Base-dependent Kinetics of Smiles Rearrangement of *N*-[2-(*p*-Nitrophenoxy)ethyl]ethylenediamine in Aqueous Solution; Intramolecular Catalysis of an Intramolecular S_NAr Reaction [1]

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Intramolecular displacement of alkoxide ion by the secondary amino group of *N*-[2-(*p*-nitrophenoxy)ethyl]ethylenediamine in water is uncatalysed by general bases, but is characterised by a pH-insensitive rate plateau and specific-base-catalysed approach to a rate limit at high pH; the rate plateau at $[OH^-]$ 0.1—0.01 M is a consequence of the dominant catalytic effect of the neighbouring amino group in promoting rate-determining deprotonation of the spiro-Meisenheimer intermediate.

In an earlier paper [2] we argued that kinetics of base-catalysed Smiles rearrangement of a series of amino-ethers SH_{a-d} could best be accommodated by the kinetic expression (1) which is a simplification of the steady-state rate expression (2) for which equation (3) holds. Equation (3) is obtained for Scheme 1 by steady-state treatment of MH and M^-.

$$k_{obs} = \frac{k_1\{k_2 + k_2^{OH}[OH^-] + k_2^{B}[B]\}}{k_{-1} + \{k_2 + k_2^{OH}[OH^-] + k_2^{B}[B]\}} \quad (1)$$

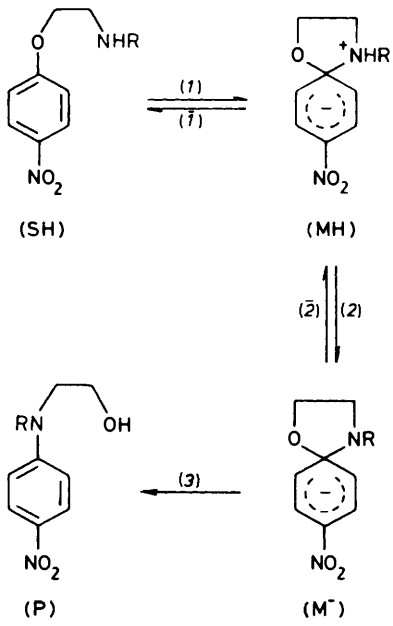
$$d[P]/dt = \frac{\{(1)(2)/[(\bar{1}) + (2)]\}(3)[SH]}{(3) + (\bar{1})(\bar{2})/[(\bar{1}) + (2)]} = k_{obs}[SH] \quad (2)$$

$$k_{obs} = \frac{(1)(2)(3)}{(3)(\bar{1}) + (3)(2) + (\bar{1})(\bar{2})} \quad (3)$$

Equation (1) is obtained from equation (3) if it is assumed that SH need not necessarily be in equilibrium with MH and that conversion of M^- into P is faster than is its rate of reprotonation to give MH [*i.e.* (3) > ($\bar{2}$)]. According to equation (1) the reaction exhibits general-base catalysis, as a consequence of rate-limiting deprotonation (r.l.d.) of MH to give M^-, but approaches a base-independent rate limit k_1 at high base concentration, *i.e.* the rate of formation of MH becomes limiting once the rate of conversion of MH into product, *via* M^-, greatly exceeds the rate of return of MH to SH.

In order to gain further evidence for rate-determining proton transfer during rearrangement of substrates SH we decided to incorporate a neighbouring base catalyst which might accelerate deprotonation of the corresponding Meisenheimer intermediate MH. It was therefore anticipated that rearrangement of SH_e, for which the conversion $MH_e \rightarrow M_e^-$ could be anchimerically assisted by the terminal amino group, should be insensitive to intermolecular general-base catalysis, and exhibit the rate limit k_1 even at moderately low base concentrations.

The kinetic results obtained upon investigation of the rearrangement of SH_e to P_e are the topic of this paper.



a; R = H
b; R = Me
c; R = Et
d; R = Pr^i
e; R = $CH_2CH_2NH_2$

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

Scheme 1.

Discussion

The substrate SH_e was synthesised from *p*-chloronitrobenzene, by reaction with sodium *N*-(2-aminoethyl)-2-aminoethoxide in DMSO, according to a recently developed procedure.[3] Although the reaction time was reduced to 5 min, SH_e was invariably obtained in admixture with the product (P_e) of its subsequent rearrangement (*ca.* 25%). Attempts to obtain a sample of SH_e which was uncontaminated by P_e were unsuccessful and, in order to obtain the kinetic results here reported, an isomeric mixture (75% SH_e, 25% P_e) was used which had satisfactory elemental analysis. The identity of the product (P_e), which was obtained in 50% yield upon Smiles rearrangement of SH_e in aqueous alkali, was confirmed by spectroscopic and elemental analysis. We have no reason to believe that the kinetics of rearrangement of SH_e (*ca.* 1×10^{-4} M) in aqueous alkaline solutions at 60 °C are influenced by the presence of P_e, and have confirmed that the

Table. Rate constants (10^5 k_{obs}/s^{-1}) for intramolecular rearrangement† of *N*-[2-(*p*-nitrophenoxy)ethyl]ethylenediamine catalysed by bases in water at 60 °C and μ 1.0 (KNO_3)

[Base]/M	1.0	0.5	0.25	0.1	0.05	0.02	0.01	0.001
NaOH	1 550	1 450	1 250	1 000	967	940	930	640
Ethanolamine*	890	930	895	910	905	895	800	900
Morpholine*	910	885	895	920	883	900	885	890

* In each case [NaOH] = 0.01M. † Monitored spectrophotometrically at 435 nm

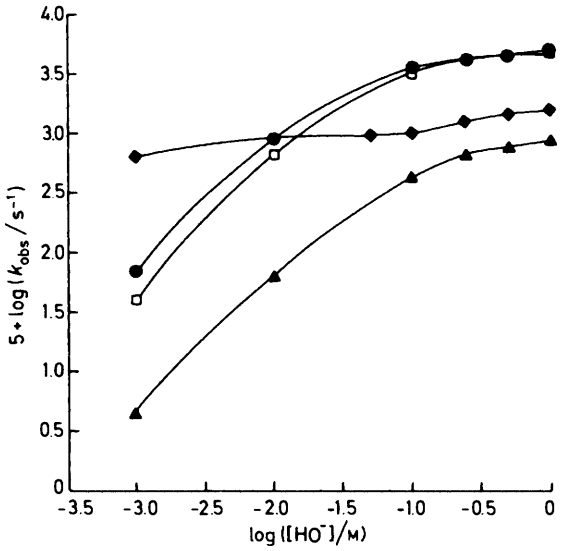


Figure 1. Plots of log k_{obs} *versus* log [HO^-] for Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine bearing *N*-Me (●, SH_b), *N*-Et (□, SH_c), *N*-Pr^i (▲, SH_d), and *N*-(2-aminoethyl) (◆, SH_e) substituents

rate constants obtained are independent of the initial concentration of SH_e and P_e.

The pseudo-first-order rate constants (k_{obs}) for intramolecular rearrangement of SH_e catalysed by hydroxide ion, morpholine, and ethanolamine at constant ionic strength (μ 1.0; *T* 60 °C) are in the Table. Sodium hydroxide (0.01M) was added to each of the morpholine and ethanolamine solutions in order to ensure that the pH exceeded the pK_a of the conjugate acid of SH_e or of the amine catalysts; reactions were monitored spectrophotometrically at 435 nm.

The results indicate that reaction of SH_e is specific-base-catalysed and that it approaches a rate limit k_1 1.65 × 10^{-2} s^{-1} at hydroxide concentrations in excess of 1.0M. Thus, while the neighbouring catalyst causes a change from general-base catalysis (*cf.* SH_{a-d}) to specific-base catalysis it has little effect on the hydroxide concentration required to achieve the rate limit k_1; comparable values 10^2 k_1/s^{-1} = 5.13, 5.00, and 1.00 have been determined for SH_{b-d}, respectively.

Furthermore, in marked contrast (see Figure 1) to the behaviour[2] of SH_{a-d} in aqueous sodium hydroxide the analogous rearrangement of SH_e exhibits a complex dependence on specific-base catalysis (there being a base-insensitive region at hydroxide concentrations of 0.01—0.1M) prior to attainment of a rate limit k_1 at high base concentration; this behaviour must be a direct consequence of neighbouring group participation by the primary amino group since it is not that expected of any of the kinetic equations * which it was necessary to inspect upon consideration of the reactivity of 2-(*p*-nitrophenoxy)ethylamines SH_{a-d}.

Modification of equation (1) by introduction of a further term (k_2^{nsp}), to take account of rapid intramolecular deprotonation of MH by the neighbouring amino group, gives equation (4) which at first sight appears to be inconsistent with the base dependence observed for reaction of SH_e. Thus, if the neighbouring group exhibits a moderately high effective concentration then equation (4) requires that the substrate attain the rate limit k_1 at low hydroxide ion concentration (relative to the hydroxide concentrations required to induce limiting behaviour of those substrates SH_{a-d} for which there is no term k_2^{nsp}); alternatively, should k_2^{nsp} fail to dominate the conversion of MH into M^-, intermolecular catalysis by general bases (β *ca.* 0.2) should again be observed.

$$k_{obs} = \frac{k_1\{k_2 + k_2^{OH}[OH^-] + k_2^{B}[B] + k_2^{nsp}\}}{k_{-1} + \{k_2 + k_2^{OH}[OH^-] + k_2^{B}[B] + k_2^{nsp}\}} \quad (4)$$

In order to explain the observed specific-base dependence with pH-insensitive rate plateau at [HO^-] 0.01—0.1M and approach to a rate limit at [HO^-] ≥ 1.0M we must therefore examine the following alternative interpretations.

(1) Equation (4) may indeed be applicable, but the intramolecular catalyst may exhibit a relatively small effective concentration (say 3—5M). This may be sufficient to dominate the influence of intermolecular catalysts of comparable basicity, but insufficient to ensure that (*2*) ≫ (*I*); consequently, attainment of the rate limit k_1 would be achieved only with the additional intermolecular catalytic influence of a strong base such as hydroxide.

(2) Introduction of the neighbouring base catalyst may cause a change in mechanism from the rate-limiting deprotonation process governed by equation (4) to the SB–GA mechanism,† for example.

(3) The mechanism of reaction of SH_{a-d} may have been incorrectly assigned; the alternative SB–GA mechanism may apply to all substrates SH_{a-e}.

We wish, at the outset, to dismiss this third alternative for the following reasons. (i) The results already reported[2] for SH_{a-d} are fully consistent with an interpretation according to equation (1). (ii) The relative values of the rate constants estimated for SH_{a-d} can be rationalised satisfactorily,[2] and the magnitude of the constants is in accord with expectations based on analogous rate constants which have been directly determined for related di- and tri-nitro systems. (iii) We have reported that the reaction of $SH_{c,d}$ is general-base-catalysed in ethanolamine solutions (0.001—1.0M) of pH ≥ 11, or in weak ethanolamine buffer solutions of pH 8.576, whereas the reaction rate becomes insensitive to high concentrations of the same buffer. This can be rationalised if it is argued that there is a change from the r.l.d. to the SB–GA mechanism as equilibration of MH and M^- becomes more rapidly established with increasing concentration of the buffer acid; furthermore, for $SH_{c,d}$ inconversion of M^- to P is apparently insensitive to general acids and the overall process should correspondingly be termed an SB mechanism. This satisfactory explanation of the behaviour of $SH_{c,d}$ could not be invoked if the SB–GA mechanism were to be assumed from the outset.

It is also important to note that explanation of the behaviour

* *I.e.* those derived from expression (2) by applying simplifying assumptions, and also those derived for an extended reaction scheme which is referred to in an earlier paper.[4]

† *I.e.* whereby MH and M^- are in an equilibrium ratio, governed by the specific base strength, and the rate-limiting conversion of M^- into P may be catalysed by the conjugate acid of any base present.

of SH_e with the initial assumption that the SB–GA mechanism applies for the series SH_{a-e} presents difficulties which are analogous to those encountered when the r.l.d. mechanism is assumed. Thus, from equation (3) one can derive equation (5) for the SB–GA mechanism, *i.e.* where $(\bar{2}) > (3)$. Incorporation of the neighbouring group will introduce terms in k_3^{ngp}, k_2^{ngp}, and k_{-2}^{ngp} but will not influence the equilibrium ratio $(\bar{2})/(2)$; thus, the rate constant for reaction of SH_e by the SB–GA mechanism would be governed by equation (6) where f is the fraction of M^- present with its terminal amino group in the form RNH_3^+.

$$k_{obs} = \frac{(1)(3)(2)/(\bar{2})}{(3)(2)/(\bar{2}) + (\bar{1})} \quad (5)$$

$$k_{obs} = \frac{k_1\{(k_3[H^+] + k_3^{OH} + k_3^{B}[BH^+] + k_3^{ngp}f)K_a^{MH}/[H^+]\}}{k_{-1} + \{(k_3[H^+] + k_3^{OH} + k_3^{B}[BH^+] + k_3^{ngp}f)K_a^{MH}/[H^+]\}} \quad (6)$$

$$\frac{1}{k_{obs}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1k_2^{OH}[OH^-]} \quad (7)$$

The qualitative similarity between equation (4) for the r.l.d. mechanism and equation (6) for the SB–GA mechanism is immediately apparent. Thus, each equation requires that if the neighbouring group exhibits a moderately high catalytic effect the substrate SH_e should attain the rate limit k_1 at low hydroxide concentration (relative to that required to induce limiting behaviour of SH_{a-d}); alternatively, intermolecular general-base catalysis (*e.g.* by ethanolamine) should be observed.

Thus, we are satisfied that amino-ethers SH_{a-d} react by the r.l.d. mechanism and we note that there is no advantage in assuming the alternative SB–GA mechanism for each substrate SH_{a-e} in order to account for the limited effect of the intramolecular catalyst. The behaviour of SH_e must therefore be a consequence of either a change to the SB–GA mechanism for this substrate alone (*cf.* the behaviour of $SH_{c,d}$ in ethanolamine buffers of high concentration)‡ or of a very modest intramolecular general-base catalytic effect on the deprotonation of MH_e according to the expected r.l.d. mechanism.

We will now present an interpretation which assumes that the r.l.d. mechanism applies to SH_e; the component rate constants will be estimated and compared with those for SH_{a-d}. The modest effect of the intramolecular catalyst will be estimated and compared with results for other examples of intramolecular general-base-catalysed deprotonation. Attention will subsequently be given to the possibility that the neighbouring base catalyst causes a change to the SB–GA mechanism for SH_e; it will be argued that this interpretation is qualitatively attractive, but quantitatively inconsistent with our combined kinetic results for SH_{a-e} and with related observations.

Interpretation of the Kinetics of Rearrangement of SH_e, according to the R.l.d. Mechanism.—Results (Table) for rearrangement of SH_e in aqueous sodium hydroxide at constant ionic strength reveal that the rate approaches a maximum at high hydroxide concentration but that there is, within experimental error, a pH-insensitive plateau for hydroxide concentrations between 0.01 and 0.1M.

For reactions of substrates SH_{a-d} in aqueous hydroxide it was convenient to invert equation (1) and to correlate $1/k_{obs}$ with $1/[HO^-]$; rectilinear correlations were obtained since k_2 is small relative to $k_2^{OH}[OH^-]$ throughout the base concentration range employed, giving equation (7). Values of k_1 and k_2^{OH}/k_{-1} were obtained from the slope and intercept in the usual manner.

The contrasting behaviour of SH_e and SH_c is apparent in Figure 2.

Inversion of the modified rate equation (4) for SH_e gives (8). It is therefore reasonable to assume that equation (9) applies for reaction in aqueous hydroxide.

$$\frac{1}{k_{obs}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1(k_2 + k_2^{OH}[OH^-] + k_2^{B}[B] + k_2^{ngp})} \quad (8)$$

$$\frac{1}{k_{obs}} = \frac{1}{k_1} + \frac{k_{-1}}{k_{-1}(k_2^{OH}[OH^-] + k_2^{ngp})} \quad (9)$$

Thus, $1/k_{obs}$ will attain the limit (intercept) $1/k_1$ when $(k_2^{OH}[OH^-] + k_2^{ngp}) \gg k_{-1}$. It is clear, from our rate study, that k_2^{ngp} alone cannot greatly exceed k_{-1}, otherwise rearrangement of SH_e would occur at constant rate (k_1) throughout the range of hydroxide concentrations employed. It is therefore to be expected that at high base concentrations $(k_2^{OH}[OH^-] > k_2^{ngp})$ equation (9) will approximate to

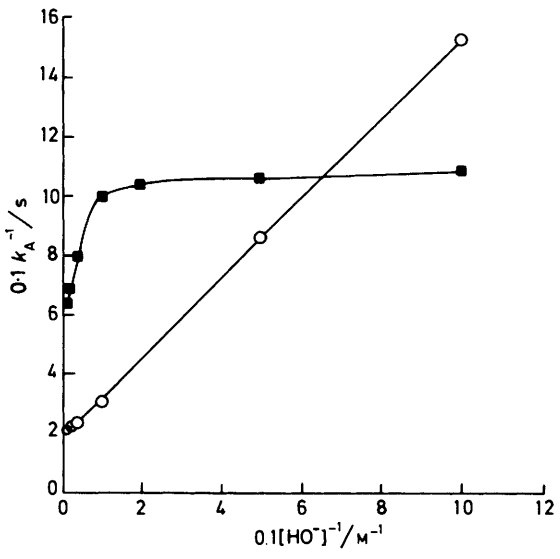


Figure 2. Contrasting plots of $1/k_{obs}$ *versus* $1/[HO^-]$ for Smiles rearrangement of 2-(*p*-nitrophenoxy)ethylamine bearing *N*-Et (○, SH_e) and *N*-(2-aminoethyl) (■, SH_e) substituents

‡ We have previously argued that for reaction of $SH_{c,d}$, in ethanolamine (E) buffer solutions of pH 8.58, a 0.5M concentration of EH^+ is sufficient to cause a change in mechanism from r.l.d. $[(\bar{2}) \ll (3)]$ to solvent-promoted ring opening of the pre-equilibrium concentration of MH, $[(\bar{2}) > (3)]$. Likewise, the pre-equilibrium condition can be claimed for reaction of SH_e if there is reason to believe that $(\bar{2})^{ngp} > (3)^{ngp}$. By analogy with $SH_{c,d}$ it is reasonable to assume that $k_{-2}^{ngp} > k_3^{ngp}$ and to expect $k_{-2}^{ngp}f$ to exceed $(k_3^{OH} + k_3^{ngp}f)$ for all solutions of sufficient acidity to ensure that $k_3^{ngp} > k_3^{OH}$; this should be achieved provided the multiple of the fraction protonated (f) and the 'effective concentration' of the neighbouring group exceeds unity (*i.e.* since E and ngp are of comparable basicity and for $SH_{c,d}$ $k_2^{E}[EH^+] > k_3^{OH}$ when $[EH^+] \geq 0.5$).

equation (7), and that a linear relationship will apply, from which $1/k_1$ and k_2^{OH}/k_{-1} can be obtained. As the hydroxide concentration is reduced, equation (9) approaches equation (10) for the further extreme where $k_2^{nsp} \gg k_2^{OH}[OH^-]$. The consequent base-independent rate plateau (from which k_2^{nsp}/k_{-1} can be obtained) should extend to lower pH until the pH approaches the highest pK_a (conjugate acid) of SH_e and the rate expression is complicated by partial protonation of the substrate; $1/k_{obs}$ should correspondingly increase at this extreme.

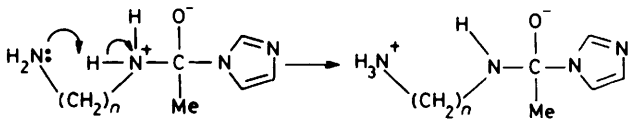
$$\frac{1}{k_{obs}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1 k_2^{nsp}} \qquad (10)$$

The relationship between $1/k_{obs}$ and $1/[OH^-]$ for SH_e (Figure 2) exhibits the trends expected of equation (9). The following rate constants have correspondingly been determined for SH_e: k_1 1.65×10^{-2} s^{-1}; k_2^{OH}/k_{-1} 10 l mol^{-1}; k_2^{nsp}/k_{-1} 1.12. The values for k_1 and k_2^{OH}/k_{-1} are consistent with those obtained[2] for SH_{a-d}. Thus, we have reported that the effect of *N*-methylation of the parent substrate SH_a is to cause k_1 to increase from 0.082×10^{-2} to 5.13×10^{-2} s^{-1} for SH_b, probably as a consequence of enhanced nucleophilicity brought about by the electron-donating effect of the methyl substituent. Although k_1 for *N*-alkyl substrates $SH_{c,d}$ is also greater (10^2 k_1/s^{-1}, 5.00 and 1.00, respectively) than for SH_a, there is a progressive decrease in k_1 with increasing complexity of the alkyl substituent; SH_e falls neatly within this series and its behaviour (10^2 k_1/s^{-1} 1.65) can be likened to that of SH_d. The comparable values of k_1 for SH_d and SH_e make it clear that the neighbouring group has no catalytic effect on the nucleophilic addition of the secondary amino group to the activated aromatic ring. This is in accord with the well established view[5] that for intermolecular S_NAr reactions of amine nucleophiles, with aromatic substrates bearing poor leaving groups, the occurrence of base catalysis cannot be attributed to deprotonation concomitant with nucleophilic addition.

The rate ratio k_2^{OH}/k_{-1} for SH_e also compares favourably with the *N*-isopropyl substrate SH_d; the respective values for SH_{a-e} are 239, 21.3, 15.4, 6.85, and 10 l mol^{-1}.

For reaction of SH_e in 0.01M-sodium hydroxide containing the general-base catalysts ethanolamine or morpholine (0.001—1.0M) the kinetic results (Table 1) fail to reveal any influence of the general base. This was a surprising result since we had established that the effect of the neighbouring group was not alone sufficient to induce deprotonation of MH_e at a rate much faster than its return to SH_e (k_2^{nsp}/k_{-1} = 1.12). However, since the behaviour of SH_e is similar to that of SH_d (particularly with regard to the rate ratio k_2^{OH}/k_{-1}) it is reasonable to suppose that for SH_e the efficacy of ethanolamine (E) will be close to that for SH_d, for which we have reported k_2^E/k_{-1} 0.26 l mol^{-1}. Correspondingly, according to the general equation (8) we would expect the rate of reaction of SH_e in 0.01M-sodium hydroxide to be increased by only *ca.* 8% upon addition of 1.0M-ethanolamine. Our failure to detect such a small change may be attributed to experimental error, possibly combined with a rate-retarding medium effect of ethanolamine at high concentration.

The inability of the neighbouring group to cause MH_e to deprotonate very much faster than it returns to SH_e (and thereby promote rate-limiting behaviour, $k_{obs} \rightarrow k_1$), requires that the intramolecular catalyst display only a modest effective concentration. An estimate $k_2^B/k_{-1} \simeq 0.32$ can be made for an intermolecular base catalyst of comparable basicity to that of the neighbouring amino group if we assume the approximate values β 0.3 (*cf.* SH_{a-d})[2] and $pK_a^{H_2O} - pK_a^{nsp} = 5$, combined with k_2^{OH}/k_{-1} 10 for SH_e. The effective molarity of the intramolecular catalyst is therefore 1.12/0.32 = 3.5M; this



Scheme 2.

relatively low value is in keeping with previous reports of intramolecular proton transfer.[6] For example, it has been estimated[6a,7] that the effective concentration of the intramolecular catalyst in promoting the conversion in Scheme 2 is 0.55, 0.94, 0.20, and 0.25M where n = 2—5, respectively.

It is reasonable* to suppose that the decrease in k_{obs} upon reduction of the hydroxide concentration to 0.001M is a consequence of partial protonation of SH_e.

Attempted Interpretation of the Kinetics of Reaction of SH_e according to the SB–GA Mechanism.—The specific-base dependence, plateau region, and approach to a rate limit observed for SH_e could also be interpreted if it is assumed that ($\bar{2}$) exceeds (*3*); this is in contrast with the behaviour of SH_{a-d} for which we have argued that conversion of M^- into P occurs much faster than return of M^- to MH [(*3*) > ($\bar{2}$)]. Thus, from equation (3) we obtain (11). Anchimeric assistance of the deprotonation step requires that its microscopic reverse be accelerated also [*i.e.* both (*2*) and ($\bar{2}$) will be augmented by n.g.p. terms]; it is therefore reasonable‡ to speculate that for reaction of SH_e the condition ($\bar{2}$) > (*3*) could prevail and that equilibration of MH_e and M_e^- might occur under the catalytic influence of the neighbouring amino group and of its conjugate acid.

$$k_{obs} = \frac{(1)(2)(3)}{(3)(2) + (\bar{1})(\bar{2})} \qquad (11)$$

Thus, since $(2)/(\bar{2}) = K_a^{MH}/[H^+]$ we obtain, from equation (11), $k_{obs} = (1)(3)K_a^{MH}/[H^+]\{k_{-1} + (3)K_a^{MH}/[H^+]\}$ and $1/k_{obs} = 1/k_1 + k_{-1}[H^+]/k_1 K_a^{MH}(3)$. Now let (*3*) be augmented by $k_3^{nsp}f$ where k_3^{nsp} is the rate constant for conversion of M^- into P catalysed by the conjugate acid (RNH_3^+) of the neighbouring group (RNH_2), and f is the fraction of M^- which exists with its terminal amino group in the RNH_3^+ form, *i.e.* $(3)^{nsp} = (k_3[H^+] + k_3^{OH} + k_3^B[BH^+] + k_3^{nsp}f)$ where $f = [RNH_3^+]/([RNH_3^+] + [RNH_2]) = 1/(1 + K_a^{nsp}/[H^+])$ and $K_a^{nsp} = [RNH_2][H^+]/[RNH_3^+]$. Thus, where $[B_{tot}] = ([B] + [BH^+])$, we obtain equations (12).

$$(3)^{nsp} = \{k_3[H^+] + k_3^{OH} + k_3^B[B_{tot}][H^+]/([H^+] + K_a^{BH}) + k_3^{nsp}[H^+]/([H^+] + K_a^{nsp})\} \qquad (12a)$$

$$1/k_{obs} = 1/k_1 + k_{-1}/k_1 K_a^{MH}\{k_3 + k_3^{OH}[OH^-]/K_w + k_3^B[B_{tot}]/([H^+] + K_a^{BH}) + k_3^{nsp}/([H^+] + K_a^{nsp})\} \qquad (12b)$$

The pH–rate profile and absence of general-base catalysis can be accommodated by equation (12b) if it is assumed that

* For SH_e there is a rectilinear relationship between $1/k_{obs}$ and $1/[OH^-]$ throughout the range $[OH^-]$ 1.0—0.01; where $[OH^-] = 0.001$ however, the departure from linearity can reasonably be attributed to 46% protonation of SH_e. The secondary amino group of SH_e should, however, be *ca.* 0.5 pK_a units more basic than that of SH_e (*cf.* 2-ethylaminoethylamine pK_a[1] 10.56, and diethylamine pK_a 11.04) which is correspondingly expected to be *ca.* 21% protonated under the same conditions. This would cause a proportionate reduction of k_{obs} which would be almost sufficient to account for the trend observed.

‡ Footnote given on p. 1903.

conversion of M_e^- into P_e is predominantly promoted by solvent (k_3^{OH}) and intramolecular (rather than intermolecular) general-acid catalysis at hydroxide concentrations of 1.0—0.1M and 0.1—0.01M, respectively. Thus, the linear relationship between $1/k_{obs}$ and $1/[OH^-]$ observed for the former range is of the form (13) while the relative insensitivity of the reaction rate to base concentration in the latter range (plateau) becomes a consequence of expression (14).

$$1/k_{obs} = 1/k_1 + k_{-1}K_w/k_1K_a^{MH}k_3^{OH}[OH^-] \quad (13)$$

$$1/k_{obs} \rightarrow 1/k_1 + k_{-1}/k_1K_a^{MH}(k_3 + k_3^{ngp}/K_a^{ngp}) \quad (14)$$

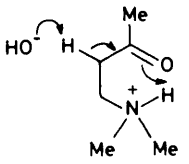
According to this alternative interpretation of the kinetics of reaction of SH_e the linear relationship between $1/k_{obs}$ and $1/[OH^-]$ at high pH will have slope $k_{-1}K_w/k_1K_a^{MH}k_3^{OH}$ and intercept $1/k_1$; the values obtained are 6.06 mol s l^{-1} and 60.6 s, respectively. Thus, upon substitution of pK_w 14.77 and (by analogy with $SH_{c,d}$) $k_{-1} \simeq 10^9$ s^{-1} and $k_3^{OH} \simeq 10^7$ s^{-1}, we obtain $pK_a^{MH\cdot} \simeq 11.77$. Furthermore, at the rate plateau ($1/k_{obs} = 110$ s) we require: (i) that $1/k_{obs} = 1/k_1$ $(1 + k_{-1}K_a^{ngp}/K_a^{MH}k_3^{ngp})$, and hence $k_3^{ngp}/K_a^{ngp} \simeq 10^9/K_a^{MH}$; (ii) that $k_3^{OH}[OH^-]/K_w < k_3^{ngp}/K_a^{ngp}$, *i.e.* for $[OH^-] < 0.1$M. One must therefore argue that $k_3^{ngp}/K_a^{ngp} > 10^7.10^{-1}/10^{-14.77} = 10^{20.77}$ and, correspondingly, $pK_a^{MH} \simeq (20.77 - 9) = 11.77$. Thus, a self-consistent interpretation of the intercept, slope, and plateau is available, *provided* $pK_a^{MH} \simeq 11.77$. However, this value is very much larger than expected* and leads us to conclude that this interpretation of the kinetics of reaction of SH_e is untenable.

Also, if we re-examine our original requirement that $f \times$ (effective concentration, x) ≥ 1 for the pre-equilibrium SB—GA mechanism to apply, where $f = 1/(1 + K_a^{ngp}/[H^+])$, we obtain $x \geq 1 + K_a^{ngp}/[H^+]$. It is most unlikely that this will apply within the range $[OH^-] = 0.01$—1.0M (pH *ca.* 12.77—14.77) since $pK_a^{ngp} \simeq 9$ (*cf.* ethylenediamine, pK_a^{60} 9.005) would demand that the neighbouring catalyst exhibit an effective concentration in excess of 10^4M; this is unprecedented for intramolecular proton-transfer mechanisms.

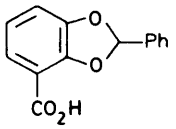
For example, an effective molarity of <1M has been estimated[6b,8] for the general-acid catalyst for the process in Scheme 3.

However, there have also been reports of high effective molarities of neighbouring general acids in reactions catalysed by intramolecular proton transfer.[9] Thus, the effective concentrations of the carboxy group catalysts of hydrolyses of (I)—(III) are 100, 5000, and 10000M, respectively.[9] These high values may be a consequence of the limited conformational mobilities of such systems, and in contrast with the behaviour to be expected of k_3^{ngp}.

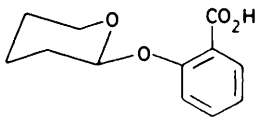
In conclusion, we are confident that the behaviour of SH_e cannot be attributed to the SB–GA mechanism since estimates of the necessary value for pK_a^{MH} in the presence of the neighbouring catalyst are inconsistent with reasonable expectations; interpretation according to the r.l.d. mechanism affords an explanation that is also consistent with our explanation of the behaviour of SH_{a-d}.



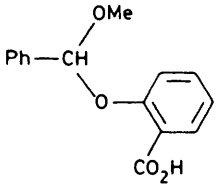
Scheme 3.



(I)



(II)



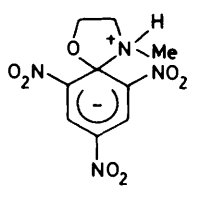
(III)

Experimental

Rate Measurements.—The kinetics of rearrangement of SH_e ($\lambda_{max.}$ *ca.* 330 nm) to P_e ($\lambda_{max.}$ 435 nm) at 60 °C, in the aqueous alkaline solutions described in the Table, were followed spectrophotometrically. Reactions were initiated by addition of a solution (10 µl) of SH_e (0.015M, in acetonitrile) to the aqueous base solution (3 cm^3) which had been thermostatted within the cell compartment of a Unicam spectrophotometer, model 1700; the increase in absorbance which occurred at 435 nm was monitored for more than seven half-lives of the rearrangement whereupon a computer (ICL1903A) was used to determine the pseudo-first-order rate constants by least-squares analysis in the usual way; in each case more than 50 data points were determined and the rate constants were reproducible to within ±1%. Reactions were repeated in triplicate and the average values obtained from runs for which the correlation coefficient exceeded 0.998 are in the Table. A calibrated thermistor was used to monitor the temperature of the reaction medium.

Preparation of N-(p-*Nitrophenoxyethyl*)*ethylenediamine* SH_e.—Sodium hydride (1.0 g; 50% suspension in oil) was added to a solution of *N*-(2-hydroxyethyl)ethylenediamine (2.08 g) in dimethyl sulphoxide (10 cm^3) whereupon *p*-chloronitrobenzene (3.1 g) was added in one portion. After 5 min dichloromethane (100 cm^3) was added and the organic layer, which separated upon addition of water (150 cm^3), was

* The magnitude of $pK_a^{MH\cdot}$ can by gauged by comparison with that[10] for (1) (pK_a 5.4 ± 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 very much smaller, say 1.5 p*K* units.



(1)

We expect that for the conjugate acid of the secondary amino-group of SH_e, $pK_a \simeq 8.32$ at 60 °C, since β-amino substitution of the *N*-ethyl group of SH_c (pK_a 8.65) should cause a pK_a decrease of *ca.* 0.33 units (*cf.* $HOCH_2CH_2NHCH_2CH_3$, pK_a 9.85, and $HOCH_2CH_2NHCH_2CH_2NH_2$, pK'_a 9.52). Thus, we estimated that $pK_a^{MH\cdot}$ is *ca.* 6.8—8.3.

extracted with hydrochloric acid (50 cm^3; 4M). The acidic extract was basified while it was being stirred vigorously with ethyl acetate at 2 °C; the ethyl acetate extract was washed with water, dried, and evaporated to yield the required product SH_e which had δ (60 MHz; $CDCl_3$) 8.14 (2 H, d, *J* 9 Hz), 6.96 (2 H, d, *J* 9 Hz), 4.20 (2 H, t, *J* 5 Hz, CH_2O), 3.4—4.0 (4 H, m), and 3.08 (2 H, t, *J* 5 Hz, CH_2NH_2).

The product was, however, in admixture with the isomeric product (P_e) of its subsequent rearrangement; elemental analysis of the mixture (75% SH_e:25% P_e), from which SH_e could not be isolated, was satisfactory (Found: C, 53.1; H, 6.9. $C_{10}H_{15}N_3O_3$ requires C, 53.3; H, 6.7%).

Preparation of N-(2-*Aminoethyl*)-N-(2-*hydroxyethyl*)-p-*nitroaniline* P_e *by Smiles Rearrangement of* SH_e.—The reaction described above, for preparation of SH_e, was repeated for an extended reaction time of 24 h; dichloromethane (100 cm^3) and water (150 cm^3) were added whereupon the product precipitated as a yellow solid which was recrystallised from benzene and obtained in 50% yield with m.p. 150 °C; δ (60 MHz; CF_3CO_2H) 7.75 (2 H, d), 6.62 (2 H, d), 3.0—3.3 (2 H, m, CH_2NH_2), and 3.3—4.0 (6 H, m) (Found: C, 52.9; H, 6.7; N, 18.0. $C_{10}H_{15}N_3O_3$ requires C, 53.3; H, 6.7; N, 18.7%); $\delta_{max.}$ (KBr disc) 3 340 and 3 280 (sharp, R-NH_2 sym. and asym. str.), 3 000—3 200, 2 700—2 950, 1 600, 1 515, 1 465, 1 435, 1 405, 1 325, 1 210, 1 160, 1 120, 1 075, 940, 825, and 755 cm^{-1}.

Acknowledgements

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