# Effects of *N*-Alkyl Substitution on the Formation and Rate-limiting Deprotonation of the Spiro-Meisenheimer Intermediate of Smiles Rearrangement of 2-(*p*-Nitrophenoxy)ethylamine, in Aqueous Solution

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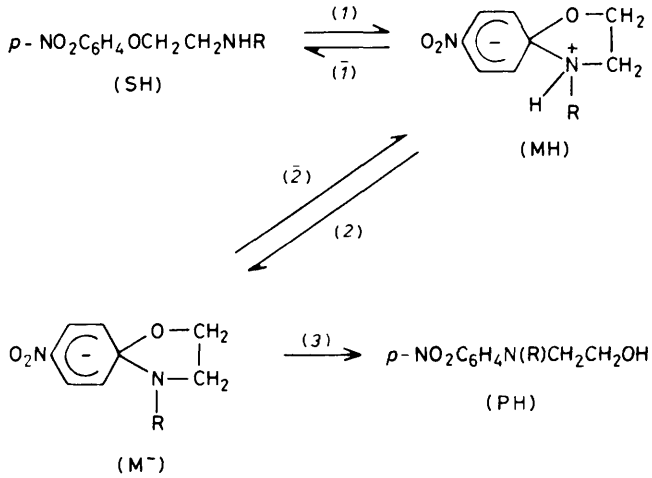
For intramolecular rearrangement of 2-(*p*-nitrophenoxy)ethylamines to the corresponding 2-(*p*-nitroanilino)ethanols the kinetic effects of *N*-alkyl substitution have been interpreted in terms of a mechanism whereby base-independent formation of a spiro-Meisenheimer intermediate is rate determined at high base concentrations but general-base-catalysed deprotonation of the intermediate (β 0.18—0.35) becomes rate determining at low base concentration. Reactions of the *N*-ethyl and *N*-isopropyl substrates are further complicated by a change to a specific-base-catalysed mechanism in ethanolamine buffers of high concentration; this observation requires that formation of the product by ring opening of the anionic spiro-Meisenheimer intermediate is not sensitive to general-acid catalysis.

In the preceding paper[1] we reported the kinetics of formation of 2-(*p*-nitroanilino)ethanol ($PH_a$) by Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine ($SH_a$) in aqueous alkali (Scheme 1). The observed general-base catalysis and tendency to approach a rate limit ($k_1$) at high base concentrations is qualitatively consistent with *either* the specific-base general-acid-catalysed (SB–GA) mechanism [kinetic expression (1)] or with a process whereby rate-limiting deprotonation (r.l.d.) of the Meisenheimer intermediate (MH) is followed by rapid conversion of $M^-$ into product PH [kinetic expression (2)].

$$k_A = \{(1)(2)/[(\bar{1}) + (2)]\}(3)/(3) + (\bar{1})(\bar{2})/[(\bar{1}) + (2)]\} \quad (1)$$

$$k_A = (1)(2)/[(\bar{1}) + (2)] \quad (2)$$

Estimates of the probable magnitudes of (3) and ($\bar{2}$), by extrapolation from values reported for analogous di- and trinitro systems, are consistent with requirements [(3) > ($\bar{2}$)] of the latter r.l.d. mechanism; furthermore, we have established[2] that kinetics of reaction of $SH_e$ (which incorporates a base catalyst as a 'neighbouring group') can only be interpreted successfully if the r.l.d. mechanism is assumed. Consequently we believe that the kinetics of Smiles rearrangement of $SH_a$ are governed by expression (2). In this paper we report the effects of *N*-alkyl substitution on the kinetics of reaction of substrates $SH_{a-d}$ for which the r.l.d. mechanism is necessarily assumed.




a; R = H
b; R = Me
c; R = Et
d; R = Pr$^i$
e; R = $CH_2CH_2NHCH_2CH_2NH_2$

(1) = $k_1$
(1̄) = $k_{-1}$
(2) = $k_2 + k_2^{OH}[OH^-] + \sum k_2^{Bi}[B_i]$
(2̄) = $k_{-2}[H^+] + k_{-2}^{OH} + \sum k_{-2}^{Bi}[B_iH^+]$
(3) = $k_3[H^+] + k_3^{OH} + k_3^{Bi}[B_iH^+]$

**Scheme 1.**

## Experimental

*N*-Alkyl-2-(*p*-nitrophenoxy)ethylamines $SH_{b-d}$ were prepared by reaction of *p*-chloronitrobenzene with the corresponding sodium 2-(alkylamino)ethoxide in dimethyl sulphoxide.[3]

It has already been indirectly established[4,5] that the corresponding *N*-alkyl-2-(*p*-nitroanilino)ethanols are obtained in high yield upon Smiles rearrangement of $SH_{b-d}$ in aqueous sodium hydroxide. Kinetics of rearrangement of $SH_{b-d}$ were determined at 60 °C by the procedure described for $SH_a$ in the preceding paper.[1] For each substrate we have determined the dependence of $k_A$ on (i) the hydroxide ion concentration in the absence of other bases, and (ii) the concentration of individual bases ($B_i$) in the presence of sufficient hydroxide ion (0.01M) to ensure (*i.e.* pH ≥ $pK_a^{SH_2} + 1$) that the substrate SH remains unprotonated. The results obtained for $SH_{b-d}$ are in Tables 1—3, respectively.

For each substrate we have also determined the kinetic dependence upon buffer concentration for reactions in ethanolamine buffer solutions (pH 9.5 at 25 °C; pH *ca.* 8.58 at 60 °C). The results are in Table 4.

## Discussion

By steady-state treatment[6] of the reaction scheme where it is assumed that (1̄)(2̄) ≪ (3) we obtain equation (2); the reaction should correspondingly be catalysed by general bases and approach a rate limit ($k_A \rightarrow k_1$) at high base concentrations [(2) ≫ (1̄)]. For hydroxide concentrations in excess of *ca.*

**Table 1.** Rate constants ($k_A$) for Smiles rearrangement of *N*-methyl-2-(*p*-nitrophenoxy)ethylamine $SH_b$ in aqueous base solutions at 60 °C (μ 1.0; $KNO_3$)

| Base | [Base]/M | $10^4 k_A/s^{-1}$ | $0.1k_A^{-1}/s$ | $k_1/k_A$ | $y = 1/\{(k_1/k_A) - 1\}$ | Correlations* |
|---|---|---|---|---|---|---|
| NaOH | 1.0 | 507 | 1.97 | 1.01 | 84.5 | |
| | 0.5 | 451 | 2.22 | 1.14 | 7.27 | |
| | 0.25 | 420 | 2.38 | 1.22 | 4.52 | $d = 0.91$ mol s l$^{-1}$ |
| | 0.1 | 357 | 2.80 | 1.44 | 2.29 | $e = 19.5 \pm 1.0$ s |
| | 0.01 | 90 | 11.1 | 5.7 | 0.213 | $\therefore k_1 = (5.13 \pm 0.25) \times 10^{-2}$ s$^{-1}$ |
| | 0.001 | 7.0 | 143.0 | 73.3 | 0.014 | $\therefore k_2^{OH}/k_{-1} = 21.3 \pm 1.5$ l mol$^{-1}$ |
| Ethanolamine | 1.0 | 360 | 2.78 | 1.43 | 2.33 | |
| (+0.01M-NaOH) | 0.5 | 280 | 3.57 | 1.84 | 1.19 | $l = k_2^B/k_{-1} = 2.0 \pm 0.01$ l mol$^{-1}$ |
| | 0.25 | 220 | 4.55 | 2.33 | 0.75 | $m = 0.26 + 0.02$ |
| | 0.1 | 160 | 6.25 | 3.22 | 0.451 | $\therefore k_2/k_{-1} = 0.047 \pm 0.035$ |
| | 0.01 | 117 | 8.55 | 4.40 | 0.294 | |
| | 0.001 | 106 | 9.48 | 4.88 | 0.258 | |
| Morpholine | 1.0 | 262 | 3.82 | 1.96 | 1.05 | |
| (+0.01M-NaOH) | 0.5 | 207 | 4.83 | 2.49 | 0.672 | $l = k_2^B/k_{-1} = 0.80 \pm 0.04$ l mol$^{-1}$ |
| | 0.25 | 169 | 5.92 | 3.05 | 0.489 | $m = 0.26 \pm 0.02$ |
| | 0.1 | 125 | 8.00 | 4.12 | 0.321 | $\therefore k_2/k_{-1} = 0.047 \pm 0.035$ |
| | 0.01 | 117 | 8.55 | 4.40 | 0.294 | |
| | 0.001 | 107 | 9.35 | 4.81 | 0.262 | |
| Morpholine | 1.0 | 192 | 5.21 | 2.67 | 0.598 | |
| (+0.001M-NaOH) | 0.5 | 155 | 6.45 | 3.30 | 0.434 | $l = k_2^B/k_{-1} = 0.75 \pm 0.03$ l mol$^{-1}$ |
| | 0.25 | 102 | 9.80 | 5.03 | 0.248 | $m = 0.05 \pm 0.015$ |
| | 0.1 | 54 | 18.5 | 9.5 | 0.118 | $\therefore k_2/k_{-1} = 0.03 \pm 0.015$ |
| | 0.01 | 32 | 31.2 | 16.0 | 0.067 | |

* See equations (3) and (8), and Figures 1 and 4.

**Table 2.** Rate constants ($k_A$) for Smiles rearrangement of *N*-ethyl-2-(*p*-nitrophenoxy)ethylamine $SH_c$ in aqueous base solution of 60 °C (μ 1.0; $KNO_3$)

| Base | [Base]/M | $10^4 k_A/s^{-1}$ | $0.1k_A^{-1}/s$ | $k_1/k_A$ | $y = 1/\{(k_1/k_A) - 1\}$ | Correlations* |
|---|---|---|---|---|---|---|
| NaOH | 1.0 | 469 | 2.13 | 1.07 | 15.13 | |
| | 0.5 | 451 | 2.22 | 1.11 | 9.20 | $d = 1.30$ mol s l$^{-1}$ |
| | 0.25 | 426 | 2.35 | 1.17 | 5.76 | $e = 20.0 \pm 1.0$ s |
| | 0.1 | 325 | 3.08 | 1.54 | 1.86 | $\therefore k_1 = (5.00 \pm 0.25) \times 10^{-2}$ s$^{-1}$ |
| | 0.01 | 66.3 | 15.1 | 7.54 | 0.153 | $\therefore k_2^{OH}/k_{-1} = 15.4 \pm 0.8$ l mol$^{-1}$ |
| | 0.001 | 4.12 | 243 | 121 | 0.008 | |
| Morpholine | 1.0 | 100 | 10.0 | 5.00 | 0.250 | |
| (+0.001M-NaOH) | 0.5 | 80.0 | 12.5 | 6.25 | 0.191 | $l = k_2^B/k_{-1} = 0.29 \pm 0.01$ mol l$^{-1}$ |
| | 0.25 | 58.2 | 17.2 | 8.60 | 0.131 | $m = 0.045 \pm 0.01$ |
| | 0.1 | 32.5 | 30.8 | 15.4 | 0.0695 | $\therefore k_2/k_{-1} = 0.03 \pm 0.01$ |
| | 0.01 | 23.0 | 43.5 | 21.7 | 0.0484 | |

* See equations (3) and (8), and Figures 2 and 5.

0.01M ($k_2 \ll k_2^{OH}[OH^-]$) the relationship (3) should be found,

$$1/k_A = d/[OH^-] + e \quad (3)$$

where $d = k_{-1}/k_1k_2^{OH}$ and $e = 1/k_1$. At low base concentrations, where (7) ≫ (2), we obtain $k_A \rightarrow (1)(2)/(7) = (k_2 + k_2^{OH}[OH^-])k_1/k_{-1} + k_2^{B_i}[B_i]k_1/k_{-1}$. Thus, in the absence of bases $B_i$ the relationship (4) should hold (where $f = k_1k_2^{OH}/k_{-1}$

$$k_A = f[OH^-] + g \quad (4)$$

and $g = k_1k_2/k_{-1}$) while for reaction with a single base B at constant pH we obtain equation (5) where $h = k_1k_2^B/k_{-1}$

$$k_A = h[B] + i \quad (5)$$

and $i = k_1(k_2 + k_2^{OH}[OH^-])/k_{-1}$.

Equation (2) can, however, be reorganised to give (6) which is applicable throughout the complete range of base concentrations. Equation (6) can be conveniently used in forms (7) and (8) where $j = k_2^{OH}/k_{-1}$, $k = k_2/k_{-1}$, and hydroxide ion is

$$y = 1/\{(k_1/k_A) - 1\} = k_2/k_{-1} + k_2^{OH}[OH^-]/k_{-1} + \Sigma k_2^{B_i}[B_i]/k_{-1} \quad (6)$$

$$y = j[OH^-] + k \quad (7)$$

$$y = l[B] + m \quad (8)$$

the only base catalyst, and where $l = k_3^B/k_{-1}$, $m = (k_2 + k_2^{OH}[OH^-])/k_{-1}$, and the reaction is catalysed by a general base B at constant pH.

For each of the substrates $SH_{a-d}$ we have generally used equation (3) in order to determine the kinetic constants $k_1$ and $k_2^{OH}/k_{-1}$, from the rectilinear correlations which are obtained; it has subsequently been convenient to use equation (8) in order to obtain $k_2^B/k_{-1}$ for each of the bases employed. The constants so obtained (from the rate constants in Table 1—3) are in Table 5.

It is clear that for each substrate $SH_{a-d}$ the rearrangement is subject to general-base catalysis and (see Figures 1—3) approaches a rate limit at high base concentration. The rate

**Table 3.** Rate constants ($k_A$) for Smiles rearrangement of *N*-isopropyl-2-(*p*-nitrophenoxy)ethylamine $SH_d$ in aqueous base solutions at 60 °C (μ 1.0; KNO 3)

| Base | [Base]/M | $10^4 k_A$/s$^{-1}$ | $0.1k_A^{-1}$/s | $k_1/k_A$ | $y = 1/\{(k_1/k_A) - 1\}$ | Correlations* |
|---|---|---|---|---|---|---|
| NaOH | 1.0 | 88.0 | 11.4 | 1.14 | 7.33 | |
| | 0.5 | 77.2 | 13.0 | 1.30 | 3.39 | |
| | 0.25 | 67.1 | 14.9 | 1.49 | 2.04 | $d$ = 14.6 mol s l$^{-1}$ |
| | 0.1 | 42.6 | 23.5 | 2.35 | 0.74 | $e$ = 100 ± 5 s |
| | 0.01 | 6.4 | 156 | 15.6 | 0.07 | ∴ $k_1$ = (1.00 ± 0.05) × 10$^{-2}$ s$^{-1}$ |
| | 0.001 | 0.465 | 2 150 | 215 | 0.004 | ∴ $k_2^{OH}/k_1$ = 6.85 ± 0.35 l mol$^{-1}$ |
| Ethanolamine (+0.01M-NaOH) | 1.0 | 21.4 | 46.7 | 4.67 | 0.272 | |
| | 0.5 | 15.7 | 63.7 | 6.37 | 0.186 | |
| | 0.25 | 11.7 | 85.5 | 8.55 | 0.132 | $l = k_2^B/k_1$ = 0.26 ± 0.01 l mol$^{-1}$ |
| | 0.1 | 8.70 | 115 | 11.5 | 0.095 | $m$ = 0.065 ± 0.005 |
| | 0.01 | 6.20 | 161 | 16.1 | 0.066 | ∴ $k_2/k_1$ = <0.005 |
| | 0.001 | 6.00 | 167 | 16.7 | 0.064 | |
| Morpholine (+0.01M-NaOH) | 1.0 | 12.0 | 83.3 | 8.33 | 0.136 | |
| | 0.5 | 9.00 | 111 | 11.1 | 0.099 | |
| | 0.25 | 7.65 | 131 | 13.1 | 0.083 | $l = k_2^B/k_1$ = 0.072 ± 0.003 l mol$^{-1}$ |
| | 0.1 | 6.70 | 149 | 14.9 | 0.072 | $m$ = 0.065 ± 0.001 |
| | 0.01 | 6.15 | 164 | 16.4 | 0.065 | ∴ $k_2/k_1$ = <0.002 |
| | 0.001 | 6.00 | 167 | 16.7 | 0.064 | |

* See equations (3) and (8), and Figures 3 and 6.

**Table 4.** Rate constants* ($k_A$) for Smiles rearrangement of *N*-alkyl-2-(*p*-nitrophenoxy)ethylamines $SH_{b-d}$ in aqueous ethanolamine buffer solutions ([B] = [$BH^+$]) at 60 °C (μ 1.0; $KNO_3$; $pK_a^{60°}$ pH 8.576†)

| Substrate | [B]/M | $10^4 k_A$/s$^{-1}$ | $0.1k_A^{-1}$/s$^{-1}$ | $k'_A$/s | $k_1/k'_A$ | $y$‡ | Correlations§ |
|---|---|---|---|---|---|---|---|
| $SH_b$ | 1.0 | 160 | 6.25 | 336 | 1.526 | 1.90 | |
| | 0.5 | 111 | 9.01 | 233 | 2.20 | 0.834 | $l = k^B/k_1$ = 1.81 l mol$^{-1}$ |
| | 0.25 | 73 | 13.7 | 153 | 3.345 | 0.426 | $m$ = 0.02 ± 0.01 |
| | 0.1 | 42 | 23.8 | 88.1 | 5.83 | 0.207 | (where $k_1$ = 5.13 × 10$^{-2}$ s$^{-1}$) |
| | 0.01 | 5.8 | 172 | 12.2 | 42.0 | 0.024 | |
| $SH_c$ | 1.0 | 58.0 | 17.2 | 126 | 3.97 | 0.337 | |
| | 0.5 | 49.5 | 20.2 | 107 | 4.65 | 0.274 | $l^¶ = k^B/k_1$ = 0.7 l mol$^{-1}$ |
| | 0.25 | 34.0 | 29.4 | 73.9 | 6.76 | 0.173 | $m$ = 0.01 ± 0.005 |
| | 0.1 | 17.6 | 56.8 | 38.2 | 13.1 | 0.083 | (where $k_1$ = 5.00 × 10$^{-2}$ s$^{-1}$) |
| | 0.01 | 3.0 | 333 | 6.52 | 76.6 | 0.013 | |
| $SH_d$ | 1.0 | 4.51 | 222 | 10.7 | 9.36 | 0.120 | $l^¶ = k^B/k_1$ = 0.26 ± 0.02 l mol$^{-1}$ |
| | 0.5 | 3.80 | 263 | 9.00 | 11.1 | 0.099 | $m$ = 0.005 ± 0.002 |
| | 0.25 | 2.64 | 379 | 6.25 | 16.0 | 0.067 | (where $k_1$ = 1.00 × 10$^{-2}$ s$^{-1}$) |
| | 0.1 | 1.36 | 735 | 3.22 | 31.1 | 0.033 | |
| | 0.01 | 0.22 | 4 540 | 0.52 | 192 | 0.005 | |

* Rate constants $k'_A$ are those for reaction of the unprotonated substrate; these have been obtained by multiplying $k_A$ by the factor $[1/(1 + a_{H^+}/K_a^{SH_2})]$ = 2.10, 2.175, and 2.368 in the case of $SH_{b-d}$ for which the conjugate acids ($SH_2$) are believed to have $pK_a^{60°}$ 8.616, 8.646, and 8.706, respectively [*i.e.* the value[1] $pK_a^{60°}$ 8.046 for $SH_a$ augmented by 0.57, 0.60, and 0.66 units to take account of *N*-methyl, *N*-ethyl, and *N*-isopropyl substitution. The correction factors were estimated as follows: The $pK_a$ values[7a] for ethanolamine and its *N*-methyl and *N*-ethyl derivatives at 25 °C are 9.498, 9.85, and 9.88, respectively; the effect of *N*-ethylation ($\Delta pK_a^{25°}$ 0.35) is greater at 50 °C, for which the $pK_a$ values for ethanolamine and its *N*-ethyl derivative are 8.813 and 9.306 ($\Delta pK_a^{50°}$ 0.49), and we have correspondingly assumed that $\Delta pK_a^{60°} \approx 0.6$. A change from *N*-ethyl to *N*-isopropyl should increase the basicity of the nitrogen by *ca.* 0.06 p*K* units: *cf.*[7a] $Pr^iNHCH_2CH_2NH_2$, $pK_{a1}^{25}$ 10.62; $EtNHCH_2CH_2NH_2$, $pK_{a1}^{25}$ 10.56; $Pr^iNHCH_2CH_2NHPr^i$, $pK_{a1}^{0°}$ 11.12; $EtNHCH_2CH_2NHEt$, $pK_{a1}^{0°}$ 11.06.] † Obtained by extrapolating results[7a] for 0—50 °C. ‡ $y = 1/\{(k_1/k'_A) - 1\}$. § See equation (8) and Figures 4 and 6. ¶ This is the initial slope of a curvilinear plot (Figures 5 and 6).

limit is expected to correspond to the rate of formation $k_1$ of the Meisenheimer intermediate MH, by intramolecular addition of the nucleophile to the activated aromatic ring. Even in the presence of high concentrations of ethanolamine or morpholine the maximum attainable rate constant may, however, fall short of $k_1$ under conditions where the substrate is appreciably protonated; under these circumstances $k_A^{max.}$ becomes $k_1[K_a^{SH_2}/(K_a^{SH_2} + a_{H^+})]$. It is apparent (see Figures 1—3), from the results in Table 4, that limiting values of $k_A$ obtained for reactions of $SH_{b-d}$ catalysed by 1.0M-ethanolamine at a buffer pH = 8.58* fall far short of those obtained for reactions catalysed by a solution of ethanolamine (1.0M) and sodium hydroxide (0.01M). That this is mainly a consequence of partial protonation of the substrate is consistent with the much greater discrepancy observed for $SH_{b-d}$ than for the less basic primary-amino-ether $SH_a$ under the same conditions.

The $pK_a$ values for the conjugate acids of the bases $SH_{b-d}$ have been estimated to be 8.62, 8.65, and 8.71, respectively (see footnote to Table 4); thus, it has been possible to correct the experimental rate constants $k_A$ to take account of the partial protonation of each substrate in ethanolamine buffer solutions. The corrected values, $k'_A$, have been used (in conjuction with the appropriate value of $k_1$) to evaluate $y$ (Table 4). The plot of $y$ *versus* [ethanolamine] for $SH_b$ is rectilinear and of near identical slope ($k_2^B/k_{-1}$) to that obtained for reactions in ethanolamine solutions which contain sodium hydroxide

* By extrapolation of $pK_a$ values[7a] for ethanolamine at 0—50 °C.

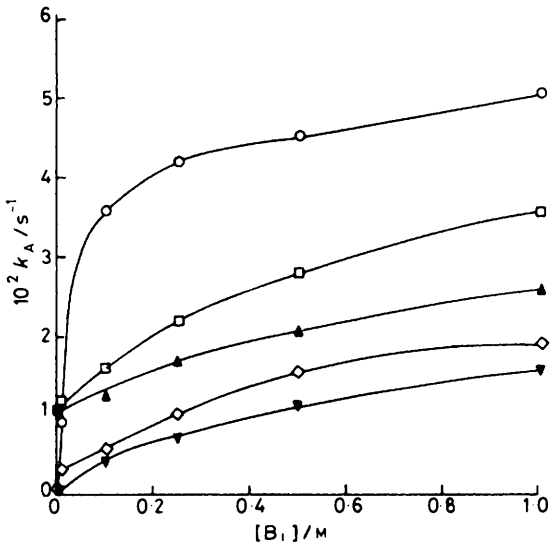



**Figure 1.** Dependence of the rate constants (see Tables 1 and 4) for Smiles rearrangement of $SH_b$ on the concentration of the catalysing base [$B_i$], in water at 60 °C (μ 1.0): ○ hydroxide ion; □ ethanolamine (in the presence of 0.01M-NaOH); ▲ morpholine (in the presence of 0.01M-NaOH); ◇ morpholine (in the presence of 0.001M-NaOH); ▼ ethanolamine buffer

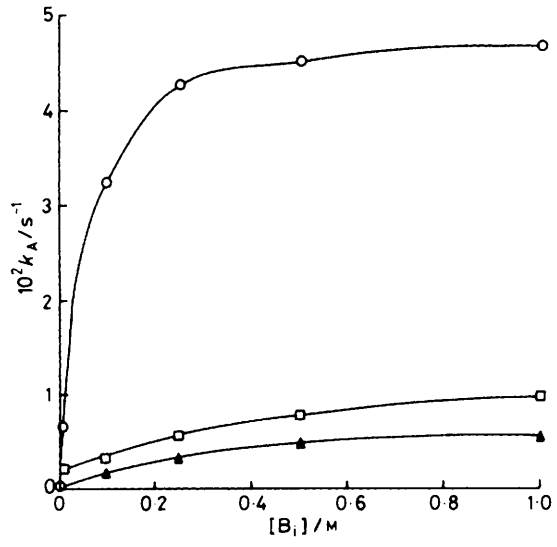



**Figure 2.** Dependence of the rate constants (see Tables 2 and 4) for Smiles rearrangement of $SH_c$ on the concentration of the catalysing base [$B_i$], in water at 60 °C (μ 1.0): ○ hydroxide ion; □ morpholine (in the presence of 0.001M-NaOH); ▲ ethanolamine buffer

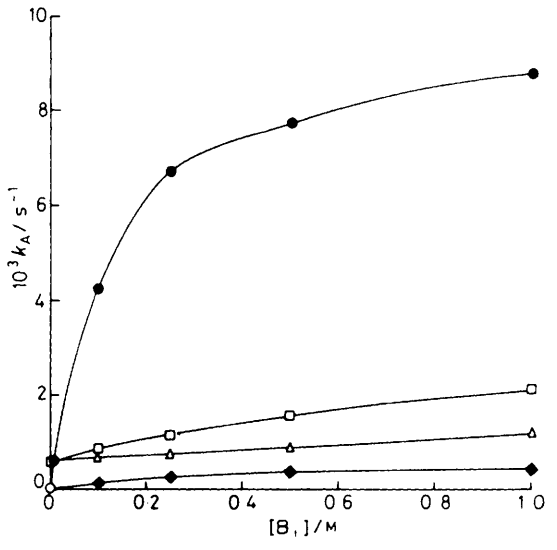



**Figure 3.** Dependence of the rate constants (see Tables 3 and 4) for Smiles rearrangement of $SH_d$ on the concentration of the catalysing base [$B_i$], in water at 60 °C (μ 1.0): ● hydroxide; □ ethanolamine (in the presence of 0.01M-NaOH); △ morpholine (in the presence of 0.01M-NaOH); ◆ ethanolamine buffer

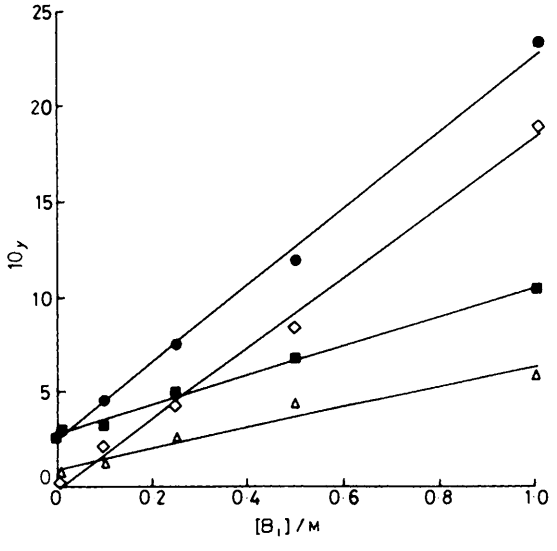



**Figure 4.** Rectilinear relationships of the form $y = l[B_i] + m$ (see Tables 1 and 4) for Smiles rearrangement of ($SH_b$) catalysed by bases $B_i$ in water at 60 °C (μ 1.0); $y = 1/\{(k_1/k_A) - 1\}$: ● ethanolamine (in the presence of 0.01M-NaOH); ■ morpholine (in the presence of 0.01M-NaOH); △ morpholine (in the presence of 0.001M-NaOH); ◇ ethanolamine buffer

(0.01M); although this implies that the reaction rate is subject to general-base catalysis it does not permit distinction between the SB–GA mechanism and one whereby general-base-catalysed deprotonation of NH is rate limiting. In this context, the results obtained for reactions of $SH_c$ and $SH_d$ (see Figures 5 and 6) are of considerable interest; in each case there is a curvilinear relationship between $y$ (based on $k'_A$) and [ethanolamine]. This behaviour is inconsistent with the single operation of either of the alternative mechanisms of general-base catalysis but can be readily explained if it is assumed that a mechanistic change occurs, as the buffer concentration is increased. Thus, from equation (1) we obtain (9) which has two well defined extremes:

$$y = 1/\{(k_1/k_A) - 1\} = (2)(3)/[(\bar{1})(3) + (\bar{1})(\bar{2})] \quad (9)$$

(i) $(\bar{2}) \ll (3)$, therefore $y \rightarrow (2)/(\bar{1})$; *i.e.* equation (6) which applies to a mechanism whereby general-base-catalysed deprotonation of MH is rate limiting and (ii) $(\bar{2}) \gg (3)$, therefore $y \rightarrow (2)(3)/(\bar{1})(\bar{2})$, *i.e.* a pre-equilibrium mechanism whereby MH and $M^-$ equilibrate prior to the conversion of $M^-$ into PH; where the latter step is general-acid-catalysed we have the SB-GA mechanism.

It has already been argued that for $SH_a$ an analysis

**Table 5.** Kinetic constants for intramolecular rearrangement of $p$-$NO_2C_6H_4OCH_2CH_2NHR$ (SH) catalysed by general bases* in water at 60 °C and μ 1.0 ($KNO_3$)

| | | Rate ratios§ (l mol$^{-1}$) | | | |
|---|---|---|---|---|---|
| R(SH) | $10^4k_1$/s$^{-1}$ | $k_2^{OH}/k_{-1}$ | $k_2^{E}/k_{-1}$ | $k_2^{M}k_{-1}$ | β† |
| H($SH_a$)‡ | 8.2 | 239 (1.0)[a] (1.0)[b] | 42.5 (5.6)[a] (1.0)[b] | 14.3 (16.7)[a] (1.0)[b] | 0.22—0.35 |
| Me($SH_b$) | 513 | 21.3 (1.0)[b] (11.2)[b] | 2.0 (10.7)[a] (21.3)[b] | 0.80 (26.6)[a] (17.8)[b] | *ca.* 0.18 |
| Et($SH_c$) | 500 | 15.4 (1.0)[a] (15.5)[b] | | 0.29 (53.1)[a] (49.3)[b] | |
| Pr$^i$($SH_d$) | 100 | 6.85 (1.0)[a] (34.9)[b] | 0.26 (26.3)[a] (163)[b] | 0.072 (95.1)[a] (199)[b] | *ca.* 0.25 |

* See correlations depicted in Tables 1—3. † Brønsted coefficient estimated from a plot of $\log(k_2^{B}/k_{-1})$ *versus* $pK_a^{BH}$ where B = $HO^-$, ethanolamine, morpholine, and (where R = H) acetate ion; the $pK_a^{BH}$ values used (14.77, 8.58, 7.74, and 4.81, respectively) are those[7a,b] for 60 °C. ‡ See ref. 1. § $k_2^{OH}$, $k_2^{E}$, and $k_2^{M}$ are catalytic rate constants $k_2^{B}$ where B = hydroxide ion, ethanolamine and morpholine respectively. All values are ±3—5%. [a] $(k_2^{OH}/k_{-1})/(k_2^{B}/k_{-1}) = k_2^{OH}/k_2^{B}$ for SH. [b] $(k_2^{B}/k_{-1})$ for $SH_a$ divided by $(k_2^{B}/k_{-1})$ for SH.

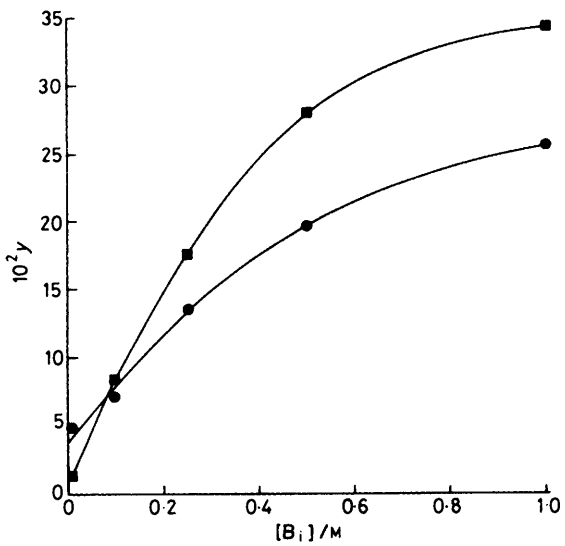



**Figure 5.** Relationships between $y$ and [$B_i$] (see Tables 2 and 4) for Smiles rearrangement of $SH_c$ catalysed by bases $B_i$ in water at 60 °C (μ 1.0); $y = 1/\{(k/k_A) - 1\}$: ● morpholine (in the presence of 0.001M-NaOH); ■ ethanolamine buffer

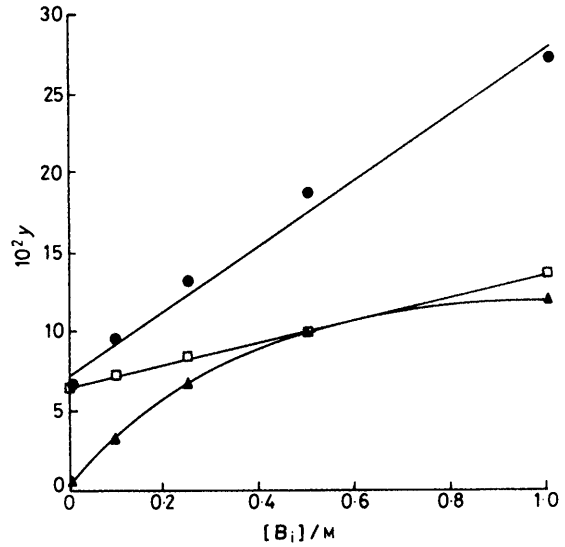



**Figure 6.** Relationships between $y$ and [$B_i$] (see Tables 3 and 4) for Smiles rearrangement of $SH_d$ catalysed by bases $B_i$ in water at 60 °C (μ 1.0); $y = 1/\{(k/k_A) - 1\}$: ● ethanolamine (in the presence of 0.01M-NaOH); □ morpholine (in the presence of 0.01M-NaOH); ▲ ethanolamine buffer

according to extreme (i) is appropriate; analogous behaviour is to be expected for reactions of $SH_{b-d}$, particularly for those reactions which are promoted by general bases at high pH (*e.g.* 0.01M-hydroxide background). There is no reason to suppose that $y$ would approach a limiting value at high concentration of the general base, unless the equation for its dependence should alter.

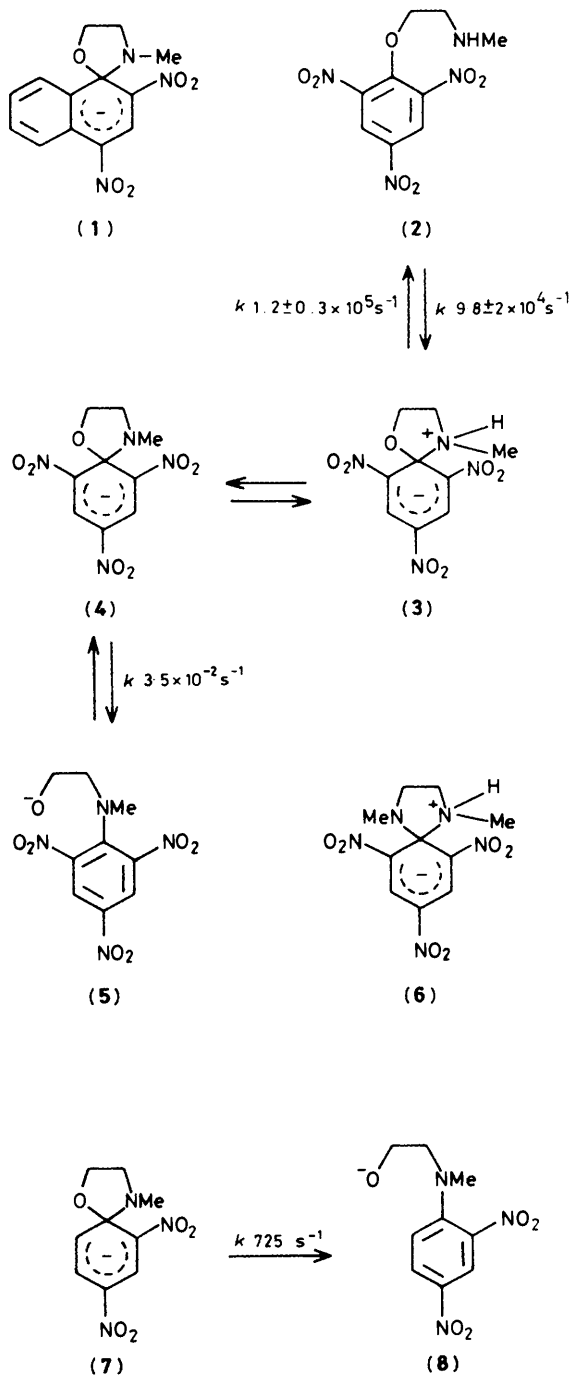
Alteration of the base dependence could, however, be caused by factors which enhance the contribution of the denominator term (1)(2), of equation (9). Thus, for example, for reactions conducted at constant pH but increasing buffer concentration the magnitude of (1)(2) could increase relative to (1)(3), provided (2) is more sensitive than (3) to the increase in concentration of buffer acid ($BH^+$). At high buffer concentration the dependence of $y$ would be given by (2)(3)/(1)(2) for extreme (ii) above.

It is apparent (see Figures 5 and 6) that for reaction of both $SH_c$ and $SH_d$, in ethanolamine buffers, $y$ approaches a maximum value at high buffer concentration. The suggested analysis requires that $y$ appproach (2)(3)/(1)(2) and it must therefore be concluded that for $SH_c$ and $SH_d$ (3) is independent of [B] and [$BH^+$], since (2)/(1)(2) is expected to be constant at fixed pH.

This is an important result since it implies that ring opening of the Meisenheimer intermediate $M^-$ is promoted predominantly by solvent, rather than by the general acid $BH^+$, even at concentrations up to 1M. In other words, *the SB–GA mechanism does not apply to this system* and its role in intermolecular analogues of this reaction must therefore be questioned. Bernasconi has reached a similar conclusion,[8] based on direct observation of the ring opening of (1), for which the respective catalytic efficacies of butylammonium ion and acetic acid are only *ca.* 2.2 and 7.3 (relative to the solvent, water).

It should be noted that the SB mechanism, which is that believed to account for the behaviour of $SH_{c,d}$ at high concentrations of ethanolamine buffer, has seldom been suggested to account for reaction of amines which activated aromatic substrates in protic solvents.[8]

Our claim that a mechanistic change from extreme (i) to (ii) occurs which increasing concentration of the ethanolamine




**Scheme 2.**

buffer at pH 8.58 is also supported by measurements of the initial slope of the plot of *y versus* [ethanolamine]. Thus, for $SH_b$ and $SH_d$, the initial slope $[k_2^B/k_{-1}$, according to equation (6) for extreme (ii)] for reaction in ethanolamine buffers (Table 4) is in close agreement with the slope of the corresponding rectilinear plot for reaction with ethanolamine in the presence of 0.01M-sodium hydroxide (Tables 1 and 3).

It is interesting that there is an increasing tendency for (7)(2) to compete with (7)(3) in the denominator of equation (9) as the *N*-alkyl substituent changes from Me($SH_b$) to Et($SH_c$) or Pr$^i$($SH_d$). This may be a straightforward consequence of increased nitrogen basicity (with concomitant increase of $k_{-2}^B$), brought about by the increasing $+I$ effect of the alkyl substituent ($\sigma^*$ 0.0, −0.10, and −0.19 for Me, Et, and Pr$^i$, respectively). Alternatively, since it is well known[9] that ring closure is entropically favoured by alkyl substituents on the acyclic chain, the effect of *N*-alkyl substituents of increasing size may be to decrease the rate of ring opening of $M^-$. Either or both of these effects could account for an increase in the ratio (2)/(3) with the change of *N*-alkyl substituent from Me to Et and Pr$^i$.

*Rates of Cyclisation* ($k_1$).—The sixty-fold increase of $k_1$ (Table 5) which is caused by *N*-alkylation (R = Me or Et) of the parent substrate ($SH_a$) can be attributed to enhanced nitrogen nucleophilicity. This effect of inductive electron donation may, however, be partially offset by the unfavourable steric effect of the alkyl substituent. Thus, the net rate enhancement is only 12-fold when R = Pr$^i$. These competing factors find parallel in intermolecular $S_NAr$ reactions of amine nucleophiles with *p*-chloronitrobenzene in ethanol.[10] The intramolecular reactions are, however, less sensitive to steric retardation; this may be tentatively attributed to compensating entropic advantage for ring closure of an acyclic chain which bears additional substituents.[9] It is not surprising that the $k_1$ value $5.13 \times 10^{-2}$ s$^{-1}$ for $SH_b$ is much smaller than for conversion of the analogous trinitro-activated system (2) into (3), for which the value $k_1 = 9.8 \pm 2 \times 10^4$ s$^{-1}$ ($T$ 25 °C) has been estimated.[11]

*Rate Ratios* ($k_2^B/k_{-1}$) *for Deprotonation of MH.*—For each substrate ($SH_{a-d}$) the logarithms of rate ratios ($k_2^B/k_{-1}$) have been plotted against the p$K_a$ of the corresponding base catalyst (hydroxide, ethanolamine, morpholine, and, in the case of $SH_a$, acetate anion) in order to determine the corresponding Brønsted coefficient for deprotonation of NH.

For $SH_a$ there is a good linear relationship between the results for ethanolamine, morpholine and acetate ion (β 0.35) but the catalytic effect of hydroxide is less than expected on this basis (β 0.20 when the hydroxide result is included). For each of the *N*-alkyl substrates ($SH_{b,d}$) the pattern of distribution of points for morpholine, ethanolamine, and hydroxide is comparable with that for $SH_a$ and the corresponding values β 0.18 and 0.25 have been determined. It is our intention to extend this study to include a wider range of base catalysts. It is already clear, however, that the reaction rate is relatively insensitive to the base strength of the catalyst; this, combined with the curvilinear nature of each Brønsted plot, is typical of proton-transfer reactions which proceeded at close to the diffusion-controlled rate limit.[12]

For a particular base B, the variation in $k_2^B/k_{-1}$ brought about by change of the *N*-substituent (R) must reflect the increase with the size of either the alkyl substituent or the base catalyst. The latter trend is well illustrated by the values of $k_2^{OH}/k_2^B$ for each substrate $SH_{a-d}$ (figures in parentheses in Table 5 which bear the superscript a). Thus, the ratios $k_2^{OH}/k_2^B$ for $SH_a$ are much less sensitive to the structure of B than are those for $SH_{b-d}$; the sensitivity increases steadily with the size of the alkyl substituent, as illustrated by the ratios $k_2^{OH}/k_2^M$ = 16.7, 26.6, 53.1, and 95.1 for $SH_{a-d}$, respectively.

*Rate Constants* $k_{-1}$.—It is reasonable to assume that for each substrate the rate constant of deprotonation of the Meisenheimer intermediate MH, by hydroxide ion, should approach the diffusion-controlled limit $k_2^{OH}$ *ca.* $10^{10}$ l mol$^{-1}$ s$^{-1}$; on this basis the values $10^{-7}$ $k_{-1}$ = *ca.* 4.2, 47, 65, and 146 s$^{-1}$ have been estimated for reaction of $SH_{a-d}$, respectively. Thus, $k_{-1}$ is very large and apparently increases with the size of the *N*-alkyl substituent. This large value is consistent with $k$ = $(1.2 \pm 0.3) \times 10^5$ s$^{-1}$ and $1.93 \times 10^5$ s$^{-1}$ for ring opening of

(3) and (6), respectively,[11,13] since it is reasonable to suppose that the mononitro system may expel the amino group several orders of magnitude faster than does the more stable trinitro system. For example, the rate of expulsion of methoxide ion from its Meisenheimer complex with 2,4-dinitroanisole occurs *ca.* $4 \times 10^4$-fold faster than from its complex with 2,4,6-trinitroanisole, in methanol.[14] Our estimates of $k_{-1}$ (*ca.* $10^9$ $s^{-1}$ for $SH_{b-d}$) are close to the theoretical limit of *ca.* $10^{10}$ $s^{-1}$ previously anticipated[13] by Bernasconi for reactions of 1-X-4-nitrobenzenes with secondary amines.

*Rate Constants* $k_3$.—An approximate estimate of $k_3^{OH}$ can be obtained for $SH_{c,d}$ from the limits $y = (2)(3)/(\bar{1})(\bar{2})$ attained at high ethanolamine buffer concentrations, for which the SB mechanism is believed to operate. Thus, since $k_3^{OH}/k_{-1} = y(\bar{2})/(2) = y[H^+]/K_a^{MH}$, we require estimates of $k_{-1}$ (*ca.* $65 \times 10^7$ for $SH_c$, and $146 \times 10^7$ $s^{-1}$ for $SH_d$), $y$ (*ca.* 0.35 for $SH_c$, and 0.13 for $SH_d$ at pH 8.58), and $K_a^{MH}$. We correspondingly obtain $pk_3^{OH} = (0.21 - pK_a^{MH_c})$ for reaction of $SH_c$ and $pk_3^{OH} = (0.31 - pK_a^{MH_d})$ for reaction of $SH_d$.

It is probable* that $pK_a^{MH_d} \simeq pK_a^{MH_c} + 0.06$ and that the values of $k_3^{OH}$ for $SH_c$ and $SH_d$ are therefore very similar; this is consistent with our expectations. The magnitude of $pK_a^{MH_c}$ can be gauged by comparison with that[15] for (3) ($pK_a = 5.4 \pm 0.3$) which is *ca.* 3.5 p$K$ units less than that for the conjugate acid of the amino-ether from which it is derived.

It is to be expected that for a less activated system (fewer nitro groups) the p$K$ difference would be much smaller, say 1.5 p$K$ units; thus, it is reasonable to suppose that $pK_a^{MH_c} \simeq 8.65 - 1.5$ (where the conjugate acid of $SH_c$ has $pK_a$ 8.65 at 60 °C).

On this basis we obtain the approximate estimate $k_3^{OH} = 10^7$ $s^{-1}$ for both $SH_c$ and $SH_d$. This figure falls in line with direct estimates of the rates of ring opening (7)→(8) and (4)→(5) for which the rate constants 725 and $3.5 \times 10^{-2}$ $s^{-1}$ ($T$ 25 °C) have been estimated.[11,16,17] Thus, the rate constant for ring opening of $M^-$ decreases from $10^7 \rightarrow 10^3 \rightarrow 10^{-2}$ $s^{-1}$ as we change from mono- and di- and then tri-nitro systems.

* *Cf.* our estimates of the likely effect, on the $pK_a$ values for the conjugate acids of secondary amines, of a change from NEt to $NPr^i$, as outlined in a footnote in Table 4.

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