How are enzymes regulated?

- By controlling their concentration
  - Control of synthesis (activation or repression)
  - Degradation
- By controlling the availability of substrate
  - Production, degradation, compartmentation of substrate
  - Reversible binding of competitive inhibitors
- By controlling the activity of the enzyme
  - Reversible binding of modulators/effectors
  - Reversible or irreversible covalent modification

Modulator binding to an allosteric enzyme influences the shape of the active site

Many allosteric enzymes have separate subunits for binding a modulator (regulatory subunit, R) & for catalyzing the reaction (catalytic subunit, C)

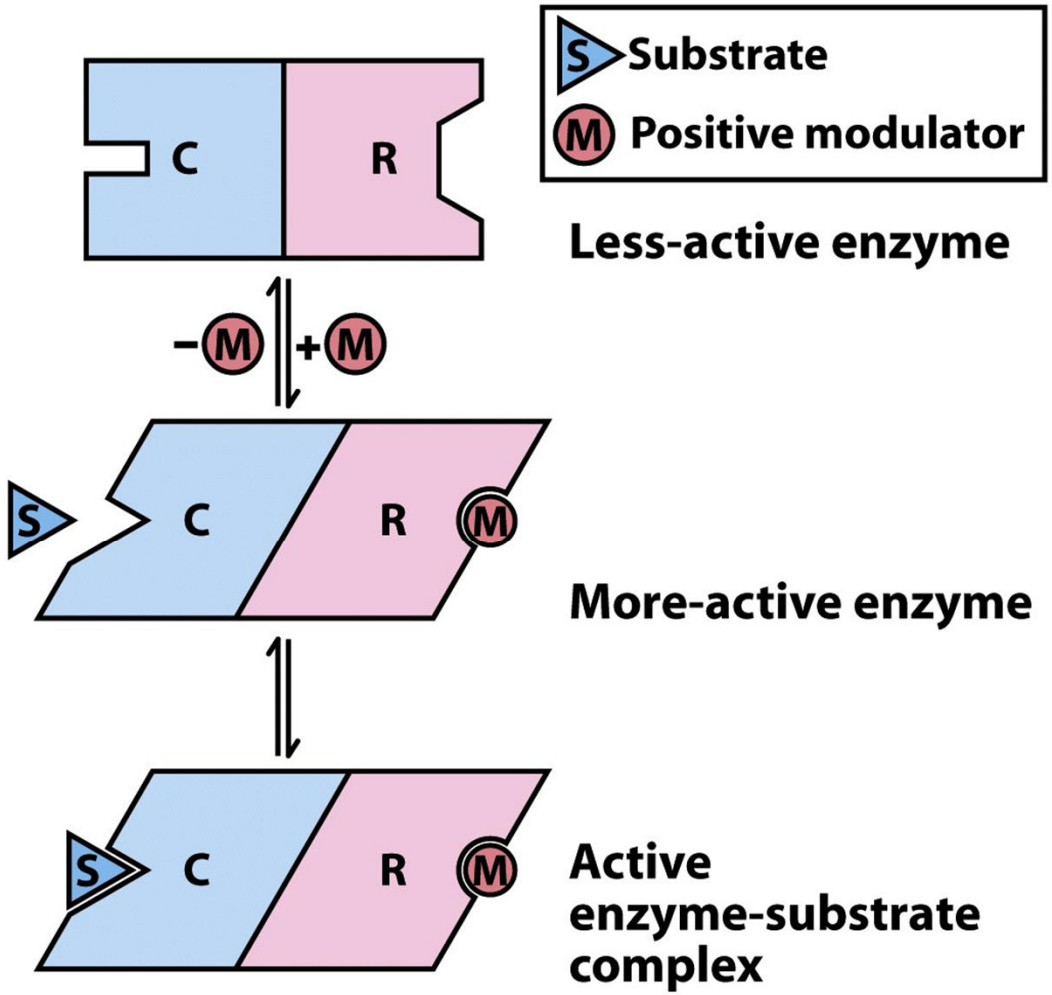

Figure 6-31
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Allosteric enzymes may show sigmoidal kinetics (positive cooperativity)

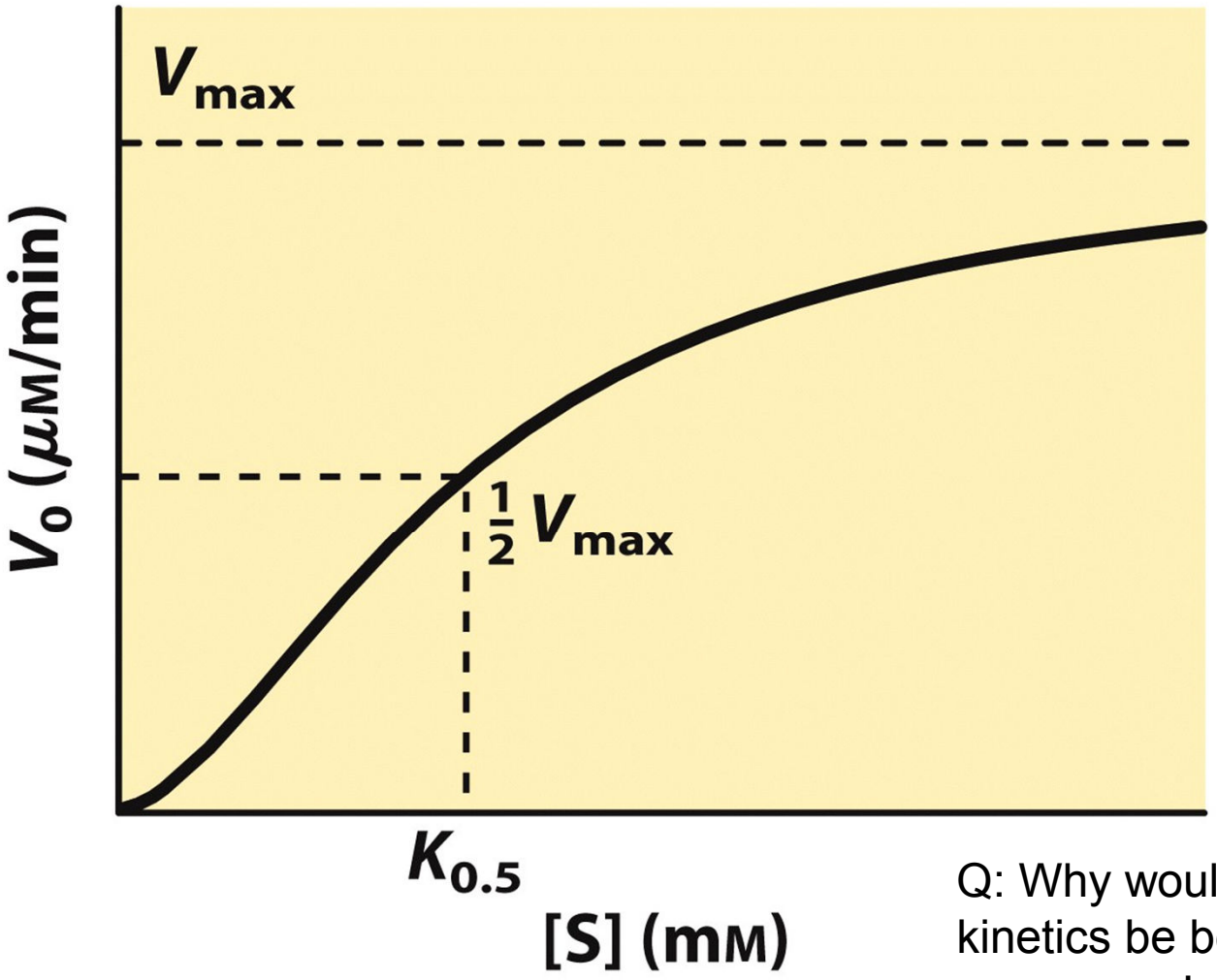

Figure 6-34a
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Q: Why would sigmoidal kinetics be beneficial to an enzyme's function?

Modulators may affect the enzyme's $K_{0.5}$

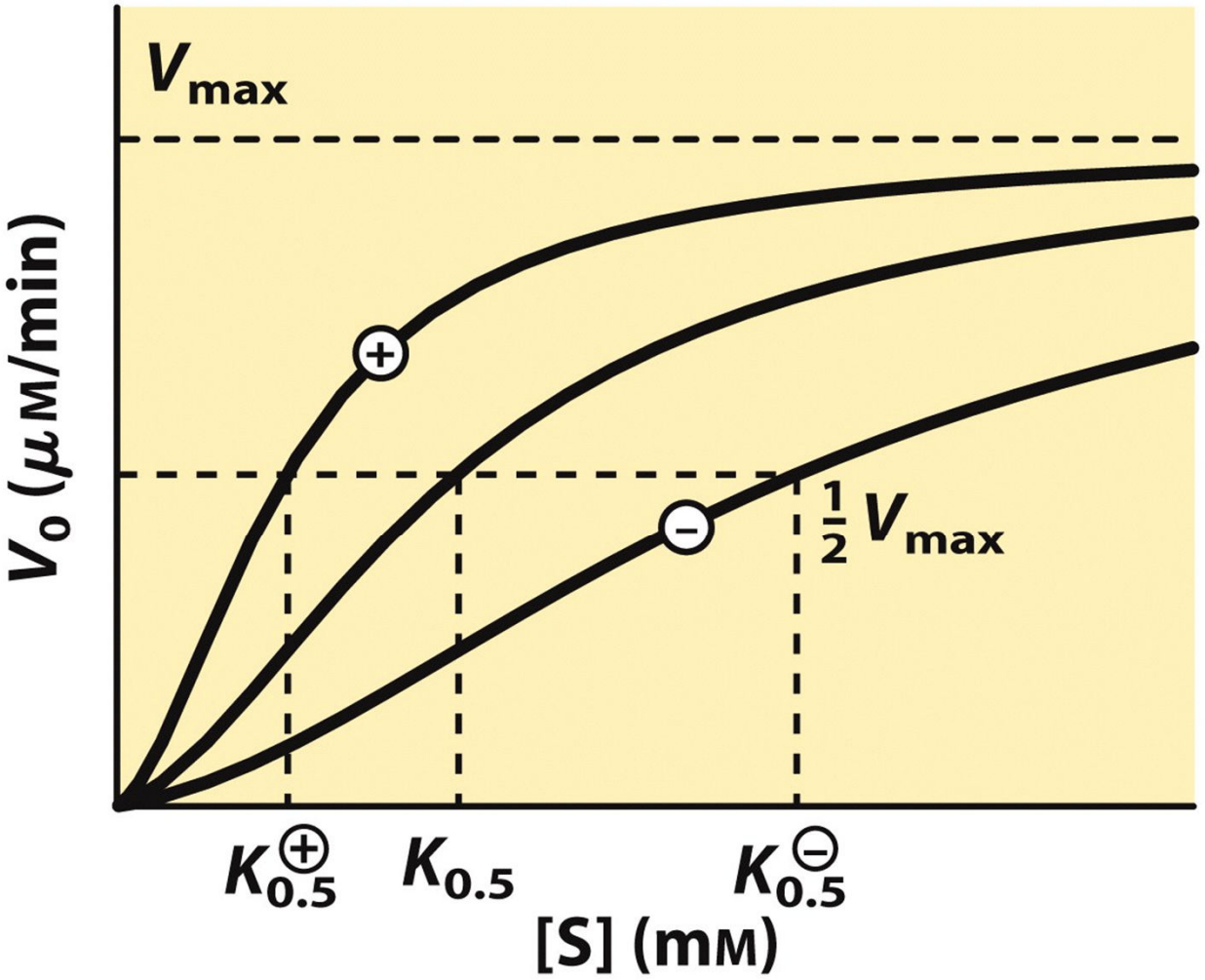

Figure 6-34b
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Modulators may affect the enzyme's V_{max}

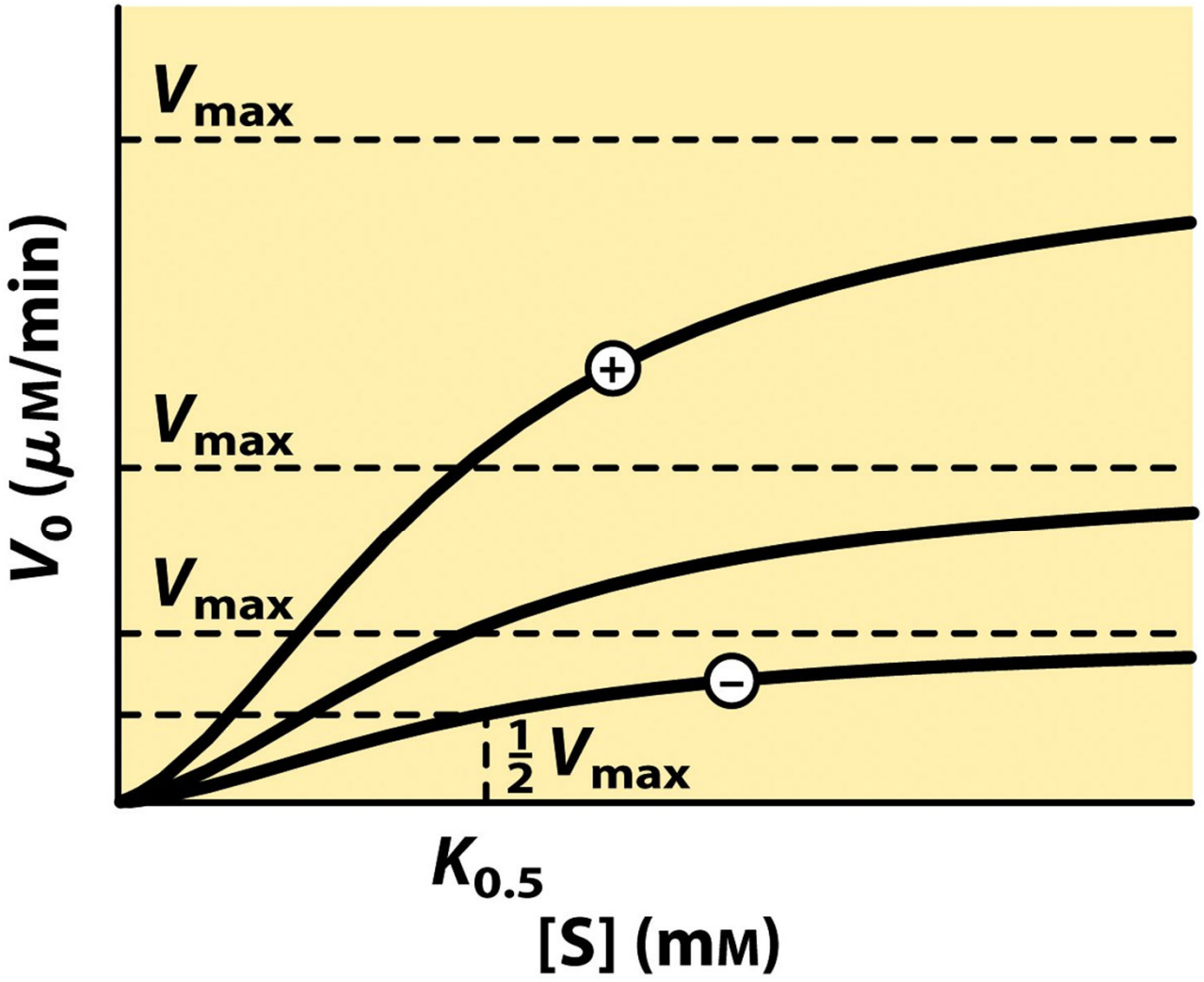

Figure 6-34c
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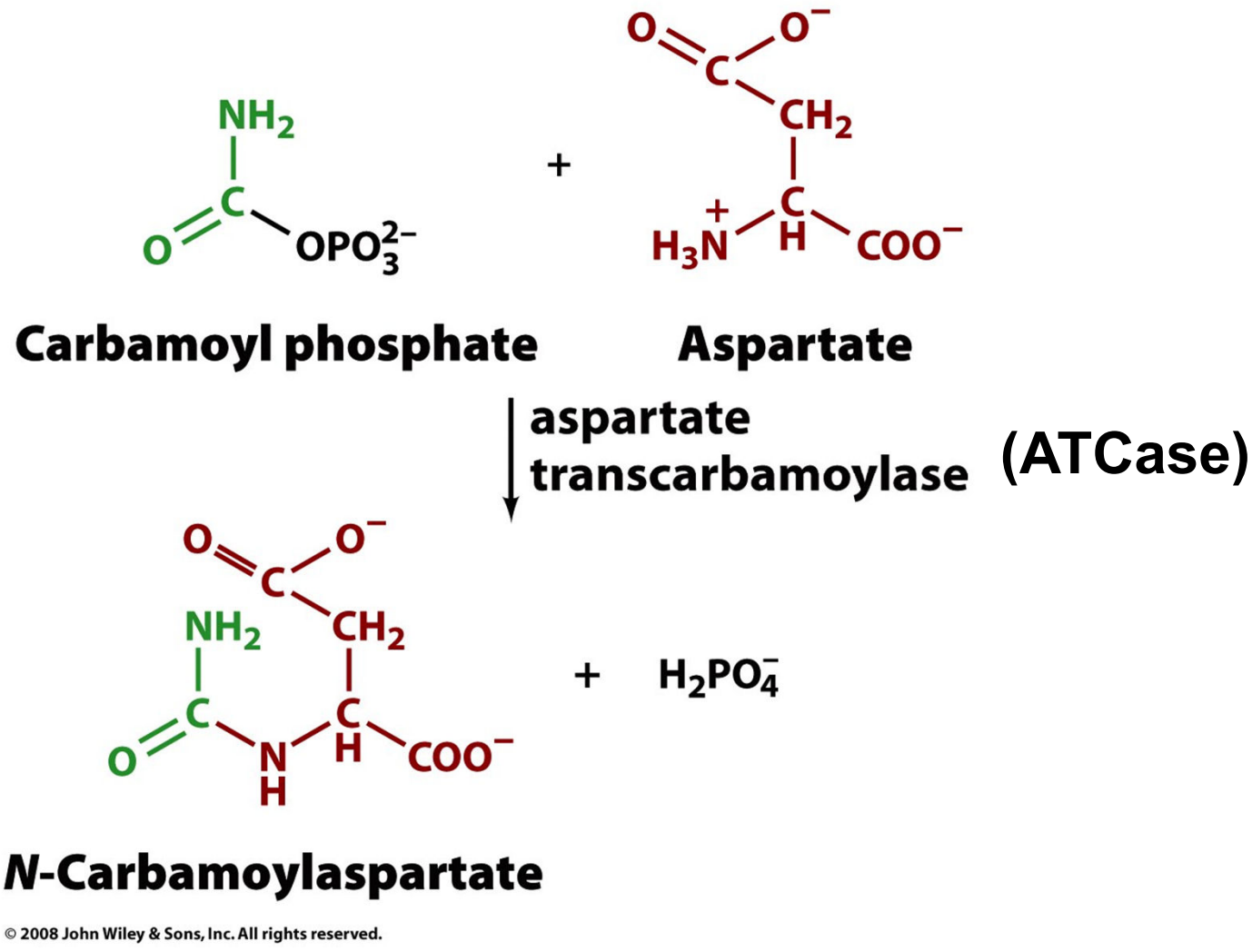
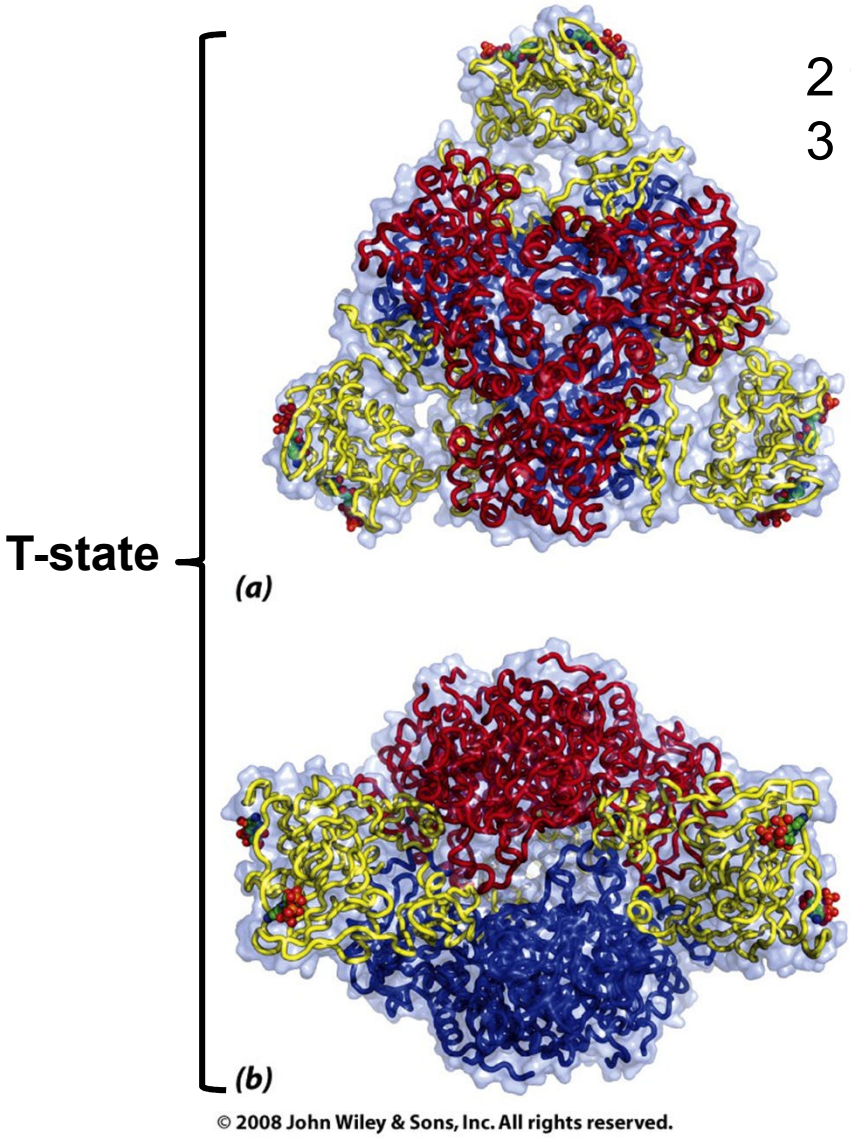
An allosteric enzyme catalyzes the first step of pyrimidine (C, T, U) nucleotide synthesis

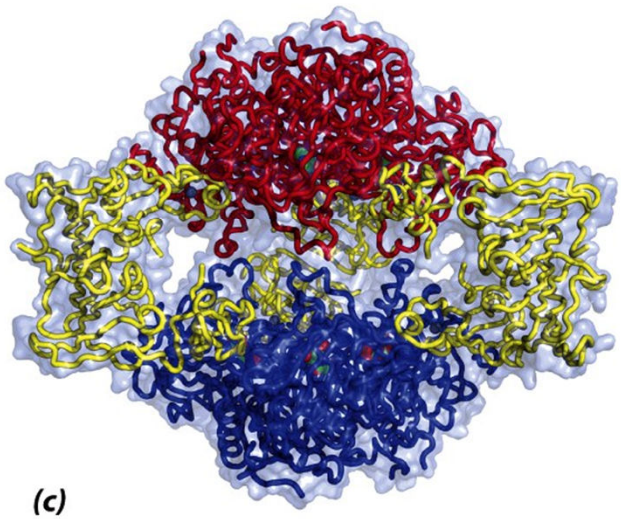


ATCase is composed of six catalytic and six regulatory subunits



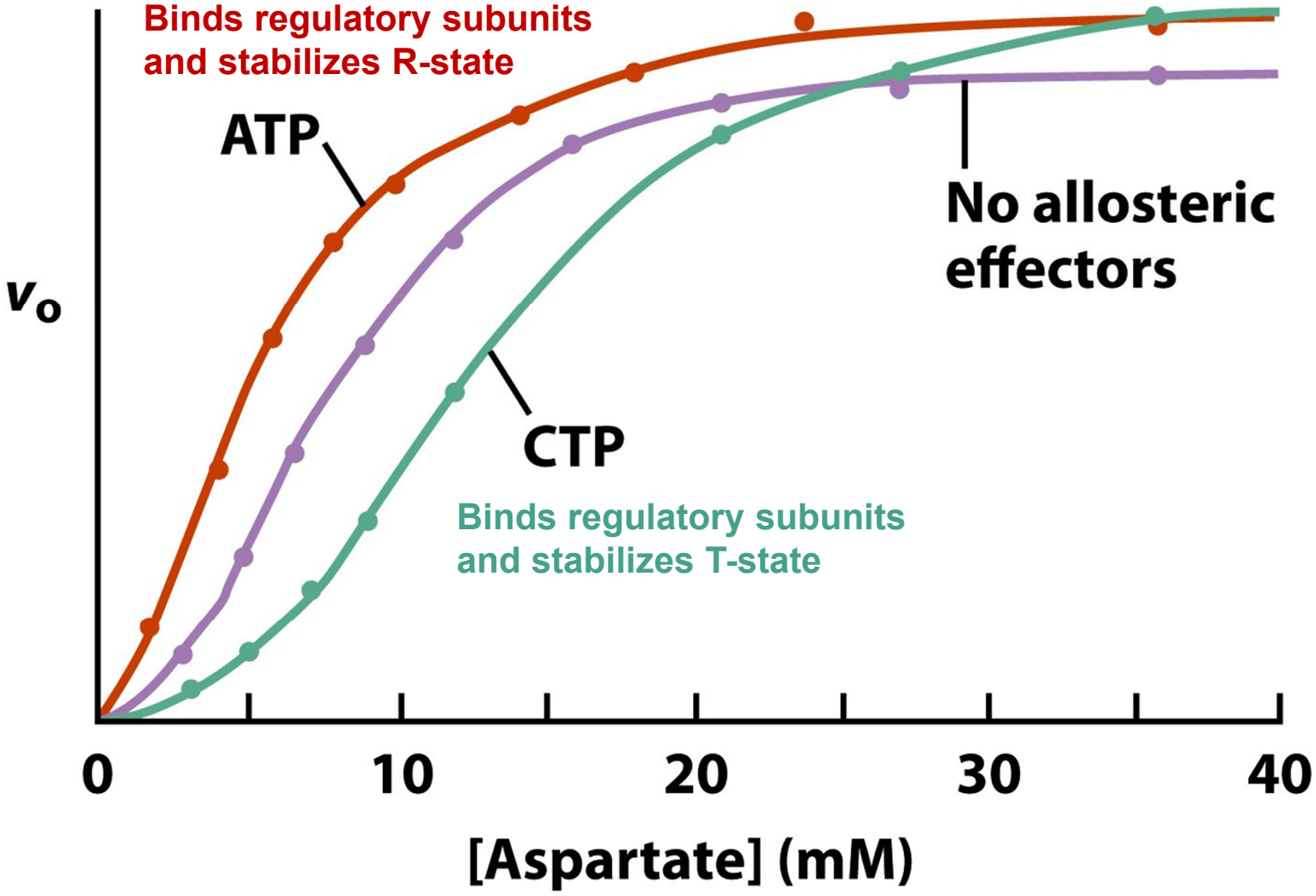
2 trimers of catalytic subunits (red, blue)
3 dimers of regulatory subunits (yellow)

R-state

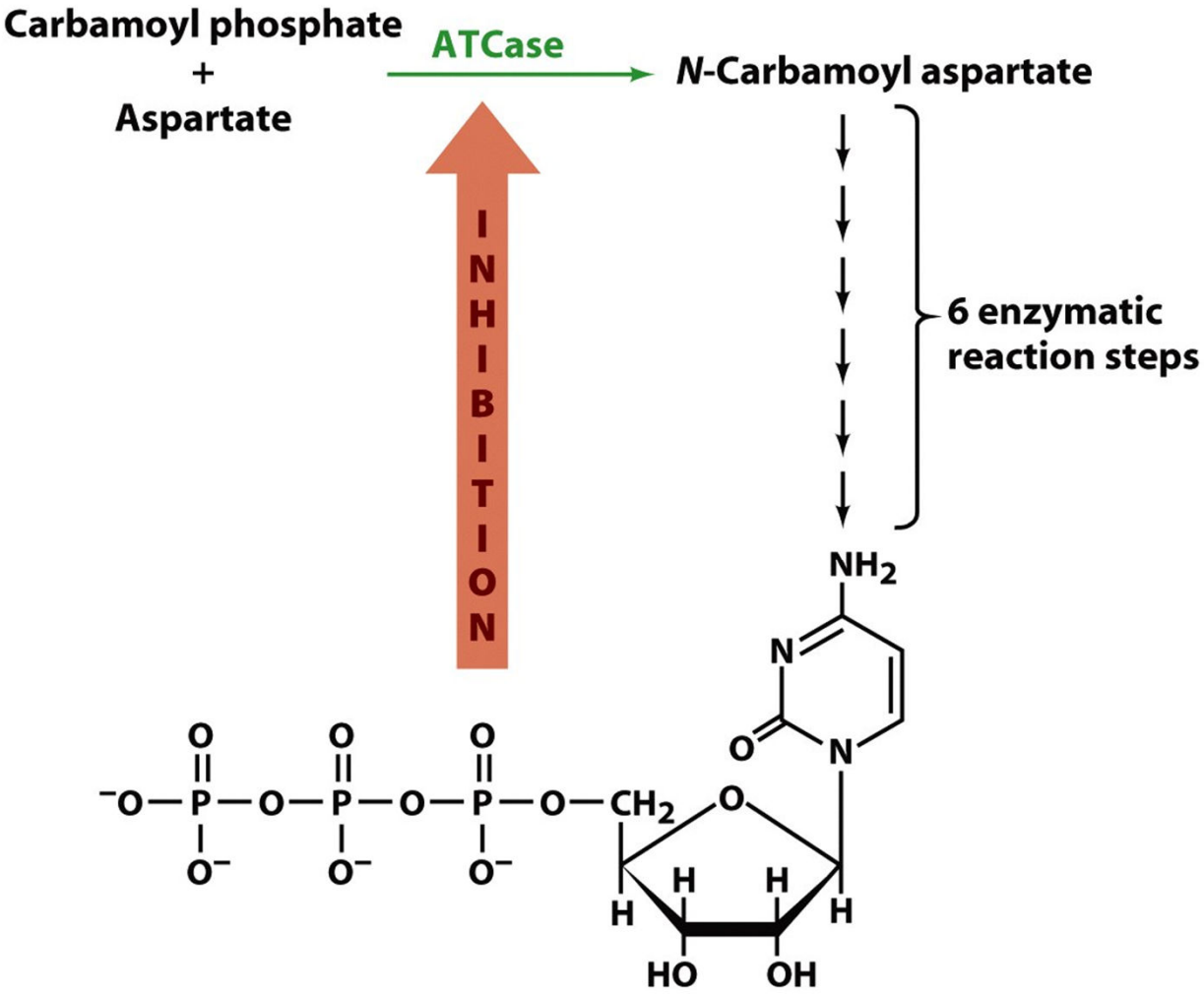


"the regulatory subunits allosterically reduce the activity of the catalytic subunits in the intact enzyme"

ATCase exhibits both homotropic and heterotropic interactions

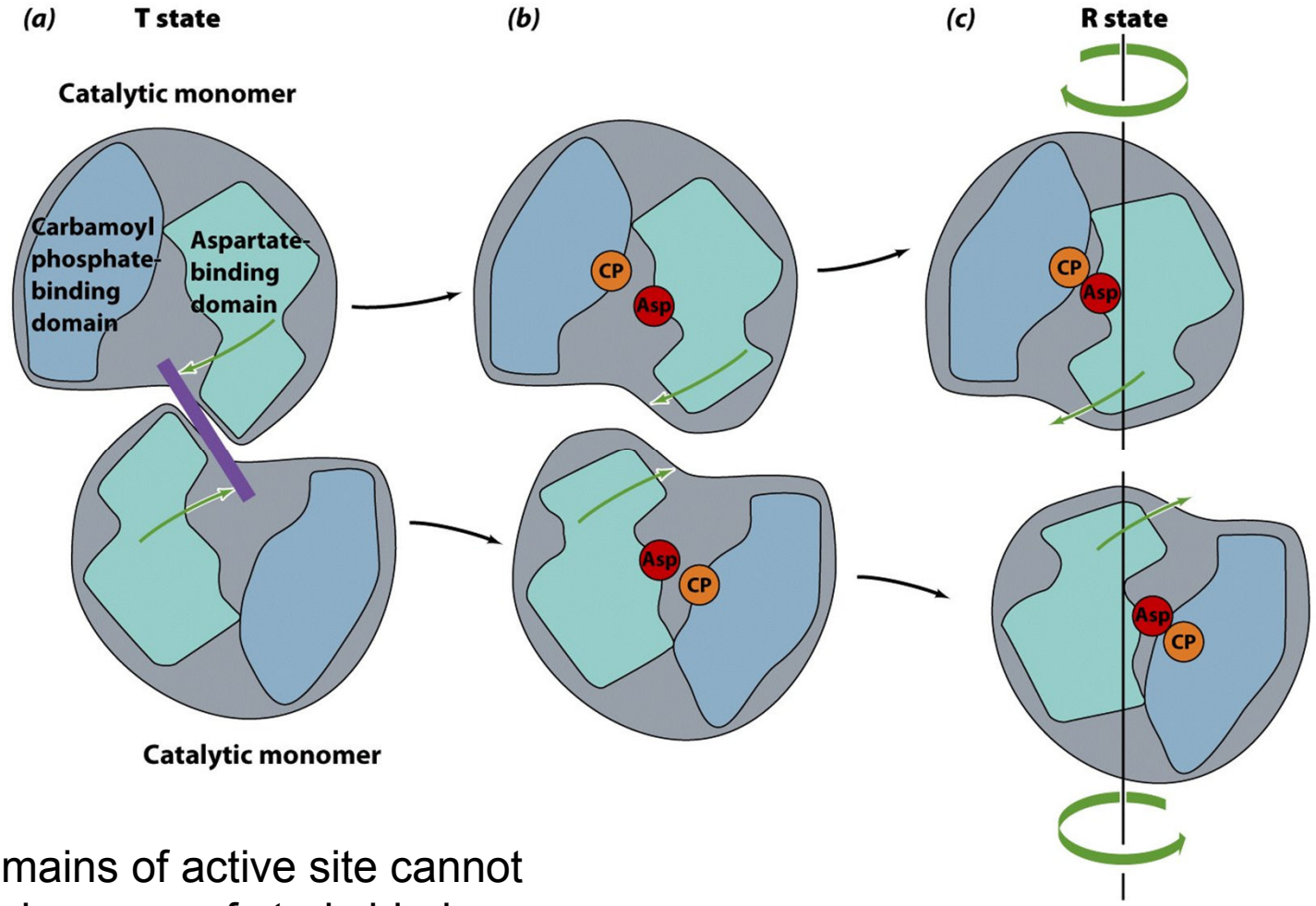


The modulator CTP is a feedback inhibitor



Cytidine triphosphate (CTP)

Binding of the substrates to ATCase induces a conformational change from T→R



Domains of active site cannot close because of steric hindrance from neighboring subunit

Substrate binding promotes separation of subunits, allowing domain closure

Enzymes may undergo many different types of covalent modification (over 500 possible!)

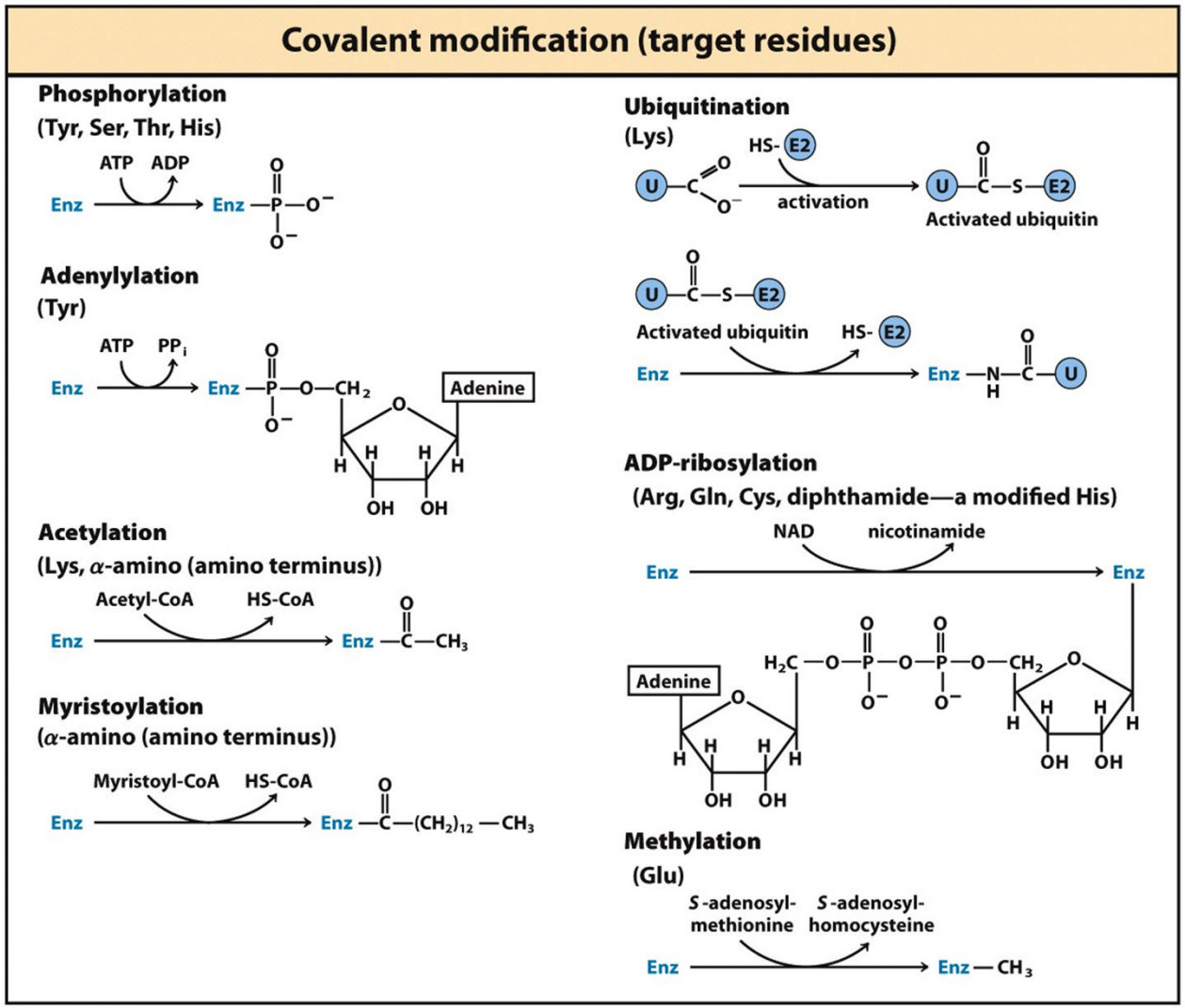


Figure 6-35
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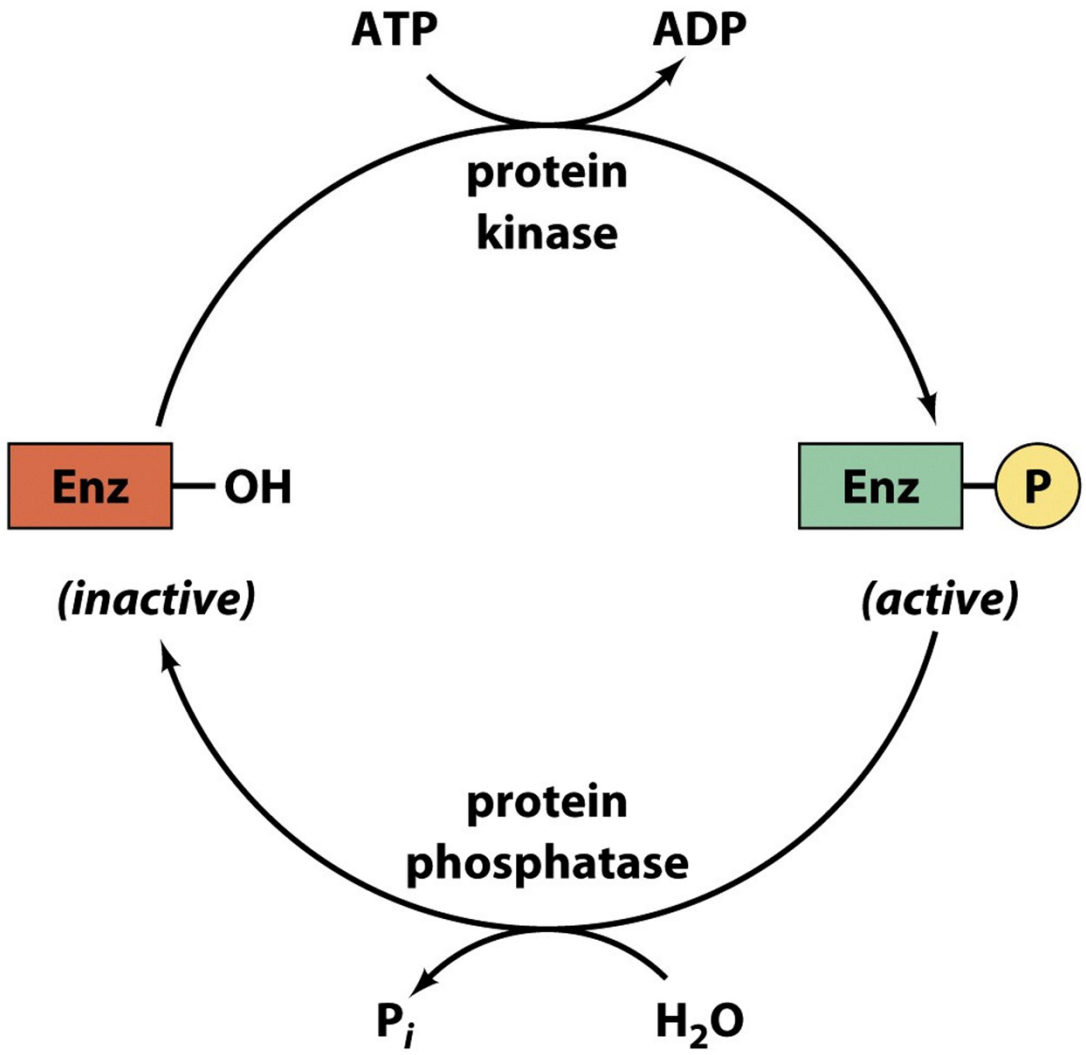
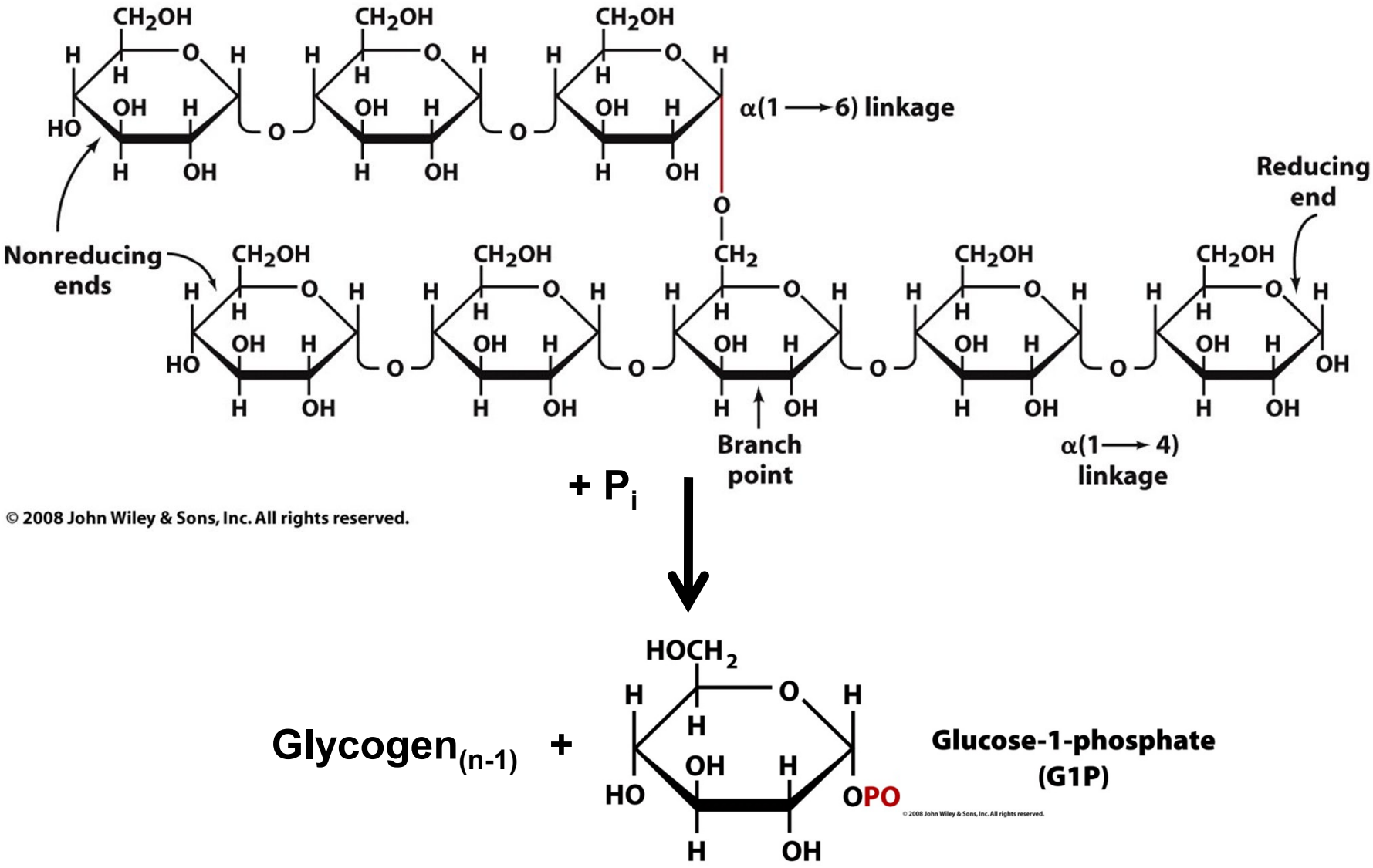
Reversible phosphorylation is a common modification for regulating enzyme activity

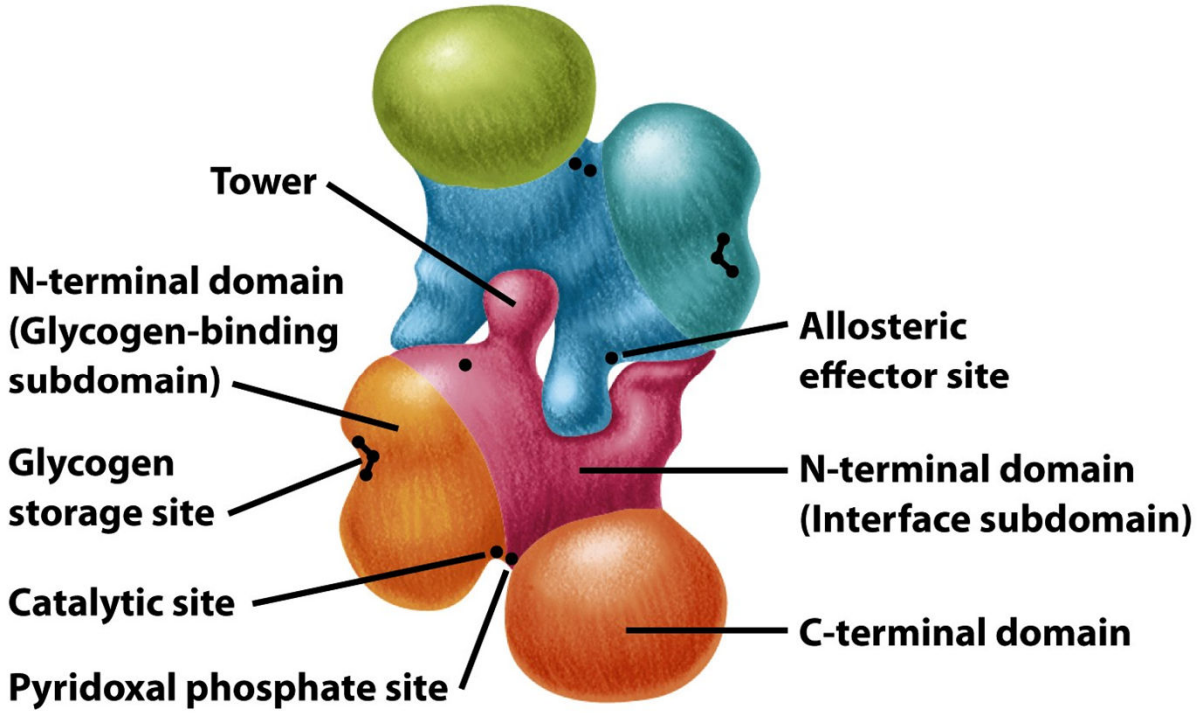


Glycogen phosphorylase catalyzes the rate-controlling step in glycogen breakdown

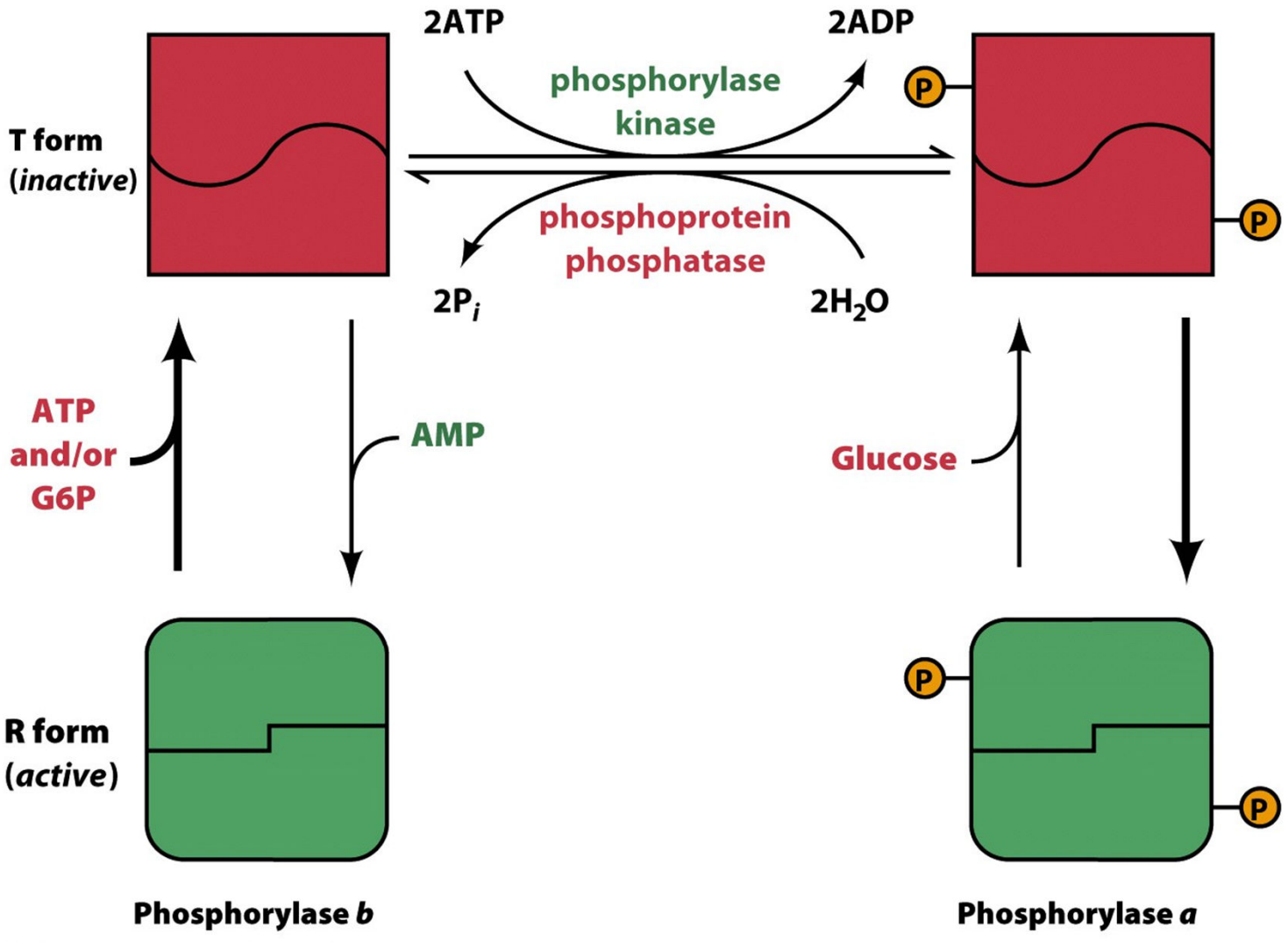


Glycogen phosphorylase is a dimer of two identical subunits

Courtesy of Stephen Sprang, University of Texas Southwestern Medical Center



Glycogen phosphorylase is regulated by phosphorylation and binding of modulators



Digestive proteases are regulated through irreversible covalent modification

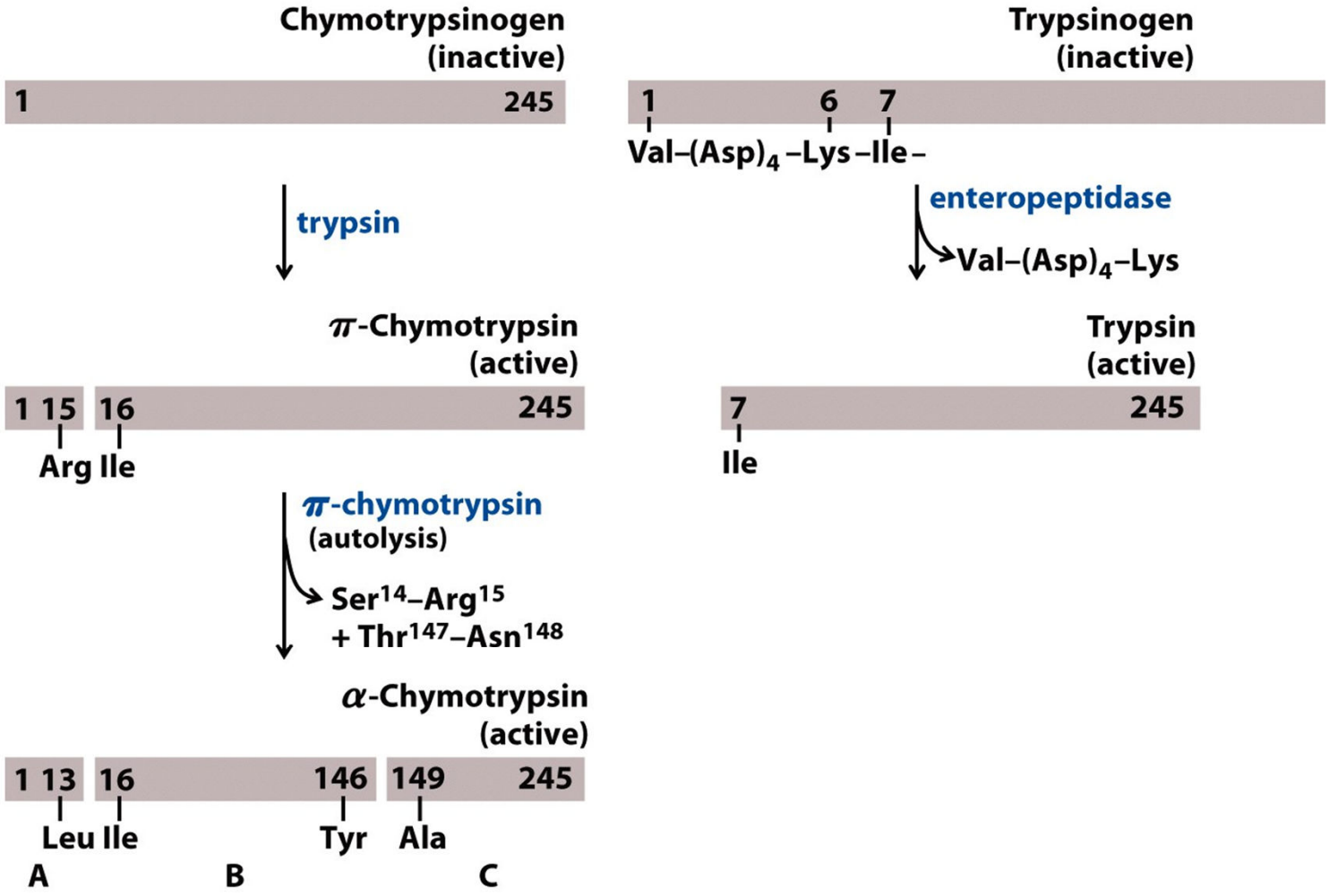


Figure 6-38
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