



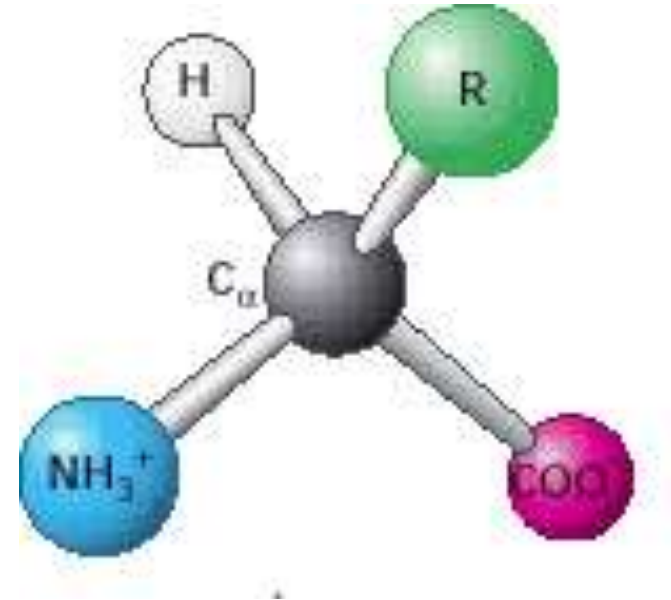
Amino acids

Prof. Mamoun Ahram

General structure



- Proteins are polymers of α -amino acids (or amino acids).
- An amino acid consists of:
 - a central carbon atom, called the α carbon, linked to four groups
 - an amino group ($-\text{NH}_2$),
 - a carboxylic acid group ($-\text{COOH}$),
 - a hydrogen atom, and
 - a specific R group (the side chain)

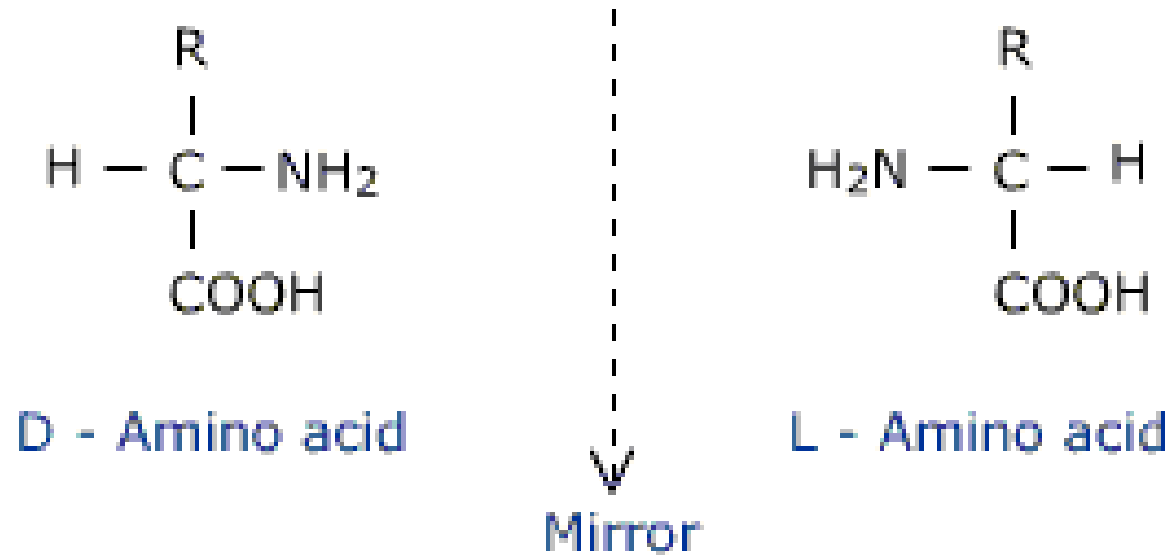


L and D isomers



- The α -carbon atom is chiral and, thus, amino acids are chiral and can be present in two forms, L and D isomers, that are mirror-images of each other (they are enantiomers).
- Only L amino acids naturally make up proteins.

Note that the amino and carboxylic groups of all amino acids are ionized at neutral pH



The amine group of L-amino acids occurs in the left-hand side when drawn in the Fischer projection, keeping the carboxylic acid group on bottom (or top) and the R group on the top, whereas the amine group of the L-amino acids occurs on the left.

Types of amino acids



- There are twenty kinds of amino acids depending on the side chains varying in
 - Size
 - Shape
 - Charge
 - Hydrogen-bonding capacity
 - Hydrophobic character
 - Chemical reactivity

Classification (according to R group)



Non-polar	Polar	Charged (positive)	Charged (negative)
Alanine	Serine	Lysine	Glutamate
Valine	Threonine	Arginine	Aspartate
Leucine	Glutamine	Histidine	
Isoleucine	Asparagine		
Methionine	Cysteine		
Tryptophan	Tyrosine		
Phenylalanine			
Proline			
Glycine			



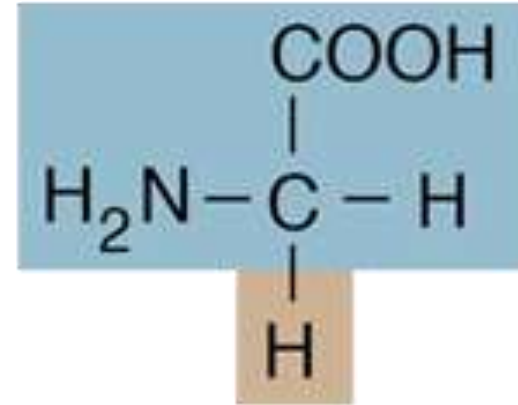
Non-polar, aliphatic amino acids

Glycine (Gly)



- Glycine is a derivative of acetic acid.

Note that the amino and carboxylic groups are normally ionized at physiological pH



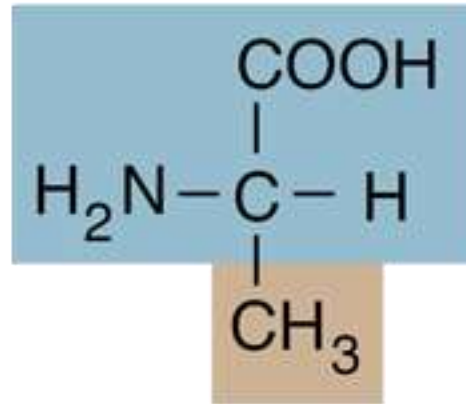
Glycine (gly)

Is it chiral?

Alanine (Ala)

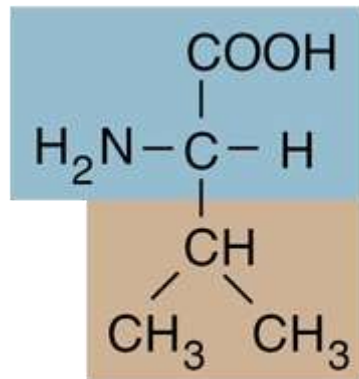


- Alanine, the next simplest amino acid, has a methyl group ($-\text{CH}_3$) as its side chain.

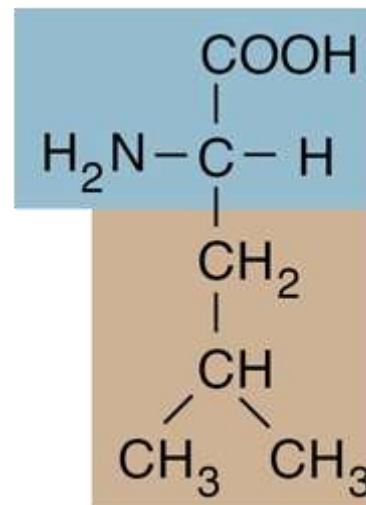


Alanine (ala)

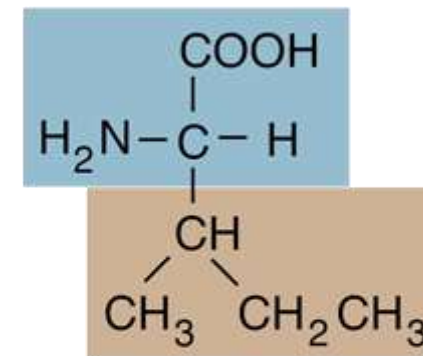
Valine (Val), leucine (Leu), and isoleucine (Ile)



Valine (val)*



Leucine (leu)*



Isoleucine (ile)*

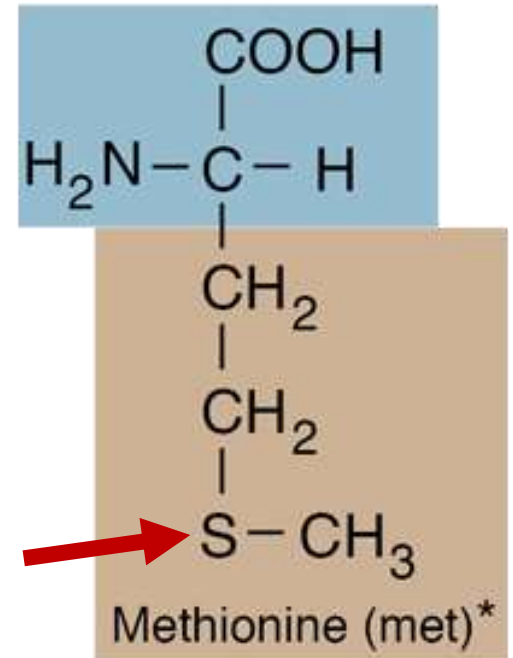
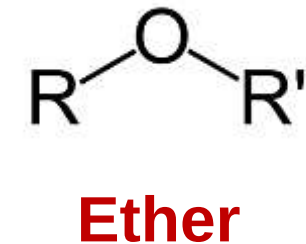
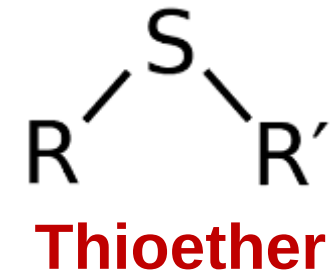
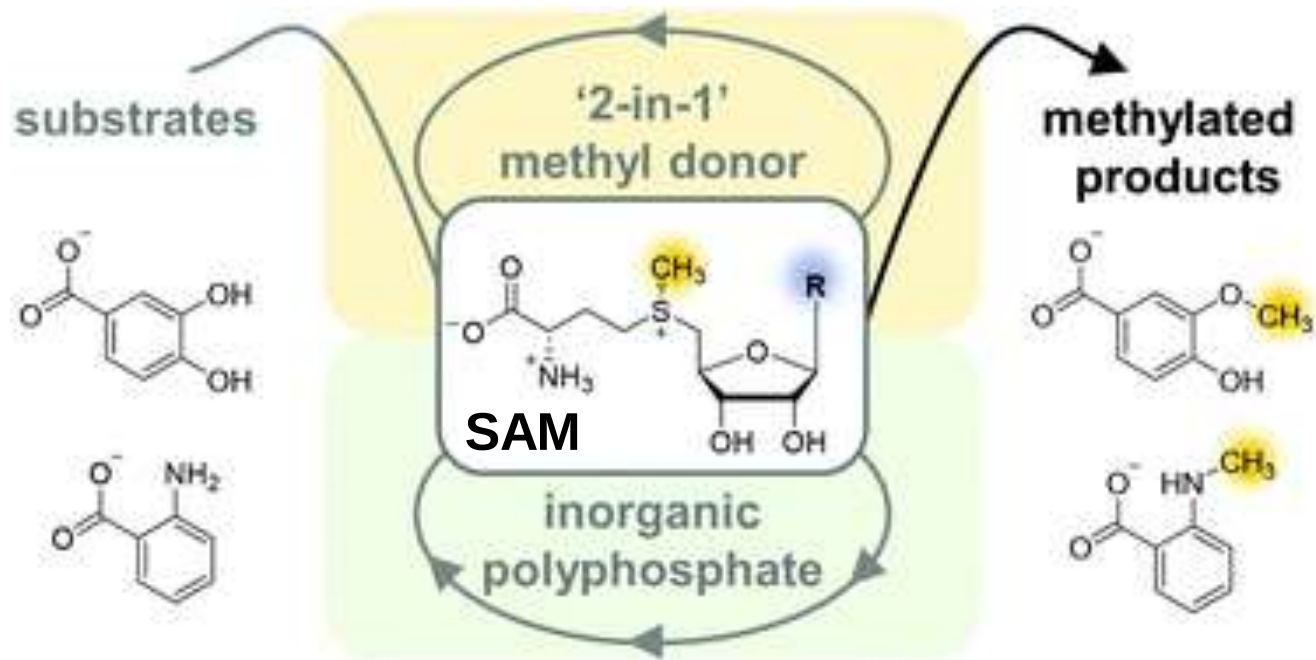
They are branched amino acids.

These are *essential amino acids* since the body cannot synthesize them.

Methionine (Met)

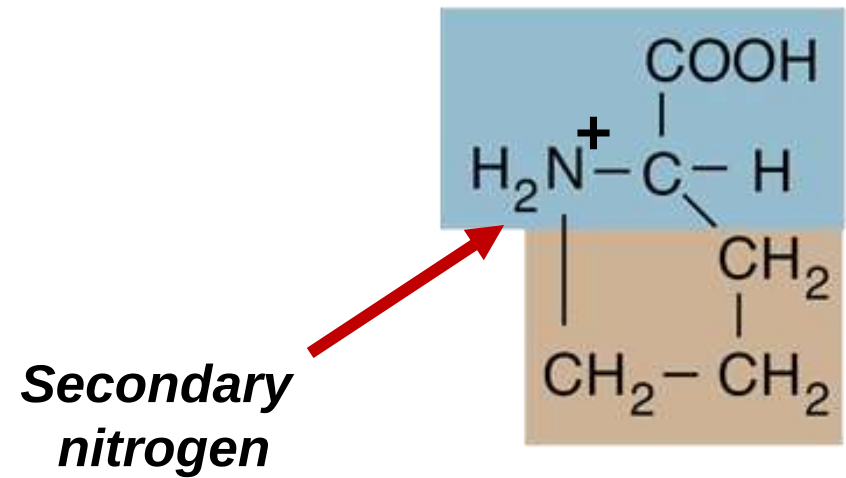


It can form S-Adenosyl-L-Methionine (SAM) which serves as a methyl donor in reactions.



Proline (Pro)

(the only cyclic amino acid)



Proline (pro)

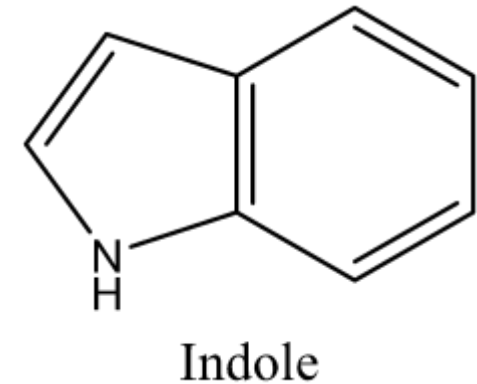
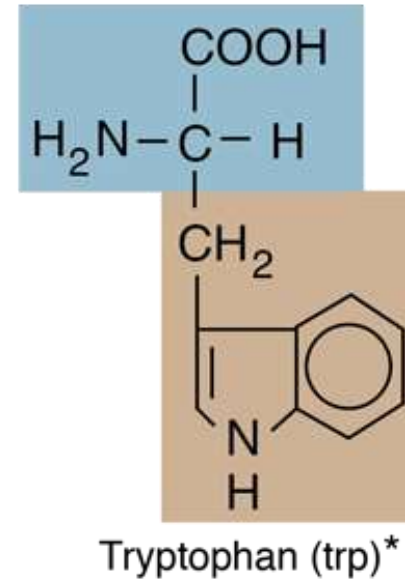
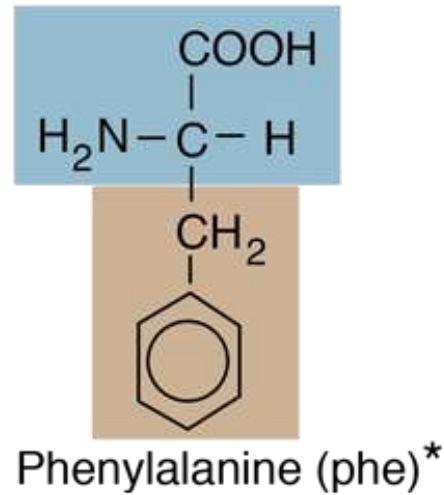
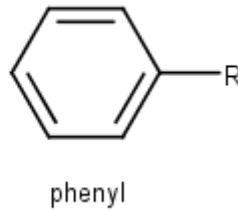
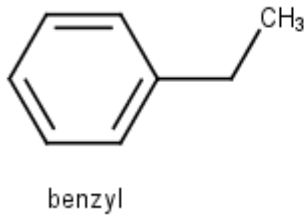


Non-polar, aromatic amino acids

Phenylalanine (Phe) and Tryptophan (Trp)



- Phenylalanine contains a phenyl ring.
- Tryptophan has an indole ring; the indole group consists of two fused rings and an NH group.



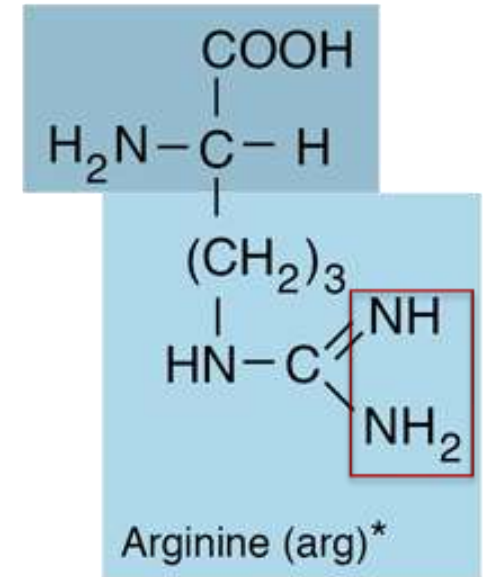
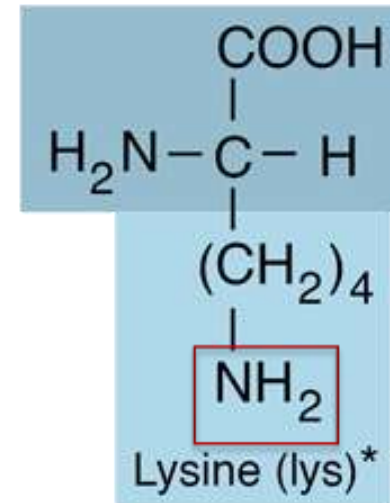


Positively-charged amino acids

Lysine (Lys) and arginine (Arg)



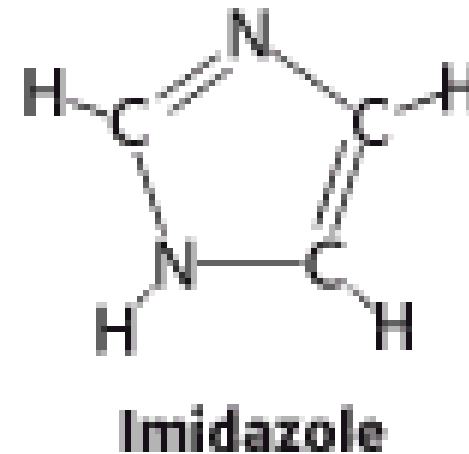
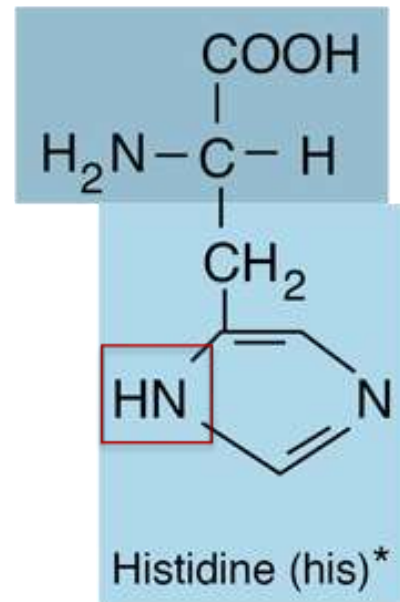
- Lysine and arginine have relatively long side chains that terminate with groups that are positively charged at a neutral pH.
- Lysine ends with a primary amino group and arginine by a guanidinium group.



Histidine (His)



- Histidine contains an imidazole group, an aromatic ring that also can be positively charged.



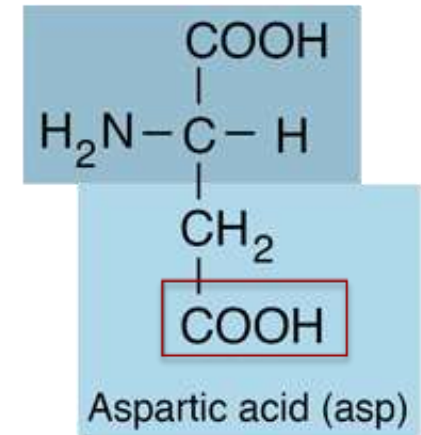
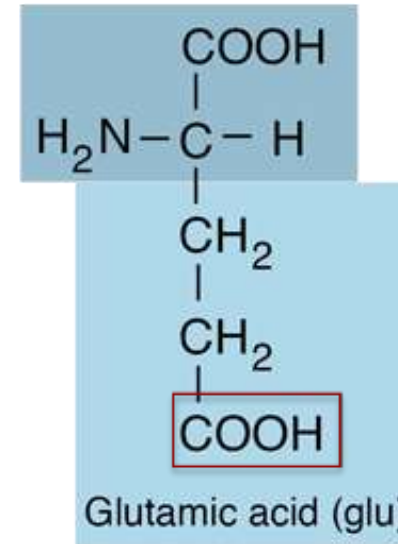


Negatively-charged amino acids

Aspartic acid (Asp) and glutamic acid (Glu)



- Two amino acids contain acidic side chains: aspartic acid and glutamic acid.
- These amino acids are often called aspartate and glutamate when they are charged.



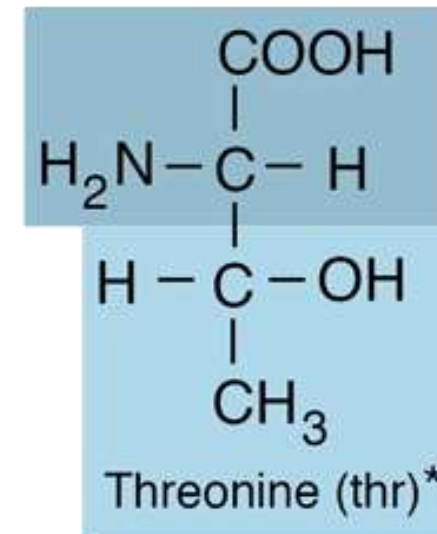
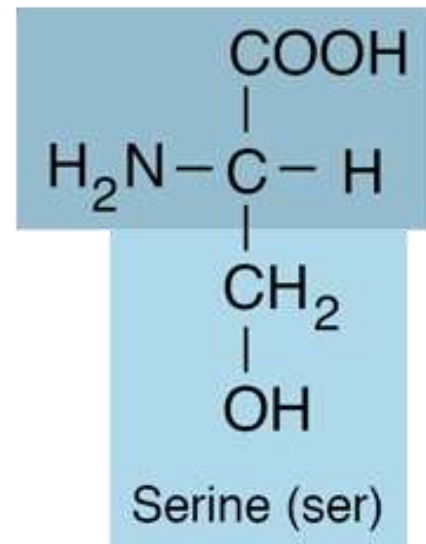


Polar, hydrophilic, neutral amino acids

Serine (Ser) and threonine (Thr)



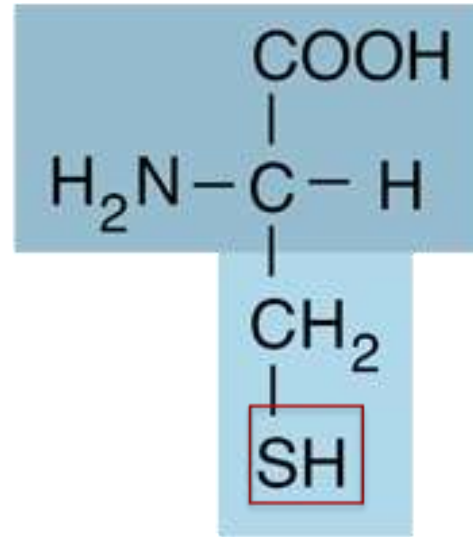
- Serine and threonine, contain aliphatic hydroxyl groups.
- The hydroxyl groups on serine and threonine make them hydrophilic and reactive.



Cysteine (Cys)



- Cysteine contains a sulfhydryl or thiol (-SH), group.
- The sulfhydryl group is reactive.

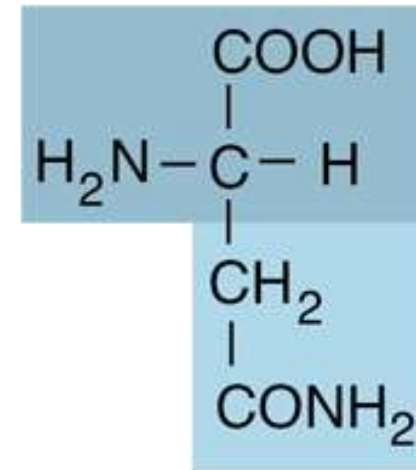
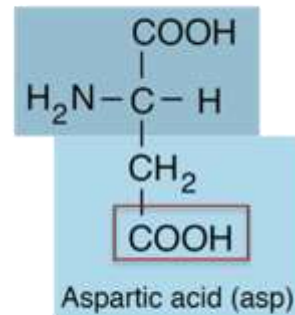
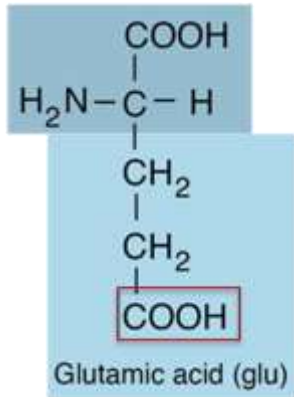


Cysteine (cys)

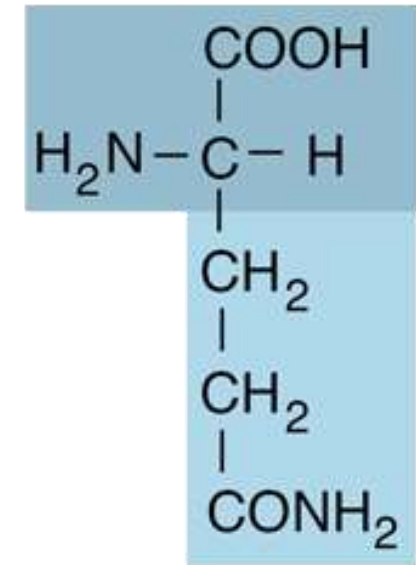
Asparagine (Asn) and glutamine (Gln)



- Asparagine and glutamine are uncharged derivatives of aspartate and glutamate.
- Each contains a terminal carboxamide in place of a carboxylic acid.



Asparagine (asn)

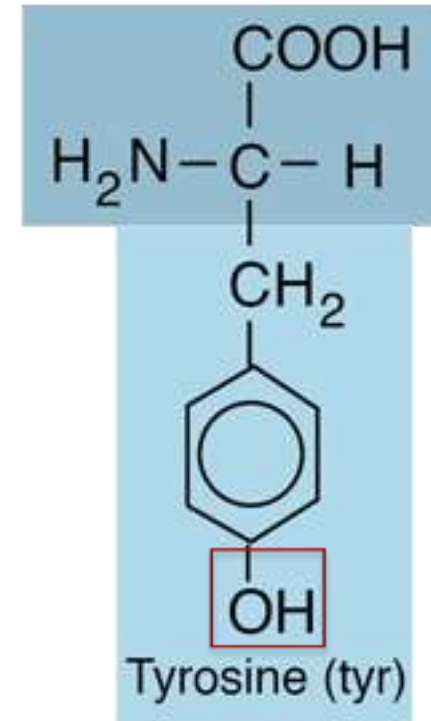
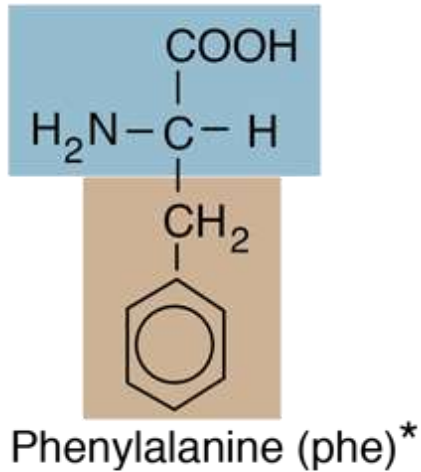


Glutamine (gln)

Tyrosine (Tyr)



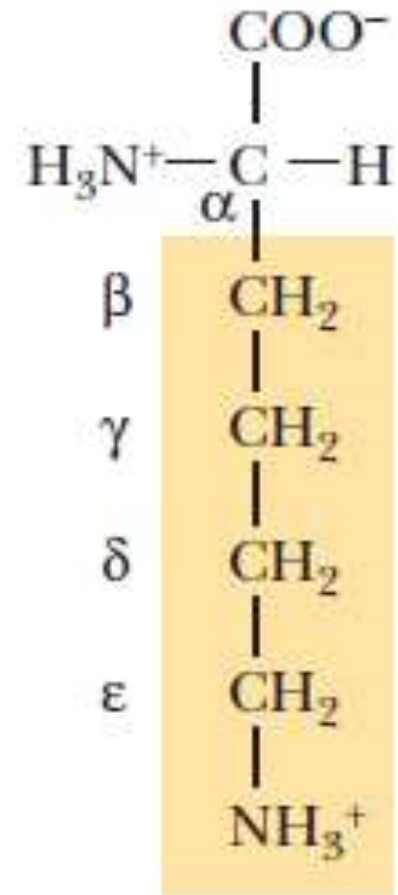
- The aromatic ring of tyrosine contains a hydroxyl group.
 - It is derived from phenylalanine.
- This hydroxyl group is reactive.



Designation of carbons



- Side-chain carbon atoms are designated with letters of the Greek alphabet, counting from the α -carbon. These carbon atoms are, in turn, the β -, γ -, δ -, and ϵ -carbons.
- If a carbon atom is terminal, it is referred to as the ω -carbon.



Questions



- Two amino acids are negatively-charged:
- The following amino acid is achiral:
- ...etc.

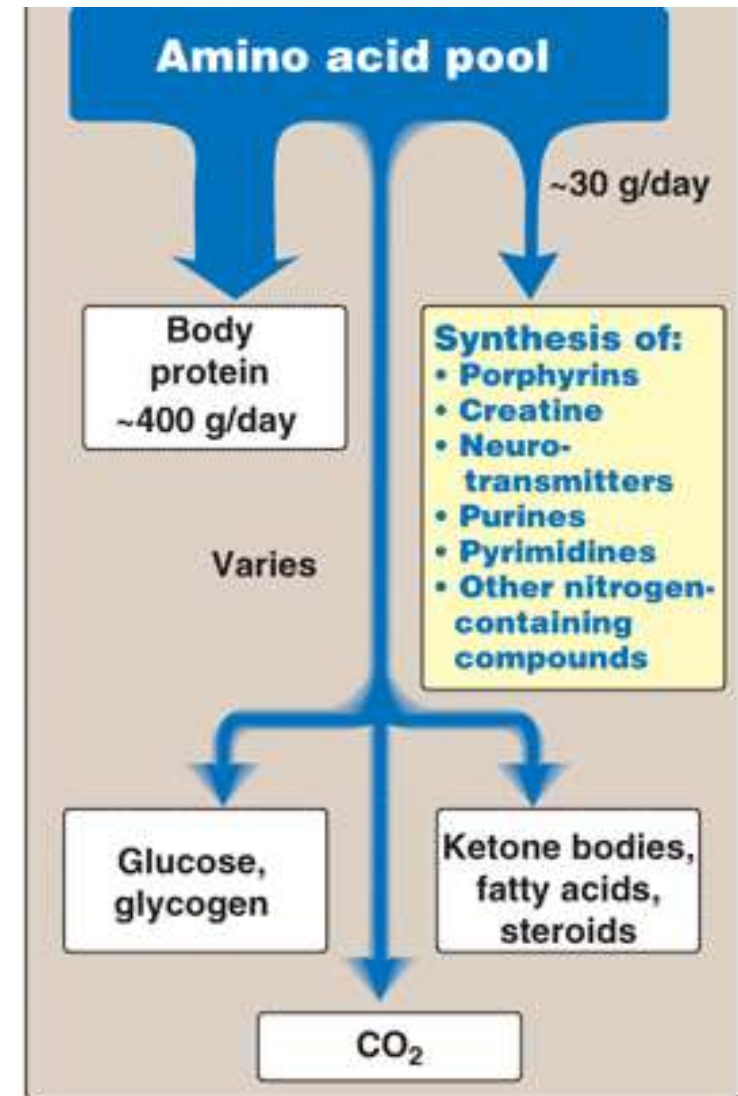


Specialized and uncommon amino acids

Biological significance of amino acids



- α -nitrogen atom of amino acids is a primary source for many nitrogenous compounds:
 - Hormones
 - Neurotransmitters
 - Biologically active peptides

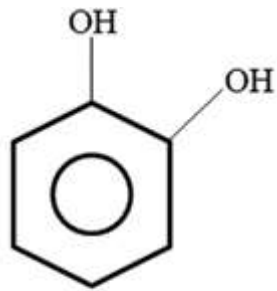


Tyrosine (1)

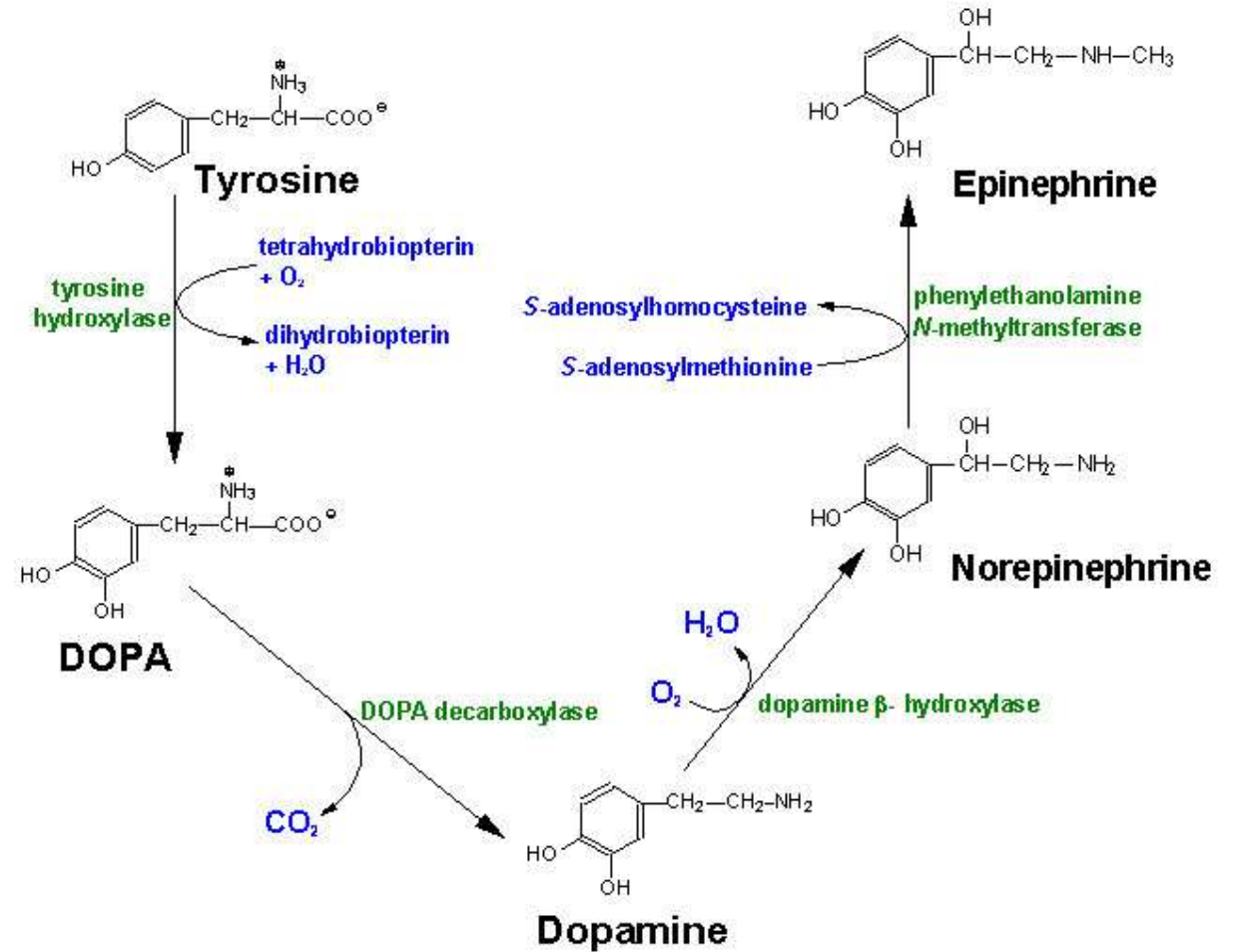


- It is converted into catecholamine neurotransmitters.

- Dopamine
- Norepinephrine
- Epinephrine
- flight or fight



catechol

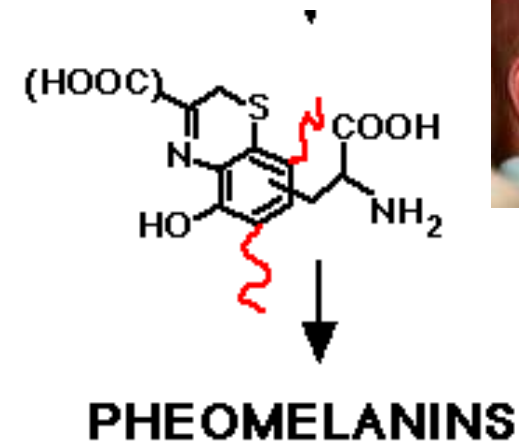
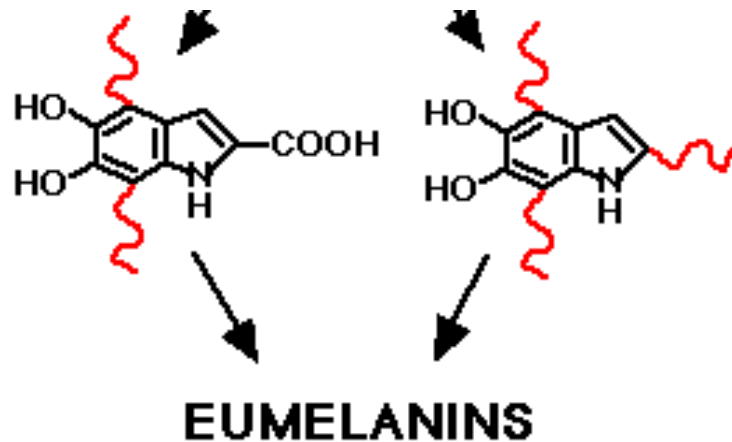
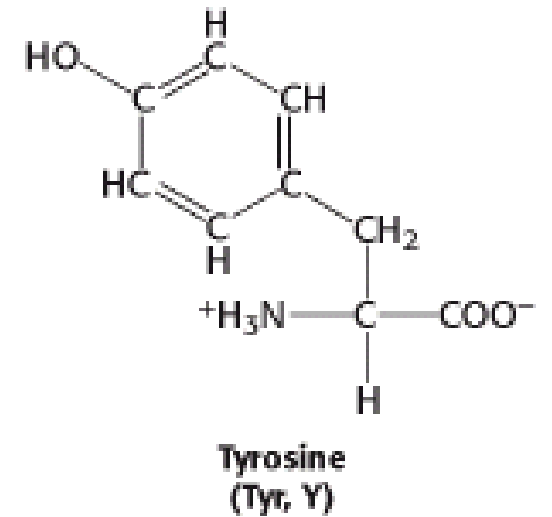
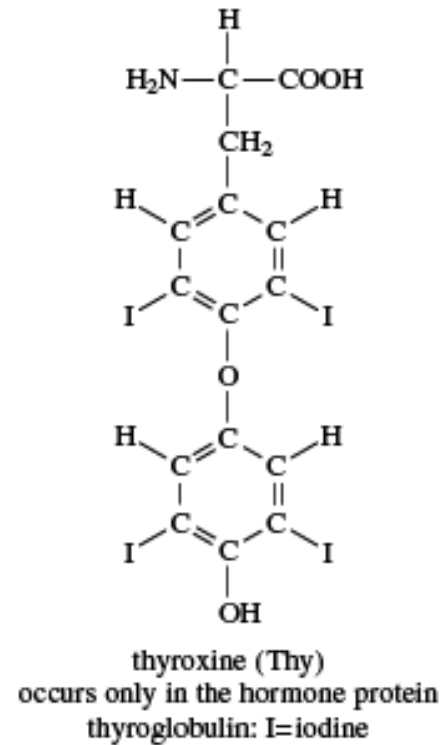


Tyrosine (2)



● Tyrosine is converted into:

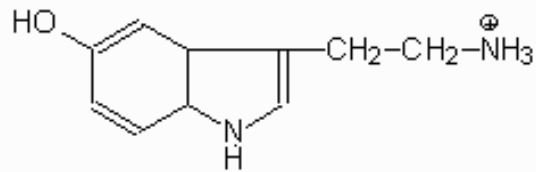
- Melanin (skin color)
- Thyroxine (hormone)



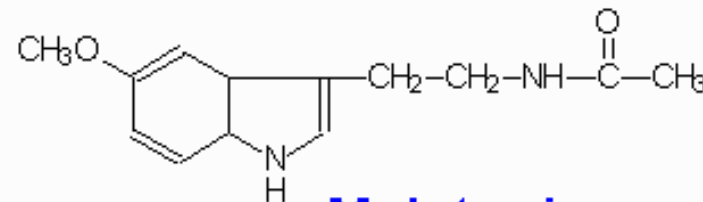
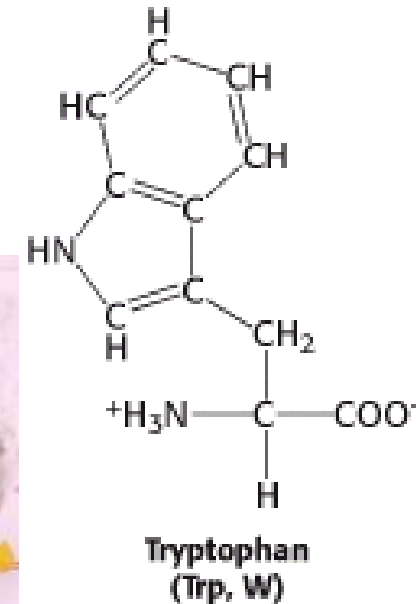
Tryptophan



- Tryptophan serves as the precursor for the synthesis of Neurotransmitters
 - Serotonin (neurotransmitter-sedative)
 - Melatonin (day-night cycle)



Serotonin
(5-hydroxytryptamine)

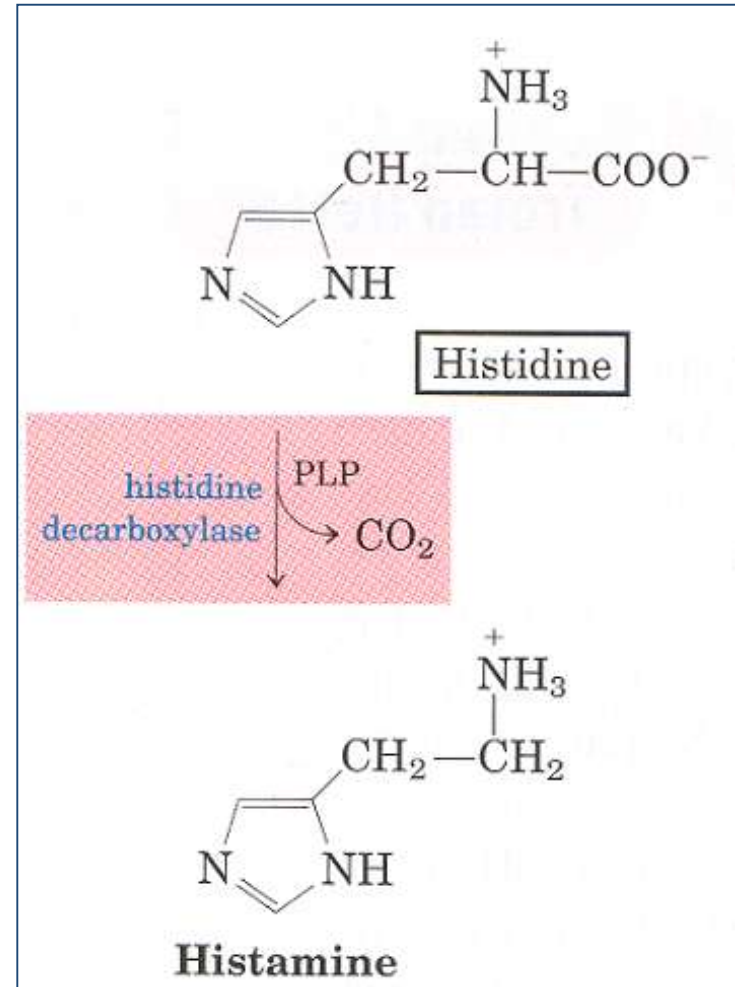


Melatonin

Histamine



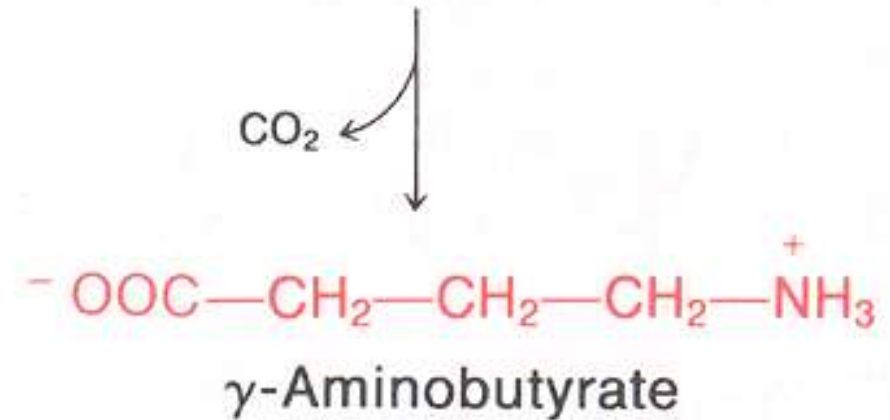
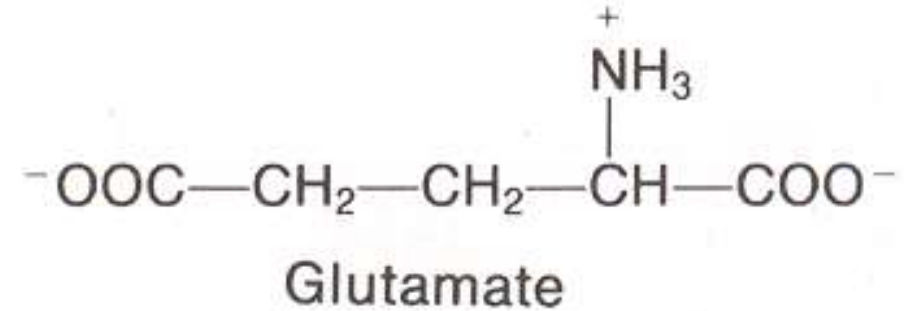
- Acts as a neurotransmitter
- Causes allergic symptoms (a major causes for asthma)



Glutamate



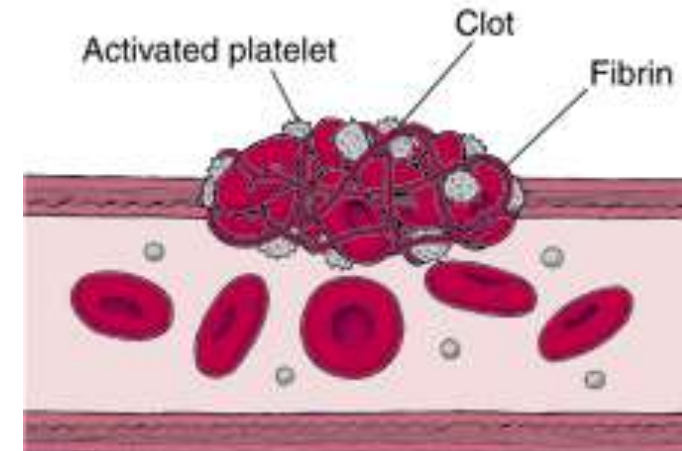
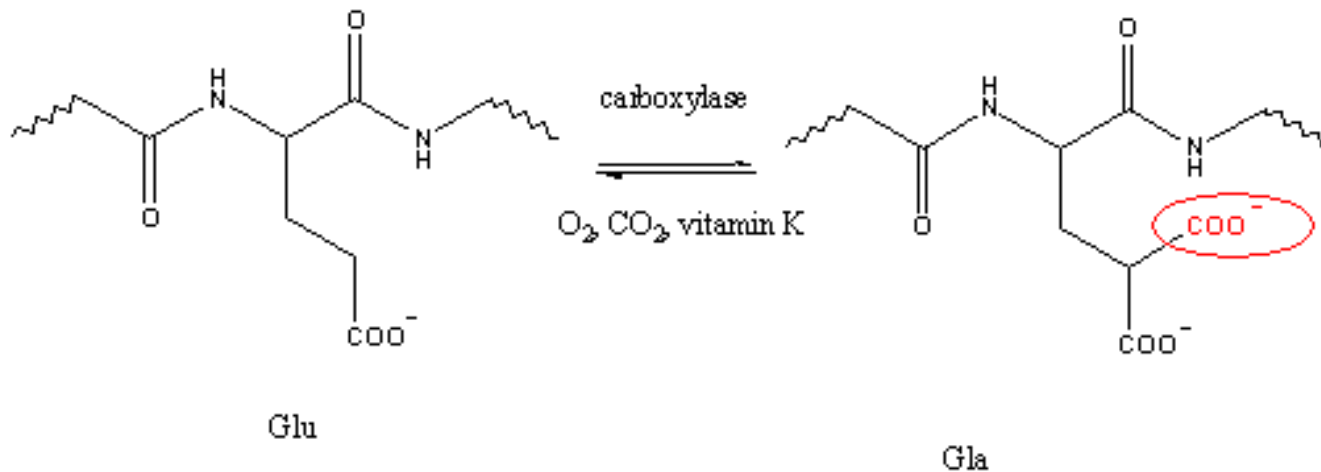
- It is a precursor of γ -aminobutyric acid (GABA), an inhibitory neurotransmitter.
- It has relaxing, anti-anxiety and anti-convulsive effects.



γ - carboxyglutamate (Gla)



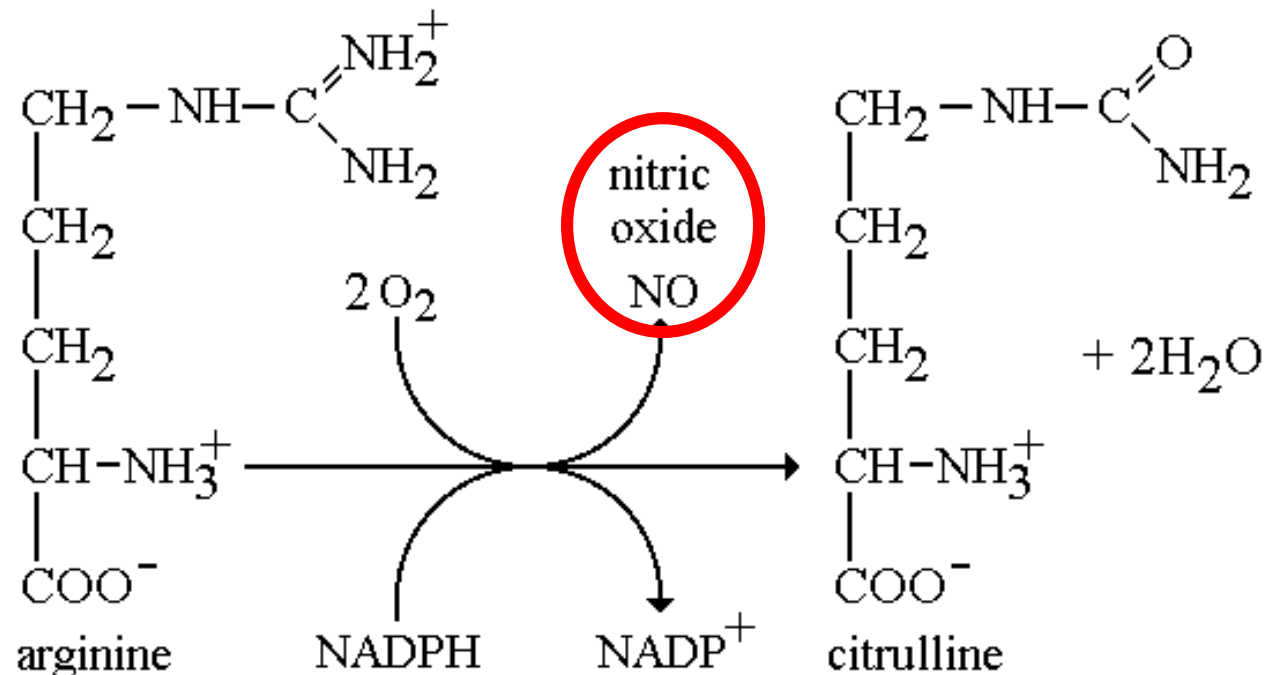
- The glutamate residues of some blood proteins factors are carboxylated to form γ - carboxyglutamate (Gla) residues.
 - Vitamin K is essential for the process
- This carboxylation is essential for blood clotting.



Arginine



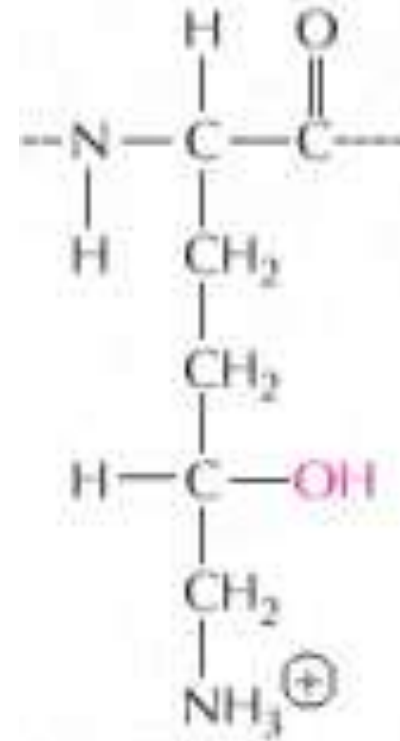
- L-arginine is the precursor of nitric oxide (NO)
- NO functions:
 - Vasodilation, inhibition of platelet adhesion, anti-inflammatory



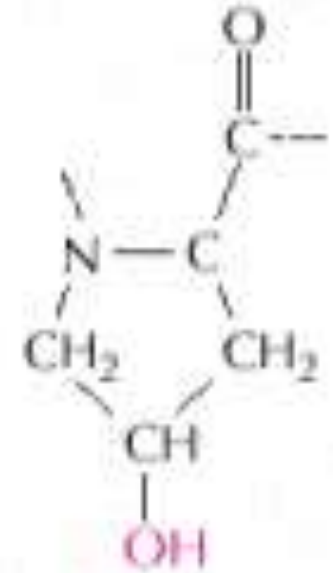
Hydroxylysine and hydroxyproline



- Lysine and proline are hydroxylated and are part of collagen structure.
- Both are modified after protein synthesis.



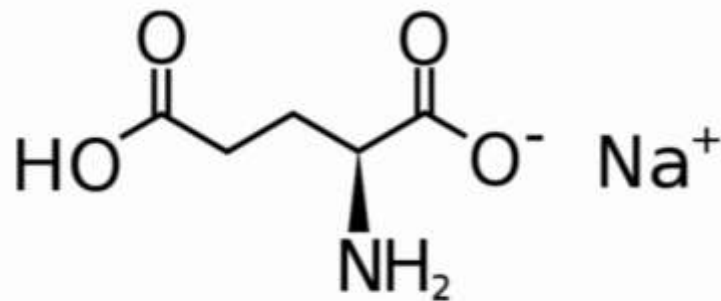
hydroxylysine
in protein



hydroxyproline
in protein



MONOSODIUM GLUTAMATE



SODIUM SALT OF GLUTAMIC ACID

Biochemical applications: Monosodium glutamate (MSG)

Glutamic acid derivative

Flavor enhancer, Asian food.

MSG causes a physiological reaction in some people (chills, headaches, and dizziness)

Chinese restaurant syndrome.



QUIZ

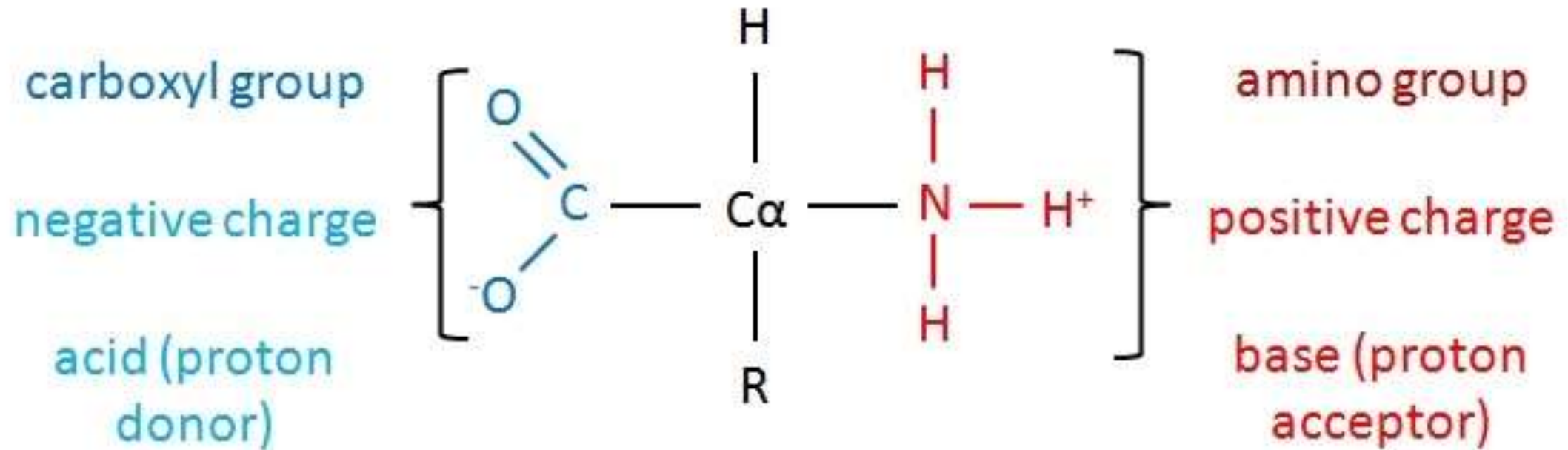


- What is special about (example: proline)?
- An acidic amino acid is _____ charged at physiological conditions.
- Name 2 amino acids that share a functional group in their side chain.



Ionization of amino acids

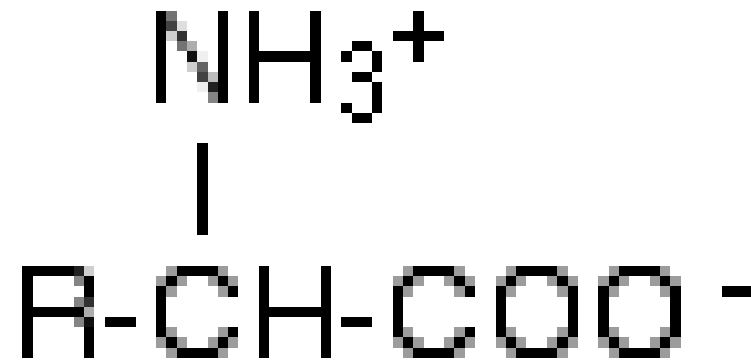
Why do amino acids get ionized?



Zwitterion and isoelectric point



- At physiological pH, amino acids (without ionizable groups) are electrically neutral.
- Zwitterion: a molecule with two opposite charges and a net charge of zero.

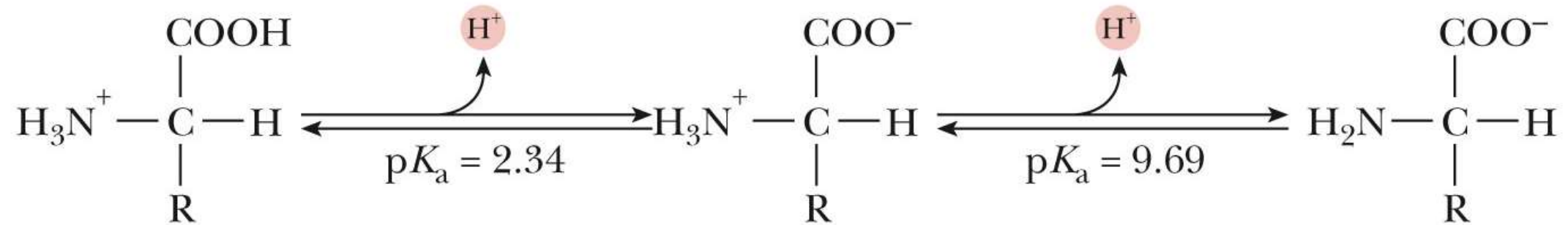


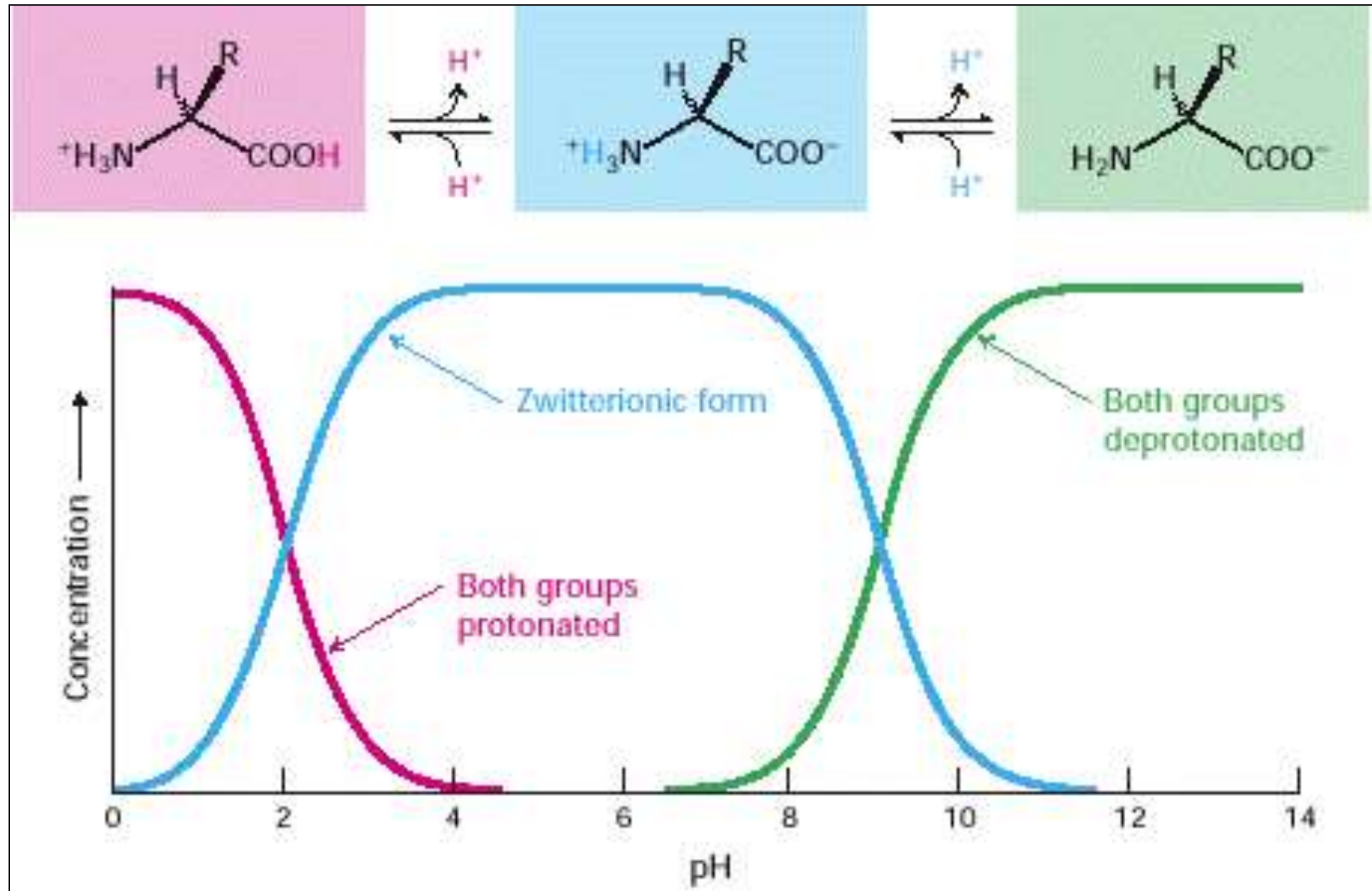
a zwitterion

Effect of pH

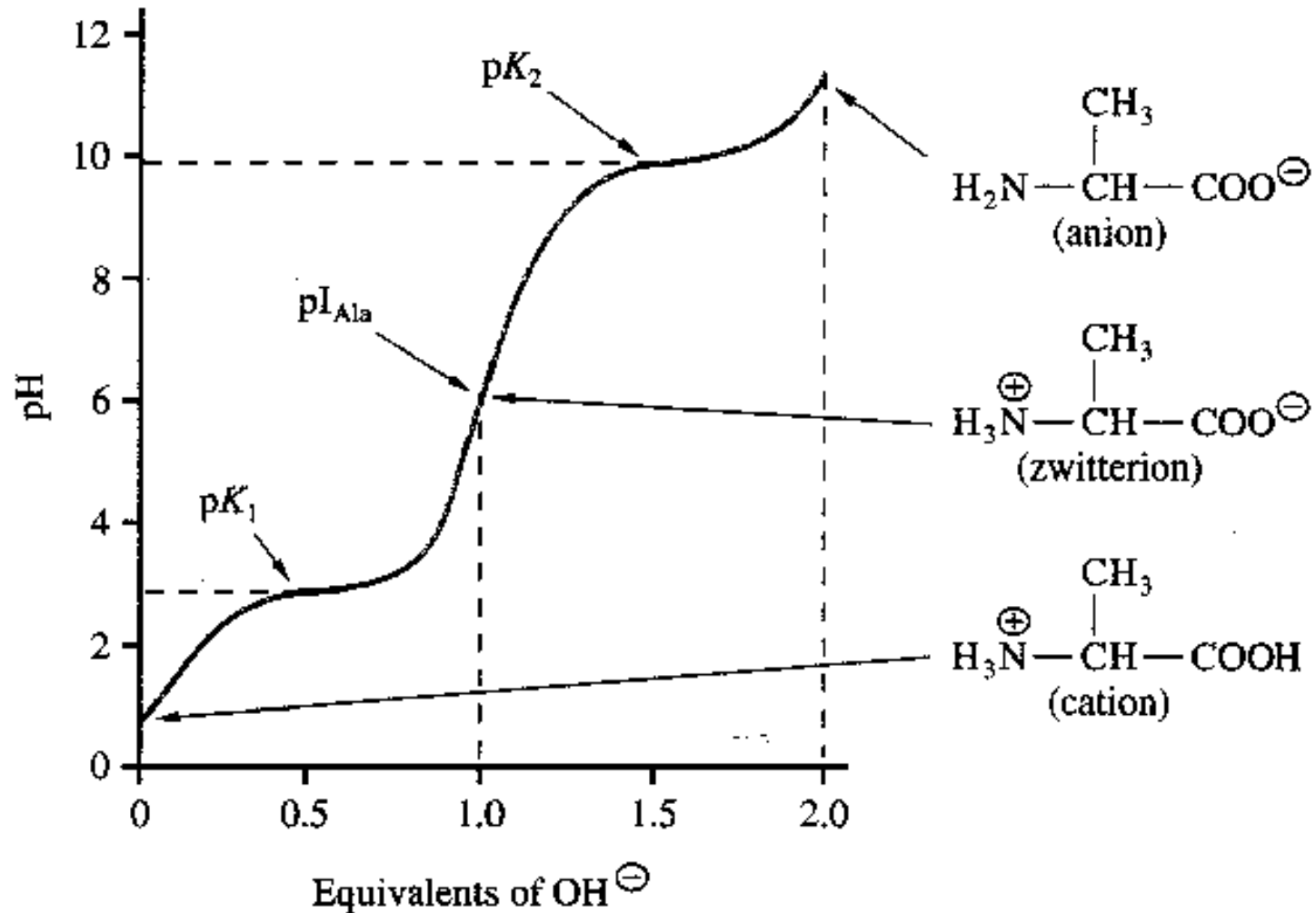


Isoelectric zwitterion





Example 1 (alanine)



$$\text{pH} = \text{pK}_a + \log \frac{[\text{conjugate base}]}{[\text{weak acid}]}$$

Isoelectric Point



- The isoelectric point or pI is the pH where the net charge of a molecule such as an amino acid or protein is zero.
- For the nonpolar and polar amino acids with two pKa's, the isoelectric point is calculated by taking the average of the pKa's of the carboxyl group and the amino group.

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

Ionization of side chains



- 7 of the 20 amino acids have ionizable side chains near physiological pH.
- These amino acids are tyrosine, cysteine, arginine, lysine, histidine, and aspartic and glutamic acids.
- Each side chain has its own pKa values for ionization of the side chains.

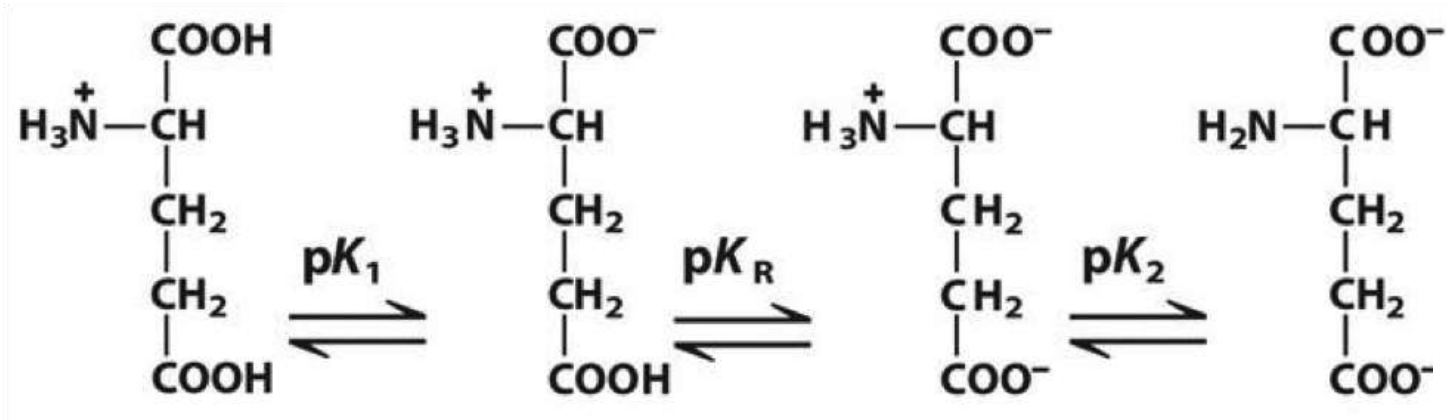
pl of amino acids



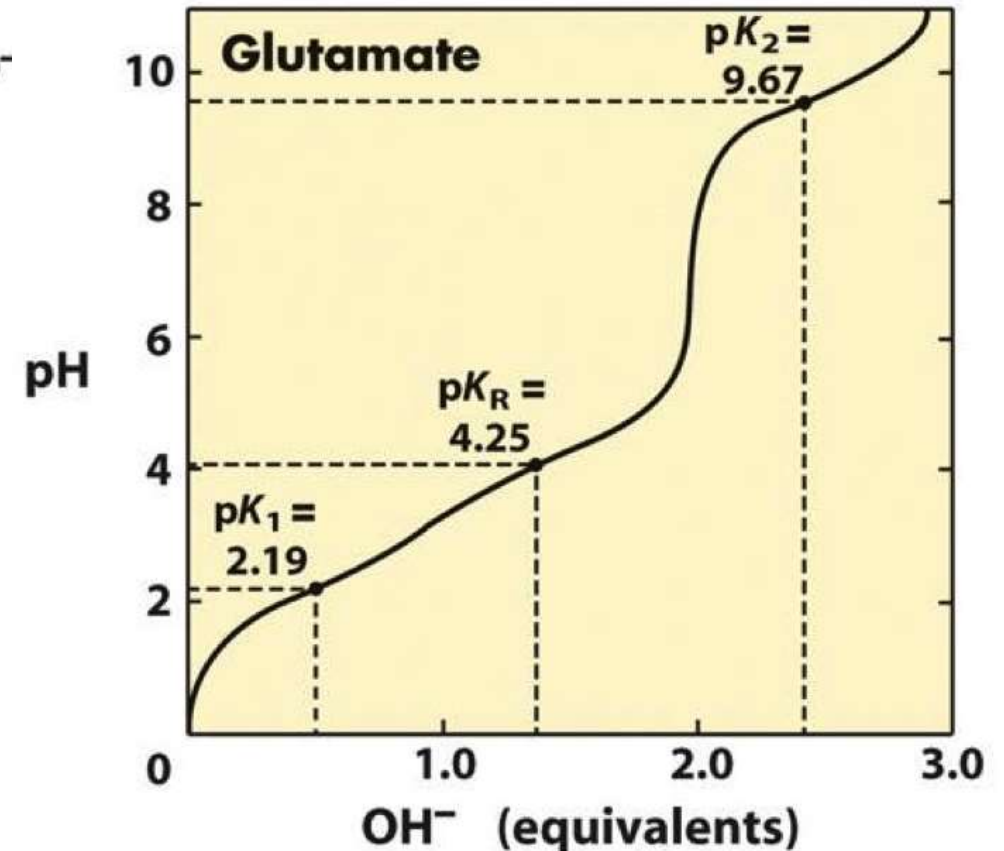
Amino Acid	Side Chain pK_a (approx.)	pI
Arginine	12.5	10.8
Aspartic Acid	4.0	3.0
Cysteine	8.0	5.0
Glutamic Acid	4.1	3.2
Histidine	6.0	7.5
Lysine	11.0	10
Tyrosine	10.0	5.5

Let's consider pK_a of $-NH_2 = 9$ and pK_a of $-COOH = 2$ for all amino acids

Example: Glutamate



- To calculate the isoelectric point of Glu, the $\text{p}K_a$'s of the two carboxyl groups are averaged.

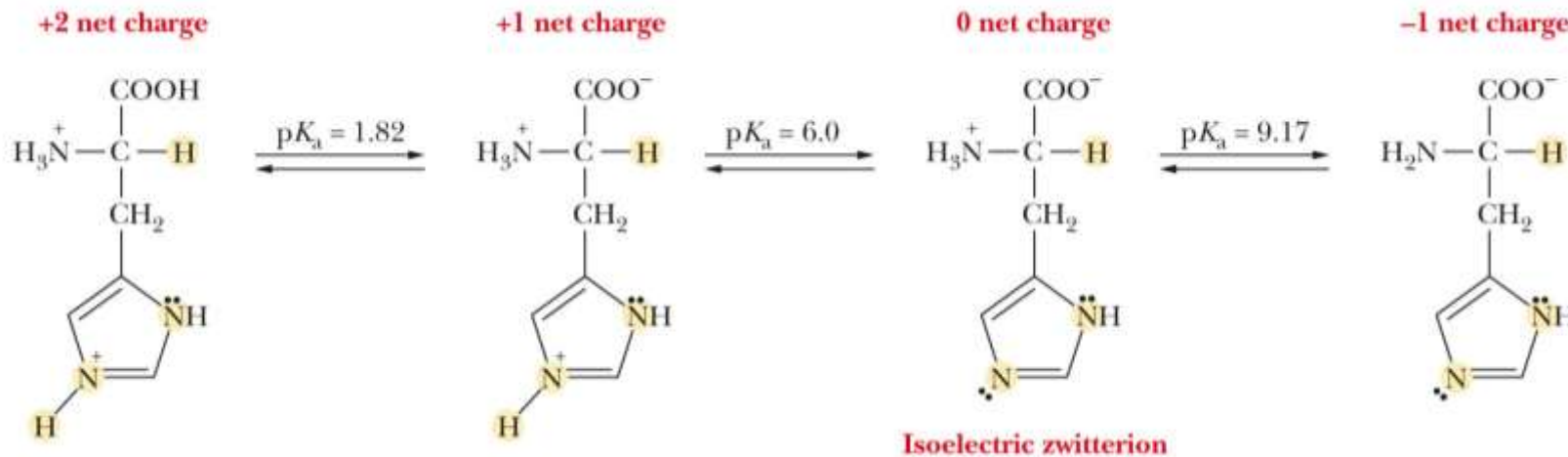
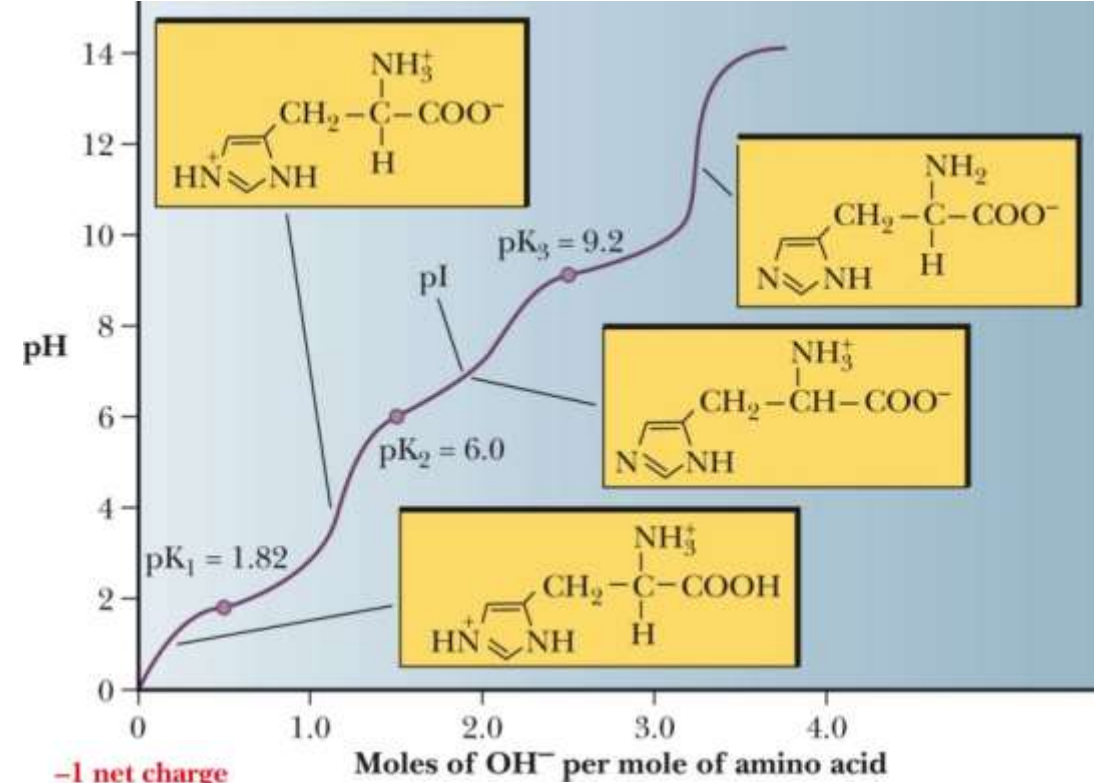


Histidine



- $pI \approx 7.5$ (The imidazole group can be uncharged or positively charged near neutral pH).

Note that the pK_a 's of the side chains are different when amino acids are part of proteins.



Questions



- Draw the titration curve of histidine.
- What is the ratio of conjugate base/acid of glutamate at pH 4.5?
- What is the total charge of lysine at pH 7?

What do you need to know?



- The names of amino acids
- The special structural features of amino acids
- Their abbreviations or designations
- The uncommon amino acids, their precursor and function (if any)
- The pKa of groups
 - not exact numbers, but which ones are acidic, basic, or near neutral



Peptides

Definitions and concepts



- A residue: each amino acid in a (poly)peptide
- Dipeptide, tripeptide, tetrapeptide, etc.
- Oligopeptide (peptide): a short chain of 20-30 amino acids
- Polypeptide: a longer peptide with no particular structure
- Protein: a polypeptide chains with an organized 3D structures
- The average molecular weight of an amino acid residue is about 110
 - The molecular weights of most proteins are between 5500 and 220,000 (calculate how many amino acids)
- We refer to the mass of a polypeptide in units of Daltons
 - A 10,000-MW protein has a mass of 10,000 Daltons (Da) or 10 kilodaltons (kDa)

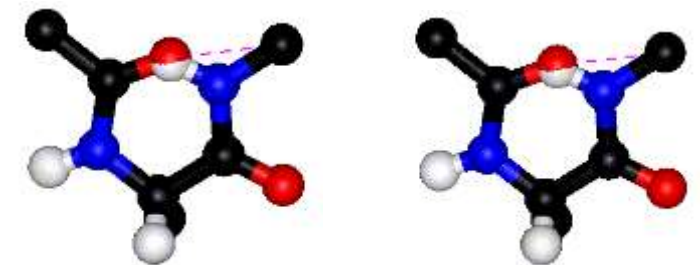
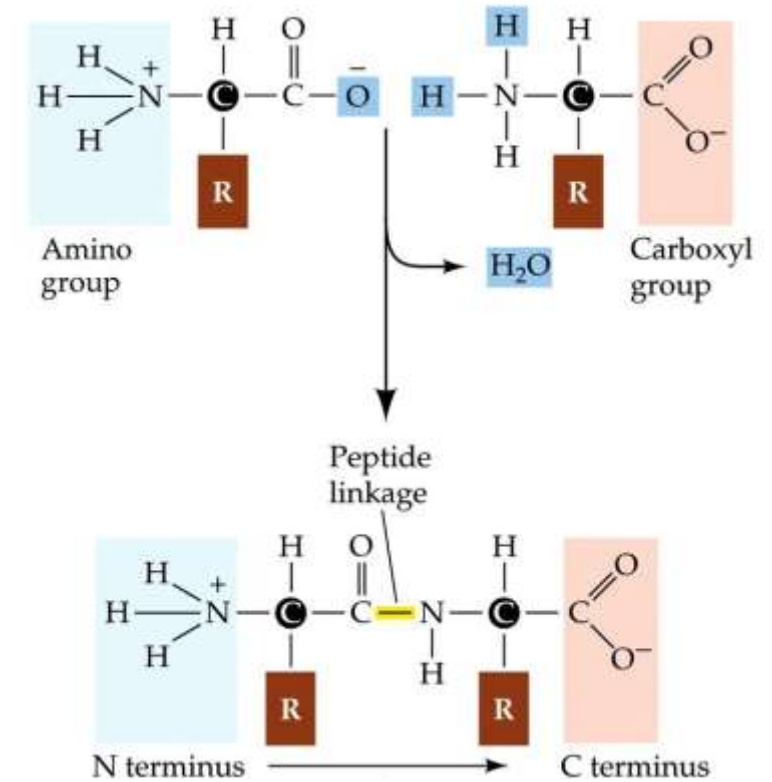
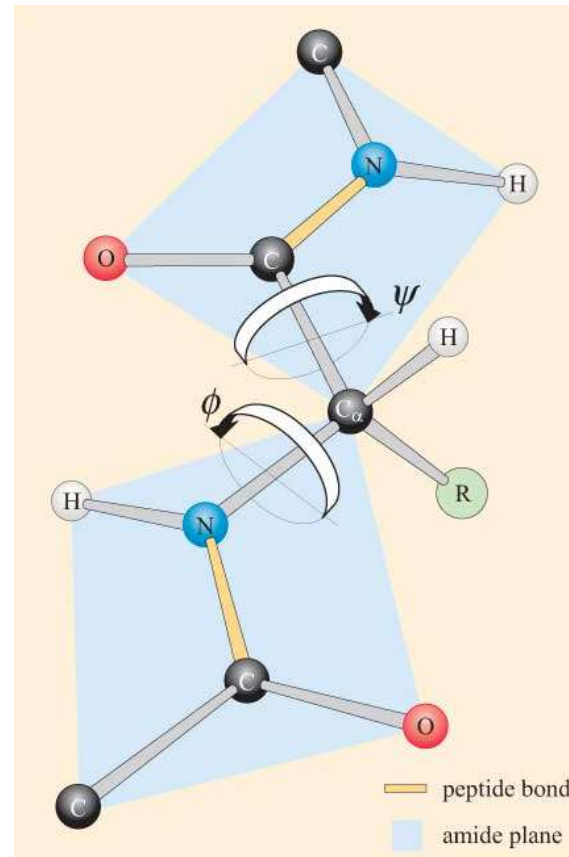
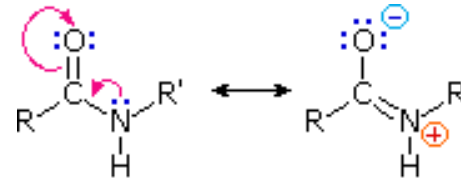
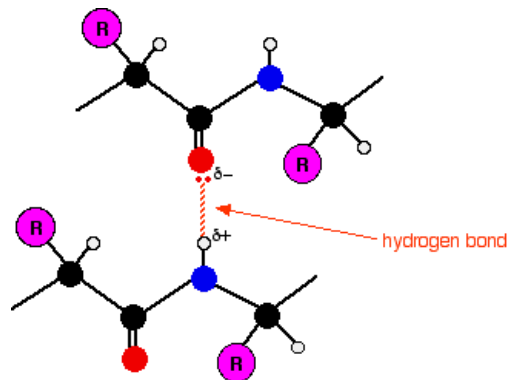
Peptide bond

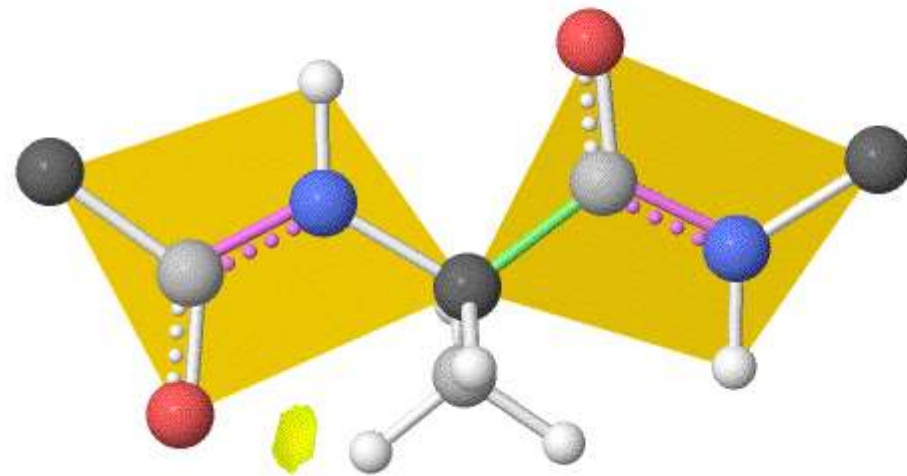


- It is called an amide bond formed via a condensation reaction.

- Features

- It has a resonance structure
- Zigzag structure
- Double bond
 - Planar, charged, Rigid, Un-rotatable
- Hydrogen bonding
 - Except proline



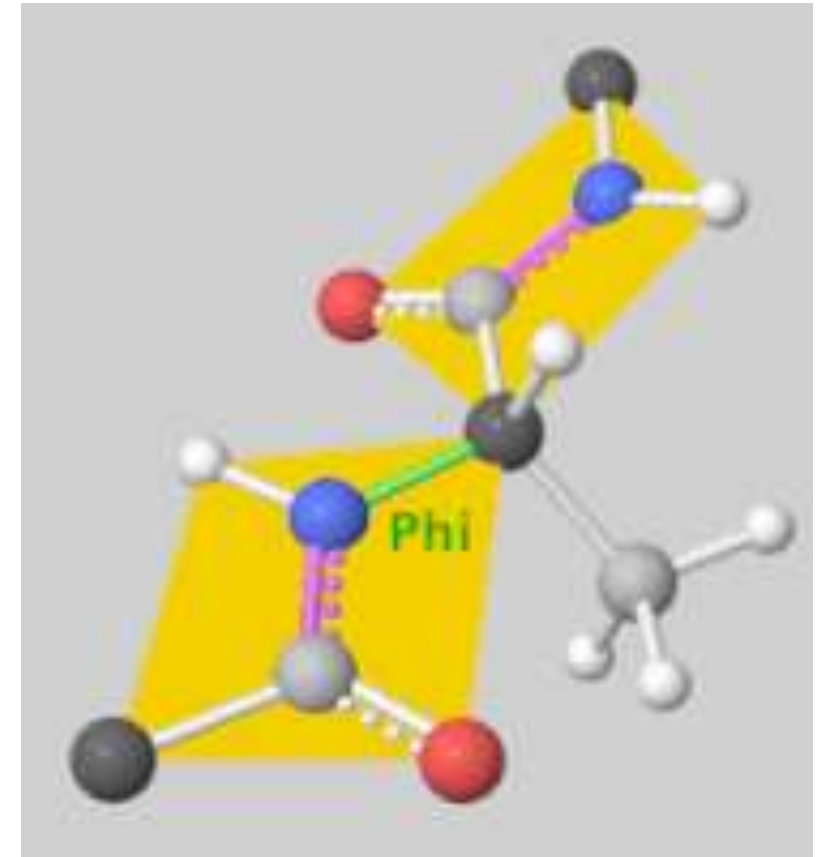


C α C H N O

○ Phi ϕ ● Psi ψ
-175° -175°

-20° +20°

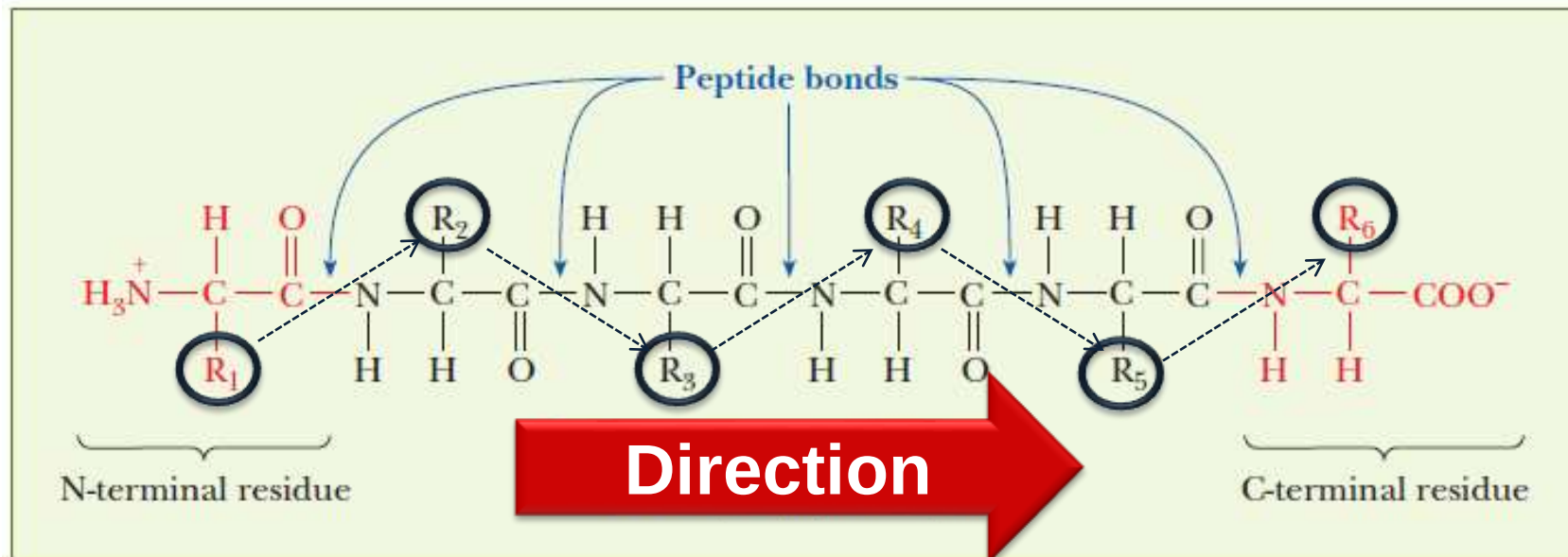
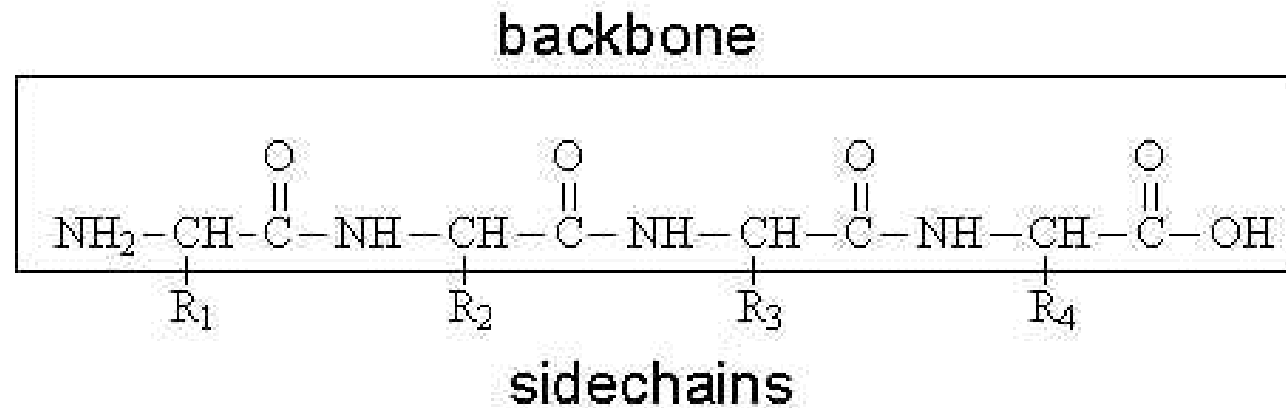
- ☐ Alanine
- ☒ Peptide Bonds
- ☒ Planes
- ☐ van der Waals⁴
- ☒ Show Clashes



Backbone, orientation and directionality



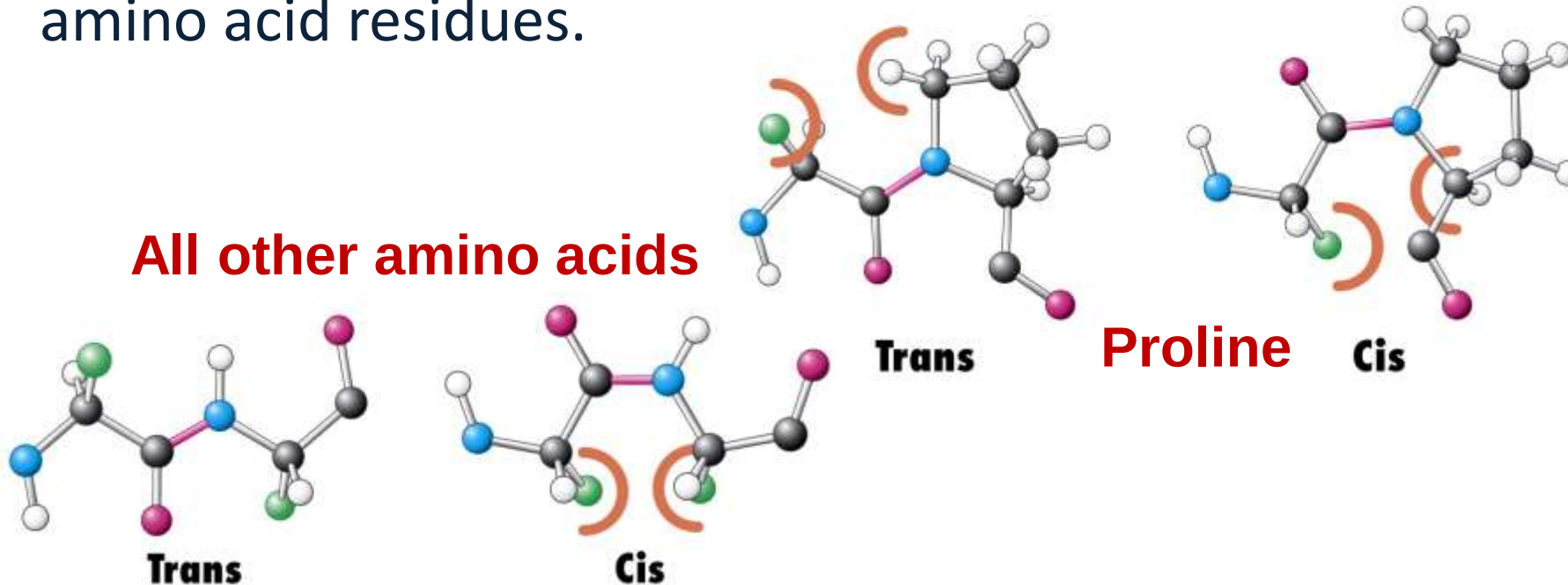
α -amide N, the α -C, and the α carbonyl C atom



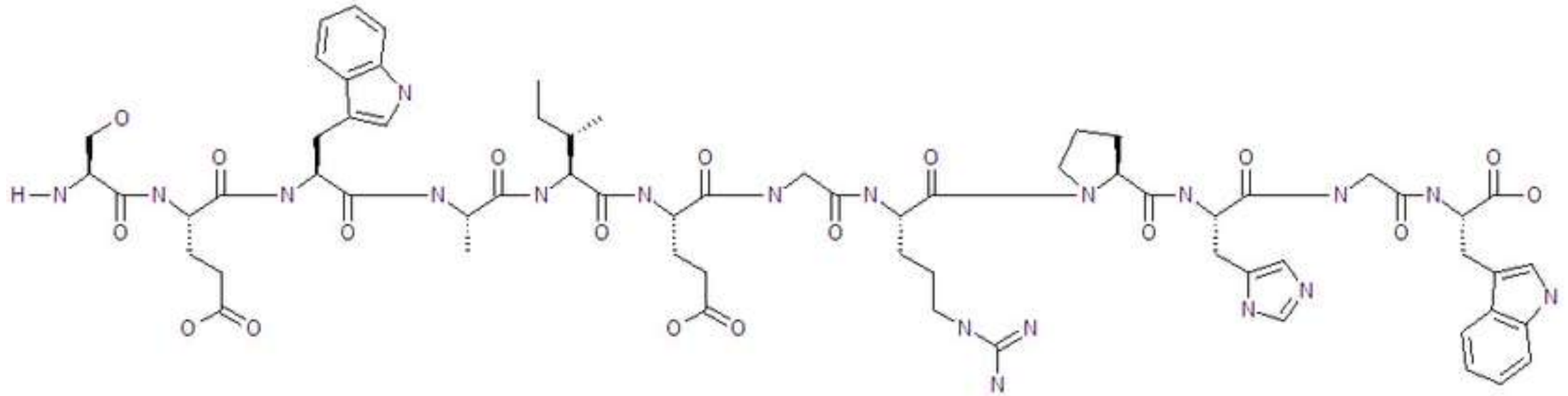
Except for proline



- Steric hindrance between the functional groups attached to the C α atoms will be greater in the cis configuration.
- In proline, both cis and trans conformations have about equivalent energies.
- Proline is thus found in the cis configuration more frequently than other amino acid residues.



Practice: *name the amino acid residues*



NH_2 —S E W A I E G R P H G W—COOH

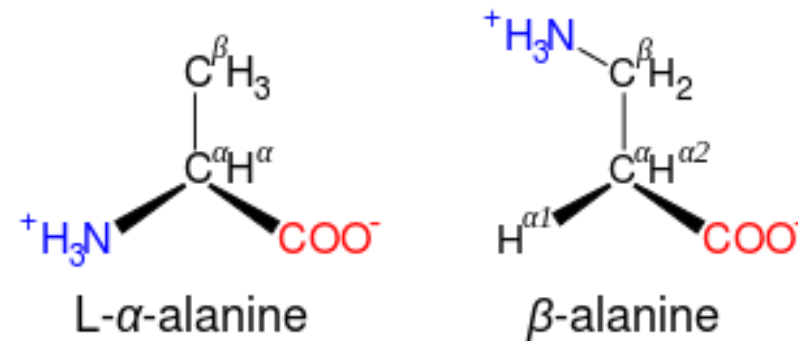
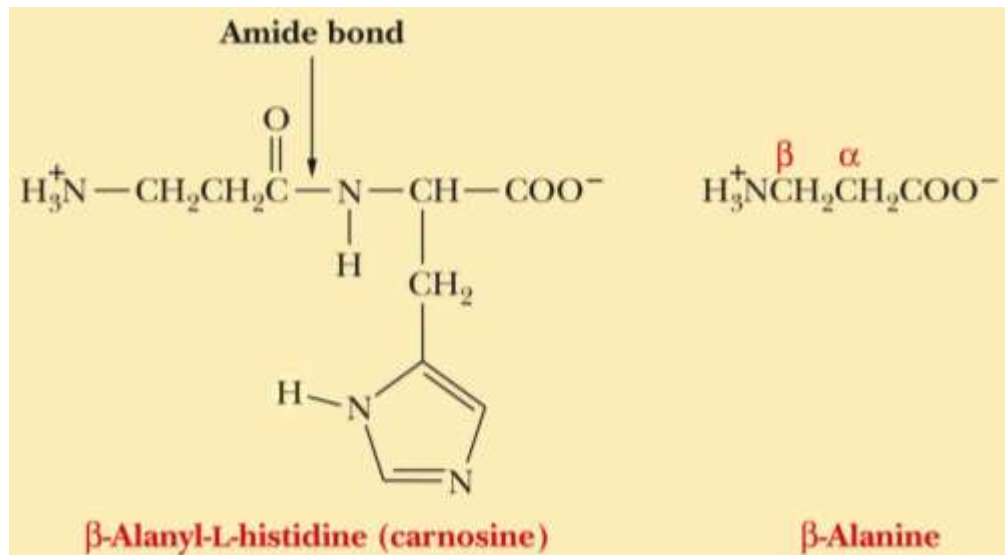


Examples of functional and exceptional peptides

Carnosine (β -alanyl-L-histidine)

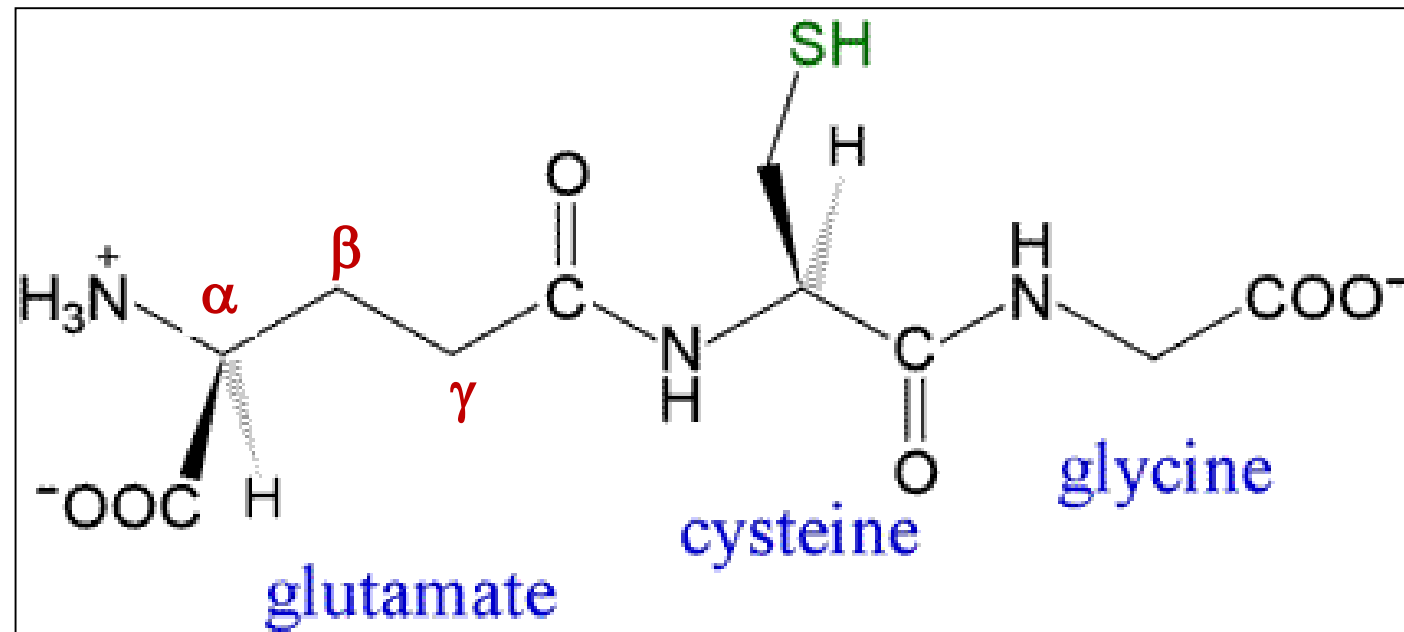
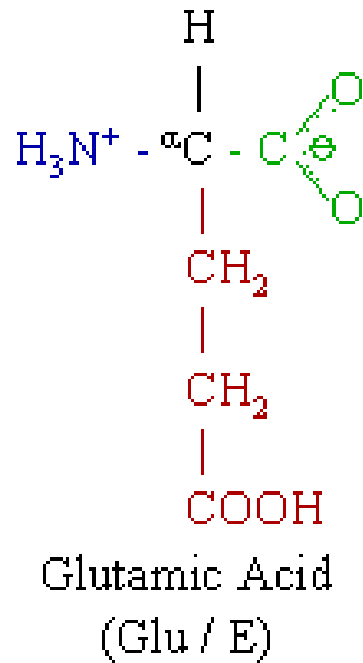


- A dipeptide of β -alanine and histidine
- The amino group is bonded to the β -carbon of alanine
- It is highly concentrated in muscle and brain tissues
 - Protection of cells from ROS (radical oxygen species) and peroxides
 - Contraction of muscle



Glutathione

(γ -glutamyl-L-cysteinylglycine)



Function of glutathione



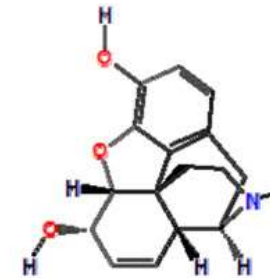
- It scavenges oxidizing agents by reacting with them.
- Two molecules of the reduced glutathione molecules form the oxidized form of glutathione by forming a disulfide bond between the —SH groups of the two cysteine residues.



Enkephalins



- Two pentapeptides found in the brain known as enkephalins, and function as analgesics (pain relievers).
 - They differ only in their C-terminal amino acids.
 - Met-enkephalin: Tyr-Gly-Gly-Phe-Met
 - Leu-enkephalin: Tyr-Gly-Gly-Phe-Leu
 - The aromatic side chains of tyrosine and phenylalanine play a role in their activities.
- There are similarities between the three-dimensional structures of opiates, such as morphine, and enkephalins.



Morphine

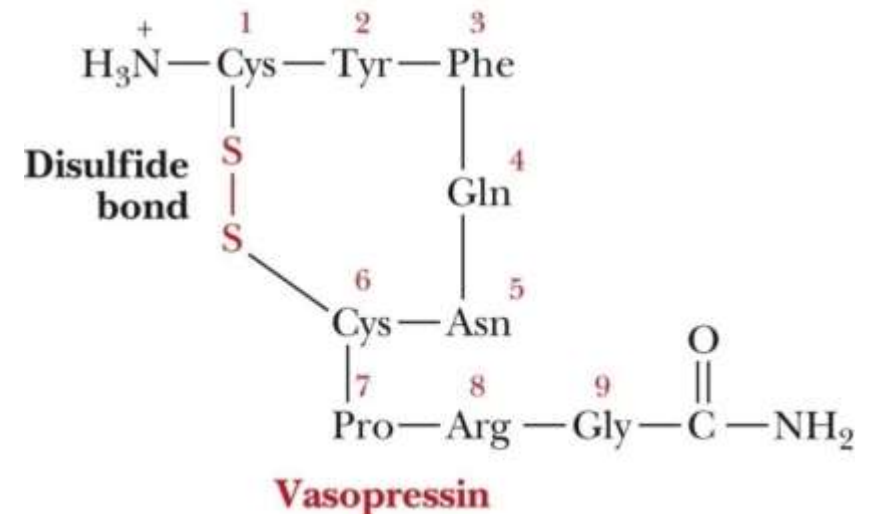
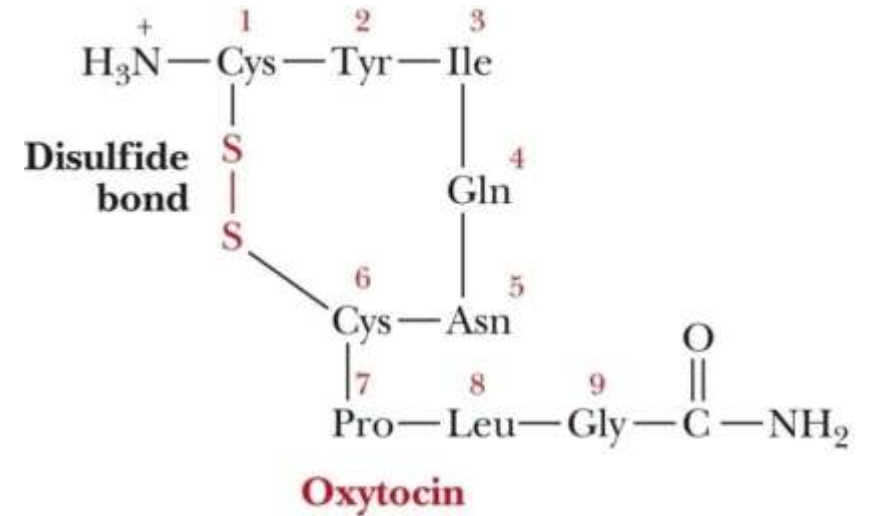


Enkephalins

Oxytocin and vasopressin



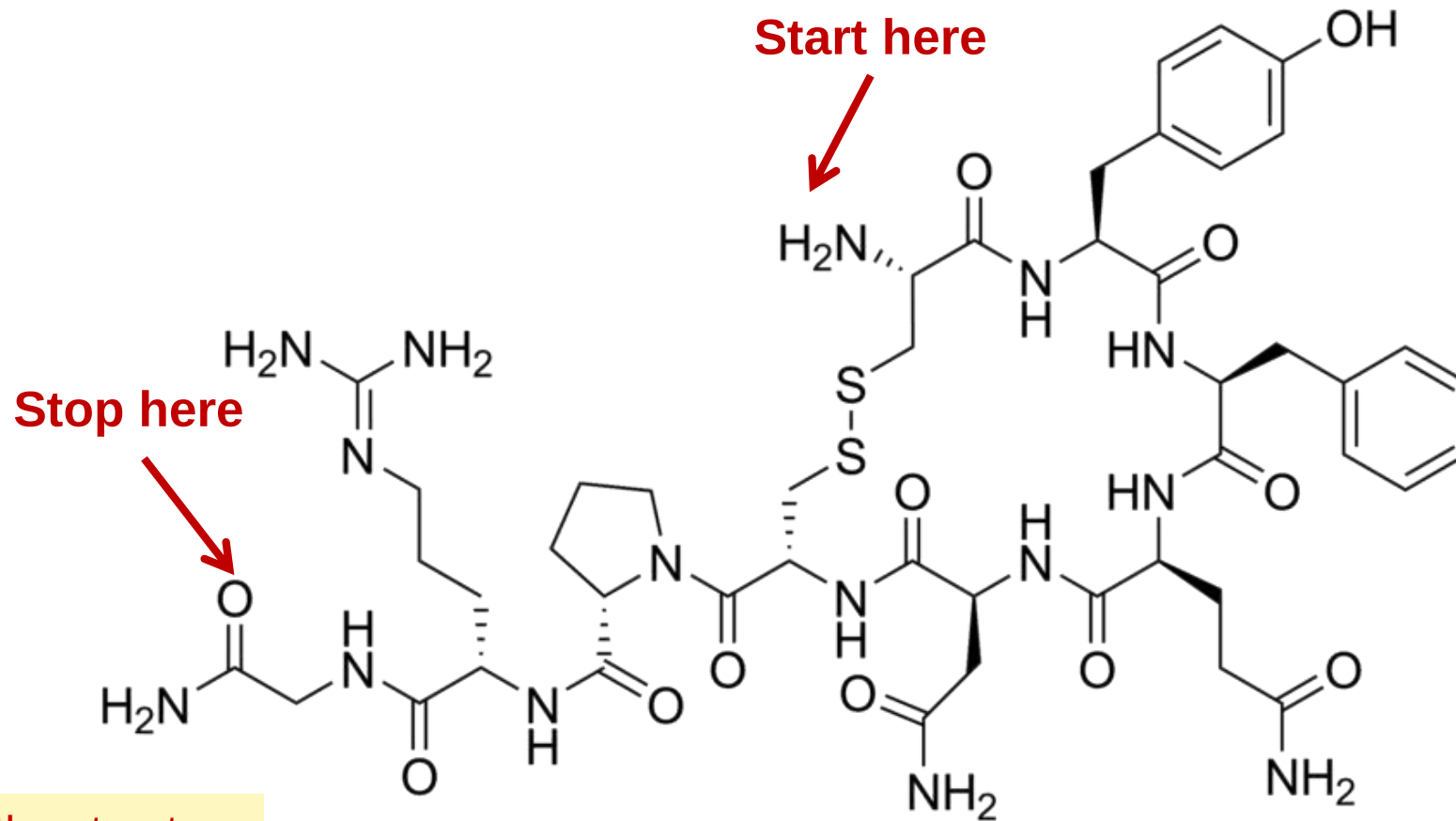
- Hormones with cyclic structures due to S-S link between Cys.
- Both have amide group at the C-terminus.
- Both contain nine residues, but:
 - Oxytocin has isoleucine and leucine.
 - Vasopressin has phenylalanine and arginine .
- Oxytocin regulates contraction of uterine muscle (labor contraction).
- Vasopressin regulates contraction of smooth muscle, increases water retention, and increases blood pressure.



Vasopressin



Practice: what is the primary structure?



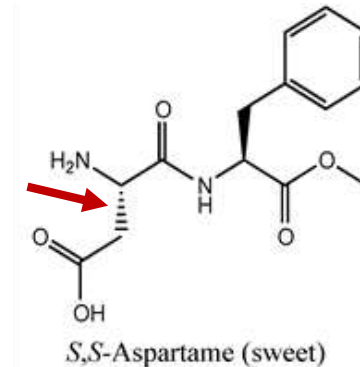
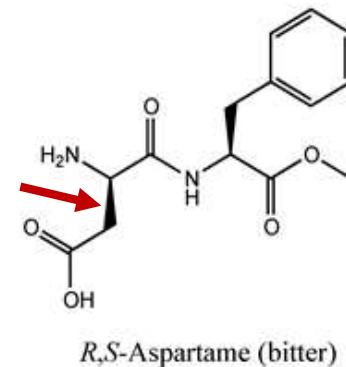
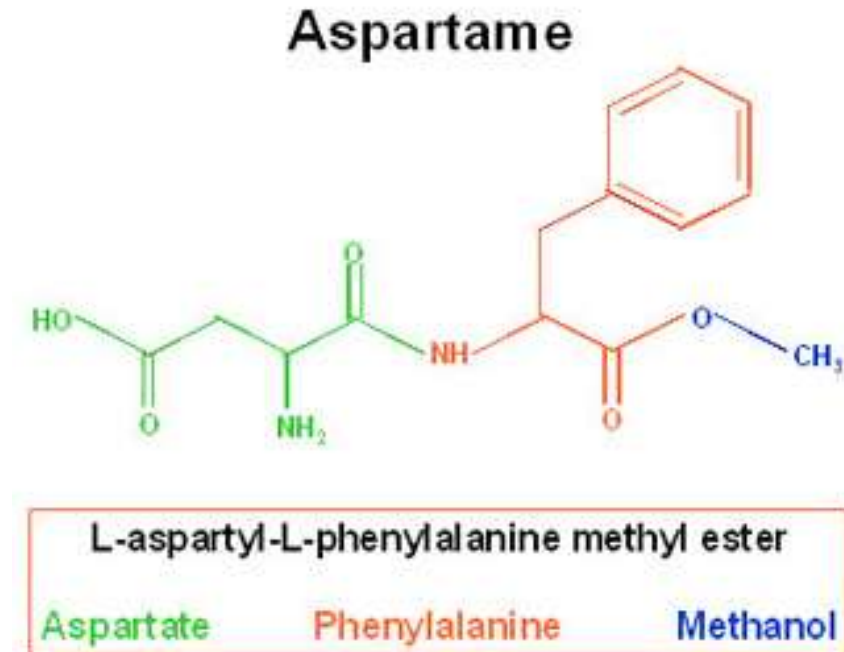
Note: the structure ends with NH₂



Aspartame

L-Aspartyl-L-phenylalanine (methyl ester)

- A dipeptide that is 200 times sweeter than sugar.
- If a D-amino acid is substituted for either amino acid or for both of them, the resulting derivative is bitter rather than sweet.



Aspartame and cancer



REUTERS®

World ▾

Business ▾

Markets ▾

Sustainability ▾

Legal ▾

Breakingviews

Technology ▾

Invest

Government Health Policy

Exclusive: WHO's cancer research agency to say aspartame sweetener a possible carcinogen -sources

By Jennifer Rigby and Richa Naidu

June 29, 2023 10:17 PM GMT+3 - Updated 7 days ago



Phenylketonuria (PKU)



- PKU is a hereditary “inborn error of metabolism” caused by defective enzyme, phenylalanine hydroxylase.
- It causes accumulation of phenylpyruvate, which causes mental retardation.
- Sources of phenylalanine such as aspartame must be limited.
- A substitute for aspartame, known as alitame, contains alanine rather than phenylalanine.

