Kinetic Evidence for the Occurrence of a Stepwise Mechanism in the Aminolysis of *N*-Ethoxycarbonylphthalimide

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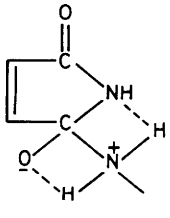
The nucleophilic second-order rate constants for the reactions of *N*-ethoxycarbonylphthalimide (ECPH) with morpholine, piperazine, 1,4-diazabicyclo[2.2.2]octane, and ethylenediamine exhibit a Brønsted plot of slope (β_{nuc}) 1.2 ± 0.3. The significantly high value of β_{nuc} reveals that the expulsion of the leaving group from a zwitterionic tetrahedral addition intermediate is the rate-determining step. The reactivity of hydroxylamine is nearly 10^5-fold larger than that expected from the Brønsted plot of slope (β_{nuc}) 1.2. The hydroxylaminolysis of ECPH reveals general base catalysis. The results obtained on the hydroxylaminolysis of ECPH in the presence of external general base, acetate, reveal that the rate-determining step changes as the buffer concentration is increased and, consequently, it provides evidence for the existence of an intermediate on the reaction co-ordinate. The rate constants for the reactions of monoprotonated 1,4-diazabicyclo[2.2.2]octane and piperazine show positive deviations from the Brønsted plot.

Although much work has been published on general acid and general base catalysis (GA–GB),[1] the mechanisms of these reactions are not yet fully understood.[2] An elegant conclusion of Jencks[2] that the driving force for GA–GB catalysis of carbonyl addition and related reactions arises ultimately from sudden large changes in the acidity and basicity of the reacting groups when there is a change in the bonding of heavy atoms does not seem to be the only driving force for the occurrence of GA–GB catalysis since we could not detect GA–GB catalysis in the reactions of maleimide with primary amines[3] while the reactions with secondary and tertiary amines[4,5] revealed GA–GB and GA catalysis, respectively. Similarly, intramolecular GB catalysis was detected in the reactions of phenyl and methyl salicylates but such catalysis could not be detected in the reactions of methyl salicylate with several secondary amines.[6–8] The huge amount of work carried out on aminolyses of esters and amides probably formed the basis of the Jencks generalization of the occurrence or non-occurrence of GA–GB catalysis in the reactions. However, may be, more observations of a different reaction series are required before any further generalized conclusions can be drawn on such catalysis. The absence of GA–GB catalysis in the reactions of primary amines with maleimide was explained qualitatively by proposing the occurrence of an internally hydrogen-bonded intermediate (**I**) which discouraged the probable occurrence of intermolecular GA–GB catalysis.



(**I**)

In the continuation of our mechanistic search on GA–GB catalysis in the cleavage of the imide bond, we have examined the aminolysis of *N*-ethoxycarbonylphthalimide (ECPH). The kinetics of the aminolysis of maleimide were complicated to some extent by the existence of both ionized and non-ionized forms of maleimide in the reaction mixtures. In order to avoid such complications, we chose ECPH and the results obtained on aminolysis of ECPH are described in this paper.

Experimental

All the chemicals used were of reagent grade and were obtained either from B.D.H. or Aldrich Chemical Company. Glass-distilled water was used in the entire kinetic studies.

Kinetic Measurements.—The reaction rates of aminolysis of *N*-ethoxycarbonylphthalimide (ECPH) were studied by monitoring the disappearance of ECPH spectrophotometrically at 300 nm. The details of the procedure and kinetic analysis are described elsewhere.[3,5]

In the hydroxylaminolysis of ECPH, it appeared that the initial product ethyl *N*-[*o*-(*N*-hydroxycarbamoyl)benzoyl]-carbamate (EBC) formed also underwent cyclization to produce *N*-hydroxyphthalimide [equation (1)]. But the ratios of

$$\text{NCPH} \xrightarrow{k_1''[NH_2OH]} \text{EBC} \xrightarrow{k_2'} \textit{N}\text{-hydroxyphthalimide} \quad (1)$$

the rate constants, k_1'/k_2' (where $k_1' = k_1''[NH_2OH]$), were $\geqslant 270$ under the experimental conditions imposed. Thus, the incursion of the k_2 step could not affect the pseudo-first-order kinetic analysis of the k_1 step.

The ionization constants of the conjugate acids of morpholine (pK_a 8.74) and 1,4-diazabicyclo[2.2.2]octane (pK_1 3.54 and pK_2 9.10) were determined potentiometrically at 30 °C and 1.0M ionic strength.

Results and Discussion

Reaction with Hydroxylamine.—A series of kinetic runs was carried out in buffer solutions of hydroxylamine at various pH. The first-order rate constants (k_{obs}) fitted reasonably to equation (2) where $[Am]_T$ represents the total amine buffer

$$k_{obs} - k_0 = k_n[Am]_T + k_{gb}[Am]_T^2 \quad (2)$$

concentration, k_n and k_{gb} represent the second- and third-order rate constants for uncatalysed and buffer-catalysed hydroxyl-

aminolysis of ECPH, respectively and k_o is the buffer-independent first-order rate constant. The values of k_o at different pH were calculated from equation (3) where k_w (water-

$$k_o = k_w + k_{OH}a_{OH} \quad (3)$$

catalysed rate constant) = (2.6 ± 0.4) × 10^{-4} s^{-1} obtained within the pH range of 3.72—6.22 and k_{OH} (hydroxide ion-catalysed rate constant) = (1.985 ± 0.196) × 10^3 dm^3 mol^{-1} s^{-1}.[9]

The fitting of observed data to equation (2) is evident from the plots shown in Figure 1 where solid lines are drawn through the calculated points. The least-squares technique was used to calculate k_n and k_{gb} as shown in Table 1.

The general rate law for the aqueous cleavage of ECPH in hydroxylamine buffer solutions may be given as

$$-\frac{d[Sub]_T}{dt} = (k_0 + k_1[Am] + k_2[Am]^2)[Sub]_T \quad (4)$$

where $[Sub]_T$ is the total concentration of substrate (ECPH) and [Am] represents the concentration of free hydroxylamine. Equation (5) may be derived from equation (4) and the observed rate law: $-d[Sub]_T/dt = k_{obs}[Sub]_T$.

$$k_{obs} - k_o = k_1 f_{bAm}[Am]_T + k_2 f_{bAm}^2[Am]_T^2 \quad (5)$$

In equation (5), f_{bAm} represents the fraction of free hydroxylamine base and k_1 and k_2 represent the nucleophilic second-order and general base-catalysed third-order rate constants, respectively. Equation (5) is similar to equation (2) with

$$k_n = k_1 f_{bAm} \quad (6)$$

and

$$k_{gb} = k_2 f_{bAm}^2 \quad (7)$$

The least-squares technique was used to calculate k_1 and k_2 from equations (6) and (7) and the results obtained are shown in Table 2. It is interesting to note that the maximum contribution of k_{gb} term in equation (2) is *ca.* 49% and minimum contribution of k_n term is *ca.* 51% (Table 1). The relative contributions of k_n and k_{gb} terms thus indicate that the derived value of k_1 is relatively more reliable than that of k_2.

Effect of Acetate Buffer on Hydroxylaminolysis of ECPH.—In order to affirm the significance of k_{gb} term in equation (2) we studied the hydroxylaminolysis in acetate buffer solutions of varying concentrations. The total hydroxylamine concentration was kept constant at 2 × 10^{-3}M. The observed data revealed a reasonable fitting to equation (8) where $k_{obs}^{corr} = k_{obs} - k_o -$

$$k_{obs}^{corr} = \frac{A_1[B]_T}{1 + A_2[B]_T} \quad (8)$$

$k_B f_{bAm}[B]_T - k_n f_{bAm}[NH_2OH]_T - k_{gb} f_{bAm}^2[NH_2OH]_T^2$ with k_o = 2.6 × 10^{-4} s^{-1}. The values of k_n and k_{gb} were obtained from equation (2) and the fractions of free hydroxylamine base f_{bAm} at different pH were calculated using the known pK_a value of hydroxylamine (Table 2). The value of the acetate buffer-catalysed second-order rate constant, k_B (= 1.23 × 10^{-3} dm^3 mol^{-1} s^{-1}), was obtained by carrying out kinetic runs in acetate buffer solutions of different concentrations and pH in the

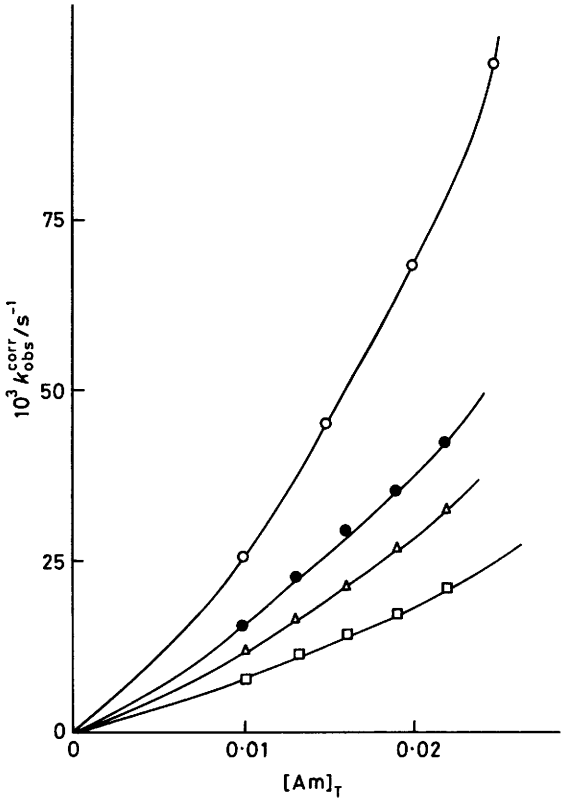


Figure 1. Plots of k_{obs}^{corr} (= $k_{obs} - k_o$) *versus* $[Am]_T$ for the reactions of ECPH with hydroxylamine at pH 4.97 (□), 5.19 (△), 5.36 (●), and 5.61 (○). The solid lines are drawn through the least-squares-calculated points using equation (2)

Table 1. Apparent second- and third-order rate constants for the hydroxylaminolysis of ECPH[a]

pH	10^3k_n/ dm^3 mol^{-1} s^{-1}	k_{gb}/ dm^6 mol^{-2} s^{-1}	$[NH_2OH]_T^b$ range	No. of runs
4.97	669.0 ± 53.1[c]	11.2 ± 2.9[c]	0.010—0.022	5
5.19	845.3 ± 18.9	27.4 ± 1.0	0.010—0.022	5
5.36	1 349 ± 109	26.1 ± 5.0	0.010—0.022	5
5.61	1 894 ± 135	73.2 ± 6.4	0.010—0.025	4

[a] Conditions: $[ECPH]_o$ 2 × 10^{-4}M, unless otherwise noted ionic strength is 1.0M, 1% MeCN in the aqueous reaction mixture, 30 °C; [b] Total amine buffer concentration range. [c] Error limits are standard deviations.

Table 2. Nucleophilic second-order rate constants for the reactions of amine nucleophiles with ECPH at 30 °C

Amine		pK_a^a	10^3k_1/ dm^3 mol^{-1} s^{-1}
Ethylenediamine	(pK_1)	7.53[b]	2.42 ± 1.20[c]
	(pK_2)	10.18[b]	8 320 ± 710 (k_3)
1,4-Diazabicyclo[2.2.2]octane	(pK_1)	3.54[d]	0.449 ± 0.034[e]
	(pK_2)	9.10[d]	406 ± 21[c](k_3)
Piperazine	(pK_1)	5.57[f](6.17)	3.77 ± 0.02
	(pK_2)	9.83[f](9.98)	1 550 ± 160 (k_3)
Morpholine		8.74[d]	85.0 ± 8.9
Hydroxylamine		5.97[g]	6 404 ± 215

[a] pK_a Of the conjugate acids of amines. [b] T. C. Bruice and R. G. Willis, *J. Am. Chem. Soc.*, 1965, **87**, 531. [c] Error limits are standard deviations. [d] This study. [e] Mean deviation. [f] Thermodynamic pK_a from reference 6 and parenthesized values are pK_a. [g] A. R. Becker, D. J. Richardson, and T. C. Bruice, *J. Am. Chem. Soc.*, 1977, **99**, 5058, and k_2 = 801 ± 74 dm^6 mol^{-2} s^{-1}.

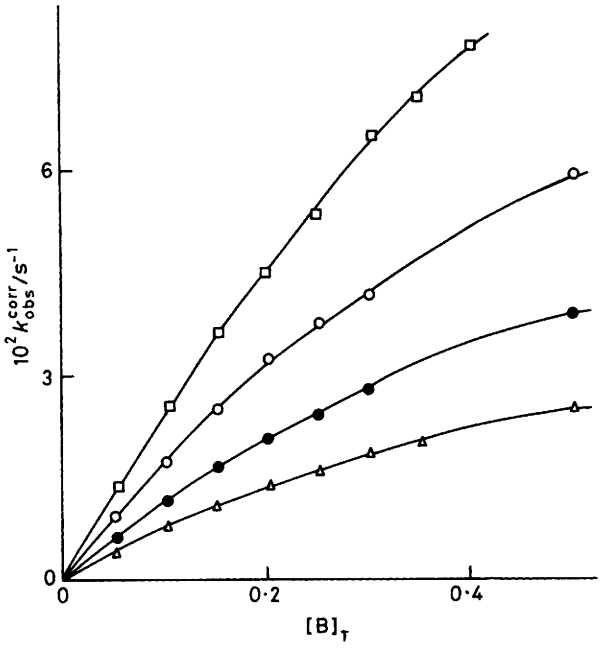


Figure 2. Plots of k_{obs}^{corr} *versus* $[B]_T$ for the nucleophilic cleavage of ECPH at a constant $[NH_2OH]_T$ of 2×10^{-3}M and at pH 4.68 (△), 4.99 (●), 5.17 (○), and 5.44 (□). The solid lines are drawn through the least-squares-calculated points using equation (8)

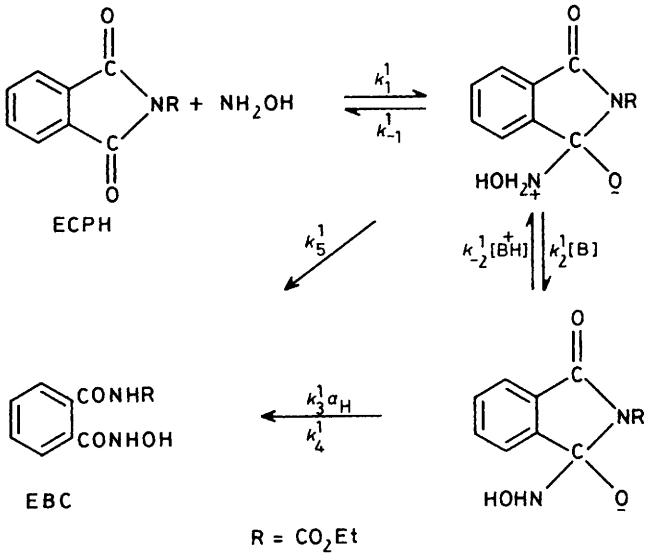
Table 3. The values of empirical parameters calculated from equation (8)[a]

pH	$10^2 A_1$/ dm^3 mol^{-1} s^{-1}	$10 A_2$/ dm^3 mol^{-1}	$[B]_T^b$ range	No. of runs
4.68 ± 0.01[c]	8.60 ± 0.22[c]	14.4 ± 1.1[c]	0.05—0.50	8
4.99 ± 0.02	13.0 ± 0.2	13.5 ± 0.8	0.05—0.50	8
5.17 ± 0.01	20.2 ± 0.6	14.2 ± 1.2	0.05—0.50	7
5.44 ± 0.02	27.2 ± 1.2	10.1 ± 1.8	0.05—0.40	8

[a] $[ECPH]_0$ 2×10^{-4}M, $[NH_2OH]_T$ 2×10^{-3}M, ionic strength is 1.0M, and 30 °C. [b] Total acetate buffer concentration range. [c] Error limits are standard deviations.

absence of hydroxylamine. In equation (8) $[B]_T$ represents the total acetate buffer concentration. The unknown parameters, A_1 and A_2, were calculated from equation (8) using the non-linear least-squares technique and the results thus obtained are summarized in Table 3. The fitting of the observed data to equation (8) is evident from the plots of Figure 2 where solid lines are drawn through the least-squares-calculated points.

The effect of acetate buffer concentrations on corrected first-order rate constants, k_{obs}^{corr}, for hydroxylaminolysis of ECPH revealed a sharp increase in k_{obs}^{corr} at low total buffer concentrations $[B]_T$ followed by a slow increase at considerably high $[B]_T$ (Figure 2). Such a non-linear dependence of k_{obs}^{corr} on $[B]_T$ reveals a change in the rate-determining step with a change in the catalyst concentration which in turn implies the formation of an intermediate on the reaction co-ordinate.[10–13] The other possible reason for the non-linear dependence such as a change in pH with change in $[B]_T$ may be ruled out by the fact that the pH was found to remain essentially constant within the observed $[B]_T$ range. Another possible reason for the non-linear dependence is that the acetate undergoes some kind of complexation with itself or with the substrate. But this possibility seems to be unlikely for the reason that such complexation could not be detected in other acetate-catalysed reactions[14–16] as well as acetate-catalysed cleavage of ECPH. The simplest mechanism which may explain the observed results is shown in the Scheme. The derived rate law,



Scheme.

based on the proposed mechanism (Scheme), is used to obtain equation (9) where $K_1^1 = k_1^1/k_{-1}^1$, $f_{bAc} = K_a^{Acetic}/(a_H + K_a^{Acetic})$,

$$k_{obs}^{corr} = \frac{K_1^1 k_2^1 f_{bAc} f_{bAm} [NH_2OH]_T [B]_T (k_4^1 + k_3^1 a_H)}{k_4^1 + k_3^1 a_H + k_{-2}^1 f_{aAc} [B]_T} \quad (9)$$

$f_{aAc} = 1 - f_{bAc}$, $f_{bAm} = K_a^{NH_2OH}/(a_H + K_a^{NH_2OH})$, $[B]_T$ and $[NH_2OH]_T$ are the total concentrations of acetate buffer and hydroxylamine, respectively, and K_a^{Acetic} and $K_a^{NH_2OH}$ represent the ionization constants of acetic acid and conjugate acid of

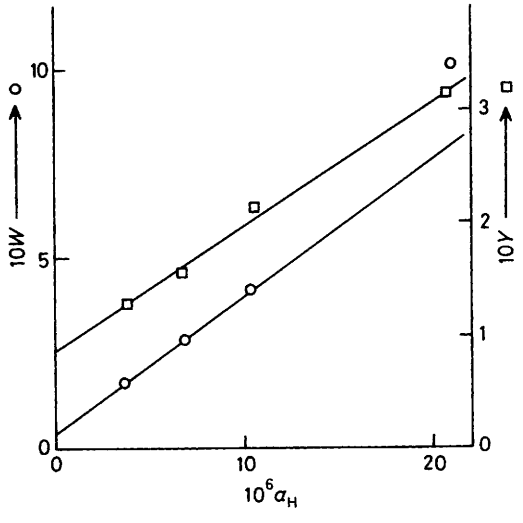


Figure 3. Plots showing the dependence of W and Y *versus* a_H for the reactions of ECPH with hydroxylamine under the presence of acetate buffer. $W = A_1 f_{aAc}/(A_2 f_{bAc} f_{bAm})$ and $Y = f_{aAc}/A_2$ where f_{aAc} is the fraction of non-ionized acetic acid in acetate buffer, $f_{bAc} = 1 - f_{aAc}$ and f_{bAm} is the fraction of free hydroxylamine in the acetate buffer. The solid lines are drawn through the least-squares-calculated points as described in the text

hydroxylamine, respectively. Equation (9) is similar to equation (8) with

$$A_1 = K_1^1 k_2^1 f_{aAc} f_{bAm}[NH_2OH]_T \quad (10)$$

and

$$A_2 = k_{-2}^1 f_{aAc}/(k_4^1 + k_3^1 a_H) \quad (11)$$

It is evident from equation (11) that a plot of f_{aAc}/A_2 *versus* a_H should be linear. Such a plot as shown in Figure 3 is essentially linear within the observed pH range. The least-squares-calculated values of intercept (k_4^1/k_{-2}^1) and slope (k_3^1/k_{-2}^1) are (8.42 ± 1.25) × 10^{-2}M and (1.12 ± 0.10) × 10^4, respectively. Equations (10) and (11) also predict that the plot of $f_{aAc}A_1/(A_2 f_{bAc} f_{bAm})$ *versus* a_H should be linear. Such a plot as shown in Figure 3 seems to be linear within the pH range 4.99—5.44. The experimental point at pH 4.68 significantly deviates from linearity. The calculated values of $A_1 f_{aAc}/(A_2 f_{bAc} f_{bAm})$ at pH 4.68, 4.99, and 5.17 are probably prone to considerable error because of the very low values of f_{bAm} at these pH. For example, the value of f_{bAm} at pH 4.68 is 0.049 and a change of this value from 0.049—0.069 will decrease the calculated value of $A_1 f_{aAc}/(A_2 f_{bAc} f_{bAm})$ by *ca.* 40%. The calculated values of the intercept ($K_1^1 k_2^1 k_4^1 [NH_2OH]_T/k_{-2}^1$) and slope ($K_1^1 k_2^1 k_3^1 [NH_2OH]_T/k_{-2}^1$) of the plot of $A_1 f_{aAc}/(A_2 f_{bAc} f_{bAm})$ *versus* a_H (based on the data points within the pH range 4.99—5.44) are (3.5 ± 0.8) × 10^{-2} s^{-1} and (3.7 ± 0.1) × 10^4 dm^3 mol^{-1} s^{-1}, respectively. Significantly low standard deviations of calculated intercept and slope are fortuitous for the reason described before.

The results obtained for the hydroxylaminolysis of ECPH in the presence of varying concentrations of acetate buffer, $[B]_T$, at constant pH may be rationalized in terms of a change in the rate-determining step with a change in $[B]_T$. At sufficiently low $[B]_T$, $k_4^1 + k_3^1 a_H > k_{-2}^1[\overset{+}{B}H]$ ($[\overset{+}{B}H]$ is the concentration of non-ionized acetic acid) which leads to the k_2^1 step as the rate-determining step and at sufficiently high $[B]_T$, $k_4^1 + k_3^1 a_H < k_{-2}^1[\overset{+}{B}H]$ and this leads to k_4^1- and k_3^1-steps as the rate-determining steps. Such a change in the rate-determining step could not be detected in the nucleophilic cleavage of ECPH in buffer solutions of hydroxylamine and the reasons for this may be given as follows: (i) the uncatalysed term [k_n, equation (2)] forms a significantly high contribution compared with the catalysed one [k_{gb}, equation (2)] under the experimental conditions employed, and (ii) the high reactivity of hydroxylamine did not allow an increase of the total hydroxylamine buffer concentrations, $[B]_T$, to an extent where the condition $k_{-2}^1[B]_T > k_4^1 + k_3^1 a_H$ could be satisfied. Thus, under the present experimental conditions of hydroxylaminolysis $k_{-2}^1[B]_T < k_4^1 + k_3^1 a^H$ and this leads to the k_2^1 step as the rate-determining step. Hence, from equation (2) and the Scheme, $k_{gb} = K_1^1 k_2^1$.

Reaction with Morpholine.—The morpholinolysis of ECPH was studied by carrying out kinetic runs in buffer solutions of morpholine at various pH. The observed first-order rate constants, k_{obs}, reasonably obeyed equation (12) where $[Am]_T$

$$k_{obs} - k_o = k_n[Am]_T \quad (12)$$

represents the total morpholine buffer concentration, k_n is the buffer-dependent second-order rate constant, and k_o is the buffer-independent first-order rate constant. The values of k_o at different pH were calculated from equation (3). The values of k_n at different pH were calculated from equation (12) using linear least-squares technique and the results obtained are summarized in Table 4. The fitting of the observed data to equation (12) is evident from the standard deviations of k_n values (Table 4).

Table 4. Apparent second-order rate constants for the reactions of amine nucleophiles with *N*-ethoxycarbonylphthalimide (ECPH)[a]

Amine	pH	10^3 k_n/ dm^3 mol^{-1} s^{-1}	$[Am]_T^b$ range M	No. of Runs
Ethylenediamine	7.12	2.51 ± 0.19[c]	0.1—0.7	5
	7.35	6.15 ± 0.35	0.1—0.7	5
	7.53	12.2 ± 0.5	0.1—0.7	5
	7.75	21.4 ± 0.8	0.1—0.6	5
	7.96	35.6 ± 1.1	0.1—0.6	5
	8.21	66.8 ± 1.9	0.1—0.7	5
1,4-Diazabicyclo[2.2.2]-octane	3.72	0.291 ± 0.019	0.1—0.7	5
	4.41	0.365 ± 0.033	0.1—0.7	5
	8.06	37.6 ± 1.0	0.01—0.30[d]	9
	8.31	60.4 ± 1.7	0.05—0.35	5
	8.63	111 ± 2	0.05—0.25	5
	8.66	97.1 ± 0.6	0.05—0.25	5
Piperazine	5.86	1.60 ± 0.01	0.05—0.35	5
	6.22	2.47 ± 0.04	0.05—0.35	5
	6.65	3.59 ± 0.06	0.047—0.329	5
	7.03	5.22 ± 0.11	0.05—0.35	5
Morpholine	8.24	18.1 ± 0.4	0.1—0.7	5
	8.44	22.2 ± 0.5	0.1—0.5	5
	8.71	47.1 ± 3.9	0.1—0.5	5

[a–c] Notation have the same meanings as mentioned in Table 1 except ionic strength is 1.5M. [d] Ionic strength is 1.0M.

The general rate law for the reactions or morpholine with ECPH may be given as

$$-\frac{d[Sub]_T}{dt} = (k_o + k_1[Am])[Sub]_T \quad (13)$$

where k_o is the buffer-independent first-order rate constant and k_1 is the nucleophilic second-order rate constant. The observed rate law: $-d[Sub]_T/df = k_{obs}[Sub]_T$ and equation (13) can be used to obtain (14) where f_{bAm} represents

$$k_{obs} - k_o = k_1 f_{bAm}[Am]_T \quad (14)$$

the fraction of free morpholine base and $[Am]_T$ is the total morpholine buffer concentration. Comparison of equations (12) and (14) gives equation (6). The value of k_1 as shown in Table 2 was calculated from equation (6) using least-squares technique.

Reaction with Diamines.—A series of kinetic runs was carried out at different pH in buffer solutions of piperazine, 1,4-diazabicyclo[2.2.2]octane and ethylenediamine. The observed first-order rate constants, k_{obs}, were found to fit to equation (12). The values of k_n at different pH were calculated from equation (12) which are summarized in Table 4. The fitting of the observed data to equation (12) is evident from the plots shown in Figure 4 for a typical amine and from standards deviations associated with k_n values (Table 4).

The general rate law for the nucleophilic cleavage of ECPH in buffer solutions of diamines may be given as

$$-\frac{d[Sub]_T}{dt} = (k_o + k_1[H_2N\overset{+}{R}NH_3] + k_3[H_2NRNH_2])[Sub]_T \quad (15)$$

where $[H_2N\overset{+}{R}NH_3]$ and $[H_2NRNH_2]$ represent the concentrations of monoprotonated and non-protonated diamines, respectively. The observed rate law (rate = k_{obs}-

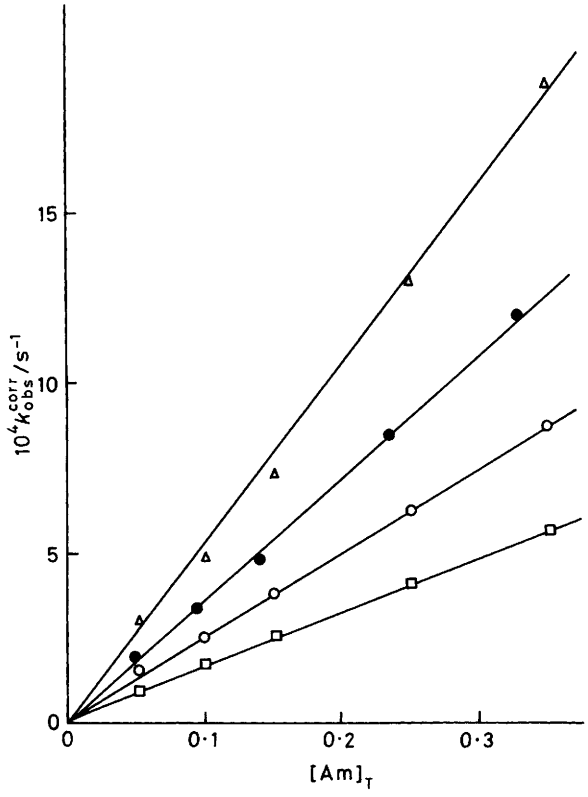


Figure 4. Plots of k_{obs}^{corr} ($= k_{obs} - k_o$) *versus* $[Am]_T$ for the reactions of ECPH with piperazine at pH 5.86 (□), 6.22 (○), 6.65 (●), and 7.03 (△). The solid lines are drawn through the least-squares-calculated points using equation (12)

$[Sub]_T$) and equations (12) and (15) were used to derive equation (16)* where $Q = a_H^2 + a_H K_1 + K_1 K_2$ and K_1 and K_2 are the ionization constants of di- and mono-protonated diamines, respectively.

$$k_n Q = k_3 K_1 K_2 + k_1 K_1 a_H \qquad (16)$$

The observed data for ethylenediamine and piperazine obeyed equation (16) and the least-squares-calculated respective values of $k_3 K_1 K_2$ (or $k_3 \gamma\gamma' K_1 K_2$ for piperazine) and $k_1 K_1$ (or $k_1 \gamma' K_1$ for piperazine) are $(16.2 \pm 1.4) \times 10^{-18}$ dm^3 mol^{-1} s^{-1} and $(7.13 \pm 3.54) \times 10^{-11}$ s^{-1} for ethylenediamine and $(10.8 \pm 1.1) \times 10^{-17}$ dm^3 mol^{-1} s^{-1} and $(2.54 \pm 0.02) \times 10^{-9}$ s^{-1} for piperazine. The calculated values of $k_3 K_1 K_2$ and $k_1 K_1$ were used to calculate k_3 and k_1 with known values of K_1 and K_2. These results are summarized in Table 2. The relatively high standard deviation (*ca.* 50%) of $k_1 K_1$ for ethylenediamine and the fact that its maximum contribution toward $k_n Q$ [equation (16)] is only *ca.* 20% (at pH 7.12) indicate that the calculated value of k_1 from $k_1 K_1$ is not very reliable.

* For piperazine whose thermodynamic ionization constants are used, equation (16) is changed to

$$k_n Q' = k_3 \gamma\gamma' K_1 K_2 + k_1 \gamma' K_1 a_H$$

where $Q' = \gamma a_H^2 + \gamma' a_H K_1 + \gamma\gamma' K_1 K_2$ and γ and γ' are the activity coefficients of mono- and di-protonated diamines, respectively. The values of γ (0.70) and γ' (0.25) at 1.0M ionic strength were calculated using the Davies equation.[17]

† The maximum contributions of k_3 term toward $k_n Q$ are *ca.* 30% at pH 7.03 for piperazine and *ca.* 100% at pH ≥ 7.96 for ethylenediamine.

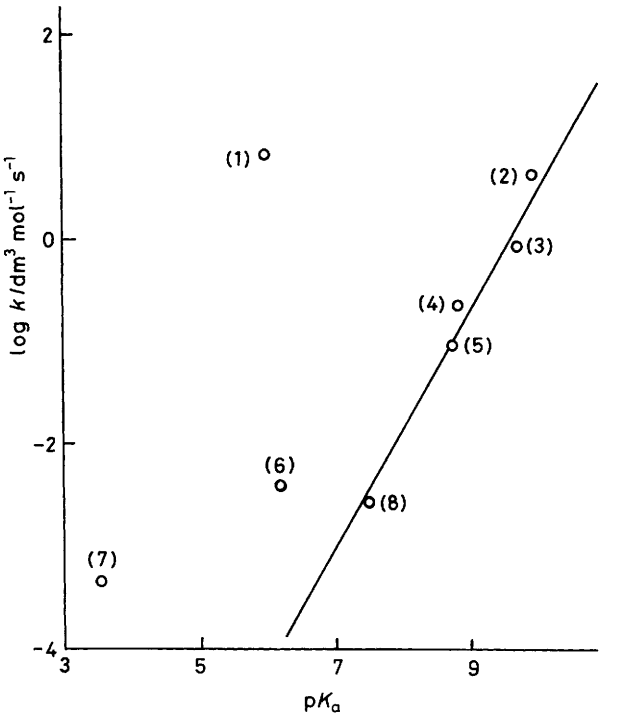


Figure 5. The dependence of the nucleophilic second-order rate constants (k_1 and k_3) for the reactions of ECPH with amine nucleophiles on the pK_a of the conjugate acid of the amine at 30 °C. The solid line is drawn through the least-squares-calculated points using Brønsted equation with slope (β_{nuc}) 1.2 and intercept (C) −11.3 dm^3 mn^{-1} s^{-1}. Statistical corrections to pK_2, and k_3 were made in the Brønsted plot for the reactivities of piperazine, 1,4-diazabicyclo[2.2.2]-octane, and ethylenediamine. In the Brønsted plot: (1) hydroxylamine, (2) ethylenediamine, (3) piperazine, (4) 1,4-ethanopiperazine, (5) morpholine, (6) piperazine-M$^+$, (7) 1,4-ethanopiperazine-H$^+$, (8) ethylenediamine-H$^+$

Unlike piperazine and ethylenediamine, the observed data on 1,4-diazabicyclo[2.2.2]octane could be analysed separately for pK_1 (pH 3.72 and 4.41) and pK_2 (pH 8.06—8.66). The values of k_n fit to equation (6) and the calculated values of k_1 and k_3 corresponding to pK_1 and pK_2 are shown in Table 2. The insignificant contribution of k_3 term compared with k_1 term [equation (15)] within the pH range of 3.72—4.41 for 1,4-diazabicyclo[2.2.2]octane and significant contributions of k_3 term† compared with k_1 term within the pH ranges 5.86—7.03 for piperazine and 7.12—8.21 for 1,2-diaminoethane may be attributed to the values of Δ pK ($= pK_2 - pK_1$) for these amines. The higher value of Δ pK (5.56) for 1,4-diazabicyclo-[2.2.2]octane compared with those for piperazine (Δ pK 4.26) and ethylenediamine (Δ pK 2.65) permits the study separately of the nucleophilic reactivities of unprotonated and monoprotonated forms of 1,4-diazabicyclo[2.2.2]octane.

It is essential to note that the $k_3[H_2NRNH_2]$ term [equation (15)] is kinetically indistinguishable from $k_{OH}[H_2NRNH_3^+][^-OH]$. But based on the observed fact that k_{OH} term could not be detected in the reactions of ECPH with morpholine and hydroxylamine, we presume the non-occurrence of such a term in the reactions with monoprotonated diamines also.

Brønsted Plot.—The second-order nucleophilic rate constants, k_1 and k_3, are shown graphically in Figure 5. A straight line (Brønsted plot) passing through the points for ethylenediamine, 1,4-diazabicyclo[2.2.2]octane, piperazine, and morpholine result in a slope (β_{nuc}) 1.2 ± 0.3 and intercept (C)

-11.3 ± 2.7 dm^3 mol^{-1} s^{-1}. The calculated value of β_{nuc} is based only on four observed points which cover a rather narrow range of pK_a values for the nucleophiles and hence it may not be considered to be reliable. However, it is comparable with those β_{nuc} which have been obtained in the related reactions such as the aminolyses of benzylpenicillin[18] ($\beta_{nuc} = 1.0$) and maleimide[3] ($\beta_{nuc} = 0.8$). The observed points for the positively charged nucleophiles (monoprotonated piperazine, 1,4-diazabicyclo[2.2.2]octane, and ethylenediamine) were not considered in the calculation of β_{nuc} because such nucleophiles may be expected to exhibit different reactivity compared with neutral nucleophiles of similar basicity.[19] The rate constant (k_1) for the reaction of monoprotonated ethylenediamine seems to fit to the Brønsted plot. But this is considered to be fortuitous since the k_1 value for this amine has been shown earlier to be unreliable. As usual, the α-effect nucleophile, hydroxylamine, exhibited nearly 10^5-fold larger reactivity compared with other amine nucleophiles of similar basicity which could fit to the Brønsted plot as shown in Figure 5.

The significantly high value of β_{nuc} (1.2) indicates that the expulsion of leaving group (k_5^1 step, Scheme) is the rate-determining step.[6,20–22] The α-effect nitrogen nucleophiles have been observed to exhibit abnormally high reactivity in nucleophilic addition–elimination reactions (at the carbonyl carbon) where expulsion of the leaving group is the rate-determining step.[23–25] But in those reactions where nucleophilic attack is rate-determining, these nucleophiles have exhibited considerably small rate enhancements (*ca.* 2- to 13-fold).[18,26] Thus, the appearance of nearly 10^5-fold higher reactivity of hydroxylamine is probably the consequence of the expulsion of the leaving group as the rate-determining step in the k_5^1 step (Scheme). Kinetically, in order for the k_5^1 step to be the rate-determining step, it is essential that $k_{-1}^1 > k_5^1$. The rate constant, k_{-1}^1 may be considered to be larger than k_5^1 for at least two reasons (i) the pK_a of the leaving in k_5^1 step is obviously larger than that in the k_5^1 step,[27] (ii) the push experienced by the leaving group in the k_{-1}^1 step is apparently larger than in the k_5^1 step.[28] However, these effects may be offset to some extent by the relief of the structural strain (if any due to the five-membered ring) in k_5^1 step.

Acknowledgements

I am grateful to the Research and Higher Degree Committee of Bayero University for a research grant to purchase the u.v.–visible spectrophotometer.

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Received 6*th April* 1987; *Paper* 7/602