

# Metal Ion Catalysis in the $\beta$ -Elimination Reactions of N-[2-(4-Pyridyl)ethyl]quinuclidinium and **N-[2-(2-Pyridyl)ethyl]quinuclidinium in Aqueous Solution**

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Catalysis of the  $\beta$ -elimination reaction of N-[2-(4-pyridyl)ethyl]quinuclidinium (1) and N-[2-(2pyridyl)ethyl]quinuclidinium (2) by  $Zn^{2+}$  and  $Cd^{2+}$  in  $OH^{-}/H_2O$  (pH = 5.20-6.35, 50 °C, and  $\mu = 1$ M KCl) has been studied. In the presence of Zn<sup>2+</sup>, the elimination reactions of both isomers occur from the Zn<sup>2+</sup>-complexed substrates (C). The equilibrium constants for the dissociation of the Zn<sup>2+</sup>complexes are as follows:  $K_d = 0.012 \pm 0.003$  M (isomer 1) and  $K_d = 0.065 \pm 0.020$  M (isomer 2). The value of  $k_{H_2O}^C$  for isomer 1 is  $4.81 \times 10^{-6}$  s<sup>-1</sup>. For isomer 2 both the rate constants for the "water" and OH<sup>-</sup>-induced reaction of the Zn<sup>2+</sup>-complexed substrate could be measured, despite the low concentration of OH<sup>-</sup> in the investigated reaction mixture  $[k_{H,O}^C = 1.97 \times 10^{-6} \text{ s}^{-1} \text{ and } k_{OH^-}^C = 21.9 \text{ M}^{-1} \text{ s}^{-1}$ , respectively]. The measured metal activating factor (MetAF), i.e., the reactivity ratio between the complexed and the uncomplexed substrate, is  $8.1 \times 10^4$  for the OH<sup>-</sup>-induced elimination of 2. This high MetAF can be compared with the corresponding proton activating factor (Alunni, S.; Conti, A.; Palmizio Errico, R. J. Chem. Soc., Perkin Trans. 2 **2000**, 453), PAF =  $1.5 \times 10^6$  and is in agreement with an E1cb irreversible mechanism ( $A_{xh}D_{E}^{*} + D_{N}$ ) (Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343). A value of  $k_{H_2O}^C \ge 23 \times 10^{-7} \text{ s}^{-1}$  is estimated for the Cd<sup>2+</sup>-complexed isomer **2**, while catalysis by Cd<sup>2+</sup> has not been observed for isomer **1**.

## Introduction

In previous studies, it was shown that  $\beta$ -elimination reactions in systems activated by a pyridine ring are strongly catalyzed by protonation of the pyridine nitrogen atom.<sup>1,3,4,5</sup> The observed proton activating factors (PAF, i.e., the ratios of second-order rate constants for Nprotonated and unprotonated substrate) are PAF = 5.3 $\times$  10<sup>4</sup> with the *N*-[2-(4-pyridyl)ethyl]quinuclidinium (1) and PAF =  $1.5 \times 10^6$  with N-[2-(2-pyridyl)ethyl]quinuclidinium (2) in OH<sup>-</sup>/H<sub>2</sub>O at 50 °C and ionic strength  $\mu$ = 1 M (KCl). This proton activation can be accounted for by an E1cb mechanism and by the high stability of the intermediate formed from the protonated substrate NH<sup>+</sup> (Scheme 1).

Reactions that are subjected to electrophilic catalysis by protons can be catalyzed by metal ions too.<sup>6,7</sup> As a matter of fact, the affinities of a substrate for both proton

#### **SCHEME 1**



and metal ions are related to its (Brønsted and/or Lewis) basicity. Lewis acid catalysis, for example, provides alternative pathways for specific acid-catalyzed enolization reactions of ketones, and comparison by metal ions and hydronium ion has recently attracted considerable interest.8-10 Thus, the Cu2+-catalyzed rate constant of

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enolization of *N*-methyl-3-acetylpyrrole<sup>11</sup> is 800 times higher than the hydronium-catalyzed rate constant. Moreover, suitable metal ions can give a "two site coordination", and this possibility leads to particularly effective catalysis. It has been shown<sup>12</sup> that complex formation between 2-acetylimidazole and Zn<sup>2+</sup> leads to rates of enolization which are up to about  $8 \times 10^3$  times larger than that of the uncomplexed substrate, while Cox<sup>13</sup> reported that the enolization of 2-acetylpyridine in the presence of  $Zn^{2+}$  is  $2\times 10^5$  faster than in the absence of the metal ion. More generally, the importance of metal ion catalysis is highlighted by the role of metal ions in enzymatic reactions. It has been suggested that metal ions hold the substrates and the reactive groups on the active site of the enzyme in the proper steric relation to each other.<sup>14</sup> For example, the Zn<sup>2+</sup>-catalyzed hydration of pyridine-2-aldehyde is a valid model for the enzyme carbonic anhydrase catalyzed hydration of aldehydes and esters. The second-order rate constant is  $6.5 \times 10^6$  faster than that for the "water" reaction, and this rate increase is only 10-fold less than that brought about by the enzyme.15

In the present paper, we report a kinetic study of the elimination reactions of **1** and **2**, in OH<sup>-</sup>/H<sub>2</sub>O at 50 °C,  $\mu = 1$  M (KCl), pH range 5.20–6.35 in the presence of Zn<sup>2+</sup> and Cd<sup>2+</sup>, with the aim of comparing the effectiveness of the proton and of the studied metal ions as reaction catalysts. Under these conditions, the studied reactions can be a model for biological and naturally occurring chemical processes in aqueous environment.

#### **Results and Discussion**

The pseudo-first-order rate constants ( $k_{obs}/s^{-1}$ , initial rate) of the elimination reaction with substrates 1 and 2 in H<sub>2</sub>O, at 50 °C and  $\mu$  = 1 M (KCl), in the presence of Zn<sup>2+</sup> and Cd<sup>2+</sup>, were measured by following spectrophotometrically the formation of 4-vinylpyridine (P) at equilibrium with its conjugated acid (PH<sup>+</sup>) at  $\lambda = 280$ nm or 2-vinylpyridine (P and PH<sup>+</sup>) at  $\lambda = 290$  nm. The concentration of 1 was about  $1.2 \times 10^{-3}$  M and that of 2 was about  $1 \times 10^{-3} \, \text{M}.$  The concentration of  $Zn^{2+}$  was in the range 0.003-0.04 M for isomer 1 and 0.004-0.04 M for isomer **2**, while the concentration of  $Cd^{2+}$  was in the range 0.005-0.2 M for isomer 1 and 0.03-0.2 M for isomer 2. The pH range studied was 5.2-6.35. The plot of  $P_{tot}$  (i.e. the total concentration [P] + [PH<sup>+</sup>]) against time (up to 3% of reaction) is strictly linear (average r =0.9998) and  $k_{obs}$  was calculated as SLOPE/[S<sub>0</sub>], where [S<sub>0</sub>] is the initial concentration of the substrate. A typical plot of  $P_{tot}$  vs time for isomer **1** at various [Zn<sup>2+</sup>] and pH = 5.19 is shown in Figure 1.

Under the reaction conditions employed, the  $pK_a^N$  of the conjugated acid of **1** is 4.85, whereas the  $pK_a^N$  of the conjugated acid of **2** is 3.81.<sup>1</sup>

**Metal Ion Catalysis by Zn**<sup>2+</sup>. The plots of  $k_{obs}$  vs [Zn<sup>2+</sup>] for isomer **1** showed a leveling off at high [Zn<sup>2+</sup>] (one example is shown in Figure 2, at pH = 6.2).

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**FIGURE 1.** Plot of  $P_{tot}/M$ , against time/min, for the elimination reaction of isomer **1** at different [Zn<sup>++</sup>]/ M, at pH = 5.19, 50 °C, and  $\mu$  = 1 M (KCl): open square, [Zn<sup>++</sup>] = 0.0350 M; solid up-triangle, [Zn<sup>++</sup>] = 0.0220 M; open circle, [Zn<sup>++</sup>] = 0.0110 M; solid square, [Zn<sup>++</sup>] = 0.0061 M.

On the other hand,  $k_{obs}$  for isomer **2** increases linearly upon increasing [Zn<sup>2+</sup>], in the [Zn<sup>2+</sup>] range 0 < [Zn<sup>2+</sup>] < 0.04 M. Nevertheless, at pH = 5.26 it was possible to increase [Zn<sup>2+</sup>] up to 0.196 M and a significant curvature was then observed (Figure 3).

A mechanism consistent with the observed results is shown in Scheme 2:

Kinetic analysis for the mechanism shown in Scheme 2 by using the steady-state approximation to I and  $I_M$  gives eqs 1–3, 6, and 7 (where eq 2 has been previously derived<sup>16</sup>).

$$v = \frac{\mathrm{d}P_{\mathrm{tot}}}{\mathrm{d}t} = k_{\mathrm{obs}}^{\mathrm{NH^{+}}}[\mathrm{NH^{+}}] + k_{\mathrm{obs}}^{\mathrm{C}}[\mathrm{C}]$$
(1)

$$k_{\rm obs}^{\rm NH^+} = k_2^{\rm NH^+} \frac{k_{\rm H_2O}^{\rm NH^+} + k_{\rm OH^-}^{\rm NH^+}[\rm OH^-]}{k_2^{\rm NH^+} + k_{\rm H_2O}^{\rm NH^+} + k_{\rm H^+}^{\rm NH^+}[\rm H^+]}$$
(2)

$$k_{\rm obs}^{\rm C} = k_2^{\rm I_M} \frac{k_{\rm H_2O}^{\rm C} + k_{\rm OH^-}^{\rm C}[\rm OH^-]}{k_2^{\rm I_M} + k_{\rm H_2O}^{\rm I_M} + k_{\rm H^+}^{\rm I_M}[\rm H^+]}$$
(3)

In all cases, the initial concentration of  $ZnCl_2$  or  $CdCl_2 = [M_0] \gg [C]$ , then  $[M_0] = [M]$ , where M is the metal ion. Under these conditions, from eq 1 and with the relationships reported in eqs 4 and 5, eq 6 can be derived.

$$K_{\rm a}^{\rm N} = \frac{[{\rm N}][{\rm H}^+]}{[{\rm N}{\rm H}^+]} \tag{4}$$

$$K_{\rm d} = \frac{[\rm N][\rm M]}{[\rm C]} \tag{5}$$

$$v = k_{obs}^{\rm NH^+} R'[S_0] + (k_{obs}^{\rm C} - k_{obs}^{\rm NH^+} R') \cdot \frac{[M_0]}{[M_0] + K_{\rm d} R} [S_0]$$
(6)

where

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**FIGURE 2.** Dependence of  $k_{obs}/s^{-1}$ , on  $[Zn^{2+}]/M$ , for the elimination reaction in OH<sup>-</sup>/H<sub>2</sub>O of isomer **1** at pH = 6.2, 50 °C,  $\mu = 1$  M (KCl).



**FIGURE 3.** Dependence of  $k_{obs}/s^{-1}$  on  $[Zn^{2+}]/M$ , for the elimination reaction in OH<sup>-</sup>/H<sub>2</sub>O of isomer **2** at pH = 5.26, 50 °C,  $\mu = 1$  M (KCl).

$$R = \frac{K_{\rm a}^{\rm N} + [{\rm H}^+]}{K_{\rm a}^{\rm N}}, \, {\rm R}' = \frac{[{\rm H}^+]}{K_{\rm a}^{\rm N} + [{\rm H}^+]}$$

and [S<sub>0</sub>] is the total concentration of the substrate. It was previously<sup>16</sup> shown that eq 2 reduces to  $k_{obs}^{NH^+} = k_{H_2O}^{NH^+} + k_{OH^-}^{NH^+}$ [OH<sup>-</sup>], owing to the operating (E1cb)<sub>1</sub> mechanism, and the values determined are as follows:  $k_{H_2O}^{NH^+} = 2.54 \times 10^{-6} \, \text{s}^{-1}$  (isomer 1) and  $k_{H_2O}^{NH^+} = 8.75 \times 10^{-7} \, \text{s}^{-1}$  (isomer 2),  $k_{OH^-}^{NH^+} = 241 \, \text{M}^{-1} \, \text{s}^{-1}$  (isomer 1), and  $k_{OH^-}^{NH^+} = 290 \, \text{M}^{-1} \, \text{s}^{-1}$  (isomer 2). From these values,  $k_{obs}^{NH^+}$  can be calculated at each pH. Even if the  $k_{H_2O}^{NH^+}$  term is associated with a large uncertainty, especially with isomer 2, this term, in the range of the pH used, does not significantly influence the calculated parameters of the mechanism. From the slope of the plot (initial rate)  $P_{tot}$  vs time it is possible to calculate  $k_{obs} = \text{SLOPE/}[S_0]$ . The expression for  $k_{obs}$  is given by eq 7:

$$k_{\rm obs} = k_{\rm obs}^{\rm NH^+} {\rm R}' + (k_{\rm obs}^{\rm C} - k_{\rm obs}^{\rm NH^+} {\rm R}') \frac{[{\rm M}_0]}{[{\rm M}_0] + K_{\rm d} {\rm R}} \quad (7)$$

$$N + Zn^{++} = C \qquad N + H^{+} = NH^{+}$$

$$C + OH^{-} \frac{k_{OH^{-}}^{C}}{k_{H_{2}O}^{H}} |_{M} + H_{2}O \qquad NH^{+} + OH^{-} \frac{k_{OH^{+}}^{NH^{+}}}{k_{H_{2}O}^{NH^{+}}} | + H_{2}O$$

$$C + H_{2}O = \frac{k_{H_{2}O}^{C}}{k_{H^{+}}^{I_{M}}} |_{M} + H_{3}O^{+} \qquad NH^{+} + H_{2}O = \frac{k_{H_{2}O}^{NH^{+}}}{k_{H^{+}}^{NH^{+}}} | + H_{3}O^{+}$$

$$L_{H} = \frac{k_{2}^{1}}{k_{H^{+}}^{NH^{+}}} P$$

$$L_{H} = \frac{k_{2}^{1}}{k_{H^{+}}^{NH^{+}}} P$$

$$N = \bigvee_{N}^{+} CH_2 \cdot CH_2 \cdot N$$

$$NH^{+} = \bigvee_{H}^{+} CH_2 \cdot CH_2 \cdot N$$

$$C = \bigvee_{H}^{+} CH_2 \cdot CH_2 \cdot N$$

$$I = \bigvee_{H}^{-} CH - CH_2 \cdot N$$

$$I_M = \bigvee_{H}^{-} CH - CH_2 \cdot N$$

$$I_M = \bigvee_{H}^{+} CH - CH_2 \cdot N$$

 $K_{\rm d}$  and  $k_{\rm obs}^{\rm C}$  can be obtained from eq 7 by two procedures. Equation 7 ( $k_{\rm obs}$  vs [M<sub>0</sub>] plot) is the equation of a curve, and the curvature, experimentally observable only for Zn<sup>2+</sup>, is an indication of a significant complexation of the metal ion with the substrate. Equation 7 can be linearized by rearranging it as in eq 8:

$$\frac{1}{k_{\rm obs} - k_{\rm obs}^{\rm NH^+} \rm R'} = \frac{1}{(k_{\rm obs}^{\rm C} - k_{\rm obs}^{\rm NH^+} \rm R')} + \frac{K_{\rm d} \rm R}{[\rm M_0](k_{\rm obs}^{\rm C} - k_{\rm obs}^{\rm NH^+} \rm R')}$$
(8)

A first procedure for the evaluation of  $K_d$  and  $k_{obs}^C$  uses a plot of  $1/(k_{obs} - k_{obs}^{NH^+}R')$  vs  $1/[M_0]$ . A straight line is expected (average r = 0.9971) whose intercept, *i*, and slope are given by eqs 9 and 10:

$$i = \frac{1}{(k_{\text{obs}}^{\text{C}} - k_{\text{obs}}^{\text{NH}^+} \text{R}')}$$
(9)

slope = 
$$\frac{K_{\rm d}R}{(k_{\rm obs}^{\rm C} - k_{\rm obs}^{\rm NH^+}R')}$$
(10)

From eqs 9 and 10, eq 11 follows:

$$\frac{\text{slope}}{i} = K_{\rm d} \mathbf{R} \tag{11}$$

 $K_{\rm d}$  can be calculated from the known value of *R*, while  $k_{\rm obs}^{\rm C}$  can be calculated from eq 12 (a rearranged form of eq 10):

$$k_{\rm obs}^{\rm C} = k_{\rm obs}^{\rm NH^+} {\rm R}' + \frac{K_{\rm d} {\rm R}}{\rm slope}$$
(12)

A second procedure for the evaluation of  $K_d$  and  $k_{obs}^C$  can be a nonlinear fitting of eq 7. According to this



**FIGURE 4.** Dependence of  $1/[k_{obs} - k_{obs}^{NH^+}R']/s$  on  $1/[M_0]$  for the elimination reaction in OH<sup>-</sup>/H<sub>2</sub>O of isomer **2** at pH = 5.26, 50 °C,  $\mu = 1$  M (KCl).



**FIGURE 5.** Dependence of  $k_{0s}^{C}$ /s<sup>-1</sup> on [OH<sup>-</sup>]/M for the elimination reaction of isomer **2** catalyzed by Zn<sup>2+</sup> in OH<sup>-</sup>/H<sub>2</sub>O at 50 °C,  $\mu$  = 1 M (KCl). The point at each pH represents the average value of two or three sets of experiments.

procedure, a  $K_d = 0.065$  M has been calculated for isomer **2** at pH = 5.26; in fact, at this low pH value it was possible to increase [Zn<sup>2+</sup>] up to 0.196 M. Under these conditions, the plot ( $k_{obs}$  vs [M<sub>0</sub>]) shows a significant curvature (Figure 3). At higher pHs a lower [Zn<sup>2+</sup>] is convenient in order to avoid precipitation of Zn(OH)<sub>2</sub>. The values of  $k_{obs}^C/s^{-1}$  with isomer **2** (calculated with the first procedure), at the four investigated pHs are 2.26 × 10<sup>-6</sup>, 2.56 × 10<sup>-6</sup>, 2.78 × 10<sup>-6</sup>, and 4.09 × 10<sup>-6</sup> at pH = 5.26, 5.6, 5.9, and 6.2, respectively. The plot of  $1/(k_{obs} - k_{obs}^{\rm NH^+} R')$  vs 1/[M<sub>0</sub>] at pH = 5.26 for isomer **2** is shown in Figure 4.

The plot of  $k_{obs}^{C}$  vs [OH<sup>-</sup>] for isomer **2** is shown in Figure 5.

A good linear correlation has been observed:  $k_{\rm obs}^{\rm C}/{\rm s}^{-1}$ = 1.97 × 10<sup>-6</sup> (sd = 1.50 × 10<sup>-7</sup>) + 21.9 (sd = 2.8) [OH<sup>-</sup>], r = 0.9842. The experimentally observed linear dependence of  $k_{\rm obs}^{\rm C}$  on [OH<sup>-</sup>] is in agreement with an E1cb irreversible mechanism. In fact, in the condition of irreversibility  $k_{2}^{\rm I_{M}} \gg k_{\rm H_{2}O}^{\rm I_{M}} + k_{\rm H^{+}}^{\rm I_{M}}[\rm H^{+}]$  and eq 3 reduces to eq 13.

$$k_{\rm obs}^{\rm C} = k_{\rm H_2O}^{\rm C} + k_{\rm OH^-}^{\rm C}[{\rm OH^-}]$$
 (13)

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On the contrary, if the intermediate I<sub>M</sub> (Scheme 1) were formed reversibly  $(k_2^{I_M} \ll k_{H_2O}^{I_M} + k_{H^+}^{I_M}[H^+])$  or if the terms  $k_{H_2O}^{I_M}$  and  $k_{H^+}^{I_M}[H^+]$  in eq 3 contributed significantly to  $k_{obs}^C$ , the plot of  $k_{obs}^C$  vs  $[OH^-]$  would not be expected to be linear. In our systems,  $k_{H_2O}^C$  and  $k_{OH^-}^C$  represent the pseudo-first-order and second-order rate constants for carbon deprotonation of the metal ion complexed substrate, C, by the base H<sub>2</sub>O and OH<sup>-</sup>, respectively. The values obtained are reported in Table 1.

The values of  $K_d$  and  $k_{obs}^C$  for isomer **1**, calculated by the above nonlinear fitting procedure (eq 7), are as follows:  $K_{\rm d} = 0.012 \pm 0.003$  M (average value at the various pHs) and  $k_{obs}^C/s^{-1} = 4.55 \times 10^{-6}$  (pH 5.19), 5.2 × 10<sup>-6</sup> (pH 5.3), 4.72 × 10<sup>-6</sup> (pH 5.6), 6.17 × 10<sup>-6</sup> (pH 5.9), 6.16  $\times$  10<sup>-6</sup> (pH 6.2), and 6.36  $\times$  10<sup>-6</sup> (pH 6.35). The variation of  $k_{obs}^{C}$  with [OH<sup>-</sup>] was very small because of the small pH range investigated. A plot of  $k_{obs}^{C}$  vs [OH<sup>-</sup>] gives, by linear regression analyses:  $k_{obs}^{C}/s^{-1} = 4.81 \times$  $10^{-6} (sd = 0.30 \times 10^{-6}) + 13.8 (sd = 4.4) [OH^{-}], r =$ 0.8425. While the value of  $k_{\rm H_2O}^{\rm C}$  (the intercept) is a reliable value, that of  $k_{OH^-}^C$  (the slope) is associated with a large standard deviation. However, given that a  $k_{\rm OH^-}^{\scriptscriptstyle \rm C}$ = 18.0  $M^{-1}$  s<sup>-1</sup> is expected from eq 13 to increase the  $k_{obs}^{C}$ of 50% on passing from pH 5.19 to pH 6.35, in the light of our experimental data we can only estimate a  $k_{OH^-}^C <$ 18.0  $M^{-1}$  s<sup>-1</sup> for isomer **1**. The values of  $K_d$  for the isomers **1** ( $K_{\rm d} = 0.012 \pm 0.003$  M) and **2** ( $K_{\rm d} = 0.065 \pm 0.020$  M) are as expected from the differences in the  $pK_a$  values of the two substrates:  ${}^{1} pK_{a}(1) = 4.85$  and  $pK_{a}(2) = 3.81$ . In fact, the more basic substrate 1 also shows a stronger complexation with Zn<sup>2+</sup>. In previously reported studies<sup>12</sup> of enolization reactions of some acetylheterocycles evidence of the formation of a complex between the metal ion (e.g., Zn<sup>2+</sup> and Cu<sup>2+</sup>) and the substrate was obtained only for the most basic investigated compound (2-acetylimidazole:  $pK_a = 3.12$ ). Moreover, a value of  $K_d = 0.028$ M has been reported by Cox<sup>13</sup> for the Zn<sup>2+</sup>-complexed 2acetylpyridine (p $K_a = 2.64$ ). However, the interaction of the metal ion with both 2-acetylimidazole and 2-acetylpyridine involves the nitrogen heterocyclic atom and the carbonyl-oxygen atom.

The ratio  $k_{OH^{-}}^{C}/k_{OH^{-}}^{N}$ , i.e. the metal activating factor (MetAF), is a measure of the activation of the elimination reaction by the interaction of  $Zn^{2+}$  and  $Cd^{2+}$  with the pyridine nitrogen atom. The MetAF found for Zn<sup>2+</sup> with isomer **2** is 8.1  $\times$  10<sup>4</sup> while with isomer **1** is < 5.2  $\times$  10 <sup>3</sup> (See above). The proton activating factors, PAF, for isomers 1 and 2, previously determined under the same conditions,<sup>1</sup> are a measure of the activation of the elimination reactions by protonation of the nitrogen atom of the pyridine ring. It was demonstrated that these baseinduced elimination reactions indeed proceed via NH<sup>+</sup>, the nitrogen protonated substrate, and that the mechanism is E1cb ( $A_{xh}D_H + D_N$ ). On the other hand the mechanism of elimination induced by OH- for the unprotonated substrates, N, can be either E2 or (E1cb)<sub>I</sub> as it was not possible to discriminate between the two pathways.<sup>1,5</sup> Consequently, it was not clear whether the PAFs observed are a measure of the activation by the proton of the rate determining carbanion intermediate

TABLE 1. Rate Constants for the Elimination Reaction Induced by H<sub>2</sub>O or OH<sup>-</sup> with 1 and 2 Complexed with Zn<sup>2+</sup> (C) in H<sub>2</sub>O at 50 °C,  $\mu = 1$  M (KCl)<sup>*a*</sup>

	$k^{ m C}_{ m H_{2}O}  imes 10^{6} \ ({ m s}^{-1})$	$k_{\rm OH^-}^{\rm C}$ (M <sup>-1</sup> s <sup>-1</sup> )	<i>K</i> <sub>d</sub> <sup><i>b</i></sup> (M)	$k_{ m OH^-}^{ m N}  imes 10^{3~c} \ ({ m M^{-1}~s^{-1}})$
1	4.81	<18	0.012	3.45
2	1.97	21.9	0.065	0.27

<sup>*a*</sup> For comparison, the rate constants, for the same reaction from N and OH<sup>-</sup> are reported. N is the unprotonated substrate. <sup>*b*</sup> Dissociation constants for Zn<sup>2+</sup>-complexed substrate (**C**). <sup>*c*</sup> Previously determined (ref 1).

## CHART 1



formation within an  $(E1cb)_{I}$  mechanism or if they are associated with a change in mechanism from E2 (N) to  $(E1cb)_{I}$  (NH<sup>+</sup>). The value of MetAF by Zn<sup>2+</sup> observed for isomer **2** is only about 10 times lower than that of the corresponding PAF ( $1.5 \times 10^{6}$ ) and accordingly the most consistent mechanism of elimination of the Zn<sup>2+</sup>-complexed substrate is probably a (E1cb)<sub>I</sub> rather than an E2 process. The comparison of the pseudo-first-order rate constant,  $k_{H_2O}^C$ , for the carbon deprotonation from the two Zn<sup>2+</sup>-complexed isomers, **C**, by the base H<sub>2</sub>O is also of interest. The measured values [ $k_{H_2O}^C = 4.81 \ (\pm 0.60) \times 10^{-6} \ s^{-1}$  for isomer **1** and  $k_{H_2O}^C = 1.97 \ (\pm 0.38) \times 10^{-6} \ s^{-1}$ for isomer **2**] are similar and this excludes a significant contribution from the negatively charged carbon atom in the reaction intermediate. In fact, the formation of a chelate complex is possible only for isomer **2** (Chart 1)

Finally the ratio  $k_{OH}^C / k_{H_2O}^C (= 1.1 \times 10^{-7} \text{ M for isomer}$ **2**) quantifies the higher reactivity of the base OH<sup>-</sup> than that of H<sub>2</sub>O in the elimination reaction of **C**, as expected from the high  $\Delta pK_a$  (H<sub>2</sub>O - H<sub>3</sub>O<sup>+</sup>) = 17.4.

**Metal Ion Catalysis by Cd**<sup>2+</sup>. The effect of the addition of Cd<sup>2+</sup> to isomer **2** showed a linear dependence of  $k_{obs}$  on [Cd<sup>2+</sup>] at all the investigated pHs and using [Cd<sup>2+</sup>] up to 0.2 M. This has been rationalized in terms of a limited complexation of **2** with Cd<sup>2+</sup>. In this situation the term  $K_d R > [Cd^{2+}]$  in eq 7 and  $k_{obs}$  is given by eq 14.

$$k_{\rm obs} = k_{\rm obs}^{\rm NH^+} \mathbf{R}' + (k_{\rm obs}^{\rm C} - k_{\rm obs}^{\rm NH^+} \mathbf{R}') \frac{[\mathbf{M}_0]}{K_{\rm d} \mathbf{R}}$$
(14)

A plot of  $k_{obs}$  vs [Cd<sup>2+</sup>] is expected to be linear with intercept, *i'* (eq 15), and slope, slope' (eq 16). Equation 16 is derived from eqs 13 and 14 assuming an E1cb irreversible mechanism in analogy with the process catalyzed by Zn<sup>2+</sup>.

$$\vec{i} = k_{\rm obs}^{\rm NH^+} R' \tag{15}$$

slope' = 
$$\frac{(k_{H_2O}^C - k_{obs}^{NH^+}R')}{K_dR} + \frac{k_{OH^-}^C}{K_dR}[OH^-]$$
 (16)

The values of slope' found at pHs = 5.29, 5.62, 5.93, 6.1, 6.2, and 6.21 are independent of pH (within the experimental errors) with an average value of slope' =

21.6 ( $\pm$  1.5)  $\times$  10<sup>-7</sup>. To a first approximation this result implies that the term  $k_{OH^-}^C[OH^-]/K_dR$  does not contribute significantly to the  $Cd^{2+}$  catalysis and that catalysis by Cd<sup>2+</sup> is observed for **2** only for the "water"-induced elimination reaction. The lack of a curvature in the plot of  $k_{obs}$  vs [Cd<sup>2+</sup>] implies an estimated  $K_d$  value > 1 M as a curvature would be expected for a 20% complexation at  $[Cd^{2+}] = 0.2$  M. Considering an average value of the  $k_{obs}^{\rm NH^+} \rm R'$  (in the pH range 5.29–6.20) of 1.2  $\times$   $10^{-7}\, s^{-1}$  and R = 1, it can be estimated that  $k_{\rm H,O}^{\rm C} \ge 23 \times 10^{-7} \, {\rm s}^{-1}$ . On the other hand no catalysis by Cd<sup>2+</sup> was observed for isomer 1, it is not clear if the reason is associated with a lower energy of stabilization by Cd<sup>2+</sup> of the intermediate with respect to that by Zn<sup>2+</sup>. It should also be considered that the water reaction in the absence of metal ion for isomer **1** is about 10 times larger than with isomer **2**, and that catalysis by Cd<sup>2+</sup> could well be covered by the water reaction.

## Conclusions

It has been demonstrated that Zn<sup>2+</sup> catalyses the  $\beta$ -elimination reactions of *N*-[2-(4-pyridyl)ethyl]quinuclidinium and of N-[2-(2-pyridyl)ethyl]quinuclidinium to 4-vinylpyridine and 2-vinylpyridine, respectively. An increase in reactivity of  $8.1 \times 10^4$  due to the interaction of Zn<sup>2+</sup> with the nitrogen atom of the pyridine ring was detected with substrate 2 when the base was OH<sup>-</sup> (pH range 5.2–6.3, 50 °C,  $\mu$  = 1 M KCl). The strong catalysis is indicative of an E1cb mechanism for the Zn<sup>2+</sup>-complexed substrate (C). The values of the pseudo-first-order rate constants for the "water" elimination reactions of C are  $k_{\rm H_2O}^{\rm C} = 4.81 \times 10^{-6} \, {\rm s}^{-1}$  and  $k_{\rm H_2O}^{\rm C} = 1.97 \times 10^{-6} \, {\rm s}^{-1}$  for isomer's 1 and 2, respectively. The similarity of these two values allows to exclude the formation of a chelate between the substrate and the metal ion in the transition state. The calculated values of the equilibrium constant for the dissociation of the  $Zn^{2+}$ -complexes are:  $K_d = 0.012$  $\pm$  0.003 M for isomer 1 and  $\mathit{K}_{\rm d}$  = 0.065  $\pm$  0.020 M for isomer **2**. In the presence of Cd<sup>2+</sup> a value of  $k_{\rm H_2O}^{\rm C} \ge 23 \times$  $10^{-7}$  s<sup>-1</sup> can be estimated for isomer **2**. No catalysis by Cd<sup>2+</sup> was observed for isomer **1**.

#### **Experimental Section**

**Materials.** Glass distilled and freshly boiled water was used throughout. Reagent grade potassium chloride and  $ZnCl_2$  and  $CdCl_2$  were commercial material, *N*-[2-(4-pyridyl)ethyl]-quinuclidinium (1) and *N*-[2-(2-pyridyl)ethyl]quinuclidinium (2) were prepared according to a previously described procedure.<sup>1</sup>

**Kinetics Measurements.** Pseudo-first-order rate constants,  $k_{obs}/s^{-1}$ , for the elimination reaction of **1** and **2** were determined by following the formation of the corresponding 4-vinylpyridine at  $\lambda = 280$  nm or 2-vinylpyridine at  $\lambda = 290$  nm, as previously described.<sup>5</sup> The p $K_a$  values of 4-vinylpyridine and of 2-vinylpyridine are 5.06 and 4.77, respectively, under the adopted experimental conditions. The relatively higher values determined previously<sup>5</sup> were 5.64 and 5.06 respectively in the presence of acetate/acetic acid buffers. Under the adopted experimental conditions, the vinylpyridine (P) is in equilibrium with a significant amount of its conjugated acid, PH<sup>+</sup>; the total concentration of the product,  $P_{tot} = P + PH^+$ , has been calculated by eq 17

$$P_{\text{tot}} = \frac{(A_t - A_0)}{\epsilon_{\text{P}} + \epsilon_{\text{PH}^+} \frac{[\text{H}^+]}{K_a^{\text{P}}}} \left(1 + \frac{[\text{H}^+]}{K_a^{\text{P}}}\right)$$
(17)

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<sup>+</sup>;  $\epsilon_P$  is the extinction coefficient of 4-vinylpyridine<sup>1</sup> [1634 M<sup>-1</sup> cm<sup>-1</sup> at 50 °C,  $\mu = 1$  M (KCl) and  $\lambda = 280$  nm] or of 2-vinylpyridine<sup>1</sup> [3584  $M^{-1}$  cm<sup>-1</sup> at 50 °C,  $\mu = 1$  M (KCl) and  $\lambda = 290$  nm] and  $\epsilon_{PH}$  is the extinction coefficient of 4-vinylpyridinium<sup>5</sup> [8987 M<sup>-1</sup> cm<sup>-1</sup> at 50 °C,  $\mu = 1$  M (KCl) and  $\lambda = 280$  nm] or of 2-vinylpyridinium<sup>5</sup> [9773 M<sup>-1</sup> cm<sup>-1</sup> at 50 °C,  $\mu = 1$  M (KCl) and  $\lambda = 290$ nm]. A plot of  $P_{\text{tot}}$  against time was linear and the  $k_{\text{obs}}/\text{s}^{-1}$ values, were calculated from  $k_{obs} = \text{SLOPE}/[S_0]$ , where  $[S_0]$  is the initial concentration of the substrate (1 or 2). The pH of the solution used in the kinetic experiments was adjusted with small amounts of HCl or KOH in order to have the same value of pH at the different  $[\mbox{Zn}^{2+}]$  values. The pH of the solution was checked in order to make sure that no variation of pH would occur during the experiments (the observed variation of pH was < 0.1 throughout). The UV spectra of the substrates and of the products were not influenced by the presence of  $Zn^{2+}$  at the concentration used in the kinetic runs at the working wavelength. The stability of a solution of 4- or

2-vinylpyridinium and Zn<sup>2+</sup> was controlled in several reaction conditions. The value of p $K_w$  at 50 °C and  $\mu$  = 1 M (KCl) is 13.23.<sup>1</sup>

**Product Analysis.** In several experiments solutions of **1** or **2** at 50 °C,  $\mu = 1$  M (KCl), at the concentration used for the kinetic runs and in the presence of  $Zn^{2+}$  or  $Cd^{2+}$  were left to react for several hours up to ~5% of the total reaction. The pH was then increased to 10–11 and the extraction with *n*-hexane gave, by GLC analysis, only 4- or 2-vinylpyridine, respectively, and quinuclidine.

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**Supporting Information Available:** Observed pseudofirst-order rate constants,  $k_{obs}/s^{-1}$ , for the  $\beta$ -elimination of N-[2-(4-pyridyl)ethyl]quinuclidinium (1) and N-[2-(2-pyridyl)ethyl]quinuclidinium (2) in H<sub>2</sub>O, 50 °C, and  $\mu = 1$  M (KCl) at different pH values and in the presence of metal ion Zn<sup>2+</sup> or Cd<sup>2+</sup>. This material is available free of charge via the Internet at http://pubs.acs.org.

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