Kinetics and Mechanism of Tertiary Amine-catalysed Aqueous Cleavage of Maleimide

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The reaction rates of the aqueous cleavage of maleimide in the presence of buffer solutions of trimethylamine, 1,4-diazabicyclo[2.2.2]octane, triethylamine, and triethanolamine have been studied at 30 °C. Both the ionized ($\bar{S}$) and non-ionized (SH) forms of maleimide are reactive towards the free base component of buffer solutions of trimethylamine and 1,4-diazabicyclo[2.2.2]octane. These amines have exhibited general acid-catalysed and uncatalysed nucleophilic attack at carbonyl carbon of both SH and S^-. Triethylamine has been found to be essentially unreactive towards SH and S^- while triethanolamine has revealed significant nucleophilic reactivity towards SH and S^-. The observed nucleophilic reactivity of triethanolamine and absence of such reactivity in the case of triethylamine have led to the proposal that the nucleophilic site in triethanolamine is the internally hydrogen-bonded hydroxy group rather than the free amine group. The absence of intermolecular general acid catalysis in the reactions of SH and S^- with triethanolamine is attributed to both the steric effect as well as probable intramolecular general acid catalysis. A pre-association stepwise mechanism is proposed for the reactions of tertiary amines with S^- while a stepwise mechanism has been favoured for the reactions of amines with SH.

The kinetics and mechanism of aminolysis of esters with leaving groups of pK_a of nearly $\leqslant 10$ have been studied extensively.[1] Similar studies on acyl substrates with leaving groups of pK_a > 10 are, by comparison, not fully explored partly because of the low reactivity of these substrates towards amines. The mechanistic aspects of the aqueous cleavages of acetylimidazole[2] and acetyltriazole[3] in the presence of amine buffers have been studied in much detail. In these reactions, the tertiary amines have been found to act as general base catalysts for hydrolysis while primary amines have revealed nucleophilic catalysis with $\beta_{nuc.}$ of 1.3—1.6. Primary, secondary, and tertiary amines exhibited nucleophilic catalysis in the cleavages of aliphatic esters.[4] But the sensitivity of the reactions of these esters to the pK_a of primary and secondary amines ($\beta_{nuc.}$ 0.8) is significantly lower than that of tertiary amines ($\beta_{nuc.}$ 1.4).

To the best of our knowledge no report has so far appeared in the literature on the kinetics of the reactions of maleimide with tertiary amines. The kinetics and mechanism of hydrolyses of a few substituted maleimides have recently been studied.[5] Because of the finding of *N*-ethylmaleimide as a potential reagent for the estimation of the sulphydryl groups of proteins,[6] a few kinetic studies on the reactions of maleimide and some of its *N*-substituted derivatives with thiols have been carried out where *N*-substituted maleimides have been revealed to act as Michael acceptors rather than acylating agents.[7] In the hydrolysis of maleimide it is difficult to distinguish kinetically between $k[\text{SH}][\bar{\text{O}}\text{H}]$ and $k[\bar{\text{S}}][\text{H}_2\text{O}]$ where SH and S^- represent non-ionized and ionized forms of maleimide. We hoped initially that the kinetics of the reactions of maleimide with tertiary amines would be capable of revealing whether or not both the SH and S^- are reactive towards the nucleophiles. Tertiary amines were chosen as nucleophiles for the reason of avoiding the probable complication produced by the Michael addition of nucleophile to the substrate (maleimide). The results and the probable mechanism are described in the present paper.

Experimental

Materials.—Reagent-grade chemicals such as 1,4-diazabicyclo[2.2.2]octane and triethanolamine were obtained from B.D.H. and trimethylammonium chloride, triethylamine, and maleimide were obtained from Aldrich. All other chemicals used were also of reagent grade. Glass-distilled water was used throughout the kinetic studies.

Kinetic Measurements.—The reaction rates were studied by monitoring the disappearance of maleimide using a spectrophotometric technique. For a typical kinetic run, a total volume of 9.5 cm^3 of aqueous reaction mixture containing required amounts of potassium chloride (to maintain the ionic strength at 1.0M) and amine buffer of desired pH was thermally equilibrated at 30 °C in a thermostatted water-bath for *ca.* 10 min. The reaction was then initiated by adding 0.0125M maleimide solution (0.5 cm^3) prepared in 1,4-dioxane. A portion of *ca.* 2.5 cm^3 was quickly withdrawn from the mixture and transferred to the quartz cuvette (3 cm^3) kept in the thermostatted cell compartment of a Beckman model 35 u.v.–visible spectrophotometer. The decrease in the absorbance as a function of time was monitored at 300 nm either by digital display (for slow reactions) or by a continuous chart recorder model 24-25 ACC (for relatively fast reactions). The temperature of the cell compartment at 30 °C was maintained electronically by the use of the temperature-control unit of the spectrophotometer.

All the buffers were prepared by partial neutralization of the amine or amine hydrochloride just before the start of the kinetic runs. The pH values of the mixtures were found to be almost the same before and after each kinetic run. The stock solutions of maleimide in 1,4-dioxane were kept frozen and reprepared frequently to avoid any probable peroxide formation.

The kinetic runs were carried out under pseudo-first-order kinetic conditions and the observed pseudo-first-order rate constants, $k_{obs.}$, were calculated from equation (1) where all the

$$A_{obs.} = E X_o \exp(-k_{obs.}t) + A_\infty \qquad (1)$$

symbols have their usual meaning as described elsewhere.[8] A non-linear least-squares technique was used to calculate three unknown parameters, $k_{obs.}$, E, and A_∞. The fitting of observed data to equation (1) is evident from the residual errors ($A_{obs.} - A_{calc.}$) which were found to be less than 1% prior to several half-lives of the reactions.

Results

A series of kinetic runs were carried out at different pH in buffer solutions of 1,4-diazabicyclo[2.2.2]octane and trimethylamine. The observed pseudo-first-order rate contants, $k_{obs.}$, were found to be well fitted by equation (2) where k_o is the first-order

$$k_{obs.} - k_o = k_n[\mathrm{Am}]_T + k_{ga}[\mathrm{Am}]_T^2 \qquad (2)$$

constant for hydrolysis, k_n and k_{ga} are second- and third-order rate constants for amine-catalysed cleavage of maleimide, and $[\mathrm{Am}]_T$ represents the total amine buffer concentration. The values of k_o at various pH were calculated from equation (3)

$$k_o = k_{OH}K_w/(a_H + K'_a) \qquad (3)$$

where $k_{OH} = 72.2$ l mol^{-1} s^{-1},[9] $K_w = 1.449 \times 10^{-14}$ mol^2 l^{-2},[10] and ionization constant of maleimide $K'_a = 1.41 \times 10^{-10}$ mol l^{-1}.[9] The rate constants, k_n and k_{ga}, were calculated from equation (2) by using a least-squares technique and the results thus obtained are summarized in Table 1. The fitting of observed data to equation (2) is evident from the plots shown in Figures 1 and 2 for 1,4-diazabicyclo[2.2.2]octane- and trimethylamine-catalysed cleavage of maleimide, respectively, where the solid lines are drawn through the least-squares calculated points.

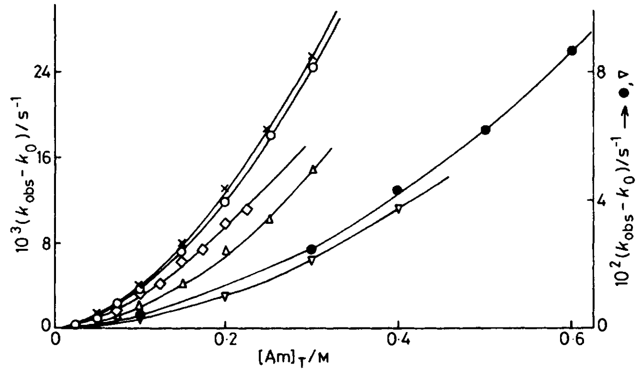


Figure 1. Plots showing the dependence of $k_{obs.} - k_o$ on the total buffer concentration of 1,4-diazabicyclo[2.2.2]octane at 30 °C and at pH 9.67 (◇), 9.21 (×), 9.17 (●), 8.92 (○), 8.65 (▽), and 8.35 (△)

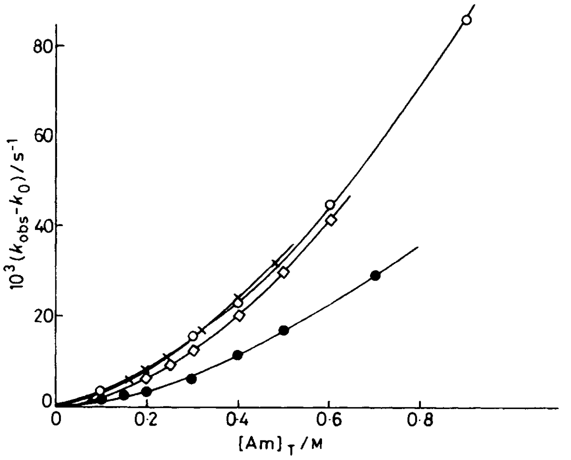


Figure 2. Plots showing the dependence of $k_{obs.} - k_o$ on the total buffer concentration of trimethylamine at 30 °C and at pH 10.08 (○), 9.87 (×), 9.50 (◇), and 9.19 (●)

Triethanolamine-catalysed cleavage of maleimide was studied at four different pH values. The observed data revealed a linear

Table 1. Apparent second- and third-order rate constants for the reactions of tertiary amines with maleimide[a]

Amine	pH	10^3k_n/l mol^{-1} s^{-1}	10^2k_{ga}/l^2 mol^{-2} s^{-1}	Concentration range (M)
1,4-Diazabicyclo[2.2.2]octane	8.35	5.427 ± 1.595[b]	14.42 ± 0.65[b]	0.025—0.300
	8.65	9.054 ± 2.423	20.84 ± 0.71	0.1—0.5
	8.92	13.31 ± 1.56	22.92 ± 0.63	0.025—0.300
	9.17	23.47 ± 4.52	20.13 ± 0.89	0.1—0.6
	9.21	18.64 ± 2.43	22.35 ± 0.98	0.025—0.300
	9.67	14.10 ± 3.40	16.35 ± 1.85	0.050—0.225
Trimethylamine	9.19	7.486 ± 1.506	4.952 ± 0.267	0.1—0.5
	9.50	13.81 ± 0.83	9.170 ± 0.170	0.1—0.6
	9.87	21.81 ± 1.61	9.380 ± 0.412	0.08—0.48
	10.08	28.47 ± 2.10	7.464 ± 0.277	0.1—0.9
Triethylamine	10.19	0.184 ± 0.126 (0.085 ± 0.563)[c]		0.04—0.28
	10.53	0.361 ± 0.284 (1.386 ± 0.540)		0.04—0.24
	11.07	2.264 ± 0.554 (0.014 ± 0.657)		0.04—0.24
	11.49	2.748 ± 1.291 (−1.790 ± 1.030)		0.04—0.24
Triethanolamine	7.70	0.360 ± 0.007 (0.348 ± 0.015)		0.1—0.7
	8.25	0.964 ± 0.026 (1.062 ± 0.023)		0.1—0.7
	8.61	1.595 ± 0.093 (2.015 ± 0.042)		0.1—0.6
	8.82	2.314 ± 0.123 (2.834 ± 0.121)		0.1—0.6

[a] Conditions: $[\text{maleimide}]_o$ 6.25 × 10^{-4}M, 30 °C, ionic strength 1.0M, 5% 1,4-dioxane into the aqueous reaction mixture. [b] Error limits are standard deviations. [c] The values in parentheses were obtained by treating the observed data with a linear equation containing two unknown parameters, k_o and k_n ($k_{obs.} = k_o + k_n[\mathrm{Am}]_T$).

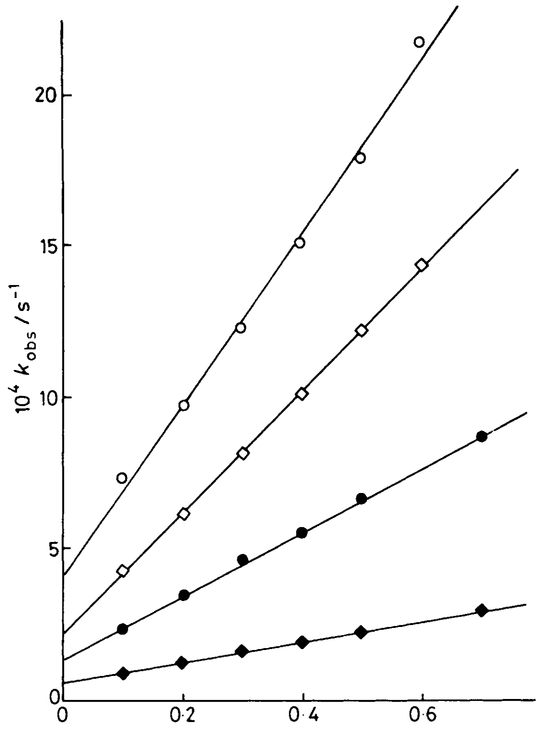


Figure 3. Observed pseudo-first-order rate constants for aminolysis of maleimide as a function of a total buffer concentration of triethanolamine at 30 °C and at pH 8.82 (○), 8.61 (◇), 8.25 (●), and 7.70 (◆)

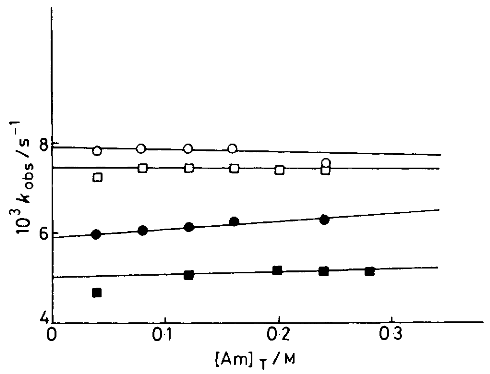


Figure 4. The plots of $k_{obs.}$ *versus* $[Am]_T$, where $[Am]_T$ represents the total buffer concentration of triethylamine, at pH 11.49 (○), 11.07 (□), 10.53 (●), and 10.19 (■)

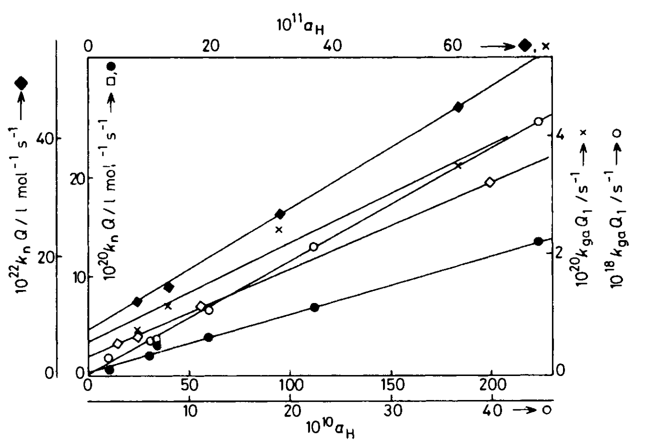


Figure 5. The plots showing the dependence of k_nQ (●, ◆, ◇) and $k_{ga}Q_1$ (×, ○) *versus* a_H for the reactions of 1,4-diazabicyclo[2.2.2]octane (○, ●), trimethylamine (×, ◆), and triethanolamine (◇) with maleimide where $Q = (a_H + K_a)(a_H + K'_a)$ and $Q_1 = Q(a_H + K_a)/a_H$. The solid lines are drawn through the least-squares calculated points using equation (6) with respective values of $k_3K_aK'_a$ and k_1K_a as 3.301 × 10^{-20} mol l^{-1} s^{-1} and 2.909 × 10^{-11} s^{-1} for (●), 7.712 × 10^{-22} mol l^{-1} s^{-1} and 5.777 × 10^{-12} s^{-1} for (◆) and 1.964 × 10^{-20} mol l^{-1} s^{-1} and 8.725 × 10^{-12} s^{-1} for (◇). Similarly the other solid lines are drawn through the least-squares calculated points using equation (7) with respective values of $k_4K_aK'_a$ and k_2K_a as 2.221 × 10^{-20} s^{-1} and 9.408 × 10^{-10} l mol^{-1} s^{-1} for (○) and 5.650 × 10^{-21} s^{-1} and 4.727 × 10^{-11} l mol^{-1} s^{-1} for (×)

relationship between $k_{obs.}$ and $[Am]_T$ as shown in Figure 3. Thus, in this case, the k_{ga} term is negligible compared with the k_n term in equation (2). The values of k_n calculated by a linear least-squares technique from equation (2) with $k_{ga} = 0$, are summarized in Table 1. The aqueous cleavage of maleimide was also studied under the buffer solutions of triethylamine. The observed results as shown graphically in Figure 4 indicate that the values of $k_{obs.}$ are almost independent of $[Am]_T$. When the observed data were treated with a linear equation containing two unknown parameters, k_o and k_n, the calculated values of k_n turned out to be either negative or positive with standard deviations of more than many 100% (Table 1). However, application of equation (2) with k_{ga} zero give k_n values as shown in Table 1. Significantly high standard deviations associated with k_n values indicate that the contribution of the k_n term compared with k_o is negligible.

Discussion

The rate law for aqueous cleavage of maleimide in the presence of the buffer solutions of tertiary amines may be given as in equation (4) where $[SH]_T$ represents the total concentration of

$$\text{rate} = k_o[SH]_T + k_1[SH][Am] + k_2[SH][Am][AmH^+] + k_3[S^-][Am] + k_4[S^-][Am][AmH^+] \quad (4)$$

maleimide. Additional terms such as $k'_3[SH][Am][\bar{O}H]$ and $k'_4[SH][Am]^2$ which are kinetically indistinguishable from the k_3 and k_4 terms, respectively, could be ruled out for the reason that intermolecular general base-catalysed tertiary amine nucleophilic attack at the carbonyl carbon of maleimide is mechanistically incomprehensible and this term has never been observed in other related studies. Equation (5) can be easily derived from (4) and the observed rate law (rate = $k_{obs.}[SH]_T$). In equation (5), K_a is the ionization constant of the amine nucleophile. Equation (5) is similar to (2) leading to equation (6) and (7). Equations (6) and (7) indicate that the

$$k_{obs.} = k_o + \frac{(k_1K_aa_H + k_3K_aK'_a)[Am]_T}{(a_H + K_a)(a_H + K'_a)} + \frac{(k_2K_aa_H^2 + k_4K_aK'_aa_H)[Am]_T^2}{(a_H + K_a)^2(a_H + K'_a)} \quad (5)$$

$$k_n = \frac{k_1K_aa_H + k_3K_aK'_a}{(a_H + K_a)(a_H + K'_a)} \quad (6)$$

$$k_{ga} = \frac{k_2K_aa_H^2 + k_4K_aK'_aa_H}{(a_H + K_a)^2(a_H + K'_a)} \quad (7)$$

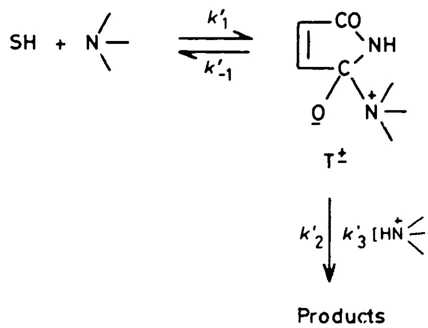
Table 2. Second- and third-order rate constants for the reactions of tertiary amines with S^- and SH

Amine	pK_a	10^2k_1/l mol^{-1} s^{-1}	k_2/l^2 mol^{-2} s^{-1}	10^2k_3/l mol^{-1} s^{-1}	$10k_4$/l^2 mol^{-2} s^{-1}
1,4-Diazabicyclo[2.2.2]octane	9.06[a]	3.340 ± 0.131[b]	1.080 ± 0.022[b]	2.688 ± 1.981[b]	1.808 ± 3.308[b]
Trimethylamine	9.95[c]	5.149 ± 0.186	0.421 ± 0.064	4.875 ± 0.486	3.571 ± 1.672
Triethanolamine	8.15	0.123 ± 0.002		1.967 ± 0.124	
Triethylamine	10.63[c]	*d*		0.32 ± 0.06[e]	

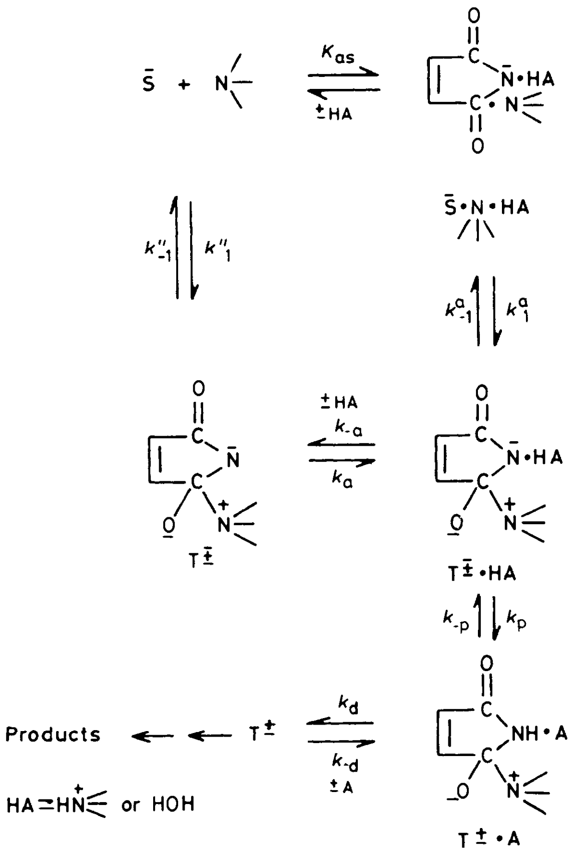
[a] B. L. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6789. [b] Error limits are standard deviations. [c] P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, 1978, **100**, 4793. [d] The estimated upper limit is even negative. [e] Value unreliable.

plots of k_nQ *versus* a_H and $k_{ga}Q_1$ *versus* a_H should be linear where $Q = (a_H + K_a)(a_H + K'_a)$ and $Q_1 = Q(a_H + K_a)/a_H$. Plots as shown in Figure 5 were found to be linear for the reactions of maleimide with trimethylamine, triethanolamine, and 1,4-diazabicyclo[2.2.2]octane. The linear least-squares technique was used to calculate k_1K_a and $k_3K_aK'_a$ from equation (6) and the respective values thus obtained are (5.777 ± 0.209) × 10^{-12} s^{-1} and (7.712 ± 0.769) × 10^{-22} mol l^{-1} s^{-1} for trimethylamine, (2.909 ± 0.114) × 10^{-11} s^{-1} and (3.301 ± 2.434) × 10^{-20} mol l^{-1} s^{-1} for 1,4-diazabicyclo[2.2.2]-octane, and (8.725 ± 0.012) × 10^{-12} s^{-1} and (1.964 ± 0.124) × 10^{-20} mol l^{-1} s^{-1} for triethanolamine. Similarly, the calculated respective values of k_2K_a and $k_4K_aK'_a$ are (4.727 ± 0.719) × 10^{-11} l mol^{-1} s^{-1} and (5.650 ± 2.646) × 10^{-21} s^{-1} for trimethylamine and (9.408 ± 0.190) × 10^{-10} l mol^{-1} s^{-1} and (2.221 ± 4.057) × 10^{-20} s^{-1} for 1,4-diazabicyclo[2.2.2]octane. These calculated values were used to evaluated k_1, k_2, k_3, and k_4 with known values of K_a and K'_a and the results thus obtained are summarized in Table 2.

The ratios of k_1/k_3 for both trimethylamine and 1,4-diazabicyclo[2.2.2]octane range from 1 to 1.2 which are nearly 6 × 10^3 fold smaller than the ratio of the bimolecular rate constants for hydroxide ion-catalysed cleavage of non-ionized (k_{OH} = 72.2 l mol^{-1} s^{-1}) and ionized (k_{OH} 0.0116 l mol^{-1} s^{-1}) maleimide.[9] In the alkaline hydrolysis of maleimide[9] we have concluded that $^-$OH nucleophilic attack at carbonyl carbon of both SH and S^- is the rate-determining step. Bender and his co-workers[11] obtained the values of the ratios of $k_n^{SH}/k_n^{S^-}$ as 7.8 and 95 for the reactions of 5-nitrophenyl 5-nitrosalicylate with imidazole and azide ion nucleophiles, respectively, where k_n^{SH} and $k_n^{S^-}$ represent the respective bimolecular nucleophilic rate constants for the reactions of non-ionized (SH) and ionized (S^-) forms of the ester with nucleophiles. These observed values indicate that a *ca.* 12 fold decrease in the rate could be expected due to electrostatic destabilization of the transition state involved in the reaction of S^- and anionic nucleophile compared with that of S^- and neutral nucleophile. This conclusion is, however, based on the assumption that the reactions of both SH and S^- with nucleophiles display Brönsted plots of similar slopes. Thus, although the ratios k_1/k_3 for neutral nucleophiles could be expected to be smaller than that for anionic nucleophiles because of the electrostatic effect, a decrease of *ca.* 6 × 10^3 fold is difficult to conceive if nucleophilic attack is considered to be the rate-determining step in the reactivity of both SH and S^- towards tertiary amine nucleophiles. The similarity of the reactivity of SH and S^- towards the tertiary amines thus indicates that the reactions of these amine nucleophiles with SH and S^- follow possibly different mechanisms. We propose that the reactions of SH with tertiary amines follow a stepwise mechanism as shown in Scheme 1 whereas the reactivity of S^- towards tertiary aimes follows a pre-association stepwise mechanism as shown in Scheme 2.*



Scheme 1.



Scheme 2.

In Scheme 1, k'_{-1} is considered to be larger than both k'_2 and $k'_3[\mathrm{Am}\overset{+}{\mathrm{H}}]$ which leads to the k'_2-and-k'_3 step as the rate-determining steps. The observed rate constant k_1 is equal to $k'_1k'_2/k'_{-1}$. The consideration that $k'_{-1} > k'_2$ and $k'_3[\mathrm{Am}\overset{+}{\mathrm{H}}]$ is

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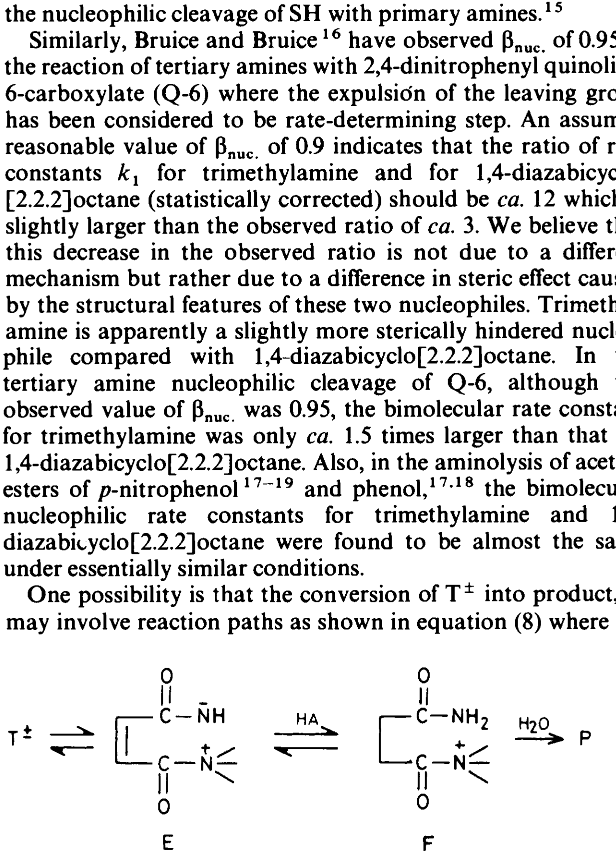
* I am very much grateful to one of the referees for suggesting this mechanism.

based on the following reasons. (i) It has been shown elegantly by Gresser and Jencks[12] that the relative leaving-group ability is controlled by various factors including the electron-donating ability of the remaining group attached to the reacting centre as well as the pK of the leaving group. In $T^{\pm}$, it is evident that the electronic push experienced by leaving group in the k'_{-1} step is more than the one in k'_2 and also the pK_a of leaving group in the k'_{-1} step (pK_a range of *ca.* 9—10) is significantly lower than that in the k'_2 step (pK_a *ca.* 14—15).[13] Thus, both the factors favour k'_{-1} being larger than k'_2. (ii) The intermediate $T^{\pm}$ might be considered to be trapped by proton transfer from water as well as protonated amine before the C–N bond cleavage in the k'_2 and k'_3 steps may occur. If this happens then general acid catalysis could be detected only if $k'_{-1} > k'_2$ and $k'_3[\mathrm{AmH}^+]$.[14] Since general acid catalysis has been detected, it is allowable to assume that $k'_{-1} > k'_2$ and $k'_3[\mathrm{AmH}^+]$.

The conclusion that k'_2 is the rate-determining step reveals that the values of k_1 should be significantly dependent on the basicity of the nucleophiles. A $\beta_{\mathrm{nuc.}}$ of 0.81 has been observed in the nucleophilic cleavage of SH with primary amines.[15]

Similarly, Bruice and Bruice[16] have observed $\beta_{\mathrm{nuc.}}$ of 0.95 in the reaction of tertiary amines with 2,4-dinitrophenyl quinoline-6-carboxylate (Q-6) where the expulsion of the leaving group has been considered to be rate-determining step. An assumed reasonable value of $\beta_{\mathrm{nuc.}}$ of 0.9 indicates that the ratio of rate constants k_1 for trimethylamine and for 1,4-diazabicyclo-[2.2.2]octane (statistically corrected) should be *ca.* 12 which is slightly larger than the observed ratio of *ca.* 3. We believe that this decrease in the observed ratio is not due to a different mechanism but rather due to a difference in steric effect caused by the structural features of these two nucleophiles. Trimethylamine is apparently a slightly more sterically hindered nucleophile compared with 1,4-diazabicyclo[2.2.2]octane. In the tertiary amine nucleophilic cleavage of Q-6, although the observed value of $\beta_{\mathrm{nuc.}}$ was 0.95, the bimolecular rate constant for trimethylamine was only *ca.* 1.5 times larger than that for 1,4-diazabicyclo[2.2.2]octane. Also, in the aminolysis of acetate esters of *p*-nitrophenol[17–19] and phenol,[17,18] the bimolecular nucleophilic rate constants for trimethylamine and 1,4-diazabicyclo[2.2.2]octane were found to be almost the same under essentially similar conditions.

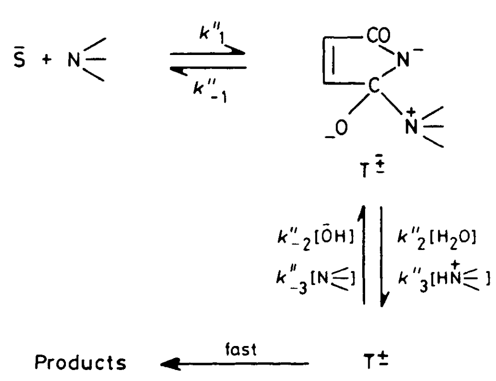
One possibility is that the conversion of $T^{\pm}$ into product, P, may involve reaction paths as shown in equation (8) where the



(8)

final intermediate, E, reverts rapidly to $T^{\pm}$, and can only proceed to F, and hence to products, when trapped by a general acid. E contains a very powerful electrophilic centre very productively, close to a good hard nucleophile, and will cyclise very rapidly indeed.* The conclusion reveals that the general acid-catalysed conversion of E into F is most likely the rate-determining step.

Triethylamine catalysis could not be detected in its reaction with SH which might be attributed to the significantly large steric hindrance to nucleophilic attack. Such steric hindrance was shown to be the reason for a change of mechanism from expected nucleophilic catalysis to the observed general base catalysis of water attack in the aqueous cleavage of Q-6.[16] The possibility of tertiary amines acting as general base catalysts for hydrolysis may be ruled out on the basis of the observed *ca.* 16-fold low reactivity of carbonate (k_1 2.27 × 10^{-3} l mol^{-1} s^{-1})[15] compared with 1,4-diazabicyclo[2.2.2]octane despite the fact that pK_a of carbonate is 0.62 pK units higher than that of 1,4-diazabicyclo[2.2.2]octane. Such a low reactivity of carbonate cannot be attributed to the difference in the structural features of the two catalysts because the second-order rate constants for the general base-catalysed hydrolysis of acetyltriazole[3] under the presence of buffer solutions of a series of bases including carbonate and other oxyanions as well as tertiary amines were found to fall on the same Brönsted plot with β 0.36. Furthermore, general base-catalysed hydrolysis of maleimide could be expected to be seen even with triethylamine because general base-catalysed water attack should presumably be less subject to the steric requirements of the tertiary amines.[16]



Scheme 3.

A search of the literature indicates that the value of the rate constant for the expulsion of an aliphatic amine nucleophile from a tetrahedral addition intermediate formed from the nucleophile and the substrate such as amide and ester is in the range 10^9—10^{10} s^{-1}.[12,20] The value of the rate constant k^{a}_{-1} is therefore expected to be significantly larger than 10^9—10^{10} s^{-1} because the electronic push experienced by the departing group in the k^{a}_{-1} step (Scheme 2) is obviously larger than the one in the k'_{-1} step (Scheme 1).† Although it is difficult to assess the magnitude of k_{-a}, it may not be unreasonable to assume that it would be $< 10^{10}$ s^{-1}. This is simply because k_{-a} is a rate constant for diffusional separation of $T^{\pm}$ and HA from encounter complex $T^{\pm}$. HA, which may be expected to be stabilized by strong hydrogen bonding. Thus, it is apparent that $k^{a}_{-1} > k_{-a}$. This condition has been shown to be necessary for the occurrence of the pre-association stepwise mechanism.[14,21]

Alternatively, since k''_{-1} could be larger than k^{a}_{-1} and therefore $k''_{-1} > k_{-a}$. This condition indicates that the reaction must proceed through a pre-association mechanism.[14a] The rate constant, k_p, represents the bimolecular rate constant for a process involving proton transfer in a presumed thermodynamically favourable direction within the encounter complex. The order of such a rate constant may be assumed to be 10^{12} l mol^{-1} s^{-1}.[22] This analysis thus reveals that $k_p > k^{a}_{-1}$ and hence k^{a}_{1} seems to be the rate-determining step.

Although in principle a stepwise mechanism or more appropriately diffusion-controlled trapping mechanism as shown in Scheme 3 is possible for the reactions of S^- with tertiary amines,

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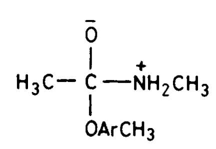
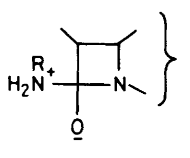
* I am very much grateful to one of the referees for suggesting this possibility of conversion of $T^{\pm}$ into P.

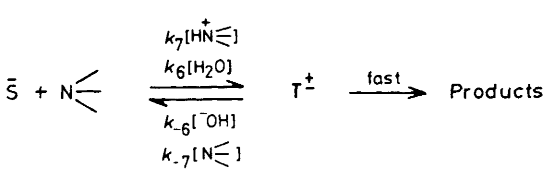
† In the expulsion of the leaving group, the electronic push exerted by >N·HA group in the k^{a}_{-1} step is apparently greater than by >NH group in k'_{-1} step.



$T_1^{\pm}$



$T_2^{\pm}$

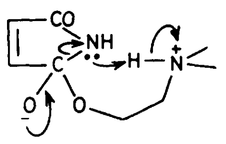


Scheme 4.

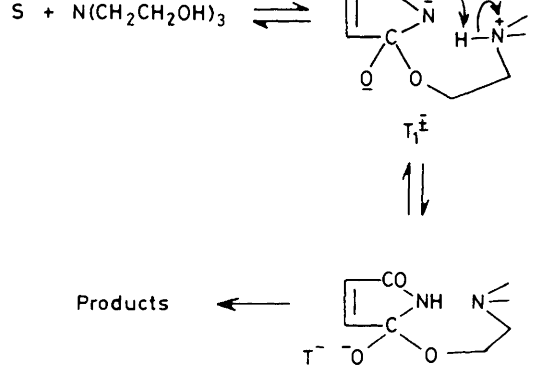
the pre-association stepwise mechanism (Scheme 2) has been preferred for the reason described as follows. In order for the k''_2 step be the rate-determining step, k''_{-1} should be greater than $k''_2[H_2O]$. Since in the k''_2 step the proton transfer takes place in a thermodynamically favourable direction, the value of $k''_2[H_2O]$ should be *ca.* 5.5×10^{11} s^{-1}. This indicates that k''_{-1} would be greater than 5.5×10^{11} s^{-1} which is conceivable for the fact that in the k''_{-1} step the expulsion of leaving group is aided by strong electron-donating powers of the remaining groups attached to the reacting centre. The first-order rate constants for the expulsion of methylamine from $T_1^{\pm}$ [12] and primary amines from $T_2^{\pm}$ (formed from benzylpenicillin and primary amines)[20] were estimated to be 3×10^9 s^{-1} and 10^9—10^{10} s^{-1}, respectively. These results may be used as the basis for the assumed value of k'_{-1} (Scheme 1) of the order of 10^9—10^{10} s^{-1}. It is apparent from the structure of $T^{\pm}$ that the value of k''_{-1} should be much larger than that of k'_{-1}. A value of k''_{-1} of $>5.5 \times 10^{11}$ s^{-1} shows that the lifetime of $T^{\pm}$ may be very close to or higher than 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.[21] Thus, the reaction is most likely forced to proceed through the pre-association stepwise mechanism. An alternative possibility of uncatalysed and general acid-catalysed conversion of $T^{\pm}$ into products may be ruled out on the basis that such mechanism would predict k_1 and k_3 to be quite different from each other in magnitude. In this mechanism, $k_3 = k''_1k''_2/k''_{-1}$ and k''_1/k''_{-1} and k''_2 should be expected to be significantly smaller than k'_1/k'_{-1} and k'_2 respectively.

An alternative mechanism as shown in Scheme 4, where k_6 and k_7 are the rate-determining steps, seems to be less probable compared with the pre-association stepwise mechanism for the reasons described as follows. (i) This mechanism would add an additional term, $k_5[Am^+H]^2[Am][S^-]$, in the rate law [equation (4)] which could not be experimentally observed. (ii) In accordance with this mechanism the observed ratio of k_1/k_3 of *ca.* 1 can be explained only if it is assumed that the ratio of k'_1/k_6 is *ca.* 55 mol l^{-1}. Since termolecular reactions are significantly less probable compared with bimolecular reactions, it may not be correct to assume that $k'_1/k_6 \simeq 55$ mol l^{-1}.

The significant reactivity of both SH and S^- towards triethanolamine is surprising for the fact that triethylamine which is *ca.* 2.5 p*K* units stronger a base compared to triethanolamine has revealed essentially no reactivity towards maleimide. These results cannot be explained in terms of steric requirements for both the amines are almost equally sterically hindered. The most plausible explanation for the significant reactivity of triethanolamine may be the nucleophilic attack by anionic oxygen (in zwitterionic form) as well as by internally hydrogen-bonded hydroxy group rather than the nitrogen of amine. It is known from the literature that in the reactions of activated esters with triethanolamine[23] and tris(hydroxymethyl)aminomethane[24,25] (TRIS) the attacking site of nucleophile is the internally hydrogen-bonded hydroxy group. Intramolecular hydrogen bonding-induced nucleophilic catalyses of aminoalcohols have been observed in the cleavages of the mostly activated esters[23,25,26] where nucleophilic attack is probably the rate-determining step. We could not observe any enhanced nucleophilic reactivity of *o*-(dimethylaminomethyl)benzyl alcohol (*o*-DBA) towards the aqueous cleavages of methyl formate, acetylcholine, and *N*-(2-bromoethyl)phthalimide where the expulsion of the leaving group might possibly be the rate-determining step.[15] A considerably lower value of k_3 compared with k_1 might be expected if the reactions of triethanolamine with SH and S^- follow same mechanism. But the observed ratio of k_3/k_1 of *ca.* 16 indicates that the reactivities of SH and S^- towards triethanolamine follow different mechanisms. We suggest that the reactivity of SH follows a stepwise mechanism which represents a rate-determining intramolecular general acid-catalysed expulsion of the leaving group involving the transition state TS. A stepwise mechanism with nucleophilic attack as the rate-determining step might be favoured for the reactivity of S^- towards triethanolamine. The tetrahedral intermediate $T_1^{\pm}$ formed as a result of the nucleophilic attack by an internally hydrogen-bonded hydroxy group might be trapped by the fast intramolecular proton transfer in a thermodynamically favourable direction as shown in equation (9) before it could collapse towards reactants. The present data are, however, not sufficient to rule out completely the occurrence of pre-association stepwise mechanism. The absence of enhanced reactivity of *o*-DBA towards methyl formate and acetylcholine might be due to a less stable nine-membered ring transition state compared with a seven-membered ring transition state (TS).



TS



(9)

The lack of intermolecular general acid catalysis in the reactions of maleimide with triethanolamine could be attributed to both steric effect as well as significantly increased rate enhancement due to intramolecular catalysis compared with analogous intermolecular catalysis. It is interesting to note that the nucleophilic bimolecular rate constant for the reaction of *p*-nitrophenyl acetate with TRIS (1.2×10^{-3} l mol^{-1} s^{-1} at 35 °C)[17] is only slightly different than that with triethanolamine

(1.35×10^{-3} l mol^{-1} s^{-1} at 30 °C).[23] But the rate constants k_1 and k_3 for triethanolamine are about four and eight times, respectively, greater than that for TRIS.

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