JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 4, 547–561 (1991)

KINETICS AND MECHANISM OF THE CLEAVAGE OF PHTHALIMIDE IN BUFFERS OF TERTIARY AND SECONDARY AMINES. EVIDENCE OF INTRAMOLECULAR GENERAL ACID–BASE CATALYSIS IN THE REACTIONS OF PHTHALIMIDE WITH SECONDARY AMINES

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The reaction rates of the cleavage of phthalimide (PTH) were studied at 30 °C in buffer solutions of trimethylamine, triethylamine, triethanolamine, carbonate, piperidine, dimethylamine, morpholine, piperazine and *N*-methylpiperazine at different pH values. The reactivity of carbonate, triethylamine and triethanolamine toward PTH could not be detected under the experimental conditions applied. However, trimethylamine revealed nucleophilic reactivity toward non-ionized PTH (SH). The steric requirements of triethylamine and triethanolamine are ascribed to the absence of nucleophilic reactivities of these amines toward SH. Secondary amines show nucleophilic reactivity toward both SH and ionized PTH (S^-). The absence of nucleophilic reactivity of trimethylamine and the presence of nucleophilic reactivity of secondary amines toward S^- are attributed to the occurrence of intramolecular general acid–base catalysis due to the presence of a mobile proton at the nucleophilic site of the nucleophile. Intermolecular general base catalysis was observed in the reactions of SH with all secondary amines except piperidine and such catalysis could be detected in the reactions of S^- with morpholine, piperazine and *N*-methylpiperazine. Nucleophilic second-order rate constants for the reactions of secondary amines with SH (k_1) and S^- (k_2) reveal the Brønsted plots of slopes of *ca* 0.8 and 0.3, respectively. Similarly, the general base-catalysed third-order rate constants (k_4) for the reactions of secondary amines with SH yield a Brønsted plot of slope 1.2. These observations suggest the occurrence of diffusion-controlled trapping stepwise and pre-association stepwise mechanisms in the aminolysis of non-ionized and ionized phthalimide, respectively.

INTRODUCTION

It is now generally believed that most enzyme-catalysed reactions involve the occurrence of intra- and intermolecular general acid–base catalysis.[1] Since this was established, a huge amount of work has been carried out to understand the mechanistic aspects of such catalyses.[2] Although some facets are well understood, there are many others which are still mysterious.[2b] Most of the well executed studies[3] on general acid–base catalysis involve reactions in which the leaving groups maintain free rotation around the bond being cleaved during the course of the product formation. We have been studying the mechanistic aspects of general acid–base catalysis in addition–elimination reactions where the leaving groups do not have free rotation around the bond being cleaved in the rate-determining step.

We have studied the kinetics and mechanism of the aminolysis of maleimide. Primary amines revealed only nucleophilic catalysis toward both non-ionized and ionized maleimide.[4] Intramolecular general acid (GA) and general base (GB) catalysis were observed in the reactions of secondary amines with ionized and non-ionized maleimide, respectively.[5] A few tertiary amines showed GA catalysis in the nucleophilic cleavage of both ionized and non-ionized maleimide.[6] The absence of GA and GB catalysis in the reactions of primary amines with ionized and non-ionized maleimide was rationalized in terms of effective occurrence of intramolecular GA–GB catalysis as shown by T_1. However, in the aminolysis of *N*-ethoxycarbonylphthalimide, GA–GB catalysis could not be observed with 1,4-diazabicyclo[2.2.2]octane (DABCO), ethylenediamine,

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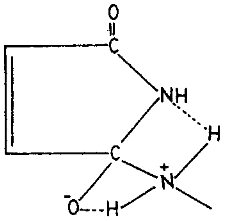
0894–3230/91/090547–15$07.50

Received 22 November 1990
Revised 1 June 1991



T_1

piperazine and morpholine, whereas GB catalysis was observed with hydroxylamine.[7] Recently, we studied the mechanistic aspects of the reactions of DABCO and propane-1,3-diamine (PDA) with phthalimide (PTH), *N*-bromopropylphthalimide (NBPPH) and *N*-hydroxyphthalimide (NHPH).[8] Intermolecular GA and GB catalyses were detected in the reactions of PDA and 2-methoxyethylamine with ionized NHPH and 2-methoxyethylamine with ionized NHPH and 2-methoxyethylamine with NBPPH, respectively.[8]

In continuation of our mechanistic study of GA–GB catalysis in the aminolysis of imide bonds and in order to obtain information on the effects of the structural moieties of maleimide and phthalimide on the rates of aminolysis, we have investigated the kinetics of the reactions of some tertiary and secondary amines with phthalimide. The results and probable explanation(s) are presented in this paper.

EXPERIMENTAL

Materials. All chemicals 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 prepared just before the start of the kinetic runs. Stock solutions of phthalimide (PTH) were prepared in acetonitrile and were always stored at low temperature whenever they were not in use.

Kinetic measurements. Reaction rates of aminolysis of PTH were studied spectrophotometrically by monitoring the disappearance of PTH as a function of time at 300 nm and 30 °C. A Beckman Model 35 UV–visible spectrophotometer was used throughout the rate studies. The details of the kinetic procedure and data analysis are described elsewhere.[9]

RESULTS

Cleavage of phthalimide (PTH) in buffer solutions of tertiary amines

The cleavage of PTH was studied in buffer solutions of trimethylamine, triethylamine and triethanolamine with different pH values at 30 °C. The observed pseudo-first-order rate constants (k_{obs}) obtained at a constant pH were treated with the equation

$$k_{obs} = k_0 + k_n[\mathrm{Buf}]_T \qquad (1)$$

where $[\mathrm{Buf}]_T$ represents the total amine buffer concentration. Buffer-independent first-order and buffer-dependent second-order rate constants, k_0 and k_n, respectively, were calculated from equation (1) by use of the least-squares technique. The results obtained are shown in Table 1.

The aqueous cleavage of PTH was also studied in buffer solutions of sodium carbonate at different pH values. The rate constants, k_{obs}, were treated with equation (1) and the least-squares calculated values of k_0 and k_n are listed in Table 1. The positive or negative values of k_n with standard deviations of more than 100% merely indicate the insignificant contribution of the $k_n[\mathrm{Buf}]_T$ term compared with the k_0 term in equation (1). Similar results were also obtained in the buffer solutions of triethylamine and triethanolamine at different pH (Table 1). However, a comparatively insignificant contribution of the $k_n[\mathrm{Buf}]_T$ term could be obtained only at high pH ($\geqslant 10{\cdot}72$) of buffer solutions of trimethylamine. The fitting of the observed data in equation (1) for trimethylamine is evident from the plots in Figure 1.

Cleavage of PTH in buffer solutions of secondary amines

The rates of aminolysis of PTH were studied at different pH in buffer solutions of piperidine, dimethylamine, morpholine, piperazine and *N*-methylpiperazine. The observed rate constants, k_{obs}, for the reactions of PTH with piperidine fitted equation (1). However, the calculated values of k_0 and k_n revealed an insignificant contribution of the k_0 term compared with the $k_n[\mathrm{Buf}]_T$ term in equation (1) under the experimental conditions applied. Hence a relatively more appropriate treatment of kinetic data with equation (1) was considered to involve k_n as the only unknown parameter. The values of k_0 at different pH were calculated from the relationship $k_0 = k'K_w/(a_H + K'_a)$, where the pH-independent rate constant for hydrolysis, k', the ionization constant, K'_a, of PTH and the ionic product of water, K_w, were taken as $26{\cdot}3\ \mathrm{dm^3\,mol^{-1}\,s^{-1}}$, $3{\cdot}05 \times 10^{-10}\ \mathrm{mol\,dm^{-3}}$ and $1{\cdot}449 \times 10^{-14}\ \mathrm{mol^2\,dm^{-6}}$, respectively.[8] The observed rate constants, k_{obs}, with known values of k_0 were used to calculate k_n from equation (1) using the linear least-squares technique. These results are shown in Table 1.

The observed rate constants, k_{obs}, for the reactions of PTH with dimethylamine, morpholine, piperazine and *N*-methylpiperazine appeared to follow the kinetic equation

$$k_{obs} - k_0 = k_n[\mathrm{Buf}]_T + k_b[\mathrm{Buf}]_T^2 \qquad (2)$$

Table 1. Apparent first- and second-order rate constants for the cleavage of phthalimide (PTH) in buffer solutions of sodium carbonate and secondary and tertiary amines[a]

Nucleophile	pH	10^3K_0[b] (s^{-1})	10^3k_n[b] ($dm^3\,mol^{-1}\,s^{-1}$)	$[Buf]_T$[c] range ($mol\,dm^{-3}$)	No. of runs
Carbonate	9·66 ± 0·01[d]	0·685 ± 0·028[d] (0·716)[e]	0·075 ± 0·130[d]	0·1–0·3	3
	10·24 ± 0·02	1·03 ± 0·04 (1·05)	0·046 ± 0·108	0·1–0·7	4
	11·03 ± 0·04	1·22 ± 0·01 (1·22)	−0·03 ± 0·03	0·1–0·7	4
Triethylamine	9·87 ± 0·06	0·840 ± 0·014 (0·858)	0·04 ± 0·08	0·035–0·280	4
	10·77 ± 0·02	1·21 ± 0·01 (1·19)	−0·10 ± 0·05	0·035–0·280	4
Triethanolamine	7·96 ± 0·02	0·040 ± 0·001 (0·032)	0·0265 ± 0·0018	0·1–0·8	5
	8·66 ± 0·01	0·083 ± 0·005 (0·146)	0·0370 ± 0·0100	0·1–0·8	5
	9·25 ± 0·06	0·385 ± 0·010 (0·426)	−0·05 ± 0·02	0·1–0·8	5
Trimethylamine	9·29 ± 0·06	0·350 ± 0·022 (0·453)	0·634 ± 0·053	0·05–0·70	5
	9·65 ± 0·06	0·618 ± 0·019 (0·723)	1·28 ± 0·05	0·05–0·70	5
	10·18 ± 0·05	1·00 ± 0·01 (1·02)	1·06 ± 0·03	0·05–0·70	5
	10·72 ± 0·05	1·22 ± 0·01 (1·18)	0·254 ± 0·036	0·05–0·70	5
	10·94 ± 0·05	1·32 ± 0·02 (1·21)	−0·07 ± 0·06	0·05–0·70	5
Piperidine	10·83 ± 0·02	(1·20)	46·6 ± 1·6	0·02–0·10	5
	10·99 ± 0·02	(1·21)	60·4 ± 2·0	0·02–0·10	5
	11·18 ± 0·06	(1·23)	82·5 ± 1·8	0·02–0·10	7
	11·52 ± 0·07	(1·24)	132 ± 2	0·02–0·10	7
Carbonate[f]	10·75 ± 0·04	1·38 ± 0·15 (1·18)	0·09 ± 0·37	0·1–0·7	5
Triethylamine[f]	11·54 ± 0·10	1·32 ± 0·07 (1·25)	−1·1 ± 0·4	0·035–0·280	4
	11·70 ± 0·09	1·29 ± 0·03 (1·25)	−1·3 ± 0·2	0·035–0·280	4

[a] Conditions: $[PTH]_0 = 3{\cdot}2 \times 10^{-4}\,mol\,dm^{-3}$; 30 °C; ionic strength, 1·0 mol dm^{-3}; $\lambda = 300$ nm; 1·6% (v/v acetonitrile added to the aqueous reaction mixture.

[b] Calculated from equation (1) as described in the text.

[c] Total buffer concentration range.

[d] Error limits are standard deviations.

[e] Parenthesized values of k_0 were calculated from the relationship $k_0 = k'K_w'/(a_H + K_a')$ with $k' = 26{\cdot}3\,dm^3\,mol^{-1}\,s^{-1}$, $K_w = 1{\cdot}449 \times 10^{-14}\,mol^2\,dm^{-6}$ and $K_a' = 3{\cdot}05 \times 10^{-10}\,mol\,dm^{-3}$.

[f] Reaction mixture contained 0·002 mol dm^{-3} dimethylamine.

where k_n and k_b represent buffer-independent and buffer-dependent nucleophilic second-order and third-order rate constants, respectively. The non-linear least-squares calculated values of k_n and k_b at different pH values for dimethylamine, morpholine, piperazine and *N*-methylpiperazine are summarized in Table 2. The fitting of the observed data to equation (2) is evident from some representative plots in Figure 2 and standard deviations associated with the calculated parameters, k_n and k_b, as shown in Table 2. The calculated values of the percentage contribution of the k_b term (Table 2) indicate an effective occurrence of general base catalysis.

A few kinetic runs were carried out in the presence of 0·002 mol dm^{-3} dimethylamine in buffer solutions of sodium carbonate (pH 10·75) and triethylamine

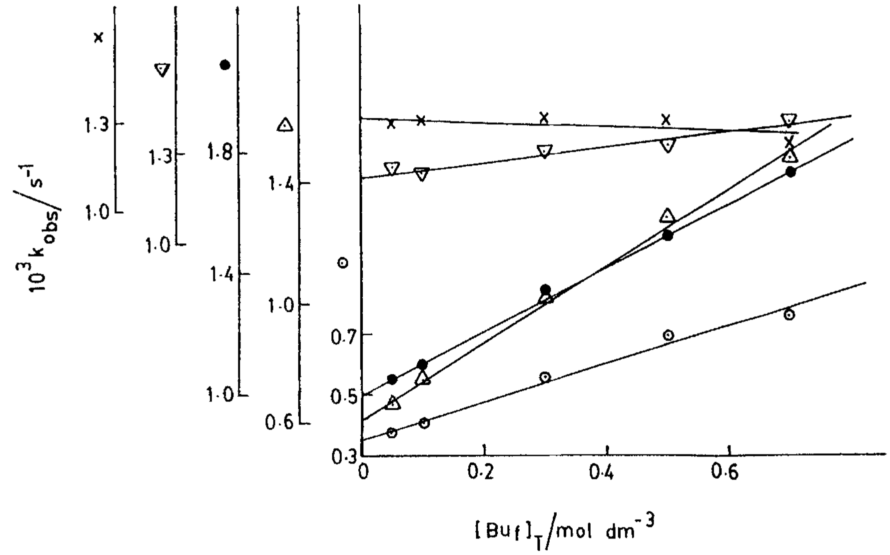


Figure 1. Effect of the total buffer concentrations of trimethylamine, $[Buf]_T$, on observed pseudo-first-order rate constants, k_{obs}, for the cleavage of phthalimide at pH 9·29 (⊙), 9·65 (△), 10·18 (●), 10·72 (▽) and 10·94 (×). The solid lines are drawn through the least-squares calculated points using equation (1) and the parameters listed in Table 1

Table 2. Apparent second- and third-order rate constants for the reactions of PTH with secondary amines[a]

Nucleophile	pH	10^3k_n[b] ($dm^3 mol^{-1} s^{-1}$)	10^3k_b[b] ($dm^6 mol^{-2} s^{-1}$)	$[Buf]_T$[c] range ($mol\ dm^{-3}$)	C[d] (%)	No. of runs
Dimethylamine	10·15 ± 0·06[e]	30·0 ± 10·4[e]	1230 ± 140[e]	0·02–0·09	45–79	8
	10·45 ± 0·04	34·7 ± 15·5	1990 ± 210	0·02–0·09	53–84	8
	10·68 ± 0·07	129 ± 16	1360 ± 220	0·02–0·09	17–49	8
	10·90 ± 0·04	174 ± 13	2170 ± 190	0·02–0·08	20–50	6
Morpholine	8·31 ± 0·02	3·22 ± 0·46	15·7 ± 0·9	0·02–0·60	9–74	8
	8·73 ± 0·01	12·1 ± 2·4	51·2 ± 4·1	0·10–0·70	30–75	5
	9·00 ± 0·01	13·6 ± 2·1	89·0 ± 5·1	0·02–0·50	12–77	9
	9·32 ± 0·02	18·6 ± 2·3	105 ± 5	0·02–0·60	10–77	8
Piperazine	6·36 ± 0·10	0·087 ± 0·011	0·151 ± 0·020	0·10–0·70	15–55	6
	6·81 ± 0·09	0·150 ± 0·019	0·414 ± 0·034	0·10–0·70	22–66	6
	6·93 ± 0·08	0·338 ± 0·025	0·675 ± 0·043	0·10–0·70	17–58	7
	7·29 ± 0·05	0·463 ± 0·150	0·903 ± 0·260	0·10–0·70	16–58	7
	9·93 ± 0·02	12·7 ± 2·0	425 ± 10	0·03–0·25	50–89	8
	10·45 ± 0·025	58·0 ± 7·9	422 ± 33	0·03–0·30	18–69	8
	10·79 ± 0·06	36·2 ± 2·3	566 ± 28	0·02–0·10	24–61	7
N-Methylpiperazine	9·63 ± 0·01	7·64 ± 2·32	157 ± 9	0·03–0·30	38–86	8
	10·15 ± 0·0	16·2 ± 2·0	170 ± 8	0·03–0·30	24–76	8
	10·65 ± 0·0	16·4 ± 1·5	97·1 ± 6·1	0·03–0·30	15–64	8

[a] Conditions: $[PTH]_0 = 3{\cdot}2 \times 10^{-4}$ mol dm^{-3}; 30 °C; ionic strength, 1·0 mol dm^{-3}; $\lambda = 300$ nm; 1·6% (v/v) MeCN acetonitrile added to the aqueous mixture.

[b] Calculated from equation (2) as described in the text.

[c] Total buffer concentration range.

[d] $C = (k_b[Buf]_T \times 100)/(k_n + k_b[Buf]_T)$.

[e] Error limits are standard deviations.

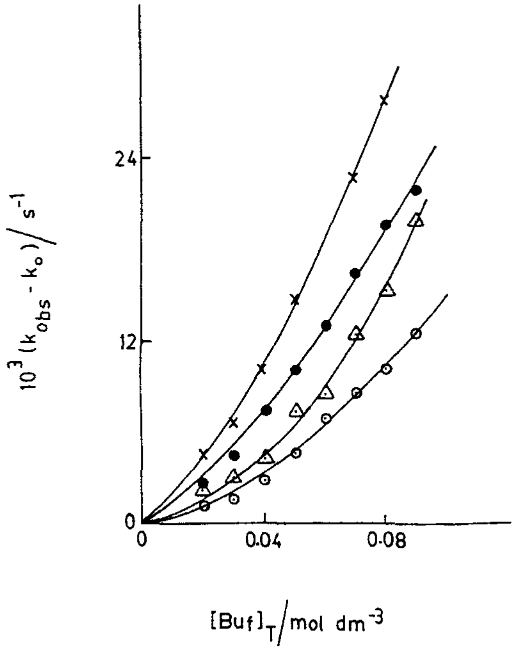


Figure 2. Plots showing the dependence of ($k_{obs} - k_0$) on the total concentrations of dimethylamine, $[Buf]_T$, in the cleavage of phthalimide at pH 10·15 (⊙), 10·45 (△), 10·68 (●) and 10·90 (×). The solid lines are drawn through the least-squares calculated points using equation (2) and the parameters listed in Table 2

(pH 11·54 and 11·70) of different concentrations. The observed rate constants, k_{obs}, did not show the occurrence of general base catalysis. These rate constants were treated with equation (1) and the calculated values of k_0 and k_n are shown in Table 1. The calculated values of k_n with >100% standard deviations reveal the absence of nucleophilic catalysis or general base catalysis for hydrolysis.

DISCUSSION

Cleavage of PTH in buffer solutions of tertiary amines

The general reaction scheme for the cleavage of PTH in buffer solutions of tertiary amines may be represented as

$$\begin{array}{ccc} SH + Am & \underset{\pm a_H}{\overset{K_a'}{\rightleftharpoons}} & S^- + Am \\ \downarrow k_1 & & \downarrow k_2 \\ & \text{Products (P)} & \end{array} \tag{3}$$

Based on this reaction scheme, the rate law for the reaction may be given as

$$\text{rate} = k_0[Sub]_T + k_1[SH][Am] + k_2[S^-][Am] \tag{4}$$

where [Am], [SH] and [S⁻] represent the concentrations of non-protonated amine and non-ionized and ionized PTH, respectively, and $[Sub]_T = [SH] + [S^-]$. The observed rate law (rate $= k_{obs}[Sub]_T$) and equation (4) can lead to the equation

$$k_{obs} = k_0 + \frac{k_2K_aK_a' + k_1K_aa_H}{(a_H + K_a)(a_H + K_a')}[Buf]_T \tag{5}$$

where K_a is the ionization constant of protonated amine and $[Buf]_T = [Am] + [AmH^+]$ with $[AmH^+]$ representing the concentration of protonated amine. Equation (5) is similar to equation (1) with

$$k_nQ = k_2K_aK_a' + k_1K_aa_H \tag{6}$$

where $Q = (a_H + K_a)(a_H + K_a')$. The observed data for the cleavage of PTH in buffer solutions of trimethylamine were treated with equation (6) and the least-squares calculated values of $k_2K_aK_a'$ and k_1K_a are $(3\cdot1 \pm 3\cdot6)\times10^{-23}$ mol dm^{-3} s^{-1} and $(6\cdot18 \pm 1\cdot29)\times10^{-13}$ s^{-1}, respectively. The calculated value of $k_2K_aK_a'$ with a standard deviation of more than 100% indicates that it is not statistically different from zero. It is interesting that the calculated value of $k_2K_aK_a'$ is nearly three times larger than the observed value of k_nQ at pH 10·72. The negative value of k_n at pH 10·94 {where $[S^-]/([S^-] + [SH]) = 0\cdot96$} further demonstrates the insignificant reactivity of S⁻ toward trimethylamine. Similar observations were obtained with 1,4-diazabicyclo[2.2.2]octane.[8]

These observations and conclusions reveal the absence of detectable reactivity of ionized PTH toward trimethylamine under the experimental conditions imposed. Thus, when the observed data were treated with equation (6) by setting k_2 equals to zero, the calculated value of k_1K_a turned out to be $(6\cdot98 \pm 0\cdot84)\times10^{-13}$ s^{-1}, which is *ca* 13% higher than that obtained without considering k_2 as zero. The calculated value of k_1K_a $(=6\cdot98\times10^{-13}$ s$^{-1})$ was used to calculate k_1 with a known value of K_a and the result is shown in Table 3.

Tertiary amine buffer-dependent cleavage of PTH may be attributed to either nucleophilic catalysis or kinetically equivalent general base catalysis of hydrolysis. We, however, rule out the possibility of the occurrence of general base catalysis of hydrolysis for the following reason. Trimethylamine and 1,4-diazabicyclo[2.2.2]octane revealed significant reactivity toward PTH. However, carbonate with a pK_2 (conjugate acid of dianion) value of 9·68[10] did not show a detectable reactivity toward PTH (Table 1). If the mechanism involving general base catalysis of hydrolysis were operating in these reactions, then it would be difficult to explain these observations. In a few related reactions[11] in which general base catalysis of hydrolysis has been unequivocally established, carbonate appeared to show the normal expected reactivity. Thus, the absence and presence of reactivity towards PTH

Table 3. Rate constants for the cleavage of PTH in buffer solutions of primary, secondary and tertiary amines

Nucleophile	pK_a[a]	$10^{11}K_1^{1}$[b] (dm^3 mol^{-1})	Buffer-catalysed and uncatalysed rate constants
Trimethylamine	9·95		$10^3k_1 = 6{\cdot}22 \pm 0{\cdot}75$[c] dm^3 mol^{-1} s^{-1} $10^3k_2 = 0$[d]
1,4-Diazabicyclo[2.2.2]octane	9·10 (pK_2)		$10^3k_1 = 2{\cdot}70$ dm^3 mol^{-1} s^{-1}[e] $10^3k_2 = 0$[d]
Triethylamine	10·63		$10^3k_1 = 0$[d] $10^3k_2 = 0$[d]
Triethanolamine	8·30		$10^3k_1 = 0$[d] $10^3k_2 = 0$[d]
Carbonate	9·68		$10^3k_1 = 0$[d] $10^3k_2 = 0$[d]
Piperidine	11·23		$10^3k_1 = 0$[d] $10^3k_2 = 173 \pm 3$[c] dm^3 mol^{-1} s^{-1}[f] $10k_4 = 0$[d] $10k_5 = 0$[d]
Dimethylamine	11·05	4910	$10^3k_1 = 0$[d] $10^3k_2 = 316 \pm 39$ dm^3 mol^{-1} s^{-1}[f] $10k_4 = 4910 \pm 430$[c] dm^6 mol^{-2} s^{-1} $10k_5 = 0$[d]
Morpholine	8·60	1·30	$10^3k_1 = 6{\cdot}61 \pm 3{\cdot}06$ dm^3 mol^{-1} s^{-1} $10^{-8}k_2^{1} = 5{\cdot}1$ s^{-1}[b] $10^3k_2 = 67{\cdot}9 \pm 27{\cdot}0$ dm^3 mol^{-1} s^{-1} $10k_4 = 1{\cdot}30 \pm 0{\cdot}07$ dm^6 mol^{-2} s^{-1} $10k_5 = 2{\cdot}60 \pm 0{\cdot}62$[c] dm^6 mol^{-2} s^{-1}
Piperazine-H$^+$	6·17 (pK_1)	0·00291	$10^3k_1 = 0{\cdot}0861 \pm 0{\cdot}0374$ dm^3 mol^{-1} s^{-1} $10^{-8}k_2^{1} = 29{\cdot}6$ s^{-1}[b] $10^3k_2 = 46$ dm^3 mol^{-1} s^{-1}[g] $10^4k_4 = 2{\cdot}91 \pm 0{\cdot}63$ dm^6 mol^{-2} s^{-1} $10k_5 = 1{\cdot}79 \pm 0{\cdot}49$ dm^6 mol^{-2} s^{-1}
Piperazine	9·98 (pK_2)	59·3	$10^3k_1 = 0$[d] $10^3k_3 = 56{\cdot}0 \pm 26{\cdot}6$ dm^3 mol^{-1} s^{-1}[h] $10k_6 = 59{\cdot}3 \pm 9{\cdot}3$ dm^6 mol^{-2} s^{-1} $10k_7 = 3{\cdot}20 \pm 2{\cdot}09$ dm^6 mol^{-2} s^{-1}
N-Methylpiperazine	9·25 (pK_2)	2·88	$10^3k_2'' = 5{\cdot}80$ dm^3 mol^{-1} s^{-1} $10^{-8}k_2^{1} = 2{\cdot}0$ s^{-1} $10^3k_3 = 19{\cdot}4 \pm 0{\cdot}6$ dm^3 mol^{-1} s^{-1}[i] $10k_6 = 2{\cdot}88 \pm 1{\cdot}20$ dm^6 mol^{-2} s^{-1} $10k_7 = 1{\cdot}84 \pm 1{\cdot}04$ dm^6 mol^{-2} s^{-1}
Propane-1,3-diamine	9·18 (pK_1)		$10^3k_1 = 66{\cdot}3$ dm^3 mol^{-1} s^{-1}[e] $k_4 = 0$[d] $k_5 = 0$[d]
	10·62 (pK_2)		$10^3k_3 = 163$ dm^3 mol^{-2} s^{-1}[e] $k_6 = 0$[d] $k_7 = 0$[d]

[a] pK_a values of conjugate acids of amines were obtained from Refs 4–9.

[b] Obtained from the relationships $k_2^{1} = k_3^{1}k_1/k_4$ and $K_1^{1} = k_4/k_3^{1}$ with $k_3^{1} = 10^{10}$ dm^3 mol^{-2} s^{-1}.

[c] Error limits are standard deviations.

[d] This term did not reveal a detectable contribution to the rate within the limits of the experimental conditions imposed.

[e] Obtained from Ref. 8.

[f] Calculated from equation (8).

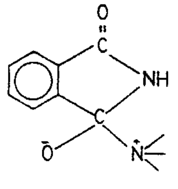
[g] The value of k_2 for PPZH$^+$ was calculated as follows. The value of k_2'' was estimated from the Brønsted plot (of slope of 0·8) which was constructed based on the observed points for PPZH$^+$ and morpholine as described in the text (broken line in Figure 3). The estimated value of k_2'' turned out to be 0·10 dm^3 mol^{-1} s^{-1}. The known values of k_2'', K_1, K_2 and K_a' were used to calculate k_2 from $k_2''K_1K_2 + k_2K_1K_a' = 16{\cdot}6 \times 10^{-18}$ [equation (17)].

[h] Calculated from the observed values of k_n as described in the text.

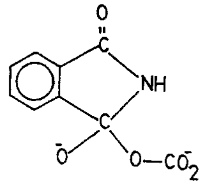
[i] Calculated from equation (21).

of carbonate and trimethylamine and of 1,4-diazabicyclo[2.2.2]octane, respectively, indicate the absence of general base catalysis of hydrolysis. It is also known[12] that in comparison with nucleophilic catalysis, general base-catalysed water attack at carbonyl carbon is less subject to the steric requirements of tertiary amines. The lack of detectable reactivity of triethylamine and triethanolamine toward PTH may therefore be attributed to the absence of general base catalysis in these reactions.

The steric requirement of carbonate may be considered to be less than that of trimethylamine and possibly than that of 1,4-diazabicyclo[2.2.2]octane and hence such an effect may not be responsible for the absence of catalytic cleavage of PTH in carbonate buffer solutions. The most plausible explanation for the presence and absence of reactivity of non-ionized PTH toward trimethylamine and carbonate, respectively, may be attributed to the relative stabilities of the addition intermediates formed during stepwise nucleophilic catalysis. Based on purely electrostatic interactions, the dipolar addition intermediate ($T^{\pm}$) formed by nucleophilic attack of a tertiary amine at the carbonyl carbon of non-ionized PTH is considered to be more stable than the dianionic addition intermediate (T^{2-}) formed by nucleophilic attack of CO_3^{2-} at the carbonyl carbon of PTH. Although the electronic push experienced by the rate-determining cleavage of the C—N bond in T^{2-} is apparently higher than that in $T^{\pm}$, the higher stability of $T^{\pm}$ compared with T^{2-} makes the overall energy barrier much higher for the reaction of non-ionized PTH with CO_3^{2-} than with tertiary amines of comparable basicity.



$T^{\pm}$



$T^{=}$

Aminolysis of PTH in buffer solutions of secondary monoamines

The cleavage of PTH in buffer solutions of piperidine showed simply a nucleophilic reaction between ionized PTH and piperidine. This shows that the contribution of the k_1 step in reaction (3) is negligible compared with the k_2 step in this case. The rate law for these reactions may be given as

$$\text{rate} = k_0[\text{Sub}]_T + k_2[S^-][\text{Am}] \qquad (7)$$

where [Am] represents the concentration of non-protonated secondary amine. The observed rate law and equations (1) and (7) can lead to the equation

$$k_n Q a_H = k_2 K_a K_a' a_H \qquad (8)$$

where $Q = (a_H + K_a)(a_H + K_a')$. The plot of $k_n Q a_H$ versus a_H appeared to be linear within the pH range of the study (10·83–11·52) and the linearity of such a plot indicates the insignificant contribution of the $k_1[SH][Am]$ term compared with the $k_2 K_a K_a' a_H$ term of equation (8). A search of the literature revealed that in several related reactions if a term similar to $k_2'[SH][Am][OH^-]$ which is kinetically indistinguishable from $k_2[S^-][Am]$ appeared in the rate law, then another term similar to $k_1[SH][Am]$ also appeared in the same rate law.[11–14] Hence the insignificant contribution of the $k_1[SH][Am]$ term rules out the significance of $k_2'[SH][Am][OH^-]$ compared with $k_2[S^-][Am]$. The least-squares calculated value of $k_2 K_a K_a'$ of $(31 \cdot 1 \pm 0 \cdot 5) \times 10^{-23}$ mol dm^{-3} s^{-1} was used to calculate k_2 and the result is shown in Table 3.

The cleavage of PTH in buffer solutions of dimethylamine and morpholine revealed the occurrence of both uncatalysed and general base-catalysed aminolysis of PTH. The general reaction scheme for such reactions may be represented by

$$\begin{tikzcd} SH + Am \arrow[rr, shift left, "K_a'"] \arrow[dr, "k_1\; k_4\,Am"'] & & S^- + Am \arrow[ll, shift left, "\pm a_H"] \arrow[dl, "k_2\; k_5\,Am"] \\ & \text{Product (P)} & \end{tikzcd} \qquad (9)$$

Based on this reaction scheme, the rate law for the reaction may be given as

$$\text{rate} = k_0[\text{Sub}]_T + k_1[SH][\text{Am}] + k_2[S^-][\text{Am}] + k_4[SH][\text{Am}]^2 + k_5[S^-][\text{Am}]^2 \qquad (10)$$

An additional term, $k_4'[S^-][Am][AmH^+]$ (where $[AmH^+]$ represents the concentration of protonated amine), which is kinetically indistinguishable from the $k_4[SH][Am]^2$ term may be ruled out for the qualitative reason that such a term could not be detected in the reactions of PTH with trimethylamine and 1,4-diazabicyclo[2.2.2]octane. The kinetic term involving general acid catalysis of tertiary amine nucleophilic-catalysed cleavage of ionized maleimide has been observed with trimethylamine and 1,4-diazabicyclo[2.2.2]octane.[6] Similarly, the kinetic term $k_5'[S^-][Am][AmH^+][OH^-]$, which is kinetically indistinguishable from $k_5[S^-][Am]^2$, may be ignored for the reasons that (i) the occurrence of such a term should result in the appearance of an additional term, $k'[S^-][Am]^2[AmH^+]$, in the rate law, which could not be observed, (ii) the occurrence of general acid-catalysed aminolysis of ionized PTH seems to be unimportant and (iii) the simultaneous occurrence of both general base or specific base and general acid catalyses in a single elementary step of a reaction is rare or almost non-existent. The reason for such catalytic behaviour was convincingly explained by Fox and Jencks.[11]

The observed rate law (rate $= k_{\text{obs}}[\text{Sub}]_T$) and equation (10) may lead to

$$k_{\text{obs}} - k_0 = \frac{k_2K_aK'_a a_H + k_1K_a a_H^2}{a_H(a_H + K_a)(a_H + K'_a)}[\text{Buf}]_T + \frac{k_5K_a^2K'_a + k_4K_a^2 a_H}{(a_H + K_a)^2(a_H + K'_a)}[\text{Buf}]_T^2 \quad (11)$$

Comparison of equations (2) and (11) gives the equations

$$k_nQa_H = k_2K_aK'_a a_H + k_1K_a a_H^2 \quad (12)$$

$$k_bQ_1 = k_5K_a^2K'_a + k_4K_a^2 a_H \quad (13)$$

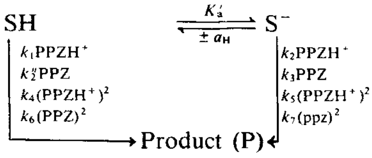
The observed rate constants, k_n, for dimethylamine revealed a linear variation of k_nQa_H against a_H within the pH range of the study. It is therefore apparent that under such experimental conditions, $k_1K_a a_H^2 \ll k_2K_aK'_a a_H$. The insignificant contribution of the k_1[SH] [Am] term shows that k'_2[SH] [Am] [OH$^-$] may be neglected in comparison with k_2[S$^-$] [Am]. These conclusions reduce equation (12) to equation (8). The linear least-squares calculated value of $k_2K_aK'_a$ is $(8\cdot59 \pm 1\cdot06) \times 10^{-22}$ mol dm^{-3} s^{-1}. The value of $k_2K_aK'_a$ of $(8\cdot59 \pm 1\cdot06) \times 10^{-22}$ mol dm^{-3} s^{-1} was used to calculate k_2 as shown in Table 3.

The observed rate constants, k_n, for morpholine showed a linear variation of k_nQ against a_H. The maximum contribution of the $k_1K_a a_H$ term toward k_nQ is *ca* 58% at pH 8·31. A kinetic term similar to k'_2[SH] [Am] [OH$^-$] term is insignificant compared with the k_2[S$^-$] [Am] term for dimethylamine and piperidine. Hence the k'_2[SH] [Am] [OH$^-$] term may be assumed to be negligible compared with the k_2[S$^-$] [Am] term for morpholine. The value of the k_2[S$^-$] [Am] term for dimethylamine and piperidine. Hence the k'_2[SH] [Am] [OH$^-$] term may be assumed to be negligible compared with the k_2[S$^-$] [Am] term for morpholine. The value of $k_2K_aK'_a$ and k_1K_a calculated from equation (12) are $(5\cdot20 \pm 2\cdot07) \times 10^{-20}$ mol dm^{-3} s^{-1} and $(1\cdot66 \pm 0\cdot77) \times 10^{-11}$ s^{-1}, respectively. These calculated values were used to calculate k_2 and k_1 as summarized in Table 3.

The observed values of k_b at different pH values for dimethylamine and morpholine obeyed equation (13). The values of $k_5K_a^2K'_a$ and $k_4K_a^2$ were calculated from equation (13) and the respective values obtained are $(-4\cdot0 \pm 1\cdot6) \times 10^{-31}$ mol dm^{-3} s^{-1} and $(4\cdot71 \pm 0\cdot38) \times 10^{-20}$ s^{-1} for dimethylamine and $(5\cdot01 \pm 1\cdot20) \times 10^{-28}$ mol dm^{-3} s^{-1} and $(8\cdot22 \pm 0\cdot45) \times 10^{-19}$ s^{-1} for morpholine. The calculated negative value of $k_5K_a^2K'_a$ for dimethylamine merely indicates that it is not statistically different from zero. Thus, by setting $k_5 = 0\cdot0$, the calculated value of $k_4K_a^2$ turned out to be $(3\cdot50 \pm 0\cdot34) \times 10^{-20}$ s^{-1}, which is *ca* 18% smaller than 4.71×10^{-20} s^{-1}. The calculated values of $k_5K_a^2K'_a$ and $k_4K_a^2$ were used to calculate k_5 and k_4 as shown in Table 3.

Aminolysis of PTH in buffer solutions of secondary diamines

The reaction rates of the cleavage of PTH were studied in buffer solutions of piperizine (PPZ) in the pH range 6·36–10·79. The general reaction scheme for the aminolysis of PTH under such buffers may be represented by



(14)

The rate law for the cleavage of PTH within the pH range 6·36–7·29 may be expressed as [reaction (14)]

$$\begin{aligned}\text{rate} = {} & k_0[\text{Sub}]_T + k_1[\text{PPZH}^+][\text{SH}] \\ & + k_2[\text{PPZH}^+][\text{S}^-] + k''_2[\text{PPZ}][\text{SH}] \\ & + k_4[\text{PPZH}^+]^2[\text{SH}] + k_5[\text{PPZH}^+]^2[\text{S}^-]\end{aligned} \quad (15)$$

where [H$^+$PPZH$^+$], [PPZH$^+$] and [PPZ] represent the concentrations of diprotonated, monoprotonated and non-protonated piperazine, respectively.

In the pH range 6·36–7·29, $[\text{PPZH}^+]/[\text{Buf}]_T = K_1/(a_H + K_1)$ and $[\text{PPZ}]/[\text{Buf}]_T = K_1K_2/[a_H(a_H + K_1)]$, where $[\text{Buf}]_T = [\text{H}^+\text{PPZH}^+] + [\text{PPZH}^+] + [\text{PPZ}]$ and K_1 and K_2 represent the ionization constants of H$^+$PPZH$^+$ and PPZH$^+$, respectively. The observed rate law and equation (15) may lead to

$$k_{\text{obs}} = k_0 + \frac{[k_1K_1a_H + k_2K_1K'_a + k''_2K_1K_2][\text{Buf}]_T}{(a_H + K'_a)(a_H + K_1)} + \frac{[k_4K_1^2a_H + k_5K_1^2K'_a][\text{Buf}]_T^2}{(a_H + K'_a)(a_H + K_1)^2} \quad (16)$$

Comparison of equations (2) and (16) gives the equations

$$k_nQ_2 = k_2K_1K'_a + k''_2K_1K_2 + k_1K_1a_H \quad (17)$$

$$k_bQ_3 = k_5K_1^2K'_a + k_4K_1^2a_H \quad (18)$$

with $Q_2 = (a_H + K'_a)(a_H + K_1)$ and $Q_3 = Q_2(a_H + K_1)$.

A plot of k_nQ_2 against a_H appeared to be linear within the pH range 6·36–7·29. The linearity of such a plot indicated that the kinetic terms such as k_3[PPZ] [S$^-$], k'_3[PPZ] [SH] [OH$^-$] and k''_3[PPZ] [S$^-$] [OH$^-$] were negligible compared with the terms in equation (17). This behaviour might be attributed to the extremely low concentrations of PPZ, S$^-$ and OH$^-$ under the experimental conditions applied. The kinetic term k'_2[PPZH$^+$] [SH] [OH$^-$], which is kinetically indistinguishable from k_2[PPZH$^+$] [S$^-$] and

$k''[\mathrm{PPZ}][\mathrm{SH}]$, may be ignored for the reason that such a term has been generally observed in related reactions at high pH with amines of relatively high basicities. Further, the $k_3'[\mathrm{PPZ}][\mathrm{SH}][\mathrm{OH}^-]$ term has been shown to be unimportant compared with the $k_3[\mathrm{PPZ}][\mathrm{S}^-]$ term in the pH range 9·93–10·79, as discussed later under Discussion. The observed data fit equation (17) reasonably well and the least-squares calculated values of $k_2K_1K_a' + k_2''K_1K_2$ and k_1K_1 are $(16{\cdot}6 \pm 6{\cdot}1) \times 10^{-18}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$ and $(5{\cdot}82 \pm 2{\cdot}53) \times 10^{-11}\ \mathrm{s^{-1}}$, respectively. The calculated value of k_1K_1 was used to calculate k_1 as shown in Table 3.

The observed data revealed a linear plot of k_bQ_3 versus a_H. Extremely low values of [PPZ] and $[\mathrm{S}^-]$ in the pH range 6·36–7·29 make the term $k_5''[\mathrm{PPZ}][\mathrm{H^+PPZH^+}][\mathrm{S}^-]$ insignificant compared with the kinetically equivalent term $k_5[\mathrm{PPZH^+}]^2[\mathrm{S}^-]$. The terms such as $k_4''[\mathrm{PPZ}][\mathrm{H^+PPZH^+}][\mathrm{SH}]$ and $k_5'[\mathrm{PPZ}][\mathrm{PPZH^+}][\mathrm{SH}]$, which are kinetically indistinguishable from $k_4[\mathrm{PPZH^+}]^2[\mathrm{SH}]$ and $k_5[\mathrm{PPZH^+}]^2[\mathrm{S}^-]$, respectively, are ignored for the reason that the presence of such terms should add an additional term $k_8[\mathrm{PPZH^+}][\mathrm{H^+PPZH^+}][\mathrm{SH}]$ in the rate law [equation (15)], but such a term has not been detected. Also, as discussed in the Appendix, the kinetic terms $k_4'[\mathrm{PPZH^+}][\mathrm{H^+PPZH^+}][\mathrm{S}^-]$ and $k_5''[\mathrm{PPZ}][\mathrm{H^+PPZH^+}][\mathrm{S}^-]$ are negligible compared with $k_4[\mathrm{PPZH^+}]^2[\mathrm{SH}]$.

The least-squares calculated values of $k_5K_1^2K_a'$ and $k_4K_1^2$ from equation (18) are $(24{\cdot}9 \pm 6{\cdot}9) \times 10^{-24}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$ and $(13.3 \pm 2{\cdot}9) \times 10^{-17}\ \mathrm{s^{-1}}$, respectively. These calculated values were used to calculate k_5 and k_4 as shown in Table 3.

Based on reaction (14), the rate law for the cleavage of PTH in buffer solutions of piperazine in the pH range 9·93–10·79 may be given as

$$\begin{aligned}\text{rate} = {} & k_0[\mathrm{Sub}]_\mathrm{T} + k_3[\mathrm{PPZ}][\mathrm{S}^-] \\ & + k_6[\mathrm{PPZ}]^2[\mathrm{SH}] + k_7[\mathrm{PPZ}]^2[\mathrm{S}^-] \qquad (19)\end{aligned}$$

The magnitudes of K_1 and K_2 make $a_\mathrm{H}^2 \ll K_1K_2 + K_1a_\mathrm{H}$ in the pH range 9·93–10·79 for piperazine. In such a pH range, $[\mathrm{PPZ}]/[\mathrm{Buf}]_\mathrm{T} = K_2/(a_\mathrm{H} + K_2)$, $[\mathrm{PPZH^+}]/[\mathrm{Buf}]_\mathrm{T} = a_\mathrm{H}/(a_\mathrm{H} + K_2)$ and $[\mathrm{H^+PPZH^+}]/[\mathrm{Buf}]_\mathrm{T} = a_\mathrm{H}^2/K_1(a_\mathrm{H} + K_2)$. The observed rate law and equation (19) give

$$\begin{aligned}k_\mathrm{obs} = {} & k_0 + \frac{k_3K_2K_a'[\mathrm{Buf}]_\mathrm{T}}{(a_\mathrm{H} + K_a')(a_\mathrm{H} + K_2)} \\ & + \frac{[k_6K_2^2a_\mathrm{H} + k_7K_2^2K_a'][\mathrm{Buf}]_\mathrm{T}^2}{(a_\mathrm{H} + K_a')(a_\mathrm{H} + K_2)^2} \qquad (20)\end{aligned}$$

Comparing equations (2) and (20), one obtains

$$k_nQ_4a_\mathrm{H} = k_3K_2K_a'a_\mathrm{H} \qquad (21)$$

$$k_bQ_5 = k_7K_2^3K_a' + k_6K_2^2a_\mathrm{H} \qquad (22)$$

with $Q_4 = (a_\mathrm{H} + K_a')(a_\mathrm{H} + k_2)$ and $Q_5 = Q_4(a_\mathrm{H} + K_2)$.

The variation of $k_nQ_4a_\mathrm{H}$ with a_H turned out to be linear and such a linearity shows that the terms such as $k_2[\mathrm{PPZH^+}][\mathrm{S}^-]$, $k_2'[\mathrm{PPZH^+}][\mathrm{SH}][\mathrm{OH}^-]$, $k_2''[\mathrm{PPZ}][\mathrm{SH}]$ and $k_1[\mathrm{PPZH^+}][\mathrm{SH}]$ are negligible compared with the $k_3[\mathrm{PPZ}][\mathrm{S}^-]$ term. The insignificant contribution of the $k_2''[\mathrm{PPZ}][\mathrm{SH}]$ term may be used as a qualitative basis to neglect $k_3'[\mathrm{PPZ}][\mathrm{SH}][\mathrm{OH}^-]$ compared with the $k_3[\mathrm{PPZ}][\mathrm{S}^-]$ term in equation (19). A kinetic term, $k_3''[\mathrm{PPZ}][\mathrm{S}^-][\mathrm{OH}^-]$, could not be kinetically detected. This is conceivable because such a term could not be detected with dimethylamine and piperidine, which are stronger bases than PPZ. The value of $k_3K_2K_a'$ was calculated from equation (21) and turned out to be $(13{\cdot}3 \pm 3{\cdot}1) \times 10^{-22}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$. However, the observed values of k_nQ_4 yielded a value of $k_3K_2K_a'$ of $(17{\cdot}9 \pm 8{\cdot}5) \times 10^{-22}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$. This value of $k_3K_2K_a'$ was used to calculate k_3 as shown in Table 3.

The plot of k_bQ_5 against a_H turned out to be linear, which indicated that $k_5[\mathrm{PPZH^+}][\mathrm{S}^-]$, $k_5''[\mathrm{PPZ}][\mathrm{H^+PPZH^+}][\mathrm{S}^-]$, $k_4[\mathrm{PPZH^+}]^2[\mathrm{SH}]$ and $k_4'[\mathrm{PPZH^+}][\mathrm{H^+PPZH^+}][\mathrm{S}^-]$ are negligible compared with $k_6[\mathrm{PPZ}]^2[\mathrm{SH}]$ and $k_7[\mathrm{PPZ}]^2[\mathrm{S}^-]$ under the experimental conditions used. Thus, within the pH range 9·93–10·79, the least-squares calculated values of $k_7K_2^2K_a'$ and $k_6K_2^2$ from equation (22) are $(1{\cdot}1 \pm 0{\cdot}7) \times 10^{-30}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$ and $(6{\cdot}50 \pm 1{\cdot}02) \times 10^{-20}\ \mathrm{s^{-1}}$, respectively. We ignore $k_6'[\mathrm{PPZ}]][\mathrm{PPZH^+}][\mathrm{S}^-]$ compared with $k_6[\mathrm{PPZ}]^2[\mathrm{SH}]$ for the qualitative reason that intermolecular general acid catalysis could not be observed in buffer solutions of trimethylamine and 1,4-diazabicyclo[2.2.2]octane. The values of k_7 and k_6 as calculated from the values of $k_7K_2^2K_a'$ and $k_6K_2^2$ are shown in Table 3.

The rates of aminolysis of PTH were studied in buffer solutions of *N*-methylpiperazine (NMPPZ) in the pH range 9·33–10·55. The general rate law shown by equation (19) with PPZ changed to NMPPZ is expected to be obeyed by these reactions. The observed values of k_n (Table 2) obtained in the pH range 9·63–10·65 obeyed equation (21). The value of $k_3K_2K_a'$ was calculated from equation (21) and turned out to be $(3{\cdot}33 \pm 0{\cdot}11) \times 10^{-21}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$. The rate constant, k_3, was calculated from the value of $k_3K_2K_a'$ $(= 3{\cdot}33 \times 10^{-21}\ \mathrm{mol\,dm^{-3}\,s^{-1}})$ and the result is shown in Table 3. The observed value of k_nQ_4 at pH 9·63, 10·15 and 10·65 gave $k_3K_2K_a' = (3{\cdot}42 \pm 0{\cdot}38) \times 10^{-21}\ \mathrm{mol\,dm^{-3}\,s^{-1}}$.

The observed value of $k_nQ_4a_\mathrm{H}$ $(= 22{\cdot}71 \times 10^{-31}\ \mathrm{mol^2\,dm^{-6}\,s^{-1}})$ at pH 9·33 revealed a significant positive deviation (*ca* 45%) from linearity of the plot of $k_nQ_4a_\mathrm{H}$ versus a_H derived from the observed points within the pH range 9·63–10·65. Nearly a 45% positive deviation of the observed point from linearity shows that the contribution of $(k_2K_a' + k_2'K_\mathrm{w} + k_2''K_2)a_\mathrm{H}^2$ {these terms are due to the inclusion of $k_2[\mathrm{NMPPZH^+}][\mathrm{S}^-]$, $k_2'[\mathrm{NMPPZH^+}][\mathrm{SH}][\mathrm{OH}^-]$ and $k_2''[\mathrm{NMPPZ}][\mathrm{SH}]$ terms in equation

(19)} toward $k_nQ_4a_H$ cannot be neglected at pH 9·33. However, the contribution of k_1[NMPPZH$^+$] [SH] compared with other terms in equation (19) can still be negligible. At pH 9·33, the value of $(k_2K_a' + k_2'K_w + k_2''K_2)a_H^2$ of $7\cdot13 \times 10^{-31}$ mol^2 dm^{-6} s^{-1} was calculated from the observed value of $k_nQ_4a_H$ and the calculated value of $k_3K_2K_a'a_H$ $(=15\cdot58 \times 10^{-31}$ mol^2 dm^{-6} s$^{-1})$. The nitrogen of the secondary amino group is presumably a more basic site than the nitrogen of the tertiary amino group in NMPPZ because dimethylamine is a stronger base than trimethylamine by nearly 1 pK unit. Hence the first protonation site in NMPPZ is the nitrogen of the secondary amino group and therefore the tertiary amino group acts as a nucleophile in NMPPZH$^+$. None of the tertiary amines in this study showed detectable nucleophilic reactivity toward ionized PTH and hence the k_2[NMPPZH$^+$] [S$^-$] term is unlikely to exist. The existence of k_2'[NMPPZH$^+$] [SH] [OH$^-$] may also be ruled out because the nitrogen of the tertiary amino group is the nucleophilic site in NMPPZH$^+$. These conclusions lead to $k_2''K_2a_H^2$ $= 7.13 \times 10^{-31}$ mol^2 dm^{-6} s^{-1} at pH 9.33 and the rate constant, k_2'', calculated from the value of $k_2''K_2a_H^2$ is shown in Table 3. Although the value of k_2'' is not very reliable, as it has been derived from a single observed point, it is comparable to the similar rate constants for trimethylamine and morpholine.

The observed intermolecular general base-catalysed rate constants, k_b, were found to fit equation (22) within the pH range 9·33–10·65. The least-squares calculated values of $k_7K_2^2K_a'$ and $k_6K_2^2$ are $(1\cdot77 \pm 1\cdot00) \times 10^{-29}$ mol dm^{-3} s^{-1} and $(9\cdot12 \pm 3\cdot78) \times 10^{-20}$ s^{-1}, respectively. The rate constants, k_7 and k_6, were calculated from the calculated values of $k_7K_2^2K_a'$ and $k_6K_2^2$, respectively, and these values are given in Table 3.

Mechanistic conclusions and speculations

General base catalysis of non-ionized PTH (SH)

Third-order rate constants, k_4 and k_6, for general base-catalysed reactions of non-ionized PTH with several secondary amines are plotted against the pK_a of the conjugate acid of general base catalysts as shown in Figure 3. All the observed points appeared to fall on a linear plot of slope $\beta_{gb} = 1\cdot24 \pm 0\cdot12$ and intercept $C = -11\cdot46 \pm 1\cdot13$ mol^{-2} dm^{-6} s^{-1}. Although all the general base catalysts in this study are neutral, except for monoprotonated piperazine (PPZH$^+$), the observed point for PPZH$^+$ does not show a significant deviation from the Brønsted plot in Figure 3. Similar observations were obtained in the general base-catalysed reactions of non-ionized maleimide with several secondary amines.[5] The cleavage of PTH in the buffer solutions of piperidine did not exhibit general base catalysis. Jencks and Carriuolo[15] observed general base catalysis in the reactions of p-nitrophenyl acetate (PNPA) with dimethylamine and n-butylamine, but such catalysis was not observed in the reactions of PNPA with piperidine and morpholine.[15]

A Brønsted β_{gb} value of 1·24 may be compared with a β value of 1·09 obtained in the general base-catalysed reactions of benzylpenicillin with primary amines.[13] Primary amine-catalysed aminolysis of 1-acetyl-1,2,4-triazole[11] and acetylimidazole[16,17] also gave a β value of 1·0. We have observed a β value of 0·79 for the secondary amine general base-catalysed

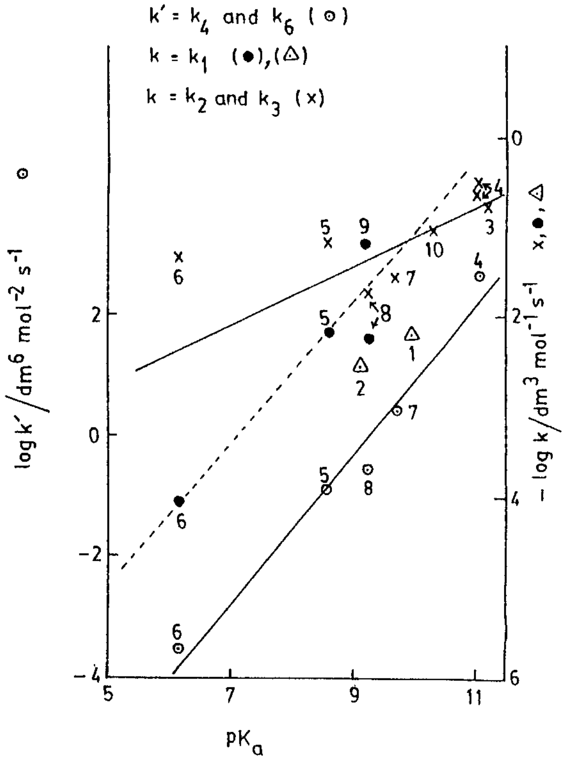
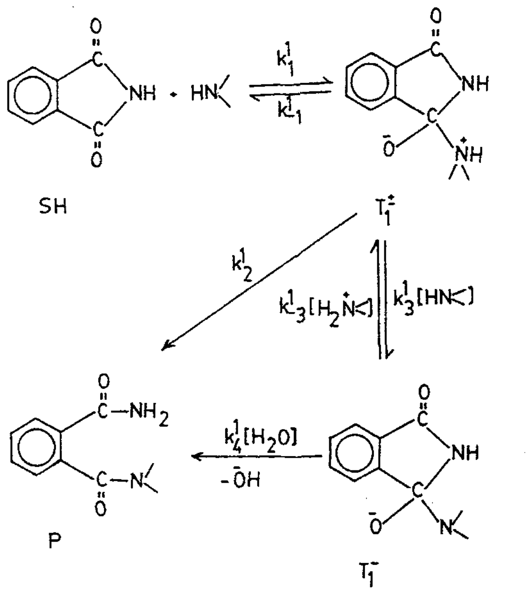


Figure 3. Dependence of the general base-catalysed third-order rate constants, k_4 and k_6 (⊙), and nucleophilic second-order rate constants, k_1 (●, △), for the reactions of non-ionized phthalimide and nucleophilic second-order rate constants, k_2 and k_3 (×), for the reactions of ionized phthalimide with secondary and tertiary amines and also a primary amine on the pK_a of the conjugate acid of amine at 30 °C. The solid lines are drawn through the least-squares calculated points from Brønsted equations: $\log k_{4 \text{ or } 6} = C + \beta_{gb}\text{p}K_a$, with (⊙) $C = -11\cdot46$ dm^6 mol^{-2} s^{-1} and $\beta_{gb} = 1\cdot24$ and (×) $\log k_{2 \text{ or } 3} = C_2 + \beta_{nuc2}\text{p}K_a$ with $C_2 = -4\cdot42$ dm^3 mol^{-1} s^{-1} and $\beta_{nuc2} = 0\cdot33$. In the Brønsted plots, 1 = triethylamine, 2 = 1,4-diazabicyclo[2.2.2]octane, 3 = piperidine, 4 = dimethylamine, 5 = morpholine, 6 = piperazine-H$^+$, 7 = piperazine, 8 = N-methylpiperazine, 9 = propane-1,3-diamine-H$^+$ and 10 = propane-1,3-diamine. Statistical corrections to pK_2 and k_3 and k_6 for the reactivity of 7 and 10 were made in the Brønsted plots

aminolysis of non-ionized maleimide.[5] A β value of *ca* unity has been also observed in the general base-catalysed aminolysis of phenyl acetate[18] and various substituted aryl quinoline-6-carboylates.[19] Our observed β_{gb} value of *ca* unity is indicative of a transition state in which a charge of $+1{\cdot}0$ has developed on the nitrogen of a nucleophile coupled with a general base. However, for the k_4 or k_6 step, both the general base and nucleophile (amine) are changing and $\beta_{gb} = \beta_1 + \beta_3$ (β_1 for k^1_1/k^1_{-1} and β_3 for k^1_3 in Scheme 1). Hence it is not possible to infer from the β_{gb} value whether in the transition state the proton is located on the attacking amine, on the catalytic amine or between two amines. The mechanism that is consistent with this observation is shown in Scheme 1. The existence of an intermediate similar to T_{I}^- in the reaction path has been kinetically ascertained in the general base-catalysed hydroxylaminolysis of *N*-ethoxycarbonylpthalimide.[7]

In Scheme 1 the rate-determining step is considered to be the k^1_3 step. This would be true only if $k^1_{-1} > k^1_3[\mathrm{HN}<]$ and $k^1_4 > k^1_{-3}[\mathrm{H_2N^+}<]$. The p$K_a$ of the protonated amino group in $T_{\mathrm{I}}^{\pm}$ is not very different from that of conjugate acid of the free amine ($\mathrm{H_2N^+}<$).[11,20–22] The proton transfer in the k^1_3 step is therefore in a thermodynamically favourable direction and hence the magnitude of the rate constant, k^1_3, is nearly $\leqslant 10^{10}\ \mathrm{dm^3\,mol^{-1}\,s^{-1}}$. The values of $k^1_3[\mathrm{HN}<]$ are therefore *ca* $\leqslant 10^9\ \mathrm{s^{-1}}$ under the experimental conditions applied. The magnitude of the first-order rate constant for the expulsion of an added amine nucleophile from addition adduct (similar to $T_{\mathrm{I}}^{\pm}$) formed in the aminolysis of benzylpenicillin[13] is shown to be 10^9–$10^{10}\ \mathrm{s^{-1}}$. It is evident from Scheme 1 that $k_1 = k^1_1 k^1_2/k^1_{-1}$ and $k_4 = k^1_1 k^1_3/k^1_{-1}$ and therefore $k_1/k_4 = k^1_2/k^1_3$. The value of k^1_3 may not be expected to differ significantly for a typical amine in its reaction with PTH and benzylpenicillin if the assumption that the pK_a of protonated amine group in $T_{\mathrm{I}}^{\pm}$ is similar to that of conjugate acid of free amine is true.[11,20–22] It is interesting that the values of k_1/k_4 for morpholine, PPZH$^+$ and *N*-methylpiperazine are comparable to the corresponding values obtained in the reactions of benzylpenicillin with primary amines of comparable basicity.[13] Hence it may be assumed that k^1_{-1} is of the order of 10^9–$10^{10}\ \mathrm{s^{-1}}$ for amines of p$K_a \leqslant 10$. Therefore, it seems that $k^1_{-1} > k^1_3[\mathrm{HN}<]$.

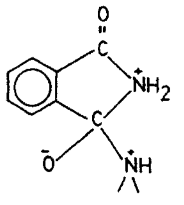
The approximate order of the values of k^1_2 and k^1_1/k^1_{-1} ($=K^1_1$) may be deduced from the relationships $k^1_2 = k^1_3 k_1/k_4$ and $K^1_1 = k_4/k^1_3$, by considering $k^1_3 = 10^{10}\ \mathrm{dm^3\,mol^{-1}\,s^{-1}}$. These results, as shown in Table 3, indicate that the values of the rate constants, k^1_2, are of the order of $10^8\ \mathrm{s^{-1}}$. As concluded elegantly by Gresser and Jenks,[23] the ease in the expulsion of a leaving group from an intermediate similar to $T_{\mathrm{I}}^{\pm}$ or T_{I}^- depends largely on the electronic push provided by atoms or groups attached to the atom from which the leaving group leaves. It is apparent from the structural features of $T_{\mathrm{I}}^{\pm}$ and T_{I}^- that the electronic push experienced by the leaving group in the k^1_4 step is much larger than that in the k^1_2 step. Hence k^1_4 is expected to be much larger than k^1_2. The values of $k^1_{-3}[\mathrm{H_2N^+}<]$ may be expected to be *ca* $\leqslant 10^9\ \mathrm{s^{-1}}$ under the experimental conditions applied. It may therefore be assumed that $k^1_4 > k^1_{-3}[\mathrm{H_2N^+}<]$. The conclusions that $k^1_{-1} > k^1_3[\mathrm{HN}<]$ and $k^1_4 > k^1_{-3}[\mathrm{H_2N^+}<]$ leads to the k^1_3 step as the rate-determining step. However, it must be noted that the estimation of the order of the magnitudes of various rate constants of Scheme 1 is based on very crude assumptions and therefore the conclusion derived from these estimated values of rate constants should be considered to be very approximate.



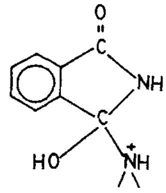
Scheme 1

Unimportance of general acid catalysis

The general acid catalysis in a stepwise mechanism (Scheme 1) may be expected to involve intermediates T_{I}^+ and T_2^+. The formation of T_{I}^- and T_2^+ involves



T_1^+



T_2^+

proton transfer in a thermodynamically favourable direction and hence these processes occur with a near zero free-energy change. However, the electronic push experienced by the leaving group in the k_4^1 step is undoubtedly much larger than that in a step which involved the conversion of T_2^+ into product, P. Hence the catalysed aminolysis of PTH is unlikely to proceed via T_2^+ in comparison with T_1^-. The ionization constants of conjugate acids of neutral amides[24] and esters[25,26] are known to be >10 and hence the formation of T_1^+ from $T_1^\pm$ involves a thermodynamically unfavourable proton transfer. The rate of conversion of $T_1^\pm$ into T_1^+ is therefore much slower than the rate at which $T_1^\pm$ converts to T_1^-. Incidentally, the intermediate T_1^+ is an *N*-protonated amide and is very unlikely to exist. For these reasons, the general acid catalysis could not be detected in the aminolysis of non-ionized PTH.

Uncatalysed pathway k_1

The rate constants, k_1, could not be obtained for the highly basic secondary amines because of the insignificant contribution of $k_1[\mathrm{SH}][\mathrm{Am}]$ in comparison with $k_2[\mathrm{S}^-][\mathrm{Am}]$ for these amines. Satisfactory values of k_1 were obtained for trimethylamine, morpholine and PPZH^+. The k_1 value for *N*-methylpiperazine was obtained from a single pH observed point. The k_1 value for trimethylamine is slightly more than twice that for 1,4-diazabicyclo[2.2.2]octane (DABCO).[8] Similar results were obtained in the reactions of trimethylamine and DABCO with non-ionized maleimide.[6] The rate constants, k_1, for trimethylamine and DABCO were found to show negative deviations *ca* seven and two-fold, respectively, from the Brønsted plot obtained from k_1 for the reactions of primary amines with non-ionized maleimide.[4] The low nucleophilic reactivity of trimethylamine compared with primary and secondary amines of comparable basicity in the related reactions is generally explained in terms of the steric requirements of these amines. Thus, although the observed data on k_1 are not sufficient to construct a satisfactory Brønsted plot, a highly unreliable two-point Brønsted plot, based on the observed k_1 for PPZH^+ and morpholine, gives a β_{nuc1} value of 0·8 (Figure 3). A value of β_{nuc1} of 0·8 is not unreliable. A search of the literature revealed that the Brønsted slopes for nucleophilic (β_{nuc}) and general base catalysis (β_{gb}) of a typical addition–elimination reaction at a carbonyl carbon are not significantly different from each other.[13,18,19] This shows that the Brønsted slope for k_1 should be near to unity because the observed value of β_{gb} is *ca* unity. The proposed reaction mechanism (Scheme 1) for uncatalysed aminolysis of PTH is consistent with $\beta_{\mathrm{nuc1}} = 0{\cdot}8$. As concluded earlier, $k_{-1}^1 \geqslant 10^9\ \mathrm{s}^{-1}$ and $k_2^1 \approx 10^8\ \mathrm{s}^{-1}$ and hence the k_2^1 step is the rate-determining step.

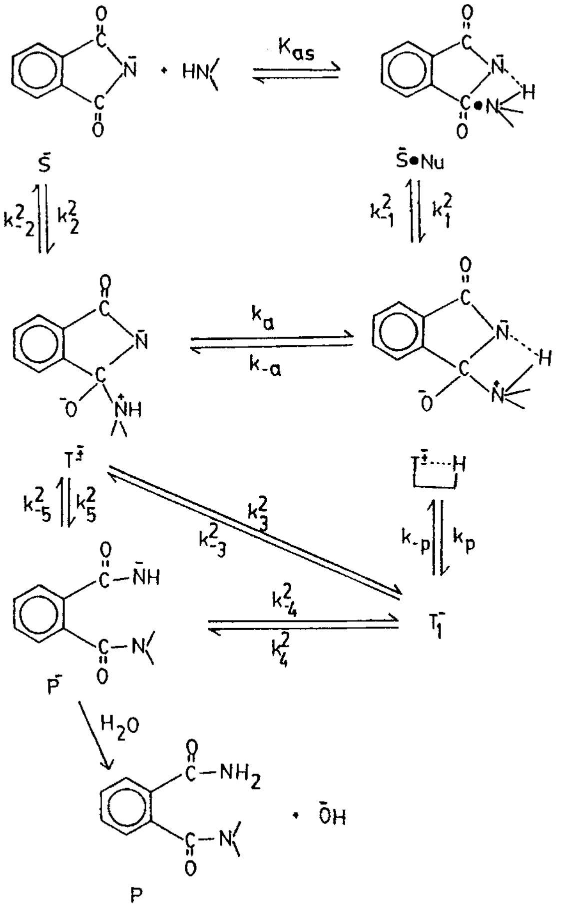
Uncatalysed aminolysis of ionized PTH (S^-)

Rate constants, k_2, for the nucleophilic reactions of piperidine, dimethylamine, morpholine, piperazine and *N*-methylpiperazine with ionized PTH appeared to fall on a Brønsted plot of slope $\beta_{\mathrm{nuc2}} = 0{\cdot}33 \pm 0{\cdot}17$ and intercept $C_2 = -4{\cdot}42 \pm 1{\cdot}70\ \mathrm{dm^3\ mol^{-1}\,s^{-1}}$ (Figure 3). It is interesting that $k_2[\mathrm{S}^-][\mathrm{HN}\!<]$ is kinetically indistinguishable from $k'_2[\mathrm{SH}][\mathrm{HN}\!<][\mathrm{OH}^-]$. Although we have ruled out the occurrence of a k'_2 term compared with a k_2 term for qualitative reason(s) mentioned earlier, perhaps a piece of additional evidence for it may be given as follows. If we assume that the k_2 term is negligible compared with the k'_2 term, then the rate constants, k'_2, may be obtained from the relationship $k'_2 = k_2K'_a/K_w$. Since K'_a/K_w is independent of the $\mathrm{p}K_a$ of amine nucleophiles, a Brønsted plot based on rate constants, k'_2, should yield a Brønsted slope (β_{sb}) identical with β_{nuc2} ($=0{\cdot}33$). However, the specific base- and general base-catalysed aminolyses of SH are expected to follow the same stepwise mechanism as shown in Scheme 1. The Brønsted slopes of the plots of $\log k'_2$ and $\log k_4$ versus $\mathrm{p}K_a$ of amine nucleophiles should therefore be nearly same. Morris and Page[13] did observe the same Brønsted slopes ($\beta = 1$) for the rate constants corresponding to specific base- and general base-catalysed aminolysis of benzylpenicillin. Although the value of β_{nuc2} is based on a very scattered Brønsted plot, it is almost certain that $\beta_{\mathrm{gb}} > \beta_{\mathrm{nuc2}}$ ($=\beta_{\mathrm{sb}}$). A significantly larger value of β_{gb} ($=1{\cdot}25$) than β_{sb} ($=0{\cdot}33$) demonstrates the non-occurrence of the k'_2 term compared with the k_2 term.

The occurrence of the kinetic term $k_2[\mathrm{S}^-][\mathrm{HN}\!<]$ cannot be expected in the reactions of *N*-bromopropylphthalimide (NBPPH) with primary and secondary amines. However, these reactions might reveal the occurrence of the kinetic term $k'_2[\mathrm{SH}][\mathrm{HN}\!<][\mathrm{OH}^-]$. We observed the occurrence of intermolecular general base catalysis in the reactions of 2-methoxyethylamine with NBPPH but a kinetic term similar to $k'_2[\mathrm{SH}][\mathrm{HN}\!<][\mathrm{OH}^-]$ could not be detected in these reactions.[8] Similarly, the kinetic term $k'_2[\mathrm{SH}][\mathrm{HN}\!<][\mathrm{OH}^-]$ was not observed in the reactions of *N*-ethoxycarbonylphthalimide with hydroxylamine and morpholine.[7] These observations also support the conclusion that $k'_2[\mathrm{SH}][\mathrm{HN}\!<][\mathrm{OH}^-]$ is unimportant compared with $k_2[\mathrm{S}^-][\mathrm{HN}\!<]$.

Although the value of β_{nuc2} is associated with a high standard deviation, it does show that β_{nuc2} is significantly smaller than β_{nuc1}. Similar results were obtained in the reactions of non-ionized and ionized maleimide with several primary amines.[4] Different values of β_{nuc2} and β_{nuc1} indicate the occurrence of different mechanisms in these reactions. In the addition–elimination reactions at a carbonyl carbon, the low values of β_{nuc} are generally attributed to the nucleophilic attack as the rate-determining step.[27] A diffusion-controlled trapping stepwise mechanism (similar to Scheme 1) with nucleophilic attack as the rate-determining step is unlikely, as discussed elsewhere in the related reactions.[5,6] The most plausible pre-association stepwise mechanism as shown in Scheme 2 ($S^- + HN< \rightarrow S^-\cdot Nu \rightarrow \underbracket{T^{\pm}\cdots H} \rightarrow T^- \rightarrow$ product) is believed to be operating in these reactions.

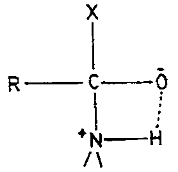
Scheme 2 represents both a diffusion-controlled trapping stepwise mechanism ($S^- + HN< \rightarrow T^{\pm} \rightarrow T^- \rightarrow$ product) and a pre-association stepwise mechanism. It is evident from Schemes 1 and 2 that the driving force to expel the leaving group in the k^2_{-1} step is significantly larger than that in the k^1_{-1} step and hence $k^2_{-1} \gg k^1_{-1}$ ($k^1_{-1} \approx 10^9$–$10^{10}\ s^{-1}$). The rate constant, k_{-a}, represents a kinetic step which involves the disruption of a very strong hydrogen bond and hence it involves a significant energy barrier. Although it is not possible to ascertain the magnitude of k_{-a}, it may be assumed that $k^2_{-1} > k_{-a}$.



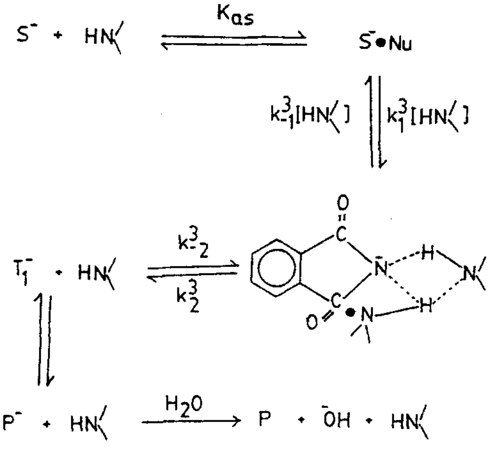
Scheme 2

In Scheme 2, the k^2_{-3} and k_{-p} steps involve proton transfer in a thermodynamically unfavourable direction. However, in the k^2_{-3} step, the proton is completely transferred from the donor site to the acceptor site whereas in the k_{-p} step the proton transfer from the donor to the acceptor site remained hydrogen bonded with the donor site. It is therefore conceivable that $k_{-p} > k^2_{-3}$. According to the principle of microscopic reversibility, if the k^2_{-1} and k_{-p} steps are the lowest energy paths for the breakdown of the intermediates, $\underbracket{T^{\pm}\cdots H}$ and T_1^-, then the k^2_1 and k_p steps must be the lowest energy paths for the formation of these intermediates. These conclusions reveal that the energetically favourable path for the reaction of S^- with $HN<$ involves the pre-association stepwise mechanism.

It is interesting that the ratios of the nucleophilic second-order rate constants, $k_n^{MeNH_2}/k_n^{Me_2NH}$, for the reactions of methylamine and dimethylamine with phenyl acetate (PA) and various substituted phenyl quinoline-6-carboxylates (Q-6)[12] are *ca* 3·6 and 1·5–0·7, respectively. However, the values of $k_n^{MeNH_2}/k_n^{Me_3N}$ ($k_n^{Me_3N}$ represents the nucleophilic or general base-catalysed hydrolytic second-order rate constants for the reactions of trimethylamine with various esters) for PA[28] and various substituted Q-6 esters[19] are *ca* 2×10^3 and 7×10–2×10^3, respectively. The nucleophilic second-order rate constants for the reactions of trimethylamine and DABCO with PA[28,29] and *p*-nitrophenyl acetate (PNPA)[28,29] have been found to be nearly identical. Similarly, only a *ca* twofold larger nucleophilic reactivity of trimethylamine compared with DABCO was observed in the reactions with non-ionized maleimide[6] and PTH.[8] Knier and Jencks[30] have reported the values of second-order rate constants for the reactions of m-$NO_2PhN^+(CH_3)_2CH_2OCH_3$ with dimethylamine and DABCO as $493\times10^{-5}\ dm^3\,mol^{-1}\ s^{-1}$ and $875\times10^{-5}\ dm^3\,mol^{-1}\,s^{-1}$, respectively. Nearly a 10^3-fold larger reactivity toward PA of methylamine or dimethylamine than trimethylamine or DABCO and a nearly twofold larger reactivity toward m-$NO_2PhN^+\ (CH_3)_2CH_2OCH_3$ of DABCO than dimethylamine cannot be explained only in terms of steric requirements and the difference in the basicities of these nucleophiles. These observations perhaps reveal the occurrence of internal hydrogen bonding in the zwitterionic tetrahedral intermediate as shown by $T_3^{\pm}$. The occurrence of such internal hydrogen bonding has been proposed and supported by



$T_3^{\pm}$



Scheme 3

Shain and Kirsch.[31] The internal hydrogen bonding, similar to that in $T_3^{\pm}$, is expected to be more facile in the aminolysis of a negatively charged substrate where the leaving group, X, carries the negative charge. The occurrence of a pre-association stepwise mechanism has been suggested in the catalysed aminolysis of neutral substrate(s).[22,32]

General base-catalysed aminolysis of ionized PTH (S^-)

General base-catalysed aminolysis of S^- could be detected only with a few amines such as morpholine, piperazine and *N*-methylpiperazine. However, the standard deviations associated with k_5 values are high. Although the observed data for general base catalysis are not sufficient to discuss any detailed mechanism, it does appear that the rate constants for general base catalysis, k_5, are almost independent of or only weakly dependent on the basicity of the general base catalysts. The suggested mechanism for general base catalysis may be as shown in Scheme 3.

ACKNOWLEDGEMENTS

M.N.K. is grateful to the Research and Higher Degree Committee of Bayero University for a research grant to purchase a UV–visible spectrophotometer. The authors thank Dr Nordin H. Lajis for providing facilities for preparing the revised version of the manuscript.

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APPENDIX

Resolution of some kinetically indistinguishable terms

The inclusion of the terms $k_4'[\mathrm{PPZH^+}][\mathrm{H^+PPZH^+}][\mathrm{S^-}]$ and $k_5''[\mathrm{PPZ}][\mathrm{H^+PPZH^+}][\mathrm{S^-}]$ in equation (15) would result in the additional term $k_5''K_1K_2K_a' + k_4'K_1K_a'a_\mathrm{H}$ in equation (18). It is apparent that the rate constant k_5'' should be larger than k_4' because PPZ is a stronger nucleophile than PPZH$^+$. The kinetic terms $(k_4K_1^2 + k_4'K_1K_a')a_\mathrm{H} + k_5''K_1K_2K_a'$ may be rearranged to $k_4'K_a'K_1a_\mathrm{H}[(k_4K_1/k_4'K_a') + 1 + (k_5''K_2/k_4'a_\mathrm{H})]$. The values of K_2/a_H vary from 2×10^{-4} to 2×10^{-3} within the pH range 6·36–7·29. The value of $k_5''K_2/k_4'a_\mathrm{H}$ would be less than unity if $k_5''/k_4' < 5 \times 10^2$. If we assume that the Brønsted slope (β) for the rate constants k_4' and k_5'' is similar to that for k_2 and k_3, then the value of β may be considered to be significantly smaller than unity. Values of β_nuc of 0·48 and 0·81 were obtained in the nucleophilic reactions of primary amines with ionized and non-ionized maleimide, respectively.[4] In the aminolysis of phthalimide, values of β_nuc of 0·33 and *ca* 1·0 have been obtained in the reactions of secondary amines with ionized and non-ionized PTH, respectively. The cleavage of *N*-ethoxycarbonylphthalimide in the presence of buffers of primary, secondary and tertiary amines yielded $\beta_\mathrm{nuc} = 1 \cdot 2$. Similarly, the reactions of primary and secondary amines with ionized phenyl salicylate produced β_nuc values which were significantly smaller than β_nuc for aminolysis of non-ionized phenyl salicylate.[9,33] Hence a presumed value of β of 0·5 would produce $k_5''/k_4' = 10^2$ and it shows that $k_5''K_2/k_4'a_\mathrm{H} < 1$.

Rate constants k_4 and k_4' represent the kinetic processes which involve intermolecular general base- and general acid-catalysed piperazinolysis of non-ionized and ionized PTH, respectively. With maleimide, the values of k_4/k_4' turned out to be *ca* 2×10^{-2} for PPZH$^+$, 0·4 for morpholine and 0·6 for *N*-methylpiperazine.[5] The rates of aminolysis and the pK_a values of maleimide and PTH are not abnormally different from each other and hence the value of k_4/k_4' of 10^{-2} may be assumed for PPZH$^+$ in the case of PTH. The magnitude of k_4/k_4' ($\approx 10^{-2}$) and K_1/K_a' ($= 2 \times 10^{-3}$) make the term $k_4K_1/k_4'K_a'$, larger than unity. It is interesting that the calculated values of k_4 for the reactions of maleimide with morpholine and PPZH$^+$ remained essentially unchanged with change in k_4' from 15·1 to 0·0 dm^6 mol^{-2} s^{-1} (i.e. $k_4/k_4' = 2 \times 10^{-2}$ to ∞) for PPZH$^+$ and from 252 to 0·0 dm^6 mol^{-2} s^{-1} (i.e. $k_4/k_4' = 0 \cdot 4$ to ∞) for morpholine. This simply revealed that the contribution of the k_4' term was negligible compared with the k_4 term under the experimental conditions applied. The arguments discussed so far reveal that $k_4K_1^2a_\mathrm{H} > k_4'K_1K_a'a_\mathrm{H} > k_5''K_1K_2K_a'$ within the pH range 6·36–7·29.