CHEM 153A Week 2

Aidan Jan

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Ionization Constants

- The tendency for any acid (HA) to lose a proton and form its conjugate base (A^-) is defined by the equilibrium constant (K_{eq}) for the reversible reaction

$$HA \rightleftharpoons H^+ + A^-$$

for which

$$K_{eq} = \frac{[H^+][A^-]}{[HA]} = K_a$$

Acid Strength Comparison: K_a and pK_a Values of Common Acids

No.	**Acid**	K_a	pK_a
1	Hydroiodic acid (HI)	3.16×10^9	-9.5
2	Hydrobromic acid (HBr)	1.0×10^9	-9
3	Hydrochloric acid (HCl)	1.0×10^6	-6
4	Sulfuric acid (H_2SO_4)	1.0×10^3	-3
5	Hydronium ion (H_3O^+)	55	-1.74
6	Nitric acid (HNO_3)	28.2	-1.45
7	Trifluoroacetic acid (CF_3COOH)	5.62×10^{-1}	0.25
8	Oxalic acid (HOOC-COOH)	5.37×10^{-2}	1.27
9	Acetic acid (CH_3COOH)	1.75×10^{-5}	4.76

pK_a

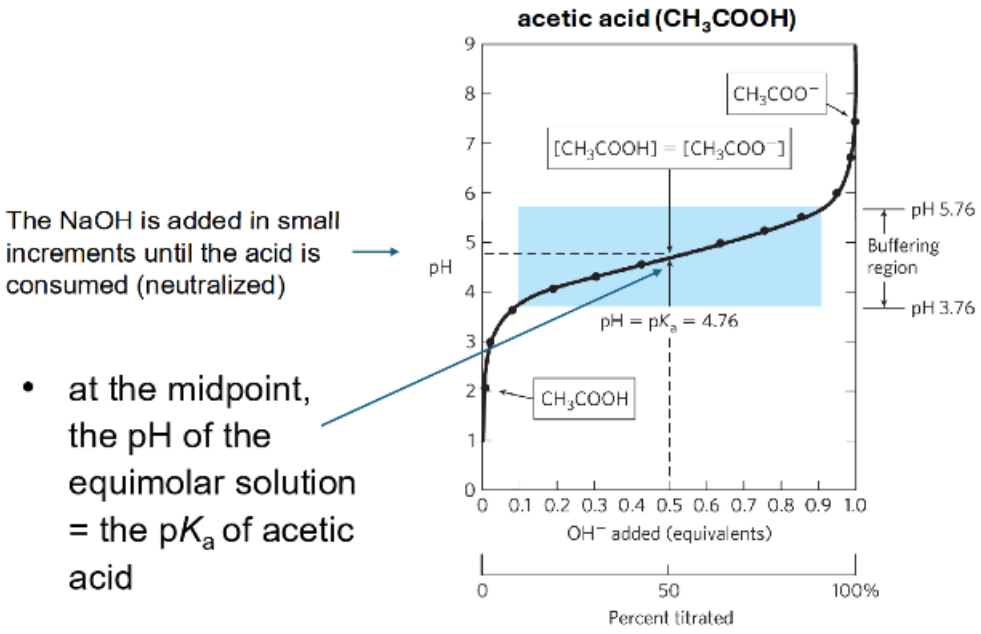
- pK_a= analogous to pH and defined by the equation

$$pK_a = \log \frac{1}{K_a} = -\log K_a$$

- the stronger the tendency to dissociate a proton, the **stronger the acid** and **the lower its pK_a**
- p$K_a$can be determined experimentally

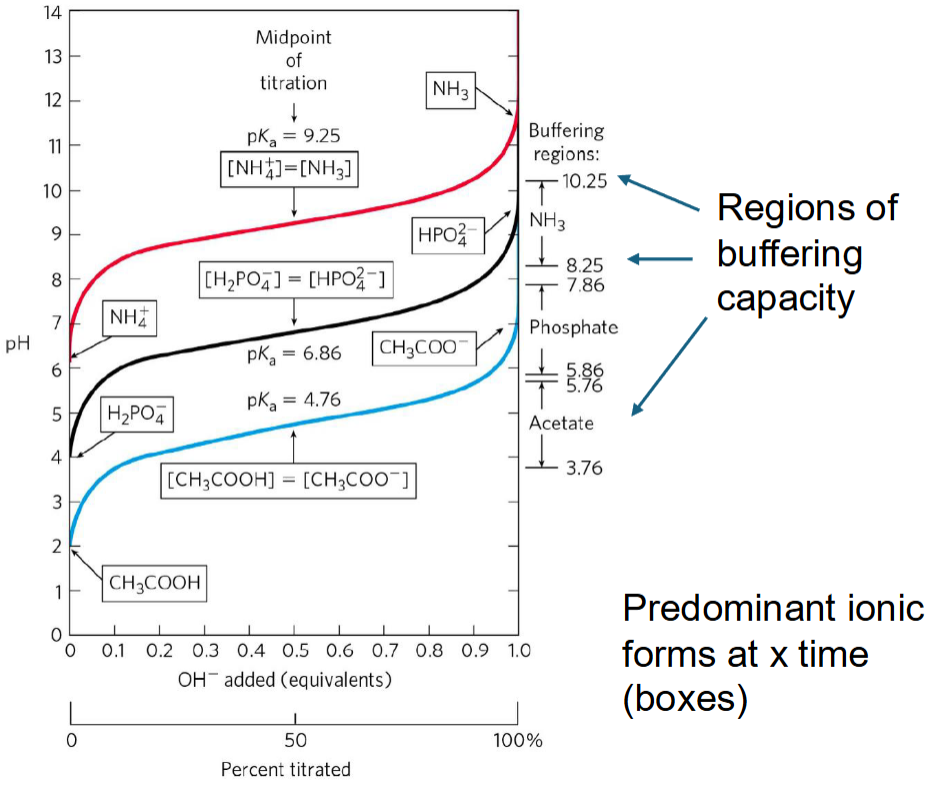
Titration Curves Reveal the p$K_a$of Weak Acids

- titration curve = a plot of pH against the amount of OH equivalents added



Comparison of the Titration Curves of Three Weak Acids

- a **weak acid** and its anion - a conjugate acid-base pair - can act as a **buffer**
- Titration curves for acetic acid, dihydrogen phosphate, and ammonium are shown below
- **Conjugate acid-base pairs are effective buffers between approximately 10% and 90% neutralization of the proton donor species**



Buffers are Mixtures of Weak Acids and Their Conjugate Bases

- buffers = aqueous systems that tend to resist changes in pH when small amounts of acid (H^+) or base (OH^-) are added
- a buffer system consists of a weak acid (the proton donor) and its conjugate acid (the proton acceptor)
- The **buffering region** is the flat zone of a titration curve (see above)
  - the boundaries of a buffer system are pH = pK_a±1 (so acetic acid buffer range is 3.76-5.76)

The buffering capacity is strongest when the ration of [HA] to [A^-] is close to 1:1. This occurs at the p$K_a$of the weak acid, where half of the weak acid is dissociated.

If the ratio of acid to base (or base to acid) becomes too large - greater than 10:1 or less than 1:10 - the buffer's capacity to neutralize added acids or bases weakens significantly

The Henderson-Hasselbalch Equation Relates pH, pK_a, and Buffer Concentration

- **Henderson-Hasselbalch equation** = describes the shape of the titration curve of any weak acid

$$\text{pH} = pK_\text{a} + \log \frac{[\text{A}^-]}{\text{HA}}$$

- Equation only works within the buffer region, outside of this it starts becoming inaccurate

Primary Uses of the Henderson-Hasselbalch Equation

1. Calculating pH of Buffers
   - Predicts pH based on acid/base ratios
2. Designing Buffers
   - Helps create buffers with a desired pH by adjusting the acid-base ratio.
3. Estimating pK_a
   - Can determine the pKa of weak acids and bases experimentally

Deriving the Henderson-Hasselbalch Equation (not needed for exam)

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]}$$

$$[\text{H}^+] = K_a \cdot \frac{[\text{HA}]}{[\text{A}^-]}$$

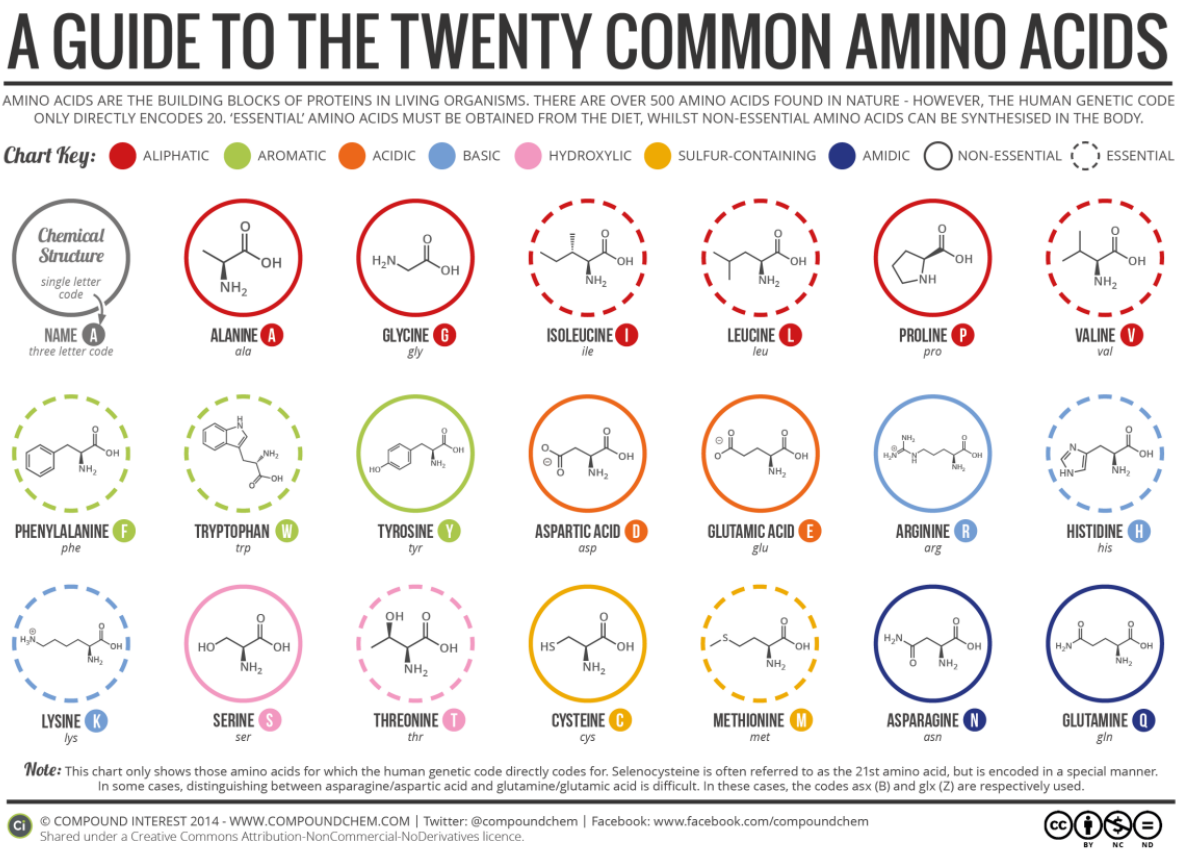
$$-\log[\text{H}^+] = -\log K_a - \log \frac{[\text{HA}]}{[\text{A}^-]}$$

$$\text{pH} = \text{p}K_\text{a} - \log \frac{[\text{HA}]}{[\text{A}^-]}$$

$$\text{pH} = \text{p}K_\text{a} + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

Amino Acids

- In every living organism, proteins are constructed from a common set of 20 amino acids*
- Each amino acid has a side chain with distinctive chemical properties. Amino acids may be regarded as the alphabet in which the language of protein structure is written.

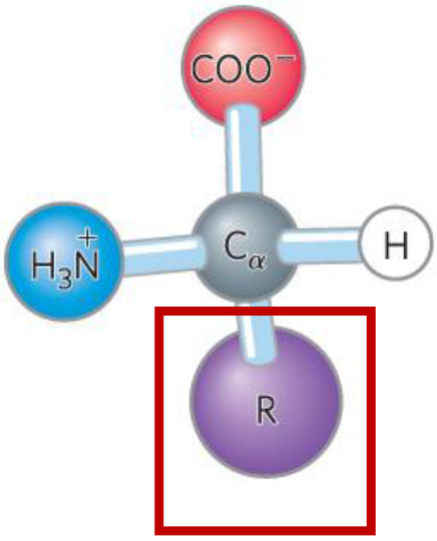


Amino Acids Share Common Structural Features

- α carbon and four substituents
- α carbon is the **chiral center** (except in Glycine, which is not chiral)
- Tetrahedral

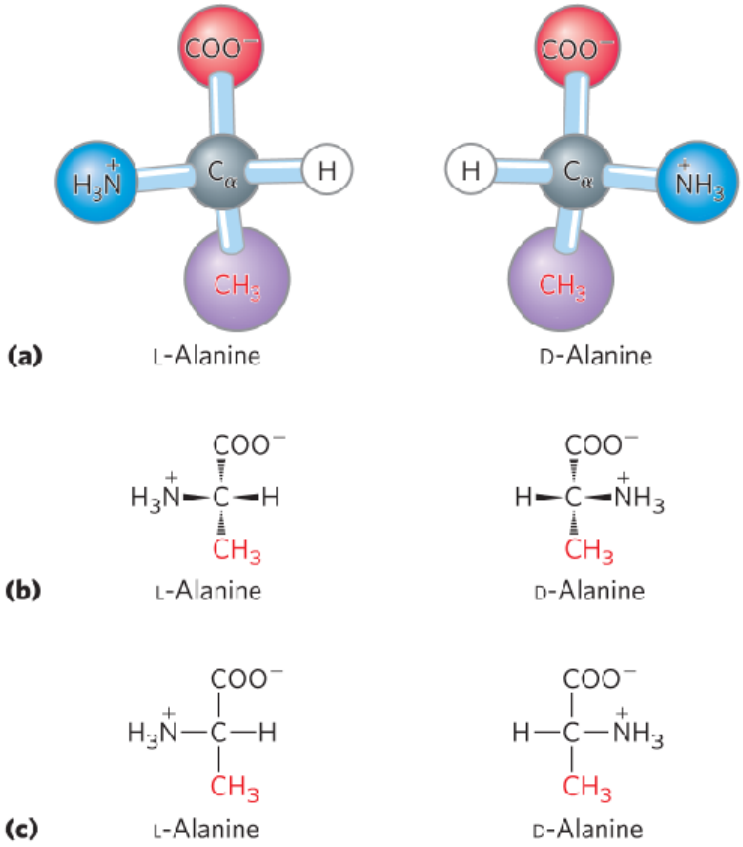
The four substituents are:

- a carboxyl group
- an amino group
- a hydrogen atom
- an **R group** (a side chain unique to each amino acid)
  - **Glycine** has a second hydrogen atom instead of an R group.



The Amino Acid Residues in Proteins are L Stereoisomers

- Two possible stereoisomers = **enantiomers**
- **optically active** = polarize light is rotated in different directions by enantiomers (Glycine is the exception)
- D, L system specifies **absolute configuration**



Amino Acids can be classified by the R Group

There are five main classes:

- Nonpolar, aliphatic (7)
- Aromatic (3)
- Polar, uncharged (5)
- Positively charged, Basic (3)
- Negatively charged, Acidic (2)

Nonpolar, Aliphatic R Groups

The **hydrophobic effect** stabilizes protein structure

- Glycine
- Alanine
- Proline
- Valine
- Leucine
- Isoleucine
- Methionine

Aromatic R Groups

R groups absorb UV light at 270-280 nm, and can contribute to the hydrophobic effect.

- Phenylalanine
- Tyrosine
- Tryptophan

Polar, Uncharged R Groups

R groups can **form hydrogen bonds**, and Cysteine can **form disulfide bonds**

- Serine
- Threonine
- Cysteine
- Asparagine
- Glutamine

Positively Charged R Groups

Have significant positive charge at pH 7.0.

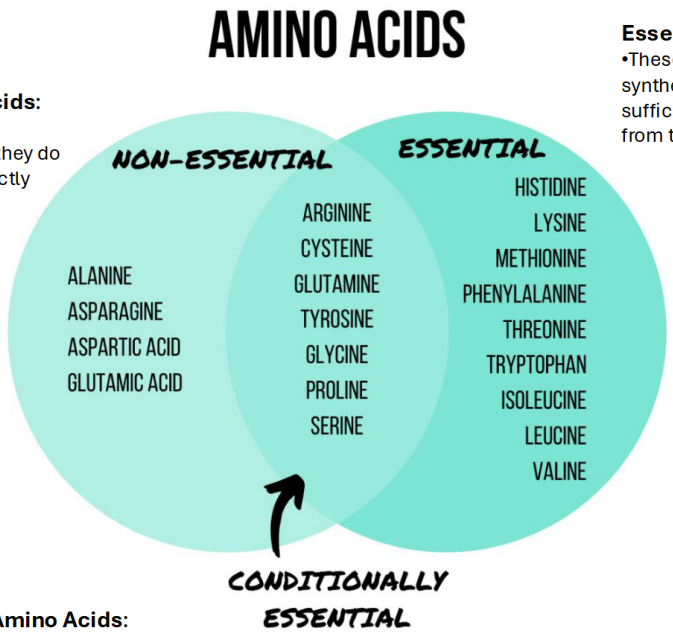
- Lysine
- Arginine
- Histidine

Negatively Charged R Groups

Have net negative charge at pH 7.0.

- Aspartate
- Glutamate

Essential Amino Acids



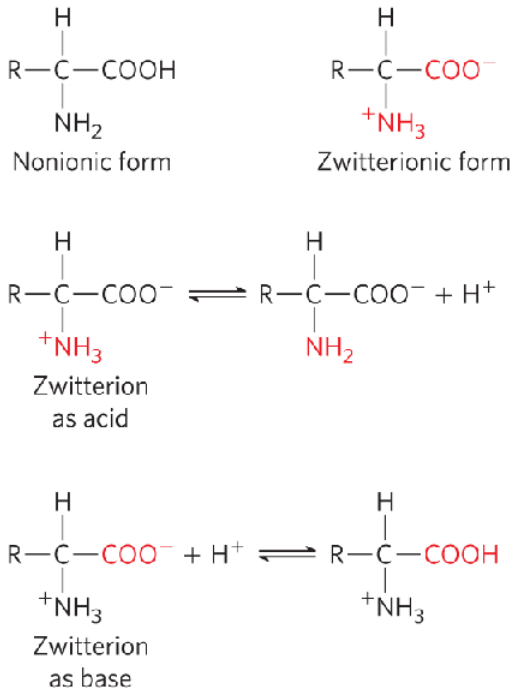
Non-Essential Amino Acids:
•These amino acids can be synthesized by the body, so they do not need to be obtained directly through the diet

Essential Amino Acids:
•These amino acids cannot be synthesized by the human body in sufficient amounts and must be obtaine from the diet

Conditionally Essential Amino Acids:
•Under normal conditions, these amino acids are synthesized by the body, but during periods of illness, stress, or growth, their production might not meet the body's demands, and they must be supplemented through the diet

Amino Acids can act as Acids or Bases

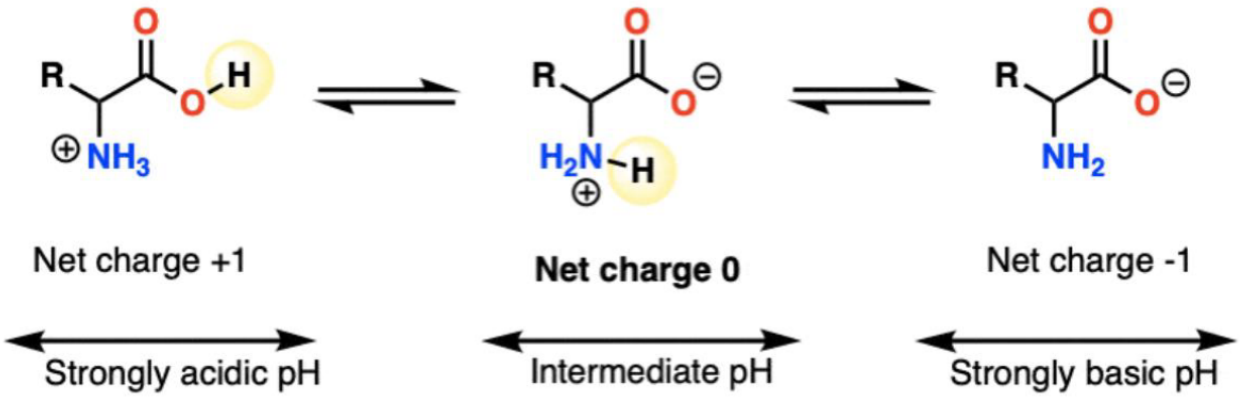
- Amino acids are **acids**. They are also **bases** containing an amino group.
- The term **amphoteric** is often used to describe amino acids, meaning that they are capable of acting as both acids and bases
- **zwitterion** occurs at neutral pH.



The pH-dependent structures of a typical amino acid

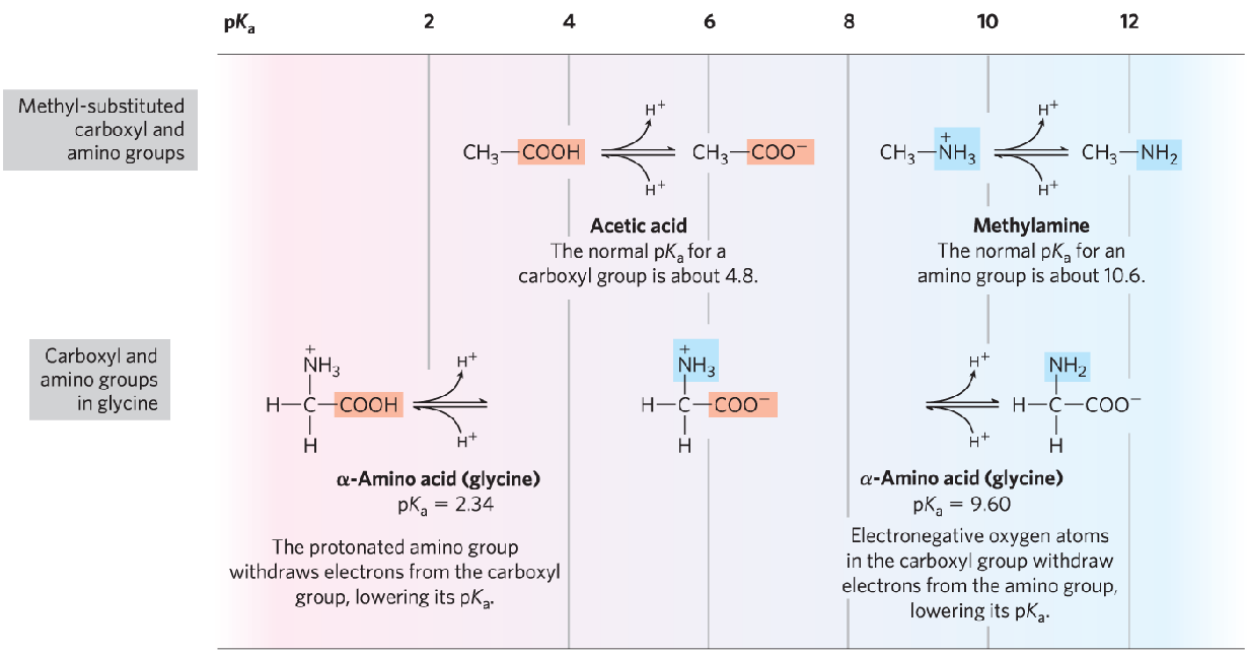
For a typical amino acid with a neutral sidechain **R**:

- the positively charged form (+1) dominates at low pH.
- the zwitterionic (neutral) form dominates at intermediate pH, and
- the negatively charged form (-1) dominates at high pH.



Effect of the Chemical Environment on pK_a

- α-carboxyl group is more acidic than in carboxylic acids
- α-amino group is less basic than in amines


pKa
2
4
6
8
10
12
Methyl-substituted carboxyl and amino groups
CH3—COOH
CH3—COO−
H+
H+
Acetic acid
The normal pKa for a carboxyl group is about 4.8.
CH3—NH3
CH3—NH2
Methylamine
The normal pKa for an amino group is about 10.6.
Carboxyl and amino groups in glycine
NH3
H—C—COOH
H
α-Amino acid (glycine)
pKa = 2.34
The protonated amino group withdraws electrons from the carboxyl group, lowering its pKa.
H—C—COO−
NH2
α-Amino acid (glycine)
pKa = 9.60
Electronegative oxygen atoms in the carboxyl group withdraw electrons from the amino group, lowering its pKa.

Structures (and pK_a) values of selected amino acids

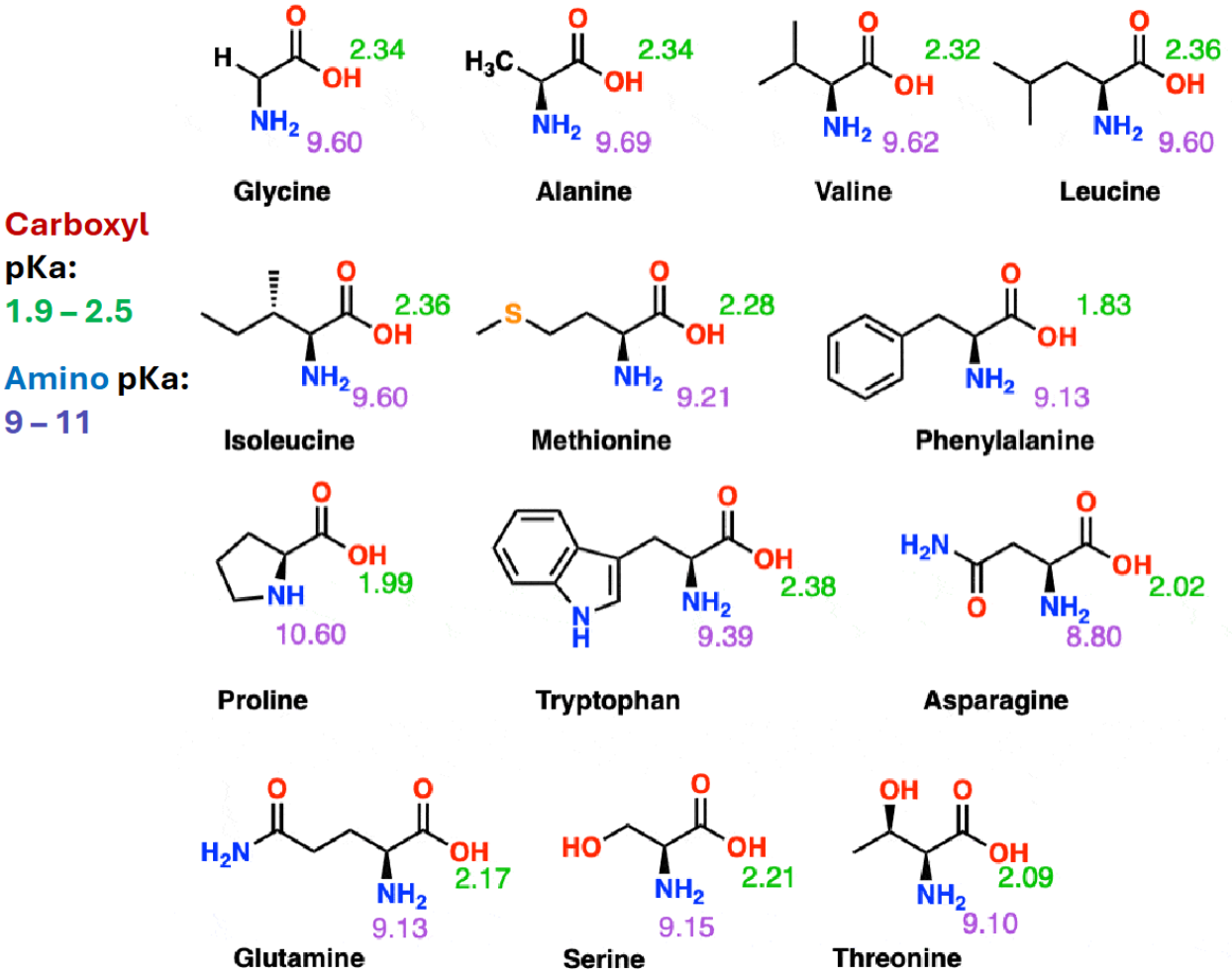


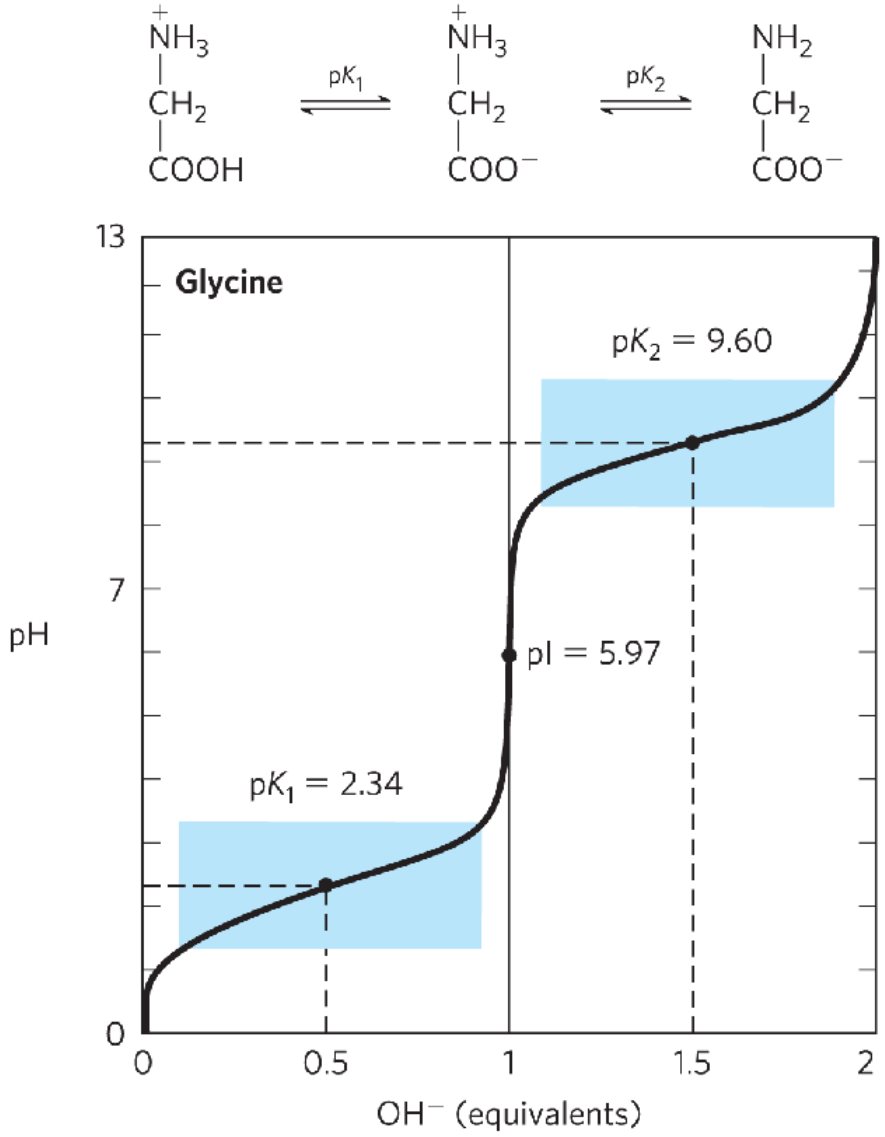
Table of Amino Acid pK_as

Functional Group	pK_a
COO^- -terminus	3.5
$^+NH_3$-terminus	8.5
α-COO^- (free amino acid)	2
α-$^+NH_3$ (free amino acid)	9.5
Aspartate R group	3.9
Glutamate R group	4.3
Histidine R group	6
Cysteine R group	8.3
Tyrosine R group	10
Lysine R group	10.8
Arginine R group	12.5

Titration of Amino Acids

- Cation $\rightleftharpoons$ zwitterion $\rightleftharpoons$ anion
- -COOH (carboxyl) has an acidic pK_a (pK_1)

- -NH_3^+ (amino) has a basic pK_a (pK_2)
- the pH at which the net electric charge is zero is the **isoelectric point (pI)**



This titration curve is a qualititative measure of the p$K_a$of each ionizing group.

- shows buffering power
  - flat regions are buffer regions. Glycine has two, one centered at p$K_1 = 2.34$, the other at p$K_2 = 9.6$
  - Buffer regions are highlighted in blue.
- shows relationship between its net charge and the pH of the solution
  - isoelectric point, or pI, can be calculated
- In the above image, glycine is present predominantly as its dipolar form, fully ionized with no net electric charge. At the point (pH = 5.97, 1eq base), glycine has an equal number of positive and negative charges.

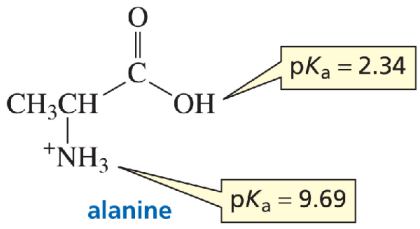
The Isoelectric Point

- The **isoelectric point (pI)** determines the pH at which a molecule carries no net electric charge
- This occurs when the positive and negative charges on the molecule are balanced. For amino acids, the pI is determined by the pKa values of its ionizable groups, such as the amino (-NH_3^+) and carboxyl (-COOH) groups, and sometimes the side chain, if it is ionizable.
- for amino acids without ionizable side chains, the **isoelectric point (pI)** is:

$$\text{pI} = \frac{\text{p}K_1 + \text{p}K_2}{2}$$

- pH = pI = net charge is zero (amino acid least soluble in water, does not migrate in electric field)
- pH > pI = net negative charge
- pH < pI = net positive charge

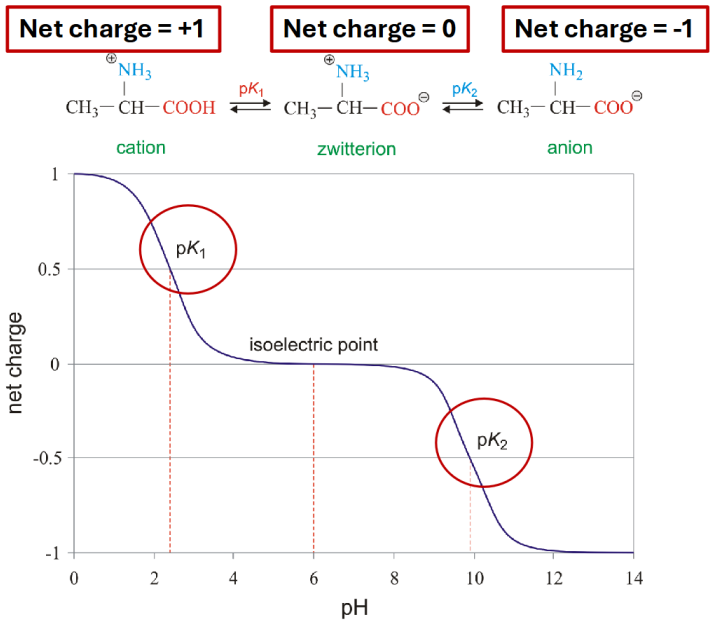
Isoelectric point - Alanine

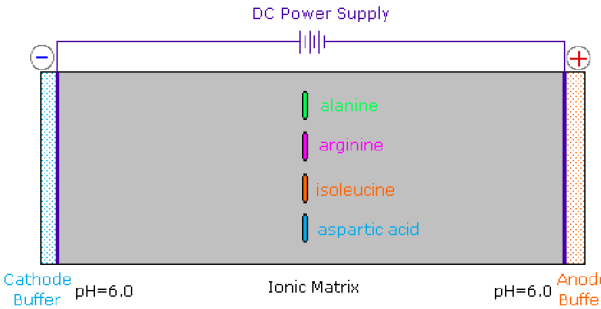


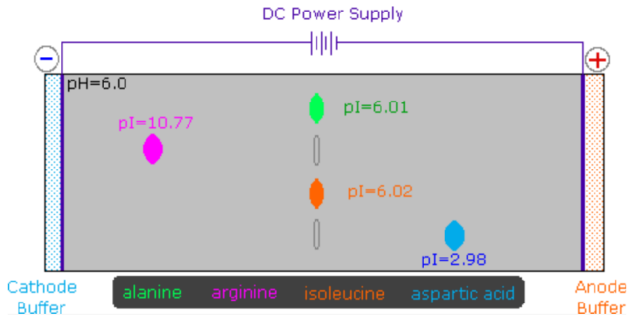
$$pI = \frac{2.34 + 9.69}{2}$$

$$pI = 6.015$$

- Not a range, we average the two pK_as around the point to get one number

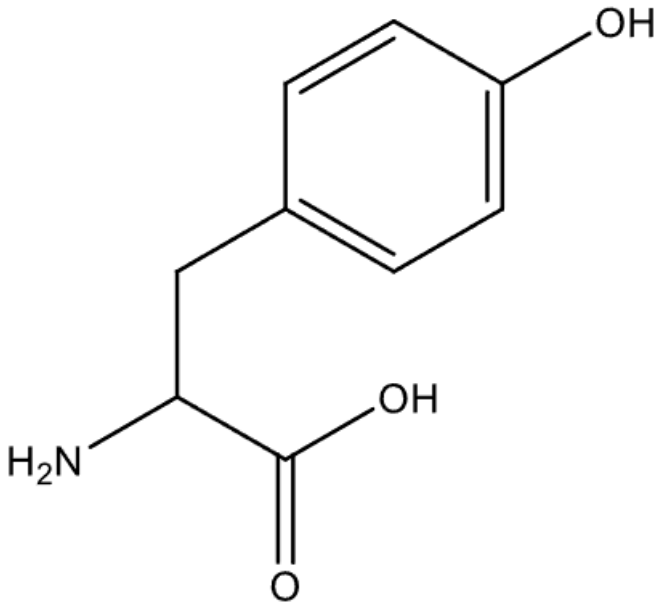






Tyrosine at different pH

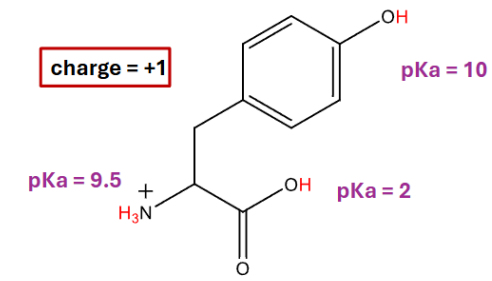
Standard Representation



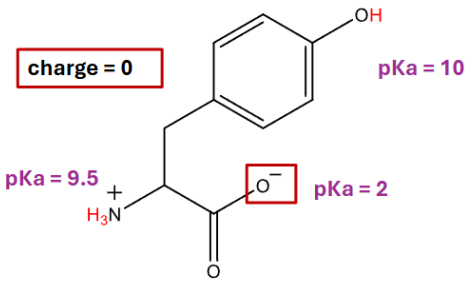
- This is the standard representation of Tyrosine, found in many online sources and textbooks
- It is important to note that **this structure does not exist at any pH**!
- The molecule is made neutral just because, to display its structure.

Representations at different pH

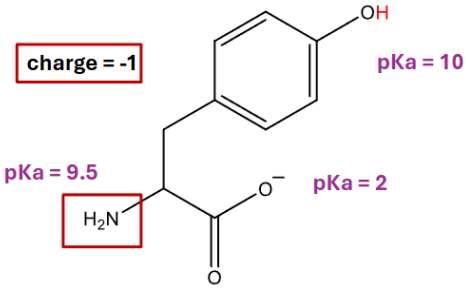
Predominant tyrosine species at pH = 1 (or any pH < 2)



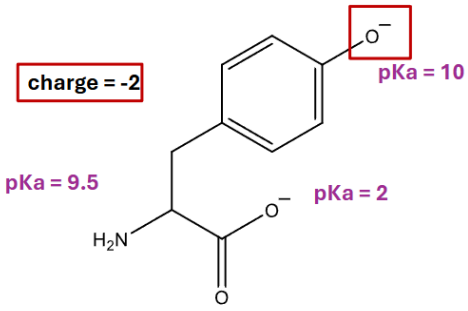
Predominant tyrosine species at pH = 7 (in range 2 < pH < 9.5)



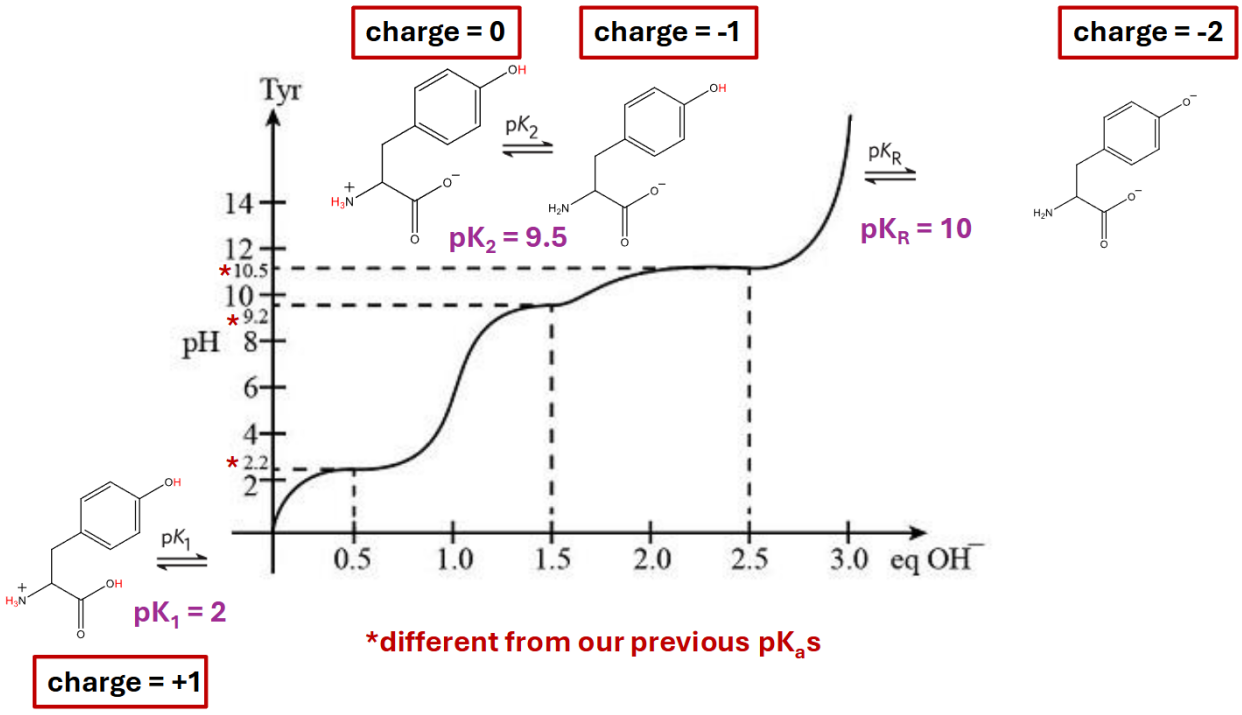
Predominant tyrosine species at pH = 9.75 (in range 9.5 < pH < 10)



Predominant tyrosine species at pH = 12 (any pH > 10)

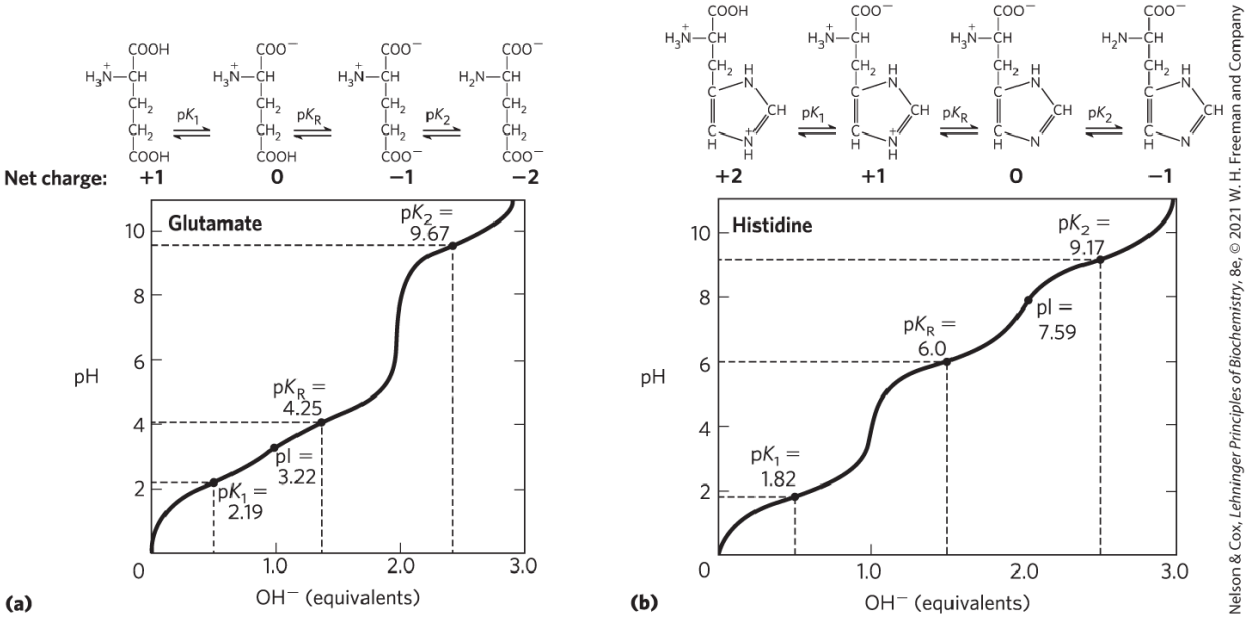


Titration of Tyrosine



- Notice there is a buffer region around each pK_a

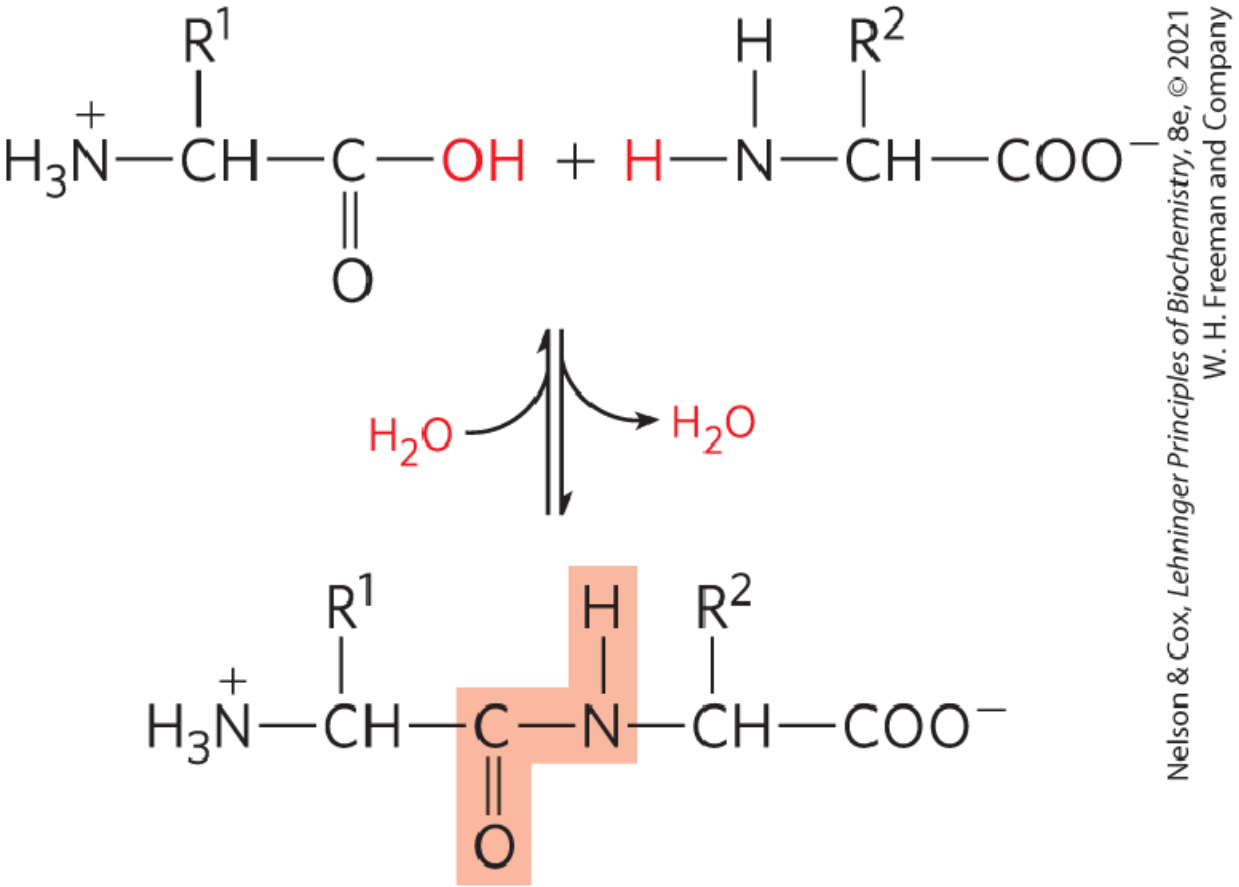
Titration of Amino Acids with an Ionizable R Group



Peptides and Proteins

In proteins, amino acids are joined in characteristic linear sequences through a common amide linkage, the peptide bond. The amino acid sequence of a protein constitutes its primary structure.

- Peptides are chains of amino acids
- Peptide bond:
  - Covalent
  - formed through **condensation**
  - broken through **hydrolysis**
- The **carboxyl group** of one amino acid loses a hydroxyl group (-OH)
- The **amino group** of the second amino acid loses a hydrogen atom (-H)



$$-CO-NH-$$

Peptide Types by the Number

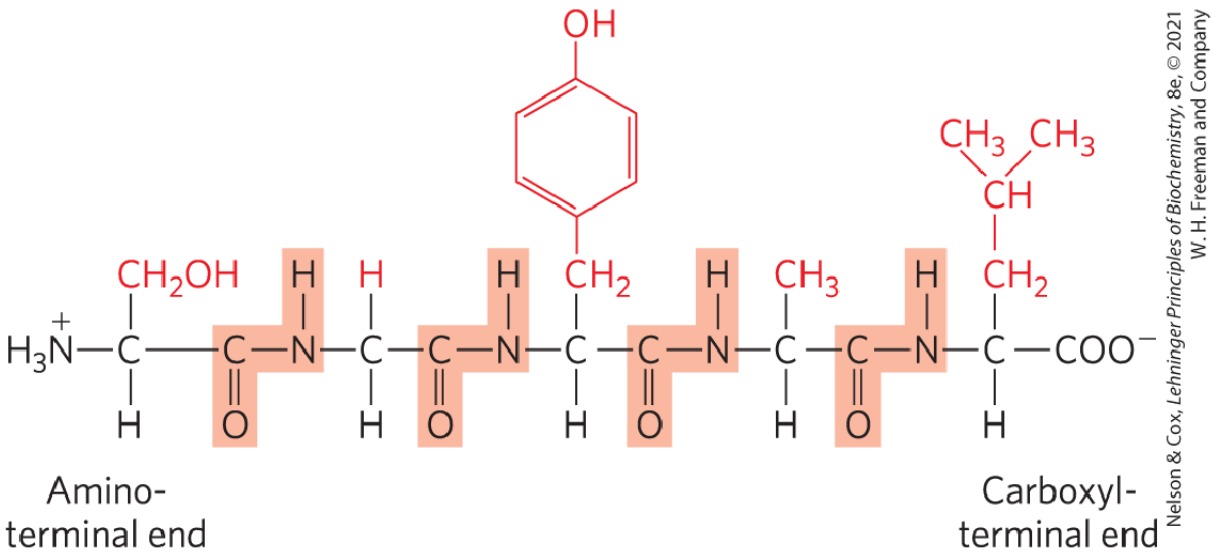
- dipeptide = 2 amino acids, 1 peptide bond
- tripeptide = 3 amino acids, 2 peptide bonds
- **oligopeptide** = a few amino acids
- **polypeptide** = many amino acids, molecular weight < 10 kDa
- **protein** = thousands of amino acids, molecular weight > 10 kDa

Aside: Daltons

- The average molecular weight of an amino acid is 110Da.
- Dalton (Da) is an alternate name for the atomic mass unit, and kilodalton (kDa) is 1000 daltons
- Thus, a protein with a mass of 64kDa has a molecular weight of 64,000 grams per mole

Peptide Terminals

Convention: numbering (and naming) starts from the **amino-terminal residue** (N-terminal)



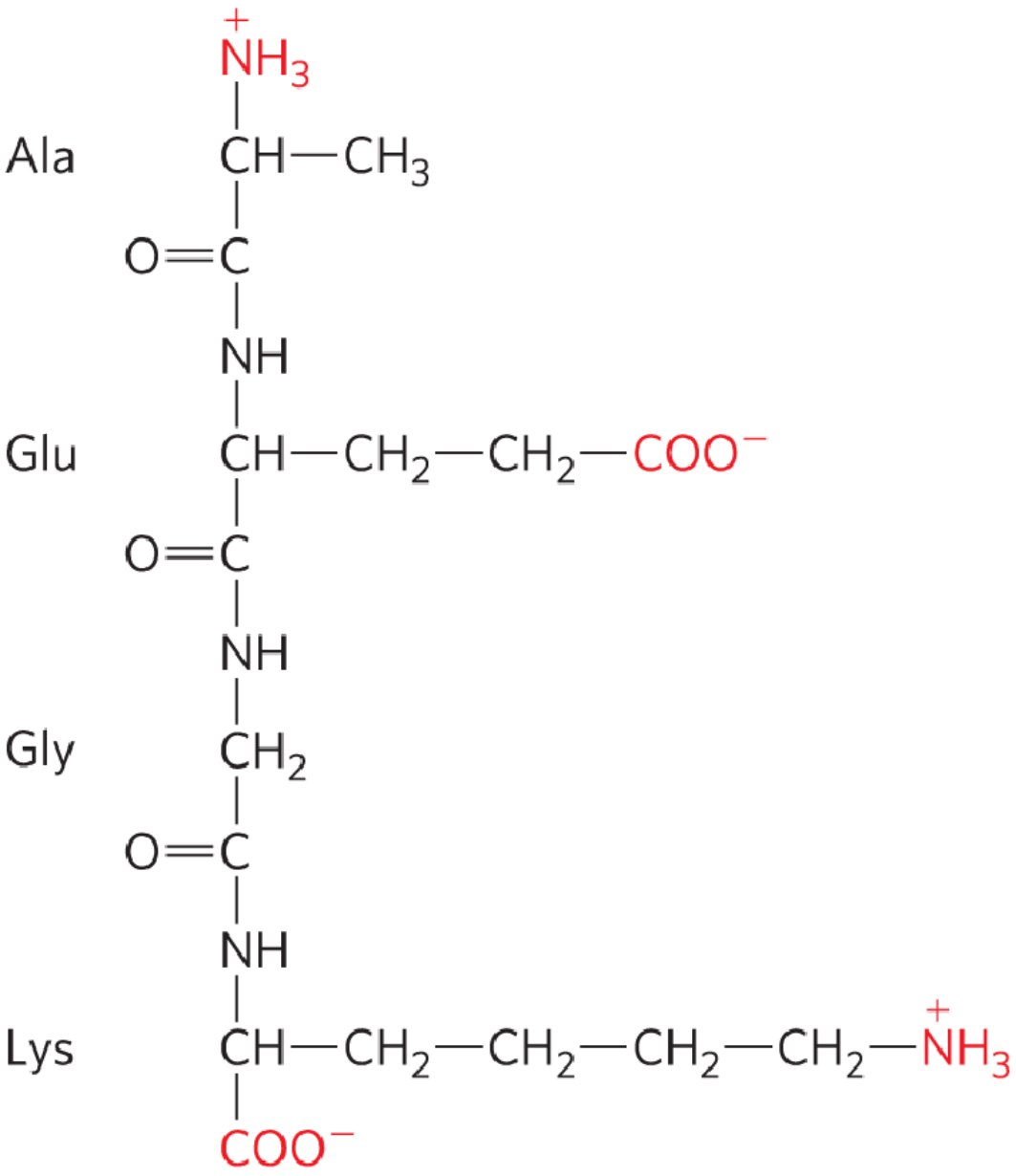
***N*-terminal** ***C*-terminal**

Naming Peptides

- Full amino acid names: serylglycyltyrosylalanylleucine
- Three letter code abbreviations: Ser-Gly-Tyr-Ala-Leu
- One letter code abbreviation: SGYAL

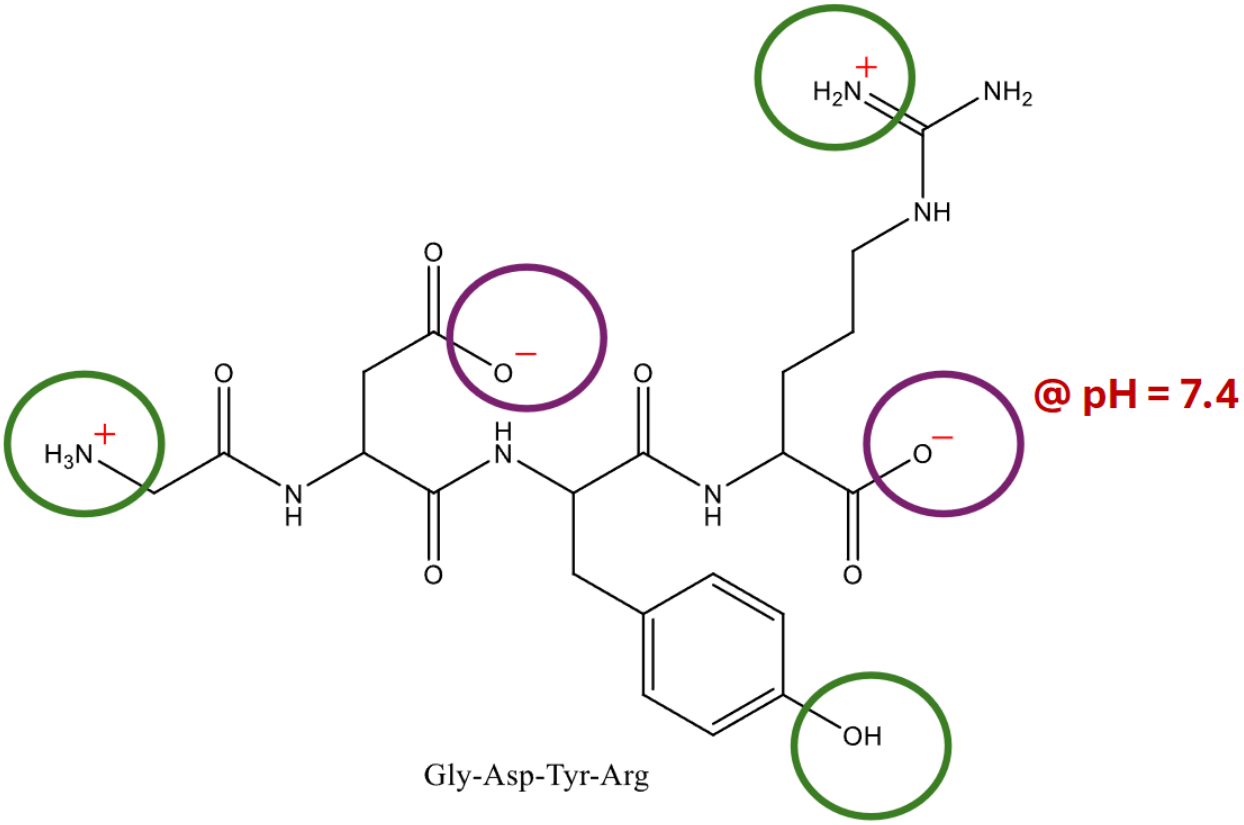
Peptides can be distinguished by their ionization behavior

- Ionizable groups in peptides:
  - one free α-amino group
  - one free α-carboxyl group
  - some R groups



Drawing oligopeptides

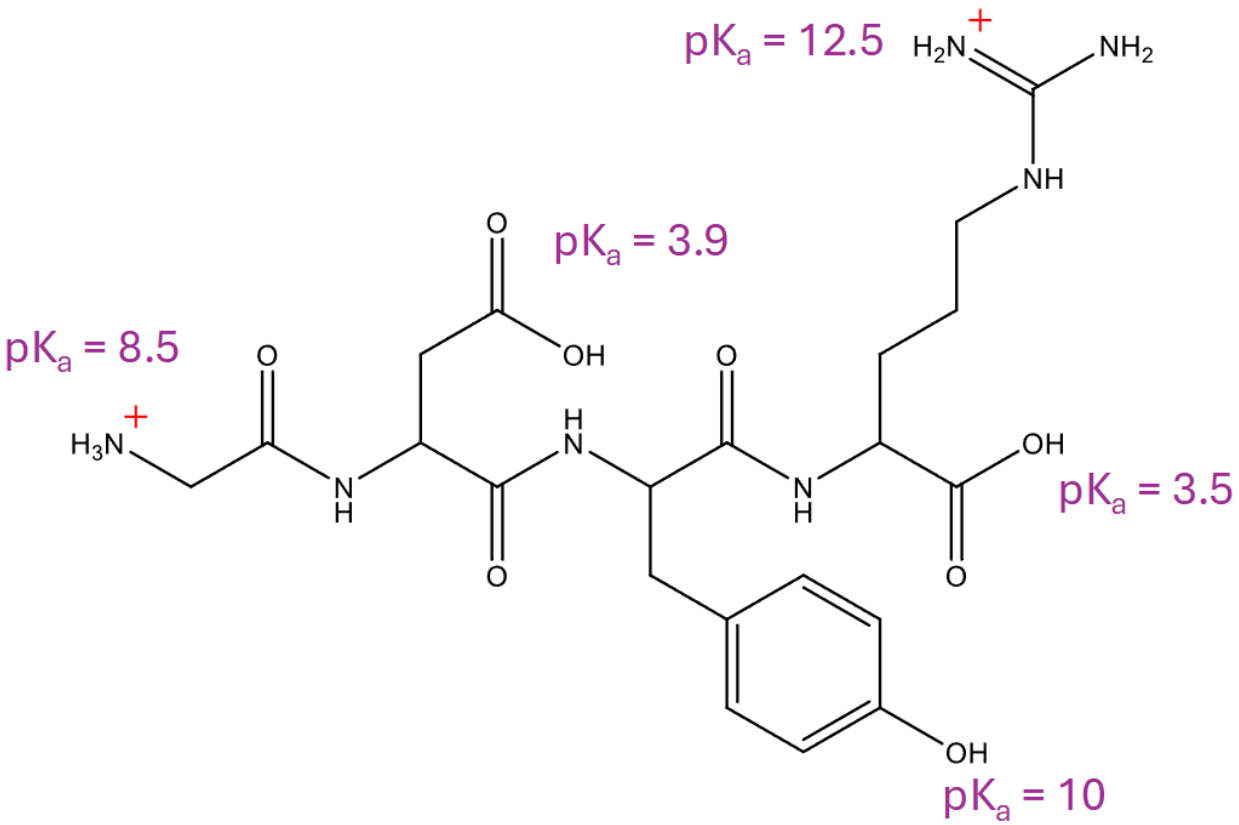
Draw the oligopeptide Gly-Asp-Tyr-Arg at physiological pH



- Refer to the functional group pH table earlier in this document.
- pH $<$ pKa: The molecule is protonated (it holds onto its protons)
- pH $>$ pKa: The molecule is deprotonated (it loses its protons)

Determining pI of peptide

1. Draw the peptide at its most protonated form (low pH)
2. Calculate overall charge
3. Calculate the change in charge as pH rises (noting pK_as)
4. Use the 2 pK_as surrounding peptide at 0 charge $\rightarrow$ average



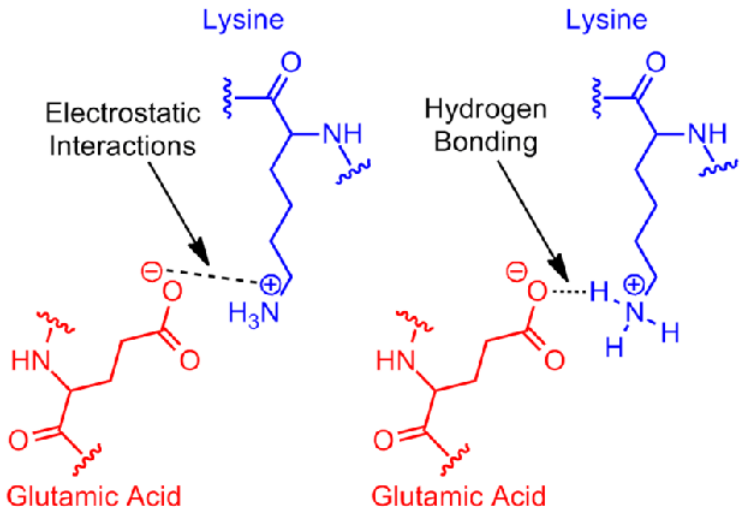
pH range	<3.5	3.5 - 3.9	3.9 - 8.5	8.5 - 10	10 - 12.5	>12.5
~net charge	+2	+1	0	-1	-2	-3

$$\text{pI} = \frac{8.5 + 3.9}{2} \boxed{= 6.2}$$

Intermolecular Interactions within Proteins

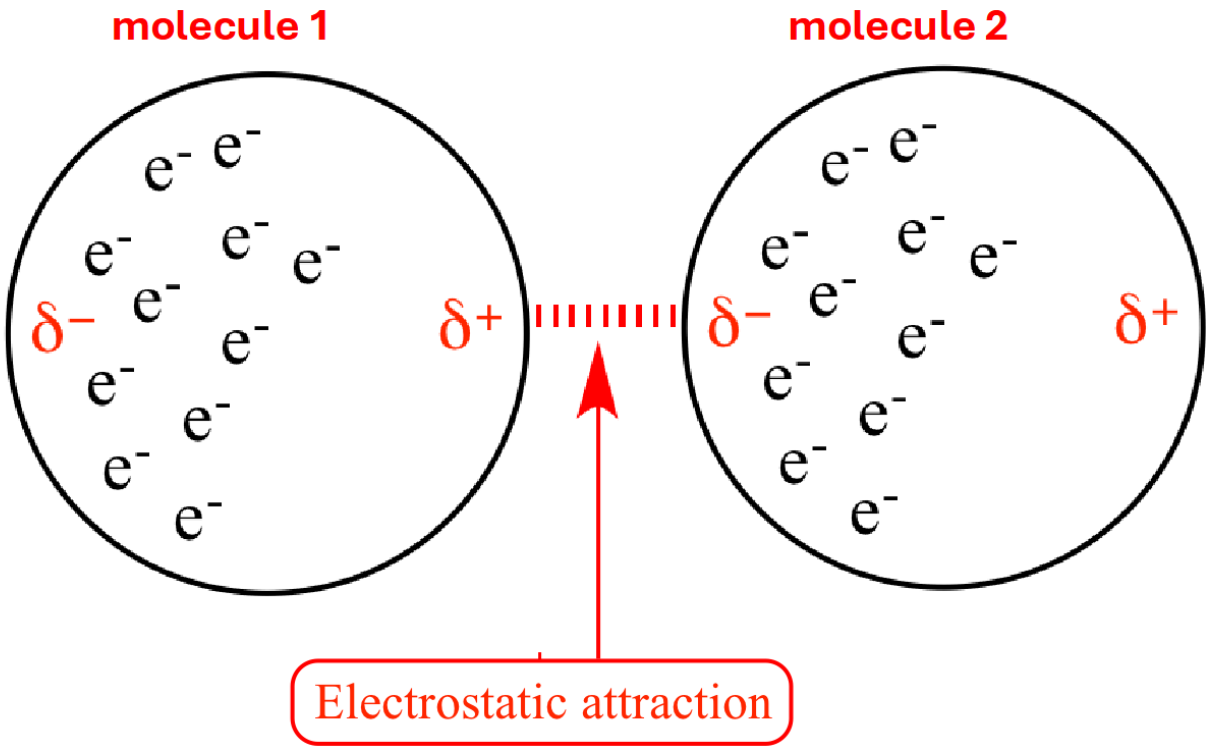
Ionic Bonds

- Strong electrostatic forces of attraction between oppositely charged ions
- Protein structures are formed by the interactions of amino acid side chains
- If an acidic chain and a basic side chain interact (e.g., Glu and Lys) **both an ionic interaction and a hydrogen bond will form**
- This is called a **salt bridge** - but most of the strength of this interaction comes from the opposing charges



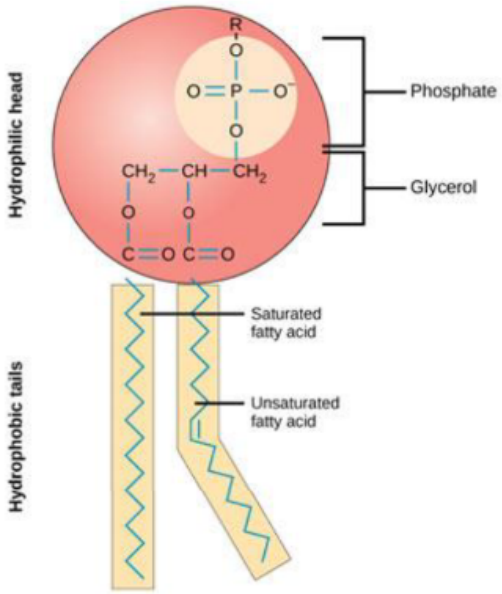
Induced Dipoles - London Dispersion Forces (LDFs)

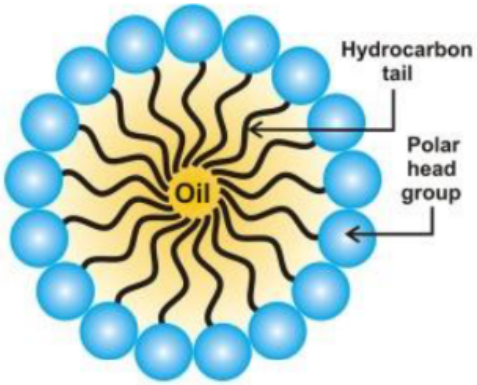
- The weakest intermolecular force
- The LDF is a temporary attractive force that results when **the electrons in two adjacent atoms occupy positions that make the atoms form temporary dipoles.** This force is sometimes called an induced dipole-induced dipole attraction.
- This is (often) the predominant force between nonpolar molecules
- The London dispersion force is sometimes called a 'Van der Waals force.' Van der Waals force is a general term that describes any attractive intermolecular force between molecules and includes both the London dispersion force and the dipole-dipole force



Micelle - Where are the LDFs?

LDFs are primarily found among the hydrophobic (nonpolar) tails of the amphiphilic molecules (like fatty acids or detergents) that form the core of the micelle.





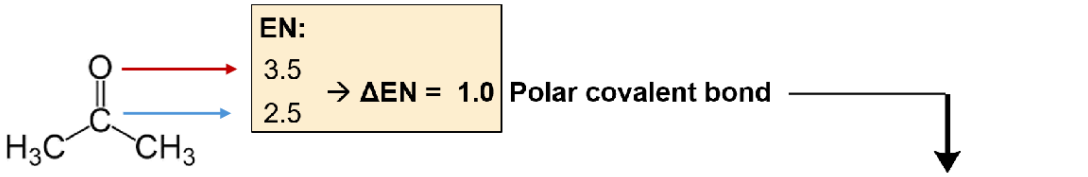
LDFs contribute to the stability of the micelle by keeping the nonpolar tails in close proximity in the micelle's core

Dipole-dipole interactions

Attractive forces that occur between polar molecules, where permanent dipoles are present due to the uneven distribution of electrons

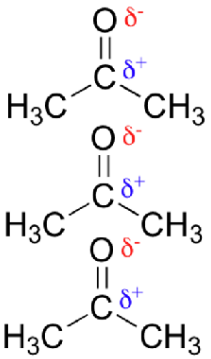
- Dipole-dipole interactions are generally stronger than London dispersion forces but weaker than hydrogen bonds or ionic interactions.

This creates a **polar bond**, where the **O :** δ^-, and the carbonyl **C:** δ^+, resulting in a **permanent dipole** in the molecule



Acetone
bp 56 °C

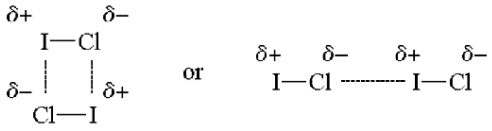
Dipole-dipole forces



Molecules with polar bonds:

- Have **permanent dipoles** that can interact with neighboring dipoles (**electrostatics** between δ^+/δ^-)

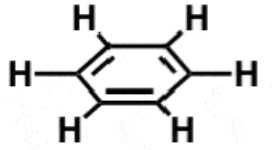
Another example:



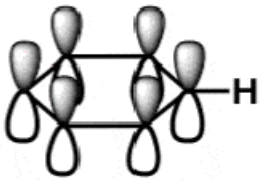
Iodine monochloride

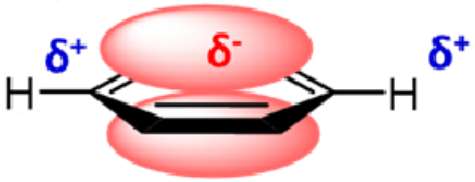
π-stacking interactions

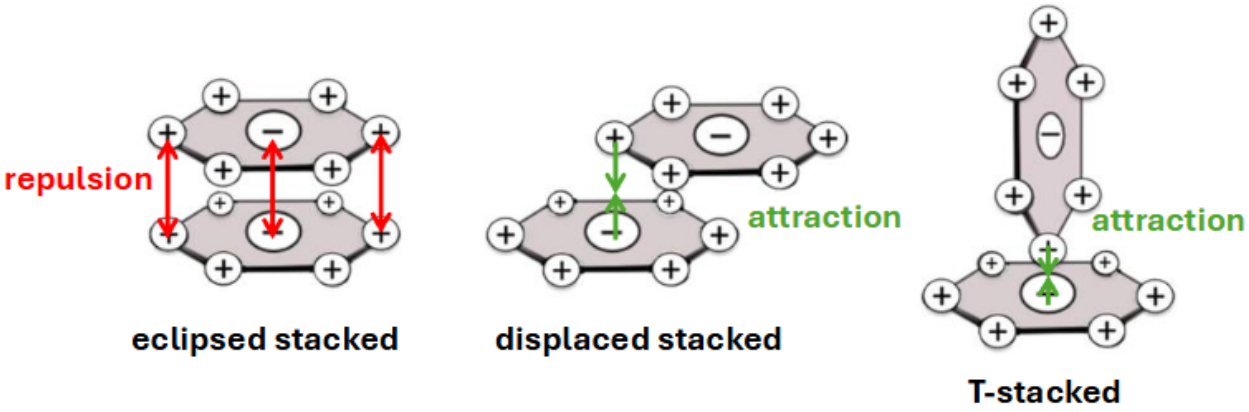
- Non-covalent interactions that occur between aromatic rings, where the delocalized π-electrons in thes systems interact with each other.
- Cyclic aromatic compounds have π orbital rings stacked above and below the molecular structure.

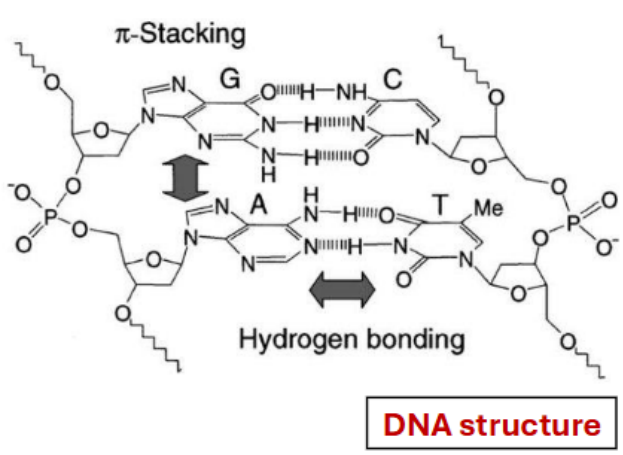


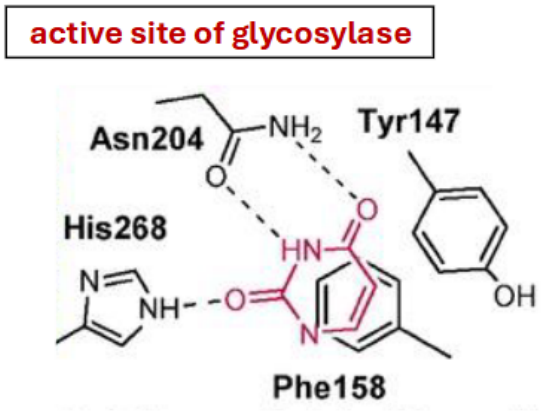
benzene











Importance of Non-Covalent Interactions

1. Protein Folding and Stability: Hydrogen bonds, hydrophobic interactions, ionic interactions, and van der Waals forces contribute to the folding of proteins into their three- dimensional structures. These forces also help stabilize protein structures, such as maintaining the secondary, tertiary, and quaternary structures
2. DNA Double Helix: Hydrogen bonds between complementary bases (A-T and G-C) and π-π stacking interactions between the aromatic bases help stabilize the DNA double helix structure
3. Membrane Formation: Hydrophobic interactions between the fatty acid tails of phospholipids drive the formation of lipid bilayers, which form the basic structure of cell membranes
4. Enzyme-Substrate Binding: Play a key role in the binding of enzymes to their substrates or cofactors, allowing for specificity and reversibility in catalysis
5. Molecular Recognition: Participate in the recognition of molecules such as ligands by receptors, or antigens by antibodies, facilitating many biological processes such as signal transduction and immune responses

The Thermodynamic Problem

- Living cells must constantly perform work, such as building complex molecules, transporting substances, and maintaining ion gradients, to stay alive. This requires an understanding of **thermodynamic principles** to predict which processes can occur naturally and how energy flows in biological systems

First Law of Thermodynamics

Energy Conservation: Energy cannot be created or destroyed, only transformed

- ΔG tells us how much energy is available to do work
- ΔH (enthalpy) represents the heat exchanged in a system
- Example: In cellular respiration, glucose releases energy ($\Delta H < 0$) that is used to produce ATP. Energy is transformed but conserved

Second Law of Thermodynamics

Entropy of the universe always increases in spontaneous processes

- ΔS (entropy) is a measure of disorder
- $\Delta G = \Delta H - T\Delta S$: A negative ΔG means a process is spontaneous and aligns with the second law (entropy increases)
- Even if a system's entropy decreases ($\Delta S < 0$), the surroundings must increase entropy for the reaction to be spontaneous
- Example: Protein folding is spontaneous ($\Delta G < 0$) even though it decreases system entropy, because heat is released, increasing the entropy of the surroundings

Third Law of Thermodynamics

As temperature approaches absolute zero, entropy approaches zero

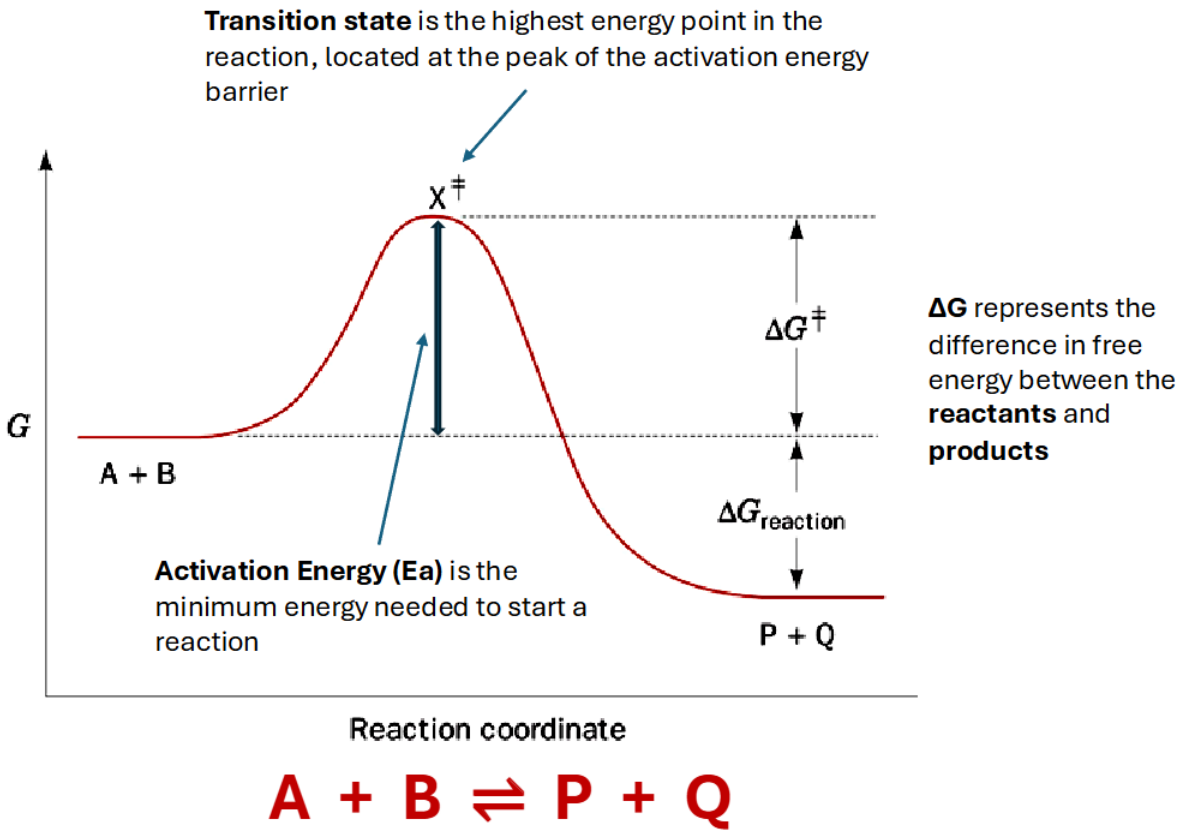
- At very low temperatures, TΔS becomes small, and ΔH dominates
- Spontaneous processes at low temperatures: Exothermic reactions ($\Delta H < 0$) are more likely to be spontaneous when entropy is low
- Example: Water freezing is spontaneous at low temperatures because it releases heat ($\Delta H < 0$) even though it decreases disorder ($\Delta S < 0$)

Gibbs Free Energy (G)

- **Gibbs free energy (G)** represents the maximum amount of energy available to perform work in a system. It's the key to understanding how cells manage energy.
- The **Gibbs free energy change (ΔG)** tells us the difference in available free energy between reactants and products. It determines whether a process will occur spontaneously (i.e., without needing an external energy input).
- ΔG determines the spontaneity of a process

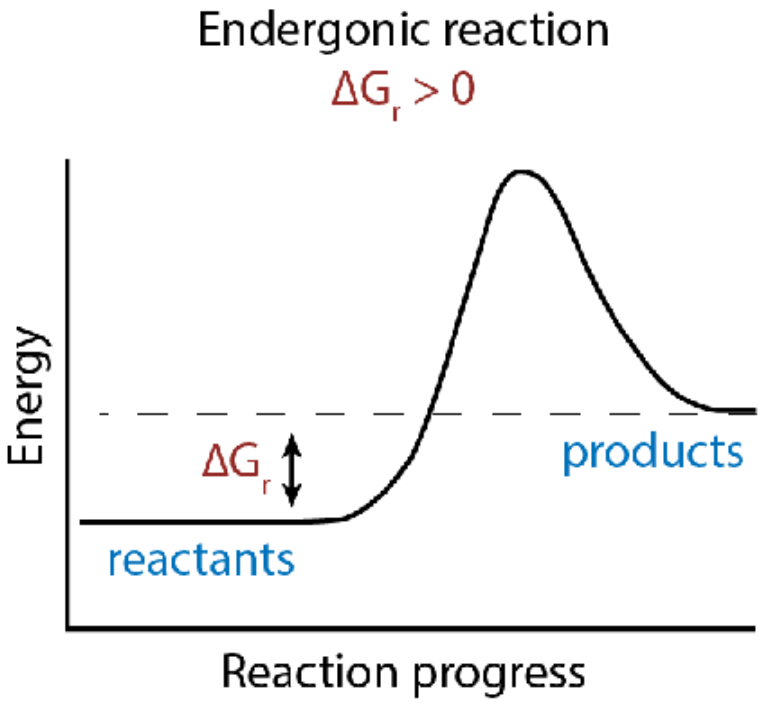
Reaction Coordinate Diagram

- A reaction coordinate diagram shows the progress of a reaction vs the overall free energy (G) as it proceeds
  - Energy flowing downhill is favorable, uphill is unfavorable.

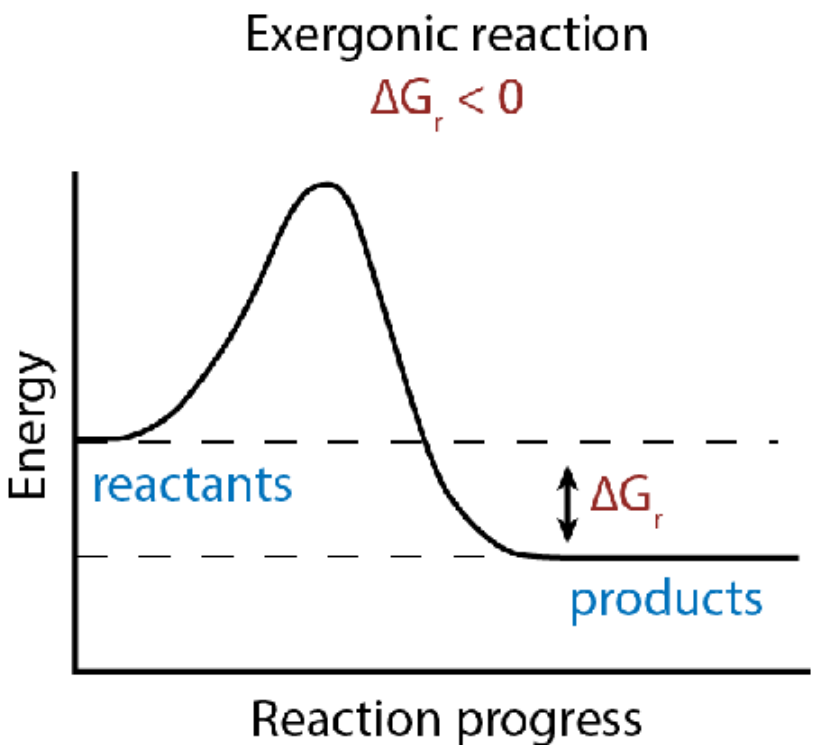


Spontaneity and ΔG: What it Really Means

- **If $\Delta G > 0$, the process is non-spontaneous** (it requires an input of energy to occur). This type of reaction is called **endergonic**.
  - **Example:** The synthesis of **glucose** from CO_2 and water during **photosynthesis** is endergonic ($\Delta G > 0$). Plants need energy from sunlight to drive this process because it doesn't happen spontaneously
- **Why:** It makes sense - if the ΔG is positive, how could you get more work out of a system without putting energy into it? In biological systems, cells **couple** endergonic reactions with exergonic ones to make them proceed.

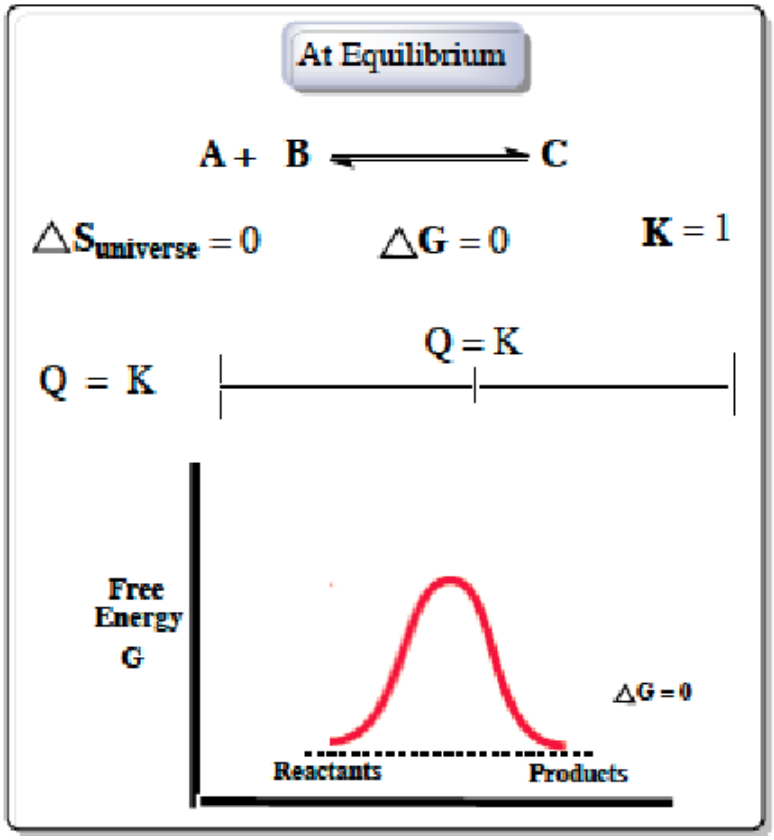


- **If $\Delta G < 0$, the process is spontaneous** (it can occur naturally without additional energy input). This is called an **exergonic** process.
  - **Example:** The breakdown of **glucose** during **cellular respiration** is exergonic ($\Delta G < 0$). When glucose is metabolized into CO_2 and H_2O, energy is released that cells can use to drive other processes (like making ATP).
- **Why:** Energy is released when bonds in glucose are broken, allowing the system to do work - such as moving ions, powering cellular machinery, or synthesizing molecules. The process moves towards equilibrium, where the system is most stable.



However

- In **biological systems, true equilibrium** is rarely reached because cells operate under a **steady state** rather than equilibrium
- In a steady state, the concentrations of molecules like glucose and ATP are kept constant, but continuous input of reactants (like glucose) and removal of products (like CO_2) allow work to be performed
- If equilibrium were reached, the system would be in a **low-energy state**, and no further work could be done. This is why biological systems keep reactions away from equilibrium to continue performing work
- **If $\Delta G = 0$, the system is at equilibrium**, meaning there's no net change in the reactants or products, and no work can be done. This happens when the forward and reverse reactions occur at the same rate.
  - **Example:** Consider **ATP** in equilibrium with **ADP** and inorganic phosphate (P_i) in a cell. If the reaction reaches equilibrium, no energy would be released or consumed, making it impossible for the cell to do any work involving ATP.



How Cells Use ΔG to Perform Work: Reaction Coupling

- Cells often use **reaction coupling** to make non-spontaneous processes occur. By coupling a reaction with **positive ΔG** (endergonic) to one with **negative ΔG** (exergonic), the overall process can still be spontaneous
  - **Example:** The phosphorylation of glucose in the first step of **glycolysis** ($\Delta G > 0$) is coupled with the **hydrolysis of ATP** to ADP and P_i ($\Delta G < 0$). **Together, these reactions allow glucose to be phosphorylated and the overall process to move forward with a net negative ΔG**
  - **Key Insight:** Cells use ATP as sort of "energy currency" to drive many otherwise non-spontaneous reactions. ATP hydrolysis ($\Delta G < 0$) provides the energy necessary to make those reactions happen

Coupled Reactions

- How does biochemistry pull off an anabolic reaction?
  - By coupling it with an energetically favorable reaction (the classic example is the hydrolysis of ATP)
  - i.e., coupling an endergonic reaction with an exergonic reaction

phosphorylation of glucose

Glucose+Pi→Glucose-6-phosphate (G6P)+H_2O

ΔG° for this reaction = **+13.8 kJ/mol** (non-spontaneous, ΔG > 0)

hydrolysis of ATP

ATP+H_2O→ADP+Pi

ΔG° for this reaction = **-30.5 kJ/mol** (spontaneous, ΔG < 0)

Glucose+ATP→Glucose-6-phosphate (G6P)+ADP

ΔG°total= (+13.8kJ/mol)+(−30.5kJ/mol)= -16.7 kJ/mol

spontaneous

Quantifying ΔG - Enthalpy

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

- H, enthalpy is the heat content locked in a system
- ΔH is the change in enthalpy

Equivalent to the difference between bonds/interactions formed and bonds/interactions broken

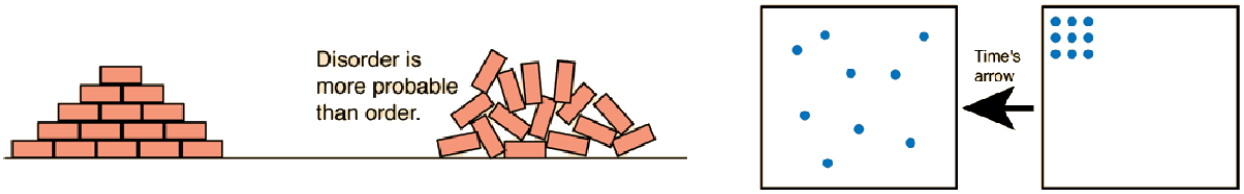
- **Bond formation** typically **releases energy** because when atoms form bonds, they move to a lower energy state. This means that energy is released as the atoms become more stable
- **Bond breaking** generally **requires energy input** because energy must be provided to overcome the stability of the bond and separate the atoms, moving them to a higher energy state

Quantifying ΔG - Entropy

- S, entropy is the degree of disorder in a system
- ΔS is the change in entropy

Equivalent to disorder of products minus disorder of reactants

- **Systems tend toward disorder**


Disorder is
more probable
than order.
Time's
arrow