Biomimetic Bond Activation via Proton-Coupled Electron Transfer

Reported by Matthew W. Boudreau 11/14/2017

Introduction: Proton-coupled electron transfer (PCET) reactions are classified by a concerted redox reaction in which a proton and an electron are concurrently exchanged to facilitate the homolytic cleavage of a bond, leading to the generation of reactive radicals that are then involved in further bond forming events (**Figure 1**)[1]. The bond dissociation free energy (BDFE) describes the energy necessary for the formation of A• from A-H. BDFE is used to describe the energy barrier for PCET reactions.

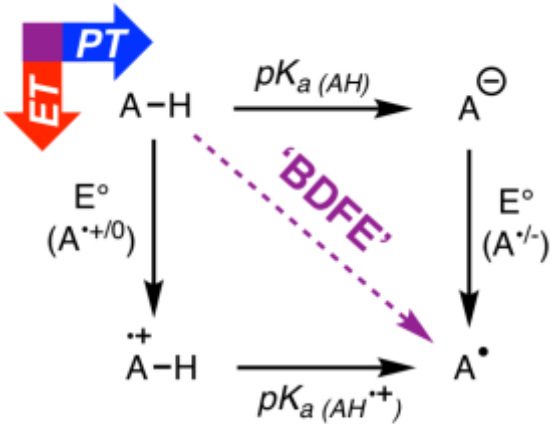

Figure 1. Thermodynamic Square-Reaction Diagram for an A-H PCET Reaction. ET: Electron Transfer PT: Proton Transfer

By coupling the movement of a proton with an electron transfer, a reaction will proceed via the diagonal of electron transfer (ET) and proton transfer (PT). The value of this approach is depicted in **Figure 2**, showing that concerted movement of a proton and electron allows for the avoidance of high energy intermediates[2]. This powerful mode of reactivity permits access to challenging reactive species, making them energetically feasible. PCET has been invoked and reported in multiple biological systems as well as recent reports in small molecule synthesis.

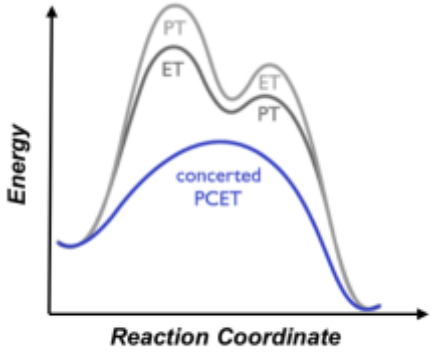

Figure 2. Graphical Representation of a PCET Reaction[2].

PCET in Biology: First hypothesized with molybdenum-based enzymes in the 1970s[3], the role of PCET to access reactive radicals in an enzyme active site has been proposed and probed across a wide range of enzymatic classes[1]. Most notable is the key role PCET has on the activity of photosystem II (PSII). PSII is responsible for the oxidation of water into the formation of O_2, an essential reaction for photosynthesis. For this oxidation to occur, a key tyrosine (Tyr) residue must be oxidized to Tyr-O•. This oxidation via a stepwise mechanism (e.g. ET then PT) utilizes a high-energy intermediate, $\Delta G = +6.0$ kcal/mol. However, a concerted PCET reaction proceeds as an exothermic reaction, $\Delta G = -8.3$ kcal/mol. Since the photo-excited state of PSII is on the order of microseconds, the avoidance of high energy intermediate formation is crucial for

PSII activity[4]. With this example and many others at the forefront, PCET is a highly enabling mode of reactivity for biological systems for the formation of critical reactive radical species.

Reductive PCET: While reports of PCET in enzymes as well as other inorganic processes are prevalent[5], the application of PCET in the field of organic synthesis is a much less explored realm. Knowles and colleagues have set out to leverage PCET as a strategy to form reactive radical species for the synthesis of small molecules in a chemo-, regio-, and diastereo-selective fashion[2]. Initial strategies utilized reductive PCET activation to form a radical species via formation of a hydrogen-bonded complex, leading to protonation of the substrate along with loss of one electron (**Figure 3**)[2]. The power of reductive PCET lies in its modularity in terms of designing conditions that will allow PCET to occur with varying substrates' BDFE. Acids with differing pK_a's and redox catalysts with diverse potentials can be employed in a modular sense to afford the BDFE's needed for a given substrate.

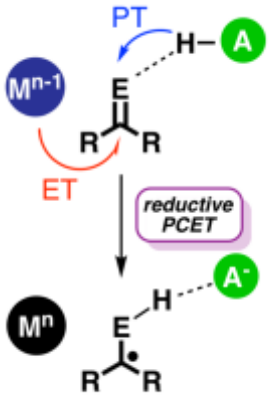

Figure 3. Reductive PCET.

Oxidative PCET: Further application of PCET has focused on utilizing oxidative PCET, in which a base deprotonates the substrate while a subsequent electron is lost, forming a radical species (**Figure 4**)[2]. Akin to reductive PCET, oxidative PCET allows for modulation of reagents to match the BDFE of a desired substrate, allowing for a broad substrate scope. Oxidative PCET has been used to activate strong N-H bonds (BDFE > 100 kcal/mol) for the formation of amidyl radicals competent in carboaminations, hydroaminations, and activation of remote C-H bonds[6,7].

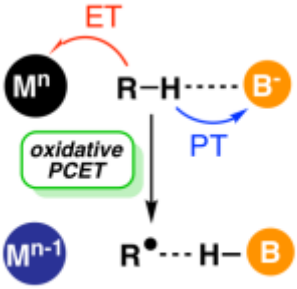

Figure 4. Oxidative PCET.

References:

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