Interpretation of the Kinetics of General-base-catalysed Smiles Rearrangement of 2-(*p*-Nitrophenoxy)ethylamine into 2-(*p*-Nitroanilino)ethanol; Rate-limiting Deprotonation of a Spiro-Meisenheimer Intermediate[1]

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The intramolecular rearrangement of 2-(*p*-nitrophenoxy)ethylamine to 2-(*p*-nitroanilino)ethanol occurs by a general-base-catalysed process in aqueous alkali; the attainment of a base-independent rate limit at high base concentration can be attributed to rate-determining formation of a spiro-Meisenheimer intermediate. The reaction kinetics can be interpreted in terms of the specific-base–general-acid-catalysed mechanism or by invoking rate-determining deprotonation of the spiro-Meisenheimer intermediate; the latter interpretation provides the best explanation of the coefficient $\beta = 0.20—0.35$ and curvilinear form of the Brønsted correlation and is consistent with the kinetics of reactions of analogous polynitro systems reported by Bernasconi.

The role of Meisenheimer intermediates in S_NAr reactions has been established largely through kinetic investigation of reactions of primary and secondary amine nucleophiles with activated aromatic systems.[2—4] The Meisenheimer intermediate formed upon nucleophilic addition of an amine to an aryl halide must undergo net dehydrohalogenation in order to form the substitution product, whereas addition of an anionic nucleophile is followed by ejection of halide ion alone. Thus, it was by demonstration that decomposition of the intermediate of the former reaction was subject to general-base catalysis that Meisenheimer intermediates found more general acceptance.

The influence of base catalysis on the observed rate constant (k_{obs}) is generally of the form $k_{obs} = k' + k''[B]$, where k' is the rate constant for the uncatalysed process and k'' is that for reaction catalysed by base B. Two broad categories of base catalysis have been discerned:[2] thus, where the conjugate acid of the leaving group has $\mathrm{p}K_a < 3$ attack of the amine on the aryl ring is believed to be assisted by hydrogen bonding, which is relatively insensitive ($k''/k' < 50\ \mathrm{l\ mol^{-1}}$) to the base strength of the catalyst; in contrast, where k'' is more sensitive to base strength ($k''/k' > 50\ \mathrm{l\ mol^{-1}}$) the catalysis is generally ascribed to decomposition of a Meisenheimer intermediate. The latter behaviour has been reported only for relatively poor leaving groups ($\mathrm{p}K_a > 3$) for which the approach of k_{obs} to a rate limit, at high catalyst concentration, is a further distinctive feature.

Studies of general-base catalysis of *intermolecular* displacement reactions between amine nucleophiles and activated aromatic systems have often been complicated by onset of competing S_NAr reactions of the catalysts; consequently, few studies[4a] have unambiguously demonstrated both general-base catalysis and attainment of the expected rate limit at high catalyst concentration. In this regard it is advantageous to study the catalytic dependence of an analogous *intramolecular* reaction (Smiles rearrangement); we have established that, by virtue of the favourable neighbouring group effect, the amino function of 2-(*p*-nitrophenoxy)ethylamine is the most effective nucleophile for S_NAr substitution of this activated aryl ether even when the reaction is conducted in 1.0M aqueous sodium hydroxide.

A detailed investigation of the general-base dependence of the intramolecular (S_NAri) reaction of 2-(*p*-nitrophenoxy)ethylamine (SH) in aqueous solution at 60 °C is the topic of this paper. At low base concentrations the rate depends upon general-base-catalysed decomposition of a spiro-Meisenheimer intermediate (MH); a base-independent rate limit (for nucleophilic addition to the activated arene) is approached at high base concentrations. The mechanism of decomposition of MH is of considerable interest[4—7] since Bernasconi has established unequivocally that proton transfer from MH to a base catalyst is rate determining for intramolecular S_NAr reactions of *NN'*-dimethyl-*N*-(2,4-dinitrophenyl)ethylenediamine[5] and *NN'*-dimethyl-*N*-picrylethylenediamine;[6] he has consequently challenged the generality of the commonly accepted specific-base–general-acid-catalysed (SB–GA) mechanism of base catalysis in aromatic substitution by amine nucleophiles.[4b,7]

We have interpreted our results with reference to several alternative reaction schemes which are the subject of the following discussion. Alternative rate expressions have been presented at length since this analysis is intended to form a foundation for subsequent papers in which the solvent- and base-dependent behaviour of *N*-alkyl and *N*-aryl derivatives of SH will be discussed.

Experimental

2-(*p*-Nitrophenoxy)ethylamine (SH) was prepared[8,9] by reaction of *p*-chloronitrobenzene with sodium 2-aminoethoxide in dimethyl sulphoxide.

Kinetics of Rearrangement of SH to 2-(p-*Nitroanilino*)*ethanol* (*PH*).—The kinetics of rearrangement of SH ($\lambda_{max.}$ 315 nm) to PH ($\lambda_{max.}$ 410 nm) at 60 °C in aqueous alkaline solutions were followed spectrophotometrically. Reactions were initiated by addition of a solution (10 µl) of SH (0.015M, in acetonitrile) to the aqueous base solution (3 cm³) which had been thermostatted within the cell compartment of a Unicam spectrophotometer, model 1700; the increase in absorbance which occurred at 410 nm was monitored for more than seven half-lives of the rearrangement whereupon a computer (ICL 1903A) was used to determine the pseudo-first-order rate constant k_A by a least-squares analysis. Reactions were repeated in triplicate and the results in Tables 1 and 2 are average values of runs for which the correlation coefficient exceeded 0.998. In each case more than 50 data points were collected and the rate constants were reproducible to within ±1%. A calibrated thermistor was used to monitor the temperature of the reaction medium.

We have determined the dependence of k_A on (i) hydroxide ion (NaOH) concentration in the absence of other bases (Table 1), (ii) concentration of individual bases B_i in the presence of sufficient hydroxide ion (0.001M) to ensure (*i.e.* $\mathrm{pH} \geq \mathrm{p}K_a^{SH_2}$

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

Base	[Base]/M^{-1}	$10^5k_A/s^{-1}$	$10^{-2}k_A^{-1}/s$	$y = 1/\{(k_1/k_A) - 1\}$	Correlations *
NaOH	1.0	95.6	10.5		
	0.5	89.9	11.1		
	0.25	84.4	11.9		
	0.10	78.7	12.7	23.8	$d = 5.1 \pm 0.02$ mol s l^{-1}
	0.010	57.6	17.4	2.4	$e = 1\,220 \pm 2$ s
	0.005	44.4	22.5	1.18	$k_1 = (82 \pm 2) \times 10^{-5}$ s^{-1}
	0.0025	28.2	35.5	0.524	
	0.0010	16.2	61.7	0.246	$k_2^{OH}/k_{-1} = 239 \pm 10$ l mol^{-1}
Ethanolamine (+0.01M-NaOH)	1.0	83.0	12.1		
	0.5	83.0	12.1		
	0.25	83.0	12.1		
	0.1	83.0	12.1		
	0.01	74.0	13.5		
	0.001	69.0	14.5		
Morpholine (+0.01M-NaOH)	1.0	83.0	12.1		
	0.5	83.0	12.1		
	0.25	82.0	12.2		
	0.1	76.0	13.2		
	0.01	69.0	14.5		
	0.001	67.0	15.0		
Morpholine (+0.001M-NaOH)	1.0	76.6	13.1	14.2	$l = k_2^B/k_{-1} = 13 \pm 3$ l mol^{-1}
	0.5	71.0	14.1	6.45	
	0.25	66.0	15.2	4.13	$m = 0.9 \pm 0.5$
	0.1	61.9	16.2	3.08	
	0.01	40.5	24.7	0.98	$k_2/k_{-1} = 0.66 \pm 0.5$
NaOAc (+0.001M-NaOH)	1.0	53.0	18.9	1.82	$l = k_2^B/k_{-1} = 1.60 \pm 0.2$ l mol^{-1}
	0.5	40.8	24.5	0.99	
	0.25	31.8	31.4	0.633	$m = 0.23 \pm 0.03$
	0.1	23.3	42.9	0.397	
	0.01	15.8	63.3	0.239	$k_2/k_{-1} = 0.0 \pm 0.04$

* See Table 3; *d*, *e*, *l*, and *m* have been interpreted with respect to reaction condition *Aa*. See also Figures 2 and 3.

Table 2. Rate constants * (k_A) for Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine (SH) in aqueous buffer solutions ($[BH^+] = [B]$) at 60 °C (μ 1.0; KNO_3)

Base B	[B]/l mol^{-1}	$10^5k_A/s^{-1}$	$10^{-2}k_A^{-1}/s$	k'_A/s^{-1}	k_1/k'_A	*y*†	Correlations §
Ethanolamine $pK_a^{60°}$ 8.576‡	1.0	61.8	16.2	80.3	1.022	45.5	
	0.5	60.3	16.6	78.4	1.047	21.3	$l = k^B/k_{-1} = 42.5 \pm 2$ l mol^{-1}
	0.25	57.6	17.35	74.9	1.095	10.5	
	0.1	53.0	18.85	68.8	1.190	5.26	$m = < 2.0$
	0.01	20.2	49.5	26.3	3.12	0.47	
Morpholine $pK_a^{60°}$ 7.735‡	1.0	25.0	40.0	76.6	1.07	14.3	
	0.5	23.5	42.5	72.1	1.136	7.35	$l = k^B/k_{-1} = 14.3 \pm 0.5$ l mol^{-1}
	0.25	21.0	47.6	64.4	1.272	3.68	
	0.1	17.3	57.8	53.0	1.545	1.84	$m = 0.2 \pm 0.2$
	0.01	6.8	147	20.8	3.94	0.34	

* By extrapolation of a plot of $1/k_A$ against $1/[B]$ the value of $1/k_A^{max.}$ is obtained. For reactions in ethanolamine and morpholine buffer solutions $k_{max.}$ values (63.1×10^{-5} and 26.8×10^{-5} s^{-1}, respectively) are 22.8 and 67.4% less than $k_1 = 82.0 \times 10^{-5}$ s^{-1}; this has been attributed to partial protonation of SH_a, for which the estimates $pK_a^{60°} = 8.056$ and 8.055 are correspondingly obtained. Rate constants k'_A, which are obtained by multiplying k_A by 1.30 (ethanolamine) or 3.06 (morpholine) are those for reaction of the unprotonated substrate. † $y = 1/\{(k_1/k'_A) - 1\}$. ‡ Obtained by extrapolating results of 0—50 °C. § See Table 3; *l* and *m* have been interpreted with respect to reaction condition *Aa*. See also Figure 3.

+ 1) that the substrate SH remains unprotonated (Table 1), and (iii) the concentration of buffers $[B_i + B_iH^+]$ at constant pH = $pK_a^{B_iH^+}$ (Table 2); in each case the ionic strength was adjusted to μ = 1.00 by addition of potassium nitrate.

Synthesis of PH by Rearrangement of SH.—A solution of the amino-ether SH (0.3 g) in acetonitrile (1.0 cm^3) was added to a vigorously stirred solution of aqueous sodium hydroxide (100 cm^3; 0.5M) thermostatted at 60 °C. The reaction mixture was stirred for 3 h, saturated with sodium chloride, cooled, and shaken with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to give a near quantitative yield of PH, m.p. 109 °C; τ(CD_3COCD_3) 1.98 (2 H, d, *J* 9 Hz, *o*- to the NO_2 group), 3.3 (2 H, d, *J* 9 Hz, *o*- to the SO_2R group), and 6.1—6.8 (4 H, m, CH_2CH_2).

Discussion

Derivation of Alternative Kinetic Expressions for Rearrangement of SH to PH.—The following scheme depicts the manifold routes for conversion of the substrate amino-ether SH into the product hydroxyaniline PH. Individual steps have been indexed *n* = 1—7 and terms (*n*) and ($\bar{n}$) represent composite rate constants for foward and reverse steps, respectively, as defined below. Component rate constants of the terms (*n*) and ($\bar{n}$), respectively, bear subscripts *n* and $-n$; the nature of the corresponding base catalyst (OH^-, B_i) is indicated by an appropriate superscript (OH, B_i) except when a solvent molecule is involved. Thus, the rate of conversion of SH into M^- by reaction (*6*) is given by the expression:

$$\begin{aligned} \mathrm{Rate}_{(SH\rightarrow M^-)} &= (6)[SH] \\ &= (k_6 + k_6^{OH}[OH^-] + \Sigma k_6^{B_i}[B_i])[SH] \end{aligned}$$

The rate of the reverse reaction is given by the expression:

$$\begin{aligned} \mathrm{Rate}_{(M^-\rightarrow SH)} &= (\bar{6})[M^-] \\ &= (k_{-6}[H^+] + k_{-6}^{OH} + \Sigma k_{-6}^{B_i}[B_iH^+])[M^-] \end{aligned}$$

It is reasonable * to treat MH, M^-, and S^- as steady-state intermediates between SH and PH; thus, the kinetic expression † for the rate of formation of PH may be derived as follows:

$$\begin{aligned} d[PH]/dt &= (3)[M^-] \\ d[M^-] = 0 &= (2)[MH] + (6)[SH] + (5)[S^-] - [(\bar{2}) + (\bar{5}) + (\bar{6}) + (3)][M^-] \\ d[MH]/dt = 0 &= (1)[SH] + (\bar{2})[M^-] - [(2) + (\bar{1})][MH] \\ \therefore [MH] &= \{(1)[SH] + (\bar{2})[M^-]\}/[(\bar{1}) + (2)] \\ d[S^-]/dt = 0 &= (4)[SH] + (\bar{5})[M^-] - [(\bar{4}) + (5)][S^-] \\ \therefore [S^-] &= \{(4)[SH] + (\bar{5})[M^-]\}/[(\bar{4}) + (5)] \\ \therefore d[M^-]/dt = 0 &= (2)\{(1)[SH] + (\bar{2})[M^-]\}/[(\bar{1}) + (2)] + (6)[SH] + \\ &\quad \{(5)(4)[SH] + (5)(\bar{5})[M^-]\}/[(\bar{4}) + (5)] - [(\bar{2}) + (\bar{5}) + (\bar{6}) + (3)][M^-] \\ \therefore d[PH]/dt &= (3)[M^-] = \\ &\frac{\{(1)(2)/[(\bar{1}) + (2)] + (6) + (4)(5)/[(\bar{4}) + (5)]\}(3)[SH]}{[(\bar{2}) + (\bar{5}) + (\bar{6}) + (3)] - (2)(\bar{2})/[(\bar{1}) + (2)] - (5)(\bar{5})/[(\bar{4}) + (5)]} = \\ &\frac{\{(1)(2)/[(\bar{1}) + (2)] + (6) + (4)(5)/[(\bar{4}) + (5)]\}(3)[SH]}{(3) + (\bar{6}) + (\bar{1})(\bar{2})/[(\bar{1}) + (2)] + (\bar{4})(\bar{5})/[(\bar{4}) + (5)]} = k_A[SH] \quad (1) \end{aligned}$$

It is convenient to consider the following simplifying extremes: (*A*) $[(\bar{6}) + (\bar{1})(\bar{2}) + (\bar{4})(\bar{5})] \ll (\bar{3})$; thus, return of M^- to SH is much slower than is its conversion into product PH and we obtain:

$$k_A = \{(6) + (1)(2)/[(\bar{1}) + (2)] + (4)(5)/[(\bar{4}) + (5)]\}$$

Thus the rate of formation of PH becomes dependent upon the rate of formation of M^- by three routes, *i.e.* from SH by intramolecular nucleophilic addition either concentrated with proton loss, followed by proton loss (*via* MH) or preceded by proton loss (*via* S^-). This expression can be simplifed further, thus: (*Aa*). Consider the formation of PH *via* MH only:

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

The reaction is *subject to general-base catalysis but approaches a rate limit* ($k_A \rightarrow k_1$) at high base concentrations $[(2) \gg (\bar{1})]$.

(*Ab*) Consider the formation of PH to occur other than *via* MH:

$$\therefore k_A = (6) + (4)(5)/[(\bar{4}) + (5)]$$

The first and second terms correspond to general- and specific-base-catalysed routes respectively; no rate limit is to be expected as pH→*ca.* 14.

(*B*) $[(\bar{6}) + (\bar{1})(\bar{2}) + (\bar{4})(\bar{5})] <|< (3)$; thus, the rate of conversion of M^- into PH does not greatly exceed the rate of return of M^- to SH, and $k_A[SH]$ is given by the full expression (1). The expression can, however, be considerably simplified if only route SH→MH→M^-→PH is considered; thus:

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

The following limiting cases are of interest.

(*Ba*). When $(\bar{1}) \ll (2)$ [or $(3) \ll (\bar{2})$] and the rate of deprotonation of MH is correspondingly fast relative to its return to SH we obtain:

$$\begin{aligned} k_A &= (1)(2)(3)/[(2)(3) + (\bar{1})(\bar{2})] \\ &= [(1)(2)(3)/(\bar{2})]/[(\bar{1}) + (2)(3)/(\bar{2})] \\ &= \{(1)(3)K_a^{MH}/[H^+]\}/\{(\bar{1}) + (3)K_a^{MH}/[H^+]\} \\ &= \frac{k_1\{k_3K_a^{MH} + k_3^{OH}K_2^{OH}[OH^-] + k_3^{B_i}K_a^{MH}[B_i]/K_a^{B_iH}\}}{k_{-1} + \{k_3K_a^{MH} + k_3^{OH}K_2^{OH}[OH^-] + k_3^{B_i}K_a^{MH}[B_i]/K_a^{B_iH}\}} \end{aligned} \quad (3)$$

In equation (3) $K_a^{MH} = [M^-][H^+]/[MH]$ and $K_2^{OH} = k_2^{OH}/k_{-2}^{OH} = [M^-]/[MH][OH^-] = K_a^{MH}/K_w$.

Thus, the reaction is *subject to general-base catalysis but approaches a rate limit* ($k_A \rightarrow k_1$) at high base concentrations; at low base concentrations $(\bar{1}) <|< (2)$ and, since (*3*) may become $\ll (\bar{1})(\bar{2})/[(\bar{1}) + (2)]$, equation (2) approaches equation (4) to give equation (4) condition (*Bb*). Conditions (*Bb*) is that where

$$k_A = [(1)(2)/(\bar{1})(\bar{2})](3) \quad (4)$$

the rate of return of M^- to SH greatly exceeds the rate of conversion of M^- into PH, such that $(\bar{1})(\bar{2}) \gg (3)$, and a pre-equilibrium condition pertains: $k_A = (3)K_1K_a^{MH}/[H^+]$, where $K_1 = k_1/k_{-1}$ and $K_a^{MH}/[H^+] = K_2^{OH}[OH^-]$.

$$\therefore k_A = k_3K_1K_a^{MH} + k_3^{OH}K_1K_2^{OH}[OH^-] + [k_3^{B_i}K_1K_a^{MH}/K_a^{B_iH}][B_i]$$

An identical result would, of course, be obtained for (*Bb*) upon inclusion of (*4*), ($\bar{4}$), (*5*), ($\bar{5}$), (*6*), and ($\bar{6}$) as alternative routes for equilibration of SH and M^-.

We have demonstrated experimentally that Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine in aqueous alkali is subject to general-base catalysis (Table 1) and that the rate limit (see Figure 1) approached at high base concentration is common to the range of bases employed (Table 4). This behaviour is consistent with conditions *Aa* and *Ba* for which it is convenient to inspect the following correlations.

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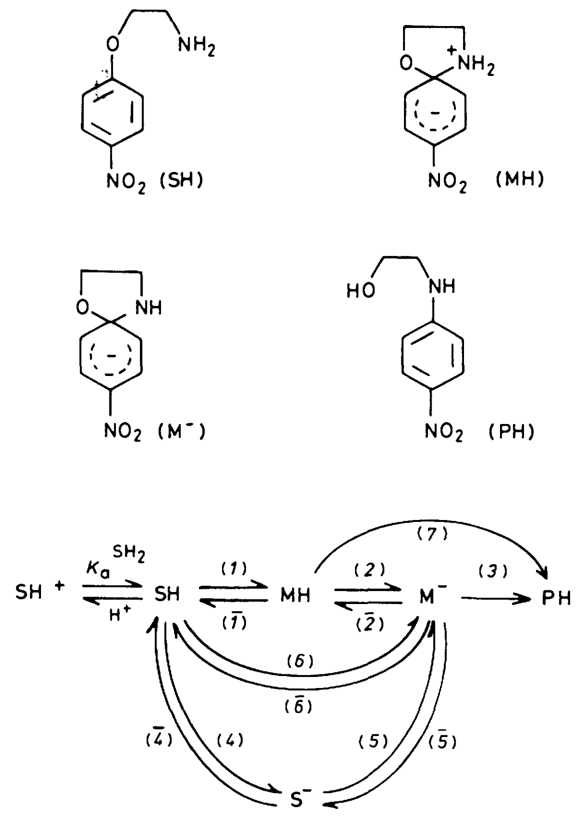
* We have been unable to detect MH, M^-, or S^- during spectroscopic investigation of the Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine.

† For mathematical convenience, route (*7*) has been omitted from this derivation; this will be given separate consideration.



$(1) = k_1$
$(2) = k_2 + k_2^{OH}[OH^-] + \sum k_2^{B_i}[B_i]$
$(3) = k_3[H^+] + k_3^{OH} + k_3^{B_i}[B_iH^+]$
$(4) = k_4 + k_4^{OH}[OH^-] + \sum k_4^{B_i}[B_i]$
$(5) = k_5$
$(6) = k_6 + k_6^{OH}[OH^-] + \sum k_6^{B_i}[B_i]$
$(7) = k_7 + k_7^{OH}[OH^-] + \sum k_7^{B_i}[B_i]$
$(\bar{1}) = k_{-1}$
$(\bar{2}) = k_{-2}[H^+] + k_{-2}^{OH} + \sum k_{-2}^{B_i}[B_iH^+]$
$(\bar{4}) = k_{-4}[H^+] + k_{-4}^{OH} + \sum k_{-4}^{B_i}[B_iH^+]$
$(\bar{5}) = k_{-5}$
$(\bar{6}) = k_{-6}[H^+] + k_{-6}^{OH} + \sum k_{-6}^{B_i}[B_iH^+]$

Scheme.

Rectilinear Correlations for Condition Aa.—

$$k_A = (1)(2)/[(\bar{1}) + (2)]$$
$$= k_1(k_2 + k_2^{OH}[OH^-] + \Sigma k_2^{B_i}[B_i])/\{k_{-1} + (k_2 + k_2^{OH}[OH^-] + \Sigma k_2^{B_i}[B_i]) \quad (5)$$

At high base concentration $(2) \rightarrow \gg (\bar{1})$, and $k_A \rightarrow k_1$; at low base concentration $(\bar{1}) \gg (2)$ and $k_A \rightarrow (1)(2)/(\bar{1})$ such that a general-base dependence is expected:

$$k_A = (k_2 + k_2^{OH}[OH^-])k_1/k_{-1} + k_2^{B_i}[B_i]k_1/k_{-1}$$

Thus, for reaction with a single base B at constant pH, a plot of k_A against [B] should be rectilinear with slope $= k_1k_2^B/k_{-1}$ and intercept $= k_1(k_2 + k_2^{OH}[OH^-])k_{-1}$; in the absence of bases B_i a plot of k_A against low concentrations of hydroxide ion should be rectilinear with slope $= k_1k_2^{OH}/k_{-1}$ and intercept $= k_1k_2/k_{-1}$. For hydroxide concentrations in excess of *ca.* 0.005M ($k_2 \ll k_2^{OH}[OH^-]$) a rectilinear plot of $1/k_A$ *versus* $1/[OH^-]$ with slope $= k_{-1}/k_1k_2^{OH}$ and intercept $= 1/k_1$ is to be expected [equation (6)].

$$1/k_A = 1/k_1 + k_{\ 1}/k_1k_2^{OH}[OH^-] \quad (6)$$

Equation (7), which can be obtained by reorganisation of equation (5) or by simplification of equation (8), is applicable over the full range of base concentrations and can be used to advantage once the rate constant limit k_1 has been determined:

$$y = 1/\{(k_1/k_A) - 1\} =$$
$$k_2/k_{-1} + k_2^{OH}[OH^-]/k_{\ 1} + k_2^{B_i}[B_i]/k_{\ 1} \quad (7)^*$$

Thus, for reactions conducted in 0.001M-sodium hydroxide containing varying amounts of general base B, a plot of *y versus* [B] should have a slope $= k_2^B/k_{-1}$ and intercept $= (k_2/k_{-1} + k_2^{OH}[OH^-]/k_{-1})$; for reactions performed in absence of bases B_i a plot of *y versus* $[OH^-]$ should have slope $= k_2^{OH}/k_{\ 1}$ and intercept $= k_2/k_{-1}$.

It is apparent that, by appropriate analysis of the dependence of k_A on $[OH^-]$ and $[B_i]$, the kinetic constants k_1, k_2^{OH}/k_{-1}, k_2/k_{-1}, and $k_2^{B_i}/k_{-1}$, and hence the relative values of the rate constants k_2, k_2^{OH}, and $k_2^{B_i}$, may be determined for reactions governed by equation (5); it is necessary to determine k_{-1} by alternative means in order to evaluate the absolute rate constants k_2, k_2^{OH}, and $k_2^{B_i}$.

Rectilinear Correlations for Condition B.—

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

At high base concentration the numerator→$(1)(3)$, the denominator→(3), and $k_A \rightarrow k_1$. At low base concentrations the denominator→$(\bar{1})(\bar{2})/[(\bar{1}) + (2)]$ and the pre-equilibrium condition *Bb* is achieved:

$$k_A = [(1)(2)/(\bar{1})(\bar{2})](3) = k_3K_1K_a^{MH} +$$
$$k_3^{OH}K_1K_2^{OH}[OH^-] + [k_3^{B_i}K_1K_a^{MH}/K_a^{B_iH}][B_i]$$

Thus, for reaction of a single base B at constant pH, under pre-equilibrium condition *Bb*, a plot of k_A *versus* [B] should be rectilinear with slope $= [k_3^BK_1K_a^{MH}/K_a^{BH}]$ and intercept $= (k_3K_1K_a^{MH} + k_3^{OH}K_1K_2^{OH}[OH^-])$; in the absence of bases B_i a plot of k_A against low concentrations of hydroxide ion should be rectilinear with slope $= k_3^{OH}K_1K_2^{OH}$ and intercept $= k_3K_1K_a^{MH}$. Equation (8) can be obtained from (2) and

$$y = 1/(k_1/k_A - 1) = (2)(3)/[(\bar{1})(3) + (\bar{1})(\bar{2})] \quad (8)$$

used to correlate the base dependence of k_A over the full range of base concentrations. Thus when condition *Ba* prevails, *i.e.* when $(3) \ll (\bar{2})$, we obtain:

$$y = 1/(k_1/k_A - 1) = (3)(2)/(\bar{1})(\bar{2}) = k_3K_a^{MH}/k_{-1} +$$
$$k_3^{OH}K_2^{OH}[OH^-]/k_{-1} + k_3^{B_i}K_a^{MH}[B_i]/k_{-1}K_a^{B_iH}$$

Thus, for reactions conducted in 0.001M-sodium hydroxide containing varying amounts of a general base B a plot of *y versus* [B] should be rectilinear with slope $= k_3^{B_i}K_a^{MH}/k_{-1}K_a^{B_iH}$ and intercept $= \{(k_3K_a^{MH}/k_{-1}) + k_3^{OH}K_2^{OH}[OH^-]/k_{-1}\}$; for reactions performed in absence of bases B_i a plot of *y*

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* $y = 1/\{(k_1/k_A) - 1\} = k_A/(k_1 - k_A) = (2)/(\bar{1})$ and consequently represents the rate of decomposition of intermediate MH in the forward direction, relative to the reverse direction.

Table 3. Summary of rectilinear kinetic relationships, between k_A and $[OH^-]$ or $[B_i]$, expected for reactions of SH

Reaction conditions	*Aa*	*Ab*(i)[a]	*Ab*(ii)[a]	*Ab*(iii)[a]	*B*
Assumptions used to simplify equation (1)	M^- is formed only *via* reactions (1) and (2)	$[(\bar{6}) + (\bar{1})(\bar{2}) + (\bar{4})(\bar{5})] \ll (3)$ M^- is formed only *via* reactions (4) and (5), or (6)			$(\bar{1})(\bar{2}) <\|< (\bar{3})$ M^- is formed only *via* reactions (1) and (2)
Rate limit[b]	k_1	None	None	None	k_1
Base dependence: (general or specific)	G	G	S	G	G
$(1/k_A = d/[OH^-] + e)$•					
d	$k_{-1}/k_1k_2^{OH}$				
e	$1/k_1$				
$(k_A = f[OH^-] + g)$‡					
f	$k_1k_2^{OH}/k_{-1}$	k_6^{OH}	$k_5K_4^{OH}$	k_4^{OH}	$[k_3^{OH}K_1K_2^{OH}]$‡[*]
g•	k_1k_2/k_{-1}	k_6	0	k_4	$[k_3K_1K_a^{MH}]$‡[†]
$(k_A = h[B_i] + i)$‡					
h	$k_1k_2^{B_i}/k_{-1}$	$k_6^{B_i}$	0	$k_4^{B_i}$	$[k_3^{B_i}K_1K_a^{MH}/k_a^{B_iH}]$‡[*]
i†	$k_1(k_2 + k_2^{OH}[OH^-])/k_{-1}$	$k_6 + k_6^{OH}[OH^-]$	$k_5K_4^{OH}[OH^-]$	$k_4 + k_4^{OH}[OH^-]$	$[K_1(k_3K_a^{MH} + k_3^{OH}K_2^{OH}[OH^-])]$‡[*]
$1/\{(k_1/K_A) - 1\} = j[OH^-] + k$					
j	k_2^{OH}/k_{-1}				$(k_3^{OH}K_2^{OH}/k_{-1})$§[†]
k•	k_2/k_{-1}				$(k_3K_a^{MH}/k_{-1})$§[†]
$1/\{(k_1/k_A) - 1\} = l[B_i] + m$					
l	k_2^{B}/k_{-1}				$(k_3^{B_i}K_a^{MH}/K_a^{B_iH}k_{-1})$§
m†	$(k_2 + k_2^{OH}[OH^-]/k_{-1}$				$\{(k_3K_a^{MH} + k_3^{OH}K_2^{OH}[OH^-])/k_{-1}]$§

[a] The expression $k_A = (6) + (4)(5)/[(\bar{4}) + (5)]$ applies to condition *Ab* for which three extremes may arise: (i) $(6) \gg (4)(5)/[(\bar{4}) + (5)]$; (ii) $(4)(5)/[(4) + (5)] \gg (6)$ and $(4) \gg (5)$; (iii) $(4)(5)/[(\bar{4}) + (5)] \gg (6)$ and $(\bar{4}) \ll (5)$. [b] At high base concentration.

• $[B_i] = 0$. † $[OH^-]$ = constant. ‡ Applicable only at low base concentration when $(\bar{1}) \gg (2)$. § Applicable only at moderately high base concentration, when $(\bar{1}) \ll (2)$; *i.e.* condition *Ba*. [*] Condition *Bb*; $(\bar{1})(\bar{2}) \gg (3)$ such that $SH \rightleftharpoons M^-$ is established. [†] Condition *Ba*; M^- is formed only *via* reactions (1) and (2), where $(\bar{1}) \ll (2)$.

versus $[OH^-]$ should have slope $= k_3^{OH}K_2^{OH}/k_{-1}$ and intercept $= k_3K_a^{MH}/k_{-1}$.

It is apparent that by appropriate analysis of the base dependence of k_A the kinetic constants k_1, $K_1K_a^{MH}k_3$, $K_1K_a^{MH}k_3^{OH}$, $K_1K_a^{MH}k_3^{B_i}/K_a^{B_iH}$, and hence the relative values of the rate constants k_3, k_3^{OH}, and $k_3^{B_i}$ may be determined for reactions governed by equation (2); it is necessary to determine k_{-1} by alternative means in order to evaluate the absolute rate constants k_3, k_3^{OH}, and $k_3^{B_i}$.

Useful rectilinear relationships are summarised in Table 3.

Interpreration of Kinetic Results for Reactions of SH.—Results in Table 1 indicate that, for reactions catalysed by sodium hydroxide alone, k_A is almost linearly dependent upon concentrations of hydroxide ion up to 0.005M; the subsequent curvilinear approach to a maximum value, which is expected to occur at high base concentration, is apparently masked by a further base-dependent process which causes a shallow increase in k_A with increase of base concentration beyond $[OH^-]$ 0.5M. A linear plot of $1/k_A$ *versus* $1/[OH^-]$ is, however, obtained for the hydroxide concentration range 0.001—0.1M; the value $k_1 = 82 \times 10^{-5}$ s^{-1} has been obtained from the intercept *e* which is believed to be a reliable estimate of $1/k_1$; $k_2^{OH}/k_{-1} = 239$ l mol^{-1} has correspondingly been evaluated from the slope *d* (see Figure 2).

It is apparent, from the results obtained (Table 2) for reaction of SH_a in ethanolamine and morpholine buffer solutions of differing total buffer concentration, that the rearrangement is general- rather than specific-base catalysed. While there is once again a curvilinear relationship between k_A and [B] (see Figure 1) the maximum value ($k_A^{max.}$) obtained is different for each buffer system and in neither case approaches the rate constant limit $k_1 = 82 \times 10^{-5}$ s^{-1}. This is to be expected since at the values of buffer pH employed the substrate SH would be partially protonated such that $k_A^{max.} = k_1[1/(1 + a_{H^+}/K_a)]$. On this basis the values of $k_A^{max.}$ for reactions in ethanolamine and morpholine buffers have been used, in conjunction with k_1 (evaulated for reactions catalysed by hydroxide ion, as described above), to estimate the average value $\mathrm{p}K_a^{SH_2} = 8.05 \pm 0.2$ (*T* 60 °C) for the protonated substrate; the values 8.05 and 8.05 were obtained at 60 °C for the respective buffer systems, it being assumed that for morpholine and ethanolamine $\mathrm{p}K_a^{60} = 7.74$ and 8.58, respectively.* The estimate $\mathrm{p}K_a^{SH_2} = 8.05$ at 60 °C is consistent with corresponding values for ethanolamine (8.58) and 2-methoxyethylamine (*ca.* 8.46) since the *p*-nitrophenoxy group should be considerably more electron withdrawing than the hydroxy or methoxy groups.†

The dependence of the reaction on general bases (ethanolamine, morpholine, and acetate) was also investigated at high pH, in order to ensure that the substrate remained unprotonated. The results obtained (Table 1) for reactions promoted by ethanolamine, morpholine, or acetate in the presence of 0.01 or 0.001M-sodium hydroxide display the expected curvilinear approach to the maximum rate constant k_1 at high concentration of the general base (see Figure 1).

The qualitative kinetic trends are consistent with those expected for conditions *Aa* and *B*, as defined in Table 3; the expected rectilinear relationships (see Figure 3) have been tested

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* See footnote to Table 2.

† For $HOCH_2$, $MeOCH_2$, and $PhOCH_2$ the Taft σ^* values are 0.555, 0.520, and 0.850, respectively; the relationship $\log K/K_0 = 1.42\sigma_R^*$ has been reported for ionisation of RCH_2OH (P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, 1960, **82**, 795).

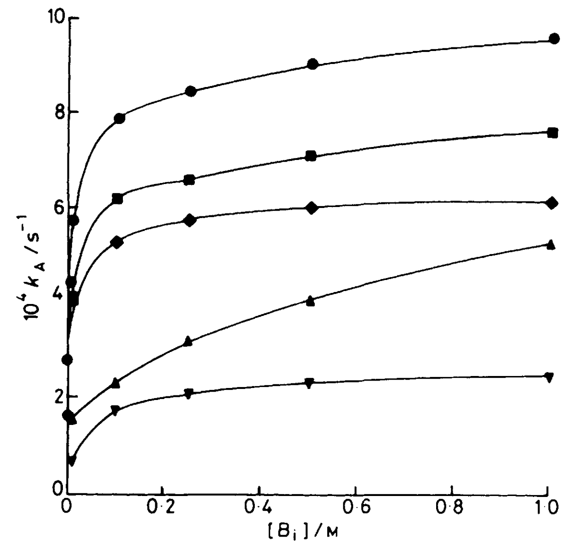


Figure 1. Dependence of the rate constants (see Tables 1 and 2) for Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine (SH) on the concentration of the catalysing base $[B_i]$, in water at 60 °C (μ 1.00): ● hydroxide ion; ■ morpholine (in the presence of 0.001M-NaOH); ▲ acetate ion (in the presence of 0.001M-NaOH); ◆ ethanolamine buffer; ▼ morpholine buffer

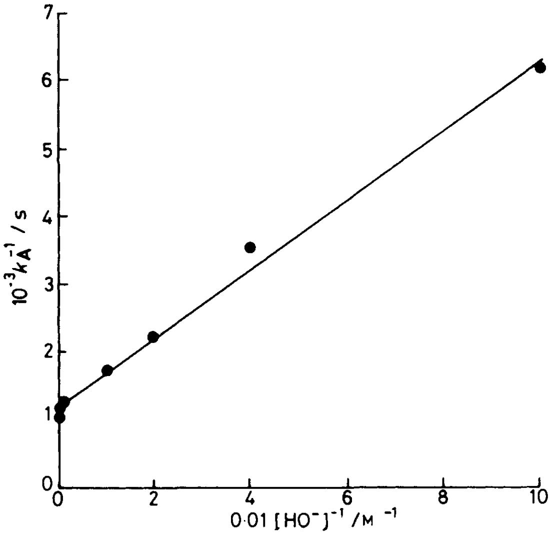


Figure 2. The rectilinear relationship of the form $1/k_A = d/[HO^-] + e$ (see Table 1) for Smiles rearrangement of SH in water at 60 °C and μ 1.00

quantitatively and the results obtained, for corresponding slopes and intercepts, are included in Tables 1 and 2.

Conditions *Aa* and *B* differ fundamentally in that they involve either rate-determining deprotonation of the spiro-Meisenheimer intermediate MH or acid-catalysed ring opening of its conjugate base M^-, respectively. By correlation of log *l* (where *l* is obtained from the rectilinear relationship $y = l[B_i] + m$) with the pK_a of the base catalyst we obtained a Brønsted plot for which there are alternative interpretations. Thus, for condition *Aa* the relationship $\log l = \log (k_2^{B_i}/k_{-1}) = -\beta \log K_2^{B_iH} + c_1$ is to be expected, whereas for condition *B* we obtain * $\log l = \log (k_3^{B_i} K^{MH}/K^{B_iH}k_{-1}) = (\alpha - 1) \log K_a^{B_iH} + c_2$.

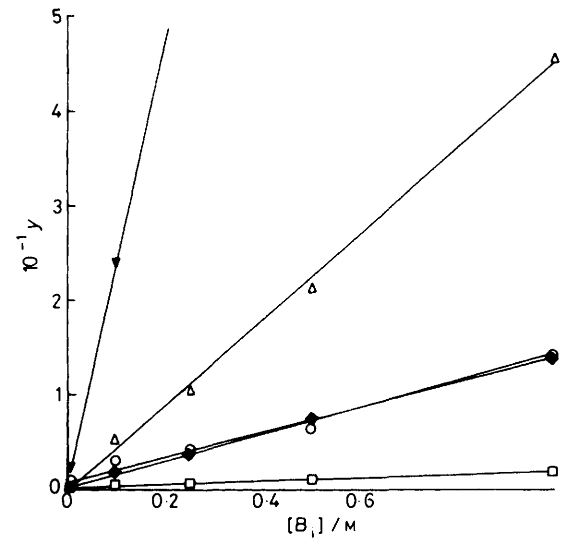


Figure 3. Rectilinear relationships of the form $y = l[B_i] + m$ (see Tables 2 and 3) for Smiles rearrangement of SH catalysed by bases B_i in water at 60 °C and μ 1.00; $y = 1/(k_1/k_A - 1)$: ▼ hydroxide ion; ○ morpholine (in the presence of 0.001M-NaOH); □ acetate ion (in the presence of 0.001M-NaOH); △ ethanolamine buffer; ◆ morpholine buffer

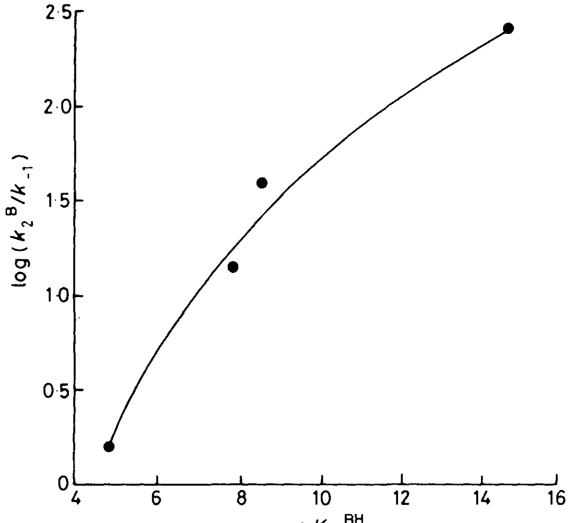
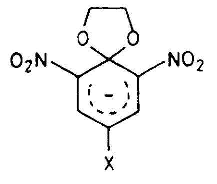
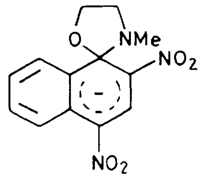


Figure 4. Brønsted relationships between $\log (k_2^B/k_{-1})$ and pK_a^{BH} for Smiles rearrangement of SH catalysed by bases B_i in water at 60 °C and μ 1.00; see Table 4



(1)



(2)

The slope of a plot of log *l* *versus* $\log K_a^{B_iH}$ may therefore be interpreted as $-\beta$ (where β is the Brønsted coefficient for general-base-catalysed deprotonation of MH) or as $\alpha - 1$ (where α is the Brønsted coefficient for acid-catalysed ring opening of M^-). The curvilinear relationship obtained (see

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* *I.e.* if $\log k_3^{B_i} = \alpha \log K_a^{B_iH} + c_3$
$= (\alpha - 1) \log K_a^{B_iH} + \log K_a^{B_iH} + c_3$
therefore $\log (c_4 \cdot k_3^{B_i}/K_a^{B_iH}) = (\alpha - 1) \log K_a^{B_iH} + c_2$

Table 4. Rate constants * obtained from correlations of the rate data, as indicated in Tables 1 and 2, it being assumed that reaction condition *Aa* applies (see Table 3)

Base B	(k_B/k_{-1})/ l mol^{-1}	$(10^5k_1$/ s$^{-1})$†	pK_a^{BH} (60 °C)	$\log(k_2^B/k_{-1})$
OH^-	239 ± 10[a]	82 ± 2[b]	14.77[c]	2.378
Ethanolamine	42.5 ± 2[d]	83 ± 1	8.58[e]	1.628
Morpholine	14.3 ± 0.5[d] (13 ± 3)[f]	83 ± 1	7.74[e]	1.155
Acetate	1.60 ± 0.2[f]	79 ± 5	4.81[g]	0.204

* The results for ethanolamine, morpholine, and acetate are larger than those reported in our preliminary communication[1] which was in error. † By extrapolation of a plot of $1/k_A$ *versus* $1/[B]$ to give intercept $1/k_1$.

[a] From *j* or *d*, *e*. [b] Based on results for $[OH^-] \leq 0.1$M. [c] p$K_w^{60°}$ = 13.017. [d] *l* for reaction with morpholine buffer solutions (Table 2). [e] 'Dissociation Constants of Organic Bases in Aqueous Solution: Supplement 1972,' ed. D. D. Perrin, Butterworths, London 1972. [f] *l* for reaction with base in the presence of 0.001M-NaOH (Table 1). [g] 'Dissociation Constants of Organic Acids in Aqueous Solution,' eds. G. Kortum, W. Vogel, and K. Andrussow, Butterworths, London, 1961.

Figure 4, for which $\beta = -$ slope $= 0.20$—0.35) is typical of those for reactions which proceed at close to the diffusion-controlled rate limit and which involve only proton transfer;[10] a value $\beta = 0.20$—0.35 would not be unexpected for condition *Aa*. A value of $\alpha = 0.80$—0.65 would, however, be inconsistent with acid-catalysed ring opening of a Meisenheimer intermediate M^-. Thus, it has been found[4c,e] that for acid-catalysed cleavage of spiro-Meisenheimer complexes (**1**), in water, the Brønsted coefficient α decreases steadily with decreasing electron-withdrawing power of substituent X (α = 0.58, 0.56, 0.54, 0.51, and 0.49 when X = SO_2CF_3, NO_2, CF_3, Cl, and H, respectively); much *smaller* values of α would be expected for ring opening of less stable analogues of (**1**). Furthermore, there is considerable evidence that general-acid catalysis of alkoxide ion expulsion from such intermediates is weak in protic solvents and generally detectable only for acids of pK_a < 6 when present in high concentration.[4b,e,7] Such considerations have prompted Bernasconi to argue that the generally accepted SB–GA mechanism of nucleophilic aromatic substitution may only become significant in aprotic media.[4b,7]

Of particular relevance to our study, it has been established that for ring opening of (**2**) catalysed by $BuNH_3^+$ in 60% dioxane–40% water or by acetic acid in 60% ethanol–40% water the ratios $k^{AH}/k^{solvent}$ are *ca.* 2.2 and 7.3. even though (p$K_a^{solvent}$ − pK_a^{AH}) are *ca.* 4 and 10, respectively.[11]

The much faster ring opening to be expected of an analogous mononitro-substituted Meisenheimer intermediate in 100% aqueous solution should be even less sensitive to the strength of an acid catalyst. Furthermore, our interpretation in terms of rate-limiting deprotonation of MH (condition *Aa*) is quite consistent with expectations based on other results for analogous di- and tri-nitro systems; this interpretation requires that conversion of M^- into PH is rapid relative to its reprotonation, $(3) > (\bar{2})$, and that $(\bar{1})$ is able to compete with (2) at moderate base concentrations. By analogy with Bernasconi's results[7b,12] for di- and tri-nitro systems it can be estimated that $k_3^{OH} > 10^5$ s$^{-1} \geq k_{-2}^{OH}$ and that k_{-1} should exceed 10^7 s^{-1} for rearrangement of a mono-nitro substrate such as SH.

Our view that Smiles rearrangement of SH proceeds by rate-determining proton transfer from the intermediate MH, rather than by the SB–GA mechanism, is further supported by results which we have obtained for *N*-alkyl analogues of SH; conditions conducive to a gradual mechanistic change to an alternative specific-base-catalysed pre-equilibrium mechanism are also described in the following paper. Thus, we have interpreted the results here reported for SH in terms of rate-limiting deprotonation of MH, in order to estimate component rate constants of equation (5). The results of this interpretation are in Table 4.

The magnitude of the rate constants obtained will be discussed in the following paper, in conjunction with those for *N*-alkyl substrates (R = Me, Et, Pr^i).

Acknowledgements

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