Molecular Dynamics Simulation of Nitroreductase in Three States

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Nitroreductase is a member of a group of enzymes that reduce a broad range of nitroaromatic compounds and has potential uses in bioremediation and chemotherapy. These enzymes facilitate NADH-driven nitroreduction reaction, which is the quintessential first step in the catabolism of a variety of NACs. Although the major processes affecting the biodegradation of NACs have been investigated qualitatively, many issues regarding a reaction mechanism and enzymatic selectivity remain unsolved.

To understand better the influence of inhibitors and NACs substrate on geometrical and time dependent properties of the enzyme we performed series of molecular dynamics (MD) simulations. The structure and dynamics of the nitroreductase enzyme from *Enterobacter cloacae* has been calculated for the oxidized form, in separate complex with benzoate inhibitor and for the two-electron reduced form. Statistical averages were sampled from 50 ns NPT classical MD simulation in the explicit water environment using AMBER force field.

In the oxidized enzyme, the FMN flavin ring system adopts a slightly bent conformation, which is also consistent with X-Ray crystallography data. This bend increases even further in the reduced form of the enzyme. The induced bend in the oxidized enzyme may favor reduction, and it may also account for the characteristic inability of the enzyme to stabilize the one electron-reduced semiquinone flavin, which is also planar. Simulation the inhibited enzyme shows increased flexibility of H6 helix. These motions may represent a mechanism for accommodating varied substrates. Other obtained results were interpreted in terms of normal mode analysis (NMA), or electrostatic interaction between principal components of the studied system.