Effect of Metal. The metal can also influence the rate of ring rotation by both electronic and steric interactions. That there are electronic effects due to interaction of the metal orbitals with porphyrin orbitals is obvious but is difficult to quantitate. Apparently of more importance in the series of compounds studied here is the indirect steric effect that results from porphyrin ring distortion to satisfy the preferred metal–nitrogen bond length.[2,3] The steric effects of the meta substituents on phenyl ring rotation are of comparable magnitude for the four metal ions examined.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. Elemental analyses were performed by Spang Microanalytical Laboratory.

Registry No. $H_2(OMe_2$-TPP), 74684-34-7; $H_2(OMe_3$-TPP), 74684-35-8; $H_2(t$-Bu_2OH-TPP), 74684-36-9; $H_2(t$-Bu_2OMe-TPP), 74684-37-0; Ru(CO)(OMe_2-TPP)(*t*-Bupy), 74684-73-4; Ru(CO)(OMe_3-TPP)(*t*-Bupy), 74684-74-5; Ru(CO)(*t*-Bu_2OH-TPP)(*t*-Bupy), 74684-75-6; Ru(CO)(*t*-Bu_2OMe-TPP)(*t*-Bupy), 74684-76-7; In(OMe_2-TPP)Cl, 74684-77-8; In(OMe_3-TPP)Cl, 74684-78-9; TiO(OMe_2-TPP), 74684-79-0; TiO(OMe_3-TPP), 74709-67-4; TiO(*t*-Bu_2OH-TPP), 74709-68-5; TiO(*t*-Bu_2OMe-TPP), 74709-69-6; Ga(OMe_2-TPP)Cl, 74684-80-3; Ga(OMe_3-TPP)Cl, 74684-81-4; Ga(*t*-Bu_2OH)-TPP)Cl, 74684-82-5; Ga(*t*-Bu_2OMe-TPP)Cl, 74709-70-9; pyrrole, 109-97-7; 3,5-dimethoxybenzaldehyde, 7311-34-4; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 3,5-*tert*-butyl-4-hydroxybenzaldehyde, 1620-98-0; 3,5-di-*tert*-butyl-4-methoxybenzaldehyde, 74684-38-1.

Mechanism of Cyclization of 2-Azido-3-benzoyl Enamines to 5-Phenacyltetrazoles: Rate-Limiting Proton Transfer and Iminium Ion Isomerization

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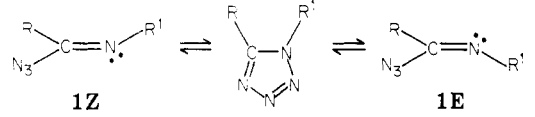
The unusual stability of the azides **5** has been investigated; these are shown to exist as the enamine tautomer **5b**. The rates of cyclization of the azides **5b** and **14** to the corresponding tetrazoles **4b** and **4c** (in water at 25 °C) vary in a complex way with pH, displaying both acid catalysis and inhibition at pH <6 and base catalysis at pH >9. A "bell-shaped" dependency of k_{obsd} on pH is observed with a maximum at pH 2.1. These results are interpreted as follows: at moderate acidities ($2 < pH < 6$) proton transfer to **5b** is the slow step, subsequent isomerization of the protonated species **7Z** and cyclization (**9E** → **4b**) being rapid. General-acid catalysis (Brønsted $\alpha = 0.57$, $k_{HOAc}/k_{DOAc} = 6.9$) is observed, but the rate-determining step can be changed at high buffer concentration (as shown by nonlinear k_{obsd} vs. [buffer] plots) or at low pH to a *Z*/*E* isomerization about the >C=$^+$N< bond of the protonated enamine (to give **7E**). Deprotonation of the latter gives (*E*)-imidoyl azide **9E** which rapidly cyclizes. The azide group therefore acts as an efficient internal trap for the imine group; only the isomer in which the lone pair on nitrogen is cis to the azide cyclizes to the tetrazole.

The existence of a tautomeric equilibrium between azidoazomethine derivatives and their corresponding tetrazoles has been established for some time.[2] In most cases the tetrazole form (**2**) is the more stable although a number of heterocyclic and acyclic azides, **1**, are known which are stable at room temperature.



1Z ⇌ **2** ⇌ **1E**

The mechanism of isomerization of **1** → **2** has been investigated by a number of authors.[3] The most recent report by Leroy et al.[4] is based on a theoretical study of the energy factors involved in the cyclization. Of particular interest is the small energy of activation for the reaction and the far higher stability predicted for the tetrazole isomer. It is suggested that the driving force for cyclization is provided by the movement of the lone pair of electrons on the imidoyl nitrogen toward the terminal nitrogen of the azide group. A subsequent study of the vinyl azide–υ-triazole isomerization[5] shows that a π system can also participate directly in the formation of the σ bond between carbon and the terminal azido nitrogen. However, a much higher activation energy (42.9 kcal/mol as against 12.6 kcal/mol) was calculated for the neutral substrate relative to the vinyl azide anion.

Several factors govern both the rate of isomerization of azide → tetrazole[6] and the equilibrium position. Electron-withdrawing substituents, higher temperatures, and an acidic medium tend to favor the azide form. Moreover, it has recently been shown,[7] in line with the theoretical finding of Leroy, that only one of the possible imidoyl azide isomers, i.e., that in which the lone pair and the azide group are cis (**1Z**), will cyclize. This isomerization step (**1E** → **1Z**) may then be rate determining for the conversion of the azide to the tetrazole.

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(2) Lwowski, W. "The Chemistry of the Azido Group"; Patai, S., Ed., Interscience: New York, 1973; p 503.

(3) Reimlinger, H. *Chem. Ber.* **1970**, *103*, 1900. Elguero, J. *Bull. Soc. Chim. Fr.* **1971**, 1925. Reynolds, G. A.; Van Allan, J. A.; Tinker, J. F. *J. Org. Chem.* **1959**, *24*, 1205.

(4) Burke, L. A.; Elguero, J.; Leroy, G.; Sana, M. *J. Am. Chem. Soc.* **1976**, *98*, 1685.

(5) Burke, L. A.; Leroy, G.; Nguyen, M. T.; Sana, M. *J. Am. Chem. Soc.* **1978**, *100*, 3668.

(6) Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 402.

(7) Hegarty, A. F.; Brady, K.; Mullane, M. *J. Chem. Soc., Chem. Commun.* **1978**, 871.

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We are particularly intrigued by the azide **3a** reported by Woodward and co-workers,[8] since in this case there appeared to be no obvious reason why cyclization to the tetrazole **4a** should not be spontaneous. Woodward reported that the tetrazole **4a** was formed from **3a** relatively slowly ($t_{1/2} \approx 100$ min in MeOH/H_2O (1/1) at 27 °C without pH control). Unlike other stable imidoyl azides it is unlikely that simple inversion of nitrogen is rate determining in this instance; the rate of nitrogen inversion is known to be highly dependent on the substituent (R^1 in **1**) attached to the imidoyl nitrogen. Thus nitrogen inversion is only slow when R^1 is an electronegative group (e.g., R^1 = nitrogen, oxygen, sulfur, or halogen) and is very rapid (at ambient temperature) when R^1 is an alkyl or aryl group (as in **3**).

3a, R = Me
b, R = Et
c, R = *t*-Bu

4a, R = Me
b, R = Et
c, R = *t*-Bu

We now report on the correct structures of azides **3b** and **3c** and on a detailed analysis of the conversion of these azides to the corresponding tetrazoles **4** in aqueous solution as a function of pH.[9] This shows that in no case is the azide cyclization step itself rate limiting—instead either proton transfer to or from the azide or imine isomerization (which must occur before cyclization) is the slow step.

Results and Discussion

Synthesis and Structure. The *N*-ethyl azide **3b** was prepared by the reaction of the *N*-(ethyl)benzoylketenimine (formed in situ from the *N*-ethyl-5-phenylisoxazolium cation) with azide ion in aqueous solution; the product was obtained as a solid, in contrast to the oil previously reported[8] for the *N*-methyl analogue (**3a**). It has recently been shown[10] that ketenimines react with carboxylic acids via rate-determining proton transfer (to give a nitrilium ion) followed by nucleophilic attack by the conjugate base rather than via direct nucleophilic attack on the neutral ketenimine. Stereoelectronic control should ensure that a single imidoyl azide isomer is formed since the reaction of nitrilium ions (–C≡N^+–) with nucleophiles leads only to formation of the *Z* isomer[11] about the C=N bond (**5a**).

Three principal tautomeric forms may be written for the azide (**5a–c**). The IR spectrum of the azide shows absorption at 2125 and 1610 cm^{-1}. Both absorptions were observed by Woodward and co-workers[8] for the azide **3a**. However, we have observed no absorption in the pure azide **5** in the 1700–1650-cm^{-1} region. This contrasts with the absorption at 1695 cm^{-1} reported[8] for **3a**. The absence of a carbonyl absorption rules out **5a** as the major tautomeric form. In addition, no N–H or O–H stretch is observed, indicating that if **5b** or **5c** is the predominant tautomer, the enaminic or enolic proton is strongly hydrogen bonded. Three maxima are observed in the UV at 210, 248, and 348 nm. These absorptions (at 245 and 348 nm) were also reported by Woodward and co-workers[8] for **3a**, together with an extra absorption at 285 nm, which we have not observed for **5**.

5a **5b** **5c**

The NMR of the azide **5** measured in CCl_4 shows three resonances of particular interest at δ 3.25 (2 H, quintet), 5.64 (1 H, s), and 11.05 (1 H, s). The singlet resonance at δ 5.64 is assigned to the proton on the β-carbon and clearly rules out **5a** (the structure originally proposed by Woodward and Olofson[8] for the azide **3**). The observation of a quintet resonance at δ 3.25 for the CH_2 protons of the ethyl group (which is reduced to a quartet on shaking of the compound with D_2O) is confirmation of structure **5b**. Dudek and Holm[12] have used such evidence to assign a ketamine structure **6** as the predominant tautomer observed in the adducts of acetylacetone with diamines.

6

The spectral evidence thus points strongly to **5b** as the major form of the azide present in solution although **5c** differs only in the position of an internally hydrogen-bonded proton and may thus be present in solution in low equilibrium concentrations. The oil reported by Woodward and co-workers[8] was most likely a mixture of the azide **3a** and the corresponding tetrazole (**4a**); the IR and UV spectral results reported[8] are entirely consistent with this (**4a** has an IR absorption at 1695 cm^{-1} and a UV maximum at 285 nm); moreover, the synthetic method used by these workers (and in particular the reaction time) would have induced (see below) appreciable azide → tetrazole isomerization.

Kinetics of the Imidoyl Azide–Tetrazole Cyclization. When heated in an inert solvent, the azide **5** cyclizes to the tetrazole **4b**. In aqueous solution cyclization occurs at 25 °C and is strongly catalyzed by both acid and base. The complex pH dependency of the rate of cyclization is shown in Figure 1. This shows basic catalysis above pH 8.5, a pH-independent region between pH 6.5 and 8.5, acid catalysis from pH 2.0 to 6.5, and acid inhibition below pH 2.0. The solid line of Figure 1 was generated by using an empirical equation (eq 1) which closely fits the observed

$$k_{obsd} = k_0 + \frac{k'K_w}{a_H} + \frac{kK_1a_H}{a_H^2 + a_HK_1 + K_1K_2} \quad (1)$$

data with $k_0 = 7.94 \times 10^{-5}$ s^{-1}, $k' = 1.82 \times 10^1$ M^{-1} s^{-1}, $k = 1.57 \times 10^{-1}$ s^{-1}, $K_1 = 2.29 \times 10^{-2}$, and $K_2 = 5.34 \times 10^{-3}$.

Base Catalysis. The rate of cyclization above pH 8.5 is directly proportional to hydroxide ion concentration (slope +1.0) and does not become pH independent even at high pH. This indicates that the pK_{a_2} of **5** (formation

(8) Woodward, R. B.; Olofson, R. A. *J. Am. Chem. Soc.* **1961**, *83*, 1007; *Tetrahedron, Suppl.* **1965**, 415.
(9) Hegarty, A. F.; Dignam, K. J.; Hickey, D. J. *Tetrahedron Lett.* **1978**, 2121.
(10) Hegarty, A. F.; McCarthy, D. G. *J. Am. Chem. Soc.* **1979**, *101*, 1345.
(11) McCormack, M. T.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1701.
(12) Dudek, G. O.; Holm, R. H. *J. Am. Chem. Soc.* **1962**, *84*, 2961.

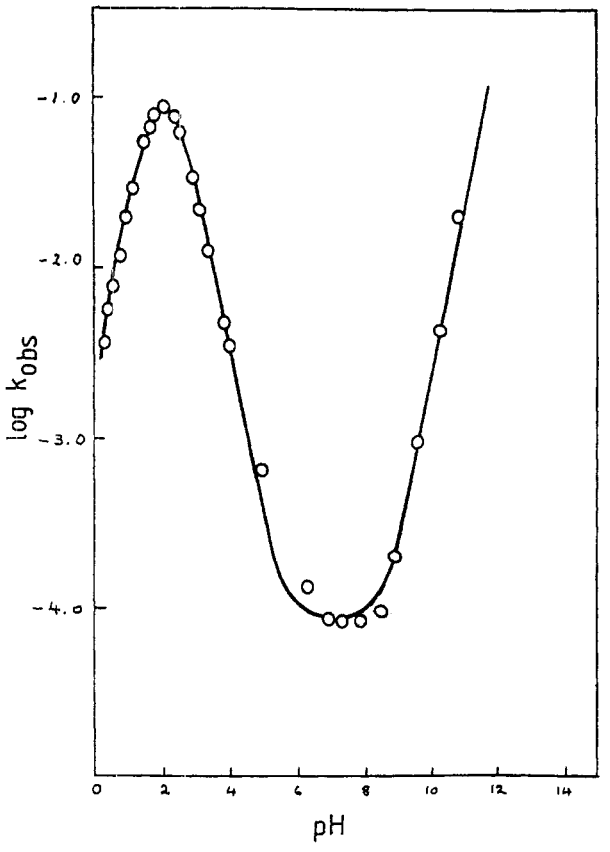
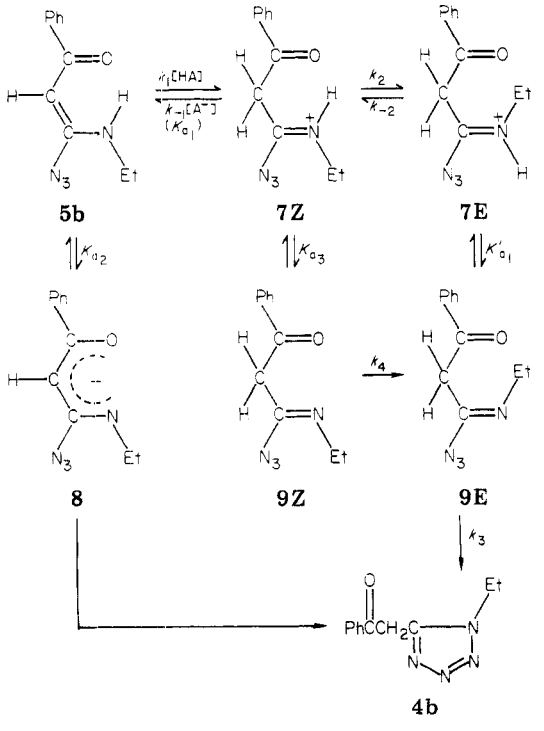


Figure 1. Plot of the logarithm of the observed rate of cyclization of the azide **5b** to the tetrazole **4b** in water at 25 °C (μ = 1.0, KCl) against pH. The points are experimental, and the line is theoretical, following eq 1.

Scheme I



of the anion 8) is greater than 13. General-base catalysis is not observed. The specific base-catalyzed rate of cyclization is consistent with proton removal from **5** to give the anion 8 which can then undergo rapid nitrogen inversion and thus cyclize to **4b** (Scheme I). The cyclization of this anion is rapid ($t_{1/2}$ < 1 s) and irreversible, consistent with previous observations that in analogous compounds[3,13]

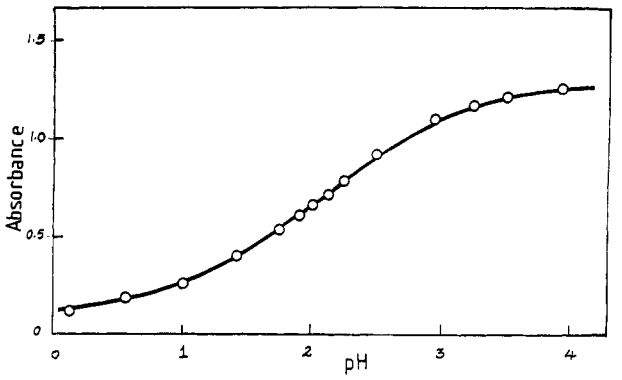


Figure 2. Plot of the absorbance of the azide **5b** at 350 nm in water at 25 °C (μ = 1.0, KCl) against pH. The solid line was drawn by assuming that this substrate has a pK_a = 2.06.

Scheme II

$$SH \overset{K_{a_1}}{\rightleftharpoons} SH_2^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} S'H_2^+ \overset{K'_{a_1}}{\rightleftharpoons} S'H \rightarrow \text{products}$$

the tetrazole isomer is strongly favored in basic solution.

Acid Catalysis and Inhibition. The kinetic behavior at pH values <6 leads to a bell-shaped dependency of the observed rate constants on pH (correlated by the third term in eq 1). The substrate undergoes a protonation–deprotonation equilibrium in this pH region as shown by the change in the ultraviolet spectrum of unreacted azide. Spectrophotometric determination of the pK_a value in this pH region provides a pK_a of 2.06 (see Figure 2). However, treatment of the kinetic data by a method analogous to that used by Bruice[14,15] leads to values of pK_1 = 1.64 and pK_2 = 2.27 (eq 1), both of which are distinctly different from the spectrophotometrically determined pK_a. It is clear, therefore, that since the substrate has only one pK_a in this region, the K_1 and K_2 values required to fit the kinetic data (eq 1) are complex functions, not merely acidity constants.

We have therefore sought a kinetic scheme which is both chemically reasonable and fits the observed data. This is shown in schematic form in Scheme II. Scheme II generates the complex empirical expression given in eq 2 (by

$$k_{obsd} = \frac{k_2 \frac{k_3}{k_{-2}} K'_{a_1} a_H}{a_H^2 + \left(\frac{k_3}{k_{-2}} K'_{a_1} + K_{a_1}\right) a_H + \frac{k_3}{k_{-2}} K'_{a_1} K_{a_1}} \quad (2)$$

assuming a steady-state concentration of $S'H_2^+$ and S'H) which may be simplified by substituting K_3 for $k_3 K'_{a_1}/k_{-2}$ (eq 3). Comparing eq 3 with the basic empirical expression

$$k_{obsd} = \frac{k_2 K_3 a_H}{a_H^2 + (K_3 + K_{a_1}) a_H + K_3 K_{a_1}} \quad (3)$$

(eq 1) provides the relationships given by eq 4–6.

$$k_2 K_3 = k K_1 \quad (4)$$

$$K_3 + K_{a_1} = K_1 \quad (5)$$

$$K_{a_1} K_3 = K_1 K_2 \quad (6)$$

Therefore, eq 2 and 3 are of the same format as eq 1,

(13) Meek, J. S.; Fowler, J. S. *J. Am. Chem. Soc.* **1967**, *89*, 1967.
(14) Alberty, R. A.; Massey, V. *Biochim. Biophys. Acta* **1954**, *13*, 347.
(15) Bruice, T. C.; Benkovic, S. J. "Bio-organic Mechanisms"; W. A. Benjamin: New York, 1966; Vol. 1, p 14.

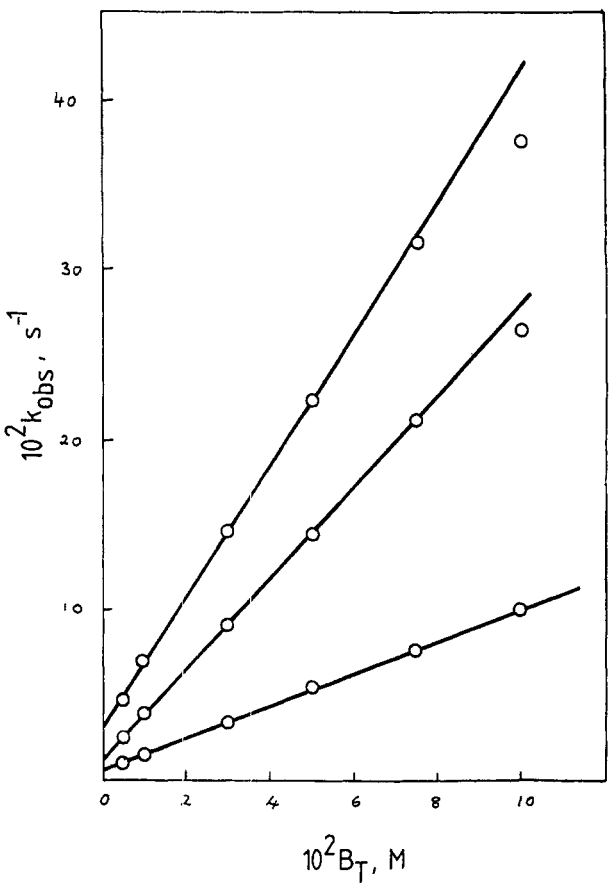


Figure 3. Plot of observed rates of cyclization of the azide **5b** to the tetrazole at constant pH's against total acetate buffer concentration. The plots are linear (see text) at the low buffer concentration used.

implying that these also fit the kinetic data. Solving eq 4–6 leads to a quadratic expression for K_{a_1} (eq 7). Two

$$K_{a_1}^2 - K_1 K_{a_1} + K_1 K_2 = 0 \qquad (7)$$

values are obtained for K_{a_1}: 8.49×10^{-3} and 1.44×10^{-2}. The former value is in excellent agreement with the acidity constant obtained spectrophotometrically ($K_{a_1} = 8.71 \times 10^{-3}$).

Equation 3 thus provides an excellent fit to the kinetic data where $k_2 = 2.5 \times 10^{-1}$ s^{-1}, $K_{a_1} = 8.49 \times 10^{-3}$, and $K_3 = 1.44 \times 10^{-2}$. A kinetic scheme which is of the same format as the empirical Scheme II is shown as Scheme I, if it is assumed that the species are in equilibrium with respect to proton transfers. For simplicity, protonation of **5b** is shown to occur on carbon although there is evidence that oxygen may be the protonation site in related keto enamines.[16] The actual site of protonation does not affect the subsequent arguments.

However, since buffer catalysis is noted at pH's >2, we must include in Scheme I the possibility that proton transfers might be rate limiting under certain conditions.

Buffer Catalysis. Above pH 2, general-acid catalysis of cyclization is observed (Figure 3) when low total buffer concentrations are employed. However, at higher total buffer concentration (>0.5 M), k_{obsd} becomes independent of buffer concentration (Figure 4). Thus proton transfer to the azide (k_1, Scheme I) is rate determining at low buffer concentration; however, at higher [HA] the subsequent step becomes rate determining (eq 2 applies) and is no longer dependent on [HA]. The apparent first-order rate

(16) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

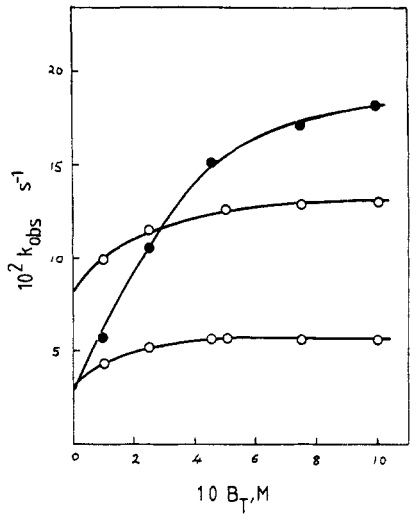


Figure 4. Plot of observed rates of cyclization of the azide **5b** to the tetrazole **4b** at constant pH's with high concentrations of acetate (pH 3.0) and chloroacetate (pH 1.8 and 1.4) buffers in water at 25 °C (μ = 1.0, KCl); the observed rates tend to reach a maximum at each pH.

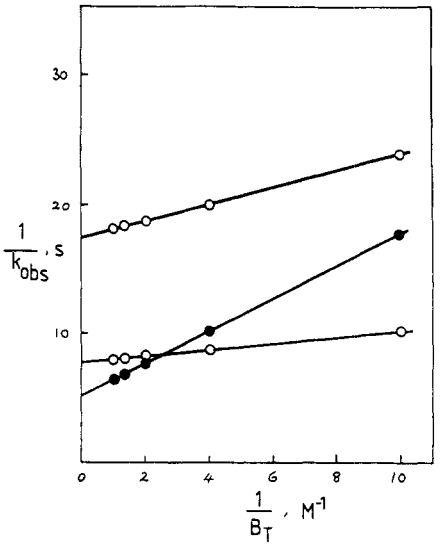


Figure 5. Double reciprocal plots of $1/k_{obsd}$ against 1/(total buffer concentration) with acetate or chloroacetate buffers (data from Figure 4); intercepts at $B_T = \infty$ give values for $(k_2)_{obsd}$.

constant under these conditions is given by eq 8 (as used recently by Page and co-workers[17]).

$$k_{obsd} = \frac{k_2 K[HA]}{1 + K[HA]} \qquad (8)$$

Plots of $1/k_{obsd}$ vs. 1/[HA] (or, more generally, the inverse of the total buffer concentration $1/B_T$) are linear with a slope of $1/k_2K$ and an intercept of $1/k_2$ (Figure 5). Thus we are able to obtain values of $(k_2)_{obsd}$ at "infinite buffer concentrations". A plot of log $(k_2)_{obsd}$ against pH is shown in Figure 6. The simple titration curve of Figure 6 gives an apparent pK_a of 2.06 which is identical with that previously determined spectrophotometrically, while the value of k_2 ($=2.75 \times 10^{-1}$ s^{-1}) obtained from Figure 6 at infinite buffer concentration at high pH is in close agreement with that calculated for k_2 (2.5×10^{-1} s^{-1}) by eq 3 (which assumes equilibrium between SH and SH_2^+). At low pH, general-acid catalysis is no longer observed (Figure 5);

(17) Gensmantel, N. P.; Gowling, E. W.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1978**, 335.

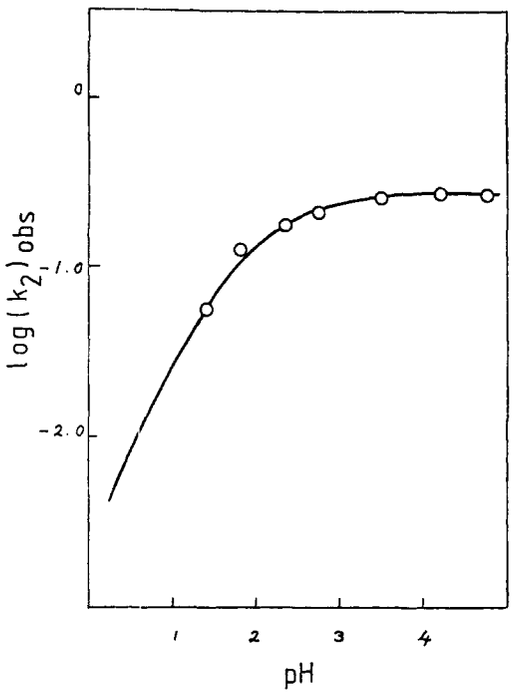


Figure 6. Plot of log $(k_2)_{obsd}$ (rates of cyclization of **5b** to **4b** at "infinite buffer concentration") as a function of pH (see Figure 5). The line is theoretical: $(k_2)_{obsd} = (k_2K_{a_1})/(a_H + K_{a_1})$ with $k_2 = 2.75 \times 10^{-1}$ s^{-1} and $K_{a_1} = 8.49 \times 10^{-3}$.

therefore, the various species (Scheme I) are in equilibrium under these conditions.

The mechanistic Scheme I accounts for these observations. At low hydrogen ion concentration (pH <2) and in the absence of large concentrations of buffer species, the proton transfer to carbon (k_1) is rate determining; once protonated (to **7Z**), the subsequent steps to the tetrazole **4b** are fast. At higher acid concentrations (pH <2 or in the presence of "infinite" general-acid concentration at pHs >2) **5b** and **7Z** are in equilibrium. The rate of formation of **4b** then depends on the equilibrium between **7Z** and **7E** (which is pH independent) and K'_{a_1}. Addition of further acid then shifts the equilibrium between **7E** and **9E** toward **7E**. This accounts for the observed acid inhibition since only **9E** in which the azido group and the lone pair on the adjacent imidoyl nitrogen are cis can cyclize to the tetrazole **4b**.

Neutral Isomerization. Between pH 6.5 and 8.5, the rate of isomerization of **5b** and **4b** is pH independent. Under these conditions the neutral **5b** is the major form of the substrate present in solution. It is, however, in equilibrium with the tautomer **9Z** which can undergo uncatalyzed nitrogen inversion (k_4) and then cyclization (k_3). There is no spectral evidence for the buildup of an intermediate, so that the cyclization of **9E** is likely to be more rapid than its formation. Thus k_0 (= 7.94×10^{-5} s^{-1}; see eq 1) = $k_4K_{a_1}/K_{a_2}$; however, the individual rate constants could not be independently determined.

Rate-Determining Proton Transfer. Proton transfer to **5b** is thus rate determining over a wide pH range (2–6.5). In their studies on the hydrolysis of related enamines, Stamhuis et al.[18] observed general-acid catalysis with rate-determining proton transfer to the β-carbon. Protonation at nitrogen also occurs in a preequilibrium. Other studies[19] on enamines also support this: while rapid protonation on nitrogen is observed, the C-protonated form

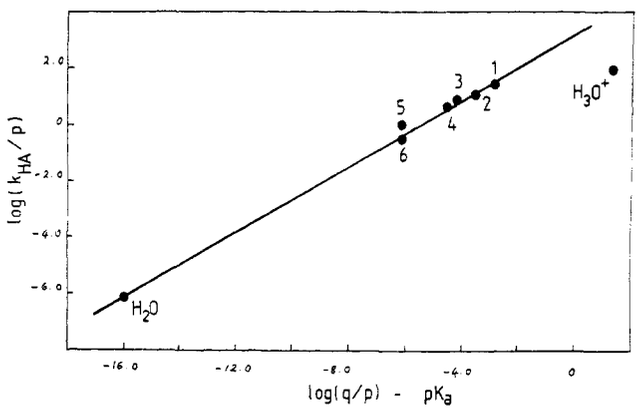
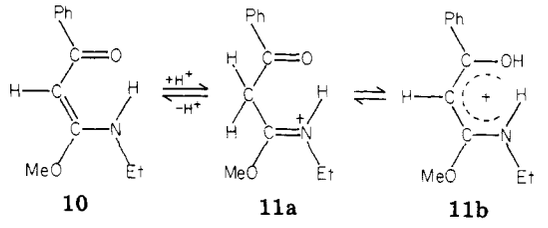


Figure 7. Brønsted plot for the general-acid-catalyzed cyclization (proton-transfer rate determining) of the azide **5b** to **4b** in water at 25 °C (μ = 1.0, KCl) against the pK_a of the acid catalyst. The oxyanion catalysts used were as follows: 1, $ClCH_2CO_2H$; 2, $MeOCH_2CO_2H$; 3, $ClCH_2CH_2CO_2H$; 4, CH_3CO_2H; 5, $H_2PO_4^-$; 6, Me_2AsOOH. The line has a slope α = 0.57.

is thermodynamically more stable (and also the reactive form in hydrolysis).

We have observed no evidence for rapid hydrolysis of the enamine-type structure **5b**. This is consistent with the great stability shown by the model compound **10**, which is hydrolyzed slowly in both acid ($k_{obsd} < 10^{-4}$ s^{-1} at 55 °C in 1.0 M H^+) and base ($k_{obsd} < 10^{-4}$ s^{-1} in 1.0 M HO^-). The enamine **10** is clearly protonated in acid solution, and we



10 **11a** **11b**

have measured a pK_a of 3.64 for the equilibrium **11** ⇌ **10**. The high stability of **11** (a protonated α-benzoylimidate) toward water attack is unusual when compared with other imidates which do not have an α-keto group.

We have also examined the rate of proton transfer to **5b** in the presence of a number of oxyacids. The results are summarized in Figure 7 which shows a plot of the derived second-order constants (k_{HA}) against the pK_a of the individual acid. The k_{HA} values were all obtained at low [HA] in order to avoid change over in the rate-determining step (to *Z*/*E* isomerization) which occurs at high [HA]. The slope (or Brønsted α value) of +0.57 calculated from these data is in the range typically observed for a proton transfer to carbon.[20] We have also observed a large primary isotope effect for the general-acid-catalyzed reaction by carrying out the cyclization of **5b** in D_2O–DOAc. Low concentrations of DOAc (0.005–0.01 M) were used close to its pK_a, and k_{obsd} vs. [DOAc] plots (not shown) were strictly linear. The derived value of the primary isotope effect (k_{HOAc}/k_{DOAc}) was 6.86. This is again consistent with a transition state **12**, involving considerable proton transfer from the acid to the carbon of **5b**.[21]

Further confirmation that protonation at carbon induces cyclization of **5b** was provided as follows. Addition of DOAc to a $CDCl_3$ solution of **5b** caused rapid cyclization to the tetrazole. Integration showed that the product was

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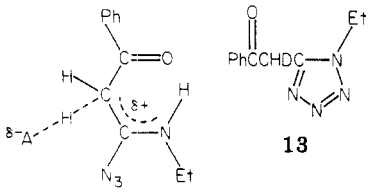

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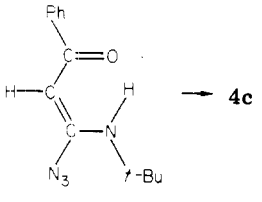
13, i.e., that cyclization was accompanied by the incorporation of just *one* deuterium in the product. This rules out preequilibrium proton transfer to the enamine-type system **5b** under these conditions. Further exchange of the methylene hydrogens with DOAc does occur, but at a rate which is much slower than the formation of **13**.

***Z/E* Isomerization.** As shown earlier, at high acidities **5** is completely converted to the protonated form **7**. The rate of isomerization of **7Z** ⇌ **7E** now becomes rate determining. A value of $k_2 = 2.75 \times 10^{-1}$ s^{-1} has been calculated from eq 2 and has been shown to be in good agreement with the experimentally determined value at "infinite" buffer concentration, thus forcing the establishment of the preequilibrium. The mechanism of *Z/E* isomerization about the carbon–nitrogen double bond may involve inversion at nitrogen (lateral-shift mechanism involving a movement of the substituent attached to nitrogen), a rotational mechanism (involving an unpairing of the π electrons in the double bond), or catalysis of the isomerization by acidic or basic species.[22-24] Most studies favor a transition state for the uncatalyzed reaction which is close to the lateral-shift extreme except in those cases where strongly electron-withdrawing substituents polarize the double bond.[25]

We have examined the effect of substitution of a bulkier group on the azide **3** as this should have a major effect on the rate of isomerization in a way which is dependent on the mechanism of isomerization. The rates of cyclization of **14** in the pH range 0–4 were thus investigated, and



14 → **4c**

Figure 8 shows the bell-shaped pH dependency which results. Using the procedure detailed previously for the analysis of these kinetic results, we have determined the relevant microconstants (see Table I). It is of particular interest that the major effect on the *tert*-butyl substituent is on the rate of *Z/E* isomerization (k_2): an 11-fold *decrease* in rate is observed on changing from an *N*-Et to an *N*-*t*-Bu group. Such a rate depression on increasing the size of the substituent attached to nitrogen is entirely explicable in terms of rate-determining C–N bond rotation (see **7Z** to **7E**); it is noted that those imines which isomerize by the nitrogen inversion mechanism undergo more rapid inversion when the bulk of the substituent on nitrogen is increased.[23] The other constants for **14** (Table I) are consistent with the slightly more electron-donating *N*-*t*-Bu group increasing the basicity of the substrate (relative to *N*-Et).

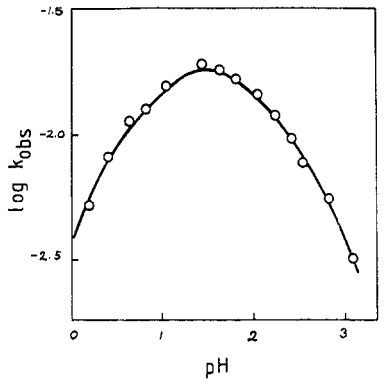


Figure 8. Plot of the logarithm of the observed rate of cyclization of the *N*-*t*-Bu azide **14** to the tetrazole **4c** at 25 °C (μ = 1.0, KCl) as a function of pH. The line is theoretical and was drawn by using eq 3 with the values for the constants given in Table I.

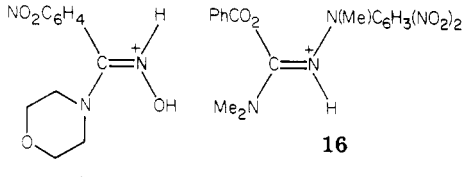
Table I. Comparison of Derived Rate and Equilibrium Constants for the Cyclization of the *N*-Et and *N*-*t*-Bu Azides 5b and 14

const	*N*-Et azide **5b**	*N*-*t*-Bu azide **14**
k_2	2.5×10^{-1} [a]	2.3×10^{-2} [b]
K_{a_1}	8.49×10^{-3} [c]	5.5×10^{-3}
K_1	2.29×10^{-2}	1.94×10^{-1}
K_2	5.34×10^{-3}	5.12×10^{-3}
K_3	1.44×10^{-2}	1.95×10^{-1}

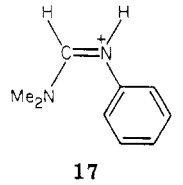
[a] A value of $k_2 = 2.75 \times 10^{-1}$ was obtained at infinite buffer concentration. [b] A value of $k_2 = 2.34 \times 10^{-2}$ was obtained at infinite buffer concentration. [c] $K_{a_1} = 8.7 \times 10^{-3}$ was obtained spectrophotometrically.

Although we have written the $Z \rightarrow E$ isomerization (**7Z** → **7E**) as occurring directly without the intervention of solvent or other nucleophilic species, the possibility does exist that rotation about the >C=$^+$N< bond may not be spontaneous. Thus there have been several reports[24] in the literature of addition–elimination catalysis of imine isomerization. The question of catalysis of *Z/E* isomerization of iminium ions will be dealt with in a future report.

Finally, the rate of *Z/E* isomerization of **7** is of the same order of magnitude as the values reported for related iminium salts also measured in water at 25 °C (k_2 = 6.8 s^{-1} for **15**,[25] 7.9×10^{-2} s^{-1} for **16**,[27] 2.5×10^{-3} s^{-1} for **17**,[28] and 2.75×10^{-1} s^{-1} for **7Z**; in each case only the thermodynamically unstable isomer is shown).



15 16



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Conclusion

The azides **5** have the benzoyl enamine structure **5b** rather than the imidoyl azide structure **5a** as originally proposed. The azides **5b** cyclize at all pHs to the more stable tetrazoles **4b**. The slow step is, however, never the azide cyclization step itself; in base, the conjugate base 8 cyclizes while at intermediate acidity the rate-determining step is proton transfer to carbon (to give the protonated substrate **7Z**). As the acidity of the solution is further increased, the overall rate of cyclization actually decreases (going through a maximum at pH ~2.0) since Z/E isomerization about the protonated imine **7Z** is rate determining. Since the spectral characteristics of the azide **5b** and the tetrazole **4b** are markedly different, the system provides a useful method for the accurate study of the precyclization (i.e., proton transfer, imine isomerization) steps.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer, and UV spectra were run on a Perkin-Elmer 124 instrument. ^{1}H NMR spectra were obtained on a Perkin-Elmer R20-A spectrometer operating at 60 MHz with tetramethylsilane as an internal standard.

Substrates. *N*-Ethylphenacylimidoyl Azides (5). To a solution of sodium azide (1.0 g, 15.4 mmol) in 10 mL of H_2O, cooled with stirring to 0 °C, was added *N*-ethyl-5-phenylisoxazolium fluoroborate[8] (0.5 g, 1.9 mmol). The mixture was stirred at 0 °C for 1–2 min and extracted rapidly with cold (0 °C) CCl_4 (4 × 10 mL). The extracts were dried over sodium sulfate and concentrated under vacuum. The *azide* (0.22 g, 51%) was precipitated from the residual solution by treatment with petroleum ether at −60 °C and dried under vacuum: mp 30–31 °C; IR $\bar{\nu}_{max}$ (CCl_4) 2125 (N_3), 1610, 1500 cm^{-1}; UV (EtOH) λ_{max} 210, 248, 348 nm; NMR (CCl_4) δ 1.15 (3 H, t), 3.25 (2 H, quintet), 5.64 (1 H, s), 7.5 (5 H, m), 11.05 (1 H, s). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.1; H, 5.5; N, 25.9. Found: C, 60.5; H, 5.5; N, 25.6. The azide was stored at −60 °C under dry ice conditions under which it remained stable indefinitely. The *N-tert*-butylphenacylimidoyl azide was prepared in the same manner from the *N-tert*-butyl-5-phenylisoxazolium salt: IR $\bar{\nu}_{max}$ (N_3) 2120 cm^{-1}; UV λ_{max} 348 nm. Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.9; H, 6.5; N, 22.95. Found: C, 63.7; H, 6.5; N, 22.65.

Methyl *N*-Ethylphenacylcarboximidate (10). *N*-Ethyl-5-phenacylisoxazolium fluoroborate was dissolved in methanol and sodium methoxide (1.1 equiv) added. The solvent was removed in vacuo and the residue taken up in ethyl acetate. This was extracted with water. The dried (Na_2SO_4) ethyl acetate was evaporated to give the *imidate* which was recrystallized from CH_2Cl_2–petroleum ether (40–60 °C): mp 34–35 °C; IR (CCl_4) $\bar{\nu}_{max}$ 1610 and 1500 cm^{-1}; UV (EtOH) λ_{max} 250, 325 nm. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.3; N, 6.8. Found: C, 70.35; H, 7.2; N, 6.8.

Kinetic Method. Kinetic data for the cyclization of **5** and **14** were obtained by following changes in the UV spectra of the substrates at wavelengths chosen from repetitive scans of the spectra of the reaction mixtures. First-order rate constants were calculated by using the experimental infinity value. Where buffer solutions were employed, either a Beckman Model 25 or a Perkin-Elmer 124 spectrophotometer was used. Kinetic studies in the absence of buffer species were carried out by using a Cary 14 spectrophotometer fitted with a pH stat. Kinetic runs were initiated by adding 2–5 drops of the substrate solution in dioxane or acetonitrile to a quartz UV cuvette (or Pyrex glass cell for the Cary 14) containing the buffer solutions previously equilibrated for 10 min. Solvents were purified by using established literature methods.[29]

pK_a Determinations. The pK_a's of the substrates **5**, **10**, and **14** were determined spectrophotometrically at wavelengths chosen from comparison of the UV spectra in neutral and acidic solutions. The selected wavelength was used as an analytical wavelength to measure the change in optical density as a function of pH. Since the substrates were reacting, especially around pH 2.0, appreciable cyclization took place during an attempted pK_a measurement. A sampling technique involving extrapolation of the observed optical density back to zero time of mixing was employed to obtain the optical density (at a given pH) of the azides.[30]

Registry No. 4b, 68375-95-1; **4c**, 74724-90-6; **5b**, 74724-91-7; **10**, 74724-92-8; **14**, 74724-93-9; *N*-ethyl-5-phenylisoxazolium fluoroborate, 1736-37-4; *N*-ethyl-5-phenacylisoxazolium fluoroborate, 74724-95-1.

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