Rates and Equilibria for Hydroxide Ion Addition to Quinolinium and Isoquinolinium Cations[1]

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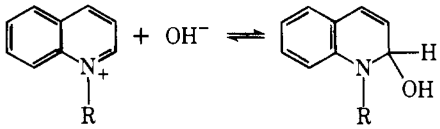
Abstract: Equilibrium constants (pK_{R^+}) have been measured (24.6 °C, ionic strength 0.1) for pseudobase formation by hydroxide ion addition to series of *N*-(X-benzyl)-5-nitroquinolinium (**3**) and 5-nitroisoquinolinium (**5**) cations bearing various meta and para substituents X in the *N*-benzyl group. Close linear correlations with the Hammett σ constant for X were obtained: pK_{R^+} (**3**) = $-1.32\sigma + 11.38$; pK_{R^+} (**5**) = $-1.14\sigma + 11.29$. Pseudo-first-order rate constants for formation ($k_f = k_{OH}[OH^-] + k_{H_2O}$) and decomposition ($k_d = k_1[H^+] + k_2$) of these pseudobases were also measured as a function of pH by the stopped-flow technique, and the parameters k_{OH}, k_{H_2O}, k_1, and k_2 were evaluated. Each of these parameters is also linearly correlated with σ(X), and of special interest are: $\log k_{OH}$ (**3**) = $0.58\sigma + 4.90$; $\log k_{OH}$ (**5**) = $0.51\sigma + 4.77$. These correlations require a linear correlation of the equilibrium (pK_{R^+}) and rate ($\log k_{OH}$) constants for hydroxide ion addition to these two series of cations. These latter correlations proved to be general for pseudobase formation from all quinolinium ($\log k_{OH} = -0.45pK_{R^+} + 10.03$) and isoquinolinium ($\log k_{OH} = -0.36pK_{R^+} + 8.84$) cations. Rate parameters for formation and decomposition of the pseudobases of the 1,5-dimethyl-1,5-naphthyridinium dication and the 1-methyl-5,7-dinitroquinolinium cation are also presented.

In 1899, Hantzsch[3] introduced the term "pseudobase" to describe the covalent hydroxide adducts of quaternary nitrogen heteroaromatic cations. Such adducts are cyclic carbinolamines (e.g., **1**) if hydroxide ion addition occurs at the carbon atom adjacent to the quaternary nitrogen atom, or simply carbinols if hydroxide addition occurs at a site in the cation that is remote from the nitrogen atom (e.g., **2**). These cation-pseudobase equilibria are exactly analogous to the carbonium ion-carbinol equilibria which have recently been the object of detailed study[4] in the triphenylmethyl carbonium ion-triphenylmethylcarbinol and related systems.



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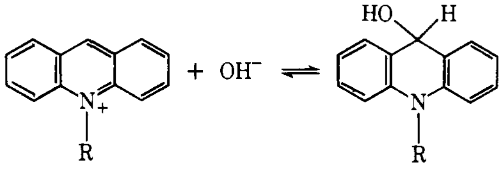

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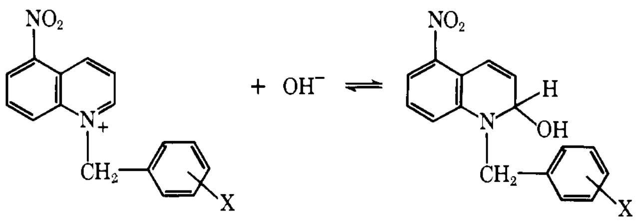
Although pseudobases have often been invoked as intermediates in reactions of heterocyclic molecules, no attempt at a detailed quantitative study of the rates and equilibria of pseudobase formation had been attempted until relatively recently. Following the measurement of the equilibrium constants for pseudobase formation from various *N*-cyano- and *N*-methylquinolinium and isoquinolinium cations by Cooksey and Johnson,[5] we have been engaged in a systematic exploration of the influence of the structure of the heterocycle and of substituent effects on the rates and equilibria of pseudobase formation from heteroaromatic cations.[6-11]

The general neglect of quantitative studies in this area in the past is somewhat surprising in view of the considerable efforts that have gone into the study of the related Meisenheimer complexes in recent years.[12] The pseudobases such as **1** and **2** formed from heteroaromatic cations may be considered to be neutral σ complexes and are exactly analogous to the anionic Meisenheimer σ complexes formed by nucleophilic addition to neutral electron-deficient aromatic systems. The pseudobase carbinolamines such as **1** are also of special interest since, unlike acyclic carbinolamines, they do not readily undergo C–N bond cleavage to give amine and carbonyl derivatives. Thus the study of the properties of carbinolamines, which are well established[13] as unstable intermediates in the formation of imines from, and hydrolysis of imines to, amines and carbonyl compounds is much facilitated in these pseudobase species.

The equilibrium constant for the heterocyclic cation (Q^+)-pseudobase (QOH) equilibrium, shown in the following equation:

$$Q^+ + H_2O \rightleftharpoons QOH + H^+ \qquad (1)$$

has the form of an acid dissociation constant, which we denote[14] as $K_{R^+} = [H^+][QOH]/[Q^+]$ in accord with general practice for cation-carbinol equilibria. In the current study, we report pK_{R^+} values for pseudobase formation by series of *N*-benzyl-5-nitroquinolinium (**3**) and 5-nitroisoquinolinium (**5**) cations bearing meta and para substituents in the benzyl ring, and also rate constants for formation and decomposition of these pseudobases. In these systems, substituent variations are sufficiently geometrically removed from the reaction



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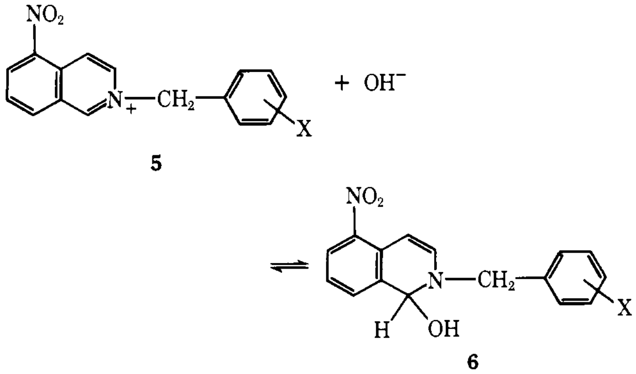

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Table I. *N*-Benzyl-5-nitroquinolinium (**3**) and 5-Nitroisoquinolinium (**5**) Cations

Cation	X	Anion	Mp, dec	^{1}H NMR spectrum (CF_3COOH), δ	Analysis
3	4-CH_3	ClO_4^-	207–209	2.4 (3 H, s), 6.3 (2 H, s), 7.3 (4 H, s), 8.3 (2 H, t), 8.7 (1 H, d), 8.9 (1 H, d), 9.3 (1 H, d), 9.8 (1 H, d)	($C_{17}H_{15}ClN_2O_6$), CHN
	H	Br^-	185–186	6.5 (2 H, s), 7.5 (5 H, s), 8.35 (2 H, m), 8.8 (1 H, d), 8.95 (1 H, d), 9.5 (1 H, d), 9.9 (1 H, d)	($C_{16}H_{13}BrN_2O_4$), CHN
	4-Br	Br^-	183–184	6.5 (2 H, s), 7.5 (4 H, q), 8.5 (2 H, m), 8.85 (2 H, t), 9.6 (1 H, d), 9.9 (1 H, d)	($C_{16}H_{12}Br_2N_2O_2$), CHN
	3-F	ClO_4^-	157–160	6.55 (2 H, s), 7.2 (4 H, m), 8.5 (2 H, m), 8.8 (2 H, t), 9.6 (1 H, d), 9.9 (1 H, d)	($C_{16}H_{12}ClFN_2O_6$) CHN
	3-CN	ClO_4^-	162–163	6.5 (2 H, s), 7.8 (4 H, m), 8.4 (2 H, m), 8.7 (1 H, s), 8.85 (1 H, d), 9.5 (1 H, d), 9.9 (1 H, d)	($C_{17}H_{12}ClN_3O_6$), CHN
	4-CN	Br^-	219–220	6.7 (2 H, s), 7.5 (4 H, q), 8.45 (2 H, q), 8.8 (2 H, m), 9.75 (1 H, d), 10.0 (1 H, d)	($C_{17}H_{12}ClN_3O_2$), CHN
	4-NO_2	Br^-	180–183	6.7 (2 H, s), 7.6 (2 H, d), 8.5 (4 H, m), 8.8 (2 H, d), 9.7 (1 H, d), 10.0 (1 H, d)	($C_{16}H_{12}BrN_3O_4$), CHN
5	4-CH_3O	Br^-	185–186	4.0 (3 H, s), 6.1 (2 H, s), 7.1 (2 H, d), 7.6 (2 H, d), 8.2 (1 H, t), 8.8 (2 H, t), 9.1 (1 H, d), 9.3 (1 H, d), 10.05 (1 H, s)	($C_{17}H_{15}BrN_2O_3$), CHN
	4-CH_3	Br^-	223–223.5	2.4 (3 H, s), 6.1 (2 H, s), 7.4 (4 H, q), 8.2 (1 H, t), 8.8 (2 H, t), 9.05 (1 H, d), 9.25 (1 H, d), 10.1 (1 H, s)	($C_{17}H_{15}BrN_2O_2$), CHN
	H	Br^-	208–209	6.2 (2 H, s), 7.6 (4 H, t), 8.25 (1 H, t), 8.9 (2 H, t), 9.1 (1 H, d), 9.3 (1 H, d), 10.15 (1 H, s)	($C_{16}H_{13}BrN_2O_4$), CHN
	4-Br	Br^-	211–213	6.2 (2 H, s), 7.6 (4 H, t), 8.3 (1 H, t), 8.9 (2 H, t), 9.1 (1 H, d), 9.35 (1 H, d), 10.15 (1 H, s)	($C_{16}H_{12}Br_2N_2O_2$), CHN
	3-F	Br^-	221–223	6.2 (2 H, s), 7.3 (4 H, m), 8.2 (1 H, t), 8.85 (2 H, t), 9.1 (1 H, d), 9.3 (1 H, d), 10.15 (1 H, s)	($C_{16}H_{12}BrFN_2O_2$), CHN
	3-CF_3	ClO_4^-	148–150	6.15 (2 H, s), 7.8 (4 H, m), 8.2 (1 H, t), 8.8 (2 H, t), 9.1 (1 H, d), 9.3 (1 H, d), 10.0 (1 H, s)	($C_{17}H_{12}ClF_3N_2O_6$), CHN
	3-CN	Br^-	257–258	6.2 (2 H, s), 7.9 (5 H, m), 8.9 (3 H, m) 9.3 (1 H, d), 10.2 (1 H, s)	($C_{17}H_{12}BrN_3O_2$), CHN
	4-CN	Br^-	259–260	6.3 (2 H, s), 7.85 (4 H, t), 8.2 (1 H, t), 8.85 (2 H, t), 9.1 (1 H, d), 9.35 (1 H, d), 10.2 (1 H, s)	($C_{17}H_{12}BrN_3O_2$), CHN

center, that substituent effects should be purely electronic effects without any significant contribution from steric or solvation effects. We find good correlations of both equilibrium and rate constants with Hammett σ constants for X and, furthermore, quite extensive linear correlations between rate and equilibrium data in both the quinolinium and isoquinolinium systems.

Experimental Section

Materials. Quaternary salts were usually prepared by refluxing the parent heterocycle with an appropriate benzyl halide, either neat or in acetone solution. When a benzyl chloride was used, a catalytic amount of sodium iodide was added to the reaction mixture. Perchlorate salts, which were found to crystallize more readily than the corresponding halide salts, were prepared by dissolving the halide salt in a minimum amount of hot water and slowly adding concentrated perchloric acid until crystallization was complete. Halide salts were recrystallized from absolute ethanol and perchlorate salts were recrystallized from water. Preparations and properties have previously been reported[9] for 1,5-dimethyl-1,5-naphthyridinium diiodide and 2-(4-nitrobenzyl)-5-nitroisoquinolinium bromide. Physical properties of the other *N*-benzyl-5-nitroquinolinium and 5-nitroisoquinolinium cations are listed in Table I.

5,7-Dinitroquinoline was prepared from 5-nitroquinoline by a method based on that of Kaufmann and Hussy.[15] 5-Nitroquinoline (1.74 g) was mixed with concentrated sulfuric acid (25 ml) and potassium nitrate (4.6 g) in a Fisher pressure bottle (200 ml). The rubber seal on the pressure bottle was protected with Teflon tape before sealing. The mixture was stirred at 145–150 °C for 3 days, and the pale-yellow product mixture was poured over ice (200 g). This solution was brought to pH 0.5–1.0 by the slow addition of concentrated aqueous ammonia, and the resulting solid was filtered off and recrystallized from ethanol–water (by dissolving in hot ethanol and adding water to induce crystallization). Yield of product = 0.36 g; mp 182 °C (lit.[15] mp 180 °C). Further neutralization of the above filtrate to pH 7 yielded approximately 1 g of unreacted 5-nitroquinoline.

1-Methyl-5,7-dinitroquinolinium Cation. 5,7-Dinitroquinoline (100 mg) was stirred in dimethyl sulfate (10 ml) for 3 days at 100 °C. The product was extracted with dilute hydrochloric acid (0.01 M). The extracts were concentrated and concentrated perchloric acid was added. Upon cooling overnight near 0 °C, brownish needles (50 mg, mp 215 °C dec) were obtained. In aqueous solution this material has an electronic spectrum almost identical with the spectrum of protonated 5,7-dinitroquinoline in >20% sulfuric acid solution (λ_{max} 308, 252 nm). The ^{1}H NMR spectrum of the aromatic protons of the product in D_2O is identical with that of 5,7-dinitroquinoline in trifluoroacetic acid [δ 10.1 (1 H), 9.6 (4 H), 8.6 (1 H); *N*-methyl signal obscured by residual H_2O].

Methods. All equilibrium and kinetic studies were carried out using techniques and conditions that we have previously described in detail.[6,7] All equilibrium and rate constants were obtained at 24.6 ± 0.2 °C and buffer ionic strength 0.1.

Results

The pK_{R^+} values for seven *N*-benzyl-5-nitroquinolinium cations (**3**) and nine *N*-benzyl-5-nitroisoquinolinium cations (**5**) are recorded in Table II at 24.6 °C and ionic strength 0.1. For the isoquinolinium cations, C-1 is the only reasonable site for nucleophilic addition to occur without disruption of the aromaticity of the homocyclic ring, and ^{1}H NMR and UV spectral studies[6,9] have corroborated this fact in all isoquinolinium cations studied to date, including **5**: X = H and **5**: X = 4-NO_2.[9] The UV spectral data for the pseudobase formed by each of the cations **5** show little variation for various X (Table II) and so support **6** as the structure for the pseudobase formed by each cation **5**. In principle, the quinolinium cations **3** can form pseudobase species by nucleophilic attack at either C-2 or C-4. The 1-methyl-5-nitroquinolinium cation has been shown[9] by ^{1}H NMR and UV spectral studies to undergo predominant C-2 attack to form the pseudobase **7**. The UV spectrum of **7** [λ_{max} 306, 405 (sh) nm] is very similar to that

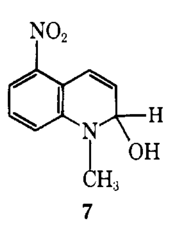

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Table II. pK_{R^+} and UV Spectral Data for Some *N*-Benzyl-5-nitroquinolinium and 5-Nitroisoquinolinium Cations

	Cation	X	pK_{R^+}[a]	pK_{R^+}[b]	λ_{max},[c] nm
1	**3**	4-CH_3	11.77 ± 0.05		301, 400 (sh)
2	**3**	H	11.26 ± 0.04		302, 400 (sh)
3	**3**	4-Br	11.05 ± 0.10	11.08 ± 0.05	305, 400 (sh)
4	**3**	3-F	11.02 ± 0.08		301, 400 (sh)
5	**3**	3-CN	10.60 ± 0.11		298, 400 (sh)
6	**3**	4-CN	10.49 ± 0.04		300, 400 (sh)
7	**3**	4-NO_2	10.36 ± 0.05		287, 400 (sh)
8	**5**	4-CH_3O	11.62 ± 0.06	11.62 ± 0.04	280, 321, 466
9	**5**	4-CH_3		11.40 ± 0.12	285, 322, 465
10	**5**	H	11.29 ± 0.05	11.32 ± 0.04	288, 321, 465
11	**5**	4-Br	11.05 ± 0.06	11.09 ± 0.06	277, 326, 467
12	**5**	3-F	10.90 ± 0.07	10.85 ± 0.08	285, 320, 463
13	**5**	3-CF_3	10.79 ± 0.07	10.77 ± 0.08	280, 320, 458
14	**5**	3-CN	10.60 ± 0.05	10.62 ± 0.16	283, 321, 465
15	**5**	4-CN	10.52 ± 0.02	10.47 ± 0.03	281, 321, 464
16	**5**	4-NO_2	10.40 ± 0.04	10.43 ± 0.03	277, 316, 458

[a] From Cary 16 K or Unicam 1800 data. [b] From stopped-flow data. [c] In aqueous KOH (0.1 M).

for the pseudobase from each of the cations **3** (Table II), and so there can be little doubt that the pseudobases **4** are the predominant forms in basic aqueous solutions of each **3**.

The equilibrations **3** $\rightleftharpoons$ **4** and **5** $\rightleftharpoons$ **6** proved to be quite rapid, but are amenable to investigation by the stopped-flow technique over ranges of 4-6 pH units for most cations. However, rates of equilibration for **3**: X = CH_3 were so fast as to be near the limit of detection with our instrument, and detailed kinetic studies were not made for this cation.

When aqueous solutions of each of the cations **3** and **5** were mixed with buffers (ionic strength 0.1) of pH greater than the corresponding pK_{R^+} values, cation-pseudobase equilibration was observable at suitable wavelengths. In all cases absorbance changes were strictly first order in heterocycle. Similarly, mixing solutions of each pseudobase in aqueous 0.005 N KOH with buffers which were of pH less than the pK_{R^+} value allowed the observation of the pseudobase to cation equilibration which was also strictly first order in heterocycle. Pseudo-first-order rate constants, k_{obsd}, were calculated at a number of pH values for each cation and are plotted as a function of pH in Figure 1 for selected **5**. Similar pH dependences for k_{obsd} were found for all **3** and **5** investigated in the present study. The observed rate constants at each pH are, of course, the sum of the individual first-order rate constants for formation (k_f) of the pseudobase from, and decomposition (k_d) of the pseudobase species to, the cation. Thus

$$k_{obsd} = k_f + k_d$$

At equilibrium

$$k_f[Q^+] = k_d[QOH]$$

and hence

$$\frac{k_f}{k_d} = \frac{[QOH]}{[Q^+]} = \frac{K_{R^+}}{[H^+]}$$

Therefore,

$$k_f = k_{obsd}/(1 + [H^+]/K_{R^+}) \tag{2}$$

and

$$k_d = k_{obsd}/(1 + K_{R^+}/[H^+]) \tag{3}$$

Values of k_f and k_d calculated from k_{obsd} using eq 2 and 3 are plotted as a function of pH in Figures 2 and 3, respectively. Each of the pH profiles in Figures 2 and 3 can be fitted by equations of the form:

$$k_d = k_1[H^+] + k_2 \tag{4}$$

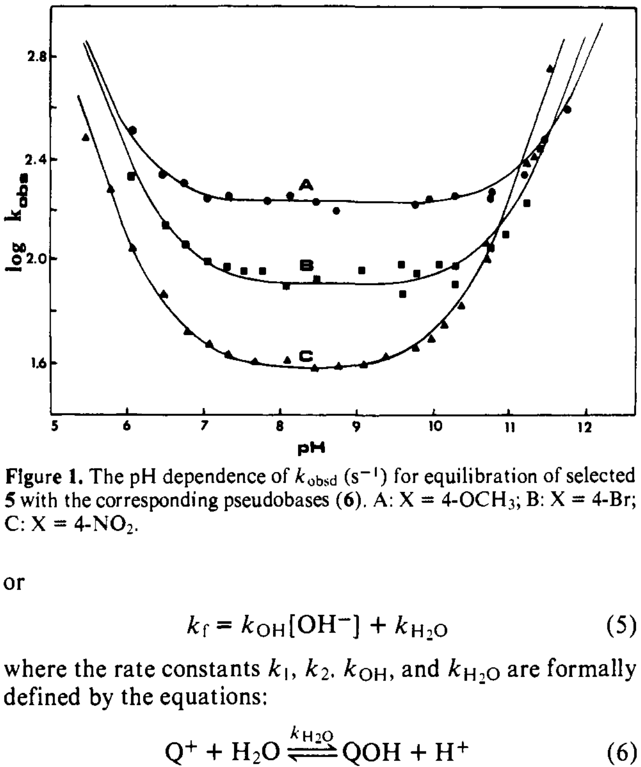


Figure 1. The pH dependence of k_{obsd} (s^{-1}) for equilibration of selected **5** with the corresponding pseudobases (**6**). A: X = 4-OCH_3; B: X = 4-Br; C: X = 4-NO_2.

or

$$k_f = k_{OH}[OH^-] + k_{H_2O} \tag{5}$$

where the rate constants k_1, k_2, k_{OH}, and k_{H_2O} are formally defined by the equations:

$$Q^+ + H_2O \underset{k_1}{\overset{k_{H_2O}}{\rightleftharpoons}} QOH + H^+ \tag{6}$$

$$Q^+ + OH^- \underset{k_2}{\overset{k_{OH}}{\rightleftharpoons}} QOH \tag{7}$$

Least-squares fitting of k_d and k_f to eq 4 and 5 gave the parameters which are collected in Table III. The curves in Figures 1-3 are calculated from eq 4 and 5 using these parameters and in general give a satisfactory fit to the experimental data.

The pK_{R^+} values for the cations **3** and **5** are plotted as functions of the Hammett σ constants[16] of the substituent X in Figure 4. Good linear correlations are apparent, and least-squares fitting gives

$$pK_{R^+}(\mathbf{3}) = -1.32\sigma + 11.38 \quad \text{(corr coeff = 0.983)} \tag{8}$$

and

$$pK_{R^+}(\mathbf{5}) = -1.14\sigma + 11.29 \quad \text{(corr coeff = 0.997)} \tag{9}$$

The rate constants k_2 for **3** and k_2 and k_{OH} for **5** also show linear dependences on σ (Figure 5). Correlation equations

Table III. Kinetic Parameters for Reversible Pseudobase Formation by *N*-Benzyl-5-nitroquinolinium (**3**) and 5-Nitroisoquinolinium (**5**) Cations

	Cation	X	k_1 (M^{-1} s^{-1}) × 10^{-8}	k_2, s^{-1}	k_{H_2O}, s^{-1}	k_{OH} (M^{-1} s^{-1}) × 10^{-5}	$10^{-7}k_{OH}/k_{H_2O}$
2	**3**	H	5.7	183	0.0031	1.01	3.3
3		4-Br	4.7	125	0.0041	1.10	2.7
4		3-F	4.2	110	0.0040	1.05	2.6
5		3-CN	3.2	59	0.0079	1.48	1.9
6		4-CN	3.4	52	0.0110	1.63	1.5
7		4-NO_2	2.5	51	0.0110	2.25	2.0
8	**5**	4-CH_3O	1.5	170		0.41	
9		4-CH_3	1.3	139		0.57	
10		H	5.7	119	0.0030	0.61	2.0
11		4-Br	1.8	81	0.0016	0.71	4.4
12		3-F	2.1	70	0.0025	0.84	3.4
13		3-CF_3	1.4	67	0.0024	1.12	4.7
14		3-CN	1.1	47	0.0027	1.17	4.3
15		4-CN	4.7	44	0.014	1.32	0.9
16		4-NO_2	0.90	38	0.0035	1.48	4.2

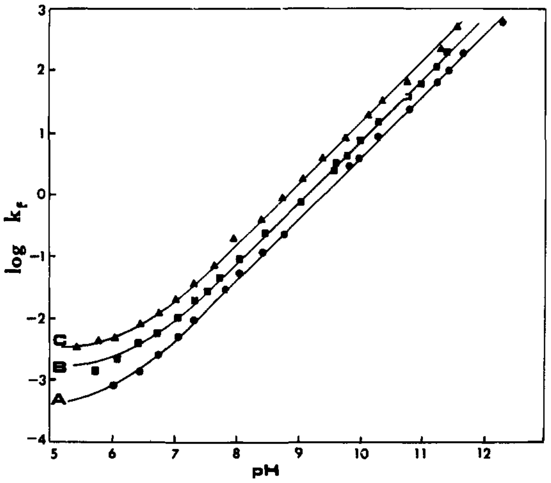


Figure 2. The pH dependence of k_f (s^{-1}) for pseudobase formation from selected **5**. A: X = 4-OCH_3; B: X = 4-Br; C: X = 4-NO_2.

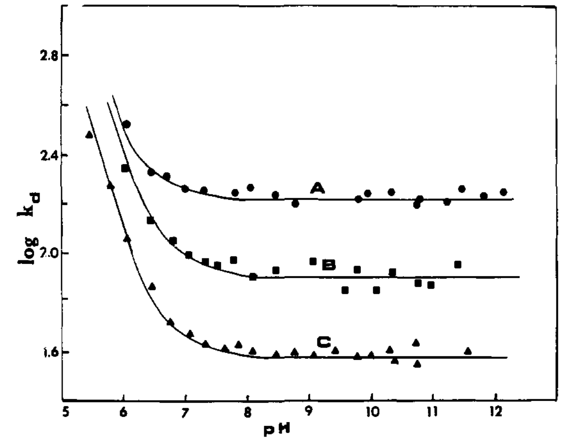


Figure 3. The pH dependence of k_d (s^{-1}) for decomposition of selected pseudobases (**6**) to the corresponding cations (**5**). A: X = 4-OCH_3; B: X = 4-Br; C: X = 4-NO_2.

are:

$$\log k_2\ (\mathbf{3}) = -0.74\sigma + 2.28 \quad \text{(corr coeff = 0.993)} \tag{10}$$

$$\log k_2\ (\mathbf{5}) = -0.61\sigma + 2.06 \quad \text{(corr coeff = 0.998)} \tag{11}$$

$$\log k_{OH}\ (\mathbf{5}) = 0.51\sigma + 4.77 \quad \text{(corr coeff = 0.992)} \tag{12}$$

The plot of log k_{OH} (**3**) against σ exhibits considerable scatter

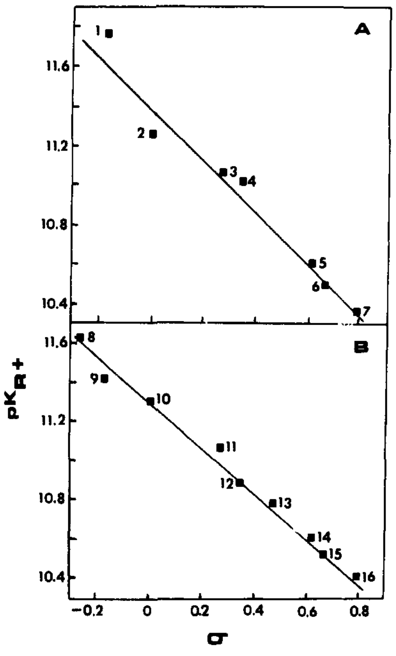


Figure 4. Dependence of pK_{R^+} on the Hammett σ constant for the cations **3** (A) and **5** (B). Cations are indicated by numbers corresponding to those in Table II.

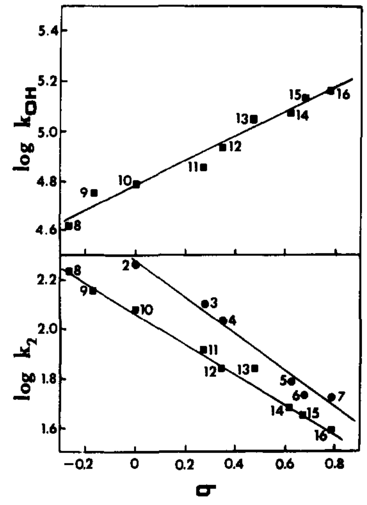


Figure 5. Dependence of log k_{OH} for **5** and log k_2 for **3** and **5** on the Hammett σ constant. Cations are indicated by numbers corresponding to those in Table II.

Table IV. Equilibrium and Kinetic Parameters for Some Heterocyclic Cations

	Cation	pK_{R^+}	k_1, $M^{-1}\,s^{-1}$	k_2, s^{-1}	k_{H_2O}, s^{-1}	k_{OH}, $M^{-1}\,s^{-1}$	$10^{-7}k_{OH}/k_{H_2O}$
17	**8**	$(5.41 \pm 0.02)^a$	2.9×10^6	0.097	$(11)^a$	$(3.8 \times 10^7)^a$	0.35
18	**10**	8.46 ± 0.11	7.2×10^7	6.4	0.27	2.2×10^6	0.81
19	**15**[b]	$(9.84)^a$	2.6×10^8	25	$(.030)^a$	$(2.8 \times 10^5)^a$	0.93
20	**16**[b]	$(9.47)^a$	1.9×10^8	14	$(.060)^a$	$(4.7 \times 10^5)^a$	0.78
21	2-Cyanomethyl-5-nitroisoquinolinium[c]	7.26	6.4×10^6	0.54	0.22	6.4×10^6	2.9
22	2-Methyl-4-nitroisoquinolinium[d]	5.11	1.3×10^5	0.011	1.04	8.8×10^6	0.85

[a] Statistically corrected for the two equivalent sites for pseudobase formation (see text). [b] Data taken from ref 10. [c] Data taken from ref 9. [d] Data taken from ref 7.

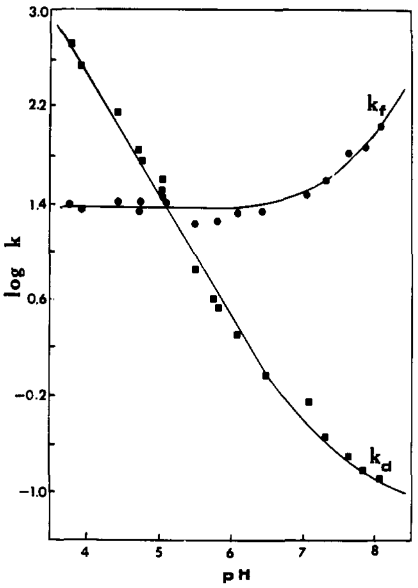


Figure 6. The pH dependence of k_f (s^{-1}) and k_d (s^{-1}) for reversible pseudobase formation from the 1,5-dimethyl-1,5-naphthyridinium dication (**8**).

since the kinetic data required to define k_{OH} were obtained near the limit of applicability of the stopped-flow spectrophotometer for several of these cations. Least-squares fitting gave:

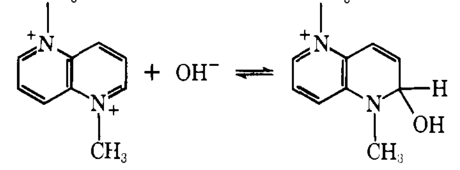
$$\log k_{OH}\ (3) = 0.45\sigma + 4.96 \qquad \text{(corr coeff} = 0.95) \qquad (13)$$

It is possible to calculate the dependence of log k_{OH} on σ in another way, since $k_{OH} = k_2K_{R^+}/K_w$ (from eq 7) where K_w is the ionic product of water. Using this expression along with eq 8 and 10 allows one to derive eq 13a which is in reasonable agreement with eq 13:

$$\log k_{OH}\ (3) = 0.58\sigma + 4.90 \qquad (13a)$$

Values of k_1 and k_{H_2O} are somewhat less precise than k_2 and k_{OH}. Consequently, no attempt is made to correlate k_1 and k_{H_2O} with σ directly.[17]

The rates of pseudobase equilibration with the 1,5-dimethyl-1,5-naphthyridinium dication (**8** ⇌ **9**; $pK_{R^+} = 5.11$)[9]



8 **9**

have also been investigated for the first time, and values of k_f and k_d as a function of pH are indicated in Figure 6. The parameters k_1, k_2, k_{OH}, and k_{H_2O} for this cation were evaluated from the data in Figure 6 and are given in Table IV.

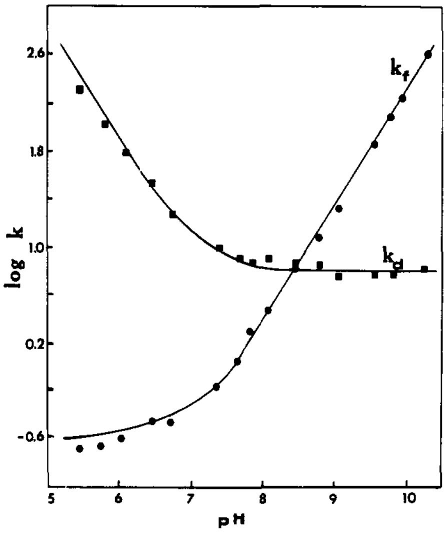
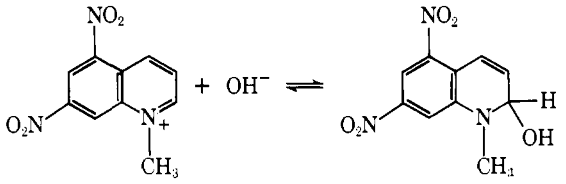


Figure 7. The pH dependence of k_f (s^{-1}) and k_d (s^{-1}) for reversible pseudobase formation from the 1-methyl-5,7-dinitroquinolinium cation (**10**).

The 1-methyl-5,7-dinitroquinolinium cation (**10**) has been



10 **11**

synthesized for the first time by methylation of 5,7-dinitroquinoline with dimethyl sulfate. This cation has a pH dependent electronic spectrum consistent with formation of the pseudobase **11** with $pK_{R^+} = 8.46$. The rates of cation-pseudobase equilibration (**10** ⇌ **11**) were investigated as usual, and the experimental data and parameters for this system are summarized in Figure 7 and Table IV.

Discussion

In the two series of cations **3** and **5**, the presence of electron-withdrawing X substituents on the benzyl ring should further increase the electron deficiency in the pyridinium ring and in particular at C-2 of **3** and C-1 of **5**. Thus the presence of electron-withdrawing X further destabilizes these cations relative to the corresponding pseudobases and consequently pK_{R^+} is predicted to decrease as X becomes increasingly electron withdrawing. The data in Table II confirm this trend and the correlations in Figure 4 indicate a linear dependence of pK_{R^+} on the Hammett σ constant for X. The ρ values of 1.32

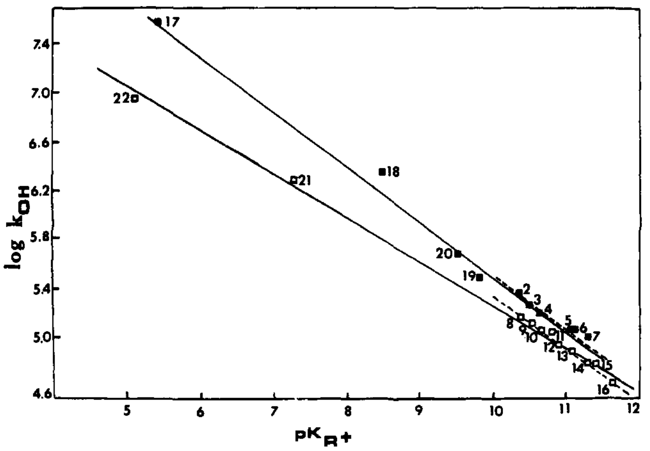
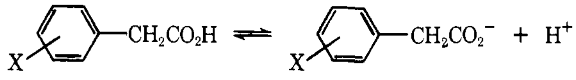
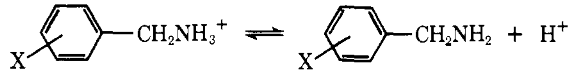


Figure 8. Relationship between log k_{OH} and pK_{R^+} for quinolinium (■) and isoquinolinium (□) cations. Cations are identified by numbers from Tables II and IV. Broken lines correspond to eq 14 and 15. Full lines correspond to eq 16 and 17.

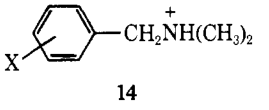
for 3 and 1.14 for 5 are quite large considering that the electronic effect of X must be transmitted to the pyridinium ring via the saturated carbon atom of the *N*-methylene unit. The ρ value for the acid dissociation of ring-substituted phenylacetic acids (**12**) is only ρ = 0.56 at 25 °C in water,[18] while for the acid dissociation of ring-substituted benzylammonium ions (**13**), ρ = 1.05.[18] This latter reaction is a useful model for the substituent effects on the equilibria for pseudobase formation from **3** and **5**, since in both cases the positive charge on a nitrogen atom is neutralized in the conversion of a benzylic ammonium ion to a neutral benzylamine. Ideally the ρ value for a series of N,N-disubstituted benzylammonium ions bearing ring substituents should be compared with $\rho(K_{R^+})$ for **3** and **5**. Such data does not appear to be available; however, by making use of ρ = 2.94 (in H_2O at 25 °C)[18] for the dissociation of anilinium ions and ρ = 3.56 (in H_2O at 20 °C)[18] for dissociation of *N,N*-dimethylanilinium ions, one may estimate $\rho = 1.05 \times 3.56/2.94 = 1.27$ for dissociation of *N,N*-dimethylbenzylammonium ions (**14**). This value is in reasonable agreement with the observed ρ values for pK_{R^+} for **3** (ρ = 1.32) and **5** (ρ = 1.14) when one considers the structural differences that still exist between **14** and **3** or **5** and the resulting differential solvation effects on the various species involved in the equilibria. Most of the difference between $\rho(K_{R^+})$ for **3** and **5** is also probably attributable to similar solvation effects.



12



13



14

We have previously reported[9] ρ^* = 4.9 and ρ^* = 3.7 for pK_{R^+} for pseudobase formation from series of N-substituted 1,8-naphthyridinium and 5-nitroisoquinolinium cations, respectively. This earlier study involved a range of different types of N-substituents in which steric effects may have been expected to play a significant role in addition to electronic effects. The ρ values for pK_{R^+} for **3** and **5** obtained in the present study, in which steric effects are unimportant, can be converted to ρ^* values using the expression $\rho^* = \rho/0.326$ derived from the relationship $\sigma^*(XC_6H_4CH_2) = 0.326\sigma(X) + \sigma^*(C_6H_5CH_2)$ due to Ritchie and Sager.[19] This gives ρ^* = 4.0 for the 5-nitroquinolinium cations (**3**) and ρ^* = 3.5 for the 5-nitroisoquinolinium cations in the present study. The latter value in particular is in excellent agreement with ρ^* = 3.7 obtained for 5-nitroisoquinolinium cations in the earlier study using a more varied assortment of N-substituent structures and confirms that the electronic effects of N-substituents heavily outweigh steric factors in influencing pK_{R^+}.

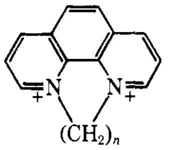
The observation that both rate and equilibrium constants for pseudobase formation from **3** and **5** are linearly dependent on σ requires that there should be a linear correlation between rate and equilibrium constants in each system. Combination of eq 8 and 13a for the quinolinium cations gives

$$\log k_{OH} = -0.44\mathrm{p}K_{R^+} + 9.90 \qquad (14)$$

and combination of eq 9 and 12 for the isoquinolinium cations gives

$$\log k_{OH} = -0.45\mathrm{p}K_{R^+} + 9.82 \qquad (15)$$

Figure 8 indicates the relationship between log k_{OH} and pK_{R^+}, and the broken lines correspond to eq 14 and 15 for **3** and **5**. Also included in Figure 8 are data for other quinolinium and isoquinolinium cations from our earlier work and for **8** and **10** from the present study. All these data are collected in Table IV. Statistical corrections have been made to both k_{OH} and pK_{R^+} for the dications **8**, **15**, and **16** to allow for the existence of two equivalent sites for hydroxide attack in each of these species. These statistical corrections involve dividing the observed values of k_{OH} by 2 and adding log 2 to the observed pK_{R^+} values.



15, *n* = 2
16, *n* = 3

From Figure 8 it is clear that the log k_{OH} vs. pK_{R^+} correlation discussed above for **3**, in fact, applies to all quinolinium cations and the correlation for **5** applies to all isoquinolinium cations. Least-squares fitting of all data in Figure 8 for quinolinium and isoquinolinium cations (independently) gives:

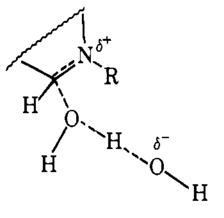
$$\text{Quinolinium: } \log k_{OH} = -0.45\mathrm{p}K_{R^+} + 10.03 \quad (\text{corr coeff} = 0.999) \qquad (16)$$

$$\text{Isoquinolinium: } \log k_{OH} = -0.36\mathrm{p}K_{R^+} + 8.84 \quad (\text{corr coeff} = 0.997) \qquad (17)$$

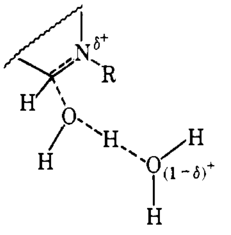
Equations 16 and 17 are in reasonable agreement with eq 14 and 15. These correlations cover six units of the pK_{R^+} scale (i.e., six orders of magnitude in K_{R^+}) and a variety of substitution patterns in the quinolinium and isoquinolinium ring systems as well as various N-substituents and so are apparently quite general correlations for pseudobase formation from isoquinolinium cations and for C-2 pseudobase formation from quinolinium cations.

It is also clear from Figure 8 that different correlation lines are required for quinolinium and isoquinolinium cations. This observation is in line with Ritchie's general conclusion[4a,b] that there is no general correlation between rate and equilibrium constants for nucleophilic addition to carbonium ions of varying structure. However, it is quite clear from Figure 8, that provided one stays within a series of very closely structurally related cations, useful linear rate-equilibrium correlations over a wide range of substituents and substitution patterns may be expected to exist.

For both **3** and **5**, $\rho(k_{OH})$ is considerably smaller in magnitude than $\rho(K_{R^+})$ and thus reflects the considerably smaller amount of charge neutralization at the ring nitrogen atom in the transition state than in the product. In fact, the relative magnitudes of $\rho(k_{OH})$ and $\rho(K_{R^+})$ suggest that the transition state associated with k_{OH} is somewhat more "reactant-like" (i.e., cationic) than "product-like" (i.e., pseudobase). We have previously concluded[7] from detailed studies on related systems that the k_{OH} term probably does not represent direct attack of hydroxide ion on the cation, but rather reflects the attack of a neutral water molecule assisted by general base catalysis by hydroxide ion (transition state A). Probably the strongest piece of evidence in favor of this mechanistic interpretation for k_{OH}, rather than a direct attack of hydroxide ion on the cation, is the fact that $\Delta S°$ is positive in such reactions (+4 to +9 eu),[7] but $\Delta S^{\ddagger}$ is quite negative (−11 to −17 eu).[7] The k_{H_2O} term similarly represents transition state B in which one molecule of water acts as a general base to assist the nucleophilic attack by another water molecule.



A



B

One outstanding feature of the data in Tables III and IV is the apparent independence of the ratio k_{OH}/k_{H_2O} on the nature of the substitution of quinolinium and isoquinolinium cations. Thus, although K_{R^+} varies 10^6-fold for the monocations collected in Tables III and IV, the ratio k_{OH}/k_{H_2O} varies only about fivefold for these same cations and can be considered to be effectively constant within experimental error for **3** and **5**. A constant k_{OH}/k_{H_2O} ratio requires that $\rho(k_{H_2O}) = \rho(k_{OH})$ and therefore suggests that the same amount of charge neutralization on N occurs in the transition state irrespective of whether k_{OH} or k_{H_2O} is in control. This idea further suggests that the same amounts of bond formation and cleavage are involved in corresponding bonds of transition states A and B, and thus the relative values of k_{OH} and k_{H_2O} are determined solely by the difference in the basicities of hydroxide ion and water. Analogous considerations apply to decomposition of the pseudobase to the cation via the k_1 and k_2 pathways, since these reactions are the microscopic reverse of k_{H_2O} and k_{OH}, respectively.

General Consideration of pH-Rate Profiles. The observed pseudo-first-order rate constant for cation-pseudobase equilibration can be expressed using eq 4 and 5 as

$$k_{obsd} = k_1[H^+] + k_2 + \frac{k_{OH}K_w}{[H^+]} + k_{H_2O} \qquad (18)$$

in which K_w is the autoprotolysis constant of water. Differentiation of k_{obsd} with respect to $[H^+]$ gives

$$\frac{d(k_{obsd})}{d[H^+]} = k_1 - \frac{k_{OH}K_w}{[H^+]^2}$$

The observed pH-rate profile (e.g., Figure 1) will pass through a minimum value when this derivative is zero: i.e., at

$$[H^+]_{min} = \left(\frac{k_{OH}K_w}{k_1}\right)^{1/2}$$

Using this relationship and eq 18, the minimum value of k_{obsd} will be

$$k_{obsd}^{min} = k_2 + k_{H_2O} + 2\sqrt{k_1 k_{OH} K_w} \qquad (19)$$

Now,

$$k_2 = k_{OH}K_w/K_{R^+} \qquad (20)$$

and

$$k_{H_2O} = k_1 K_{R^+} \qquad (21)$$

The data presented in this paper indicate that, in general, for pseudobase formation from isoquinolinium cations and at C-2 of quinolinium cations $k_{OH}/k_{H_2O} \approx 10^7$. Making this assumption, eq 21 may be rearranged to

$$k_1 = \frac{10^{-7}k_{OH}}{K_{R^+}}$$

Thus,

$$[H^+]_{min} = \sqrt{10^7 K_w K_{R^+}}$$

and

$$pH_{min} = 3.5 + 0.5pK_{R^+} \text{ at } 25\ °C, \text{ when } K_w = 10^{-14}$$

Equation 19 becomes

$$k_{obsd}^{min} = k_{OH}K_w/K_{R^+} + 10^{-7}k_{OH} + 2k_{OH}\sqrt{10^{-7}K_w/K_{R^+}}$$
$$= k_{OH}\,(10^{-14}/K_{R^+} + 10^{-7} + 6.3 \times 10^{-11}/\sqrt{K_{R^+}}) \qquad (19a)$$

while eq 18 becomes

$$k_{obsd} = k_{OH}[(10^{-7}[H^+] + 10^{-14})/K_{R^+} + [OH^-] + 10^{-7}] \qquad (18a)$$

Clearly, substitution of eq 16 or 17 into 18a and 19a gives k_{obsd} and k_{obsd}^{min} as a function of K_{R^+} alone. Thus, for quinolinium and isoquinolinium cations, the measurement of pK_{R^+} allows calculation of the complete pH profile provided eq 16 or 17 is applicable and with the only other assumption being that $k_{OH}/k_{H_2O} = 10^7$. In general, of course, one would prefer to independently determine the pH-rate profile from kinetic measurements; however, the above expressions for k_{obsd}, k_{obsd}^{min}, and pH_{min} in terms of K_{R^+} allow a useful preliminary determination of the pH region that is likely to be amenable to investigation by the stopped-flow technique.

In our earlier work[9] we had routinely explored the equilibration rates at a pH equal to pK_{R^+} on the assumption that the minimum value of k_{obsd} would occur in this vicinity. The above derivation indicates that this is not in general a useful assumption, and that k_{obsd}^{min} only occurs at pH = pK_{R^+} when pK_{R^+} is in the vicinity of 7.0. Clearly, the above derivations can be modified for other systems in which k_{OH}/k_{H_2O} takes values other than 10^7.

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(2) National Research Council of Canada Postdoctoral Fellow, 1975–1977.
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(14) We have previously followed Cooksey and Johnson[5] and used K_{ROH} in place of K_{R^+}. We have now decided to use K_{R^+} for the equilibrium constant for pseudobase formation since this is general practice for other cation–carbinol equilibria.
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(17) As discussed later, k_{OH}/k_{H_2O} is approximately constant for these cations; this requires that $\rho(k_{H_2O}) \approx \rho(k_{OH}) \approx 0.5$ for both **3** and **5**. Also, from eq 21 one may then estimate $\rho(k_1) \approx -0.84$ for **3** and $\rho(k_1) \approx -0.62$ for **5**.
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Elimination–Addition Mechanisms of Acyl Group Transfer: Hydrolysis and Aminolysis of Aryl Phenylmethanesulfonates[1]

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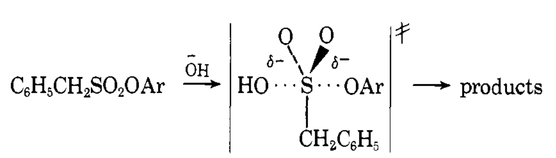
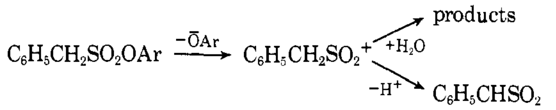
Abstract: The following evidence is consistent with an E1cB mechanism involving a sulfene intermediate for the alkaline hydrolysis and aminolysis of aryl phenylmethanesulfonates in water: (1) The Brønsted plot of hydroxide rate constant vs. phenol acidity possesses a sharp break at $pK_a \sim 6.5$. (2) Alkaline hydrolysis of the esters of weakly acidic phenols possesses a high selectivity ($\beta_{LG} = 2.4$) compared with that for esters (1.2) undergoing an addition–elimination mechanism. (3) The rate constant for phenol release is not linearly dependent on amine buffer concentration. (4) Trapping experiments with amines indicate a common intermediate for aminolysis of the esters. (5) The hydroxide rate constant for the 4-nitrophenyl ester is 1000-fold larger than for the corresponding benzene- and methanesulfonates. (6) Esters of the acidic phenols hydrolyze with general base catalysis and a high primary deuterium isotope effect. (7) Esters of the weakly acidic phenols undergo only specific base-catalyzed hydrolysis and involve no primary isotope effect. The lifetime of the conjugate base from esters of phenols with $pK_a < 6$ is too short ($<10^{-13}$ s) for it to exist as a discrete intermediate and an E2 elimination occurs with an unsymmetrical transition state involving no S–OAr bond cleavage and half advanced proton transfer. The inactivation of α-chymotrypsin by phenylmethanesulfonyl fluoride is shown not to be via a sulfene intermediate.

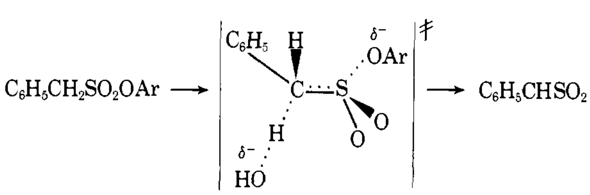
Recent discussion has centered on the existence of E2 mechanisms[2] as opposed to E1 or E1cB pathways for elimination and especially on the critical evaluation of evidence previously thought to support a concerted timing.[3-5] The status of the E1cB mechanism was reviewed in 1967[6] and little evidence was available in favor of this pathway. Later, detailed studies established the stepwise path in selected systems and have led to an empirical understanding of mechanistic control.[7]

Four major types of reaction mechanism are envisaged for sulfonate group transfer. The addition–elimination mechanism (eq 1) is the process currently thought to operate for simple sulfonate transfers such as the hydrolysis of aryl benzenesulfonates.[8] There is some doubt, however, as to whether this process is stepwise involving a pentacovalent intermediate or concerted. The S_N1 path is a possible mechanism for sulfonyl halide hydrolysis,[9] although there is as yet no evidence for the E1 component involving proton transfer. One of the elimination mechanisms (eq 3 and 4) almost certainly participates in sulfene formation in the presence of base from sulfonyl halides possessing an α-proton.


(1)


(2)

$$C_6H_5CH_2SO_2OAr \overset{B}{\rightleftharpoons} C_6H_5\bar{C}HSO_2OAr \longrightarrow C_6H_5CHSO_2 \quad (3)$$


(4)

The E1cB mechanism for acyl group transfer has recently become established,[10] but there is still no credible evidence for the operation of E2 timing for reactions in aqueous solution; we decided to investigate the possibility of E2 mechanisms of acyl group transfer for phenylmethanesulfonate esters where the intermediate is a sulfene. Regarding our knowledge of mechanistic control of the olefin forming reaction we thought that the high pK_a of the carbon acid[11] combined with an active leaving group might provide conditions for a concerted process which should be revealed in a Brønsted type plot vs. leaving group basicity; previous work[12] provides much evidence consistent with an E1cB-like (paenecarbanion) E2 process or an $E1cB_I$ (proton transfer rate limiting) mechanism for the formation of sulfenes from active sulfonates in nonaqueous solvents.

The inactivation of α-chymotrypsin by phenylmethanesulfonyl fluoride[13] is usually assumed to involve binding of the phenyl group in a hydrophobic pocket followed by an S_N2 attack of the nucleophile on the enzyme. An alternative explanation is that the enzyme catalyzes the formation of sulfene, which then attacks the nucleophile;[14] this mechanism is capable of being directly tested by use of a primary deuterium isotope effect.