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Iron(III) Complexation by Rhizoferrin, a Fungal Siderophore

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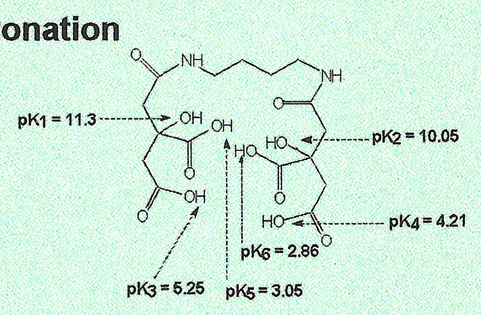
✦ Introduction

Rhizoferrin is a polycarboxylate siderophore excreted by the pathogenic fungi wich belong to *Rhizopus* family[1-3]. These fungi are responsible for mucormycosis and their virulence is enhanced by medical treatment with Desferal[4,5] (deferriferrioxamine B, Ciba-Geigy). For a better understanding of the development of these fungi which requires iron uptake outside the cells and release inside, we have carried out thermodynamic, electrochemical and kinetic studies which point out the major parameters involved in the coordination and transport of iron by rhizoferrin under physiological conditions.

✦ Thermodynamics

• Protonation

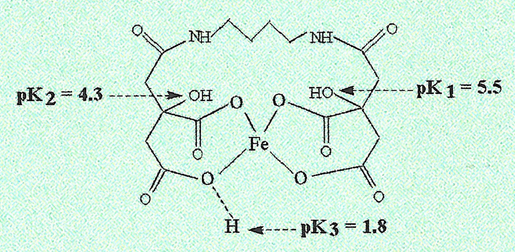


Solvent: water; I = 2.0; T = (25.0 ± 0.2)°C

Ligands	pK1	pK2	pK3	pK4
glutaric acid	4.64	4.09		
tartaric acid	3.93	2.79		
citric acid	13	5.7	4.32	2.92

The pK values were attributed by comparison with carboxylic acids

• Ferric Complexes



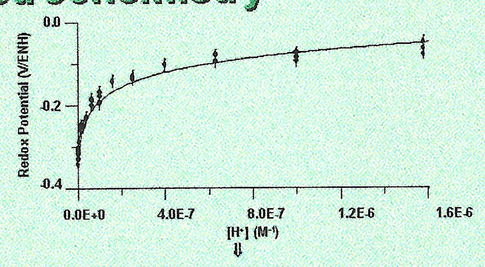
Solvent: water; I = 2.0; T = (25.0 ± 0.2)°C

Coordination Sites	Ligands	pFe(III)
3 catecholates	Enterobactin	35.5
3 hydroxamates	Ferrioxamine B	26.6
2 hydroxamates 1 hydroxyacid	Aerobactin	23.3
2 carboxylic acids 2 hydroxyacids	Rhizoferrin	19.7

pFe(III) = - log [Fe^{3+}] with $[L]_{tot} = 10^{-5}$ M; $[Fe]_{tot} = 10^{-6}$ M; p[H] = 7.4

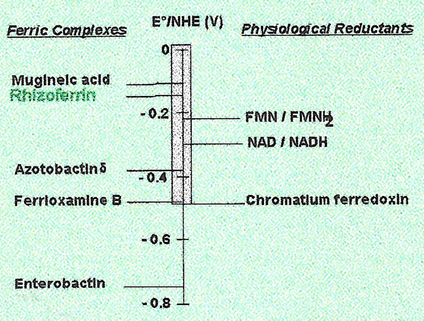
Rhizoferrin ferric complexes are less stable than catecholates or hydroxamates siderophores

✦ Electrochemistry



$$E_{redox}(V) = E_0 + 0.059 \log \frac{[Fe(III)L](1 + K_{[Fe(III)LH]}[H^+] + K_{[Fe(III)LH]}K_{[Fe(III)LH_2]}[H^+]^2)}{[Fe(II)L](1 + K_{[Fe(II)LH]}[H^+] + K_{[Fe(II)LH]}K_{[Fe(II)LH_2]}[H^+]^2)}$$

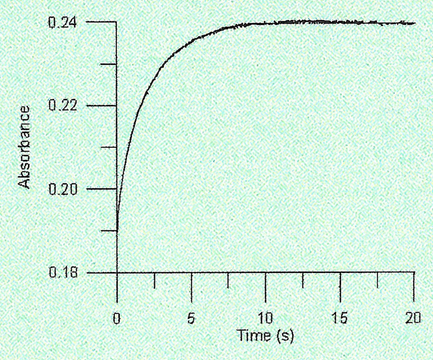
$$K_{Fe(II)LH} = (3 \pm 1) \times 10^8\ M^{-1}$$
$$K_{Fe(II)LH_2} = (8 \pm 1) \times 10^7\ M^{-1}$$
$$\log K_{LFe(II)} = 3 \pm 1$$

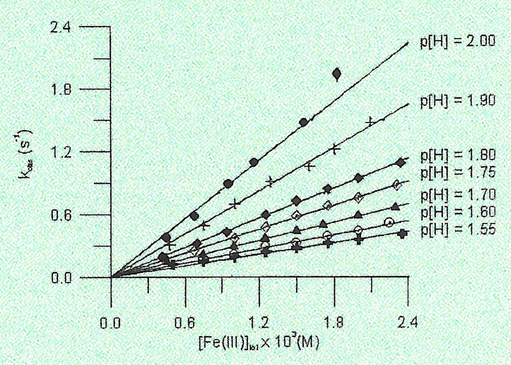


The reduction potential of ferric rhizoferrin at p[H] = 7 is similar to those of carboxylic complexes and less negative than those of ferrioxamine B and enterobactin ferric complexes

✦ Kinetics

• Iron(III) Uptake Mechanism





$[Fe(III)] = 12.5 \times 10^{-4}$ M ; $[L]_{tot} = 5 \times 10^{-4}$ M ; p[H] = 1.75 ; l = 0.2 cm ; λ = 283 nm

$[L]_{tot} = 5 \times 10^{-4}$ M

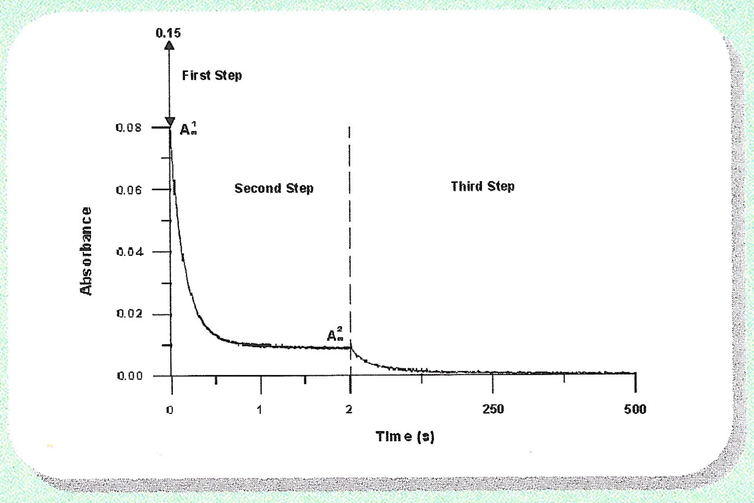
Solvent : water ; I = 2.0 ; T = (25.0 ± 0.2)°C

$$LH_6 + FeOH^{2+} \xrightarrow{k_1} LH_5Fe + H_2O$$
$$H^+ \uparrow\downarrow$$
$$LH_5^- + FeOH^{2+} \xrightarrow{k_2} LH_5Fe + OH^-$$

Ligands	k_1 ($FeOH^{2+}$) ($M^{-1}s^{-1}$)
hydroxamic acids	(2.3 to 5) x 10^3
substitued cathecolates	(1.5 to 3.1) x 10^3
deferriferrioxamine B	3.5 x 10^3
hydroxyacids	(3.6 to 6.1) x 10^3
rhizoferrin LH_6	(1.3 ± 0.3) x 10^3
rhizoferrin LH_5^-	(5 ± 1) x 10^4

The rate determining step for $FeOH^{2+}$ is the first water molecule release from the coordination sphere of the metal: Eigen-Wilkins mechanism

• Iron(III) Release Mechanism



Solvent: water; T = 25.0°C; I = 2; $[LFe^{3-}] = 6.6 \times 10^{5}$ M; $[H^+] = 0.8$ M; λ = 330 nm; l = 1 cm.

First step : $LFe^{3-} + 5H^+ \underset{}{\overset{fast}{\rightleftharpoons}} LH_5Fe^{2+}$

Second step : $LH_5Fe^{2+} \rightleftharpoons LH_5Fe^{2+*}$

Third step : $LH_5Fe^{2+*} + H^+ \longrightarrow LH_6 + Fe^{3+}$

Two rates limiting steps

✦ Conclusion

- Under physiological conditions the rhizoferrin ferric complexes are at least 6 orders of magnitude less stable than tri-hydroxamate Fe(III) species
- The reduction of the ferric rhizoferrin complexes is accessible to biological reductants
- The chelation mechanism of iron(III) under acidic conditions is a fast process
- Release mechanism: solwest steps related to the dissociation of the final carboxylic group

✦ Perspectives

- Spectrophotometric determination of the intermediate complexes by diode arrays stopped-flow measurements
- Determination of the activation parameters

✦ References

1) Drechsel, H.;Metzger, J.; Freund, S.; Boelaert, J.R.; Winkelmann, *BioMetals* 1991, 4, 238. 2) Carrano, C.J.; Drechsel, H.; Kaiser, D.; Jung, G.; Matzanke, B.; Winkelmann, G.; Rochel, N.; Albrecht-Gary, A.-M. *Inorg. Chem*, 1996, 35, 6429. 3) Drechsel, H.; Jung, G.; Zähner, H.; Winkelmann, G. *BioMetals* 1992, 5, 141. 4) Boelaert, J.R.; de Locht, M.; Schneider, Y.J. *J. Infect. Dis.* 1994, 169, 231. 5) Boelaert, J.R.; de Locht, M.; Van Cutsem, *Rev. Med. Microbiol.* 1993, 4, 171.