(ε 6260), 274 (6350), and 280 sh nm (4660); $\delta_{TMS}^{DMSO-d_6}$ 6.53–8.32 (m, 13, aryl and pyridyl), 5.71 (s, 1, –OH), 4.44–4.77 (m, 1, >C*H*C(OH)<), and 3.22–3.58 (m, 2, α-methylene).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.88. Found: C, 83.40; H, 5.91; N, 4.69.

Reaction of 3 with Benzaldehyde. The dianion (**3**) was generated from 2.5 g (15.3 mmol) of 3,8-dimethyl-2-methoxyazocine and 1.2 g (30.7 mg-atoms) of potassium. To a suspension of this salt in anhydrous tetrahydrofuran (*ca.* 40 ml) was added 3.26 g (30.7 mmol) of freshly distilled benzaldehyde. A blue color did not develop in this instance. The reaction mixture was stirred at room temperature under dry nitrogen for 43 hr and evaporated to give a dark residue. Water (65 ml) was carefully added and the products were extracted with three 60-ml portions of methylene chloride. The combined organic layers were washed once with water, dried, and evaporated to afford a dark viscous oil which was chromatographed on Florisil (45 g). Elution with petroleum ether and ether–petroleum ether (1:4) yielded a viscous yellow gum (1.13 g) which resisted crystallization and further purification. Elution with ether–petroleum ether (1:1) afforded in the earlier fractions 132 mg of a colorless crystalline solid, mp 107–108° (ethyl acetate–hexane), which contained no nitrogen and was not examined further. The infrared spectrum showed peaks at 3330, 1670, 1605, and 1585 cm^{-1}. The nmr spectrum exhibited a multiplet at δ 7.26–8.29 and singlets at 4.55 and 4.45.

The later fractions contained a dark gum (705 mg). This gum and residues from the preceding recrystallization were combined and rechromatographed on Woelm neutral alumina (10 g, activity grade I). Elution with ether–benzene (7:3) gave 225 mg (6.1%) of **13**, mp 120–120.5°, from hexane; ν_{max}^{KBr} 3230, 1600, 1580, 753, and 703 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 279 (ε 6850) and 286 sh nm (4650); $\delta_{TMS}^{CDCl_3}$ 7.64 (s, 5, aryl), 6.83 (d, J = 8.0 Hz, 1, pyridyl), 6.65 (d, J = 8.0 Hz, 1, pyridyl), 4.73 (d, J = 9.0 Hz, 1, <C*H*OH), 4.21 (s, 1, –OH), 3.63 (d of q, J = 7.0 and 1.8 Hz, 1, α-methylene), 3.18 (d of m, J = 9.0 Hz, 1, >C*H*C(OH)<), 2.41 (s, 3, methyl), and 1.45 (d, J = 7.0 Hz, 3, methyl).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85: Found: C, 80.25; H, 7.12; N, 5.74.

Elution of the original column with 5% methanol in ether led to the isolation of colorless plates (210 mg), mp 124–125°, from ethyl acetate: ν_{max}^{KBr} 1690, 1630, and 1580 cm^{-1}; $\delta_{TMS}^{DMSO-d_6}$ 8.36–8.73 (series of multiplets).

Anal. Found: C, 69.30; H, 5.89.

This substance has not been identified.

Base-Induced Aromatization of 3,4-Dihydro-3,8-dimethyl-2-methoxyazocine (18). A mixture of 0.50 g (3.0 mmol) of **18**[1] and 1.12 g (19 mmol) of powdered potassium *tert*-butoxide in 10 ml of dry tetrahydrofuran was heated at reflux with stirring under anhydrous conditions for 24 hr. After cooling, water (50 ml) was added and the aqueous mixture was extracted with three 50-ml portions of ether. The combined ethereal extracts were dried, filtered, and evaporated and the residual oil was molecularly distilled. There was obtained 340 mg (85%) of **20** as a mobile colorless liquid with a penetrating odor. Vpc analysis (10% SF-96 on 60–80 mesh Chromosorb G at 145°) showed a single peak. The analytical sample was prepared by preparative scale vpc: ν_{max}^{film} 1600, 1580, and 818 cm^{-1}; $\lambda_{max}^{C_2H_5OH}$ 276 (ε 6760), 278 sh (6660), and 285 sh nm (5550); $\delta_{TMS}^{CDCl_3}$ 7.26 (d, J = 7.5 Hz, 1, pyridyl), 6.95 (d, J = 7.5 Hz, 1, pyridyl), 3.77 (m, 1, α-methine), 3.26 (d of d, J = 14.0 and 5.0 Hz, 1, β-methylene), 2.54 (d of m, J = 14 Hz, 1, β-methylene), 2.52 (s, 3, methyl), and 1.43 (d, J = 7.0 Hz, 3, methyl).

Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.33. Found: C, 80.80; H, 8.45.

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Reactions of Acetylimidazole and Acetylimidazolium Ion with Nucleophilic Reagents. Structure–Reactivity Relationships[1a]

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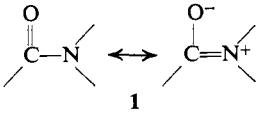
Abstract: The reactions of amines with acetylimidazolium ion exhibit a large dependence on amine basicity, $\beta = 1.0$, for amines both more and less basic than the leaving imidazole. The rapid reaction of *N*-methylimidazole with acetylimidazolium ion (and of imidazole with acetyl-*N*-methylimidazolium ion) shows that concerted proton transfer is not important in these reactions. The nucleophilic reactions with tertiary amines are inhibited by very low concentrations of added imidazole. The dependence of oxyanion reactivity upon basicity varies markedly; β values decrease with increasing basicity over the entire range from approximately 1.7 to 0. The reactions of tertiary amines with free acetylimidazole are not inhibited by imidazole and represent general base catalysis of hydrolysis; the triethylenediamine reaction exhibits a solvent deuterium isotope effect $k_{H_2O}/k_{D_2O} = 2.1$. The β values for general base catalysis of hydrolysis are 0.34 for acetylimidazolium ion and 0.55 for acetylimidazole. The β value for the nucleophilic reaction of phenolate anions with free acetylimidazole is 1.3. It is argued that the nucleophilic reactions of trifluoroethoxide ion with acetylimidazole and acetylimidazolium ion cannot proceed through a tetrahedral addition intermediate that is at equilibrium with respect to proton transfer.

In this and the following paper we describe a study of structure–reactivity relationships and mechanisms of catalysis in the reactions of a model amide, acetylimidazole, with nucleophilic reagents. Mechanistic studies on the reactions of ordinary amides are technically difficult because of the low reactivity of resonance-stabilized amides (**1**) under conditions suitable for the



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kinetic study of reactions with nucleophiles. Acetylimidazole (**2**) and its conjugate acid, acetylimidazolium ion (**3**), have a greatly enhanced reactivity because the

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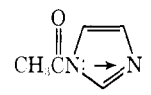

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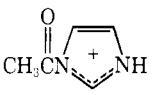

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electron pair which is normally involved in resonance with the carbonyl groups is tied up in the aromatic imidazole ring; furthermore, the ultraviolet absorption of acetylimidazole at 245 nm greatly facilitates kinetic studies.[2-4] We were particularly interested in studying the reactions of acetylimidazolium ion with amines of both greater and lesser basicity than the leaving imidazole group, to complement a study of the reactions of a series of acetate esters with alkoxide ions of varying basicity.[5] The study also complements a recent examination of the reactions of nucleophiles with substituted acetylpyridinium ions in which, for technical reasons, a more limited series of reagents was studied.[6] The reactions of acetylimidazole are also of special interest because of the possibility of examining at the same time the reactions of an amide with a good leaving group, acetylimidazolium ion with a leaving group of pK 7, and an amide with a poor leaving group, free acetylimidazole, in which the leaving group has a pK of 14.2.[7] The results confirm the general impression that reactions of amides with nucleophiles are dominated by a tendency to add a proton to the leaving amine and that acyl compounds with poorer leaving groups display an enhanced sensitivity to the basicity of the attacking group and to catalysis.

Experimental Section

Acetylimidazole (Eastman Organic Chemicals) was recrystallized from isopropenyl acetate (mp 101–102°). The chloride salt of *N*-acetyltriethylenediamine cation was prepared by the dropwise addition of triethylenediamine (1.12 g) in 20 ml of dry ether to redistilled acetyl chloride (0.71 ml) in 70 ml of dry ether at −78° (Dry Ice–acetone). The white precipitate was washed several times with cold ether, kept as a suspension in ether at −78°, and used within 2 hr. The product decomposes rapidly at room temperature and no attempt was made to measure its physical properties. However, a small quantity of the ether suspension added to neutral aqueous hydroxylamine solution and then to ferric chloride gave the purple color characteristic of active acetyl compounds;[8] acetyl chloride gave no color under the same conditions. All other reagents were commercial materials recrystallized or distilled before use. The reactions were carried out in glass-distilled water.

The kinetic measurements were carried out as described previously.[4,9] The pH was measured after each run, the temperature was 25.0°, and, unless otherwise stated, the ionic strength was maintained with tetramethylammonium chloride.

The products of the reactions of acetylimidazole with trifluoroethanol and piperidine were analyzed for ester and amine by the alkaline[10] and neutral[11] hydroxylamine methods, respectively. For the amide analysis 0.5 ml of sample was heated at 100° for 2 hr with 1.5 ml of a solution consisting of 1.5 vol of 40% hydroxylamine hydrochloride, 1.0 vol of 3.5 *M* sodium hydroxide, and 0.6 vol of water. After cooling, 1.5 ml of 7% $FeCl_3 \cdot 6H_2O$ in 1.5 *M* hydrochloric acid was added and the absorbance was read at 540 nm. Standards of acetylpiperidine, acetohydroxamic acid, and the acetylimidazole solution used for the experiment were subjected to the same procedure; acetylpiperidine gives a color yield of approximately 70% compared to acetohydroxamic acid under these conditions. In runs containing 0.1, 0.2, and 0.4 *M* piperidine, 20% free base, and as the hydrochloride in imidazole buffer, 50% base, in which the reactions proportional to [piperidine]^2 and to [piperidine-H$^+$], respectively, accounted for almost all of the observed reaction with acetylimidazole, the calculated yields of acetylpiperidine were obtained, indicating that these two reactions represent nucleophilic attack of piperidine on acetylimidazole. The products of the uncatalyzed reaction proportional to [piperidine] are difficult to analyze, because there is no pH value at which this reaction accounts for almost all of the observed reaction. However, in borate buffer at pH 9.3 containing 0.1, 0.2, and 0.4 *M* total piperidine, the observed yields of acetylpiperidine were found to be 38, 44, and 55%, respectively. The expected yields for the other two contributing reactions are 10, 21, and 38%, while the expected yields if all three reactions represent nucleophilic attack are 36, 56, and 76%, respectively. These results show that at least the major part of the uncatalyzed piperidine reaction represents nucleophilic attack. A semiquantitative experiment using the alkaline hydroxylamine method with 0.5 *M* trifluoroethanol in 0.1 *M* imidazole buffer, 80% base, conditions in which almost all of the reaction involves trifluoroethoxide ion, showed that most or all of this reaction involves nucleophilic attack on acetylimidazole to give the ester.

Results

Hydrolysis. The pH–rate profile for the hydrolysis of acetylimidazole in 1 *M* tetramethylammonium chloride was found to follow the rate law of eq 1, which

$$v = 2.26[\mathrm{AcImH^+}] + 0.006[\mathrm{AcIm}] + 16{,}000[\mathrm{AcIm}]a_{\mathrm{OH^-}} \quad (1)$$

is very similar to that previously reported for lower ionic strength.[4] Rate measurements in triethylenediamine and imidazole buffers were extrapolated to zero buffer concentration; other measurements were made in dilute hydrochloric acid or in 0.03 *M* acetate buffers, in which the reaction with acetate contributes less than 3% to the observed rate. The hydrolysis rate levels off at low pH as acetylimidazole is completely converted to the acetylimidazolium ion, following a pK for this ionization of 3.86 under these conditions.

Reactions with Nucleophiles. The reactions of acetylimidazole with amines follow the rate law of eq 2 in

$$v = k_1[\geqslant\mathrm{NH^+}][\mathrm{AcIm}] + k_2[\geqslant\mathrm{NH^+}][\mathrm{AcIm}][\mathrm{B}] + k_3[\geqslant\mathrm{N}][\mathrm{AcIm}] + k_4[\geqslant\mathrm{N}][\mathrm{AcIm}][\mathrm{B}] \quad (2a)$$

$$= k_1'[\geqslant\mathrm{N}][\mathrm{AcImH^+}] + k_2'[\geqslant\mathrm{N}][\mathrm{AcImH^+}][\mathrm{B}] + k_3[\geqslant\mathrm{N}][\mathrm{AcIm}] + k_4[\geqslant\mathrm{N}][\mathrm{AcIm}][\mathrm{B}] \quad (2b)$$

which B represents a second molecule of amine that catalyzes the reaction.[4] The rate constants are usually determined experimentally according to eq 2a, but may also be expressed according to the kinetically equivalent rate law of eq 2b, in which the free base form of the amine is assumed to be the reactive species.[9] The two rate constants are interrelated by the ratio of the acid dissociation constants for the conjugate acid of the nucleophile, $K_{\mathrm{NH^+}}$, and for acetylimidazolium ion, $K_{\mathrm{AcImH^+}}$, so that $k_1' = k_1 K_{\mathrm{AcImH^+}}/K_{\mathrm{NH^+}}$ and $k_2' = k_2 \cdot K_{\mathrm{AcImH^+}}/K_{\mathrm{NH^+}}$. The experimental conditions for the rate measurements and the observed rate constants are given in Table I and the derived rate constants are summarized in Table II.

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Table I. Rate Constants for the Reactions of Acetylimidazole with Nucleophiles at 25° and Ionic Strength 1.0 M ($(CH_3)_4NCl$)

Nucleophile	% free base	pH	No. of points	Concn range, M	k_{obsd},[a] M^{-1} min^{-1}	k_{cat},[b] M^{-2} min^{-1}	k_0,[c] min^{-1}
Piperidine	1.7×10^{-5}–1.6×10^{-4}	6.6–7.6	9	0.50	0.43[d,e]		
	4×10^{-3}	7.08	6[f]	0.191	0.40		
	0.06	8.23	6[g]	0–0.60	0.50		
	2.2	9.80	6[h]	0–0.10	5.7		
	4.0	10.07	6[h]	0–0.10	11.6	*i*	
	6.6	10.29	6[h]	0–0.10	20	*i*	
	9.1	10.45	7[h]	0–0.12	30	*i*	
	9.9	10.48	12[h]	0–0.10	32	*i*	
Ethylamine[d,e]	5.1×10^{-5}	6.66	3	0.50	0.53		
	1.5×10^{-4}	7.13	3	0.50	0.56		
	4.5×10^{-4}	7.60	3	0.50	0.58		
Piperazine	27	5.58	4	0.08–0.40	1.22		0.050
	48	5.99	4	0.08–0.40	1.15		0.025
	65	6.28	5	0.08–0.40	1.13		0.008
Glycine	10	8.87	14	0.05–0.3	*Ca.* 0.9	46	
	20	9.12	14	0.05–0.3	*Ca.* 1.5	113	
	40	9.58	13	0.0125–0.075	*Ca.* 2.7	450	
Triethylenediamine	16	8.29	5	0.08–0.40	0.60		0.030
	30	8.65	5	0.08–0.40	1.22		0.070
	50	8.98	5	0.08–0.40	2.03		0.185
In D_2O	30	9.31[j]	6	0.04–0.40	0.66		0.072
	50	9.72[j]	5	0.08–0.40	0.98		0.21
	70	10.09[j]	6	0.04–0.40	1.40		0.40
Triethylenediamine-H^+	99.90[k]	6.00	5	0.08–0.40	0.040[l]		
	99.97[k]	6.53	5	0.08–0.40	0.025[l]		
Morpholine	20	8.19	5	0.08–0.40	1.11	3.6	
	30	8.43	5	0.08–0.40	1.14	8.5	
	39	8.59	5	0.08–0.40	1.20	14.4	
	50	8.74	5	0.08–0.40	1.20	23.4	
	80	9.29	4	0.036–0.097	1.30	60	
In D_2O	53	9.78	5	0.08–0.40	0.50	4.0	
	80	9.86	5	0.04–0.20		15	
Methylimidazole	10	6.23	3[m]	0.04–0.16	12.6[n]		
	20	6.59	6[m]	0.02–0.10	10.8[n]		
	50	7.21	3[m]	0.05–0.20	6		
	70	7.58	3[m]	0.08–0.40	4.7		
	80	7.84	2[m]	0.10–0.25	3.2		
	95	8.45	5	0.10–0.50	1.09		
	96	8.53[h]	1[m]	0.40	1.04		
	98	8.90[h]	1[m]	0.40	0.87		
Imidazole	7	6.00	5	0.10–0.50	0.018		0.023
	12	6.25	5	0.10–0.50	0.032		0.017
	20	6.52	5	0.10–0.50	0.035		0.0121
	50	7.08	5	0.08–0.40	0.055		0.0083
	80	7.75	5	0.08–0.40	0.078		0.0144
Trifluoroethylamine	20	5.19	4	0.1–0.5	1.21	0.46	
	40	5.65	5	0.1–0.5	0.89	0.92	
	50	5.80	5	0.1–0.5	0.86	0.87	
	80	6.47	5	0.1–0.5	0.33	0.66	
	84	6.54	*d, o*	0.10	0.21		
	95	7.19[p]	5	0.1–0.5	0.17	0.55	
	95	7.11	*d, o*	0.10	0.14		
	98	7.69	*d, o*	0.10	0.10		
Methoxyamine	94	6.22	4	0.02	16[u]		
	99	6.70	4	0.02	5.8[u]		
	100	7.16	4	0.02	3.0[u]		
	100	7.62	4	0.02	2.0[u]		
	100	8.10	4	0.02	2.3[u]		
H_2O		1.1–1.8	3				2.26
		3.73[q]	1				1.30
		3.85[q]	1				1.15
		3.98[q]	1				0.99
		4.12[q]	1				0.82
		4.22[q]	1				0.69
		4.34[q]	1				0.58
		4.41[q]	1				0.51
Trifluoroethanol	5.75×10^{-5}	6.19	*d*	0.564	0.324		
	1.05×10^{-4}	6.46	*d*	0.4	0.50		
	4.57×10^{-4}	7.10	5	0.1–0.5	1.45[r]		
	1.66×10^{-3}	7.65	*d*	0.2	5.10		
Hydrogen peroxide[e,s]	1.8×10^{-6}–1.5×10^{-5}	5.85–6.77	5	6.5×10^{-3}	30[t]		
	4.3×10^{-5}	7.24	5	8.4–28×10^{-4}	430		
	1.26×10^{-4}	7.71	3	8.4–28×10^{-4}	1090		

Footnotes to Table I

[a] Observed second-order rate constant, based on total concentration of nucleophile [N + NH^+]. [b] Observed third-order rate constant, based on total concentration [N + NH^+]. [c] Extrapolated to zero nucleophile concentration. [d] Extrapolated to zero imidazole buffer concentration (D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 188 (1970). [e] Ionic strength maintained at 1.0 with potassium chloride. [f] Extrapolated to zero imidazole buffer concentration. [g] In 0.08 *M* Tris buffer. [h] In 0.1 *M* borate buffer. [i] See text. [j] pH meter reading + 0.41 [A. K. Covington, M. Paabo, R. A. Robinson, and R. G. Bates, *Anal. Chem.*, **40**, 700 (1968)]. [k] Calculated from pH and 3.47 for the second p*K*.[5] [l] Obtained in 0.01 *M* phosphate buffer and corrected for reaction with unprotonated triethylenediamine. [m] Run in 5-cm path length cuvettes. [n] The values of k_2 decrease with increasing amine concentration and were extrapolated to zero amine concentration. [o] Corrected for catalysis by the free amine. [p] In 0.1 *M* imidazole buffer. Rate constants corrected by up to 50% for catalysis by imidazole. [q] In 0.03 *M* acetate buffer. Buffer catalysis accounts for <3% of k_{obsd}. [r] Corrected by 5% for catalysis by 0.1 *M* imidazole buffer. [s] In 0.025–0.05 *M* imidazole buffers. No buffer catalysis was detected in 0.025–0.1 *M* buffers at pH 7.24. [t] Extrapolated to pH-independent reaction. [u] Extrapolated to zero buffer concentration from experiments in 0.015–0.3 *M* imidazole buffers. Ionic strength 0.3, maintained with tetramethylammonium chloride.

Table II. Summary of Rate Constants for Reactions with Acetylimidazole at 25°, Ionic Strength of 1.0 (Tetramethylammonium Chloride)[a]

Nucleophile	p*K*	$k_{3\ B}^{AcIm}$, M^{-1} min^{-1}	$k_{1\ BH+}^{AcIm}$, M^{-1} min^{-1}	$k_{1\ B}^{\prime\ AcImH+}$, M^{-1} min^{-1}	$k_{4\ B,B}^{AcIm}$, M^{-2} min^{-1}	$k_{2\ B,BH+}^{AcIm}$, M^{-2} min^{-1}
Piperidine	11.44	280	0.40	1.52×10^7	72,000	
			0.43[b]	1.82×10^7 [b]		
Ethylamine[b]	10.97[c]		0.54	7.6×10^6		
Piperazine	10.10[c]		0.98	1.71×10^6		
Glycine	9.77	2 ± 2	1.61	1.3×10^6	2,400	200
Triethylenediamine	9.00	4.1	0.017 ± 0.004	$(2.3 \pm 0.3) \times 10^3$	<5[d]	
In D_2O		1.99				
Morpholine	8.74	1.4	1.04	7.89×10^4	95	<1.5
In D_2O					20	
Methylimidazole	7.20	0.5 ± 0.2	13.5	2.96×10^4	<0.52	<10[e]
Imidazole	7.11	0.092	0.020	36		
Piperazine-H^+	6.01		1.31	303		
Trifluoroethylamine	5.81	0.06 ± 0.02	1.45	129	0.4 ± 0.2	2.9 ± 0.3
Methoxyamine[f]	4.73[c]	1.7		3200		
Hydroxide ion	15.75	1.6×10^4	1.1×10^{-4} [g]	7.00×10^7 [g]		
Trifluoroethoxide anion	12.37[h]	2.6×10^5	0.15	3.9×10^7		
		2×10^4 [i]				
Hydrogen peroxide anion	11.6[j]	1×10^7	30	1.65×10^9		
Water	−1.7	1.1×10^{-4} [g]		0.041		

[a] The rate constants are defined in eq 2. [b] Ionic strength maintained at 1.0 with potassium chloride. [c] 1.0 *M* potassium chloride (ref 5 and T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 3817 (1968)). [d] Assuming a 20% rate increase was not seen. [e] Obtained from the slope of $(k_{obsd} - k_0)/[MeIm]_{total}$ in an experiment at 95% free base and using a value for k_0 40% greater than the approximate value from the pH profile to exaggerate the curvature (the "correct" value for k_0 gave no measurable slope). [f] Ionic strength 0.3, maintained with tetramethylammonium chloride. [g] The reactions of water with AcIm (= $k_w/55.5$) and of hydroxide ion with $AcImH^+$ are kinetically indistinguishable; both rate constants are given. [h] Thermodynamic p*K*, P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960). [i] Calculated (see text). [j] A. J. Everett and G. J. Minkoff, *Trans. Faraday Soc.*, **49**, 410 (1953).

The procedure used for determining the rate constants will be described for the reaction with morpholine, as an example. At most pH values the observed rate constants for this reaction increase more rapidly than the morpholine concentration because of catalysis by a second mole of amine. The observed second-order rate constants, based on total morpholine concentration, are plotted as a function of morpholine buffer concentration at a series of different buffer compositions in Figure 1. The ordinate intercepts of these lines, k_{obsd}, represent the uncatalyzed (or water-catalyzed) reactions with morpholine and the slopes, k_{cat}, the catalyzed reactions. In Figure 2, k_{obsd} and k_{cat}/(fraction free base) are plotted against the fraction of free base in the buffer to separate the terms. It is apparent that the uncatalyzed reaction consists of almost equal contributions of the k_1 and k_3 terms of eq 2a, obtained from the intercepts at 0 and 100% free morpholine, respectively, whereas for the catalyzed reaction only the k_4 term, obtained from the intercept at 100% free morpholine, is significant. These rate constants and others derived in a similar manner are summarized in Table II. Upper limits are given for a number of rate constants when no reaction was detected; these were usually estimated from the assumption that a 20% increase in rate, caused by the term in question, was not detected.

The catalytic constants for the reaction with piperidine free base were difficult to determine in a single experiment because of the rapid rate of the reaction. The rate constants for free piperidine were obtained from the results of a large number of experiments at different pH values which were corrected for hydrolysis (k_0) and for the k_1 reaction (Figure 3). The value of k_1 was determined at low pH values at which the free base reactions are insignificant. Least-squares treatment of the experimental second-order rate constants from these data gave values for k_3 and k_4 of 280 M^{-1} min^{-1} and 72,000, respectively. These rate constants were used to calculate the solid line in Figure 3, which provides a satisfactory fit to the experimental results.

The reaction of acetylimidazole with oxygen nucleophiles follows the rate law of eq 3.[2,4,12] As in the

$$v = k_1[ROH][AcIm] + k_2[ROH][AcIm][B] + k_3[RO^-][AcIm] \quad (3)$$

amine reactions, the k_1 terms may be expressed as

(12) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **86**, 4651 (1964); J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4655 (1964).

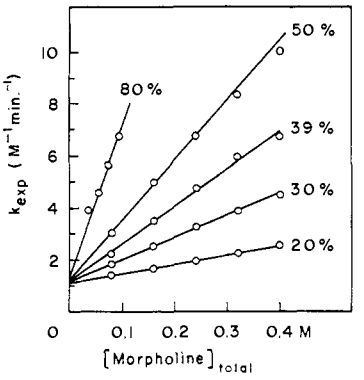


Figure 1. Experimental second-order rate constants for the reaction of acetylimidazole with morpholine as a function of morpholine buffer concentration at 25° and ionic strength 1.0, maintained with tetramethylammonium chloride. The fraction of free base in each buffer is indicated.

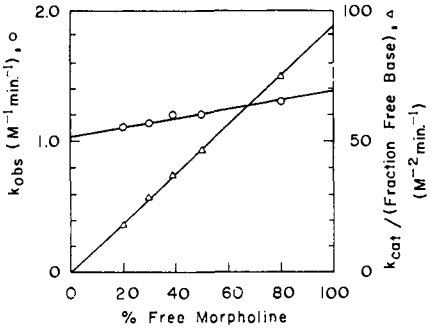


Figure 2. Dependence of second-order rate constants, k_{obsd} (○), and catalytic rate constants, k_{cat} (△), for the reaction of acetylimidazole with morpholine on the fraction of morpholine as the free base at 25°, ionic strength 1.0.

k_1'[AcImH$^+$][RO$^-$] in view of the fact that these reactions, with the partial exception of water, actually involve the kinetically equivalent reaction of alkoxide ion with acetylimidazolium ion.[9] Both k_1 and k_3 terms are important for the reactions of hydrogen peroxide and trifluoroethanol, extrapolated to zero concentration of imidazole buffer (Tables I and II); catalysis by imidazole was detected only for the trifluoroethanol reaction.

The rate constants for the nucleophilic reactions of phenolate anions with free acetylimidazole were calculated from the rate constants for the hydroxide ion catalyzed reactions of imidazole with substituted phenyl acetates and the equilibrium constants for the reactions (eq 4).[12,13] It is difficult to measure k_3 directly be-

$$RO^- + AcIm \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} ROAc + Im + OH^- \qquad (4)$$

cause of interference by other reactions. The rate constant k_{-3} for the reaction with phenyl acetate and a limiting value for the reaction with *p*-nitrophenyl acetate have been determined previously.[13] The values for *p*-chlorophenyl acetate and *m*-nitrophenyl acetate have now been determined by the same method and are given, along with the values of k_3, for the reactions of phenolate anions, in Table III. A similar calculation for trifluoroethoxide attack on acetylimidazole gives a value of $k_3 = 2.0 \times 10^4\ M^{-1}$ min^{-1}, significantly below the observed value of $2.6 \times 10^5\ M^{-1}$ min^{-1}; however,

(13) J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 86, 833, 837 (1964).

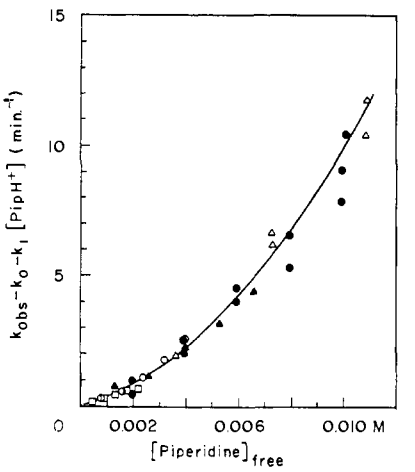
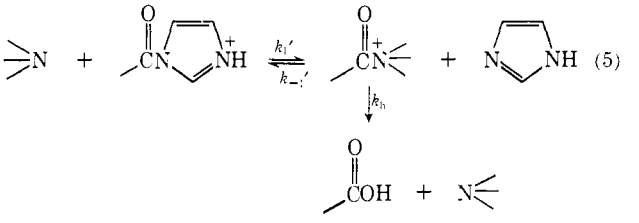


Figure 3. Dependence of the rate constant for the reaction of acetylimidazole with free piperidine on piperidine concentration in 0.1 *M* borate buffer at 25°, ionic strength 1.0. Fraction free piperidine: 9.9%, ●; 9.1%, △; 6.6% ▲; 4.0%, ○; 2.2%, □. The solid line was calculated from $k_3 = 280\ M^{-1}$ min^{-1} and $k_4 = 72{,}000\ M^{-2}$ min^{-1}.

the poor agreement is not surprising in view of the uncertainty in the equilibrium constant for trifluoroethyl acetate hydrolysis caused by the necessity for multiple extrapolations in its determination,[12] and the several other equilibrium, ionization, and rate constants involved in the comparison. The equilibria for the reactions of phenyl acetates with imidazole were measured directly,[12] and there should be little error in the relative values of the rate constants, the principal point of interest here.

Mechanisms of Reactions of Tertiary Amines with Acetylimidazole. A distinction between nucleophilic and general base catalysis of the hydrolysis of acetylimidazole by tertiary amines was made by examining the inhibition of the reaction by added imidazole; this also permitted calculation of the rate constant for the reaction of imidazole with acetyl-*N*-methylimidazolium ion. The nucleophilic reaction proceeds according to eq 5 and the hydrolysis reaction will be inhibited when



sufficient imidazole is added to react with the intermediate to regenerate acetylimidazole (k_{-1}'[Im]) faster than it undergoes hydrolysis (k_h). The general base catalyzed hydrolysis will not be inhibited by low concentrations of imidazole. The fact that catalysis of the hydrolysis of acetylimidazole by *N*-methylimidazole at pH 6.8 is completely inhibited by low concentrations of imidazole (Figure 4) shows that this reaction represents nucleophilic catalysis and permits calculation of the rate constant for nucleophilic attack of this tertiary amine on acetylimidazolium ion according to the $k_1 - k_1'$ term of eq 2. Because of the extreme sensitivity of the reaction to imidazole, it was necessary to follow these reactions with $3 \times 10^{-5}\ M$ acetylimidazole in

Table III. The Rate Constants for Hydroxide Ion Catalyzed Reactions of Imidazole with Phenyl Acetates and for the Reactions of Phenoxide Ions with Free Acetylimidazole at 25° and Ionic Strength 1.0[a]

Ester	[Imidazole], M	[OH^-], M	No. of runs	k_{-3}, M^{-2} min^{-1}	k_3,[b] M^{-1} min^{-1}
Phenyl acetate[c]				210	1.0
p-Chlorophenyl acetate	0.4	0–0.085	12	345	0.22
m-Nitrophenyl acetate	0.1	0–0.025	12	840	9.4×10^{-3}
p-Nitrophenyl acetate[c]				<4700	$<8.3 \times 10^{-4}$

[a] Maintained with potassium chloride. [b] Calculated from k_{-3} and the equilibrium constant for the reaction.[12] [c] Reference 13.

5-cm cuvettes, in order that imidazole released during the reaction should not cause inhibition. No indication was observed of a term second order with respect to methylimidazole buffer, which would indicate catalysis of the reaction by methylimidazole or methylimidazolium ion. However, the second-order rate constants were found to decrease at high methylimidazole concentrations at low pH, suggesting the existence of an inhibition caused by an activity coefficient effect or complexation with the substrate, and it is possible that a small amount of catalysis might be masked by this effect.

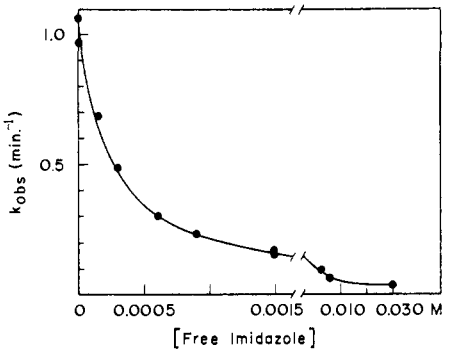


Figure 4. Inhibition by imidazole of the reaction of acetylimidazole with 0.2 M *N*-methylimidazole, 30% free base, by reaction with the acetyl-*N*-methylimidazolium ion intermediate to regenerate starting materials.

The steady-state expression for the nucleophilic reaction of a tertiary amine with acetylimidazolium ion is given in eq 6. If k_{min} is the residual observed rate

$$k_{nuc} = \frac{k_1' k_h [R_3N]}{k_{-1}'[Im] + k_h} \quad (6)$$

when increasing imidazole concentration causes no further rate decrease, then $k_{nuc} = k_{obsd} - k_{min}$. A plot of $1/(k_{obsd} - k_{min})$ against the concentration of free imidazole gives a straight line from which the ratio k_h/k_{-1}' and the concentration of imidazole which gives 50% inhibition (2.2×10^{-4} M) may be calculated. The value of k_h for the hydrolysis of acetyl-*N*-methylimidazolium ion in 0.2 M *N*-methylimidazole buffer, 30% base, was found to be 5.2 min^{-1} from which the value of k_{-1} for the reaction of imidazole with acetyl-*N*-methylimidazolium ion is 23,000 M^{-1} min^{-1}. This value is similar to the value of 29,600 M^{-1} min^{-1} for the reaction of *N*-methylimidazole with acetylimidazolium ion, calculated from the observed rate constants (Table I) and a pK value of 3.86 for the acid dissociation of this ion.

The reaction of acetylimidazole with the bicyclic tertiary amine triethylenediamine at low pH involves terms proportional to the concentrations of triethylenediamine mono- and dications, and is partially inhibited by imidazole, indicating that nucleophilic catalysis contributes to at least one of these reactions (Table IV). The concentration of imidazole required to give

Table IV. Second-Order Rate Constants for Reactions of Acetylimidazole with Triethylenediamine (TED) at 25°, Ionic Strength 1.0

	k_{exp}, M^{-1} min^{-1} pH 6.00	pH 6.53
(1) Observed[a] with no imidazole	0.044	0.039
(2) Free TED reaction[b]	0.004	0.014
(3) (1) − (2): for $TEDH^+$ and $TEDH_2^{2+}$	0.040	0.025
(4) For $TEDH_2^{+}$ [c]	0.023	0.008
(5) (3) − (4): for $TEDH^+$	0.017	0.017
(6) Observed with addition of 0.02 M imidazole	0.024	0.023
(7) (1) − (6): inhibition = nucleophilic reaction	0.020	0.016

[a] Slope of k_{obsd} *vs.* total triethylenediamine concentration (see Table I). [b] Calculated from the second-order rate constants for free triethylenediamine, obtained in experiments at high pH. [c] Obtained from the intercept at 100% triethylenediamine-H_2^{2+} concentration of (3) plotted against the percentage of fully protonated amine, calculated from the pH and pK 3.47.[5]

50% of maximal inhibition is approximately 2.3×10^{-4} M (free base) in the presence of 0.4 M triethylenediamine hydrochloride and 0.02 M phosphate buffer, pH 6.47. The inhibition may be accounted for if it is assumed that the reaction proportional to the concentration of triethylenediamine monocation is entirely nucleophilic and that proportional to the concentration of the dication represents general base catalysis of hydrolysis (Table IV). These reactions are assigned to the kinetically equivalent reactions of free triethylenediamine and triethylenediamine monocation with acetylimidazolium ion; the agreement of the rate constants with those expected for nucleophilic reaction and general base catalysis, respectively, by amines with the basicity of these compounds supports these assignments (see below).

In contrast to their nucleophilic reactions with acetylimidazolium cation, the reactions of tertiary amines with free acetylimidazole proceed largely or entirely by general base catalysis of hydrolysis. At pH 7.8, at which >94% of the reaction of acetylimidazole with 0.5 M triethylenediamine involves the free base species of both reactants, there is no inhibition of the reaction by 0.32 M imidazole; there is also no inhibition of the reaction of triethylenediamine, 5% free base, by 0.1 M imidazole.

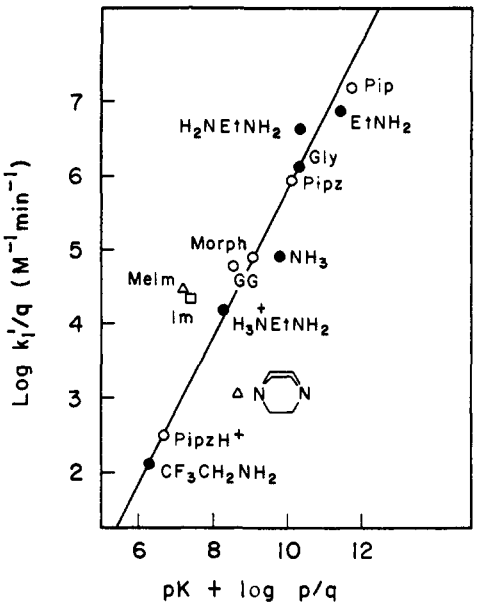


Figure 5. Effect of basicity on the rate constants for reactions of amines with acetylimidazolium ion at 25° (Table II and ref 4 and 22). The imidazole rate constant is for reaction with acetyl-*N*-methylimidazolium ion.

The experiments with methylimidazole and triethylenediamine at low pH indicate that the acylated tertiary amines should react readily with imidazole and this was confirmed qualitatively by the addition of the solid chloride salt of *N*-acetyltriethylenediamine cation to 0.4 *M* imidazole buffer, 50% free base, to give acetylimidazole, which gave a strong color of the hydroxamic acid after reaction with hydroxylamine and addition of ferric chloride. Approximately the same amount of the salt gave a similar color if added directly to hydroxylamine, but no color if added to water immediately before the addition of hydroxylamine and ferric chloride. The solvent isotope effect for the hydrolysis of acetylimidazole catalyzed by free triethylenediamine, $k_{H_2O}/k_{D_2O} = 2.1$ (Table II), supports the assignment of general base catalysis for this reaction.

At high pH a relatively slow reaction of methylimidazole with free acetylimidazole becomes significant. At 98 and 96% free methylimidazole the total reaction with methylimidazole is inhibitable by imidazole to the extent of 44 and 69%, respectively; at 98% free base half-maximal inhibition is observed with 0.002 *M* imidazole. The reaction with acetylimidazolium ion accounts for 32 and 52% of the observed reaction at the two buffer concentrations, respectively, so that most of the remaining reaction of methylimidazole with free acetylimidazole is noninhibitable and represents general base catalysis. From these results an upper limit for the rate constant $k_3 \leqslant 0.2\ M^{-1}\ min^{-1}$ was calculated for the nucleophilic reaction of methylimidazole with free acetylimidazole.

The dependence on pH of the catalysis of acetylimidazole hydrolysis by imidazole itself indicates that there is a small component of hydrolysis proportional to the concentration of imidazole cation (Table I) which was not detected in earlier experiments carried out in the presence of sodium chloride.[4] This reaction is interpreted as the kinetically equivalent catalysis by imidazole of the hydrolysis of the acetylimidazolium cation and the rate constant of 36 $M^{-1}\ min^{-1}$ for this reaction is comparable to the value of 18 $M^{-1}\ min^{-1}$ for methylimidazole catalysis of the hydrolysis of acetyl-*N*-methylimidazolium ion.[9] This type of catalysis was first reported for the hydrolysis of simple acylimidazoles by Fife.[14]

Discussion

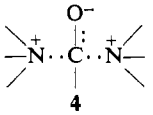
Reactions of Acetylimidazolium Ion. The predominant mechanism for the reaction of most nucleophilic reagents with acetylimidazole involves a pH-independent pathway near neutral pH. This is a consequence of the fact that the nucleophile exists primarily as the unreactive, protonated species in this pH region and the reactive species of acetylimidazole is the acetylimidazolium ion, so that a change in pH causes an equal and opposite change in the concentrations of both reactive species.[4,9] Acetylimidazole, therefore, behaves like most amides in that it reacts preferentially through an acid-catalyzed reaction pathway, with protonation of the leaving amine; imidazole (pK 7.0) is a far better leaving group than imidazole anion (pK 14.2),[7] and can be expelled by nucleophilic reagents of moderate basicity. Acetylimidazole differs from ordinary amides in that its basicity (the pK_a of acetylimidazolium ion is 3.8) permits easy protonation of the leaving amine, so that there is a significant concentration of the reactive species present near neutrality; ordinary amides are less basic (p$K < 0$) and are protonated predominantly on the carbonyl oxygen atom, so that the concentration of the N-protonated species is very small.

A Brønsted plot of reaction rate against basicity for the acetylimidazolium ion and amine nucleophiles, based upon statistically corrected[15] rate and dissociation constants, is shown in Figure 5. The point for the analogous reaction of imidazole with acetyl-*N*-methylimidazolium ion is included and agrees well with that for the nucleophilic reaction of *N*-methylimidazole with acetylimidazolium ion. The rate constants for primary and secondary amines fall close to a line of slope $\beta = 1.0$ except for the most basic amines, which show a small negative deviation that becomes much more pronounced in the acetylpyridinium series.[6] An interesting consequence of this slope of 1.0 is that the observed rate constants of amines of widely varying basicity are almost identical at pH values below their pK because, in contrast to most nucleophilic reactions, the lower concentration of the free base form of a more basic amine is fully compensated by its increased reactivity, compared to less basic amines. Although triethylenediamine shows a negative deviation, presumably because of steric hindrance, imidazole and *N*-methylimidazole are even more reactive than primary and secondary amines of comparable basicity; similar relative reactivities are observed in the reactions of these amines with phenyl acetates.[5] The fact that the reactivity of these tertiary amines is not greatly depressed compared to that of primary and secondary amines establishes the important conclusion that, as in the reactions with phenyl esters,[5] *proton removal from the attacking nucleophile is not necessary for reactions with acetylimid-*

(14) T. H. Fife, *J. Amer. Chem. Soc.*, 87, 4597 (1965); J. A. Fee and T. H. Fife, *J. Org. Chem.*, 31, 2343 (1966).
(15) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, 291, 297 (1966).

azolium ion. This does not mean that such partial proton removal does not occur, in the "water" reaction for example, but only that any such removal does not lead to a large rate acceleration; in fact, there is evidence that the reactions of weakly basic amines are subject to general base catalysis by this mechanism.[16] The absence of significant proton transfer is also consistent with the β value of 1.0 because such proton removal would tend to reduce the β value by decreasing the amount of charge development on the attacking nitrogen atom.

The Brønsted plot of Figure 5 is almost identical with that for *p*-nitrophenyl acetate and, in fact, logarithmic plots of the rate constants for the reactions of primary and secondary amines with acetylimidazolium ion against those for the same reactions with *p*-nitrophenyl acetate[5] are linear with slopes of 1.1 (not shown). It is noteworthy that the pK's of the leaving groups of the two compounds are the same, although the absolute rates of the acetylimidazolium ion reactions are three to four orders of magnitude faster. The β value of 1.0 means that in the transition state there is a large amount of bond formation and charge development on the attacking amine, comparable to that for complete protonation of the amine Since complete transfer of an acetyl group to a series of amines exhibits a β value of 1.7,[6] this means that the transition state is at least halfway along the reaction coordinate toward products with respect to charge development and bond formation on the attacking amine. In neither reaction series is there evidence of a break that would suggest a change in the nature of the transition state or rate-determining step. In conjunction with the β values for leaving group variation in acetylpyridinium ion reactions, these results indicate that the acetylimidazolium ion reactions fall into the class II category of almost symmetrical acyl transfer reactions, which may be described by transition state **4**.[6]



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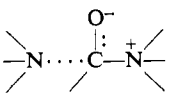
An aminolysis reaction of this kind with identical entering and leaving groups is symmetrical. If there is a tetrahedral addition intermediate, it would be expected that as the attacking amine is made more basic than the leaving group it would be expelled from the intermediate less easily and the attack step would become rate determining; conversely, breakdown of the intermediate would become rate determining for weakly basic attacking amines, so that a change in rate-determining step would be expected in the region of equal basicity of attacking and leaving groups. The linearity of the Brønsted plot of Figure 5 and of the correlation with the reactions of *p*-nitrophenyl acetate, with no indication of a break for amines up to three orders of magnitude more basic than the leaving imidazole, means that the transition states for these reactions are of similar structure over a large range of amine basicity and suggests that they should be formulated in terms of either a concerted mechanism, with no discrete addition intermediate, or as stepwise reactions with almost identical transition states for formation and breakdown of the intermediate.[6,17] The reactions do not proceed through a class I, asymmetric, early transition state for the formation of a tetrahedral addition intermediate (**5**). A formulation in terms of a class III, asymmetric transition state for rate-determining breakdown of a tetrahedral intermediate (the mirror image of **5**) is also not in agreement with the observed β values for the attacking and leaving groups in acetylimidazolium and acetylpyridinium[6] ion reactions; such a formulation would also require that imidazole be a poorer leaving group than amines of 10^3 greater basicity.



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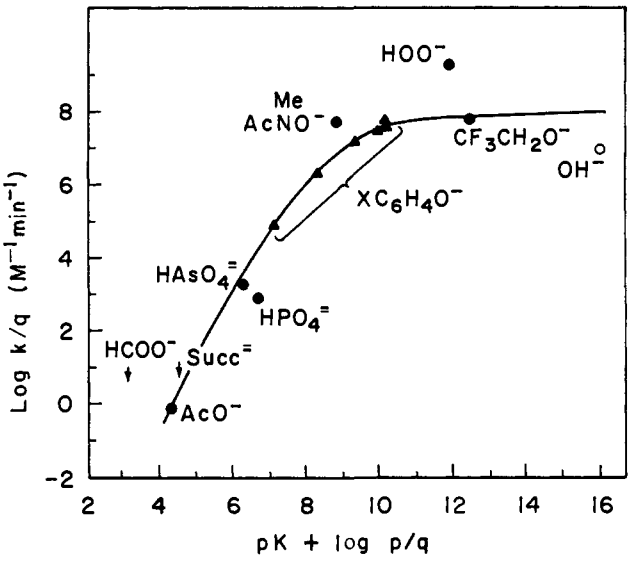


Figure 6. Effect of basicity on the rate constants for reactions of oxyanions with acetylimidazolium ion at 25° (Table II and ref 4, 12, and 18).

The Brønsted plot for the reactions of oxyanion nucleophiles with acetylimidazolium ion is shown in Figure 6. The point for acetate ion is for the nucleophilic reaction,[18] but those for succinate and formate are observed rate constants that include general base catalysis of hydrolysis and are, therefore, given as limits. Hydroperoxide and *N*-methylacetohydroxamate anions ("α-effect" compounds) exhibit an enhanced reactivity and hydroxide ion a reduced reactivity, as has been observed for other acyl group reactions.[5,6,12] The sharp curvature of this plot is similar, but more marked, compared to the corresponding plots for the reactions of oxyanions with substituted phenyl esters and, in both cases, is in contrast to the almost linear plots observed for amine nucleophiles.[5] The curvature in the acetylimidazole reactions is the converse of the curvature in the plot for the reactions of imidazole with acetate esters, which exhibits a change from a moderate to a very large dependence of reaction rate on the basicity of the leaving group as the leaving group becomes worse.[13] The two curves are related by the equilibrium

(16) D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *J. Amer. Chem. Soc.*, 92, 188 (1970).

(17) Fife and coworkers[14] have suggested that the small or inverse steric effects in the hydrolysis of acylimidazoles result from relief of strain in a transition state that resembles products, but this interpretation does not necessarily imply a concerted mechanism.

(18) W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Amer. Chem. Soc.*, 88, 4464 (1966).

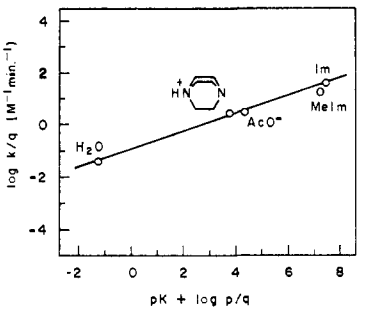


Figure 7. Brønsted plot for general base catalysis of the hydrolysis of acetylimidazolium ion. The point for acetate ion is corrected for the nucleophilic component of the observed reaction.[18] The point for methylimidazole refers to catalysis of the hydrolysis of acetyl-*N*-methylimidazolium ion.[9]

constants for the acyl transfer reactions, which show an almost linear logarithmic dependence on the pK of the alcohol.[12] The leveling off of the dependence on basicity for the reactions of acetylimidazolium ion with strongly basic anions is strikingly illustrated by the almost equal reaction rates of phenolate and trifluoroethoxide anions, in spite of the 100-fold greater basicity and smaller steric requirements of the latter compound. It is possible that the rate constants for reactions of the phenolate ions are increased to a small extent by some specific interaction with acetylimidazole, but (i) there is no evidence for any such complexation, (ii) any interaction that does occur must overcome the increased steric demands of the phenyl group which usually amount to an order of magnitude,[13] and (iii) the rate constants for phenolates are still well below that for *N*-methylacetohydroxamate ion, so that it is unlikely that any such effect causes a major perturbation. The β values from portions of the curve should not be taken as exact values because of the fact that structurally different oxygen nucleophiles are being compared, but the observed limiting β values of 1.7 for weakly basic nucleophiles and 0 for strongly basic nucleophiles emphasize the marked change in the nature of the transition state with changing structure of the nucleophile and span the entire range of reaction types from those with little or no dependence to those with the maximal dependence on the structure of the attacking and leaving groups, since the β value for the equilibrium constant of the overall acyl transfer reaction is also 1.7.[6,12] These reactions illustrate directly, for the first time in a single reaction series, the three limiting classes of acyl transfer reactions, I, II, and III, with transition states resembling starting materials, a symmetrical intermediate or transition state, and products, respectively.[6] The reason for the difference in the behavior of oxygen and nitrogen nucleophiles in this and related[5,6] reactions has not been established, although differing effects of solvation on basicity and reactivity are undoubtedly important contributing factors. In particular, hydrogen bonding to the solvent of relatively strong oxygen acids, such as carboxylic acids, will stabilize the acid, but not the transition state for nucleophilic reaction of the anion, with a consequent steepening of the Brønsted plot of reactivity against basicity.

The Brønsted plot for general base catalyzed hydrolysis of acetylimidazolium ion has a slope, β, of 0.34 (Figure 7). The rate constant for the imidazole-catalyzed hydrolysis of acetylimidazolium ion is very similar to that for the methylimidazole-catalyzed hydrolysis of acetyl-*N*-methylimidazolium ion.[9] The rate constant for the reaction of triethylenediamine monocation with acetylimidazolium ion is consistent with the above-mentioned assignment of this reaction to general base catalyzed hydrolysis, which is not inhibitable by imidazole. The rate constants for the reactions with formate and succinate ions[4] also fall near this line and may represent general base catalysis.

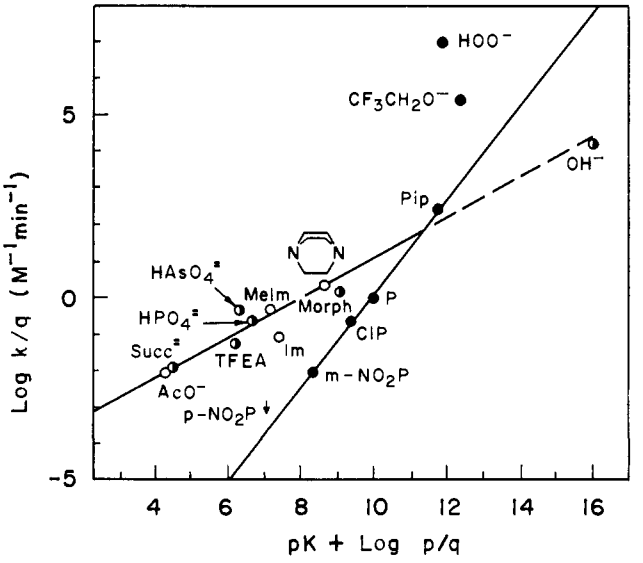


Figure 8. Rate constants for reactions of bases with free acetylimidazole at 25° as a function of their basicity (Table II and ref 4 and 18): nucleophilic reactions, ●; general base catalysis of hydrolysis, ○; mechanism not determined, ◑; phenols, P.

Reactions of Acetylimidazole. The reactions of free acetylimidazole with nucleophilic reagents reflect the fact that expulsion of an amine anion from an amide in aqueous solution is difficult or impossible without assistance by general acid–base catalysis. That these reactions occur at all with acetylimidazole is largely a consequence of the much greater stability of the imidazole anion (pK_a = 14.2)[7] compared to anions of other amines. The poor leaving ability of the imidazole anion, compared to free imidazole, is responsible for the following results: (i) the unassisted reactions of nucleophilic reagents with free acetylimidazole are slow and often masked by other reactions, (ii) the nucleophilic reactions have transition states resembling products, with a very large sensitivity to the basicity of the nucleophile, (iii) the observed unassisted reactions of acetylimidazole with nucleophiles of moderate or weak basicity represent general base catalysis of hydrolysis rather than nucleophilic attack, and (iv) the nucleophilic reactions are extremely sensitive to intermolecular and intramolecular general acid–base catalysis. In many respects these reactions resemble the reactions of simple aliphatic esters, which have leaving groups of similar pK.

The rate constants for the reactions of nucleophilic reagents with free acetylimidazole are shown as a function of their basicity in Figure 8. The solid circles represent nucleophilic reactions, the open circles represent general base catalysis of hydrolysis, and the half-filled circles represent rate constants similar to those for the general base catalyzed reactions, but which have not

been directly demonstrated to represent general base catalysis.[19] That the acetate[18] and tertiary amine reactions do indeed represent general base catalysis of hydrolysis rather than nucleophilic attack was demonstrated by the observations (i) that the observed reaction is not inhibited by imidazole, which reacts with the immediate product of the nucleophilic reactions to regenerate starting materials, and (ii) the reaction with triethylenediamine exhibits a solvent deuterium isotope effect $k_{H_2O}/k_{D_2O} = 2.1$, as expected for general base catalysis, but not for a nucleophilic reaction,[20] and (iii) the Brønsted β value for these reactions is 0.55. The nucleophilic reactions of amines with acetylimidazolium ion exhibit a β value of 1.0 and it would be expected that with the poorer leaving group of free acetylimidazole the β value would be still larger. The observed value of β is, therefore, inconsistent with a nucleophilic reaction, but shows the expected increase compared to the value of 0.34 for general base catalysis of the hydrolysis of acetylimidazolium ion. The reaction with imidazole itself must represent catalysis of hydrolysis, since the nucleophilic reaction only regenerates starting material.[4]

The line for general base catalyzed hydrolysis in Figure 8 intercepts the steeper line for nucleophilic reactions near the rate constant for the piperidine reaction. The piperidine and trifluoroethoxide reactions were shown by analysis of reaction products to represent mainly nucleophilic reactions. The rate constants for phenolate ions represent nucleophilic reactions because they were calculated from the directly measured equilibrium constants and rate constants for the reverse reactions. The slope of the line, defined by the rate constants for the oxyanion reactions, is 1.3; the point for trifluoroethoxide ion exhibits a positive deviation from this line that is accounted for, at least in part, by the relatively small steric requirements of this nucleophile. The difference between the acetylimidazole and acetylimidazolium reactions and the greatly enhanced importance of nucleophile basicity in the former group is illustrated dramatically by a comparison of the rate constants for reactions of phenolate and trifluoroethoxide ions—these nucleophiles have an equal reactivity toward acetylimidazolium ion, but the more basic trifluoroethoxide ion has a reactivity more than 10^5 greater than that of phenolate ion toward free acetylimidazole. It is of interest that the enhanced reactivity of hydroperoxide ion, which may be an "α-effect" compound, compared to trifluoroethoxide ion, toward free acetylimidazole is only slightly larger than toward acetylimidazolium ion. This suggests that its abnormal reactivity does not result from some sort of increase in effective basicity and is a further indication that different factors, such as basicity and polarizability, may exert independent influences on reactivity in acyl transfer reactions,[6] so that changes in position along the reaction coordinate in these reactions ("Hammond postulate" effects) should be evaluated separately with respect to different contributing factors to the reaction.

(19) Analysis of reaction products has shown that the phosphate dianion reaction (in contrast to the reaction with acetylimidazolium ion[2]) includes a large contribution of general base catalysis of hydrolysis (W. P. Jencks and K. Salvesen, unpublished experiments).

(20) B. M. Anderson, E. Cordes, and W. P. Jencks, *J. Biol. Chem.*, 236, 455 (1961).

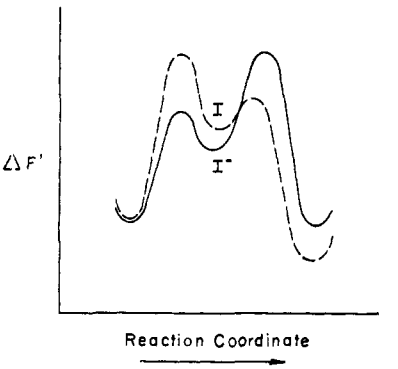
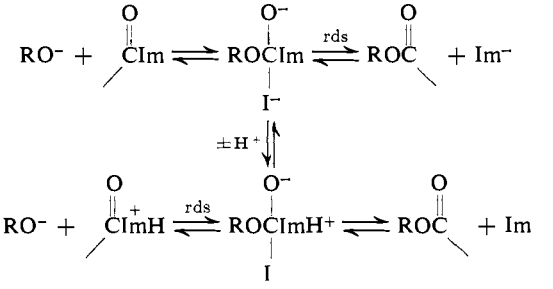


Figure 9. Transition-state diagrams for the reaction of trifluoroethoxide ion with acetylimidazole (solid line) and with acetylimidazolium ion (dashed line), assuming the intermediate formation of tetrahedral addition compounds I⁻ and I (eq 7).

The importance of proton transfer in reactions of free acetylimidazole is immediately apparent from the predominance of terms second order with respect to amine at all but the lowest amine concentrations (Figures 1 and 3). As in the aminolysis of simple alkyl esters,[20,21] the general base catalyzed reaction of compounds with relatively poor leaving groups is so important as to make the first-order reaction difficult to measure. It is because general base catalyzed proton transfer is so important that ethylenediamine shows a rate enhancement of over 10^3 compared to other amines in its reaction with free acetylimidazole, whereas it shows little or no rate enhancement in its reaction with acetylimidazolium ion (Figure 5), for which proton transfer is of much less importance.[22] The mechanism of this general base catalysis will be discussed in the following paper.

If there is a tetrahedral addition intermediate formed during the reaction, the reactions of trifluoroethoxide ion with acetylimidazole and acetylimidazolium ion may be written according to eq 7. Since the reactions



(7)

of oxyanions with acetylimidazole exhibit a β value with respect to nucleophile basicity of 1.3, it is certain that the transition state for the reaction of trifluoroethoxide ion with free acetylimidazole resembles products and, if there is an intermediate, must represent breakdown of the intermediate to products with expulsion of imidazole anion. Since the rate constant for the reaction of trifluoroethoxide ion with acetylimidazolium ion falls on a portion of the Brønsted plot for this reaction of slope *ca.* zero, it is equally certain that the transition state for this reaction must resemble starting materials and, if there is an intermediate, must represent rate-determining attack to form the intermediate. This

(21) J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, 82, 665 (1960); M. Blackburn and W. P. Jencks, *ibid.*, 90, 2638 (1968).

(22) W. P. Jencks and K. Salvesen, *Chem. Commun.*, 548 (1970).

conclusion is in accord with the very large sensitivity to the nature of the leaving group of the reactions of imidazole with esters that have poor leaving groups, including trifluoroethyl acetate; this reaction may be interpreted in terms of the same rate-determining step (rds) in the reverse reaction, *i.e.*, the breakdown of a tetrahedral intermediate to expel trifluoroethoxide ion.[13] Now, these two assignments are impossible if, as is usually assumed, the tetrahedral intermediate is at equilibrium with respect to proton transfer so that the interconversion of I and I^- is fast relative to the other steps of the reaction. If such an equilibrium existed, the intermediate could be formed by the upper path and break down by the lower path of eq 7, thus avoiding both of the assigned rate-determining steps. Such a crossover should be possible because the reactions with anionic and with neutral transition states take place concurrently at the same pH value. The problem is shown schematically in the transition state diagrams of Figure 9, in which the solid line represents the anionic reaction and the dashed line the neutral reaction; the free energies have been normalized to a pH value at which both reaction paths are of equal importance, *i.e.*, a pH at which both transition states have the same free energy relative to the starting materials. Since this mechanism does not account for the observed properties of the reactions, we are forced to conclude either (i) one or both reactions proceed by a concerted pathway without the formation of a tetrahedral addition intermediate or (ii) there is an addition intermediate, but its lifetime is too short for it to reach equilibrium with respect to proton transfer,[23] so that the intermediates I and I^- are not at equilibrium with each other and the upper and lower pathways may proceed concurrently without crossover.

(23) A. Moffat and H. Hunt, *J. Amer. Chem. Soc.*, 81, 2082 (1959); R. E. Barnett and W. P. Jencks, *ibid.*, 91, 2358 (1969).

Reactions of Acetylimidazole and Acetylimidazolium Ion with Nucleophilic Reagents. Mechanisms of Catalysis[1a]

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Abstract: The agreement within a factor of 2 over a range of 10^9 of the rate constants for reactions of nucleophiles with 1-acetyl-3-methylimidazolium ion ($AcImMe^+$) and acetylimidazolium ion ($AcImH^+$) confirm the conclusion[2] that $AcImMe^+$ is a satisfactory model for reactions of $AcImH^+$. The absence of detectable catalysis by methylimidazole of the reactions of ammonia and ethylamine with $AcImMe^+$ shows that $AcImMe^+$ is not a model for the imidazolium ion catalyzed reaction of these compounds with acetylimidazole. It is suggested that this catalysis involves proton donation from the catalyst to the leaving imidazole. The observed catalysis by methylimidazole of the reactions of methoxyamine and trifluoroethylamine with $AcImMe^+$ shows that $AcImMe^+$ is a model for the kinetically equivalent imidazole-catalyzed reactions of these weakly basic amines with $AcImH^+$. It is suggested that the mechanism of catalysis for weakly basic amines involves proton abstraction from the attacking amine, in accord with the symmetry of the overall reaction. The mechanisms of other general acid–base catalyzed reactions of acetylimidazole and the application to these reactions of structure–reactivity relationships for such catalysis are discussed.

Catalysis by imidazole of the hydrolysis and transfer of the acetyl group of acetylimidazole[3] is analogous to the first reported example of general base catalysis of acyl group transfer, the acetate-catalyzed hydrolysis of acetic anhydride,[4] in that nucleophilic displacement of the acyl group by the catalyst can only regenerate starting material. Previous studies of this reaction have demonstrated imidazole catalysis of acyl transfer to a variety of hydroxyl compounds, amines, and thiols and have identified several terms in the rate laws for these reactions.[3,5–7] It was concluded initially that the mechanism of imidazole catalysis involves proton abstraction from the attacking nucleophile, largely because no such catalysis was observed for reactions of nucleophiles with no proton on the attacking atom.[3] While this conclusion is valid for some reactions, its experimental basis has been eroded by the finding that the reactions of acetylimidazole with some nucleophiles with no proton on the attacking atom represent general base catalysis of hydrolysis rather than nucleophilic attack.[8,9] For this reason and because these interesting reactions appeared deserving of a more thorough in-

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