Hydrolysis of 1-Benzylimino-1,3-dihydroisobenzofuran. Implications for the Mechanism of Lactonization of 2-Hydroxymethylbenzamides

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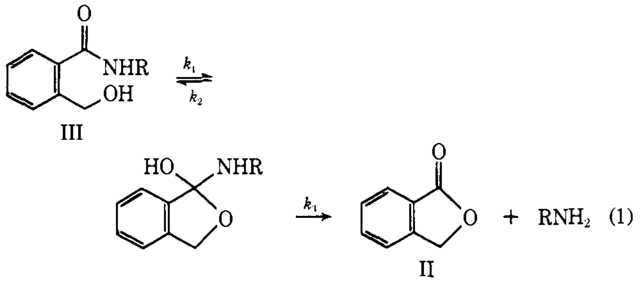
Received July 5, 1972

Abstract: The hydrolysis of the iminolactone I has been studied at 30° in the pH range 3–9. The effects of pH and of buffers on the nature of the hydrolysis products are analogous to those observed earlier with imidate esters and have been explained in terms of a mechanism including tetrahedral addition intermediates. The properties of these intermediates appear to be inconsistent with a recently proposed mechanism for the lactonization of 2-hydroxymethylbenzamides. The influence of bicarbonate buffers on the rate of lactonization of *N*-benzyl-2-hydroxymethylbenzamide has been investigated and found to be more complex than previously reported.

A recent kinetic study of the lactonization of 2-hydroxymethylbenzamides in aqueous solution led to the proposal of the mechanism shown (in abbreviated form) in eq 1.[2] It was suggested that there occurs a change in rate-determining step at about pH 8, with formation of an intermediate (step k_1) being rate-limiting at more alkaline pH. At pH <8, the solvent and buffer catalyzed conversion of the intermediate to products (step k_3) was stated to be rate-limiting. Put another way, at pH >8, $k_3 \gg k_2$, while the reverse inequality holds at pH <8, with the intermediate present at low, steady-state concentration.



Our interest in this reaction stems from the fact that the results of an earlier study of the lactonization of 4-hydroxybutyranilide, taken conjointly with those of the hydrolysis of the iminolactone 2-phenyliminotetrahydrofuran, were interpreted in precisely the opposite sense.[3-5] From the knowledge of the influence of pH on the nature of the products of hydrolysis of the iminolactone, it was concluded that lactonization of 4-hydroxybutyranilide involved rate-limiting formation of a tetrahedral addition intermediate at pH <7, with transition to rate-determining breakdown of the intermediate at higher pH. If this mechanism is correct, and general, the aminolysis of esters (which is the microscopic reverse of the alcoholysis of amides) should proceed with rate-determining formation of intermediate at pH >7, and this was proposed to be the case in the reaction of methyl formate with aliphatic amines.[6]

It is possible, though we considered it unlikely, that the rate-limiting steps at high and low pH in the lactonization of 2-hydroxymethylbenzamides might be different from what would be expected on the basis of the earlier studies.[3-6] To obtain additional information on the mechanism of these reactions, we chose to employ the approach used previously,[3-5] that is, to generate the intermediate of eq 1 by hydration of the iminolactone I (see Scheme I) and to examine its initial hydrolysis products as a function of pH. If the mechanism proposed by Belke, Su, and Shafer[2] is valid, then, at pH <8, where $k_2 > k_3$ (eq 1), the product of the hydrolysis of I should be the hydroxymethyl amide III, while the predominant products at pH >8 should be phthalide and benzylamine.

Results

Iminolactone Hydrolysis. The pH–rate profile (Figure 1) for the hydrolysis of the iminolactone I at 30° (3% ethanol–water, μ = 0.49) exhibits pH-independent regions at acid and alkaline pH. Rate constants were measured at low concentrations of buffers and are not corrected for possible buffer effects, which are expected to be small. Increasing the concentration of borate buffer from 0.02 to 0.04 *M* (pH 8.15) did not alter the rate of hydrolysis of I.

The shape of the pH–rate profile for the hydrolysis of I is characteristic of imines and imidate esters of relatively high basicity.[7-10] In agreement with previous formulations,[9-12] it is proposed that the rate-determining step in the hydrolysis of I consists of the attack of water or hydroxide ion on the protonated iminolactone to yield unstable intermediates which rapidly decompose to products (Scheme I). The solid line (Figure 1) is based on eq 2,[9,13] with k_1 =

$$k_{\text{obsd}} = \frac{[\text{H}^+](k_1 + k_7[\text{OH}^-])}{[\text{H}^+] + K_1} \tag{2}$$

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(1) On leave from the Faculty of Engineering Science, Osaka University.

(2) C. J. Belke, S. C. K. Su, and J. A. Shafer, *J. Amer. Chem. Soc.*, **93**, 4552 (1971).

(3) B. A. Cunningham and G. L. Schmir, *ibid.*, **89**, 917 (1967).

(4) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965).

(5) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

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

(7) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961).

(8) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).

(9) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **90**, 4413 (1968).

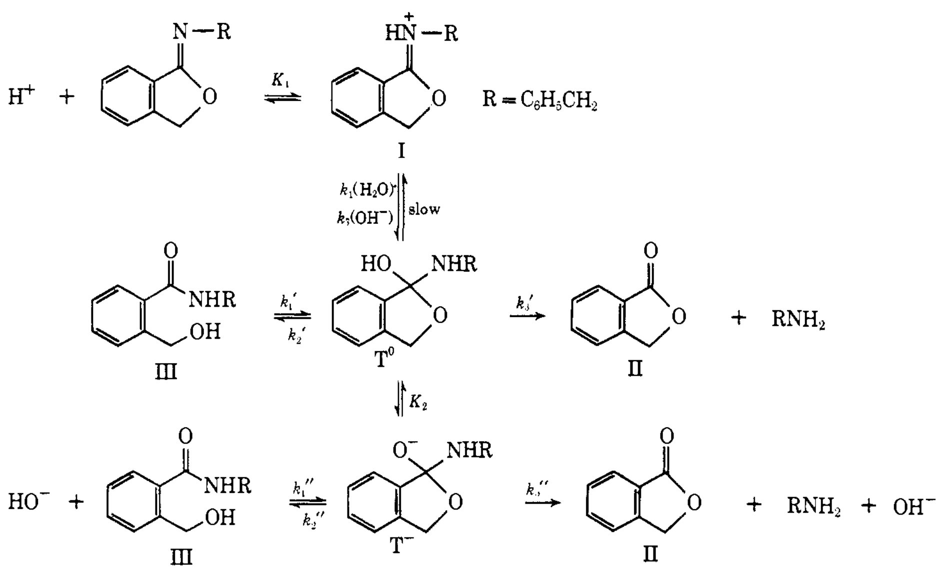
(10) T. C. Pletcher, S. Koehler, and E. H. Cordes, *ibid.*, **90**, 7072 (1968).

(11) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(12) Reference 4 and earlier studies cited therein.

(13) Equation 2 is based on the assumption of a steady state in the carbinolamine intermediates, and is a special case of the general expression derived earlier.[4] pK_w is taken as 13.83.

Scheme I



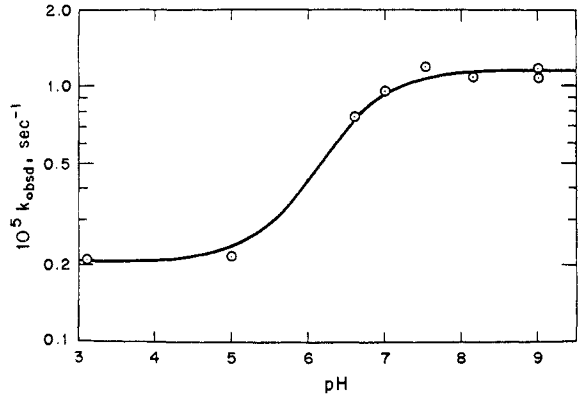


Figure 1. pH-rate profile for hydrolysis of iminolactone I in 3% ethanol-water, 30°. The solid line is calculated from eq 2, using the constants given in the text.

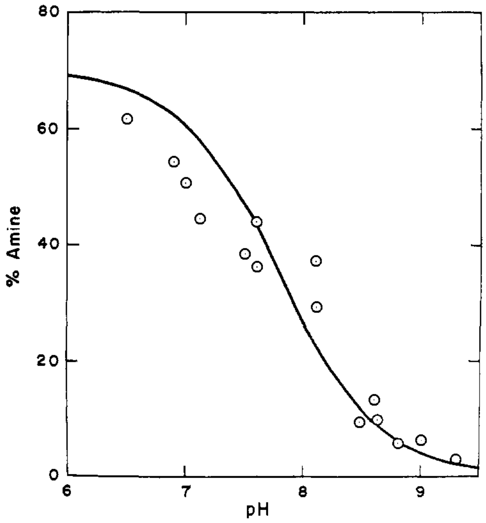


Figure 2. Effect of pH on the yield of benzylamine produced on hydrolysis of iminolactone I. The solid line is the calculated titration curve for a monovalent acid of pK = 7.8. Borate buffer: pH 6.5–7.1, 0.1 M; pH 7.5–7.8, 0.05 M; pH 8–9.3, 0.02 M.

2.05×10^{-6} sec^{-1}, k_7 = 248 M^{-1} sec^{-1}, and pK_1 = 6.50. The latter value is in reasonable accord with that of 6.63, determined by spectrophotometric titration of I. The ratio k_7/k_1, which describes the relative rates of attack of hydroxide ion and water on the protonated substrate, is relatively high[9] (1.2×10^8 M^{-1}), thus accounting for the observation that the pH-independent rate at alkaline pH is greater than that at low pH. In weakly acidic solution, the iminolactone I ($t_{1/2}$ 94 hr) is one of the most stable imidate esters for which kinetic data have been published, and is at least 25 times less reactive than ethyl benzimidate.[14]

The products of the hydrolysis of I vary with pH (Figure 2). The iminolactone is cleaved mainly to benzylamine (and phthalide) at pH <7, while the major product in more alkaline solution is the hydroxymethyl amide III. The yield of amine follows approximately a sigmoid dependence on pH in the range 6–9, and seems to approach a limiting value of about 70%. At lower pH, using acetate buffers (pH 5–6), yields of 100 ± 1% are obtained. As with other imidate esters,[4,6,9,10] the effect of pH on the nature of the products does not parallel its effect on the rate of the reaction, thus providing strong evidence for the existence of at least one intermediate on the hydrolysis reaction pathway. In the present case, the product transition occurs at pH 8 while the rate law reflects the change from nucleophilic attack by water to attack by hydroxide ion at pH 5.75. Control experiments established that formation of benzylamine at acid pH is not the result of the hydrolysis of initially formed amide III; less than 2% and 11% hydrolysis of III took place at pH 7 and 5, respectively, during the time necessary for total disappearance of the iminolactone. The transition from the formation of amine at pH <7 to that of amide at higher pH is in accord with observations made with other imidate esters derived from aniline[4] and aliphatic amines,[6,9,10] which exhibited similar product transitions in the range of pH 7–9.

Consonant with the behavior of cyclic[4] and acyclic[9] imidate esters, the yield of amine produced on hydrolysis of I is markedly increased in the presence of low concentrations of phosphate and bicarbonate buffers

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(14) E. S. Hand and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 3505 (1962).

Table I. Effect of Phosphate and Bicarbonate Buffers on the Yield of Benzylamine Obtained from Hydrolysis of the Iminolactone I[a]

pH	[Buffer],[b] M	Amine,[c] %	Amine,[d] %, corrected	K_{app},[e] M
		a. Bicarbonate		
8.15		39.1	37.3	0.0034 ± 0.0007
8.18	0.002	59.5		
8.18	0.004	72.5		
8.19	0.008	85.0		
8.21	0.02	90.8		
8.24	0.05	95.4	93.9	
9.03		10.9	6.3	0.014 ± 0.002
9.04	0.001	15.3	10.4	
9.04	0.002	20.7	14.5	
9.05	0.005	38.6	31.0	
9.05	0.01	49.1	39.2	
9.07	0.02	66.0	56.4	
9.09	0.04	78.9	69.2	
9.10	0.08	84.9	71.5	
9.10	0.15	94.6	85.5	
		b. Phosphate		
8.15		39.1	37.3	0.0068 ± 0.0013
8.17	0.002	54.6		
8.17	0.004	58.0		
8.17	0.008	74.0		
8.18	0.02	84.3		
8.20	0.05	92.0	90.4	
9.03		10.9	6.3	0.053 ± 0.012
9.05	0.002	12.0	6.0	
9.05	0.005	17.8	11.0	
9.06	0.01	25.2	18.0	
9.06	0.02	36.5	26.4	
9.08	0.04	52.5	43.0	
9.09	0.06	62.9	53.0	
9.10	0.10	67.3	56.5	

[a] At 30° in 3% ethanol-water, μ = 0.49. [b] All reaction mixtures contain 0.02 M borate buffer. [c] Total yield of benzylamine in reaction mixture. [d] Yield of benzylamine formed directly from iminolactone. For method of correction, see Experimental Section. At pH 8.15, corrections are very small and were carried out in a few cases only. [e] Standard deviations are given.

(Table I). These pronounced buffer effects are manifested on the product distribution only, without corresponding changes in the rate of hydrolysis of the iminolactone. Thus, the rate constant for hydrolysis of I in 0.02 M borate buffer (pH 9.0) was not altered detectably by the addition of 0.15 M bicarbonate buffer; under these conditions, the yields of benzylamine were found to be 6.3 and 85.5%, respectively.

The dependence of the yield of amine on the concentration of catalytic buffers can be fitted to a rectangular hyperbola, according to eq 3 (ΔA = increase

$$\Delta A/\Delta A_{\max} = [\text{buffer}]/([\text{buffer}] + K_{\text{app}}) \qquad (3)$$

in amine yield above that produced in the absence of a reactive buffer; $\Delta A_{\max}$ = maximum increase possible; K_{app} = concentration of buffer required to produce half the maximum possible increase in yield).[5] Maximum yields calculated for hydrolysis in the presence of phosphate or bicarbonate buffer at pH 8.2 were 90–100%, and 90–95% at pH 9. The high sensitivity of product formation to low concentrations of these buffers is indicated by the K_{app} values listed in Table I.

Lactonization of *N*-Benzyl-2-hydroxymethylbenzamide. For reasons explained in the Discussion, the influence of bicarbonate buffer on the rate of cyclization of the amide III was investigated at pH 9. It had previously been reported[2] that bicarbonate buffer accelerated the lactonization of III. To establish the dependence of the rate of lactonization both at low and high buffer concentrations, 0.02 M borate buffer was employed to maintain constant pH in the presence of concentrations of bicarbonate buffer ranging from 0.001 to 0.30 M. The principal result of this study (Table II and Figure 3) is that the *plot of k_{obsd} vs. total buffer concentration is not linear*, the reaction rate at low buffer concentration exhibiting a greater dependence on buffer than that at high buffer concentration. At concentrations of bicarbonate buffer exceeding 0.08 M, increases in rate are approximately proportional to buffer concentration, but with a slope about $^1/_3$ that of the rate constants at low buffer concentration.

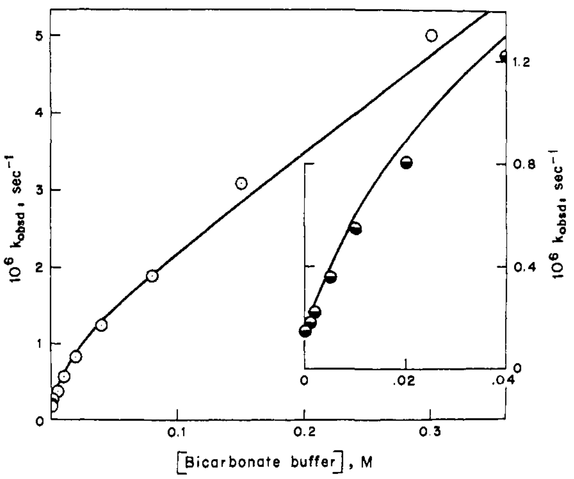


Figure 3. Effect of bicarbonate buffer at pH 9 on the rate of lactonization of amide III. All reaction mixtures contain 0.02 M borate buffer. The insert shows the data at low bicarbonate concentration, using an expanded scale. The solid curves are calculated from eq 5, using the constants given in the text.

Table II. Effect of Bicarbonate Buffer on the Rate of Lactonization of III[a]

pH	[Buffer],[b] M	$k_{\text{obsd}} \times 10^6$, sec^{-1}
9.03		0.14
9.02	0.001	0.18
9.03	0.002	0.22
9.03	0.005	0.36
9.03	0.01	0.54
9.03	0.02	0.81
9.03	0.04	1.22
9.08	0.08	1.88
9.07	0.15	3.08
9.07	0.30	5.00

[a] At 30° in 3% ethanol-water, μ = 0.49. [b] All reaction mixtures contain 0.02 M borate buffer.

Discussion

Iminolactone Hydrolysis and the Rate-Determining Step of the Lactonization of III. The dependence of the rates and products of hydrolysis of the iminolactone I on pH is completely analogous to that of other imidate esters, and the same reaction mechanism is suggested to account for the behavior of I (Scheme I). The arguments in support of this proposal have been presented in detail in earlier studies[4,9,10] and need not be restated here. For the present purpose, we stress only the following points: (a) the independent effects of pH on rates and products of the hydrolysis of I provide strong evidence for the existence of intermediates on the reaction pathway; (b) this conclusion is supported by the dependence of amine yield but not of rate of hydrolysis on buffer concentration at constant pH; (c) the pathway of lowest energy for the breakdown of intermediates in acidic solution results in the expulsion of amine, while in alkaline medium, the most favorable reaction path leads to the formation of amide and alcohol; this statement describes the behavior of the intermediates generated from all the imidate esters thus far studied, with the exception of those derived from amines of $\mathrm{p}K_a < 0$.[15]

If it is assumed that the intermediates formed by hydration of imidate esters are identical or closely related to those of the corresponding ester aminolysis or amide alcoholysis, the preferred pathways of intermediate breakdown at various pH values in the acyl transfer reaction may be specified in some detail.[3,6,16] This reasoning led to the conclusion that in the lactonization of 4-hydroxybutyranilide,[3] the rate-determining step at pH <7 was formation of the intermediate(s), since the lowest-energy path for decomposition in that pH range led to amine expulsion (*i.e.*, $k_3 \gg k_2$ in eq 1). For the aminolysis of methyl formate,[6] it was similarly concluded that intermediate breakdown was rate-limiting at pH values below neutrality, in agreement with the lactonization study, and as required by the principle of microscopic reversibility. Since the properties of the intermediates formed from I parallel those of similar species, we conclude that the lactonization of III proceeds *via* a mechanism qualitatively similar to that previously established for 4-hydroxybutyranilide, and that the rate-limiting step at pH below neutrality is the formation of intermediates, while at high pH, intermediate breakdown (*i.e.*, amine expulsion) becomes rate-determining. This conclusion contradicts that offered by Belke, *et al.*,[2] but seems required by the experimental results of the present and earlier studies.

For simplicity, it has been assumed that the neutral (or zwitterionic) and anionic intermediates of Scheme I (T^0 and T^-) are in acid–base equilibrium, *i.e.*, that proton transfers between T^0 and T^- are fast relative to the making and breaking of bonds to carbon. That this assumption may not be true for all such reactions has recently become evident;[17,18] however, the conclusions concerning the favored pathways of intermediate decomposition at low and high pH are not altered, even if, for example, the expulsion of amine from the intermediates requires a (relatively) slow proton transfer (*e.g.*, to convert T^0 to its zwitterionic form), which may under certain conditions become a rate-determining step for the acyl transfer reaction.

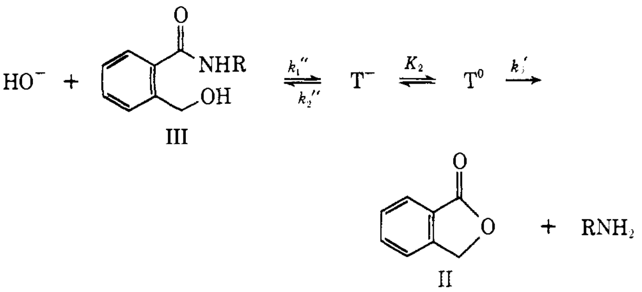
Buffer Catalysis and the Kinetics of the Lactonization of III. To simplify the discussion that follows, it is assumed that the neutral intermediate T^0 breaks down largely to amine (*i.e.*, $k_3' > k_2'$) and that the anionic species T^- yields mainly the amide III ($k_2'' > k_3''$), in accord with observation. As previously mentioned,[3,5,9] it is suggested that the effects of buffers on the amine yield are the result of catalysis of step k_3'. That these catalysts accelerate amine expulsion from the intermediates more than alcohol expulsion is evident from the fact that amine yields approach (but probably are not equal to) 100% at high buffer concentration.[16]

Scheme II describes the simplified mechanism for the lactonization of III *via* intermediates T^- and T^0, which break down to amide and amine, respectively. This mechanism holds in the pH range 5–9, *i.e.*, does not account for specific base-catalyzed lactonization at pH >10,[2,3] nor for pH-independent or acid-catalyzed paths at low pH. It is consistent, however, with the transition from hydroxide ion catalysis to pH-independent pathways as pH is increased from 5 to 9.[2,3] The steady-state expression (eq 4) indicates that there occurs a

$$k_{\mathrm{obsd}} = k_1''K_w/([\mathrm{H}^+] + K'') \tag{4}$$

change in rate-limiting step at pH = pK'' (where $K'' = k_2''K_2/k_3'$, and is numerically equal to the pH where the product transition in iminolactone hydrolysis occurs).[3,16] According to eq 4, the rate-determining step at pH < pK'' is the hydroxide-catalyzed formation of T^-, while at pH > pK'', the rate controlling step is the breakdown of intermediate to product *via* a neutral transition state.

Scheme II



If catalysts such as phosphate or bicarbonate buffers accelerated solely step k_3', catalysis would be seen at pH > pK'' and k_{obsd} should increase with buffer concentration only until the uncatalyzed formation of T^- became rate-determining.[3,16] The data of Figure 3 suggest that both formation and breakdown of intermediates are susceptible to catalysis, since k_{obsd} shows no tendency to become independent of buffer concentration at high buffer. The curvature of the plot can be accounted for by a mechanism in which the rate-limiting breakdown of T^0 is catalyzed at low buffer until a transition occurs to partial or complete rate-limiting formation of T^-, which is also susceptible, but to a lesser extent, to catalysis by bicarbonate buffer (Scheme III). The assignment of the nature of the buffer species involved in catalysis is plausible but largely arbitrary and is not important for the argument that follows. The steady-state rate law (eq 5, where $K_a = [\mathrm{B}][\mathrm{H}^+]/$

$$k_{\mathrm{obsd}} = \frac{(k_1''K_w + k_1'''K_a[\mathrm{BH}])(1 + k_3'''[\mathrm{BH}]/k_3')}{([\mathrm{H}^+] + K'') + k_3'''([\mathrm{H}^+] + K''')[\mathrm{BH}]/k_3'} \tag{5}$$

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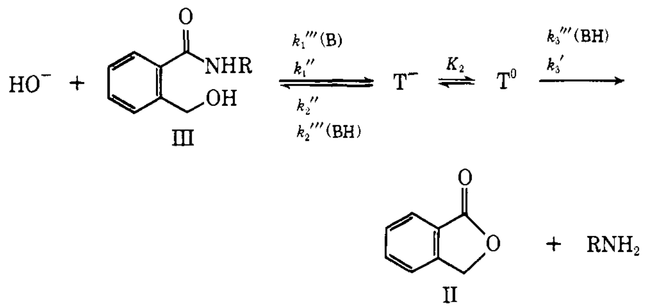
(15) (a) T. Okuyama, T. C. Pletcher, D. J. Sahn, and G. L. Schmir, *J. Amer. Chem. Soc.*, in press. (b) The reason for the apparent discrepancy between the limiting value of 70% for the benzylamine yield at low pH estimated from Figure 2, and the observed yield of 100% in acetate buffers, is not clear. Possibly, the postulated neutral intermediate T^0 (Scheme I) breaks down to yield only 70% of the amine, except in the presence of bifunctional catalysts (*e.g.* bicarbonate ion, acetic acid) which divert its decomposition to yield amine quantitatively. Alternatively, the observed yield of 100% at pH ≤5 may be the result of product formation *via* a cationic intermediate.

(16) G. L. Schmir, *J. Amer. Chem. Soc.*, 90, 3478 (1968).

(17) (a) R. E. Barnett and W. P. Jencks, *ibid.*, 91, 2358 (1969); (b) R. K. Chaturvedi and G. L. Schmir, *ibid.*, 91, 737 (1969).

(18) W. P. Jencks, *Chem. Rev.*, 72, 705 (1972).

Scheme III



[BH], and $K''' = k_2'''K_2/k_3'''$) indicates that, at high buffer, k_{obsd} becomes linearly dependent on buffer concentration (eq 6). The slopes of such lines will vary

$$k_{obsd} = \frac{k_1'''K_a[BH]}{[H^+] + K'''} = k_{BH}[BH] \qquad (6)$$

with pH; at low pH, the rate-limiting step at limitingly high buffer concentration is the general base-catalyzed formation of T⁻ ($k_{obsd} = k_1'''$[B]), and at high pH and high buffer concentration, the rate-limiting step is the general acid-catalyzed breakdown of T⁰ ($k_{obsd} = k_1'''K_a \cdot [BH]/K'''$). The pH at which there occurs a change in rate-limiting step at limitingly high buffer concentration is given by pK'''. The important point is that at constant pH, the nature of the rate-limiting step at zero buffer (*cf.* eq 4) will be the same as that at high buffer (eq 6) *only if* $K'' = K'''$ (eq 7), k_{obsd} remaining linearly

$$k_{obsd} = \frac{k_1''K_w + k_1'''K_a[BH]}{[H^+] + K''} \qquad (7)$$

dependent on buffer at all buffer concentrations. In the general case, the rate-limiting step will be partially or completely changed as buffer concentration is increased at constant pH, and therefore curvature in the plot of k_{obsd} *vs.* buffer is generally expected. Put another way, the requirement that $K'' = K'''$ is equivalent to the requirement that the Brønsted slopes defined by the two catalysts being compared (*i.e.*, BH and H_2O, in this case) be equal for steps 2 and 3. In view of the probable bifunctional nature[3–5] of catalysis on step 3 (but not necessarily of catalysis on step 2) this requirement is not likely to be met. Figure 4 illustrates the foregoing discussion. The cross-hatched section is the region of pH where the nature of the rate-limiting step varies significantly at constant pH in going from zero buffer (upper curve) to the limiting situation at high buffer (lower curve). No curvature in the dependence of rate on buffer would be expected at pH ≪ pK'' and pK''' or pH ≫ pK'' and pK''', since the rate-limiting step remains the same both at zero and high buffer concentrations.

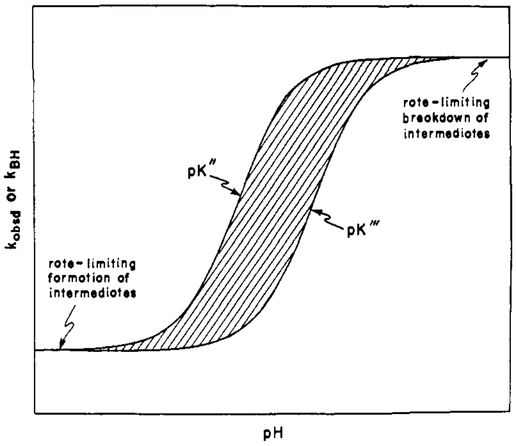


Figure 4. Schematic representation of the effect of pH on the rate-limiting step of the lactonization of III. Upper curve: pH dependence of the solvent-catalyzed reaction (eq 4). Lower curve: pH dependence of the slopes (k_{BH}) of linear plots of k_{obsd} *vs.* buffer at high buffer concentration (eq 6). The cross-hatched section represents the pH range where the rate-limiting step changes partially or completely on going from zero buffer to high buffer at constant pH.

What does the assumption that buffer catalyzes the breakdown of both T⁰ and T⁻ (Scheme III) mean with respect to the maximum yield of amine to be expected from hydrolysis of the iminolactone? For this situation, the yield of amine will show the usual hyperbolic dependence on buffer concentration (eq 8),[16] but the

$$\%\ \text{amine} = \frac{\left(\dfrac{[H^+]}{[H^+] + K'''}\right)\left(\dfrac{k_3'}{k_3'''} + [BH]\right)}{\dfrac{k_3'}{k_3'''}\left(\dfrac{[H^+] + K''}{[H^+] + K'''}\right) + [BH]} \times 100 \qquad (8)$$

asymptotic yield of amine at constant pH (eq 9) will no

$$\text{maximum yield of amine} = [H^+]/([H^+] + K''') \qquad (9)$$

longer be 100%, and will vary with pH.

The solid line in Figure 3 was calculated from eq 5 using the following constants: $k_1''K_w = 1.54 \times 10^{-15}$ M sec⁻¹, $k_1'''K_a = 1.43 \times 10^{-14}$ sec⁻¹, p$K'' = 8.0$, p$K''' = 9.75$, and $k_3'''/k_3' = 520\ M^{-1}$. The first two terms are estimated from the rate of lactonization of III in the absence of added bicarbonate buffer and from the limiting slope at high buffer, respectively; the last three terms can be estimated from the effect of pH on amine yields from I in the absence of catalytic buffers, and from the dependence of amine yield at pH 9.0 on the concentration of added bicarbonate buffer.[19] In view of the absence of buffer catalysis data at other pH values the absolute values of these constants may be somewhat in error. The calculation is simply meant to illustrate the quantitative relationship which may be expected to hold between the pH and buffer data on iminolactone hydrolysis and on the lactonization of III.[16] In summary, the lactonization of III at pH 9 is believed to occur with mainly rate-determining breakdown of intermediate in the absence of added bicarbonate buffer (pH > pK''); increasing concentrations of bicarbonate buffer cause a transition to mainly rate-determining formation of intermediates (pH < pK'''), so that the slope of the limiting line reflects predominantly catalysis on the formation step k_1.

The very slow rates of hydrolysis of I and of lactonization of III discouraged us from a more extensive study of these reactions. The results of this limited investigation, however, strongly suggest that the solvent-catalyzed lactonization of III proceeds *via* the mechanism first suggested for 4-hydroxybutyranilide,[3] at least with regard to the identification of the rate-limiting steps at high and low pH, and appear inconsistent with

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[19] The five terms of eq 5 to which numerical values are assigned are not independently variable. The equilibrium restriction $k_1''K_w/k_2'' = k_1'''K_a/k_2'''$ requires that $k_1'''K_a = k_1''K_wK'''k_3'''/K''k_3'$, so that selection of values for four parameters determines the value of the fifth.

the proposal of Belke, Su, and Shafer.[2] The observed nonlinear dependence of rate on buffer concentration is in accord with expectation based on the response of the hydrolysis of the iminolactone to the same buffer. Belke, *et al.*,[2] did not seem to have observed curvature in similar studies of buffer catalysis of the lactonization of III, probably owing to the fact that sufficiently low concentrations of buffer were not employed. The present study raises serious questions concerning the validity both of the published Brønsted plots for buffer catalysis and of their interpretation in terms of the mechanism of lactonization of III.

Experimental Section[20]

1-Benzylimino-1,3-dihydroisobenzofuran Hydrobromide (I). 2-Bromomethylbenzoyl bromide[21] was prepared in 68% yield by treating 15.0 g (0.11 mol) of phthalide (Aldrich) with 47.7 g (0.11 mol) of phosphorus pentabromide (Pfaltz and Bauer) at 95° for 2 hr, followed by distillation *in vacuo*. Conversion to the iminolactone hydrobromide was acccomplished in low yield according to Stirling:[22] mp 147–148° (lit.[22] 145–146°); infrared spectrum (Nujol mull) 5.93 μ (C=$^+$NH–); ultraviolet spectrum in ethanol containing 4 equiv of NaOH, $\lambda_{\max}$ 284 mμ (ε 5900), 277 mμ (ε 4580), 243 mμ (ε 15,700), in ethanol containing 4 equiv of HCl, $\lambda_{\max}$ 292 mμ (ε 3600), 284 (4640), 249 (18,200) (lit.[22] $\lambda_{\max}$ 284 mμ (ε 5500), 242 (15,400) for iminolactone free base in ethanol); mass spectrum molecular ion (–HBr) at *m/e* 223 (relative abundance 63%).

The pK_a of I was determined by spectrophotometric titration of the iminolactone (6.7% CH_3CN-H_2O, μ = 0.53–0.59, 30°) at 292 mμ where the free base exhibits negligible absorption. The resulting data were analyzed by the method of Reed and Berkson,[23] yielding pK_a = 6.63.

N-Benzyl-2-hydroxymethylbenzamide[2] (III) had mp 136–137° (lit.[2] mp 134–135°); infrared spectrum 6.15 μ (C=O); ultraviolet spectrum in ethanol, no $\lambda_{\max}$ at >220 mμ, shoulders at 267 mμ (ε 950) and 263 (110). **Benzylamine hydrochloride**, prepared by passing gaseous HCl into the ethereal solution of the amine, was recrystallized from ethanol–ether and had mp 263°.

Kinetic Measurements. Buffers and inorganic salts were of reagent grade and were used without further purification. Freshly boiled, glass-distilled water was used for all rate determinations and product analyses for reactions at pH >6.

The hydrolysis of the iminolactone I was studied at 30° in 3% ethanol–water (μ = 0.49, KCl) by determining the rate of decrease of absorbance usually at 282 mμ. At pH ≤8, any phthalide produced either is completely stable to ring opening or undergoes hydrolysis so slowly that this reaction does not interfere with the calculation of the rate constants for the disappearance of I. At pH 9, phthalide is hydrolyzed at a rate ($t_{1/2}$ *ca.* 30 hr, 0.04 *M* borate buffer) comparable to that of I. At that pH, however, in borate alone, I is converted almost exclusively to the hydroxymethyl amide III, which exhibits negligible absorbance at 282 mμ. To avoid complications resulting from competing phthalide hydrolysis, the disappearance of I at pH 9 in borate buffers containing added bicarbonate or phosphate (where the reaction products are mainly phthalide and benzylamine) was measured at 258 mμ, an isosbestic wavelength for phthalide and 2-hydroxymethyl benzoate ion.

Buffers used in the hydrolysis of I were HCl (pH 3), acetate (0.005 *M*, pH 5.0), 2-*N*-morpholinoethanesulfonate (0.02 *M*, pH 6.6), and borate (0.1 *M* at pH 7–7.5, 0.02 *M* at pH 8–9). The concentration of I was generally 1.1 × 10^{-4} *M*. First-order rate constants were calculated by use of the Guggenheim procedure[24] or of a modified Guggenheim procedure.[25]

The lactonization of III at 30° in 3% ethanol–water (μ = 0.49, KCl) was followed by measuring the rate of appearance of benzylamine by means of a colorimetric method described below. All reactions were carried out in sealed glass ampoules. The faster reactions were followed to completion, and substrate concentration was 1.2 × 10^{-4} *M*. Slower reactions (in reaction mixtures containing <0.01 *M* bicarbonate) were followed to 25–40% completion, with III initially at 7 × 10^{-4} *M*. In the latter cases, rate constant calculations were based on the theoretical yield of benzylamine.

Product Analysis. The extent of C–N bond cleavage which occurred during the hydrolysis of I or the lactonization of III was determined by measuring the concentration of benzylamine produced either as a function of time (with III) or after 6 half-lives of reaction (with I). Benzylamine was determined by means of a modification[26] of the method of Dahlgren,[27] using benzylamine hydrochloride as a standard. Under the usual assay conditions, a 1-ml aliquot containing amine at 1 × 10^{-4} *M* gives an absorbance of about 0.520 at 540 mμ. An equivalent amount of the amide III exhibits an absorbance of <0.01 in the assay.

The presence of low concentrations of bromide ion is known to increase the color yield of amines measured by this method.[27] Since the substrate used for the hydrolysis of I was the iminolactone hydrobromide, an equivalent concentration of potassium bromide (*ca.* 1.1 × 10^{-4} *M*) was included in the standard solution of benzylamine. Under these conditions, a 1-ml aliquot containing benzylamine at 1 × 10^{-4} *M* gave an absorbance of 0.610, while the same concentration of III showed an absorbance of 0.04.

Control experiments showed that a pH 7–8 (borate buffer) lactonization of III produced <3% benzylamine during the time needed for complete hydrolysis of I, so that the amine formed in that pH range is the initial product of the hydrolysis of I. At pH 9, and to a lesser extent at pH 8 also, in the presence of bicarbonate and phosphate buffer, separate experiments showed that part of the amine found after six half-lives of hydrolysis of I was derived from secondary hydrolysis of some initially produced III. Observed amine yields (from I) were corrected as follows to calculate the yield of amine directly obtained on hydrolysis of I.

For Scheme IV, where A_1 = amine formed directly from I, and A_2 = amine formed by hydrolysis of III, the time dependence of the concentration of A_1 and A_2 is given by eq 10 and 11, respectively

Scheme IV

$$\begin{tikzcd}
\mathrm{I} \arrow[r, "k_1"] \arrow[d, "k_1'"'] & \mathrm{III} \arrow[r, "k_2"] & \mathrm{A_2} \\
\mathrm{A_1} & &
\end{tikzcd}$$

$$\frac{A_1}{I_0} = \frac{k_1'}{k_0}(1 - e^{-k_0t}) \tag{10}$$

$$\frac{A_2}{I_0} = \frac{k_1}{(k_2 - k_0)k_0}[k_2(1 - e^{-k_0t}) - k_0(1 - e^{-k_2t})] \tag{11}$$

(where $k_0 = k_1 + k_1'$ and I_0 = I present at $t = 0$).[28] For 6 or more half-lives of reaction of I ($e^{-k_0t} << 1$), eq 10 and 11 are reduced to eq 12 and 13, respectively, yielding eq 14 for *A*, the total concentration of amine observed at time *t*. The desired mole fraction k_1'/k_0 is easily evaluated from eq 14 or 15 (where *F* is defined in eq 16)

$$A_1/I_0 = k_1'/k_0 \tag{12}$$

$$\frac{A_2}{I_0} = \frac{k_1}{k_0} + \frac{k_1}{k_2 - k_0}e^{-k_2t} \tag{13}$$

$$\frac{A}{I_0} = \frac{A_1 + A_2}{I_0} = \frac{k_1'}{k_0} + \frac{k_1}{k_0}\left(\frac{k_2 - k_0(1 - e^{-k_2t})}{k_2 - k_0}\right) \tag{14}$$

$$\frac{k_1'}{k_0} = \frac{(\text{mol fraction of amine from I}) - F}{1 - F} \tag{15}$$

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(20) Melting points are uncorrected.

(21) L. Reichel and W. Hampel, *Z. Chem.*, 3, 190 (1963).

(22) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).

(23) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams and Wilkins, Baltimore, Md., 1960, p 154. Equation 38 should be corrected to read: pK' – p[L]$_f$ = log *C*.

(24) E. A. Guggenheim, *Phil. Mag.*, 2, 538 (1926).

(25) (a) F. J. Kezdy, J. Jaz, and A. Bruylants, *Bull. Soc. Chim. Belg.*, 67, 687 (1958). (b) E. S. Swinbourne, *J. Chem. Soc.*, 2371 (1960).

(26) R. K. Chaturvedi, A. E. McMahon, and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 6984 (1967).

(27) G. Dahlgren, *Anal. Chem.*, **36**, 596 (1964).

(28) The derivation of eq 10 and 11 is similar to that described for the simple consecutive first-order reaction scheme A → B → C.[29]

(29) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 166.

$$F = \frac{k_2 - k_0(1 - e^{-k_2 t})}{k_2 - k_0} = \frac{k_2 - k_0(\text{mol fraction of amine from III})}{k_2 - k_0} \quad (16)$$

if k_2 is known from independent measurement of the rate of lactonization of III. For the hydrolysis of I in bicarbonate buffer at pH 9, k_2 was accurately known (Table II). In other experiments, corrections were based on single point determinations of the yield of amine from samples of III which had been allowed to undergo lactonization for a time period equal to that used in the complete hydrolysis of I. Observed and corrected yields of benzylamine are listed in Table I.

Values of K_{app} and ΔA_{max} were calculated by means of a computer fit of the data to the two-parameter rectangular hyperbola.[26]

Acknowledgment. Support of this research by a grant from the National Science Foundation is gratefully acknowledged.

Medium and Temperature Dependence of Acid-Catalyzed Hydrolysis of N-Methylated Methylbenzimidates and Benzoylimidazole. An Investigation into the Mechanism of Amide Hydrolysis

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Abstract: The kinetics of hydrolysis of methylbenzimidate, *N,O*-dimethylbenzimidatium fluoroborate, and *N,N,-O*-trimethylbenzimidatium fluoroborate have been studied in 1–65% aqueous sulfuric acid over the temperature range 25–85°. The hydrolysis of benzoylimidazole was studied in 10–75% sulfuric acid over the temperature range 15–65°. The benzimidates yielded esters as primary hydrolysis products in dilute acid but gave amides as products in more concentrated acids, indicating different rate-determining steps in dilute and concentrated acids. The order of reactivity with successive N-methylation was primary > secondary > tertiary and there were monotonic decreases in both the enthalpy and entropy of activation with successive N-methylation. By comparing rate constants, activation parameters, product studies and ^{18}O exchange results for the N-methylated methylbenzimidates and the corresponding N-methylated benzamides, it is concluded that none or not all of the benzamides hydrolyze in acid solution *via* the accepted tetrahedral intermediate mechanism (involving an O-protonated amide) as do the benzimidates. Inspection of data for benzoylimidazole (as a model for an N-protonated amide) does not contradict this conclusion.

Despite the importance of acid-catalyzed hydrolysis of amides, the mechanism of this reaction is still uncertain. A number of mechanisms can be envisaged, but the two most reasonable mechanistic pathways are outlined in Scheme I. These can be designated as $A_O{}^T2$ (acid-catalyzed, bimolecular, O-protonated cation, tetrahedral intermediate mechanism) and $A_N{}^D2$ (acid-catalyzed, bimolecular, N-protonated cation, direct displacement mechanism), respectively.[1] Various authors have regarded one or another of these mechanisms as being correct, with the majority favoring the $A_O{}^T2$ mechanism. However, there is no evidence whatever to rule out either; thus the correct mechanism is not established.

It was shown previously[2] that changes in first-order rate constants and enthalpies of activation for the acid-catalyzed hydrolysis of benzamide are not monotonic with successive N-methylation. It was clear that these changes were either the result of a mechanistic change with successive N-methylation or some unexplained phenomenon of a unique mechanism of amide hydrolysis. Edward and Meacock[3] have proposed that methylbenzimidate would be a good chemical model for benzamide hydrolyzing *via* the O-protonated form ($A_O{}^T2$ mechanism) since imidates in general react through tetrahedral intermediates.[3,4] In this paper, the effect of successive N-methylation of methylbenzimidate on hydrolysis rate constants and activation parameters will be examined. If the benzamides and benzimidates react *via* similar tetrahedral intermediates, the reaction parameters for these two types of substrate should exhibit similar changes with successive N-methylation. The substrates to be compared are listed in Chart I. The amides are represented in their predominant O-protonated form[5] and the benzimidates in their protonated or cationic forms.

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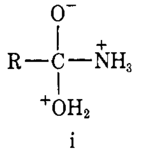
[1] One other mechanism is possible which closely resembles the $A_N{}^D2$ mechanism. In this process water attacks the N-protonated species to give a discrete tetrahedral intermediate ($A_N{}^T2$). However, because of the highly dipolar nature of such an intermediate (i), it is



$$R-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle {}^+OH_2}{|}}{C}}-\overset{+}{N}H_3$$

i

considered to represent a less reasonable mechanistic pathway, although the possible intermediates involved in these two alternative mechanisms would be very difficult to distinguish experimentally.

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