6.2: Transititon State Analogs and Catalytic Antibodies

Transition State Analog inhibitors

All chemical reactions progress through a transition state, a transient and unstable species between a substrate and a product, which contains the highest energy in the reaction progress. To reach the transition state, activation energy is required.

Without the participation of an enzyme, the activation energy is large, and as a result, the chance of the reaction to happen is small. In the presence of an enzyme, the activation energy will be lowered significantly to facilitate the reaction. This could lead to an increase in rates of some reactions by trillions of folds.

If energy does not simply appear or disappear, then, how does an enzyme lower the activation energy? This is because the enzyme could bind to the transition state extremely tightly, resulting in releasing a large amount of binding energy that is utilized to "compensate" the activation energy (to make it look smaller).

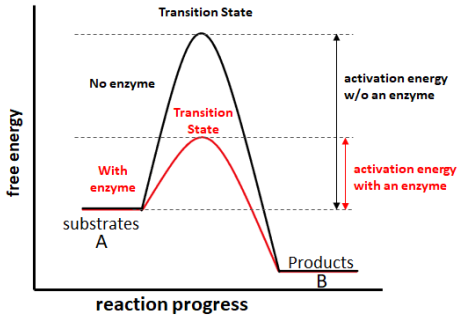

Figure 6.2.1: The energies of the stages of a chemical reaction. Without enzyme (Black line), substrates need a lot of activation energy to reach a transition state, which then decays into lower-energy products. When enzyme catalyzed (Red line), the enzyme binds the substrates (A), then stabilizes the transition state ($ES^{\ddagger}$) to reduce the activation energy required to produce products (B) which are finally released.

A transition state analog, one exhibiting the same properties such as shape and charge of the original transition molecule, may come in and bind. Although the analog displays similar properties as the original transition molecule, but it has higher affinity for the enzyme than the natural substrate and will ultimately deactivate and inhibit the enzyme and prevent it from binding to a substrate. The analogs can "function as antimetabolites".

Catalytic Antibody

Transition-state analogs have been used for generating catalytic antibodies, antibodies that catalyze chemical reactions. Enzymes lower activation energy and accelerate catalysis by tightly binding to the transition state. If an antibody could bind the transition state tightly like an enzyme, and it should also catalyze the reaction just like an enzyme. The transition state has short lifetimes (suggested to be as short as 10^{-13} S) and cannot be used to generate antibodies as antigens. Their stable mimics, the transition-state analogs, which have long half-lives and could be synthesized chemically, may function as an antigen to generate the antibody.

One example of catalytic antibody is the one that catalyzes the chelation of ferrous iron into the porphyrin plane of protoporphyrin IX which is naturally catalyzed by ferrochelatase in living organisms, the last enzyme in the synthetic pathway of heme. During catalysis, ferrochelatase significantly bends the planar porphyrin plane into a bowl-liked ring as the transition state. N-methylmesoporphyrin, a chemical causing hepatic protoporphyria mice, resembles the transition state by containing a bent and stable porphyrin ring. When N-methylmesoporphyrin was injected to animals as the antigen, monoclonal tightly binding antibodies were produced. Some of the produced antibodies were capable to distort the planary planar porphyrin plane into a bowl-liked ring and insert of iron into protoporphyrin IX, just like ferrochelatase. to facilitate the entry of ferrous iron. Using a similar technique, antibodies that catalyze ester and amide hydrolysis, transesterification, and photoinduced cleavage, among other reactions, have been developed.

Contributors

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