

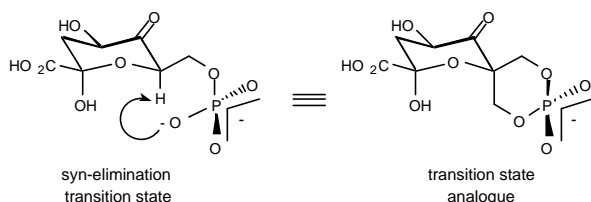
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Enzymes during catalyzed turnover of substrate into product selectively stabilize reactive intermediates and transition states. This stabilization lowers the activation barriers between individual steps in the enzyme-catalyzed process



thereby increasing the rate of enzyme-catalyzed reactions. By synthesizing analogues which structurally mimic reactive intermediates or transition states, tight binding interactions between enzyme and reactive intermediate analogue or transition state analogue can be achieved. This inhibition can lead to molecules which possess useful medicinal and therapeutic properties. Molecules being synthesized in this group are intended for ultimate use as antibiotics and agents for treatment of mental disorders.

The primary challenge in synthesizing reactive intermediate and transition state analogues is that the reactive intermediates and transition states generally only exist within the confines of the enzyme's active site. Since the analogues which are synthesized must be stable in

solution, structural changes must be introduced which enhance stability while not interfering with binding of the analogue to the enzyme.

Inhibition of DHQ synthase, an enzyme involved in aromatic amino acid biosynthesis, is one example of the aforementioned challenges and goals. During catalytic turnover, the phosphate monoester of a reactive intermediate mediates its own *syn* elimination. We have recently synthesized a transition state analogue which mimics this *syn* elimination. The synthesis of this transition state analogue provides a flavor of the extensive synthetic efforts which are required to synthesize putative inhibitors. After binding to the enzyme's active site, oxidation of the C-4 alcohol of the synthesized analogue by DHQ synthase provides the desired transition state analogue. Synthetic chemists in the group also do all of the enzyme purification and kinetic evaluation required to determine how the synthesized reactive intermediate and transition state analogues interact with enzymes targeted for inhibition.

