FIRST SEMESTER (CLINICAL ENZYMOLOGY)

MECHANISM OF ENZYME ACTION: LOCK AND KEY MODEL AND INDUCED FIT THEORY

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four Stage المرحلـــــــــــــة الرابعة

محاضرة رقم 3 الجانب النظري

Lecture No. 3 Theoretical

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Enzymes speed up reactions by binding a specific substrate to their active site, forming an enzyme-substrate complex, which lowers the activation energy. This complex then transforms into an enzyme-product complex, with the enzyme releasing the free product and remaining unchanged to catalyze further reactions. This process occurs through models like Lock and Key and Induced Fit, which explain how the active site's shape and flexibility facilitate the reaction.

The Step-by-Step Mechanism

1- Substrate Binding: A substrate molecule binds to the enzyme's active site, a specific region on the enzyme with a precise shape and chemical properties.

2- Enzyme-Substrate Complex Formation: This binding forms a temporary, high-energy complex called the enzyme-substrate complex.

3- Catalysis (Lowering Activation Energy): The enzyme's active site provides a unique environment that lowers the activation energy required to convert the substrate into a product.

4- Product Formation: Within the active site, chemical bonds are rearranged or broken, transforming the substrate into a product.

5- Product Release: The new product(s) are released from the enzyme's active site, freeing the enzyme to bind to another substrate molecule.

MECHANISM OF ENZYME ACTION

- The catalytic efficiency of enzymes is explained by two perspectives:

Thermodynamic changes

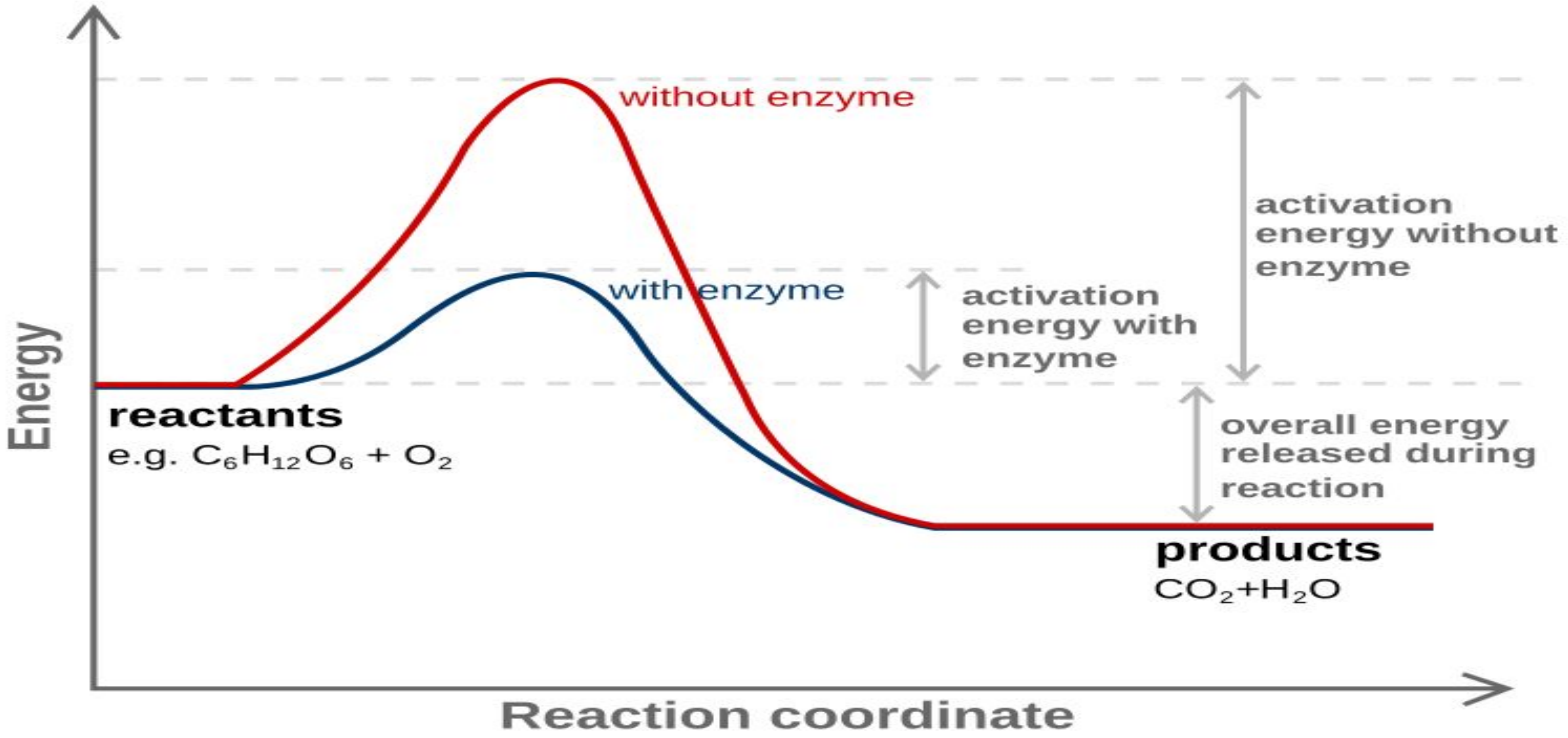
Processes at the active site

THE THERMODYNAMICS OF ENZYME ACTION

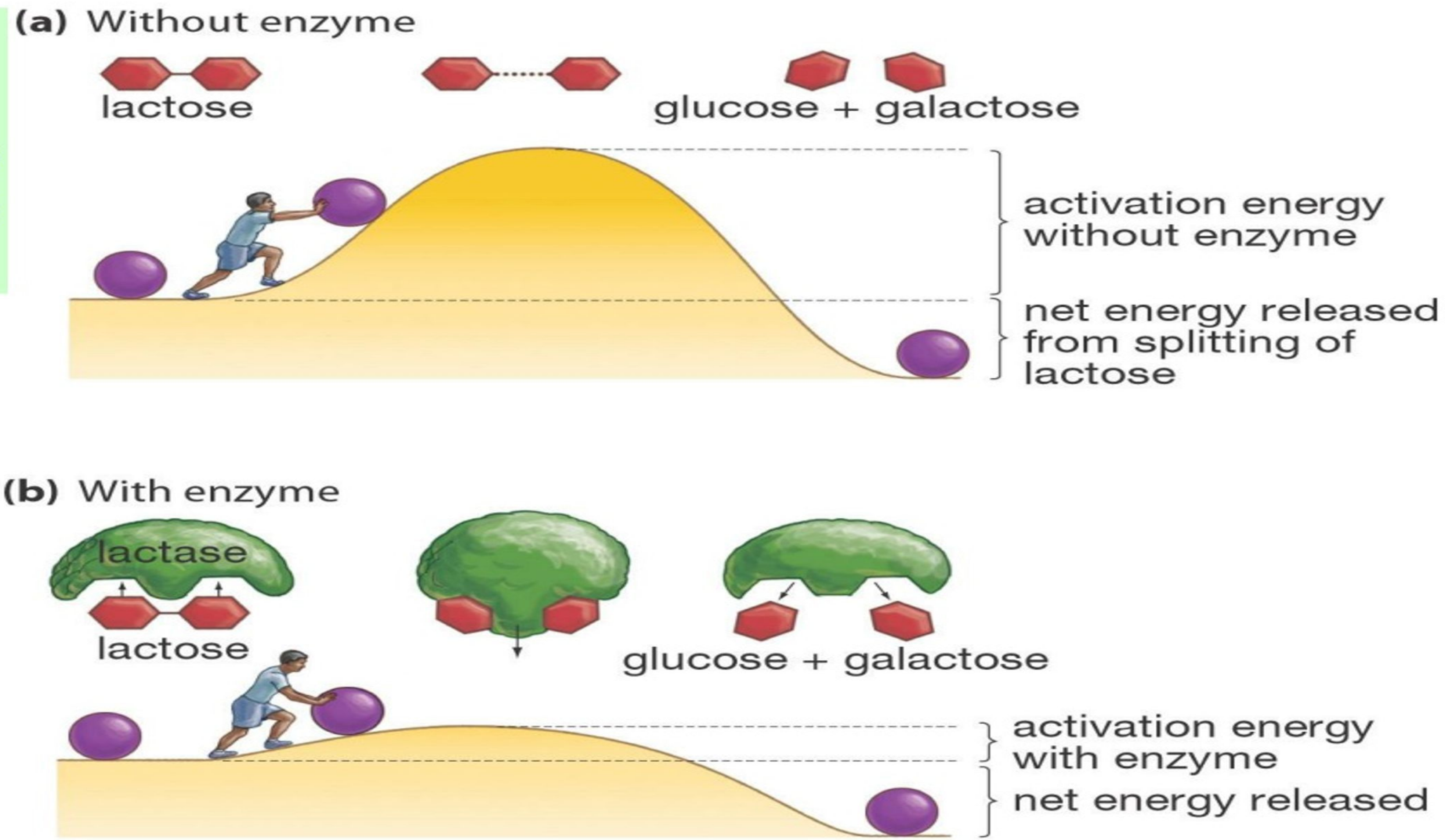
explain how enzymes increase reaction rates by lowering the activation energy without changing the overall free energy change or the position of chemical equilibrium.

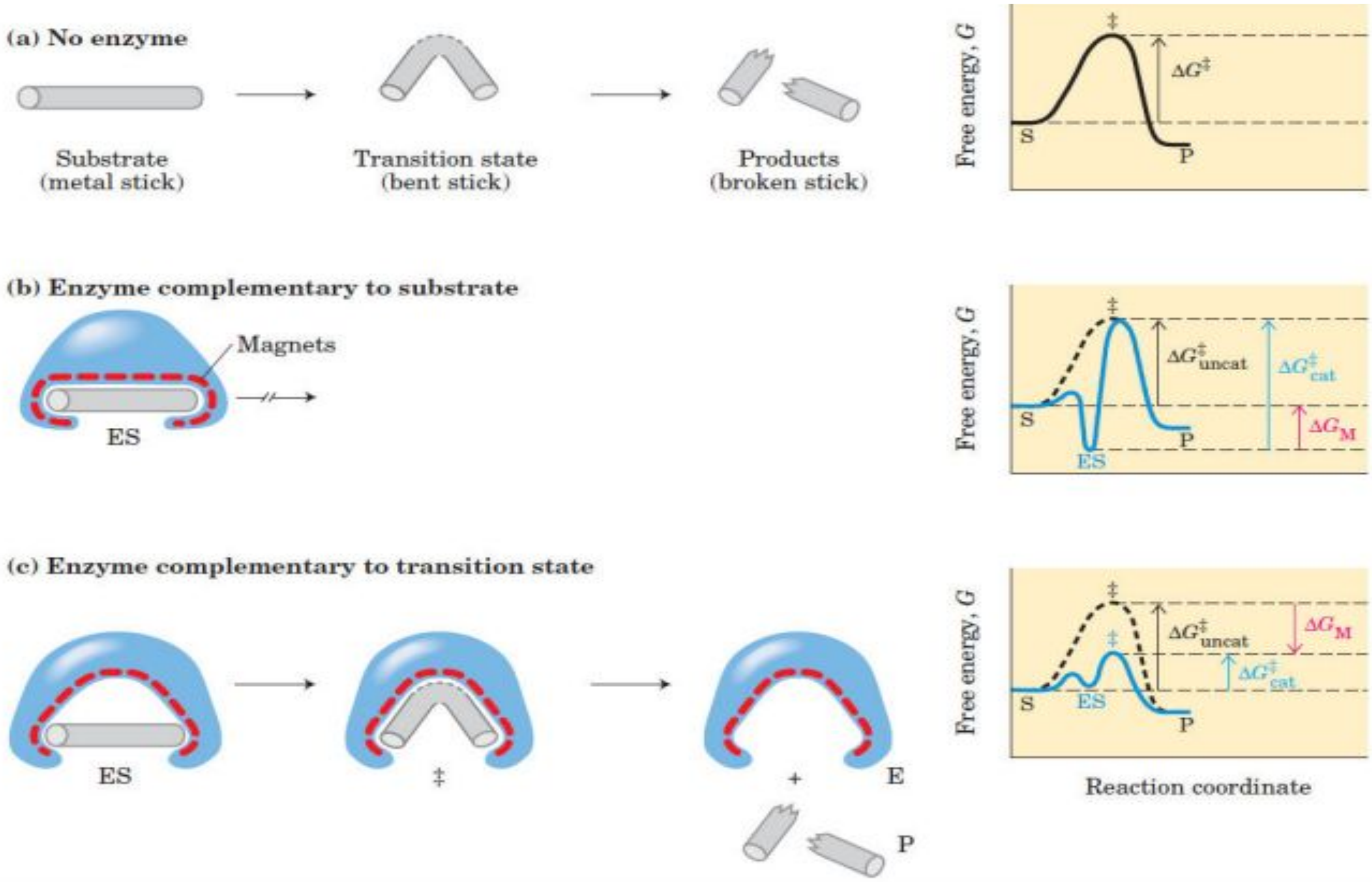
How Enzymes Work Thermodynamically:

1- Binding to the Transition State:
Enzymes bind to the high-energy, transient transition state of the reaction, not just the substrate itself.
2- Stabilizing the Transition State:
The binding of the enzyme to the transition state releases binding energy, which is used to stabilize the transition state, effectively lowering the energy barrier.
3- Lowering Activation Energy:
By stabilizing the transition state, the enzyme reduces the activation energy required for the reaction.
4- Altering the Reaction Coordinate:
Enzymes provide an alternative reaction pathway with a lower energy peak.


without enzyme
with enzyme
activation energy without enzyme
activation energy with enzyme
Energy
reactants
e.g. $C_6H_{12}O_6 + O_2$
overall energy released during reaction
products
CO_2+H_2O
Reaction coordinate

Enzymes Lower a Reaction's Activation Energy





(a) No enzyme
Substrate
(metal stick)
Transition state
(bent stick)
Products
(broken stick)
(b) Enzyme complementary to substrate
Magnets
ES
(c) Enzyme complementary to transition state
ES
‡
+
E
P
Free energy, G
‡
$\Delta G^{\ddagger}$
S
P
$\Delta G^{\ddagger}_{uncat}$
$\Delta G^{\ddagger}_{cat}$
ΔG_{M}
ES
Reaction coordinate

processes at the active site

Covalent Catalysis:
An amino acid residue in the active site forms a temporary covalent bond with the substrate, stabilizing the transition state.

Acid-Base Catalysis:
Amino acids can act as proton donors or acceptors to facilitate the reaction.

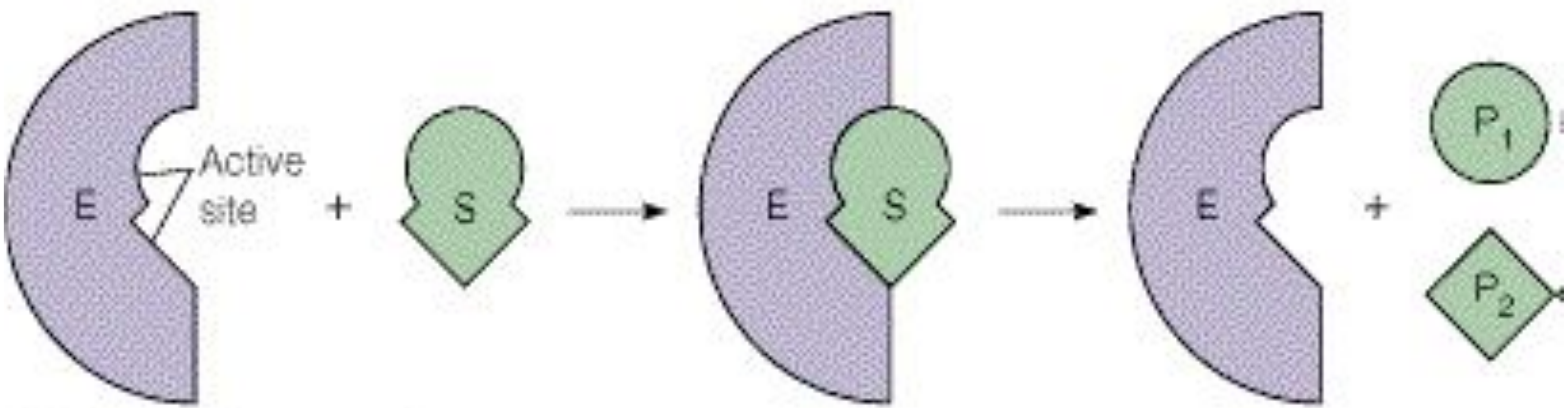
Catalysis by Approximation (Proximity):
The active site increases the local concentration of substrate molecules, bringing them into close proximity and ideal orientation for bond formation.

Catalysis by Strain:
The binding of the substrate to the active site can cause structural strain or reorientation, weakening the bonds within the substrate and making them easier to break.

LOCK AND KEY HYPOTHESIS

- Enzymes are very specific and it was suggested by Fischer in 1890 that this was because the enzyme had a particular shape into which the substrate or substrates fit exactly.This is often referred as Lock and Key hypothesis.
- Lock and Key model:
  - According to this model, shape of active site of enzyme is complementary to the shape of substrate molecules. the substrate is like a key whose shape is complementary to the enzyme which is supposed to be lock and they fit perfectly.
  - Enzymes catalyze only those substrates which fit perfectly on the active site of that enzyme.
  - Most enzymes are far larger than the substrates molecules that act on and the active site is usually a very small portion of the enzyme, between 3 and 12 amino acids. The remaining amino acids which make the bulk of the enzyme, function to maintain the correct globular shape of the enzyme.
  - Once the product is formed, they no longer fit into the active site and escape into surrounding medium.
  - According to lock and key model, enzymes behave as rigid molecules. However, most enzymes are globular and are flexible with varying shape.

LOCK AND KEY HYPOTHESIS

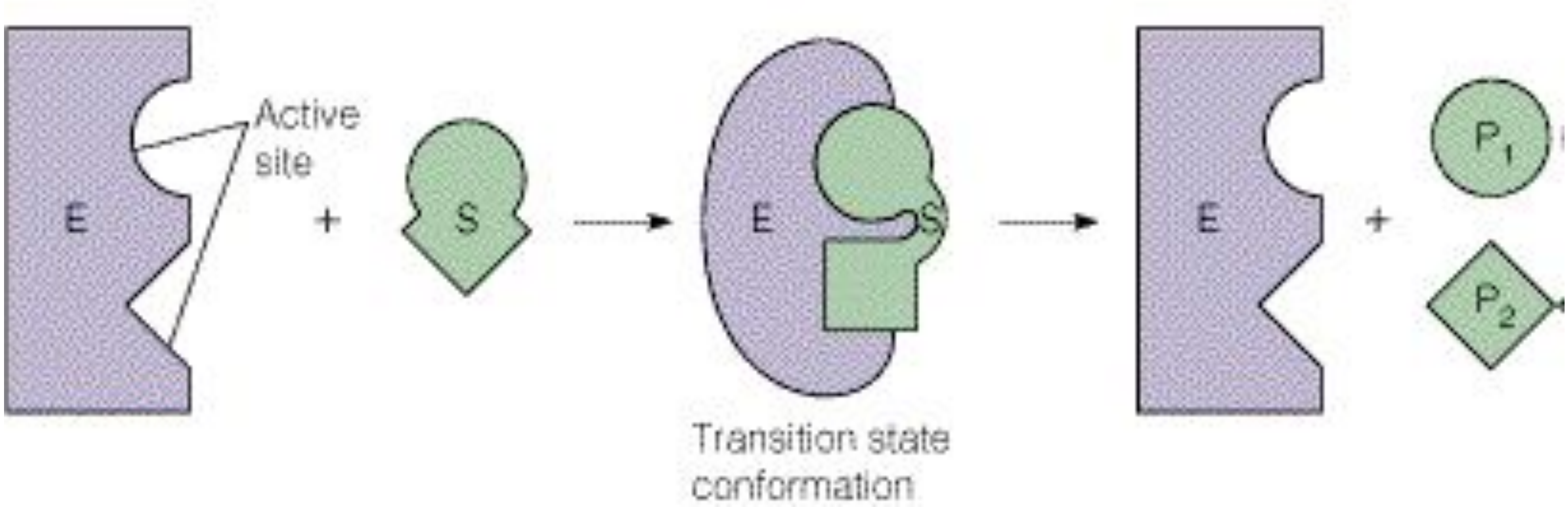


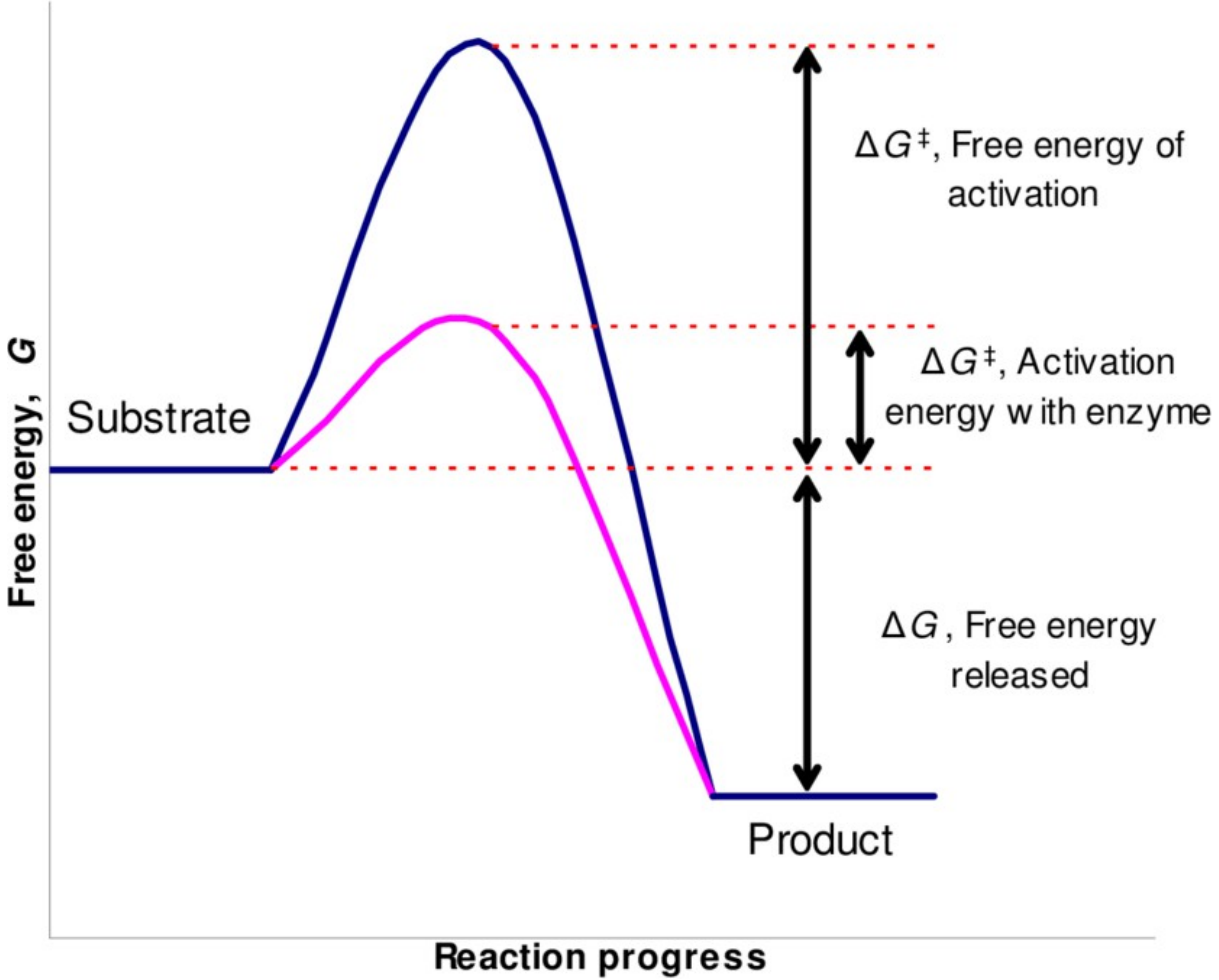
(a) Lock-and-key model

INDUCED FIT MODEL

- In 1959, Koshland suggested a modification to the ‘Lock and Key’ hypothesis which is known as ‘Induced fit’ hypothesis.
- Working from evidence that suggested that some enzymes and their active site are more flexible. To this, he proposed that the active site can modify its shape as the substrate interact with the enzyme.
- The amino acids which make up the active site are moulded into precise shape which enable the enzyme to perform its catalytic function most efficiently.
- For instance, a suitable analogy to describe Induced fit model would be that of a hand changing the shape of the glove as the individual put on the glove. Therefore in this case, glove is the active site of enzyme and the hand is substrate.
- However, in some cases, the substrate molecules changes slightly as it enters the active site before binding

INDUCED FIT MODEL





Free energy, G
Substrate
ΔG‡, Free energy of activation
ΔG‡, Activation energy with enzyme
ΔG, Free energy released
Product
Reaction progress

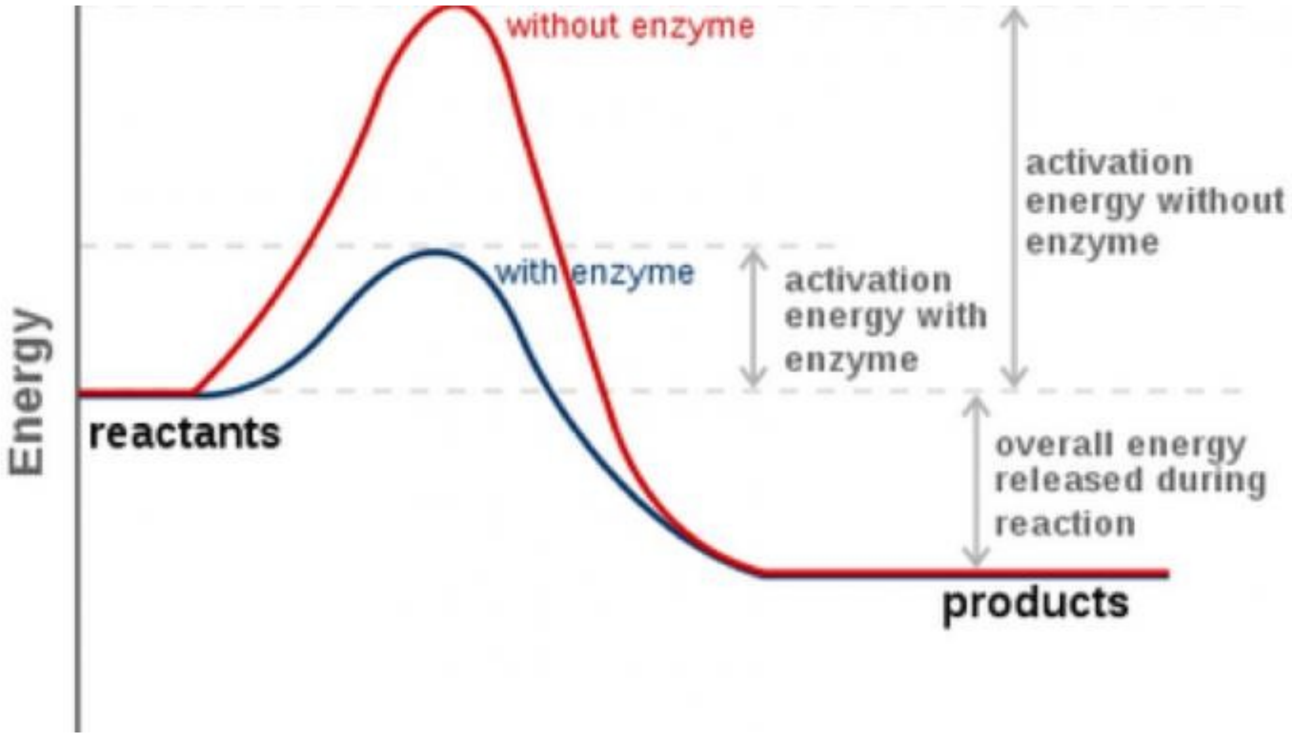
HOW ENZYME CATALYSE A REACTION?

- Enzymes are catalyst that accelerate the rate of biochemical reaction by decreasing the energy of activation.
- Every chemical reaction have energy barrier that must be crossed by the reactant molecules in order to convert itself into the product.
- The amount of energy supplied to reactant molecules in order to cross the energy barrier to from product is known as Energy of activation.
- If energy of activation is higher, rate of reaction is slower and if it is lower, the rate of reaction is faster.
- The role of enzyme in biochemical reaction is to reduce the amount of energy of activation such that the rate of reaction increases.
- During enzyme catalysis, active site of enzyme binds with substrate molecules to form Enzyme-substrate (ES) complex. During this binding some binding energy is released which is utilized to activate the substrate (reactant) molecules to form product. Thus the requirement of the amount of activation energy is decreased such that rate of reaction increases. The amount of activation decrease is equal to the amount of binding energy released during binding of enzyme and substrate.

RATE OF ENZYME REACTIONS

RATE OF ENZYME REACTIONS

- The rate of enzyme reaction is measured by the amount of **substrate changed** or **amount of product formed** during a period of time.
- The rate is determined by measuring the slope of the tangent to the curve in the initial stage of the reaction. The steeper the slope, the greater is the rate.
- If enzyme activity is measured over a period of time, the rate of reaction usually falls, most commonly as a result of a fall in the substrate concentration.



Any questions?