The Intramolecular Participation of the Pyridyl Group in the Acid Hydrolysis of Dinitropyridyl Dipeptides

Angelo Signor and Emilio Bordignon

Centro Nazionale di Chimica delle Macromolecole and the Istituto di Chimica Organica, Universita' di Padova, Padova, Italy

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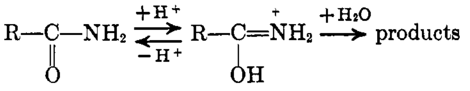
Measurements are reported on the kinetics of hydrolysis of dinitro-2-pyridylalanylglycine in solutions of hydrochloric acid up to 10 *M;* acid-catalyzed hydrolysis of the amide bond occurs when the acid concentration is 2 *M* or higher and the rate of hydrolysis is accurately proportional to H_0; classification of the reaction according to Bunnett gives an ω value of zero and this indicates that water does not participate in transformation of SH^+ to a transition state. Furthermore the kinetic results for other dinitro-2-pyridyl dipeptides show that the catalytic effect is a general phenomenon. On the other hand, the hydrolysis of dinitro-2-pyridylalanylglycine is about 10^2–10^3 times as fast as the hydrolyses of dinitrophenylalanylglycine and of dinitro-4-pyridylalanylglycine. These results suggest that the acid-catalyzed hydrolysis of dinitro-2-pyridyl dipeptides is an electrophilic–nucleophilic catalyzed reaction involving a cyclic acylpyridinium intermediate.

It is well known that the rates of the acid-catalyzed hydrolysis of several aliphatic and aromatic amides go through a maximum as the concentration of acid is increased.[1] These results may be explained in terms of the generally accepted mechanism for the hydrolysis of amides, in which the rate-determining step is the attack of a water molecule on the conjugate acid of the amide.

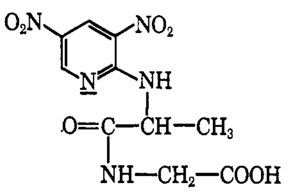

$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NH_2} \underset{-H^+}{\overset{+H^+}{\rightleftarrows}} \mathrm{R{-}\underset{\underset{OH}{|}}{C}{=}\overset{+}{N}H_2} \xrightarrow{+H_2O} \text{products}$$
(1)

Amides are strong enough bases to be appreciably protonated in 3–6 *M* mineral acids. Below the concentration for maximum rate, the effect of increasing acid strength is chiefly to increase the concentration of the protonated intermediate; above the concentration for maximum rate the effect is chiefly to decrease the activity of water.

Many studies have been made on the hydrolysis of peptides and proteins in aqueous acids, but there appear to have been no attempts to discover whether the rates pass through a maximum as the concentration of acid is increased. Edward and Meacock[2] show that the rate of hydrolysis of acetylglycine was maximal in about 5 *M* HCl at 61°; no maximum was found, however, in the rate of hydrolysis of piperazine-2,5-dione or of gelatin as the concentration of hydrochloric acid was increased to 10 *M*. The absence of a maximum rate in this range of acid concentration indicates a pK_a of the peptide linkage below −4.

There are, moreover, a whole host of reactions in which one carboxylic acid derivative is converted to free acid by the catalytic action of a nucleophile. Nucleophilic catalysis of organic reactions is a general phenomenon; substances that can participate in nucleophilic catalysis of the hydrolysis of carboxylic acid derivatives include carboxylate ion, phosphate ion, or tertiary amines. Furthermore, sterically favorable intramolecular reactions proceed more rapidly than the corresponding intermolecular processes; in intramolecular reactions catalysis should be favored and should therefore be of special importance.

It was our desire in the present study to determine not only if it is possible that a pyridine group as an intramolecular participant can bring the nucleophilic displacement of amine from amide bonds, but to determine the effectiveness of the pyridine group in the intramolecular catalysis of aliphatic amide hydrolysis. The work described here constitutes a study of neighboring-group participation through the comparison of acid hydrolyses of dinitro-2-pyridylalanylglycine (I) and dinitrophenylalanylglycine (II).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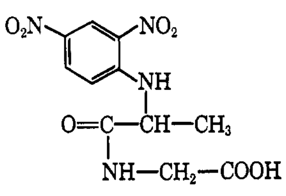
II

Experimental Section

Materials.—Fluka CHR[3] peptides were employed without further purification; the peptides were all tested for purity by elementary analysis and by chromatography on paper in at least two different solvent systems. Dinitrophenylalanylglycine was prepared from alanylglycine and dinitrofluorobenzene according to Sanger's procedure[4]; the dinitropyridyl dipeptides used in this investigation were described in a previous paper.[5]

Procedure.—Approximately 2×10^{-3} *M* solutions of substrates were prepared in water and then diluted to 2 vol. with hydrochloric acid. The resulting mixture was kept in a glass-stoppered vessel in a thermostated water bath whose temperature was held constant to ±0.05°, and 1-ml. portions were withdrawn at intervals for analysis. The extent of hydrolysis was measured by analysis of samples of the neutralized reaction solution according to the ninhydrin procedure of Moore and Stein.[6]

Portions of each hydrolysis mixture were subjected to complete hydrolysis by heating for 5 hr. at 60°; at this temperature all dinitropyridyl amino acids are stable,[5] and the ninhydrin reaction is relative only to the C-terminal amino acid of the dipeptide. Optical density measurements were carried out with a Beckman DU spectrophotometer at a wave length of 570 mμ.

The procedure described previously was used for all runs except for the comparative hydrolysis of 2,4-dinitrophenylalanylglycine and 3,5-dinitro-2-pyridylalanylglycine performed at 60° in constant-boiling HCl with 20% formic acid added.

pK_a Determination.—The ionization constants of dinitro-2-pyridylalanylglycine and dinitro-2-pyridylalanine were determined by a photometric method. All spectral measurements were made with a Model DU Beckman spectrophotometer in sulfuric acid solution at 25°; temperature control was main-

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[1] V. K. Krieble and K. A. Holst, *J. Am. Chem. Soc.*, **60**, 2976 (1938). J. T. Edward, H. P. Hutchinson, and S .C. Meacock, *J. Chem. Soc.*, 2520 (1955).

[2] J. T. Edward and S. C. Meacock, *ibid.*, 2000 (1957).

[3] Chromatographically pure.

[4] F. Sanger, *Biochem. J.*, **39**, 507 (1945).

[5] A. Signor, L. Biondi, M. Terbojevich, and P. Pajetta, *Gazz. chim. ital.*, **94**, 619 (1964).

[6] D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

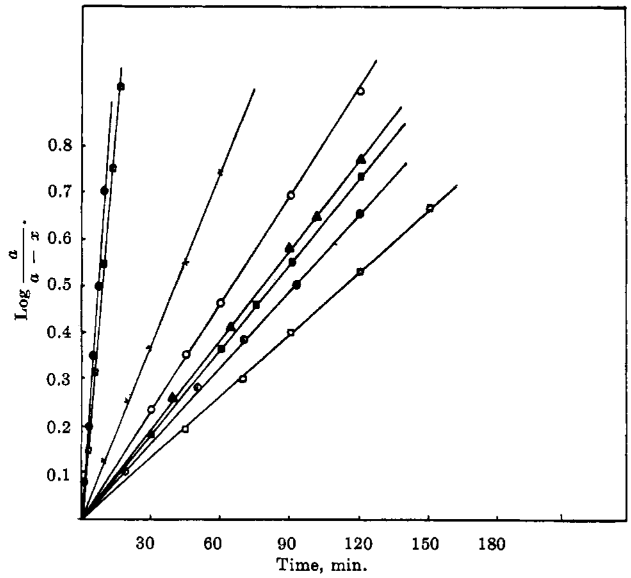

Figure 1.—Kinetics of hydrolysis of representative dinitropyridyl dipeptides in 6 N HCl at 60° plotted according to the first-order law: ●, DNPyr-Ala-Gly; □, DNPyr-Ala-Ala; ×, DNPyr-Ala-Phe; ○, DNPyr-Leu-Leu; ▲, DNPyr-Gly-Gly; ■, DNPyr-Pro-Gly; ⊙, DNPyr-Gly-Ser; ⊡, DNPyr-Gly-Ala.

tained in the cell compartment and in all cases the solution to be measured was kept at 25 ± 0.1° until immediately before use. Duplicate readings were made on all samples, and, if agreement was not better than 0.5%, an average of three or more readings was used. The readings were taken against a blank containing the same medium as that used in the cell containing the pyridine derivative. Because of the facile hydrolysis of dinitro-2-pyridylalanylglycine in concentrated acid solutions, the optical density for these solutions has been obtained by extrapolation to time zero of the photometric measurements as a function of time. As a check on gross errors the isosbestic points for both compounds were determined, and the absorbancies at five wave lengths that were 1 mμ apart and passed through the isosbestic point were measured along with the absorbancies at the wave length selected for the equilibrium measurements (330 mμ). The experimental values for the two compounds were found to be in close agreement and are −2.80 for dinitro-2-pyridylalanine and −3.20 for dinitro-2-pyridylalanylglycine.

Results

Peptide Bond Hydrolysis.—In order to establish first-order dependence of the rate of hydrolysis on substrate concentration under the conditions of hydrolysis employed throughout the course of this investigation, apparent rate constants between successive points of observation for the hydrolysis of dinitro-2-pyridylalanylglycine in 6 N HCl were calculated from appropriate optical density measurements. The results conform to the kinetics of a pseudo-first-order reaction at constant acid concentration. The kinetic results for various dinitropyridyl dipeptides showed that the reactions were first order in amide throughout; typical first-order plots are shown in Figure 1.

The first-order rate constants k_{obsd} calculated by the method of least squares are shown in Table I together with the relative rates of hydrolysis. From Table I it is seen that the rates of hydrolysis of dinitro-2-pyridylalanyl-X are in each instance higher than those of dinitro-2-pyridylglycyl-X; furthermore, no appreciable difference in rate constants is observed between dinitro-2-pyridylglycylglycine and dinitro-2-pyridylleucylleucine.

TABLE I

RELATIVE RATES OF HYDROLYSIS OF DINITROPYRIDYL DIPEPTIDES[a]

Compd.[b]	k_{obsd}, min.$^{-1}$	Relative rate of hydrolysis
DNPyr-2-Gly-Gly	0.015	1.00
DNPyr-2-Gly-Ala	0.009	0.60
DNPyr-2-Pro-Gly	0.014	0.93
DNPyr-2-Gly-Ser	0.015	1.00
DNPyr-2-Leu-Leu	0.019	1.25
DNPyr-2-Ala-Phe	0.035	2.20
DNPyr-2 Ala-Ala	0.140	9.30
DNPyr-2-Ala-Gly	0.170	11.00

[a] In 6 N HCl at 60 ± 0.05°. [b] The significance of symbols is DNPyr = dinitropyridyl, Gly = glycine, Ala = alanine, Pro = proline, Ser = serine, Leu = leucine, and Phe = phenylalanine.

The significance of these results in relation to the more general problems of acid hydrolysis of free dipeptides is of particular interest: Synge[7] and Harris, *et al.*,[8] show that, when the rate constants for the acid hydrolysis of free dipeptides are expressed on a common scale (glycylglycine being taken as 1), valyl and leucyl peptides are the most resistant to acid hydrolysis while glycyl and seryl peptides are significantly more labile. It is reasonable, as a first approximation, to assume that stability to hydrolysis of peptide bond in dinitropyridyl dipeptides is modified by the presence of the masking group at the N-terminal end.

In order to determine how powerful catalysis by an intramolecular pyridine group could be, we have investigated the hydrolysis of 3,5-dinitro-2-pyridylalanylglycine in comparison with 2,4-dinitrophenylalanylglycine. In Table II is shown a summary of the kinetic results.

TABLE II

COMPARATIVE ACID HYDROLYSIS OF DINITRO-2-PYRIDYLALANYLGLYCINE (I) AND DINITROPHENYLALANYLGLYCINE (II)[a]

HCl concn., M	$k_{\text{I}} \times 10^2$, min.$^{-1}$	$k_{\text{II}} \times 10^4$, min.$^{-1}$	$\frac{k_{\text{I}}}{k_{\text{II}}}$
1.0	0.35	0.82	42.8
2.0	1.20	1.80	66.6
4.0	6.50	4.00	162.0
6.0	40.00	7.50	534.0

[a] At 60 ± 0.05°. The experiments were carried out in the presence of formic acid (20%) owing to the small solubility of dinitrophenylalanylglycine in aqueous hydrochloric acid.

A chromatographic examination of the reaction products showed that the two processes are analogous.

$$\text{DNPyr-2-Ala-Gly} \xrightarrow{\text{H}^+} \text{DNPyr-2-Ala} + \text{Gly} \quad (2)$$

$$\text{DNP-Ala-Gly} \xrightarrow{\text{H}^+} \text{DNP-Ala} + \text{Gly} \quad (3)$$

A comparison of rate constants of hydrolysis for the two substrates is significant in considering the behavior of the pyridine derivative; the hydrolysis of dinitro-2-pyridylalanylglycine is 10^2–10^3 times as fast as that of dinitrophenylalanylglycine with a comparable concentration of hydrogen ion. On the other hand, the rate of hydrolysis of dinitro-4-pyridylalanylglycine at 60° (k_{obsd} = 0.30 × 10^{-3} min.$^{-1}$ in 6 N HCl with 20%

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(7) R. L. M. Synge, *Biochem. J.*, **39**, 351 (1945).

(8) J. I. Harris, R. D. Cole, and N. G. Pon, *ibid.*, **62**, 154 (1956).

formic acid added) is even smaller than that of dinitrophenylalanylglycine.

Hydrogen Ion Dependence.—Table III gives data on the acid-catalyzed hydrolysis of dinitro-2-pyridylalanylglycine in aqueous solutions at 25°. For all runs listed amide concentration was in the range 0.0005–0.001 *M*. The most striking point about the data of Table III is the lack of correlation between rate and concentration of hydrogen ion; for example, an increase in hydrochloric acid concentration of from 3.00 to 6.00 *M* causes the value of k_{obsd} to increase by almost 16-fold. If instead of the molar concentration of hydrogen ion one considers the acidity of the solutions as measured by H_0, the observed variations in the rate are entirely sensible. The values of H_0 are obtained from the data of Bell, Dowding, and Noble[9]; Figure 2 gives a plot of log k_{obsd} *vs.* $-H_0$. The solid line in this figure is drawn with a slope of 1.00, the theoretical slope for first-order dependence on the acidity as measured by H_0; it can be seen that the experimental data for all the solutions fall very close to a line of this slope. As Hammett[10] has pointed out, this correlation is to be expected if the hydrolysis mechanism involves a first-order rate-determining reaction of the conjugate acid of dinitro-2-pyridylalanylglycine.

TABLE III

RATES OF HYDROLYSIS OF DINITRO-2-PYRIDYLALANYLGLYCINE[a]

HCl concn., *M*	$-H_0$	$k_{obsd} \times 10^4$, min.$^{-1}$	Log k_{obsd} + 4
1.48	0.35	0.92	−0.036
2.11	0.59	1.70	0.230
3.05	0.92	3.80	0.579
3.97	1.30	10.80	1.033
4.45	1.45	12.40	1.093
5.00	1.62	18.00	1.255
5.86	2.03	60.00	1.778
8.11	2.89	280.00	2.450
10.04	3.60	1580.00	3.200

[a] In hydrochloric acid solutions at 25 ± 0.05°.

$$\left.\begin{array}{ll} S + H^+ \rightleftarrows SH^+ & \text{equilibrium} \\ SH^+ \longrightarrow M^+ & \text{rate determining} \\ M^+ + H_2O \longrightarrow \text{products} + H^+ & \text{fast} \end{array}\right\} \quad \text{A-1}$$

Using Ingold's terminology,[11,12] the notation A-1 denotes an acid reaction characterized by an essentially unimolecular rate step, regardless of the over-all kinetics. Applying the Brønsted equation for the effects of changes in the medium to the rate-determining step

$$\text{rate} = k'C_{SH^+}\frac{f_{SH^+}}{f_{M^+}} = kC_S\, a_{H^+}\frac{f_S}{f_{M^+}}$$

where the constant *k* includes the rate constant *k'* and the equilibrium constant.

In considering the dependence of reaction rate on HCl concentration, it is important to recognize separately the dependence of the equilibrium, $S + H^+ \rightleftarrows SH^+$, and of the rate of reaction of the protonated substrate, $SH^+ \rightarrow$ products, on acid concentration. For that we have determined experimentally the variation of $[SH^+]/[S]$ on HCl concentration for dinitro-2-pyridylalanylglycine; in Table IV values of $[SH^+]/[S]$ as a function of HCl concentration are reported both for dinitro-2-pyridylalanylglycine and for dinitro-2-pyridylalanine.

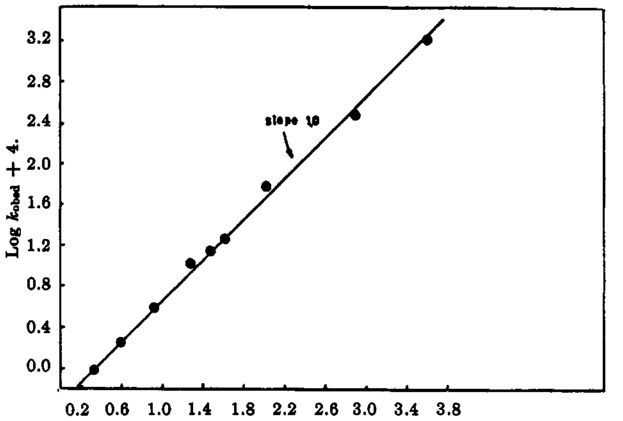

Figure 2.—Rate of acid-catalyzed hydrolysis of dinitro-2-pyridylalanylglycine *vs.* H_0 in HCl at 25°.

TABLE IV

EQUILIBRIUM PROTONATION OF DINITRO-2-PYRIDYLALANYLGLYCINE (I) AND OF DINITRO-2-PYRIDYLALANINE AS A FUNCTION OF HYDROCHLORIC ACID CONCENTRATION[a]

HCl concn.,	[S]/[SH+]	
M	DNPyr-2-Ala-Gly	DNPyr-2-Ala
5.52	0.042	0.174
6.02	0.079	0.282
6.90	0.188	0.563
7.62	0.407	0.832
8.41	0.617	1.480
9.15	1.111	2.300
9.75	2.040	3.990
10.58	4.060	...
11.35	8.500	...

[a] The experiments were carried out at 25°.

Temperature Dependence.—The rates of hydrolysis of dinitro-2-pyridylalanylglycine were measured at 25, 30, 35, 45, 52, and 60 ± 0.05° in 6 *N* HCl. The rate constants derived from these experiments are summarized in Table V together with the temperatures used in each case.

TABLE V

RATE CONSTANTS OF HYDROLYSIS OF DINITRO-2-PYRIDYLALANYLGLYCINE AT VARIOUS TEMPERATURES[a]

Temp., °K.	$1/T \times 10^3$	Log k_{obsd}
298	3.356	−2.18
303	3.300	−1.95
308	3.246	−1.72
318	3.144	−1.30
325	3.076	−1.02
333	3.003	−0.72

[a] The experiments were carried out in 6 *N* HCl.

The heat of activation, ΔH^*, was calculated from the activation energy E_a by means of the relationship $\Delta H^* = E_a - RT$ using a mean temperature *T* of 318°K. The frequency factor *A* was used to calculate the entropy of activation ΔS^* using the following equation.

$$A = (ekT/h)\exp(\Delta S^*/R) \qquad (4)$$

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[9] R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

[10] L. P. Hammett, *Chem. Rev.*, **16**, 67 (1935).

[11] J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

[12] S. C. Datta, J. N. E. Day, and C. K. Ingold, *J. Chem. Soc.*, **838** (1939).

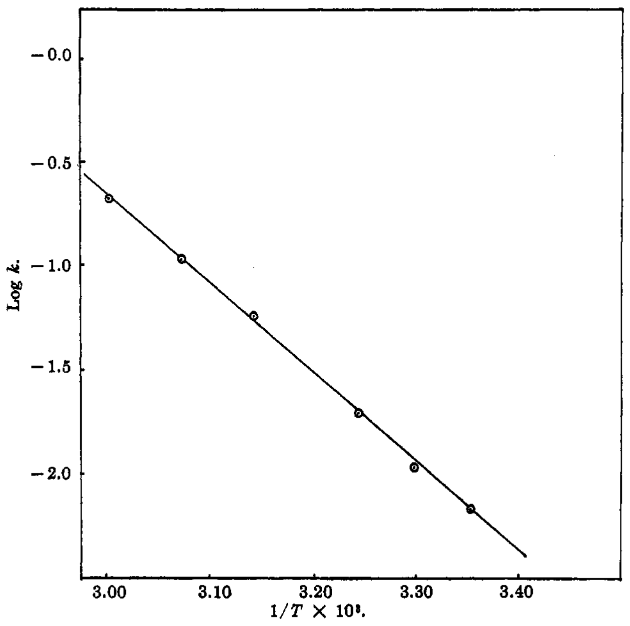


Figure 3.—Log k against $1/T$ for dinitro-2-pyridylalanylglycine at 25, 30, 35, 45, 52, and 60 ± 0.05° in 6 N HCl.

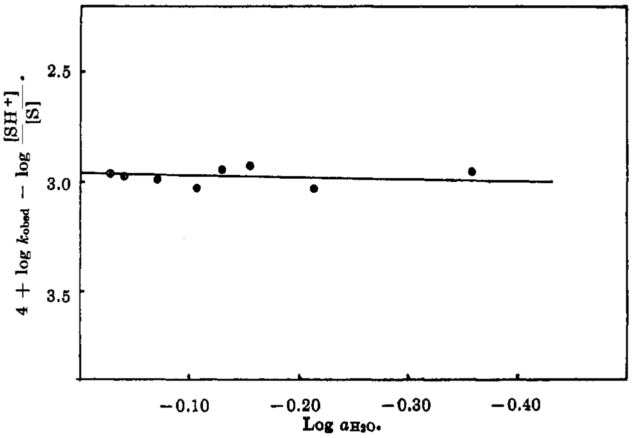


Figure 4.—Hydrolysis of dinitro-2-pyridylalanylglycine in hydrochloric acid solutions; plot of {log k_{obsd} − log([SH$^+$]/[S]$_{st}$} against log a_{H_2O}. The slope ω is 0.00 − *[S]$_{st}$ = [S] + [SH$^+$].

The free energy of activation ΔG^* was obtained from $\Delta H^* - T\Delta S^*$ using the mean temperature T of 318°K. In Figure 3 the Arrhenius curve for the hydrolysis of dinitro-2-pyridylalanylglycine has been drawn using all the data in Table V. The values are $\Delta H^* = +18.4$ kcal., $\Delta G^* = +20.6$ kcal., and $\Delta S^* = -7.00$ e.u.

Discussion

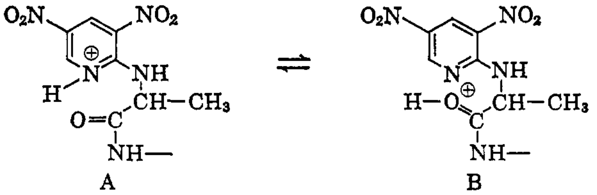
Acid-catalyzed reactions have generally been classified in one or another of two categories defined by Zucker and Hammett[13]; reactions which gave linear plots of log k_{obsd} *vs.* $-H_0$ formed the one category, and those which gave linear plots of log k_{obsd} *vs.* log [HX] constituted the other. Recently Bunnett[14] observed that for most acid-catalyzed reactions plots of (log $k_{obsd} + H_0$) *vs.* log a_{H_2O} are linear or approximately so. The slope in such a plot constitutes a parameter, called ω, which describes the manner in which the particular reaction responds to catalysis by strong mineral acids. Rather than being assigned to one set category or another, reactions are classified according to their ω values; reactions which in the Zucker–Hammett treatment give linear plots of log k_{obsd} *vs.* $-H_0$ with slope unity have ω of zero, while slopes slightly greater than unity correspond to small negative ω values. In other words ω becomes virtually the kinetic order in water of the transformation of protonated substrate SH$^+$ to transition state; empirically reactions in which transformation of SH$^+$ to transition state requires no water are associated with ω values of zero to −2.5, while reactions in which water acts as a nucleophile in the rate-determining step are associated with ω values of 1.2–3.3. Furthermore, plots of (log k_{obsd} − log [HX]) against log a_{H_2O} might also be linear; the slope in such a plot is taken to define another parameter ω^*, which is an alternative representation of the response of the reaction to catalysis by strong acids. These linear relationships suggest that the activity of water may be a fundamental variable in these systems.

As previously seen, the chief feature of the hydrolysis of normal amides in strongly acid aqueous solutions is a rate maximum and the approximate dependence of the rate on the acid concentration up to the position of the maximum; a plot of the new type for a reaction (acetylglycine hydrolysis) which passes through a rate maximum gives an experimental ω value of +1.41. A tendency for like reactions to have like ω values can be observed; thus ω is about 1–2.5 for carboxylic amide hydrolyses and about 4–6 for carboxylic ester hydrolyses. Divergences from typical values can sometimes be associated with differences in mechanism; for example, ω for hydrolyses of three pyridinecarboxamides are unusually high, indicating a mechanism different from hydrolyses of benzamide or acetamide. In order to determine the ω value for the hydrolysis of protonated I, we have plotted {log k_{obsd} − log ([SH$^+$]/[S]$_{st}$)} against log a_{H_2O} (Figure 4); the ω value is than computed objectively from the experimental data with use of log a_{H_2O} values from the literature.[14a] We have also obtained the ω^* value by plotting (log k_{obsd} − log [HCl]) against log a_{H_2O} (Figure 5).

According to Bunnett,[15] an extreme interpretation of ω^* value would be that it represents the number of water molecules of change of hydration between reactants and transition states, and that ω represents the same quantity on an adjusted scale. Therefore the observed values (least squares) of $\omega^* = -6.37$ and $\omega = 0.00$ strongly indicate that water does not participate in the transformation of SH$^+$ to transition state.

Figure 4 clearly shows that in the hydrolysis of dinitro-2-pyridylalanylglycine the rate of glycine liberation is proportional to concentration of protonated I; a complication, however, is that two isomeric forms of monoprotonated I need to be taken into account.

The ω values obtained as described above probably represent the effect of acid concentration on the A ⇄ B equilibrium.



A B

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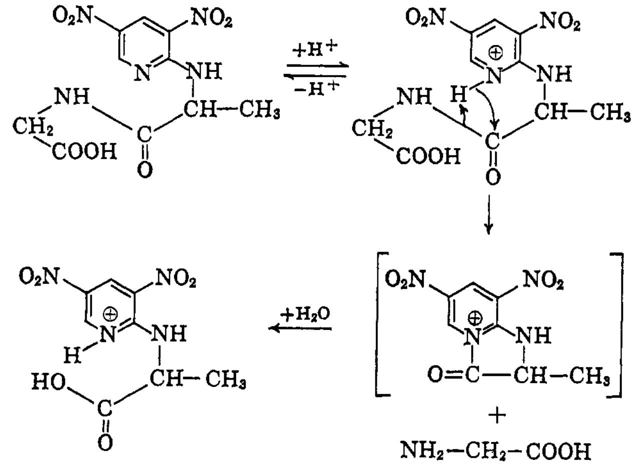
[13] L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

[14] (a) J. F. Bunnett, *ibid.*, **83**, 4956 (1961); (b) *ibid.*, **83**, 4968 (1961).

[15] J. F. Bunnett, *ibid.*, **83**, 4973 (1961); 4978 (1961).

On the other hand, the concept that catalysis solely by a nucleophile or by an electrophile can be surpassed in efficiency by the concerted catalysis of a nucleophile and an electrophile has received much attention in recent years. For example the amide of γ-(4-imidazolyl)butyric acid is hydrolyzed at a rate which indicates that the imidazolyl group participates in the reaction in its protonated form.[16] The specific rate for the participation of protonated imidazolyl group in the hydrolysis of γ-(4-imidazolyl)butyramide is greater than that of the participation of the imidazolyl group in the hydrolysis of the corresponding ester. These results lend credence to the concerted electrophilic-nucleophilic mechanism proposed for the intramolecular catalysis of amide hydrolysis.

Therefore, we strongly favor the proposition that A is the form reactive in hydrolysis and that pyridinium ion performs both functions of a bifunctional catalyst, attacking the carbonyl carbon of the amide and simultaneously donating a proton to the departing glycine molecule, with the formation of a cyclic acylpyridinium ion. The water molecule then adds in a following fast reaction. Although the reaction involving proton transfer in a fast pre-equilibrium followed by reaction of the conjugate base with the protonated substrate in the rate-determining step is kinetically a general acid catalysis, we think that mechanistically it is not a general acid catalysis at all but rather a electrophilic-nucleophilic catalysis.



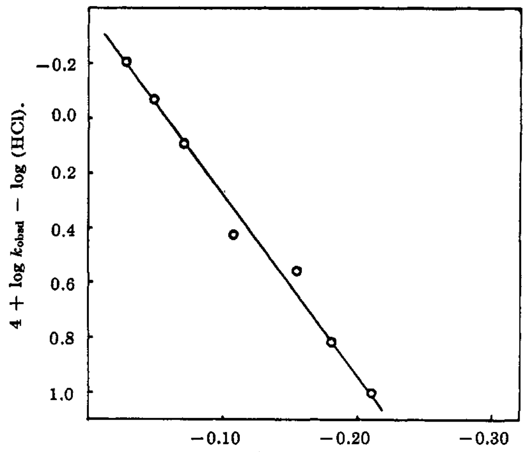


Figure 5.—Hydrolysis of dinitro-2-pyridylalanylglycine in hydrochloric acid solutions; plot of (log k_{obsd} − log [HCl]) against log a_{H_2O}. The slope ω^* is −6.37.

A comparison of rate constants of hydrolysis of dinitro-2-pyridylalanylglycine (I) and dinitro-4-pyridylalanylglycine is instructive in considering the extraordinary behavior of I; the rate of hydrolysis of dinitro-4-pyridylalanylglycine is even smaller than that of dinitrophenylalanylglycine (II), indicating a neighboring-group participation in the case of I.

Further evidence for a favored intramolecular process for the acid hydrolysis of I is provided by the small, negative entropy of activation.[17]

Acknowledgment.—The authors wish to thank Professor E. Scoffone and D. U. Miotti for helpful discussion and Mr. E. De Menego for his technical assistance.

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[16] T. C. Bruice and J. M. Sturtevant, *J. Am. Chem. Soc.*, **81**, 2860 (1959).

[17] M. L. Bender and M. C. Neveu, *ibid.*, **80**, 5388 (1958).

The Synthesis and Reactions of 1-(Dimethylamino)-3-phenyloxindole

Robert F. Meyer

Research Division, Parke, Davis and Company, Ann Arbor, Michigan

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The reaction of α-chlorodiphenylacetyl chloride with 1,1-dimethylhydrazine was found to give 1-(dimethylamino)-3-phenyloxindole in high yield under very mild conditions. A mechanism involving an α-lactam intermediate was proposed. The title compound was subjected to various reactions, mainly substitutions at the 3 position and variations of the carbonyl function.

In recent years there has been in increasing interest in reactions of α-haloamides which culminated in the isolation of the first α-lactams by Baumgarten[1] and Sheehan.[2] Sarel[3] studied the sodamide-promoted rearrangement of α-chloro-α,α-diphenylacetanilide to afford mainly N-phenyl-N-benzhydrylurea. Earlier, Sheehan[4] investigated in detail the reaction of α-chloro-α,α-diphenylacetanilide with sodium hydride and identified "three compounds of the oxindole and indoxyl type."

The reaction of α-chlorodiphenylacetyl chloride with acylhydrazines is reported to give oxadiazinones.[5] Bird[6] obtained a diazetidinone by reaction of α-

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