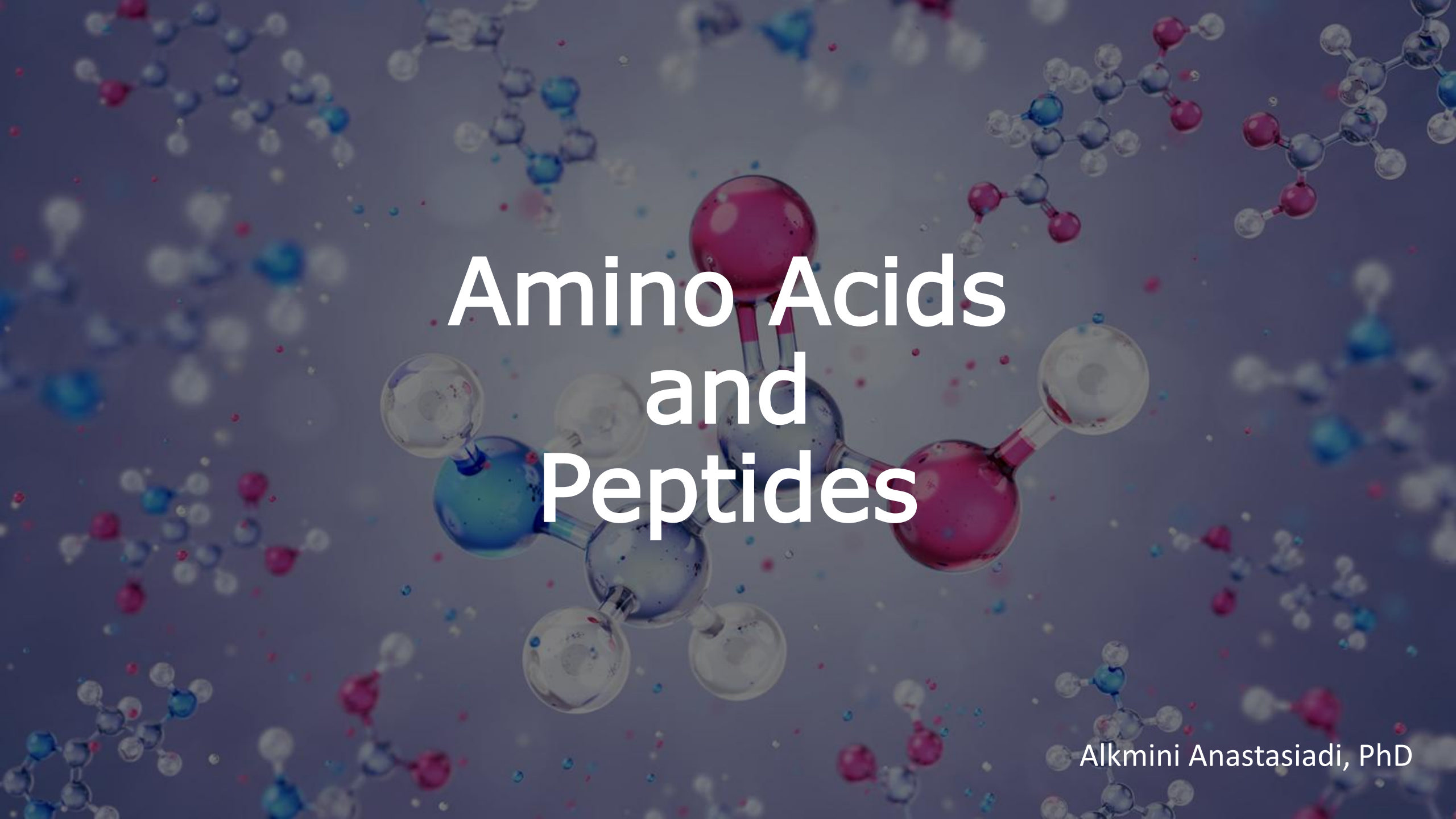


The background of the slide is a dark blue-grey color, populated with numerous molecular models. These models consist of small spheres representing atoms (colored red, blue, and white) connected by thin rods representing chemical bonds. The molecules are scattered across the frame, with some appearing more prominent and in focus than others, creating a sense of depth. The overall aesthetic is scientific and modern.

Amino Acids and Peptides

Alkmini Anastasiadi, PhD

Intrinsic Characteristics of Amino Acids

- Amino acids = building blocks of proteins
- The abundance of proteins is based on the **intrinsic characteristics** of the 20 common amino acids:
 1. Chirality
 2. Acid-base properties
 3. Side chains with multiple structures and chemical characteristics
 4. Polymerization ability

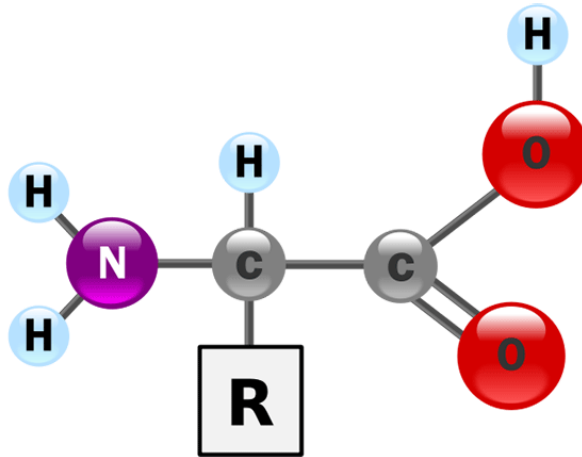
Intrinsic Characteristics of Amino Acids

Chirality

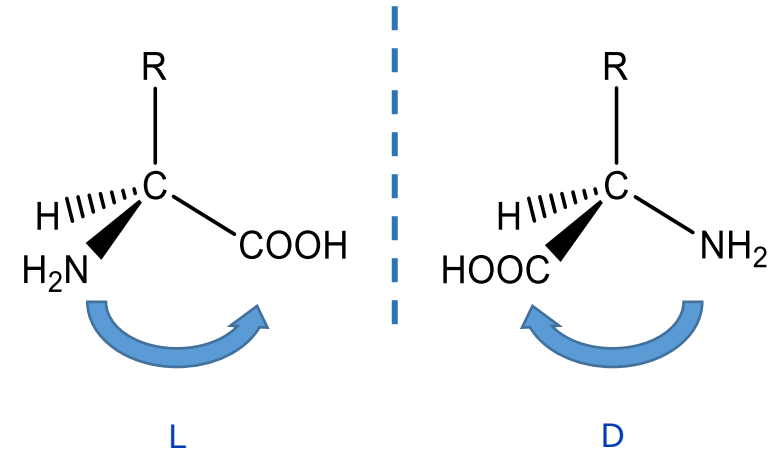
■ Typical amino acids:

- Central carbon atom (C_α)
- Amino group (NH_3^+)
- Carboxyl group (COO^-)
- Hydrogen (H)
- Side chain (R)

Central carbon = asymmetric because it is linked to 4 different groups



Enantiomers



Chirality: a structural property of a molecule that renders it non-superimposable on its mirror image → a chiral molecule and its mirror-image = enantiomers

Intrinsic Characteristics of Amino Acids

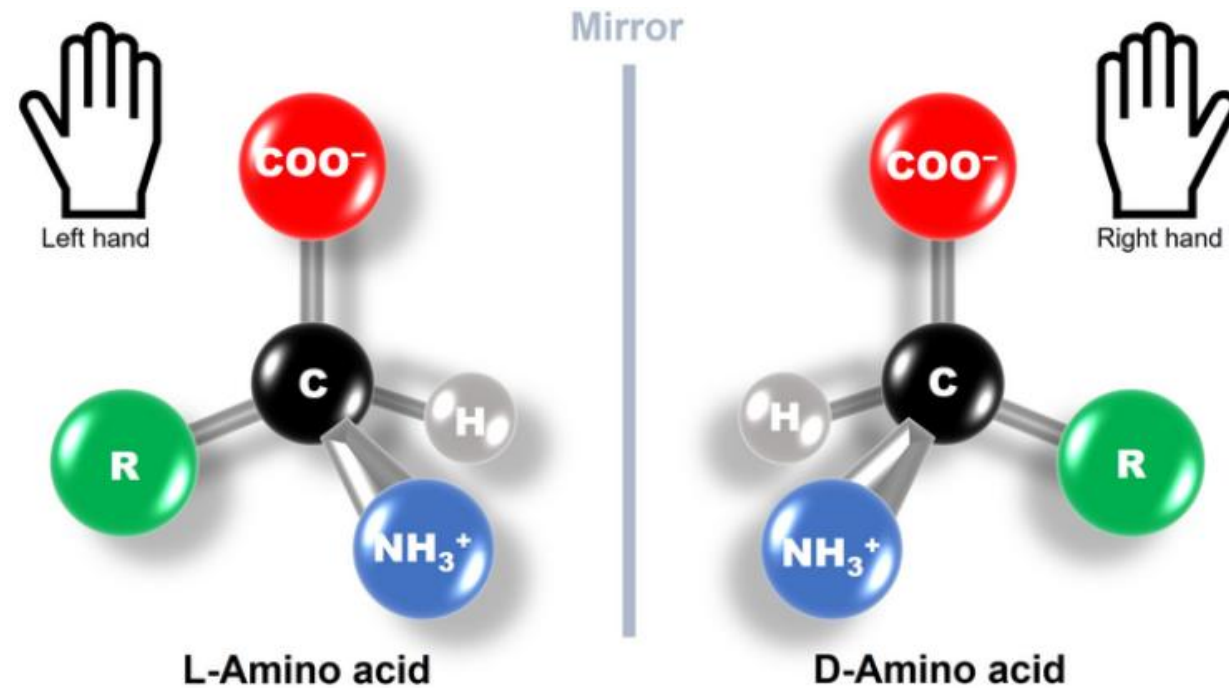
Chirality

- Most amino acids (except for glycine) are chiral
 - ➔ it means they exist in two forms-mirror images:
 - L-amino acid (levo)
 - D-amino acid (dextro)
 - ➔ They have the exact **same chemical composition**, but **different arrangement** around the asymmetric carbon atom.
 - ➔ It's like your left and right hand: they are alike but don't "fit" when you put one on top of the other.

Intrinsic Characteristics of Amino Acids

Chirality

- Enantiomers' chemical properties are the same
- They differ in the way they interact with other chiral molecules → **important in the biological context** (e.g., enzyme function)
- In nature, the amino acids that participate in the structure of proteins are **L-amino acids**.

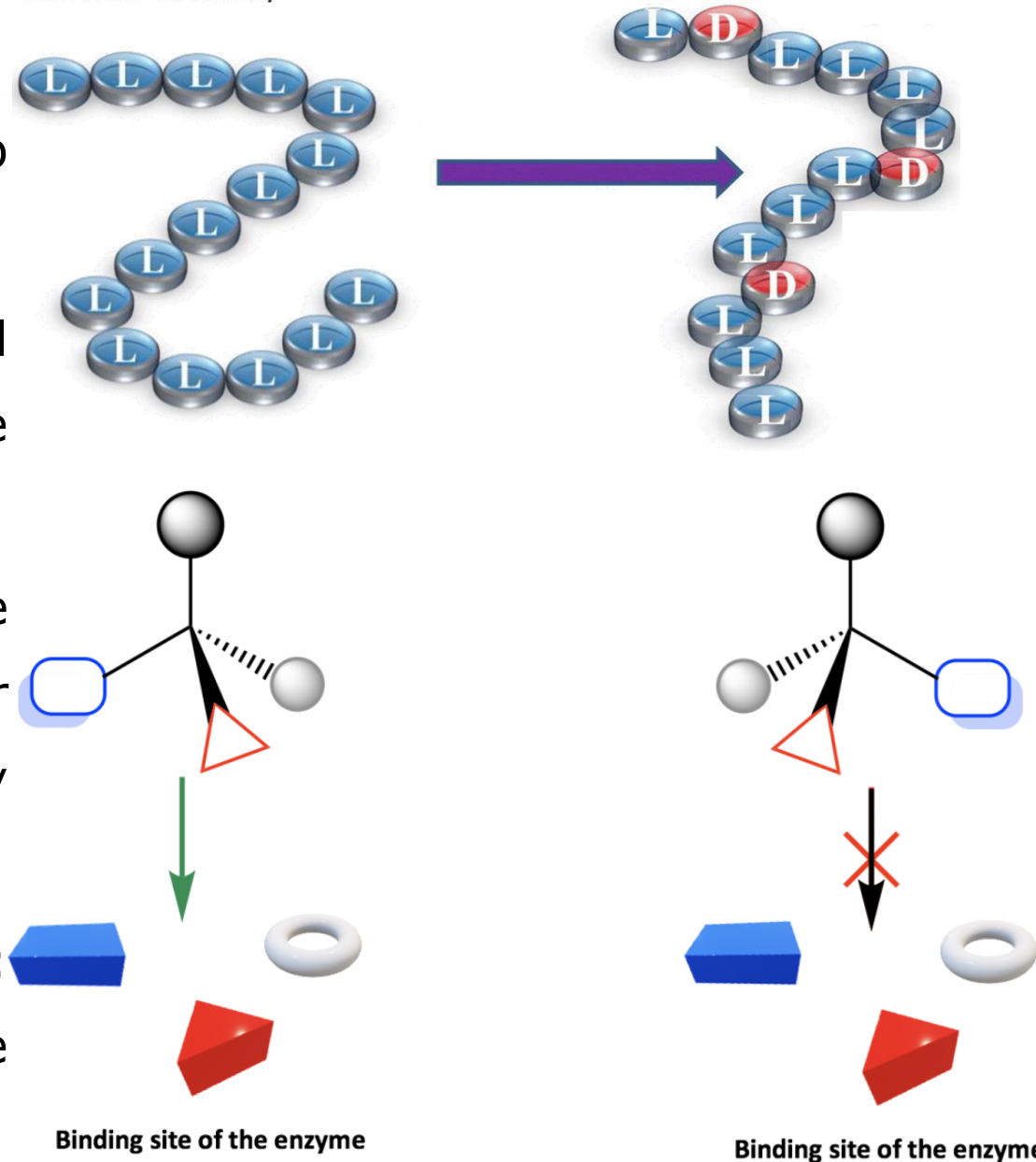


Intrinsic Characteristics of Amino Acids

Chirality

- «Consequences» of the prevalence of L-amino acids:

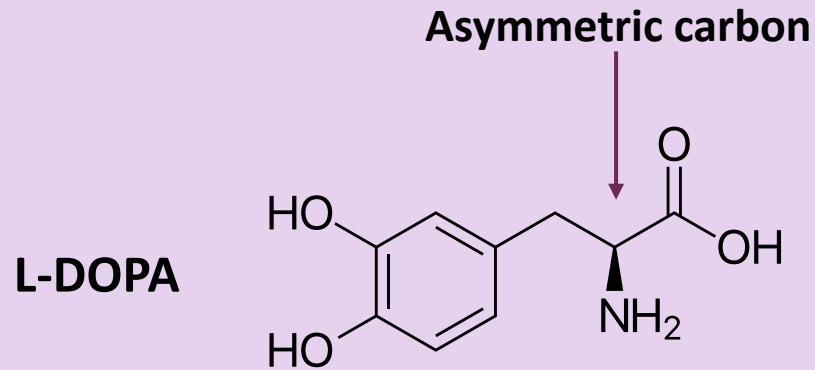
- Uniformity in protein structure:** Since all amino acids are in the L-form, proteins acquire stable, predictable three-dimensional structures.
- Enzyme specificity:** If D-amino acids are present they cannot be incorporated or metabolized because enzymes are highly stereospecific.
- Sensitivity and recognition of biomolecules:** Just like enzymes, receptors and transporters are also stereospecific



Intrinsic Characteristics of Amino Acids

Chirality

Do we care about chirality in the medical setting?



- Parkinson's disease → the dopaminergic neurons degenerate
→ dopamine depletion → problems in movement
(bradykinesia, rigidity, tremor)
- Dopamine cannot cross the blood-brain barrier

- L-DOPA can cross it since it is an amino acid and can be transported by the amino acid **transporter** LAT1
- In the brain a **decarboxylase** transforms it to dopamine
- The surviving neurons store it and release it when needed

Both the transporter and the enzyme are stereospecific: they interact ONLY with the L-form

Intrinsic Characteristics of Amino Acids

Chirality

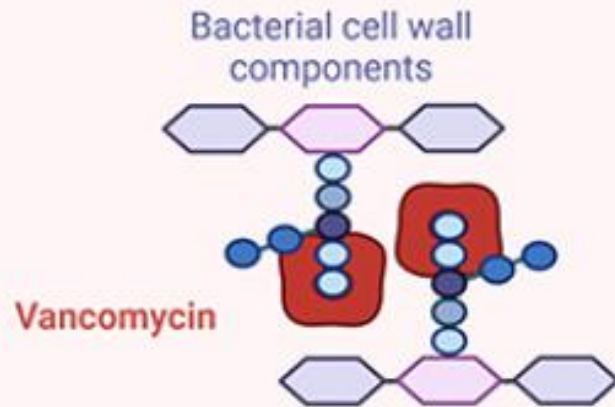
Do we care about chirality in the medical setting?

i

Vancomycin-treated bacterial cell wall

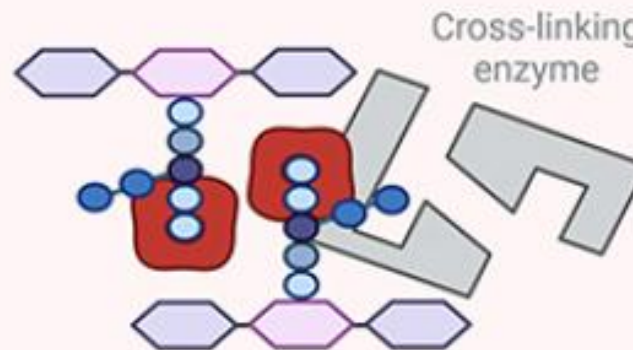
①

Vancomycin targets bacteria cell wall and binds to two D-alanine residues on the end of the peptide chains



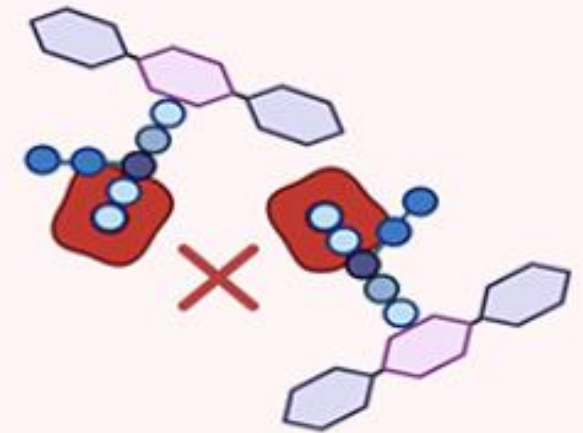
②

Vancomycin prevents cross-linking enzyme from binding to residues



③

Vancomycin prevents cell wall strands from cross-linking, leading to cell wall rupture



We can have drugs that target a chiral “signature” that the human body does not have

Intrinsic Characteristics of Amino Acids

Chirality

Do we care about chirality in the medical setting?

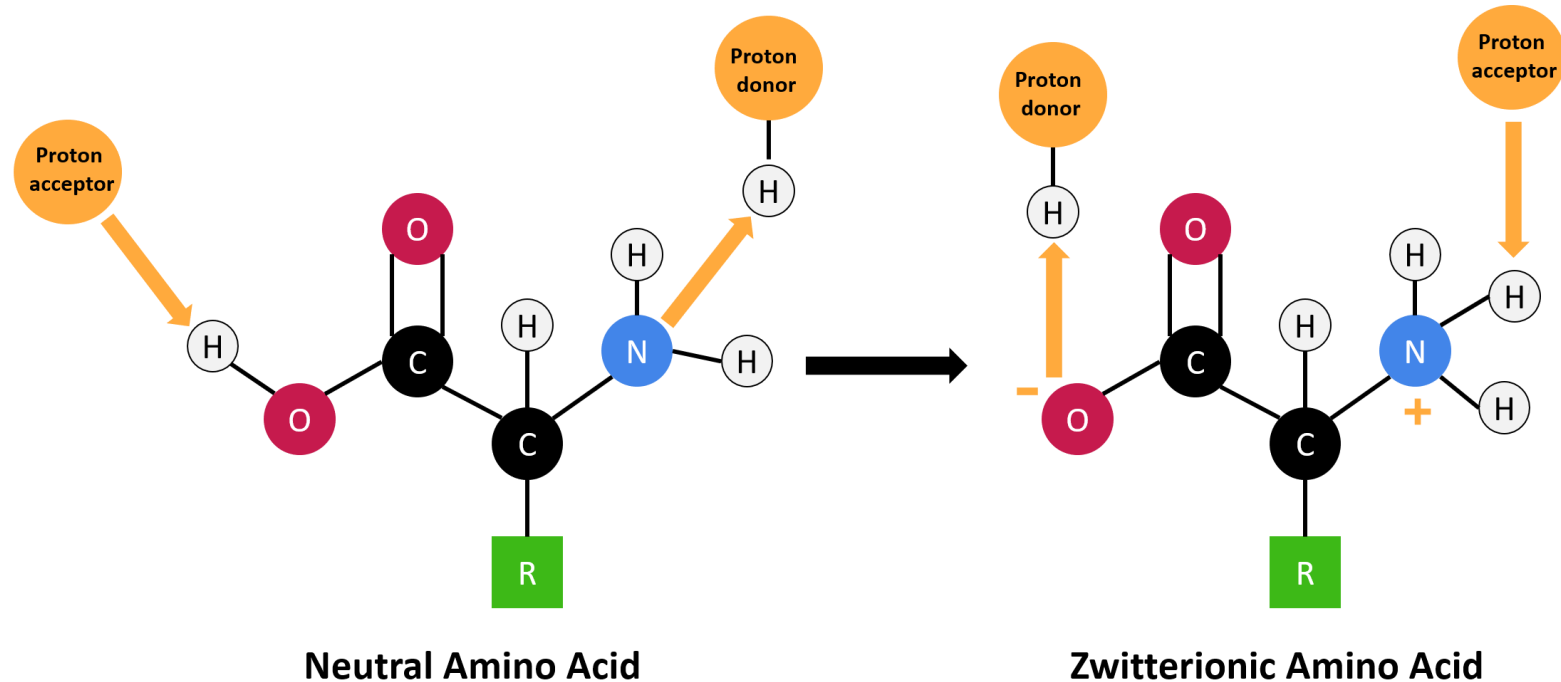
Chirality is not static: time “wears down” stereochemistry → **racemization**: a spontaneous, non-enzymatic chemical modification of proteins where amino acid residues gradually **invert from their natural L-form to their D-form** (enantiomer) over time.

- Ocular lens proteins present extensive D-aspartate accumulation over decades → aid in the development of age-related cataract formation
- D-aspartate accumulates in tooth dentin at a steady, predictable rate → D/L aspartate ratio in teeth widely used in forensic medicine to estimate chronological age.

Intrinsic Characteristics of Amino Acids

Acid-Base Properties

- Every amino acid contains at least:
 - A carboxyl group ($-\text{COOH}$) $\rightarrow$ acts as an **acid**
 - An amino group ($-\text{NH}_2$) $\rightarrow$ acts as a **base**
- $\rightarrow$ it can act both as a proton (H^+) donor and acceptor $\rightarrow$ **ampholyte**.

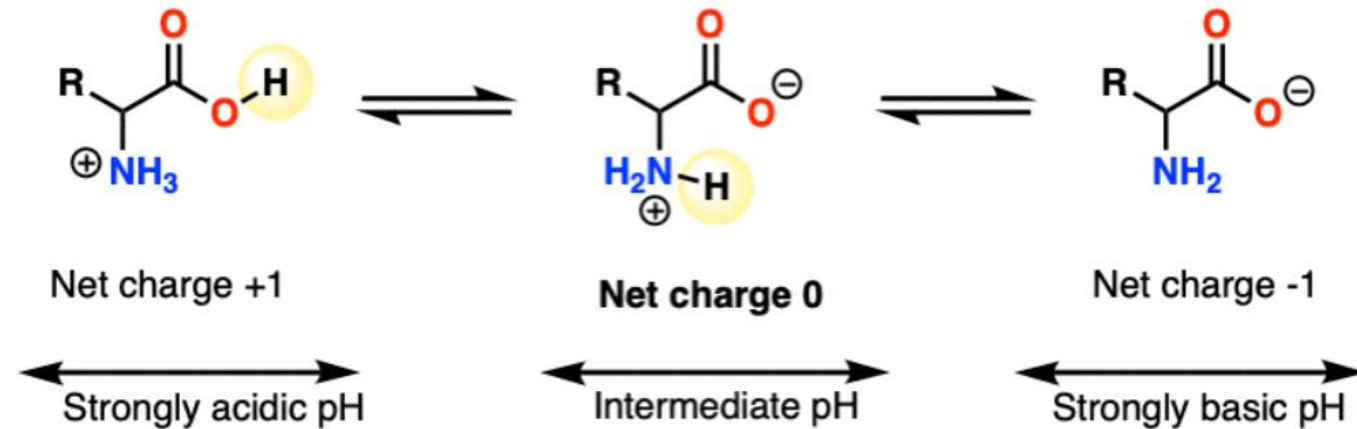


Intrinsic Characteristics of Amino Acids

Acid-Base Properties

Due to the presence of the amino group and the carboxyl group → based on pH → different charge

- Low pH: amino groups and carboxyl groups are protonated → positive charge
- Increase in pH: the carboxyl group loses its proton first → neutral charge
- Extra increase in pH: the amino group also loses its proton → negative charge



Zwitterion: in a specific pH, the amino acid carries both a positive and a negative charge in equal amounts → dipole ion

Intrinsic Characteristics of Amino Acids

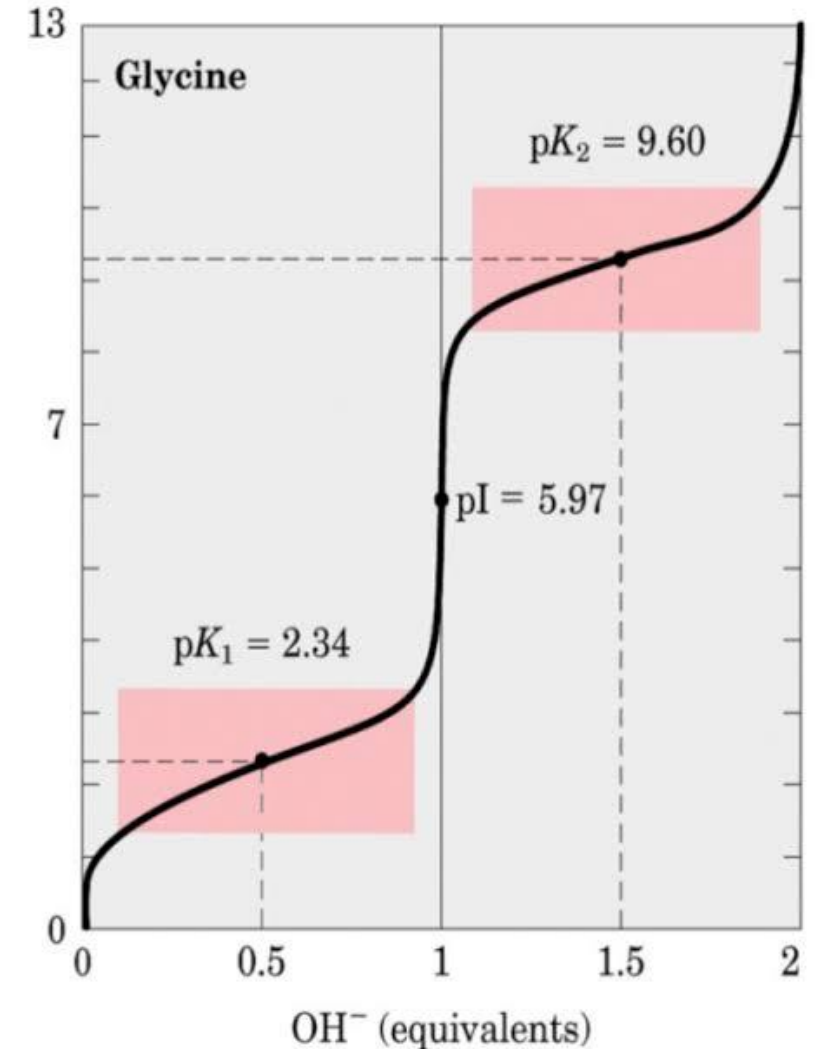
Acid-Base Properties

- When net charge = neutral → amino acid's **isoelectric form** → the **least soluble form**

- This happens in a specific pH value, which is unique for every amino acid and is called the isoelectric point (pI)

$$pI = \frac{pK_1 + pK_2}{2}$$

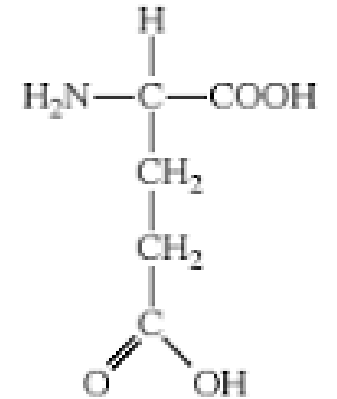
- The pK_1 and pK_2 values are the pH values at which half the number of molecules have converted to the anionic and cationic forms, respectively.



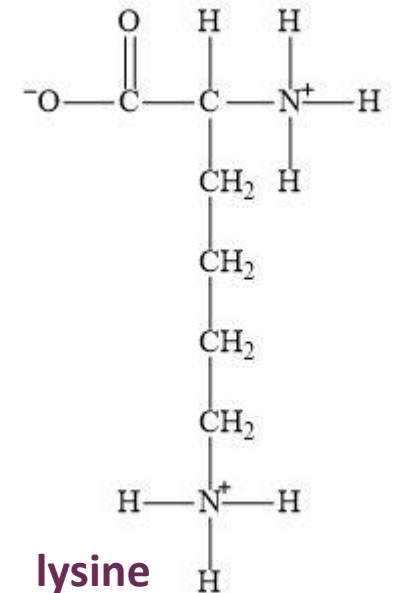
Intrinsic Characteristics of Amino Acids

Acid-Base Properties

- The pI value depends on the **side chain** of the amino acid:
 - e.g., The pI of glutamic acid (its side chain contains a carboxyl group) $\rightarrow \sim 3.2$
 - e.g., The pI of lysine (its side chain contains an amino group) $\rightarrow >9$



Glutamic acid

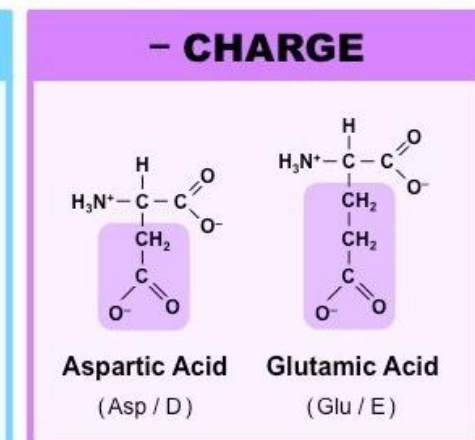
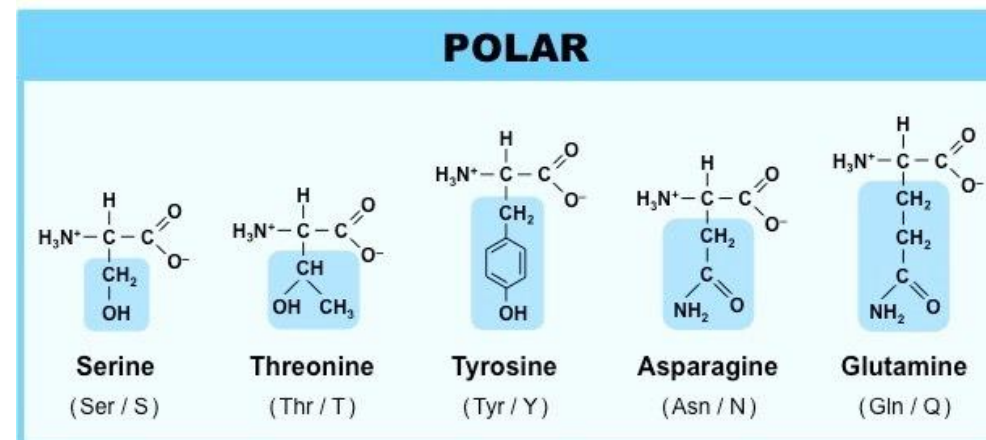
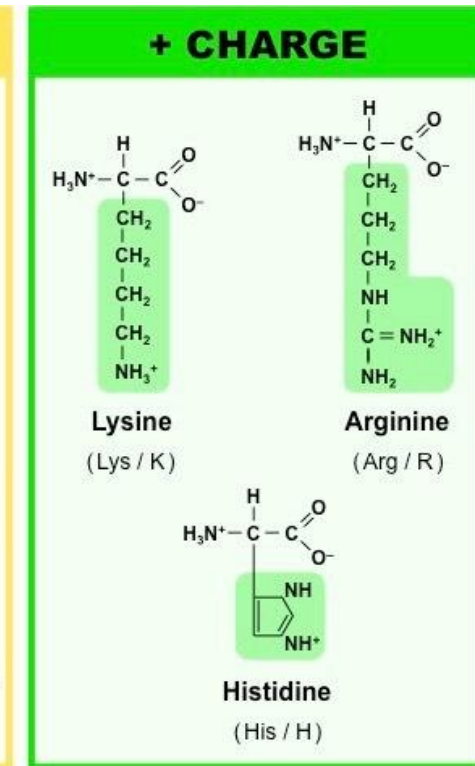
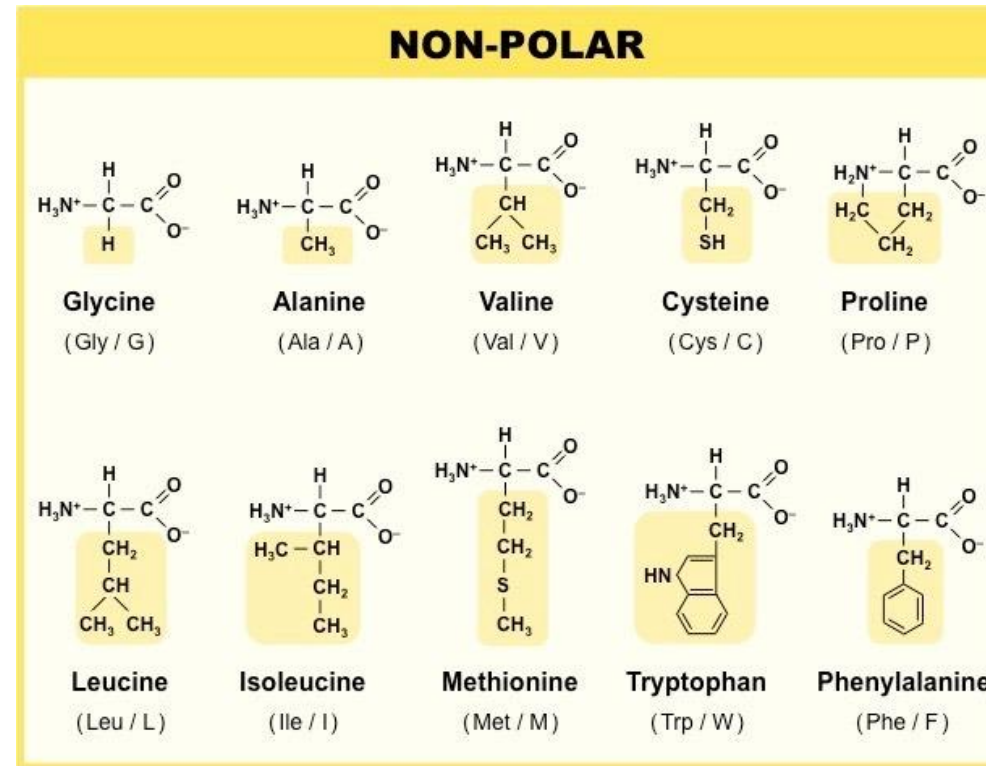


lysine

Intrinsic Characteristics of Amino Acids

Side chain (R)

- It gives proteins their chemical properties
- It is used as a method for classifying amino acids:
 - Non-polar or hydrophobic amino acids
 - Neutral but polar amino acids
 - Acidic amino acids (at pH 7)
 - Basic amino acids (at pH 7)

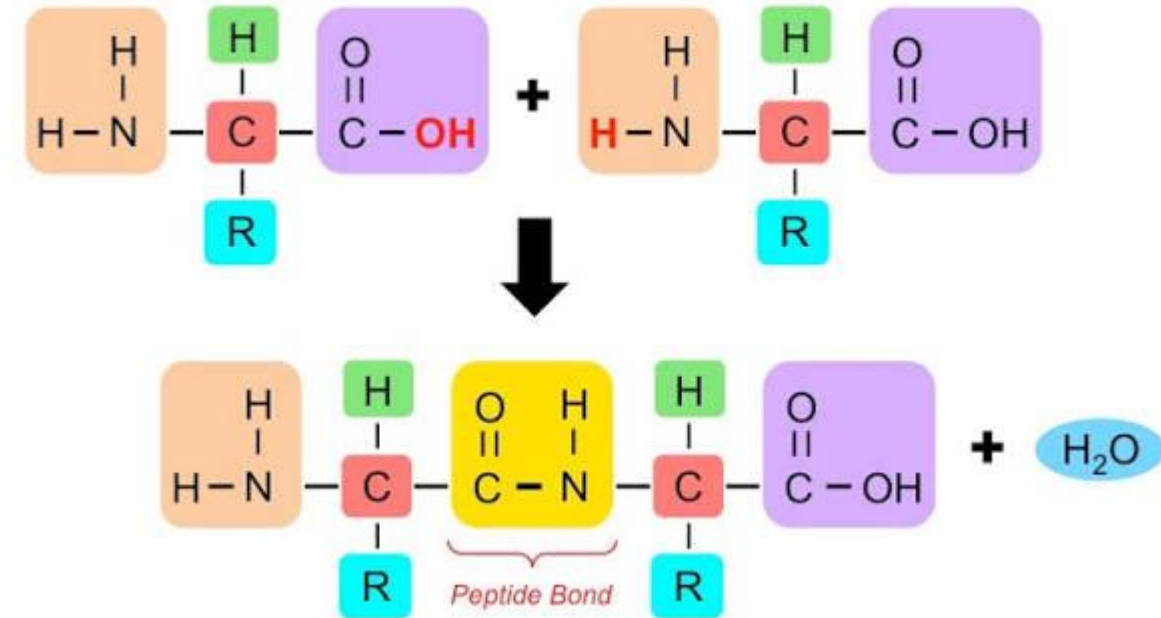


Intrinsic Characteristics of Amino Acids

Polymerization capacity

The carboxyl end of an amino acid can connect with the amino end of another = **peptide bond**

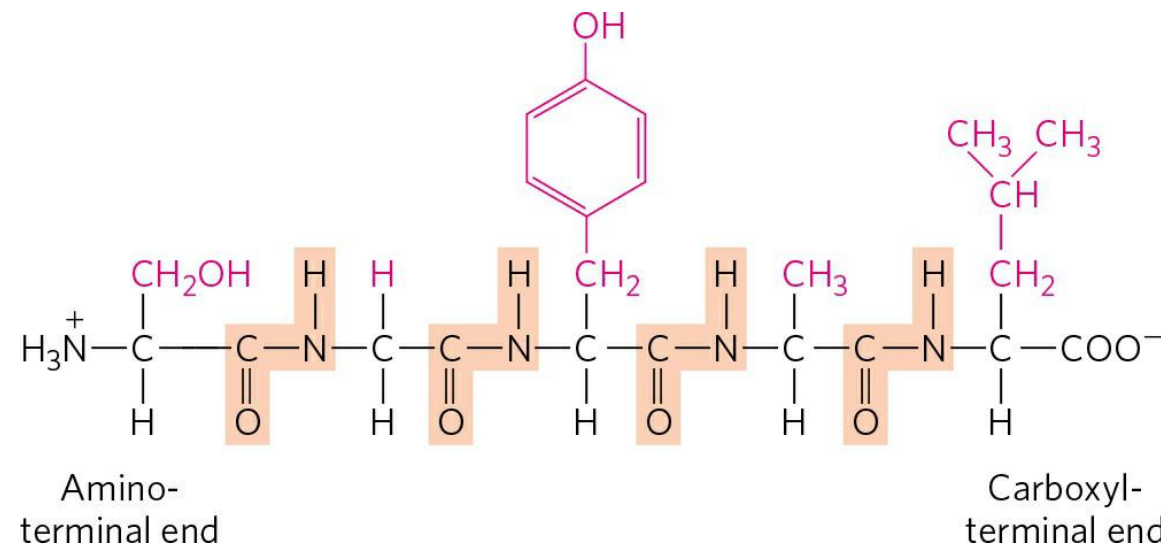
- Covalent bond
- Condensation reaction (water removal)



Intrinsic Characteristics of Amino Acids

Polymerization capacity

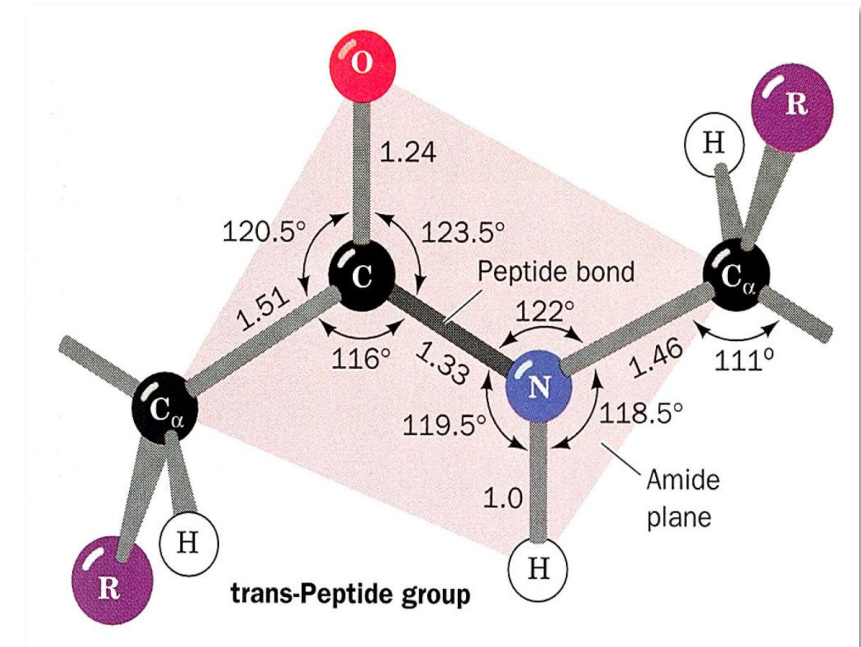
- The product of this condensation: peptide (dipeptide, tripeptide, ... , oligopeptide, polypeptide)
- Peptides have a free amino-terminal end (N-terminal) and a free carboxyl-terminal end (C-terminal)
- We write the N-terminal end on the left and the C-terminal end on the right.



Intrinsic Characteristics of Amino Acids

Polymerization capacity

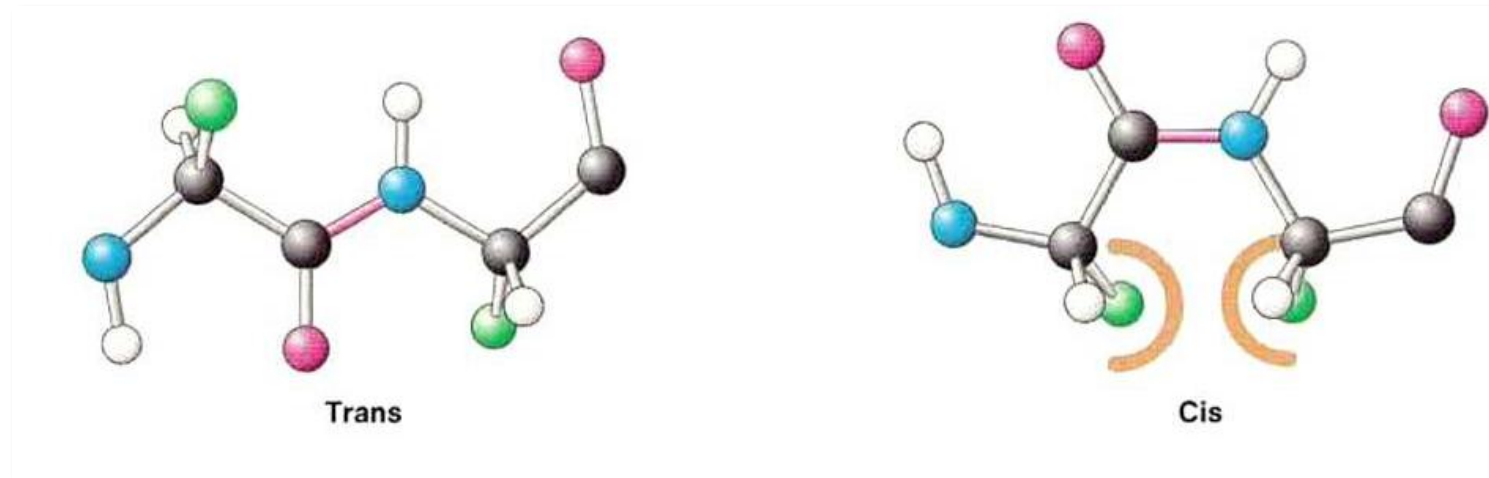
- Essentially, the “backbone” of the peptide consists of repeating -N-C α -C- sequences.
- The peptide bond behaves partially (40%) as a double bond:
 - No free rotation around it**
 - All atoms involved in the bond lie in the same plane**
 - The length between C and N is shorter than that of a single bond and longer than that of a double bond**



Intrinsic Characteristics of Amino Acids

Polymerization capacity

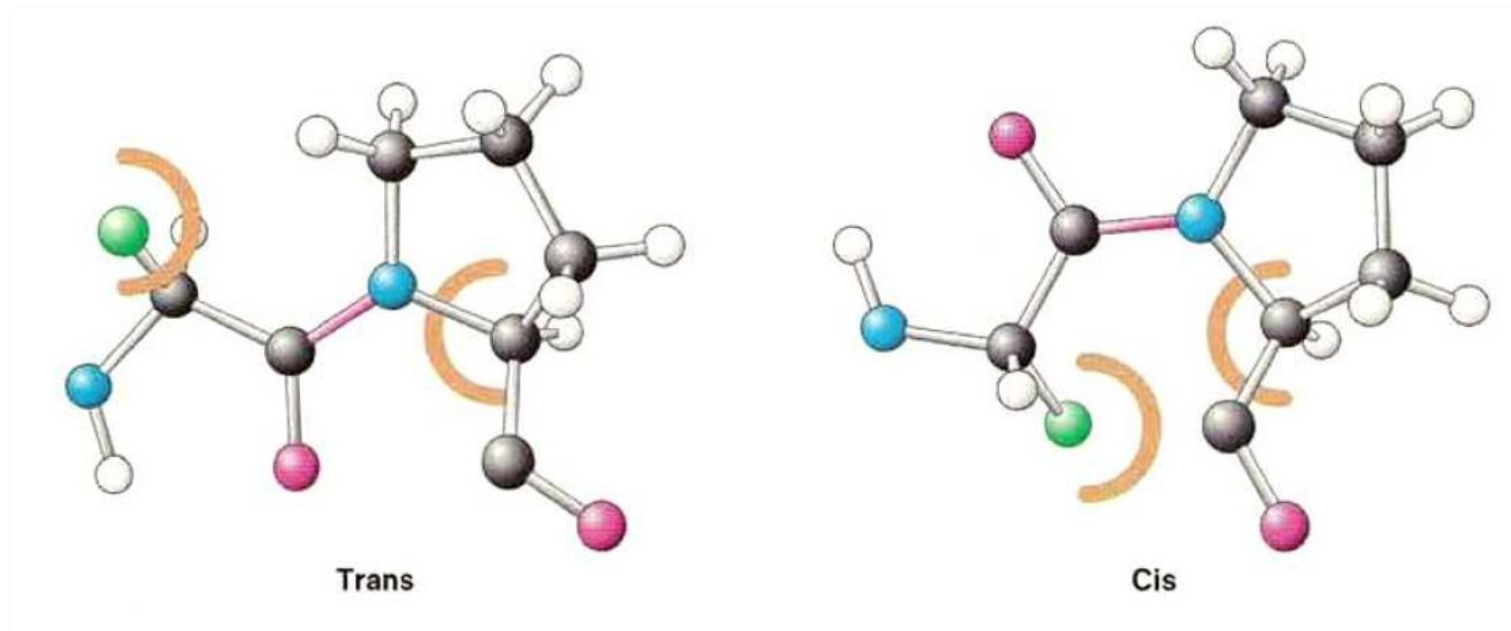
- Depending on the position of the two C α atoms of the two amino acids in the peptide bond → two possible conformations:
 - cis: they are on the same side
 - trans: they are on opposite sides



Intrinsic Characteristics of Amino Acids

Polymerization capacity

- Most peptide bonds → trans because they are more energetically stable
- Exception: peptide bonds with proline, mainly in the cis stereoconfiguration

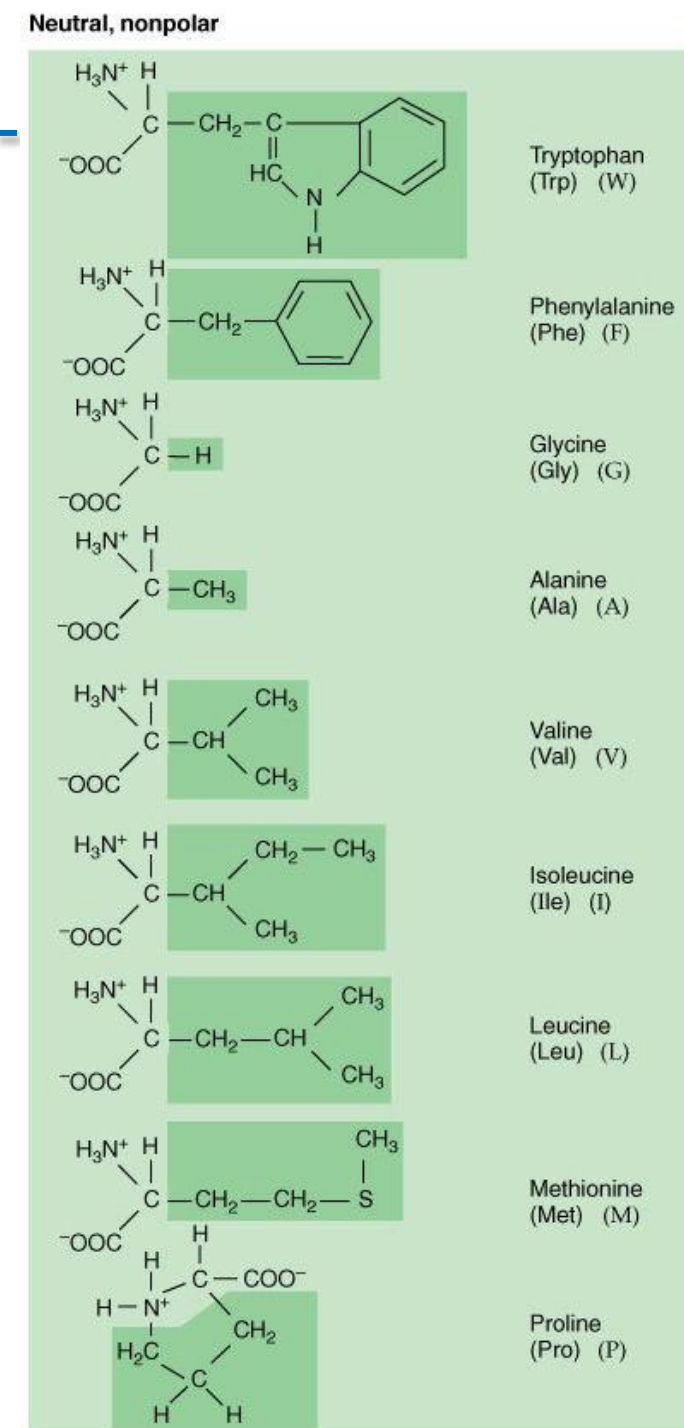
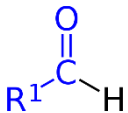
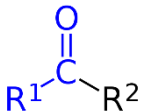


Classification

Based on the polarity/charge of the side chain

1. Non-polar or hydrophobic amino acids

- Of utmost importance for protein folding
- These include:
 - Glycine = the simplest amino acid/ side chain= **hydrogen**
 - Amino acids with **acyl-groups** in the side chain (alanine, valine, leucine, isoleucine)
 - Amino acids with a distinctive **circular** structure (proline)
 - Amino acids with a **sulfhydryl group within** the chain (methionine)
 - **Aromatic** amino acids (tryptophan, phenylalanine)



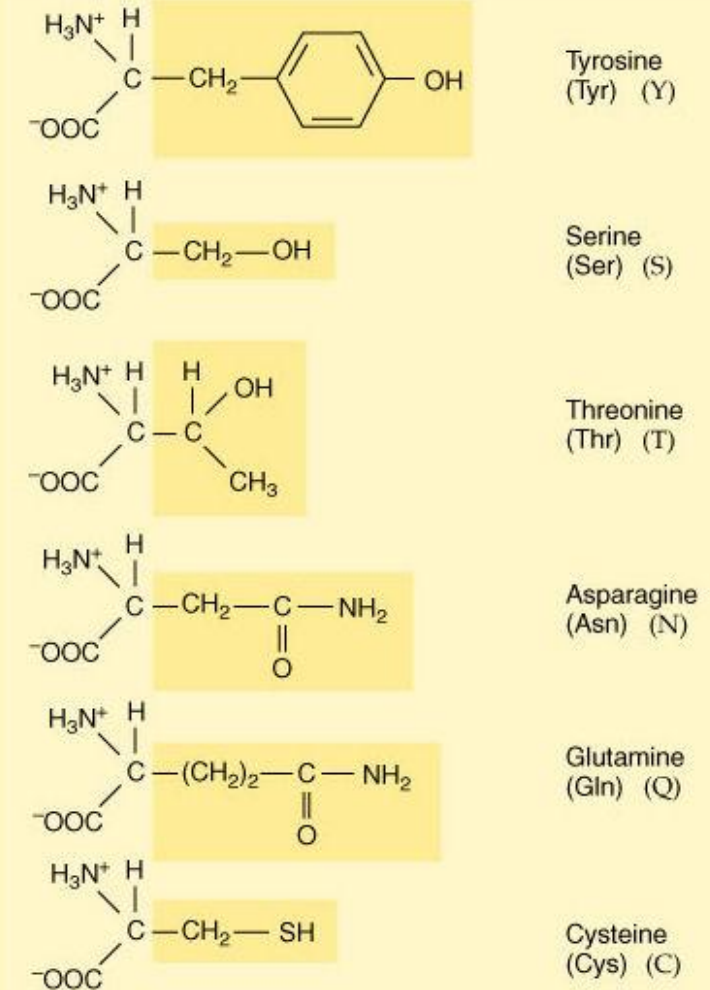
Classification

Based on the polarity/charge of the side chain

2. Neutral but polar amino acids

- They can form hydrogen bonds with water molecules
- Important in enzymatic reactions
- These include:
 - Amino acids with an **amide group** (asparagine, glutamine)
 - Amino acids with a **hydroxyl group** (serine, threonine, tyrosine)
 - Amino acids with a **sulfhydryl group at the end** of the chain (cysteine)

Neutral, polar



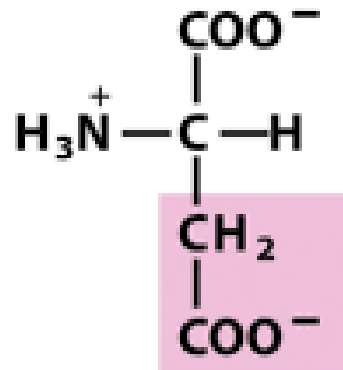
Classification

Based on the polarity/charge of the side chain

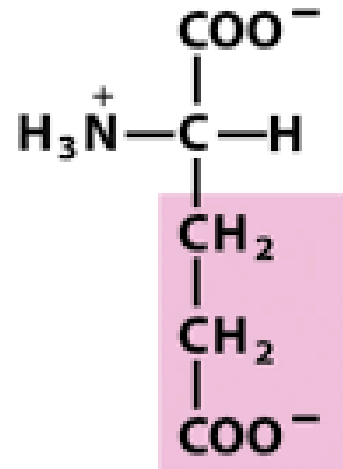
3. Acidic amino acids

- They confer metal-binding capacity on proteins
- They include amino acids with a **carboxyl group** (aspartic acid, glutamic acid)

Negatively charged R groups



Aspartate



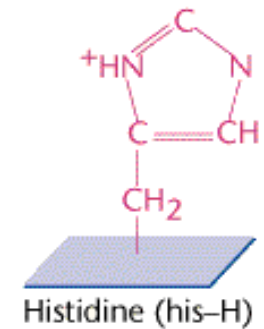
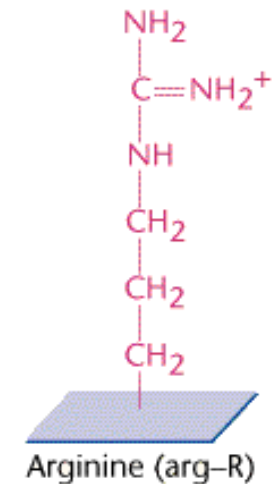
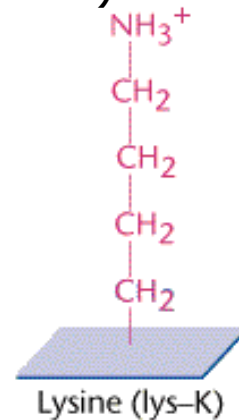
Glutamate

Classification

Based on the polarity/charge of the side chain

4. Basic amino acids

- They are often found in regions of the protein that bind ATP
- These include:
 - Amino acids with an **amino group** (arginine, lysine)
 - Amino acids with an **imidazole group** (histidine)



Classification

Based on structure

- Aliphatic (glycine, leucine, isoleucine, alanine, valine)
- Aromatic (phenylalanine, tyrosine, tryptophan)
- With carboxyl (glutamic acid, aspartic acid) or amide groups (glutamine, asparagine)
- With hydroxyl groups (threonine, serine)
- With basic groups (arginine, lysine, histidine)
- With sulfur atoms (cysteine, methionine)
- Proline (contains a secondary amine)

Classification

Based on dietary requirements

In 1936, William Cumming Rose discovered threonine and, at the same time, the necessity of obtaining it from food. He believed that there must be other essential amino acids as well... Indeed there are!

→ Essential amino acids (must be obtained from food because **our body does not produce them**): leucine, isoleucine, valine, lysine, tryptophane, threonine, methionine, phenylalanine, histidine

Some amino acids are considered essential for certain subgroups of people (e.g., newborns)

Classification

Based on dietary requirements

There are also cases in which the intake of a certain essential amino acid must be reduced while the intake of a non-essential one must be increased...

→ phenylketonuria: the enzyme that converts phenylalanine to tyrosine does not function → accumulation of phenylalanine and reduced tyrosine

