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The Mechanism of Hydrolysis of Phthalamic and N-Phenylphthalamic Acid

The Spectrophotometric Detection of Phthalic Anhydride as an Intermediate[1]

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Phthalic anhydride has been detected spectrophotometrically in the hydrolysis of phthalamic acid and *N*-phenylphthalamic acid in solutions which were made up to *5 M* with sodium perchlorate. In solutions of lower ionic strength the variation of k_{obs} with acid concentration follows the equation, $k_{obs} = (k_1 + k_2\,[H_3O^+])/(1 + K_a/[H_3O^+])$, and the values of k_1 and k_2 are both enhanced. The ρ values for the variation of k_1 and k_2 with the aryl group for the hydrolysis of *N*-arylphthalamic acids are −1.23 and −0.94. A mechanism involving nucleophilic catalysis by the carboxyl group in which breakdown of the tetrahedral intermediate is rate-limiting was proposed.

In a classic paper on intramolecular catalysis Bender, Chow, and Chloupek provided evidence that phthalic anhydride is an intermediate in the hydrolysis of phthalamic acid by means of an elegant double labeling experiment (*1*). Strictly, this experiment only demonstrated the intervention of a symmetrical intermediate, and in order to confirm that this is phthalic anhydride we have attempted to detect it spectrophotometrically. To do this use was made of the large rate-decreasing effect that perchlorates have on the hydrolysis of anhydrides (*2*), and it was thought that if the hydrolysis of phthalamic acid were studied in the presence of sodium perchlorate the hydrolysis of phthalic anhydride would be sufficiently slow for it to be detectable, if it were an intermediate. The intervention of an intermediate with a uv spectrum similar to that of phthalic anhydride was demonstrated by repeatedly scanning the spectrum of solutions in 0.02 *M* perchloric acid which contained sodium perchlorate (4.98 *M*). The uv spectra of phthalamic acid (10^{-3} *M*), phthalic acid (10^{-3} *M*), and phthalic anhydride (5×10^{-4} *M*) are shown in Fig. 1. Phthalic anhydride is much more strongly absorbing in the region of 250–325 nm than either phthalamic or phthalic acid and has peaks at 300 and 262 nm. At 48°C the absorbance of the solution of phthalamic acid increased rapidly at both these wave lengths, reached a maximum after 7 to 8 min (cf. Fig. 2), and thereafter decreased until eventually the spectrum changed to that of phthalic acid. This clearly demonstrates the intervention of an intermediate with a uv spectrum similar to that of phthalic anhydride. The only other species likely to be present in these solutions which is more strongly absorbing than phthalic and phthalamic acid at 300 nm is phthalimide, but its absorbance at 262 nm is not sufficiently great to explain the increase in absorbance

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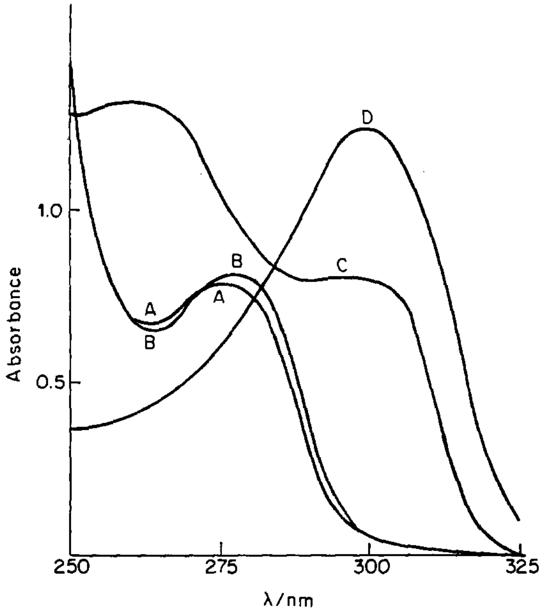


FIG. 1. The uv spectra (10-mm cells), in 0.02 M $HClO_4$–4.98 M $NaClO_4$, of: phthalamic acid (10^{-3} M), curve A; phthalic acid (10^{-3} M), curve B; phthalic anhydride (5×10^{-4} M), curve C; phthalimide (5×10^{-4} M), curve D.

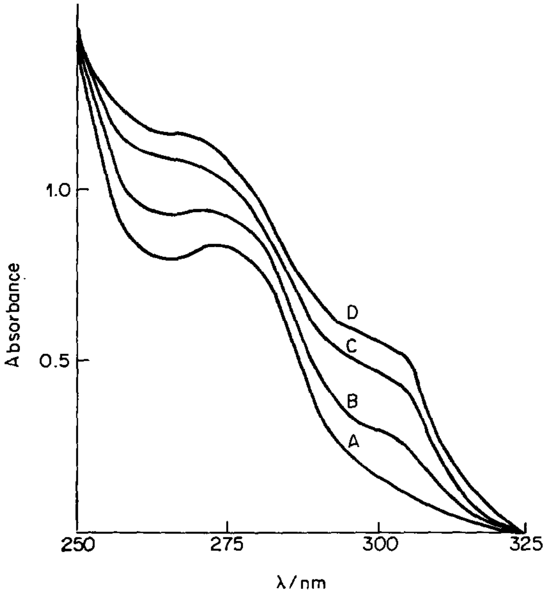


FIG. 2. The uv spectrum of a solution, originally 10^{-3} M phthalamic acid, in 0.02 M $HClO_4$–4.98 M $NaClO_4$ at 48°C: immediately, curve A; after ca. 2 min, curve B; after ca. 4 min, curve C; after ca. 7 and 8 min (spectra identical), curve D.

at this wavelength of reacting solutions of phthalamic acid (see Fig. 1). Furthermore, it is stable under the reaction conditions. The plot of absorbance at 310 nm against time of a reacting solution of phthalamic acid is shown in Fig. 3. Toward the end of the reaction the concentration of phthalamic acid should be very small, and the major reaction should be the conversion of the intermediate into phthalic acid. The first-order rate constant was calculated from the results after 30 min to give a value identical with that determined independently for the hydrolysis of phthalic anhydride ($2.6 \times 10^{-3} \text{sec}^{-1}$). It is therefore concluded that the intermediate is phthalic anhydride. Similar behavior was obtained in buffers of pH 2–3 and in solutions of perchloric acid, 0.01 to 5 *M*, when the total ionic strength was made up to 5*M* with sodium perchlorate.

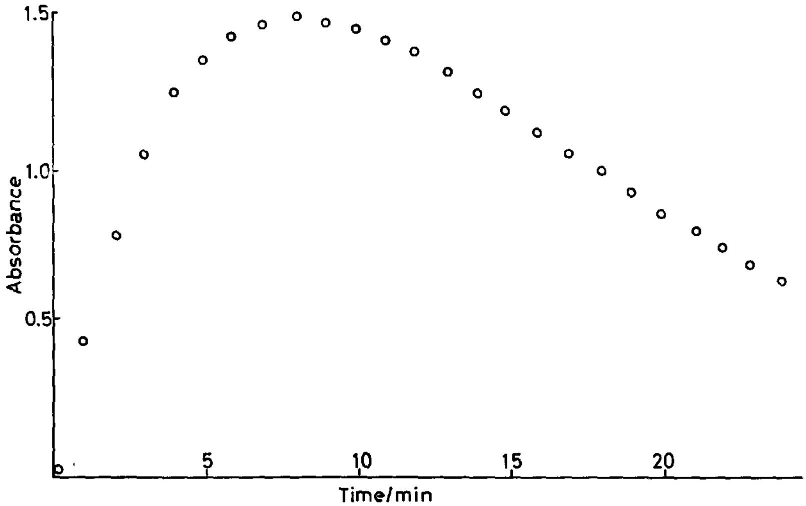


FIG. 3. Plot of absorbance at 310 nm against time for a solution of phthalamic acid (2×10^{-3} *M*) in 0.01 *M* $HClO_4$ and 4.99 *M* $NaClO_4$ at 48°C.

The change in absorbance with time was analyzed by means of the kinetic equations for two consecutive first-order reactions:

$$A \xrightarrow{k_A} B \xrightarrow{k_B} C.$$

The change in absorbance (A_t) with time (t) is given by the equation (*3*):

$$A_t = [A]_0 \varepsilon_A \times e^{-k_A t} + \varepsilon_B \times k_A(e^{-k_A t} - e^{-k_B t})/(k_B - k_A) + \varepsilon_C(1 - (k_A \times e^{-k_B t} - k_B \times e^{-k_A t})/(k_A - k_B)),$$

where $[A]_0$ is the starting concentration of A. The values of the molar extinction coefficients ε_A, ε_B, and ε_C, and of k_B were determined by independent experiment, and the value of k_A which gave the best fit to the experimental results was determined by an iterative method using a simple computer program. In the pH range 3 to 4 the plot of absorbance against time did not show a maximum, but was not following first-order behavior, and the results were analyzed similarly. At pH values greater than 4, $k_B \gg k_A$, (cf. Fig. 4 and 5), phthalic anhydride is not detectable, so the results were analyzed by the first-order rate equation to give k_A directly. Between pH 5 and 1.5 the plot of k_A

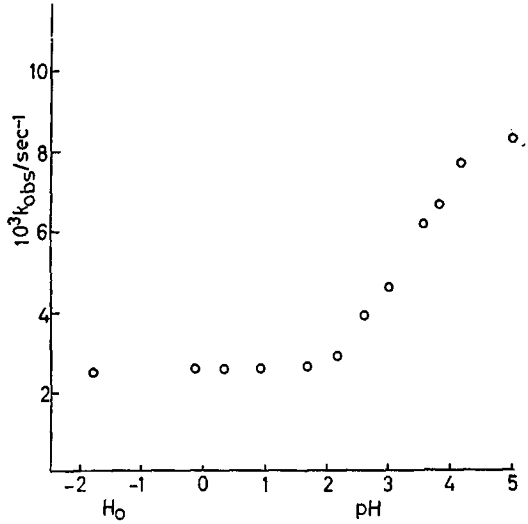


FIG. 4. Plot of 10^3k_{obs}/sec^{-1} against pH and H_0 for the hydrolysis of phthalic anhydride at 48°C in solutions made up to an ionic strength of 5 *M* with sodium perchlorate.

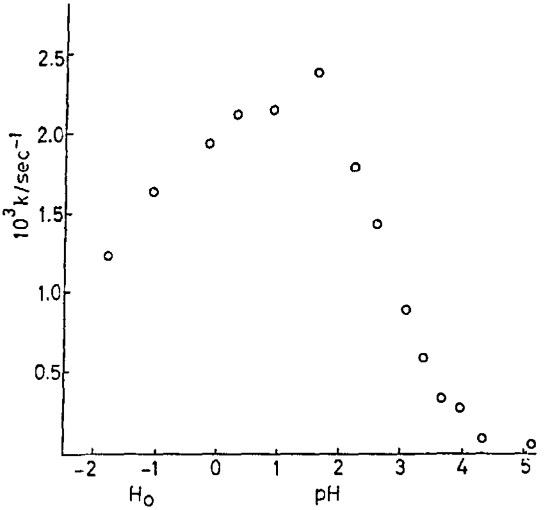


FIG. 5. Plot of 10^3k/sec^{-1} against pH or H_0 for the disappearance of phthalamic acid at 48°C in solutions made up to 5 *M* with sodium perchlorate.

against pH was sigmoid with k_A increasing with decreasing pH which indicates a rate law:

$$k_A = k_1 \text{ [unionized form]}.$$

The kinetic pK_a was 2.82, in good agreement with the spectrophotometrically determined values of pK_a^c, 2.83 ± 0.10. In this region of pH the kinetic behavior is therefore similar to that reported for lower ionic strength by Bender, Chow, and Chloupek (*1*). It is therefore reasonable that a similar mechanism should be followed under the two sets of conditions.

In solutions more strongly acidic than 0.1 *M* perchloric acid, in which the ionic strength was maintained at 5 *M* by sodium perchlorate, the value of k_A decreased slightly with increasing acid concentration. This behavior is different from that found by Bender, Chow, and Chloupek for solutions in hydrochloric acid, which contained no other electrolyte to keep the ionic strength constant (*1*). Under these conditions k_{obs} is proportional to $[H_3O^+]$ up to about 6 *M* acid, passes through a maximum, and then decreases with increasing acidity at higher acid concentrations. It was assumed that under these conditions the hydrolysis of phthalamic acid followed the normal mechanism for amide hydrolysis. However, the second-order constant calculated from the results in 1 to 5 *M* hydrochloric acid is 5.4×10^{-4} $M^{-1}\text{sec}^{-1}$ at 47.3°C, which is about 500 times greater for that for the hydrolysis of terephthalamic acid at the same temperature, viz., ca. 10^{-6} $M^{-1}\text{sec}^{-1}$. The rate law for the hydrolysis of phthalamic acid in buffers of ionic strength 0.12 *M* and hydrochloric acid of concentrations up to 5 *M* is therefore:

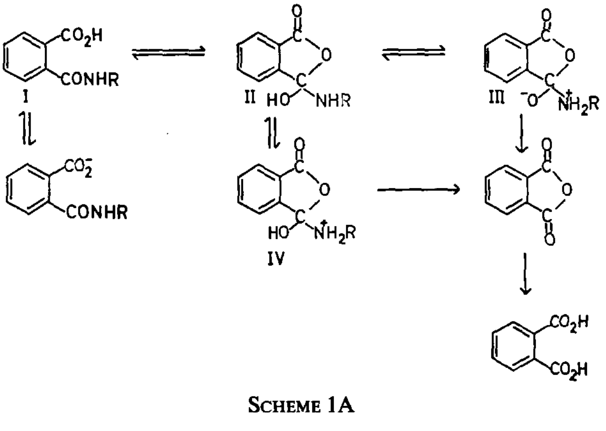
$$k_{obs}\,[\text{total substrate}] = k_1\,[\text{unionized form}] + k_2\,[\text{unionized form}]\,[H_3O^+],$$

or

$$k_{obs} = (k_1 + k_2\,[H_3O^+])/(1 + K_a/[H_3O^+]); \qquad [1]$$

k_2 as well as k_1 arises from an anchimerically assisted pathway (*4*). If there is no change in mechanism in going from 5 *M* hydrochloric acid to 5*M* perchloric acid, this must also involve phthalic anhydride as an intermediate since this was detected in the latter.

A reasonable mechanism which explains all these observations is given in Scheme 1A (R = H). In this the k_1-term of the rate law corresponds to the pathway via species II and III, and the k_2-term to hydrolysis via species II and IV. A tetrahedral intermediate such as II would be expected to preferentially expel carboxylate rather than amide ion, and so it should be in equilibrium with I, and the rate-limiting step should be its breakdown to phthalic anhydride (*5*). Also it is known from the work of Bender and Thomas (*6*) that a tetrahedral intermediate such as II does not readily expel amide ion and reacts via the zwitterionic form like III.



SCHEME 1A

This mechanism was tested for compounds with R = Ar by studying the hydrolysis of *N*-phenylphthamic acid. In buffers made up to ionic strength 5.0 *M* with sodium perchlorate the behavior was similar to that already described for phthalamic acid, and phthalic anhydride could be detected as an intermediate. At ionic strength 0.05 the pH–rate profile for a series of substituted *N*-phenylphthalamic acids followed Eq. (1). The values of k_1 and k_2, determined by a generalized least-squares method (*7*), are given in Table 1. The values of ρ_1 and ρ_2 for the variation of k_1 and k_2 with structure are −1.23 and −0.94, respectively, in reasonable agreement with those reported recently by Hawkins (−1.05 and −1.29) (*8*). These values are very different from the ρ values for the acid-catalyzed hydrolysis of *N*-arylbenzamides (*9*), which is +0.56, and *N*-arylbutyramides (*10*), which is +0.42. The latter can be explained by considering the initial state which can be regarded as a resonance hybrid (V↔VI) with a partial positive charge on the nitrogen.

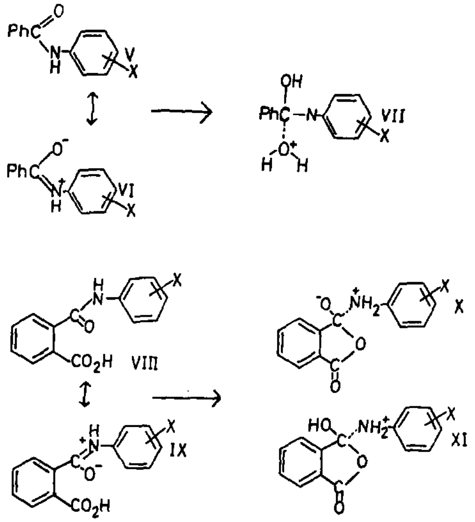
TABLE 1

RATE CONSTANTS AND DISSOCIATION CONSTANTS FOR THE HYDROLYSIS OF *N*-ARYLPHTHALAMIC ACIDS AT 50.15°C (±0.05°)

Aryl group	$10^4k_1/\mathrm{sec}^{-1}$ [a]	$10^3k_2/M^{-1}\mathrm{sec}^{-1}$ [b]	$10^4K_a/M^{-1}$
m-Methylphenyl	35.7	15.7	2.80
Phenyl	27.4	12.5	1.62
m-Methoxyphenyl	23.2	13.1	1.63
m-Chlorophenyl	9.94	5.83	1.52

[a] $\rho = -1.23$, SD = 0.12, $r = 0.991$.

[b] $\rho = -0.991$, SD = 0.089, $r = 0.991$.



SCHEME 1B

The reactions are not accompanied by exchange of the carbonyl oxygen with the solvent, so the rate-limiting step should be the attack of water on the *O*-protonated conjugate acid with the transition state (VII). This is the highest point on the free-energy reaction coordinate profile, and here the positive charge on the nitrogen has been reduced because the resonance V↔VI is not now possible. A reduction in the positive charge should be facilitated by electron-withdrawing substituents leading to a small positive ρ-value as found. With the *N*-arylphthalamic acids (Scheme 1A, R = substituted phenyl) the initial state (VIII↔IX) is similar to that for the *N*-arylbenzamides, but if the mechanism of this scheme were followed, the nitrogen would carry an increased positive charge in the rate-limiting transition states for both pathways (X, XI), provided the C–N bond breaking were not too well advanced. This would not be favored by electron-withdrawing substituents and negative ρ values should be obtained, as found.

Therefore we favor the mechanism of Scheme 1A for the hydrolysis of phthalamic acid and *N*-arylphthalamic acids. It accounts for the intervention of phthalic anhydride as an intermediate at low and high acid concentrations, the enhanced values of k_1 and k_2, and the ρ values for the variation of k_1 and k_2 with the aryl group.

EXPERIMENTAL

Materials

Phthalamic acid (mp 149°C, Eastman Kodak Ltd)., phthalic acid (mp 230°C, recrystallized from water), phthalic anhydride (mp 131°C, sublimed), and phthalimide (mp 230–232°C) were commercial samples. The *N*-arylphthalamic acids were prepared by the reaction of the amine and phthalic anhydride. Their infrared spectra all showed $\nu = 3310$ (N–H stretch), 1720 (C=O stretch of carboxylic acid), 1640 (amide I), and 3200–2500 cm^{-1} (broad, carboxylic acid OH). Analytical figures are given in Table II.

TABLE 2

ANALYTICAL FIGURES FOR *N*-ARYLPHTHALAMIC ACIDS

	Analysis					
	Found (%)			Calculated (%)		
Substituents	C	H	N	C	H	N
m-Methyl	69.8	5.5	5.5	70.6	5.1	5.55
Hydrogen	69.7	4.7	5.8	69.7	4.6	5.8
m-Methoxy	66.4	4.9	4.9	66.4	4.8	5.2
m-Chloro	61.25	3.7	4.95	61.0	3.7	5.1

Methods

Kinetic measurements were carried out in a Unicam SP800 spectrophotometer filled with a thermostatted cell block and a transmitting potentiometer which was connected to a slave recorder. First-order rate constants were calculated by a generalized least-squares method (7) and the data from the first-order consecutive reactions by the iterative method described above. The values of k_{obs} at different pH values were fitted to

Eq. (1) by a generalized least-squares method to yield k_1 and k_2. The values of pK_a^c for phthalamic and *N*-phenylphthalamic acid were determined in solutions made up to ionic strength 5 *M* with lithium perchlorate by the spectrophotometric method. Calculations were carried out on Glasgow University's KDF 9 computer or on a Digico Micro 16P computer.

ACKNOWLEDGMENT

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