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A Change in the Rate-Determining Step in the E1cB Reactions of *N*-(2-(4-Nitrophenyl)ethyl)pyridinium Cations

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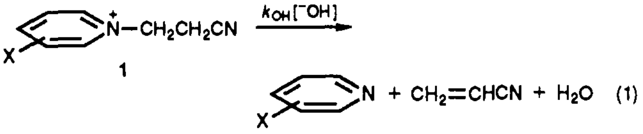
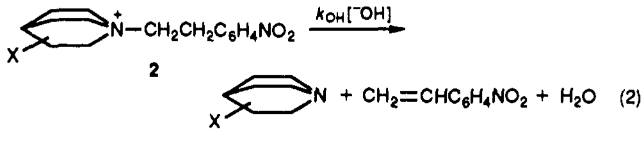
Abstract: Second-order rate constants have been measured (aqueous solution, $I = 1.0$, 25 °C) for the hydroxide ion catalyzed elimination reactions of 12 *N*-(2-(4-nitrophenyl)ethyl)pyridinium cations (**3**) bearing a variety of substituents in the pyridine ring. Brønsted plots as a function of the basicity of the pyridine leaving group are concave-down, which is consistent with a change in rate-determining step within an E1cB mechanism. These plots are characterized by $\beta_{lg} = -0.17$ for the rate-determining deprotonation for $pK_{BH} < 6.5$, and $\beta_{lg} = -0.39$ for the rate-determining expulsion of the pyridine nucleofuge from the carbanionic intermediate for $pK_{BH} > 6.5$. Elimination reactions in basic D_2O occur without any significant incorporation of deuterium into the 4-nitrostyrene product, and require the presence of a hydrogen-bonded carbanionic intermediate in which nucleofuge expulsion occurs faster than exchange of hydrogen-bonding water molecules. Rate-determining deprotonation in these elimination reactions occurs 50-fold more slowly than for the corresponding reactions of the *N*-[2-(4-nitrophenyl)ethyl]quinuclidinium cations that have also been reported to have $\beta_{lg} = -0.17$, but which do not show an analogous change in the rate-determining step upon variation of the nucleofuge basicity. The analogous elimination of the 1-methyl-3-[2-(4-nitrophenyl)ethyl]imidazolium cation occurs a further 30-fold more slowly than that predicted for **3** having a pyridine leaving group of the same basicity as 1-methylimidazole. The E1cB reactions of **3** are similar to the analogous reactions of *N*-(2-cyanoethyl)pyridinium cations (**1**) in displaying a change in the rate-determining step with nucleofuge basicity; however, the β_{lg} values for **1** and **3** are quite different for both k_1 and k_2/k_{-1}.

We have recently reported[1] a detailed kinetic study of the hydroxide ion catalyzed elimination of pyridines from *N*-(2-cyanoethyl)pyridinium cations (**1**) in aqueous solution for pyridine leaving groups having pK_{BH} in the range 1.5–9.7. Brønsted plots as a function of pK_{BH} showed a clear change in the rate-determining step within an E1cB mechanism. Thus, $\beta_{lg} = -0.30$ for rate-determining deprotonation (i.e. $(E1cB)_{irrev}$ or $A_{xh}D_H{}^{\ddagger} + D_N)$[2] for $pK_{BH} < 5.8$ is transformed into $\beta_{lg} = -0.93$ for rate-determining leaving group expulsion from the carbanionic intermediate (i.e. $(E1cB)_{rev}$ or $A_{xh}D_H + D_N{}^{\ddagger}$) for $pK_{BH} > 5.8$.



(1)

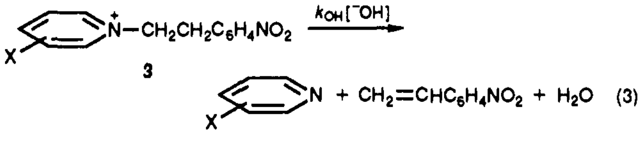
A closely related reaction, the hydroxide ion catalyzed elimination of quinuclidines from *N*-(2-(4-nitrophenyl)ethyl)quinuclidinium cations (**2**), showed[3-5] no such change in the rate-determining step with leaving-group basicity, although other evidence firmly established the E1cB mechanism for these reactions. Rate-determining deprotonation, with $\beta_{lg} = -0.17$, was found for quinuclidine leaving groups having pK_{BH} covering the range 3–11.



(2)

Since **1** and **2** differ in having different activating groups as well as different leaving groups, it is not immediately obvious whether it is the nature of the leaving group or of the activating group that is more important in imposing the change in the rate-determining step that is observed for **1**. Both reactions involve the fission of a carbon–nitrogen bond and the loss of neutral nitrogen-based leaving groups of similar basicity. While this appears to implicate the quite different activating groups (cyano and 4-nitrophenyl) as the determinants of the rate-determining step in these E1cB eliminations, there is at least one clear example[6] of a reaction in which pyridines are much poorer nucleofuges when compared with quinuclidines of the same basicity.

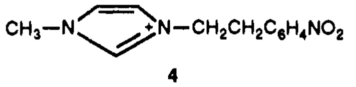
We felt that considerable insight into the above conjecture would be obtained from a study of the kinetics and mechanism of the elimination reactions of *N*-(2-(4-nitrophenyl)ethyl)pyridinium cations (**3**), since these species contain the same leaving groups as **1** and the same activating group as **2**. We now report such a study for pyridine leaving groups having pK_{BH} in the range 2.8–9.7.



(3)

Experimental Section

Syntheses. Bromide salts ($3\cdot Br^-$) of the *N*-(2-(4-nitrophenyl)ethyl)pyridinium cations were synthesized by refluxing the appropriate ring-substituted pyridine (0.1 mol) with 1-bromo-2-(4-nitrophenyl)ethane (0.1 mol) in ethanol (30 mL) for periods ranging from 12 to 144 h depending upon the nucleophilicity (basicity) of the substituted pyridine.[7] The bromide salt was precipitated by swamping the ethanolic solution with diethyl ether, and this crude product was then recrystallized several times from propanol or butanol. Yields of purified material were in the range 69–84%. Melting points and ^1H NMR spectral data for all $3\cdot Br^-$ are listed in Table I. 1-Methyl-3-(2-(4-nitrophenyl)ethyl)imidazolium bromide ($4\cdot Br^-$) was similarly prepared from 1-methylimidazole, and appropriate data for this salt are also included in Table I.



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Kinetic Studies. All kinetic data were obtained by monitoring the appearance of 4-nitrostyrene at 335 nm ($\epsilon = 8640$) in the Cary 210 spectrophotometer in aqueous solutions of constant ionic strength (KOH + KCl) at 25 °C with initial $[3\cdot Br^-] = 0.05$ mM. All runs proved to be strictly pseudo-first-order in [**3**] over greater than 90% of the complete

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(7) 4-Amino-3-bromopyridine was a gift from Professor O. S. Tee of Concordia University, Montreal, Quebec; 4-morpholinopyridine was available from an earlier study[1] in our laboratory; all other pyridines, 1-methylimidazole, and 4-nitrophenethyl bromide were obtained commercially.

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Table I. Characterization of the Bromide Salts of **3** and **4**

cation	X	mp, °C	^{1}H NMR,[a] δ
3a	3-Cl	200–202	2.88 (2 H, t), 4.31 (2 H, t), 6.68 (2 H, d), 7.45 (2 H, d), 7.60 (3 H, m), 8.08 (1 H, s)
3b	3-CH_2CN	199–201	2.70 (2 H, t), 3.43 (2 H, s), 4.23 (2 H, t), 6.53 (2 H, d), 7.27 (2 H, d), 7.8–8.2 (4 H, m)
3c	3-C_6H_5	213–215	2.86 (2 H, t), 4.36 (2 H, t), 6.73 (2 H, d), 6.76 (5 H, s), 7.33 (3 H, m), 7.93 (2 H, d), 8.13 (1 H, s)
3d	H	167–169	3.02 (2 H, t), 4.48 (2 H, t), 6.71 (2 H, d), 7.28 (4 H, m), 7.64 (1 H, m), 7.91 (2 H, d)
3e	3-CH_3	222–224	2.02 (3 H, s), 2.93 (2 H, t), 4.37 (2 H, t), 6.83 (2 H, d), 7.64 (2 H, d), 7.5–8.1 (4 H, m)
3f	2-CH_3	219–221	2.23 (3 H, s), 2.93 (2 H, t), 4.37 (2 H, t), 6.83 (2 H, d), 7.64 (2 H, d), 7.5–8.1 (4 H, m)
3g	4-CH_3	224–226	2.03 (3 H, s), 2.86 (2 H, t), 4.30 (2 H, t), 6.73 (2 H, d), 7.16 (2 H, d), 7.53 (2 H, d), 7.86 (2 H, d)
3h	3,4-$(CH_3)_2$	179–181	2.27 (3 H, s), 2.37 (3 H, s), 3.30 (2 H, t), 4.64 (2 H, t), 7.17 (2 H, d), 7.37 (2 H, d), 7.97 (2 H, d), 8.14 (1 H, s)
3i	3-Br, 4-NH_2	258–260	2.74 (2 H, t), 3.97 (2 H, t), 6.54 (1 H, d), 6.84 (2 H, d), 7.37 (1 H, d), 7.54 (1 H, s), 7.67 (2 H, d)
3j	4-morpholino	228–230	2.73 (2 H, t), 3.16 (4 H, d), 3.43 (4 H, d), 3.89 (2 H, t), 6.39 (2 H, d), 6.76 (2 H, d), 7.32 (2 H, d), 7.59 (2 H, d)
3k	4-NH_2	229–231	2.73 (2 H, t), 3.90 (2 H, t), 6.30 (2 H, d), 6.77 (2 H, d), 7.20 (2 H, d), 7.57 (2 H, d)
3l	4-$N(CH_3)_2$	223–225	2.54 (6 H, s), 2.67 (2 H, t), 3.87 (2 H, t), 6.20 (2 H, d), 6.74 (2 H, d), 7.20 (2 H, d), 7.57 (2 H, d)
4		184–186	2.81 (2 H, t), 3.34 (3 H, s), 4.04 (2 H, t), 6.84 (4 H, d), 7.61 (2 H, d), 8.00 (1 H, s)

[a] In CF_3CO_2H; δ relative to $(CH_3)_4Si$.

Table II. Second-Order Rate Constants for Hydroxide Ion Catalyzed Eliminations from **3** and **4**

		k_{OH} (10^{-4} M^{-1} s^{-1})			
cation	X	*a*	*b*	*c*	pK_{BH}[d]
3a	3-Cl	8.11	5.94	13.2	2.84
3b	3-CH_2CN	4.39			4.08
3c	3-C_6H_5	3.40	2.14	6.46	4.88[e]
3d	H	3.46	2.21	5.13	5.16
3e	3-CH_3	2.75			5.82
3f	2-CH_3	2.25			6.04[e]
3g	4-CH_3	2.23			6.15
3h	3,4-$(CH_3)_2$	1.81			6.45
3i	3-Br, 4-NH_2	1.01			7.15
3j	4-morpholino	0.261			8.80
3k	4-NH_2	0.154			9.21
3l	4-$N(CH_3)_2$	0.100			9.68
4		0.0629			7.21

[a] In aqueous solution containing 0.8 M KOH + 0.2 M KCl. [b] In aqueous solution containing 0.1 M KOH + 0.9 M KCl. [c] In aqueous solution containing 0.1 M KOH only. [d] Acid dissociation constant (at ionic strength 0.1) of the appropriate ring-substituted pyridinium cation.[1] [e] Current work.

reaction. All pseudo-first-order rate constants (k_{obsd}) were calculated as previously described.[1] All rate constants reported in Table II are the averages of the rate constants from triplicate runs in which k_{obsd} usually varied by less than 1%.

pK_{BH} values for 3-phenylpyridine and 2-methylpyridine were measured spectrophotometrically at ionic strength 0.1 and 25 °C so as to be consistent with the data that we have previously reported[1] for the other pyridines. ^{1}H NMR spectral studies made use of a Varian Gemini 200 spectrometer.

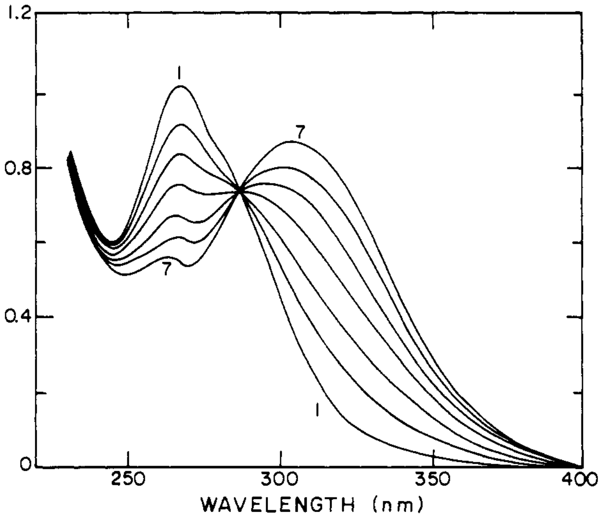


Figure 1. Time dependence of the electronic absorption spectrum of **3i** (0.05 mM) in aqueous 1 M KOH. Spectra 1–7 were recorded at 0, 1200, 4200, 7200, 12000, 15000, and 22200 s, respectively, after the start of the reaction.

Results

The time dependence of the electronic absorption spectrum of the bromide salt of **3i** in aqueous 1 M KOH is shown in Figure 1. The formation of the characteristic absorption spectrum of 4-nitrostyrene (λ_{max} = 311 nm) is quite obvious; the final spectrum is identical with that of a 1:1 mole ratio mixture of 4-amino-3-bromopyridine and 4-nitrostyrene. Similar spectral observations were made for each **3**·Br^- in aqueous base.

The clean formation of the elimination products from **3** in aqueous base was also confirmed by ^{1}H NMR spectroscopy. Solutions of **3**·Br^- (0.07 M) in 0.7 M NaOD in D_2O became heterogeneous; however, addition of acetonitrile (50% by volume) led to homogeneous reaction mixtures in which the signals corresponding to the appropriately substituted pyridine and 4-nitrostyrene were readily assignable. In no case was there any experimentally detectable incorporation (i.e. <5%) of deuterium into the vinylic protons (δ 5.96 (d, J = 12 Hz), 6.46 (d, J = 18 Hz), and 7.25 (dd, J = 12 and 18 Hz)) of the 4-nitrostyrene product. Thus elimination occurs *without* exchange of the protons on the carbon atom adjacent to the 4-nitrophenyl ring.

The dependence of k_{obsd} upon [$^-$OH] for each cation **3** at constant ionic strength 1.0 (KOH + KCl) shows a slight upward curvature, which results in second-order rate constants, $k_{OH} = k_{obsd}/[^-OH]$, that increase with [$^-$OH]. Exactly analogous results were obtained for the elimination reactions of **2** by Jencks and co-workers,[3-5] who attributed this phenomenon to specific ion effects upon the replacement of chloride ion by hydroxide ion in these ionic strength solutions. This interpretation is consistent with the cationic substrates that are involved in both series of elimination reactions. In Table II, we have chosen to report values of k_{OH} calculated in 0.8 M KOH to allow a direct comparison with the data for the hydroxide ion catalyzed eliminations from **2**. For some of the less reactive **3** we have found it difficult to obtain accurate kinetic data in other than the most concentrated KOH solutions. Table II also includes some values of k_{OH} calculated from data in 0.1 M KOH solutions at both ionic strengths 0.1 and 1.0 (in the presence of 0.9 M KCl). Although we have not made a detailed study, the variation in k_{OH} over the three sets of experimental conditions in Table II is consistent with an inhibition by chloride ion, presumably as a result of ion pairing with these pyridinium cations. The magnitudes of these effects are quantitatively similar to those reported[3-5] for the corresponding quinuclidinium cations.

Discussion

All spectral observations are consistent with the *N*-(2-(4-nitrophenyl)ethyl)pyridinium cations (**3**) undergoing a clean elimination in aqueous base to give the appropriately substituted

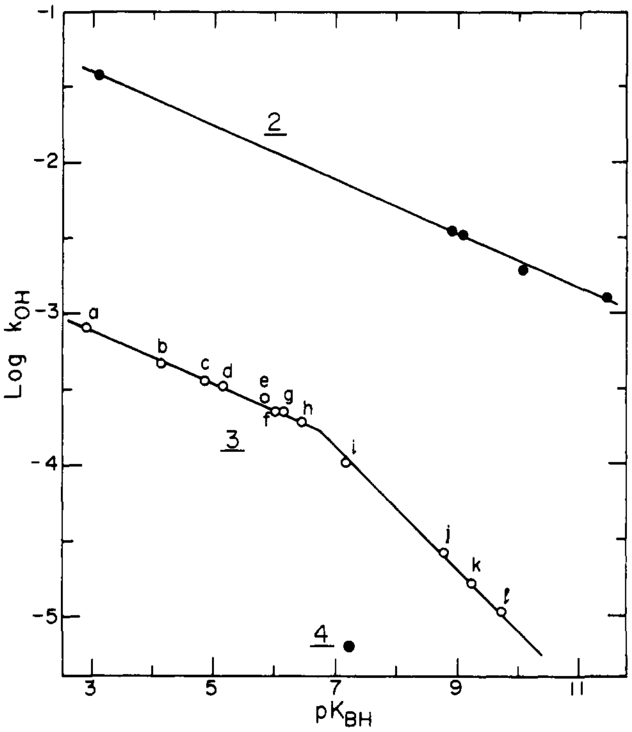


Figure 2. Brønsted plots for the elimination reactions of **2** (data from ref 3), **3**, and **4** (data from Table II). All data are for solutions containing 0.8 M KOH + 0.2 M KCl.

pyridine and 4-nitrostyrene (eq 3). The Brønsted plot of the data from Table II as a function of leaving-group basicity is shown in Figure 2. This figure appears to describe two distinct linear regions, with $\beta_{lg} = -0.17$ for $pK_{BH} < 6.5$ and $\beta_{lg} = -0.39$ for $pK_{BH} > 6.5$ (eqs 4 and 5, respectively). Such a "concave-down" Brønsted plot is consistent with a change in the rate-determining step and is most simply interpreted in terms of an E1cB mechanism in which deprotonation is rate-determining for $pK_{BH} < 6.5$, and leaving-group departure from the carbanionic intermediate is rate-determining for $pK_{BH} > 6.5$.

$$\log k_{OH} = -0.17\ (\pm 0.01)pK_{BH} - 2.64\ (\pm 0.06) \tag{4}$$

$$\log k_{OH} = -0.39\ (\pm 0.02)pK_{BH} - 1.2\ (\pm 0.2) \tag{5}$$

All **3** proved to be much less reactive than the corresponding *N*-(2-(4-nitrophenyl)ethyl)quinuclidinium cations (**2**) toward hydroxide ion catalyzed elimination reactions. The literature data for **2** are indicated in Figure 2. It is also clear from this figure that the 1-methyl-3-(2-(4-nitrophenyl)ethyl)imidazolium cation (**4**) is 30-fold less reactive than a pyridine leaving group having similar basicity to 1-methylimidazole.

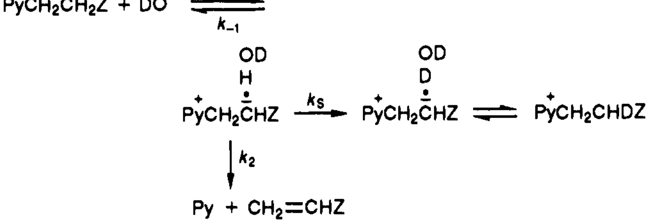
The $\beta_{lg} = -0.17$ reported[5] for **2** is identical with β_{lg} for **3** for $pK_{BH} < 6.5$. Thus the interpretation of these data as the rate-determining deprotonation of **2** and **3**, respectively, indicates a 50-fold greater kinetic acidity for **2** than for **3** when one compares derivatives of quinuclidine and pyridine having the same basicity, as far as protonation of the nitrogen base is concerned. Whether this difference in the kinetic acidities of **2** and **3** is also a reflection of the difference in the thermodynamic acidities of these two classes of carbon acids is unclear at present. The greater kinetic acidity of **2** than of **3** is suggestive of a greater effective positive charge on the quinuclidinium nitrogen than upon the pyridinium nitrogen atom. Such a difference probably results from a combination of two influences: differences in the solvation in the vicinity of the charged atoms in these two series of cations, and a greater delocalization of charge in the aromatic pyridinium cation than in the saturated quinuclidinium cation. The thermodynamic parameters for the protonation of quinuclidines and pyridines indicate that there are important differences in the solvation of the cationic conjugate acids of these two classes of nitrogen base. Thus, 1,4-diazabicyclo[2.2.2]octane ($pK_{BH} = 8.82$, $\Delta H° = 7.3$ kcal mol^{-1}, $\Delta S° = -15.9$ cal deg^{-1} mol^{-1})[8] and 4-(dimethylamino)pyridine ($pK_{BH} = 9.68$, $\Delta H° = 11.9$ kcal mol^{-1}, $\Delta S° = -4.4$ cal deg^{-1} mol^{-1})[9] are of similar basicity, but the entropies of protonation, in particular, indicate significant differences in solvation.

Table III. Kinetic Acidities of 4-Nitrophenyl- and Cyano-Activated Carbon Acids in Aqueous Solution

	k_{OH} (M^{-1} s^{-1})		
carbon acid	Z = 4-NO$_2$C$_6$H$_4$	Z = CN	k_{OH}^{CN}/k_{OH}^{NP} [a]
$ZCH_2C_6H_3(2,4\text{-}(NO_2)_2)$	2.15[b,c]	3.6×10^5 [b,d]	1.7×10^5
$ZCH_2C_6H_4(4\text{-}NO_2)$	~0.09[b,e]	2.55×10^4 [b,d]	$\sim 3 \times 10^5$
$ZCH_2CH_2N^+C_5H_5$	5.13×10^{-4} [f]	28[g]	5.5×10^4
ZCH_3	4×10^{-12} [h]	4×10^{-5} [i]	10^7 (5×10^3)[j]

[a] Relative second-order rate constants for deprotonation of cyano and 4-nitrophenyl (NP) activated carbon acids by hydroxide ion. [b] In 50% dimethyl sulfoxide–50% water (v/v). [c] Terrier, F.; Farrell, P. G.; Lelievre, J.; Chatrousse, A. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1479. [d] Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343. [e] Fogel, P.; Farrell, P. G.; Lelivre, J.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **1985**, 711. [f] Current work at ionic strength 0.1. [g] At ionic strength 0.1, from ref 1. [h] $k_{OH} = k_{H_2O}K_a/K_w$, where $k_{H_2O} = 0.012$ s^{-1} for the protonation of the 4-nitrobenzyl carbanion by water,[11] and pK_a is estimated[12] as 23.5 for 4-nitrotoluene in aqueous solution. [i] k_{OD} in D$_2$O.[13] [j] Relative kinetic acidities for deprotonation by ethoxide ion in ethanolic solution.[14]

Scheme I



Both **2** and **3** undergo hydroxide ion catalyzed deprotonation much more slowly than does **1**. For pyridine itself as the leaving group, k_{OH} for **3d** is 5.5×10^4-fold smaller than for **1** (X = H). This difference must represent a direct reflection of the relative kinetic acidities of cyano-activated and 4-nitrophenyl-activated carbon acids. Such a difference is consistent with literature data (Table III) for the relative kinetic acidities of analogous cyano-activated and 4-nitrophenyl-activated carbon acids. The kinetic acidity of **3** ($\beta_{lg} = -0.17$) is also less sensitive to the substitution in the pyridine ring than is the kinetic acidity of **1** ($\beta_{lg} = -0.30$). This latter observation must ultimately be traceable to differences in the carbanionic electron density in the transition-state species for the deprotonation of cyano-activated and 4-nitrophenyl-activated carbon acids.

While **1** and **3** both display a change in the rate-determining step from deprotonation to leaving-group departure for pyridine leaving groups of $pK_{BH} \approx 6$, there are important experimental differences between these two classes of elimination reactions. We have commented above upon the large difference in the second-order rate constants for these two series of reactions, and the difference in β_{lg} when deprotonation is rate-determining. There is an even more dramatic difference in β_{lg} when leaving-group departure from the carbanionic intermediate is rate-determining: $\beta_{lg} = -0.93$ for **1** and $\beta_{lg} = -0.39$ for **3**. The interpretation of this latter observation must be considered in the light of the observed rapid hydrogen/deuterium exchange in basic D$_2$O for the acidic methylene group in **1** for $pK_{BH} > 6$, but the absence of any experimentally observable exchange for **3** for the same leaving groups.

The absence of any exchange of deuterium into **3**, even when leaving-group departure is rate-determining, can be accommodated

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Table IV. Thermodynamic Acidities of 4-Nitrophenyl- and Cyano-Activated Carbon Acids[a]

carbon acid	pK_a Z = 4-$NO_2C_6H_4$	pK_a Z = CN	ΔpK_a
ZCH_2NO_2	5.89[b]	4.86[c]	1.03
ZCH_2CN	13.4[d]	11.14[e]	2.3
(4-ZCH_2)$C_5H_4N^+CH_3$	>13[f]	8.93[f]	>4
$ZCH_2C_6H_3$(2,4-$(NO_2)_2$)	12.19[g,h]	8.06[g,i]	4.13
$ZCH_2COC_6H_5$	>12[f]	7.77[j]	>4.2
$ZCH_2C_6H_4$(4-NO_2)	14.94[g,i]	12.62[g,i]	2.32
ZCH_3	23.5[k]	~25[l], 28.6[m]	~-3

[a] In aqueous solution, unless otherwise indicated. [b] Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907. [c] Ried, W.; Kohler, E. *Liebigs Ann. Chem.* **1956**, *598*, 145. [d] Stearns, R. S.; Wheland, G. W. *J. Am. Chem. Soc.* **1947**, *69*, 2025. [e] Hojatti, M.; Kresge, A. J.; Wang, W. H. *J. Am. Chem. Soc.* **1987**. *109*, 4023. [f] Unpublished results from our laboratory. [g] In 50% dimethyl sulfoxide–50% water (v/v). [h] Terrier, F.; Farrell, P. G.; Lelievre, J.; Chatrousse, A. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1479. [i] Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343. [j] Pihl, V.; Siilbek, H.; Tenno, T.; Ranne, A.; Talvik, A. *Reakts. Sposobn. Org. Soedin.* **1968**, *5*, 27; *Chem. Abstr.* **1968**. *69*, 100208. [k] Estimated in ref 12. [l] Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439. [m] Jorgensen, W. L.: Briggs. J. M.; Gao, J. *J. Am. Chem. Soc.* **1987**, *109*. 6857.

within the E1cB reaction mechanism by the inclusion of a hydrogen-bonded carbanionic intermediate as in Scheme I ($Z = C_6H_4NO_2$). This mechanism has been considered in detail by Fishbein and Jencks[10] in their studies of the elimination reactions of 2-cyanoethyl sulfides. Provided $k_{-1} > k_2 > k_S$, this scheme allows rate-determining leaving-group departure without exchange of solvent deuterium into unreacted **3**, and corresponds to what has been termed an $(E1cB)_{\text{ion pair}}$ $(A_{xh}D_H{}^*D_N)$ mechanism for an elimination that is promoted by a neutral general-base species.

The observed incorporation of deuterium α to the cyano group in **1** for $pK_{BH} > 6$ can also be accommodated within Scheme I (Z = CN) provided $k_{-1} > k_2$ and $k_s > k_2$. Now, k_s has been estimated[10] as $\approx 10^{11}$ s^{-1}, and should be similar for both **1** and **3**. Thus $k_2 > 10^{11}$ s^{-1} for **3**, but $k_2 < 10^{11}$ s^{-1} for **1**, and departure of the *same* pyridine leaving group is faster from a 4-nitrophenyl-stabilized carbanion than from a cyano-stabilized carbanion. We thus have that the 4-nitrophenyl-stabilized carbanion is formed more slowly (k_1) than the corresponding cyano-stabilized carbanion, but this 4-nitrophenyl-stabilized carbanion ejects a pyridine nucleofuge more rapidly (k_2) than the corresponding cyano-stabilized carbanion. These results then strongly suggest that the 4-nitrophenyl-stabilized carbanion is thermodynamically less stable than its cyano analogue. Such a conclusion is supported by several comparisons between the thermodynamic acidities of cyano- and 4-nitrophenyl-activated carbon acids in aqueous solution (Table IV). Curiously, the estimated thermodynamic acidities of acetonitrile and 4-nitrotoluene in aqueous solution are not consistent with these observations, although they are consistent with the observation that 4-nitrotoluene is more acidic than acetonitrile in dimethyl sulfoxide solution[15] and also in the gas phase.[16]

When k_2 is rate-determining as in the case for eq 5, Scheme I predicts that $k_{OH} = k_1k_2/k_{-1}$. Combination of eq 4 ($k_{OH} = k_1$) and eq 5 then generates eq 6. Analogous treatment of the data[1] for **1** gives eq 7. These two equations indicate that the partitioning of the carbanionic intermediate between nucleofuge expulsion and reprotonation is much more dependent upon the basicity of the leaving group for cyano-stabilized carbanions than for 4-nitrophenyl-stabilized carbanions.

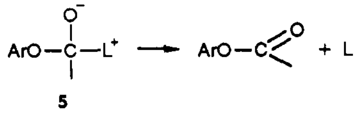
$$\log k_2/k_{-1} = -0.22\ pK_{BH} + 1.44 \text{ (for 3)} \tag{6}$$

$$\log k_2/k_{-1} = -0.63\ pK_{BH} + 3.6 \text{ (for 1)} \tag{7}$$

We expect that k_2 will be considerably more sensitive to substituent effects than will k_{-1} for elimination reactions from both **1** and **3**. Thus the significantly different Brønsted slopes for **1** and **3** in eqs 7 and 6, respectively, (and also the different β_{lg} for rate-determining leaving-groups departure in **1** and **3**) must be mainly a reflection of the different sensitivities of k_2 to substituent effects in the departure of the substituted pyridine nucleofuge from the conjugate bases of these two series of reactants. Thus $\beta(k_2)$ for **1** is considerably larger than $\beta(k_2)$ for **3**, and implies a greater fraction of C–N bond fission in the k_2 transition state in Scheme I when Z is cyano than when Z is 4-nitrophenyl. Such a transition-state effect is not unexpected, although its magnitude and direction may not be readily predictable, when one considers that there will be considerable difference in the delocalization of the carbanionic electron density into the cyano and 4-nitrophenyl groups. In fact, the hydrogen-bonded zwitterionic intermediate that is implied in Scheme I for Z = 4-$NO_2C_6H_4$ is almost certainly not the thermodynamically most stable conjugate base species since significant delocalization of negative charge onto the nitro group would be expected. Such electronic reorganization will result in significant solvational changes in the vicinity of the nitro group, and also diminish the hydrogen bonding that is shown to the carbanionic center in the kinetically controlled deprotonation product in Scheme I. The lack of significant incorporation of solvent deuterium into the 4-nitrostyrene product, and the relative magnitudes discussed above for the rate constants in Scheme I, imply that the solvent reorganization that would accompany the formation of the thermodynamically most stable conjugate base species must be slower than either the k_{-1} or k_2 steps.

Although a change in the rate-determining step with nucleofuge basicity was not demonstrated[3-5] for the hydroxide ion catalyzed elimination reactions of the *N*-[2-(4-nitrophenyl)ethyl]-quinuclidinium cations (**2**), the rate-determining step of such elimination reactions was shown to be dependent upon the concentration of general base catalyst species.[5] Analysis of the kinetic data for the elimination reactions of **2** promoted by the acetohydroxamate anion lead to $\beta(k_1) = -0.17$, $\beta(k_2/k_{-1}) = -0.47$, and $\beta(k_1k_2/k_{-1}) = -0.64$. The relative order of these three β_{lg} values is the same as that found for both **1** and **3**. However, the different numerical values observed for β_{lg} in each of these three systems indicates that the transition-state electron density distributions in each of the k_1, k_{-1}, and k_2 steps are quite sensitive to the nature of both the resonance-stabilizing substituent (cyano or 4-nitrophenyl) and the nucleofuge.

We cannot make any quantitative estimates of k_2 for quinuclidines and pyridines of similar basicity since a change in the rate-determining step to leaving-group departure is not observed for **2**. This result does suggest, however, that k_2 for quinuclidine loss from the carbanionic intermediate should be considerably greater than for the loss of a pyridine of the same basicity. The current experimental data in turn demonstrate that k_2 for a pyridine leaving group is considerably larger than for an imidazole of the same basicity. These results are consistent with the observations of Gresser and Jencks[6] of the relative rates of breakdown of tetrahedral intermediates (**5**) for quinuclidine, pyridine, and imidazole leaving groups. For leaving groups of the same basicity, the observed order of nucleofugalities from **5** is quinuclidine > pyridine > imidazole.



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On the basis of the current work and our earlier study,[1] we have now demonstrated a change in the rate-determining step in an E1cB reaction for the same class of leaving group (pyridines) with

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two quite different activating groups (cyano and 4-nitrophenyl). The significant difference in the reactivities of the *N*-(4-nitrophenethyl)pyridinium and quinuclidinium cations (**3** and **2**, respectively) is unexpected, particularly in terms of the lack of a change in the rate-determining step for the latter at about the same nucleofuge basicity for which such a change is clearly apparent for the former. More comprehensive studies of these two general classes of nucleofuge will be required to elucidate the detailed reasons behind their quite different reactivities, despite their similarities as nitrogen-derived leaving groups of the same electrical charge and similar basicity.

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Registry No. **3a**·Br, 135041-77-9; **3b**·Br, 135041-78-0; **3c**·Br, 135041-79-1; **3d**·Br, 120392-43-0; **3e**·Br, 135041-80-4; **3f**·Br, 135105-70-3; **3g**·Br, 135041-81-5; **3h**·Br, 135041-82-6; **3i**·Br, 135041-83-7; **3j**·Br, 135041-84-8; **3k**·Br, 135041-85-9; **3l**·Br, 135041-86-0; **4**·Br, 135041-87-1; 1-bromo-2-(4-nitrophenyl)ethane, 5339-26-4; 3-chloropyridine, 626-60-8; 3-(cyanomethyl)pyridine, 6443-85-2; 3-phenylpyridine, 1008-88-4; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 2-methylpyridine, 109-06-8; 4-methylpyridine, 108-89-4; 3,4-dimethylpyridine, 583-58-4; 4-amino-3-bromopyridine, 13534-98-0; 4-morpholinopyridine, 2767-91-1; 4-aminopyridine, 504-24-5; 4-(dimethylamino)pyridine, 1122-58-3; 1-methylimidazole, 616-47-7.

Cation Radical–Nucleophile Combination Reactions. Reactions of Nitrogen-Centered Nucleophiles with Cation Radicals Derived from Anthracenes

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Abstract: Cation radicals derived from anthracene and 9-substituted anthracenes react with pyridine and substituted pyridines to form pyridinium salts. 9-Nitro- and 9-cyano-substituted cation radicals were observed to be about 10^2 times as reactive as unsubstituted anthracene (AH) cation radicals while the 9-phenylanthracene (PAH) cation radical was found to be from 2 to 7 times less reactive than $AH^{•+}$. The reactivities of the nitrogen-centered nucleophiles were observed to depend upon both electronic and steric factors. The mechanism of the reactions involves nucleophilic attack by the nitrogen lone pair at the 10-position of the cation radical. The reactions are accompanied by a change in hybridization, sp^2 to sp^3, at the anthracene 10-position, giving rise to inverse deuterium kinetic isotope effects ranging from 0.7 to 0.8 when the 10-position is substituted with deuterium. An electron-transfer mechanism for the substitution reactions was ruled out on the basis of energetic considerations.

Introduction

Although cation radical–nucleophile combination reactions have been studied extensively,[1] the mechanism of the reactions remains an active topic of discussion. A central issue has been concerned with the energetics of the attack of a nucleophile on a cation radical. Work reported from our laboratory[2-4] indicates that the overall reaction (1), where Ar–H is an aromatic compound and compound N is a nucleophile, in the absence of special constraints such as steric factors, can be an essentially barrier-free reaction.

$$\text{Ar–H}^{•+} + \text{N} \rightarrow \text{Ar}^{•}(\text{H})(\text{N}^{+}) \qquad (1)$$

This is in spite of the fact[5,6] that since the product of reaction 1 is a doubly excited configuration with respect to reactants, the reaction is formally "forbidden" and can only have a low barrier under certain conditions. Specifically, when Ar–H is anthracene or 9-phenylanthracene and N is pyridine, reaction 1 is predicted to be slow.[6]

The early studies on cation radical–nucleophile reactivity[7,8] involved cation radicals of low reactivity such as those from 9,10-diphenylanthracene (DPA). This was an intentional feature of these studies made necessary by the fact that it was not possible to study the kinetics of more reactive cation radicals with the available kinetic techniques. The kinetic studies showed that in these systems, complex rate laws are followed that implicate the intermediacy of doubly charged species.[1] The apparent low reactivity[9] of cation radicals toward nucleophiles led Pross to examine the reaction theoretically, by using the configuration-mixing (CM) model.[5]

Cation radicals derived from 9-phenylanthracene (PAH), in contrast to $DPA^{•+}$, are highly reactive toward nucleophiles.[2,10,11]

Table I. Oxidation Peak Potentials of Anthracenes and Nitrogen-Centered Nucleophiles in Acetonitrile–Bu_4NPF_6 (0.1 M)

substance	$E^{p\,a}$
anthracene	0.88
9-phenylanthracene	0.85
9-cyanoanthracene	1.25
9-nitroanthracene	1.26
4-methylpyridine	2.44
pyridine	2.46
2-methylpyridine	2.31
4-cyanopyridine	2.90[b]
2,6-dimethylpyridine	2.13

[a] Peak potentials for the oxidation of the substrate in V vs $Fc/Fc^{•+}$ in CH_3CN–$LiClO_4$ (0.1 M) at 298 K. Fc refers to ferrocene. [b] 4-Cyanopyridine did not show a well-defined oxidation peak. A shoulder was observed at about 2.9 V vs $Fc/Fc^{•+}$.

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