lengths were used for kinetics: for BI, *p*-Cl, 260 nm; *p*-H, 250 nm; *p*-CH_3, 260 nm; for BMI^+, *p*-H, 250 nm; *p*-CH_3, 265 nm; *p*-OCH_3, 295 nm. Within experimental error the reaction was found to follow good pseudo-first-order kinetics for at least 4 half-lives.

A least-squares treatment of each set of kinetic data was carried out by the use of a modified version of the computer program LSKIN1.[44]

Acknowledgments. Support by the U. S. Public Health Service, the National Science Foundation, and the University of Pennsylvania Computer Center is gratefully acknowledged.

(44) D. F. De Tar and C. E. De Tar in "Computer Programs for Chemistry," Vol. I, D. F. De Tar, Ed., W. A. Benjamin, New York, N. Y., 1968, Chapter 6.

General Acid and General Base Catalysis of the Methoxyaminolysis of 1-Acetyl-1,2,4-triazole[1]

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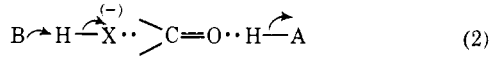
Abstract: Brønsted plots for general acid and for general base catalysis of the methoxyaminolysis of 1-acetyl-1,2,4-triazole are nonlinear, with equal limiting rate constants for strong acid and strong base catalysts. The data are consistent with mechanisms in which the rate-determining step is (I) a simple proton transfer that is diffusion controlled in the favorable direction or (II) diffusion-controlled encounter of an intermediate $T^{\pm}$ with the catalyst for strong catalysts and the breakdown of $T^{\pm}$ or T^0 for weak catalysts. Estimated p*K* values of the intermediate and structure–reactivity considerations favor mechanism II. The change from a mechanism that gives a linear Brønsted plot for kinetic general acid catalysis of the hydrazine–acetylimidazole reaction is consistent with the change in structure of the reactants. Rate constants for the reactions of acetyltriazole with water, buffers, and amines are reported and compared with those for the corresponding reactions of acetylimidazole.

We have been concerned with the problem of the driving force, detailed mechanism, and "concertedness" of general and specific acid–base catalysis of acyl transfer and related reactions. The experiments reported here were originally carried out in an attempt to detect concerted, bifunctional acid–base catalysis of an acyl transfer reaction, in which both an acid and a base catalyst are present in the transition state and give rise to a term in the rate law containing both of these species (eq 1). Examples of such catalysis in aqueous solution

$$v = k[\text{H–X}][\text{—C(=O)Y}][\text{HA}][\text{B}] \qquad (1)$$

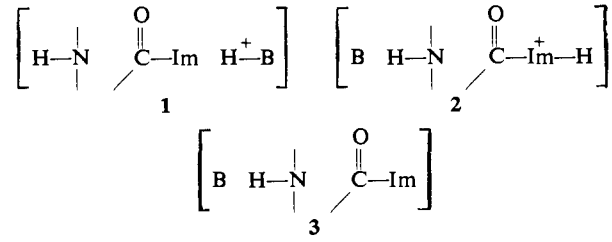
are rare or nonexistent and we suspected that one reason for this is that catalysis at one end of a system is likely to decrease the importance of catalysis at the other end. For example, a base that removes a proton from an attacking nucleophile H–X increases the effective basicity of the nucleophile (eq 2), and, since it is known that



(2)

carbonyl addition reactions are subject to concerted general acid catalysis only if the attacking nucleophile is a weak base, general base catalysis will tend to decrease the importance of general acid catalysis so that concerted acid–base catalysis becomes insignificant.[2]

Acetylimidazole and related compounds are useful models for studying acyl transfer reactions of amides because of their high reactivity and convenient ultraviolet absorption. By the use of *N*-methylacetylimidazolium ion as a model for acetylimidazolium ion, evidence has been obtained that general acid catalysis of the reaction of acetylimidazole with strongly basic amines involves proton donation to the leaving imidazole group (**1**), whereas this catalysis with weakly basic amines involves the kinetically equivalent general base catalysis of a reaction with the acetylimidazolium ion (**2**). Furthermore, it is known that the aminolysis of free acetylimidazole, with a much poorer leaving group, is subject to general base catalysis (**3**).[3] (The formulas **1**–**3** are shown only to suggest the relative locations of



the catalyst and reactants in the transition state, without any implication as to whether the formation or breakdown of a tetrahedral intermediate is rate determining or as to a detailed mechanism of catalysis.) We hoped to detect bifunctional acid and base catalysis of the reaction of 1-acetyl-1,2,4-triazole (**4**) with weakly basic amines on the basis of the following, rather naive, reasoning. General acid catalysis of leaving group expulsion from acetylimidazole is not observed with

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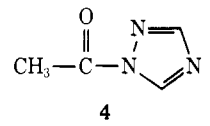
(2) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 196, 198.

(3) D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *J. Amer. Chem. Soc.*, **93**, 188 (1971).



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weakly basic amine nucleophiles (**2**, $\alpha = 1.0$), but is observed with strongly basic nucleophiles (**1**, $\alpha < 1.0$). and we thought that by substituting 1,2,4-triazole, a better, less basic leaving group, for imidazole the amount of proton transfer to the leaving group in the transition state would be decreased and general acid catalysis ($\alpha = <1.0$) would become significant even for weakly basic amines.[3,4] Furthermore, general base catalysis should increase the effective basicity of the attacking amine and thereby make it more like a basic amine, which shows this type of catalysis.[3] Since general base catalysis involving the attacking amine is known with both a good leaving group (acetylimidazolium ion) and a relatively poor leaving group (free acetylimidazole), we expected that it would also be significant for acetyltriazole, with a leaving group intermediate in basicity between imidazole and imidazole anion.

Experiments with acetyltriazole quickly showed that bifunctional acid and base terms (eq 1) are not significant for the reactions of this compound with weakly basic amines, although separate terms for acid and base catalysis are readily detectable. The reason for this became apparent when it was found that the Brønsted plots for both acid and base catalysis are nonlinear, suggesting a stepwise mechanism for the catalyzed reactions with intermediates that are not at equilibrium with respect to transport processes.[4] In this manuscript we describe the properties of these reactions, discuss possible mechanisms of catalysis, and compare these mechanisms to those for the reaction of the more basic hydrazine with the less reactive acetylimidazole, which shows a similar nonlinear Brønsted plot for general base catalysis but a linear plot, suggesting a "concerted" mechanism, for general acid catalysis.[5] A preliminary communication of this work has appeared.[6]

Experimental Section

Materials. 1-Acetyl-1,2,4-triazole, which has been shown to be the 1-acetyl isomer, was prepared by a published procedure: mp 39.5–40.5° (lit. 40–42°); uv (H_2O) λ 222 nm (ϵ 7.1 × 10^3) (lit. uv (tetrahydrofuran) λ_{max} 221.5 nm (ϵ 7.8 × 10^3)); nmr (CCl_4) δ 8.90:7.97:2.72 (1:1:3) (lit. nmr (CH_3CN) δ 8.95 and 8.03).[7] Methoxyamine hydrochloride (Eastman) was twice recrystallized from ethanol, mp 151–153°. Unless otherwise stated, inorganic salts and acetic acid were analytical reagent grade and were used without further purification. Other carboxylic acids and commercially available primary and tertiary amines were purified by distillation or recrystallization. *N*-Methylpiperidine was stored as the hydrochloride salt in 0.01 *M* hydrochloric acid.

The equivalent weights and pK_a values of disodium methylarsonate (Alfa inorganic, recrystallized from aqueous ethanol), trichloromethylphosphonate (Pfaltz and Bauer, recrystallized as the dipotassium salt from aqueous ethanol),[8] and potassium ethylphosphonate[8] were determined by pH titration with standard hydrochloric acid. Dipotassium trichloromethylphosphonate was found to be a dihydrate as determined from the equivalent weight of 154 ($K_2O_3PCCl_3$, equiv wt 138; $K_2O_3PCCl_3 \cdot 2H_2O$, equiv wt 156).

Kinetic Measurements. The disappearance of 1-acetyl-1,2,4-triazole was followed by the decrease in absorbance at 222 nm using a Gilford Model 2000 spectrophotometer equipped with a thermostated cell holder. The temperature was maintained at 25.0° with a circulating water bath. Buffer solutions were prepared within 3 hr before a series of kinetic runs. The ionic strength was maintained at 1.0 *M* with either tetramethylammonium chloride or potassium chloride.

The pH was measured both prior to and at the completion of a kinetic measurement using a Radiometer pH meter 26 with a GK 2321 C combined electrode. If the pH change during a reaction was greater than 0.04, the run was rejected. The variation of pH with buffer concentration was usually less than 0.1 for the range of concentrations used. Potassium chloride solutions that were adjusted with hydrochloric acid to the same pH as concentrated buffer solutions were used to dilute buffers of substituted acetic acids with pK below 3.0 and 1,2,4-triazole. Pseudo-first-order rate constants were corrected for the variation of the rate of H_3O^+ and OH^- catalyzed hydrolysis with pH. Pseudo-first-order rate constants for reactions of methoxyamine in the presence of buffer were also corrected for variation of the rate of the methoxyamine reaction with pH. Corrections due to pH variations resulted in less than a 5% correction to catalytic rate constants derived from the slopes of plots of the observed rate constants against buffer concentrations. The pK_a values of buffers at ionic strength 1.0 *M* were determined from the pH of solutions of known fraction free base, extrapolated to infinite dilution, or by titration of 0.05–0.1 *M* solutions. For acids of pK_a < 3.0, approximate pK_a values were obtained from the observed pH of concentrated buffer solutions; for difluoroacetic acid buffers a correction was made for dissociation of the acid component.[9] The rate constants for hydrolysis in strong acid solutions were plotted as a function of the acidity function H_A for the dissociation of protonated amides.[10] Values of H_0 for LiCl-HCl solutions were obtained by interpolation according to eq 3, in which Q is the activity coefficient ratio f_B/f_{H^+}.

$$H_0 = -\log C_{H^+} - \log Q_H - [\log Q_L - \log Q_H][LiCl]/8 \quad (3)$$

f_{BH^+}; $\log Q_H = 1.96$ in 8 *M* HCl and $\log Q_L = 2.49$ in 8 *M* LiCl.[11] Values of H_A were obtained from these H_0 values.[10]

Methoxyamine solutions were prepared separately, mixed with buffer solutions, and incubated for 5–10 min at 25°. Reactions were initiated by the addition of 0.01–0.02 ml of acetyltriazole in cold 50% acetonitrile to 3.0 ml of solution contained in a 1-cm path length cuvette. Initial concentrations of acetyltriazole were 0.5–2.0 × 10^{-4} *M*. Experiments with buffers that absorb significantly at 222 nm were carried out with a final concentration of 0.8–1.5 × 10^{-3} *M* acetyltriazole using a path length of 0.05 cm obtained by the use of quartz inserts; with imidazole and trichloromethylphosphonate the reactions were followed at 230 and 225 nm, respectively.

Reaction mixtures were monitored for reaction between methoxyamine and the added buffers by measurement of the pH over periods of time that were greater than several half-lives for the reaction with acetyltriazole, and by comparison of the rate constants observed after initially mixing methoxyamine and the buffer and rate constants observed several hours after mixing. Methoxyamine was found to react slowly with chloroacetate above pH 4. This side reaction was avoided by initiating reactions by the addition of acetyltriazole to reaction mixtures immediately after mixing, without the usual 5–10-min preincubation at 25°.

Methoxyamine was also found to react with bicarbonate buffer to form a carbamate, as indicated by a time-dependent increase in pH observed upon the addition of methoxyamine to bicarbonate buffers, 0.1 fraction dianion. The equilibrium constant $K = [CH_3ONHCO_2^-][H^+]/[CH_3ONH_2][CO_2]$ at 25° and ionic strength 1.0 *M* (KCl) was estimated to be 2 × 10^{-7} from the observed pH change. This value may be compared with a previously reported

(4) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972); R. Barnett, *Accounts Chem. Res.*, **6**, 41 (1973).
(5) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8828 (1972).
(6) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4729 (1972).
(7) (a) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956); (b) K. T. Potts and T. H. Crawford, *J. Org. Chem.*, **27**, 2631 (1962).
(8) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **95**, 5637 (1973).
(9) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 4377 (1968).
(10) K. Yates and J. C. Riordan, *Can. J. Chem.*, **43**, 2328 (1965).
(11) C H. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, p 39; D. Rosenthal, I. T. Oiwa, A. D. Saxton, and L. R. Lieto, *J. Phys. Chem.*, **69**, 1589 (1965); D. Rosenthal and J. S. Dwyer, *ibid.*, **66**, 2687 (1962).

value $K = 10^{-6}$ at 10° and ionic strength 1.0 M (KCl).[12] Under the conditions of the kinetic experiments the maximum amount of carbamate corresponded to 3% of the total methoxyamine concentration. Correction for carbamate formation decreased the derived rate constant for catalysis by carbonate dianion by <10% but increased the catalytic constant for bicarbonate from 8.3 to 17 M^{-2} sec^{-1}; the latter rate constant is, accordingly, only an approximate value.

All rate constants were determined under pseudo-first-order conditions with the concentrations of nucleophile and buffer in large excess over that of the substrate. Plots of log $(A_t - A_\infty)/(A_0 - A_\infty)$ against time were linear over 3 to 4 half-lives. Experiments were generally carried out at 5-7 different buffer concentrations in the presence and absence of methoxyamine. Duplicate rate constants agreed to within 2-5%.

Kinetic Analysis. Plots of the experimental pseudo-first-order rate constants, k_{obsd}, against total buffer concentration were found to be linear for the reactions of 1-acetyl-1,2,4-triazole with buffers of substituted acetic, phosphonic, phosphoric, cacodylic, arsonic, boric, and carbonic acids, tertiary amines, and alcohols. The intercepts of these plots are k_0 (sec^{-1}) for hydrolysis and the slopes are second-order rate constants k_B' (M^{-1} sec^{-1}). The values of k_B' were plotted against the fraction free base of the buffer, α', to obtain the rate constant for reaction with the base, k_B, as the intercept at $\alpha' = 1.0$ and the rate constant for reaction with the acid, k_{BH^+}, as the intercept at $\alpha' = 0$.

Similar experiments were carried out in the presence of a constant concentration of added methoxyamine and the intercepts and slopes were corrected by the values of k_0 and k_B' obtained in the absence of methoxyamine. The corrected intercepts k_{MA} correspond to the sum of the rate constants for the reactions of methoxyamine that are not catalyzed by the added buffer. The corrected slopes were divided by the concentration of free methoxyamine and the resulting rate constants, k_{cat}, were plotted against α' to obtain the rate constants k_3 for catalysis of the methoxyamine reaction by the basic component of the buffer and k_4 for catalysis by the acidic component, from the intercepts at $\alpha' = 1.0$ and $\alpha' = 0$, respectively.

The rate constants for the reactions with primary amines in the absence of other buffer components are described by eq 4.[13,14]

$$k_{obsd} - k_0 = k_1[RNH_2] + k_2[RNH_3^+] + k_3[RNH_2]^2 + k_4[RNH_2][RNH_3^+] + k_3'[RNH_2][OH^-] \quad (4)$$

Plots of $(k_{obsd} - k_0)/[RNH_2]_T$ against $[RNH_2]_T$ were linear. The intercepts k_1 (M^{-1} sec^{-1}) correspond to the second-order rate constants $k_1\alpha + k_2(1 - \alpha) + k_3'\alpha a_{OH^-}$, in which α is the fraction free base of the amine. The slope k_S (M^{-2} sec^{-1}) corresponds to $k_3\alpha^2 + k_4\alpha(1 - \alpha)$. Intercepts, k_1, and slopes, k_S, were determined at three to five different buffer ratios. Plots of k_1 against the fraction free base of the amine exhibited a slight concave upward curvature indicative of catalysis by hydroxide ion for reactions of ammonia, methoxyethylamine, allylamine, and propylamine. The values of k_3' and k_1 for these amines were obtained from the slopes and intercepts, respectively, of plots of k_1/α against a_{OH^-}, under experimental conditions such that $k_1\alpha \gg k_2(1 - \alpha)$. For other amines k_1 was plotted against α and the values of k_1 and k_2 were obtained from the intercepts at $\alpha = 1.0$ and $\alpha = 0$, respectively. Plots of k_S/α against the fraction free base of the amine were linear and the values of k_3 and k_4 were obtained from the intercepts at $\alpha = 1.0$ and $\alpha = 0$, respectively.

The rate constants for the methoxyamine reaction obtained in methoxyamine buffers by the above procedure were found to account, within 10%, for the corrected intercepts, k_{MA}, that were obtained in the experiments with added buffers.

Product analysis also provided evidence for a term in the rate law corresponding to specific base catalysis of the aminolysis reactions with strongly basic amines. The amides formed in the reactions of acetyltriazole with 0.1 M ammonia, 0.05 M allylamine, and 0.05 M n-propylamine in 0.1 N potassium hydroxide with the ionic strength maintained at 1.0 M (KCl) were assayed by the neutral hydroxylamine method.[13] Acetohydroxamic acid, N-methylacetamide, and the acetyltriazole solution used in the experiments were subjected to the same assay procedure. N-Methylacetamide gave a color yield of 100% compared to acetohydroxamic acid. The observed yields of amide from the reactions with the three amines were 35, 90, and 83%, respectively. The calculated yields assuming hydroxide ion catalysis of aminolysis (eq 4) were 83, 97, and 96%, respectively. In the absence of specific base catalysis of aminolysis the expected yields under these conditions would be 12, 26, and 35%, respectively.

For buffers that showed little or no catalysis, an upper limit for the catalytic constant was estimated by assuming that a 10% increase in the rate at the highest buffer concentration examined was caused by the buffer, but not detected. The upper limit for the rate constant corresponding to catalysis by hydroxide ion was obtained from experiments with 0.08 M methoxyamine in 0.01 M bicarbonate and borate buffers in the pH range 8.5-9.9. A 20% increase in the rate of reaction, after correction for hydrolysis, was observed with increasing pH. However, this increase could be accounted for by buffer catalysis in the case of the bicarbonate buffers. If the increase in rate observed with borate buffers was attributed to buffer catalysis by borate anion, the rate constant k_4 for this catalysis was estimated to be $<3.3 \times 10^1$ M^{-2} sec^{-1}. The upper limit estimated for the rate constant corresponding to catalysis by hydroxide ion is 7×10^3 M^{-2} sec^{-1} if the observed increase in rate is attributed entirely to this catalysis.

Results

The pH–rate profile for the hydrolysis of 1-acetyl-1,2,4-triazole (Figure 1) is similar to that for acetylimidazole,[13] but with faster pH-independent and hydroxide ion reactions and a break, caused by protonation of acetyltriazole, at a lower pH. The rate law is given in eq 5 and the rate constants in 1.0 M tetramethylammonium chloride are $k_{H^+} = 0.22$ M^{-1} sec^{-1}, $k_{H_2O} = 1.7 \times 10^{-3}$ sec^{-1} (1.5×10^{-3} sec^{-1} in 1.0 M potassium chloride), and $k_{OH^-} = 2.7 \times 10^3$ M^{-1} sec^{-1}. Staab has previously reported a rate constant of 1.75×10^{-3} sec^{-1} for the hydrolysis of 1-acetyl-1,2,4-triazole in water at 25°.[7a]

$$k_{obsd} = k_{H^+}a_{H^+} + k_{H_2O} + k_{OH^-}a_{OH^-} \quad (5)$$

In acid solutions the rate levels off, because of protonation of acetyltriazole, and then shows acid inhibition above 2 M hydrochloric acid, as was observed previously with acetylimidazolium ion.[15] In order to separate the effects of protonation and acid inhibition it was assumed that the per cent inhibition by acid of the hydrolysis of acetyltriazolium and acetylimidazolium ions is the same and that the ionization of acetyltriazolium ion follows the acidity function h_A.[10] The observed rate constant in acid solution is then given by eq 6, in

$$k_{obsd} = k_H^0 Q\left(\frac{h_A}{h_A + K_{AT}}\right) \quad (6)$$

which k_H^0 is the rate constant for hydrolysis of acetyltriazolium ion at zero ionic strength, K_{AT} is the ionization constant of acetyltriazolium ion, and Q is the activity coefficient ratio $f_{AcTrH^+}a_{H_2O}/f^{\pm}$ that describes the acid inhibition, estimated from the acid inhibition of acetylimidazolium ion hydrolysis.[15] The best fit of the data to eq 6 was obtained with $K_{AT} = 1.5$ M and $k_H^0 = 0.38$ sec^{-1} and the calculated line based on these constants is drawn through the points in Figure 1. The dashed line in Figure 1 shows the expected rate in the absence of acid inhibition and in the presence of 1.0 M tetramethylammonium chloride, for which the value of Q is 0.8.[15] There is no inhibition by hydrochloric acid

(12) M. Caplow, *J. Amer. Chem. Soc.*, 90, 6795 (1968).
(13) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).
(14) D. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, **93**, 178 (1971). The numbering of the rate constants in this paper corresponds to that in this reference.
(15) S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.* 84, 232 (1962).

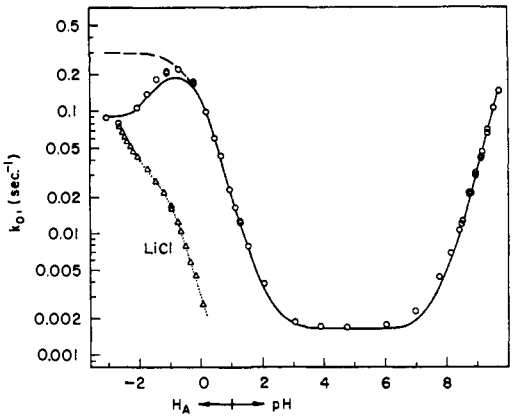


Figure 1. Dependence on pH of the hydrolysis of 1-acetyl-1,2,4-triazole at 25°. Above pH 0 the ionic strength was maintained at 1.0 *M* with tetramethylammonium chloride or potassium chloride. The experiments were carried out in hydrochloric acid below pH 3 and in 0.01 *M* acetate, phosphate, and borate buffers above pH 3; reactions with these buffers do not significantly affect the pH–rate profile: (——) calculated from the rate constants given in the text and eq 5 and 6; (△) ionic strength maintained at 8.0 *M* with lithium chloride; (---) expected rate in the absence of acid inhibition.

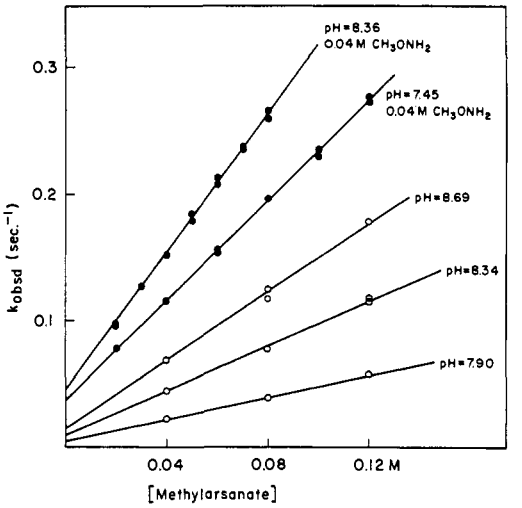


Figure 2. Pseudo-first-order rate constants for the disappearance of acetyltriazole in the presence and absence of methoxyamine as a function of the concentration of methylarsonate buffers at 25°, ionic strength 1.0 *M* (KCl).

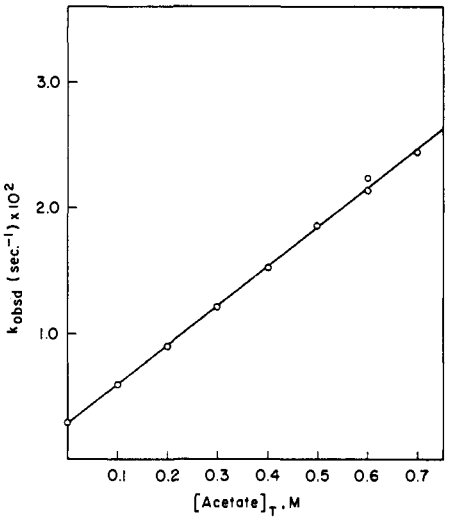


Figure 3. Dependence on acetate buffer concentration (80% potassium acetate) of the observed rate constants for the reaction of acetyltriazole with 0.15 *M* trifluoroethylamine at pH 5.14, 25°, ionic strength 1.0 *M* (KCl).

if the ionic strength is maintained constant at 8.0 *M* by the addition of lithium chloride (Figure 1, triangles). The small rate increase in the most acidic solutions may represent an imbalance of activity coefficient effects or an acid-catalyzed reaction of the acetyltriazolium ion.

The pK_a of acetyltriazolium ion of −0.2 is 2.8 units below that of triazolium ion, similar to the decrease of 3.2 units in the pK_a of imidazolium ion upon acetylation to acetylimidazolium ion.[16]

The second-order rate constants for the disappearance of acetyltriazole in the presence of a series of buffers and nucleophiles and the third-order rate constants for catalysis by these buffers of the reaction of methoxyamine with acetyltriazole are given in Table I.[19] The data obtained with methylarsonate buffers are shown in Figure 2. This example was chosen because it represents the most unfavorable case examined with respect to the fraction of the total catalyzed reaction that represents reaction with methoxyamine. The rate of the catalyzed reaction was found to be strictly linear with respect to buffer concentration in every case. A plot of k_{obsd} as a function of acetate buffer concentration up to 0.7 *M* for the reaction with trifluoroethylamine is shown in Figure 3.

The rate constants for the methoxyamine reaction were separated into the components corresponding to the acidic and basic species of the reactant or catalyst according to eq 7, in which k_0 is the hydrolysis rate in the absence of buffer, as described in the experimental section. In Figure 4 are shown examples of plots of k_{cat} against the fraction free base of the buffer, for the reactions of methoxyamine catalyzed by chloroacetate, methylarsonate, and cacodylate buffers. These rate constants are summarized in Table II. The assignment of the rate constants for catalysis by trichloromethylphosphonate, phosphate, ethylphosphonate, methylarsonate and bicarbonate monoanions is ambiguous, since these compounds can act as either base or acid catalysts. By comparison with the rate constants for other catalysts of comparable p*K*, trichloromethylphosphonate and phosphate presumably act as acid catalysts, methylarsonate and bicarbonate as base catalysts, and ethylphosphonate as both an acid and a base catalyst.

$$k_{obsd} = k_0 + k_B[B] + k_{BH^+}[BH^+] + k_1[CH_3ONH_2] + k_2[CH_3ONH_3^+] + k_3[B][CH_3ONH_2] + k_4[BH^+][CH_3ONH_2] \quad (7)$$

(16) Since 1-methyl-1,2,4-triazole undergoes protonation at the 4 (not the 2) position,[17] 1,2,4-triazolium ion is expected to have protons on the 1 and 4 nitrogen atoms and 1-acetyl-1,2,4-triazolium ion to be protonated on the 4 position. The pK_a of 1-methyl-1,2,4-triazolium ion is 1.0 unit lower than that of the 4-methyl compound (ref 18). This suggests that the ionization of 1,2,4-triazolium ion occurs at the 4 position and the 1-H compound is the stable isomer of free 1,2,4-triazole. Since the protonation of 1-acetyl-1,2,4-triazole also occurs at the 4 position, the substituent effect of the acetyl group refers to protonation of the same nitrogen atom in the free and acetylated triazoles. However, the reactions of acetyltriazolium ion with nucleophiles give as the immediate product the isomer of 1,2,4-triazole with the proton at the 4 position, which is some tenfold less stable than the 1-H compound.

(17) G. B. Barlin and T. J. Batterham, *J. Chem. Soc. B*, 516 (1967).

(18) C. F. Kröger and W. Freiberg, *Chimia*, 21, 161 (1967); *Z. Chem.*, 5, 381 (1965).

(19) See paragraph at end of paper regarding supplementary material.

Table II. Summary of Derived Rate Constants at 25°, Ionic Strength 1.0 *M* (KCl)

Buffer	pK_a	k_B, M^{-1} sec^{-1}	k_{BH^+}, M^{-1} sec^{-1}	k_3, M^{-2} sec^{-1}	k_4, M^{-2} sec^{-1}
Difluoroacetate	1.05[a]		$\leq 1.0 \times 10^{-2}$	≤ 0.12	≤ 100
Cyanoacetate	2.23	5×10^{-4}	1.2×10^{-3}	0.57	83
Chloroacetate	2.65	8.3×10^{-4}	1.0×10^{-3}	1.2	63
Methoxyacetate	3.33	1.8×10^{-3}	$\leq 8 \times 10^{-5}$	4.0	53
Acetate	4.60	3.8×10^{-3}	$\leq 3.3 \times 10^{-4}$	15	40
Cacodylate	6.16	1.2×10^{-1}		38	13
Hexafluoro-2-propanol	9.30	3.5×10^{2}			
Sulfate	1.97[b]			≤ 1.3	
Trichloromethylphosphonate	4.20	8.0×10^{-3}		12	30
Phosphate	6.49 (1.72)[c]	3.3×10^{-2}	4.2×10^{-3}	75	25
Ethylphosphonate	7.60 (2.23)[d]	5.6×10^{-2}	3×10^{-3}	72	8.3
Methylarsonate	8.50 (3.98)[d]	2.3		83	22
Borate	9.4	9.7×10^{-1} [e]			
Carbonate	9.78	1.1		120 (130)[f]	17[g] (8.3)[f,g]
1,2,4-Triazole	2.58	1.0×10^{-3}	$\leq 1.7 \times 10^{-4}$	1.7	140
Imidazole	7.21[h]				1.3
Morpholineethanesulfonic acid	6.30	1.4×10^{-3}		2.7	1.4
N-Allylmorpholine	7.35	7.3×10^{-3}		4.8	≤ 1.0
N-Methylmorpholine	7.84[e]	3.2×10^{-2} [e]		7.7	≤ 0.5
N,N'-Dimethylpiperazine	8.99 (4.65)[d]	1.8×10^{-1}		27	3.3
N-Methylpiperidine	10.53[d]	1.5		50	
Methoxyamine	4.72			10	25
2,2,2-Trifluoroethylamine	5.81[i]				6.0
Glycine ethyl ester	7.90[h]				<0.33[j]
Cyanoethylamine	8.17[k]				<0.14[j]
Morpholine	8.74[l]				<0.24[j]

[a] pK_a corrected for dissociation of the acidic species.[9] [b] pK_a at zero ionic strength: M. Kerker, *J. Amer. Chem. Soc.*, **79**, 3664 (1957). [c] First ionization at μ = 1.0 *M*, KCl.[9] [d] First ionization at μ = 1.0 *M*, KCl determined by pH titration. [e] μ = 1.0 *M*, $(CH_3)_4NCl$. [f] Uncorrected for carbamate formation. [g] Approximate value. [h] μ = 1.0 *M*, KCl: W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968). [i] μ = 1.0 *M*, KCl: T. St. Pierre and W. P. Jencks, *ibid.*, **90**, 3817 (1968). [j] Reported as an upper limit. The reaction was run at only one buffer ratio. [k] μ = 1.0 *M* KCl: M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8818 (1972). [l] μ = 1.0 *M* $(CH_3)_4NCl$.[14]

Table IV. Summary of Derived Rate Constants for Reactions of 1-Acetyl-1,2,4-triazole with Primary Amines at 25°, Ionic Strength Maintained at 1.0 *M* with Tetramethylammonium Chloride

Amine	pK_a	k_1, M^{-1} sec^{-1}	k_2, M^{-1} sec^{-1}	k_3, M^{-2} sec^{-1}	k_4, M^{-2} sec^{-1}	k_5, M^{-2} sec^{-1}
Methoxyamine	4.74	0.52	0.10	11	30	
	4.72[a]	0.52	0.12	10	25	$<7 \times 10^3$
2,2,2-Trifluoroethylamine	5.81[a,b]		<0.003	0.68	0.28	
Cyanoethylamine	8.08	0.083		57	3.3	
Ammonia	9.48	1.5		3.8×10^3		1.3×10^5 [d]
Methoxyethylamine	9.68	1.7		2.5×10^3	<8	1.3×10^5 [d]
Allylamine	9.89	8.3		9.5×10^3		8.3×10^5 [d]
n-Propylamine	10.82[c]	0.53		5.8×10^4		2.2×10^6 [d]

[a] Ionic strength 1.0 *M*, KCl. [b] T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 3817 (1968). [c] Determined by titration. [d] Approximate values.

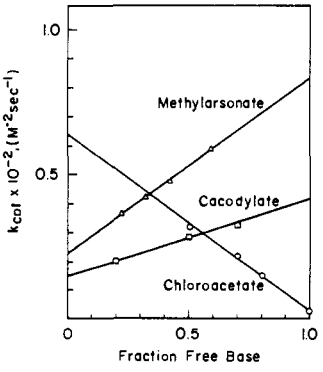


Figure 4. Observed catalytic constants for the reaction with methoxyamine plotted against the fraction free base of the buffer, to separate the terms representing catalysis by the acid and base forms of the buffers.

Solvent effects and specific salt effects are not sufficiently large to cause serious uncertainty in most of the catalytic constants. A 7% decrease in rate was observed upon the addition of 1.0 *M* 2-propanol to the reaction with 0.06 *M* methoxyamine, pH 4.76. An increase in ionic strength from 1.0 to 3.0 *M* with potassium chloride was found to cause a 30% decrease in the rate with 0.04 *M* methoxyamine, pH 5.16, and substitution of 1.0 *M* tetramethylammonium chloride for 1.0 *M* potassium chloride causes only small changes in the rate constants for the reactions of methoxyamine (Table IV).

Although nucleophilic catalysis by triazole of the hydrolysis of 1-acetyl-1,2,4-triazole through the intermediate formation of the 4-acetyl compound is possible in principle, the observed reaction probably represents general base catalysis of hydrolysis by the weakly basic triazole. The 4-acetyl- and 1-acetyltriazoles are expected to have similar properties since there is a difference of only 1 p*K* unit between the basicities of the 1 and 4 nitrogen atoms of 1,2,4-triazole.[16] As the triazole concentration is increased the observed rate of

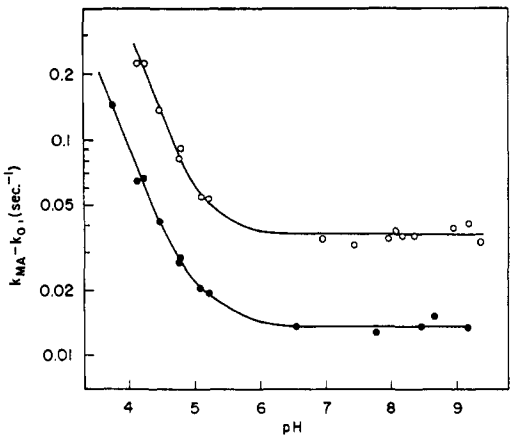


Figure 5. Dependence on pH of the observed rate constants for the reaction of acetyltriazole with methoxyamine at constant free base concentration of 0.02 *M* (●) and 0.04 *M* (○), ionic strength 1.0 *M* (HCl).

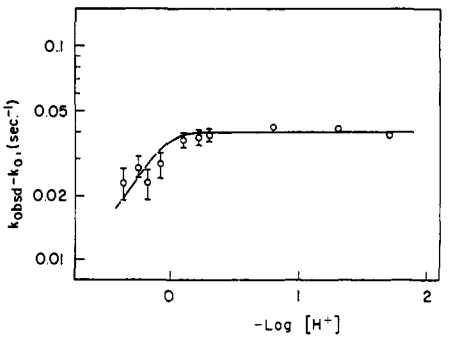


Figure 6. The effect of acid concentration on the rate of reaction of acetyltriazole with 0.4 *M* methoxyammonium ion at 25°, ionic strength 3.0 *M* (KCl).

hydrolysis should level off at the rate of hydrolysis of the 4-acetyl compound when the 1-acetyl is completely converted to the 4-acetyl isomer, so that the plot of k_{obsd} against triazole concentration is expected to be nonlinear. The observed linear plot supports the general base catalysis mechanism. Nucleophilic catalysis of hydrolysis by *N*-methylmorpholine would generate the *N*-acetyl-*N*-methylmorpholinium ion as an intermediate and the observed hydrolysis would be inhibited if this intermediate reacted with added triazole to regenerate starting materials.[20] No such inhibition was observed in the presence of 0.3 *M N*-methylmorpholine ± 0.1 *M* triazole at pH 8.2.

The enhanced rate of disappearance of acetyltriazole in the presence of carboxylate ions almost certainly represents general base catalysis of hydrolysis, since the reaction of acetate ion with acetylimidazolium ion, a compound with a much better leaving group, is only 22% nucleophilic.[20]

The reaction of 1,2,4-triazole (0.02–0.05 *M*) with acetic anhydride (1.2×10^{-4} *M*) was measured in acetate buffers at pH 4.0, 4.6, and 5.2, ionic strength 1.0 *M* (KCl), by following the appearance of acetyltriazole at 222 nm. The reaction was found to proceed to completion in the presence of added acetate buffers, up to 0.4 *M* at pH 4.0 and 0.2 *M* at pH 4.6, and no rapid decrease in the absorbance of acetyltriazole was observed upon addition to concentrated acetate buffers. Thus, a nucleophilic back-reaction of acetate or acetic acid with acetyltriazole could not be detected.

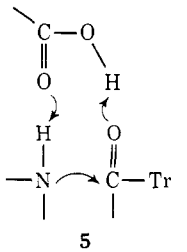
The reactions of acetyltriazole with primary amines are kinetically more complex (eq 4) because of catalysis by hydroxide ion and by a second molecule of amine or ammonium ion that causes upward curvature in plots of k_{obsd} against total amine concentration, as observed previously for the reactions of acetylimidazole.[13,14] For basic amines the dominant reaction path involves general base catalysis (k_3); the specific and general acid catalyzed pathways (k_2 and k_4) become important for weakly basic amines. The rate constants for the reaction with methoxyamine, at a constant concentration of free base and extrapolated to zero buffer concentration, are shown as a function of pH in Figure 5. The increase in the observed rate below pH 6 corresponds to these acid-catalyzed pathways. There is a small, but definite, increase in the observed rate constants for several amines at high pH that corresponds to catalysis by hydroxide ion. A correction was made for this hydroxide ion catalysis k_3', which is approximately proportional to k_3, in the determination of k_1, but the catalysis was not large enough to permit accurate determination of the rate constants k_3'. The experimental rate constants are summarized in Table III[19] and the derived rate constants in Table IV.

The rate of reaction of acetyltriazole with 0.4 *M* methoxyammonium ion in acid solution is shown in Figure 6. There is no decrease in rate with increasing acidity other than that expected from the conversion of acetyltriazole to acetyltriazolium ion ($pK_a = -0.2$).

Discussion

General Acid and Base Catalysis. Bifunctional, concerted general acid and base catalysis by two molecules of buffer, as described by the rate law of eq 1, would result in a greater than first-order dependence of the observed rate constants upon buffer concentration because of the product term [HA][B] in the rate law. The dependence of the observed second-order rate constants for the reactions of amines with acetyltriazole upon the concentration of buffer catalysts was found to be strictly linear in all cases, including catalysis of the reaction of acetyltriazole with trifluoroethylamine by acetate buffers of up to 0.7 *M* (Figure 3). Thus, there is no significant product term (and also no significant self-complexation of the buffers that gives a negative deviation from linearity) under the conditions of our experiments.

Concerted bifunctional catalysis can also occur with a single molecule of buffer that has both acidic and basic sites (*e.g.*, **5**) and has been proposed to explain the smaller Bronsted α values for carboxylic acids compared to ammonium ions in the general acid catalyzed me-



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

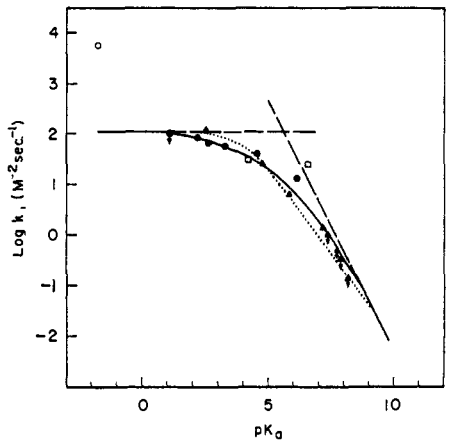


Figure 7. Brønsted plot for general acid catalysis of the reaction of methoxyamine with acetyltriazole at 25°: (●) carboxylic and cacodylic acids; (▲) protonated amines; (□) trichloromethylphosphonate and phosphate monoanions; (○) solvated proton. The solid line is calculated for the simple proton transfer mechanism of eq 8 and the dotted line for the mechanism proceeding through k_o of eq 12.

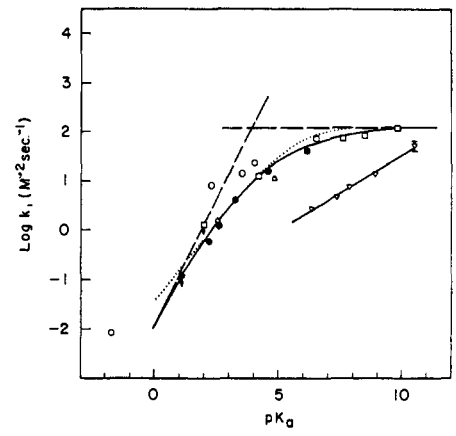


Figure 8. Brønsted plot for general base catalysis of the reaction of methoxyamine with acetyltriazole at 25°: (●) carboxylate and cacodylate monoanions; (○) ethylphosphonate, bicarbonate and methylarsonate monoanions; (□) oxygen dianions; (△) triazole and methoxyamine; (▽) *N*-alkylmorpholines and piperidines. The solid line is calculated for the simple proton transfer mechanism of eq 8 and the dotted line for the mechanism proceeding through k_o' of eq 9.

thoxyaminolysis of *p*-nitrophenyl acetate.[21] In the methoxyaminolysis of acetyltriazole, the catalytic constants for triazolium and methoxyammonium ions, which have no basic site for bifunctional catalysis, are equal to those for carboxylic acids; furthermore, oxyanions, which have no acidic site, are the most effective base catalysts examined (Table II).[22] The catalytic constants for phosphate monoanion as an acid catalyst and for bicarbonate and methylarsonate monoanions as base catalysts are about twofold larger and that for ethylphosphonate monoanion as a base catalyst is about tenfold larger than those for other catalysts of comparable pK. However, part of the observed catalytic constant for ethylphosphonate monoanion represents general acid catalysis by this species (pK_a = 7.6). Thus, concerted, bifunctional acid–base catalysis of the methoxyaminolysis of acetyltriazole by relatively strong acids and bases is not significant, although there may be a small rate enhancement with bifunctional catalysts of intermediate pK. The pK values of the reactants and the addition intermediate (see Appendix) are such that no large free energy advantage is to be expected from concerted bifunctional catalysis; such catalysis would require that two initially unfavorable proton transfers become favorable during the formation or breakdown of the intermediate.[4,23]

The nonlinear Brønsted plots for general acid and general base catalysis shown in Figures 7 and 8, respectively, provide experimental support for stepwise reaction mechanisms. The evidence that these Brønsted plots are nonlinear is as follows. The catalytic constants for carboxylic and cacodylic acids establish a Brønsted α value of ≤ 0.2 for acidic catalysts (closed circles, Figure 7). Catalysis by protonated amines is similar to that for carboxylic acids for the more acidic catalysts, but drops off for the weaker acids to a slope $\alpha \geq 0.6$ (triangles, Figure 7). It is possible that the limiting slope is steeper than that shown since no catalysis was detected with the least acidic catalysts and the rate constants are given only as upper limits, shown by arrows in the figure. For general base catalysis, the rate constants for oxygen dianions establish a Brønsted β value of ≤ 0.2 for the basic catalysts (squares, Figure 8). For less basic dianions and monoanions the catalytic constants fall below this slope and for carboxylate anions the slope β is ≥ 0.6 (closed circles, Figure 8). An upper limit for the catalytic constant of hydroxide ion of $\leq 7 \times 10^3$ M^{-2} sec^{-1} falls below the Brønsted line established by the carboxylate ions by a factor of 10^4–10^5. The catalytic constants for triazole and methoxyamine (triangles) are similar to those for carboxylate ions of comparable basicity, but the constants for N-substituted morpholines and piperidines (inverted triangles) fall below those for the other basic catalysts. These negative deviations have been observed in other systems and are presumably a consequence of the special steric and conformational requirements of these molecules, as discussed elsewhere.[5,8,24] The open circles in Figure 8 and a square in Figure 7 show the small positive deviations of the points for phosphate, ethylphosphonate, methylarsonate, and bicarbonate monoanions. The pK_a values refer to the observed dissociation at ionic strength 1.0 M except for that of sulfate, which was not determined under the conditions of the experiments; correction to ionic strength 1.0 M would shift the upper limit for this rate constant to the left in Figure 8. The catalytic constants have not been statistically corrected, for reasons which are discussed elsewhere;[5,8] such corrections decrease the amount of the negative deviations for N-substituted morpholines and piperidines, but do not otherwise change the shape of the plots significantly.

The nonlinear Brønsted plots of Figures 7 and 8 provide evidence for a change in the nature of the rate-determining step with changing pK of the catalyst and for a stepwise mechanism in which an intermediate is not at equilibrium with the medium with respect to transport processes, in both the acid and the base catalyzed reaction pathways.[4] Furthermore, the limiting

(21) L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *J. Amer. Chem. Soc.*, 89, 3537 (1967).

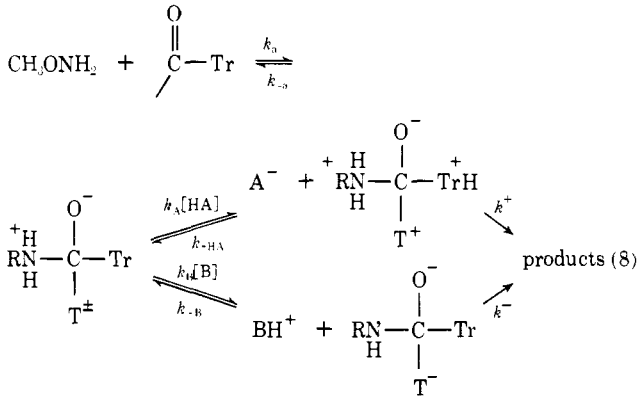
(22) A similar argument may be applied to the methoxyaminolysis of *p*-nitrophenyl acetate, for which methoxyammonium ion is also an effective catalyst.[21]

(23) W. P. Jencks, *J. Amer. Chem. Soc.*, 94, 4731 (1972).

(24) J. Hine and J. Mulders, *J. Org. Chem.*, 32, 2200 (1967).

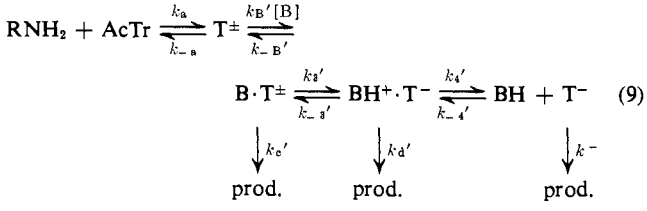
rate constants are the same for the acid and the base catalyzed reactions, suggesting an identical or closely similar rate-determining step for these two reactions. We offer two limiting interpretations that are consistent with these data.

The first interpretation, I, is that a simple proton transfer between the catalyst and an intermediate is the rate-determining step and that the rate of this proton transfer step is diffusion controlled in the favorable direction when the ΔpK between the catalyst and the intermediate is large. The data are consistent with an approach to limiting Brønsted slopes of 0 and 1.0, shown by the dashed lines in the figures. The solid lines in the figures show the curvature actually observed for such simple proton transfers by Eigen and coworkers[25] and are consistent with the data. Equation 8



shows a mechanism of this kind, with rate-determining protonation of the dipolar addition intermediate $T^{\pm}$ for general acid catalysis and rate-determining proton abstraction from the intermediate for general base catalysis.

According to the second interpretation, II, the limiting rate constants for strong acids and bases represent diffusion-controlled encounter of the catalyst with $T^{\pm}$ that leads to product formation in one or more additional steps, as in mechanism I, but the descending limbs of the Brønsted curves for weak acids and bases represent general acid or base catalyzed breakdown of the addition intermediate. For general base catalysis the rate-determining step with weak base catalysts is the concerted general base catalyzed decomposition of $T^{\pm}$ with the rate constant k_c' (eq 9). A concerted mechanism of



decomposition is required if the immediate product of proton removal, T^-, has too short a lifetime to exist as a discrete intermediate ($k_d' > 10^{13}$ sec^{-1}) so that k_3' and k_d' cannot represent separate steps. It has been suggested previously that the corresponding intermediate T^- in the acetylimidazole–hydrazine reaction has, at most, a borderline existence[5] and triazole ($pK_a = 10.1$) is a better leaving group than imidazole ($pK_a = 14.2$).[26] The steady-state rate expression for this mechanism is given in eq 10 and the dotted line in Figure 8 is calculated

$$k_{obsd} = \frac{k_B' k_c' K_{add}}{k_{-B}' + k_c'} \qquad (10)$$

from this equation and the Brønsted eq 11 for the concerted decomposition step. The value of $K_{add}k_B'$ is 100 M^{-2} sec^{-1}, the experimental limiting rate constant for strong bases ($K_{add} = k_a/k_{-a}$ and $K_{add}k_B'$ represents the diffusion-controlled formation of encounter complexes between the catalysts and $T^{\pm}$), the value of k_{-B}', for the separation of these complexes, is taken[8] as 10^{11} sec^{-1}, and the constants in eq 11 are based on the experimental points for weak base catalysts. The calculated line provides a satisfactory fit to the data, keeping in mind the expected small differences in the rates of encounter and catalysis for different classes of catalysts. An analogous situation has been observed previously in the general base catalyzed breakdown of hemithioacetals.[27] In this reaction the general base catalyzed decomposition is rate determining for most bases, but with the strong base hydroxide ion the rate of breakdown reaches the diffusion-controlled limit and there is a change in rate-determining step to the diffusion-controlled encounter of the base and the substrate.

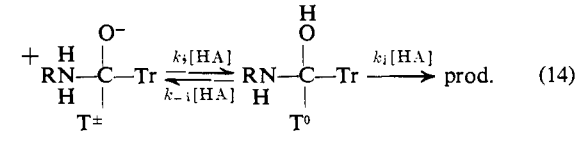
$$\log k_c' = 0.6pK_a + 7.5 \qquad (11)$$

For general acid catalysis, the descending limb of the Brønsted plot may be assigned to a concerted general acid catalyzed decomposition of $T^{\pm}$ (mechanism IIa; k_c eq 12) or to general acid catalyzed decomposition of the uncharged intermediate T^0 (mechanism IIb; k_j, eq 14). Mechanism IIa (eq 12) will be followed if protonation takes place on the triazole group and the resulting "intermediate" T^+ is too unstable to have a finite existence ($k_d > 10^{13}$ sec^{-1}). The Brønsted curve for this mechanism was calculated in the same way as that for the analogous base-catalyzed reaction, based on eq 13

$$\log k_c = -0.7pK_a + 13.9 \qquad (13)$$

for the concerted decomposition step and $K_{add}k_{HA}' = 100\ M^{-2}$ sec^{-1}, the same limiting rate constant for diffusion-controlled encounter of $T^{\pm}$ with the catalyst as in the base-catalyzed reaction. The calculated curve is shown as the dotted line in Figure 7 and provides a satisfactory fit to the data.

Mechanism IIb will be followed if protonation occurs initially on the more basic oxygen atom of $T^{\pm}$, followed by the rapid loss of a proton from the cationic methoxyammonium group and by general acid catalyzed breakdown of the resulting intermediate T^0. The essential features of mechanism IIb are described by eq 14 and by



(25) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).
(26) K. T. Potts, *Chem. Rev.*, 61, 87 (1961); G. Yagil, *Tetrahedron*, 23, 2855 (1967).
(27) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, 91, 6758 (1969).

the steady-state eq 15. If the breakdown step k_j is

$$k_{obsd} = \frac{k_i k_j K_a}{k_{-i} + k_j} \quad (15)$$

concerted it may be described by the Brønsted eq 16.

$$\log k_j = -0.7pK + 5.5 \quad (16)$$

The equilibrium constant k_i/k_{-i} is estimated to be $10^{6.4}$ from the pK_a values given in the Appendix, $K_{add}k_i'$ is 100 M^{-2} sec^{-1}, and k_{-i} is taken as $10^9/10^{6.4} = 10^{2.6}$ M^{-1} sec^{-1}. Equations 15 and 16 give a calculated curve identical with that obtained from eq 10 and 11, shown as the dotted line in Figure 7. If the breakdown is stepwise with rate-determining proton transfer to the weakly basic triazole group of T^0, the descending limb of the Brønsted plot will have a slope of -1.0 and will be identical or parallel with the dashed line in Figure 7. The data do not distinguish between these two mechanisms for the breakdown of T^0, although the degree of curvature provides somewhat better agreement with the concerted mechanism. Rate-limiting protonation of the oxygen atom of $T^{\pm}$ has been proposed previously for the general acid catalyzed aminolysis of thiol esters.[28,29] The ring closure reaction of *o*-aminoacetanilide to 2-methylbenzimidazole, which involves expulsion of the carbonyl oxygen atom after the rate-determining step, may involve a similar rate-determining protonation of the oxygen atom of $T^{\pm}$.[30] The rate constants for catalysis of this reaction by acetic acid and by phosphate monoanion are identical and are closely similar with that for catalysis by hydroxide ion, which could trap $T^{\pm}$ by abstracting a proton from the attacking nitrogen atom.

The reaction paths of mechanism II provide considerably better agreement with the observed position of the breaks in the nonlinear Brønsted plots for acid and base catalysis than do the simple proton transfer reactions of mechanism I. Simple proton transfer reactions are diffusion controlled in the favorable direction and exhibit breaks near the point at which the pK values of the proton donor and acceptor are equal.[25] The breaks in Figures 7 and 8, at the intersection point of the limiting lines of slope 0 and 1.0, occur at pK values of 5.5 and 4.0 for acid and base catalysis, respectively. The estimated pK_a of $T^{\pm}$ = 6.5 (see Appendix) is 2.5 units above the break point at pK_a = 4.0 for general base catalysis. This difference is probably beyond the combined errors of the estimations of the pK values; a correction for electrostatic effects with the anion catalysts[25] increases the difference. The concerted mechanism for the base-catalyzed breakdown of $T^{\pm}$ *via* k_c' provides a faster path for the reaction with relatively weak bases than does the simple proton transfer mechanism[5] and therefore leads to a break in the curve at a lower pK_a' as observed.

The break in the curve for acid catalysis should occur close to the pK_a of the protonated triazole in the addition intermediate if proton transfer to this group is rate determining, and close to the pK_a of the hydroxyl group if oxygen protonation is rate determining. The pK_a of triazolium ion is 2.6 and it would be expected that this value would be decreased further in T^+ because of the electron-withdrawing substituents in this intermediate. The pK_a of imidazolium ion is decreased by 1.8 units in a tetrahedral addition intermediate formed from imidazole and a phthalimidium ion.[31] The pK_a of the hydroxyl group is estimated to be 8.1 (see Appendix). Neither of these values is close to the observed break point of 5.5 for general acid catalysis. Mechanism IIa raises the pK at which the break occurs above the pK of protonated triazole by providing a faster path for the breakdown of $T^{\pm}$ with relatively weak acids through the concerted reaction *via* k_c. Mechanism IIb lowers the pK_a at which the break occurs below that of the hydroxyl group by providing a step subsequent to the protonation of $T^{\pm}$ that becomes rate-determining with relatively weak acids.

Mechanisms I and II are both consistent with the equal limiting values of the observed rate constants for strongly acidic and basic catalysts; these rate constants represent diffusion-controlled encounter of the catalysts with a small concentration of the unstable intermediate $T^{\pm}$. Both mechanisms require that the intermediate revert to starting materials faster than it is trapped by encounter with a molecule of strong acid or base catalyst. Since the observed rate constants were found to increase linearly with increasing buffer concentration up to 0.4 M, the step involving the buffer is rate controlling and k_{-a} must be fast ($\geq 10^9$ sec^{-1}). The subsequent proton transfer or breakdown steps must also be fast for the strong acid and base catalysts. If the limiting values of k_{HA} and k_B (or k_{HA}' and k_B') are taken as 10^9 M^{-1} sec^{-1}, the equilibrium constant K_{add} for the formation of $T^{\pm}$ from methoxyamine and acetyltriazole is approximately 10^{-7} M^{-1} for both mechanisms. This is similar to the estimate of K_{add} 10^{-6} M^{-1} for the addition of the more basic hydrazine to the less reactive acetylimidazole molecule.[5] The equilibrium constants for the formation of the uncharged intermediates T^0, calculated from these values and the estimated ionization constants of the intermediates (see Appendix),[5] are on the order of 5×10^{-3} M^{-1} for the hydrazine–acetylimidazole reaction and 0.25 M^{-1} for the methoxyamine–acetyltriazole reaction, respectively. If a concerted mechanism is assumed also for weak base catalysts in the acetylimidazole reaction, the value of k_c' for a base catalyst of pK = 6 is about 20 times larger for breakdown of the intermediate formed from methoxyamine and acetyltriazole than for that formed from hydrazine and acetylimidazole, consistent with the better leaving ability of triazole than of imidazole anion.

An alternative pathway for the formation of $B \cdot T^{\pm}$ involves the initial association of the reactants in an encounter complex, with an equilibrium constant K_A, followed by bond formation to give $B \cdot T^{\pm}$ (k_a', eq 17).

$$\begin{array}{ccc} RNH_2 + AcTr & \overset{K_A}{\rightleftharpoons} & B \cdot RNH_2 \cdot AcTr \\ & \underset{\pm B}{} & \\ k_a \downarrow \uparrow k_{-a} & & k_a' \downarrow \uparrow k_{-a}' \\ T^+ & \overset{k_B'[B]}{\underset{k_{-B}}{\rightleftharpoons}} & B \cdot T^+ \end{array} \quad (17)$$

This "preassociation" or "spectator" mechanism will be the lowest energy path when the lifetime of $T^{\pm}$ is so

(28) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2358 (1969).
(29) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, **91**, 737 (1969); G. M. Blackburn, *Chem. Commun.*, 249 (1970).
(30) K. J. Morgan and A. M. Turner, *Tetrahedron*, **25**, 915 (1969).
(31) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 499 (1974).

short that the rate constant k_{-a}' for its breakdown to reactants is larger than the rate constant k_{-B}' for separation of the $B \cdot T^{\pm}$ complex, *ca.* 10^{11} sec^{-1}.[5,32,33] An analogous mechanism, with closely similar rate and equilibrium constants, exists for the formation of $T^{\pm} \cdot HA$ in the acid catalyzed pathway. Although this mechanism will be followed if k_{-a}' is sufficiently large, and will give identical observed limiting rate constants for the acid and base catalyzed reactions, it does not provide an explanation for the discrepancy between the positions of the breaks in the Brønsted plots and the estimated pK_a values of the intermediates. A pathway of this kind provides a lower energy, faster route to the intermediate and will cause the break in the acid-catalyzed reaction to occur at lower pK and in the base-catalyzed reaction at higher pK, in the opposite direction from the observed discrepancy.[8]

It was suggested previously that the intermediate T^- in the acetylimidazole–hydrazine reaction may be so unstable that it breaks down faster than the diffusion away of BH^+ from the $BH^+ \cdot T^-$ complex or has no lifetime at all.[5] The former alternative is analogous to that just discussed, but refers to the terminal rather than the initial part of the reaction. Such a mechanism will be the preferred reaction path when T^- has a very short lifetime and the rate constant for the breakdown of T^-, k_d' in eq 9, is larger than k_4'. It might be supposed that such a mechanism would decrease the pK_a value at which the break occurs in the Brønsted plot and, indeed, it was suggested that this may occur in the acetylimidazole reaction. However, this interpretation neglects the rate of the proton transfer step itself, k_3' in eq 9. The observed rate constants for simple proton transfer reactions fall below the predicted rate constants for simple diffusion-controlled reactions when the difference in pK between the proton donor and acceptor becomes small, because the proton transfer step itself (including associated solvation changes) becomes partly rate determining.[25] The observed curvature of these Brønsted plots may be fitted by assuming that the rate constants for the separation of an encounter complex are 10^{11} sec^{-1} and that the rate constant k_3' for the proton transfer step within the complex follows eq 18.[8] Since

$$\log k_3' = 0.5\Delta pK + 10 \qquad (18)$$

the same proton transfer step, k_3', is required in the preassociation, "spectator" mechanisms, the observed rate constants will fall below the line corresponding to $\beta = 0$ at approximately the same position as in the simple diffusion-controlled proton transfer mechanism. Calculation of the Brønsted plots for such a modified mechanism using eq 18 and the appropriate steady-state rate equation[8] shows that this mechanism does not resolve the discrepancy in pK's for either the base- or acid-catalyzed pathways. Thus, mechanism II appears to provide the most satisfactory resolution of these discrepancies in the acetyltriazole reactions, and also provides a reasonable mechanism for the base-catalyzed acetylimidazole reaction.

It is unlikely that the proton transfer step k_3' is itself rate determining[33] for the reactions catalyzed by strong bases even if (as is certainly the case) eq 18 does not hold over a large range of base strength. The circumstances under which k_3' may be rate limiting are very restricted. For a simple proton transfer mechanism, diffusion-controlled encounter is rate determining for strong bases.[25] For a preassociation mechanism (eq 9 and 17), rate-determining proton transfer requires not only that $k_{-a}' > k_{-B}'$, but also that $k_{-a}' > k_3'$.[34] It is unlikely that C–N bond cleavage (k_{-a}'), with its associated changes in charge and solvation, will be faster than the thermodynamically favored transfer of a proton to a strong base (k_3'), which is expected to have a rate constant on the order of 10^{13} sec^{-1}.[35] Analogous arguments may be made for strong acids in the mechanism of eq 12, and for weak acids and bases by considering the reverse reactions.

The "water" reaction of methoxyamine with acetyltriazole is somewhat faster than expected from the Brønsted plot of Figure 8 (open circle) if water is acting as a base catalyst. This reaction may represent an uncatalyzed reaction with expulsion of triazole anion, analogous to the uncatalyzed reactions of phenyl acetates with amines.[36]

It remains to explain the change from a "concerted" reaction mechanism with a linear Brønsted plot for general acid catalysis in the hydrazinolysis of acetylimidazole[5] to the stepwise mechanism with a nonlinear Brønsted plot for general acid catalysis of the methoxyaminolysis of acetyltriazole. The rate constants for several of the acid catalysts in the acetylimidazole reaction are larger than the limiting rate constants for general base catalysis, so that a diffusion-controlled reaction with a common intermediate cannot be involved in both reactions. The concerted general acid catalysis in the acetylimidazole reaction was interpreted as the kinetically equivalent general base catalysis of the hydrazinolysis of the acetylimidazolium ion ($pK_a = 3.8$), formed in a rapid equilibrium step (k_4', eq 19).[5] The concerted

$$v = k_4[N_2H_4][BH^+][AcIm] = k_4'[N_2H_4][B][AcImH^+] \qquad (19)$$

nature of the reaction was attributed to the extreme instability of the "intermediates" $RNH\text{–}RCO\text{–}ImH^{-+}$ and $RNH_2\text{–}RCO\text{–}ImH^{+-+}$, which are thought to be too unstable to exist. The corresponding mechanism for the methoxyamine–acetyltriazole reaction will be considerably less favorable because of the lower basicity of triazole (pK_a of acetyltriazolium ion $= -0.2$). Furthermore, the greater chemical reactivity and smaller thermodynamic stability of acetyltriazole and the good leaving ability of protonated triazole will facilitate the mechanism of eq 12 for general acid catalysis. Thus, the change in mechanism for the general acid catalysts is consistent with the changes in structure of the reactants.

The catalytic constant for the solvated proton in the acetyltriazole–methoxyamine reaction falls 50-fold above the Brønsted plot in Figure 7, suggesting a different mechanism for this catalysis. It is probable that catalysis by the proton involves protonation of acetyl-

(32) W. P. Jencks and K. Salvesen, *J. Amer. Chem. Soc.*, **93**, 1419 (1971).

(33) L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 2014 (1971); R. L. Schowen, *Progr. Phys. Org. Chem.*, **9**, 275 (1972).

(34) It is assumed here that translation (k_B') is the rate-determining step of a diffusion-controlled proton transfer, but analogous arguments may be made, with different assignments of the rate constants, if rotation within an encounter complex is rate determining.

(35) E. Grunwald, *Progr. Phys. Org. Chem.*, **3**, 317 (1965).

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

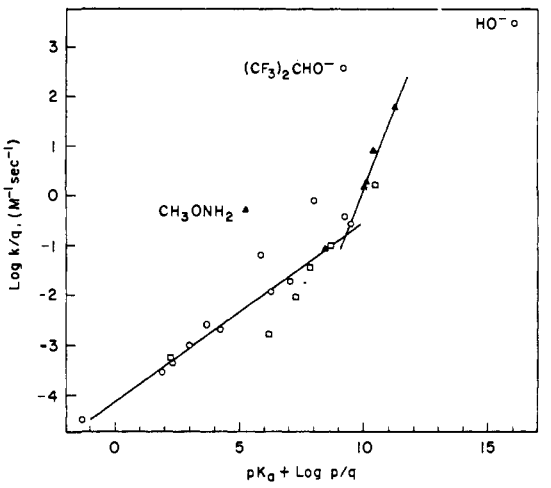


Figure 9. Statistically corrected second-order rate constants for the reactions of a series of buffer bases and nucleophiles with acetyltriazole as a function of basicity at 25°, ionic strength 1.0 *M*: (○) oxyanions; (□) tertiary amines; (▲) primary amines.

triazole in a fast equilibrium step, *i.e.*, specific acid catalysis. If a Brønsted line with a slope of −0.72 (as in the acetylimidazole reaction) is drawn through the point for the proton in the acetyltriazole reaction, it falls below the observed catalytic constants for all of the other acids. In other words, even if the same mechanism exists for the acetyltriazole and acetylimidazole reactions, the catalytic constants for this mechanism would be too small to be detected for the acetyltriazole reaction, except for that of the solvated proton. It is reasonable that an equilibrium protonation mechanism be followed for the proton in the acetyltriazole reaction because proton transfer from this acid to acetyltriazole is thermodynamically favorable, and if the starting material is already protonated on the leaving group a mechanism involving proton transfer to this group in the rate-determining step is not feasible.[23]

Hydrolysis. The acid-catalyzed hydrolysis of acetyltriazole is slower than that of acetylimidazole[14] by a factor of 10^3 (k_{H^+} = 0.22 and 250 M^{-1} sec^{-1}). This is a reflection of the 10^4 lower basicity of acetyltriazole than of acetylimidazole, which is only slightly offset by a tenfold faster hydrolysis of acetyltriazolium ion compared to acetylimidazolium ion (k = 0.38 and 0.038 sec^{-1}). Triazole is not as good a leaving group as might be expected from the pK_a of triazolium ion because the immediate product of the reaction is the isomer of 1,2,4-triazole with the proton on the 4 position, which is tenfold less stable than the 1-protonated isomer.[16] *N*-Acetylbenzotriazole (pK_a benzotriazolium ion = 1.6) is even less susceptible to acid catalysis, with no significant acid-catalyzed reaction above pH 2.[37]

The hydrolysis of the acetyltriazolium ion, like that of acetylimidazolium ion,[15] is inhibited by concentrated acid and salt solutions. The fact that the inhibition by hydrochloric acid is abolished if the experiments are carried out at a constant ionic strength of 8.0 *M*, maintained with lithium chloride (Figure 1), suggests that this inhibition represents a salt effect rather than a change in rate-determining step with increasing acidity.

(37) M. Ravaux, M. Laloi-Diard, and M. Vilkas, *Tetrahedron Lett.*, 43, 4015 (1971).

The pH-independent hydrolysis of free acetyltriazole is 17-fold faster than that of acetylimidazole (k_0 = 1.7 × 10^{-3} and 1.0 × 10^{-4} sec^{-1}) and the alkaline hydrolysis is 100-fold faster (k_{OH^-} = 2.7 × 10^3 and 27 M^{-1} sec^{-1}). A plot of log k against the pK of the leaving group for the "water" hydrolysis of the free and protonated species of acetyltriazole and acetylimidazole has a slope β_{lg} of −0.35, with a small negative deviation for the acetyltriazolium ion. This value is somewhat smaller than the values β_{lg} = −0.50 for substituted *N*-acetylpyridinium ions[38] and β_{lg} = −0.55 for substituted *N*-acetylimidazolium ions.[39]

Reactions with Acids. Acetyltriazole shows a significant reaction with methoxyammonium ion (Figure 5), a barely detectable reaction with several acidic carboxylic acids, and no detectable reaction with acetic or methoxyacetic acids (Table II). Phosphate and ethylphosphonate monoanions react 4–8 times faster than carboxylate anions of comparable pK and may react, in part, as the acid. The comparable reactions of acids with acetylimidazole actually represent the kinetically equivalent reaction of the conjugate base with acetylimidazolium ion (eq 20) either as a nucleophilic reagent

$$v = k_2[BH^+][AcIm] = k_2'[B][AcImH^+] \quad (20)$$

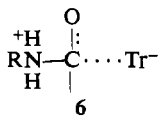
or as a general base catalyst for hydrolysis; the acetic acid reaction represents 22% nucleophilic attack and 78% catalysis of hydrolysis.[3,20,40] This path through acetylimidazolium ion represents the predominant mechanism for most reactions of acetylimidazole at or below neutral pH. The corresponding path through acetyltriazolium ion is relatively insignificant because of the smaller basicity of acetyltriazole, as discussed above.

Reactions with Bases. The statistically corrected[41] second-order rate constants for the reactions of acetyltriazole with a series of bases exhibit a relatively small dependence on basicity for most weak bases and a much larger dependence for a series of more basic primary amines (Figure 9). Similar behavior was observed previously with acetylimidazole.[14] The reactions of the weak bases are attributed to general base catalysis of hydrolysis. The Brønsted β value for these bases is 0.36 (Figure 9), which may be compared with β values of 0.34 and 0.55 for the general base catalyzed hydrolysis of acetylimidazolium ion and acetylimidazole, respectively.[14] Evidence that the reactions of triazole, carboxylate anions, and *N*-methylmorpholine represent general base catalyzed hydrolysis is presented in the Results. The points for methoxyamine and for hexafluoroisopropoxide and hydroxide anions show large positive deviations from this line that are attributed to nucleophilic reactions. The smaller positive deviations of the points for cacodylate and methylarsonate anions may also represent nucleophilic reactions.

The rate constants for the uncatalyzed reactions of basic primary amines and ammonia with acetyltriazole fall on a line of slope $\beta \simeq 1.3$, slightly less than the

(38) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5432 (1970).
(39) E. Guibe-Jampel and M. Wakselman, *Bull. Soc. Chim.Fr.*, 7, 2554 (1971).
(40) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, 83, 4390 (1961).
(41) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A*, **291**, 297 (1966).

slope of $\beta = 1.6$ observed with acetylimidazole;[42] a logarithmic plot of the rate constants for acetyltriazole against those for acetylimidazole has a slope of 0.85. The value of $\beta \simeq 1.3$ is larger than that for the addition of a proton with the development of a full positive charge on an amine, and approaches the value of $\beta = 1.6$ for the equilibrium formation of a cationic amide with a positive charge on the nitrogen atom.[43] This large β value indicates that the transition state of the aminolysis reaction has a large development of positive charge on the attacking nitrogen atom and must resemble a cationic amide product; *i.e.*, the transition state is late and does not involve significant proton removal from the attacking amine (**6**). It is a



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corollary of this conclusion that bond formation between the amine and the carbonyl group is essentially complete and that the rate-determining step involves expulsion of triazole anion; *i.e.*, a tetrahedral intermediate $T^{\pm}$ formed from an amine and acetyltriazole breaks down most frequently with expulsion of the attacking amine, so that triazole anion ($pK = 10.1$) must be a poorer leaving group than primary amines of pK_a up to 10.8. Surprisingly, in spite of this late transition state that must certainly involve bond breaking of the leaving group, the absolute rate constants for the acetyltriazole reactions are only about tenfold faster than those for acetylimidazole. Evidently, the triazole anion, with a nitrogen atom adjacent to the leaving nitrogen atom, is a less good leaving group than might have been expected from its pK.

It has been suggested that the late transition state for the acetylimidazole reactions may represent a rate-determining separation of the product ion pair $RNH_2^+Ac \cdot Im^-$ and the estimated rate constant for the rate-determining step of the reverse reaction through RNH_2^+Ac and Im^- is equal to that expected for a diffusion-controlled reaction, consistent with this interpretation.[42] An analogous calculation for the acetyltriazole reaction gives rate constants in the range 10^4–10^5 M^{-1} sec^{-1} for the same step in the reaction of triazole anion with N-protonated amides. This shows that the separation of an ion pair is not the rate-determining step in the forward reaction of acetyltriazole, consistent with the smaller value of β_{nuc} for the acetyltriazole reactions and the expected smaller ratio k_{-2}/k_3 for triazole anion than for imidazole anion in the scheme of eq 21. The free energy of hydrolysis

$$RNH_2 + AcTr \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T^{\pm} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \overset{+}{A}cNH_2R \cdot Tr^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}}$$

$$\overset{+}{A}cNH_2R + Tr^- \rightleftharpoons AcNHR + TrH \quad (21)$$

of acetyltriazole, which is required for this calculation, was estimated to be -11 kcal/mol, based on the value -9.5 kcal/mol for acetylimidazole, the difference of 1.5 kcal/mol in the heats of hydrolysis of the two compounds, and the assumption that the entropies of hydrolysis of the two compounds are the same.[44,45] This value is consistent with a limiting value for the equilibrium constant of the reaction of acetyltriazole with acetic anhydride (eq 22). The free

$$Ac_2O + TrH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AcOH + AcTr \quad (22)$$

energy of hydrolysis of acetic anhydride is -15.7 kcal/mol[20] and the equilibrium constant $K = k_1/k_{-1} \geq 2500$, from values of $k_1 = 0.83$ M^{-1} sec^{-1} and $k_{-1} \leq 3.3 \times 10^{-4}$ M^{-1} sec^{-1}. This gives a value of ΔG° for acetyltriazole hydrolysis that is equal to or more positive than -11 kcal/mol.

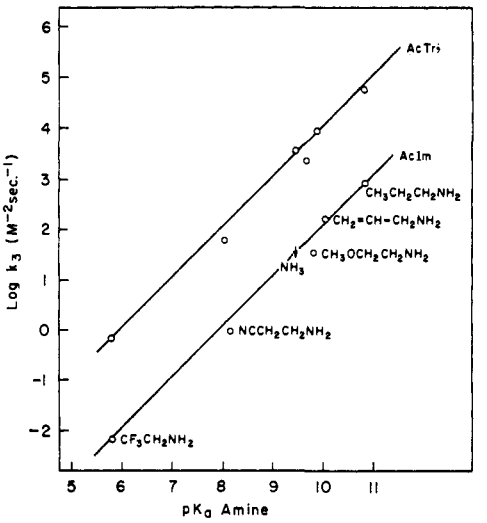


Figure 10. Rate constants k_3 for the amine-catalyzed reactions of amines with acetyltriazole (upper line, ionic strength 1.0 M $(CH_3)_4NCl$) and acetylimidazole (lower line, ionic strength 1.0 M KCl) as a function of amine basicity. The lines have a slope of 1.0.

Other Base-Catalyzed Aminolyses. The amine-catalyzed reactions of amines according to the rate constant $k_3[RNH_2]^2$ give a β value of 1.0 and are 100 times faster than the corresponding reactions with acetylimidazole,[3,42] which also follow a slope of 1.0 (Figure 10). The β value of 1.0 means that the reaction behaves as if there is a development of a charge of $+1.0$ on nitrogen in the transition state. This is consistent with the hypothesis that the rate-determining step in the reaction involves a reaction of the addition intermediate $T^{\pm}$ with a second molecule of amine according to the mechanism of eq 9.[5]

The electron-withdrawing effect of the carbonyl group is responsible for the destabilization of amides by electron-withdrawing substituents on the amine, with a β value of -0.6.[43] The difference in the rate constants for these reactions of acetylimidazole and acetyltriazole corresponds to a β_{lg} value of -0.5, based on pK_a values of 14.2 and 10.1 for imidazole and triazole, respectively. This is in reasonable agreement with the expected difference in the equilibrium constants for the formation of tetrahedral addition compounds from acetylimidazole and acetyltriazole, if it is assumed that most of the electron-withdrawing effect of the carbonyl group is lost upon addition compound forma-

(42) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, 94, 3263, 8818 (1972).

(43) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 92, 5432 (1970); A. R. Fersht and Y. Requena, *ibid.*, 93, 3499 (1971); W. P. Jencks, B. Schaffhausen, K. Tornheim, and H. White, *ibid.*, 93, 3917 (1971).

(44) J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, 86, 4655 (1964).

(45) I. Wadsö, *Acta Chem. Scand.*, 14, 903 (1960). This value refers to acetone solutions; for the pure substances the difference is 2.5 kcal/mol.

tion. The difference in the heats of hydrolysis of acetylimidazole and acetyltriazole in acetone solution of 1.5 kcal/mol[44] is somewhat smaller than these differences, but does not take account of differences in entropy or solvation in the two hydrolysis reactions. The estimated equilibrium constants of 5×10^{-3} and 0.25 M^{-1} for the formation of uncharged addition compounds in the hydrazine–acetylimidazole and methoxyamine–acetyltriazole reactions give a β value of −0.42. Since the effect of amine basicity on the equilibrium constants for the formation of uncharged addition compounds is small,[31] this value is in satisfactory agreement with these estimates.

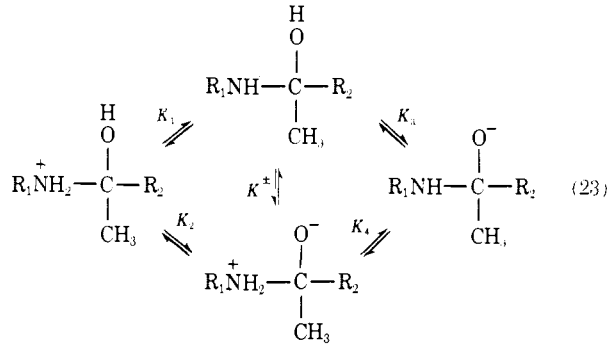
Acknowledgment. We are most grateful to Dr. Jane Sayer for her helpful advice and suggestions.

Appendix

Estimation of pK Values. Structure–Reactivity Correlations. The acidities of substituted alcohols and *gem*-diols XCR_1R_2OH have been satisfactorily correlated with a value of $\rho^* = -1.32$;[46] correction by a factor[47] of 6.23 gives a value of $\rho_I = -8.2$.

Correlations for aliphatic ammonium ions are less satisfactory. Hall[48] reported a ρ^* value of -3.2 ± 0.1 for primary, secondary, and tertiary ammonium ions, $XNHR_1R_2^+$, which corresponds to a value of $\rho_I = -8.0$ for $XCR_3R_4NHR_1R_2^+$ after correction by a factor of 6.23 and for transmission through a carbon atom by a factor of 2.5.[49] However, the slope of Hall's plots is determined largely by substituted hydroxylammonium ions. A correlation (not shown) for 28 primary ammonium ions including trifluoroethylammonium and cyanomethylammonium ions[50] gives a least-squares value of $\rho_I = -8.6$. A similar correlation for tertiary amines gives a ρ_I value of −9.3, but inclusion of a series of N-substituted morphinolinium ions gives $\rho_I = -7.3$. We conclude that the ρ_I value for the dissociation of substituted ammonium ions is -8.3 ± 1.0 and that within the error of the available data there is no evidence for a significant difference in the ρ_I values for the dissociation of alcohols and ammonium ions. We will take $\rho_I = -8.4$ for both series and use this value over as small a range of structural variation as possible, by choosing appropriate reference compounds. The assumption of a single ρ value is equivalent to the assumption that the equilibrium constant $K^{\pm}$ for the interconversion of neutral and zwitterionic forms of an addition intermediate (eq 23) is independent of polar substituent effects on the central carbon atom.

We estimate the ionization constants for the addition compound formed from methoxyamine and acetyltriazole according to eq 23 with $R_1 = CH_3O$ and R_2 = triazole. Values of σ_I are taken from Charton[47] and from Ritchie and Sager.[51] The values of σ_I for triazole and methoxyamine are not known and



(23)

have been taken as 0.18, intermediate between the values 0.1 for amine and 0.25 for amide substituents; the value for hydrazine is 0.15.[51]

Estimation of pK_1. (a) The addition of a hydroxyl group to the methyl group of a secondary ammonium ion $CH_3N^+H_2R$ decreases the pK_a by approximately 1.88 units.[52,53] Substitution of CH_3 for H in the α position increases the pK_a of a number of alcohols and ammonium ions by 0.3 unit[46,48] and the triazole substituent is expected to decrease the pK_a by $0.18 \times 8.4 = 1.5$ units. Based on a pK_a of 4.75 for $CH_3NH_2OCH_3^+$,[54] the value of pK_1 is 1.7

(b) Again starting with $CH_3NH_2OCH_3^+$, pK_a = 4.75, correction for HO ($-8.4 \times 0.25 = -2.1$), CH_3 (0.3) and triazole (−1.5) gives pK_1 = 1.5.

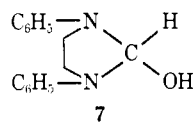
(c) Again following Hine, *et al.*,[53] pK_a ($HOCH_2NH_2CH_3^+$) ≃ 8.83 based on pK_a ($(CH_3)_2NH_2^+$) = 10.71 at 25°.[55] Substitution of CH_3O for CH_3 lowers the pK_a of methylamine by 6 units.[48] Assuming the same substituent effect for the hydroxymethylamine and correcting for the methyl (0.3) and triazole (−1.5) substituents give pK_1 = 1.6.

(d) The addition of a hydroxymethyl group to a primary amine to give a secondary hydroxymethylamine results in a decrease in pK_a of 1.3 units according to Hall's correlation.[48] Based on a pK_a of 4.60 for $CH_3ONH_3^+$,[54] this gives a pK_a of 3.3 for $CH_3ONH_2CH_2OH^+$ and, after correction for methyl (0.3) and triazole (−1.5) substituents, a value of pK_1 = 2.1.

The best value of pK_1 is taken as 1.7.

Estimation of pK_2. The pK of the hydroxyl group of $CH_3NH_2CH_2OH^+$ has been estimated to be 9.98.[53] Correction for a methyl group (0.3), triazole (−1.5), and substitution of CH_3ONH for CH_3NH ($-8.4(0.18-0.10) = -0.7$) gives pK_2 = 8.1.

Estimation of pK_3. Based on a pK_a of 15.9 for CH_3CH_2OH,[46] correction for methoxyamine and triazole substituents ($-8.4(0.18 + 0.18) = -3.0$) gives pK_3 = 12.9. This may be compared to the measured pK_a of 7 = 12.75.[56]



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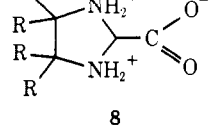

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(46) S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971); J. Hine and G. F. Koser, *ibid.*, **36**, 1348 (1971).
(47) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
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(50) W. P. Jencks and J. Regenstein, "Handbook of Biochemistry," 2nd ed, H. A. Sober, Ed., Chemical Rubber Co., Cleveland, Ohio, 1970, p J-187.
(51) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 323 (1964).
(52) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5864 (1966).
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(54) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Amer. Chem. Soc.*, **79**, 796 (1957).
(55) N. F. Hall and M. R. Sprinkle, *J. Amer. Chem. Soc.*, **54**, 3469 (1932).
(56) D. R. Robinson, *J. Amer. Chem. Soc.*, **92**, 3138 (1970).

The value of pK_4 is then $pK_1 + pK_3 - pK_2 = 6.5$. The electrostatic effect of the development of a positive charge upon the ionization of the hydroxyl group and of a negative charge on the ionization of the ammonium group is in each case $pK_3 - pK_2 = pK_4 - pK_1 = 4.8$ units, in agreement with a previous estimate of 4.7 units.[5] The (uncorrected) electrostatic effect of the positive charge on the ionization of **8** (R = H,CH_3) at ionic strength 1.0 *M* is 4–5 p*K* units.[57]

We estimate that the individual pK_a values are probably accurate to within 1 p*K* unit. The estimates are based, as far as possible, on pK_a values at low or zero ionic strength and shifts on the order of 0.1–0.2 unit, upwards for ammonium and downwards for hydroxyl ionizations, may be expected at ionic strength 1.0 *M*.

(57) A. Hilton and D. L. Leussing, *J. Amer. Chem. Soc.*, **93**, 6831 (1971). Professor Leussing has kindly informed us that the correct values of log K_{12} are 4.81 and 3.1 for 8, R = H and CH_3, respectively.

Supplementary Material Available. Tables I and III will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1436.

Photogeneration of Fluorescent Hydrocarbons from Cyclic 1,2- and 1,4-Dicarboxylic Anhydrides

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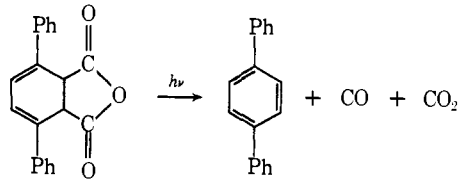
Abstract: Several cyclic 1,2- and 1,4-dicarboxylic anhydrides were prepared. Their photochemistry was examined and spectroscopic changes in fluorescence as well as absorption were monitored. Both types of anhydrides underwent efficient direct, but not sensitized, photofragmentation, generating carbon monoxide, carbon dioxide, and new unsaturation. These photoreactions proceeded without discernible differences in mechanism. Extended Hückel molecular orbital calculations were carried out in an attempt to trace how anhydride orbitals may evolve into product orbitals with or without crossing of filled and empty orbitals. Although these calculations suggested the possibility that product molecules from 1,4-cyclic anhydrides might emerge from the reaction coordinate in an excited singlet state, detailed dynamic photoluminescence measurements conducted during the course of photolysis of 9,10-diphenyl-1,4-dihydroanthracene-1,4-dicarboxylic anhydride provided no support. These measurements showed that not more than 1 in 10,000 of the 9,10-diphenylanthracene product molecules emerge from the reaction coordinate in an excited singlet state.

The fluorescence of a product can be a useful characteristic for probing the potential energy surface of photochemical reactions since prompt product fluorescence resulting from reactant absorption indicates an adiabatic excited singlet state transformation.[1] The photogeneration of fluorescent products also has imaging applications.[2] Since *p*-terphenyl is an efficient fluorescer[3] its reported[4-6] photogeneration together with carbon monoxide and carbon dioxide in high yield from 1,4-diphenyl-1,3-cyclohexadiene-5,6-dicarboxylic anhydride led us to further investigations of anhydride photolyses. We have previously described



related photochemical studies with aza-[7] and diaza-[8] succinic anhydrides. Reported here are the results of studies on the photofragmentation of several dihydroanthracene anhydrides and 2,3-diphenylsuccinic anhydride.

Dihydroanthracene Dicarboxylic Anhydrides. Although several 9,10-dihydroanthracene-9,10-dicarboxylic anhydrides (**3**) are known,[9,10] no photochemical studies have been reported for these or other anhydrides of 1,4-dicarboxylic acids. Their investigation attracted our attention because of the well-characterized excited-state properties, including generally high quantum yields of fluorescence of the anticipated anthracene photoproducts. In addition, comparisons with investigations on anhydrides of 1,2-dicarboxylic acids could provide mechanistic information on the nature of the fragmentation processes.

Anhydrides **3a** and **3b** were prepared from the corresponding anthracene by slight modification of literature procedures[9] (Chart I). Difficulties were encountered, however, in the cyclization of the cis diacid

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