

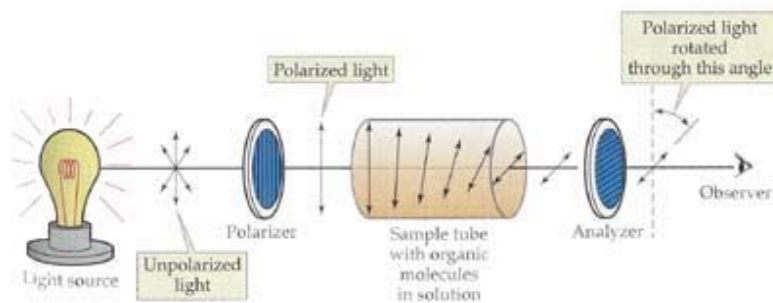
Chapter 18

Amino Acids and Proteins

Chapter 18 suggested problems: none

Class Notes

- I. A review of isomerism
 - A. Stereochemistry: the study of the three dimensionality of molecules
 - B. Constitutional isomers (structural isomers): same molecular formula, different connectivity i.e., differ in spatial arrangement of atoms or groups
 - C. Stereoisomers: same connectivity but with different relative orientations
 1. Chiral: an object is chiral if it is not superimposable on its mirror image
 - a. A molecule is chiral if its two mirror-image forms are not superimposable in three dimensional space
 - b. Chiral objects are "handed," i.e. either right-handed or left-handed
 2. Achiral: not chiral; an object is achiral if it is superimposable on its mirror image
 - a. A molecule is achiral if its two mirror-image forms are superimposable in three dimensional space
 3. Stereoisomers are classed as either enantiomers or as diastereomers
 4. Enantiomers: nonsuperimposable mirror images
 - a. Enantiomers have identical physical properties except for the way in which they rotate plane polarized light (see Ch 22.2 and Figure 22.1)



- b. Enantiomers have identical chemical properties except for the way they behave when interacting with other optically active compounds

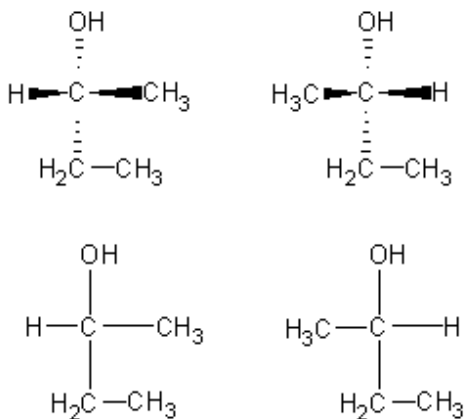
5. Diastereomers: stereoisomers that are not enantiomers

- a. Example of diastereomers: geometric isomers due to double bonds or to cis-trans ring compounds
- b. Diastereomers have similar - not identical - chemical properties
- c. Diastereomers have different physical properties - M.P., B.P., solubilities, densities, etc.

II. Enantiomers

- A. Molecules that are not superimposable on their mirror images are chiral (e.g., CWYZ)
- B. A compound with chiral molecules can exist as enantiomers, a compound without chiral molecules cannot exist as enantiomers
- C. Chiral molecules have at least one chiral atom (tetrahedral stereocenter) i.e., an atom attached to four different groups
 1. All double bonds count as a bond to two of the same atom; the central atom cannot be chiral

D. Representations of chiral molecules using 2-butanol



1. Wedge-bond representation: dashes are vertical and away, wedges are horizontal and toward

2. Fisher representation: vertical is away, horizontal is toward

E. Rules for testing the chirality of compounds

1. Is there a tetrahedral stereocenter?
2. Draw one of the molecules and then draw its mirror image
3. The molecules may be slid or rotated but may not be removed from the plane of the paper

F. Interpreting structural formulas of enantiomers: examples

1. Butane
2. 1-chlorobutane
3. 2-chlorobutane
4. 1,1-dichlorobutane
5. 1,2-dichlorobutane
6. 1,3-dichlorobutane
7. 1,4-dichlorobutane
8. 2,2-dichlorobutane
9. 2,3-dichlorobutane

G. The importance of chirality in the pharmaceutical industry

from C&EN, Vol. 82, No. 24; June 14, 2004, p. 51.

CHIRAL BLOCKBUSTERS
In nine of top 10 drugs, the active ingredients are chiral

| BRAND | GLOBAL 2003 SALES (\$ BILLIONS) | ACTIVE INGREDIENT(S) | FORM OF ACTIVE INGREDIENT(S) | THERAPEUTIC EFFECT |
|--------------|---------------------------------|----------------------|------------------------------|--|
| Lipitor | \$10.3 | Atorvastatin | Single enantiomer | Lipid-lowering agent |
| Zocor | 6.1 | Simvastatin | Single enantiomer | Lipid-lowering agent |
| Zyprexa | 4.8 | Olanzapine | Achiral | Psychotropic agent |
| Norvasc | 4.5 | Amlodipine | Racemate | Calcium channel blocker |
| Procrit | 4.0 | Epoetin α | Protein | Stimulant of blood cell production |
| Prevacid | 4.0 | Lansoprazole | Racemate | Inhibitor of gastric acid secretions |
| Nexium | 3.8 | Esomeprazole | Single enantiomer | Inhibitor of gastric acid secretions |
| Plavix | 3.7 | Clopidogrel | Single enantiomer | Inhibitor of platelet aggregation |
| Advair | 3.7 | Salmeterol | Racemate | β_2 -adrenergic bronchodilator |
| | | Fluticasone | Single enantiomer | Anti-inflammatory agent |
| Zoloft | 3.4 | Sertraline | Single enantiomer | Selective serotonin reuptake inhibitor |
| TOTAL | \$48.3 | | | |

NOTE: Sales figures from IMS Health.

III. Properties of enantiomers

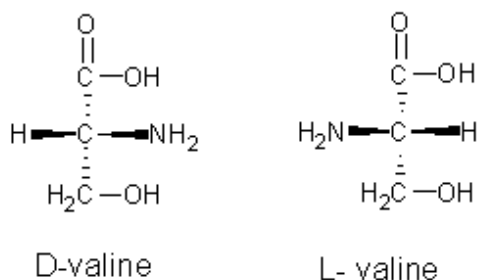
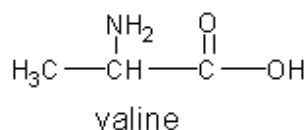
A. Different enantiomers of the same compound rotate plane polarized light

differently from each other

- B. Each enantiomer will rotate plane polarized light the same amount but in opposite directions, either clockwise (+, dextrorotatory) or anti-clockwise (-, levorotatory)
- C. The spatial orientations responsible for + and - behavior can be classed as (D-, L-) (or (R)- / (S)-), but there is not a correlation between +/- rotation and D-/L-orientation; absolute determinations can be made using various techniques, including x-ray diffraction

IV. Nomenclature of enantiomers: rules for determining D/L configuration (note: will not cover how to determine R/S configuration in this class)

- A. The tetrahedral stereocenter must be bonded to an H, heteroatom, and two different R groups
- B. R groups drawn away (up and down), most substituted R (lowest numbered carbon) drawn up and least substituted (highest numbered carbon) drawn down
- C. H and heteroatom are drawn toward (left and right)
- D. Enantiomer with heteroatom on right is the D-enantiomer; enantiomer with heteroatom on left is L-enantiomer
- E. Example: valine



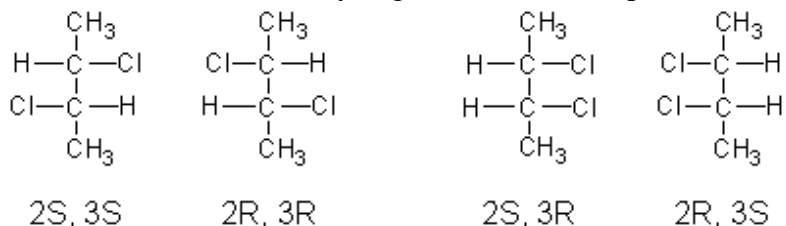
V. Compounds containing two or more tetrahedral stereocenters

- A. There are 2^n possible stereoisomers in a compound with n tetrahedral stereocenters
- B. Usually there are $1/2 2^n$ pairs of enantiomers forming the complete set of diastereomers
 1. Two tetrahedral stereocenters, two pairs of enantiomers for a total of 4 diastereomers
 2. Three tetrahedral stereocenters, four pairs of enantiomers for a total of 8 diastereomers

- Four tetrahedral stereocenters, eight pairs of enantiomers for a total of 16 diastereomers

C. Meso compounds: achiral compounds (i.e., not optically active) even though they contain chiral centers

- Meso compounds are often recognized because one half of the molecule is the mirror image of the other half
- The molecules are superimposable on their mirror images, so only one form exists
- The rotation caused by one molecule is equal but opposite to the rotation of another molecule so they negate each other's optical activity (?)



VI. Cyclic compounds containing tetrahedral stereocenters

A. A ring carbon is chiral if

- It is bonded to two different non-ring substituents
- The ring is not symmetric w.r.t. the carbon

VII. An introduction to biochemistry

A. Biochemistry: the chemistry of life and living systems

- An example: the contents of a bacterium include abt. 10^{10} molecules

| Molecule | Weight percentage | Number of Types |
|---|-------------------|-----------------|
| Water | 70 | 1 |
| Inorganic ions | 1 | 20 |
| Sugars and precursors | 1 | 250 |
| Amino acids and precursors | 0.4 | 100 |
| Nucleotides and precursors | 0.4 | 100 |
| Fatty acids and precursors | 1 | 50 |
| Other small molecules | 0.2 | ~300 |
| Macromolecules (proteins, nucleic acids, and polysaccharides) | 26 | ~3000 |
| Total | | ~4,000 |

B. Principal classes of biomolecules

1. Proteins
2. Carbohydrates
3. Lipids
4. Nucleic acids

C. Functional groups of importance in biochemistry (Table 18.1, p. 504)

| functional group | structure | type of biomolecule |
|---------------------------|--------------------------------|--|
| amino group | $-\text{NH}_2, -\text{NH}_3^+$ | amino acids and proteins |
| hydroxyl group | $-\text{OH}$ | monosaccharides and glycerol |
| carbonyl group | $-\text{CO}$ | monosaccharides, acetyl groups |
| carboxylic acids | $-\text{COOH}$ | amino acids, proteins, and fatty acids |
| amide group | $-\text{CONR}_2$ | proteins |
| carboxylic acid esters | $-\text{COOC}-$ | triacylglycerols |
| mono, di & tri phosphates | $-\text{C-OPO}_3$ & etc. | ATP and metabolic intermediates |
| hemiacetal group | | cyclic monosaccharides |
| acetal group | | di and polysaccharides |

VIII. An overview of proteins

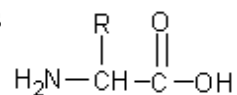
- A. Most plentiful organic chemicals in the body, responsible for more than half of its dry weight
- B. Covalent compounds, all contain C, H, O, and N; nearly all contain S; many also contain P, Fe, Zn, or Cu
- C. Proteins have high MW (from 5700 to several million) but on acid hydrolysis yield smaller organic building blocks, amino acids, which all contain at least one carboxylic acid group and one alpha-amino group; amino acids are linked head-to-toe by amide linkages (peptide bonds) in chains called polypeptides
 1. Most naturally occurring peptide chains consist of 50-2,000 AA with masses of 5,000 d - 220,000 d (1 Dalton (d) = 1 amu)
 2. Proteins consist of one or more polypeptide chain and can have MW in excess of several million
- D. There are roughly 3,000 different proteins in *E. coli*, and there may be as many as 100,000 different proteins in humans. Each species of organism has its own chemically distinct sets of proteins and nucleic acids. Since there are over 1.5

million known species, the total number of different proteins in all species of all living organisms is estimated to be around 10^{10} - 10^{12} ! (Lehninger: 6)

- E. A protein has a three dimensional shape, also known as its conformation, which is largely responsible for its function; discussed more below
1. The biological function (effect) of a peptide is determined by its amino acids and their sequence
 2. With only 20 common AA, how many peptide sequences are possible?
 3. For N amino acids, there are N! possible unique arrangement using each AA only once
 - a. For two AA (A & B): A-B and B-A ($2! = 2$)
 - b. For a polypeptide with three AA(A, B, & C): A-B-C, A-C-B, B-A-C, B-C-A, C-A-B, and C-B-A ($3! = 6$)
 - c. For a polypeptide with twenty AA: $20! = 2 \times 10^{18}$, small chain with MW of abt. 2,600
 - d. For a protein with a MW of 34,000 with equal numbers of just 12 different AA, there are about 10^{300} different possible sequence isomers
 4. Despite the sometimes enormous length of peptide chains, the variation of as few as a single amino acid in the chain can partially or completely alter the peptide structure and consequently impair or destroy its biological function
 - a. Sickle-cell anemia is the result of the replacement of glutamate with valine in each of the two hemoglobin peptides
- F. Proteins can be categorized based on their conformations, simple or conjugated, or based on function
1. Fibrous and globular proteins
 - a. Fibrous proteins - polypeptide chains arranged in parallel along a single axis to yield long fibers or sheets; the basic structural materials in connective tissue of higher animals
 - i. Keratins, collagens, elastins, myosins, and fibrin
 - b. Globular proteins - polypeptide chains are tightly folded into compact spherical or globular shapes
 - i. Insulin, ribonuclease, immunoglobulins, hemoglobin, and albumins
 2. Simple and conjugated proteins

- a. Simple proteins - on hydrolysis yield only amino acids
 - b. Conjugated proteins - on hydrolysis yield amino acids and other organic or inorganic groups
 - i. Nucleoproteins - amino acids + nucleic acids
 - ii. Lipoproteins - amino acids + lipids
 - iii. Phosphoproteins - amino acids + phosphate ester
 - iv. Metalloproteins - amino acids + Fe, Zn, Cu, Mo, etc.
 - v. Glycoproteins - amino acids + saccharides
3. Biological functions
- a. Enzymes serve as biological catalysts; several thousand known enzymes
 - b. Storage proteins: storage of amino acids as nutrients and building blocks for growing embryos,- e.g., ovalbumin (eggs), casein (milk), gliadin (wheat)
 - c. Transport proteins: binding and transporting specific types of substances through the blood and within cells, e.g. hemoglobin
 - d. Contractile proteins: serve as means of locomotion, e.g. actin and myosin
 - e. Protective proteins: include antibodies, complement, fibrinogen and thrombin, and bacterial, plant, and animal toxins
 - f. Hormones: stimulate and regulate biological processes, e.g., insulin and growth hormone
 - g. Structural proteins: provide, directly or indirectly, for structure at various levels within a living organism, e.g. keratin, collagen, and elastin

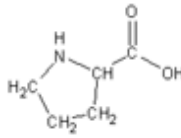
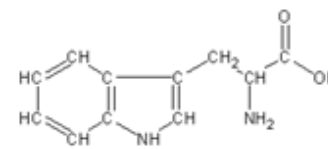
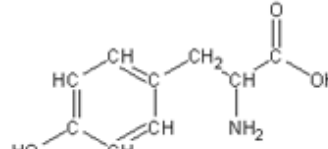
IX. α -amino acids: the building blocks of proteins

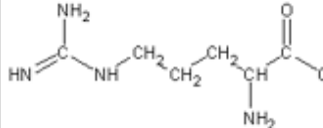
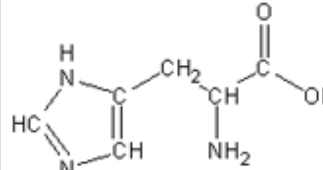


- A. There are 20(+?) common amino acids found in proteins as well as a handful of rare amino acids, as well as over 150 non-protein amino acids
- B. Classes of essential amino acids
 1. Nonpolar neutral (9)
 2. Polar neutral (6)
 3. Polar acidic (2)

4. Polar basic (3)the side chain

5.

| name | code | code | R group |
|-------------------------|------|------|---|
| <i>nonpolar neutral</i> | | | |
| glycine | Gly | G | H- |
| alanine | Ala | A | CH ₃ - (methyl) |
| valine | Val | V | (CH ₃) ₂ CH- (isopropyl) |
| leucine | Leu | L | (CH ₃) ₂ CHCH ₂ - (isobutyl) |
| isoleucine | Ile | I | CH ₃ CH ₂ CH(CH ₃)- (sec-butyl) |
| proline | Pro | P |  <p>note that proline incorporates the amino acid into a pyrrolidine group (see Ch. 15 notes)</p> |
| phenylalanine | Phe | F | C ₆ H ₅ CH ₂ - (alanine's methyl group with an H replaced by a phenyl group) |
| tryptophan | Trp | W |  <p>the side chain is indole (Ch. 15 notes)</p> |
| methionine | Met | M | CH ₃ SCH ₂ CH ₂ - |
| <i>polar neutral</i> | | | |
| serine | Ser | S | HOCH ₂ - (methanol side chain) |
| threonine | Thr | T | CH ₃ CH(OH)- (ethanol side chain) |
| cysteine | Cys | C | HSCH ₂ - (methanethiol side chain) |
| tyrosine | Tyr | Y |  <p>the side chain is a p-hydroxytoluene group</p> |
| asparagine | Asn | N | H ₂ NCOCH ₂ - (acetamide side chain) |
| glutamine | Gln | Q | H ₂ NCOCH ₂ CH ₂ - (propanamide side chain) |
| <i>polar acidic</i> | | | |
| aspartic acid | Asp | D | HOOCCH ₂ - (acetic acid aide chain) |
| glutamic acid | Glu | E | HOOCCH ₂ CH ₂ - (propanoic acid side chain) |
| <i>polar basic</i> | | | |
| lysine | Lys | K | H ₂ NCH ₂ CH ₂ CH ₂ CH ₂ - (1-aminobutane side chain) |

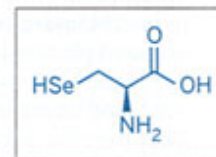
| | | | |
|-----------|-----|---|--|
| arginine | Arg | R |  <p>the side chain is a 1-propylguanidine group</p> |
| histidine | His | H |  <p>the side chain is a 2-methyl-1-pyrrole group</p> |

6. Note on selenocysteine

from C&EN, Vol 85, No. 1; January 1, 2007, p. 22.

SELENOCYSTEINE'S BIOSYNTHESIS

Most proteins are built from 20 types of amino acids. But some organisms, including humans, use a 21st amino acid, selenocysteine (shown), in their proteins. The selenium in selenocysteine is believed to play an essential protective role in the body, including preventing cancer and heart disease and delaying aging. Dolph L. Hatfield of the National Cancer Institute and his coworkers have now discovered the previously unknown selenocysteine biosynthetic pathway (*PLoS Biol.*, DOI: 10.1371/journal.pbio.0050004). They used comparative genomics studies to identify proteins that occur only in organisms that use selenocysteine. When one of these proteins, soluble liver antigen, was given appropriate substrates, it catalyzed the synthesis of selenocysteine. With this selenocysteine synthase in hand, Hatfield and coworkers were able to elucidate the entire pathway of selenocysteine biosynthesis in mammals. The study suggests that "this pathway is also active in other eukaryotes and archaea that synthesize selenoproteins," the researchers note.



C. Noncovalent forces between amino acid side chains are important contributors to the shape (and therefore function) of proteins

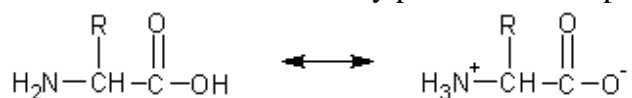
1. The predominant intramolecular bonding force in peptides is covalent bonding
2. Bonding interactions other than covalent bonds are referred to as "noncovalent forces" and can be either intramolecular or intermolecular, esp. in large molecules like peptides
3. Individually these forces are weak (1-3 orders of magnitude weaker than covalent bonds, 0.1 - 10 kcal/mol vs ~100 kcal/mol for covalent bonds) but the collective force of many of them operating simultaneously on a peptide have profound affect on its structure, i.e., they determine how a peptide folds
4. Nonpolar side chains are hydrophobic and behave - in some respects - similarly to fatty acids in micelle formation
5. Polar, acidic, and basic side chains are hydrophilic and may interact easily

with water, which affects the aqueous solubility of the peptide chains

6. Noncovalent forces include the following
 - a. Charge-charge interactions
 - i. Between charged functional groups
 - ii. Strong and can occur over relatively long distances (several Angstroms)
 - iii. Can be either attractive or repulsive, depending on charge
 - b. Hydrogen bonds
 - c. Van der Waals forces: weak and short-range, usually dipole-dipole or dipole-induced dipole interactions
 - d. Hydrophobic interactions

X. The acid-base behavior of α -amino acids

- A. Generally, at physiological pH, amino acids exist not in their neutral form but as molecules that simultaneously possess both a positive and a negative charge

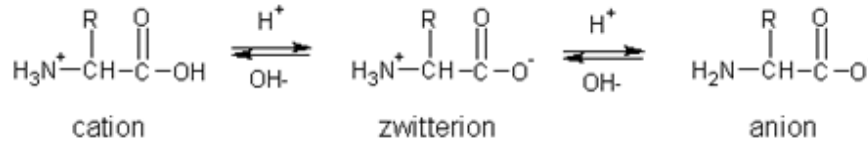


- B. These molecules are called zwitterions, or dipolar ions, and are amphoteric: simultaneously positively and negatively charged

1. (source: <http://www.psigate.ac.uk/newsite/reference/plambeck/chem1/p01155.htm>)
The term amphiprotic in modern acid-base chemistry is the replacement for the older term amphoteric. An amphiprotic substance is a substance which can act both as an acid and as a base because it contains at least one proton which can be given up and at least one site at which a proton can be acquired.
2. Most polyprotic acids have at least one amphiprotic ion. Using phosphoric acid as an example, the monohydrogen phosphate ion and the dihydrogen phosphate ion are both amphiprotic while phosphoric acid itself can only be an acid and the phosphate ion can only be a base.
3. Organic compounds which contain both a carboxylic acid group and an amine group on the same molecule are called amino acids. When an amino acid such as glycine, $\text{H}_2\text{NCH}_2\text{COOH}$, is dissolved in water, the carboxylic acid group loses a proton which is gained by the more basic amine group. This produces an ionic structure with opposite charges on both ends, a zwitterion. The zwitterion structure of glycine is $^+\text{H}_3\text{NCH}_2\text{COO}^-$. The protonated form of this amphiprotic zwitterion, $^+\text{H}_3\text{NCH}_2\text{COOH}$, is the glycinium ion.
4. When an amphiprotic substance alone is dissolved in water, it will act

both as an acid and as a base.

- C. These molecules are electrically neutral despite bearing simultaneous positive and negative charges
- D. This behavior is dependent on the isoelectric point (pI) of the amino acid, i.e., the pH at which 99.9% of the amino acid exist in its neutral but zwitterionic form



- E. Generally amino acids behave as self-buffering systems in that they resist ionization as a function of changes in pH
- F. At pH changes of 2 units above or below the pI of the amino acid about 97% still exists in zwitterion form
- G. Zwitterions tend to aggregate, forming solids with relatively high MPs, and limiting solubility in aqueous solution at the pI
- H. Peptides exist as chains of zwitterions

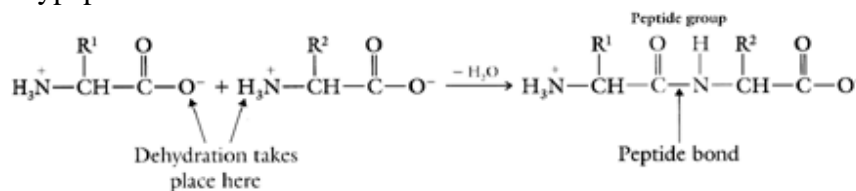
XI. The chirality of amino acids

- A. All amino acids that appear in proteins are L-amino acids
- B. D-amino acids are commonly found in bacterial cell walls and in peptide antibiotics like gramicidin and actinomycin

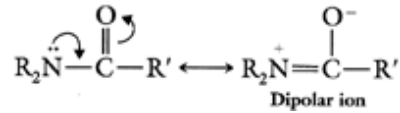
XII. Peptides: chains of amino acids linked together by peptide bonds (amide linkages)

- A. Peptides can be referred to generically based on the number of amino acids linked together
1. Dipeptides: 2 AA
 2. Tripeptides: 3 AA
 3. Tetra, penta, hexapeptides, etc.
 4. Oligopeptides: 10-20 AA
 5. Polypeptides: large peptide chains

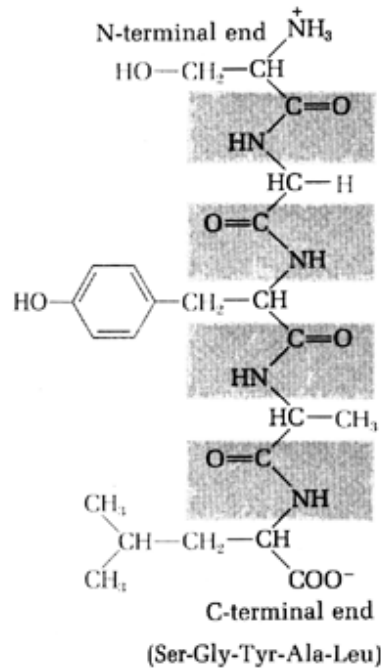
B. Polypeptide bonds



1. Due to resonance the C-N bond has abt. 40% imine character and the C=O has abt. 40% single bond character
2. The bond is much stronger than predicted, shorter bond length, and hindered rotation around what might seem to be a sigma bond (C-N bond)



3. The chain of peptide linkages forms the backbone of the protein and is responsible for its primary structure



- C. By convention peptides and proteins are written such that the amino terminal is always written on the left and the carboxy terminal is always written on their right

XIII. Three-dimensional structure of proteins: the 3-D structure of a protein determines its function

A. Interactions that determine the shape of proteins

1. Hydrogen bonding between neighboring backbone segments
 - a. Interactions occur between the amide's N-H group and carbonyl oxygen atoms
 - b. Can be either intramolecular or intermolecular
2. Hydrogen bonding of side chains with the backbone or with each other
3. Charge-charge interactions: when attractive interactions occur a "salt bridge" is formed
4. Hydrophobic interactions

5. Covalent sulfur-sulfur bonds (disulfide bridges) between cysteine molecules
- B. Primary structure: refers to the backbone of polypeptide linkages i.e., to the amino acid sequence
- C. Secondary structure: the spatial arrangement of polypeptide backbones
1. The backbone can form regular, repeating structures held together by the attractions between amide linkages, i.e. some proteins contain one or more sequences of amino acids that take on a characteristic 3-D structure that become repeating units within the peptide
 2. Some proteins have extensive regions of secondary structure, e.g. fibrous proteins arranged in alpha-helices and beta sheets
 3. Some proteins have small or negligible regions of secondary structure, e.g. globular proteins
- D. Tertiary structure: how the peptide is bent and folded in three dimensions
1. While secondary structure depends mainly on bonding atoms between backbone atoms, tertiary structure depends on interactions between amino acid side chains located some distance away from each other along the backbone
 2. The bending and folding of a peptide is not random but occurs in such a manner that it results in the most stable configuration for the peptide
- E. Quaternary structure: if a protein consists of two or more peptides, how the chains arrange in three dimensions with respect to one another to form a single unit

XIV. Chemical reactions of peptides

- A. Disulfide bridges between the sulfhydryl groups of cysteine groups
1. Two cysteine AAs joined by a disulfide bridge are called cystine
- B. Denaturation: reactions (or processes) that result in a loss of conformation by interrupting bonds between AA molecules within peptides
1. Organic chemicals: soaps, detergents, urea, beta-mercaptoethanol, alcohols, etc.
 2. Inorganic chemicals: esp. heavy metal ions such as lead and mercury
 3. Oxidizing and reducing agents
 4. Changes in pH
 5. Increased temperature
 6. UV and ionizing radiation

7. Mechanical energy (e.g., whipping egg whites)

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