



Diels-Alderase: Computational Design of a Novel Enzyme

Alex George, Jason DeChancie and Kendall Houk

Swarthmore College

and

Department of Chemistry and Biochemistry, UCLA

The ability to design enzymes would be of considerable therapeutic and synthetic importance. Here we use computational methods to design an enzyme to catalyze the Diels-Alder reaction, a reaction of immense synthetic importance with no known biological catalysts. To ensure water-soluble reagents and to facilitate enzymatic binding of the substrates, we selected as the target of catalysis the reaction of methacrolein with a diene with an attached glucose moiety. We plan to catalyze this reaction via the formation of an iminium intermediate between methacrolein and a lysine side chain. We used Gaussian03 software to perform quantum mechanical calculations to calculate the difference in energy between the transition state and reagents for a reduced model system of the reaction, using a methoxy group as a substitute for the glucose moiety, with and without iminium catalysis. The calculations indicated that iminium catalysis reduces the difference in energy by 23.5 kcal/mol, well in excess of the 10 kcal/mol required for effective enzymatic catalysis. We are currently using similar calculations to determine the optimal geometry of the transition state for the reaction. Once that has been determined, known glucose-binding protein structures from the Protein Data Bank will be modified such that they will support the optimized transition state geometry and the nucleophilic lysine required for iminium formation.

As an enzyme's catalytic ability is dependant on its active site and prediction of protein folding remains beyond our capabilities, it is key to focus on active site design as a method of designing novel enzymes.

Words Count: 250