INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Fundamentals of Medicinal and Pharmaceutical Chemistry

FUNCHEM.14 Introduction to Organic Chemistry II

Professor Dan Wu

DATE: 8th November 2024

Learning outcomes

At the end of this lecture, the learner will be able to

- Identify the following functional groups (alkane, alkene, alkyne, alcohol, thiol, ether, sulphide, aldehyde, ketone, carboxylic acid, amine, amide, ester, acid halide, aromatic).
- Recall Covalent bonding, 3D Shape of Organic Compounds, Writing Structural Formulas, Geometric Isomers (cis/trans isomers)
- Identify and describe aliphatic and aromatic hydrocarbons.
- Describe and identify examples of structural, geometric, chiral molecules and optical isomers.
- Interpret and construct Lewis structures, condensed structures and line structures of organic compounds.
- Identify and describe structural geometry and bonding present in organic compounds according to valence bond theory.
- Compare properties of organic and inorganic compounds.

Recommended reading

- Organic chemistry with biological application (John McMurry)
- Chapter 3: Organic Compounds:
  alkanes and their stereochemistry
- Chapter 4: Organic Compounds:
  Cycloalkanes and their stereochemistry
- Chapter 6: an overview of organic reactions

Covalent Bonding

Organic compounds – compounds of carbon – are held together by covalent bonds

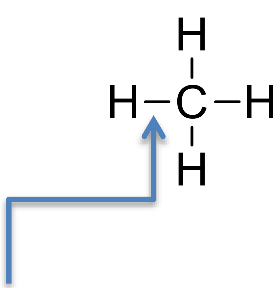
Covalent bonds are formed by sharing of electrons;

In organic chemistry the term bond is used to designate a shared pair of electrons

Carbon has four valence electrons; this means it can form a maximum of four covalent bonds

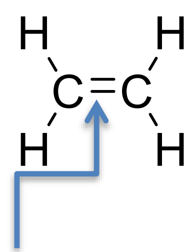
Bonds are represented by a straight line connecting the atoms with each bond representing a shared pair of electrons

methane
CH_4
four single bonds to carbon



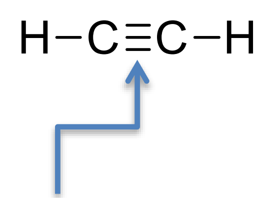
2 electrons in this δ bond

ethene
CH_2CH_2
double bond between carbons



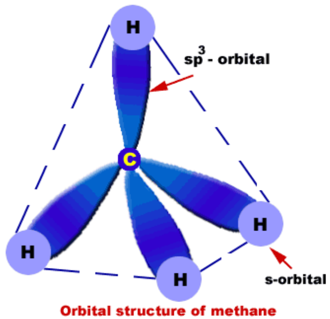
2 electrons in a δ bond and 2 electrons in a π bond

ethyne
CHCH
triple bond between carbons



2 electrons in a δ bond and 2 electrons each in two π bonds

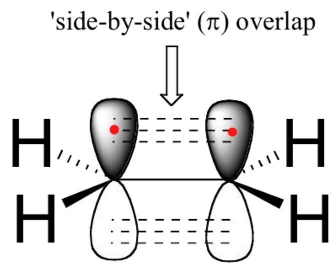
Covalent Bonding



methane

A sigma (σ) bond is a covalent bond formed by head-on overlap of atomic orbitals

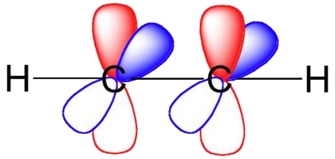
All four C-H bonds are identical and spatially orientated towards a regular tetrahedron



ethene

A pi (π) bond is a covalent bond formed by sideways overlap of atomic orbitals,

e.g. carbon-carbon double bonds contain one sigma bond and one pi bond formed by sideways overlap of two *p* orbitals



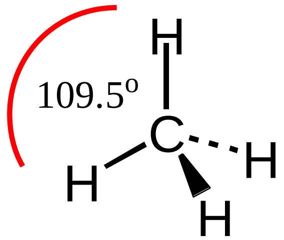
π overlap

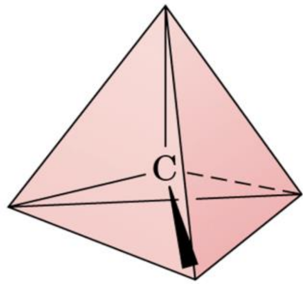
ethyne

e.g. carbon-carbon triple bonds contain one sigma bond and two pi bonds (formed by sideways overlap of two *p* orbitals)

3D Shape of Organic Compounds

Methane





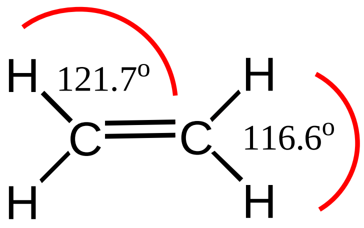
Tetrahedral geometry

all four C-H bonds are identical and spatially orientated towards a regular tetrahedron

all C–H bonds are the same length (110 pm); angles between any pair of bonds is 109.5°

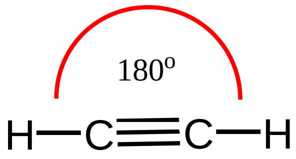
solid line lies in the plane of the page;
the dashed line goes behind the plane;
the solid wedge extends out of the plane

Ethene



carbon-carbon double bonds containing one sigma bond and one pi bond with length of 133 pm;
C-H bond angle of 121.7°

Ethyne



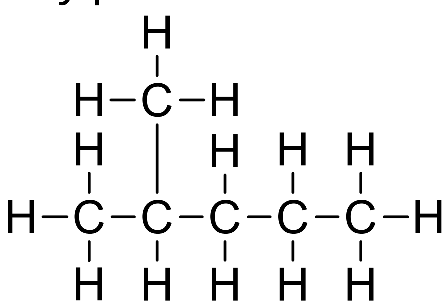
carbon-carbon triple bonds contain one sigma bond and two pi bonds with length of 120 pm;
bond angle of 180°

Writing Structural Formulas

Structural formulas are often abbreviated

When carbon–hydrogen and carbon–carbon bonds are not shown they are understood to be present

2-Methylpentane



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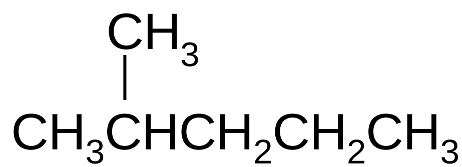
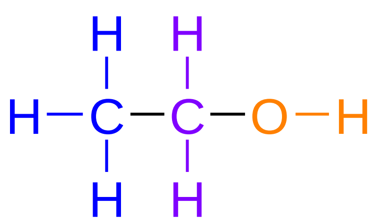


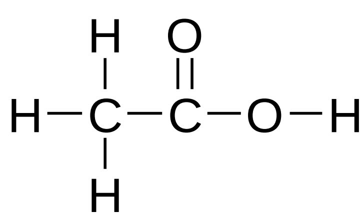
= $(CH_3)_2CH(CH_2)_2CH_3$

Ethanol



= CH_3—CH_2—OH = CH_3CH_2OH

Acetic acid



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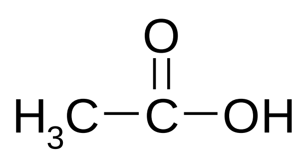
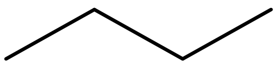


= CH_3CO_2H

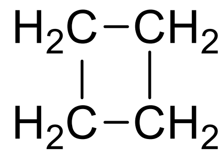
expanded = *condensed* = *more condensed*

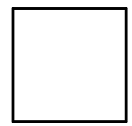
Use of Lines to Represent the Carbon Framework

$CH_3(CH_2)_2CH_3$



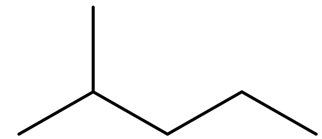
butane





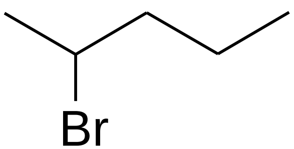
cyclobutane

$(CH_3)_2CH(CH_2)_2CH_3$



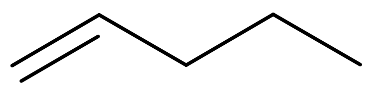
2-methylpentane

$CH_3CH(Br)(CH_2)_2CH_3$



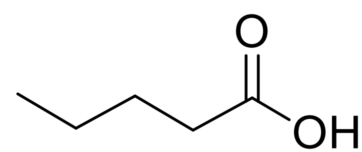
2-bromopentane

$CH_2CH(CH_2)_2CH_3$



1-pentene

$CH_3(CH_2)_3CO_2H$



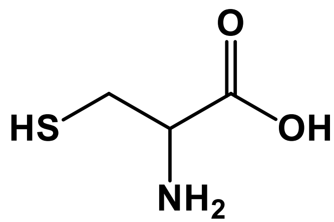
pentanoic acid

Line formulae have a carbon atom at each end and at the intersections

Carbon and hydrogen atoms are not usually shown

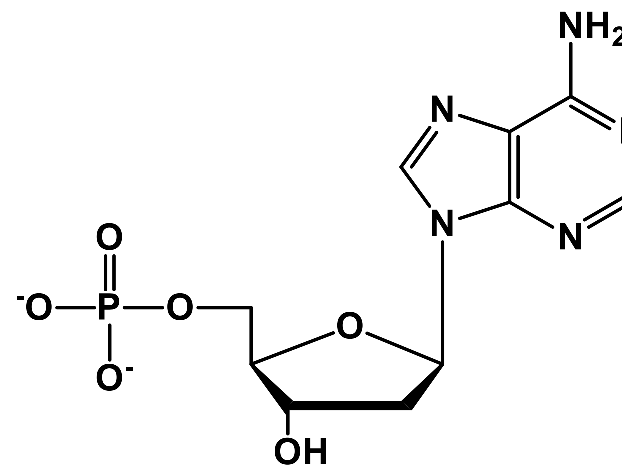
Atoms other than carbon and hydrogen are shown

Line Formula in Complex Biomolecules and Drugs



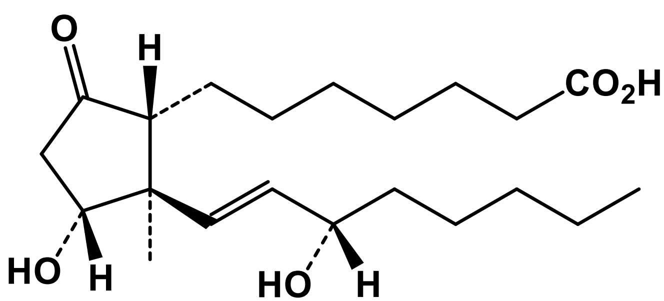
Cysteine

(Amino acid)

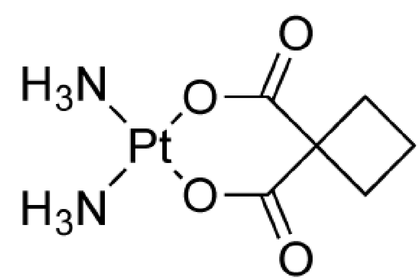


2’-Deoxyadenosine 5’-phophate

(Deoxyribonucleotide)



Prostaglandin E_1



carboplatin

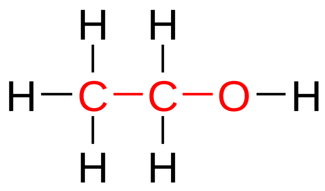
Structural Isomers

Compounds can have identical molecular formula but different structural formulas.

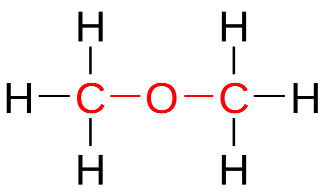
Structural (or constitutional) isomers differ in atom to atom connectivity.

Isomers can have totally different physical and biological properties.

Compare



Ethanol
(liquid)



Dimethyl ether
(gas)

Molecular formula	C_2H_6O	C_2H_6O
Boiling point	78.5 ° C	-23.6 ° C
Melting point	-114.3 ° C	-138.5 ° C
Solubility in water	Soluble in all proportions	Slightly soluble

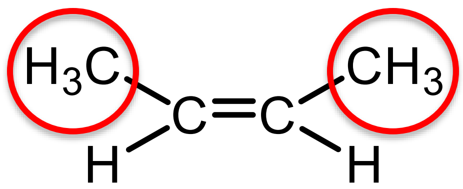
Geometric Isomers (*cis/trans* isomers)

(arise due to the lack of free rotation around a double bond)

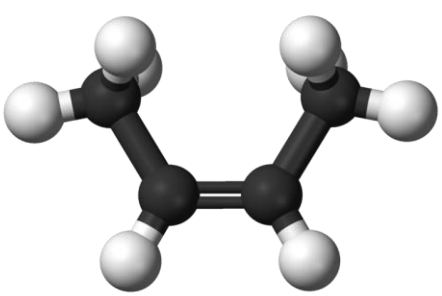
The same order of attachment of their atoms but a different arrangement of their atoms in space

cis-but-2-ene

C_4H_4: b.p. 4 °C

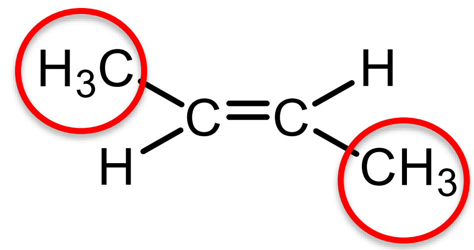


cis
(substituents on the same side)

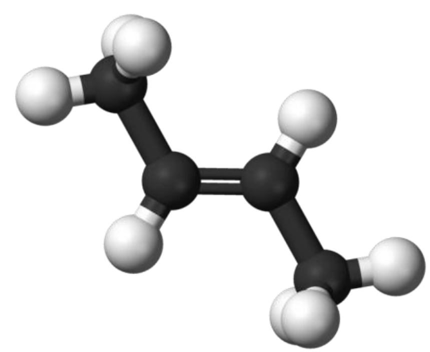


trans-but-2-ene

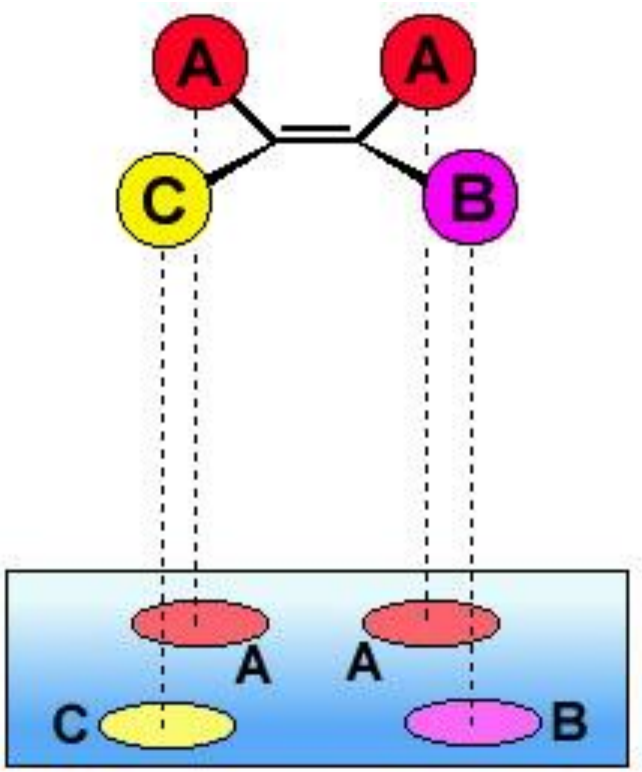
C_4H_4: b.p. 1 °C



trans
(substituents on opposite sides)



Geometric Isomers (*cis/trans* isomers)

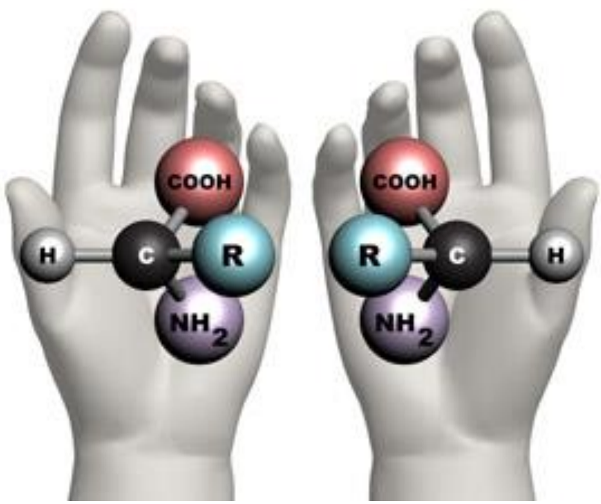


Group B and C *cis*

Specific interactions between molecules and biological receptors

Optical Isomers: Chirality and Enantiomers

The mirror image of a chiral molecule cannot be superimposed on the molecule itself.



A pair of molecules that are related as non-superimposable mirror images are called enantiomers.

Chiral molecules are chemically identical to each other but possess unique three-dimensional shapes, making them mirror-images that are not superimposable on each other.

Although chemically identical, chiral molecules may possess very different biological properties.

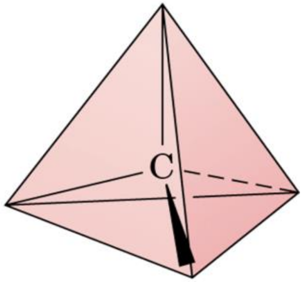
This is very important in drug – enzyme / receptor interactions.

Chiral Molecules

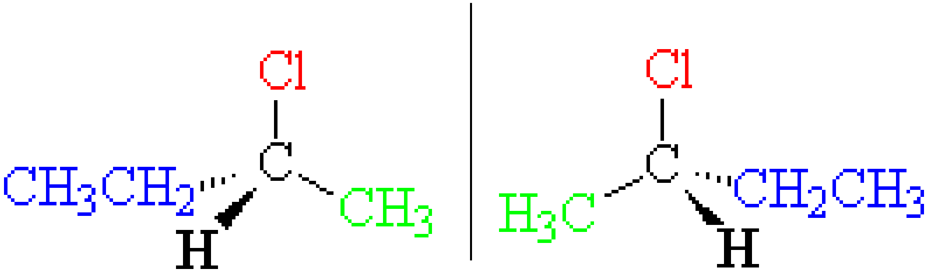
A carbon atom with four <u>different</u> groups attached to it
called a stereogenic centre as it gives rise to two stereoisomers

Chiral molecules do not have a plane of symmetry.

e.g. 2-chlorobutane



Carbon has tetrahedral geometry

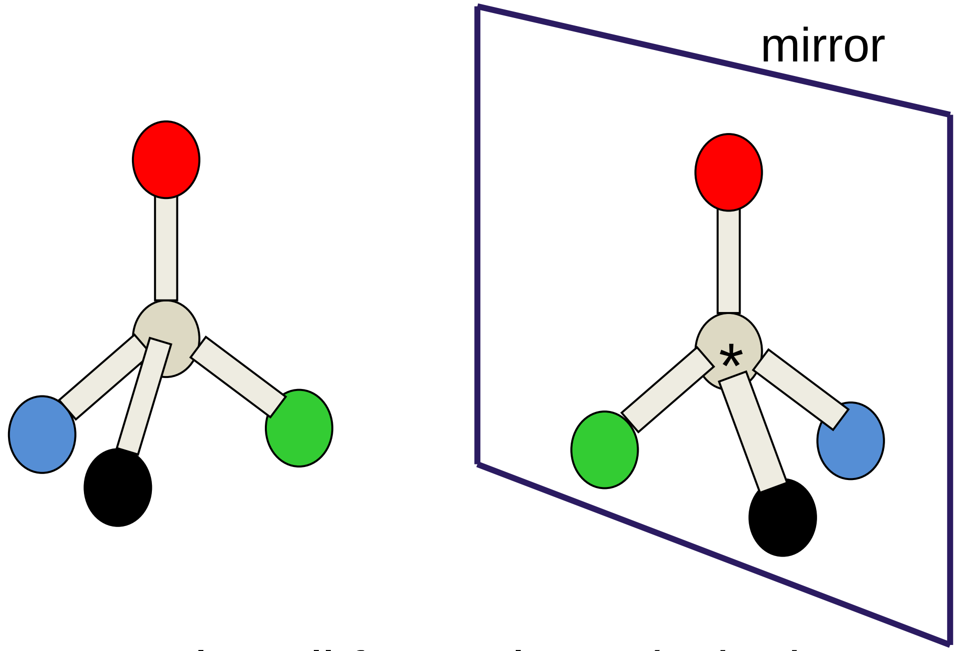


The arrangement of groups is called configuration.
Enantiomers have opposite configurations.

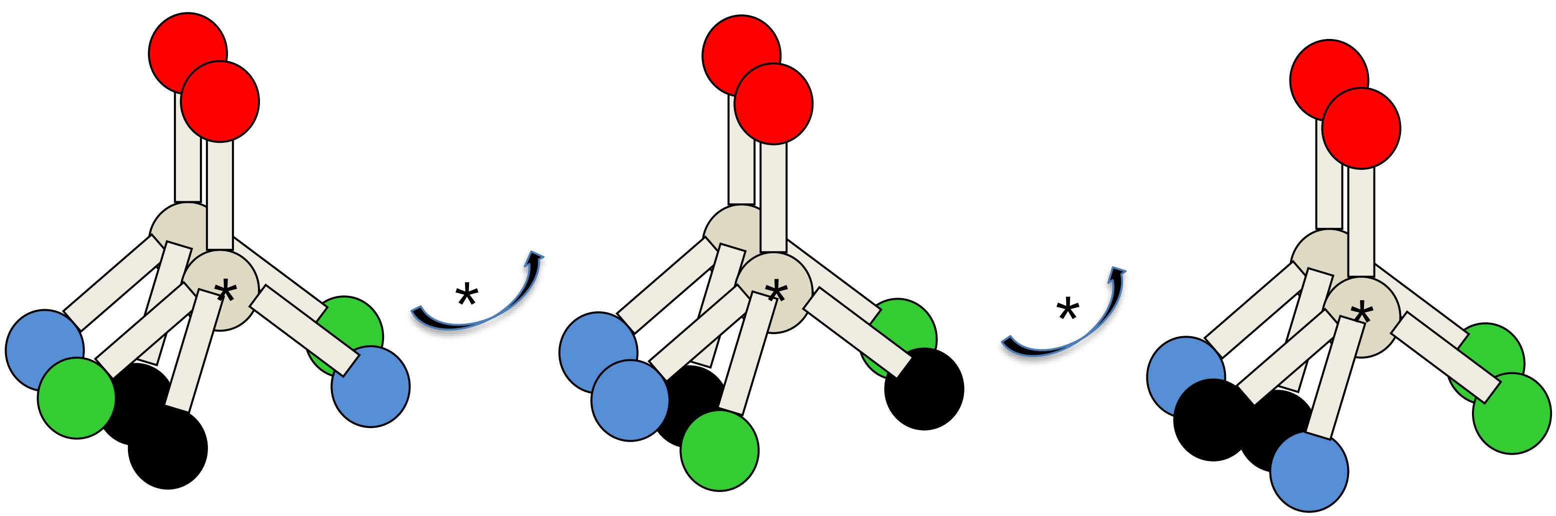
Any molecule with a plane of symmetry (i.e. two or more substituents on carbon are the same) is called achiral

Note: this is a challenging concept but you will see more on this topic next semester

Enantiomers: Non-superimposable Mirror Images



You cannot overlap all four colours (substituents on carbon)

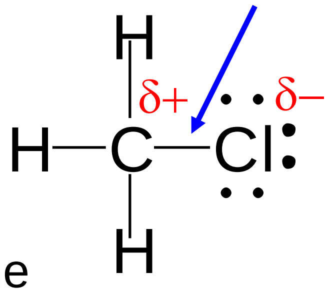


Note: this is a challenging concept but you will see more on this topic next semester

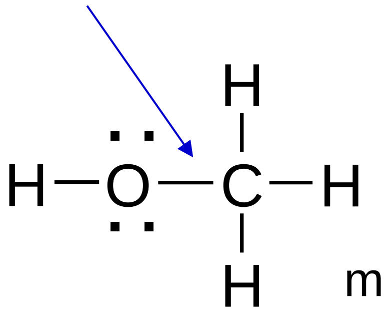
Covalent Bonding (reminder from previous lecture)

Polar covalent bond:
a covalent bond where electron pair is not shared equally between the atoms

Polar Covalent Bond



chloromethane



methanol

Electronegativity values
C = 2.5
Cl = 3.1

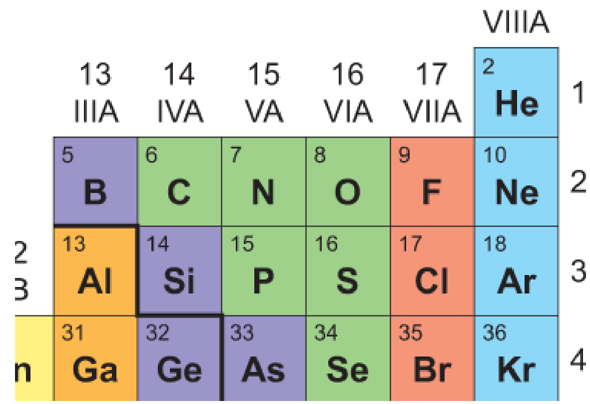
Electronegativity values
C = 2.5
O = 3.5

Electronegativity determines bond polarization
(unequal sharing of electrons in covalent bond).

Notes: C (2.5) and H (2.2) have very close electronegativity values.

Covalent Bonding (reminder from previous lecture)

From left to right within a given period in periodic table, the elements become *more* electronegative, owing to increasing charge on the nucleus;
From top to bottom of the table within a given group, the elements become *less* electronegative because the valence electrons are shielded from the nucleus by an increasing number of inner-shell electrons.



Biologically relevant examples:

$\overset{\delta+}{C}-\overset{\delta-}{N}$ $\overset{\delta+}{C}-\overset{\delta-}{O}$ $\overset{\delta+}{H}-\overset{\delta-}{O}$ $\overset{\delta+}{C}-\overset{\delta-}{Cl}$ $\overset{\delta+}{C}-\overset{\delta-}{F}$

δ+ is partial positive charge; δ - is partial negative charge

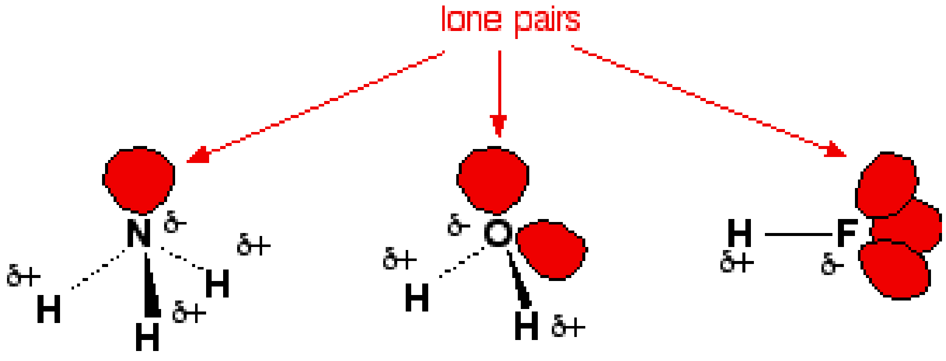
Hydrogen Bonds

Hydrogen bond

Interaction between hydrogen atoms bonded to a highly electronegative atom (O, N, F)

and the non-bonding electron pair (lone pair) on another highly electronegative atom

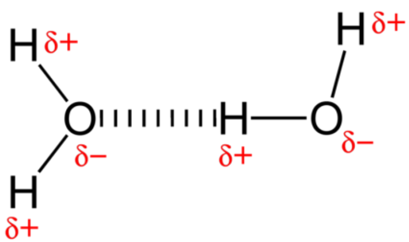
Examples of molecules capable of hydrogen bonding



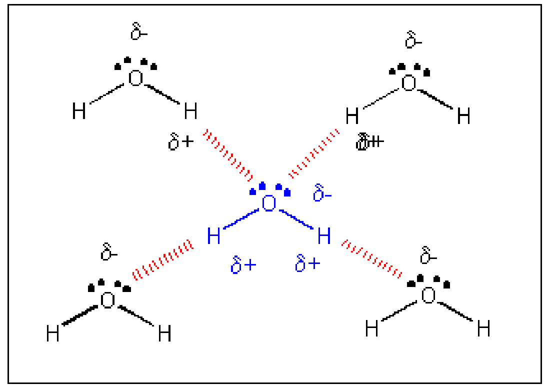
$\ddot{N}H_3$ $H_2\ddot{O}:$ $H\underset{\cdot\cdot}{\ddot{F}}:$

Hydrogen Bonding in Water and Alcohols

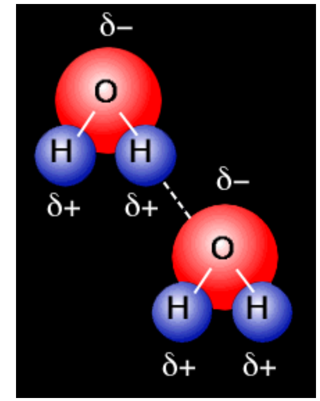
(can act as both H-donor and H-acceptor)



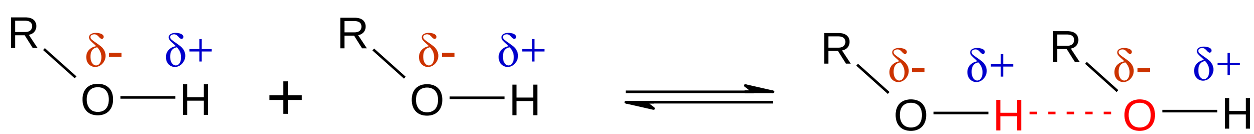
attraction of opposite partial charges



network of hydrogen bonds



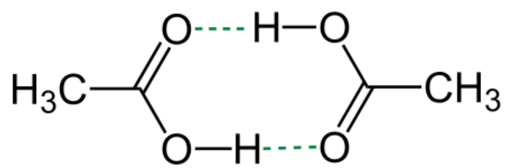
Force of attraction between molecules; Increase melting and boiling points



two separate alcohol molecules

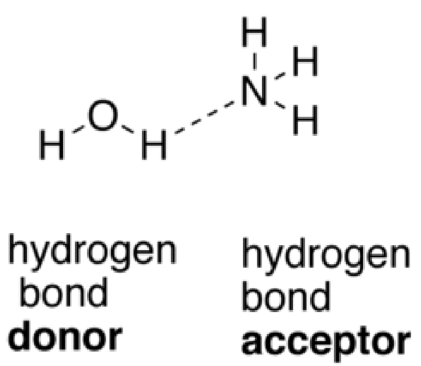
a hydrogen bond

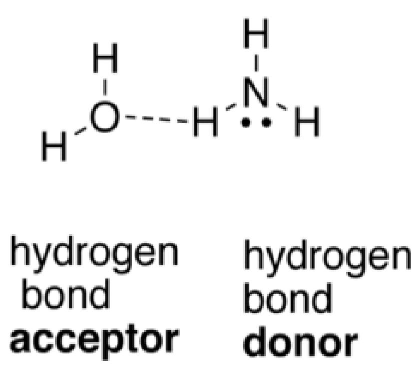
Hydrogen Bonding in Carboxylic acids

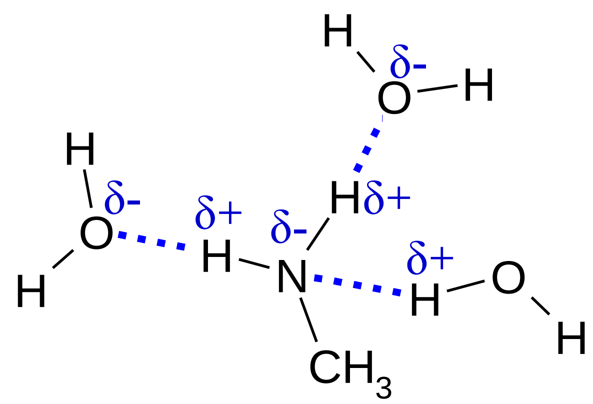


Head to head dimer formed (gives rise to increased boiling point)

Hydrogen bonds between different compounds







Methylamine in water

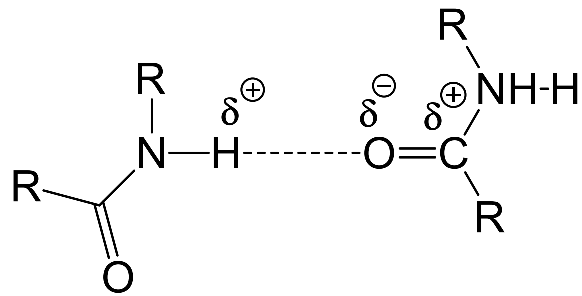
For instance, alcohols and amines can readily form H bonding with water

This accounts for the high miscibility of amines and alcohols with water

Hydrogen Bonds in Proteins

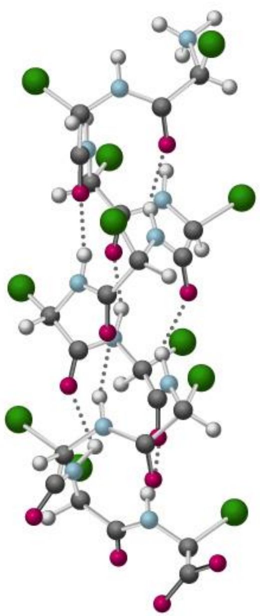
between -N-H and -C=O

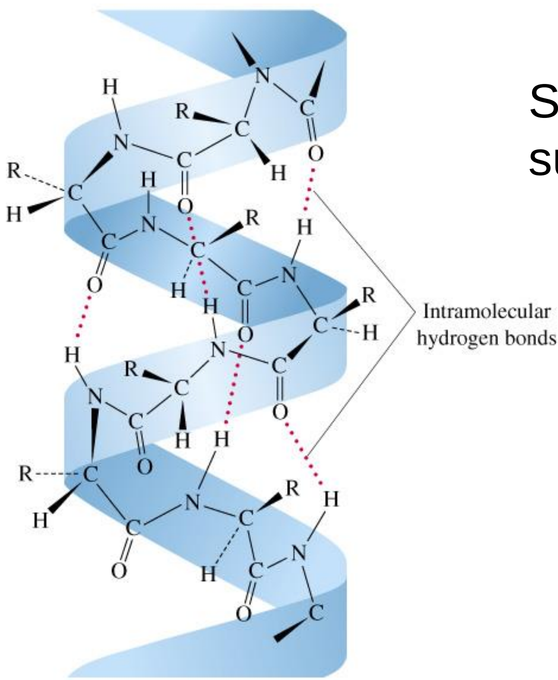
The force of attraction between the partial positive charge on the hydrogen (of the NH) and the partial negative charge on the oxygen of the carbonyl.



amide bond covalently links each amino acid

α-helix



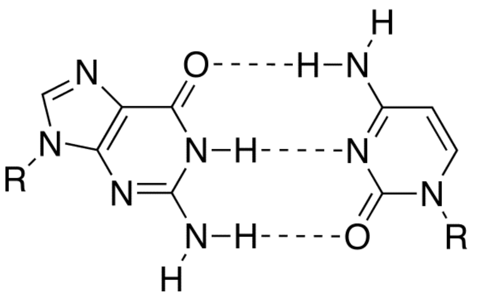


(b)

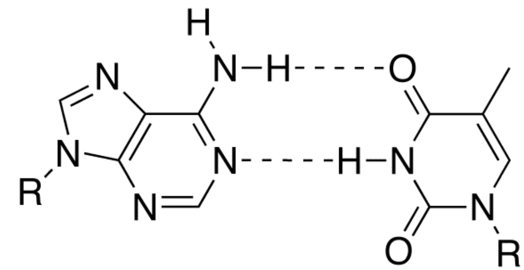
Stabilises secondary protein structures such as α-helix and β-pleated sheets

Hydrogen Bonds between DNA Base Pairs

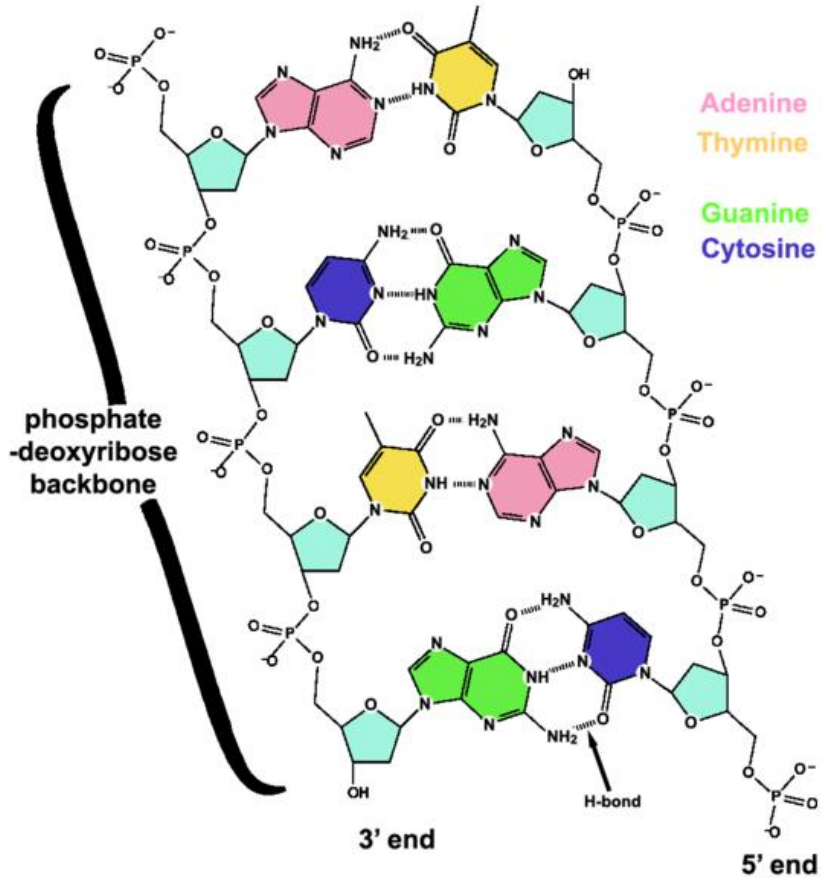
between -N-H and -C=O *or* -C=N-



Guanine Cytosine

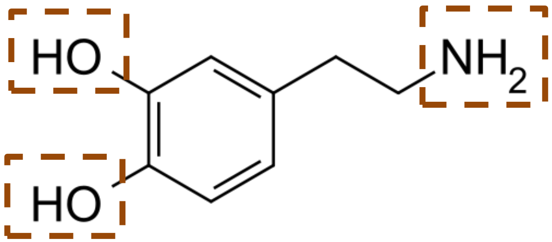


Adenine Thymine

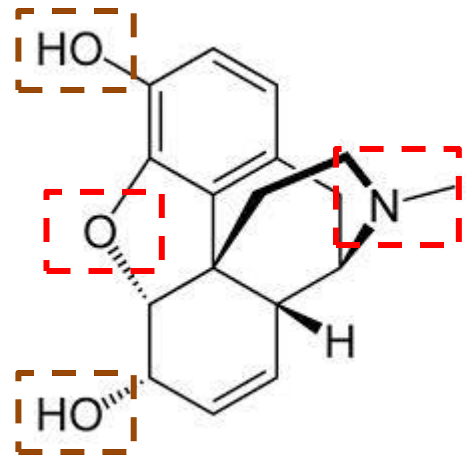


Hydrogen Bonding Sites in CNS Active Compounds

Dopamine
neurotransmitter



Morphine
opiate analgesic drug



hydrogen bond **donor** | hydrogen bond **acceptor** | hydrogen bond **acceptor** | hydrogen bond **donor**

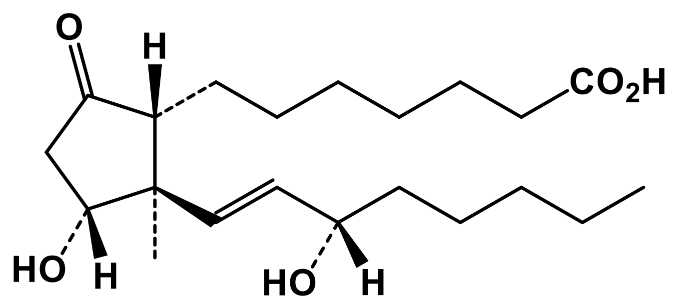
hydrogen bond acceptor

hydrogen bond donor and/or acceptor

hydrogen bond donor

Practice Example

The structure of prostaglandin E_1 is given below



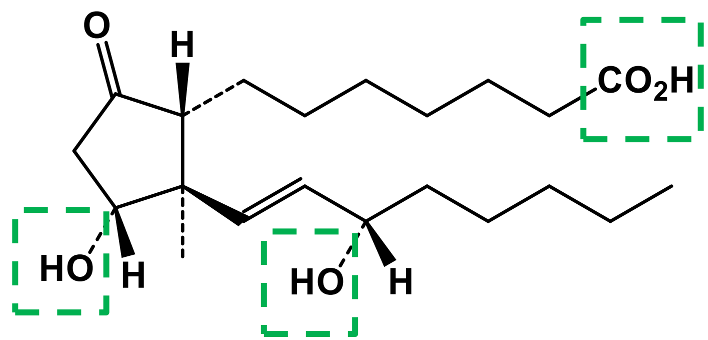
a) Identify all hydrogen bond donor sites

b) Identify all hydrogen bond acceptor sites

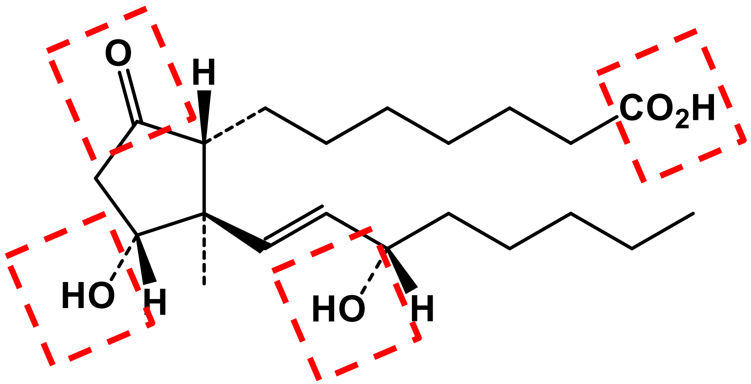
c) Identify any stereogenic centre(s) in the molecule

Practice Example

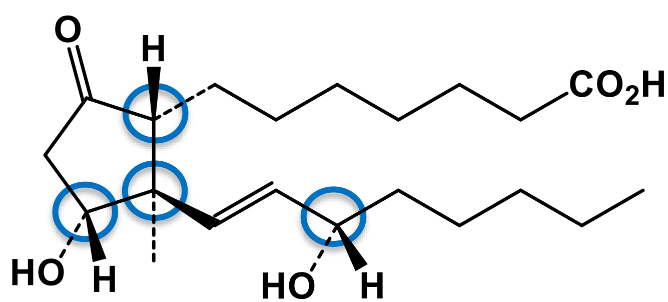
Hydrogen bond donors



Hydrogen bond acceptors



Stereogenic centres



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