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Review

Substrate entasis and electronic coupling elements in electron transfer from Fe^{II} in a multicopper ferroxidase

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Dedicated to Edward Solomon

Abstract

Outersphere electron transfer in multicopper oxidases occurs at the type 1, blue Cu^{II}. One class of MCO proteins exhibits a specificity in this reaction towards Fe^{II}. In work carried out in collaboration with the Solomon lab over the past 7 years, we have delineated the structural motifs that support this ferroxidase specificity and have quantified the contributions that each makes to this outersphere electron transfer reaction from Fe^{II} to the type 1 Cu^{II}. Two features of this electron transfer catalysis stand out. First, the protein provides a binding site for Fe^{II} that actually favors Fe^{III}; this coordination sphere places the bound Fe^{II} in a state of "entasis" that can be relieved by loss of an electron. In short, the E° of the bound Fe^{II} is lowered relative to that of aqueous ferrous iron making electron transfer *thermodynamically favorable*. Second, carboxylates within this coordination sphere provide an electronic coupling pathway for the electron transfer *via* their H-bond network with type 1 Cu histidine ligands thus making electron transfer *kinetically efficient*. This brief report breaks down these contributions to ferroxidase specificity in terms of the semi-classical Marcus equation describing outersphere electron transfer.
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1. Introduction

Professor Edward Solomon has turned 60 in this academic year of 2006–2007 but another birthday is coming up in 2008, the 40th birthday of ''entasis'', first described by R.J.P. Williams and Bert Vallee in 1968 [1]. On the occasion of Professor Solomon's birthday it is certainly appropriate to base an article on the work and ideas of two scientists who were ''present at the creation'' of bioinorganic chemistry in the mid-20th century (Fig. 1).

Professor Vallee was at Harvard when Professor Williams spent a sabbatical from Oxford with him at the Peter Bent Brigham Hospital. Each had published numerous papers that had as a theme the extra(literally)-ordinary properties of metal ions bound as protein prosthetic groups in comparison to the same metal ion's properties in flexible coordination complexes of typical poly-dentate ligands. This *entatic* state implied to them a ''catalytically poised state *intrinsic to the active site* (their italics)'' of the protein to which the metal ion was bound; the IUPAC definition very clearly puts an ''entatic'' metal ion in this context with ''A state of an atom or group which, due to its binding in a protein, has its geometric or electronic condition adapted for function''. In other words, metal ions bound to specific sites on proteins found themselves in *reactant*-state coordination complexes that were anything but *ground*-state in energy.

Ironically, Drs. Vallee and Williams had less to say when it came to enzyme catalysis in the sense that their focus remained tightly on metal ion as prosthetic group, *e.g.* a heme or catalytic Zn^{II}, and not about how a metal ion bound as *substrate* might be in a state of entasis also. Coincidentally (or not) in the same period, to explain catalysis generally the notions of orbital steering, propinquity, and the chelate effect were being vigorously discussed among physical organic chemists-turned enzymologists (*e.g.* Drs. Jencks, Bruice and Koshland); while ''entasis'' was never used to rationalize the reactivity of amides in the active site of chymotrypsin, more recent discussions of these same concepts (*e.g.* the Circe Effect, Reactant State Stabilization) by computational chemists like Drs. Wolynes and Warshel have effectively brought the entasis story full circle. The specificity that the multicopper oxidase, Fet3p from *Saccharomyces cerevisiae*, exhibits towards Fe^{II} as substrate is arguably one of the clearest examples of *substrate* entasis in bioinorganic chemistry.

Professor Solomon shares his 60th birthday with another, the 50th ''birthday'' of Rudy Markus' first full paper (in 1956) [2] on what became the Marcus Theory of electron transfer [3], a theory that, in effect, tells us *what* entasis *on* Fe^{II} Fet3p *could* perform in order to make ferrous iron a better e^--transfer partner in the ferroxidase reaction. In this brief story, then, the intent is to describe how the Fet3p reaction with Fe^{II} reflects these two, defining aspects of bioinorganic chemistry that were in place over the course of Ed's first 32 years as a member of the club.

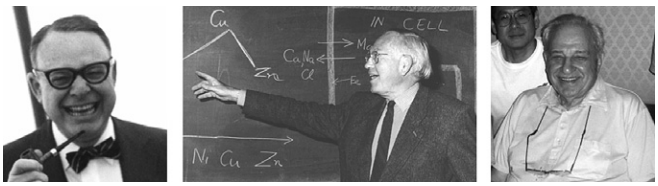

Fig. 1. Three who were present at the creation of metalloenzynie structure and reactivity; from the left: Bert Vallee, R.J.P. Williams, and Rudy Marcus.

2. The Fet3 protein: function and structure

The Fet3 protein expressed by fungi is a prototypical three-cupredoxin domain multicopper oxidase with two additional structural motifs: an amino-terminal signal sequence that targets the nascient Fet3 polypeptide to the endoplasmic reticulum (ER) and a carboxyl-terminal transmembrane domain that tethers the chain to the lumenal face of the ER and thence to the exocytoplasmic face of the plasma membrane [4,5]. In the ER, the *apo*-Fet3p is core-glycosylated and associates with the Ftr1 protein, a

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