Kinetic Evidence for the Occurrence of a Stepwise Mechanism in the Aminolysis of Maleimide. General Acid and Base Catalysis by Secondary Amines

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The reaction rates for nucleophilic cleavage of maleimide have been studied for buffered solutions of eight secondary amines. The reactions of secondary amines with ionized and non-ionized maleimide are subject to general acid and general base catalysis, respectively. Non-linear plots of the apparent second-order rate constants at a given pH against total buffer concentrations reveal that the rate-determining step changes as the buffer concentration is increased; this provides evidence for the existence of an intermediate on the reaction path. The rate constants for specific acid-catalysed cleavage of an oxy monoanionic tetrahedral addition intermediate (T^-) display a Brønsted plot of slope (β_{nuc}) 0.37. The rate constants for general base-catalysed cleavage of non-ionized maleimide (SH) reveal a Brønsted plot of slope (β_{nuc_1}) 0.79. The significantly high value of β_{nuc_1} is attributed to a normal stepwise mechanism (*i.e.* diffusion-controlled trapping mechanism) in which a zwitterionic tetrahedral addition intermediate ($T^{\pm}$) is converted into T^- by general base catalysis. The rate constants for general acid-catalysed cleavage of ionized maleimide ($\bar{S}$) fit a Brønsted plot of slope (β'_{nuc_1}) 0.47. The low value of β'_{nuc_1} compared with that of β_{nuc_1} is explained by assuming a preassociation stepwise mechanism in which the highest energy barrier on the reaction co-ordinate involved in the formation of T^- is for nucleophilic attack within the encounter complex. An uncatalysed term in the rate law for the cleavage of maleimide could not be detected under the experimental conditions.

Although much work has already been published on general acid–base catalysis, the mechanisms of these reactions are not yet fully understood. It is generally believed that the driving force for general acid–base catalysis of carbonyl addition and related reactions arises from the existence of highly unstable intermediates and transition states on the reaction path.[1] General acid catalysis was detected in the reaction of maleimide with tertiary amines[2] but no general acid–base catalysis could be found in that with primary amines.[3]

In the alkaline hydrolysis of amides[4] and imides,[5] the occurrence of a stepwise mechanism has been proposed on the basis of the observed break in the pH–rate profiles. Similarly, the breaks in the plots of rate constants *versus* total buffer concentrations in the buffer catalysed reactions are generally attributed to the existence of short-lived intermediates on the reaction path.[6] This characteristic led to the proposal of the occurrence of a stepwise mechanism in the aqueous cleavage of 2,4-dinitrophenyl 4-chloro-2-nitrophenylmethanesulphonate in the presence of cacodylic acid buffers,[7] tertiary amine-catalysed enolization of oxaloacetic acid[8] and diethyl oxaloacetate,[9] hydroxylaminolysis of amides,[10] and cyclization of methyl 2-aminophenylacetate at pH <7.[11]

Studies on aminolysis of imides have not been carried out as extensively as those of esters partly because of the comparatively low reactivity of imides toward amine nucleophiles. The magnitudes of the Brønsted coefficients obtained in uncatalysed and general acid–base-catalysed aminolyses of esters and related compounds have been attributed to the measure of the charge development in the transition states.[12–14] Thus, a β value of 1.0 obtained in the general base-catalysed aminolysis of acetylimidazole[15] revealed the development of a charge of +1.0 on nitrogen in the transition state. This work was initiated with the aim of exploring whether or not the secondary amine-catalysed cleavage of maleimide is subject to general acid–base catalysis. The results and the probable mechanism are described here.

Experimental

Reagent grade chemicals such as morpholine and piperazine (B.D.H.), *N*-methylpiperazine (Fluka AG), and maleimide, pyrrolidine, diethanolamine, diethylamine, dimethylamine hydrochloride, and piperidine hydrochloride (Aldrich) were commercially available. Other chemicals were also of reagent grade. Glass-distilled water was used throughout.

Kinetic Measurements.—The reaction rate of aminolysis of maleimide was studied by monitoring the disappearance of maleimide spectrophotometrically at 300 nm. The details of the procedure and the kinetic analysis are described elsewhere.[2,3]

The pK_a values for piperazine, *N*-methylpiperazine, diethanolamine, and diethylamine were determined potentiometrically as described elsewhere.[3]

Product Characterization.—The nucleophilic catalysis exhibited by primary and secondary amines towards maleimide may be considered as due to nucleophilic attack at either carbonyl carbon leading to *NN*-dialkymaleamide or at the ethylene carbon leading to Michael addition. Michael addition may be ruled out as described below.

To 0.4M-dimethylamine buffer (3.0 cm^3; 50% free base) was added 0.0125M-maleimide (1.0 cm^3). The absorbance at 300 nm (A_{300}) was found to drop from a maximum to a minimum within *ca.* 30 s ($k_{\mathrm{obs}} \simeq 0.8$—$0.87$ s^{-1}); 10 min from the start of the run, 2.5M-NaOH (16 cm^3) was added and the production of ammonia was measured periodically by a nesslerization technique.[16] The kinetics was monitored up to *ca.* 70 h and the observed pseudo-first-order rate constant (k'_{obs}) was found to be $(1.3 \pm 0.2) \times 10^{-3}$ min^{-1} at 30 °C which may be compared with k''_{obs} $(1.6 \pm 0.2) \times 10^{-3}$ min^{-1} at 2.0M-NaOH and 30 °C[17] and 25×10^{-3} min^{-1} at 2.0M-NaOH and 65 °C[18] obtained for the alkaline hydrolysis of maleamic acid. The close similarity of k'_{obs} and k''_{obs} indicates that k'_{obs} corresponds to the alkaline hydrolysis of maleamic acid. This is conceivable from the fact that $k_{1\mathrm{obs}} \simeq 1.8 \times 10^3 k_{2\mathrm{obs}}$ where $k_{1\mathrm{obs}}$ and $k_{2\mathrm{obs}}$ are the respective second-order rate constants for the first and second steps of the alkaline hydrolysis of maleamide.[18] Thus, the instantaneously formed *NN*-dimethylmaleamide, as a result of the nucleophilic reaction of dimethylamine with maleimide, is quickly converted into maleamic acid with a rate constant, $k'_{1\mathrm{obs}}$, of *ca.* 2.9 min^{-1} assuming a value of $k'_{1\mathrm{obs}}/k'_{2\mathrm{obs}}$ of 1.8×10^3. The overall reaction is shown in equation (1) where $k_{\mathrm{II}}[\overline{\mathrm{O}}\mathrm{H}] = k'_{1\mathrm{obs}}$ and $k_{\mathrm{III}}[\overline{\mathrm{O}}\mathrm{H}] = k'_{2\mathrm{obs}}$. The non-appearance of ammonia

$$\begin{tikzcd}
\text{maleimide} + \mathrm{Me_2NH} \arrow[r, "k_1", "\text{very fast}"'] & NN\text{-dimethylmaleamide} \arrow[d, "k_{\mathrm{II}}[\overline{\mathrm{O}}\mathrm{H}]", "{\text{very fast} \atop -\mathrm{Me_2NH}}"'] \\
\text{maleic acid} + \mathrm{NH_3} & \text{maleamic acid} \arrow[l, "{k_{\mathrm{III}}[\overline{\mathrm{O}}\mathrm{H}]}"', "\text{slow}"]
\end{tikzcd} \qquad (1)$$

in the k_{II} step is expected since these are examples which indicate that, generally, tertiary amides were hydrolysed faster than secondary and primary amides.[19]

The Michael addition product of dimethylamine and maleimide is expected to be a substituted succinimide and the production of ammonia in the alkaline hydrolysis of succinimide has been shown to follow an irreversible consecutive reaction path.[20] Since the production of ammonia in the present reaction system followed a simple first-order rate law, it is probable that the reaction of dimethylamine with maleimide did not produce a Michael addition adduct. Furthermore, dimethylamine is a hard nucleophile and ethylene carbon is a soft electrophile compared with carbonyl carbon and therefore nucleophilic attack by dimethylamine at a carbonyl carbon is more probable than at an ethylene carbon. A recent report also concluded that primary amines are unlikely to produce Michael addition adducts with maleimide.[3] This analysis thus does not favour Michael addition in the reaction of maleimide with primary and secondary amines. The possibility that secondary amines are acting as general base catalysts for hydrolysis of maleimide has been ruled out elsewhere.[3]

Results and Discussion

The aqueous cleavage of maleimide was studied at different pH values in buffer solutions of several secondary amines. The results for a few typical amines are shown in Figures 1 and 2.

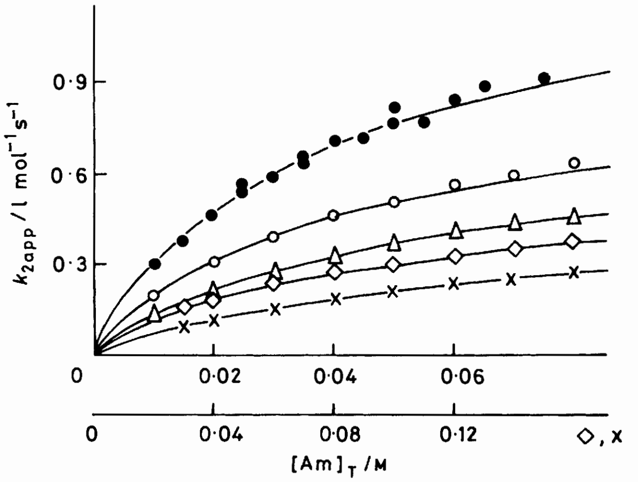


Figure 1. Plots of k_{napp} *versus* $[\mathrm{Am}]_\mathrm{T}$ for the reactions of maleimide with morpholine at pH: 7.97 (×), 8.09 (□), 8.35 (△), 8.51 (○), and 8.79 (●). The solid lines are those calculated from equation (2)

These results indicate that the slopes of the plots change from higher to lower values as the total amine buffer concentrations ($[\mathrm{Am}]_\mathrm{T}$) change from lower to higher ones. Such plots were also observed in various reactions[6–11] and the biphasic nature of the plots was attributed to the presence of an intermediate on the reaction path. The observed data were well fitted to the empirical equation (2) where the apparent second-order rate

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

constant $k_{\mathrm{napp}} = (k_{\mathrm{obs}} - k_\mathrm{o})/[\mathrm{Am}]_\mathrm{T}$; k_o is the buffer-independent first-order rate constant and k_{obs} is the observed pseudo-first-order rate constant. The fitting of the observed data to equation (2) reveals that the uncatalysed nucleophilic second-order rate constant term is negligible compared with the catalysed term under the experimental conditions employed in the present study. The values of k_o at different pH values were calculated from equation (3) where $k_{\mathrm{OH}} = 72.2$ l mol^{-1} s^{-1},[17] $K_\mathrm{w} =$

$$k_\mathrm{o} = k_{\mathrm{OH}}K_\mathrm{w}/(a_\mathrm{H} + K'_\mathrm{a}) \qquad (3)$$

1.449×10^{-14} mol^{-1} l^{-1},[21] and the ionization constant of maleimide, $K'_\mathrm{a} = 1.41 \times 10^{-10}$ mol l^{-1}.[17]

The empirical parameters A_1 and A_2 were calculated from equation (2) by a least-squares technique and the results are shown in Table 1 for the reactions of maleimide with piperazine, morpholine, *N*-methylpiperazine, and diethanolamine. These results indicate that both A_1 and A_2 increase with increase in pH values. The extent of the fitting of the observed data to equation (2) is evident from the standard deviations of A_1 and A_2 and the plots shown in Figures 1 and 2 where solid lines are drawn through the calculated points. It is evident from Table 1 that, within the observed total buffer concentration range, the change in k_{napp} is *ca.* 100—200% for morpholine, *N*-methylpiperazine, and monoprotonated piperazine while a change of *ca.* 25—43% in k_{napp} was obtained for piperazine and diethanolamine.

The distinct non-linear plots of k_{napp} *versus* $[\mathrm{Am}]_\mathrm{T}$ shown for a few typical amines in Figures 1 and 2 reveal a change in the

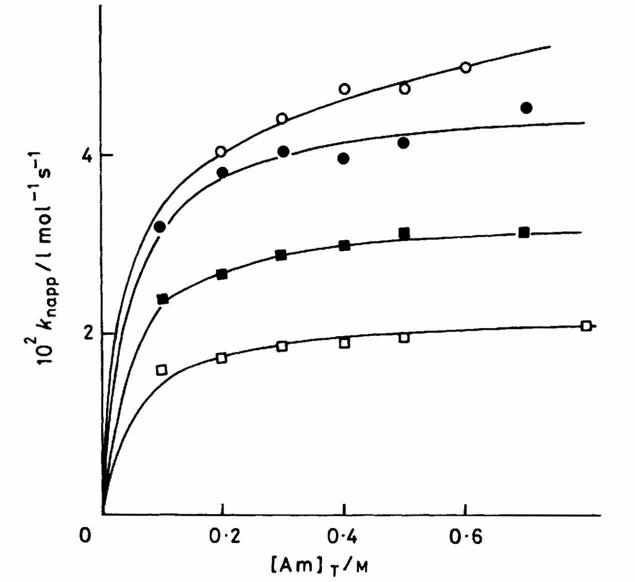


Figure 2. Plots of k_{napp} *versus* $[\mathrm{Am}]_\mathrm{T}$ for the reactions of maleimide with diethanolamine at pH: 8.65 (□), 8.94 (■), 9.21 (●), and 9.70 (○). The solid lines are drawn through the least-squares-calculated points using equation (2)

Table 1. The values of empirical parameters calculated from equation (2)[a]

Amine	pH	$10A_1$/l^2 mol^{-2} s^{-1}	A_2/l mol^{-1}	$\left(\frac{f_a f_{SH}}{f_{aH} f_{S^-}}\right)^b$	Ψ^c (%)	No. of runs	$[\text{Am}]_T$/M range
Piperazine	5.63	0.331 ± 0.021[d]	0.786 ± 0.193[d]	6.5×10^3	192	6	0.16—0.60
	6.07	0.832 ± 0.038	1.45 ± 0.18	6.5×10^3	150	6	0.16—0.60
	6.41	1.40 ± 0.03	2.56 ± 0.13	6.5×10^3	126	6	0.12—0.45
	7.15	3.04 ± 0.28	3.09 ± 0.57	6.4×10^3	112	5	0.12—0.45
	9.07	907 ± 128	71.9 ± 17.2	0.71	25	5	0.015—0.025
	9.28	1 273 ± 164	68.6 ± 15.2	0.71	26	5	0.015—0.025
	9.49	1 654 ± 225	54.6 ± 13.7	0.71	37	4	0.015—0.030
	9.69	1 896 ± 174	37.4 ± 7.9	0.71	35	5	0.015—0.025
Morpholine	7.97	38.0 ± 1.3	7.92 ± 0.56	19	181	8	0.03—0.16
	8.09	70.8 ± 2.1	13.4 ± 0.7	23	138	8	0.03—0.16
	8.35	146 ± 5	19.0 ± 1.2	18	251	8	0.01—0.08
	8.51	215 ± 11	21.6 ± 2.0	18	227	8	0.01—0.08
	8.79	352 ± 18	25.1 ± 2.3	19	202	16	0.01—0.075
N-Methylpiperazine	8.56	163 ± 32	25.2 ± 6.9	4	157	8	0.02—0.16
	8.66	224 ± 8	21.4 ± 1.4	4	246	8	0.01—0.08
	8.90	401 ± 16	30.1 ± 1.9	4	195	8	0.01—0.08
	9.08	616 ± 26	41.8 ± 2.7	4	162	12	0.01—0.065
Diethanolamine	8.65	5.58 ± 1.28	26.4 ± 6.8	4.5	33	6	0.1—0.8
	8.94	8.08 ± 0.72	24.3 ± 2.5	4.5	31	6	0.1—0.7
	9.21	10.4 ± 2.0	22.5 ± 4.9	4.2	42	6	0.1—0.7
	9.70	9.37 ± 0.83	17.5 ± 1.8	4.5	43	6	0.1—0.6

[a] Conditions: [Maleimide] 6.25×10^{-4}M, 30 °C, ionic strength 1.0M, 5% 1,4-dioxane in the aqueous reaction mixture. [b] $f_a = K_a/(a_H + K_a)$, $f_{aH} = 1 - f_a$, $f_{S^-} = K'_a/(a_H + K'_a)$, $f_{SH} = 1 - f_{S^-}$, and K_a and K'_a represent the ionization constant of conjugate acid of amine and maleimide, respectively. [c] $\Psi = 100\,(k_{2h} - k_{2l})/k_{2l}$ where k_{2l} and k_{2h} represent k_{napp} obtained at the lowest and highest total amine buffer concentrations ($[\text{Am}]_T$) attained. [d] Error limits are standard deviations.

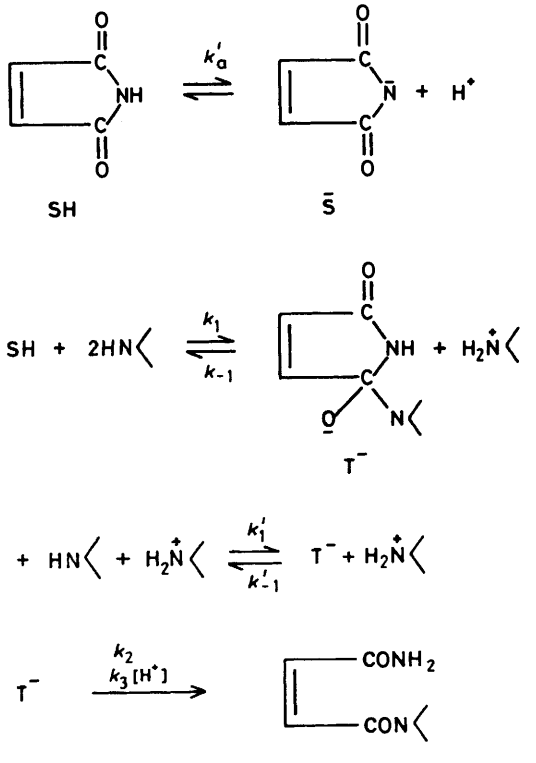
rate-determining step with change in the catalyst concentration which in turn implies the formation of an intermediate on the reaction co-ordinate. The other possible reason for the non-linear dependence of k_{napp} on $[\text{Am}]_T$ such as a change in pH with change in the total buffer concentration, $[\text{Am}]_T$, may be ruled out by the fact that pH values were found to remain essentially constant within the observed $[\text{Am}]_T$ range. Another possible reason for the non-linearity is that morpholine undergoes some kind of complexation with the substrate or with itself. But this possibility could also be ruled out for the reason that such complexation is unlikely to occur with all other secondary amines of the present study. The results could be explained by the overall simplified mechanism shown in Scheme 1 for the reactions of non-ionized (SH) and ionized ($\bar{S}$) maleimide with secondary amines. A similar mechanism has been proposed by Jencks *et al.* in the hydroxylaminolysis of amides.[10] The derived rate law, on the basis of the proposed mechanism (Scheme 1), could lead to equation (4) where $f_a = K_a/(a_H + K_a)$,* $f_{aH} = 1 - f_a$, $f_{S^-} = K'_a/(a_H + K'_a)$, $f_{SH} = 1 - f_{S^-}$, and K_a is the ionization constant of the conjugate acid of the amine base. Equation (4) is similar to equation (2) with the conditions (5) and (6).

$$k_{napp} = \frac{(k_1 f_a^2 f_{SH} + k'_1 f_a f_{aH} f_{S^-})(k_2 + k_{3aH})[\text{Am}]_T}{k_2 + k_3 a_H + (k_{-1} + k'_{-1}) f_{aH}[\text{Am}]_T} \qquad (4)$$

$$A_1 = k_1 f_a^2 f_{SH} + k'_1 f_a f_{aH} f_{S^-} \qquad (5)$$

$$A_2 = (k_{-1} + k'_{-1}) f_{aH}/(k_2 + k_3 a_H) \qquad (6)$$

The validity of equation (6) could be tested experimentally by using the observed values of A_2 at different pH values as shown in Table 1. It is evident from equation (6) that plots of f_{aH}/A_2 *versus* a_H should be linear. These plots are shown in Figure 3 and are essentially linear within the observed pH range. The intercept $[k_2/(k_{-1} + k'_{-1})]$ and slope $[k_3/(k_{-1} + k'_{-1})]$ were calculated by a linear least-squares technique and the results



Scheme 1.

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* For amines whose thermodynamic ionization constants are known, $f_a = \gamma K_a/(a_H + \gamma K_a)$ for monoamine, $f_a = \gamma K_2/(a_H + \gamma K_2)$ for diamine where K_2 is the ionization constant of monoprotonated diamine, $f_a = \gamma' K_1/(a_H\gamma + \gamma' K_1)$ for diamine where K_1 is the ionization constant of diprotonated diamine and γ and γ' are the activity coefficient of mono- and di-protonated diamine, respectively.

obtained are shown in Table 2. The calculated values of $k_2/(k_{-1} + k'_{-1})$ with standard deviations of more than 100% indicate the insignificant contribution of the k_2 step compared with that of k_3 in the reactions of maleimide with morpholine, *N*-methylpiperazine, and monoprotonated piperazine.

The values of k_1 and k'_1 for those amines which followed equation (2) and for which, therefore, A_1 values were available, were derived as follows. It is evident from Scheme 1 and equation (5) that k_1 is kinetically indistinguishable from k'_1. However, the relative values of k_1 and k'_1 could be qualitatively estimated as described in the Appendix. The estimated values of k_1/k'_1 are 0.58, 0.40, and 0.04 for the reactions of maleimide with *N*-methylpiperazine, morpholine, and monoprotonated piperazine (piperazine–$\overset{+}{\text{H}}$), respectively. The values of $f_af_{SH}/f_{aH}f_{S^-}$ were calculated at different pH values with known values of K_a and K'_a and the results obtained are shown in Tables 1 and 3.

The known values of k_1/k'_1 and $f_af_{SH}/f_{aH}f_{S^-}$ were used to calculate the contributions of $k_1f_a^2f_{SH}$ and $k'_1f_af_{aH}f_{S^-}$ toward A_1 [equation (5)] which are shown in Table 4. The values of $k_1f_a^2f_{SH}$ and $k'_1f_af_{aH}f_{S^-}$ were calculated from observed values of A_1 and calculated values of $k_1f_af_{SH}/k'_1f_{aH}f_{S^-}$. The calculated values of $k_1f_a^2f_{SH}$ and $k'_1f_af_{aH}f_{S^-}$ at different pH values were used to calculated k_1 and k'_1 with known values of f_a, f_{aH}, f_{SH}, and f_{S^-}. The average values of k_1 and k'_1 thus calculated are shown in Table 4. The calculated values of k_1 and k'_1 for

Table 2. The values of $k_2/(k_{-1} + k'_{-1})$ and $k_3/(k_{-1} + k'_{-1})$ calculated from equation (6)

Amine	pK_a^a	$10^2\left(\frac{k_2}{k_{-1} + k'_{-1}}\right)$	$10^{-5}\left(\frac{k_3}{k_{-1} + k'_{-1}}\right)$
Morpholine	8.60[b]	−0.15 ± 0.76[c]	91.4 ± 13.2[c]
N-Methylpiperazine	9.10[d]	0.84 ± 0.71 (0.0971)[e]	105 ± 37
Piperazine–H$^+$	5.57[d]	−2.15 ± 1.66	5.68 ± 0.13
Piperazine	9.83[d]	0.619[e]	224[f]
Diethanolamine	9.04[f]	0.0414	106
Piperidine	11.23[g]	0.0269	746
Dimethylamine	11.05[h]	0.0238	639
Pyrrolidine	11.32[g]	0.110	806
Diethylamine	11.07[d]	0.0146	650

[a] pK_a Of conjugate acid of free amine. [b] P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, 1974, **96**, 5533. [c] Error limits are standard deviations. [d] This study. [e] Estimated from the calculated values of $Yk_2/(k_{-1} + k'_{-1})$ (Table 5) and Y as described in the text. [f] Estimated from equation (10): $\log[k_3/(k_{-1} + k'_{-1})] = 3.68 + 0.37\ pK_a$ (Figure 6). [g] A. R. Becker, D. J. Richardson, and T. C. Bruice, *J. Am. Chem. Soc.*, 1977, **99**, 5058. [h] D. Z. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, 1979, **101**, 4713.

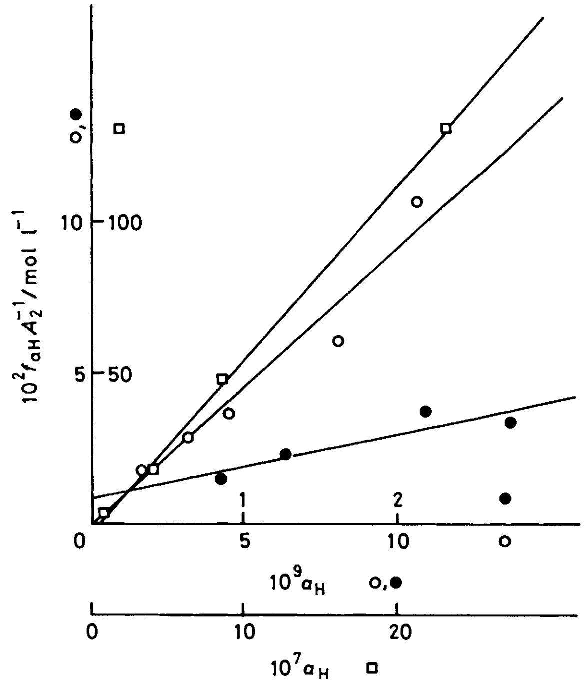


Figure 3. Plots of $f_{aH}A_2^{-1}$ *versus* a_H for the reactions of maleimide with morpholine (○), *N*-methylpiperazine (●), and piperazine–H$^+$ (□). The solid lines are those calculated from equation (6) with parameters listed in Table 2

Table 3. Apparent second-order rate constants calculated from equation (8)[a]

Amine	pH	10^2k_{napp}/l mol^{-1} s^{-1}	$\frac{f_{aH}f_{S^-}}{f_af_{SH}}$	W^b range	$[\text{Am}]_T$/M range	No. of runs
Piperidine	10.12	93.7 ± 1.7[c]	24	5—25	0.03—0.14	10
	10.27	104 ± 1	24	6—14	0.030—0.065	8
	10.46	110 ± 1	24	9—19	0.030—0.065	8
	10.67	118 ± 1	24	9—23	0.020—0.055	8
	10.94	118 ± 1	24	11—28	0.020—0.055	8
	11.05	122 ± 1	24	12—33	0.020—0.055	8
Dimethylamine	9.91	202 ± 4	16	3—5	0.020—0.034	8
	10.10	240 ± 3	16	4—6	0.020—0.034	8
	10.23	263 ± 3	16	4—8	0.020—0.034	8
	10.71	293 ± 3	16	10—17	0.022—0.034	8
Pyrrolidine	10.30	157 ± 7	30	3—5	0.0175—0.0250	4
	10.60	197 ± 7	30	4—7	0.0150—0.0250	5
	10.84	251 ± 6	30	7—18	0.020—0.050	5
	10.92	253 ± 7	30	5—8	0.0125—0.0250	6
	11.03	279 ± 8	30	4—9	0.0125—0.0250	6
	11.14	312 ± 8	29	5—9	0.0125—0.0250	6
Diethylamine	10.72	7.37 ± 0.14	23	35—96	0.060—0.165	5
	11.07	7.31 ± 0.16	28	16—42	0.020—0.055	5
	11.36	6.35 ± 0.10	21	55—150	0.060—0.165	5
	11.63	4.80 ± 0.18	28	57—143	0.060—0.165	5

[a] Reaction conditions are the same as described in Table 1; f_a, f_{aH}, f_{S^-}, and f_{SH} have the same meanings as described in Table 1. [b] $W = (k_{-1} + k'_{-1})f_{aH}[\text{Am}]_T/(k_2 + k_3a_H)$. [c] Error limits are standard deviations.

Table 4. General base- (k_1) and general acid-catalysed (k'_1) rate constants for the formation of T^- (Scheme 1) in the reactions of secondary amines with SH and S^-, respectively

Amine	pK_a	k_1/l^2 mol^{-2} s^{-1}	k'_1/l^2 mol^{-2} s^{-1}	X_1^a	X_2^b
Morpholine	8.60	96.6	241	0.877	0.123
		$(98.5 \pm 7.7^d)^c$	$(252 \pm 22^d)^c$	$(0.878)^e$	$(0.122)^e$
		$(112 \pm 9^d)^f$	0.0		
N-Methylpiperazine	9.10	520	895	0.695	0.305
		(368 ± 56)	(623 ± 88)	$(0.699)^e$	$(0.301)^e$
		$(546 \pm 68)^f$	0.0		
Piperazine–H$^+$	5.57	0.423	9.70	0.995	0.005
		(0.341 ± 0.059)	(15.1 ± 3.1)	$(0.996)^e$	$(0.004)^e$
		$(0.342 \pm 0.060)^f$	0.0		
Piperazine	9.83	1.81×10^3	1.84×10^3	0.419	0.581
		$(1.68 \pm 0.49) \times 10^3$	$(1.81 \pm 0.65) \times 10^3$	$(0.419)^e$	$(0.581)^e$
Diethanolamine	9.04	10.4	19.3	0.709	0.291
		(4.80 ± 2.90)	(8.77 ± 5.22)	$(0.709)^e$	$(0.291)^e$
Piperidine	11.23	8.65×10^3	3.01×10^3	0.107	0.893
Dimethylamine	11.05	1.47×10^4	5.90×10^3	0.136	0.864
Pyrrolidine	11.32	1.31×10^4	4.30×10^3	0.094	0.906
Diethylamine	11.07	585	232	0.096	9.904

[a] $X_1 = k_1K_a^2/(k_1K_a^2 + k'_1K_aK'_a)$. [b] $X_2 = k'_1K_aK'_a/(k_1K_a^2 + k'_1K_aK'_a)$: K'_a is the ionization constant of maleimide. [c] Parenthesized values were calculated from the observed values of A_1 as described in the text. [d] Error limits are standard deviations. [e] $X_1 = k_1f_af_{SH}/(k_1f_af_{SH} + k'_1f_{S^-}f_{aH})$; $X_2 = k'_1f_{aH}f_{S^-}/(k_1f_af_{SH} + k'_1f_{S^-}f_{aH})$ and f_a, f_{aH}, f_{S^-}, and f_{SH} have the same meanings as described in Table 1. [f] Calculated from A_1 assuming $k'_1 = 0.0$

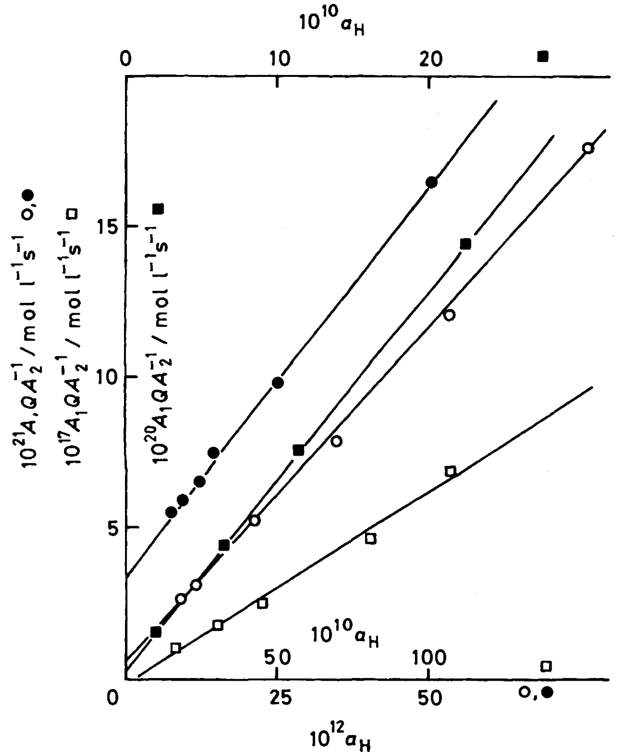


Figure 4. Plots showing the dependence of $A_1QA_2^{-1}$ on a_H for the reactions of maleimide with piperidine (○), pyrrolidine (●), morpholine (□), and diethanolamine (■). The solid lines are drawn through the least-squares-calculated points. $Q = (a_H + K_a)(a_H + K'_a)$ for piperidine, pyrrolidine, and morpholine, and $Q = (a_H + \gamma K_a)(a_H + K'_a)$ for diethanolamine where γ and K_a are the respective activity coefficient and thermodynamic ionization constants of protonated diethanolamine

piperazine and diethanolamine are, however, not very reliable because they are obtained from A_1 values which are derived from equation (2) where the variations in k_{napp}, within the total $[Am]_T$ range are not very significant (Table 1). It is interesting to note that the values of k_1 (for piperazine–H$^+$, morpholine, and *N*-methylpiperazine), calculated on the assumption that $k'_1 = 0.0$, are not significantly different from those calculated without considering this assumption (Table 4).

Table 5. The calculated intercepts and slopes of the plots of A_1Q/A_2 *versus* a_H [equation (7)]

Amine	pK_a	$Yk_2/(k_{-1} + k'_{-1})^a$/ mol l^{-1} s^{-1}	$Yk_3/(k_{-1} + k'_{-1})^a$/ s^{-1}
Morpholine	8.60	$(-1.9 \pm 2.4^b) \times 10^{-18}$	$(6.35 \pm 0.38^b) \times 10^{-9}$
N-Methylpiperazine	9.10	$(3.2 \pm 12.2) \times 10^{-19}$	$(2.41 \pm 0.64) \times 10^{-9}$
Piperazine–H$^+$	5.57	$(1.36 \pm 0.88) \times 10^{-14}$	$(9.99 \pm 0.70) \times 10^{-8}$
Piperazine	9.83	$(28.6 \pm 5.8) \times 10^{-20}$	$(1.03 \pm 0.11) \times 10^{-9}$
Diethanolamine	9.04	$(3.69 \pm 1.00) \times 10^{-20}$	$(6.31 \pm 0.28) \times 10^{-11}$
Piperidine	11.23	$(7.55 \pm 0.68) \times 10^{-22}$	$(2.09 \pm 0.02) \times 10^{-10}$
Dimethylamine	11.05	$(30.0 \pm 3.8) \times 10^{-22}$	$(5.49 \pm 0.05) \times 10^{-10}$
Pyrrolidine	11.32	$(35.1 \pm 1.2) \times 10^{-22}$	$(2.58 \pm 0.05) \times 10^{-10}$
Diethylamine	11.07	$(3.14 \pm 0.66) \times 10^{-23}$	$(1.40 \pm 0.06) \times 10^{-11}$

[a] $Y = k_1K_a^2 + k'_1K_aK'_a$ where K'_a is the ionization constant of maleimide.
[b] Error limits are standard deviations.

An alternative method of calculating k_1 and k'_1 for all the amines and for which A_1/A_2 values at different pH are available may be explained as follows. Equations (5) and (6) could be used to obtain (7) where $Q = (a_H + K_a)(a_H + K'_a)$ and $Y = k_1K_a^2 + k'_1K_aK'_a$.

$$A_1Q/A_2 = Y(k_2 + k_3a_H)/(k_{-1} + k'_{-1}) \qquad (7)$$

Plots of A_1Q/A_2 *versus* a_H are essentially linear as evident from the plots shown in Figure 4 for a few typical amines. The values of $Yk_2/(k_{-1} + k'_{-1})$ and $Yk_3(k_{-1} + k'_{-1})$ were calculated from equation (7) and the results obtained are shown in Table 5. The estimated values of k_1/k'_1 and observed values of $k_3/(k_{-1} + k'_{-1})$ (Table 2) and $Yk_3/(k_{-1} + k'_{-1})$ (Table 5) were used to calculated k_1 and k'_1 with known values of K_a and K'_a. These results are summarized in Table 4.

The observed rate constants for the reactions of maleimide with piperidine, dimethylamine, pyrrolidine, and diethylamine obeyed equation (8) within the pH range studied. These results

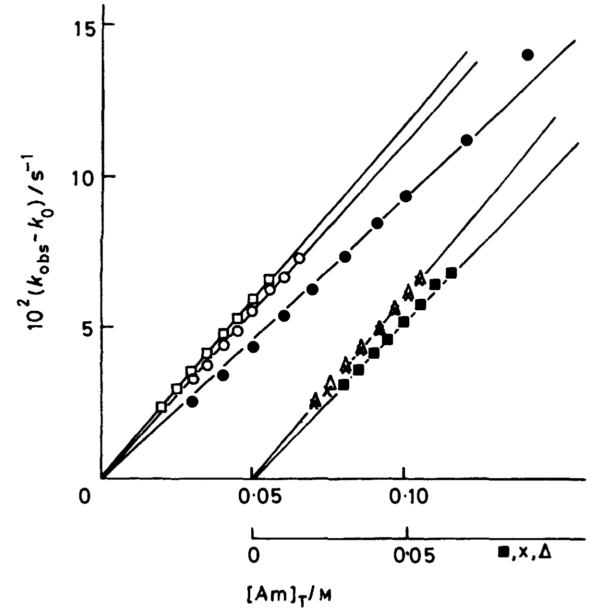


Figure 5. Plots showing the dependence of $k_{obs} - k_o$ on $[Am]_T$ for the reactions of maleimide with piperidine at pH 10.12 (●), 10.27 (■), 10.46 (○), 10.67 (□), 10.94 (×), and 11.05 (△). The solid lines are drawn through the least-squares-calculated points using equation (8)

$$k_{obs} - k_o = k_{napp}[Am]_T \qquad (8)$$

are thus anomalous in view of those for other amines which followed equation (2). The observed results for one typical amine are shown in Figure 5. The apparent second-order rate constants, k_{napp}, were calculated from equation (8) and are summarized in Table 3. The fitting of the observed data to equation (8) is evident from the standard deviations associated with k_{napp}. If we assume that these amines also obey the mechanism of Scheme 1 then, under the present experimental conditions, $(k_2 + k_3a_H)/(k_{-1} + k'_{-1})$ should be negligible compared with $f_{aH}[Am]_T$. Application of this condition reduced equation (4) to (9) which is similar to equation (8) with $k_{napp} = A_1/A_2$.

$$k_{obs} - k_o = A_1[Am]_T/A_2 \qquad (9)$$

The values of k_1 and k'_1 for the amines which followed equation (9) were calculated as described in the following lines. The observed values of k_{napp} $(=A_1/A_2)$ were found to fit equation (7). The fitting of the observed data to equation (7) is evident from the plots shown in Figure 4 for a few typical amines. The least-squares-calculated values of $Yk_2(k_{-1} + k'_{-1})$ and $Yk_3(k_{-1} + k'_{-1})$ are summarized in Table 5. Because of the unavailability of A_2 values, $k_3(k_{-1} + k'_{-1})$ values for these amines could not be obtained. However, these values were estimated as follows. The values of $k_3(k_{-1} + k'_{-1})$ for the amines (Table 2) which obeyed equation (2) and for which, therefore, A_2 values were available, were found to follow equation (10). The least-squares-calculated values of C and β_{app}

$$\log\left(\frac{k_3}{k_{-1} + k'_{-1}}\right) = C + \beta_{app}pK_a \qquad (10)$$

are 3.68 ± 0.26 and 0.37 ± 0.03, respectively. The fitting of the observed data to equation (10) is evident from the plot shown in Figure 6. In this calculation, the observed points considered were only for morpholine, *N*-methylpiperazine, and piperazine–H$^+$. The values of $k_3/(k_{-1} + k'_{-1})$ for the amines which followed equation (9) were estimated from equation (10) with known values of C, β_{app}, and pK_a. These results are shown in Table 2. The estimated values of $k_3/(k_{-1} + k'_{-1})$ were used to calculate $k_2(k_{-1} + k'_{-1})$ and $Y(= k_1K_a^2 + k'_1K_aK'_a)$ from the least-squares-calculated values of $Yk_3/(k_{-1} + k'_{-1})$ and $Yk_2/(k_{-1} + k'_{-1})$. The calculated values of $k_2(k_{-1} + k'_{-1})$ are shown in Table 2. As described in the Appendix, the estimated values of k_1/k'_1 and calculated values of Y were used to calculate k_1 and k'_1. The results thus obtained are shown in Table 4.

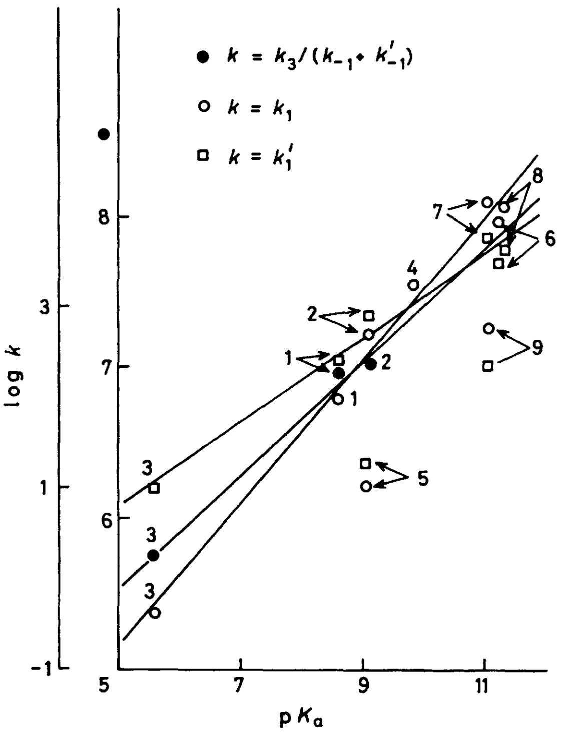


Figure 6. The dependence of $\log[k_3/(k_{-1} + k'_{-1})]$ (●), $\log k_1$ (○), and $\log k'_1$ (□) on the pK of the conjugate acid of the amines at 30 °C. The solid lines are drawn through the least-squares-calculated points from the Brønsted equation with β_{nuc} 0.37 and slope 3.68 for (●), β_{nuc_1} 0.79 and C_1 −4.68 for (○), and β'_{nuc_1} 0.47 and C'_1 −1.53 for (□). In the Brønsted plots: 1 morpholine; 2 *N*-methylpiperazine, 3 piperazine–H$^+$; 4 piperazine; 5 diethanolamine; 6 piperidine; 7 dimethylamine; 8 pyrrolidine; and 9 diethylanide

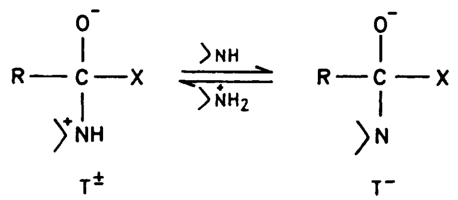
The values of k_2 were found to be negligible compared with k_3a_H for piperazine–H$^+$, *N*-methylpiperazine, and morpholine within the pH range of the present study (Table 2). The values of $f_{aH}[Am]_T$ $(k_{-1} + k'_{-1})/(k_2 + k_3a_H)$ were calculated at different $[Am]_T$ values with known values of $k_2/(k_{-1} + k'_{-1})$, $k_3/(k_{-1} + k'_{-1})$ (Table 2), and pH (Table 3) and the ranges of these calculated values are summarized in Table 3. It may be concluded from these calculated values that $(k_2 + k_3a_H)$ could be negligible compared with $(k_{-1} + k'_{-1})f_{aH}[Am]_T$ if the ratio $(k_{-1} + k'_{-1})f_{aH}[Am]_T/(k_2 + k_3a_A) \geqslant 4$.

The rate constants k_1 and k'_1 (Table 4) were well fitted to the respective Brønsted equations (11) and (12) as shown

$$\log k_1 = C_1 + \beta_{nuc_1}pK_a \qquad (11)$$

$$\log k'_1 = C'_1 + \beta'_{nuc_1}pK_a \qquad (12)$$

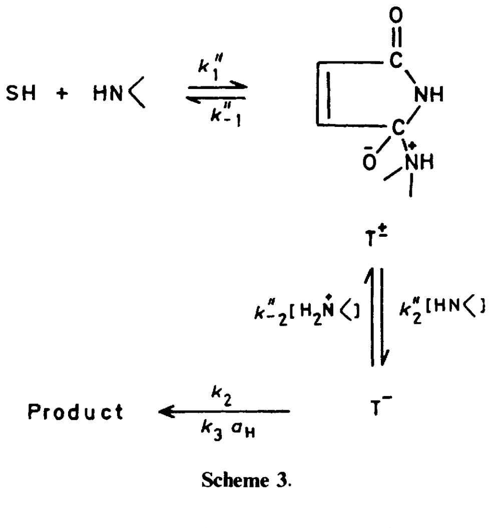
graphically in Figure 6. The least-squares-calculated values of C_1, C'_1, β_{nuc_1}, and β'_{nuc_1} are −4.68 ± 0.39 l^2 mol^{-2} s^{-1}, −1.53 ± 0.39 l^2 mol^{-2} s^{-1}, 0.79 ± 0.04, and 0.47 ± 0.04, respectively. In the calculation of β_{nuc_1} and β'_{nuc_1}, the rate constants for diethylamine and diethanolamine were not included because these nucleophiles are believed to be more sterically hindered compared with the other amine nucleophiles in the present study. The Brønsted slopes of 1.09 and 1.08 were obtained in the amine general base-catalysed cleavages of benzylpenicillin[13] and phenyl acetate,[22] respectively. Fox and Jencks[12] observed a Brønsted slope of $\geqslant 0.6$ in the carboxylate anion general base-catalysed methoxyaminolysis of acetyltriazole while catalytic constants for primary amine general base-catalysed aminolysis of acetyltriazole gave Brønsted plots of slope *ca.* 1.0. In these reactions, the Brønsted slope of approximately unity was generally attributed to intermolecular general base-catalysed conversion of a zwitterionic tetrahedral addition intermediate ($T^{\pm}$) into an anionic tetrahedral addition intermediate (T^-) as shown in Scheme 2.



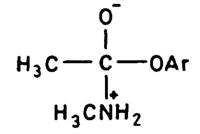
Scheme 2.

It has been elegantly argued by Jencks and others[12–15] that the values of the Brønsted coefficients obtained in the uncatalysed and general acid- and base-catalysed nucleophilic substitution reactions at carbonyl carbon are a measure of the extent of charge development in the critical transition states. Thus, significantly different values of β_{nuc_1} (0.79) and β'_{nuc_1} (0.47) demonstrate the occurrence of transition states for different structures in the reactions of non-ionized (SH) and ionized (S^-) maleimide with secondary amines. This, in turn, implies the involvement of different mechanisms in the reactions of SH and S^- with secondary amines.

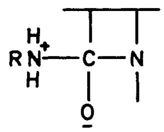
The value of β_{nuc_1} of 0.79 implies that the reaction behaves as if *ca.* 0.79 positive charge is developed in the transition state which is distributed between nucleophilic and catalysing amine molecules. The simplest mechanism that is consistent with this observation is shown in Scheme 3. The nature of the rate-determining step may be characterized as follows. Since k''_2 is the rate constant for the process involving thermodynamically favourable proton from $T^{\pm}$ to HN<, therefore its value will presumably be $\leqslant 10^{10}$ l mol^{-1} s^{-1} because the value of the rate constant for the proton transfer from $\mathrm{H_3\overset{+}{O}}$ to imidazole is 1.5×10^{10} l mol^{-1} s^{-1}.[23] The maximum value of $k''_2[\mathrm{HN}<]$ may be shown to be $\leqslant 4 \times 10^8$ s^{-1} under the experimental conditions for all amines. The reported values of the rate constants for the expulsion of methylamine and amine nucleophiles from (I)[24] and (II)[13] are 3×10^9 and 10^9—10^{10} s^{-1}, respectively. On the basis of these results, perhaps it may not be unreasonable to assume that the value of k''_{-1} is $> 10^9$ s^{-1}. This analysis thus reveals that $k''_{-1} > k''_2[\mathrm{HN}<]$ and consequently the rate constants k_1 and k_{-1} of Scheme 1 are equal to $k''_1 k''_2 / k''_{-1}$ and k''_{-2}, respectively. It has been discussed earlier that in the case of those amines where the observed data obeyed equation (9), the values of $(k_{-1} + k'_{-1})[\mathrm{H_2\overset{+}{N}}<]/(k_2 + k_3 a_{\mathrm{H}})$ are *ca.* $\geqslant 4$. This shows that $(k_{-1} + k'_{-1})[\mathrm{H_2\overset{+}{N}}<] \geqslant 4(k_2 + k_3 a_{\mathrm{A}})$. Thus for these amines, the conclusions that $k''_{-1} > k''_2[\mathrm{HN}<]$ and $(k_{-1} + k'_{-1})[\mathrm{H_2\overset{+}{N}}<] > (k_2 + k_3 a_{\mathrm{H}})$ lead to the k_2 and k_3 steps as rate limiting. In the reactions of maleimide with those secondary amines for which equation (4) was followed, it can be shown that, at a constant pH, $(k_2 + k_3 a_{\mathrm{H}}) > (k_{-1} + k'_{-1})[\mathrm{H_2\overset{+}{N}}<]$ at low $[\mathrm{Am}]_{\mathrm{T}}$ leading to the k''_2 step as rate limiting and $(k_2 + k_3 a_{\mathrm{H}}) < (k_{-1} + k'_{-1})[\mathrm{H_2\overset{+}{N}}<]$ at high $[\mathrm{Am}]_{\mathrm{T}}$ which leads to the k_2 and k_3 steps as rate limiting. Alternatively, it may be concluded that the distinction between equations (9) and (4) is that between the breakdown of T^- as rate limiting, *i.e.* very efficient catalysis (strong bases), and either $T^{\pm}$ or T^- as rate-limiting, according to amine concentration, *i.e.* less efficient catalysis.*



Scheme 3.



(I)



(II)

The value of β'_{nuc_1} of 0.47 indicates that *ca.* 0.47 positive charge is developed on the nucleophilic nitrogen atom in the transition state. A concerted mechanism for the rate-limiting general base-catalysed formation of T^- from S^- and R_2NH may be considered to be highly improbable. The most probable preassociation stepwise mechanism which could explain the observed values of β'_{nuc_1} may be shown in Scheme 4. A similar mechanism has been proposed in the reactions of maleimide with tertiary and primary amines.[2,3] Recently, Gesser and Jencks[24] have well demonstrated that, in addition–elimination reactions, the expulsion of a leaving group depends largely upon the push provided by the other groups attached to the reaction centre as well as the pull provided by the leaving group. The estimated values of the rate constants for the nitrogen leaving group from (I)[24] and (II)[13] are 3×10^9 and 10^9—10^{10} s^{-1}, respectively. On the basis of these results, the values of the rate constants k^{a}_{-1} and k'''_{-1} could be assumed to be $\geqslant 10^9$—10^{10} s^{-1} because the magnitudes of the push provided by the groups attached to the reaction centre to expel the cationic nitrogen leaving group from $T^{\pm}$ and $T^{\pm}\cdot\mathrm{H_2\overset{+}{N}}<$ are presumably larger than the push experienced by the cationic nitrogen leaving group from (I) or (II). In Scheme 4, $k_{-\mathrm{a}}$ represents the rate constant for a process involving diffusional separation of $\mathrm{H_2\overset{+}{N}}<$ and $T^{\pm}$ from an intermolecular encounter complex

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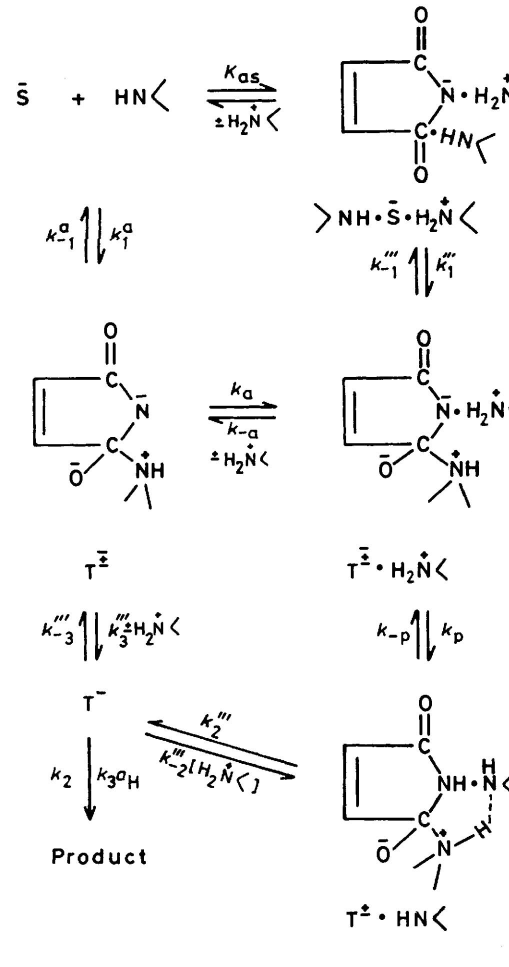
* I thank a referee for pointing this out.



Scheme 4.

$(T^{\pm}\cdot H_2\overset{+}{N}<)$. This diffusional separation is presumably retarded by the strong hydrogen bonding between the negatively charged nitrogen atom of $T^{\pm}$ and the hydrogen atom of the cationic amine $(H_2\overset{+}{N}<)$. The rate constant for the diffusional separation of two molecules from an intermolecular encounter complex, where such strong hydrogen bonding cannot exist, is of the order of 10^{10} s^{-1}.[1] The value of k_{-a} is therefore expected to be $< 10^{10}$ s^{-1}. These conclusions reveal that $k'''_{-1} > k_{-a}$ and thus the reaction must proceed through the preassociation stepwise mechanism[25] (*i.e.* path K_{as}, k'''_1, k_p, k'''_2, T^-).

On the other hand, if we assume that the normal stepwise mechanism (*i.e.* path k^{a}_1, k'''_3, T^-) is feasible then in order to account for the low value of β'_{nuc_1}, k'_1 should be equal to k^{a}_1.[26] In order for k^{a}_1 to be equal to k'_1, $k'''_3[H_2\overset{+}{N}<]$ should be larger than k^{a}_{-1}. The value of k^{a}_{-1} is considered to be $\gg 10^9$—10^{10} s^{-1}. The k'''_3 step involves the proton transfer in a thermodyanamically favourable direction and hence the magnitude of $k'''_3[H_2\overset{+}{N}<]$ could be expected to be of the order of 10^8—10^9 s^{-1} under the experimental conditions of the present study. Thus it appears that $k^{a}_{-1} > k'''_3[H_2\overset{+}{N}<]$ which is against the expected relationship (*i.e.* k^{a}_{-1} should be smaller than $k'''_3[H_2\overset{+}{N}]$). It has been concluded in the reactions of S^- with tertiary amines[2] that the value of k^{a}_{-1} is larger than 10^{11} s^{-1}. It is therefore likely that the lifetime of the intermediate $T^{\pm}$ may be very close to the period of a critical molecular vibration (*ca.* 10^{-13} s) and hence under such conditions $T^{\pm}$ might not be considered as a discrete intermediate on the reaction path.

In the preassociation stepwise mechanism (Scheme 4), k_p represents the rate constant for a process in which intermolecular proton transfer takes place in a thermodynamically favourable direction within the intermolecular encounter complex. Although it is difficult to estimate the value of $k_p[H_2\overset{+}{N}<]$, it may perhaps not be unreasonable to assume it to be $>10^{10}$—10^{11} s^{-1} (under the present experimental conditions) because the value of the rate constant for thermodynamically favourable intermolecular proton transfer in reversed micelles is 10^{12} l mol^{-1} s^{-1}.[27] The value of k'''_{-1} is $\leqslant 10^9$—10^{10} s^{-1} and therefore it may be assumed that $k_p[H_2\overset{+}{N}<] > k'''_{-1}$. The rate constant k_{-p} is assigned to a process where proton transfer takes place in a presumably thermodynamically unfavourable direction while the k'''_2 step involves thermodynamically favourable proton transfer and therefore k'''_2 may be considered to be larger than k_{-p}. The analysis that $k_p[H_2\overset{+}{N}] > k'''_{-1}$ and $k'''_2 > k_{-p}$ reveals that, in Scheme 1, $k'_1 = k'''_1K_{as}$ and $k'_{-1} = k'''_{-1}k_{-p}k'''_{-2}/k_pk'''_2$. The plot of log k'_1 *versus* pK_a of amine is expected to give a moderately low value of β'_{nuc_1} which is in agreement with the observed value of β'_{nuc_1} of 0.47.

The results obtained for the reactions of maleimide with morpholine, *N*-methylpiperazine, and piperazine show that the rate-determining step changes with change in the total amine buffer concentration, $[Am]_T$. In these reactions, it can be easily shown that at a constant pH, the value of $(k_{-1} + k'_{-1})[H_2\overset{+}{N}<]/(k_2 + k_3a_A) < 1$ at low $[Am]_T$ which leads to the k'''_1 step as rate limiting, while at sufficiently high $[Am]_T$ $[H_2\overset{+}{N}<](k_{-1} + k'_{-1})/(k_2 + k_3a_H) > 1$ and this leads to the k_2 and k_3 steps as rate limiting.

It is interesting to note that the observed rate constants which obeyed equation (8) could alternatively be interpreted by considering the rate law (13) where $[SH]_T$ represents the total

$$d[SH]_T/dt = k_o[SH]_T + k_{n1}[SH][Am] + k_{n2}[S^-][Am] \quad (13)$$

concentration of maleimide, [SH] and $[S^-]$ represent the respective concentrations of non-ionized and ionized maleimide, and [Am] is the concentration of free amine base. Comparing equation (13) with the observed rate law, $-d[SH]_T/dt = k_{obs}[SH]_T$, one gets equation (14).

$$\frac{(k_{obs} - k_o)}{[Am]_T}(a_H + K_a)(a_H + K'_a) = k_{n2}K_aK'_a + k_{n1}K_aa_H \quad (14)$$

Equation (14) is similar to equation (7) with $(k_{obs} - k_o)/[Am]_T = k_{napp}$ and $k_{napp} = A_1/A_2$ [equation (9)]. Equation (13) was found to be obeyed by the reactions of several primary amines with maleimide.[3] The rate constants k_{n1} and k_{n2} calculated from equation (14) may be compared with the corresponding rate constants obtained for the reactions of maleimide with primary amines (Table 6). It appears from Table 6 that k_{n1} for dimethylamine is *ca.* 16 times larger than that for methylamine while k_{n2} for methylamine is slightly larger than k_{n2} for dimethylamine. Furthermore, k_{n1} for diethylamine is twice as large as that for n-propylamine and k_{n2} for n-propylamine is *ca.* 10 times larger than that for diethylamine. It is known from the literature that the nucleophilic second-order rate constants for the reactions of phenyl acetate with methylamine, dimethylamine, piperidine, and n-butylamine are nearly the same (Table 6) and they constitute a single Brønsted plot along with other primary and secondary amines.[22] The

Table 6. Second-order nucleophilic rate constants for the reactions of nucleophiles with SH (k_{n1}) and S^- (k_{n2}) at 30 °C [equation (14)]

Amine	pK_a	10^2k_{n1}/l mol^{-1} s^{-1}	10^2k_{n2}/l mol^{-1} s^{-1}	k_n^a/l mol^{-1} min^{-1}
Piperidine	11.23	3 551 ± 28[b]	90.9 ± 8.1[b]	4.3
Dimethylamine	11.05	6 324 ± 561	167 ± 49	4.5
Pyrrolidine	11.32	5 392 ± 100	521 ± 18	
Diethylamine	11.07	236 ± 10	3.74 ± 0.79	
Methylamine	10.85	382[c] ± 30	296[c] ± 11	
n-Propylamine	10.79	110 ± 3	36.5 ± 0.3	
n-Butylamine	10.59			4.5

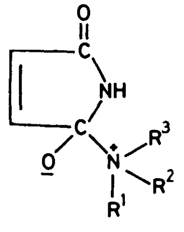
[a] Second-order rate constants for the nucleophilic cleavage of phenyl acetate were obtained from ref. 31. [b] Error limits are standard deviations. [c] These values were obtained from ref. 3.

nucleophilic reactivity of diethylamine toward maleimide may be expected to be significantly smaller compared to that of n-propylamine because of the comparatively large steric requirement of diethylamine. The nucleophilic rate constant for the reaction of *p*-nitrophenyl phosphate with diethylamine turned out to be more than *ca.* 4-, 10-, 8-, and 9-fold smaller compared with that with n-butylamine, methylamine, dimethylamine, and piperidine, respectively.[28] The absence of nucleophilic reactivity of triethylamine toward maleimide was attributed to a steric effect.[2] Thus, the larger reactivity of diethylamine and dimethylamine (toward S^-) compared with that of n-propylamine and methylamine, respectively, is difficult to conceive if both primary and secondary amines are believed to follow the same reaction mechanism. Similarly, the nearly nine times larger reactivity of piperidine compared with that of methylamine is difficult to understand if both reactions have to follow the same reaction mechanism because for the reactions of ionized phenyl salicylate with piperidine and methylamine, where the same mechanism has been shown to be followed by both amines, the nucleophilic second-order rate constants are nearly the same.[29] We propose that the reactions of all the secondary amines with maleimide reported in this paper follow the mechanism shown in Scheme 1. The question why the reactions of maleimide with secondary amines, in contrast to those with primary amines, are subject to intermolecular general base catalysis is difficult to answer because of our incomplete understanding of the nature of general acid–base catalysis.[1] Kirby and Jencks[30] observed that the reactions of *p*-nitrophenyl phosphate with secondary amines were subject to general base catalysis while no such catalysis was observed with primary amines.

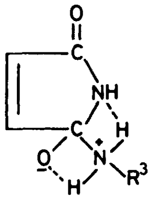
In a classic review on enforced general acid-base catalysis, Jencks[1] attempted to answer the vexing question why certain reactions are sensitive to general acid–base catalysis while others are not. The most extensively studied class of reactions is probably the aminolysis of esters. The reactions of phenyl acetate with glycine, ammonia, glycylglycine, glycine ethyl ester, n-butylamine, hydroxylamine, and dimethylamine revealed a general base-catalysed term ($k_{gb}[RNH_2]^2$) in the rate law while no such term was detected with piperidine, morpholine, and methoxyamine.[31] Bruice and Willis[32] reported the presence and absence of k_{gb} terms in the reactions of phenyl acetate with morpholine and n-butylamine, respectively.

We could not detect general acid–base catalysis in the reactions of maleimide with several primary amines[3] while general acid catalysis was detected in the reactions of maleimide with trimethylamine and 1,4-diazabicyclo[2.2.2]octane.[2] In the present paper, we have shown that the reactions of non-ionized (SH) and ionized (S) maleimide with several secondary amines are subject to general base and general acid catalysis, respectively. The aminolysis of maleimide appeared to have quite different characteristics compared with the aminolyses of phenyl acetate[22] (PA), 1-acetyl-1,2,4-triazole[12] (AcTr), and benzylpenicillin.[13] In the nucleophilic cleavage of PA and AcTr, ammonia revealed essentially similar reactivity compared with primary and secondary amines of similar basicity, while in the nucleophilic cleavage of maleimide it showed a *ca.* 50-fold lowering in comparative reactivity.

The respective absence and presence of general acid–base catalysis in the reactions of maleimide with primary and secondary amines could be considered as unexpected in terms of the steric requirements of primary and secondary amines. But probably other requirements of these reactions such as stereochemical or stereoelectronic are dominant over the steric requirements of the attacking amines. One of the various possible causes for differing characteristics of the reactivity of maleimide toward primary, secondary, and tertiary amines probably lies in the structural features of maleimide. The leaving group (for product formation) in (**III**) is not free to rotate and hence when $R^1 = R^2 = H$ (*i.e.* primary amine) then no general acid–base catalysis could be detected simply because the uncatalysed reaction possibly involves an intramolecular general acid–base catalysis as shown in (**IV**). But when $R^1 = H$ (*i.e.* secondary amine), then the possibility of the labile proton being in the vicinity of the leaving group is less compared with when $R^1 = R^2 = H$ and hence intermolecular general acid–base catalysis begins to show an effect on the rate. These are of course qualitative explanations and any meaningful generalizations about when and where general acid–base catalysis could occur should await more results on related reactions.



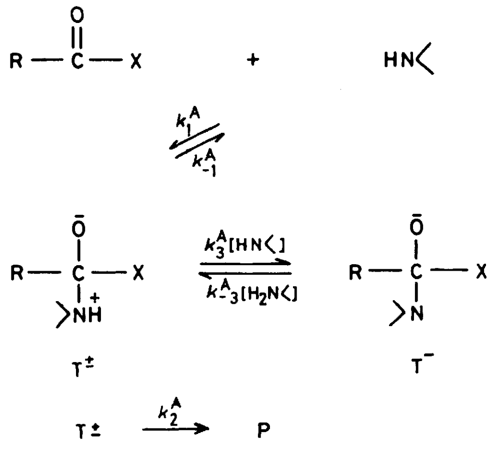
(**III**)



(**IV**)

Appendix

In Scheme 5, the uncatalysed nucleophile second-order rate constant k_n and general base-catalysed third-order rate constant



Scheme 5.

k_gb may be expressed as $k_2^\mathrm{A}k_1^\mathrm{A}/k_{-1}^\mathrm{A}$ and $k_3^\mathrm{A}k_1^\mathrm{A}/k_{-1}^\mathrm{A}$, respectively, if $k_{-1}^\mathrm{A} > k_3^\mathrm{A}[\mathrm{HN}<]$ and k_2^A. The Brønsted slope (β) for the rate constant k_3^A would be nearly zero because in the k_3^A step the proton transfer is presumably thermodynamically favourable.[13,33] The observed β value corresponding to k_gb is therefore for the equilibrium constant $(k_1^\mathrm{A}/k_{-1}^\mathrm{A})$ of the formation of $\mathrm{T}^\pm$ (Scheme 5). Since the observed β values for k_n and k_gb are essentially the same in the aminolysis of benzylpenicillin,[13] phenyl acetate,[22] and various substituted arylquinoline-6-carboxylates[34] (Q-6), the β value for the rate constant k_2^A (Scheme 5) should be nearly zero. This analysis is in agreement with the conclusion that the rate constant for leaving group expulsion from $\mathrm{T}^\pm$ (Scheme 5) is independent of the nature of the attacking nitrogen nucleophile.[26] It is also evident from the aminolysis of phenyl acetate[22] and other related reactions[34] that the rate constants k_n for the reactions of structurally similar primary and secondary amines with the same substrate fall on the same Brønsted plot. We observed that the uncatalysed rate constants for the reactions of maleimide with 1,4-diazabicyclo-[2.2.2]octane and primary amines of similar basicity were not significantly different from each other.[2,3] Thus, the assumption that the rate constants for uncatalysed reactions of maleimide with primary and secondary amines would constitute a single Brønsted plot may not be unreasonable. Following these conclusions, it is apparent that if equations (i) and (ii) hold then we have relationships (iii) and (iv) where k_n^SH and $k_\mathrm{gb}^\mathrm{SH}$ are rate

$$\log(k_\mathrm{n}^\mathrm{SH}/k_\mathrm{no}^\mathrm{SH}) = \beta_\mathrm{nuc}\mathrm{p}K_\mathrm{a} \qquad \text{(i)}$$

$$\log(k_\mathrm{n}^{\mathrm{S}^-}/k_\mathrm{no}^{\mathrm{S}^-}) = \beta'_\mathrm{nuc}\mathrm{p}K_\mathrm{a} \qquad \text{(ii)}$$

$$\log(k_\mathrm{gb}^\mathrm{SH}/k_\mathrm{gbo}^\mathrm{SH}) \simeq \beta_\mathrm{nuc}\mathrm{p}K_\mathrm{a} \qquad \text{(iii)}$$

$$\log(k_\mathrm{ga}^{\mathrm{S}^-}/k_\mathrm{gao}^{\mathrm{S}^-}) \simeq \beta'_\mathrm{nuc}\mathrm{p}K_\mathrm{a} \qquad \text{(iv)}$$

contants for nucleophilic and amine general base-catalysed cleavage of SH, respectively, and $k_\mathrm{n}^{\mathrm{S}^-}$ and $k_\mathrm{ga}^{\mathrm{S}^-}$ are for the respective nucleophilic and amine general acid-catalysed cleavage of S^-. Comparing Schemes 1 and 5, $k_1 = k_\mathrm{gb}^\mathrm{SH}$ and $k'_1 = k_\mathrm{ga}^{\mathrm{S}^-}$, equation (v) may be derived from (iii) and (iv) assuming

$$\log(k_1/k'_1) = \log(k_\mathrm{no}^\mathrm{SH}/k_\mathrm{no}^{\mathrm{S}^-}) + (\beta_\mathrm{nuc} - \beta'_\mathrm{nuc})\,\mathrm{p}K_\mathrm{a} \qquad \text{(v)}$$

that although $k_\mathrm{gbo}^\mathrm{SH}$ and $k_\mathrm{gao}^{\mathrm{S}^-}$ are not equal to $k_\mathrm{no}^\mathrm{SH}$ and $k_\mathrm{no}^{\mathrm{S}^-}$, respectively, $(k_\mathrm{gbo}^\mathrm{SH}/k_\mathrm{gao}^{\mathrm{S}^-}) \simeq (k_\mathrm{no}^\mathrm{SH}/k_\mathrm{no}^{\mathrm{S}^-})$. The values of k_1/k'_1 were calculated from equation (v) with known values of $\mathrm{p}K_\mathrm{a}$ and $\log(k_\mathrm{no}^\mathrm{SH}/k_\mathrm{no}^\mathrm{S})$ of -3.25,[3] and $\beta_\mathrm{nuc} - \beta'_\mathrm{nuc}$ of 0.33.[3]

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