Biology of Cells & Tissues

Lecture 1: Chemistry of Amino Acids

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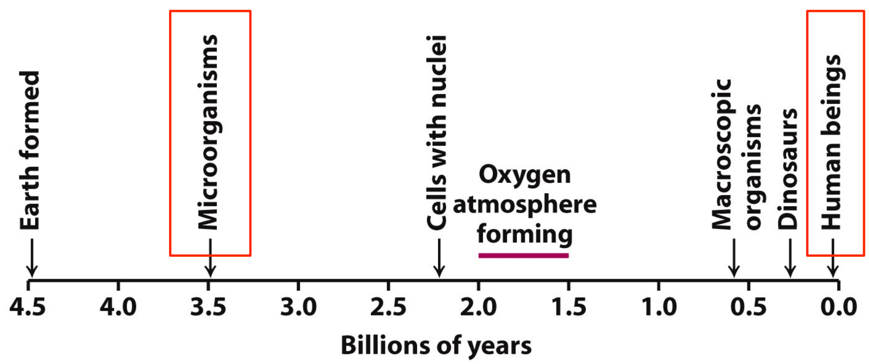
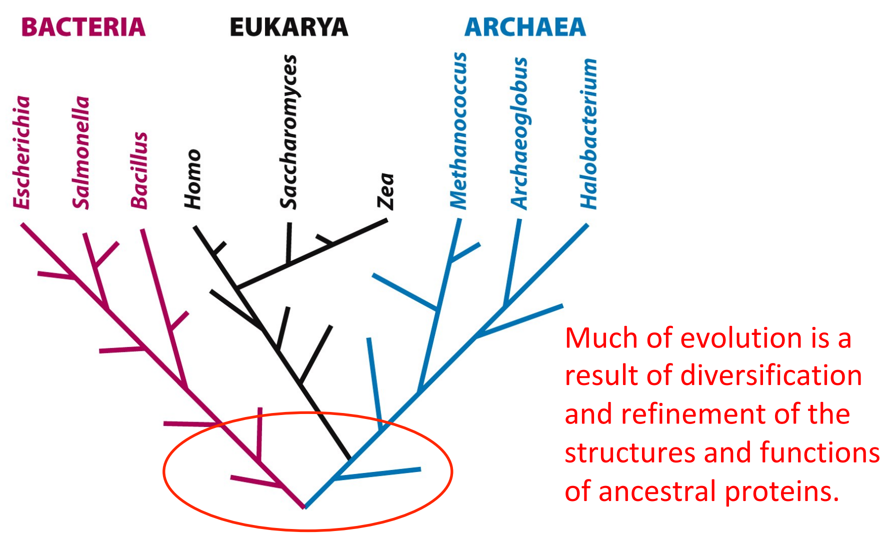
Lecture Plan

1. Essential biological and chemical principles for biochemistry
2. pH control in biological systems
3. Structures and properties of amino acids

Biochemical processes have been evolving for 3.5 billion years...



...and those common to all life are very ancient.



The 10 ancient amino acids

Leu	Hydrophobic
Ile	Hydrophobic
Val	Hydrophobic
Pro	Kinky
Ala	Flexible
Gly	Flexible
Ser	Hydrophilic
Thr	Hydrophilic
Glu	Charged
Asp	Charged

Missing:
- Aromatic
- Positive charge
- Amides
- Sulfur

Life is non-equilibrium thermodynamics

Gibbs free energy/four equations:

<u>Question</u>: If a reaction results in a net increase in S (i.e. ΔS is positive), does raising T increase or decrease the favorability of the reaction?

<u>Question</u>: What effect does increasing substrate concentration or decreasing product concentration have on the favorability of the reaction?

Chemical bonding in biochemistry

1. Covalent bonds
   - SP2 and SP3 hybridization
   - Bond lengths: 1 – 1.5 Å (1 Å = 0.1 nm)
   - Bond strengths:

C – C	83 kcal/mole
C – H	100 kcal/mole
C – O	86 kcal/mole
C – N	74 kcal/mole

Chemical bonding in biochemistry

2. Ionic bonds
   - "Coulombic attraction"
   - Strength varies by $1/R^2$ (square of distance)
   - Depending on distance can be 2X stronger than a covalent bond

Chemical bonding in biochemistry

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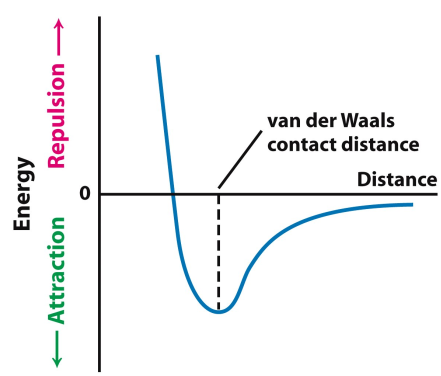
3. Hydrogen bonds
   - Bond length 1.5 – 2.5 Å
   - Proton is shared between two electronegative atoms (combinations of N and O)
   - Bond strength 2 – 7 kcal/mole

Hydrogen bonds form by sharing of a proton between electronegative atoms

Hydrogen-bond donor	Hydrogen-bond acceptor	Bond strength
N—H (δ^- δ^+)	------- N (δ^-)	3 kcal/mole
N—H	------- O	2 kcal/mole
O—H	------- N	7 kcal/mole
O—H	------- O	5 kcal/mole

Chemical bonding in biochemistry

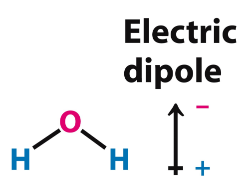
4. Van der Waals forces
   - Electrostatic force between uncharged atoms from transient movements of electron clouds
   - Strength varies by $1/R^6$
   - Is a very weak force
   - Requires very close contact



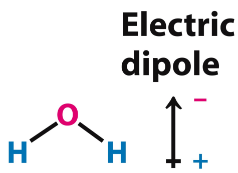
Chemical bonding in biochemistry

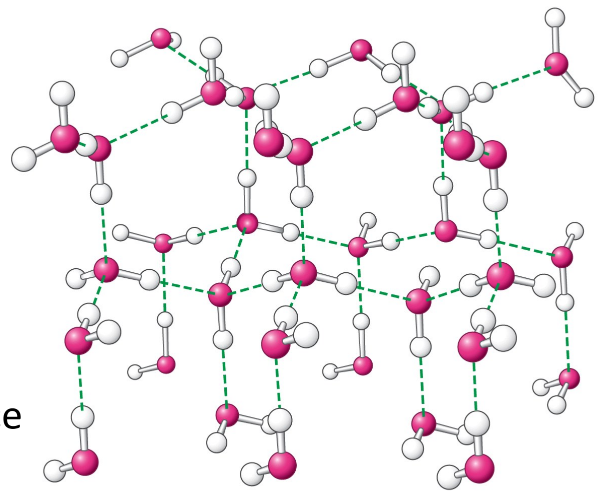
Hydrophobic effect
- Is not an attractive force (i.e. not a “bond”)
- Is driven by entropy of the solvent water
- Entropy IS NOT disorder
- Entropy IS a lack of constraint

Water molecules are electric dipoles...



...and they readily form intermolecular hydrogen bonds

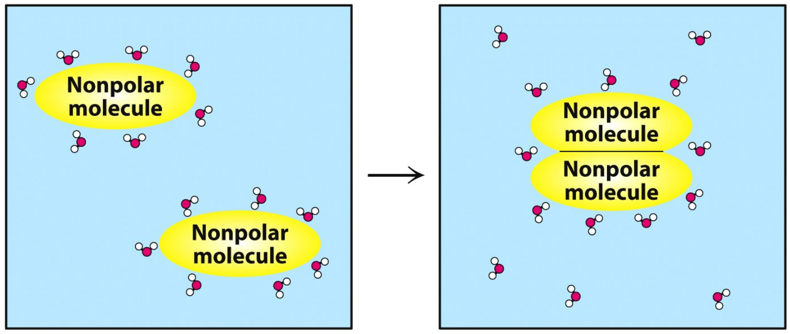




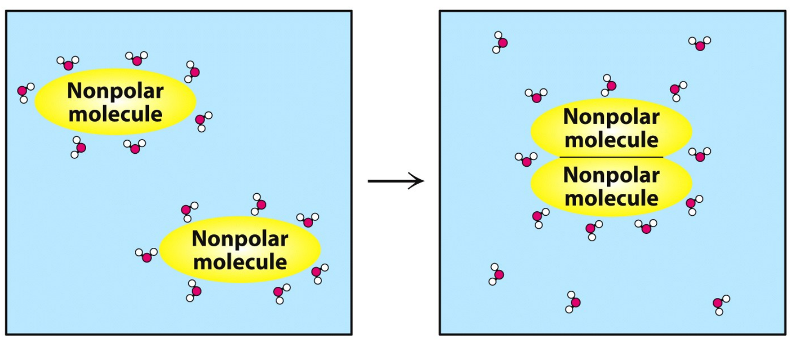
H-bonded structure of ice

Molecular dynamics modeling of water

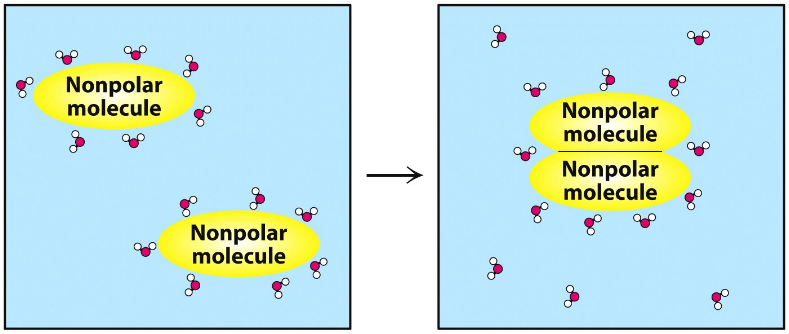
https://www.youtube.com/watch?v=Zl74NCVbA5A



- Nonpolar molecules in aqueous solution constrain the free motion and intermolecular H-bonding of the water molecules



- Nonpolar molecules in aqueous solution constrain the free motion and intermolecular H-bonding of the water molecules
- The entropy of the system increases when the nonpolar molecules associate with each other leaving water free to make H-bonds without constraint



- Nonpolar molecules in aqueous solution constrain the free motion and intermolecular H-bonding of the water molecules
- The entropy of the system increases when the nonpolar molecules associate with each other leaving water free to make H-bonds without constraint
- The increased entropy makes ΔG more negative, thus making the reaction more thermodynamically favorable

Common reactions in biochemistry

MANY reactions are nucleophilic substitutions

1. Reaction with the carbonyl of an aldehyde:

Common reactions in biochemistry

MANY reactions are nucleophilic substitutions

2. Reaction with the carbonyl of a carboxylic acid:

Common reactions in biochemistry

MANY reactions are nucleophilic substitutions

3. Reaction with phosphate:

4. Reaction between two acids to form acid anhydrides:

Question:

What do grilled steak, toasted marshmallows, cataracts, and hemoglobin A1C have in common?

A. Allergic reaction
B. Maillard reaction
C. Grignard reaction
D. Redox reaction
E. Nuclear reaction

Biochemistry mostly uses a modified Lowry-Brønsted definition of acids and bases:

An <u>acid</u> dissociates in aqueous solution to produce a proton (H^+) and a conjugate base.

Generically: $$HA \underset{}{\overset{K_a}{\rightleftharpoons}} H^+ + A^-$$

$$pK_a < 7$$

Biochemistry mostly uses a modified Lowry-Brønsted definition of acids and bases:

A <u>base</u> associates in aqueous solution with H^+ to produce a conjugate acid.

Generically: $$B\text{-}H^+ \overset{K_a}{\rightleftharpoons} H^+ + B:$$

$$pK_a > 7$$

Biochemistry mostly uses a modified Lowry-Brønsted definition of acids and bases:

$$HA \overset{K_a}{\rightleftharpoons} H^+ + A^- \quad pK_a < 7$$

$$B\text{-}H^+ \overset{K_a}{\rightleftharpoons} H^+ + B: \quad pK_a > 7$$

Note that both reactions are written as acid dissociations with K_a dissociation constants.

Biochemistry mostly uses a modified Lowry-Brønsted definition of acids and bases:

For dissociation of a weak acid, the mass action equation is:

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

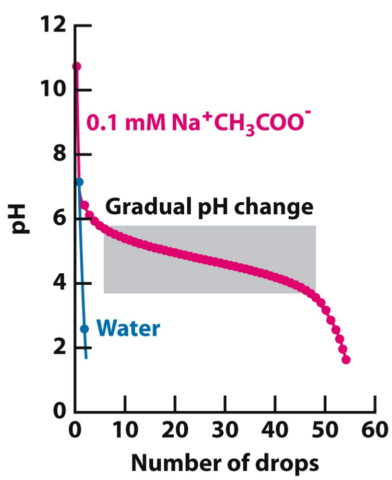
Biochemistry mostly uses a modified Lowry-Brønsted definition of acids and bases:

<u>Example</u>: dissociation of acetic acid

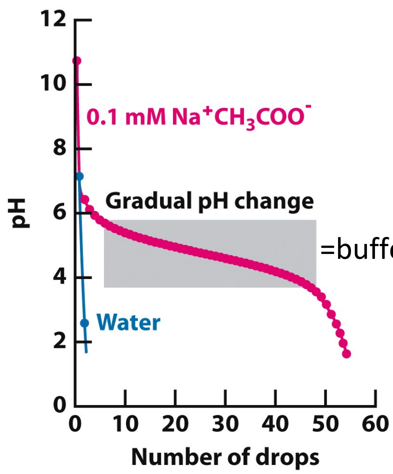
$$CH_3COOH \underset{}{\overset{K_a}{\rightleftharpoons}} H^+ + CH_3COO^-$$

$$K_a = \frac{[H^+]\,[CH_3COO^-]}{[CH_3COOH]}$$

Titration of acetate with acid

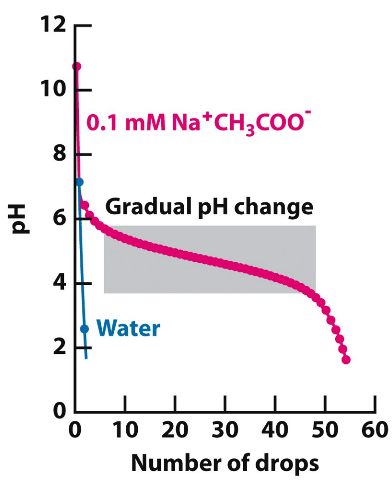


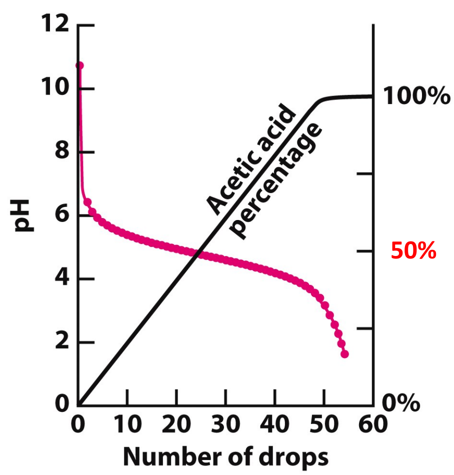
Titration of acetate with acid



=buffer range

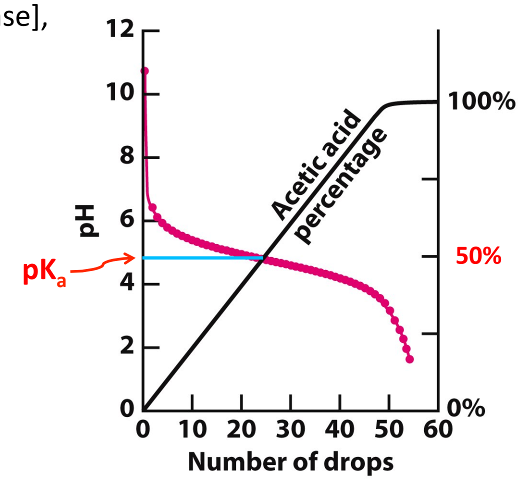
Titration of acetate with acid





Titration of acetate with acid

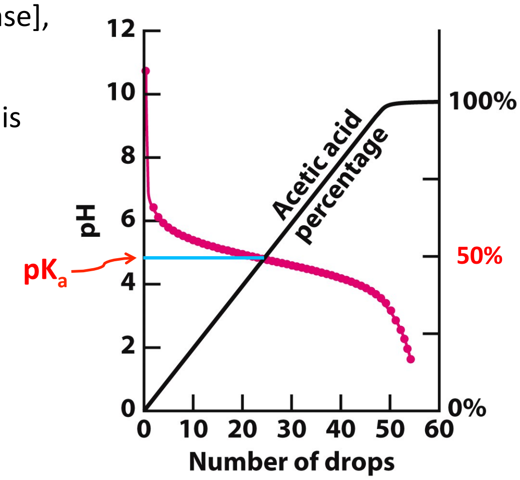
When [acid] = [conjugate base], $pH = pK_a$



Titration of acetate with acid

When [acid] = [conjugate base], $pH = pK_a$

Most effective buffer range is $pK_a \pm 1$



The Henderson-Hasselbalch equation is easily derived from the mass action equation for dissociation of a weak acid:

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

Question:

In a buffered solution, increasing the concentration of the conjugate base causes

A. an increase in pH.
B. a decrease in pH.
C. no change in pH because it's a buffer.
D. a pK_a shift in the acidic direction.
E. a pK_a shift in the basic direction.

Questions:

1. What is the pH relative to pK_a when [acid] = [conjugate base]?
2. What is the pH relative to pK_a when [acid] is 10 times higher than [conjugate base]?
3. What is the pH relative to pK_a when [conjugate base] is 10 times higher than [acid]?
4. What is the pH relative to pK_a when [acid] is 2 times higher than [conjugate base]?
5. What is the pH relative to pK_a when [conjugate base] is 20 times higher than [acid]?

The predominant buffer in biology is the CO_2/bicarbonate system:

$$CO_{2(g)} + H_2O \rightleftharpoons H_2CO_{3(aq)} \overset{K_a}{\rightleftharpoons} HCO_3^- + H^+$$

$pK_a = 6.1$

normal $[HCO_3^-]$ = 20 mM

$[H_2CO_3]$ (mM) = $0.03 \times pCO_2$ (Torr)

Thus:

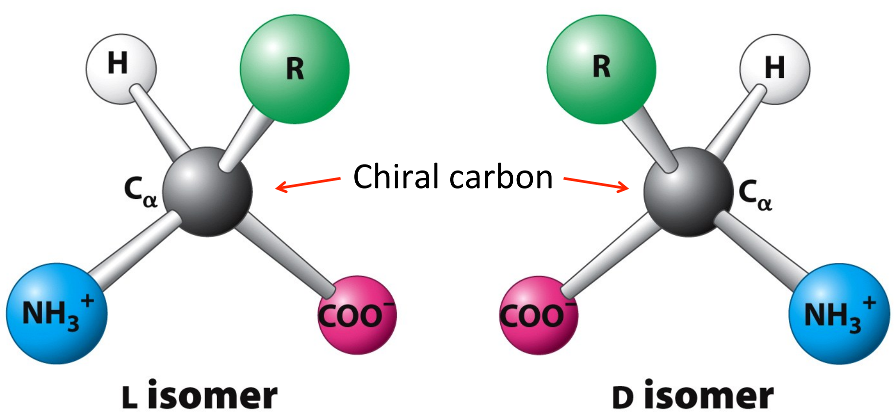
Questions:

1. What is the ratio of [conjugate base] to [acid] when pH = 7.4?
2. What pCO_2 is required to produce this ratio?
3. Is the CO_2/bicarbonate system an effective buffer at physiological pH?
4. What, if anything, is the advantage of this system?

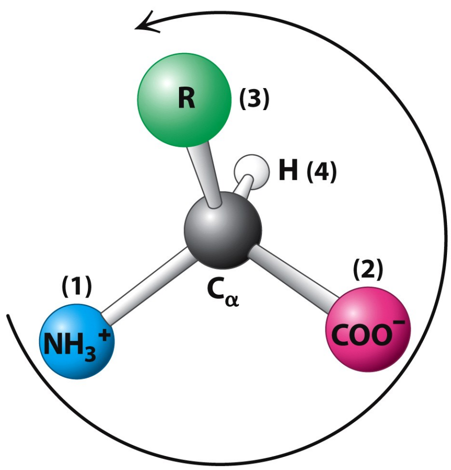
Amino acids

Generic structure of an α-amino acid

α-amino acids have two possible isomeric structures



Only the L isomers are prevalent in biology



D-amino acids:
In bacterial cell walls
D-Ser as co-agonist of NMDA receptor

Study tip: learn the dicarboxylic acids

Oh	Oxalic	C2
My	Malonic	C3
Such	Succinic	C4
Good	Glutaric	C5
Apple	Adipic	C6
Pie	Pimelic	C7

Structures of the 20 proteinogenic amino acids

W F Y

Structures of the 20 proteinogenic amino acids

W F Y

Structures of the 20 proteinogenic amino acids

L I V M

Structures of the 20 proteinogenic amino acids

L I V M

Structures of the 20 proteinogenic amino acids

P A G

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P A G

Structures of the 20 proteinogenic amino acids

CST

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CST

Structures of the 20 proteinogenic amino acids

H N Q

Structures of the 20 proteinogenic amino acids

H N Q

Structures of the 20 proteinogenic amino acids

D E K R

Structures of the 20 proteinogenic amino acids

D E K R

Table 2.1 Typical pK_a values of ionizable groups in proteins

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
Tyrosine		⇌		10.9
Lysine		⇌		10.8
Arginine		⇌		12.5

*pK_a values depend on temperature, ionic strength, and the microenvironment of the ionizable group.

Know approximate pK_a values:

3

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8

11

12

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Which forms are predominant at physiological pH?

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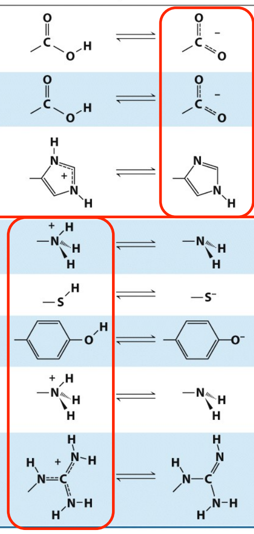

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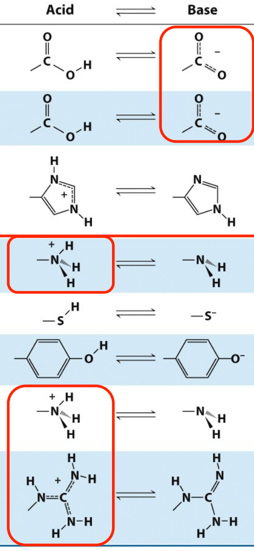

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Know approximate pK_a values:

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6

7

8

11

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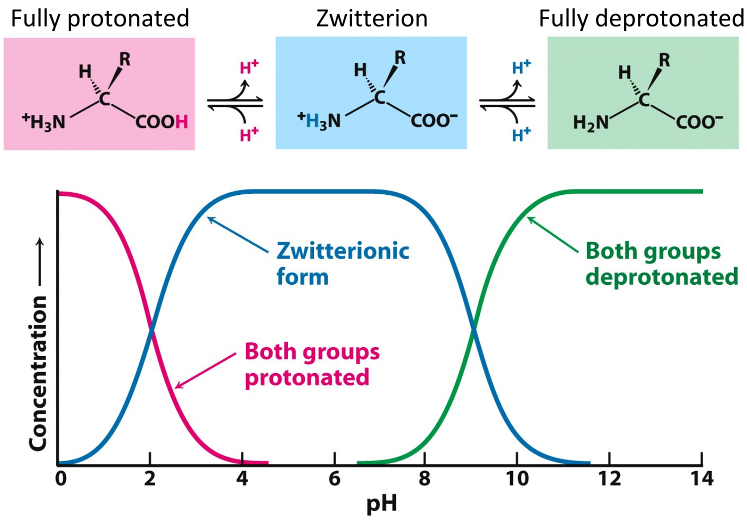
Which forms are predominant at physiological pH?

Which groups will be mostly charged at physiological pH?

Amino acids are zwitterions at neutral pH



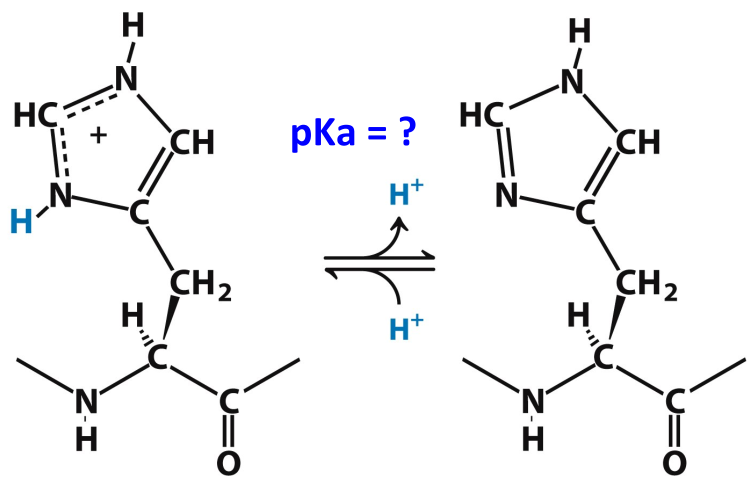
Amino acids have N+1 protonation states

N= number of ionizable groups
N= 2 if side chain is not ionizable
N= 3 if side chain is ionizable

Example: titration of glutamic acid

Understanding titration of side chains is important for understanding isoelectric point of a protein

Ability to accept and delocalize charge makes histidine's side chain useful for catalysis



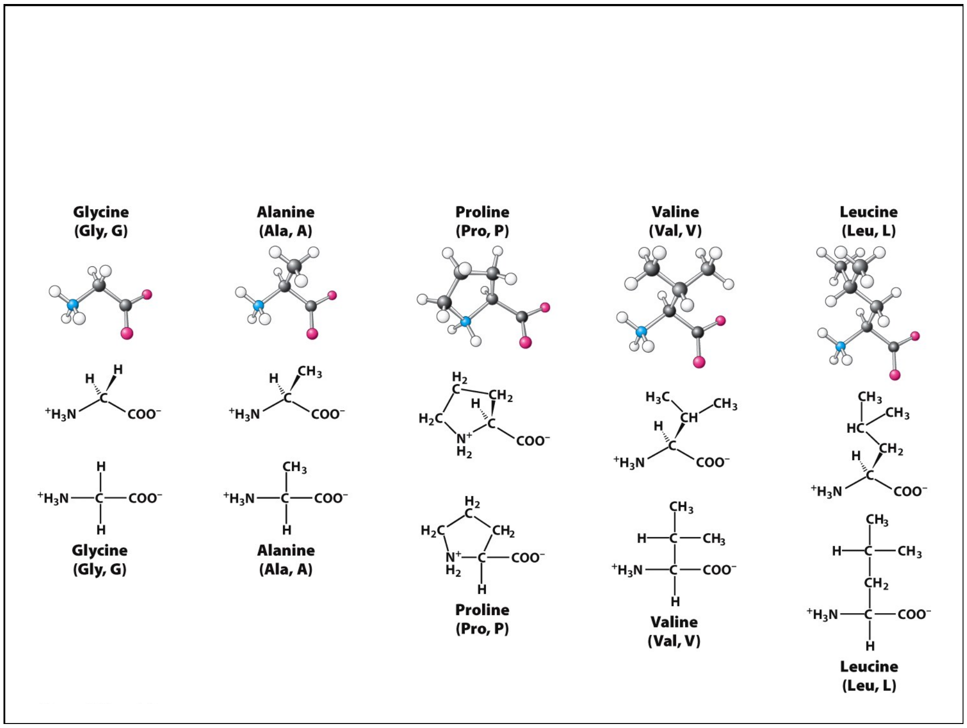
Lecture 1 Recap

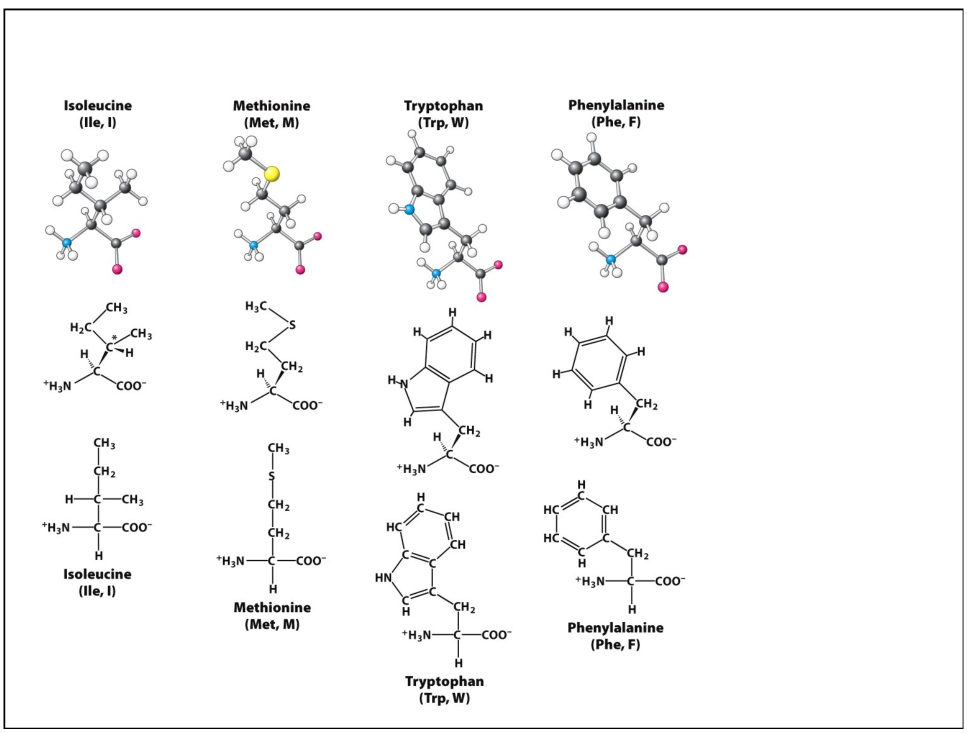
1. Review of chemical bonding, thermodynamics, and nucleophilic reactions
2. Acid-base chemistry in biological systems
3. Amino acid structures and properties

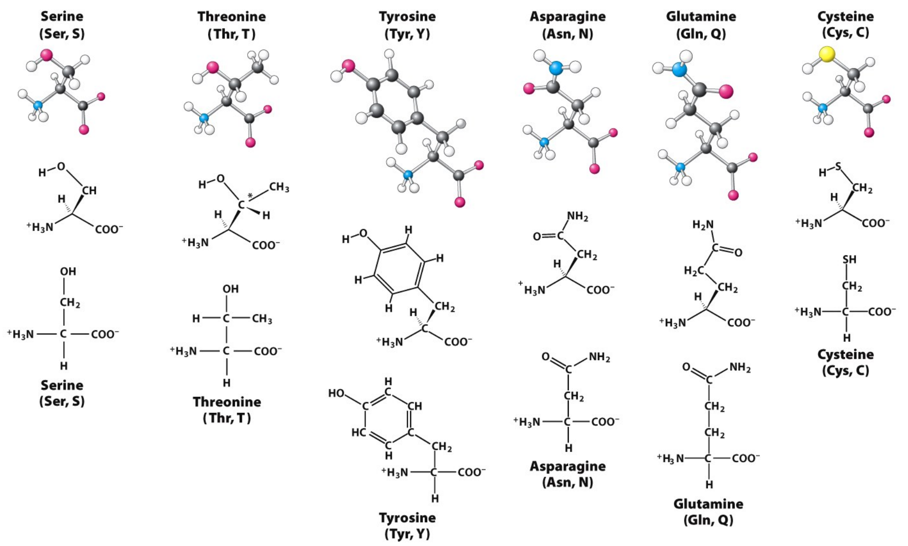
Appendix

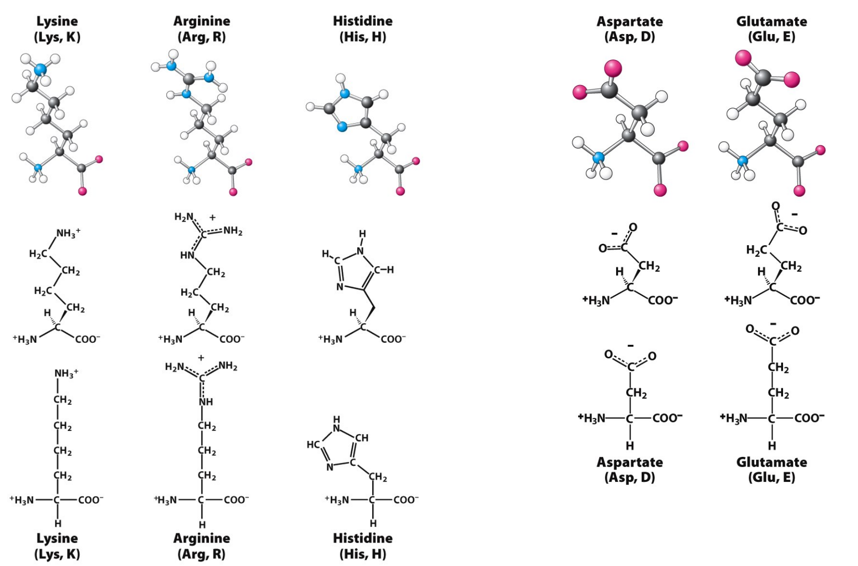
Table 2.2 Abbreviations for amino acids

Amino acid	Three-letter abbreviation	One-letter abbreviation	Amino acid	Three-letter abbreviation	One-letter abbreviation
Alanine	Ala	A	Methionine	Met	M
Arginine	Arg	R	Phenylalanine	Phe	F
Asparagine	Asn	N	Proline	Pro	P
Aspartic acid	Asp	D	Serine	Ser	S
Cysteine	Cys	C	Threonine	Thr	T
Glutamine	Gln	Q	Tryptophan	Trp	W
Glutamic acid	Glu	E	Tyrosine	Tyr	Y
Glycine	Gly	G	Valine	Val	V
Histidine	His	H	Asparagine or aspartic acid	Asx	B
Isoleucine	Ile	I	Glutamine or glutamic acid	Glx	Z
Leucine	Leu	L			
Lysine	Lys	K			


Glycine
(Gly, G)
Alanine
(Ala, A)
Proline
(Pro, P)
Valine
(Val, V)
Leucine
(Leu, L)


Isoleucine
(Ile, I)
Methionine
(Met, M)
Tryptophan
(Trp, W)
Phenylalanine
(Phe, F)


Serine
(Ser, S)
Threonine
(Thr, T)
Tyrosine
(Tyr, Y)
Asparagine
(Asn, N)
Glutamine
(Gln, Q)
Cysteine
(Cys, C)


Lysine
(Lys, K)
Arginine
(Arg, R)
Histidine
(His, H)
Aspartate
(Asp, D)
Glutamate
(Glu, E)