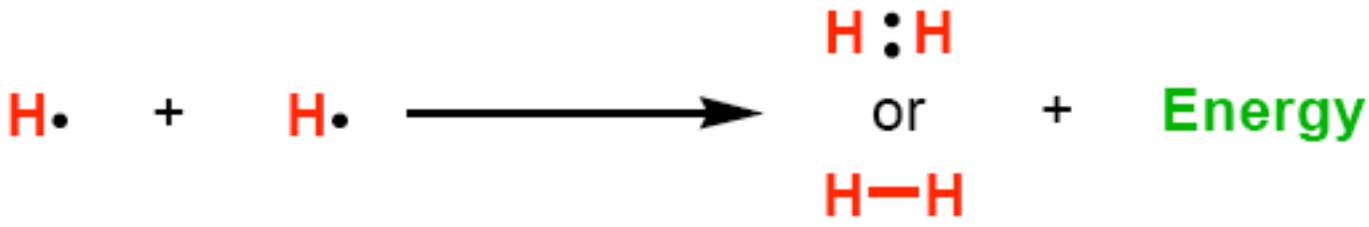
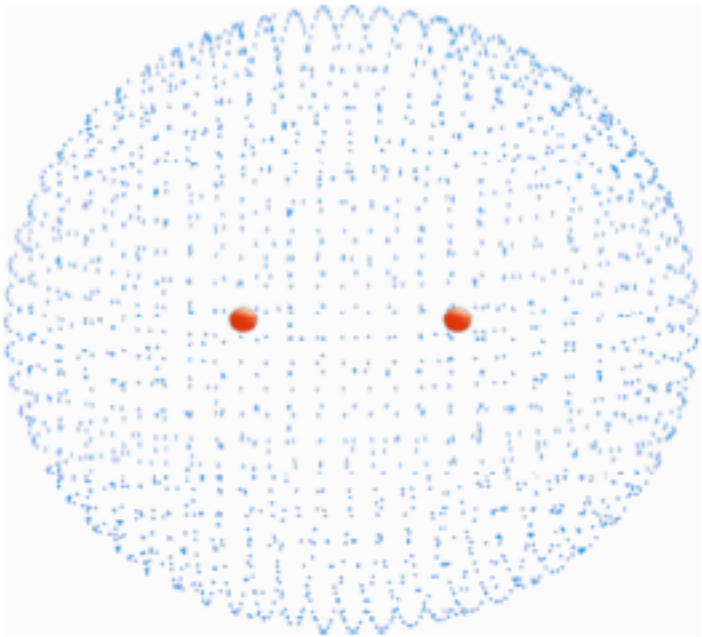
Topic 1 Organic Structures and Interactions of Drugs

Understanding Structural Diagrams of Organic Molecules

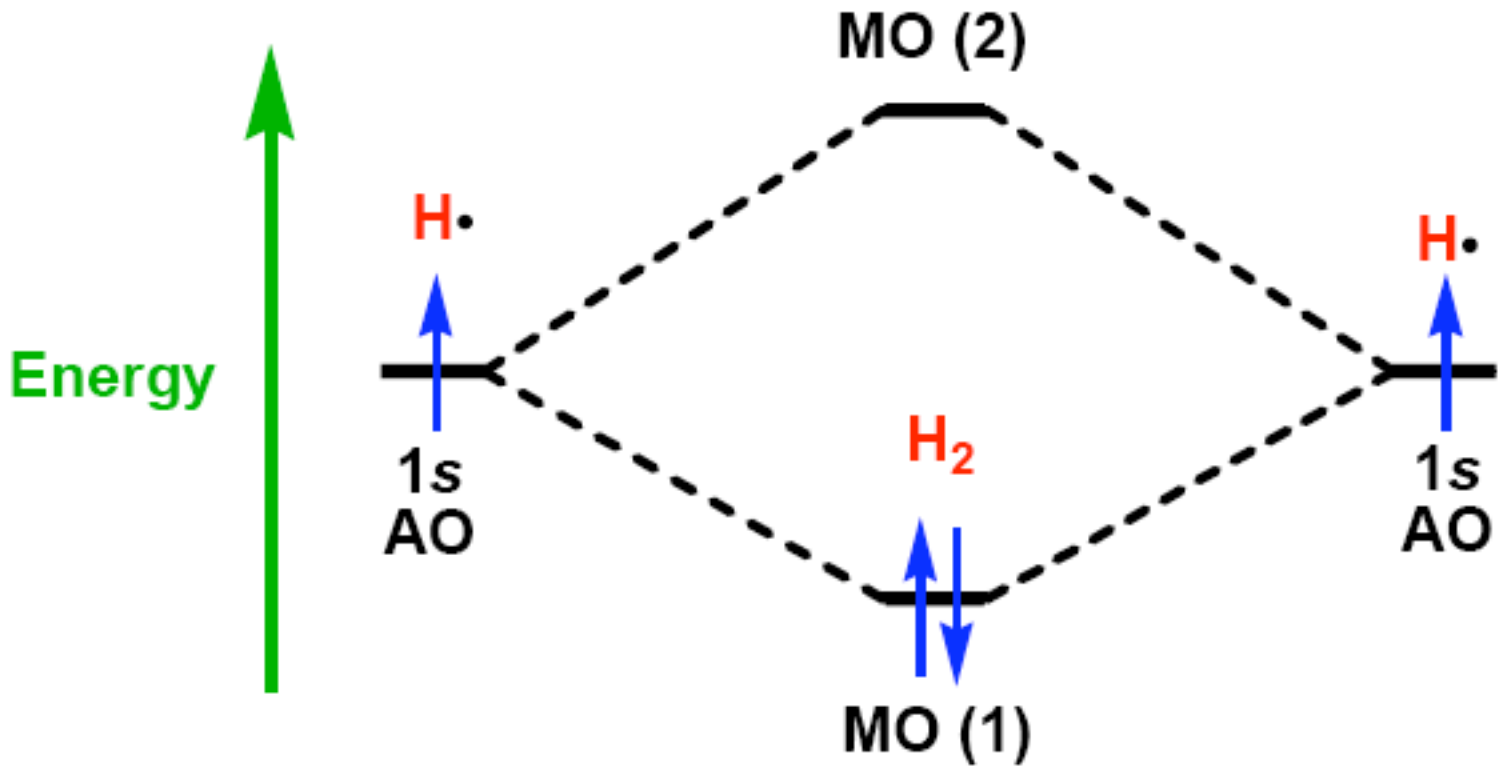
The simplest molecule, H_2





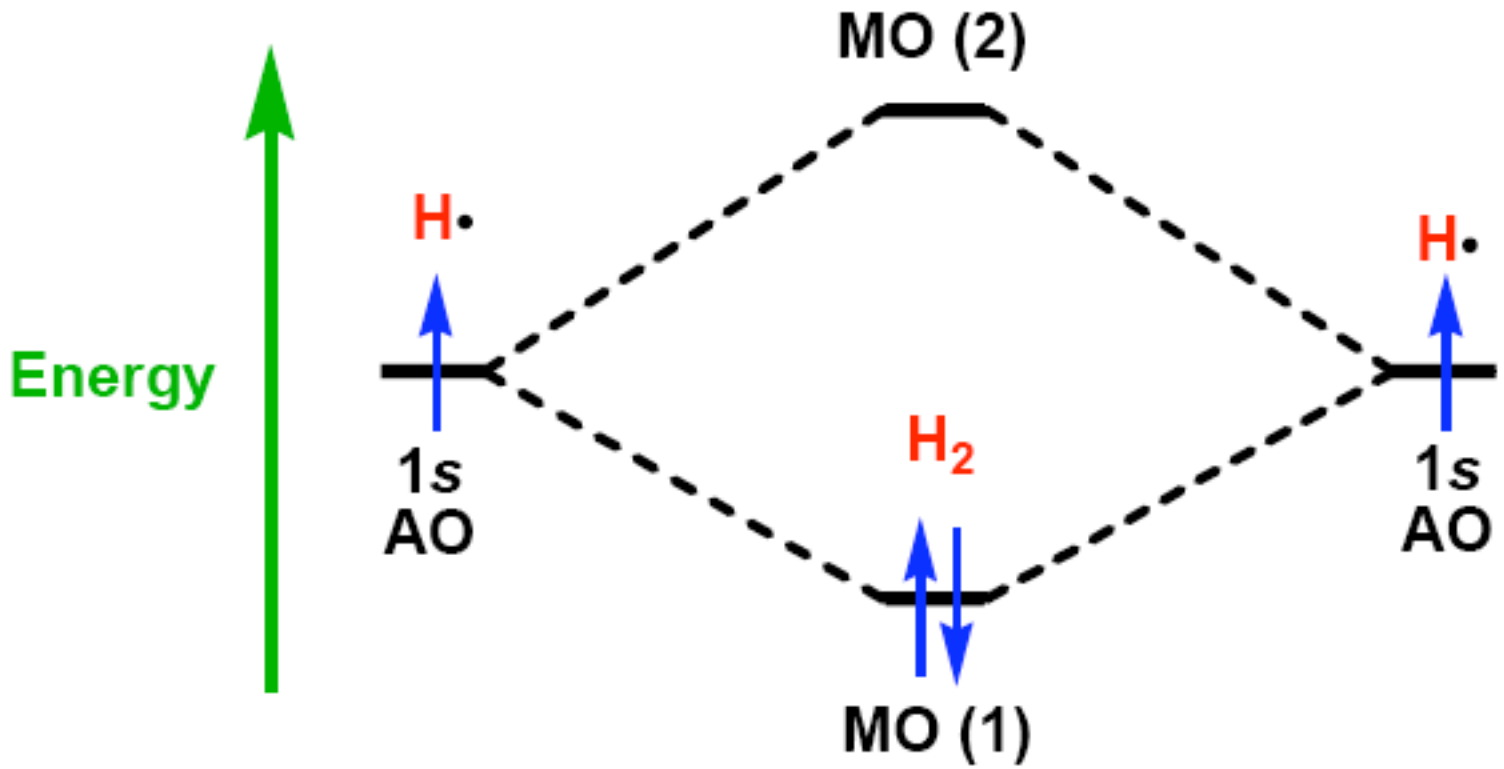
Understanding Structural Diagrams of Organic Molecules

The nature of the chemical bond



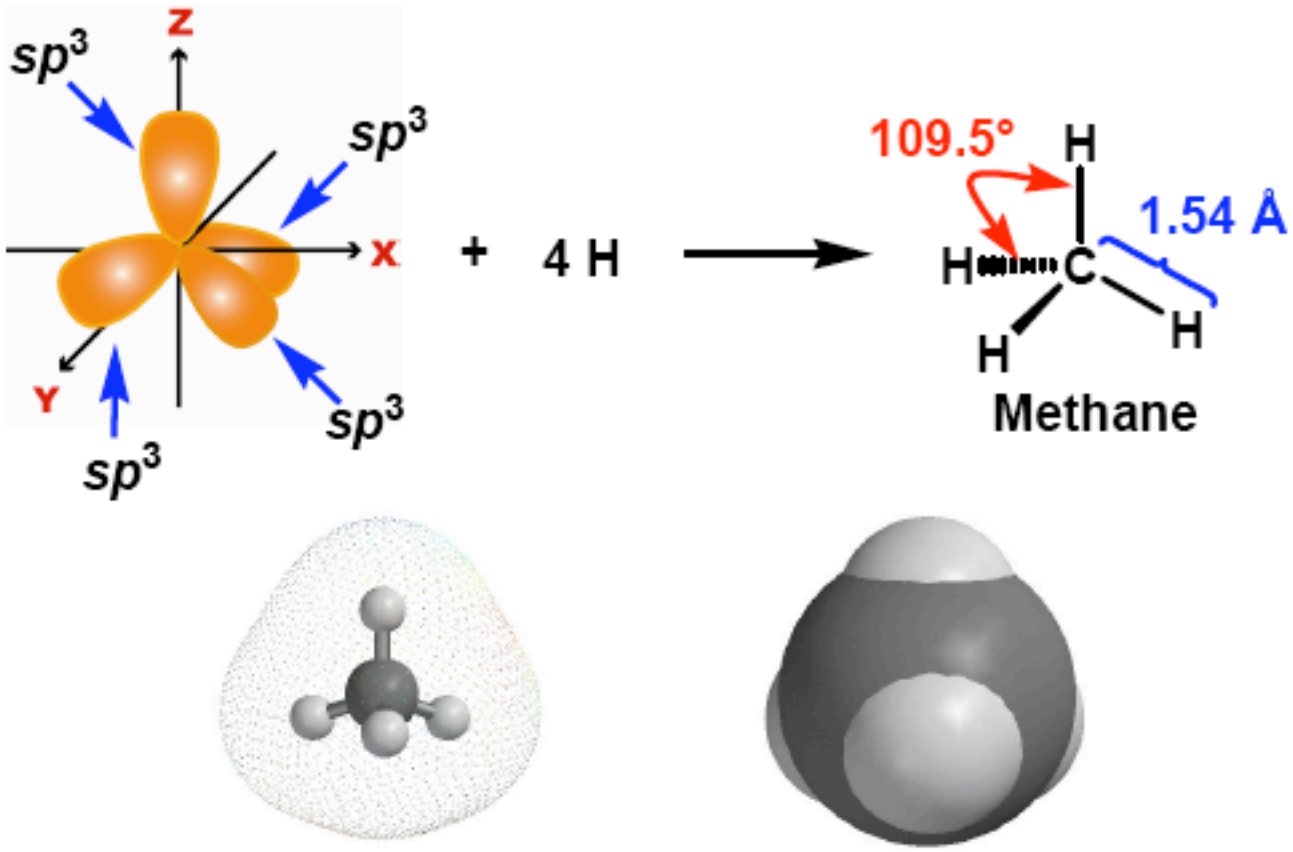
Understanding Structural Diagrams of Organic Molecules

The nature of the chemical bond

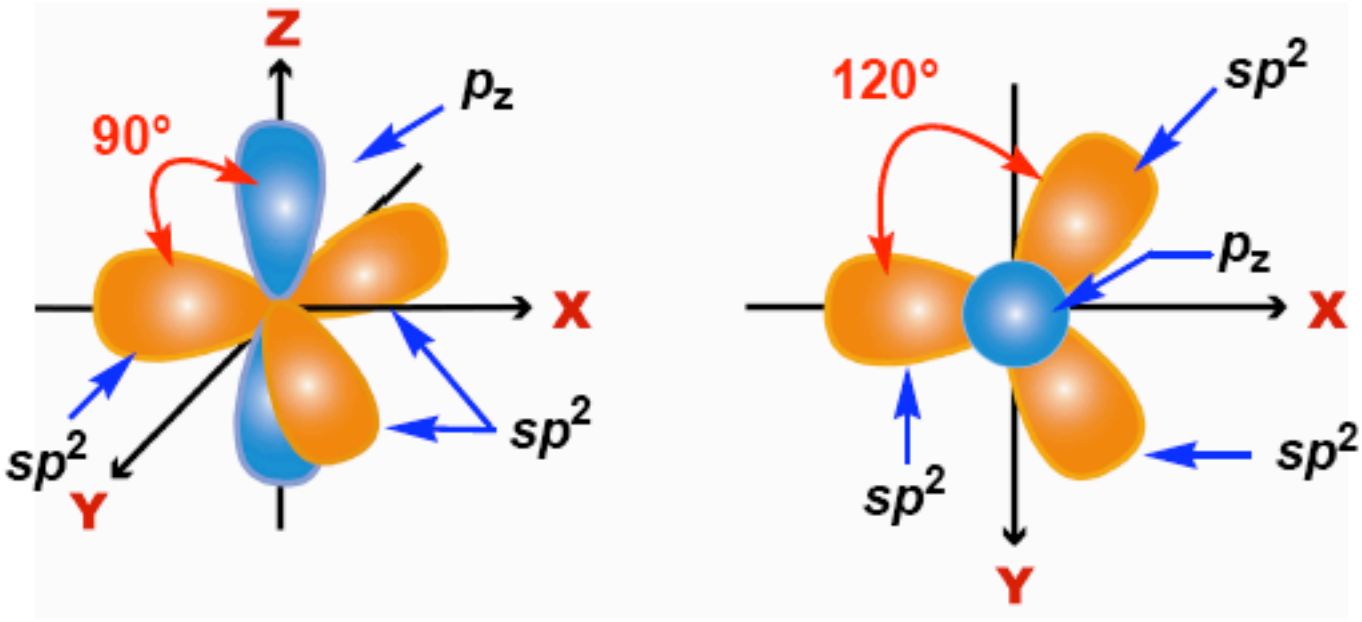


Understanding Structural Diagrams of Organic Molecules

Hybrid Orbitals for Tetracoordinate Carbon



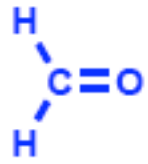
Understanding Structural Diagrams of Organic Molecules
Tricoordinate Carbon Compounds. The double bond I.



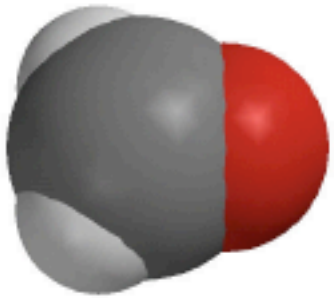
Side-on view **Top-on view**

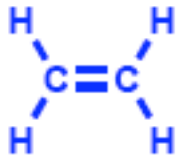
Understanding Structural Diagrams of Organic Molecules

Tricoordinate Carbon Compounds. The double bond II.

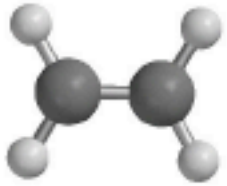


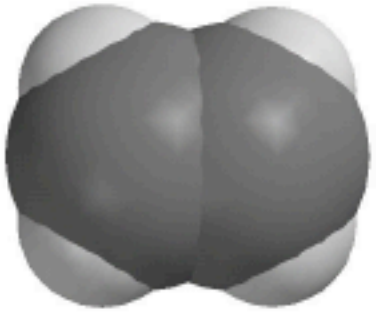
Formaldehyde





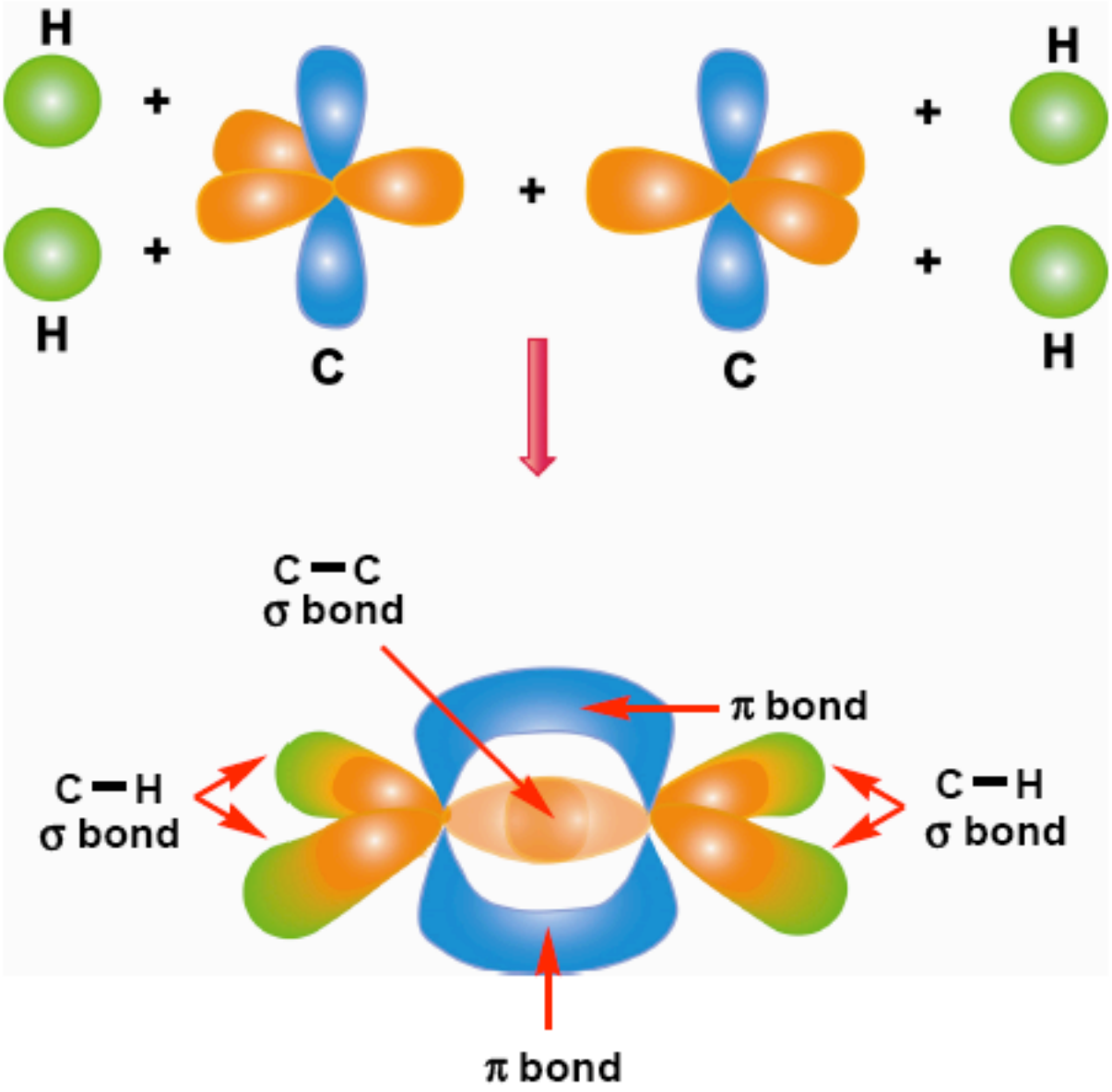
Ethylene



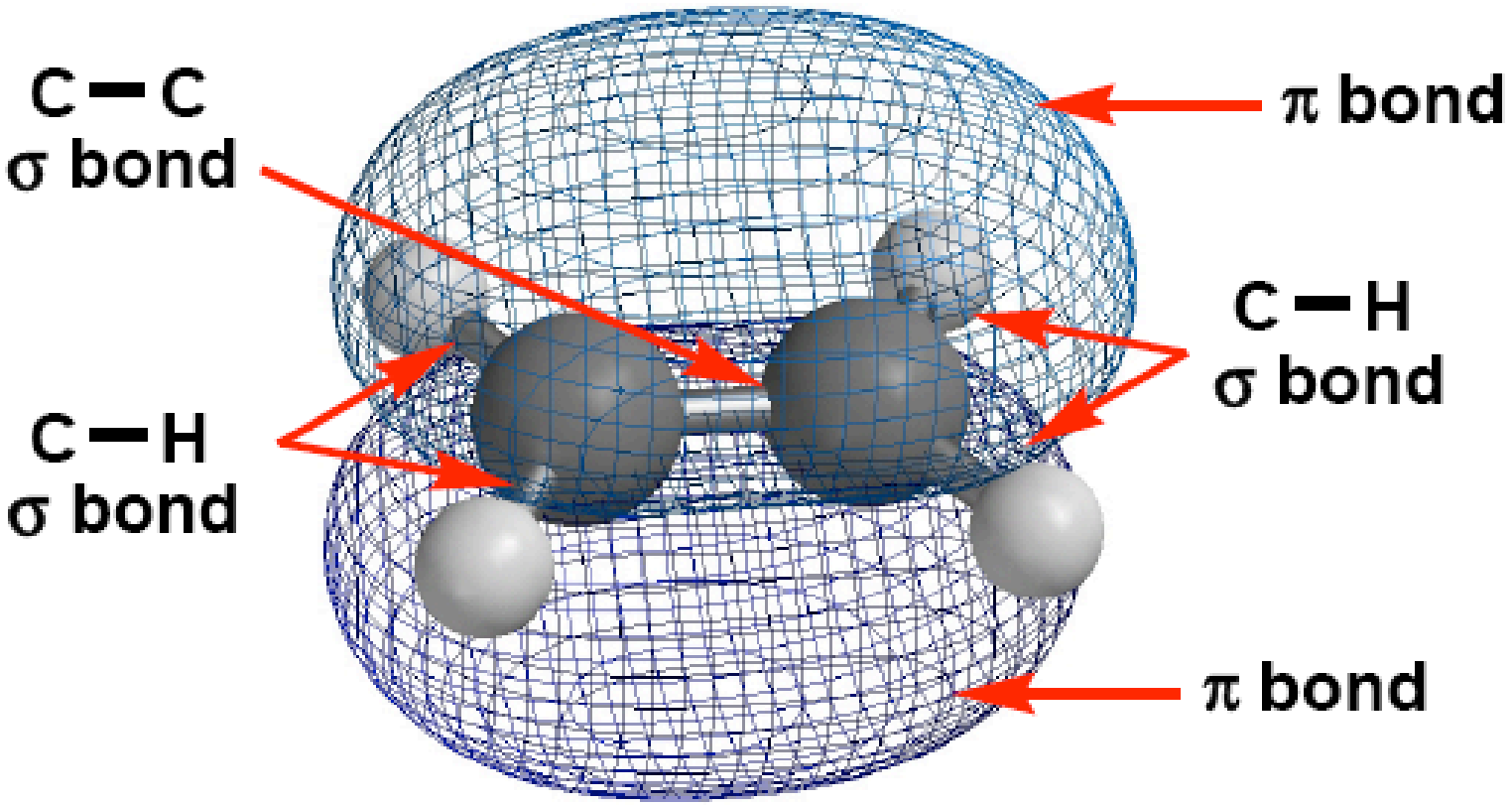


Understanding Structural Diagrams of Organic Molecules

Tricoordinate Carbon Compounds. The double bond III.

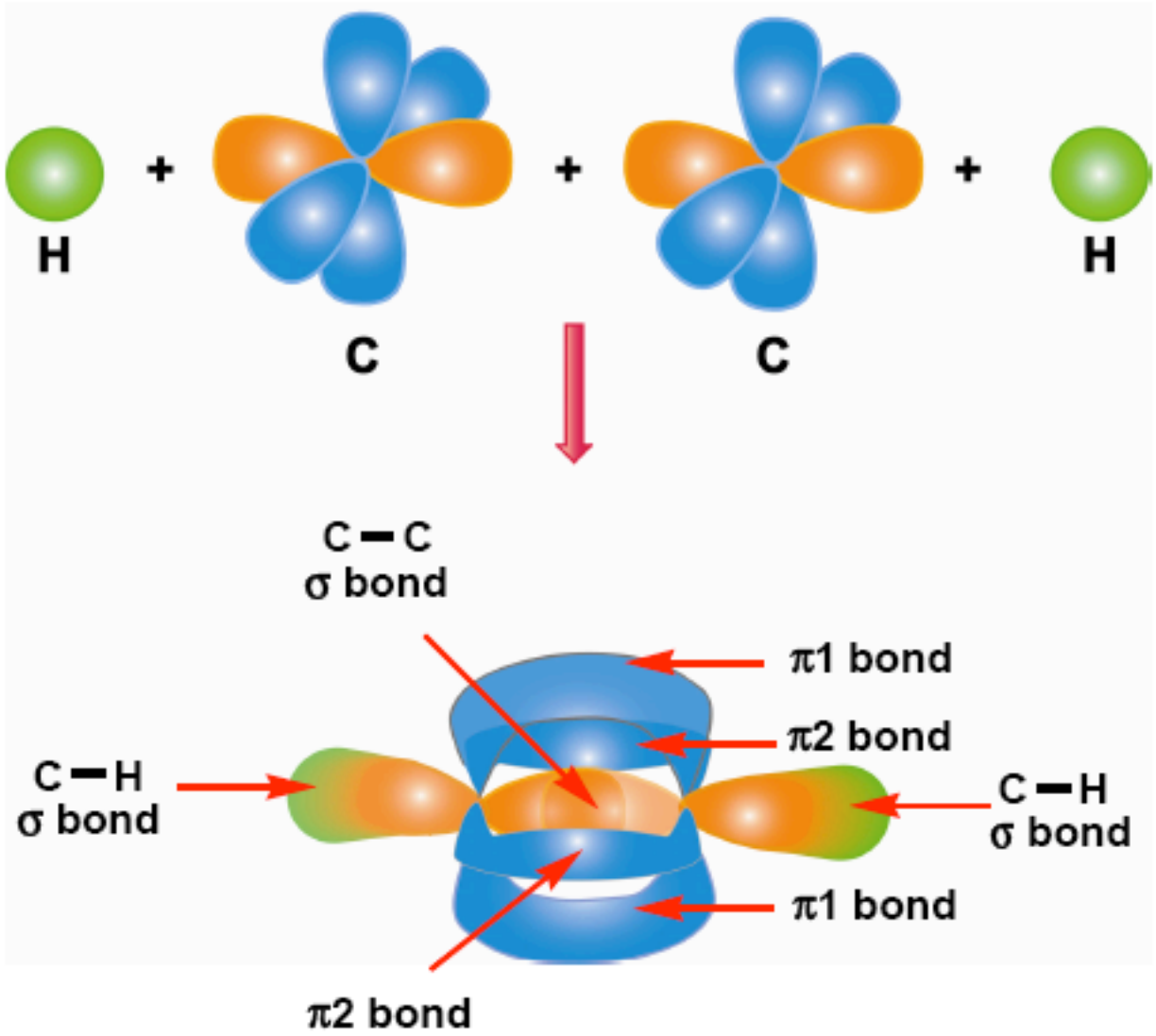


Understanding Structural Diagrams of Organic Molecules
Tricoordinate Carbon Compounds. The double bond IV.



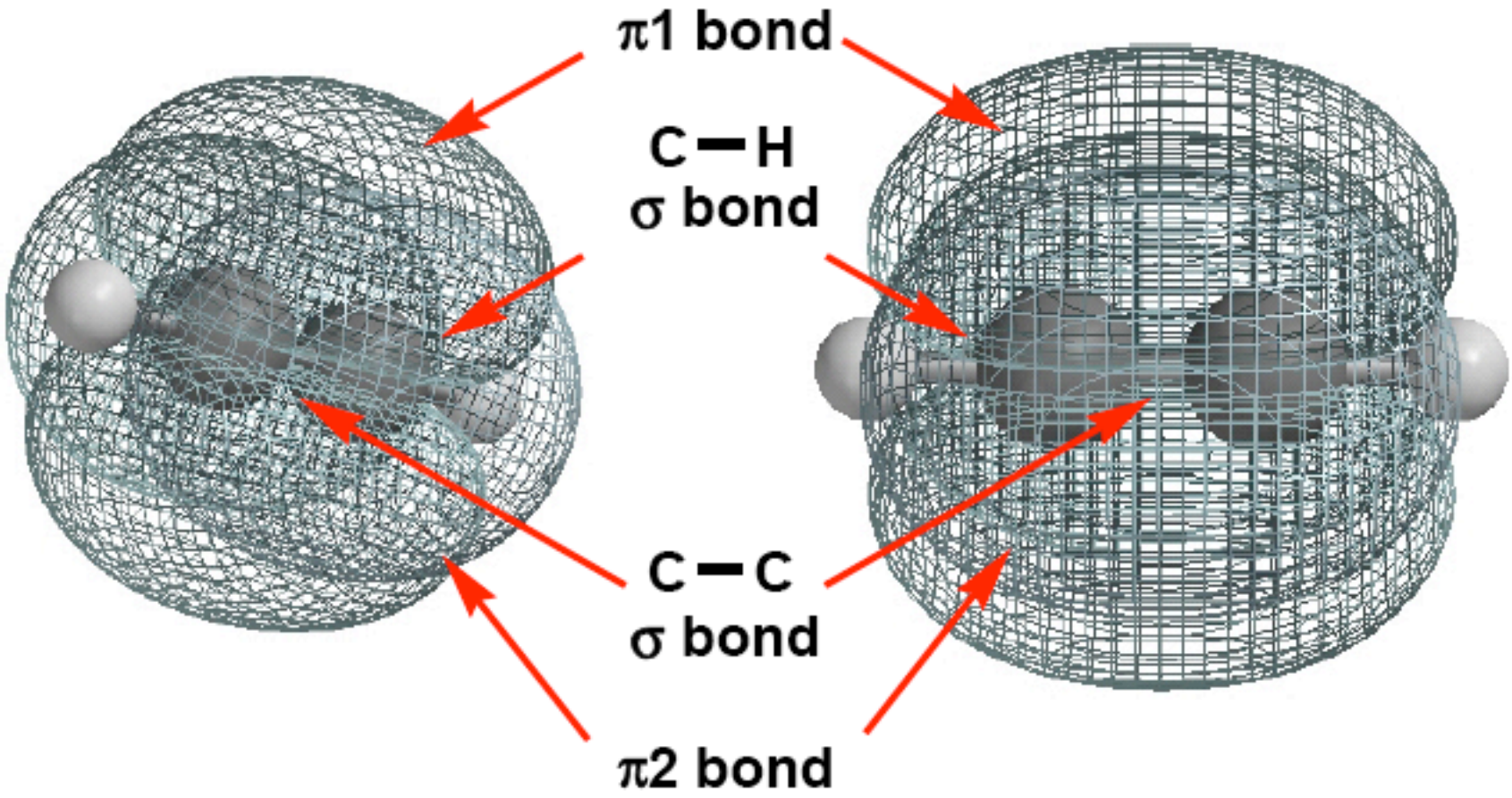
Understanding Structural Diagrams of Organic Molecules

Dicoordinate Carbon Compounds. The triple bond III.



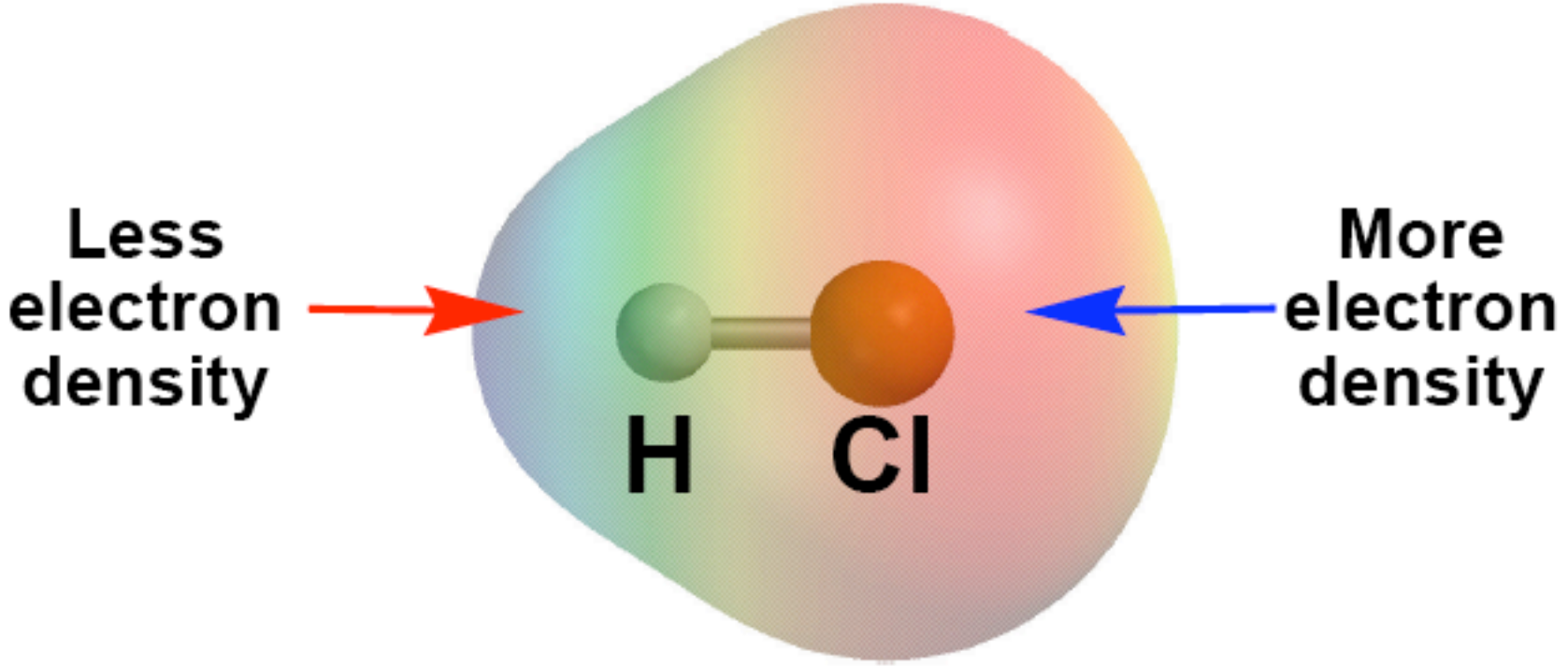
Understanding Structural Diagrams of Organic Molecules

Dicoordinate Carbon Compounds. The triple bond IV.



Understanding Structural Diagrams of Organic Molecules

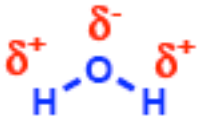
Bonds of Intermediate Polarity I.



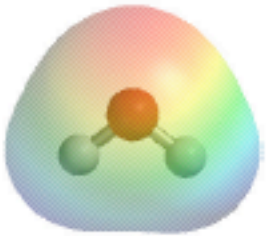
$$HCl + H_2O \longrightarrow HOH_2^+(H_2O)_n + Cl^-(H_2O)_n$$

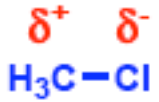
Understanding Structural Diagrams of Organic Molecules

Bonds of Intermediate Polarity II.

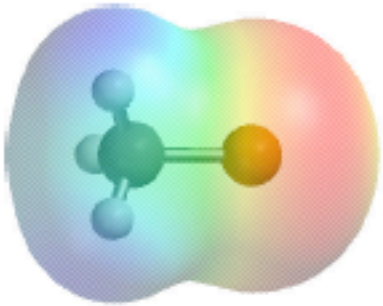


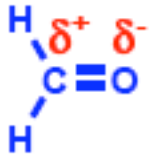
Water



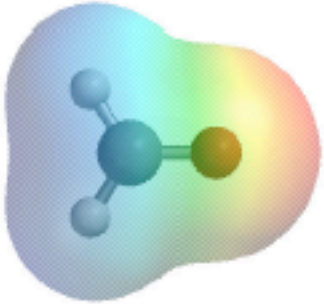


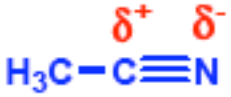
Methyl Chloride



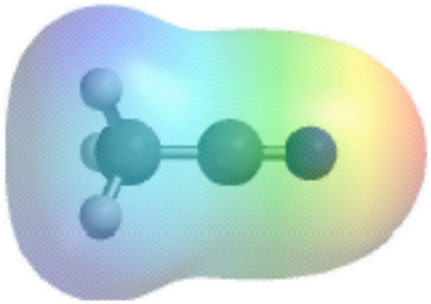


Form-aldehyde



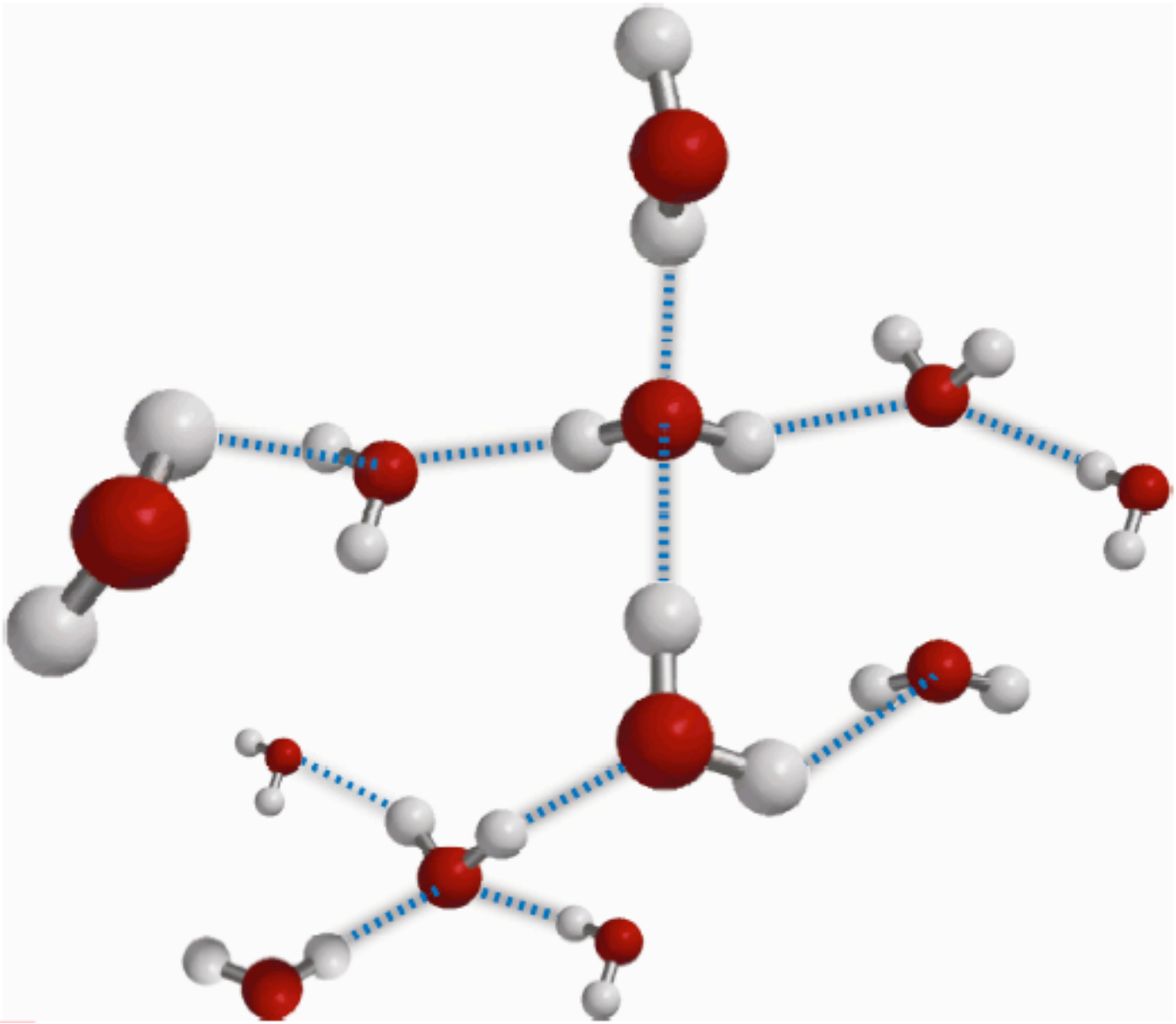


Acetonitrile



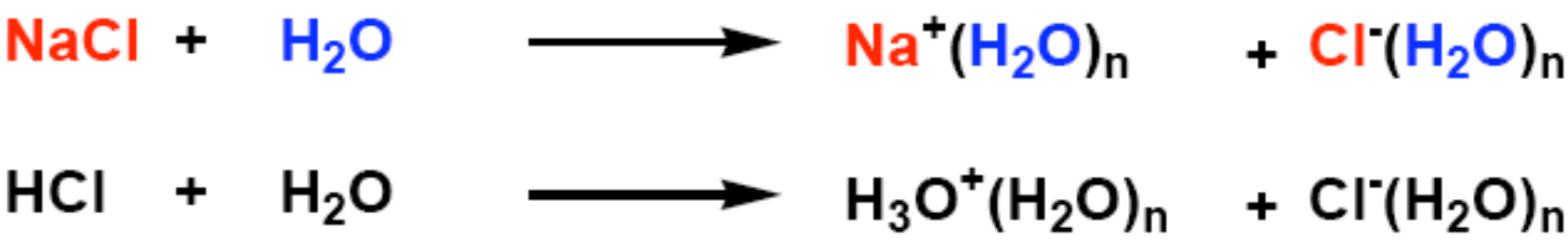
Understanding Structural Diagrams of Organic Molecules

Molecular Polarity and Hydrogen Bonding



Understanding Structural Diagrams of Organic Molecules

Aqueous Solvation of Ions

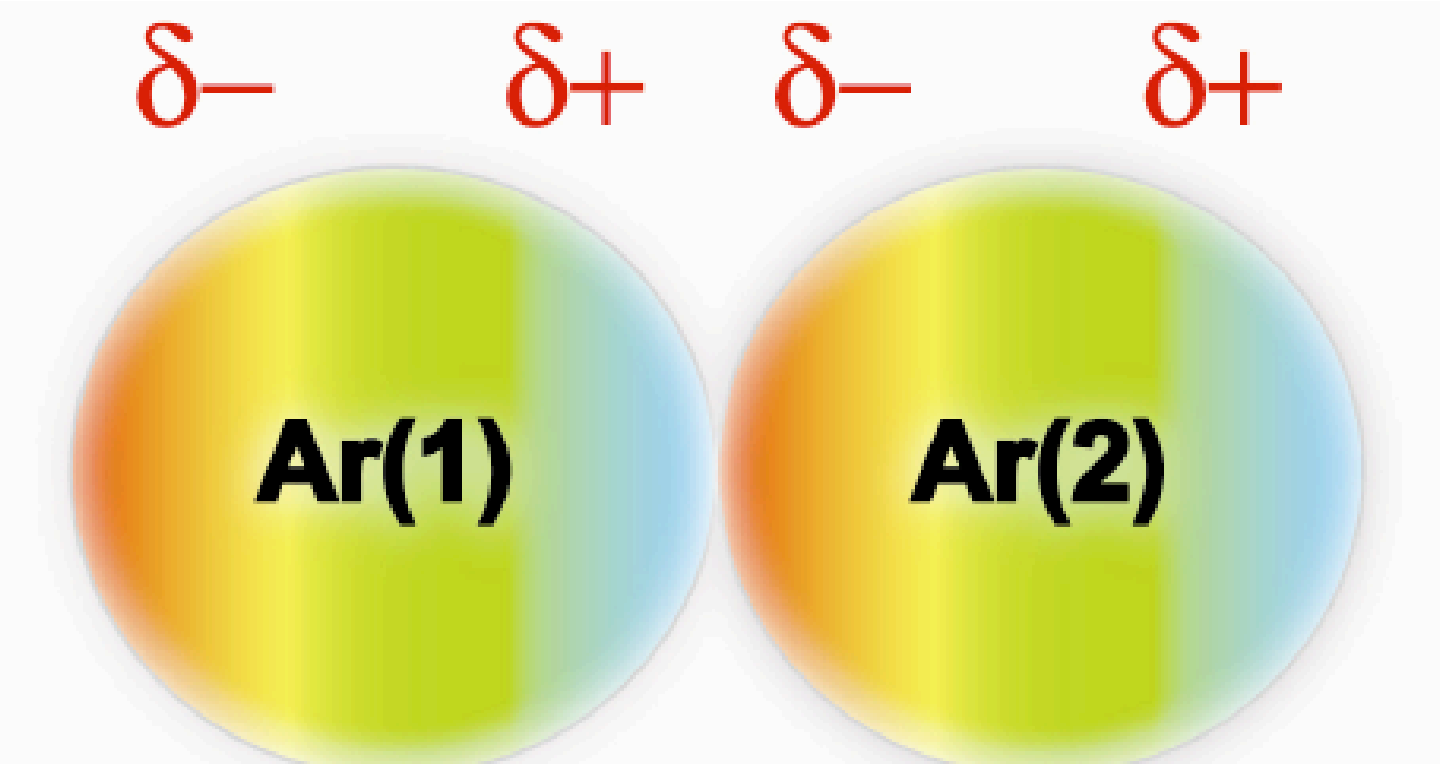


Enthalpy of Hydration (H_{hyd} **kJ/mol**) of Some Typical Ions

Ion	H_{hyd}	**Ion**	H_{hyd}	**Ion**	H_{hyd}
H^+	-1130	Al^{3+}	-4665	Fe^{3+}	-4430
--					
Li^+	-520	Be^{2+}	-2494	F^-	-505
Na^+	-406	Mg^{2+}	-1921	Cl^-	-363
K^+	-322	Ca^{2+}	-1577	Br^-	-336
Rb^+	-297	Sr^{2+}	-1443	I^-	-295
Cs^+	-276	Ba^{2+}	-1305	ClO_4^-	-238
--					
Cr^{2+}	-1904	Mn^{2+}	-1841	Fe^{2+}	-1946
Co^{2+}	-1996	Ni^{2+}	-2105	Cu^{2+}	-2100
Zn^{2+}	-2046	Cd^{2+}	-1807	Hg^{2+}	-1824

Understanding Structural Diagrams of Organic Molecules

Interactions Between Nonpolar Molecules I.



Understanding Structural Diagrams of Organic Molecules

Interactions Between Nonpolar Molecules II.

Propane (-44.5 °C)

Butane (-0.5 °C)

Pentane (36 °C)

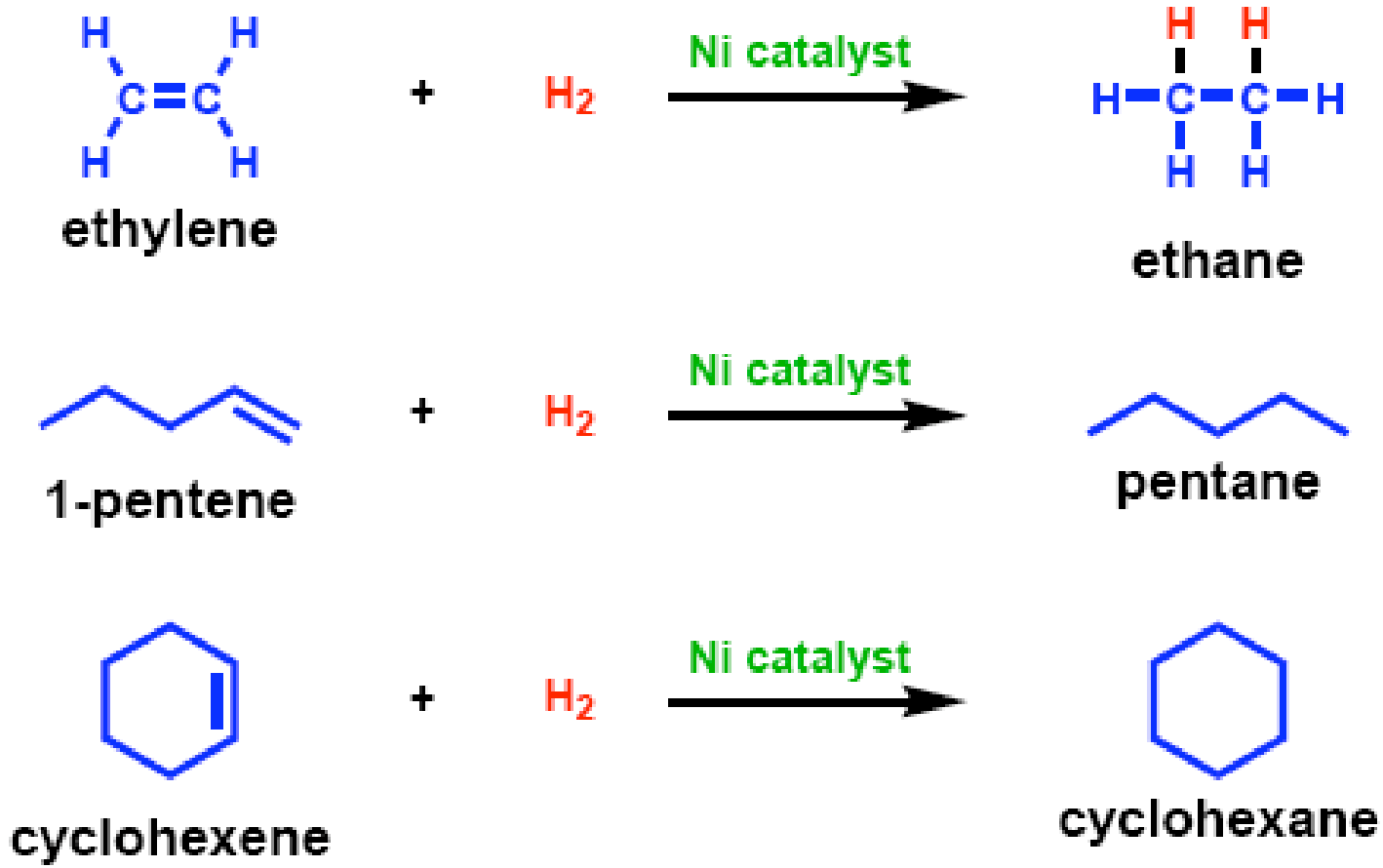
Hexane (69 °C)

Octane (126 °C)

Decane (174 °C)

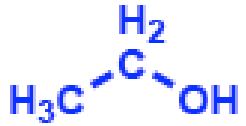
Understanding Structural Diagrams of Organic Molecules

Functional Groups I.

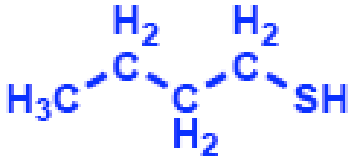
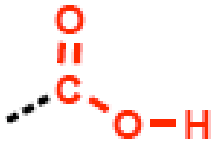
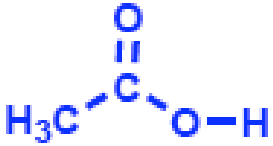
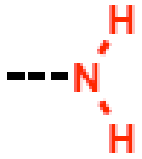
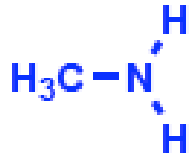


Understanding Structural Diagrams of Organic Molecules

Functional Groups II.

FUNCTIONAL GROUP	EXAMPLE
 double bond	$H_2C{=}CH_2$ ethylene
---C≡C--- triple bond	$HC{\equiv}C{-}CH_3$ methylacetylene
---O–H hydroxyl	 ethanol

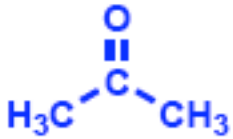
Understanding Structural Diagrams of Organic Molecules
Functional Groups III.

FUNCTIONAL GROUP	EXAMPLE
	
thiol	butanethiol
	
carboxyl	acetic acid
	
amine	methylamine

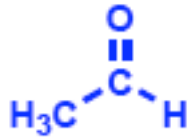
Understanding Structural Diagrams of Organic Molecules
Functional Groups IV.

FUNCTIONAL GROUP **EXAMPLE**

carbonyl



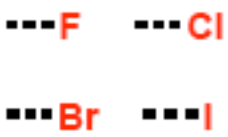
acetone



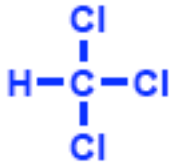
acetaldehyde

nitro

nitromethane



halogen



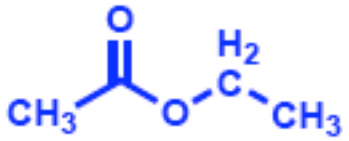
chloroform

Understanding Structural Diagrams of Organic Molecules

Functional Groups V.

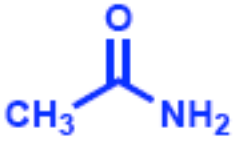
butadiene

vinyl chloride

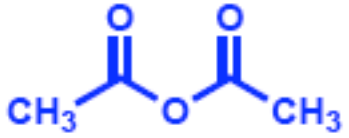


ethyl acetate
(an ester)

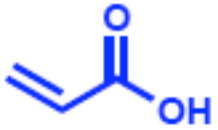
urea



acetamide
(an amide)



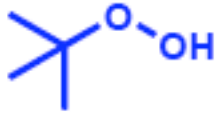
acetic anhydride
(an anhydride)



acrylic acid

acrylonitrile
(a nitrile)

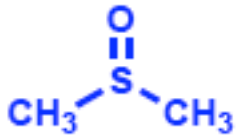
dimethyl
disulfide



tertiary-butyl
hydroperoxide

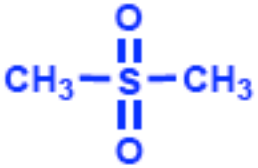
Understanding Structural Diagrams of Organic Molecules

Functional Groups VI.



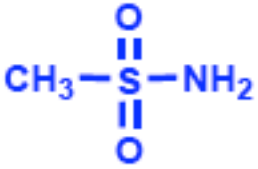
dimethyl sulfoxide
(a sulfoxide)

diethylphosphoric acid
(a phosphoric acid ester)

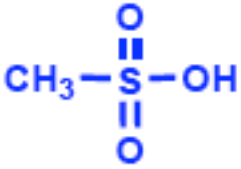


dimethyl sulfone
(a sulfone)

dimethylpyrophosphoric acid
(a pyrophosphate)



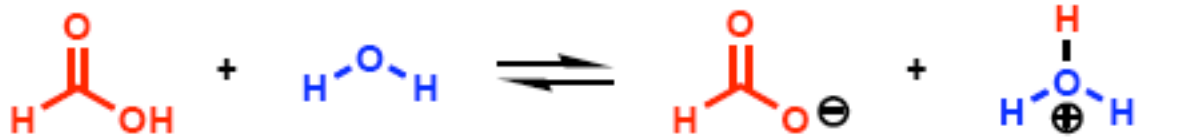
methanesulfonamide
(a sulfonamide)



methanesulfonic acid
(a sulfonic acid)

Understanding Structural Diagrams of Organic Molecules

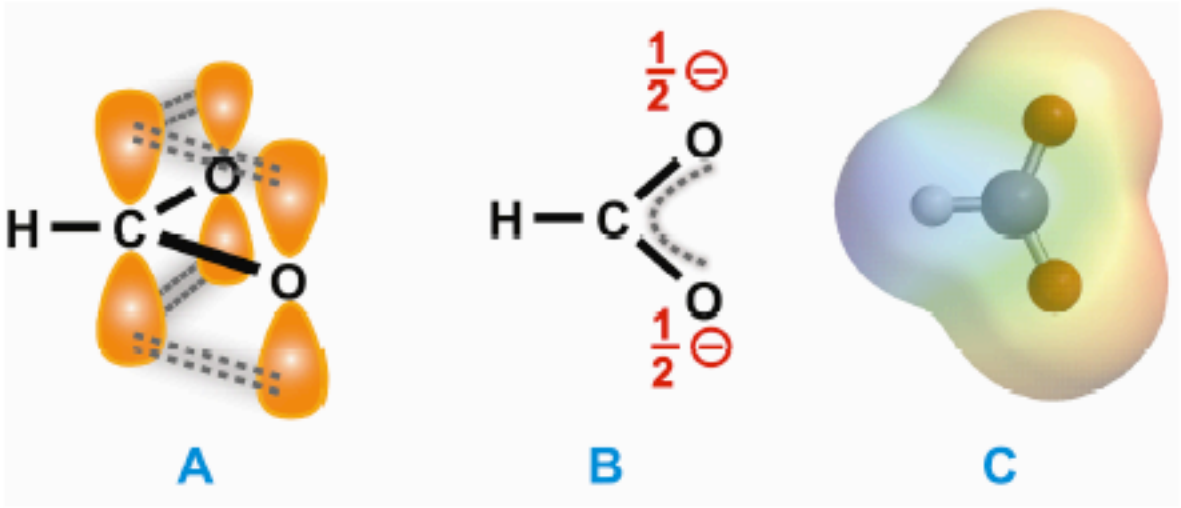
Functional Groups – Carboxylic Acids I.

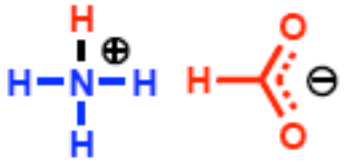


formic acid

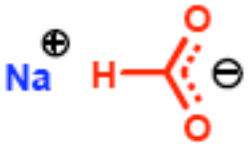
formate ion (hydrated)

(hydrated)





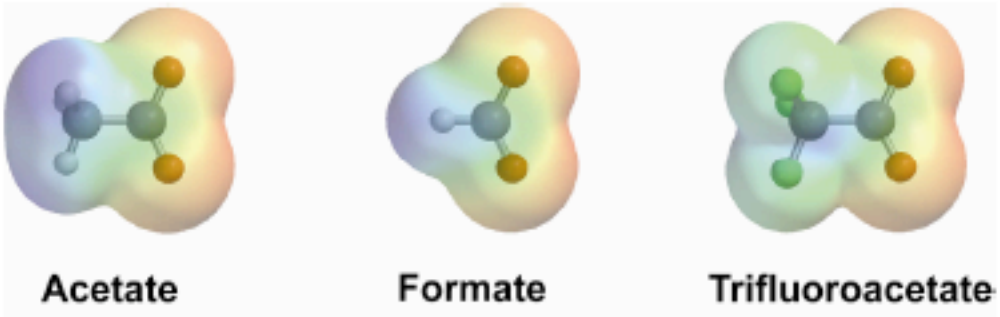
ammonium formate

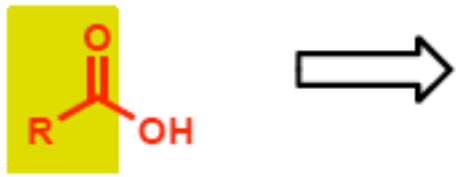


sodium formate

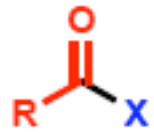
Understanding Structural Diagrams of Organic Molecules

Functional Groups – Carboxylic Acids II.

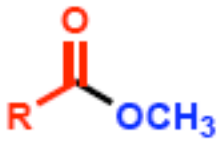




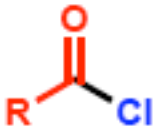
carboxylic acid



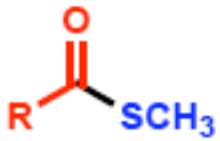
carboxylic acid derivative



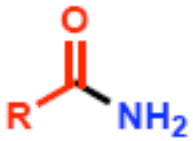
methyl ester



acyl chloride

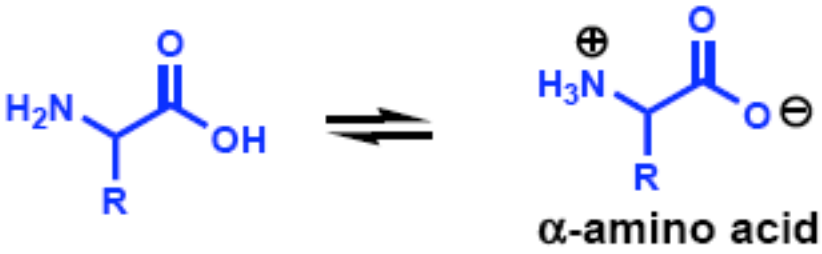


methyl thiolester

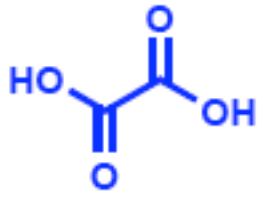
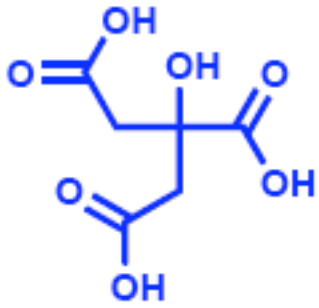


amide

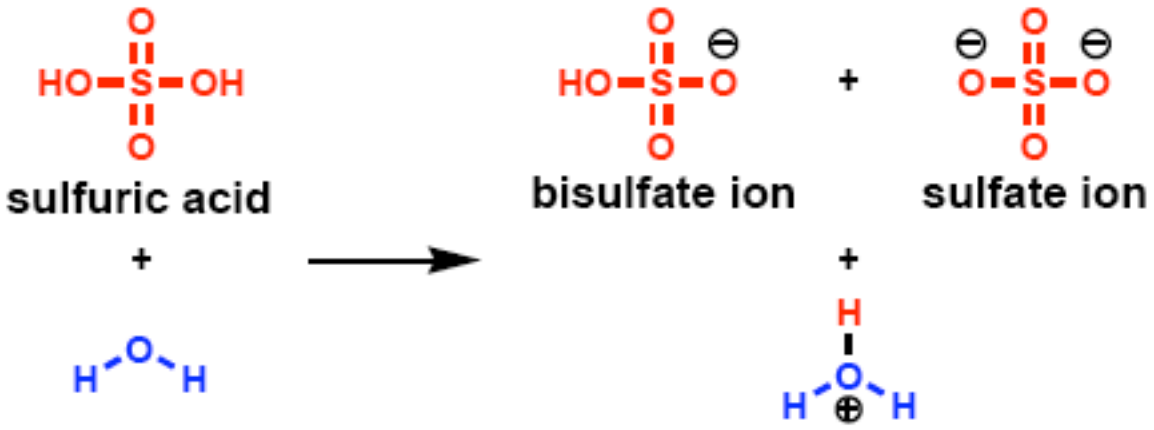
Understanding Structural Diagrams of Organic Molecules
Functional Groups – Polyfunctional Carboxylic Acids I.

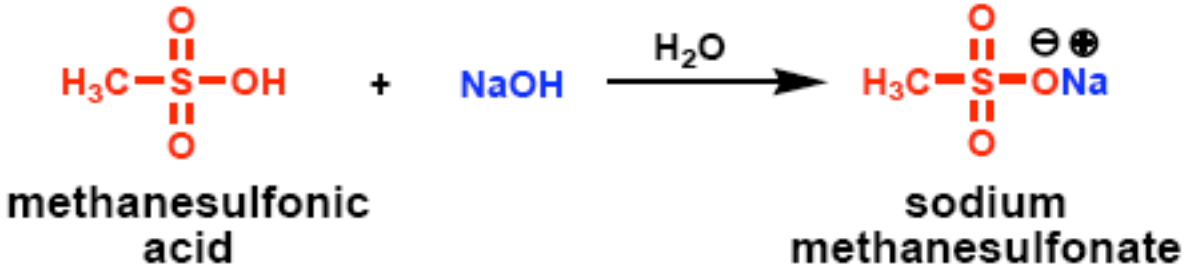
COMPOUND	DESCRIPTION
 glycine	the simplest α-amino acid and one of the building blocks of proteins
 α-amino acid	general formula for the class of α-amino acids

Understanding Structural Diagrams of Organic Molecules
Functional Groups – Polyfunctional Carboxylic Acids II.

COMPOUND	DESCRIPTION
 oxalic acid	oxalic acid, the acidic component of rhubarb
 malonic acid	malonic acid, a building block for the synthesis of fats *in vivo*
 citric acid	citric acid, the acidic component of lemons, oranges and other fruits.

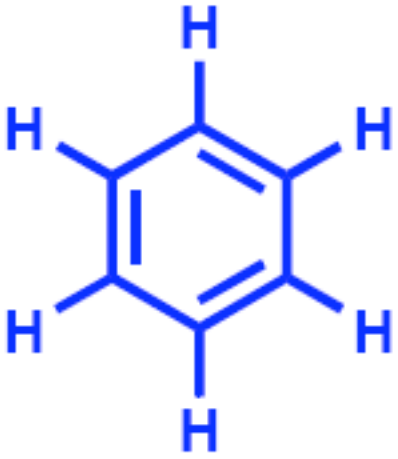
Understanding Structural Diagrams of Organic Molecules
Functional Groups – Sulfur and Phosphorous Acids I.





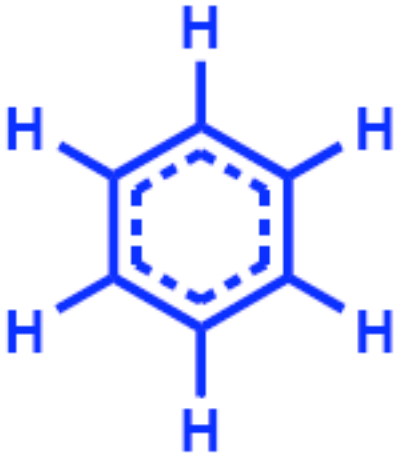
Understanding Structural Diagrams of Organic Molecules

Benzene – Structure and Stabilization I.



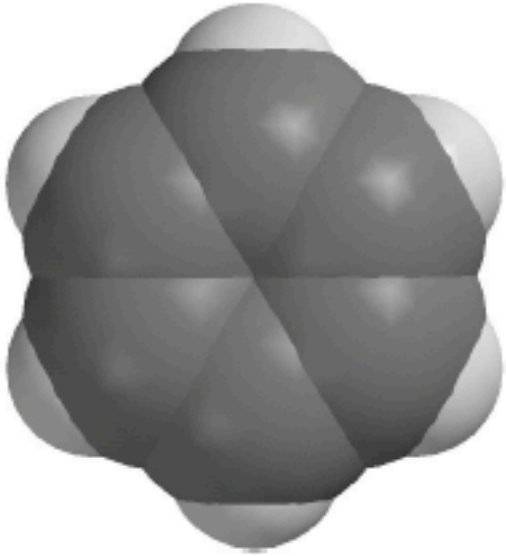
A

π-bonds localized



B

π-bonds delocalized

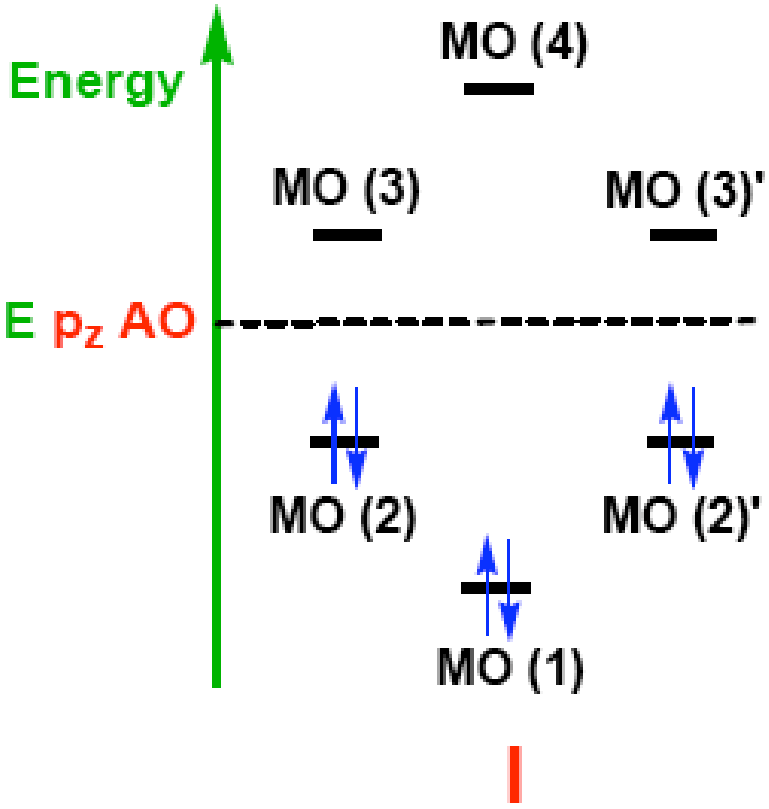


C

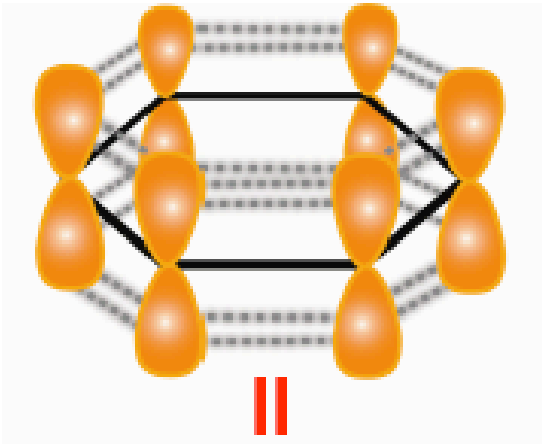
space-filling model

Understanding Structural Diagrams of Organic Molecules

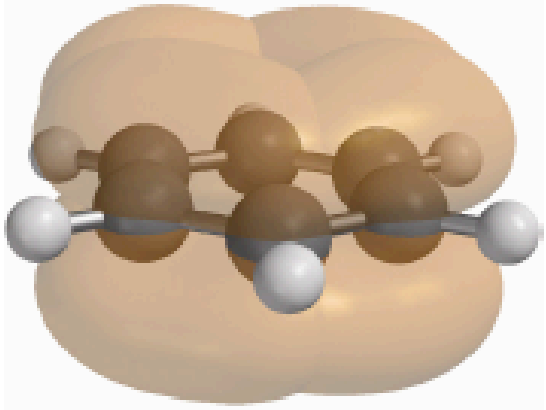
Benzene – Structure and Stabilization II.



I



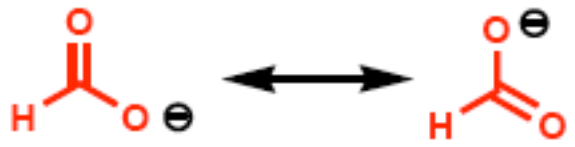
II



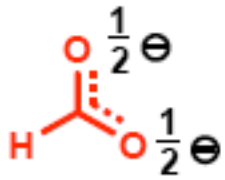
III

Understanding Structural Diagrams of Organic Molecules

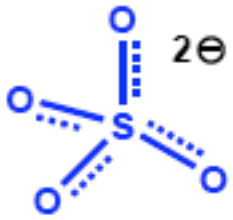
Representation of Structures with Delocalized π-Electrons



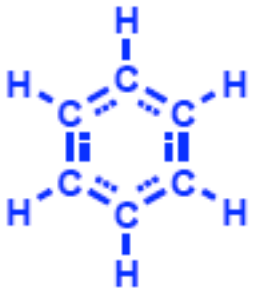
two extremes



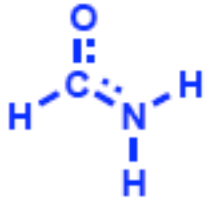
delocalized hybrid structure



sulfate ion



benzene



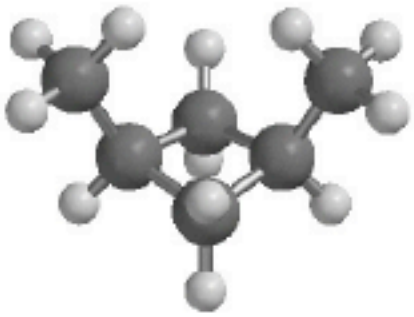
formamide

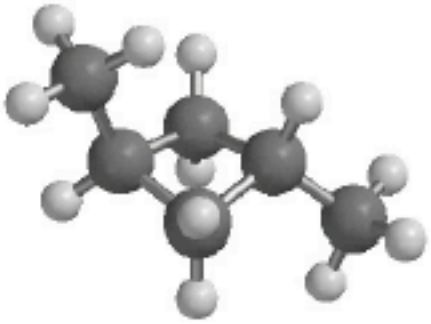
Understanding Structural Diagrams of Organic Molecules

Geometrical Isomers I.

***cis*-1,3-dimethyl-cyclobutane**

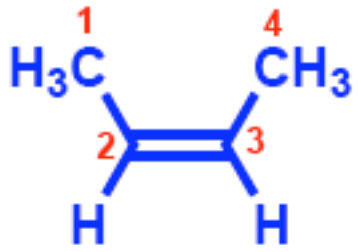
***trans*-1,3-dimethyl-cyclobutane**





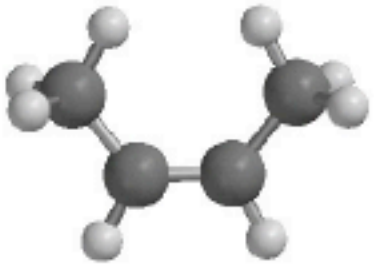
Understanding Structural Diagrams of Organic Molecules

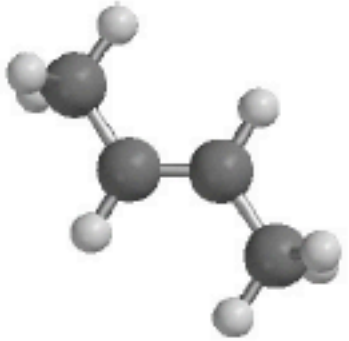
Geometrical Isomers II.



***cis*-2-butene**

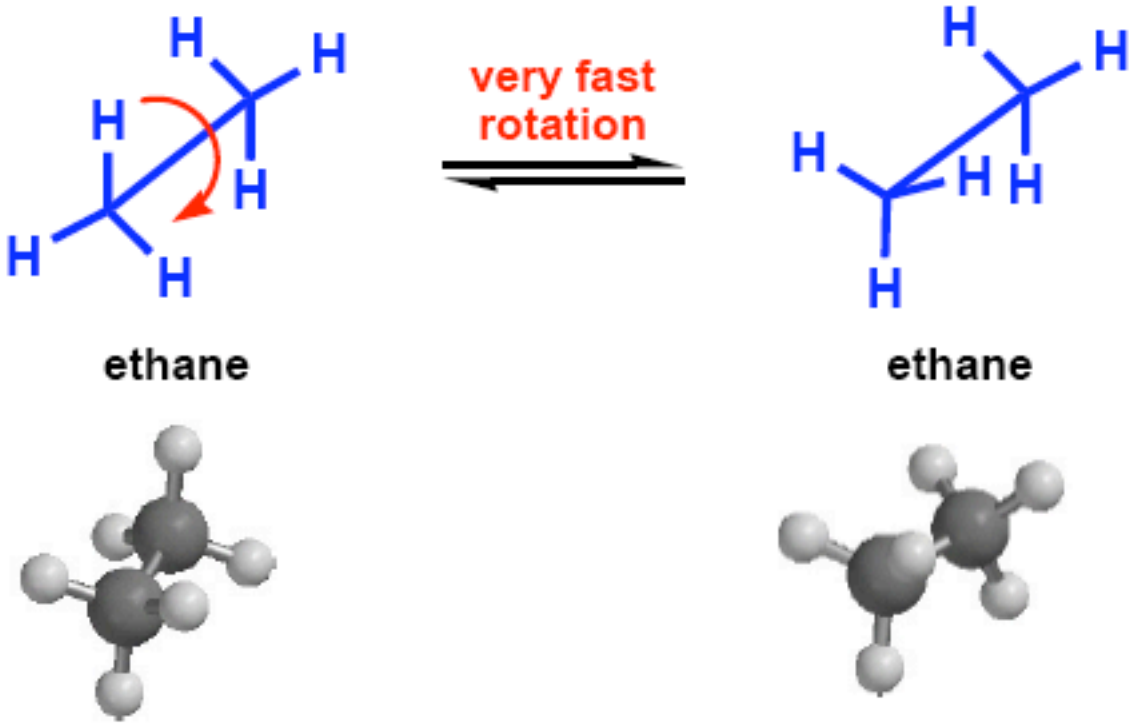
***trans*-2-butene**





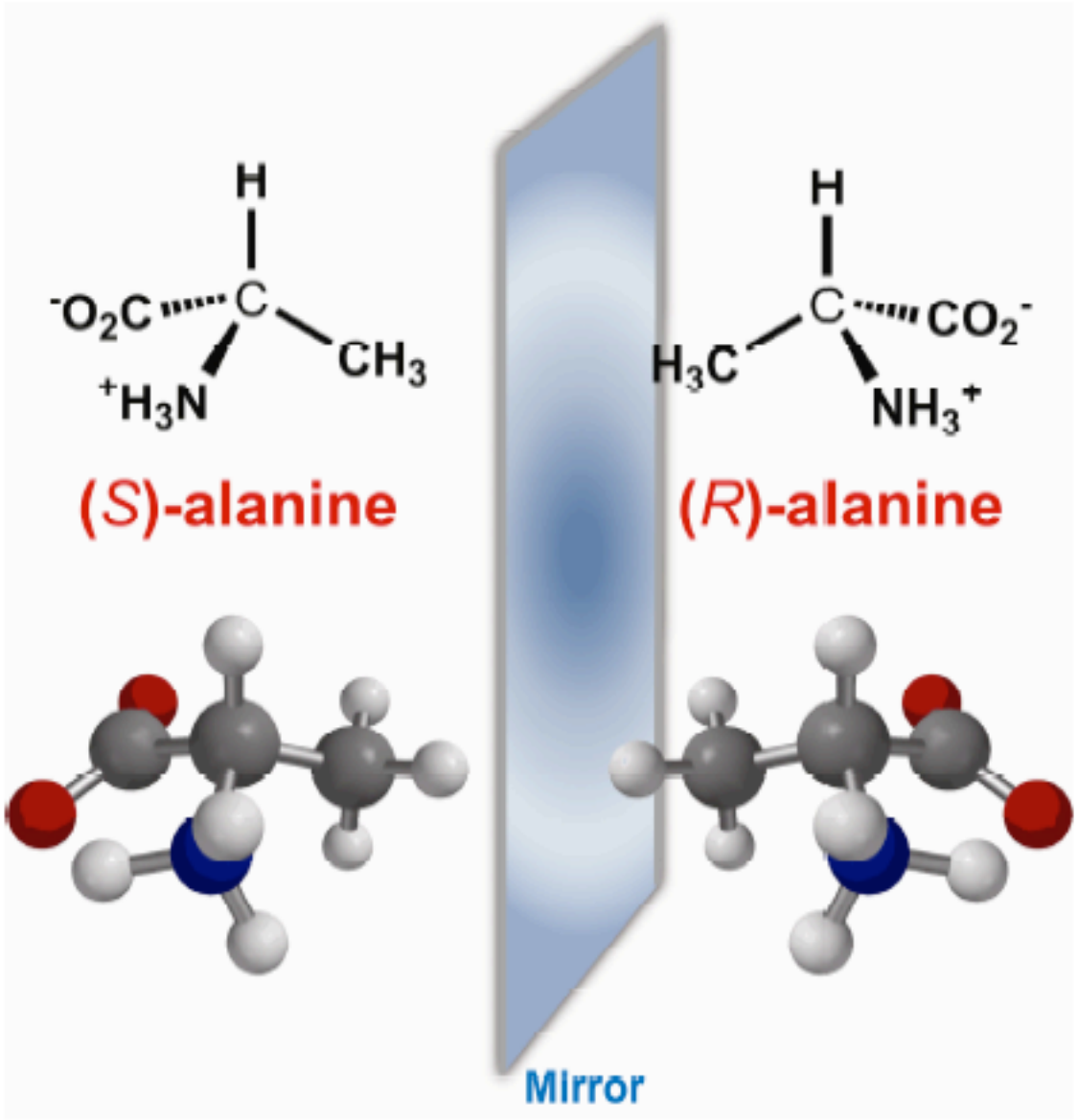
Understanding Structural Diagrams of Organic Molecules

Geometrical Isomers III.



Understanding Structural Diagrams of Organic Molecules

Chirality Isomerism (Stereoisomerism) III.



Drug Targeting Principles

Chapter 2-Patrick

Drug targets

Lipids

Cell membrane lipids

Proteins

Receptors
Enzymes
Carrier proteins
Structural proteins (tubulin)

Nucleic acids

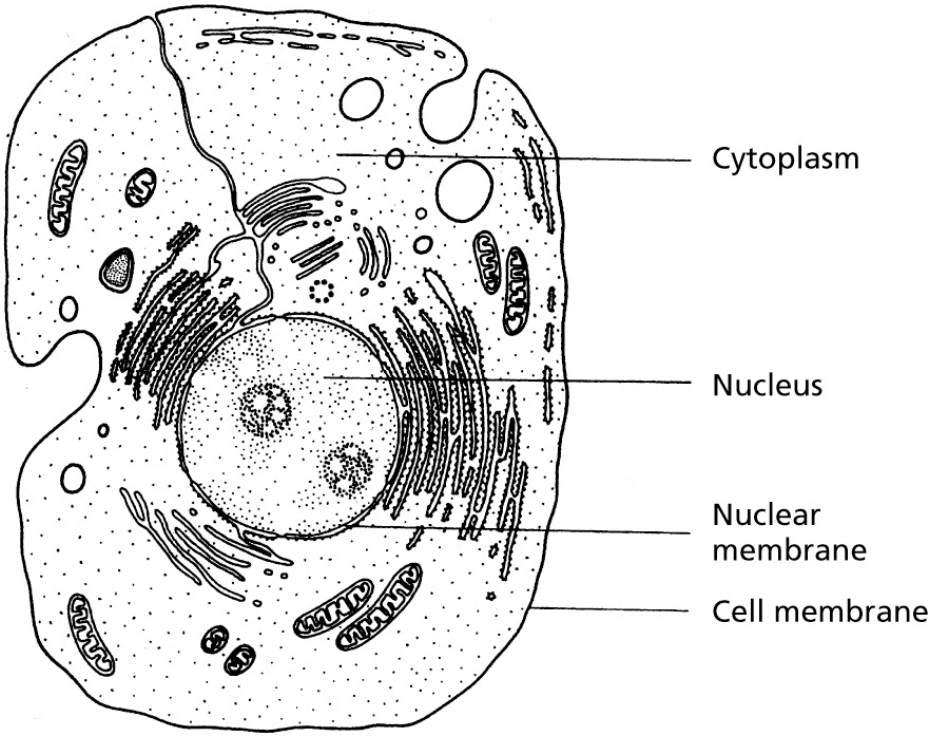
DNA
RNA

Carbohydrates

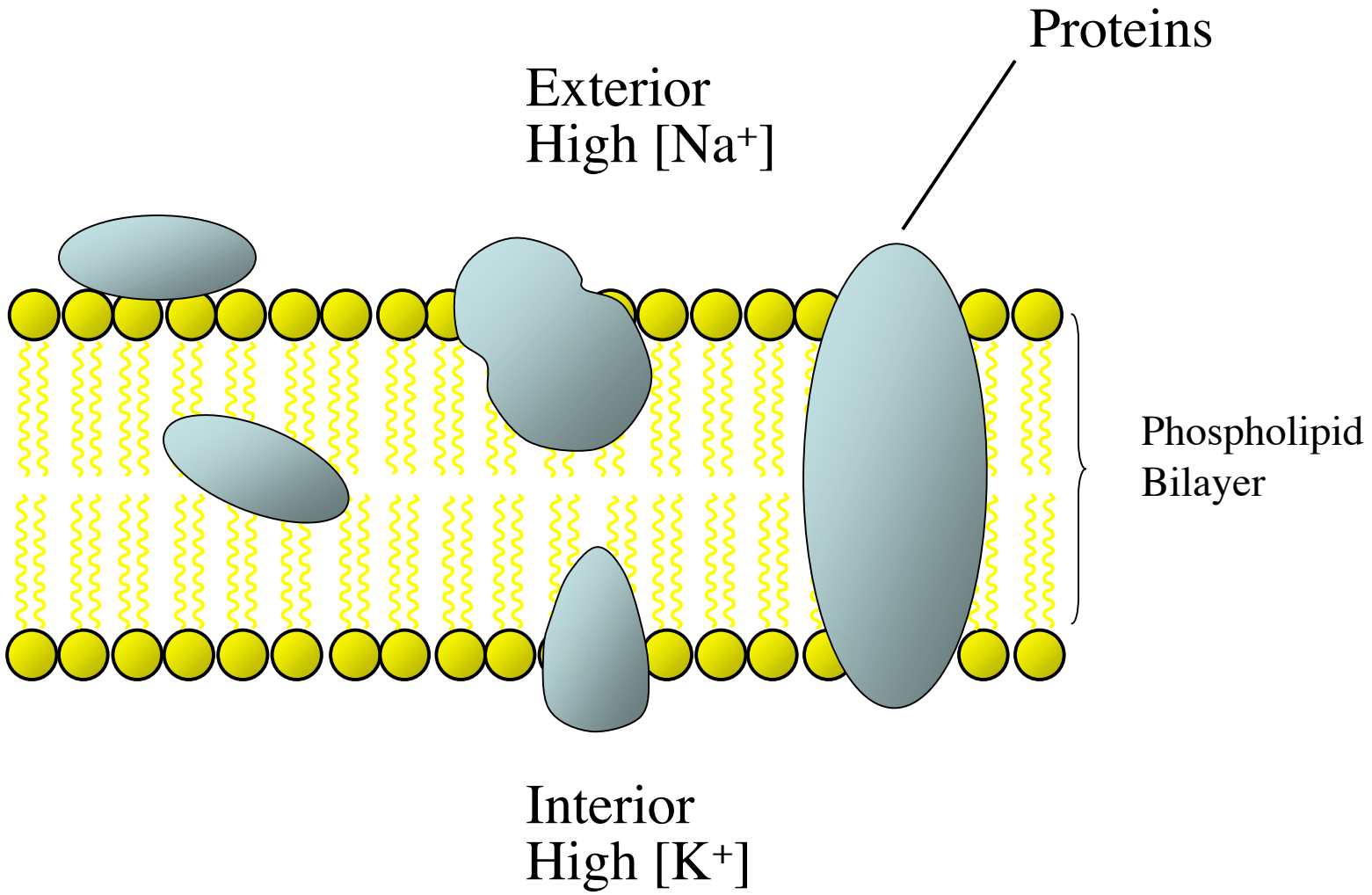
Cell surface carbohydrates
Antigens and recognition molecules

Cell Structure

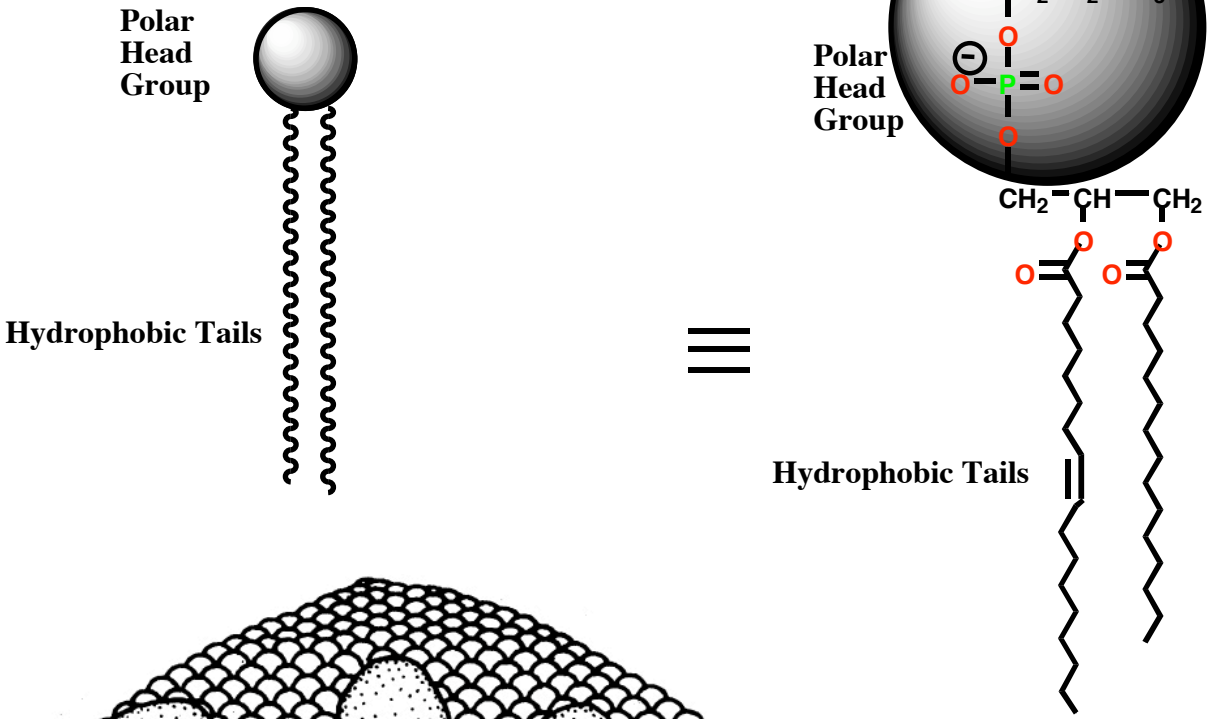
- **Human, animal and plant cells are eukaryotic cells**
- **The nucleus contains the genetic blueprint for life (DNA)**
- **The fluid contents of the cell are known as the cytoplasm**
- **Structures within the cell are known as organelles**
- **Mitochondria are the source of energy production**
- **Ribosomes are the cell's protein 'factories'**
- **Rough endoplasmic reticulum is the location for protein synthesis**

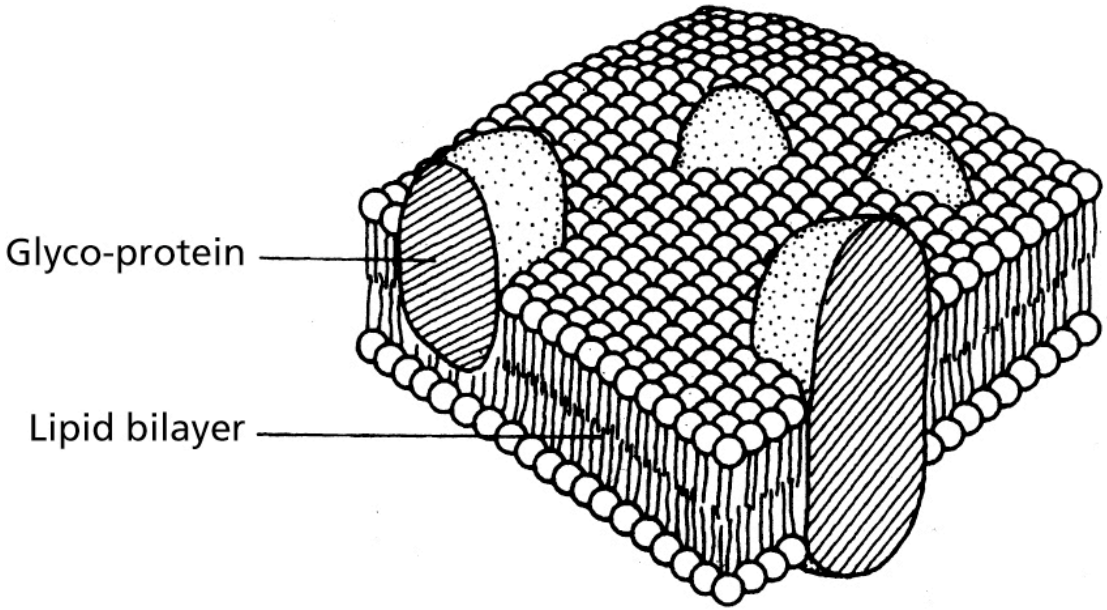


Cell Membrane



Cell Membrane





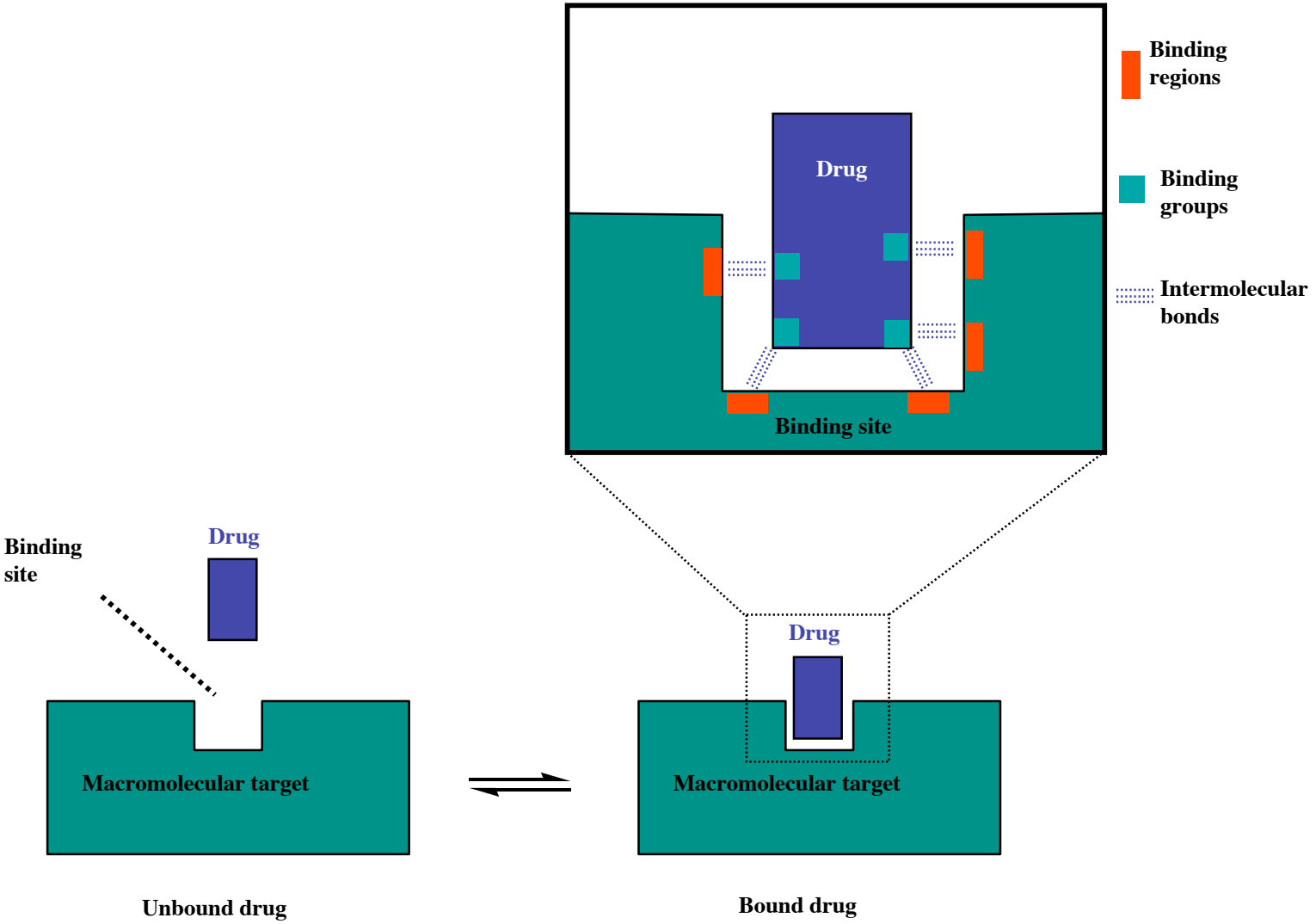
Cell Membrane

- **The cell membrane is made up of a phospholipid bilayer**
- **The hydrophobic tails interact with each other by van der Waals interactions and are hidden from the aqueous media**
- **The polar head groups interact with water at the inner and outer surfaces of the membrane**
- **The cell membrane provides a hydrophobic barrier around the cell, preventing the passage of water and polar molecules**
- **Proteins are present, floating in the cell membrane**
- **Some act as ion channels and carrier proteins**

Drug targets

- Drug targets are large molecules - macromolecules
- Drugs are generally much smaller than their targets
- Drugs interact with their targets by binding to binding sites
- Binding sites are typically hydrophobic pockets on the surface of macromolecules
- Binding interactions typically involve intermolecular bonds
- Most drugs are in equilibrium between being bound and unbound to their target
- Functional groups on the drug are involved in binding interactions and are called binding groups
- Specific regions within the binding site that are involved in binding interactions are called binding regions

Drug targets



Drug targets

- **Binding interactions usually result in an induced fit where the binding site changes shape to accommodate the drug**

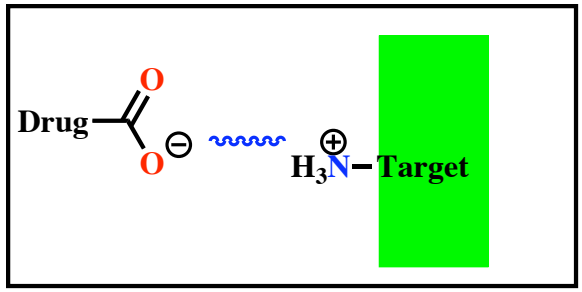
- **The induced fit may also alter the overall shape of the drug target**

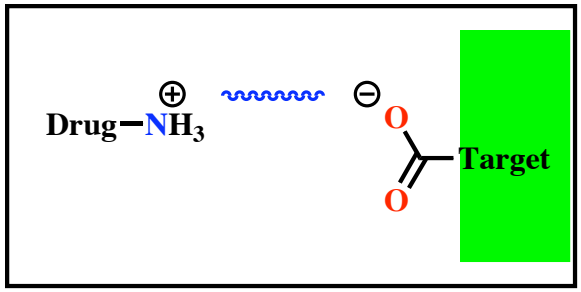
- **Important to the pharmacological effect of the drug**

Intermolecular bonding forces

Electrostatic or ionic bond

- Strongest of the intermolecular bonds (20-40 kJ mol^{-1})
- Takes place between groups of opposite charge
- The strength of the ionic interaction is inversely proportional to the distance between the two charged groups
- Stronger interactions occur in hydrophobic environments
- The strength of interaction drops off less rapidly with distance than with other forms of intermolecular interactions
- Ionic bonds are the most important initial interactions as a drug enters the binding site





Intermolecular bonding forces

Electrostatic or ionic bond

Electrostatic interactions: governed by Coulomb's law

Where V is the interaction energy between two charges in kJ/mol

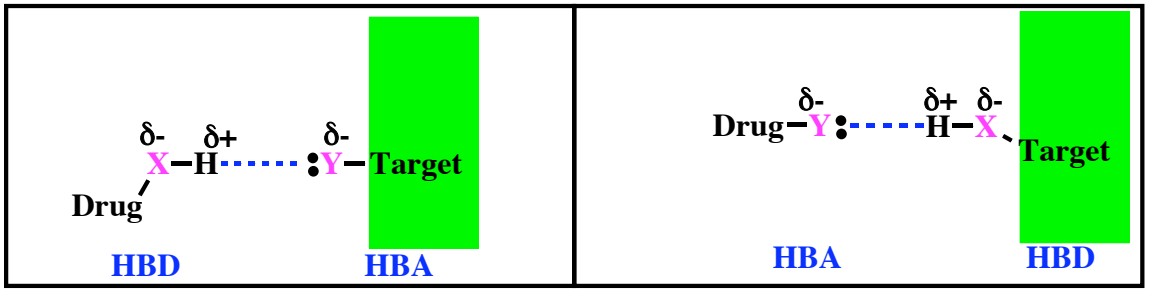
- q_1 and q_2 are charges in multiples of the protonic charge
- e is the dielectric constant of the medium(a measure of polarity)
- r is distance in Å (10^{-10} M)

$$V = \frac{1390 q_1 q_2}{\varepsilon r}$$

Intermolecular bonding forces

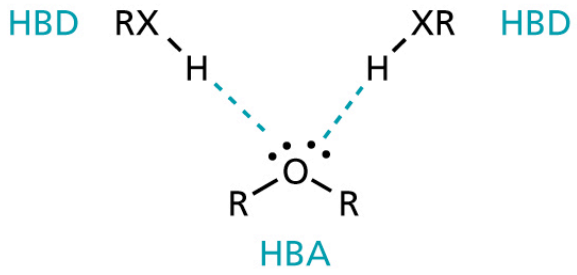
Hydrogen bonds

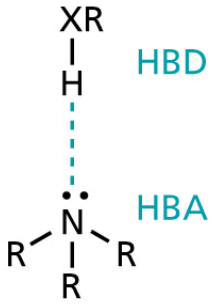
- Vary in strength
- Weaker than electrostatic interactions but stronger than van der Waals interactions
- A hydrogen bond takes place between an electron deficient hydrogen and an electron rich heteroatom (N or O)
- The electron deficient hydrogen is usually attached to a heteroatom (O or N)
- The electron deficient hydrogen is called a hydrogen bond donor
- The electron rich heteroatom is called a hydrogen bond acceptor

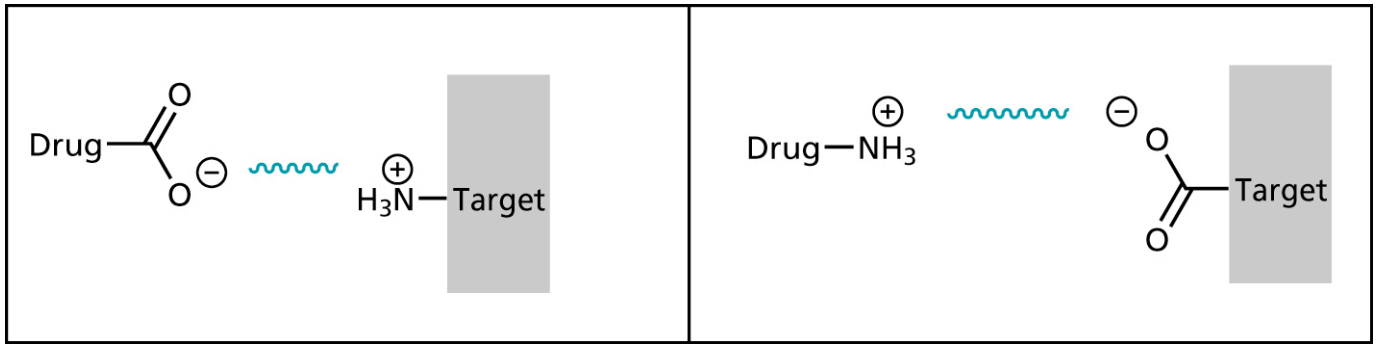


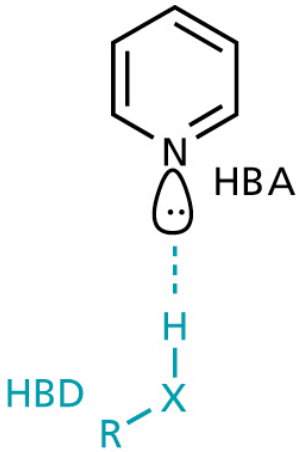
Intermolecular bonding forces

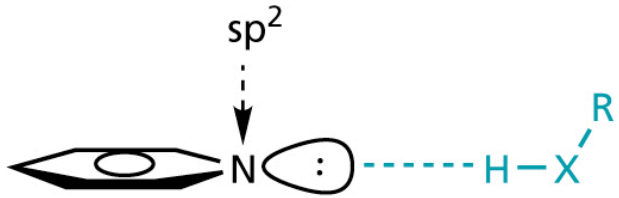
Hydrogen bonds









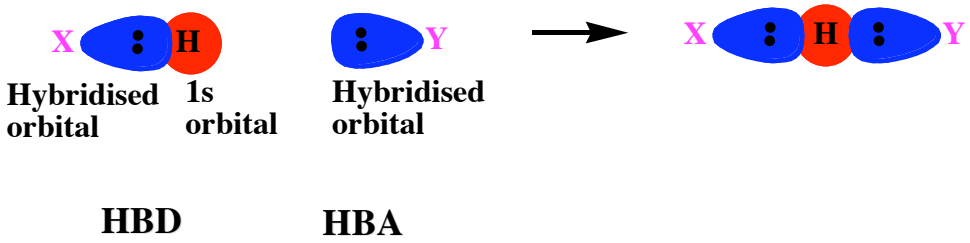


Intermolecular bonding forces

Hydrogen bonds

- **The interaction involves orbitals and is directional**

- **Optimum orientation is where the X-H bond points directly to the lone pair on Y such that the angle between X, H and Y is 180^{o}**



Intermolecular bonding forces

Hydrogen bonds

- **Examples of strong hydrogen bond acceptors**
  - carboxylate ion, phosphate ion, tertiary amine

- **Examples of moderate hydrogen bond acceptors**
  - carboxylic acid, amide oxygen, ketone, ester, ether, alcohol

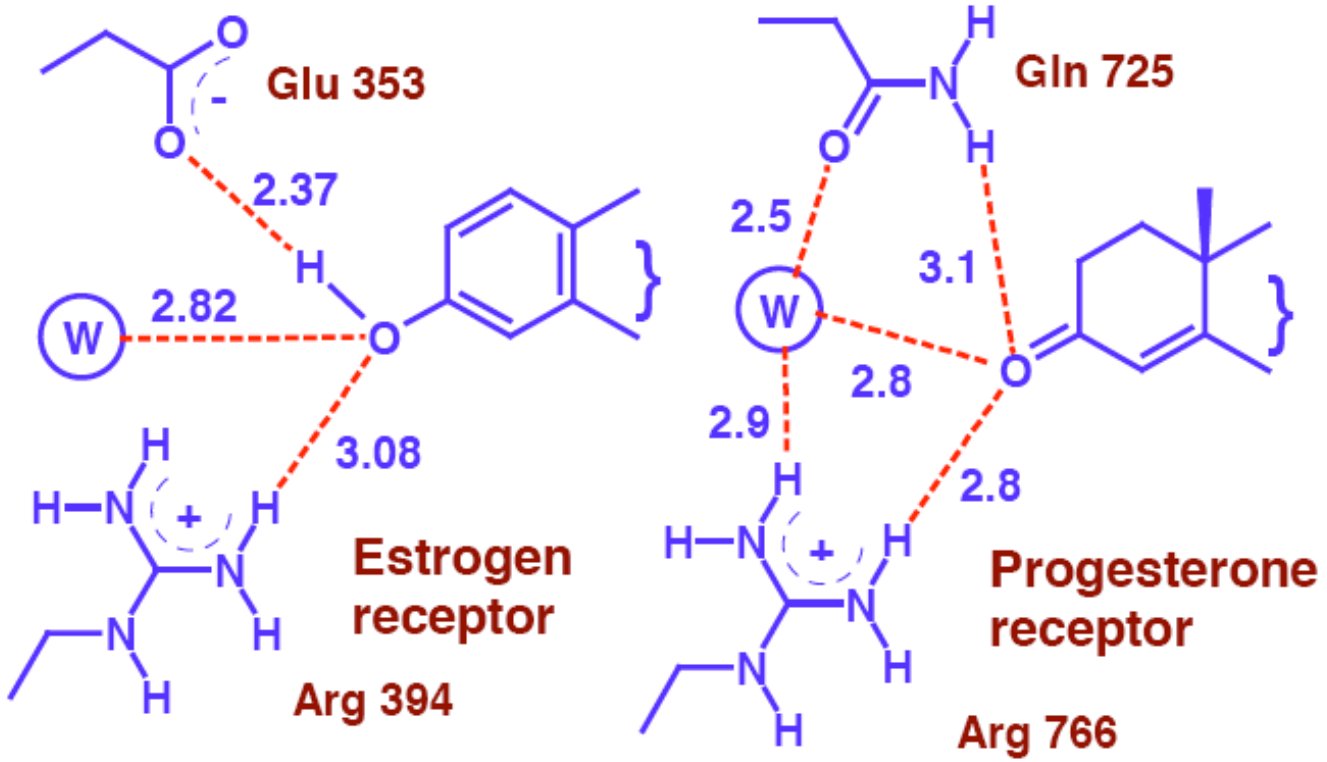
- **Examples of poor hydrogen bond acceptors**
  - sulfur, fluorine, chlorine, aromatic ring, amide nitrogen, aromatic amine

- **Example of good hydrogen bond donors**
  - Quaternary ammonium ion

Intermolecular bonding forces

Hydrogen bonds-The importance of hydrogen bonds, e.g.

Ligand Recognition - Specificity of Estrogen and Progesterone Receptors

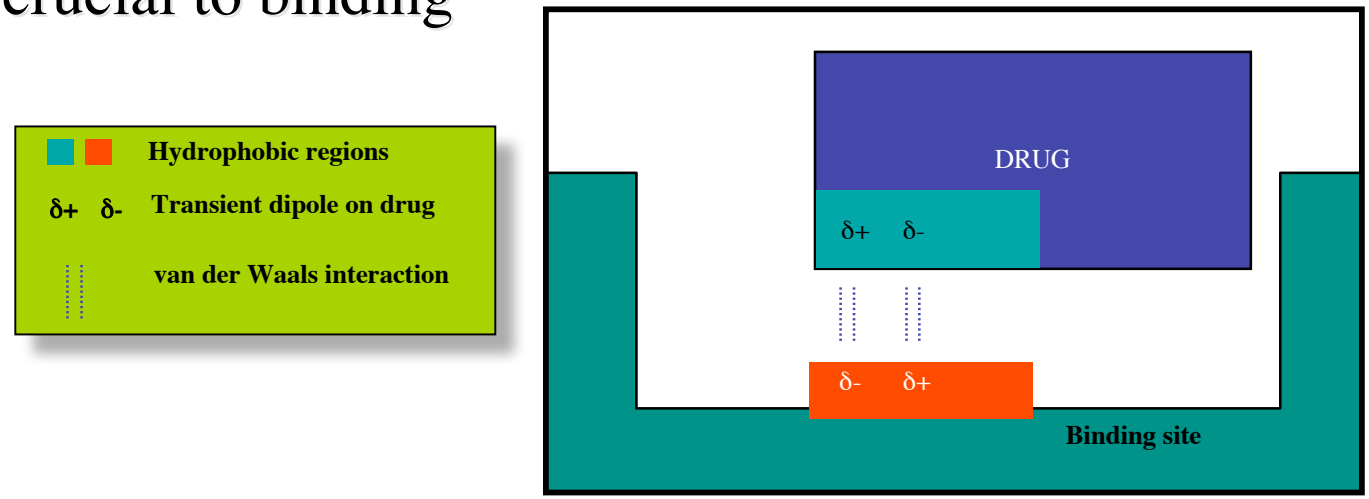


A. M. Brzozowski et al., Nature 389, 753-758 (1997)
S. P. Williams and P. B. Sigler, Nature 393, 392-396 (1998)

Intermolecular bonding forces

Van der Waals interactions

- Very weak interactions (2-4 kJmol^{-1},~4 kJ/Å^2 contact)
- Occur between hydrophobic(and other) regions of the drug and the target
- Due to transient areas of high and low electron densities leading to temporary dipoles
- Interactions drop off rapidly with distance
- Drug must be close to the binding region for interactions to occur
- The overall contribution of van der Waals interactions can be crucial to binding



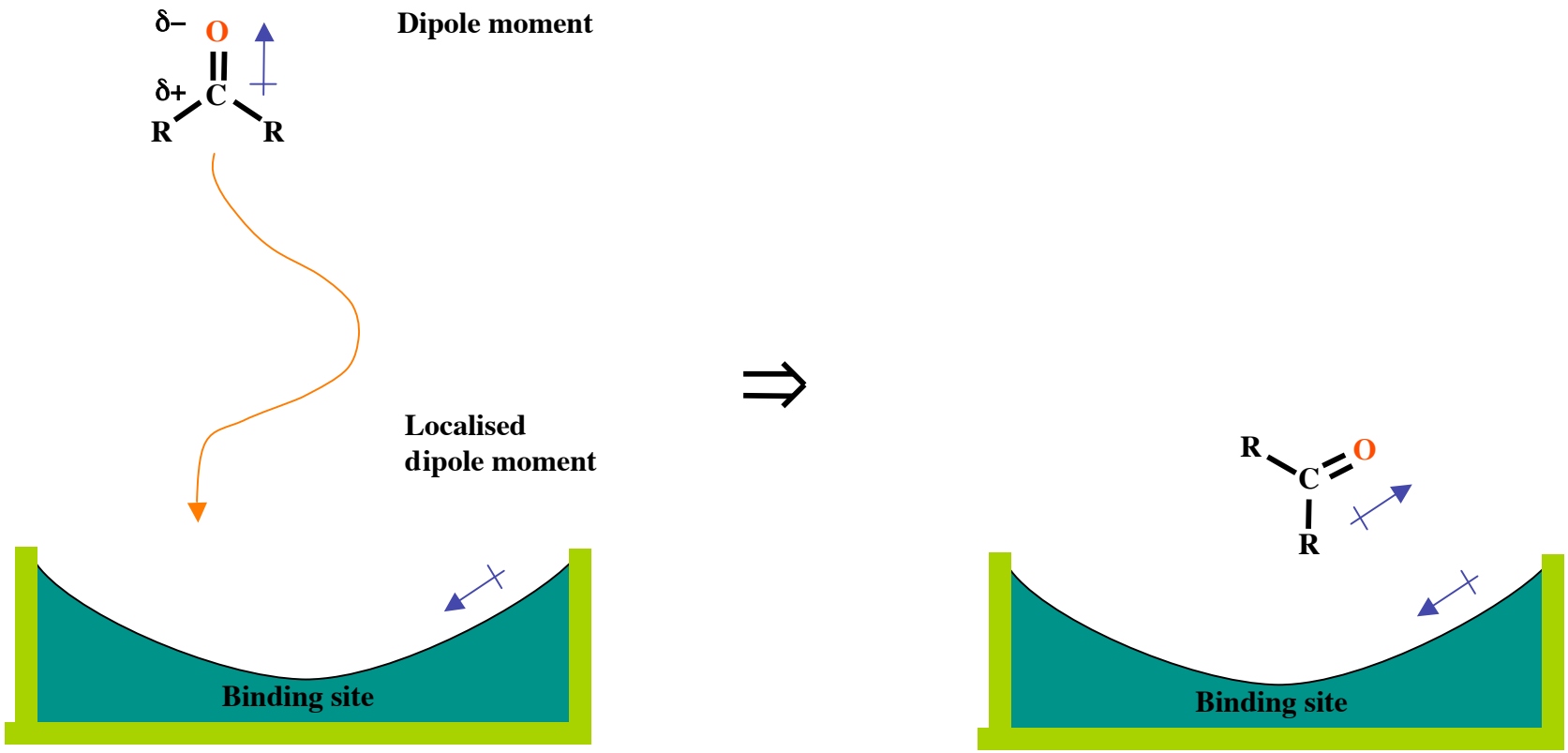
Intermolecular bonding forces

Dipole-dipole interactions

- Can occur if the drug and the binding site have dipole moments
- Dipoles align with each other as the drug enters the binding site
- Dipole alignment orientates the molecule in the binding site
- Orientation is beneficial if other binding groups are positioned correctly with respect to the corresponding binding regions
- Orientation is detrimental if the binding groups are not positioned correctly with respect to corresponding binding regions
- The strength of the interaction decreases with distance more quickly than with electrostatic interactions, but less quickly than with van der Waals interactions

Intermolecular bonding forces

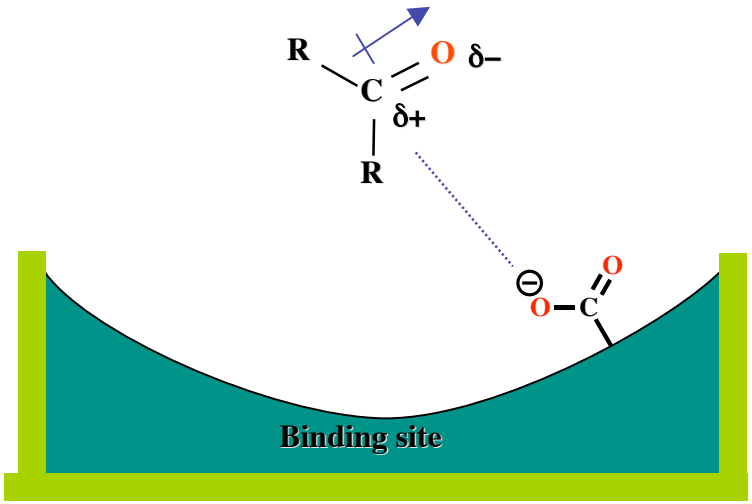
Dipole-dipole interactions

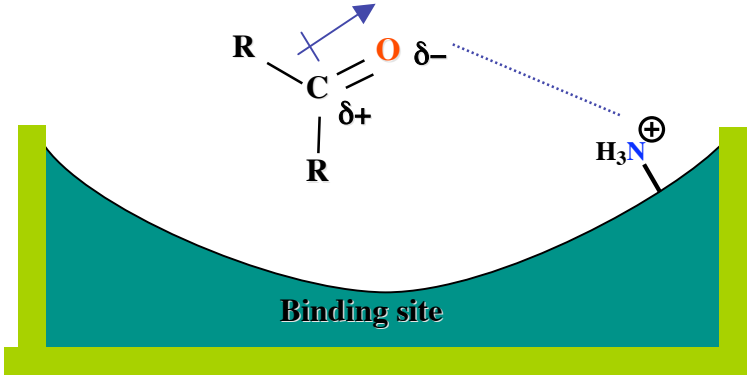


Intermolecular bonding forces

Ion-dipole interactions

- Occur where the charge on one molecule interacts with the dipole moment of another
- Stronger than a dipole-dipole interaction
- Strength of interaction falls off less rapidly with distance than for a dipole-dipole interaction

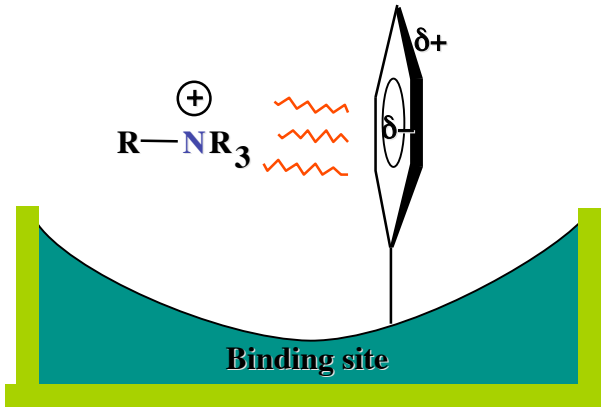




Intermolecular bonding forces

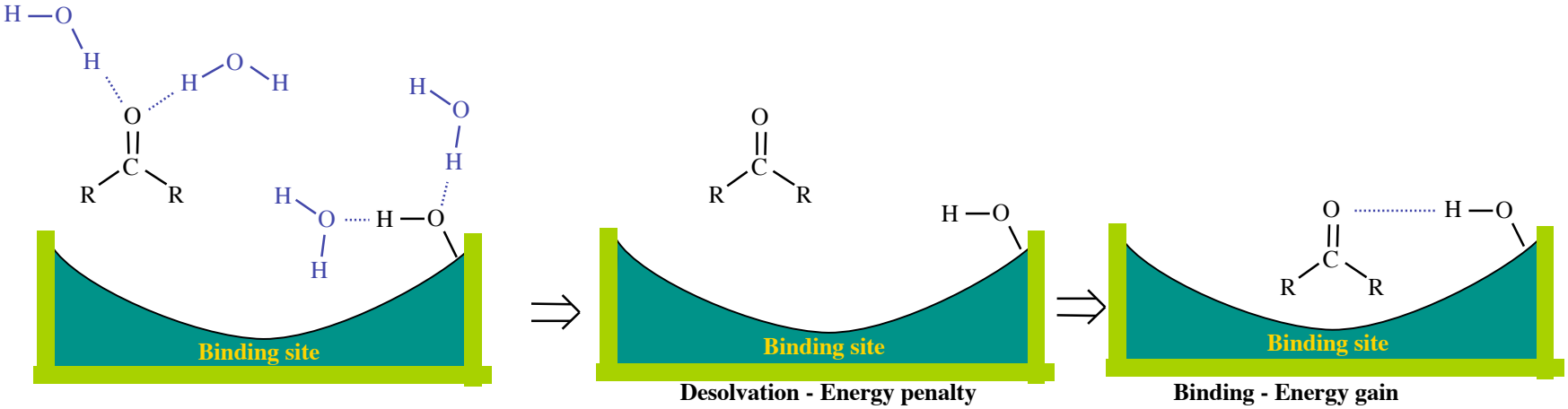
Induced dipole interactions

- Occur where the charge on one molecule induces a dipole on another
- Occurs between a quaternary ammonium ion and an aromatic ring



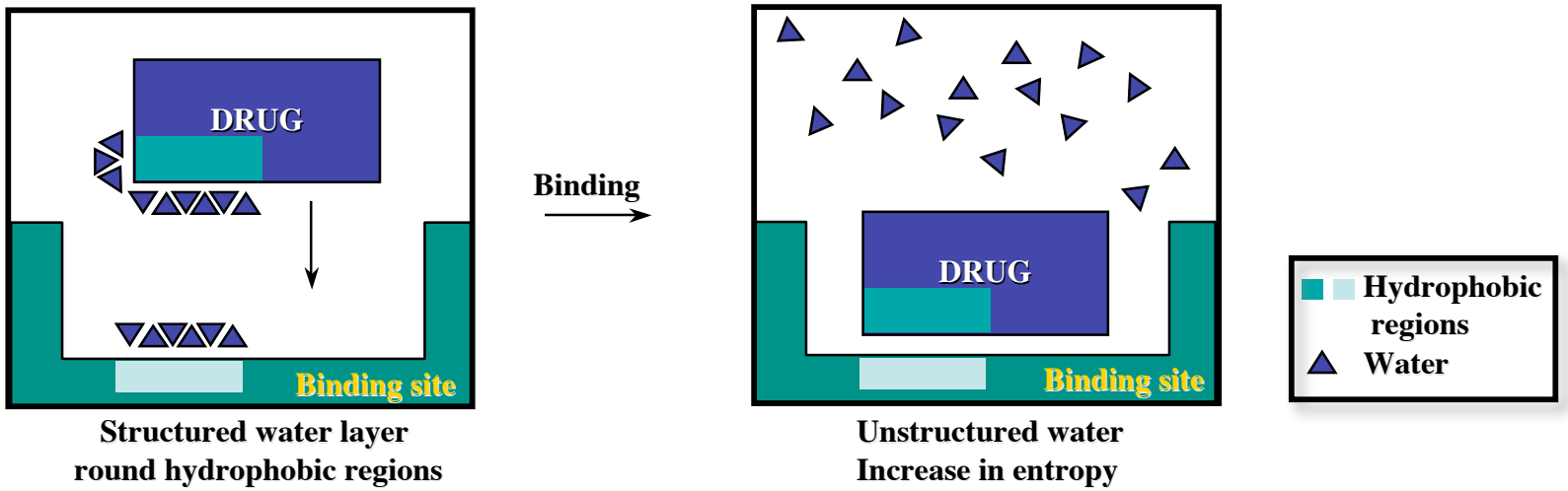
Desolvation penalties

- Polar regions of a drug and its target are solvated prior to interaction
- Desolvation is necessary and requires energy
- The energy gained by drug-target interactions must be greater than the energy required for desolvation



Hydrophobic interactions

- Hydrophobic regions of a drug and its target are not solvated
- Water molecules interact with each other and form an ordered layer next to hydrophobic regions - negative entropy
- Interactions between the hydrophobic interactions of a drug and its target ‘free up’ the ordered water molecules
- Results in an increase in entropy
- Beneficial to binding energy



Structured water layer round hydrophobic regions

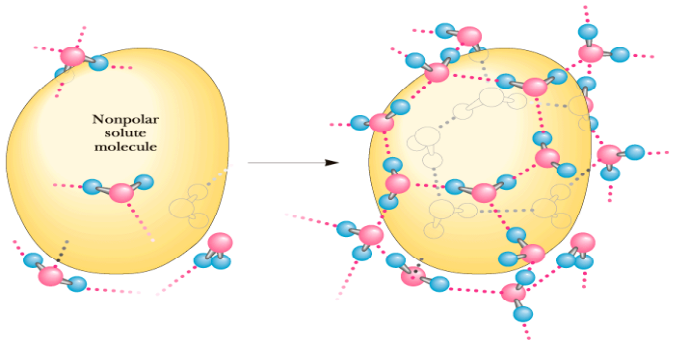
Unstructured water Increase in entropy

Hydrophobic interactions

- A nonpolar solute "organizes" water
- The H-bond network of water reorganizes to accommodate the nonpolar solute
- T his is an increase in "order" of water-This is a decrease in ENTROPY

Transfer reaction (25˚C)	**ΔH kcal/mol**	**ΔS cal/K mol**	**ΔG kcal/mol**
CH_4 in benzene→ CH_4 in water	-2.8	-18	+2.6
CH_4 in ether→ CH_4 in water	-2.4	-19	+3.3
CH_4 in CCl_4→ CH_4 in water	-2.5	-18	+2.9
C_3H_8 liquid→ C_3H_8 in water	-1.8	-23	+5.1

Recall **ΔG=ΔH-TΔS**

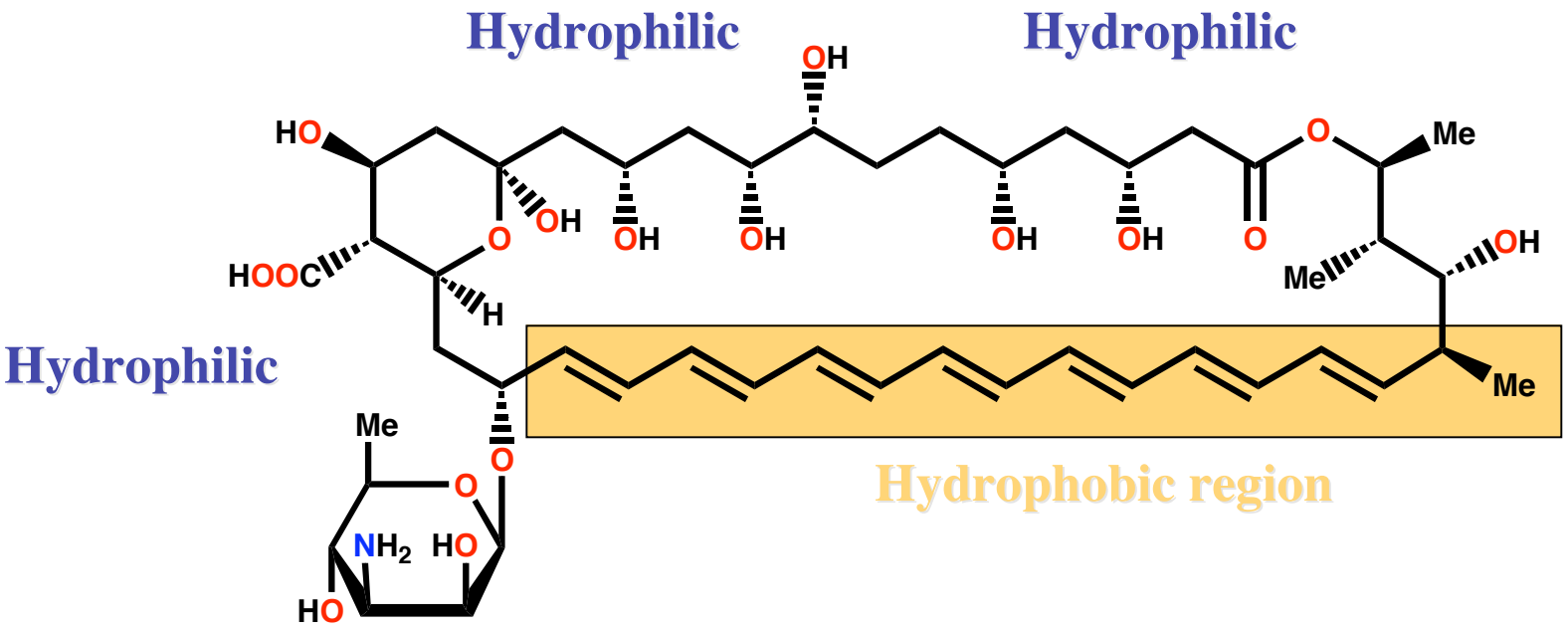


Drug Targets - Cell Membrane Lipids

Drugs acting on cell membrane lipids - Anaesthetics and some antibiotics

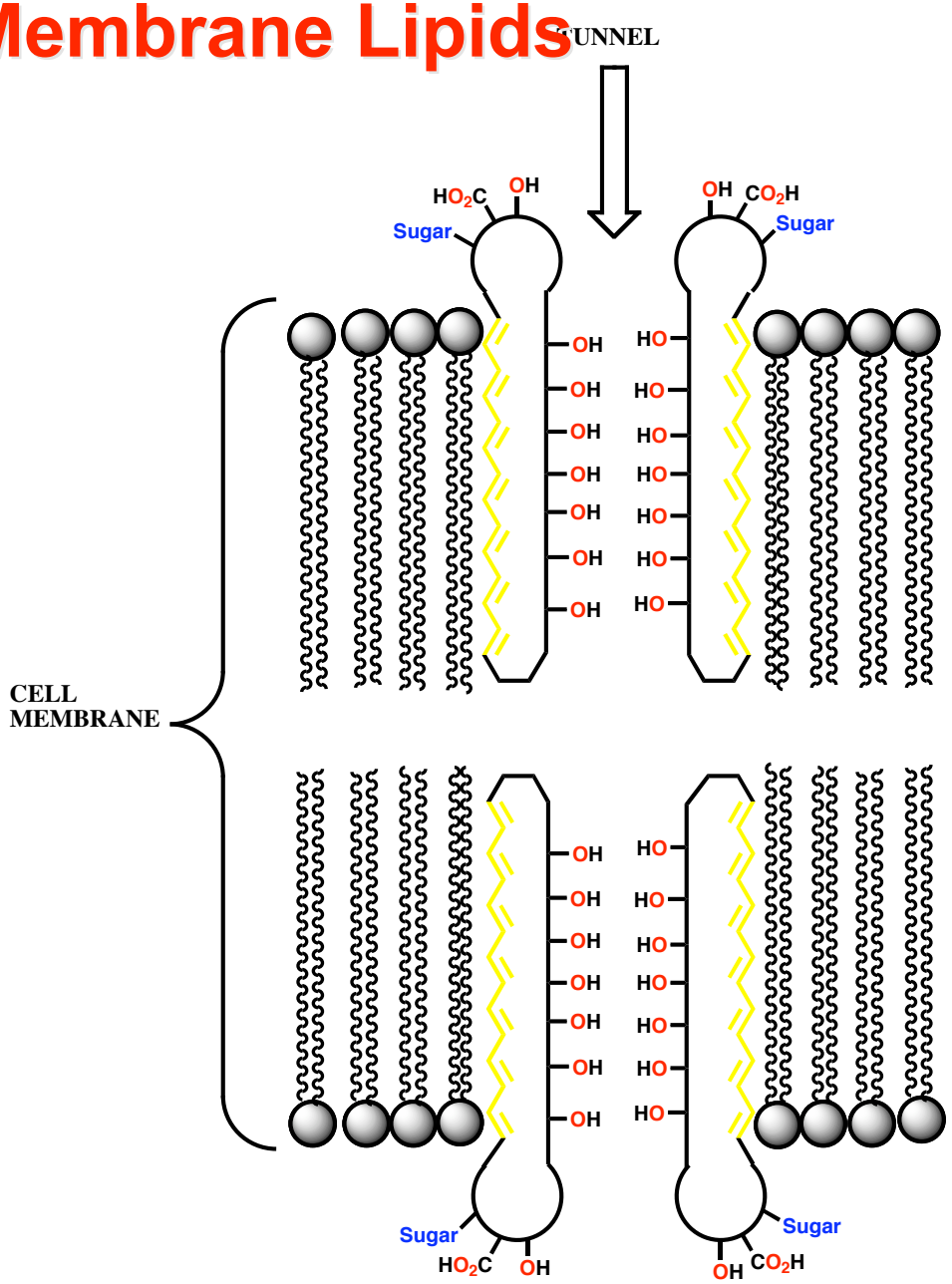
Action of amphotericin B (antifungal agent)

- builds tunnels/defects through membrane and drains cell



Drug Targets - Cell Membrane Lipids

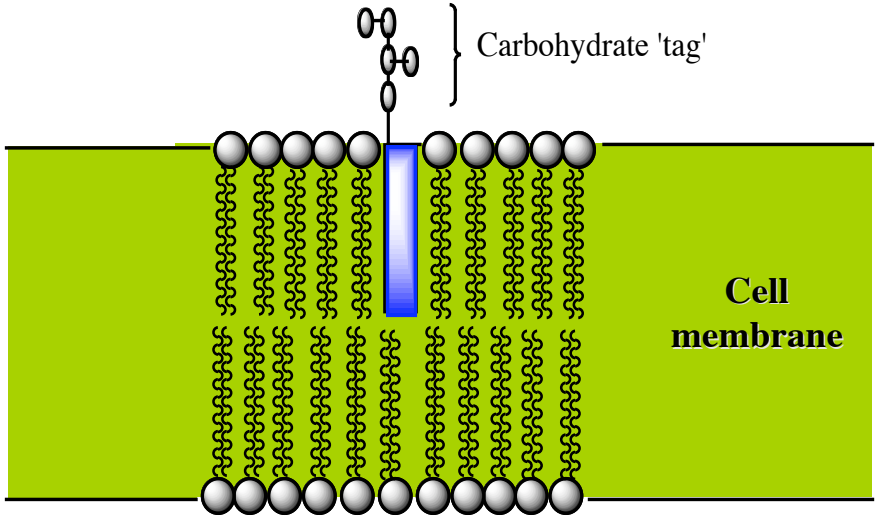
Polar tunnel formed
Escape route for ions



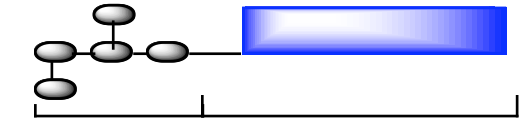
Probably not correct model, but correct concept

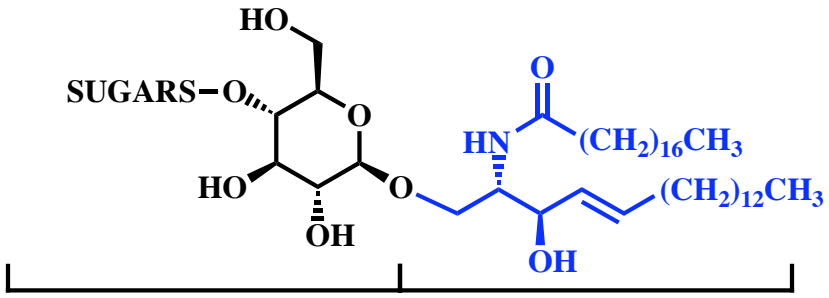
Drug Targets - Carbohydrates

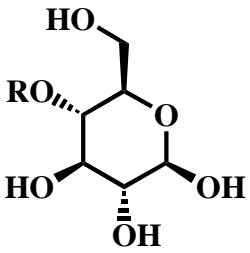
- Carbohydrates play important roles in cell recognition, regulation and growth
- Potential targets for the treatment of bacterial and viral infection, cancer and autoimmune disease
- Carbohydrates act as antigens



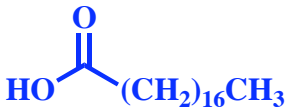
Drug Targets - Carbohydrates



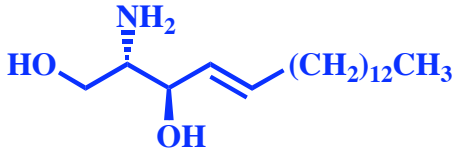




Carbohydrate
(R=various carbohydrate structures)



Fatty Acid (e.g. Stearic acid)



Sphingosine

Drug Targets - Proteins and Nucleic acids up later!