# Intramolecular General Acid–Base Catalysis and the Rate-determining Steps in the Nucleophilic Cleavage of Maleimide with Primary Amines

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The kinetics of nucleophilic cleavage of maleimide have been studied at 30 °C under the buffer solutions of 13 primary amines including three diamines and carbonate. Both ionized ($S^-$) and non-ionized (SH) forms of maleimide have been found to exhibit significant reactivity toward amines and carbonate anion. The respective bimolecular rate constants $k_1$ and $k_2$ for the reactions of nucleophiles with non-ionized and ionized forms of maleimide display Brönsted plots with respective slopes of $\beta nuc_1 = 0.81 \pm 0.15$ and $\beta nuc_2 = 0.48 \pm 0.19$. The significantly different values of $\beta nuc_1$ and $\beta nuc_2$ reveal the involvement of different rate-determining steps in the nucleophilic cleavage of non-ionized and ionized maleimide. The high value of $\beta nuc_1$ is attributed to the expulsion of the leaving group as the rate-determining step while the value of $\beta nuc_2$ of 0.48 indicates the nucleophilic attack within the encounter complex as the rate-determining step. The values of $\beta nuc_1$ and $\beta nuc_2$ for the nucleophilic reactivity of diamines were found to be $0.52 \pm 0.02$ and $0.13 \pm 0.02$, respectively. The value of $\beta nuc_1$ of 0.52 has been attributed to intramolecular general acid–base-catalysed expulsion of the leaving group as the rate-determining step. The low value of $\beta nuc_2$ (0.13) reveals the nucleophilic attack as the rate-determining step. A pre-association stepwise mechanism is proposed for the reactions of amines with $S^-$ while a diffusion-controlled trapping mechanism is favoured for the reactions of amines with SH. The rate constants $k_1$ and $k_2$ for TRIS, 2-amino-2-methylpropane-1,3-diol, ammonia, and carbonate have been found to show significant negative deviations while hydrazine revealed a large positive deviation from Brönsted plots.

The detailed mechanistic studies of the aminolysis of acetylimidazole ($pK_{lg} \simeq 14$) have been carried out by Jencks and his co-workers and the reaction has been found to be sensitive to general acid and general base catalysis.[1] General acid catalysis of nucleophilic cleavage of acetylimidazole could be detected with strongly basic amine nucleophiles.[1] Intra- and inter-molecular general base as well as intramolecular general acid catalysis are detected in the aminolysis of benzylpenicillin where the effective $pK_a$ of the leaving group could be estimated to be *ca.* 10 rather than normal values of *ca.* 30 for ordinary amines.[2] Fife *et al.* have observed general acid and general base catalysis in the intramolecular nucleophilic cyclization of 2-aminomethylbenzamide[3] ($pK_{lg}$ *ca.* 30). Since the $pK_a$ of the leaving group in the nucleophilic cleavage of maleimide is nearly the same as that of imidazole, we hoped initially to observe intermolecular general acid and general base catalysis in the aminolysis of maleimide. Also, it is not easily possible to differentiate between kinetically indistinguishable rate laws: $k[\bar{O}H][SH]$ and $k'[H_2O][\bar{S}]$ in the alkaline hydrolysis of imides and amides with leaving groups carrying a labile proton.[4] We initiated the present study with a hope to get a rate law consisting of $k[Am][SH]$ and $k'[Am][\bar{S}]$ if ionized maleimide is also involved in the nucleophilic cleavage. The aim of the present study is also to see whether there are Brönsted plots of different slopes for the reactivity of ionized and non-ionized maleimide toward nucleophiles as we have recently observed in the aminolysis of phenyl salicylate.[5] In the present paper we describe the experiments on aminolysis of maleimide and propose the possible mechanisms.

## Experimental

*Materials.*—Reagent grade chemicals such as tris(hydroxymethyl)aminomethane (TRIS), 2-methoxyethylamine, n-propylamine, 1-aminopropan-2-ol, 3-aminopropan-1-ol, ethanolamine, 2-amino-2-methylpropane-1,3-diol, 1,3-diaminopropane, 1,4-diaminobutane, and maleimide were obtained from Aldrich Chemical Co., and 1,2-diaminoethane, ammonium chloride, hydrazinium chloride, methylammonium chloride, and 1,4-dioxane were obtained from B.D.H. All other chemicals used were also of reagent grade.

*Kinetics.*—All kinetic experiments reported herein were carried out in aqueous solution (5% 1,4-dioxane) at 30 °C, $\mu = 1.0$M with potassium chloride. Stock solutions ($1.25 \times 10^{-2}$M) of maleimide prepared in 1,4-dioxane were always kept frozen and reprepared frequently in order to avoid any peroxide formation. The total volume of the reaction mixtures was maintained at either 10 or 50 $cm^3$. For a typical kinetic run, the reaction mixture containing all the reaction ingredients except maleimide was incubated at 30 °C for *ca.* 10—15 min in a thermostatted water bath. The reaction was initiated by adding 0.5 or 2.5 $cm^3$ (depending upon the total volume of the reaction mixture) of stock solution of maleimide. A portion (*ca.* 2.5 $cm^3$) was quickly withdrawn from the mixture and transferred to a 3 $cm^3$ quartz cuvette kept in the thermostatted cell holder of the spectrophotometer. The transfer of a portion from reaction vessel to the cuvette normally took 15—25 s. The constant temperature (30 °C) of the cell holder was controlled electronically by the use of the temperature control unit of the spectrophotometer. The reaction rates were studied spectrophotometrically by following the disappearance of maleimide at 300 nm. The spectrophotometer used in the entire kinetic studies was a Beckman model 35 u.v.–visible spectrophotometer equipped with digital display as well as chart recorder model 24-25 ACC.

The amines were used both as nucleophiles and as buffers, to maintain constant pH. All the buffer solutions were prepared just prior to the kinetic run by the addition of standardized hydrochloric acid or sodium hydroxide to the solutions of the free amine or amine hydrochloride. All solutions were prepared in freshly glass-distilled water. The pH values of the kinetic solutions were determined both prior to and after each kinetic experiment with Philips digital pH meter model PW 9409. Any kinetic run showing a pH drift of greater than 0.03 pH units was rejected.

All the kinetic runs were carried out under pseudo-first-order kinetic conditions. The observed pseudo-first-order rate constants $k_{obs}$ were calculated from equation (1) with the use of

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

the non-linear least-squares technique. In equation (1), $k_{obs}$, apparent extinction coefficient, $E_{app}$, and absorbance at $t = \infty$, $A_\infty$, were considered as unknown parameters. $A_{obs}$ is the absorbance value at any time, $t$, and $X_o$ is the initial concentration of maleimide. Almost all the kinetic runs were carried out for more than 3—4 half-lives. The lowest limits of $k_{obs}$ of the order of $10^{-3}$ s$^{-1}$ were observed for all nucleophiles except ammonia, 2-amino-2-methylpropane-1,3-diol, TRIS, and carbonate where the order of the lowest $k_{obs}$ was found to be $10^{-4}$ s$^{-1}$. The fitting of the observed data to equation (1) was significantly good as evident from the residual errors ($A_{obs} - A_{calc}$) of $< 1\%$ prior to 3—4 half-lives for almost all the kinetic runs.

The cyclic imide group such as in maleimide has a characteristic absorption maximum at *ca.* 300 nm and maleamic acid as well as diamides of maleic acid have essentially very low absorption at *ca.* 300 nm. Thus, the decrease in the absorption peak at 300 nm with the progress of the reaction demonstrates that during the aminolysis of maleimide the imide bond cleaves. In order to find out whether highly basic amines are acting as nucleophiles or general base catalysts we, however, carried out a few kinetic runs in which the production of ammonia was monitored periodically using Nessler's reagent.[4] For a typical kinetic run, the reaction was initiated by adding $1.25 \times 10^{-2}$M-maleimide solution (1.0 cm$^3$) to the reaction mixture containing 0.06M-Me$_2$NH buffer (50% free base) in a total volume of 19 cm$^3$. The optical density at 300 nm, $A_{300}$, was found to drop from a maximum to a minimum value within *ca.* 45 s and then there was no change in $A_{300}$ for a further few minutes. After nearly 20 min, *ca.* 10.5M-HCl solution (1.0 cm$^3$) was added to the reaction mixture in order to make it acidic. This was done in order to find out whether the product formed was *N,N*-dimethylmaleamide or maleamic acid. It is known from the literature that the acid hydrolysis of maleamic acid is much faster ($k_{obs}$ $5.28 \times 10^{-3}$ min$^{-1}$ at 30 °C)[6] than that of maleamide (*ca.* $3.4 \times 10^{-3}$ min$^{-1}$ at 65 °C and *ca.* 0.5M-HCl).[7] The reaction was carried out for 691 h and the observed pseudo-first-order rate constant was found to be $2.46 \times 10^{-5}$ min$^{-1}$ at 30 °C which is nearly 200 times smaller than the rate constant obtained for acid hydrolysis of maleamic acid under essentially similar conditions. These observations thus indicate that the dimethylamine is not acting as a general base catalyst in the aqueous cleavage of maleimide.

The possibility of Michael addition of primary amines to maleimide could be ruled out for some qualitative reasons as follows. (i) It is known that the aliphatic amines are hard nucleophiles and $>$CO is a relatively hard electrophile compared with C$_2$H$_4$. Therefore, nucleophilic attack by amines at carbonyl carbon may be expected to be significantly faster than at carbon–carbon double bond in maleimide. Probably because of this reason no Michael addition product was obtained in the hydrolysis of maleimide[8] and *N*-alkylmaleimides.[9] (ii) Bimolecular nucleophilic rate constants obtained for the reactions of maleimide with primary and tertiary amines[10] of comparable basicity have been found to be nearly the same. Since the nucleophilic attack by tertiary amine at –CH=CH– may not be expected to result in Michael addition, it is unlikely that the reaction of primary amines with maleimide will give Michael addition products.

The p$K_a$ values for 1-aminopropan-2-ol, 3-aminopropan-1-ol, and 2-amino-2-methylpropane-1,3-diol were determined potentiometrically as described elsewhere.[5]

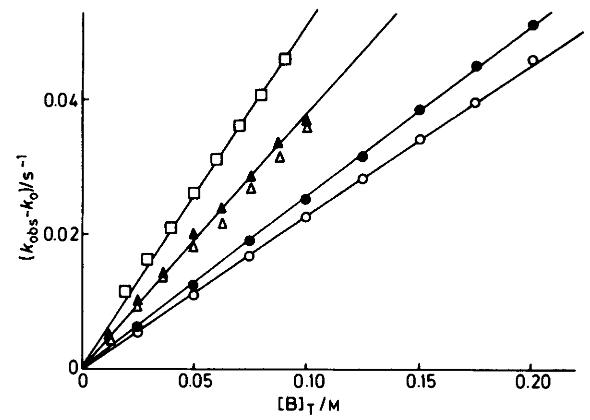

**Figure 1.** The plots showing the dependence of corrected pseudo-first-order rate constants on total amine (1,2-diaminoethane) buffer concentrations for the aminolysis of maleimide at 30 °C and at pH values of 9.34 (○), 9.45 (●), 9.66 (△), 9.71 (▲), and 10.15 (□)

## Results and Discussion

The observed pseudo-first-order rate constants, $k_{obs}$, at constant pH were first tried to fit equation (2) where $k_o$ and $k_n$ are rate

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

constants for the nucleophilic cleavage of maleimide catalysed by hydroxide ion as well as water and by buffer components, respectively. $[B]_T$ represents the total buffer concentration. The unknown parameters $k_o$ and $k_n$ were calculated with linear least-squares techniques.* The values of $k_o$ obtained at various pH values were found to be negative, associated with unusually high standard deviations for most of the highly basic amines. This has occurred because of the insignificant contribution of the $k_o$ term compared with $k_n$ in equation (2). The calculated values of $k_o$ from equation (2) were thus considered to be not very reliable, at least for most reactive amines, and therefore more reliable values of $k_o$ were obtained from equation (3)

$$k_o = A_1K_w/(a_H + K'_a) \qquad (3)$$

where $K'_a$ ($=1.41 \times 10^{-10}$ mol l$^{-1}$) is the acidity constant of maleimide, $K_W = 1.449 \times 10^{-14}$ mol$^{-2}$ l$^{-2}$ and $A_1 = 72.2$ l mol$^{-1}$ s$^{-1}$ as summarized elsewhere.[8] The values of $k_n$ were calculated from equation (4) with the linear least-square

$$k^{corr} = k_n[B]_T \qquad (4)$$

technique and the results obtained are summarized in Table 1. In equation (4), $k^{corr} = k_{obs} - k_o$. The fitting of observed data to equation (4) is evident from the plots shown in Figure 1 for a typical amine and from the standard deviations of $k_n$ listed in Table 1. The difference between the respective values of $k_n$ obtained from equations (2) and (4) were found to be $<3\%$. The general rate law for aminolysis of maleimide may be given by

$$-d[MH]_T/dt = k_o[MH]_T + k_1[MH][B] + k_2[M^-][B] \qquad (5)$$

equation (5) where $[MH]_T$ represents the total concentration of maleimide. [MH] and [M$^-$] represent the concentration of non-ionized and ionized maleimide, respectively, and [B]

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* The linear least-squares computer program in BASIC was developed and entire computations were carried out on a VAX-11 digital computer.

**Table 1.** Apparent second-order rate constants for the reactions of nucleophiles with maleimide[a]

| Amine | pH | $10^2k_n$/ l mol$^{-1}$ s$^{-1}$ | $[B]_T$[b]/ M | No of runs |
|---|---|---|---|---|
| 2-Methoxyethylamine | 8.83 | 3.57 ± 0.04[c] | 0.200 | 8 |
| | 9.13 | 6.20 ± 0.04 | 0.200 | 8 |
| | 9.53 | 11.6 ± 0.1 | 0.090 | 8 |
| | 9.93 | 16.2 ± 0.1 | 0.090 | 8 |
| Methylamine | 9.68 | 17.3 ± 0.1 | 0.200 | 8 |
| | 10.06 | 33.9 ± 0.1 | 0.090 | 8 |
| | 10.37 | 59.3 ± 0.4 | 0.090 | 8 |
| | 10.64 | 78.4 ± 0.5 | 0.055 | 8 |
| n-Propylamine | 10.21 | 10.0 ± 0.8 | 0.060 | 5 |
| | 10.57 | 15.7 ± 0.4 | 0.055 | 5 |
| | 10.84 | 21.1 ± 0.4 | 0.055 | 5 |
| | 11.17 | 26.8 ± 0.2 | 0.055 | 5 |
| 1-Aminopropan-2-ol | 9.03 | 4.05 ± 0.05 | 0.300 | 5 |
| | 9.22 | 4.40 ± 0.11 | 0.300 | 5 |
| | 9.71 | 10.7 ± 0.3 | 0.150 | 5 |
| | 10.28 | 15.0 ± 0.5 | 0.150 | 5 |
| 3-Aminopropan-1-ol | 9.55 | 6.03 ± 0.19 | 0.250 | 6 |
| | 9.73 | 7.98 ± 0.21 | 0.250 | 6 |
| | 9.96 | 11.1 ± 0.4 | 0.125 | 6 |
| | 10.15 | 15.3 ± 0.4 | 0.125 | 6 |
| | 10.38 | 20.2 ± 0.5 | 0.125 | 6 |
| Ethanolamine | 8.96 | 2.84 ± 0.06 | 0.300 | 6 |
| | 9.26 | 5.09 ± 0.13 | 0.300 | 6 |
| | 9.71 | 10.2 ± 0.4 | 0.125 | 6 |
| | 9.98 | 13.7 ± 0.4 | 0.150 | 6 |
| | 10.26 | 15.8 ± 0.6 | 0.125 | 6 |
| Ammonia | 9.15 | 0.108 ± 0.007 | 0.800 | 5 |
| | 9.40 | 0.184 ± 0.026 | 0.300 | 5 |
| | 9.64 | 0.258 ± 0.016 | 0.800 | 5 |
| | 9.87 | 0.444 ± 0.016 | 0.800 | 5 |
| Hydrazine | 7.59 | 33.6 ± 0.4 | 0.050 | 5 |
| | 7.89 | 60.0 ± 1.4 | 0.050 | 5 |
| | 8.19 | 84.8 ± 1.6 | 0.050 | 5 |
| | 8.73 | 153 ± 3 | 0.050 | 5 |
| 2-Amino-2-methylpropane-1,3-diol | 8.52 | 0.0329 ± 0.0015 | 0.70 | 5 |
| | 9.04 | 0.0574 ± 0.148 | 0.52 | 5 |
| | 9.57 | 0.113 ± 0.016 | 0.375 | 5 |
| TRIS | 8.20 | 0.0209 ± 0.0009 | 0.70 | 4 |
| | 8.82 | 0.557 ± 0.0038 | 0.40 | 7 |
| Carbonate | 9.37 | 0.054 | 0.70 | 2 |
| | 9.77 | 0.081 | 0.70 | 2 |
| | 9.99 | 0.087 | 0.70 | 2 |
| | 10.42 | 0.076 | 0.70 | 2 |
| 1,2-Diaminoethane | 7.29 | 1.16 ± 0.01 | 0.50 | 8 |
| | 7.69 | 1.91 ± 0.02 | 0.50 | 8 |
| | 7.85 | 2.35 ± 0.01 | 0.50 | 8 |
| | 8.55 | 7.15 ± 0.13 | 0.50 | 8 |
| | 9.34 | 22.6 ± 0.1 | 0.20 | 8 |
| | 9.45 | 25.5 ± 0.1 | 0.20 | 8 |
| | 9.66 | 35.6 ± 0.2 | 0.10 | 8 |
| | 9.71 | 37.8 ± 0.4 | 0.10 | 8 |
| | 10.15 | 51.3 ± 0.4 | 0.09 | 8 |
| 1,3-Diaminopropane | 8.64 | 4.73 ± 0.08 | 0.120 | 5 |
| | 8.89 | 8.36 ± 0.13 | 0.120 | 5 |
| | 9.19 | 12.6 ± 0.2 | 0.100 | 5 |
| | 9.57 | 22.1 ± 0.5 | 0.050 | 5 |
| | 10.20 | 46.7 ± 0.5 | 0.050 | 5 |
| | 10.40 | 60.2 ± 0.4 | 0.050 | 5 |
| | 10.78 | 72.7 ± 1.4 | 0.050 | 5 |
| | 11.18 | 82.9 ± 1.1 | 0.050 | 5 |
| 1,4-Diaminobutane | 9.38 | 12.0 ± 0.4 | 0.060 | 5 |
| | 9.63 | 19.0 ± 0.4 | 0.060 | 5 |
| | 9.86 | 25.5 ± 0.6 | 0.060 | 5 |
| | 10.17 | 37.0 ± 0.5 | 0.050 | 5 |
| | 10.46 | 53.1 ± 0.6 | 0.120 | 5 |
| | 10.57 | 58.1 ± 0.5 | 0.120 | 5 |
| | 10.62 | 58.3 ± 0.5 | 0.060 | 5 |
| | 10.71 | 59.6 ± 1.4 | 0.150 | 5 |
| | 10.79 | 64.6 ± 0.5 | 0.060 | 5 |
| | 11.01 | 70.1 ± 0.4 | 0.050 | 5 |
| | 11.39 | 72.2 ± 0.8 | 0.050 | 5 |

[a] Temperature 30 °C, ionic strength 1.0M. [b] Maximum total buffer concentration attained at the particular pH. [c] Error limits are the standard deviations.

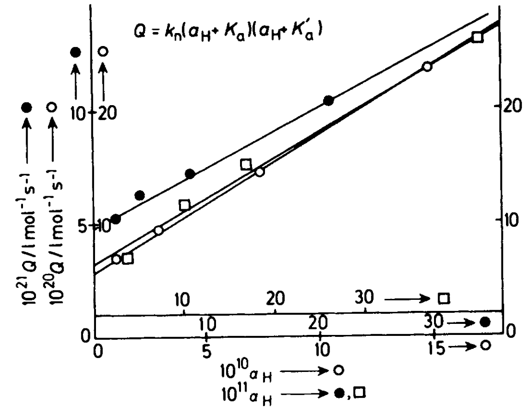

**Figure 2.** The plots of $k_n(a_H + K_a)(a_H + K'_a)$ against $a_H$ for the reaction of methylamine (●), 2-methoxyethylamine (○), and carbonate anion (□) with maleimide. The solid lines are drawn through the least-squares-calculated points

represents the concentration of free monoamine or carbonate nucleophile. From equations (4) and (5), it can be shown that (6)

$$k_nQ = k_2K_aK'_a + k_1K_aa_H \qquad (6)$$

holds where $Q = (a_H + K_a)(a_H + K'_a)$ and $K_a$ is the acidity constant of protonated monoamine.*

The plots of $k_nQ$ against $a_H$ were found to be linear for the reactions of maleimide with all monoamine and carbonate nucleophiles employed in this study as shown for a few typical nucleophiles in Figures 2 and 3. The linearity of these plots indicates that a most likely kinetic term $k'_3[M^-][B][\bar{O}H]$ is unimportant in the rate law [equation (5)]. This is conceivable since the significance of such a term has been observed in the reactions of esters with considerably highly basic amines and where general base catalysis was found to exist.[11,12] An additional kinetic term $k'_4[MH][B][\bar{O}H]$ which is indistinguishable from $k_2[M^-][B]$ could be ruled out simply because of the absence of general base catalysis. This conclusion is further strengthened by the observed occurrence of the $k_2$ term in the reactions of maleimide with tertiary amines[10] where the $k_2$ term cannot be interpreted in terms of the kinetically equivalent term $k'_4[MH][B][\bar{O}H]$. The intercept ($k_2K_aK'_a$) and slope ($k_1K_a$) were calculated from equation (6) by the use of linear least-squares techniques and the respective values thus obtained were used to calculate $k_2$ and $k_1$ with known values of

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* For the amines whose thermodynamic acidity constants ($K_a$) were determined in this study, equation (6) is modified to $k_nQ = k_2K'_aK_a\text{v} + k_1K_a\text{v}a_H$ where $Q = (a_H + K'_a)(a_H + \text{v}K_a)$ and v is the activity coefficient.

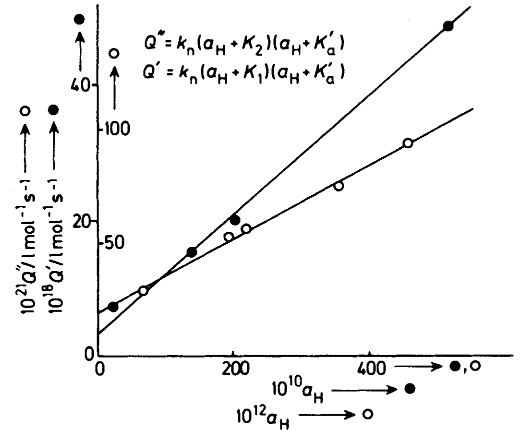


**Figure 3.** The plots showing the dependence of $k_n(a_H + K)(a_H + K'_a)$ on $a_H$ for the reactions of 1,2-diaminoethane (● $K = K_1$, and ○ $K = K_2$) with maleimide. The solid lines are drawn through the last-squares-calculated points

**Table 2.** Second-order nucleophilic rate constants for the reactions of nucleophiles with non-ionized ($k_1$) and ionized ($k_2$) maleimide at 30 °C, ionic strength 1.0M

| Nucleophile | p$K_a$[a] | $10^2k_1$/ l mol$^{-1}$ s$^{-1}$ | $10^2k_2$/ l mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|
| 2-Methoxyethylamine | 9.45[b] | 17.2 ± 0.3[c] | 23.8 ± 0.7[c] |
| Methylamine | 10.85[d] | 382 ± 30 | 206 ± 11 |
| n-Propylamine | 10.79[e] | 110 ± 2 | 36.5 ± 0.3 |
| 1-Aminopropan-2-ol | 9.58[f] | 27.9 ± 2.8 | 19.6 ± 4.8 |
| 3-Aminopropan-1-ol | 10.16[f] | 47.2 ± 3.2 | 34.9 ± 1.6 |
| Ethanolamine | 9.60[g] | 13.6 ± 0.2 | 20.7 ± 0.2 |
| Ammonia | 9.21[d] | 0.014 ± 0.067 | 0.673 ± 0.086 |
| Hydrazine | 8.15[h] | 153 ± 5 | 482 ± 22 |
| 2-Amino-2-methyl-propane-1,3-diol | 8.86[f] | 0.138 ± 0.013 | 0.102 ± 0.073 |
| TRIS | 8.14[h] | 0.028 | 0.247 |
| Carbonate | 9.68[d] | 0.227 | 0.0986 |
| 1,2-Diaminoethane | 7.53 (p$K_1$)[i] | 2.92 ± 0.13 | 21.3 |
| | 10.18 (p$K_2$)[i] | 102 ($k_3$) | 83.9 ± 10.2 ($k_4$) |
| 1,3-Diaminopropane | 9.18 (p$K_1$)[i] | 18.6 ± 1.3 | 28.5 |
| | 10.62 (p$K_2$)[i] | 173 ($k_3$) | 101 ± 8 ($k_4$) |
| 1,4-Diaminobutane | 9.94 (p$K_1$)[i] | 52.8 ± 2.5 | 43.4 |
| | 10.77 (p$K_2$)[i] | 207 ($k_3$) | 83.0 ± 3.0 ($k_4$) |

[a] The p$K_a$ of the conjugate acid of nucleophiles. [b] T. H. Fife, R. J. Bambory, and B. R. DeMark, *J. Am. Chem. Soc.*, 1978, **100**, 5500. [c] Error limits are standard deviations. [d] D. Z. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, 1979, **101**, 4713. [e] J. J. Morris and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1980, 220. [f] This study. [g] T. H. Fife and B. R. DeMark, *J. Am. Chem. Soc.*, 1977, **99**, 3075. [h] A. R. Becker, D. J. Richardson, and T. C. Bruice, *J. Am. Chem. Soc.*, 1977, **99**, 5058. [i] T. C. Bruice and R. C. Willis, *J. Am. Chem. Soc.*, 1965, **87**, 531.

$K_a$ and $K'_a$. These values, for various monoamines as well as carbonate, are summarized in Table 2.

The general rate law for the reactions of maleimide with diamines, studied within the pH range where the significant amounts of the fully deprotonated diamines ($H_2NRNH_2$) and $M^-$ could not exist, may be given as equation (7). From equations

$$-d[MH]_T/dt = k_o[MH]_T + k_1[MH][H_2NR\overset{+}{N}H_3] + k_2[M^-][H_2NR\overset{+}{N}H_3] + k_3[MH][H_2NRNH_2] \quad (7)$$

(4) and (7), we have (8) where $Q' = (a_H + K'_a)(a_H + K_1)$ and $K_1$ is the first ionization constant of the fully protonated diamine.

$$k_nQ' = k_2K_1K'_a + k_3K_1K_2 + k_1K_1a_H \quad (8)$$

The plots of $k_nQ'$ against $a_H$ were found to be linear for the reactions of maleimide with all diamines. The linear least-squares technique was used to calculate $k_2K_1K'_a + k_3K_1K_2$ and $k_1K_1$ from equation (8). The calculated values of $k_1K_1$ for all diamines were used to calculate $k_1$ with known values of $K_1$ and the results thus obtained are shown in Table 2. The least-squares-calculated values of $k_2K_1K'_a + k_3K_1K_2$ were used to evaluate $k_2$ and $k_3$ as described in the Appendix.

For the kinetic runs carried out within the pH range where substantial amounts of $H_2NRNH_2$ and $M^-$ could exist, the general rate law should include an additional term $k_4$ $[M^-][H_2NRNH_2]$. By the inclusion of this term in equation (7), and following equation (4), we get equation (9) where $Q'' = (a_H + K'_a)(a_H + K_2)$ and $K_2$ is the second ionization constant of diamine.

$$k_nQ'' = k_4K_2K'_a + (k_3K_2 + k_2K'_a)a_H + k_1a_H^2 \quad (9)$$

The plots of $k_nQ''$ against $a_H$ for the reactivity of fully free diamines were found to be linear as shown in Figure 3 for 1,2-diaminoethane in the pH range 9.34—10.15. The linearity of the plots of $k_nQ''$ against $a_H$ indicates that $k_1a_H^2 \ll k_4K_2K'_a + (k_3K_2 + k_2K'_a)a_H$. The maximum relative contribution of the $k_1$ term should be expected at the lowest observed pH 9.34 for 1,2-diaminoethane and the calculated value of $k_1a_H^2$ ($k_1 = 0.029$ l mol$^{-1}$ s$^{-1}$ obtained from the experiments carried out within the pH range 7.29—8.57) at pH 9.34 revealed a *ca.* 6% contribution to the total rate. Thus, within the observed pH range, the $k_1$ term could be neglected compared with the other terms in equation (9) which in turn further reduced it to (10). The respective values of the intercept ($k_4K_2K'_a$) and slope ($k_3K_2 + k_2K'_a$) were calculated by the linear least-squares technique from equation (10).

$$k_nQ'' = k_4K_2K'_a + (k_3K_2 + k_2K'_a)a_H \quad (10)$$

The values of $k_4$ for all diamines as calculated from the least-squares-calculated intercept ($k_4K_2K'_a$) with known values of $K_2$ and $K'_a$ are summarized in Table 2. The calculated values of the slope ($k_3K_2 + k_2K'_a$) were used to calculate $k_2$ and $k_3$ as described in the Appendix.

The reactivity of TRIS has been studied at two different pH values, 8.20 and 8.82. A plot of $k_nQ$ against $a_H$ through two observed points gave the intercept ($k_2K_aK'_a$) and slope ($k_1K_a$) as $5.90 \times 10^{-21}$ mol l$^{-1}$ s$^{-1}$ and $2.05 \times 10^{-12}$ s$^{-1}$, respectively. The values of $k_1$ and $k_2$ calculated from the slope and intercept are summarized in Table 2.

The nucleophilic reactivity of $C\bar{O}^{3-}$ toward maleimide was found to be extremely low compared with its basicity. The kinetics were measured at only two total buffer concentrations (0.1 and 0.7M). The values of the slope ($k_n$) obtained from plots drawn through two observed points are shown in Table 1. A plot of $k_nQ$ against $a_H$ is shown in Figure 2. The least-squares-calculated values of $k_2K_aK'_a$ and $k_1K_a$ are $(6.28 \pm 0.97) \times 10^{-23}$ mol l$^{-1}$ s$^{-1}$ and $(4.73 \pm 0.41) \times 10^{-13}$ s$^{-1}$, respectively. The values of $k_1$ and $k_2$ were obtained from $k_1K_a$ and $k_2K_aK'_a$, respectively. These values are shown in Table 2.

*Proposed Mechanism.*—(1) *Reaction of monoamines.* The rate constants $k_1$ and $k_2$ have been found to follow the Brönsted equations (11) and (12), respectively. The Brönsted coefficients βnuc$_1$, βnuc$_2$, and intercepts $C_1$ and $C_2$ were calculated by the

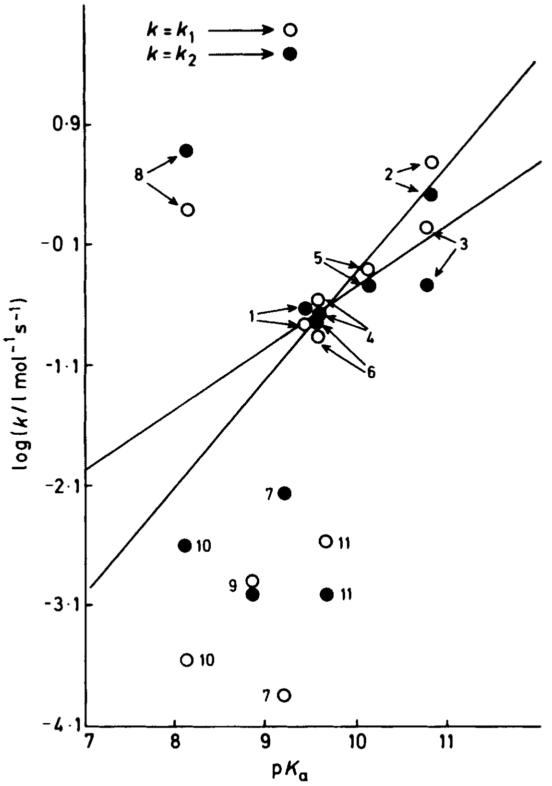


**Figure 4.** The dependence of the nucleophilic bimolecular rate constants for the reactions of ionized ($k_2$, ●) and non-ionized maleimide ($k_1$, ○) with primary monoamines on the p$K$ of the conjugate acid of the amine at 30 °C. The solid lines are drawn through the least-squares-calculated points from equation (11) with $\beta$nuc$_1$ = 0.81, $C_1$ = $-8.50$ l mol$^{-1}$ s$^{-1}$ for (○) and equation (12) with $\beta$nuc$_2$ = 0.48, $C_2$ = $-5.25$ l mol$^{-1}$ s$^{-1}$ for (●). In the Brönsted plots: 1, 2-methoxyethylamine; 2, methylamine; 3, n-propylamine; 4, 1-aminopropan-2-ol; 5, 3-aminopropan-1-ol; 6, ethanolamine; 7, ammonia; 8, hydrazine; 9, 2-amino-2-methylpropane-1,3-diol; 10, TRIS; and 11, carbonate

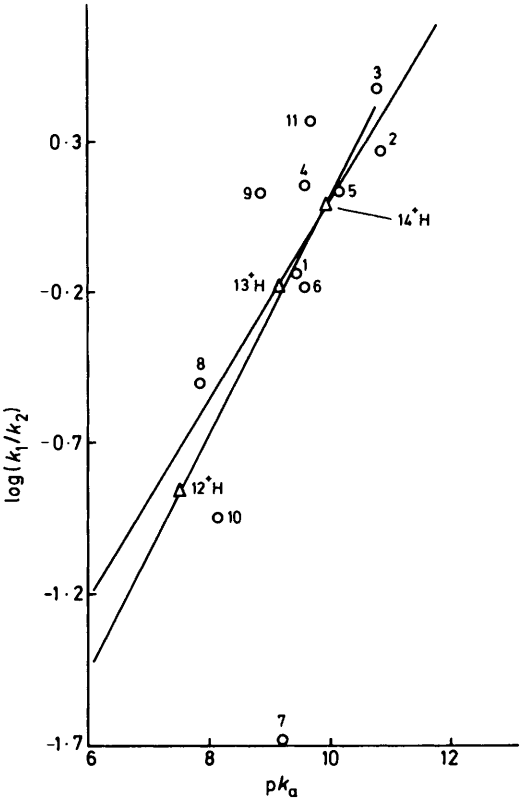


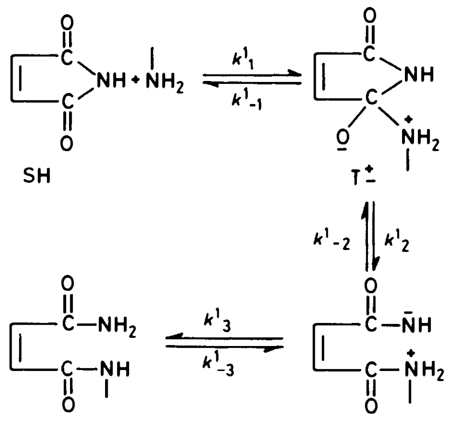
**Figure 5.** Plots showing the dependence of log($k_1/k_2$) *versus* p$K_a$ of the nucleophile where $k_1$ and $k_2$ represent the bimolecular rate constants for the reactions of nucleophile with non-ionized and ionized maleimide, respectively. Abbreviations for nucleophiles are as described in the captions of Figures 4 and 6. Statistical corrections were considered for the rate constants and p$K$ of the hydrazine only. ○ For monoamines including carbonate and hydrazine and △ for monocation of diamines

$$\log k_1 = C_1 + \beta\text{nuc}_1\ \text{p}K_a \qquad (11)$$

$$\log k_2 = C_2 + \beta\text{nuc}_2\ \text{p}K_a \qquad (12)$$

linear least-squares technique. The respective values of $\beta$nuc$_1$, $\beta$nuc$_2$, $C_1$, and $C_2$ are 0.81 ± 0.15, 0.48 ± 0.19, $-8.50 \pm 1.55$ l mol$^{-1}$ s$^{-1}$, and $-5.25 \pm 1.89$ l mol$^{-1}$ s$^{-1}$. The amines used in the calculation of $\beta$nuc$_1$ and $\beta$nuc$_2$ were 2-methoxyethylamine, methylamine, n-propylamine, 1-aminopropan-2-ol, 3-aminopropan-1-ol, and ethanolamine. The fittings of observed data to equations (11) and (12) are evident from the plots shown in Figure 4 where the solid lines are drawn through the least-squares-calculated points. A better plot to show the difference between $\beta$nuc$_1$ and $\beta$nuc$_2$ might be to plot the logarithm of $k_1/k_2$ against p$K$ of the amine. Such a plot is shown in Figure 5 which is essentially linear. The linear least-squares-calculated slope of the plot was found to be 0.33 ± 0.11 by considering only those amines which were used in the Brönsted correlations. However, the consideration of all monoamines including ammonia and hydrazine resulted in a slope of 0.43 ± 0.02. The value of the slope of 0.33 clearly demonstrates that $\beta$nuc$_1$ and $\beta$nuc$_2$ are significantly different from each other. It is interesting to note that the observed point for the most reactive amine for its basicity (hydrazine) falls very close to the plot with slope of 0.33 while the observed point for ammonia has the largest negative deviation from the plot. Hydrazine thus appears to behave very similarly to other monoamines in its reactivity toward non-ionized and ionized substrate.

The significantly different values of $\beta$nuc$_1$ and $\beta$nuc$_2$ indicate the involvement of different types of transition states in the nucleophilic cleavage of non-ionized and ionized maleimide. The rate constants for TRIS and 2-amino-2-methylpropane-1,3-diol reactivity were not included in the least-squares calculation of $\beta$nuc$_1$ and $\beta$nuc$_2$ simply because at least TRIS is known to have a negative deviation from Brönsted plot due to probable steric hindrance.[13] Hydrazine has been found to show a large positive deviation from Brönsted plot which could be attributed to the so-called α-effect. Surprisingly, both the rate constants $k_1$ and $k_2$ for ammonia revealed considerable large negative deviations from Brönsted plots (Figure 4). These deviations indicate that the ammonia possibily does not belong to a series of homologous primary amines in its nucleophilic reactivity toward maleimide. n-Propylamine was found to show significant negative deviations from Brönsted plots for its reactivity toward both MH and M$^-$. In the nucleophilic cleavage of acetyltriazole, Jencks and his co-workers[14] have also observed a *ca.* 300 times lower reactivity of n-propylamine compared with less hindered monoamines of similar basicity. The exclusion of the rate constants for n-propylamine in the least-squares calculation of $\beta$nuc$_1$ and $\beta$nuc$_2$ resulted in their respective values as being 0.96 ± 0.15 and 0.75 ± 0.07. The value of $\beta$nuc$_1$ is significantly different from those obtained in the nucleophilic cleavage of acetylimidazole[15] ($\beta$nuc 1.6) and acetyltriazole[14] ($\beta$nuc 1.3) with basic primary amines. But it is

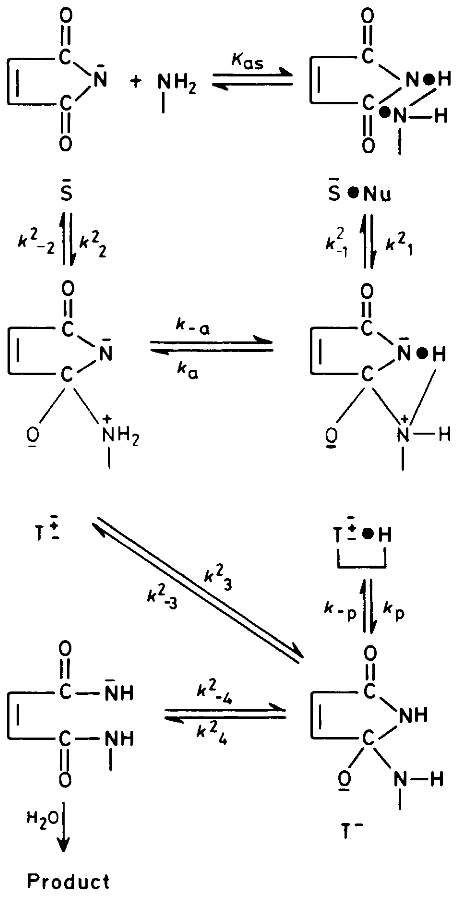


Scheme 1.

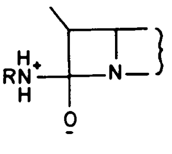
comparable with βnuc (1.0) obtained in the nucleophilic cleavage of benzylpenicillin with primary amines.[2]

The value of $\beta nuc_1$ of 0.81 indicates that 0.81 unit positive charge is developed on the nitrogen atom of the attacking amine in the transition state.[2,16,17] The large value of $\beta nuc_1$ reveals the appearance of late transition state on the reaction co-ordinate with complete development of nearly a unit positive charge on the nitrogen atom of the nucleophile and thus suggests that the explusion of leaving group is most likely the rate-determining step.[2,16,18] The mechanism of the nucleophilic cleavage of non-ionized maleimide may be as shown in Scheme 1. In order for $k^1_2$ to be rate determining (Scheme 1), the assumption that $k^1_{-1} > k^1_2$ should be true. The assumption that $k^1_{-1} > k^1_2$ is conceivable for two reasons: (i) the nucleophiles (p$K_a$ *ca.* 8—11) are better leaving groups than the leaving group of the substrate (p$K_a$ *ca.* 14—16),* and (ii) the expulsion of the nitrogen atom of nucleophile is aided by a push from both the amide nitrogen atom and the anionic oxygen atom while the expulsion of the nitrogen atom of the amide is aided only by the anionic oxygen atom.

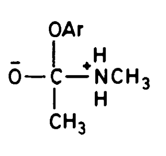
The value of $\beta nuc_2$ of 0.48 indicates that the nucleophilic reactions of amines with ionized maleimide behave as if 0.48 unit positive charge has developed on the nitrogen atom of the nucleophile in the critical rate-determining step. The simplest preassociation stepwise mechanism that is consistent with the observed results may be as shown in Scheme 2. Recently, Gresser and Jencks[20] have well demonstrated that the rate of expulsion of a 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 in (**I**)[21] and (**II**)[16] have been found to be $10^9$—$10^{10}$ and $3 \times 10^9$ $s^{-1}$, respectively. On the basis of these results, the value of the rate constant $k^2_{-2}$ (Scheme 2) could be assumed to be significantly larger than $10^9$—$10^{10}$ $s^{-1}$ because the push provided by the groups attached to the reaction centre to expel the cationic nitrogen leaving group from $T^{\pm}$ would most likely be more in $T^{\pm}$ than in (**I**) or in (**II**). In Scheme 2, the rate constant $k_a$ represents the diffusional separation of $>\bar{N}$ and $H_2\overset{+}{N}<$ groups from an intramolecular encounter complex ($\underbrace{T^{\pm}\cdot H}$). This diffusional separation is presumably retarded by the strong hydrogen bonding between the negatively charged nitrogen atom and hydrogen atom of cationic amine. Although it is difficult to assess the exact value of $k_a$, it may not be unreasonable to assume that $k_a < 10^{10}$ $s^{-1}$ because the value of the rate constant for diffusional separation of two molecules from an intermolecular encounter complex where such a strong hydrogen bonding could not be envisaged is of the order of $10^{10}$ $s^{-1}$.[22] Thus, it appears that $k^2_{-2} > k_a$. This condition reveals that the reaction must proceed through the preassociation stepwise mechanism[22] (*i.e.* path $\xrightleftharpoons{K_{as}}$ $S^-$ ·Nu $\xrightleftharpoons{k^2_1}$ $\underbrace{T^{\pm}\cdot H}$ $\xrightleftharpoons{k_p}$ $T^-$ $\xrightleftharpoons{k^2_4}$). In the reaction of $S^-$ with tertiary amines,[10] we have demonstrated that the value of $k^2_{-2}$ is $> 10^{11}$ $s^{-1}$. Thus, it is 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.[23]



Scheme 2.



(I)



(II)

In the preassociation stepwise mechanism (Scheme 2), $k_p$ represents the rate constant for a process in which intramolecular proton transfer takes place in a thermodynamically favourable direction within the intramolecular encounter complex involving a four-membered ring transition state. The value of $k_p$ may be considered to be in the range of $10^{11}$—$10^{12}$ $s^{-1}$ because the upper limit of the order of the rate constant of intermolecular proton transfer in a thermodynamically favourable direction within an ion pair is $10^{12}$ l $mol^{-1}$ $s^{-1}$.[24] Although

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* An approximate p$K_a$ range of 14—16 has been considered arbitrarily on the basis of the reported p$K_a$ values of benzamide and acetamide of 14—15 and 15.4,[19] respectively.

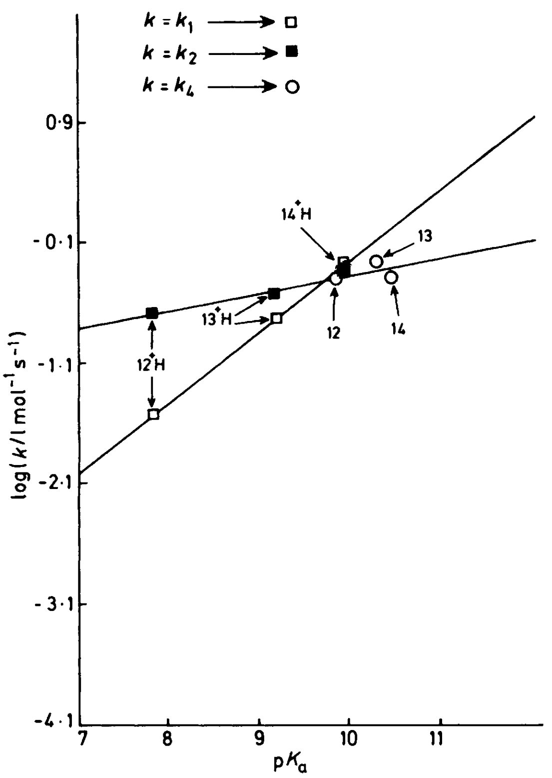
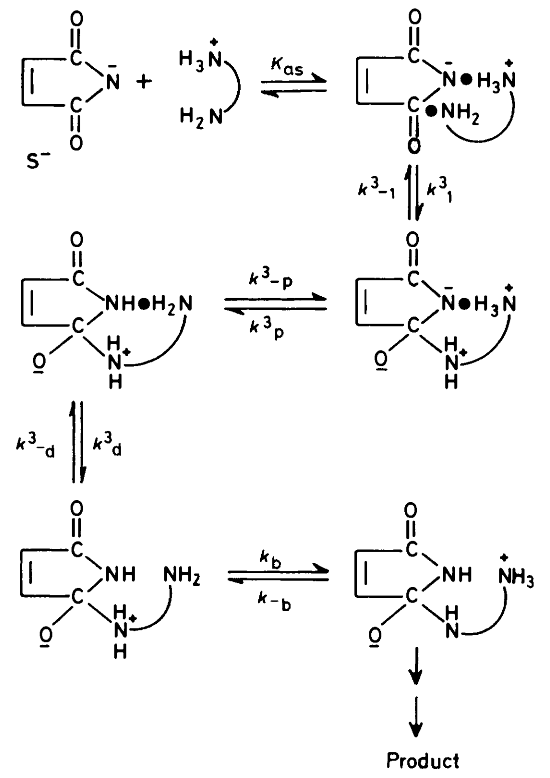


**Figure 6.** The dependence of the nucleophilic bimolecular rate constants for the reactions of ionized ($k_2$, ■ and $k_4$, ○) and non-ionized maleimide ($k_1$, □) with primary diamines on the p$K$ of the conjugate acid of the amine at 30 °C. The solid lines are drawn through the least-squares-calculated points from equation (11) with βnuc$_1$ = 0.52, $C_1$ = −5.43 l mol$^{-1}$ s$^{-1}$ for (□) and equation (12) with βnuc$_2$ = 0.13, $C_2$ = −1.64 l mol$^{-1}$ s$^{-1}$ for (■, ○). Statistical corrections were made to both $k_4$ and $k_2$ for diamines. In the Brönsted plots: 12H$^+$, 13$^+$H, and 14H$^+$ are the monocation of 1,2-diaminoethane, 1,3-diaminopropane, and 1,4-diaminobutane, respectively. 12, 13, and 14 are free 1,2-diaminoethane, 1,3-diaminopropane, and 1,4-diaminobutane, respectively

the value of $k^2_{-1}$ could be greater than $10^9$—$10^{10}$ s$^{-1}$, it may not possibly be equal or greater than $10^{11}$—$10^{12}$ s$^{-1}$. The analysis thus indicates that $k_p > k^2_{-1}$ which leads to $k^2_1$ as the rate-determining step. In Scheme 2, $k_{-p}$ represents the rate constant for proton transfer in a thermodynamically unfavourable direction and hence $k_{-p}$ may be smaller than $k^2_4$ because in the $k^2_4$ step, the expulsion of the leaving group is facilitated by the push provided by the anionic oxygen and nitrogen atom of the nucleophile. Thus, the conclusions that $k_p > k^2_{-1}$ and $k^2_4 > k_{-p}$ show that $k^2_1$ is most likely the rate-determining step. An alternative evidence that $k^2_4$ is not rate limiting is the moderately large Brönsted β value. The reactivities of carbonate with S$^-$ and SH are *ca.* 300- and *ca.* 100-fold less than that predicted from Brönsted plots. The actual decrease in the reactivity of carbonate compared with amine of similar basicity is partially offset by the larger carbon basicity of oxy anions than of amines, for a given basicity toward the proton.[20]

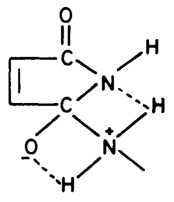
(2) *Reaction of diamines.* The reactivity of diamines toward both non-ionized and ionized maleimide has been found to obey Brönsted equations (11) and (12), respectively, as shown graphically in Figure 6. The Brönsted coefficients βnuc$_1$, βnuc$_2$, and intercepts $C_1$, $C_2$ were found to be 0.52 ± 0.02, 0.13 ± 0.02, −5.43 ± 0.23 l mol$^{-1}$ s$^{-1}$, and −1.64 ± 0.24 l mol$^{-1}$ s$^{-1}$, respectively. The difference in the values of βnuc$_1$ and βnuc$_2$ could also be seen from the plot of log ($k_1/k_2$) against the p$K$ of the amine as shown in Figure 5. The least-squares-calculated slope of the plot was found to be 0.40 ± 0.01. The values of βnuc$_1$ and βnuc$_2$ are significantly different than the corresponding values obtained with primary monoamines. This indicates that the mechanisms involved in the reactions of diamines with non-ionized and ionized maleimide are different from those proposed in the similar reactions with primary monoamines. The value of βnuc$_1$ of 0.52 indicates that the reaction behaves as if 0.52 unit positive charge is developed on the attacking nitrogen in the critical transition state. We propose that the expulsion of leaving group is the rate-determining step but it is facilitated somehow by intramolecular general acid–base catalysis. This intramolecular general acid–base catalysis makes the transition state to occur earlier on the reaction co-ordinate compared to one where there is no such possibility of intramolecular general acid–base catalysis.



**Scheme 3.**

The value of βnuc$_2$ (0.13) indicates an insignificant amount of positive charge development on the attacking nitrogen in the transition state. This could be attributed to the nucleophilic attack as the rate-determining step. The mechanism for the nucleophilic cleavage of ionized maleimide with diamines may be as shown in Scheme 3. The mechanistic analysis as described for the reaction of S$^-$ with monoamines (Scheme 2) may lead $k^3_1$ as the rate-determining step.

*Conclusions.*—The absence of general acid and general base catalyses in the reactions of primary amines with maleimide reveals that the empirical condition that such catalyses are required in the reactions only if bond formation and bond fission between heavy atoms involve sufficiently large changes in the acidity of the reacting site[22,25] may be necessary but certainly not sufficient. The significantly large value of βnuc$_1$ (0.81) is comparable with the βnuc of 1.00 obtained in the aminolysis of benzylpenicillin[2] where expulsion of the leaving group has been suggested as the rate-determining step. The unimportance of general acid and general base catalyses in the



(III)

present system is surprising in the domain of the existing knowledge of such catalyses. However, the occurrence and non-occurrence of these catalyses even in the most extensively studied reactions (aminolysis of esters and amides) are not fully understood.[22] The qualitative explanation for the absence of general acid–base catalysis may be discussed in terms of the conformational requirements. The extent of the probable intramolecular hydrogen bonding (**III**) possibly tends to decrease the significance of the intermolecular general acid–base catalysis. The suggested preassociation stepwise mechanism for the reactions of primary mono- and di-amines with ionized maleimide ($S^-$) has been shown to occur simply because the estimated lifetime of the intermediate $T^{\pm}$(Scheme 2) formed in a simple stepwise mechanism becomes shorter than the period of critical vibration (*ca.* $10^{-13}$ s). This is based on the conclusion drawn by Jencks on related studies.[23,26]

## Appendix

From equation (8), the calculated intercept $C$ may be taken from equation (i). Similarly, the calculated slope $S$ from

$$C = k_2K_1K_a' + k_3K_1K_2 \qquad \text{(i)}$$

equation (9) may be taken from (ii). The values of $k_3$ for all

$$S = k_2K_a' + k_3K_2 \qquad \text{(ii)}$$

diamines were estimated as follows: the unambiguously observed values of $k_1$ for all three diamines were found to show a reasonably good fit to equation (iii) with least-squares-

$$\log k_1 = C_1 + \beta\text{nuc}_1\ \text{p}K_a \qquad \text{(iii)}$$

calculated values of $C_1$ and $\beta\text{nuc}_1$ as $-5.43 \pm 0.23$ and $0.52 \pm 0.02$, respectively. Since both $k_1$ and $k_3$ represent the rate constants for the reactions of the non-ionized maleimide with nucleophiles, it may not be unreasonable to assume that $k_3$ would also obey equation (iii). Thus, the values of $k_3$ as listed in Table 2 were calculated from equation (iii) with $k_1$ replaced by $k_3$. These calculated values of $k_3$ were used to calculate $k_2$ from equations (i) and (ii). The values of $k_2$ obtained from equation (i) are $(13.7 \pm 4.7) \times 10^{-2}$, $(28.8 \pm 3.7) \times 10^{-2}$, and $(49.1 \pm 1.6) \times 10^{-2}$ l mol$^{-1}$ s$^{-1}$ for 1,2-diaminoethanes, 1,3-diaminopropane, and 1,4-diaminobutane, respectively. Similarly, equation (ii) gave values of $k_2$ of $(28.9 \pm 1.4) \times 10^{-2}$, $(28.3 \pm 3.5) \times 10^{-2}$, and $(37.6 \pm 1.8) \times 10^{-2}$ l mol$^{-1}$ s$^{-1}$ for 1,2-diaminoethane, 1,3-diaminopropane, and 1,4-diaminobutane, respectively. The average of two values of $k_2$ obtained from equation (i) and (ii) has been considered as its appropriate value. These average values are summarized in Table 2.

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