Tyrosine and Tryptophan Mediated-Proton-Coupled Electron Transfer Reactions

Tyrosine (Y) or tryptophan (W) residues are frequently utilized to drive charge transfer reactions in biological processes such as photosynthesis, cellular respiration, and the synthesis of DNA. The large size of these systems and high overpotentials needed to oxidize Y/W residues prohibits extensive experimental characterization of Y/W redox potentials in the protein environment. This precludes understanding the role of the solvated protein environment and influence of chemical substituents in amino acid mediated PCET reactions. My thesis project aims to systematically study these effects at a fundamental level using a designed protein scaffold, α_3X, which is a small helical bundle with a single Y or W residue buried in the interior. I will use this α_3X system (Collaborator: Cecilia Tommos) as a base to build an extensive computational study of the redox chemistry of both natural and synthetic Y/W derivatives. Two main approaches will be employed, which will provide the necessary information for the culminating study on PCET kinetics. In my first approach, I will isolate the effect of the protein environment by computing the redox potential of W/Y derivatives using density functional theory (DFT) in both implicit solvent and with electrostatic embedding of the protein environment. I will establish a protocol for computing the proton-coupled redox potential of redox active amino acids in the protein environment, which is not standardized. In my second approach, I will use molecular dynamics to probe the role of water and protein conformational changes in the generation and decay of the tyrosyl or tryptophanyl radical. These studies will provide the information needed to compute the PCET rate constant.

Besides working with the α_3X model system, I seek to investigate how protein conformational changes control Y/W-mediated PCET reactions in pertinent biological systems, such as ribonucleotide reductase. *E.coli* ribonucleotide reductase (RNR) utilizes a series of

tyrosine residues spanning a distance of ~35 Å to translocate a radical species from the generating iron center to the bound ribonucleotide. This PCET mechanism is one of the most elaborate existing in biology and is imperative to life. I will be using molecular dynamics simulations to probe conformational gating, water structure, and the effect of mutations on a recently solved structure of the active RNR complex (Collaborators: Catherine Drennan and Joanne Stubbe). This work could help interpret the many years of experimental measurements and hypotheses formed about the nature of this PCET-pathway, which was highly speculative due to a lack of structural data.

From:	Clorice Reinhardt
To:	Cox, Katie
Subject:	Disseration Prospectus-Clorice Reinhardt
Date:	Thursday, July 25, 2019 9:54:12 AM
Attachments:	Prospectus_Prov_Reinhardt.pdf

Hi Katie,

Thank you for the clear email and instructions last week. I'm attaching my prospectus, my PI-Sharon Hammes-Schiffer has approved this. The title is "Tyrosine and Tryptophan Mediated-Proton-Coupled Electron Transfer Reactions"

Thank you for your time,
Clorice