Heterocyclic Organic Chemistry CHEM 341

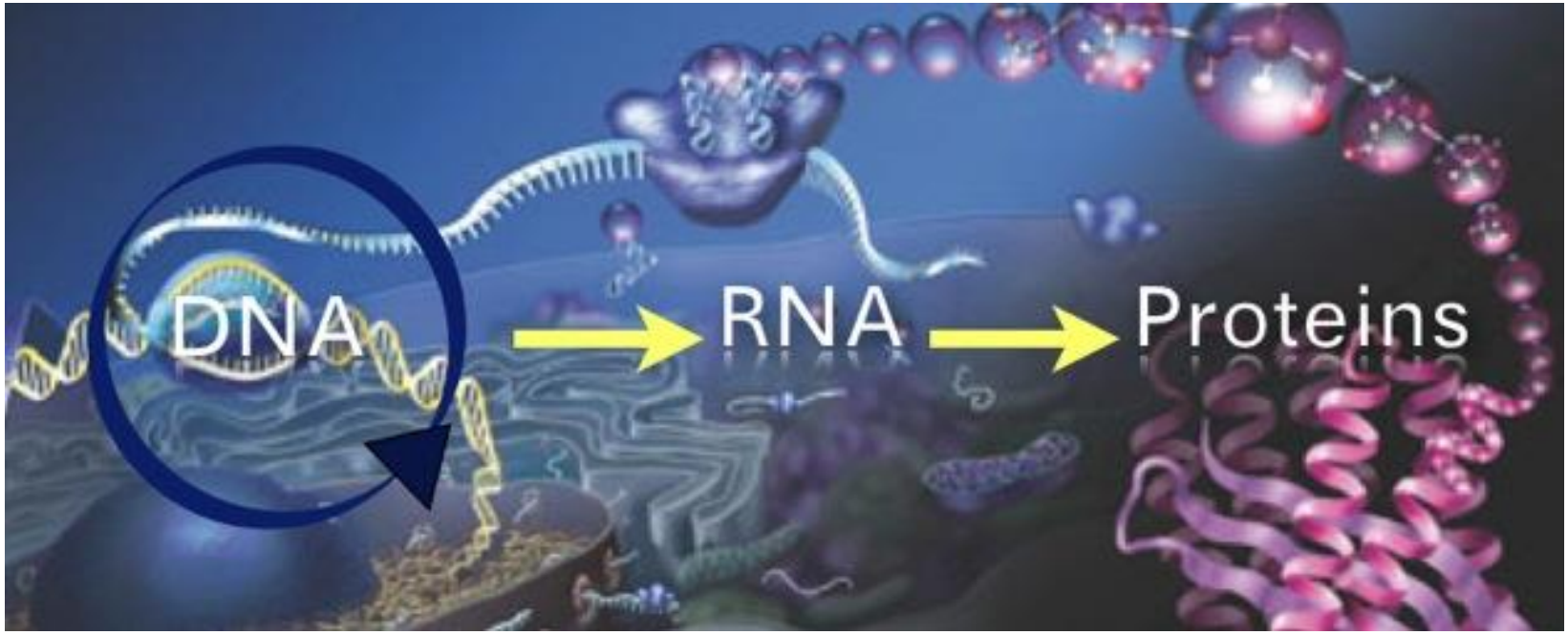
Dr. Assem Barakat
Associate Professor
Organic Chemistry
King Saud University
Room: 2B94; Email: ambarakat@ksu.edu.sa

Amino Acids and the Peptide Bond

Learning Objectives

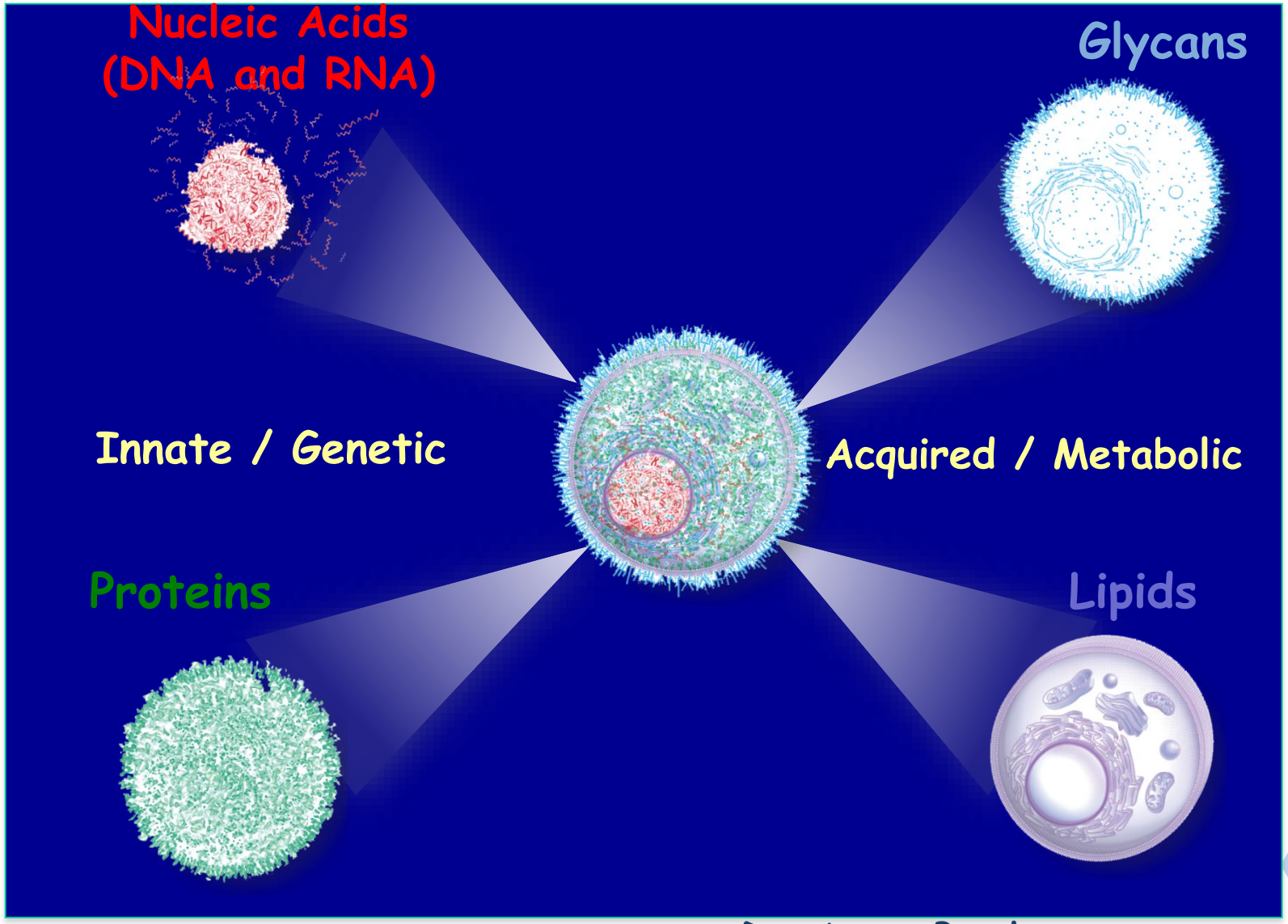
- Know your 20 standard AA's
- Be able to classify based on side chain: ionizable, aliphatic, aromatic, sulfur-containing, polar, non-polar, etc..
- Be able to draw a peptide bond and understand the amide character
- Be aware of PTM's
- Appreciate that function of proteins are dictated in large part by side chain properties of AA's

Central Dogma of Molecular Biology



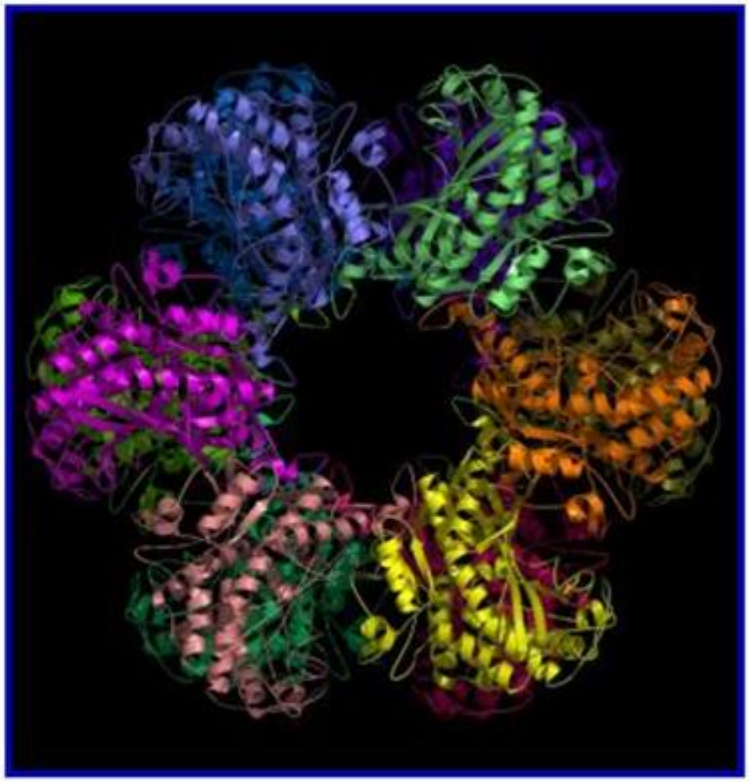
http://www.labgrab.com/users/labgrab/blog/central-dogma-genetics-incomplete_id%3D904

Four Main Families of Biomolecules in Cells

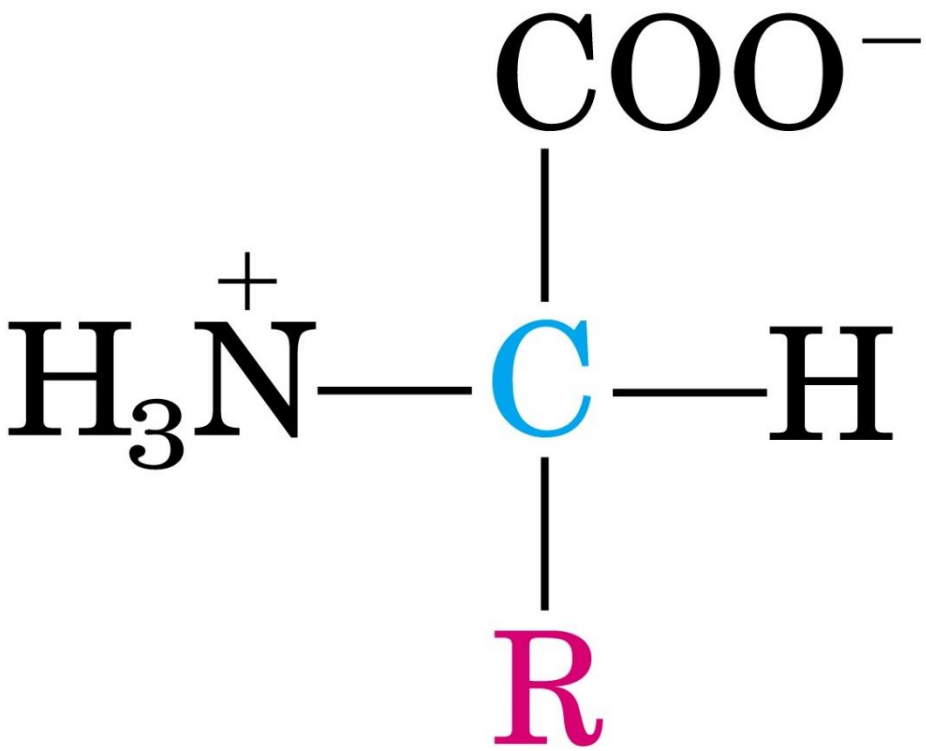


Protein Functions

- Structural – muscle, skin, hair
- Signalling – insulin, growth hormone, EPO
- Catalysts – enzymes
- Immunity – antibodies
- Regulation – DNA-binding proteins
- Poisons – toxins in snakes/spiders etc
- Transport – **hemoglobin**



Structure of Amino acid



Classification of Amino Acids

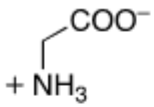
Nutritional

- Essential
- Non-essential

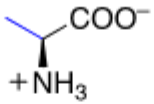
Based on R group

- Non polar aliphatic R group
- Polar uncharged R group
- Aromatic R group
- Positively charged R group
- Negatively charged R group

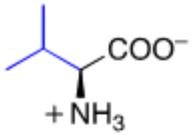
Nonpolar, aliphatic R group



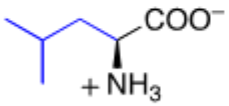
Glycine *(Gly, G)*



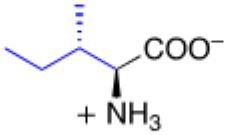
(S)-(+)-Alanine *(Ala, A)*



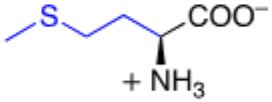
(S)-(+)-Valine *(Val, V)*



(S)-(–)-Leucine *(Leu, L)*



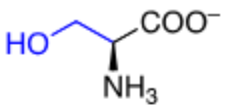
(2S,3S)-(+)-Isoleucine *(Ile, I)*



(S)-(–)-Methionine *(Met, M)*

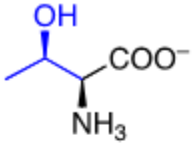
The hydrocarbon R group in this class of amino acids is nonpolar and hydrophobic. Glycine has the simplest amino acid structure. The bulky side chain of valine, isoleucine and leucine are important in promoting hydrophobic interactions within protein structures.

Polar, uncharged R groups



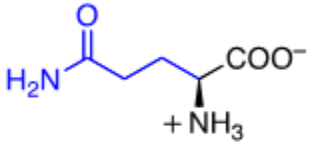
(S)-(–)-Serine *(Ser, S)*

pKa ~ 13

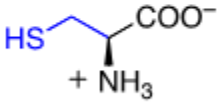


(2S,3R)-(–)-Threonine *(Thr, T)*

pKa ~ 13

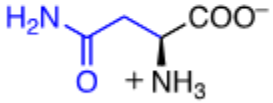


(S)-(+)-Glutamine *(Gln, Q)*



(R)-(–)-Cysteine *(Cys, C)*

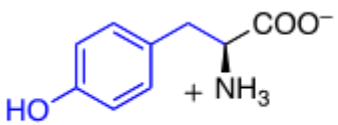
pKa ~ 8.2



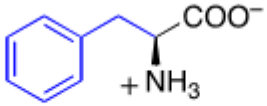
(S)-(–)-Asparagine *(Asn, N)*

The R group of these amino acids is more soluble in water, or hydrophilic than those of non polar amino acids, because they contain functional groups that form hydrogen bond with water

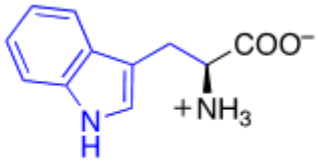
Aromatic R groups



(S)-(–)-Tyrosine *(Tyr, Y)*



(S)-(–)-Phenylalanine *(Phe, F)*

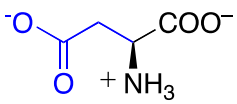


(S)-(–)-Tryptophan *(Trp, W)*

Their aromatic side chains are relatively nonpolar. All can participate in hydrophobic interactions. The OH group of tyrosine can form hydrogen bond and can act as an important functional group in the activity of some enzymes.

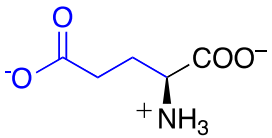
Negatively / Positively charged R groups

Acidic:



(S)-(+)-Aspartic Acid *(Asp, D)*

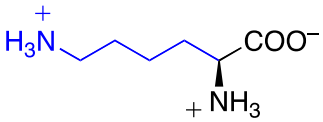
pKa ~ 3.6



(S)-(+)-Glutamic Acid *(Glu, E)*

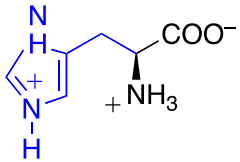
pKa ~ 4.2

Basic:



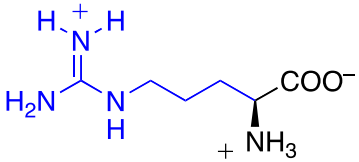
(S)-(+)-Lysine *(Lys, K)*

pKa ~ 10.5



(S)-(–)-Histidine *(His, H)*

pKa ~ 6.0



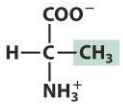
(S)-(+)-Arginine *(Arg, R)*

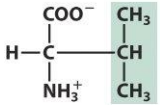
pKa ~ 12.5

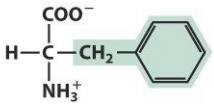
The amino acids in which the R group have a net positive charge or negative charge it depend on the pH.

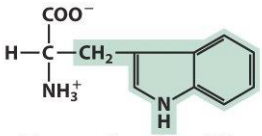
Structures and abbreviations of the standard amino acids

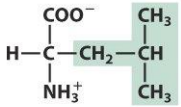
Hydrophobic amino acids

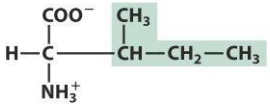

Alanine (Ala, A)

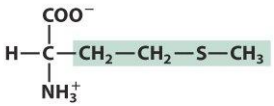

Valine (Val, V)

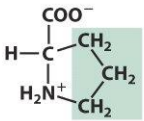

Phenylalanine (Phe, F)


Tryptophan (Trp, W)

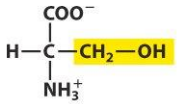

Leucine (Leu, L)

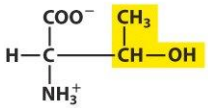

Isoleucine (Ile, I)

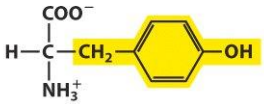

Methionine (Met, M)

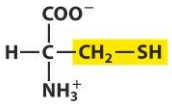

Proline (Pro, P)

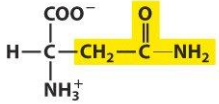
Polar amino acids

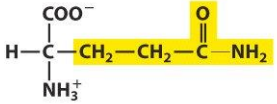

Serine (Ser, S)

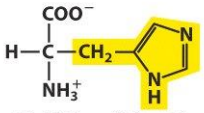

Threonine (Thr, T)

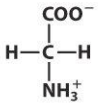

Tyrosine (Tyr, Y)


Cysteine (Cys, C)

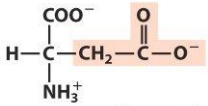

Asparagine (Asn, N)

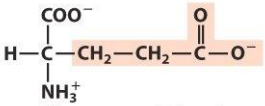

Glutamine (Gln, Q)

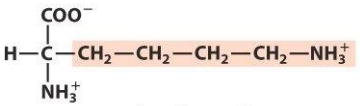

Histidine (His, H)

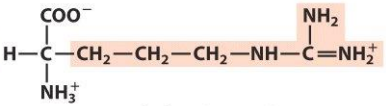

Glycine (Gly, G)

Charged amino acids


Aspartate (Asp, D)


Glutamate (Glu, E)


Lysine (Lys, K)


Arginine (Arg, R)

Nutritional Classification of Amino acids

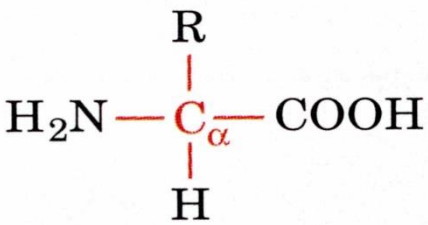
Essential Amino Acids:
Need to supplied in daily diet

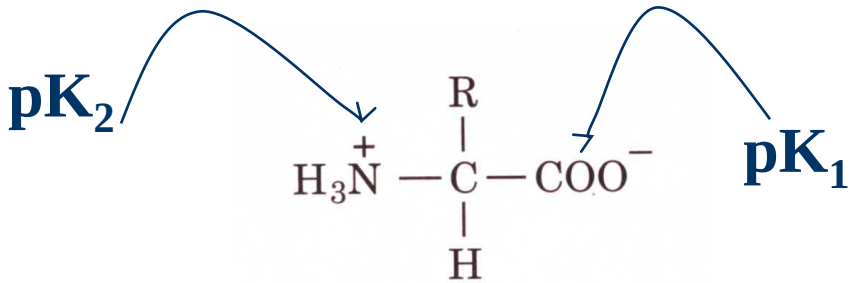
1. Lysine
2. Leucine
3. Isoleucine
4. Metionine
5. Tryptophan
6. Phenylalanine
7. Threonine
8. Valine
9. Histidine

Nonessential Amino Acids:
Need not be supplied in daily diet

- Alanine
- Asparagine
- Glycine
- Tyrosine
- Serine
- Proline
- Cysteine
- Cystine
- Histidine(essential for children)
- Glutamine(conditionally essential)
- Arginine(conditionally essential)
- Glutamate

Amino Acids:
The building blocks of proteins





a amino acids because of the a carboxylic and a amino groups pK_1 and pK_2 respectively pKR is for R group pK's

$pK_1 \approx 2.2$ while $pK_2 \approx 9.4$

In the physiological pH range, both carboxylic and amino groups are completely ionized

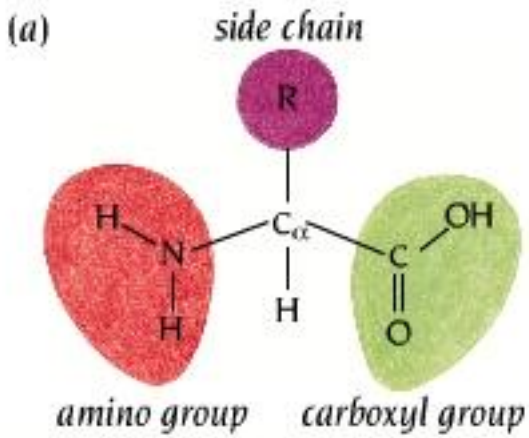
Amino acids are Ampholytes

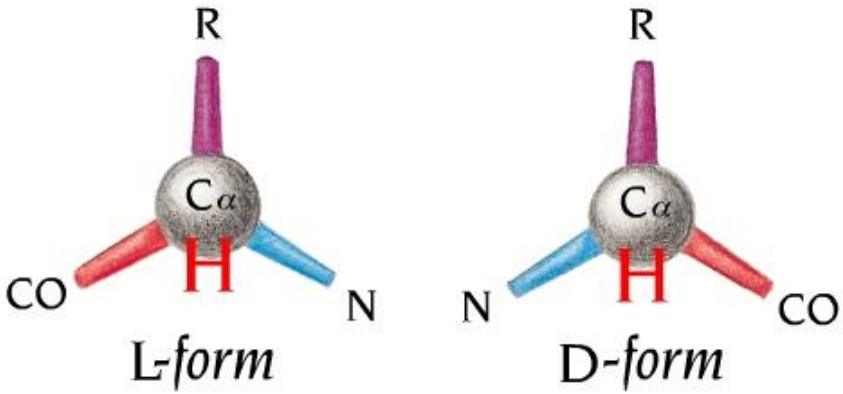
They can act as either an acid or a base

They are Zwitterions or molecules that have both a positive and a negative charge

Amino acids are the building blocks of proteins

- Three major parts: carboxyl group, amino group, and side chain.
- Central C atom called *alpha carbon*.
- Amino acids can differ in their side chains (R).
- The alpha carbon is a *chiral center*. (except for one amino acid)
- L-form found almost exculsively in proteins (CORN)





Sources, Classification and Structure of Amino Acids

- The amino acids are known by common names.
- Each also has a three-letter abbreviation based on this name, which is used when writing the formulas of peptides, and a one-letter abbreviation used to describe the amino acid sequence in a protein.

  For example; Glycine= Gly; Alanine = Ala; Valine = Val, etc..
- The amino acids are classified into:
  - Essential amino acids

    Eight amino cannot be synthesized by adult humans and therefore must be included in the diet in the form of proteins.

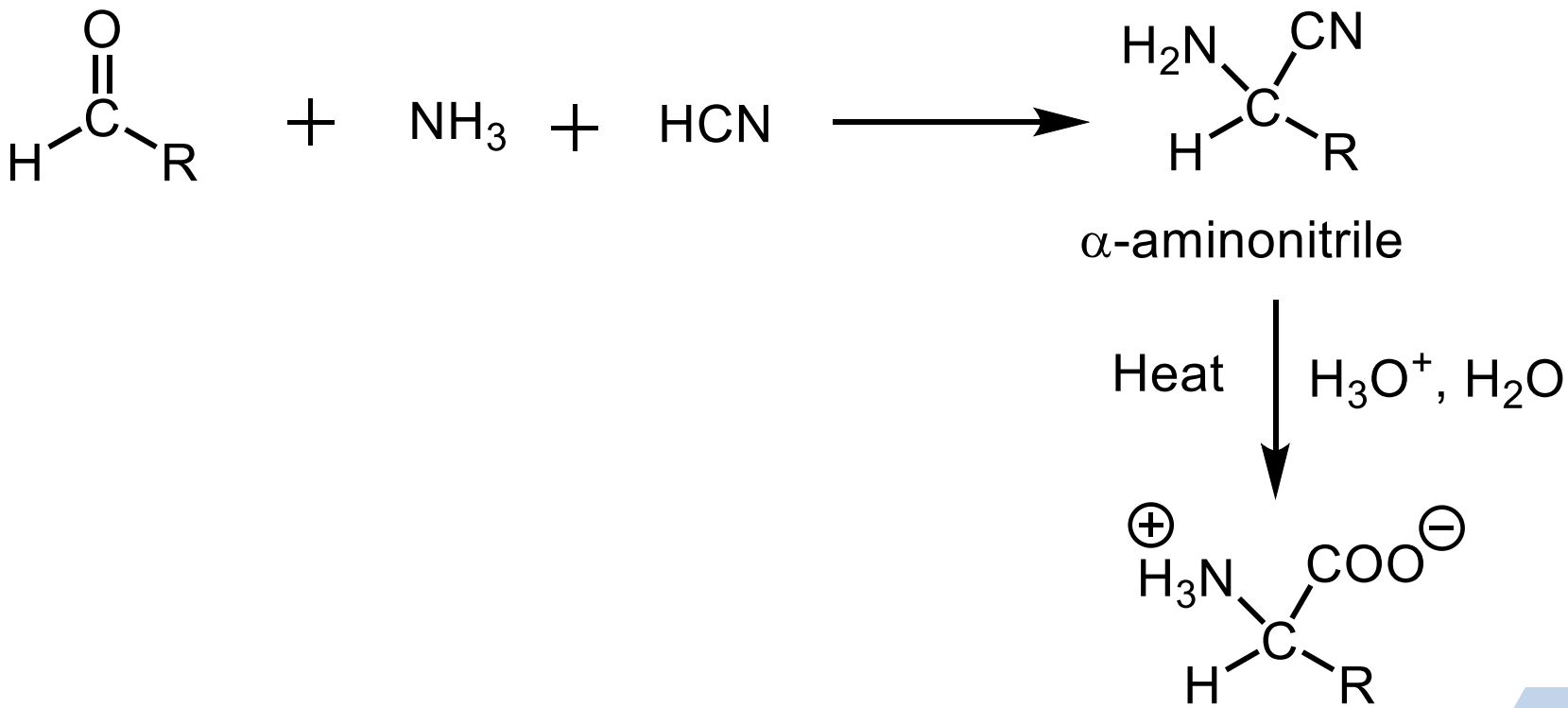
    e.g. Valine, Leucine, Isoleucine, Threonine, Methionine, Phenylalanine, Tryptophan, and Lysine.
  - Non-essential amino acids

    Twelve amino acids can be synthesized in the body from other foods.

    e.g. Glycine, Alanine, Serine, Cysteine, Proline, Tyrosine, Aspartic acid, Glutamic acid, Asparagine, Glutamine, Arginine, and Histidine.

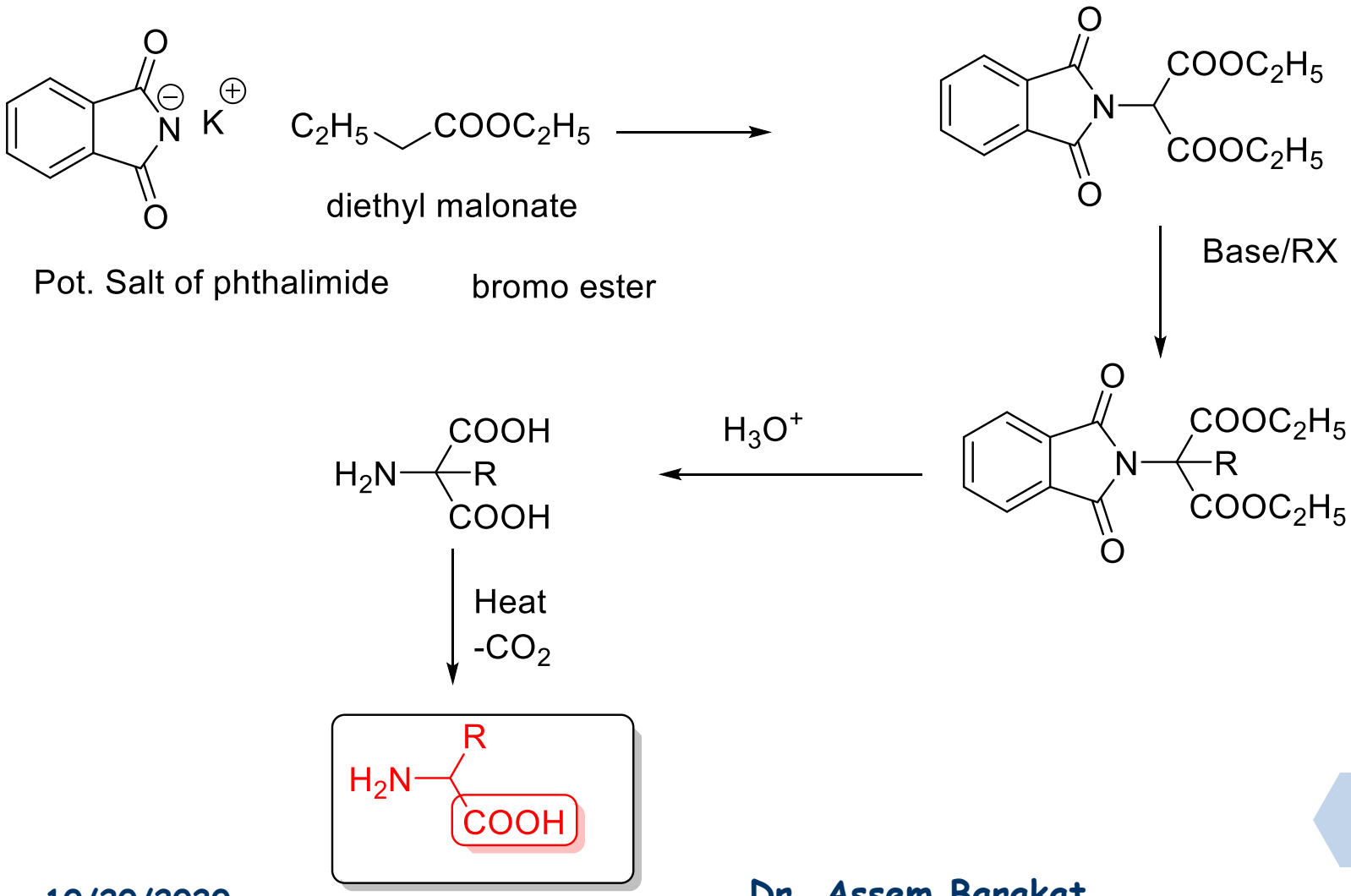
Synthesis of Amino Acids

Strecker Synthesis: **Recall reductive amination and Cyanohydrin formation.**



Synthesis of Amino Acids

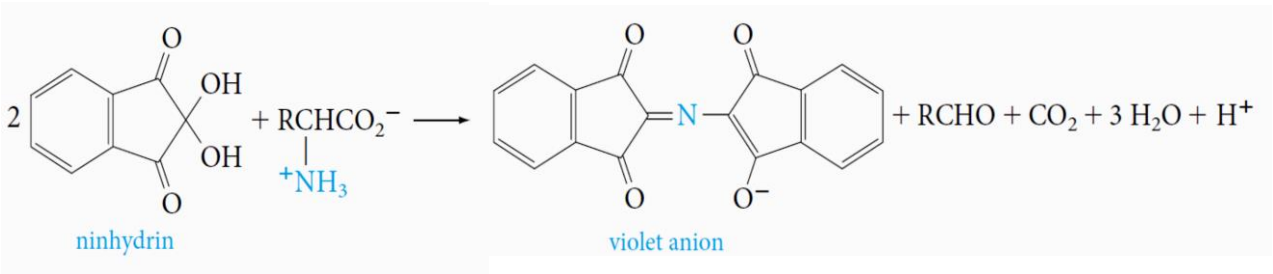
Gabriel Method:



Reactions of Amino Acids

1) The Ninhydrin Reaction

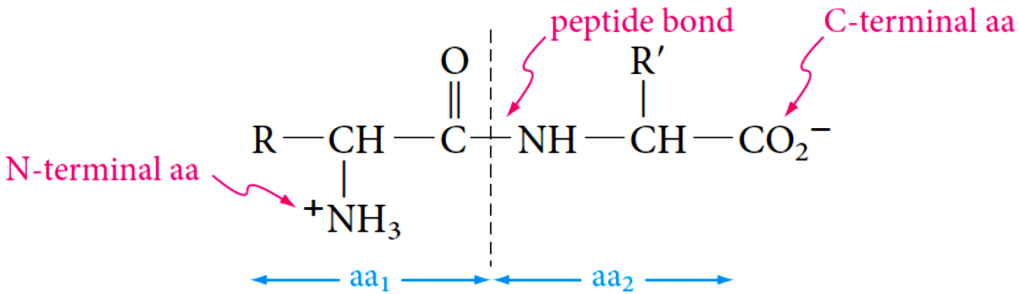
- **Ninhydrin is a useful reagent for detecting amino acids and determining the concentrations of their solutions.**
  - ***Ninhydrin** is the hydrate of a cyclic triketone, and when it reacts with an amino acid, a violet dye is produced.*



- **Only the nitrogen atom of the violet dye comes from the amino acid (primary amino group); the rest of the amino acid is converted to an aldehyde and carbon dioxide.**
- **Only proline, which has a secondary amino group, reacts differently to give a yellow dye, but this, too, can be used for analysis.**

2) Formation of an amide linkage (The peptide bond: Proteins)

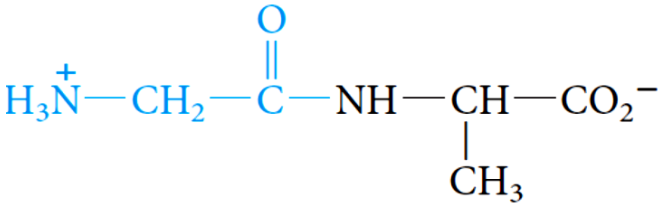
- **Amino acids** are linked in **peptides and proteins** by an amide bond (***peptide bond***) between the carboxyl group of one amino acid and the α-amino group of another amino acid.
- A molecule containing only *two* amino acids (the shorthand aa is used for amino acid) joined in this way is a **dipeptide**:



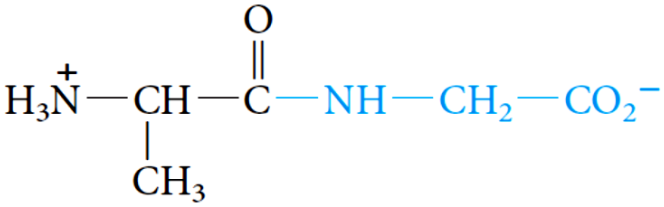
- By convention, the **peptide bond** is written with the amino acid having a free $^{+}NH_3$ group at the left and the amino acid with a free CO_2^- group at the right.
- These amino acids are called, respectively, the **N-terminal amino** acid and the **C-terminal** amino acid.

- We often write the formulas for peptides in a kind of shorthand by simply linking the **three-letter abbreviations for each amino acid**, *starting with the N-terminal one at the left.*

- **For example;** glycylalanine is Gly—Ala, and alanylglycine is Ala—Gly.

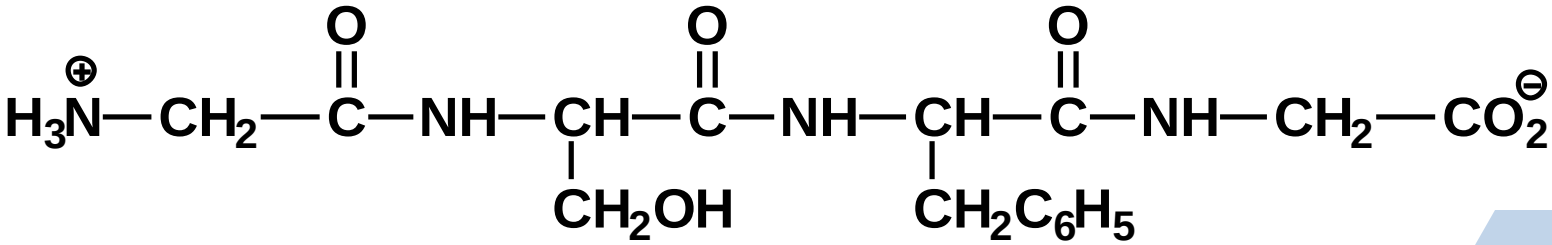


glycylalanine



alanylglycine

A tetrapeptide glycylserylphenylalanylglycine = gly-ser-phe-gly



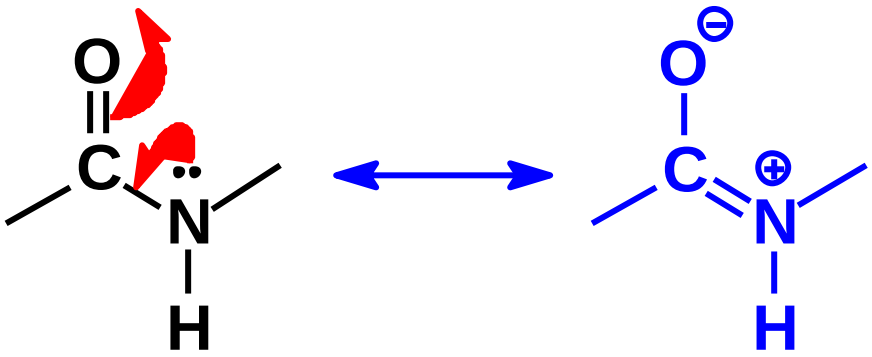
The peptide bond: Proteins

The Peptide (Amide) Bond

The amide nitrogen is sp^2 hybridized and the lone pair is conjugated with the carbonyl group

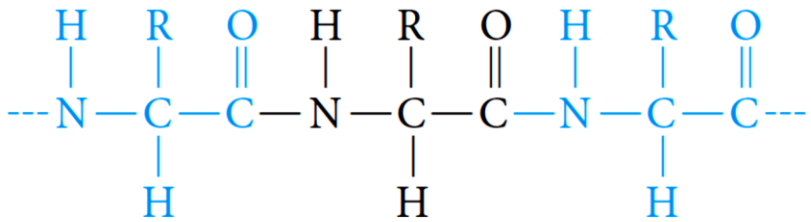
There is considerable C–N double-bond character

Rotation about the C–N bond is difficult



The Primary Structure of Proteins

- The **backbone of proteins** is a repeating sequence of one nitrogen and two carbon atoms.



protein chain, showing amino acids linked by amide bonds

- **Peptides and proteins** can be hydrolyzed to their amino acid components by heating with 6 M HCl.
- An instrument called an **amino acid analyzer** is used to determine the amino acids mixture.

Peptide Synthesis

- Many methods have been developed to link amino acids in a controlled manner.

To link the carboxyl group of one amino acid to the amino group of a second amino acid. Several steps must be followed

1-Protection Step: the amino group of the first amino acid and the carboxyl group of the second must be protected.

2- Coupling step: the two protected amino acids

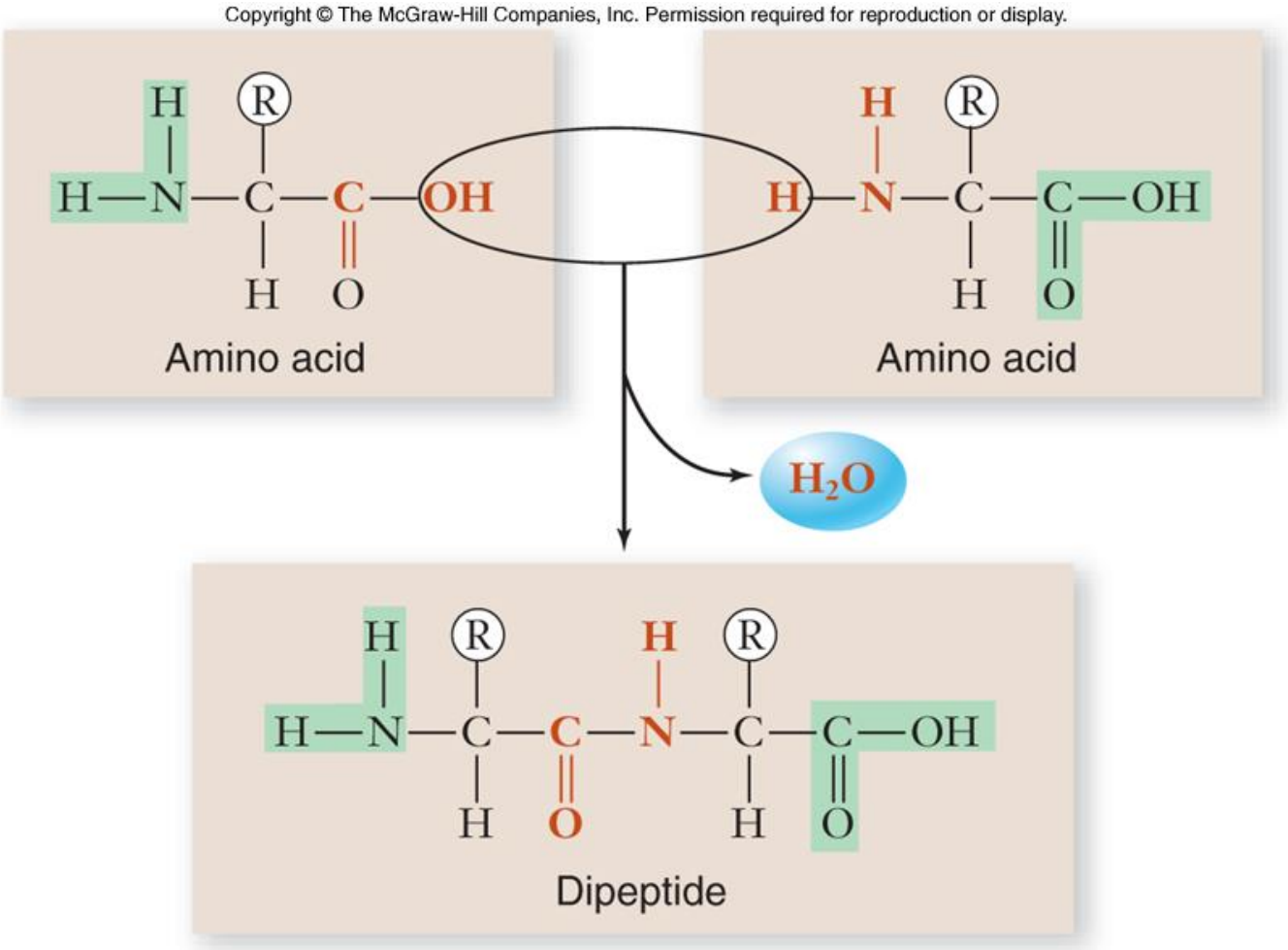
3- Deprotection Step: removing the protecting groups.

(Note that all the protecting group must be removed under normal conditions)

In this way, we can control the linking of the two amino acids so that the carboxyl group of aa_1 combines with the amino group of aa_2.

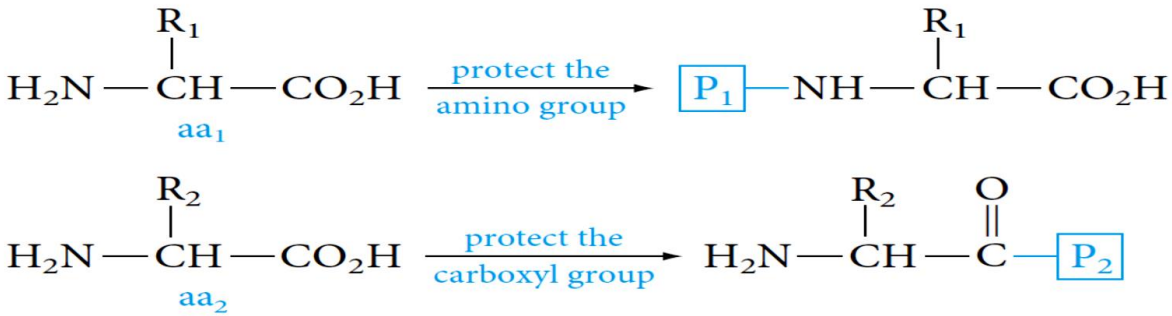
Peptide Synthesis

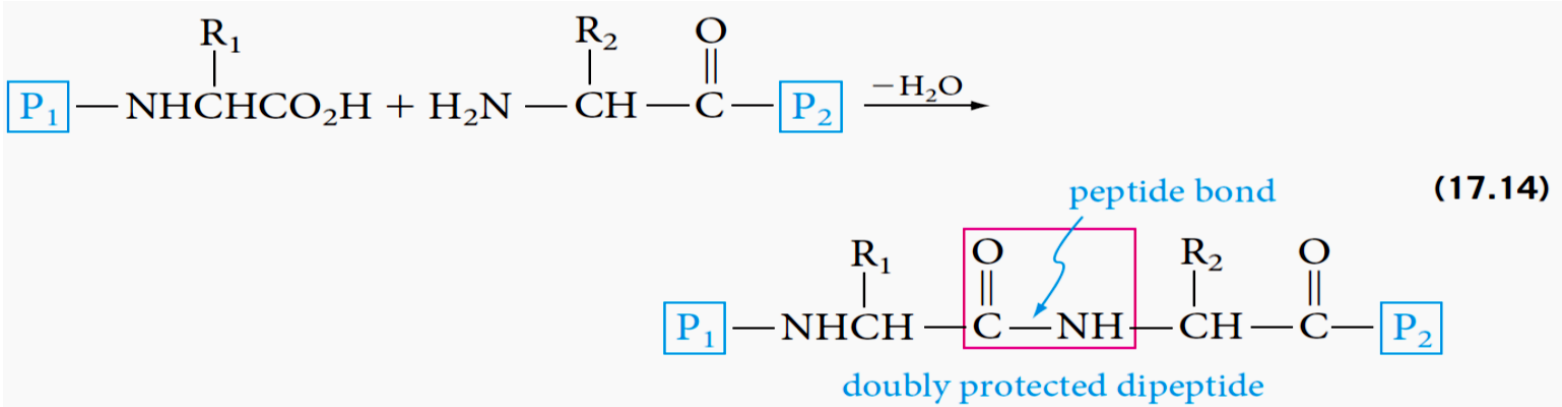
Condensation reaction



Peptide Synthesis

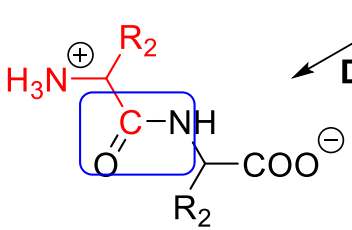
1-Protection Step





(17.14)

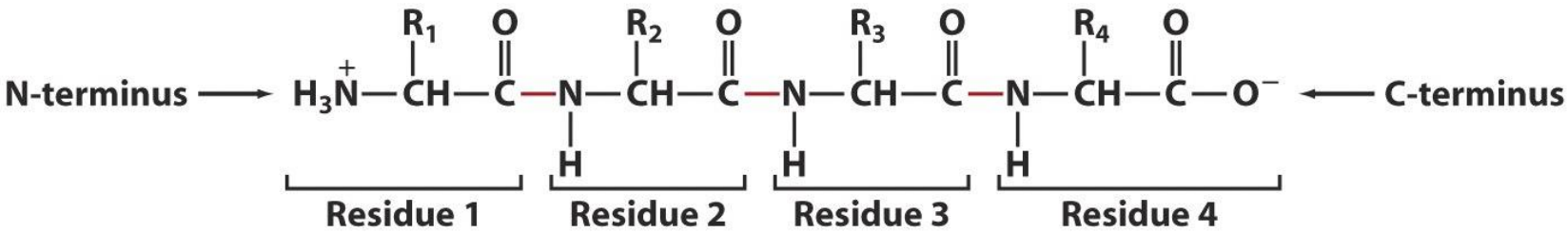
3- Deprotection Step

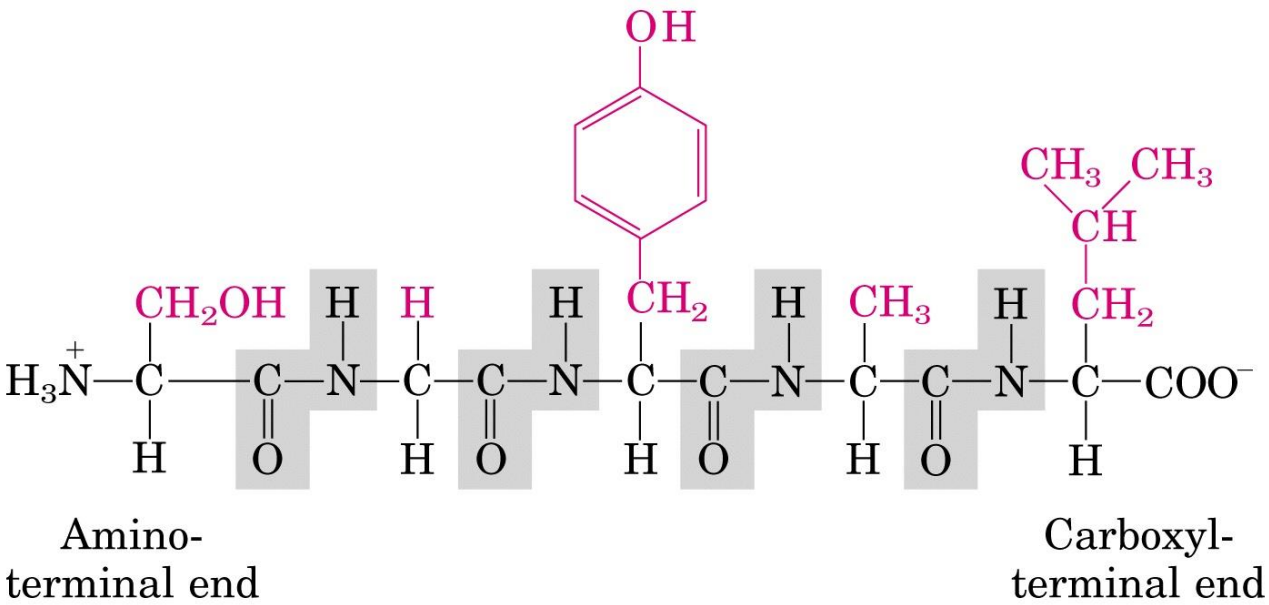


Deprotection
removing of the protecting groups

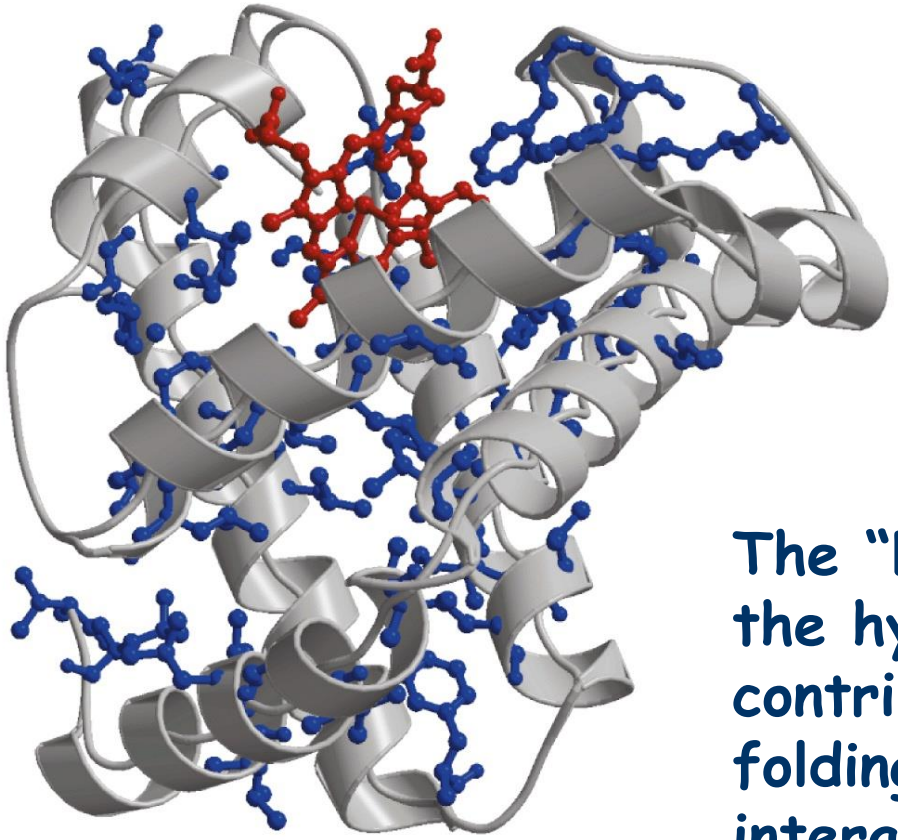
Free dipeptide

Amino acid residues





Non-polar R-groups tend to be buried in the cores of soluble proteins



(d)

<u>Myoglobin</u>

Blue = non-polar R-group

Red = Heme

The "Bricks" that make up the hydrophobic core and contribute significantly to folding (hydrophobic interactions)

Uses of Amino Acids

- **Amino acids**, often referred to as the building blocks of proteins, are compounds that play many critical roles in your body.
- They're needed for vital processes like the building of proteins and synthesis of hormones and neurotransmitters.
- **Phenylalanine** plays an integral role in the structure and function of proteins and enzymes and the production of other amino acids.
- **Valine** helps stimulate muscle growth and regeneration and is involved in energy production.
- **Threonine** is a principal part of structural proteins such as collagen and elastin, which are important components of the skin and connective tissue. It also plays a role in fat metabolism and immune function.
- **Tryptophan** is needed to maintain proper nitrogen balance and is a precursor to serotonin, a neurotransmitter that regulates your appetite, sleep and mood.

Uses of Amino Acids

- **Methionine** plays an important role in metabolism and detoxification. It's also necessary for tissue growth and the absorption of zinc and selenium, minerals that are vital to your health.
- **Leucine** helps to regulate blood sugar levels, stimulates wound healing and produces growth hormones.
- **Isoleucine** is involved in muscle metabolism and is heavily concentrated in muscle tissue. It's also important for immune function, hemoglobin production and energy regulation.
- **Lysine** plays major roles in protein synthesis, hormone and enzyme production and the absorption of calcium. It's also important for energy production, immune function and the production of collagen and elastin.
- **Histidine:** Histidine is used to produce histamine, a neurotransmitter that is vital to immune response, digestion, sexual function and sleep-wake cycles. It's critical for maintaining the myelin sheath, a protective barrier that surrounds your nerve cells