filtered, washed, dried and weighed, following the procedure described by Iddles.[12] The results are included in Table III.

Three of the 2,4-dinitrophenylhydrazones are new: (1) 2,4-dinitrophenylhydrazone of *p*-carbethoxybenzaldehyde, m.p. 248–249° dec. *Anal.* Calcd. for $C_{16}H_{14}N_4O_6$: C, 53.6; H, 3.94; N, 15.6. Found: C, 53.61; H, 3.93; N, 15.37. (2) Bis-2,4-dinitrophenylhydrazone of fumaric dialdehyde, m.p. 260° dec. *Anal.* Calcd. for $C_{16}H_{12}N_8O_8$: C, 43.2; H, 2.80; N, 25.2. Found: C, 43.90; H, 2.76; N, 22.7. (3) 2,4-Dinitrophenylhydrazone of cyclobutanecarboxaldehyde, m.p. 155–156°. *Anal.* Calcd. for $C_{11}H_{11}N_4O_4$: C, 50.1; H, 4.2; N, 21.2. Found: C, 50.28; H, 4.25; N, 21.27.

(12) H. A. Iddles, A. W. Low, B. D. Rosen and R. T. Hart, *Anal. Ed.*, **11**, 103 (1939).

LAFAYETTE, IND.

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

Intramolecular Catalysis of Hydrolytic Reactions. II. The Hydrolysis of Phthalamic Acid[1,2]

BY MYRON L. BENDER, YUAN-LANG CHOW AND FRANK CHLOUPEK

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The hydrolysis of phthalamic acid in aqueous solution exhibits kinetic dependence on the undissociated phthalamic acid and independence of external hydrogen ion from *p*H 1 to 5. At *p*H 3 the hydrolysis of phthalamic acid is about 10^5 faster than the hydrolysis of benzamide and about 10^6 faster than the hydrolysis of *o*-nitrobenzamide. On the other hand the hydrolysis of terephthalamic acid is somewhat slower than that of benzamide. The large rate enhancements in the former case suggest that the *o*-carboxylic acid group does not exert a substituent effect but rather catalyzes the amide hydrolysis by a direct intramolecular process. It is suggested that this process is an electrophilic–nucleophilic catalyzed reaction involving the intermediate formation of phthalic anhydride. A tracer experiment involving the hydrolysis of phthalamic acid-*carboxamide*-C^{13} in H_2O^{18} provides indirect evidence for the formation of a symmetrical phthalic anhydride intermediate. The hydrolysis of phthalamic acid in concentrated hydrochloric acid exhibits a rate maximum and appears to involve the direct attack of water on the protonated amide; apparently the undissociated carboxylic acid group cannot function as a nucleophile toward a protonated amide group as effectively as the carboxylate ion can.

Introduction

Recently nucleophilic catalysis[3] of ester hydrolysis has been demonstrated in the hydrolyses of *p*-nitrophenyl acetate, 2,4-dinitrophenyl acetate, phenyl acetate, ethyl thiolacetate and methyl pyrrolidylacetylsalicylate hydrochloride using the nucleophiles pyridine, 3- and 4-picoline, trimethylamine, imidazole, N-methylimidazole, a number of 4,5-substituted imidazoles, quinoline and acetate ion.[4–7]

Investigations of intramolecular catalysis have now been initiated.[2] The purpose of these investigations is to compare the kinds and effectiveness of intramolecular and intermolecular catalysis. Intramolecular catalysis implies that there are groups attached to a molecule that can catalyze the reactions of other groups. This interpretation immediately excludes consideration of hydronium ion and hydroxide ion as intramolecular catalysts (except for certain ion exchange resins) and focuses attention on general (Brönsted) catalysts.

The earlier experiments described above suggested that in favorable systems nucleophilic catalysis of the hydrolysis of carboxylic acid derivatives can occur. It was then thought feasible to investigate the possibility of nucleophilic and/or electrophilic catalysis in intramolecular cases where steric factors would favor such processes. Much work has been done on anchimeric or synartetic assistance to the solvolysis at saturated carbon atoms.[8] The present research is an extrapolation of such intramolecularly-assisted reactions to the hydrolysis of carboxylic acid derivatives.

Leach and Lindley observed that the hydrolysis of two aliphatic amides is subject to what they have called an internal mechanism.[9] They determined the kinetics of the hydrolysis of the amide links of glycyl-L-asparagine and L-leucyl-L-asparagine in aqueous solution from *p*H 1.2 to 3.5. Each reaction was first order in organic reactant with an undissociated carboxyl group and was independent of the external hydrogen ion concentration over this *p*H range. These authors concluded that the first-order character of the reactions, the independence of the external hydrogen ion concentration and the small, negative entropies of activation were consistent with an internal mechanism of hydrolysis involving an (internal) proton transfer from the un-ionized carboxyl group at one end of the molecule to the amide group at the other end. It was postulated that the peptides exist in solution in a six-membered cyclic hydrogen-bonded structure which is close to the postulated activated complex of a protonated amide group. In order to

(1) This research was supported by Grant H-2416 of the National Institutes of Health.

(2) A preliminary report of part of this research was given by M. L. Bender, THIS JOURNAL, **79**, 1258 (1957), and was presented at a symposium on "Reaction Mechanisms and Solvent Effects" at Queen Mary College, London, July, 1957.

(3) Originally the term general basic catalysis was used to describe this phenomenon but it is suggested that nucleophilic catalysis be adopted as the proper term in order to distinguish a mechanism involving the addition of a nucleophile to the substrate producing an unstable intermediate from the classical mechanism of general basic catalyses involving a rate-determining proton transfer.

(4) M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1656 (1957).

(5) T. C. Bruice and G. L. Schmir, *Arch. Biochem. & Biophys.*, **63**, 484 (1956); THIS JOURNAL, **79**, 1663 (1957).

(6) D. M. Brouwer, M. J. v. d. Vlugt and E. Havinga, *Proc. Koninkl. Nederl. Akad. Wetenschap*, in press.

(7) E. R. Garrett, THIS JOURNAL, **79**, 3206 (1957).

(8) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *ibid.* **75**, 147 (1953); C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 511.

(9) S. J. Leach and H. Lindley, *Trans. Faraday Soc.*, **49**, 921 (1953).

determine how powerful catalysis by an intramolecular carboxylic acid group could be, we have investigated the hydrolysis of phthalamic acid, the half-amide of phthalic acid.

Experimental

Materials.—Phthalamic acid was prepared from the reaction of phthalic anhydride and concentrated aqueous ammonia, and subsequent treatment of the ammonium phthalamate with cold concentrated hydrochloric acid.[10] Phthalamic acid also was prepared by treatment of phthalimide with excess 25% potassium hydroxide, followed by treatment of the sodium phthalamate with cold concentrated hydrochloric acid,[11] m.p. 147–148°, resolidification 153–157°, remelting 230° (phthalamic acid is converted to phthalimide above its melting point).

Terephthalamic acid was prepared by oxidation of *p*-tolunitrile (Eastman Kodak Co.) or *p*-toluamide with potassium permanganate in aqueous solution.[12] After the manganese dioxide was removed by filtration, the filtrate was extracted with ether and then acidified with concd. hydrochloric acid. The precipitate was extracted continuously with acetone in a soxhlet apparatus in order to remove *p*-toluic acid and *p*-toluamide. The white amorphous material sublimed at 250° and did not melt at 300°. It is very insoluble in most organic solvents and only slightly soluble in water. *Anal.* Calcd. for $C_8H_7O_2N$: C, 58.25; H, 4.28; N, 8.49. Found: C, 58.79; H, 4.41; N, 8.39.

Phthalamic acid-*carboxamide*-C^{13} was prepared by conversion of ethyl *o*-aminobenzoate to ethyl-*o*-cyano-C^{13}-benzoate by diazotization and treatment with cuprous cyanide[13] prepared from potassium cyanide containing 22 atom % carbon-13 (Eastman Kodak Co.). The crude material was recrystallized from benzene–petroleum ether yielding white platelets, m.p. 66.5–67°. The melting point of a mixture with an authentic unlabeled ethyl *o*-cyanobenzoate showed no depression.

Ethyl *o*-cyano-C^{13}-benzoate (2.5 g.) was suspended in 20 ml. of ethanol and 40 ml. of water. Over a period of 5 hours at 55°, 4.5 ml. of 6 *N* sodium hydroxide was added, during which time the ester dissolved completely. The solution then was brought to *p*H 7 and the ethanol was distilled *in vacuo*. *o*-Cyano-C^{13}-benzoic acid then was precipitated by adding concd. hydrochloric acid and purified by dissolving in 20% sodium carbonate solution followed by reprecipitation and recrystallization from ethanol–benzene; yield 1.2 g. (58%), m.p. 185–187°; resolidification occurred immediately after melting, yielding phthalimide. The relatively low yield of *o*-cyano-C^{13}-benzoic acid is probably due to further hydrolysis to phthalic acid (a 10% yield of phthalic acid was isolated). The facile hydrolysis of the cyanide group under such mild conditions can be interpreted as proceeding through an intramolecular catalysis by *o*-carboxylate ion as postulated in the case of methyl hydrogen phthalate.[14]

Pulverized *o*-cyano-C^{13}-benzoic acid was added in portions with stirring to 0.7 ml. of chilled concd. sulfuric acid in an ice-bath. The reaction was allowed to proceed for 15 min. at ice-bath temperature and then stirred into 4 g. of crushed ice and the flask was rinsed with three 0.7-ml. portions of ice-water. From the combined solution, a white precipitate of phthalamic acid-*carboxamide*-C^{13} settled out, and was filtered and washed with three 0.3-ml. portions of ice-water and then benzene, yield 490 mg., 91%, m.p. 146.5–147°, resolidification, 153°. The melting point of a mixture with authentic unlabeled phthalamic acid was 146–147°.[15]

The Hydrolysis of Phthalamic Acid-carboxamide-C^{13} in H_2O^{18}.—Phthalamic acid-*carboxamide*-C^{13} (50 mg.) was dissolved in 0.6 ml. of water containing 10% oxygen-18 (Weizmann Institute of Science, Rehovoth, Israel). The hydrolysis was allowed to proceed for two hours at reflux temperature. The solution was cooled, 2 drops of concd. hydrochloric acid was added, and crystallization yielded 45 mg. of phthalic acid, m.p. 208° dec.

Mass Spectrometric Analysis.—For determination of the isotopic content of the carboxylic acid groups, phthalic acid was suspended in water and concd. ammonium hydroxide added to dissolve the acid. The excess ammonia was boiled off. Silver nitrate was added dropwise to the cooled solution with stirring. The silver phthalate was filtered, washed with water, ethanol, and petroleum ether, dried under vacuum at 100° for 48 hours and pulverized. The silver phthalate was decarboxylated by treatment with bromine in carbon tetrachloride solution in a stream of helium according to the method of Jeffery and Fry[16] using in addition to a Dry Ice condenser followed by a liquid nitrogen trap, a purification system for the carbon dioxide involving three fractional distillations from Dry Ice to liquid nitrogen. The yield of carbon dioxide, measured in a constant volume manometer, was 48–52% for silver phthalate and 10% for silver phthalamate. The combustion for carbon-13 analysis of phthalamic acid-*carboxamide*-C^{13} was carried out according to the method of Wilzbach and Sykes.[17] Isotopic analysis of the carbon dioxide samples was made in a Consolidated–Nier isotope ratio mass spectrometer, model 21-201.

Infrared Analysis.—It is not possible to observe the carbonyl region of the infrared spectrum in aqueous (H_2O) solution because of an intense water band, but in deuterium oxide solution this region is relatively unobstructed and observations of the carbonyl absorptions of organic compounds in deuterium oxide solution may be conveniently carried out.[18] A Perkin–Elmer model 12 double beam recording infrared spectrophotometer was used with calcium fluoride matched cells with 0.1 mm. spacing.

Kinetics of Hydrolysis.—The kinetics of hydrolysis of phthalamic acid were followed continuously in a thermostated Beckman DU spectrophotometer at 292 mμ (ε 764); for terephthalamic acid with Beckman DK2 spectrophotometer at 245 mμ. Because of the longer times involved in the latter experiments, ampoules were employed in each measurement. The method of Guggenheim was used for the determination of the first-order rate constants.[19] In the phthalamic acid hydrolyses the buffers for *p*H's 3–5 were citric acid–disodium hydrogen phosphate buffers. The concentration of phthalamic acid was approximately 6×10^{-4} *M*. From *p*H 1–3 the *p*H was controlled by an excess of hydrochloric acid. It was found that a change in the ionic strength from 0.016 to 0.12 *M* produced no change in the rate constant at *p*H 3 so that no special precautions were taken to maintain constant ionic strength. The *p*H of the solution after reaction was found to be identical with the initial *p*H by measurement with a Beckman model G *p*H meter.

Results and Discussion

Dilute Acid Solution.—The infrared spectrum of phthalamic acid in deuterium oxide solution exhibited intense absorption bands at 1690 and 1625 cm.$^{-1}$ corresponding to the deuteriocarboxylic acid and deuteriocarboxamide group, respectively.[20] The carboxylic acid band remained constant with time, but the carboxamide group was replaced by a new carboxylate band at 1560 cm.$^{-1}$ in a few hours at room temperature, a very unusual phenomenon for an amide. Phthalic acid was isolated from the system after 24 hours at room temperature.

Measurements of the kinetics of hydrolysis of phthalamic acid from *p*H 1 to 5 by ultraviolet spectrophotometry are summarized in Fig. 1. The variation of the rate constant from *p*H 1 to 5 indicates kinetic dependence on the undissociated

(10) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1793 (1925).

(11) O. Aschan, *Ber.*, **19**, 1402 (1886).

(12) P. Kattwinkel and R. Wolffenstein, *ibid.*, **37**, 3227 (1904).

(13) Organic Syntheses, Coll. Vol. I, 2nd Ed., J. Wiley and Sons Inc., New York, N. Y., 1941, p. 514.

(14) M. L. Bender, F. Chloupek and M. C. Neveu, THIS JOURNAL, **80**, 5384 (1958).

(15) This method follows that of M. M. S. Hoogewerff and W. A. v. Dorp, *Rec. trav. chim.*, **11**, 100 (1892).

(16) D. Jeffery and A. Fry, *J. Org. Chem.*, **22**, 735 (1957).

(17) K. E. Wilzbach and W. Y. Sykes, *Science*, **120**, 494 (1954).

(18) G. Ehrlich, THIS JOURNAL, **76**, 5263 (1954); G. Ehrlich and G. B. B. M. Sutherland, *ibid.*, **76**, 5268 (1954), and references cited therein.

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

(20) These absorption bands are displaced to lower frequencies with respect to their protio analogs as described in detail in ref. 17.

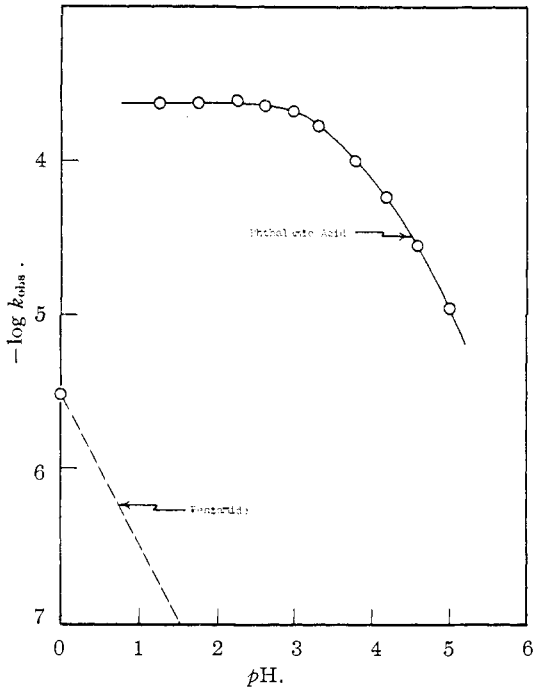


Fig. 1.—The hydrolysis of phthalamic acid and benzamide in aqueous solution. The phthalamic acid data are at 47.3° while the benzamide data are extrapolated at 48.7° (B. Rabinovitch and C. A. Winkler, *Can. J. Res.*, **20B**, 73 (1942)).

phthalamic acid and independence of the external hydrogen ion concentration. This *p*H dependence is characterized by constancy of the rate constant from *p*H 1 to 3 and a decrease in the rate constant from *p*H 3 to 5 as the phthalamic acid ionizes. The kinetic dependence on undissociated phthalamic acid in this region is quantitatively confirmed by the linearity of a plot of $1/k_{obs}$ *vs.* $1/H^+$ shown in Fig. 2.[21] From the slope of this line it is possible to estimate the ionization constant of phthalamic acid as 2.0×10^{-4} which compares favorably with the literature value of 1.6×10^{-4}.[22]

A comparison of rate constants of hydrolysis for a number of benzamide derivatives as shown in Table I is instructive in considering the extraordinary behavior of phthalamic acid.

As seen from Table I, the hydrolysis of phthalamic acid is about 10^5 times faster than the hydrolysis of benzamide with a comparable concentration of hydrogen ion (*p*H 3). Furthermore *o*-nitrobenzamide is about one-tenth as fast as benzamide so that the hydrolysis of phthalamic acid is about 10^6 faster than *o*-nitrobenzamide, a compound having a substituent of similar electronic and steric properties to the *o*-carboxylic acid group. These large rate enhancements suggest that the *o*-carboxylic acid group does not exert a substituent effect in the usual sense but rather catalyzes the amide hydrolysis by a direct intramolecular process.

(21) If it is assumed that $RCO_2H \overset{K}{\rightleftharpoons} RCO_2^- + H^+$ and that $RCO_2H \overset{k}{\longrightarrow}$ products, it can be shown that $1/k_{obs} = 1/k + (K/k)(1/H^+)$.

(22) W. Ostwald, *Z. physik. Chem.*, **3**, 379 (1889).

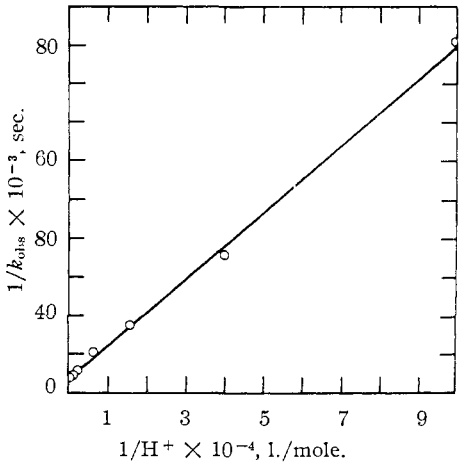


Fig. 2.—The hydrolysis of phthalamic acid.

It is seen from Table I that the rate of hydrolysis of terephthalamic acid *p*-carboxybenzamide is somewhat slower than for benzamide itself, indicating further that an electronic effect cannot explain the large rate enhancement of the *o*-isomer. It has been suggested by Prof. A. Bruylants[23] that the kinetics and the large rate of enhancement of phthalamic acid could be explained by a substituent effect of the *o*-carboxylate ion as the amide group is hydrogen-bonded to a hydronium ion and attacked by a water molecule. It would be expected that the *p*-isomer would also exhibit this effect, although to a lesser extent. However, the *p*-isomer is even slower than the parent compound benzamide. It will also be seen later that this interpretation is not in accord with the results of an isotopic tracer experiment.

TABLE I

THE ACID HYDROLYSIS OF SUBSTITUTED BENZAMIDES

Reaction	T, °C.	H^+, M	$k_1 \times 10^5$, sec.$^{-1}$	$k_2 \times 10^3$, l./mole sec.	Reference
Phthalamic acid	47.3	0.001	23,500		
Benzamide + acetic acid[a]	47.3	0.001			
Benzamide + H^+	48.7	4	1,000		*b*
Benzamide + H^+	48.7	0.001	0.31		*c*
o-Nitrobenzamide + H^+	100	0.538	1,000		*d*
Benzamide + H^+	100	1.0	35,000	0.35	*d*
Terephthalamic acid + H^+	109	5.6	133,000	0.238	

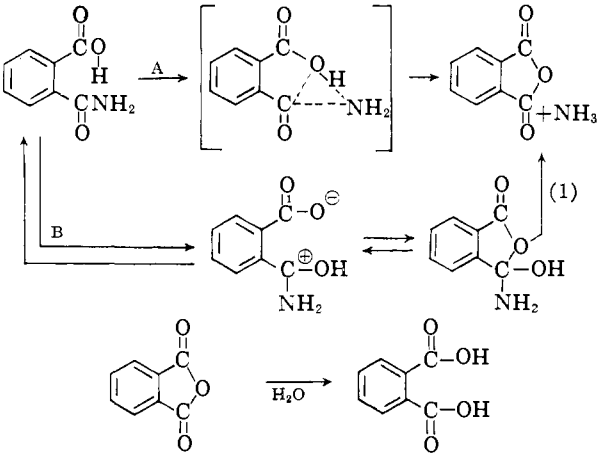
[a] Private communication of Prof. A. Bruylants, University of Louvain, indicates that Prof. Smets of the University of Louvain has found a small amount of hydrolysis of acetamide catalyzed by molecular acetic acid at 110°. Under the milder conditions employed here, no reaction was detected. [b] B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **20B**, 76 (1942). [c] Extrapolated from *b* assuming a linear dependence of the rate constant on H^+ below 1 *M*. [d] E. E. Reid, *Am. Chem. J.*, 21, 327, 332 (1899).

It was mentioned earlier that an internal mechanism occurring in the hydrolysis of glycyl-L-asparagine and L-leucyl-L-asparagine was postulated to proceed through an internal proton transfer.[9] However, the relatively high basicity of amides precludes this as the full explanation. Edward and Meacock[24] have shown that the *pK*

(23) A. Bruylants, personal communication.

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

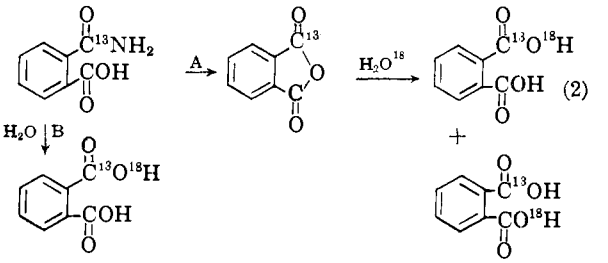
of benzamide is −1.85. Benzamide would be expected to be half-protonated in 4 *M* hydrochloric acid (at which $H_0 = -1.85$). If the protonation is the rate-determining factor, a half-protonated benzamide should be comparable in rate to phthalamic acid. But yet the rate constant of benzamide hydrolysis in 4 *M* hydrochloric acid is still much less than that of phthalamic acid at *p*H 3 (Table I).



It is therefore suggested that these intramolecular processes are electrophilic–nucleophilic-catalyzed reactions and that the *o*-carboxylic acid performs both functions of a bifunctional catalyst as shown in eq. 1 (route A), attacking the carbonyl atom of the amide and simultaneously donating a proton to the departing ammonia molecule with the formation of phthalic anhydride. The phthalic anhydride is then hydrolyzed in a fast step to phthalic acid.[25] An alternate route (B) to phthalic anhydride is also shown in eq. 1 in which the (proton transfer) electrophilic catalysis and the nucleophilic catalysis (attack by carboxylate ion on the carbonyl carbon atom of the amide) occur in separate steps. It is suggested that the proton is transferred to the oxygen atom of the amide group which is not in unequivocal assignment because of the possible resonance stabilization of the charge with the nitrogen atom, the oxygen atom and with the π-electrons of the benzene ring.

It was possible to obtain direct spectrophotometric evidence for the acetylimidazole intermediate postulated in the imidazole-catalyzed hydrolysis of an ester.[4] Direct evidence for the existence of anhydride intermediates is not obtainable since the subsequent hydrolysis of the anhydride is usually faster than its formation. However, the existence of a symmetrical phthalic anhydride intermediate is strongly suggested by the double-label isotopic tracer experiment described in eq. 2, involving both carbon-13 and oxygen-18.

If the water (H_2O^{18}) attacks the phthalamic acid amide group directly as in an ordinary amide hydrolysis (path B) all the oxygen-18 would occupy the carboxylic group labeled with carbon-13. If on



the other hand, the water attacks the symmetrical phthalic anhydride intermediate, the oxygen-18 atoms will be equally divided between the two carboxylic acid groups as shown in path A. Table II indicates the isotopic analyses calculated for the two mechanistic courses starting with 14.5 atom % carbon-13 and 10 atom % oxygen-18 as well as the mass spectrometric results of the tracer experiments. The mass spectrometric determinations were performed on the carbon dioxide resulting from the decarboxylation of the silver phthalates with bromine under anhydrous conditions. Significant differences are not to be expected for the two mechanistic paths with respect to carbon dioxide of masses 45 and 46. However, with respect to carbon dioxide of mass 47, the intramolecular process differs from the intermolecular process by a factor of two.

TABLE II

THE HYDROLYSIS OF PHTHALAMIC ACID-*carboxamide*-C^{13} IN H_2O^{18}[a]

Acid	Mass 45,[b] mole %	Carbon dioxide mass 46[c] mole %	Mass 47[b,c] mole %
Phthalamic acid-C^{13} (carboxamide group)	14.5	..	...
Phthalamic acid-C^{13} (carboxylic acid group)[e]	Normal	..	...
Phthalic acid (intramolecular path)	7.43	4.69	0.363
Phthalic acid (intermolecular path	7.05	4.35	.725
Phthalic acid (experimental)[e,d]	7.3	3.73[f]	.31[f,g] .34

[a] The *p*H at the beginning of the experiment was 2; the *p*H rose slightly in the unbuffered solution as the reaction proceeded. [b] Based on the natural abundance of C^{13} in the standard = 1.108 atom %. [c] Based on the natural abundance of O^{18} in the standard = 0.204 atom %. [d] Determined by combustion of the entire molecule to carbon dioxide. [e] Determined by decarboxylation of the silver salt. [f] The non-linearity of the mass spectrometer at high enrichment may account for the slightly low values of masses 46 and 47. [g] It was demonstrated that equilibration of oxygen atoms between carbon dioxide molecules does not occur under the anhydrous conditions used here.

The mass spectrometric determination of carbon dioxide of mass 47 is consistent with the result predicted on the basis of the intramolecular process and adds credence to the hypothesis that the hydrolysis of phthalamic acid in dilute solution proceeds through a phthalic anhydride intermediate.

Concentrated Acid Solution.—Below *p*H 1, the hydrolysis of phthalamic acid has been found to be subject to hydrogen ion catalysis. The kinetics of hydrolysis in concentrated hydrochloric acid presented in Fig. 3 exhibits the characteristics of the

(25) A. C. D. Rivett and N. V. Sidgwick, *J. Chem. Soc.*, **97**, 1683 (1910).

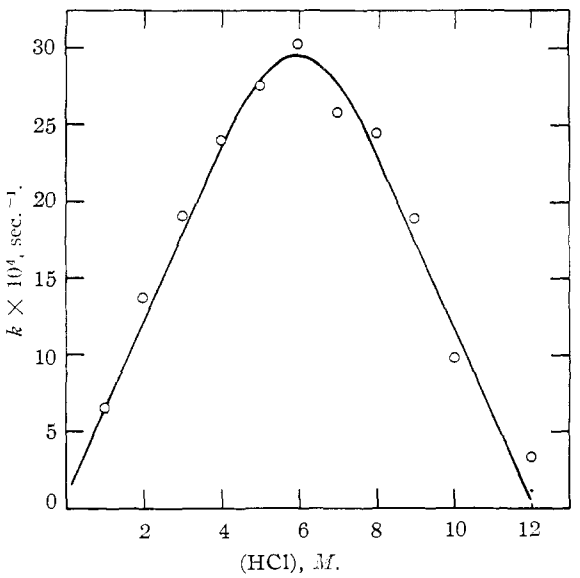


Fig. 3.—The hydrolysis of phthalamic acid in concentrated hydrochloric acid at 47.3°.

hydrolysis of normal amides including a rate maximum at about 6 M hydrochloric acid and the approximate dependence of the rate on the stoichiometric acid concentration up to the position of the maximum. This behavior is exhibited by benzamide, for example, as well as by a number of other simple amides. The position of the rate maximum is related to the ionization constant of the protonated amide and leads to an estimate of the pK of -2.5 for the protonation of phthalamic acid. It was not possible to determine this ionization constant directly because of the facile hydrolysis of phthalamic acid in concentrated acid solution.

The similarity in behavior of phthalamic acid in concentrated acid solution to the behavior of benzamide suggests that under these conditions phthalamic acid hydrolyzes *via* the direct attack of a water molecule on the protonated amide group. This change in mechanism of the hydrolysis of phthalamic acid from dilute to concentrated acid solution is apparent in the relative rate constants shown in Table III. The difference in rates of benzamide and phthalamic acid at 0.001 M HCl is 75,800 whereas it is only 240 at 4 M HCl, reflecting a change in mechanism.

TABLE III

A COMPARISON OF THE HYDROLYSIS OF BENZAMIDE AND PHTHALAMIC ACID

Amide	k_1, sec.$^{-1}$ 0.001 M HCl	k_1, sec.$^{-1}$ 4 M HCl
Phthalamic acid	2.35×10^{-4}	240×10^{-5}
Benzamide	3.1×10^{-9}	1×10^{-5}
Phthalamic acid/benzamide	75,800	240

Unfortunately it is not possible to test this hypothesis by conducting a (double-label) tracer experiment in concentrated hydrochloric acid since exchange of oxygen-18 between the reactant or product and the solvent is too fast in this medium. The change in mechanism in concentrated acid is consistent with the mechanism proposed earlier since the undissociated *o*-carboxylic acid group could not serve as a nucleophile as well as the *o*-carboxylate ion, thereby permitting an external water molecule to serve as nucleophile in the rate-determining attack on the protonated amide group.

Acknowledgment.—The authors acknowledge with pleasure valuable discussions with Drs. G. J. Buist, J. T. Edward, E. S. Kosower, F. A. Long and R. W. Taft, Jr., and wish to express their appreciation to Dr. H. Taube of the University of Chicago through whose courtesy the mass spectrometer under AEC Contract At(11-1)92 was made available. We thank the Simonize Co. for its contribution to the departmental fund for research.

CHICAGO 16, ILL.

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

Intramolecular Catalysis of Hydrolytic Reactions. III. Intramolecular Catalysis by Carboxylate Ion in the Hydrolysis of Methyl Hydrogen Phthalate[1,2]

BY MYRON L. BENDER, FRANK CHLOUPEK AND MAURICE C. NEVEU

RECEIVED MARCH 14, 1958

The hydrolytic reaction of methyl hydrogen phthalate is characterized by a region near neutrality in which the observed first-order rate constant is independent of the pH. This phenomenon has been observed previously in the hydrolyses of mono-*p*-nitrophenyl glutarate and acetylsalicylic acid and has been interpreted as catalysis of the hydrolytic reaction by an internal nucleophile, carboxylate ion. It is suggested that in addition to the phenyl esters, aspirin and mono-*p*-nitrophenyl glutarate, the methyl ester, methyl hydrogen phthalate, is subject to intramolecular catalysis of hydrolysis by carboxylate ion, involving an anhydride intermediate. This reaction is the first example of the hydrolysis of an unactivated ester by a nucleophilic catalyst. The enthalpy and entropy of activation, 33.7 kcal./mole and 7.5 e.u., respectively, are consistent with an intramolecular process. The finding that oxygen-18 labeled salicylic acid is formed in the hydrolysis of aspirin in H_2O^{18} at pH 6 is consistent with intramolecular catalysis in this process. These observations lend credence to the hypothesis that intramolecular catalysis by carboxylate ion occurs during the catalytic process of the enzymes ficin and papain.

A general investigation has been initiated to ascertain what hydrolytic processes can be catalyzed by internal nucleophiles and/or electrophiles.[2,3] One nucleophile that occurs in many organic compounds is the carboxylate ion. Carboxylate ion is

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(2) Previous paper in this series, M. L. Bender, Y. L. Chow and F. Chloupek, THIS JOURNAL, **80**, 5380 (1958). A portion of this research was presented at a symposium on "Reaction Mechanisms and Solvent Effects" at Queen Mary College, London, July, 1957.

(3) M. L. Bender, *ibid.*, **79**, 1258 (1957).