Reaction of Substituted Nitrosobenzenes with Formaldehyde

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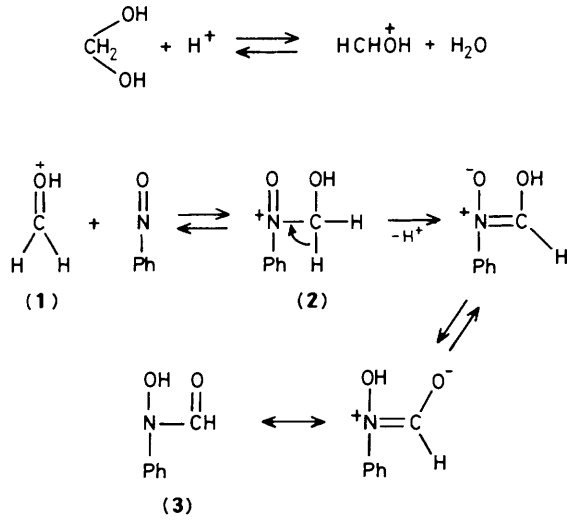
Substituted nitrosobenzenes react with formaldehyde in an acid-catalysed reaction giving *N*-phenylhydroxamic acids.

Hydroxamic acids are of current interest owing to the variety of their industrial and pharmaceutical applications, as well as their role as a model system for natural siderophores.[1—4] *N*-Phenylhydroxamic acids have been obtained, *e.g.* by thiamine-catalysed enzymatic conversion of nitroso aromatics[5a] and by direct reaction of glyoxylic acid with nitrosobenzenes.[5b] However, earlier attempts to obtain *N*-phenylhydroxamic acids from the reaction of nitrosobenzenes with formaldehyde or trifluoroacetaldehyde were unsuccessful.[5b,c]

We now report that substituted nitrosobenzenes react with formaldehyde in aqueous acidic media to give the corresponding *N*-phenylhydroxamic acids. The reaction proceeds by nucleophilic attack of nitroso nitrogen on protonated formaldehyde (**1**), followed by rate-determining proton transfer from the resulting intermediate (**2**) (Scheme 1).

This mechanism is supported by the following observations. (a) The reaction proceeds to completion and the only product is the corresponding hydroxamic acid (**3**), as shown by spectroscopic evidence. (b) At constant proton concentration, the observed reaction kinetics are second order overall, and first order with respect to both formaldehyde and nitrosobenzene. (c) Linear dependence of the reaction rate on H_3O^+ concentration, with zero intercept, in the concentration range 0.01—0.2 M, and a solvent deuterium isotope effect k_{D_2O}/k_{H_2O} of 1.64 + 0.10 (in 91% deuterium oxide) was observed. Both these facts are consistent with the pre-equilibrium protonation of formaldehyde which leads to acid catalysis.† (d) The order of reactivity of substituted nitrosobenzenes in this reaction is that of the electron-donating properties of the ring substituents, R′ (see Table 1). Although the number of derivatives examined is relatively small, the Hammett plot of log *k* *vs.* σ values illustrates this situation (Figure 1). In the closely similar



Scheme 1

reaction of nitrosobenzenes with glyoxylic acid an analogous order of reactivity was observed, and the occurrence of a nucleophilic attack of nitroso group on aldehyde group carbon of glyoxylic acid was proposed.[5b] (e) The added neutral salt ($NaClO_4$) significantly increases the reaction rate in the ionic strength range 0.1—2.0 M, while no 'primary salt effect' in the range 0.01—0.1 M was observed. This suggests that at least one of the reaction species is uncharged.‡ (f) A primary kinetic deuterium isotope effect k_H/k_D of 7.8 ± 0.32 between formaldehyde and [$^2H_2$]formaldehyde in this reaction was

† The observed acid catalysis may be also a consequence of protonation (occurring after nucleophilic addition), on the intermediate (**2**).

‡ The rate acceleration above 0.1 M may be due in part to the proton activity changes arising from ionic strength variations of the reaction medium.

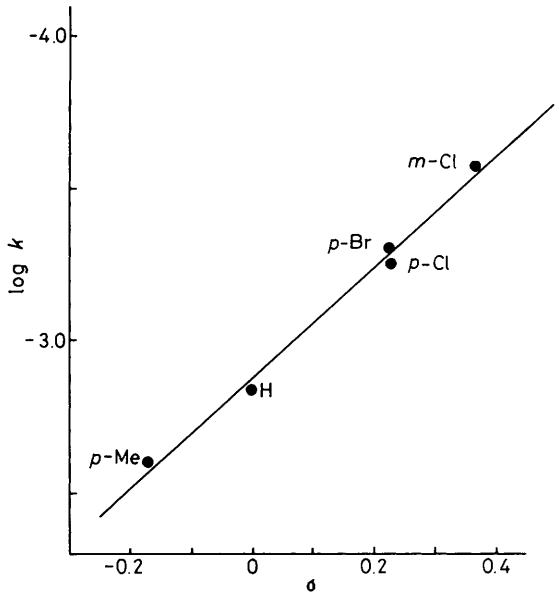


Figure 1. Plot of log $k_{obs.}$ for the title reaction *vs.* Hammett σ constants.

observed. The magnitude of this isotope effect is near the maximum for the rate-determining proton transfer from carbon.[6] The primary effect is complicated by a secondary isotope effect in the same direction arising from the change in sp^3 towards sp^2 hybridisation between the hydrated reactant and the transition state for dehydration. Nevertheless, it seems reasonable to conclude that the observed isotope effect suggests that proton transfer from intermediate (**2**) leading to the product, hydroxamic acid (**3**), is rate-determining for this reaction.

We found that trifluoroacetaldehyde also reacts with nitrosobenzene to give the corresponding hydroxamic acid. Although evidence for this reaction was only qualitative, we believe that it proceeds in the same way as that of formaldehyde and nitrosobenzenes, *i.e.* the single proton adjacent to the carbonyl carbon in trifluoroacetaldehyde becomes sufficiently acidic in the reaction intermediate [analogous to (**2**)] to be transferred in a rate-determining step leading to the product, hydroxamic acid.

Table 1. Rates of the reaction of substituted nitrosobenzenes R–C_6H_4–NO with formaldehyde.[a,b]

	R				
	p-Me	H	*p*-Cl	*p*-Br	*m*-Cl
$10^3 k_{obs.}$ [c,d]/s^{-1}	2.49	1.49	0.63	0.58	0.27

[a] In water, at 25 °C and the ionic strength 2.0 M ($NaClO_4$). [b] Kinetics are performed spectrophotometrically by following the disappearance of the absorbance of nitrosobenzene at 360 nm. [c] Rates expressed as pseudo-first order rate constants $k_{obs.} = k$ [HCHO][H^+] according to the rate law: rate = k [HCHO][H^+][Ph–NO] where concentrations of formaldehyde and H_3O^+ are constant throughout the reaction. [d] Average of several runs. Concentrations of formaldehyde and H_3O^+ ($HClO_4$) are 0.688 and 0.050 M respectively. Initial concentration of R–C_6H_4–NO was usually 5×10^{-4} M.

To our knowledge, there are few reactions such as the one reported here in which the nitroso group acts as a nucleophile,[5b] providing an easy and convenient synthetic route to *N*-phenylhydroxamic acids in potentially quantitative yields.

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