6. Reactions of Carbonyl Group with Nitroso Compounds: Reaction of Formaldehyde with Substituted Nitrosobenzenes

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Formaldehyde reacts with substituted nitrosobenzenes giving the corresponding N-phenylhydroxamic acids. A mechanism involving three sequential steps in this reaction is proposed. The first step is the nucleophilic attack of the nitroso group on the carbonyl group which leads to the formation of the unstable tetrahedral zwitterionic intermediate. This step is followed by the proton transfer to the zwitterionic intermediate to form more stable nitrosocarbinolic cation intermediate, which in the subsequent step undergoes the rate-controlling elimination of proton from the C-atom of nitrosocarbinolic group, leading to the final product, hydroxamic acid. The first and the second step appear to be reversible. The experimental evidence obtained, which is the basis for such a description of the investigated reaction, includes: a) the order of reactivity of substituted nitrosobenzenes, as demonstrated by the plot of log k_{obs} *vs.* σ *Hammett* parameters with slope of -1.74; b) the observation of a general-acid catalysis; c) the observation of the inverse solvent deuterium isotope effect of *ca.* 1.8 in the reaction; d) the observation of kinetic primary deuterium isotope effect of *ca.* 8 related to the 'water' reaction in the reactions of formaldehyde with substituted nitrosobenzenes; e) the observation of general-base catalysis in the reaction; f) the observation of the kinetic primary deuterium isotope effect of *ca.* 2.1 for the acetate-ion-catalyzed reaction.

Introduction. – Chemistry of hydroxamic acids has received considerable attention [1–8], and this interest is also connected with a variety of their pharmaceutical and industrial applications [4–6]. Particularly important is their role as siderophores, as well as a model system for natural siderophores [7–9]. Siderophores are low-molecular-weight multidentate ligands which serve as Fe^{III}-specific chelators of biological importance. Natural trishydroxamic acid desferioxamine, for instance, is currently the only really clinically useful drug for the transfusion-induced iron overload treatment [9]. On the other hand, it is well known that the reactions involving C=O group present a large fraction of chemical and an even larger fraction of biochemical reactions.

It was reported that nitrosobenzenes react in water medium with C=O group of glyoxylic acid [10], and in water acidic medium with formaldehyde [11], trifluoroacetalde-hyde [11], acetaldehyde [12] [13], and pyruvic acid [13], giving the corresponding hydroxamic acids. Aliphatic nitroso compounds also react with formaldehyde giving hydroxamic acids [14]. It seems that these reactions proceed by the mechanism bearing resemblance to the addition reactions of nitrogen nucleophiles, such as amine, hydroxylamine, *etc.*, to the C=O group [15–19]. The case of the reaction of formaldehyde with nitrosobenzene is illustrated in the *Scheme*. Although nitrosobenzenes are considered to have electrophilic rather than nucleophilic properties, the evidence obtained suggests that the first step is nucleophilic addition of the NO group to the C=O group, resulting in the formation of unstable tetrahedral zwitterionic intermediate. This intermediate is trapped by the proton transfer from an acid catalyst, to form a more stable cation intermediate, unless it reverts into the reactants. The cation intermediate undergoes the subsequent

Scheme
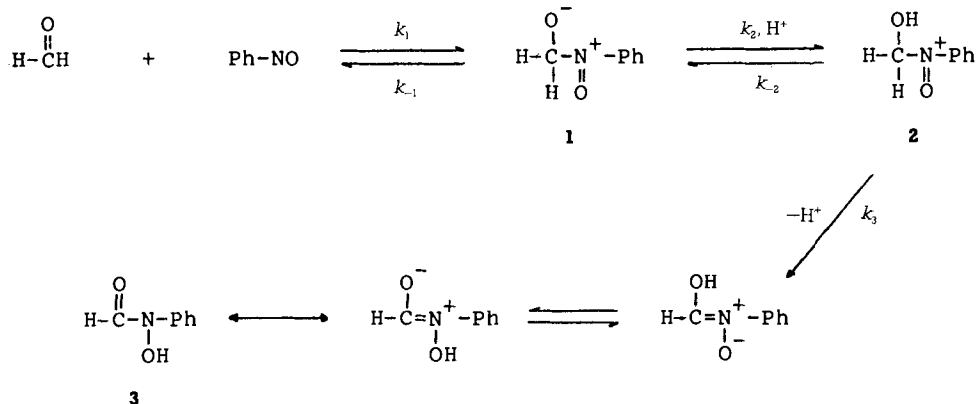
1   **2**

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rate-controlling elimination of proton from the C-atom of nitrosocarbinolic group (or decarboxylation in the case of an oxo-acid [13]). The elimination step is general-base catalyzed, and the final product is the corresponding hydroxamic acid. In this paper, evidence is presented in support of such a description of the reaction of formaldehyde with substituted nitrosobenzenes[1]). This reaction is one of the few known reactions of carbonyl compound with nitrosobenzenes which lead to hydroxamic acids, and the first case where an aldehyde is included in this type of reaction.

Results and Discussion. – The reaction of formaldehyde with nitrosobenzenes proceeds, under the conditions employed, to completion, giving the corresponding hydroxamic acid **3**. Evidence for this comes from UV spectra, product analysis[2]), and VIS spectra of the (monohydroxamato)iron(III) complexes. At constant hydrogen-ion concentration, the observed pseudo-first-order rate constants depend linearly on the aldehyde concentration in excess, suggesting that the reaction is of the first order with respect both to formaldehyde and nitrosobenzene. In the range of 0.001–0.030M H_3O^+, the observed pseudo-first-order rate constants depend linearly on the hydrogen-ion concentration. Above 0.03M H_3O^+, this dependence became nonlinear, and in the pH range of 0.907–0.040, log k_{obs} correlate linearly ($r = 0.997$) with pH (as measured by the glass electrode). At the constant ionic strength, for example in 2.0M $NaClO_4/HClO_4$, linear dependence on $[H^+]$ was obtained up to 0.150M H_3O^+. The observed rate law is

$$k_{obs} = k \, [HCHO] \, [H^+] \, [PhNO].$$

Rate constants for the five substituted nitrosobenzenes were determined. The order of reactivity established is that of the electron-donating properties of ring substituents. Linear plot ($r = 0.99$) of log k_{obs} vs. *Hammett* σ parameters with slope of -1.74 was obtained.

The inverse solvent deuterium isotope effect $k(D_2O)/k(H_2O)$ is observed in this reaction. The value $k(D_2O)/k(H_2O)$ is 1.79 (in 98% D_2O) at 0.0150M H_3O^+, and 1.64 (in 91% D_2O) at 0.0307M H_3O^+, which lead to the value of *ca.* 1.8 in 100% D_2O.

[1])   A preliminary account of a portion of this work was presented in [11].
[2])   The synthetic use of this reaction was described in [12].

Table. *Rate Constants for the Acid- and Base-Catalyzed Reaction of Formaldehyde with Substituted Nitrosobenzenes*[a])[b])

R	Catalyst [M]	$10^{-1} k_H$ [$M^{-2}s^{-1}$]	Catalyst	k_{HA} [$M^{-2}s^{-1}$]
H	H_3O^+, 0.001	2.98	CH_3COOH	0.13
	H_3O^+, 0.010	2.86	HCOOH	0.84
	H_3O^+, 0.005	10.02[c])	$CH_2ClCOOH$	0.88[d])
	H_3O^+, 0.050	9.84[c])	$CHCl_2COOH$	0.93[d])
	H_3O^+, 0.052	19.43[e])		
	H_3O^+, 1.031	23.39	CH_3COO^-	0.15[f])
$p-CH_3$	H_3O^+, 0.050	16.45[c])		
$p-Cl$		4.16[c])		
$p-Br$		3.84[c])		
$m-Cl$		1.77[c])		

[a]) Taking 4.4×10^{-4} for the equilibrium constant for dehydration of formaldehyde [27c]. Rate constants are expressed starting from experimentally obtained pseudo-first-order rate constants.
[b]) In water, at 25° and without added neutral salt except otherwise noted.
[c]) Ionic strength 2.0 ($NaClO_4$).
[d]) Extrapolated to the zero ionic strength.
[e]) Ionic strength 1.0 (NaCl).
[f]) Ionic strength 3.5 ($NaCl/CH_3COONa$).

General-acid catalysis was observed in this reaction (*cf.* the *Table*). The catalytic rate constants for dichloroacetic[3]), chloroacetic, and formic acid are of the same order of magnitude, differing little one from another. The ratio between catalytic rate constant for hydronium ion (at 0.001M H_3O^+) and catalytic rate constant for the formic acid is 35, while the corresponding rate ratio for acetic acid differs for *ca.* one order of magnitude in comparison with catalysts of lower pK_a. These results suggest that the proton transfer from catalysts with pK_a of 3.77 (the pK_a value of formic acid) or less is strongly thermodynamically favorable, while for catalysts of pK_a above this value the proton transfer process becomes thermodynamically less favorable.

General-base catalysis by acetate ion was observed in this reaction. The rate ratio established between acetate-catalyzed and water-catalyzed reactions is *ca.* 60 (taking 55.5M for the water concentration).

Primary kinetic deuterium isotope effect k_H/k_D of 7.78 (0.32) between formaldehyde and (D_2)formaldehyde was observed in the investigated reaction. The corresponding isotope effect in the reaction of formaldehyde with *p*-chloronitrosobenzene was 7.99 (0.21) and 7.93 (0.23) in the reaction with *p*-bromonitrosobenzene. All these isotope effects should be related to the 'water' reaction, since no other base catalyst were included.

The corresponding kinetic primary deuterium isotope effect in the reaction of formaldehyde and nitrosobenzene in acetate buffer (2M CH_3COOH/4M CH_3COONa, pH *ca.* 5) was also determined. At least 80% of reaction, *i.e.* proton transfer from nitroso-carbinolic cation intermediate, proceeds under these conditions by the acetate-catalyzed

[3]) The apparent catalytic rate constant for dichloroacetic acid perhaps is too high, owing to some contribution from dichloroacetate-ion-catalyzed proton-transfer process from the C-atom of intermediate **2**.

reaction path. The observed isotope effect is 2.08 (0.07), indicating the change in degree of the proton transfer with change of pK_a of the proton acceptor, in transition state.

A mechanism consistent with the above experimental observations is proposed in the *Scheme*. The first reaction step is considered to involve the formation of a tetrahedral zwitterionic intermediate **1**. This proposal is supported by the following evidence. *1*) The order of reactivity of substituted nitrosobenzenes is that of electron-donating properties, as demonstrated by the plot of $\log k_{obs}$ *vs. Hammett σ* parameters. This order of reactivity suggests the occurring of nucleophilic attack of NO group on the C=O C-atom which would lead to the C−N bond formation and a tetrahedral zwitterionic intermediate **1**. *2*) The C−N bond formation and existence of the tetrahedral addition intermediate such as **1** are consistent with the structure of the product, hydroxamic acid. *3*) The formation of the tetrahedral addition intermediate is ordinarily the first step in many of the addition reactions to the C=O group [15–19]. Although the rates of the formation of tetrahedral addition intermediates in these reactions are often too fast to be measured, even with flow techniques, the existence of such intermediates was confirmed experimentally many years ago, among others, by spectroscopic evidence [20]. *4*) Occurrence of nucleophilic attack of NO N-atom on the C=O C-atom in the first addition step was also proposed in the cases of closely similar reactions of glyoxylic [10] and pyruvic acid [13] with substituted nitrosobenzenes. *5*) The observed independence of the catalytic rate constants for relatively strong acids ($pK_a < 4$) on the pK_a of acid catalyst can be accounted for by the existence of a zwitterionic addition intermediate. Generally, trapping of such an intermediate by the proton transfer from an acid catalyst would lead to acid catalysis [19]. If the proton transfer from an acid catalyst is strongly thermodynamically favorable and, therefore, diffusion-controlled, the observed catalytic rate constants should be independent on the pK_a of the catalyst [21]. In such a case, the slope of the *Brønsted* plot for catalysis should be close to zero, which is considered to be one of the experimental manifestations of the general-acid catalysis by trapping of an unstable intermediate, where the simple proton transfer to it gives rise to a more stable product [19] [22]. The observed ratio of *ca.* 35, between the catalytic rate constant for hydronium ion and catalytic rate constants for catalysts with $pK_a < 4$, is consistent with the expected one for general-acid catalysis by trapping, where the proton transfer is diffusion-controlled. It is known that the rates for the diffusion-controlled proton transfer for proton and hydroxide ion are 10–50-fold greater than the rates for diffusion-controlled proton transfer for other catalysts [21].

According to the *Scheme*, the first addition step, which includes the formation of the unstable zwitterionic addition intermediate **1**, is followed by the trapping of this intermediate by the proton transfer, to form more stable nitrosocarbinolic cation intermediate **2**. The observed general-acid catalysis seems to be acceptably interpreted in terms of such a process, as already discussed. The next line of experimental evidence, which is related to the second step of the *Scheme*, is the observation of the inverse solvent deuterium isotope effect in this reaction. An inverse solvent deuterium isotope effect is normally expected, if there is a pre-equilibrium protonation preceding a slow step in a complex reaction. The solvent deuterium isotope effect $K(D_2O)/K(H_2O)$, arising from an equilibrium protonation is usually 2–4 [23], although effects that fall below the lower limit are not excluded[4]).

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[4])   For example, $K(D_2O)/K(H_2O)$ of 1.41 in the case of benzalacetophenone was reported [24].

The observed solvent deuterium isotope effect in this reaction is *ca.* 1.8. However, the magnitude of the solvent isotope effect in this reaction could be greater than the observed one. Formaldehyde is extensively hydrated, and the appearance of the solvent isotope effect on hydration of formaldehyde cannot be excluded. The observed solvent deuterium isotope effect $K(D_2O)/K(H_2O)$ on hydration of, for example, acetaldehyde [25] is 1.16, and 1.18 in the case of fluoroacetone [26]. Therefore, if there is solvent isotope effect on hydration of formaldehyde similar to the corresponding isotope effect for acetaldehyde or fluoroacetone, then the inverse solvent isotope effect $K(D_2O)/K(H_2O)$ in our reaction could be as high as 2.1. This figure is within the limits expected for solvent deuterium isotope effect, arising from equilibrium protonation of a basic substrate [23].

It should be noted that the observation of the catalysis by hydronium ion and the observed solvent deuterium isotope effect can be interpreted in terms of an alternative reaction path. This alternative reaction would include formation of nitrosocarbinolic cation intermediate **2** as a result of the nucleophilic attack of nitrosobenzene on the protonated formaldehyde. The pK_a for protonated formaldehyde is not known, but is believed to be more negative than -2.8, the pK_a for protonated acetone [27a, b]. The equilibrium constant K_{deh} for dehydration of formaldehyde hydrate is 4.4×10^{-4} [27c]. If the pK_a of protonated formaldehyde is *ca.* -4.0 (see also [27a]) then, in conditions employed, the concentration of protonated formaldehyde could be of the order of 10^{-8} M or less. Taking into account the observed rate constants, the specific rate for the attack of nitroso nucleophile on the protonated aldehyde would approach 10^6–10^7 M^{-1} s^{-1}, a value not far from the diffusion-controlled limit. Although this value seems to be very high, the possibility that the protonated formaldehyde is involved in the reaction perhaps cannot be already excluded. For instance, the rate constant for a nucleophilic attack of trimethylamine on formaldehyde [28] is 1.3×10^7 M^{-1} s^{-1}, and the apparent great difference in basicity between trimethylamine and nitrosobenzene can be, at least in part, compensated by the expected greater reactivity of the protonated aldehyde in comparison with aldehyde alone.

The two reactions are kinetically indistinguishable. The observation that the catalytic rate constants for hydronium ion and, for example, for formic acid differ by *ca.* one order of magnitude one from another, suggests the occurrence of the reaction over a zwitterionic intermediate. But this fact does not rule out a possible concurrent reaction over the protonated formaldehyde. The observed solvent deuterium isotope effect also cannot serve for distinguishing between two reaction paths, since both reactions would include equilibrium protonation which can lead to the inverse solvent isotope effect. The problem remains unsolved at this stage.

The observed primary kinetic deuterium isotope effects k_H/k_D between formaldehyde and (D$_2$)formaldehyde in the reactions with nitrosobenzene, *p*-chloronitrosobenzene, and *p*-bromonitrosobenzene are sizeable, strongly suggesting the occurrence of the rate-controlling proton transfer in this reaction. The structure of the final product, hydroxamic acid **3**, indicates that the proton transferred is the one from formaldehyde C-atom. The magnitude of effects observed is near the maximum expected for the rate-controlling proton transfer from carbon [29]. These observations suggest the existence of the third reaction step in the reaction of formaldehyde with nitrosobenzene, the elimination of proton from the C-atom of nitrosocarbinolic cation intermediate **2**. The values of 7.78, 7.99, and 7.93 for k_H/k_D observed in reactions of formaldehyde with nitrosobenzene,

p-chloronitrosobenzene, and p-bromonitrosobenzene, respectively, are slightly greater than the maximum expected for the rate-controlling proton transfer from the C-atom. This difference can appear due to the secondary isotope effect, arising from the change in sp^3 towards sp^2 hybridization in the transition state for elimination of proton from the C-atom of **2**. Some other secondary isotope effects can arise from the addition to the C=O group, but it does not seem probable that they contribute significantly to the isotope effect observed[5]).

The observed primary isotope effects should be related to the 'water' reaction, since other base catalysts were not present in significant concentration, under conditions employed. It is known that kinetic primary deuterium isotope effect approaches the maximum where ΔpK_a between a proton donor and proton acceptor is zero (*cf.* pp. 216–233 in [29]). Therefore, the observed isotope effects which are very close to the maximum expected can be indicative of what the pK_a value of proton donor is, *i.e.*, pK_a of the carbon acid originating from the nitrosocarbinolic intermediate **2**. This figure can be, thereafter, close to the pK_a of hydronium ion. On the other hand, if a more basic catalyst would be included, leading to ΔpK_a different from zero, the resulting isotope effect should be different in magnitude from the maximum expected. Indeed, this is what is observed for the acetate-ion-catalyzed reaction, where the observed primary deuterium kinetic isotope effect between formaldehyde and (D_2)formaldehyde was 2.08 (0.07). This observation further corroborates the mechanism proposed, suggesting also that in this case the leaving proton in transition state for elimination is more than 'half-transfered' to the acceptor, *i.e.* acetate-ion catalyst.

Assuming the steady-state conditions for the system described in the *Scheme*, the rate-law will have the following form

$$\text{Rate} \;=\; \frac{k_1 k_2 k_3}{k_{-1}(k_{-2} + k_3) + k_2 k_3\,[\text{H}^+]}\;[\text{HCHO}]\,[\text{H}^+]\,[\text{PhNO}]$$

The value of k_2, the rate of protonation of zwitterionic addition intermediate would be of the order of magnitude characteristic for an oxy anion (*Chapt.* 6 in [29]), *i.e.* 10^{10} M^{-1} s^{-1}. The value of k_{-2} can be of the order 10^2–10^4 s^{-1}, assuming that the pK_a of nitrosocarbinolic cation intermediate **2** is *ca.* 8 or less[6]). The rate constant for the breakdown of zwitterionic addition intermediate k_{-1} can be 10^{-9} s^{-1} or even greater[7]).

The rate constant for the proton transfer from the C-atom of **2**, k_3, most likely is much smaller than rate constants k_2, k_{-1}, and k_{-2}, since proton transfer from a carbon acid ordinarily is relatively slow (*Chapt.6* in [29]). Hence, $k_2 k_3\,[\text{H}^+]$ in denominator will be significantly smaller than $k_{-1}(k_{-2} + k_3)$, and k_3 can be neglected in the latter. Taking $k_1/k_{-1} = K_1$ and $k_2/k_{-2} = K_2$, the rate-law is of the form

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[5]) For example, the observed equilibrium isotope effect K_D/K_H for addition of hydroxylamine to benzaldehyde is 1.37, and the same value was observed for addition of water to acetaldehyde [30]. One would expect mutual cancellation of the isotope effects arising from addition of water and nitroso nucleophiles to the C=O group.

[6]) pK_a of **2** derived from p-nitrobenzaldehyde and methoxyamine (pK_a 4.73), for example, is 7.9 [17]. The nitrosocarbinolic cation intermediate **2** derived from formaldehyde and nitrosobenzene perhaps is more acidic, since nitrosobenzene is much less basic than an amine.

[7]) The rate constant for the breakdown of dipolar addition intermediate formed from benzaldehyde and semicarbazide is 2×10^9 s^{-1} [18]. Nitrosobenzene is certainly less basic than semicarbazide (pK_a 3.9), and our intermediate can be less stable than the former.

$$\text{Rate} = k_3 K_1 K_2 \,[\text{HCHO}]\,[\text{H}^+]\,[\text{PhNO}]$$

in accordance with that obtained from the experiment. Obviously, solvent deuterium as well as substrate isotope effects can be nicely related to this rate law.

The proposed *Scheme* permits to draw some analogy with addition reactions of nitrogen nucleophiles. The reaction sequence in our reaction consists of the fundamental reaction steps that are analogous to, for instance, reaction of an aldehyde with an amine [15–19], *i.e.* the first step being the addition on the C=O group and formation of the unstable zwitterionic tetrahedral intermediate, the second step in which zwitterionic intermediate is trapped by the proton transfer from an acid catalyst to give the more stable cation intermediate, and the elimination in the final step, leading to the product.

The point among the experimental evidence obtained here which still deserves to look back is the nonlinear dependence of the reaction rate on the hydrogen-ion concentration. Above 0.02M H_3O^+, the reaction rate constant increases more rapidly than in direct proportion to hydrogen-ion concentration. This effect is sometimes considered as reminiscent of the 'acidity function behavior', commonly observed in concentrated aqueous acids [31]. Perhaps, the rate acceleration observed here is the result of a combination of factors, such as change in hydration of aldehyde due to salt effects and salting-out effects on the activity of the carbonyl compound.

Experimental. – *Reagents and Apparatus.* Nitrosobenzenes were prepared from the corresponding nitrobenzenes (*Fluka*) as described in [12] [32]. Formaldehyde and (D_2) formaldehyde (*Merck*, anal. grade purity, 99% D) were used without further purification. Chloroacetic and dichloroacetic acid were recrystallized before use. All other chemicals were of anal. grade purity. Line-distilled water was redistilled before use. Buffer solns. are prepared according to standard procedure [33]. A *Cary* model *16 K* spectrophotometer and a *Pye-Unicam* model *SP 8-100* spectrophotometer, both equipped with thermostated cell compartments, were used for collection of kinetic data and for UV and VIS scans. Radiometer *PHM 84* digital pH-meter equipped with glass and calomel electrodes (radiometer *G202C* and *K 401*) was used for the pH measurements.

Kinetics. Pseudo-first-order kinetics were performed spectrophotometrically by following the disappearance of the absorbance of nitrosobenzenes at 360 or 370 nm. Usually, kinetics are initiated by adding of soln. of nitrosobenzene in MeOH (15 µl) to the reaction mixture (3 ml, in well stoppered and thermostated silica cell) containing formaldehyde, perchloric acid, and, if necessary, sodium perchlorate. Formaldehyde and proton concentration exceeded 10–1500 times that of nitrosobenzenes. Rate constants were computed using a nonlinear least-square fitting program, and very well first-order kinetics (correlation coefficient was always better than 0.9997) was obtained for a more than five half-life times.

Solvent deuterium kinetic isotope effects as well as kinetic deuterium isotope effects between formaldehyde and (D_2) formaldehyde were determined from the paired experiments using thermostated cell compartment with carefully maintained temp. control within ±0.05°. Primary kinetic deuterium isotope effects were obtained from four paired measurements and solvent deuterium isotope effects from two to four paired measurements.

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