COMPUTATIONAL INSIGHTS INTO EPOXIDE HYDROLASE ASYMMETRIC HYDRATIONS OF EPOXIDES

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Among optically active chiral compounds, enantiopure epoxides are recognized as high valuable synthons in organic synthesis for the manufacturing of pharmaceuticals, agrochemicals and fine chemicals. Producing such compounds in high stereo- and regioselectivities with reasonable yields is still a major challenge using conventional strategies. Epoxide hydrolases (EHs) have caught the pharmaceutical industry attention as they have shown promising features for the preparation of enantiopure epoxides and diols during the selective hydrolysis of epoxides racemic mixtures. Indeed, EHs exhibit different enantiopreferences depending on the substrate epoxide structure and its substituents. For instance, in EH from *Bacillus megaterium* (BmEH)[1] a switch in its *(R)*-selectivity towards aryl glycidyl ethers (PGE) is observed when a nitro group is included at the *orto position* (*o*-NO_2) of the PGE substrate.[2] The factors that are governing the stereo- and regioselectivities of the process remain unknown, despite different mechanistic studies put forward to get insights into those fine details of the catalytic reaction.[3-4] In this study, we evaluate through conventional nanosecond time-scale Molecular Dynamics (MD) simulations in combination with enhanced sampling techniques (i.e. accelerated Molecular Dynamics (aMD)) the enzyme conformational dynamics, and active site preorganization. We also explore the enzyme active site channels, and its binding affinities towards different aromatic epoxides substrates and their corresponding products. Quantum Mechanics (QM) calculations are also applied to study the reaction mechanism and the effect of the substrate substituents.[5]

Our results provide valuable insights into the mechanism and the origins of selectivity in BmEH that pave the way to the proper rational design of synthetically useful EHs for the hydrolysis of racemic epoxides.

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