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Photobiocatalysis has recently emerged as a valuable strategy for conducting chemical reactions that are challenging with conventional organic chemistry tools. This approach involves the use of photenzymes, i.e. enzymes that absorb light to promote substrate conversion. The photexcitation of these catalysts enables access to electronic excited states with different properties compared to the ground state, thus providing new reaction modes. Additionally, the chiral active sites of these enzymes can control the stereoselective outcomes of these processes.

Although natural photoenzymes are rare, enzymes containing cofactors with latent photochemical properties can be activated by irradiation, thereby expanding the repertoire of available catalysts. Notably, Todd Hyster and coworkers discovered that the photoexcitation of flavin-dependent ene-reductases (EREDs) can facilitate non-natural transformations involving radical intermediates, such as the 5-exo-trig radical cyclization of alkene-tethered α-chloroacetamides to yield a chiral γ-lactam [1]. Specifically, they found that the triple mutant T36A-K317M-Y343F of Gluconobacter oxydans ene-reductase (GluER-G6) was very efficient in promoting this activity [2]. In a previous study [3] we explored the origin of the enantioselectivity of this reaction and we proposed an enatioinduction scenario in which the relative stability of prochiral transition states is dependent on a degree of freedom within the substrate, which is controlled by the enzyme through conformational selection.

Here, we present a computational study focused on the initial steps of the process promoted by GluER-G6, specifically the photoexcitation of the electron donor-acceptor (EDA) complex formed between the flavin cofactor and the substrate within the active site, and the mesolytic cleavage of the C-Cl bond. We employ a multiscale approach based on Molecular Dynamics (MD), Quantum Mechanics (QM), and the Perturbed Matrix Method (PMM) [4] to characterize the excited states, compute the spectrum of the EDA complex within the enzyme, and determine the kinetic constant for the mesolytic cleavage. We explain the low experimental quantum yield with a limited population (<10%) of EDA complex conformers (named EDAin) with a charge transfer state competent for the mesolytic cleavage. The accessibility of this state requires substrate bending positioning the chlorine atom near to the styrenic moiety [4]. We also find that the radical species obtained after the C-Cl bond breaking displays the correct prochirality for the stereoselective cyclization. This demonstrates that the conformational selection of EDA complex governs both mesolytic cleavage and enantioselectivity.

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