98–99°; mixture melting point with an authentic sample[32] of the natural abundance compound 97–99°.

Reaction of Ethanesulfonyl Chloride with D_2O. Ethanesulfonyl chloride (4.52 g.) was dissolved in dry dioxane (25 ml.) containing D_2O (18 ml.). Triethylamine (50 ml.) was added over a period of 5 min. and the solution was allowed to stand for an additional 5 min., then worked up as in the case of methanesulfonyl chloride yielding monodeuterated ethanesulfonyl chloride (3.17 g., 71%) b.p. 65–66° (15 mm.), $n^{25}D$ 1.4506. Johnson and Sprague[31] report $n^{25}D$ 1.4506 for the natural abundance isomer. *Anal.* Calcd. for $C_2H_4DSO_2Cl$: 20.00 atom % excess D. Found: 18.55 atom % excess D. The n.m.r. spectrum (CCl_4) showed a doublet (J = 7.2 c.p.s.) of triplets (J = 1.1 c.p.s.) at 1.62 and a quartet (J = 7.2 c.p.s.) of triplets (J = 2.2 c.p.s.) at 3.65 p.p.m. The relative areas were 3:1.1.

The aniline and *p*-toluidine derivatives of the deuterated ethanesulfonyl chloride were prepared in the same way as those of the methanesulfonyl chloride; anilide m.p.[33] (i) from $CH_3CH_2SO_2Cl$, 57–58°; (ii) from CH_3CHDSO_2Cl, 56–58°; m.m.p. (i) and (ii), 56–58°; toluidides m.p.[34] (i) from $CH_3CH_2SO_2Cl$, 76–78°; (ii) from CH_3CHDSO_2Cl, 77–78°; m.m.p. (i) and (ii), 76–78°.

Reaction of 2-Phenylethanesulfonyl Chloride with D_2O. 2-Phenylethanesulfonyl chloride[35] (410 mg.) was dissolved in dioxane (20 ml.) containing D_2O (5 ml.). Triethylamine (2.0 ml.) was added as quickly as possible. The reaction was allowed to stand at room temperature for 10 min. and then worked up as in the solvolysis of phenylmethanesulfonyl chloride. Silica gel chromatography of the product obtained from the phosphorus pentachloride reaction, gave an oil (315 mg.) on elution with 1:1 petroleum ether–benzene. Recrystallization from petroleum ether gave long white needles, m.p. 31–33°, mixture melting point with a sample of natural abundance 2-phenylethanesulfonyl chloride 31–33°. The n.m.r. spectrum showed aromatic protons at 7.20 (singlet) and aliphatic protons at 3.95 to 3.10 p.p.m. (complex multiplet) in the ratio of 5:3. *Anal.* Calcd. for $C_8H_8DSO_2Cl$: 11.11 atom % excess D. Found: 10.45 atom % excess D.

Hydrolysis of Phenylmethanesulfonyl-1,1-d_2 Chloride without Added Base. Phenylmethanesulfonyl-1,1-d_2 chloride (400 mg.) was dissolved in dioxane (12 ml.) and water (12 ml.) and the solution was warmed at 50° for 90 min. The reaction mixture was extracted with ether; the product (97 mg., 24%) obtained on evaporation of the ether was identified as phenylmethanesulfonyl-1,1-d_2 chloride by its infrared spectrum. The aqueous layer was taken down to dryness. Treatment of the residue with phosphorus pentachloride in the usual manner gave $PhCD_2SO_2Cl$ (211 mg., 53%), m.p. 90–92°. The infrared spectrum was identical with that of an authentic sample.

Methanolysis of Phenylmethanesulfonyl-1,1-d_2 Chloride without Added Base. Phenylmethanesulfonyl-1,1-d_2 chloride (690 mg.) was dissolved in methanol (Fisher Spectranalyzed, 25 ml.) and warmed in an oil bath at 50° for 90 min. The methanol was evaporated and the product was chromatographed on silica gel (30 g.). Elution with 1:1 petroleum ether–benzene gave phenylmethanesulfonyl-1,1-d_2 chloride (304 mg., 49%) whose infrared spectrum was identical with that of the starting material. Elution with 9:1 benzene–ether yielded methyl phenylmethanesulfonate-1,1-d_2 (236 mg., 35%), m.p. 61–62°, mixture melting point with the natural abundance ester 61–62°. *Anal.* Calcd. for $C_8H_8D_2SO_3$: 20.00 atom % excess D. Found: 19.50 atom % excess D. N.m.r. bands ($CDCl_3$) were found at 7.38 (singlet) and 3.73 p.p.m. (singlet). Infrared peaks below 1500 cm.$^{-1}$ (0.5 *M*, $CHCl_3$) were 1495 (m), 1451 (s), 1360 (vs), 1282 (m), 1180 (vs), 1150 (sh), 1053 (w), 1038 (w), 1028 (m), 1012 (vs), 993 (vs), 915 (w), 850 (s), 806 (s), 700 (s) cm.$^{-1}$. C–D stretching bands were at 2240 (vw) and 2156 (vw) cm.$^{-1}$.

(33) W. Autenrieth and P. Rudolph, *Ber.*, **34**, 3467 (1901).
(34) N. N. Mel'nikov, E. M. Sokolova, and P. P. Trunov, *Zh. Obshch. Khim.*, **29**, 529 (1959).
(35) E. B. Evans, E. E. Mabbot, and E. E. Turner, *J. Chem. Soc.*, 1159 (1927).

Iminolactones. I. The Mechanism of Hydrolysis

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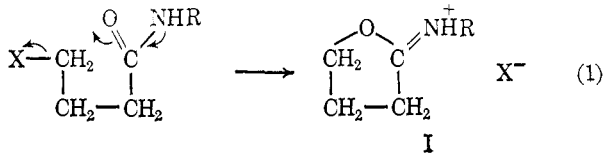
Contribution from the Department of Biochemistry, Yale University, New Haven, Connecticut 06510. *Received August 18, 1965*

The hydrolysis of the iminolactone 2-phenyliminotetrahydrofuran (III) has been investigated in the pH range 0–14 at 30°. The rate–pH profile resembles those reported for the hydrolyses of thiazolines, oxazolines, and Schiff bases. The nature of the hydrolysis products, however, varies with pH. There occurs a gradual transition from the formation of aniline (and butyrolactone) at acid pH to the appearance of γ-hydroxybutyranilide in basic solution; at about pH 7.1, equal amounts of the two products are formed. These findings have necessitated an alteration of the accepted mechanism of imine hydrolysis; it is suggested that, depending upon pH, the hydrolysis of III proceeds either through a neutral carbinolamine intermediate or through its conjugate base, the choice of pathway dictating the identity of the product.

(1) This work is taken from a dissertation to be presented by B. A. C. in partial fulfillment of the requirements for the Ph.D. Degree, Yale University, 1966.

Introduction

N-Substituted iminolactones[2] (I) arise as a result of intramolecular nucleophilic displacement by the amide carbonyl function upon a neighboring electrophilic center (eq. 1).



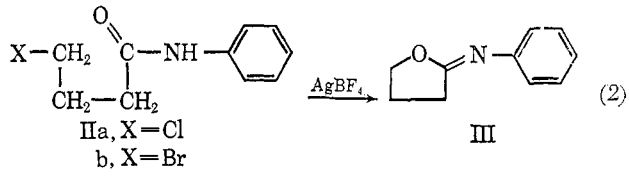
I (1)

While iminolactones (or their salts) have been isolated in a few instances,[3] there are known a number of reactions where the transitory existence of iminolactone intermediates has been postulated. Notable among these are the oxidative cleavages of peptides of tryptophan,[4] tyrosine,[5] and phenylalanine,[6] and the solvolytic cleavage of S-alkylated methionine peptides.[7] These, and additional reactions involving fugitive iminolactones, have been intensively studied in recent years particularly in relation to the development of selective, nonenzymatic methods for the fission of peptide bonds in proteins and oligopeptides.[8] Much emphasis has been placed upon the elaboration of systems capable of yielding, *via* transient iminolactones, the products of cleavage of the amide function; nevertheless, the factors governing the rates and modes of breakdown of iminolactones in aqueous media are little understood.

The present investigation of the hydrolysis of a simple iminolactone was undertaken with two aims: (a) to provide information which might be relevant to the rational design of chemical methods for the specific cleavage of peptide bonds, and (b) to compare the mechanisms of iminolactone hydrolysis to those previously proposed for the hydrolysis of closely related imines (*e.g.*, thiazolines and oxazolines).[9] In the present communication, we report our observation of a striking effect of pH upon the products of hydrolysis of 2-phenyliminotetrahydrofuran (III). This and other findings described here have led us to propose, at least for this one instance, a modification of the generally accepted mechanism of imine hydrolysis.[9]

Results

Synthesis. Stirling[3] has described the preparation of several iminolactones by fusion or ethanolysis of γ- and δ-bromoamides, but has reported that attempts to convert γ-bromobutyranilide (IIb) to the corresponding iminolactone (III) led only to the isolation of aniline and butyrolactone. The successful preparation of 2-(*p*-tolylimino)tetrahydrofuran, isolated as the hydrofluoroborate salt, was achieved by Meerwein, *et al.*,[10a] by reaction of O-ethylbutyrolactonium tetrafluoroborate with *p*-toluidine. A recent report by Mukaiyama and Sato[10b] describes the synthesis of 2-phenyliminotetrahydrofuran (III) by treatment of 2,2-diethoxytetrahydrofuran with aniline at elevated temperatures. The product was found to be a distillable oil, which polymerized on prolonged heating. In the present work, the desired iminolactone III was obtained as a low-melting, crystalline solid upon treatment of γ-chlorobutyranilide (IIa) with silver tetrafluoroborate, according to the general procedure of Peter, *et al.*[11] (eq. 2).



IIa, X=Cl
b, X=Br

III (2)

The assignment of structure III to the product of the silver tetrafluoroborate reaction is supported by the presence of a strong infrared absorption band at 5.88 μ,[12] the quantitative formation of γ-butyrolactone (v.p.c.) and aniline after mild acid hydrolysis, and the kinetic behavior described below.

Kinetic Studies. The observed first-order rate constants for the hydrolysis of the iminolactone III in 10% acetonitrile–water (30°) are presented in Figure 1. In the pH range 4.1–7.7, the rate constants were extrapolated to zero buffer concentration (acetate, phosphate, and imidazole buffers). No effect of varying buffer concentration was noted at pH 8–11 (Tris and carbonate buffers). Reactions at pH greater than 12 were carried out in 10% ethanol–water, since base-catalyzed decomposition of the acetonitrile solvent occurred during the extended period of rate measurement at high pH. Data obtained at pH 11 indicated

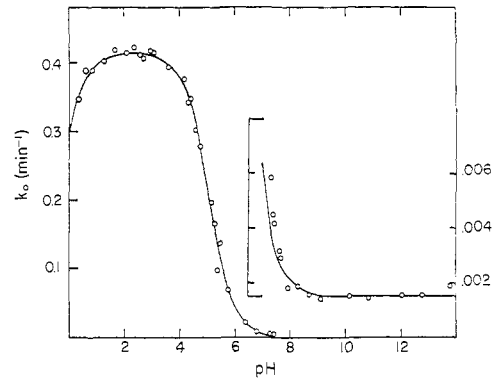


Figure 1. pH–rate profile for hydrolysis of iminolactone III at 30°: pH 0–7, left ordinate; pH 7–14, right ordinate. Solid curve is calculated from eq. 8, using constants of Table II.

(2) For convenience, the trivial term *iminolactone* will be used to designate substances of type I. More accurately, these compounds should be named as derivatives of 2-iminotetrahydrofuran.

(3) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960), and earlier studies cited therein.

(4) A. Patchornik, W. B. Lawson, E. Gross, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 5923 (1960).

(5) G. L. Schmir, L. A. Cohen, and B. Witkop, *ibid.*, **81**, 2228 (1959); E. J. Corey and L. F. Haefele, *ibid.*, **81**, 2225 (1959).

(6) M. Wilchek and A. Patchornik, *ibid.*, **84**, 4613 (1962).

(7) W. B. Lawson, E. Gross, C. M. Foltz, and B. Witkop, *ibid.*, **84**, 1715 (1962); E. Gross and B. Witkop, *J. Biol. Chem.*, **237**, 1856 (1962).

(8) For reviews of these reactions, and for applications to proteins, see B. Witkop, *Advan. Protein Chem.*, **16**, 221 (1961); L. A. Cohen and B. Witkop, *Angew. Chem.*, **73**, 253 (1961); B. Witkop and L. K. Ramachandran, *Metabolism*, **13**, 1016 (1964).

(9) (a) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959); (b) G. L. Schmir, *ibid.*, **87**, 2743 (1965), and references cited therein.

(10) (a) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Ber.*, **89**, 2060 (1956); (b) T. Mukaiyama and K. Sato, *Bull. Chem. Soc. Japan*, **36**, 99 (1963).

(11) H. Peter, M. Brugger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 577 (1963).

(12) The C=NR function of several iminolactones has been found to absorb at 5.87–5.91 μ; H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *J. Org. Chem.*, **28**, 1795 (1963), and ref. 11.

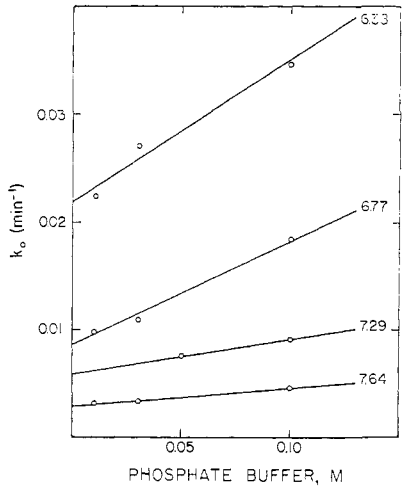
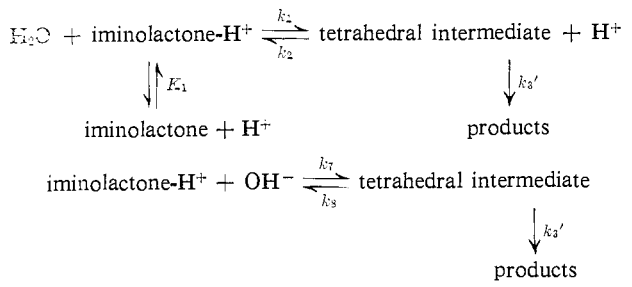


Figure 2. Effect of phosphate buffer on rate of iminolactone hydrolysis. Numbers indicate pH for each series of experiments.

that replacement of acetonitrile by ethanol did not affect sensibly the rate of hydrolysis.

Maximal reactivity is found in the pH region 1–4, where the iminolactone has a half-life of about 2 min. The rate of hydrolysis decreases progressively with increasing pH and becomes constant in the pH range 9–14, where the half-life of hydrolysis is 7.5 hr. The rate–pH profile of Figure 1 is analogous to those reported for the hydrolyses of 2-methylthiazoline,[9] 2-methyl-5,6-dihydro-1,3-thiazine,[13] Schiff bases,[14] and 2-methyloxazoline.[15] Consequently, a preliminary analysis of the kinetic data was made in terms of the mechanism which appears to provide a satisfactory description of imine hydrolysis.[9,13,14] Although certain useful conclusions could be drawn from this analysis, it will be shown in the sequel that the mechanism of Scheme I does not account for all the features of the

Scheme I



hydrolysis of the iminolactone III. According to Scheme I, hydrolysis at pH values below 7 proceeds *via* attack of water upon protonated iminolactone to yield an uncharged tetrahedral intermediate. With decreasing pH, a transition occurs from rate-limiting hydration to rate-limiting decomposition of the carbinolamine intermediate. At alkaline pH, the predominant event is reaction of protonated iminolactone with hydroxide ion. Assumption of a steady state in the intermediate leads to eq. 3 for the dependence of observed first-order rate constant for iminolactone disappearance (k_0) on pH.[16] The first term of the right-hand side of eq. 3 represents the contribution of the

$$k_0 = \frac{(k_1k_3'/k_2)[H]}{([H] + K_1)([H] + (k_3' + k_8)/k_2)} + \frac{(k_7k_3'/k_2)K_w}{([H] + K_1)([H] + (k_3' + k_8)/k_2)} \quad (3)$$

water reaction, while the second describes the process involving nucleophilic hydroxide ion attack. If it is assumed[13] that $k_8 \ll k_3'$, and since at alkaline pH $K_1 \gg [H]$, and $k_3'/k_2 \gg [H]$, the simplified eq. 4 is obtained.

$$k_0 = \frac{(k_1k_3'/k_2)[H]}{([H] + K_1)([H] + (k_3'/k_2))} + \frac{k_7K_w}{K_1} \quad (4)$$

The best values of the constants k_1, k_3'/k_2, and K_1 were found by fitting the observed rate constants (corrected for the contribution of the alkaline reaction) to the first term of the assumed rate eq. 4, by means of an IBM 7094 computer.[17] The resulting values were: $k_1 = 0.415$ min.$^{-1}$, $K_1 = 8.75 \times 10^{-6}$ M (p$K_1 = 5.06$), and $k_3'/k_2 = 2.5$ M. These constants, together with the value of 1.55×10^{-3} min.$^{-1}$ for the pH-independent rate constant (k_7K_w/K_1), were employed to calculate the curve shown in Figure 1. Agreement between observation and the theory expressed in Scheme I is seen to be good.

The hydrolysis of iminolactone III is subject to catalysis by buffer species. The effect of phosphate buffer at four different pH values is shown in Figure 2. Similar data describing catalysis by acetate and imidazole buffers are summarized in Table I.

Table I. General Base Catalysis of Iminolactone Hydrolysis[a]

Buffer	pK_2	pH	Intercept,[b] min.$^{-1}$	Slope,[b] M^{-1} min.$^{-1}$	k_1', M^{-1} min.$^{-1}$
Acetate[c]	4.76	4.31	0.34	0.20	
		4.38	0.35	0.24	
		4.55	0.30	0.36	1.1
		4.76	0.28	0.41	
		5.15	0.20	0.37	
		5.48	0.14	0.28	
Phosphate	6.77	6.38	0.0220	0.131	
		6.77	0.0084	0.100	8.9
		7.29	0.0058	0.034	
		7.64	0.0029	0.017	
Imidazole[d]	7.02	7.39	0.0045	0.013	4.1

[a] At 30° in 10% acetonitrile–water; $\mu = 0.5$. [b] Intercept and slope are those of plots of k_0 *vs.* B_0 as defined by eq. 5. [c] Total buffer concentration varied between 0.02 and 0.20 M. [d] Total buffer concentration varied between 0.01 and 0.20 M.

General base catalysis (in terms of protonated substrate) has been demonstrated for the hydrolysis of thiazolines,[18] Schiff bases,[14b,c] and imidates.[19] Assuming that the buffer effects on the hydrolysis of III represent general base catalysis of the hydration of protonated iminolactone, it may be shown (see Ap-

(13) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, 83, 4830 (1961).
(14) (a) E. H. Cordes and W. P. Jencks, *ibid.*, 84, 832 (1962); (b) E. H. Cordes and W. P. Jencks, *ibid.*, 85, 2843 (1963); (c) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, 86, 2413 (1964).
(15) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, 41, 1662 (1963).
(16) (a) An analogous expression is given in ref. 13 for the hydrolysis of 2-methyl-5,6-dihydro-1,3-thiazine; (b) K_w = ion product of water.
(17) We are grateful to Professor W. W. Cleland, of the University of Wisconsin, for providing us with the necessary computer program.
(18) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, 29, 3197 (1964).
(19) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 3505 (1962).

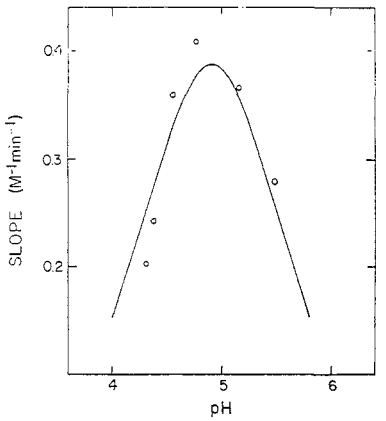


Figure 3. Effect of acetate buffer on rate of iminolactone hydrolysis. The slopes of plots analogous to those of Figure 2 are plotted against pH. Solid line is calculated from the expression slope = $(k_1'K_2[H])/([H] + K_1)([H] + K_2)$, with $pK_1 = 5.06$, $pK_2 = 4.77$, and $k_1' = 1.1\ M^{-1}$ min.$^{-1}$.

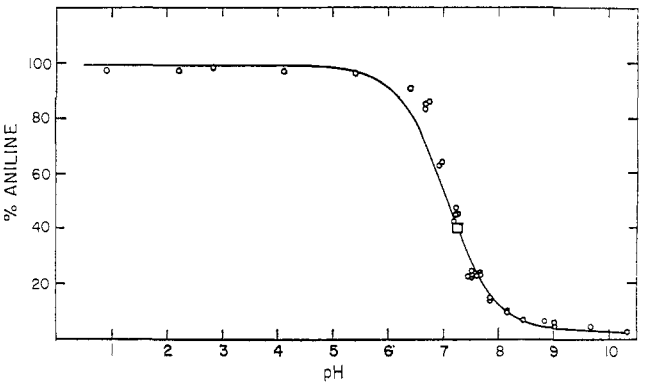


Figure 4. Effect of pH on the nature of the products of iminolactone hydrolysis. Solid line is calculated from eq. 9, with $K' = K_3k_9/k_8 = 8.5 \times 10^{-8}\ M$ ($pK' = 7.07$). The square symbol represents eight experimental points.

pendix, part A) that the dependence of k_0 on total buffer concentration (B_0) is given by eq. 5. (K_2 = acid dis-

$$k_0 = \left(\frac{k_1[H]}{[H] + K_1}\right) + B_0\left(\frac{k_1'K_2[H]}{([H] + K_1)([H] + K_2)}\right) \quad (5)$$

sociation constant of buffer; k_1' = second-order rate constant for reaction of basic species of buffer with protonated iminolactone.) Consequently, plots of k_0 *vs.* B_0 at fixed pH should be linear (Figure 2). The slopes of such plots should vary with pH as a bell-shaped curve, the maximum of which will be at pH = $(pK_1 + pK_2)/2$.

The rate measurements in phosphate buffer were carried out at pH values more alkaline than the calculated pH for maximum buffer effect (pH 5.9). As expected, therefore, the slopes of the lines in Figure 2 *increase* with decreasing pH. Determination of rates in acetate buffer could be made over a pH region wide enough to demonstrate the bell-shaped character of the buffer effect. The pH variation of the slopes of plots of k_0 *vs.* total buffer concentration at six pH values is shown in Figure 3. The solid line is calculated from the coefficient of B_0 in eq. 5, using $pK_1 = 5.06$, $pK_2 = 4.77$, and $k_1' = 1.1\ M^{-1}$ min.$^{-1}$. The agreement between observation and theory provides independent confirmation of the validity of the pK value of 5.06 assigned to the iminolactone on the basis of the pH–rate profile (Figure 1) and eq. 4. Average values of k_1' calculated from eq. 5 for all three buffers are listed in the last column of Table I. In accord with expectation for general acid–base catalysis, k_1' for imidazole is similar to that for phosphate. It will be noted that although k_1' for phosphate is eight times greater than k_1' for acetate, phosphate buffers appear generally less effective than acetate buffers in catalyzing iminolactone hydrolysis. This observation is simply the consequence of the fact that the product of the concentrations of protonated iminolactone and phosphate dianion is necessarily always small. The absence of base catalysis above pH 8 is in agreement with the proposal that the pH-independent reaction in alkaline medium represents reaction of hydroxide ion with protonated iminolactone, and not the kinetically equivalent reaction of water with iminolactone free base. A similar conclusion has been drawn[14b] for Schiff base hydrolysis.

The Nature of the Products. The yield of aniline produced upon hydrolysis of the iminolactone III is pH dependent. A modified Bratton–Marshall diazotization assay for aniline was performed, after 7–10 half-lives of reaction, on hydrolyses carried out in the pH range 1–11. The results of these determinations, expressed as per cent conversion of iminolactone to aniline, are shown in Figure 4. It is seen that, while aniline is the major reaction product at pH values below 6, it is formed in negligible amount above pH 8.5. These experiments, and others summarized below, suggest that hydrolysis of III in acid solution results in quantitative formation of aniline (and butyrolactone); in alkaline milieu, the predominant (and perhaps exclusive) product is *γ-hydroxybutyranilide.* These conclusions are supported by the following evidence.

(a) Ultraviolet spectra of reactions carried out below pH 5.5, measured at completion of reaction, were identical with those of aniline or anilinium ion. Spectra of reactions at pH 10.5 were identical with that of γ-hydroxybutyranilide.

(b) γ-Hydroxybutyranilide was isolated after hydrolysis of the iminolactone at pH 10.5.

(c) The quantitative formation of γ-butyrolactone after hydrolysis of the iminolactone in 0.15 *N* HCl was demonstrated by vapor phase chromatography.

(d) The transient presence of the anilide could be demonstrated kinetically when the hydrolysis of III was carried out in 0.56 *N* NaOH. The spectral changes at 237 mμ occurring during the hydrolytic process are shown in Figure 5. It was assumed that the absorbance increase reflected conversion of iminolactone to hydroxyanilide (rate constant k_a) while the absorbance decrease resulted from hydrolysis of the anilide (rate constant k_b). The constants k_a and k_b, evaluated from the data of Figure 5, were: $k_a = 1.9 \times 10^{-3}$ min.$^{-1}$ and $k_b = 7.6 \times 10^{-4}$ min.$^{-1}$. The theoretical curve of Figure 5 is the result of a calculation based on these values.

The rate of hydrolysis of γ-hydroxybutyranilide is linearly dependent upon hydroxide ion concentration and presumably occurs *via* intramolecular nucleophilic attack of the neighboring oxide anion.[20] The ob-

(20) *Cf.* T. C. Bruice and F.-H. Marquardt, *J. Am. Chem. Soc.*, 84, 365 (1962), who studied the alkaline hydrolysis of γ-hydroxybutyramide.

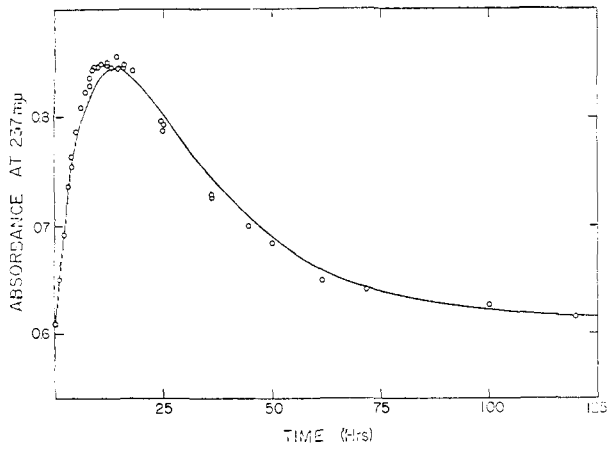


Figure 5. Absorbance changes during the hydrolysis of III in 0.56 *N* NaOH. Solid line is theoretical curve for consecutive first-order reactions, calculated as described in the Experimental Section.

served first-order rate constant for its hydrolysis in 0.56 *N* NaOH was found to be 7.7×10^{-4} min.$^{-1}$, in good agreement with the rate constant k_b for the disappearance of the intermediate. Determinations of the yield of aniline produced from iminolactone were not carried out above pH 11, since release of aniline from γ-hydroxybutyranilide begins to take place at a significant rate (relative to the rate of iminolactone hydrolysis) above pH 12.

(e) The formation of aniline at pH 1–11 is not the result of hydrolysis of intermediate γ-hydroxybutyranilide. When solutions of the anilide were maintained at pH 5–10.5 (30°) for periods of 48–72 hr., less than 0.5% hydrolysis to aniline was observed. Below pH 3, acid-catalyzed hydrolysis occurred at a measurable rate ($t_{1/2}$ at pH 0.9 was about 22 hr.). The lability of the anilide in acid solution is reminiscent of the behavior of γ-hydroxybutyramide[20,21] and probably is the result of intramolecular participation by the hydroxyl group. The much more rapid hydrolysis of the iminolactone in acid solution allowed aniline determination to be performed without interference by possible anilide hydrolysis.

The appearance of γ-hydroxybutyranilide is not the result of a secondary reaction between initially formed aniline and γ-butyrolactone. Exposure of aniline (10^{-3} *M*) to 10 equiv. of butyrolactone at pH 10.5 for 91 hr. led to no disappearance of aniline. The lack of reactivity of γ-butyrolactone towards aromatic amines has been reported.[22]

Discussion

Little information is recorded in the literature concerning the mechanism of hydrolysis of iminolactones. In a kinetic study of the hydrolysis of an N-unsubstituted iminolactone, Kuhn and Weiser[23] noted that the rate of hydrolysis was greatest at pH 1–3 and decreased both in more acid and more alkaline solution. The sole reaction product was the corresponding lactone.

(21) R. B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, 29, 158 (1964).
(22) Y. Knobler, E. Bonni, and T. Sheradsky, *ibid.*, 29, 1229 (1964).
(23) R. Kuhn and D. Weiser, *Angew. Chem.*, **69**, 371 (1957).

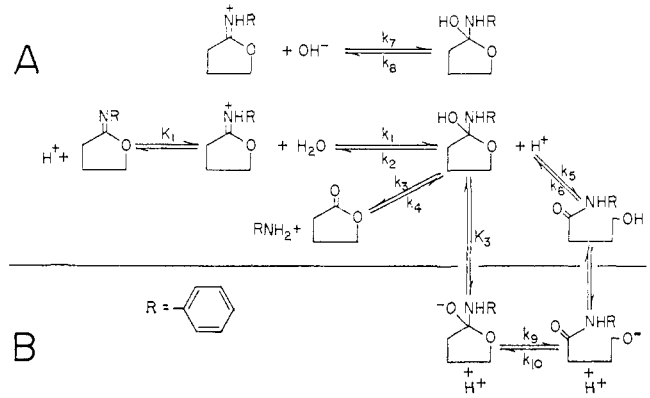
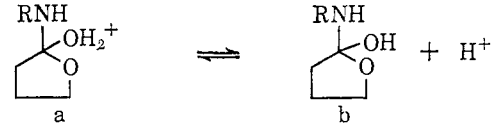


Figure 6. Mechanism of iminolactone hydrolysis.

The kinetic behavior of 2-phenyliminotetrahydrofuran (III) appears to be, in all particulars, similar to that found for other imines in several recent investigations. The pH–rate profile (Figure 1) exhibits the now familiar bell-shaped dependence of rate on pH in weakly acid solution and the constant rate of hydrolysis throughout the alkaline range. Hydrolysis is subject to general base catalysis (in terms of protonated imine) on the alkaline side of the pH optimum, but not in the pH-independent region. Other imines, the hydrolyses of which possess the above features, are thiazolines,[9] a dihydrothiazine,[13] 2-methyloxazoline,[15,24a] and aliphatic Schiff bases.[14b,c] Accordingly, it might be proposed that the common mechanism which encompasses the several aspects of the hydrolyses of these imines also describes the behavior of III. Some salient components of this mechanism (Figure 6A; Scheme I) are as follows. In acidic medium, reaction of water with protonated iminolactone leads to a *neutral tetrahedral intermediate*, whose partitioning to products is described by the rate constant ratio k_3/k_5. In alkaline solution, addition of hydroxide ion to protonated iminolactone yields the same neutral intermediate. This mechanism predicts,[13,18] therefore, that the product ratio will be *independent of pH*, both in the pH region of water addition and in the alkaline range.

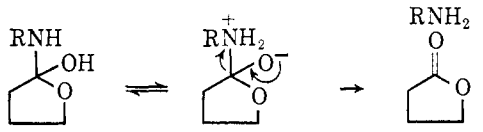
The data presented in Figure 4 are at variance with this conclusion. It is proposed, therefore, that, at least for the special case of III, the general mechanism be modified as shown in Figure 6. According to this

(24) (a) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, 83, 4835 (1961). (b) It has been pointed out by a referee that the moderate rate decrease at values of pH below 2 might reflect a change in the activity of water, rather than a transition in rate-determining step. Similar uncertainty exists in the interpretation of the acid inhibition of the hydrolysis of 2-methyloxazoline.[24c] In addition, although the hydrolysis of aliphatic Schiff bases[14b,c] proceeds *via* a neutral (zwitterionic) tetrahedral intermediate, the hydrolysis of the aromatic Schiff base *p*-chlorobenzylideneaniline[14a] involves the decomposition of a cationic intermediate at acid pH. If the rate decrease at pH <2 is not the result of a transition in rate-determining step and the hydrolysis of III in acid solution proceeds *via* the cationic intermediate a, the observed product variation can be explained on the assumption that a yields largely aniline

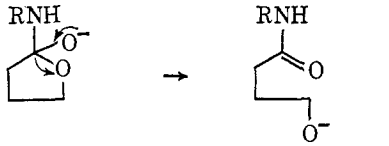


while b breaks down to γ-hydroxybutyranilide. Kinetic analysis indicates that this situation would be described by an expression identical with eq. 9, with K_3 now denoting the equilibrium constant for the process a ⇌ b. Available data do not rigorously rule out this alternate mechanism.

hypothesis, hydrolysis of the iminolactone proceeds *via* two kinetically significant tetrahedral intermediates. In acidic solution there occurs decomposition of the *neutral carbinolamine*[24b] to give largely aniline and butyrolactone. At higher pH, product formation occurs mainly as a result of breakdown of an *anionic carbinolamine*, yielding γ-hydroxybutyranilide. A possible explanation for the change in product structure as a result of ionization of the tetrahedral intermediate is shown in eq. 6 and 7. Breakdown of the neutral



(6)

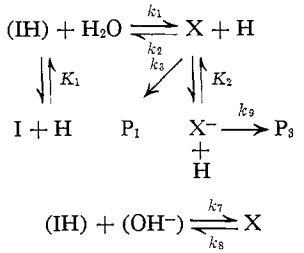


(7)

intermediate *via* its zwitterionic form would allow expulsion of the neutral amine molecule. The inability of the anionic intermediate to similarly facilitate departure of the amine leaving group, and the poor leaving tendency of amine anion, would result in C–O bond breakage, with expulsion of the more acidic oxide ion.

The following considerations indicate that the mechanism of Figure 6 appears to account quantitatively for the rate–pH profile and the product–pH dependence of the hydrolysis of III. For purposes of kinetic analysis in the pH range 0–11, the following assumptions seem reasonable: (a) the reactions involving product interconversion occur at negligible rates (steps k_4, k_6, and k_{10}); (b) $k_3 \gg k_5$, as shown by the predominance of aniline in the product of acid hydolysis. The kinetically important stages of the complete mechanism are outlined in Scheme II.[25]

Scheme II



Assumption of a steady state in the tetrahedral intermediates X and X^- leads to eq. 8 for dependence of k_0 on pH (see Appendix, part B). It is seen that eq. 8

$$k_0 = \frac{(k_1k_3/k_2)[H]}{([H] + K_1)([H] + (k_3/k_2))} + \frac{k_7K_w}{K_1} \qquad (8)$$

is essentially identical with eq. 4, the latter describing the dependence of k_0 on pH predicted by the incomplete mechanism of Scheme I. This result follows simply from the fact that it is assumed (Appendix, part B) that tetrahedral intermediate ionization is important only in the pH region where hydration of protonated iminolactone (and not carbinolamine decomposition) is rate limiting. Therefore, events such as the ionization of the intermediate and the consequent change in product composition are not reflected in the kinetics of disappearance of the iminolactone.

It is easily shown (Appendix, part C) that the fraction of aniline (% P_1) in the total product will depend upon pH according to eq. 9. This expression

$$\% P_1 = \frac{[H]}{[H] + (K_3k_9)/k_3} \times 100 \qquad (9)$$

states that the aniline yield will vary with pH as the titration curve of a hypothetical ionizing group of apparent dissociation constant $K' = K_3k_9/k_3$. The curve drawn in Figure 4 is calculated from eq. 9 with the assumptions that $(K_3k_9/k_3) = 8.5 \times 10^{-8}$ M ($pK' = 7.07$) and that the aniline yields at the extremes of pH are 99% (in acid) and 1% (in alkali). Clearly, the results of the present study do not allow evaluation of the dissociation constant K_3. The position of the inflection point of the curve in Figure 4 is simply a quantitative expression of the interaction of the equilibrium process described by K_3 with the rate processes denoted by the constants k_3 and k_9.

The rate and equilibrium constants of iminolactone hydrolysis evaluated in this study are summarized in Table II. The ratio of the rates of nucleophilic hydroxide attack to water attack on protonated iminolactone (k_7/k_1) is seen to be 3.3×10^6 M^{-1}, in the range of the values of 10^6 to 10^8 M^{-1} summarized elsewhere[9b] for several related imines.

Table II. Rate and Equilibrium Constants[a] for Iminolactone Hydrolysis[b]

K_1, M	8.75×10^{-6}	$pK_1 = 5.06$
k_1, min.$^{-1}$	0.415	
k_3/k_2, M	2.5	
k_7, M^{-1} min.$^{-1}$	1.4×10^6	
K_3k_9/k_3, M	8.5×10^{-8}	$pK' = 7.07$

[a] Constants are defined for processes shown in Scheme II. [b] At 30° in 10% acetonitrile–water, $\mu = 0.5$.

An alternative mechanism, which could account both for the observed rate–pH profile and the change in product with pH, merits consideration. Nucleophilic displacement by hydroxide ion on protonated iminolactone at position 5 of the tetrahydrofuran nucleus would obviously result in the formation of γ-hydroxybutyranilide. It can be shown that expressions analogous to eq. 8 and 9 would result from a mechanism including normal water addition at the imine function together with nucleophilic displacement by hydroxide ion at position 5. Such displacement reactions are well known in the chemistry of imidates[26] and oxazolines[27] and have even been described for iminolactones of type III.[10]

This alternative explanation may be rejected on the following grounds. (a) Consideration of the known pathways of reaction between nucleophilic reagents and ambident cations, thoroughly reviewed by Hünig,[27b] strongly suggests that the *addition* of hydroxide ion to

(25) I = iminolactone in free base form; (IH) = protonated iminolactone; X = neutral carbinolamine; (X^-) = anionic carbinolamine; P_1 = aniline + butyrolactone; P_2 = γ-hydroxybutyranilide.

(26) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(27) (a) *Cf.* E. M. Fry, *J. Org. Chem.*, **15**, 438, 802 (1950); (b) S. Hünig, *Angew. Chem. Intern. Ed. Engl.*, **3**, 548 (1964).

the immonium function would be kinetically favored over *displacement* by hydroxide ion on C-5. (b) The inflection point (pK') of the curve relating mole fraction of aniline to pH should occur at the pH where the rates of water addition and hydroxide ion displacement are equal, if the alternative mechanism is correct; the observed value of 7.07 for pK' is not in accord with a calculated value of 7.49. (c) Certain substances, *e.g.*, phosphate buffers, have been found to influence the nature of the hydrolysis products in a complex manner; this phenomenon (to be described fully in a future communication) is not easily explicable on the basis of the displacement mechanism. Clearly, the mechanistic ambiguity would be best resolved by experiments carried out in H_2O^{18} solvent.

The formation of amides by hydrolytic fission of imidates is not a general phenomenon. Under conditions of acid hydrolysis, acyclic imidates[26,28] and iminolactones[3] yield esters (lactones) and amines. The alkaline hydrolysis of N-unsubstituted imidates results in the isolation of nitriles.[19,28d] In the case of an iminolactone derived from N-methylvaline, there exists[11] suggestive evidence that hydrolysis in bicarbonate solution may have led to C–O bond fission and the formation of a γ-hydroxybutyramide derivative. It is well known[15,24a,29a] that oxazolines (cyclic N-substituted imidates) afford substituted amides on hydrolysis. The *initial* product of oxazoline ring fission is, however, an O-acyl amino alcohol.[15,24a] The eventual isolation of N-acyl amino alcohols is the consequence of the well-established intramolecular O → N acyl shift.[15,18,24a,29]

The postulation of more than one kinetically significant ionic state of the tetrahedral intermediate (with the consequent occurrence of alternate reaction paths) is found in a number of recent investigations, among which may be cited those of the hydrolysis of anilides,[30a-c] N-acetylsalicylamide,[30d] and *p*-chlorobenzylideneaniline,[14a] the hydroxylaminolysis of thiol esters,[31a] the aminolysis of imidates,[19] semicarbazone formation,[31b] and acyl migration in O-acetylethanolamine.[29b]

Experimental Section[32a]

2-Phenyliminotetrahydrofuran (III). A solution of 3.25% (w./w.) silver tetrafluoroborate[11,32b] (18 mmoles) in benzene–methylene chloride was added dropwise with continuous stirring to a solution of 3.16 g. (16 mmoles) of 4-chlorobutyranilide[33] in 250 ml. of anhydrous methylene chloride at −18°. The reaction mixture was kept at −18° for 1 hr. (magnetic stirring), at 0° for another hour, and at room temperature for an additional 1.5 hr. Excess silver tetrafluoroborate was destroyed by addition of 1 g. of triethylamine hydrochloride, and the silver chloride was removed by filtration. The filtrate was washed twice with 2 *N* Na_2CO_3, three times with saturated aqueous NaCl solution, and was dried over $MgSO_4$. The colorless solution was reduced to a yellow oil by evaporation *in vacuo*. Crystallization occurred on cooling to −20°. The crude product was recrystallized by solution in the minimum volume of anhydrous ether at room temperature, cooling to −20°, and seeding. After removal of the supernatant liquid with a pipet, the iminolactone was recrystallized four times from anhydrous ether, isolated by filtration at 4°, washed with cold petroleum ether (b.p. 30–60°), and dried *in vacuo* over P_2O_5 (0.62 g., 24%, m.p. 32–33°). An additional 0.77 g. of product was isolated after addition of petroleum ether to the combined mother liquors, total yield, 54%. *Anal.* Calcd. for $C_{10}H_{11}NO$ (161.20): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.15; H, 7.04; N, 8.70.

Spectral properties of the iminolactone are collected in Table III, together with the corresponding data for the isomeric 1-phenylpyrrolid-2-one.

Table III. Spectral Properties of Iminolactone and Related Compounds

Compd.	M.p., °C.	Ultraviolet[a] λ_{max}, mμ	ϵ_{max}	Infrared[b] (λ), μ	
III	32–33	243	6,900	5.88	C=N
1-Phenylpyrrolid-2-one[c]	66–67[d]	245	12,600	5.94	C=O
γ-Hydroxybutyranilide	78–79	242	15,000	5.96	C=O

[a] In ethanol. [b] In chloroform. [c] Prepared from IIb according to method of H. W. Heine, P. Love, and J. L. Bove, *J. Am. Chem. Soc.*, 77, 5420 (1955). [d] Lit.[3] m.p. 66–68°.

4-Hydroxybutyranilide was prepared in 55% yield by the method of Horii, *et al.*,[34] and had m.p. 78–79° (lit. m.p. 83–84°,[34] 74–75°.[22]). *Anal.* Calcd. for $C_{10}H_{13}NO_2$ (179.21): C, 67.02; H, 7.31; N, 7.82. Found: C, 67.30; H, 7.28; N, 7.77. Spectral data are shown in Table III.

Kinetic Measurements. Acetonitrile was purified by treatment with calcium hydride and distillation from P_2O_5, according to method D of Coetzee, *et al.*[35] Imidazole (Eastman Kodak Co.) was recrystallized from acetone–petroleum ether.

With the exception of rate measurements performed above pH 12, the medium used for the kinetic studies was 10% acetonitrile–water (v./v.), at ionic strength 0.50, adjusted with added KCl. Constant pH was maintained with HCl, chloroacetate, acetate, phosphate, imidazole, Tris, borate, and carbonate buffers in the appropriate ranges. At pH 2–4, the concentrations of chloroacetate or acetate buffers were 0.01–0.05 *M*. Buffer concentrations in the pH range 4–8 are indicated in Table I and Figure 2. Above pH 8, borate buffers were at 0.03 *M*, and Tris and carbonate varied

(28) (a) J. Stieglitz, *Am. Chem. J.*, **39**, 29 (1908); (b) I. H. Derby, *ibid.*, **39**, 437 (1908); (c) W. McCracken, *ibid.*, **39**, 586 (1908); (d) H. I. Schlesinger, *ibid.*, **39**, 719 (1908).

(29) (a) G. R. Porter, H. N. Rydon, and D. A. Schofield, *J. Chem. Soc.*, 2686 (1960); (b) B. Hansen, *Acta Chem. Scand.*, **17**, 1307 (1963).

(30) (a) S. S. Biechler and R. W. Taft, *J. Am. Chem. Soc.*, **79**, 4927 (1957); (b) M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4183 (1961); (c) P. M. Mader, *ibid.*, **87**, 3191 (1965); (d) M. T. Behme and E. H. Cordes, *J. Org. Chem.*, **29**, 1255 (1964).

(31) (a) T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86**, 4886 (1964); (b) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

(32) (a) All melting points are uncorrected. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ultraviolet spectra were determined by means of a Perkin-Elmer Model 350 recording spectrophotometer. Infrared spectra were recorded on a Beckman Model IR-5 spectrophotometer. (b) Silver tetrafluoroborate obtained from Ozark-Mahoning Co., Tulsa, Okla., also proved satisfactory for the preparation of III.

(33) P. Lipp and F. Caspers, *Ber.*, **58**, 1011 (1925).

(34) Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).

(35) J. F. Coetzee, G. P. Cunningham, D. K. McGuire, and G. R. Padmanabhan, *Anal. Chem.*, **34**, 1139 (1962).

between 0.01 and 0.2 M, with no effect of buffer concentration being observed for the latter two.

Above pH 12, pH was maintained with NaOH, and the solvent used was 10% ethanol–water, since acetonitrile appeared to decompose upon prolonged exposure to strongly alkaline solutions. Measurements of pH were made with the glass electrode, using either a Leeds and Northrup Model 7664 pH meter or a Radiometer TTTlc pH meter equipped with scale expander.

The rate of hydrolysis of the iminolactone (*ca.* 1–2 $\times 10^{-4}$ M) was determined spectrophotometrically by the decrease in absorbance at 245 mμ (below pH 7) or, at alkaline pH, the absorbance decrease at 270 mμ or increase at 240 mμ. Slow reactions were carried out in stoppered volumetric flasks or sealed ampoules immersed in a constant temperature bath at 30°. The changes in absorbance of aliquots were measured with a Beckman Model DU spectrophotometer. Fast reactions were carried out in a rectangular, 4-ml. Beckman cuvette inserted in a water-jacketed cuvette holder maintained at 30° by means of a circulating bath. Changes in absorbance were recorded at appropriate intervals. Alternatively, the rapid reaction was followed using a Beckman Model DU spectrophotometer converted to a linear direct reading instrument by a Gilford Model 220 optical density converter. Absorbance was recorded continuously by means of a Honeywell-Brown electronic recorder. The reaction mixture was kept at 30° with Beckman thermospacers connected to a circulating bath. Reaction was initiated by addition of 100 μl. of an acetonitrile solution of the iminolactone to the buffer solution, previously equilibrated at 30° in the cuvette holder. Mixing was accomplished with a stream of air bubbles, the cell was stoppered, and recording was begun immediately.

Final optical densities were obtained generally after 7–10 half-lives of reaction, and the observed first-order rate constants were calculated using the integrated form of the first-order rate equation. When the hydrolysis of the iminolactone was followed at pH 12–13, calculated (rather than observed) final optical densities were used for the evaluation of the rate constants, since the reaction product (γ-hydroxybutyranilide) was hydrolyzed slowly under these conditions.

The rate of hydrolysis of III in 0.56 N NaOH was measured at 237 mμ. The consecutive increase and decrease in absorbance were interpreted according to the equation that follows, and the rate constants k_a

$$\text{III} \xrightarrow{k_a} \text{hydroxybutyranilide} \xrightarrow{k_b} \text{aniline}$$

and k_b were evaluated by means of consecutive first-order reaction theory, as previously described.[36,37] The molar extinction coefficients at 237 mμ employed in the calculations were: iminolactone, 6200; γ-hydroxybutyranilide, 10,800; aniline, 6400. After evaluation of the two rate constants, the variation of absorbance at 237 mμ with time was calculated according to the theoretical expression,[36] and the computed curve is compared to the experimental data in Figure 5.

(36) G. L. Schmir and C. Zioudrou, *Biochemistry*, **2**, 1305 (1963).
(37) Equation 13 of ref. 36 should be corrected to read

$$\frac{D}{A_t} = (\epsilon_A - \epsilon_C)e^{-\tau} + \frac{(\epsilon_B - \epsilon_C)}{\kappa - 1}(e^{-\tau} - e^{-\kappa\tau}) + \epsilon_C$$

The definition of τ should be amended to read $\tau = k_1 t$.

The rate of hydrolysis of γ-hydroxybutyranilide in 0.56 N NaOH was determined spectrophotometrically by the decrease in absorbance at 237 mμ.

pK Determinations. pK_a values were determined for acetate, imidazole, and phosphate buffers by titration at 30° in 10% acetonitrile–water. Calculated ionic strength at the midpoint of the titration was 0.50. The titration data were analyzed by the method of Reed and Berkson[38] and the resulting pK_a values are listed in Table I.

Determination of Products. A. Aniline Assay. Reaction mixtures were analyzed for aniline after 7–10 half-lives of hydrolysis, by means of a modification of the Bratton–Marshall procedure.[39] Aliquots (0.5–2.0 ml., containing 1–10 μg. of aniline) were added to 3.5 ml. of 2 M sodium phosphate adjusted to pH 1.7 with HCl. Total volume was made up to 5.5 ml. with water (if necessary), and 0.5 ml. of 0.1% aqueous sodium nitrite was added. After 5 min., excess nitrite was destroyed by addition of 0.5 ml. of 0.5% aqueous ammonium sulfamate. Three minutes later, 0.5 ml. of 0.1% N-(1-naphthyl)ethylenediamine dihydrochloride was added; after 3 hr. of color development, absorbance at 546 mμ was measured. Standard curves were based on distilled aniline or on the more stable and more conveniently handled aniline hydrochloride.

For product analysis, hydrolytic reactions were carried out under conditions identical with those used in the kinetic measurements, with the exceptions that only imidazole and Tris buffers were employed at pH 6–8. Variation in the concentrations of imidazole and Tris buffers did not materially affect the fraction of iminolactone converted to aniline. In phosphate buffers, however, the nature of the reaction products was dependent on buffer concentration.

B. γ-Butyrolactone. After hydrolysis of 22.4 mg. of III in 2 ml. of 0.15 N HCl (10% acetonitrile), the presence of γ-butyrolactone was demonstrated by vapor phase chromatography of 3-μl. samples, using columns (72 × 1/8 in.) packed with 20% silicone gum rubber SE-30 on Anakrom ABS (90-100 mesh). Retention time was identical with that of authentic material and comparison of peak areas to standard samples indicated formation of butyrolactone in 96% yield.

C. Isolation of γ-Hydroxybutyranilide. A solution of 174 mg. (1.08 mmoles) of III in a mixture of 135 ml. of acetonitrile and 200 ml. of aqueous sodium borate buffer (0.03 M, pH 10.5) was kept at 30° for 3 days. After adjustment of pH to neutrality with 6 N HCl, the reaction mixture was reduced to 20 ml. by evaporation *in vacuo*. Five milliliters of 1.3 M Na_2CO_3 was added and the solution was saturated with NaCl. The suspension was thoroughly extracted with ethyl acetate, and the organic phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. Removal of solvent *in vacuo* yielded a residual oil, which was taken up into anhydrous ether. The ethereal solution was reduced in volume until crystallization began. The crystalline product (59 mg.) was collected by filtra-

(38) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams and Wilkins Co., Baltimore, Md., 1960, p. 149.
(39) (a) A. C. Bratton and E. K. Marshall, *J. Biol. Chem.*, **128**, 537 (1939); (b) L. Lukens and J. Flaks in "Methods in Enzymology," Vol. 6, S. P. Colowick and N. O. Kaplan, Ed., Academic Press Inc., New York, N. Y., 1963, p. 671.

tion and dried over P_2O_5. An additional 11.7 mg. was isolated from the mother liquor, by addition of petroleum ether, total yield 70.7 mg. (37%), m.p. 78–79° with no depression on admixture with authentic γ-hydroxybutyranilide. The infrared spectrum of the product in chloroform was identical with that of the anilide.

Appendix

A. The Effect of General Bases. Derivation of Eq. 5. In the presence of general bases (B), Scheme I is modified by the addition of eq. 10, where IH is protonated iminolactone and X is the neutral tetrahedral intermediate. The rate of disappearance of total

$$\mathrm{IH} + \mathrm{B} + \mathrm{H_2O} \underset{k_2'}{\overset{k_1'}{\rightleftharpoons}} \mathrm{X} + \mathrm{BH} \qquad (10)$$

$$\mathrm{X} \xrightarrow{k_3'} \text{products}$$

iminolactone (I_t) at pH <7 (where the reaction involving hydroxide ion may be neglected) is given by eq. 11.

$$\frac{-\mathrm{d}I_t}{\mathrm{d}t} = [\mathrm{IH}](k_1 + k_1'[\mathrm{B}]) - [\mathrm{X}](k_2[\mathrm{H}] + k_2'[\mathrm{BH}]) \qquad (11)$$

Assume that the intermediate maintains a steady state with respect to the reactants. Then

$$\frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}t} = [\mathrm{IH}](k_1 + k_1'[\mathrm{B}]) - (k_2[\mathrm{H}] + k_2'[\mathrm{BH}] + k_3')[\mathrm{X}] = 0$$

$$[\mathrm{X}] = \frac{[\mathrm{IH}](k_1 + k_1'[\mathrm{B}])}{k_2[\mathrm{H}] + k_2'[\mathrm{BH}] + k_3'} \qquad (12)$$

Let

$$-\frac{\mathrm{d}I_t}{\mathrm{d}t} = k_0 I_t$$

From eq. 11 and 12, and employing the relationship $I_t = [\mathrm{I}] + [\mathrm{IH}]$ and $[\mathrm{I}][\mathrm{H}]/[\mathrm{IH}] = K_1$

$$k_0 = \frac{((k_1 + k_1'[\mathrm{B}])k_3'/k_2)[\mathrm{H}]}{([\mathrm{H}] + K_1)([\mathrm{H}] + (k_2'[\mathrm{BH}] + k_3')/k_2)} \qquad (13)$$

Under conditions of rate-limiting hydration of protonated iminolactone (pH >4), $k_3'/k_2 \gg [\mathrm{H}]$ and at low buffer concentrations $k_3' \gg k_2'[\mathrm{BH}]$, so that

$$k_0 = \frac{(k_1 + k_1'[\mathrm{B}])[\mathrm{H}]}{[\mathrm{H}] + K_1} \qquad (14)$$

In terms of total buffer concentrations, B_0, and employing the expressions $[\mathrm{B}] + [\mathrm{BH}] = B_0$ and $[\mathrm{B}][\mathrm{H}]/[\mathrm{BH}] = K_2$

$$k_0 = \left(\frac{k_1[\mathrm{H}]}{[\mathrm{H}] + K_1}\right) + B_0\left(\frac{k_1'K_2[\mathrm{H}]}{([\mathrm{H}] + K_1)([\mathrm{H}] + K_2)}\right) \qquad (5)$$

B. Dependence of k_0 on pH. Derivation of Eq. 8. From the favored mechanism (Figure 6, Scheme II), the rate of disappearance of iminolactone (I_t) is given by

$$\frac{-\mathrm{d}I_t}{\mathrm{d}t} = [\mathrm{IH}](k_1 + k_7[\mathrm{OH}]) - [\mathrm{X}](k_2[\mathrm{H}] + k_8) \qquad (15)$$

Assume that the two forms of the tetrahedral intermediate, X and X^-, maintain steady states with respect to reactants. Then

$$\frac{\mathrm{d}([\mathrm{X}] + [\mathrm{X}^-])}{\mathrm{d}t} = [\mathrm{IH}](k_1 + k_7[\mathrm{OH}]) - [\mathrm{X}](k_2[\mathrm{H}] + k_3 + k_8) - k_9[\mathrm{X}^-] = 0 \qquad (16)$$

Since $[\mathrm{X}^-][\mathrm{H}]/[\mathrm{X}] = K_3$

$$[\mathrm{X}] = \frac{[\mathrm{IH}](k_1 + k_7[\mathrm{OH}])}{\left(k_2[\mathrm{H}] + k_3 + k_8 + \frac{K_3k_9}{[\mathrm{H}]}\right)} \qquad (17)$$

Let

$$\frac{-\mathrm{d}I_t}{\mathrm{d}t} = k_0 I_t$$

From eq. 15 and 17, and employing the relationships $I_t = [\mathrm{I}] + [\mathrm{IH}]$ and $[\mathrm{I}][\mathrm{H}]/[\mathrm{IH}] = K_1$

$$k_0 = \frac{[\mathrm{H}](k_1 + k_7[\mathrm{OH}])\left(k_3 + \frac{K_3k_9}{[\mathrm{H}]}\right)\Big/k_2}{([\mathrm{H}] + K_1)\left([\mathrm{H}] + \left(k_3 + k_8 + \frac{K_3k_9}{[\mathrm{H}]}\right)\Big/k_2\right)} \qquad (18)$$

Interpretation of eq. 18 is simplified by the following assumptions, which permit transformation of eq. 18 to eq. 8.

$$k_3 \gg k_8 \qquad (a)$$

$$k_3 \gg (K_3k_9)/[\mathrm{H}], \text{ at least below pH 3} \qquad (b)$$

above pH 3, $\left(k_3 + \frac{K_3k_9}{[\mathrm{H}]}\right)\Big/k_2 \gg$ [H] and, above pH 6, $K_1 \gg [\mathrm{H}]$ (c)

Then

$$k_0 = \frac{(k_1k_3/k_2)[\mathrm{H}]}{([\mathrm{H}] + K_1)([\mathrm{H}] + (k_3/k_2))} + \frac{k_7K_w}{K_1} \qquad (8)$$

C. Dependence of Product Composition on pH. Derivation of Eq. 9. The rate of formation of aniline ($\mathrm{P_1}$) is given by

$$\frac{\mathrm{d}[\mathrm{P_1}]}{\mathrm{d}t} = k_3[\mathrm{X}] = k_3''I_t \qquad (19)$$

From eq. 17 and 19, and the expressions relating [IH] and I_t

$$k_3'' = \frac{[\mathrm{H}]k_3/(k_1 + k_7[\mathrm{OH}])/k_2}{([\mathrm{H}] + K_1)\left([\mathrm{H}] + \left(k_3 + k_8 + \frac{K_3k_9}{[\mathrm{H}]}\right)\Big/k_2\right)} \qquad (20)$$

The rate of formation of γ-hydroxybutyranilide ($\mathrm{P_2}$) is given by

$$\frac{\mathrm{d}[\mathrm{P_2}]}{\mathrm{d}t} = k_9[\mathrm{X}^-] = k_9''I_t \qquad (21)$$

From eq. 17 and 21, and the expression $[\mathrm{X}^-][\mathrm{H}]/[\mathrm{X}] = K_3$

$$k_9'' = \frac{K_3k_9(k_1 + k_7[\mathrm{OH}])/k_2}{([\mathrm{H}] + K_1)\left([\mathrm{H}] + \left(k_3 + k_8 + \frac{K_3k_9}{[\mathrm{H}]}\right)\Big/k_2\right)} \qquad (22)$$

It follows from eq. 20 and 22 that the fraction of aniline (% $\mathrm{P_1}$) in the total product is given by

$$\%\,\mathrm{P_1} = \frac{k_3''}{k_3'' + k_9''} \times 100 = \frac{[\mathrm{H}]}{[\mathrm{H}] + (K_3k_9)/k_3} \times 100 \qquad (9)$$

Acknowledgment. We are grateful to the National Institutes of Health for financial support (Grant No. AM-04288). During this investigation, B. A. C. was supported by a Training Grant (2G-53) of the U. S. Public Health Service (1963–1964) and was a Predoctoral Fellow of the National Institute of General Medical Sciences, U. S. Public Health Service (1964–1965).

The Reactions of 2- and 4-Picoline N-Oxide with Phenylacetic Anhydride[1]

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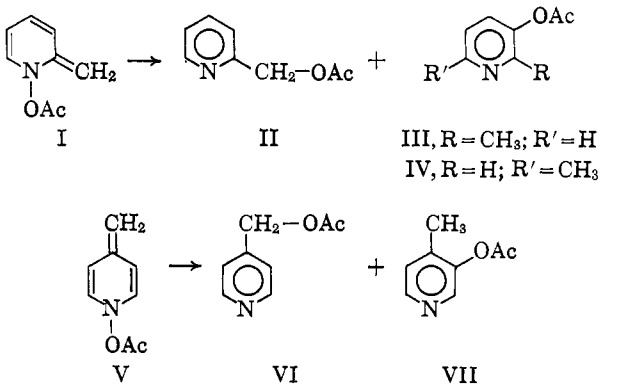
The reactions of 2- and 4-picoline N-oxide with phenylacetic anhydride yield the oxidation–reduction products, benzaldehyde, carbon dioxide, picolines, and small quantities of diphenylmaleic anhydride (XII), in addition to rearrangement products. The latter consist predominantly of 2-pyridinemethanol phenylacetate (X) and 2-phenylethylpyridine (XI), in a ratio of about 1.5:1 in the case of 2-picoline N-oxide, and of 4-pyridinemethanol phenylacetate (XIV) and 4-phenylethylpyridine (XV), in a ratio of about 0.06:1 in the case of 4-picoline N-oxide. The product composition is unchanged when the reactions are performed in the presence of the radical trap m-dinitrobenzene. The rearrangement but not the oxidation products are thought to arise via the anhydrobase intermediates XIX and XX. The ester products in this case (and in the corresponding acetic anhydride reaction with 2-picoline N-oxide) are thought to be formed by nonradical paths while the phenylethylpyridines are probably formed by geminate recombination of benzyl and picolyl radicals or ions which are produced by fragmentation of the anhydrobases XIX and XX.

Introduction

The reaction of 2-picoline N-oxide (VIII) with acetic anhydride yields mainly 2-pyridinemethanol acetate[2] (II) and smaller quantities of 3-acetoxy-2-picoline (III) and 5-acetoxy-2-picoline (IV).[3–5] Under similar conditions 4-picoline N-oxide (XIII) yields a binary ester mixture which is richer in 4-pyridinemethanol acetate (VI)[2] than in 3-acetoxy-4-picoline (VII).[8] The mechanism in both cases is generally believed to involve acetylation of the N-oxide function followed by the removal of a proton from the ring methyl group of the resulting N-acetoxypicolinium ion to yield an anhydrobase intermediate (I or V).[9] (The postulation of the intermediate formation of these anhydrobases (I and V) is also reasonable in view of the great ease of these reactions compared to that of acetic anhydride with pyridine N-oxide, a reaction in which an anhydrobase is precluded. In unpublished work, we have shown that 4-picoline N-oxide (XIII) reacts with acetic anhydride in refluxing benzene and that the 2-isomer (VIII) reacts at room temperature in pyridine solution. On the other hand, pyridine N-oxide reacts with this anhydride very slowly at temperatures below 100°.[10])



Recent tracer studies utilizing O^{18}-labeled acetic anhydride[11] indicate that both in the presence and

(1) (a) This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research Grant No. AF-AFOSR 344-63; (b) presented in part at the XIXth International Congress of Pure and Applied Chemistry, London, July 1963; (c) taken from the Ph.D. thesis of J. H. Fager, University of Pittsburgh, April 1965.

(2) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954); O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

(3) S. Okuda, *Pharm. Bull. Japan*, **3**, 316 (1955). Okuda's report that these three esters are formed in the ratio of 3:1:1 has frequently been ignored in the literature, the product being treated as consisting only of 2-pyridinemethanol acetate (II). We have confirmed by gas chromatography that the ester mixture obtained in this reaction contains three components in the ratio 3:1:1 and that the major component is 2-pyridinemethanol acetate (II). In very recent work, Ford and Swan,[4] utilizing v.p.c., n.m.r., and mass spectrometry, have further confirmed the nature of this reaction mixture.

(4) P. W. Ford and J. M. Swan, *Australian J. Chem.*, **18**, 867 (1965).

(5) An earlier report,[6] that the reaction of 2-picoline N-oxide with acetic anhydride produces, after hydrolysis, a 5:2 mixture of 2-pyridinemethanol and 6-methyl-2-pyridone, is probably in error. The latter compound was identified by its melting point (163–165°), its conversion to an acetate ester, and the hydrolysis of this ester back to the compound, m.p. 163–165°. In view of the fact that this pyridone was not isolated by several other groups,[2–4] there appears to be no reason to believe that this substance is not either 2-methyl-3-pyridinol, m.p. 163–165°,[8] 169–170°,[7] or 2-methyl-5-pyridinol, m.p. 167°,[8] both of which were later identified by Okuda[3] as products of this reaction.

(6) G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, 1, 347 (1953).

(7) N. Clauson-Kaas, N. Elming, and Z. Tyle, *Acta Chem. Scand.*, 9, 1 (1955).

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(9) For a recent discussion of the substantial evidence for these steps in the reaction of 2-picoline N-oxide, see V. J. Traynelis and P. L. Pacini, *ibid.*, **86**, 4917 (1964).

(10) T. Cohen, Ph.D. Thesis, University of Southern California, 1955, p. 65; J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Am. Chem. Soc.*, **85**, 958 (1963).

(11) (a) S. Oae, T. Kitao, and Y. Kitaoka, *ibid.*, **84**, 3359 (1962); (b) S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron*, **20**, 2685 (1964).