Metal binding in the radical SAM enzyme QueE – influencing the mechanistic outcome of radical reactions

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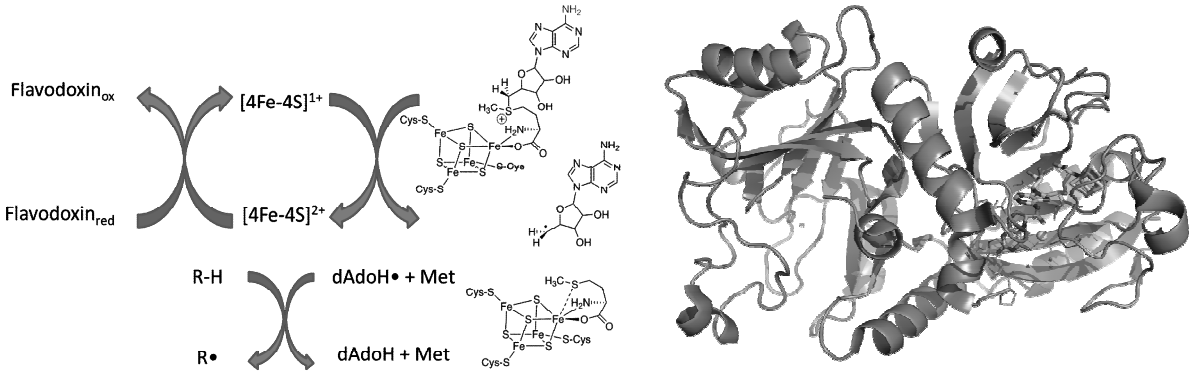
Radical enzymes have attracted recent interest because of their involvement in chemical processes leading to products of potential use for anti-viral, anti-cancer and antibiotic treatments. As such, they are excellent targets for protein engineering to access a variety of new drugs that are difficult to access via traditional synthetic methods. One of the most diverse radical enzyme families is the so-called radical SAM enzyme family,[1] the members of which all share a central S-adenosyl methionine (SAM) molecule as either a cofactor or co-substrate for catalysis. The manifold diversity of chemical reactions catalysed by these enzymes is outstanding, including methyl transfer, sulphur insertion and complex chemical rearrangements. While a general framework for the initial catalytic mechanism has been established over the past years[2] (see Figure), much less is known about the subsequent chemical rearrangements in most cases.

7 carboxy-7-deazaguanine (CDG) synthase (QueE) is one of the very recently solved enzyme structures that uses SAM as cofactor.[3] It catalysis the rearrangement of 6-carboxy-5,6,7,8-tetrahydropterin (CPH4) into CDG and also shows a clear dependence on the presence of Mg^{2+} in the active site - a complete novel feature reported for radical SAM enzymes. Still unclear is how the ion influences the catalysis of the chemical rearrangement.

We show first results from *ab initio* and DFT calculations on a model system to investigate effect of the ion on the chemical rearrangement and first molecular-dynamics simulations of the enzyme to investigate the dynamical behaviour of the entire protein-substrate complex and its influence on metal and substrate binding. Further, we will outline our systematic approach to investigate the enzyme's catalytic mechanism in detail.



[1] Sofia, H. J.; Chen, G.; Hetzler, B. G.; Reyes-Spindola, J. F.; Miller, N. E. *Nucleic acids research* **2001**, *29*, 1097.
[2] Broderick, J. B.; Duffus, B. R.; Duschene, K. S.; Shepard, E. M. *Chem. Rev.* **2014**, *114*, 4229.
[3] Dowling, D. P.; Bruender, N. A.; Young, A. P.; McCarty, R. M.; Bandarian, V.; Drennan, C. L. *Nat. Chem. Biol.* **2014**, *10*, 106.