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Acylium Ion Formation in the Reactions of Carboxylic Acid Derivatives. I. Application of the H_R Acidity Function to the Diazotization of Benzamide in Sulfuric Acid[1]

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The kinetics and oxygen exchange in the diazotization of benzamide were investigated. Correlation of the rate data with the H_R acidity function indicates prior ionization of nitrous acid to the nitrosonium ion, which reacts with unprotonated benzamide in the slow step. The remainder of the reaction involves a series of fast proton transfers yielding the acyldiazonium ion which in turn decomposes to form the acylium ion and nitrogen gas. Diazotization of benzamide is shown to be faster than hydrolysis by a factor of 2.5×10^7. The absence of oxygen exchange during the diazotization reaction provides additional evidence for the proposed mechanistic scheme.

Introduction

A number of investigations involving kinetics and oxygen exchange have elucidated the mechanism of the acid- and base-catalyzed hydrolysis of esters and amides of benzoic acid.[2-5] It was thought that the kinetic and oxygen exchange criteria applied in these cases would also be applicable in establishing the mechanism of reactions of carboxylic acid derivatives which have been presumed to proceed through acylium ion intermediates. Reactions falling into the latter category include the hydrolysis of methyl mesitoate in concentrated acid solutions and the hydrolysis of acid chlorides.

When methyl mesitoate is dissolved in 100% sulfuric acid, an "*i*" factor of 5 is measured cryoscopically, whereas methyl benzoate yields an initial "*i*" factor of two.[6] This has been interpreted to indicate the presence of an acylium ion, RCO^+, in the former case. Furthermore, the rate of hydrolysis of methyl mesitoate has been shown to follow the Hammett acidity function in strong (1–6 *M*) sulfuric acid and does not follow the concentration of the hydronium ion.[7] This evidence is interpreted to mean that water does not participate in the rate-determining step of the reaction and further means that the acylium ion is formed during the hydrolysis. On the other hand, it is well-known that in dilute acid solution, the hydrolysis of methyl mesitoate is much slower than the hydrolysis of methyl benzoate. The relative rate data can be explained most easily on the basis of the rate-determining formation of a tetrahedral addition intermediate which is sterically strained in the case of methyl mesitoate. Studies of the hydrolysis of substituted benzoyl chlorides in mixed solvents have indicated that the mechanism of the reaction is sensitive to changes in water concentration of the solvent. The effect of solvent composition,[8,9] temperature,[8] substituents[10] and inert and common-ion salts[11] indicate that in media low in water content, the reaction of benzoyl chloride and those chlorides substituted with electron-donating groups proceeds almost exclusively by the bimolecular SN2 mechanism, whereas with an increase in water concentration there is a gradual shift to a unimolecular SN1 ionization involving formation of an acylium ion. The tendency for acylium ion formation is dependent on the ionizing power of the solvent and the structure of the aryl radical. Of all the compounds tested, the importance of structure will be most clearly expressed in the hydrolysis of mesitoyl chloride. Here the formation of the acylium ion would be facilitated by the steric, hyperconjugative and inductive effects of the methyl groups. Hudson reports that in 95% aqueous acetone the rate of hydrolysis is higher than for any of the other acyl halides and further that the addition of hydroxide ion produces no effect on the rate. These results are readily interpretable on the basis of a rate-determining formation of an acylium ion intermediate. Contradictory evidence has appeared indicating that hydroxide ion does exert a large effect on the hydrolysis of mesitoyl chloride in 95% aqueous dioxane[12] and furthermore that the carboxyl oxygen atom of mesitoyl chloride exchanges with the solvent during the hydrolysis.[5] Both of these results are incompatible with acylium ion formation and support a mechanism involving the formation of a tetrahedral addition intermediate in a bimolecular reaction.

The ambiguous and sometimes conflicting data in the reaction of methyl mesitoate and mesitoyl chloride indicate the possibility of complicated or possibly multiple pathways in these reactions which are presumed to proceed through acylium ion intermediates. It was therefore decided to initiate a study of reactions involving acylium ion intermediates by choosing a reaction where the SN1 path could be shown to play the predominant role. If such a reaction could be found, it was thought that it would then be possible to determine the possible oxygen exchange in an acylium ion process for comparison with the oxygen exchange in a process involving a tetrahedral intermediate. It is

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(1) This research was supported by a grant from the National Science Foundation.

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(3) M. L. Bender, R. D. Ginger and K. C. Kemp, *ibid.*, **76**, 3350 (1954).

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(9) D. A. Brown and R. F. Hudson, *ibid.*, 3352 (1953).

(10) D. A. Brown and R. F. Hudson, *ibid.*, 883 (1953).

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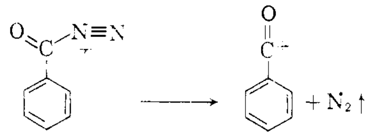
(12) C. A. Bunton and T. A. Lewis, *Chemistry & Industry*, 180 (1956).

predicted that whereas reactions involving tetrahedral intermediates proceed with concurrent oxygen exchange, reactions involving acylium ion intermediates should proceed with no concurrent oxygen exchange.

With these ends in mind, the diazotization of benzamide was selected as the model for the ionization mechanism of a carboxylic acid derivative, assuming the formation of I which loses nitrogen to give the acylium ion II, by analogy with the phenyldiazonium ion. The diazotization of benzamide also provides the opportunity for a mechanistic study of this widely-used synthetic tool for the preparation of acids from their amides,[13] as well as a test of the correlation of rate data with the H_R acidity function.[14,15]


I II

Experimental

Materials.—Sodium hydroxide was standardized against potassium hydrogen phthalate using potentiometric titration. Sulfuric acid diluted from the concentrated material (B and A product, C.P. grade) was standardized against sodium hydroxide solution by potentiometric titration. Quinoline (Matheson Co.) was purified by distillation from zinc dust[16]; b.p. 47.2° (0.15 mm.). Mercuric chloride was Fisher reagent grade. The concentration of sodium nitrite (Fisher certified, A.C.S. reagent) stock solutions was determined spectrophotometrically, using previously determined extinction coefficients.[17] Benzamide (Matheson Co.) was recrystallized twice from water, m.p. 126.5–127.0°.

Kinetic Measurements.—The diazotization of benzamide was followed by changes in optical density at 255 mμ, using a thermostated Beckman DK2 recording spectrophotometer. Spectral studies of nitrous acid, benzoic acid and benzamide in sulfuric acid solution indicated abnormal changes with acidity. Changes in both extinction coefficient and absorption maximum which cannot be correlated with changes in concentrations of the acidic and basic forms of the compounds were observed.[18-20] Therefore it was necessary to obtain spectra of benzamide and benzoic acid for every sulfuric acid concentration in which the reaction was observed to determine the optimum wave length (255 mμ) for following the reaction. Agreement with the literature was found.[20] The final absorption quantitatively corresponds to that calculated for benzoic acid.

The volatility of nitrous acid makes the determination of its stoichiometric concentration difficult and prevents the complete transfer of nitrous acid solutions.[18] Therefore the nitrous acid was prepared *in situ*. The water, stock solutions of benzamide and sodium nitrite were added to a ground glass-stoppered optical cell. The cell was chilled in an ice–water mixture, and sulfuric acid was added as quickly as possible (less than 10 sec.) and the cell capped. It was shaken, immersed in water at thermostat temperature, wiped dry and inserted into the spectrophotometer. The opposing effects of heat of dilution and external cooling brought the resulting temperature to no less than five degrees below the temperature of the thermostat. By pouring the sulfuric acid over the solution, the nitrous acid is essentially trapped in the viscous acid medium. Capping the cells prevented any volatility loss as shown by constancy of absorption with time.[18]

Because the extinction coefficients of the various materials are high, the solutions were of the order of 5×10^{-5} to 10^{-4} *M* in nitrous acid and benzamide, respectively. The stoichiometric concentrations of nitrous acid and sulfuric acid could not be directly calculated from the known concentrations of the stock solutions because of the appreciable volume contraction on mixing. In order to calculate the final volume of the solution, a blank reaction was run using water instead of the sodium nitrite and benzamide solutions. After mixing, the volume was experimentally determined from the weight and concentration of the final sulfuric acid solution. The over-all range of acidities studied in this reaction is restricted by practical considerations. Nitrous acid was used in 20–100 fold stoichiometric excess to ensure a pseudo-order constancy and to minimize errors due to volatility. A possible side reaction, the decomposition of nitrous acid, has been extensively studied and is quite small under these conditions.[18c,21]

Oxygen Exchange.—Solutions of benzamide-O^{18} were cooled and sulfuric acid was added to give the same acidities as in the kinetic experiments. Sodium nitrite solutions were added last, with the mouth of the pipet at the bottom of the flask. This procedure, the reverse of that described above, is necessitated by the large volume (and heats of dilution) of sulfuric acid that had to be added in these runs. After being thermostated for the desired times (corresponding to 0–65% reaction), the contents were poured onto a slurry of ice and sodium carbonate to quench the reaction and prevent heating due to the neutralization. The *p*H was adjusted to 8–9 and the benzamide was extracted with six to seven 30-ml. portions of methylene chloride. The methylene chloride solutions were combined, dried, evaporated and the residual benzamide was recrystallized from water.

The oxygen-18 content of the benzamide samples was determined by analysis of the carbon dioxide obtained on pyrolysis of the amide with mercuric chloride at 530° for 1.8 hours following the method of Rittenberg and Ponticorvo.[22] The carbon dioxide was analyzed with a Consolidated-Nier model 21-201 isotope ratio mass spectrometer.

Quinoline was found preferable to 5,6-benzoquinoline for reaction with the by-product hydrogen chloride formed in the pyrolysis reaction, because of its ready availability and the ease of manipulation of the liquid. It was found desirable to carry out a second treatment of the pyrolysis gas with fresh quinoline in order to be absolutely sure that all traces of hydrogen chloride were removed before mass spectrometric analysis.

The atom fraction (X) of oxygen 18 in an organic compound containing one oxygen atom was calculated from the mass spectrometric data in the following way. The pyrolysis reaction may be written as

$$y\text{RO}^{18} + y\text{RO}^{16} + y\text{C} \longrightarrow y\text{CO}_2$$

XyA = number of O^{18} molecules in y moles of RO (A = Avogadro's number). Assuming statistical distribution of O^{18} in CO_2, and assuming $CO^{18}O^{18}$ is negligible compared to the other species

the fraction of $CO^{18}O^{16} = 2(X - X^2)$
the fraction of $CO^{16}O^{16} = (1 - X)^2$

The mass spectrometer readings are proportional to the mass 46/44 ratios, R_s and R_u being the mass spectrometer readings for standard and unknown carbon dioxide, respectively.

$$R_s = 2k(0.00204)/(0.99796)$$

where k is the proportionality constant and the normal isotopic composition is assumed to be 0.204% O^{18}.

$$R_u = 2kX(1 \pm X)yA/(1 - X)^2y\text{A} = 2kX/(1 - X)$$

Therefore $X = (0.00204R_u/R_s)/(0.99796 + 0.00204R_u/R_s)$.

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[13] S. Sarel and M. S. Newman, THIS JOURNAL, **78**, 5416 (1956), and references therein.

[14] N. C. Deno, J. J. Jaruzelski and A. Schriesheim, *ibid.*, **77**, 3044 (1955).

[15] (a) N. C. Deno and R. Stein, *ibid.*, **78**, 578 (1956); (b) N. C. Deno, H. E. Berkheimer, W. L. Evans and H. J. Peterson, *ibid.*, **81**, 2344 (1959).

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[19] (a) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, **57**, 2103 (1935); (b) C. T. Davis and T. A. Geissman, *ibid.*, **76**, 3507 (1954).

[20] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).

[21] E. D. Hughes, C. K. Ingold and J. H. Ridd, *ibid.*, 62 (1958).

[22] D. Rittenberg and L. Ponticorvo, *J. Appl. Radiation and Isotopes*, **1**, 208 (1956).

Results and Discussion

Kinetics.—A basic assumption is made in this discussion that diazotization of the amide is analogous to the corresponding reaction of arylamines in that the reaction involves the attack of an electrophilic nitrosating agent on the nucleophilic nitrogen center. This mechanism has been demonstrated in the case of the amine by extensive investigations of Ingold and co-workers.[23] The results of the kinetic study of the diazotization of benzamide are given in Fig. 1 and Table I. The spectrophotometric data, from which the first-order rate constants, k_{obs}, are obtained, express the rate of disappearance of the protonated benzamide or the production of unprotonated benzoic acid.

TABLE I

KINETICS OF THE DIAZOTIZATION OF BENZAMIDE IN CONCENTRATED SULFURIC ACID[a]

Run	H_2SO_4, M	$(HONO)_{stoich}$, $\times 10^3$, M	$k_{obs} \times 10^4$,[h] sec.$^{-1}$	ROH $(HONO_{mol})$,[i] %
20	4.58[b]	20.0	4.72	99.99
12	5.40[c]	11.3	5.82	99.94
14	5.40	8.10	4.24	99.94
13	5.40	5.67	3.14	99.94
15	5.40	4.05	1.92	99.94
21	6.02[d]	6.68	4.32	99.74
17	6.70[e]	4.26	3.92	98.78
18	6.70	2.62	2.34	98.78
19	7.45[f]	1.23	4.32	95.12
22	8.55[g]	0.804	2.58	47.70

[a] 26.2 ± 0.2°, except for runs 20–22, for which the temperature was 25.0 ± 0.1°. [b] $h_0 = 126$, $H_R = -4.05$. [c] $h_0 = 287$, $H_R = -4.88$. [d] $h_0 = 603$, $H_R = -5.52$. [e] $h_0 = 1380$, $H_R = -6.20$. [f] $h_0 = 3715$, $H_R = -6.82$. [g] $h_0 = 15{,}490$, $H_R = -8.15$; h_0 and H_R values taken from F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 1 (1957), and ref. 14, respectively. [h] These rate constants were calculated according to the method of E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926). [i] See Discussion.

The concentration of protonated and unprotonated species can be calculated from a knowledge of the pK_a's of their conjugate acids and the H_0 of the medium.[19a,20] The pK_a's of the protonated benzamide and benzoic acid are −1.85 and −7.26, respectively. The kinetic data do not allow a decision as to which species of benzamide is actually involved in the nitrosation step. The first-order dependence of the Guggenheim plot requires that either benzamide or protonated benzamide must be consumed in the nitrosation step. By analogy with the amine reaction, it is concluded that benzamide is the true reactant, with the protonated form acting as a reservoir. It is difficult to conceive of a reaction (see later) proceeding by electrophilic attack on a positively charged species.

In determining the nature of the nitrosating agent, the results of two spectrophotometric investigations of the behavior of nitrous acid in perchloric acid solution are pertinent.[18] Ionization of the neutral species, HONO, to nitrosonium ion, NO^+, was demonstrated to increase with the acidity of the medium. The two species account for the stoichiometric concentration of nitrous acid in perchloric acid, within 5% error. There is no indication of the existence of other species in appreciable amounts, such as H_2ONO^+, as previously reported. The nitrosating agent, dinitrogen trioxide, which Ingold showed to be the species generally involved with amines in neutral solution, does not exist in concentrated acid solution but rather is converted to the nitrosonium ion.

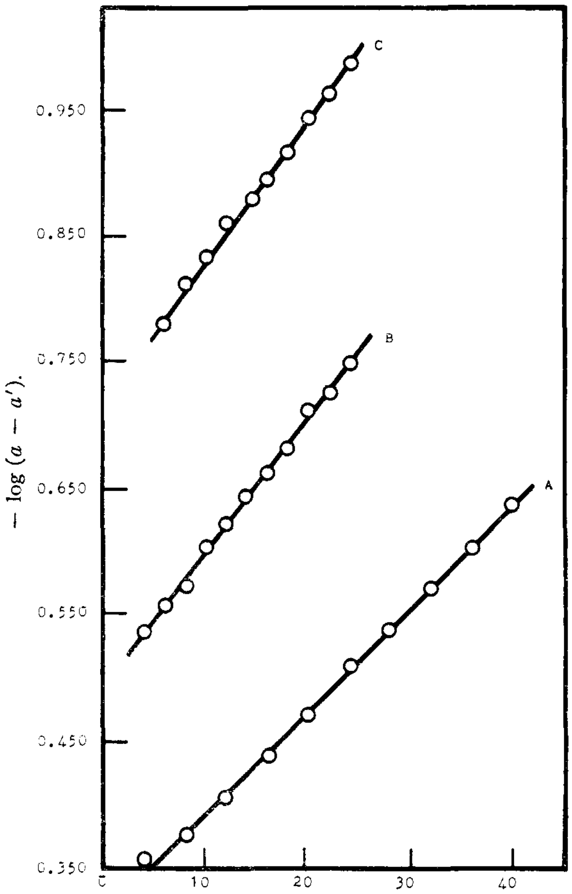

Fig. 1.—Representative Guggenheim plots of the kinetics of diazotization at 26°: A, run 13; B, run 17; C, run 19.

It is reasonable to assume that the nitrous acid–nitrosonium ion equilibrium measurements obtained in perchloric acid[18] can be extrapolated to concentrated sulfuric acid solutions used in the present work where spectrophotometric measurements are not feasible as pointed out earlier. The nitrosonium ion concentration can be calculated by use of the equation[15b]

$$\log (R^+/ROH) = pK_{R^+} - H_R \qquad (1)$$

where R^+ = concentration of nitrosonium ion, NO^+, ROH = concentration of molecular nitrous acid, HONO, and pK_{R+} refers to the reverse of equations 4 and 7; H_R is explained below. pK_{R+} for the nitrous acid–nitrosonium ion equilibrium has been evaluated as −8.11 (25°) by Deno and co-workers[14] from the data of Singer and Vamplew.[18a] The percentage of ROH, calculated from equation 1, is given in the last column of Table I. We have made the reasonable assumption that pK_{R+} and H_R are independent of the nature of the acid medium.

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(23) E. D. Hughes, C. K. Ingold and J. H. Ridd, *J. Chem. Soc.*, 88 (1958), and five previous papers.

Identification of NO^+ as the nitrosating carrier does not rest solely upon the physical evidence of the spectrophotometric investigation. The following kinetic analysis offers convincing support for the role of the nitrosonium ion.

The above considerations and the data in Table I indicate the following points that are relevant to the reaction mechanism: (1) the reaction is first order in unprotonated benzamide; and (2) the reaction in nitrosonium ion is first order as seen by dividing column 4 of Table I by the concentration of nitrosonium ion, at any given acidity, such as in runs 12–15 and 17–18.

If one assumes that the rate-determining step of the diazotization of benzamide is

$$\text{rate} = k_8(\text{benzamide})(\text{NO}^+) \qquad (2)$$

it is immediately apparent that the rate should be a function of the acidity function, H_R. The H_R acidity function is related to the Hammett acidity function, H_0, which has been extensively used for the elucidation of mechanisms of acid-catalyzed reactions.[24] The H_R acidity function has been defined by Deno[14,15b] as

$$H_R = pK_{R^+} + \log(\text{ROH})/(\text{R}^+) = -\log \frac{a_{H^+}}{a_{H_2O}} \times \frac{f_{ROH}}{f_{R^+}} \qquad (3)$$

which refers to the reverse of the equilibrium

$$\text{ROH} + \text{H}^+ \rightleftarrows \text{R}^+ + \text{H}_2\text{O} \qquad (4)$$

Furthermore, it has been shown that for reactions of the general form

$$\text{ROH} + \text{H}^+ \rightleftarrows \text{R}^+ + \text{H}_2\text{O} \quad \text{fast} \qquad (5)$$

$$\text{R}^+ + \text{B} \longrightarrow \text{products} \quad \text{rate-determining} \qquad (6)$$

a plot of the logarithm of the rate constant *versus* $-H_R$ will have a slope of unity if $f_{X^\ddagger}/f_{ROH}f_B = f_{R^+}/f_{ROH}$, where $X^\ddagger$ is the transition state for reaction path 6.[15a] The diazotization of benzamide in concentrated sulfuric acid can be written in a scheme formally analogous to eqs. 5 and 6

$$\text{HONO} + \text{H}^+ \overset{K_7}{\rightleftarrows} \text{NO}^+ + \text{H}_2\text{O} \quad \text{fast} \qquad (7)$$

$$\text{NO}^+ + \text{benzamide} \xrightarrow{k_8} \text{products} \quad \text{rate-determining} \qquad (8)$$

Therefore, if the assumption of the ratios of activity coefficients holds, one would expect a linear relation between $-H_R$ and log of a second-order rate constant. Such a relationship has been observed in the reaction of nitrous acid with formic acid in perchloric acid.[25] A slope of between 0.93 and 1.12 was observed, depending on the degree of correction for a side-reaction of formic acid.[14] It is therefore reasonable to expect that in this reaction of nitrous acid in sulfuric acid the same relationship may hold. Equation 8 then can be expressed in terms of the Brönsted rate equation, utilizing the equilibrium constant of equation 7, to yield

$$\mathrm{d}P/\mathrm{d}t = k_8K_7(\text{HONO})(\text{B})f_B f_{HONO}a_{H^+}/f_{X^\ddagger}a_{H_2O} \qquad (9)$$

If one assumes the equivalence of the activity coefficients given above, eq. 9 can be transformed with the use of eq. 3 to eq. 10

$$\mathrm{d}P/\mathrm{d}t = -\mathrm{d}((\text{B}) + (\text{BH}^+))/\mathrm{d}t = k_8K_7(\text{HONO})(\text{B})h_R \qquad (10)$$

The benzamide reaction is complicated by the equilibrium involving the protonation of benzamide.

$$\text{B} + \text{H}^+ \overset{K_{11}}{\rightleftarrows} \text{BH}^+ \qquad (11)$$

This equilibrium has been investigated by Edward.[20] The equilibrium constant can be expressed

$$K_{11} = (\text{BH}^+)/(\text{B})h_0 \qquad (12)$$

In the present experiments the decrease in the species BH^+ was measured spectrophotometrically leading to a pseudo-first order expression

$$k_{obs} = (-\mathrm{d}(\text{BH}^+)/\mathrm{d}t)(1/(\text{BH}^+)) \qquad (13)$$

Dividing eq. 10 by (BH^+), and substituting from eq. 12 yields

$$\frac{-1}{(\text{BH}^+)}\frac{\mathrm{d}((\text{B}) + (\text{BH}^+))}{\mathrm{d}t} = \frac{-1}{(\text{BH}^+)}\frac{\mathrm{d}((\text{BH}^+))}{\mathrm{d}t}\left(\frac{1}{K_{11}h_0} + 1\right) = k_8K_7(\text{HONO})\frac{(\text{B})}{(\text{BH}^+)}h_R \qquad (12a)$$

It follows that

$$k_{obs} = k_8K_7(\text{HONO})h_R/(K_{11}h_0 + 1) \qquad (14)$$

A new second-order rate constant, k', may be defined in terms of the reaction of unprotonated benzamide

$$k' = k_{obs}(K_{11}h_0 + 1)/(\text{HONO}) = k_8K_7h_R \qquad (15)$$

which predicts a linear relationship between log k' and $-H_R$ with slope 1. A plot of this kind is shown in Fig. 2. The data for this plot are in Table I. Equation 14 indicates that only at a given acidity will k_{obs} be proportional to the molecular concentration of nitrous acid. As discussed previously, this is found for those runs which were investigated as a function of nitrous acid concentration. In comparing rate constants at different acidities, changes of k_{obs} with nitrous acid concentration are not to be expected, since the two acidity functions h_R and h_0 respond differently to change in acidity.

The slope of the line in Fig. 2 containing data at six concentrations of sulfuric acid is 0.96. Considering the errors in interpolation, the errors due to volatility of nitrous acid and the possible non-equivalence of the activity coefficient ratio, the slope is in satisfactory accord with the prediction of equation 15. It is possible that the point at the highest acidity exhibits a negative deviation. This would be expected for a situation in which the concentration of the NO^+ ion is no longer negligible with respect to that of HONO.[26] Furthermore, it has been shown that the amount of decomposition is at a maximum when the concentrations of NO^+ and HONO are approximately equal,[18c] as they are in this case. Thus, the true k' would be higher than calculated here. It therefore may be concluded that the two pre-equilibria (eqs. 7 and 11) and the rate-determining step (eq. 8) postulated above are consistent with the kinetic data so that the correlation with the H_R acidity function provides confirmation for the role of NO^+ as the nitrosating agent.

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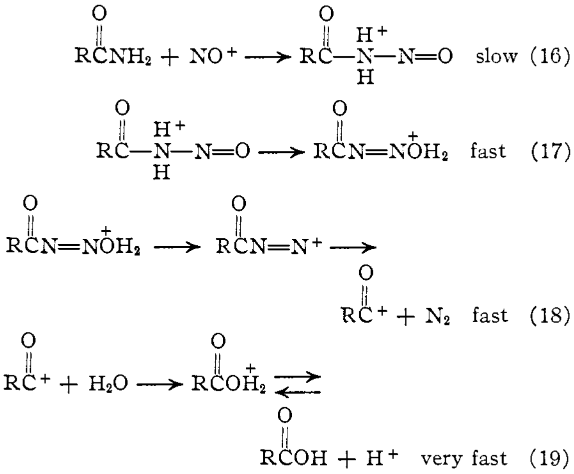
(24) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957).

(25) J. V. L. Longstaff and K. Singer, *J. Chem. Soc.*, 2604 (1954).

(26) R. W. Taft, Jr., N. C. Deno and P. S. Skell, *Ann. Rev. Phys. Chem.*, **9**, 305 (1958).

The kinetic data fail to yield information on the nature of the product of the slow step, or of any of the subsequent reactions that must occur to give the final products, benzoic acid and nitrogen gas. The following is based upon a slight modification of the amine reaction.[27]



$$R\overset{\overset{O}{\|}}{C}NH_2 + NO^+ \longrightarrow R\overset{\overset{O}{\|}}{C}-\underset{H}{\overset{H^+}{N}}-N{=}O \quad \text{slow} \quad (16)$$

$$R\overset{\overset{O}{\|}}{C}-\underset{H}{\overset{H^+}{N}}-N{=}O \longrightarrow R\overset{\overset{O}{\|}}{C}N{=}\overset{+}{N}OH_2 \quad \text{fast} \quad (17)$$

$$R\overset{\overset{O}{\|}}{C}N{=}\overset{+}{N}OH_2 \longrightarrow R\overset{\overset{O}{\|}}{C}N{=}N^+ \longrightarrow R\overset{\overset{O}{\|}}{C}^+ + N_2 \quad \text{fast} \quad (18)$$

$$R\overset{\overset{O}{\|}}{C}^+ + H_2O \longrightarrow R\overset{\overset{O}{\|}}{C}\overset{+}{O}H_2 \rightleftarrows R\overset{\overset{O}{\|}}{C}OH + H^+ \quad \text{very fast} \quad (19)$$

No claim is made that decomposition by other paths is impossible. For example, the protonated nitrosoamide produced in eq. 16 could cleave to yield the acylium ion and NH_2NO, the conjugate base of the proposed intermediate in the nitrosation of ammonia, which in acid solution will be protonated and rapidly undergo reaction to give nitrogen, water and a proton. Several possible paths exist in which an acylium ion would not be present as intermediate at all. For example, the protonated nitrosoamide could be attacked by water to produce carboxylic acid and NH_2NO directly. This reaction would be analogous to the attack of water on a protonated benzamide and thus one would expect a similarity of this reaction to the acid-catalyzed hydrolysis of benzamide, which would lead to a hydrolysis rate of comparable magnitude to that of diazotization. The observed rate constants for the diazotization and hydrolysis of benzamide are not strictly comparable because they are functions of different species. It is worthwhile to note that the observed rate constant of the diazotization of benzamide at 4.58 *M* sulfuric acid exceeds that of the hydrolysis by 1,060-fold, and at 7.45 *M* sulfuric acid by 7,780-fold. Furthermore, enough data are now available from Edward's work to permit the determination of the true second-order rate constant for hydrolysis, k_2, for comparison with that for diazotization, k_8. The latter can be evaluated through eq. 15, the logarithmic form of which yields a linear equation with an intercept equal to log k_8K_7. Using the slope of 0.96, one obtains from Fig. 2, log $k_8K_7 = -5.43$ (this assumes that no diazotization occurs at $H_R = 0$ due to HONO), from which k_8, the diazotization rate constant, is 479 l. mole^{-1} sec.$^{-1}$. The second-order rate constant for hydrolysis of benzamide, involving the attack of water on protonated benzamide, is derived from the equation

$$k_{obs} = k_2(H_3O^+)/(K + h_0) \qquad (20)$$

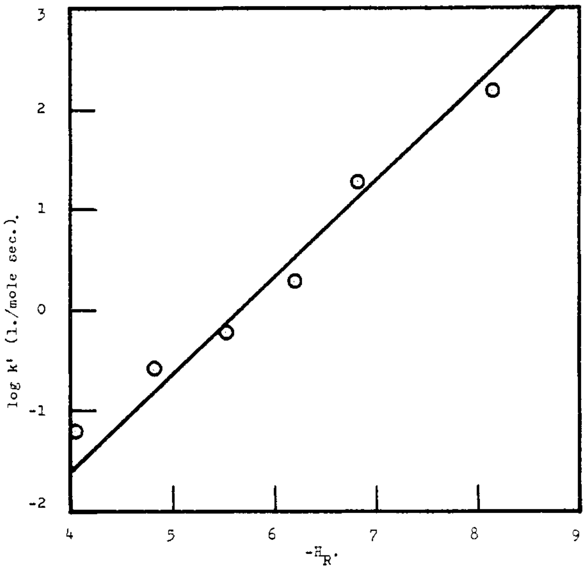


Fig. 2.—Correlation of the H_R acidity function with the diazotization rate constants.

where K is the reciprocal of K_{11} in eq. 11. The values of H_3O^+ were obtained by interpolation from the literature,[28] as were values of h_0 (see Table I); $k_2 = 1.95 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$. The large difference in rates of diazotization and hydrolysis is strikingly emphasized in the ratio of these two rate constants, $k_8/k_2 = 2.5 \times 10^7$. The reactivity of the nitrosonium ion may be compared to that of the nitrosating agent, NOCl, which has been proposed in a recent study in the diazotization of acetamide in hydrochloric acid.[29] These authors presume the slow step to be the attack of nitrosyl chloride on the nitrogen function of the amide. Nitrosyl chloride was found to be ineffective in the diazotization of arylamines, which was not the case with nitrosyl bromide or iodide.[23] By using more recent literature data to correct certain constants used in their work, the ratio of the two diazotization rate constants $k_{NO^+}/k_{NOCl} = 6000$. This value reflects the relative electrophilicity of the two agents.

It therefore seems reasonable to assume that an acylium ion is produced in this diazotization reaction just as a carbonium ion is produced in the diazotization of an amine, and that in both instances the formation of the positive species is facilitated by the formation of the stable nitrogen molecule. A recent investigation offering cryoscopic evidence for the instability of the benzoyl acylium ion in nearly anhydrous sulfuric acid indicates that either the first part of reaction 19 must be extremely rapid[30] or that removal of nitrogen and attack by water are simultaneous in the last step of eq. 18.

Oxygen Exchange.—The results of the determination of the oxygen exchange of benzamide-O^{18} during the diazotization reaction are shown in Table II.

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TABLE II

OXYGEN EXCHANGE DURING THE DIAZOTIZATION OF BENZAMIDE-O^{18}

Reaction, %	Atom per cent O^{18}
Unreacted	0.576[b]
Unreacted[a]	.550
50	.563
65	.558

[a] This sample was subjected to the entire procedure except that no sodium nitrite was introduced. The difference in the O^{18} content of this sample and the first sample indicates the small error due to isolation. [b] The O^{18} content of this labeled benzamide previously had been measured as 0.589 using the modified Doering and Dorfman pyrolysis.[31]

The data of Table II show no oxygen exchange during the diazotization of benzamide, within experimental error. The lack of oxygen exchange leads to no definite conclusion concerning the mechanistic pathway. In general, lack of exchange does not add much information to the mechanistic conclusions. For example, in the acid hydrolysis of benzamide, lack of exchange does not differentiate between an addition intermediate and the direct displacement by water. Again, in the present instance, the lack of oxygen exchange does not differentiate among a number of possibilities which include the paths mentioned above, although exchange would eliminate the proposed mechanism.

The use of benzamide-O^{18} thus does not differentiate between an addition intermediate and an acylium ion intermediate. The acyldiazonium ion is a species of such high instability that it must certainly react by an S_N1 mechanism. In other cases involving acid chloride hydrolyses and hydrolysis of esters in strong acids, the oxygen exchange criterion should be of more importance.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Hydrolysis of *p*-Nitrophenyl Acetate Catalyzed by *o*-Mercaptobenzoic Acid[1]

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The rate of the reaction of *p*-nitrophenyl acetate with *o*-mercaptobenzoic acid in approximately neutral solution at 25° was determined both by spectrophotometric measurement of the liberated *p*-nitrophenol and by iodine titration of the remaining *o*-mercaptobenzoic acid. The results indicate that the dianion of *o*-mercaptobenzoic acid is the effective species in reaction with *p*-nitrophenyl acetate. The second-order rate constants obtained by the two methods are considered consistent with one another. The initial product of the reaction is thioaspirin; thioaspirin hydrolyzes in neutral solution but at a rate slower than its formation. The hydrolysis of thioaspirin is postulated to proceed *via* intramolecular catalysis aided by the *o*-carboxylate ion, analogously to the aspirin hydrolysis. The two steps: (a) conversion of *p*-nitrophenyl acetate to thioaspirin and (b) hydrolysis of thioaspirin to acetate ion and *o*-mercaptobenzoic acid constitute an over-all catalytic process (brought about by the reagent *o*-mercaptobenzoic acid), the rate-determining step being the second step. The functional groups involved, the *pK*'s of these groups and the over-all *p*H dependence of this catalytic process parallel those postulated for the action of the enzyme, papain, and reproduce in part those postulated for the action of the enzyme, ficin.

Introduction

In recent years increasing attention has been paid to the study of the mechanism of ester hydrolysis in the presence of nucleophiles other than hydroxide ion. For example it has been shown that imidazole and other tertiary amines catalyze the hydrolysis of certain esters.[2,3] The reasons for this interest in nucleophilic catalysis of ester hydrolysis are twofold: (1) the elucidation of the reaction mechanism in the system under investigation and (2) the possibility that such studies will aid our understanding of more complex catalytic processes, *e.g.*, enzymatic catalysis.

It has been postulated that the efficiency of enzymatic processes may be due to the combination of a number of factors including (a) the fixation of the substrate at the enzymatic catalytic site by specific adsorption[4-6]; (b) the use of more than one functional group giving rise to a concerted process; and (c) the use of coupled reactions, that is, interaction of the catalytic groups of the enzyme with the substrate in a consecutive fashion.[7,8] It has been shown that certain kinds of nucleophilic catalysis in simple organic systems approximate the processes mentioned above. A number of examples of intramolecular catalysis approximate the conditions set forth in (a)[4-6] although the fixation in this instance is not due to adsorption. A classical example of (b) is the bifunctional action of 2-hydroxypyridine in the mutarotation of tetramethylglucose.[9] The consecutive processes involved in the imidazole-catalyzed hydrolysis of *p*-nitrophenyl acetate[1,3] and the spontaneous hydrolysis of aspirin[10] exemplify point (c) in simple systems.

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