1. D. Jayatilaka, D. J. Grimwood, *Acta Cryst A* **57**, 76 (2001).

2. W. L. Clinton, A. J. Galli, L. J. Massa, *Phys. Rev.* **177**, 7 (1969).

3. A. Genoni, *J. Phys. Chem. Lett.* **4**,1093 (2013).

4. A. Genoni, *J. Chem. Theory Comput.* **9**, 3004 (2013).

5. B. Meyer, P. Macchi, A. Genoni, *submitted.*

6. N. Casati, A. Kleppe, A. J. Jephcoat, P. Macchi, *Nat. Commun.* **7**, 10901, doi:10.1038/ncomms10901 (2016).

**Keywords:** X-ray Constrained Wave Function, Electron Density, Extremely Localized Molecular Orbitals, Valence Bond Theory

## MS46-O2 Synergistic 'Substrate Activation' and 'Oxygen Activation' in Salicylate Dioxygenase from QM/MM Simulations

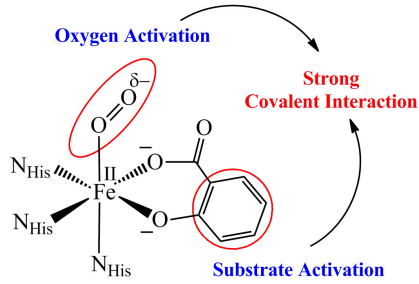
Johannes Keastner[1], Subhendu Roy[1]

1. University of Stuttgart, Institute for Theoretical Chemistry

email: kaestner@theochem.uni-stuttgart.de

Salicylate 1,2-Dioxygenase (SDO) is the first enzyme discovered to catalyze the oxidative cleavage of a monohydroxylated aromatic compound, salicylate, in contrast to the well-known electron-rich substrates. We have investigated the mechanism of dioxygen activation in SDO by QM/MM calculations. Our study reveals that the non-heme $Fe^{II}$ center in SDO activates salicylate and $O_2$ synergistically by a strong covalent interaction to facilitate the reductive cleavage of $O_2$. A covalent Salicylate-$Fe^{II}$-$O_2$ complex is the reactive oxygen species in this case, where the electronic structure is best described as between the two limiting cases, $Fe^{II}$-$O_2$ and $Fe^{II}$-$O_2^-$ with partial electron transfer from the activated salicylate to $O_2$ via the Fe center. Thus, SDO employs a synergistic strategy of 'substrate activation' and 'oxygen activation' to carry out the catalytic reaction, which is unprecedented in the family of iron dioxygenases. Moreover, $O_2$ activation in SDO happens without the assistance of a proton source. Our study essentially opens up a new window in the mechanism of $O_2$ activation.

[1] S. Roy and J. Kästner Angew. Chem. Int. Ed. 55, 1168 (2016)




(His = Histidine)

**Figure 1.** Dioxygen is activated in Salicylate 1,2-Dioxygenase (SDO) by a stron covalent interaction with the non-heme iron cofactor and the substrate.

**Keywords:** DIOXYGENASE, METALLOENZYMES, QM/MM, ACTIVATION