Evidence for Rate-limiting Deprotonation of a Spiro-Meisenheimer Intermediate During Smiles' Rearrangement of 2-(*p*-Nitrophenoxy)ethylamine

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Summary Kinetic studies of intramolecular nucleophilic aromatic displacement of alkoxide ion by the amino group in 2-(*p*-nitrophenoxy)ethylamine support a mechanism whereby, at low base concentrations, the rate of Smiles' rearrangement is dependent upon the rate of general base-catalysed deprotonation of a spiro-Meisenheimer intermediate; at high base concentrations the base independent rate of formation of the Meisenheimer intermediate becomes rate limiting.

INTEREST in the kinetics of S_NAr reactions of primary and secondary amines with activated aromatic ring systems has recently been revived.[1] The mechanism suggested[2] for many such intermolecular reactions involves a fast acid-base equilibrium between an initially formed zwitterionic Meisenheimer intermediate and its conjugated base, followed by rate limiting expulsion of the leaving group catalysed by general acids including the conjugate acid of the base B; this mechanism accounts for the general base catalysis observed in such cases.

More recently, it has been suggested by Bernasconi[3] that the base dependence observed for intramolecular S_NAr reaction of an amino-group with a neighbouring activated ring system [as in the case of *NN'*-dimethyl-*N*-(2,4-dinitrophenylethylenediamine and *NN'*-dimethyl-*N*-picrylethylenediamine] may alternatively be attributed to rate-limiting deprotonation of the Meisenheimer intermediate, even in strongly basic media. Such claims have, so far, been limited to reactions of di- and tri-nitro-aromatic systems for which the relatively slow proton transfers have been ascribed to intramolecular hydrogen bonding.

TABLE

Rate constants for intramolecular rearrangement of 2(*p*-nitrophenoxy)ethylamine catalysed by general bases in water at 60 °C, $\mu = 1{\cdot}0$.

Base B	$k_1/10^{-5}\ s^{-1}$	pK_a^{BH}	$(k_2^B/k_{-1})/l\ mol^{-1}$
$CH_3CO_2^-$	79·8	4·75	0·71
Morpholine	79·8	8·33	5·90
Ethanolamine	80·1	9·5	28·8
OH^-	78·6	15·74	$254{\cdot}0 = k_2^{OH}/k_{-1}$
H_2O	—	−1·74	$0{\cdot}0002 = \frac{k_2/k_{-1}}{[H_2O]}$

We have recently[4] perfected the synthesis of 2-(*p*-nitrophenoxy)ethylamine (λ_{max} 315 nm) and its *N*-alkyl derivatives and now report kinetic results obtained from a study of the base dependence of its Smiles' rearrangement to 2-(*p*-nitroanilino)ethanol (λ_{max} 410 nm) in aqueous solution at constant ionic strength ($\mu = 1{\cdot}0$). The rate of reaction, which was monitored by u.v. spectrophotometry, is linearly dependent on OH^- concentrations below 0·01 M but becomes insensitive to base concentrations in excess of 0·1 M and approaches a limiting value; the same rate limit is approached in the presence of alternative general bases.† Our results are consistent with the mechanism shown in the Scheme.‡

By analogy with Bernasconi's results[5] for di- and tri-nitro-systems it can be estimated that $k_P > 10^5\ \mathrm{s}^{-1} \geqslant k_{-2}^{OH}$. Under these conditions the rate of return of M^- to SH may be appreciably slower than that of its conversion into P and steady state treatment of the reactive intermediates MH and M^- gives rise to the expression shown in equation (1) for the observed rate of formation of P.

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

Values obtained§ for k_1 (approached at high base concentrations) and k_2^B/k_{-1} (appropriately evaluated at low base concentrations) are given in the Table for reactions of a range of general bases B.

The curvilinear Brønsted relationship ($\beta = 0{\cdot}15 - 0{\cdot}4$) between log k_2^B/k_{-1} and $\mathrm{p}K_a^{BH}$ is typical of those for reactions which proceed at close to the diffusion controlled rate limit and which involve only proton transfer. The estimate k_{-1} *ca.* $10^6\ \mathrm{s}^{-1}$ can also be made since k_2^{OH} should be close to $10^9\ \mathrm{l\ mol^{-1}\ s^{-1}}$.

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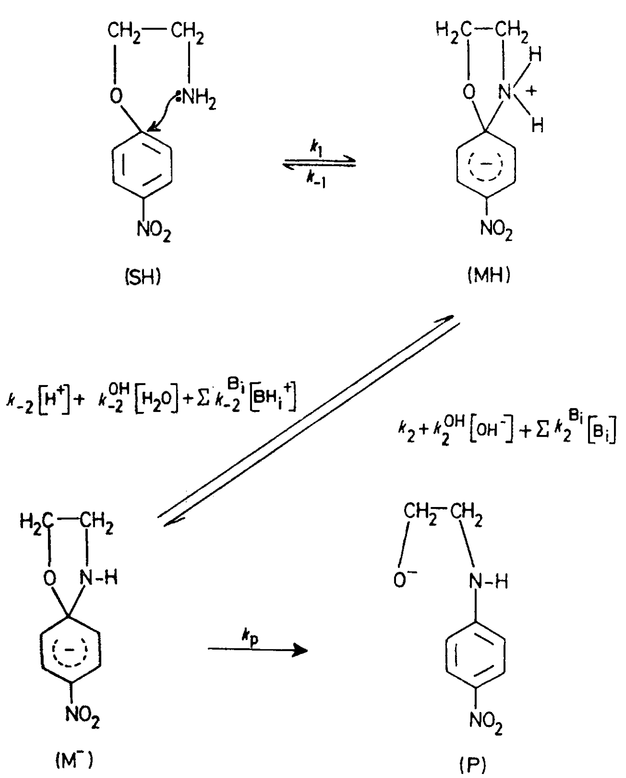

Scheme

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† For reactions conducted in the presence of a general base, sodium hydroxide (0·001 M) was added to maintain pH $\geqslant \mathrm{p}K^{SH_2} + 1$.

‡ The kinetic observations do not rule out the possibility of the formation of P from MH, by a concerted base-catalysed process, without the intermediacy of M^-.

§ For hydroxide ion concentrations in excess of 0·01 M ($k_2 << k_2^{OH}$ [OH⁻]), the equation $1/k_{obs} = 1/k_1 + k_{-1}/k_1k_2^{OH}[OH^-]$ applies for reaction in absence of other bases; from the rectilinear plot of $1/k_{obs}$ *vs.* $1/[OH^-]$ the constant k_1 has been evaluated. The equation $1/\{(k_1/k_{obs}) - 1\} = k_2/k_{-1} + k_2^{OH}[OH^-]/k_{-1} + k_2^{B}[B]/k_{-1}$ can also be derived from equation (1). For reactions conducted in aqueous sodium hydroxide (0·001 M) containing varying amounts of a general base B, a plot of $1/\{(k_1/k_{obs}) - 1\}$ *vs.* [B] has a slope of k_2/k_{-1} and an intercept of $k_2/k_{-1} + k_2^{OH}[OH^-]/k_{-1}$.

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