Reaction control in radical SAM enzymes: How nature plays with radical and redox reactivity

Christian Suess[1], Floriane L. Martins[1], Samuel Gaughan[1,2], Jonathan Hirst[1,2], Anna K. Croft[1] and Christof M. Jäger[1]

[1]*Department of Chemical and Environmental Engineering, University of Nottingham, Nottingham, NG7 2RD, UK*
[2]*School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK*

christof.jaeger@nottingham.ac.uk

How enzymes have developed to catalyse and control specific reactions is one of the most complex questions necessary to understand in order to be able to rationally influence enzyme activity and selectivity for medicinal and biotechnological applications. Intriguingly interesting in this concept are enzymes that need to control highly reactive intermediates that tend to undergo rapid stabilising side reactions, like radicals.

Radical *S*-adenosylmethionine (SAM) dependent enzymes [1] share the communality to initiate radical intermediates vie hydrogen abstraction reactions controlled by SAM and the redox chemistry associated with central iron sulfur clusters. They are perfectly designed to control these highly reactive intermediates in order to facilitate and drive the desired reaction involved in number of biosynthetic pathways towards anti-viral, anti-cancer and antibiotic products. [2]

Complex radical ring rearrangements like in the example of 7-carboxy-7-deazaguanine (CDG) synthase (QueE) [3] are a particular speciality of rSAM enzymes and we recently demonstrated how these rearrangements need to be fine-tuned by controlling the thermodynamics of the central radical clock reaction. [4] Here, we show how the enzymes control the reactivity of the radical rearrangement and how efficient computational assessment of thermodynamic reaction profiles through calculating radical stabilization energies (RSEs) [5] of key intermediates from simulation ensembles can be used for screening for alternative substrates and designing radical enzymes with improved substrate range and turnover.

A second key influencing parameter for many examples in enzyme catalysis is the internal electrostatic field in the enzyme active site, often referred to as electrostatic preorganization. [6] Recently Shaik *et al.* [7] and others demonstrated how externally orientated electric fields can influence biocatalytic reaction rates by orders of magnitude. Hydrogen abstraction reactions and effects on the reactivity of metal clusters in enzymes, both important in radical SAM enzyme catalysis, are prone to be highly influenced by changes in the surrounding electrostatic field. Along similar lines to the example of QueE, we will discuss very recent investigations on the role of orientated electric fields at different stages of rSAM enzyme catalysis.

References

1) Broderick, J. B. et al., *Chem. Rev.*, **2014**, *114*, 4229-4317
2) Jäger, C. M., Croft, A. K., *Chem. Bio. Eng. Rev.* **2018,** *5*, 143-162.
3) Dowling, D. P. *et al.*, *Nat. Chem. Biol.*, 2014, *10*, 106-112
4) a) Jäger, C. M.; Croft, A. K., *Chem. Eur. J.*, **2017,** *23*, 953-962, b) Suess, C.; *et al., J. Chem. Inf. Model.,* **2019**, *in revision, DOI: 10.26434/chemrxiv.7379945*
5) Hioe, J.; Zipse, H., *Faraday Discussions*, **2010**, *145*, 301-313.
6) Warshel, A.; *et al., Chem. Rev.* **2006**, *106*, 3210-3215.
7) Shaik, S., Mandal, D., Ramanan, R., *Nat. Chem.*, 2016, *8*, 1091-1098.