

BCH 4053 Spring 2001 Chapter 16 Lecture Notes

Slide 4

Some Important Catalytic Mechanisms

- Destabilizing ES complex
 - 1. Entropy loss in ES formation (Fig. 16.4)
 - 2. Strain, desolvation, electrostatic effects (Figures 16.5 and 16.6)
- Stabilizing EX[‡]
 - 3. Covalent catalysis (Fig. 16.9)
 - 4. General acid or base catalysis (Fig. 16.11)
 - 5. Metal ion catalysis (Fig. 16.13)
 - 6. Proximity and Orientation (Figures 16.14 and 16.15) (same concept as in item 1 above)

Slide 5

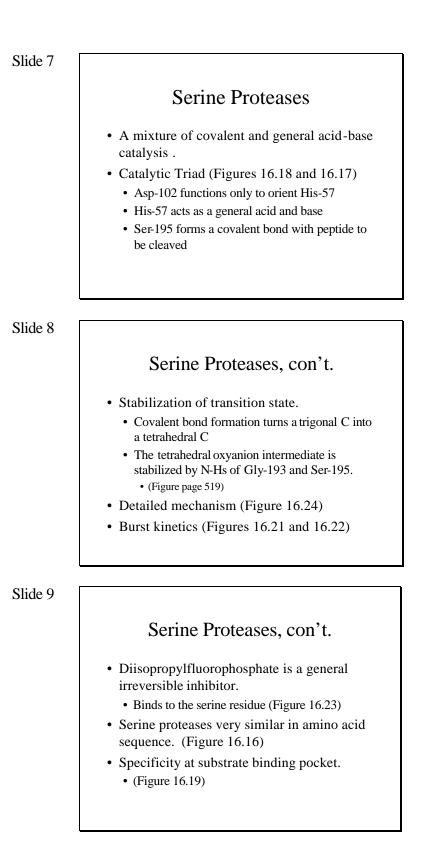
Transition State Analogs

- The affinity of the enzyme for the transition state may be 10⁻¹⁵ M!
- Analogs of the transition state are very good inhibitors.
 - Proline racemase reaction (Fig. 16.7)
 - Aldolase and adenosine deaminase (Fig. 16.8)

Slide 6

Some Example Mechanisms

- Serine proteases
- Aspartic proteases
- Lysozyme



Slide 10

The Aspartic Proteases Pepsin, chymosin, cathepsin D, renin and HIV-1 protease · All involve two Asp residues at the active site • Two Asps work together as general acid-base catalysts, one has a relatively low pK_a, the other has a relatively high pK_a • Deprotonated Asp acts as general base, accepting a proton from HOH, forming OH in the transition state • Protonated Asp (general acid) donates a proton, facilitating formation of tetrahedral intermediate • (Mechanism, Fig. 16.27; pH profile, Fig. Page 525) Slide Lysozyme

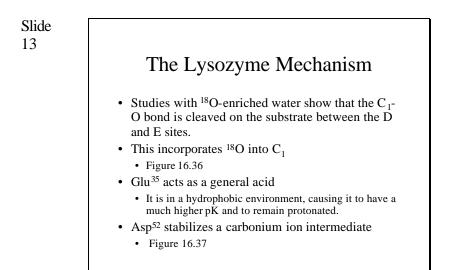
- The first enzyme whose structure was solved by X-ray crystallography (by David Phillips in 1965)
- Lysozyme hydrolyzes polysaccharide chains and ruptures certain bacterial cells by breaking down the cell wall.
 - Hydrolyzes at glycosidic bond of Nacetylmuramic acid residue. (See Figure 16.31)

Slide 12

11

Lysozyme Substrate Analog Studies

- Natural substrates are not stable in the active site for structural studies
- But analogs can be used like (NAG)₃
 - Figure 16.33
- Fitting a NAG into the D site requires a distortion of the sugar.
 - (Figures 16.34 and 16.35)
- This argues for stabilization of a transition state via destabilization (distortion and strain) of the substrate.



Chapter 16, page 5