droxyl group of the phthalimide reduces the dependence of the observed equilibrium constants on acidity. Although the spectrophotometric evidence suggests that the phthalimide does not undergo protonation on a carbonyl group, direct physical measurements indicate that simple alcohols are partially protonated in the range of acid strengths examined; in more dilute acid solutions there is a significant decrease in the activity coefficient of alcohols, as measured by distribution techniques for example, presumably because the alcohol is involved in solvation of the proton.[48-50] The degree of alcohol protonation shows a relatively shallow dependence on acid strength so that the phthalimide is expected to undergo only a small increase in degree of protonation in the range 8–10 M perchloric acid, from 0.30 to 0.49 by analogy with the protonation of ethanol.[49] Thus, dehydration to the phthalimidium ion results in the uptake of less than 1.0 mol of acid and curvature in the H_0 plots as a consequence of this degree of ionization would be difficult to detect over the range of acid concentrations examined.[51]

The *rate of the reverse, ring closure reaction* shows a much smaller dependence on acidity, with a slope of log k_r against $-H_0$ of approximately 0.11 (Figure 8); a plot of log k against log [$HClO_4$] in the range 8–10 M has a slope of approximately 2.7. A plot of (log k_r + H_0) against (H_0 + log H^+) gives a slope of $\varphi = 0.91$. Even allowing for partial protonation of the alcohol, this dependence on H_0 is much smaller than that for butyrolactone formation[31] or the dehydration of alcohols to carbonium ions,[52] which follow H_0; however, it is similar to that for amide hydrolysis.[33,39,40,53] Evidently, the intramolecular attack of the hydroxyl group of an alcohol is not grossly different from the intermolecular attack of the hydroxyl group of water on an amide; in both cases the activity of the attacking hydroxyl group is decreased by solvation and protonation, and additional water molecules are required for proton transfer and solvation of the transition state. A strongly hydrated transition state with the characteristics of **4** for the ring closure reaction is consistent with the results; similar transition states containing a total of three water molecules have been suggested for amide hydrolysis from the dependence on water activity of the rate of reaction of the protonated amide.[54]

Acknowledgment. We are grateful to Professor J. Bunnett for his advice on the utilization of the φ function.

(48) R. E. Weston, Jr., S. Ehrenson, and K. Heinzinger, *J. Amer. Chem. Soc.*, **89**, 481 (1967); E. M. Arnett, R. P. Quirk, and J. J. Burke, *ibid.*, **92**, 1260 (1970).

(49) D. G. Lee and R. Cameron, *J. Amer. Chem. Soc.*, **93**, 4724 (1971).

(50) L. S. Levitt and B. W. Levitt, *Tetrahedron*, 27, 3777 (1971), and references therein.

(51) In the absence of experimental data for the protonation of the hydroxyl group of the phthalimide in perchloric acid it seems preferable to include its solvation and protonation in an overall activity coefficient, as is usually done in analogous systems in which water is a reactant, rather than attempting to correct for its degree of protonation.

(52) C. H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, p 162.

(53) H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.*, **57**, 900 (1953); H. H. G. Jellinek and A. Gordon, *ibid.*, **53**, 996 (1949).

(54) R. B. Moodie, P. D. Wale, and T. J. Whaite, *J. Chem. Soc.*, 4273 (1963); K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965).

The Mechanism of Formation and Breakdown of Amine Tetrahedral Addition Compounds of a Phthalimidium Cation. The Relative Leaving Group Abilities of Amines and Alkoxide Ions[1]

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Abstract: The breakdown of amine addition compounds formed from *N,O*-trimethylenephthalimidium cation shows no buffer catalysis and apparently proceeds by a stepwise mechanism of specific acid catalysis; the reverse reaction involves the uncatalyzed attack of the free amine. A negative deviation from structure–reactivity correlations for the reaction of protonated *N,N'*-dimethylhydrazine adduct may reflect a change to rate-determining protonation of this weakly basic adduct. Rate constants for acid-catalyzed breakdown and for amine attack show only a small dependence on amine basicity ($\beta_{lg} = 0.1$ and $\beta_{nuc} = 0.1$) and the equilibrium constants for formation of the uncharged adducts are independent of amine basicity. Rate constants for breakdown of the protonated adducts are highly sensitive to amine basicity ($\beta = -0.9$), indicating a late transition state. Direct comparison of the rate constants for expulsion of amines to those for expulsion of alkoxide ions shows that for a given basicity the amines are better leaving groups by a factor of *ca.* 10^5. This suggests that alkoxide departure will ordinarily be rate determining in the uncatalyzed aminolysis of esters. Imidazole is an abnormally poor leaving group.

In this paper we report the results of our studies on the rate and equilibrium constants and on the mechanism for the breakdown and formation of amine tetrahedral addition compounds of a phthalimidium cation (eq 1). We also describe a comparison of the leaving group abilities of amines and alkoxide ions of a given basicity that is relevant to the question of

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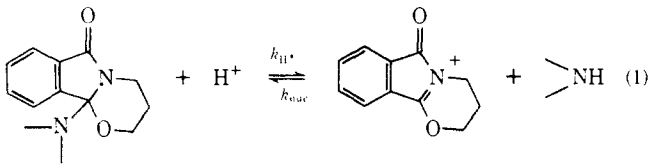


whether the formation or breakdown of a tetrahedral addition intermediate is the rate-determining step in acyl transfer reactions in which such an intermediate exists and which are not complicated by kinetically significant proton transfer.

Experimental Section

Materials. Amine hydrochlorides or dihydrochlorides and tetramethylammonium chloride were recrystallized twice. Imidazole was recrystallized twice from carbon tetrachloride and triethylenediamine was recrystallized twice from acetone and then sublimed. Piperidine, morpholine, and *N*-methylimidazole were redistilled under nitrogen at reduced pressure and stored under argon at 0°.

1,2-Dimethylthiosemicarbazide (mp 130–131°) was synthesized according to the procedure of Jensen, *et al.*[2] The piperidine addition compound (mp 98–100°) was synthesized from *N,O*-trimethylenephthalimidium perchlorate according to the procedure of Hünig and Geldern.[3] The product was recrystallized twice from methylene chloride–cyclohexane and had an infrared spectrum identical with that reported.[3]

Other amine adducts were freshly prepared in acetonitrile solution prior to each experiment. One molar equivalent each of amine and of triethylenediamine in acetonitrile were added to a weighed sample of phthalimidium perchlorate in a small glass-stoppered test tube to give a final concentration of addition compound of 0.026 *M*. In the case of the dibasic amines, piperazine and *N,N'*-dimethylhydrazine, 2.0 molar equiv each of the amine dihydrochloride and of triethylenediamine were used in order to avoid formation of amine diadducts. For experiments carried out at pH values more than 2 units below the p*K* values of the parent amines, at which the back-reaction of free amine is negligible, adducts were prepared from 2.0 molar equiv of piperidine and morpholine without triethylenediamine.

Kinetics. Rate constants were determined by following the appearance of phthalimide absorption at 300 nm using stopped-flow, rapid-injection syringe, or conventional spectroscopy as described previously.[4] The reactions were initiated by the addition of 0.03–0.10 ml of amine adduct in acetonitrile. For the stopped-flow experiments one syringe typically contained 0.001 *M* amine adduct in 10^{-3} *M* sodium hydroxide and sufficient salt to give identical refractive indices for the solution in the two syringes. The final ionic strength was brought to 1.0 *M* with tetramethylammonium chloride in each case. In order to avoid or correct for imidazole inhibition of the hydrolysis of the imidazole adduct, the experiments were carried out in 5-cm cuvettes using low adduct concentrations, or the rate constants were extrapolated to zero imidazole concentration from plots of $1/k_{obsd}$ against the concentration of added imidazole.

A limiting rate constant for the breakdown of the piperidine adduct in alkali was determined in the presence of 0.005 *M* sodium hydroxide and 10^{-4} *M* ethylenediaminetetraacetate under argon by following the disappearance of adduct at 255, 258, and 260 nm. The hydrolysis product is the phthalamic acid anion under these conditions. Aliquots of the solution were made 0.05 *M* in sodium hydroxide before measurement of absorbancies. The absorbance of the product at time infinity was measured repeatedly throughout the course of the experiment by acidification of aliquots followed by addition of sodium hydroxide to a final concentration of 0.05 *M*.

pK_a Determinations. The pK_a of 1,2-dimethylthiosemicarbazide at ionic strength 1.0 (tetramethylammonium chloride) and 25° was determined spectrophotometrically in a series of acid solutions and phosphate buffers at 250 and 230 nm. The pK_a values for *N,N'*-dimethylhydrazine, piperidine, morpholine, piperazine, and *N*-methylpiperazine were measured by potentiometric titration under the same conditions.

Amine Nucleophilicity. Rate constants for the attack of amines on the phthalimidium cation were obtained from the directly measured rate of attack of water[4] and the ratio of the rate constants for attack of water and amine. This ratio was determined by measuring the amount of inhibition by added amine of the hydrolysis of an addition compound formed from the same amine or from the ratio of products formed from phthalimidium ion in the presence of varying amine concentrations.

The inhibition of hydrolysis by added amine was determined in acetate buffers for *N*-methylpiperazine and piperazine monohydrochlorides and in *N*-methylimidazole buffer for imidazole, morpholine and piperidine at two different buffer ratios and at buffer concentrations in the range 0.004–0.008 *M*. The total amine concentrations ranged up to 0.005 *M* for imidazole, 0.07 *M* for the amine monohydrochlorides, 0.08 *M* for morpholine, and 1.0 *M* for piperidine. A total of at least 22 experiments was carried out for each amine.

Product ratios were measured at different amine concentrations from the reaction of phthalimidium cation that was generated *in situ* from the imidazole adduct. Hydrolysis of the imidazole adduct is fast compared to that of the other amine adducts. At pH values below 8 the amount of phthalimide product was determined at 300 nm and the ratio of amine adduct to phthalimide hydrolysis product was obtained from eq 2, in which α is the

$$\frac{\alpha}{1-\alpha} = \frac{(A_0 - A_N)}{(A_N - A_\infty)} \quad (2)$$

fraction of amine adduct product, A_0 is the absorbance at zero amine concentration, A_∞ is the absorbance at infinite amine concentration, and A_N is the absorbance at a given amine concentration. The value of A_∞ was obtained from the reciprocal of the ordinate intercept of a plot of $1/(A_0 - A_N)$ against 1/[amine] at relatively high amine free base concentrations.

At pH values above 8 the phthalimide undergoes significant hydrolysis to phthalamic acid and the product ratios were determined by measuring the concentration of amine adduct by following the absorption of phthalimide upon acid hydrolysis. Phthalimide formation was measured by the change in absorbance at 300 nm upon the addition of 0.01 ml of concentrated hydrochloric acid to 3 ml of solution. The ratio of products was obtained from eq 3, in which ΔA refers to the change in absorbance

$$\frac{\alpha}{1-\alpha} = \frac{(\Delta A_N - \Delta A_0)}{(\Delta A_\infty - \Delta A_N)} \quad (3)$$

and the other symbols have the same meaning as previously.

Identification of Products. The piperidine adduct was shown to give phthalimidium cation upon addition to concentrated perchloric acid solutions. The product had an identical absorption spectrum, extinction coefficient, and rate constants for approach to equilibrium (1.42×10^{-2} and $4.5 \pm 0.1 \times 10^{-3}$ sec^{-1} in 8.18 and 8.79 *M* perchloric acid, respectively) compared to authentic phthalimidium cation. It has been noted previously that the immediate product of the acid-catalyzed breakdown of the morpholine adduct has the same kinetic behavior as authentic phthalimidium cation in concentrated sodium perchlorate solutions and that the water addition intermediate formed during morpholine adduct breakdown exhibits the same kinetic behavior as the intermediate formed directly from phthalimidium cation.[4]

The ultraviolet spectra of all of the amine adducts were found to be very similar to each other and to the spectra of the alcohol and water addition compounds.[4,5] The final breakdown product from each of the adducts was shown to be the phthalimide by comparison of ultraviolet spectra.

Results

Breakdown of Amine Addition Compounds. In Figure 1 are shown the dependencies on pH of the rate constants for the hydrolysis of the amine addition compounds formed from the phthalimidium ion and piperidine, morpholine, imidazole, piperazine, *N*-methylpiperazine, *N,N'*-dimethylhydrazine, *N,O*-

(2) K. A. Jensen, U. Anthoni, B. Kägi, C. Larson, and C. Th. Pedersen, *Acta Chem. Scand.*, 22, 1 (1968).

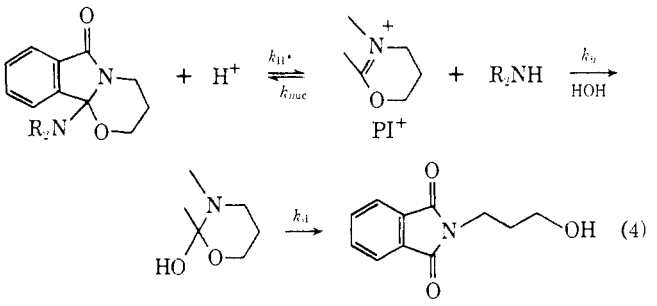
(3) S. Hünig and L. Geldern, *J. Prakt. Chem.*, 24, 246 (1964).

(4) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, 96, 489 (1974).

(5) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, 96, 507 (1974).

dimethylhydroxylamine, and 1,2-dimethylthiosemicarbazide. The rate constants were found to be independent of buffer concentration under the conditions indicated in the legend to Figure 1. From the observed absence of buffer catalysis the Brønsted coefficient, α, for general acid catalysis was estimated to be >0.9 for the breakdown of the piperidine and morpholine addition compounds and >0.8 for the 1,2-dimethylthiosemicarbazide addition compound.

The acid-catalyzed breakdown of the amine adducts gives the phthalimidium ion as the initial product, which then reacts rapidly with water to give the water addition compound and finally the phthalimide (eq 4).



(4)

The range of pH over which the rate of adduct breakdown could be followed was limited by the rate of phthalimide formation from the water addition compound at low pH values (k_d = 1.84 sec^{-1} + k_B[B]).[4] The range that could be examined without interference from this reaction was extended to pH 4 for the piperidine adduct and to pH 4.9 for the imidazole adduct, by carrying out the reactions at high buffer concentrations since the breakdown of the water adduct, but not the amine adducts, is buffer catalyzed.

The linear plots of log k against pH, with slopes of −1.0 over most of the pH range examined (Figure 1), and the absence of buffer catalysis indicate that breakdown of the amine adducts is specific acid catalyzed. Hydrolysis of the piperidine adduct at pH 6.6 was found to result in the uptake of 1.06 mol of acid. This shows that the hydrolysis involves acid catalysis of the reaction of the uncharged adduct, as shown in eq 4, and not an acid-catalyzed reaction of an adduct that is already protonated on nitrogen under the conditions of the experiments. A leveling off of the curves because of protonation of the adduct is observed only for the imidazole and *N,N'*-dimethylhydrazine adducts, which can be protonated on a site other than the nitrogen atom that is bound directly to the phthalimide nucleus; in the case of *N,N'*-dimethylhydrazine a second increase in rate at low pH reflects an acid-catalyzed reaction of the monoprotonated species. Values of pK_a = 5.38 and 4.56 were obtained for the protonated imidazole and *N,N'*-dimethylhydrazine adducts, respectively, from the slopes ($-K_a$) of plots of k_{obsd} against k_{obsd}/a_{H^+}; the ordinate intercepts of the plots gave rate constants of 16.5 and 0.54 sec^{-1}, respectively, for the breakdown of the protonated adducts.

In the case of the piperazine and *N*-methylpiperazine adducts the observed hydrolysis is attributed to an acid-catalyzed reaction of the species that is fully protonated on the distal nitrogen atom. An acid-catalyzed reaction of the unprotonated species is detectable for the *N*-methylpiperazine adduct as a small increase in rate at the highest pH values examined (Figure 1) and

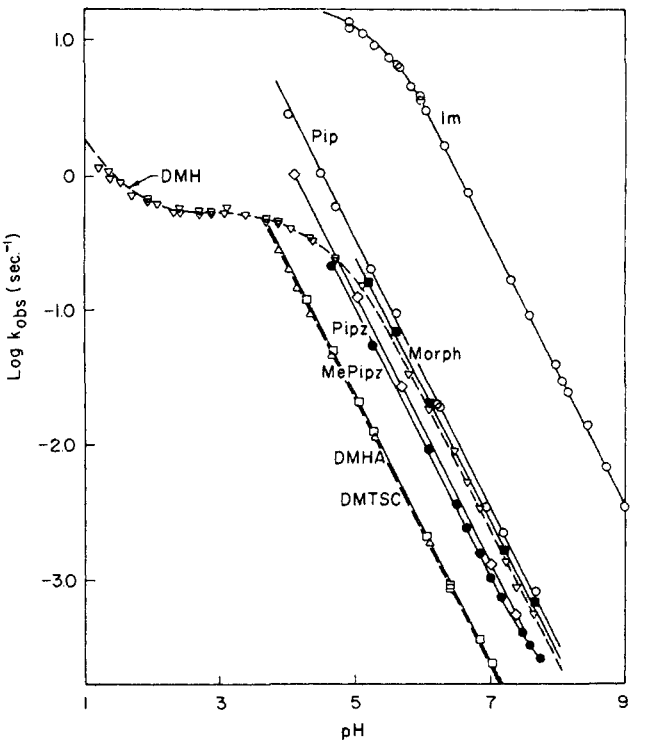


Figure 1. Dependence on pH of the pseudo-first-order rate constants for the breakdown of the following amine addition compounds formed from phthalimidium cation: imidazole (○), piperidine (○), morpholine (■), *N,N'*-dimethylhydrazine (▽), piperazine (◇), *N*-methylpiperazine (●) *N,O*-dimethylhydroxylamine (□), and 1,2-dimethylthiosemicarbazide (△) at 25° and ionic strength 1.0 (tetramethylammonium chloride). The following buffers were used: hydrochloric acid at pH <1.7, chloroacetate at pH 1.7–3.9 (0.02–0.06 *M*), formate at pH 3.13–4.38 (0.04–0.8 *M*), acetate at pH 4.37–6.32 (0.04–0.8 *M*), phosphate at pH 6.2–7.2 (0.02 *M*), *N*-methylimidazole at pH 6.5–8.2 (0.02–0.4 *M*), and triethylenediamine at pH >8.2 (0.05 *M*). The lines represent the theoretical curves for the kinetic constants listed in Table I.

the rate constants for the acid-catalyzed breakdown of the protonated and uncharged species were estimated from a plot of k_{obsd} against a_{H^+}.[6] The rate constants for adduct breakdown are summarized in Table I and the calculated lines in Figure 1 are based on these rate constants and the estimated pK_a values for those adducts that undergo a significant amount of protonation.

The observed rate constant for breakdown of the piperidine adduct at pH 11.51 of 1.1 × 10^{-7} sec^{-1} (measured over 1.5 months) was found to be identical with that calculated from the observed acid-catalyzed rates at lower pH. The rate constant for pH-independent breakdown of the adduct was accordingly

(6) Although the deviation from linearity is small in the logarithmic plot of Figure 1, the intercept of the plot of k_{obsd} against a_{H^-} that corresponds to the pH-independent breakdown of the monoprotonated adduct is 7.8 × 10^{-5} sec^{-1}, significantly larger than zero; the slope of this plot of 1.10 × 10^4 M^{-1} sec^{-1} is the rate constant for the acid-catalyzed breakdown of the monoprotonated adduct. The pK_a of the protonated adduct was estimated to be 8.4 from the pK_a of 8.89 for *N,N'*-dimethylpiperazine-H$^+$,[7] the observed decrease in pK of 3.1 units upon substitution of the phthalimide nucleus for hydrogen in *N,N'*-dimethylhydrazine and a fall-off factor of 0.4 × 0.4 = 0.16 for the additional intervening carbon atoms in *N,N'*-dimethylpiperazine.[8] A value of k_{H^+} = 2 × 10^4 M^{-1} sec^{-1} for the acid-catalyzed breakdown of the neutral adduct was then calculated from the equation $k_{H^+} = k_{AdH^+}/K_a$.

(7) A. Satterthwait, unpublished data.

(8) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968, p 39.

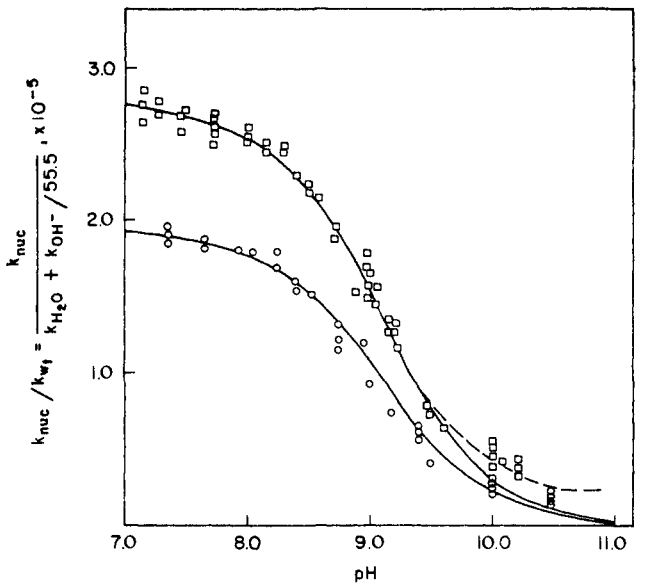


Figure 2. The pH dependence of the product ratio for the reaction of phthalimidium ion with piperidine (□) and morpholine (○) at 25°. The lines are theoretical curves calculated from eq 7 and the rate constants in Table I. The dashed line represents a best fit through the lower piperidine points for the occurrence of a hydroxide ion catalyzed term for piperidine.

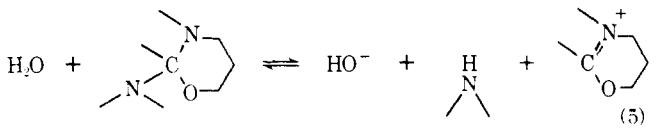
Table I. Summary of Rate Constants for the Amine–Phthalimidium Reactions. Acid-Catalyzed Amine–Adduct Breakdown, Amine Nucleophilic Attack, and the Calculated Equilibrium Constant for Adduct Breakdown at 25°, Ionic Strength 1.0 (Tetramethylammonium Chloride)

Amine	pK_a'[a]	$k_{H^+} \times 10^{-4}$, M^{-1} sec^{-1}	$k_{nuc} \times 10^{-4}$, M^{-1} sec^{-1}	K_{eq}[b]
Piperidine	11.44	3.29	28	0.12
N-Methylpiperazine	9.32	2.0		
Morpholine	8.89	2.60	19.8	0.13
N,N'-Dimethylhydrazine	7.69	2.14		
Imidazole	7.21	392	4.7	84
Piperazine–H^+	6.01	1.3	7.3	0.18
N-Methylpiperazine–H^+	5.19 6.31[c]	1.10	6.7	0.16
N,O-Dimethylhydroxylamine	4.88	0.24		
1,2-Dimethylthiosemicarbazide	1.31	0.23		
N,N'-Dimethylhydrazine–H^+	−2.1[d]	0.0012		

[a] Determined by titration at 25° and ionic strength 1.0 (tetramethylammonium chloride) unless otherwise noted. [b] Calculated from k_{H^+}/k_{nuc}. [c] Microscopic dissociation constant of the secondary amino group of the dication. Calculated from the ratio of the dissociation constants of piperazine, 9.88×10^{-7} *M*, and *N,N'*-dimethylpiperazine, 2.51×10^{-5} *M* (A. Satterthwait, unpublished) and the appropriate statistical corrections. [d] Estimated value, see text.

estimated to be less than 3.3×10^{-8} sec^{-1}. A pH-independent breakdown of the adduct would correspond to amine attack on phthalimidium ion catalyzed by hydroxide ion in the reverse direction (eq 5). Since breakdown of the amine adducts proceeds without significant buffer catalysis or a pH-independent reaction of the base species, the reverse reactions must proceed without significant buffer or hydroxide ion catalysis.

Reactions of Amines with the Phthalimidium Cation.


(5)

Second-order rate constants k_{nuc} for the attack of amines on the phthalimidium cation (Table I) were determined by a competition method, from the known hydrolysis rate constants[4] and the yields of amine adduct and phthalimide formed from the phthalimidium ion (see Experimental Section), and by measuring the inhibition of adduct breakdown in the presence of increasing concentrations of added amine. Equilibrium constants for the acid-catalyzed elimination of these amines from the addition compounds were calculated from k_{H^+}/k_{nuc} and are also given in Table I.

The most accurate data were obtained from the amine inhibition method and the rate constants in Table I are based on these results. In the presence of amine the observed rate of hydrolysis of the addition compound formed from the same amine is inhibited because the phthalimidium ion intermediate reacts with the amine to regenerate the adduct (k_{nuc}, eq 4) faster than it adds water (k_h). In the presence of excess amine the rate constants are related by eq 6 and

$$\frac{1}{k_{obsd}} = \frac{1}{k_{H^-}a_{H^+}} + \frac{k_{nuc}[R_2NH]}{k_{H^+}a_{H^+}k_h} \quad (6)$$

the values of $k_{nuc}/k_{H^+}a_{H^+}k_h$ and $1/k_{H^+}a_{H^+}$ were obtained from the slopes and ordinate intercepts, respectively, of plots of $1/k_{obsd}$ against $[R_2NH]$. Since k_h and k_{H^+} are known, k_{nuc} is readily calculated.[9]

The ratio of the products from amine and water attack on the phthalimidium ion is given by eq 7, in

$$\frac{\alpha[H_2O]}{(1-\alpha)[R_2NH]} = \frac{k_{nuc}}{k_{wt}} = \frac{k_{nuc}}{k_{H_2O} + k_{OH^-}a_{OH^-}/[H_2O] + k_B[B]} \quad (7)$$

which k_{wt} is a (second order) rate constant for hydrolysis at a given pH and buffer concentration and k_{H_2O}, k_{OH^-}, and k_B are rate constants for the pH-independent, hydroxide ion, and general base catalyzed attack of water on the phthalimidium ion, respectively. Values of k_{nuc} calculated from product ratios were found to agree with those obtained by the amine inhibition method. The value of k_B for catalysis of water attack by triethylenediamine buffers was calculated from the effect of buffer concentration on the product ratio according to this equation.[4]

The effect of pH on the product ratios for reactions of morpholine and piperidine with the phthalimidium ion is shown in Figure 2. The decrease in the yield of amine adduct with increasing pH is a consequence of the additional hydrolysis caused by hydroxide ion. A rate constant of $4.6 \pm 0.5 \times 10^6$ M^{-1} sec^{-1} for this hydrolysis was obtained from the slopes of plots of k_h/k_{nuc} against a_{OH^-} and the values of k_{nuc} for piperidine and morpholine (Table I). The solid lines in Figure 2 were calculated from these rate constants. Some of the points for the piperidine reaction are above the theoret-

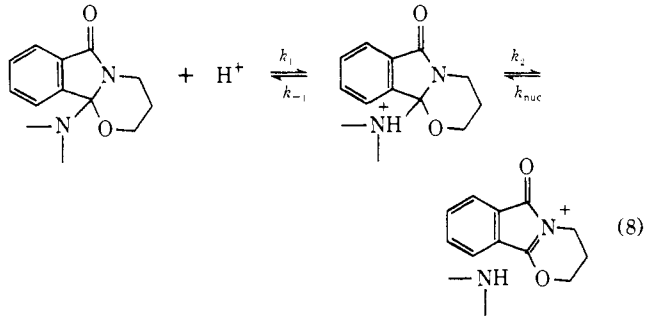
(9) At pH values at which a significant amount of free amine was released upon hydrolysis of the adduct, eq 6 was used in some experiments to obtain values of k_{H^+}.

ical line and it might be argued that the curve levels off to a constant value at high pH as a consequence of a hydroxide ion catalyzed attack of piperidine that competes effectively with the hydroxide ion catalyzed hydrolysis; the dashed line is drawn for such a reaction with a rate constant of $2 \times 10^9\ M^{-2}\ sec^{-1}$. However, this possibility can be ruled out by calculating the rate constant for hydroxide ion catalysis of piperidine attack (eq 5) from the upper limit for the rate constant of the same reaction in the reverse direction of $<3.3 \times 10^{-8}\ sec^{-1}$ and the known equilibrium constant (Table I); the resulting value of $4 \times 10^7\ M^{-2}\ sec^{-1}$ would not give a detectable amount of amine adduct under the experimental conditions so that the deviations from the solid line in Figure 2 must be attributed to the uncertainty of the data at high pH and low yields of amine adduct.

The addition of phthalimidium ion to solutions of primary amines in water or acetonitrile was found to give stable products with spectra resembling that of the phthalimidium ion, presumably the corresponding amidinium ions.

Discussion

The absence of detectable buffer catalysis or a "water" reaction of the unprotonated species suggests that the breakdown of the amine adducts proceeds by a stepwise mechanism of specific acid catalysis, in which a fast equilibrium protonation of the leaving nitrogen atom is followed by rate-determining expulsion of the protonated amine (eq 8). In the reverse direction this

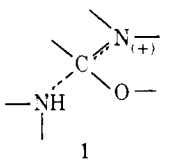


(8)

mechanism corresponds to the attack of free amine on the phthalimidium ion, without general base catalysis. The addition of amines to ethyl benzimidate also occurs without detectable buffer catalysis.[10] We believe that this mechanism is general for addition–elimination reactions of moderately basic amines at iminium or carbonyl centers when the addition intermediate has a lifetime sufficient to permit equilibration with respect to proton transfer. The addition compounds formed from the phthalimidium ion and basic amines have a sufficient lifetime and basicity to permit the mechanism of eq 8 (see below) and there is no documented example of concerted general acid–base catalysis involving the nitrogen atom for the addition or expulsion of moderately basic amines when the addition product has a significant lifetime. The general acid–base catalysis that has been observed for some reactions of this kind has been ascribed to a stepwise mechanism in which proton transfer is necessary in order to allow a second step to occur or to stabilize an otherwise highly unstable intermediate; however, if the "intermediate" is so unstable that it has no significant lifetime to permit proton transfer, a concerted mechanism of catalysis may be required.[11,12]

The phthalimide nucleus causes a large decrease in the basicity of amines in the tetrahedral addition compounds. The pK_a values of the distal nitrogen atoms of imidazole and *N,N'*-dimethylhydrazine are reduced by approximately 2 and 3 p*K* units, respectively, in the corresponding adducts. The fact that there is no deviation from linearity of the log *k*–pH plot for breakdown of the piperidine adduct down to pH 4 means that the pK_a of the conjugate acid of the piperidine adduct must be ≤ 3.0. A $\rho_I\sigma_I$ correlation based on a ρ_I value of -8.5 gives a predicted pK_a of 4.7 for the piperidine adduct, based on a pK_a of 10.1 for *N*-methylpiperidinium ion.[13] Additional base-weakening may arise from unfavorable steric and solvation effects in the crowded environment adjacent to the phthalimide nucleus and from electron donation to the 2p orbital of the carbon atom induced by the electron-withdrawing substituents on this atom.[14] Estimations of the pK_a of the piperidine adduct from the observed decrease in the pK_a of the *N,N'*-dimethylhydrazine adduct give a value of 1.4, using an attenuation factor of 0.39 for the transmission of polar substituent effects through nitrogen from the benzylamine–phenylhydrazine series, and a value of 5.9, using an attenuation factor of 0.73 from the alkylhydrazine–alkylamine series.[15] It appears from these estimates that the pK_a of the piperidine adduct is probably on the order of 3.0 and this value of 3.0, corresponding to a decrease in pK_a of 8.4 units, was used to estimate a rate constant $k_2 = 33\ sec^{-1}$ for the breakdown of the protonated adduct.

Rate constants for the breakdown of other protonated amine adducts were estimated in the same way, assuming a constant substituent effect corresponding to 8.4 pK_a units for the phthalimide nucleus, and are summarized in Table II. These rate constants show a large dependence upon the pK_a of the amine and a plot of log k_2 against pK_a has a slope $\beta_{lg} = -0.9$ (Figure 3). This suggests a transition state with a large amount of carbon–nitrogen bond breaking and little charge on the departing nitrogen atom (**1**). The addition com-



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pounds formed from the "α-effect" compounds *N,N'*-dimethylhydrazine, *N,O*-dimethylhydroxylamine, and 1,2-dimethylthiosemicarbazide break down with rate

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(11) (a) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 3262 (1972); (b) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *ibid.*, **94**, 4729 (1972); (c) M. I. Page and W. P. Jencks, *ibid.*, **94**, 8828 (1972); (d) H. Diebler and R. N. F. Thorneley, *ibid.*, **95**, 896 (1973).

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(13) The σ_I values for C_6H_5, RO, and RCONH were taken from C. D. Ritchie and W. F. Sager [*Progr. Phys. Org. Chem.*, 2, 323 (1964)]; the ρ_I value was estimated by J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, in press.

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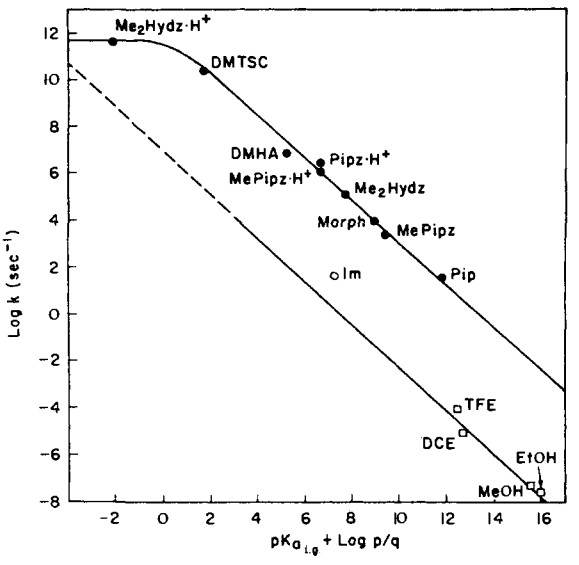

Figure 3. Dependence of the reaction rates on the statistically corrected pK_a (see ref 16) of the leaving group for the breakdown of alcohol (□) (see ref 5) and protonated amine (●) addition compounds at 25°. Trifluoroethanol is TFE and dichloroethanol is DCE.

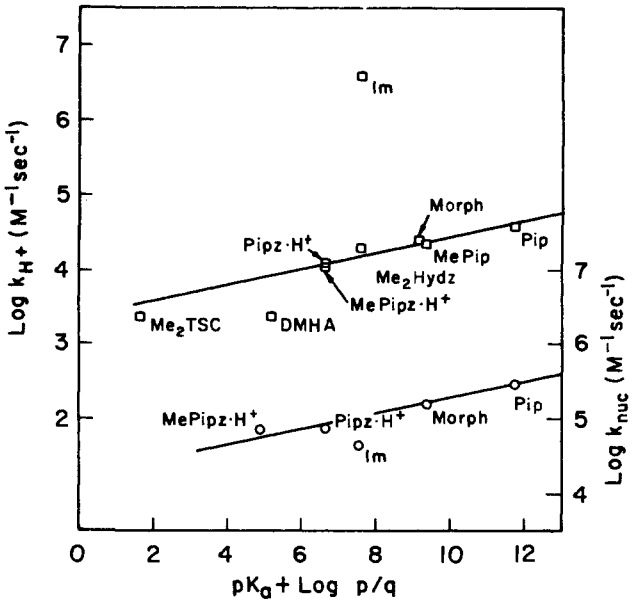

Figure 4. Dependence of the rate constants for acid-catalyzed amine–adduct breakdown (□) and amine nucleophilic attack on the phthalimidium cation (○) on the statistically corrected[16] amine basicity at 25°.

Table II. Calculated Rate and Equilibrium Constants for Protonated Amine–Adduct Breakdown at 25°

Amine–adduct	Estimated[a] pK_a of adduct	k_2,[b] sec^{-1}	K_{eq}',[c] M
Piperidine–H^+	3.0	3.3×10^1	1.2×10^{-4}
N-Methylpiperazine–H^+	0.9	3.6×10^3	
Morpholine–H^+	0.49	8.4×10^3	4.2×10^{-2}
N,N'-Dimethylhydrazine–H^+	−0.8	1.4×10^5	
Imidazole–H^+	5.38[d]	1.64×10^1	3.3×10^{-4}
Piperazine–H^+	−2.4	3.2×10^6	4.5×10^1
N-Methylpiperazine–H^+	−2.1	1.4×10^6	2.1×10^1
N,O-Dimethylhydroxylamine–H^+	−3.5	7.4×10^6	
1,2-Dimethylthiosemicarbazide–H^+	−7.1	2.9×10^{10}	
N,N'-Dimethylhydrazine-$2H^+$	−10.9	9×10^{11}	

[a] Calculated from $pK^{adduct} = pK^{amine} - 8.4$ (see text). [b] First-order rate constant for protonated amine–adduct breakdown calculated from $k_2 = k_{H^+}K_a$(adduct). [c] $K_{eq}' = k_2/k_{nuc} = [R_2NH]\cdot[PI^+]/[AdH^+]$. [d] Observed value from kinetic measurements (Figure 1).

constants that are not significantly different from those for other amine adducts, regardless of whether the rate constants are expressed for the acid-catalyzed reactions (k_{H^+}, Figure 4) or for the breakdown of the protonated adducts (k_2, Figure 3). Thus, there is no indication of any special destabilization of the product-like transition state of these reactions, by interaction of adjacent lone pair electrons, for example, that causes a reduced rate constant compared to "normal" amines.

In the reverse direction, the rate constants for the attack of amines on the phthalimidium ion display little sensitivity to the statistically corrected[16] pK of the amine, with a slope $\beta_{nuc} = 0.1$ (Figure 4). This corresponds to an early transition state with little charge on the attacking nitrogen atom and is also consistent with **1**. Small values of β_{nuc} have been reported for the reactions of basic amines with highly reactive acyl compounds such as acetic anhydride,[17] 1-acetoxy-4-methoxypyridinium cation,[18] and *N*-acetylpyridinium cations,[19] but considerably larger values are found for the reactions of less basic amines with these compounds. The reaction of primary amines with the carbonium ion malachite green exhibits a β_{nuc} value of 0.41 for simple primary amines.[20] Although malachite green is several orders of magnitude less reactive than the phthalimidium ion, very similar behavior has been observed for other carbonium ions with a reactivity comparable to that of the phthalimidium ion.[21] A β_{nuc} value of 0.4 has also been reported for the reaction of the oxocarbonium ions derived from methyl orthobenzoates with hydroxylamine, methoxyamine, and semicarbazide.[22] The smaller value of β_{nuc} for the phthalimidium ion reactions indicates that there is a significant dependence of the nature of the transition states on the structure of the electrophile in these reaction series and that the desolvation energy of the amine is not the only factor that determines the sensitivity of the reaction rates to amine basicity. However, the ratio log $(k_{OH^-}/55.5k_{H_2O}) = 4.9$ for attack on the phthalimidium ion is similar to the ratio of 4.5 for the corresponding carbonium ion reactions.[23]

Figure 4 shows that the rate constants for adduct breakdown, expressed as an acid-catalyzed reaction of the uncharged adduct, also show only a small dependence on the basicity of the nitrogen atom (β =

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(20) J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3248 (1971).

(21) C. D. Ritchie and P. O. I. Virtanen, *J. Amer. Chem. Soc.*, **95**, 1882 (1973).

(22) K. Koehler and E. H. Cordes, *J. Amer. Chem. Soc.*, **92**, 1576 (1970).

(23) C. D. Ritchie and P. O. I. Virtanen, *J. Amer. Chem. Soc.*, 94, 4966 (1972).

0.1). Thus, the equilibrium constants for adduct formation (Table I) show essentially no dependence on the pK of the amine over a range of 5 pK units. The same independence of amine basicity is observed for the equilibrium addition of amines to carbonyl compounds,[24] although a small dependence (β = 0.23) has been reported in one series.[25]

It is likely that breakdown of the diamine adducts involves protonation of the proximal nitrogen atom followed by expulsion of the free amine (eq 9), rather

$$\mathrm{Ad{-}\overset{+}{N}H{-}NH} \rightleftharpoons \mathrm{PI^+ + HN{-}NH} \qquad (9)$$

than a reaction of the species protonated on the distal nitrogen atom which would give the unstable dipolar ion RN^{-}–NRH_2^{+} as the immediate product (eq 10).

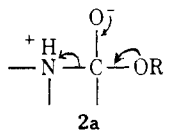
$$\mathrm{Ad{-}N{-}\overset{+}{N}H_2} \rightleftharpoons \mathrm{PI^+ + \bar{N}{-}\overset{+}{N}H_2} \qquad (10)$$

In the reverse direction the former mechanism involves attack of the free amine, rather than the dipolar ion. This interpretation is supported by the fact that the rate constants for the diamines and diamine adducts fall on the same correlation lines as those for simple amines (Figures 3 and 4).

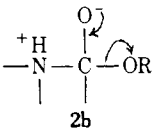
The rate of protonation of the adducts formed from basic amines, which is presumably diffusion controlled, is more than adequate to account for the observed rate of the overall reaction. For the weakly basic 1,2-dimethylthiosemicarbazide adduct, with an estimated pK_a of 1.3 − 8.4 = −7.1, the rate constant for protonation is approximately $55 \times 10^{10}/10^{7.1} = 4 \times 10^4\ M^{-1}\ \mathrm{sec}^{-1}$, which is still adequate to account for the observed rate constant $k_{H^+} = 2.3 \times 10^3\ M^{-1}\ \mathrm{sec}^{-1}$. For these compounds the rate of proton transfer to the solvent (k_{-1}, eq 8) is faster than the rate of breakdown of the protonated addition compound (k_2), in accord with a mechanism of specific acid catalysis. However, the acid-catalyzed decomposition of the still less basic monoprotonated N,N'-dimethylhydrazine adduct is approximately 200 times slower than that of any of the other adducts (Table I) and the calculated first-order rate constant of $9 \times 10^{11}\ \mathrm{sec}^{-1}$ for decomposition of the diprotonated species shows a negative deviation in the correlation of Figure 3. This decrease in rate may be a consequence of a change in rate-determining step, from decomposition to protonation of the adduct (k_1, eq 8). The observed rate constant $k_{H^+} = 12\ M^{-1}\ \mathrm{sec}^{-1}$ corresponds to rate-determining proton transfer (k_1) if the reverse proton transfer occurs with a rate constant $k_{-1} = 55 \times 10^{10}\ \mathrm{sec}^{-1}$ and the pK_a of the adduct is −10.6. The pK_a of $CH_3NH_2NH_2CH_3^{2+}$ was estimated to be 7.7 − 10.2 = −2.5 from the pK_a of $CH_3NHNH_2CH_3^{+}$ and $\rho^*\sigma^*$ correlations,[26] and the pK_a of the adduct is expected to be some 8.4 units lower or −10.9. A pK_a of −10.9 would give a rate constant for proton transfer, $k_1 = 6\ M^{-1}\ \mathrm{sec}^{-1}$. The agreement with the observed rate constant of $12\ M^{-1}\ \mathrm{sec}^{-1}$ is closer than one has any right to expect, but even this crude calculation indicates that a change to rate-determining proton transfer is a reasonable mechanism to account for the relatively slow breakdown of this adduct. Since the Brønsted α value should be 1.0 for the protonation of weak bases by the solvated proton and buffer acids (the reaction is diffusion-controlled with β = 0 in the reverse direction), the proton reaction will dominate and catalysis by buffers is neither expected nor found.

The estimated rate constant of $9 \times 10^{11}\ \mathrm{sec}^{-1}$ for breakdown of the diprotonated dimethylhydrazine adduct indicates that the lifetime of this intermediate is borderline, at best, and that more normal tetrahedral "intermediates" with a greater driving force for amine expulsion are likely to have a lifetime that is less than a vibration frequency; *i.e.*, they will be too unstable to exist. The "intermediate" formed in the aminolysis of an amide, for example, will have a much stronger driving force for expulsion of the attacking amine arising from the electron pairs of an anionic oxygen atom and an unencumbered nitrogen atom. This is consistent with the conclusion that addition "intermediates" formed in the hydrazinolysis of acetylimidazole and acetylimidazolium ion have a very short or no lifetime.[11c]

Relative Leaving Abilities of Amines and Alkoxide Ions. The rate-determining step for the breakdown of a dipolar tetrahedral addition compound that is formed in ester aminolysis or amide alcoholysis (or hydrolysis) is determined by the relative rates of expulsion of the amine and alkoxide leaving groups. These rates are determined largely by the intrinsic leaving abilities of each group, but also by the driving force provided by the other group. Amine expulsion from **2a** is aided by electron donation from the alcohol oxygen atom, for example, but there is no assistance to oxygen expulsion by electron donation from a saturated cationic amine in **2b**. The phthalimidium addition com-



2a



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pounds provide a useful system for comparing the leaving abilities of amines and alkoxide ions because the driving force for expulsion of the leaving group is the same for both the amine and alcohol adducts.

In Figure 3 the estimated rate constants for the expulsion of amines are compared with those for the expulsion of alkoxide ions[5] from the respective phthalimide tetrahedral addition compounds. Except for the imidazole and the protonated dimethylhydrazine addition compounds, the amine and oxyanion series are both described by lines of slope −0.9. Although it is not possible to compare amines and alkoxide ions of identical pK, piperidine and trifluoroethoxide ion differ by only 1 pK unit and the relative position of the lines is clearly established by the data. The rate constants for expulsion of the protonated amines are 2×10^5 larger than those for expulsion of alkoxide ions of comparable pK. The factor of 2×10^5 is not precise because of uncertainties in the pK_a estimates for the amine adducts and the experimental data, and it should be kept in mind that the comparison involves protonated secondary amines and less bulky primary alcohols. Nevertheless, the data establish that for a given basicity

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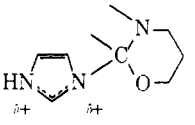
secondary amines are expelled much more rapidly than alkoxide ions and that there is no justification for the common assumption that amines and alkoxide ions of equal pK have equal leaving ability. In ester aminolysis electron donation from the alcohol oxygen atom (**2a**) will provide an additional factor favoring amine expulsion, in the absence of proton transfer. This result is consistent with the conclusion that the rate-determining step in the breakdown of tetrahedral intermediates formed in the uncatalyzed reactions of amines with phenyl acetate is the expulsion of phenoxide ion.[11b]

Imidazole. The imidazole adduct represents an instructive special case that is relevant to the mechanism of reactions of acetylimidazole. The acid-catalyzed breakdown of the imidazole adduct is approximately 100 times faster than that of any other amine adduct (Table I), but the breakdown of the protonated adduct is some 10^4 *slower* than expected for the adduct of an amine of pK = 7 (Figure 3). The imidazole adduct is protonated to give the reactive species (pK_a = 5.38) much more easily than other amine adducts, but the adduct, once protonated, is much less reactive than other protonated adducts. This is a consequence of the fact that protonation of the imidazole adduct takes place on the distal nitrogen atom to give **3**, which has



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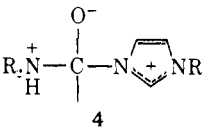
its positive charge divided between the two nitrogen atoms and is a poorer leaving group than a protonated adduct with a full positive charge on the proximal nitrogen atom. The strong electron-withdrawing effect of the phthalimide nucleus has a relatively small effect on the equilibrium for protonation of imidazole in the adduct (about 10^6 less than for other amine adducts) because a major part of the positive charge can be localized on the distal nitrogen atom, away from the phthalimide substituent. Consequently, there is relatively little positive charge on the proximal nitrogen atom. Protonated secondary amines have a full positive charge on this nitrogen atom in a crowded, unfavorable environment immediately adjacent to the phthalimide nucleus and will therefore be expelled more rapidly. It is clear that correlations between reactivity and pK_a cannot be extended to compounds with significantly different structure and resonance stabilization; *i.e.*, the difference in structure between imidazole and simple amines has a very different effect on the relative stabilities of the conjugate acids and the transition states.

These observations have two consequences for the interpretation of the mechanism of reactions of acetylimidazole. First, the 100-fold increased reactivity of the imidazole–phthalimide adduct toward acid-catalyzed breakdown suggests that the great facility with which acetylimidazole undergoes acid-catalyzed reactions is also, in part, a consequence of the ease of protonation of imidazole on the distal nitrogen atom and is not caused entirely by the inhibition of normal amide resonance in acetylimidazole. Second, the relatively poor leaving ability of protonated imidazole means that in the breakdown of any tetrahedral adducts that are formed in the aminolysis of acetylimidazole, **4**, pro-



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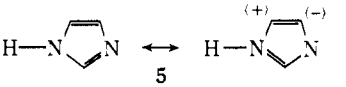
tonated imidazole or methylimidazole will behave like a protonated amine of pK_a *ca.* 11; *i.e.*, most attacking amines will leave more easily than imidazole and the rate-determining step will be breakdown of the intermediate with imidazole expulsion. A similar situation is expected to hold for pyridines that are stabilized by electron-donating groups, such as 4-methoxypyridine. This may account for the break in the structure–reactivity correlations for the reactions of substituted acetylpyridinium ions with amines of increasing basicity; a small negative deviation of the rate constant for the reaction of piperidine with acetylimidazolium ion may reflect an incipient similar change in the nature of the rate-determining step.[19,27] There is some indication that tetrahedral adducts may have lifetimes too short to permit their recognition as discrete intermediates in these reactions;[11c] however, a change in the nature of the rate-determining step may occur even if no discrete intermediate exists.[28]

The rate constant for the *attack* of imidazole on the phthalimidium ion is about twofold less than that of ordinary amines (Table I). This is similar to the behavior of imidazole with highly reactive acyl compounds, but very different from the reactions with less reactive esters in which imidazole shows an abnormally high reactivity,[29] presumably because of stabilization of the transition state for rate-determining departure of the alcoholate ion by resonance with the aromatic imidazole ring; such resonance stabilization is, of course, not possible with a protonated amine nucleophile.

The *equilibrium constant* $1/K_{eq}$ for the addition of imidazole to the phthalimidium ion to form the uncharged adduct is about 500 times less favorable than that for other amines (Table I). A similar, but smaller, difference has been observed for the addition of imidazole to formaldehyde.[24a] These differences are attributed, at least in large part, to loss of the hydrogen bond between the acidic proton (pK = 14.2)[30] of imidazole (**5**) and the solvent upon adduct formation.



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The protons of ordinary amines are too weakly acidic to provide significant stabilization by such hydrogen bonding.

Acknowledgment. We thank Professor C. D. Ritchie for communicating to us results from his laboratory on the reactions of amines with carbonium ions prior to publication.

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(29) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).
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