

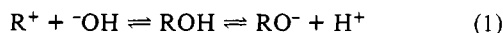
# pH Dependence of the Elimination of Isoquinolines from *N*-(2-Cyanoethyl)isoquinolinium Cations

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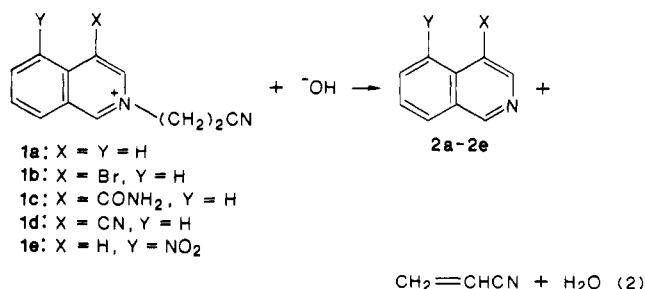
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**Abstract:** The reactions of *N*-(2-cyanoethyl)isoquinolinium cations (**1a** (unsubstituted), **1b** (4-bromo), **1c** (4-aminocarbonyl), **1d** (4-cyano), **1e** (5-nitro)) have been investigated in basic aqueous solution (pH 9–13) at 25 °C and ionic strength 0.1. In these solutions, these cations are rapidly equilibrated with their C-1 pseudobases, and pseudobase alkoxide ions, and  $pK_R^+$  and  $pK_{RO^-}$  have been evaluated. Subsequently, **1a**–**1c** and **1e** undergo hydroxide ion catalyzed eliminations to give the appropriately substituted isoquinoline and acrylonitrile. The pH rate profiles for these reactions are very dependent upon  $pK_R^+$  and  $pK_{RO^-}$  for the isoquinolinium cation. It is shown that the nonreactivity of **1d** under these conditions is readily rationalized in terms of the overwhelming predominance of the nonproductive pseudobase species (and/or its alkoxide ion) over the entire pH region under study. Second-order rate constants ( $k_{OH}$ ) for the elimination reaction correlate with the  $pK_a$  of the isoquinolinium cation, with  $\beta_{lg} = -0.43$ . Elimination in basic  $D_2O$  resulted in no observable incorporation of deuterium into the acrylonitrile product. These observations are shown to be consistent with either an E2 mechanism or an E1cB mechanism involving a hydrogen-bonded carbanionic intermediate in which internal return of the proton and loss of the nucleofuge are both faster than exchange with solvent.

The reactivities of heteroaromatic cations in basic solutions are influenced by the equilibration of these species with their pseudobases.<sup>1</sup> In aqueous solutions these pseudobases (hydroxide adducts) are also in equilibrium with their alkoxide ion conjugate bases (eq 1). Such equilibria may profoundly influence the pH rate profiles for reactions of heteroaromatic cations in aqueous solution.



Several earlier studies from our laboratory have demonstrated and analyzed this phenomenon for reactions in which the pseudobase or its alkoxide ion is the reactive species.<sup>1–5</sup> We now present a detailed examination of the pH rate profiles for a reaction in which the heteroaromatic cation is the reactive species but in which neither the pseudobase nor its alkoxide ion undergoes reaction. The reaction under investigation is the base-catalyzed elimination of an isoquinoline from an *N*-(2-cyanoethyl)isoquinolinium cation (eq 2). We demonstrate that the relative reactivities of such heterocyclic cations in this reaction are quite pH-dependent and that a complete pH rate profile is essential to the interpretation of reactivity in reactions of this type.



## Experimental Section

Isoquinoline, 4-bromoisquinoline, 5-nitroisoquinoline, and 3-bromopropionitrile are commercial products (Aldrich Chemical Co.). 4-Cyanoisoquinoline and 4-isoquinolinecarboxamide were prepared as previously described.<sup>6</sup>

**Table I.** *N*-(2-Cyanoethyl)isoquinolinium Bromides (1-Br<sup>+</sup>)

cation	mp, °C	<sup>1</sup> H NMR (in D <sub>2</sub> O), <sup>a</sup> δ
<b>1a</b>	243–245	3.6 (2 H, t), 5.28 (2 H, t), 7.83–8.83 (6 H, m), 9.96 (1 H, d)
<b>1b</b>	203–205	3.63 (2 H, t), 5.2 (2 H, t), 7.98–8.73 (4 H, m), 9.1 (1 H, d), 10.03 (1 H, d)
<b>1c</b>	222–223	3.57 (2 H, t), 5.23 (2 H, t), 8.0–8.83 (4 H, m), 9.0 (1 H, d), 10.07 (1 H, d)
<b>1d</b>	229–230	3.67 (2 H, t), 5.47 (2 H, t), 7.92–9.17 (4 H, m), 9.33 (1 H, s), 10.23 (1 H, s) <sup>b</sup>
<b>1e</b>	224–225	3.57 (2 H, t), 5.53 (2 H, t), 8.37 (1 H, dd), 8.83–9.6 (4 H, m), 10.28 (1 H, d)

<sup>a</sup> The following coupling constants are observed for all **1**:  $J = 6$  Hz for the CH<sub>2</sub> triplets of the cyanoethyl substituent;  $J \approx 1$  Hz for H-1 ( $\delta \approx 10.1$ ) and H-3 ( $\delta \approx 9.2$ ). <sup>b</sup> In CF<sub>3</sub>CO<sub>2</sub>H. These solutions are unstable, and time-dependent spectral changes occur. We have traced this phenomenon to a reaction (product not identified) between the cyano substituents and this solvent. We have also observed similar processes for cyanopyridinium cations in CF<sub>3</sub>CO<sub>2</sub>H.

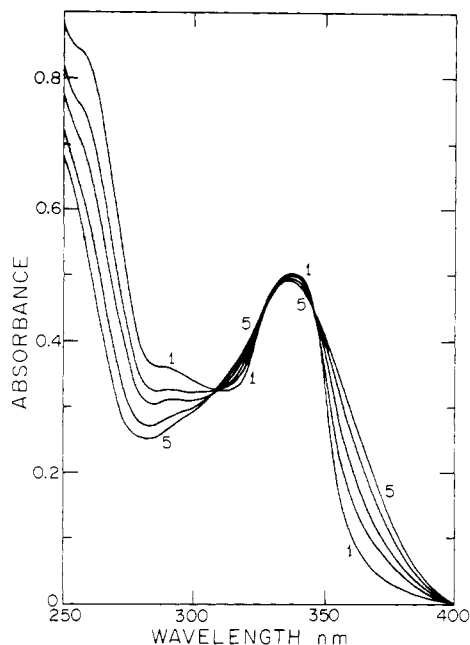
***N*-(2-Cyanoethyl)isoquinolinium Bromides (1-Br<sup>+</sup>).** The most efficient routes to these salts proved to be via prolonged reflux (several days) of the appropriate isoquinoline with a slight excess of 3-bromopropionitrile in a mixture of ethanol and acrylonitrile. The salts were precipitated in approximately 50% yields by swamping the reaction products with ether. In the absence of acrylonitrile, these products were contaminated with significant amounts of the isoquinoline hydrobromides, which were presumably formed via isoquinoline catalyzed elimination reactions of either **1** or 3-bromopropionitrile.<sup>7</sup> The addition of the hydrohalides of heterocyclic bases to acrylonitrile has been reported<sup>8</sup> as a synthetic route to these species; however, we have been unable to accomplish efficient syntheses of **1** under the reported reaction conditions. The crude salts (**1-Br<sup>+</sup>**) were recrystallized several times from either ethanol or methanol after treatment with sodium carbonate to neutralize any contamination by isoquinoline hydrobromide. They were characterized by <sup>1</sup>H NMR spectroscopy (Table I) and Volhard titration of the bromide ion (100 (±2)%).

**Reaction Products.** The electronic absorption spectra of all reaction products were compared with authentic mixtures (in 1:1 molar ratio) of the appropriate isoquinoline and acrylonitrile. These products were also observed by <sup>1</sup>H NMR spectroscopy. In a typical experiment, a solution of **1a-Br<sup>+</sup>** (0.2 M) was prepared in a mixture of D<sub>2</sub>O (0.35 mL containing 0.4 M Na<sub>2</sub>CO<sub>3</sub>) and acetonitrile (0.15 mL). The product spectrum displayed isoquinoline ( $\delta$  9.3 (1 H, s), 8.5 (1 H, d), 8.33–7.6 (5 H, m)) and acrylonitrile ( $\delta$  6.67–5.83 (3 H, m)) in 1:1 molar ratio and identical with the spectrum of an authentic 1:1 mixture of these two species in the

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**Figure 1.** Time dependence of the electronic absorption spectrum of the 2-(2-cyanoethyl)-5-nitroisoquinolinium cation (**1e**) (0.1 mM) in aqueous solution of pH 8.5. Curves: 1 at 0 min; 2 at 25 min; 3 at 46 min; 4 at 96 min; 5 at 435 min.

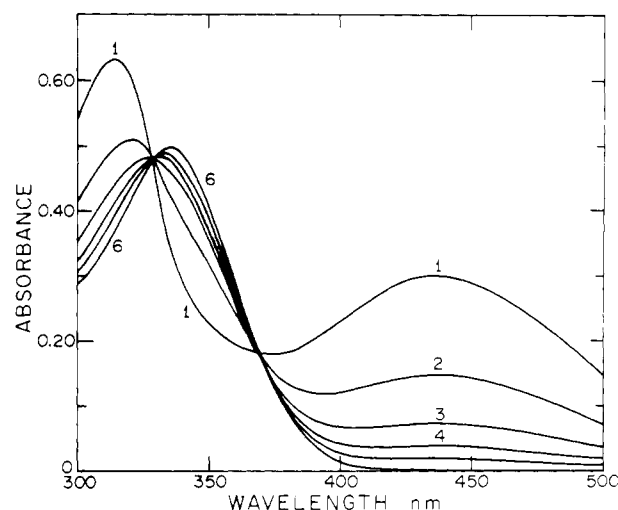
same solvent. Similar analyses were used for the characterization of the reaction products from **1b** (in 0.4 M Na<sub>2</sub>CO<sub>3</sub>), **1c**, and **1e** (each in phosphate buffer of pH 8).

**Kinetic Studies.** All reactions were followed in aqueous solution at 25 °C in buffers of ionic strength 0.1 at appropriate wavelengths (**1a**, 335 nm; **1b**, 345 or 298 nm (pH > 11.4); **1c**, 300 or 340 nm (pH < 11.3); **1e**, 445 or 500 nm), using either a Cary 210 spectrophotometer or a Durrum stopped-flow spectrophotometer (for  $t_{1/2} < 10$  s). Concentrations of **1**·Br<sup>−</sup> were in the range 0.1–0.2 mM. All reactions proved to be kinetically first-order in the isoquinoline species for at least 95% of the reaction. The kinetic studies were conducted in either 2-amino-2-(hydroxymethyl)-1,3-propanediol (Tris) buffers (pH 8–9), carbonate buffers (pH 9.4–10.5), or KOH + KCl solutions (pH 10.7–13). We were unable to observe any buffer catalysis in the Tris buffers, while weak catalysis by the carbonate buffers was found in the case of **1a** only. In this case, data at each pH were obtained at four different carbonate concentrations and extrapolated to give  $k_{obs}$  at [CO<sub>3</sub><sup>2−</sup>] = 0.

**Equilibrium Constants.** All pK values (pK<sub>a</sub>, pK<sub>R+</sub>, pK<sub>RO−</sub>) were measured spectrophotometrically at 25 °C and ionic strength 0.1 from the absorbance of at least 10 solutions in the range pH = pK ± 1.

## Results

**Reaction Products.** The time dependence of the electronic absorption spectrum of the 2-(2-cyanoethyl)-5-nitroisoquinolinium cation (**1e**) is shown in Figures 1 (pH 8.5) and 2 (pH 11.5). Although the spectra of the initial species present in these two solutions are different, the final spectra are identical with one another and are also identical with the spectrum of an authentic sample of an aqueous solution of 5-nitroisoquinoline (**2e**). The initial long wavelength absorption maximum at 436 nm in Figure 2 is typical of that previously observed for the C-1 hydroxide adducts (pseudobases) of many other 5-nitroisoquinolinium cations.<sup>9</sup> The pH dependence of this initial absorbance is con-



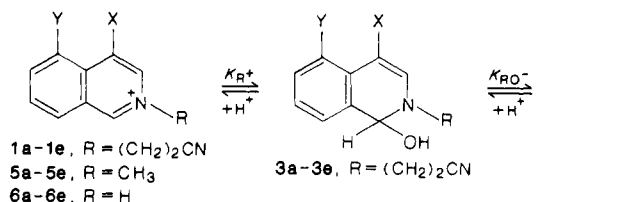
**Figure 2.** Time dependence of the electronic absorption spectrum of the 2-(2-cyanoethyl)-5-nitroisoquinolinium cation (**1e**) (0.1 mM) in aqueous solution of pH 11.5. Curves: 1 at 16 s; 2 at 95 s; 3 at 180 s; 4 at 255 s; 5 at 340 s; 6 at 1060 s.

**Table II.** pK Values for Isoquinolinium Cations<sup>a</sup>

X	Y	cation 1		cation 5:	
		pK <sub>R+</sub>	pK <sub>RO−</sub>	pK <sub>R+</sub>	pK <sub>a</sub> (6)
H	H	(14.6) <sup>b</sup>	(14.3) <sup>c</sup>	16.29 <sup>d</sup>	5.55 ± 0.01
Br	H	11.67 ± 0.03	(13.5) <sup>c</sup>	13.4 <sup>e</sup>	3.55 ± 0.03
CONH <sub>2</sub>	H	9.62 ± 0.03	12.87 ± 0.02	11.49 <sup>f</sup>	3.78 ± 0.01
CN	H	5.77 ± 0.03	12.20 ± 0.03	7.80 <sup>f</sup>	2.06 ± 0.2
H	NO <sub>2</sub>	9.93 ± 0.02	12.49 ± 0.05	11.7 <sup>g</sup>	3.48 ± 0.01

<sup>a</sup> All data evaluated spectrophotometrically in aqueous solution at 25 °C; ionic strength 0.1. <sup>b</sup> Estimated from pK<sub>R+</sub><sup>1</sup> = 1.05 (±0.01)pK<sub>R+</sub><sup>5</sup> − 2.5 (±0.01) ( $r = 0.9998$ ), which is derived from the data for the other four isoquinolines in this table. Note that pK<sub>a</sub> for the (2-cyanoethyl)diethylammonium cation is 2.6 units less than for the methyldiethylammonium cation.<sup>10</sup> <sup>c</sup> Calculated from<sup>5</sup> pK<sub>RO−</sub> = 0.29pK<sub>R+</sub> + 10.1. <sup>d</sup> From ref 11. <sup>e</sup> This work (ionic strength 0.1). <sup>f</sup> From ref 6. <sup>g</sup> From ref 12.

sistent with an acid–base equilibration of pK<sub>a</sub> 9.9, which we assign to pK<sub>R+</sub> for pseudobase (**3e**) formation from **1e**.



The time-dependent electronic absorption spectra of each of **1b** and **1c** also indicate that both the cation (at low pH) and the pseudobase (at high pH) are clearly converted into the corresponding isoquinoline. For the 4-carboxamide (**1c**), an alternative reaction begins to become apparent for pH > 12, since such solutions begin to display a pH-dependent yellow coloration. This yellow color arises from a species having  $\lambda_{max} = 410$  nm; there is only a trace of this species in the product mixture at pH 12, but its concentration increases with pH in more basic solutions. The reaction leading to this colored species seems to be unique to the 4-carboxamide derivative, since it is not observed for any other *N*-(2-cyanoethyl)isoquinolinium cation in the current study. Consistent with this interpretation, we have found that the corresponding *N*-methyl cation (**5c**) of isoquinoline-4-carboxamide generates a similar, and possibly identical, yellow species in aqueous base. We have not examined this reaction in any detail

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(13) For C-4 substituted isoquinolinium cations, pK<sub>a</sub> correlates<sup>14</sup> with Hammett  $\sigma_m$  for the C-4 substituent, while pK<sub>R+</sub> correlates<sup>6</sup> with  $\sigma_p^-$ .

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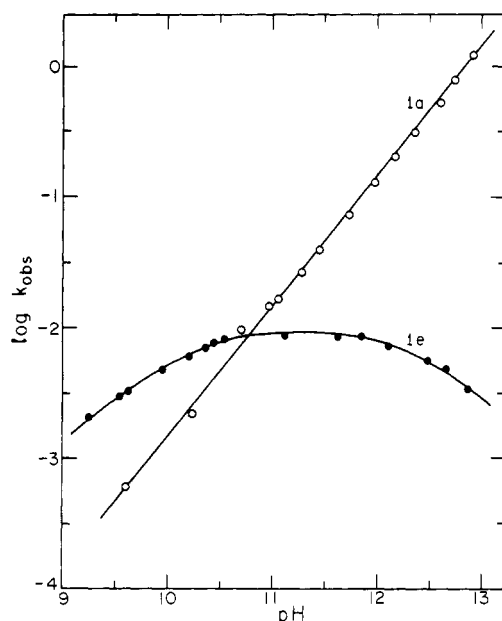


Figure 3. pH dependence of the pseudo-first-order rate constant ( $k_{\text{obs}}$ ,  $\text{s}^{-1}$ ) for the elimination reaction of **1a** and **1e**.

at present and have avoided it in the present work by limiting our study of the elimination reaction (eq 2) of **1c** to  $\text{pH} < 12$ .

For the parent *N*-(2-cyanoethyl)isoquinolinium cation (**1a**) the initial species in all solutions of  $\text{pH} < 13$  (the upper limit in the current studies) is that of the cation, which is cleanly converted into isoquinoline (**2a**).

The spectrum of the *N*-(2-cyanoethyl)-4-cyanoisoquinolinium cation (**1c**) displays a pH dependence that is consistent with the formation of **3d** and **4d**, but the spectrum of each of these species seems to be stable for at least 15 h at 25 °C, with no apparent formation of any significant amount of **2d**.

Values of  $\text{p}K_{\text{R}^+}$  were evaluated from the pH dependence of the initial spectra of **1b–1d**, while  $\text{p}K_{\text{RO}^-}$  was similarly obtained for **3c–3e**. These  $\text{p}K_{\text{R}^+}$  and  $\text{p}K_{\text{RO}^-}$  values are collected in Table II, which also contains literature values for the analogous equilibria for the correspondingly substituted *N*-methylisoquinolinium cations and the  $\text{p}K_{\text{a}}$  values for deprotonation of the isoquinolinium cation conjugate acids of **2**.

The occurrence of the reaction of eq 2 in these systems was confirmed from the  $^1\text{H}$  NMR spectra of basic  $\text{D}_2\text{O}$  solutions of these cations. The most basic solutions of **1b–1e** could not be examined in such studies because of the precipitation of the pseudobase species. However, for each of **1a–1c** and **1e** at  $\text{pD} < \text{p}K_{\text{R}^+}$ , the conversion of **1** to **2** and acrylonitrile was cleanly observable by  $^1\text{H}$  NMR spectroscopy. The signals of the three protons in the acrylonitrile product were clearly seen in these studies; there was no exchange of these hydrogen atoms for solvent deuterium within the experimental error of the integrated spectrum.

**Kinetic Studies.** The conversions of the isoquinolinium cations (**1**), their pseudobases (**3**), or the alkoxide ions (**4**) to the corresponding isoquinolines (**2**) were followed spectrophotometrically at convenient wavelengths as indicated in the Experimental Section. The pH dependences of the pseudo-first-order rate constants ( $k_{\text{obs}}$ ) are displayed in Figures 3 and 4. In each case, these pH rate profiles are cleanly first-order in  $[\text{OH}^-]$  at low pH but flatten to a plateau region for  $\text{pH} > \text{p}K_{\text{R}^+}$ . For **1e**, a subsequent decrease in  $k_{\text{obs}}$  is also apparent in the most basic solutions. The pH dependences detailed in Figures 3 and 4 can be described by eq 3 derived on the basis of Scheme I, where  $\text{IQ}^+$ ,  $\text{IQ}$ ,  $\text{IQOH}$ , and  $\text{IQO}^-$  represent **1–4**, respectively.

The 5-nitro derivative (**1e**) is the only case in which all terms of eq 3 are clearly important to the pH rate profiles in Figures

$$k_{\text{obs}} = \frac{k_{\text{OH}}[\text{OH}^-]}{1 + K_{\text{R}^+}/[\text{H}^+] + K_{\text{R}^+}K_{\text{RO}^-}/[\text{H}^+]^2} \quad (3)$$

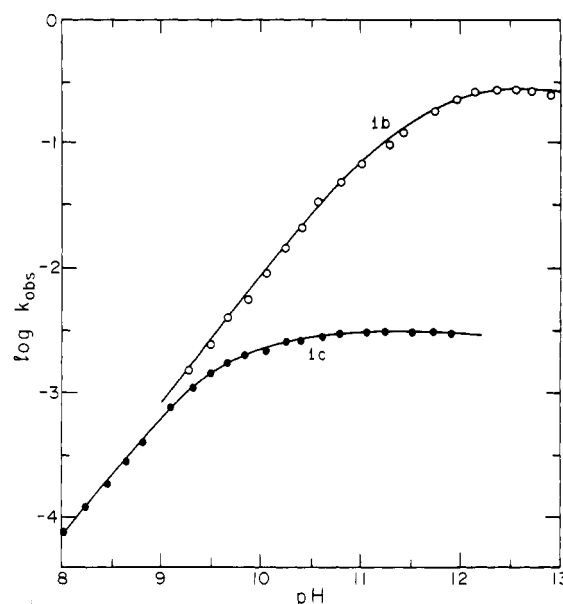


Figure 4. pH dependence of the pseudo-first-order rate constant ( $k_{\text{obs}}$ ,  $\text{s}^{-1}$ ) for the elimination reaction of **1b** and **1c**.

#### Scheme I

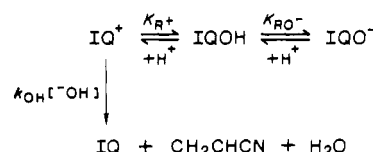


Table III. Kinetic Parameters for Hydroxide Ion Catalyzed Elimination from **1**<sup>a</sup>

cation	$k_{\text{OH}}$ , $\text{M}^{-1} \text{s}^{-1}$	$\text{p}K_{\text{R}^+}$	$\text{p}K_{\text{RO}^-}$
<b>1a</b>	$14 \pm 1$		
<b>1b</b>	$90 \pm 5$	$11.51 \pm 0.03$	
<b>1c</b>	$77 \pm 2$	$9.59 \pm 0.01$	
<b>1d</b>	$(410)^b$		
<b>1e</b>	$121 \pm 6$	$9.90 \pm 0.03$	$12.66 \pm 0.03$

<sup>a</sup> All data in aqueous solution at 25 °C, ionic strength 0.1. All parameters evaluated by fitting the experimental data of Figures 3 and 4 to eq 3–5, as appropriate. <sup>b</sup> Calculated from eq 6, with  $\text{p}K_{\text{a}} = 2.06$ .

3 and 4. For **1b** and **1c** the term in  $K_{\text{R}^+}K_{\text{RO}^-}/[\text{H}^+]^2$  is insignificant in the pH range examined in Figure 4 ( $\text{pH} < \text{p}K_{\text{RO}^-}$ , see Table II), and for these two cases eq 3 may be simplified to eq 4. For

$$k_{\text{obs}} = \frac{k_{\text{OH}}[\text{OH}^-]}{1 + K_{\text{R}^+}/[\text{H}^+]} \quad (4)$$

**1a**, the pH range of Figure 3 is much less than either  $\text{p}K_{\text{R}^+}$  or  $\text{p}K_{\text{RO}^-}$ , and in this case eq 3 is further simplified to eq 5.

$$k_{\text{obs}} = k_{\text{OH}}[\text{OH}^-] \quad (5)$$

Values of  $k_{\text{OH}}$ ,  $\text{p}K_{\text{R}^+}$ , and  $\text{p}K_{\text{RO}^-}$  were evaluated by nonlinear iterative regression analysis fitting the data of Figures 3 and 4 to eq 3–5 as appropriate. Values for these kinetically derived parameters are listed in Table III. The kinetically evaluated  $\text{p}K_{\text{R}^+}$  and  $\text{p}K_{\text{RO}^-}$  values of Table III are in acceptable experimental agreement with the spectrophotometrically evaluated equilibrium constants of Table II.

#### Discussion

Electronic absorption and  $^1\text{H}$  NMR spectral observations clearly indicate that the cations (**1a–1c**, **1e**) and their pseudobases (**3**) are cleanly converted into the corresponding isoquinolines (**2**) and acrylonitrile in basic aqueous solutions. The pH dependences of the pseudo-first-order rate constants for these reactions are consistent with these processes being hydroxide ion catalyzed elim-

inations from the isoquinolinium cations (**1**). Although such a reaction mechanism is kinetically equivalent to a process that occurs via an uncatalyzed reaction of the pseudobase species (**3**), we eliminate this latter possibility on the basis that we can conceive of no simple chemically acceptable reaction mechanism for such a process. Furthermore, such an uncatalyzed reaction of **3** would have a very unusual substituent dependence and would be difficult to reconcile with the extremely low reactivity of the 4-cyano derivative (**3d**). As discussed below, this low apparent reactivity of the 4-cyano derivative is readily understood in terms of the base-catalyzed reaction via the isoquinolinium cation as outlined in Scheme I.

The  $k_{OH}$  values of Table III reflect the leaving abilities of these isoquinolines in these elimination reactions and are closely related to the  $pK_a$  values for deprotonation of the corresponding isoquinolinium cations **6** (Table II). From the dependence of  $\log k_{OH}$  upon  $pK_a$  (eq 6), we estimate a Brønsted  $\beta_{lg} = -0.43$  for this

$$\log k_{OH} = -0.43 (\pm 0.03) pK_a + 3.5 (\pm 0.1) \quad (6)$$

reaction. Extrapolation of eq 6 to the  $pK_a$  of the 4-cyanoisoquinolinium cation, allows the estimation of  $k_{OH} = 410 \text{ M}^{-1} \text{ s}^{-1}$  for elimination of **2d** from **1d**.

Although the reactivities of the isoquinolinium cations (**1**) in these elimination reactions are correlated (eq 6) with the leaving abilities of the substituted isoquinolines as expressed by their basicities, the apparent reactivities within the series of derivatives **a-e** are very pH-dependent. This phenomenon arises because the substituent effects upon pseudobase formation from **1** follow a similar, although not identical, order to substituent effects<sup>13</sup> upon the basicities of **2**. Since leaving abilities (nucleofugalities) follow the reverse of basicities, this observation then implies that the best leaving groups are found in those *N*-(2-cyanoethyl)isoquinolinium cations that are most susceptible to formation of pseudobase species. Such species are nonproductive in so far as the elimination reaction is concerned, and this then leads to the 4-cyano derivative, which has the best leaving group (largest  $k_{OH}$ ), being essentially unreactive in the current study under conditions in which the elimination reaction is readily observable for the other isoquinolinium cations. The true order of reactivity of various **1** toward base-catalyzed elimination will only be observable in the pH region in which *all* substituted **1** predominate over their pseudobases (pH < 6 for **1a-e**).

Combination of eq 3 and 6 gives eq 7, which may in turn be modified to eq 8, by making use of the approximate relationship

$$k_{obs} = \frac{10^{(3.5-0.43pK_a)} [-OH]}{1 + K_{R^+}/[H^+] + K_R K_{RO^-}/[H^+]^2} \quad (7)$$

$$k_{obs} = \frac{10^{(3.5-0.43pK_a)} [-OH]}{1 + K_{R^+}/[H^+] (1 + 10^{-10.1} K_R^{0.29}/[H^+])} \quad (8)$$

previously reported<sup>5</sup> between  $pK_{RO^-}$  and  $pK_{R^+}$ . Equations 7 and 8 allow the prediction of the pH rate profile for the reaction of eq 2 for any *N*-(2-cyanoethyl)isoquinolinium cation for which  $pK_{R^+}$  and  $pK_a$  are available.

We have calculated pH rate profiles for eq 2 for each of the cations **1a-e** from eq 7 and the equilibrium constants in Table II. These calculated pH rate profiles are displayed in Figure 5. For the 4-cyano derivative (**1d**), the maximum pseudo-first-order rate constant for elimination is calculated to be  $2.4 \times 10^{-6} \text{ s}^{-1}$ , which corresponds to a half-time of 80 h in the pH-independent region for **1d** in Figure 5.

It is obvious from the pH rate profiles in Figure 5 that, depending upon the pH chosen, essentially any order of substituent effects upon the rates of elimination can be found. Such data make it clear that it is absolutely essential that a complete pH rate analysis be completed before drawing conclusions upon substituent effects for any reaction under conditions in which the equilibration of a heteroaromatic cation with its pseudobase is possible. Williams<sup>15</sup> gives an interesting recent example where the low

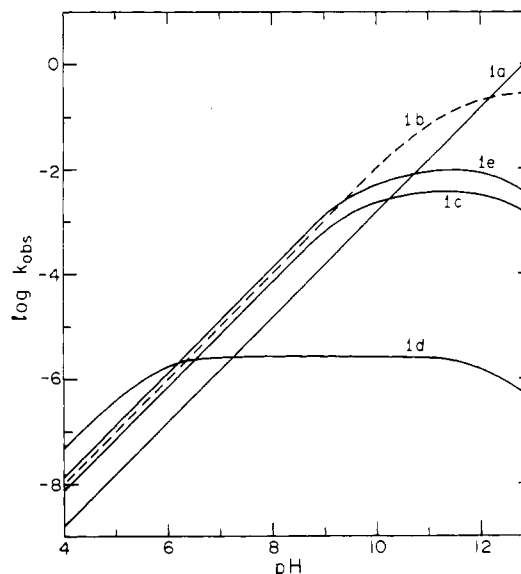
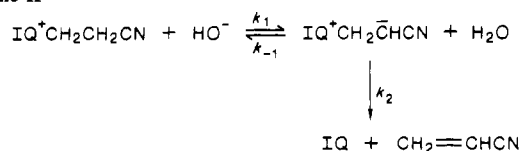


Figure 5. Calculated pH rate profiles for elimination from **1a-e**. Curves ( $k_{obs}$ ,  $\text{s}^{-1}$ ) are calculated from eq 7 using  $pK_a$ ,  $pK_{R^+}$ , and  $pK_{RO^-}$  from Table II.

#### Scheme II



reactivity of an isoquinolinium cation relative to a series of pyridinium cations can be traced to the presence of a nonproductive pseudobase species in the more basic solutions that were investigated.

In a very recent study, Fishbein and Jencks<sup>16</sup> have reported kinetic data for hydroxide ion catalyzed elimination from a variety of 3-arylthiopropionitriles ( $\text{ArSCH}_2\text{CH}_2\text{CN}$ ) that have leaving groups of similar basicity to the isoquinolines of our current study. The *N*-(2-cyanoethyl)isoquinolinium cations (**1**) appear to undergo elimination with hydroxide ion approximately 1300-fold faster than these 2-cyanoethyl sulfides. The sulfides have a slightly larger  $\beta_{lg} = -0.54$  than reported above for isoquinolinium cations.

There appear to be very few other kinetic data available that are directly comparable with the  $k_{OH}$  values of Table III. Stirling and co-workers<sup>17,18</sup> have reported kinetic data for base-catalyzed eliminations from many 3-substituted propanonitriles ( $\text{XCH}_2\text{CH}_2\text{CN}$ ); however, all of their data appear to be in ethanolic solution. We note that the *N,N*-dimethylaniline leaving group, of similar charge type and basicity to isoquinoline, appears to be one of the best leaving groups in their study. This dimethylaniline is also reported<sup>18</sup> to react approximately 10<sup>6</sup>-fold faster than the corresponding thiophenoxide.

While the current study was not specifically designed to give detailed mechanistic information, the data collected do allow the narrowing of the mechanistic possibilities for this  $\beta$ -elimination reaction. An E1 elimination via a carbocationic intermediate is not expected and is ruled out by the observed base catalysis. The presence of hydroxide ion catalysis and a significant dependence upon the nucleofugality of the leaving group are consistent with an E2 process. However, there seems to be widespread agreement<sup>16-19</sup> that eliminations in which the  $\beta$ -proton is activated by

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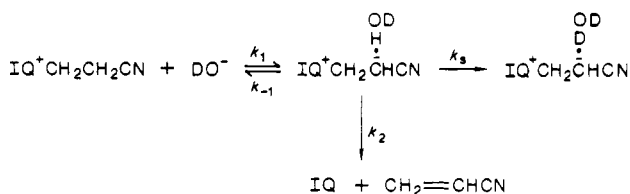
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## Scheme III



a group, such as the cyano group, are best described as occurring via one of the variants of the E1cB mechanistic spectrum. The simplest case of the E1cB mechanism for the present reaction is presented in Scheme II, which predicts the observed pseudo-first-order rate constant of eq 9.

$$k_{\text{obs}} = k_1 k_2 [\text{HO}^-] / (k_{-1} + k_2) \quad (9)$$

An (E1cB)<sub>1</sub> mechanism<sup>19</sup> is formally consistent with our observation that there is apparently no deuterium incorporation into the acrylonitrile product when the reaction is run in basic D<sub>2</sub>O. However, for such a mechanism  $k_2 \gg k_{-1}$  of Scheme II, and thus  $k_{\text{obs}}$  of eq 9 simplifies to  $k_1[\text{HO}^-]$ . To a first approximation, we can assume that  $k_1$  should be essentially independent of the substituent on the isoquinoline ring, and this then indicates that (E1cB)<sub>1</sub> is not consistent with the observed  $\beta_{1g} = -0.43$  of eq 6. On the other hand, while the (E1cB)<sub>R</sub> mechanism ( $k_{-1} > k_2$ ) for which  $k_{\text{obs}} \approx k_1 k_2 [\text{HO}^-] / k_{-1}$  does contain a contribution from  $k_2$  that is consistent with the observed  $\beta_{1g}$ , a simple (E1cB)<sub>R</sub> mechanism based upon Scheme II would predict significant incorporation of deuterium into the acrylonitrile product in basic D<sub>2</sub>O. However, the absence of deuterium incorporation into the acrylonitrile product in the current study can be accommodated within an (E1cB)<sub>R</sub> mechanism if Scheme II is modified as in Scheme III with  $k_{-1} > k_2 > k_s$ , i.e., provided protonation of the carbanion by HOD ( $k_{-1}$ ) and loss of isoquinoline from the carbanion ( $k_2$ ) are both faster than exchange of HOD of the solvated carbanion for solvent D<sub>2</sub>O ( $k_s$ ). Scheme III is essentially the mechanism deduced by Fishbein and Jencks<sup>16</sup> for base-catalyzed elimination reactions of RSCH<sub>2</sub>CH<sub>2</sub>CN and implies a carbanionic species that is strongly hydrogen-bonded to a water molecule via the proton, which has been abstracted from the substrate methylene group. Such a hydrogen-bonded carbanion intermediate in which internal return is faster than exchange with solvent has been recognized<sup>20</sup> as a special case of the (E1cB)<sub>ip</sub> mechanism

and has been considered<sup>21</sup> in considerable detail for some eliminations in alcoholic solutions.

Fishbein and Jencks<sup>16</sup> estimated that  $k_s$  of Scheme III is of the order of  $10^{11} \text{ s}^{-1}$ , which is a lower limit to both  $k_{-1}$  and  $k_2$  of this scheme (see above). Upper limits to  $k_{-1}$  and  $k_2$  may be assigned from the stretching frequencies of the O-H ( $\approx 3500 \text{ cm}^{-1}$ ) and C-N ( $\approx 1100 \text{ cm}^{-1}$ ) bonds. Thus,  $10^{11} \leq k_2 \leq 3 \times 10^{13} \text{ s}^{-1}$  and  $k_2 \leq k_{-1} \leq 10^{14} \text{ s}^{-1}$ . By analogy with the data of Stirling and co-workers,<sup>18,22</sup>  $k_2$  is expected to be greater in the current reaction of eq 2 than for hydroxide ion catalyzed elimination from RSCH<sub>2</sub>CH<sub>2</sub>CN. For this latter reaction, values of log  $k_2$  in the range 9.4–12.4 were calculated.<sup>16</sup> It is thus clear that, in terms of Scheme III for the reaction of eq 2,  $k_2$  must approach the upper limit of  $3 \times 10^{13} \text{ s}^{-1}$ , and similarly  $k_{-1}$  must approach  $10^{14} \text{ s}^{-1}$ .

These considerations, and the 1300-fold greater reactivity for *N*-(2-cyanoethyl)isoquinolinium cations than for 2-cyanoethyl aryl sulfides, suggest that the lifetime of the carbanion in Scheme III cannot be very much greater than the vibration time of the C-N bond. This in turn suggests that the elimination reactions of eq 2 must lie close to the borderline for the merging of the E1cB and E<sub>2</sub> mechanisms, and in fact the E<sub>2</sub> mechanism may be enforced for the most reactive substrates (largest  $k_{\text{OH}}$ ) of Table III. Final establishment of Scheme III or the kinetically equivalent E<sub>2</sub> mechanism must await the availability of data from the sophisticated deuterium solvent and kinetic isotope effects, general-base catalytic effects, and substituent effect studies that have been developed<sup>23–25</sup> as probes of the E1cB mechanistic spectrum.

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**Registry No.** 1a, 118798-86-0; 1b, 118798-87-1; 1c, 118798-88-2; 1d, 118798-89-3; 1e, 118798-90-6.

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