CROATICA CHEMICA ACTA CCACAA **69** (4) 1633–1638 (1996)

ISSN-0011-1643
CCA–2401

Preliminary Communication

Formation of Hydroxamic Acids Promoted by Metal Ions. Interaction of Nitroso Group with Coordinated Carbonyl Group*

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Received September 1, 1996; revised October 5, 1996; accepted October 11, 1996

Hydroxamic acids are formed in the interaction of nitroso group of substituted nitrosobenzenes with carbonyl group of glyoxylate coordinated on iron(III) ion.

Interaction of nitroso compounds having a nitroso group on carbon (C-nitroso group) with carbonyl group of α-oxo acids[1] and aldehydes[1a,b,2] leads to the formation of hydroxamic acids, a class of compounds of exceptional biochemical, pharmaceutical and industrial importance.[3–5] For example, the roles of hydroxamic acids as enzime inhibitors[4] or neoplastic cell differentiation inducers[5] are currently investigated. Nitroso group is known to act as an electrophile in many of its reactions,[6] but it also possesses nucleophilic properties. This fact, predicted also by theoretical studies,[7] was demonstrated by both solution and solid-state NMR spectroscopy,[8,9] as well as by kinetic studies of its nucleophilic reactions.[1,2] These include, among others, interactions of substituted nitrosobenzenes and aliphatic nitroso compound 2-methyl-2-nitrosopropane with biochemically important carbonyl substrates

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* Dedicated to the memory of Professor Stanko Borčić.

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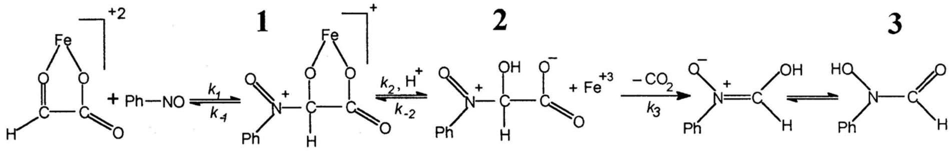
such as glyoxylate,[1a,c] pyruvic acid,[1b] glyoxylic acid,[1a] and acetaldehyde.[1b] Products of these reactions are, as mentioned, hydroxamic acids. The reactions are complex, and nitroso group acts as a nucleophile in the first reaction step, where nucleophilic attack of nitroso nitrogen on carbonyl carbon results in the C–N bond formation, leading to the corresponding dipolar addition intermediate.[2a] To our knowledge, there is no evidence reported that nitroso group can interact in analogous manner with carbonyl group coordinated on a metal ion.

In this work, we report that substituted nitrosobenzenes react with glyoxylate coordinated on iron(III) ion, giving the corresponding *N*-phenyl hydroxamic acids. The reaction involves the formation of the complex intermediate (**1**), Scheme 1, resulting from the interaction of nitroso nucleophile with α-oxo group of glyoxylate coordinated on iron(III) ion, thus catalyzing the subsequent formation of the nitrosocarbinolic intermediate (**2**) which leads to the product, hydroxamic acid (**3**). The evidence includes:



Scheme 1.

i) The observation that the reaction product of the reaction of nitroso nulceophile with glyoxylic carbonyl group, under the conditions where the rate of the reaction *via* uncomplexed glyoxylate/glyoxylic acid was kinetically insignificant in the overall process, was the corresponding hydroxamic acid.

ii) The observation of the metal ion catalysis (Figure 1). The catalysis is rationalized by the obtained linear dependence of the pseudo-first order rate constants for the formation of hydroxamic acid on the concentration of mono glyoxylato iron(III) complex, Figure 2, expressed by $k_{obs} = k_o + k_1$ [FeL^{2+}] (L$^-$ = glyoxylate), where k_o refers to the ferric ion uncatalysed reaction path, as described in detail earlier.[1,2] Values of k_o[13] and k_1 are 0.0067 s^{-1} and 0.516 s^{-1} M^{-1} respectively, under the conditions employed.

iii) The slope of the straight line of log k_{obs} *vs.* Hammett σ^+ parameters, obtained for the reaction of glyoxylate with substituted nitrosobenzenes in the presence of ferric ions differs substantially from that of the corresponding line of log k_{obs} *vs.* Hammett σ^+ parameters in the absence of iron(III) ions (Figure 3). The negative value of this slope in the case of reaction of

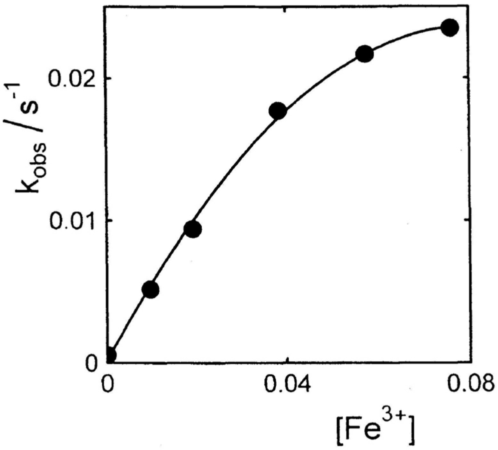


Figure 1. Dependence of the pseudo-first order rate constants for the formation of *N*-phenylformohydroxamic acid in the reaction of glyoxylic acid/glyoxylate with nitrosobenzene on the iron(III) ion concentration at pH = 1.56. Individual rate constants are determined using the methods reported.[1a,b;2a,c] In water, at 25 °C, ionic strength: 2.0 M ($NaClO_4/Fe(ClO_4)_3$), total glyoxylate /glyoxylic acid: 0.05 M.[10,13]

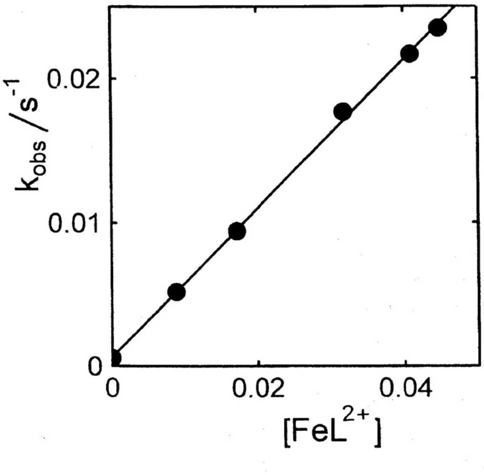


Figure 2. Dependence of the pseudo-first order rate constants for the formation of *N*-phenylformohydroxamic acid in the reaction of glyoxylic acid/glyoxylate with nitrosobenzene on the monoglyoxylato iron(III) complex concentration.[13] At pH = 1.56, in water, at 25 °C, ionic strength: 2.0 M ($NaClO_4/Fe(ClO_4)_3$), total glyoxylate/glyoxylic acid: 0.05 M. Rate constants were determined as described earlier.[1a,b;2a, c] Fraction of FeL^{2+} complex was calculated (L^- = glyoxylate) using an equilibrium quotient K_{eq} = 7.76, defined as $FeL^{2+} \cdot H^+/Fe^{3+} \cdot HL$ for the formation of monoglyoxylato iron(III) complex, as determined spectrophotometrically, at pH = 1.56, (under the conditions employed in kinetic measurements, by measuring the increase of absorbance at 450 nm due to the formation of the complex).

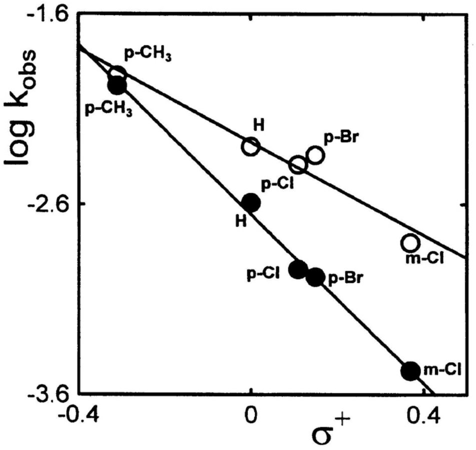


Figure 3. Plot of the k_{obs} *vs.* Hammett σ^+ parameters for the reactions of glyoxylate with the substituted nitrosobenzenes R-Ph-NO. In the presence of 0.009 M Fe^{3+}, (total glyoxylate = 0.194 M, pH = 1.55, ionic strenght = 0.2 M), $\rho^+ = -1.22$, $r = 0.970$, (open circles). In the absence of Fe^{3+}, (total glyoxylate = 0.194 M, pH = 1.55, ionic strength = 0.2 M), $\rho^+ = -2.20$, $r = 0.998$, (solid circles).

glyoxylate/glyoxylic acid with substituted nitrosobenzenes, as well as in similar reactions,[1,2] was related to the nucleophilic attack of nitroso nucleophile in the first reaction step. Therefore, it seems reasonable to conclude from the evidence obtained that the metal ion intervenes in this reaction step.

iv) The observed solvent deuterium isotope effects k_{D_2O}/k_{H_2O} (uncorrected) were as follows: 1.11 (0.07) at Fe^{3+} = 0.073 M, total glyoxylate = 0.01 M, pH = 1.15, pD(reading) = 0.80, in 95% D_2O; 1.19 (0.08) at Fe^{3+} = 0.073 M, total glyoxylate = 0.05 M, pH = 1.32, pD(reading) = 1.03, in 95% D_2O; 1.01 (0.01)[14] at Fe^{3+} = 0.008 M, total glyoxylate = 0.084 M, pH = 1.32, pD(reading) = 1.02, in 84% D_2O. These isotope effects are small and inverse. This is consistent with the preequilibrium protonation[15,16] of (**1**) which leads to the nitrosocarbinolic polar intermediate (**2**). Such a preequilibrium protonation could lead to the inverse solvent deuterium isotope effect (k_{D_2O}/k_{H_2O}) of a magnitude of 2–4.[15,16] However, the observed small inverse solvent deuterium isotope effects should result from the mutual cancellation of the corresponding solvent isotope effect on iron(III) complexation[17] with glyoxylate (under the conditions employed) and the solvent isotope effect on preequilibrium protonation of complex intermediate (**1**).

It should be noted that C-nitroso compounds could be of interest as antiretroviral[18] and citotoxic[19] agents. Hence, a better insight into its reactivity toward the coordinated carbonyl compounds of biochemical importance could be helpfull in C-nitroso drug design.

Acknowledgments. – We thank Miss Jelena Bužančić for collaboration and the Croatian Research Council for support.

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10. Glyoxylate and glyoxylic acid are present in solution mainly in the form of hydrated species[11] and glyoxylic acid ($\mathrm{p}K_\mathrm{a} \approx 2$, for the dehydrated glyoxylic acid, see for example Ref. 12) is much more hydrated than glyoxylate itself.
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13. Under the conditions employed, the uncatalyzed reaction does not contribute significantly to the overall rate of the reaction. k_o of 0.0067 s^{-1} refers to the total glyoxylate concentration of 1 M.
14. In the case of this solvent isotope effect, there is about 30% of uncatalysed reaction. Solvent deuterium isotope effect on k_o is $k_{\mathrm{D_2O}}/k_{\mathrm{H_2O}} = 1.92$, at pH = 1.24. Therefore, cancellation of the inverse isotope effect could be partly a consequence of the normal isotope effect in uncatalyzed reaction.
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16. See also discussion in Ref. 1b and 2a.

17. Obviously, normal solvent deuterium isotope effect on the equilibrium of the complex formation of FeL^{2+} should be expected. It is well known that ΔpK_a between D_2O and H_2O for most weak acids lies between 0.3 and 0.6.[15]
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SAŽETAK

Nastajanje hidroksamskih kiselina potpomognuto kovinskim ionima. Međudjelovanje nitrozo-skupine i koordinirane karbonilne skupine

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Međudjelovanjem karbonilne skupine glioksilata koordinirane na ion Fe(III) s nitrozo-skupinom supstituiranih nitrozobenzena nastaju odgovarajuće *N*-fenil supstituirane hidroksamske kiseline.