

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

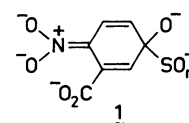
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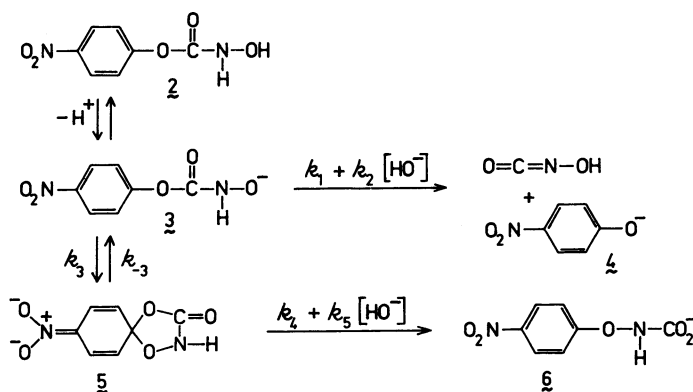
In alkaline solution, 4-nitrophenyl N-hydroxycarbamate undergoes reaction by elimination to yield 4-nitrophenoxide ion, and by rearrangement to yield N-carboxy-4-nitrophenoxamine. The effect of pH on the yield of the rearrangement product establishes that a transient spiro Meisenheimer complex is formed 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.<sup>1)</sup> In 1965, Kirby and Jencks<sup>2)</sup> 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.<sup>3)</sup> 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*<sub>-</sub> ≈ 18) in which it is generated. Indeed, when **1** is oxidized by air ultimately to the -SO<sub>3</sub><sup>-</sup> 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,<sup>4)</sup> spiro complexes of *mononitro* derivatives have been less well documented, even as transient intermediates.<sup>5)</sup> 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 (**5**).<sup>6)</sup> 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-nitrophenoxyamine<sup>7)</sup> (**6**) in proportions which vary with pH.<sup>6)</sup> The formation of both **4** and **6** obeys a strict first-order rate law, and  $k_{\text{obsd}}$  is independent of the concentration of buffers. Both products are formed in parallel, since  $k_{\text{obsd}}$  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;  $\text{SH} = \text{2}$ ).<sup>8)</sup> The yield of 4-nitrophenoxide ion (**4**) is minimal at pH 12 (Fig. 1), and the yield of rearrangement product (**6**,  $\lambda_{\text{max}} \approx 315 \text{ nm}$ )<sup>6)</sup> shows a corresponding maximum.

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

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

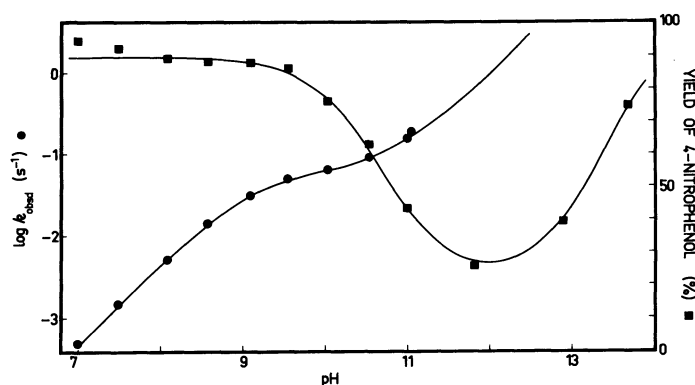


Fig. 1. Decomposition of 4-nitrophenyl N-hydroxycarbamate (**2**,  $1 \times 10^{-4} \text{ M}$ ) as a function of pH at 25°C in 1.64% (v/v) acetonitrile [ $\mu = 1(\text{KCl})$ ]: (●)  $\log k_{\text{obsd}}$ . The line is theoretical for Eq. 1 with  $\text{p}K'_a$ , 9.12;  $k_{\text{HO}^-}$ ,  $2.70 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ ;  $k'_{\text{HO}^-}$ ,  $56 \text{ M}^{-1} \text{ s}^{-1}$ ;  $K_w$  (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  $k_{\text{obsd}}$  and the fractional yield ( $f$ ) of the 4-nitrophenoxide ion (**4**):

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

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

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

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

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

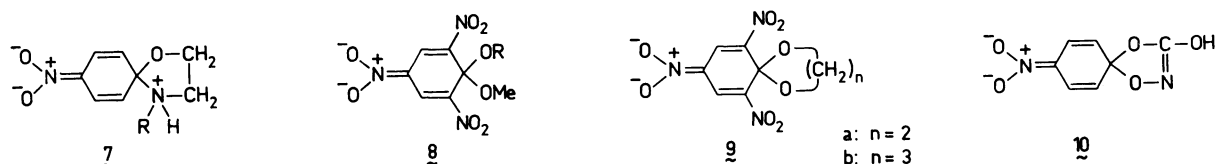
The results show that  $k_{\text{HO}^-}$  and  $k'_{\text{HO}^-}$  are independent of pH in the range of interest as required by Eq. 2.<sup>8)</sup> Moreover, the scheme requires that the kinetically

determined  $pK'_a$  (Eq. 1) is that of **2**, and the observed value of  $9.12 \pm 0.05$  is entirely reasonable for the  $pK'_a$  of a hydroxamic acid.<sup>9)</sup>

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 [ $25^\circ\text{C}$ ,  $k_1 = 5.3 \pm 0.2 \times 10^{-2} \text{ s}^{-1}$ ;  $k_2 = 0.65 \pm 0.1 \text{ M}^{-1} \text{ s}^{-1}$ ;  $k_3 = 0.21 \pm 0.04 \text{ s}^{-1}$ ;  $k_3 k_4 / (k_{-3} + k_4) = 5.9 \pm 0.2 \times 10^{-3} \text{ s}^{-1}$ ;  $k_{-3}/k_4 = 34.0 \pm 6$ ;  $k_5/k_4 = 9.7 \pm 2 \times 10^3 \text{ M}^{-1}$ ] were used to calculate the theoretical curve for  $f$  (Eq. 4) shown in Fig. 1.

The elimination of N-hydroxycyanic acid from a prototropic form<sup>9)</sup> 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,<sup>10)</sup> and for various phenyl N-phenyl-carbamates.<sup>11)</sup> The value of  $k_2$  ( $0.65 \text{ M}^{-1} \text{ s}^{-1}$ ) for the hydroxide promoted decomposition of **3** is much greater than that for the attack of hydroxide ion on 4-nitrophenyl dimethylcarbamate ( $4.0 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  at  $25^\circ\text{C}$ )<sup>10a)</sup> or 4-nitrophenyl phosphate ( $8.2 \times 10^{-9} \text{ M}^{-1} \text{ s}^{-1}$  at  $39^\circ\text{C}$ ).<sup>2)</sup> 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 ( $t_{1/2} < 3 \text{ s}$  at  $25^\circ\text{C}$ )<sup>9)</sup> is greater than that of 2-(4-nitrophenoxy)ethylamines to form **7** ( $R = \text{Me}$ ;  $t_{1/2} = 13 \text{ s}$  at  $60^\circ\text{C}$ )<sup>5b)</sup> 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  $\text{RO}^-$  from the Meisenheimer complex **8** show a normal dependence on the  $pK'_a$  of  $\text{ROH}$ .<sup>12)</sup> Further, the possibility of major thermochemical strain in the spiro Meisenheimer complex **9a** relative to **8** ( $R = \text{Me}$ ), 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** ( $R = \text{Me}$ ),<sup>4b)</sup> 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**.<sup>13)</sup>

The above facts comment significantly on the mechanism of the aromatization of **5**. Since  $k_{-3}/k_4 = 34$ , it is thus exceedingly unlikely that a carbamate ion ( $pK'_a \leq 5$ )<sup>14)</sup> is ejected in the  $k_4$  step in direct competition with hydroxamate ion ( $pK'_a = 9.12$ ) in the  $k_{-3}$  step. However, since **5** is an internal carbamate ester,<sup>10)</sup> the rate-limiting general base catalyzed conversion of **5** to **10** ( $k_4$ ,  $\text{H}_2\text{O}$ ;  $k_5$ ,  $\text{HO}^-$ ) 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.<sup>5b)</sup>

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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