

### Enzyme Catalysis 3

#### I. Fundamental principle of enzyme catalysis

A. Enzymes lower the free energy of the transition state ( $\Delta G^\ddagger$ ) pp. 196 - 197

This is accomplished by binding and stabilizing the transition state

B. The energy to force the substrate into the transition state comes from substrate binding

C. The transition state is bound more tightly than substrate

1.  $|\Delta G_{b,\ddagger}| > |\Delta G_{b,s}|$

2. The active site is chemically complementary to the transition state

- a. The same weak forces used to bind substrate binds transition state

- b. The shape of the active site is complementary to the transition state

- c. Charges in transition state are near opposites in the enzyme's active site

#### II. A hypothetical enzyme : Stickase [from Lehninger, Nelson & Cox]

A. Stickase breaks sticks into two pieces

B. The transition state for breaking a stick is a bent, strained stick

1. Upon bending, strain accumulates in the stick's center and eventually the stick breaks

2. Free-standing sticks do not spontaneously bend and break.

The activation energy is too high for this to occur by random fluctuation

C. The binding site of stickase forces the stick to bend in order to gain more contact with the enzyme

A bent stick has more weak interactions with the enzyme than a straight stick

D. A stick containing a natural bend will bind more tightly to stickase than a straight stick

1. This bent stick is a **transition state analog**

2. Transition state analogs are potent competitive inhibitors of enzymes

#### III. Lowering $\Delta G^\ddagger$

p. 228

A. Entropy effects (catalysis by approximation)

1. Enzymes juxtapose substrates in their optimally reactive orientation

Substrates coming together by random collisions generally do not contact with reactive portions.

2. Example: Adenylate kinase [ATP + AMP  $\rightleftharpoons$  ADP + ADP]

The enzyme brings the terminal phosphate of ATP adjacent to the phosphate of AMP, facilitating transfer of the phosphate

B. Enthalpy effects

1. Acid-base catalysis

Enzymes supply or remove  $H^+$  to bring about catalysis

2. Covalent catalysis

The creation on a new intermediate with a covalent bond to the enzyme lowers the energy of the transition state

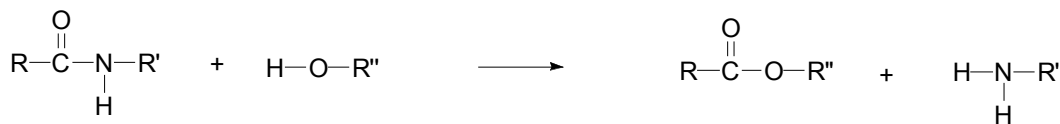
3. Metal catalysis

- a. Metals can enhance the acidity and basicity of water

- b. Metals can aid oxidation-reduction reactions by providing electron sinks and sources

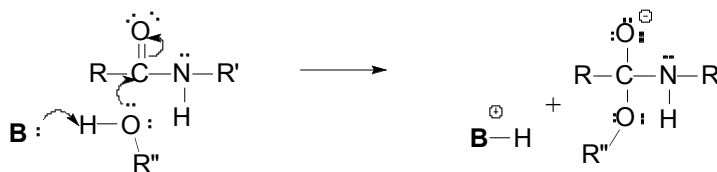
- c. Metals can also stabilize and orient substrate (an entropic effect)

## IV. Example: Cleavage of an amide bond

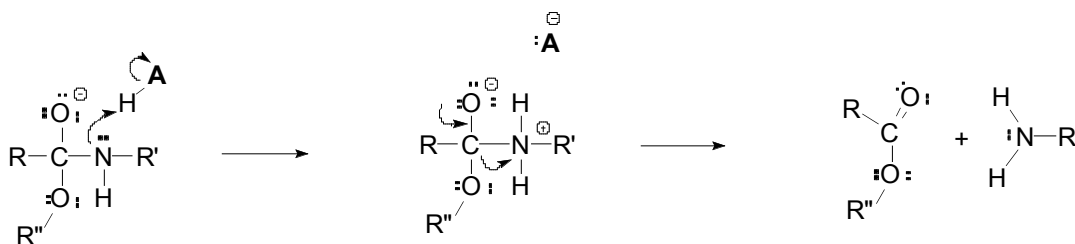


One scheme for hydrolyzing an amide bond

General base mechanism acts in the first step:

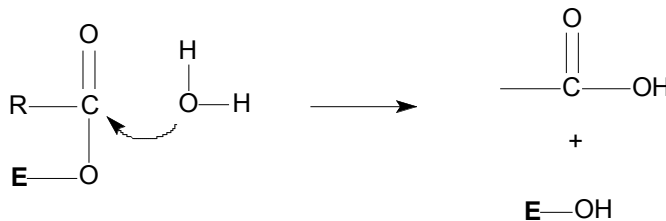
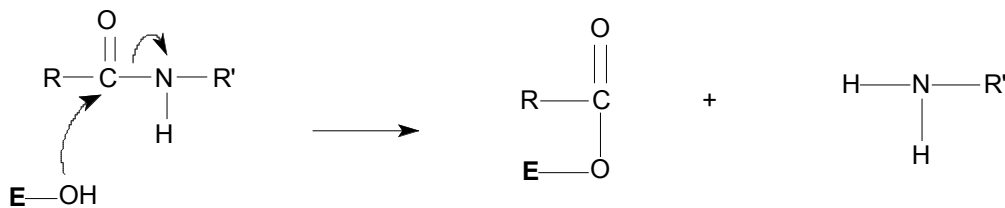


General acid mechanism acts in the second step::



Which amino acid side chains can perform the jobs of **B:** and **A-H**?

A different mechanism uses covalent catalysis:



These different strategies may be combined.