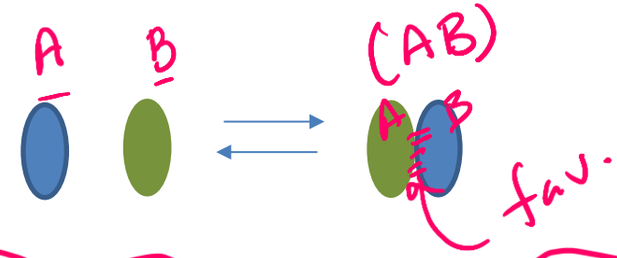
Lecture 1
Chemistry and Biology Fundamentals II

- Chirality of carbon, chiral drugs
- Molecular interactions
- pH and charge
- Protein Structure and Stability
- Ligand Binding
- Proteins as enzymes (PKU disease)

Molecular Interactions



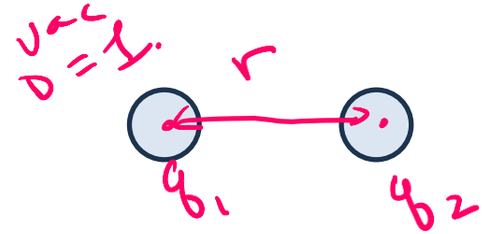
$$\Delta E = E_{AB} - (E_A + E_B) \sim E_{A \cup B}$$

The energy change when two things come together can be approximated to be due to ***new*** inter-molecular interactions: $E_{A \cup B}$.

Interaction	Interaction	Energy (kJ/mol)
Electrostatic interactions (in water)	Full charges	~5 kJ/mol/single interaction
Van der Waals: Dipole-Dipole	Perm. partial charges	~0.05 kJ/A^2 x 100 A^2 = 5 kJ/mol for 100 A^2
Van der Waals: Induced-dipole	Induced partial charges	~0.02 kJ/A^2 x 100 A^2 = **2 kJ/mol for 100 A^2**
H-Bonds	Electrostatic + e sharing	~20 kJ/mol gross, **~5 kJ/mol net**

i) Electrostatics: The interaction energy between two charged particles is:

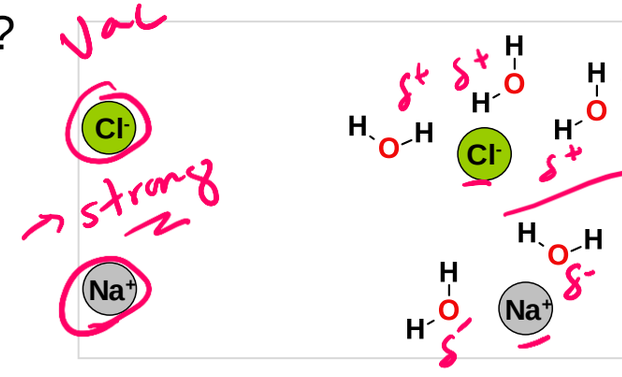
$$E = \frac{1}{D}\frac{1}{4\pi\varepsilon_o}\frac{q_1 q_2}{r}$$



The energy depends on the charges of the particles (q_1, q_2), distance (r) between the two charges, and the dielectric constant (D) of the media.

How strong are electrostatic interactions?
$Na^+ Cl^-$ = ~ -700 kJ/mol *in vacuum (D=1) when r = 2A*

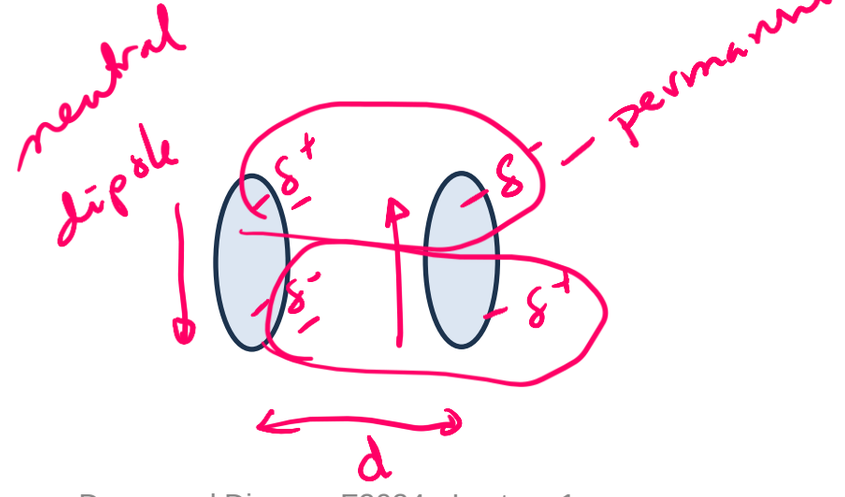
Water has a high dielectric constant of 80 due to its polar nature. How does this affect the energy of interaction?

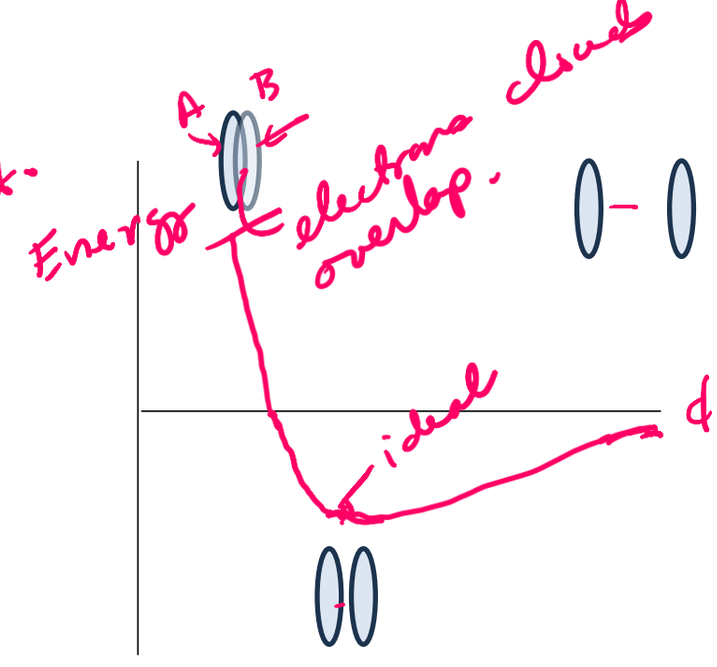


Electrostatic energy of *point* charges.

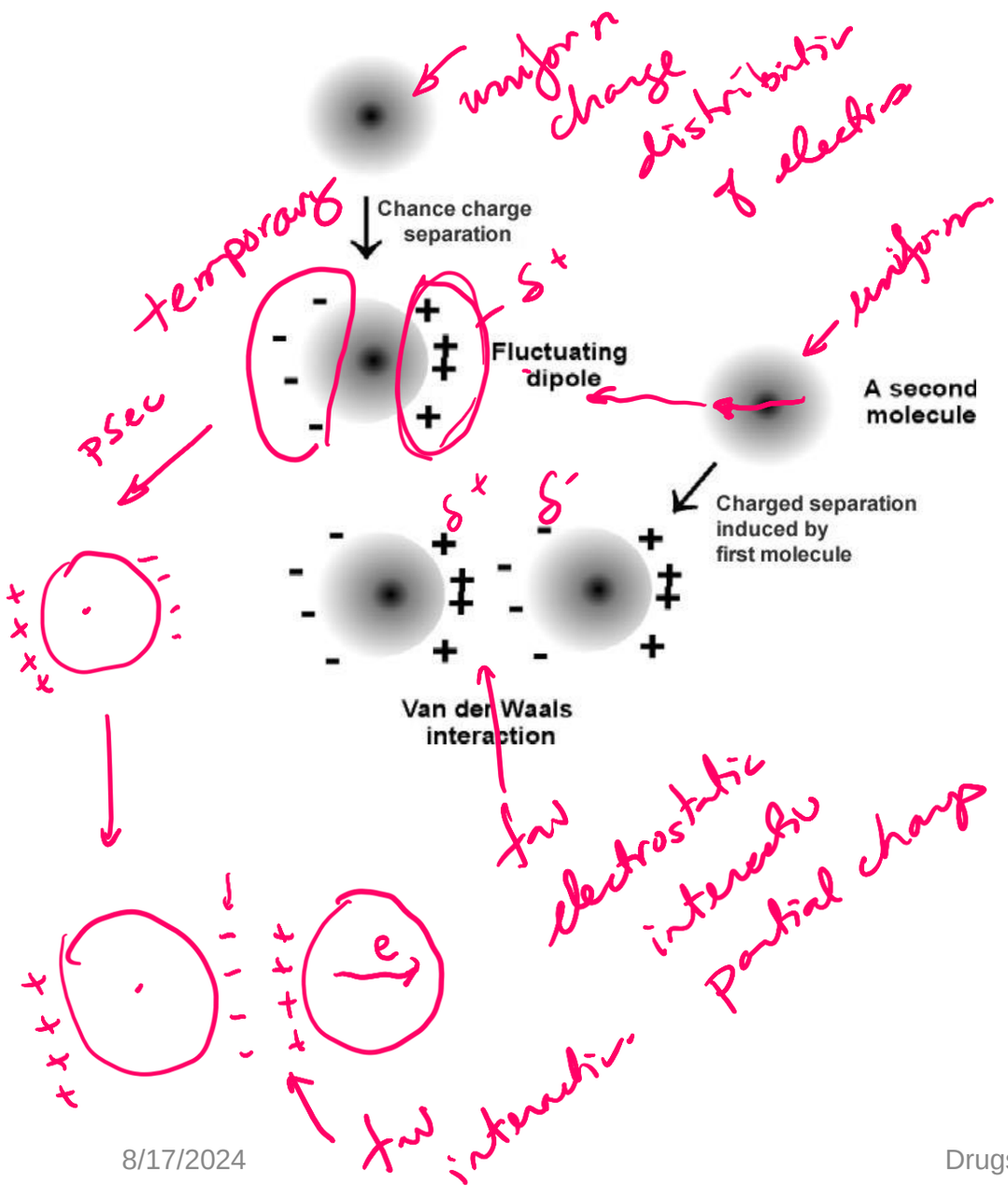
Van Der Waals Forces:

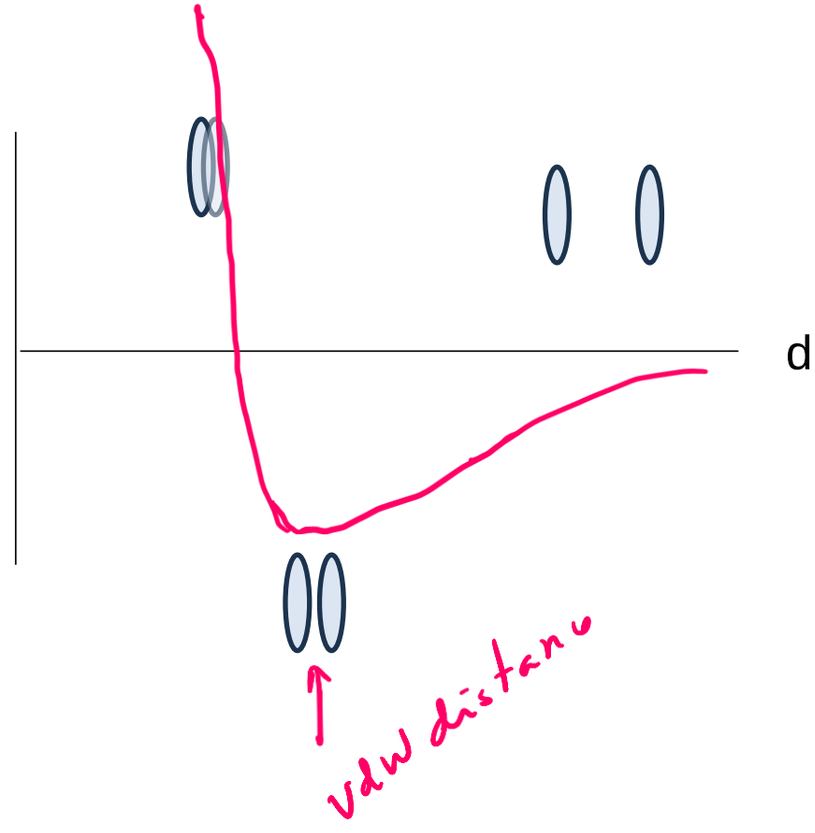
ii) Dipole-dipole – an electrostatic interaction that involves permanent ***partial*** charges (these are sometimes called Keesom forces).





iii) **Induced dipole** (often referred to as London Dispersion)



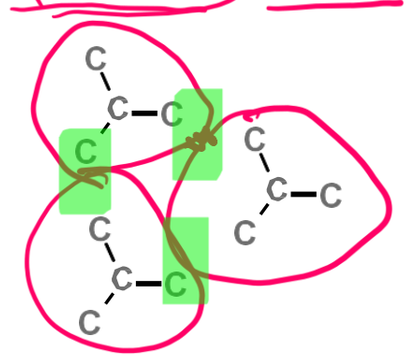


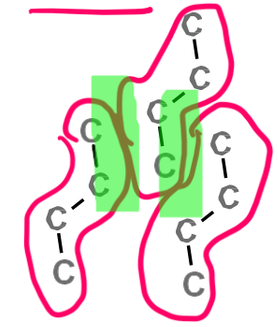
iii) Induced dipole (often referred to as London Dispersion)

Although weak, the effects of van der Waals are easily observed: Boiling points of two hydrocarbons:

isobutane: 261 K

butane: 272 K





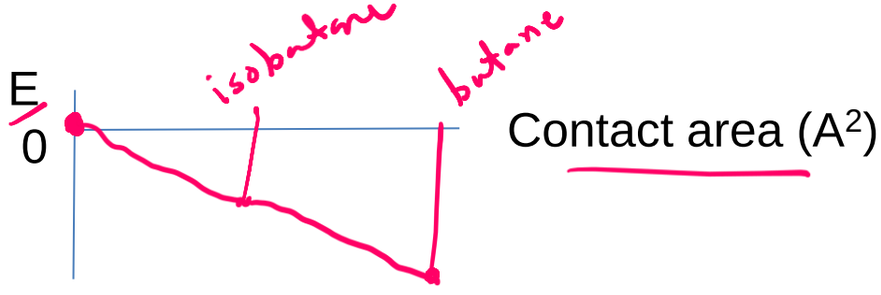
Δ = 11 K.

1. Same number of carbons, why the difference in boiling points?

electrostatic (complete charge)

vdw ?

2. How will van der Waals interaction energies scale with contact area?

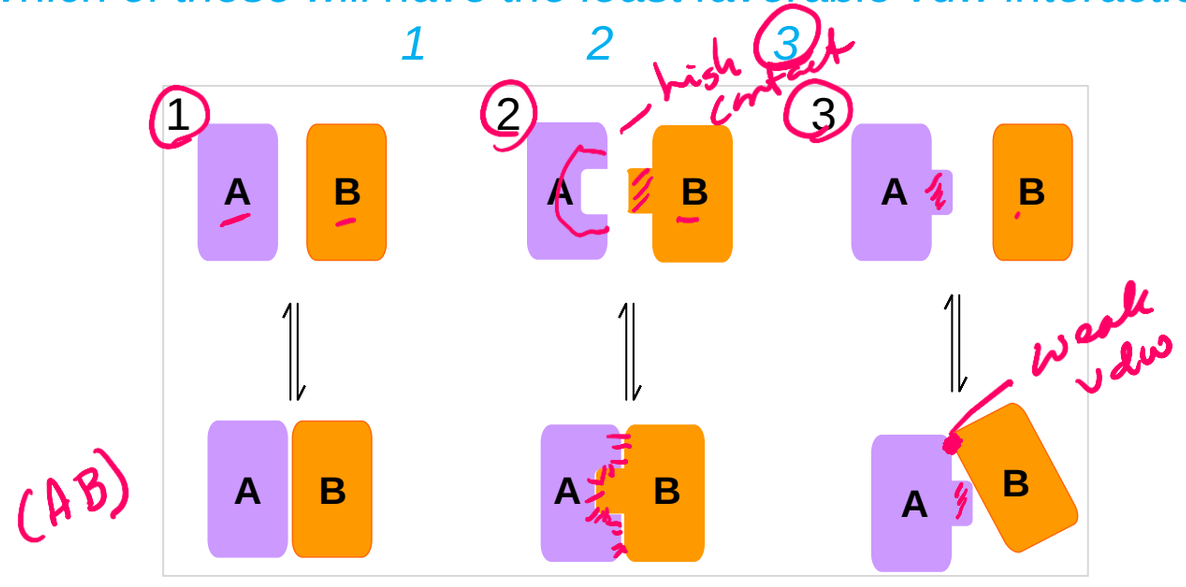


3. Which of these will have the most favorable vdw interaction:

1 2 3

4. Which of these will have the least favorable vdw interaction:

1 2 3



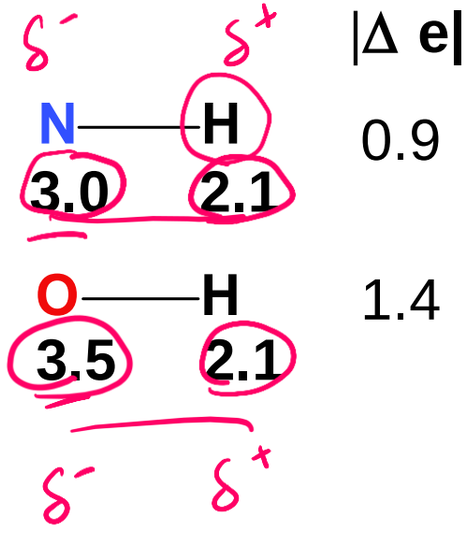
https://www.youtube.com/watch?v=uhfXbSSrabw

iv) Hydrogen Bonds

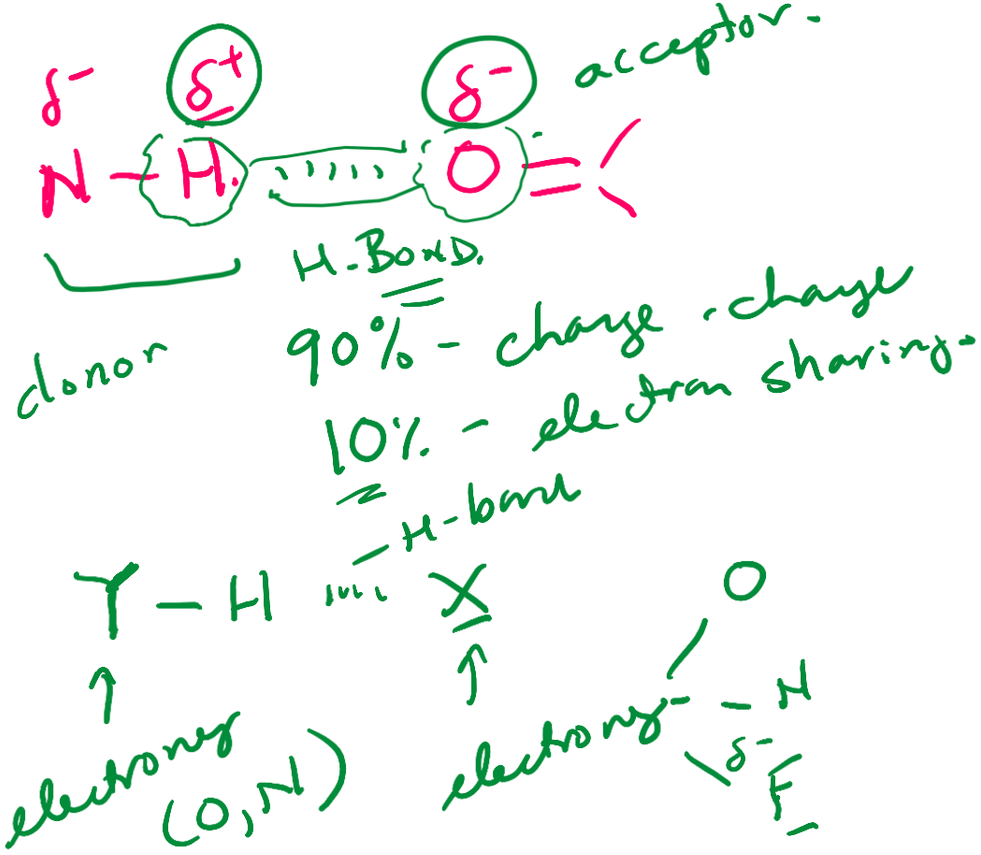
- H-bonds are primarily (90%) an electrostatic attraction between:
  - Electropositive hydrogen, attached to an electronegative atom is the hydrogen bond donor (i.e. NH).
  - Electronegative hydrogen bond acceptor (e.g. the lone pairs of oxygen, or C=O group of an amide).

A "bond" implies electron sharing – about 10% of the electron is shared from one molecule to the next in the case of H-bonds

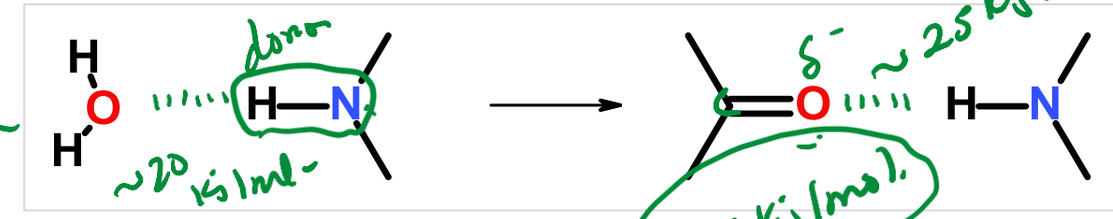
*Note that the proton is **NOT** transferred to the acceptor, it remains covalently bonded to the donor atom. The Hydrogen Bond is the **interaction** between the X-H donor and electronegative acceptor.*



	|Δ e|
N—H	0.9
O—H	1.4



- The energy released when an H-bond forms depends on the distance and angle of the bond.
- Usually hydrogen bonds are exchanged, resulting in small ***net*** energy differences:



Relative Energy of Interactions

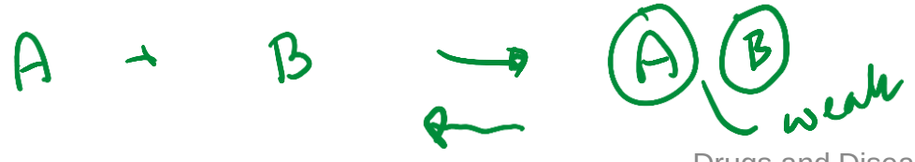
Interaction	Interaction	Energy (kJ/mol)
Covalent Bond	Electron sharing	200-400 kJ/mol
Electrostatic interactions (in water)	Full charges	~5 kJ/mol/single interaction
VdW - Dipole-dipole (Keesom)	Perm. partial charges	~0.05 kJ/A^2 x 100 A^2 = 5 kJ/mol for 100 A^2
VdW – Induced dipole (London)	Induced partial charges	~0.02 kJ/A^2 x 100 A^2 = **2 kJ/mol for 100 A^2**
H-Bonds	Electrostatic + e sharing	~20 kJ/mol gross, **~5 kJ/mol net**

1. How does the energy of the last four interactions compare to covalent bonds?

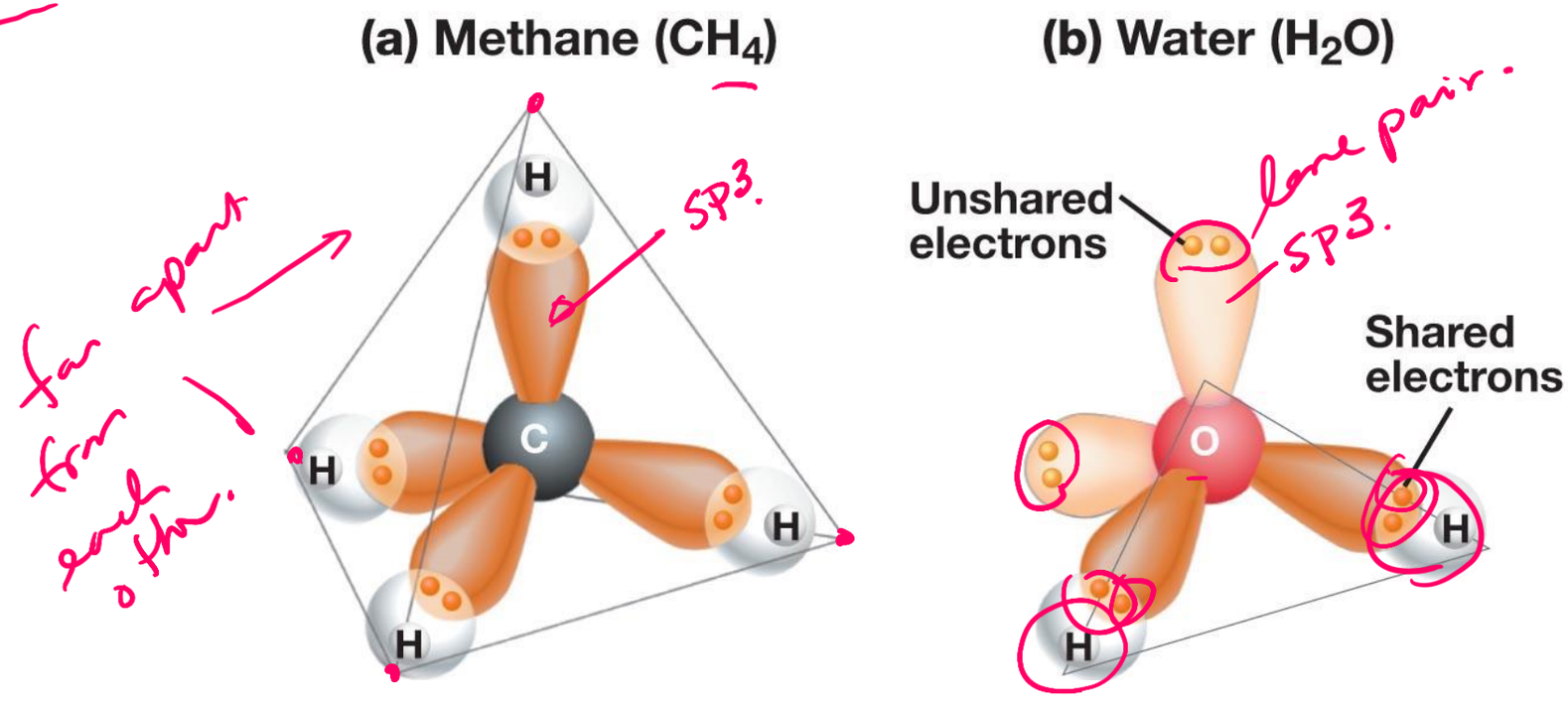
1. Stronger 2. Weaker 3. The Same

2. Which of these are closer to thermal energy, kT = 2.5 kJ/mol @ room temp.

3. What is the advantage of a weak interaction in biology?



The Geometry of Simple Molecules

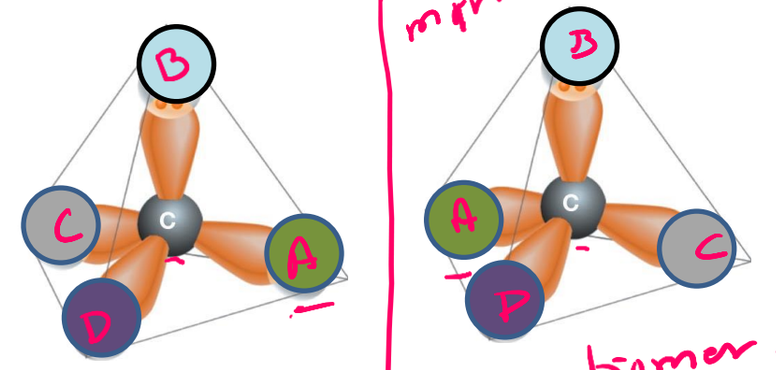


The shape of a molecule is determined by the geometry of its bonds.

Carbon, oxygen, and nitrogen often form bonds with a tetrahedral geometry

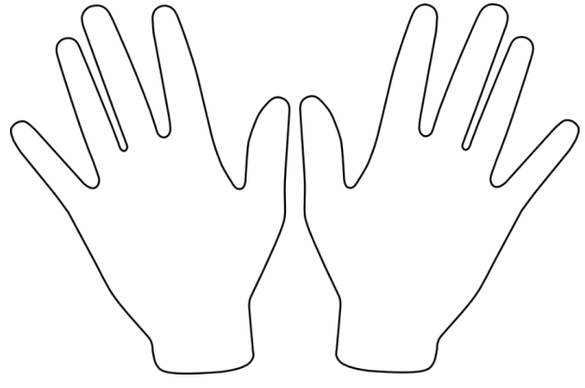
Unique Feature of Tetrahedral Carbon - Chirality

- A single tetrahedral carbon atom can have four groups attached (group = collection of atoms)
- If the four groups are different, then two forms of the molecule are possible, they are **mirror images** of each other.
- The carbon that has four different *groups* is called a **chiral carbon.**
- The two different mirror-image molecules are called **enantiomers**
- These two *cannot be superimposed* on each other (superimposed = rotated so that the same atoms overlap)
- A mixture of both enantiomers is called a **racemic mixture**.
- One naming system to distinguish enantiomers is D & L

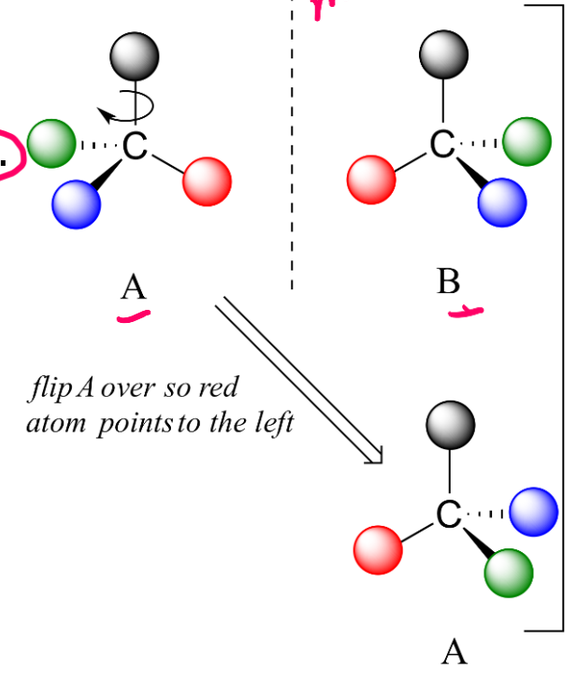


mirror plane

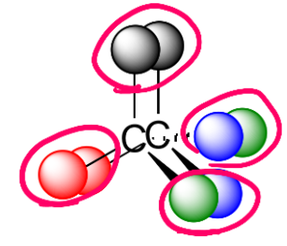
enantiomer.



50% A
50% B



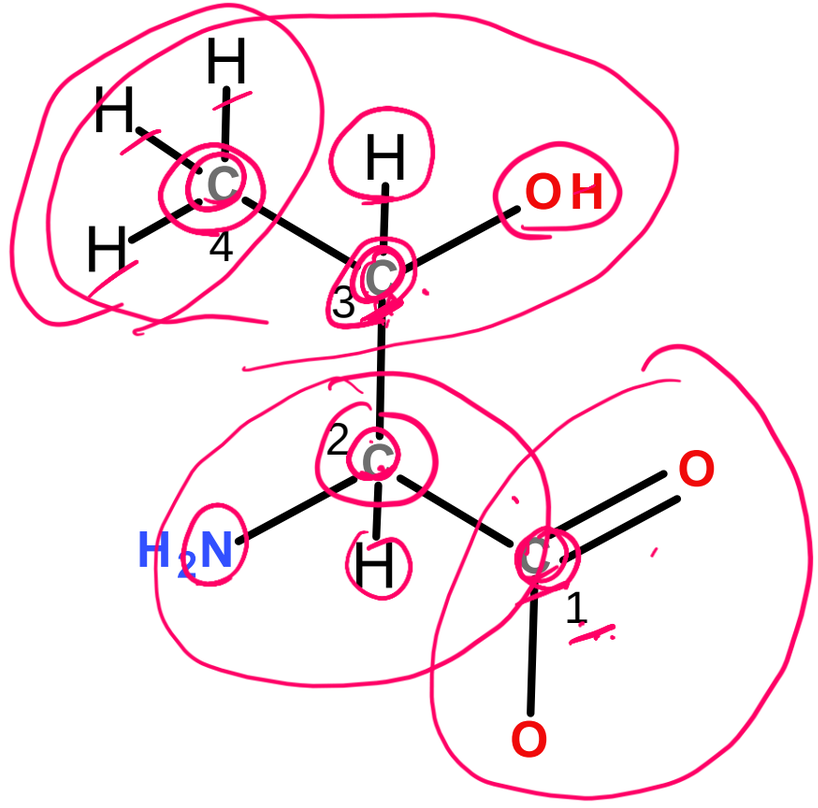
mirror.



*A and B cannot be superimposed: they are **not** the same molecule!*

Identify the Chiral Centers on Threonine

Can you identify chiral centers?



Which carbon is chiral?

1 Yes or No?

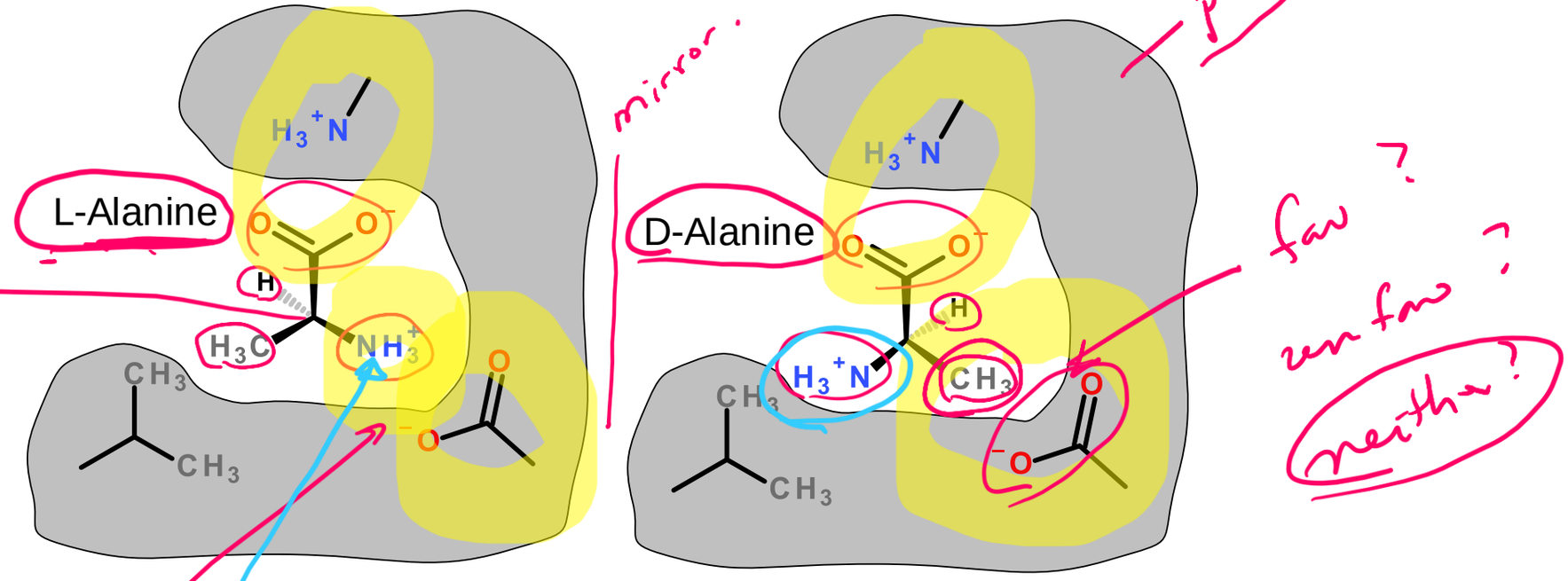
2 Yes or No?

3 Yes or No?

4 Yes or No?

Chirality and Molecular Interactions

Two Different enantiomers (L and D alanine) binding to the same receptor protein



L-Alanine binds better because of more favorable electrostatic interact. *interactions.*

Drugs with Chiral Centers

Nobel Prize for Chiral Synthesis 2001

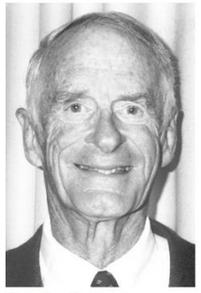


Photo from the Nobel Foundation archive.
William S. Knowles


Photo from the Nobel Foundation archive.
Ryoji Noyori

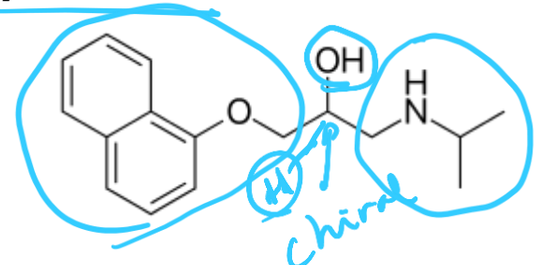

Photo from the Nobel Foundation archive.
K. Barry Sharpless

and a fun game:

https://educationalgames.nobelprize.org/educational/chemistry/chiral/game/game.html

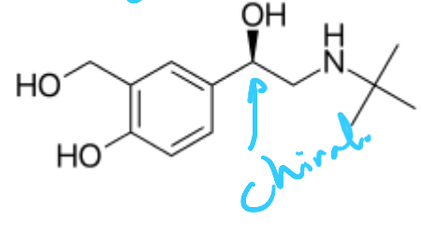
1) one form more active
2) other form can be toxic.
naproxin → headache
→ liver toxin.

Propranolol



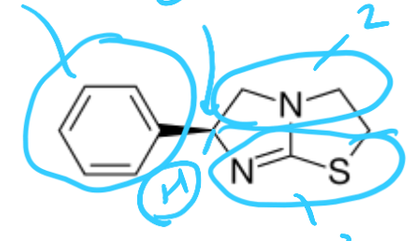
1. Racemic mixture is used to treat high blood pressure.

levalbuterol



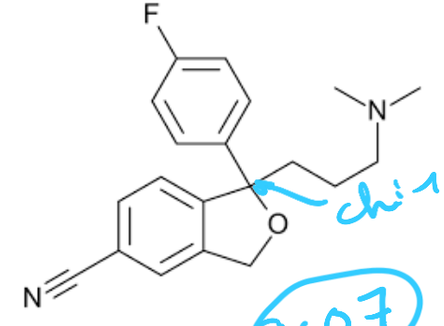
2. R-enantiomer used to treat asthma

levamisole



3. L-form used to treat parasitic worm infections

citalopram



4. Antidepressent (escitalopram is L)

9:02 → 9:07

pH, Strong Acids & Bases

- $pH = -\log [H^+] = -\log[H_3O^+]$
- The pH of a solution tells us how acidic the solution is.
- The pH scale is used to transform the large range of possible [H+] values to more manageable numbers.
- **Note a low pH is a high [H+].**

The pH is a property of the solvent (water) and can be changed by the addition of a strong acid or base, such as HCl or NaOH.

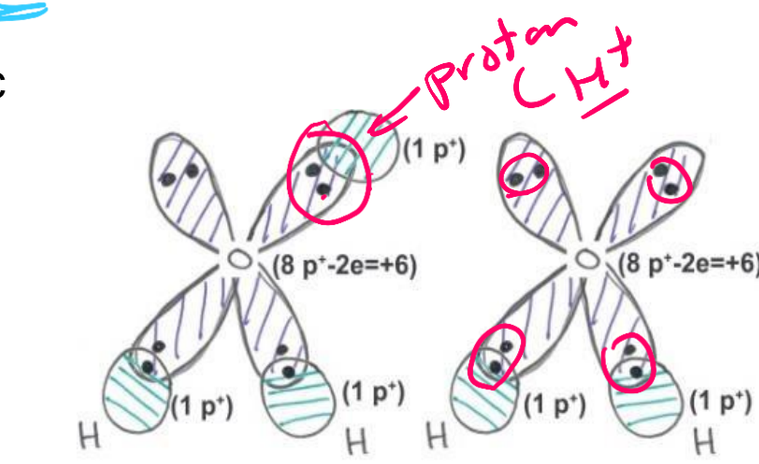
- Acids release protons and will lower the pH of the solution, e.g.

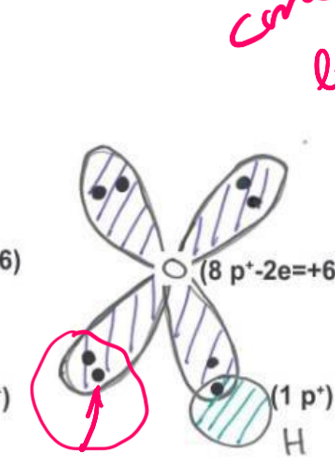
  $HCl + H_2O \rightarrow H_3O^+ + Cl^-$

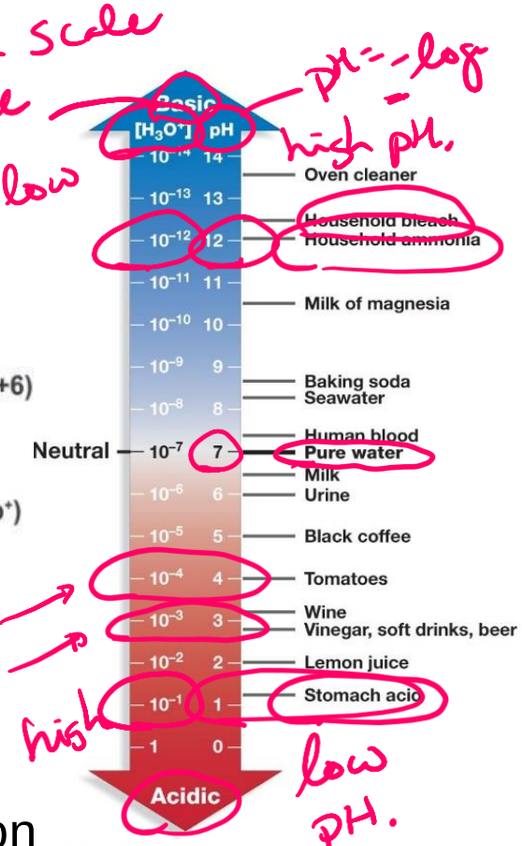
- Bases (e.g. ammonia, sodium hydroxide) will absorb protons and lower the hydrogen ion concentration. These increase the pH.

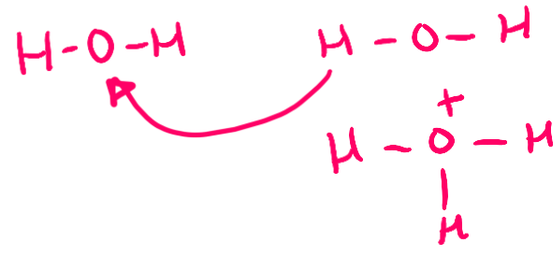
  $NaOH \Rightarrow Na^+ + OH^-$

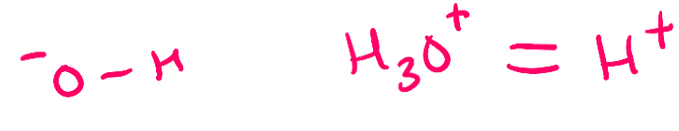
  $OH^- + H_3O^+ \rightarrow 2\ H_2O$











10 fold

1. Which solution has a higher H^+ concentration, pH=3 or pH 4.

2. How large is the difference?

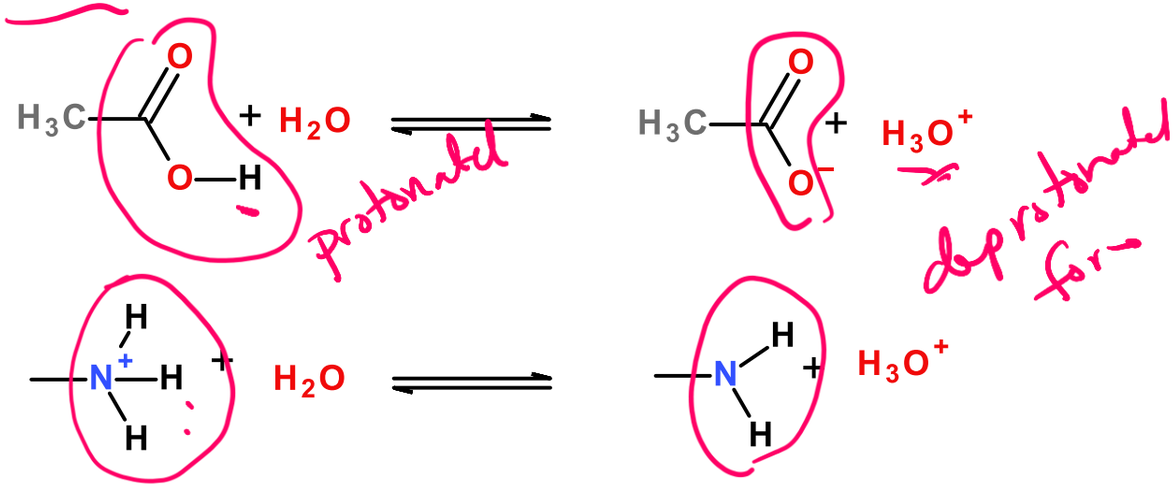
pH 3 $[H^+] = 10^{-3}$ pH 4 $[H^+] = 10^{-4}$

Acids and Bases.

Strong acid – complete ionization in solution. e.g.

$HCl \longrightarrow H^+ + Cl^-$

Weak Acid – incomplete ionization in solution.

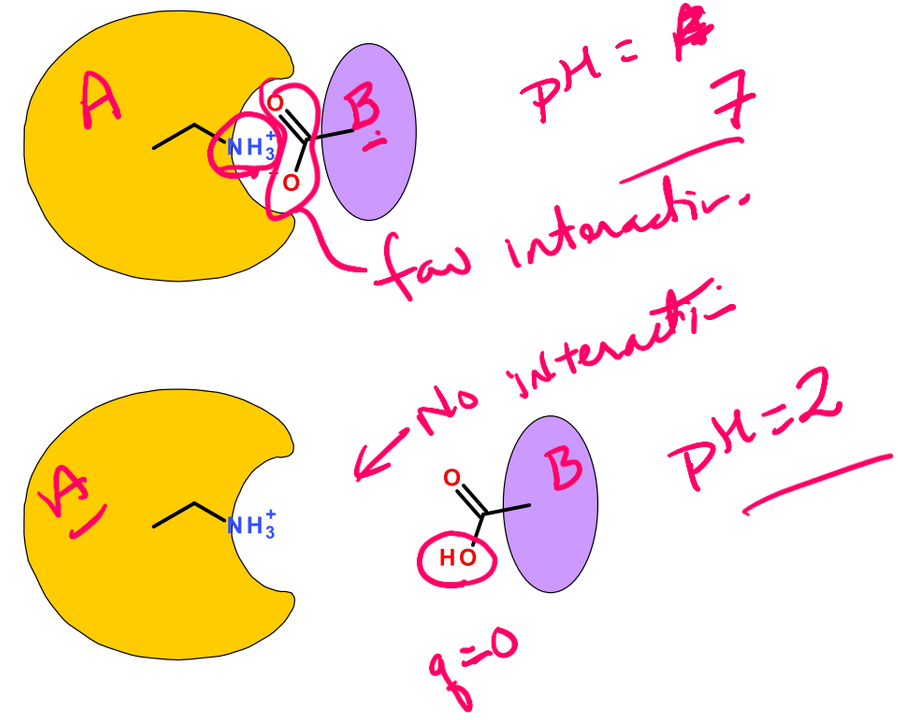


“HA”=protonated form

“A”=deprotonated form (conjugate base)

Why this is important:

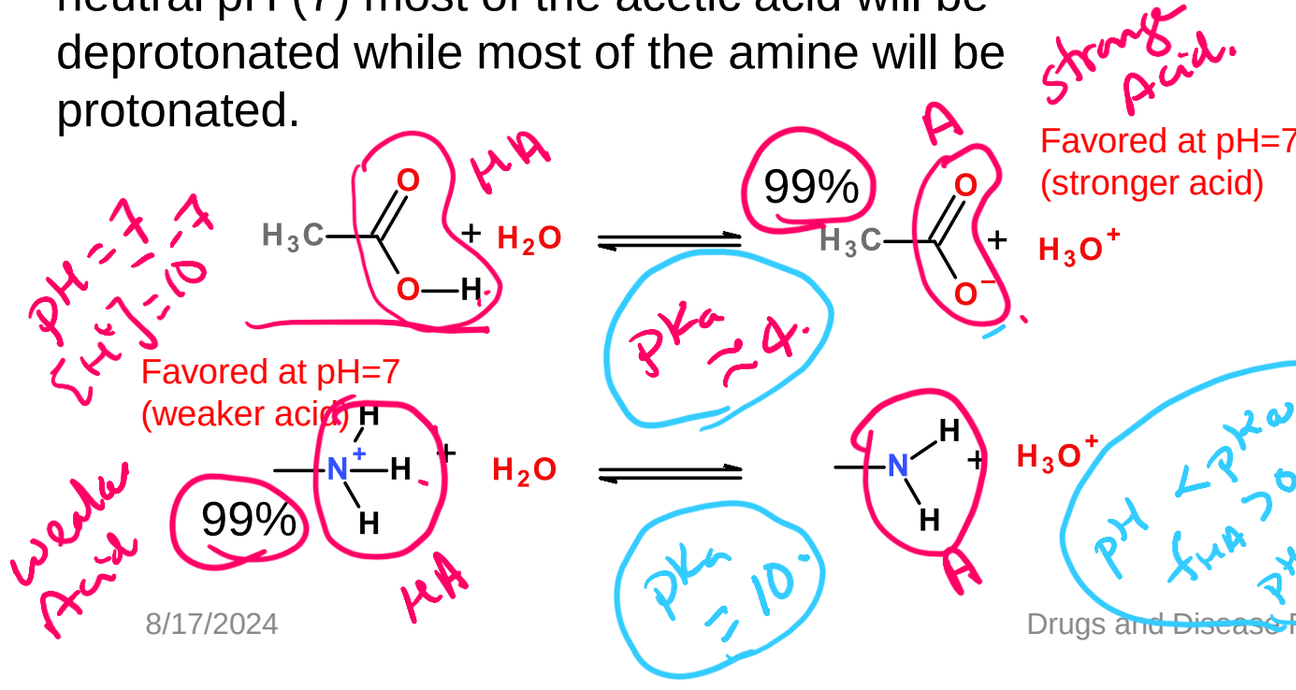
protonation/deprotonation changes the ***charge*** on species, either creating or destroying strong electrostatic interactions!



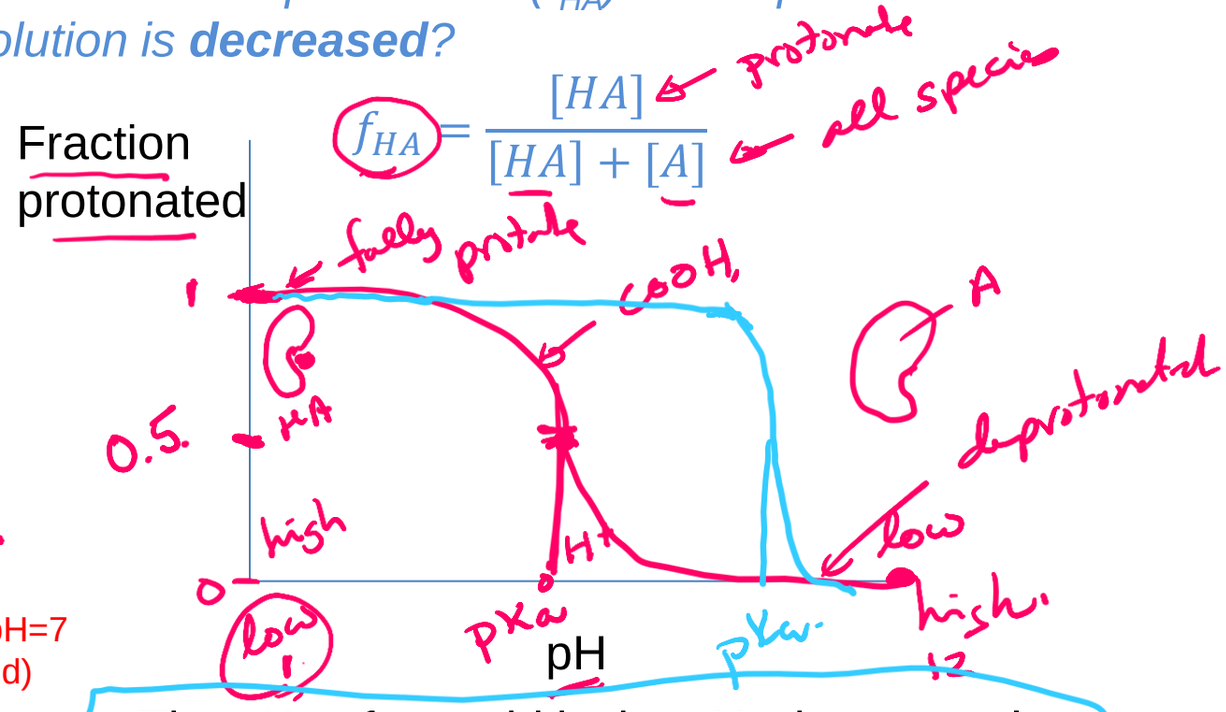
What Affects the Degree of Protonation?

1. The extent of protonation/deprotonation depends on the pH of the solution:
   - Low pH values will favor protonation of acids since there are many protons that will collide with (A) to make (HA).
   - High pH values will favor deprotonation of acids since there are fewer protons to protonate the acid.

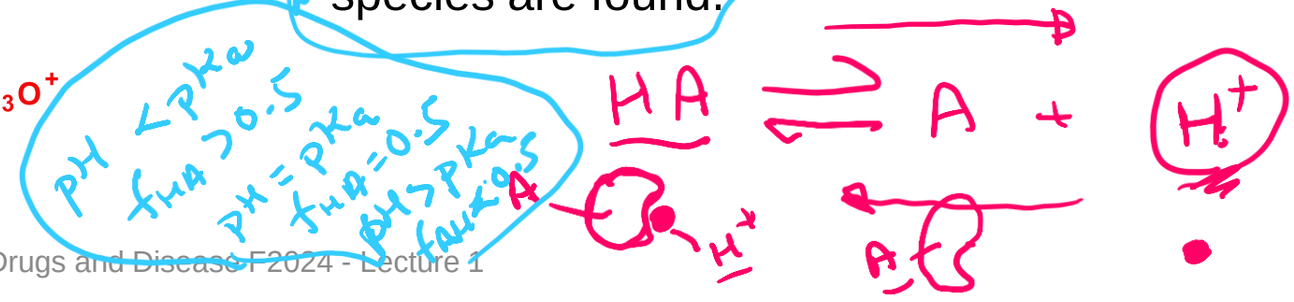
2. The amount of protonated/deprotonated species *also* depends on the chemical properties of the acid. Comparing acetic acid to a protonated amine. At neutral pH (7) most of the acetic acid will be deprotonated while most of the amine will be protonated.



*What would you expect to happen to the fraction of the acid that is protonated (f_{HA}) as the pH of the solution is **decreased**?*



The pKa of an acid is the pH where equal amounts of protonated and deprotonated species are found.



Key Points & Expectations

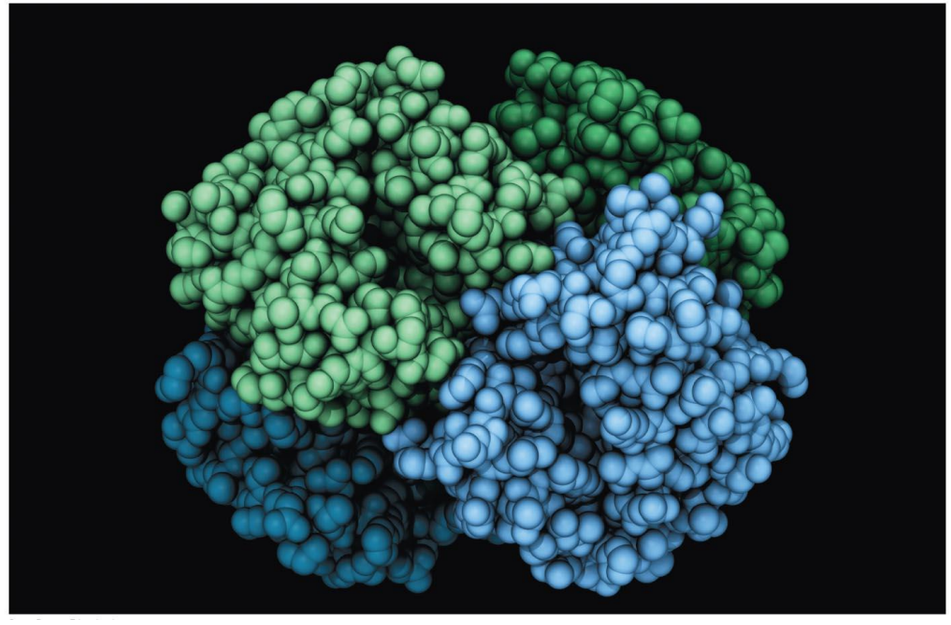
Chemistry

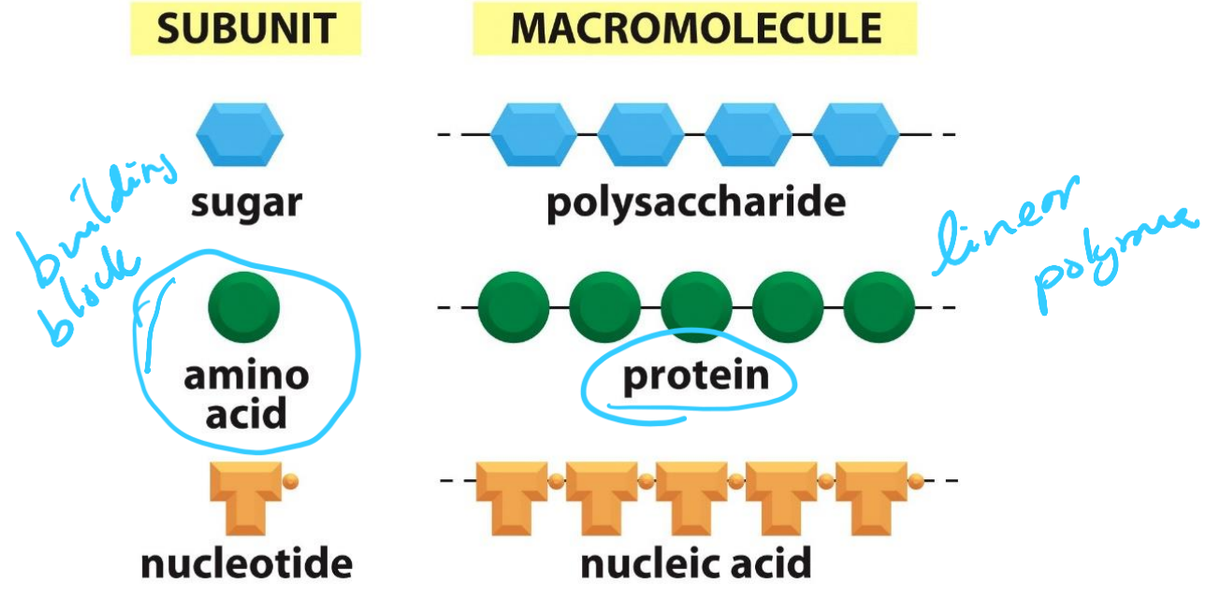
- Number of bonds formed by common elements:

  (N=3, C=4, O=2, S=2, H=1).

- You should be able to complete chemical structures by adding hydrogens to carbons.
- Chiral carbon and enantiomers - different enantiomers can have different properties. You need to identify chiral carbons.
- Polar (unequal charge distribution, e.g. N-H) versus non-polar bonds (e.g. C-H). You need to be able to identify polar and non-polar bonds.
- H-bond - Partial charges due to X-H interacting with Y (X & Y electronegative)
- H-bond - Identify donors and acceptors, partial charges
- pH – be able to predict the charge on a group, given the pH of the solution and the pKa of the acid.

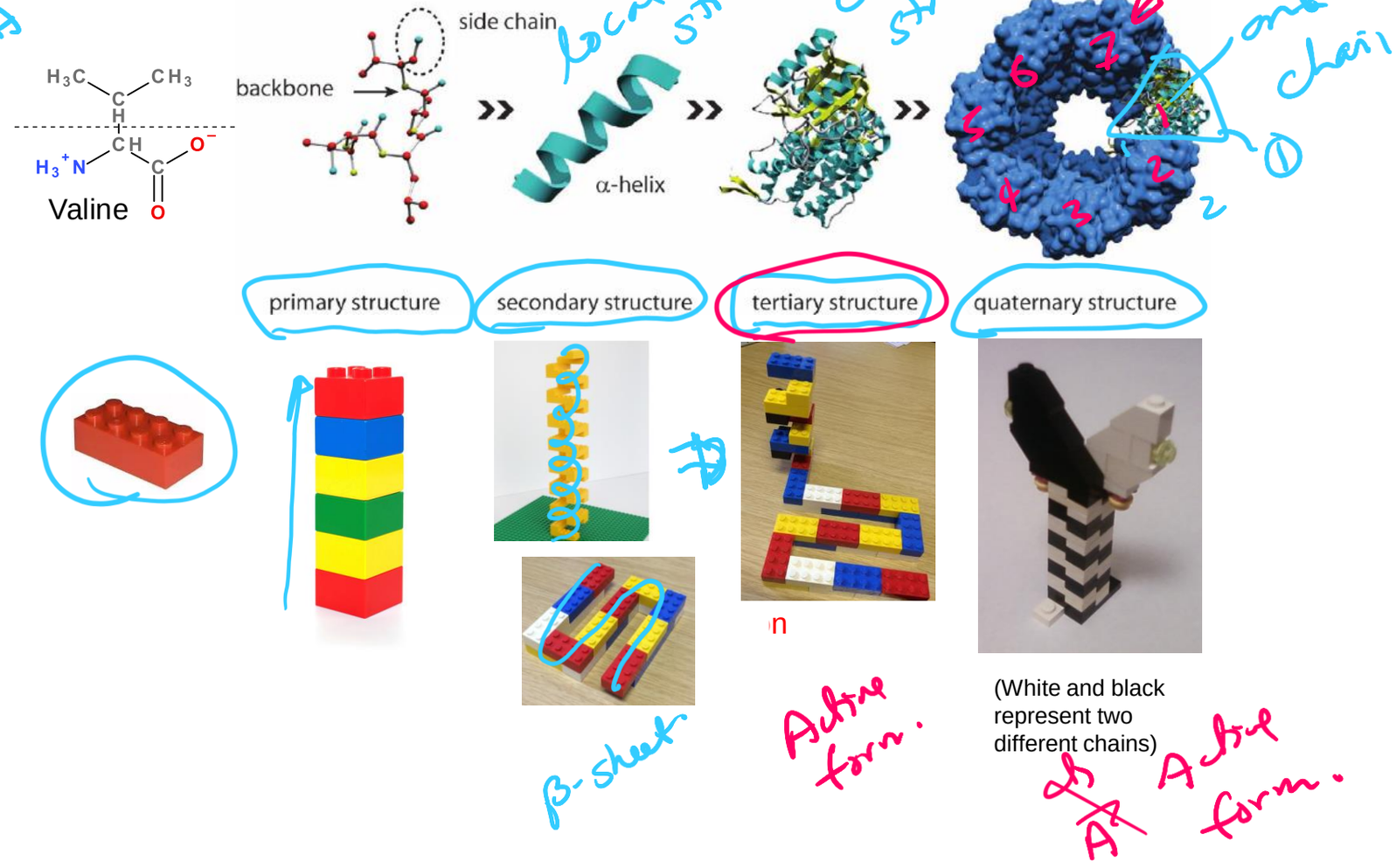
Proteins and Amino Acids

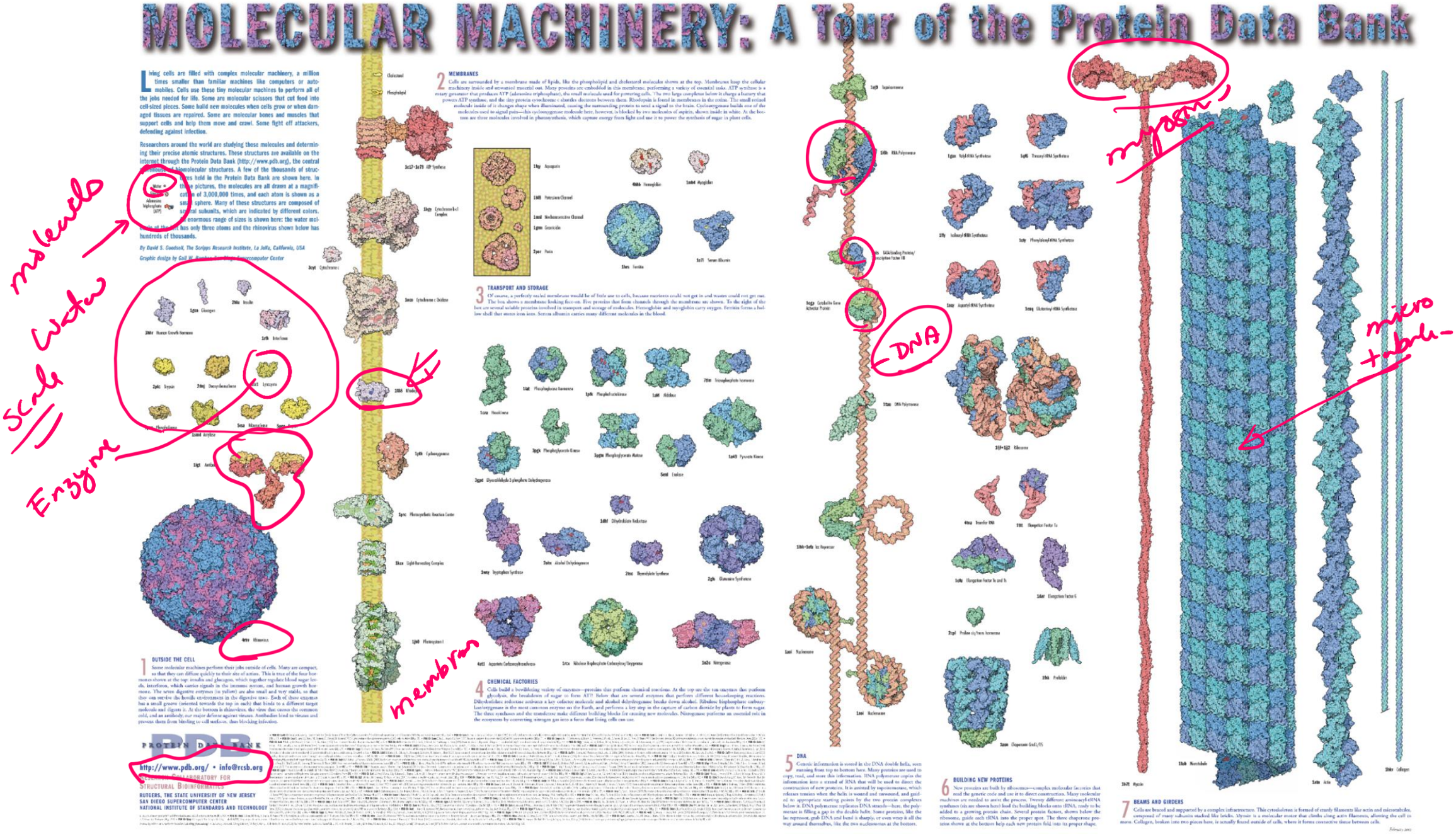




Structural Hierarchy of Proteins

- Primary - sequence of amino acids, no 3D structural information
- Secondary - local structural elements, only mainchain atoms involved
- Tertiary - 3D position of ***all*** atoms, functional form of many proteins.
- Quaternary - multiple chains – multiple chains often required for function.




MOLECULAR MACHINERY: A Tour of the Protein Data Bank
Living cells are filled with complex molecular machinery, a million times smaller than familiar machines like computers or automobiles. Cells use these tiny molecular machines to perform all of the jobs needed for life. Some are molecular scissors that cut food into cell-sized pieces. Some build new molecules when cells grow or when damaged tissues are repaired. Some are molecular bones and muscles that support cells and help them move and crawl. Some fight off attackers, defending against infection.
Researchers around the world are studying these molecules and determining their precise atomic structures. These structures are available on the internet through the Protein Data Bank (http://www.pdb.org), the central repository of biomolecular structures. A few of the thousands of structures held in the Protein Data Bank are shown here. In these pictures, the molecules are all drawn at a magnification of 3,000,000 times, and each atom is shown as a small sphere. Many of these structures are composed of several subunits, which are indicated by different colors. The enormous range of sizes is shown here: the water molecule at the left has only three atoms and the rhinovirus shown below has hundreds of thousands.
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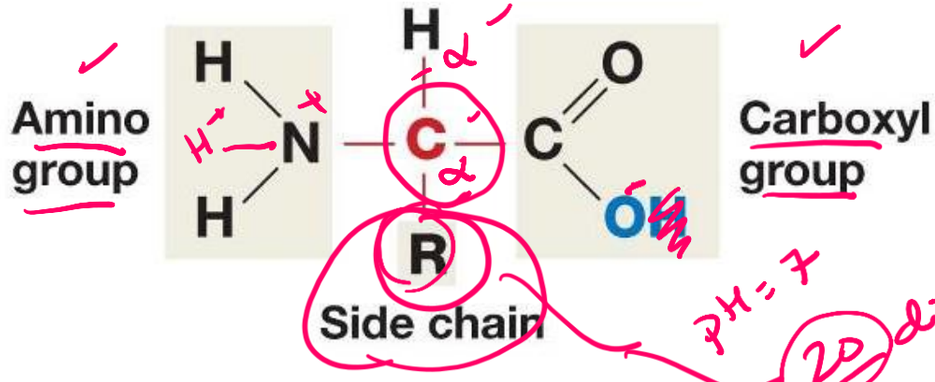
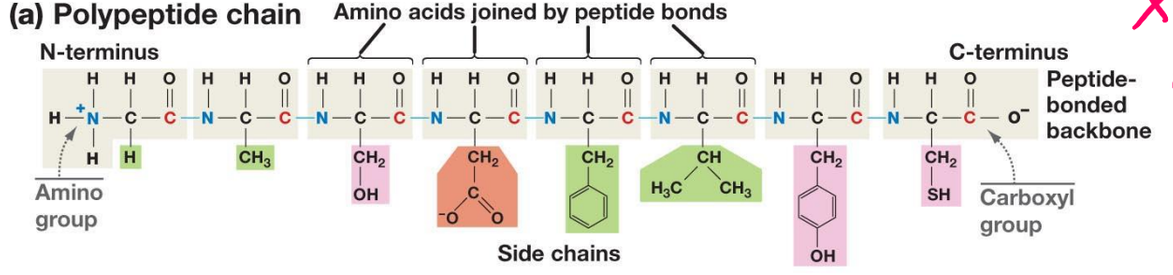
Graphic design by Gail W. Rumbaugh, San Diego Supercomputer Center
1 OUTSIDE THE CELL
Some molecular machines perform their jobs outside of cells. Many are compact, so that they can diffuse quickly to their site of action. This is true of the four hormones shown at the top: insulin and glucagon, which together regulate blood sugar levels, interferon, which carries signals in the immune system, and human growth hormone. The seven digestive enzymes (in yellow) are also small and very stable, so that they can survive the hostile environment in the digestive tract. Each of these enzymes has a small groove (oriented towards the top in each) that binds to a different target molecule and digests it. At the bottom is rhinovirus, the virus that causes the common cold, and an antibody, our major defense against viruses. Antibodies bind to viruses and prevent them from binding to cell surfaces, thus blocking infection.
2 MEMBRANES
Cells are surrounded by a membrane made of lipids, like the phospholipid and cholesterol molecules shown at the top. Membranes keep the cellular machinery inside and unwanted material out. Many proteins are embedded in this membrane, performing a variety of essential tasks. ATP synthase is a rotary generator that produces ATP (adenosine triphosphate), the small molecule used for powering cells. The two large complexes below it charge a battery that powers ATP synthase, and the tiny protein cytochrome c shuttles electrons between them. Rhodopsin is found in membranes in the retina. The small retinal molecule inside of it changes shape when illuminated, causing the surrounding protein to send a signal to the brain. Cyclooxygenase builds one of the molecules used to signal pain—this cyclooxygenase molecule here, however, is blocked by two molecules of aspirin, shown inside in white. At the bottom are three molecules involved in photosynthesis, which capture energy from light and use it to power the synthesis of sugar in plant cells.
3 TRANSPORT AND STORAGE
Of course, a perfectly sealed membrane would be of little use to cells, because nutrients could not get in and wastes could not get out. The box shows a membrane looking face-on. Five proteins that form channels through the membrane are shown. To the right of the box are several soluble proteins involved in transport and storage of molecules. Hemoglobin and myoglobin carry oxygen. Ferritin forms a hollow shell that stores iron ions. Serum albumin carries many different molecules in the blood.
4 CHEMICAL FACTORIES
Cells build a bewildering variety of enzymes—proteins that perform chemical reactions. At the top are the ten enzymes that perform glycolysis, the breakdown of sugar to form ATP. Below that are several enzymes that perform different housekeeping reactions. Dihydrofolate reductase produces a key cofactor molecule and alcohol dehydrogenase breaks down alcohol. Ribulose bisphosphate carboxylase/oxygenase is the most common enzyme on the Earth, and performs a key step in the capture of carbon dioxide by plants to form sugar. The three synthases and the transferase make different building blocks for creating new molecules. Nitrogenase performs an essential role in the ecosystem by converting nitrogen gas into a form that living cells can use.
5 DNA
Genetic information is stored in the DNA double helix, seen running from top to bottom here. Many proteins are used to copy, read, and store this information. RNA polymerase copies the information into a strand of RNA that will be used to direct the construction of new proteins. It is assisted by topoisomerase, which releases tension when the helix is wound and unwound, and guided to appropriate starting points by the two protein complexes below it. DNA polymerase replicates DNA strands—here, the polymerase is filling a gap in the double helix. Some proteins, like the lac repressor, grab DNA and bend it sharply, or even wrap it all the way around themselves, like the two nucleosomes at the bottom.
6 BUILDING NEW PROTEINS
New proteins are built by ribosomes—complex molecular factories that read the genetic code and use it to direct constructions. Many molecular machines are needed to assist the process. Twenty different aminoacyl-tRNA synthases (six are shown here) load the building blocks onto tRNA, ready to be added to a growing protein chain. Several protein factors, shown below the ribosome, guide each tRNA into the proper spot. The three chaperone proteins shown at the bottom help each new protein fold into its proper shape.
7 BEAMS AND GIRDERS
Cells are braced and supported by a complex infrastructure. This cytoskeleton is formed of sturdy filaments like actin and microtubules, composed of many subunits stacked like bricks. Myosin is a molecular motor that climbs along actin filaments, allowing the cell to move. Collagen, broken into two pieces here, is actually found outside of cells, where it forms connective tissue between cells.
PDB
PROTEIN DATA BANK
http://www.pdb.org/ • info@rcsb.org
RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATICS
RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY
SAN DIEGO SUPERCOMPUTER CENTER
NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
molecule
Scale water
Enzyme
membrane
DNA
myosin
micro tubu-

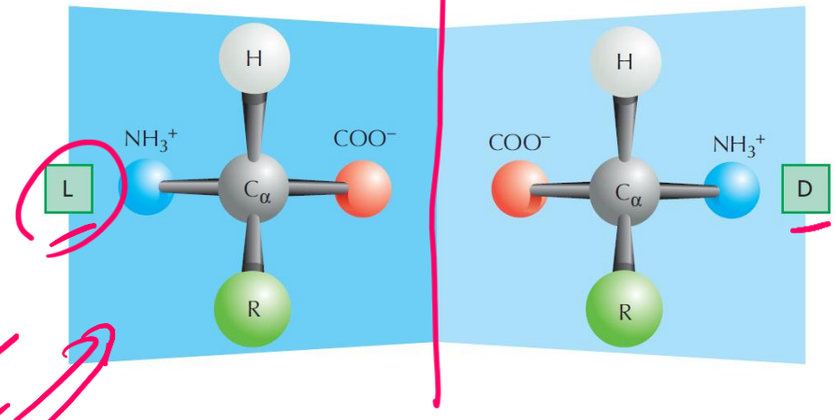
The Structure of Amino Acids and Proteins



- *The amino group, Cα (and one hydrogen), and the carbonyl group are common to all amino acids*
- *The N-Cα-C=O are the mainchain of the protein polymer.*
- *The R groups are different –there are 20 common R groups they are the sidechain of the protein polymer – their* ***sequence*** *defines the properties of the protein.*



Is there a chiral carbon on amino acids?



Proteins consist exclusively of L-amino acids.
(as does the ribosome that make them)

Primary Structure

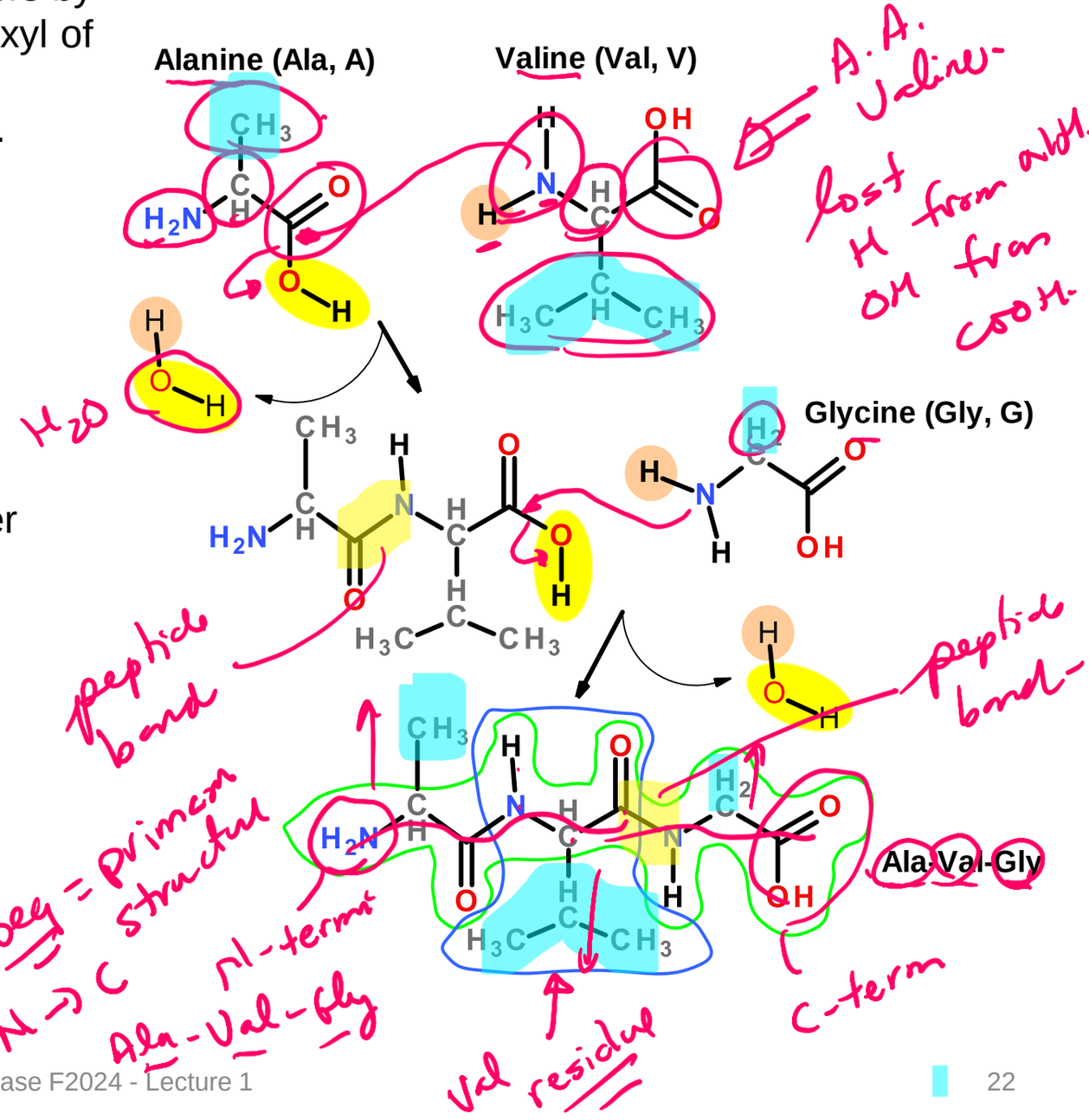
- Amino acids are joined together to form linear polymers by the formation of a **peptide bond** between the carboxyl of one amino acids and the amino group of the next.
- This reaction releases water: a **dehydration** reaction.
- The peptide bond can be broken (*lysis*) by the addition of water = **hydrolysis**.

Incorporated amino acid = *residue* (atoms are lost when the peptide bond is formed).

Polarity of chain direction – amino (N) terminus to carboxy(C) terminus = order of amino acids = *sequence* = *primary structure*

Mainchain (or backbone) – linear atoms of the polymer

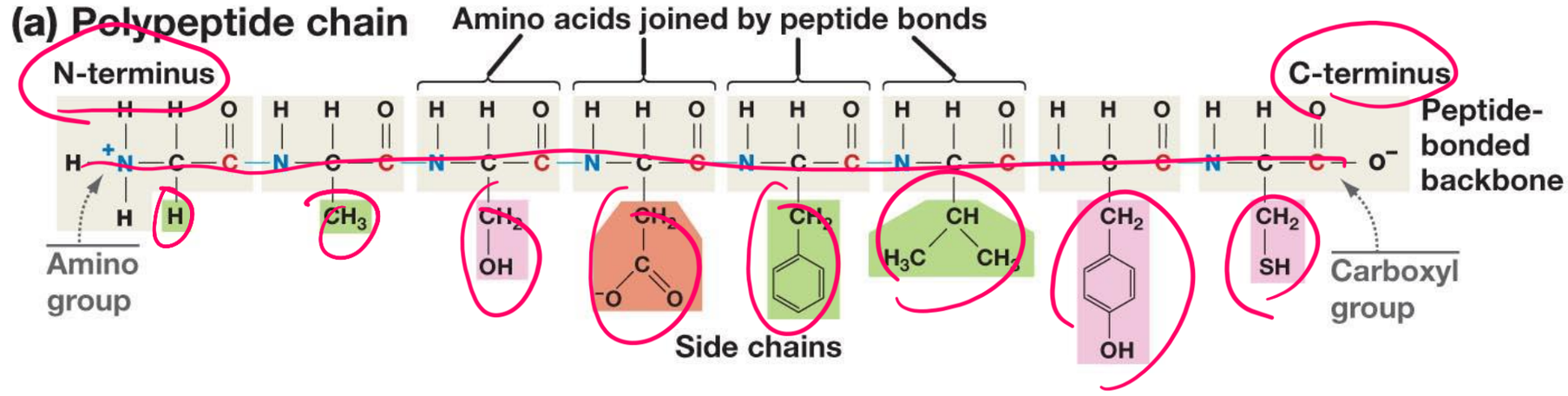
Sidechain – atoms off the Ca carbon



Primary Structure – Expectations

- Draw chemical structure given the sequence.
- Determine the seq. from chemical structure.
- Distinguish/identify:
  - **Mainchain** & **Sidechain** atoms,
  - **Residue** = aa in polymer,
  - N & C terminus,
  - Peptide bond(s).

Sidechain *Functional* Groups Affect Behavior (and the order is important)

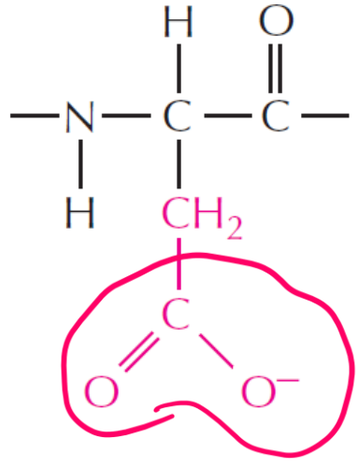


- Sidechains (R-groups) differ in their size, shape, reactivity, and interactions with water.
  1. Nonpolar Sidechains: **hydrophobic**; do not form hydrogen bonds; coalesce in water - typically form the core of folded proteins.
  2. Polar Sidechains: **hydrophilic**; form hydrogen bonds; readily dissolve in water
  3. **Ionizable** Sidechains: Can be charged at certain pH values. Interact strongly with water.

ACIDIC SIDE CHAINS

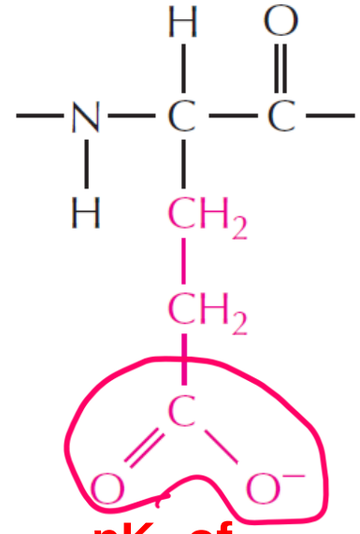
aspartic acid

(Asp, or D)



glutamic acid

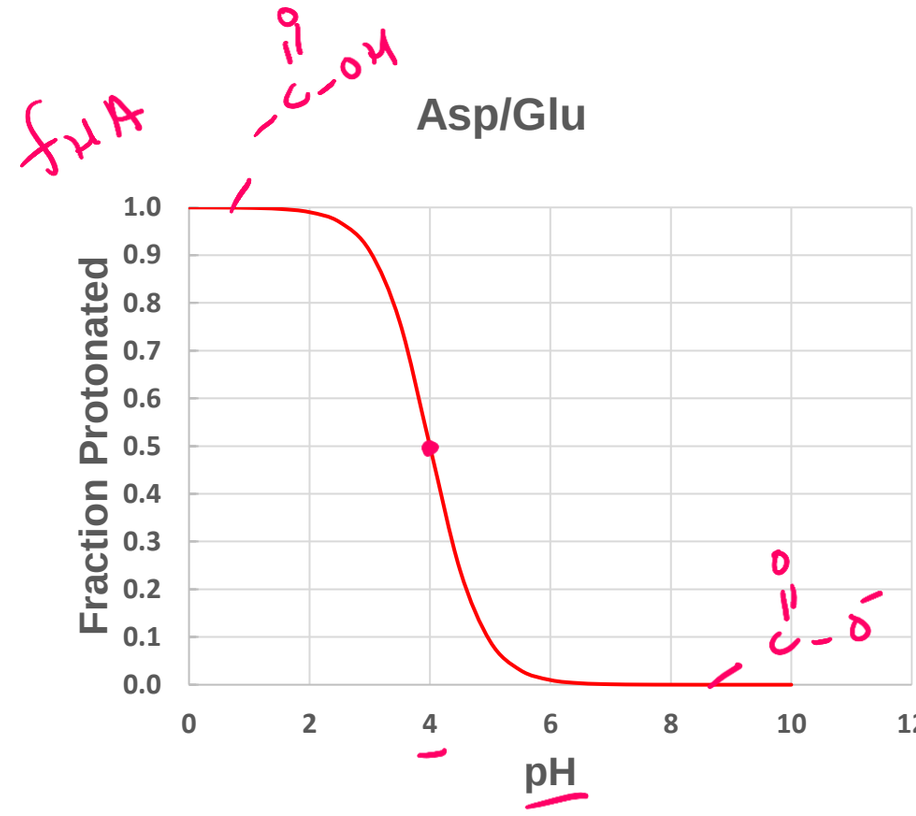
(Glu, or E)



pK_a of sidechain ~ 4

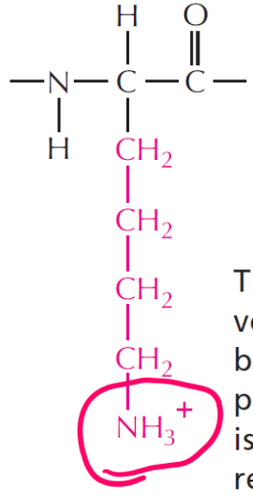
pK_a of sidechain ~ 4

Have a net negative charge at pH 7.0



BASIC SIDE CHAINS

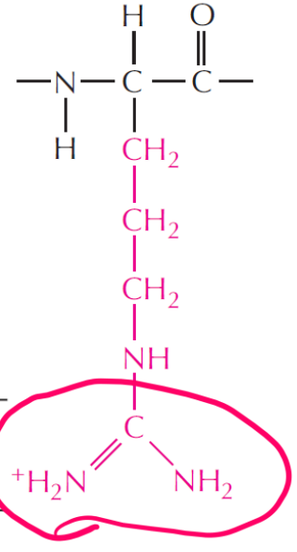
lysine
(Lys, or K)



This group is very basic because its positive charge is stabilized by resonance.

pK_a ~ 10

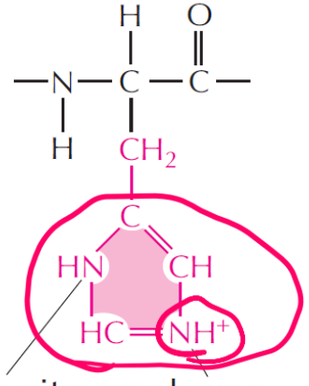
arginine
(Arg, or R)



pK_a ~ 12

Have a net positive charge at pH 7.0

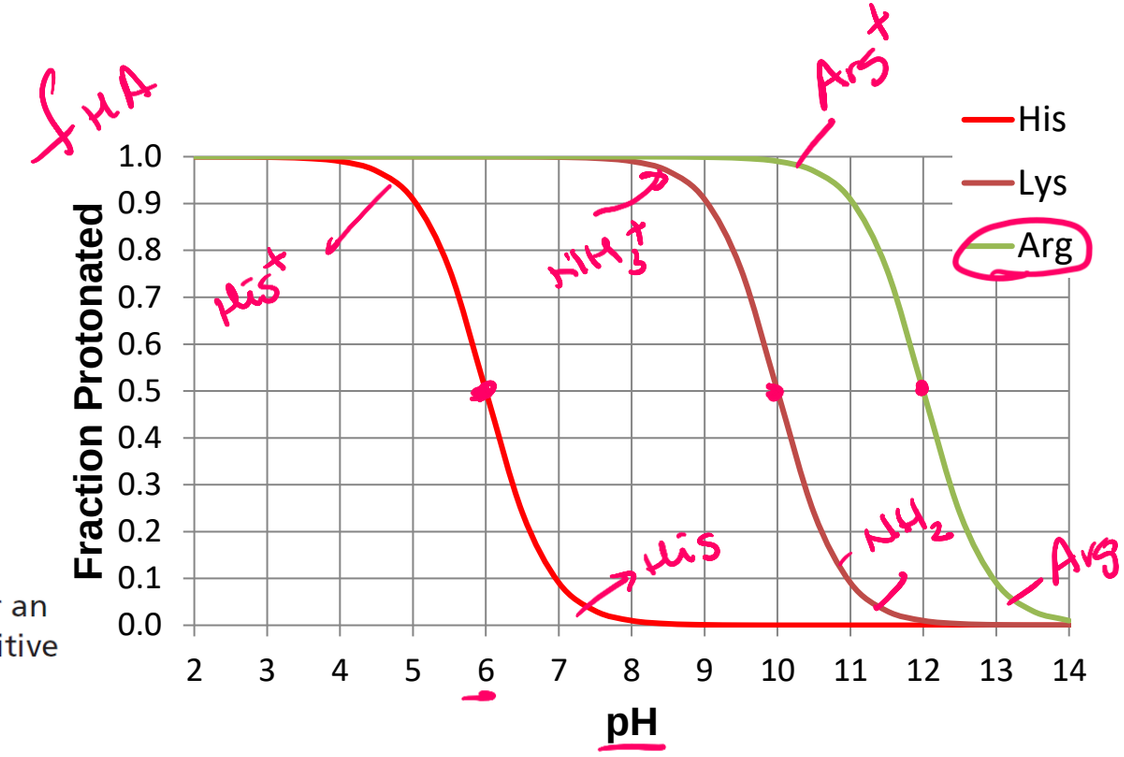
histidine
(His, or H)



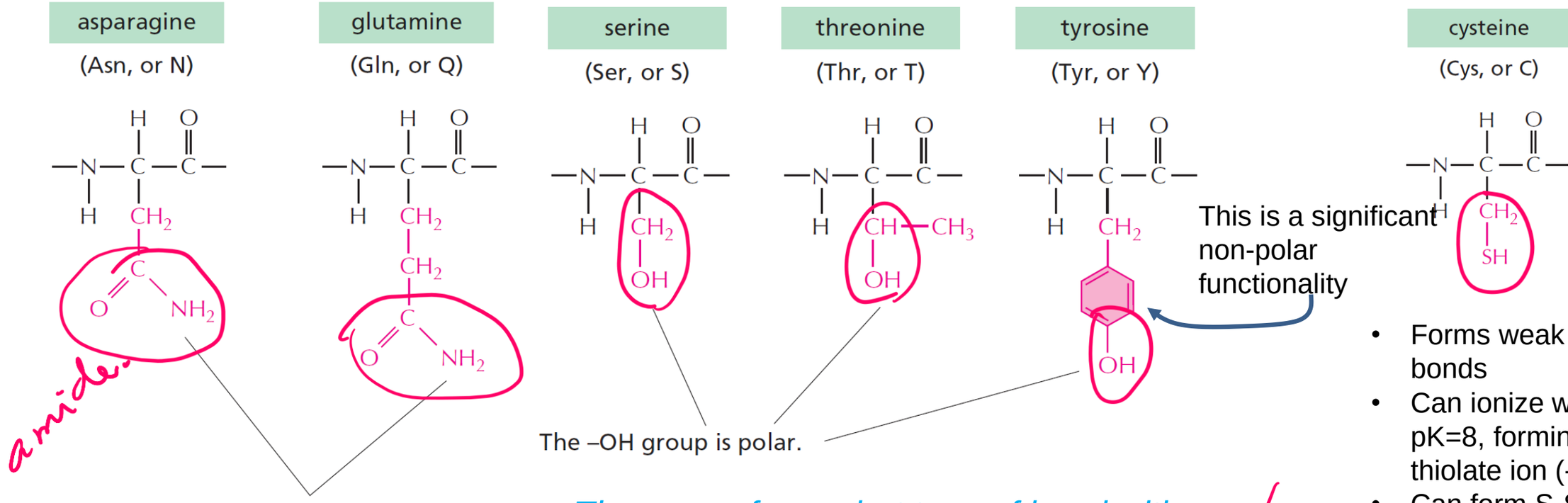
These nitrogens have a relatively weak affinity for an H^+ and are only partly positive at neutral pH.

pK_a ~ 6

Positive charge when protonated
10% Protonated at pH 7.0



UNCHARGED POLAR SIDE CHAINS



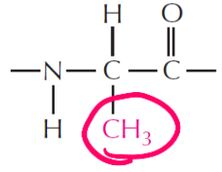
- Forms weak H-bonds
- Can ionize with a pK=8, forming thiolate ion ($-S^-$)
- Can form S-S disulfide bonds with other Cys residues

These can form what type of bond with water?

NONPOLAR SIDE CHAINS

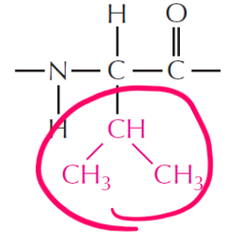
alanine

(Ala, or A)



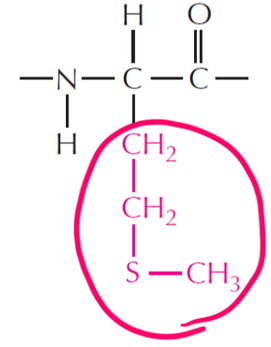
valine

(Val, or V)



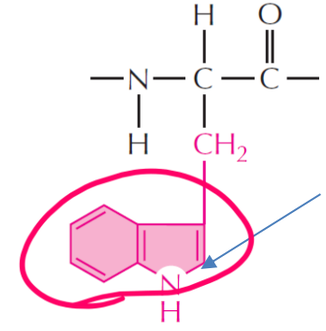
methionine

(Met, or M)



tryptophan

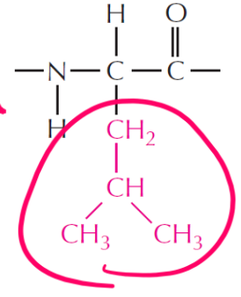
(Trp, or W)



H-bond donor
(polar functionality)

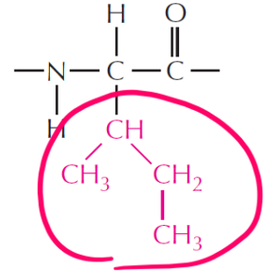
leucine

(Leu, or L)



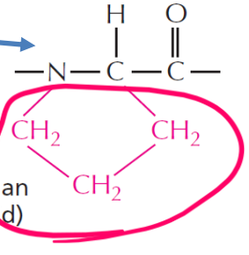
isoleucine

(Ile, or I)



proline

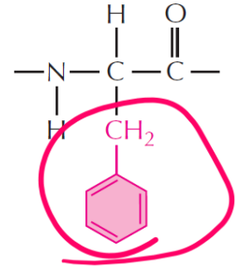
(Pro, or P)



(actually an imino acid)

phenylalanine

(Phe, or F)

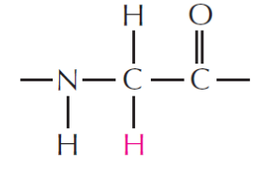


Ring results in no NH group for H-bonding

AND LASTLY THERE IS GLYCINE:

glycine

(Gly, or G)



No real functionality for its R group (H)
Only AA that is achiral

Summary of what you should know about amino acids:

- All amino acids have a carbon atom bonded to an amino group, a hydrogen atom and a carboxyl group. What makes each amino acid unique is its **sidechain**.
- The common atoms will form the **mainchain** of the protein.
- Most amino acids have at least one chiral center - the alpha carbon, exception is glycine, which is achiral.
- You should be able to look at the functional groups on the ***side-chain*** and determine how they will interact with water:
  - Polar
  - Charged
  - Non-polar (hydrophobic). You should be able to justify large differences in hydrophobicity, e.g. Val versus Ala

Relative Hydrophobicity of Sidechains (one of many)