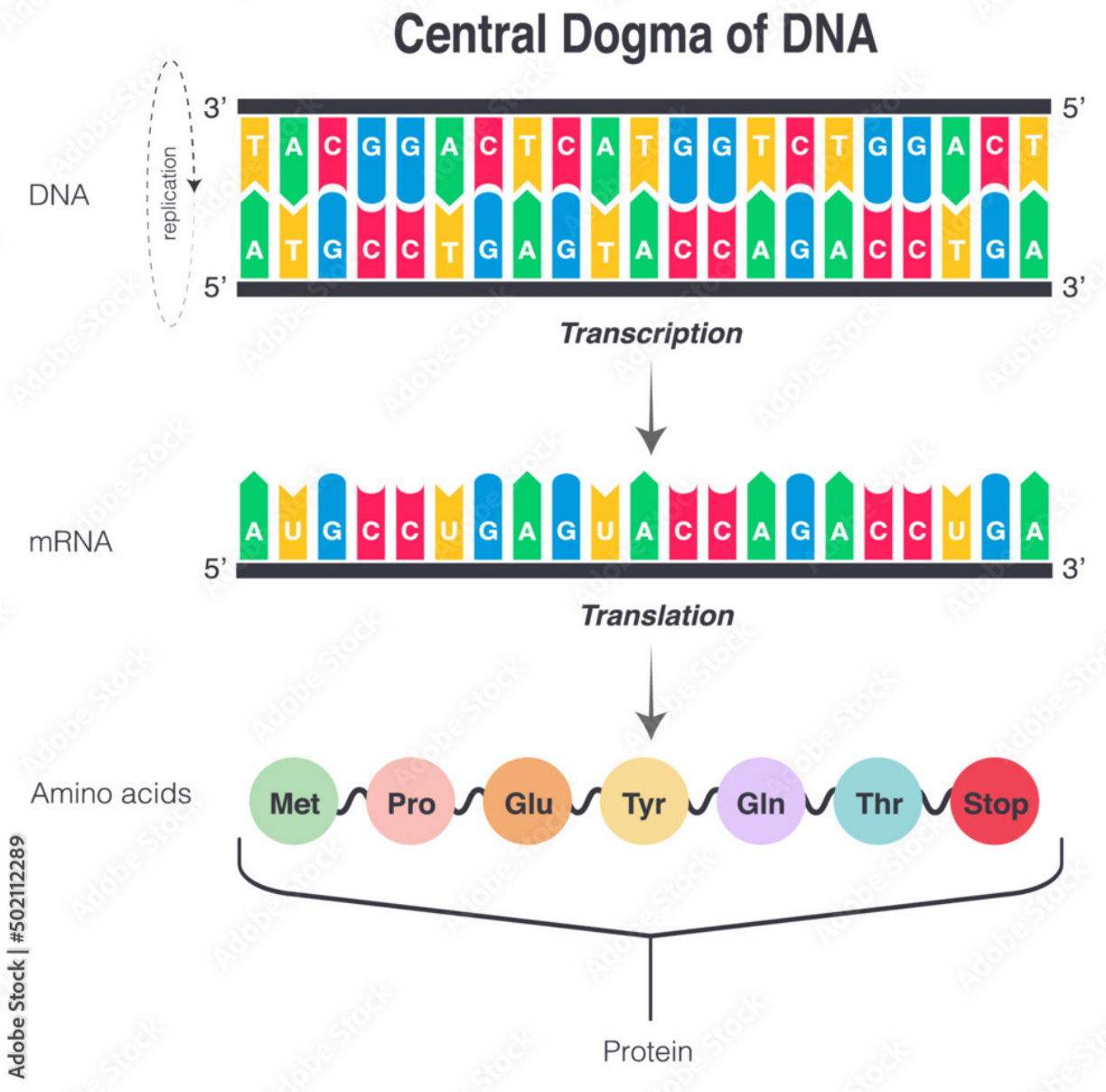
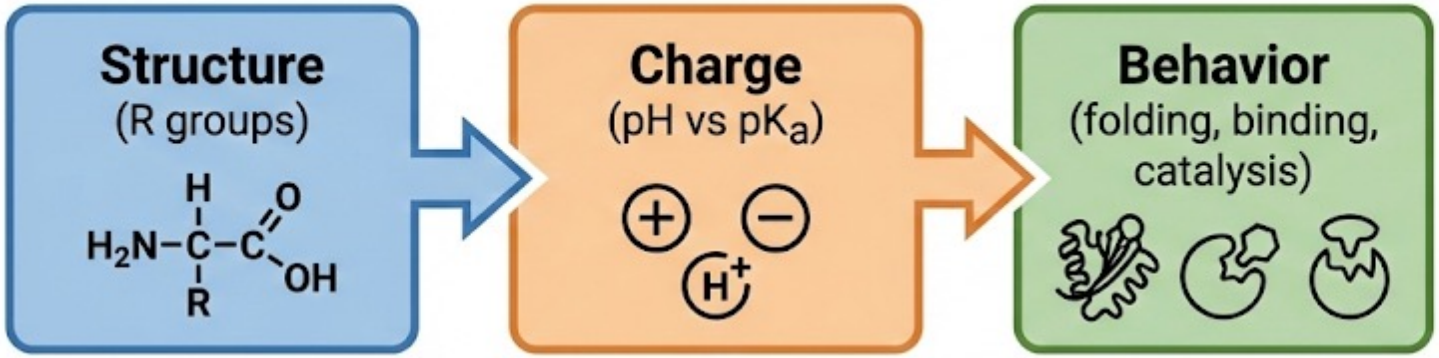
CHAPTER 3
Amino Acids



Chapter 3 Targets:
What you should be able to do today

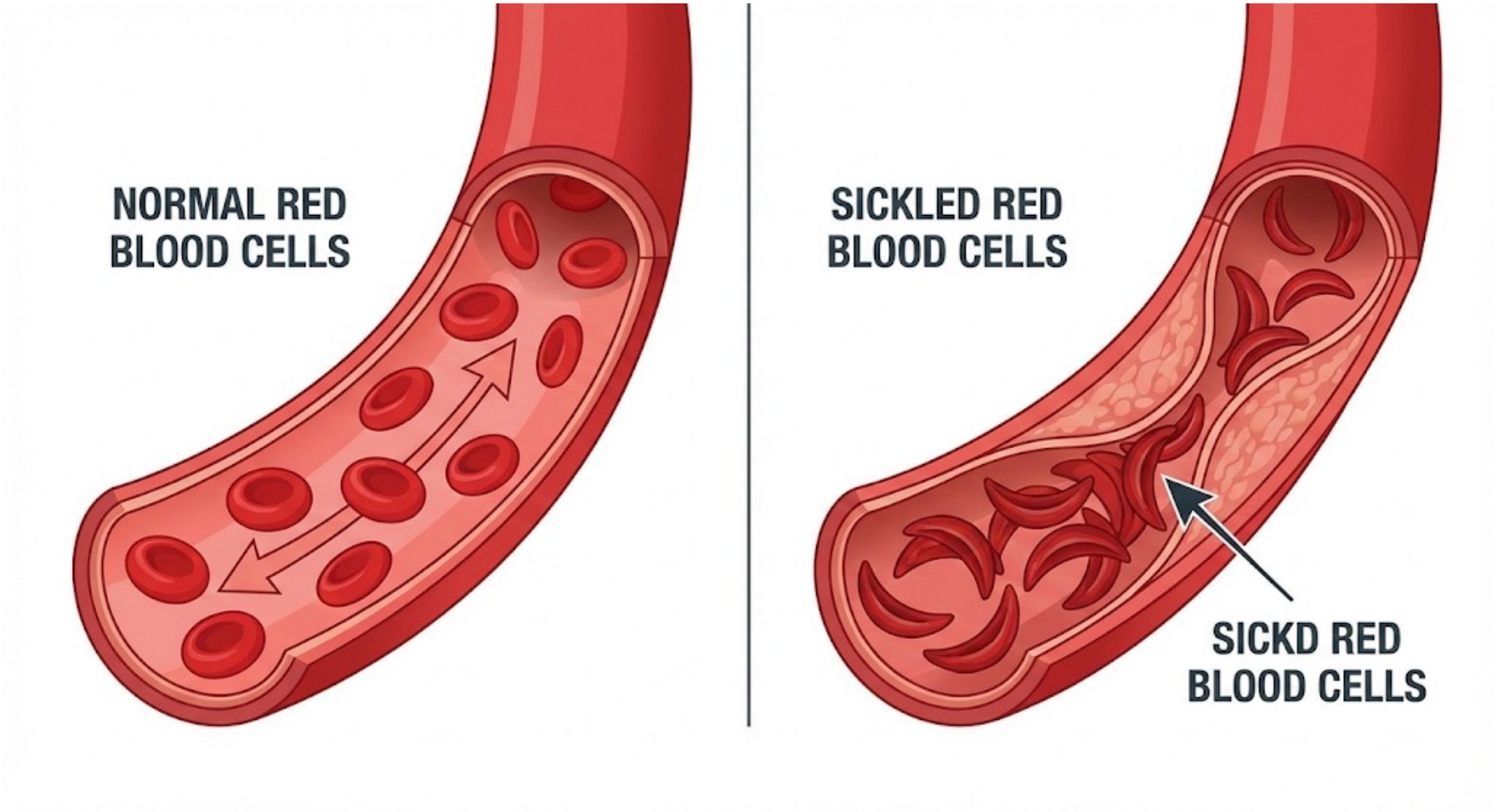


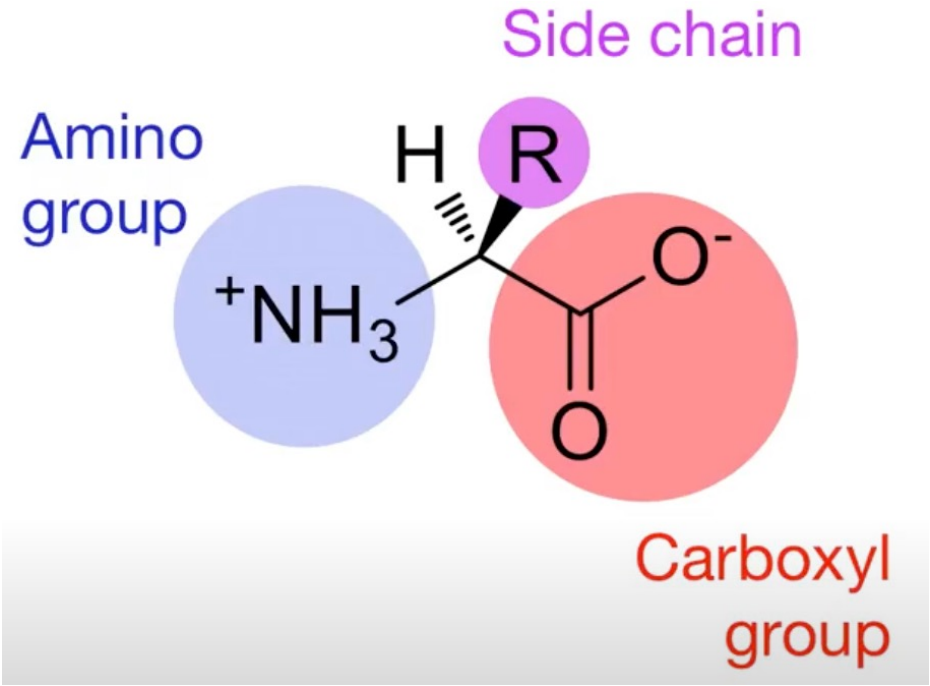
Today is about **structure** → **charge** → **behavior**.

You are here

- ☑ Define amino acid, proteogenic, essential
- ☑ Sort into 4 major R-group classes
- ☑ Predict net charge using pK_a logic
- ☑ Explain zwitterions and pI
- ☑ Anticipate protein behavior (folding, binding, catalysis)

One amino acid can change everything.



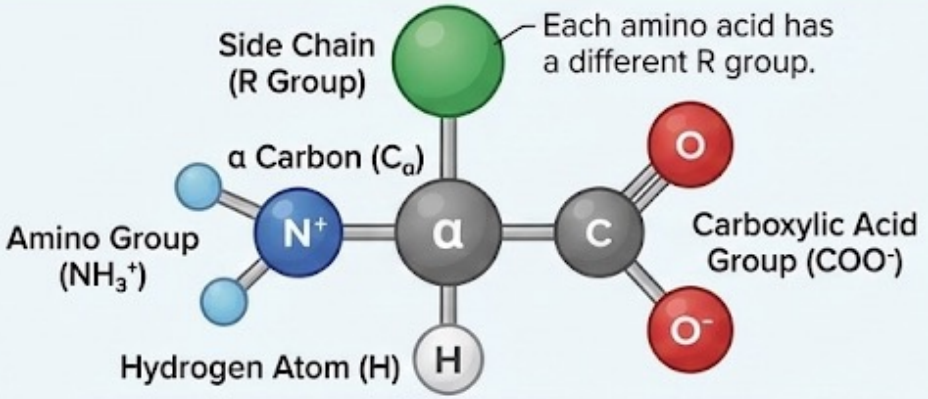


Section 3.1 Proteins Are Build from a Repertoire of 20 Amino Acids

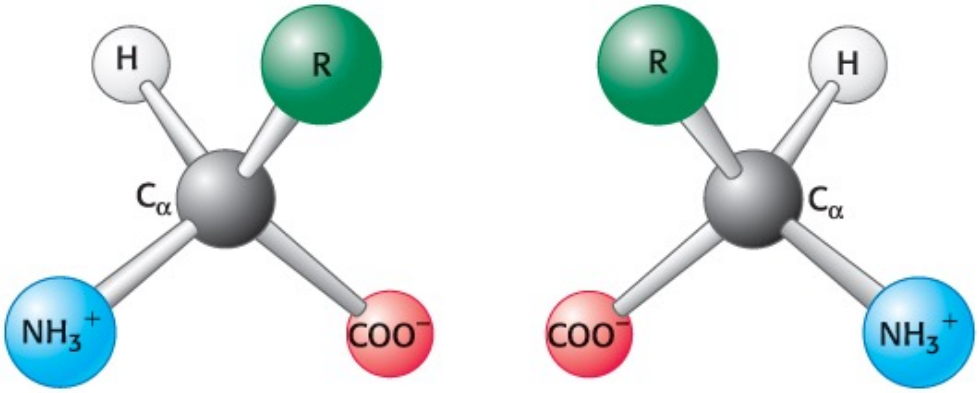
- **Learning objective 1: Identify the main classes of amino acids.**
  - An α-amino acid is composed of a central carbon atom called the α-carbon.
  - The α-carbon is linked to an amino group, a carboxylic acid, a hydrogen atom, and a distinctive side chain, called the R group.

Proteogenic Amino Acids: The Building Blocks of Proteins

General Structure



Stereochemistry



L Isomer

D Isomer

The Proteogenic Set (20)

The same set of 20 amino acids construct all proteins in all bacterial, archaeal, and eukaryotic species.

Synthesis & Essential Amino Acids

Microorganisms
Most can synthesize the entire basic set of 20 proteogenic amino acids.

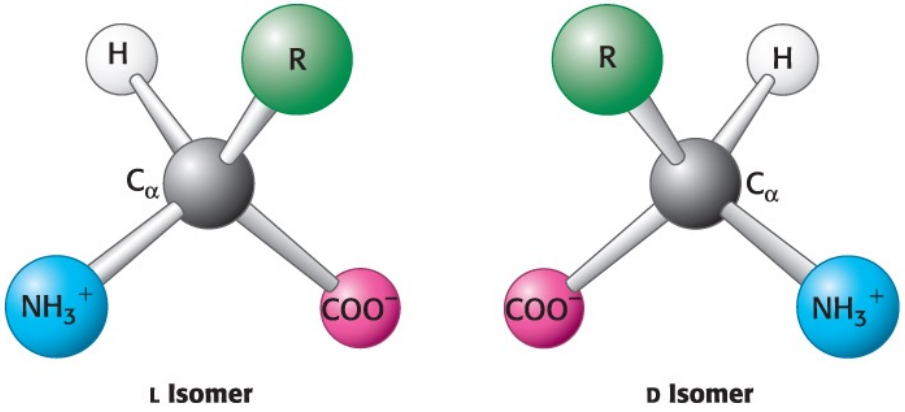
Humans
Can make only 11 of them.

Essential Amino Acids
The remaining essential amino acids (9) must be supplied by the diet.

- Also referred to as α-amino carboxylic acids.

Most Amino Acids Exist in Two Mirror-Image Forms

- When four different groups are bonded to the a-carbon, the amino acids are chiral, which means that they exist as two mirror-image forms called the L isomer and the D isomer.
- Only the L isomers are found in proteins.



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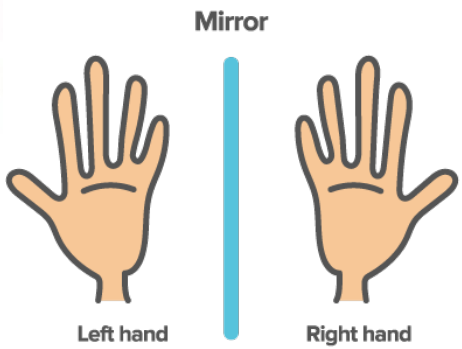
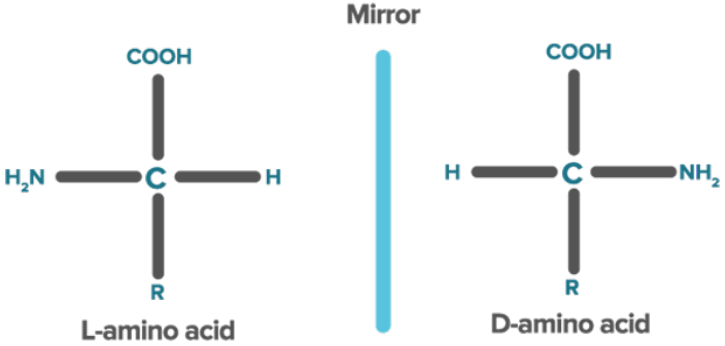
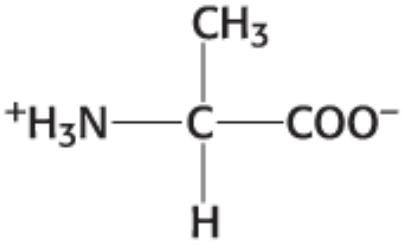




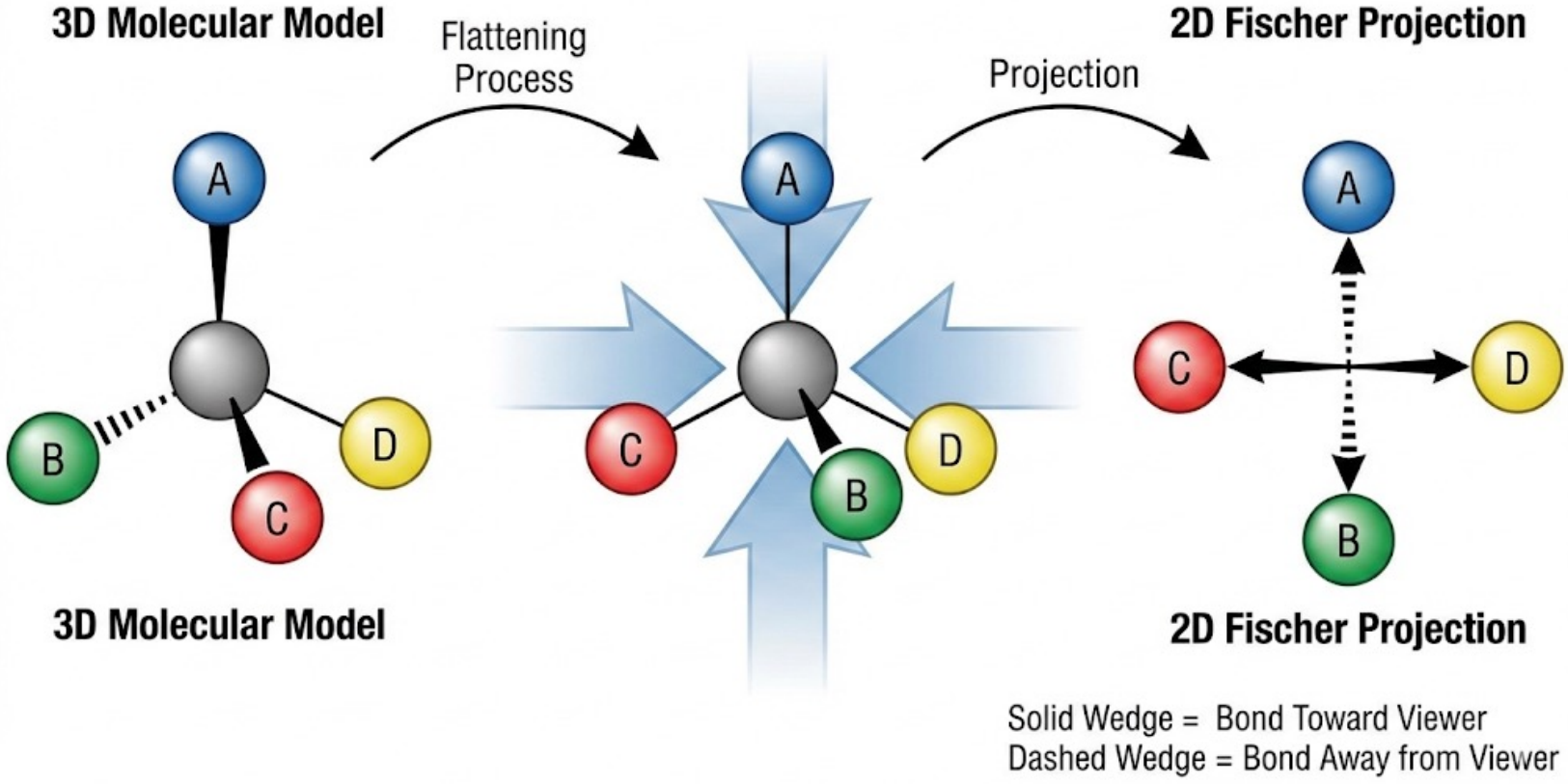
Why are all biological amino acids L-form?

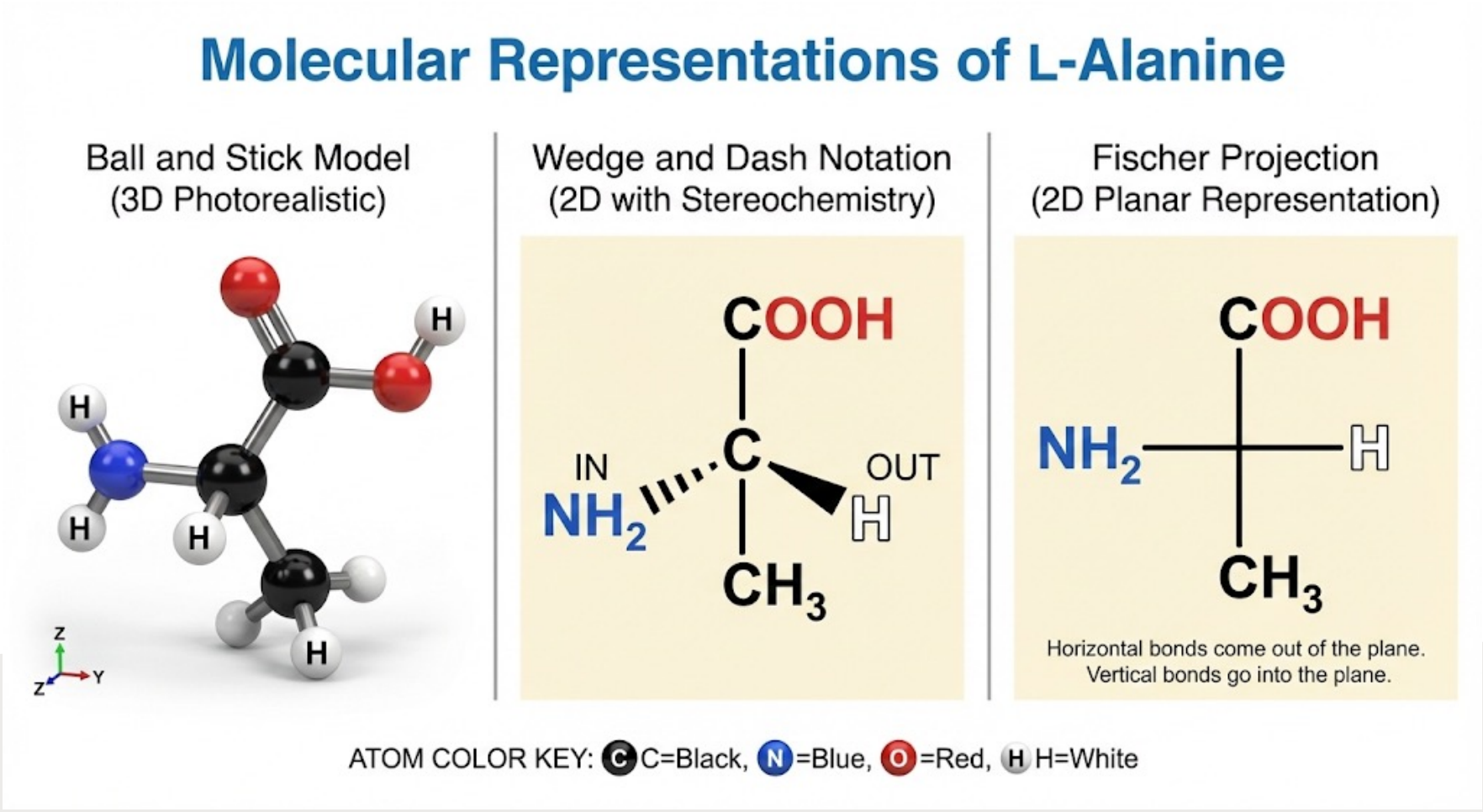
Two Different Ways of Depicting How Biomolecules Will Be Used



Fischer projection of alanine

- Fischer projections are useful for visualizing the constituent atoms of the molecule.
- Every atom is identified, and the bonds to the central atom are depicted as vertical and horizontal lines. The horizontal bonds are taken to project out of the plane toward the viewer, whereas the vertical bonds are assumed to project behind the plane away from the viewer.

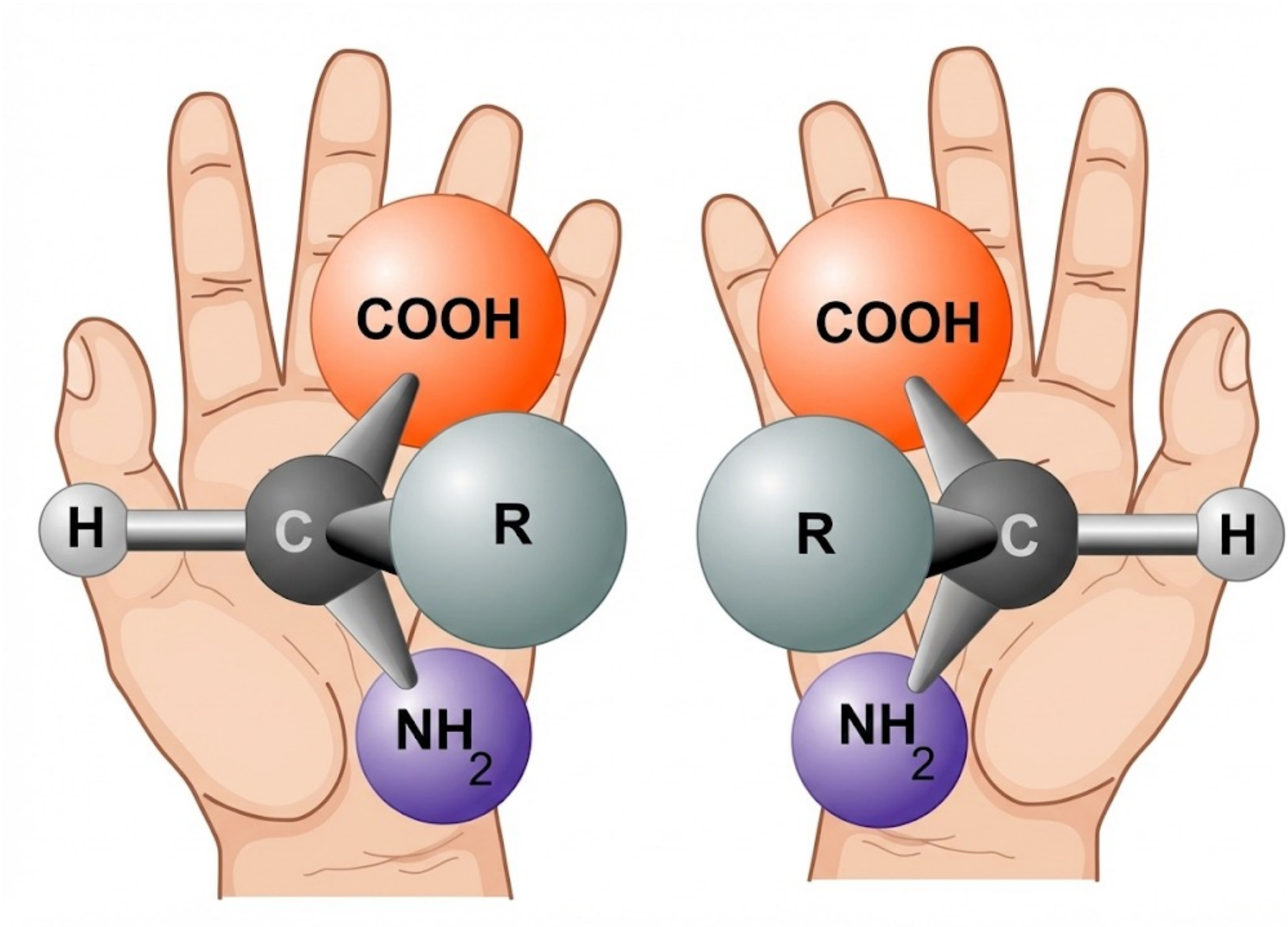




Two Different Ways of Depicting How Biomolecules Will Be Used

- Stereochemical renderings are useful for visualizing the shape of the molecule.
- Wedges are used to depict the direction of bond projection. A solid wedge shows the bond projecting toward the viewer out of the plane. A dashed wedge shows the bond projecting behind the plane, away from the viewer. The remaining bonds are depicted as straight lines.

CORN Rule for isomer orientation



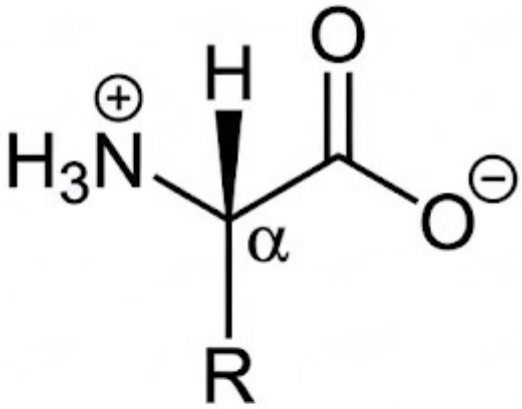
L configuration.

D configuration.

Amino Acid Ionization & Zwitterions

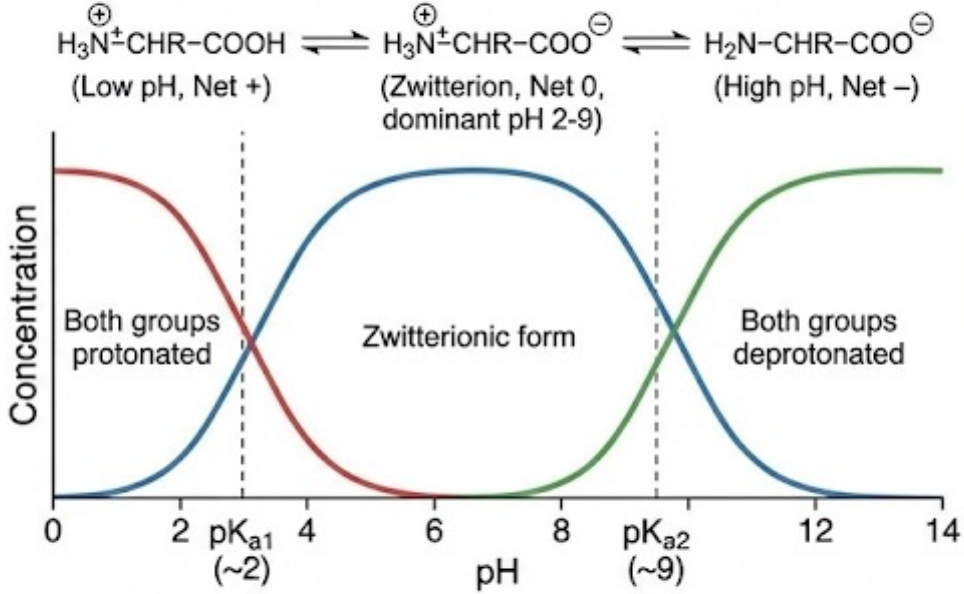
1. The Zwitterion Concept

Under physiological conditions, amino acids exist as **zwitterions** (dipolar ions with both positive and negative charges).



Amino group protonated (NH3+), Carboxyl group deprotonated (COO-).

2. Ionization & pH Dependence



Ionization varies with pH. In acid, both groups are protonated. Carboxylic acid loses proton first (pKa ~2). Zwitterion predominates until pH passes ~9. In base, amino group is deprotonated.

Sorting and Characteristics of Proteogenic Amino Acid R Groups

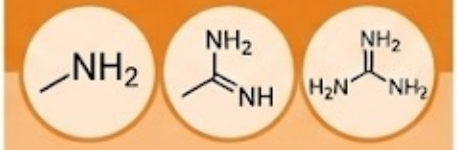
1. Hydrophobic (Nonpolar) R Groups

- Includes thioethers
- Vary in size, shape
- High hydrophobic character
- Nonpolar, no charge
- Found in protein cores.

2. Polar, Neutral R Groups

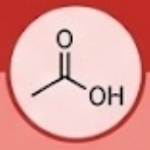
- Includes alcohols, thiols, carboxamides
- Uneven charge distribution
- Hydrogen-bonding capacity
- Chemical reactivity
- Neutral at physiological pH.

3. Positively Charged R Groups (pH ≈ 7.4)



- Variety of basic groups
- Positive charge at physiological pH
- Hydrogen-bonding capacity
- Chemical reactivity.

4. Negatively Charged R Groups (pH ≈ 7.4)

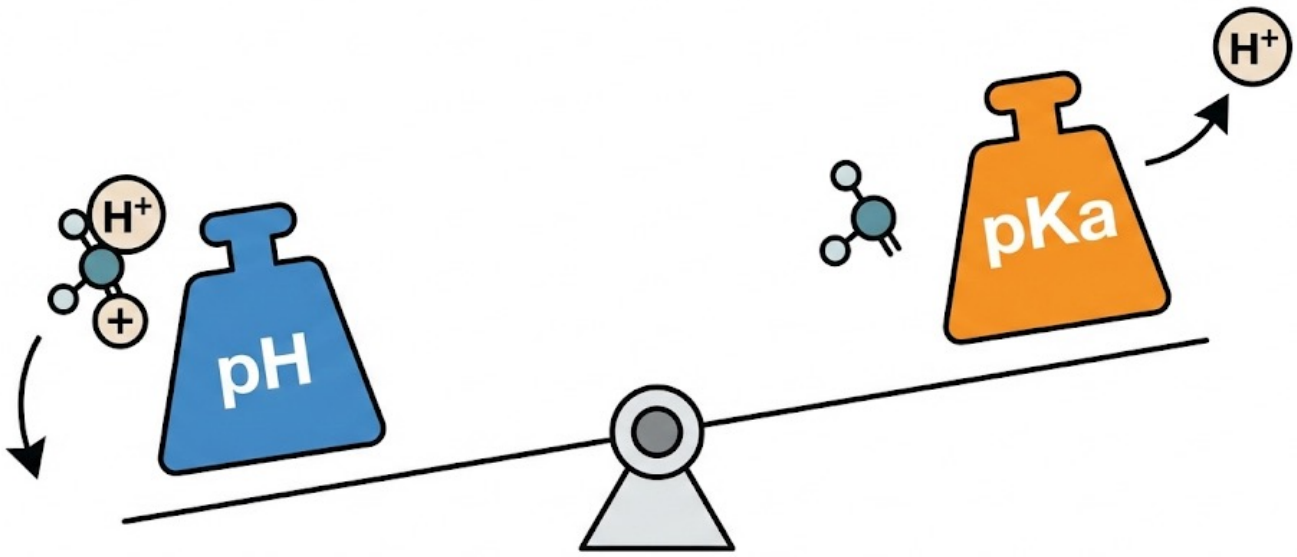


- Includes carboxylic acids
- Negative charge at physiological pH
- Hydrogen-bonding capacity
- Chemical reactivity.

- Amino acid side chains vary in size, shape, charge, hydrogen-bonding, hydrophobic character, and chemical reactivity.
- Functional groups dictate these properties.

Which R-group category would you expect in a membrane-spanning helix?

The pH/pKa Rule You'll Use Forever

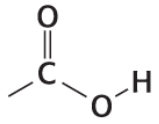
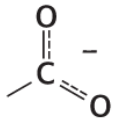
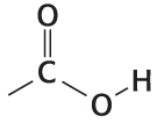
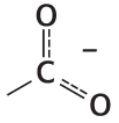
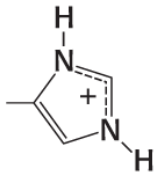
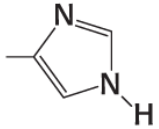
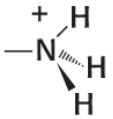
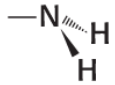
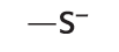
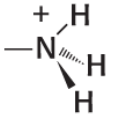
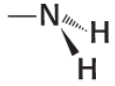
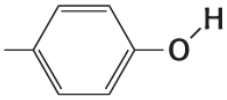
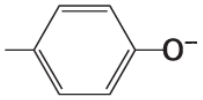
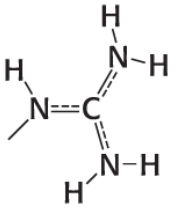
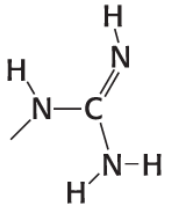


Lower pH:
Proton attached (H+)

Higher pH:
Proton flies away (H+)

The Ionizable Side Chains Enhance Reactivity and Bonding

- Seven of the 20 amino acids—tyrosine, cysteine, arginine, lysine, histidine, and aspartic and glutamic acids—have readily ionizable side chains.
- These seven amino acids are able to form ionic bonds as well as to donate or accept protons (called acid–base catalysis) to facilitate reactions.

Group	Acid	Base	Typical pK_a
Terminal α-carboxyl group			3.1
Aspartic acid Glutamic acid			4.1
Histidine			6.0
Terminal α-amino group			8.0
Cysteine			8.3
Lysine			10.8
Tyrosine			10.9
Arginine			12.5

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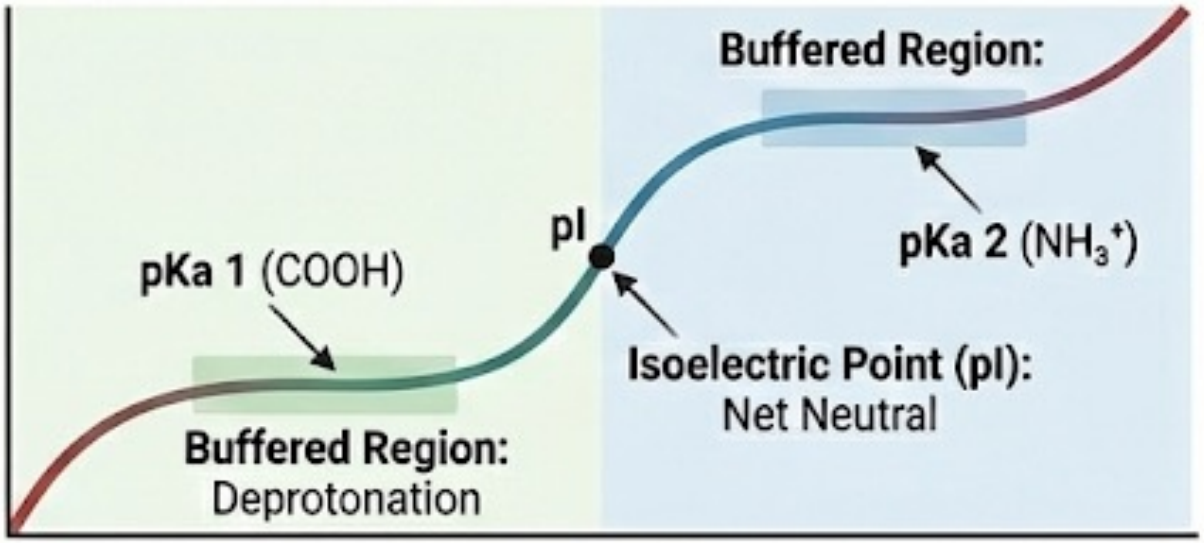
The Titration Process & Curve

Add Acid or Base
(Burette)

Monitor pH
(pH Meter)

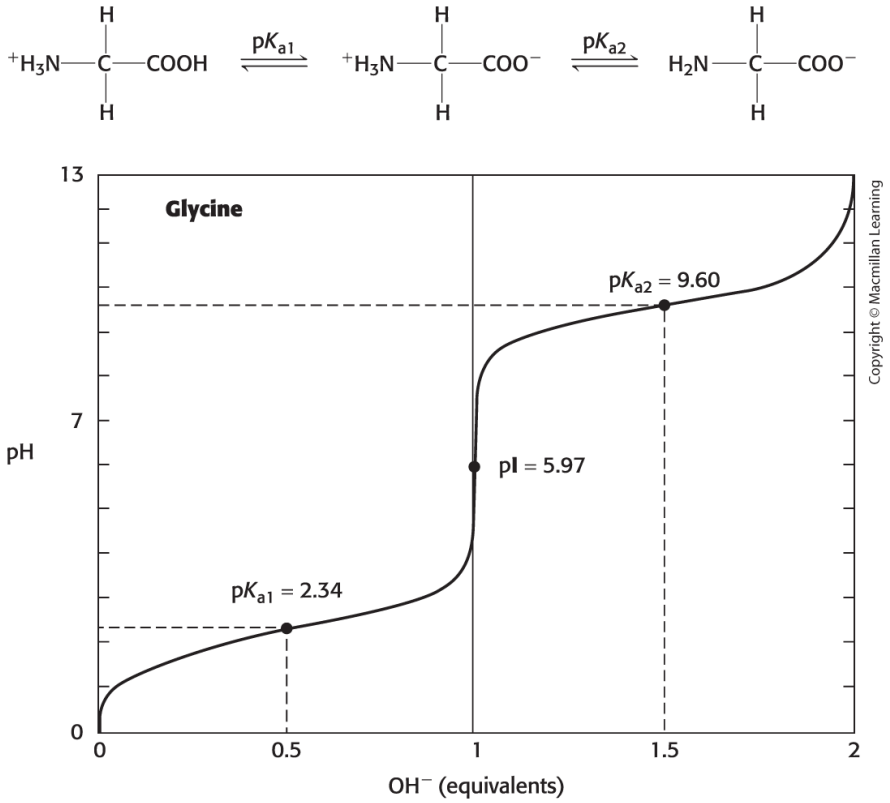
Plot Curve
(pH vs. Volume Added)



Curve reveals:

- pKa values of ionizable groups.
- Isoelectric point (pI) where net charge is zero.

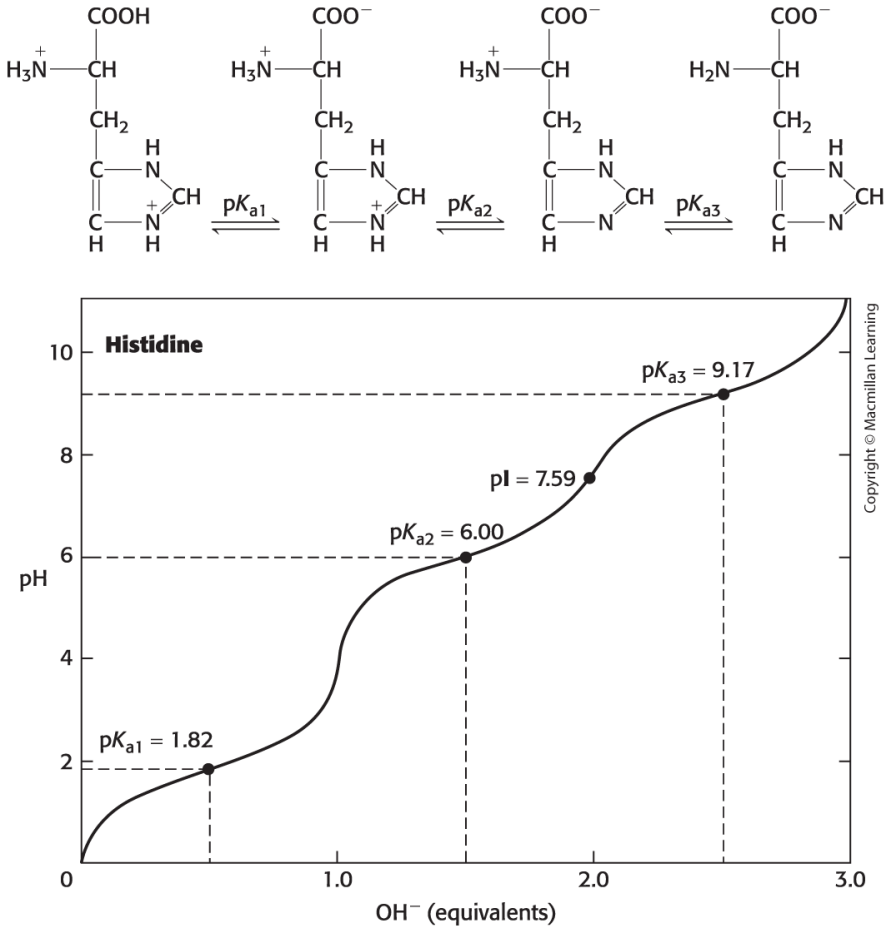
Titration of Glycine (with a strong base)



Three inflection points.

1. 2.34 = pK_a value of the carboxylate
2. 5.97 = pI value
3. 9.60 = pK_a value of the amino group

Titration of Histidine

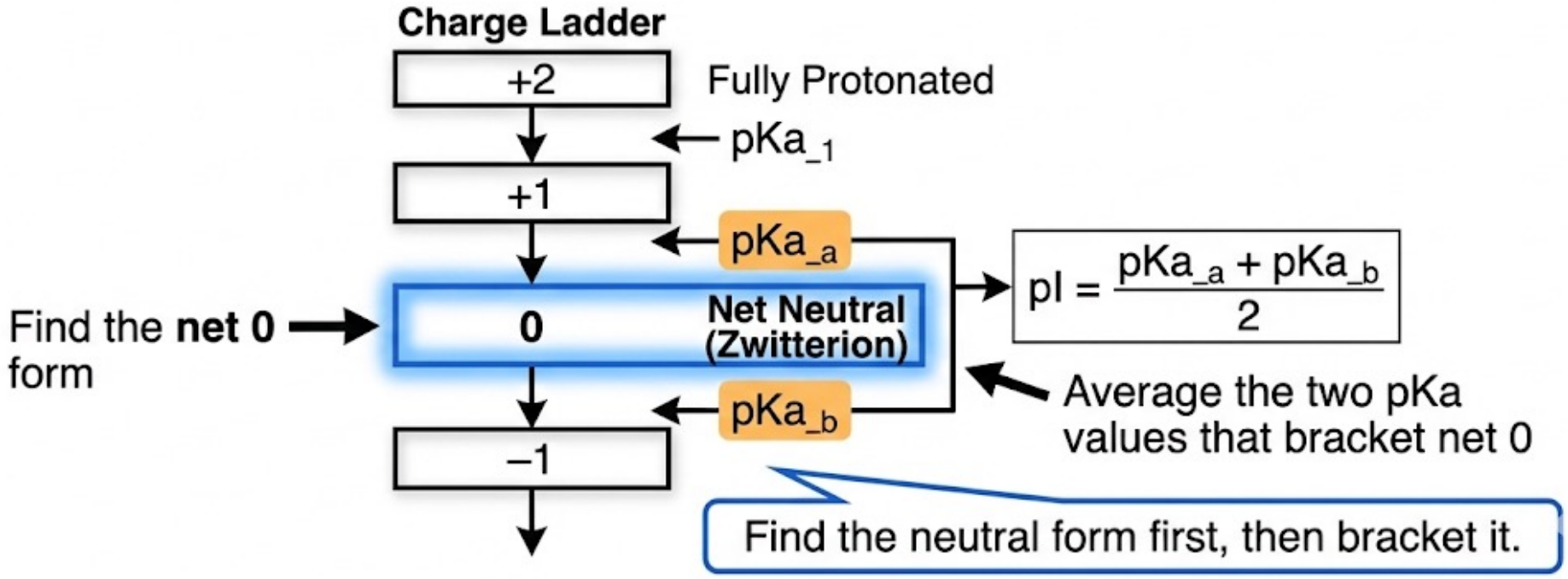


Four inflection points.

1. 1.82 = pK_a value of the carboxylate group
2. 6.00 = pK_a value of the imidazole group
3. 7.59 = pI value
4. 9.17 = pK_a value of the amino group

pI shortcut rule (when there is an ionizable side chain)

- Identify the neutral (net 0) species on the charge ladder
- pI is between the two pK_a values that bracket that neutral species
- For amino acids with an ionizable side chain, average the two like-charged pK_a values
- Sanity check: pI must fall between two pK_a values



Remember!

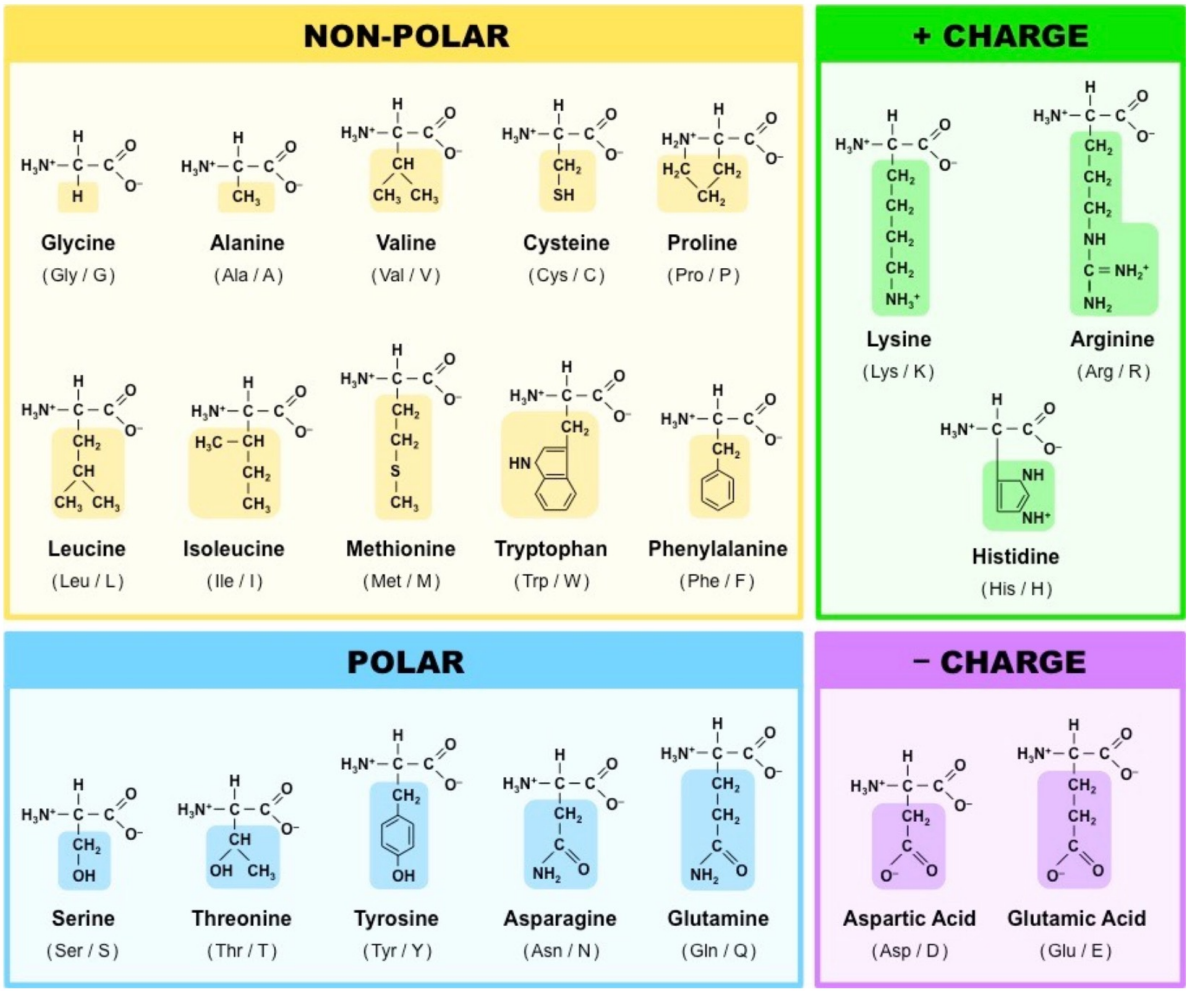
All amino acids can exist in one of several varying charged or uncharged states.

An amino acid's predominate state depends on

1. the pK_a values of the amino acid's various functional groups, and
2. the pH of the solution the amino acid is in.

Section 3.2 Amino Acids Contain a Wide Array of Functional Groups

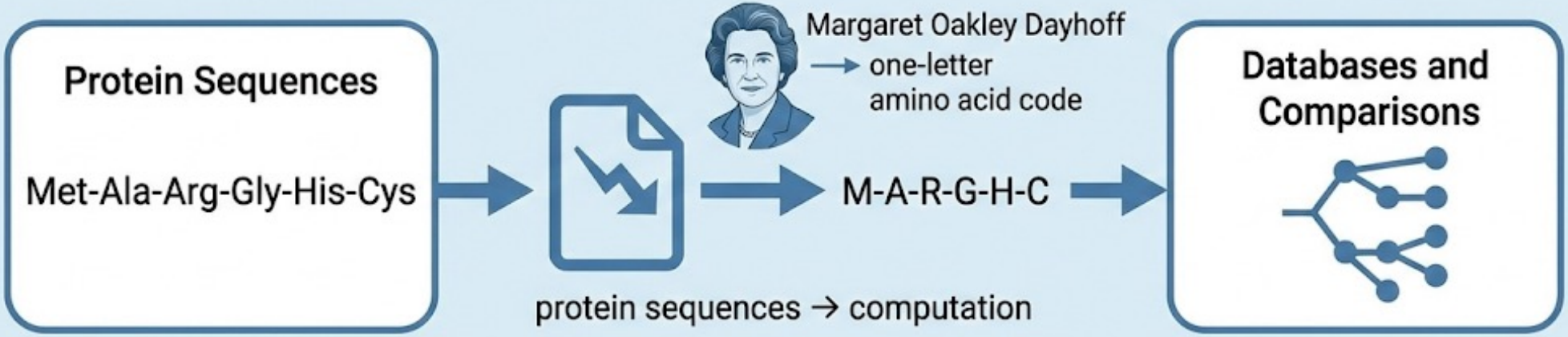
- The 20 amino acids found in proteins contain unique side chains that vary in size, shape, charge, hydrogen-bonding capacity, hydrophobic character, and chemical reactivity.
- Amino acids have three-letter abbreviations and one-letter symbols.
- Amino acids can be sorted into four groups on the basis of the general characteristics of their R groups:
  - Hydrophobic amino acids (non-polar)
  - Polar amino acids (hydrophilic)
  - Positively charged amino acids (hydrophilic)
  - Negatively charged amino acids (hydrophilic)



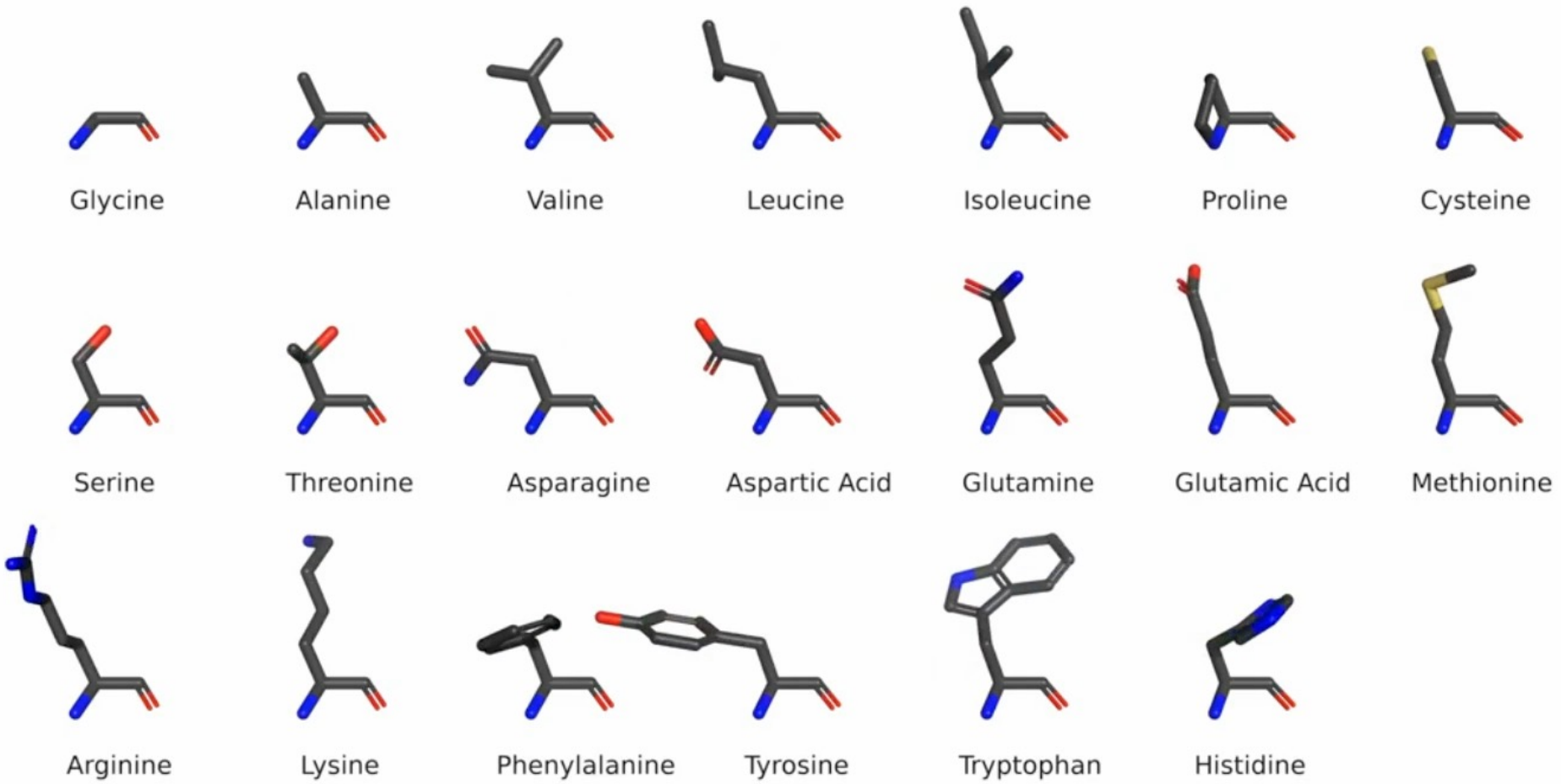
What you need to know: R-group structure, 3 letter abbreviation, one letter ab., property

Why one-letter codes exist: Dayhoff and early bioinformatics

- Protein sequences became data before “biology as data” was fashionable
- Margaret Oakley Dayhoff helped standardize protein sequence handling
- One-letter codes helped shrink early storage and simplify computation
- This enabled early comparisons of sequences and evolutionary relationships



The alphabet exists because proteins became information.



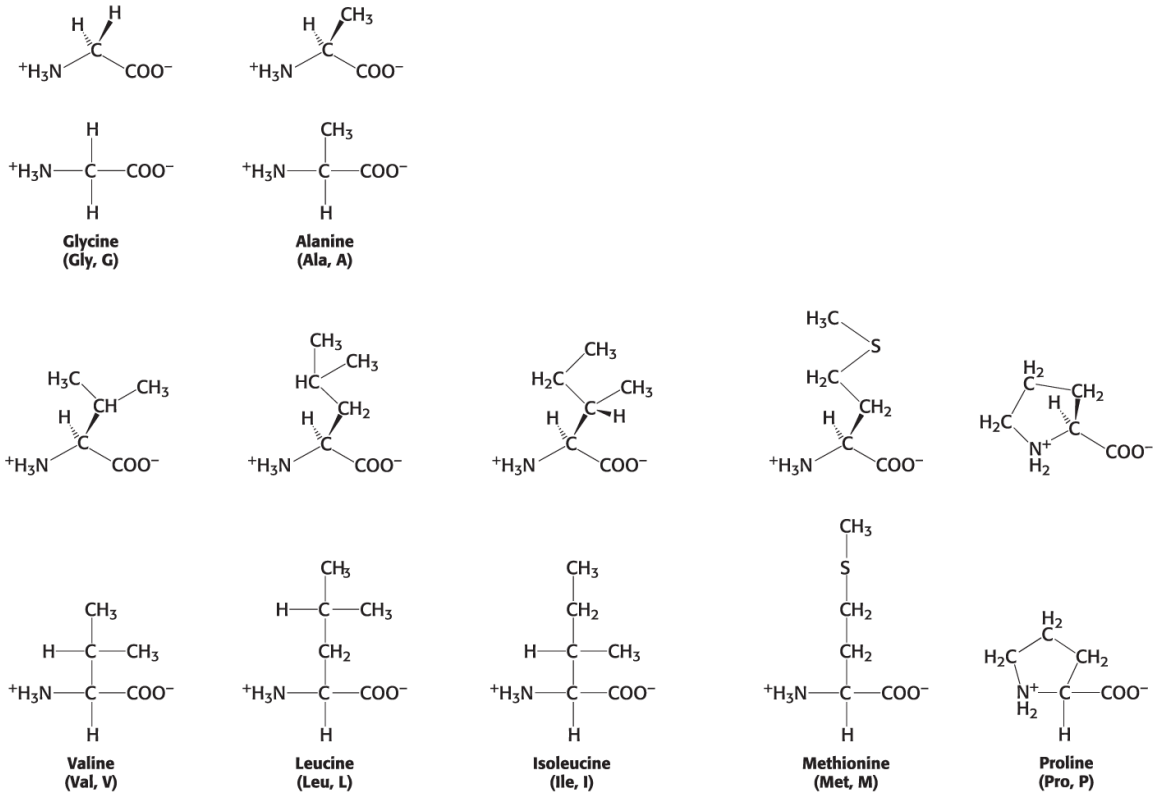
Why is glycine found at tight turns in proteins?

Hydrophobic Amino Acids Have Mainly Hydrocarbon Side Chains

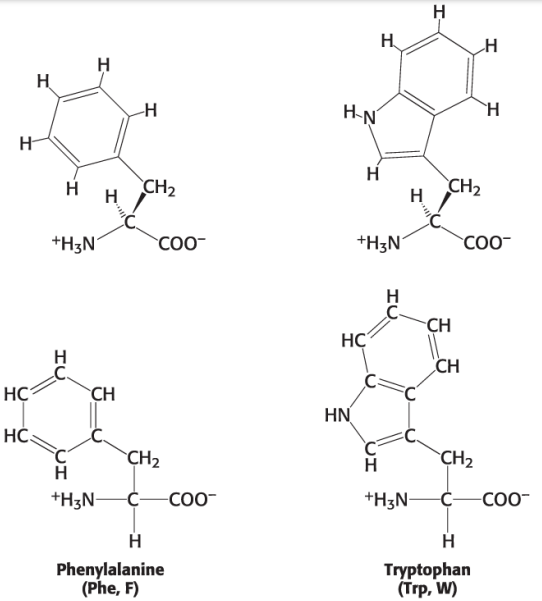
- The amino acids having side chains consisting only of hydrogen and carbon are hydrophobic.
- The hydrophobic amino acids, particularly the larger aliphatic and aromatic ones, tend to cluster together inside the protein away from the aqueous environment of the cell.

hydrophobic amino acids

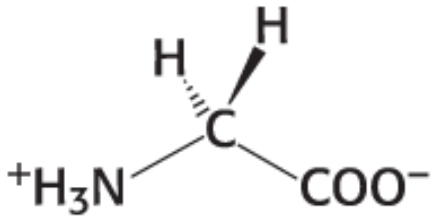
Alkyl

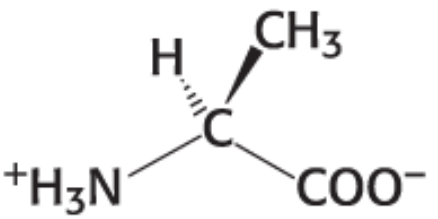


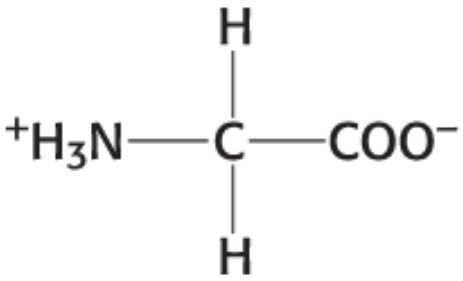
Aromatic



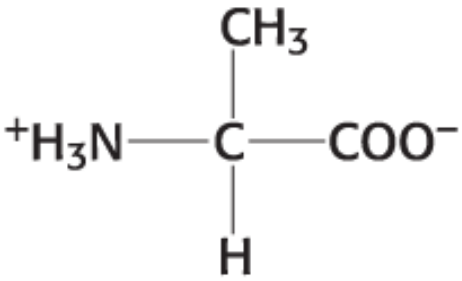
Small Hydrophobic Amino Acids Glycine and Alanine



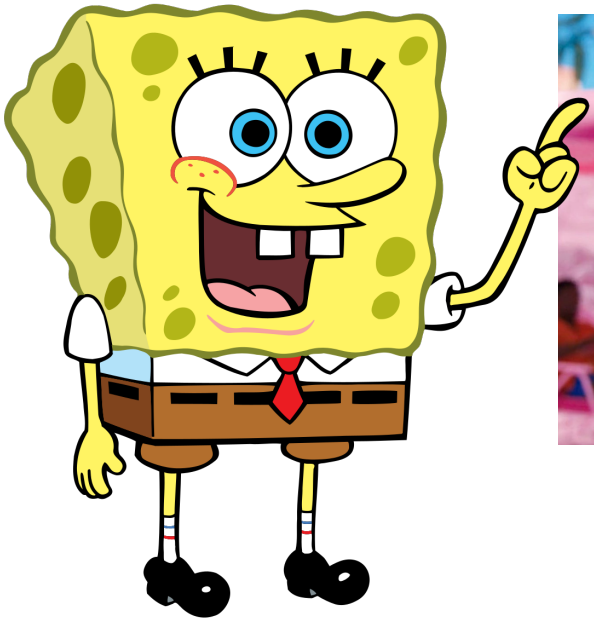




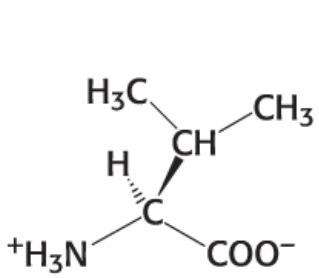
Glycine (Gly, G)

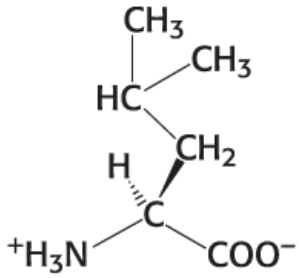


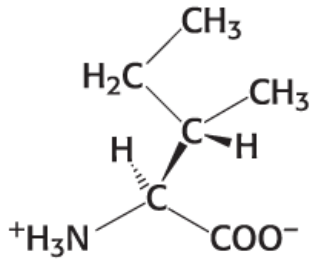
Alanine (Ala, A)

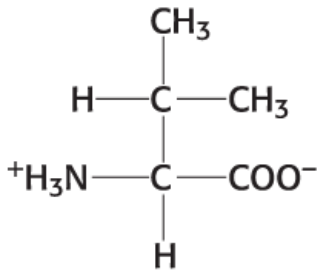


Hydrophobic Amino Acids Valine, Leucine, and Isoleucine

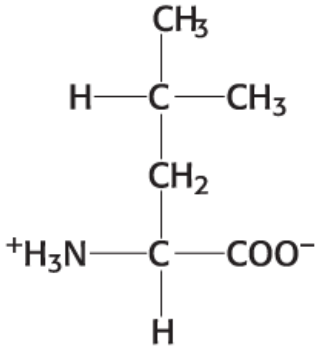




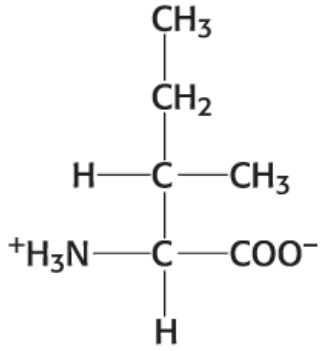




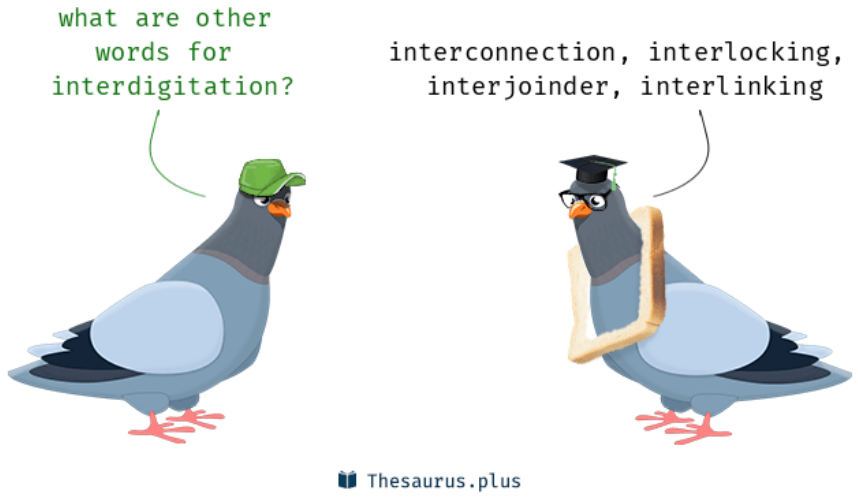
Valine
(Val, V)



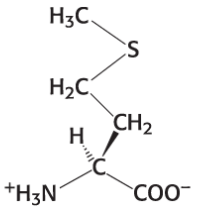
Leucine
(Leu, L)

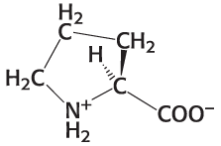


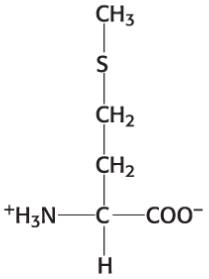
Isoleucine
(Ile, I)



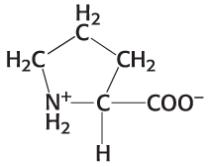
Hydrophobic Amino Acids Methionine, Proline, Phenylalanine, and Tryptophan



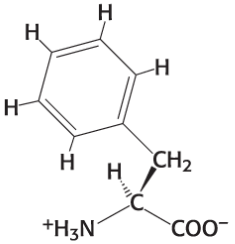


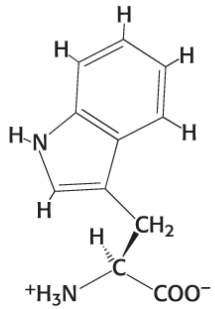


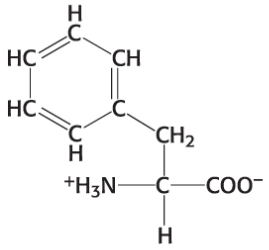
Methionine
(Met, M)



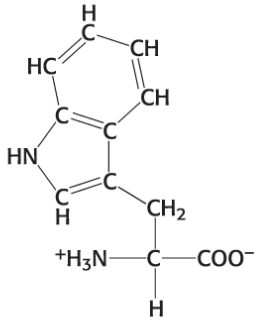
Proline
(Pro, P)







Phenylalanine
(Phe, F)

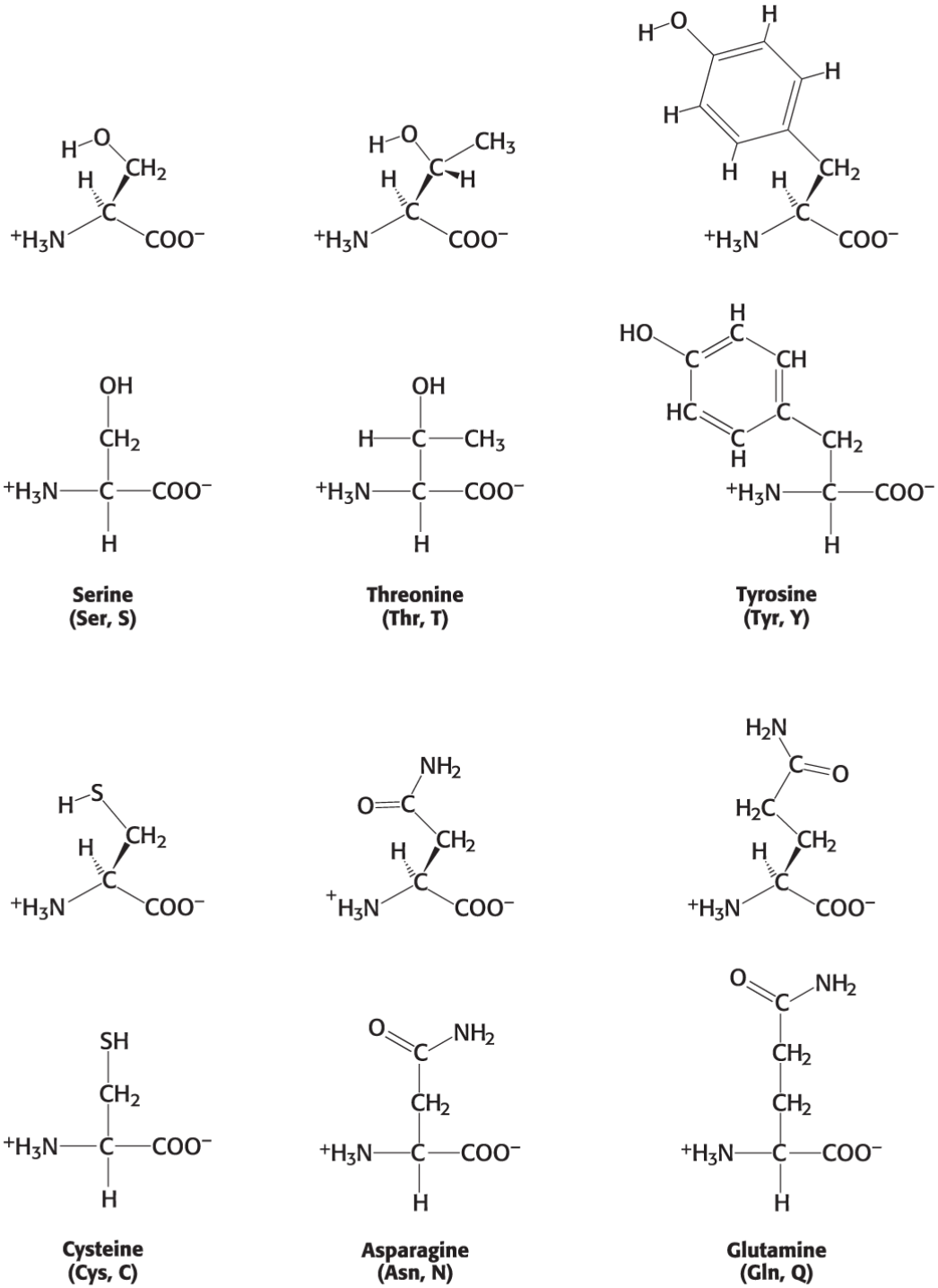


Tryptophan
(Trp, W)

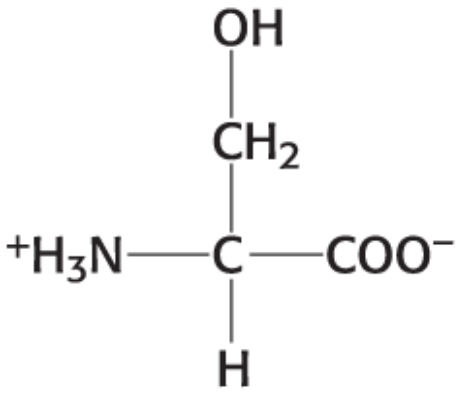
Break

Polar Amino Acids Have Side Chains That Contain an Electronegative Atom

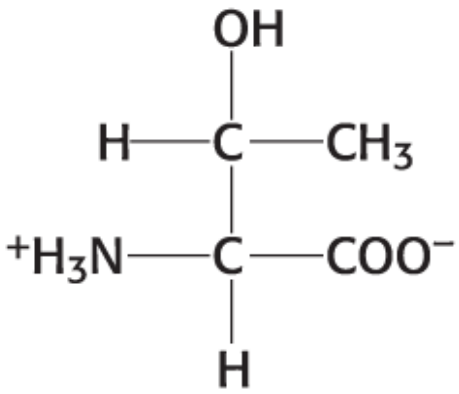
- Polar amino acids are neutral overall, yet they are polar because the R group contains an electronegative atom that hoards electrons.
- Glutamine plays a number of important roles in rapidly dividing cells, including cancer cells. In addition to being used in protein synthesis, glutamine enhances fuel metabolism by providing components for the TCA cycle, which oxidizes carbon fuels. Glutamine also provides nitrogens for the synthesis of nucleotides, which are required for RNA and DNA synthesis



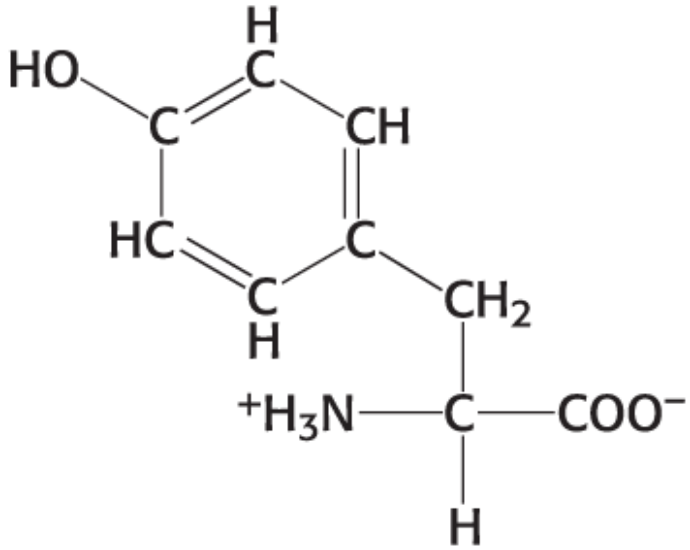
Polar Amino Acids Serine, Threonine, and Tyrosine



Serine
(Ser, S)

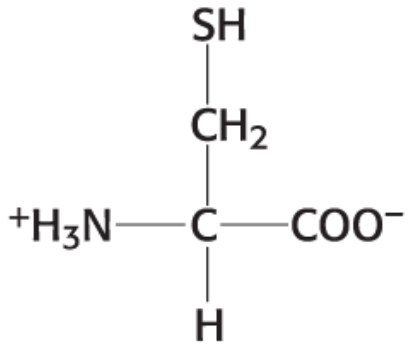


Threonine
(Thr, T)

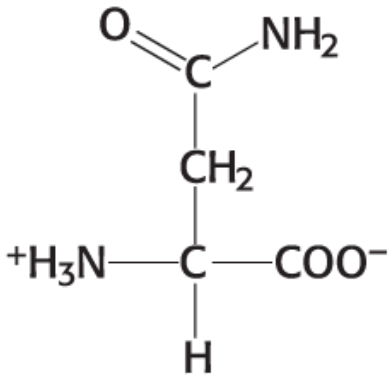


Tyrosine
(Tyr, Y)

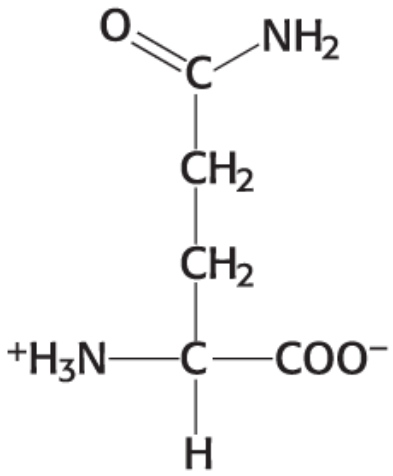
Polar Amino Acids Cysteine, Asparagine, and Glutamine



Cysteine
(Cys, C)



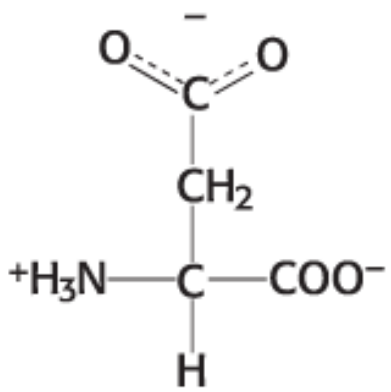
Asparagine
(Asn, N)



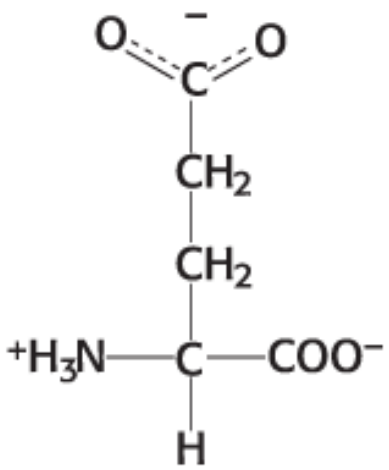
Glutamine
(Gln, Q)

Charged Amino Acids

Negative

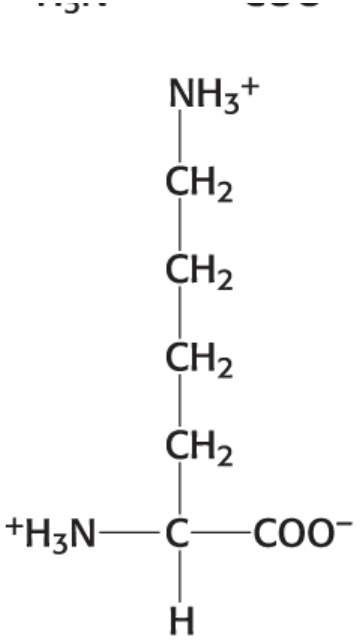


Aspartate
(Asp, D)

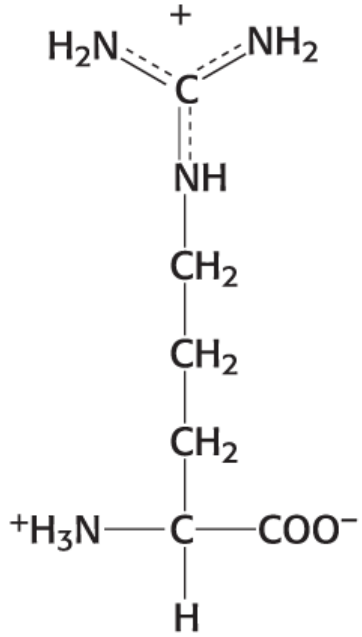


Glutamate
(Glu, E)

Positive



Lysine
(Lys, K)

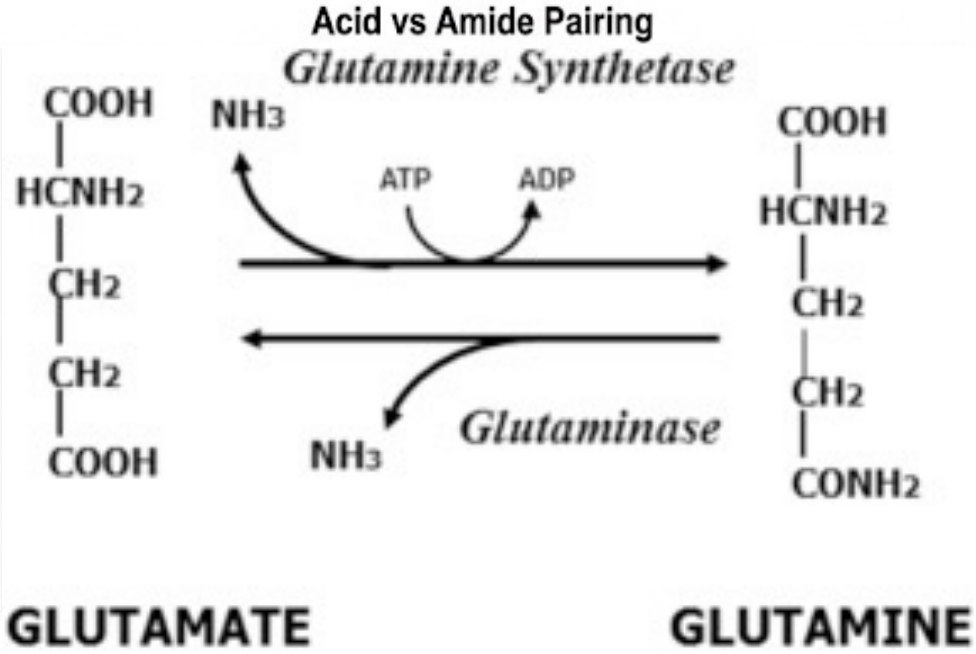


Arginine
(Arg, R)

Aspartate and Glutamate: the names are a hint

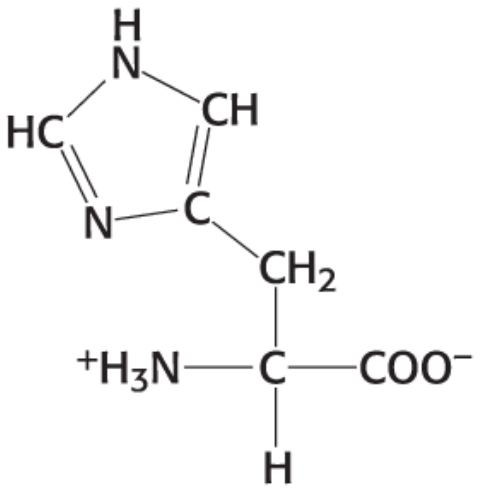
- At physiological pH, Asp and Glu side chains are usually deprotonated (negative)
- “Aspartate / glutamate” emphasizes charged form (not the acid)
- Asp/Glu are to Asn/Gln as carboxylate is to carboxamide
- This naming helps you predict net charge fast

“-ate” is your reminder: negative at pH ~7.4.



What pKa would be ideal for a catalytic residue?

Histidine: The Most Important Charged Amino Acid You've Never Heard Of

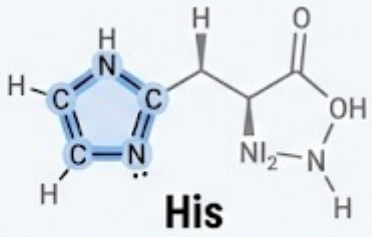


Histidine
(His, H)

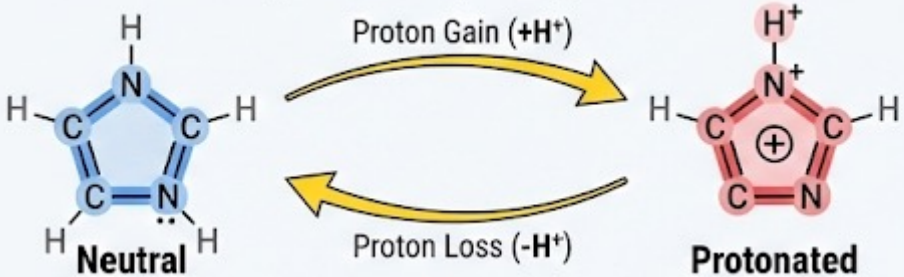
- pKa ~6.0 → can be + or neutral at physiological pH
- - "This makes His the Swiss Army knife of catalysis"
- - Preview: hemoglobin, enzymes, metal binding

Histidine: The pKa Shape Shifter

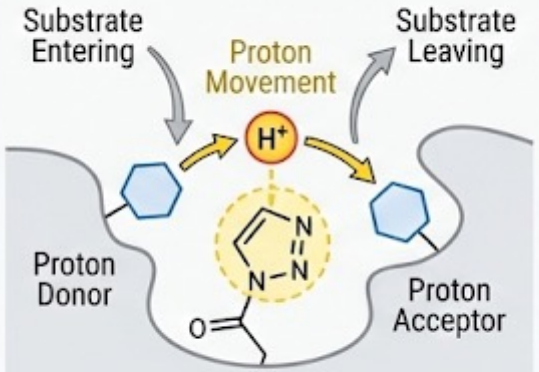
Why one amino acid changes everything in enzyme chemistry



pKa Concept Diagram



Histidine in Action

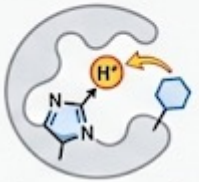


Histidine as a proton shuttle

Why histidine is the exam question residue:

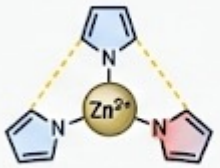
Its pKa is uniquely close to physiological pH;
It toggles charge states with tiny environmental shifts;
It enables catalysis, signaling, pH sensing, and metal binding.

Why This Matters

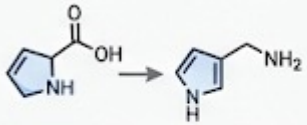


Acid/Base Catalysis

pH Sensor
Local pH Sensitivity



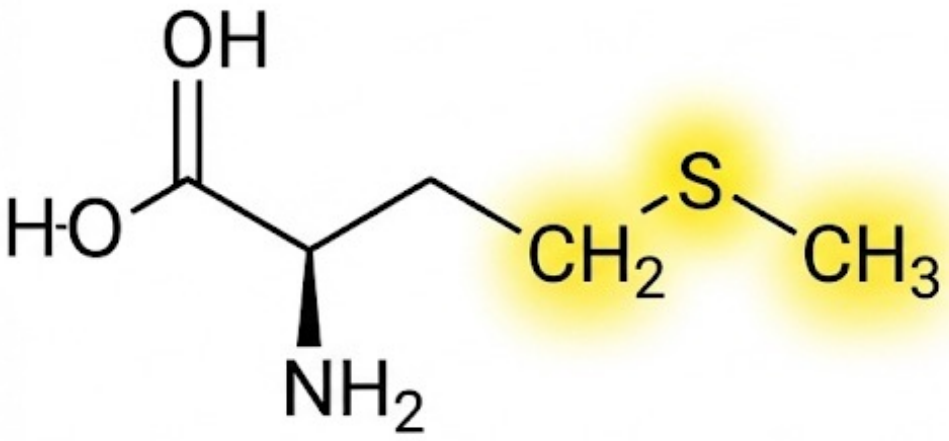
Metal Binding
Metal Coordination



Precursor to Histamine
Histamine Pathway

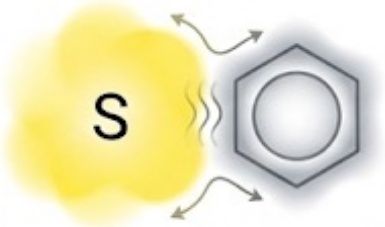
Sulfur containing amino acids

Why Methionine Has Sulfur



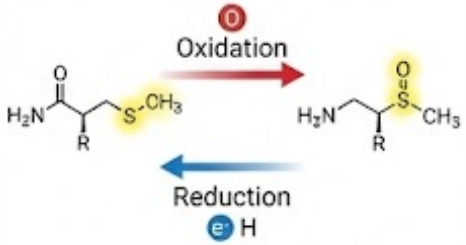
Methionine (Met)

Soft and Polarizable



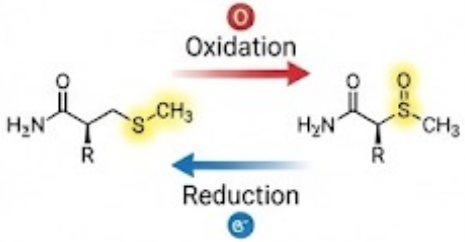
Sulfur allows adaptable packing and subtle interactions.

Reversible Oxidation



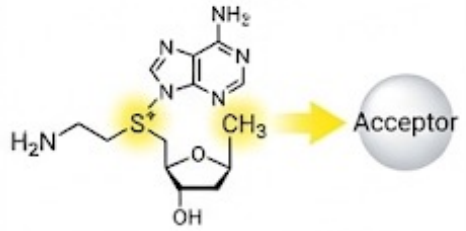
Acts as a mild oxidative stress buffer.

Reversible Oxidation



Acts as a mild oxidative stress buffer.

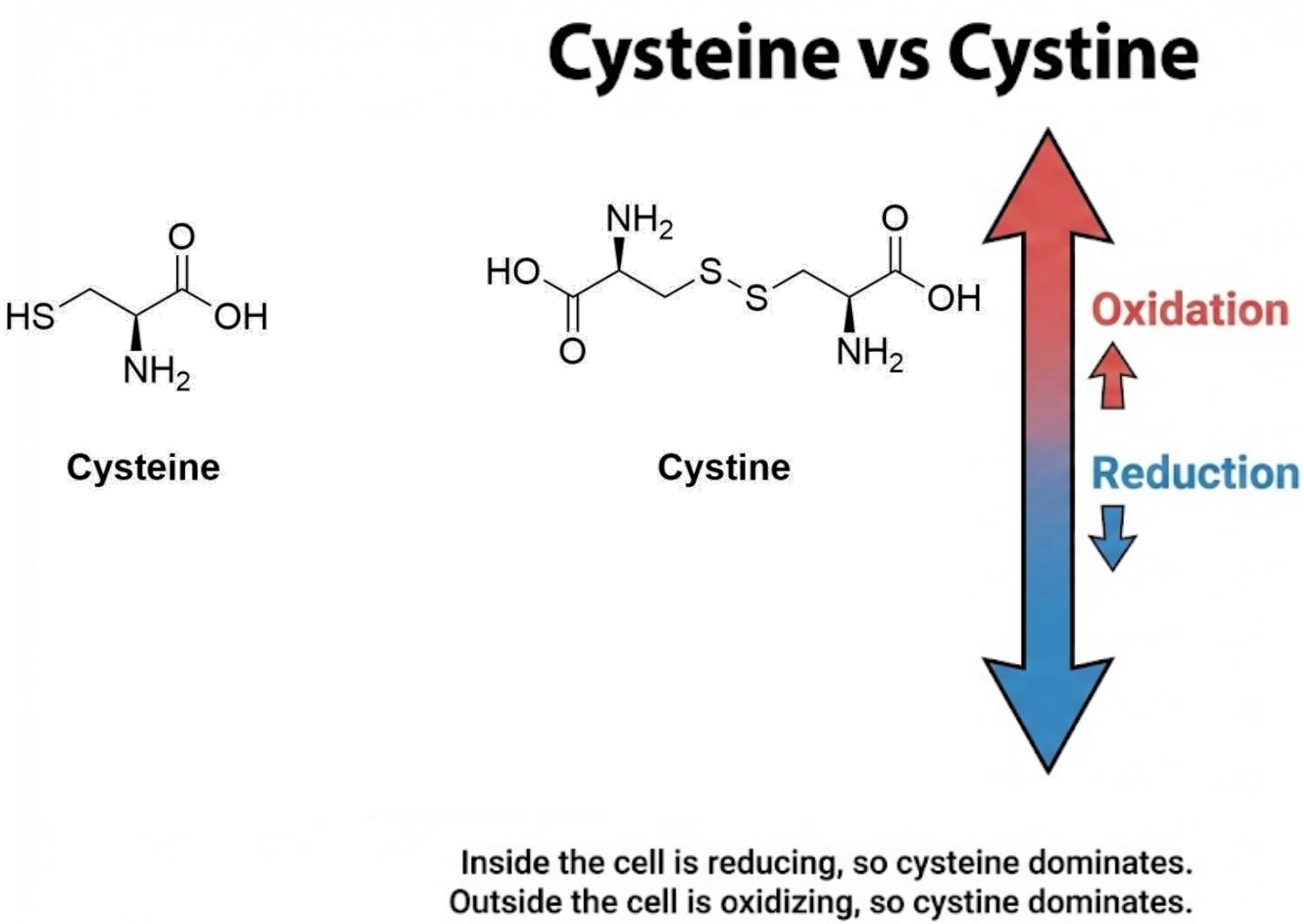
Source of SAM



Methionine becomes SAM, the universal methyl donor.

Sulfur gives methionine flexibility, mild redox activity, and metabolic significance.

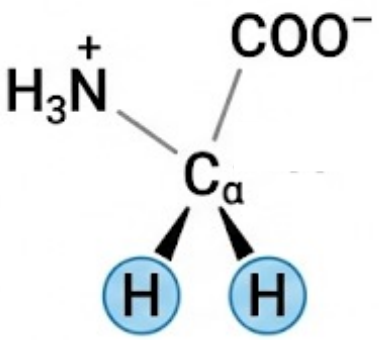
Sulfur containing amino acids



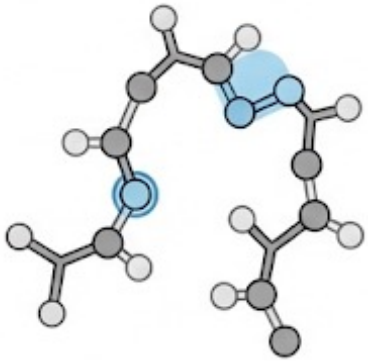
Why does your hair hold a curl after a perm?
Where do disulfide bonds form in the cell?

The Two Exceptions: Glycine and Proline

Glycine

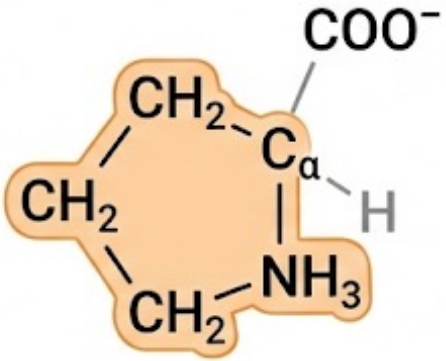


Achiral: R group is H.

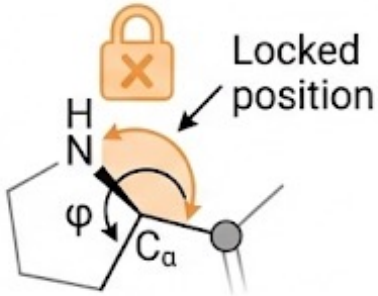


Allows extreme flexibility.

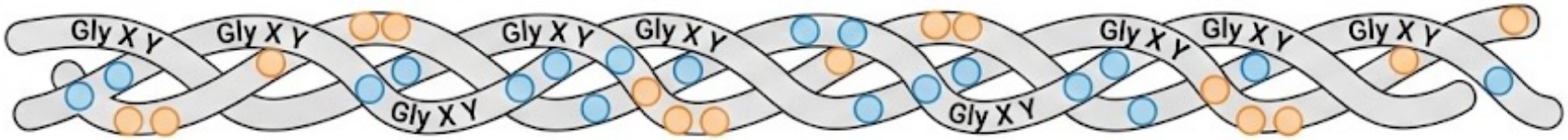
Proline



Rigid cyclic structure.



Restricted phi rotation.



Collagen relies on glycine for tight packing and proline for structural kinks.

Quick Quiz

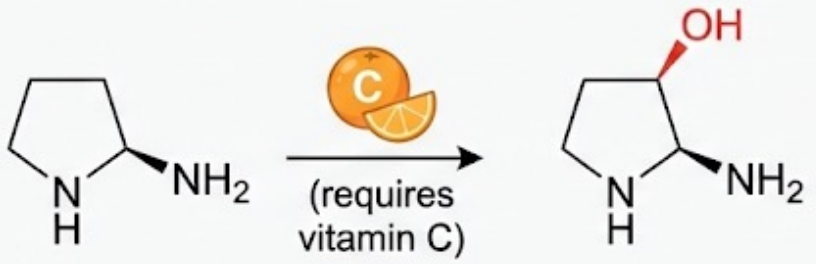
QUICK QUIZ Name three amino acids that are positively charged at neutral pH. Name three amino acids that contain hydroxyl groups.

Rule: 20

Exceptions

Exceptions and add-ons: amino acids beyond “the 20”

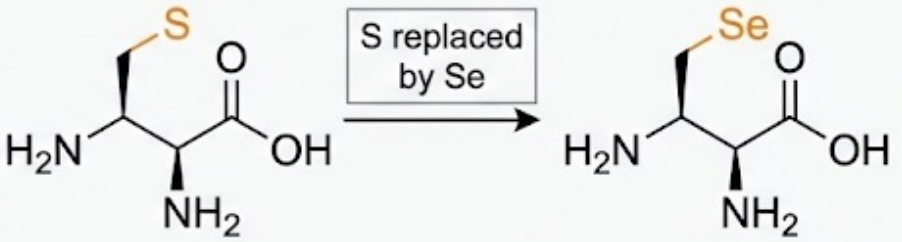
Modified after protein synthesis



Proline

Hydroxyproline
(requires vitamin C)

Rare encoded exception

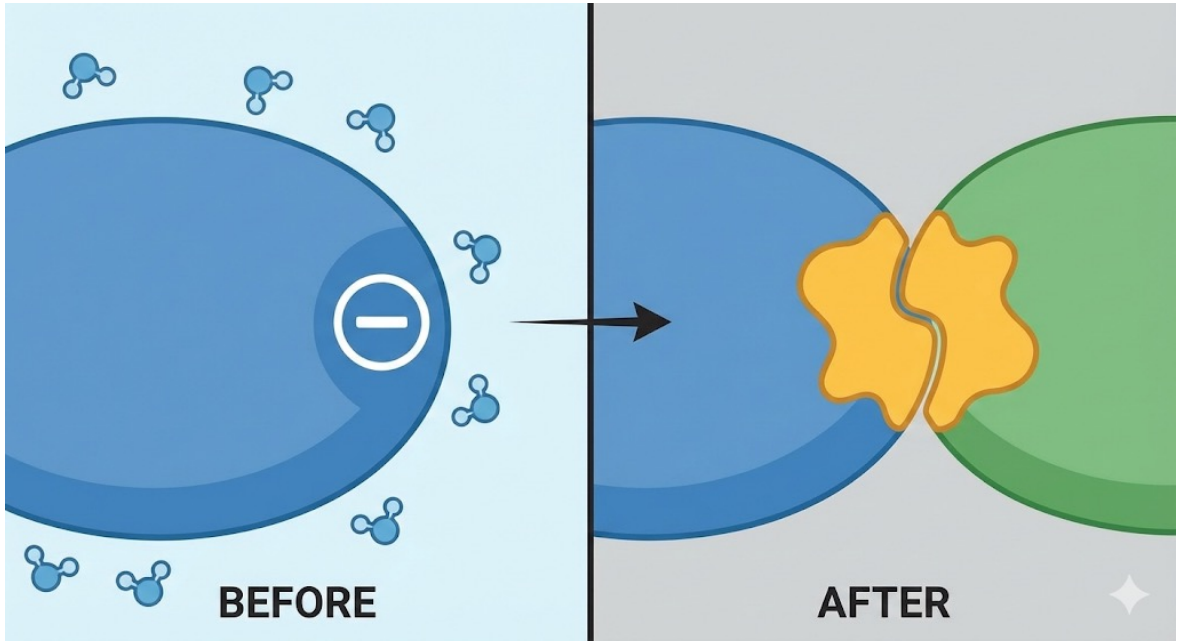


Cysteine

Selenocysteine
(often called the 21st)

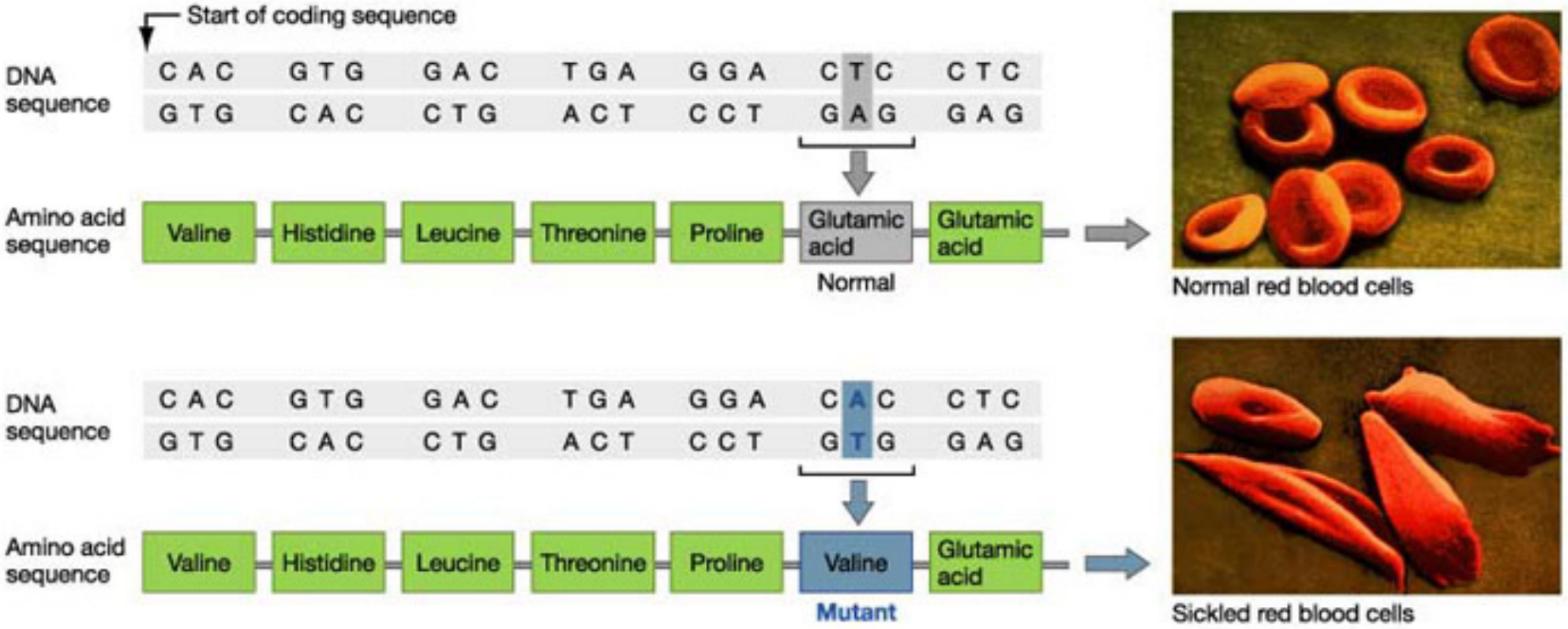
The rule is 20, biology still keeps a few weird receipts.

Return to the Mystery



- "You now know: R-groups determine properties"
- "Charge depends on pH”
- "One change can flip hydrophilic → hydrophobic"
- "Let's solve the sickle cell case."

Changes to amino acids underlie most genetic disorders

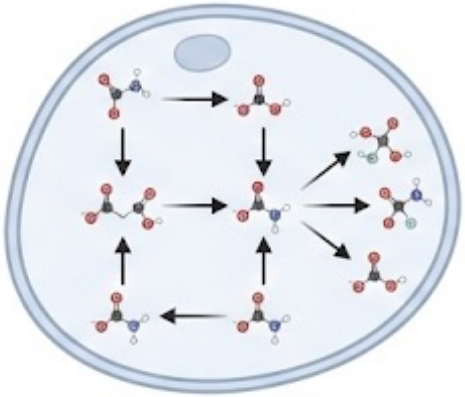


The change in amino acid sequence causes hemoglobin molecules to crystallize when oxygen levels in the blood are low. As a result, red blood cells sickle and get stuck in small blood vessels.

Essential vs Nonessential Amino Acids

Nonessential Amino Acids

- Alanine
- Arginine*
- Asparagine
- Aspartate
- Cysteine*
- Glutamate
- Glutamine
- Glycine
- Proline*
- Serine
- Tyrosine*



Body can synthesize.

Must come from diet.

Essential Amino Acids

- Histidine
- Isoleucine
- Leucine
- Lysine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine

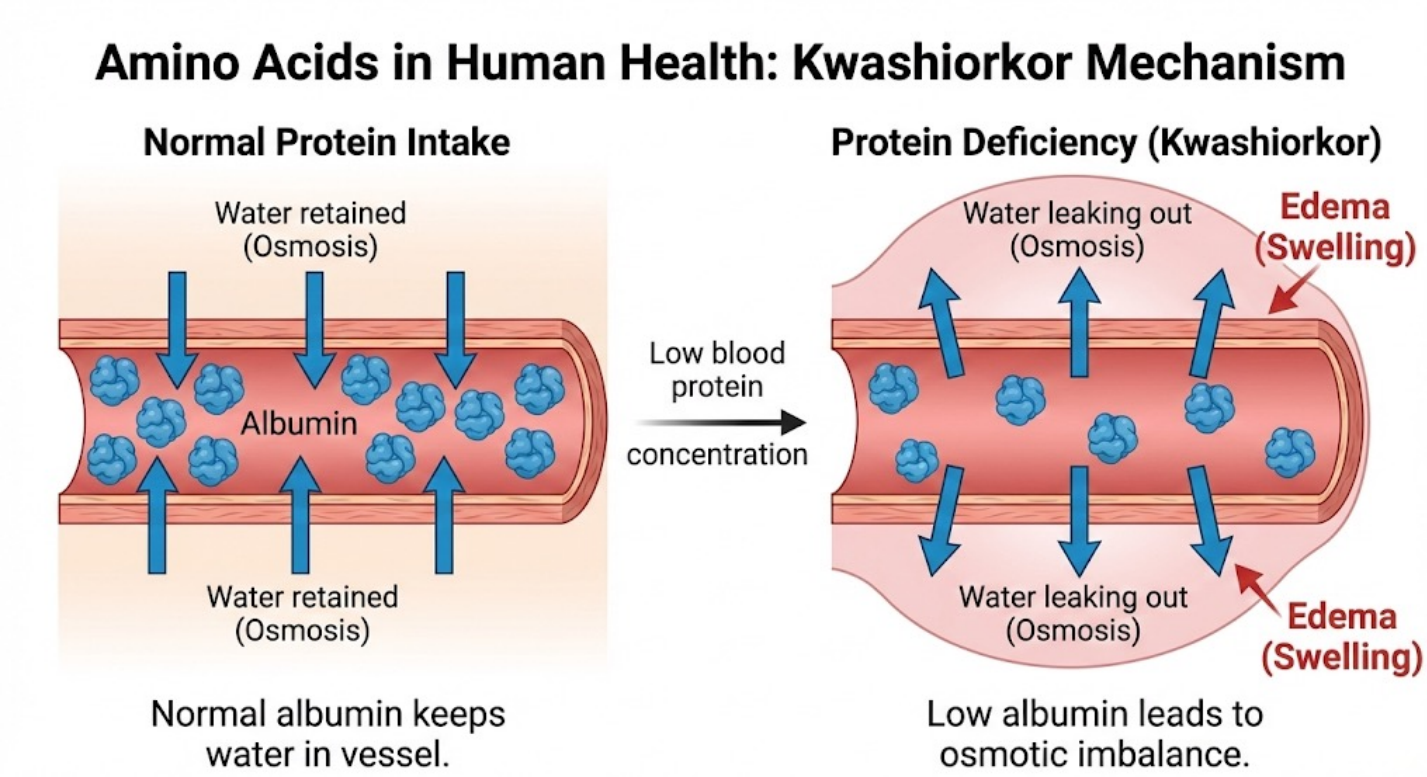
*Conditionally essential under stress or growth.

All 20 amino acids matter. Essential ones must be eaten. Nonessential ones the body makes as needed.

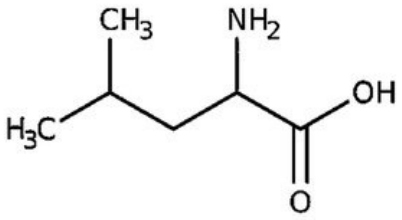
Section 3.3 Essential Amino Acids Must be Obtained from the Diet

- Most microorganisms can synthesize the entire basic set of 20 amino acids, whereas human beings can make only 11 of them.
- Amino acids that cannot be generated in the body must be supplied by the diet and are termed *essential amino acids*. The others are called nonessential amino acids.
- Kwashiorkor is a form of malnutrition resulting from inadequate consumption of amino acids usually ingested as proteins.

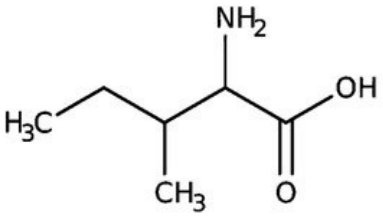
Mauro Fermariello/Science Source.



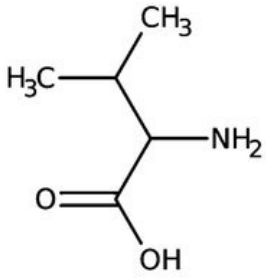
Branch chain amino acids



Leucine



Isoleucine



Valine

- BCAAs have several important roles in the body:
- **Protein synthesis and muscle growth**: Leucine, in particular, has been shown to stimulate the synthesis of muscle protein. For this reason, BCAAs, especially leucine, are often used as dietary supplements to stimulate muscle growth and enhance athletic performance.
- **Energy production**: During prolonged exercise, BCAAs can be broken down in muscle to provide an additional energy source.
- **Glucose homeostasis**: BCAAs, especially valine and isoleucine, can promote glucose uptake by muscles, helping to maintain blood sugar levels.
- **Preventing muscle wasting**: BCAAs can help to prevent protein breakdown and muscle wasting, particularly in individuals who are bedridden or suffering from diseases like cancer or AIDS.

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