Intermolecular Forces at Play in the Active Site of Lactoperoxidase

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Abstract

Lactoperoxidase (LPO) is an enzyme that fights in the first line of defense against infection. LPO catalyzes the formation of toxic chemicals which indiscriminately kill foreign microbes and viruses caught in the mucous membranes of vulnerable body parts (namely, the eyes and upper airways). Because of its importance for the immune system, LPO is largely studied for potential applications in medical therapies. However, while much research has been done to determine the protein's structure and its efficacy against various pathogens, the chemical mechanism by which the enzyme's active-site transforms common ions into germ-killing agents is not known in detail. The aim of this project is to apply methods of computational chemistry and bioinformatics implemented in state-of-the-art software to elucidate the catalytic mechanism of LPO with common substrates found in the body fluids.

After comparing the three-dimentional structures of LPO available in the Protein Data Bank to estimate the variability and flexibility of the active-site and the overall protein, an active-site model was constructed. In this work, the spacial distribution and strength of intermolecular forces at play in the LPO active-site were computed with a force field optimized for proteins. The resulting implications to substrate binding and catalysis were analyzed.

The detailed catalytic mechanism at the molecular level by which this enzyme generates antipathogenic substances is essential for chemists to create synthetic enzymes that mimic the antimicrobial function of LPO. A synthetic enzyme can be modified to vary the specificity for substrates, can be tuned to perform under broader physiological conditions,

can have a longer shelf life than the natural enzyme, and can be dispensed in a variety of pharmaceutical forms without the enzyme losing effectiveness.

The full catalytic mechanism of LPO computed by quantum chemical methods will be published in a peer-reviewed journal.