Enzyme Kinetics
And
Inhibition

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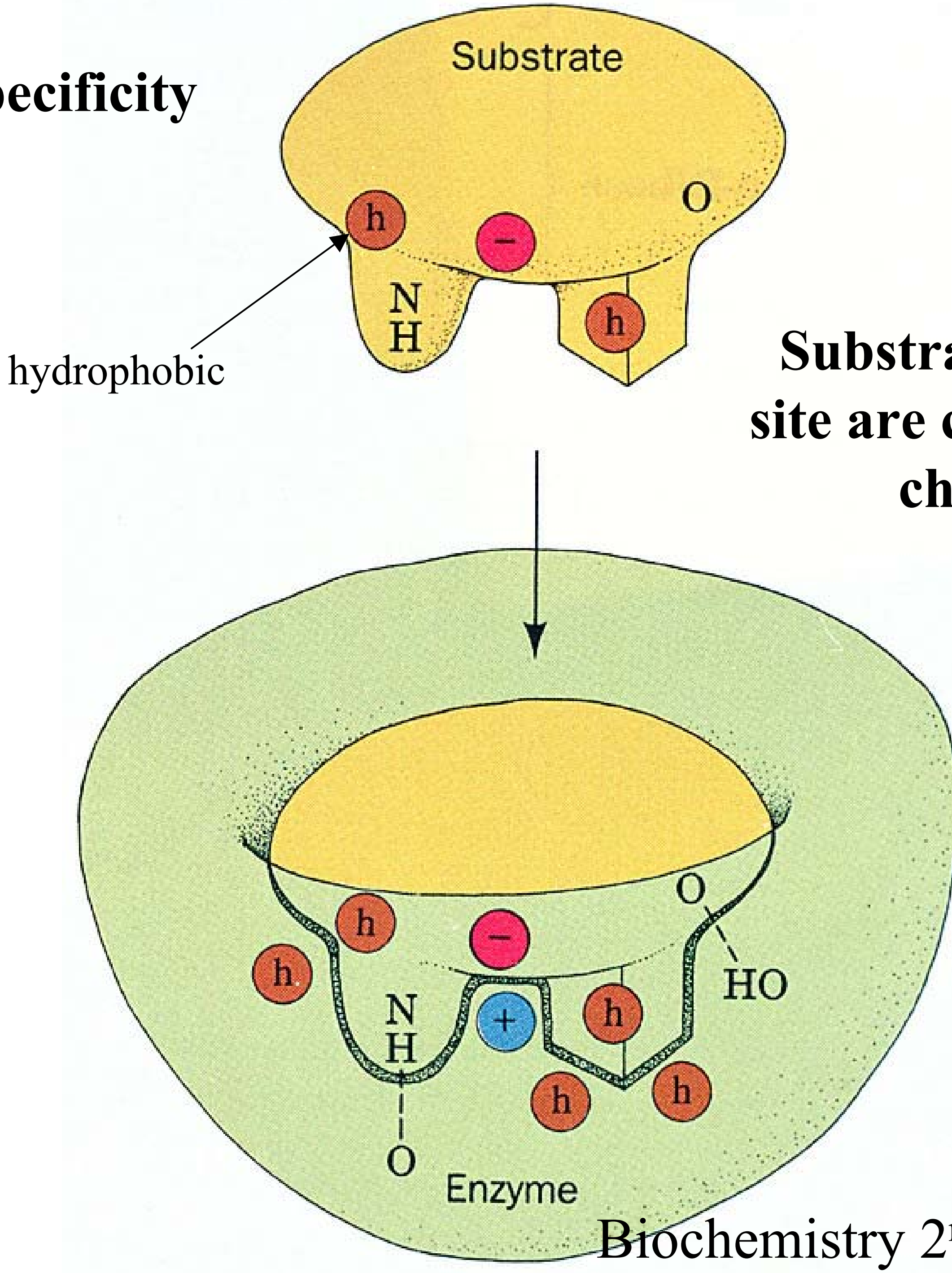
Table 11.1

Table 11.1 **A Comparison of Enzyme-Catalyzed Reactions and Their Uncatalyzed Counterparts**

Reaction	Enzyme	Uncatalyzed Rate, v_u (sec^{-1})	Catalyzed Rate, v_e (sec^{-1})	v_e/v_u
$CH_3{-}O{-}PO_3^{2-} + H_2O \longrightarrow CH_3OH + HPO_4^{2-}$	Alkaline phosphatase	1×10^{-15}	14	1.4×10^{16}
$H_2N{-}C({=}O){-}NH_2 + 2\,H_2O + H^+ \longrightarrow 2\,NH_4^+ + HCO_3^-$	Urease	3×10^{-10}	3×10^4	1×10^{14}
$R{-}C({=}O){-}O{-}CH_2CH_3 + H_2O \longrightarrow RCOOH + HOCH_2CH_3$	Chymotrypsin	1×10^{-10}	1×10^2	1×10^{12}
Glycogen (n) + $P_i \longrightarrow$ Glycogen $(n-1)$ + Glucose-1-P	Glycogen phosphorylase	$<5 \times 10^{-15}$	1.6×10^{-3}	$>3.2 \times 10^{11}$
Glucose + ATP $\longrightarrow$ Glucose-6-P + ADP	Hexokinase	$<1 \times 10^{-13}$	1.3×10^{-3}	$>1.3 \times 10^{10}$
$CH_3CH_2OH + NAD^+ \longrightarrow CH_3C({=}O)H + NADH + H^+$	Alcohol dehydrogenase	$<6 \times 10^{-12}$	2.7×10^{-5}	$>4.5 \times 10^6$
$CO_2 + H_2O \longrightarrow HCO_3^- + H^+$	Carbonic anhydrase	10^{-2}	10^5	1×10^7
Creatine + ATP $\longrightarrow$ Cr-P + ADP	Creatine kinase	$<3 \times 10^{-9}$	4×10^{-5}	$>1.33 \times 10^4$

Adapted from Koshland, D., 1956. *Journal of Cellular Comparative Physiology,* Supp. 1 **47:**217.

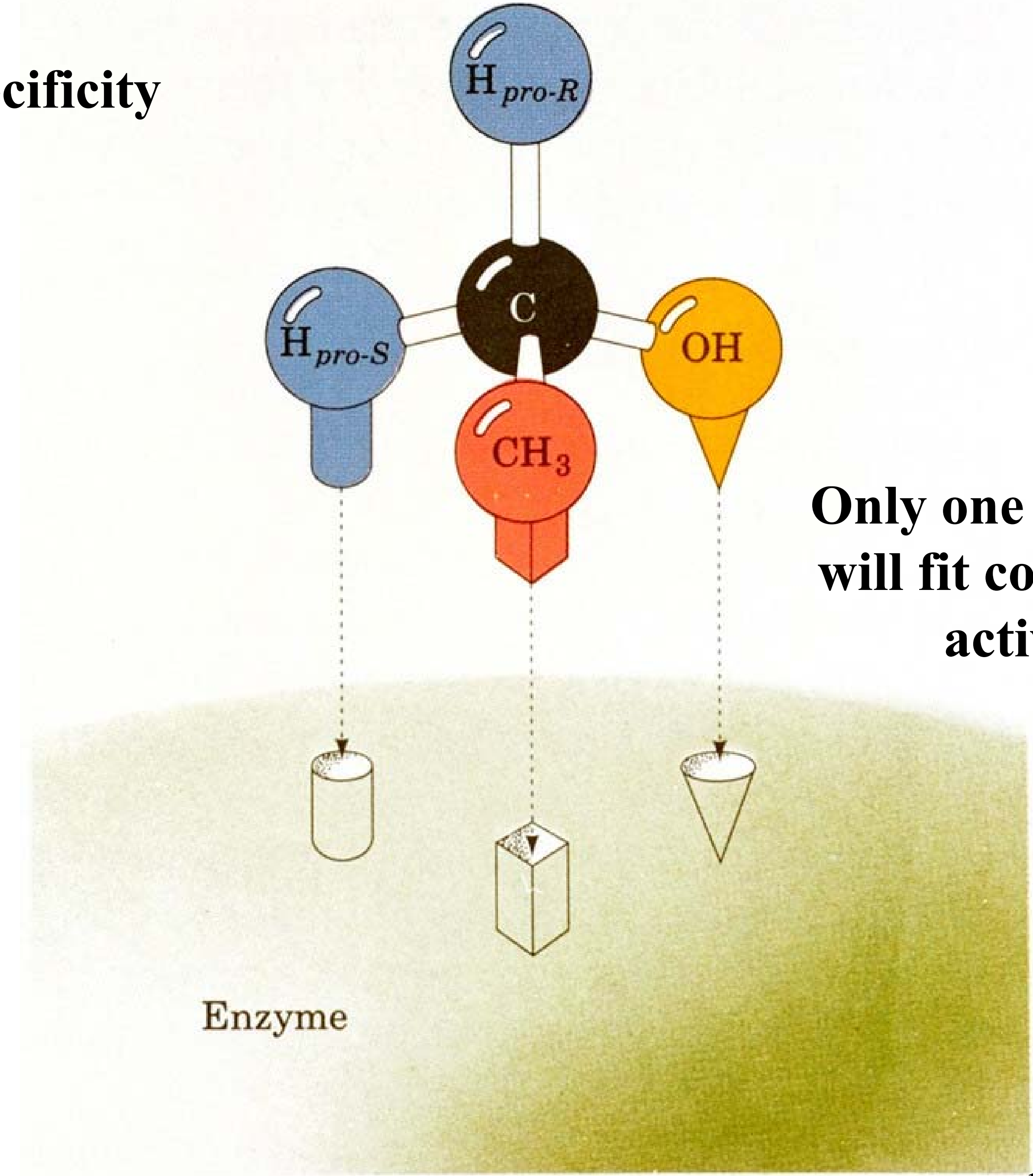
Substrate Specificity



Substrate and Active site are complementary chemically.

Biochemistry 2nd ed, Voet/Voet

Stereospecificity



Only one enantiomer will fit correctly into active site

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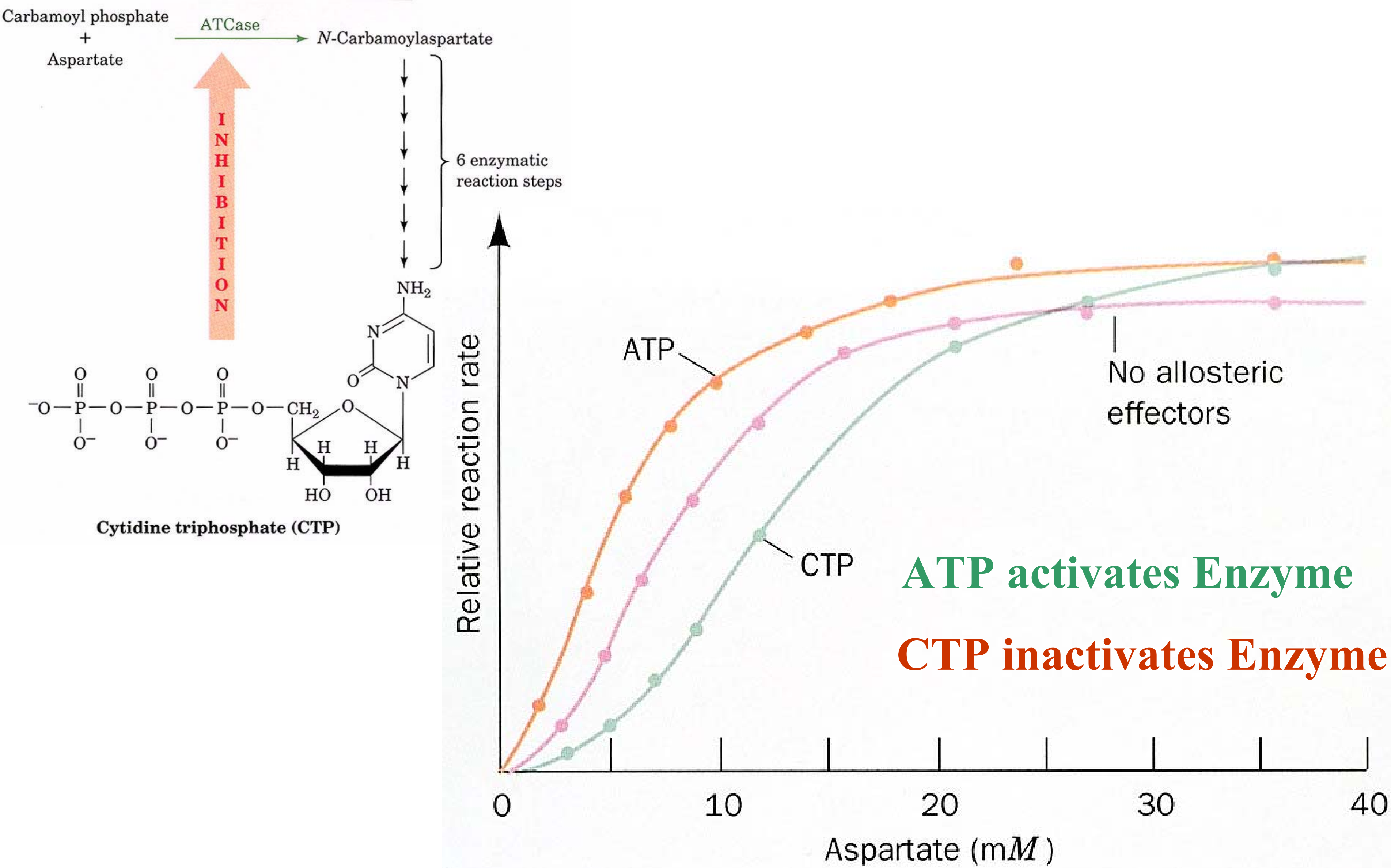
Allosteric and Feedback Regulation of ACTase



ATP activates Enzyme

CTP inactivates Enzyme

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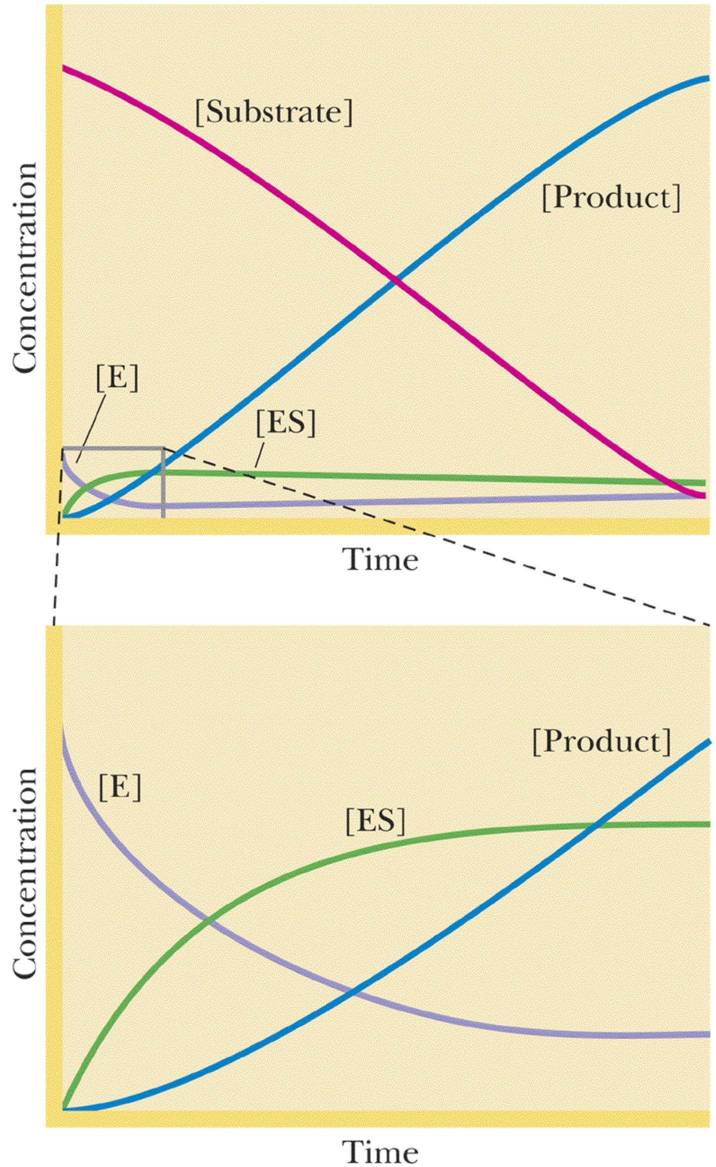
Figure 10.8



Lineweaver-Burke Plot

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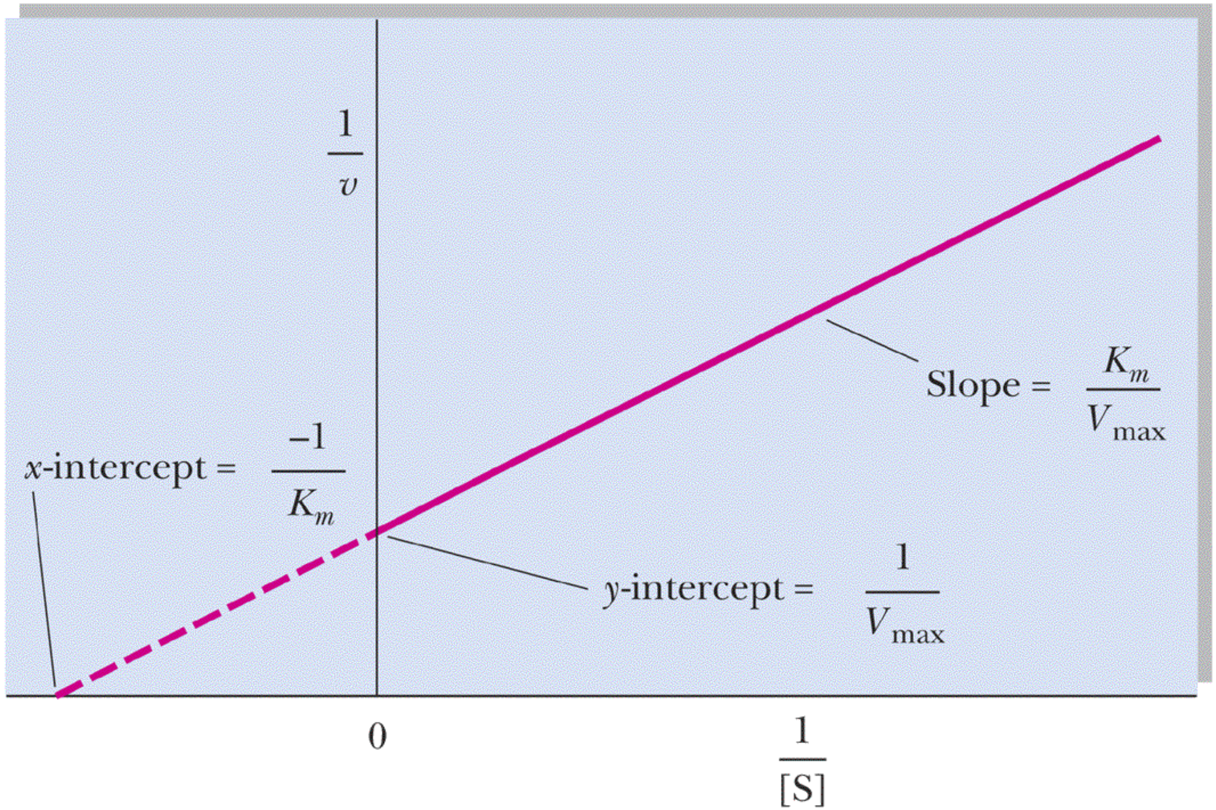
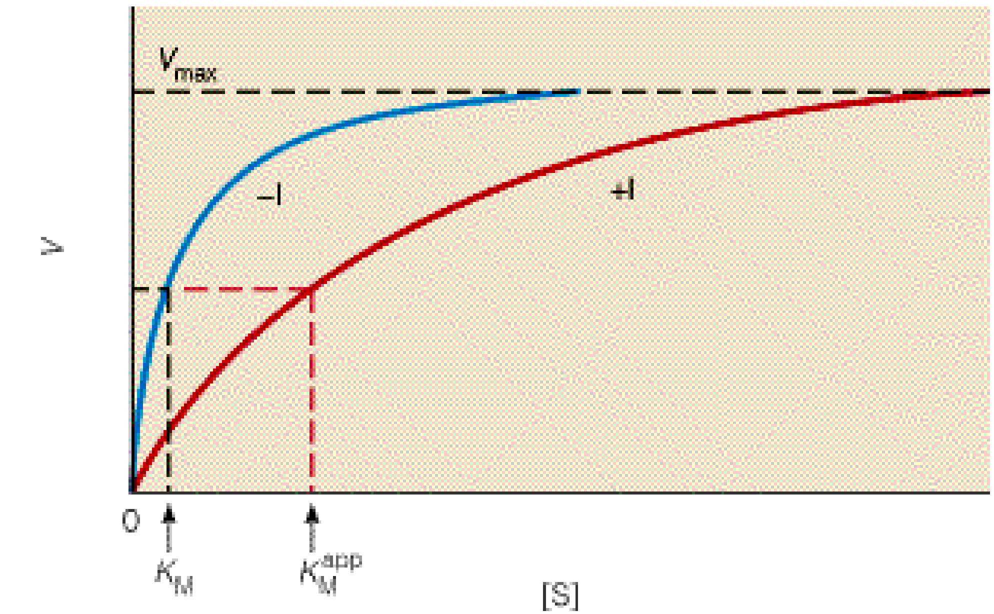
Figure 10.9

$$\frac{1}{v} = \frac{K_m}{V_{max}}\left(\frac{1}{[S]}\right) + \frac{1}{V_{max}}$$

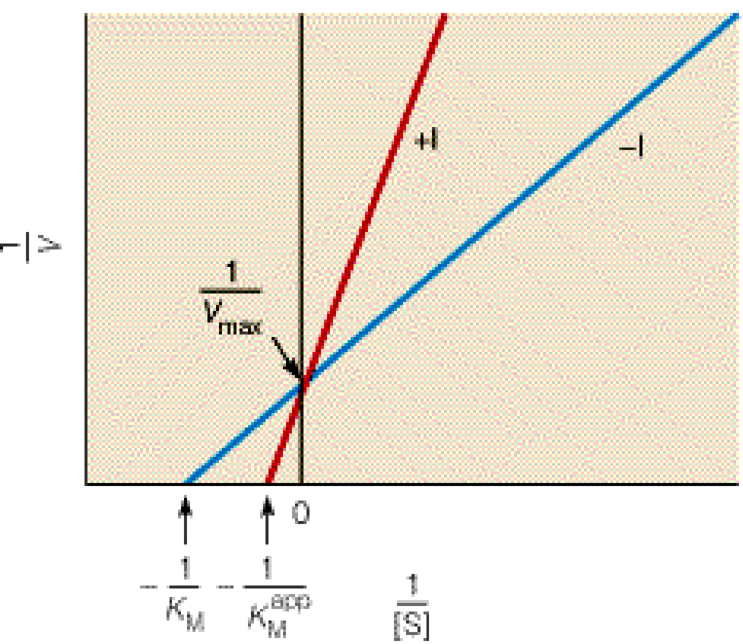


Competitive Inhibition

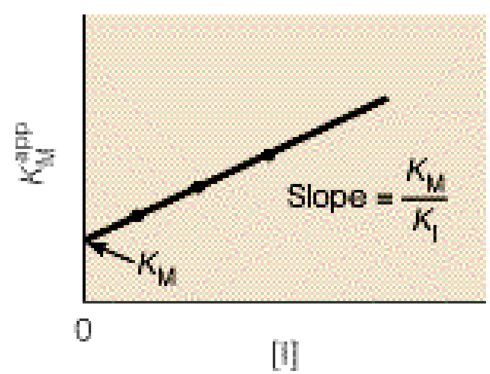


(a)

Because the inhibitor competes with substrate, Km is changed.



(b)



(c)

Vmax stays the same because ES → EP is same rate once S is bound.

From Biochemistry, Matthews/VanHolde

Competitive Inhibition

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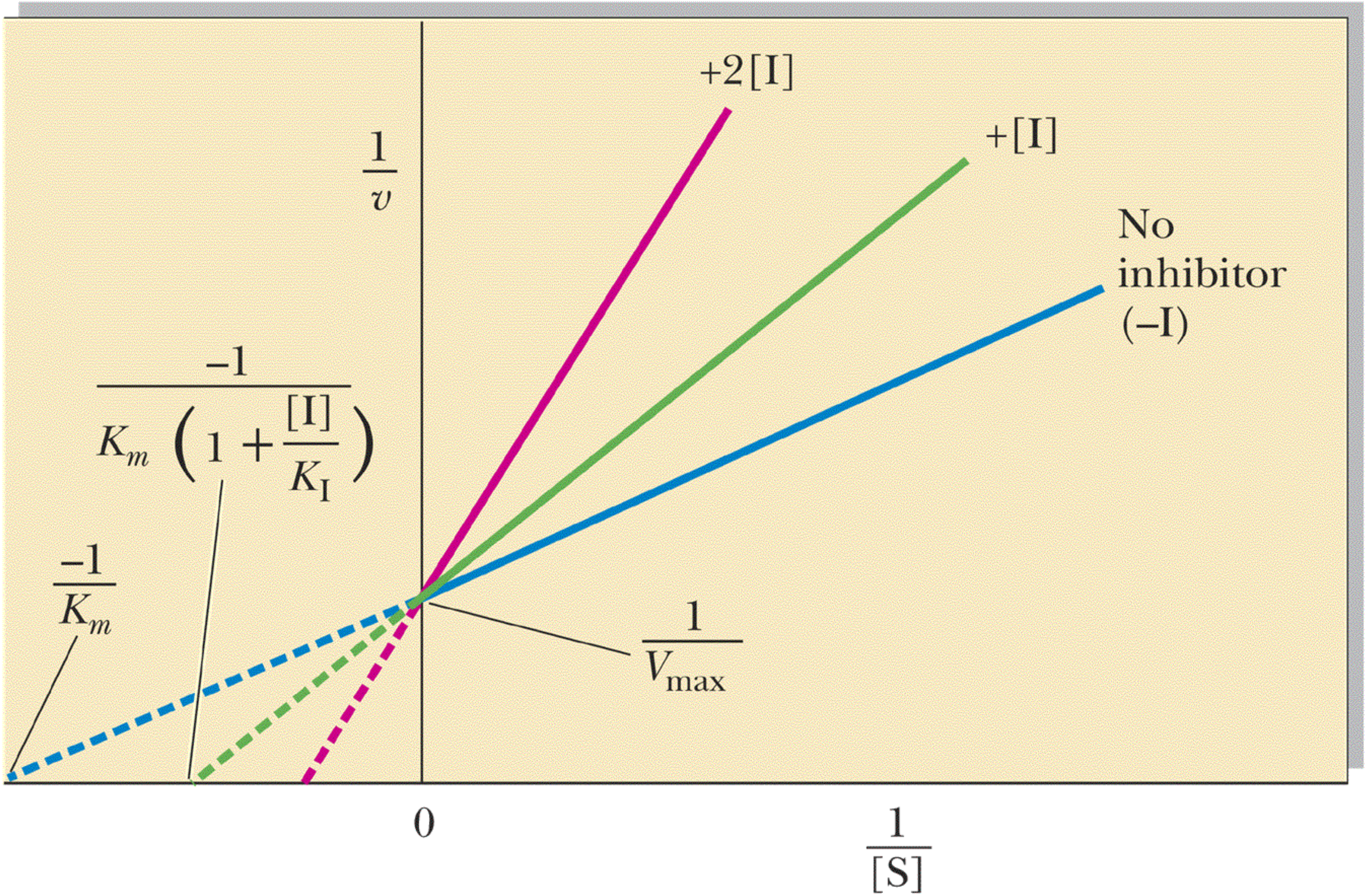
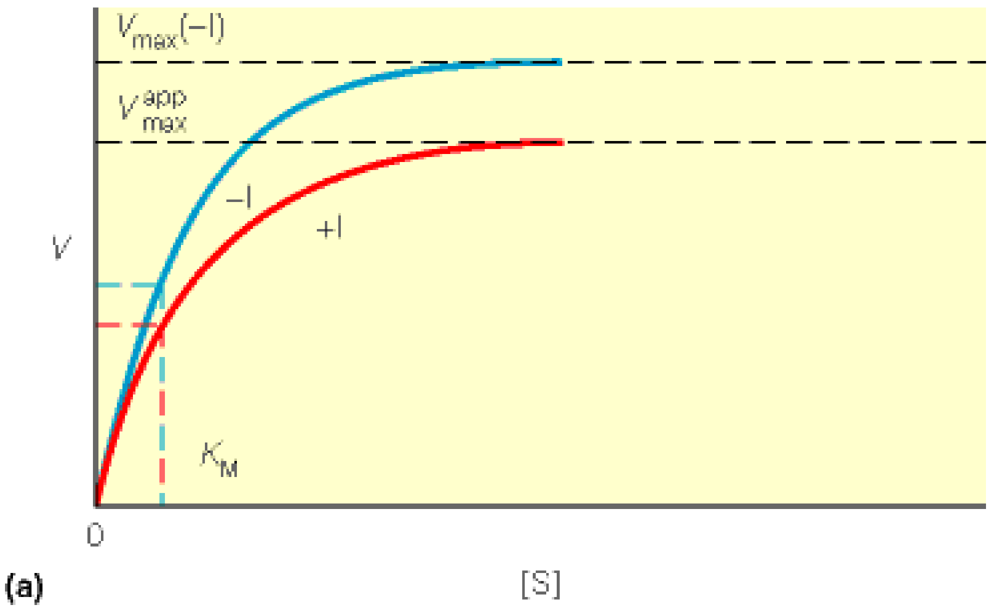
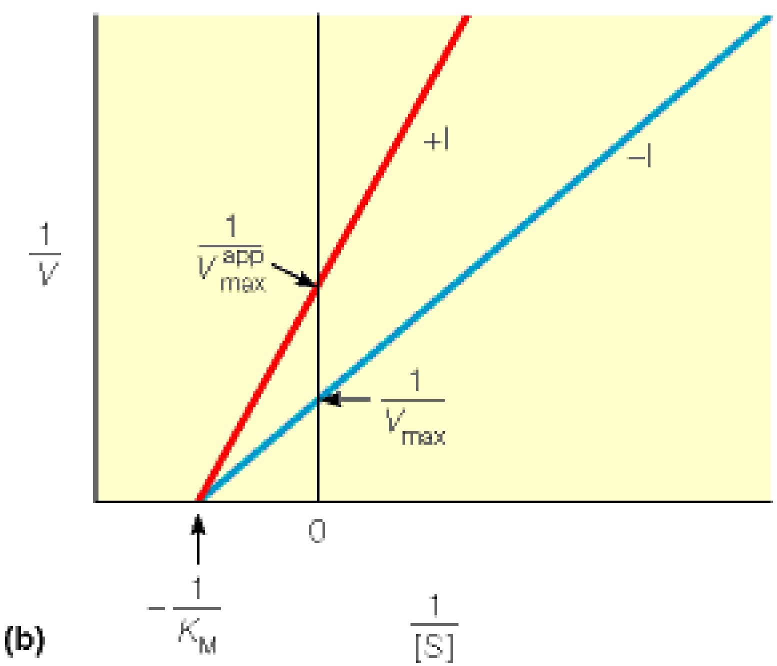
Figure 10.12

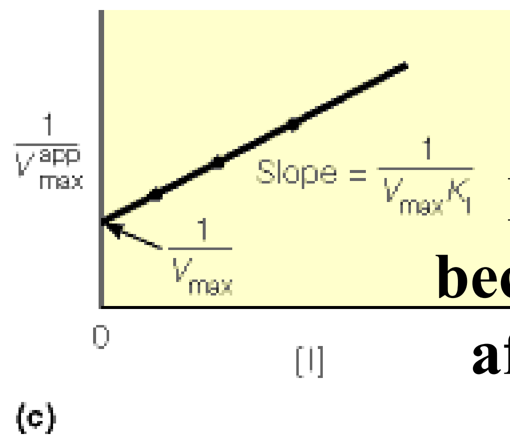


Non-Competitive Inhibition



Because the inhibitor changes the rate of catalysis by inducing a conformational change in E, Vmax is changed.





Km stays the same because S binding is not affected by I binding.

From Biochemistry, Matthews/VanHolde

Non-competitive Inhibition

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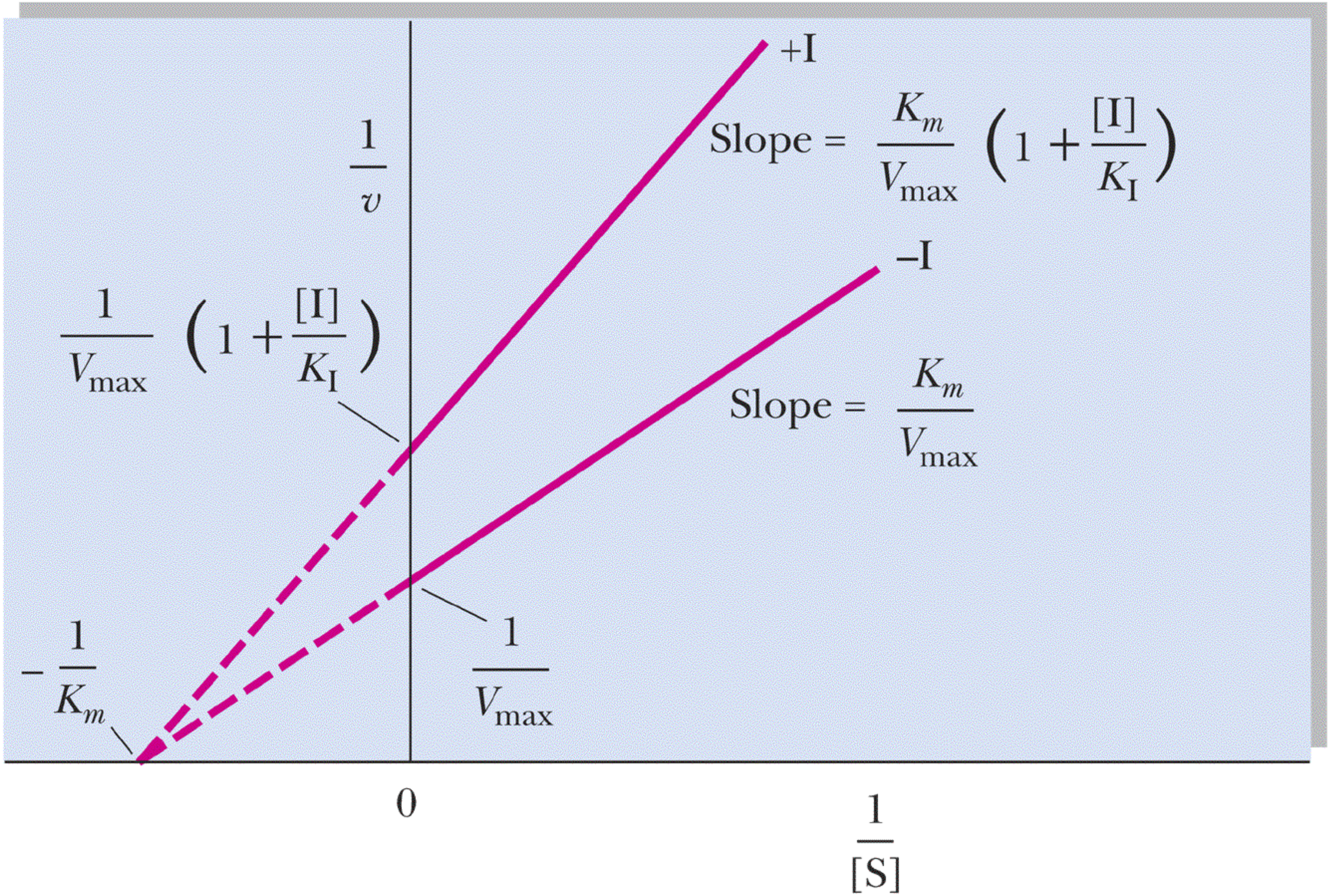
Figure 10.14



Mixed Inhibition

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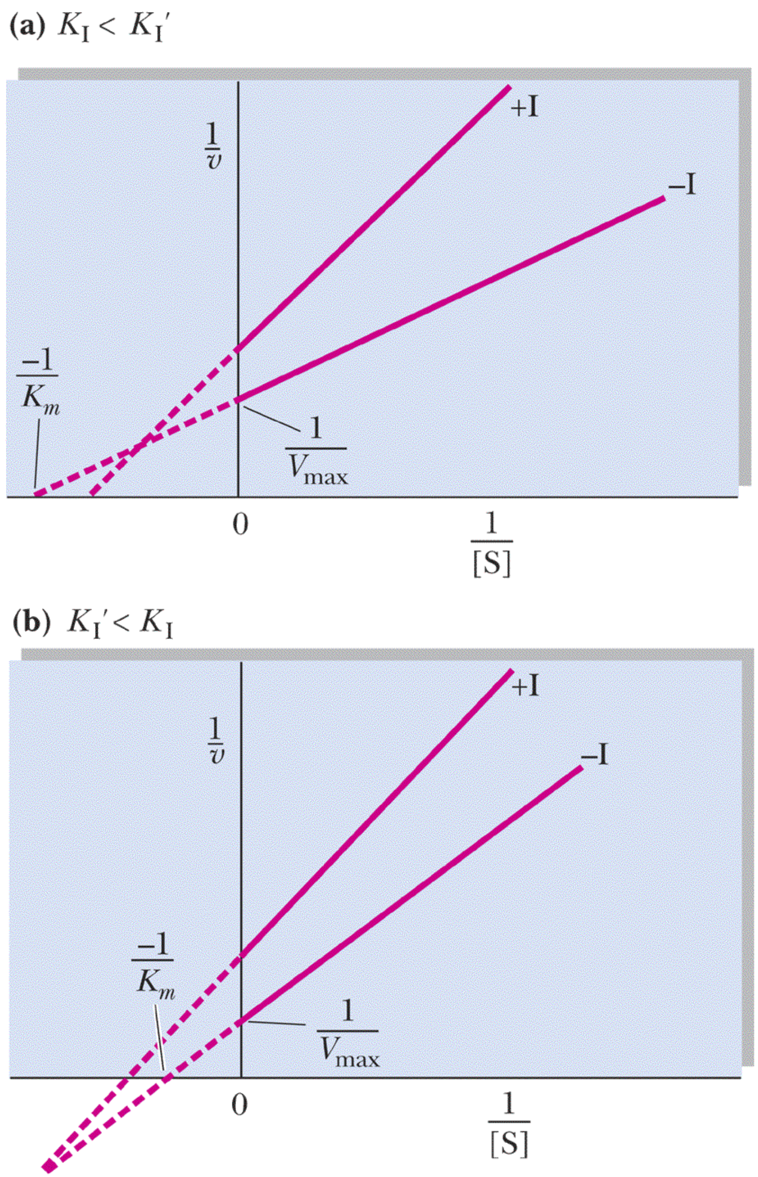
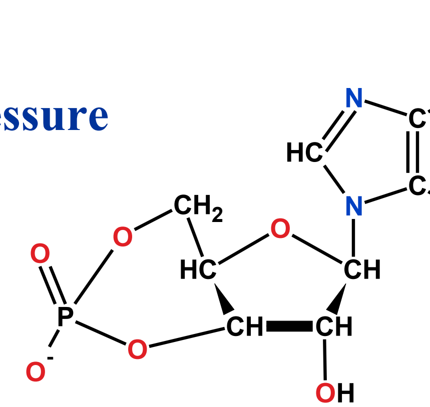
Figure 10.15



Inhibitor binds remotely from the active site but changes both catalysis rate (Vmax) and substrate binding (Km)

Phosphodiesterase Inhibitor

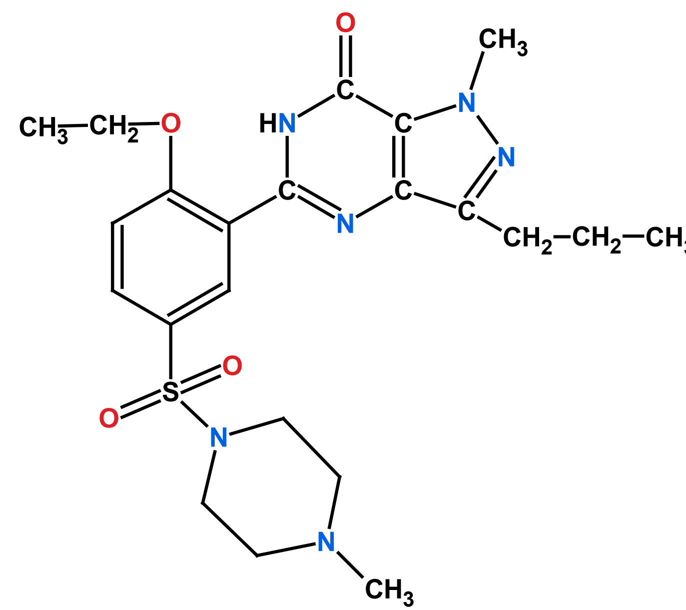
If can get smooth muscle of blood vessel walls to relax, then treat angina and high blood pressure



cGMP

Smooth muscle cells relax:

- ↑ $NO^{\cdot}$ nitrous oxide ~ neurotransmitter
- ↑ cGMP ~ cyclic GMP (top structure)
- ↓ Intracellular Ca^{2+} concentration decreases
- ↑ Muscle relaxation



Phosphodiesterases (PDE) cleave cGMP to GMP causing muscle contraction

Inhibit PDE 5 (isozyme prevalent in vascular tissue)
At least 9 isozymes.

Competitive inhibitor of PDE developed and marketed
Didn't work well