

### **Covalent Catalysis: In Enzymes**

- Proteases and peptidases
  - chymotrypsin, elastase, subtilisin
  - reactive surfle nucleophile
- Spirle aldehode Gehydrogenase
  - glyceraldehyde-3phosphate dehydrogenase
  - reactive thiolate nucleophile
- Aldolases and decarboxylases
  - amine nucleophile
- Dehalogenases



## **Mechanisms of catalysis**

## Conformational distortion (also known as substrate strain) (Transition state stabilization)

- "Strain" is a classic concept in which it was supposed that binding of the substrate to the enzyme some low caused the substrate to become distorectionard the application state (this is the assumption of induced-ft model – substrates induces conformational change in enzyme active site to fit substrate (induced fit) and enzyme applies bond strain on the substrate)
  - It's unlikely that there is enough energy available in substrate binding to actually *distort* the substrate toward the transition state
  - It's possible that the substrate and enzyme interact unfavorably and this unfavorable interaction is relieved in the transition state
  - It's more likely that the *enzyme* is strained, as for example in induced fit
- Transition state stabilization is a more modern concept: it is not the substrate that is distorted but rather that the transition state makes better contacts with the enzyme than the substrate does, so the full binding energy is not achieved until the transition state is reached

# Mechanisms of catalysis Conformational distortion (Transition state stabilization) 29 0 • The procence of transmontal distortion (or against it) :

- - 1. Quantitative studies showed that observed
    - rate enhancement cannot only be explained with above mechanisms and
    - we know that enzymes are conformationally dynamic
  - 1. The measure of good/bad substrate by comparing  $K_m$  and  $k_{rat}$ 
    - K<sub>m</sub> (based on binding of substrates in their ground state)
    - k<sub>et</sub> (based on the chemical steps subsequent to initial substrate binding)
- Jencks (1969)  $\rightarrow$  for a reversible reaction, distortion is necassary: • having an active site best matched to a structure intermediate between the product and substrate states: the transition state

# Examples of metal ion catalysis

- Cu<sup>2+</sup> or Zn<sup>2+</sup> can stabilize the transition state (TS). The metal binds to the charged intermediate
- This charge stabilization of the TS is often called electrostatic catalysis
- This method is likely to be found in many enzymes since nearly 1/3 of all enzymes require metal ions

