

Mechanistic insights into photodecarboxylation of fatty acids from classical and QM/MM simulations

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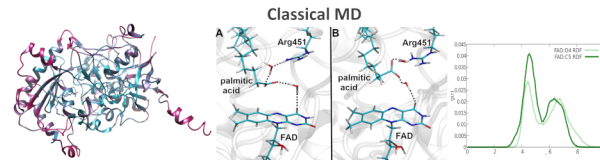
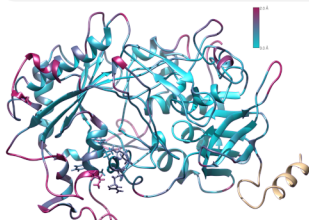


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Background

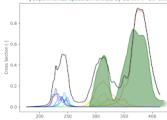
Light-activated biological systems are vital to life and often highly complex, involving multiple proteins, chromophores, and complex structural and electronic relationships. Photoenzymes are a subset of these systems that are relatively small (<1000 protein residues) and use light for biological catalysis. Fatty acid photodecarboxylase (FAP) is a newly discovered photoenzyme that converts fatty acids to hydrocarbon chains and CO₂, driven by blue light. However, the reaction mechanism is not yet known. We have examined the excited state dynamics and charge transfer steps of the catalytic cycle using a combination of molecular dynamics (MD) simulations, QM/MM, and excited state methods. We found that the protein environment and solvent play a critical role in sampling favorable substrate and chromophore orientations.



Comparison between calculated RMSF values (left) and crystal structures β -factors (above) demonstrates similar regions of stability near the chromophore and movement near the active site and in the hydrophobic substrate cavity.

Populations of the conformational ensemble selected as initial geometries for QM/MM simulations. The dominant population (left) has a substrate-chromophore distance of ~4Å. This distance is ~6Å for the minor population (right).

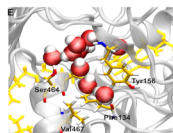
— experimental spectrum (shifted by 80 nm (-0.7 eV))



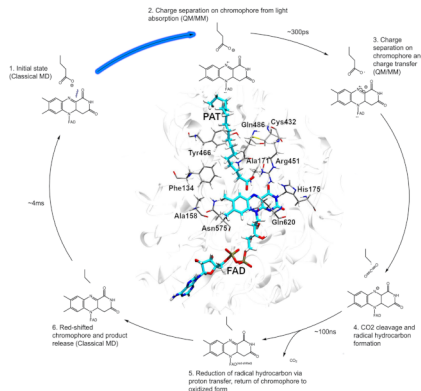
Theoretical UV-Vis spectrum calculated from classical MD structures. It includes the correct distance between S₁ and S₀ as well as a particular shoulder in S₁. This indicates that four excited states (2 bright, 2 dark) is sufficient to reproduce the initial experimental results. The experimental spectrum is overlaid in green.

Methods

MD: PDBID: 5NCC, prepared with MolProbity and Modeller, AMBER ff14SB/OL3/gaff parameters, OpenMM production (1µs per trajectory)
QM/MM: TeraChem, TDDFT-wPBE (6-31G**, $\omega=0.5$) (1 ps per trajectory)
284 atoms in QM region

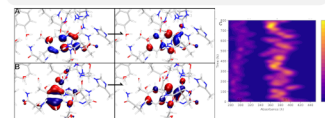


Small water tunnel seen in active site near hydrophobic cavity. This allows for water to diffuse in and out of the active site, and could be involved in CO₂ product release.

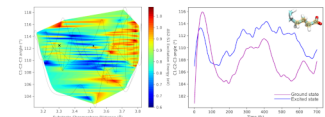


QM/MM

Once a favorable geometry is adopted, we observe that the oscillator strength of S₂ increases slightly by 0.1 a.u., while the energy gap between S₁ and S₂ decreases by 0.9 eV. These results suggest that the charge transfer step of the reaction requires population transfer between the first two excited states.



The natural orbitals for the S₂ state, where the electronic density is moving off of the substrate and onto the chromophore.



The predominant structural change while simulating on the excited state includes several angle distortions along the substrate. The C1-C2-C3 angle (above) changes the most relative to the ground state MD trajectory. Within a 3.4 Å distance, distortion of the angle to 114 and 109 degrees from the ground state 104 appears to promote the lowering of the gap between S₁ and S₂.

Conclusions and Future Directions

We have probed the initial steps of the mechanism of FAP using classical and quantum methods. We have shown that the unusual conformation of the chromophore, as well as the flexibility of the substrate in the open active site, are likely crucial to the mechanism. We will investigate further steps of the mechanism and the charge transfer mechanism along with effects of mutagenesis simulations.



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