Pergamon

Tetrahedron Letters, Vol. 36, No. 52, pp. 9547-9550, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)02044-6

Formation of Hydroxamic Acids Promoted by Metal Ions. Interaction of Aldehyde Carbonyl Group with C-Nitroso Group in the Presence of Ferric Ions.

Stanko Uršić*, Biljana Nigović, Valerije Vrček and Viktor Pilepić

Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, Zagreb, Croatia

Abstract: Formation of N-phenyl substituted hydroxamic acids in the reaction of formaldehyde with substituted nitrosobenzene is strongly catalysed by Fe^{3+} ions, which stabilize the transition state for the rate-controlling proton transfer from the carbon of nitrosocarbinolic cation intermediate leading to the product, hydroxamic acid.

Formation of hydroxamic acids *via* the interaction of carbonyl group of aldehydes[1, 2a] and α-oxo acids[1c, 2] with aromatic or aliphatic[2a] C-nitroso group, belongs to the small number of nucleophilic reactions of the C-nitroso group known so far.[1-3] In contrast, there are large numbers of addition reactions of the C-nitroso compounds where the nitroso group acts as an electrophile.[3] Nucleophilic reactions of the C-nitroso group include carbonyl substrates of exceptional biochemical significance, such as pyruvic acid, glyoxylate and acetaldehyde. The great biochemical, pharmaceutical and industrial importance of hydroxamic acids is well known.[4, 5] For example, D-threonohydroxamic acid is a potent xylose isomerase inhibitor, [5a] and the inhibitory effect of some natural occuring hydroxamates on cancerous cell growth,[5b] as well as synergistic effect of hydroxamates on the anti-human immunodeficiency virus type 1 are reported.[5c]

We now report the observation that a ferric ion strongly catalyses the formation of N-phenyl substituted hydroxamic acids from formaldehyde and substituted nitrosobenzenes.[6] The evidence obtained strongly

Table 1.

catalyst	R	p-CH_3	H	p-Cl	p-Br	m-Cl
H^+	k_H/k_D	8.99 (0.09)	7.71 (0.65)	8.07 (0.07)	6.99 (0.06)	7.17 (0.19)
H^+, Fe^{3+}	k_H/k_D	9.21 (0.08)	8.57 (0.19)	7.71 (0.23)	6.83 (0.23)	6.52 (0.04)

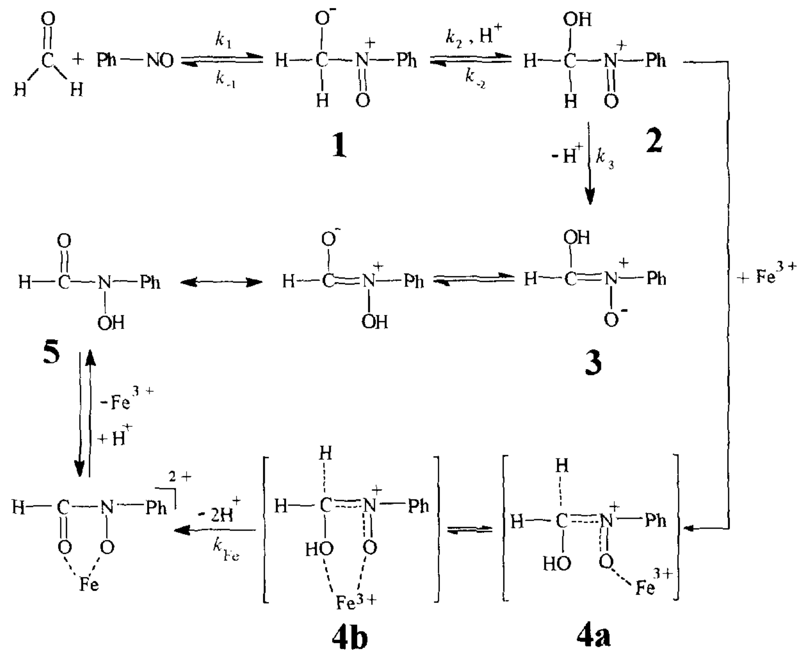
Table 1. Kinetic primary deuterium isotope effects between formaldehyde and formaldehyde-d_2 in the reaction with substituted nitrosobenzenes R-PhNO in the presence and the absence of Fe^{3+} ions. At 25°C and in 4 M $NaClO_4$ solution. Rate constants are determined as described earlier.[1, 2a, 7] In the presence of Fe^{3+} ions, appearance of absorbance due to formation of Fe-(III)-monohydroxamato complex at 530 nm was followed.[1c, 2a] Isotope effects are ratios of six paired measurements.

suggests that the catalytic role of ferric ions is reflected in the stabilisation of the transition state for the rate-controlling proton transfer from the carbon of nitrosocarbinolic cation intermediate (2), Scheme 1.[6] This leads to a transition state similar to (4a) or (4b), Scheme 1, which are converted to the hydroxamic acid (5). The evidence supporting such a description of the mechanism of the catalysis includes:

i) The observation that the reaction products are the corresponding hydroxamic acids;

ii) The observation of the catalysis by Fe^{3+} ions. The catalysis is obvious from the experimentally obtained linear dependence (R = .999) of the pseudo-first order rate constants for the formation of hydroxamic acid on the concentration of Fe^{3+} ions: $k_{obs} = k' + k'' [Fe^{3+}]$. At 0.05 M H^+ (in 4.0 M $NaClO_4$ solution and in the range of 0.0010-0.0765 M Fe^{3+}), k'' has the value 0.0714 $mol^{-3}\ dm^9\ s^{-1}$, and k' is 0.0022 $mol^{-2}\ dm^6\ s^{-1}$. Parameter k' refers to the ferric ion uncatalysed reaction path, (1 → 2 → 3 → 5 in Scheme 1), and its meaning was explained in detail earlier.[1b]

Scheme 1.



Following Scheme 1 and with regard to considerations mentioned[1b] and evidence obtained, k'' could be of the form $k'' = k_{Fe} K_1 K_2 [HCHO] [H^+]$ where [1b] $K_1 = k_1 / k_{-1}$ and $K_2 = k_2 / k_{-2}$, which permits the comparison of k_{Fe} and k_3.

iii) Observation that the plots of log k_{obs} vs. Hammett σ parameters , Fig. 1, have essentially the same ρ values for the reaction of the formaldehyde and substituted nitrosobenzenes in absence of Fe^{3+} ions, and in the situation where 72 % of the overall reaction goes *via* the Fe^{3+} catalysed reaction pathway. The corresponding plots for the cases of formaldehyde-d_2 differ only slightly from each other. Therefore, it seems reasonable to conclude that Fe^{3+} is not involved at this stage of the formation of dipolar addition intermediate (1).

iv) The inverse solvent deuterium isotope effect k_{D_2O} / k_{H_2O} of 1.79 (0.01) observed in the presence of Fe^{3+} ions, where at least 72 % of the reaction follows the Fe^{3+} catalysed reaction pathway, is the same in magnitude as in the absence of ferric ions.[1a, b, 7] This means that Fe^{3+} is not included in the process of trapping of highly unstable dipolar addition intermediate (1) leading to nitrosocarbinolic cation intermediate (2), Scheme 1.

v) Primary kinetic deuterium isotope effects k_H/k_D between formaldehyde and formaldehyde-d_2 in the ferric ion catalysed reaction and the uncatalysed reaction,[7] Table 1, are essentially the same or differ only slightly for the two reactions. Therefore, it seems that the action of Fe^{3+} ions manifests itself in stabilisation of the transition state for the rate-controlling proton transfer from nitrosocarbinolic cation intermediate (2), which could be described as transition states (4a) or (4b) in Scheme 1.[10]

Fig 1.

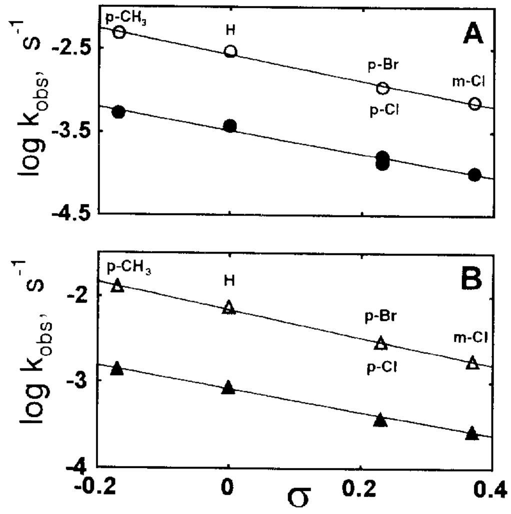


Fig 1. Plot of the k_{obs} vs. Hammett σ parameters for the reactions of formaldehyde and formaldehyde-d_2 with the substituted nitrosobenzenes R-Ph-NO in the absence (A) of Fe^{3+} ions (open circles and solid circles, respectively), and **in the presence (B)** of Fe^{3+} (open triangles and solid triangles). ρ values are as follows: -1.57 (0.07) and 1.41 (0.12) for the formaldehyde and formaldehyde-d_2, respectively and in the absence of Fe^{3+}. The corresponding ρ values for the reactions in the presence of Fe^{3+} are -1.62 (0.04) and -1.34 (0.06). Correlation coefficients for the plots are in the range of 0.990 to 0.999.

We have also observed the appearance of the highly characteristic peak of the iron(III)-mono-N-phenylhydroxamate complex in the reaction of uridine 2′, 3′-dialdehyde with nitrosobenzene in the presence of Fe^{3+} ions. At 0.25M H^+ and 0.38 M Fe^{3+} and nucleoside 0.10 M, the observed pseudo-first order rate constants are of the order of magnitude 0.001 s^{-1}. It should be emphasized that the reaction does not work in the absence of Fe^{3+} under the conditions employed. The significance of this observation could be in the possibility of developing of the corresponding synthetic approach to new 2′-substituted nucleosides, whose importance is well known.[8, 9] This is the objective of our efforts.

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

REFERENCES AND NOTES:

1. a) Kronja, O.; Matijević-Sosa, J.; Uršić, S. *J. Chem. Soc. Chem. Commun.* **1987**, 463. b) Uršić, S. *Helv. Chim. Acta* **1993**, *76*, 131. c) Uršić, S.; Pilepić, V.; Vrček, V.; Gabričević, M.; Zorc, B. *J. Chem. Soc. Perkin Trans. 2* **1993**, 509.

2. a) Pilepić, V.; Uršić, S. *Tetrahedron Lett.* **1994**, 35, 7425-7428. b) Corbett, M. D.; Corbett, B. R. *J. Org. Chem.* **1980**, 45, 2834.

3. Zuman, P.; Shah, B. *Chem. Rev.* **1994**, 1621.

4. a) Matzanke, B. F.; Mueler-Matzanke, G.; Raymond, K. N. Siderophore Mediated Iron Transport; Chemistry, Biology and Physical Properties. In *Physical Bioorganic Chemistry*; Loehr, T. M.; Gray, H. B.; Lever, A. B. P. Eds.; VCH Publishers: New York, 1989; b) Hider, C.; Hall, A. D.; In *Perspectives in Bioinorganic Chemistry*; Hay, R. W.; Dilworth, J. R.; Nolan, K. B. Eds.; JAI Press: London 1991; vol. 1; pp. 209-255. c) Miller, M. J.; Malouin, F. *Acc. Chem. Res.* **1993**, 25, 241.

5. a) Allen, K. N.; Lavie, A.; Petsko, G. A.; Ringe, D. *Biochemistry* **1995**, 34, (11), 3742. b) Zhang, X.; Habib, F. K.; Ross, M.; Burger, U. ; Lewenstein, A.; Rose, K.; Jaton, J. C. *J. Med. Chem* **1995**, 38, (4), 735. c) Malley, S. D.; Grange, J. M.; Hamedisangsari, F.; Vila, J. R. *Proc. Natl. Acad. Sci. U. S. A.* **1994**, 91, (23), 11017.

6. Reaction of formaldehyde with substituted nitrosobenzenes was described in detail in reference 1b. The part of Scheme 1 describing the ferric ion uncatalysed reaction path was taken from this reference.

7. See also discussion in ref. 1b and 1c.

8. Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, 92, 1745.

9. Eaton, B. E.; Pieken, W. A. *Annu. Rev. Biochem.* **1995**, 64, 837.

10. The other line of evidence suggested by the referee. could be the correlation between k_{obs} and stability constants $K_{FeL^{2+}}$ (FeL^{2+} monohydroxamato iron (III) complex) within the series examined. Indeed, this correlation is linear ($r = 0.998$). However, one should take into account that $\log K_{FeL^{2+}}$ also correlates with Hammett σ parameters ($\rho = -0.744$, $r = 0.999$)[11] and that the differences in the ρ values of the corresponding Hammett plots (see Fig. 1) and the differences in the kinetic primary isotope effects (see Table 1) for both, the Fe^{3+} catalysed and the uncatalysed reaction are probably insignificant, suggesting rather weak interaction between Fe^{3+} and the reactive intermediate in 4b or 4a (Scheme 1).

11. Uršić, S.; Pilepić, V.; Ljubas, D.; Vrček, V.; Nigović, B. manuscript in preparation.

(*Received in UK* 22 *September* 1995; *revised* 26 *October* 1995; *accepted* 27 *October* 1995)