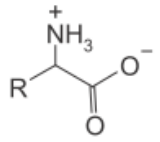
Amino acids and peptides

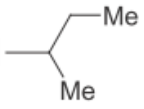
Amino acids, as the name implies, contain both an amino and a carboxylic acid group, and are the building blocks of proteins. Twenty different amino acids are used to synthesize proteins, and these are alanine (Ala, A), arginine (Arg, R), asparagine (Asn, N), aspartic acid (Asp, D), cysteine (Cys, C), glutamine (Gln, Q), glutamic acid (Glu, E), glycine (Gly, G), histidine (His, H), isoleucine (Ile, I), leucine (Leu, L), lysine (Lys, K), methionine (Met, M), phenylalanine (Phe, F), proline (Pro, P), serine (Ser, S), threonine (Thr, T), tryptophan (Trp, W), tyrosine (Tyr, Y) and valine (Val, V). The shape and other properties of each protein are dictated by the precise sequence of amino acids in it. Most amino acids are optically active, and almost all the 20 naturally occurring amino acids that comprise proteins are of the L-form. While the (*R*) and (*S*)-system can be used to describe the absolute stereochemistry of amino acids, conventionally the D and L-system is more popular for amino acids.

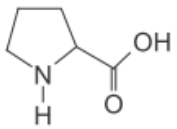
Aliphatic aminoacids



Alanine R = Me
Glycine R = H
Leucine R = $CH_2CH(CH_3)_2$
Valine R = $CH(CH_3)_2$

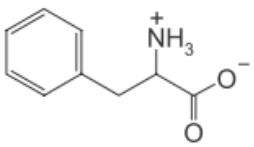
Isoleucine R =



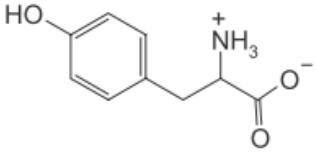


Proline
A cyclic amino acid

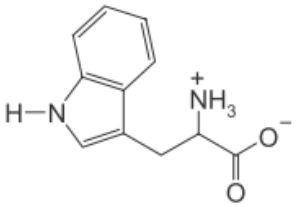
Aromatic amino acids



Phenyl alanine

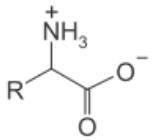


Tyrosine



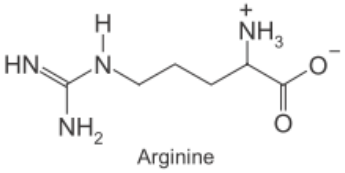
Tryptophan

Acidic amino acids

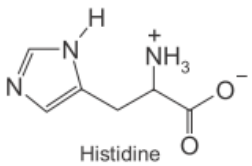


Aspartic acid R = CH_2COOH
Glutamic acid R = CH_2CH_2COOH

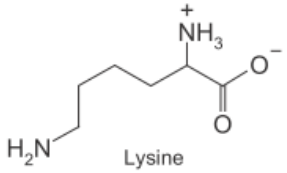
Basic amino acids



Arginine

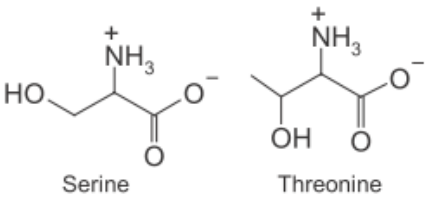


Histidine

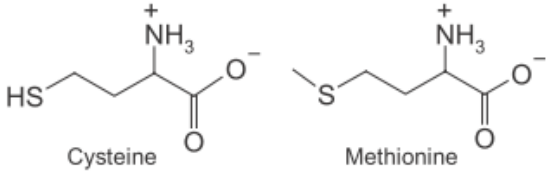


Lysine

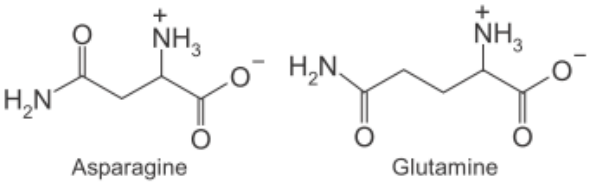
Hydroxylic amino acids



Sulphur-containing amino acids

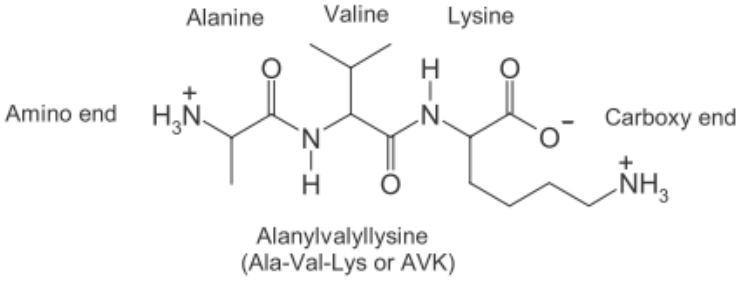


Amidic amino acids



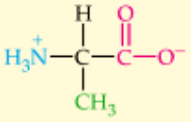
Peptides are biologically important polymers in which α-amino acids are joined into chains through amide linkages, called *peptide bonds*. A peptide bond is formed from the amino group ($-NH_2$) of one amino acid and the carboxylic acid group ($-COOH$) of another. The term *peptide bond* implies the existence of the peptide group, which is commonly written in text as $-CONH-$. Two molecules (amino acids) linked by a peptide bond form a *dipeptide*. A chain of molecules linked by peptide bonds is called a *polypeptide*. Proteins are large peptides. A protein is made up of one or more polypeptide chains, each of which consists of amino acids. Instead of writing out complex formulae, sequences of amino acids are commonly written using the three- or one-letter codes e.g. Ala–Val–Lys (three letter) or

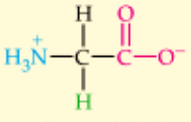
AVK (one letter). The ends of a peptide are labelled as the amino end or amino terminus, and the carboxy end or carboxy terminus.

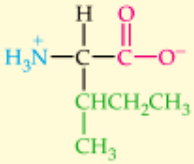


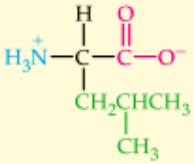
Large peptides of biological significance are known by their trivial names; e.g., insulin is an important peptide composed of 51 amino acid residues.

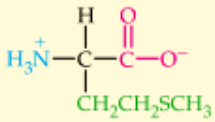
Nonpolar Side Chains

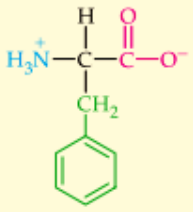

Alanine, Ala (6.0)

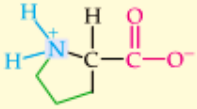

Glycine, Gly (6.0)

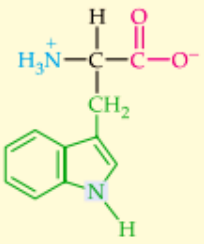

Isoleucine, Ile (6.0)

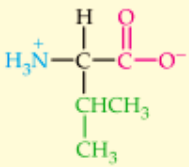

Leucine, Leu (6.0)


Methionine, Met (5.7)

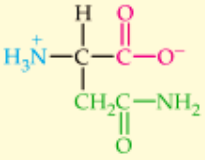

Phenylalanine, Phe (5.5)

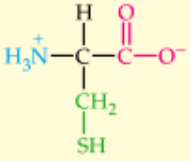

Proline, Pro (6.3)

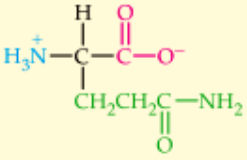

Tryptophan, Trp (5.9)

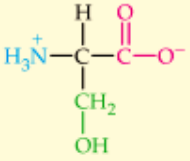

Valine, Val (6.0)

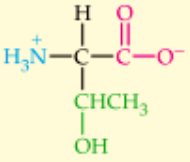
Polar, Neutral Side Chains

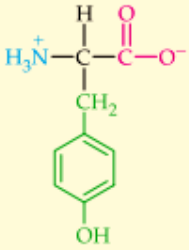

Asparagine, Asn (5.4)


Cysteine, Cys (5.0)

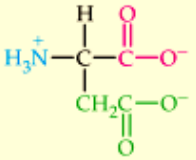

Glutamine, Gln (5.7)

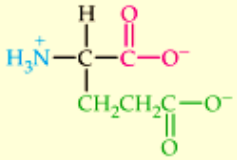

Serine, Ser (5.7)


Threonine, Thr (5.6)

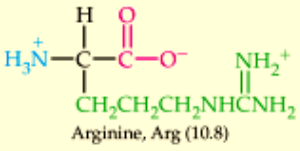

Tyrosine, Tyr (5.7)

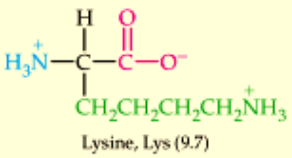
Acidic Side Chains

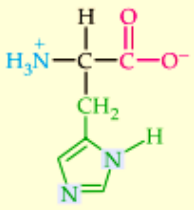

Aspartic acid, Asp (3.0)
(Aspartate)


Glutamic acid, Glu (3.2)
(Glutamate)

Basic Side Chains

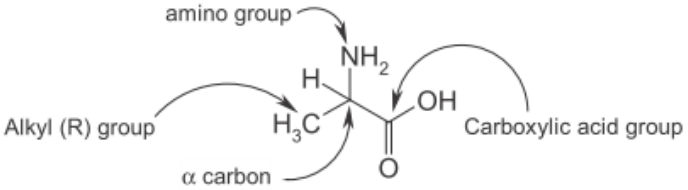

Arginine, Arg (10.8)


Lysine, Lys (9.7)

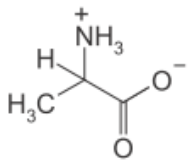

Histidine, His (7.6)

Fundamental structural features of amino acids

Each amino acid consists of a carbon atom to which is attached a hydrogen atom, an amino group ($-NH_2$), a carboxyl group ($-COOH$) and one of 20 different 'R' groups. It is the structure of the R group (side chain) that determines the identity of an amino acid and its special properties. The side chain (R group), depending on the functional groups, can be aliphatic, aromatic, acidic, basic, hydroxylic, sulphur containing or amidic (containing amide group). However, proline has an unusual ring structure, where the side chain is bonded at its terminus to the main chain nitrogen.



Alanine
An amino acid



The zwitterionic
structure of alanine

An amino acid, with an overall charge of zero, can contain within the same molecule two groups of opposite charge. Molecules containing oppositely charged groups are known as *zwitterions*. For amino acids, a *zwitterionic* structure is possible because the basic amino group can accept a proton and the acidic carboxylic group can donate a proton.

Essential amino acids

All living organisms can synthesize amino acids. However, many higher animals are deficient in their ability to synthesize all of the amino acids they need for their proteins. Thus, these higher animals require certain amino acids as a part of their diet. Human beings also must include in their diet adequate amounts of eight different amino acids, which they cannot synthesize in their body. These are known as *essential* amino acids. The eight essential amino acids are valine, leucine, isoleucine, phenylalanine, tryptophan, threonine, methionine and lysine. Sometimes, arginine and histidine are also included in the category of essential amino acids.

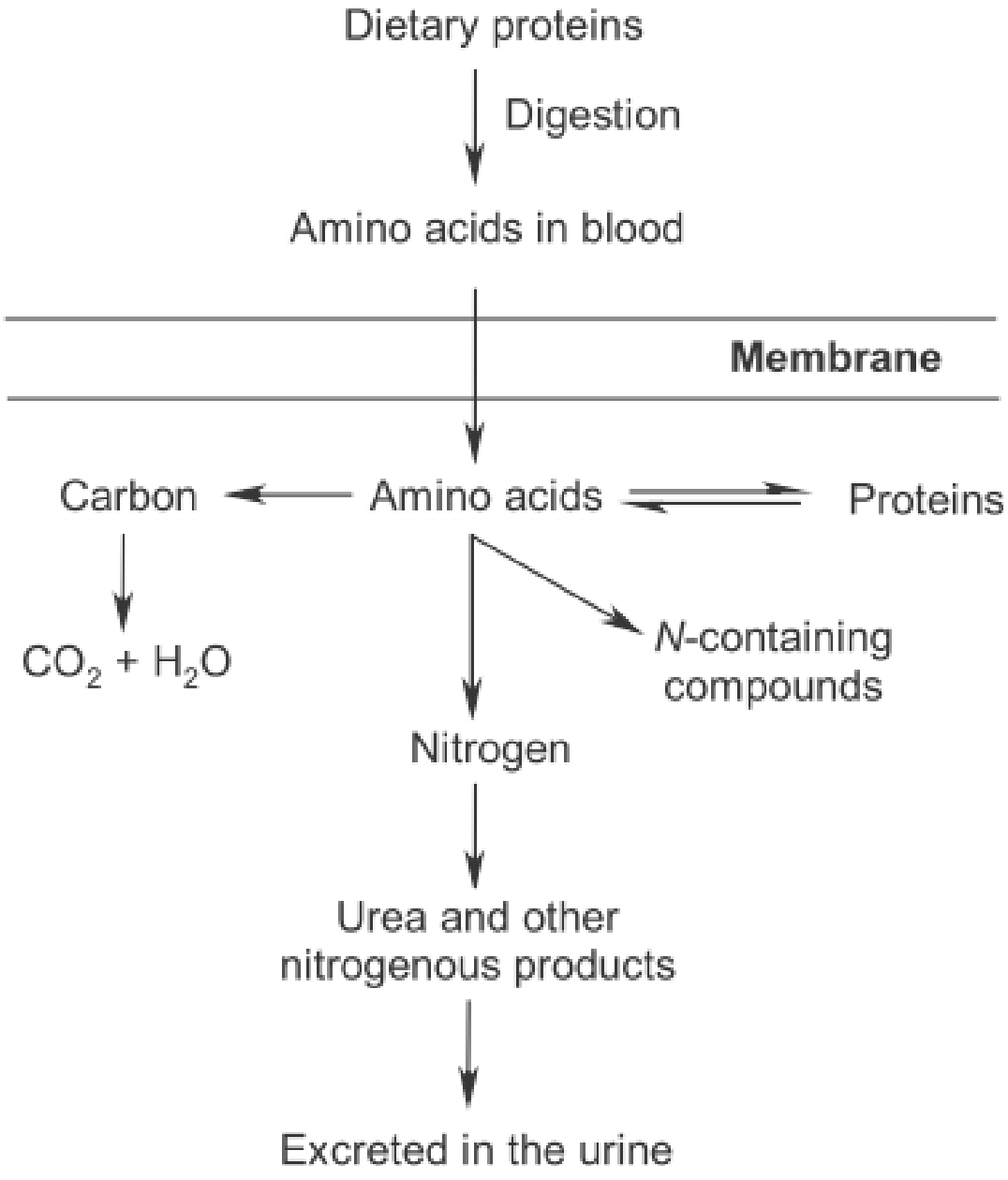
Glucogenic and ketogenic amino acids

The carbon skeletons of the amino acids can be used to produce metabolic energy. Several amino acids can be classified as *glucogenic* and *ketogenic* because of their degradation products.

Amino acids in human body

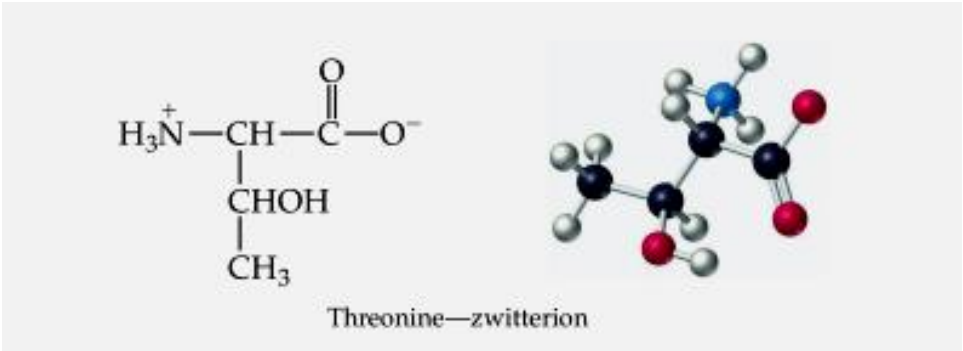
All human tissues are capable of synthesizing the nonessential amino acids, amino acid remodelling and conversion of non-amino-acid carbon skeletons into amino acids and other derivatives that contain nitrogen. However, the liver is the major site of metabolism of nitrogenous compounds in the body. Dietary proteins are the primary source of essential amino acids (or nitrogen). Digestion of dietary proteins produces amino acids, which are absorbed through epithelial cells and enter the blood. Various cells take up these amino acids that enter the cellular pools.

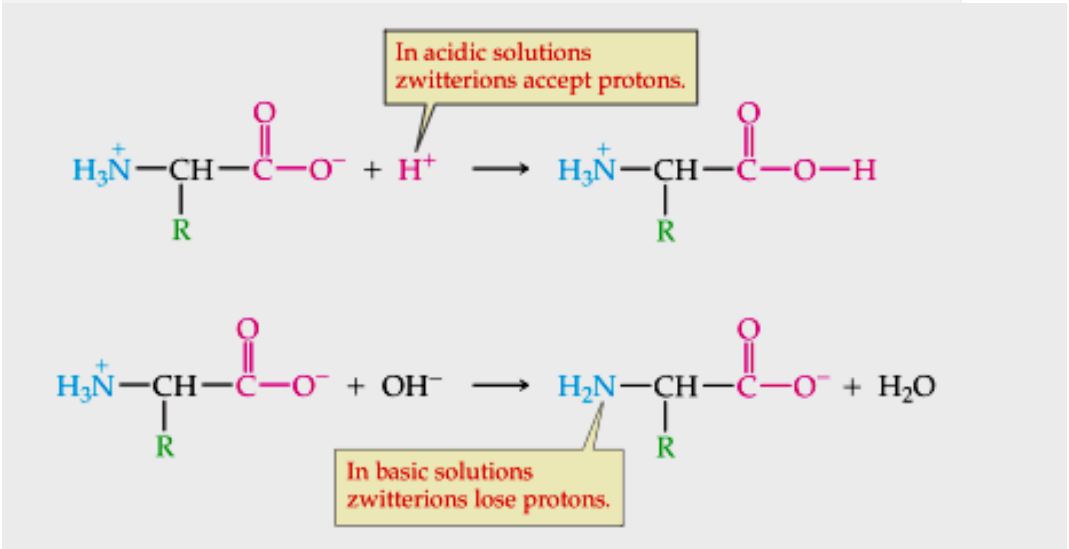
In our bodies, amino acids are used for the synthesis of proteins and other nitrogen-containing compounds, or they are oxidized to produce energy. Cellular proteins, hormones (thyroxine, epinephrine and insulin), neurotransmitters, creatine phosphate, the haem of haemoglobin, cytochrome, melanin (skin pigment) and nucleic acid bases (purine and pyrimidine) are examples of amino-acid-derived nitrogen-containing biologically important group of compounds found in humans.



Acid–base properties of amino acids

The neutral forms of amino acids are *zwitterions*. This is why amino acids are insoluble in apolar aprotic solvents, e.g. ether, but most nonprotonated amines and unionized carboxylic acids dissolve in ether. For the same reason, amino acids usually have high melting points, e.g. the m.p. of glycine is 262 °C, and large dipole moments. The high melting points and greater water solubility than in ether are saltlike characteristics, not the characteristics of uncharged organic molecules. This saltlike characteristic is found in all zwitterionic compounds. Water is the best solvent for most amino acids because it solvates ionic groups much as it solvates the ions of a salt. A large dipole moment is characteristic of zwitterionic compounds that contain great deal of separated charge. The pK_a values for amino acids are also typical of zwitterionic forms of neutral molecules. Peptides can also exist as zwitterions; i.e., at pH values near 7, amino groups are protonated and carboxylic acid groups are ionized.





Isoelectric points of amino acids and peptides

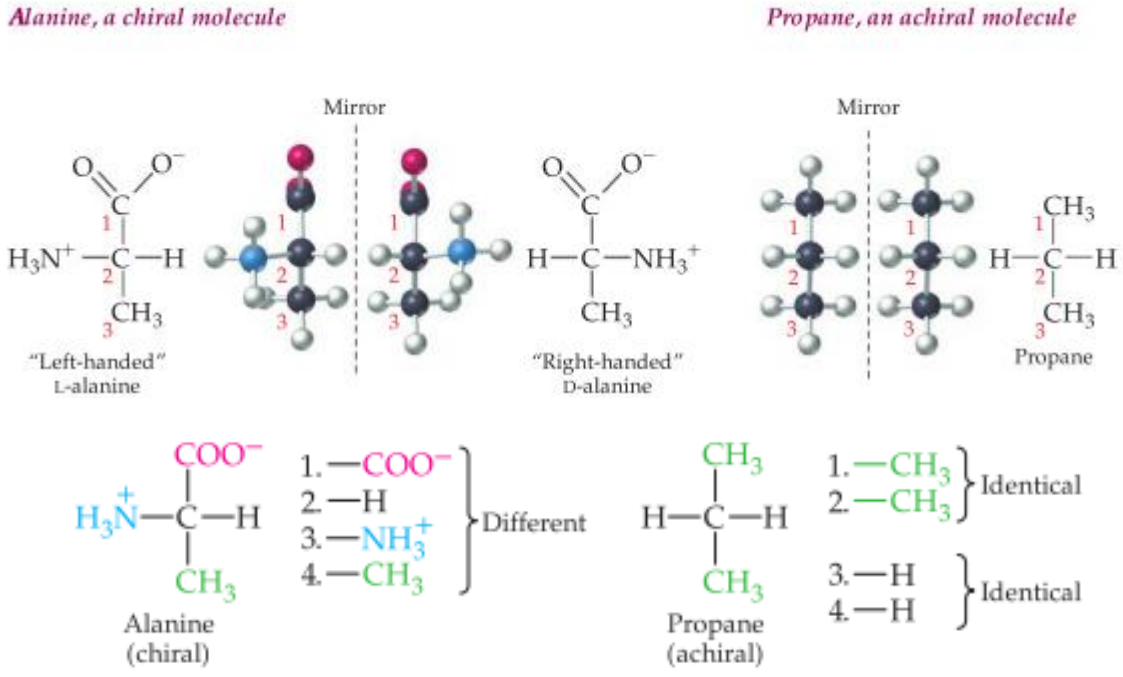
Isoelectric point (*pI*) or *isoelectric pH* is the pH at which a molecule carries no net electrical charge, i.e. zero charge. It is an important measure of the acidity or basicity of an amino acid. To have a sharp *isoelectric point*, a molecule must be amphoteric, i.e. it must have both acidic and basic functional groups, as found in amino acids. For an amino acid with only one amino and one carboxylic acid group, the p*I* can be calculated from the pK_a values of this molecule.

$$pI = \frac{pK_{a1} + pK_{a2}}{2}$$

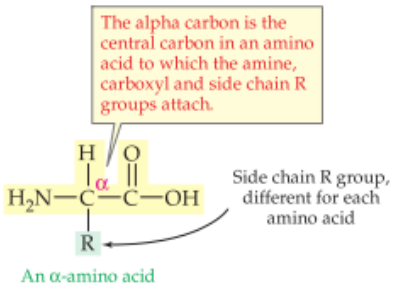
For amino acids with more than two ionizable groups, e.g. lysine, the same formula is used but the two pK_a values used are those of the two groups that lose and gain a charge from the neutral form of the amino acid.

The process that separates proteins according to their isoelectric point is called *isoelectric focusing*. At a pH below the p*I* proteins carry a net positive charge, whereas above the p*I* they carry a net negative charge. Appling this principle, *gel electrophoretic methods* have been developed to separate proteins. The pH of an electrophoretic gel is determined by the buffer used for that gel. If the pH of the buffer is above the p*I* of the protein being run, the protein will migrate to the positive pole (negative charge is attracted to a positive pole). Similarly, if the pH of the buffer is below the p*I* of the protein being run, the protein will migrate to the negative pole of the gel (positive charge is attracted to the negative pole). If the protein is run with a buffer pH that is equal to the p*I*, it will not migrate at all. This also applies for individual amino acids.

Optical isomerism of aminoacids



Proteins are polymers of **amino acids**. Every amino acid in a protein contains an amine group a carboxyl group (COOH), and an R group called a **side chain**, all bonded to a central carbon atom known as the alpha (α) carbon. The amino acids in proteins are **alpha-amino (α-amino) acids**—the amine group in each is connected to the carbon atom "*alpha* to" (next to) the carboxylic acid group. The R groups may be hydrocarbons, or they may contain a functional group:



Protein A large biological molecule made of many amino acids linked together through amide (peptide) bonds.

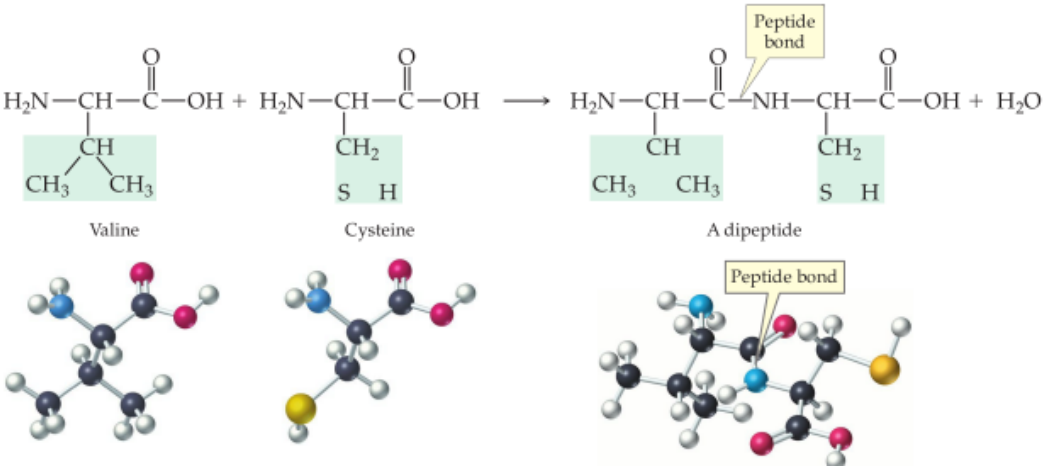
Amino acid A molecule that contains both an amino group and a carboxylic acid functional group.

Side chain (amino acid) The group bonded to the carbon next to the carboxyl group in an amino acid; different in different amino acids.

Alpha- ($\alpha-$) amino acid An amino acid in which the amino group is bonded to the carbon atom next to the —COOH group.

Two or more amino acids can link together by forming amide bonds (, Section 17.4), which are known as **peptide bonds** when they occur in proteins. A *dipeptide* results from the formation of a peptide bond between the $—NH_2$ group of one amino acid and the —COOH group of a second amino acid. For example, valine and cysteine are connected in a dipeptide as follows:

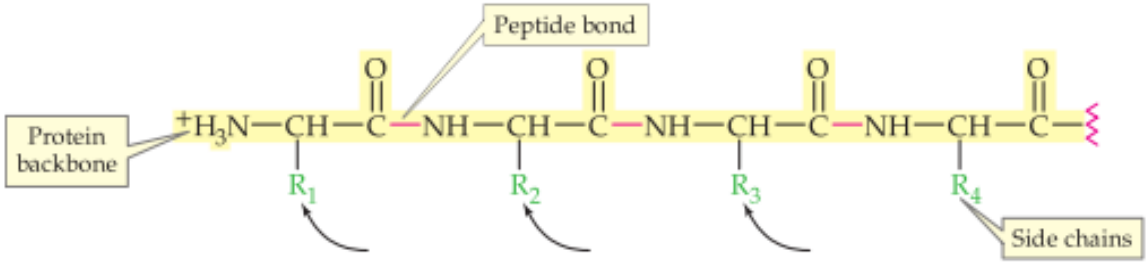
Peptide bond An amide bond that links two amino acids together.



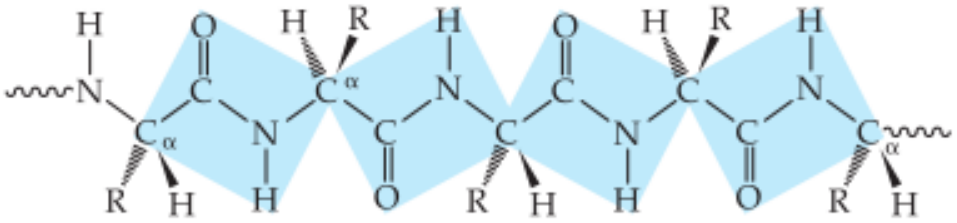
Proteins have four levels of structure, each of which is explored later in this chapter.

- *Primary structure* is the sequence of amino acids in a protein chain (Section 18.7).
- *Secondary structure* is the regular and repeating spatial organization of neighboring segments of single protein chains (Section 18.9).
- *Tertiary structure* is the overall shape of a protein molecule (Section 18.10) produced by regions of secondary structure combined with the overall bending and folding of the protein chain.
- *Quaternary structure* refers to the overall structure of proteins composed of more than one polypeptide chain (Section 18.11).

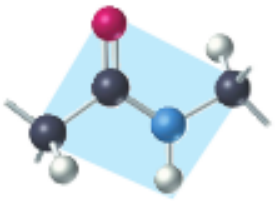
Primary Protein Structure

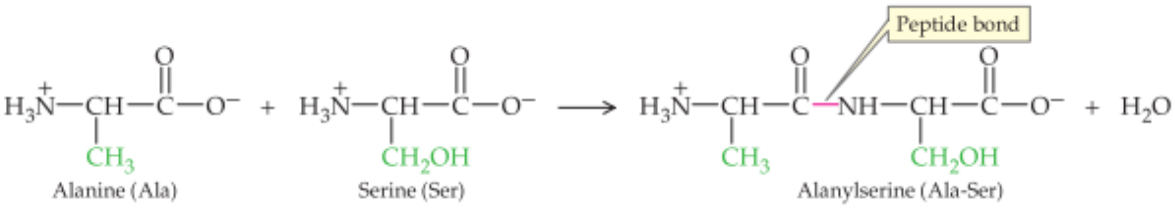


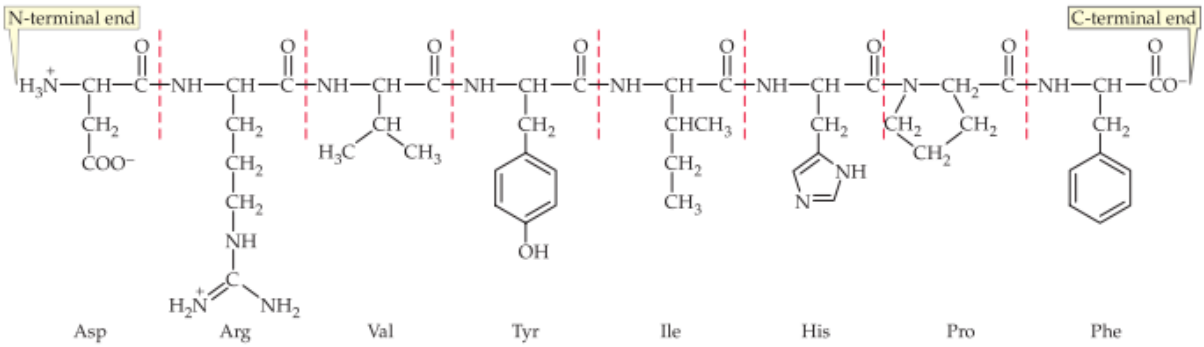
Planar units along a protein chain



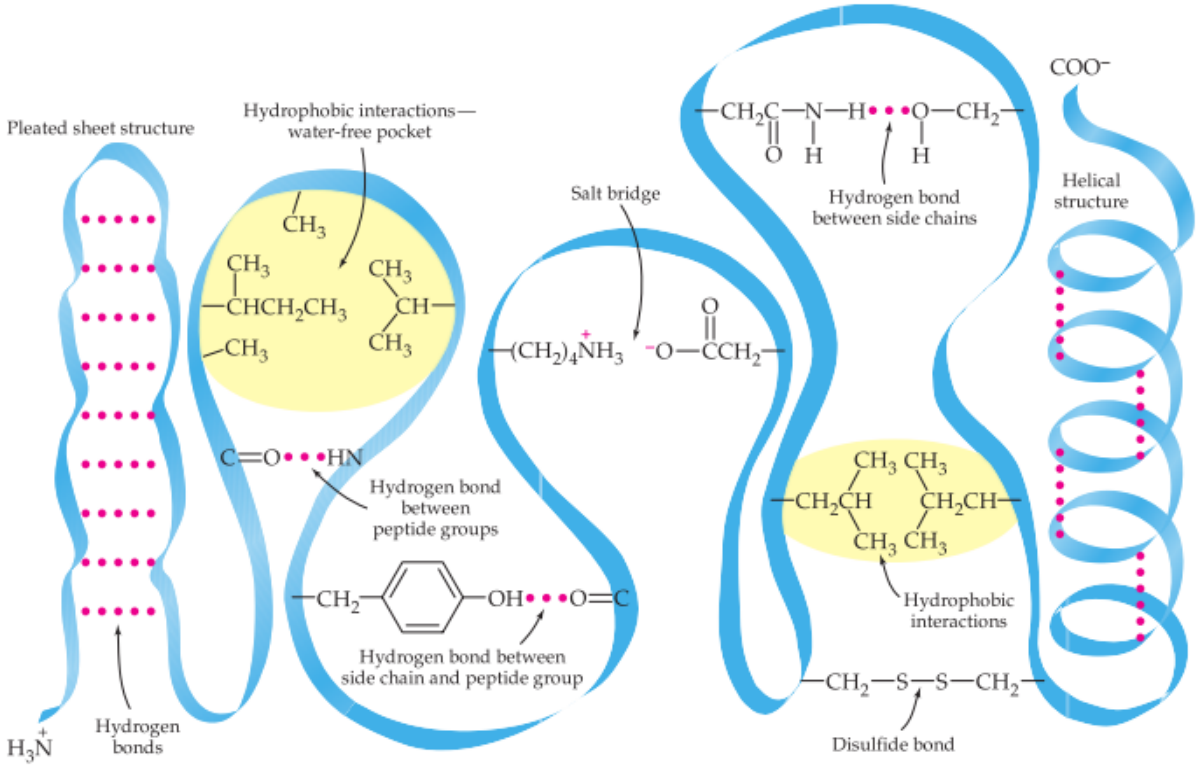
One planar unit

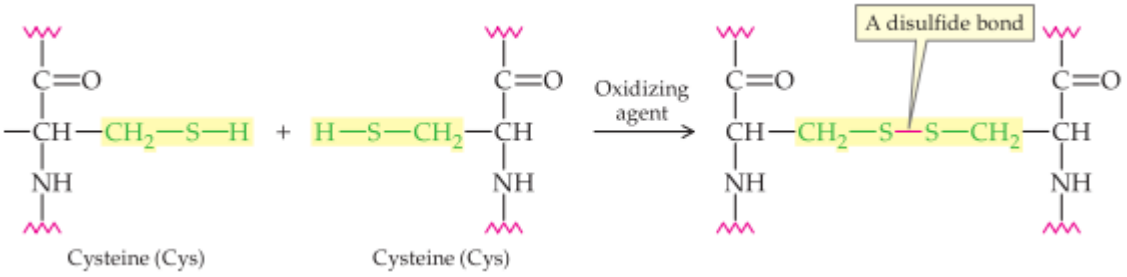


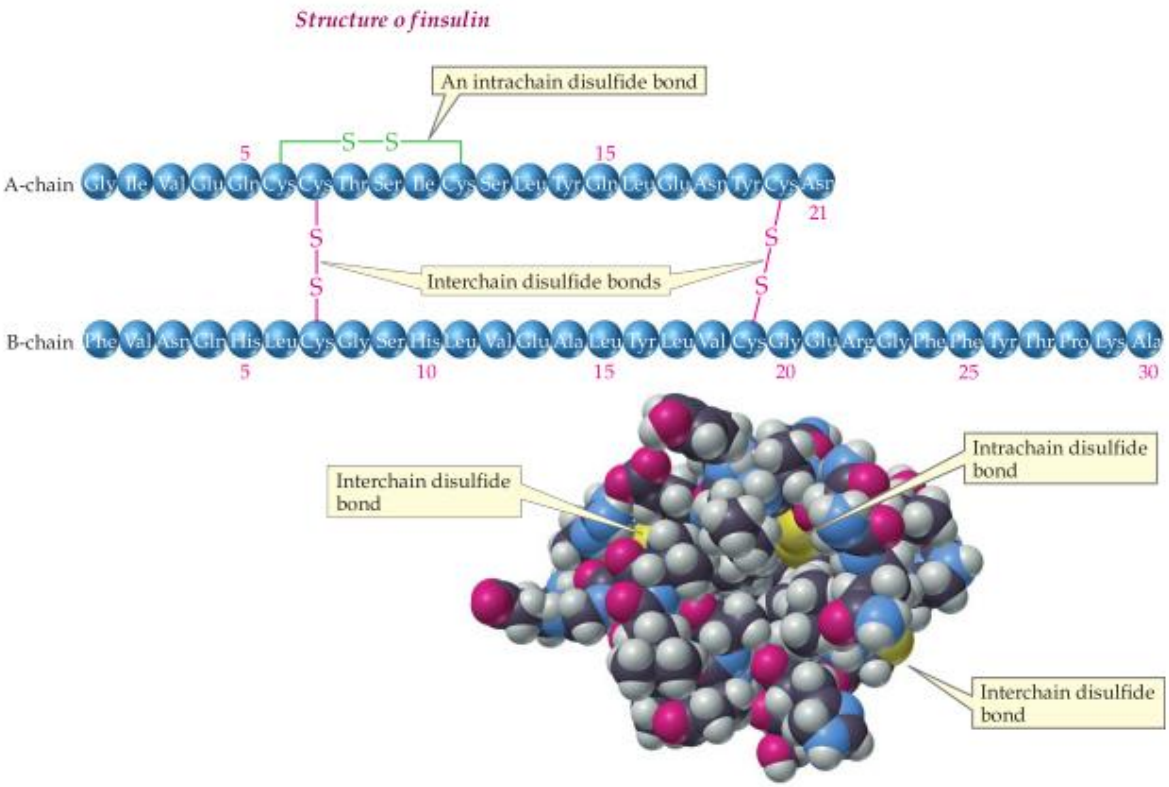




Secondary structure

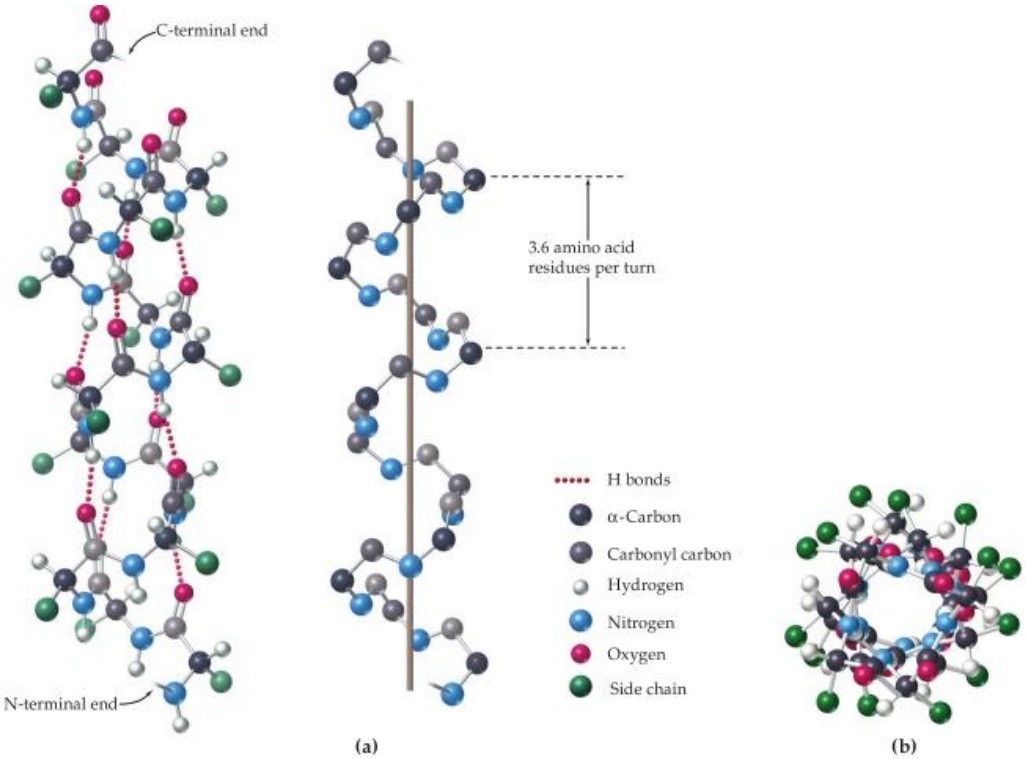




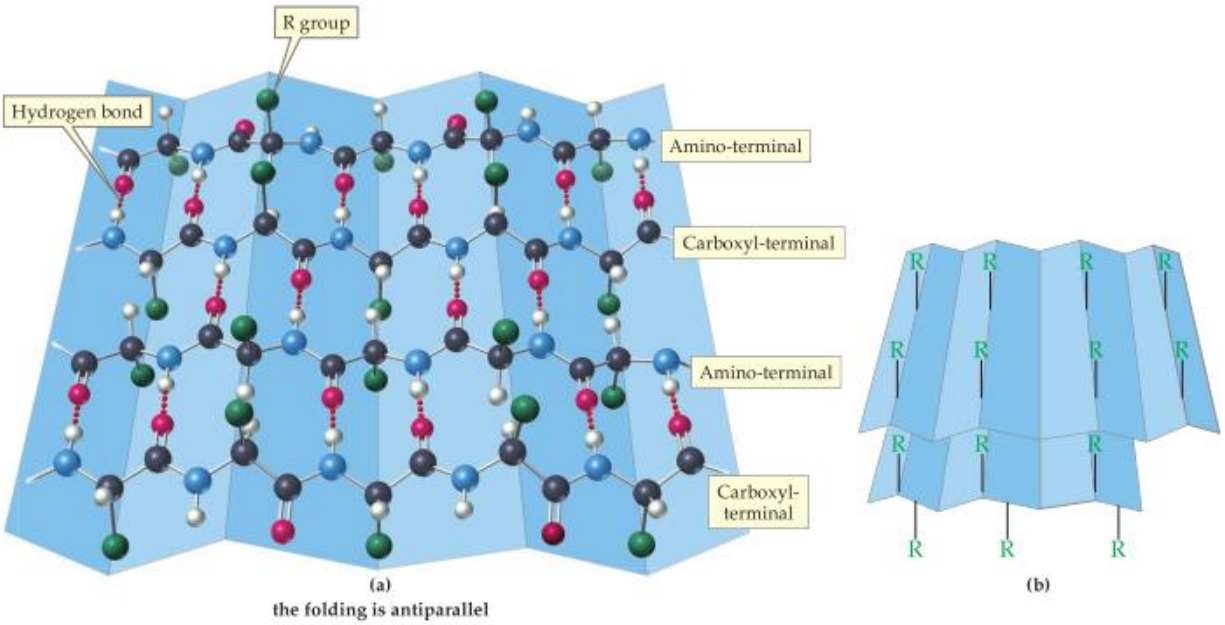


Secondary Protein Structure

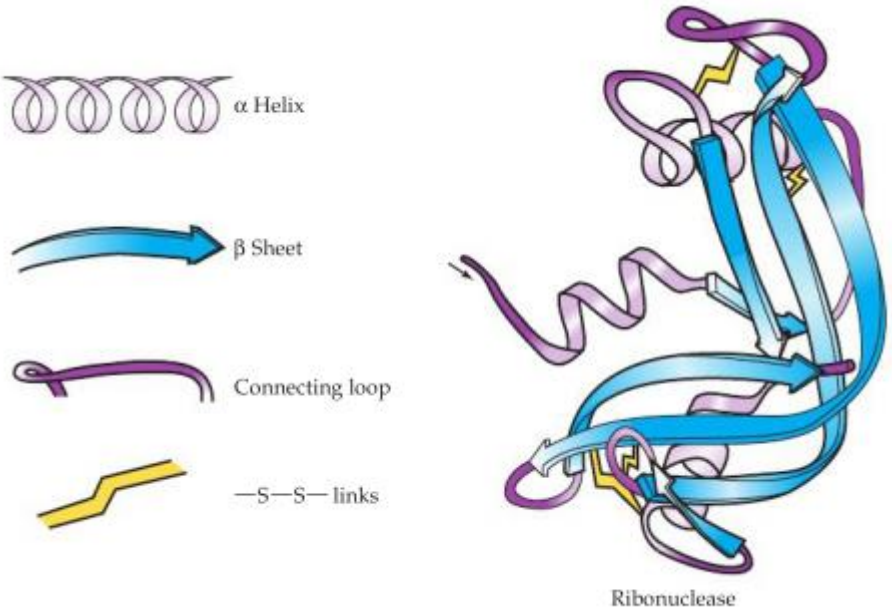
A-helix



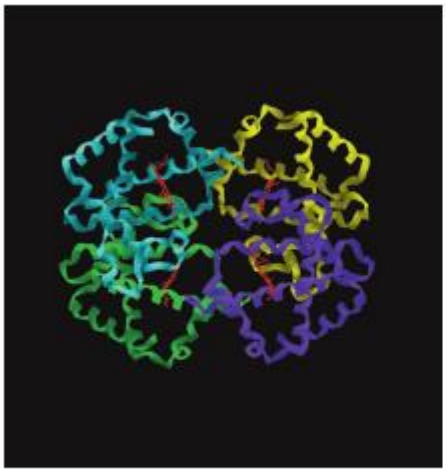
β-Sheet

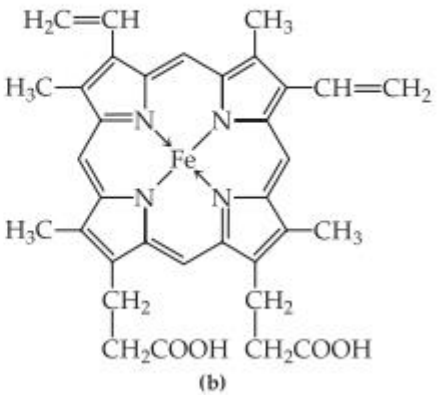


Tertiary Protein Structure



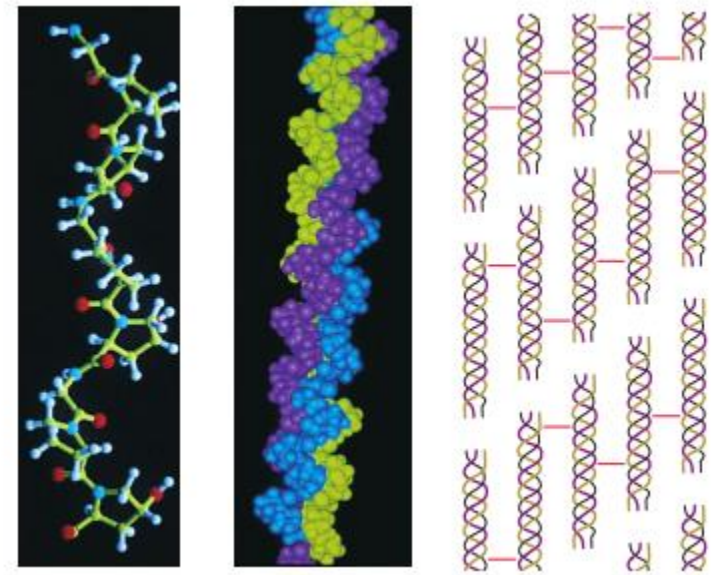
Quaternary Protein Structure


(a)



(b)

hemoglobine



collagene

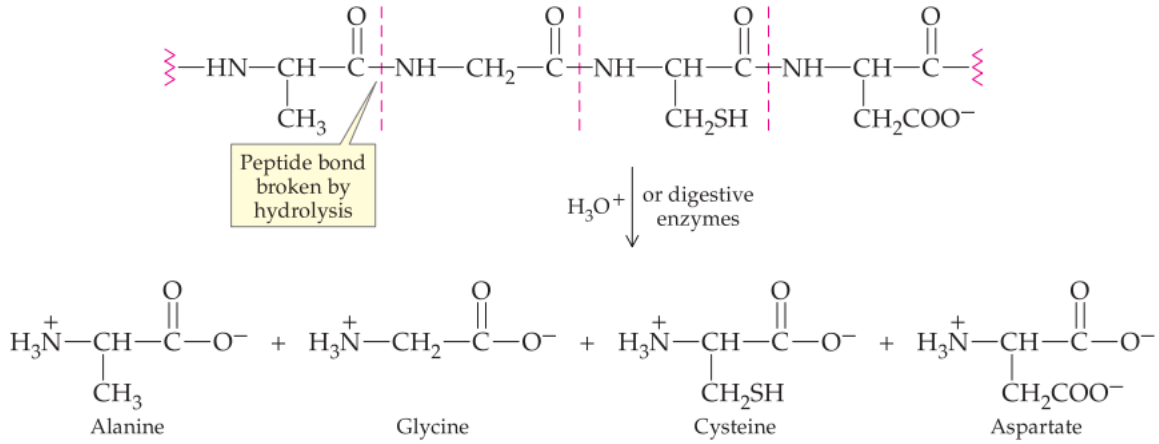
- **Classes of proteins**
- *Fibrous proteins* are tough, insoluble, and composed of fibers and sheets; *globular proteins* are water-soluble and have chains folded into compact shapes.
- *Simple proteins* contain only amino acid residues; *conjugated proteins* include one or more non–amino acid units.

Classification of peptides by function

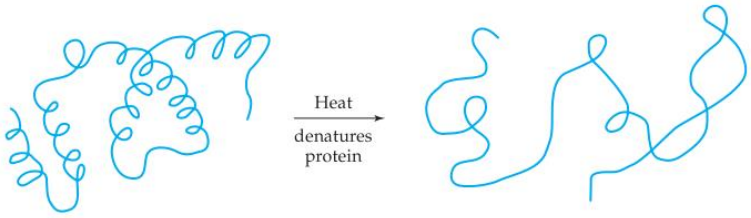
TYPE	FUNCTION	EXAMPLE
Enzymes	Catalysts	*Amylase*—begins digestion of carbohydrates by hydrolysis
Hormones	Regulate body functions by carrying messages to receptors	*Insulin*—facilitates use of glucose for energy generation
Storage proteins	Make essential substances available when needed	*Myoglobin*—stores oxygen in muscles
Transport proteins	Carry substances through body fluids	*Serum albumin*—carries fatty acids in blood
Structural proteins	Provide mechanical shape and support	*Collagen*—provides structure to tendons and cartilage
Protective proteins	Defend the body against foreign matter	*Immunoglobulin*—aids in destruction of invading bacteria
Contractile proteins	Do mechanical work	*Myosin and actin*—govern muscle movement

Chemical Properties of Proteins

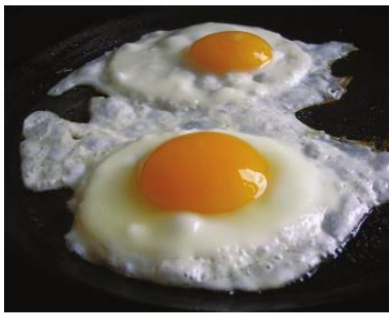
Protein Hydrolysis



Protein Denaturation



Denaturation is accompanied by changes in physical, chemical, and biological properties. Solubility is often decreased by denaturation, as occurs when egg white is cooked and the albumins coagulate into an insoluble white mass. Enzymes lose their catalytic activity and other proteins are no longer able to carry out their biological functions when their shapes are altered by denaturation.



▲ Protein denaturation in action: The egg white denatures as the egg fries.

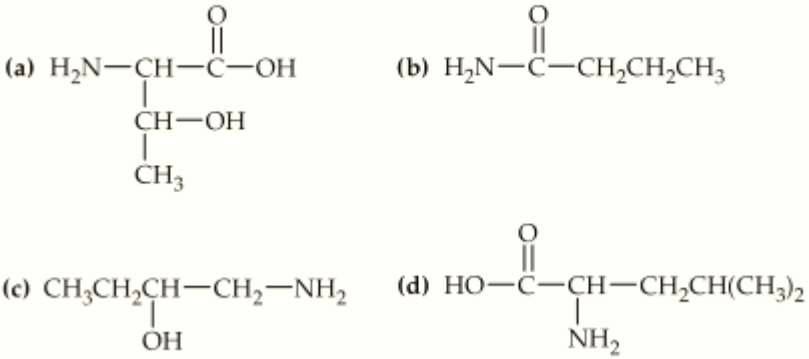
Agents that cause denaturation include heat, mechanical agitation, detergents, organic solvents, extremely acidic or basic pH, and inorganic salts.

- **Heat** The weak side-chain attractions in globular proteins are easily disrupted by heating, in many cases only to temperatures above 50 °C. Cooking meat converts some of the insoluble collagen into soluble gelatin, which can be used in glue and for thickening sauces.
- **Mechanical agitation** The most familiar example of denaturation by agitation is the foam produced by beating egg whites. Denaturation of proteins at the surface of the air bubbles stiffens the protein and causes the bubbles to be held in place.
- **Detergents** Even very low concentrations of detergents can cause denaturation by disrupting the association of hydrophobic side chains.
- **Organic compounds** Polar solvents such as acetone and ethanol interfere with hydrogen bonding by competing for bonding sites. The disinfectant action of ethanol, for example, results from its ability to denature bacterial protein.
- **pH change** Excess H^+ or OH^- ions react with the basic or acidic side chains in amino acid residues and disrupt salt bridges. One familiar example of denaturation by pH change is the protein coagulation that occurs when milk turns sour because it has become acidic.
- **Inorganic salts** Sufficiently high concentrations of ions can disturb salt bridges.

PROBLEMS

1.

Indicate whether each of the molecules shown below is an α-amino acid or not and explain why.



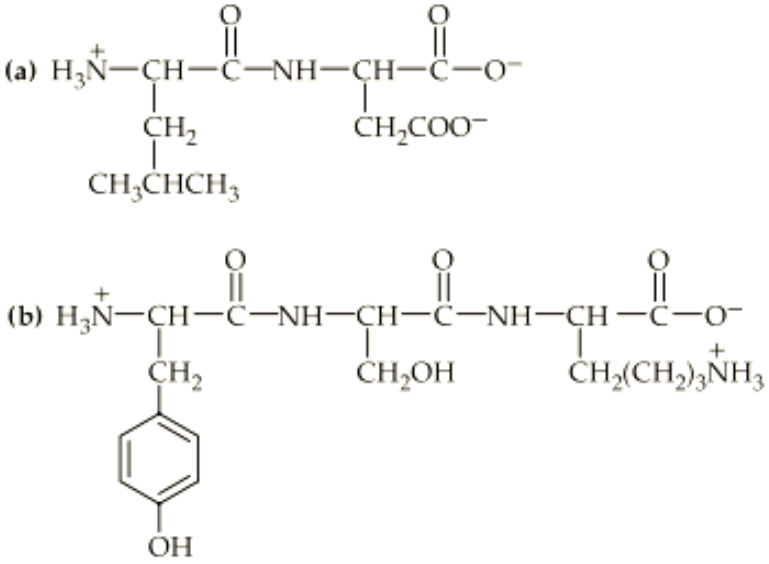
2. Draw alanine showing the tetrahedral geometry of its α carbon.

3.

Name the common amino acids that contain an aromatic ring, contain sulfur, are alcohols, and have alkyl-group side chains.

4.

Identify the amino acids in the following dipeptide and tripeptide, and write the abbreviated forms of the peptide names.



5.

Draw the structure of the following tripeptides at low pH and high pH. At each pH, assume that all functional groups that might do so are ionized.

(a) Val-Gly-Leu **(b)** Arg-Lys-His
(c) Tyr-Pro-Ser **(d)** Glu-Asp-Phe
(e) Gln-Ala-Asn **(f)** Met-Trp-Cys

Literature:

1. Sarker, Satyajit D. Chemistry for pharmacy students: general, organic, and natural product chemistry / Satyajit D. Sarker, Lutfun Nahar. John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England
2. Fundamentals of general, organic, and biological chemistry/John McMurry, Mary E. Castellion, David S. Ballantine. 6th ed. Prentice Hall: New York, Boston, San Francisco, London, Toronto, Sydney, Tokyo, Singapore, Madrid, Mexico City, Munich, Paris, Cape Town, Hong Kong, Montreal © 2007. - 901 p.