# Drugs & Disease – Spring 2025

**Course Overview:**

1. Introductory Biochemistry
2. DNA, RNA, protein synthesis, biotechnology
3. Immunology & Immunotherapy
4. Drug Discovery – Enzyme Inhibitors
5. Genome Editing – CRISPR
6. Final presentations

**Expectations:**

- 5 Problem sets (***First one posted***)
- One mid-class exam
- Presentation (10 min, topic of choice)
- Short paper (Same topic as presentation)

**My Story**

- Born in Ottawa Canada
- Undergraduate: University of Waterloo, largely physics
- MS: Penn State University
- PhD: Carnegie Mellon
- Post-doc: Stanford University
- Faculty: University of Virginia then Carnegie Mellon

**Research area:**

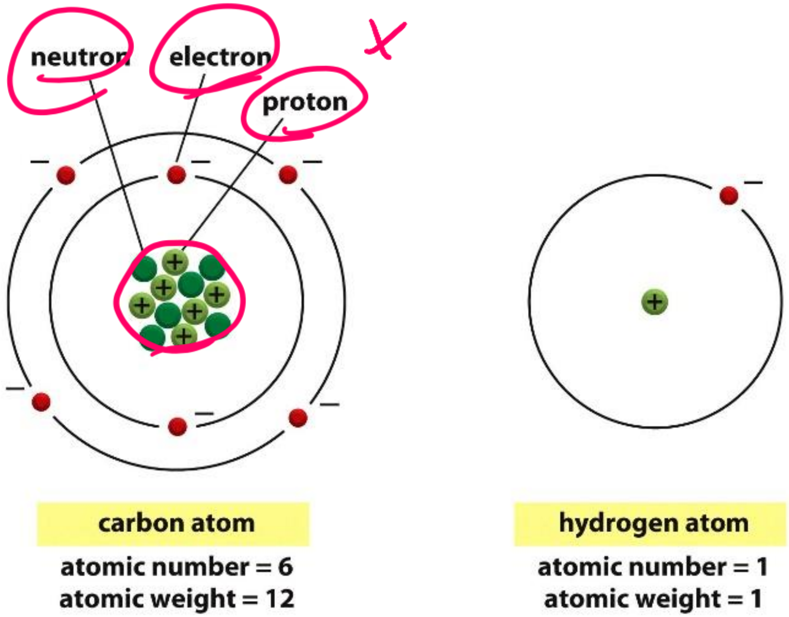
- Protein structure and dynamics
- Drug discovery

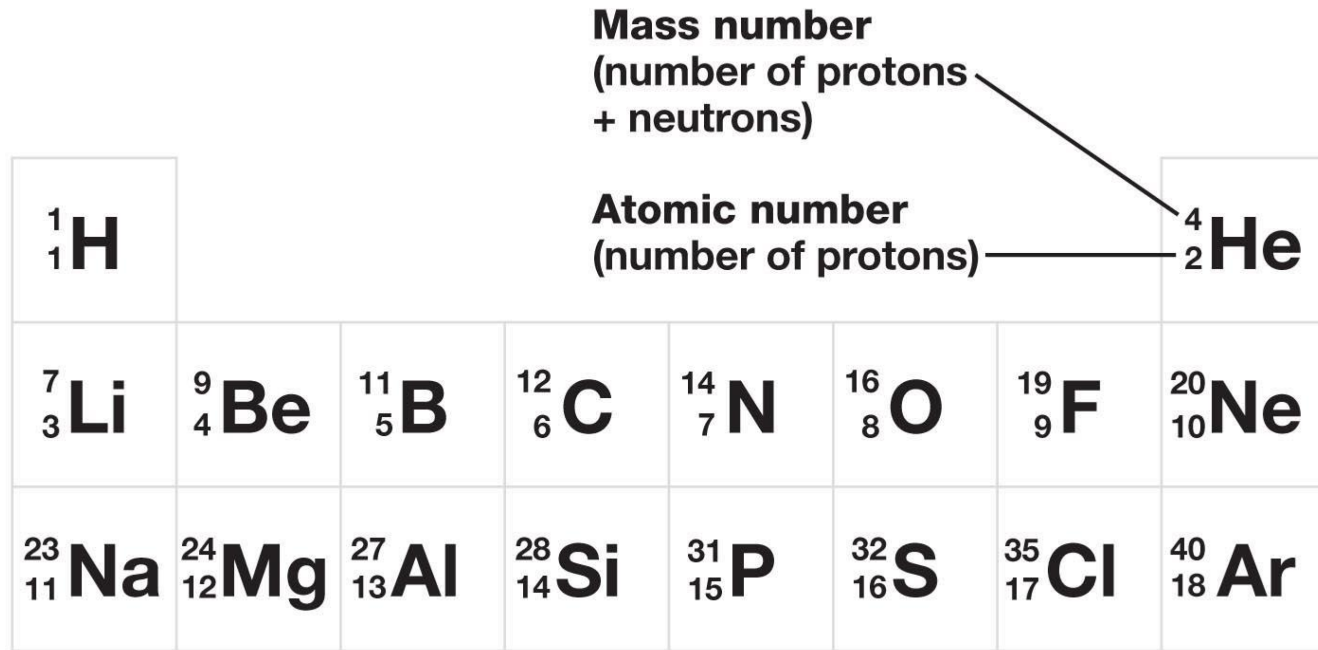
**Take-home exercise:**
Send me an email with a short paragraph describing why you took the course and what you hope to take away from the course.

**Course materials:**
https://www.andrew.cmu.edu/user/rule/Drugs_Disease/

# Lecture 1
# Chemistry and Biology Fundamentals

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

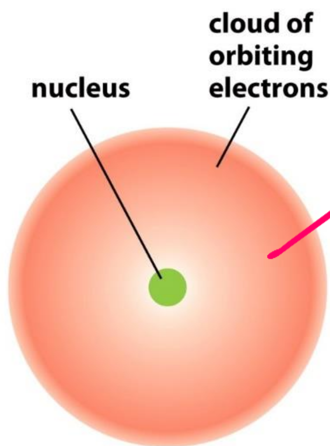



- Atoms are composed of:
  - Protons – positively charged particles
  - Neutrons – neutral particles
  - Electrons – negatively charged particles
- Protons and neutrons are located in the nucleus.
- Electrons are found in **orbitals** surrounding the nucleus.
- The overall charge on an element is neutral (#electrons = # protons).

Atomic number = # of protons = # electrons in element

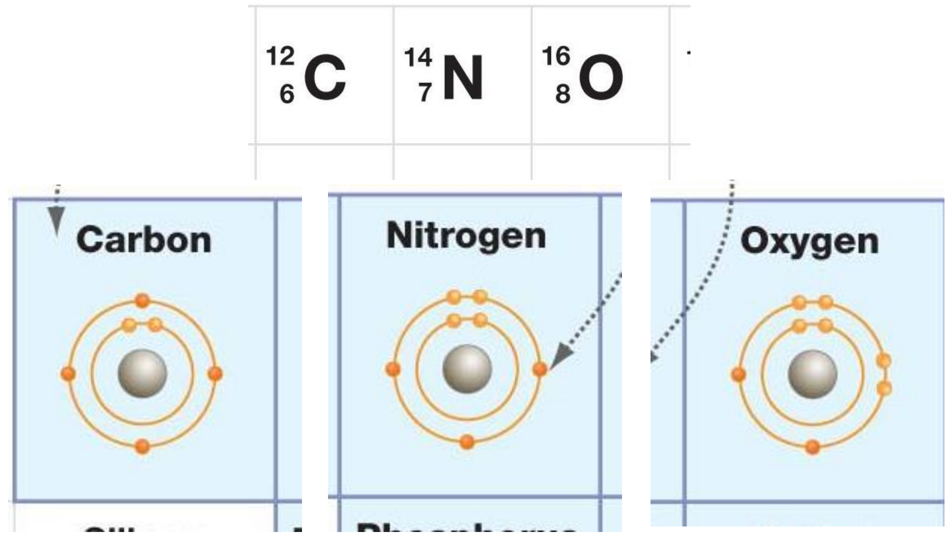
Isotope = different # of neutrons = same bonding capability

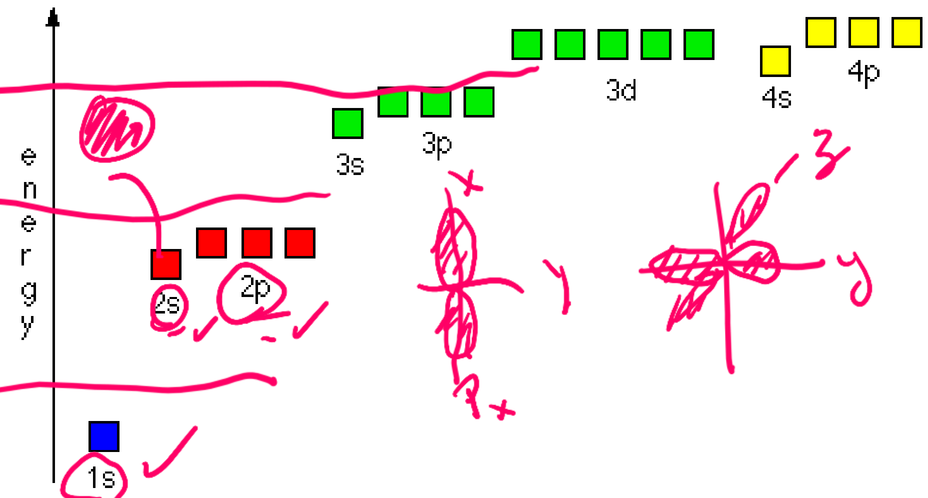



electron cloud ⇒ bonding interaction

# Electron Orbitals

- 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 via electron sharing.
- The most stable configuration is a complete (full) outer shell.

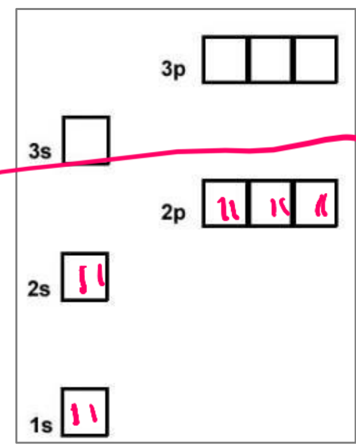



**Shells:** 1st = 1s, 2nd = 2s + 2p, 3rd = 3s + 3p

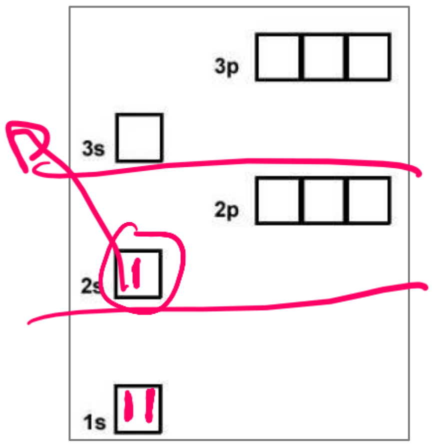
Shell is a collection of orbitals with similar energy

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



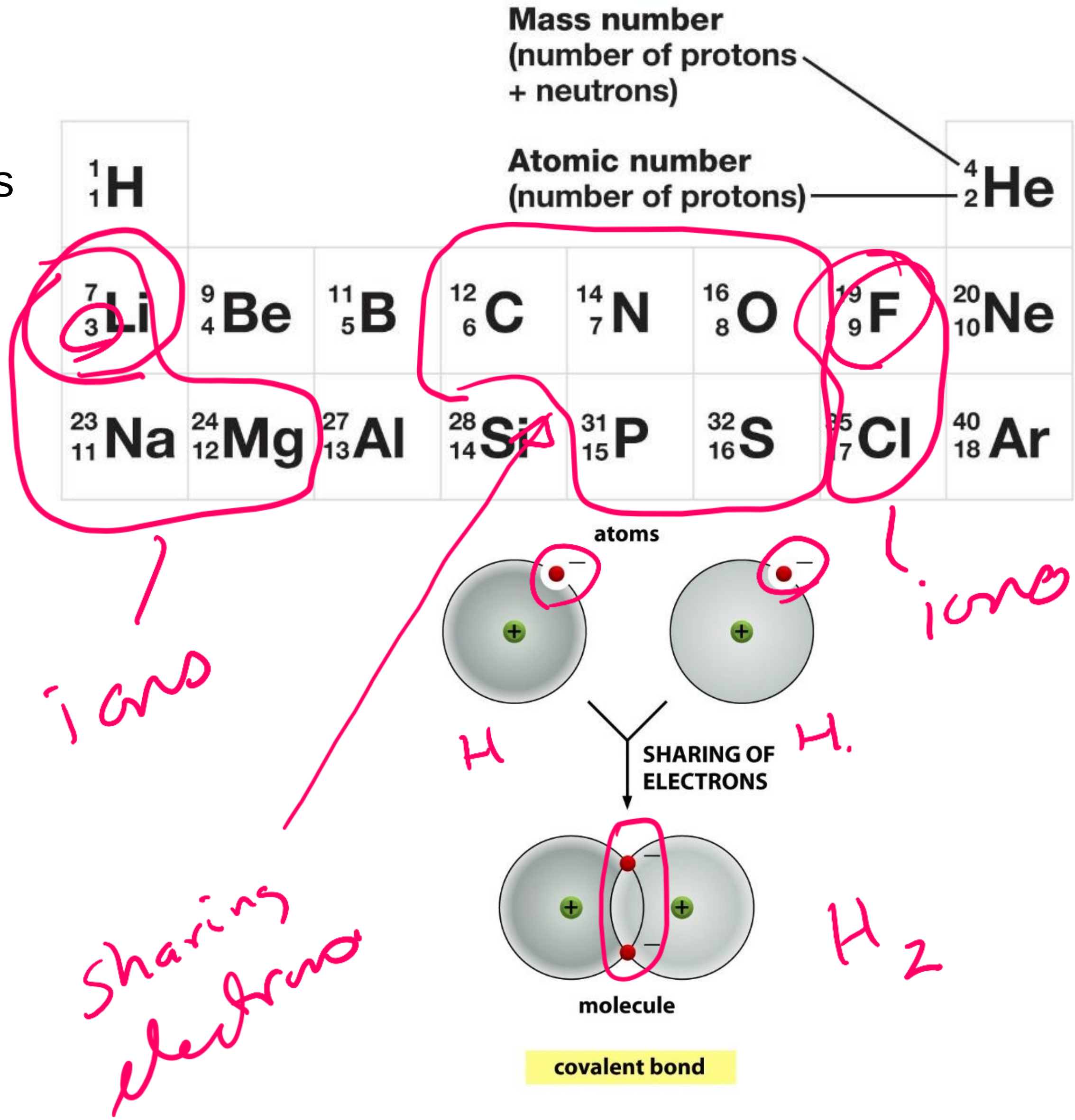
# Ions or Covalent Chemical Bonds – What's an Element going to do?

- Elements like Li, Na, F, Cl, Mg, readily form ions to generate a complete outer shell.




Example:
Li with 3 electrons

- 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



# Covalent Bonds – Filling the Outer Shell by Sharing

- 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.

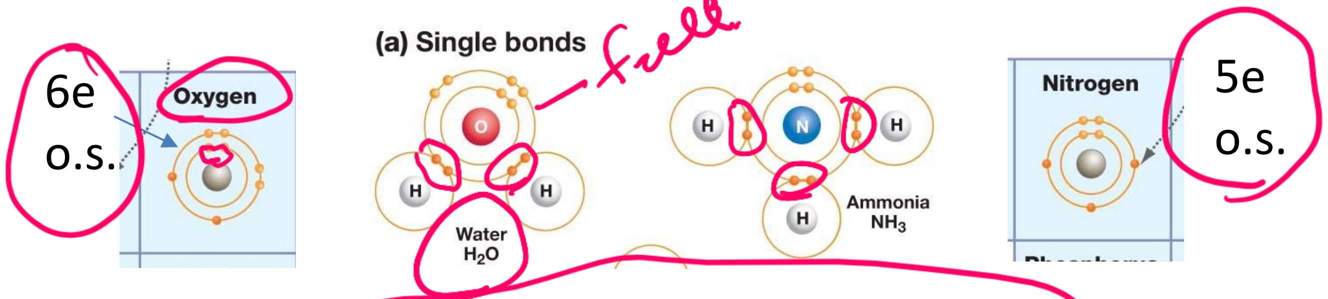
- Oxygen = 2 bonds
- Nitrogen = 3 bonds
- Carbon = ______
- Sulfur = 2 bonds (in biological systems)
- Hydrogen = 1 bond
- Phosphorous = 5 bonds in biological molecules

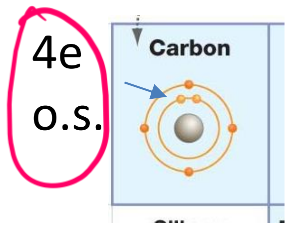
**You must know these numbers.**

**Abbreviated Chemical Drawings:**

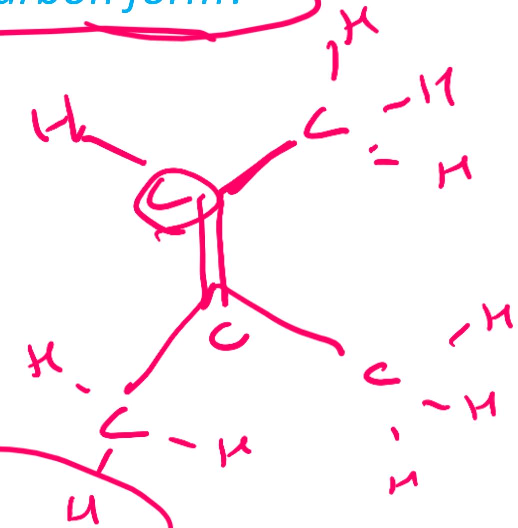
- "C" for carbon is not drawn, but carbons are found at the ends of lines and when lines join or "kink"
- Hydrogens attached to carbon are not shown, you need to add them to complete to complete the valence of the carbon atoms.

**You must know how to do this.**

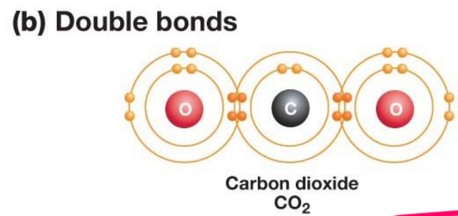



*How many bonds will carbon form?*

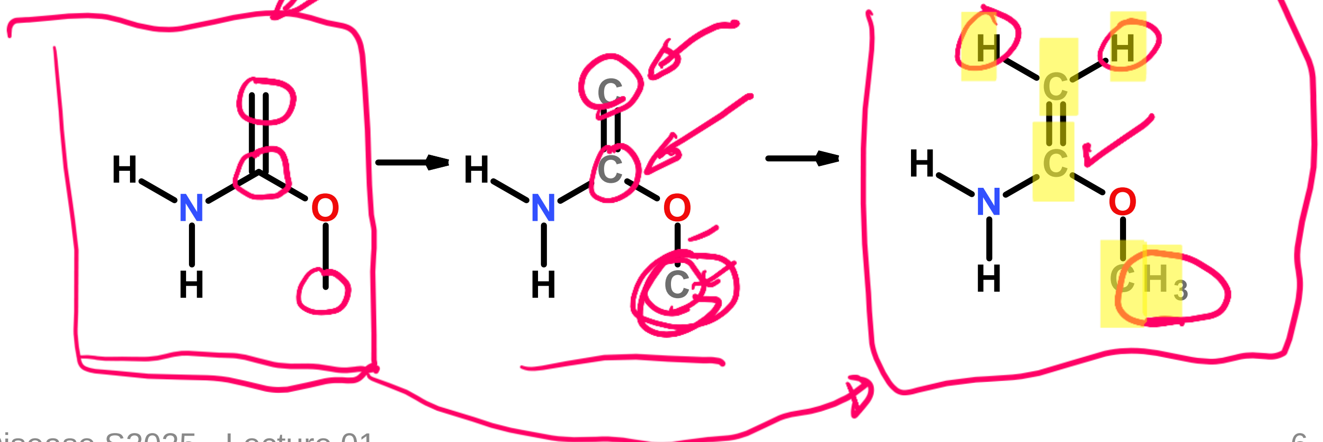


$O=C=O$

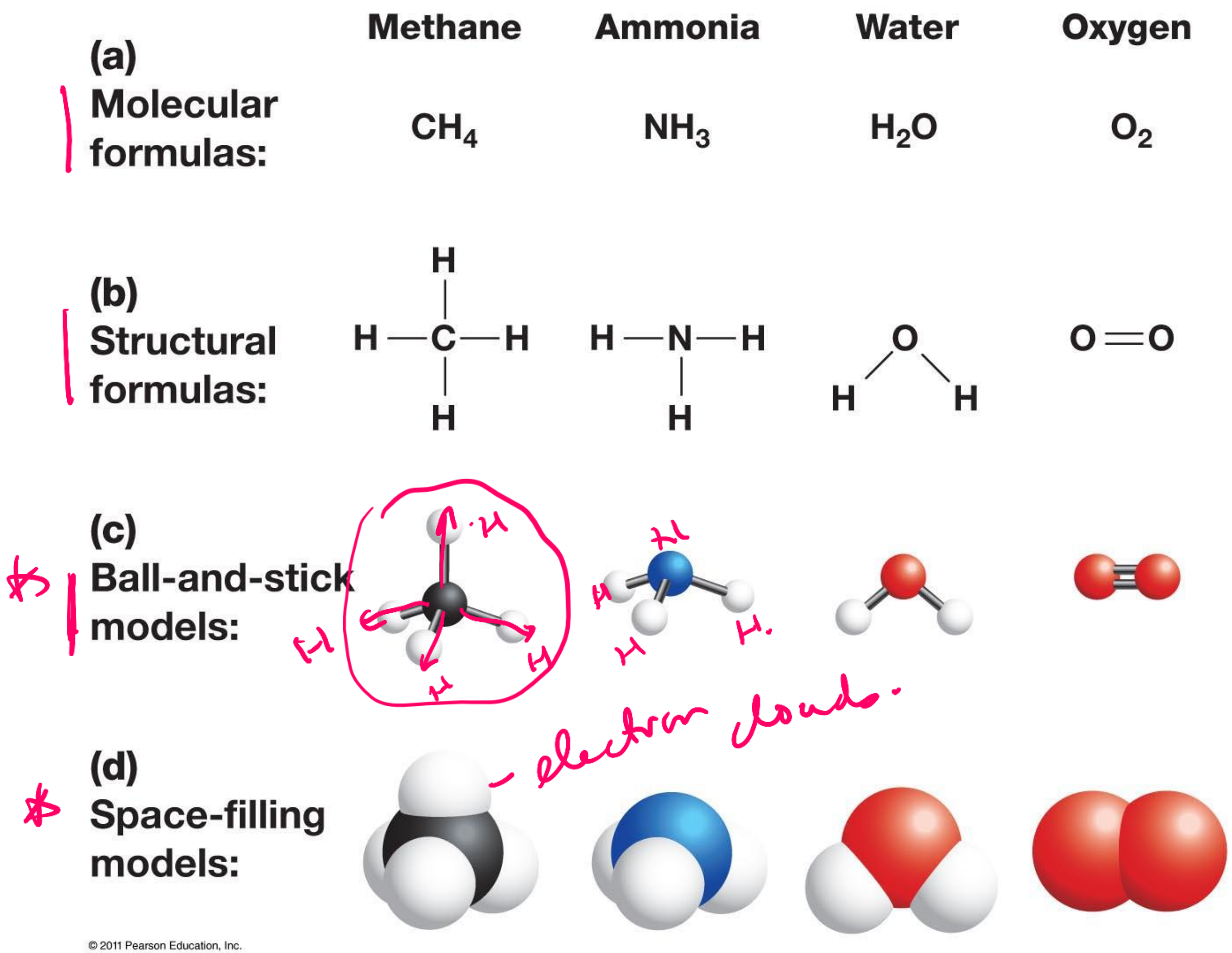



"C" for carbons

Complete valence with H



# Representation of Molecules

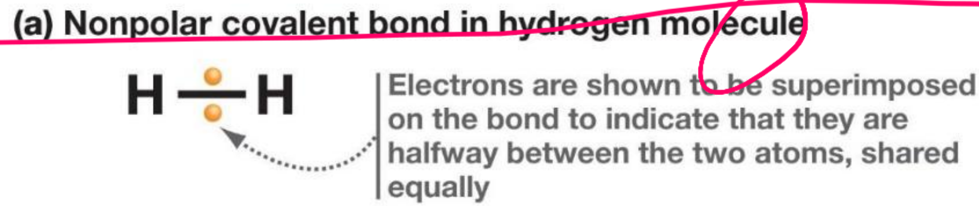


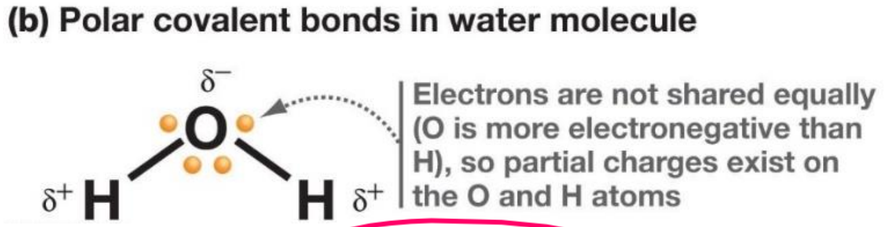
# Electron Sharing and Bond Polarity – Are All Bonds Equal?

- Polar bonds = different electron density of each atom.
- 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:

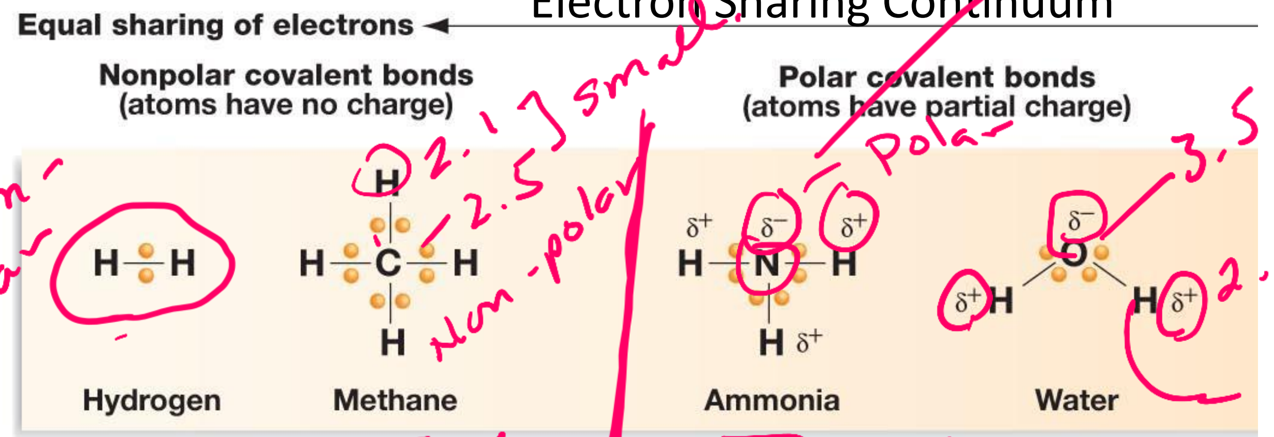
  H ~ C < N < O

*Increased pos. charge of nucleus.*


Electron Sharing Continuum

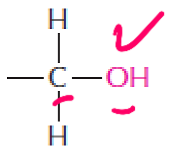


# Functional Groups – You should Become Familiar with These

## C–O COMPOUNDS

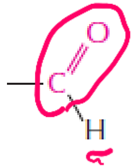
Many biological compounds contain a carbon bonded to an oxygen. For example,

alcohol

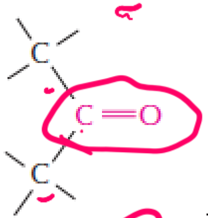


The –OH is called a hydroxyl group.

aldehyde

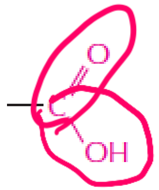


ketone



The C=O is called a carbonyl group.

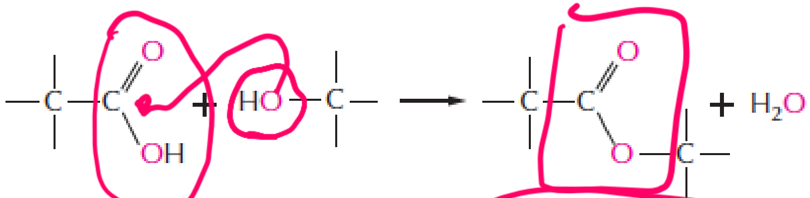
carboxylic acid



The –COOH is called a carboxyl group. In water this loses an $H^+$ ion to become $–COO^–$.

esters

Esters are formed by combining an acid and an alcohol.

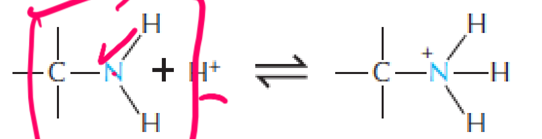


acid alcohol ester

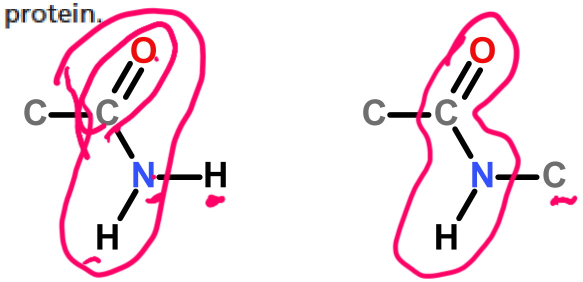
## C–N COMPOUNDS

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.

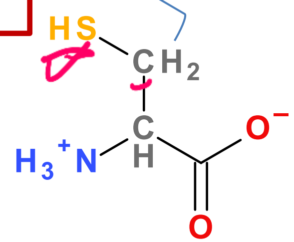


Amides are formed by combining an acid and an amine. Unlike amines, amides are uncharged in water. An example is the peptide bond that joins amino acids in a protein.



## C–S COMPOUNDS

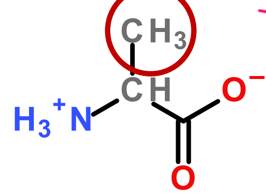
thiol



Cysteine (amino acid)

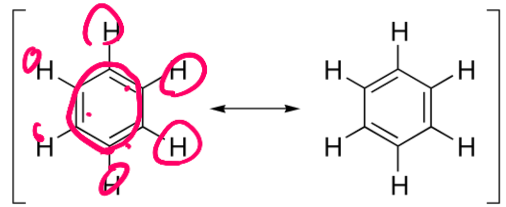
## C–H GROUPS (HYDROPHOBIC)

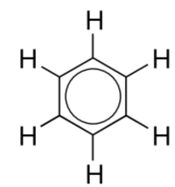
Methyl



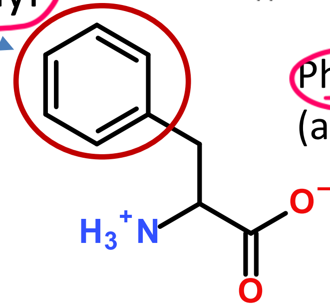
Alanine (amino acid)

**Aromatic** – planer rings, alt double bonds





Phenyl



Phenylalanine (amino acid)

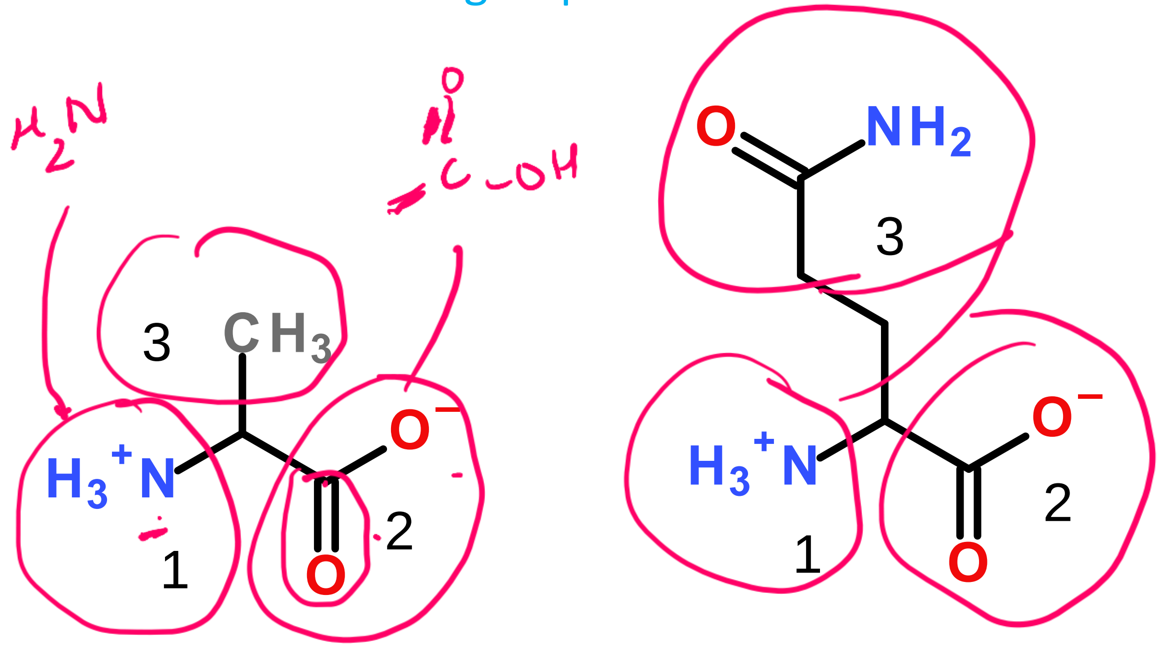
# Key Points & Expectations

**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.
- Predict degree of bond polarity based on electronegativies, N-H and O-H and C=O are polar, C-H is not.
- Be able to draw the following functional groups & identify them on larger molecules.
  - Non-polar:
    - Methyl
    - Phenyl
  - Polar:
    - Alcohol (C-OH)
    - Thiol (C-SH)
    - Carboxylate (ketone, aldehyde) (C=O)
    - Ester
    - Carboxylic acid
    - Amide
    - Amino

A. Give the names of the functional groups on these two amino acids.

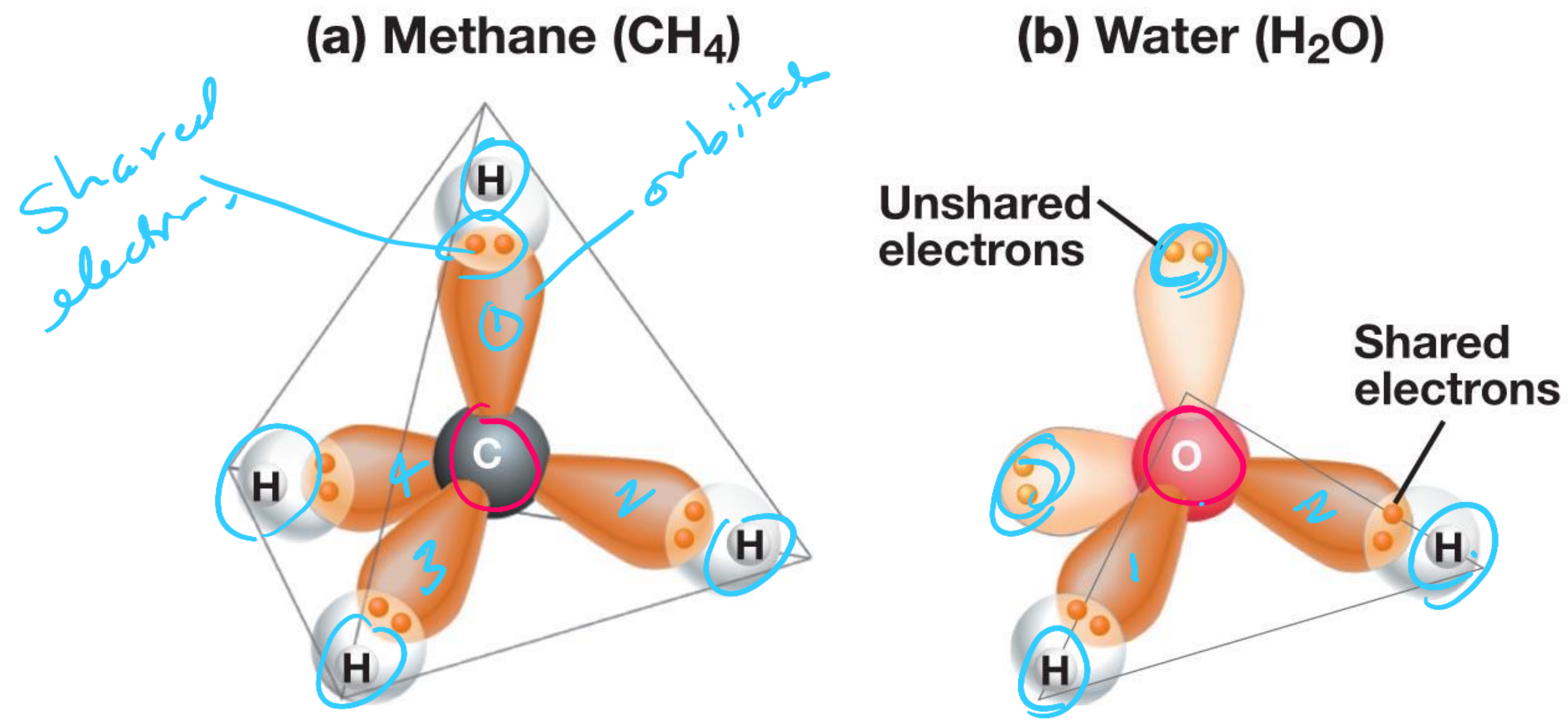
B. Which functional groups are common?




1.
2.
3.

1.
2.
3.

# The Geometry of Simple Molecules

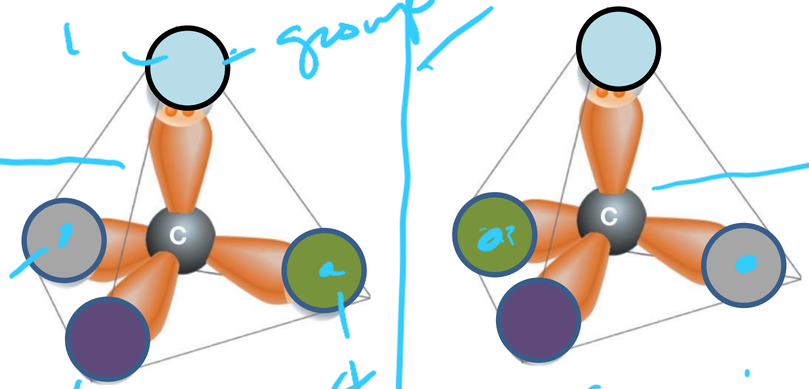


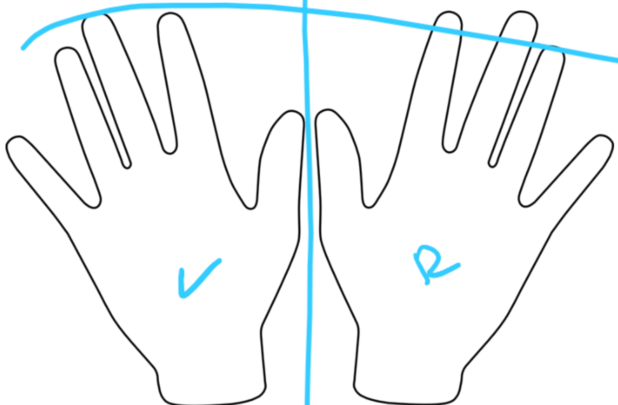

**The shape of a molecule is determined by the geometry of its bonds.**

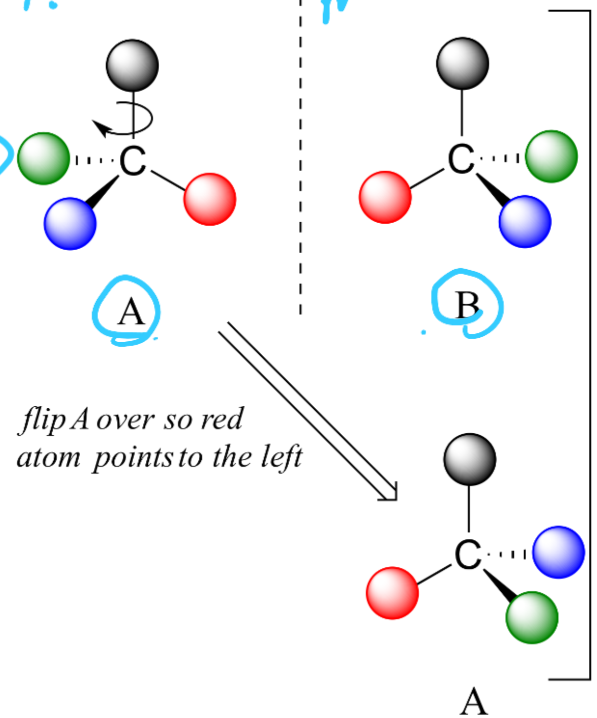
**Carbon, oxygen, and nitrogen often form bonds with a tetrahedral geometry**

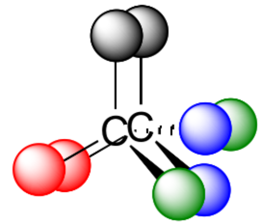
# Unique Feature of Tetrahedral Carbon - Chirality

- 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



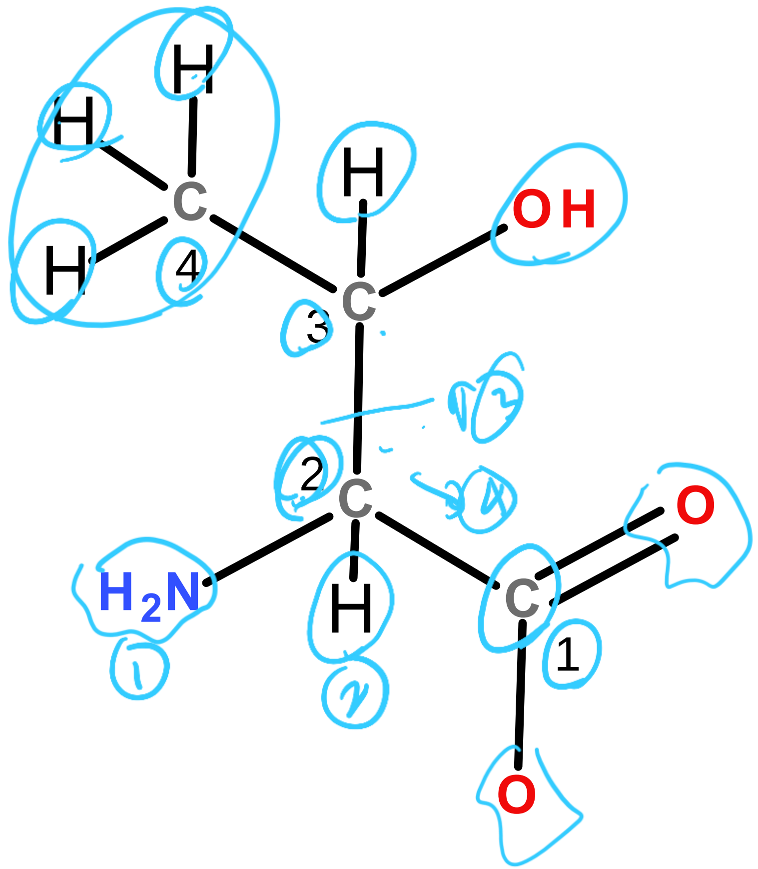



*A and B cannot be superimposed: they are **not** the same molecule!*

# 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?

# Drugs with Chiral Centers

## Nobel Prize for Chiral Synthesis 2001

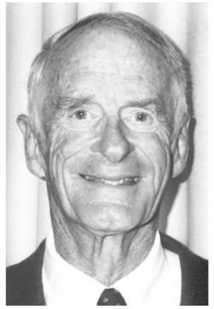


Photo from the Nobel Foundation archive.
William S. Knowles


Photo from the Nobel Foundation archive.
Ryoji Noyori

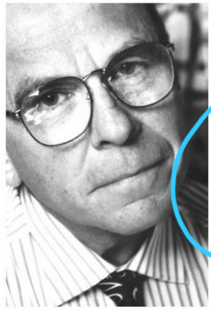
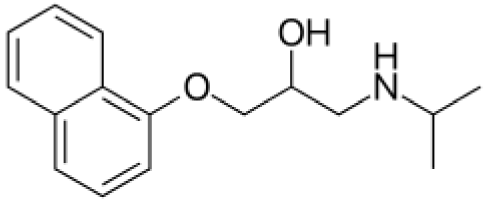


Photo from the Nobel Foundation archive.
K. Barry Sharpless

and a fun game:

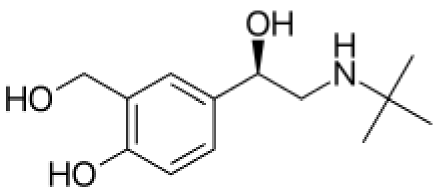
https://educationalgames.nobelprize.org/educational/chemistry/chiral/game/game.html

***Propranolol***



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

**levalbuterol**

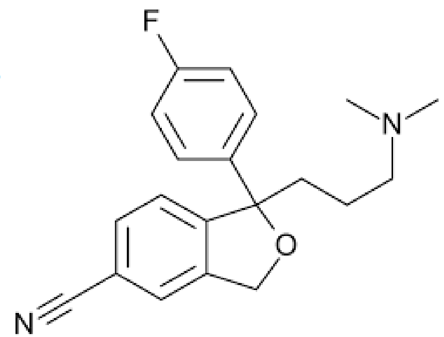


2. R-enantiomer used to treat asthma

**levamisole**

3. L-form used to treat parasitic worm infections

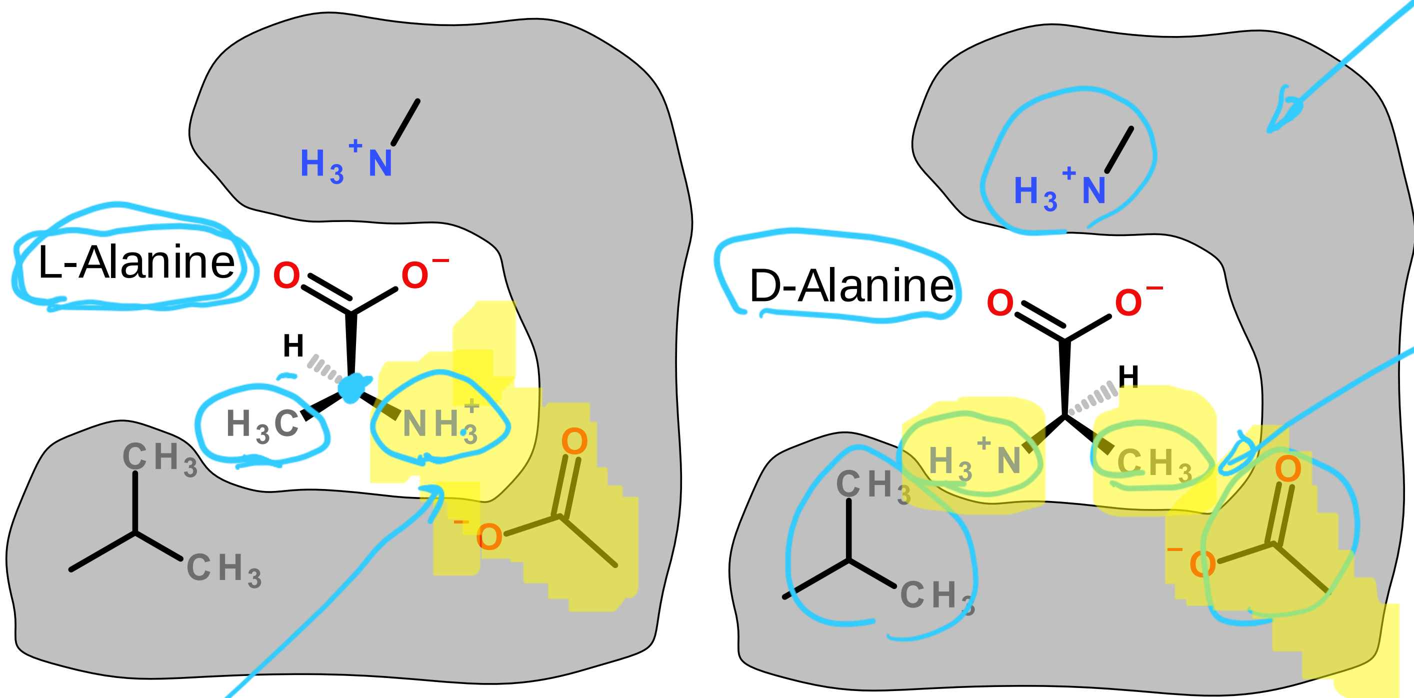
**citalopram**



4. Antidepressent (escitalopram is L)

# Why Chirality Matters

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




*L-Alanine binds better because of more*

*favorable* ___________________ *interactions.*

# 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.*

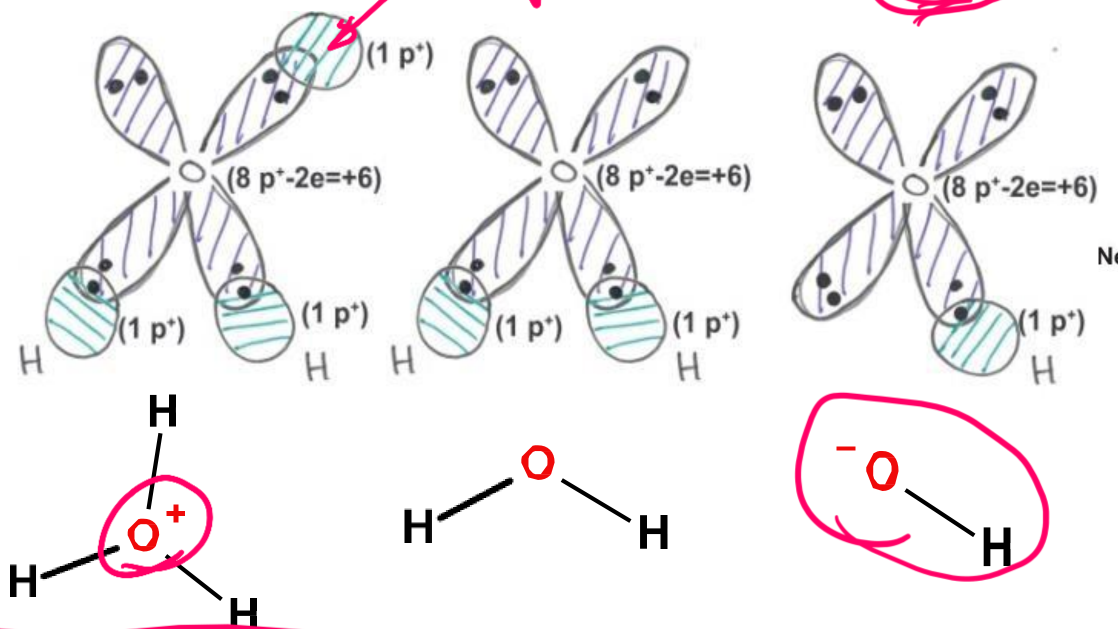
- Acids release protons and will lower the pH of the solution, e.g.

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

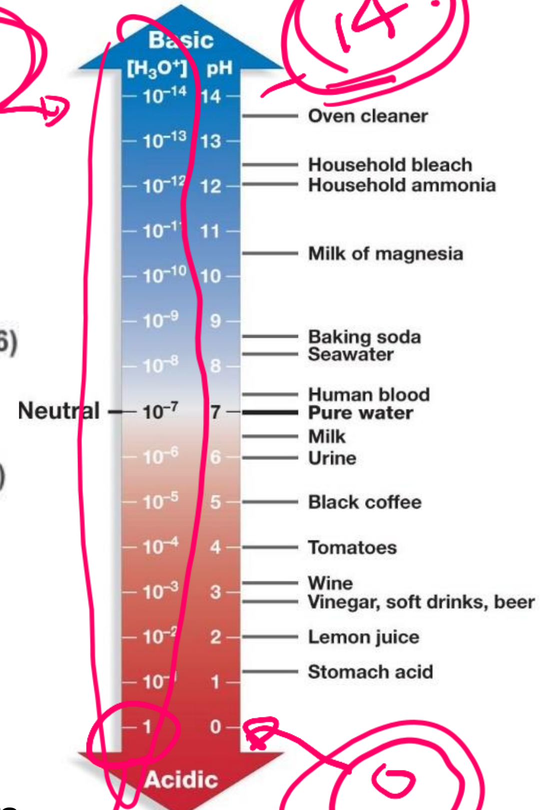
- Bases (e.g. ammonia, sodium hydroxide) will absorb protons and lower the hydrogen ion concentration. These increase the pH.

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

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




Hydronium ion  Water  Hydroxide ion

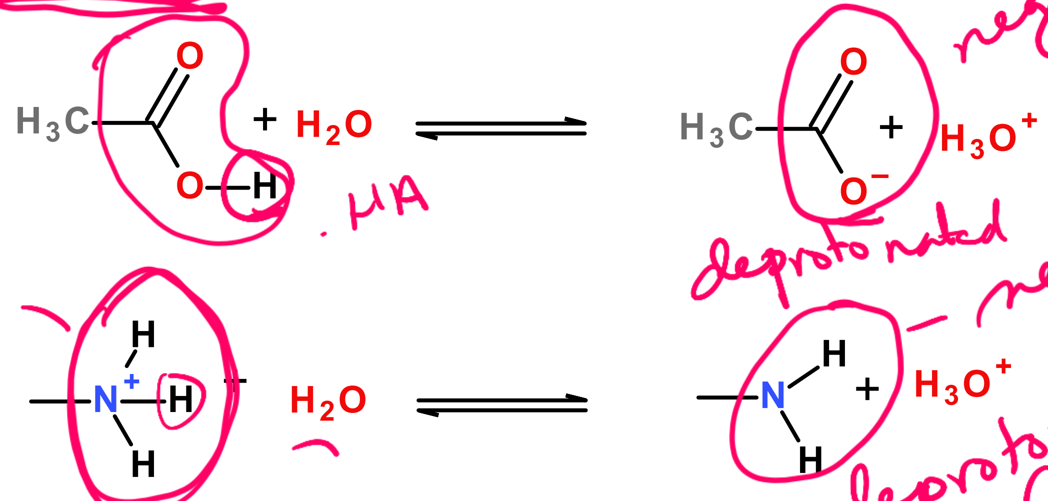



*1. Which solution has a higher H⁺ concentration, pH=3 or pH 4.*
*2. How large is the difference?*

# Acids and Bases.

Strong acid – complete ionization in solution. e.g.
$HCl \longrightarrow H^+ + Cl^-$

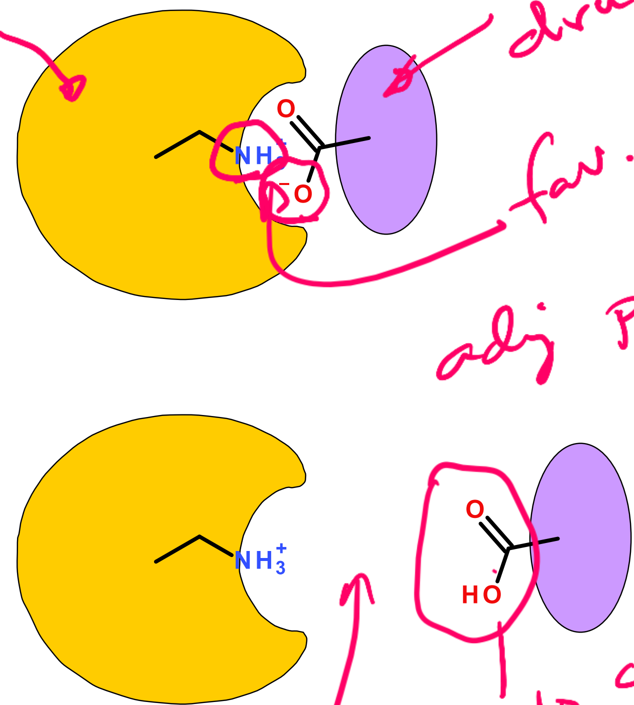
Weak Acid – incomplete ionization in solution.




**“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.

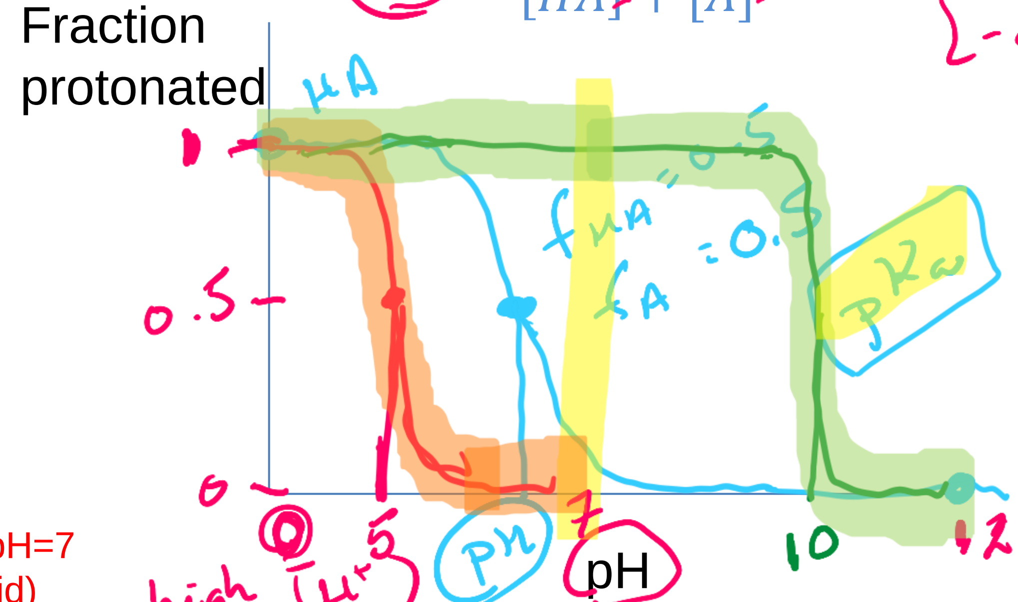
2. The amount of protonated/deprotonated species *also* depends on the chemical properties of the acid. Comparing acetic acid to a protonated amine. At neutral pH (7) most of the acetic acid will be deprotonated while most of the amine will be protonated.


Favored at pH=7
(stronger acid)

Favored at pH=7
(weaker acid)


*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**?*

$$f_{HA} = \frac{[HA]}{[HA] + [A]}$$




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

# Key Points & Expectations

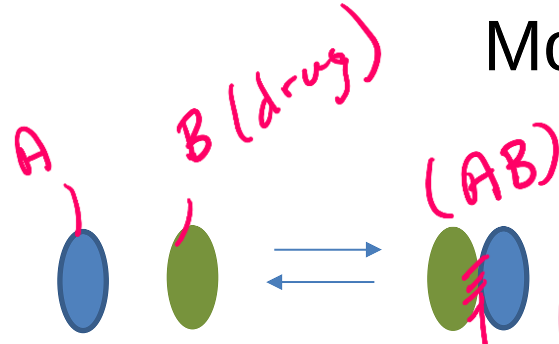
**Chemistry**

- 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.

# Molecular Interactions




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

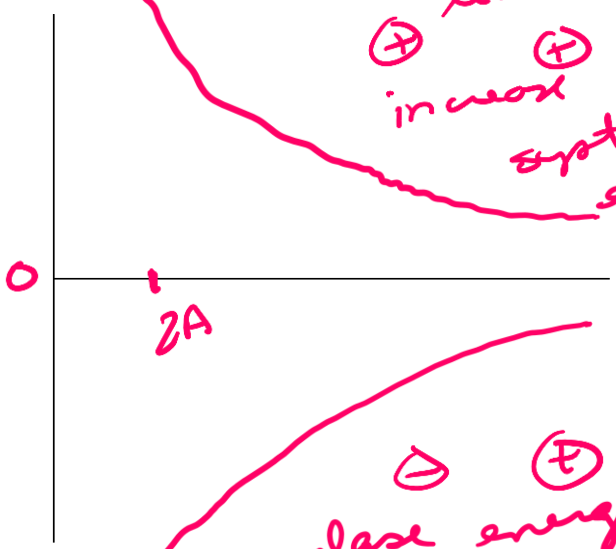
$$\Delta E = E_{AB} - (E_A + E_B) \sim E_{A\cup B}$$

| 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:

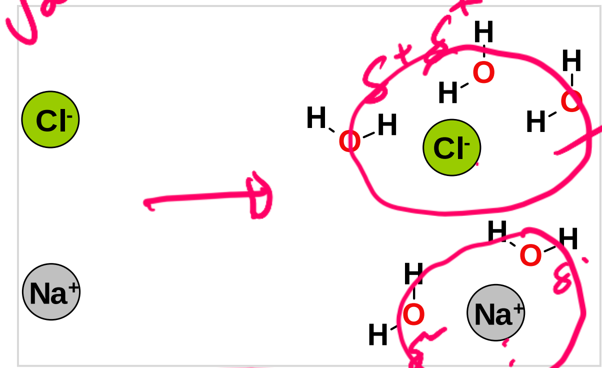
$$E = \frac{1}{D}\frac{1}{4\pi\varepsilon_o}\frac{q_1 q_2}{r}$$

Electrostatic energy of *point* charges.



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.

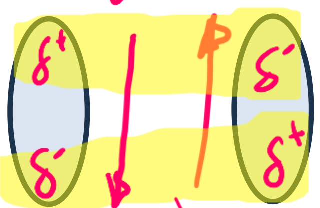
How strong are electrostatic interactions?
$Na^+Cl^-$ = ~ -700 kJ/mol *in vacuum (D=1) when r = 2A*

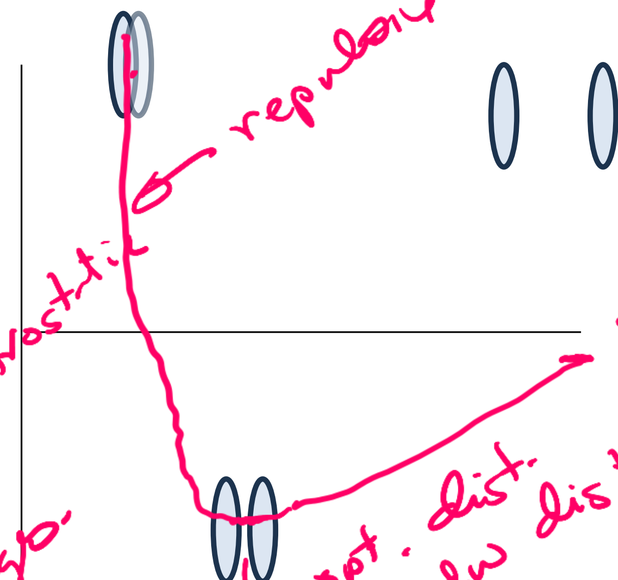



*Water has a high dielectric constant of 80 due to its polar nature. How does this affect the energy of interaction?*

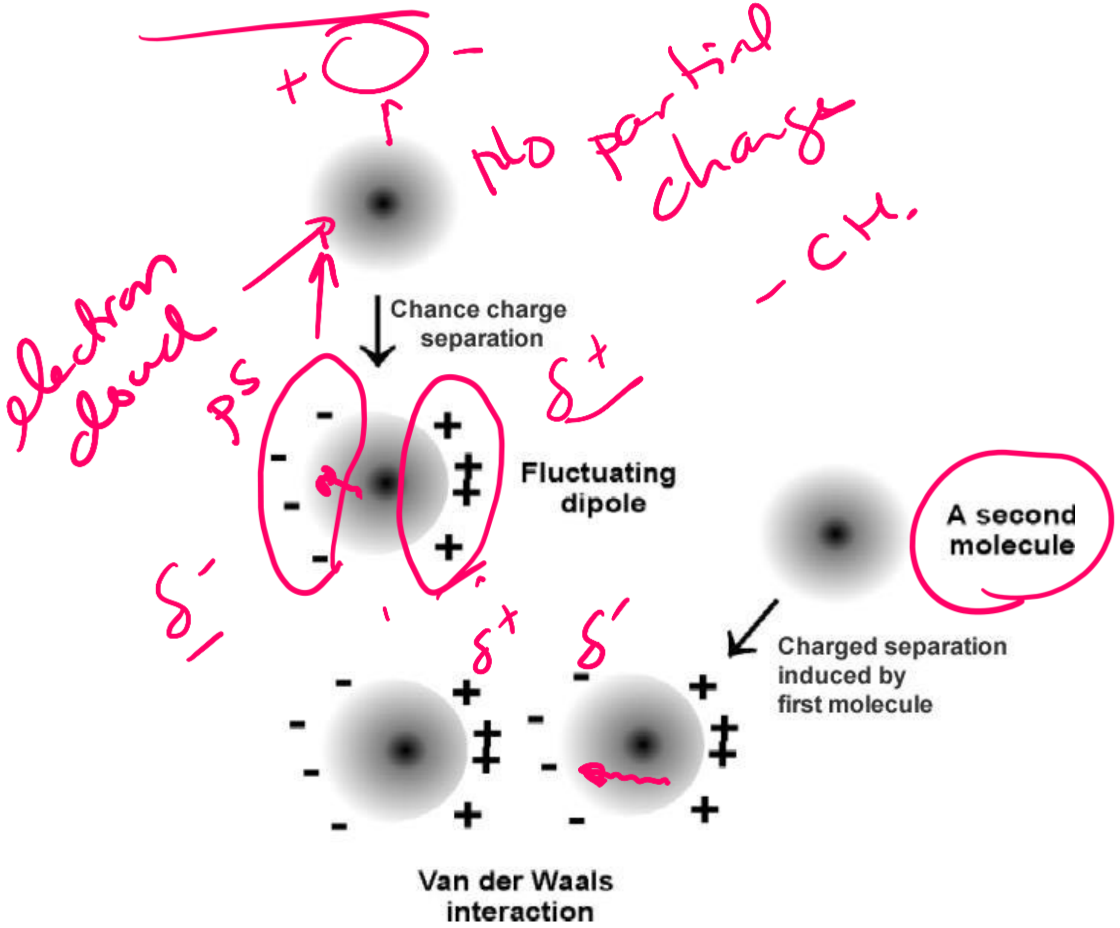
**Van Der Waals Forces:**

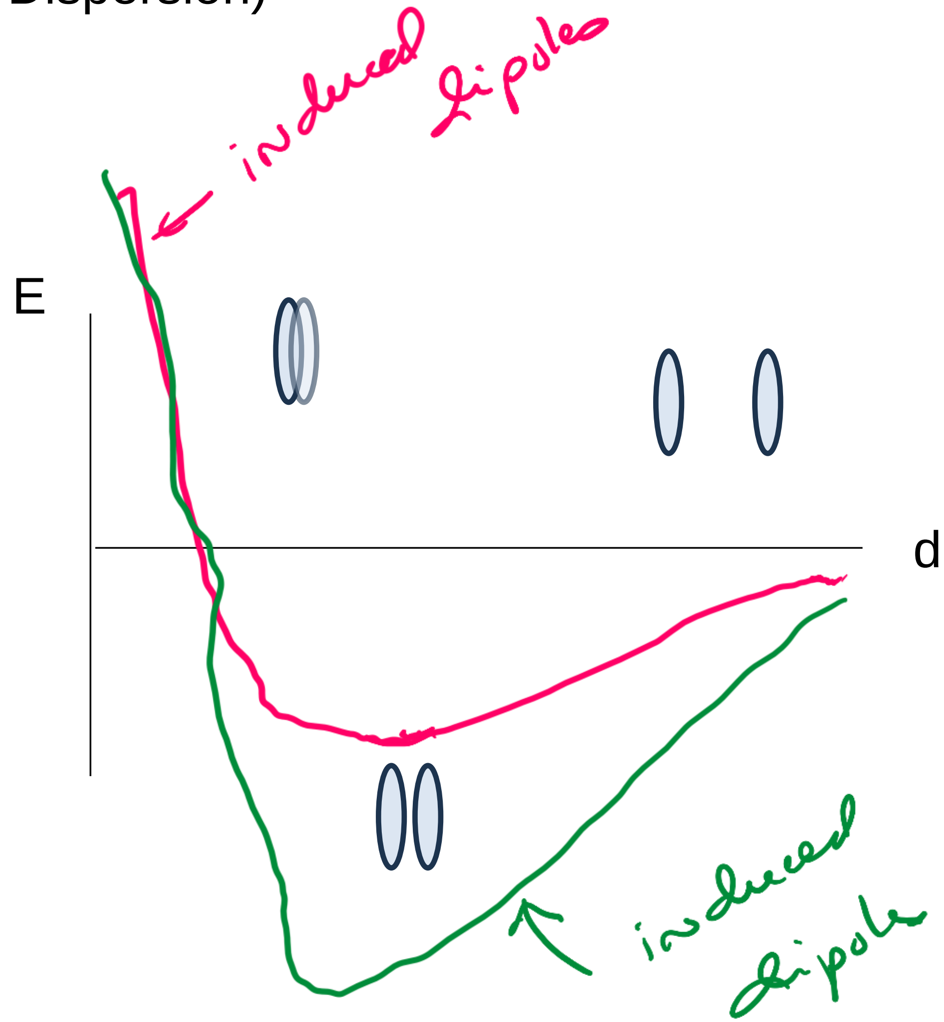
**ii) Dipole-dipole** – an electrostatic interaction that involves permanent ***partial*** charges (these are sometimes called Keesom forces).





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

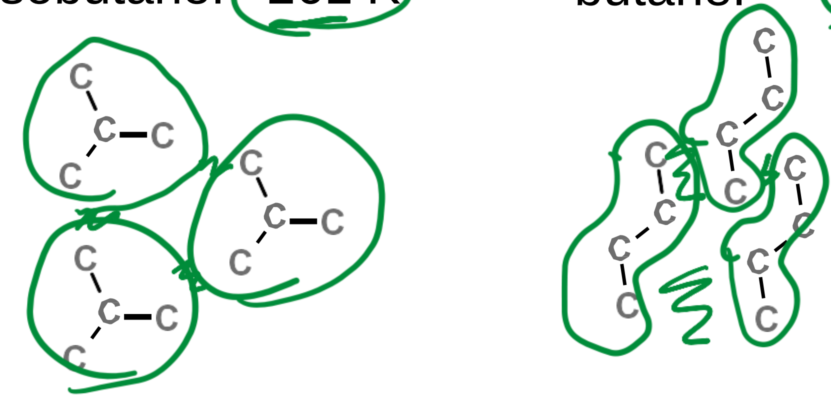


## iii) **Induced dipole** (often referred to as London Dispersion)

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

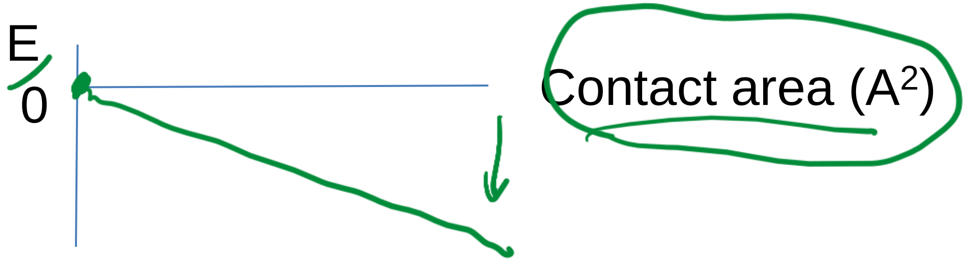
isobutane: 261 K     butane: 272 K




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

vdw

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

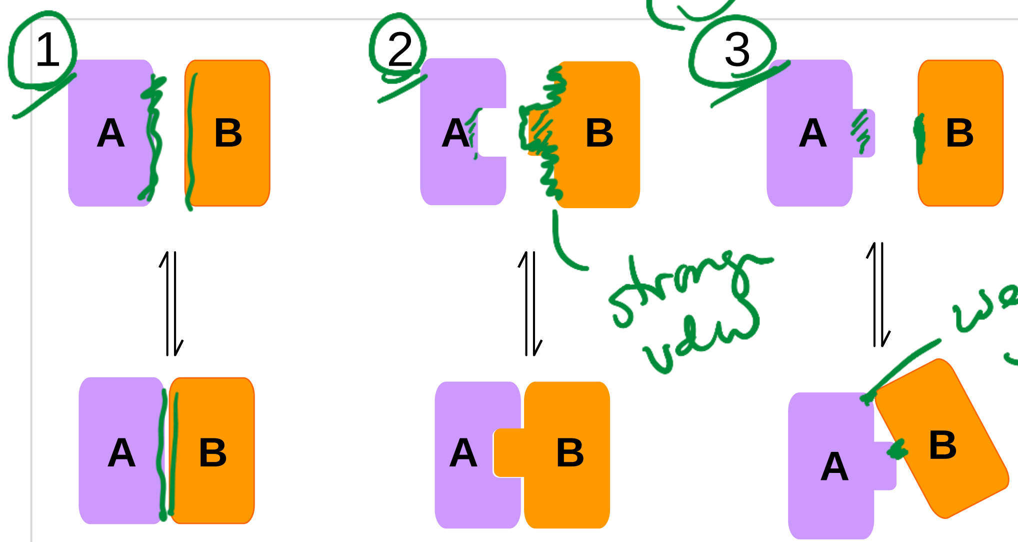



*3. Which of these will have the most favorable vdw interaction:*

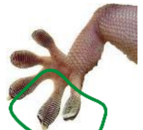
*1     2     3*

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

*1     2     3*




complex



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