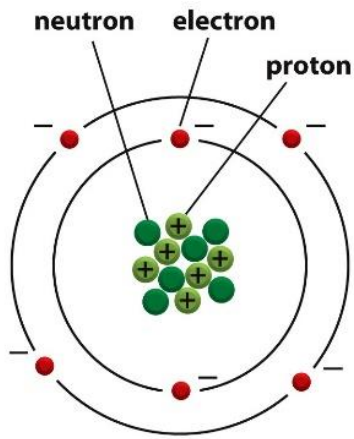


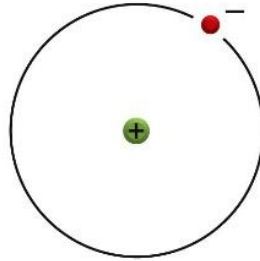
Lecture 1:

Chemistry and Biology Fundamentals

- Chemical Bonding
- Functional Groups \rightarrow pH
- Protein Structure and Stability
- Ligand Binding
- Proteins as enzymes
- Carbohydrates



carbon atom
atomic number = 6
atomic weight = 12



hydrogen atom
atomic number = 1
atomic weight = 1

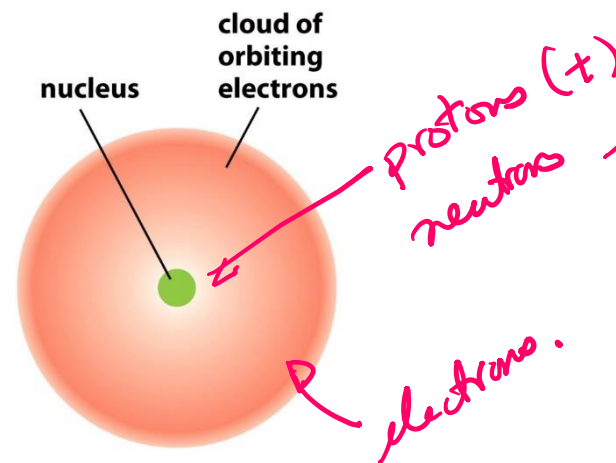
- Atoms are composed of:
 - Protons – positively charged particles
 - Neutrons – neutral particles
 - Electrons – negatively charged particles
- Protons and neutrons are located in the nucleus.
- Electrons are found in **orbitals** surrounding the nucleus.

Mass number
(number of protons + neutrons)

Atomic number
(number of protons)

<div>1 1H</div>	<div>Atomic number (number of protons)</div>						<div>4 2He</div>
<div>7 3Li</div>	<div>9 4Be</div>	<div>11 5B</div>	<div>12 6C</div>	<div>14 7N</div>	<div>16 8O</div>	<div>19 9F</div>	<div>20 10Ne</div>
<div>23 11Na</div>	<div>24 12Mg</div>	<div>27 13Al</div>	<div>28 14Si</div>	<div>31 15P</div>	<div>32 16S</div>	<div>35 17Cl</div>	<div>40 18Ar</div>

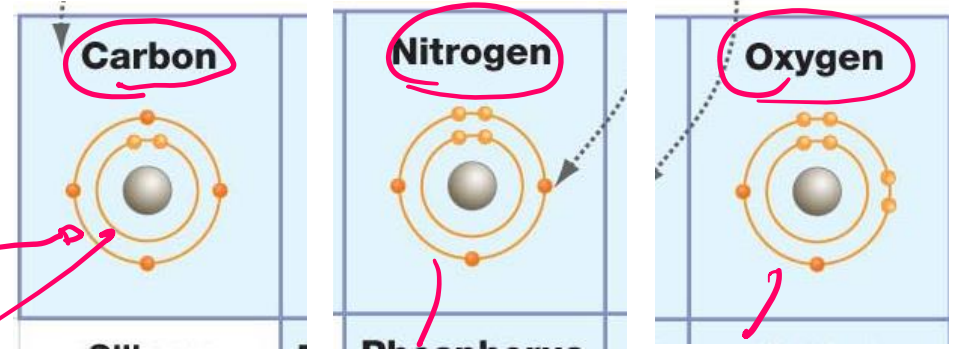
Atomic number = # of protons = # electrons in element



- Electrons arranged around the nucleus in specific regions called orbitals.
 - Each orbital can only hold two electrons
- Orbitals are grouped into electron shells
 - Numbered 1,2,3...
 - Lower numbers = shells closer to the nucleus
 - First shell can hold a maximum of 2 electrons
 - Second shell can hold up to 8
 - Third shell can also hold 8
- Orbitals are usually filled from lowest energy (inner shell) to highest energy (outer shell)
- Outer shell is the **valence shell** and is used for forming bonds with other elements.
- The most stable configuration is a complete (full) outer shell.

Electron Orbitals

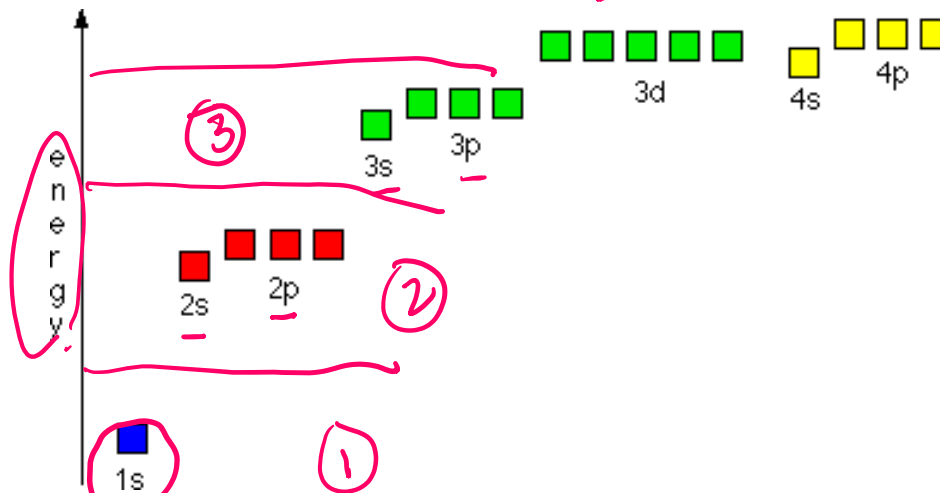
12 6 C	14 7 N	16 8 O
---------------------	---------------------	---------------------



1st shell 2

5e

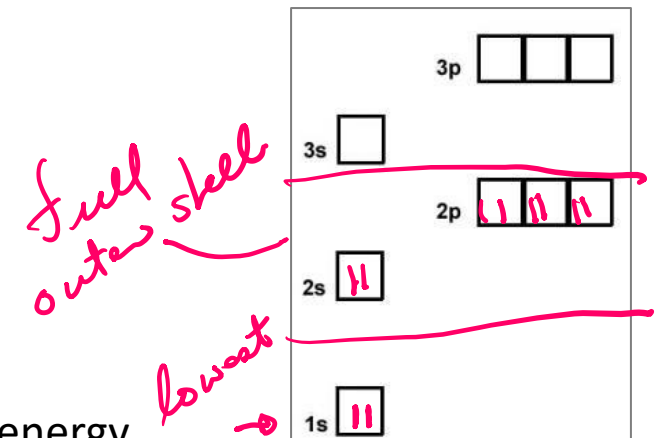
6e



Shells: 1st = 1s, 2nd = 2s + 2p, 3rd = 3s + 3p

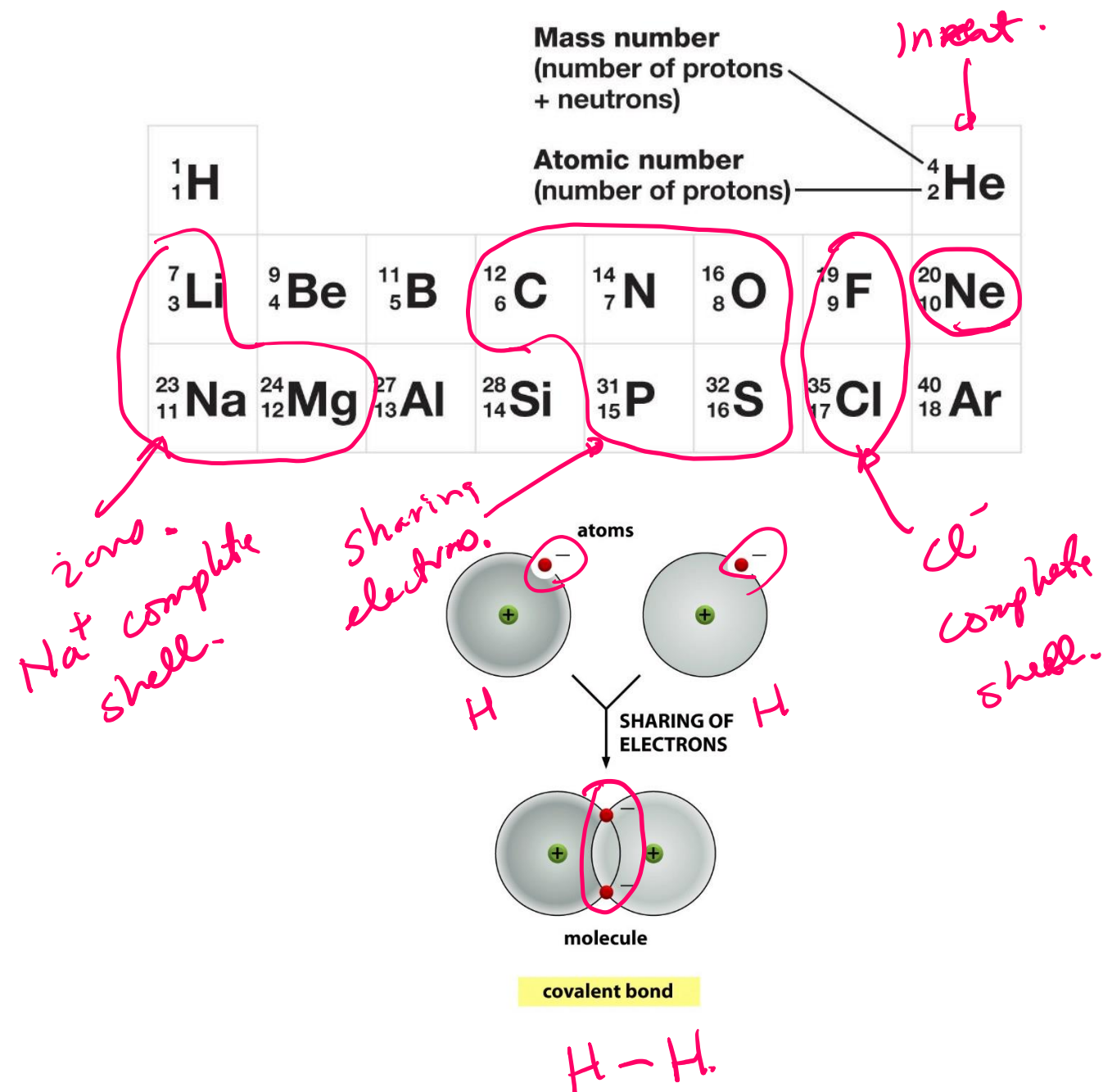
Shell is a collection of orbitals with similar energy

Electron Configuration of Ne – an inert gas (10e)

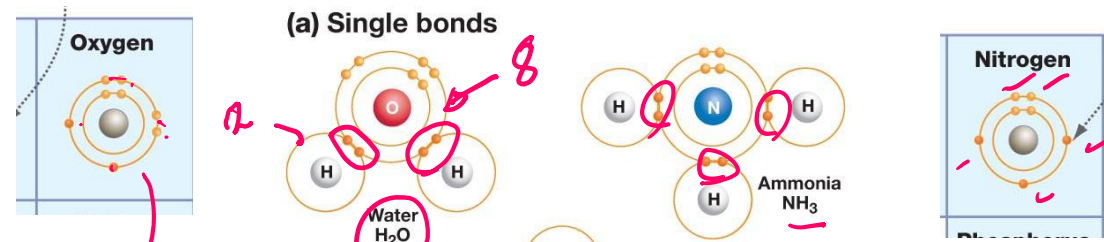


Covalent Chemical Bonds

- Elements like Li, Na, F, Cl, Mg, readily form ions to generate a complete outer shell.
- Some elements cannot form stable ions because it would involve the loss or gain of too many electrons. This includes C, N, and O – which are common in biological systems.
- Unfilled electron orbitals on elements like C, N, and O allow for the formation of **covalent bonds**, and atoms are most stable when each electron orbital is filled.
 - Each atom's unpaired **valence** electrons are shared by both nuclei to fill their orbitals.
 - Substances held together by covalent bonds are called molecules



- The number of unpaired electrons (in the outer shell) determines the number of bonds an atom can make.
- Multiple bonds form when atoms share multiple electrons.



The number of covalent bonds (valence) formed by common elements.

- Oxygen = 2 bonds ✓
- Nitrogen = 3 bonds ✓
- Carbon = 4 ✓
- Sulfur = 2 bonds (in biological systems) ✓
- Hydrogen = 1 bond ✓
- Phosphorous = 5 bonds in biological molecules ✓

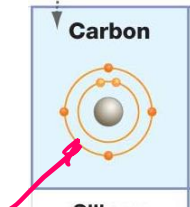
You must know these numbers.

In chemical drawings:

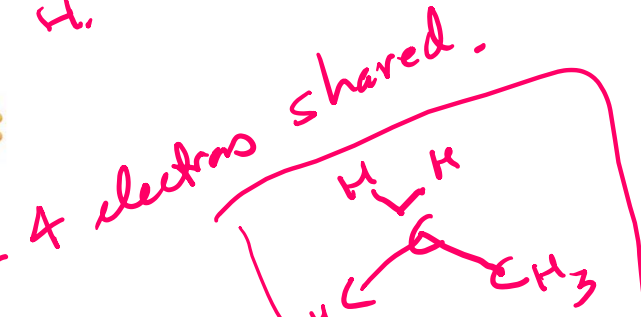
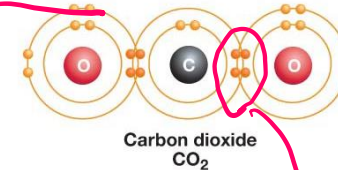
- "C" for carbon is not drawn, but carbons are found at the ends of lines and when lines join or "kink"
- Hydrogens attached to carbon are not shown, you need to add them to complete to complete the valence of the carbon atoms.

You must know how to do this.

How many bonds will carbon form?

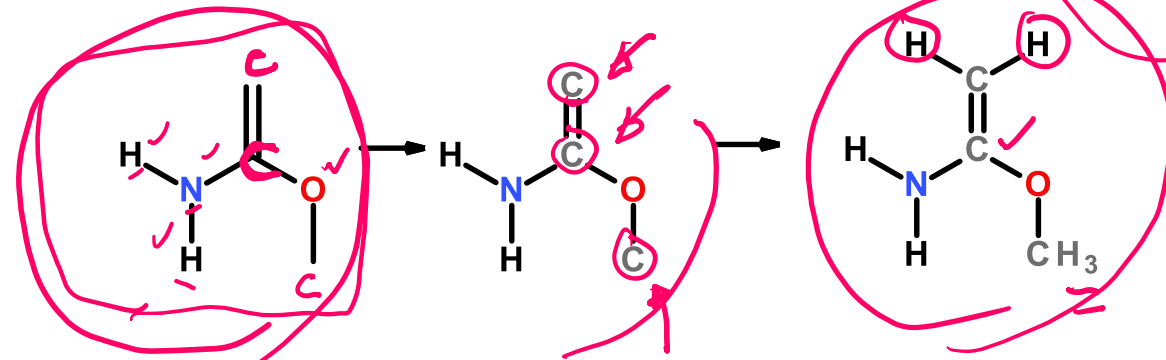


(b) Double bonds

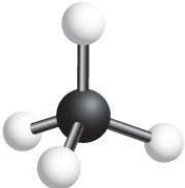
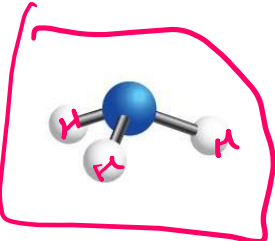

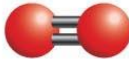
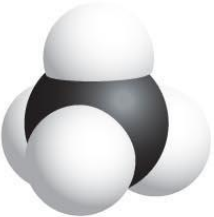





"C" for carbons

Complete valence with H



Representation of Molecules

	Methane	Ammonia	Water	Oxygen
(a) Molecular formulas:	<u>CH₄</u>	NH ₃	H ₂ O	O ₂
(b) <u>Structural formulas:</u>	$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{H}-\text{N}-\text{H} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{O} \\ / \quad \backslash \\ \text{H} \quad \text{H} \end{array}$	O=O
(c) <u>Ball-and-stick models:</u>				
(d) Space-filling models:				

*direction
in space*

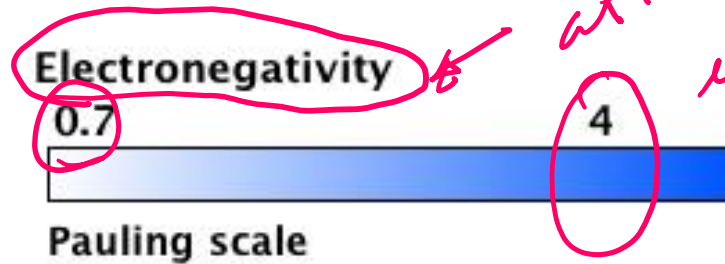
*extent of
electron
cloud **

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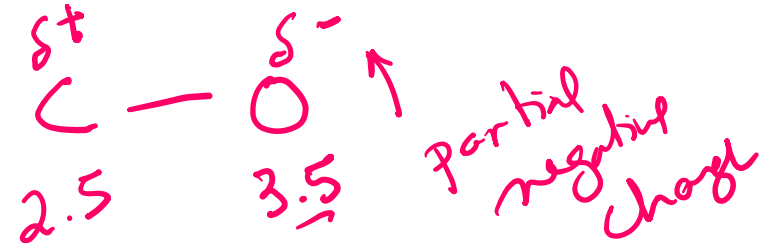
Electron Sharing and Bond Polarity

- The polarity of a bond depends on the electronegativity of the atoms.
- Electronegativity - ability of atoms to pull electrons from other atoms.
- Atoms with higher electronegativity will develop a partial negative charge, the atom they are bonded will have a partial positive charge.
- The order of electronegativity is:
 $H \sim C < N < O$

1		2
H 2.1		
Li 1.0	Be 1.5	



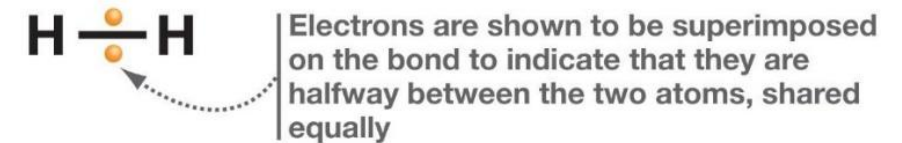
13	14	15	16	17	18
B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	He --



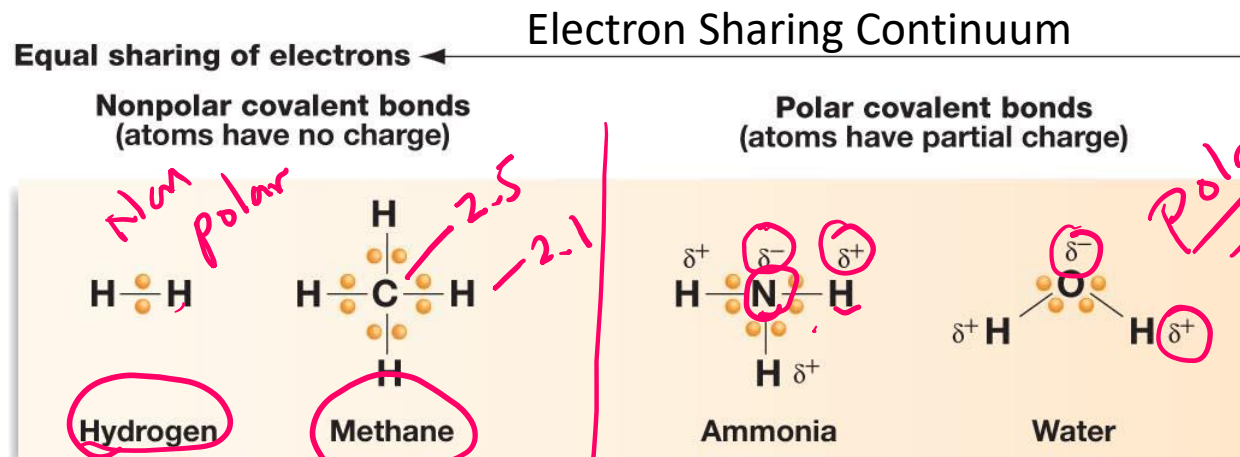
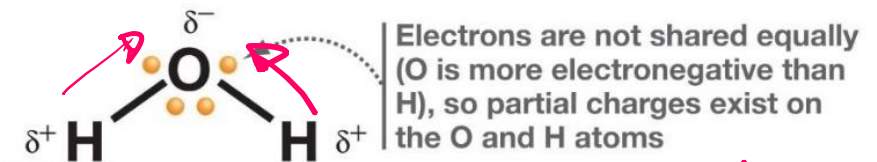
increasing electroneg.

Increased pos. charge of nucleus.

(a) Nonpolar covalent bond in hydrogen molecule



(b) Polar covalent bonds in water molecule

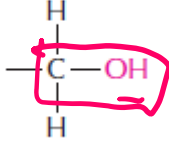


Functional Groups – You should Become Familiar with These

C-O COMPOUNDS

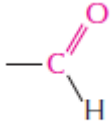
Many biological compounds contain a carbon bonded to an oxygen. For example,

alcohol

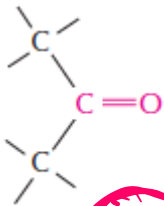


The -OH is called a **hydroxyl** group.

aldehyde

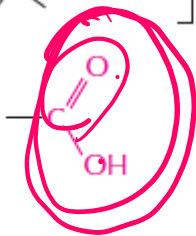


ketone



The C=O is called a **carbonyl** group.

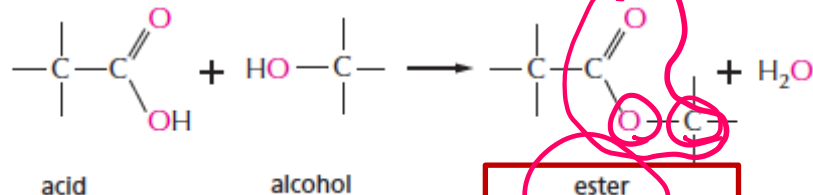
carboxylic acid



The -COOH is called a **carboxyl** group. In water this loses an H^+ ion to become $-\text{COO}^-$.

esters

Esters are formed by combining an acid and an alcohol.



acid

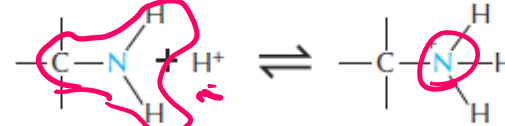
alcohol

ester

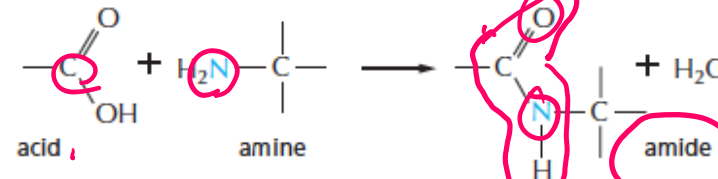
C-N COMPOUNDS

Amines and amides are two important examples of compounds containing a carbon linked to a nitrogen.

Amines in water combine with an H^+ ion to become positively charged.

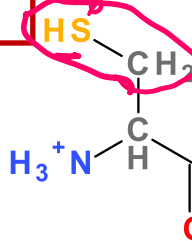


Amides are formed by combining an acid and an amine. Unlike amines, amides are uncharged in water. An example is the peptide bond that joins amino acids in a protein.



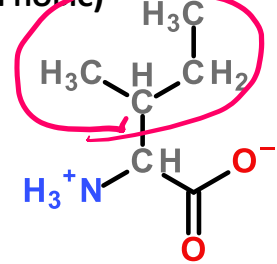
C-S COMPOUNDS

thiol



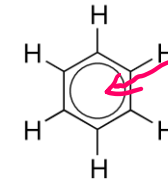
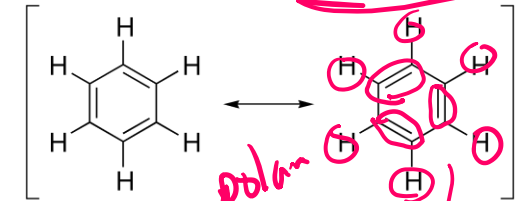
Cysteine (amino acid)

C-H GROUPS
(HYDROPHOBIC)



Isoleucine (amino acid)

Aromatic – planer rings

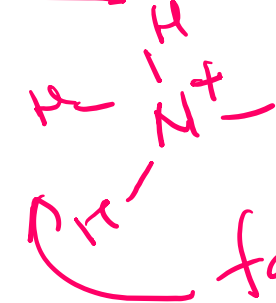
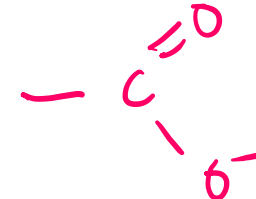


Inter-molecular Interactions in Biology

①

- **Electrostatic interactions** between fully charged molecules (ionic interactions)
 - Like charges repel
 - Opposite charges attract

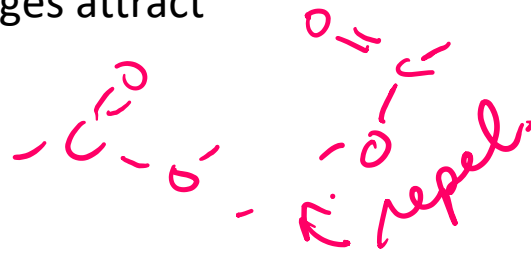
- full charge



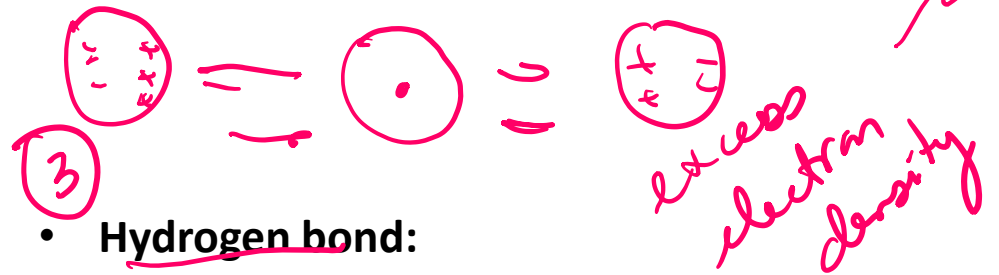
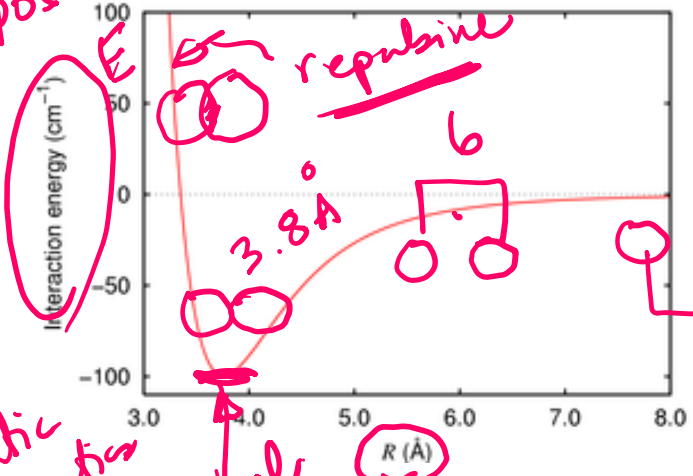
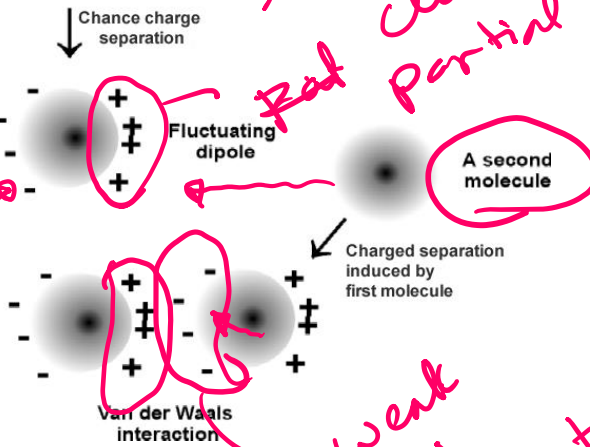
fav interaction

②

- **van der Waals** interactions between:
 - Molecules with partial charges (polar)
 - Molecules with no charge (non-polar)



neutral electron cloud - partial positive



③

- **Hydrogen bond:**

X & Y are electronegative (N and O usually)

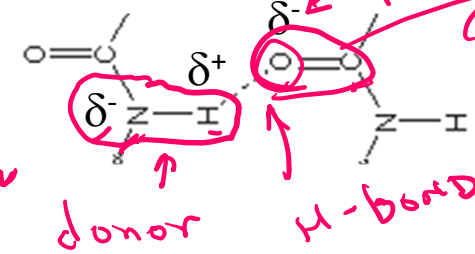
X-H = Donor of the hydrogen bond, it provides the hydrogen (the hydrogen remains in a covalent bond to X)

Y = Acceptor of the hydrogen bond



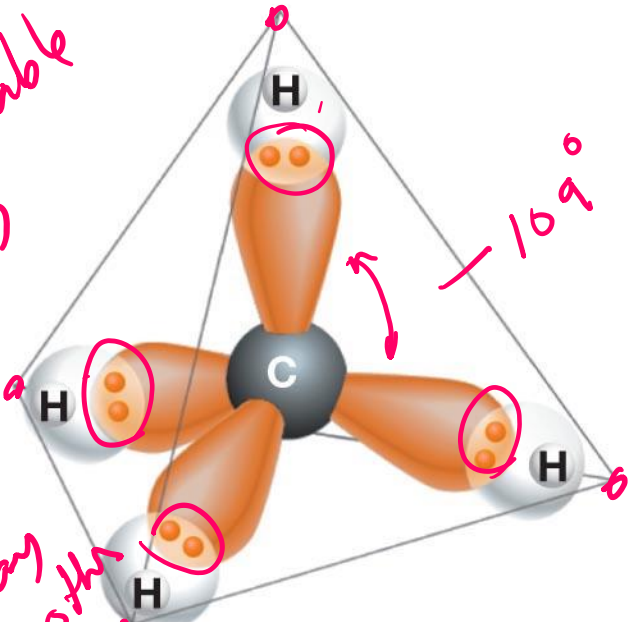
electro neg, fav electrostatic

Hydrogen bond between NH and O=C



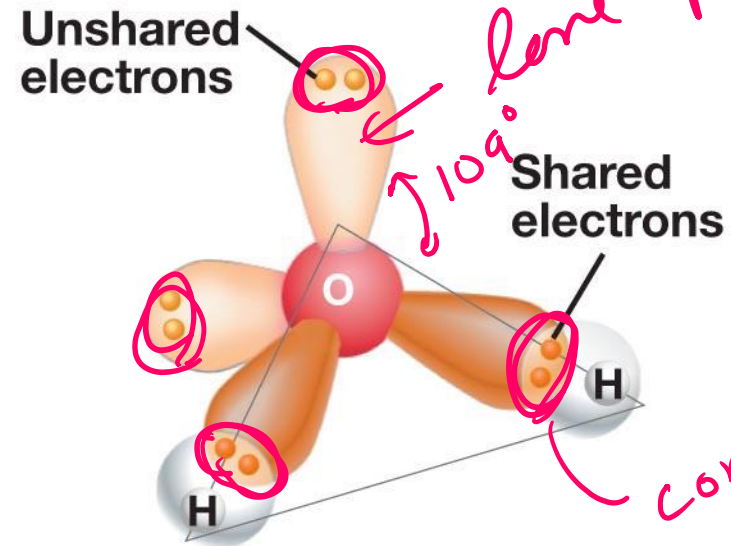
The Geometry of Simple Molecules

(a) Methane (CH_4)



most stable geometry because H are far away from each other as possible.

(b) Water (H_2O)



lone pair in electron orbital.

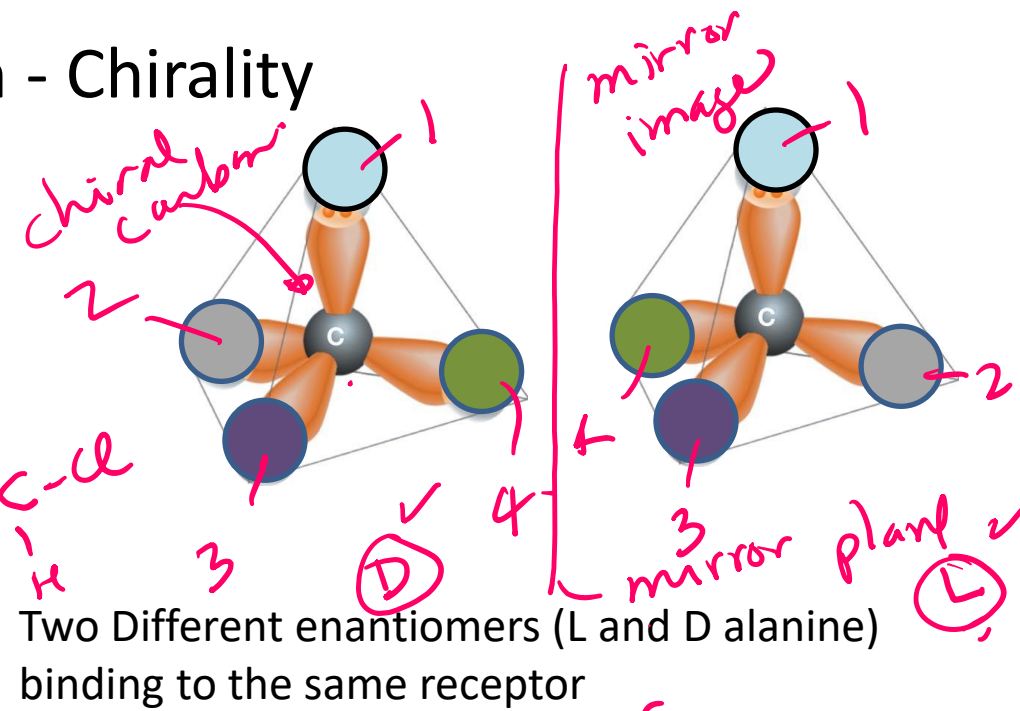
corner of tetrahedron

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

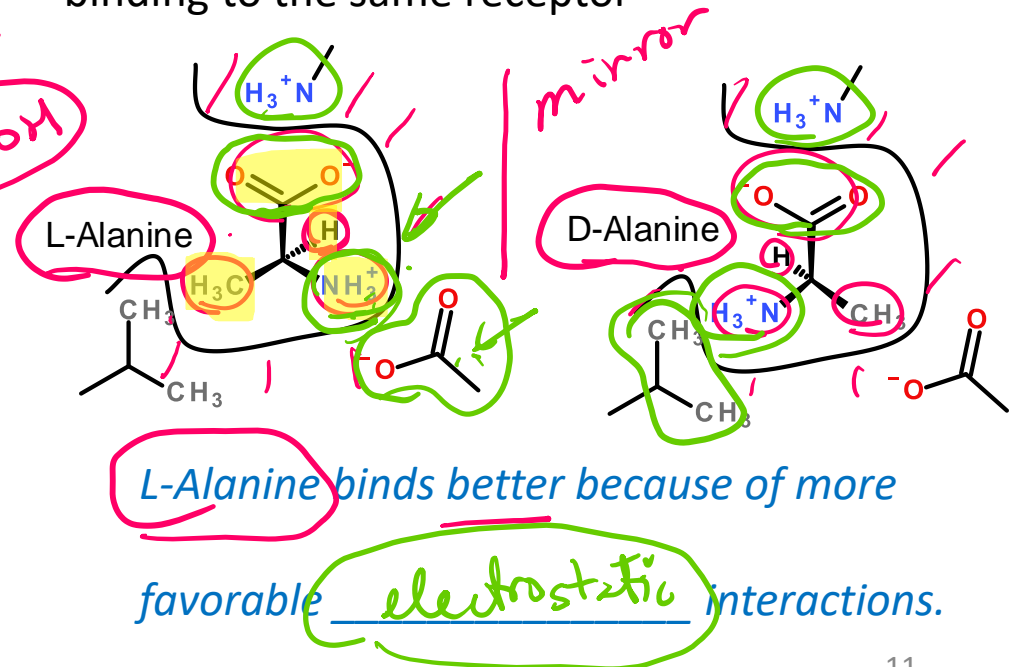
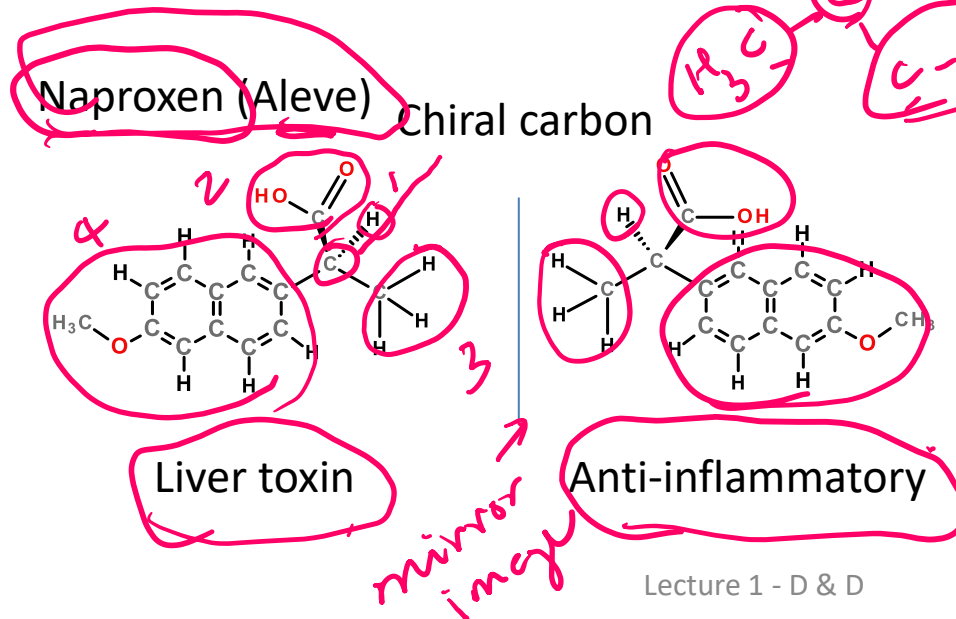
Carbon, oxygen, and nitrogen often form bonds with a tetrahedral geometry

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

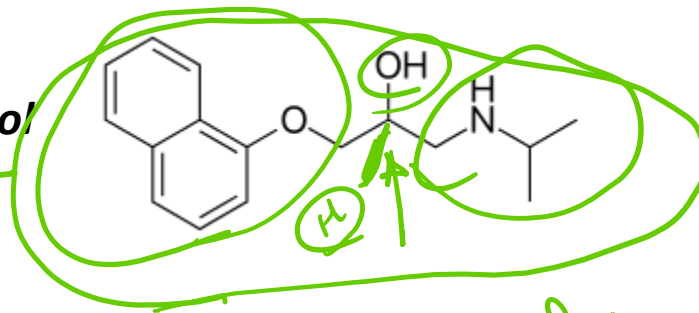


- The biological properties of each enantiomer may be quite different, because they may interact with different receptors in the cell.



Propranolol

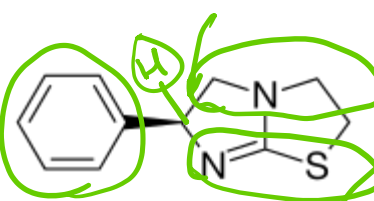
1.



beta blocker

levamisole

4.

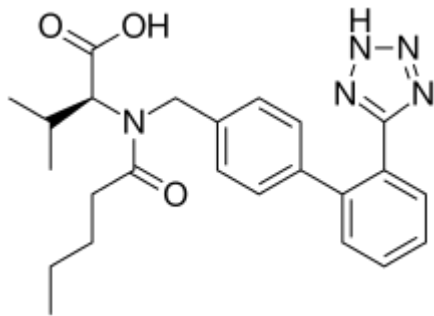


L-form

Instructions: Go to the google slide with the same number as your breakout room

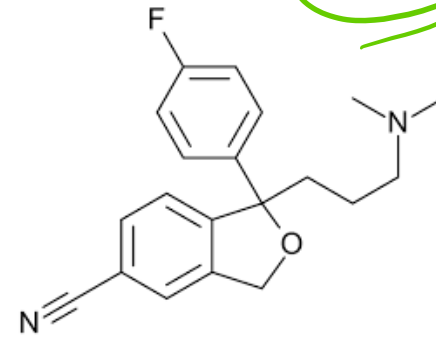
Valsartan

2.



citalopram

5.

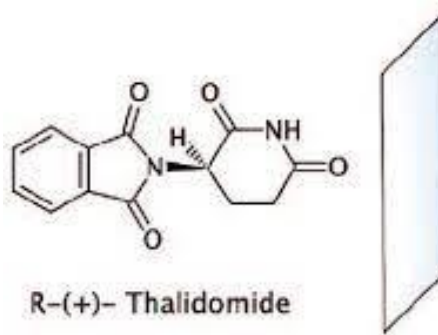


9:02

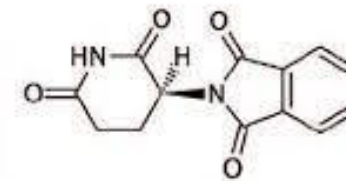
9:08

Thalidomide

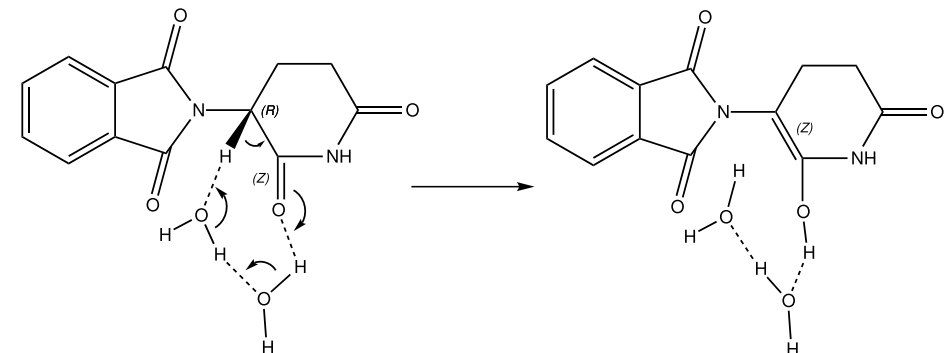
6.



R-(+)- Thalidomide



S-(-)-Thalidomide



<https://docs.google.com/presentation/d/1PJ33ZCi55w4Bdjg4KVQ0qf2HrCfwVHKLcdkvIbUbdfw/edit?usp=sharing>

pH, Strong Acids & Bases

$\text{pH} = -\log [\text{H}^+]$

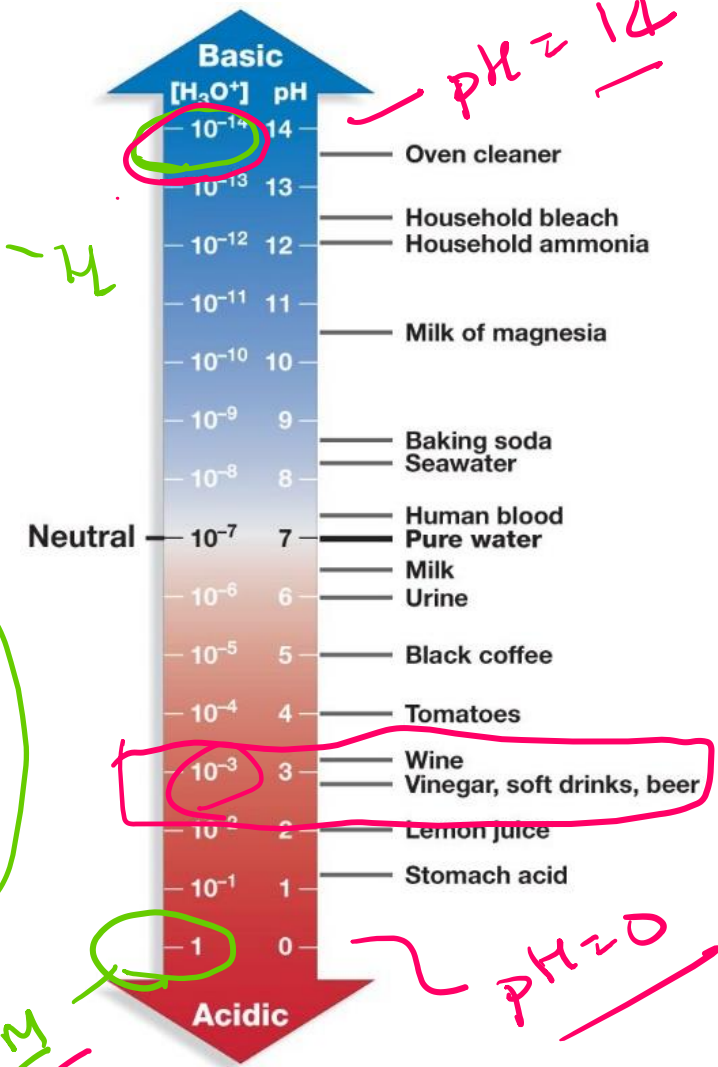
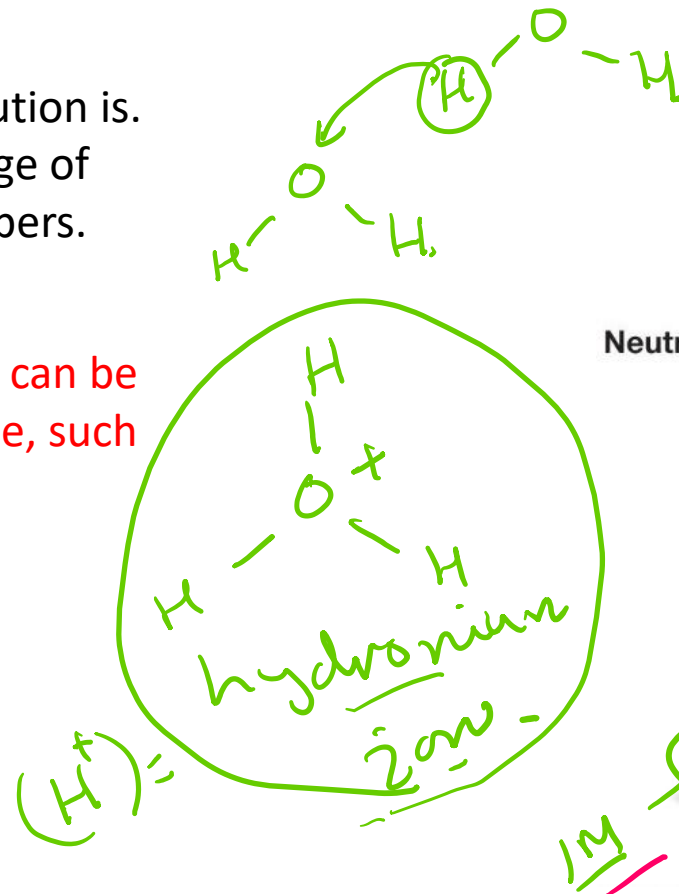
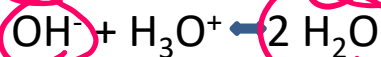
- The pH of a solution tells us how acidic the solution is.
- The pH scale is used to transform the large range of possible $[\text{H}^+]$ values to more manageable numbers.
- Note a low pH is a high $[\text{H}^+]$.**

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.



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

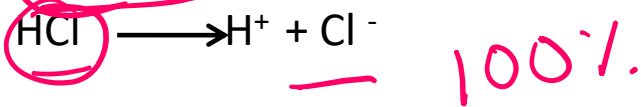


- Which solution has a higher H^+ concentration, pH=3 or pH 4.
- How large is the difference?

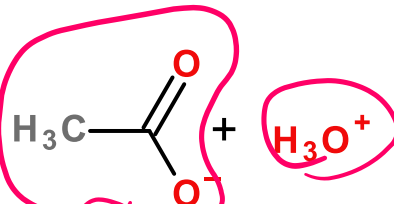
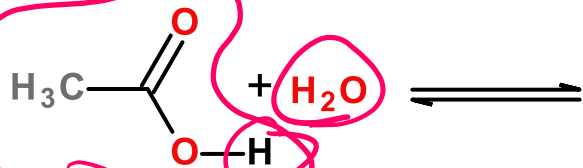
Handwritten notes: "10⁻³", "10⁻⁴", "10 fold diff.", and "chart".

Acids and Bases.

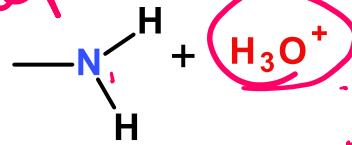
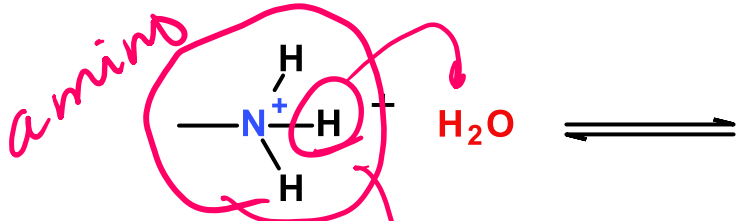
Strong acid – complete ionization in solution. e.g.



Weak Acid – incomplete ionization in solution.



deprotonated neg.

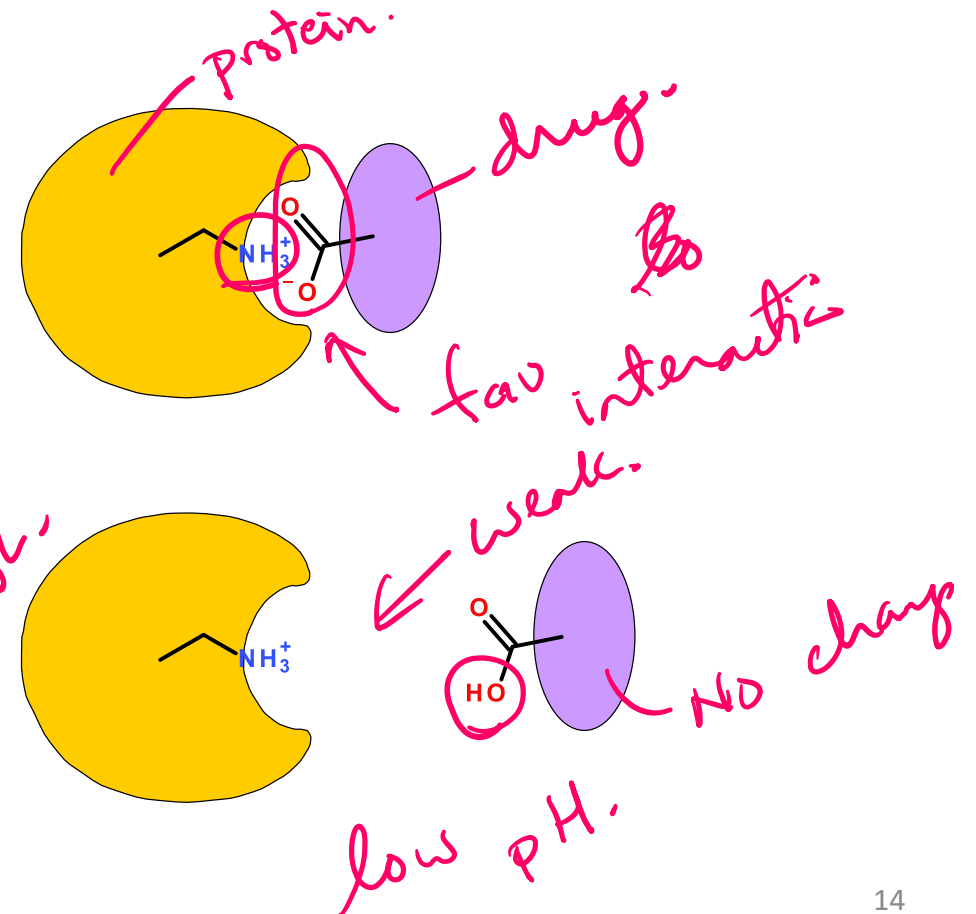


neutral in charge

“HA”=protonated form
low pH. x charge

“A”=deprotonated form
(conjugate base)
high pH.

Why this is important: protonation/deprotonation changes the **charge** on species, either creating or destroying strong electrostatic interactions!



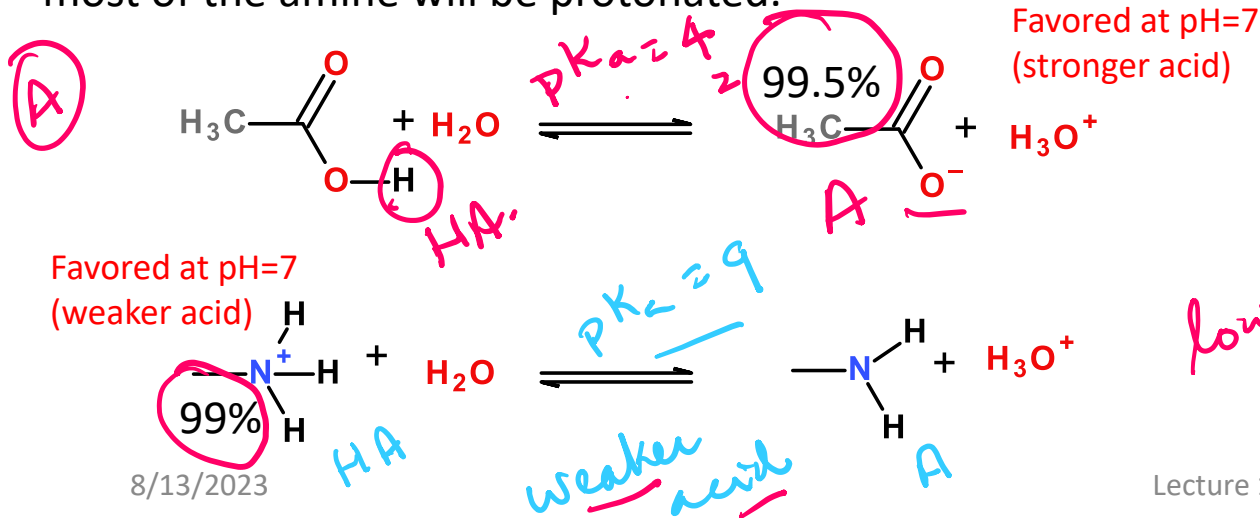
What Affects the Degree of Protonation?

1. The extent of protonation/deprotonation depends on the pH of the solution:

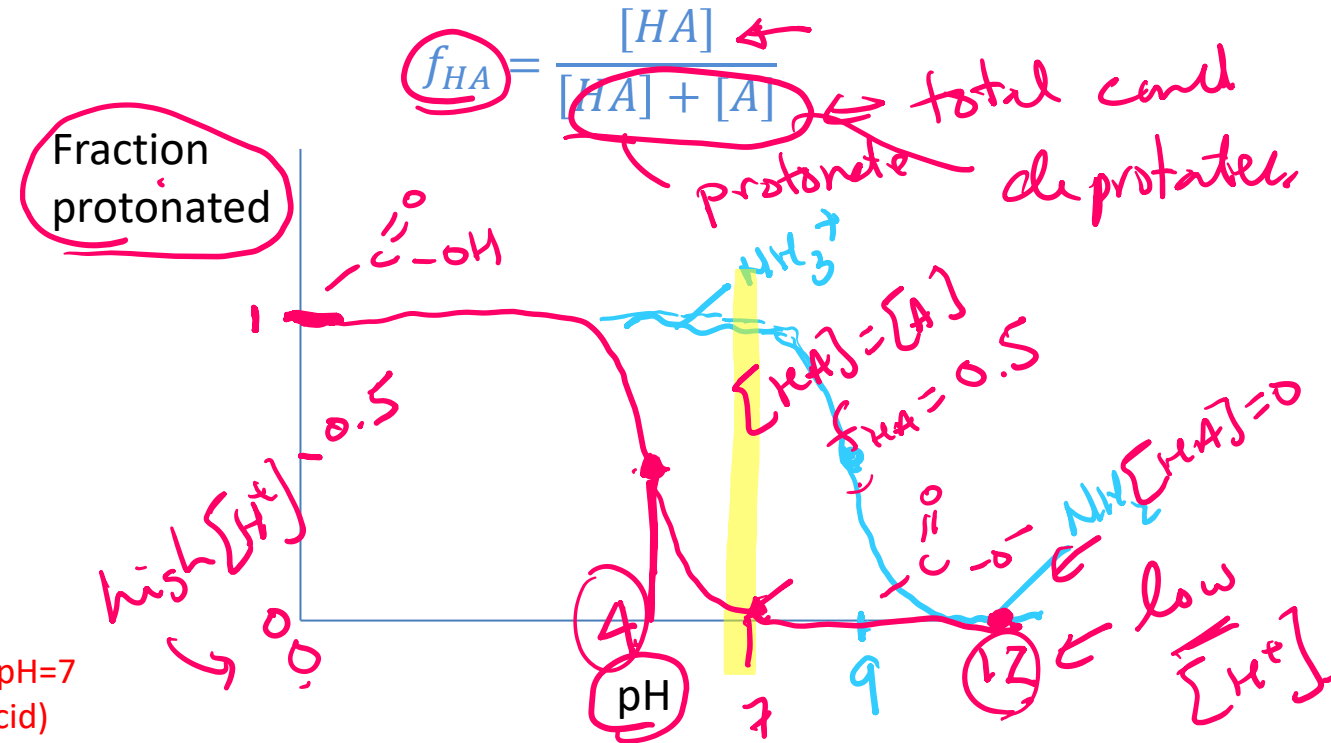
- Low pH values will favor protonation of acids since there are many protons that will collide with (A) to make (HA).
- High pH values will favor deprotonation of acids since there are fewer protons to protonate the acid.

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

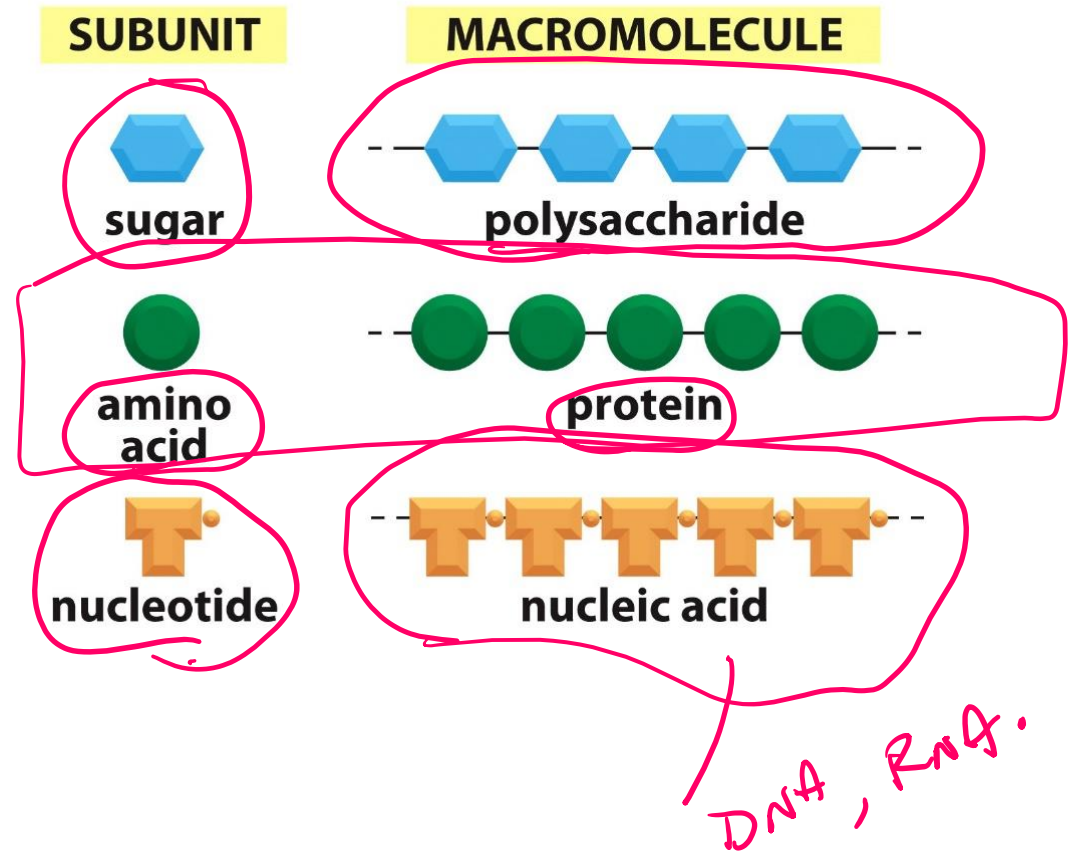
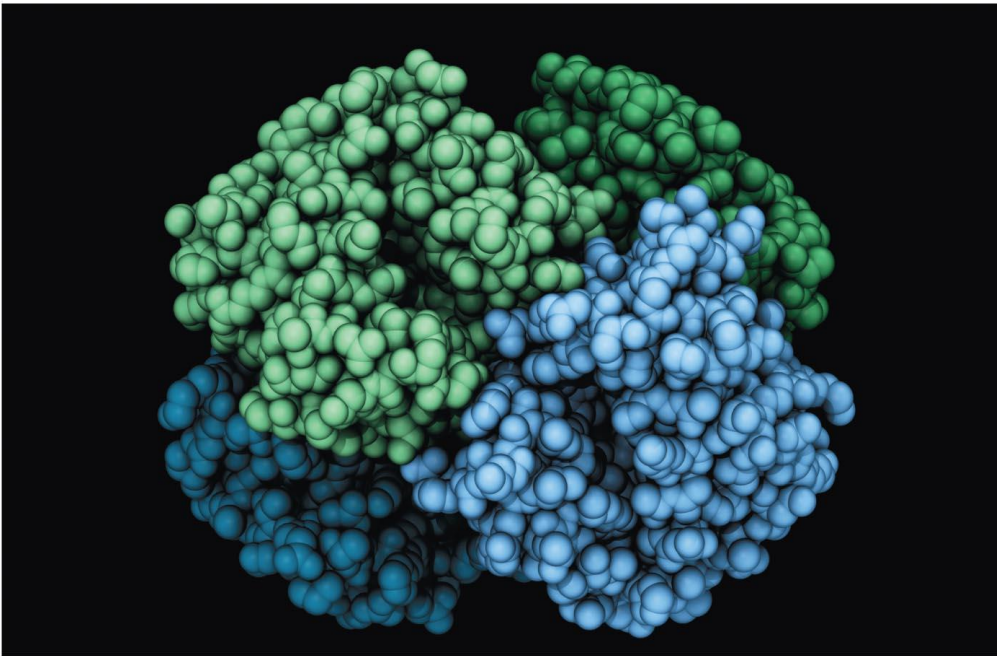
Chemistry

- 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



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 storehouse 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. An 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.

By David S. Goodsell, The Scripps Research Institute, La Jolla, California, USA
Graphic design by Gail W. Bamber, San Diego Supercomputer Center

MEMBRANES

L Cells are surrounded by a membrane made of lipids, like the phospholipids and cholesterol molecules shown at the top. Membranes lock 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 molecules used for powering cells. The two large complexes here either charge a battery that powers ATP synthase, or the light protein cytochrome *c* shuttles electrons between them. Rhodospirillum rubrum, a purple bacterium in the cyan. The small red dots are small molecules called signaling molecules that carry a message. A signal is a molecule that carries a message. A signal is a molecule that carries a message. The molecules used to signal pain—the 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.

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.

CHEMICAL FACTORIES

4 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 biosynthesizing reactions. Dihydroxyacetone reductase activates a key cofactor molecule and alcohol dehydrogenase breaks down alcohol. Ribulose biphosphate 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 transaminase 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.

DN

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 bind it sharply, or even wrap it all the way around themselves, like the two nucleosomes at the bottom.

BUILDING NEW PROTEINS

b New proteins are built by ribosomes—complex molecular factories that read the genetic code and use it to direct construction. Many molecular machines are needed to assist the process. Twenty different aminoacyl-tRNA synthetases (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.

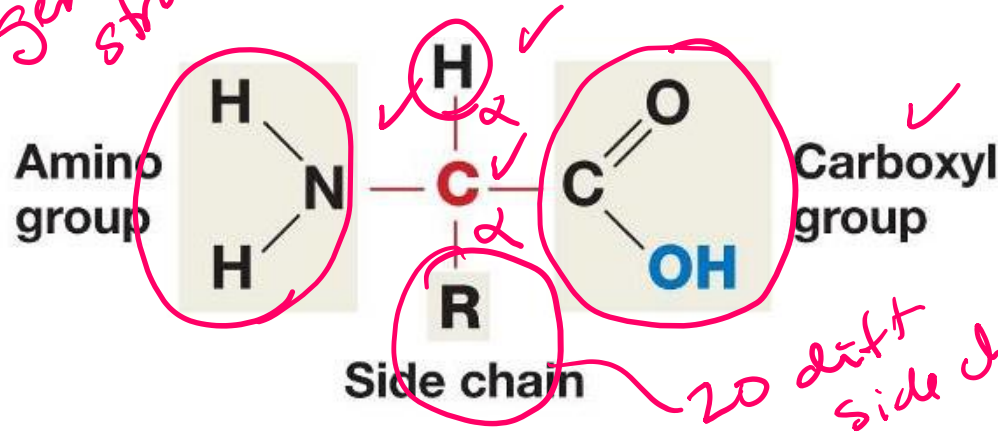
7 BEAMS AND GIRDERS

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 glides 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.

References + 2002

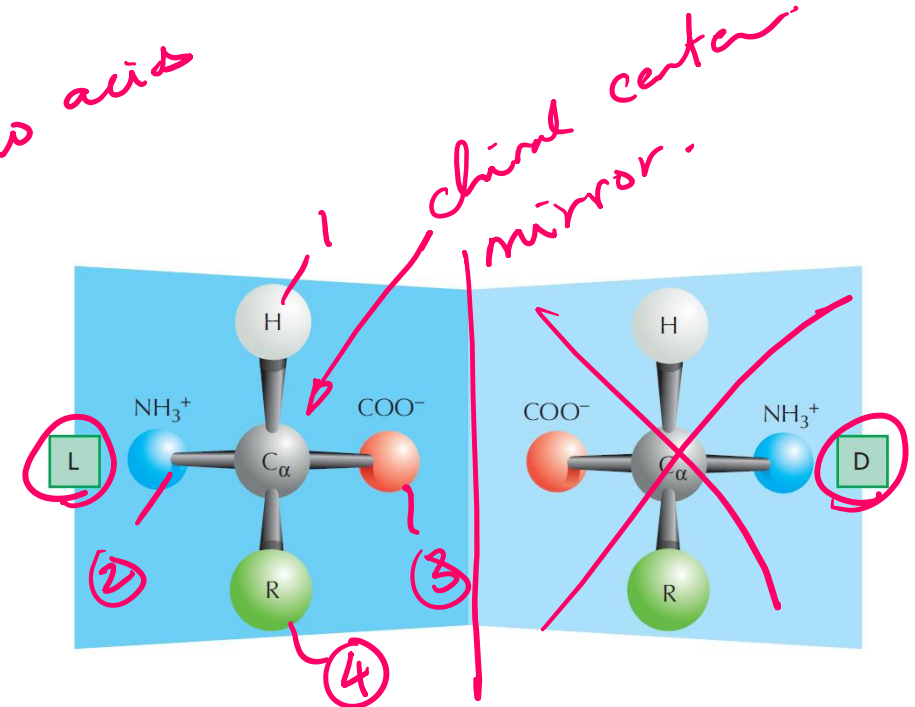
The Structure of Amino Acids and Proteins

General structure



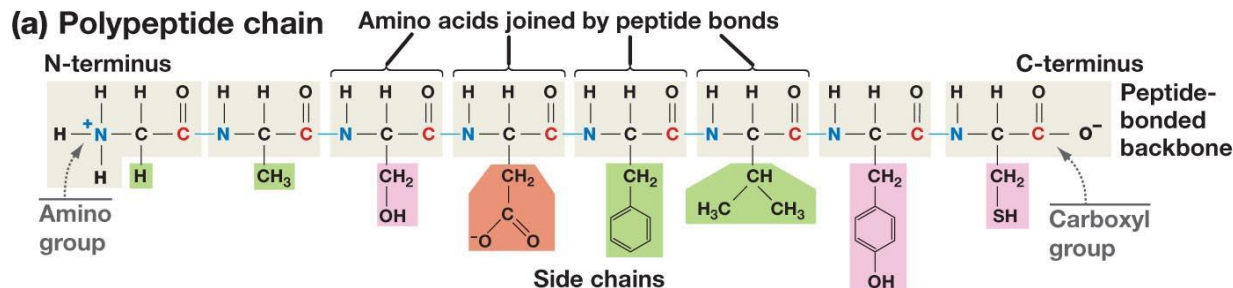
Is there a chiral carbon on amino acids?

- The amino group, C_α (and one hydrogen), and the carbonyl group are common to all amino acids
- The $N-C_\alpha-C=O$ 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.



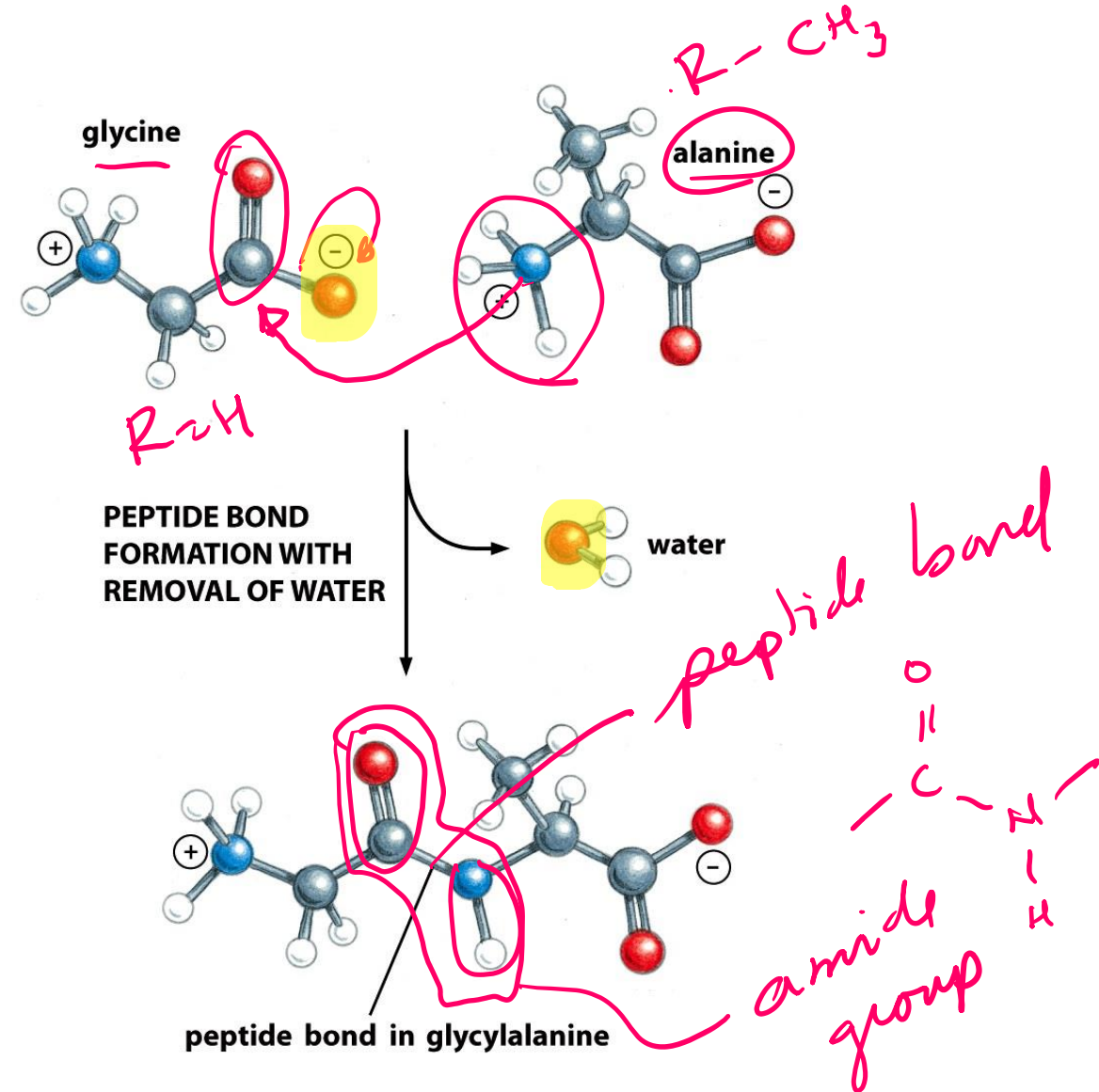
Proteins consist exclusively of L-amino acids.
(as does the ribosome that make them)

L-form is common found in all protein



Proteins are generated by formation of Peptide Bonds

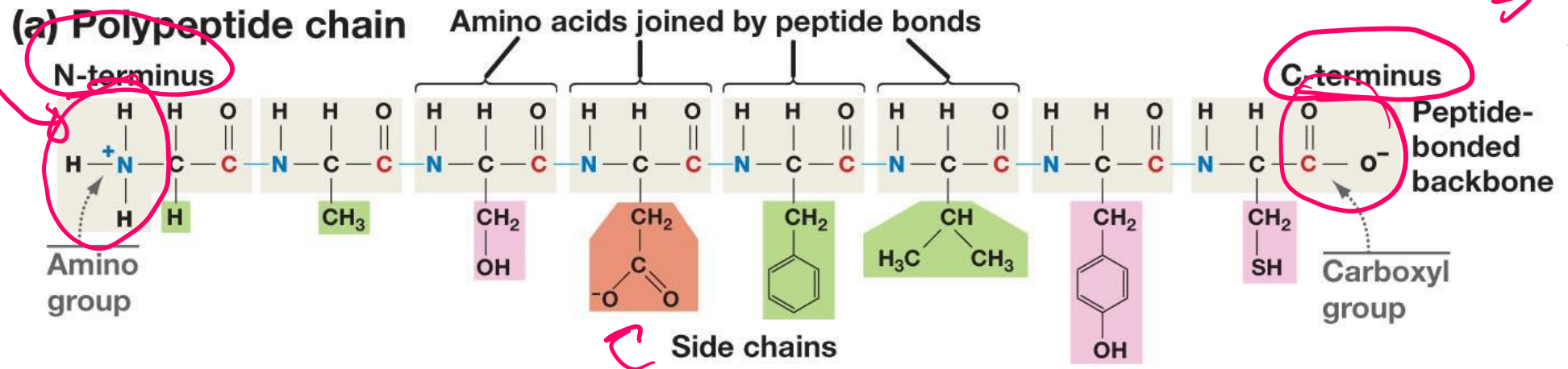
- Amino acids are linked to form **linear** polymers:
- Dehydration reactions bond the carboxyl group of one amino acid to the amino group of another to form a **peptide bond**.
- A chain of amino acids linked by peptide bonds is called a **polypeptide**.
 - Polypeptides containing fewer than 50 amino acids are called **oligopeptides (peptides)**.
 - Polypeptides containing more than 50 amino acids are called **proteins**.
 - The four atoms involved in the peptide bond all lie on the same plane.
 - The C=O is usually across from the N-H (trans conformation)



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

main chain

Seq of protein = order of AA
Starting from Amino terminus

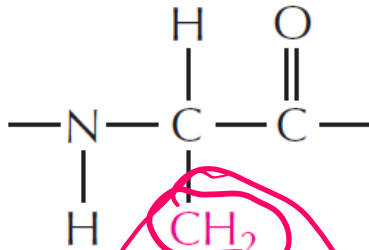


- Sidechains (R-groups) differ in their size, shape, reactivity, and interactions with water.
 - Nonpolar Sidechains: **hydrophobic**; do not form hydrogen bonds; coalesce in water - typically form the core of folded proteins.
 - Polar Sidechains: **hydrophilic**; form hydrogen bonds; readily dissolve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

ACIDIC SIDE CHAINS

aspartic acid

(Asp, or D)

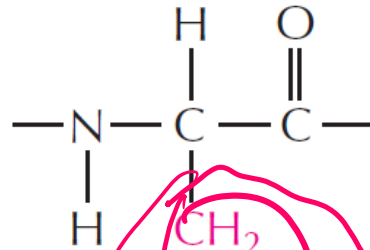


pK_a of sidechain ~ 4

Have a net negative charge at pH 7.0

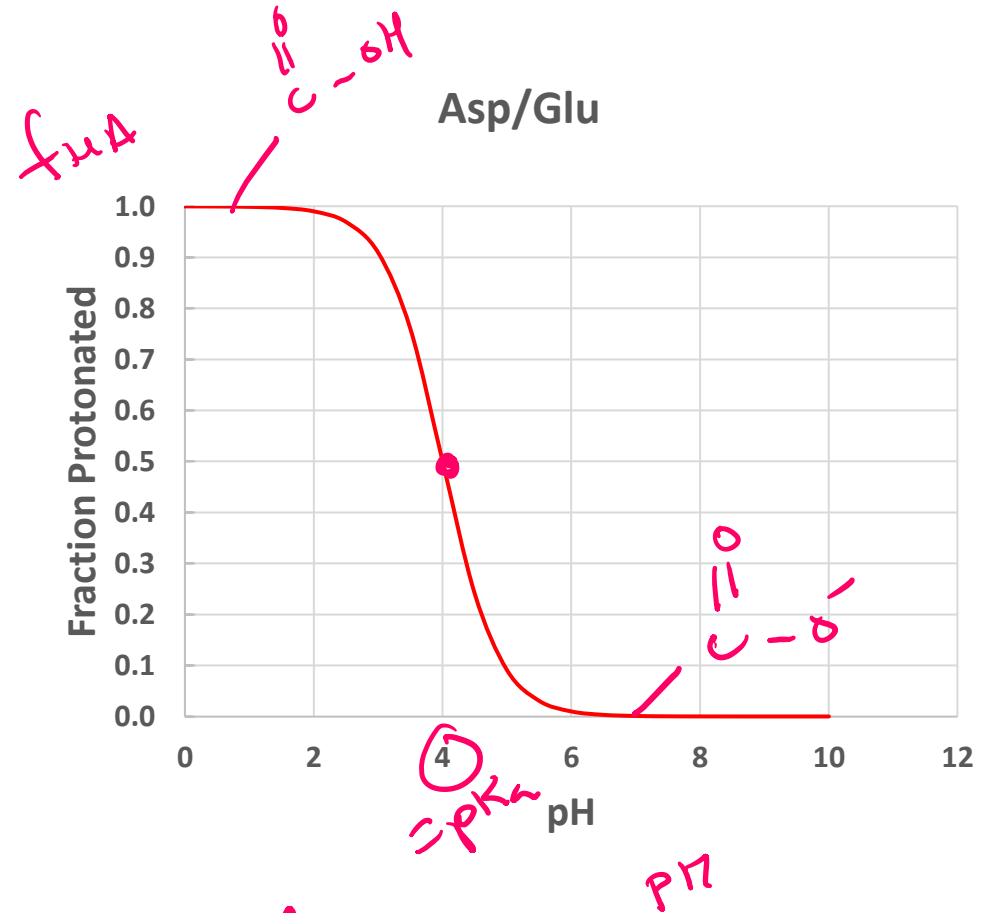
glutamic acid

(Glu, or E)



pK_a of sidechain ~ 4

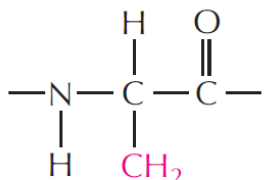
Same functional group



BASIC SIDE CHAINS

lysine

(Lys, or K)



CH₂

CH₂

CH₂

CH₂

CH₂

NH₃⁺

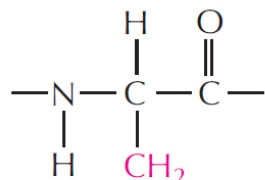
This group is very basic because its positive charge is stabilized by resonance.

pK_a ~ 10

Have a net positive charge at pH 7.0

arginine

(Arg, or R)



CH₂

CH₂

CH₂

CH₂

NH

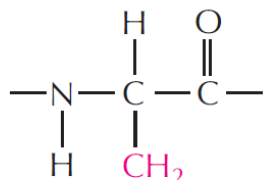
C

NH₂

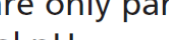
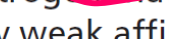
pK_a ~ 12

histidine

(His, or H)



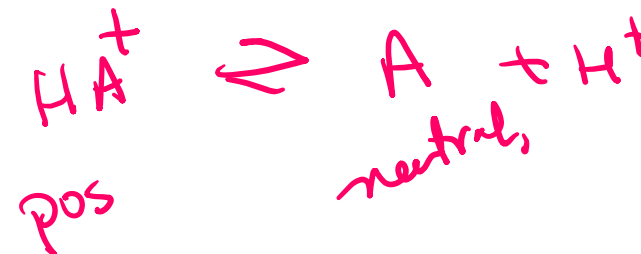
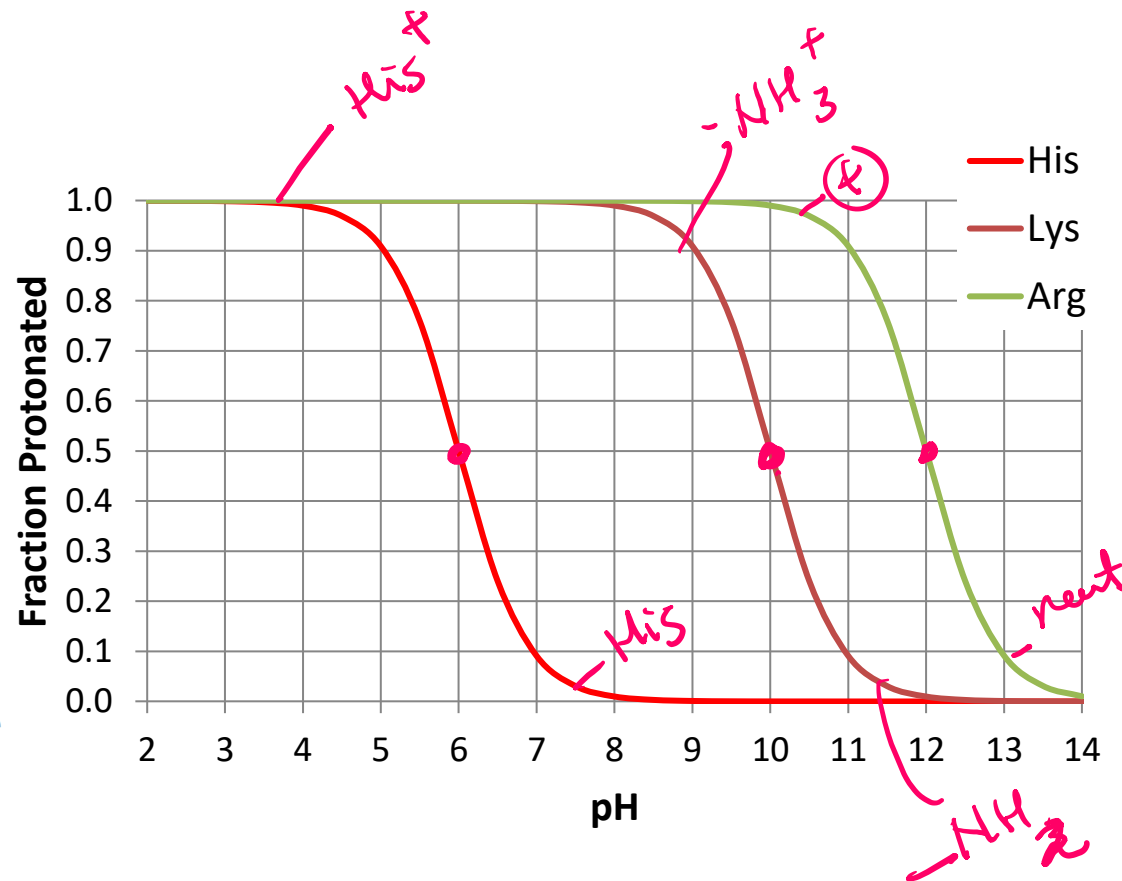
CH₂



pK_a ~ 6

Positive charge when protonated
10% Protonated at pH 7.0

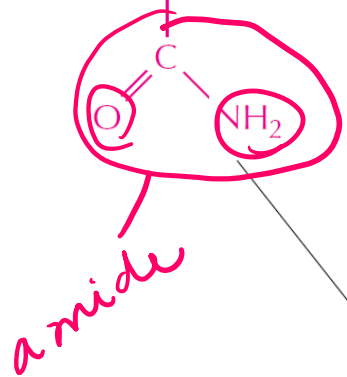
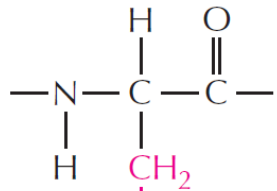
weaker acids
pos charge when protonated.



UNCHARGED POLAR SIDE CHAINS

asparagine

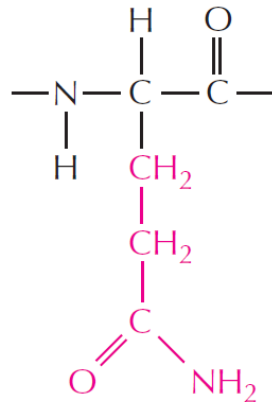
(Asn, or N)



Although the amide N is not charged at neutral pH, it is polar.

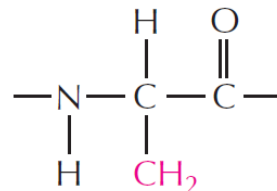
glutamine

(Gln, or Q)



serine

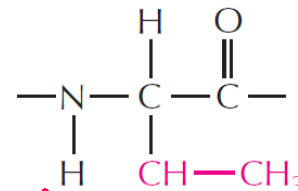
(Ser, or S)



The -OH group is polar.

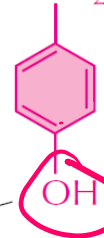
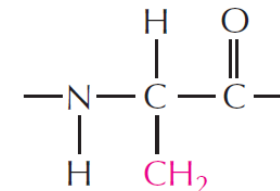
threonine

(Thr, or T)



tyrosine

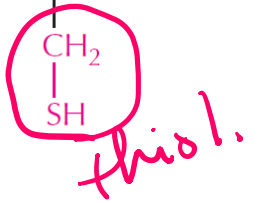
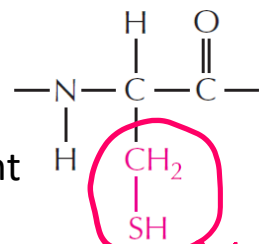
(Tyr, or Y)



This is a significant non-polar functionality

cysteine

(Cys, or C)

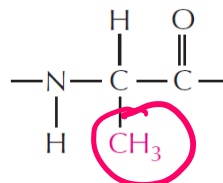


- Forms weak H-bonds
- Can ionize with a pK=8, forming thiolate ion (-S⁻)
- Can form S-S disulfide bonds with other Cys residues

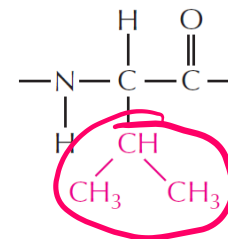
These can form what type of bond with water?

NONPOLAR SIDE CHAINS

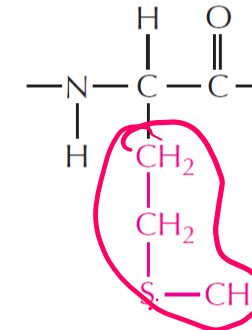
alanine
(Ala, or A)



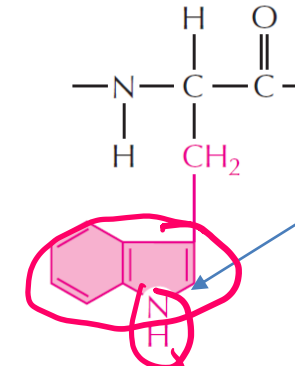
valine
(Val, or V)



methionine
(Met, or M)



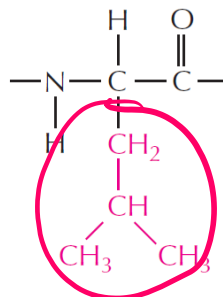
tryptophan
(Trp, or W)



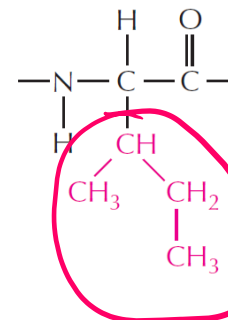
H-bond donor
(polar functionality)

polar
-OH.

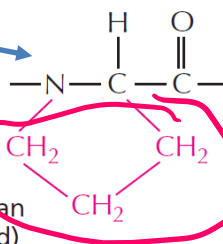
leucine
(Leu, or L)



isoleucine
(Ile, or I)



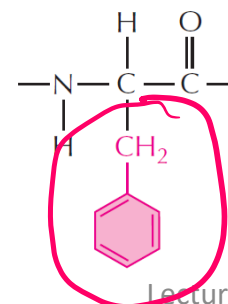
proline
(Pro, or P)



Ring results
in no NH
group for
H-bonding

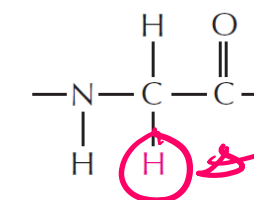
(actually an
imino acid)

phenylalanine
(Phe, or F)



AND AT LAST THERE IS GLYCINE:

glycine
(Gly, or G)

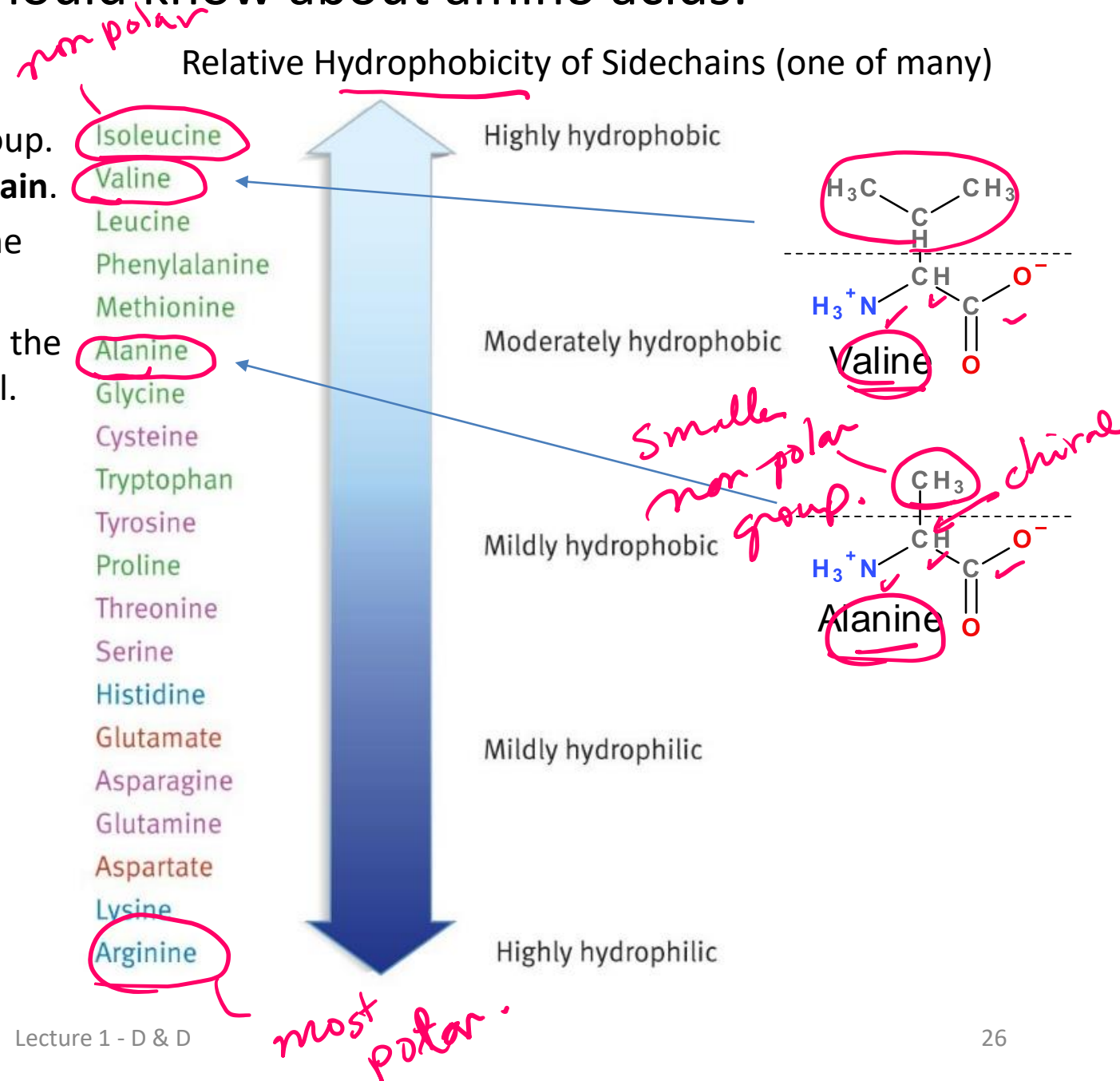


No real functionality for its R group (H)
Only AA that is achiral

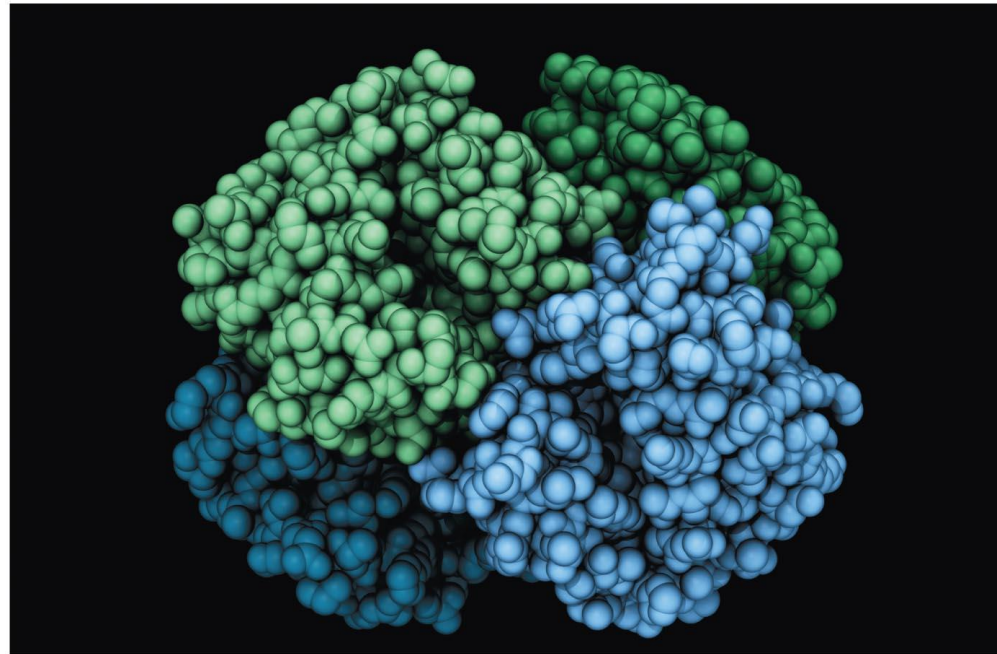
no functionality

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 ✓



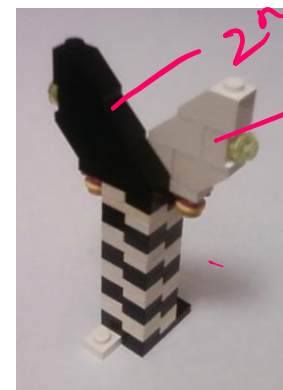
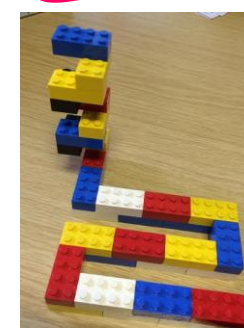
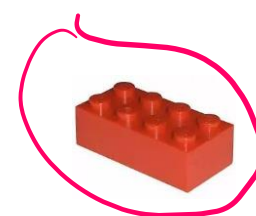
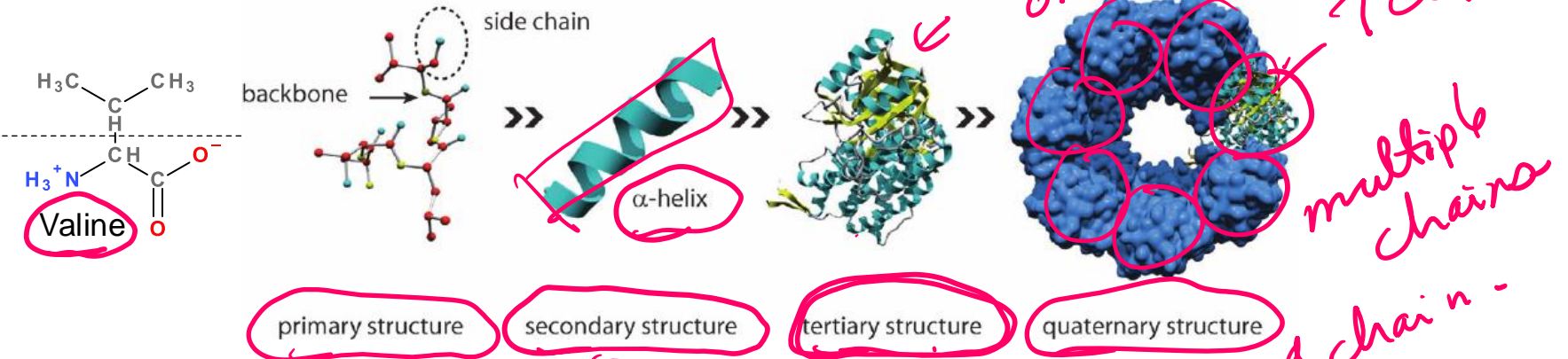
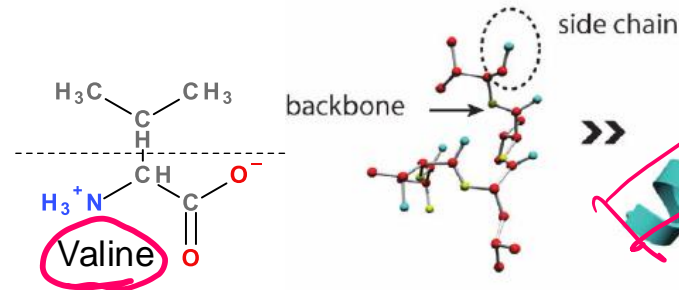
Protein Structure and Stability



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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.



(White and black represent two different chains)

Chemical
Structure
linking
AA by
peptide
bond



β -strands

functional form.

(White and represent different

functional form

28

Secondary Structure

“Building blocks of proteins”

- **Hydrogen bonds** between the *mainchain* carbonyl group of one amino acid and the *mainchain* amino group of another form a protein's **secondary structure**.
 - A polypeptide must bend to allow this hydrogen bonding, forming:
 - α -helices
 - β -pleated sheets
- The large number of hydrogen bonds in a protein's secondary structure increases its stability - each hydrogen bond that is formed releases some energy.
- All amino acids can be incorporated into either secondary structure
(However, some are found more frequently in one structure)



General Rule for Hydrogen Bonds:



X & Y are electronegative (N and O usually)

X-H = Donor of the hydrogen bond

Y = Acceptor of the hydrogen bond

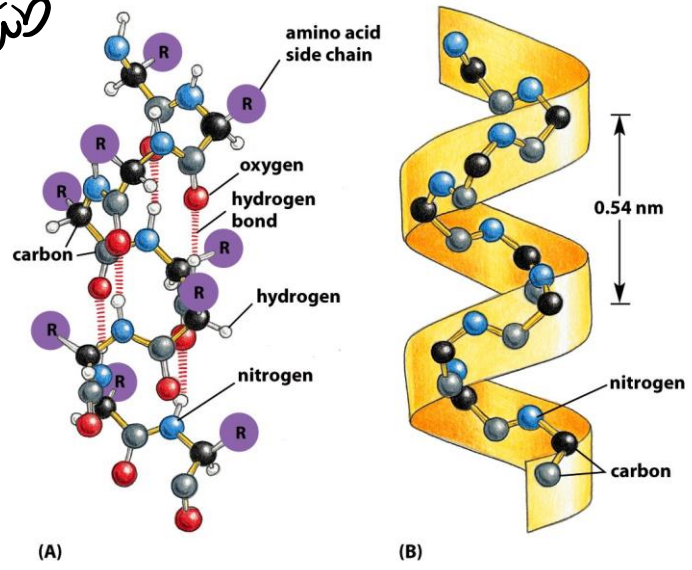
Mainchain hydrogen bonds



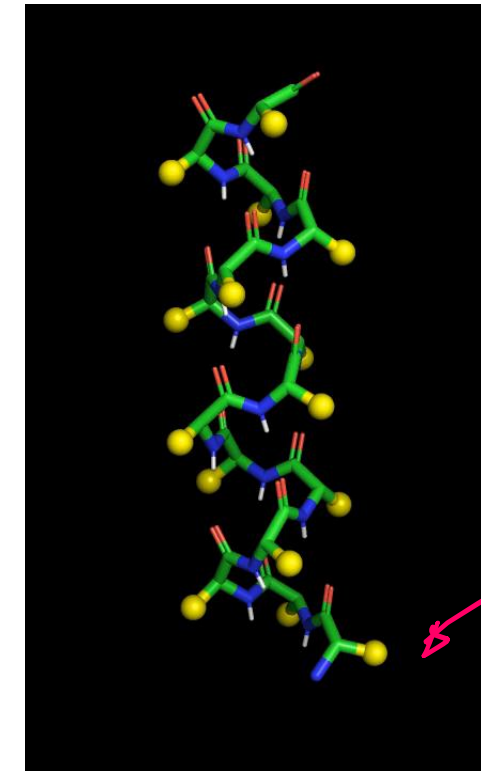
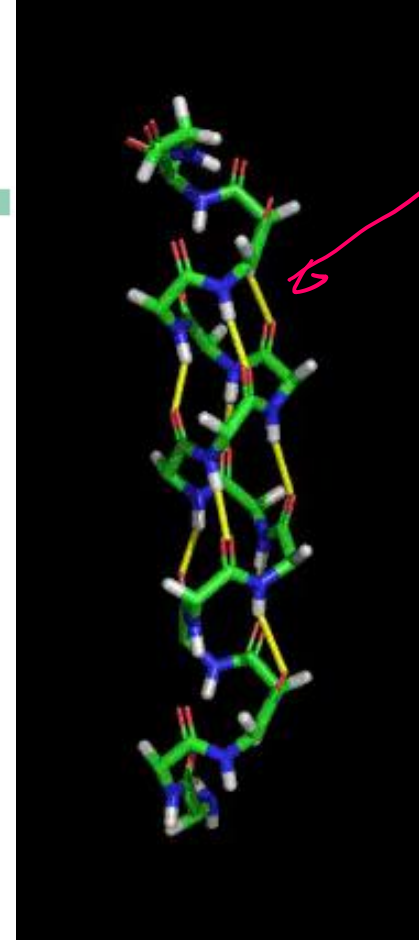
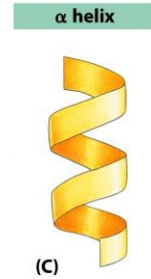
The NH is the hydrogen bond donor.

The C=O is the hydrogen bond acceptor.

main chain
H-bonds
Side chain



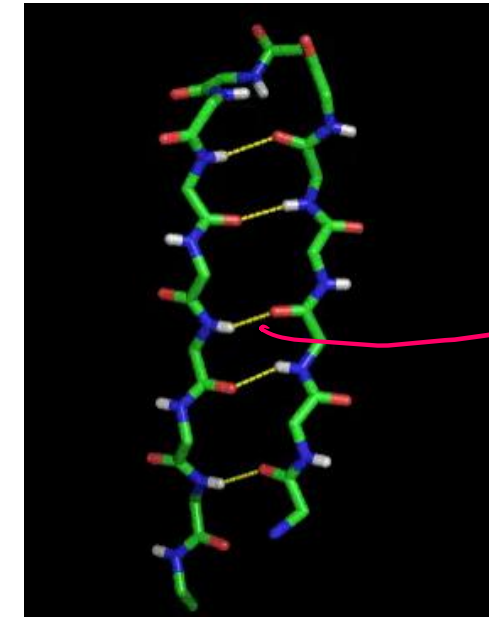
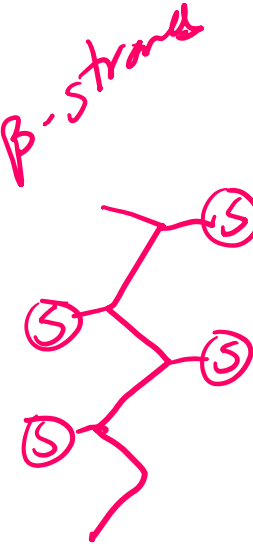
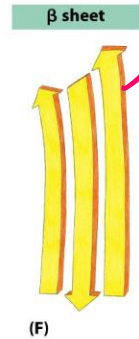
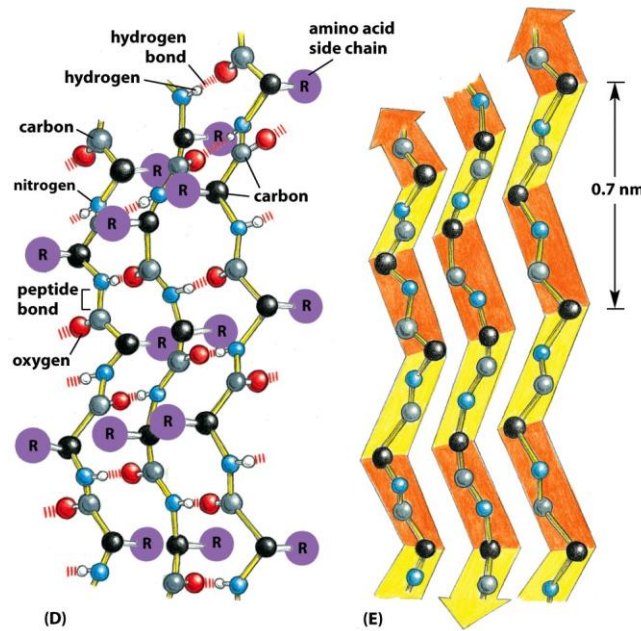
Alpha Helix



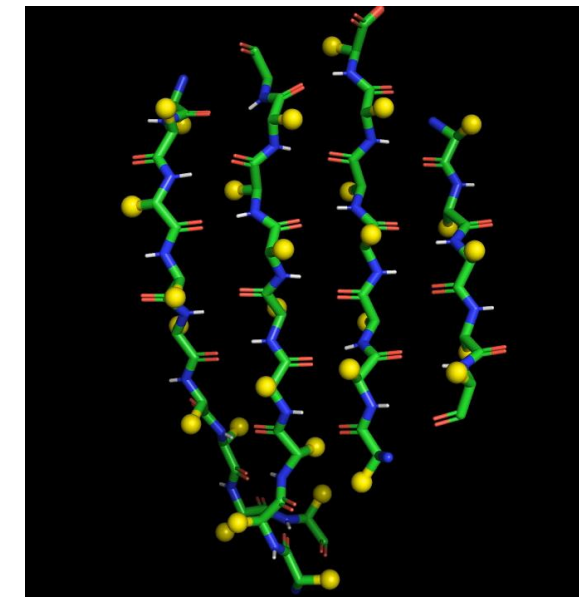
Spiral conformation (*helix*) in which every backbone N-H group donates a hydrogen bond to the backbone C=O group of the amino acid four residues earlier:

- Intra-strand H-bonds, parallel to helix axis.
- Side-chains project outwards.

Beta Sheet



N-H ... O=C
⊥ to strands.

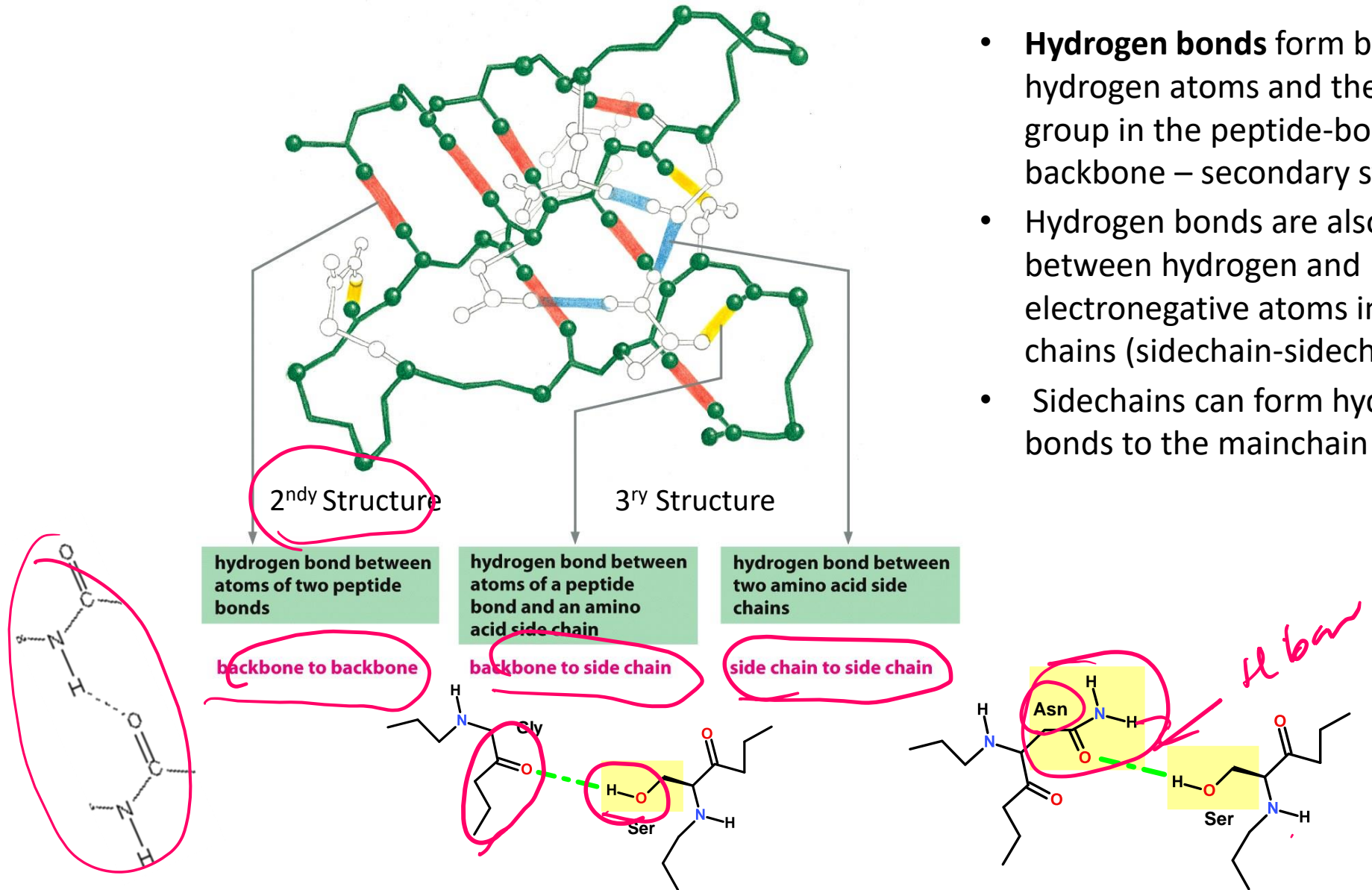


4-strands
side chain

- Beta-Strands connected laterally by backbone hydrogen bonds that are perpendicular to the strand, forming a generally twisted, pleated sheet.
- Sheets can have two or more strands
- Side-chains:
 - project up and down along a strand.
 - project in the same direction going from strand to strand across the sheet.

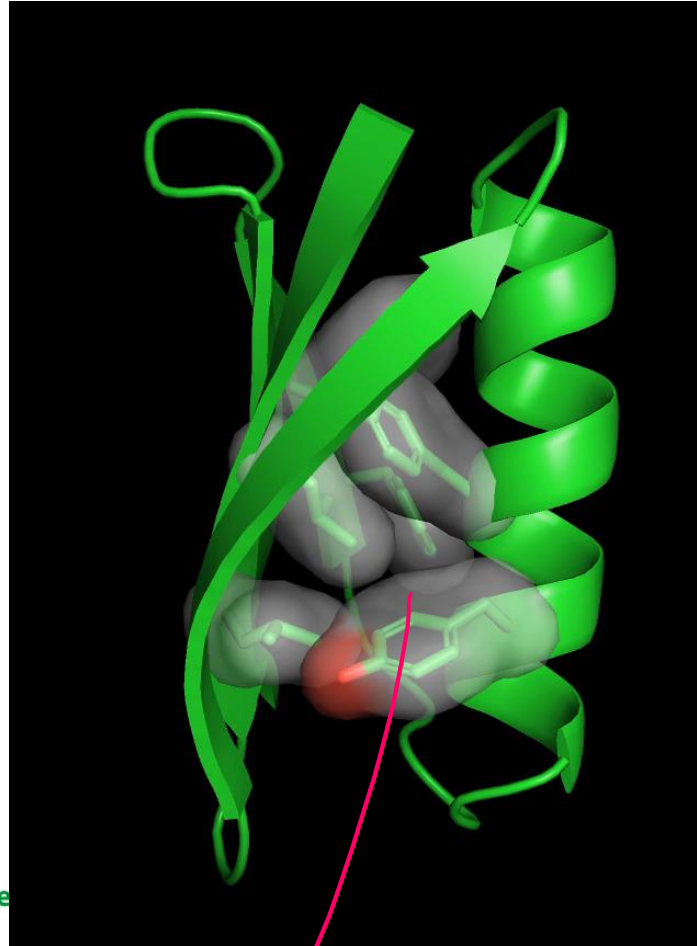
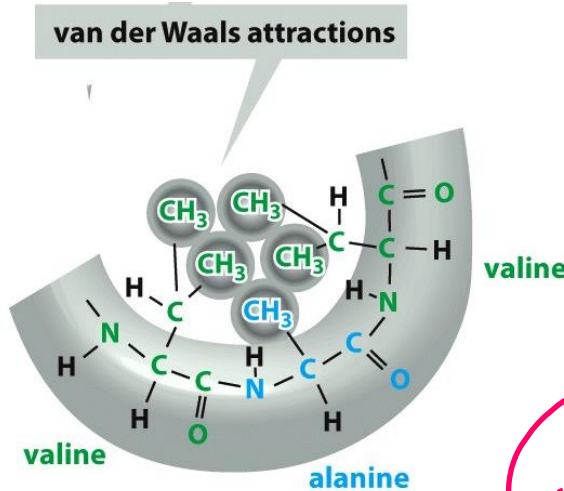
Hydrogen Bonding Stabilizes the Tertiary Structure

- **Hydrogen bonds** form between hydrogen atoms and the carbonyl group in the peptide-bonded backbone – secondary structure
- Hydrogen bonds are also found between hydrogen and electronegative atoms in side chains (sidechain-sidechain)
- Sidechains can form hydrogen bonds to the mainchain too.

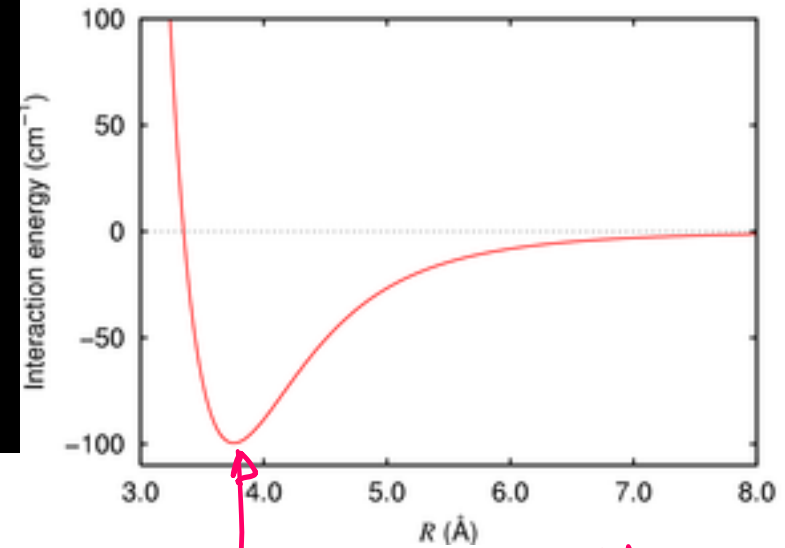
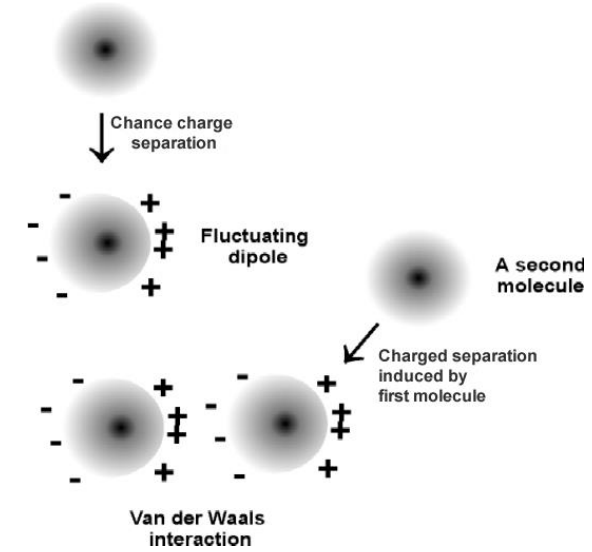


Van der Waals (VdW) interactions Stabilize the Folded State

- VdW are weak electrostatic interactions between side chains due to temporary (fluctuating) charges.
- Attractive from long distance
- Distance at lowest energy is at the van der Waals radii of the atoms.
- Optimized in the core of folded proteins by “knobs fitting into holes”
- Strength proportional to contact area.



well packed core.



opt vdw distance

Strength of Van der Waals Depends on the Surface Area



Hydrophobic Interactions are Critical for Stabilizing Folded Proteins

Hydrophobic interactions within a folded protein increase stability of surrounding water molecules by releasing the ordered water that surrounded exposed non-polar groups when the protein is unfolded, **increasing the entropy of the water – disorder is favorable.**

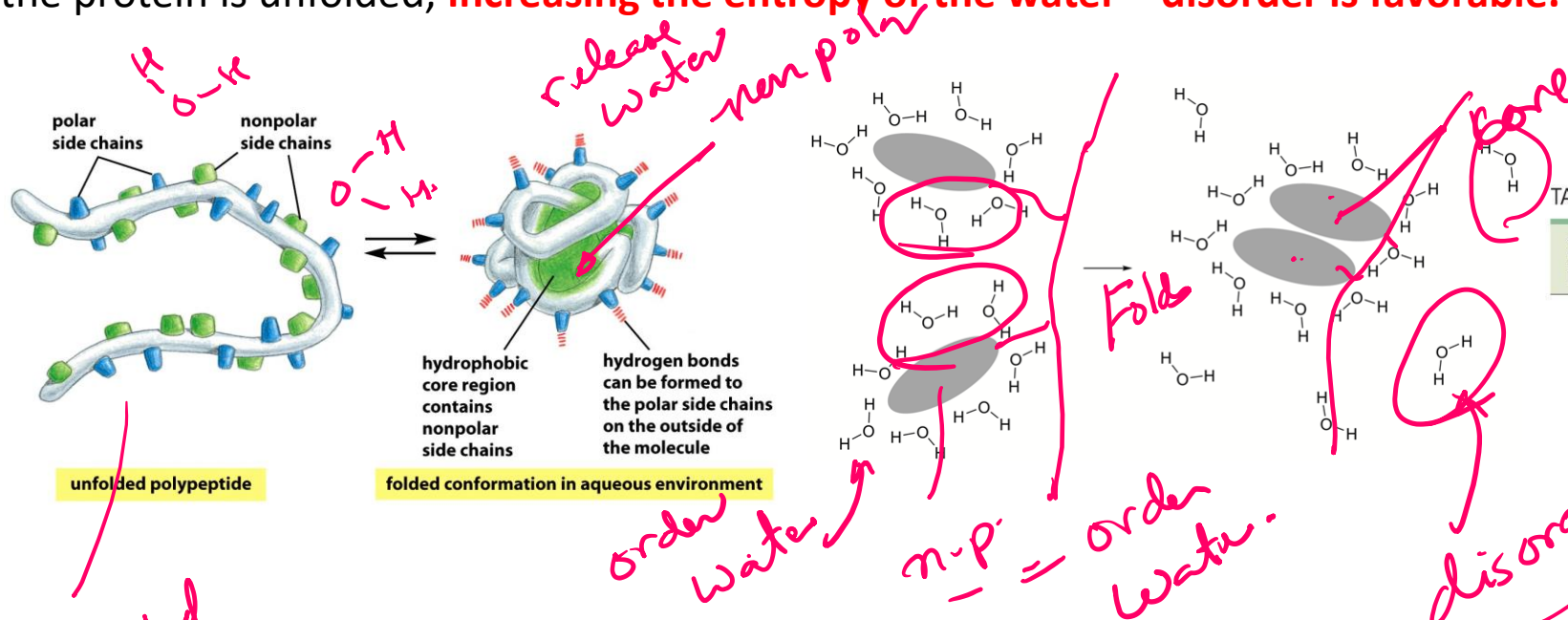
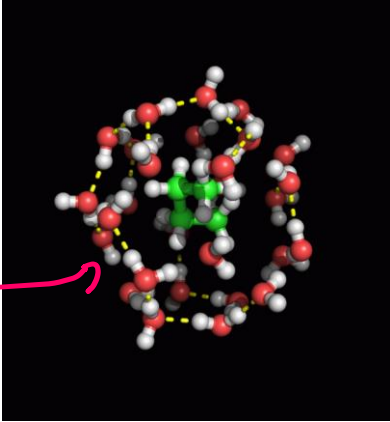
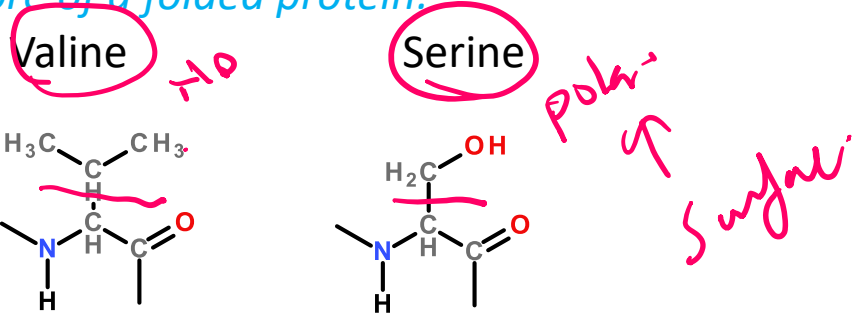


TABLE 3.1 How Amino Acids Interact with Water

20 amino acids are ranked according to how likely they are to interact with water. Color codes are based on Figure 3.3.

Isoleucine	Highly hydrophobic
Valine	
Leucine	
Phenylalanine	
Methionine	
Alanine	Moderately hydrophobic
Glycine	
Cysteine	
Tryptophan	
Tyrosine	
Proline	Mildly hydrophobic
Threonine	
Serine	
Histidine	
Glutamate	
Asparagine	Mildly hydrophilic
Glutamine	
Aspartate	
Lysine	
Arginine	
	Highly hydrophilic

Which amino acid is most likely to be found in the core of a folded protein:



disorder
favoured

unfolded protein.

