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Kinetic Evidence for the Occurrence of a Stepwise Mechanism in Hydrazinolysis of Phthalimide

M. Niyaz Khan

Department of Chemistry, Universiti Malaya, Lembah Pantai, 59100 Kuala Lumpur, Malaysia

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The apparent second-order rate constants, k_{napp}, for the reaction of hydrazine with phthalimide at a constant pH follow the empirical relationship $k_{napp} = A_1[Am]_T/(1 + A_2[Am]_T)$, where $[Am]_T$ represents the total hydrazine buffer concentration. The nonlinear variation of k_{napp} against $[Am]_T$ is attributed to the change in the rate-determining step with change in $[Am]_T$ at a constant pH, and this provides evidence for the existence of an intermediate on the reaction path. The cyclization of *o*-(aminocarbamoyl)benzamide to 2,3-dihydrophthalazine-1,4-dione involves *N*-aminophthalimide as the intermediate.

Introduction

The mechanistic aspects of general acid–base (GA-GB) catalysis have been extensively studied partly because of the occurrence of these catalyses in many enzymatic reactions.[1] But many facets of the mechanism of these catalyses are still mysterious. We have been studying these catalyses in addition–elimination reactions where the leaving groups do not have free rotation around the bond being cleaved in the rate-determining step.[2] Kinetic studies on GA-GB catalyzed reactions provide unequivocal evidence for the occurrence of a stepwise mechanism if the plot of the nucleophilic second-order rate constant versus total buffer concentration turns out to be nonlinear with positive slope. This is, however, true only if the nonlinearity does not occur due to (i) self-association of catalyst, (ii) ionization of the substrate, and (iii) complex formation between the catalyst and substrate.

The reaction of hydrazine with phthalimide or its N-substituted derivatives is used in the synthesis of primary amines, and this procedure is known as the Ing-Mnske procedure.[3] The general reaction scheme is shown in Scheme 1.[3]

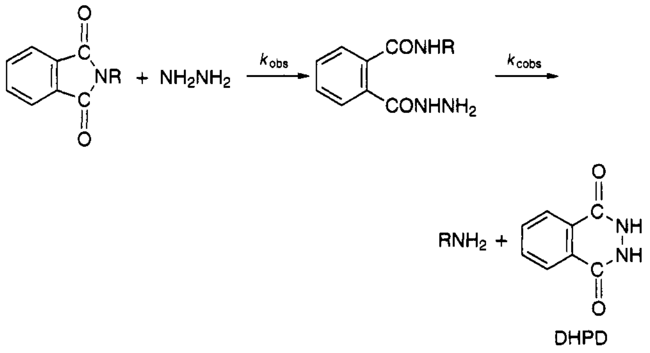
Studies on the mechanistic details of hydrazinolysis of phthalimide may be used to optimize the reaction conditions for the Ing-Mnske procedure. In a continuation of our mechanistic search on GA-GB catalyses in the cleavage of the imide bond, we have examined the hydrazinolysis of phthalimide. The results and the probable explanation(s) are presented in this paper.

Experimental Section

Materials. All the chemicals used were of reagent grade and were obtained from BDH, Aldrich, and Fluka. Glass-distilled water was used throughout, and the stock solutions of the buffers were freshly prrepared just before the start of the kinetic runs. Stock solutions of phthalimide were prepared in acetonitrile.

Kinetic Measurements. Hydrazinolysis of Phthalimide. The rates of hydrazinolysis of phthalimide were studied spectrophotometrically by monitoring the disappearance of phthalimide as a function of time at 300 nm and 30 °C. The details of the kinetic procedure and data analysis have been described elsewhere.[4]

Scheme 1



Cyclization of the Product of Hydrazinolysis of Phthalmide. Kinetic studies on cyclization of the product {*o*-(aminocarbamoyl)benzamide} obtained from hydrazinolysis of phthalimide were carried out as follows. For a typical kinetic run, the reaction mixture containing required amounts of hydrazine (100% free base) and KCl (to maintain ionic strength) was temperature equilibrated at 30 °C for a few minutes. The hydrazinolysis of phthalimide was initiated by adding 0.05 cm^3 of 0.02 mol dm^{-3} phthalimide to the temperature-equilibrated reaction mixture. After the hydrazinolysis of phthalimide was completed (i.e. when the observed absorbance A_{obs} at 300 nm was leveled off), the cyclization of the product {*o*-(aminocarbamoyl)benzamide} was initiated by adding the required volume of 1.0 mol dm^{-3} Na_2CO_3 buffer of desired pH (Na_2CO_3 buffer solution was also temperature equilibrated at 30 °C). It may be noted that the complete conversion of phthalimide to product *o*-(aminocarbamoyl)benzamide took <40 s under the experimental conditions of the present study. The rate of cyclization was monitored by recording the increase in A_{obs} at 300 nm as a function of time *t*. The observed data (A_{obs} vs *t*) were found to fit to the first-order kinetic equation (eq 1)

$$A_{obs} = \epsilon_{app}[X]_0(1 - e^{-k_{cobs}t}) + A_0 \qquad (1)$$

where $[X]_0$ is the initial concentration of phthalimide. The unknown parameters ϵ_{app} (apparent molar extinction coefficient), k_{cobs} (pseudo-first-order rate constant for cyclization), and A_0 (absorbance at $t = 0$) were calculated from eq 1 using the nonlinear least-squares technique. The extent of the reliability of the fitting of the observed data to eq 1 is evident from a few representative plots of Figure 1 where solid lines are drawn through the least-squares calculated points.

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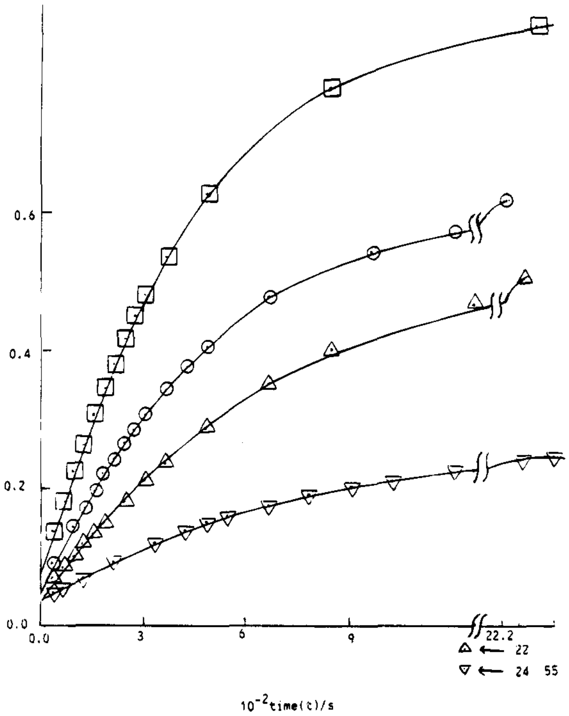

Figure 1. Plots showing the dependence of observed absorbance (A_{obs}) at 300 nm versus time (t) for cyclization of product of hydrazinolysis of phthalimide at pH 10.59, 0.1 mol dm^{-3} Na_2CO_3 and 0.1 mol dm^{-3} NH_2NH_2 (▽); 9.56, 0.6 mol dm^{-3} Na_2CO_3 and 0.1 mol dm^{-3} NH_2NH_2 (△); 10.20, 0.5 mol dm^{-3} Na_2CO_3 and 0.12 mol dm^{-3} NH_2NH_2 (⊙), and 10.51, 0.5 mol dm^{-3} Na_2CO_3 and 0.35 mol dm^{-3} NH_2NH_2 (□). Solid lines are drawn through the calculated points.

Cyclized Product Characterization. Although the cyclized product in related reactions is reported to be 2,3-dihydrophthalazine-1,4-dione (DHPD),[3] we carried out the following qualitative test in the presence of DHPD in the present reaction. To the reaction mixture (containing 2×10^{-4} mol dm^{-3} phthalamide, 0.12 mol dm^{-3} NH_2NH_2, and 0.5 mol dm^{-3} Na_2CO_3 buffer of pH 10.20 and total volume 5 cm^3) of a typical kinetic run for cyclization was added 0.5 cm^3 of 5 mol dm^{-3} NaOH at 40 min (nearly 7 half-lives) since the start of the cyclization reaction. The resulting reaction mixture contained 0.11 mol dm^{-3} NH_2NH_2, 0.45 mol dm^{-3} Na_2CO_3, and 0.45 mol dm^{-3} NaOH. The observed absorbance at 300 nm (A_{obs} = 0.62) of the resulting reaction mixture remained unchanged within the period of 25 min since the addition of 0.5 cm^3 of 5 mol dm^{-3} NaOH. Similar osbervations (i.e. no detectable change in A_{obs} within the reaction period of 25 s to 50 min) were obtained for another kinetic run on cyclization reaction where 2 cm^3 of 5 mol dm^{-3} NaOH was added to the reaction mixture (with total volume 5 cm^3) containing 0.15 mol dm^{-3} Na_2NH_2 and 0.5 mol dm^{-3} Na_2CO_3 buffer (pH 9.75) at nearly 8 half-lives of the reaction. These observations revealed that the alkaline hydrolysis of the cyclized product was extremely slow.

Since the most likely cyclized product is 2,3-dihydrophthalazine-1,4-dione (DHPD), we studied the effects of [NaOH] on alkaline hydrolysis of luminol (a compound similar to DHPD except that it contains an amino group at 5-position). The absorbance of a reaction mixture containing $\leq 2 \times 10^{-4}$ mol dm^{-3} luminol, 0.4 mol dm^{-3} NaOH, 2%, v/v, MeCN, 98%, v/v, H_2O, and 1.0 mol dm^{-3} ionic strnegth (by KCl) was recorded periodically at 300 nm and 30 °C. The observed absorbance (A_{obs} = 1.01) remained unchanged within the reaction period of 25 s to 130 min. Similar results were obtained at 0.1 mol dm^{-3} NaOH. It is interesting to note that the molar extinction coefficient (ϵ) of luminol ($\geq$5000 dm^3 mol^{-1} cm^{-1} at 0.1 and 0.4 mol dm^{-3} NaOH and $\geq$4100 dm^3 mol^{-1} cm^{-1} at 0.0 mol dm^{-3} NaOH) is not significantly different from ϵ_{app} (= 4100 dm^3 mol^{-1} cm^{-1}) of cyclized product obtained at pH 9.81 and 10.51 for the reaction mixtures containing 0.35 mol dm^{-3} NH_2NH_2 and 0.5 mol dm^{-3} Na_2CO_3 buffer. We will discuss latter that the cyclized product cannot be expected to be 100% of the initial concentration of phthalimide. These observations indicate that the cyclized product is most likely DHPD.

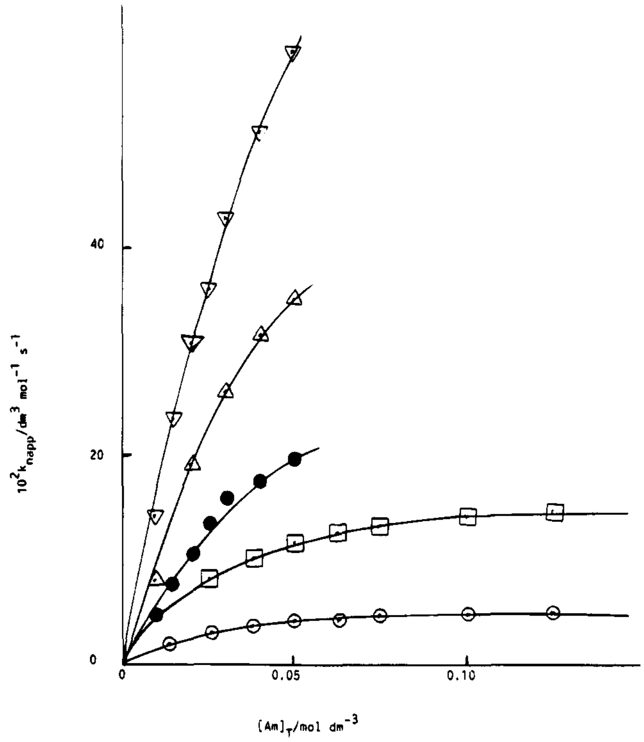

Figure 2. Plots of k_{napp} versus $[Am]_T$, at pH 7.85 (⊙), 8.19 (□), 8.41 (●), 8.66 (△), and 9.06 (▽).

Results and Discussion

Reaction with Hydrazine. A series of kinetic runs was carried out in the buffer solutions of hydrazine at different pH ranging from 7.85 to 9.06. The apparent nucleophilic second-order rate constants, k_{napp} {= (k_{obs} − k_0)/$[Am]_T$, where k_{obs} is the observed pseudo-first-order rate constant, k_0 is the buffer-independent first-order rate constant, and $[Am]_T$ is the total hydrazine buffer concentration}, are shown graphically in Figure 2. The plots in Figure 2 indicate a change in the slopes from higher to lower values as the $[Am]_T$ changes from lower to higher. The biphasic nature of these plots may not be ascribed to either self-association of buffer components or complex formation between phthalimide and hydrazine molecules because such characteristic plots were not obtained in the hydrazinolysis of maleimide,[5] penicillin,[6] phenyl salicylate,[7] methyl salicylate,[7] and phenyl acetate[8] under similar experimental conditions. The rate constants, k_{napp}, were well fitted to the empirical eq 2.

$$k_{napp} = \frac{A_1[Am]_T}{1 + A_2[Am]_T} \qquad (2)$$

The fitting of the observed data to eq 2 shows that the uncatalyzed nucleophilic second-order rate constant term is negligible compared with the catalyzed term under the

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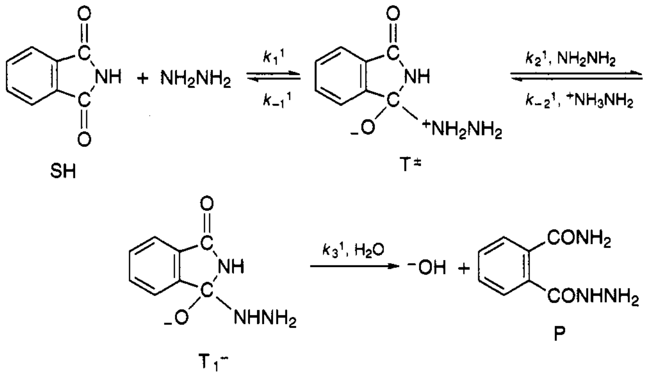
Table 1. Values of Empirical Parameters Calculated from Eq 2[a]

pH	A_1, $dm^6\ mol^{-2}\ s^{-1}$	A_2, $dm^3\ mol^{-1}$	$[Am]_T$[b] range	no. of runs
7.85	2.07 ± 0.12[c]	35.1 ± 3.0[c]	0.0125–0.125	8
8.19	6.09 ± 0.24	33.8 ± 1.9	0.025–0.125	7
8.41	6.50 ± 0.79	11.9 ± 4.8	0.01–0.05	7
8.66	11.1 ± 1.4	11.2 ± 4.6	0.01–0.05	5
9.06	18.1 ± 0.9	10.5 ± 1.9	0.01–0.05	7

[a] Conditions: $[\text{phthalimide}]_0 = 2 \times 10^{-4}$ mol dm^{-3}, 30 °C, ionic strength 1.0 mol dm^{-3} (maintained by KCl), 1%, v/v, CH_3CN in the aqueous reaction mixture. [b] Total hydrazine buffer concentration range. [c] Error limits are standard deviations.

Scheme 2



experimental conditions of the present study. The relationship $k_0 = k_{OH}K_w/(a_H + K_a')$, where the hydroxide ion-catalyzed second-order rate constant, k_{OH}, for hydrolysis of nonionized phthalimide, SH, the ionization constant, K_a', of SH, and the ionic product of water, K_w, were taken as 26.3 $dm^3\ mol^{-1}\ s^{-1}$, 3.05×10^{-10} mol dm^{-3}, and 1.449×10^{-14} $mol^2\ dm^{-6}$, respectively.[2] The empirical parameters, A_1 and A_2, were calculated from eq 2 by the nonlinear least-squares technique, and the results are shown in Table 1. The extent of the fitting of the observed data to eq 2 is evident from the standard deviations of A_1 and A_2 and from the plots of Figure 2 where solid lines are drawn through the calculated points.

The nonlinear dependence of k_{napp} on $[Am]_T$ (Figure 2) reveals a change in the rate-determining step with change in $[Am]_T$ which in turn implies the formation of an intermediate on the reaction coordinate.[9-12] The simplest mechanism which may explain the observed results is shown in Scheme 2.

Although both nonionized (SH) and ionized (S^-) forms of phthalimide are known to react with primary and secondary amines, the reaction steps for the hydrazinolysis of S^- are not included in Scheme 2. The reason may be described as follows. Hydrazine revealed nearly 3-fold larger nucleophilic reactivity toward ionized maleimide compared to nonionized maleimide.[5] If we assume that a similar reactivity pattern exists in the hydrazinolysis of phthalimide, then the insignificance of hydrazinolysis of S^- compared to that of SH is conceivable for the reason that the ratio $[SH]/[S^-]$ varies from 49 to 3 with change in pH from 7.85 to 9.06.

The observed rate law, rate = $k_{obs}[PTH]_T$, where $[PTH]_T$ represents the total concentration of phthalimide, and

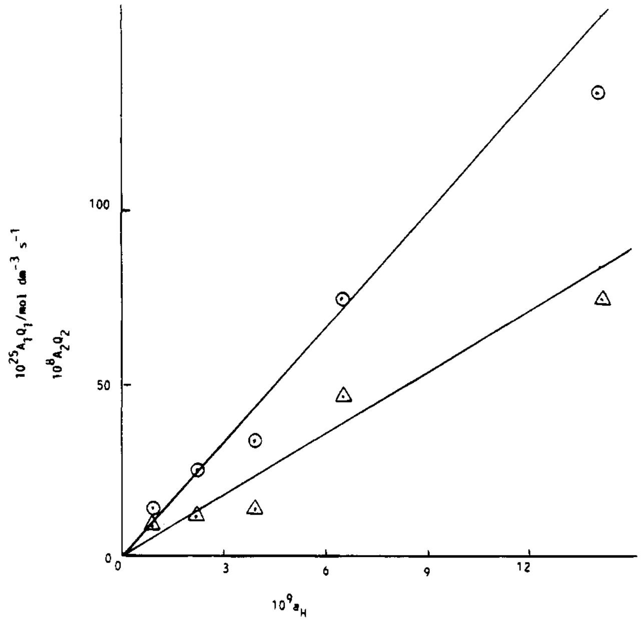


Figure 3. Plots of A_1Q_1 (⊙) and A_2Q_2 (△) versus a_H where $Q_1 = (a_H + K_a)^2(a_H + K'_a)$ and $Q_2 = a_H + K_a$.

Scheme 2 can lead to eq 3

$$k_{napp} = \frac{K_1^1 k_2^1 k_3^1 f_{bAm}^2 f_{SH}[Am]_T}{k_3^1 + k_{-2}^1 f_{aAm}[Am]_T} \qquad (3)$$

where $[Am]_T = [NH_2NH_2] + [NH_2NH_3^+]$, $K_1^1 = k_1^1/k_{-1}^1$, $f_{bAm} = K_a/(a_H + K_a)$ with $K_a = a_H[NH_2NH_2]/[NH_2NH_3^+]$ and $f_{aAm} = 1 - f_{bAm}$ and $f_{SH} = a_H/(a_H + K_a')$. Equation 3 is similar to eq 2 with

$$A_1 = K_1^1 k_2^1 f_{bAm}^2 f_{SH} \qquad (4)$$

and

$$A_2 = k_{-2}^1 f_{aAm}/k_3^1 \qquad (5)$$

Equations 4 and 5 predict that the plots of $A_1(a_H + K_a)^2(a_H + K_a')$ and $A_2(a_H + K_a)$ vs a_H must be linear with essentially zero intercepts. Such plots, as shown in Figure 3, appear to be linear. The least-squares calculated values of the slopes, $K_1^1K_a^2k_2^1$ and k_{-2}^1/k_3^1, of the plots based upon eqs 4 and 5 are $(11.2 \pm 2.7) \times 10^{-16}\ s^{-1}$ and 60.1 ± 24.1 $dm^3\ mol^{-1}$, respectively. The value of $K_1^1k_2^1$ (= 22.4 ± 5.4 $dm^6\ mol^{-2}\ s^{-1}$, calculated from the value of $K_1^1K_a^2k_2^1$ with $pK_a = 8.15$) may be compared with the corresponding rate constants $k_4 = 491$ $dm^6\ mol^{-2}\ s^{-1}$ and $k_6 = 5.9$ $dm^6\ mol^{-2}\ s^{-1}$ obtained for the reaction of SH with dimethylamine and piperazine, respectively.[13] Although the value of k_3^1/k_{-2}^1 (= 1.66×10^{-2} mol dm^{-3}) is associated with considerably large standard deviation, it may be compared with k_3^1/k_{-2}^1 (= 8.42×10^{-2} mol dm^{-3}) for hydroxylaminolysis of *N*-(ethoxycarbonyl)phthalimide (NCPH) in the acetate buffer.[14] The magnitude of k_{-2}^1 may be considered to be same for both phthalimide and NCPH because proton transfer in the k_{-2}^1 step is very near to the diffusion controlled limit. Thus, a nearly 5-fold larger value of k_3^1/k_{-2}^1 for NCPH than for phthalimide may be attributed to the larger

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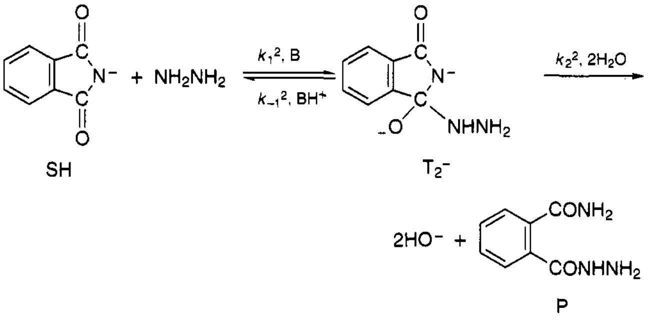
Table 2. Effects of Carbonate and Tris Buffers on Hydrazinolysis of Phthalimide[a]

buffer	$[Buf]_T$, mol dm^{-3}	pH	10^4k_{obs}, s^{-1}	$10^4k_{obs}^{corr}$, s^{-1}	10^3Y,[b] s^{-1}	10^4Z,[c] s^{-1}
Corbonate	0.1	9.91	33.6 ± 1.2[d]	24.7	2.08	
	0.3	9.85	28.1 ± 1.8	19.6	1.98	
	0.5	9.77	21.0 ± 1.2	13.0	1.68	
	0.7	9.70	18.1 ± 1.0	10.5	1.70	
Tris	0.02	8.38	6.81 ± 0.63	5.96		6.74
	0.10	8.08	4.26 ± 0.38	3.82		3.44

[a] Conditions: $[\text{phthalimide}]_0 = 2 \times 10^{-4}$ mol dm^{-3}, 30 °C, $[NH_2NH_2] = 0.01$ mol dm^{-3}, 1%, v/v, CH_3CN in the aqueous reaction mixture. [b] $Y = k_1^2k_2^2[Am]_T/k_{-1}^2 = k_{obs}^{corr}f_{aB}/f_{bAm}f_{S^-}$ {calculated from eq 7 with $pK_a = 8.15$, $pK_{aB} = 9.68$}, ionic strength 2.0 mol dm^{-3} (maintained by KCl). [c] Calculated from the relationship $Z = A_1[Am]_T^2/(1 + A_2[Am]_T)$, where $[Am]_T = 0.01$ mol dm^{-3} and A_1 and A_2 are calculated from eqs 4 and 5, respectively, ionic strength 1.0 mol dm^{-3} (maintained by KCl). [d] Error limits are standard deviations.

Scheme 3



value of k_3^1 for NCPH than for phthalimide. This is conceivable for the reason that the k_3^1 step involves a much better leaving group for NCPH than for phthalimide.

Effect of Carbonate Buffer on Hydrazinolysis of Phthalimide. In order to affirm the significance of the general base-catalyzed term in hydrazinolysis of phthalimide, we studied the cleavage of phthalimide in carbonate buffer solutions of different concentrations (0.1–0.7 mol dm^{-3}) containing 0.01 mol dm^{-3} hydrazine. The observed pseudo-first-order rate constants, k_{obs}, are summarized in Table 2. The ratio, $[S^-]/[SH]$, varies from 1.5 to 2.4 with change in pH from 9.70 to 9.90. Since the nucleophilic reactivity of hydrazine with S^- is expected to be larger than that with SH, the reaction of hydrazine with SH may be neglected compared with S^- under the pH range 9.70–9.91. The simplest mechanism, in the presence of carbonate bufer of pH range 9.70–9.91, may be shown in Scheme 3.

The observed rate law, rate = $k_{obs}[PTH]_T$, and Scheme 3 can yield eq 6

$$k_{obs}^{corr} = \frac{k_1^2k_2^2f_{bB}f_{bAm}f_{S^-}[Buf]_T[Am]_T}{k_2^2 + k_{-1}^2f_{aB}[Buf]_T} \qquad (6)$$

where $k_{obs}^{corr} = k_{obs} - k_0$, $[Buf]_T = [CO_3^{2-}] + [HCO_3^-]$, $f_{bB} = K_{aB}/(a_H + K_{aB})$, $f_{aB} = 1 - f_{bB}$, and $K_{aB} = [CO_3^{2-}]a_H/[HCO_3^-]$. At a constant $[Am]_T = 0.01$ mol dm^{-3}, the increase in $[Buf]_T$ from 0.1 to 0.7 mol dm^{-3} did not reveal an increase in k_{obs}^{corr} (Table 2). Nearly a 2.5-fold decrease in k_{obs}^{corr} with increase in $[Buf]_T$ from 0.1 to 0.7 mol dm^{-3} is possibly due to decrease in pH from 9.91 to 9.70 (Table 2). Under such conditions, it appears that $k_{-1}^2f_{aB}[Buf]_T \gg k_2^2$ and this inequality reduces eq 6 to eq 7.

$$k_{obs}^{corr} = k_1^2k_2^2f_{bB}f_{bAm}f_{S^-}[Am]_T/k_{-1}^2f_{aB} \qquad (7)$$

The values of $k_1^2k_2^2[Am]_T/k_{-1}^2$ at different pH were calculated from eq 7 and are summarized in Table 2. The average value of $k_1^2k_2^2[Am]_T/k_{-1}^2$ turned out to be $(1.86 \pm 0.20) \times 10^{-3}$ s^{-1} which gave $k_1^2k_2^2/k_{-1}^2 = 0.186$ dm^3 mol^{-1} s^{-1} because $[Am]_T = 0.01$ mol dm^{-3}. The lowest value of $f_{bB}[Buf]_T$ at which $k_{-1}^2f_{aB}[Buf]_T \gg k_2^2$ is 0.037 mol dm^{-3}. This shows that $k_{-1}^2/k_2^2 \gg 27$ dm^3 mol^{-1}. Since $k_1^2k_2^2/k_{-1}^2 = 0.186$ dm^3 mol^{-1} s^{-1}, therefore $k_1^2 \gg 5.0$ dm^6 mol^{-2} s^{-1}. The calculated values of $K_1^1k_2^1$ (= 22.4 dm^6 mol^{-2} s^{-1}) and k_1^2 ($\gg$ 5.0 dm^6 mol^{-2} s^{-1}) are conceivable for the reason that k_1^2 is expected to be similar or slightly larger than $K_1^1k_2^1$.

Effect of Trihydroxy(methylamino)methane (Tris) Buffer on Hydrazinolysis of Phthalimide. The rate of hydrazinolysis of phthalimide was studied at 0.01 mol dm^{-3} total hydrazine concentration under two different total Tris buffer concentrations, 0.02 and 0.10 mol dm^{-3}, of pH 8.38 and 8.08, respectively. The observed pseudo-first-order rate constants, k_{obs}, are summarized in Table 2. These results indicate an absence of the effect of Tris buffer on rate of hydrazinolysis of pthalimide. Equation 3 was used to calculate pseudo-first-order rate constants, k_{calcd}, at 0.01 mol dm^{-3} $[Am]_T$ and at pH 8.38 and 8.08. The values of k_{obs} and k_{calcd} are not significantly different from each other at the same pH. The absence of the effect of Tris buffer may be attributed to the probable steric requirements of the Tris molecule.

Cyclization of *o*-(Aminocarbamoyl)benzamide (OHB) to 2,3-Dihydrophthalazine-1,4-dione (DHPD). A few kinetic runs were carried out on cyclization of OHB at different pH, total hydrazine concentrations ($[NH_2NH_2]_T$), and total carbonate buffer concentations ($[Na_2CO_3]_T$). The temperature and ionic strength of the reaction medium were kept constant at 30 °C and 2.0 mol dm^{-3}, respectively. The observed data (A_{obs} vs t) were used to calculate k_{cobs}, ϵ_{app}, and A_0 from eq 1, and these results are summarized in Table 3. The calculated values of A_∞ (= $A_0 + \epsilon_{app}[X]_0$, where $[X]_0$ represents the initial concentration of phthalimide) at different $[NH_2NH_2]_T$, $[Na_2CO_3]_T$, and pH are also shown in Table 3.

The values of A_0 appear to be independent of $[NH_2NH_2]_T$ and $[Na_2CO_3]_T$ under the experimental conditions where hydrazine exists almost 100% in free base form (Table 3). These results indicate that the rate of cyclization of OHB to phthalimide is negligible compared with the rate of hydrazinolysis of phthalimide under the experimental conditions imposed.

It is evident from Table 3 that the increase in $[NH_2NH_2]_T$ at a constant value of $[Na_2CO_3]_T$ increases the magnitude of A_∞. Similar results have been obtained with increase in $[Na_2CO_3]_T$ at a constant $[NH_2NH_2]_T$. These observations show that at low $[NH_2NH_2]_T$ the product, OHB, obtained from hydrazinolysis of phthalimide does not convert fully (100%) to DHPD. Thus, the disappearance of OHB invovles the formation of DHPD as well as a side product (P_1) which does not absorb at 300 nm. If the formation of DHPD from OHB does not involve any stable intermediate (i.e. this transformation occurs in a single step), then the most likely side products (P_1) are phthalamic acid and *o*-(aminocarbamoyl)benzoic acid, which are formed due to hdyrolysis of OHB. But the rate of hydrolysis of OHB may be expected to be extremely slow under the experimental conditions of the present study. The maximum value of first-order rate

Table 3. Values of k_{cobs}, ϵ_{app}, and A_0 Calculated from Eq 1[a]

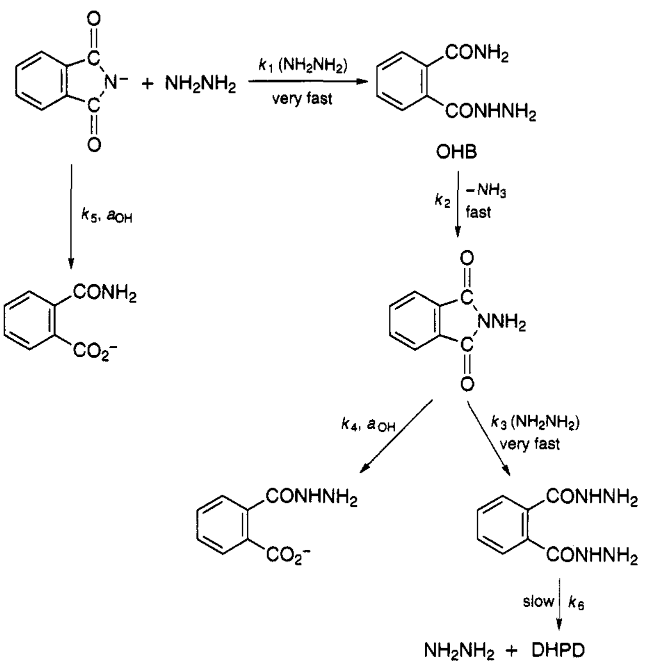
pH	$[NH_2NH_2]_T$, mol dm^{-3}	$[Na_2CO_3]_T$, mol dm^{-3}	$10^3 k_{cobs}$, s^{-3}	ϵ_{app}, dm^3 mol^{-1} cm^{-1}	A_0	A_∞[b]
10.43	0.05	0.5	3.87 ± 0.10[c]	1698 ± 18[c]	0.047 ± 0.003[c]	0.38
10.51	0.12[d]	0.5	3.16 ± 0.05	2930 ± 20	0.033 ± 0.03	0.61
10.44	0.15	0.5	2.34 ± 0.05	3349 ± 28	0.034 ± 0.004	0.69
10.40	0.25	0.5	2.20 ± 0.04	3918 ± 25	0.054 ± 0.004	0.81
10.51	0.35	0.5	2.24 ± 0.04	4134 ± 27	0.073 ± 0.004	0.89
10.59	0.10	0.1	1.60 ± 0.04	1065 ± 10	0.035 ± 0.001	0.24
10.63	0.10	0.3	2.15 ± 0.07	2089 ± 26	0.021 ± 0.004	0.43
10.63	0.10	0.4	2.43 ± 0.08	2392 ± 25	0.025 ± 0.004	0.48
10.49	0.10	0.5	2.72 ± 0.08	2641 ± 30	0.040 ± 0.005	0.56
10.42	0.10	0.6	3.11 ± 0.08	2937 ± 32	0.027 ± 0.005	0.60
9.47	0.05	0.5	2.04 ± 0.17	1543 ± 51	0.055 ± 0.005	0.28
9.69	0.12	0.5	1.18 ± 0.04	2618 ± 37	0.030 ± 0.004	0.53
9.75	0.15	0.5	0.981 ± 0.017	3046 ± 23	0.030 ± 0.004	0.53
9.81	0.25	0.5	0.837 ± 0.014	3697 ± 24	0.061 ± 0.001	0.74
9.81	0.35	0.5	0.836 ± 0.017	4067 ± 34	0.070 ± 0.02	0.79
9.86	0.1	0.1	0.621 ± 0.006	1129 ± 4	0.038 ± 0.001	0.26
9.74	0.1	0.3	1.04 ± 0.03	1901 ± 21	0.031 ± 0.003	0.40
9.71	0.1	0.4	1.23 ± 0.05	2132 ± 35	0.032 ± 0.004	0.45
9.63	0.1	0.5	1.36 ± 0.05	2248 ± 33	0.044 ± 0.005	0.48
9.56	0.1	0.6	1.52 ± 0.08	2440 ± 48	0.037 ± 0.005	0.49
10.19	0.12	0.5	1.98 ± 0.03	2868 ± 15	0.050 ± 0.002	0.62

[a] Conditions: $[\text{phthalimide}]_0 = 2 \times 10^{-4}$ mol dm^{-3}, 30 °C, $\lambda = 300$ nm, ionic strength 2.0 mol dm^{-3} (maintained by KCl), 1%, v/v, CH_3CN in the aqueous reaction mixture. [b] Calculated from the relationship $A_\infty = \epsilon_{app}[X]_0 + A_0$, where $[X]_0 = 2 \times 10^{-4}$ mol dm^{-3}. [c] Error limits are standard deviations. [d] Ionic strength 1.5 mol dm^{-3}.

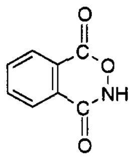
constant (at pH 10.70) for hydrolysis of OHB may be estimated to be $<10^{-7}$ s^{-1} {the values of the second-order rate constants, k_{OH}, for $^-$OH-catalyzed hydrolysis of benzamide[15,16] and *o*-methoxybenzamide[15] at 100 °C are (6.6–9.5) × 10^{-2} dm^3 mol^{-1} s^{-1} and 6.6 × 10^{-2} dm^3 mol^{-1} s^{-1}, respectively}. The estimated value ($<10^{-7}$ s^{-1}) of rate constant for hydrolysis of OHB is even smaller than the lowest standard deviation of k_{cobs} {= (621± 6) × 10^{-6} s^{-1}} as listed in Table 3. Thus, this analysis reveals that the low values of A_∞ with change in $[NH_2NH_2]_T$ cannot be attributed to the probable hydrolysis of OHB. It may be noted that the maximum contribution of the rate of hydrolysis (the value of rate constant for $^-$OH-catalyzed hydrolysis of phthalimide is 26.3 dm^{-3} mol^{-1} s^{-1} at 30 °C[2]) compared with rate of hydrazinolysis of phthalimide is ≤2%. Thus, the observed change in A_∞ with change in $[NH_2NH_2]_T$ as listed in Table 3 cannot be attributed solely to the hydrolysis of phthalimide to phthalamic acid.

The simplest mechanism which may explain, at least qualitatively, the observed values of A_∞ as a function of $[NH_2NH_2]_T$ or $[Na_2CO_3]_T$ is shown in Scheme 4.

Scheme 4



As explained earlier in the Experimental Section, the rates of formation of DHPD from OHB follow strictly first-order rate law under the experimental conditions imposed. In terms of Scheme 4, this would be true only if $k_2/k_6 > 5$. A search of literature reveals that the $^-$OH-catalyzed second-order rate constants, k_{OH}, for phthalamide,[17] *o*-(aminomethyl)benzamide,[18] and *o*-(hydroxymethyl)benzamide[19] are 4.9, 0.16, and 0.15 dm^3 mol^{-1} s^{-1}, respectively. A nearly more than 30-fold larger rate of cyclization of phthalamide compared to that of *o*-(aminomethyl)bezamide indicates tht probably $k_2/k_6 > 5$. It may be noted that in the hydroxylaminolysis of *N*-hydroxyphthalimide (NHPH), the equilibrium between NHPH and the product *o*-(hydroxycarbamoyl)benzohydroxamic acid (OHBH) was attained within less than 20 s (the equilibrium cosntant turned out to be 4.6) while the rate constant for the formation of **1** from OHBH was 1.3 × 10^{-3} s^{-1} at pH 7.03 and 0.132 mol dm^{-3} $[NH_2NH_2]_T$.[20]



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These results show that if we assume the half-life period of the formation of OHBH from NHPH as ca. 5 s then, the value of k_{-1}^{NHPH}/k_2^1 (k_{-1}^{NHPH} and k_2^1 represent

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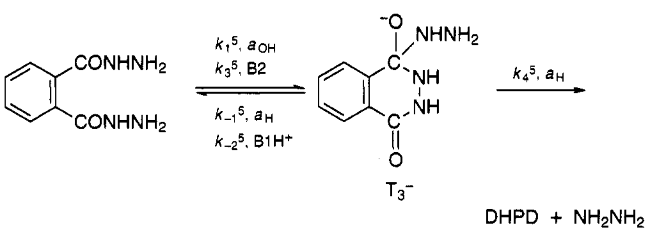
Scheme 5



first-order rate constants for the respective formation of NHPH and **1** from OHBH) turns out to be 20.

The hydroxide ion-catalyzed second-order rate constants, k_{OH}, for N-substituted phthalimides gave a satisfactory Taft plot,[21] and this plot was used to calculate k_{OH} ($\equiv k_4$ in Scheme 4) for the proposed stable intermediate *N*-aminophthalimide $\sigma_I^{NH_2} = 0.12$[22]). The calculated value of k_4 turned out to be 66 $dm^3\ mol^{-1}\ s^{-1}$ which is nearly 2.5-fold larger than k_5 (Scheme 4). Furthermore, the fraction of nonionized phthalimide is <50% under the experimental conditions imposed. The rate of hydrolysis of nonionized NHPH is sensitive to general base catalysis.[23] Both k_3 and k_4 steps (Scheme 4) are expected to involve general base catalysis. The change in the observed values of A_∞ as a function of $[NH_2NH_2]_T$ or $[Na_2CO_3]_T$ (Table 3) may be attribtued to the relatively larger rate of alkaline hydrolysis of *N*-aminophthalimide compared to that of phthalimide under similar experimental conditions.

The rate constants k_{cobs} reveal an increase with increase in $[Na_2CO_3]_T$ at a constant $[NH_2NH_2]_T$. Similarly, the increase in $[NH_2NH_2]_T$ causes a nonlinear decrease in k_{cobs} at a constant $[Na_2CO_3]_T$ (Table 3). These observations indicate that the k_6 step of Scheme 4 involves a transient intermediate on the reaction path whose formation and disappearance involve general base and general acid catalysis, respectively. The reaction mechanism for k_6 step of Scheme 4 may be shown in Scheme 5. The kinetic term $k_{-3}^5[HCO_3^-]$ for the conversion of T_3^- to *N,N'*-diaminophthalimide is ignored compared with $k_{-2}^5[NH_2NH_3^+]$ for the reason that HCO_3^- is a weaker acid than $NH_2NH_3^+$. Similarly, the kinetic term $k_2^5[NH_2NH_2]$ is neglected compared with $k_3^5[CO_3^{2-}]$ because CO_3^{2-} is a stronger base than NH_2NH_2. All the kinetic steps shown in Scheme 5 are known to occur in the related reactions.

The observed rate law (rate = $k_{cobs}[sub]_T$) and Scheme 5 may lead to eq 8

$$k_{cobs} = \frac{k_4^5 a_H (k_1^5 a_{OH} + k_3^5 f_b [B2]_T)}{(k_{-1}^5 + k_4^5) a_H + k_{-2}^5 f_a [B1]_T} \qquad (8)$$

where B1 = NH_2NH_2, B2 = CO_3^{2-}, $f_b = K_a^{B2}/(a_H + K_a^{B2})$, $f_b = a_H/(a_H + K_a^{B1})$, and K_a^{B1} and K_a^{B2} are the ionization constants of conjugate acids of B1 and B2, respectively. Although the observed changes in the magnitudes of k_{cobs} as a function of pH, $[NH_2NH_2]_T$, and $[Na_2CO_3]_T$ may be explained qualitatively using eq 8, a quantiative fit of k_{cobs} to eq 8 could not be obtained because of the complexity in both the observed data and eq 8.

Conclusion

The effects of total concentrations of hydrazine and carbonate buffers on rate of hydrazinolysis of phthalimide revealed the occurrence of a stepwise mechanism involving intermolecular general base catalysis. The rate of reaction of hydrazine with phthalimide was found to be independent of total buffer concentration of Tris. The product {*o*-(aminocarbamoyl)benzamide, (OHB)} of hydrazinolysis of phthalimide cyclizes to 2,3-dihydrophthalazine-1,4-dione (DHPD) under the buffer solutions of carbonate. The cyclization of OHB to DHPD has been concluded to involve *N*-aminophthalimide and *N,N'*-diaminophthalimide as the stable intermediates.

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