If $k_{-1} \simeq k_2$ and $\rho k_{-1} > \rho k_2$ (as is presumably the case here since the reaction center for removal of a proton from carbon (k_{-1}) is closer and more directly linked to the aromatic ring than that for addition of hydroxide ion to the aldehyde (k_2)) then $\rho(k_{-1} + k_2) \simeq \rho k_{-1}$ and

$$\rho k = \rho k_1 - \rho k_{-1}$$
$$= -\rho K_a$$

A value of -1.0 (the observed[3] ρk) is not at all unreasonable for $-\rho K_a$.

We conclude then that Scheme IV best represents the mechanism of hydrolysis of benzoylacetaldehyde. It is essentially the scheme of Pearson and Mayerle (Scheme I) but takes into account the fact that protonation of the enolate anion by water can become rate limiting at high pH in cases of sufficiently strongly acidic dicarbonyl compounds. The situation is thus likely common. Another example is probably that of thenoyltrifluoroacetone, whose hydrate is reported to cleave rapidly in alkali but whose enolate is inert.[16]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

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1,3-Dicarbonyl-2-ketimines. Hydrolysis of 1,3-Dimethyl-5-(*p*-tolylimino)barbituric Acid[1a]

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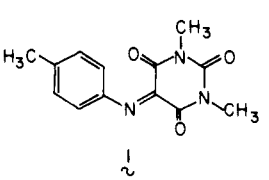
Abstract: The hydrolysis of 1,3-dimethyl-5-(*p*-tolylimino)barbituric acid (**1**) in dilute aqueous solution at zero buffer concentration follows a rate law, $v = k_H[\mathbf{1}][H_3O^+] + k_{OH}[\mathbf{1}][OH^-]$. Under neutral and basic conditions attack by hydroxide ion occurs at an acyl carbon of **1** to give 1,3-dimethyl-5-(*p*-tolylamino)hydantoin in dilute solution. Analogies between the base hydrolysis of **1** and that of 3-methyl-10-arylisoalloxazines are discussed. In acidic solution nucleophilic attack of water occurs at the imino carbon of **1** to give *p*-toluidine and 1,3-dimethylalloxan, as a result of the greatly increased electrophilicity of the protonated imino group. Hydrolysis of **1** under acidic conditions is subject to general acid catalysis with $\alpha = 0.72$, corresponding mechanistically to general base catalysis of rate-determining water attack upon the protonated imino group with $\beta = 0.28$. The lack of a substantial difference between the Brønsted β values for catalysis of water attack on protonated **1** and on protonated simple aromatic aldimines suggests that there is little or no change in the extent of proton transfer in the transition state with increasing electron withdrawal at the central carbon atom in these reactions.

In 1971, Hamilton[2] noted that the C4a–N5 bond of oxidized flavins resembles, in some respects, the carbon–nitrogen double bond of an imine, and in light of this similarity, he suggested that nucleophilic attack of a substrate at C4a might provide a reasonable first step for a hypothetical mechanism of enzymatic oxidation of substrates mediated by flavin coenzymes. Subsequent investigations[3] of flavins and isoalloxazines have indicated that both C4a and N5, as well as C4 and C10a, are capable of electrophilic behavior toward different nucleophiles. Hamilton's suggestion concerning the electrophilic character of the C4a–N5 bond has prompted our interest in the detailed mechanisms of reactions of simple imines of electron-deficient carbonyl compounds that, analogous to isoalloxazines, possess strongly resonance electron-withdrawing substituents at carbon. 1,3-Dicarbonyl-2-ketimines are compounds of this type. In this paper we describe the kinetics and products of hydrolysis of 1,3-dimethyl-5-*p*-tolylimino)barbituric acid (**1**), a reaction that exhibits analogies to the hydrolysis of substituted isoalloxazines.[3d]



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Experimental Section

Materials. Reagent grade inorganic compounds and formic and acetic acids were used without further purification. Other organic reagents were recrystallized or distilled before use. Acetonitrile used in the kinetic experiments was distilled. Glass-distilled or distilled and deionized water was used in all experiments.

1,3-Dimethylbarbituric acid was prepared[4] from 38 mL of diethyl malonate, 5.75 g of sodium, and 22 g of dimethylurea, mp 115–120 °C (lit.[5] 123 °C).

1,3-Dimethylalloxan was prepared by the method of Otsuji, Wake, and Imoto[6] from 10.6 g of dimethylbarbituric acid and 7.5 g of selenium dioxide. It was recrystallized from a large volume of benzene and petroleum ether, or, preferably, from a small volume of acetonitrile and benzene. The identity of the product was confirmed by elemental analysis of a carefully dried sample. Anal. ($C_6H_6N_2O_4$) C, H, N.

1,3-Dimethyl-5-(*p*-tolylimino)barbituric Acid (1). Dimethylalloxan (510 mg, 3.0 mmol) was dissolved in 100 mL of benzene and 3 Å molecular sieves (1.0 g) were added. To the heated benzene solution was added 320 mg (3.0 mmol) of *p*-toluidine dissolved in a small amount of benzene. The solution was refluxed for 3–4 h, decanted from the molecular sieves, and evaporated to dryness, and the product was crystallized by addition of ether–petroleum ether (bp 66–75 °C), mp 133–137 °C. An analytical sample, sublimed in vacuo, gave mp 137–138 °C. Anal. ($C_{13}H_{13}N_3O_3$) C, H, N.

NMR (CD_3CN, Me_4Si) δ 2.36 (s, 3 H, CH_3), 3.20 (s, 3 H, NCH_3), 3.36 (s, 3 H, NCH_3), 6.77 (d, 2 H, aromatic), and 7.25 ppm (d, 2 H, aromatic); mass spectrum *m/e* 259 (M) and 261 (M + 2).

Kinetics. Rates of reaction were measured by following the decrease in absorbance of **1** at 470 nm using a spectrophotometer with a cell compartment thermostated at 25 °C. Reactions were initiated by addition of 50 μL of a 1.75×10^{-2} M solution of **1** in acetonitrile to 3.0 mL of aqueous buffer solutions. An ionic strength of 1.0 M was maintained by addition of potassium chloride. The reaction was ordinarily followed for 2–3 half-lives, and satisfactory pseudo-first-order kinetics were observed for this period.

Product Identification. (1) In Acidic Solution. The NMR spectrum of a solution of 26 mg of **1** in 0.5 mL of CD_3CN was determined before and after addition of 0.5 mL of 0.5 M formic acid–sodium formate buffer (D_2O), 50% anion. Shortly after addition of the buffer a parallel decrease in the areas of the peaks at 3.4 and 2.4 ppm, an increase in the area of the peak at 3.2 ppm, and the appearance of a new peak at 2.3 ppm were observed. In a separate experiment, *p*-toluidine was identified as a product of the reaction by extraction from a solution of **1** in 50% acetonitrile–water solution containing 0.25 M sodium formate buffer, 50% anion, that had been allowed to stand for 4 h until all the red color of **1** had disappeared. The solution, after adjustment to pH 11, was extracted three times with ether, and the ether extract was shown to contain *p*-toluidine by thin layer chromatography (ether solvent) with an authentic sample of *p*-toluidine.

(2) In Neutral and Basic Solution. 1,3-Dimethyl-5-(*p*-tolylamino) hydantoin (2). To a solution of **1** (251 mg) in 5 mL of acetonitrile was added 5 mL of 0.4 M potassium hydroxide. A stream of nitrogen was passed through the reaction mixture during mixing and for about 2 min thereafter. The mixture was acidified to a pH of approximately 2 with 0.4 M hydrochloric acid and extracted three times with ether. The ether solution was dried over sodium sulfate and evaporated. Treatment of the residue with carbon tetrachloride gave crystals of crude 1,3-dimethyl-5-(*p*-tolylamino)hydantoin (**2**) which were isolated by filtration. Thin layer chromatography of the filtrate indicated that it contained a mixture of **2** and a product whose chromatographic mobility corresponded to 1,3-dimethyl-5-(*p*-tolylimino)hydantoin (**3**). Additional **2** was isolated from this mixture by preparative layer chromatography on silica using ether as a solvent. The total isolated yield of crude **2** was 112.5 mg (50%). After sublimation and repeated crystallization from carbon tetrachloride **2** was obtained as a white, crystalline solid: mp 113–116 °C; NMR ($CDCl_3$, Me_4Si) δ 2.24 (s, 3 H, CH_3), 2.95 (s, 3 H, NCH_3), 3.05 (s, 3 H, NCH_3) 4.23 (s, broad, 1 H, NH), 5.07 (s, 1 H, CH), 6.57 (d, 2 H, aromatic), and 7.02 ppm (d, 2 H, aromatic); mass spectrum *m/e* 233 (M). A similarly prepared sample of **2**, after purification by recrystallization from carbon tetrachloride, sublimation, and subsequent recrystallization from ether, had mp 115–116 °C. Anal. ($C_{12}H_{15}N_3O_2$) C, H, N.

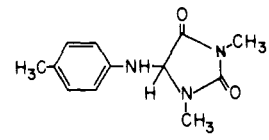
1,3-Dimethyl-5-(*p*-tolylimino)hydantoin (3). To a solution of 200 mg of **1** in 10 mL of acetonitrile was added 10 mL of 0.1 M potassium phosphate buffer, 67% dianion. The reaction mixture was allowed to stand in the dark at room temperature for 5 h. Upon completion of the reaction the pH of the reaction mixture was adjusted to approximately 4 and the mixture was extracted with ether. The ether solution was concentrated and subjected to column chromatography on silica using ether as solvent. The yellow band, which was the fastest moving constituent of the reaction mixture, was collected. Evaporation of the solvent gave a yellow oil which did not crystallize and was not purified further: NMR (CCl_4, Me_4Si) δ 2.3 (s, 3 H, CH_3), 3.0 (s, 3 H, NCH_3), 3.2 (s, 3 H, NCH_3), 6.8 (d, 2 H, aromatic), and 7.1 ppm (d, 2 H, aromatic). Absorption at 1.1–1.35 ppm in this sample was assigned to an impurity. The compound was converted into **2** by treatment with excess dithiothreitol[3c] in 50% aqueous acetonitrile containing 0.05 M potassium phosphate–biphosphate buffer, 80% dianion. After completion of reaction, as indicated by thin layer chromatography of the reaction mixture, the mixture was acidified and extracted with ether. The ether layer was repeatedly extracted with water, dried, and evaporated, and the residue was crystallized from carbon tetrachloride, mp 111–113 °C, mmp with **2** 113–114 °C.

Identification of 2 from Hydrolysis of 1 in Dilute, Neutral Solution. To 100 mL of 0.1 M aqueous potassium phosphate–biphosphate buffer (76% dianion), ionic strength 1.0 M (KCl), was added 1.7 mL of a solution of **1** in acetonitrile, to give a final concentration of 3.2×10^{-4} M **1**. After 1.5 h the mixture was extracted three times with ether. The ether extract was dried and concentrated. Thin layer chromatography of the concentrated product on silica using ether as solvent gave a large spot which cochromatographed with **2**, plus a trace of material corresponding to unreacted starting material.

Results

1,3-Dimethyl-5-(*p*-tolylimino)barbituric acid (**1**) undergoes hydrolysis in aqueous acid and base solutions. Under acidic conditions the hydrolysis of 0.1 M **1** in 50% CD_3CN–D_2O was followed by NMR spectroscopy (Figure 1); the disappearance of the peaks corresponding to **1** is accompanied by an increase in peaks characteristic of dimethylalloxan and *p*-toluidine. Formation of *p*-toluidine under these conditions was confirmed by extraction of *p*-toluidine which was identified by thin layer chromatography.

In strongly basic solution hydrolysis of 0.1 M **1** yields 1,3-dimethyl-5-(*p*-tolylamino)hydantoin (**2**). Identification of this



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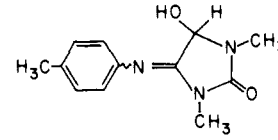
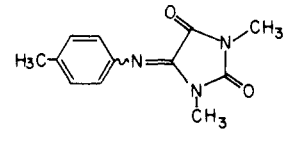


2a

product was based on the elemental analysis and NMR spectrum of the isolated compound. The peak at δ 5.07 ppm proved especially useful in the assignment of structure; this proton did not exchange with solvent D_2O but exchanged immediately in the presence of small amounts of deuterioxide ion, an observation which suggested the assignment of this peak to an acidic C–H proton. Existence of a tautomeric equilibrium between **2** and the hydroxy imine **2a** is possible. We believe that structure **2** is the more likely, based on the infrared spectrum (in $CDCl_3$) which exhibits peaks at ca. 1720 and 1780 cm^{-1}, consistent with reported values[7] of 1694–1712 and 1730–1780 cm^{-1} for the 2- and 4-carbonyl groups, respectively, of substituted hydantoins. The oxidation product, **3**, which cannot



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exist in tautomeric forms, shows a strong absorbance at 1680 cm^{-1} that is absent in **2** and is most reasonably assigned to the C=N group. Hence we conclude that the predominant tautomeric form of **2** is most likely to be the amino form, which lacks the C=N group, rather than the imino form **2a**.

Aminohydantoin **2** is the only product detectable by thin layer chromatography of an ether extract of a reaction mixture containing 3.2×10^{-4} M **1** in 0.1 M aqueous phosphate buffer (76% dianion), conditions approximating those of the kinetic

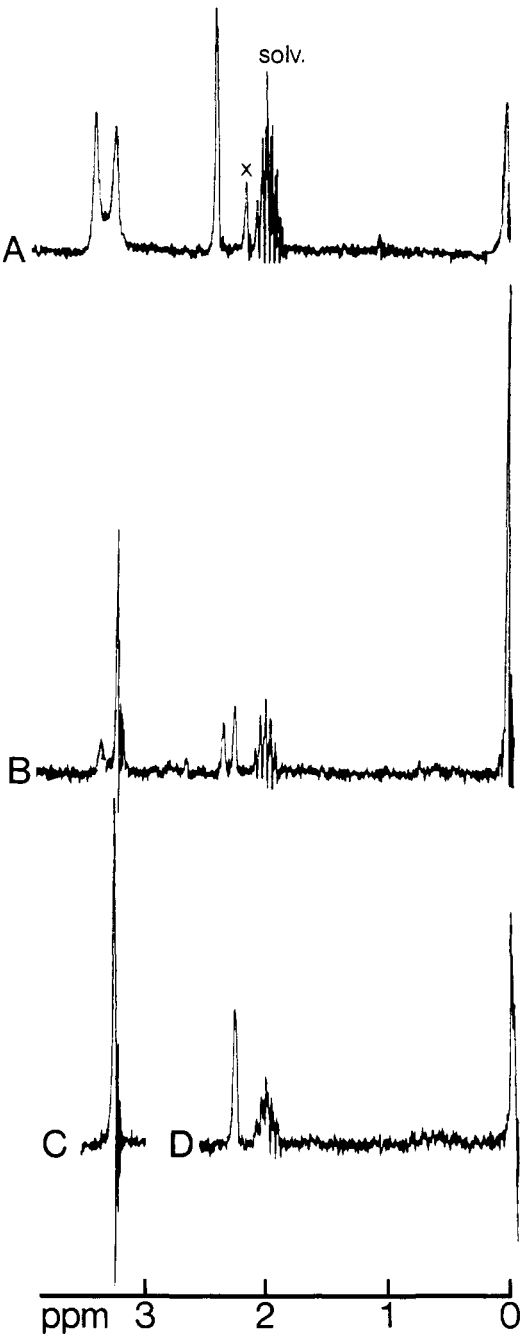


Figure 1. NMR spectra of **1** in CD_3CN (A); reaction mixture of 0.1 M **1** with formic acid-sodium formate buffer, 50% base, in 50% CD_3CN-D_2O, corresponding to approximately 72% hydrolysis of **1** (B); authentic dimethylalloxan (C) and *p*-toluidine (D) in the above buffer. The peak marked X in spectrum A is due to a trace of water in the acetonitrile solvent.

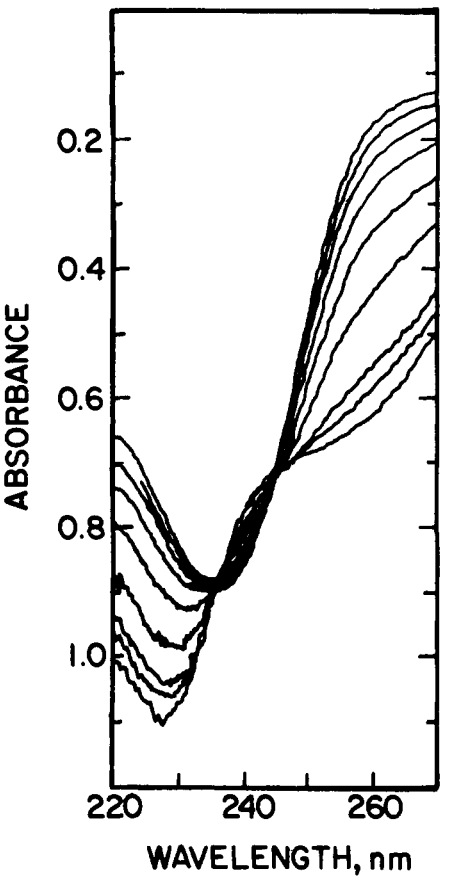


Figure 2. Ultraviolet spectra as a function of time for the hydrolysis of ~7 × 10^{-5} M **1** in 0.1 M potassium phosphate-biphosphate buffer, 76% dianion, ionic strength 1.0 M. Absorbance at highest and lowest wavelengths shown decreases with time. Initial scan, 15 s; final, 23.4 min.

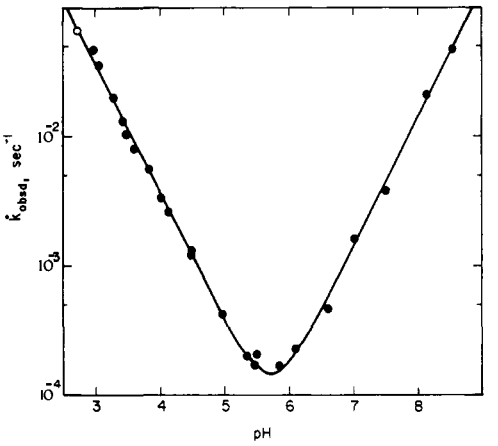


Figure 3. Effect of pH on the pseudo-first-order rate constants, k^0_{obsd}, for hydrolysis of **1** at 25 °C, ionic strength 1.0 M, in dilute hydrochloric acid solution (○) or extrapolated to zero buffer concentration (●). The line is a theoretical curve corresponding to the rate constants k_H and k_{OH} given in the text.

experiments. Attempts to isolate **2** from more concentrated neutral reaction mixtures resulted instead in the isolation of iminohydantoin **3**. Based on this concentration dependence and the observation that carrying out the reaction under nitrogen did not significantly affect the relative amounts of **2** and **3** produced (as shown by thin layer chromatography) we speculate that **3** is formed by a bimolecular oxidation of **2** or some precursor thereof in which unreacted **1**, rather than molecular oxygen, acts as the oxidant.

Kinetics of the hydrolysis of **1** in dilute aqueous solutions at 25 °C were followed spectrophotometrically. A typical scan of the ultraviolet spectral changes observed in neutral solution as a function of time is shown in Figure 2. Figure 3 shows the effect of the pH on the pseudo-first-order rate constants, k^0_{obsd}, for disappearance of **1**, at zero buffer concentration. The reaction follows a rate law, $v = k^0_{obsd}[\mathbf{1}] = k_H[H_3O^+][\mathbf{1}] + k_{OH}[OH^-][\mathbf{1}]$, with k_H and k_{OH} equal to 38 M^{-1} s^{-1} and 1.4 × 10^4 M^{-1} s^{-1} (in terms of antilog [−pH] or antilog [pH − 14]), respectively. Buffer catalysis of hydrolysis is observed on the acid limb of the pH-rate profile but no detectable general catalysis (less than 20% acceleration of the reaction

Table I. General Acid Catalysis of Hydrolysis of 1,3-Dimethyl-5-(*p*-tolylimino)barbituric Acid[a]

Acid	pK_a'	Fraction conj acid	Concn range,[b] M	k_{app},[c] $M^{-2}\,s^{-1}$	k_{cat} (av), $M^{-2}\,s^{-1}$
Chloroacetic (CA)	2.70[d]	0.10	0.02-0.20	0.014	
		0.20	0.02-0.20	0.028	0.14
Methoxyacetic (MA)	3.40[d]	0.43	0.02-0.55	0.020	
		0.67	0.02-0.55	0.036	0.050
Formic (F)	3.56[d]	0.20	0.02-0.40	0.0068	
		0.50	0.02-0.20	0.012	
		0.64	0.02-0.40	0.034	0.037
β-Chloropropionic (BCP)	3.93[d]	0.21	0.02-0.30	0.003	
		0.46	0.02-0.30	0.012	
		0.73	0.02-0.30	0.017	0.021
Acetic (A)	4.65[d]	0.31	0.02-0.60	0.0023	
		0.60	0.04-0.60	0.0039[e]	
		0.80	0.04-0.60	0.0053[e]	0.0068
Dimethylmalonic (DMM)	5.44[d]	0.30	0.025-0.20	0.00068	
		0.50	0.01-0.10	0.0012	0.0023

[a] At 25 °C, ionic strengh 1.0 M (KCl). [b] Total buffer concentration. [c] In terms of total buffer. [d] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6353-6361 (1969). [e] Based on the linear portion only of plots of k_{obsd} against buffer concentration.

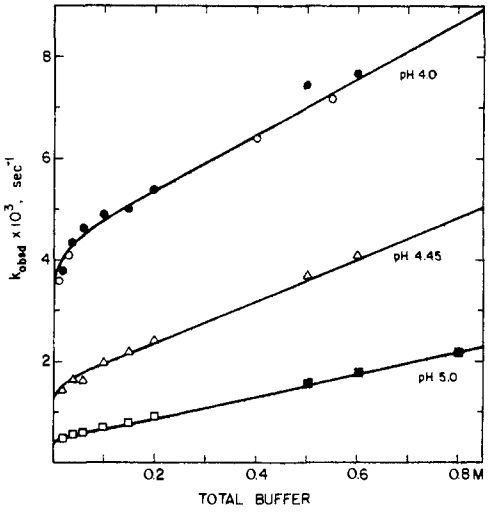


Figure 4. Catalysis of hydrolysis of **1** by acetic acid-acetate buffers at 25 °C, ionic strength 1.0 M. The lines are theoretical curves based on eq 7 and the individual rate constants given in the text. Solid and open symbols represent results of separate experiments.

in the presence of 0.2 M imidazole and triethylenediamine buffers) is found in basic solution. The buffer catalysis in acid solutions is kinetically general acid catalysis and follows the rate law given by eq 1, with $k_{cat} = k_{app}/\alpha$, where α equals the fraction of buffer present as the conjugate acid. Catalytic constants for a series of carboxylic acid buffers are summarized in Table I.

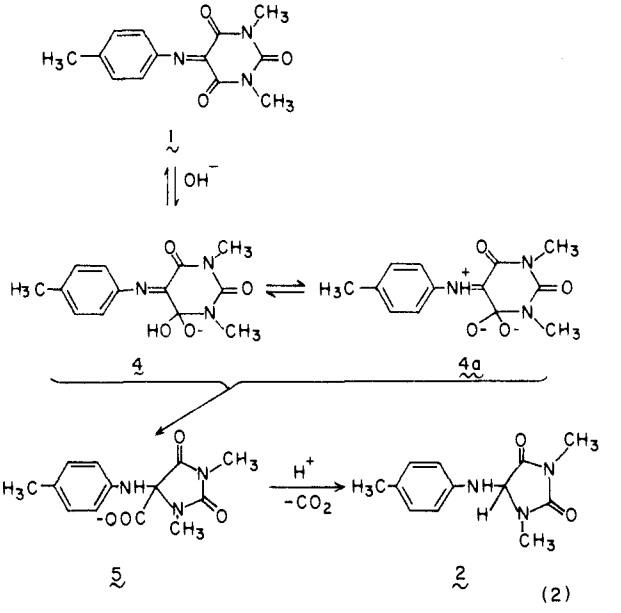
$$v = k^0_{obsd}[\mathbf{1}] + k_{app}[\text{total buffer}][\mathbf{1}] = k^0_{obsd}[\mathbf{1}] + k_{cat}[HA][\mathbf{1}] \quad (1)$$

Catalysis of the hydrolysis of **1** in acetic acid-acetate buffer solution, pH 4.0, shows a nonlinear dependence on buffer concentration (Figure 4). This small effect, which resulted in a maximum deviation of the rate constants for the reaction below 0.05 M buffer of 15-20% from the line established at higher buffer concentrations, was detectable only with acetate buffer at pH 4.0 but was reproducible in two separate experiments under these conditions.

Discussion

The present results show that, like isoalloxazines, a simple 1,3-dicarbonyl-2-ketimine **1** is capable of acting as an ambident electrophile. In the hydrolysis of this compound the predominant site of nucleophilic attack changes from an acyl to an imino carbon as the pH is decreased and reaction of the protonated imine becomes the predominant reaction pathway.

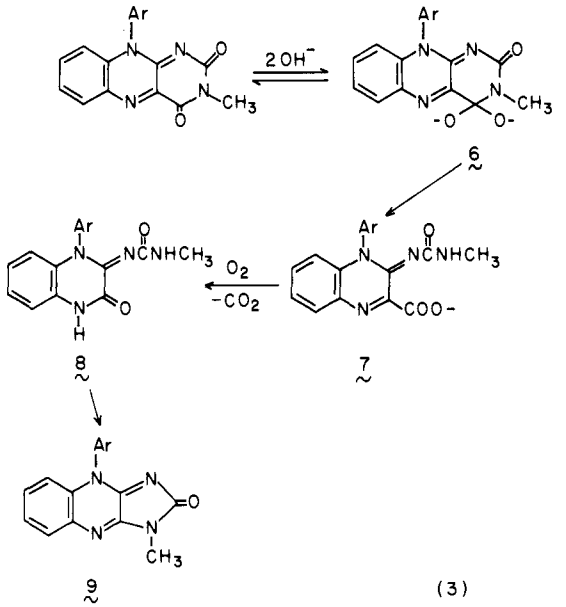
Base Hydrolysis. Proposed mechanisms for the reactions of the simple imine **1** and 3-methyl-10-arylisoalloxazines[3d] with aqueous base are summarized in eq 2 and 3, respectively. The



formation of **2** from **1** shows that base hydrolysis of 1,3-dimethyl-5-(*p*-tolylimino)barbituric acid is initiated by nucleophilic attack at an acyl, rather than the imino, carbon, analogous to attack at C4 of isoalloxazines. The observation of ring contraction in the reaction products is also common to both reactions, although the mechanism of this ring contraction is different in the two systems.

Two major differences exist between the reaction of **1** and that of the isoalloxazine derivatives.

(1) The base hydrolysis (at pH 10-14) of 3-methyl-10-arylisoalloxazines is second order in hydroxide ion whereas that of **1** is first order in hydroxide ion. The second-order dependence on hydroxide ion was attributed by Smith and Bruice[3d] to rate-determining expulsion of nitrogen from the dianionic adduct **6**. Our observations that the reaction of **1** is first order in hydroxide ion up to pH 8.5 and shows no detectable general

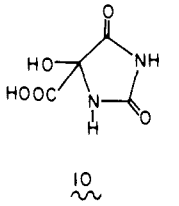


(3)

base catalysis are consistent either with rate-determining attack of hydroxide ion on **1** or rearrangement of monoanion **4** or **4a.** Although sharp isosbestic points were not obtained, spectral curves for the hydrolysis of **1** (Figure 2) do not indicate the buildup of significant quantities of any intermediates during the first 4 half-lives of the reaction at pH ca. 7.

The reaction of **1** at pH 10 is at least 10^5 times faster than that of 3-methyl-10-arylisoalloxazines based on extrapolation of Figure 3. Since **1** must be nonplanar as a result of interference between an ortho hydrogen of the benzene ring and a carbonyl group, the much smaller reactivity of the isoalloxazine derivatives relative to **1** is probably a result of the greater kinetic and thermodynamic stability of the planar, resonance-stabilized isoalloxazine system.

(2) The product, **2,** of hydrolysis of **1** in dilute solution on the alkaline limb of the pH-rate profile results from nonoxidative decarboxylation, probably via the β-carboxamido acid **5.** Precedent for an intermediate such as **5** is provided by the formation of alloxanic acid (**10**) in the base-catalyzed rearrangement of alloxan,[8] the parent ketone of **1,** via migration of nitrogen from an acyl to a carbonyl carbon. An oxidized derivative of **2** (corresponding to the product, **9,** obtained under aerobic conditions from isoalloxazine hydrolysis) is obtained only in the presence of high concentrations of **1,** which presumably acts as the oxidant. This is in contrast to the isoalloxazine reaction,[3d] in which decarboxylation does not occur in the absence of oxidation and the reduced form of the ring-contraction product **11** (analogous to **5**) is not an intermediate in the formation of **9.**



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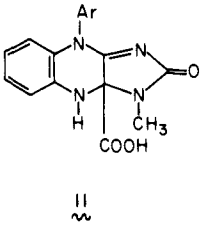

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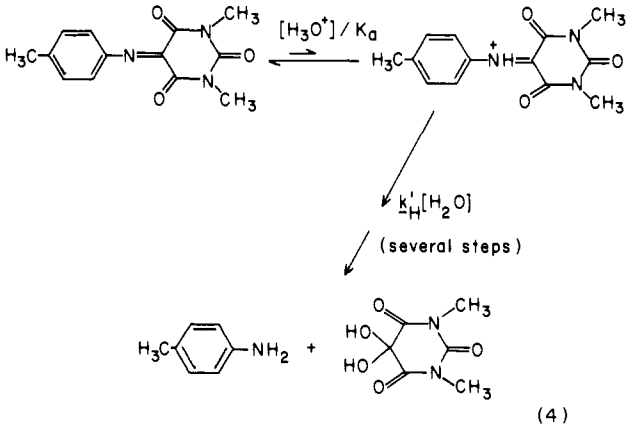
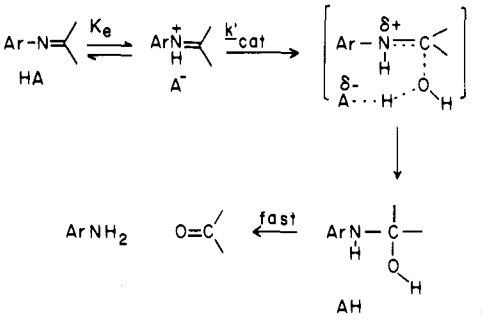
Acid Hydrolysis. Although the product of hydrolysis of **1** on the basic limb of the pH-rate profile corresponds to attack of hydroxide ion at C4 (or C6), the products of acid hydrolysis, *p*-toluidine and dimethylalloxan, indicate that under acid conditions nucleophilic attack of water occurs in the more "normal" position for an imine, i.e., at the imino carbon, C5. This change in the electrophilic position of the molecule with pH is a result of the greater ease of protonation of nitrogen than of oxygen and the increased electrophilicity of the protonated imino group. Hence under weakly acidic conditions attack of water on the protonated imine[9-12] becomes the predominant reaction pathway (eq 4), with an observed second-order rate constant, k_H, given by $k_H = k_H'/K_a$. This mechanism becomes favorable even at pH values well above the pK_a of the iminium ion, where the fraction of **1** in the protonated form is extremely small, because of the very high reactivity (large k_H') of the iminium ion; evidence for a similar effect of cation formation at the N5 position of a flavin on the electrophilicity of C4a is provided by the formation of the C4a carbinolamine of 5-ethyl-3-methyllumiflavinium perchlorate[13] with an equilibrium constant K_{OH} = [>C(OH)-N<]/[>C=N<$^+$][OH$^-$] of 9.5 × 10^9 M^{-1}.



(4)

The hydrolysis of **1** under acidic conditions is subject to catalysis by buffers, according to the rate law given in eq 1. By analogy with other reactions of imines[10,11] we assign this catalysis to general base catalysis of rate-limiting water attack (k'_{cal}) on the protonated imine (eq 5). No detectable break in



(5)

the pH-rate profile corresponding to a change from rate-limiting water attack to expulsion of *p*-toluidine[9-12] with changing pH is observed, but there is evidence for a partial change in the rate-limiting step with increasing concentration of acetic acid buffers. At pH 4.0 a plot of pseudo-first-order rate constants for the reaction against buffer concentration is nonlinear at buffer concentrations less than 0.05 M (Figure 4). At higher pH values the deviation from linearity is so small and occurs at such low buffer concentrations that it is experimentally undetectable. Explanations for this nonlinearity involving buffer self-association, specific salt effects, or medium effects are unlikely since the break occurs in a concentration range where these effects are expected to be negligible. Evi-

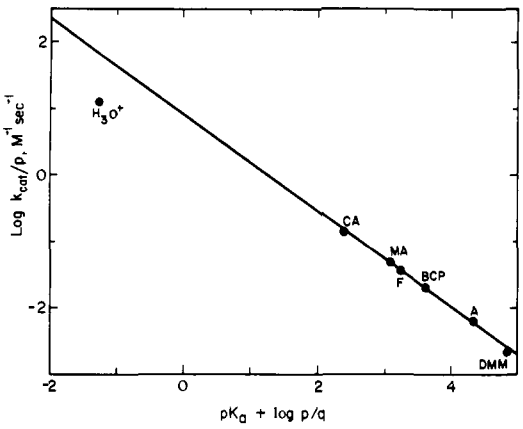
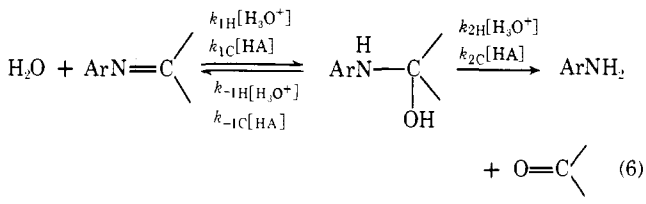


Figure 5. Brønsted plot for general acid catalysis of hydrolysis of **1** by carboxylic acids and hydronium ion. The acids are identified in Table I. Statistical corrections were made according to the method of R. P. Bell and P. G. Evans [(*Proc. R. Soc. London, Ser. A*, **291**, 297-323 (1966)]. The least-squares slope of the line (with H_3O^+ omitted) is 0.72.

dence has been obtained for a lack of kinetically significant self-association of acetate buffers at concentrations up to 2.0 M.[14] The most reasonable explanation for the curvature of the buffer-rate plot, based on the behavior of similar systems,[15] involves a change from partially rate-determining breakdown of the intermediate to fully rate-determining water attack as the buffer concentration is increased (eq 6). At low or zero



(6)

buffer concentration expulsion of the amine occurs at a rate comparable to loss of water from the intermediate, so that amine expulsion is partly rate determining. If this step is much more sensitive to buffer catalysis than attack and loss of water,[15] increasing the buffer concentration will increase the rate of amine expulsion more than it increases the rate of attack and loss of water, so that at moderate or high buffer concentrations amine expulsion is very fast, the attack step becomes entirely rate determining, and k_{cal}(eq 1) = k_{1C}. The steady-state rate law for this mechanism is given by eq 7, where $K_h = k_{1H}/k_{-1H} = k_{1C}/k_{-1C}$.

$$k_{obsd} = \frac{K_h(k_{1H}[H_3O^+] + k_{1C}[HA])(k_{2H}[H_3O^+] + k_{2C}[HA])}{(k_{1H} + K_h k_{2H})[H_3O^+] + (k_{1C} + K_h k_{2C})[HA]} \quad (7)$$

The data of Figure 4 at three pH values can be fit by curves calculated from eq 7 with $k_{1H} = 44\ M^{-1}\ s^{-1}$, $k_{1C} = 6.8 \times 10^{-3}\ M^{-1}\ s^{-1}$, $K_h k_{2H} = 170\ M^{-1}\ s^{-1}$, and $K_h k_{2C} = 1.5\ M^{-1}\ s^{-1}$. Because of the very small contribution of amine expulsion to k_{obsd}, even at low buffer concentrations, values of $K_h k_{2H}$ and $K_h k_{2C}$ can only be estimated approximately. Even at zero buffer concentration, where the hydronium ion catalyzed expulsion of amine (k_{2H}) makes its maximal contribution to the observed rate constant, this step is approximately four times faster than the expulsion of water (k_{-1H}) since $k_{2H}/k_{-1H} = K_h k_{2H}/k_{1H}$. Hence under most experimental conditions, involving finite buffer concentrations, the first step is almost entirely rate determining. As the pH and base:acid ratio of the buffer are increased the break in the plots (Figure 4) occurs at increasingly lower buffer concentrations and is experimentally undetectable at pH 4.45 and 5.0.

The Bronsted α value for catalysis of hydrolysis of **1** by carboxylic acids (Figure 5) is 0.72, corresponding to a β value for general base catalysis (k'_{cal}; eq 5) of 0.28, or an α value for the reverse reaction, general acid catalysis of carbinolamine dehydration, of 0.72. The point for hydronium ion shows a negative deviation of slightly less than an order of magnitude from the line determined for carboxylic acids.[16] A line including the hydronium ion has a least-squares slope of 0.6. The observed Brønsted coefficients for **1** are similar to the β value of 0.27 for general base catalysis of water attack on the benzhydrylidenedimethylammonium ion,[10] α values of 0.6-0.77 for general-acid-catalyzed dehydration of carbinolamines derived from 4-chlorobenzaldehyde and substituted hydrazines[17] and hydroxylamine,[11] and α values of 0.65-0.8 for dehydration of the phenylhydrazine carbinolamines of 2-, 3-, and 4-formyl-1-methylpyridinium iodides.[18] If the assumption[19] is made that a Brønsted β value of 0.28 means that the reaction behaves "as if" approximately 0.3 of the negative charge on the carboxylate ion has been neutralized in the transition state and the proton transfer to the catalyst is about 0.3 complete, then the similarity in Brønsted coefficients for the hydrolysis of **1** and imines derived from much less electron deficient substituted benzaldehydes means that the extent of proton transfer in the transition state must be about the same for "normal" imines and the electron-deficient compound **1**. This result was unexpected in light of the prediction from structure-reactivity considerations[20] that increasing the electrophilic character of the central carbon atom and destabilizing the protonated imine by electron withdrawal should shift the transition state on the reaction coordinate-free energy surface toward a structure involving less proton transfer from water to the base catalyst and hence a smaller β value. The lack of any regular decrease in β value with increasing electron withdrawal at carbon for base-catalyzed formation of carbinolamines from imines of 4-chlorobenzaldehyde, 1-methylpyridinium aldehydes,[18] and alloxan suggests that the extent of proton transfer in these reactions is relatively insensitive to substituents on the central carbon atom. These reactions may provide another example[21] of a system in which the "Hammond postulate" prediction of decreasing selectivity with increasing reactivity is not experimentally demonstrable. The reasons for the apparent dissimilarity between general-acid-catalyzed carbinolamine dehydration and the analogous expulsion of phenol from substituted benzaldehyde methyl phenyl acetals,[22] in which α varies from 0.7 to 1.0 as the benzaldehyde substituent is varied from *p*-methoxy to *m*-nitro, is at present unclear.

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References and Notes

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(16) A small uncertainty in the value of k_H results from the extrapolation of plots of k_{obsd} to zero buffer concentration, because of the possible contribution of partially rate-determining amine expulsion (k_{2H}; see text) to some of these extrapolated rate constants used in the determination of k_H. Based on the values for the individual rate constants cited in the text, the experimental value of k_H differs from k_{1H} for fully rate-determining water attack by no more than 20%. This uncertainty is insufficient to account for the observed deviation of k_H from the Brønsted plot for general acid catalysis of the attack step.
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Elimination–Addition Mechanisms of Acyl Group Transfer: The Hydrolysis and Synthesis of Carbamates

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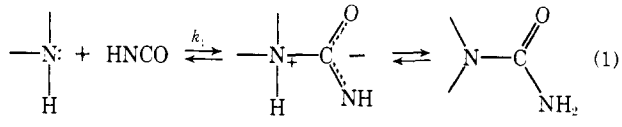
Abstract: The equilibrium constants for formation of aryl carbamates from isocyanic acid and a series of phenols have been measured. The Bronsted β_N value for the reaction of phenolate anion with isocyanic acid and the selectivity of the equilibrium constant for formation of carbamate anion $ArO^- + HNCO \rightleftarrows ArOC(NH)O^-$ are consistent with a transition state half-way between reactants and product. The Bronsted selectivity for the latter equilibrium indicates that the carbamide group $[-CO(NH)^-]$ is significantly more electropositive than a proton in electrophilic attack on aryl oxide ions. The formation and decomposition of carbamoyl phosphate, an important metabolite, does not involve intramolecular proton transfer concerted with C–O bond fission.

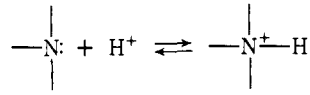
Introduction

It was recently shown[1,2] that attack of strong amines on isocyanic acid (eq 1) possesses a relatively low Bronsted selectivity (β_N) with respect to changing ammonium ion structure. Decomposition of the zwitterionic intermediate becomes rate limiting at low amine basicity, giving rise to a higher β_N value derived from a composite rate constant. Low selectivities have also been observed for attack of nucleophiles on a number of heterocumulenes.[3,4] The β_N obtained from the Bronsted type relationship essentially measures the selectivity of a reaction vs. the ionization of the conjugate acid of the nucleophile and therefore does not provide strong evidence for the structure of the transition state of the reaction. Comparison of reactivity change with change in equilibrium constant for the reaction yields more meaningful β_N quantities, and this type of result is available for many acyl transfer reactions[5] and recently for reaction of alcoholate anions with carbon dioxide.[4] This type of selectivity is somewhat difficult to obtain because of the scarcity of good data on equilibrium constants, so it is not surprising that the ionization equilibria are used as general standards.

The equilibrium constant for formation of the zwitterion (eq 1) from amine and isocyanic acid is unfavorable[2] whereas the



(1)


(2)

low value for β_N (vs. the pK_a of the ammonium ion) suggests an early transition state apparently violating the Hammond postulate.[6] "Anti-Hammond" behavior could arise from three sources: (1) the β_N may not be a good measure of the position of the transition state because the ionization of the conjugate acid of the nucleophile is not a good comparison with the equilibrium, (2) the Hammond postulate refers to potential energies whereas reactivities and equilibria are free energies and possess an entropy component which may not be negligible or cancel, (3) some subtle effect such as that discussed by Pross[7] may be operating.

This work seeks to obtain the effect of structure variation on the equilibrium constant and individual rate constants for the reaction of phenolate anions with isocyanic acid.

Experimental Section

Materials. Phenyl carbamate was purchased from Aldrich and other aryl carbamates were prepared by the following procedure. Phenol (0.2 mol) was dissolved in carbon tetrachloride (100 mL) and dry, powdered sodium cyanate (13 g) was added. The mixture was stirred while a solution of trichloroacetic acid (33 g) in carbon tetrachloride (80 mL) was added. Stirring was continued at 55 °C for 3 h, water added, and the organic layer separated. The carbon tetrachloride solution was dried with Na_2SO_4, evaporated, and the residue recrystallized from a suitable solvent (Table I). This procedure worked well