[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Ortho Esters, Imidic Esters and Amidines. III. The Acid-catalyzed Hydrolysis of N,N'-Diphenylformamidine in Aqueous Dioxane Solutions[1]

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The hydrolysis of N,N'-diphenylformamidine in aqueous dioxane buffer solutions has been studied dilatometrically and found to exhibit general acid catalysis. The catalytic coefficients of hydronium ion and acetic acid were determined; the latter was found to vary inversely with the buffer ratio, (HOAc)/(OAc$^-$). This result is explained by the assumption that only the free base, N,N'-diphenylformamidine, and not its conjugate acid undergoes hydrolysis. This is confirmed by the following: (a) in strong (hydrochloric) acid solutions, the hydrolysis rate is independent of acid concentration; (b) in very weak acid (*p*-nitrophenol) solutions, the weak acid catalytic coefficient is constant at different buffer ratios; (c) the K_b of N,N'-diphenylformamidine in 30.7% dioxane solution is determined and used in calculating the true catalytic coefficient for acetic acid which is independent of buffer ratio. A general rate equation is formulated for the hydrolysis of N,N'-diphenylformamidine in 30.7% aqueous dioxane acetate buffer solutions:

$$k = \frac{1}{1 + 3.0([\mathrm{HOAc}]/[\mathrm{OAc}^-])}(6 \times 10^{-5} + 4.8 \times 10^{-4}[\mathrm{HOAc}]/[\mathrm{OAc}^-] + 0.013[\mathrm{HOAc}])$$

With increasing dioxane concentrations, the hydrolysis rate passes through a maximum at *ca.* 35% dioxane. This is explained as a result of two conflicting factors. A mechanism compatible with experimental data is proposed for the acid-catalyzed hydrolysis of N,N'-diphenylformamidine.

Tobias,[3] in 1882, reported that when N,N'-diphenylformamidine was refluxed in aqueous alcohol it was partially hydrolyzed to give formanilide and aniline (equation 1).

$$\mathrm{C_6H_5NHCH{=}NC_6H_5 + H_2O = C_6H_5NH_2 + C_6H_5NHCHO} \quad (1)$$

Hydrolysis of N,N'-diphenylformamidine is briefly mentioned in two other early publications,[4,5] but no quantitative data concerning the rate of the reaction appear in the literature.

The purpose of this investigation was to study the kinetics of hydrolysis of N,N'-diphenylformamidine in aqueous dioxane buffer solutions. Aqueous dioxane was chosen as the reaction medium because of the low solubility of diphenylformamidine[6] in water. The effects of dioxane concentration, buffer ratio and ionic strength upon the rate of the reaction have been investigated, and explanations for most of these effects are offered.

Experimental

The dioxane used in the buffer solutions was purified by the procedure of Fieser.[7] Reagent grades of acetic acid, sodium hydroxide, sodium chloride, hydrochloric acid and picric acid were used. The *p*-nitrophenol was recrystallized from dilute hydrochloric acid and its purity checked by determining its melting point. All solutions were made up using distilled water. Diphenylformamidine was prepared from ethyl orthoformate and aniline by the method of Claisen[8] and recrystallized from mixtures of benzene and petroleum ether. The pure product melted at 139–140°.

Stock acetic acid–sodium acetate buffers were made up by adding glacial acetic acid to known volumes of standard sodium hydroxide solution and diluting to the calibration mark of the volumetric flask with water. The stock buffers were titrated with standard sodium hydroxide solution to the phenolphthalein end-point to determine the concentration of acetic acid.

Acetic acid–sodium acetate buffer solutions were prepared by pipetting the desired amounts of stock buffer, dioxane and sodium chloride solution into a volumetric flask and filling to the mark with distilled water. In making up the *p*-nitrophenol—*p*-nitrophenolate buffers, weighed samples of *p*-nitrophenol were washed into the volumetric flask, known volumes of standard sodium hydroxide solution, dioxane and sodium chloride solution were added, and the flask filled to the mark with distilled water.

A run was started by allowing the solution to reach thermal equilibrium with the thermostat, then adding the sample of diphenylformamidine (0.1 to 0.4 g. per 100 ml. of solution) dissolved in a known volume of dioxane. Dioxane concentrations in the reaction mixtures were determined by measuring the refractive indices of blank solutions containing only the measured volume of dioxane and distilled water; the weight per cent. dioxane in the solutions was calculated from their refractive indices, using the data of Stallard and Amis.[9] All runs were made at 35.0° in a thermostat which maintained the temperature constant to within ±0.002°. Whenever the solubility of diphenylformamidine in the buffer solutions was sufficiently great, the reaction was followed dilatometrically. The dilatometer consisted of a glass bulb of approximately 105-ml. capacity, to which was attached a filling tube equipped with a stopcock and a long capillary tube of about 0.6-mm. bore. A linear scale was attached to the capillary tube for determining the meniscus height. It was necessary to expel dissolved air from the reaction solution before starting a run to prevent the formation of gas bubbles in the dilatometer bulb. This was accomplished by refluxing the solution for a few seconds shortly before starting the run. After almost filling the bulb of the dilatometer, a small amount of mercury was introduced by means of the stopcock into the sidearm between the bulb and the stopcock, to prevent possible leakage of the solution past the stopcock.

The hydrolysis of diphenylformamidine is accompanied by a significant volume increase which is proportional to the amount of diphenylformamidine hydrolyzed. A blank run and one made on formanilide gave no measurable volume increase. It seems unlikely that the formanilide formed by the initial hydrolysis reaction would hydrolyze at an appreciable rate in acetic acid buffer solutions, since Karve and Kelkar[10] found that formanilide hydrolyzes at a relatively slow rate ($k = 1.2 \times 10^{-4}$/sec.) in 50% ethanol which is 0.25 *N* in sulfuric acid, at 35°. Calculation of the first-order reaction rate constant, k, was usually made from the slope of the straight lines obtained by plotting log $(r_\infty - r_t)$ *vs.* t, where r_∞ is the final dilatometer reading and r_t is the reading at time t, in accordance with the equation

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(1) (a) For the previous article in this series see R. M. Roberts, R. H. DeWolfe and J. H. Ross, THIS JOURNAL, **73**, 2277 (1951); (b) most of the work reported in this article was taken from the M.A. thesis of Robert H. DeWolfe, 1951.

(2) Dow Chemical Company Fellow, 1950–1951.

(3) G. Tobias, *Ber.*, **15**, 2443 (1882).

(4) R. Walther, *J. prakt. Chem.*, [2] **53**, 472 (1896).

(5) F. B. Dains, *Ber.*, **35**, 2496 (1902).

(6) For the sake of simplicity, the prefix letters "N,N'-" are dropped throughout most of the discussion.

(7) L. F. Fieser, "Experiments in Organic Chemistry," Part II, D. C. Heath and Company, New York, N. Y., 1941, p. 368.

(8) L. Claisen, *Ann.*, **287**, 366 (1895).

(9) R. D. Stallard and E. S. Amis, THIS JOURNAL, **74**, 1781 (1952).

(10) D. D. Karve and B. W. Kelkar, *Proc. Indian Acad. Sci.*, **24A**, 254 (1946).

$$k = -2.303 \frac{\mathrm{d} \log (r_\infty - r_t)}{\mathrm{d}t}$$

or by plotting the data according to the method of Guggenheim,[11] in which

$$k = -2.303 \frac{\mathrm{d} \log (r_2 - r_1)}{\mathrm{d}t}$$

where r_1 and r_2 are dilatometer readings at times t_1 and t_2, with the interval $t_2 - t_1$ being constant throughout a run. The second method has the advantage of not attaching undue weight to the final reading. In several cases where duplicate hydrolysis runs were made, the reaction rate constants agreed within better than 3%.

The solubility of diphenylformamidine in some of the solutions was too small to permit the use of the dilatometric method. In these cases the reaction was followed by analyzing aliquots of the reaction mixtures by quantitative precipitation of unchanged diphenylformamidine as its picrate salt. The aliquots were added to about twice their volume of cold saturated aqueous picric acid solution, the mixtures were cooled for 30 minutes in an ice-bath, and the precipitates were collected in sintered glass filter crucibles, washed with cold water on the filter, and dried. The dried precipitates were weighed, and the rate constants were calculated from the slopes of the straight lines obtained by plotting log *w* *vs.* *t*, where *w* is the weight of picrate precipitated at time *t* (the volume of all aliquots being the same), according to the equation

$$k = -2.303\ (\mathrm{d} \log w/\mathrm{d}t)$$

Results and Discussion

Preliminary experiments showed that the hydrolysis of diphenylformamidine is quite sensitive to acid catalysis and is relatively insensitive to catalysis by bases (OH^- and OAc^-). The reaction is general acid catalyzed; when a series of hydrolysis runs were performed in acetic acid–sodium acetate buffers in which the buffer ratio $(HOAc)/(OAc^-)$, ionic strength and dioxane concentration were held constant and the acetic acid concentration was varied, the first-order rate constants increased linearly with increasing acetic acid concentration. Figure 1 shows the results obtained for several different dioxane concentrations; Table I gives the experimental data and results for this series of runs.

The rate of hydrolysis appears not to be measurably affected by the ionic strength of the medium. Two runs made in 50% dioxane ($(HOAc)/(OAc^-) = 0.606$, $(OAc^-) = 0.109$, $T = 35.0°$) which differed only by the ionic strength in one being twice that of the other (0.218 and 0.109) gave identical rate constants (2.89×10^{-4}/sec.).

The reaction rate was found to exhibit a maximum at about 35% dioxane when the dioxane concentration of the reaction medium was varied while the buffer ratio, buffer concentration and temperature were maintained constant (Fig. 2). It can be seen from Fig. 1 that approximately the same maximum is exhibited at each of three buffer concentrations.

In buffer solutions, the specific rate of a general acid-catalyzed reaction which is not appreciably catalyzed by bases may be represented by an expression of the form

$$k = k_0 + k_H(H_3O^+) + k_{HA}(HA)$$

where k_0 is the rate of the spontaneous, or solvent-catalyzed reaction, and k_H and k_{HA} are the catalytic coefficients of hydronium ion and the weak acid,

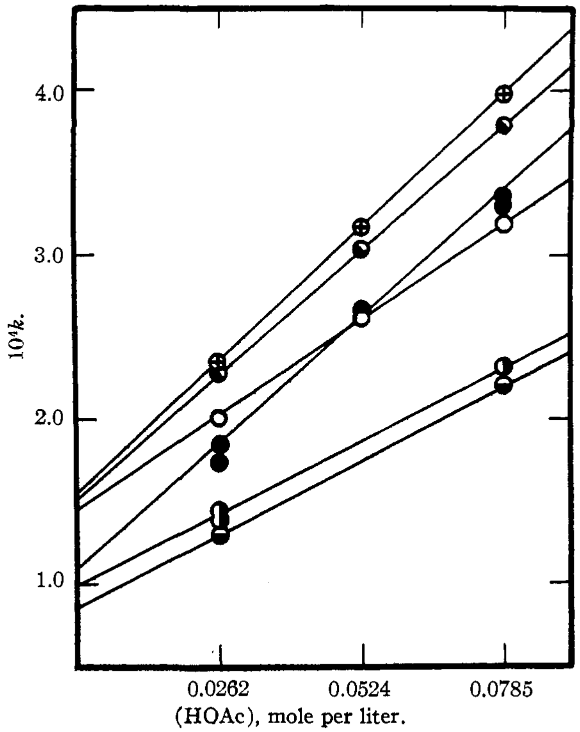

Fig. 1.—Variation of catalytic coefficients with dioxane concentration: ⊖, 58.0% dioxane; ●, 48.9% dioxane; ⊕, 39.8% dioxane; ◔, 30.7% dioxane; ○, 21.4% dioxane; ◐, 12.5% dioxane; temperature, 35°; ionic strength, 0.0870.

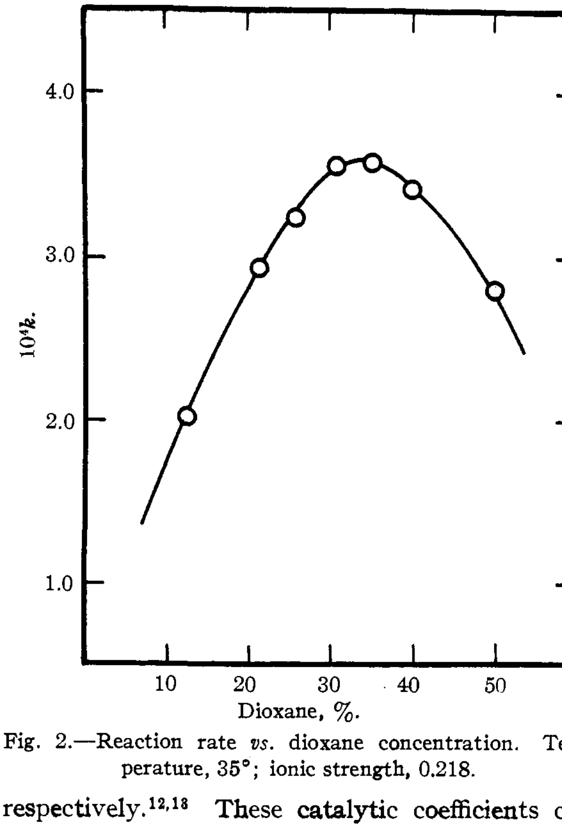

Fig. 2.—Reaction rate *vs.* dioxane concentration. Temperature, 35°; ionic strength, 0.218.

respectively.[12,13] These catalytic coefficients can

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[11] E. A. Guggenheim, *Phil. Mag.*, [7] 2, 538 (1926).

[12] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 219.

[13] J. N. Brönsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 25, 59 (1929).

be evaluated from kinetic data by plotting rate constants for the reaction against concentration of the weak acid in the buffer, as in Fig. 1. A straight line is obtained for each series of runs performed in solutions of constant dioxane concentration and constant buffer ratio. k_{HA} is equal to the slope of this line. The apparent catalytic coefficient of acetic acid exhibits a maximum at around 30% dioxane. k_H cannot be accurately evaluated unless k_0 and the ionization constant of the weak acid are known. Ionization constants of acetic acid in aqueous dioxane solutions may be calculated from the data of Harned and Fallon.[14] k_0 could not be evaluated for the hydrolysis reaction occurring in acetic acid–sodium acetate buffer solutions; however, the rate of hydrolysis of diphenylformamidine in very dilute sodium hydroxide solutions was found to be 6 × 10^{-5}/sec. in 30.7% dioxane and 3 × 10^{-5}/sec. in 40% dioxane, and k_0 should be only a fraction of these rates, for reasons to be discussed later. Since k_0 is usually considerably smaller than $k_H(H_3O^+)$, it may be neglected in making rough calculations. k_H may be calculated from the relation

$$k_H = (k' - k_0)/RK_i$$

where k' is the rate constant obtained by extrapolating the k *vs.* (HA) plot to (HA) = 0, R is (HOAc)/(OAc⁻), and K_i is the ionization constant of acetic acid at the dioxane concentration concerned. If k_0 is neglected, k_H can be calculated from known values of k', R and K_i. k_H is found to increase rapidly as the dioxane concentration increases. Values of k_{HA}, k_H and K_i in different concentrations of dioxane are given in Table I.

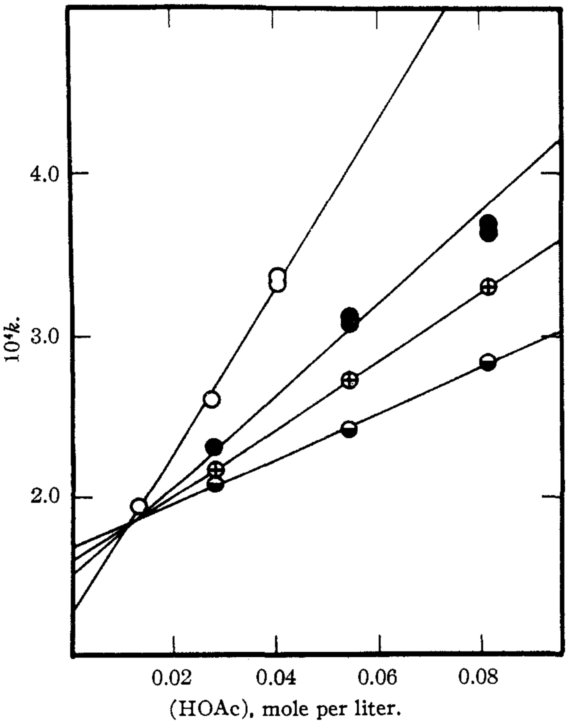

Fig. 3.—Variation of catalytic coefficients with buffer ratio in 30.7% dioxane; buffer ratios: ○, 0.533; ●, 1.605; ⊕, 1.60; ◒, 3.19.

TABLE I

THE IONIZATION CONSTANT OF ACETIC ACID AND CATALYTIC COEFFICIENTS FOR THE HYDROLYSIS OF N,N'-DIPHENYLFORMAMIDINE IN DIFFERENT CONCENTRATIONS OF DIOXANE AT 35°

Wt. % dioxane	K_i	10^3k_{HA}	k_H
12.5	8.29 × 10^{-6}	1.68	13
21.4	4.41 × 10^{-6}	2.23	35
30.7	2.04 × 10^{-6}	2.89	80
39.8	7.99 × 10^{-7}	3.11	200
48.9	2.49 × 10^{-7}	2.78	600
58.0	5.74 × 10^{-8}	1.76	2000

When a series of runs was made in 30.7% dioxane in buffers of several different buffer ratios, it was found that the apparent catalytic coefficient of acetic acid varies inversely with the buffer ratio of the solution. The same effect, although much less pronounced, was observed in 40% dioxane. The data for 30.7% dioxane appear in Fig. 3, and the results for both 30.7 and 40% dioxane are given in Table II. The observed variation of k_{HA} with R was unexpected, since catalytic coefficients are usually constant for a given reaction in a given medium. The explanation of this anomaly became apparent when it was found that diphenylformamidine is hydrolyzed only slowly in solutions which are strongly acidic, even though the reaction is highly sensitive to acid catalysis. Since diphenylformamidine is a weak base, these facts indicate that the free base, B, undergoes acid-catalyzed hydrolysis and that its conjugate acid, BH⁺, does not do so at an appreciable rate.[15]

TABLE II

VARIATION OF k_{HA} WITH BUFFER RATIO FOR THE HYDROLYSIS OF N,N'-DIPHENYLFORMAMIDINE IN AQUEOUS DIOXANE–ACETIC ACID BUFFER SOLUTIONS AT 35°

Ionic strength = 0.077

Wt. % dioxane	(HOAc)/(OAc⁻)	k_{HA}
30.7	0.533	0.0050
30.7	1.065	.0028
30.7	1.60	.0021
30.7	3.19	.0013
39.8	0.615	.0043
39.8	1.156	.0030
39.8	1.683	.0028

In acidic solution the following equilibrium should exist between diphenylformamidine and its conjugate acid

$$B + H^+ = BH^+$$

$$K_b = (BH^+)/(B)(H^+) \qquad (1)$$

When some diphenylformamidine is added to an acetic acid–sodium acetate buffer, in which

$$(H^+) = K_i \times (HOAc)/(OAc^-) \qquad (2)$$

it follows from (1) that

$$(B) = (BH^+)/K_b(H^+)$$
$$= (BH^+)(OAc^-)/K_bK_i(HOAc) \qquad (3)$$

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[14] H. S. Harned and L. D. Fallon, THIS JOURNAL, 61, 2374 (1939).

[15] A similar case of dependence of reaction rate upon pH is the acid-catalyzed reaction of semicarbazide with carbonyl compounds, investigated by J. B. Conant and P. D. Bartlett, THIS JOURNAL, 54, 2881 (1932).

where (B) represents the actual concentration of diphenylformamidine present in the solution. At any given time, however, the total amount of diphenylformamidine remaining unhydrolyzed is (B) + (BH^+). As B is hydrolyzed, BH^+ dissociates at a rate such that

$$(\mathrm{B})/(\mathrm{BH^+}) = (\mathrm{OAc^-})/K_bK_i(\mathrm{HOAc}) = \text{a constant}$$

Because part of the diphenylformamidine in the solution is present as diphenylformamidinium ion, which is not hydrolyzed, the observed rate of hydrolysis, *k*, will be only a fraction of what the rate would be if all of the diphenylformamidine were present as the free base; that is

$$k = \frac{(\mathrm{B}) + (\mathrm{BH^+})}{(\mathrm{B})} \times k_t \qquad (4)$$

where k_t is the true first-order rate constant of the hydrolysis reaction. Neglecting catalysis by bases, the following relation should be valid.

$$k_t = k_0' + k_H'(\mathrm{H^+}) + k_{HA}'(\mathrm{HOAc}) \qquad (5)$$

where k_0', k_H' and k_{HA}' are the true values of the catalytic constants, as distinguished from the unprimed observed values. From equations (4) and (5)

$$k = \frac{\mathrm{B}}{(\mathrm{B}) + (\mathrm{BH^+})}\,[k_0' + k_H'(\mathrm{H^+}) + k_{HA}'(\mathrm{HOAc})]$$

From equation (3), it can be shown that

$$\frac{(\mathrm{B})}{(\mathrm{B}) + (\mathrm{BH^+})} = \frac{1}{1 + K_bK_iR}$$

Therefore

$$k = \frac{1}{1 + K_bK_iR}\,[k_0' + k_H'\,(\mathrm{H^+}) + k_{HA}'(\mathrm{HOAc})] \qquad (6)$$

The component of the rate constant due to acetic acid catalysis alone is

$$k_{HOAc} = k_{HA}'[\mathrm{HOAc}]/(1 + K_bK_iR) \qquad (7)$$

Inspection of this equation shows that as the buffer ratio increases, the observed catalytic coefficient of acetic acid decreases. This is in excellent qualitative agreement with the experimental results, if it is assumed that the product K_bK_iR has a large enough value to affect appreciably the value of the denominator of equation (7), *i.e.*, that an appreciable fraction of the diphenylformamidine is present as diphenylformamidinium ion in acetic acid buffer solutions. This assumption is supported by the observation that in 21.4 and 30.7% dioxane solutions diphenylformamidine is much more soluble in acetic acid buffers than in alkaline solutions or *p*-nitrophenol buffers.

In dilute solutions of a strong acid such as hydrochloric acid, substitution of (H^+) for RK_i and the obvious simplifications reduce equation (6) to

$$k = k_H'/K_b \qquad (8)$$

This follows since K_b for a weak base has a large positive value, and $1 + K_b(H^+) \cong K_b(\mathrm{H^+})$. This relation predicts that the rate of hydrolysis of diphenylformamidine in dilute hydrochloric acid solutions should be practically independent of the acid concentration, all other factors being constant. This was found to be the case. The rate constant in 0.21 *N* hydrochloric acid was 1.64×10^{-4}/sec. and that in 0.084 *N* hydrochloric acid was 1.66×10^{-4}/sec. (30.7% dioxane solutions).

K_b can be calculated from equation (8) if k_H is known. It was not possible to determine k_H from the data obtained for 30.7% dioxane–acetic acid buffers, since k_H varied with buffer ratio, and differed by an unknown factor from k_H'. However, it should be possible to carry out hydrolysis runs in buffers of an acid which is sufficiently weak for practically all of the diphenylformamidine to be present as the free base, *i.e.*, for which $K_bK_i \ll 1$. Under these conditions, $k_H \cong k_H$, and k_H could be evaluated as described by Brönsted and Wynne-Jones.[13]

p-Nitrophenol was found to be a sufficiently weak acid for these determinations. Hydrolysis runs were made in *p*-nitrophenol buffers of three different buffer ratios, three runs at different *p*-nitrophenol concentrations being made for each buffer ratio, the ionic strength and dioxane concentration being maintained constant. The data and results for this series of runs appear in Table III. When the rate constants for this series of runs were plotted against *p*-nitrophenol concentration, three approximately parallel straight lines were obtained, as predicted by theoretical considerations. Values of *k'* (the rate constant at zero *p*-nitrophenol concentration) were determined by extrapolation of these lines to zero *p*-nitrophenol concentration. The value of the rate constant for the hydrolysis of diphenylformamidine in very slightly alkaline 30.7% dioxane was found to be 6.0×10^{-5}/sec., and is assumed to be equal to *k'* at $R = 0$. k_H was then calculated from the ionization constant of *p*-nitrophenol and the slope of the line obtained by plotting the four values of *k'*, determined as described above, against the buffer ratio of the *p*-nitrophenol buffers, according to equation (9)

$$k_H' = \frac{1}{K_i} \times \frac{\Delta k'}{\Delta R} = \frac{1}{K_i} \times 4.0 \times 10^{-6} \qquad (9)$$

The slope of the *k'* *vs.* *R* plot could not be determined as precisely as was hoped, since the values of *k'* from the *k* *vs.* (p-$NO_2C_6H_4OH$) plot differed by only a little more than the order of magnitude of the average deviation of the experimentally determined reaction rate constants. This is true because the hydronium ion concentration of the *p*-nitrophenol buffers is so low that the values of *k'* are only slightly different for buffer ratios varying between 2.6 and 7.0. Before equation (9) could be solved for k_H' it was necessary to determine K_i, the ionization constant of *p*-nitrophenol in 30.7% dioxane. This was done by comparing the rate of hydrolysis of ethyl orthoformate in an acetic acid buffer of known hydrogen ion concentration with its rate of hydrolysis in a *p*-nitrophenol buffer of known buffer ratio, the dioxane concentration and ionic strength being the same for both buffers. Since the hydrolysis of ethyl orthoformate is a specific acid-catalyzed reaction,[13] its rate of hydrolysis in a buffer solution is

$$k = k_HRK_i \qquad (10)$$

For a 30.7% dioxane–acetic acid buffer, $K_i = 2.04 \times 10^{-6}$; when $R = 0.137$, *k* was found to be 1.51×10^{-3}/sec. Substituting these values into equation (10) gives $k_H = 5.4 \times 10^3$ for the hydrolysis of ethyl orthoformate in 30.7% dioxane. When a run was carried out in a 30.7% dioxane–*p*-nitrophenol buffer in which $R = 1.13$, k was found to be 1.08×10^{-4}/sec. Using these two values and $k_{\text{H}} = 5.4 \times 10^{3}$, equation (10) was solved for K_{i}, the ionization constant of *p*-nitrophenol. This gave $K_{\text{i}} = 1.8 \times 10^{-8}$. Substitution of K_{i} into equation (9) gave $k'_{\text{H}} = 230$, where k'_{H} is the true catalytic coefficient of hydronium ion for the hydrolysis of diphenylformamidine in 30.7% dioxane.

TABLE III

DATA AND REACTION RATE CONSTANTS FOR HYDROLYSIS OF N,N'-DIPHENYLFORMAMIDINE IN 30.7% DIOXANE–*p*-NITROPHENOL BUFFERS AT 35.0°

Ionic strength = 0.036

(p-$NO_2C_6H_4OH$)	(p-$NO_2C_6H_4OH$)/-(p-$NO_2C_6H_4O^-$)	10^4k
0.092	7.02	2.37
.061	7.02	1.87
.031	7.02	1.36
.092	4.67	2.25
.061	4.67	1.79
.031	4.67	1.28
.092	2.58	2.22
.061	2.58	1.75
.031	2.58	1.32

Substitution of the known values of k and k'_{H} into equation (8) gives $K_{\text{b}} = 1.4 \times 10^{6}$ for diphenylformamidine in 30.7% dioxane. Using this value of K_{b} it was possible to check the validity of equations (6) and (7). The observed catalytic coefficients of acetic acid in 30.7% dioxane are equal to the actual coefficient multiplied by the fraction of diphenylformamidine which is present as the free base (see equation (7)). Since k_{HA}, K_{b}, K_{i} and R were known, it was possible to calculate values for k_{HA}' for each buffer ratio. The values thus obtained were fairly constant and independent of the buffer ratio, as was predicted. The average value obtained for k_{HA}' was 0.013. Using this value of k_{HA}' and previously determined constants, it was possible to formulate a general equation for the hydrolysis of diphenylformamidine in 30.7% dioxane–acetic acid buffers. Referring to equation (6), it is seen that K_{b}, K_{i}, k_0', k'_{H} and k_{HA}' are constants, and R and (HOAc) are experimental variables. Substitution of known values of the constants into equation (6) gives

$$k = \frac{1}{1 + 3.0R}\,[6 \times 10^{-5} + 4.8 \times 10^{-4}\,R + 0.013(\text{HOAc})]$$

Values of R and (HOAc) for all runs made in 30.7% dioxane–acetic acid buffers were substituted into this equation, and k, the rate constant, was calculated for each run. The observed and calculated values of k agree well, considering the numerous possible sources of error (see Table IV).

The maximum exhibited by the reaction rate constant at about 35% dioxane in acetic acid buffers can be explained qualitatively by considering the effect of dioxane concentration upon K_{i} of acetic acid and K_{b} of diphenylformamidine. The ionization constant of a carboxylic acid falls off rapidly with increasing dioxane concentration in aqueous dioxane solutions,[14] due to the decrease in the dielectric constant of the solvent. However, the acidic dissociation constant, K_{a}, of the conjugate acid of a nitrogen base usually increases slightly with increasing dioxane concentration. This is probably due to the fact that dissociation of the conjugate acid of an amine does not involve separation of charge, but only the transfer of a proton between the base and the solvent. For example, James and Knox[16] found that as dioxane concentration increases from 0 to 80%, K_{i} for carboxylic acids decreases by about four powers of ten, while K_{a} for aniline and other aromatic primary amines increases by about one power of ten. Since $K_{\text{b}} = 1/K_{\text{a}}$, in equation (6) the term $K_{\text{b}}K_{\text{i}}R = (K_{\text{i}}/K_{\text{a}})R$, where K_{i} is the ionization constant of acetic acid, and K_{a} is the dissociation constant of diphenylformamidinium ion. It is evident that if K_{i} diminishes and K_{a} increases with increasing dioxane concentration, the term $K_{\text{b}}K_{\text{i}}R$ of equation (6) will decrease sharply in value as the dioxane concentration is increased. Referring to equation (6), it is seen that this variation of K_{i} and K_{a} means that as the dioxane concentration increases, the fraction of diphenylformamidine present as the free base approaches unity, and as the dioxane concentration decreases the fraction of diphenylformamidine present as the conjugate acid increases. These considerations are in qualitative agreement with the experimental observation that the variation of the apparent catalytic coefficient, k_{HA}, with buffer ratio is much more pronounced in 30.7% dioxane than in 40% dioxane (Table II). The maximum shown by the plot of rate constant *vs.* % dioxane is then explainable in terms of the effects of two conflicting factors upon the reaction rate. In low concentrations of dioxane, (H^+) and k_{HA} are larger than in high concentrations of dioxane, and these facts tend to increase the rate of the reaction. However, a much smaller fraction of the diphenylformamidine is present in the basic (hydrolyzable) form in low dioxane concentrations than in high dioxane concentrations. These two opposing factors cause the rate constant to pass through a maximum at about 35% dioxane in acetic acid buffers.

TABLE IV

OBSERVED AND CALCULATED RATE CONSTANTS FOR THE HYDROLYSIS OF N,N'-DIPHENYLFORMAMIDINE IN 30.7% DIOXANE–ACETIC ACID BUFFER SOLUTIONS

$k_{\text{obsd.}}$	$k_{\text{calcd.}}$	$k_{\text{obsd.}}$	$k_{\text{calcd.}}$
2.28	2.2	2.33	2.2
3.36	3.2	3.30	3.2
3.32	3.2	2.73	2.7
2.61	2.5	2.18	2.1
1.94	1.9	2.84	2.5
3.63	3.8	2.43	2.2
3.69	3.8	2.09	1.9
3.08	3.0	3.04	3.1
3.11	3.0	3.79	3.9

The kinetic experiments described above shed some light on the mechanism of the hydrolysis reaction. It appears certain that the free base and not its conjugate acid, undergoes hydrolysis. The absence of salt effects in this reaction makes it seem probable that a complex of an ion and an un-

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(16) J. C. James and J. G. Knox, *Trans. Faraday Soc.*, **46**, 254 (1950).

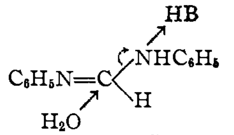
charged molecule is involved in the rate determining step (reference 12, page 128). Diphenylformamidine is known to form a monohydrochloride salt.[17] Two monobasic conjugate acids of diphenylformamidine are possible.

$$C_6H_5\overset{+}{N}H{=}CHNHC_6H_5 \qquad C_6H_5N{=}CH\overset{+}{N}H_2C_6H_5$$
$$\text{I} \qquad\qquad\qquad \text{II}$$

Of these two, the one in which the proton is attached to the imino nitrogen atom (I) would be stabilized by resonance to a much greater extent than the other, and probably is the unreactive conjugate acid. The greater stability of I resides in the fact that its resonance hybrid possesses two identical contributing structures

$$C_6H_5\overset{+}{N}H{=}CHNHC_6H_5 \longleftrightarrow C_6H_5NHCH{=}\overset{+}{N}HC_6H_5$$

The acid-catalyzed hydrolysis reaction probably involves attachment of a proton to the amino nitrogen atom of diphenylformamidine to form the conjugate acid II, which reacts with water to form the products. It seems quite likely[18] that the attack of a water molecule may be concerted with the attachment of the proton, the rate-determining step involving III in the transition state



III

where HB is H_3O^+ or HOAc.[19]

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[17] R. M. Roberts, THIS JOURNAL, **72**, 3608 (1950).

[18] See C. G. Swain, *ibid.*, **72**, 4582 (1950), for a suggestion regarding the mechanism of the closely related hydrolysis of ortho esters.

[19] The referee suggested that the experimental observations could be accounted for in an equally satisfactory manner by a second mechanism involving general base-catalyzed hydrolysis of the conjugate acid of diphenylformamidine. This alternate mechanism would explain the observed variation of k_{HA} with buffer ratio in acetic acid buffers, and also the constant rate of hydrolysis in dilute solutions of hydrochloric acid. However, the authors feel that their proposed mechanism is more probable than the base-catalyzed mechanism for the following reason: when the rate constants obtained in *p*-nitrophenol buffers (see Table III) are plotted against *p*-nitrophenol concentration, three separate, parallel straight lines are obtained, one for each buffer ratio. This result is expected if the reaction is general acid-catalyzed hydrolysis of the free base, but cannot be explained on the basis of general base-catalyzed hydrolysis of the conjugate acid of diphenylformamidine. Theoretical considerations indicate that in buffers in which practically all of the substrate is present as the free base, a single straight line should be obtained when k is plotted against [HA], if the reaction involved is general base-catalyzed hydrolysis of the conjugate acid of the substrate.

AUSTIN 12, TEXAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Cleavage of Heterocycles with Raney Nickel and with Lithium

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Dibenzofuran has been found to be susceptible to cleavage by lithium in dioxane and in ether and dibenzothiophene undergoes a similar cleavage in dioxane. The cleavage of dibenzofuran in dioxane yields only *o*-hydroxybiphenyl after carbonation and hydrolysis while 3,4-benzocoumarin was obtained when the reaction was carried out in ether. The cleavage of dibenzothiophene in dioxane yielded only *o*-mercaptobiphenyl and biphenyl after carbonation and hydrolysis.

The development of methods for the proof of structure of derivatives of various heterocycles has long been of interest in connection with general studies of heterocyclic compounds which have been carried out in this Laboratory. The ideal method of a simple, direct, and one-step reaction has seldom been achieved. The reports by Blicke and Sheets[1] on the successful desulfurization of thianaphthene and several of its derivatives and of dibenzothiophene over Raney nickel presented what appeared to be an approach to the ideal reaction.

A brief investigation of the application of Raney nickel desulfurization to the proof of structure of dibenzothiophene and of its derivatives was carried out. The results were rather disappointing. With 2-bromodibenzothiophene only biphenyl was isolated, indicating that debromination occurred along with the desulfurization. No identified product was obtained when an attempt was made to remove the sulfur from dibenzothiophene-5-monoxide and from dibenzothiophene-5-dioxide. Some difficulty was encountered in attempts to repeat the cleavage of dibenzothiophene with Raney nickel,[1] the activity of the Raney nickel was indicated to be a critical factor in the success of the desulfurization.

Earlier work in this Laboratory[2] showed that when dibenzofuran was treated with lithium in dioxane or ether good yields of *o*-hydroxybiphenyl were obtained. This cleavage reaction was of interest not only from the structure-proof view, but also in connection with the reactions of metals with heterocycles in general since the treatment of dibenzofuran with sodium–potassium alloy yields 4-dibenzofurylpotassium[3] while treatment of dibenzofuran[4] with sodium in ethanol and of dibenzothiophene[5] with sodium in liquid ammonia leads to reduction of the benzenoid ring.

It was found possible to carry out the cleavage of dibenzofuran with lithium in dioxane using an atmosphere of either dry air or nitrogen and terminating the reaction by hydrolysis or by carbonation. A possible mode of reaction would involve the cleavage of an oxygen–carbon bond to form an oxygen–lithium bond and a carbon–lithium bond.

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[1] F. F. Blicke and D. G. Sheets, THIS JOURNAL, **70**, 3768 (1948); *ibid.*, **71**, 4010 (1949).

[2] C. W. Bradley, unpublished studies.

[3] H. Gilman and R. V. Young, THIS JOURNAL, **56**, 1415 (1934).

[4] H. Gilman, E. W. Smith and L. C. Cheney, *ibid.*, **57**, 2095 (1935).

[5] H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).