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Reactions of the Aldehyde Carbonyl Group with Nitrosobenzenes. Kinetic Studies Leading to a New Synthetic Route to the *N*-Phenylhydroxamic Acids

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Five *N*-phenylhydroxamic acids were synthesized in high yields starting from substituted nitrosobenzenes and formaldehyde, in water acidic medium under the specific acid catalysis conditions as well as under the general acid-catalysis conditions for the reaction of nitrosobenzenes with formaldehyde.

INTRODUCTION

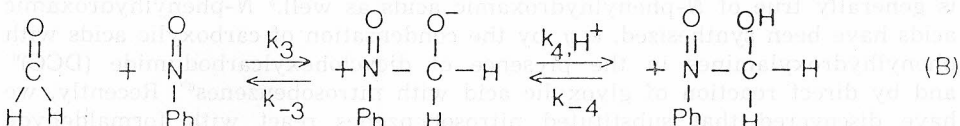
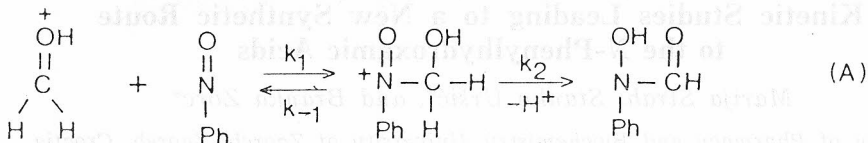
The chemistry and application of hydroxamic acids has received appreciable attention, owing to the variety of their industrial and pharmaceutical use as well as their role as a model system for natural siderophores.¹⁻⁵ This is generally true of *N*-phenylhydroxamic acids as well.⁵ *N*-phenylhydroxamic acids have been synthesized, *e. g.* by the condensation of carboxylic acids with phenylhydroxylamines in the presence of dicyclohexylcarbodiimide (DCC)^{6a} and by direct reaction of glyoxylic acid with nitrosobenzenes^{6b}. Recently, we have discovered that substituted nitrosobenzenes react with formaldehyde giving *N*-phenylhydroxamic acids.⁷ Dealing with the mechanism of this new reaction, at that time, we did not examine its synthetic utility. Now, starting from earlier⁷ and extended⁸ mechanistic investigations on the reaction of formaldehyde with nitrosobenzenes, we have developed two novel and useful synthetic procedures to the *N*-phenylhydroxamic acids. These synthetic routes are a) formation of the *N*-phenylhydroxamic acids from nitrosobenzenes and formaldehyde in water, catalyzed by specific acids and accelerated by the addition of neutral salt, and b) general acid catalyzed formation of the *N*-phenylhydroxamic acids from nitrosobenzenes and formaldehyde in acetic acid/water solvent without addition of neutral salt.

RESULTS AND DISCUSSION

It was recently demonstrated that the acid-catalyzed addition step of the reaction of formaldehyde with substituted nitrosobenzenes proceeds *via* two separate and concurrent processes^{7,8} (see Scheme). So, at pH values above 2 and in the absence of significant concentration of the neutral salt, the predominant process is the diffusion-controlled protonation of the zwitterionic intermediate I_{\pm} (pathway B in the Scheme). The second process, similar to that described as pathway A, which includes a »protonated«

formaldehyde as the reactant, becomes increasingly more important as the proton activity increases. Both processes, (A) and (B) are sensitive to the specific acid catalysis. Process (B) is also sensitive to the general-acid catalysis by the proton transfer from general acid to the zwitterionic intermediate I_{\pm} . Some experiments which illustrate this situation are presented in Table I.

Scheme 1



Added neutral salts accelerate both processes (A and B). This is the consequence of a) salting-out effects on the activity coefficient of aldehyde, and b) effective dehydration of the aldehyde hydrate because of the lowering of the water activity caused by the added salt. The addition of neutral salt into the water solution increases the proton activity too due to partial dehydration of the hydrated proton. This effect reflects only on the rate of process (A), since protonation of the zwitterionic intermediate I_{\pm} is diffusion-controlled, except in the case of general acids having $\text{p}K_a$ near or greater of $\text{p}K_a$ of the zwitterionic intermediate.⁹

In order to make use of these general considerations for synthetic purposes, we have performed reaction of five nitrosobenzenes (nitrosobenzene, 4-methylnitrosobenzene, 4-bromonitrosobenzene, 4-chloronitrosobenzene and

3-chloronitrosobenzene with formaldehyde, in acidified (*ca.* 0.05 M HCl) concentrated solution of sodium chloride in water (Method A in Experimental), and reaction of nitrosobenzene with formaldehyde in 50% v/v water solution of acetic acid (Method B in Experimental). Both methods have proved to be elegant, fast and very successful, with nearly quantitative yields of the corresponding *N*-phenylhydroxamic acids.

This holds especially in the case of method B, which is not so fast as method A but has some advantages over it, because difficulties connected with low solubility of nitrosobenzenes in water solutions were avoided using the acetic acid as solvent. The main role of acetic acid here, of course, is its function as proton-transfer agent in the general-acid catalyzed process.

The effect of the added neutral salt is shown in Figure 1 and Table I. Plotting of $\log k_{\text{obs}}/a_w$ (a_w = water activity) *vs.* concentration of the neutral salt gives the straight line indicating the significance of the salting-out effects for the observed rate acceleration.⁸ The influence of the organic cosolvent on the reaction rate is illustrated in Figure 2. The diminution of the rate is the highly unstable zwitterionic intermediate I_{\pm} , as a consequence of the rather large, and is probably caused mainly by the decrease in stability of decrease of solvent polarity going on from water to the mixed solvent.

TABLE I

Dependence of the rate of reaction between nitrosobenzene and formaldehyde on hydrogen ion and buffer acid concentration^{a,b}

Acid	mol dm ⁻³	10 ³ k_{obs}/s^{-1}
HClO ₄	0.0100	0.087
HCl	0.0104	0.090
HCl	0.0010	0.009
HCl	0.1469	2.511
HCl	0.2938	6.76
HCl	1.0093	73.036
ClHAc	0.0671	0.124
ClHAc	0.5242	0.451
ClAcNa	0.1153	
HCl	0.1469	3.653
ClHAc	0.9231	

^a In water, at 25 °C. HAc = acetic acid, ClHAc = chloroacetic acid, ClAcNa = sodium chloroacetate. ^b Average of several runs. Rate expressed as pseudo-first order rate constant $k_{\text{obs}} = k [\text{HCHO}] [\text{H}^+]$, according to the rate law: *rate* = $k [\text{HCHO}] [\text{H}^+]$ [Ph—NO], at 0.688 M HCHO. (Ph—NO = nitrosobenzene).

In order to obtain further information about the reaction of the aldehyde carbonyl group with nitrosobenzene, an attempt was made to examine the case of acetaldehyde. The result is partially surprising: acetaldehyde reacts with nitrosobenzene in 4 M NaCl solution and in the presence of strong acid (0.05–0.1 M), giving *N*-phenylacetohydroxamic acid. This is, to our knowledge, the first report dealing with this reaction. Investigation of its mechanism is in progress in this laboratory.

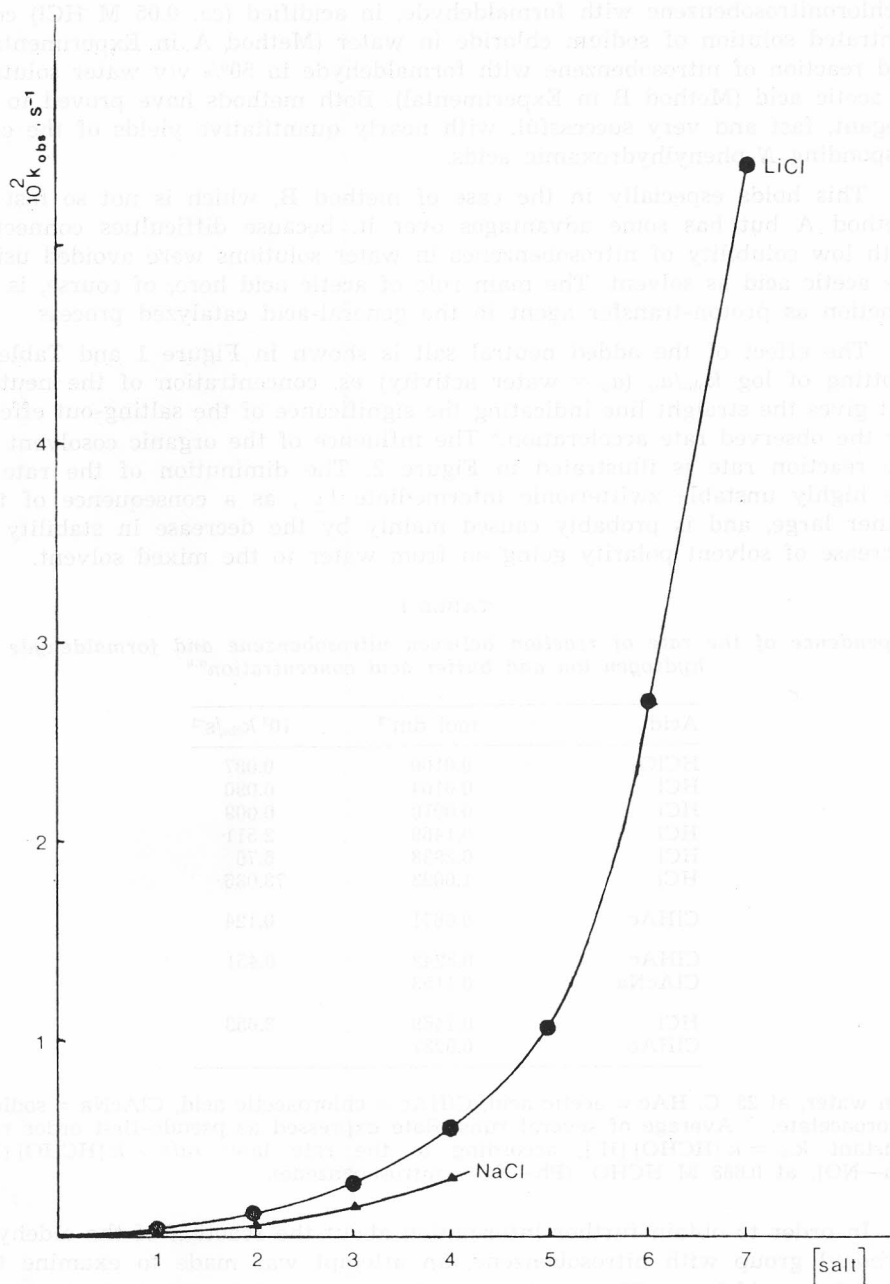


Figure 1. Effect of the added neutral salt on the rate of the reaction of nitrosobenzene with formaldehyde at 25°C. Rate constants were determined as described in Experimental.

TABLE II

Effect of the neutral salt on the rates of reaction of nitrosobenzene with formaldehyde^{a,b}

Added salt	mol dm ⁻³	10 ³ k _{obs} /s ⁻¹
none		0.44
NaCl	2.0	7.70
LiCl	2.0	13.47
LiCl	7.0	561.42
NaClO ₄	2.0	1.49
NaClO ₄ (in 40% v/v MeOH)	2.0	0.10

^a In water, at 25 °C. ^b Average of several runs. Rates expressed as pseudo-first order rate constants $k_{\text{obs}} = k[\text{HCHO}][\text{H}^+]$ as earlier (see Table I), where concentrations of formaldehyde and H₃O⁺ are 0.688 and 0.050, respectively, and are constant throughout the reaction.

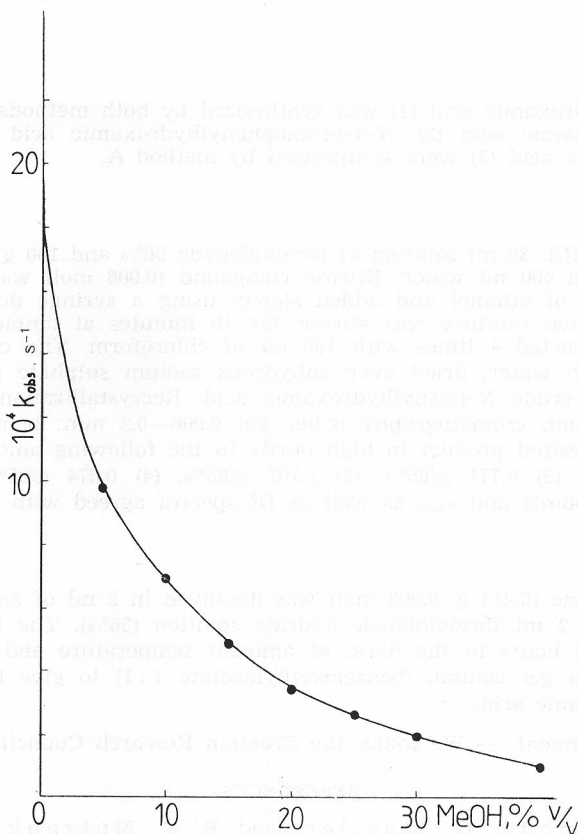


Figure 2. Dependence of rate constants for the reaction of formaldehyde with nitrosobenzene on the added methanol. Conditions: 0.688 M HCHO, 0.050 M HClO₄, 2 M NaClO₄, 25 °C. Rate constants were determined as described in Experimental.

EXPERIMENTAL

Reagents and Apparatus

All substituted aromatic nitroso compounds were prepared from the corresponding nitro aromatics following literature (nitrosobenzene,^{10a} 4-methylnitrosobenzene,^{10b} 4-bromonitrosobenzene,^{10c} 4-chloronitrosobenzene,^{10c} 3-chloronitrosobenzene^{10d}). Nitro aromatics for the preparation of nitroso compounds were commercially available. Formaldehyde dihydrate solution was Merck, 36%. Other chemicals and solvents were of analytical grade purity. Solvents were redistilled prior to use. Line distilled water was redistilled in full glass apparatus.

UV spectra were recorded on a Pye-Unicam Sp 8-100 spectrophotometer, IR spectra were taken on a Perkin-Elmer 547 spectrometer. Melting points were determined in open glass capillaries and are uncorrected. For thin-layer chromatography silica gel sheets Kieselgel 60 F₂₅₄, Merck, were used. Yields are not optimized.

Kinetics

Kinetics was performed by following the disappearance of the absorbance of nitrosobenzene at 360 nm, as reported.⁷⁻⁸ Individual rate constants were computed using a nonlinear least-square program. Very good pseudo-first order rate constant were obtained within 5 half-lives, and individual runs agreed within several percent.

Synthesis

N-phenylhydroxamic acid (1) was synthesized by both methods, while *N*-4-methylphenylhydroxamic acid (2), *N*-4-bromophenylhydroxamic acid (3), *N*-4-chlorophenylhydroxamic acid (5) were synthesized by method A.

Method A.

4 ml conc. HCl, 30 ml solution of formaldehyde 36% and 100 g sodium chloride were dissolved in 400 ml water. Nitroso compound (0.006 mol) was dissolved in a minimal amount of ethanol and added slowly using a syringe during 30–50 minutes. The reaction mixture was stirred for 10 minutes at ambient temperature, filtered and extracted 4 times with 100 ml of chloroform. The combined extract was washed with water, dried over anhydrous sodium sulphate and rotary evaporated to give crude *N*-phenylhydroxamic acid. Recrystallization from ether/petroleum ether or column chromatography (silica gel 0.006–0.2 mm; benzene/ethylacetate 1:1) gave the desired product in high purity in the following amounts and yields: (1), 0.749 g/91%, (2) 0.771 g/85%, (3) 1.101 g/85%, (4) 0.874 g/85% and (5) 0.926 g/90%. Melting points and λ_{\max} , as well as IR spectra agreed with literature data.^{6b}

Method B.

Nitrosobenzene (0.214 g, 0.002 mol) was dissolved in 2 ml of acetic acid (99.6%) and mixed with 2 ml formaldehyde hydrate solution (36%). The reaction mixture was kept for 2.5 hours in the dark, at ambient temperature and then chromatographed on silica gel column (benzene/ethylacetate 1:1) to give 0.260 g (95%) of *N*-phenylhydroxamic acid.

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SAŽETAK

Reakcija aldehidne karbonilne skupine s nitrozobenzenima. Sinteze N-fenilhidroksamskih kiselina iz nitrozobenzena i formaldehida

M. Strah, S. Uršić i B. Zorc

Reakcijom nitrozobenzena s formaldehidom sintetizirano je pet N-fenilhidroksamskih kiselina u visokim iskorištenjima. Reakcije su provedene u vodeno-kiselom mediju primjenom specifične kisele i opće kisele katalize. Proučavan je i diskutiran utjecaj dodatka neutralne soli i organskog kosolventa na tok reakcije.