

Role of Intramolecular Catalysis in the Kinetics of Smiles' Rearrangement of *N*-[2-(*p*-Nitrophenoxy)ethyl]ethylenediamine

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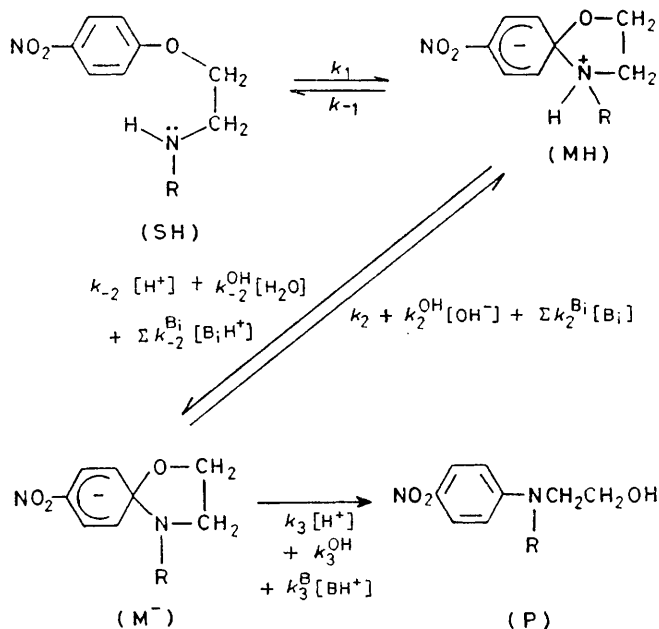
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Summary Intramolecular displacement of alkoxide ion by the secondary amino group of *N*-[2-(*p*-nitrophenoxy)ethyl]ethylenediamine is not catalysed by general bases, but occurs by a specific base catalysed mechanism with a pH-insensitive rate plateau and approaches to a rate limit at high pH; the rate plateau at $[\text{OH}^-] = 0.1\text{--}0.01\text{ M}$ is a consequence of the dominant catalytic effect of the neighbouring primary amino group in promoting rate determining deprotonation of the spiro-Meisenheimer intermediate.

WE recently reported¹ that Smiles' rearrangement of 2-(*p*-nitrophenoxy)ethylamine (**SHa**), whereby alkoxide ion is intramolecularly displaced by the amine nucleophile, is subject to general base catalysis at low concentrations of added base. We argued that under such conditions the rate of reaction is limited by the rate of deprotonation of a spiro-Meisenheimer intermediate (as a consequence of the magnitude of k_{-1} and k_p) and that the rate limit observed at high base concentrations corresponds to the base independent formation (k_1) of (**MH**).

Rate constants (k_{obs}) observed¹ for rearrangement of (**SHa**) [and its *N*-alkyl derivatives² (**SHb**—**d**)] can be correlated by the rate expression (1) which is obtained by a

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



SCHEME. a, R = H; b, R = Me; c, R = Et; d, R = Pri; e, R = $\text{CH}_2\text{CH}_2\text{NH}_2$. The rate constants k_{-1} , k_2^{OH} , k_{-2}^{OH} , and k_3^{OH} are expected to be of magnitude $10^7\text{--}8$, $10^9\text{--}10$, $<10^5$, and $>10^5\text{ s}^{-1}$, respectively (ref. 1).

steady state treatment of intermediates (**MH**) and (**M**⁻) in the Scheme; 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**). Consequently, we believed that a substrate (*e.g.*, **She**) for which the proton transfer (**MH**→**M**⁻) could be anchimerically assisted should be insensitive to intermolecular general base catalysis and exhibit the rate limit (k_1) even at moderately low base concentrations; the results obtained upon investigation of the base dependent kinetics of reaction of (**She**) are the topic of this communication. The substrate (**She**) was synthesised from *p*-chloronitrobenzene by reaction with sodium *N*-(2-aminoethyl)-2-aminoethoxide in Me_2SO by a standard procedure.³ Although the reaction time was reduced to 5 min the (**She**) obtained was invariably in admixture with *ca.* 25% of the product (**Pe**, m.p. 150 °C, λ_{max} 435 nm) of its subsequent rearrangement; this isomeric mixture, which had satisfactory elemental analyses, was used to determine the pseudo first order rate constants reported in the Table.

TABLE. Rate constants^a ($k_{\text{obs}}/10^{-5}\text{ s}^{-1}$) for intramolecular rearrangement^b of *N*-[2-(*p*-nitrophenoxy)ethyl]ethylenediamine catalysed by bases in water at 60 °C, $\mu = 1.0$ (KNO₃).

[Base]/M	1.0	0.5	0.25	0.1	0.01	0.001
NaOH	1550	1450	1250	1000	910	640
	(6.45) ^a	(6.90)	(8.00)	(10.0)	(11.0)	(15.6)
Ethanolamine ^c	890	930	895	910	890	900
Morpholine ^c	910	885	895	920	885	890

^a Bracketed figures = $10^4\text{ s}^{-1}/k_{\text{obs}}$ for reactions in aqueous NaOH; all values are $\pm 2\%$. ^b Monitored spectrophotometrically at 435 nm. ^c In each case $[\text{NaOH}] = 0.01\text{ M}$.

The results indicate that reaction of (**She**) is specific base catalysed and that it approaches a rate limit $k_1 = 1.65 \times 10^{-2}\text{ s}^{-1}$ at hydroxide concentrations in excess of 1.0 M. Thus, while the neighbouring catalyst causes a change from general base catalysis (*cf.* **SHa**—**d**) to specific base catalysis it has little effect on the hydroxide concentration required to achieve the rate limit k_1 ; substrates (**SHb**—**d**) achieve comparable rate limits k_1 under similar conditions.²

However, in contrast with (**SHa**—**d**) (for which the rate of reaction decreases smoothly with decrease of hydroxide ion concentration) the rate of reaction of (**She**) becomes insensitive to concentrations of the specific base catalyst in the range 0.1—0.01 M.

Thus, interpretation of the results obtained for (**She**) must account for (i) the absence of general base catalysis, (ii) the pH-rate plateau, and (iii) the inability of the neighbouring group to promote limiting behaviour ($k_{\text{obs}} \rightarrow k_1$) at moderately low base concentrations.

The absence of general base catalysis can be attributed to rate limiting deprotonation of (**MHe**), dominated by the catalytic effect of the intramolecular catalyst; intermolecular deprotonation of (**MHe**) becomes competitive at hydroxide ion concentrations $>0.1\text{ M}$. According to this interpretation the slope and intercept of a plot of $1/k_{\text{obs}}$ vs. $1/[\text{HO}^-]$

at high hydroxide concentrations (>0.1 M) equal $k_{-1}/k_1k_2^{\text{OH}}$ and $1/k_1$, respectively; the values $k_1 = 1.65 \times 10^{-2} \text{ s}^{-1}$ and $k_2^{\text{OH}}/k_{-1} = 11 \text{ M}^{-1}$ have correspondingly been obtained from the rectilinear relationship observed. These values are consistent with those obtained² for **(SHa—d)**, respectively: $k_1/10^{-2} \text{ s}^{-1} = 0.082, 5.13, 5.00, \text{ and } 1.00$; $k_2^{\text{OH}}/k_{-1} \text{ M}^{-1} = 239, 21.3, 15.4, \text{ and } 6.85$. For $[\text{HO}^-] < 0.1 \text{ M}$ the rate of deprotonation of **(MHe)** becomes dominated by the intramolecular component k_2^{ngp} , and the rate ratio $k_2^{\text{ngp}}/k_{-1} = 1.12$ can be estimated since $k_{\text{obs}} \rightarrow k_1k_2^{\text{ngp}}/(k_{-1} + k_2^{\text{ngp}})$ (ngp = neighbouring group participation).

Thus, the rate of deprotonation by the neighbouring amino group is comparable with the rate of return of **(MHe)** to **(SHe)**; we were therefore surprised not to detect an intermolecular catalytic influence of ethanolamine (E) on reaction of **(SHe)** particularly since we have determined $k_2^{\text{E}}/k_{-1} = 2.0 \text{ M}^{-1}$ for reaction of **(SHb)**. Our subsequent estimate² of a much smaller ratio ($k_2^{\text{E}}/k_{-1} = 0.26 \text{ M}^{-1}$) for reaction of **(SHe)** suggests that the value for **(SHe)** may indeed be sufficiently small to account for our failure to observe catalysis by ethanolamine in competition with catalysis by the neighbouring group.

The inability of the neighbouring group to cause **(MHe)** to deprotonate at a rate very much faster than it returns to **(SHd)** (and thereby promote rate-limiting behaviour, $k_{\text{obs}} \rightarrow k_1$) is a consequence of the small† 'effective concentration' displayed by this intramolecular catalyst. This degree of catalytic efficiency is in keeping with previous reports of intramolecular proton transfer.⁴

We believe that the results obtained can be satisfactorily explained by the interpretation above; the decrease in rate upon further reduction of the hydroxide concentration to 0.001 M is consistent with the expected partial protonation of the neighbouring catalyst. We have also given careful consideration to the alternative SB-GA mechanism, dominated by intramolecular catalysis; while it offers an attractive interpretation of the rate plateau and specific base catalysis we have been unable to justify the quantitative requirements, particularly in regard to an unusually high $\text{p}K_{\text{a}}$ for the conjugate acid of the neighbouring catalyst.

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† If we assume the approximate values (refs. 1 and 2) $\beta \text{ ca. } 0.3$, and $\text{p}K_{\text{a}}^{\text{H}_2\text{O}} - \text{p}K_{\text{a}}^{\text{ngp}} = 5$, we can use $k_2^{\text{OH}}/k_{-1} = 11 \text{ M}^{-1}$ in order to obtain $k_2^{\text{E}}/k_{-1} \text{ ca. } 0.35 \text{ M}^{-1}$ for intermolecular reaction of **(MHe)** with a base of comparable basicity to that of the neighbouring group. Thus, the effective molarity of the intramolecular catalyst = $1.12/0.35 = 3.2 \text{ M}$.

¹ A. C. Knipe, J. Lound-Keast, and N. Sridhar, *J.C.S. Chem. Comm.*, 1976, 765.

² A. C. Knipe, N. Sridhar, and J. Lound-Keast, *Tetrahedron Letters*, 1979, 2541.

³ A. C. Knipe and N. Sridhar, *Synthesis*, 1976, 606.

⁴ See B. Capon in 'Proton Transfer Reactions,' eds. E. Caldin and V. Gold, Chapman and Hall, London, 1975, ch. 11, pp. 359, 374, and 378.