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Kinetics and Mechanism of Aminolysis of Phthalimide and *N*-Substituted Phthalimides. Evidence for the Occurrence of Intramolecular General Acid–Base Catalysis in the Reactions of Ionized Phthalimides with Primary Amines

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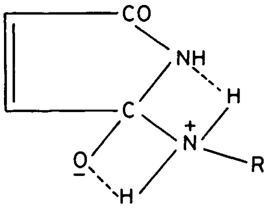
The kinetics and mechanism of the reactions of propane-1,3-diamine (PDA) and 1,4-diazabicyclo-[2.2.2]octane (DABCO) with phthalimide (PTH), *N*-hydroxyphthalimide (NHPH), and *N*-bromopropylphthalimide (NBPPH) and 2-methoxyethylamine with NHPH and NBPPH are described. Both ionized and non-ionized PTH are reactive toward PDA while only ionized NHPH showed reactivity toward PDA and 2-methoxyethylamine under the experimental conditions imposed. The presence and absence of or weak nucleophilic reactivity of DABCO toward neutral and ionized imides, respectively, are noted for PTH and NHPH. Significant nucleophilic reactivity of primary amines and the absence or considerably low nucleophilic reactivity of DABCO toward ionized PTH and NHPH are attributed to the occurrence of intramolecular general acid–base (GA–GB) catalysis due to the presence of a mobile proton at the nucleophilic site of the nucleophile. This intramolecular GA–GB catalysis seems to decrease with increased steric requirements of the leaving group. Diffusion-controlled trapping stepwise and preassociation stepwise mechanisms are suggested in the aminolysis of non-ionized phthalimides and ionized phthalimides, respectively. Intermolecular GA and GB catalysis has been detected in the reactions of PDA and 2-methoxyethylamine with ionized NHPH and 2-methoxylethylamine with NHPH and ionized NHPH, respectively. Specific-base catalysis could be detected in the reactions of 2-methoxyethylamine with ionized NHPH. The reactions of monoprotonated PDA with ionized NHPH reveal few of favourable electrostatic effects.

The mechanistic aspects of general acid–base (GA–GB) catalysis in organic reactions have been studied extensively. Many elegant but qualitative inferences have been drawn from these studies.[1–5] It is, however, still not clear why certain reactions show GA–GB catalysis while others of the same class do not show such catalysis. Most of these extensively and well executed studies[6] involve reactions at the carbonyl carbon of esters, aldehydes and a few activated amides where the leaving group maintains free rotation around the bond between the electrophilic atom and the leaving group during the course of the reaction. We have been interested in studying the nature of GA–GB catalysis in addition–elimination reactions where the leaving group does not have free rotation around the bond being cleaved in the rate determining step.

We studied the kinetics and mechanism of aminolysis of maleimide where both non-ionized and ionized maleimide appeared to react with amines. Several secondary amines exhibited GA and GB catalysis in the cleavage of ionized and non-ionized maleimide, respectively.[7] A few tertiary amines showed GA catalysis in the nucleophilic cleavage of both ionized and non-ionized maleimide.[8] Primary amines on the other hand, did not show GA–GB catalysis in their reactivity toward maleimide.[9] These observations were rationalized in terms of a proposal that an initial addition the adduct (1) formed between nucleophile and maleimide was stabilized by internal hydrogen bonding. Such internal hydrogen bonding masked completely the probable occurrence of intermolecular GA–GB catalysis. In the reactions with secondary amines, this internal hydrogen bonding was not strong enough and intermolecular GA–GB resulted. Recently, we studied the aminolysis of *N*-ethoxycarbonylphthalimide[10] where the apparent selective reactivity of primary, secondary and tertiary amines, as was obtained with maleimide, could not be observed.



(1)

This apparent difference in reactivity of maleimide and *N*-ethoxycarbonylphthalimide might be attributed to the intrinsic structural difference between these imides and the comparatively larger group attached to the nitrogen of *N*-ethoxycarbonylphthalimide.

In continuation of our mechanistic studies on GA–GB catalysis in the cleavage of the imide bond and in order to obtain information on the effects of (*i*) the groups attached to the nitrogen and (*ii*) the mobility of the negative charge on leaving groups on aminolysis of phthalimides, we studied the kinetics of the reactions of primary and tertiary amines with phthalimide and two *N*-substituted phthalimides. The results and their probable explanation(s) are described in this paper.

Experimental

Materials.—Reagent grade chemicals such as *N*-hydroxyphthalimide (NHPH), *N*-bromopropylphthalimide (NBPPH), propane-1,3-diamine (PDA), and 2-methoxyethylamine were obtained from Aldrich, and phthalimide (PTH) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were obtained from

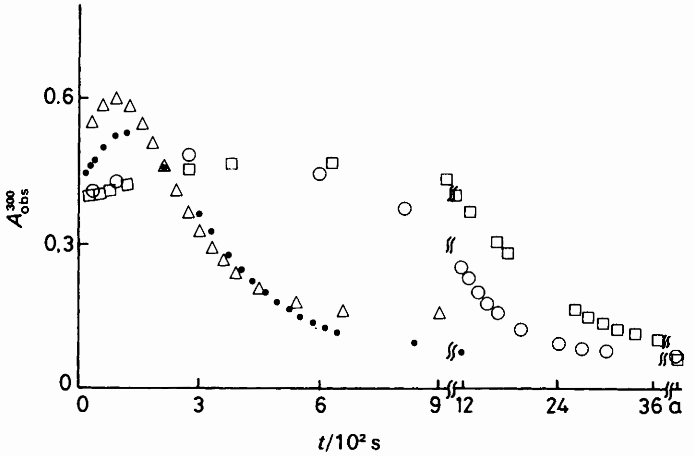


Figure 1. Plots showing the dependence of A^{300}_{obs} *versus* time for the reactions of propane-1,3-diamine (PDA) and 2-methoxyethylamine with *N*-hydroxyphthalimide (NHPH) at pH 9.01, 0.05 mol dm^{-3} PDA (○) and 0.30 mol dm^{-3} PDA (△) and at pH 9.59, 0.05 mol dm^{-3} $MeOCH_2CH_2NH_2$(□) and 0.30 mol dm^{-3} $MeOCH_2CH_2NH_2$ (●), respectively. The initial concentration of NHPH was 4 × 10^{-4} mol dm^{-3} in each kinetic run and A^{300}_{obs} represents absorbance at 300 nm. a = 6 420 s (○); a = *7 380 s* (□).

BDH. All other chemicals used were also of reagent grade. Glass-distilled water was used throughout the studies. The stock solutions of PTH, NHPH, and NBPPH were prepared in acetonitrile and were always stored at low temperature whenever they were not in use.

Kinetics Measurements.—PTH and its *N*-alkyl substituted derivatives absorb strongly at 300 nm (molar extinction coefficient at 300 nm, ε_{300}, $\simeq$2 000–2 500 dm^3 mol^{-1} cm^{-1}) while phthalamic acid and *N*-alkyl substituted phthalamic acids as well as phthalamide and *N*-alkyl substituted phthalamides have essentially no absorption at 300 nm. Therefore, the reaction rates of aminolysis of PTH and NBPPH were studied spectrophotometrically by monitoring the disappearance of PTH or NBPPH at 300 nm. The desired ionic strength of the reaction medium was kept constant with potassium chloride. The buffer solution of desired pH was prepared just before the start of the kinetic runs.

In a typical kinetic run, all the reaction ingredients except PTH or NBPPH required for an appropriate experimental condition were placed in a 25 cm^3 reaction vessel which was in turn placed in a thermostatted water bath. A total volume of 4.95 cm^3 of reaction solution was allowed to equilibrate for 5–10 minutes at 30 °C. The reaction was then initiated by adding 0.05 cm^3 (using 50 mm^3 syringe) of 0.02 mol dm^{-3} PTH or NBPPH solution prepared in acetonitrile. This procedure thus ensured 1% acetonitrile content in the aqueous reaction mixture. An aliquot of *ca.* 2.5 cm^3 was quickly withdrawn from the reaction mixture and transferred to a 3 cm^3 quartz cuvette kept in the thermostatted cell compartment of the spectrophotometer. The decrease in the absorbance at 300 nm with time was monitored by the use of either a digital display (for slow reactions) or a chart recorder (for fast reactions) of a Beckman Model 35 spectrophotometer. The constant temperature (30 °C) of the cell compartment was controlled electronically by the use of the temperature control unit of the spectrophotometer equipped with digital display as well as chart recorder Model 24–25 ACC. For slow reactions, four kinetic runs were carried out simultaneously by the use of the manually controlled sample changer of the spectrophotometer. The pH values of the reaction mixtures were determined with Philips digital pH meter Model PW 9409 and the pH for each kinetic run was found to be constant during the course of the reaction.

All the kinetic runs were carried out under pseudo-first-order kinetic conditions. The observed pseudo-first-order rate constants (k_{obs}) were calculated from equation (1) with the non-linear least-squares technique considering ε_{app} (apparent molar

$$A_{obs} = \varepsilon_{app}[X]_0 \exp(-k_{obs}t) + A_\infty \qquad (1)$$

extinction coefficient) and A_∞ (the absorbance at $t = \infty$) also as unknown parameters. In equation (1), A_{obs} is the absorbance value at any time t, and $[X]_0$ is the initial concentration of PTH or NBPPH. The reactions were carried out for up to 4–10 half-lives and observed data fitted well into equation (1).

The kinetics of the reactions of PDA with NHPH were studied by monitoring the change in absorbance at 300 nm under the buffer solution of PDA of pH 9.01. The observed data, absorbance (A^{300}_{obs}) *versus* time (t) (Figure 1) did not fit equation (1). Similar observations (Figure 1) were obtained for the reactions of 2-methoxyethylamine with NHPH at pH 9.59. The first-order kinetics for these reactions were complicated by the incursion of a stable intermediate on the reaction path which also absorbed strongly at 300 nm. This stable intermediate, phthalamic acid, phthalamide, and *N*-alkyl-substituted phthalamides appeared to have no absorption at 410 nm. Ionized NHPH (NHP^-), however, absorbs significantly at 410 nm ($\varepsilon^{410} \simeq 885$ dm^3 mol^{-1} cm^{-1}). The rates of the reactions of NHP^- with PDA and 2-methoxyethylamine were studied by monitoring the disappearance of NHP^- at 410 nm. The observed data obeyed perfectly first-order kinetics *i.e.* equation (1). The reactions were generally carried for up to 8–12 half-lives of the reactions.

In the determination of pK_a of ionized *o*-carboxybenzohydroxamic acid (o-$\bar{O}_2CC_6H_4CONHOH$) we observed that its molar extinction coefficient is similar to that of ionized *N*-hydroxyphthalimide at pH 9.68 and 300 nm. Because of this, the detectable change in the observed absorbance at 300 nm, A^{300}_{obs}, could not be observed during the period of *ca.* 24 h for the reactions carried out at pH 9.68 and within a total DABCO buffer concentration range of 0.2–1.0 mol dm^{-3}. However, neither non-ionized nor ionized *o*-carboxybenzohydroxamic acid absorbs at 410 nm and hence the effects of the presence of different concentrations of DABCO on the rates of cleavage of NHPH were studied by monitoring the disappearance of NHP^- at 410 nm. The observed data obeyed equation (1) perfectly. All the reactions were carried out for more than four half-lives of the reactions.

Results

Hydrolysis of Phthalimide (PTH), N-*Hydroxyphthalimide (NHPH) and* N-*Bromopropylphthalimide (NBPPH) in DABCO Buffers.*—The nucleophilic cleavages of PTH, NHPH, and NBPPH were studied in DABCO buffer solutions of different pH at 30 °C. The observed pseudo-first-order rate constants (k_{obs}) obtained at a constant pH obeyed equation (2) where

$$k_{obs} = k_o + k_n[\text{Buf}]_T \qquad (2)$$

$[\text{Buf}]_T$ represents the total amine buffer concentration and k_o and k_n are first-order (buffer-independent) and second-order (buffer-dependent) rate constants, respectively. The least squares technique was used to calculate the unknown parameters, k_o and k_n. The results obtained are summarized in Table 1. The fitting of the observed data to equation (2) is evident from some typical plots of Figure 2 and the magnitudes of the standard deviations associated with k_o and k_n (Table 1).

Table 1. Apparent first- and second-order rate constants for the cleavage of *N*-substituted phthalimide in the buffer solutions of 1,4-diazabicyclo[2.2.2]octane (DABCO).

$C_6H_4(CO)_2NR^a$ R	pH	$k_o{}^b$/ 10^{-4} s^{-1}	$k_n{}^b$/ 10^{-4} dm^3 mol^{-1} s^{-1}	$[Buf]_T^c$ range/ mol dm^{-3}	No. of runs
H	8.64	1.82 ± 0.22[d]	6.07 ± 0.32[d]	0.2–1.0	4
(pK_a = 9.51)[e]	9.06	3.55 ± 0.17	11.1 ± 0.8	0.05–0.35	5
	9.14	3.89 ± 0.14	8.84 ± 0.21	0.2–1.0	5
	9.53	6.93 ± 0.21	8.50 ± 1.00	0.05–0.35	5
	10.19	10.5 ± 0.2	0.33 ± 0.33	0.2–1.0	5
$(CH_2)_3Br$	8.64	1.73 ± 0.16	5.30 ± 0.23	0.2–1.0	4
	9.18	5.74 ± 0.65	10.4 ± 0.9	0.2–1.0	4
	9.67	17.1 ± 0.8	14.4 ± 1.1	0.2–1.0	4
OH[f]	8.40	0.062 ± 0.009	0.861 ± 0.011	0.3–1.2	5
(pK_a = 5.99)[g]	8.99	0.257 ± 0.071	1.48 ± 0.08	0.3–1.2	5
	9.28	0.551 ± 0.024	1.72 ± 0.03	0.3–1.2	5
	9.51	0.842 ± 0.060	1.57 ± 0.07	0.3–1.2	5

[a] Conditions 30 °C, ionic strength 1.0 mol dm^{-3}, λ = 300 nm, 1% MeCN in the aqueous reaction mixture, $[C_6H_4(CO)_2NR]_0 = 2 \times 10^{-4}$ mol dm^{-3} for R = H, $(CH_2)_3Br$. [b] Calculated from equation (2) as described in the text. [c] Total buffer concentration range. [d] Error limits are standard deviations. [e] pK_a of phthalimide. [f] Ionic strength 1.0 mol dm^{-3}, λ = 410 nm, 2% MeCN into the aqueous reaction mixture, and $[C_6H_4(CO)_2NOH]_0 = 12 \times 10^{-4}$ mol dm^{-3}. [g] pK_a of *N*-hydroxyphthalimide.

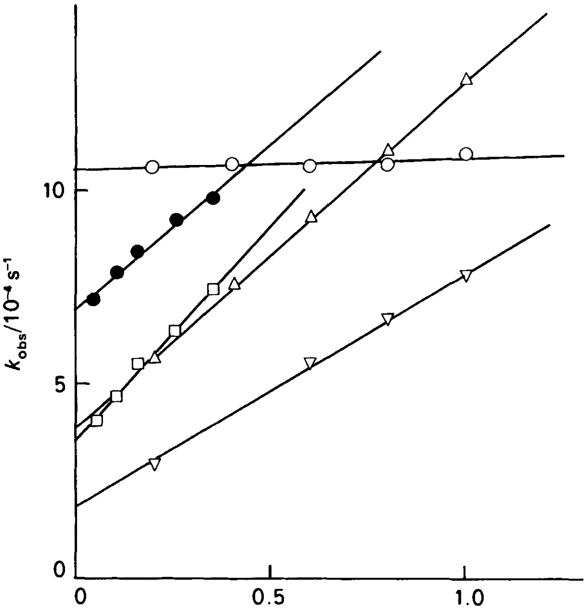


Figure 2. The effect of the total buffer concentration of 1,4-diazabicyclo[2.2.2]octane, $[Buf]_T$, on observed pseudo-first-order rate constants (k_{obs}) for the cleavage of phthalimide at pH 8.64 (▽), 9.06 (□), 9.14 (△), 9.53 (●) and 10.19 (○). The solid lines are drawn through the least-squares-calculated points using equation (2) and the parameters listed in Table 1.

Cleavage of Phthalimide (PTH) and N-*Bromopropylphthalimide (NBPPH) in Propane*-1,3-*diamine (PDA) Buffers*.—The effects of the buffer solutions of PDA on the nucleophilic cleavages of PTH and NBPPH were studied at different pH. The rate constants, k_{obs}, obeyed equation (2) where k_n was considered as the only unknown parameter. The values of k_o at different pH were calculated from the relationships: $k_o = k_{OH} K_w/(a_H + K_a)$ for PTH with k_{OH} = 26.3 dm^3 mol^{-1} s^{-1}, K_a = 3.05 × 10^{-10} mol dm^{-3} and K_w = 1.449 × 10^{-14} mol^2 dm^{-6},[11] and $k_o = k_{OH}\, a_{OH}$ for NBPPH with k_{OH} = 26.3 dm^3 mol^{-1} s^{-1}. The calculated values of k_n are shown in Table 2. The observed data were also treated with equation (2) where both k_o and k_n were considered as unknown parameters. The calculated values of k_n were not significantly different from those obtained by considering only k_n as the unknown parameter. This happened simply because the contributions of the k_o term compared with the $k_n[Buf]_T$ term were negligible at most of the pH values for PTH, and NBPPH. It is evident from the values of k_n shown in Tables 1 and 2 that PDA and 2-methoxyethylamine are more reactive than DABCO.

Aminolysis of N-*Bromopropylphthalimide (NBPPH) in* 2-*Methoxyethylamine Buffers and* N-*Hydroxyphthalimide (NHPH) in Propane*-1,3-*diamine (PDA) and* 2-*Methoxyethylamine Buffers*.—The reactions of PDA with NHPH and 2-methoxyethylamine with NBPPH and NHPH were found to exhibit intermolecular GA–GB catalysis. The observed rate constants (k_{obs}) obeyed equation (3) where k_n and k_B represent

$$k_{obs} - k_o = k_n[Buf]_T + k_B[Buf]_T^2 \qquad (3)$$

uncatalysed second-order and buffer-catalysed third-order rate constants, respectively. The hydrolysis of NHPH appeared to be extremely slow within the pH range *ca.* 7.66–10.10 at 30 °C. We therefore neglected k_o in comparison with k_{obs} within the limits of the present experimental conditions. The rate constants, k_n and k_B, as summarized in Table 2 were calculated from equation (3) using the least-squares technique. The fitting of the observed data to equation (3) is evident from a few representative plots of Figure 3 and standard deviations of k_n and k_B (Table 2). It is interesting to note that within the limits of experimental conditions, the contributions due to the $k_B[Buf]_T^2$ term were 34–93 and 14–38% for the reactions of 2-methoxyethylamine with NBPPH and NHPH, respectively, and 7–28% for the reactions of PDA with NHPH.

Discussion

Cleavage of Phthalimide (PTH) N-*Hydroxyphthalimide (NHPH) and* N-*Bromopropylphthalimide (NBPPH) in DABCO Buffers*.—The general rate law for the aqueous cleavage of PTH, NHPH, and NBPPH in the presence of DABCO may be given as equation (4) where $[SH]_T$ represents the total

$$\text{rate} = k_o[SH]_T + k_1[DABCO][SH] + k_2[DABCO][S^-] \qquad (4)$$

concentration of imides, [SH] and $[S^-]$ represent the

Table 2. Apparent second- and third-order rate constants for the reactions of *N*-substituted phthalimides with primary amines at 30 °C.

$C_6H_4(CO)_2NR$[a] R	Amine	pH	k_n[b]/ 10^{-3} dm^3 mol^{-1} s^{-1}	k_B[b]/ 10^{-3} dm^6 mol^{-2} s^{-1}	$[Buf]_T$[c] range/ mol dm^{-3}	No. of Runs	% C[d] range
H	$H_2N(CH_2)_3NH_2$	8.24[e]	9.87 ± 0.20[f]	—	0.2–0.7	5	
		8.57	19.3 ± 0.1	—	0.05–0.35	5	
		8.77	50.7 ± 0.5	—	0.05–0.35	5	
		9.04	80.8 ± 0.4	—	0.05–0.35	5	
		10.63[g]	453 ± 10	—	0.02–0.07	5	
		10.90	363 ± 2	—	0.02–0.06	5	
		11.01	341 ± 1	—	0.02–0.06	5	
		11.24	291 ± 5	—	0.02–0.06	5	
$(CH_2)_3Br$	$H_2N(CH_2)_3NH_2$	8.52	3.22 ± 0.12	—	0.10–0.35	5	
		8.73	6.15 ± 0.12	—	0.10–0.35	5	
		8.97	13.8 ± 0.3	—	0.05–0.35	5	
		9.13	22.2 ± 0.2	—	0.05–0.35	5	
$(CH_2)_3Br$	$MeOCH_2CH_2NH_2$	9.37[g]	2.13 ± 0.12	11.0 ± 0.2[f]	0.1–0.6	5	34–76
		9.60	2.60 ± 0.32	19.7 ± 0.6	0.1–0.7	7	43–84
		9.91	1.62 ± 1.51	29.0 ± 2.6	0.1–0.7	7	64–93
		10.07	4.64 ± 1.60	33.1 ± 2.8	0.1–0.7	7	42–83
OH	$H_2N(CH_2)_3\overset{+}{N}H_3$	7.66[e]	2.16 ± 0.10	2.06 ± 0.34	0.10–0.35	5	9–25
		8.37	10.0 ± 0.8	9.28 ± 2.73	0.10–0.35	5	8–25
		8.76	24.2 ± 0.6	27.5 ± 2.1	0.10–0.35	5	10–28
		8.99	35.5 ± 1.1	30.6 ± 3.8	0.10–0.35	6	8–23
		9.22	60.4 ± 3.3	47.9 ± 11.5	0.10–0.35	6	7–22
OH	$MeOCH_2CH_2NH_2$	9.27[g]	9.45 ± 0.56	19.1 ± 2.0	0.10–0.34	6	17–41
		9.42	12.8 ± 0.5	22.2 ± 1.8	0.10–0.35	6	15–38
		9.66	17.2 ± 0.8	28.4 ± 2.9	0.10–0.35	6	14–37
		10.10	27.0 ± 2.1	41.4 ± 7.3	0.10–0.35	6	13–35

[a] $[C_6H_4(CO)_2NR]_0 = 2 \times 10^{-4}$ mol dm^{-3}, 1% MeCN in the reaction mixture, $\lambda = 300$ nm for R = H, and $(CH_2)_3Br$ and $[C_6H_4(CO)_2NR]_0 = 12 \times 10^{-4}$ mol dm^{-3}, 3% MeCN into the reaction mixture, $\lambda = 410$ nm for R = OH. [b] Calculated from equations (2) and (3) as described in the text. [c] Total buffer concentration range. [d] $\% C = 100\, k_B[Buf]_T^2/(k_n[Buf]_T + k_B[Buf]_T^2)$. [e] Ionic strength 1.5 mol dm^{-3}. [f] Error limits are standard deviations. [g] Ionic strength 1.0 mol dm^{-3}.

concentration of non-ionized and ionized forms of imide, respectively, and [DABCO] is the concentration of non-protonated DABCO. The observed rate law, rate = $k_{obs}[SH]_T$, and equations (2) and (4) may easily produce equation (5) where

$$k_nQ_2 = k_2K_aK_2 + k_1K_2a_H \qquad (5)$$

$Q_2 = (a_H + K_a)\,(a_H + K_2)$ and K_a and K_2 represent the ionization constant of PTH and monoprotonated DABCO ($DABCOH^+$), respectively.

The aqueous cleavage of PTH was studied at four different pH in the buffer solutions of DABCO. The observed data were treated with equation (5) and the least-squares calculated values of $k_2K_aK_2$ and k_1K_2 are $(-0.53 \pm 1.40) \times 10^{-22}$ mol dm^{-3} s^{-1} and $(2.18 \pm 0.12) \times 10^{-12}$ s^{-1}, respectively. The fitting of the observed data to equation (5) is evident from the standard deviations of the calculated parameters. The negative value of $k_2K_aK_2$ with a standard deviation of more than 100% indicates that $k_2K_aK_2$ is negligible compared with $k_1K_2a_H$ under the experimental conditions imposed. Thus, it seems that ionized phthalimide is non-reactive towards DABCO. This conclusion reduces equation (5) to equation (6). The value of k_1K_2 as

$$k_nQ_2 = k_1K_2a_H \qquad (6)$$

calculated from equation (6) is $(2.14 \pm 0.07) \times 10^{-12}$ s^{-1}. The fitting of the observed data to equation (6) is evident from the standard deviation associated with calculated value of k_1K_2. The calculated value of k_1K_2 was used to calculate k_1 with known value of K_2 which is summarized in Table 3.

Buffer solutions of DABCO of four different pH were used to study the effects of DABCO on the cleavage of NHPH. The observed data were found to obey equation (5) and the least-squares calculated values of $k_2K_aK_2$ and k_1K_2 are $(18.9 \pm 2.1) \times 10^{-20}$ dm^3 mol^{-1} s^{-1} and $(6.00 \pm 0.99) \times 10^{-11}$ s^{-1}, respectively. The calculated values of $k_2K_aK_2$ and k_1K_2 were used to calculate k_2 and k_1 with known values of K_a and K_2. These results are shown in Table 3.

Since NBPPH does not contain any easily ionizable protons, equation (6) will therefore be reduced to $k_nQ_2 = k_1K_2$ for this imide, where $Q_2 = a_H + K_2$. The values of k_nQ_2 were obtained at 3 different pH values ranging from 8.64 to 9.67. The average value of k_1K_2 turned out to be $(15.3 \pm 0.9) \times 10^{-3}$ s^{-1} which was used to calculate k_1 as shown in Table 3.

Aminolysis of Phthalimide (*PTH*) *in Propane*-1,3-*diamine* (*PDA*) *Buffers*.—The nucleophilic cleavage of PTH was studied within the pH range of 8.24–11.24 under the buffer solutions PDA. The general rate law for the cleavage of PTH, within the pH range 8.24–9.04, may be given as equation (7) where

$$\begin{aligned} \text{rate} = {} & k_0[SH]_T + k_1[H_2NCH_2CH_2CH_2\overset{+}{N}H_3][SH] \\ & + k_2[H_2NCH_2CH_2CH_2\overset{+}{N}H_3][S^-] \\ & + k'_2[H_2NCH_2CH_2CH_2NH_2][SH] \end{aligned} \qquad (7)$$

$[H_2NCH_2CH_2CH_2\overset{+}{N}H_3]$ and $[H_2NCH_2CH_2CH_2NH_2]$ represent the concentration of monoprotonated and non-protonated PDA, respectively. The observed rate law and equations (2)

$$k_nQ_1 = k_2K_1K_a + k'_2K_1K_2 + k_1K_1a_H \qquad (8)$$

and (7) may lead to equation (8) where $Q_1 = (a_H + K_a)(a_H + K_1)$ and K_1 and K_2 are the ionization constants for di-

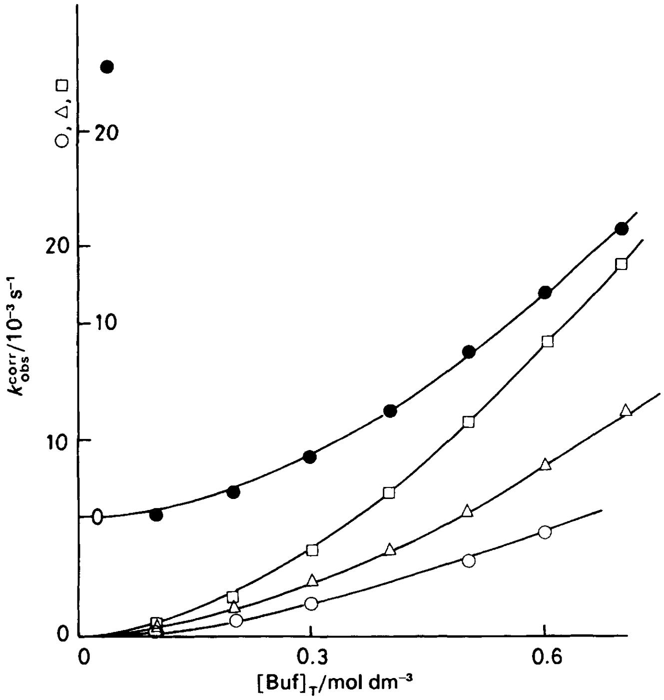


Figure 3. Plots showing the dependence of $k^{\text{corr}}_{\text{obs}}$ upon the total buffer concentrations of 2-methoxyethylamine, $[\text{Buf}]_T$, in the cleavage of *N*-bromopropylphthalimide at pH 9.37 (○), 9.60 (△), 9.91 (●), and 10.07 (□). The solid lines are drawn through the least-squares-calculated points using equation (3) and the parameters listed in Table 2. $k^{\text{corr}}_{\text{obs}} = k_{\text{obs}} - k_{\text{o}}$.

and mono-protonated PDA, respectively. The observed data were treated with equation (8) and the least-squares-calculated values of $k_2K_1K_a + k'_2K_1K_2$ and k_1K_1 values are $(12.2 \pm 4.1) \times 10^{-20}$ mol dm^{-3} s^{-1} and $(4.38 \pm 1.24) \times 10^{-11}$ s^{-1}, respectively. The kinetically indistinguishable term such as $k''_2[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][^{-}\text{OH}][\text{SH}]$ has been considered to be unimportant for the reasons that intermolecular general-base catalysis could not be detected in these reactions and generally such catalysis could be detected with highly basic amines at considerably high pH. Furthermore, the occurrence of k''_2 term leaves unexplained the question as to why a term such as $k'_3[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2][^{-}\text{OH}][\text{SH}]$ could not be detected.

The general rate law for the reaction kinetics studied within the pH range 10.63–11.24 may be given as equation (9).

$$\begin{aligned}\text{rate} = k_\text{o}[\text{SH}]_\text{T} + k_2[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][\text{S}^-] +\\ k'_2[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2][\text{SH}] +\\ k_3[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2][\text{S}^-]\end{aligned} \quad (9)$$

Equation (10) can be easily derived from observed rate law and

$$k_nQ_2 = k_3K_2K_a + (k_2K_a + k'_2K_2)a_\text{H} \quad (10)$$

equations (2) and (9). In equation (10), $Q_2 = (a_\text{H} + K_a)(a_\text{H} + K_2)$. The observed data fitted well into equation (10) and the least-squares calculated values of $k_3K_aK_2$ and $k_2K_a + k'_2K_2$ are $(11.9 \pm 1.0) \times 10^{-22}$ mol dm^{-3} s^{-1} and $(248 \pm 7) \times 10^{-12}$ s^{-1}, respectively. The values of k_1 and k_3 were calculated from the calculated values of k_1K_1 and $k_3K_2K_a$ using known values of K_1, K_2, and K_a. These results are shown in Table 3.

Aminolysis of N-*Bromopropylphthalimide* (*NBPPH*) *in PDA Buffers*.—The nucleophilic cleavage of NBPPH was studied in the buffer solutions of PDA of varying pH (8.52–9.13). The general rate law may be given as equation (11). Equation (11)

$$\begin{aligned}\text{rate} = \{k_\text{o} + k_1[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3]\\ + k'_2[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2]\}[\text{SH}]_\text{T}\end{aligned} \quad (11)$$

coupled with equation (2) and the observed rate law gave

$$k_nQ_3 = k_1K_1 + \frac{k'_2K_1K_2}{K_w}a_{\text{OH}} \quad (12)$$

equation (12) where $Q_3 = a_\text{H} + K_1$, a_{OH} is the activity of the hydroxide ion and K_w is the ionic product of water. The plot of k_nQ_3 *versus* a_{OH} turned out to be essentially linear. The least-squares calculated values of k_1K_1 and $k_2K_1K_2/K_w$ from equation (12) are $(54.9 \pm 5.0) \times 10^{-13}$ s^{-1} and $(13.2 \pm 0.4) \times 10^{-7}$ dm^3 mol^{-1} s^{-1}, respectively. These values were used to calculate k_1 and k_2 which are shown in Table 3.

Rearrangement of equation (12) yields equation (13). The observed data were also treated with equation (13) and the

$$k_nQ_3a_\text{H} = k'_2K_1K_2 + k_1K_1a_\text{H} \quad (13)$$

calculated values of $k'_2K_1K_2$ and k_1K_1 are $(19.3 \pm 0.6) \times 10^{-21}$ mol dm^{-3} s^{-1} and $(5.42 \pm 0.30) \times 10^{-12}$ s^{-1}, respectively. These values were also used to calculate k_1 and k'_2 which are shown in Table 3.

Aminolysis of N-*Hydroxyphthalimide* (*NHPH*) *in PDA Buffers*.—The reaction rates of the cleavage of NHPH were studied under the buffer solutions of PDA of pH ranging from 7.66–9.22. The general rate law for the reaction may be given as equation (14).

$$\begin{aligned}\text{rate} = k_1[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][\text{SH}] +\\ k_2[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][\text{S}^-] +\\ k'_2[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2][\text{SH}] +\\ k_3[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2][\text{S}^-] +\\ k_5[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3] \times\\ [\text{H}_3\overset{+}{\text{N}}\text{CH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][\text{S}^-] +\\ k_6[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2] \times\\ [\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][\text{S}^-] +\\ k_7[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3]^2[\text{S}^-] +\\ k'_5[\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2] \times\\ [\text{H}_3\overset{+}{\text{N}}\text{CH}_2\text{CH}_2\text{CH}_2\overset{+}{\text{N}}\text{H}_3][\text{S}^-]\end{aligned} \quad (14)$$

The observed rate law and equation (14) can easily yield equation (15).

$$k_{\text{obs}} = \frac{(k_3K_1K_2K_aa_\text{H}^{-1} + k_2K_1K_a + k'_2K_1K_2 + k_1K_1a_\text{H})[\text{Buf}]_\text{T}}{(a_\text{H} + K_a)(a_\text{H} + K_1)} + \frac{(k_6K_1^2K_2K_a + (k_7K_1^2K_a + k'_5K_1K_2K_a)a_\text{H} + k_5K_1K_aa_\text{H}^2)[\text{Buf}]_\text{T}^2}{(a_\text{H} + K_a)(a_\text{H} + K_1)^2a_\text{H}} \quad (15)$$

Comparison of equations (3) and (15) produces the following equations.

$$k_\text{n} = \frac{k_3K_1K_2K_a + (k_2K_1K_a + k'_2K_1K_2)a_\text{H} + k_1K_1a_\text{H}^2}{(a_\text{H} + K_a)(a_\text{H} + K_1)a_\text{H}} \quad (16)$$

Table 3. Rate constants for the cleavage of *N*-substituted phthalimide in the buffer solutions of primary and tertiary amines.

$C_6H_4(CO)_2NR$ R	Amine	pK_a[a]	Buffer–catalysed and non-catalysed rate constants
H	DABCO[b]	9.10 (pK_2)	$10^3k_1 = 2.70 \pm 0.09^c$ dm^3 mol^{-1} s^{-1}
			$k_2 = d$
$(CH_2)_3Br$			$10^3k_1 = 1.93 \pm 0.11$ dm^3 mol^{-1} s^{-1}
OH			$10^3k_1 = 75.5 \pm 12.5$ dm^3 mol^{-1} s^{-1}
O^-			$10^3k_2 = 0.232 \pm 0.026$ dm^3 mol^{-1} s^{-1}
CO_2Et^e			$10^3k_1 = 406$ dm^3 mol^{-1} s^{-1}
H	$PDAH^{+\,f}$	9.18 (pK_1)	$10^3k_1 = 66.3 \pm 18.8$ dm^3 mol^{-1} s^{-1}
$(CH_2)_3Br$			$10^3k_1 = 8.31 \pm 0.76^g$ dm^3 mol^{-1} s^{-1}
			$= 8.20 \pm 0.45^h$ dm^3 mol^{-1} s^{-1}
OH			$k_1 = d$
			$10^3\,k_2 = 74.4 \pm 0.6$ dm^3 mol^{-1} s$^{-1\,i}$
			$= 71.3 \pm 3.0$ dm^3 mol^{-1} s$^{-1\,j}$
			$10^3k_5 = 70.1 \pm 1.8$ dm^6 mol^{-2} s^{-1}
			$k'_5 = 3.10 \pm 0.75$ dm^6 mol^{-2} s^{-1}
H	PDA[k]	10.62 (pK_2)	$10k_3 = 1.63 \pm 0.14$ dm^3 mol^{-1} s^{-1}
$(CH_2)_3Br$			$k'_2 = 1.21 \pm 0.04$ dm^3 mol^{-1} s$^{-1\,g}$
			$= 1.22 \pm 0.04$ dm^3 mol^{-1} s$^{-1\,h}$
OH			$10k_3 = 7.27 \pm 2.4$ dm^3 mol^{-1} s$^{-1\,i}$
			$= 10.4 \pm 1.3$ dm^3 mol^{-1} s$^{-1\,j}$
$(CH_2)_3Br$	$MeOCH_2CH_2NH_2$	9.45	$10^3k_1 = 4.24 \pm 0.86$ dm^3 mol^{-1} s^{-1}
			$10^3k_{GB} = 52.4 \pm 1.3$ dm^6 mol^{-2} s^{-1}
OH			$k_1 = d$
			$10^3k_2 = 22.4 \pm 1.3$ dm^3 mol^{-1} s^{-1}
			$= 23.6 \pm 1.0$ dm^3 mol^{-1} s^{-1}
			$10k''_3 = 747 \pm 323$ dm^6 mol^{-2} s^{-1}
			$= 529 \pm 99$ dm^6 mol^{-2} s^{-1}
			$10^3k_5 = 45.7 \pm 3.8$ dm^6 mol^{-2} s-1
			$10^3k_7 = 48.9 \pm 4.0$ dm^6 mol^{-2} s^{-1}

[a] pK_a values of the conjugate acids of amines were obtained from references 8–10. [b] DABCO = 1,4-diazabicyclo[2.2.2]octane. [c] Error limits are standard deviations. [d] This term did not reveal detectable contribution to the rate within the limits of the experimental conditions imposed. [e] Obtained from reference 10. [f] $PADH^+ = H_3\overset{+}{N}(CH_2)_3NH_2$. [g] Calculated from equation (12). [h] Calculated from equation (13). [i] Calculated from equation (18). [j] Calculated from equation (19). [k] PDA = $H_2N(CH_2)_3NH_2$. [l] Calculated from equation (22). [m] Obtained as described in the text.

$$k_B = \frac{k_6K_1^2K^2K_a + (k_7K_1^2K_a + k'_5K_1K_2K_a)a_H + k_5K_1K_aa_H^2}{(a_H + K_a)(a_H + K_1)^2a_H} \qquad (17)$$

A plot of $k_nQ_1a_H$ *versus* a_H was found to be linear which implies that $k_1K_1a_H^2 \ll k_3K_1K_2K_a + (k_2K_1K_a + k'_2K_1K_2)a_H$. This conclusion simplifies equation (16) to equation (18). The least-squares-calculated values of $k_3K_1K_2K_a$ and $k_2K_1K_a +$ $k'_2K_1K_2$ are $(1.18 \pm 0.39) \times 10^{-26}$ mol^2 dm^{-6} s^{-1} and $(5.03 \pm 0.04) \times 10^{-17}$ mol dm^{-3} s^{-1}, respectively. The insignificant contribution of the $k_1K_1a_H^2$ term compared with other terms of equation (16) could be attributed to the extremely low concentration of non-ionized NHPH ([SH]) within the pH range of the present study. This shows that all the terms such as $k'_2[H_2NCH_2CH_2CH_2NH_2][SH]$, $k''_2[H_2NCH_2CH_2CH_2\overset{+}{N}H_3][\bar{O}H][SH]$, and $k'_3[H_2NCH_2CH_2CH_2NH_2][\bar{O}H][SH]$ may be neglected compared with the corresponding equivalent terms involving $[S^-]$. The kinetic term, $k''_3[H_2NCH_2CH_2CH_2\overset{+}{N}H_3][\bar{O}H][S^-]$ was neglected for the reason that the similar probable term, $k_4[H_2NCH_2CH_2CH_2NH_2][\bar{O}H][S^-]$ could not be detected. The calculated values of $k_3K_1K_2K_a$ ($= 1.18 \times 10^{-26}$ mol^2 dm^{-6} s^{-1}) and $k_2K_1K_a$ ($= 5.03 \times 10^{-17}$ mol dm^{-3} s^{-1}) were used to calculate k_3 and k_2. These results are shown in Table 3.

$$k_nQ_1a_H = k_3K_1K_2K_a + (k_2K_1K_a + k'_2K_1K_2)a_H \qquad (18)$$

Equation (18) can be rearranged to equation (19) by considering $k_2K_1K_a + k'_2K_1K_2 \simeq k_2K_1K_a$. The observed data obeyed equation (19). The least-squares calculated values of $k_2K_1K_a$ and $k_3K_1K_2K_a/K_w$ are $(4.82 \pm 0.20) \times 10^{-17}$ mol dm^{-3} s^{-1} and $(1.17 \pm 0.15) \times 10^{-12}$ s^{-1}, respectively. These values were also used to calculate the values of k_2 and k_3 which are shown in Table 3.

$$k_nQ_1 = k_2K_1K_a + k_3K_1K_2K_aK_w^{-1}a_{OH} \qquad (19)$$

The observed data for the buffer-catalysed cleavage of NHPH revealed a linear plot of k_BQ_4 *versus* a_H where $Q_4 = (a_H + K_a)(a_H + K_1)^2$. The linearity of the plot implies that the k_6 term is insignificant compared with other terms of equation (17). The kinetically indistinguishable k_7 term may be neglected compared with k'_5 term for the reason that the contribution of k_6 term is insignificant. The reaction appeared to involve GA catalysis. Diprotonated PDA ($H_3\overset{+}{N}CH_2CH_2CH_2\overset{+}{N}H_3$), being a stronger GA than monoprotonated ($H_2NCH_2CH_2CH_2\overset{+}{N}H_3$), made the k_5 and k'_5 terms more significant compared with the k_6 and k_7 terms, equation (17). The least-squares calculated values of the slope ($= k_5K_1K_a$) and intercept ($= k'_5K_1K_2K_a$) of the plot of k_BQ_4 *versus* a_H are $(4.74 \pm 0.12) \times 10^{-17}$ s^{-1} and $(5.02 \pm 1.21) \times 10^{-26}$ mol dm^{-3} s^{-1}, respectively. These values were used to calculate k_5 and k'_5 which are summarized in Table 3.

Aminolysis of N-*Hydroxyphthalimide* (*NHPH*) *in 2-Methoxyethylamine Buffers.*—The rates of reactions of 2-methoxyethylamine with NHPH was studied within the pH range 9.27–10.10. The general rate law for this reaction may be given as

$$\text{rate} = \{k_1[\text{SH}] + k_2[\text{S}^-] + k_3''[\text{S}^-][\overset{-}{\text{O}}\text{H}]\}[\text{RNH}_2] + \{k_5[\text{S}^-][\text{R}\overset{+}{\text{N}}\text{H}_3] + k_7[\text{S}^-][\text{RNH}_2]\}[\text{RNH}_2] \quad (20)$$

Based on the general rate law [equation (20)], the derived kinetic equation may be given as equation (21) where K_a' is the ionization constant of conjugate acid of 2-methoxyethylamine. Equation (21) is related to equation (3) by equations (22) and (23).

$$k_{\text{obs}} = \frac{\{k_3''K_aK_a'K_w + k_2K_aK_a'a_H + k_1K_a'a_H^2\}[\text{Buf}]_T}{(a_H + K_a)(a_H + K_a')a_H} + \frac{\{k_7K_aK_a'^2 + k_5K_aK_a'a_H\}[\text{Buf}]_T^2}{(a_H + K_a)(a_H + K_a')^2} \quad (21)$$

$$k_n = \frac{k_3''K_aK_a'K_w + k_2K_aK_a'a_H + k_1K_a'a_H^2}{(a_H + K_a)(a_H + K_a')a_H} \quad (22)$$

$$k_B = \frac{k_7K_aK_a'^2 + k_5K_aK_a'a_H}{(a_H + K_a)(a_H + K_a')^2} \quad (23)$$

The plot of $k_nQ_5a_H$ *versus* a_H, where $Q_5 = (a_H + K_a)(a_H + K_a')$, was found to be linear. The linearity of this plot shows that $k_1K_a'a_H^2$ is negligible compared with other terms of equation (22). The extremely low [SH] makes the k_1 term negligible compared with other terms involving $[\text{S}^-]$. For this reason we have neglected the kinetically indistinguishable term, $k_2'[\text{SH}][\text{RNH}_2][\overset{-}{\text{O}}\text{H}]$. The GA-specific base catalysis term, $k_7''[\text{S}^-][\text{RNH}_2][\text{R}\overset{+}{\text{N}}\text{H}_3][\overset{-}{\text{O}}\text{H}]$ which is kinetically indistinguishable from the k_7 term, has also been neglected for the qualitative reason that the occurrence of such term should also add a term $k[\text{S}^-][\text{RNH}_2]^2[\text{R}\overset{+}{\text{N}}\text{H}_3]$ to the rate law. However, such a term could not be detected. The intercept ($= k_3''K_aK_a'K_w$) and slope ($=k_2K_aK_a'$) of the plot of $k_nQ_5a_H$ *versus* a_H turned out to be $(3.93 \pm 1.70) \times 10^{-28}$ mol^2 dm^{-6} s^{-1} and $(8.13 \pm 0.49) \times 10^{-18}$ mol dm^{-3} s^{-1}, respectively. These values were used to calculate k_3'' and k_2 as shown in Table 3. The values of k_3'' and k_2 were also calculated from the slope ($= k_3''K_aK_a$) and intercept ($= k_2K_aK_a'$) of the plot of k_nQ_5 *versus* a_{OH}. These results are shown in Table 3.

Equation (23) indicates that the plot of $k_B(a_H + K_a)(a_H + K_a')^2$ *versus* a_H should be linear. Such a plot was found to be linear. The calculated values of $k_7K_aK_a'^2$ and $k_5K_aK_a'$ are $(6.30 \pm 0.51) \times 10^{-27}$ mol dm^{-3} s^{-1} and $(1.66 \pm 0.14) \times 10^{-17}$ s^{-1}, respectively. These values were used to calculate k_7 and k_5 as shown in Table 3.

Aminolysis of N-*Bromopropylphthalimide* (*NBPPH*) *in* 2-*Methoxyethylamine Buffers*.—The reactions of 2-methoxyethylamine with NBPPH were studied within the pH range 9.37–10.07. The observed data appeared to obey rate law (24) where $[\text{Sub}]_T$ represents the total concentration of

$$\text{rate} = \{k_o + k_1[\text{RNH}_2] + k_{GB}[\text{RNH}_2]^2\}[\text{Sub}]_T \quad (24)$$

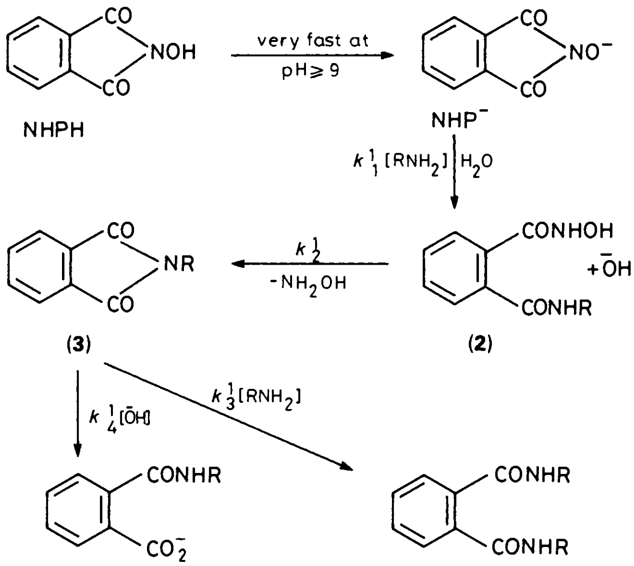
NBPPH. Equations (24), (3), and the observed rate law yield equations (25) and (26). The observed data were treated with

$$k_n = k_1K_a'/(a_H + K_a') \quad (25)$$

$$k_B = k_{GB}K_a'^2/(a_H + K_a')^2 \quad (26)$$

equations (25) and (26) and the calculated values of k_1 and k_{GB} are $(4.24 \pm 0.86) \times 10^{-3}$ mol dm^{-3} s^{-1} and $(52.4 \pm 1.3) \times 10^{-3}$ dm^6 mol^{-2} s^{-1}, respectively.

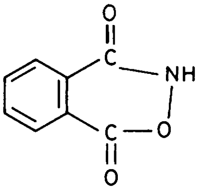
Consecutive Nature of the Reactions of N-*Hydroxyphthalimide* (*NHPH*) *with Propane*-1,3-*diamine* (*PDA*) *and* 2-*Methoxyethylamine*.—The rates of reactions of PDA with NHPH were studied in the total buffer concentration range 0.05–0.35 mol dm^{-3} at pH 9.01 and 300 nm. In contrast with usual expected decrease in absorbance values at 300 nm (A_{obs}^{300}) (as has been observed in the reactions of PDA with PTH and NBPPH under essentially similar experimental conditions), the values of A_{obs}^{300} show a distinct increase in the initial phase of the reaction followed by a smooth decrease with time in the latter phase of the reaction. This is evident from a few representative plots of Figure 1. Similar observations were obtained for the reactions of 2-methoxyethylamine with NHPH at pH 9.59 and total amine buffer concentration range of 0.05–0.35 mol dm^{-3}. These observations indicate the formation of a stable intermediate on the reaction path, the molar extinction coefficient (ε^{300}) of which is higher than that of NHP$^-$ at 300 nm. The values of ε^{300} of NHP$^-$ and *N*-alkyl substituted phthalimides are 1 250 dm^3 mol^{-1} cm^{-1} and *ca.* 2 000–2 500 dm^3 mol^{-1} cm^{-1}, respectively. We suggest that the intermediate is most likely the *N*-alkyl substituted phthalimide. The simplest reaction scheme which could explain these observations may be shown in Scheme 1.



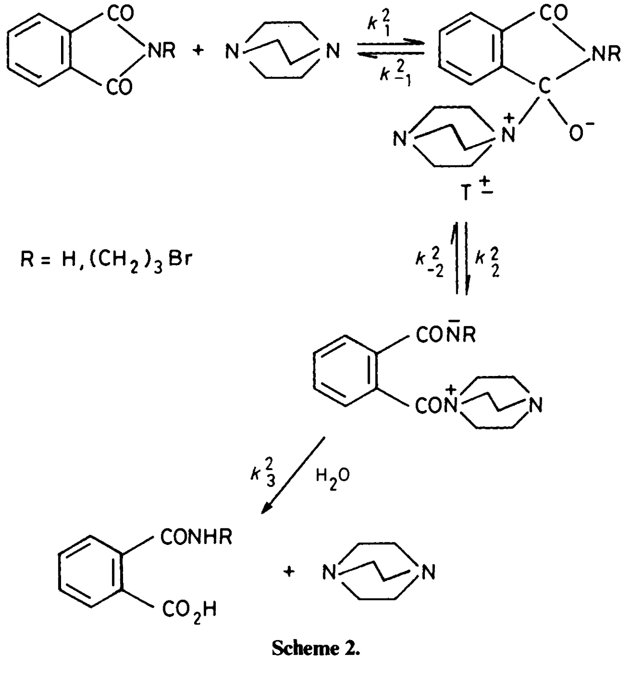
Scheme 1.

The k_2^1 step involves a hydroxide-ion-catalysed nucleophilic substitution reaction. The rate constants, k_2^1, for hydroxide-ion-catalysed cyclization reactions of the methyl *o*-carbamoylbenzoate, methyl *o*-aminomethylbenzoate, phthalimide, ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]carbamate (EBC) and *o*-(*N*-hydroxycarbamoyl)benzohydroxamic acid are 3.1 × 10^3 (25.9 °C),[12] 7 × 10^3 (30 °C),[13] 4.9 (25.9 °C,[12] 4.1 × 10^4 (30 °C)[14] and *ca.* 10^7 dm^3 mol^{-1} s^{-1} (30 °C),[14] respectively. These results suggest that the value of $k_2^1[^-\text{OH}]$ might be much larger than 10^{-3} s^{-1} at pH ≥ 9.0. The rate constants, $k_1^1[\text{RNH}_2]$, were determined by monitoring the disappearance of NHP$^-$ as a function of time at 410 nm. The final phase of the plots of A_{obs}^{300} *versus* time (Figure 1) were used to calculate the values of $k_3^1[\text{RNH}_2]$ using equation (1). Although the calculated values of $k_3^1[\text{RNH}_2]$ are not very reliable because of the consecutive nature of the reaction (Scheme 1), the values of $k_3^1[\text{RNH}_2]$ for the reactions of NHP$^-$ with PDA and 2-methoxyethylamine are *ca.* 1.5 times larger than those obtained for the reactions of NBPPH with PDA and 2-methoxyethylamine under similar experimental conditions. The values of k_1^1/k_3^1 turned out to be *ca.* 2 for the reactions of both PDA and 2-methoxyethylamine with NHP^-. Both rate constants, $k_1^1[RNH_2]$ and $k_3^1[RNH_2]$ are of the order of 10^{-3} s^{-1}. Thus, it is apparent that $k_2^1 \gg k_1^1 > k_3^1$.

The probable formation of (**4**) in the k_2^1 step may be ruled out for the following reasons. (*i*) The observed data on related reactions show that the magnitude of k_2^1 is highly dependent on the basicity of the leaving group while it is essentially independent of the basicity of the nucleophile.[12–14] The conjugate acid of HO$\bar{N}$H is presumably much stronger than that of R$\bar{N}$H with R as an alkyl group. Thus, the formation of (**4**) is unlikely compared with that of (**3**) in the k_2^1 step. (*ii*) We did not observe the formation of (**4**) in the cyclization of EBC. (*iii*) A product similar to (**4**) was obtained in the cyclization of ethyl *N*-[*o*-(*N*-hydroxy-*N*-methylcarbamoyl)benzoyl]carbamate.


(**4**)

We did not observe the occurrence of k_2^1 step (Scheme 1) in the reactions of PDA with PTH and NBPPH and 2-methoxyethylamine with NBPPH. The most obvious reason for this may be explained as follows. The magnitude of k_2^1 may be expected to be in the region of 4.9 dm^3 mol^{-1} s^{-1} which is the value of the second-order rate constant for hydroxide-ion-catalysed cyclization of phthalamide to phthalimide. The value of $k_2^1[^-OH]$ is therefore *ca.* $\leqslant 10^{-4}$ s^{-1} at pH $\leqslant$ 10.0. Under such conditions, the values of $k_1^1[RNH_2]$ are large enough compared with $k_2^1[^-OH]$ to diminish completely the consecutive nature of the reaction and observed data obeyed equation (1) perfectly.

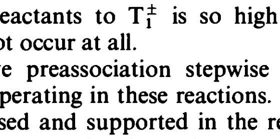


Scheme 2.

Mechanistic Conclusions

Cleavage of Phthalimide and N-*Substituted Phthalimides in DABCO Buffers.*—The nucleophilic second-order rate constants for the reactions of DABCO with non-ionized PTH, NHPH, NBPPH, and *N*-ethoxycarbonylphthalimide (k_1) and ionized NHPH (k_2) appeared to be significantly dependent on the leaving ability of the leaving groups. Although the present data are not sufficient to favour either a stepwise mechanism or a concerted mechanism involving simultaneous occurrence of bond formation and bond cleavage between the nucleophile and electrophilic centres and the leaving group and electrophilic centres, respectively, we prefer the stepwise mechanism as shown in Scheme 2. Our preference for the stepwise mechanism (Scheme 2) is based on the fact that the occurrence of such mechanism has been ascertained in the hydroxylaminolysis of *N*-ethoxycarbonylphthalimide.[10] It may be concluded that $k_{-1}^2 > k_2^2$.[7–9,15,16] The k_3^2 step presumably involves intramolecular general-base catalysis and hence we assume that $k_3^2[H_2O] > k_{-2}^2$. However, the magnitudes of $k_3^2[H_2O]$ and k_{-2}^2 cannot be easily ascertained. These conclusions lead to k_2^2 step as the rate-determining step. The rate constant k_1 [equation (5)] is therefore equal to $k_2^2k_1^2/k_{-1}^2$.

The ionized forms of PTH did not show the detectable reactivity toward DABCO. If the reactions of DABCO with ionized PTH are assumed to follow the mechanism as shown in Scheme 2, then it can be shown that the lifetime of tetrahedral addition intermediate, $T_1^{\pm}$, would be $>$ *ca.* 5.5 × 10^{-11} s.[8] The lifetime of $>$ *ca.* 10^{-11} s of $T_1^{\pm}$ is not significantly different from the period of a critical molecular vibration (10^{-13} s). Under such circumstances $T_1^{\pm}$ may not be expected to exist as a discrete intermediate with a definite potential well on the reaction path.[4,14] Thus, it seems that the activation barrier for the conversion of reactants to $T_1^{\pm}$ is so high that the reaction virtually does not occur at all.

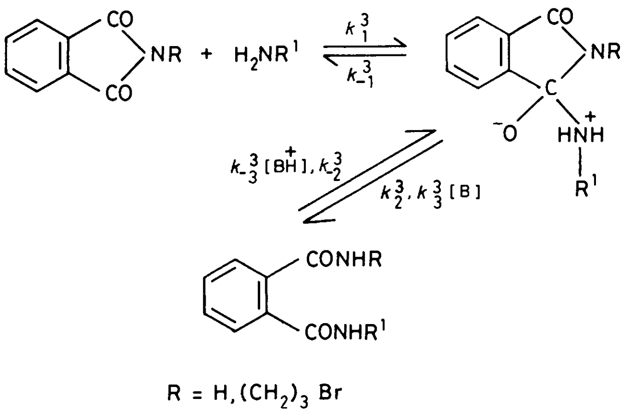


$T_1^{\pm}$

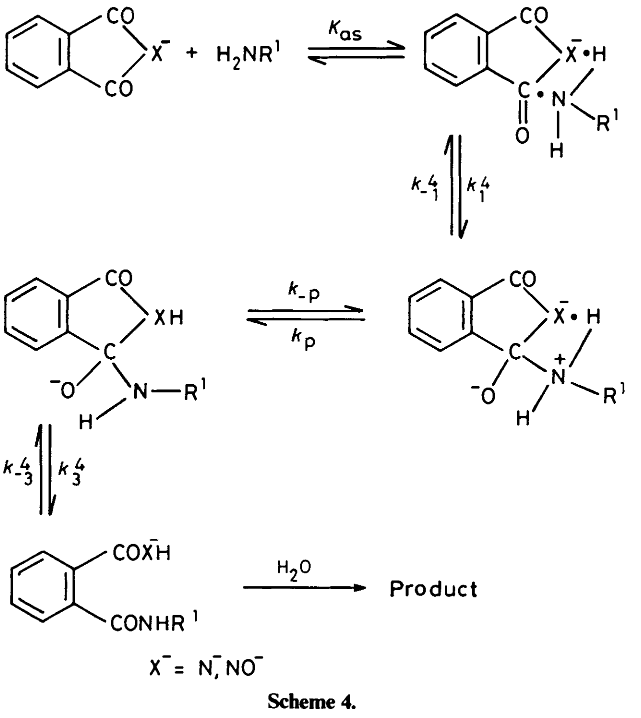
An alternative preassociation stepwise mechanism seems also not to be operating in these reactions. Such a mechanism has been proposed and supported in the reactions of ionized maleimide with DABCO where the rate law revealed both uncatalysed and GA-catalysed nucleophilic catalysis terms. But GA catalysis could not be detected in the reactions of ionized PTH with DABCO. The nucleophilic second-order rate constants for the reaction of DABCO with maleimide[8] is nearly 12 times larger than that with PTH. Thus, the significantly low reactivity of DABCO toward PTH might be one of the various reasons for the absence of GA catalysis in these reactions.

Aminolysis of Phthalimide and N-*Substituted Phthalimides in Primary Amine Buffers.*—It is interesting and surprising to note that the reaction of 2-methoxyethylamine with ionized NHPH involves specific-base catalysis while such catalysis could not be detected in the reaction of 2-methoxyethylamine with NBPPH. On purely electrostatic ground, the specific base catalysis should be more effective in case of NBPPH than ionized NHPH. One of the possible reasons for these observations might be attributed to the considerably low contribution of intermolecular GB catalysis in the 2-methoxyethylaminolysis of ionized NHPH compared with that of NBPPH (Table 2).

The nucleophilic second-order constant, k_2, for the reaction of monoprotonated PDA ($PDAH^+$) with ionized NHPH is slightly larger than those (k_1) for the reactions of $PDAH^+$ with non-ionized PTH. The observed value of k_2 for the reaction of $PDAH^+$ with ionized NHPH is *ca.* 600 times larger than that expected from the relative nucleophilic reactivities of $PDAH^+$ toward NBPPH and PTH with $\sigma_O{}^{-*} = -0.75$ (the source of Taft substituent constant, $\sigma_O{}^{-*}$, is described in the Appendix). These observations indicate that the reactions of primary amines with neutral and ionized phthalimides follow different mechanisms. The significantly larger reactivity of $PDAH^+$ with ionized NHPH compared with that expected from the nucleophilic reactivities of $PDAH^+$ with neutral phthalimides cannot be attributed solely to favourable electrostatic effects due to the presence of a cationic amino group in $PDAH^+$. This is evident from the values of $k_n^{NHP^-}/k_n^{NBPPH}$ of *ca.* 5 for $MeOCH_2CH_2NH_2$, *ca.* 9 for $PDAH^+$ and $k_n^{PDAH^+}/k_n^{MeOCH_2CH_2NH_2}$ of *ca.* 2 for NBPPH and *ca.* 3 for NHP^- where $k_n^{NHP^-}$ and k_n^{NBPPH} represent nucleophilic second-order rate constants for the reactions of amines with NHP^- and NBPPH, respectively. Similarly, $k_n^{PDAH^+}$ and $k_n^{MeOCH_2CH_2NH_2}$ represent nucleophilic second-order rate constants of the reactions of imides with $PDAH^+$ and $MeOCH_2CH_2NH_2$, respectively. These observations may be explained in terms of mechanisms shown in Schemes 3 (diffusion-controlled trapping, stepwise mechanism for the reactions of primary amines with neutral phthalimides) and 4 (pre-association stepwise mechanism for the reactions of primary amines with ionized phthalimides).

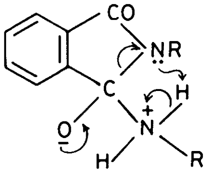


Scheme 3.

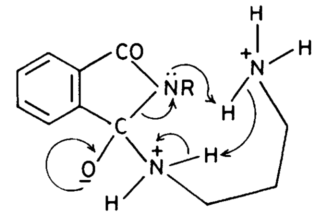


Scheme 4.

Recently, we proposed and supported mechanisms similar to those shown in Schemes 3 and 4 for the aminolysis of maleimide.[9] It is interesting to note that the values of $k_1^{PDAH^+}/k_1^{DABCO}$ are 25 and 4 for PTH and NBPPH, respectively. Similarly, the value of $k_1^{MeOCH_2CH_2NH_2}/k_1^{DABCO}$ is *ca.* 2 for NBPPH. These observations could be explained in terms of the probable occurrence of intramolecular GA catalysis in the k_2^3 step as shown by TS1. When $R^1 = CH_2CH_2CH_2\overset{+}{N}H_3$, the occurrence of TS2 cannot be completely ruled out. The principle of the least nuclear motion (PLNM) effect[17] favours TS1 while the four-membered cyclic strained transition state, TS1, is less favoured over the more flexible TS2 in terms strain energy requirements. As the molecular size of the R group increases, steric factors probably decrease the importance of this intramolecular GA catalysis. This characteristic might be responsible for considerably large proportion of intermolecular GB catalysis in the reaction of 2-methoxyethylamine with NBPPH (Table 2). Although the influence of the intramolecular GA–GB catalysis as shown by TS1 and TS2 seems to be considerably decreased in the reaction of $PDAH^+$ with NBPPH compared with that with PTH, its effect was large enough to offset completely the occurrence of intermolecular GB catalysis within the limits of the experimental conditions.

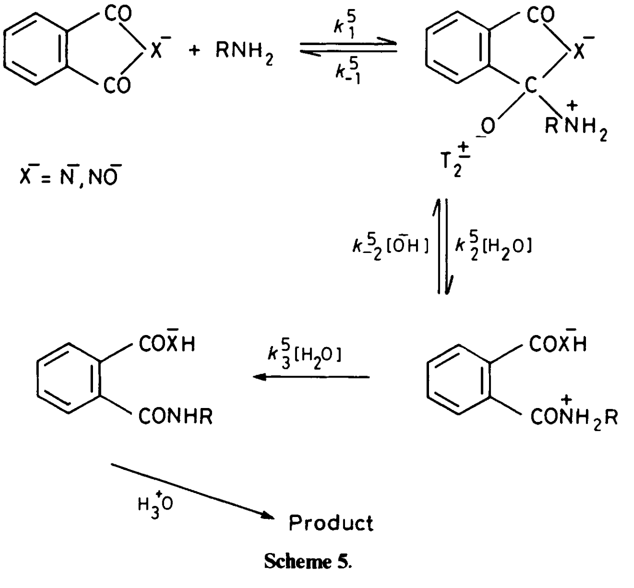


TS1



TS2

A sceptic might argue that the reactions of primary amines with ionized PTH and NBPPH follow a nucleophilic diffusion-controlled trapping, stepwise mechanism as shown in Scheme 5. The k_3^5 step presumably involves proton transfer in a thermodynamically favourable direction and hence $k_3^5[H_2O] \simeq 5.5 \times 10^{11}\ s^{-1}$. Thus, it may be possible that $k_{-2}^5[^-OH]$



Scheme 5.

$\ll k_3^5[H_2O]$ and therefore the k_2^5 step is the rate-determining step. In the reactions with DABCO, the k_3^5 step does not exist and hence product formation does not occur. We are, however, reluctant to favour this mechanism for the following reasons. (*i*) In the light of the mechanism of Scheme 5 it is difficult to explain the presence and absence of nucleophilic reactivity of DABCO toward non-ionized and ionized PTH, respectively. (*ii*) It is difficult to explain why the values of $k_n^{NHP^-}/k_n^{NBPPH}$ are *ca.* 9 for $PADH^+$, *ca.* 5 for $MeOCH_2CH_2NH_2$ and *ca.* 0.04 for ^-OH. (*iii*) It has been concluded earlier in the text that the lifetime of $T_2^{\pm}$ (Scheme 5) is extremely short and it is difficult to consider it as a discrete intermediate with a definite potential well on the reaction path.

Appendix

The Taft substituent constant (σ^*) for O^- was calculated from the relationship[18]

$$\sigma^* = 6.23\,\sigma_I$$

where σ_I for O^- is -0.12.[19]

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