

Transition State Optimization of Biochemical Systems for the Acceleration of Biomaterial Discovery

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The formation of side products is often a significant detriment to the efficiency of chemical reactions, reducing output, increasing waste, and requiring additional time for purification. Purification is especially a concern for the synthesis of biomaterials. The optimization of reactions to eliminate such products however, proves both expensive and time consuming. In this regard, understanding the mechanisms of bio-conjugation through use of DFT calculations may help to accelerate this process.

Here we present transition-state optimization to improve the kinetic control of several types of coupling reactions. First we show that through manipulation of the substituents in phenyloxadiazolyl methylsulfone derivatives, we can accelerate coupling with a cysteine analogue. To elaborate, the TS barrier was found to be inversely proportional to the amount of positive charge at the reaction site, providing insight to tailor future reactants. Coupling between sugars is more challenging. Different reaction pathways follow different transition states, which result in different products. We explore the chemical space of potential protecting groups to propose a means of manipulating the transition state of the reaction. Finally, we show that for a simple mechanochemical system, by simply manipulating the exerted pressure we can alter the reaction mechanism, leading to different products. The application of similar methodologies to other biochemical systems may accelerate biomaterial discovery in a more efficient and eco-friendly way.