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-

(1) (a) Publication No. 748 of the Graduate Department of Biochemistry, Brandeis University, Waltham, Mass. Supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD-1247). (b) To whom correspondence should be addressed.

(2) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, 83, 4390 (1961).

(3) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 234, 1272, 1280 (1959).

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(5) J. Gerstein and W. P. Jencks, *ibid.*, 86, 4655 (1964).

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(8) W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *ibid.*, 88, 4464 (1966).

(9) D. G. Oakenfull and W. P. Jencks, *ibid.*, 93, 178 (1971).

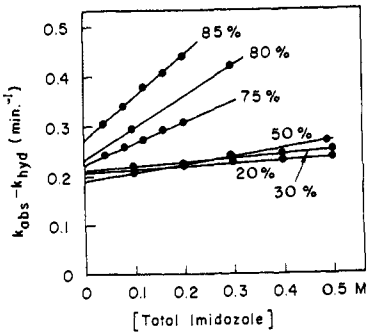


Figure 1. Catalysis of the reaction of 0.2 *M* morpholine with acetylimidazole by imidazole buffers at the indicated fractions of free base at 25°.

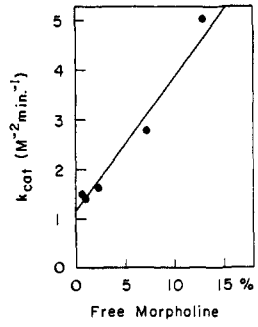
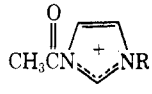


Figure 2. Dependence of the catalytic constants for imidazole (as the free base) on the fraction of morpholine as the free base.

vestigation, we undertook a further examination of their mechanism, with special attention to a comparison of the reactions of acetylimidazole with those of 1-acetyl-3-methylimidazolium ion (AcImMe$^+$, **1**, R = CH_3), which is a useful model for the reactive form of acetylimidazole, acetylimidazolium ion (AcImH$^+$, **1**, R = H).[2] Some of these results have been reported in a preliminary communication.[10]



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Experimental Section

The materials and methods used in these experiments were the same as described previously.[2,3,9] Experiments with 1-acetyl-3-methylimidazolium chloride were carried out by adding a particle of the solid to 3 ml of reaction mixture in the thermostated cell compartment of a Gilford recording spectrophotometer and following the reaction at 245 or 250 nm. It was possible to measure first-order rate constants of up to 20 min^{-1} by this technique without the use of special equipment.

Results

Catalysis of the reaction of morpholine with acetylimidazole by a series of imidazole buffers is shown in Figure 1. Morpholine is predominantly protonated at these pH values and the observed catalytic constants increase more rapidly than the imidazole free base concentration. A plot of the observed catalytic constant, based on free imidazole, against the fraction of morpholine present as the free base (Figure 2) shows that the catalysis involves reactions with both cationic and neutral transition states, according to the k_2 and k_4 terms of eq 1a. This confirms previous results for

$$v = k_1[\geq NH^+][AcIm] + k_2[\geq NH^+][AcIm][B] + k_3[\geq N][AcIm] + k_4[\geq N][AcIm][B] \quad (1a)$$

$$= k_1'[\geq N][AcImH^+] + k_2''[\geq N][AcIm][BH^+] + k_3[\geq N][AcIm] + k_4[\geq N][AcIm][B] \quad (1b)$$

other amines[3] and is the same form of the rate law as for catalysis by a second molecule of amine or its conjugate acid.[9] The experimental data may also be described by the kinetically equivalent rate law of eq 1b. Experimental conditions and observed catalytic constants as well as values of k_2'' and k_4 for imidazole catalysis of the reactions of a series of amines, from this and earlier work, are summarized in Table I.

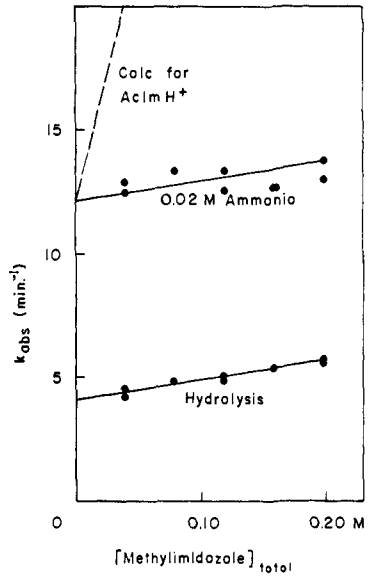


Figure 3. The dependence of the hydrolysis and reaction with 0.02 *M* ammonia of acetyl-*N*-methylimidazolium ion on the concentration of methylimidazole buffer, 50% base, at 25°. The dashed line shows the rate increase expected if AcImMe$^+$ were a model for the imidazole-catalyzed reaction of acetylimidazole, based on the rate constant k_2' (Table II).

Experimental conditions and rate constants for imidazole catalysis of the reaction of acetylimidazole with trifluoroethanol are also given in Table I. The rate law for this reaction follows eq 2, which contains the same

$$v = k_1[ROH][AcIm] + k_2[ROH][AcIm][B] + k_3[RO^-][AcIm] \quad (2)$$

terms that have been noted previously for reactions with water, acetohydroxamic acid, and ethanol.[3,5,11] Although catalysis of the ethanol reaction is certain,[11] the possible influence of solvent effects makes the catalytic constants uncertain and they are given only as limits in Table I.

Rate constants for the reactions of nucleophilic reagents with AcImMe$^+$ were measured in methylimidazole buffers. Values of k_1' for the reaction of the basic form of the nucleophile were obtained by extrapolation to zero buffer concentration as shown in Figures 3 and 4 and are summarized in Table II, along with some pre-

(10) W. P. Jencks, D. G. Oakenfull, and K. Salvesen, *J. Amer. Chem. Soc.*, 92, 3201 (1970).

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

Table I. Imidazole Catalysis of Reactions of Acetylimidazole with Amines and Alcohols at 25°

	pK	% free imidazole	No. of points	Concn of[a] N + NH+, M	Concn of Im + ImH+, M	k_{cat}^{AcIm} N + NH+; Im,[a] M^{-2} min^{-1}	$k_2''^{AcIm}$ N, ImH+,[a] M^{-2} min^{-1}	$k_{4N, Im}^{AcIm}$,[a] M^{-2} min^{-1}
					Amine			
Piperidine[b]	11.44	50	6	0.5	0.04–0.40	<0.4	$<8 \times 10^3$	
Ethylamine[c]	10.95	20	3	0.5	0.025–0.10	2.28		
		50	3	0.5	0.025–0.10	4.70	6.8×10^4	<5000
		80	3	0.5	0.025–0.10	8.24		
Glycine[b]	9.77	20	3	0.1	0.05–0.2	5.5		
		50	6	0.1	0.025–0.2	6.0	2200	530
		80	5	0.1	0.05–0.2	10.9		
		90	6	0.1	0.025–0.2	14.1		
Ammonia[d]	9.25						1700	
Morpholine[b]	8.74	20	5	0.20	0.1–0.5	1.50		
		30	5	0.20	0.1–0.5	1.43		
		50	3	0.18	0.1–0.5	1.74	52	26
		75	5	0.20	0.04–0.20	2.80		
		85	5	0.20	0.04–0.20	5.03		
Glycylglycine[d]	8.10						190	*Ca.* 80
Trifluoroethyl-amine[b]	5.81	20	4	0.10	0.03–0.17	7.1		
		50	5	0.10	0.03–0.17	5.5	1.0	4.9
		80	5	0.10	0.03–0.17	5.3		
Methoxyamine[e]	4.60	10	4	0.02	0.03–0.30	37		
		25	4	0.02	0.03–0.30	56		
		50	4	0.02	0.03–0.30	66	33	100
		75	4	0.02	0.015–0.15	80		
		90	4	0.02	0.015–0.15	95		
Semicarbazide[d]	3.86						<1	18
					Alcohol			
Ethanol[b]	16	50	3	0.4	0.04–0.35	$\leqslant$0.08	$\leqslant 1 \times 10^8$	
		80	3	0.4	0.04–0.40	$\leqslant$0.13		
Trifluoroethanol[b]	12.37	11.4	5	0.56	0.1–0.5	0.9 ± 0.2		
		20	5	0.4	0.1–0.5	0.9 ± 0.4	$(1.9 \pm 0.4) \times 10^5$	
		50	5	0.4	0.1–0.5	1.0 ± 0.3		
		80	5	0.2	0.1–0.5	1.1 ± 0.6		

[a] N refers to the free base form of the amine or the anion of the alcohol. [b] Ionic strength maintained at 1.0 with tetramethylammonium chloride. [c] Ionic strength maintained at 1.0 with potassium chloride. [d] Reference 3 (ionic strength maintained at 0.2 with sodium chloride). [e] Ionic strength maintained at 0.3 with tetramethylammonium chloride.

viously obtained values.[2] Catalytic constants for catalysis of the reactions by *N*-methylimidazole were obtained from the slopes of plots of k_{obsd} against buffer concentration after correction for catalysis of hydrolysis. No catalysis was detected for the reactions of trifluoroethoxide, ammonia (Figure 3), and ethylamine. Catalysis was observed for the reactions with trifluoroethylamine[10] and methoxyamine (Figure 4) and the catalytic constants k_2' are summarized in Table II. The k_2' terms are kinetically equivalent, by substitution of the appropriate ionization constants, to the k_2'' and k_2 terms of eq 1a and 1b as shown in eq 3. Since the

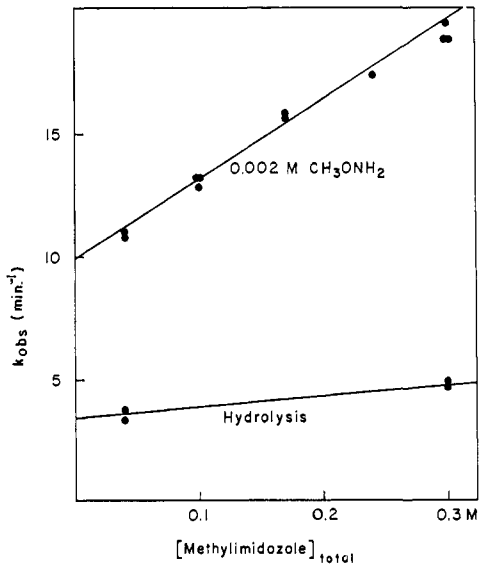


Figure 4. Catalysis of the reaction of acetyl-*N*-methylimidazolium ion with 0.002 *M* methoxyamine by methylimidazole buffers, 30% base, at 25°.

$$k_2'[RNH_2][AcImR^+][B] = k_2''[RNH_2][AcIm][BH^+] = k_2[RNH_3^+][AcIm][B] \quad (3)$$

salt concentration was not the same in all of these experiments, the effect of varying the nature and concentration of salt was examined in a few cases and found not to be large (Table II).

Discussion

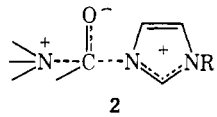
Imidazole Catalysis with a Cationic Transition State. The k_2–k_2'–k_2'' Reaction. The rate constants k_1' for the reactions of nucleophilic reagents with $AcImMe^+$ agree well, to within less than a factor of 2 over a range of 10^9, with the corresponding rate constants for the reactions of $AcImH^+$, except for the reaction with hydroxide ion (Table II). This confirms a previous conclusion[2] that $AcImMe^+$ is a good model for the reactive form of acetylimidazole, $AcImH^+$, and that the k_1 term of eq 1a should be formulated as a reaction of the basic form of the nucleophile with $AcImH^+$ ac-

Table II. Comparison of Rate Constants for Reactions of Nucleophiles with Acetyl-*N*-methylimidazolium and Acetylimidazolium Ions at 25°

Nucleophile	% free MeIm	No. of points	Concn of[a] N + NH^+, *M*	Concn of MeIm + $MeImH^+$, *M*	$k_1'^{AcImMe^+}_{N}$, [a] M^{-1} min^{-1}	$k_1'^{AcImH^+}_{N}$, [a] M^{-1} min^{-1}	$k_2'^{AcImMe^+}_{N, MeIm}$, [a] M^{-2} min^{-1}	$k_2'^{AcImH^+}_{N, Im}$, [a] M^{-2} min^{-1}
Water					0.051[b]	0.051[b]		
Acetate$^-$					17[b]	19[b]		
Succinate^{2-}					42[b]	78[b]		
Phosphate^{2-}					2230[b]	2100[b]		
Trifluoroethoxide$^-$	30	6	0.03–0.06	0.04	7.1×10^7 [c]	3.9×10^7 [d,e]	$<3 \times 10^7$	$2.7–4.1 \times 10^8$ [e]
	40	9	0.03	0.04–0.30	7.4×10^7 [c]		<130[f]	
Hydroxide$^-$					9×10^6 [b]	13×10^7 [b]		
Methoxyamine	30	11	0.002	0.04–0.30	3250[c]	3200[c]	4.6×10^4 [c]	5.9×10^4 [c]
Trifluoroethylamine	30	13	0.05	0.04–0.30	151[c]	129[e]	1560[c]	1780[e]
Imidazole					2.3×10^4 [d,e]			
Methylimidazole						2.96×10^4 [d,e]		
Ammonia	50	9	0.02	0.04–0.20	5.6×10^4 [g]		*h*	3×10^6 [b]
					6.2×10^4 [b]	8.1×10^4 [b]		
Ethylamine	40	15	0.01	0.04–0.30	6.1×10^6 [c]	7.6×10^6 [i]	*h*	1.2×10^8 [i]
						6.8×10^6 [c]		1.0×10^8 [c]

[a] N refers to the free base form of the amine or the anion of the alcohol. [b] Reference 2 (ionic strength maintained at 0.2 with sodium chloride). [c] Ionic strength maintained at 0.3 with tetramethylammonium chloride. [d] Reference 9. [e] Ionic strength maintained at 1.0 with tetramethylammonium chloride. [f] Based on total alcohol concentration. [g] Ionic strength maintained at 0.2 with tetramethylammonium chloride. [h] No catalysis by methylimidazole except for hydrolysis. [i] Ionic strength maintained at 1.0 with potassium chloride.

cording to the k_1' term of eq 1b and transition state **2**, without taking a position as to whether a metastable tetrahedral addition intermediate is formed along the reaction path. In particular, the equivalence of these



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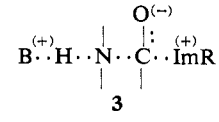
rate constants means that concerted proton transfer to the leaving imidazole, by the solvated proton, is not important for these reactions, since such proton transfer is not possible for the $AcImMe^+$ reactions. The same conclusion holds for the reaction of trifluoroethoxide ion with $AcImMe^+$ and $AcImH^+$ and the transition state for this reaction is analogous to **2**. However, the 14-fold larger value of k_1' for the reaction of hydroxide ion with $AcImH^+$ compared to $AcImMe^+$ means that an additional mechanism must be available for the former reaction, which is equivalent to the "water" hydrolysis of free acetylimidazole, so that the greater part of this reaction cannot be formulated in terms of a rapid equilibrium protonation of AcIm followed by attack of hydroxide ion.[2]

Two mechanisms for imidazole catalysis of the aminolysis of acetylimidazole according to the k_2–k_2'–k_2'' terms of eq 1 and 3 are shown in transition states **3** and **4** (which again are not meant to imply that



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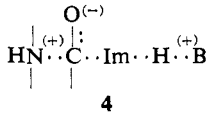

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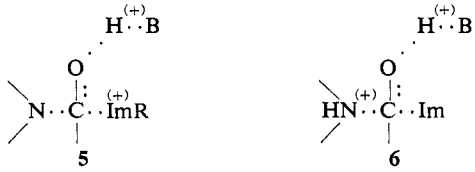
a tetrahedral addition intermediate is or is not formed). Mechanism **3**, which corresponds to the rate constant k_2', involves general base catalysis by imidazole of the removal of a proton from the attacking nucleophile with protonated imidazole as the leaving group. Mechanism **4**, which corresponds to the kinetically equivalent rate constant k_2'', involves the free amine nucleophile and protonation of the leaving imidazole group by imidazolium ion. A mechanism corresponding to the rate constant k_2 is unlikely, because this term involves the protonated amine, which has no free electron pair to attack the acyl group. As in the second-order k_1' reactions, $AcImMe^+$ should serve as a model for $AcImH^+$, so that if mechanism **3** is correct the observed rate constant k_2' for methylimidazole catalysis of the reaction with $AcImMe^+$ should agree with the rate constant for the observed catalysis with acetylimidazole expressed in terms of k_2' (eq 3) according to mechanism **3**. As shown in Figure 3, there is no detectable catalysis of the reaction of ammonia with $AcImMe^+$ by methylimidazole. Catalysis of a magnitude sufficient to account for the observed catalysis with acetylimidazole would have been easily detectable if the latter catalysis occurred by this mechanism, as shown by the dashed line in the figure. The same result was obtained for ethylamine under conditions in which catalysis by the same mechanism for acetylimidazole would have given an increase in rate constant of 12–16 min^{-1}. These results show that $AcImMe^+$ is *not* a model for these catalyzed reactions and rule out mechanism **3**; they are consistent with mechanism **4** for imidazole catalysis of the reactions of these strongly basic amines with acetylimidazole.

Now, the aminolysis of an amide is a symmetrical reaction and it is intuitively unsatisfying to conclude that the unsymmetrical catalytic mechanism **4** holds for all such reactions. In the ethylamine and ammonia reactions a strong base is displacing imidazole, a weaker base, and catalysis according to mechanism **4** involves proton donation to this weaker base. From considerations of microscopic reversibility it seemed possible that attack of a weaker base might be catalyzed by proton removal from the attacking base according to mechanism **3** (the reverse of this reaction would involve the attack of the relatively strong base imidazole with proton donation to the leaving weak base by a catalyst). Accordingly, catalysis by methylimidazole of the reactions of the weak bases trifluoroethylamine and methoxyamine with $AcImMe^+$ was sought for and, as shown in Figure 4, was found. The rate constants for these reactions agree well with those for the observed catalysis

by imidazole of the same reactions with $AcImH^+$ expressed according to k_2' (Table II). $AcImMe^+$ is, therefore, a model and transition state **3** is a satisfactory mechanism for the catalyzed reactions of weakly basic amines with acetylimidazole.

Mechanisms involving a protonated carbonyl oxygen atom or catalysis of proton transfer to or from this oxygen atom (*e.g.*, **5** or **6**) must also be considered for these



5 **6**

reactions. It is difficult to explain the observed catalysis by such mechanisms, principally because of the symmetry and the apparent importance of protonation of the leaving imidazole in these reactions. The fact that $AcImMe^+$ is a satisfactory model for the second-order reactions of acetylimidazole and the catalyzed reactions of weakly basic amines means that a proton is located on the leaving imidazole group, rather than on the carbonyl group, in these cases. It is expected that partial or concerted protonation should occur also in the corresponding reactions with strongly basic amines. If mechanisms **5** and **6** hold generally, the "water" reaction must follow mechanism **5**, presumably with water hydrogen bonded to the carbonyl oxygen atom, since $AcImMe^+$ is a satisfactory model for this reaction for all amines. There would then have to be a change in mechanism or rate-determining step, for no obvious reason, in the imidazole-catalyzed reactions to account for the fact that $AcImMe^+$ is a model for only the reactions of weakly basic amines. Furthermore, the fact that tertiary amines react normally with $AcImH^+$ means that proton removal from the attacking amine is not required in these reactions[9] and means that mechanisms requiring such proton removal, such as **5**, are not general.

The reactions of amides are generally dominated by the requirement for protonation of the leaving amine, in order that the leaving group not be the extremely unstable N^- anion; conversely, because of the symmetry of the reaction a proton must be removed from the attacking amine. This proton may be fully attached to the leaving group (probably in an equilibrium protonation step before C–N bond cleavage occurs) so that the Brønsted $\alpha = 1.0$, or it may be added as the amine leaves, *i.e.*, $\alpha < 1.0$ and the reaction is subject to general acid catalysis. The converse holds for the attacking amine: the proton may remain fully attached in the transition state ($\beta = 0$; no general base catalysis) or may be removed as C–N bond formation occurs ($\beta > 0$; general base catalysis). The position of the proton which gives the lowest energy transition state for amine attack depends upon the basicity of the amine and the amount of assistance to C–N bond formation that is brought about by proton abstraction. The results reported here suggest (i) that strongly basic amines are effective nucleophiles without proton abstraction, whereas with less nucleophilic, weakly basic amines a significant advantage is gained from partial proton abstraction and general base catalysis is observed, and (ii) that the expulsion of imidazole by weakly basic amines requires full protonation of the leaving group, whereas the greater electron density at the reaction center that is developed by strongly basic amines is sufficient to expel imidazole with only partial protonation ($\alpha < 1.0$). From the symmetry of the reaction and microscopic reversibility one may further conclude (iii) that the expulsion of strongly basic amines, which are poor leaving groups, requires full protonation and (iv) amines with electron-withdrawing substituents which are protonated less easily and are intrinsically better leaving groups are expelled with only partial protonation. Although the above discussion has been presented without explicit consideration of the possible existence of a tetrahedral addition intermediate, similar considerations hold if there is such an intermediate. It is not certain whether an analogous mechanism holds for the hydroxylaminolysis of amides, but a suggested mechanism for this reaction[12] is in accord with these considerations to the extent that a "water" reaction, with full proton transfer to the leaving amine, is important for ammonia, but not for hydroxylamine expulsion. A somewhat similar situation has been suggested for the expulsion of hydroxide ion from the addition compound formed from amines and aldehydes: here too, general acid–base catalysis of proton transfer is significant only for weakly basic amines which do not have the driving force to easily expel the hydroxide ion without such assistance.[13]

These conclusions are in accord with eq 4 and 5, which relate nucleophilic reactivity, n, to Brønsted α or β values and may be of assistance in assigning reaction mechanisms.[14] Equation 4 states that as the

$$n_i c_5 = \beta_0 - \beta_i \tag{4}$$

$$n_k = c_2(\alpha_0 - \alpha_k) \tag{5}$$

nucleophilicity of an amine that is attacking $AcImMe^+$ or $AcImH^+$ is increased, the value of β will decrease, in agreement with the observed presence of general base catalysis for weakly basic, but not strongly basic nucleophiles for which $\beta = 0$. Equation 5 states that as the amine nucleophilicity is increased the value of α will decrease, in agreement with the observed general acid catalysis for the expulsion of imidazole from acetylimidazole with strongly basic amines and the absence of such catalysis for weakly basic amines, for which $\alpha = 1.0$. The conclusions are also in accord with the "solvation" and "reacting-bond" rules of Swain and coworkers.[15]

Equations 6 and 7, in which pK_1 and pK_2 are measures

$$pK_2 - pK_1 = c_5(s_1 - s_2) \tag{6}$$

$$pK_2 - pK_1 = c_2(s_2 - s_1) \tag{7}$$

of the basicity or acidity of two catalysts and s is a measure of the sensitivity of the substrate to the nucleophilic reactivity of the nucleophile, are corollaries of eq 4 and 5. These equations state that the sensitivity of a substrate to the nucleophilicity of an attacking

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(13) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, 91, 6353 (1969).

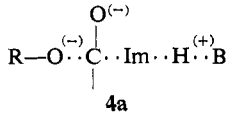
(14) E. G. Cordes and W. P. Jencks, *ibid.*, 84, 4319 (1962); G. E. Llenhard and W. P. Jencks, *ibid.*, 88, 3982 (1966).

(15) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *ibid.*, 87, 1553 (1965); C. G. Swain and J. C. Worosz, *Tetrahedron Lett.*, 36, 3199 (1965).

reagent decreases with increasing basicity of a base catalyst (eq 6) or acidity of an acid catalyst (eq 7). (The equations apply only to true, mechanistic general acid or base catalysis.) The fact that general base catalysis by imidazole or methylimidazole for reactions with $AcImR^+$ is observed only for weakly basic nucleophiles means that the sensitivity of the "water" reaction to the basicity of the nucleophile is larger than that of the imidazole-catalyzed reaction, in accord with eq 6. The fact that general acid catalysis by imidazolium ion for reactions of acetylimidazole is observed only for strongly basic nucleophiles means that the sensitivity of the imidazolium-catalyzed reaction to the basicity of the nucleophile is larger than that of the proton-catalyzed reaction (*i.e.*, the reaction of $AcImH^+$). This is in accord with eq 7.

Mechanism **2**, with general base catalysis of amine attack, is the same mechanism that has been established for the aminolysis of esters under conditions in which the attack of amine on the ester is rate determining.[16] The analogy extends to the effect of structure upon reactivity: catalysis by this mechanism with strongly basic amines is important only for esters with poor leaving groups; it is not important for *p*-nitrophenyl acetate or $AcImR^+$.[17] However, for the weakly basic methoxyamine general base catalysis is observed with *p*-nitrophenyl acetate[18] and $AcImR^+$, both of which have leaving groups with $pK = 7.0$.

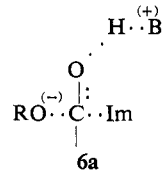
Transition state **4**a, analogous to **4**, provides the simplest mechanism for imidazole catalysis of the reactions of acetylimidazole with hydroxylic nucleophiles according to the k_2'' or the kinetically equivalent k_2 term of eq 2 and 8. As is the case with strongly basic amines, no



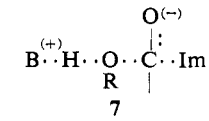
4a

$$k_2''[RO^-][AcIm][BH^+] = k_2[ROH][AcIm][B] \quad (8)$$

catalysis was found of the reaction of $AcImMe^+$ with trifluoroethanol. This result is not unexpected since there are no protons on the trifluoroethoxide ion, the presumed nucleophilic species in this reaction. The imidazole-catalyzed reaction of imidazole with *p*-nitrophenyl benzoates represents the same reaction in reverse and in this case also there is no catalysis if methylimidazole is substituted for imidazole.[19] The similarity of the proposed mechanisms for catalysis of alkoxide and amine reactions is in accord with the comparable reactivities and basicities of these nucleophiles. Mechanism **4**a involves proton donation to the leaving imidazole and, for the reaction in the reverse direction, the attack of imidazole on an ester, involves removal of a proton from the attacking amine. This is the same mechanism as has been demonstrated for catalysis of the aminolysis of methyl formate, which provides additional support, by analogy, for mechanism **4a**. Mechanism **6a** is less likely because the proton-catalyzed



6a



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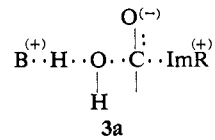
reaction definitely involves proton donation to the leaving imidazole, as shown by the equivalence of the rate constants for the reactions of trifluoroethoxide ion with $AcImH^+$ and $AcImMe^+$ (Table II). The same objection applies to mechanism **7** and, in addition, imidazole catalysis of the reaction of the weakly basic trifluoroethanol molecule with free acetylimidazole would require a rate constant many orders of magnitude larger than that predicted from the observed rates of the imidazole-catalyzed reactions of other nucleophiles with free acetylimidazole (see below).

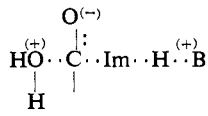
The hydrolysis of acylimidazoles is catalyzed by imidazolium ion,[6,9] according to the rate law of eq 9. The

$$k_5[AcIm][BH^+] = k_5'[AcImH^+][B] \quad (9)$$

rate constant for this catalysis may be expressed in the kinetically equivalent form $k_5' = 36\ M^{-1}\ min^{-1}$ for $AcImH^+$ and imidazole, and the similarity of this value to the corresponding value of $k_5' = 18\ M^{-1}\ min^{-1}$ for the methylimidazole-catalyzed hydrolysis of $AcImMe^+$[2,9] indicates that $AcImMe^+$ is a satisfactory model for at least a large part of the catalyzed hydrolysis of acetylimidazole. This rules out **8** and **9** as the predominant reaction mechanism and suggests that the catalyzed reaction of the weakly basic water molecule is analogous to that of weakly basic amines, according to mechanism **3**a.



3a



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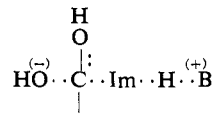

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In all of these mechanisms the possibility should be kept in mind that catalysis of a second proton transfer by the catalyzing acid or base takes place immediately before or after the rate-determining transition state, in a "one-encounter" mechanism.[20] However, the fact that $AcImMe^+$ is a model for many reactions of $AcImH^+$ means that any such pre- or post-transition-state proton transfer involving the imidazole group cannot affect the reaction rate significantly in these reactions, because the methyl group is not subject to such transfer (*i.e.*, the overall free energy profile along the reaction coordinate is similar for both reactions, with no indication of a required proton transfer step which would become kinetically significant if diffusion to the reacting complex from the bulk solution, rather than proton transfer within the reacting complex, were required).

Imidazole Catalysis with a Neutral Transition State. The k_4 Reaction. The primary problem in reactions of

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(19) M. Caplow and W. P. Jencks, *Biochemistry*, **1**, 883 (1962).
(20) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 211.

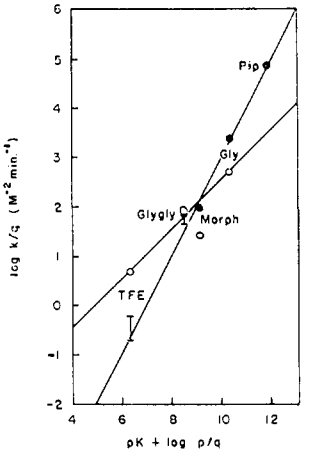
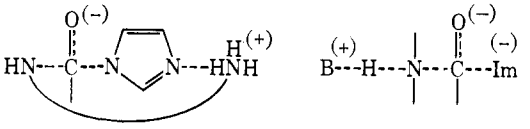


Figure 5. Dependence on basicity of the reactions of amines with free acetylimidazole catalyzed by a second molecule of amine[3,9] (●) and by imidazole (○).

free acetylimidazole is the expulsion of the unstable imidazole anion (pK = 14.2[21]) by less basic nucleophilic reagents[9] and it would be expected that the mechanism of catalysis would reflect a facilitation of this process. Inspection of Pauling–Corey molecular models suggests that in the facile intramolecularly catalyzed reaction of ethylenediamine with acetylimidazole, proton transfer from the catalyzing group to the distal nitrogen atom of the imidazole group (**10**) is difficult or impossible;[22]



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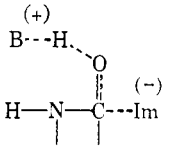
11



12

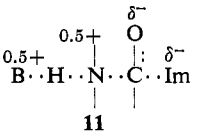
protonation of the proximal nitrogen is unlikely to be of importance in catalysis in view of the fact that AcImMe$^+$ is a satisfactory model for AcImH$^+$. Reasonable mechanisms for both the intramolecular and intermolecular catalysis are **11** and **12**. Mechanism **12** is possible only if a proton has been removed from the attacking amine before the rate-determining step and if there is a metastable tetrahedral addition intermediate on the reaction pathway, which has not yet been demonstrated. Since the acidity of imidazole (pK_a = 14.2) is similar to that of methanol (pK_a = 15.5[23]), it is reasonable to suggest that the mechanism of catalysis is **11**, the same as that which has been demonstrated for the attack step in the aminolysis of methyl formate,[16] again without taking a position as to the possible role of a tetrahedral addition intermediate. Removal of the proton according to mechanism **11** prevents expulsion of the attacking reagent to regenerate starting materials and provides sufficient electron density at the reaction center to expel the imidazole anion, which is now the best leaving group.

General base catalysis has also been demonstrated for the hydroxylaminolysis and hydrazinolysis of trifluoroacetanilide.[24] Since the aniline anion is a very poor leaving group, it is probable that a proton is donated to the leaving aniline in this reaction.

The sensitivity to amine basicity of the reaction with amines catalyzed by a second molecule of amine, according to the rate law of eq 10, is shown in Figure 5;

$$v = k_4[\mathrm{AcIm}][\mathrm{RNH_2}]^2 \qquad (10)$$

the slope of the line, β, is 1.0. The sensitivity of the imidazole-catalyzed reaction to the basicity of the attacking amine is smaller; a line of slope β = 0.5 is drawn through points for three primary amines in Figure 5. The difference of approximately 0.5 between these two β values must represent the sensitivity of the reaction to the basicity of the *catalyzing* amine. The β value of 0.5 for the imidazole-catalyzed reaction means that the reaction behaves as if there is a development of a net charge of 0.5 on the nucleophilic nitrogen atom, so that the charge distribution in the transition state according to mechanism **11** is approximately that shown.



11

The β value of 0.5 is *not* a direct measure of the amount of N—C bond formation, because charge is being removed from the attacking amine as the proton is abstracted by the catalyst. If this catalysis also involves the development of approximately 0.5 positive charge on the catalyzing base, as suggested by the Brønsted β values, and a comparable degree of charge removal from the attacking nitrogen atom, a large amount of N—C bond formation has taken place, comparable to that which would occur in an uncatalyzed reaction with a β value of 0.5 + 0.5 = 1.0. This decrease in the observed β value for the nucleophile with general base catalysis has been observed previously in intramolecular general base catalyzed aminolyses of aspirin and aspirin analogs[25] and has been suggested as a mechanism to account for the very low sensitivity of reactions of acylchymotrypsin to the basicity of the nucleophile.[26] The β value for the catalyzing base of 0.5 is similar to the value of approximately 0.45 for catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate by carboxylate ions.[18]

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(25) T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 3817 (1968); S. M. Felton and T. C. Bruice, *ibid.*, **91**, 6721 (1969).
(26) P. W. Inward and W. P. Jencks, *J. Biol. Chem.*, **240**, 1986 (1965).