

Quantum Entatic State/Rack Mechanism for Catalysis by Solvent Environments

Robert K. Szilagyi, Emerald Ellis, Jennifer L. Du Bois

Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT 59717 USA
szilagyi@montana.edu elementologia.org

Sustainability in chemistry can be achieved through catalysis, in which the catalyst commonly either lowers the activation barrier or opens up new reaction pathways with new intermediates and reduced activation barriers in comparison to corresponding non-catalytic processes. A more sophisticated catalytic effect is described by the entatic state [1] or the analogous rack-induced bonding [2] theories. In a metalloenzyme, entatic state is achieved by protein-bound groups forming a so-called 'rack'. Rack-induced bonding occurs when the protein-shaped active site stabilizes the products (increases driving force) or destabilizes the reactants (lowers activation barrier). Strain stored in a rack for this energetic tuning is commonly perceived to be of steric origins, such as quenched protein folding, distinctive conformational features, or simply the crowdedness of side chains around a prosthetic group.

By studying the family of cofactor-independent oxidases that utilize molecular oxygen (as green oxidant) for catalytic oxidation of flavin-like substrate molecules without the presence of any transition metal ion or organic prosthetic group, we discovered a new manifestation of the entatic state. The rack-induced strain can emerge solely due to electronic and electrostatic interactions from the external chemical environment without steric strain. We strategically composed a systematic series of neat solvents by considering properties of solvent molecules to mimic specific amino acid side-chains that line the active site pocket of nogalamycin monooxygenase [3]. In a combined spectroscopic and computational approach, we mapped out the chemical speciation of the substrate dithranol/anthralin, its tautomeric forms, and partial or fully ionized states [4]. We defined a staircase-like potential energy surface that explains how the diamagnetic, organic substrate can spontaneously react with the paramagnetic dioxygen in specific neat solvents.

Our discovery has a direct impact on Emergence-of-Life research, particularly, the research into reaction networks that were essential for the chemical evolution of the building blocks of life. We propose a close consideration of the external chemical environment (solvation, inorganic/organic templates, micelles, colloids, etc.), network of electrostatic polarization and dispersion interactions as catalytic driving forces for achieving kinetic acceleration in the interconversion of small, inert molecules under Hadean physicochemical conditions toward more complex substrates with higher chemical potentials.

Acknowledgement

Financial support for this work is from the US NSF grant MCB1715176.

References

1. Vallee B.L., Williams R.J.: **Metalloenzymes: The entatic nature of their active sites** *PNAS* 1968, 59(2), 498–505 (DOI: 10.1073/pnas.59.2.498)
2. Malmström, B.G.: Rack-induced bonding in blue-copper proteins *European Journal of Biochemistry* 1994, 223, 711–718 (DOI: 10.1111/j.1432-1033.1994.tb19044.x)
3. Machovina M.M., Usselman R.J., Du Bois* J.L.: **Monooxygenase substrates mimic flavin to catalyze cofactorless oxygenations** *Journal of Biological Chemistry*, 2016, 291, 17816–17828 (DOI: 10.1074/jbc.M116.730051)
4. Ellis E., MacHale L.T., Szilagyi* R.K., Du Bois* J.L.: **How chemical environment activates anthralin and molecular oxygen for direct reaction** *Journal of Organic Chemistry*, 2019, ASAP (DOI: 10.1021/acs.joc.9b03133)