General Base and Acid Catalysis in the Hydrazinolysis of Acetylimidazole[1]

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Abstract: The Brønsted plot for general base catalysis of the reaction of hydrazine with free acetylimidazole is nonlinear with limiting slopes of $\beta \leqslant 0.2$ and $\beta > 0.7$ for strong and weak bases, respectively. The curvature is similar to that for simple proton transfer reactions between electronegative atoms. It is concluded that there is a change in the nature of the rate-determining step with changing basicity of the catalyst and it is suggested that this change is a consequence of a kinetically significant transport step involving the catalyst and at least one ionic species of a tetrahedral addition intermediate. Possible detailed mechanisms and their relationship to the lifetime of the intermediate and the position of the break in the Brønsted plot are described. In contrast, the Brønsted plot for general acid catalyzed hydrazinolysis shows no evidence of nonlinearity. It is suggested that this reaction involves the kinetically equivalent general base catalysis of the hydrazinolysis of acetylimidazolium ion and that this catalysis occurs through a "concerted" mechanism. It is proposed that one or more ionic species of the tetrahedral "intermediate" formed from acetylimidazolium ion may be too unstable to exist, so that a "concerted" mechanism is required in order to avoid the formation of an unstable N-protonated amide product.

Most acyl transfer reactions require one or more proton transfers at some time during the course of the reaction and there is evidence that metastable tetrahedral addition compounds are intermediates in many such reactions.[2] The timing of the proton transfer(s) and its relationship to the various ionic species of tetrahedral addition intermediates constitute a central problem in our attempts to understand the mechanisms of these reactions. If a particular ionic species of a tetrahedral intermediate has a lifetime of $>10^{-3}$ sec, it can usually reach equilibrium with the bulk solvent with respect to proton transfer.[3] With shorter lifetimes there may be insufficient time to reach equilibrium in the absence of catalysts for proton transfer, so that the pathway with the lowest free energy for the overall reaction may not include proton transfer steps that are thermodynamically favorable or a proton transfer step may itself become rate determining.[4-10] If the tetrahedral addition "intermediate" is still less stable, it may not represent a significant potential energy minimum along the reaction coordinate; if this is the case discrete proton transfer steps to or from this "intermediate" are not possible.

We describe here a study of the hydrazinolysis of acetylimidazole catalyzed by general bases and acids that illustrates the two types of experimental manifestations of general acid–base catalysis with a single acyl compound. The hydrazinolysis of free acetylimidazole, which has a relatively poor leaving group of $pK = 14.2$,[11] appears to proceed through the formation of an intermediate that has a lifetime sufficient to permit the occurrence of kinetically significant transport steps involving the catalyst, but insufficient to reach equilibrium with respect to proton transfer. In the hydrazinolysis of acetylimidazolium ion, which has a much better leaving group of $pK = 7$, it appears that the lifetime of an "intermediate" is insufficient to permit stepwise proton transfer to take place and proton transfer occurs by a "concerted" mechanism.[12] Hydrazine was chosen as the nucleophile for this study because its high reactivity made it possible to obtain Brønsted plots for general acid and base catalysis of its reactions.[13] General base catalysis of acyl aminolysis reactions is usually manifested by a term second order with respect to amine so that it is difficult or impossible to change the catalyst without also changing the nucleophile.[14]

Some of these results have been described in a preliminary communication.[15]

Experimental Section

The materials and methods used in these experiments were the same as described previously.[16-19] *N*-Propargylmorpholine (mp 168–169°) was prepared by Mr. A. Satterthwait.[20] The pH

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Table I. Rate Constants for the Buffer-Catalyzed Reaction of Hydrazine with Acetylimidazole at 25° and Ionic Strength 1.0 *M* (KCl)

Buffer	Fraction free base	pH	No. of points	Total buffer concn, *M*	Total hydrazine concn, *M*	k_{cat},[a] M^{-1} sec^{-1}
Formate[b]	0.33	3.29	7	0.04–0.4	4×10^{-2}	1.01×10^{-1}
	0.48	3.50	8	0.02–0.4	4×10^{-2}	1.20×10^{-1}
	0.67	3.85	8	0.02–0.4	4×10^{-2}	1.56×10^{-1}
	0.86	4.33	8	0.02–0.4	4×10^{-2}	1.10×10^{-1}
Acetate[b]	0.15	3.83	18	0.02–0.4	1×10^{-2}	4.40×10^{-2}
	0.30	4.22	14	0.04–0.4	1×10^{-2}	6.12×10^{-2}
	0.50	4.59	14	0.04–0.4	1×10^{-2}	6.40×10^{-2}
	0.70	4.95	14	0.04–0.4	1×10^{-2}	5.63×10^{-2}
	1.0[c]	7.45	10	0.04–0.20	5×10^{-2}	5.3×10^{-2}
	1.0	7.70	14	0.04–0.60	5×10^{-2}	7.8×10^{-2}
Malonate[b]	0.30	4.72	10	0.04–0.2	1×10^{-2}	4.85×10^{-2}
	0.50	5.06	10	0.04–0.2	1×10^{-2}	4.52×10^{-2}
	0.70	5.39	10	0.04–0.2	1×10^{-2}	4.28×10^{-2}
	0.90	5.99	10	0.04–0.2	1×10^{-2}	4.03×10^{-2}
	1.0[c]	7.71	12	0.05–0.60	5×10^{-2}	1.04×10^{-1}
	1.0	7.82	12	0.09–0.54	5×10^{-2}	5.5×10^{-2}
N-Propargyl-morpholine	0.70	5.97	16	0.04–0.2	1×10^{-2}	7.0×10^{-3}
	0.90	6.60	12	0.04–0.2	1×10^{-2}	9.0×10^{-3}
Trifluoroethylamine	0.10	4.87	12	0.025–0.4	1×10^{-2}	4.6×10^{-3}
	0.70	6.19	12	0.025–0.4	1×10^{-2}	2.86×10^{-2}
	0.80	6.45	12	0.025–0.4	1×10^{-2}	3.27×10^{-2}
	0.90	6.79	12	0.025–0.4	1×10^{-2}	3.38×10^{-2}
	1.0[c]	7.72	14	0.04–0.60	5×10^{-2}	3.52×10^{-1}
	1.0	7.90	14	0.04–0.60	3×10^{-2}	2.25×10^{-1}
Cacodylate	0.70	6.50	7	0.04–0.4	1×10^{-2}	9.4×10^{-2}
	0.90	7.11	7	0.04–0.4	1×10^{-2}	1.15×10^{-1}
	1.0[c]	7.65	7	0.04–0.6	5×10^{-2}	8.9×10^{-1}
	1.0	7.90	7	0.04–0.6	3×10^{-2}	5.8×10^{-1}
Imidazole	0.10	6.30	12	0.025–0.4	1×10^{-2}	2.44×10^{-2}
	0.50	7.25	10	0.04–0.2	1×10^{-2}	3.17×10^{-1}
	0.70	7.66	10	0.04–0.2	5×10^{-3}	3.44×10^{-1}
	0.90	8.21	12	0.025–0.4	5×10^{-3}	8.89×10^{-1}
N-Methylmorpholine	0.30	7.46	10	0.04–0.2	1×10^{-2}	5.10×10^{-2}
	0.50	7.83	10	0.04–0.2	1×10^{-2}	1.64×10^{-1}
	0.70	8.20	10	0.04–0.2	1×10^{-2}	3.83×10^{-1}
2-Cyanoethylamine	0.20	7.57	12	0.04–0.3	1×10^{-2}	1.13×10^{-1}
	0.50	8.16	12	0.04–0.3	5×10^{-3}	3.45×10^{-1}
Hydrazine[d]	0.10	7.24	10	0–0.05		11.0
	0.20	7.57	10	0–0.05		30.0
	0.30	7.84	10	0–0.05		64.0
	0.40	8.00	10	0–0.05		101.0
Morpholine	0.20	8.20	14	0.04–0.40	5×10^{-3}	1.35×10^{-1}
	0.50	8.85	10	0.04–0.20	5×10^{-3}	6.05×10^{-1}
Triethylenediamine	0.20	8.62	10	0.02–0.25	4×10^{-3}	3.48×10^{-1}
	0.50	9.20	10	0.025–0.30	5×10^{-3}	1.41
	0.70	9.56	10	0.01–0.15	5×10^{-3}	1.98
Hexafluoroisopropyl alcohol	0.10	8.26	10	0.04–0.2	5×10^{-3}	2.7×10^{-1}
	0.30	8.84	10	0.04–0.2	5×10^{-3}	9.8×10^{-1}
	0.50	9.23	10	0.04–0.2	5×10^{-3}	1.82
2-Methoxyethylamine	0.10	8.70	10	0.04–0.2	1×10^{-2}	4.15×10^{-1}
	0.20	9.06	10	0.04–0.2	1×10^{-2}	9.9×10^{-1}
3-Quinuclidinol	0.10	9.25	10	0.025–0.3	5×10^{-3}	2.44×10^{-1}
	0.20	9.62	10	0.02–0.3	1×10^{-2}	9.2×10^{-1}
	0.30	9.86	10	0.02–0.2	1×10^{-2}	1.58
	0.20	9.61	10	0.02–0.2	2×10^{-2}	2.03
Quinuclidine	0.10	10.60	10	0.04–0.2	5×10^{-3}	6.25×10^{-1}
	0.15	10.81	8	0.08–0.2	5×10^{-3}	6.95×10^{-1}
	0.15	10.81	8	0.04–0.16	5×10^{-3}	8.6×10^{-1}
Hydronium ion		2.15	6		0.1–0.4	6.8×10^{-2}
		1.08	6		0.1–0.289	6.9×10^{-2}

[a] Based on total buffer concentration; see text, eq 3 and 5. [b] These species showed an extra term in the rate law given by $k[HA][N_2H_4][H^+] \cdot [AcIm]$, see text. [c] Hydrazine used as the buffer. [d] Tetramethylammonium chloride used to maintain ionic strength.

was measured before and after each run and the temperature was 25.0°. Unless otherwise stated the ionic strength was 1.0 *M*, maintained with potassium chloride.

The hydrazinolysis experiments were usually carried out with 0.005–0.02 *M* hydrazine in the presence of increasing concentrations of buffer solutions prepared from the catalyst being examined. Individual rate constants were generally determined from data collected up to 3 half-lives (always at least 2 half-lives) and were found to be strictly pseudo-first-order. These constants were determined in duplicate. Because of its volatility, experiments with trifluoroethylamine were carried out in tightly stoppered cuvettes with a small air space, using solutions of the hydrochloride that had been neutralized in an ice bath immediately before use. The measured pH of the solutions was found to be that expected from the amount of alkali added and was the same before and after each run. For weakly basic catalysts the acid catalysis term is large and the catalytic constant for the basic component was determined from experiments carried out in hydrazine buffers, in which the contribution of acid catalysis is small or negligible. Parallel experiments were carried out with all buffer solutions in

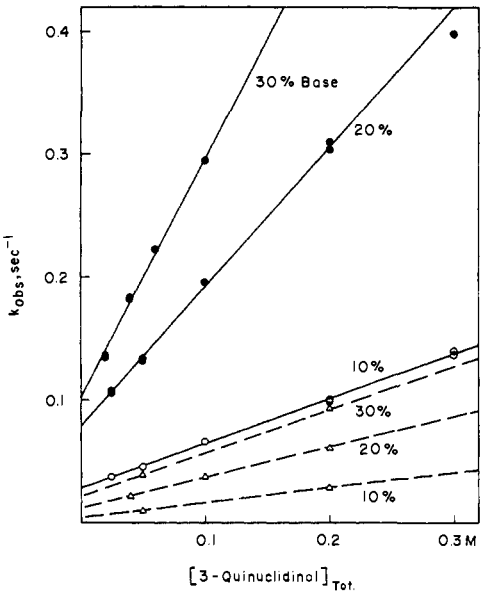


Figure 1. Observed pseudo-first-order rate constants for the reaction of acetylimidazole with hydrazine (solid lines) as a function of 3-quinuclidinol buffer concentration at the indicated fractions of free base at 25°, ionic strength 1.0 *M*: upper lines, 0.01 *M* hydrazine; lower line, 0.005 *M* hydrazine. The dashed lines show the rate constants in the same buffers but in the absence of hydrazine.

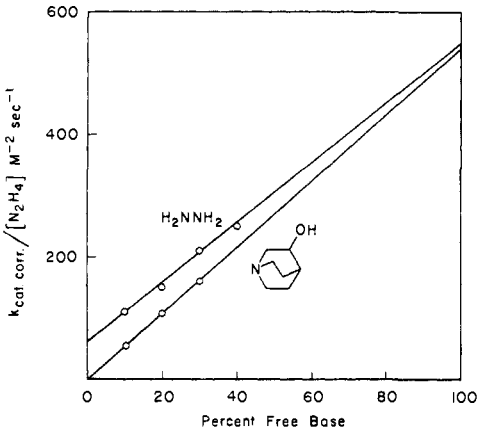


Figure 2. Dependence of the observed rate constants for catalysis of the reaction of acetylimidazole with hydrazine by 3-quinuclidinol and by hydrazine buffers on the fraction free base of the buffer. The left and right ordinate intercepts give the catalytic constants for the acidic and basic species of the buffer.

the absence of hydrazine and the observed pseudo-first-order rate constants were corrected for the contribution of all buffer-dependent terms that do not involve hydrazine. The intercepts of the plots against buffer concentration were found to agree closely with the rate constants calculated from the sum of the various hydrolysis and hydrazinolysis terms expected under the conditions of the experiment. The corrections for hydrolysis were generally small. In the case of quinuclidine, the most basic catalyst examined, the corrections for catalysis of hydrolysis were as large as 40% of the observed catalysis at 15% free base and the catalytic constants for hydrazinolysis by this base are accordingly less accurate than for the other bases examined. A downward curvature was observed at high buffer concentrations in plots of rate constants against the concentration of acetate and formate buffers. The plots were linear up to 0.2 *M* and the catalytic constants were obtained from the initial slopes. Experiments at low pH values were corrected for the partial conversion of acetylimidazole into acetylimidazolium ion (pK_a = 3.86[18]) by multiplying the observed rate constants by $K_a/(K_a + a_{H^+})$.

With malonate and acetate ions as the bases, all of the observed rate increases with increasing base concentration could be accounted

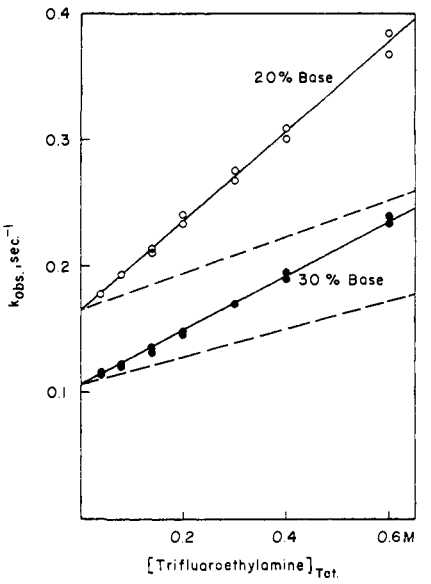


Figure 3. Observed pseudo-first-order rate constants for the reaction of acetylimidazole with hydrazine, as a function of added trifluoroethylamine concentration at 25°, ionic strength 1.0 *M*. The buffers were 0.05 *M* hydrazine, 20% base, and 0.03 *M* hydrazine, 30% base. The dashed lines show the rate constants expected if there were no reaction of hydrazine, free trifluoroethylamine, and acetylimidazole.

for by catalytic terms other than general base catalyzed hydrazinolysis. Upper limits were therefore obtained for these rate constants by assuming that a 20% rate increase would not have been detected and assigning all of this increase to the base-catalyzed term k_3. For those catalysts in which the catalytic coefficient for one ionic species is much larger than that for the other, an upper or error limit was obtained by assuming a 10% error for the catalytic coefficient determined at the highest or lowest fraction of free base. The limit for hydroxide ion catalysis was obtained from comparison of the observed intercepts of plots against buffer concentration with those calculated from known rate constants. No evidence for hydroxide catalysis was found; a catalytic constant equal to the limiting value of $<10^5$ M^{-2} sec^{-1} would have given intercepts up to 200% larger than those observed.

Results

The experimental conditions and results are given in Table I; k_{cat} is the slope of a plot of k_{obsd} against the total concentration of each buffer or catalyst, corrected for terms second order in buffer concentration when these are significant. Examples of the experimental results are shown in Figures 1–3. Figure 1 shows catalysis of hydrazinolysis by quinuclidinol buffers of increasing fraction free base; the dashed lines show the catalysis of hydrolysis in the absence of hydrazine. Plots of the catalytic constants for hydrazinolysis against the fraction of free base in the buffer show that for quinuclidinol only the free base form of the buffer gives detectable catalysis (Figure 2); however, for hydrazine itself and other less basic catalysts both general acid and base catalyses are observed (Figure 2, upper line). For trifluoroethylamine, the catalytic constant is much larger for the acid than for the free base species and the constant for base catalysis was obtained from experiments in hydrazine buffers (Figure 3); even under these conditions catalysis by the acid species (included in the dashed line) makes a significant contribution to the observed catalysis.

The rate constants for catalysis of hydrazinolysis by the acidic and basic species of a series of catalysts were

Table II. Summary of Rate Constants for Reactions of Hydrazine with Acetylimidazole Catalyzed by Acids and Bases at 25°, Ionic Strength 1.0 M

Base	pK_a[a]	k_3(B, N_2H_4, AcIm) M^{-2} sec^{-1}	k_4(BH^+, N_2H_4, AcIm), M^{-2} sec^{-1}	k_4'(B, N_2H_4, $AcImH^+$), M^{-2} sec^{-1}
Water	−1.74	0.027	2.4×10^8	6.3×10^2
Malonate monoanion (MAL)[b]	2.62		2.2×10^6	1.3×10^5
Formate (Form)	3.56[c]	*d*	1.2×10^5	6.2×10^4
Acetate (Ac)	4.59	<2.5	1.5×10^4	8.1×10^4
Malonate dianion	5.03	<4.7	5.8×10^3	1.2×10^6
N-Propargylmorpholine (PM)	5.60	<5.0	$\leq 4.4 \times 10^2$	$\leq 2.4 \times 10^4$
Trifluoroethylamine (TFE)	5.84[e]	17.2	8.7×10^2	9.0×10^4
Cacodylate (CAC)	6.15[f]	30.5	1.7×10^3	3.4×10^5
Imidazole (Im)	7.21[e]	370	273	5.9×10^5
N-Methylmorpholine (NMM)	7.83	116	≤ 3	$<2.8 \times 10^4$
2-Cyanoethylamine (CEA)	8.20	306	≤ 10	$<2.2 \times 10^5$
Hydrazine	8.25	550	64	1.48×10^6
Morpholine	8.82	305	<5	$<4.5 \times 10^6$
Triethylenediamine (Dabco)	9.22[c]	570	≤ 10	$<2.2 \times 10^6$
Hexafluoroisopropoxide anion (HFIP)	9.22[c]	724	40 ± 10	8.9×10^6
2-Methoxyethylamine (MEA)	9.72[e]	565	<10	$<6.2 \times 10^6$
3-Quinuclidinol (QDL)	10.20	540	*d*	*d*
Quinuclidine (Q)	11.55	1100 ± 200	*d*	*d*
Hydroxide ion	15.74	$<10^5$	2.7×10^{-2}	2.0×10^{10}

[a] The pK_a of the conjugate acid was determined from measurements of the pH of partially neutralized solutions or from titration curves under the conditions of the kinetic experiments, unless otherwise noted. [b] The k_3 term of 5.8×10^3 for the monoanion is assigned to general acid catalysis; the k_4 term refers to free malonic acid. [c] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 6353 (1969). [d] No detectable reaction. [e] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968). [f] J. M. Sayer, unpublished data.

obtained from the left- and right-hand ordinate intercepts of Figure 2 and similar plots and are summarized in Table II. The assignments are based on the rate law for the reaction of acetylimidazole with hydrazine given in eq 1.

$$\text{rate} = (k_1[N_2H_4] + k_2[N_2H_5^+] + k_3[N_2H_4][B] + k_4[N_2H_4][BH^+])[AcIm] \quad (1)$$

In experiments at low pH values an additional term $k_5[N_2H_4][BH^+][AcImH^+]$ was found to be significant. The values of k_5 were found to be 3.1×10^5, 4.3×10^5, and 1.2×10^7 M^{-2} sec^{-1} for acetic acid, formic acid, and the hydronium ion, respectively. This term could represent general acid catalysis of the reaction of hydrazine with acetylimidazolium ion, general base catalysis of the reaction of hydrazine monocation with acetylimidazolium ion, or general acid catalysis of the reaction of hydrazinium ion with free acetylimidazole. The k_4 term for malonic acid is kinetically ambiguous and may contain a contribution of acid catalysis by the monoanion according to this k_5 term.

No inhibition of quinuclidinol catalysis of the hydrazinolysis reaction by imidazole could be detected at concentrations up to 0.1 M at pH 9.24. Imidazole could cause inhibition of reactions that involve nucleophilic catalysis by tertiary amines to form $AcNR_3^+$ by reacting with this intermediate to regenerate starting materials.[18] However, a nucleophilic reaction of this kind should not contribute to the observed catalysis of hydrazinolysis, in any case, because it would give hydrolysis in the absence of hydrazine and, therefore, would be included in the observed catalysis of hydrolysis (Figure 1, dashed lines).

Discussion

General Base Catalysis. The Brønsted plot for general base catalysis of the reaction of hydrazine with free acetylimidazole (Figure 4) cannot be described by a single straight line nor by a series of straight lines for the different classes of catalysts that were examined. Catalysis by relatively strong bases shows only a small dependence on basicity ($\beta \lesssim 0.2$), whereas catalysis by weak bases shows a much stronger dependence ($\beta > 0.7$). A curved line is required to describe the data for catalysis by primary amines (open circles). Curvature in the oxyanion series is also supported by the absence of detectable catalysis by hydroxide ion. The upper limit of 10^5 M^{-2} sec^{-1} for the rate constant for such catalysis falls below a Brønsted line of slope 1.0 (drawn through the point for cacodylate) by a factor of 10^6 and below a line of slope 0.7 by a factor of 10^3. In the region of $\beta \lesssim 0.2$ primary and tertiary amines of the

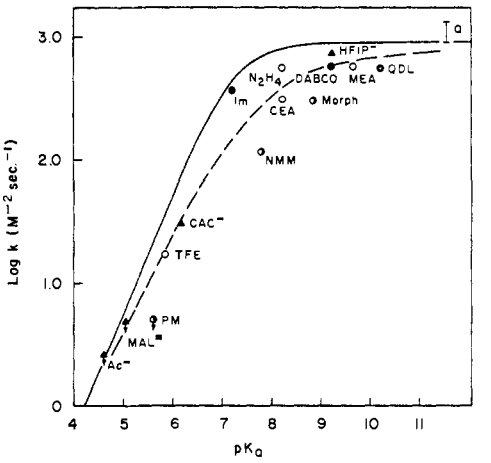


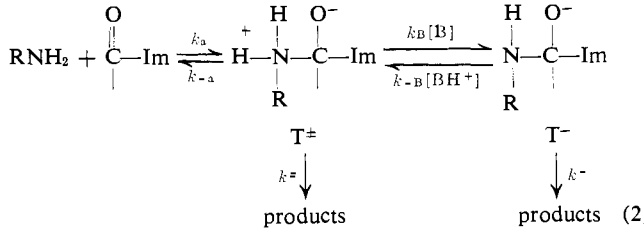
Figure 4. Brønsted plot for general base catalysis of the hydrazinolysis of acetylimidazole at 25°. Upper limits for the rate constant when no base catalysis could be detected are indicated by arrows and the abbreviations are identified in Table II. The solid line is that expected for a simple proton transfer that proceeds at a diffusion-controlled rate in the thermodynamically favorable direction and the dashed line shows the curvature actually observed for a simple proton transfer reaction.[3]

same pK have almost identical rate constants; hexafluoroisopropoxide anion has a slightly larger rate constant. Negative deviations are observed for morpholine and its derivatives, which may reflect steric and conformational requirements of these catalysts associated with preferential proton transfer to the equatorial or axial position.[21] However, statistical corrections of the rate and dissociation constants[22] bring the rate constant for morpholine itself and also those for hydrazine and triethylenediamine (Dabco) into the range observed for other amines of similar pK. Such statistical corrections do not alter the above conclusions regarding nonlinearity and limits for the Brønsted β values.[23]

Nonlinear Brønsted plots that reflect a gradual change in transition state structure may be expected for simple general base catalyzed reactions over a sufficiently wide range of variation of the pK of the catalyst and substrate.[24-26] However, the break in Figure 4 is sharper than expected or observed for reactions with a moderately large free energy of activation, including a number of simple proton abstractions from carbon acids.[3,25-27] This nonlinearity means that there is a large change in the nature of the rate-determining step over a relatively small range of catalyst basicity and is most easily explained if a transport step involving the catalyst for proton transfer becomes significant for the limiting rate constants on at least one limb of the curve of Figure 4.[3,26] The simplest interpretation is that the rate-determining step of the catalyzed aminolysis is a simple proton transfer reaction for which the limiting rate constants are in large part controlled by the rate of encounter of the proton donor and acceptor in the thermodynamically favorable direction. The solid line in Figure 4 is the theoretical curve for a rate-determining proton transfer reaction between an unstable intermediate and the catalyst that is completely diffusion controlled in the thermodynamically favorable direction and the dashed line shows the shape of the curve for the observed rates of proton transfer between ammonium ion and a series of oxyanion bases.[3] In the region in which the rate is independent of base strength such proton transfers are thought to take place at almost every encounter of the reactants, whereas in the region of strong dependence on base strength the thermodynamically favorable proton transfer in the reverse direction is encounter controlled and the rate in the forward direction is directly proportional to the equilibrium constant of the reaction, giving a slope β approaching 1.0. It is possible that the final rate-determining step in the limiting regions may be a rotation rather than a translation. In the intermediate region of curvature the experimental points fall below the theoretical curve and the proton transfer process itself, or associated processes involving the solvent, is thought to become partially rate determining.[3,26] It should be noted that experimental limitations make it difficult to measure rate constants in the limiting regions of the curve, as is also the case for simple proton transfer reactions,[3] so that the observed rate constants generally fall in the intermediate region of curvature and only approach the limiting lines of slope 0 and 1.0 that are expected for fully rate-controlling transport processes in the two directions. The position of the break in the Brønsted plot is defined by the intersection of the limiting lines of slope 0 and 1.0 and is expected to be near the point at which the equilibrium constant for the proton transfer is 1.0 ($\Delta pK = 0$).

The greater sensitivity of the catalytic constants to base strength for weak than for strong bases means that the catalyst resembles its conjugate acid more closely for the weak bases, with a larger amount of charge development and proton transfer in the transition state. It does not seem probable that a simple solvation or hydrogen-bonding mechanism of catalysis, in which the proton is in its most stable position in the transition state, would give this result. If the proton were in the stable potential well of a hydrogen bond it would be expected to be closer to the stronger bases in the transition state, the opposite of the observed behavior.

The simplest mechanism for the catalyzed reaction is shown in eq 2. According to this mechanism the



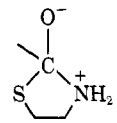
(2)

extremely unstable dipolar tetrahedral addition intermediate $T^{\pm}$ reverts to starting materials by expulsion of the attacking amine (k_{-a}) unless it is trapped by an encounter with a base that results in the removal of a proton to form the anionic intermediate T^{-}, which rapidly breaks down to products. The strategy of this catalysis is similar to that of the previously described trapping of a dipolar adduct in thiol ester aminolysis by protonation of the oxygen anion[5] and the base-catalyzed deprotonation of the dipolar adduct initially formed in the addition of 2-methylthiosemicarbazide to p-chlorobenzaldehyde.[8]

In order that the k_B step of eq 2 be rate determining, it is necessary that $k_{-a} > k_B[B]$. This means that k_{-a} must be at least 10^8–10^9 sec^{-1}, since k_B is presumably in the range 10^9–10^{10} M^{-1} sec^{-1} for strong bases and no nonlinearity suggestive of a change in rate-determining step was observed in the buffer plots up to 0.1 M free

(21) J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967).
(22) R. P. Bell and P. G. Evans, *Proc. Roy. Soc. (London), Ser. A*, **291**, 297 (1966).
(23) A completely diffusion-controlled reaction should not require a statistical correction of the rate constant in the thermodynamically favored direction, but should require it in the reverse direction for which the rate is determined by the overall equilibrium constant as well as the diffusion rate. However, the rate constants for proton transfer involving different structural types of proton donors and acceptors suggest that some encounters of improperly oriented reactants do not lead to reaction, so that these reactions may not be completely diffusion controlled and a statistical or other probability factor correction may be justified (E. Grunwald, *Progr. Phys. Org. Chem.*, **3**, 317 (1965); ref 3). In the absence of more complete information, a claim for nonlinearity in a Brønsted plot associated with diffusion-controlled proton transfer should be consistent with the data for structurally related catalysts both with and without statistical corrections.
(24) J. N. Brønsted and K. Pedersen, *Z. Phys. Chem.*, **108**, 185 (1924).
(25) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 155–182.
(26) A. O. Cohen and R. A. Marcus, *J. Phys. Chem.*, **72**, 4249 (1968).
(27) M. L. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys.Chem.*, **74**, 380 (1970); M. M. Kreevoy and D. E. Konasewich, *Advan. Chem. Phys.*, **21**, 243 (1971); A. Streitwieser, Jr., W. B. Hollyhead, A. H. Pudjaatmaka, P. H. Owens, T. L. Kruger, P. A. Rubenstein, R. A. MacQuarrie, M. L. Brokaw, W. K. C. Chu, and H. M. Niemeyer, *J. Amer. Chem. Soc.*, **93**, 5088 (1971); A. Streitwieser, Jr., W. B. Hollyhead, G. Sonnichsen, A. H. Pudjaatmaka, C. J. Chang, and T. L. Kruger, *ibid.*, **93**, 5096 (1971), and references therein.

base. A value of k_{-a} in this range is not unreasonable, since the rate constant for the expulsion of a more basic amine from the intermediate **1** that is formed in

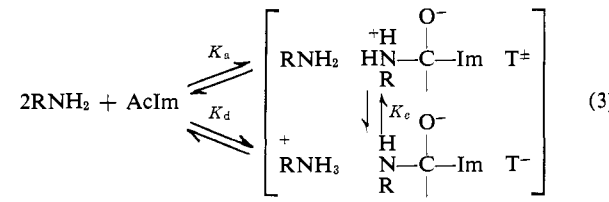


1

the intramolecular aminolysis of a thiol ester has been estimated[5] to be 6.6×10^8 sec^{-1} and electron donation by resonance from the imidazole group should provide an additional driving force for amine expulsion. The equilibrium constant K_a for the formation of T^- from reactants is approximately 10^{-6} M^{-1} if the rate-determining step has a rate constant k_B for a diffusion-controlled reaction of 10^9 M^{-1} sec^{-1} and $k_{obsd} = K_a k_B = 10^3$ M^{-2} sec^{-1}. In the absence of catalyst the intermediate $T^{\pm}$ can decompose directly ($k^{\pm}$) through a transition state that very closely resembles the unstable immediate products imidazole anion and N-protonated acetamide.[19,28] The rate constant for this "water" reaction is $k_w = K_a k^{\pm} = 1.5$ M^{-1} sec^{-1}, so that the rate constant $k^{\pm}$ for the expulsion of imidazole anion from $T^{\pm}$ must be $\geq 10^6$ sec^{-1}. This rate constant k_w can be converted into a third-order rate constant for base or acid catalysis by water by dividing by 55 M. The resulting rate constant shows a positive deviation from the Brønsted plots for both general base and general acid catalysis, as would be expected if it occurred through a different mechanism, without catalysis.

A stepwise mechanism of catalysis such as that shown in eq 2 is in accord with a recently proposed *rule* which states that concerted catalysis of reactions with an appreciable activation energy can occur only when a large change in the pK of the proton donor site during the course of the reaction converts an unfavorable to a favorable proton transfer; *i.e.*, when the pK of the base catalyst is intermediate between the pK values of the proton donor sites in the starting material and product.[29] The pK_a of the intermediate $T^{\pm}$ is not very different from that of the conjugate acid of the attacking amine,[30] so that the requirements of the rule are not met for many of the catalysts examined and a stepwise mechanism of catalysis is expected. So long as the intermediate has an appreciable lifetime, the encounter of $T^{\pm}$ with a relatively strong base will result in extremely rapid proton transfer ($<10^{-11}$ sec) to give T^-, which will then break down to products in a subsequent step(s). The proton removal serves to (a) prevent the expulsion of hydrazine from the intermediate to regenerate starting materials, (b) liberate the lone-pair electrons on the nitrogen atom to help expel the leaving group, and (c) avoid the formation of the unstable N-protonated acetamide product $CH_3CONH_2R^+$ (pK $\simeq -10$)[33] and the unstable transition state leading to its formation that would be required in the absence of proton removal.

The rate constants for the general base catalyzed aminolysis of acetylimidazole by a series of amines, with a second molecule of the same amine as the catalyst, are directly proportional to amine basicity with a value of $\beta_{nuc} = 1.0$.[18,19] This means that the reaction behaves as if approximately one positive charge has been developed in the transition state that is distributed between the nucleophilic and catalyzing amine molecules. This β value is consistent with a mechanism in which the bond between the attacking amine and the acyl carbon atom is fully formed and the proton is on either the attacking or the catalyzing amine in the transition state (eq 3), as expected for the



(3)

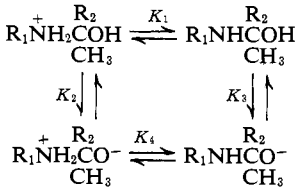
mechanism of eq 2. The equilibrium constant for the formation of $T^{\pm}$ will obviously be increased by an increase in amine basicity; in the case in which the proton is on the catalyzing amine the equilibrium formation of T^- will be favored by proton donation to a more basic catalyzing amine. The β values of 0.9 for the general base catalyzed aminolysis of methyl formate[34] and phenyl acetate[35] are consistent with the same interpretation.

Finally, a mechanism of the kind shown in eq 2 is consistent with the properties of an intramolecularly catalyzed aminolysis of acetylimidazole by ethylenediamine and related compounds.[19] Although diamines show a large rate acceleration relative to the uncatalyzed reaction of primary amines, this rate acceleration is largely a consequence of the large sensitivity of the reaction to general base catalysis and the "effective concentration" of the catalyzing amine group in ethylenediamine is low, on the order of 1 M. This result and the very small sensitivity of the catalyzed reaction to changes in structure of the diamine suggest that the entropic requirements of the transition state are very small; *i.e.* the reaction can occur with a large number of different relative positions of the catalyst

(28) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 3263 (1972).

(29) W. P. Jencks, *ibid.*, **94**, 4731 (1972).

(30) The pK_a of $T^{\pm}$ was estimated as follows. For $R_1 = CH_3$ and $R_2 = H$, pK_3 was found to be 15.1 by $\rho_I\sigma_I$ correlations, based on the pK



of ethanol and aldehyde hydrates[31] and pK_2 to be 10.4 ± 0.1 according to the treatment of Hine, *et al.*[32] Thus, the electrostatic effect of RNH_2^+ on the ionization of the hydroxyl group is 4.7 pK units and, since pK_3 − pK_2 = pK_4 − pK_1, the electrostatic effect of O^- must be to increase the pK of the ammonium group by 4.7 units. Again following the procedure of Hine, *et al.*,[32] and assuming that for imidazole $\sigma_I = 0.15 \pm 0.05$ the value of pK_4 is approximately 10 ± 0.5 for $R_1 = NH_2$ and R_2 = imidazole. The other ionization constants for $T^{\pm}$ are estimated to be pK_1 = 5.1 ± 0.5, pK_2 = 8.8 ± 0.5, and pK_3 = 13.5 ± 0.5.

(31) J. Hine and G. F. Koser, *J. Org. Chem.*, **36**, 1348 (1971); S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971); H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957). A mean value of $\rho_I = 8.4$ was used for the ionization constants of both alcohols and ammonium ions (J. Fox and M. I. Page, unpublished): C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 334 (1964).

(32) (a) J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970); (b) J. Hine, J. C. Craig, Jr., J. G. Underwood II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

(33) A. R. Fersht, *ibid.*, **93**, 3504 (1971).

(34) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

(35) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

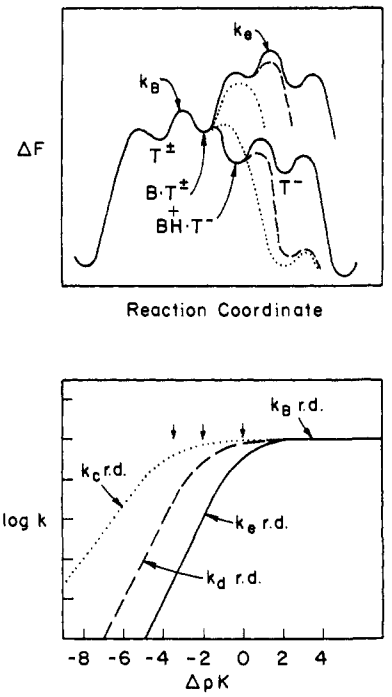
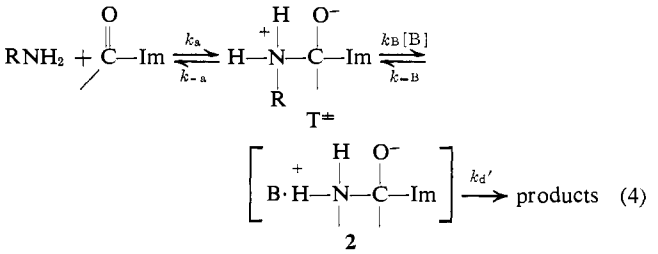


Figure 5. Diagrams to show the expected behavior of Brønsted plots for the reaction mechanisms of eq 4 and 5: solid line, simple proton transfer mechanism with diffusion-controlled rates in the favorable direction; dashed line, rate-determining breakdown of $BH^+{\cdot}T^-$ with weak bases; $k_d > k_e$; dotted line, concerted reaction mechanism when T^- does not have a significant lifetime. In the upper figure the lower lines are for strong bases and the upper lines for weak bases. In all cases the encounter of B and $T^{\pm}$ is rate determining with strong bases.

and substrate, as expected for a reaction in which diffusion or rotation of the catalyzing group is largely or entirely rate determining.

There are several modifications of this mechanism that should be considered for this (and other) reactions.

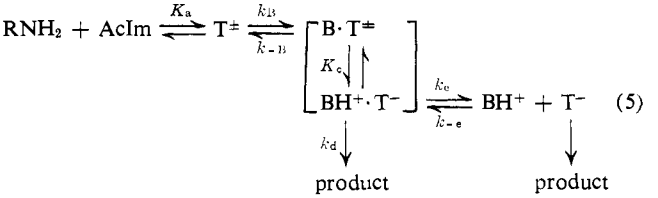
(1) Mechanisms of the kind shown in eq 2 are only possible for a limited range of lifetimes of the tetrahedral addition intermediates $T^{\pm}$ and T^-—if the intermediates are relatively stable they will be at equilibrium with respect to proton transfer and no catalysis will be observed, and if they are too unstable they cannot exist as discrete intermediates. The lifetime of the intermediate T^- of eq 2 is expected to be extremely short. The rate constant for expulsion of the amino group ($pK = 9.1$) from **1** has been estimated[5] to be 6.6×10^8 sec^{-1}. The imidazole anion of T^- is a poorer leaving group (pK_a(imidazole) = 14.2[11]), but there is a very large driving force for its expulsion that arises from the lone-pair electrons on the hydrazine nitrogen atom, as well as from those on the oxygen anion, and from the developing resonance of the amide product, amounting to about 17 kcal of stabilization energy.[33] The rate constant for the expulsion of imidazole anion from the intermediate $T^{\pm}$, which lacks this driving force from the nitrogen lone-pair electrons and developing resonance stabilization, has been estimated to be $\geq 10^6$ sec^{-1}. If the lifetime of T^- is less than about 10^{-13} sec it cannot exist as an intermediate at all, and even with a somewhat longer lifetime it will break down before diffusion away of the catalyst. Under these circumstances the mechanism of eq 2 must be modified to that of eq 4. The diffusion controlled encounter of $T^{\pm}$ with a base will



(4)

result directly in proton transfer and product formation if the pK of the catalyst is equal to or even somewhat smaller than that of $T^{\pm}$. This would give rise to the pK-independent portion of the Brønsted plot in Figure 4. However, with sufficiently weak bases, for which the proton transfer is thermodynamically unfavorable, reaction will not occur on every encounter. If T^- has a small but finite lifetime, the rate-determining step will then be its breakdown within the encounter complex before the dissociation of BH^+ and T^- can take place. If T^- has too short a lifetime to exist as an intermediate, the breakdown catalyzed by weak bases will occur through a "concerted" process with an appreciable activation energy, in which there has been considerable movement of the proton toward the catalyst in the transition state. In either case, this change in rate-determining step results in a downward curvature of the Brønsted plot to give $\beta > 0$ for weak bases, as is observed. This mechanism is analogous to that suggested previously for the breakdown of hemithioacetals formed from acidic thiols.[36]

When the intermediate T^- has a significant lifetime, the reaction may be described by eq 5 and the steady-



(5)

state rate eq 6, in which $\alpha = [BH^+{\cdot}T^-]/[B{\cdot}T^{\pm} + BH^+{\cdot}T^-]$. For the mechanism of eq 2 the break in the Brønsted plot will occur close to the pK_a of the intermediate $T^{\pm}$ when $k_e > k_d$ and $\Delta pK = 0$, as for simple proton transfer reactions;[3] *i.e.*, $K_c \approx 1.0$, $\alpha \approx 0.5$, and $k_e \approx k_{-B}$. If, however, $k_d > k_e$ so that breakdown occurs before dissociation of the complex the change in rate-determining step that causes the break will occur at a lower pK value, by an amount $\approx \log k_d/k_{-B}$ when $K_c = 1.0$. If T^- has no finite existence at all, the break will occur at a still lower pK. The break in the Brønsted plot of Figure 4 occurs at about $pK = 7.2$, whereas the pK_a of $T^{\pm}$ is estimated to be 10 ± 0.5.[30] This difference provides suggestive evidence in favor of the modified mechanism, but the pK estimates are too uncertain to make the evidence conclusive.

$$\text{rate} = \frac{k_B K_a (k_d + k_e)\alpha}{k_{-B}(1 - \alpha) + (k_d + k_e)\alpha}[RNH_2][AcIm][B] \quad (6)$$

The relationship between these different situations is shown in the reaction coordinate diagram and Brønsted plots of Figure 5. For strong bases the rate-deter-

(36) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, 91, 6758 (1969).

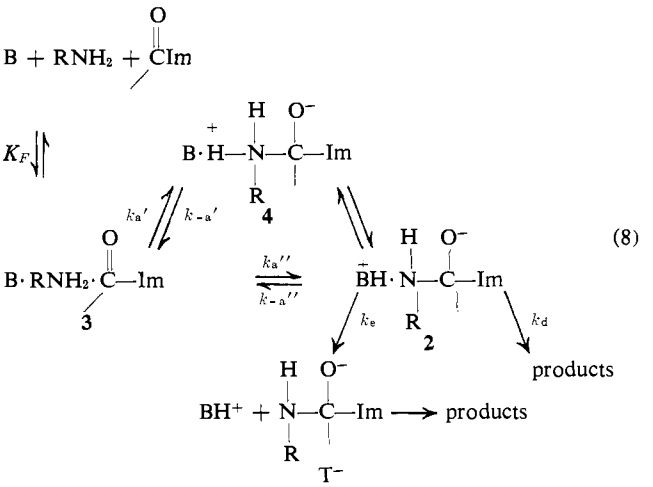
mining step is the diffusion-controlled encounter of B and $T^{\pm}$ and the observed catalytic constant is independent of the pK of the catalyst for all three cases. For the simple proton transfer mechanism of eq 2 (solid lines) the break in the Brønsted plot, determined by the intersection of the extrapolated Brønsted lines of slope 0 and 1.0, occurs near $\Delta pK = 0$ and the rate-determining step for weak bases may be regarded as the separation of BH^+ and T^-. For the case in which $k_d > k_e$ (dashed lines) the break occurs at a lower pK value and the rate-determining step with weak bases is the expulsion of imidazole anion from T^- within the encounter complex. If T^- has no significant lifetime (dotted lines) the break will occur at a still lower pK value and the rate-determining step (k_c) for weak bases is the concerted breakdown of $T^{\pm}$ catalyzed by B, with a value of $\beta < 1.0$.

(2) The rate-determining step of the reaction could be the breakdown of T^- to products as a result of the diffusion-controlled protonation of T^- by BH^+ on oxygen or on the distal nitrogen atom of imidazole (eq 7). However, since O^- is expected to be more basic

$$T^{\pm} \underset{k_{-B}[BH^+]}{\overset{k_B[B]}{\rightleftharpoons}} T^- \underset{k_{-B}'[B]}{\overset{k_B'[BH^+]}{\rightleftharpoons}} \text{products} \qquad (7)$$

than the hydrazine nitrogen atom[30] and has an added electrostatic advantage for reaction with BH^+, it is probable that $k_B' \geq k_{-B}$, so that k_B' cannot be rate determining. Trapping of T^- by protonation on the imidazole nitrogen atom will be slower than by protonation of the more basic oxygen anion when BH^+ is of intermediate or low acidity. When BH^+ is a relatively strong acid, protonation of T^- will occur on the imidazole and hydrazine nitrogen atoms at comparable rates, so that in the forward reaction proton removal from $T^{\pm}$ must be at least partly rate determining. Furthermore, the mechanism of intramolecular catalysis in the ethylenediamine reaction almost certainly cannot involve proton transfer to the leaving imidazole because of the small size of the diamine.[19] Finally, these mechanisms require addition intermediates that have a short lifetime at best to exist long enough to permit two sequential proton transfer steps, rather than the single proton transfer required for the previously described mechanisms. For these reasons and in view of the expected rapid breakdown of T^- without catalysis, the mechanism of eq 7 is less probable than those of eq 2 or 4.

(3) If the rate of diffusion apart of the complex 4 (eq 8) is slower than the breakdown of $T^{\pm}$ to starting materials, k_{-a}', the lowest energy path for the breakdown of **4** will give the complex **3** as the immediate product. Conversely, as a consequence of the principle of microscopic reversibility, the lowest energy path for the formation of **4** will be through a preassociation[7] or ("spectator"[9]) mechanism in which the catalyst forms the loose complex **3** with the reactants before $T^{\pm}$ is formed (eq 8). In this class of mechanism the catalyst does not directly assist the formation of T^+, but must be present during this step in order to make further reaction possible. For strong bases the rate-determining step, k_a', is the formation of the N–C bond within the encounter complex **3** and $\beta = 0$. If the lifetime of $T^{\pm}$ is still shorter, so that it cannot exist an as intermediate at all, the complex **2** may be



(8)

formed directly in a concerted reaction (k_a''). In this case the value of β will be >0 for the strongest bases, but unless B is a very strong base (BH^+ is a weak acid) the breakdown of **2** to reactants *via* k_{-a}'' will be fast and the rate-determining step will be k_d or k_e. In all cases sufficiently weak bases will give a value of $\beta = 1.0$ as k_d or k_e becomes rate determining. These situations are the converse of those described in (1) above and the shapes of the reaction coordinate diagrams for the different cases will be similar to those shown in the upper part of Figure 5, but in the reverse direction. Just as the modified mechanism 1 predicts a break in the Brønsted plot at a pK below the pK of $T^{\pm}$, mechanism 3 predicts a break at a pK above that expected for $T^{\pm}$. This is in the opposite direction from that observed experimentally, so that the modified mechanism 1 is preferred. Since the modifications depend on the lifetimes of the intermediates $T^{\pm}$ and T^-, this suggests that $T^{\pm}$ may have a longer lifetime than T^-, which is not unreasonable in view of the additional driving force for the breakdown of T^- from the lone-pair electrons on the hydrazine nitrogen atom and the developing resonance stabilization of the amide.

(4) Kershner and Schowen have made the important suggestion that a value of α or $\beta \neq 0$ or 1.0 could be observed with rate-determining proton transfer between two electronegative atoms if the overall reaction involves a sequence of two such proton transfers without diffusion away of the catalyst.[9] In principle, a mechanism of this kind might give rise to a change in rate-determining step, from one proton transfer to the other, with changing basicity of the catalyst if the value of β for one step were quite different from the value of $1 - \alpha$ for the other step. We believe that this situation is unlikely for the acetylimidazole reaction, however, because even if two sequential proton transfer steps were fast relative to diffusion apart of the intermediate and one catalyst, it is unlikely that this would hold over a large range of pK for a series of catalysts if the proton transfer steps show a large and the diffusion step a small dependence on pK. Furthermore, there does not appear to be a requirement on chemical grounds for protonation of the carbonyl oxygen atom in the course of the reaction, once a proton has been removed from the attacking nitrogen atom.

The General Acid Catalyzed Reaction. The k_1 term for general acid catalysis of the hydrazinolysis of

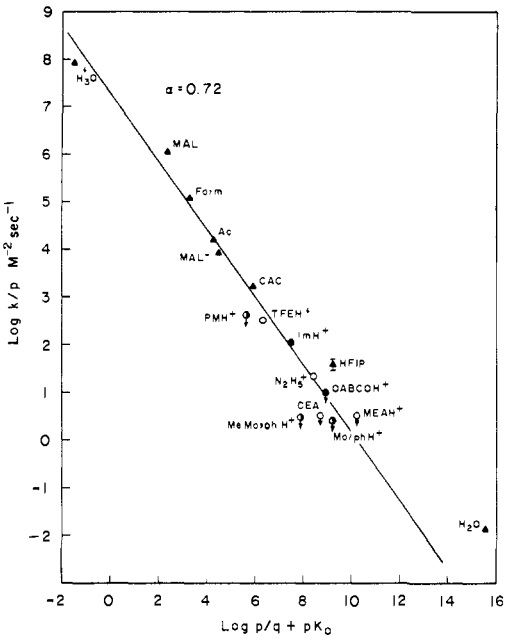
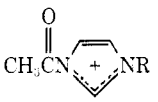


Figure 6. Brønsted plot for general acid catalysis of the hydrazinolysis of acetylimidazole at 25°. Upper limits where no catalytic rate constant could be assigned are indicated by arrows and the abbreviations are identified in Table II.

acetylimidazole can also be interpreted as the kinetically equivalent general base catalyzed reaction of hydrazine with protonated acetylimidazole, as shown in eq 9;

$$k_4[N_2H_4][BH^+][AcIm] = k_4'[N_2H_4][B][AcImH^+] \quad (9)$$

the only requirement from the kinetics is that the transition state contain the elements of acetylimidazole, hydrazine, the catalyst for proton transfer, and a proton. The values of k_4' are also given in Table II. The use of *N*-methylacetylimidazolium ion (**4**, R = CH_3) as a model for protonated acetylimidazole (**4**, R = H) has provided evidence that both of these mechanisms are significant for the catalysis of acetylimidazole aminolysis, depending on the basicity of the attacking amine.[18] The fact that catalysis according to the k_4' term is observed for the reactions of trifluoroethylamine and methoxyamine with *N*-methylacetylimidazolium ion shows that **5** is a satisfactory model for the reaction



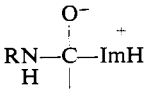
5

of acetylimidazole with amines of low basicity and that the catalysis in the corresponding imidazole reaction proceeds through acetylimidazolium ion according to the k_4' term of eq 9. However, no such catalysis is detectable for the reactions of ethylamine and ammonia with *N*-methylimidazolium ion (**5**, R = CH_3). This suggests that the observed general acid catalysis of the reaction of acetylimidazole with strongly basic amines involves proton donation from the acidic form of the catalyst, according to the k_4 term of eq 9, which is not possible for *N*-methylacetylimidazolium ion. Hydrazine is of intermediate basicity and might be expected to react by either mechanism.

The Brønsted plot for general acid catalysis of the hydrazinolysis of acetylimidazole, based on statistically corrected[22] rate and ionization constants, is shown in Figure 6. In contrast to the general base catalyzed reaction (Figure 4), there is no evidence for a break in the correlation and the experimental points are consistent with a straight line of slope $\alpha = 0.72$. The complementary Brønsted slope β is 0.28 for general base catalysis, if the rate constants are expressed in the kinetically equivalent form k_4'. Malonic acid shows a small positive deviation from the line that may represent a contribution of the k_5 term to the observed catalytic constant and negative deviations are observed for catalysts in the morpholine series. The point for the hydronium ion is close to the line of Figure 6 and that for the "water" reaction exhibits a positive deviation.

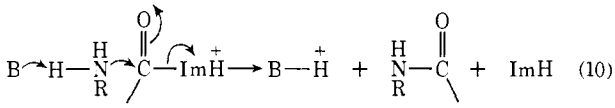
The nature of this Brønsted plot and the absolute values of the rate constants require that the general acid catalyzed reaction proceed through a mechanism that is fundamentally different from that of the general base catalyzed reaction. The nonlinear Bronsted plot for the latter reaction suggests a stepwise mechanism in which the proton is closely associated with either the catalyst or substrate in the transition state. The absence of evidence for a break and the fact that the Bronsted coefficient has a value intermediate between 0 and 1.0 in a region well removed from the expected pK value of any intermediate suggest that the acid-catalyzed reaction proceeds by a mechanism that is in some sense "concerted,"[12] with the proton at an intermediate position between the catalyst and substrate in the transition state. Furthermore, the absolute values of the rate constants k_4 for several catalysts are larger than those for general base catalysis, k_3, by several orders of magnitude (Table II). If the general base catalyzed reaction k_3 involves a diffusion-controlled reaction of the catalyst with an intermediate, the larger rate constant for the general acid catalyzed reaction excludes a mechanism that involves proton transfer to the same intermediate.

The simplest and most attractive mechanism that is consistent with the data involves acetylimidazolium ion as the acyl reactant and catalysis through a more or less concerted proton removal from the attacking amine by a general base according to the k_4' mechanism of eq 9. It has been suggested above that the tetrahedral intermediate T^- (eq 2), with a leaving group of pK = 14, has an extremely short lifetime if it exists at all. The intermediate **6** has a similar structure, with a strong



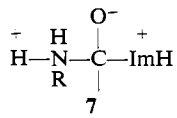
6

driving force for breakdown provided by the electron pairs on the oxyanion and nitrogen atoms and the developing resonance of the amide product, but it has a much better leaving group of pK = 7. We suggest that the structure **6** may be too unstable to exist as an intermediate, so that the reaction cannot proceed through this intermediate by a stepwise mechanism. The reaction may then proceed directly from acetylimidazolium ion to products without intermediates or major relocation of the reacting atoms during the entire process (eq 10). This mechanism is consistent with the previously demonstrated general base catalysis of the reactions of *N*-methylacetylimidazolium ion with



(10)

amines of relatively low basicity[18] and with the evidence that the aminolysis of more stable acyl compounds may be catalyzed by proton removal from the attacking amine.[29,34] If the addition compound **7** has sufficient



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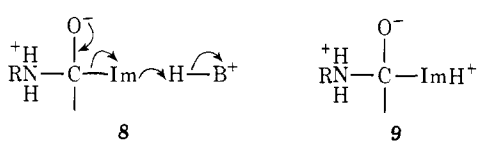
stability, it might exist as a transient intermediate along the reaction path. However, its reactions with bases that are strong enough to give an encounter-controlled proton transfer and breakdown should be independent of the pK of the base. Such a change from a concerted to an encounter-controlled rate-determining step should give rise to curvature in the Brønsted plot, for which there is no indication.

Again, the driving force for catalysis in this reaction arises from the change in the acidity of the attacking amine, which is converted during the course of the reaction from an extremely weak acid (p$K_a \simeq 30$) to the N-protonated amide $CH_3CONH_2R^+$ with a pK of approximately -10,[33] if a proton is not removed at some point. A concerted mechanism of general base catalysis for this reaction path is consistent with the above-mentioned rule.[29] Concerted catalysis by a base with a basicity similar to that of the attacking amine is not expected for acyl aminolysis reactions that proceed through stable addition intermediates, because the pK of the intermediate is not very different from that of the conjugate acid of the catalyzing amine, so that there is no large driving force for the proton transfer. However, if such an addition intermediate does not exist, a concerted mechanism is made possible by this large change in the pK of the attacking amine in proceeding from starting materials to the initial product.

Several alternative mechanisms for true general acid catalysis of the reaction according to the k_4 term of eq 9 can be excluded on the following grounds. The mechanism cannot involve concerted catalysis of the breakdown of the tetrahedral intermediate T± **8** because, as long as the protonated intermediate **9** has a



8 **9**

finite lifetime, an encounter of T± with a relatively strong general acid will simply result in fast proton transfer to give **9** which will break down in a subsequent step, in accord with the above-mentioned rule. The same argument may be used to exclude a concerted mechanism for breakdown of an uncharged tetrahedral intermediate. If the intermediate **9** does not have an appreciable lifetime, breakdown will occur at every encounter of T± with a relatively strong acid. The value of α will then be zero, which is inconsistent with the experimental data (Figure 6). Furthermore, it has already been pointed out that if the general base catalyzed reaction involves a diffusion-limited reaction with the intermediate T±, the faster general acid catalyzed reaction cannot involve the same intermediate.[37] Catalysis cannot involve the protonation of imidazole anion in an ion pair $CH_3CONH_2^+R \cdot Im^-$, because this would also give an α value of zero, and it cannot involve the rate-determining protonation of acetylimidazole itself, because the acetylimidazolium ion (pK = 3.86) is a compound with a known lifetime and reactivity that certainly does not react with a nucleophile every time it is formed. It cannot involve concerted catalysis by protonation of the acetylimidazole nitrogen, because a significant fraction of acetylimidazole would already exist in the protonated form at equilibrium in the presence of the stronger acid catalysts, and it cannot involve concerted base catalysis of the attack of hydrazine on acetylimidazolium ion to form a tetrahedral addition intermediate, because proton transfer from the intermediate T± to the base is not thermodynamically favorable for most of the catalysts examined; these two points are in accord with the above-mentioned rule.

Mechanisms that involve concerted catalysis of proton transfer to or from the carbonyl oxygen atom cannot be rigorously excluded, but are less likely and less attractive for the following reasons. (a) If the general base catalyzed reaction proceeds by a stepwise mechanism involving the catalyst and T±, it is not clear why the corresponding acid-catalyzed reaction should not also proceed by a stepwise mechanism. There is not a large difference between the pK values of the nitrogen and oxygen atoms of the intermediate[30,32] and the small ΔpK between the least acidic catalysts examined and this oxygen atom means that there will be little free-energy advantage from such catalysis, even if it does not violate the above-mentioned rule. There is evidence that catalysis involving proton transfer to the carbonyl oxygen atom in other acyl aminolysis reactions proceeds by a stepwise mechanism.[5,6] (b) Such mechanisms require the occurrence of several sequential proton transfers to or from unstable tetrahedral addition intermediates during the course of the reaction. There is some question whether these intermediates have sufficient stability to exist at all and it is still less probable that they would have a lifetime sufficient to permit several proton transfers. (c) There is considerable evidence, described here and elsewhere,[17,18] that reactions of acetylimidazole are generally aided by proton removal from the attacking amine and protonation of the leaving imidazole.

Comparison with Other Reactions. Evidence has been reported previously that indicates that the reactions of thiols with acetylimidazole proceed through pathways that are not at equilibrium with respect to proton transfer.[7] The reaction of thiol anion with acetylimidazolium ion appears to proceed directly, without evidence for intermediates or catalysis. This is in accord with the proposed mechanism for the hydrazine reaction with acetylimidazolium ion, since there is no proton to remove by general base catalysis on the attacking thiol anion. The reaction of thiol anion with free acetylimidazole, with its poorer leaving

(37) This type of mechanism is not ruled out for general acid catalyzed reactions of basic amines, such as ethylamine and ammonia, for which N-methylacetylimidazolium ion is not a model and which have not been shown to exhibit linear Brønsted plots.[18]

group, proceeds through an intermediate and is subject to catalysis, which has been interpreted as proton donation to the leaving imidazole. Again, the absence of a proton on the thiol anion or the sulfur atom in the addition intermediate precludes general base catalysis of the kind suggested here for aminolysis reactions and catalysis of imidazole expulsion is brought about by protonation of the leaving group.

The thiol reaction undergoes a change in rate-determining step at high catalyst concentrations. This is interpreted as a change to rate-determining attack of thiol anion, which occurs as a consequence of the relatively high affinity (small k_{-a}, eq 2) of sulfur toward carbonyl carbon; no such change in rate-determining step is seen in aminolysis, presumably because of the rapid rate of expulsion of protonated amine. The rate constant k_a for the attack of mercaptoethanol anion on acetylimidazole is 2.3×10^3 M^{-1} sec^{-1}, whereas the rate constant for the uncatalyzed reaction of hydrazine with acetylimidazole is only 1.5 M^{-1} sec^{-1}; the corresponding ratio $k_{RS^-}/k_{N_2H_4}$ is 1.8 for the reactions of these compounds with *p*-nitrophenyl acetate.[13] This suggests that the rate constant k_a for the attack of hydrazine on acetylimidazole is >1.5 and is consistent with an estimated value of $k_a \geq 100$ M^{-1} sec^{-1}, assuming the previously noted values of $K_a = k_a/k_{-a} = 10^{-6}$ M^{-1} and $k_{-a} \geq 10^8$ sec^{-1}. In other words, this comparison suggests that the attack of hydrazine on acetylimidazole to form $T^{\pm}$ is sufficiently fast that it does not become rate determining, in agreement with the proposed mechanisms.

In summary, the available data for acyl aminolysis reactions are consistent with a sequence of mechanisms that are determined by the nature of the leaving group: (a) for methyl formate, with a relatively poor leaving group, there is a stepwise mechanism of catalysis but the free intermediate has a sufficient lifetime that its breakdown may become rate determining at low pH values;[29,34] (b) for somewhat better leaving groups (*e.g.*, free acetylimidazole) there is a stepwise mechanism of catalysis and an intermediate, but the lifetime of the intermediate is so short that the rates of proton transfer steps are always kinetically significant for the catalyzed reaction pathway. Breakdown of the immediate product of the proton transfer step, T^-, can occur either before or after diffusion away of BH^-, depending on its lifetime; (c) for still better leaving groups (*e.g.*, acetylimidazolium ion) the "intermediate" is too unstable to exist and the reaction must proceed through a concerted rather than a stepwise mechanism. It may be significant that many of the cases in which addition intermediates have been demonstrated, kinetically or otherwise, involve acyl-activated compounds with relatively poor leaving groups;[2] in other cases the reason that such intermediates have not been detected may be simply that they do not exist.

Synthesis and Thermal Rearrangements of Spiro[2.3]hexadiene and Spiro[2.3]hex-4-ene Derivatives

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Abstract: The reaction of *n*-butyllithium and hexachlorocyclobutene in the presence of alkenes produced 4,5,6,6-tetrachlorospiro[2.3]hex-4-ene derivatives; with 2-butyne in place of the alkenes, the corresponding spiro[2.3]-hexadiene was obtained in 40% yield. With *n*-butyllithium and 3-*H*-pentachlorocyclobutene, reaction occurs predominately by α dechlorination and, in the presence of alkenes, leads to 4,5,6-trichlorospiro[2.3]hex-4-enes. The latter compounds were also obtained in a more efficient way, by controlled potential electroreduction of the 4,5,6,6-tetrachlorospiro[2.3]hex-4-enes and the 4,5,6,6-tetrachlorospiro[2.3]hexadiene. The formation of spirocycles in these reactions is in contrast to earlier reports where tetrachlorocyclobutadiene was postulated as intermediate in related reactions. The spirocycles are generally stable toward isomerization at ambient temperature but rearranged at elevated temperatures (265–450° in a flow system, 60° and above in solution). The spiro[2.3]-hexadienes produce labile products which are tentatively identified as allylidenecyclopropenes, while the spiro[2.3]-hex-4-enes undergo ring opening to allylidenecyclopropanes, which rearrange further to derivatives of 3-methylene-cyclopentene. In certain cases, the latter products spontaneously lose hydrogen chloride to afford a series of fulvenes.

Spirocyclic molecules consist of two perpendicular rings joined by a common carbon atom of tetrahedral geometry. This special geometry has provoked detailed theoretical studies of unique π-electron delocalization (spiroconjugation,[1] spiroaromaticity[2]) and provides an array of molecular rearrangements, especially in highly strained or highly unsaturated spirocycles. In this paper we report the synthesis of the first unsaturated representatives of the spiro[2.3]hexane ring system (*e.g.*, **1**–**3**) and the series of molecular rearrangements which occur at elevated temperatures.[3]

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