interpretation, base catalysis permits the formation of product by removing a proton from the unstable dipolar intermediate $T^{\pm}$, which would otherwise break down rapidly to starting materials.[6] Other, more complex, interpretations are possible, but the data suggest (a) that the addition reaction involves at least two steps and an intermediate and (b) at least one of these steps involves transport of the catalyst for proton transfer.

The equilibrium constant K_1 for the formation of $T^{\pm}$ from amine and aldehyde may be estimated from the overall equilibrium constant for the addition step, K_{ov}, and the equilibrium constant $K^{\pm}$ for the formation of $T^{\pm}$ from T^0. The extreme instability of $T^{\pm}$ is apparent in the value log $K_1 = -11.3 \pm 1.0$, obtained from estimates[7] of log $K_{ov} = -0.64$ and log $K^{\pm} = -10.7 \pm 1.0$. The observed rate constant of the 3-quinuclidinol-catalyzed reaction then corresponds to a value of log $k_t = 10.8 \pm 1.0$ (M^{-1} sec^{-1}) for this strong base catalyst. Thus, if $T^{\pm}$ is formed as an intermediate, it must react with the catalyst with a rate constant in the range expected for a diffusion-controlled reaction.[5] The expulsion of methylthiosemicarbazide ($pK_a' = 1.2$) from $T^{\pm}$ (k_{-1}) must be extremely fast; the corresponding adducts formed from still weaker nucleophiles will have too short a lifetime to exist as intermediates, so that the addition of such nucleophiles must occur through a more or less concerted mechanism of catalysis.

(6) J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, 88, 3973 (1966).

(7) K_{ov} was calculated from an observed equilibrium constant of 8.1 M^{-1} for the addition of 2-methylthiosemicarbazide to pyridine-4-aldehyde (25°, ionic strength 1.0) and the relationship $K_{ov}^{pyr\text{-}4\text{-}ald}/K_{ov}^{PCBA} = 35$ (E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, 90, 6154 (1968)). The value of $K^{\pm}$ was estimated from the value log $K^{\pm} = -1.3 \pm 0.6$ for carbinolamines formed from primary aliphatic amines[8] and the assumption that substituent effects on the ionization of substituted ammonium ions are additive. The same value was obtained from estimates of the individual ionization constants for the interconversion of $T^{\pm}$ and T^0 (ref 8; H. K. Hall, Jr., *J. Amer. Chem. Soc.*, 79, 5441 (1957); S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, 36, 1205 (1971)).

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

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The Uncatalyzed Aminolysis of Acetylimidazole. A Limiting Product-Like Transition State for Acyl Transfer[1]

Sir:

We wish to report an unusually large sensitivity to the basicity of the attacking amine in the uncatalyzed aminolysis of acetylimidazole. The value of β_{nuc} of approximately 1.6 indicates that little or no proton removal has occurred from the attacking amine in the product-like transition state of this reaction.

Acyl compounds with good leaving groups (phenyl acetates,[2] acetylimidazolium ion[3]) readily undergo aminolysis without proton removal from the attacking amine, as shown by the similar reactivities of primary, secondary, and tertiary amines. These reactions generally show a large sensitivity to the basicity of the attacking amine with values of β_{nuc} (the slope of plots of log k against the pK_a of the conjugate acid of the amine) in the range 0.8–1.0. With poor leaving groups (*e.g.*, methyl formate[4]) this uncatalyzed reaction path is unfavorable and leaving group expulsion is made possible by proton transfer. Free acetylimidazole, with a leaving group of $pK_a = 14.2$,[5] appears to be in an intermediate position. Although the predominant aminolysis reaction occurs with general base catalysis and weakly basic amines simply act as general base catalysts of hydrolysis,[3] strongly basic amines react with acetylimidazole in an uncatalyzed, second-order aminolysis reaction which is faster than general base catalyzed hydrolysis and exhibits a value of β_{nuc} of approximately 1.6 (Figure 1). The rate constants (Table I) were obtained from the intercepts of plots of observed second-order rate constants against amine concentration, corrected for any reaction of amine with acetylimidazolium ion (based on rate constants obtained at lower pH values).[3]

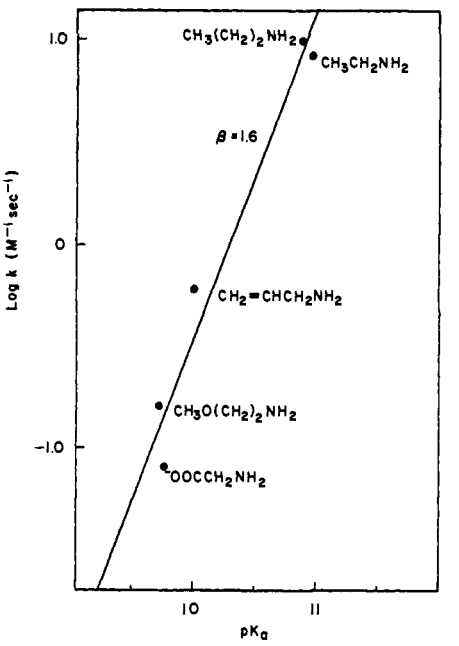

Figure 1. Dependence of the second-order rate constants for the uncatalyzed aminolysis of free acetylimidazole on the basicity of the amine at 25°, ionic strength 1.0.

Table I. Rate Constants for the Uncatalyzed Reactions of Primary Amines with Free Acetylimidazole[a]

Amine	pK_a	k, M^{-1} sec^{-1}
n-Propylamine	10.89	10
Ethylamine	10.97	8.2
Allylamine	10.02	0.6
Glycine	9.76	0.08
Methoxyethylamine	9.72	0.16

[a] 25°, ionic strength 1.0 (KCl).

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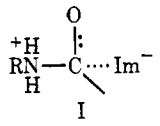
(2) T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, 80, 2265 (1958); W. P. Jencks and M. Gilchrist, *ibid.*, 90, 2622 (1968).

(3) D. G. Oakenfull and W. P. Jencks, *ibid.*, 93, 178 (1971); D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *ibid.*, 93, 188 (1971).

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

(5) G. Yagil, *Tetrahedron*, 23, 2855 (1967).

The very large sensitivity of this reaction to the basicity of the attacking amine (Figure 1) means that the transition state is more sensitive to polar substituents on the nitrogen atom than is the equilibrium for the addition of a proton; the reaction behaves *as if* some 1.6 positive charge is generated at the amine nitrogen atom in the transition state. The value of β_{nuc} for the *equilibrium* transfer of an acyl group to an amine or pyridine to give a cationic product is also 1.6,[6,7] so that the transition state for the aminolysis reaction (I) closely resembles the product that is formed without proton transfer. Since proton removal would



I

decrease the amount of positive charge development on the nitrogen atom, this β value means that little or no proton removal from the attacking amine has occurred in the transition state. The pK_a of an N-protonated amide[8] is about -7.6, so that there is no significant proton removal through general base catalysis by water and the proton transfer process does not appear to be at an equilibrium position in the transition state.[9] Apparently the advantage gained from general base catalysis by water is insufficient to offset the unfavorable free energy required for the positioning of a water molecule and the transfer of a proton in the transition state.

The limiting interpretation of the data is that *complete* cleavage of the C–N bond has occurred in the transition state; *i.e.*, that the rate-determining step is the dissociation of the ion pair $RNH_2^+Ac\cdot Im^-$ to solvent-separated ions (eq 1). If the dissociation step,

$$RNH_2 + AcIm \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RNH_2^+Ac\cdot Im^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} RNH_2^+Ac + Im^- \quad (1)$$

$$K_A \Big\uparrow \Big\downarrow \pm H^+ \qquad \pm H^+ \Big\uparrow \Big\downarrow K_I$$

$$RNHAc \qquad ImH$$

k_2, is rate determining in the forward direction, encounter of the ions with the rate constant k_{-2} is rate determining in the reverse direction. Since the overall equilibrium constant K_{ov} may be calculated from the free energies of hydrolysis of acetylimidazole[10] and acetamide,[7,11] a rough estimate of the reverse rate constant k_{-2} according to this interpretation may be obtained from the observed forward rate constant $k_f = k_1k_2/k_{-1}$ and the pK values of the N-protonated amide[7] and imidazole of -7.6 and 14.2, respectively, according to eq 2. The resulting value of $k_{-2} = 3 \times 10^9\ M^{-1}$

$$k_{-2} = \frac{k_1k_2K_A}{k_{-1}K_{ov}K_I} = \frac{k_fK_A}{K_{ov}K_I} \quad (2)$$

sec^{-1} for the reaction of imidazole anion with the protonated amide is in the range expected for a diffusion-controlled reaction. This is consistent with (but of course does not prove) this limiting interpretation of the mechanism. The fact that the observed rate constants for the reactions of acetylpyridinium ions with less basic amines and hydroperoxide ion are close to the diffusion-controlled limit[12] is also in accord with this interpretation.

The reactions of amines with methyl formate[4] are several orders of magnitude slower, with a β value of 0.7, indicating a different mechanism for this reaction in spite of the comparable pK_a values of methanol (15.5)[13] and imidazole. A calculation similar to that for the acetylimidazole reaction gives a value of $1.5 \times 10^{14}\ M^{-1}\ sec^{-1}$, greater than the diffusion-controlled limit, for the reaction of methoxide ion with N-protonated *N*-propylformamide. The limiting mechanism of eq 1 evidently cannot be significant for methyl formate. This is a consequence of the greater stability (smaller K_{ov}) of methyl formate[8] that results from enhanced resonance stabilization compared to acetylimidazole.

(6) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5432 (1970); W. P. Jencks, B. Schaffhausen, K. Tornheim, and H. White, *ibid.*, **93**, 3917 (1971).
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(8) A. R. Fersht, *ibid.*, **93**, 3504 (1971).
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(12) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5442 (1970).
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Conformations of Saturated Phosphorus Heterocycles. Effect of Europium Dipivaloylmethane and Europium Heptafluorodimethyloctanedione on Conformational Equilibria of 2-Substituted 5-*tert*-Butyl-2-oxo-1,3,2-dioxaphosphorinanes

Sir:

Recent studies have demonstrated the potential utility of europium shift reagents in the determination of molecular geometry.[1] Both coupling constants from spectra simplified by added shift reagent and the accompanying chemical-shift behavior are useful in this regard. We present here results which clearly show, however, that mobile conformational equilibria can be greatly perturbed by added shift reagents and which emphasize that care must be used in interpreting nmr data of this type.[2] In addition, our findings demonstrate further the importance of electronic as well as steric effects in determining conformations in six-membered rings containing heterocyclic atoms.

It had been found[3] earlier that the AA'BB'XY pmr spectrum of **1** could be readily simplified by the addition of $Eu(DPM)_3$ to a solution of **1** in $CDCl_3$.

(1) Some recent examples include: (a) B. D. Cuddy, K. Treon, and B. J. Walker, *Tetrahedron Lett.*, 4433 (1971); (b) J. R. Corfield and S. Trippett, *J. Chem. Soc. D.*, 721 (1971); (c) J. F. Caputo and A. R. Martin, *Tetrahedron Lett.*, 4547 (1971); (d) R. Caple and S. C. Kuo, *ibid.*, 4413 (1971); (e) C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971); (f) J. Briggs, F. A. Hart, and G. P. Moss, *J. Chem. Soc. D*, 1506 (1970); (g) R. R. Fraser and Y. Y. Wigfield, *ibid.*, 1471 (1970); (h) P. V. Demarço, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).
(2) It has previously been recognized that results from conformationally mobile systems do not lend themselves to ready interpretation.[1c,g] Our results show these effects clearly in terms of identifiable changes in conformer populations.
(3) K. C. Yee and W. G. Bentrude, *Tetrahedron Lett.*, 2775 (1971).