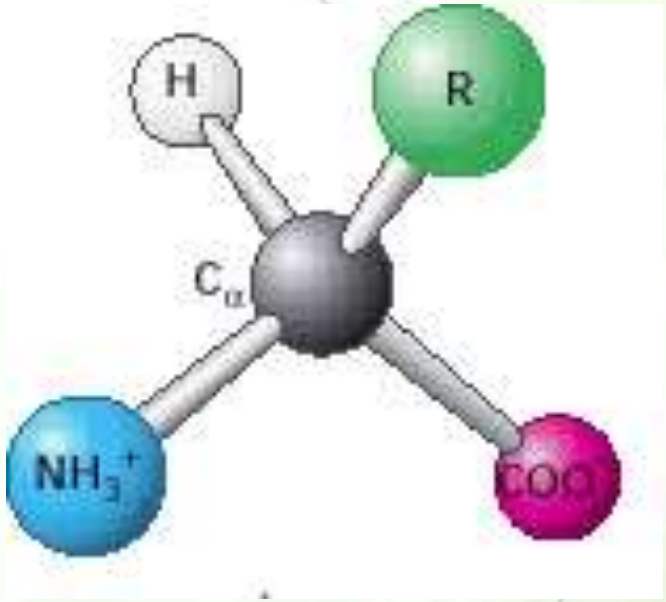
Amino acids

Summer 2023

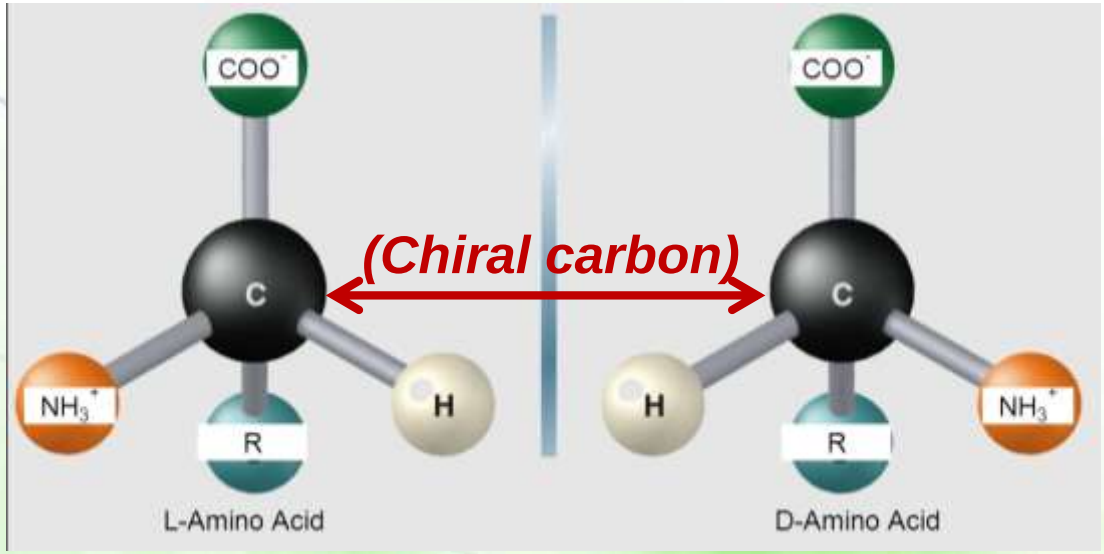
General structure

- 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 (-NH2),
  - a carboxylic acid group (-COOH),
  - a hydrogen atom, and
  - a specific R group (the side chain)

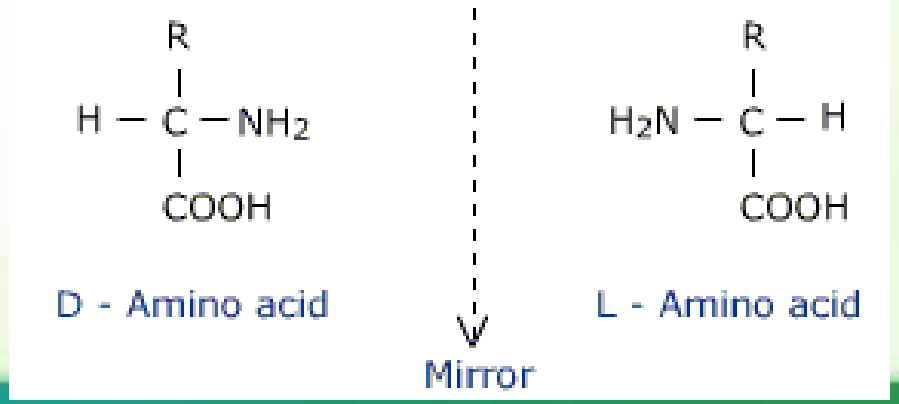


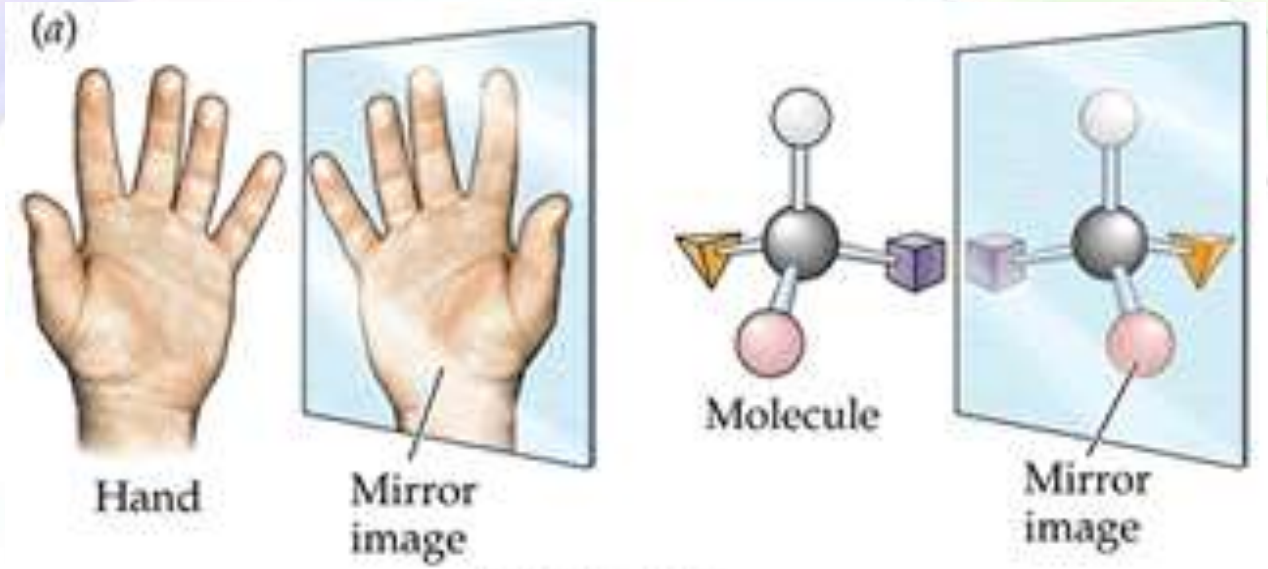
L and D isomers

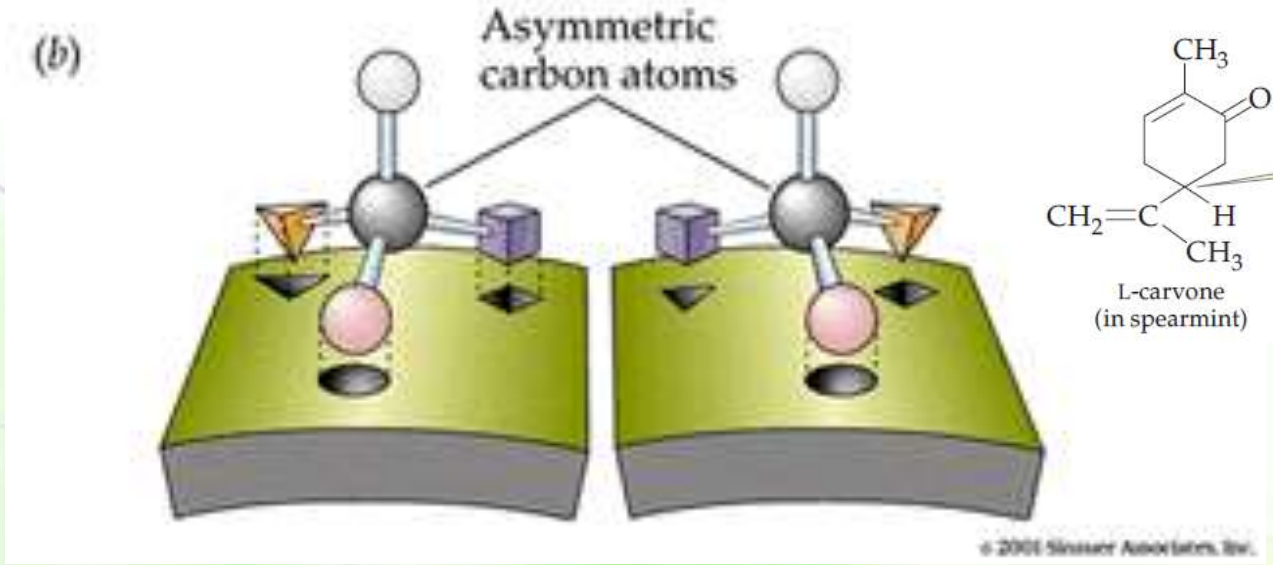
- The α-carbon atom is chiral and, thus, amino acids can be present in two forms that are mirror-images of each other (they are enantiomers).
- The amino acids are chiral (when a central carbon is bonded to four different groups).
- They are called L isomer and D isomer.
- Only L amino acids naturally make up proteins.

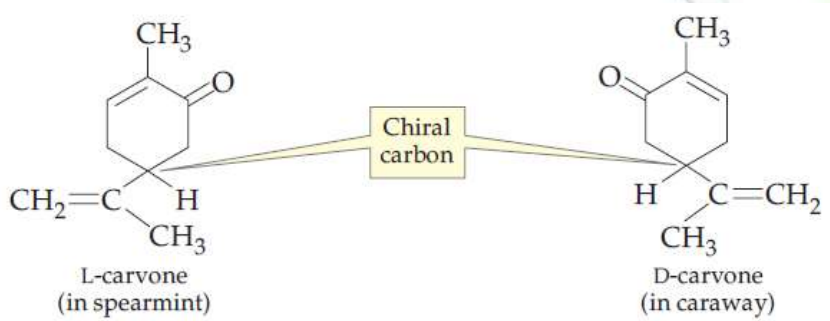


The amine group of L-amino acids occurs in the left-hand side when drawn in the Fischer projection, keeping the carboxylic acid group on bottom (or top) and the carbon chain in the top, whereas the amine group of the L-amino acids occurs in the left.




(a)
Hand
Mirror image
Molecule
Mirror image


(b)
Asymmetric carbon atoms


CH3
O
CH2=C
H
CH3
Chiral carbon
CH3
O
H
C=CH2
CH3
L-carvone (in spearmint)
D-carvone (in caraway)

Types of amino acids

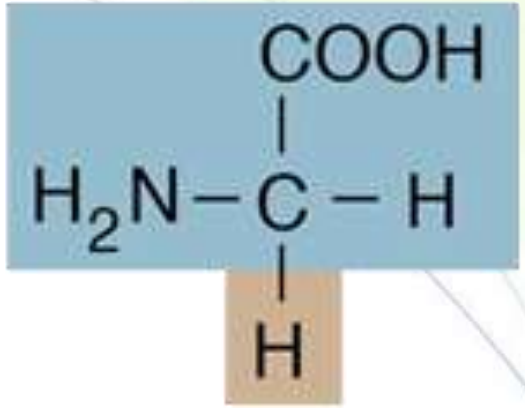
- There are twenty kinds of amino acids depending on the side chains varying in
  - Size
  - Shape
  - Charge
  - Hydrogen-bonding capacity
  - Hydrophobic character
  - Chemical reactivity

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			

Glycine

- Glycine is a derivative of acetic acid.
- It could be considered a derivative of aminoethane.



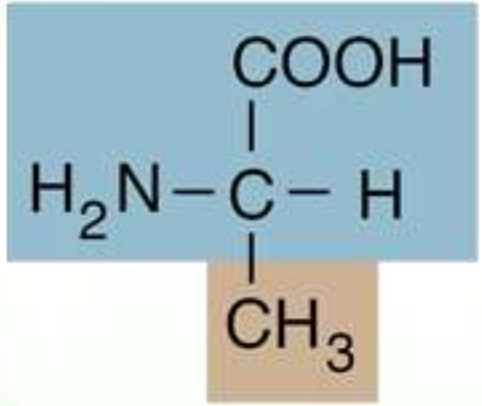
Glycine (gly)

Is it chiral?

Non-polar, aliphatic amino acids

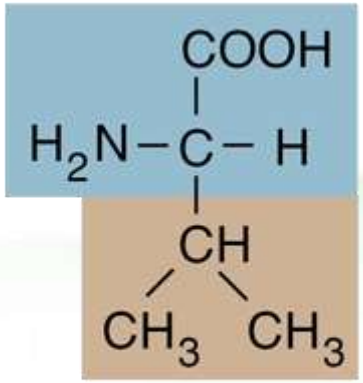
Alanine

- Alanine, the next simplest amino acid, has a methyl group (-CH3) as its side chain.

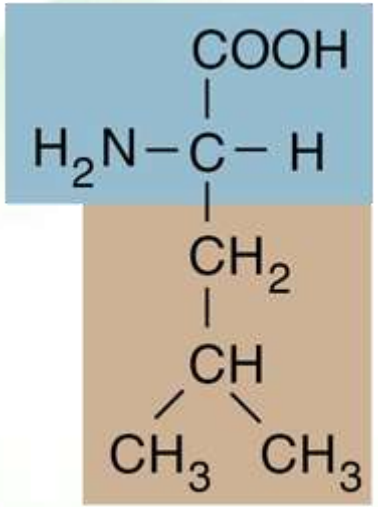


Alanine (ala)

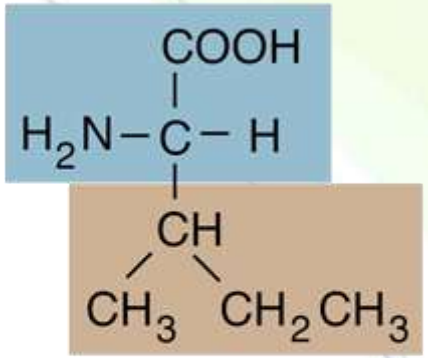
Valine, leucine, and isoleucine



Valine (val)*



Leucine (leu)*

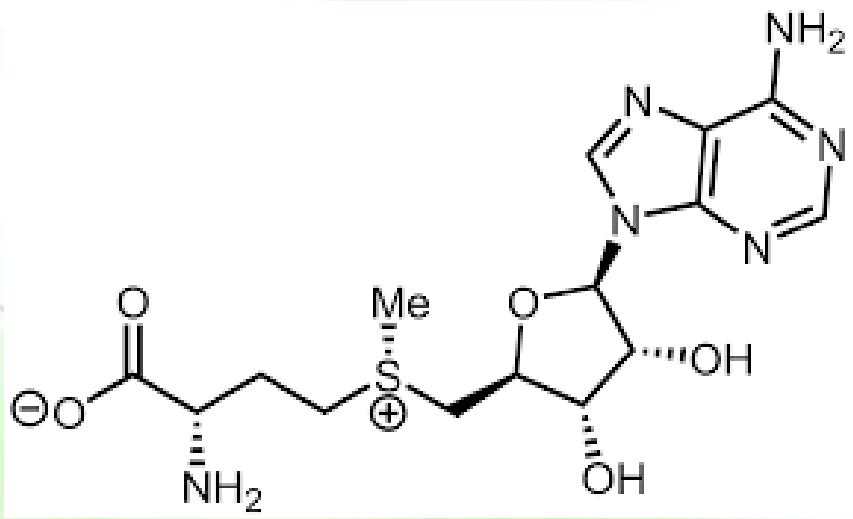


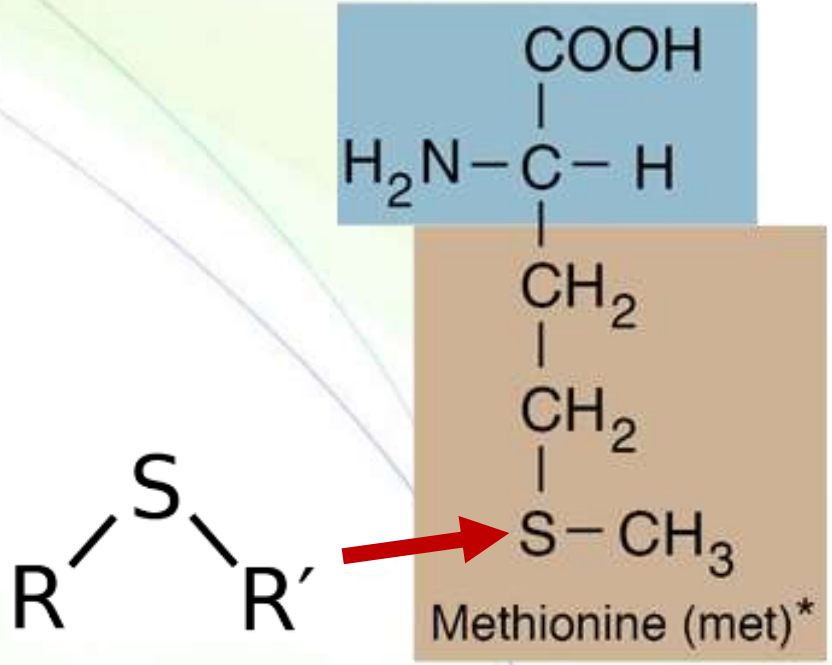
Isoleucine (ile)*

They are branched amino acids.
These are *essential amino acids in the sense that the body* cannot synthesize them.

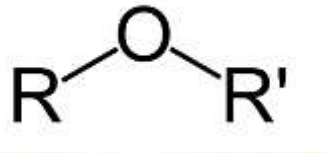
Methionine

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



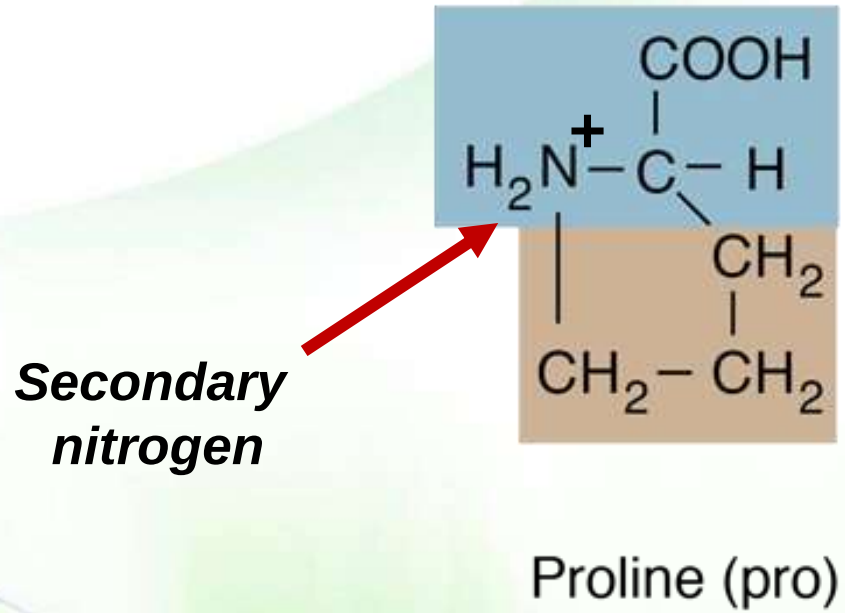


Thioether



Ether

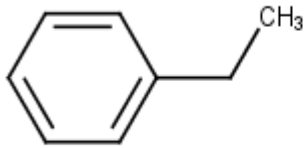
Proline (the only cyclic amino acid)



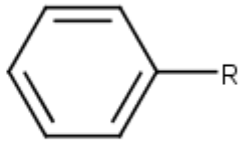
Proline (pro)

Phenylalanine and Tryptophan

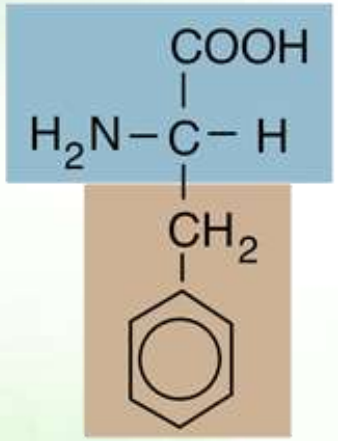
- Phenylalanine contains a phenyl ring.
- Tryptophan has an indole ring; the indole group consists of two fused rings and an NH group.



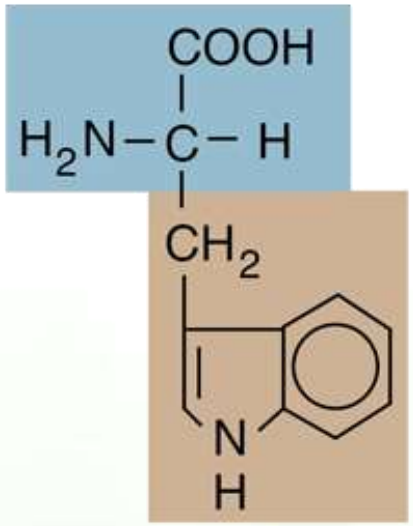
benzyl



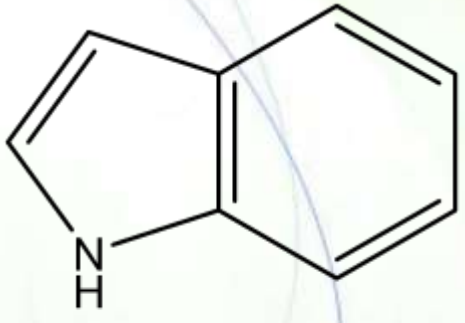
phenyl



Phenylalanine (phe)*



Tryptophan (trp)*

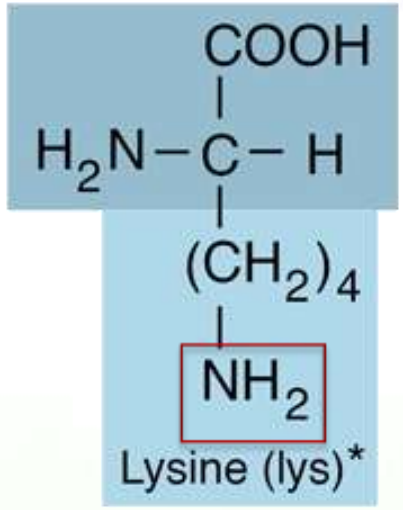


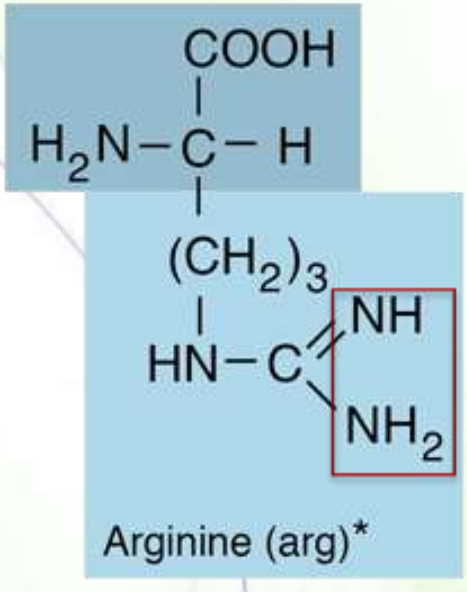
Indole

Positively-charged amino acids

Lysine and arginine

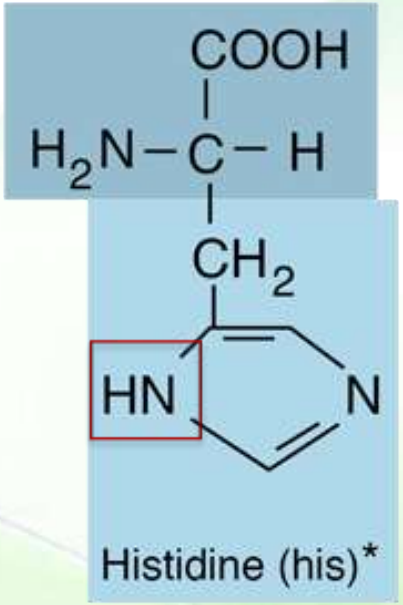
- Lysine and arginine have relatively long side chains that terminate with groups that are positively charged at neutral pH.
- Lysine ends with a primary amino group and arginine by a guanidinium group.

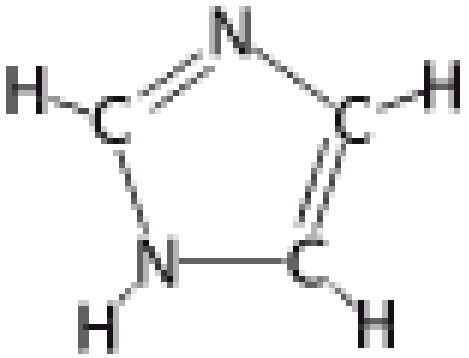




Histidine

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



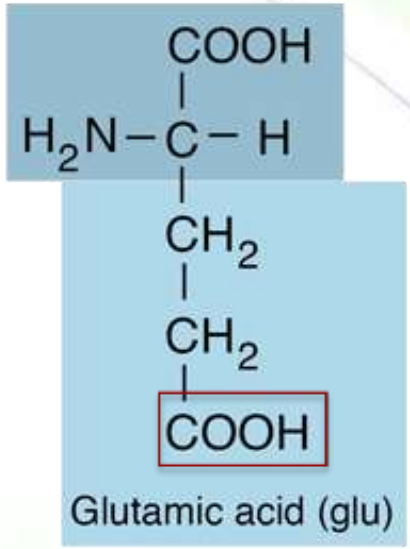


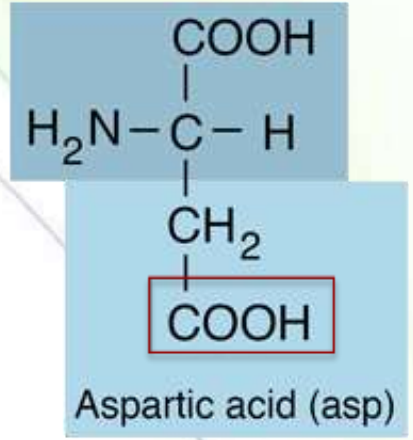
Imidazole

Negatively-charged amino acids

Aspartic acid and glutamic acid

- 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.

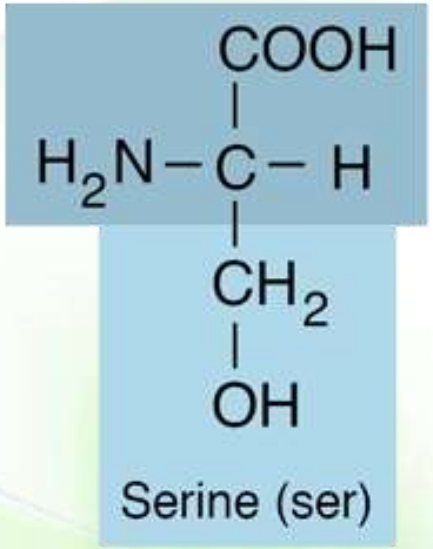




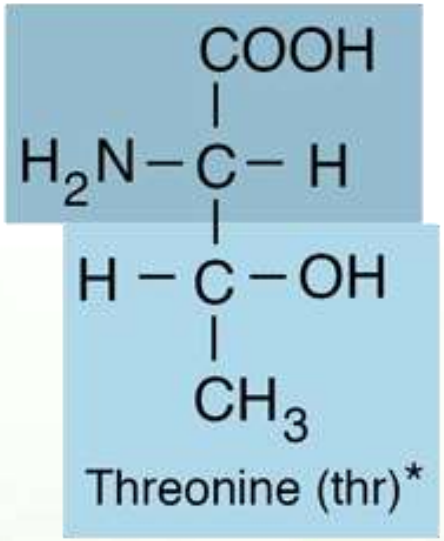
Polar, hydrophilic, neutral amino acids

Serine and threonine

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



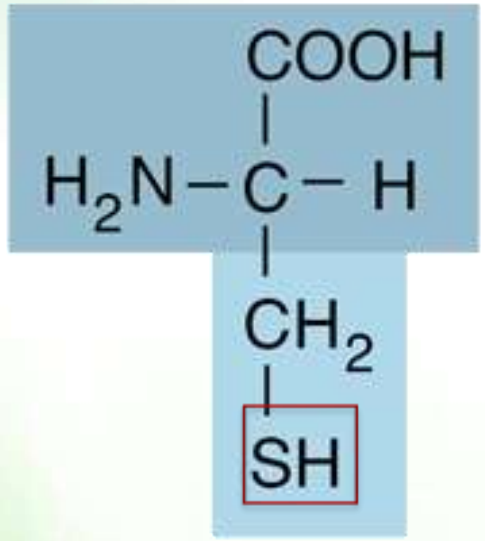
Serine (ser)



Threonine (thr)*

Cysteine (Cys)

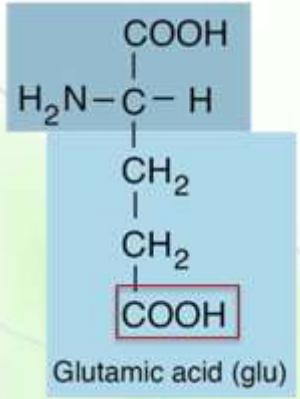
- Cysteine contains a sulfhydryl or thiol (-SH), group.
- The sulfhydryl group is reactive.



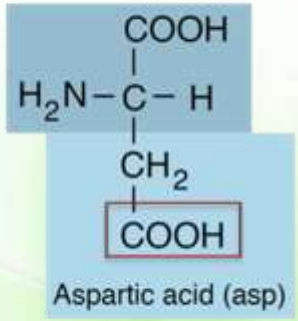
Cysteine (cys)

Asparagine and glutamine

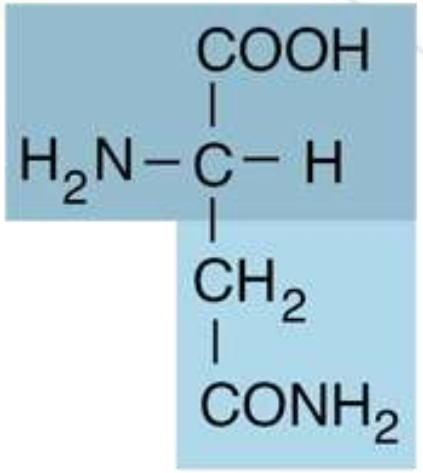
- Asparagine and glutamine are uncharged derivatives of aspartate and glutamate.
- Each contains a terminal carboxamide in place of a carboxylic acid.



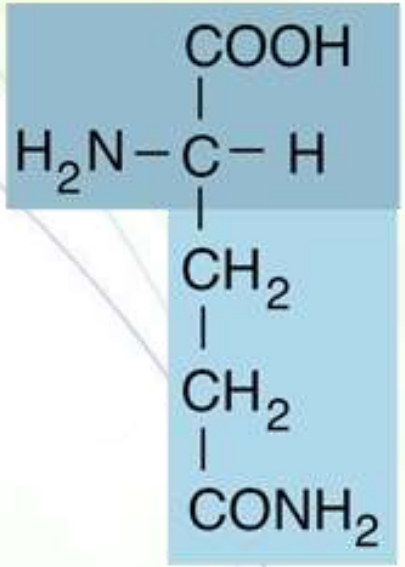
Glutamic acid (glu)



Aspartic acid (asp)



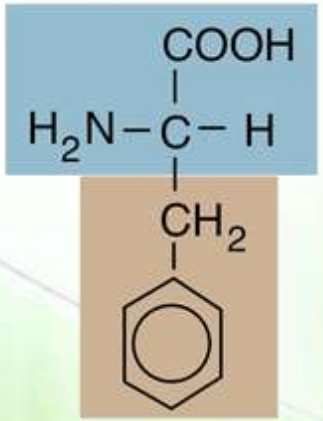
Asparagine (asn)



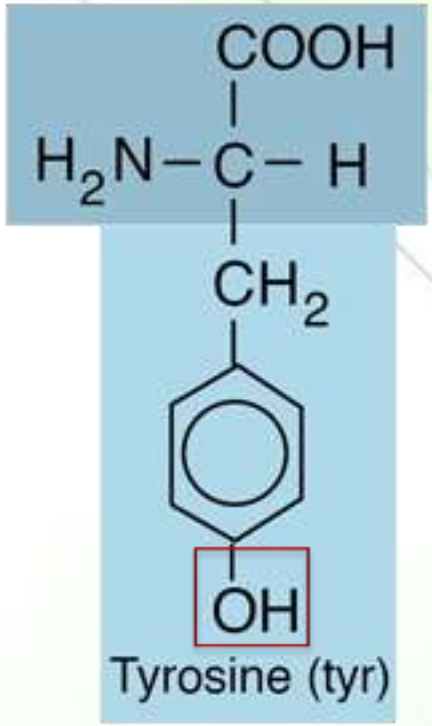
Glutamine (gln)

Tyrosine

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



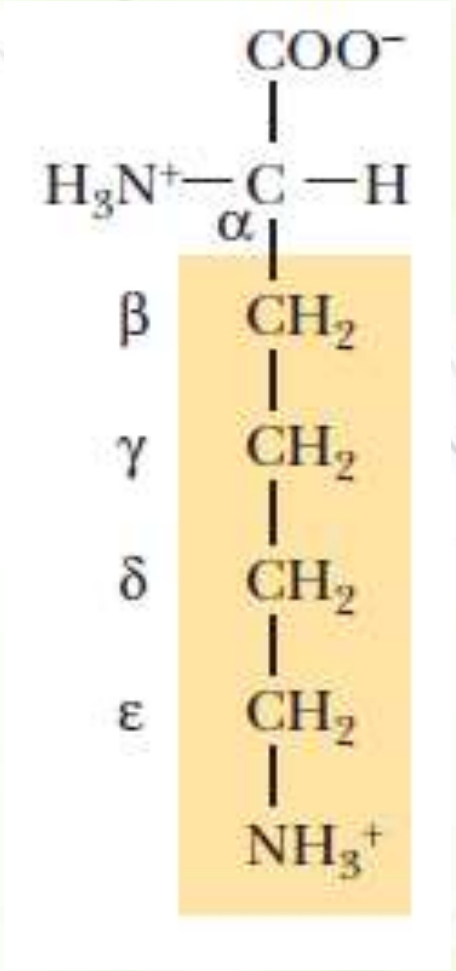
Phenylalanine (phe)*



Tyrosine (tyr)

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.



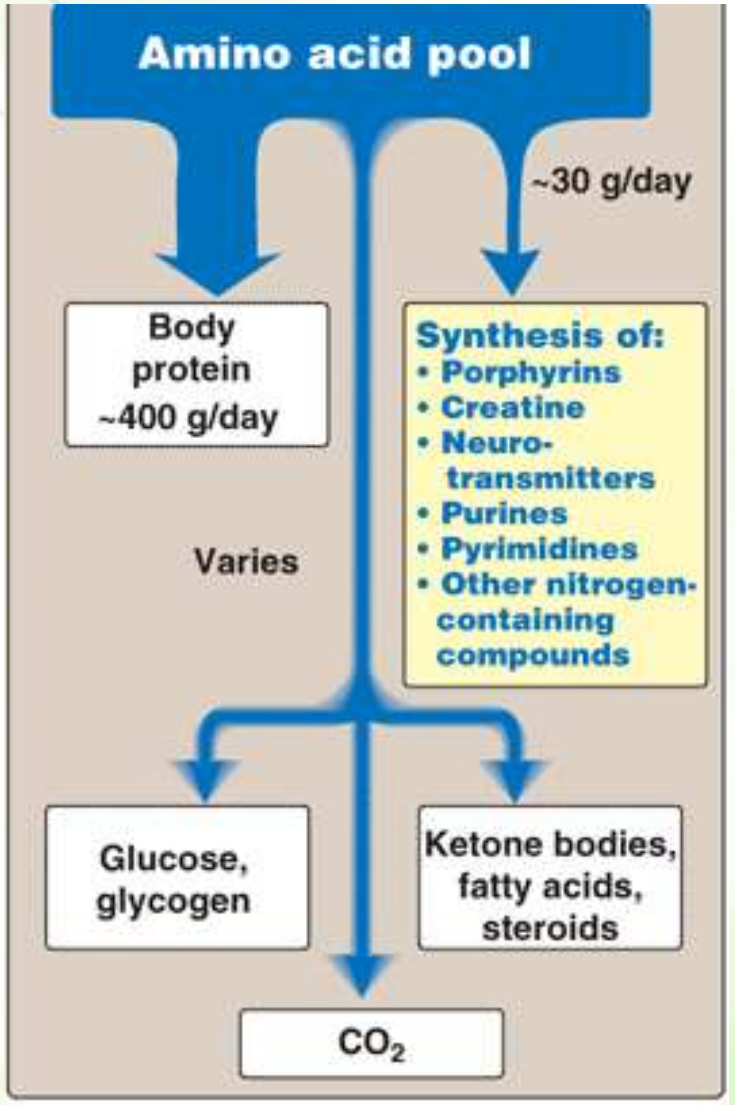
Questions

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

Specialized and uncommon amino acids

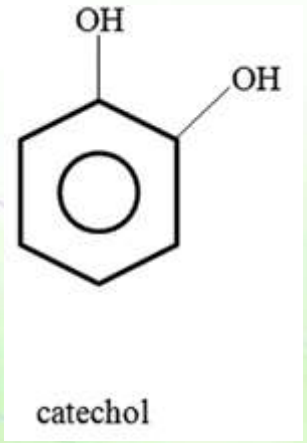
Biological significance of amino acids

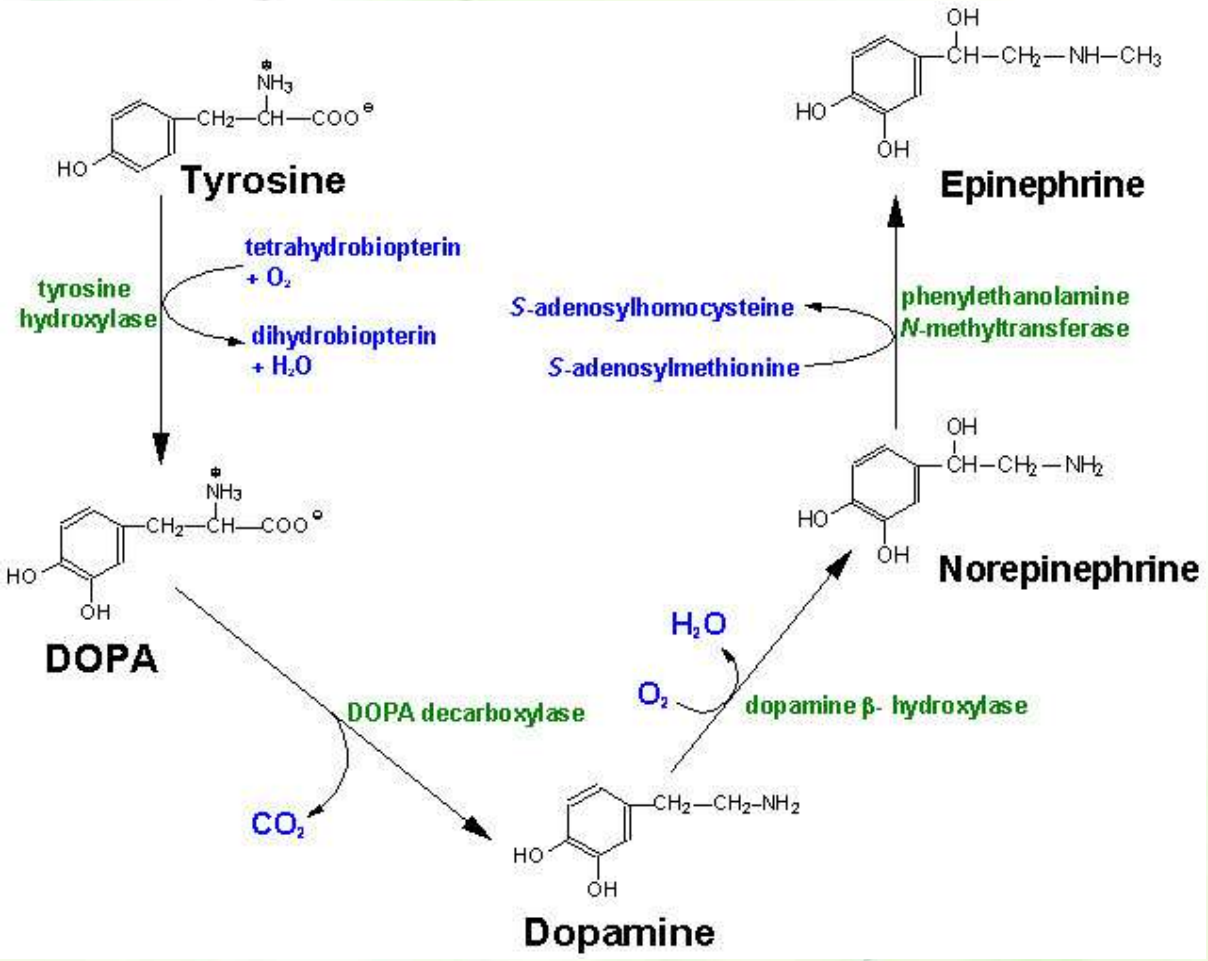
- α-nitrogen atom of amino acids is a primary source for many nitrogenous compounds:
  - Hormones
  - Neurotransmitters
  - Biologically active peptides



Tyrosine (1)

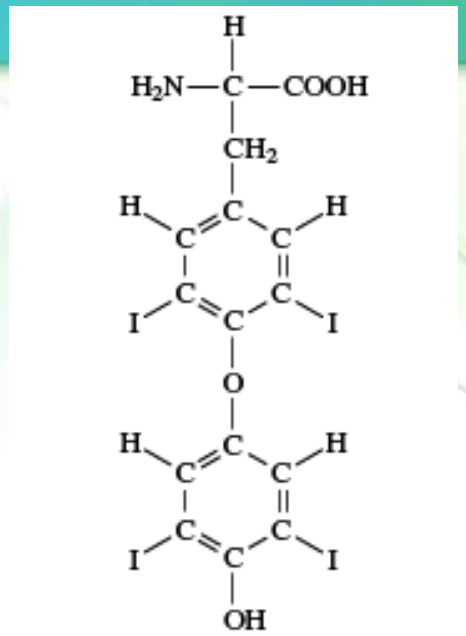
- It is converted into catecholamine neurotransmitters
  - Dopamine
  - Norepinephrine
  - Epinephrine
    - flight or fight

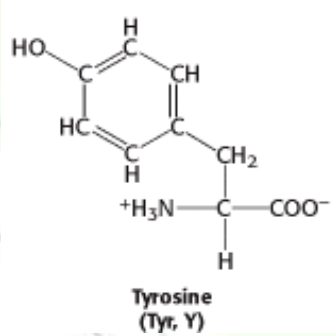


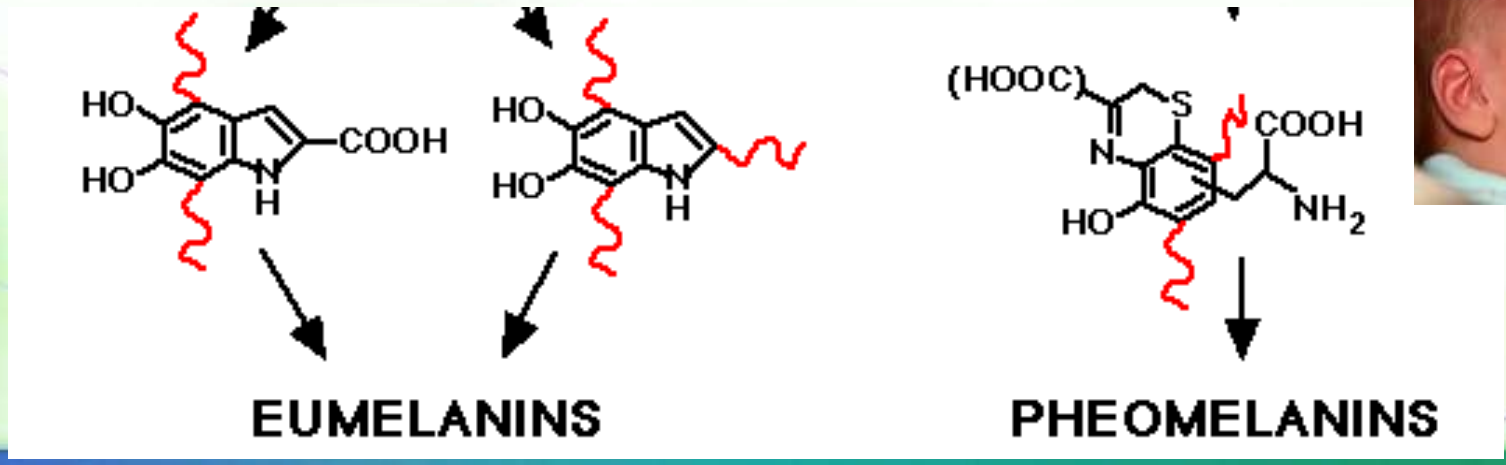


Tyrosine (2)

- Tyrosine is converted into
  - Melanin (skin color)
  - Thyroxine (hormone)

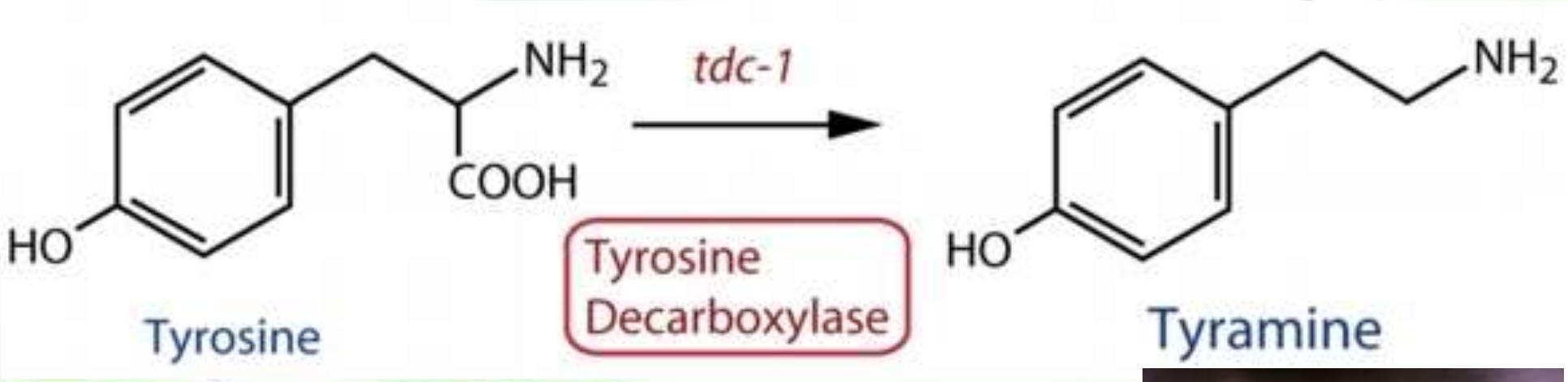






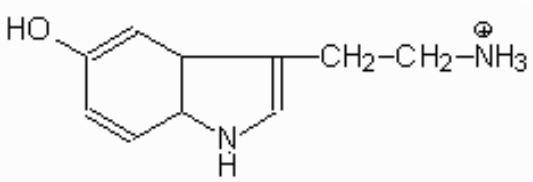
Tyrosine and life

- Cheese contain high amounts of tyramine, which mimics epinephrine; for many people a cheese omelet in the morning is a favorite way to start the day.

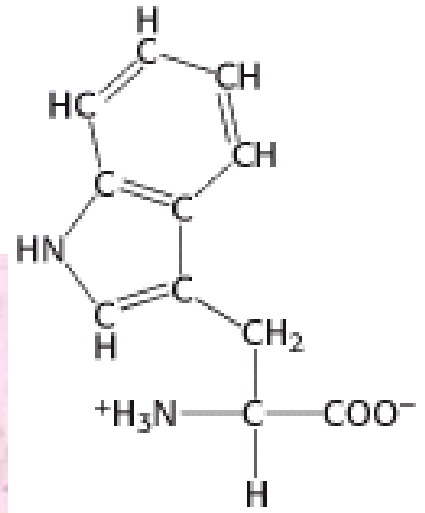


Tryptophan

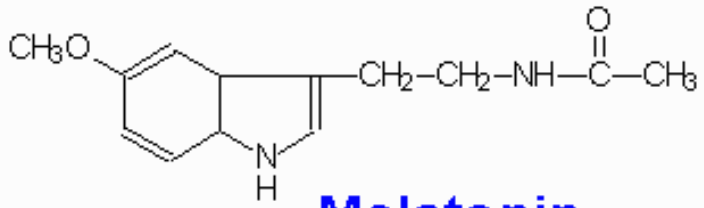
- Tryptophan serves as the precursor for the synthesis of Neurotransmitters
  - Serotonin (neurotransmitter-sedative)
  - Melatonin (day-night cycle)



Serotonin
(5-hydroxytryptamine)



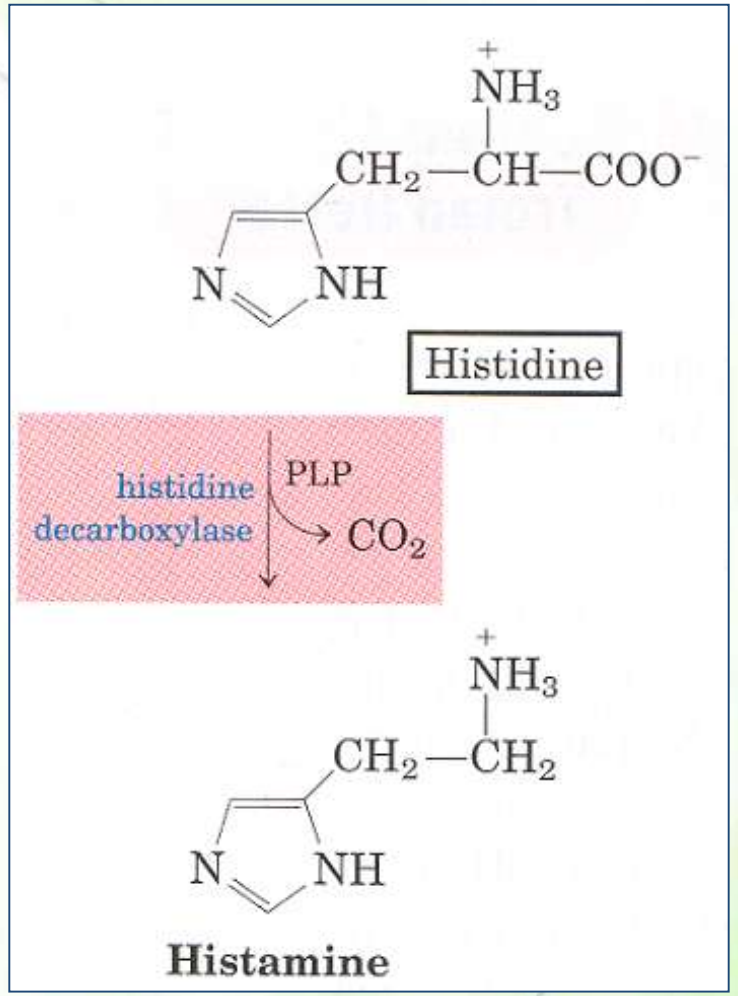
Tryptophan
(Trp, W)



Melatonin

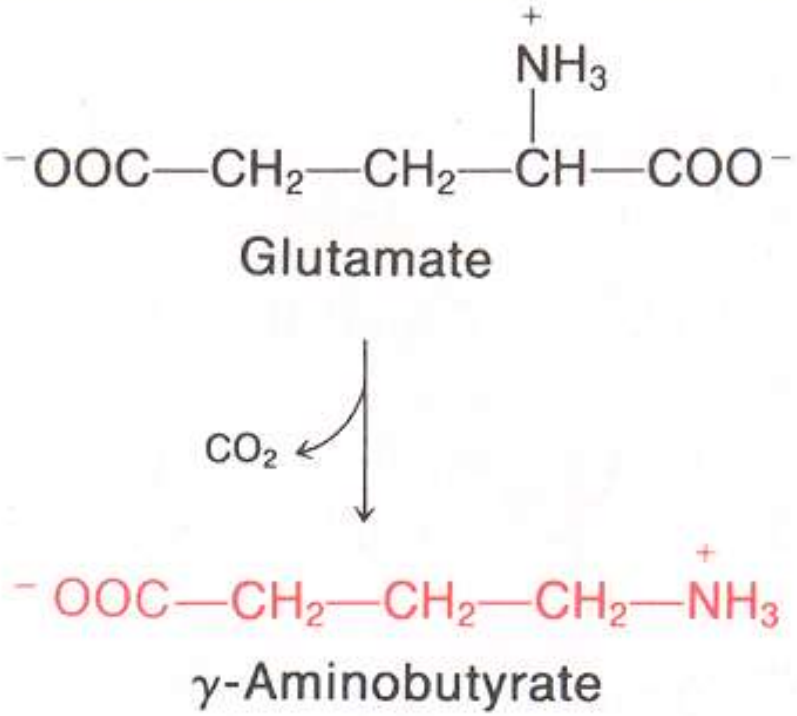
Histamine

- Regulates physiological function in the gut
- Acts as a neurotransmitter
- Causes allergic symptoms (a major causes for asthma)
- Contributes to inflammatory response
- Causes constriction of smooth muscle



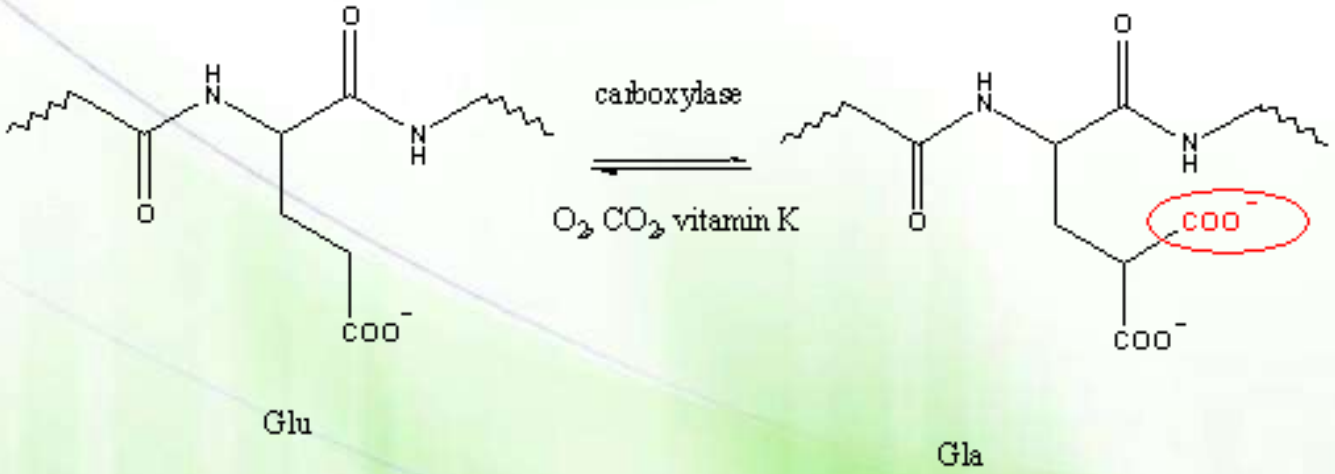
Glutamate

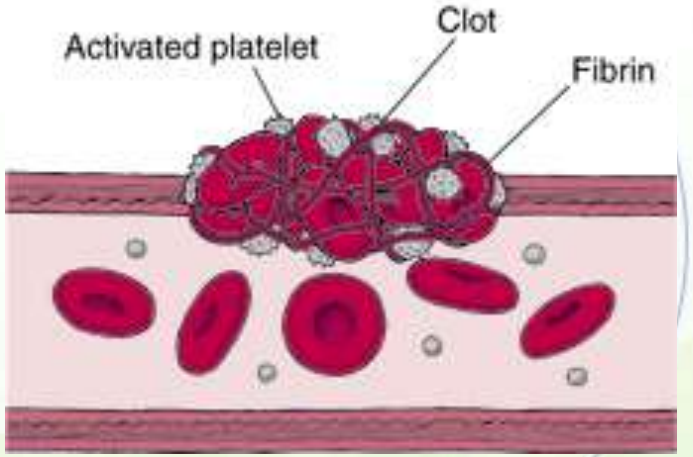
- It is a precursor of g- aminobutyric acid (GABA)
- It is an inhibitory neurotransmitter (CNS) that reduces neuronal excitability.
- It is synthesized in brain because it does not cross the BBB.
- It has relaxing, anti-anxiety, and anti-convulsive effects.



γ- carboxyglutamate (Gla)

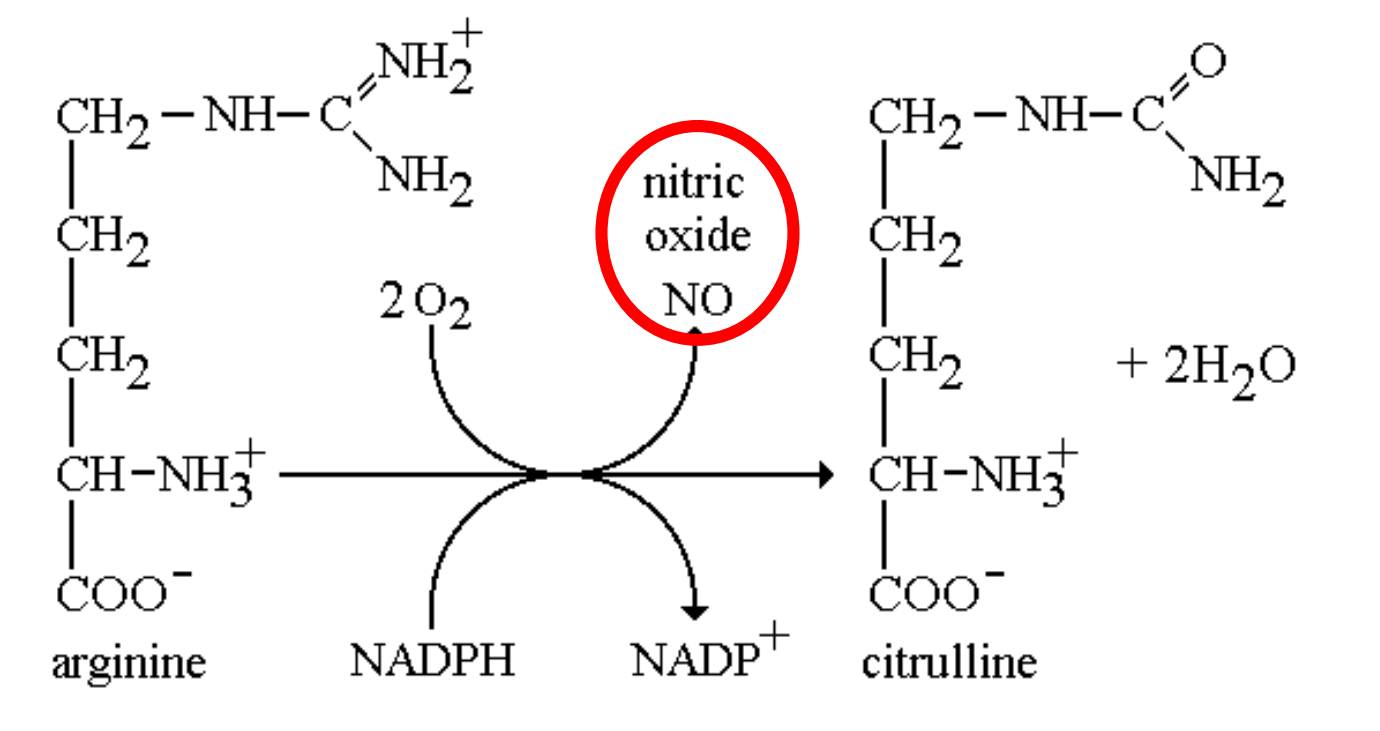
- The glutamate residues of some clotting factors are carboxylated to form γ- carboxyglutamate (Gla) residues.
  - Vitamin K is essential for the process
- This carboxylation is essential for the function of the clotting factors.





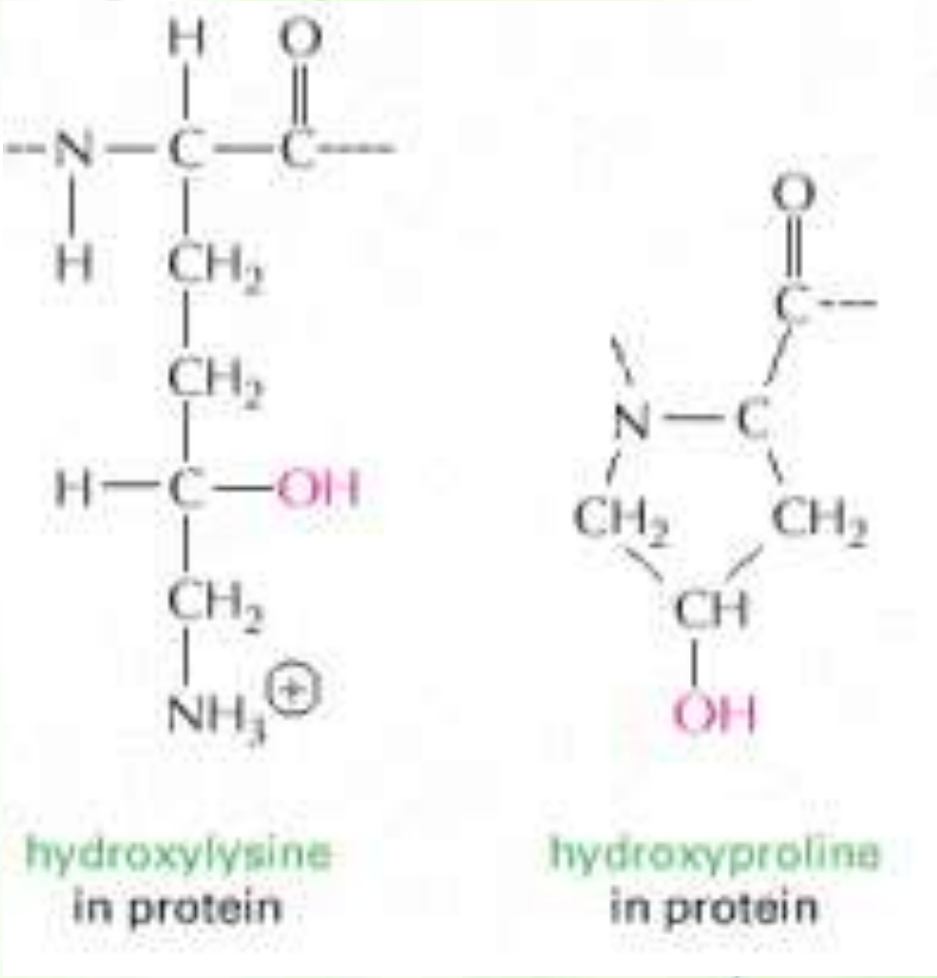
Arginine

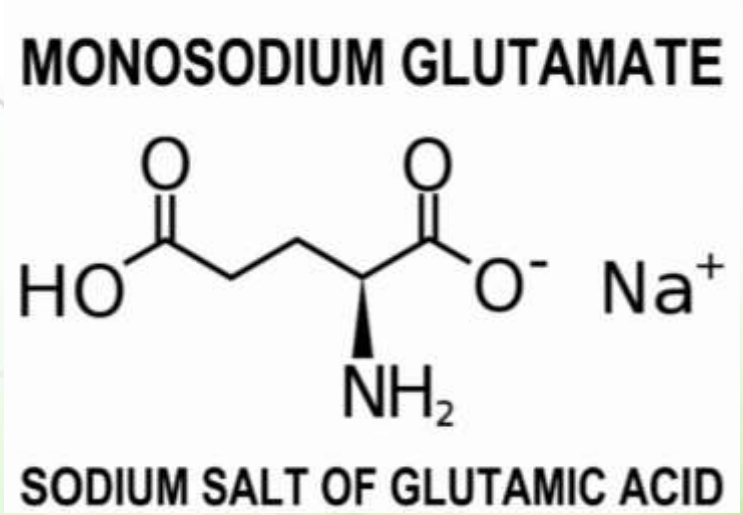
- L-arginine is the precursor of nitric oxide (NO)
- NO functions:
  - Vasodilation, inhibition of platelet adhesion, inhibition of leukocyte adhesion, antiproliferative action, scavenging superoxide anion (anti-inflammatory)



Hydroxylysine and hydroxyproline

- Both are hydroxylated and are part of collagen structure.
- Both are derived from the common amino acids.
- Both are produced by modification of the parent amino acid after protein synthesis, posttranslational modification.





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

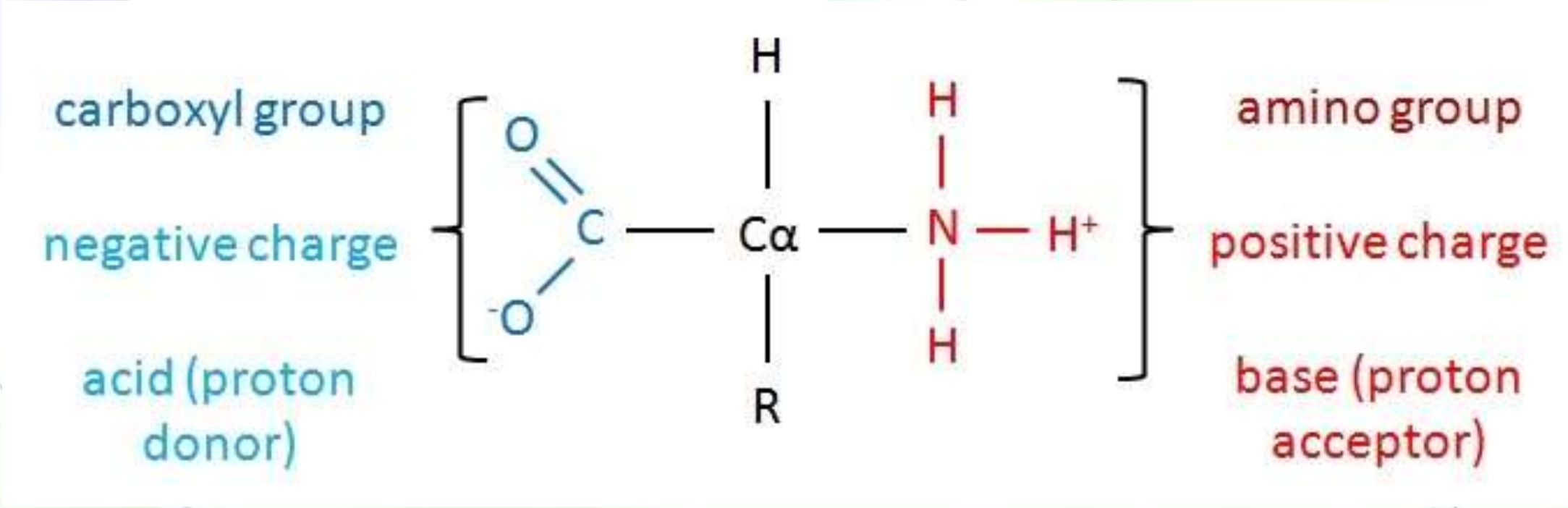
- What is special about (example: proline)?
- An acidic amino acid is_____ charged at physiological conditions.
- Name 2 amino acids that share a functional group in their side chain.

- Amino acid and protein molecular weight.
- The average molecular weight of an amino acid residue is about 110.
  - The molecular weights of most proteins are between 5500 and 220,000.

- 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).

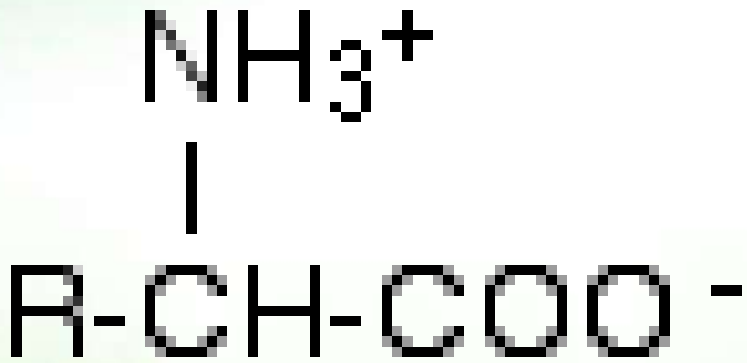
Ionization of amino acids

Why do amino acids get ionized?



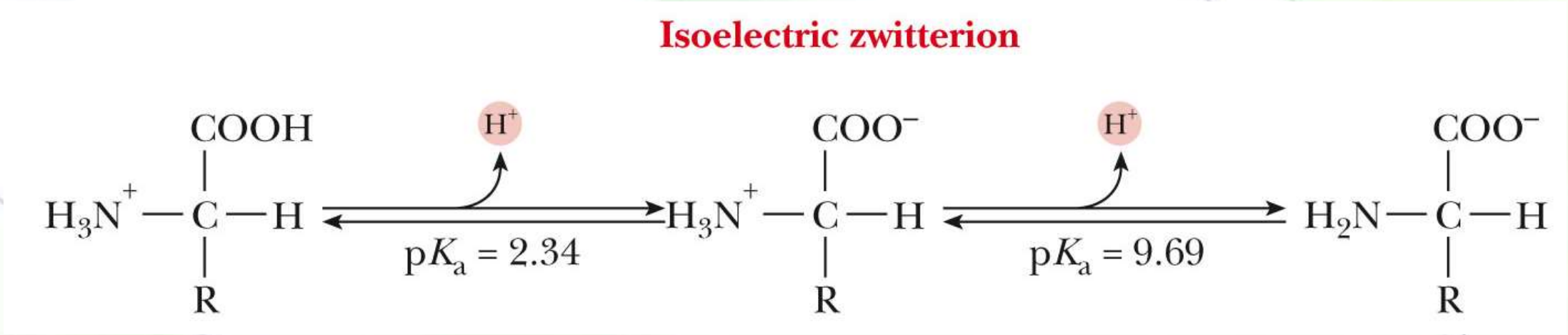
Zwitterion and isoelectric point

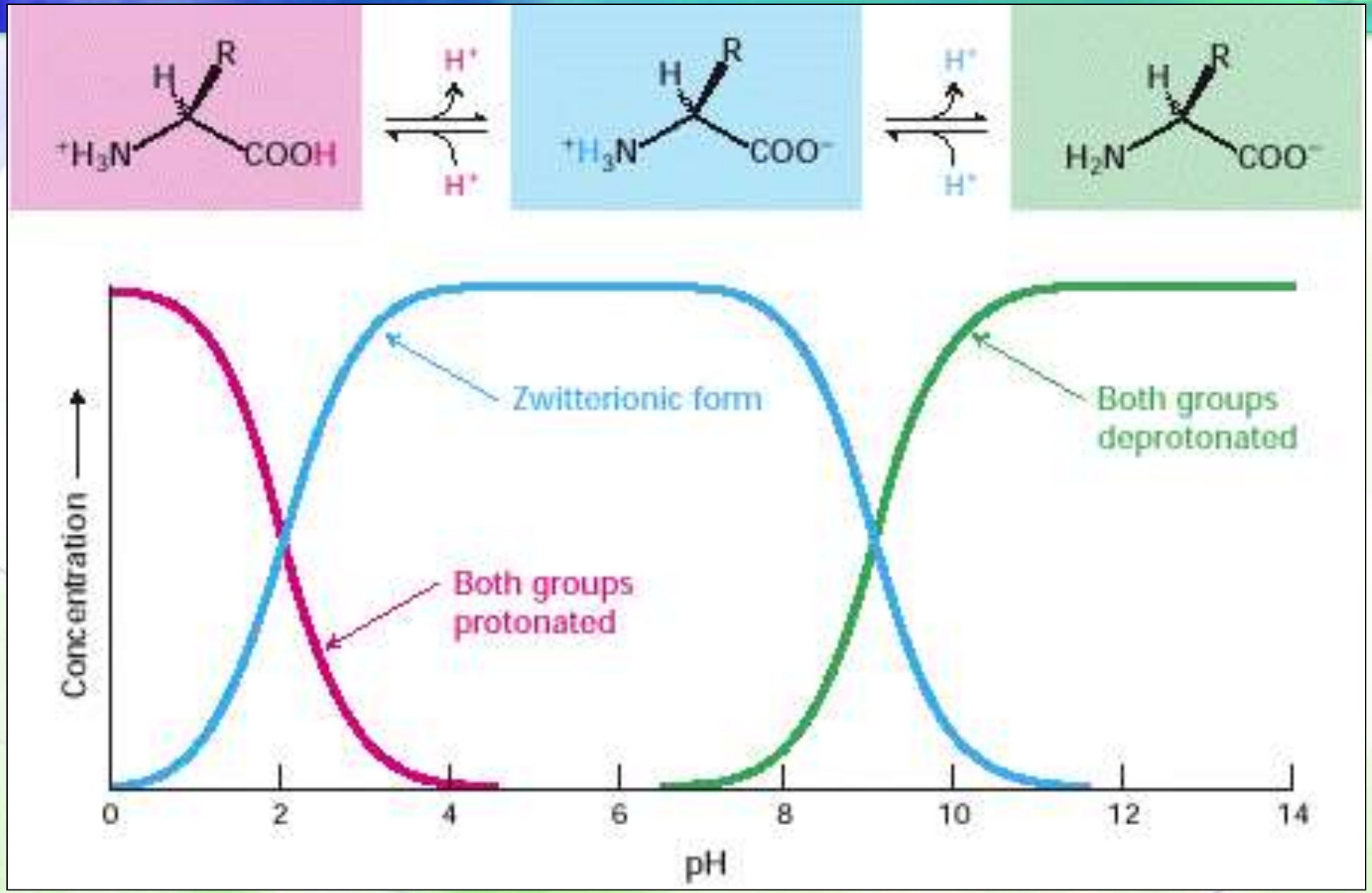
- At physiological pH, amino acids (without ionizable groups) are electrically neutral.
- Zwitterion: a molecule with two opposite charges and a net charge of zero.



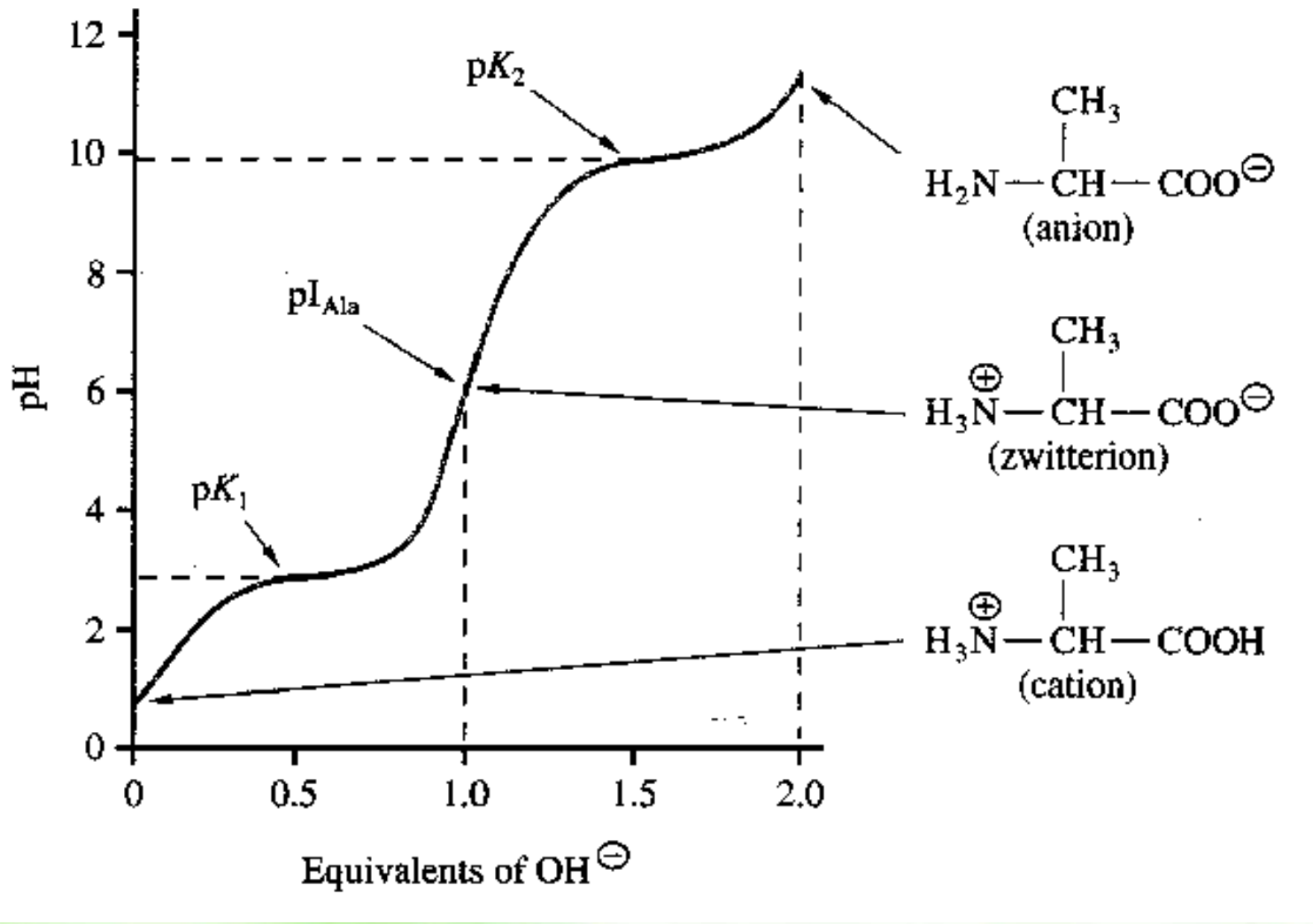
a zwitterion

Effect of pH


Isoelectric zwitterion
COOH
H+
COO−
H+
COO−
H3N+ — C — H
H3N+ — C — H
H2N — C — H
R
R
R
pKa = 2.34
pKa = 9.69


H
R
+H3N
COOH
H+
H+
H
R
+H3N
COO−
H+
H+
H
R
H2N
COO−
Zwitterionic form
Both groups
deprotonated
Both groups
protonated
Concentration
0
2
4
6
8
10
12
14
pH

Example 1 (alanine)



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

Isoelectric Point

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

$$\mathrm{pI} = \frac{\mathrm{p}K_{\mathrm{a1}} + \mathrm{p}K_{\mathrm{a2}}}{2}$$

Ionization of side chains

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

pI of amino acids

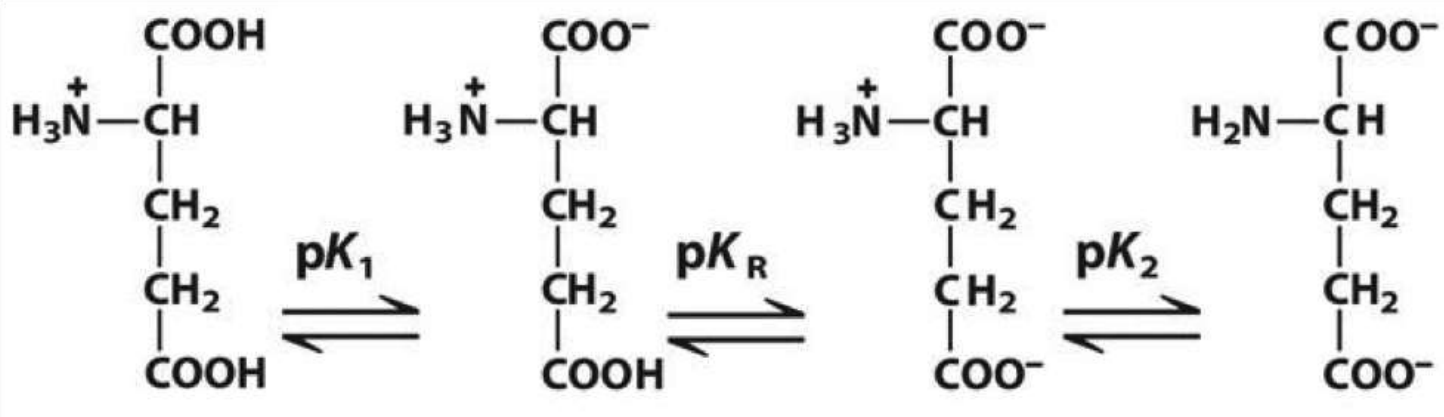
Amino Acid	Side Chain pK_a [3]	pI
Arginine	12.5	10.8
Aspartic Acid	4.0	3.0
Cysteine	8.0	5.0
Glutamic Acid	4.1	3.2
Histidine	6.0	7.5
Lysine	11.0	10

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

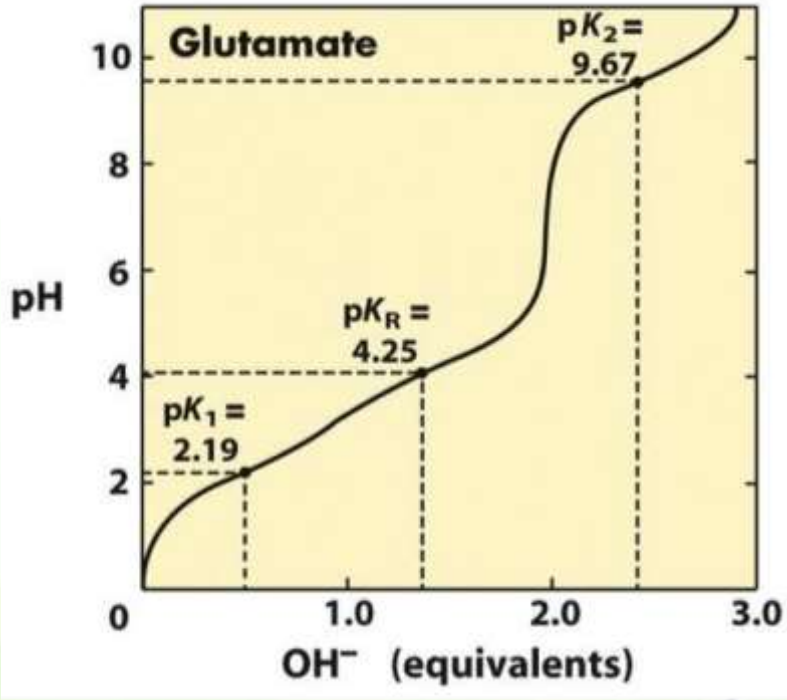
Calculation of pI of amino acids with ionizable R groups

- The isoelectric point for these amino acids is calculated by taking the average of the pKa's of the groups with same charge when ionized
- In this case, the total charge on the groups with like charge must equal one (1) so that it can be balanced by the one (1) opposite charge present on the molecule

Example: Glutamate

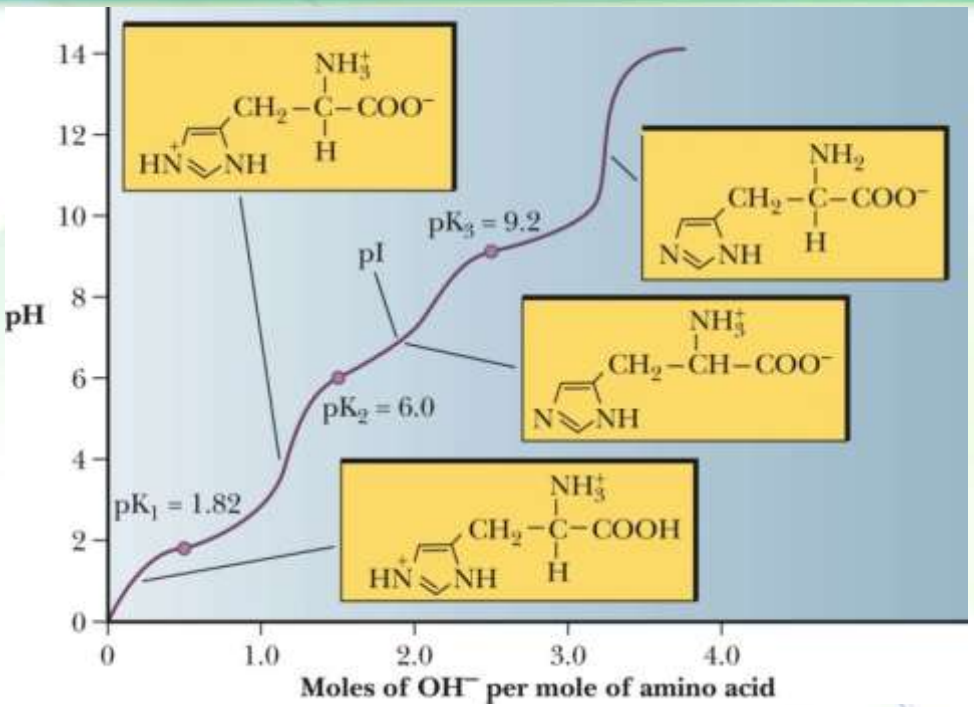


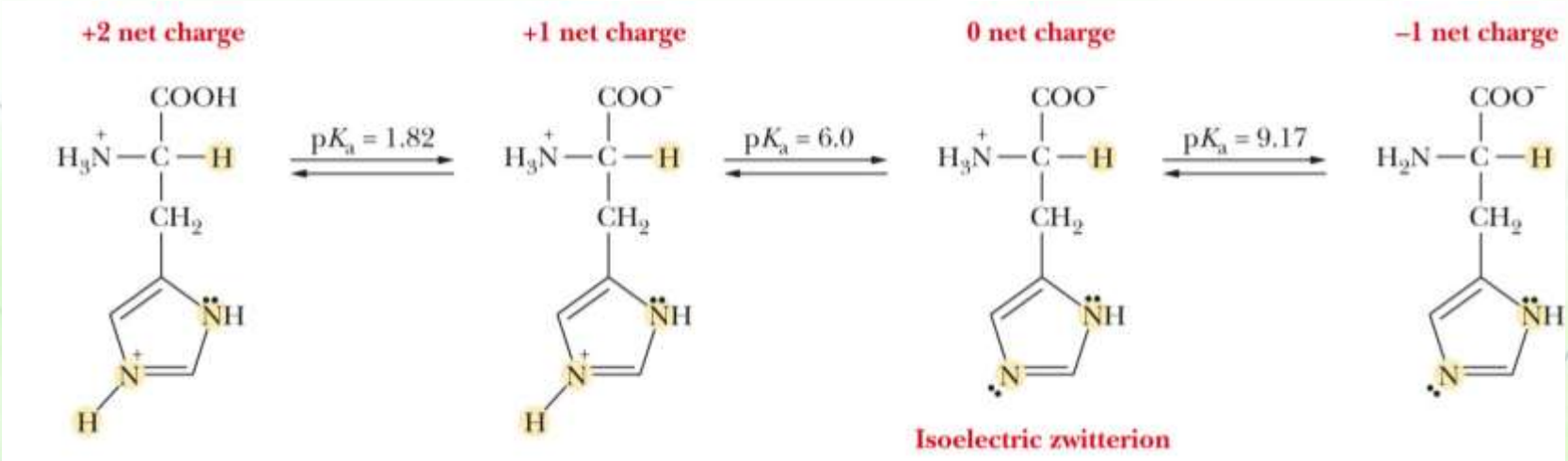
- To calculate the isoelectric point of Glu, the pKa's of the two carboxyl groups are averaged.



Histidine

- pI = ~7.5 (The imidazole group can be uncharged or positively charged near neutral pH).





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