KINETIC STUDIES OF THE REACTIONS OF PHTHALIMIDE WITH AMMONIA AND PYRROLIDINE

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The kinetics of the nucleophilic cleavage of phthalimide (PTH) in buffer solutions of ammonia and pyrrolidine were determined. The reaction rates for ammonolysis of PTH revealed a buffer-catalysed second-order term in the rate law, but the reaction rates for pyrrolidinolysis of PTH showed buffer-catalysed second- and third-order terms in the rate law. Both ammonia and pyrrolidine revealed nucleophilic reactivity towards ionized PTH (S^-) only within the pH range of the present study. This is attributed to the occurrence of intramolecular general base–acid catalysis. General base catalysis is detected in the reactions of pyrrolidine with both non-ionized PTH (SH) and S^-. The general base-catalysed third-order rate constant for pyrrolidinolysis of SH is nearly 28 times larger than that of S^-.

INTRODUCTION

Kinetic studies on the reactions of amines (primary, secondary and tertiary) with esters, aldehydes, ketones and amides have been carried out in great detail.[1] The fine details of the mechanisms of most of these reactions have been also worked out, but why in a particular reaction certain amines display either general base (GB) or general acid (GA) catalysis while other amines of the same class do not show such catalysis still remains a great puzzle. We observed GA catalysis in the reactions of maleimide with a few tertiary amines[2] but the same amines did not reveal such catalysis with phthalimide.[3] Several secondary amines including piperidine and pyrrolidine[4] showed GA–GB catalysis whereas several primary amines[5] did not snow such catalysis in their reactions with maleimide. Bunett and co-workers have demonstrated a spectacular difference between the behaviour of pyrrolidine and piperidine towards the reaction with 2,4-dinitro-1-naphthyl ethyl ether[6] and 2,4-dinitro-6-methylphenyl phenyl ether.[7] They also observed the presence and absence of specific base catalysis in the reactions of 2,4-dinitrophenyl phenyl ether with piperidine[8] and pyrrolidine,[9] respectively. These two cyclic amines are very similar in structure, pK_a values[10] and electron delocalization between pyrrolidino or piperidino groups and unsaturated systems to which they are attached,[11] so why they should behave so differently is curious. The differing behaviour of pyrrolidine and piperidine as nucleophiles in these addition–elimination reactions prompted us to study the reaction of pyrrolidine with phthalimide.

Ammonia does not belong to the general class of primary amines and hence it may be expected to show different reactivity compared with primary amines toward a substrate. However, in many addition–elimination reactions at carbonyl carbon,[12-17] sulphonic acid sultone sulphur[18] and phosphonate phosphorus,[19] the reactivity of ammonia did not display any significant deviation from Brønsted plots derived from the reactivity of primary and secondary amines. Significant negative deviations from Brønsted plots of primary amines were obtained for ammonia in its reactions with ionized and non-ionized maleimide[5] and ionized phenyl salicylate.[20] In order to see whether or not ammonia shows unusual reactivity toward phthalimide, we carried out a few kinetic runs on the ammonolysis of phthalimide. The results are described and discussed in this paper.

EXPERIMENTAL

Materials. Reagent-grade ammonia and pyrrolidine were obtained from BDH and Aldrich, respectively. All other chemicals were also of reagent grade. Glass-distilled water was used throughout and the stock solutions of buffers were freshly prepared just before the

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start of the kinetic runs. Stock solutions of PTH were prepared in acetonitrile.

Kinetic measurements. The rates of reactions of PTH with ammonia and pyrrolidine were studied spectrophotometrically by monitoring the disappearance of PTH as a function of time at 300 nm and 30 °C. The details of the kinetic procedure and data analysis are described elsewhere.[20]

Ammonolysis of phthalimide (PTH)

The rates of ammonolysis of PTH were studied at different pH in buffer solutions of ammonia where ammonia acted both as the reactant and the buffer concurrently. The observed pseudo-first-order rate constants (k_{obs}) obtained at a constant pH were found to
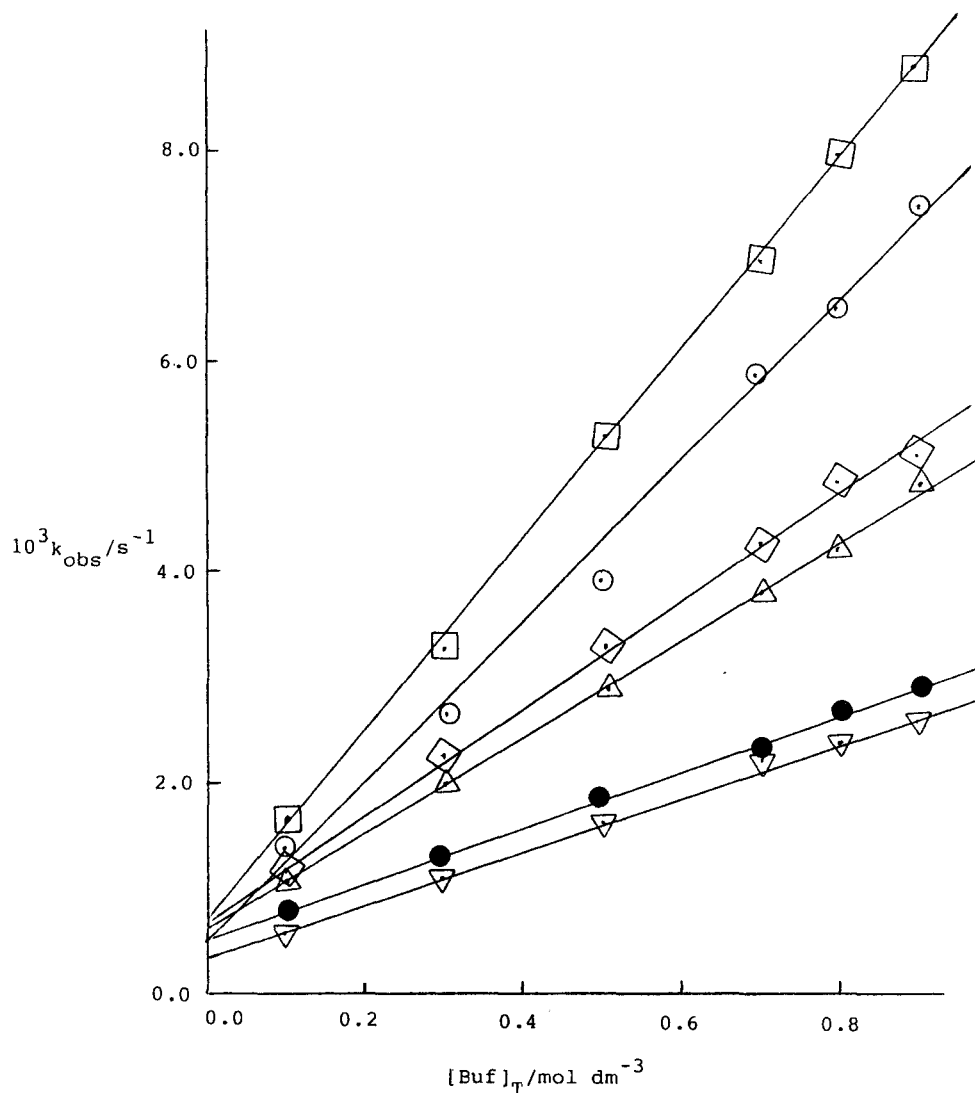

Figure 1. Effects of the total buffer concentration of ammonia ([Buf]$_T$) on the observed pseudo-first-order rate constants (k_{obs}) for the cleavage of PTH at pH (▫) 10·41, (◉) 10·33, (◇) 10·02, (△) 9·89, (●) 9·70 and (▽) 9·53

Table 1. Apparent first-, second- and third-order rate constants for the reactions of PTH with ammonia and pyrrolidine[a]

Amine	pH	$10^3 k_0$ (s^{-1})	$10^3 k_n$ $(dm^3 mol^{-1} s^{-1})$	$10^2 k_b$ $(dm^6 mol^{-2} s^{-1})$	C (%)[b]	$[Buf]_T^c$ $(mol\,dm^{-3})$
Ammonia	$9\cdot53 \pm 0\cdot01$[d]	$0\cdot35 \pm 0\cdot05$[d,e]	$2\cdot55 \pm 0\cdot08$[d,e]	—		$0\cdot1-0\cdot9$
	$9\cdot70 \pm 0\cdot00$	$0\cdot52 \pm 0\cdot04$	$2\cdot68 \pm 0\cdot07$	—		$0\cdot1-0\cdot9$
	$9\cdot89 \pm 0\cdot01$	$0\cdot61 \pm 0\cdot05$	$4\cdot56 \pm 0\cdot09$	—		$0\cdot1-0\cdot9$
	$10\cdot02 \pm 0\cdot01$	$0\cdot66 \pm 0\cdot09$	$5\cdot10 \pm 0\cdot15$	—		$0\cdot1-0\cdot9$
	$10\cdot33 \pm 0\cdot01$	$0\cdot52 \pm 0\cdot20$	$7\cdot54 \pm 0\cdot31$	—		$0\cdot1-0\cdot9$
	$10\cdot41 \pm 0\cdot01$	$0\cdot69 \pm 0\cdot08$	$9\cdot02 \pm 0\cdot13$	—		$0\cdot1-0\cdot9$
Pyrrolidine	$10\cdot94 \pm 0\cdot06$	$(1\cdot21)$[f]	188 ± 20[f,g]	251 ± 23[f,g]	$21-57$	$0\cdot02-0\cdot1$
	$11\cdot10 \pm 0\cdot08$	$(1\cdot23)$	280 ± 62	284 ± 73	$17-50$	$0\cdot02-0\cdot1$
	$11\cdot27 \pm 0\cdot06$	$(1\cdot23)$	349 ± 31	465 ± 37	$21-57$	$0\cdot02-0\cdot1$
	$11\cdot62 \pm 0\cdot05$	$(1\cdot25)$	522 ± 92	766 ± 211	$23-54$	$0\cdot02-0\cdot08$

[a] Conditions: $[PTH]_0 = 3\cdot2 \times 10^{-4}$ mol dm^{-3}, $30\,^\circ$C, ionic strength $1\cdot0$ mol dm^{-3}, $\lambda = 300$ nm, $1\cdot6\%$ (v/v) acetonitrile added to aqueous reaction mixture for each kinetic run.
[b] C (%) $= 100 k_b [Buf]_T^2/(k_n [Buf]_T + k_b [Buf]_T^2)$
[c] Total amine buffer concentration range.
[d] Error limits are standard deviations.
[e] Calculated from equation (1) as described in the text.
[f] Calculated from the relationship $k_0 = k_{OH} K_w/(a_H + K_a')$ as described in the text.
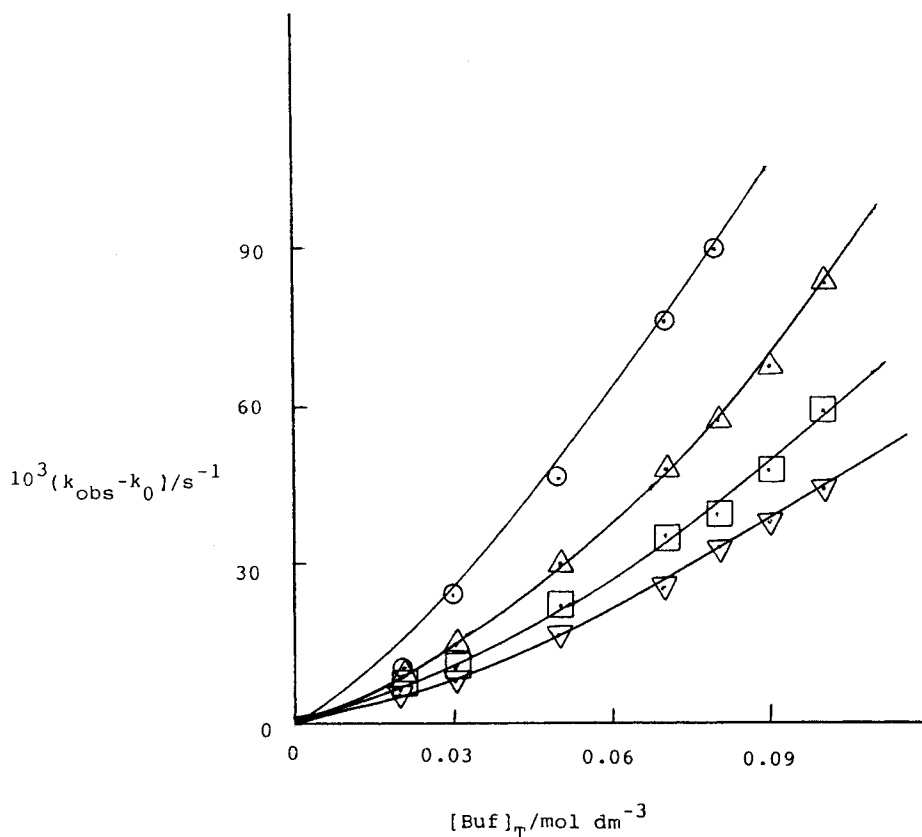[g] Calculated from equation (2) as described in the text.

Figure 2. Plots showing the dependence of $k_{obs} - k_0$ on the total buffer concentration of pyrrolidine ([Buf]$_T$) at $30\,^\circ$C and at pH
(⊙) $11\cdot62$, (△) $11\cdot20$, (▣) $11\cdot0$ and (▽) $10\cdot94$

fit the equation

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

where $[\text{Buf}]_T$ represents the total ammonia buffer concentration, i.e. $[\text{Buf}]_T = [\text{Am}] + [\text{AmH}^+]$ with $[\text{Am}]$ and $[\text{AmH}^+]$ representing the concentrations of free and protonated amine, respectively. The linear least-squares technique was used to calculate buffer-independent first-order and buffer-dependent second-order rate constants, k_0 and k_n, respectively. These results, at different pH, are summarized in Table 1. The fitting of the observed data to equation (1) is evident from the plots in Figure 1, where the solid lines are drawn through the least-squares calculated points.

Pyrrolidinolysis of PTH

The cleavage of PTH was studied at different total pyrrolidine buffer concentrations, $[\text{Buf}]_T$, (where pyrrolidine acted both as the reactant and the buffer concurrently) at a constant pH and temperature ($30\,^\circ$C). The observed pseudo-first-order rate constants, k_{obs}, were treated with the equation

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

where k_0, k_n and k_b represent buffer-independent first-order, buffer-dependent second- and third-order rate constants, respectively. The calculated values of k_0, k_n and k_b revealed an insignificant contribution of the k_0 term compared with $k_n[\text{Buf}]_T + k_b[\text{Buf}]_T^2$ terms in equation (2) under the experimental conditions imposed. Hence a relatively more appropriate treatment of the kinetic data with equation (2) was considered with k_n and k_b as the only unknown parameters. The values of k_0 at different pH were calculated from the relationship $k_0 = k_{OH}K_w/(a_H + K_a')$* where the

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* The equation

$$k_0 = k_{OH}K_w/(a_H + K_a') \qquad (i)$$

may be derived as follows. The observed pseudo-first-order rate constant, k_w, for water-catalysed cleavage of PTH has been reported to be $9 \cdot 0 \times 10^{-6}\,\text{s}^{-1}$ at $100\,^\circ$C.[21] Similarly, the value of k_w for the hydrolysis of p-nitrophenyl acetate is $5 \cdot 5 \times 10^{-7}\,\text{s}^{-1}$ at $25\,^\circ$C.[16] The buffer-independent observed pseudo-first-order rate constants, k_0, obtained within the pH range $7 \cdot 29 - 11 \cdot 03$ showed a good fit to the equation (i). This shows that $k_w[\text{SH}]$ is negligible compared with $k_{OH}[\text{OH}^-][\text{SH}]$ even at pH $7 \cdot 29$ and $30\,^\circ$C where $k_0 = 7 \cdot 6 \times 10^{-6}\,\text{s}^{-1}$ ($k_0 = 0 \cdot 0208\,\text{s}^{-1}$ at $100\,^\circ$C). Hence, within the pH range 9–12, the buffer-independent rate of cleavage of PTH may be given as

$$\text{rate} = k_{OH}[\text{OH}^-][\text{SH}]$$
$$= k_{OH}K_w[\text{Sub}]_T/(a_H + K_a') \qquad (ii)$$

where $[\text{Sub}]_T = [\text{SH}] + [\text{S}^-]$. Comparison of the observed rate law, $\text{rate} = k_0[\text{Sub}]_T$, with equation (ii) gives equation (i).

hydroxide ion-catalysed second-order rate constant for hydrolysis of non-ionized phthalimide (SH), k_{OH}, the ionization constant of SH, K_a', and the ionic product of water, K_w, were taken as $26 \cdot 3\,\text{dm}^3\text{mol}^{-1}\text{s}^{-1}$, $3 \cdot 05 \times 10^{-10}\,\text{mol}\,\text{dm}^{-3}$ and $1 \cdot 449 \times 10^{-14}\,\text{mol}^2\,\text{dm}^{-6}$, respectively.[22] The observed rate constants, k_{obs}, with known values of k_0 were used to calculate k_n and k_b from equation (2) using the least-squares method. These calculated values of k_n and k_b at different pH values are summarized in Table 1. The fitting of the observed data to equation (2) is evident from the plots in Figure 2 and the standard deviations associated with the calculated parameters, k_n and k_b, as shown in Table 1.

DISCUSSION

Cleavage of PTH in buffer solutions of ammonia

Both non-ionized (SH) and ionized (S^-) forms of PTH are known to be reactive towards amine nucleophiles with hydrogen attached to nitrogen. Thus, the general reaction scheme for the cleavage of PTH in the buffer solutions of ammonia may be given as shown in Scheme 1.

Based on Scheme 1, the rate law for the cleavage of PTH may be given as

$$\text{rate} = k_{OH}[\text{OH}^-][\text{SH}] + k_1[\text{Am}][\text{SH}]$$
$$+ k_2[\text{Am}][\text{S}^-] \qquad (3)$$

where $[\text{Am}]$ is the concentration of free amine nucleophile. The observed rate law ($\text{rate} = k_{obs}[\text{Sub}]_T$ where $[\text{Sub}]_T = [\text{SH}] + [\text{S}^-]$) and equation (3) yield

$$k_{obs} = k_0 + \frac{k_2 K_a K_a' + k_1 K_a a_H}{(a_H + K_a')(a_H + K_a)}[\text{Buf}]_T \qquad (4)$$

where K_a represents the ionization constant of protonated amine, AmH^+, and $k_0 = k_{OH}K_w/(a_H + K_a')$. Equation (4) is similar to equation (1) with

$$k_n Q a_H = k_2 K_a K_a' a_H + k_1 K_a a_H^2 \qquad (5)$$

where $Q = (a_H + K_a')(a_H + K_a)$. The plot of $k_n Q a_H$ versus a_H turned out to be linear within the pH range of the study ($9 \cdot 53 - 10 \cdot 41$) and the linearity of such a plot indicates the insignificant contribution of the $k_1[\text{SH}][\text{Am}]$ term compared with the $k_2[\text{S}^-][\text{Am}]$ term in equation (3). It is essential to note that
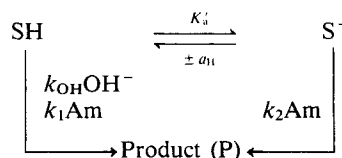
Scheme 1

k_2[S⁻][Am] term is kinetically indistinguishable from k_2'[SH][Am][OH⁻]. However, the presence of k_2'[SH][Am][OH⁻] may be ruled out because in several related reactions if a term similar to k_2'[SH][Am][OH⁻] appeared in the rate law, then another term similar to k_1[SH][Am] also appeared in the same rate law[12,23-25] and the latter term could not be detected in the observed rate law.

The least-squares method was used to calculate $k_2 K_a K_a'$ from equation (5) by neglecting $k_1 K_a a_H^2$ compared with $k_2 K_a K_a' a_H$ and the calculated value of $k_2 K_a K_a'$ of $(1 \cdot 54 \pm 0 \cdot 31) \times 10^{-21}$ mol dm⁻³ s⁻¹ yielded k_2 as summarized in Table 2 with p$K_a = 9 \cdot 21$. An attempt to fit the observed data to the equation $k_n Q a_H = \alpha + \beta a_H$ resulted in values of α and β of $(1 \cdot 65 \pm 1 \cdot 99) \times 10^{-32}$ mol² dm⁻⁶ s⁻¹ and $(1 \cdot 26 \pm 0 \cdot 12) \times 10^{-21}$ mol dm⁻³ s⁻¹, respectively. The calculated value of α with a relative standard deviation of more than 100% indicates that it is not statistically different from zero.

The reactivity of ammonia is expected to show a negative deviation from the Brønsted plot of the reactivities of primary amines. This is merely due to the larger solvation shell for ammonia than for primary amines. However, in many addition–elimination reactions at carbonyl carbon,[12-17] sultone sulphur[18] and phosphonate phosphorus,[19] ammonia did not reveal an unusually low reactivity compared with primary amines of similar pK_a. However, in most of these reactions, the nucleophilic reactivity of both primary and secondary amines constituted a single Brønsted plot. In the aminolysis of both non-ionized and ionized maleimide[5] and ionized phenyl salicylate,[20] primary and secondary amines were found to form Brønsted plots of different slopes. In these reactions, the nucleophilic reactivity of ammonia showed significant negative deviations from the Brønsted plots of nucleophilic reactivity of primary amines.

The value of k_2 ($8 \cdot 08 \times 10^{-3}$ dm³ mol⁻¹ s⁻¹) may be

compared with the corresponding value of k_2 ($6 \cdot 7 \times 10^{-3}$ dm³ mol⁻¹ s⁻¹) for ammonolysis of ionized maleimide.[5] Although the rate constant, k_1, could not be detected in the ammonolysis of PTH under the experimental conditions imposed, the value of k_1 for ammonolysis of maleimide turned out to be $1 \cdot 4 \times 10^{-4}$ dm³ mol⁻¹ s⁻¹, which is nearly 50 times smaller than k_2. If we assume that the ratio k_2/k_1 is nearly 50 for the reaction of ammonia with PTH, then the value of $k_1 K_a a_H^2 / k_2 K_a K_a' a_H$ ranges from $0 \cdot 02$ to $0 \cdot 003$ because the ratio a_H/K_a' varies from 1 to $0 \cdot 13$ within the pH range $9 \cdot 53$–$10 \cdot 43$. This shows that $k_2 K_a' K_a a_H > 50 k_1 K_a a_H^2$ within the limits of the experimental conditions imposed. It appears from earlier and the present studies on addition–elimination reactions that a significantly low nucleophilic reactivity of ammonia compared with other primary amines occurs in those reactions where primary and secondary amines constitute Brønsted plots of different slopes.

Cleavage of PTH in buffer solutions of pyrrolidine

The cleavage of PTH in buffer solutions of pyrrolidine revealed the occurrence of both uncatalysed and general base-catalysed terms in the rate law. Hence the general reaction scheme for such reactions may be given as shown in Scheme 2.
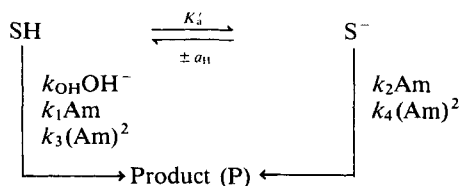
Based on Scheme 2, the rate law for the reaction may be given as

$$\text{rate} = k_{OH}[\text{OH}^-][\text{SH}] + (k_1[\text{SH}] + k_2[\text{S}^-])[\text{Am}]$$
$$+ (k_3[\text{SH}] + k_4[\text{S}^-])[\text{Am}]^2 \qquad (6)$$

The additional terms, k_3'[S⁻][Am][AmH⁺] and k_4'[S⁻][Am][AmH⁺][OH⁻], which are kinetically indistinguishable from the k_3[SH][Am]² and k_4[S⁻][Am]² terms, respectively, may be ignored for the qualitative reasons described elsewhere for related reactions.[22]

The observed rate law (rate $= k_{obs}$[Sub]ₜ) and equation (6) give

$$k_{obs} = k_0 + \frac{k_2 K_a K_a' + k_1 K_a a_H}{(a_H + K_a')(a_H + K_a)} [\text{Buf}]_T$$
$$+ \frac{k_4 K_a' K_a^2 + k_3 K_a^2 a_H}{(a_H + K_a')(a_H + K_a)^2} [\text{Buf}]_T^2 \qquad (7)$$

Table 2. Rate constants for the cleavage of PTH in buffer solutions of ammonia and pyrrolidine

Nucleophile	pK_a[a]	Buffer-catalysed and uncatalysed rate constants[b]
Ammonia	9·21	k_1[c]
		$10^3 k_2 \simeq 8 \cdot 08 \pm 1 \cdot 65$ dm³ mol⁻¹ s⁻¹
Pyrrolidine	11·32	k_1[c]
		$k_2 < 0 \cdot 742 \pm 0 \cdot 055$ dm³ mol⁻¹ s⁻¹
		$k_3 \simeq 393 \pm 122$ dm⁶ mol⁻² s⁻¹
		$k_4 \simeq 13 \cdot 6 \pm 3 \cdot 0$ dm⁶ mol⁻² s⁻¹

[a] pK_a values of the conjugate acids of amines were obtained from Refs 4 and 5.
[b] Error limits are standard deviations.
[c] This term did not reveal a detectable contribution to the rate within the limits of the experimental conditions imposed.

SH $\overset{K_a'}{\underset{\pm a_H}{\rightleftharpoons}}$ S⁻

k_{OH}OH⁻
k_1Am
k_3(Am)²

k_2Am
k_4(Am)²

⟶ Product (P) ⟵

Scheme 2

Comparison of equations (2) and (7) gives

$$k_n Q a_H = k_2 K_a K_a' a_H + k_1 K_a a_H^2 \qquad (8)$$

$$k_b Q_1 = k_4 K_a' K_a^2 + k_3 K_a^2 a_H \qquad (9)$$

where $Q_1 = (a_H + K_a')(a_H + K_a^2)$.

The plot of $k_n Q a_H$ versus a_H was found to be linear, which implies that $k_1 K_a a_H^2 \ll k_2 K_a K_a' a_H$. A similar observation was made in the cleavage of PTH in buffer solutions of piperidine.[22] The observed nucleophilic second-order rate constants, k_n, were used to calculate $k_2 K_a K_a'$ from equation (8) by neglecting $k_1 K_a a_H^2$ compared with $k_2 K_a K_a' a_H$. The least-squares calculated value of $k_2 K_a K_a'$ is $(10 \cdot 83 \pm 0 \cdot 80) \times 10^{-22}$ mol dm^{-3} s^{-1}. This value of $k_2 K_a K_a'$ was used to calculate k_2 with known values of K_a (p$K_a = 11 \cdot 32$) and K_a' and such a calculated value of k_2 is shown in Table 2. A crude value of k_1 can be estimated from the extrapolation of the Brønsted plot for k_1 derived for only four data points as shown in Ref. 22. Such a value of k_1 is nearly 1 dm^3 mol^{-1} s^{-1}. Thus, the ratio k_1/k_2 is nearly $1 \cdot 5$ for the reaction of pyrrolidine with PTH. If we consider the value of $k_1/k_2 = 1 \cdot 5$, the values of $k_1 K_a a_H^2/k_2 K_a K_a' a_H$ vary from $0 \cdot 06$ to $0 \cdot 012$ within the pH range $10 \cdot 94 - 11 \cdot 62$ (the values of a_H/K_a' vary from $0 \cdot 04$ to $0 \cdot 008$ within this pH range). This analysis shows that $k_2 K_a K_a' a_H > 16 k_1 K_a a_H^2$ within the experimental conditions of the present study.

The observed buffer-catalysed third-order rate constants, k_b, at different pH were found to obey equation (9). The least-squares calculated values of $k_4 K_a' K_a^2$ and $k_3 K_a^2$ are $(9 \cdot 50 \pm 2 \cdot 12) \times 10^{-32}$ mol dm^{-3} s^{-1} and $(9 \cdot 00 \pm 2 \cdot 81) \times 10^{-21}$ s^{-1}, respectively. The rate constants k_3 and k_4 were calculated from the values of $k_3 K_a^2$ and $k_4 K_a' K_a^2$ and are summarized in Table 2. The value of k_3 (393 dm^6 mol^{-2} s^{-1}) is nearly 20% smaller than the corresponding rate constant[22] obtained for dimethylaminolysis of PTH under essentially similar experimental conditions.

The absence of k_1 [SH] [Am] term in the rate law [equation (6)] shows that k_2' [SH] [Am] [OH$^-$] may be neglected compared with k_2 [S$^-$] [Am]. However, the presence of the k_3 [SH] [Am]^2 term implies the probable occurrence of the k_4' [SH] [Am] [OH$^-$] term. If we assume that k_2 [S$^-$] [Am] is negligible compared with k_2' [SH] [Am] [OH$^-$], then the calculated value of the slope $(10 \cdot 83 \pm 0 \cdot 80) \times 10^{-22}$ mol dm^{-3} s^{-1}) of the plot of $k_n Q a_H$ versus a_H [equation (8) where $k_2 K_a K_a' a_H$ is replaced with $k_2' K_a K_w a_H$] will give $k_2' = 1 \cdot 5 \times 10^4$ dm^6 mol^{-2} s^{-1}, which is nearly 38 times larger than k_3. Thus, it is apparent that $k_2'/k_3 < 38$ because the k_2 [S$^-$] [Am] term cannot be considered to be negligible in the pH range of the study. The ratio k_2'/k_3 was found to be 88 for propylaminolysis of benzylpenicillin.[24] Similarly, the reported values of k_2'/k_3 for the aminolysis of phenyl acetate are 32,[13] 60[25] for methylamine and 180[13] and 91[25] for ethylamine.

These results reveal that the anticipated value of $k_2'/k_3 < 38$ is probably not an unreasonable one because pyrrolidine is a stronger base than methylamine by nearly $0 \cdot 5$ pK unit. This shows that the value of k_2 is less than $0 \cdot 742$ dm^3 mol^{-1} s^{-1}.

The respective absence and presence of nucleophilic reactivity of both ammonia and pyrrolidine towards non-ionized PTH (SH) and ionized PTH (S$^-$) indicate the occurrence of either intramolecular general base–acid catalysis* involving intermediate T$_1$ or solvent-mediated intramolecular general base–acid catalysis involving intermediate T$_2$ in a preassociation stepwise mechanism (a mechanism suggested and supported for the reactions of S$^-$ with a few secondary amines[22]). The values of the second-order rate constant (k_2) for the reactions of S$^-$ with pyrrolidine ($k_2 < 0 \cdot 742$ dm^3 mol^{-1} s^{-1}), dimethylamine ($k_2 = 0 \cdot 316$ dm^3 mol^{-1} s^{-1}) and piperidine ($k_2 = 0 \cdot 173$ dm^3 mol^{-1} s^{-1}) indicate that these reactions probably follow the same reaction mechanism.

It is interesting that the rate constant k_4 could not be detected in the reaction of PTH with dimethylamine.[22] However, the rate constants, k_4, obtained in the reactions of PTH with morpholine, piperazine and N-methylpiperazine appeared to be weakly dependent on the basicity of the general base catalysts.[22] The value of k_4 ($13 \cdot 6$ dm^6 mol^{-2} s^{-1}) obtained in the pyrrolidinolysis of PTH is nearly 75 and 50-times larger than k_4 for the reactions of PTH with monoprotonated piperazine and morpholine, respectively.[22] These results are consistent with the occurrence of a preassociation stepwise mechanism where the association complex is T$_3$.

Pyrrolidine and piperidine have very similar pK_a values.[10] The occurrence of general base catalysis in the reaction of PTH with pyrrolidine and the absence of such catalysis in the piperidinolysis of PTH is therefore difficult to explain in terms of polar effects. Such a differing behaviour of pyrrolidine and piperidine as nucleophiles toward maleimide was not observed.[4] However, Bunnett and co-workers[6,7] observed a differing behaviour of these alicyclic amines as nucleophiles toward a few aromatic nucleophilic substitution reactions. Pyrrolidine and piperidine showed almost similar reactivity towards amine-catalysed elimination from a β-acetoxy ketone,[26] nucleophilic displacement on the arene oxides of phenanthrene[27] and the reactions of amines with cyanic acid.[17] A nearly 100 times larger reactivity of pyrrolidine compared with piperidine

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* The usage of intramolecular general base–acid catalysis in the present system (T$_1$, T$_2$ or T$_3$) is peculiar in the sense that the leaving group (anionic nitrogen of S$^-$) acts as the intramolecular general base catalyst to facilitate the nucleophilic attack by the amine nucleophile and in the process the attacking amine nucleophile acts as the intramolecular general acid catalyst to increase the leaving ability of the leaving group (anionic nitrogen of S$^-$).
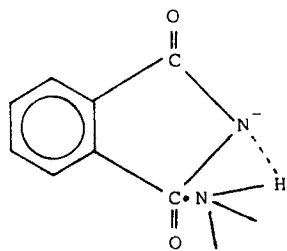
T_1
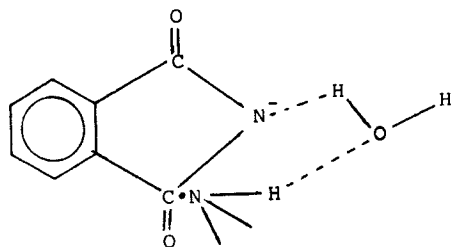
T_2
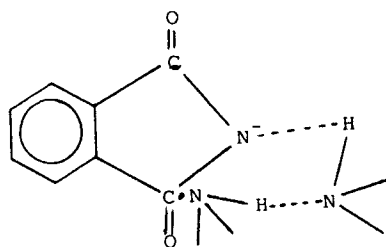
T_3

towards amine catalysis of β-ketol dehydration has been reported by Hupe *et al.*[28] It is interesting that the nucleophilic second-order rate constant, k_2, for the reaction of ionized PTH with piperidine $(k_2 = 0\cdot173$ dm^3 mol^{-1} s^{-1})[22] is not unusually different from that with pyrrolidine $(k_2 < 0\cdot742$ dm^3 mol^{-1} s$^{-1})$.

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REFERENCES

1. W. P. Jencks, *Catalysis in Chemistry and Enzymology*. McGraw-Hill, New York (1969); T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms*. Benjamin, New York (1966); W. P. Jencks, *Acc. Chem. Res.* **9**, 425 (1976); **13**, 16 (1980).
2. M. N. Khan, *J. Chem. Soc., Perkin Trans. 2* 891 (1985).
3. M. N. Khan, *J. Chem. Soc., Perkin Trans. 2* 435 (1990).
4. M. N. Khan, *J. Chem. Soc., Perkin Trans. 2* 819 (1987).
5. M. N. Khan, *J. Chem. Soc., Perkin Trans. 2* 1977 (1985).
6. J. F. Burnett, S. Sekiguchi and L. A. Smith, *J. Am. Chem. Soc.* **103**, 4865 (1981).
7. J. F. Bunnett and A. V. Cartano, *J. Am. Chem. Soc.* **103**, 4861 (1981).
8. J. F. Bunnett and C. F. Bernasconi, *J. Am. Chem. Soc.* **87**, 5209 (1965).
9. J. F. Bunnett and D. H. Hermann, *Biochemistry* **9**, 816 (1970).
10. A. R. Becker, D. J. Richardson and T. C. Bruice, *J. Am. Chem. Soc.* **99**, 5058 (1977).
11. W. Schwotzer and W. von Philipsborn, *Helv. Chim. Acta* **60**, 1501 (1977).
12. J. P. Fox and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 1436 (1974).
13. T. C. Bruice, A. Donzel, R. W. Huffman and A. R. Butler, *J. Am. Chem. Soc.* **89**, 2106 (1967).
14. T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.* **82**, 3067 (1960).
15. J. Fastrez, *J. Chem. Soc., Perkin Trans. 2* 1067 (1980).
16. W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.* **82**, 1778 (1960).
17. A. Williams and W. P. Jencks, *J. Chem. Soc., Perkin Trans. 2* 1753 (1974).
18. T. Deacon, A. Steltner and A. Williams, *J. Chem. Soc. Perkin Trans. 2* 1778 (1975).
19. N. Bourne and A. Williams, *J. Am. Chem. Soc.* **106**, 7591 (1984).
20. M. N. Khan, *J. Chem. Soc., Perkin Trans. 2* 199 (1989).
21. B. Zerner and M. L. Bender, *J. Am. Chem. Soc.* **83**, 2267 (1961).
22. M. N. Khan and J. E. Ohayagha, *J. Phys. Org, Chem.* **4**, 547 (1991), and references cited therein.
23. P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.* **96**, 5523 (1974).
24. J. J. Morris and M. I. Page, *J. Chem. Soc., Perkin Trans. 2* 212 (1980).
25. W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* **88**, 104 (1966).
26. D. J. Hupe, M. C. R. Kendal and T. A. Spencer, *J. Am. Chem. Soc.* **94**, 1254 (1972).
27. P. Y. Bruice, T. C. Bruice, H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.* **98**, 2973 (1976).
28. D. J. Hupe, M. C. R. Kendal and T. A. Spencer, *J. Am. Chem. Soc.* **95**, 2271 (1973).