

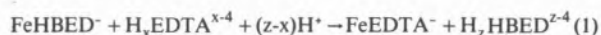


PS5.19 — TU

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# AN INVESTIGATION OF THE KINETICS AND MECHANISM OF IRON(III) RELEASE FROM *N,N'*-DI(2-HYDROXY-BENZYL)ETHYLENEDIAMINE-*N,N'*-DIACETIC ACID AS A MODEL FOR IRON EXCHANGE FROM TRANSFERRIN

The kinetics and mechanism of the release of iron(III) from *N,N'*-di(2-hydroxybenzyl)ethylene-diamine-*N,N'*-diacetic acid (HBED) [1] has been investigated. Because the donor groups of HBED (phenol, carboxylate, amine) provide a hexadentate binding site which has a high affinity for iron(III) and which has certain similarities to transferrin [2], this reaction may serve to mimic iron dissociation reactions from transferrin. Our initial study of this complex was made by investigating the following iron(III) exchange reaction.



The rate law for this exchange reaction over the pH range from 2.5 to 6.0 expressed in terms of  $\text{EDTA}^{4-}$  is as follows.

$$\text{Rate} = (k_2[\text{H}^+]^2 + k_3[\text{H}^+]^3 + k_4[\text{H}^+]^4 + k_5[\text{H}^+]^5)[\text{FeHBED}^-][\text{EDTA}^{4-}] \quad (2)$$

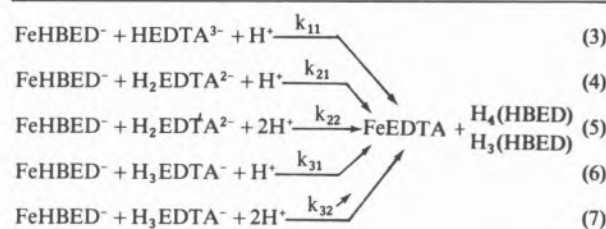
These observations are consistent with five parallel paths to products as shown in the Reaction Scheme.

The values for the microscopic rate constants and pH range where each path contributes significantly to product formation are as follows: (3) pH 6.0-4.5,  $k_{11} = 1.4 \text{ M}^{-2}\text{s}^{-1}$ ; (4) pH 6.0-2.5,  $k_{21} = 1.0 \text{ M}^{-2}\text{s}^{-1}$ ; (5) pH 4.5-2.5,  $k_{22} \leq 7.5 \times 10^2 \text{ M}^{-3}\text{s}^{-1}$ .

(6) pH 3.8-2.5,  $k_{31} = 1.6 \text{ M}^{-2}\text{s}^{-1}$ ; (7) pH 3.8-2.5,  $k_{32} \leq 2.5 \times 10^3 \text{ M}^{-3}\text{s}^{-1}$ . Apparently the microscopic rate constants are not influenced by the degree of protonation of EDTA. This is consistent with a carboxylate group, unprotonated over the entire pH range, being the site of primary attack by the EDTA leading to ternary complex formation. Protonation of one or both of the phenolate groups of HBED further assists the iron exchange.

The influence of acetohydroxamic acid as a catalyst for reaction (1) was investigated. A significant rate enhancement was observed at physiological pH. Possible mechanisms for this catalytic effect will be discussed.

### Reaction Scheme



In order to determine the usefulness of HBED as a kinetic model for transferrin, certain experiments previously reported for transferrin [3,4] were duplicated using  $\text{FeHBED}^-$ . Initial rate studies for iron(III) exchange between  $\text{FeHBED}^-$  and EDTA, thioglycolate, and pyrophosphate were carried out at physiological pH. These results are compared with results from the corresponding transferrin reactions in the Table. Also included in the Table are redox reactions using dithionite and thioglycolate reductants and bathophenanthroline-disulfonic acid (BPS) as a trap for the dissociated iron(II). The transferrin system reacts  $10^2$  to  $10^5$  times faster than  $\text{FeHBED}^-$  toward competing chelating agents. In the reduction reactions, however, the thioglycolate reaction proceeds at comparable rates and the dithionite reaction is  $10^2$  faster for  $\text{FeHBED}^-$  than transferrin. Furthermore, the  $\text{FeHBED}^-$  system exhibits a wider reactivity range than does transferrin (variation in  $k$  by  $10^6$  for  $\text{FeHBED}^-$  and 40 for transferrin). Apparently HBED is not a good kinetic model for transferrin, despite the binding site similarities.

Table  
Comparison of ligand exchange kinetics for FeHBED and Fe-Transferrin at pH 7.4<sup>a)</sup>

	X = HBED	X = Transferrin	
	$k_{\text{HBED}}, \text{s}^{-1}$	$k_{\text{Tf}}, \text{s}^{-1}$	$k_{\text{Tf}}/k_{\text{HBED}}$
FeX + L $\longrightarrow$ FeL + X			
L = 0.05 M EDTA	$2.7 \times 10^{-9}$	$4.1 \times 10^{-4} \text{ b)}$	$1.5 \times 10^5$
L = 0.1 M Thioglycolate	$3.5 \times 10^{-6}$	$3.6 \times 10^{-4} \text{ c)}$	$1.0 \times 10^2$
L = 0.06 M Pyrophosphate	$1.3 \times 10^{-7}$	$1.9 \times 10^{-3} \text{ c)}$	$1.5 \times 10^4$
Fe <sup>III</sup> X + BPS $\xrightarrow{\text{R}}$ Fe <sup>II</sup> (BPS) <sub>3</sub> + X			
R = 0.03 M Dithionite	$5.7 \times 10^{-3}$	$4.3 \times 10^{-5} \text{ c)}$	$7.5 \times 10^{-3}$
R = 0.1 M Thioglycolate	$4.2 \times 10^{-5}$	$3.6 \times 10^{-4} \text{ c)}$	8.6

a) All data 25°C, I = 0.1 M KNO<sub>3</sub>. b) [3]. c) [4].

The implications of this observation in terms of the role of the protein and/or HCO<sub>3</sub><sup>-</sup>/CO<sub>3</sub><sup>=</sup> in influencing the lability of the iron in transferrin will be discussed.

## REFERENCES

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## NET ELECTRON ACCEPTOR/DONOR CHARACTER OF ISOCYANIDES AND DINITROGEN AT THE IRON(II) CENTRE {FeH(Ph<sub>2</sub>PCH<sub>2</sub>CH<sub>2</sub>PPh<sub>2</sub>)<sub>2</sub>}<sup>+</sup>: AN ELECTROCHEMICAL STUDY

### 1 — INTRODUCTION AND RESULTS

Isocyanides (C≡NR) have been used as probes for the study of the electronic and chemical properties of dinitrogen activated by a transition metal centre [1].

Hence, *e.g.*, an analogy of chemical behaviour between N<sub>2</sub> and CNR was detected when they bind a d<sup>6</sup> Mo or W phosphinic centre, both substrates being activated towards ready electrophilic attack. The net electron donor/acceptor character