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 pHindependent 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-4nitrophenoxyamine (\S).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-nitrophenoxide 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-nitrophenoxide ion (4) is minimal at pH 12 (Fig. 1), and the yield of rearrangement product (6, $\lambda_{max} \approx 315 \text{ nm}$)⁶⁾ shows a corresponding maximum.

$$k_{\text{obsd}} = (k_{\text{HO}^-} K_{\text{w}} / K_{\text{a}}' + K_{\text{HO}^-} [\text{HO}^-]) / (1 + [\text{H}^+] / K_{\text{a}}')$$
(1)

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



Fig. 1. Decomposition of 4-nitrophenyl N-hydroxycarbamate (2, 1×10^{-4} M) as a function of pH at 25°C in 1.64% (v/v) acetonitrile [$\mu = 1$ (KCI)]: (\bigcirc) log k_{obsd} . The line is theoretical for Eq. 1 with pK', 9.12; k_{HO^-} , 2.70 × 10³ M⁻¹ s⁻¹; k_{HO^-} , 56 M⁻¹ s⁻¹; K_w (ion product of water), 1.69 × 10⁻¹⁴ M². (\blacksquare) 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 $k_{\rm obsd}$ and the fractional yield (f) of the 4-nitrophenoxide ion (4):

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

$$f = (k_1 + k_2 [HO^-]) / k_{obsd} (1 + [H^+] / K'_a)$$
(4)

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

$$k_{\rm HO^-} = (K_a'/K_w) (k_1 + k_3k_4 / (k_{-3} + k_4 + k_5 [\rm HO^-]))$$
(5)

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

The results show that k_{HO}^{-} and $k_{HO}^{\prime}^{-}$ 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 2, 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 $[25^{\circ}C, k_1 = 5.3\pm0.2 \times 10^{-2} \text{ s}^{-1}; k_2 = 0.65\pm0.1 \text{ M}^{-1} \text{ s}^{-1}; k_3 = 0.21\pm0.04 \text{ s}^{-1}; k_3k_4/(k_{-3}+k_4) = 5.9\pm0.2 \times 10^{-3} \text{ s}^{-1}; k_{-3}/k_4 = 34.0\pm6; k_5/k_4 = 9.7\pm2\times10^3 \text{ M}^{-1}]$ 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 3 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 M⁻¹ s⁻¹) for the hydroxide promoted decomposition of 3 is much greater than that for the attack of hydroxide ion on 4-nitrophenyl dimethylcarbamate (4.0 × 10⁻⁴ M⁻¹ s⁻¹ at 25°C)^{10a)} or 4-nitrophenyl phosphate (8.2 × 10⁻⁹ M⁻¹ 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 3, and concerted removal of a proton accompanied by elimination appears more likely than pre-equilibrium formation of the dianion of 2.

The reactivity of the hydroxamate ion (3) towards cyclisation ($t_1 \le 3$ s at 25°C)⁹⁾ is greater than that of 2-(4-nitrophenoxy)ethylamines to form 7 (R = Me; $t_1 = 13$ 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 3.



The rate constants for the departure of RO⁻ from the Meisenheimer complex § show a normal dependence on the pK'_a of ROH.¹²⁾ Further, the possibility of major thermochemical strain in the spiro Meisenheimer complex 9a relative to 8 (R = Me), gains little support from kinetic data: (i) although the rate constant for aromatization of 9a by loss of alkoxide ion is ~170-fold higher than that of 8 (R = Me),^{4b)} ethylene glycol is a stronger acid than methanol by 0.77 pK'_a units; (ii) the rate constant for the loss of alkoxide ion from 9b is only 19-fold larger than that from 9a.¹³⁾

The above facts comment significantly on the mechanism of the aromatization of 5. Since $k_{-3}/k_{+} = 34$, it is thus exceedingly unlikely that a carbamate ion $(pK'_{a} \leq 5)^{14}$ is ejected in the k_{+} step in direct competition with hydroxamate ion $(pK'_{a} = 9.12)$ in the k_{-3} step. However, since 5 is an internal carbamate ester,¹⁰ the rate-limiting general base catalyzed conversion of 5 to 10 (k_{+} , H₂O; k_{5} , HO⁻) would provide a subsequently rapid route to 6 because of the low pK'_{a} of the iminocarbonate nucleofuge in 10. Further, this mechanism finds analogy in the general base catalyzed removal of a proton from 7 on the pathway to aromatization by loss of alkoxide ion.^{5b)}

These results therefore establish unequivocally the involvement of 5 as a reaction intermediate, and demonstrate the power of detailed kinetics allied to product distribution studies.

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References

- 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.*, <u>70</u>, 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).
- a) C. F. Bernasconi, Acc. Chem. Res., <u>11</u>, 147 (1978); b) M. R. Crampton and M. J. Willison, J. Chem. Soc., Perkin Trans. 2, 1974, 1681.
- a) A. C. Knipe, J. Lound-Keast, and N. Sridhar, J. Chem. Soc., Chem. Commun., <u>1976</u>, 765; A. H. Khuthier, T. Y. Ahmed, and L. I. Jalbo, *ibid.*, <u>1976</u>, 1001; A. C. Knipe and N. Sridhar, *ibid.*, <u>1979</u>, 791; b) A. C. Knipe, N. Sridhar, and J. Lound-Keast, *Tetrahedron Lett.*, <u>1979</u>, 2541.
- 6) R.L. Blakeley and B. Zerner, *Chem. Ind. (London)*, <u>1973</u>, 133. Compound 2 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*, <u>28</u>, 3833 (1972); Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, <u>1977</u>, 1.
- 8) The parameters $k_{\rm HO}^{-}$, $k_{\rm HO}^{\prime}^{-}$ and K_{a}^{\prime} in Eq. 1 were evaluated by plotting $k_{\rm obsd}$ ([H⁺] + K_{a}^{\prime}) vs 1/[H⁺] (pH 8.1-10.5) for a range of assumed values of K_{a}^{\prime} . The maximum correlation coefficient (0.9988) by linear least squares analysis was obtained with a pK_{a}^{\prime} 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 3 will therefore be a function of the unknown prototropic equilibrium constant.
- a) L. W. Dittert and T. Higuchi, J. Pharm. Sci., <u>52</u>, 852 (1963); b) M. L. Bender and R. Homer, J. Org. Chem., <u>30</u>, 3975 (1965); N. E. Dixon, P. W. Riddles, C. Gazzola, R. L. Blakeley, and B. Zerner, Can. J. Biochem., <u>58</u>, 1335 (1980); erratum, <u>59</u>, 564 (1981).
- 11) A. Williams, J. Chem. Soc., Perkin Trans. 2, <u>1972</u>, 808; A. F. Hegarty and L. N. Frost, *ibid.*, <u>1973</u>, 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., <u>44</u>, 3189 (1979). The same relationship is apparently obeyed in the alternate pathways for aromatization of the spiro Meisenheimer complex derived from Nmethyl-2-(2,4,6-trinitrophenoxy)ethylamine: C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, J. Am. Chem. Soc., <u>98</u>, 8451 (1976).
- 13) C. F. Bernasconi and J. R. Gandler, J. Org. Chem., 42, 3387 (1977).
- S. L. Johnson and D. L. Morrison, J. Am. Chem. Soc., <u>94</u>, 1323 (1972); S. P. Ewing, D. Lockshon, and W. P. Jencks, *ibid.*, 102, 3072 (1980).

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32