

THE SMILES REARRANGEMENT OF 4-NITROPHENYL N-HYDROXYCARBAMATE: THE INVOLVEMENT OF A SPIRO MEISENHEIMER COMPLEX OF A MONONITROBENZENE DERIVATIVE AS A TRANSIENT REACTION INTERMEDIATE

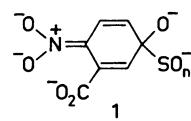
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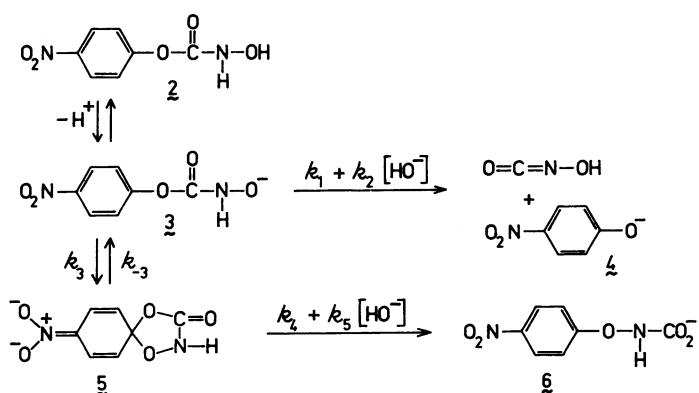
In alkaline solution, 4-nitrophenyl N-hydroxycarbamate undergoes reaction by elimination to yield 4-nitrophenoxide ion, and by rearrangement to yield N-carboxy-4-nitrophenoxyamine. The effect of pH on the yield of the rearrangement product establishes that a transient spiro Meisenheimer complex is formed reversibly. Aromatization of this species occurs by two competing pH-independent reactions: one involves expulsion of a hydroxamate ion; the other involves the formation of a carbamate ion *via* a general base catalyzed collapse of the complex.

Meisenheimer complexes of mononitro derivatives of benzene have often been suggested as unstable intermediates in nucleophilic aromatic substitution reactions.¹⁾ In 1965, Kirby and Jencks²⁾ used a change in rate-limiting step, brought about by increasing concentrations of dimethylamine, to establish that substitution in 4-nitrophenyl phosphate involved the formation of the Meisenheimer complex as a transient intermediate.

The first *stable* Meisenheimer complex of a mononitro benzene derivative (1, n = 1,2) was reported in 1980.³⁾ The peculiar feature of the stability of 1 is its lack of a good nucleofuge in the highly basic medium (15.3 M KOH, $H_- \approx 18$) in which it is generated. Indeed, when 1 is oxidized by air ultimately to the $-SO_3^-$ derivative, sulfite is lost with the formation of 3-carboxy-4-nitrophenolate ion.



While spiro Meisenheimer complexes of *polynitro* benzene derivatives have found extensive application as models for the intermediates in nucleophilic aromatic substitution reactions,⁴⁾ spiro complexes of mononitro derivatives have been less well documented, even as transient intermediates.⁵⁾ In 1973, we postulated that a spiro Meisenheimer intermediate (5, Scheme 1) occurs in the



Scheme 1.

Smiles rearrangement of 4-nitrophenyl N-hydroxycarbamate (2) to form N-carboxy-4-nitrophenoxyamine (6).⁶⁾ We have now analyzed the effect of extensive variation of pH on the rate and products of the degradation of 2 in aqueous buffers at 25°C, and clearly establish the reversible formation of 5 as a transient intermediate.

Compound 2 decomposes in aqueous solution to form both 4-nitrophenoxyde ion (4) and N-carboxy-4-nitrophenoxyamine⁷⁾ (6) in proportions which vary with pH.⁶⁾ The formation of both 4 and 6 obeys a strict first-order rate law, and k_{obsd} is independent of the concentration of buffers. Both products are formed in parallel, since k_{obsd} is independent of the wavelength at which it is monitored. Fig. 1 shows that the results are consistent with Eq. 1 which is derived from a two-term rate expression (Eq. 2; SH = 2).⁸⁾ The yield of 4-nitrophenoxyde ion (4) is minimal at pH 12 (Fig. 1), and the yield of rearrangement product (6, $\lambda_{\text{max}} \approx 315 \text{ nm}$)⁶⁾ shows a corresponding maximum.

$$k_{\text{obsd}} = (k_{\text{HO}^-} K_w / K_a' + K_a' [HO^-]) / (1 + [H^+] / K_a') \quad (1)$$

$$-\frac{d[S]_{\text{total}}}{dt} = k_{\text{HO}^-} [HO^-] [SH] + k_a' [HO^-] [S^-] \quad (2)$$

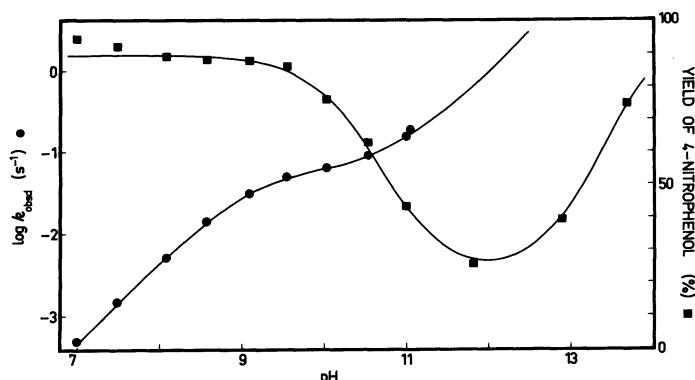


Fig. 1. Decomposition of 4-nitrophenyl N-hydroxycarbamate (2, $1 \times 10^{-4} \text{ M}$) as a function of pH at 25°C in 1.64% (v/v) acetonitrile [$\mu = 1$ (KCl)]: (●) $\log k_{\text{obsd}}$. The line is theoretical for Eq. 1 with pK_a' , 9.12; k_{HO^-}' , $2.70 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$; k_{HO^-} , $56 \text{ M}^{-1} \text{ s}^{-1}$; K_w (ion product of water), $1.69 \times 10^{-14} \text{ M}^2$. (■) percent yield of 4-nitrophenol at ten half-lives, determined from A_{400} . The line is theoretical for Eq. 4 and the experimentally determined parameters.

These results may be understood in terms of Scheme 1. Using the steady-state assumption for the concentration of the spiro Meisenheimer complex (5), the following equations may be derived for k_{obsd} and the fractional yield (f) of the 4-nitrophenoxyde ion (4):

$$k_{\text{obsd}} = (k_1 + k_2 [HO^-] + k_3 (k_4 + k_5 [HO^-])) / (k_{-3} + k_4 + k_5 [HO^-]) / (1 + [H^+] / K_a') \quad (3)$$

$$f = (k_1 + k_2 [HO^-]) / k_{\text{obsd}} (1 + [H^+] / K_a') \quad (4)$$

Reconciliation of Eq. 1 with Eq. 3 requires the following relationships:

$$k_{\text{HO}^-} = (K_a' / K_w) (k_1 + k_3 k_4 / (k_{-3} + k_4 + k_5 [HO^-])) \quad (5)$$

$$k_{\text{HO}^-}' = k_2 + k_3 k_5 / (k_{-3} + k_4 + k_5 [HO^-]) \quad (6)$$

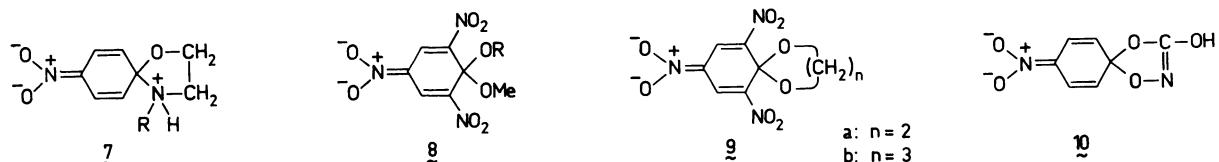
The results show that k_{HO^-} and k_{HO^-}' are independent of pH in the range of interest as required by Eq. 2.⁸⁾ Moreover, the scheme requires that the kinetically

determined pK'_a (Eq. 1) is that of $\underline{\underline{\beta}}$, and the observed value of 9.12 ± 0.05 is entirely reasonable for the pK'_a of a hydroxamic acid.⁹⁾

Rate constants and steady-state parameters were estimated by consideration of the reactions which are dominant in three different regions of pH, and these approximate values were refined by iteration. The results [25°C , $k_1 = 5.3 \pm 0.2 \times 10^{-2} \text{ s}^{-1}$; $k_2 = 0.65 \pm 0.1 \text{ M}^{-1} \text{ s}^{-1}$; $k_3 = 0.21 \pm 0.04 \text{ s}^{-1}$; $k_3 k_4 / (k_{-3} + k_4) = 5.9 \pm 0.2 \times 10^{-3} \text{ s}^{-1}$; $k_{-3}/k_4 = 34.0 \pm 6$; $k_5/k_4 = 9.7 \pm 2 \times 10^3 \text{ M}^{-1}$] were used to calculate the theoretical curve for f (Eq. 4) shown in Fig. 1.

The elimination of N-hydroxycyanic acid from a prototropic form⁹⁾ of $\underline{\underline{\beta}}$ in the k_1 step is consistent with the mechanism which has been established for the elimination of derivatives of cyanic acid in the decomposition of 4-nitrophenyl carbamate and its N-methyl analogue,¹⁰⁾ and for various phenyl N-phenyl-carbamates.¹¹⁾ The value of k_2 ($0.65 \text{ M}^{-1} \text{ s}^{-1}$) for the hydroxide promoted decomposition of $\underline{\underline{\beta}}$ is much greater than that for the attack of hydroxide ion on 4-nitrophenyl dimethylcarbamate ($4.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ at 25°C)^{10a)} or 4-nitrophenyl phosphate ($8.2 \times 10^{-9} \text{ M}^{-1} \text{ s}^{-1}$ at 39°C).²⁾ These last two reactions are considered to involve attack of hydroxide ion on a carbonyl carbon and on an aromatic carbon, respectively. It is therefore eminently reasonable that k_2 refers to the elimination of N-oxycyanate ion from $\underline{\underline{\beta}}$, and concerted removal of a proton accompanied by elimination appears more likely than pre-equilibrium formation of the dianion of $\underline{\underline{\beta}}$.

The reactivity of the hydroxamate ion ($\underline{\underline{\beta}}$) towards cyclisation ($t_{1/2} < 3 \text{ s}$ at 25°C)⁹⁾ is greater than that of 2-(4-nitrophenoxy)ethylamines to form $\underline{\underline{\gamma}}$ ($\text{R} = \text{Me}$; $t_{1/2} = 13 \text{ s}$ at 60°C)^{5b)} even though the nucleophilic groups would have similar basicity. However, this difference in reactivity must reflect in part the electron-withdrawing effect of the carbonyl group in $\underline{\underline{\beta}}$.



The rate constants for the departure of RO^- from the Meisenheimer complex $\underline{\underline{\beta}}$ show a normal dependence on the pK'_a of ROH .¹²⁾ Further, the possibility of major thermochemical strain in the spiro Meisenheimer complex $\underline{\underline{\beta}}\text{a}$ relative to $\underline{\underline{\beta}}$ ($\text{R} = \text{Me}$), gains little support from kinetic data: (i) although the rate constant for aromatization of $\underline{\underline{\beta}}\text{a}$ by loss of alkoxide ion is ~ 170 -fold higher than that of $\underline{\underline{\beta}}$ ($\text{R} = \text{Me}$),^{4b)} ethylene glycol is a stronger acid than methanol by $0.77 \text{ pK}'_a$ units; (ii) the rate constant for the loss of alkoxide ion from $\underline{\underline{\beta}}\text{b}$ is only 19-fold larger than that from $\underline{\underline{\beta}}\text{a}$.¹³⁾

The above facts comment significantly on the mechanism of the aromatization of $\underline{\underline{\beta}}$. Since $k_{-3}/k_4 = 34$, it is thus exceedingly unlikely that a carbamate ion ($\text{pK}'_a < 5$)¹⁴⁾ is ejected in the k_4 step in direct competition with hydroxamate ion ($\text{pK}'_a = 9.12$) in the k_{-3} step. However, since $\underline{\underline{\beta}}$ is an internal carbamate ester,¹⁰⁾ the rate-limiting general base catalyzed conversion of $\underline{\underline{\beta}}$ to $\underline{\underline{\gamma}}$ ($k_4, \text{H}_2\text{O}; k_5, \text{HO}^-$) would provide a subsequently rapid route to $\underline{\underline{\gamma}}$ because of the low pK'_a of the iminocarbonate nucleofuge in $\underline{\underline{\gamma}}$. Further, this mechanism finds analogy in the general base catalyzed removal of a proton from $\underline{\underline{\gamma}}$ on the pathway to aromatization

by loss of alkoxide ion.^{5b)}

These results therefore establish unequivocally the involvement of $\tilde{\gamma}$ as a reaction intermediate, and demonstrate the power of detailed kinetics allied to product distribution studies.

This work was supported in part by the Australian Research Grants Scheme and by the University of Queensland.

References

- 1) Th. J. de Boer and I. P. Dirkx, "The Chemistry of the Nitro and Nitroso Groups," ed by H. Feuer, Interscience, New York (1969), Part 1, p. 487; T. N. Hall and C. F. Poranski, Jr., *ibid.*, Part 2, p. 329 (1970); M. J. Strauss, *Chem. Rev.*, 70, 667 (1970).
- 2) A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, 87, 3217 (1965).
- 3) R. L. Blakeley and B. Zerner, *J. Am. Chem. Soc.*, 102, 6586 (1980).
- 4) a) C. F. Bernasconi, *Acc. Chem. Res.*, 11, 147 (1978); b) M. R. Crampton and M. J. Willison, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1681.
- 5) a) A. C. Knipe, J. Lound-Keast, and N. Sridhar, *J. Chem. Soc., Chem. Commun.*, 1976, 765; A. H. Khuthier, T. Y. Ahmed, and L. I. Jalbo, *ibid.*, 1976, 1001; A. C. Knipe and N. Sridhar, *ibid.*, 1979, 791; b) A. C. Knipe, N. Sridhar, and J. Lound-Keast, *Tetrahedron Lett.*, 1979, 2541.
- 6) R. L. Blakeley and B. Zerner, *Chem. Ind. (London)*, 1973, 133. Compound $\tilde{\gamma}$ crystallizes in two interconvertible forms whose properties in solution are identical but whose infrared spectra (KBr disc) are distinctly different.
- 7) Acid-promoted decarboxylation of N-carboxy-4-nitrophenoxyamine (6) produces 4-nitrophenoxyamine (see ref. 6) which is an aminating agent: T. Sheradsky, G. Salemnick, and Z. Nir, *Tetrahedron*, 28, 3833 (1972); Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, 1977, 1.
- 8) The parameters k_{HO^-} , k'_{HO^-} and K'_a in Eq. 1 were evaluated by plotting $k_{obsd} ([H^+] + K'_a) vs 1/[H^+]$ (pH 8.1-10.5) for a range of assumed values of K'_a . The maximum correlation coefficient (0.9988) by linear least squares analysis was obtained with a pK'_a of 9.12.
- 9) The O-anion of the conjugate base of a hydroxamic acid (e.g. 3) is in prototropic equilibrium with the corresponding N-anion (not shown), but the position of equilibrium is not known: S. Mizukami and K. Nagata, *Coord. Chem. Rev.*, 3, 267 (1968); L. Bauer and O. Exner, *Angew. Chem. Int. Ed. Engl.*, 13, 376 (1974). Rate constants leading away from $\tilde{\gamma}$ will therefore be a function of the unknown prototropic equilibrium constant.
- 10) a) L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 52, 852 (1963); b) M. L. Bender and R. Homer, *J. Org. Chem.*, 30, 3975 (1965); N. E. Dixon, P. W. Riddles, C. Gazzola, R. L. Blakeley, and B. Zerner, *Can. J. Biochem.*, 58, 1335 (1980); *erratum*, 59, 564 (1981).
- 11) A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1972, 808; A. F. Hegarty and L. N. Frost, *ibid.*, 1973, 1719.
- 12) For a variety of reactions (including the aromatization of 8) which involve the departure of alkoxide and phenoxide anions, the Brønsted β for the leaving group is in the range -0.65 to -1.29 (ref. 4a). Rate constants for departure of amines from Meisenheimer complexes of 1,3,5-trinitrobenzene are comparable to those of alkoxide ions for a given basicity: ref 4a; C. F. Bernasconi, M. C. Muller, and P. Schmid, *J. Org. Chem.*, 44, 3189 (1979). The same relationship is apparently obeyed in the alternate pathways for aromatization of the spiro Meisenheimer complex derived from N-methyl-2-(2,4,6-trinitrophenoxy)ethylamine: C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *J. Am. Chem. Soc.*, 98, 8451 (1976).
- 13) C. F. Bernasconi and J. R. Gandler, *J. Org. Chem.*, 42, 3387 (1977).
- 14) S. L. Johnson and D. L. Morrison, *J. Am. Chem. Soc.*, 94, 1323 (1972); S. P. Ewing, D. Lockshon, and W. P. Jencks, *ibid.*, 102, 3072 (1980).

(Received September 19, 1983)