

# Amino Acids and Protein Structure

By lyobosa lyare

# General Structure

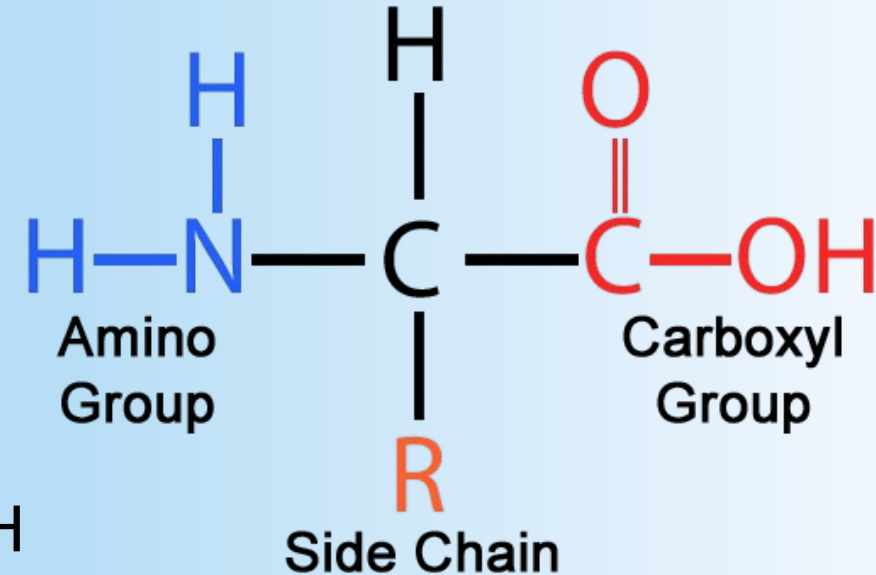
## ❖ Basic building blocks of proteins

### ❖ Each amino acid has:

1. A central ( $\alpha$ ) carbon, An amino group ( $-\text{NH}_2$ )
2. A carboxyl group ( $-\text{COOH}$ )
3. A hydrogen atom ( $-\text{H}$ )
4. A unique side chain (R group)

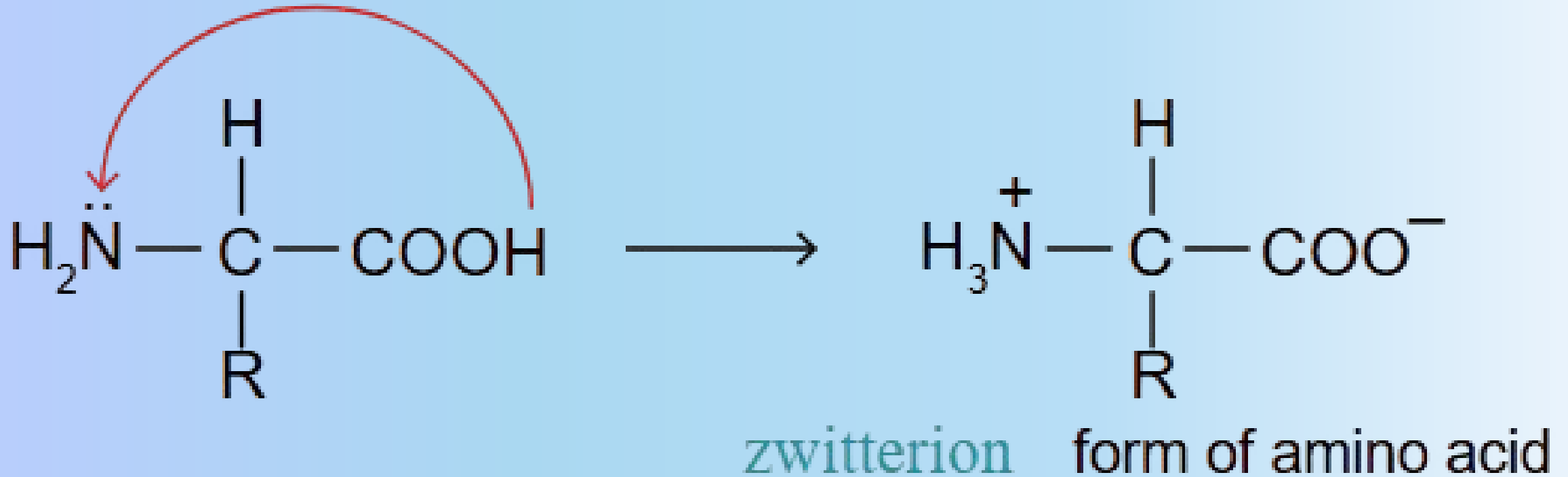
❖ Exist mainly in zwitterion form at physiological pH (7.4)

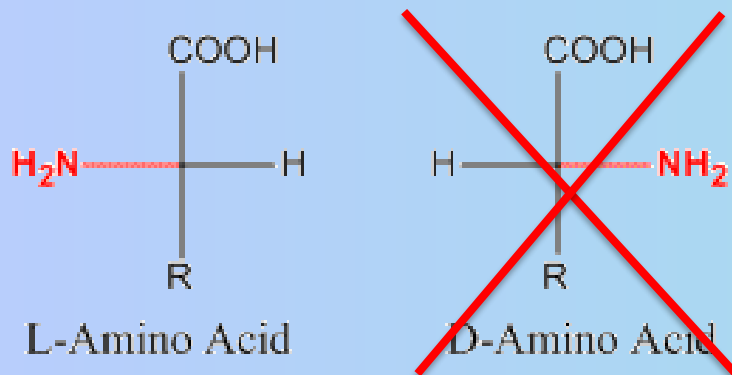
❖ Linked by peptide bonds to form proteins



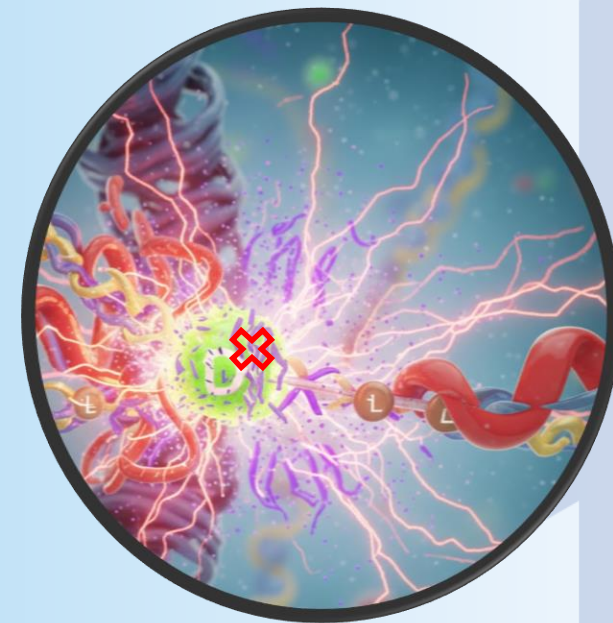
*Zwitter ions = Dipolar ions: ion possessing both pos and neg electrical charges*  
*All **FREE** aa are water soluble at physiological pH*

# Zwitterions





# L- $\alpha$ -amino acids



- ❖ Naturally occurring amino acids in proteins are **L- $\alpha$ -amino acids**
- ❖ “ $\alpha$ ” carbon = central carbon attached to amino, carboxyl, hydrogen, and R group
- ❖ **Only L-forms are used in human proteins**
- ❖ Exhibit **chirality** (except glycine, which is achiral)



Chiral carbon = a carbon with 4 single bonds and **4 different groups** attached to it

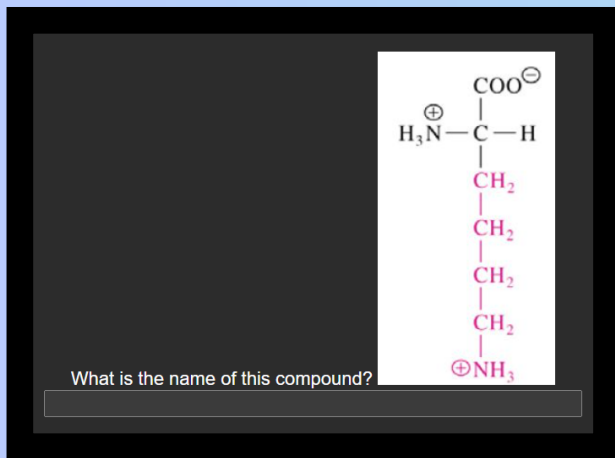
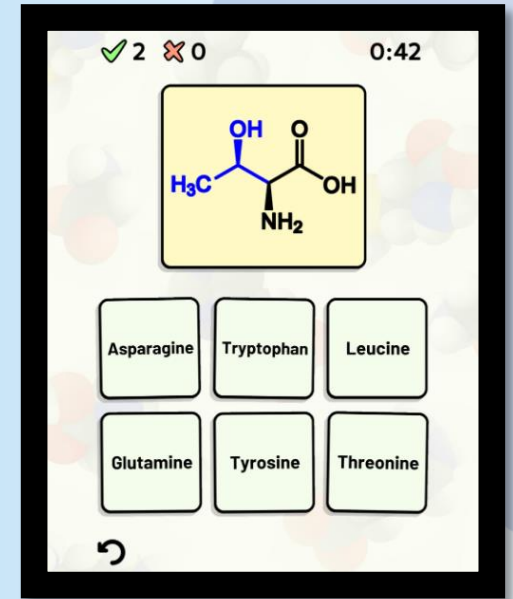
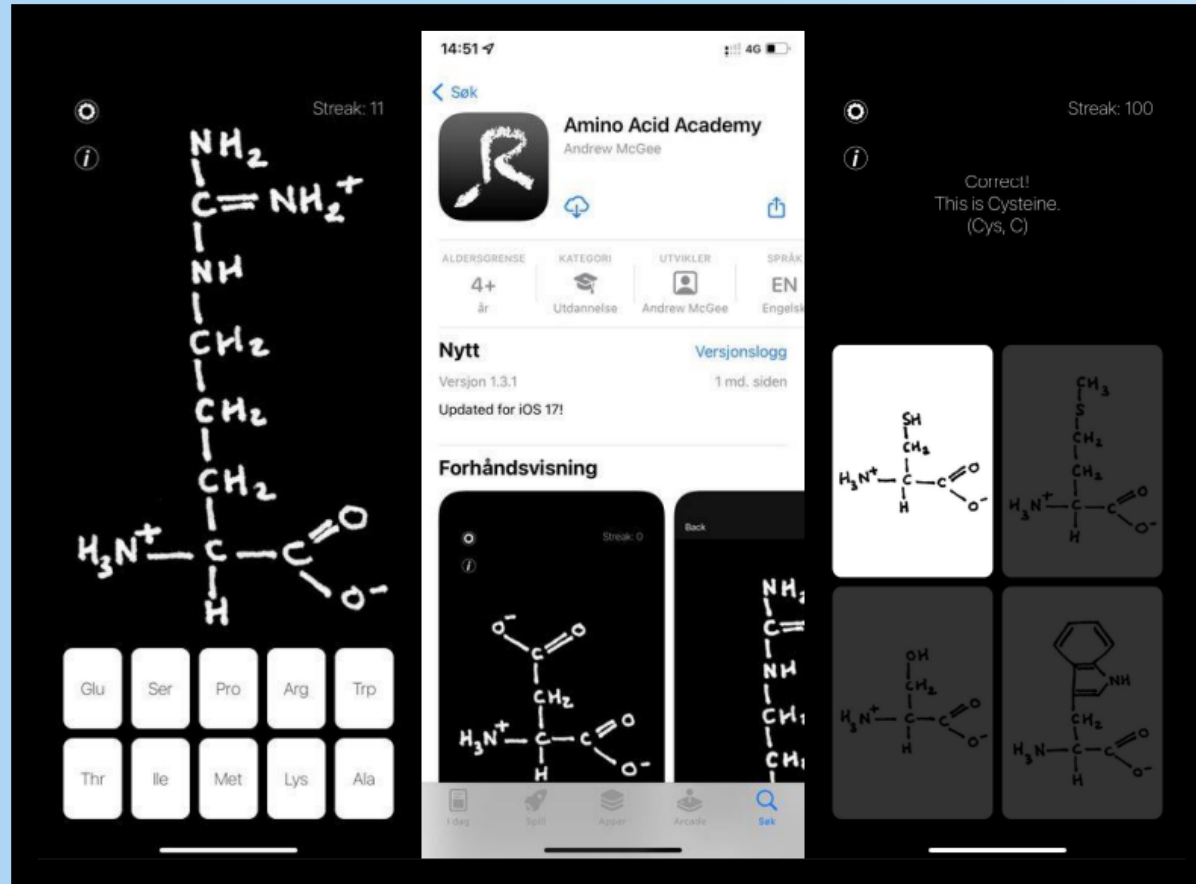
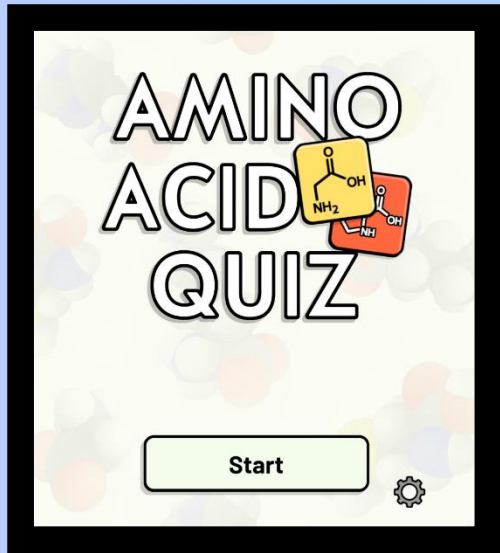


NOTE

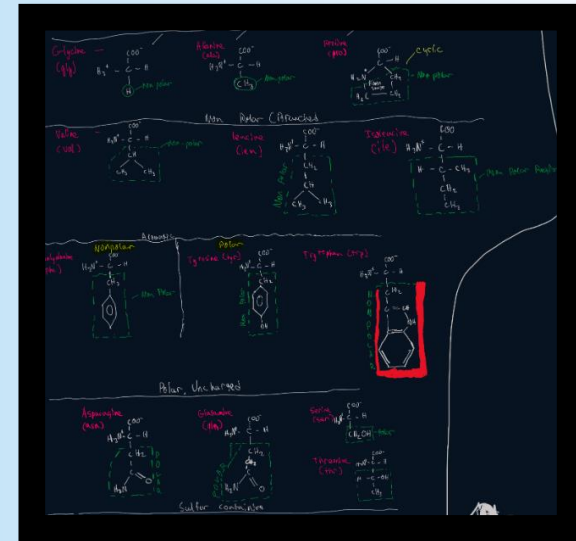
# REAL IMPORTANT!!!

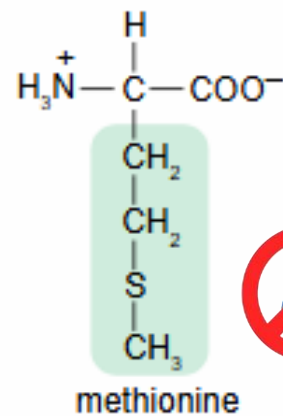
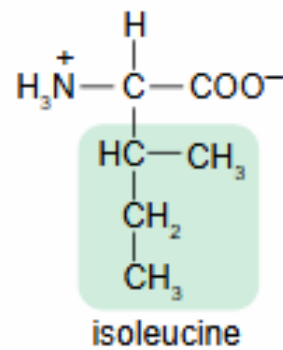
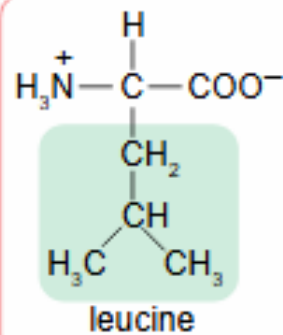
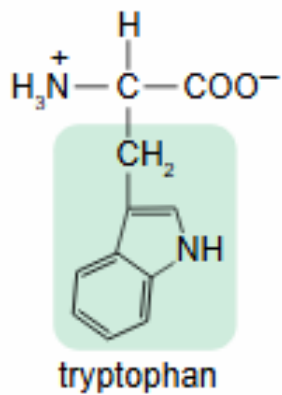
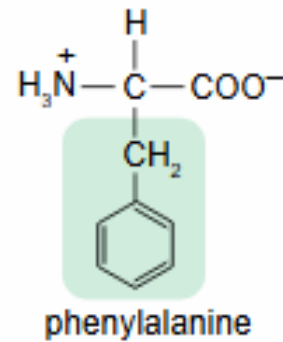
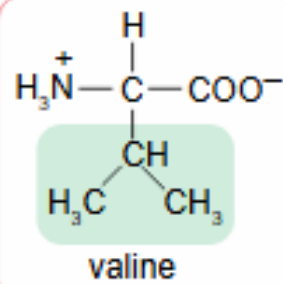
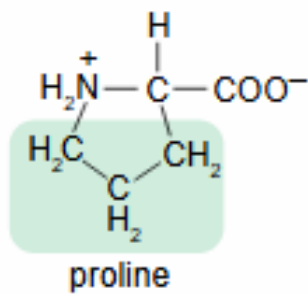
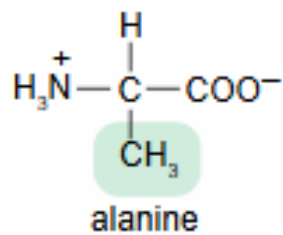
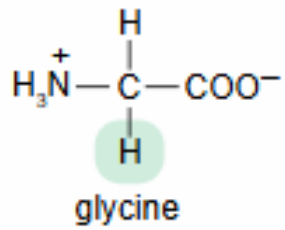
- ❖ Non-Polar Amino Acids will be depicted in the colour **RED**
- ❖ Polar Amino Acids will be depicted with the colour **Blue**

# How to Remember the 20 structures?



Whether it is Anki, Amino Acid Academy/Quiz, or straight brute force – Repetition is Key



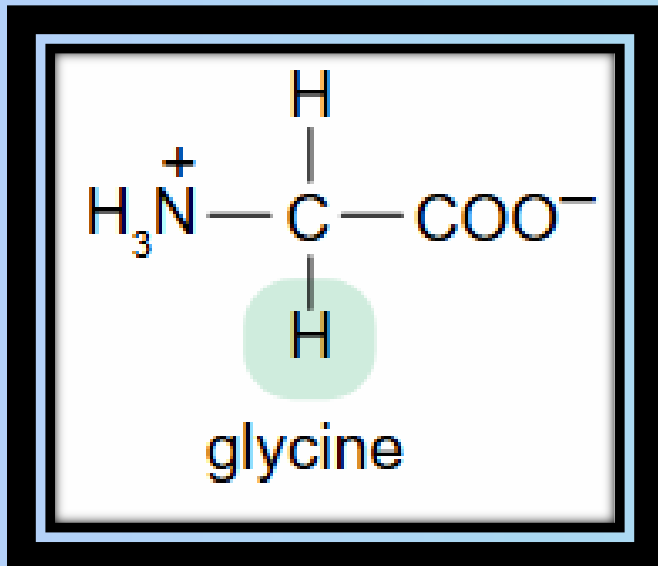


- ❖ Have **hydrocarbon side chains** that are nonpolar and hydrophobic
- ❖ **Do not form hydrogen bonds** or interact well with water
- ❖ Tend to be located in the **interior of proteins** (away from aqueous environments)
- ❖ Important for maintaining the **hydrophobic core and protein stability**

# Non-Polar Amino Acids

# Glycine

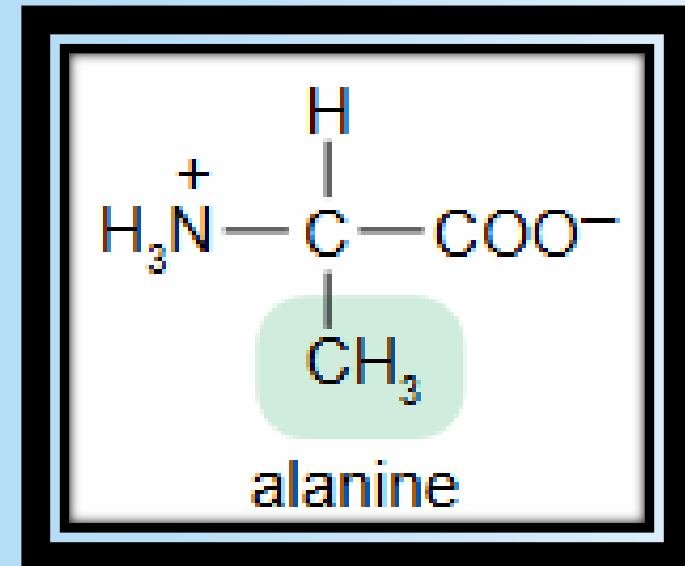
- ❖ Smallest amino acid
- ❖ Non-polar and hydrophobic
- ❖ No chiral center (R group = H)
- ❖ Provides flexibility (**Good and Bad**)
- ❖ Often found in **tight turns** or **collagen**



Gly, G

# Alanine

- ❖ Non-polar and hydrophobic
- ❖ Side chain is a simple **methyl group (-CH<sub>3</sub>)**
  - ❖ Common in **α-helices**
- ❖ *Plays a role in the **glucose-alanine cycle***

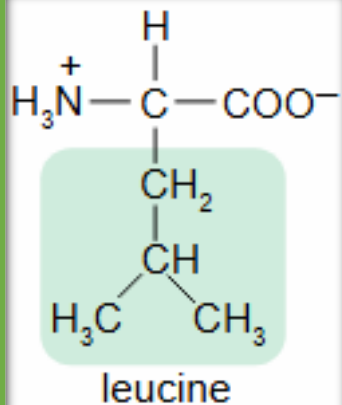


Ala, A

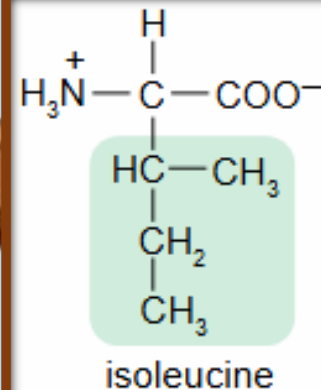
# Branched-Chain Amino Acids

- ❖ Include **Leucine**, **Isoleucine**, and **Valine**
- ❖ Have branched aliphatic side chains
  - ❖ Non-polar and hydrophobic
- ❖ Important for muscle metabolism and energy
- ❖ Leucine stimulates muscle protein synthesis
- ❖ Metabolized mainly in skeletal muscle, not the liver

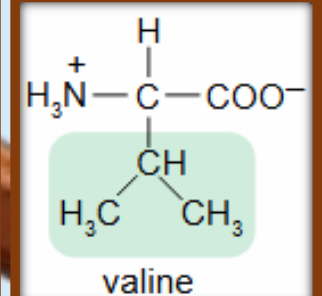
**Leu, L**



**Ile, I**



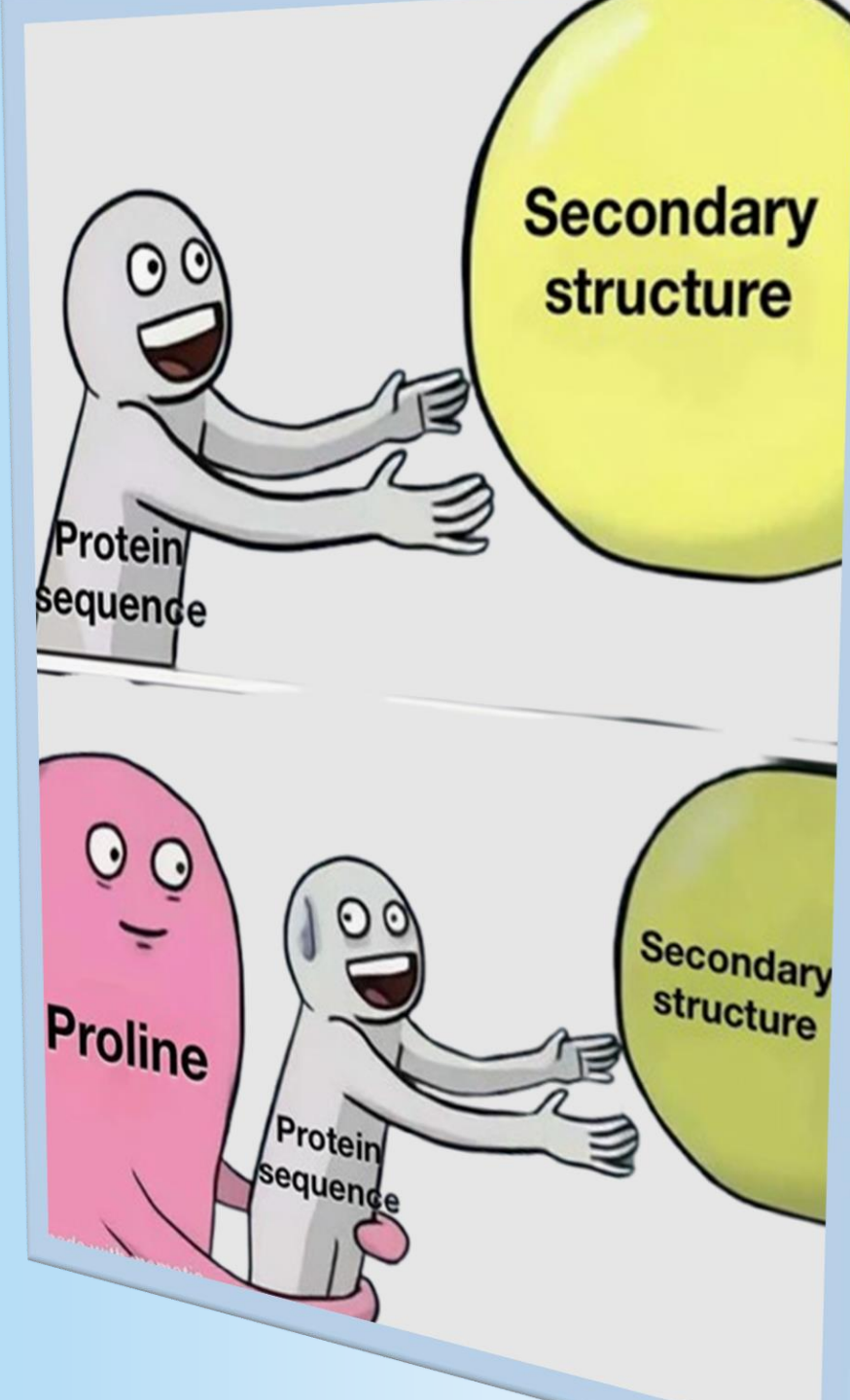
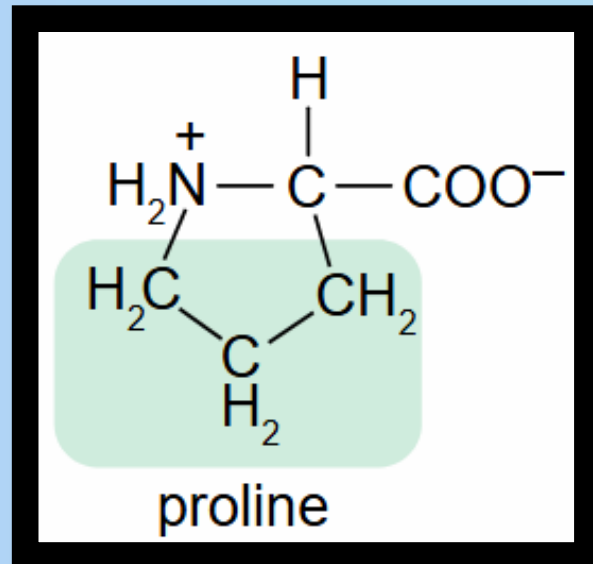
**Val, V**





# Proline

- ❖ Non-polar, hydrophobic amino acid
- ❖ Side chain forms a cyclic structure with the amino group
- ❖ **Side chain = unique nitrogen containing ring**
- ❖ Causes *kinks or bends* in protein chains
- ❖ **Disrupts  $\alpha$ -helices** due to its rigid structure

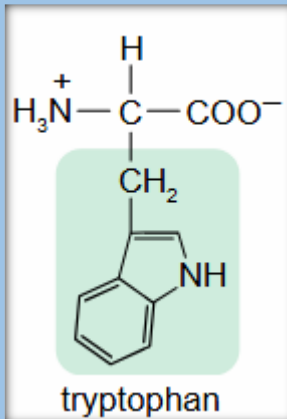


# Aromatic Amino Acids

- ❖ Aromatic = six membered carbon-hydrogen ring with three conjugated double bonds (benzene or phenyl)
- ❖ **Absorbs UV-light**

## Tryptophan

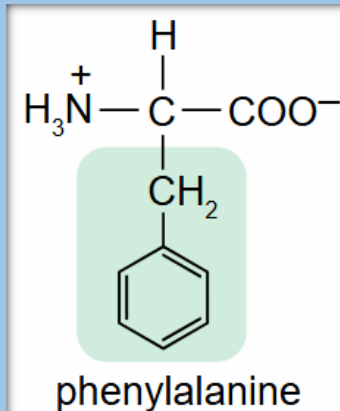
- ❖ **Non-polar, hydrophobic** amino acid
- ❖ Contains a **bulky aromatic indole ring**
- ❖ Precursor for **serotonin, melatonin, and niacin**



Trp, W

## Phenylalanine

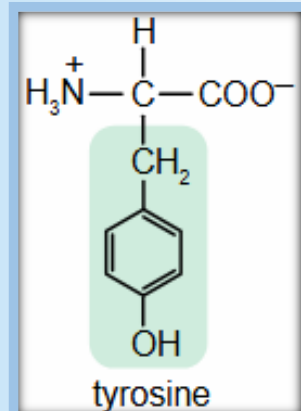
- ❖ **Non-polar and hydrophobic** amino acid
- ❖ Contains a **benzyl aromatic side chain**
- ❖ Precursor for **tyrosine, dopamine, norepinephrine, and epinephrine**



Phe, F

## Tyrosine

- ❖ **POLAR and Uncharged AMINO ACID**
- ❖ Phenol side chain (–OH allows H-bonds)
- ❖ Precursor for **dopamine, norepinephrine, epinephrine, thyroid hormones**



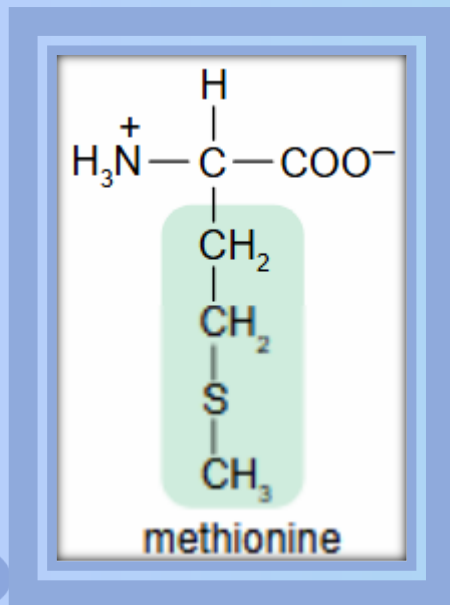
Tyr, Y



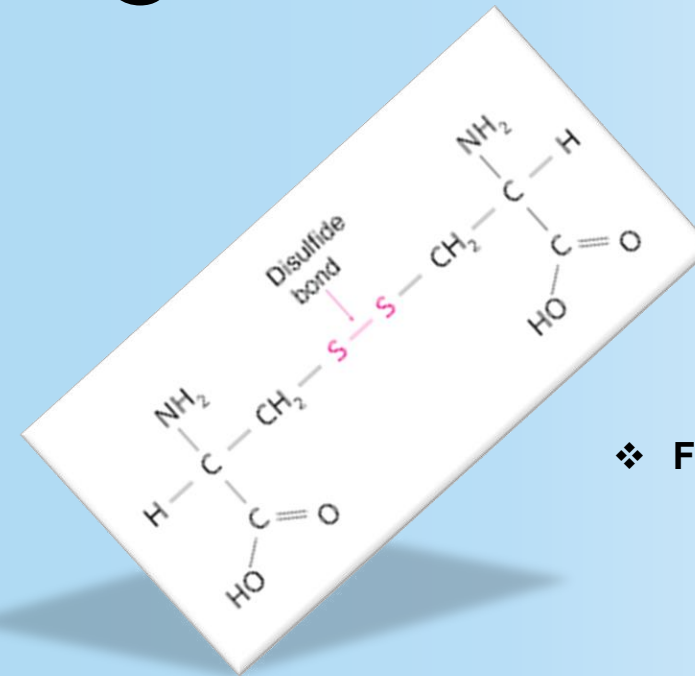
# Sulfur-Containing Amino Acids

## Methionine

- ❖ Non polar
- ❖ Does not contain sulfhydryl group
- ❖ Cannot form disulfide bond



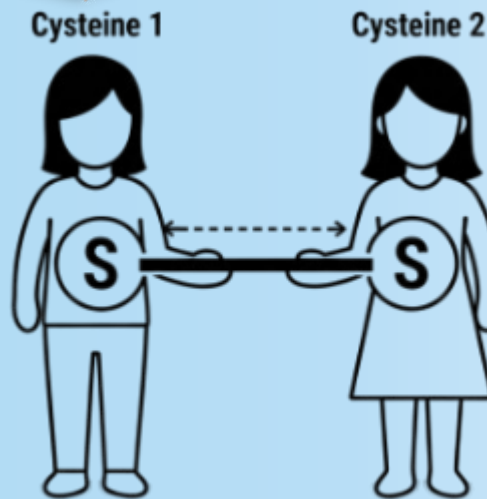
**Memory Key-** Meth =  
Illegal = hiding of S



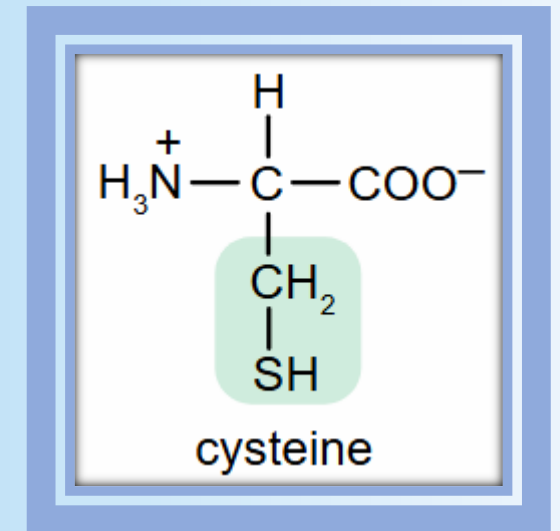
## Cysteine



- ❖ POLAR
- ❖ Sulfhydryl group
- ❖ Forms disulfide bond with another cysteine



Two **cys**ters holding hands  
= **cys**ter connection



Cys, C

# POLAR AMINO ACIDS

| AMINO ACID                  |   |
|-----------------------------|---|
| Positively charged R groups | $  \begin{array}{c}  \text{COO}^- \\    \\  \text{H}_3\text{N}^+ - \text{C} - \text{H} \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{NH}_3^+  \end{array}  $ <p>Lysine</p>                    |
|                             | $  \begin{array}{c}  \text{COO}^- \\    \\  \text{H}_3\text{N}^+ - \text{C} - \text{H} \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{NH} \\    \\  \text{C} = \text{NH}_2^+ \\    \\  \text{NH}_2  \end{array}  $ <p>Arginine</p>         |
|                             | $  \begin{array}{c}  \text{COO}^- \\    \\  \text{H}_3\text{N}^+ - \text{C} - \text{H} \\    \\  \text{CH}_2 \\    \\  \text{C} - \text{NH}^+ \\    \quad \backslash \\  \text{H} \quad \text{CH} \\    \quad // \\  \text{H} \quad \text{N}  \end{array}  $ <p>Histidine</p> |
| Negatively charged R groups | $  \begin{array}{c}  \text{COO}^- \\    \\  \text{H}_3\text{N}^+ - \text{C} - \text{H} \\    \\  \text{CH}_2 \\    \\  \text{COO}^-  \end{array}  $ <p>Aspartate</p>  |
|                             | $  \begin{array}{c}  \text{COO}^- \\    \\  \text{H}_3\text{N}^+ - \text{C} - \text{H} \\    \\  \text{CH}_2 \\    \\  \text{CH}_2 \\    \\  \text{COO}^-  \end{array}  $ <p>Glutamate</p>  |


| Neutral, polar   |                         |
|--|-------------------------|
| $  \begin{array}{c}  \text{H}_3\text{N}^+ \quad \text{H} \\  \backslash \quad / \\  \text{C} \\  / \quad \backslash \\  \text{OOC} \quad \text{CH}_2 - \text{C}_6\text{H}_4 - \text{OH}  \end{array}  $  | Tyrosine<br>(Tyr) (Y)   |
| $  \begin{array}{c}  \text{H}_3\text{N}^+ \quad \text{H} \\  \backslash \quad / \\  \text{C} \\  / \quad \backslash \\  \text{OOC} \quad \text{CH}_2 - \text{OH}  \end{array}  $   | Serine<br>(Ser) (S)     |
| $  \begin{array}{c}  \text{H}_3\text{N}^+ \quad \text{H} \quad \text{H} \quad \text{OH} \\  \backslash \quad / \quad \backslash \quad / \\  \text{C} \quad \text{C} \\  / \quad \backslash \quad \backslash \quad / \\  \text{OOC} \quad \text{CH} \quad \text{CH}_3  \end{array}  $ | Threonine<br>(Thr) (T)  |
| $  \begin{array}{c}  \text{H}_3\text{N}^+ \quad \text{H} \\  \backslash \quad / \\  \text{C} \\  / \quad \backslash \\  \text{OOC} \quad \text{CH}_2 - \text{C} - \text{NH}_2 \\  \quad \quad \quad    \\  \quad \quad \quad \text{O}  \end{array}  $                                | Asparagine<br>(Asn) (N) |
| $  \begin{array}{c}  \text{H}_3\text{N}^+ \quad \text{H} \\  \backslash \quad / \\  \text{C} \\  / \quad \backslash \\  \text{OOC} \quad \text{C} - \text{NH}_2 \\  \quad \quad \quad    \\  \quad \quad \quad \text{O}  \end{array}  $  | Glutamine<br>(Gln) (Q)  |
| $  \begin{array}{c}  \text{H}_3\text{N}^+ \quad \text{H} \\  \backslash \quad / \\  \text{C} \\  / \quad \backslash \\  \text{OOC} \quad \text{CH}_2 - \text{SH}  \end{array}  $   | Cysteine<br>(Cys) (C)   |

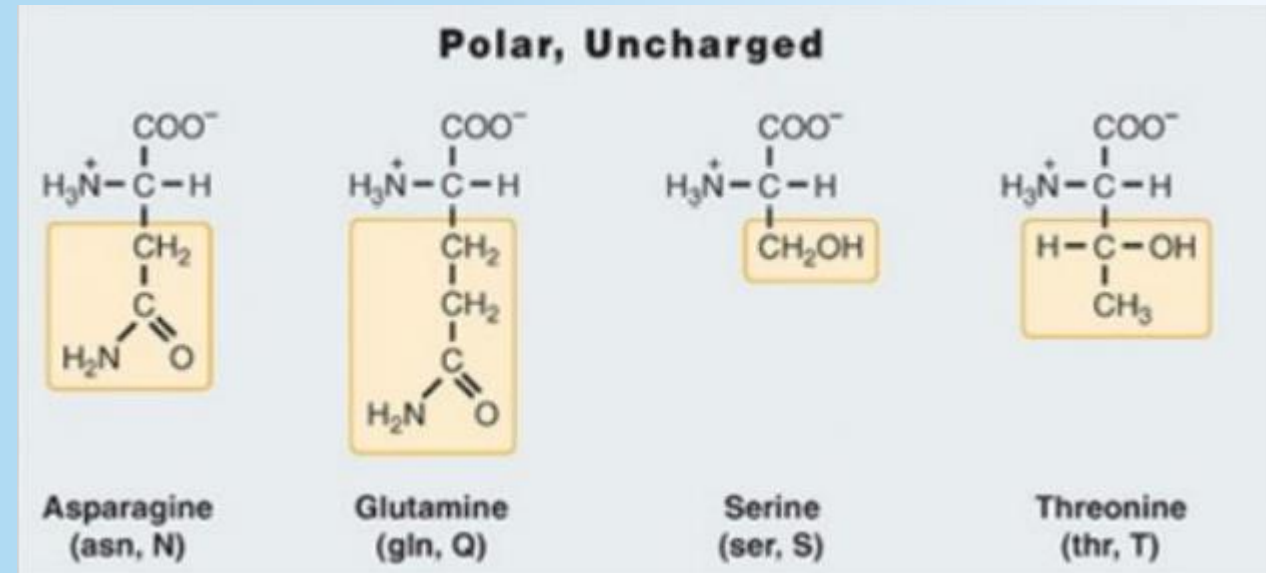




# Polar, Uncharged

Hydrogen bond =  
 $H \rightarrow N, O \text{ or } F$

- ❖ Hydrophilic = water 
- ❖ **Asparagine and Glutamine**
  - Amide group (N)  $\rightarrow$  hydrogen bonds
- ❖ **Serine and Threonine**
  - Hydroxyl group (OH)  $\rightarrow$  hydrogen bonds



# Charged

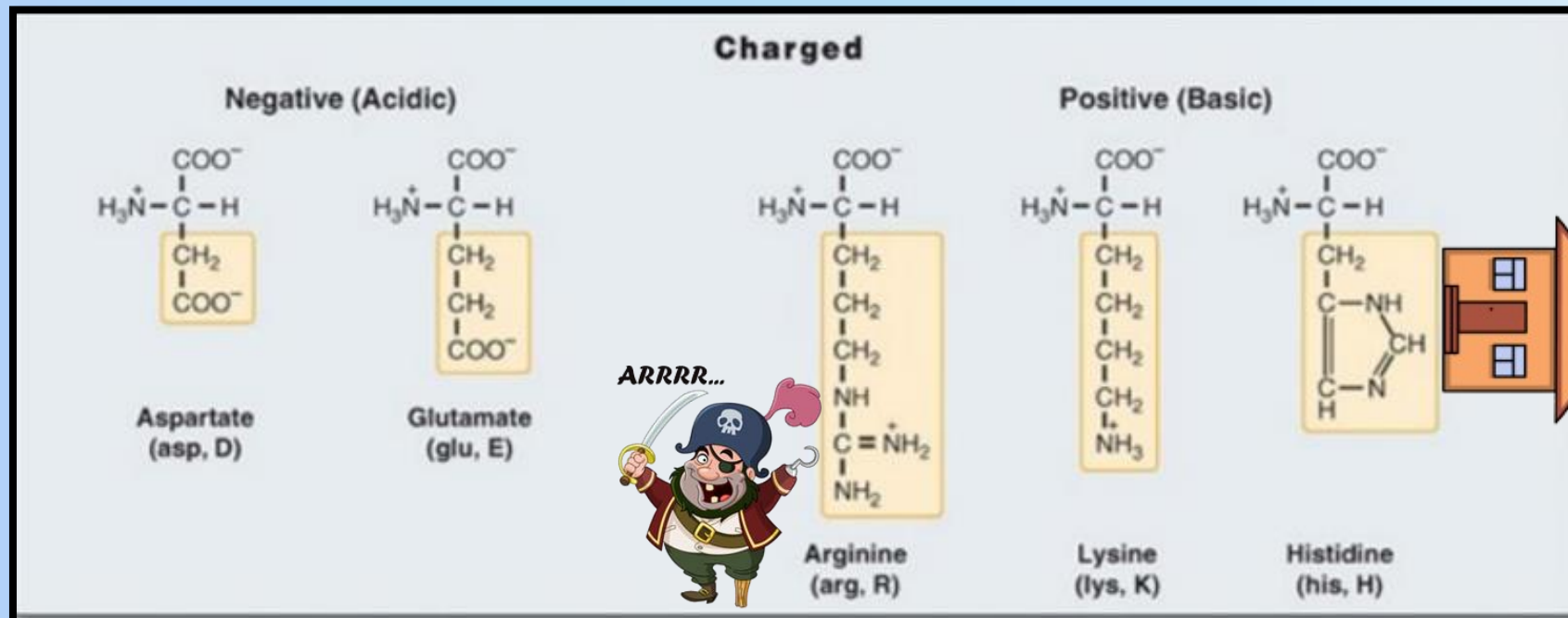


## Acidic

- Carboxylic acid group
- **Negative** charge at physiological pH
- Polar
- Ionic and hydrogen bonds, salt bridges

## Basic

- Nitrogen that can be protonated
- **Positive** charge at physiological pH
- Polar
- Ionic and hydrogen bonds, salt bridges

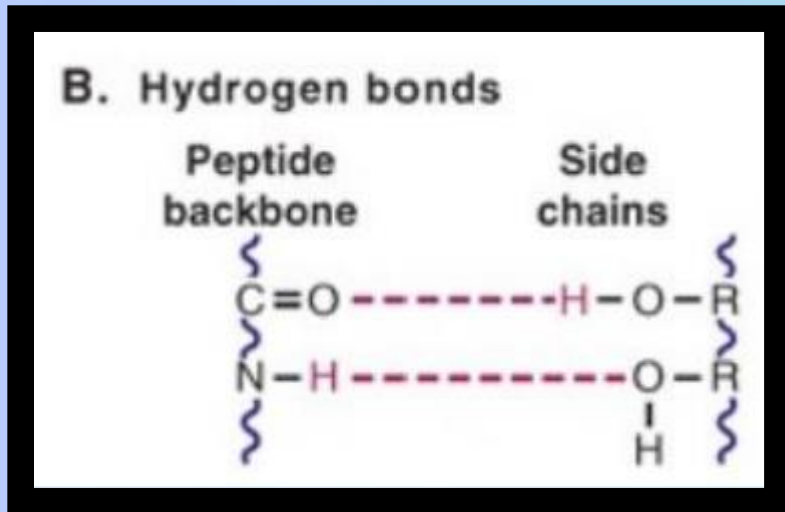


**HALal**

# Bonds from side chains

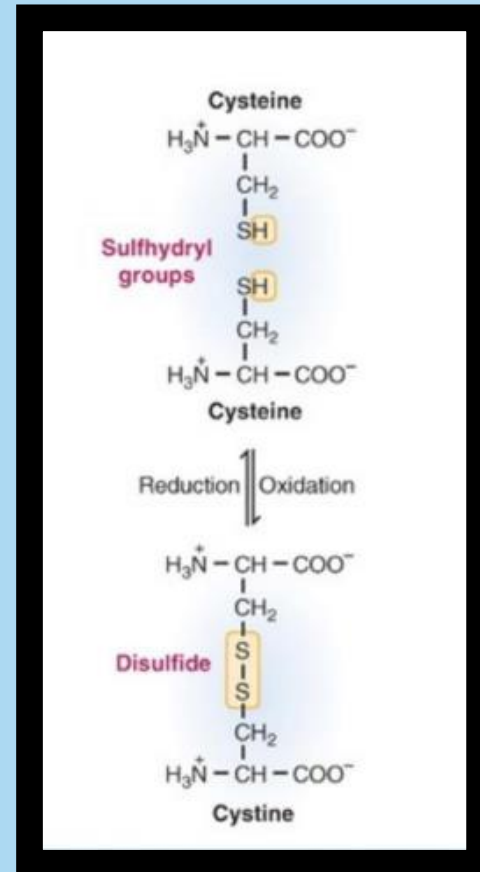
## Hydrogen Bonds

- Polar
- Hydrogen with N O F



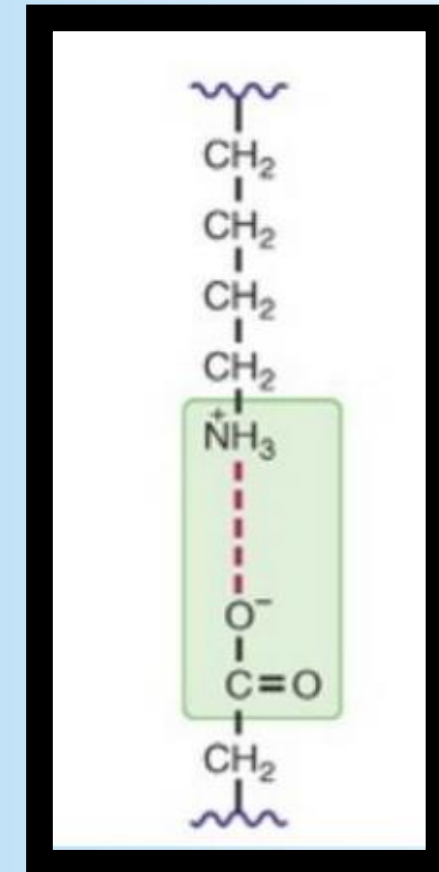
## Disulfide bond

Cys - Cys



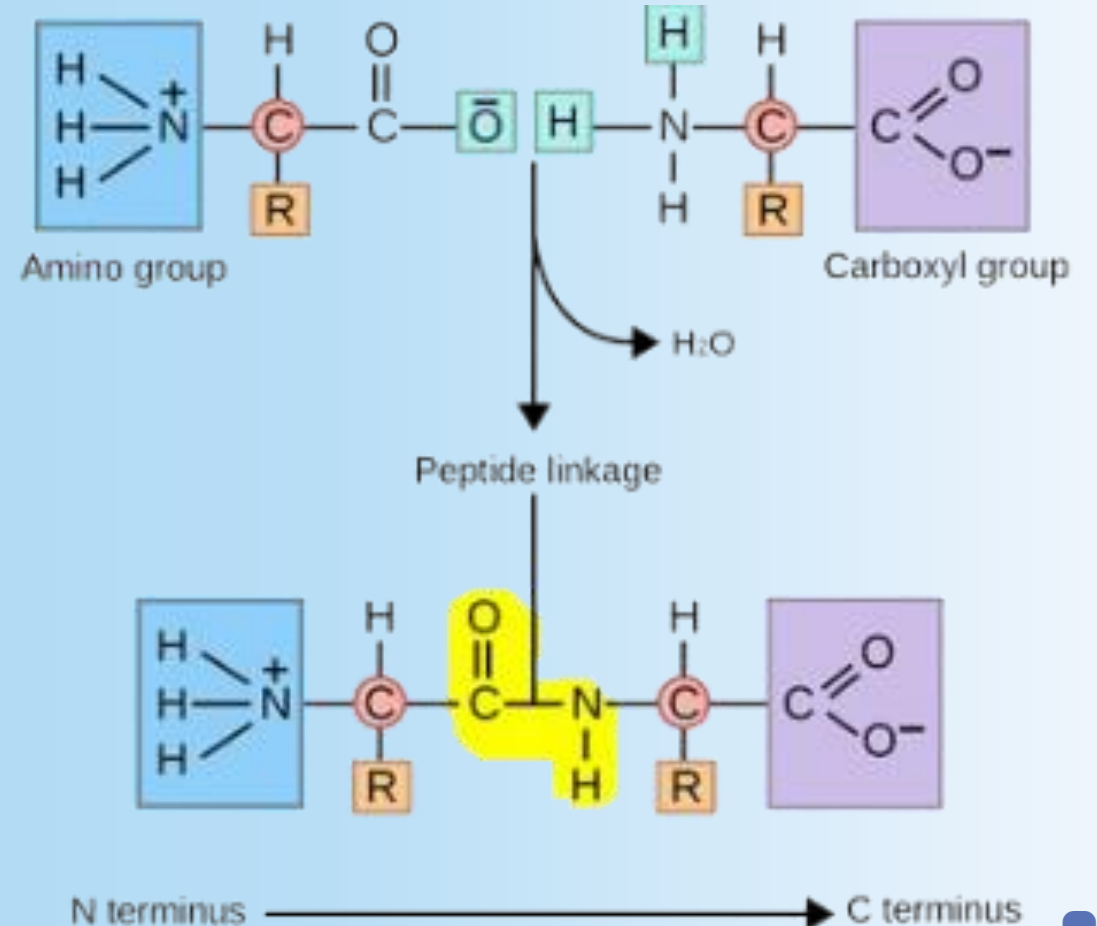
## Ionic

Neg AA - pos AA



# Peptide

- ❖ **CONH**
- ❖ Condensation reaction (lose H)
- ❖ Make polypeptides
- ❖ Always planar → very little rotation  
→ stabilize protein structure
- ❖ Usually trans configuration
- ❖ *Always read from N → C*



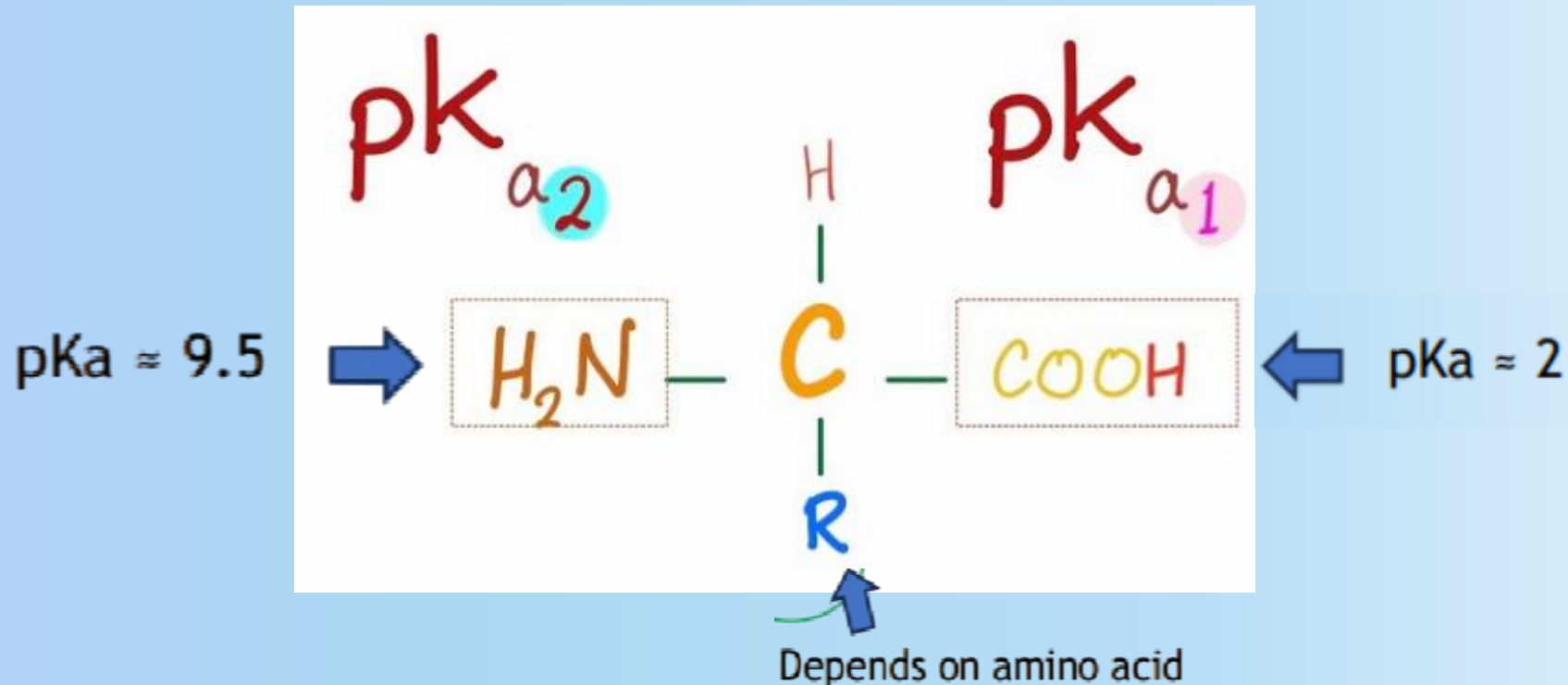
# Mr pKa



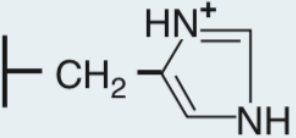
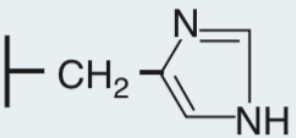
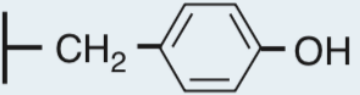
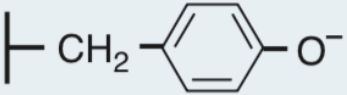
- pKa = the **pH at which 50%** of the molecules' specific ionizable groups have lost their proton.
- The pKa is like the tipping point - it tells us the pH where a group is **halfway between holding onto its proton and letting it go.**
- **Example (carboxyl group -COOH): pKa  $\approx$  2.3**
- At pH < 2.3, most molecules keep H<sup>+</sup> → positive charge.
- At pH = 2.3, half keep it, half lose it → this is the pKa.
- At pH > 2.3, most molecules lose H<sup>+</sup> → negative charge.

# pKa

- ❖ Each group that has a dissociable proton, has a pKa
- In polypeptides only the **first amino group**, the **last carboxyl group** + **side chains** have pKas



- The  $\alpha$ -COOH and  $\alpha$ -NH<sub>3</sub><sup>+</sup> pKa values are **similar across amino acids**, but **slightly shifted** depending on the **side chain**. That's why the **pI differs slightly** between amino acids.
- $\alpha$ -COOH = ~2.0 - 2.5 and  $\alpha$ -NH<sub>3</sub><sup>+</sup> = ~9.0 - 10.5

|                  | Form that predominates below the $pK_a$   | $pK_a$                     | Form that predominates above the $pK_a$   |
|------------------|---|----------------------------|---|
| <b>Aspartate</b> | $\text{—CH}_2\text{—COOH}$  | $\longleftrightarrow$ 3.9  | $\text{—CH}_2\text{—COO}^- + \text{H}^+$  |
| <b>Glutamate</b> | $\text{—CH}_2\text{—CH}_2\text{—COOH}$  | $\longleftrightarrow$ 4.1  | $\text{—CH}_2\text{—CH}_2\text{—COO}^- + \text{H}^+$  |
| <b>Histidine</b> | $\text{—CH}_2\text{—}$                       | $\longleftrightarrow$ 6.0  | $\text{—CH}_2\text{—}$  $+ \text{H}^+$ |
| <b>Cysteine</b>  | $\text{—CH}_2\text{SH}$   | $\longleftrightarrow$ 8.4  | $\text{—CH}_2\text{S}^- + \text{H}^+$   |
| <b>Tyrosine</b>  | $\text{—CH}_2\text{—}$                       | $\longleftrightarrow$ 10.5 | $\text{—CH}_2\text{—}$  $+ \text{H}^+$ |
| <b>Lysine</b>    | $\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—}\overset{+}{\text{N}}\text{H}_3$                                     | $\longleftrightarrow$ 10.5 | $\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—NH}_2 + \text{H}^+$   |
| <b>Arginine</b>  | $\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—NH—C} \begin{matrix} \overset{+}{\text{N}}\text{H}_2 \\ \text{NH}_2 \end{matrix}$ | $\longleftrightarrow$ 12.5 | $\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—NH—C} \begin{matrix} \text{NH} \\ \text{NH}_2 \end{matrix} + \text{H}^+$      |

# Isoelectric Point

- ❖ The *isoelectric point* (*pI*) is the pH at which an amino acid has no overall electric charge – it is neutral.

**pH at which the NET charge is 0**

- ❖ If 3 pKa → use the ones on each side of the net charge 0

$$pI = \frac{pKa_1 + pKa_2}{2}$$

↑ Free H<sup>+</sup>

Molecules wants to  
KEEP H for themself

↓ Free H<sup>+</sup>

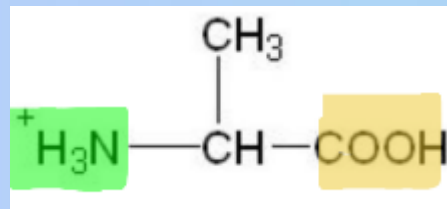
Molecules wants  
to GIVE H away



pH

↑ Free H<sup>+</sup>

Molecules wants to  
KEEP H for themselves

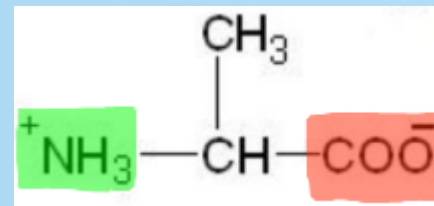


+1

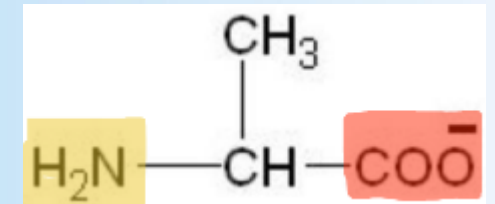
## Alanine in different pH pKa 1 = 2,3, pKa2 = 9,7

↓ Free H<sup>+</sup>

Molecules wants  
to GIVE H away



0



-1

2,3

9,7

$$pI = \frac{2,3 + 9,7}{2} = 6$$

pH

↑  
Physiological pH:  
Charge = 0

Arginine shows 3 pKas at 1.8, 9.0 and 12.5. What is the charge at physiological pH (7.4) and the pI value?

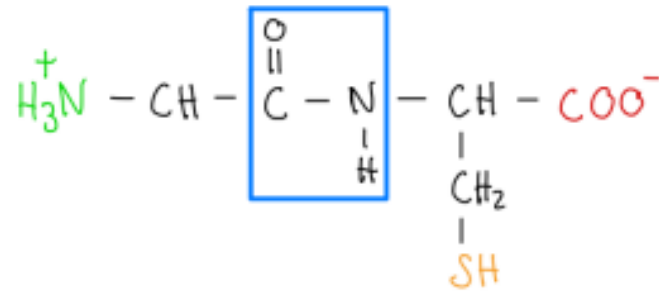


Draw all possible ionic forms of dipeptide Ala-Cys and choose which form is predominant at:

a)  $\text{pH} = \text{pI}$

b)  $\text{pH} > \text{pI}$

c)  $\text{pH} < \text{pI}$



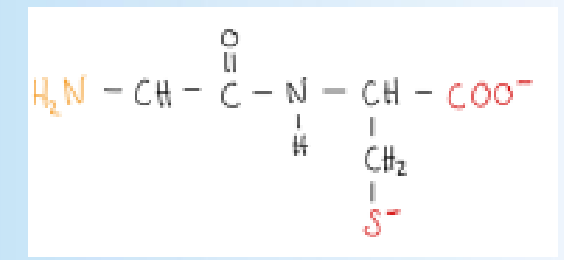
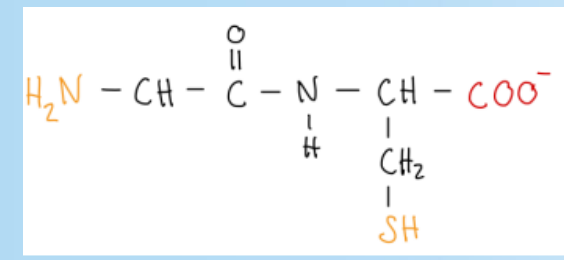
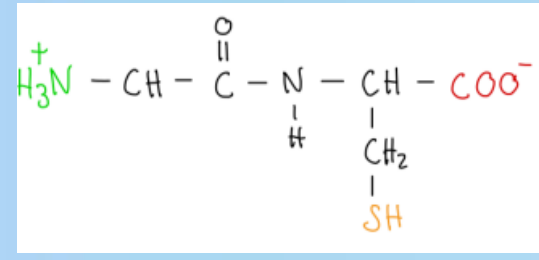
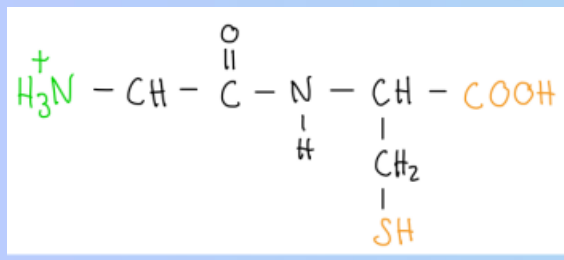
Ala:  $\text{pK}_a(\text{COOH}) = 2,4$ ,  $\text{pK}_a(\text{NH}_3^+) = 9,69$ ;

Cys:  $\text{pK}_a(\text{COOH}) = 2,0$ ,  $\text{pK}_a(\text{NH}_3^+) = 9,2$ ,  $\text{pK}_a(\text{SH}) = 10,3$

↑ Free H<sup>+</sup>

↓ Free H<sup>+</sup>

Ala: pKa(NH<sub>3</sub><sup>+</sup>)= 9,69;  
Cys: pKa(COOH)= 2,0, pKa(SH)= 10,3



+1

0

-1

-2

pH < pI

2

pH = pI

9,69

pH > pI

10,3

pH >> pI

Physiological pH:  
Charge = 0

pH

$$pI = \frac{2 + 9,69}{2} = 5,845$$

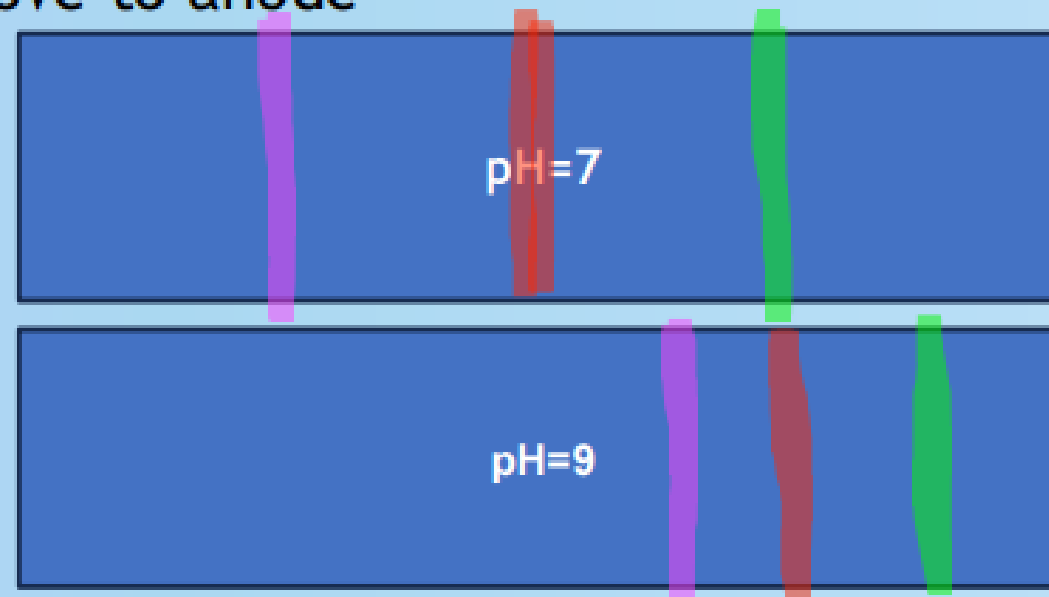
# Electrophoretic separation

- ❖ Use electrical charge to separate AA and proteins
- ❖ If  $\text{pH} = \text{pI}$  the protein will stand still
- ❖ If  $\text{pH} < \text{pI} \rightarrow$  move to cathode
- ❖ If  $\text{pH} > \text{pI} \rightarrow$  move to anode

$\text{pI}$  = the pH where net charge is 0!!!

Cathode

-



- ❖  $\text{pI} = 6$ ,  $\text{pI} = 7$ ,  $\text{pI} = 8$

Anode

+



**TAKE**

**5min**



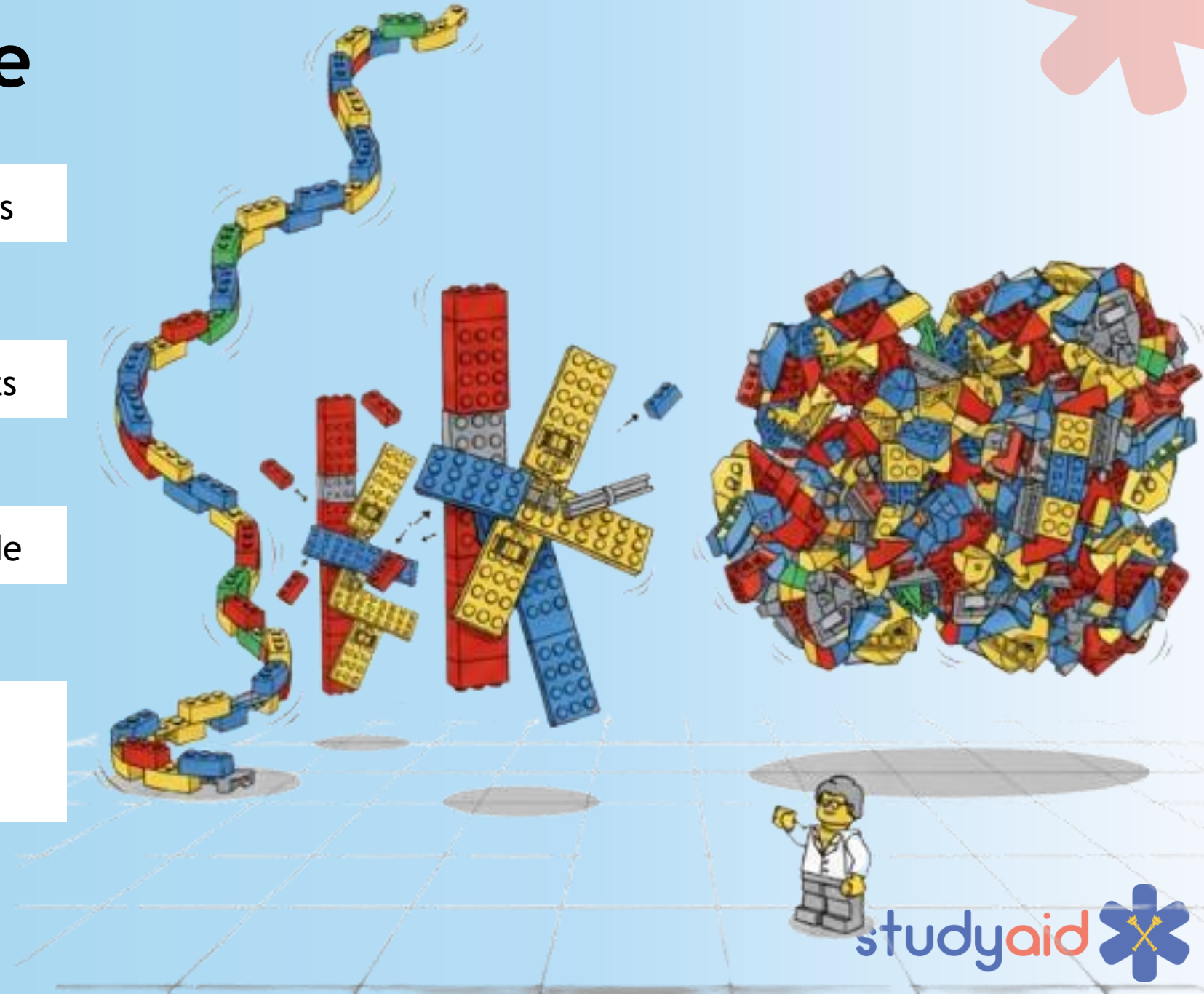
# Protein Structure

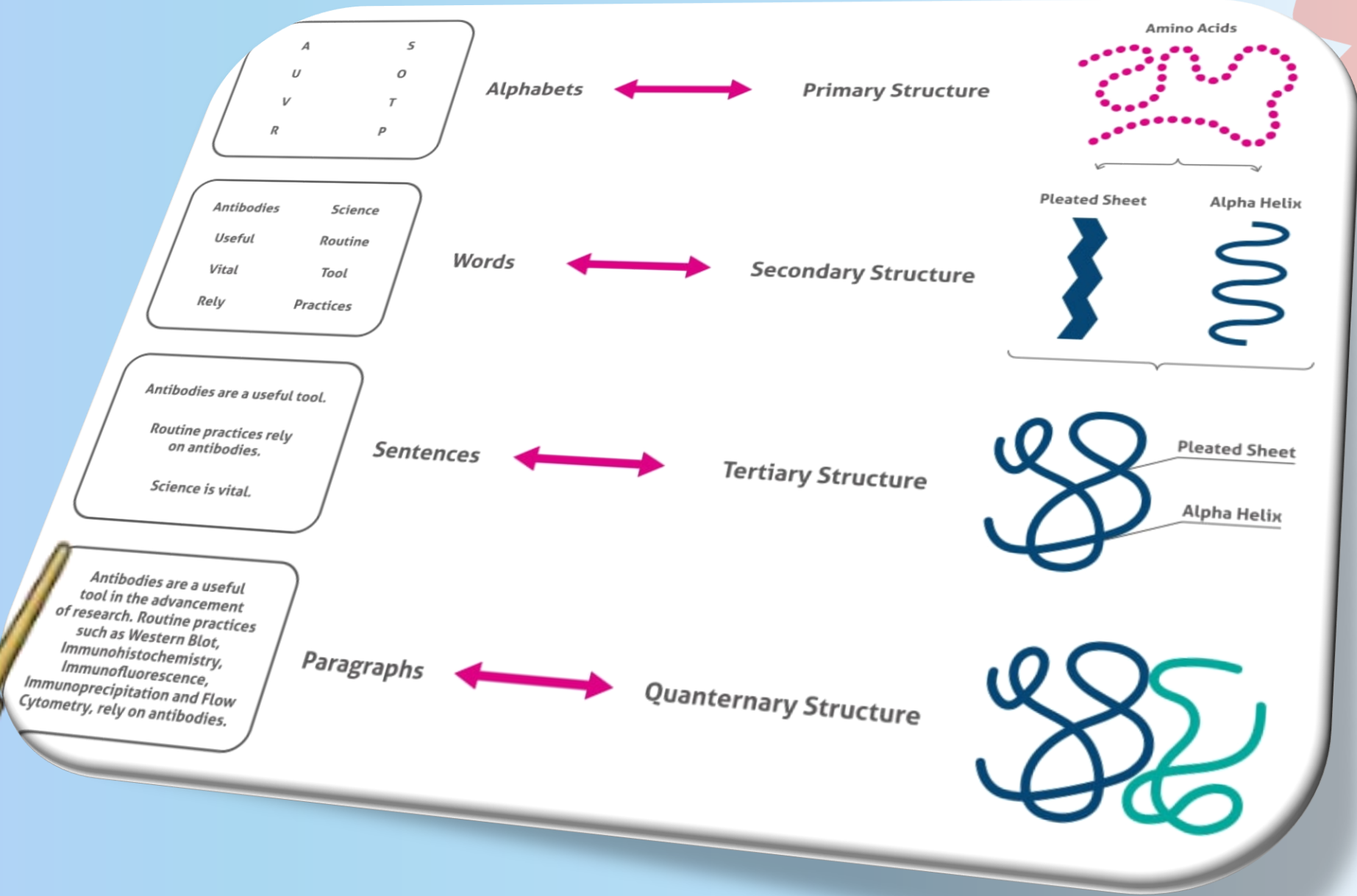
Primary- The sequence of amino acids

Secondary-alpha helix and beta sheets

Tertiary- 3D folding of one polypeptide

Quaternary - multiple polypeptides together





# Primary Structure

The two ends

- **A**mino terminus (N-terminus) and **C**arboxyl terminus (C-terminus)
- The sequence is read from N→C

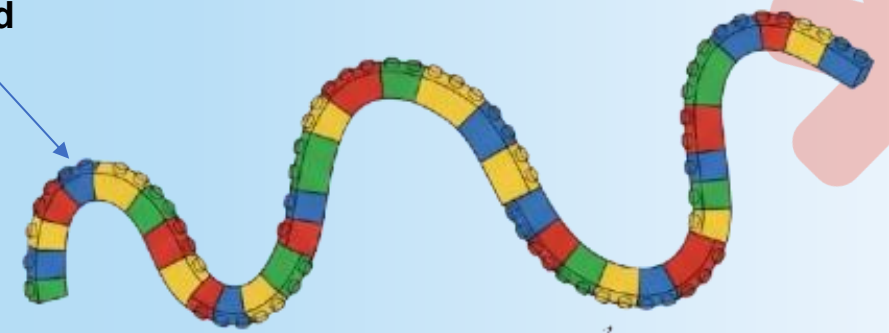
## Bonds

- **Peptide bonds** - between C and N terminus of sequential AA

Determined by the gene corresponding to the protein

**ALL of the info** about folding is in the primary sequence

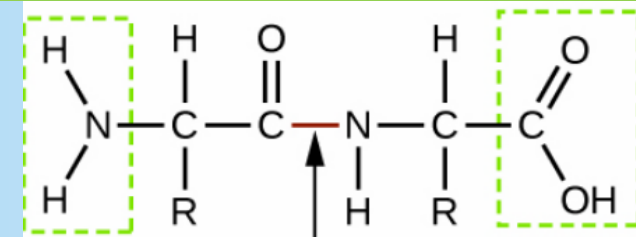
Amino Acid



Primary Structure



Primary- The sequence of amino acids



Peptide bond

# What actually holds an $\alpha$ -helix or $\beta$ -sheet together?

- A. Side chains
- B. Peptide bond rotation
- C. Backbone hydrogen bonds
- D. Sheer willpower

# What actually holds an $\alpha$ -helix or $\beta$ -sheet together?

- A. Side chains
- B. Peptide bond rotation
- C. **Backbone hydrogen bonds (Correct!)**
- D. Sheer willpower

# Secondary Structure

Hydrogen bond =  
 $H \rightarrow N, O \text{ or } F$

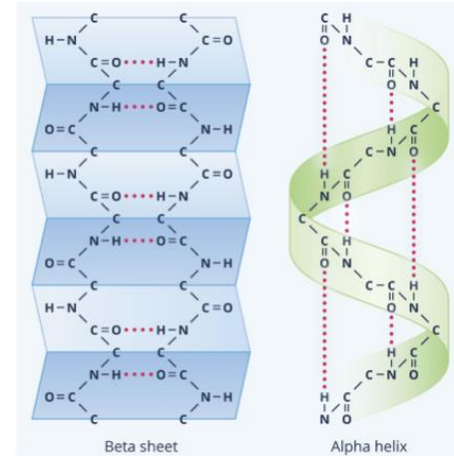
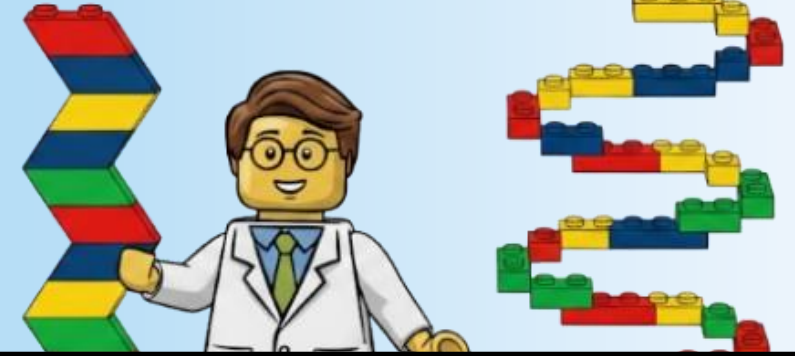
The main types of secondary structure:

- $\alpha$ -helix
- $\beta$ -strand or  $\beta$ -sheets

Defined by patterns of hydrogen bonds between the main-chain peptide groups.

## Beta-Pleated Sheet

## Alpha Helix



**Fig 1. Secondary Structure:** Notice how the beta sheet has two amino acid chains running side by side, whilst the alpha helix has coiling. The red dots are hydrogen bonds which hold together both the beta pleated sheets and the alpha helix.

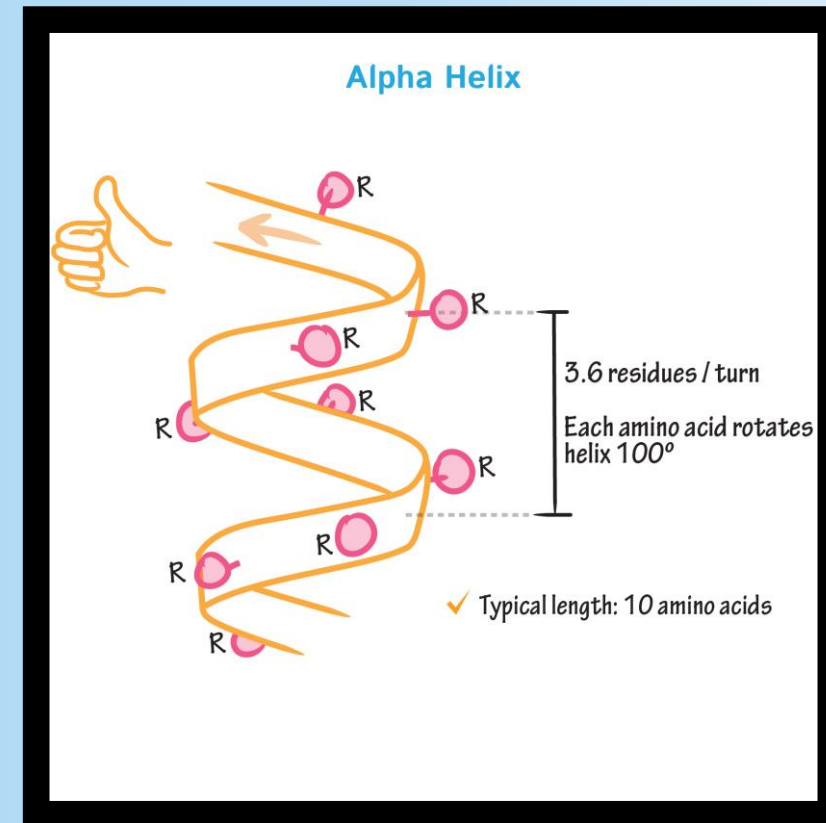
NOTE

- Irregular types of secondary structure: Bends, Loops, Turns, Motifs, and Coils

# Alpha Helix

Hydrogen bond =  
 $H \rightarrow N, O \text{ or } F$

- **Right-handed spiral helix!!!!**
- **3.6 residues per turn**
- Side chains project outward!!
- Hydrogen bonds project parallel
- **H-bonds:  $i \rightarrow i+4$** 
  - Donor: the N-H of residue  $i + 4$
  - Acceptor: the C=O of residue  $i$



- Alpha helix is **RIGHT HANDED** while the collagen triple helix is **LEFT HANDED**!



# Which amino acids break helices?

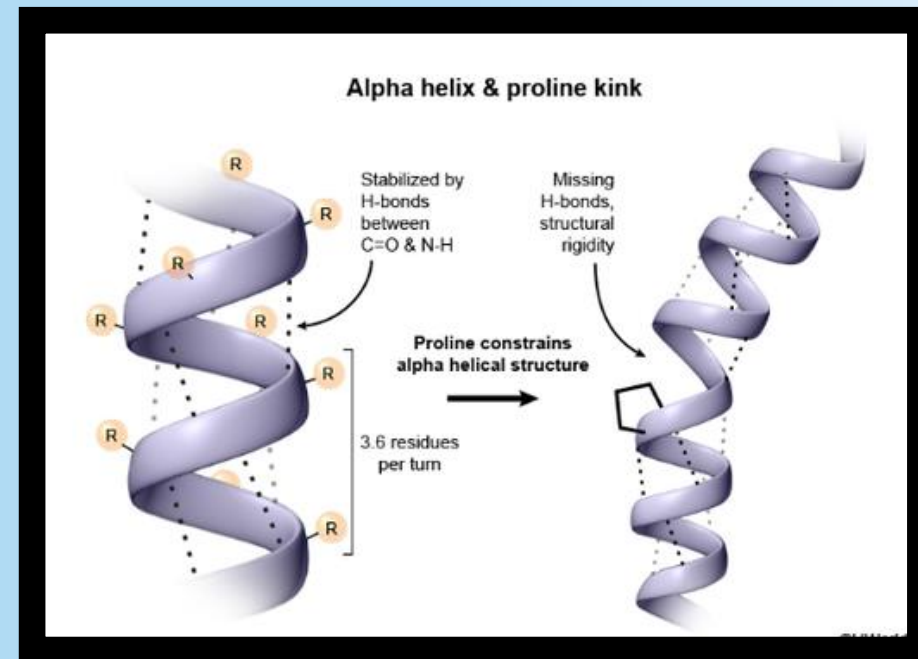
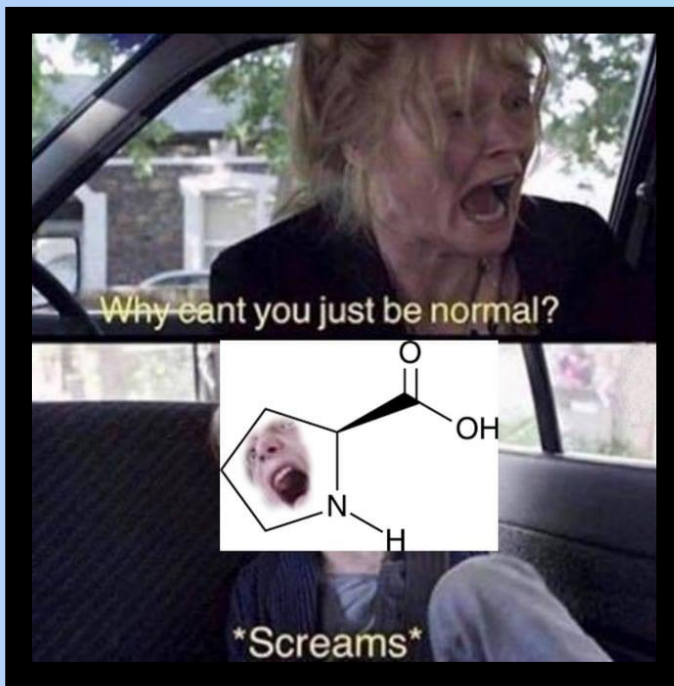


# Alpha Helix Breakers



**Proline** breaks  $\alpha$ -helices because its rigid ring removes the N-H needed for H-bonding and forces a kink in the backbone

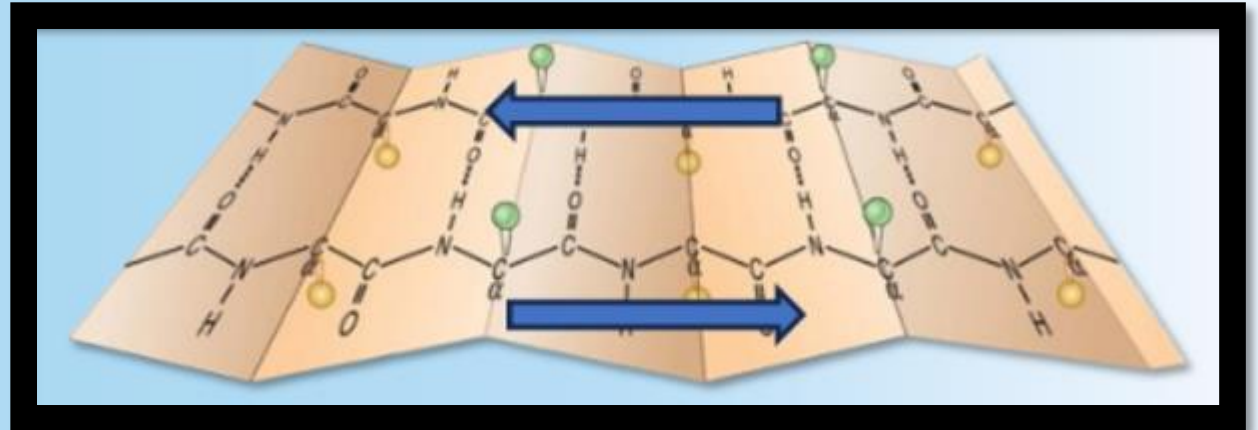
**Glycine** destabilizes  $\alpha$ -helices because its tiny size makes it too flexible to maintain the helix's strict geometry



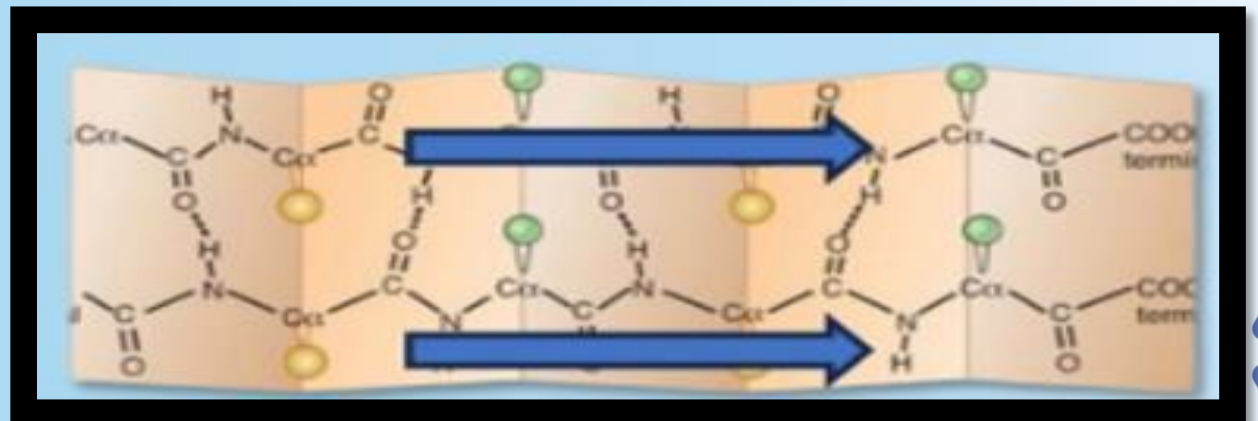
# Beta-pleated sheets

- Composed of **beta strands**
- Side chains project on both sides of the sheets (“over and under”)
- **Antiparallel sheets:** stronger, more linear H-bonds

**AntiParallel**

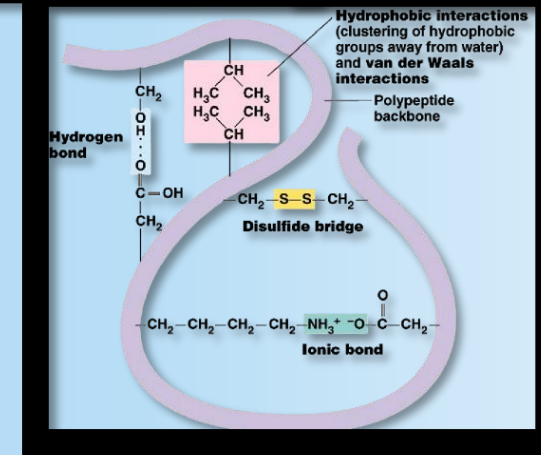
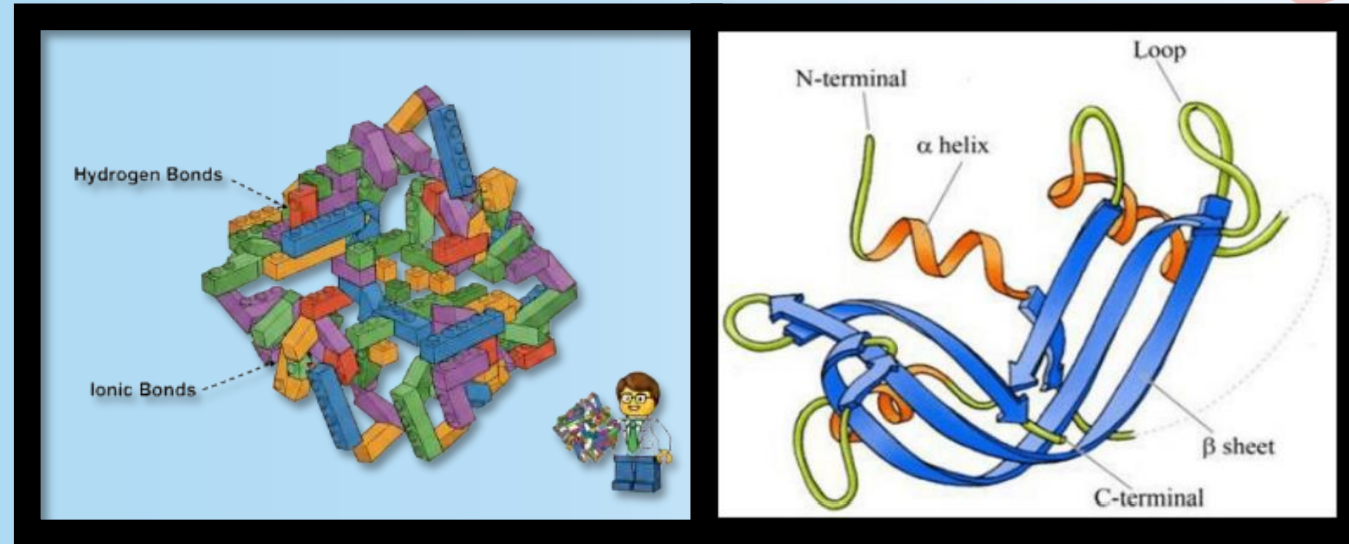


**Parallel**

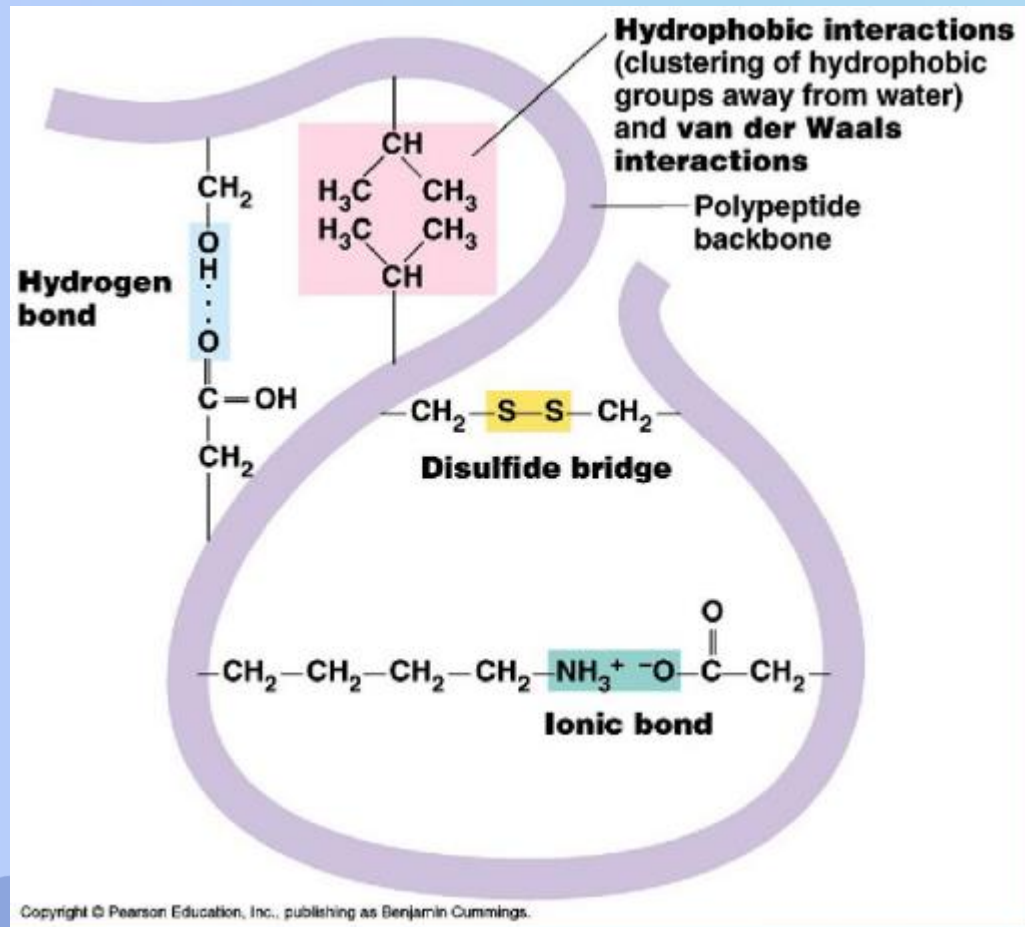


# Tertiary Structure

- the three-dimensional structure created by a **single polypeptide chain**
- Stabilized by interactions between **R-groups** (side chains)
- The  $\alpha$ -helixes and  $\beta$ -pleated sheets are folded into a compact globular structure



# Bonds



## Types of bonds

1. **H**ydrophobic interactions
2. **I**onic bonds
3. **V**an der Waals interactions
4. **H**ydrogen bonds
5. **D**isulfide bridges

(Remember **HIV** in **HD**)

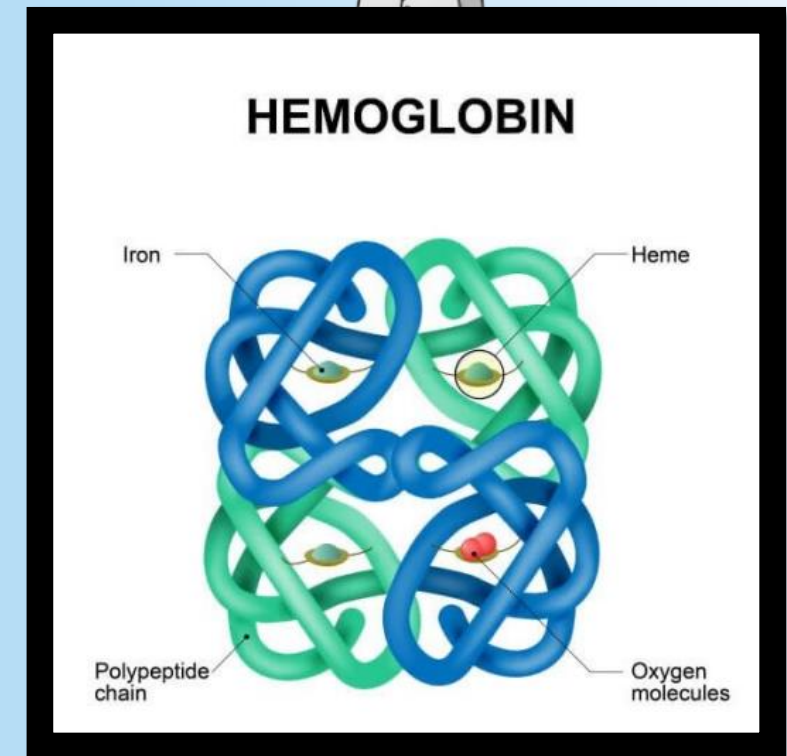


Hydrophobic collapse forms the basic fold, but specific interactions (H-bonds, salt bridges, disulfides) lock the protein into a stable final structure

# Quaternary structure

- Formed when **two or more polypeptide chains (subunits) come together to function as one unit**
- The assembled protein complex is called a multimer
- Stabilized by the same interactions as tertiary structure: **HIV in HD**
- Many possible organizations: **dimers, trimers, tetramers, etc.**

Example: Hemoglobin ( $\alpha_2\beta_2$  tetramer)



# Summary of bonds/interactions

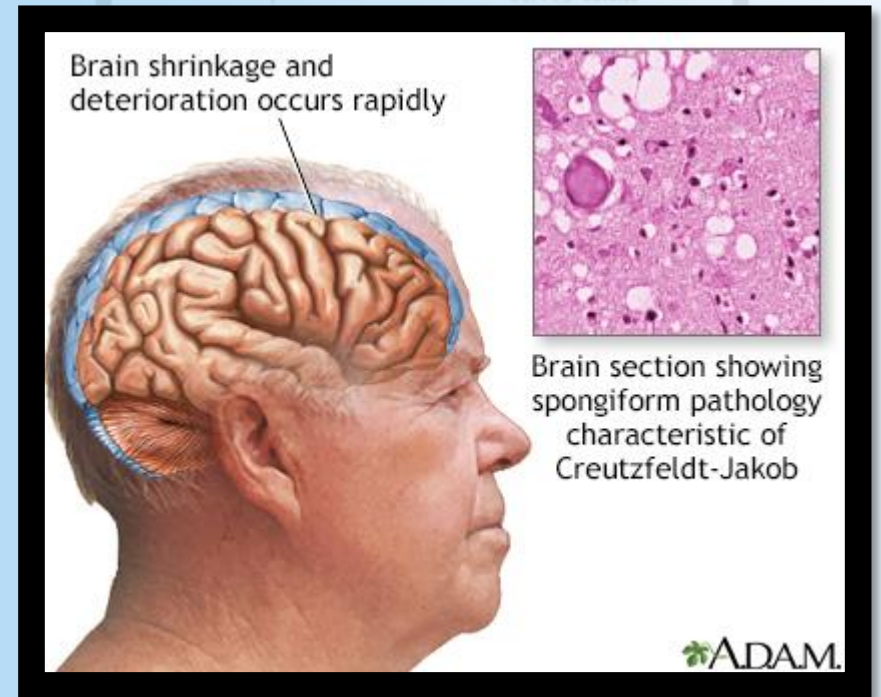
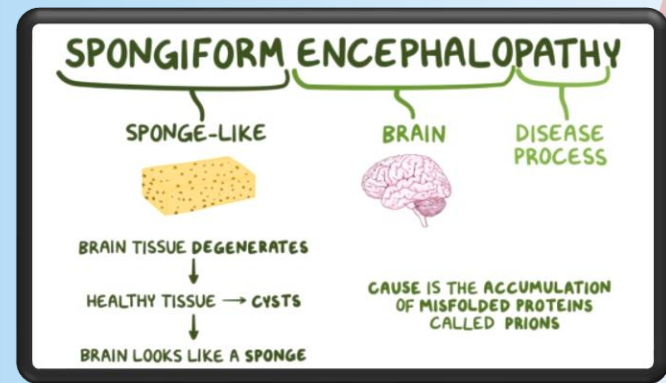
|                | PRIMARY STRUCTURE | SECONDARY STRUCTURE | TERTIARY STRUCTURE   | QUATERNARY STRUCTURE  |
|----------------|-------------------|---------------------|--|---|
| TYPES OF BONDS | Peptide bonds     | Hydrogen bonds      | <p>Hydrophobic interactions</p> <p>Ionic bonds</p> <p>Van der Waals interactions</p> <p>Hydrogen bonds</p> <p>Disulfide bridges<br/>(Remember HIV in HD)</p> | <p>Non-covalent bonds:</p> <ul style="list-style-type: none"> <li>Hydrogen bonds and van der waals forces between nonpolar side chains</li> <li>Occasional ionic bonds or salt bridges</li> </ul> <p>Disulfide bridges (rare)</p> |

# Prions

- Prions cause misfolding of proteins
- PrP<sup>c</sup> = normal,  $\alpha$ -helix-rich
- PrP<sup>sc</sup> = abnormal,  $\beta$ -sheet-rich, resistant to degradation

## Prions Cause

1. Creutzfeldt-Jakob disease (CJD)
2. Mad cow disease



Prions → misfolded proteins → neuron death → holes in the brain → fatal neurologic decline

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Event code  
**AGDJTT**

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~~Party Hard!~~

**Do your best!**

THE END

