Inorganica Chimica Acta, 56 (1981) L43–L44

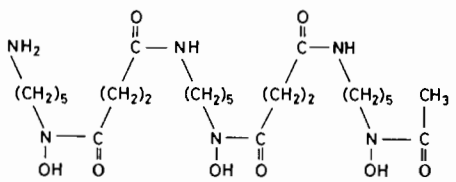
Mechanistic and Equilibrium Study of the Iron(III) Complexation by Deferriferrioxamine B in Aqueous Acidic Solution. Evidence for the Formation of Binuclear Diferrioxamine B

MLADEN BIRUŠ, ZDRAVKO BRADIĆ, NIKOLA KUJUNDŽIĆ, and MARIJAN PRIBANIĆ*

Department of Chemistry, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia, Yugoslavia

Received March 11, 1981

A very important bioinorganic reaction, currently stirring wide interest, appears to be the ligand substitution on high-spin iron(III) by hydroxamic acid chelators [1–4]. The dominant role among hydroxamic acid chelators is played by the naturally produced deferriferrioxamine B (DFB) which is marketed as ®Desferal by Ciba Geigy Corporation. DFB has been beneficial in the treatment of both iron toxicity and iron storage diseases [5]. The structure of DFB is shown in (*I*):



(*I*)

Deferriferrioxamine B (DFB)

The overall second-order rate constant for the reaction of iron(III) with the hexadentate chelating ligand DFB was reported, claiming failure of pseudo first-order rate studies [6]. No detailed kinetic or mechanistic analysis on this system is available. A very recent preliminary report [7] on the reverse reaction, notably on the kinetics and mechanism of the final stage of ferrioxamine B (FeDFB)** aquation in aqueous acid prompted us to report our results of the mechanistic and equilibrium study of complexation of iron(III) by DFB. The present work represents the continuation of investigations in our laboratory, of the formation of iron(III) hydroxamato complexes [2, 8].

Contrary to the statement in the literature [6] the complexation of iron(III) by deferriferrioxamine B can be analysed in terms of the pseudo first-order kinetics. A linear plot is obtained when the experimentally observed pseudo first-order rate constants, k_{obs}, are plotted against the DFB concentrations under conditions described in Fig. 1. Under these conditions good pseudo first-order kinetics are observed. The increase in transmittance at 335 nm is due to the loss of aqueous iron(III) ions as a result of the formation of the hydroxamato complexes, what at the same time decreases transmittance at 440 nm. The data obtained at 335 nm and 440 nm are in good agreement as is shown in Fig.1.

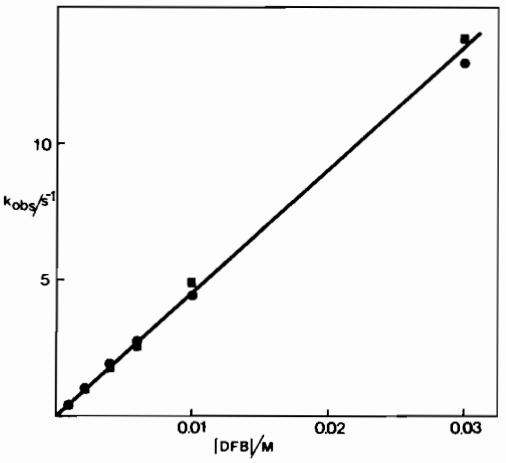


Fig. 1. Plot of pseudo first-order rate constant, k_{obs}, for the reaction of iron(III) with DFB. Conditions: 0.0001 *M* $FeCl_3$, 0.1 *M* HCl, I = 1.0 *M* (maintained with NaCl), and 25 °C. The reaction kinetics were recorded on a Durrum model D-110 stopped-flow spectrophotometer measuring both a decrease in transmittance at 440 nm (●) and an increase in transmittance at 335 nm (■). Each data point represents the average of three individual determinations.

However, at lower acidity than quoted in Fig. 1, at least two kinetic relaxations clearly appear. Furthermore, in an excess of iron(III) over DFB concentration we observed an additional slope. The overall kinetic display is shown in Fig. 2.

A detailed spectral and kinetic analysis of the iron (III) complexation by DFB [9] allows us to ascribe the first slope in Fig. 2 to the formation of the tetradentate bonded DFB iron(III) complex involving intermediate formation of a bidentate bonded species. The second slope in Fig. 2 is assigned to the formation of a hexadentate bonded complex (ferrioxamine B) exhibiting higher transmittance at 560 nm than that of the tetradentate bonded species [9].

Finally, the third slope in Fig. 2 representing a decrease in transmittance is observed only in an excess of iron(III) over DFB concentrations, indicating formation of the binuclear species diferrioxamine B, Fe_2(DFB). Binding of two iron(III) ions per one

*Author to whom correspondence should be addressed.
**The overall charge on the complex molecules is not shown throughout the paper.

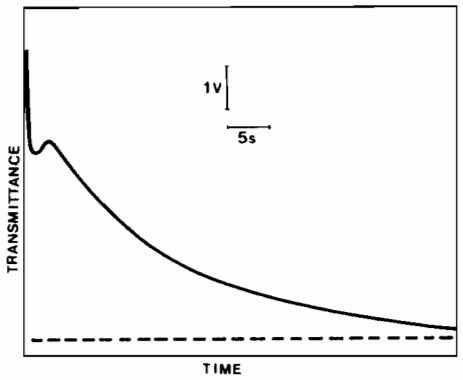


Fig. 2. Transmittance change with time in 1.0 *M* ionic strength (maintained with NaCl) at 560 nm and 25 °C was monitored by a Durrum model D-110 stopped-flow apparatus. The initial concentrations are: 0.002 *M* $FeCl_3$, 0.0001 *M* DFB, and 0.1 *M* HCl.

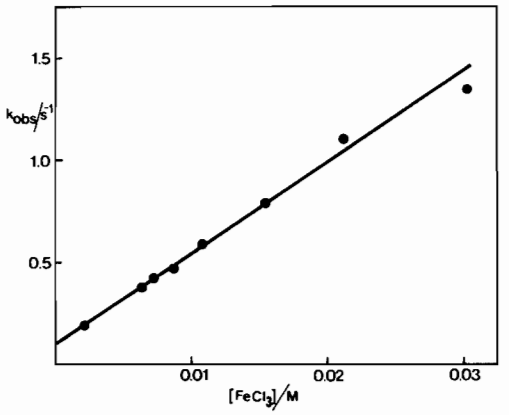


Fig. 3. Diagram of pseudo first-order constant for the reaction of ferrioxamine B with $FeCl_3$ at 25 °C, I = 1.0 *M* (maintained with NaCl), 0.0001 *M* Fe(DFB), 0.04 *M* HCl. Each data point represents the average of the determinations at wavelengths 650, 560, 495, and 440 nm.

polymer unit containing three hydroxamato groups, analogously to DFB, has been recently reported [10].

Furthermore, the formation of diferrioxamine B is substantiated by the spectral and kinetic analysis [9] of both the complexation of iron(III) with DFB as well as the separate reaction of the ferrioxamine B complex with iron(III). The influence of the $FeCl_3$ concentration on the experimentally observed pseudo first-order rate constant for the reaction of ferrioxamine B complex with $FeCl_3$ is shown in Fig. 3. The obtained linearity suggests that only one iron(III) coordinates to ferrioxamine B resulting in the formation of diferrioxamine B.

The diferrioxamine B formation constant defined as $K = [Fe_2(DFB)]/([Fe^{3+}][Fe(DFB)])$ was calculated from the kinetic data of Fig. 3 using the formation constants of the mononuclear DFB–Fe complexes [9]. The obtained value of $K = 520\ M^{-1}$ is in agreement with that obtained by spectrophotometric titration.

Our results indicate that the formation of diferrioxamine B should be considered in the interaction studies of deferriferrioxamine B with iron(III) ions.

Acknowledgement

The authors appreciate the financial support of the Croatian Council for Research (SIZ II).

References

1 B. Monzyk and A. L. Crumbliss, *J. Am. Chem. Soc., 101,* 6203 (1979) and references therein.
2 Previous paper in this series: M. Biruš, N. Kujundžić and M. Pribanić, *Inorg. Chim. Acta, 55,* 65 (1980).
3 J. Eisenlauer and E. Matijević, *J. Colloid Interface Sci., 75,* 199 (1980).
4 S. R. Cooper, J. V. McArdle and K. N. Raymond, *Proc. Natl. Acad. Sci. USA, 75,* 3551 (1978).
5 'Development of Iron Chelators for Chemical Use', W. F. Anderson and M. C. Hiller, Eds., Dept. Health, Education and Welfare Publication, U.S. Govt. Printing Office, Washington, D. C., 1977, No. (NIH) 77–994.
6 D. J. Lentz, G. H. Henderson and E. M. Eyring, *Mol. Pharmacol., 6,* 514 (1973).
7 B. Monzyk and A. L. Crumbliss, *Inorg. Chim. Acta, 55,* L5 (1981).
8 N. Kujundžić and M. Pribanić, *J. Inorg. Nucl. Chem., 40,* 789 (1978); N. Kujundžić, M. Biruš and M. Pribanić, *Acta Pharm. Jugosl., 28,* 161 (1978).
9 To be published from our laboratory.
10 A. Winston and D. Kirchner, *Macromolecules, 11,* 597 (1978).