The Hydrolysis and Cyclization of Some Phthalamic Acid Derivatives

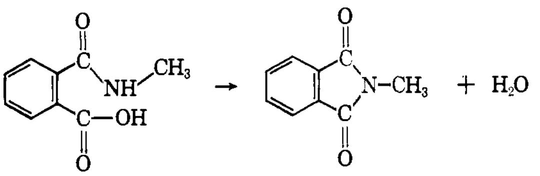
J. Brown, S. C. K. Su, and J. A. Shafer[1]

Contribution from the Department of Biological Chemistry, The University of Michigan, Ann Arbor, Michigan *Received April 13, 1966*

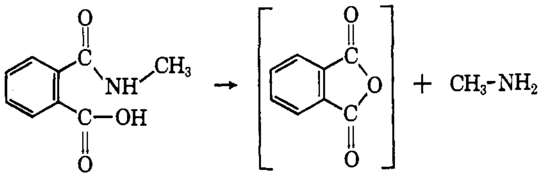
Abstract: The cyclization to imide and the hydrolysis to phthalic acid of phthalamic acid, N-methylphthalamic acid, and N-acetylphthalamic acid were studied in aqueous solution, as a function of the hydrogen ion concentration. The observed pseudo-first-order rate constant for the hydrolysis of N-methylphthalamic acid is proportional to the concentration of the un-ionized acid. The relationship required to represent the hydrogen ion dependence of the cyclization reaction is more complicated, and indicates intermediates are involved in the formation of N-methylphthalimide. This cyclization reaction points out the effectiveness of an amide group as a nucleophile under physiological conditions, since cyclization involves the displacement of a hydroxyl group by an amide. Possible mechanisms are discussed. Activation parameters for the cyclization and hydrolysis of N-methylphthalamic acid were evaluated. In acid solution (0.04 *N* HCl–0.16 *N* KCl) the hydrolysis of phthalamic acid is more than 300 times faster than cyclization to phthalimide, while the hydrolysis of N-methylphthalamic acid is less than five times faster than cyclization to N-methylphthalimide. The equilibrium constant for N-methylphthalimide formation (shown in eq 10) is 24 times greater than the corresponding equilibrium constant for phthalimide formation. The temperature dependence of the equilibrium constant for N-methylphthalimide formation was evaluated in order to estimate the enthalpy and entropy changes. The cyclization of N-acetylphthalamic acid to N-acetylphthalimide in 0.1 *N* HCl, 100°, was inferred from the appearance of phthalimide, and the observation that phthalimide is rapidly produced from N-acetylphthalimide under these conditions. The hydrolysis of N-acetylphthalamic acid was found to be much less susceptible to catalysis by the neighboring carboxyl group than the hydrolysis of phthalamic acid.

The apparent labilization of amide bonds by neighboring un-ionized carboxyl groups first was discussed in detail by Bender and co-workers.[2,3] Figure 1 depicts the two possible mechanisms suggested for the hydrolysis of phthalamic acid.[2] Both mechanisms are consistent with the existing proportionality between the fraction of un-ionized phthalamic acid and the observed pseudo-first-order rate constant.[2,3] The existence of the phthalic anhydride intermediate was inferred from the results of isotope tracer experiments.[2] These results demand a symmetrical intermediate. In the transition state, the plane of the carboxyl residue was assumed to be in the plane of the aromatic ring, and perpendicular to the plane defined by the carboxamide group, because *o*-carboxyphthalimide (a compound which cannot easily assume this favorable conformation) is more stable, and does not exhibit the same relationship between the observed hydrolytic rate constant and the fraction of un-ionized carboxyl residues.[3]

In an investigation of the decomposition of N-methylphthalamic acid we observed the elimination of water by the neighboring amide group (eq 1) in addition to the expected elimination of methylamine by the neighboring acid group (eq 2). In order to compare the reaction mechanisms of the carboxyl and amide groups, and evaluate the thermodynamic parameters characteristic of the equilibrium between phthalamic acid and cyclic imide, the cyclization and hydrolysis of some phthalamic acid derivatives were investigated.



(1)



(2)

Experimental Section

Materials. Phthalamic acid was prepared from phthalic anhydride and ammonia,[4] dec pt 146–147° cor, lit.[4] 147–148°.

N-Methylphthalamic acid was prepared by the procedure of Chapman and Stephen[4] using 30–35% aqueous methylamine in place of ammonia, dec pt 131–133° cor, lit.[5] 130–135°.

N-Acetylphthalimide was obtained by heating overnight under reflux 30 g of phthalimide in 200 ml of acetic anhydride. The product was recrystallized twice from benzene, mp 135–136° cor, lit.[6] 135°.

N-Acetylphthalamic acid was prepared by hydrolyzing N-acetylphthalimide in 5% sodium carbonate.[6] A mixture of 5 g of N-acetylphthalimide (~26 mmoles) and 26 ml of 5% sodium carbonate (24.6 mequiv) was stirred vigorously at 55–65° for about 20 min. The resulting solution was cooled in an ice bath (some precipitation occurred on cooling) and neutralized to congo red with 1 *N* hydrochloric acid. The product was collected and recrystallized from water and then methanol, dec pt 162–163° cor, lit.[6] 165. *Anal.* Calcd for $C_{10}H_9NO_3$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.63; H, 4.33; N, 6.56.

Phthalimide was obtained from Eastman Organic Chemicals and recrystallized twice from 95% ethanol, mp 235–236° cor, lit.[7] 233.5°.

N-Methylphthalimide was also obtained from Eastman Organic Chemicals and recrystallized twice from 95% ethanol, mp 134–135° cor, lit.[8] 133–134°.

---

[1] To whom inquiries regarding this work should be made.

[2] (a) M. L. Bender, *J. Am. Chem. Soc.*, **79**, 1258 (1957); (b) M. L. Bender, Y-L. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

[3] B. Zerner and M. L. Bender, *ibid.*, **83**, 2267 (1961).

[4] E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1791 (1925).

[5] M. M. S. Hoogewerff and W. A. Van Dorp, *Rec. Trav. Chim.*, **13**, 98 (1894).

[6] A. W. Titherley and W. L. Hicks, *J. Chem. Soc.*, **89**, 708 (1906).

[7] C. Graebe, *Ann. Chem.*, **247**, 294 (1888).

The distilled water supplied to the laboratory was run through a demineralizer and redistilled in an all-glass still.

All other chemicals used were Mallinckrodt or Baker-Adamson analytical reagents.

Methods. Measurements of pH at 25–37° were made using a Radiometer Model 4b pH meter which was standardized with a 1:1 phosphate, NBS primary standard solution.[9] The response of the glass electrode was checked with another NBS primary standard solution (either borax or phthalate). Any nonideality in the glass electrode response was corrected with the temperature compensator. This correction never corresponded to more than 1° per pH unit difference between the primary standards. Measurements of pH were made before and after each kinetic run, and the average value of pH was used. The total change in pH during a kinetic run rarely exceeded 0.03 unit.

The hydrogen ion concentration was estimated from the pH and the mean activity coefficient of hydrogen chloride in potassium chloride solutions. The mean activity coefficients used (0.746 at 37° and 0.750 at 25°, ionic strength of 0.2) were interpolated from the data listed in Harned and Owen.[10] Below pH 3, the hydrogen ion concentration was obtained by titration. Buffers were used to maintain constant hydrogen ion concentration. Below pH 3 hydrochloric acid was used.

For the studies of the decomposition of N-methylphthalamic acid the other buffers used were: succinic acid–sodium hydrogen succinate, pH 3.4–4.0; acetic acid–sodium acetate, 4.0–5.2; disodium phosphate–potassium hydrogen phosphate, 6.0–8.0; boric acid–sodium borate, 8–10. Unless otherwise specified the total concentration of acid plus conjugate base was 0.05 *M*. The ionic strength was adjusted to 0.2 by the addition of potassium chloride.

In order to reproduce the conditions of Zerner and Bender,[3] 0.1 *M* total acetate buffers and $^1/_{15}$ *M* phosphate buffers were used to control the hydrogen ion concentration during the decomposition of N-acetylphthalamic acid. The pH of these solutions at 100° were estimated from measurements made at 25° (using the procedure employed by Zerner and Bender[3]). No extra potassium chloride was added to these solutions. Ammonia was determined with Nessler's reagent and ammonium sulfate standards.

Rate Measurements. The rates of disappearance of starting materials or the appearance of products were followed spectrophotometrically on a Zeiss PMQ II spectrophotometer. The decomposition of N-methylphthalamic acid was followed at 294, 300, 310, 315, and 320 mμ. At the higher wavelengths, the increase in absorbance attributable to the production of phthalic acid becomes negligible, compared to the absorbance of N-methylphthalimide. The decomposition of phthalamic acid was followed at 300 mμ. The decomposition of N-acetylphthalamic acid was followed at 259 mμ after cooling a portion of the reaction mixture to room temperature and diluting an aliquot with phosphate buffer. The phosphate buffer was 0.5 *M* KH_2PO_4–0.5 *M* Na_2HPO_4, plus extra sodium hydroxide equivalent to the hydrochloric acid in the reaction mixture. Unless otherwise specified, the approach of the absorbance (A) to its final value (A_∞) was first order. The first-order rate constants were determined by the method of Guggenheim[11] or from the slopes of the linear $-\ln(A - A_\infty)$ or $-\ln(A_\infty - A)$ *vs.* time plots. The independence of the observed rate constants on the initial concentration of starting material (see the tabulated data) also established the first-order nature of the reaction. The temperature of the reacting solution was controlled by a thermostated temperature bath (±0.01° at 25 and 37°, and ±0.03° at 100°) or by a circulating bath attached to the Zeiss heatable cell holder (±0.05°), when the reaction was carried out in a cuvette equipped with a ground-glass stopper. The temperatures of the reacting solutions were measured with NBS certified thermometers.

The rate constants for the hydrolysis (k_1') to phthalic acid and the cyclization (k_2') to N-methylphthalimide for N-methylphthalamic acid were related to the initial velocity by

$$\frac{dA}{dt} = (k_1' + k_2')[R^0]\frac{E_{Im}k_1'}{k_1' + k_2'} + \frac{E_{Ac}k_2'}{k_1' + k_2'} - E_{Am} \tag{3}$$

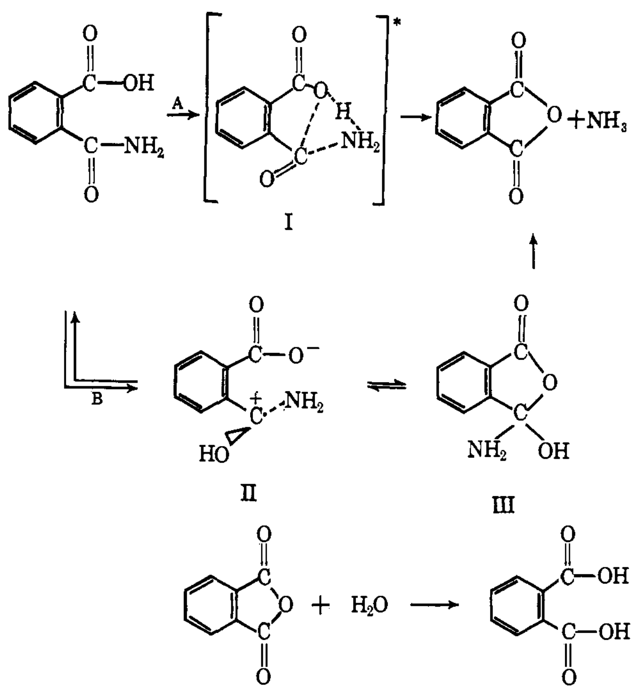


Figure 1. Possible mechanisms for the *o*-carboxyl-catalyzed hydrolysis of phthalamic acid.[2]

where dA/dt is the initial slope of the absorbance *vs.* time plot at 300 mμ. The extinction coefficients of N-methylphthalimide, phthalic acid, and N-methylphthalamic acid at 300 mμ are represented by E_{Im}, E_{Ac}, and E_{Am}, respectively. The initial concentration of N-methylphthalamic acid is given by [R⁰]. Between pH 1 and 4.3, the value of $k_1'/(k_1' + k_2')$ was obtained from the product composition. Above pH 7, $k_1' \gg k_2'$.

$$\frac{dA}{dt} = k_1'[R^0](E_{Im} - E_{Am}) \tag{4}$$

Between pH 4.3 and 7, the rate of hydrolysis of phthalimide to phthalamic acid is significant, and final spectra cannot be used to determine $k_1'/(k_1' + k_2')$ so that initial rate measurements at two wavelengths were necessary to determine k_1'. Thus

$$k_1' = \frac{\dfrac{1}{[R^\circ]}\dfrac{dA}{dt}\left[(E_{Ac}' - E_{Am}') - \dfrac{dA'}{dt}(E_{Ac} - E_{Am})\right]}{(E_{Ac}' - E_{Am}')(E_{Im} - E_{Am}) - (E_{Im}' - E_{Am}')(E_{Ac} - E_{Am})} \tag{5}$$

The primes correspond to values at 310 mμ. All initial rates were obtained from absorbance values corresponding to less than 5% conversion.

The Products of Reaction. After each kinetic run an ultraviolet absorption spectrum was determined on a Cary Model 15 recording spectrophotometer. These final spectra always agreed (to 5% or 0.005 absorbance unit) with the spectra obtained from the postulated reaction products.

Results

Cyclization *vs.* Hydrolysis. The decomposition of N-methylphthalamic acid in dilute aqueous solution may be followed conveniently by observing the increase in absorbance at 294–320 mμ. When the solution is buffered, the approach of the absorbance (A) to its final value[12] (A_∞) is first order. The rate constants

---

(8) M. Freund and H. Beck, *Ber.*, 37, 1945 (1904).

(9) R. G. Bates, "Determination of pH Theory and Practice," John Wiley and Sons, Inc., New York, N. Y., 1964, pp 62–94, 123–130.

(10) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, p 748.

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

(12) Although "infinity" readings were taken at times corresponding to at least eight half-lives for the decomposition of N-methylphthalamic acid, the hydrolysis of N-methylphthalimide was too slow to affect these final readings.

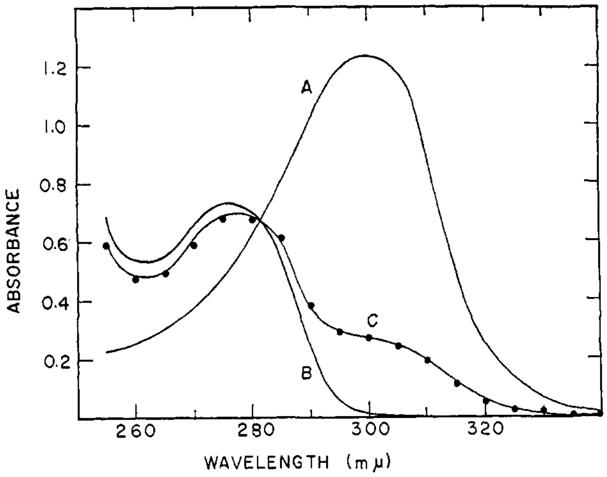


Figure 2. Ultraviolet spectra in 0.2 *N* HCl: (A) N-methylphthalimide (5.68×10^{-4} *M*), (B) phthalic acid (5.68×10^{-4} *M*), (C) products of the decomposition of N-methylphthalamic acid (5.68×10^{-4} *M*) at 37°; solid line, observed; ●, calculated for a solution containing 1.14×10^{-4} *M* N-methylphthalimide and 4.54×10^{-4} *M* phthalic acid.

obtained from the slope of the linear plots of $-\ln (A_\infty - A)$ *vs.* time are independent of the wavelength. Ultraviolet spectra taken after the absorbance becomes constant[12] could be rationalized quantitatively by assuming a mixture of N-methylphthalimide and phthalic acid at concentrations of x and $[R^0] - x$, respectively. The initial concentration of N-methylphthalamic acid is represented by $[R^0]$. Figure 2 illustrates the agreement between the expected and observed ultraviolet spectra of the reaction products. Additional evidence that the presence of N-methylphthalimide causes the deviation of the product spectra from that of phthalic acid was obtained by keeping product mixtures above pH 10 for a few minutes. Above pH 10 N-methylphthalimide rapidly decomposes to N-methylphthalamic acid, and the part of the ultraviolet spectrum attributed to N-methylphthalimide disappears.

The apparent first-order rate constant for a substance undergoing a parallel first-order reaction is equal to the sum of the rate constants, while the ratio of the products at any time is equal to the ratio of the rate constants.[13] The individual rate constants for cyclization (k_1') and hydrolysis (k_2') of N-methylphthalamic acid at several hydrogen ion concentrations were obtained from the over-all rate constants and product compositions (Table I). As expected for a first-order reaction, the rate constants are independent of the initial concentration of N-methylphthalamic acid.

Table II indicates that only k_2' is proportional to the fraction of un-ionized N-methylphthalamic acid. That is

$$k_2' = \frac{A_0}{1 + \dfrac{K}{[H^+]}} \tag{6}$$

The value of the ionization constant (K) which fits the data best (2.14×10^{-4} *M*) is in reasonable agreement with the ionization constant determined from the titration of N-methylphthalamic acid (2.5×10^{-4} *M* ± 10% at $\mu = 0.2$, 37°).

Table I. Rate Constants for the Hydrolysis and the Cyclization of N-Methylphthalamic Acid at 37° (μ = 0.2)

$10^6[H^+]$, *M*	Fraction of N-methylphthalimide	$10^5k_1'$, sec^{-1} Obsd	Calcd[f]	$10^5k_2'$, sec^{-1} Obsd	Calcd[g]
200,000[a]	0.193	0.68	0.68	2.85	2.68
200,000[b]	0.201	0.68	0.68	2.68	2.68
40,000[a]	0.174	0.60	0.57	2.85	2.68
40,000[b]	0.176	0.57	0.57	2.69	2.68
2,000[b]	0.178	0.52	0.53	2.39	2.40
370[b]	0.208	0.44	0.44	1.68	1.70
147[b]	0.262	0.38	0.37	1.08	1.09
147[c]	0.266	0.40	0.37	1.05	1.09
147[d]		0.39[e]	0.37		
63[b]	0.343	0.32	0.31	0.62	0.61
43[d]		0.29[e]	0.29		
17[d]		0.26[e]	0.25		
6.3[d]		0.20[e]	0.21		
0.88[d]		0.12[e]	0.13		
0.28[d]		0.104[e]	0.108		

[a-d] Initial concentration of N-methylphthalamic acid: [a] 1.07×10^{-3} *M*; [b] 3.41×10^{-3} *M*; [c] 0.6×10^{-3} *M*; [d] 9.8×10^{-3} *M*. [e] Rate constant from initial rate. [f] Calculated from eq 13. [g] Calculated from eq 9.

Table II. Temperature Dependence of Cyclization and Hydrolysis of N-Methylphthalamic Acid at Ionic Strength 0.2[a]

Temp, °C	$[H^+]$, *M*	$10^5k_1'$, sec^{-1}	10^5k_{1A}, sec^{-1}[b]	10^5k_2, sec^{-1}
25.0	0.04	0.133		0.48
	0.2	0.157		0.48
			0.127	
37.0	0.04	0.58		2.8
	0.2	0.68		2.8
			0.55	
47.3	0.04	1.75		11.0
	0.2	2.15		11.1
			1.65	
54	0.04	3.49		25.8
	0.2	4.52		25.8
			3.23	

[a] For the first-order cyclization of un-ionized acid, $\Delta S^* = -15.0$ eu, $\Delta H^* = 21.0$ kcal/mole. For the first-order hydrolysis of un-ionized acid, $\Delta S^* = +4.3$ eu, $\Delta H^* = 26.0$ kcal/mole. [b] k_{1A} is the first-order rate constant which might be attributed to cyclization of un-ionized N-methylphthalamic acid.

If low concentrations of the reactive intermediates are in equilibrium with the starting material along with the required combination of water, hydrogen ions, and hydroxide ions, and if the decomposition of these intermediates is catalyzed by various combinations of water, hydrogen ions, and hydroxide ions, then the hydrogen ion concentration dependence of the observed rate constant will be given by

$$k' = \frac{A_n[H^+]^n}{1 + \dfrac{K}{[H^+]}} + \ldots + \frac{A_1[H^+]}{1 + \dfrac{K}{[H^+]}} + \frac{A_0[H^+]^0}{1 + \dfrac{K}{[H^+]}} + \frac{A_{-1}[H^+]^{-1}}{1 + \dfrac{K}{[H^+]}} + \ldots + \frac{A_{-n}[H^+]^{-n}}{1 + \dfrac{K}{[H^+]}} \tag{7}$$

Each term represents the contribution from a given group of mechanisms. The mechanisms are grouped by the sum of the charges on the entities participating in the rate-limiting step, assuming charges arise only from the addition and subtraction of protons and hydroxide ions. The terms in which $[H^+]$ appears to the +1, 0,

---

(13) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, pp 160–162.

and -1 powers in the numerator represent the contribution from the mechanisms in which the total charges on the species participating in the rate-determining step are $+1$, 0, and -1, respectively.

Applying this relationship to the decomposition of N-methylphthalamic acid, a finite value need only be assigned to A_0 in order to represent the hydrogen ion concentration dependence of k_2', while a finite value of A_1, A_0, and A_{-1} is required to represent the hydrogen ion concentration dependence of k_1' below pH 4.3. Between pH 1 and 4.3 at 37°

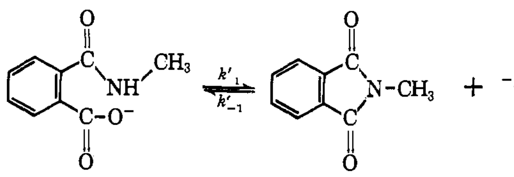
$$k_1' = \frac{0.55 \times 10^{-5}}{1 + \dfrac{K}{[\mathrm{H^+}]}} + \frac{0.60 \times 10^{-5}[\mathrm{H^+}]}{1 + \dfrac{K}{[\mathrm{H^+}]}} + \frac{5.4 \times 10^{-10}[\mathrm{H^+}]^{-1}}{1 + \dfrac{K}{[\mathrm{H^+}]}} \tag{8}$$

$$k_2' = \frac{2.68 \times 10^{-5}}{1 + \dfrac{K}{[\mathrm{H^+}]}} \tag{9}$$

As indicated above each term may be attributed to contributions from different groups of mechanisms; however the relative contributions of the various mechanisms within a group cannot be evaluated from the pH-rate profile. For example, the term containing $[\mathrm{H^+}]^{-1}$ in the numerator may represent contributions from the hydroxide ion catalyzed cyclization of any number of uncharged intermediates including un-ionized N-methylphthalamic acid, and it may also contain a contribution from the water-catalyzed cyclization of one or more intermediates with unit negative charge, including N-methylphthalamate. The rate constants for any other reactions contributing to the cyclization rate will also appear in this term, as long as the total charge on the species participating in the rate-limiting step is -1. Equation 8 predicts that k_1' will approach a constant at low hydrogen ion concentrations. The observed constancy of k_1' (to within 10%) between pH 7 and 8 is in qualitative agreement with this prediction. The limiting value of k_1' is $1.0 \times 10^{-6} \pm 10\%$; however, the predicted value is 2.5×10^{-6} sec^{-1}. Equation 8 must be modified to obtain quantitative agreement with all of the data. Removal of the requirement that $K = 2.1 \times 10^{-4}$ M would improve the fit of 8 to the observed pH dependence of k_1'.

The activation parameters for cyclization and hydrolysis were obtained from the temperature dependence of the rate constants given in Table II.

The Equilibrium between N-Methylphthalamate and N-Methylphthalimide. The rate of hydrolysis of N-methylphthalamate becomes negligible relative to the rate of imide formation at low hydrogen ion concentrations, so that the equilibrium



(10)

can be studied conveniently above pH 7. Below pH 7, the analysis is difficult because the irreversible decomposition of N-methylphthalamic acid to phthalic acid can no longer be neglected. Since the equilibrium favors N-methylphthalamate in the pH region investigated, accurate estimation of equilibrium compositions were made only when equilibrium was approached from N-methylphthalamate. The approach of N-methylphthalimide and N-methylphthalamate to their final absorbance at 300 or 310 mμ was first order. The slopes of the first-order plots were equal when the reactions were carried out under the same conditions. An analysis of this type of process (ref 12, pp 185–86) indicates that these slopes are equal to $k_{-1}' + k_1'$. Since k_{-1}' is proportional to the hydroxide ion concentration above pH 7, and since k_1' is essentially independent of the hydroxide ion concentration in this region, the pseudo-first-order rate constant for the approach to equilibrium ($k' = k_{-1}' + k_1'$) should be a linear function of the hydroxide ion concentration, *i.e.*, $k' = k_1' + k_{-1}''[\mathrm{OH^-}]$. Figure 3 illustrates that the value of k' is independent of the side from which equilibrium is approached.

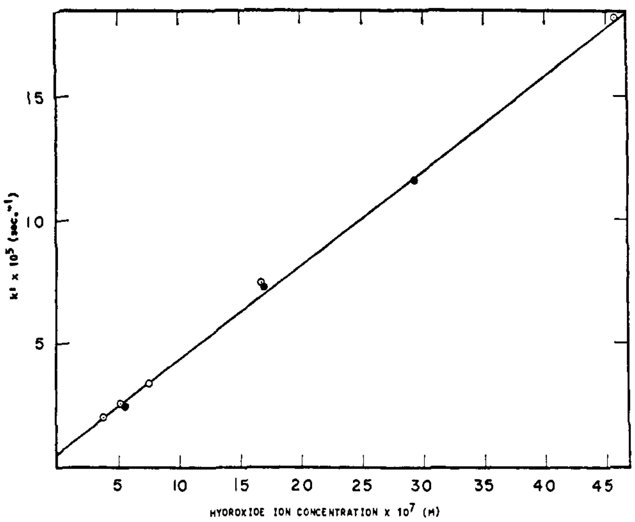


Figure 3. Dependence on hydrogen ion concentration of the approach to equilibrium at 37° and ionic strength 0.2: ○, starting with N-methylphthalamic acid; ●, starting with N-methylphthalimide.

Values of k_1' estimated from the initial rates of cyclization (eq 4) were in reasonable agreement (±10%) with the corresponding rate constants obtained from the rate of approach to equilibrium and the composition of the reaction mixture at equilibrium. Values of the equilibrium constant calculated from the product composition, and the hydroxide ion concentration, are listed in Table III. As expected, the equilibrium constant is independent of OH$^-$ concentration. From the temperature dependence of the equilibrium constant, $\Delta H = 15.5$ kcal/mole (assuming $\ln \gamma_{\mathrm{Im}}\gamma_{\mathrm{OH^-}}/\gamma_{\mathrm{Am^-}}$ is independent of temperature) and $\Delta S - R \ln \gamma_{\mathrm{Im}}\gamma_{\mathrm{OH^-}}/\gamma_{\mathrm{Am^-}} = 15.2$ eu, where γ_{Im}, $\gamma_{\mathrm{OH^-}}$, and $\gamma_{\mathrm{Am^-}}$ represent the activity coefficients of N-methylphthalimide, hydroxide ion, and N-methylphthalamate, respectively, at 0.2 ionic strength.

In order to further characterize the equilibrium between amic acid and imide the decomposition of phthalamic acid was reinvestigated, but the low yields of imide (usually less than 0.2%) made it inordinately difficult to assign accurate values to the rate constant

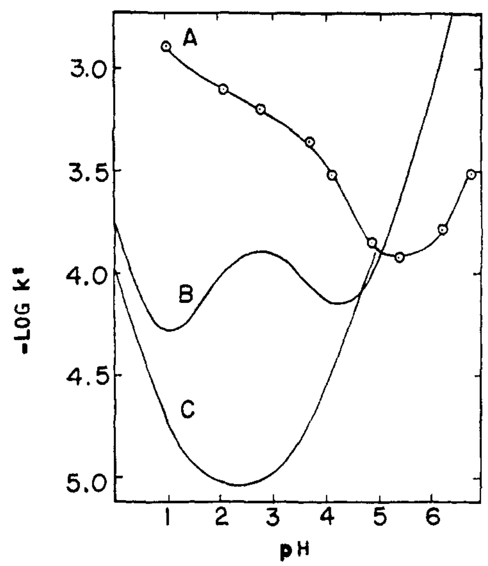
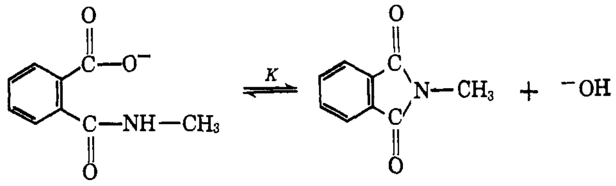


Figure 4. pH dependence of decomposition rates at 100°: (A) N-acetylphthalamic acid, (B) *o*-carboxyphthalimide, (C) phthalimide (curves B and C from ref 3).

(k_1') for imide formation. In 0.04 *N* HCl–0.16 *N* KCl at 37°, k_1' is approximately 3×10^{-7} sec^{-1}, while k_2' is 9.2×10^{-5} sec^{-1}. The fraction of imide formed equals $k_1'/(k_1' + k_2')$; therefore the low yield of imide characteristic of unsubstituted phthalamic acid is attributed to both an increase in k_2' and a decrease in k_1'.

Table III. Formal Equilibrium Constants for the Reaction (μ = 0.2)

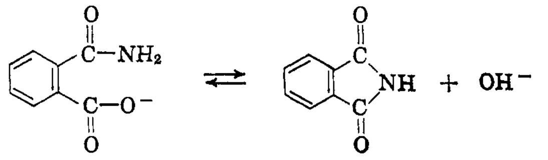


[Am⁻] Im

$10^7 \times$ [OH⁻],[a] *M*	[Im]/ [Am⁻]	10^8K	Temp, °C
4.0	0.061	2.4	37
7.5	0.031	2.3	37
16.7	0.0147	2.5	37
46	0.0050	2.3	37
7.6	0.0116	0.88	25
36	0.0153	5.5	47.3

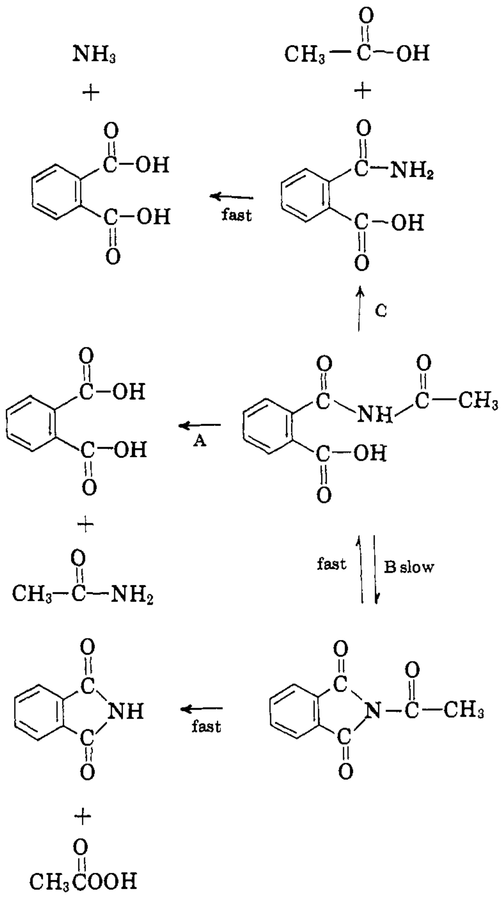
[a] Hydroxide ion concentration obtained from the measured pH, the activity coefficients of hydrogen ion, and the formal dissociation constants for water, *i.e.*, $K_w\alpha_{H_2O}/\gamma_{H^+}\gamma_{OH^-}$, which were interpolated from data listed in ref 10.

A value of 1×10^{-9} *M* was assigned to the equilibrium constant for the reaction


(11)

at 37°, from the equilibrium composition, at a given hydroxide ion concentration. The difficulty in determining the small amount of imide present at equilibrium (0.18% at 5.6×10^{-7} *M* hydroxide ion) decreases the accuracy of the value assigned to this equilibrium constant. In light of the small amount of imide present at equilibrium, the agreement (within 20%) between the first-order approaches to equilibrium from both sides is tolerable.

Hydrolysis of N-Acetylphthalamic Acid. Figure 4 illustrates the different pH–rate profiles associated with phthalimide, *o*-carboxyphthalimide, and N-acetylphthalamic acid. In contrast to phthalamic acid, no simple proportionality exists between the fraction of un-ionized carboxyl groups and the observed rate constant (k') for the decomposition of either *o*-carboxyimide. Since the decomposition of N-acetylphthalamic acid might be attributed to at least three distinct reactions



(12)

interpretation of the hydrogen ion dependence of the observed rate constant is difficult. Reaction B is thought to occur, because the formation of phthalimide during the decomposition of N-acetylphthalamic acid could be demonstrated by analyzing the ultraviolet spectra of decomposed N-acetylphthalamic acid.[14] The yields of phthalimide from the decomposition of phthalamic acid, N-acetylphthalamic acid, and N-acetylphthalimide (at initial concentrations of 5×10^{-3}

---

(14) At pH values above 3.5 the rate of phthalimide decomposition becomes comparable to the decomposition of N-acetylphthalamic acid, and the fraction of phthalimide formed cannot be estimated from the spectrum of reacted N-acetylphthalamic acid. As expected, under the conditions used to follow the decomposition of N-acetylphthalamic acid, any decomposition of the small amount of phthalimide produced did not cause deviations from first-order kinetics.

Table IV. Definition of the Adjustable Parameters in Eq 13

	b_1	b_2	b_3	b_4	b_5
If $k_{-3} \gg k_4$	$K_a k_{-1}/k_{-3}$	$k_3 k_2 K_a/k_{-3}$	$k_3 k_4/k_{-3}$	$k_3 k_6/k_{-3} K_b$	$K_a k_2/k_{-3}$
If $k_4 \gg k_{-3}$	$K_a k_{-2}/k_4$	$k_3 k_{-1} K_a/k_{-3}$	k_3	k_5/K_2	$K_a k_{-1}/k_4$
Value used to fit data in Table I	1×10^{-6}	5.4×10^{-10}	5.5×10^{-6}	6.0×10^{-6}	1.7×10^{-6}

M in 0.1 *N* HCl at 100°) were 0.2, 3.9, and 59%, respectively. These results indicate that cyclization of phthalamic acid is not a significant source of phthalimide. The rapid formation (too fast to measure at 100°) of phthalimide during the hydrolysis of N-acetylphthalimide is consistent with the possibility that reaction B is the main source of phthalimide. Phthalimide could not be detected in solutions of phthalic acid and acetamide (both initially at 5×10^{-3} *M*) in 0.1 *N* HCl at 100°, after times equivalent to several half-lives for the decomposition of N-acetylphthalamic acid.

The appearance of ammonia during the decomposition of N-acetylphthalamic acid was taken as evidence for reaction C. The hydrolysis of acetamide (initial concentration, 5×10^{-3} *M*) could not account for the ammonia. Only 1.3×10^{-4} mole of ammonia/l. was liberated after 18 min (one half-life for the decomposition of N-acetylphthalamic acid) at 100° in 0.01 *N* HCl. A 5.0×10^{-3} *M* solution of N-acetylphthalamic acid liberated 3.0×10^{-4} mole of ammonia/l. under identical conditions.

Discussion

Cyclization *vs.* **Hydrolysis.** All attempts to satisfactorily represent the pH dependence of k_1' with eq 7 failed when K was held at 2.1×10^{-4} *M*. This result may be taken as kinetic evidence for the formation of intermediates during the cyclization of N-methylphthalamic acid. If the intermediates were present in low concentrations, but their steady concentrations deviated from the equilibrium values, one could rationalize the data with the potentiometrically determined ionization constant.[15] A scheme for the cyclization reaction involving the formation of tetrahedral intermediates is given in Figure 5.

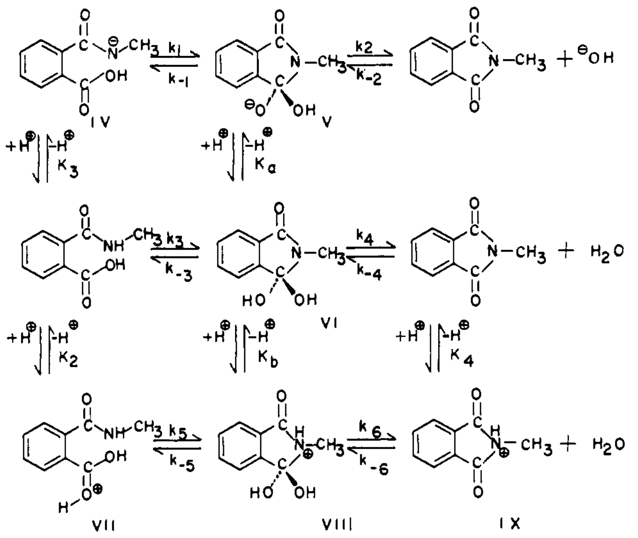


Figure 5. Cyclization of N-methylphthalamic acid.

Assuming $(k_6/K_b)[H^+] + (k_{-5}/K_b)[H^+] \ll k_4 + k_{-3}$, the predicted relationship between the observed rate constant and the hydrogen ion concentration for the reaction scheme illustrated in Figure 5 is

$$k_1' = \frac{(1 + b_1[H^+]^{-1})(b_2[H^+]^{-1} + b_3 + b_4[H^+])}{\left(1 + \dfrac{2.14 \times 10^{-4}}{[H^+]}\right)(1 + b_1[H^+]^{-1} + b_5[H^+]^{-1})} \tag{13}$$

The adjustable parameters in eq 13 are defined in Table IV. Although additional information is needed to establish the mechanism of cyclization, interesting conclusions follow from eq 13. Values of 1.7 or 0.60 can be assigned to k_2/k_{-1} (Table IV). These values are comparable to the corresponding ratios for benzamide[16] (k_2/k_{-1} = 2.86 at 35°) and ethyl benzoate[17] (k_2/k_{-1} = 0.42 at 25°) obtained from studies of concurrent oxygen-18 exchange and hydrolysis. Using these values of k_2/k_{-1} for cyclization one may conclude that

$$\frac{k_{-2}[\text{imide}][\text{OH}]}{k_{-1}[\text{intermediate}]} = 2.7 \text{ or } 1.6$$

or the rate of elimination of amide anion from the tetrahedral intermediate in the base-catalyzed hydrolysis of N-methylphthalimide is partially rate limiting. This result suggests that the ratio of the rate constants for the hydroxide ion catalyzed hydrolysis of phthalimide (to phthalamic acid) and benzamide (2.5×10^6 at 100°, Table V) probably reflects the relative rates at which amide anions[18] and amine anions[18] are eliminated from the tetrahedral intermediates, since the

Table V. Second-Order Rate Constants for Acid- and Base-Catalyzed Hydrolysis of Benzamide and Phthalimide at 100°

	$k_{[H_2O]}$, sec^{-1}	$k_{[OH^-]}$, M^{-1} sec^{-1}	$k_{[H^+]}$, M^{-1} sec^{-1}
Benzamide		$1.64 \times 10^{-3\,a}$	$0.35 \times 10^{-3\,b}$
Phthalimide	8.98×10^{-6}	$4.08 \times 10^{3\,c}$	$0.0983 \times 10^{-3\,c}$

[a] Interpolated from temperature dependence of rate constants listed in ref 14. [b] E. E. Reid, *Am. Chem. J.*, **21**, 327, 332 (1899). [c] From ref 3.

---

(15) If the intermediates were in equilibrium with N-methylphthalamic acid, and their concentrations were comparable to N-methylphthalamic acid, one could also justify the failure of eq 8 to represent the data. For a discussion of such situations see T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **81**, 4552 (1959).

(16) M. L. Bender, R. D. Ginger, and J. P. Unik, *ibid.*, **80**, 1044 (1958).

(17) M. L. Bender and R. D. Ginger, *Suomen Kemistilehti*, **33B**, 25 (1960).

(18) It is understood that these anions are probably associated with one or more molecules of water before they are liberated from the tetrahedral intermediate.

elimination of ammonia (as an anion[18]) from the tetrahedral intermediate is rate controlling in the base-catalyzed hydrolysis of benzamide.[17]

The large difference in the entropies of activation (see Table IV) for the cyclization and hydrolysis of undissociated N-methylphthalamic acid cannot be attributed to the different conformational changes associated with the transition from N-methylphthalamic acid to the transition states for the rate-controlling steps of both reactions, because the entropy changes accompanying partial protonation or deprotonation, and hydration or dehydration reactions, which might be involved in the formation of the transition state, could distort the influence of conformation on the activation entropy.

The Equilibrium between N-Methylphthalamate and N-Methylphthalimide. The formation of imide under physiological conditions indicates that a reaction between the free carboxyls of glutamic and aspartic acid, and amide groups, could conceivably occur in proteins. It is also interesting to note that the amide group is the only residue present on proteins which has been demonstrated to efficiently catalyze all of the reactions commonly catalyzed by the proteolytic enzymes, namely the elimination of -NHR,[19] -OR,[20,21] and -OH from carbonyl carbon atoms. The significance of these observations is doubtful at present, since there is no evidence for the involvement of an amide residue in the action of proteolytic enzymes.

Hydrolysis of N-Acetylphthalamic Acid. Neglecting reactions B and C, the rate constant for the decomposition of N-acetylphthalamic acid at 100° in 0.01 *N* HCl might be taken as an upper limit for the first-order, carboxyl-catalyzed elimination of acetamide from N-acetylphthalamic acid. This assumes that reactions not involving the neighboring carboxyl group do not contribute to this rate constant. For example, we have not excluded the possibility that direct catalysis of reaction A by hydrogen ion and by water accounts for part or even all of the rate attributed to the carboxyl-catalyzed reaction.

If intramolecular catalysis by the neighboring un-ionized carboxyl contributes to the observed rate of decomposition of N-acetylphthalamic acid, the largest rate constant which could be assigned to this reaction (7.7×10^{-4} sec^{-1} at 100°) is lower than the rate constant associated with the *o*-carboxyl-catalyzed hydrolysis of phthalamic acid (2.3×10^{-2} sec^{-1}, at 100°, calculated from the data of Bender[2]). The rate constant for neighboring carboxyl group participation in the hydrolysis of methyl hydrogen phthalate[22] (3.3×10^{-4} sec^{-1} at 100°) is also smaller than the rate constant for the carboxyl-catalyzed hydrolysis of phthalamic acid. Since the second-order rate constants for the acid-catalyzed hydrolysis of ethyl benzoate ($k \sim 0.39 \times 10^{-3}$ M^{-1} sec^{-1}),[23] benzamide, and phthalimide are similar (Table V), it seems significant that the neighboring carboxyl group catalyzes the hydrolysis of phthalamic acid more effectively than it catalyzes the hydrolysis of N-acetylphthalamic acid or methyl hydrogen phthalate. This result could be rationalized by assuming that the addition of the neighboring carboxylate to the carbonyl carbon atom of the protonated amide is faster than the addition of the carboxylate to the carbonyl carbon atom of the protonated ester or imide. The increased susceptibility of the protonated amide group to attack by a neighboring carboxylate could be a consequence of electronic effects. The π electron cloud of the carbonyl carbon atom in the amide might be more polarizable and interact to a greater extent with the bonding electrons of the attacking carboxylate. Unfavorable stereochemistry could also be responsible for the low rate of hydrolysis of N-acetylphthalamic acid and methyl hydrogen phthalate. The favored conformation for the formation of the activated complex is believed to require that the plane determined by the carbamido group be perpendicular to the plane of the aromatic ring[24] (see Figure 1). To support this thesis, Zerner and Bender point out that the hydrolysis of *o*-carboxyphthalimide, a compound which cannot assume the required conformation, is not susceptible to catalysis by the un-ionized *o*-carboxyl group. The increased resonance expected on acetylation of phthalamic acid may keep the plane of the carbamido group in the plane of the ring, and thereby inhibit the formation of the activated complex. Although there is no reason to believe that the relative conformation of amide and carboxyl proposed by Zerner and Bender is incorrect, the low reactivity of *o*-carboxylphthalimide could be a characteristic of imides in general. In light of this uncertainty, it is difficult to assess the importance of steric and electronic effects on the rate of hydrolysis of the phthalamic acid derivatives.

Acknowledgment. Financial support of the National Institutes of Health through Research Grant AM-09276-01 is gratefully acknowledged.

---

(19) P. Crooy, Doctoral Dissertation, Catholic University, Louvain, 1961.

(20) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962).

(21) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963).

(22) J. W. Thanassi and T. C. Bruice, *J. Am. Chem. Soc.*, **88**, 747 (1966).

(23) From the rate in 1 *M* HCl at 99° reported by M. L. Bender, *ibid.*, **73**, 1626 (1951).

(24) This conformation is thought to favor the electronic interactions between the bonding electrons of the carboxylate and the π electrons of the protonated amide group (see ref 3).