

# Protein Structure. 1



1

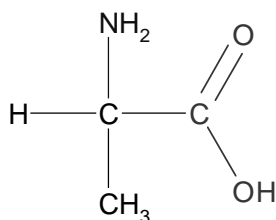
Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## How does protein structure determine its function?

the amino acid, alanine



- Proteins are made of long chains of amino acids linked by peptide bonds.
- What are amino acids?
- Amino acids are compounds with an *amino* group and a carboxylic *acid* group attached to the same carbon.

2

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Amino Acids

- The amino group is called an  $\alpha$ -amino group because it is attached to the first carbon attached to the carboxyl group.
- The second carbon attached to the carboxyl group (if there is one) is called the  $\beta$ -carbon, the third the  $\gamma$ -carbon, and so on.
- There are twenty different amino acids commonly found in proteins
- What makes these amino acids different?

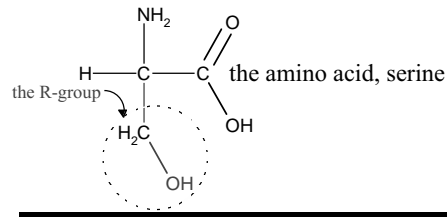
3

## Four Bonds

- The  $\alpha$ -carbon of amino acids has four bonds:
- one to the carboxyl group
- one to the  $\alpha$ -amino group
- one to a hydrogen atom
- one to a fourth group of atoms.

4

## The “R” Group



- The fourth group of atoms is often referred to as the “R” group.
- The “R” group is what differs among the common amino acids.

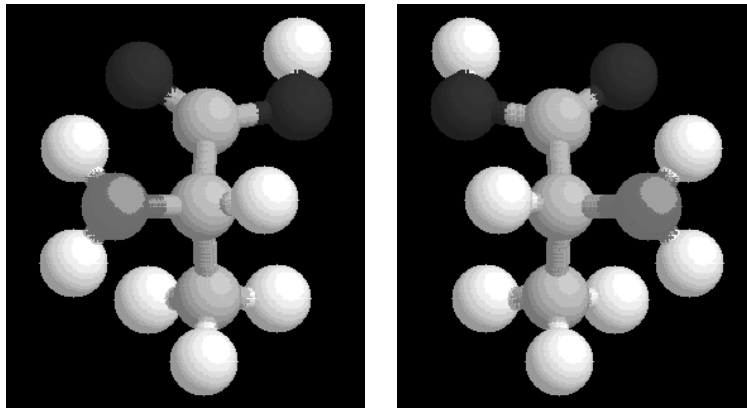
5

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## How do these two amino acids differ?



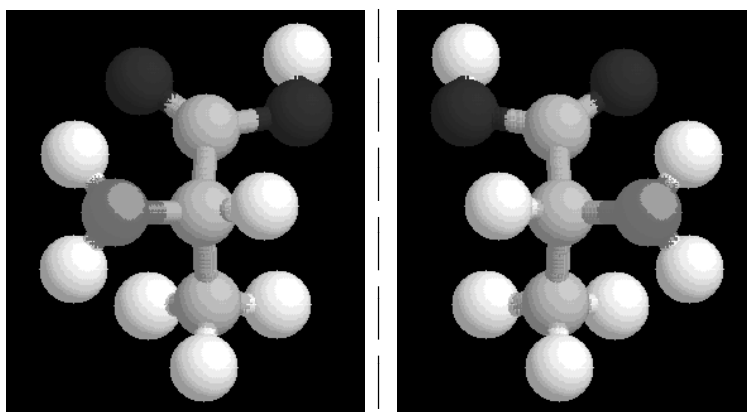
6

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Nonsuperimposable Mirror Images



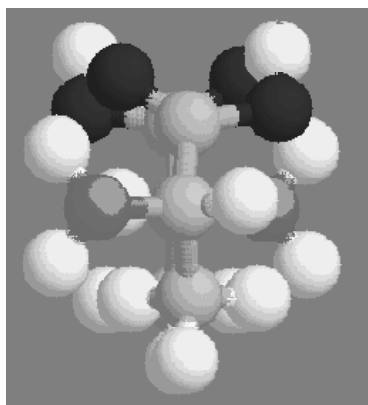
7

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Nonsuperimposable Mirror Images



- These compounds are enantiomers.
- Enantiomers (nonsuperimposable mirror images) exist when there is at least one chiral (asymmetric) carbon in the molecule.
- A carbon is chiral if it has four different substituents.
- The  $\alpha$ -carbon in most amino acids is chiral.

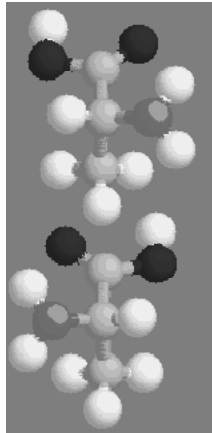
8

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## How can we designate these different compounds?



**D**

- Orient the molecule with the carboxyl up and back, the R group down and back, and the amino and hydrogen forward.
- If the amino is on the right it is the D-configuration, if it is on the left it is the L-configuration.
- Nearly all of the amino acids found in nature have the L-configuration.

**L**

9

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## How does the protein catalyze reactions?

- The protein chain wraps up into a specific structure.
- Part of the protein chain usually forms a pocket that has a shape that accommodates the reactants and associates with them by noncovalent bonds.
- This pocket is called the “active site”.

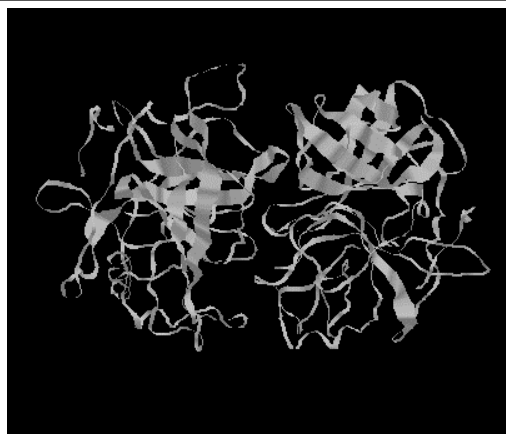
10

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## $\alpha$ -chymotrypsin (ribbon model)



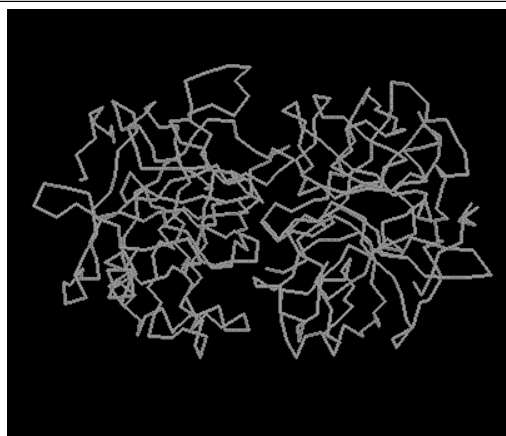
11

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## $\alpha$ -chymotrypsin (backbone)



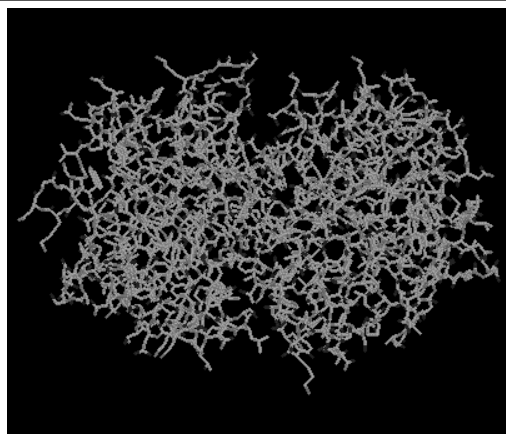
12

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## $\alpha$ -chymotrypsin (stick model)



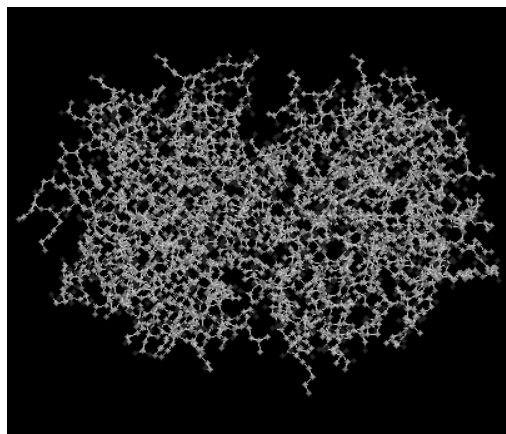
13

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## $\alpha$ -chymotrypsin (ball & stick model)



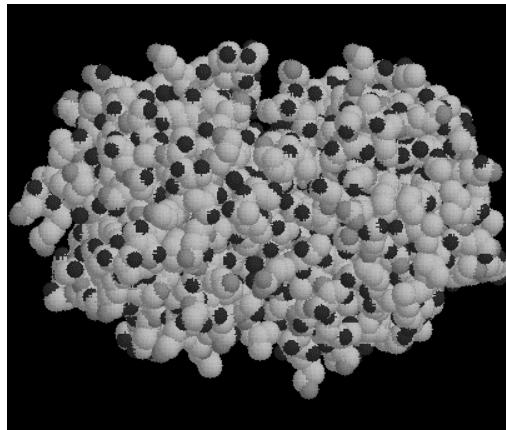
14

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## **$\alpha$ -chymotrypsin (space filling model)**



15

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## **The Enzyme Active Site**

- **The active site holds the reactants in an orientation that provides an alternate reaction path that has a lower reaction barrier.**
- **The alternate reaction path is favored by the position and type of the R groups of the few amino acids at the active site.**
- **Therefore the nature of the R groups plays an important role in the catalytic activity of the enzyme.**

16

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## **An Example: Chymotrypsin**

- **Chymotrypsin catalyzes the hydrolysis of amide bonds in proteins.**
- **The shape of the active site of chymotrypsin complements the shape of a part of the reacting protein chain.**
- **R groups at the active site of chymotrypsin facilitate the hydrolysis reaction by temporarily forming bonds to the amide bond being hydrolyzed.**

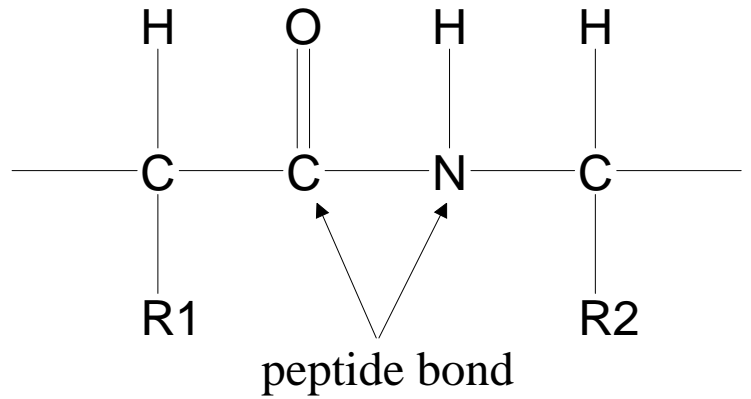
17

## **The Protein Backbone**

- **To understand the action of chymotrypsin one must first know more about protein structure.**
- **The amino acids in a protein are linked by peptide bonds.**
- **Peptide bonds are amide bonds that link two amino acids in a protein or peptide**

18

## Peptide Bonds



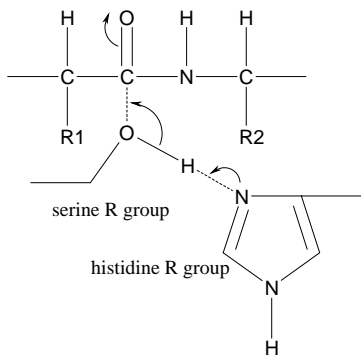
19

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Hydrolysis of Peptide Bonds



- The hydroxyl of the serine R group forms a bond to the carbonyl of the peptide bond.
- The imidazole of the histidine R group takes H from the serine hydroxyl, making the hydroxyl oxygen more reactive.

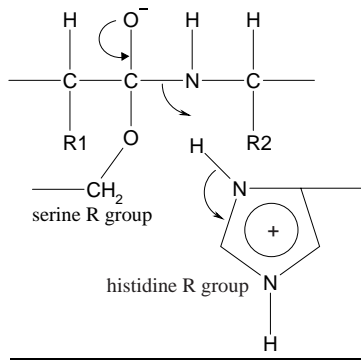
20

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## A Tetrahedral Intermediate



- The tetrahedral intermediate rearranges resulting in breaking the amide bond leaving the acyl group attached to the serine oxygen.

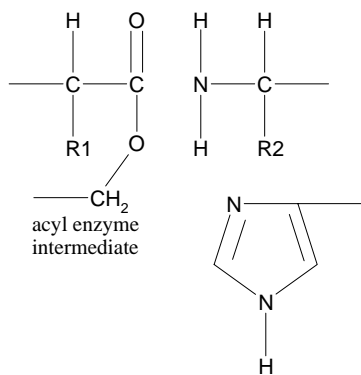
21

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## The Acyl Enzyme



- The acyl enzyme intermediate is hydrolyzed in the next step regenerating the free enzyme.

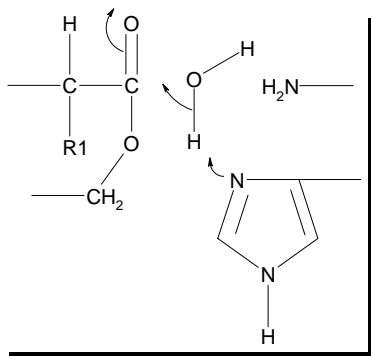
22

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Acyl-Enzyme Hydrolysis



- The imidazole N removes  $H^+$  from water making the water O more reactive, and therefore more likely to form a bond to the carbonyl C.
- This forms a second tetrahedral intermediate.

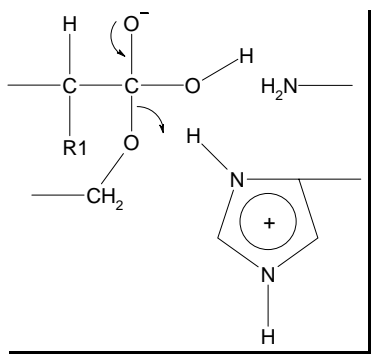
23

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## The Second Tetrahedral Intermediate



- When the carbonyl group reforms either C—O bond may break.
- If the C—OH bond breaks, the acyl enzyme is regenerated, i.e., no net reaction.
- If the C—O—CH<sub>2</sub> bond breaks, the original enzyme is regenerated and the hydrolysis is complete.

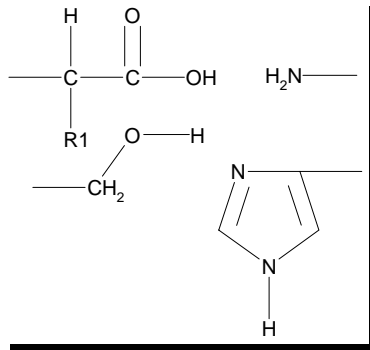
24

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## The Regenerated Enzyme



- The enzyme is now in its original state.
- The hydrolysed protein or peptide fragments leave the active site.
- And the enzyme can catalyze another reaction.

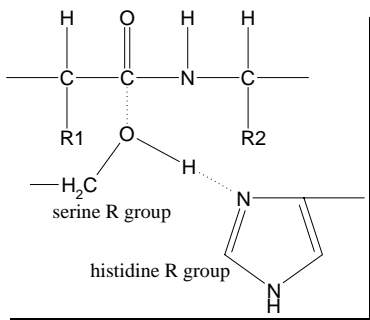
25

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## The Source of the Catalysis



- The enzyme accelerates the reaction because it has the serine hydroxyl in a favorable position to form a bond to the amide carbonyl...
- and because the serine hydroxyl is activated by bonding of its hydrogen atom to the nearby histidine.
- This lowers the energy of the transition state.

26

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Lowering the Energy of the Transition State

- **The energy of the transition state is lowered because the active site of the enzyme interacts with it favorably.**
  - these interactions may include hydrogen-bonding, electrostatic interactions, hydrophobic forces or others
- **Since the transition state energy is lowered, the reaction barrier is lowered and the rate is accelerated.**

27

## The Critical Role of Enzyme Conformation

- **The enzyme functions because key R groups are held in an optimum position to lower the energy of the transition state and thus facilitate the chemical reaction.**
- **Therefore, protein conformation is critical to the effective function of the enzyme.**
- **If the shape of the protein is altered, it will no longer catalyze the reaction.**
- **What maintains protein conformation?**
- **What holds the protein chain in such a specific and complex orientation?**

28

## Questions For Discussion

29

## Protein Monomers

**What are the monomeric components of proteins?**

**Draw the molecular structure of a typical amino acid and indicate the carboxyl group, the amino group and the R group.**

30

## **The Common Amino Acids**

**How many different amino acids are commonly found in living organisms and what parts of the molecular structure differ? What parts of the molecular structure are the same?**

31

## **Enantiomers**

**What are enantiomers?**

**For which molecules do enantiomers exist?**

32

## Chiral Carbons

Which carbon in most amino acids is chiral?

33

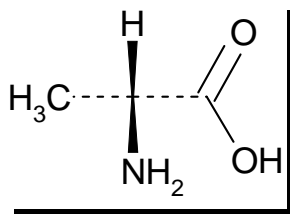
## Amino Acid Stereoconfiguration

How is an amino acid oriented to determine its D- or L-configuration?

34

## Assigning Configuration

What is the D/L-configuration of the following amino acid?



35

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## Amino Acid Linkages

By what type of chemical bond are amino acids linked in proteins?

Draw an example of this bond using two typical amino acids.

36

Copyright © 1998 W.R.Midden  
All Rights Reserved

Bowling Green State University

Protein Structure I

## **The Active Site**

**What is the role of the active site of an enzyme?**

37

## **Enzyme Structure and Catalysis**

**What features of the molecular structure of the active site of a protein are responsible for the ability of the enzyme to catalyze a chemical reaction?**

38

## **Chymotrypsin Reaction**

**What chemical reaction is catalyzed by chymotrypsin?**

39

## **Hydrolysis of the Peptide Bond**

**Draw the molecular structure of a peptide bond showing the interaction of the serine hydroxyl and the histidine imidazole at the active site of chymotrypsin.**

40

## The Tetrahedral Intermediate

**Draw the molecular structure of the tetrahedral intermediate in the reaction catalyzed by chymotrypsin. Show how this intermediate is converted to products.**

41

## Regenerating Free Enzyme

**What has to happen to the acyl-enzyme for chymotrypsin to be able to catalyze another reaction?**

42

## The Hydrolysis Products

**Draw the molecular structures of the products formed in the reaction catalyzed by chymotrypsin.**

43

## Active Site Functional Groups

**Briefly explain which functional groups of chymotrypsin are most directly involved in catalysis and how they are involved in catalysing the reaction.**

44

## A Serine Protease

**What is the role of serine at the active site of chymotrypsin?**

**Why is chymotrypsin called a “serine protease”?**

45

## Serine Reactivity

**The R group of which amino acid increases the reactivity of the serine in chymotrypsin?**

**Explain how this interaction increases serine reactivity and why this is a crucial part of the catalytic process.**

46

## **Enzyme Conformation**

**Explain why the conformation of an enzyme is critical to its catalytic activity.**

47