Difference in the Reactions of *N*-Methylhydroxylamine and *N*-Phenylhydroxylamine with Nitrosobenzene

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The reaction of nitrosobenzene with *N*-methylhydroxylamine was studied. The pH-rate profile exhibits a negative break at between pH 0.5 and 3.0, which is considered to be caused by a change in the rate-determining step of the reaction from an attack of the amine on nitrosobenzene at low pH, to the dehydration of an addition intermediate previously formed between the reagents at higher pH. This behavior is different from that of the reaction between *N*-phenylhydroxylamine and nitrosobenzene where, over the entire pH range, the only rate-determining step is dehydration of the addition intermediate. This fact confirms the special behavior of phenylhydroxylamine as a nucleophile, as was observed in its reactions with aromatic aldehydes.

Nitrosobenzene is formed in biological systems,[1,2] and under physiological conditions can react with various nucleophiles. It thus seems to be of biological interest to investigate the mechanisms of the reaction of nitrosobenzene with nucleophiles.

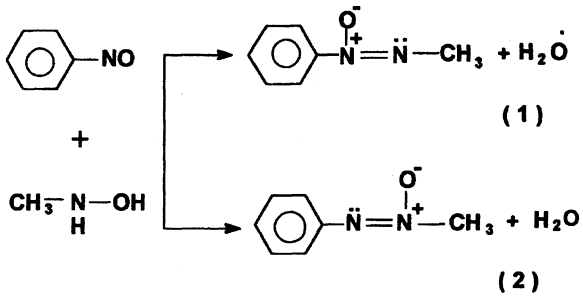
It was also demonstrated that the rate constant of the reaction of nitrosobenzene with *N*-phenylhydroxylamine between pH 1—5 is determined by the oxonium-ion-catalyzed dehydration of an addition intermediate formed between the reagents.[3] Surprisingly this rate constant is three-times larger than that for the rate-determining oxonium-ion-catalyzed attack of aniline to the nitrosobenzene to form a similar addition intermediate.[4] Thus, it is evident that the attack step of *N*-phenylhydroxylamine on the nitrosobenzene should be significantly faster than that of aniline in spite of phenylhydroxylamine to be 500-times less basic.

It was proposed that the reaction of benzaldehyde with *N*-phenylhydroxylamine follows a pre-association mechanism in an attack step that is different from the mechanism of other amines.[5] This pre-association mechanism was demonstrated to have special steric requirements.

In this study we analyzed the reaction of nitrosobenzene with *N*-methylhydroxylamine, which exhibits different steric characteristics which respect to *N*-phenylhydroxylamine, in order to obtain insights about this kind of mechanism.

Results and Discussion

The reaction of nitrosobenzene with *N*-methylhydroxylamine could give two products according Scheme 1.



Scheme 1.

An analysis of the reaction products by HRGC MS indicates that compound (**1**) is the only one formed in this reaction, as was observed previously by Freeman.[6]

The reaction was studied in the pH range 0—12 in water, and the concentration of *N*-methylhydroxylamine was in the required excess in order to obtain pseudo-first-order reaction conditions.

The pH dependence of the second-order rate constants (k_{2ap}) extrapolated to zero buffer concentration is shown in Fig. 1. Between pH 0 and 5 a nonlinear pH-rate profile generally shows a negative deviation caused by a change in the rate-determining step, as observed in the reaction of nitrone formation from *p*-chlorobenzaldehyde and *N*-methylhydroxylamine[7] and between *p*-nitrosobenzene and aniline.[8]

Thus it is assumed that the reaction mechanism of nitrosobenzene with *N*-methylhydroxylamine is a two-step process: a first-step, (rate-determining between pH $\approx$ 3.0 and pH $\approx$ 0) the attack of the nucleophile on the nitrosobenzene to give an *N*,*N*′-dihydroxy intermediate (Eq. 1) and a second step (rate-determining between pH $\approx$ 3.0 and pH $\approx$ 12) involving the dehydration of this intermediate to products (Eq. 2).

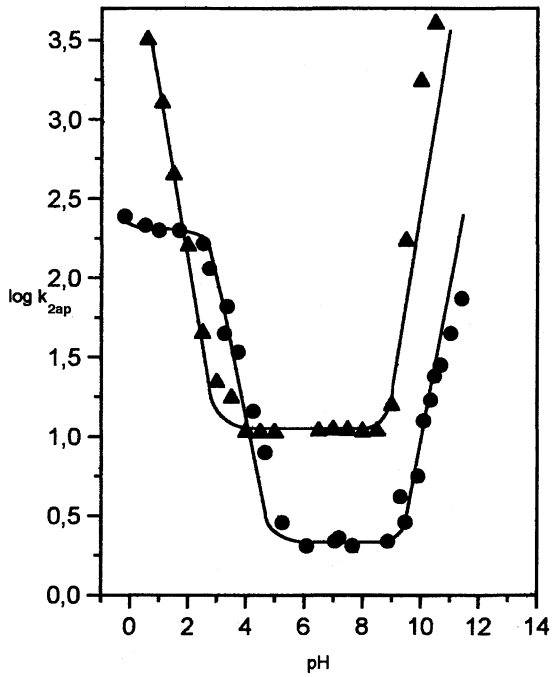
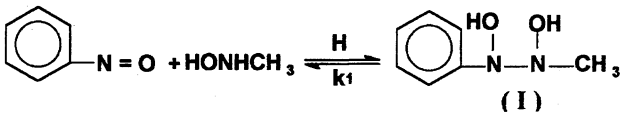
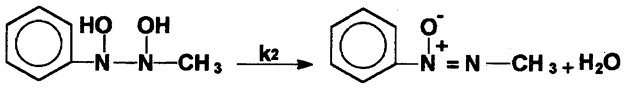


Fig. 1. pH-dependence of the logarithms of second-order rate constants for reaction of *N*-methylhyroxylamine (●) and *N*-phenylhydroxylamine (▲) which nitrosobenzene in water, 25 °C and ionic strength 1 M (KCl).



(1)



(2)

After the third-order rate constant, determined in presence of buffers, was plotted against the molar fraction of free acid for several different concentrations, a least-squares fit was made. The right-hand intercept gives the catalytic constant for the acidic component of the buffer (k_{AH}, Table 1), whereas the left-hand intercept gives the catalytic constant for the basic component of the buffer (k_B, Table 1).

Table 1. Rate Constants for General-Acid (k_{AH}) and General-Basic (k_B) Catalyzed 1-Methyl-2-phenyldiazene 2-Oxide Formation from *N*-Methylhydroxylamine and Nitrosobenzene[a)]

Catalyst	pK_a	logk_{AH}	logk_B
H_3O^+	−1.70	5.14	—
HCO_2H	3.69	2.94	—
CH_3CO_2H	4.67	2.57	2.17
$CH_2(CO_2H)_2$	5.48	2.90	2.16
$H_2PO_4^-$	6.78	2.68	2.41
Imidazolium	7.02	2.03	2.65
Morpholinium	8.87	1.41	2.80
H_2O	15.70	−1.44	4.94

a) *N*-Methylhydroxylamine 10^{-3} M, nitrosobenzene 8.33×10^{-5} M, in water, 25 °C and ionic strength 1.0 M (KCl).

General Acid Catalysis. The catalytic rate constants for different acids follow the Brønsted equation (Fig. 2) and give a value of $\alpha = 0.34$ ($r = 0.99$). Experiments with different concentrations of acetic acid at pH = 3.0 showed that the value agrees acceptably with that obtained from a plot of the third-order rate constants vs. the molar fraction of free acid, indicating that the mechanism is a true general-acid catalysis. The points corresponding to the oxonium ion as an acid catalyst satisfactorily fit the line of correlation, which is expected for a concerted mechanism with proton participation in the formation or rupture of bonds from heavy atoms in the transition state. The point corresponding to water also fits the Brønsted line, showing that this molecule participates in this mechanism as a general acid catalyst.

Specific and General-Base Catalysis. The catalytic constants for different bases give a Brønsted plot with $\beta = 0.20$ ($r = 0.98$) (Fig. 3). It is important to observe that the point corresponding to the hydroxide ion shows a positive deviation of ten times. This fact was also observed in the reaction of *N*-phenylhydroxylamine with nitrosobenzene, and was considered to be strong evidence for specific-base catalysis by the hydroxide ion.[3)]

Another line of evidence is pK_a of the first ionization of one hydroxy group of the *N*,*N*′-dihydroxy intermediate of the reaction. From pK_a of a similar intermediate of the reaction of nitrosobenzene and *N*-phenylhydroxylamine, which was calculated to be 11.61,[3)] it is possible to calculate the difference introduced by the change of one phenyl for a methyl group.

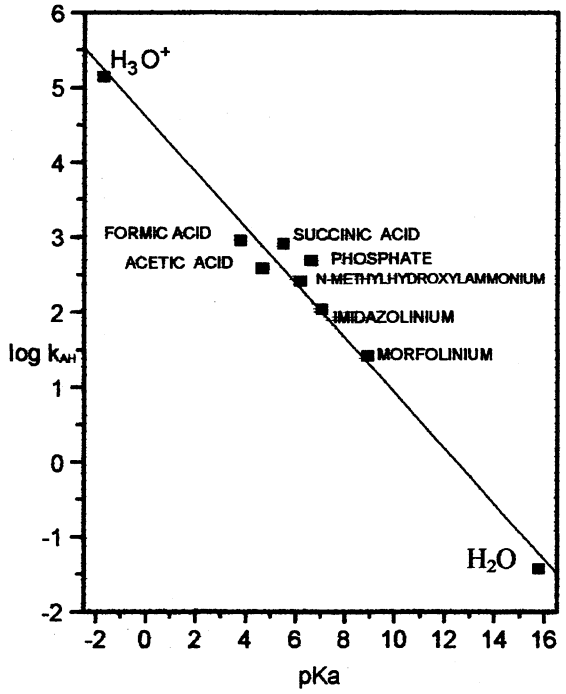


Fig. 2. Brønsted plot for general-acid catalysis of the dehydration step of the reaction between *N*-methylhydroxylamine and nitrosobenzene, in water, 25 °C and ionic strength 1 M (KCl) $\alpha = 0.34$ ($r = 0.99$).

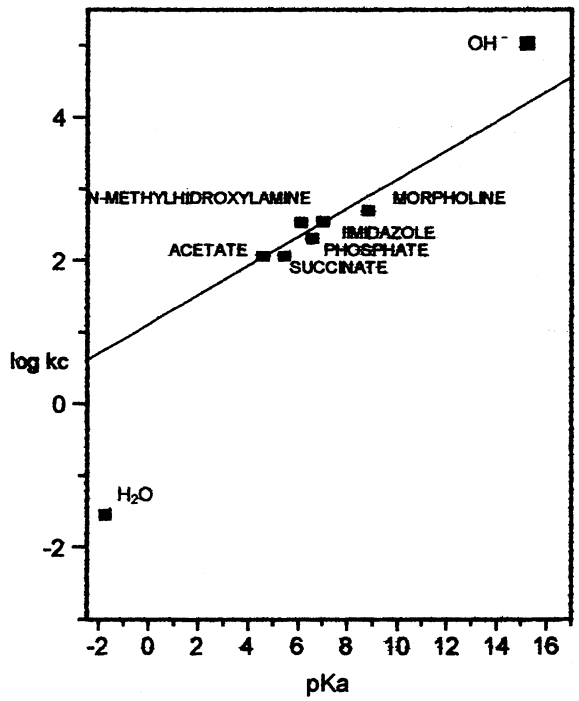


Fig. 3. Brønsted plot for general-base catalysis of the dehydration step of the reaction between *N*-methylhydroxylamine and nitrosobenzene, in water, 25 °C and ionic strength 1 M (KCl) $\beta = 0.20$ ($r = 0.98$).

The acid-strengthening effect of the phenyl group can be calculated from its σ^* (0.75[9]) and the equation $-\Delta pK_a = 0.06+0.63\sigma^*$ [9] as −0.53; however, since the phenyl ring is directly bonded to the functional group, the effect, assuming normal behavior, will be $-0.53/0.4 = -1.32$. The effect of the methyl group, which has $\sigma^* = 0.00$, is +0.06. Thus, pK_a of the *N*,*N*′-dihydroxy intermediate as an acid will be $11.61+0.06-(-1.32) = 12.87$. Even with a calculus error of one unit pK_a of the *N*,*N*′-dihydroxy intermediate is smaller than that of the hydroxide ion, supporting the idea that the mechanism of its catalysis is base-specific, considering that to act as a true general catalyst, the pK_a value of the catalyst must lie between those of the initial and final substrate sites.[10]

Mechanism of the Reaction. The condensation between *N*-methylhydroxylamine and nitrosobenzene gives the product 1-methyl-2-phenyldiazene 2-oxide (**1**), but not 1-methyl-2-phenyldiazene 1-oxide; that is, considering the resonance effect, the more stable product. Evidently the reaction is kinetically controlled because a departure of the 1-hydroxy group is favorable with respect to the 2-hydroxy group due to the inductive effects of the methyl and phenyl groups.

It is interesting to observe that: i) The reaction of *N*-methylhydroxylamine with nitrosobenzene exhibits a negative deviation of the plot of $\log k_2$ vs. pH, which should be considered to be evidence for a change in the rate-determining step from an dehydration of an addition intermediate, formed between the reagents, at higher pH to an attack of the nucleophile on the nitroso compound at lower pH.[11] The reaction of *N*-phenylhydroxylamine with nitrosobenzene shows no evidence of this kind of deviation. ii) Also, the rate constant of the oxonium-ion catalyzed dehydration of the reaction between *N*-phenylhydroxylamine with nitrosobenzene ($k_{H^+} = 1.44\times10^4$ dm^{-6} mol^{-2} min^{-1}) is six-times as large as the rate constant of the concerted hydroxonium-ion, catalyzed attack of *N*-methylhydroxylamine on nitrosobenzene ($k_{H^+} = 2.23\times10^3$ dm^{-6} mol^{-2} min^{-1}) between pH ≈ 0.5 an pH ≈ 0, and eighty-times as large as the rate constant of an uncatalyzed attack of *N*-methylhydroxylamine on nitrosobenzene ($k_2 = 1.77\times10^2$ dm^{-6} mol^{-2} min^{-1}) between pH ≈ 3.0 and pH ≈ 1.5 (Fig. 1) in spite of *N*-phenylhydroxylamine being approximately 10^4-times less basic. These facts are evidence that the reaction of an attack of *N*-phenylhydroxylamine on nitrosobenzene follows an special mechanism, as was shown for the similar reaction of *N*-phenylhydroxylamine with benzaldehyde.[5]

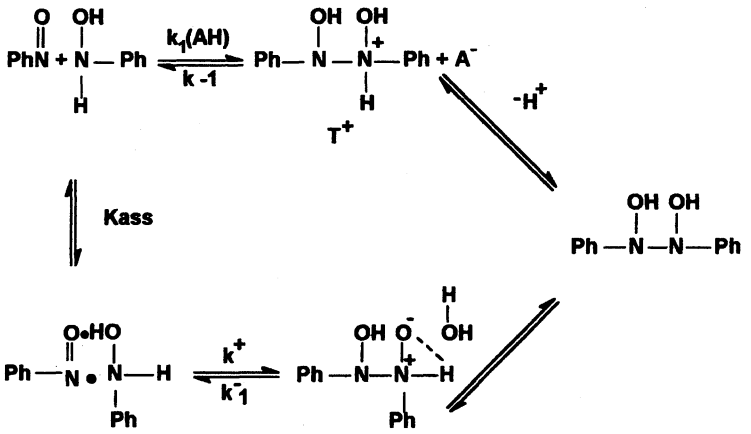
Ogata et al.[12] observed that the reaction of *p*-chloronitrosobenzene and *N*-phenylhydroxylamine lead to the formation of four azoxy-compounds. They suggest that a rapid redox pre-equilibrium with a proton transfer is established (Eq. 3) and that the condensation of all possible reactant pairs leads to the observed products:

$$p\text{-ClC}_6\text{H}_4\text{NO} + \text{PhNHOH} \rightleftharpoons p\text{-ClC}_6\text{H}_4\text{NHOH} + \text{PhNO} \quad (3)$$

Darchen and Moinet[13] have suggested a mechanism due to free radicals through a *N*-hydroxy-*N*′-oxide intermediate that was demonstrated not to be correct.[3] In a study of the reaction of *p*-substituted nitrosobenzene with *N*-alkyl-*N*-arylhydroxylamines Knight and Loadman[14] suggest that the reaction proceeds via an intermediate nitroxyl radical pair required by an electron-transfer mechanism. However, evidence for a symmetrical *N*,*N*′-dihydroxy intermediate and for a rapid equilibrium for its formation was given by Shemyakin et al.[15] from ^{15}N studies; then, from ^{18}O labelled *N*-phenylhydroxylamine[11] Becker and Sterson[17] gave more evidences for the formation of an symmetrical intermediate which is in rapid equilibrium with nitrosobenzene and *N*-phenylhydroxylamine.

In this study it was demonstrated that the rate-pH profile of the reaction of *N*-methylhydroxylamine with nitrosobenzene is completely similar to that of *N*-methylhydroxylamine with *p*-chlorobenzaldehyde,[7] which provides evidence that both reactions follow the same mechanism. For this reason "in the absence of any compelling evidence for a radical mechanism"[7] it is possible to conclude that these reactions occur by an ionic mechanism similar to that of oxime formation.[18]

The present result cannot exclude the existence of free radicals on or off the reaction pathway of azoxybenzene formation, but permit us to consider an alternative mechanism where there is a pre-association between nitrosobenzene and *N*-phenylhydroxylamine, probably formed in two steps: in the first one, a hydrogen bonding between the hydroxy group of the *N*-phenylhydroxylamine and the oxygen of the nitrosyl group occurs; in the second step an attack of the nucleophilic nitrogen of *N*-phenylhydroxylamine on the electrophilic nitrogen of the nitrosobenzene occurs. This "encounter com-



Scheme 2.

plex" has special steric and electronic requirements that are not satisfied in the case of nitrosobenzene and *N*-methylhydroxylamine that follow by a concerted acid-catalyzed attack of the nucleophile on the nitrosobenzene (Scheme 2).

Experimental

Materials: Nitrosobenzene was synthetized and purified by sublimation, as indicated in the literature.[19] Commercial *N*-methylhydroxylamine was purified by recrystallization from ethanol.

Kinetic Procedure: The reactions were followed spectrometrically at 25 °C by monitoring the formation of the product at 250 nm. The reactions were carried out in water at 25 °C and ionic strength 1.0 M (KCl) (1 M = 1 mol dm^{-3}). The solutions were prepared immediately before use and degassed with nitrogen. The initial concentrations were 8.33×10^{-5} and 10^{-3} M for nitrosobenzene and *N*-methylhydroxylamine, respectively.

The reactions were followed for three half-lives under the indicated pseudo-first-order conditions. The first-order rate constants (k_{obsd}) were calculated with a computer. The second-order rate constants were calculated by dividing k_{obsd} by the concentration of *N*-methylhydroxylamine as a free base. Apparent second-order rate constants (k_{2ap}) were calculated by dividing the k_{obsd} by the concentration of *N*-methylhydroxylamine as a free base. Apparent second-order rate constants (k_{2ap}) were calculated by dividing the k_{obsd} by the concentration of the free amine,

$$k_{2ap} = (k_{obsd}/[Nu]_1)fc \quad (4)$$

where $fc = 1+K_{ad}\,[Nu]_1$; since $[Nu]_1\,K_{ad}$ is very small, $fc = 1$. The concentration of the free amine calculated by Henderson–Hasslbalch equation.

Steady-state treatment of the mechanism in Scheme 3 yields

$$k_{ad} = k_{1H^+} + k_2, \quad (5)$$

$$k_{deh} = k_3k_{ad}[H^+]/1 + k_3k_{ad}[H^+], \quad (6)$$

for product formation in the regions of the rate-determing neutral intermediate (I^0) formation (k_{ad}) and dehydration (k_{deh}) respectively.

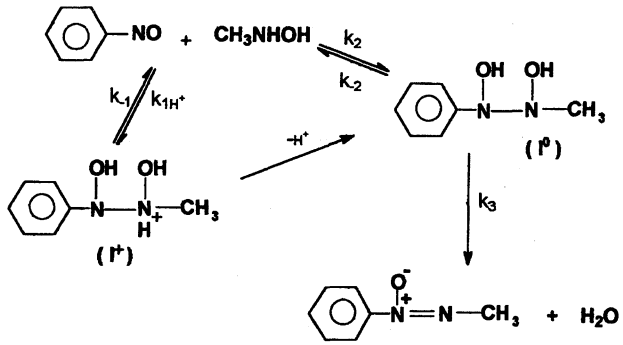
k_{2ap} was calculated employing

$$k_{2ap} = k_{ad}k_d/k_{ad} + k_d, \quad (7)$$

together with the rate constants in Table 2.

The Product Analysis: The formation of only one product was also followed by GC analysis on a Shimadzu GC model 14A equipped with a flame-ionization detector. The column was a 0.25 mm×25 m fused-silica capillary column (OV-1). The oven temperature was programmed to increase 5 °C min^{-1} from 40 to 190 °C. Hydrogen was used as the carrier gas. The structural elucidation was made by ^{1}H NMR using a Bruker AM-200 spectrometer, giving a sinal 3.4 ppm (H, CH$_3$) according to the literature.[6]

Mass spectra were obtained on a Shimadzu-CGMS-QP-2000 spectrometer interfaced to a model 14B Shimadzu GC. The mass spectrum showed a molecular peak at *m/z* 136 and major fragments at *m/z* 120 (*m*−16), 119 (*m*−16−1), 108 (*m*−28), 107 (*m*−29), and 77 (*m*−59).



Scheme 3.

Table 2. Kinetic Constant for Product Formation from the Reaction of Nitrosobenzene and *N*-Methylhydroxylamine[a]

Constant kinectic		Value
k_{1H^+}	(dm^{-6} mol^{-2} min^{-1})	2.23×10^3
k_2	(dm^{-6} mol^{-1} min^{-1})	1.77×10^3
k_3K_{ad}	(dm^{-6} min^{-1})	2.30×10^3

a) *N*-Methylhydroxylamine 10^{-3} M, nitrosobenzene 8.33×10^{-5} M, in water, 25 °C and ionic strength 1.0 M (KCl).

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