

Enzymatic Transition States: Cancer, Autoimmunity, Malaria and Antibiotics

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The dynamic description of an enzymatic transition state is the instant of bond breaking within the time of a single bond vibration. Transition state structure can be probed by kinetic isotope effects coupled to quantum chemical structures of proposed transition states. Transition state structure provides information for the design of transition state analogues. Mimics of enzymatic transition states convert the energy of catalysis into binding energy.

Our drug design program is producing powerful transition state analogues for several targets through the protocol:

- Select a target enzyme with potential for disease intervention
- Synthesize the substrates with isotopic labels near the reaction center
- Measure intrinsic kinetic isotope effects (KIE) (those on the chemical step)
- Compute a transition state structure matching the intrinsic KIE
- Calculate the molecular electrostatic potential map
- Synthesize chemically stable analogues that match the electrostatic potential
- Test analogues against the enzymes and in biological models of the disease

Powerful inhibitors with promise for T-cell leukemia, B-cell leukemia, autoimmune diseases, prostate cancer, head and neck cancer, malaria and bacterial antibiotics are being developed in this program. Two compounds, Immucillin-H and DADMe-Immucillin-H are in clinical trials for T-cell diseases. Computational dynamics is providing insights into the atomic motions needed to form enzymatic transition states