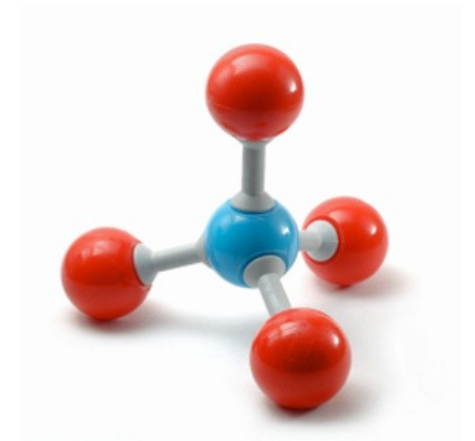


Ch16

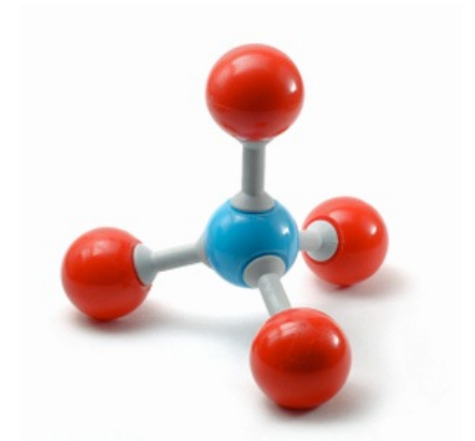
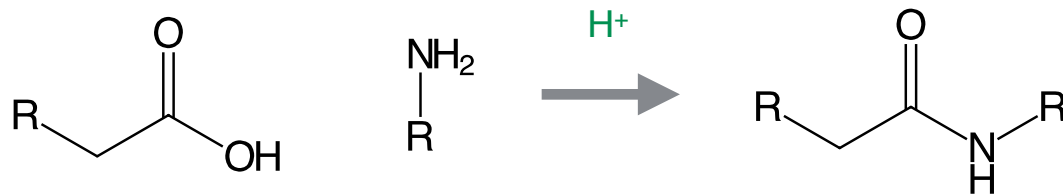
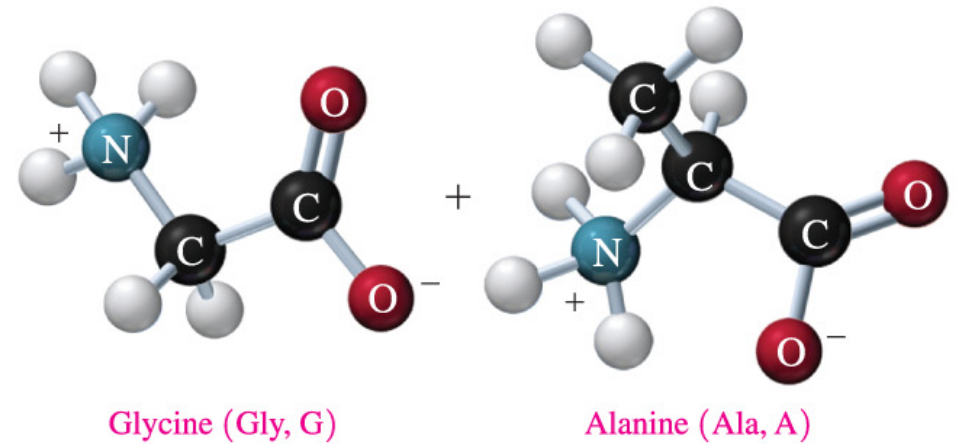
Peptides

Amino Acids and proteins we make from them.
A whole new scale of biomolecule.



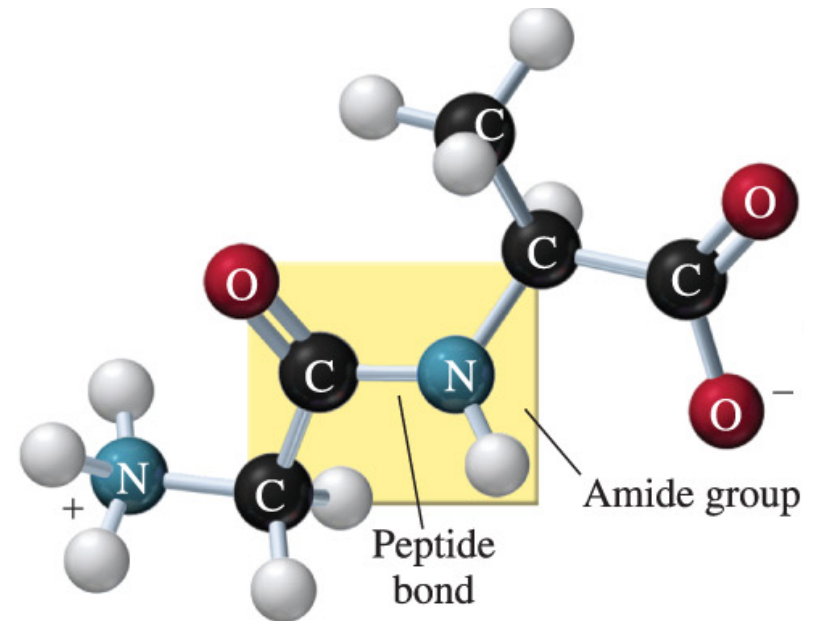
Peptide Bonds

- ▶ A **peptide bond** is an amide bond that forms when the $-\text{COO}^{1-}$ group of one amino acid reacts with the $-\text{NH}_3^+$ group of the next amino acid.

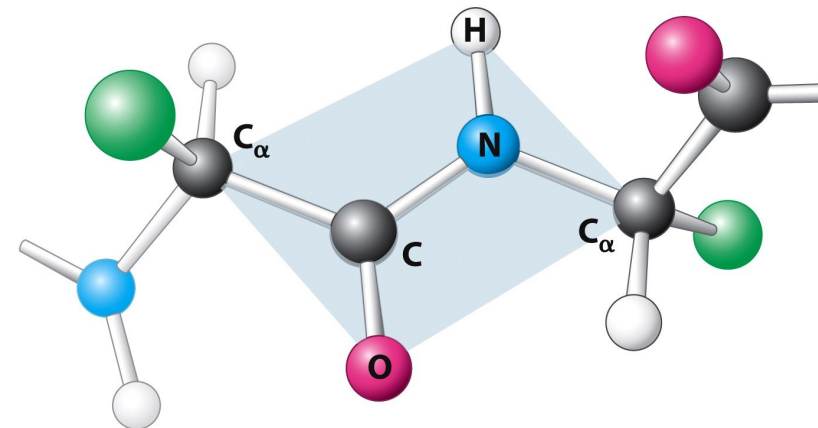
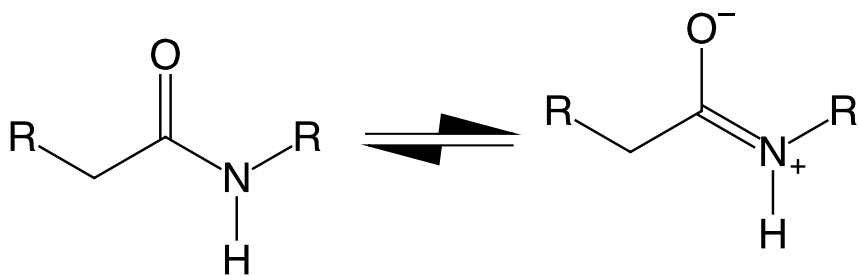


Peptide Bonds

- ▶ A **peptide bond** is an amide bond that forms when the $-\text{COO}^{1-}$ group of one amino acid reacts with the $-\text{NH}_3^+$ group of the next amino acid.
- ▶ Because of resonance, the C-N bond has **partial double bond character**.
- ▶ Amide bonds, peptide bonds, are strong.
- ▶ It also results in a planar structure of the four atoms attached to either side of the C-N bond.
- ▶ Peptide bonds have **trans** stereochemistry between the attached carbons.



Glycylalanine (Gly-Ala, GA)

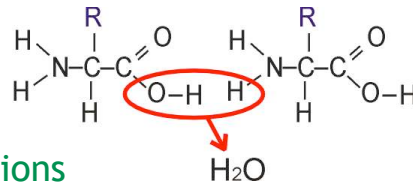


Peptides

▶ Peptides

▶ Peptide Bonds

- ▶ Structure & Reactions



▶ Tertiary Structure

- ▶ Types of Interactions

▶ Denaturation

▶ Enzymes

▶ Catalysis

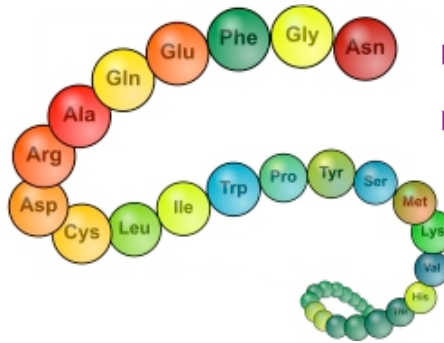
▶ Enzyme activity

▶ Inhibition



▶ Peptides

- ▶ Terminals
- ▶ Sequencing
- ▶ Names



▶ Proteins are Big Peptides

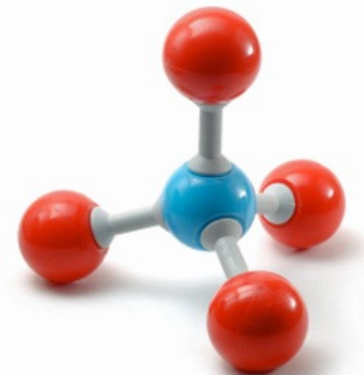
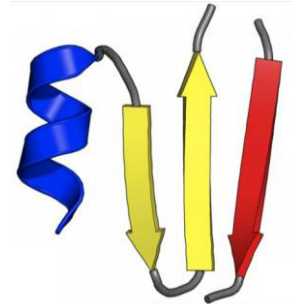
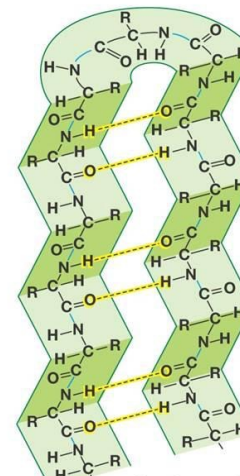
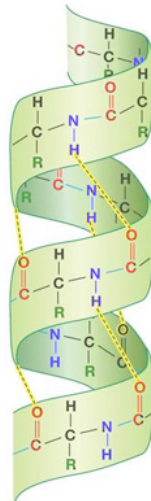
▶ Definition

▶ Primary Structure

- ▶ Sequence

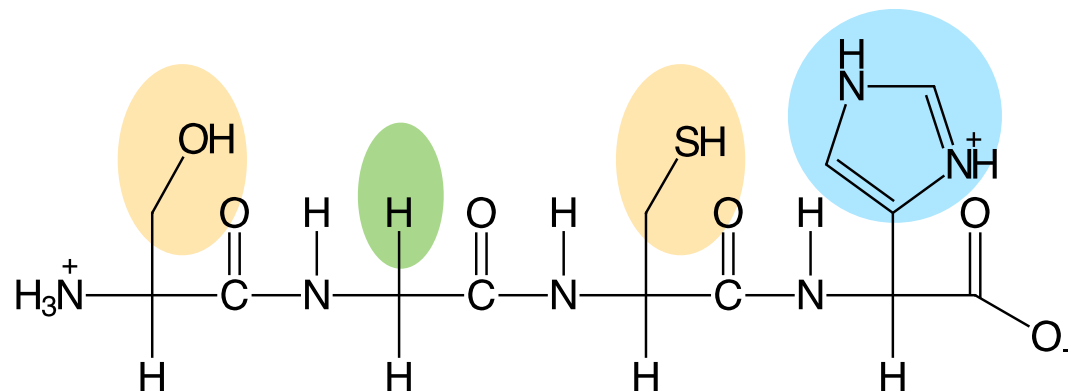
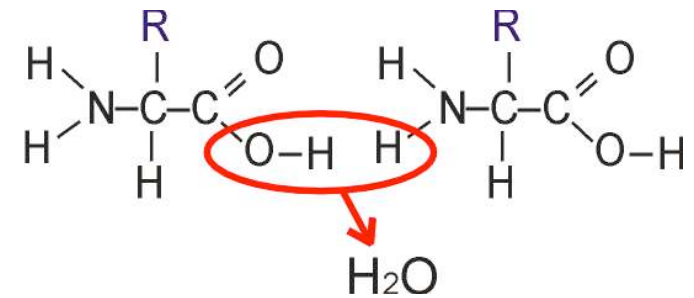
▶ Secondary Structure

- ▶ α Helix
- ▶ β Sheets
- ▶ Triple helix



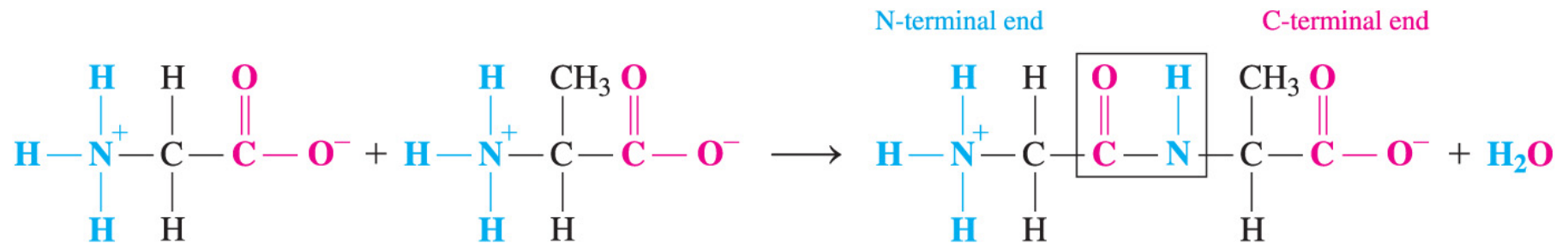
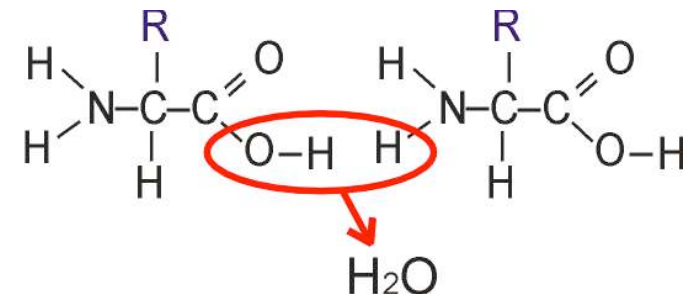
Peptides

- ▶ A **peptide** is two or more amino acids linked by peptide bonds.
- ▶ Peptides formed from
 - ▶ 2 amino acids are dipeptides
 - ▶ 3 amino acids are tripeptides
 - ▶ 4 amino acids are tetrapeptides
 - ▶ 5 amino acids are pentapeptides
 - ▶ more than that are polypeptides



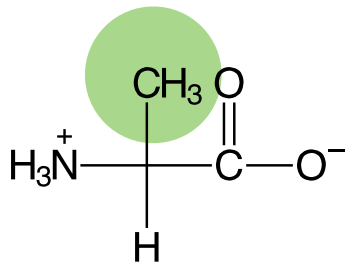
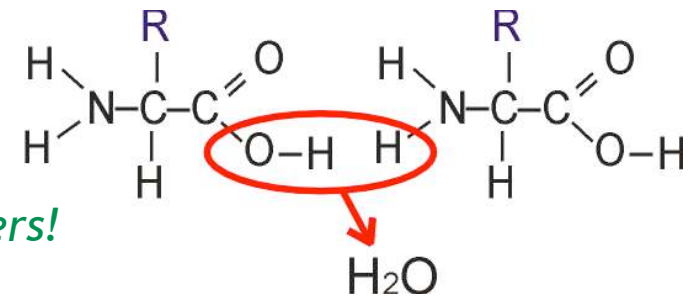
Peptides

- ▶ A **peptide** is two or more amino acids linked by peptide bonds.
- ▶ Each peptide has two ends:
 - ▶ N-terminal End
 - ▶ C-terminal End

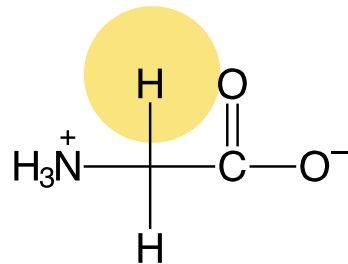


Peptides

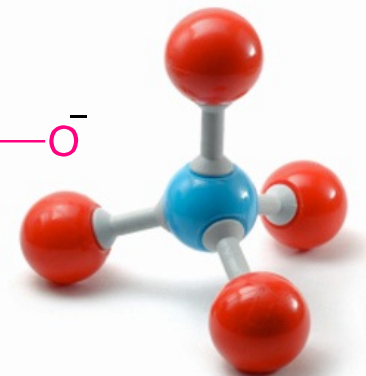
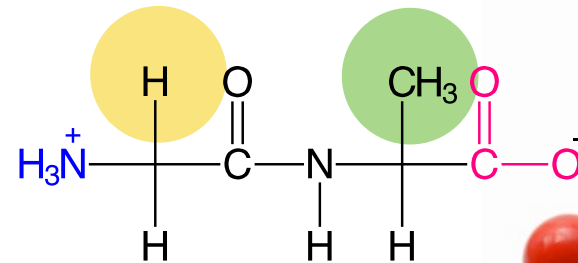
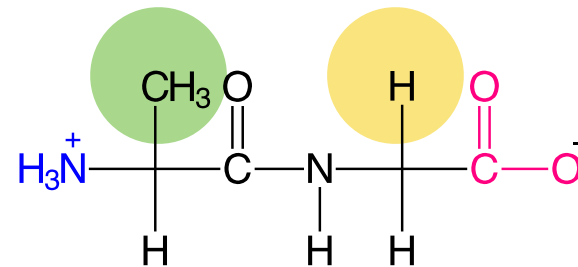
- ▶ A **peptide** is two or more amino acids linked by peptide bonds.
- ▶ Each peptide has two ends:
 - ▶ N-terminal End
 - ▶ C-terminal End
- ▶ Because the two ends are different, *the order matters!*



Glycine

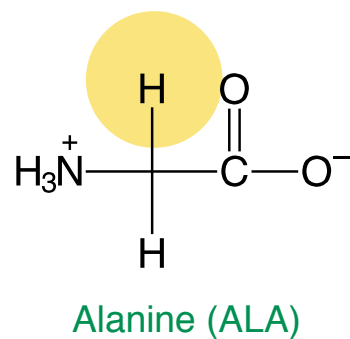
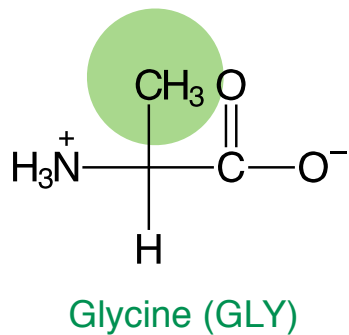


Alanine

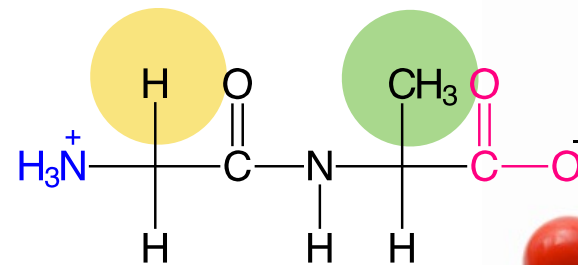
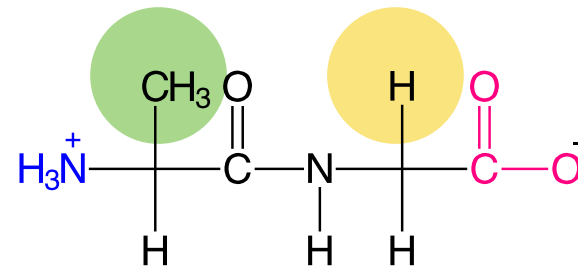


Peptides

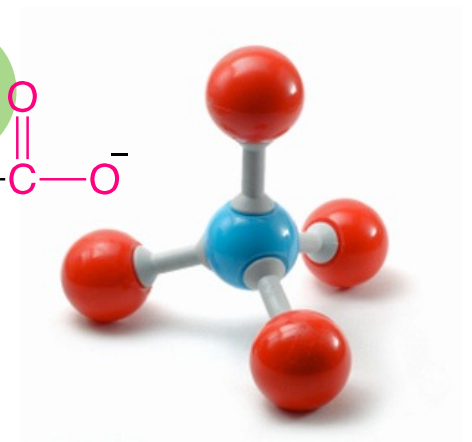
- ▶ **Sequence** is the order in which amino acids appear in a peptide.
- ▶ Sequence always begins with the **N-terminal End**.
- ▶ The **C-terminal End** is always last.
- ▶ Sequence is given by providing the three letter codes for each amino acid separated by dashes.



GLY-ALA

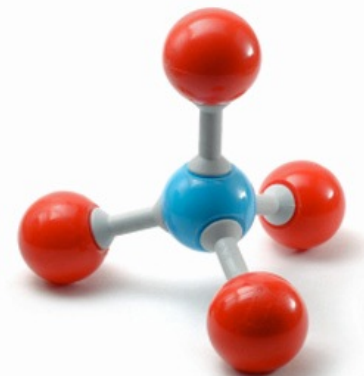
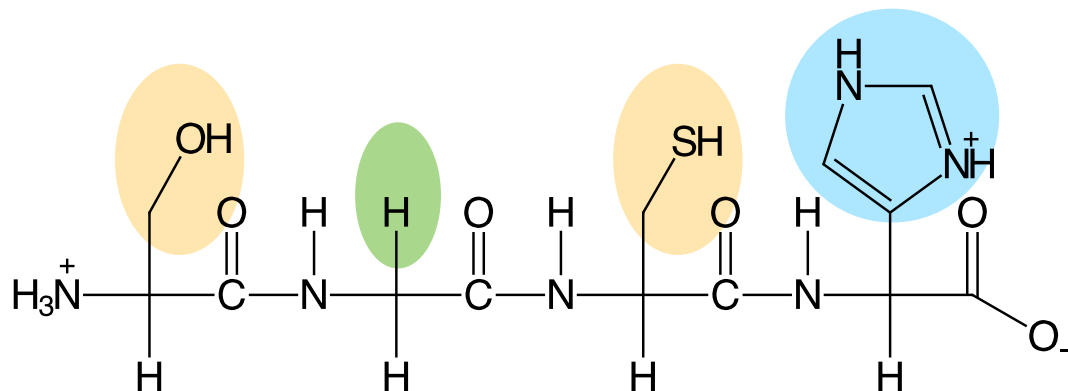
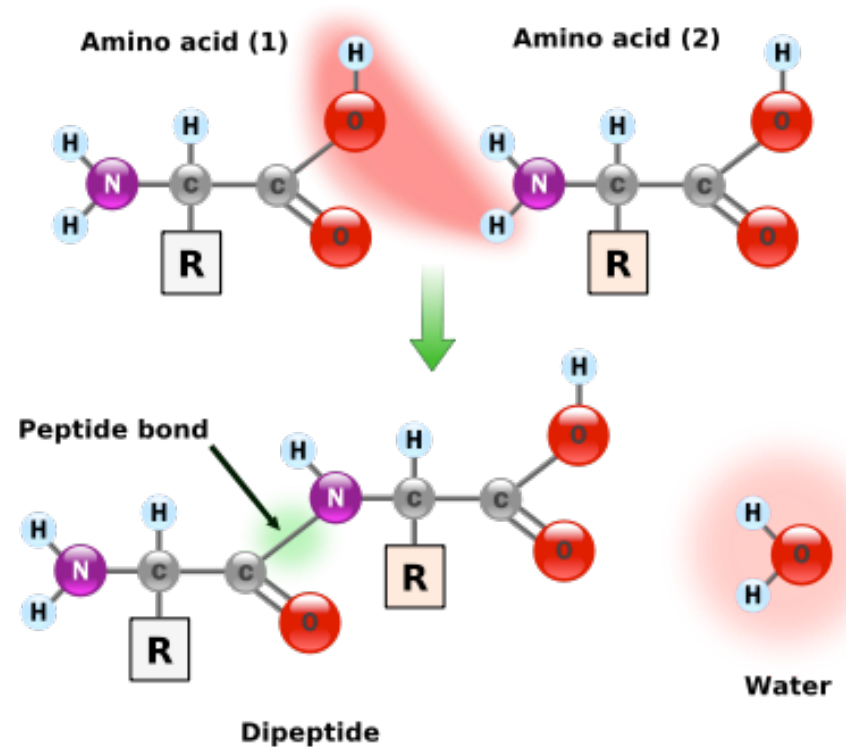


ALA-GLY



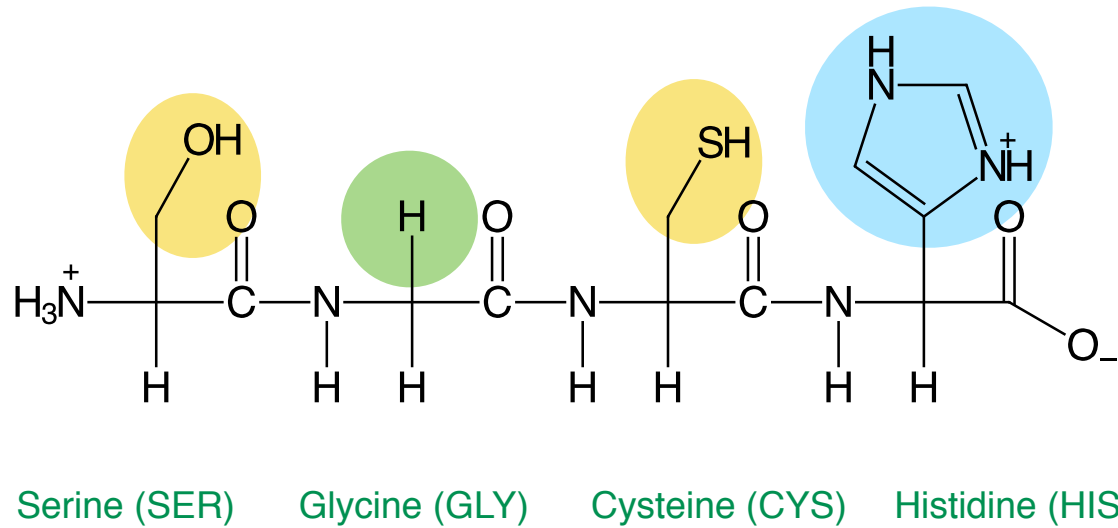
Peptides

- ▶ A **peptide bond** is an amide bond that forms when the $-\text{COO}^{1-}$ group of one amino acid reacts with the $-\text{NH}_3^+$ group of the next amino acid.
- ▶ The linking of two or more amino acids by peptide bonds forms a peptide.
- ▶ Peptides formed from
 - ▶ two amino acids are called dipeptides
 - ▶ three amino acids are called tripeptides
 - ▶ four amino acids are called tetrapeptides
 - ▶ five amino acids are called pentapeptides
 - ▶ more than that are called polypeptides

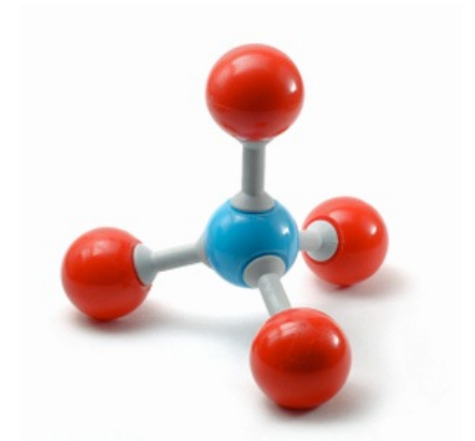


Try it.

- ▶ What's the sequence of the following peptide?



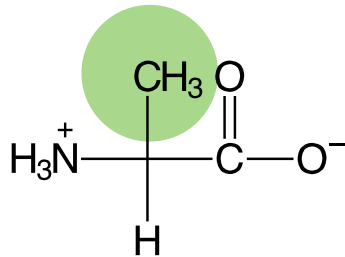
SER-GLY-CYS-HIS



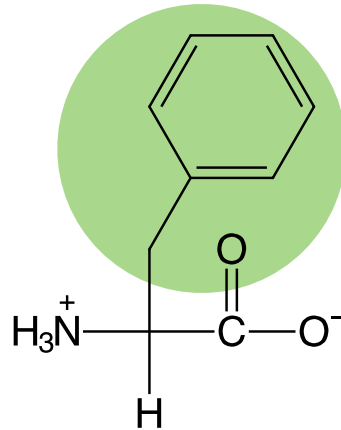
Try it.

- ▶ Draw the tripeptide with the sequence ALA-PHE-VAL.

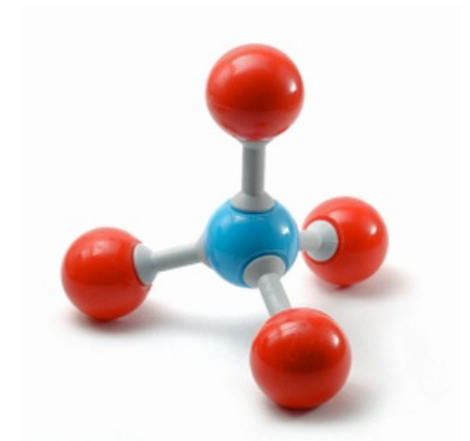
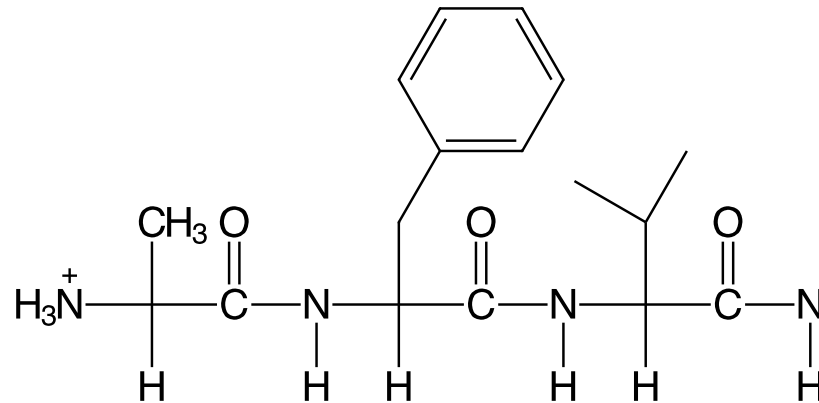
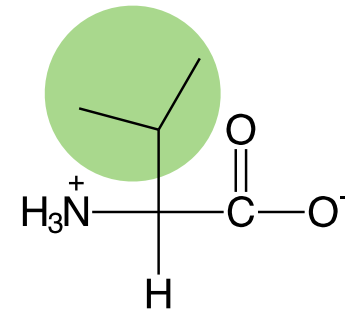
Alanine (ALA)



Phenylalanine (PHE)



Valine (VAL)

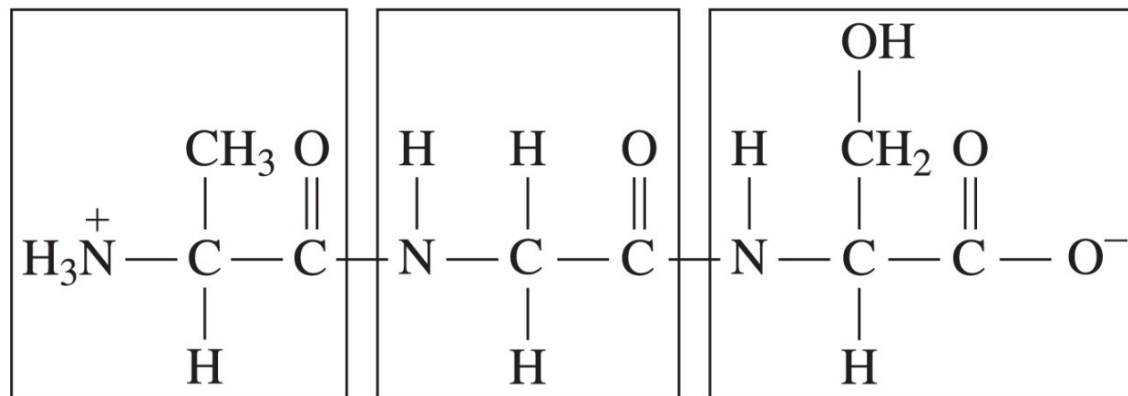


Peptides

- ▶ Peptides are named by stringing together the names of their amino acids in order of sequence.
- ▶ With the exception of the C-terminal amino acid, the names of all the other amino acids in a peptide end with **-yl** instead of **-ine**.

N-terminal end

C-terminal end



Always start with the amino end — this is first amino acid in the peptide.

Always end with the acid end — this is the last amino acid in the peptide.

(from alanine)

(from glycine)

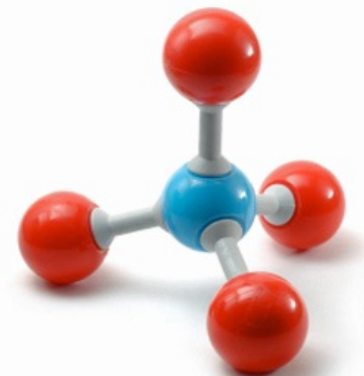
(from serine)

Alanyl

Glycyl

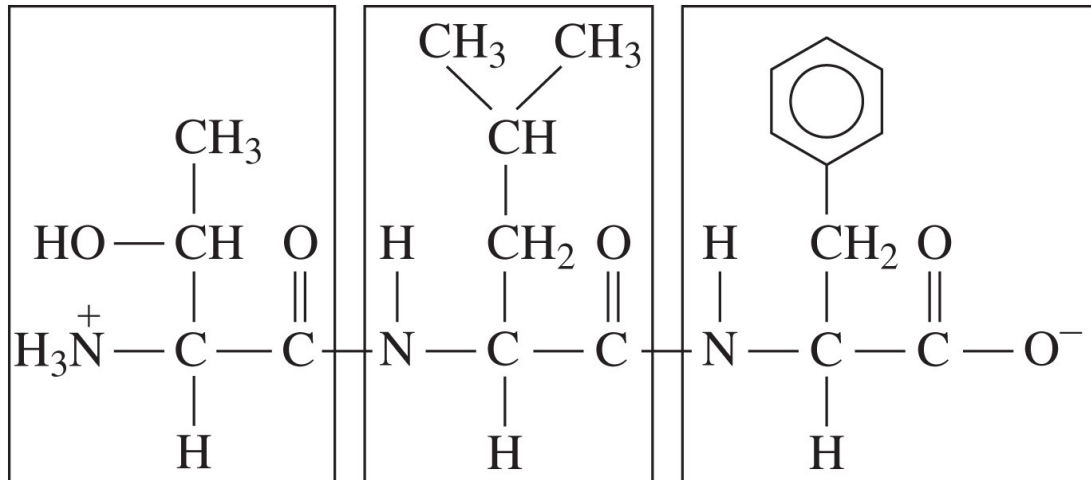
Serine

Alanylglycylserine



Try it.

- ▶ What's the name of this peptide?
(you'll be provided with a list of amino acid structures on the exam)



(from threonine)

Threonyl

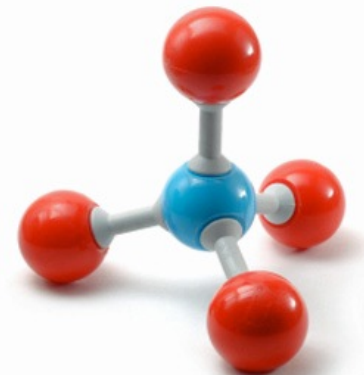
(from isoleucine)

Isoleucyl

(from phenylalanine)

Phenylalanine

Threonylisoleucylphenylalanine



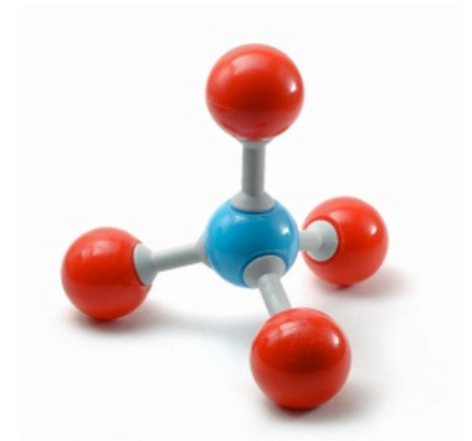
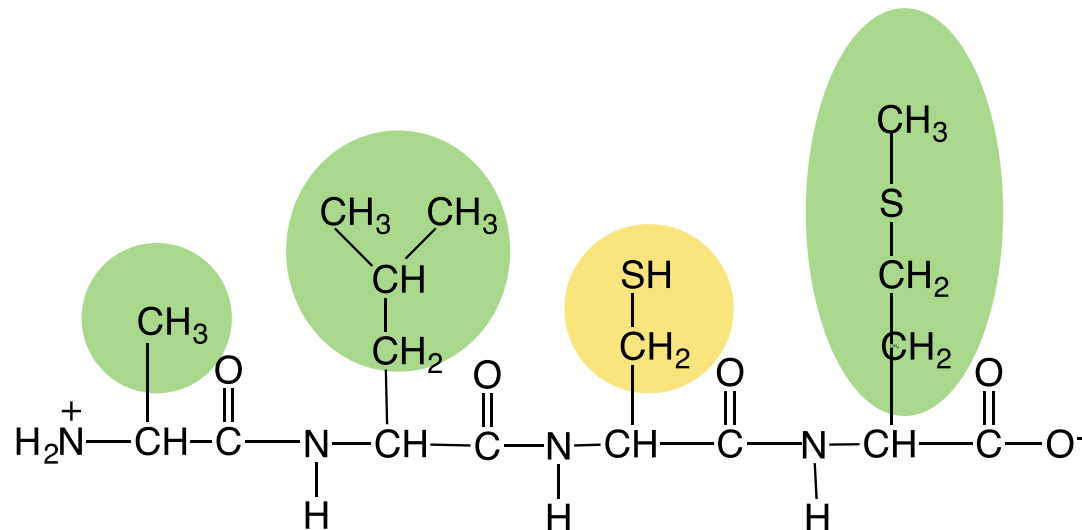
Try it.

- ▶ What's the name of the tetra peptide sequenced ALA-LEU-CYS-MET?
(you'll be provided with a list of amino acid structures on the exam)

ALA (alanine) LEU (leucine) CYS (cysteine) MET (methionine)

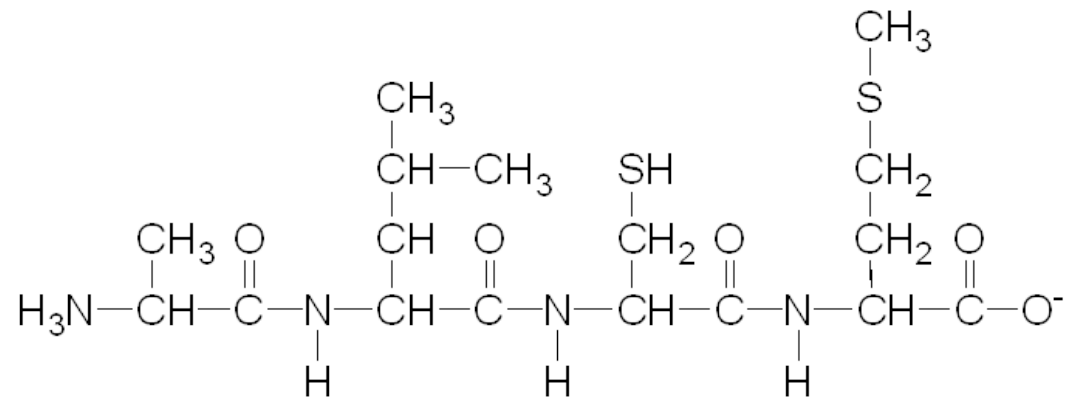
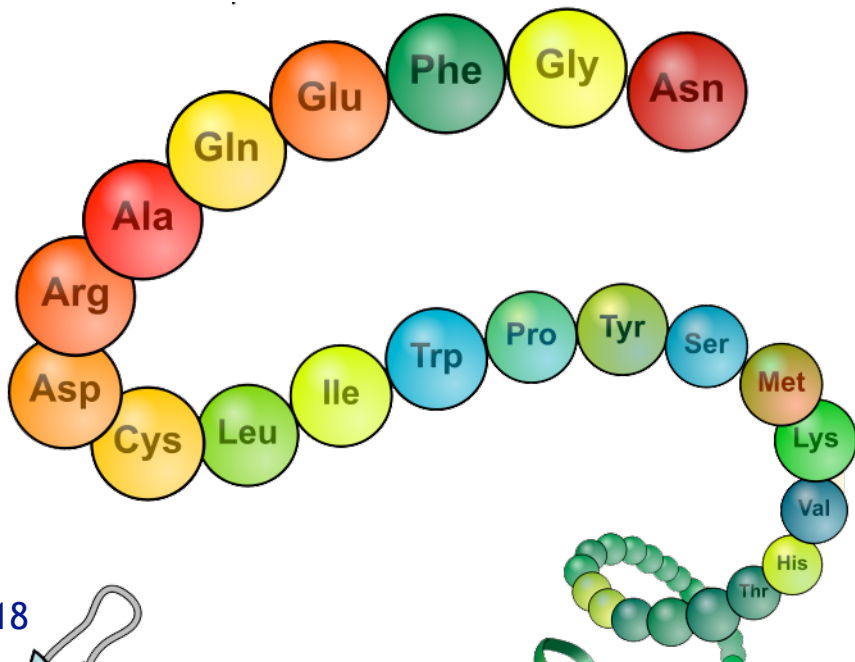
Alanylleucylcystylmethionine

- ▶ Draw the structure of Alanylleucylcystylmethionine.

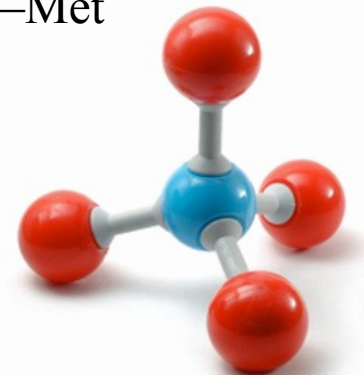


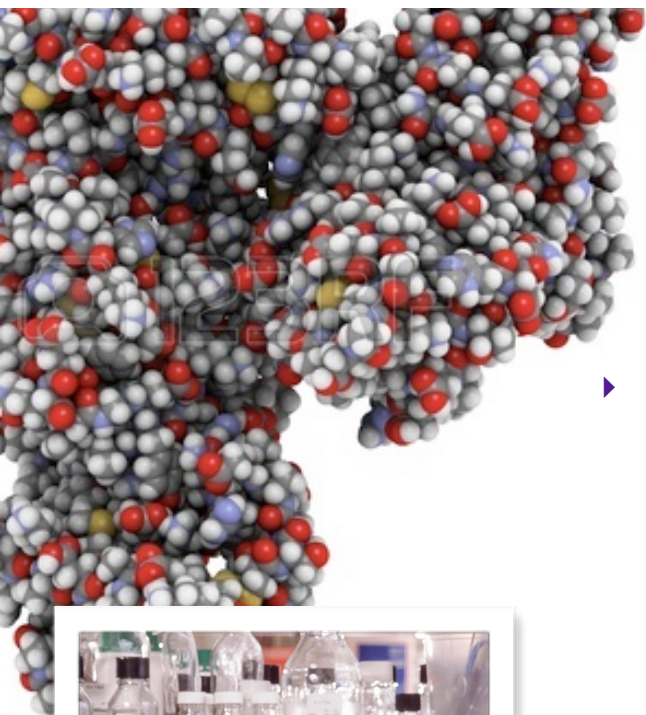
Primary Structure

- ▶ A **protein** is a polypeptide of 50 or more amino acids that has biological activity.
- ▶ The **primary structure** of a protein is its sequence of amino acids.



Ala–Leu–Cys–Met



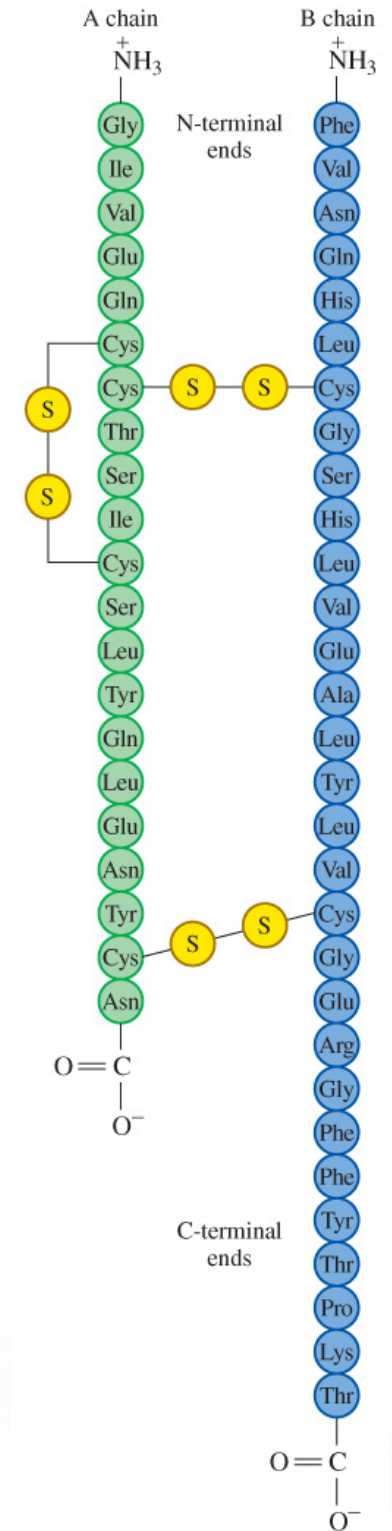
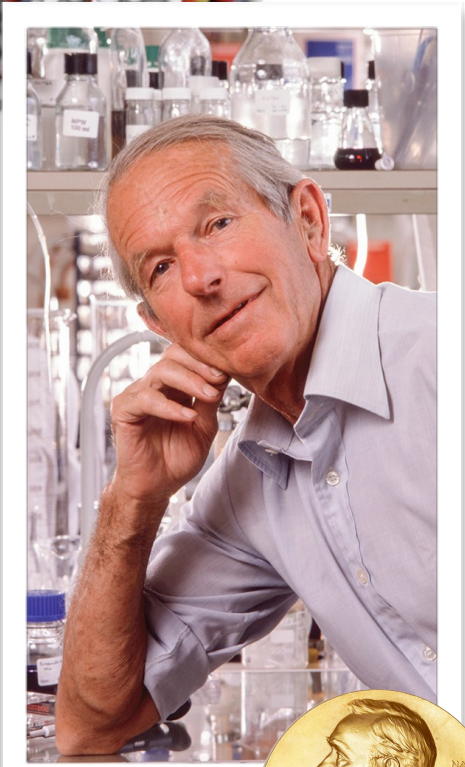


Insulin

▶ Insulin

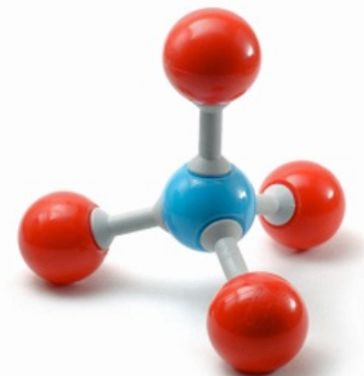
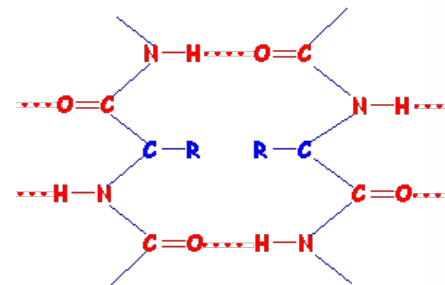
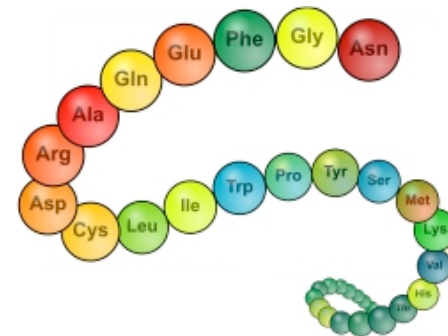
- ▶ Insulin was first identified in 1869.
- ▶ Insulin was sequenced by Frederick Sanger in 1953 (84 years later).
- ▶ This was the first protein to have its primary structure determined.
- ▶ Sanger was awarded the 1958 Nobel Prize in Chemistry for this work.
- ▶ The primary structure of two polypeptide chains linked by disulfide bonds
- ▶ The A chain of insulin has 21 amino acids.
- ▶ The B chain has 30 amino acids

- ▶ Insulin is a small protein. Many proteins have more than a thousand amino acids.
- ▶ Identifying which of the 20 primary amino acids exists at each position of some 1000 acid chains has taken decades of research.
- ▶ It's like solving a combination lock with 1000 wheels each having 20 possible settings.

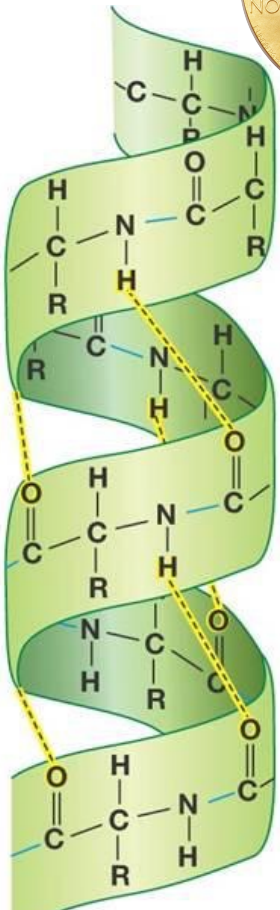
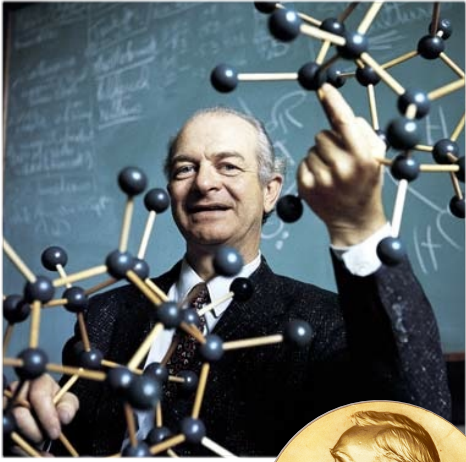


Secondary Structure

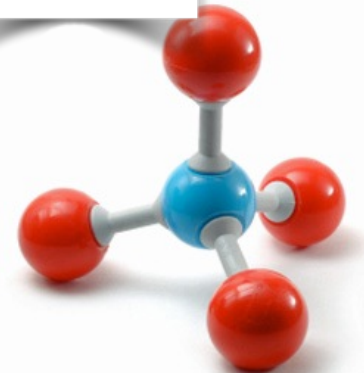
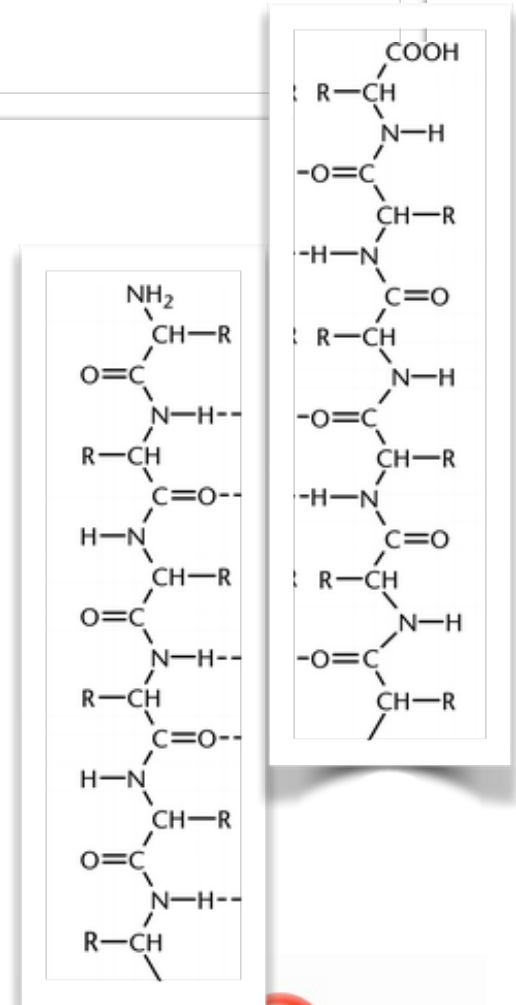
- ▶ The primary structure of a protein doesn't tell the whole story.
- ▶ A string of a thousand amino acids, each with:
 - ▶ a hydrogen bond donor (the amide)
 - ▶ and a hydrogen bond acceptor (the carbonyl)
- ▶ The huge number of amide carbonyl hydrogen bonds causes the string to adhere to itself.
- ▶ This internal hydrogen bonding causes the string to ball up and fold over itself.
 - ▶ Some amino acids can cause the chain to kink up, to bend or turn.
 - ▶ Others cause it to straighten out.
- ▶ So different sequences may prefer to 'ball up' or fold over or run straight...
- ▶ The way a protein string packs on itself with the intramolecular hydrogen bonds is its **secondary structure**.
- ▶ Secondary structure considers only amide-carbonyl intramolecular hydrogen bonds.



Secondary Structure

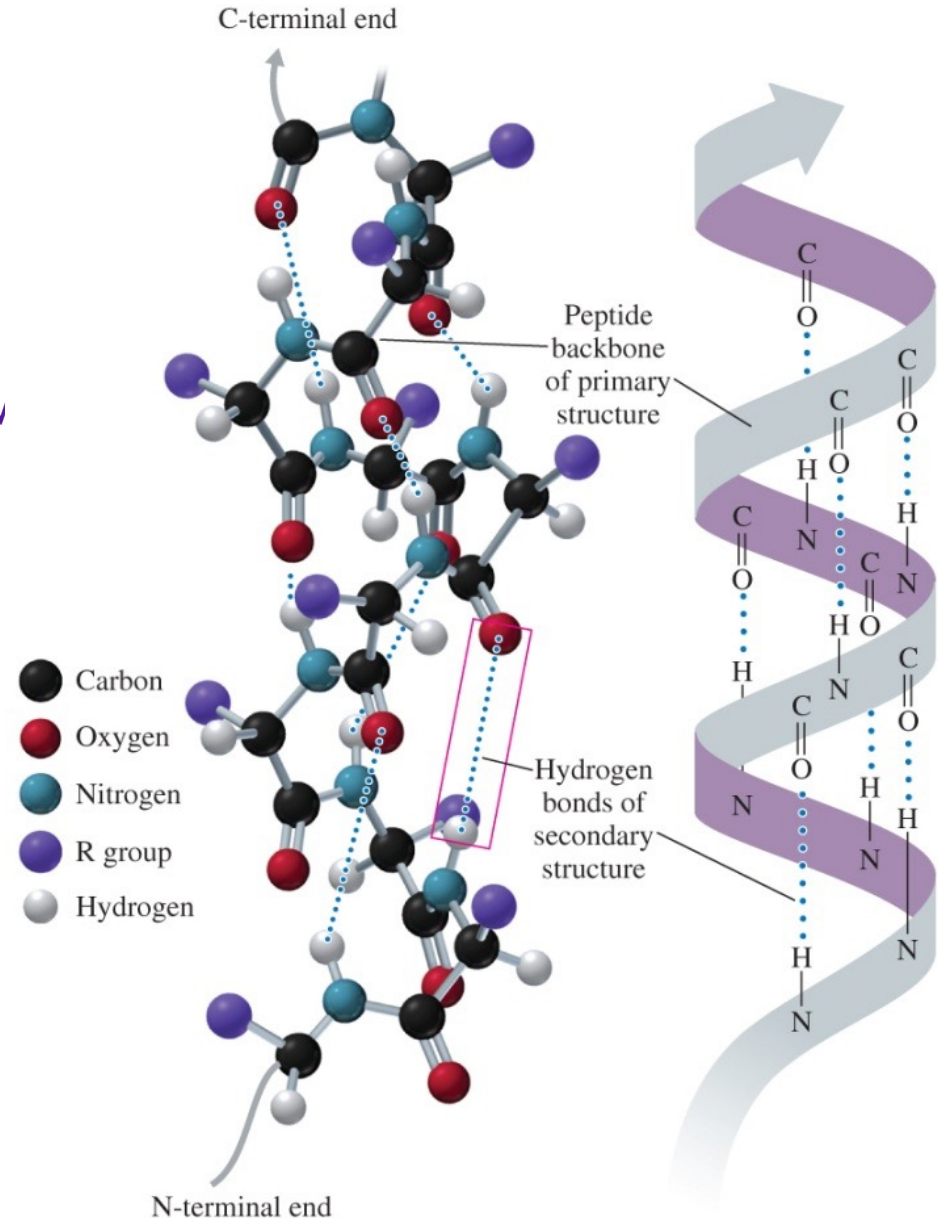
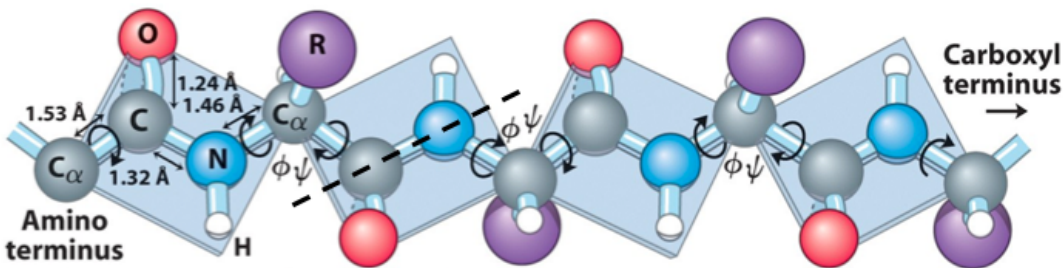


- ▶ Proteins that are forced to straighten out lose many of the properties they demonstrate when their secondary structure is active.
- ▶ Understanding this secondary structure is an important part of understanding the nature of a particular protein.
- ▶ Chemists used to write out parts of amino acid sequences on paper and slide one paper against another to try and visualize what hydrogen bonding might work best.
- ▶ In 1948, while in bed recovering from a cold, Linus Pauling made a crude paper model of a particular polypeptide chain.
- ▶ But instead of sliding the paper edges, he rolled it – and found a better bonding pattern.
- ▶ He concluded that the polypeptide chain was a single-stranded helix, which he named the alpha-helix.
- ▶ Linus Pauling received the Nobel prize in chemistry for this in 1954.



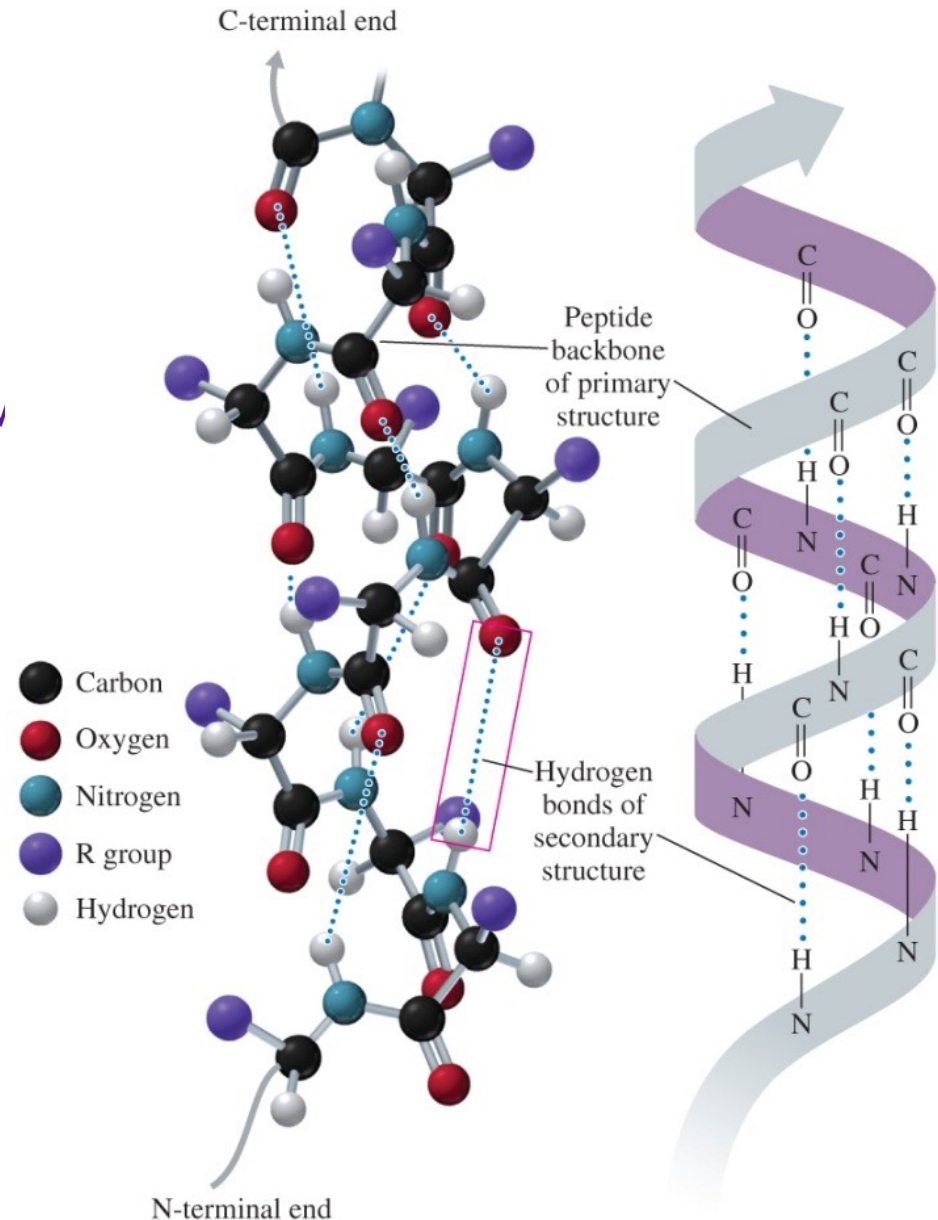
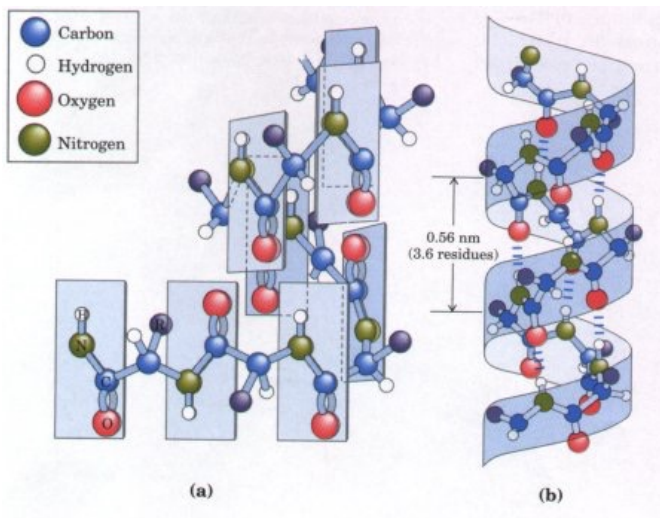
Secondary Structure: α Helix

- ▶ The α helix secondary structure is common to many proteins.
- ▶ The planar peptide bond with sp^3 carbons every fourth atom makes a natural curve in peptides, like a spiral staircase.
- ▶ The sp^3 bond angle brings periodic amides and carbonyls into close proximity and allow easy hydrogen bonding.
- ▶ The side branches (R groups) are always pointed to the outside of the alpha helix.



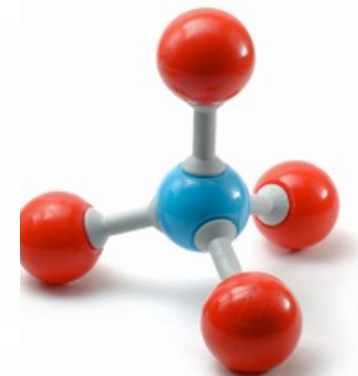
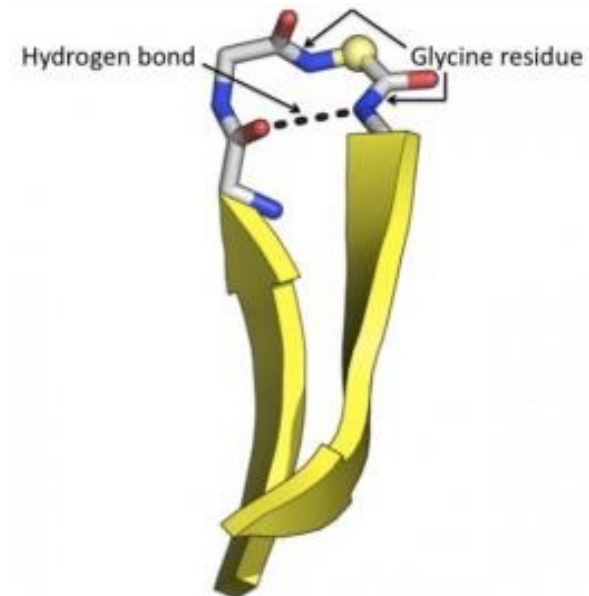
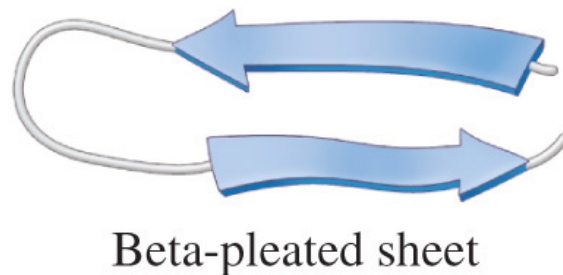
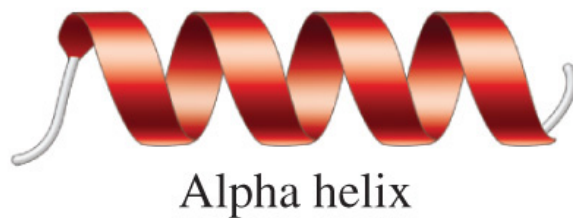
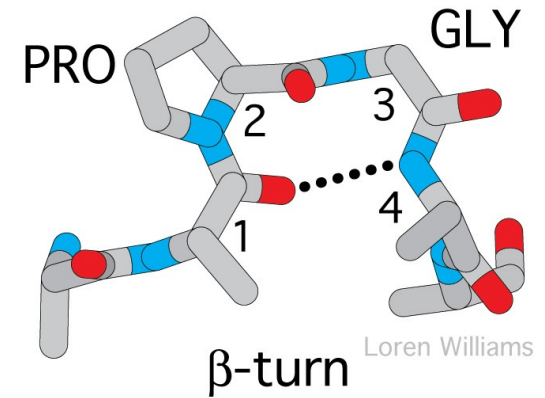
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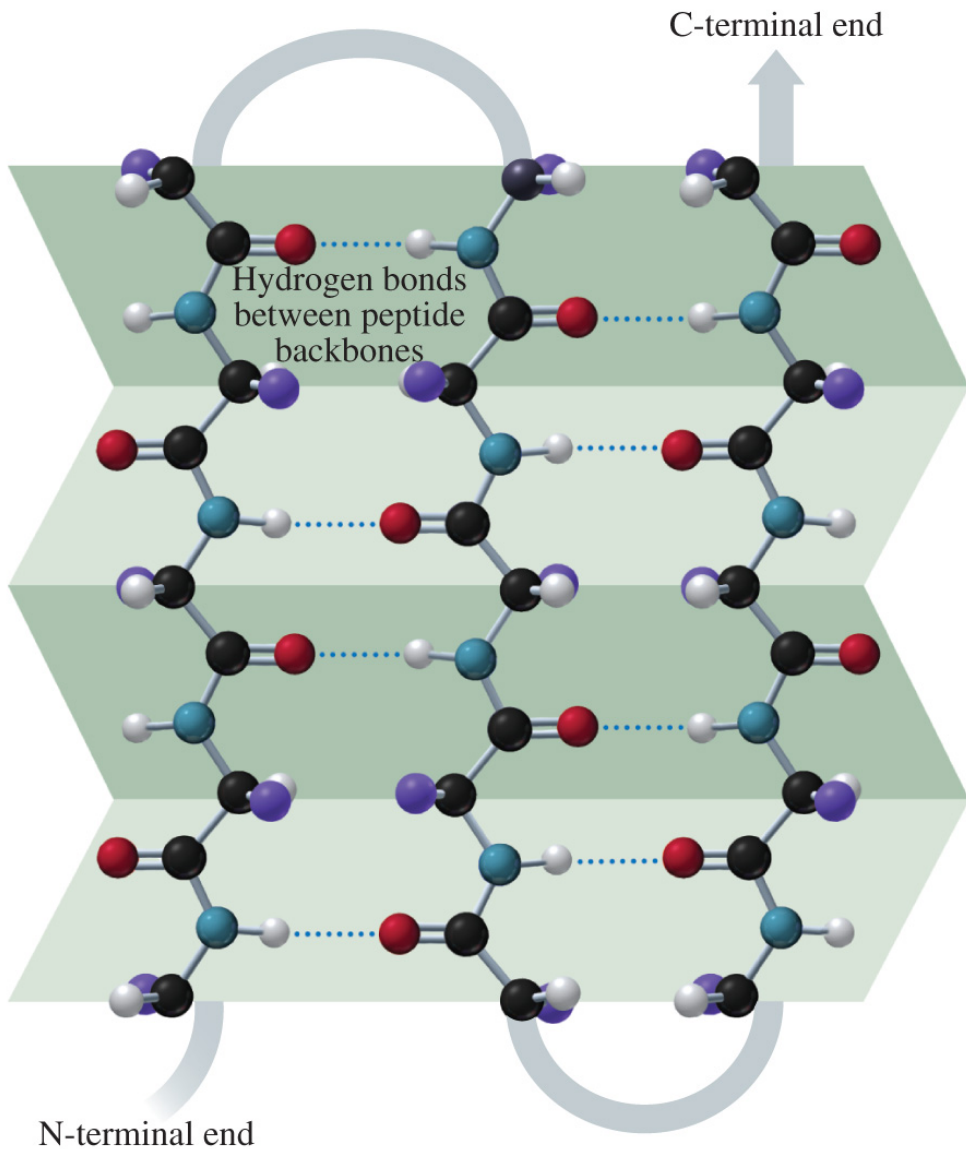


Secondary Structure: β Sheets

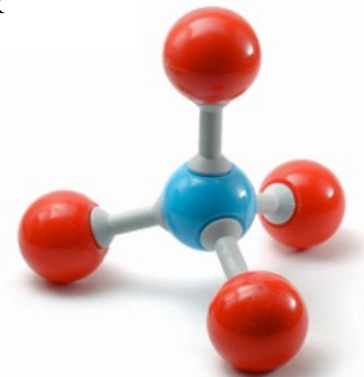
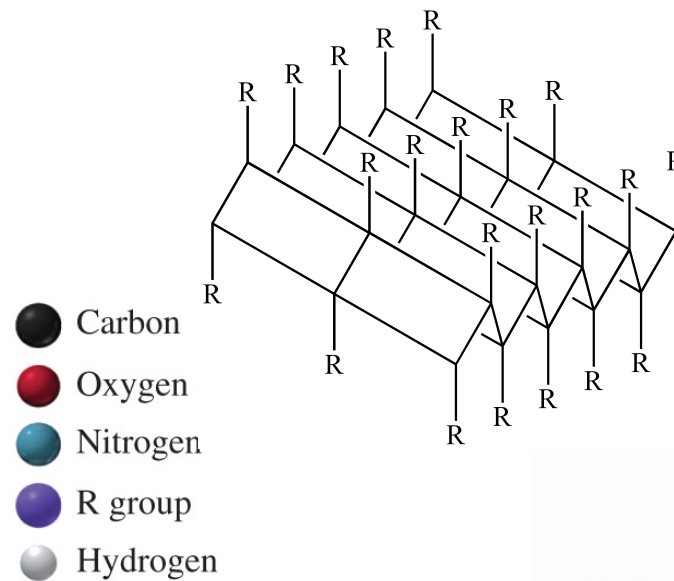
- ▶ Other secondary structures are possible.
- ▶ β Sheets are another secondary structure.
- ▶ With some sequences periodic patterns of amino acids cause the chain to flip back on itself.
- ▶ These are called β -turns.
 - ▶ Small glycine next to fixed proline can cause a beta turn.
- ▶ When a β -turns occurs this can cause the chain can close like a zipper.



Secondary Structure: β Sheets



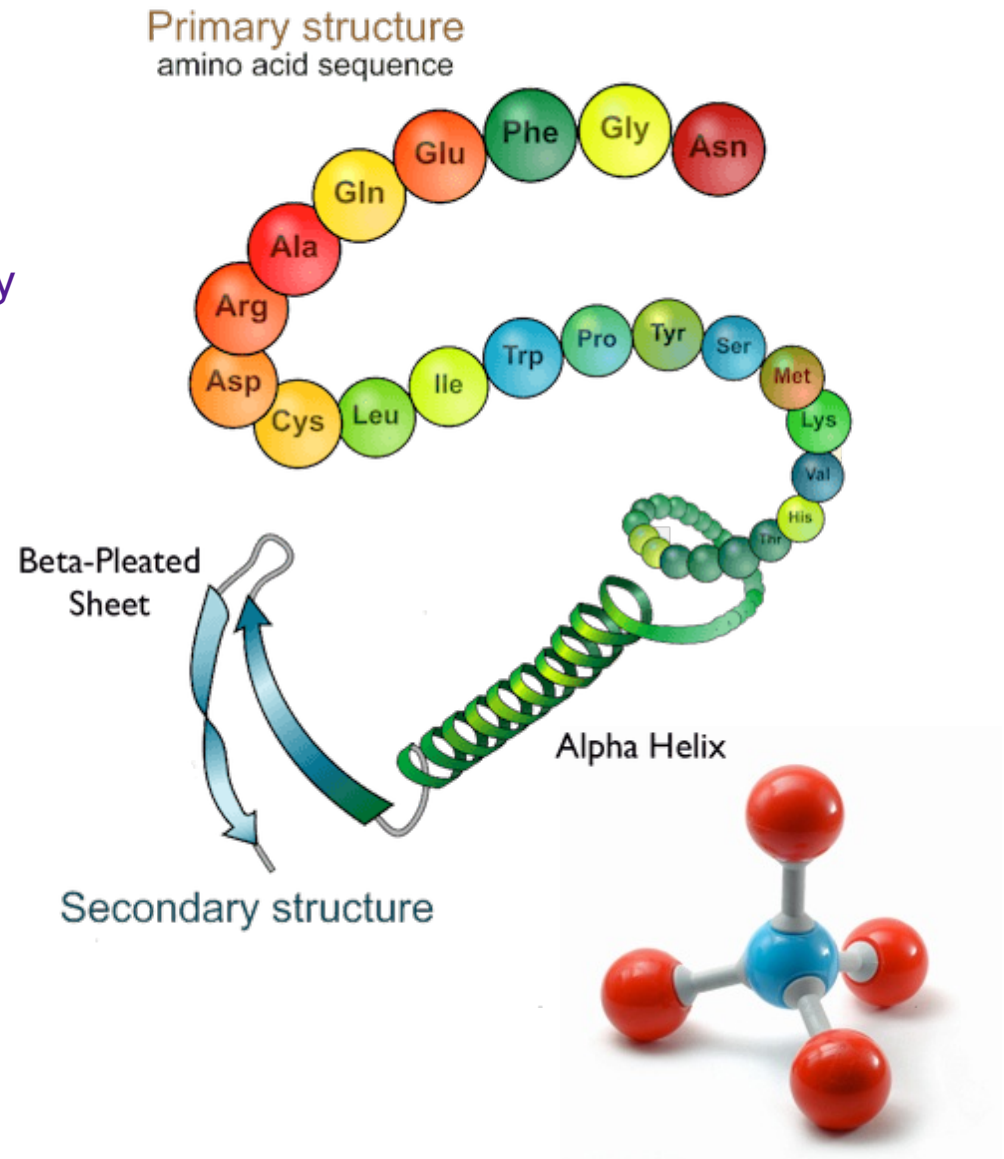
- ▶ β Sheets may have more than one β turn.
- ▶ In β sheets the side chains (R groups) are all pointed in parallel, either above or below the plane.



N-terminal end

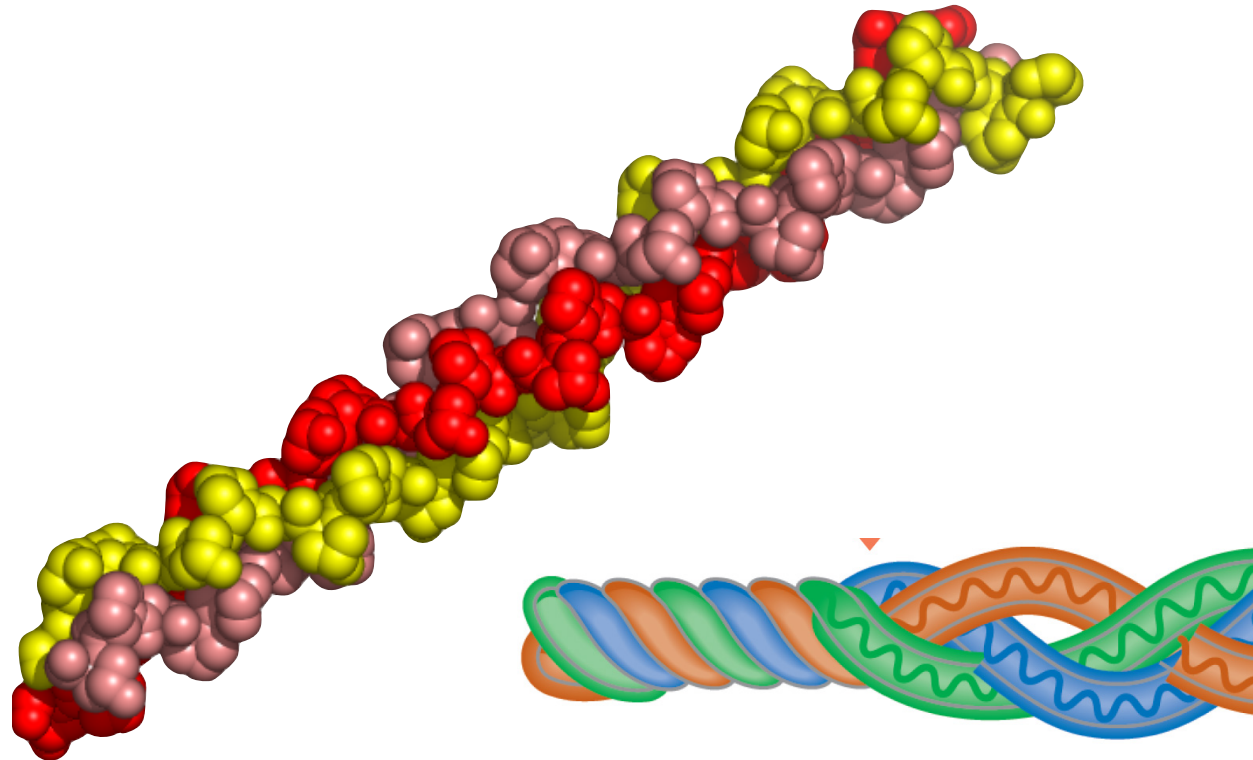
Secondary Structure

- ▶ Different parts of the same protein may form different secondary structures.



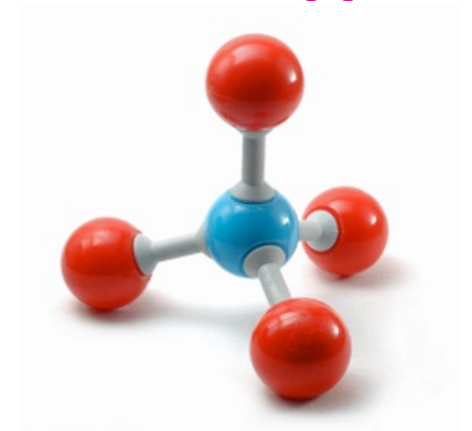
Secondary Structure: Triple Helix

- ▶ Another secondary structure is the triple helix.
- ▶ In a triple helix three polypeptide chains are woven together.
- ▶ As with all secondary structures, hydrogen bonds between amides and carbonyls hold the structure together.
- ▶ In the case they are intermolecular hydrogen bonds. Bonds between separate molecules.
- ▶ A triple helix has added strength and is typical of collagen, connective tissue, skin, tendons, and cartilage



Triple helix

3 peptide chains



Peptides

▶ Peptides

▶ Peptide Bonds

- ▶ Structure & Reactions

▶ Peptides

- ▶ Terminals
- ▶ Sequencing
- ▶ Names

▶ Proteins are Big Peptides

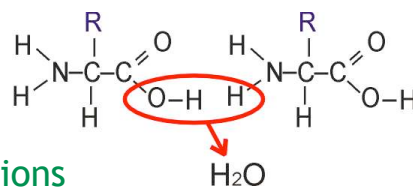
▶ Definition

▶ Primary Structure

- ▶ Sequence

▶ Secondary Structure

- ▶ α Helix
- ▶ β Sheets
- ▶ Triple helix



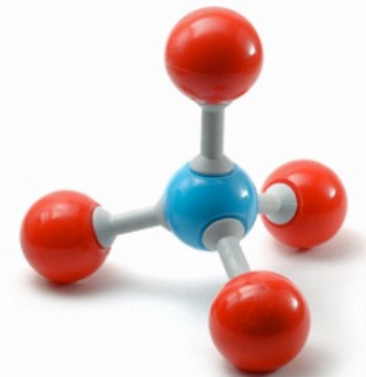
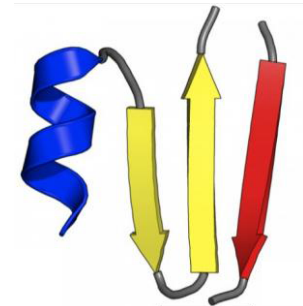
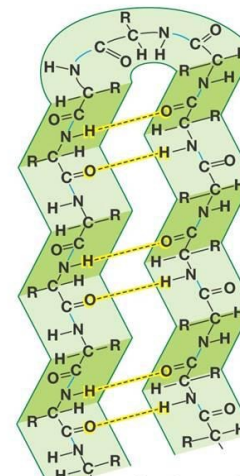
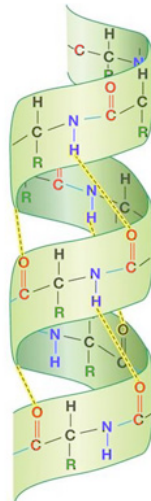
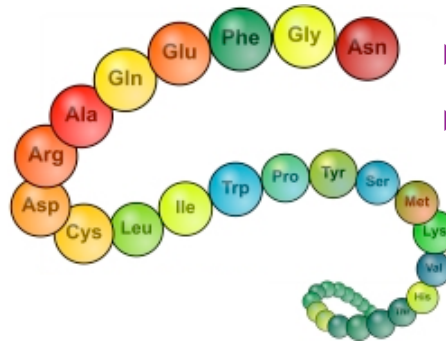
Tertiary Structure

- ▶ Types of Interactions

▶ Denaturation

▶ Enzymes

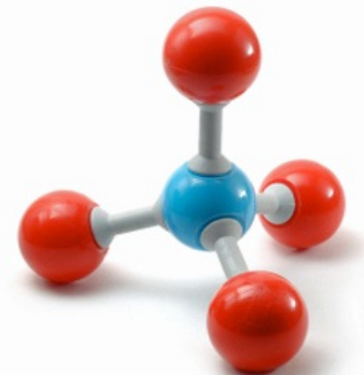
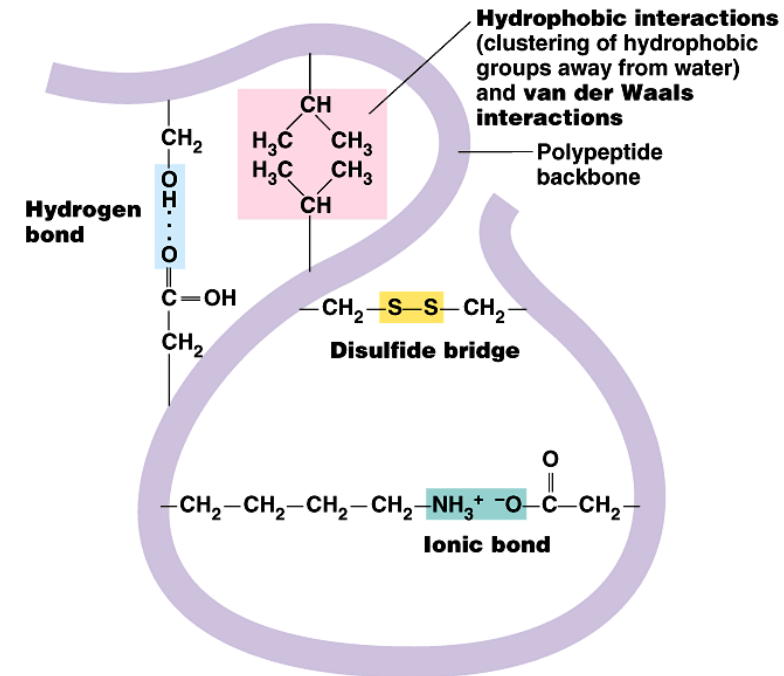
- ▶ Catalysis
- ▶ Enzyme activity
- ▶ Inhibition



Tertiary Structure

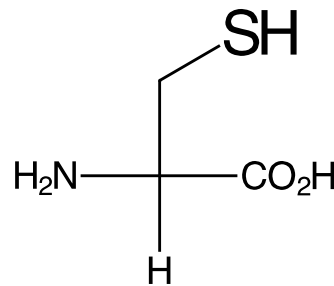
- ▶ Beyond primary and secondary structure, peptides have other interactions that produce other shapes.
 - ▶ Primary structure is sequence.
 - ▶ Secondary structure is carbonyl-amide hydrogen bonding.
- ▶ Tertiary structure results from interaction of the side chains (with each other or the environment).
- ▶ This can be attractive or repulsive interactions.
- ▶ There are at least five kinds of tertiary interaction.

1. Hydrophilic
2. Hydrophobic (or lipophilic)
3. Salt bridges (ionic bonding)
4. Hydrogen bonding (between side chains)
5. Disulfide Bonds



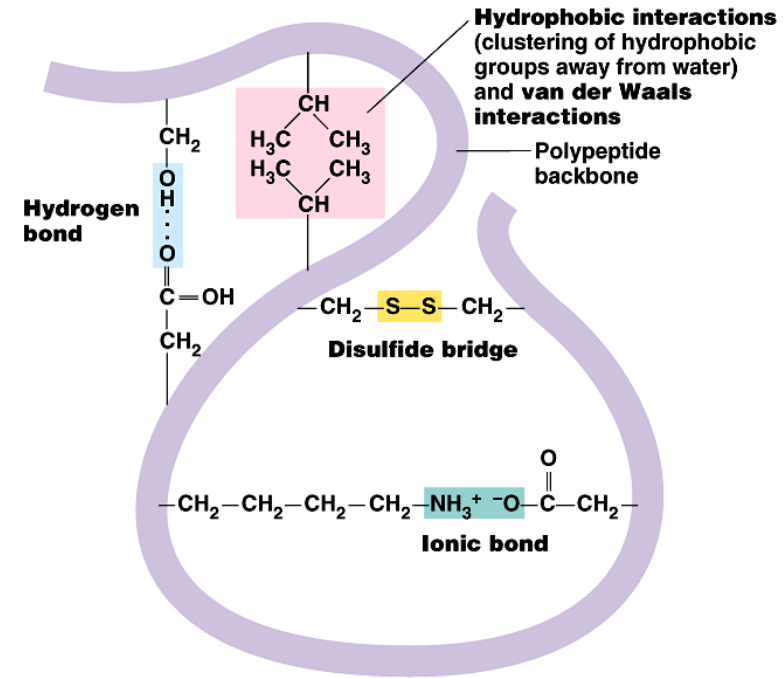
Tertiary Structure

- ▶ Disulfide bonds can only occur when two Cysteine molecules become oxidized.

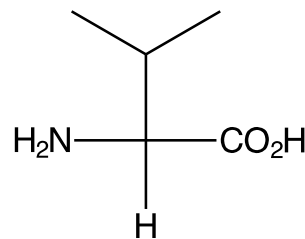


Cystine

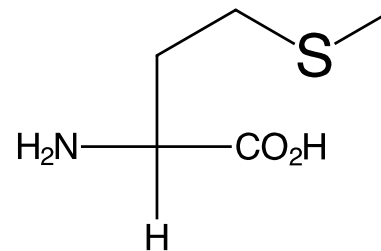
- ▶ Hydrophobic (lipophilic) tertiary interactions occur between “floppy” or cyclic (aromatic) non-polar amino acids.
- ▶ Smaller amino acids like alanine and glycine do not contribute this interaction but valine does.



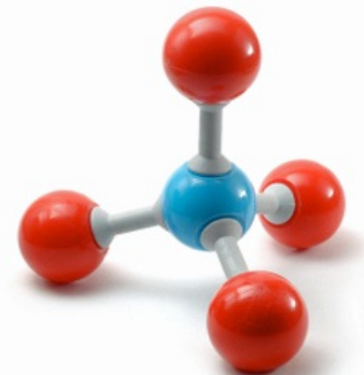
examples:



Valine



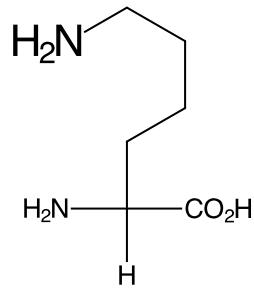
Methionine



Tertiary Structure

- ▶ **Salt bridges** form between a polar acidic and polar basic amino acid.

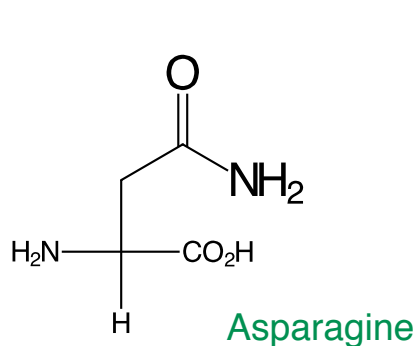
examples:



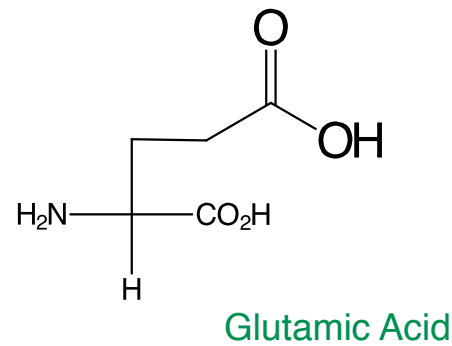
Lysine

- ▶ **Tertiary hydrogen bonding** occurs when a polar side chain hydrogen-bonds to an amide, carbonyl or other side chain.
- ▶ Do not confuse this with hydrogen bonding in secondary structures!

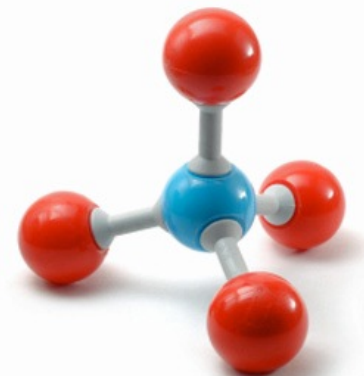
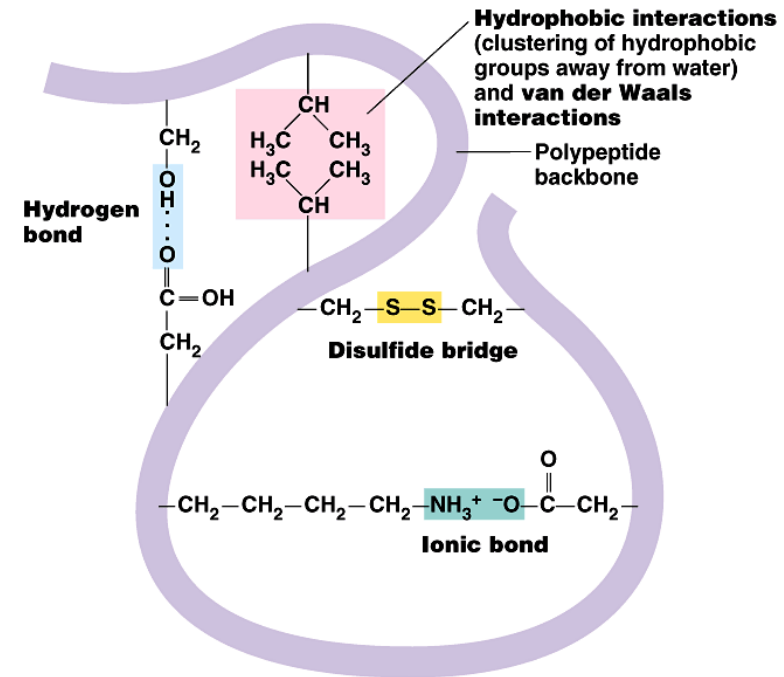
examples:



Asparagine

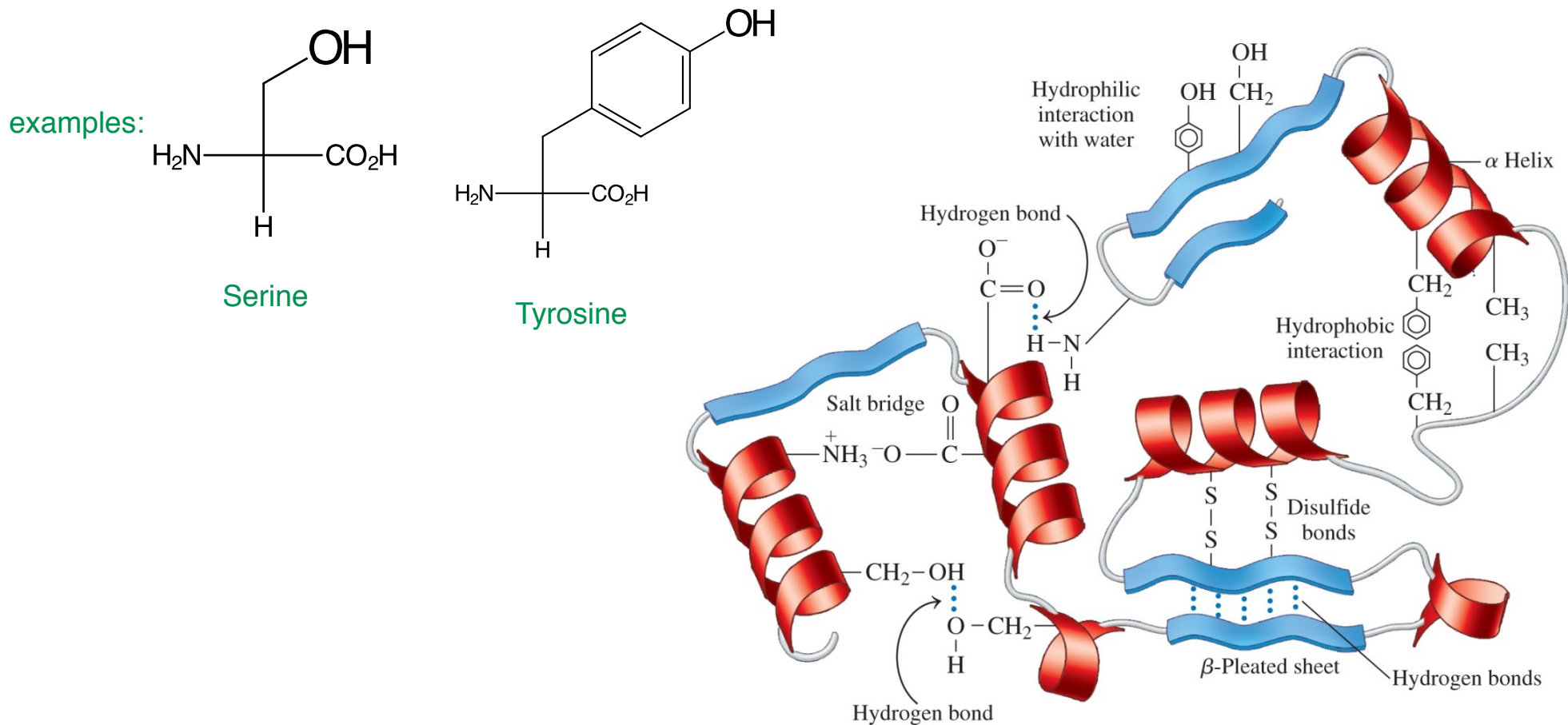


Glutamic Acid



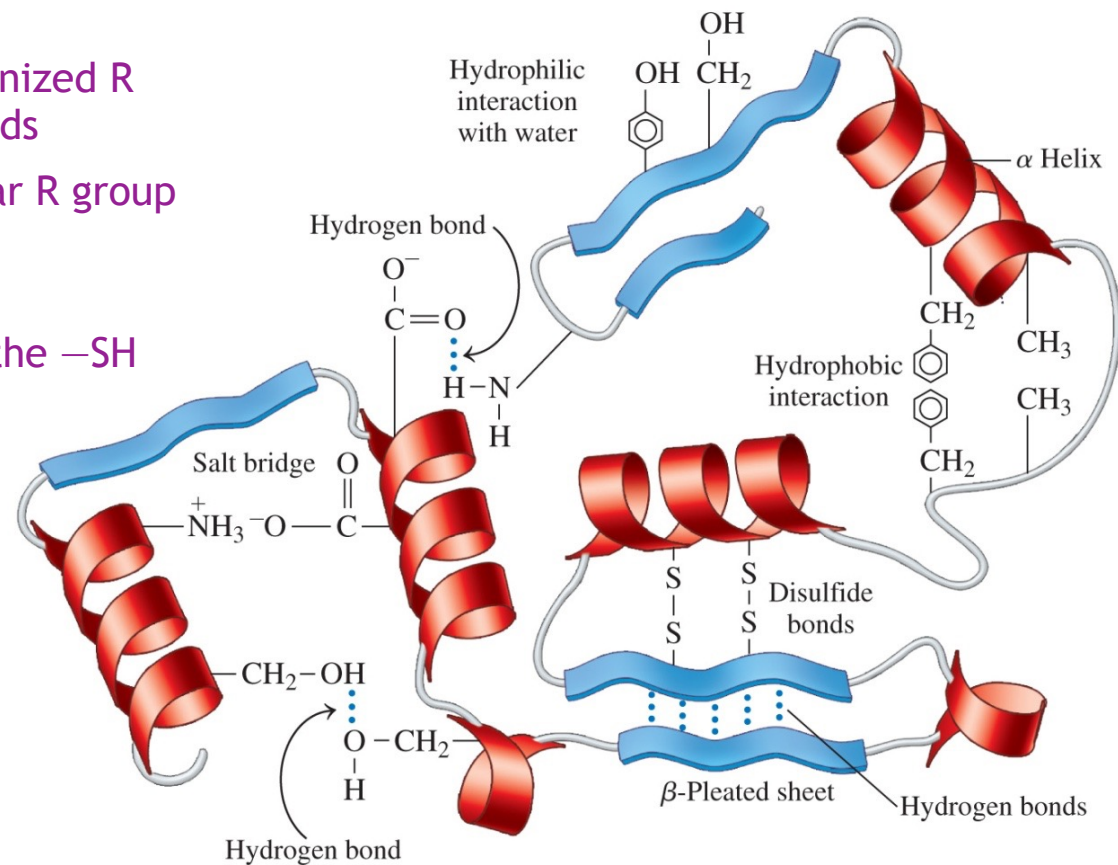
Tertiary Structure

- ▶ **Hydrophilic** interactions from amino acids with hydroxy groups pull proteins open by being attracted to the aqueous environment outside them.



Tertiary Structure

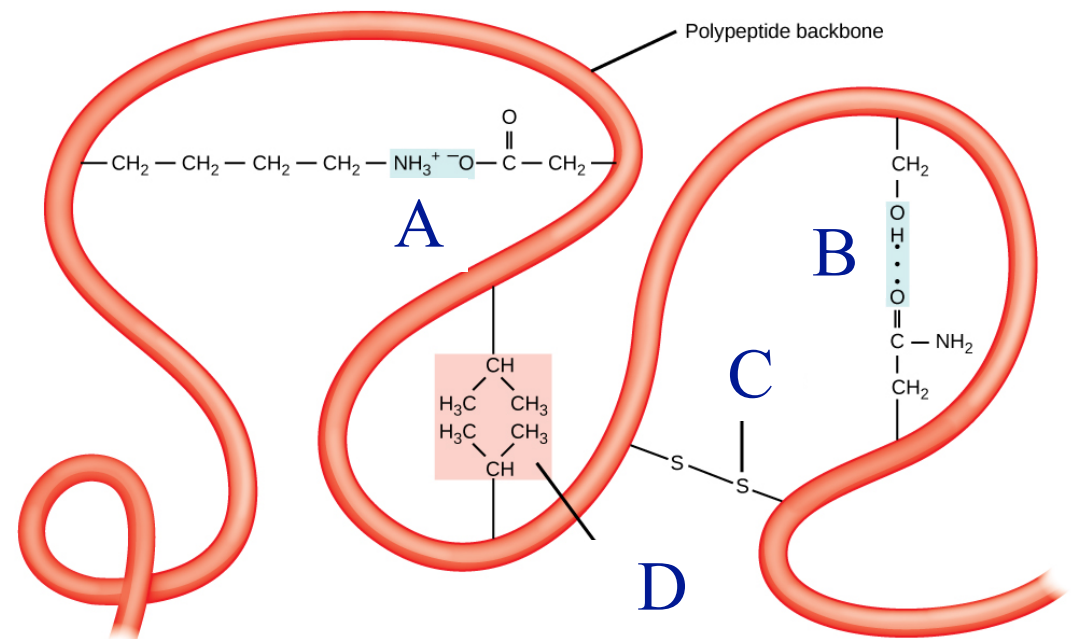
- ▶ Sections of a protein interact to create the tertiary structure of a protein due to
 - ▶ **hydrophobic interactions** between two nonpolar amino acids
 - ▶ **hydrophilic interactions** between the external aqueous environment and the R groups of polar amino acids
 - ▶ **salt bridges**, ionic bonds between ionized R groups of basic and acidic amino acids
 - ▶ **hydrogen bonds** between H of a polar R group and the O or N of another amino acid
 - ▶ **disulfide bonds** — S — S — between the —SH groups of cysteine amino acids



Try it.

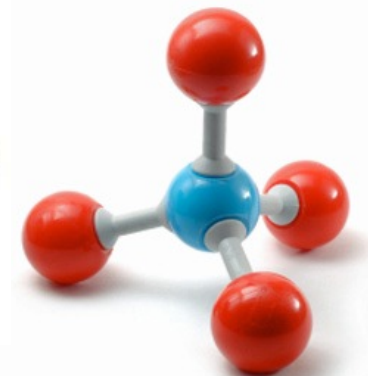
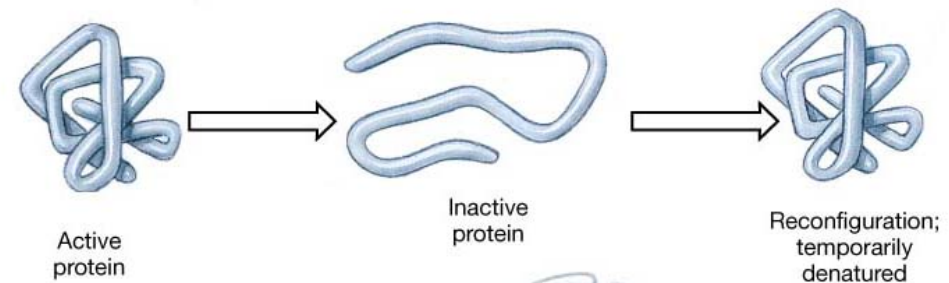
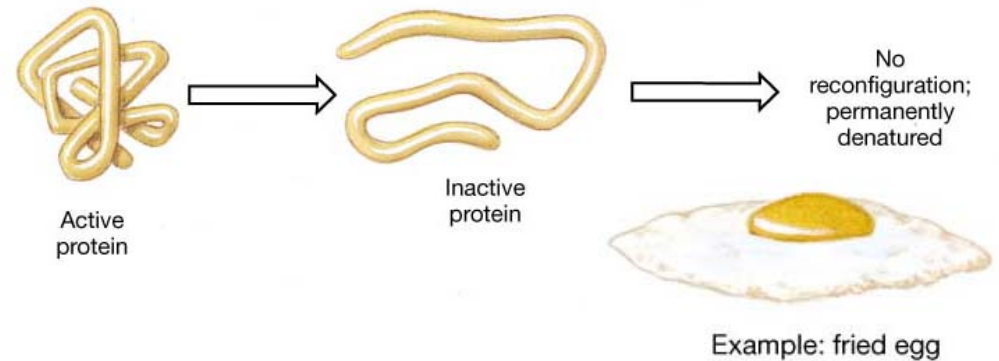
► What type of tertiary interaction is indicated with each letter below?

- A. Salt bridge
- B. Hydrogen Bonding (tertiary)
- C. Disulfide Bond
- D. Hydrophobic (or lipophilic)



Denaturation

- ▶ Many properties of proteins depend on their advanced structures (secondary and beyond).
- ▶ Removing those interactions changes the substance.
- ▶ **Denaturation** is removing advanced interactions.
- ▶ Two ways to accomplish denaturation of proteins are with acid or with heat.
- ▶ Denaturation can be reversible or irreversible.
 - ▶ Eggs can be denatured irreversibly by heating.
 - ▶ Milk can be denatured reversibly by heating.
 - ▶ When cooled the milk returns to its natured form.



Peptides

▶ Peptides

▶ Peptide Bonds

- ▶ Structure & Reactions

▶ Peptides

- ▶ Terminals
- ▶ Sequencing
- ▶ Names

▶ Proteins are Big Peptides

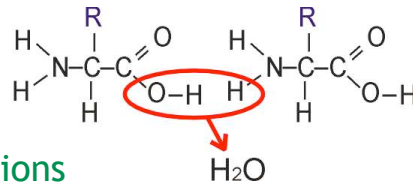
▶ Definition

▶ Primary Structure

- ▶ Sequence

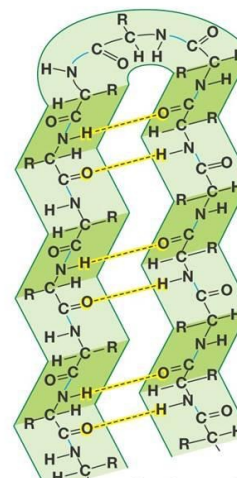
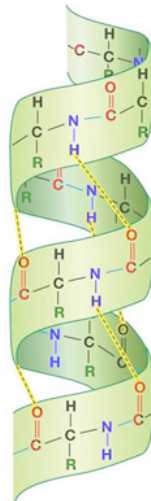
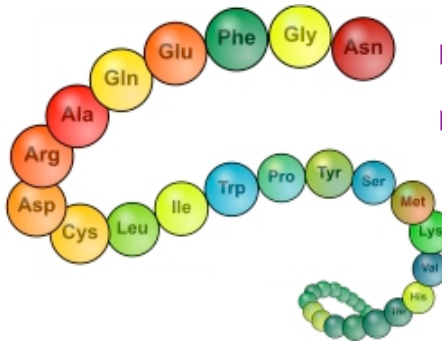
▶ Secondary Structure

- ▶ α Helix
- ▶ β Sheets
- ▶ Triple helix



Enzymes

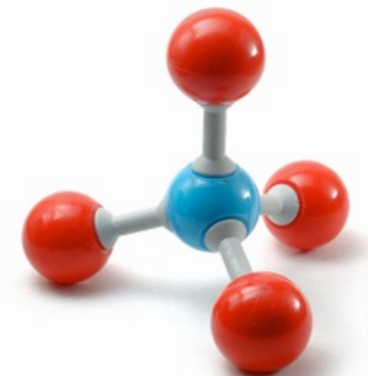
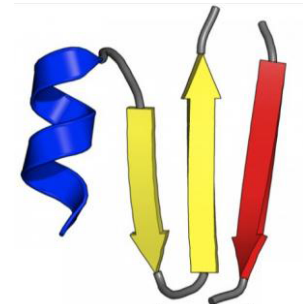
- ▶ Catalysis
- ▶ Enzyme activity
- ▶ Inhibition



▶ Tertiary Structure

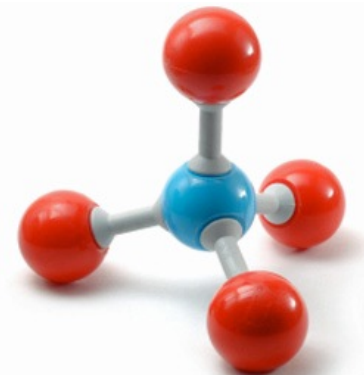
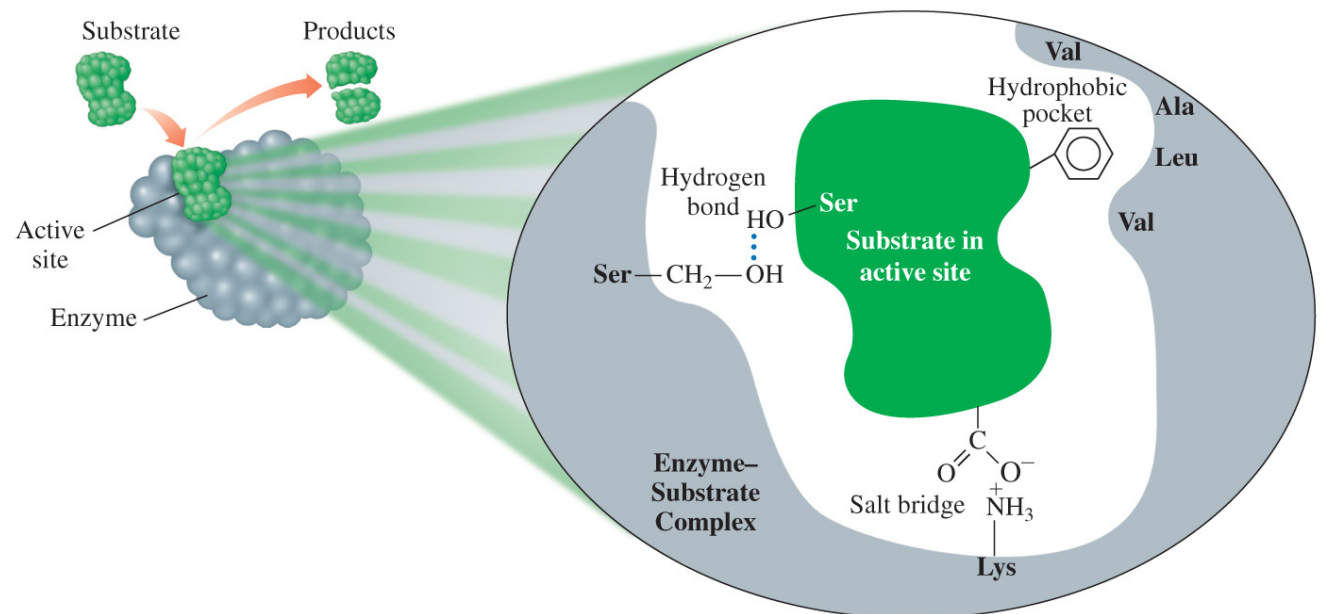
- ▶ Types of Interactions

▶ Denaturation



Enzymes

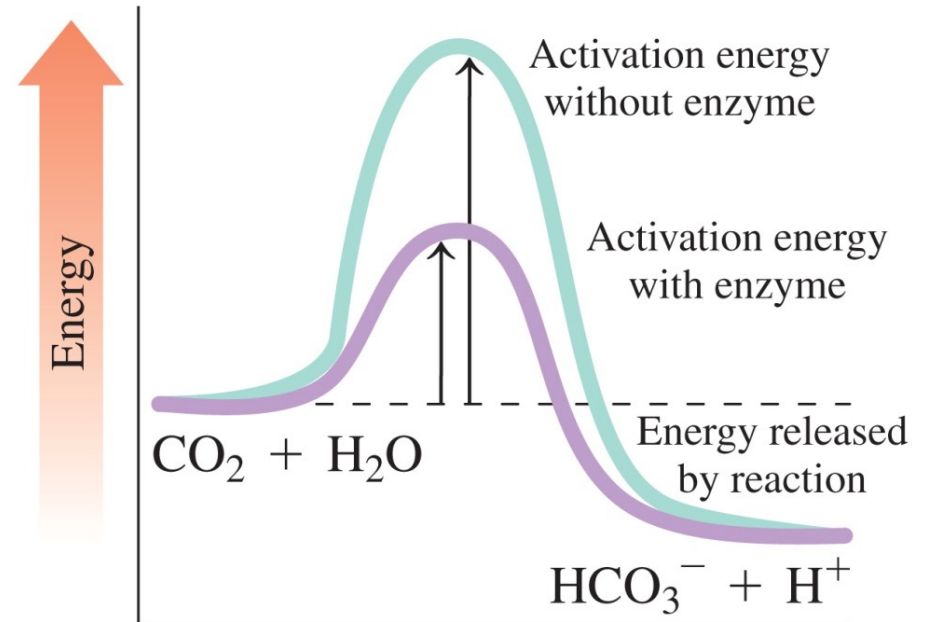
- ▶ Enzymes are proteins that act as biological catalysts. On the surface of an enzyme, a small region called an active site binds a substrate and catalyzes a specific reaction for that substrate.



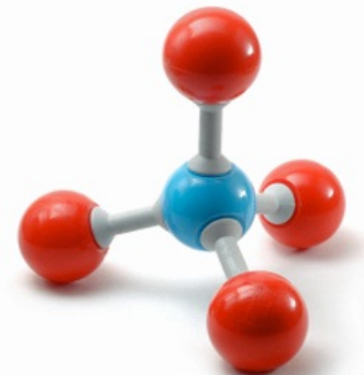
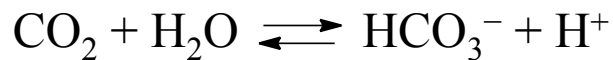
Enzymes

▶ Enzymes

- ▶ catalyze nearly all the chemical reactions taking place in the cells of the body
- ▶ increase the rate of reaction by lowering the energy of activation

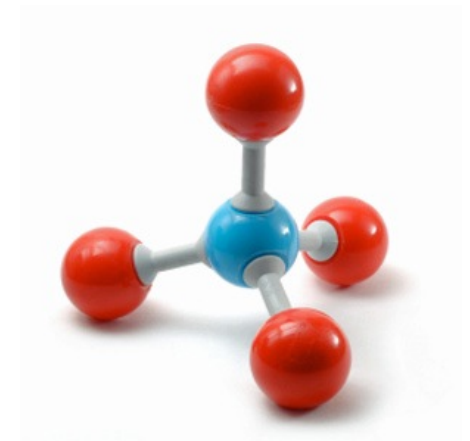


The enzyme carbonic anhydrase lowers the activation energy for the reaction:



Enzymes

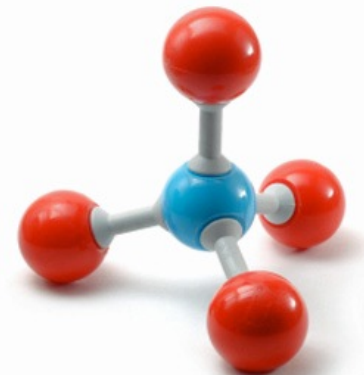
- ▶ The name of an enzyme
 - ▶ is derived by replacing the end of the name of the reaction or reacting compound with the suffix ase
 - ▶ identifies the reacting substance—for example, sucrase catalyzes the reaction of sucrose
 - ▶ describes the compound or the reaction that is catalyzed—for example, oxidase catalyzes an oxidation reaction
 - ▶ could be a common name, particularly for the digestion enzymes, such as pepsin and trypsin



Enzymes

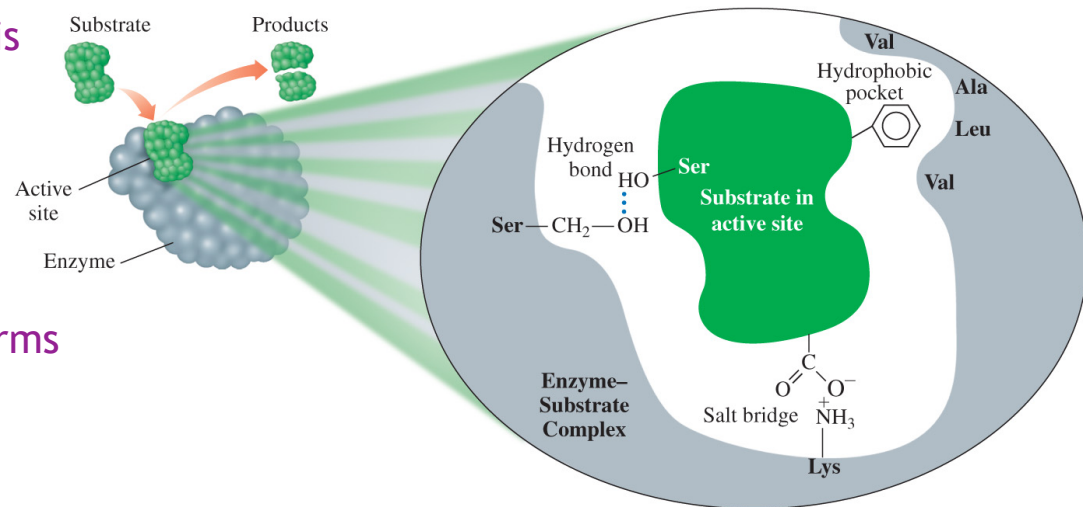
- ▶ Enzymes are classified by the reaction they catalyze. There are six main classes of enzymes.

<u>Class</u>	<u>Type of Reactions Catalyzed</u>
Oxidoreductases	Oxidation–reduction
Transferases	Transfer groups of atoms
Hydrolases	Hydrolysis
Lyases	Add or remove atoms to or from a double bond
Isomerases	Rearrange atoms
Ligases	Use ATP to combine small molecules



Active Sites

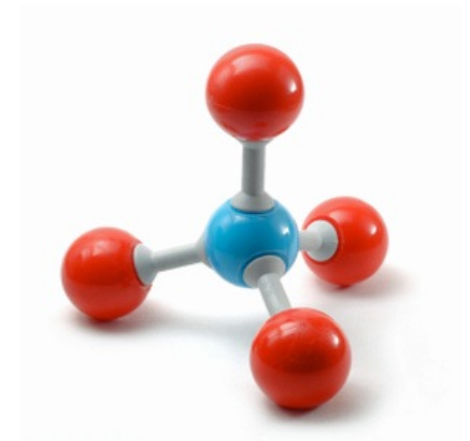
- ▶ On the surface of an enzyme, a small region called an active site binds a substrate and catalyzes a reaction of that substrate.
- ▶ The active site
 - ▶ is a region within an enzyme that fits the shape of the reacting molecule called a substrate
 - ▶ contains amino acid R groups that bind the substrate
 - ▶ releases products when the reaction is complete
- ▶ In an enzyme-catalyzed reaction,
 - ▶ a substrate attaches to the active site
 - ▶ an enzyme-substrate (ES) complex forms
 - ▶ reaction occurs and products are released
 - ▶ an enzyme is used over and over



Enzyme Action: Lock-and-Key Model

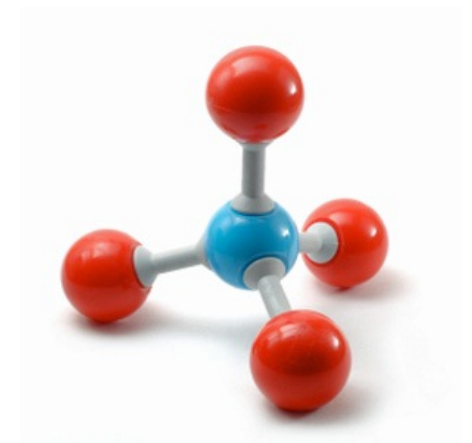
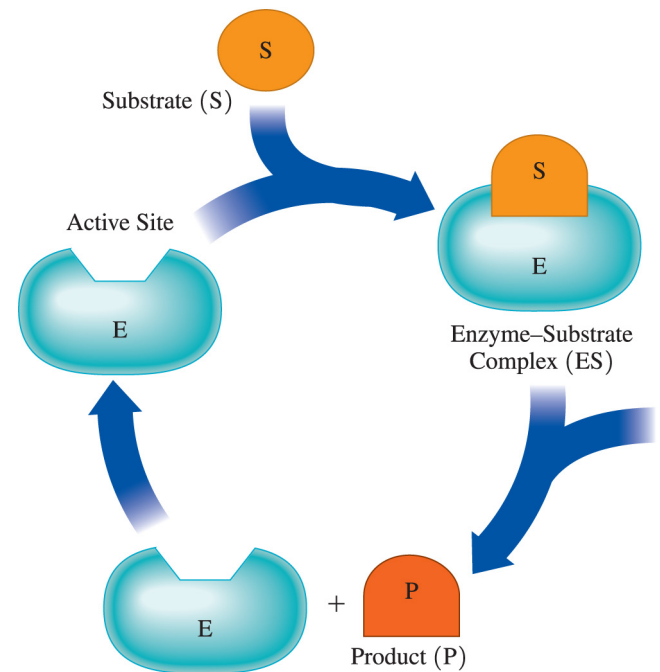
- ▶ In the lock-and-key model, the
 - ▶ active site has a rigid, nonflexible shape
 - ▶ enzyme binds only substrates that exactly fit the active site like a lock
 - ▶ substrate is the key that fits that lock

- ▶ This model was a static one that did not include the flexibility of the tertiary shape of an enzyme and the way the active site can adjust to the shape of a substrate.



Enzyme Action

- ▶ In the induced-fit model,
 - ▶ enzyme structure is flexible, not rigid, and adjusts to the shape of the active site in order to bind the substrate
 - ▶ the range of substrate specificity increases
 - ▶ shape changes improve catalysis during reaction
- ▶ In the induced-fit model, substrate and enzyme work together to acquire a geometrical arrangement that lowers the activation energy of the reaction.



Peptides

▶ Peptides

▶ Peptide Bonds

▶ Structure & Reactions

▶ Peptides

▶ Terminals

▶ Sequencing

▶ Names

▶ Proteins are Big Peptides

▶ Definition

▶ Primary Structure

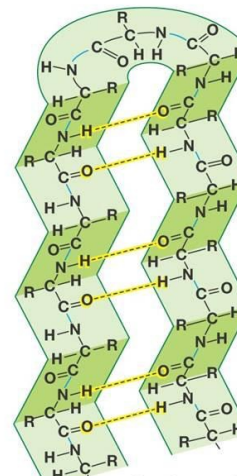
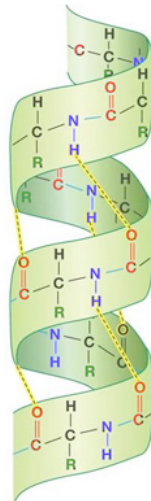
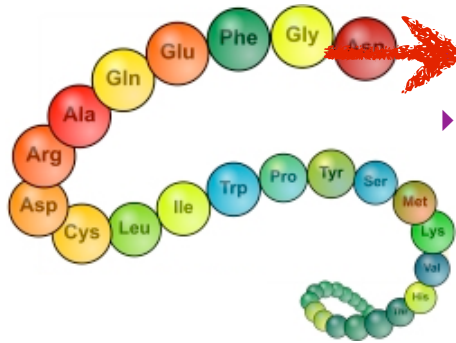
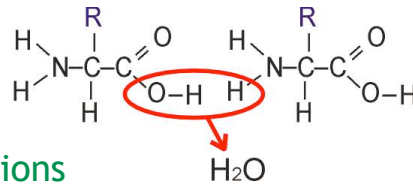
▶ Sequence

▶ Secondary Structure

▶ α Helix

▶ β Sheets

▶ Triple helix



▶ Tertiary Structure

▶ Types of Interactions

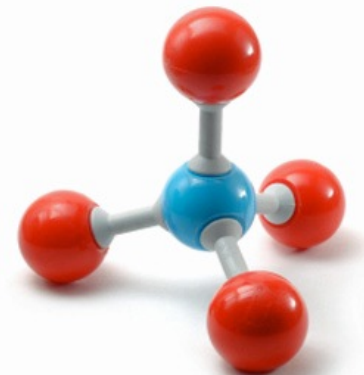
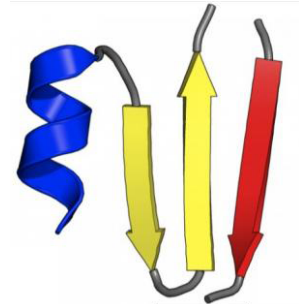
▶ Denaturation

▶ Enzymes

▶ Catalysis

▶ Enzyme activity

▶ Inhibition

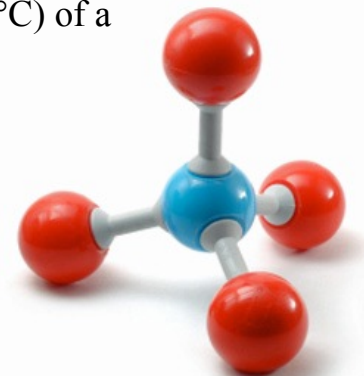


Affecting Enzyme Activity

- ▶ The activity of an enzyme
 - ▶ describes how fast an enzyme catalyzes the reaction that converts a substrate to product
 - ▶ is strongly affected by reaction conditions, which include temperature, pH, and the presence of inhibitors



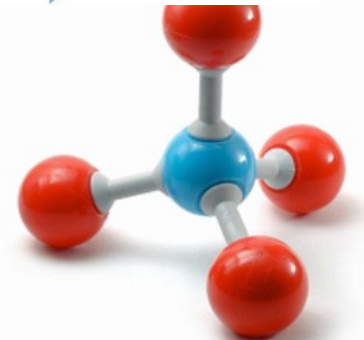
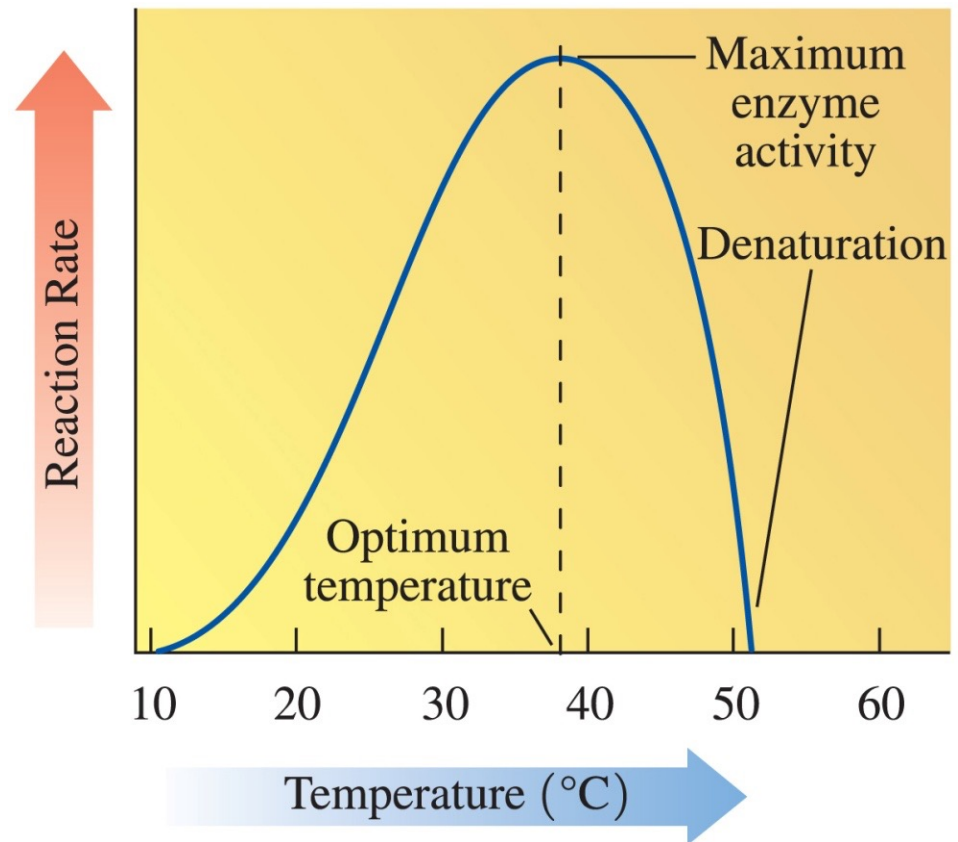
Thermophiles survive in the high temperatures (50 °C to 120 °C) of a hot spring.



Temperature and Enzyme Activity

Enzymes

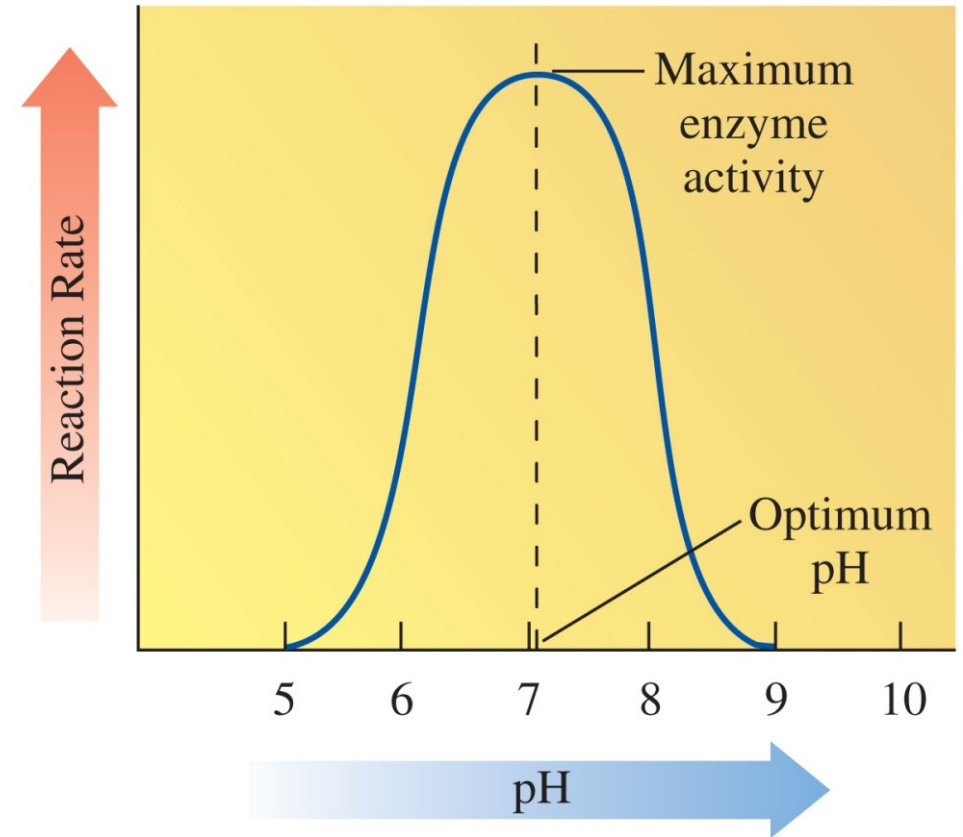
- ▶ are most active at an optimum temperature (usually 37 °C in humans)
- ▶ show little activity at low temperatures.
- ▶ lose activity at temperatures above 50 °C as denaturation occurs with loss of catalytic activity



pH and Enzyme Activity

Enzymes

- ▶ are most active at optimum pH
- ▶ contain R groups of amino acids with proper charges at optimum pH
- ▶ lose activity in low or high pH as tertiary structure is disrupted



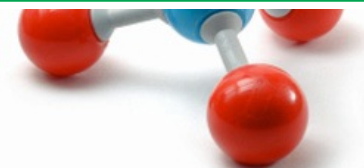
Optimum pH Values

Enzymes in

- ▶ the body have an optimum pH of about 7.4
- ▶ certain organs operate at lower and higher optimum pH values

TABLE 16.11 Optimum pH for Selected Enzymes

Enzyme	Location	Substrate	Optimum pH
Pepsin	Stomach	Peptide bonds	1.5–2.0
Sucrase	Small intestine	Sucrose	6.2
Amylase	Pancreas	Amylose	6.7–7.0
Urease	Liver	Urea	7.0
Trypsin	Small intestine	Peptide bonds	7.7–8.0
Lipase	Pancreas	Lipid (ester bonds)	8.0
Arginase	Liver	Arginine	9.7



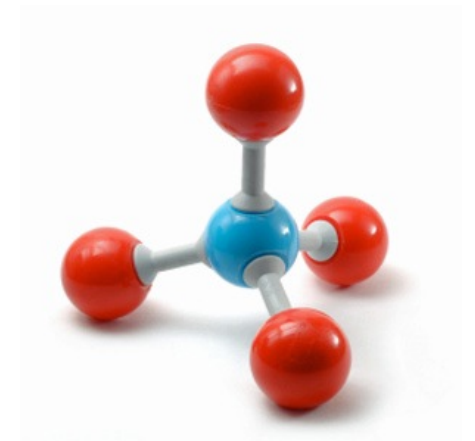
Competitive Inhibition

Inhibitors

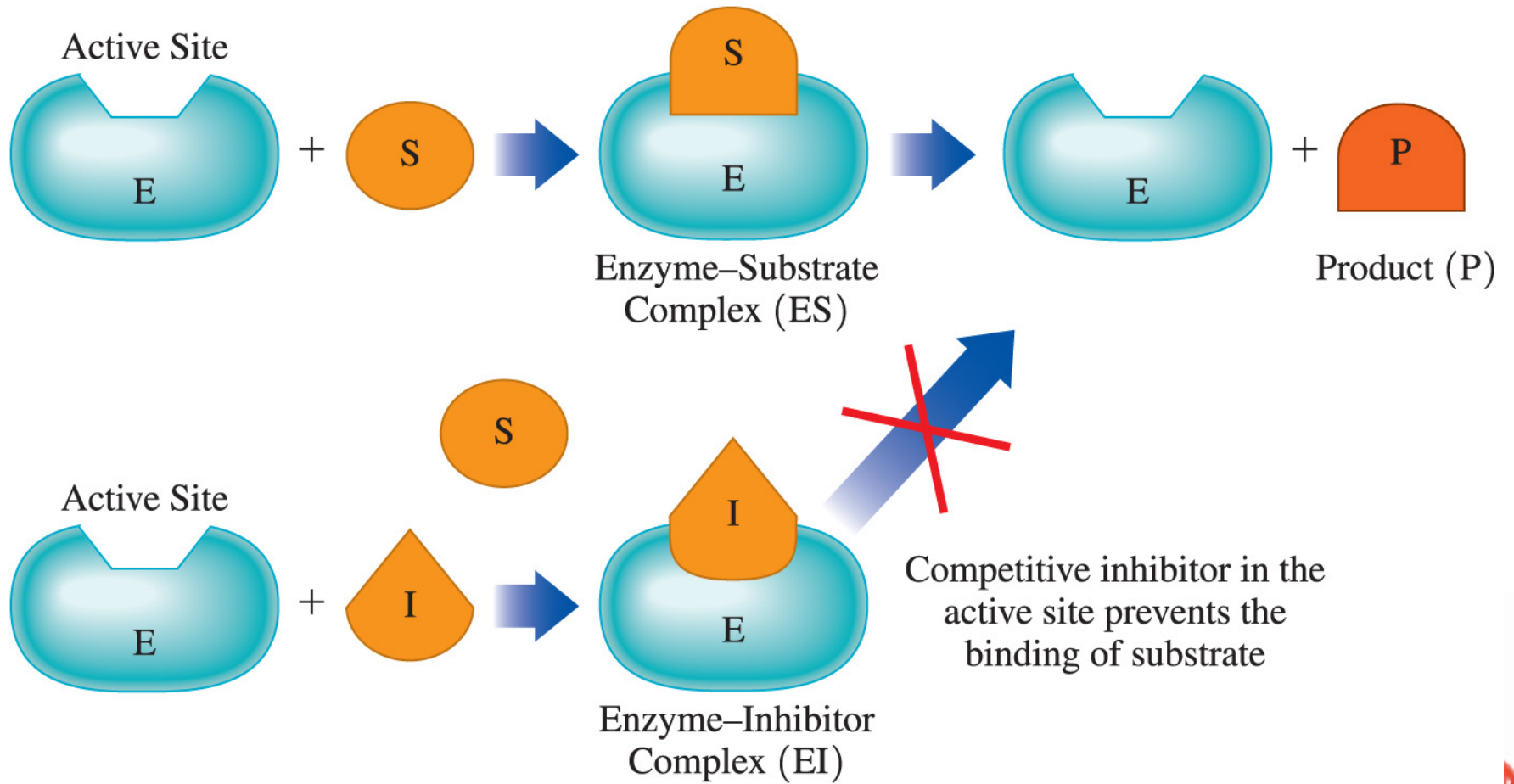
are molecules that cause a loss of catalytic activity
prevent substrates from fitting into the active sites

A competitive inhibitor

- ▶ has a structure that is similar to that of the substrate
- ▶ competes with the substrate for the active site
- ▶ has its effect reversed by increasing substrate concentration



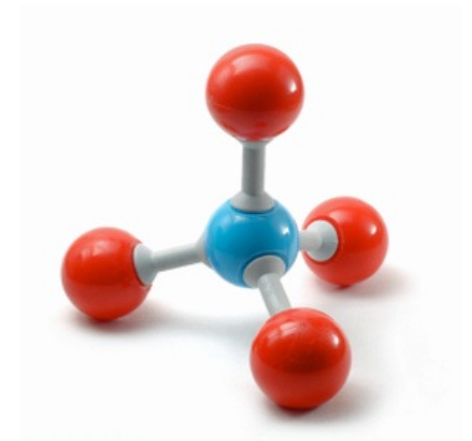
Competitive Inhibition



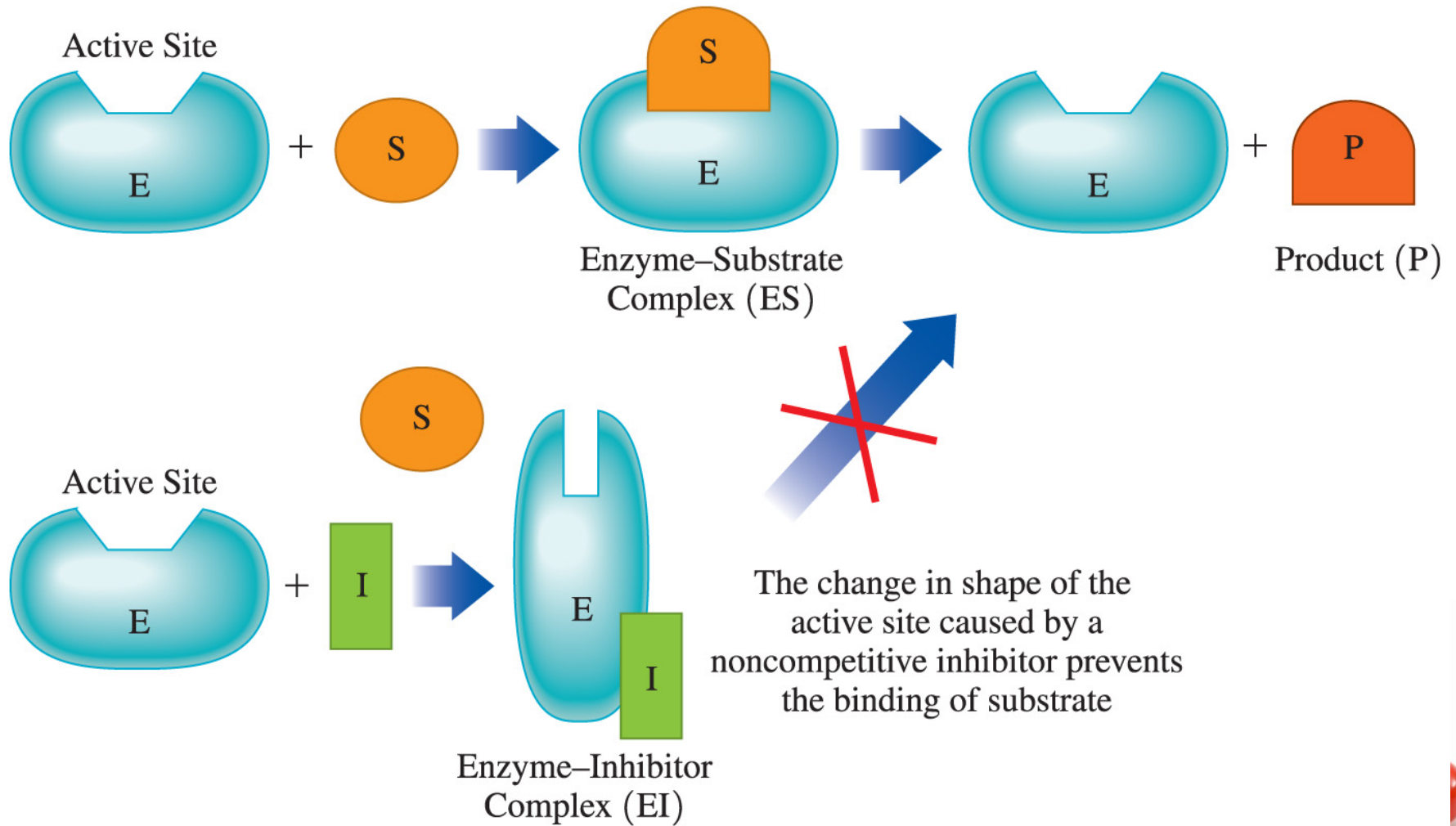
Noncompetitive Inhibition

A noncompetitive inhibitor

- ▶ has a structure that is much different than that of the substrate
- ▶ binds to an enzyme at a site other than the active site and distorts the shape of the enzyme by altering the shape of the active site
- ▶ prevents the binding of the substrate
- ▶ cannot have its effect reversed by adding more substrate



Noncompetitive Inhibition

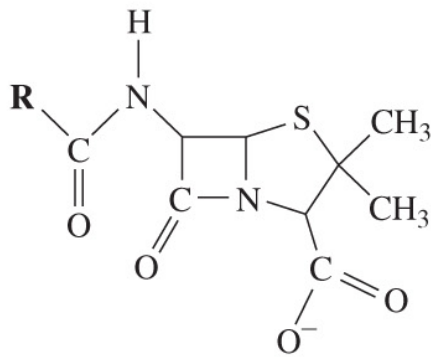


Irreversible Inhibition

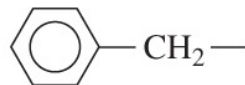
An irreversible inhibitor

- ▶ is a molecule that causes the enzyme to lose all activity
- ▶ is often a toxic substance that destroys enzymes
- ▶ usually forms a covalent bond with an amino acid side chain preventing catalytic activity
- ▶ may be a nerve gas, an insecticide, or an antibiotic

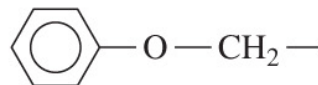
R Groups for Penicillin Derivatives



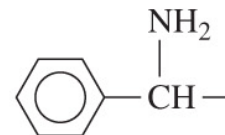
Penicillin



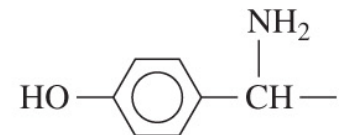
Penicillin G



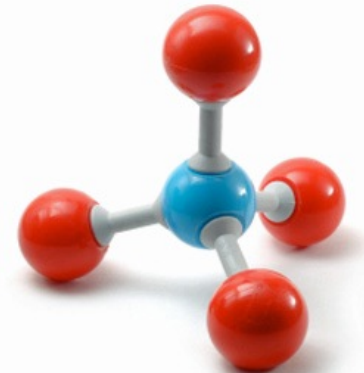
Penicillin V



Ampicillin



Amoxicillin



Competitive, Noncompetitive, and Irreversible Inhibitors

TABLE 16.12 Summary of Competitive, Noncompetitive, and Irreversible Inhibitors

Characteristics	Competitive	Noncompetitive	Irreversible
Shape of Inhibitor	similar shape to the substrate	does not have a similar shape to the substrate	does not have a similar shape to the substrate
Binding to Enzyme	competes for and binds at the active site	binds away from the active site to change the shape of the enzyme and its activity	forms a covalent bond with the enzyme
Reversibility	adding more substrate reverses the inhibition	not reversed by adding more substrate, but by a chemical change that removes the inhibitor	permanent, not reversible



Questions?

