Amino Acids and Peptides

Nafith Abu Tarboush
DDS, MSc, PhD
natarboush@ju.edu.jo
www.facebook.com/natarboush

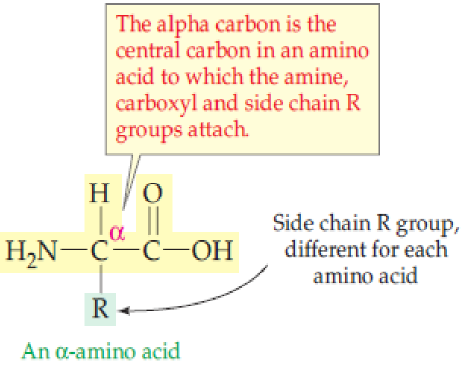
Protein structure and function

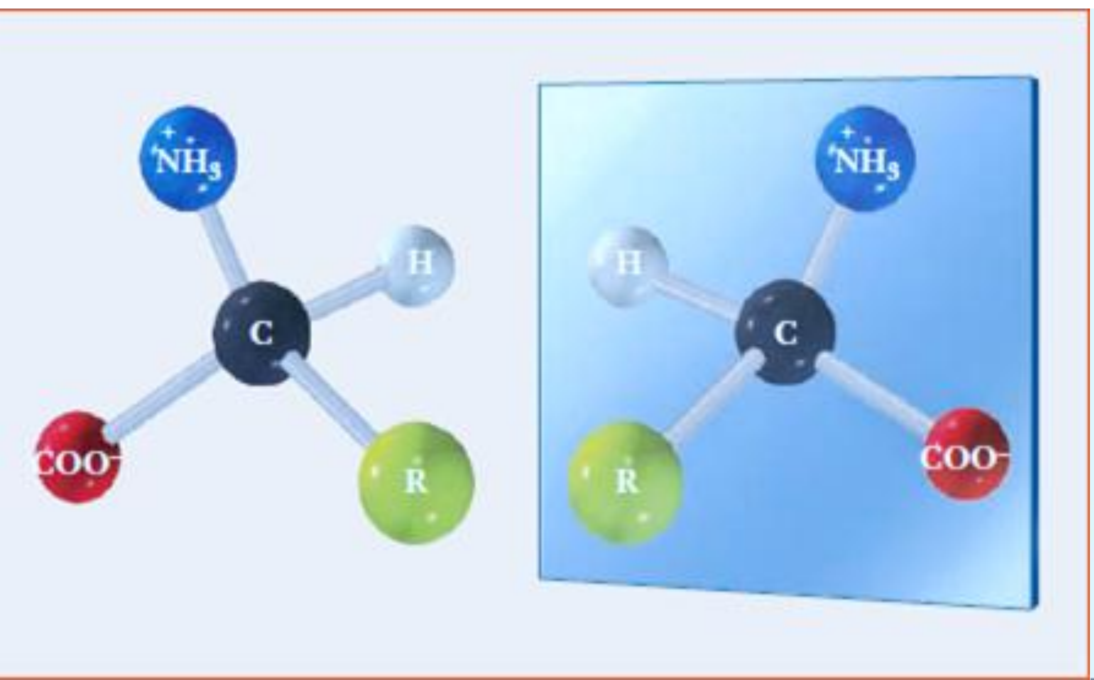
- Greek: proteios, primary (importance)
- 50 % of body's dry weight is protein
- Wide range of different functions
- Polymers of amino acids

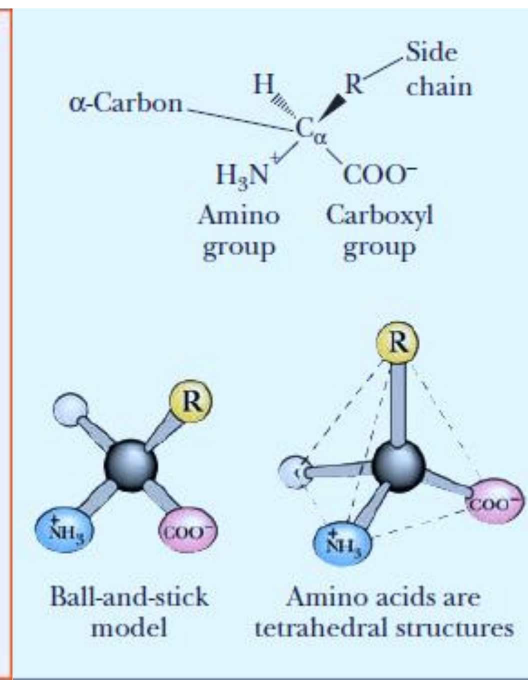
TYPE	FUNCTION	EXAMPLE
Enzymes	Catalysts	*Amylase*—begins digestion of carbohydrates by hydrolysis
Hormones	Regulate body functions by carrying messages to receptors	*Insulin*—facilitates use of glucose for energy generation
Storage proteins	Make essential substances available when needed	*Myoglobin*—stores oxygen in muscles
Transport proteins	Carry substances through body fluids	*Serum albumin*—carries fatty acids in blood
Structural proteins	Provide mechanical shape and support	*Collagen*—provides structure to tendons and cartilage
Protective proteins	Defend the body against foreign matter	*Immunoglobulin*—aids in destruction of invading bacteria
Contractile proteins	Do mechanical work	*Myosin and actin*—govern muscle movement

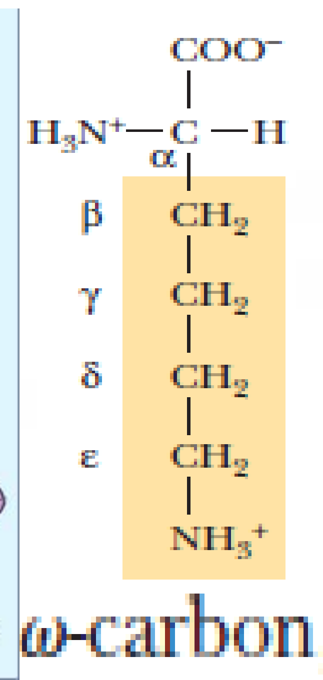
Structure of the amino acids

- General structure(amino, carboxylic, H, R)
- The basis of their classification
- Two vs. 3-dimentional (handedness, chirality, chiral vs. achiral, left vs. right, L vs. D)

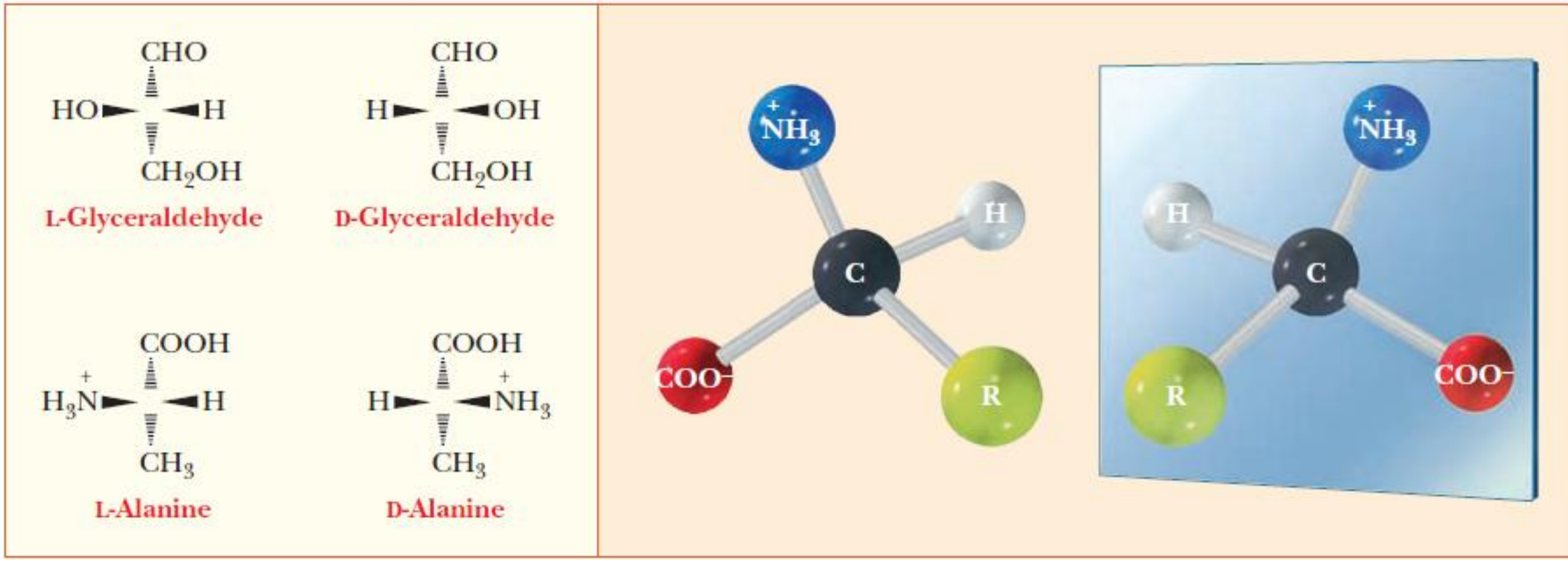








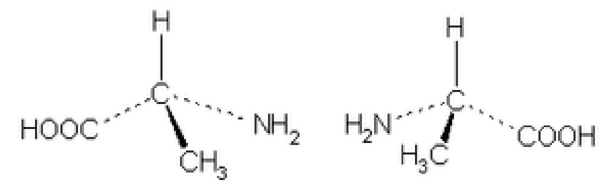
Isomers, stereoisomers, enantiomers



- If two molecules have the same number of atoms, they are isomers
- If the isomers have the same atomic connectivity, but differ spatially, they are stereoisomers
- If the stereoisomers are mirror images of each other, they are enantiomers

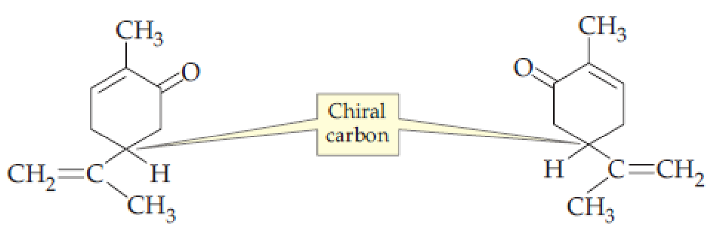
What should not be forgotten?

- There are a lot of amino acids in life
- There are 20 encoded by the genetic code
- Naturally occurring amino acids in proteins are all “L”
- Chirality makes a difference
- What follows……



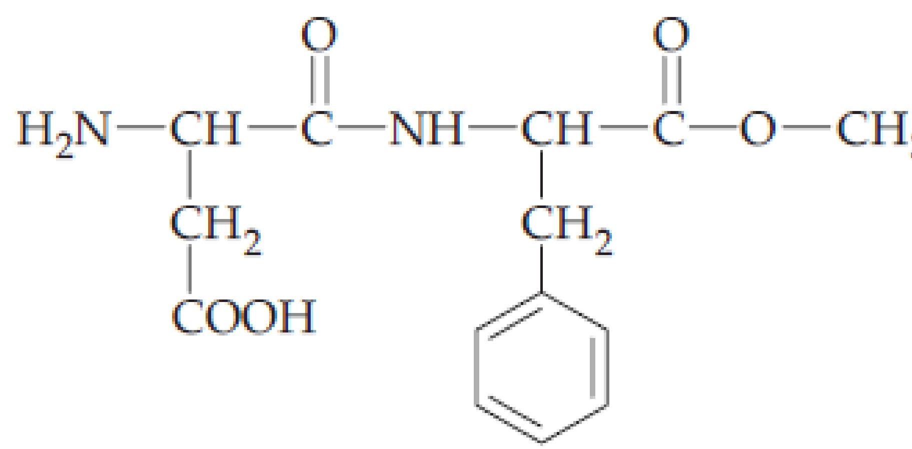
D-Amino acid L-amino acid

Clockwise vs. counter-clockwise “CO – R – N”



L-carvone (in spearmint)

D-carvone (in caraway)



Aspartame (methyl ester of aspartylphenylalanine)

Names and codes

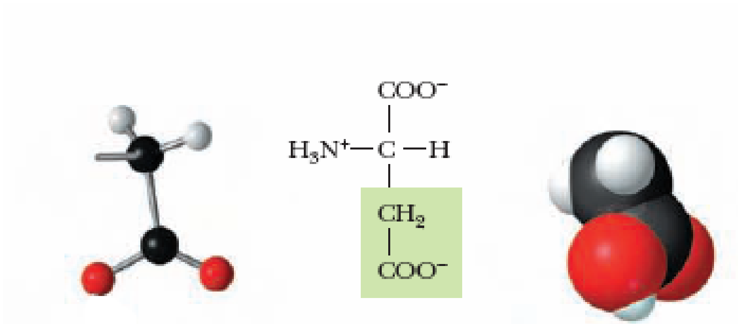
Amino Acid	3-letter code	1-letter code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamic acid	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I

Amino Acid	3-letter code	1-letter code
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

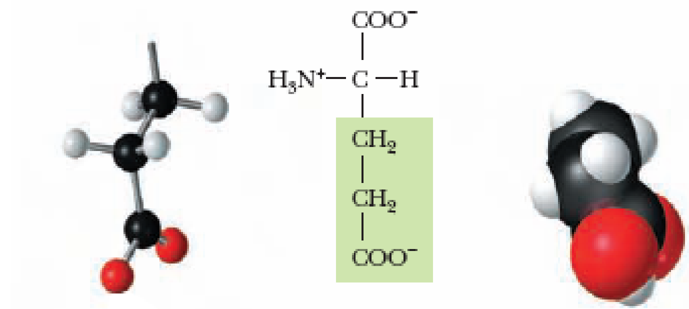
Classification

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

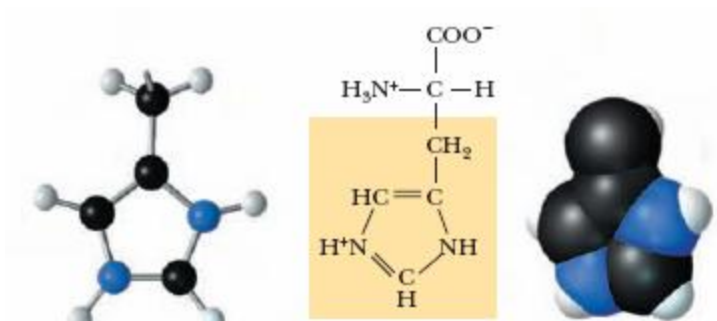
Charged



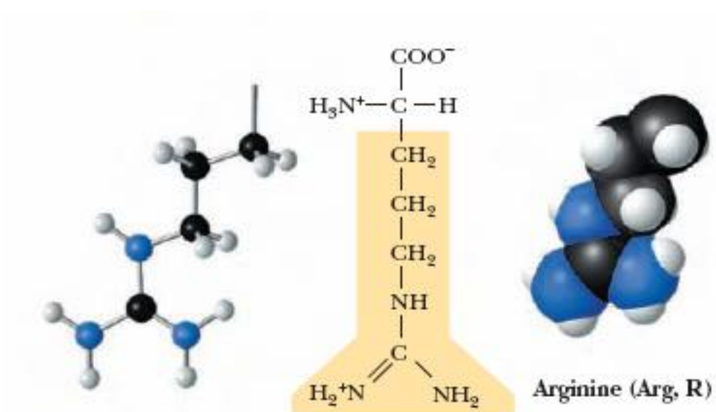
Aspartic acid (Asp, D)



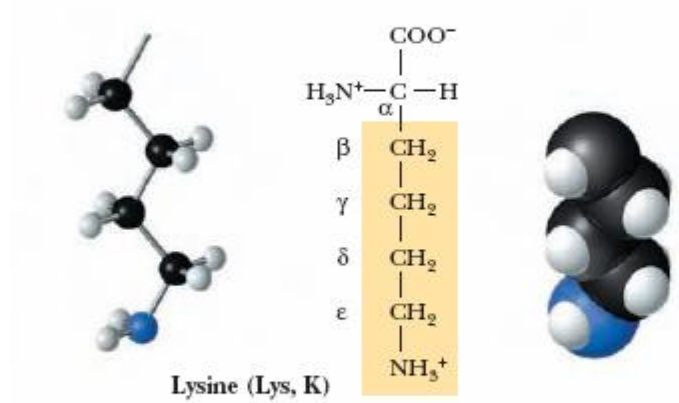
Glutamic acid (Glu, E)



Histidine (His, H)

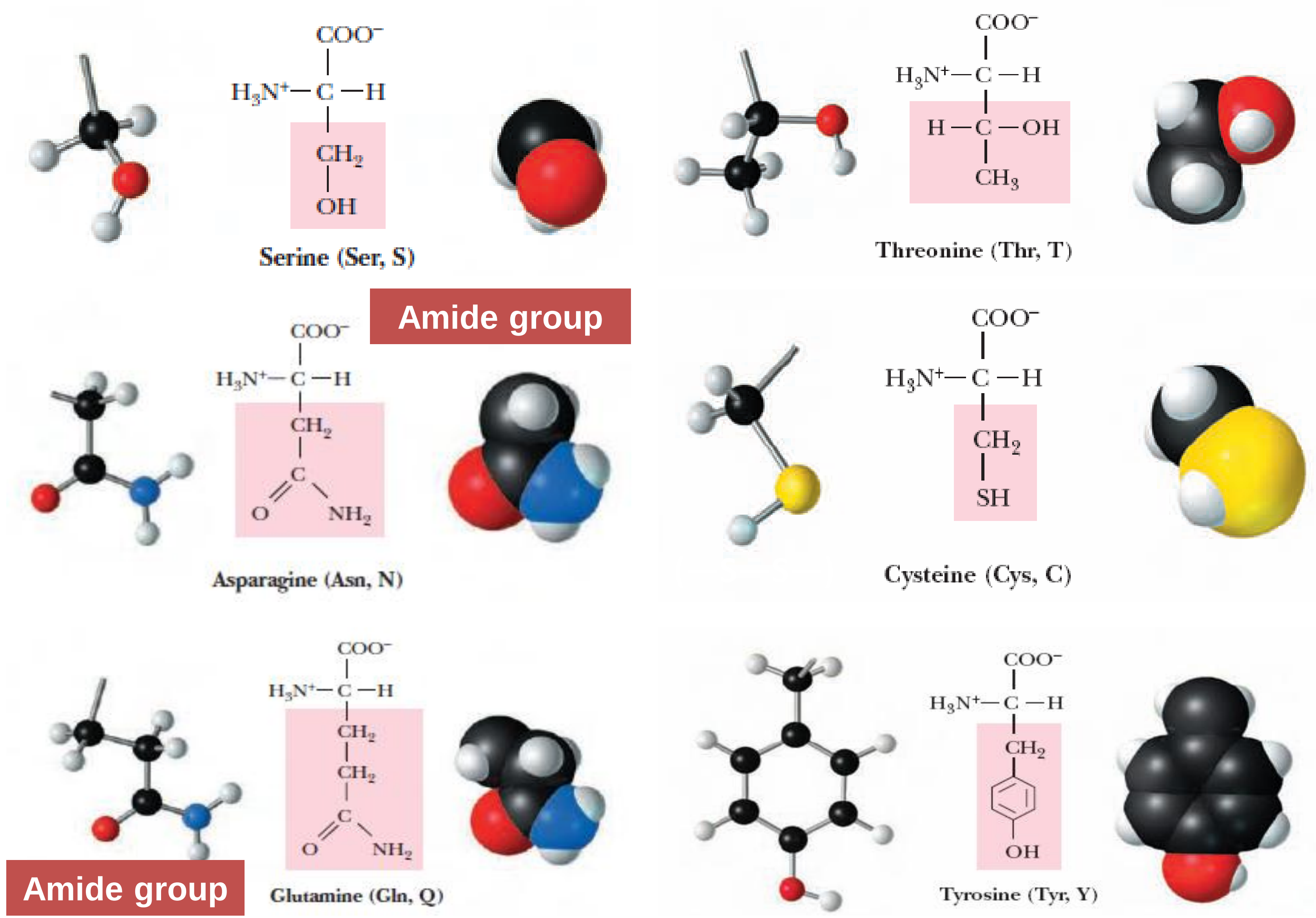


Arginine (Arg, R)

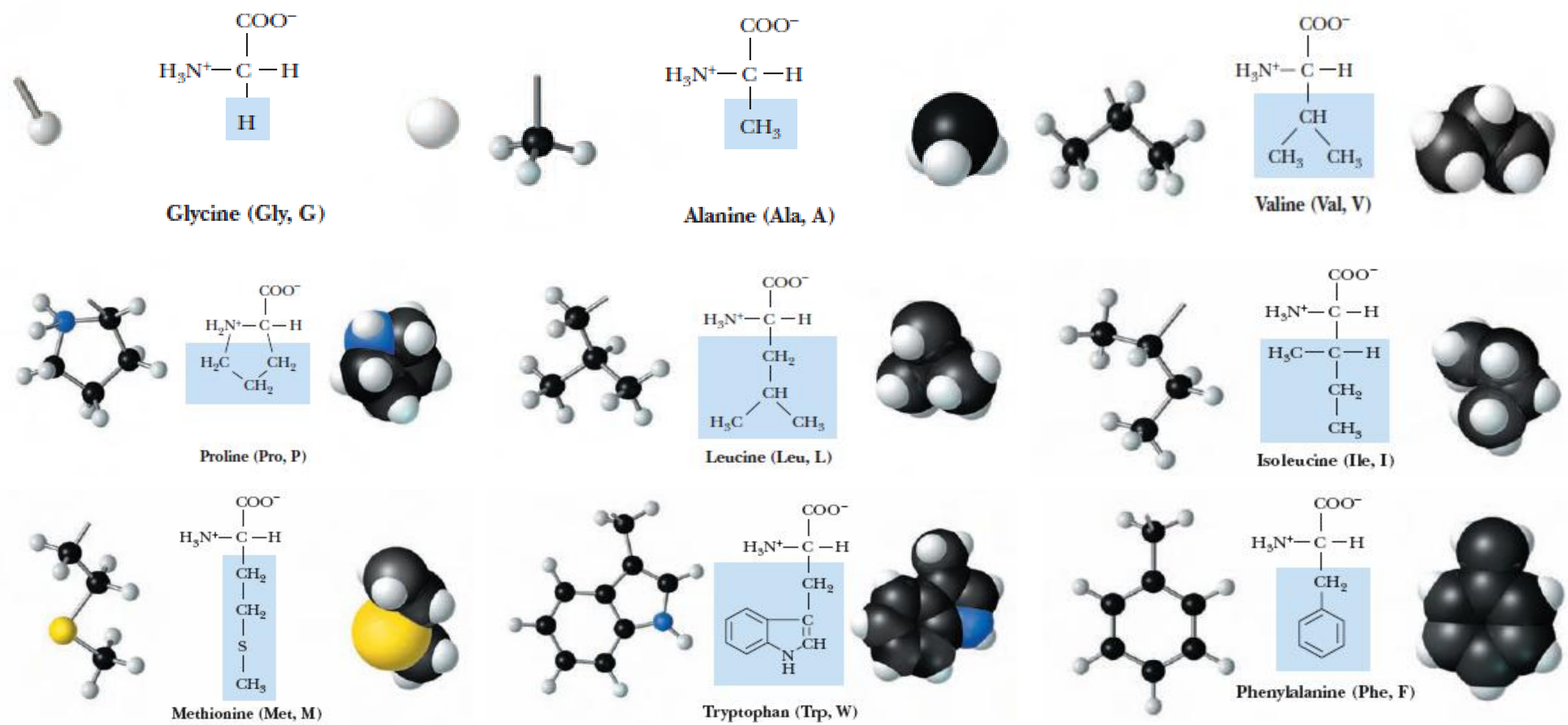


Lysine (Lys, K)

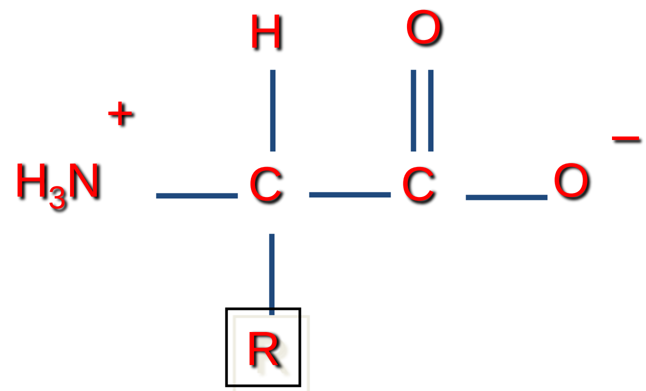
Polar, Uncharged



Non-polar, Uncharged



Amino acids – general structure

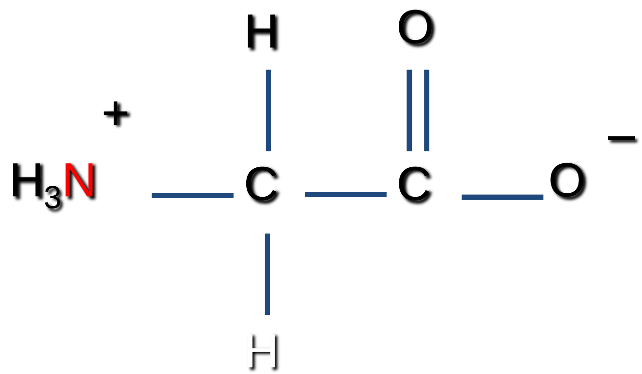


- The amino acids obtained by hydrolysis of proteins differ in respect to R (the side chain)
- The properties of the amino acid vary as the structure of R varies

Glycine

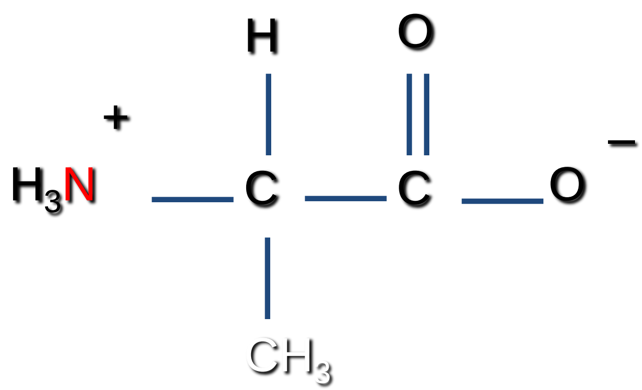
Glycine

(Gly or G)



- Glycine is the simplest amino acid. It is the only one that is achiral
- In all of the other amino acids the α-carbon is a stereogenic center

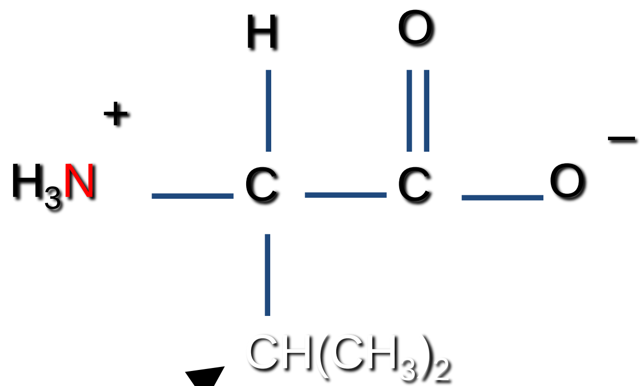
Alanine



Alanine

(Ala or A)

Valine

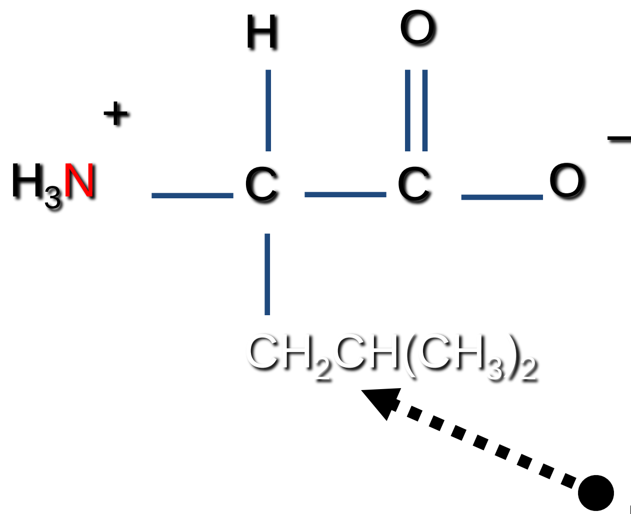


Branched

Valine

(Val or V)

Leucine

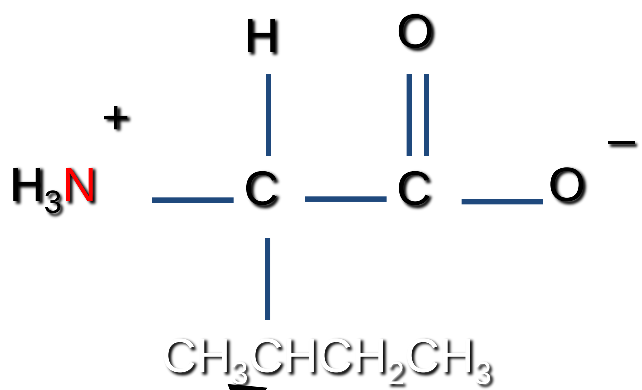


Branched

Leucine

(Leu or L)

Isoleucine

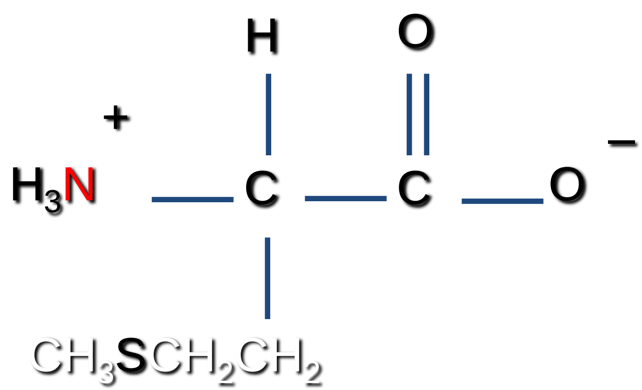


Branched

Isoleucine

(Ile or I)

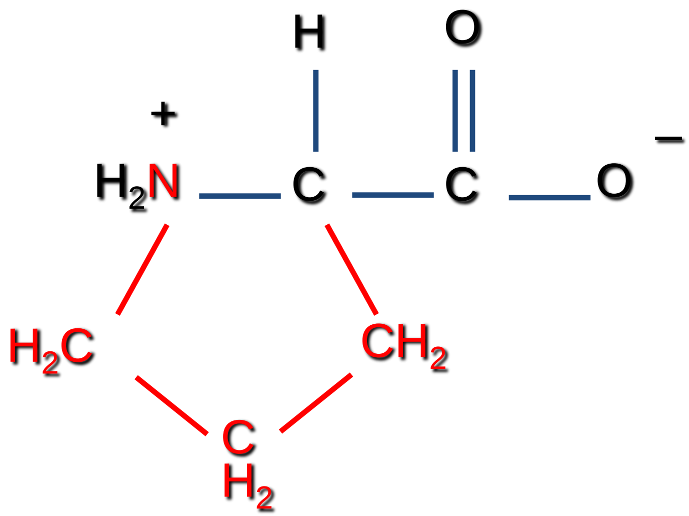
Methionine



Methionine

(Met or M)

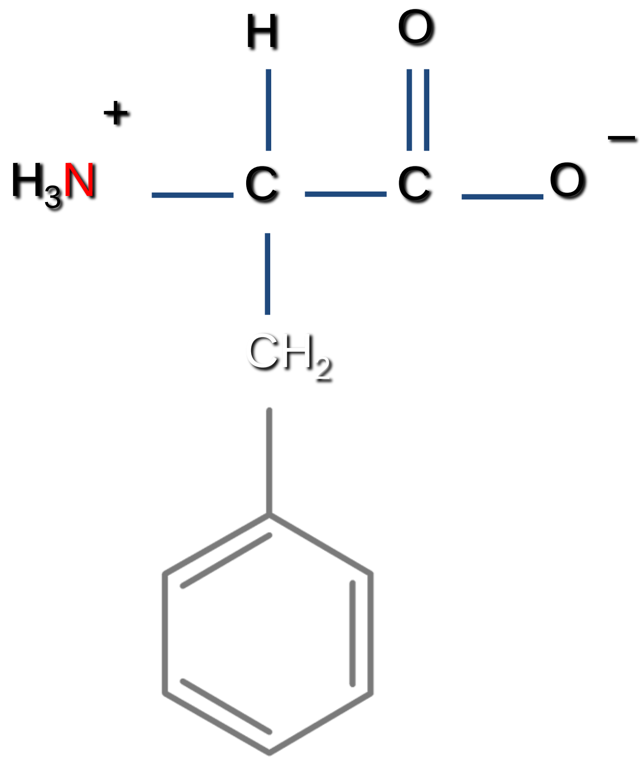
Proline (imino)



Proline

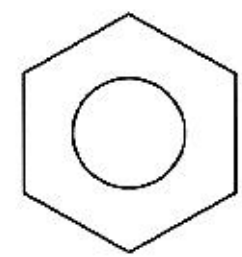
(Pro or P)

Phenylalanine (aromatic)



Phenylalanine

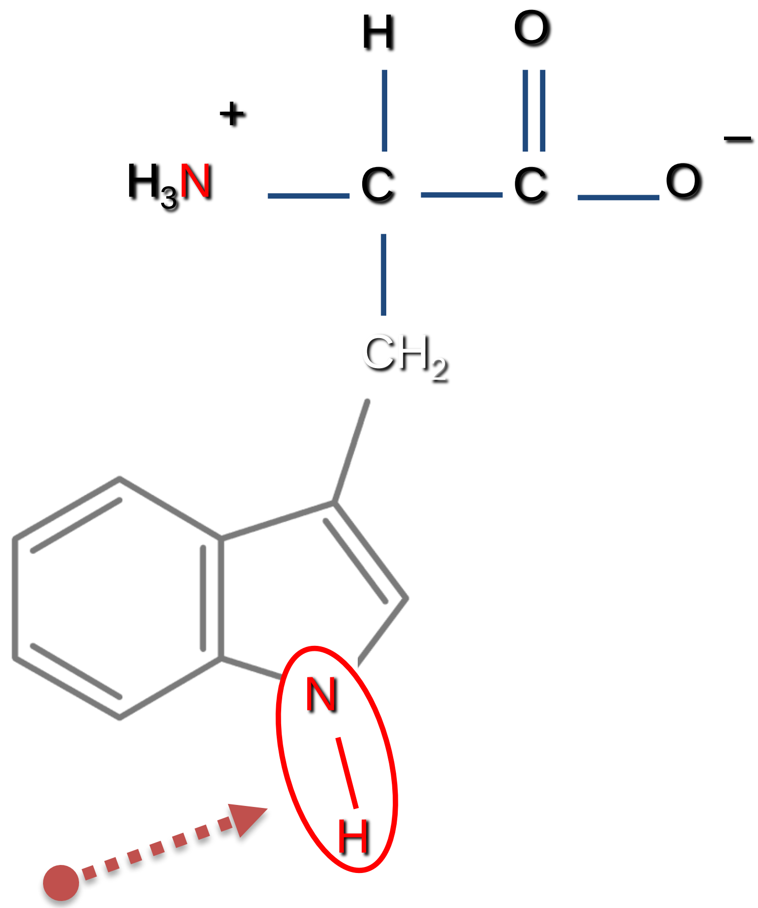
(Phe or F)

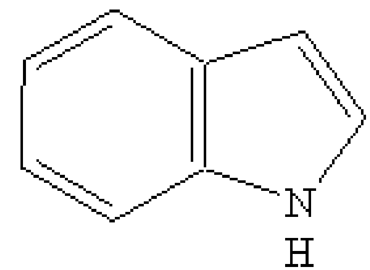


Benzene

C_6H_6

Tryptophan (aromatic)



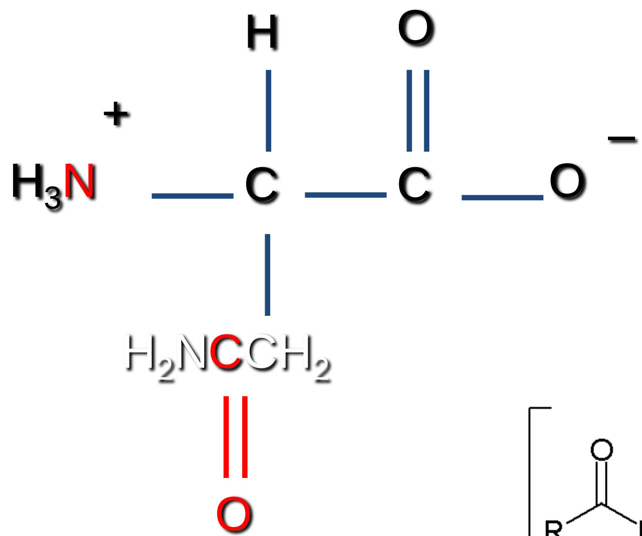


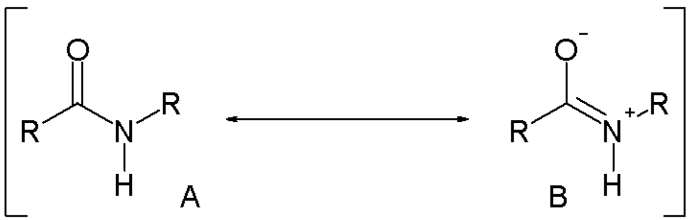
Indole

Tryptophan

(Trp or W)

Asparagine

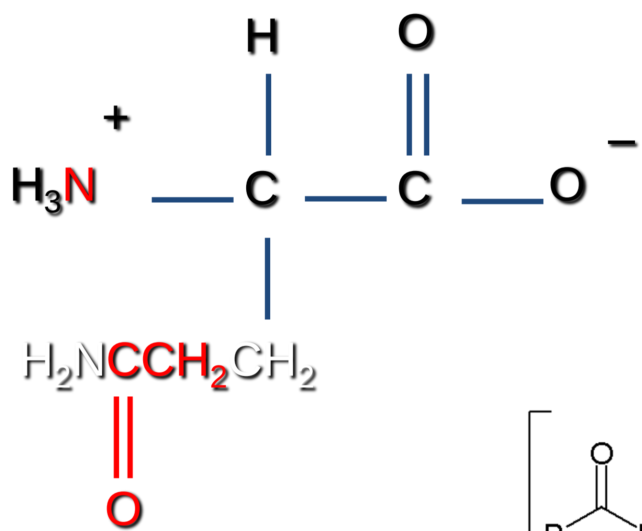


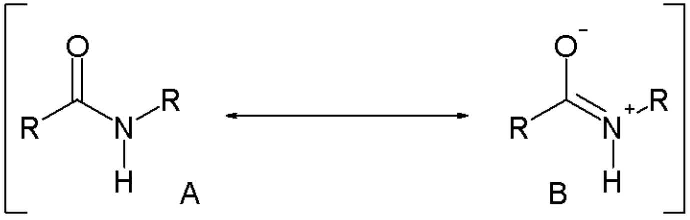


Asparagine

(Asn or N)

Glutamine

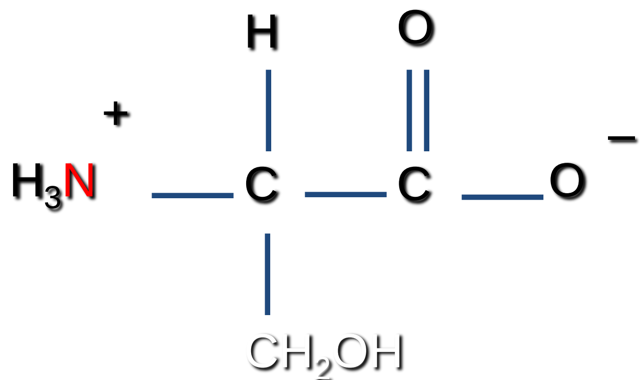




Glutamine

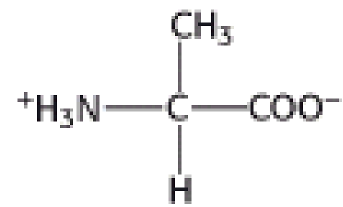
(Gln or Q)

Serine



Serine

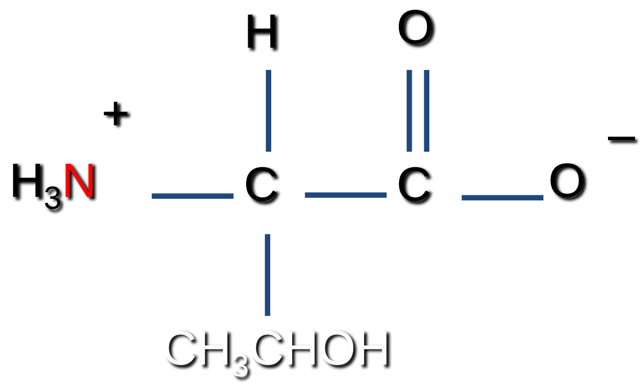
(Ser or S)

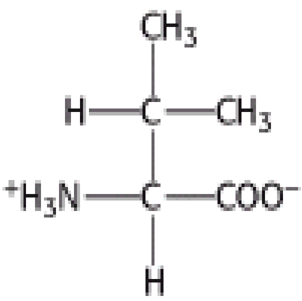


Alanine
(Ala, A)

How close?

Threonine





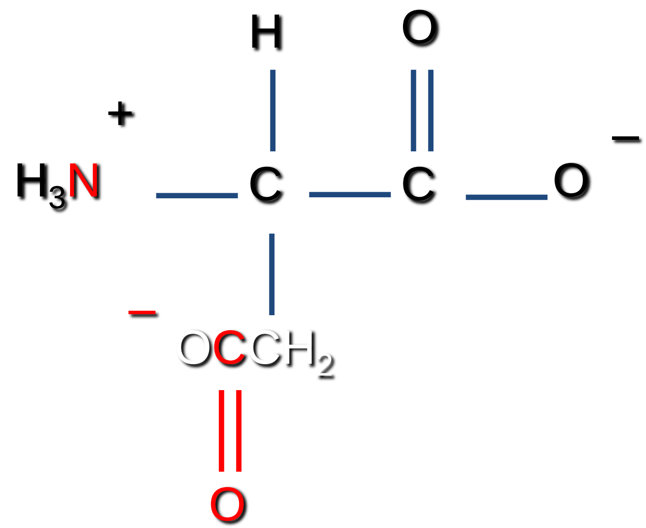
Valine
(Val, V)

How close?

Threonine

(Thr or T)

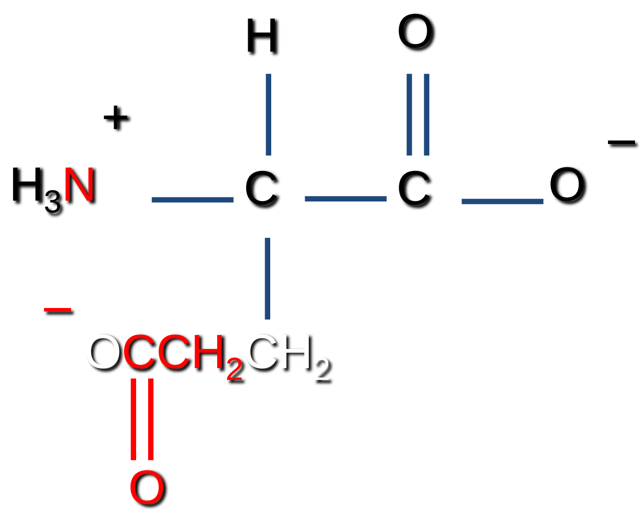
Aspartic Acid



Aspartic Acid

(Asp or D)

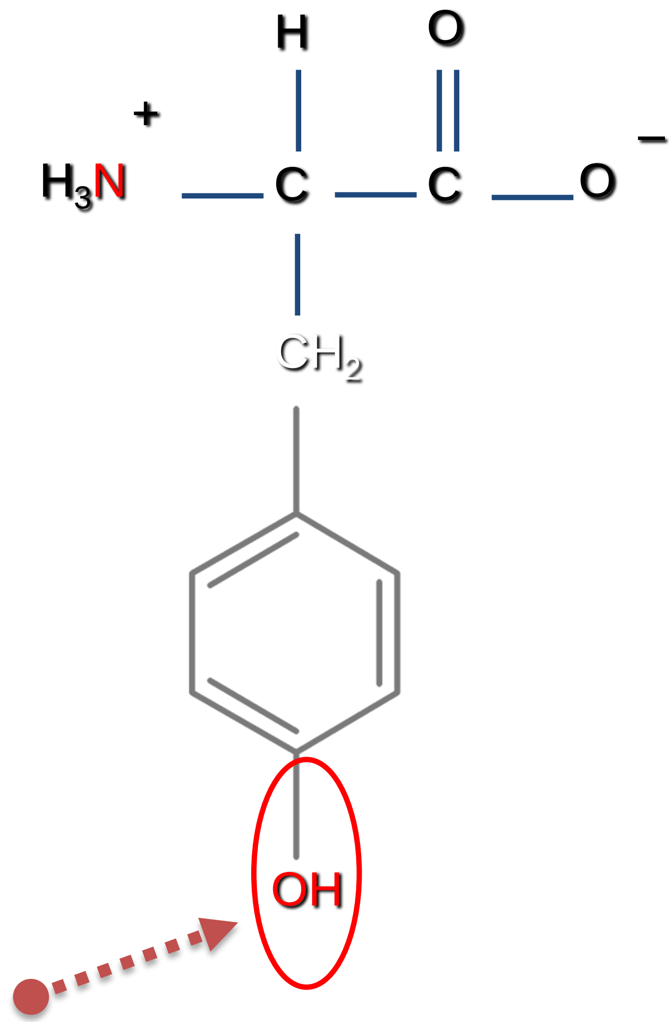
Glutamic Acid

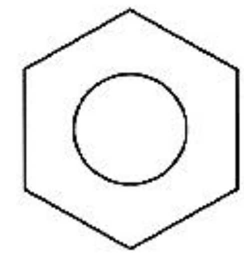


Glutamic Acid

(Glu or E)

Tyrosine (aromatic)





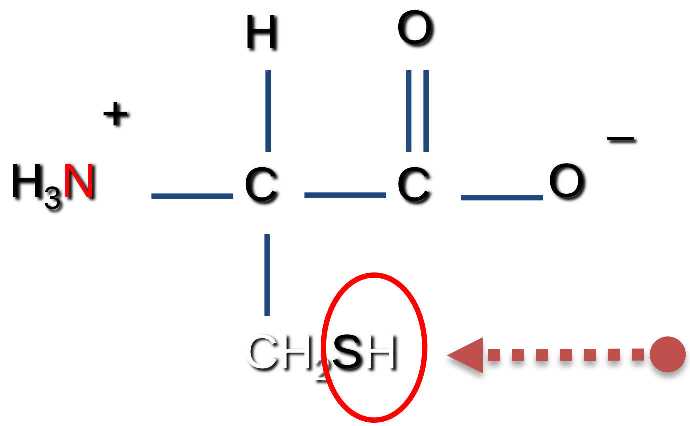
Benzene

C_6H_6

Tyrosine

(Tyr or Y)

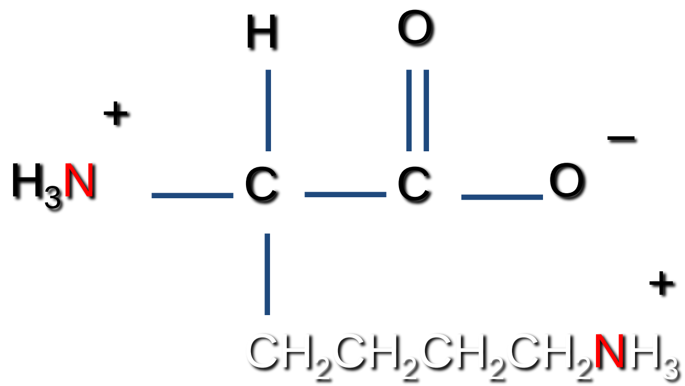
Cysteine



Cysteine

(Cys or C)

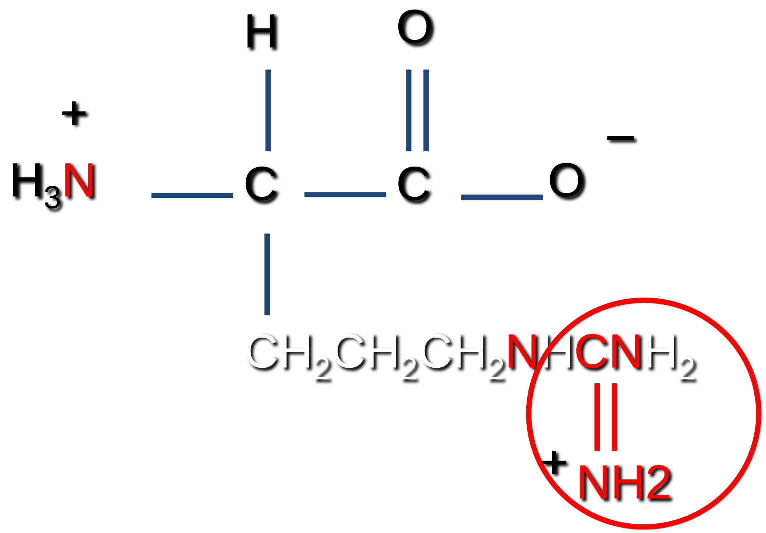
Lysine



Lysine

(Lys or K)

Arginine



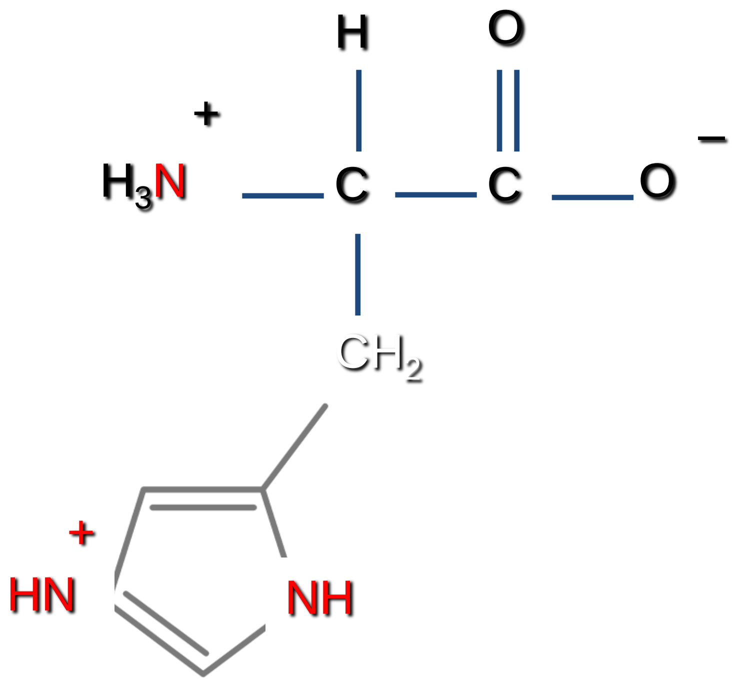
Guanidino group

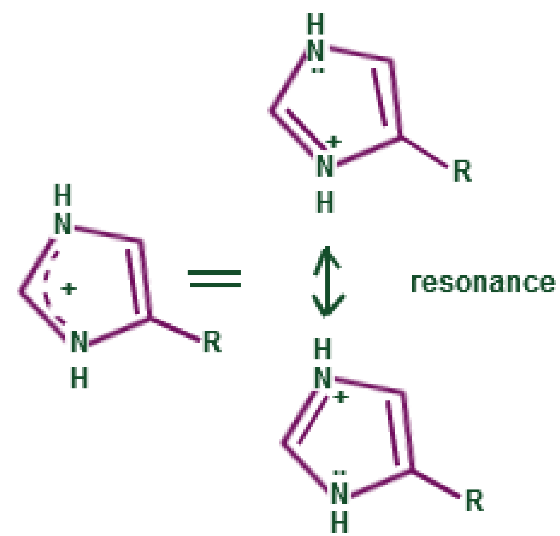
Arginine

(Arg or R)

Strong base; used in production of plastics & explosives

Histidine (imidazole ring)

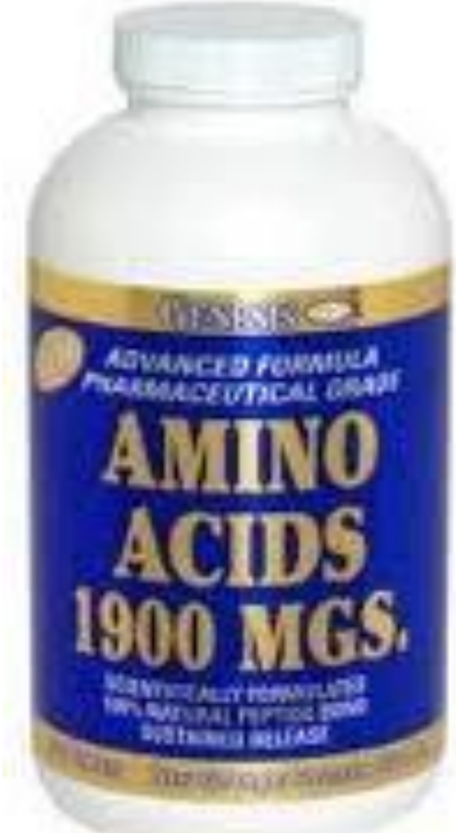




Histidine

(His or H)

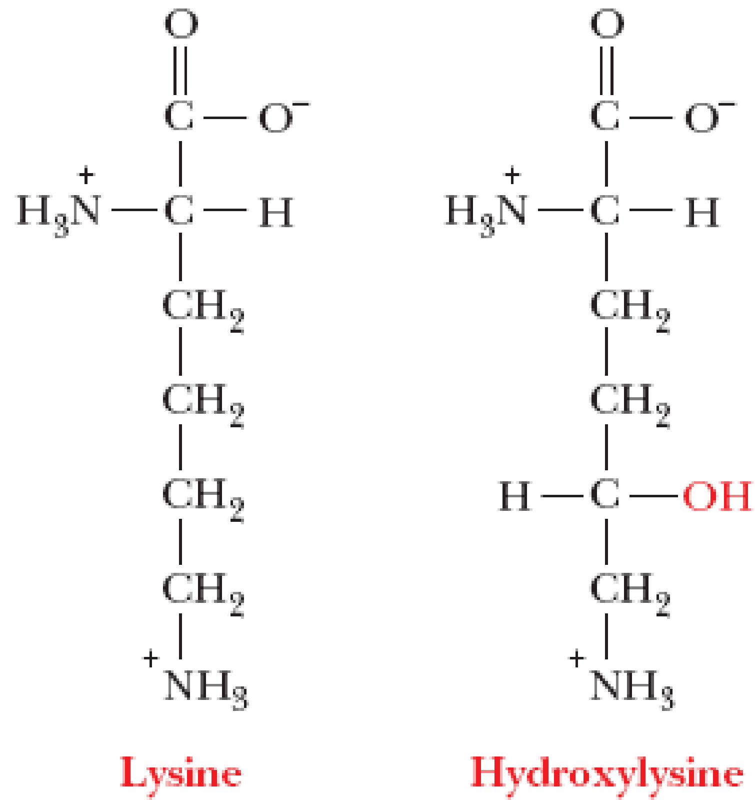
Amino Acids & life

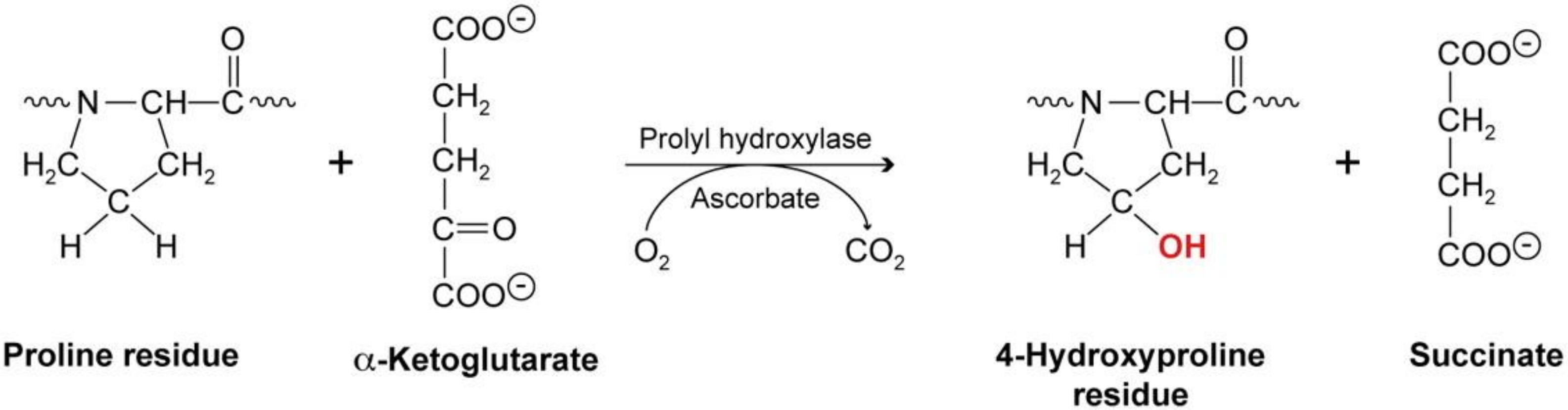


Modified Amino Acids

Lysine & Proline

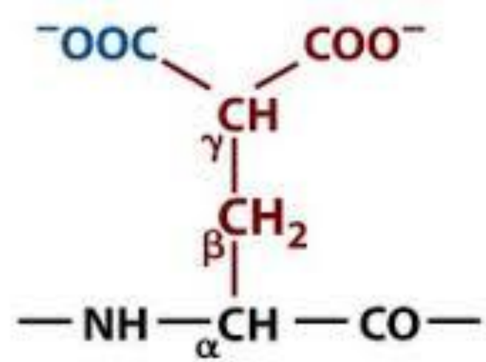
- Both are hydroxylated & are part of collagen structure



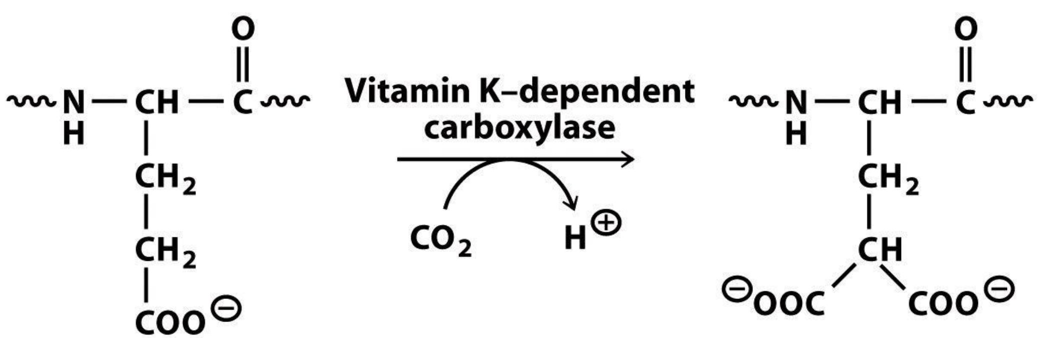


Glutamate (Glu) & γ- carboxyglutamate (Gla)

- 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

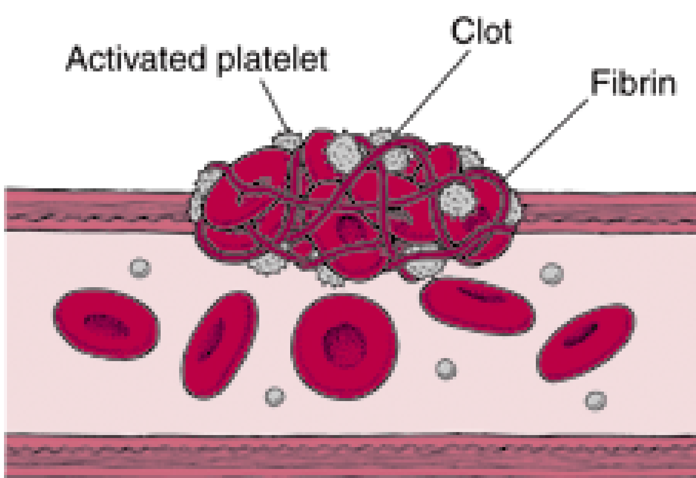


γ-Carboxyglutamate



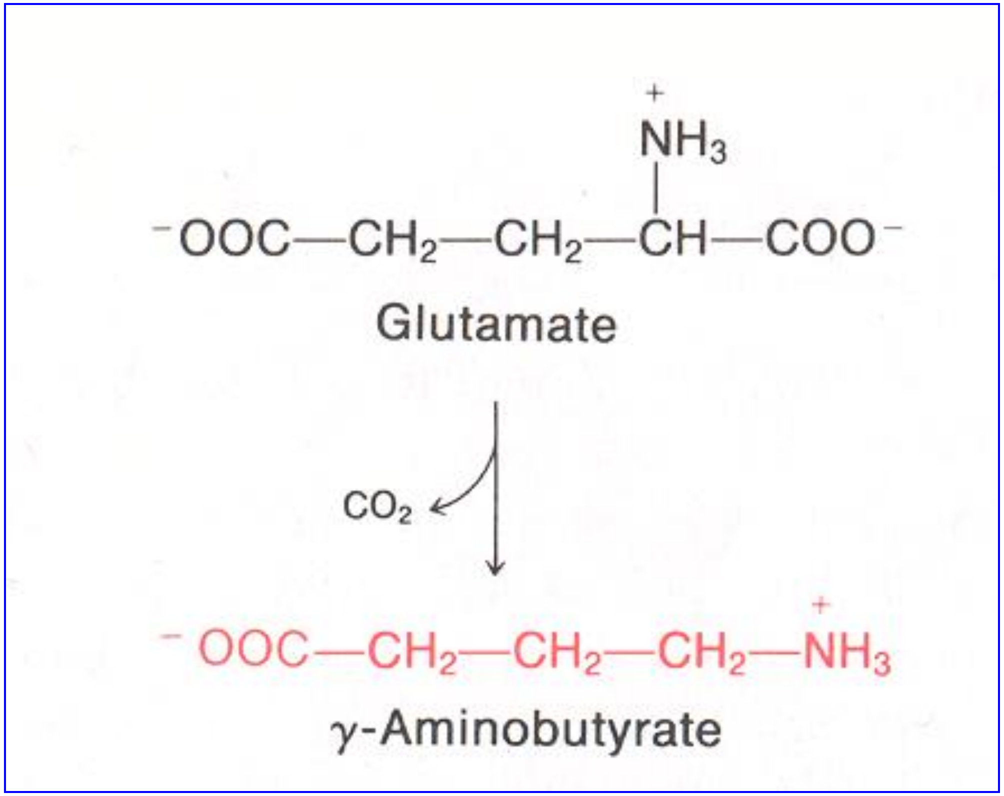
Glutamate residue

γ-Carboxyglutamate residue



Glutamate & GABA

- Is a precursor of γ- aminobutyric acid (GABA)
  - Inhibitory neurotransmitter (CNS)

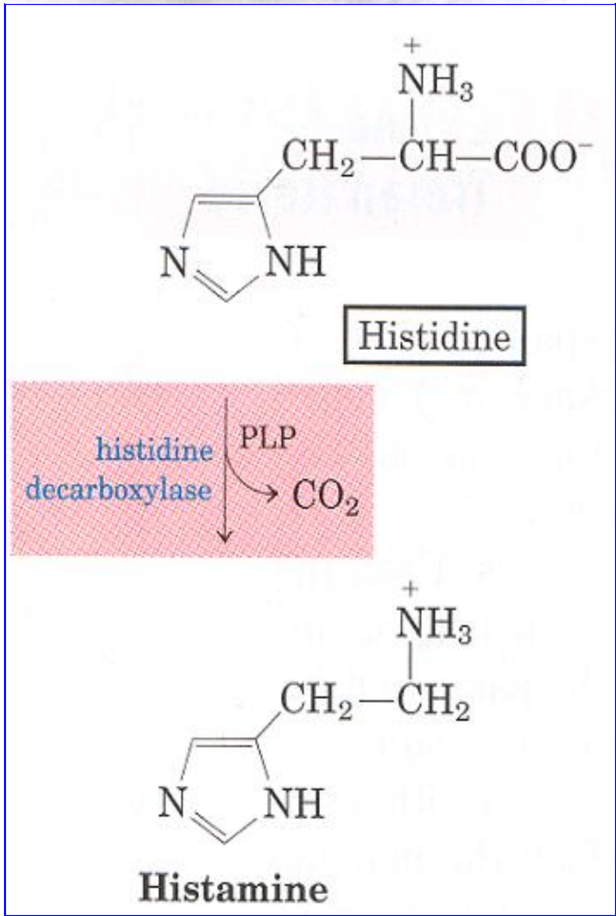


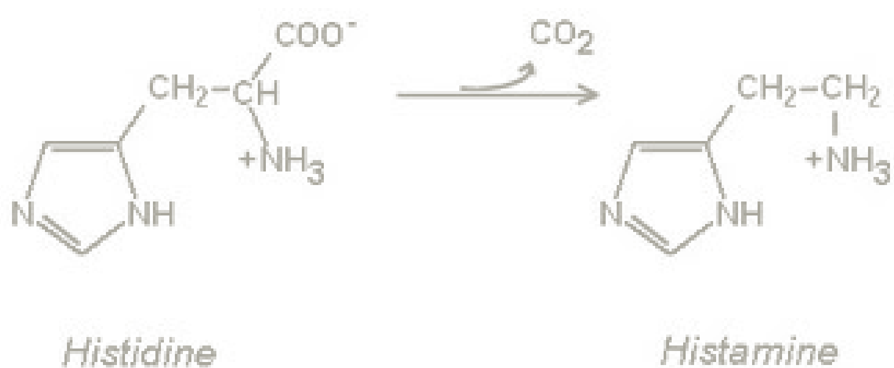
Glutamate & MSG in food

- Monosodium glutamate, or MSG, is a derivative of glutamic acid used as a flavor enhancer
- MSG may cause Chinese restaurant syndrome (chills, headaches, & dizziness)

Histidine & Histamine

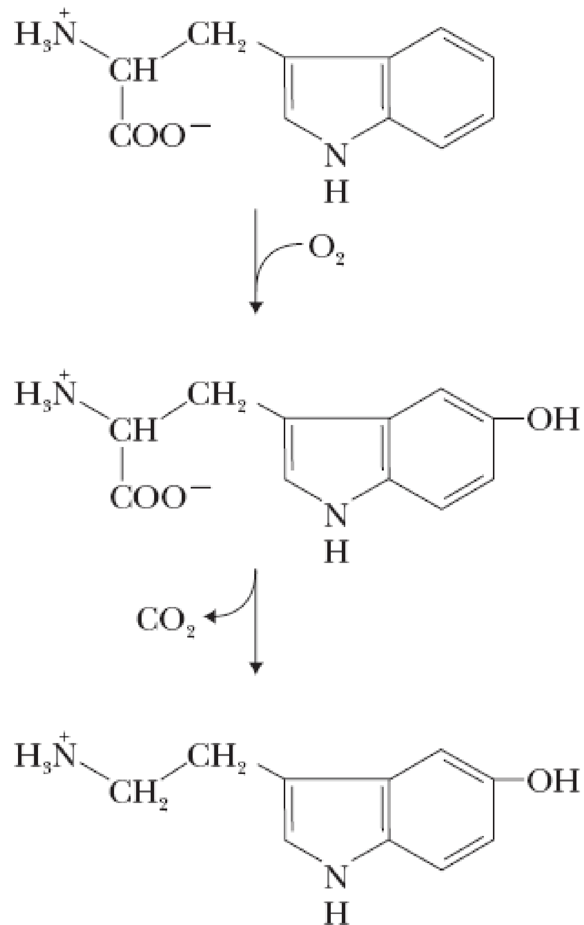
- Regulates physiological function in the gut
- Acts as a neurotransmitter
- Causes allergic symptoms (a major causes for asthma)
- Contributes to inflammatory response
- Causes constriction of smooth muscle





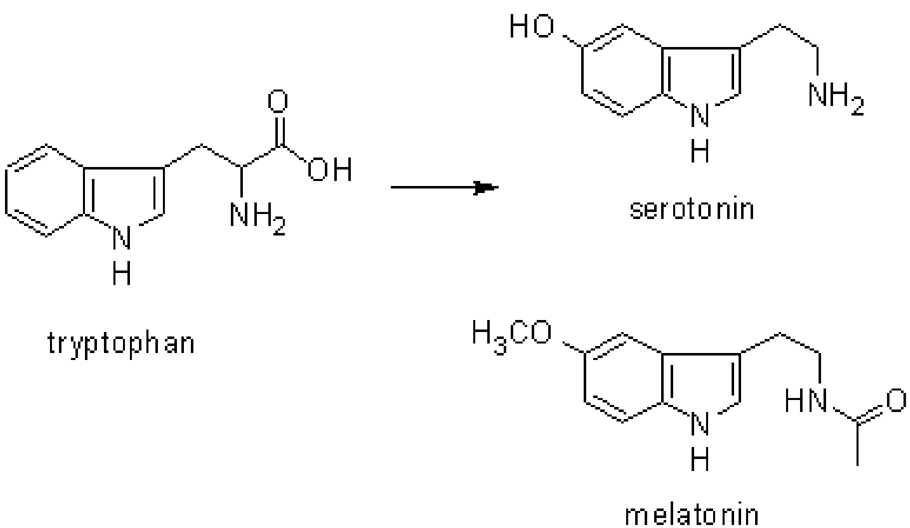
Tryptophan & Serotonin

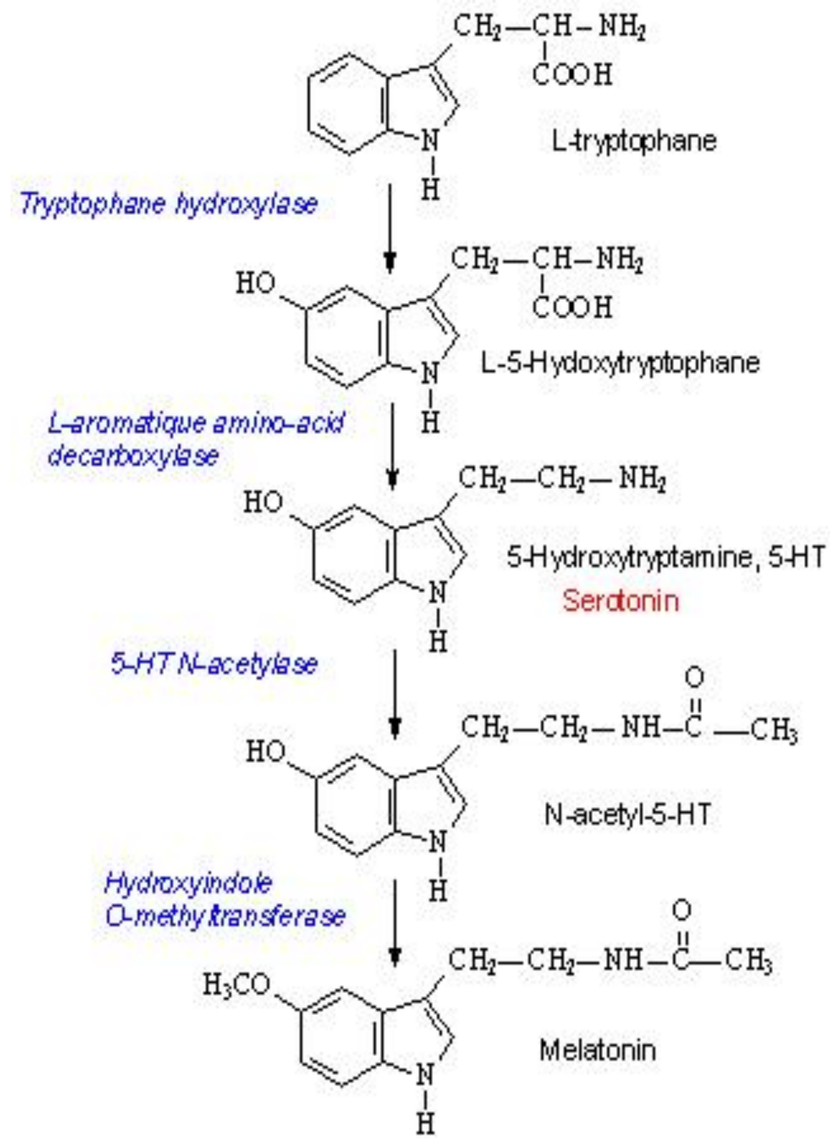
- Converted to 5-hydroxytryptamine (**serotonin**, sedative effect)
- Very low levels are associated with depression, while extremely high levels result in manic state
- Tryptophan, milk & sleep



Tryptophan & Melatonin

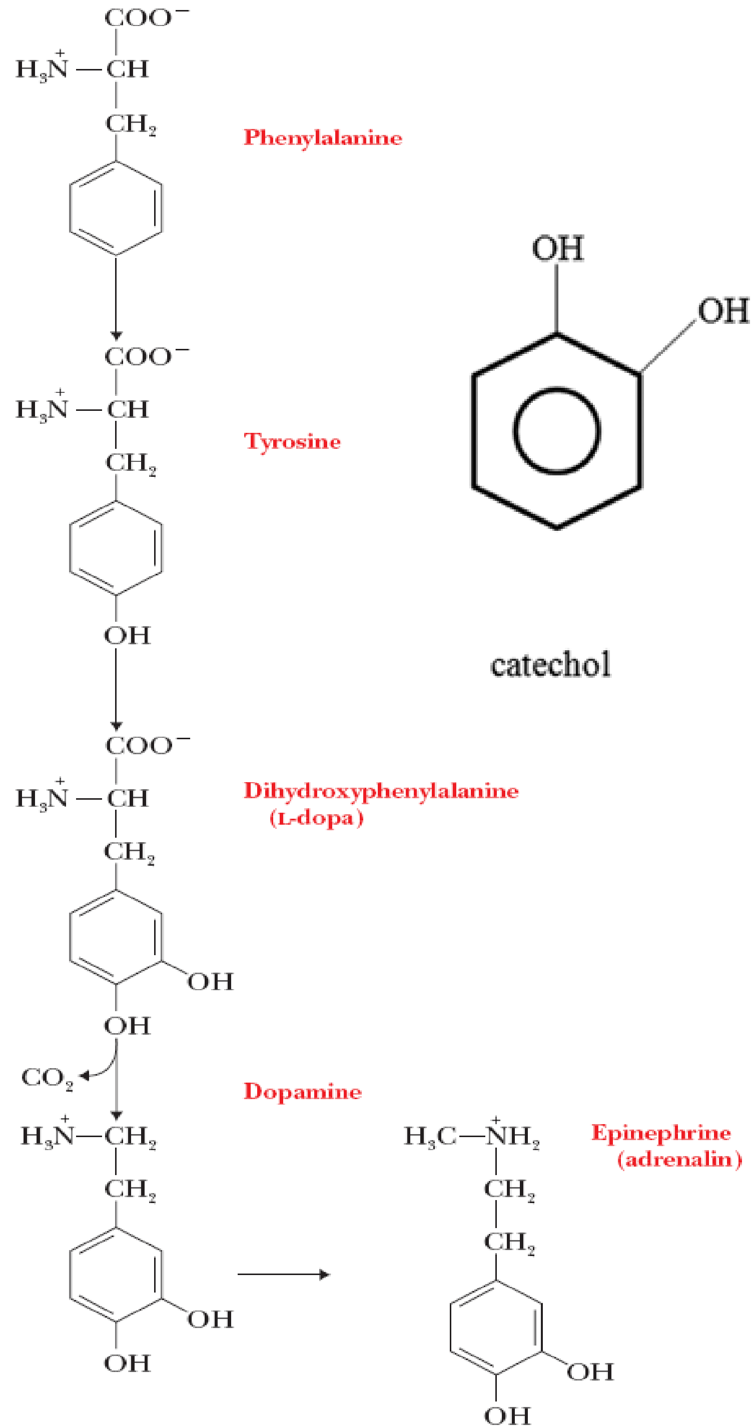
- Melatonin is a hormone secreted by the pineal gland in the brain
- It helps regulate other hormones & maintains the body's circadian rhythm (day-night cycle)





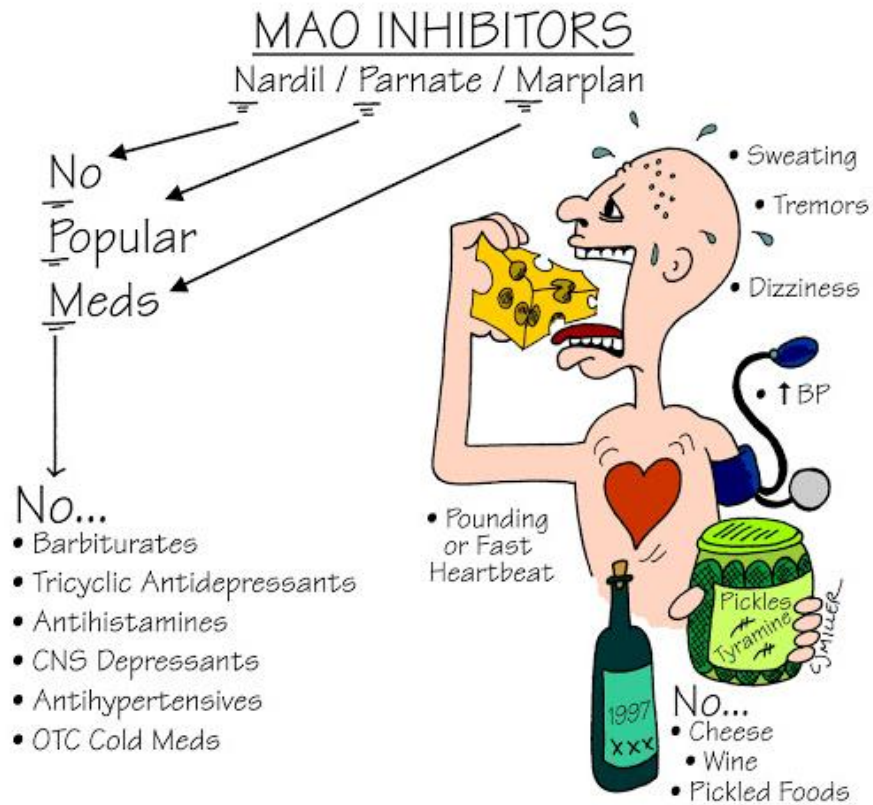
Tyrosine & Catecholamine's

- Converted into catecholamine neurotransmitters
  - L-DOPA
  - Dopamine
  - Norepinephrine
  - Epinephrine
    - flight or fight



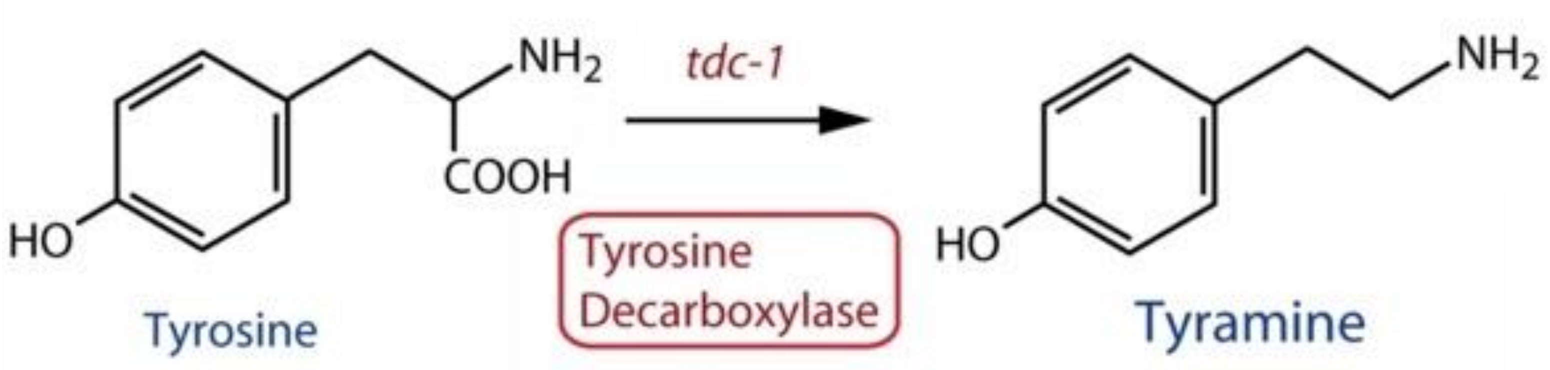
Tyrosine & MAOs

- The active products are monoamine derivatives (MA). MAOs
- *A Beautiful Mind, focused on Dopamine*
- MAO$_i$ makes metabolism slow



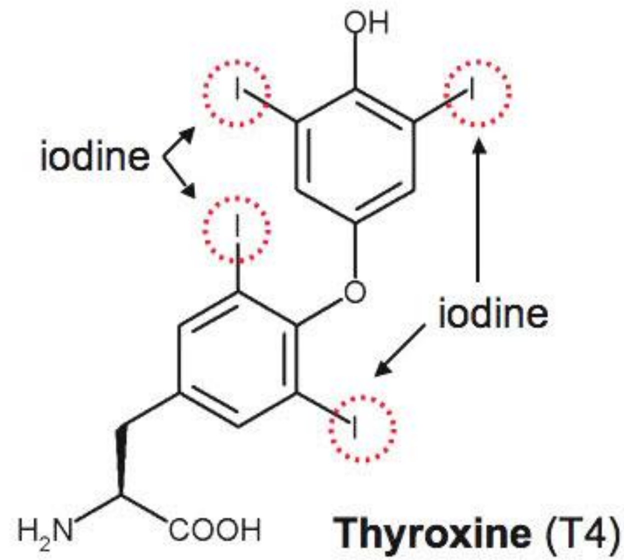
Tyrosine & Tyramine

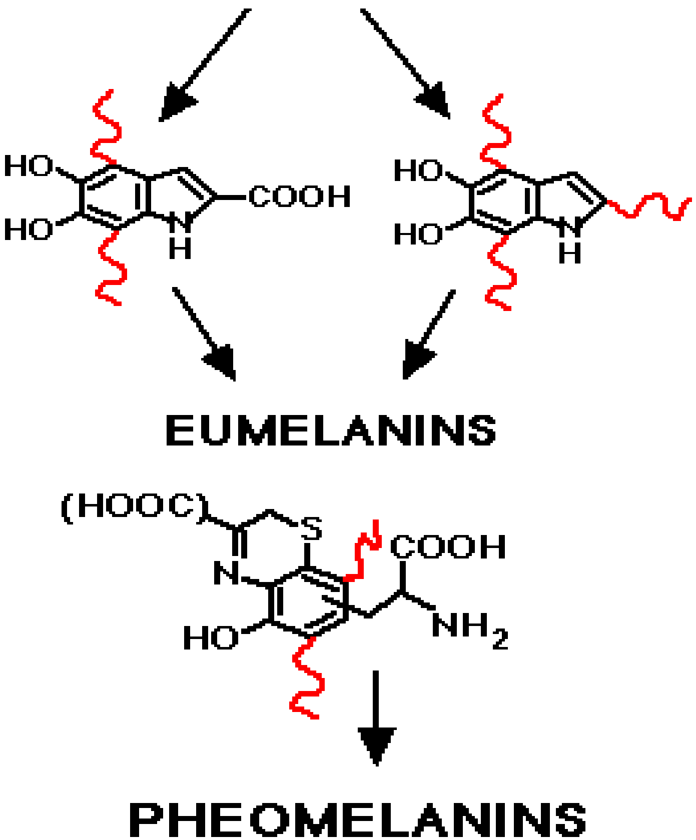
- **Tyrosine supplements & morning lift**
- **Cheese & red wines (tyramine; mimics epinephrine); a cheese omelet is a favorite way to start the day**

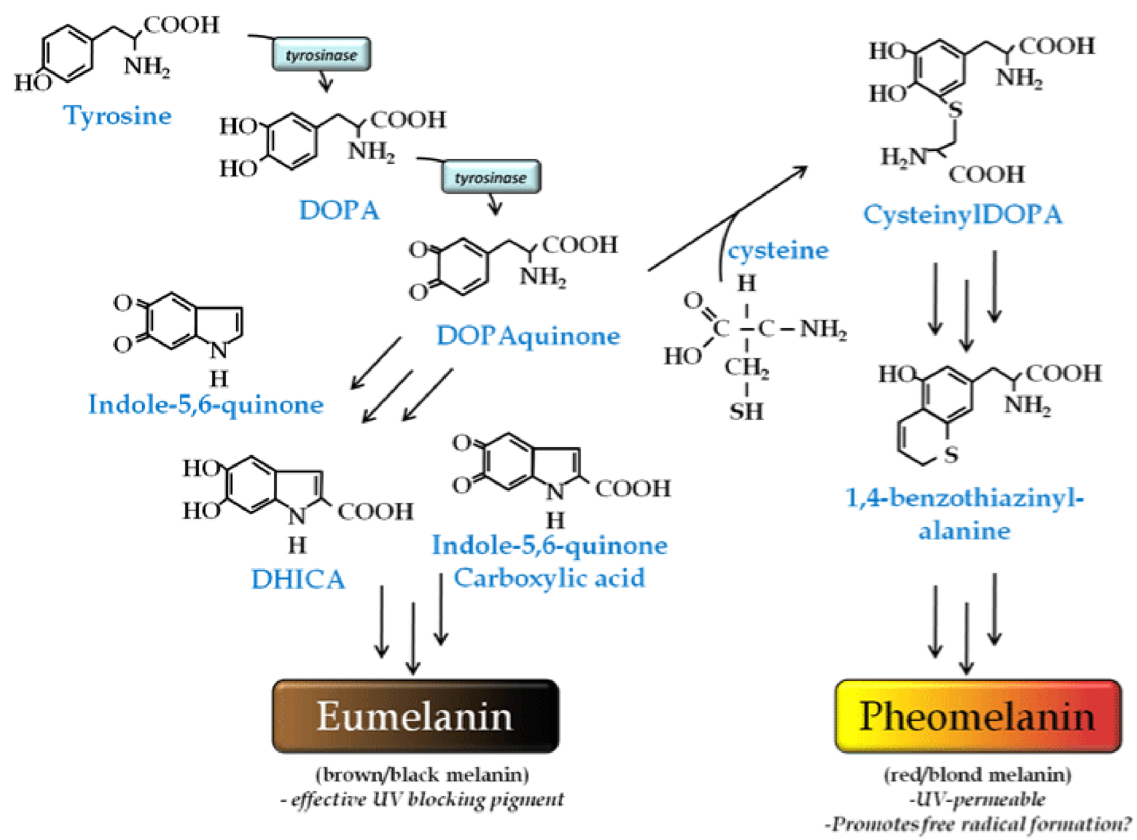


Tyrosine, Thyroxine & Melanin

- Thyroxine (hormone)
- Melanin (skin color)

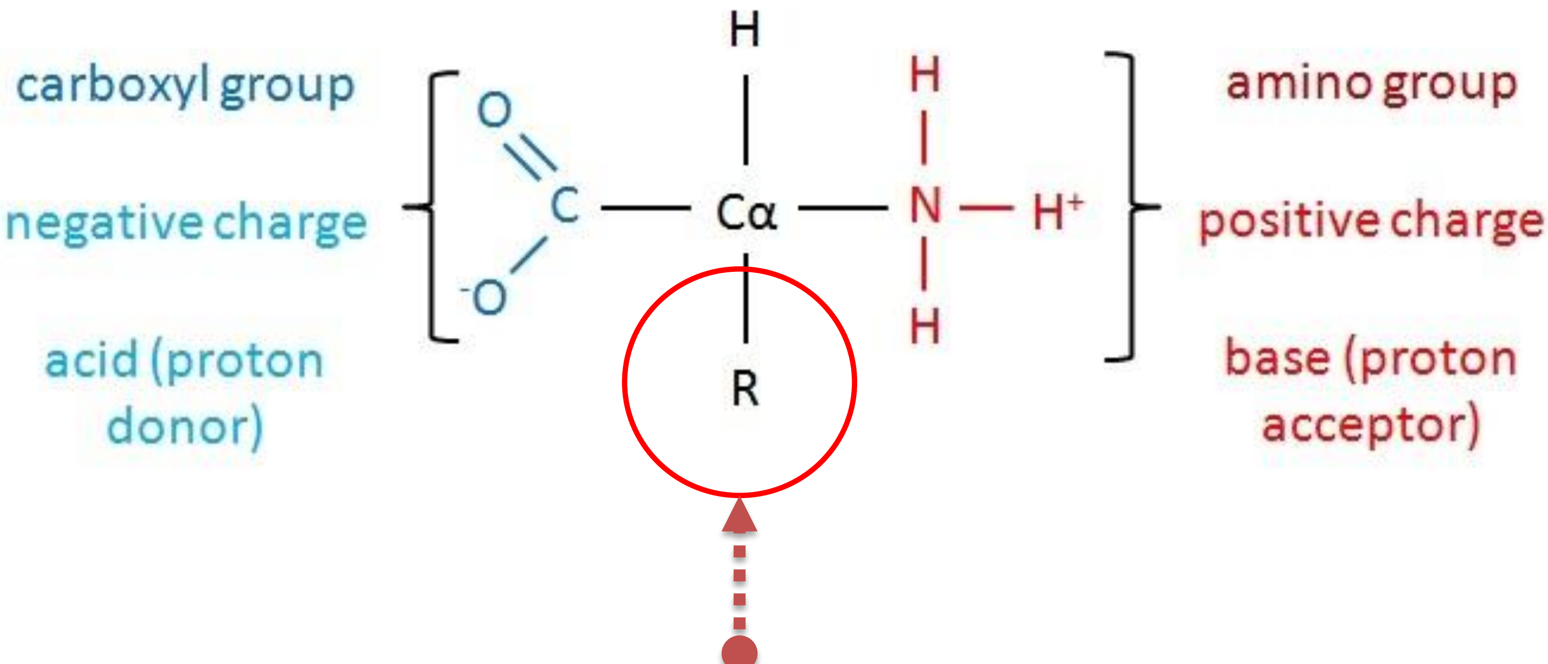






Ionization of amino acids

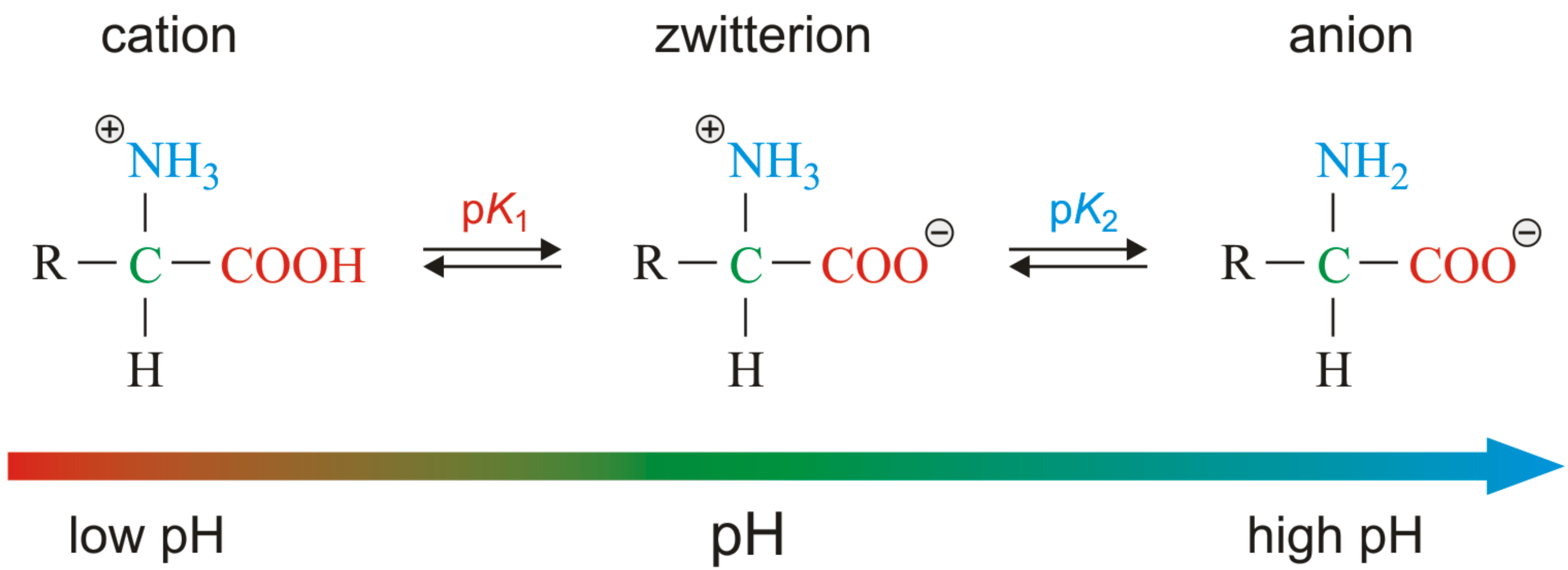
Why do amino acids get ionized?



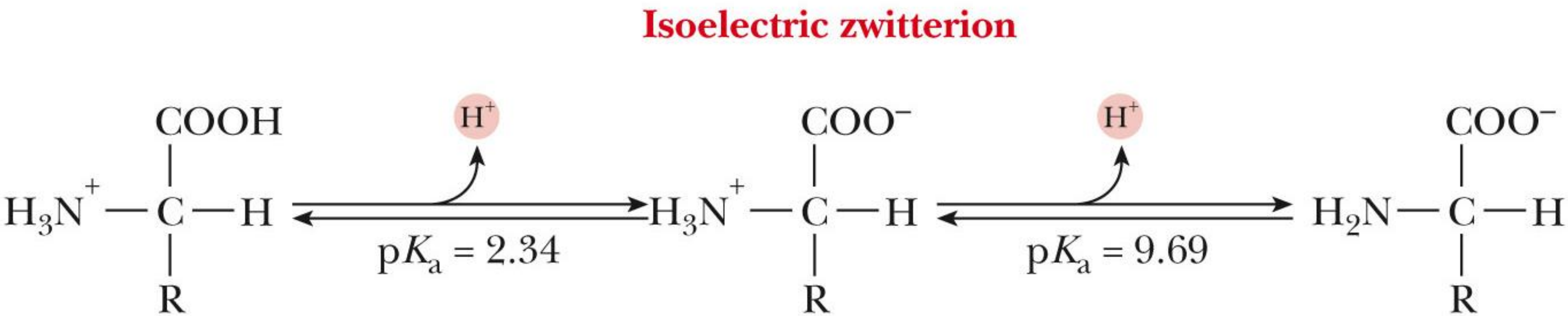
Is it ionizable?

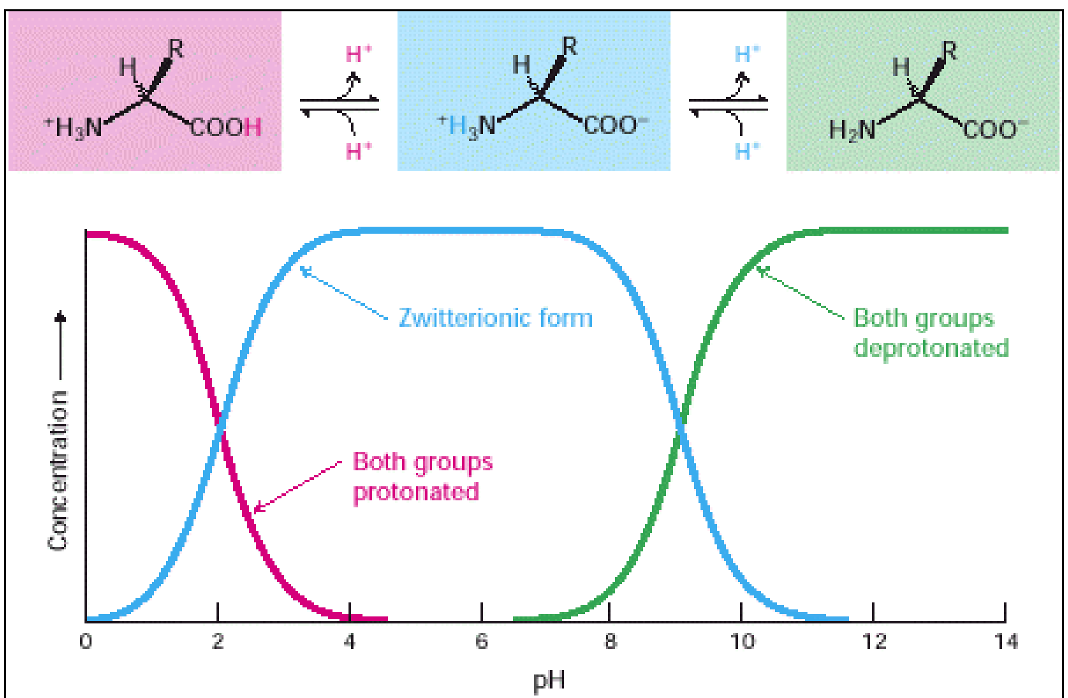
Why do amino acids get ionized?

- At physiological pH, amino acids (without ionizable groups) are electrically neutral
- **Zwitterion**: a molecule with a net charge of zero (**Isoelectric point; pI**)



Effect of pH


Isoelectric zwitterion
COOH
H_3N^+—C—H
R
H^+
pK_a = 2.34
COO⁻
H_3N^+—C—H
R
H^+
pK_a = 9.69
COO⁻
H_2N—C—H
R

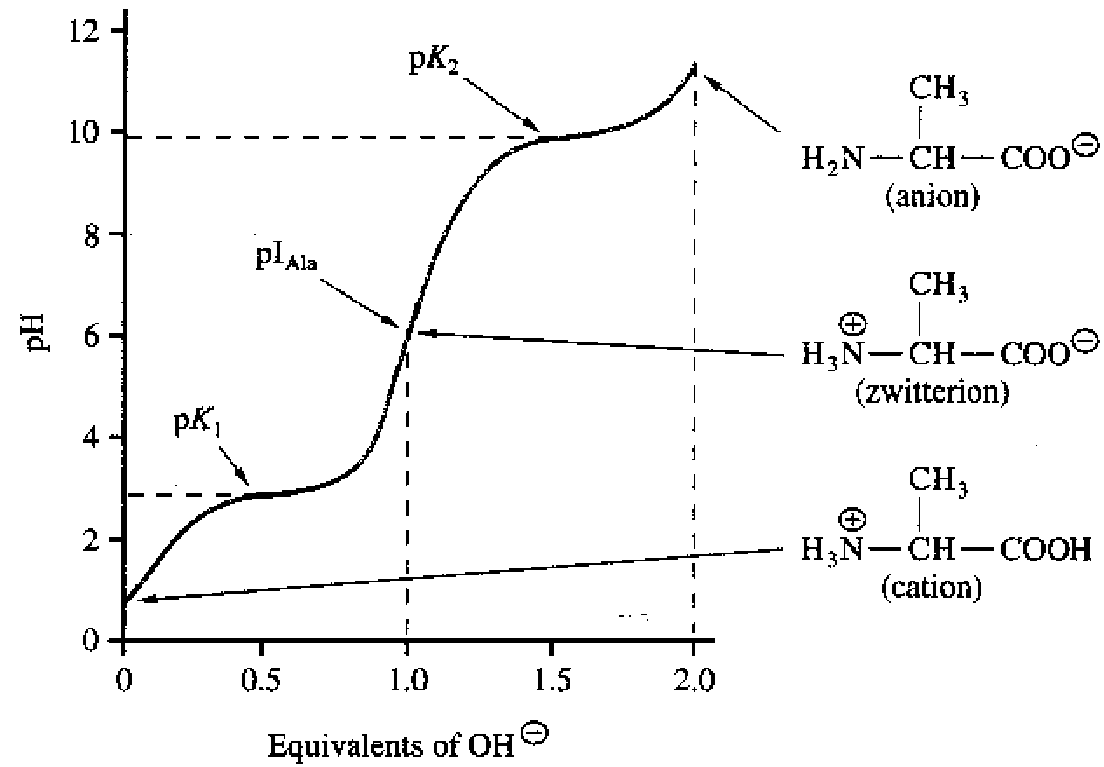

H
R
^+H_3N
COOH
H^+
H^+
H
R
^+H_3N
COO⁻
H^+
H^+
H
R
H_2N
COO⁻
Concentration
Zwitterionic form
Both groups deprotonated
Both groups protonated
0
2
4
6
8
10
12
14
pH

Henderson-Hasselbalch Equation

- We have calculated the ratio of acid to conjugate base for an α-carboxyl group and an α-amino group at pH 7.0
- We can do this for any weak acid and its conjugate base at any pH using the **Henderson-Hasselbalch equation**

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

Example 1 (Alanine)



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

Ionization of side chains

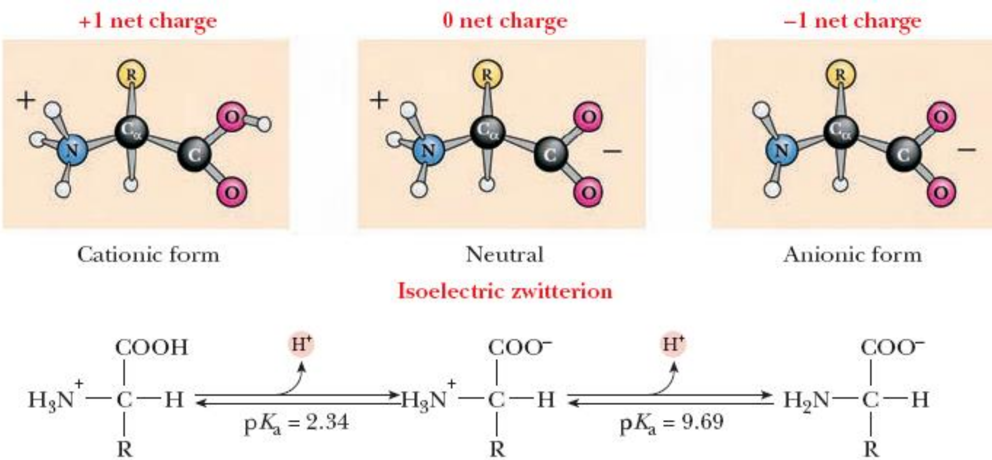
- Nine of the 20 amino acids have ionizable side chains
- These amino acids are:
  - Tyrosine, Cysteine, Serine, Threonine
  - Arginine, Lysine, Histidine
  - Aspartate, Glutamate
- Each side chain has its own pK_a value for ionization

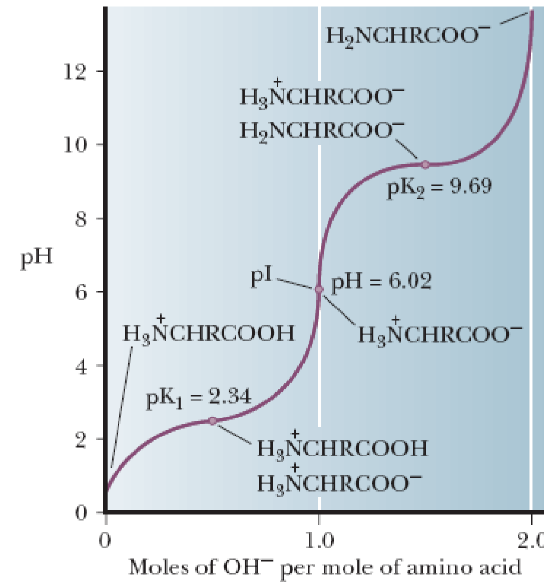
pI$_s$ of amino acids

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

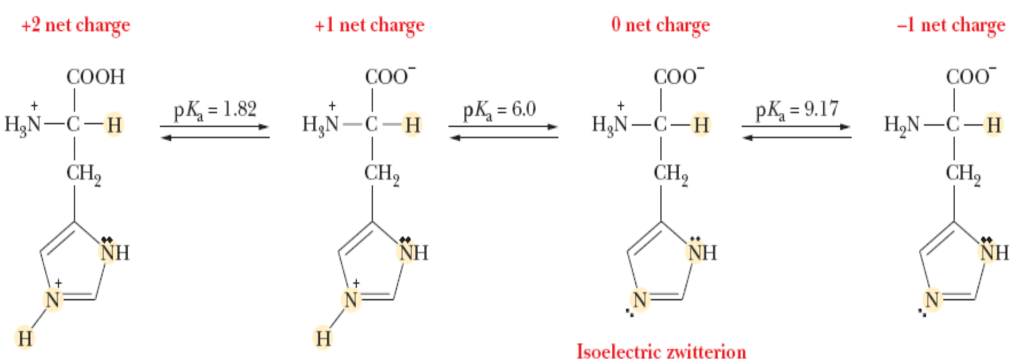
Let's consider pKa of -NH_2 = 9 and pKa of –COOH = 2 for all amino acids

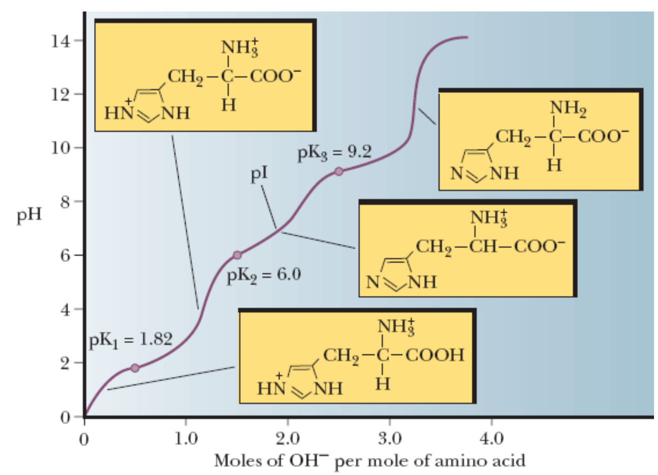
Titration of amino acids: what happens?





$$\mathbf{pI = (pK}a_1 + pKa_2\mathbf{)/2}$$



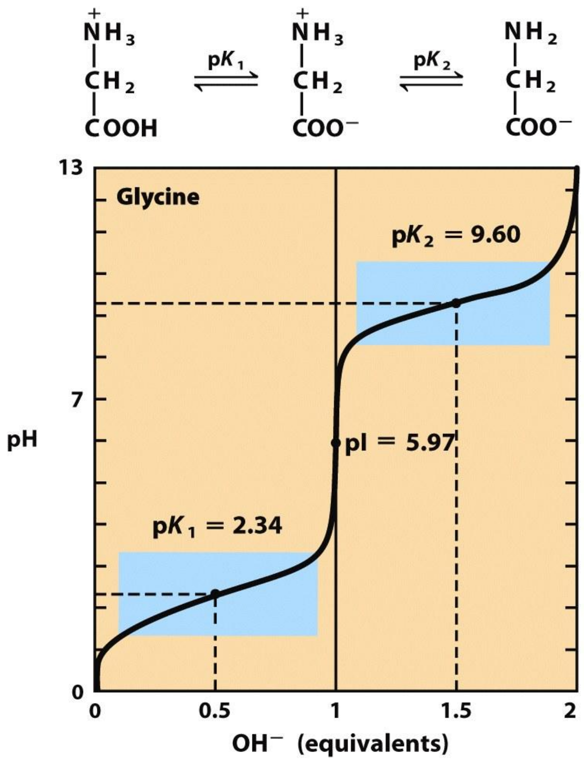


General rules for amino acid ionization

- **Alpha carboxylic acids ionize at acidic pH & have pKs < 6; So in titration, alpha carboxylic acids lose the proton first**

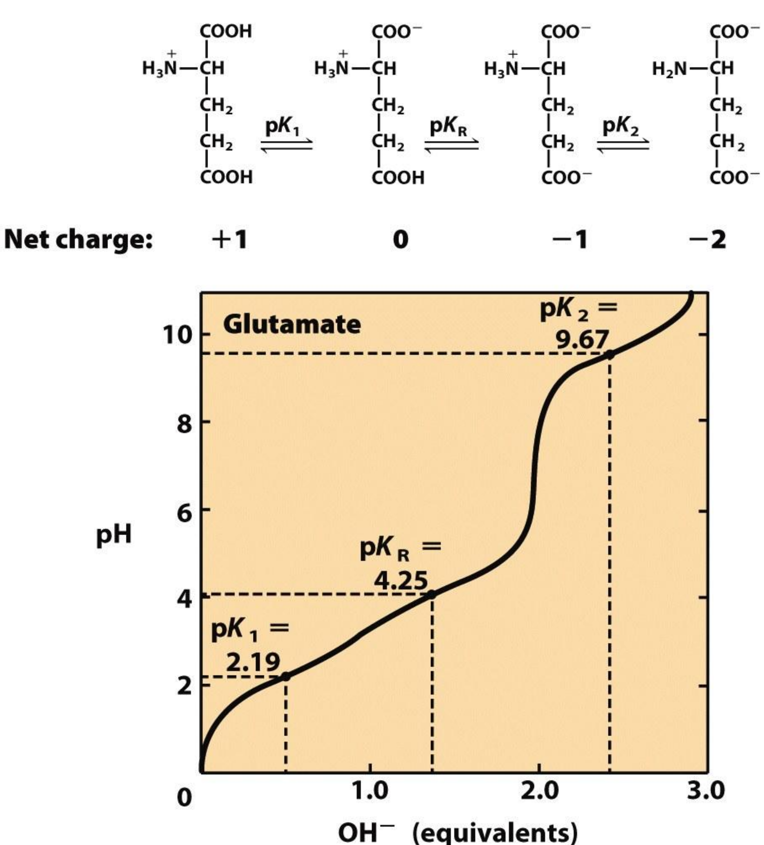
- **Alpha amino groups ionize at basic pH & have pKs > 8; So after acids lose their protons, amino groups lose their proton**

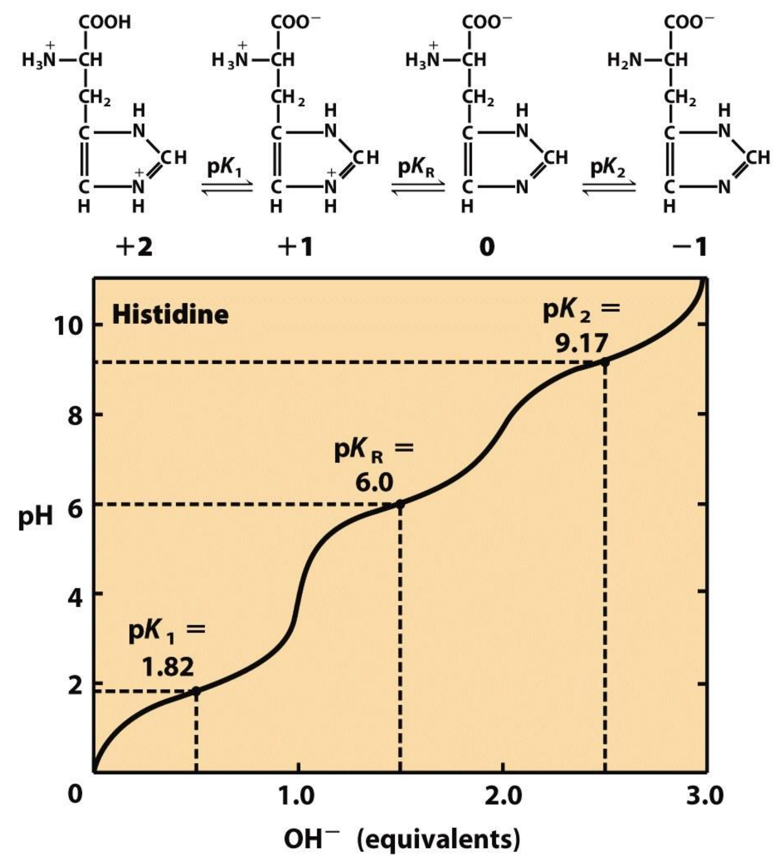
- **Most of the 20 amino acids are similar to Gly**



General rules for amino acid ionization

- **Aromatic amines "His" have a pK about pH 6**
- **On titration: alpha carboxylic acids lose their proton first, then side chain carboxylic acids, then aromatic amine side chains (His), then alpha amino groups, then side chain amino groups**
- **These rules apply to small peptides, and proteins also**

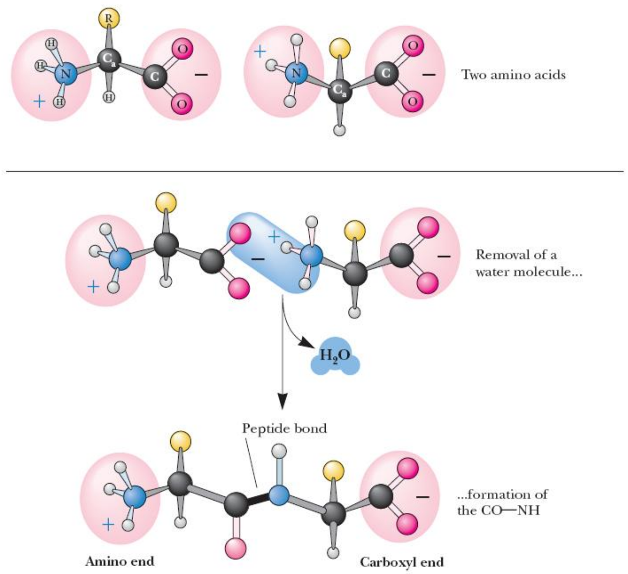


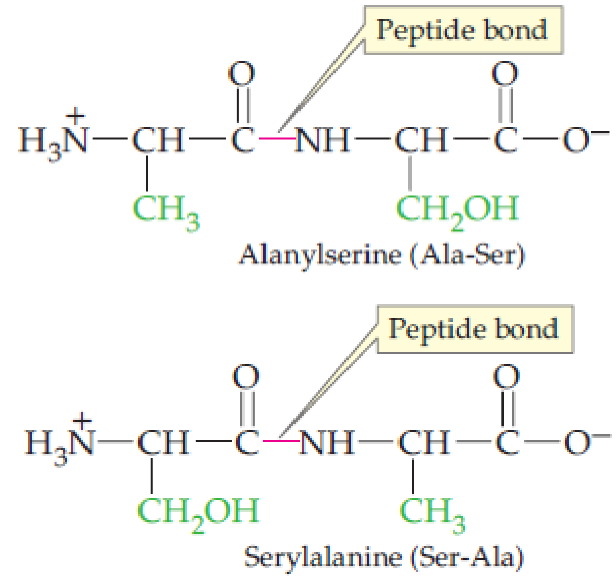


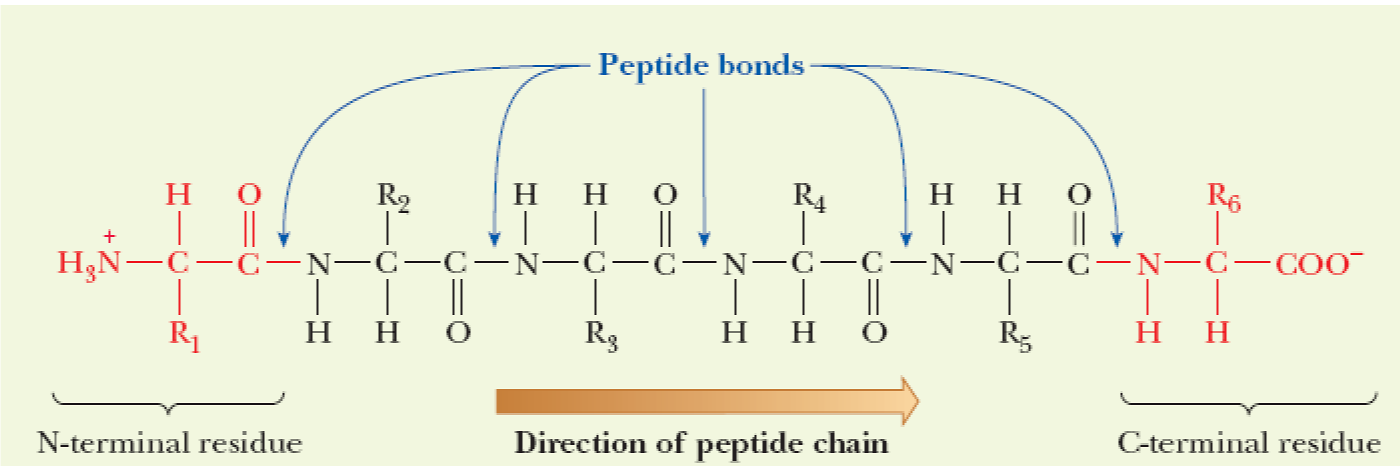
Peptides

The peptide bond, peptides, & proteins

- Amide bond
- Condensation reaction
- Directionality





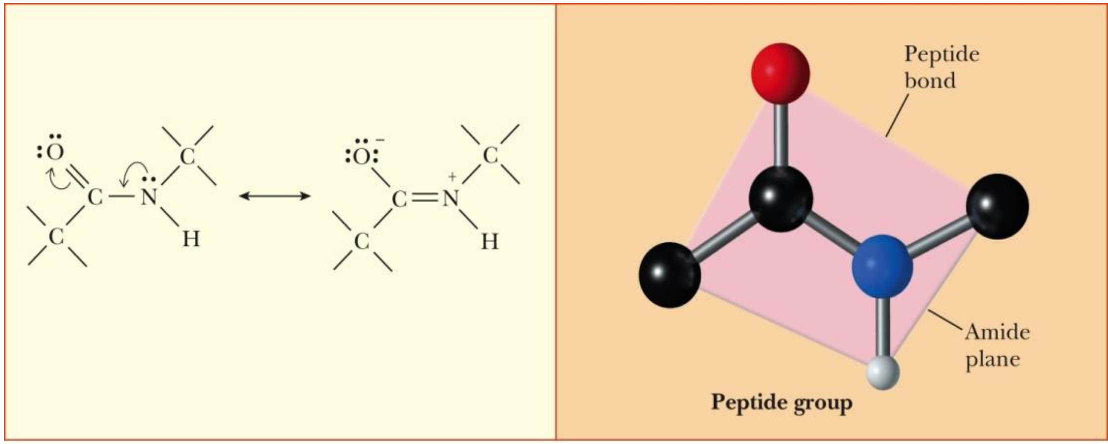


Definitions and concepts

- 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 Da
  - 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)

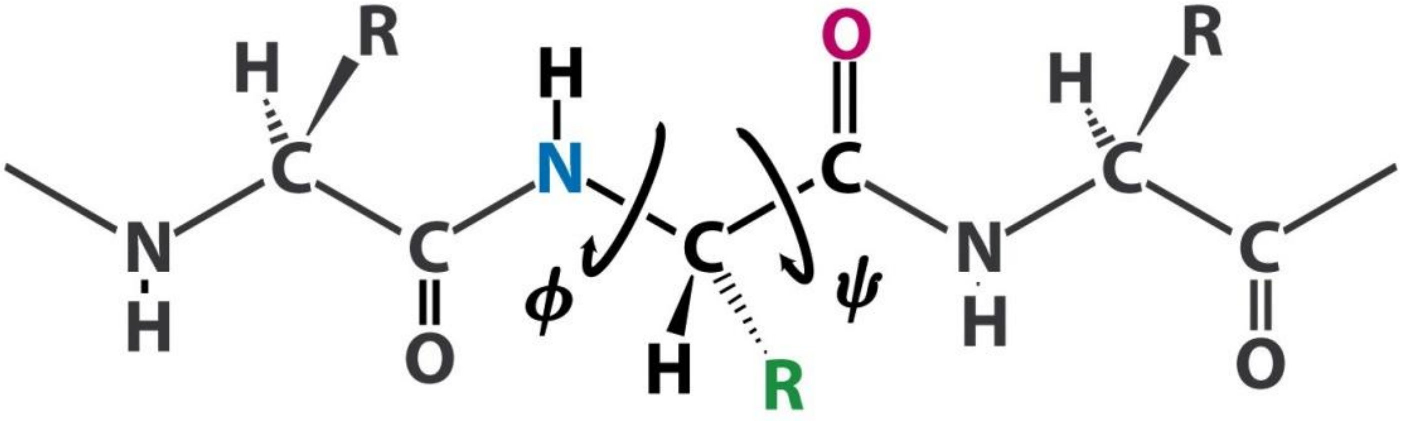
Features of the peptide bond

- Resonance structure makes peptide bond
  - Zigzag structure
  - Planar
  - (Un)charged
  - Rigid (double bond)
  - Un-rotatable



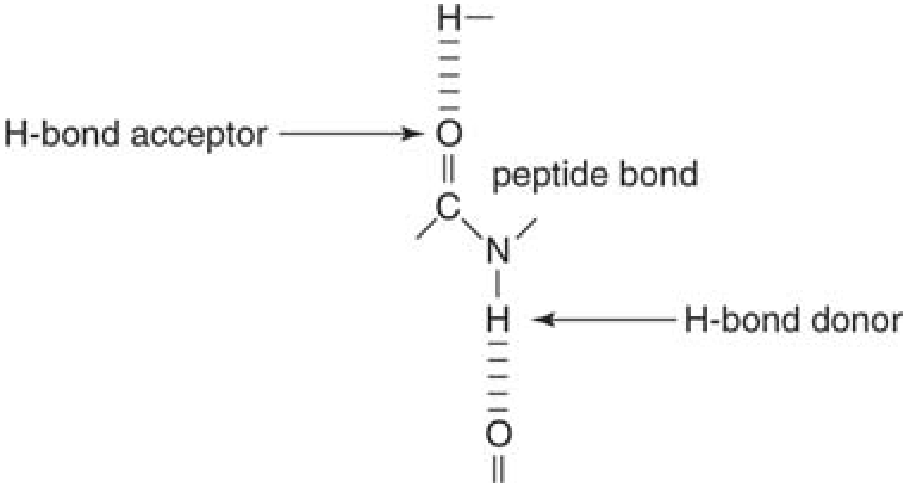
A Resonance structures of the peptide group.

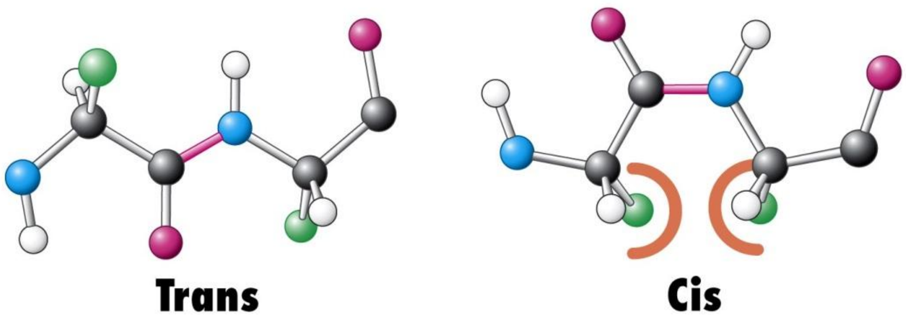
B The planar peptide group.

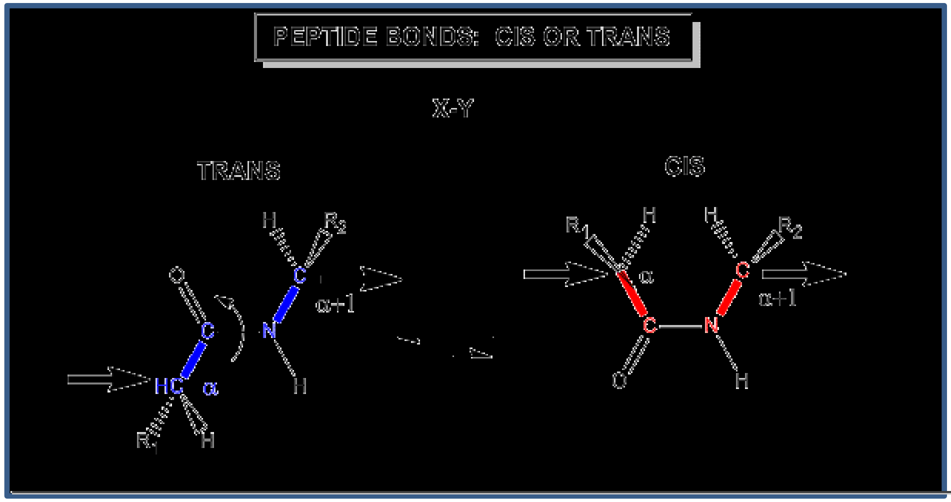


Features of the peptide bond

- Hydrogen bonding (exception: proline)
- Cis vs. trans configurations
- Why is it all trans?

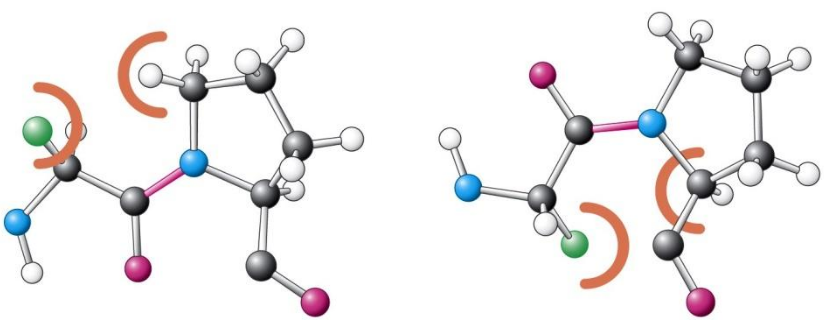




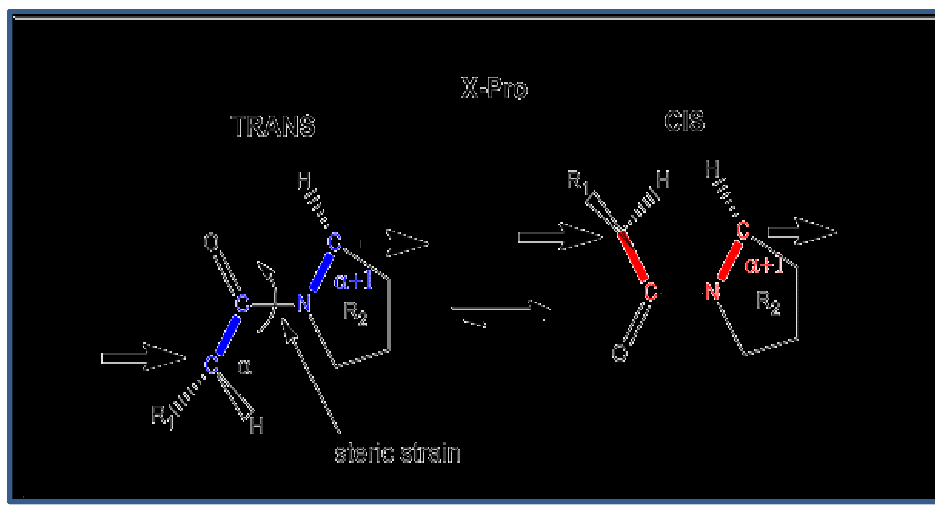


Except for proline

- 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

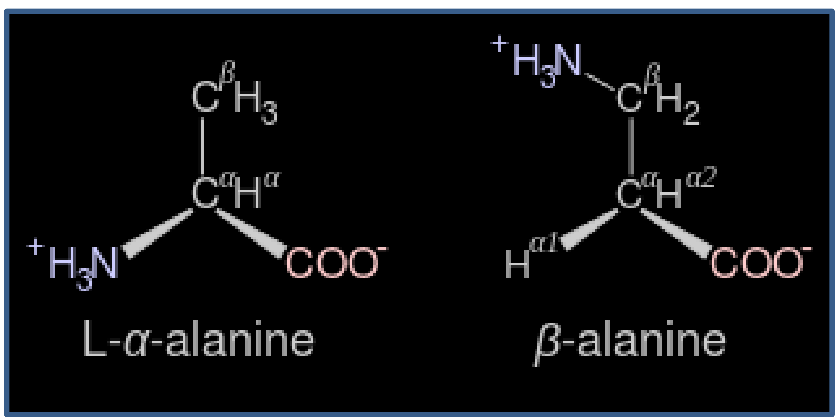


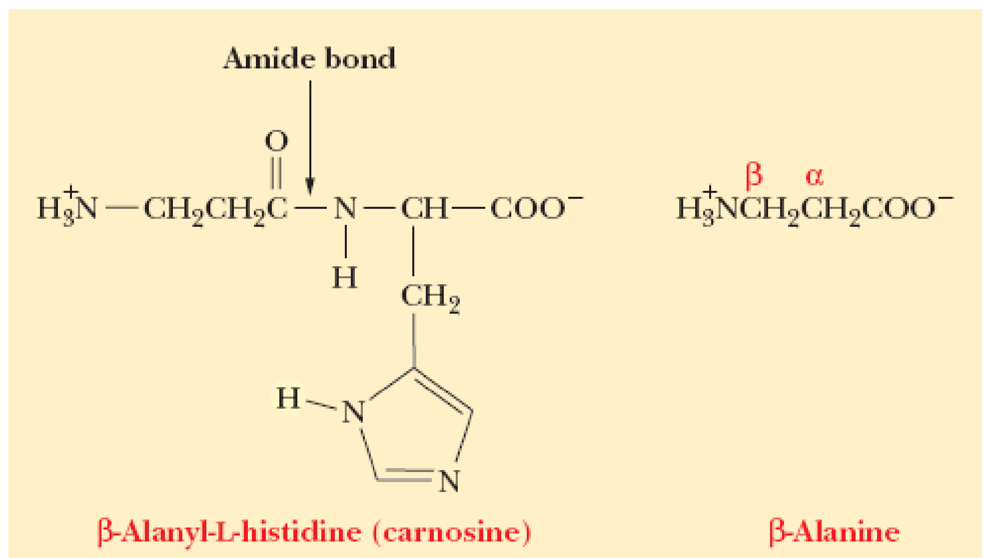
Trans Cis



Small Peptides with Physiological Activity

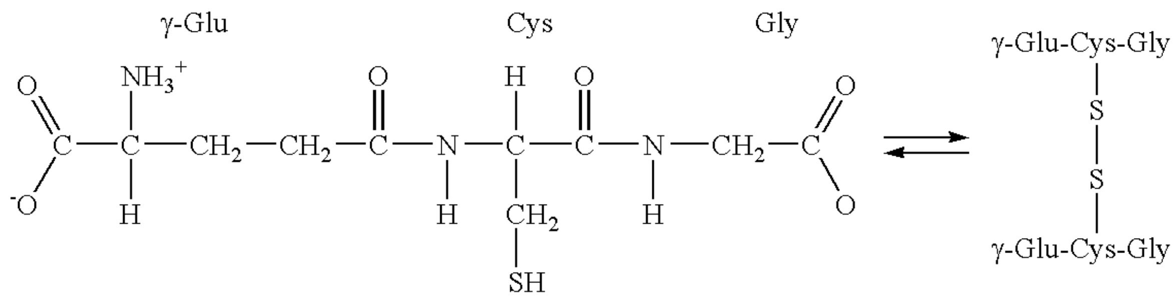
- Carnosine (dipeptide), (β-alanyl-L-histidine)
- It is highly concentrated in muscle & brain tissues
  - Antioxidant; protection of cells from ROS (radical oxygen species)
  - Contraction of muscle

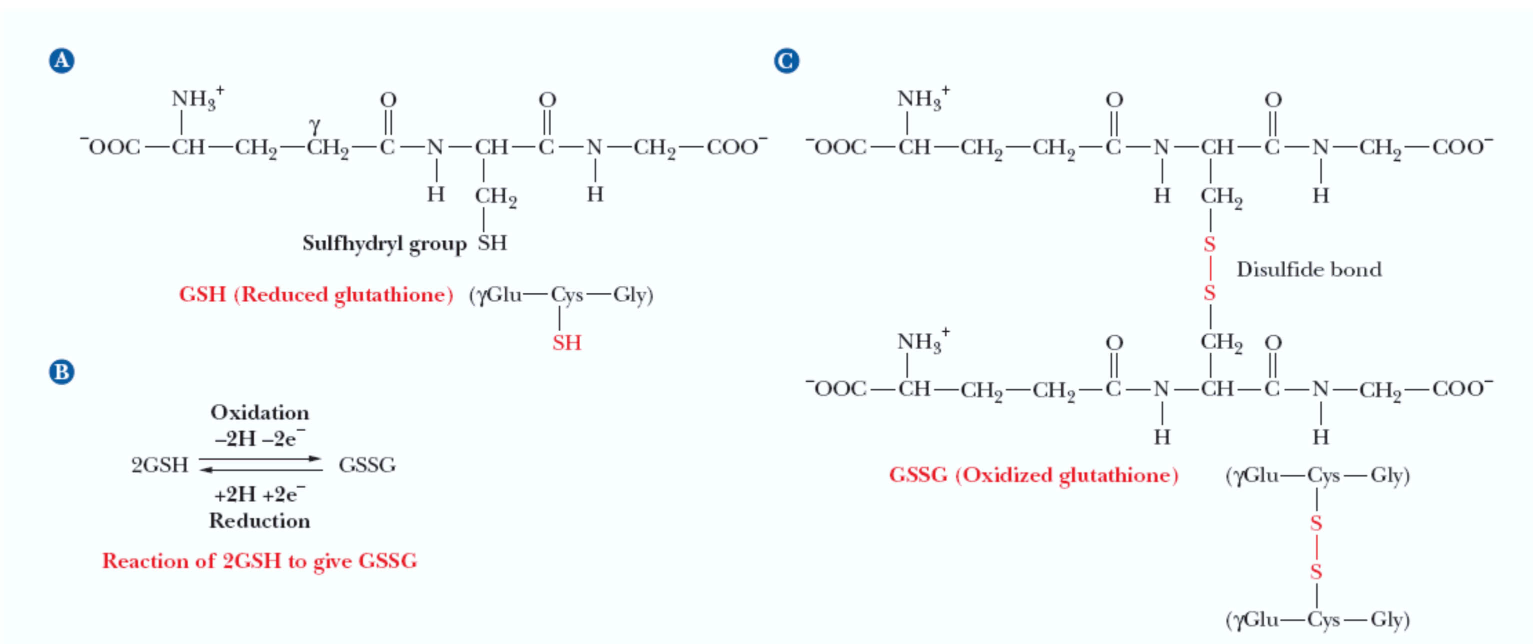




Small Peptides with Physiological Activity

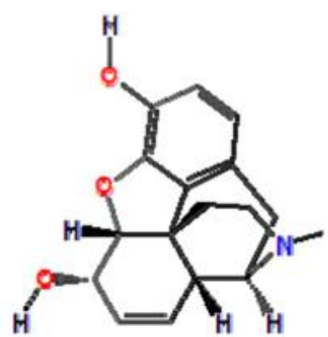
- Glutathione (tripeptide)
- (γ-glutamyl-L-cysteinylglycine)
- A scavenger for oxidizing agents





Small Peptides with Physiological Activity

- Enkephalins (pentapeptides), naturally occurring analgesics
- Found in the brain
  - ✓Tyr—Gly—Gly—Phe—Leu (Leucine enkephalin)
  - ✓Tyr—Gly—Gly—Phe—Met (Methionine enkephalin)
- The aromatic side chains of tyrosine and phenylalanine play a role in their activities
- Similarities of three-dimensional structures to opiates (e.x, morphine)

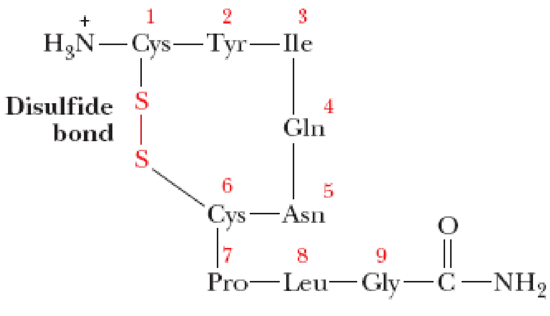


Morphine

Enkephalins

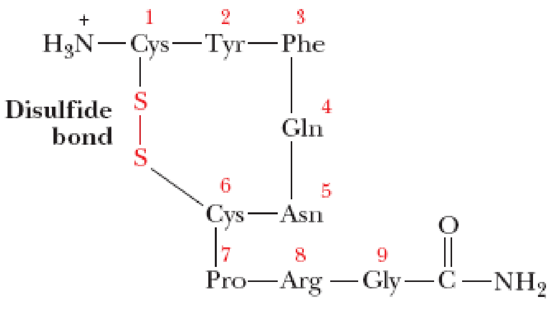
Small Peptides with Physiological Activity

- Some important peptides have cyclic structures. Two well-known hormone examples, oxytocin & vasopressin
- S-S linkages between Cys
- Amide group at the C-terminus
- Nine residues, but:
  - Oxytocin has Ile & L
  - Vasopressin has Phe & Arg



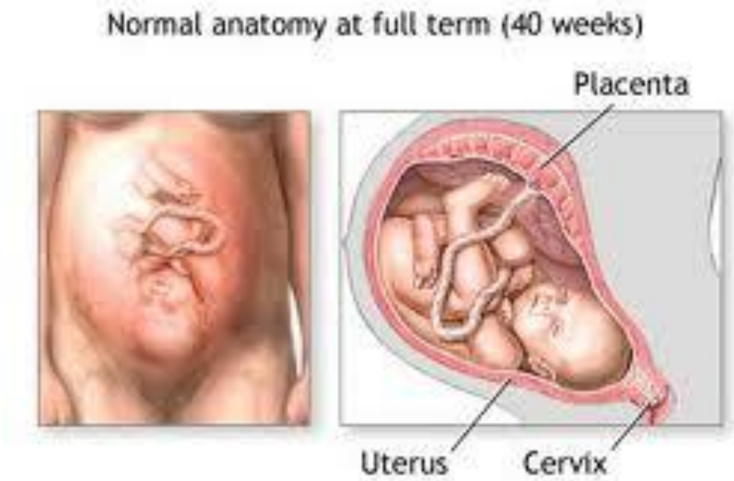
Oxytocin

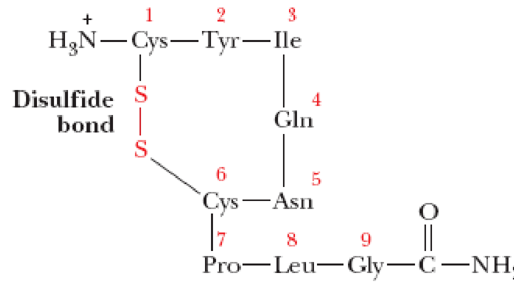
- Oxytocin regulates contraction of uterine muscle (labor contraction)
- Vasopressin regulates contraction of smooth muscle, increases water retention, & increases blood pressure



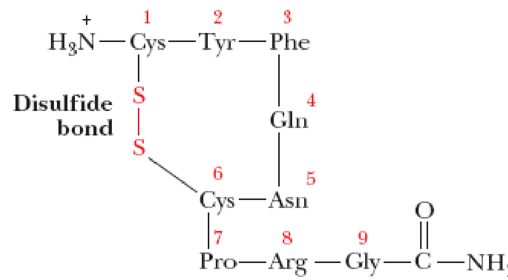
Vasopressin

Peptide Hormones-Small Molecules with Big Effects

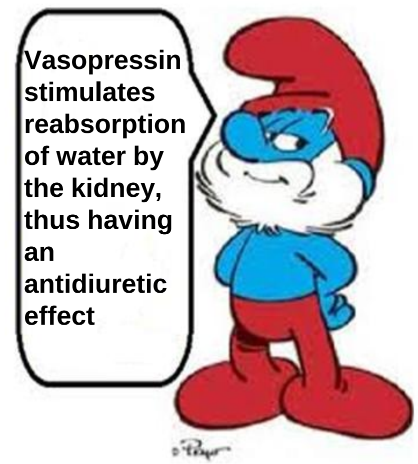




Oxytocin

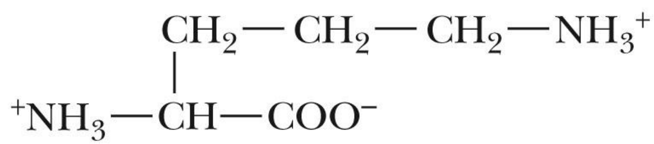


Vasopressin



Small Peptides with Physiological Activity

- Gramicidin S & tyrocidine A
- Cyclic decapeptides, act as antibiotics (Bacillus brevis)
- Contain D- & L-amino acids
- Both contain ornithine (Orn), which does not occur in proteins



Ornithine (Orn)

L-Val — L-Orn — L-Leu — D-Phe — L-Pro
L-Pro — L-Phe — L-Leu — D-Orn — L-Val

Direction of peptide bond

Gramicidin S

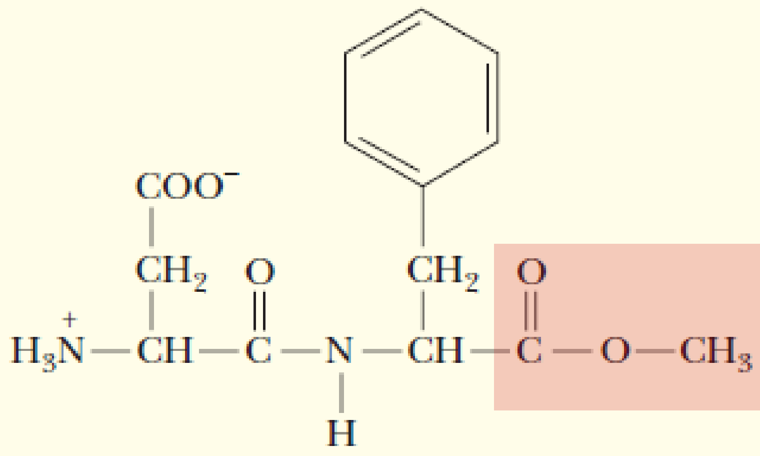
L-Val — L-Orn — L-Leu — D-Phe — L-Pro
L-Tyr — L-Glu — L-Asp — D-Phe — L-Phe

Direction of peptide bond

Tyrocidine A

Aspartame, the Sweet Peptide

- L-aspartyl-L-phenylalanine, commercial importance
- The methyl ester derivative is called *aspartame*
- 200 times sweeter than sugar



L-Aspartyl-L-phenylalanine (methyl ester)

Phenylketonuria

- Inborn errors of metabolism; errors in enzymes of amino acids metabolism
- May have disastrous consequences (mental retardation)
- Phenylketonuria (PKU) is a well-known example
- PKU can be easily detected and managed in newborns
- Aspartame carry a warning
- Alatame (Ala instead of Phe) is a substituent