Second Semester (2020-2021)

Pharmaceutical Chemistry I

Topic 1

Physicochemical Properties in Relation to Biological Activities

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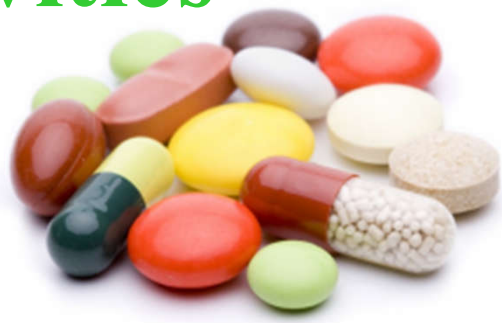
Pharmaceutical Chemistry and Drug Control



مصادر المواد الدوائية وطرق اكتشافها

1. Natural source
2. Synthetic source

A. Primitive Medicine; Folklore, witchcraft, etc.

B. Screening of Natural Products

C. Happy Chance (Serendipity)

D. Rational Drug Design (SAR)

Rational drug design is a more focused approach that uses greater knowledge (structural information) about the drug receptor (targets) or one of its natural ligands as a basis to design, identify, or create drug "leads."

Testing is usually done with one or two models (e.g., specific receptor systems or enzymes) based on the therapeutic target.

The drug design component often involves molecular modeling and the use of quantitative structure–activity relationships (QSARs) to better define the physicochemical properties and the pharmacophoric groups that are essential for biologic activity.

The development of QSARs relies on the ability to examine multiple relationships between physical properties and biologic activities.

In classic QSAR, an equation defines biologic activity as a linear free-energy relationship between physicochemical and/or structural properties.

It permits evaluation of the nature of interaction forces between a drug and its biological target, as well as the ability to predict activity in molecules.

These approaches are better for the development of a lead compound into a drug candidate than for the discovery of a lead compound.

ما هي الكيمياء الصيدلانية وبماذا تهتم؟

- تخصص علمي يجمع بين الكيمياء والصيدلة
- تبحث في المواد الدوائية:

a) استخلاص Extraction المركبات الفعالة وعزلها Isolation

b) تحديد بنيتها الكيميائية العامة والفراغية Structure
واصطناعها في المختبر Synthesis

c) Identification, design, synthesis, and development of new drugs

d) قياس درجة ثباتها Stability وسرعة تخربها Degradation

e) وضع الطرق الخاصة لمعايرتها Assay وتحديد ذاتيتها Identification

MOLECULAR STRUCTURE AND BIOLOGIC ACTIVITY

- Molecular structure influences the biologic activity of chemical entities
- **Alterations in structure produce changes in biologic action.**

Structure activity relationship (SAR)

- The type of pharmacologic effect that the molecule possesses (i.e., SAR) is determined by:

1. The structure of a molecule
2. The composition of a molecule
3. Arrangement of functional groups

- Molecular structure and biological activity are correlated by *observing the results of systematic structural modification on defined biological endpoints.*
- Quantitative SARs (QSAR)as a special case of SARs (when relationships become quantified)

Physicochemical properties of drugs

1) Acid-Base Properties

الخواص الحمضية ـ القاعدية

2) Water Solubility of Drugs

الانحلالية المائية للأدوية

3) Stereochemistry

الكيمياء الفراغية

1 ACID-BASE PROPERTIES

- The human body is 70 to 75% water, which amounts to approximately 51 to 55 L of water for a 73-kg individual.
- For an average drug molecule with a molecular weight of 200 g/mol and a dose of 20 mg, this leads to a solution concentration of approximately 2×10^{-6} M (2 mM).
- When considering the solution behavior of a drug within the body, we are dealing with a dilute solution, for which the **Brönsted-Lowry acid–base theory** is most appropriate to explain and predict acid–base behavior.

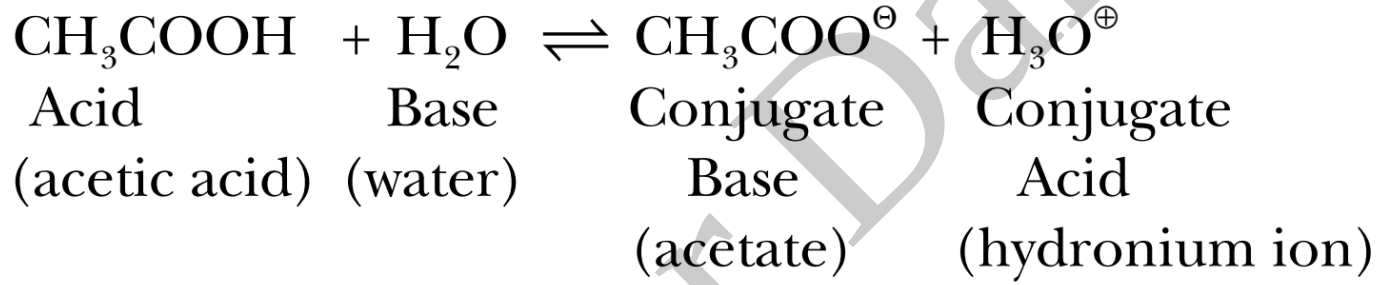
قاعدة مُرافقة + حمض مُرافق ⇌ حمض + قاعدة

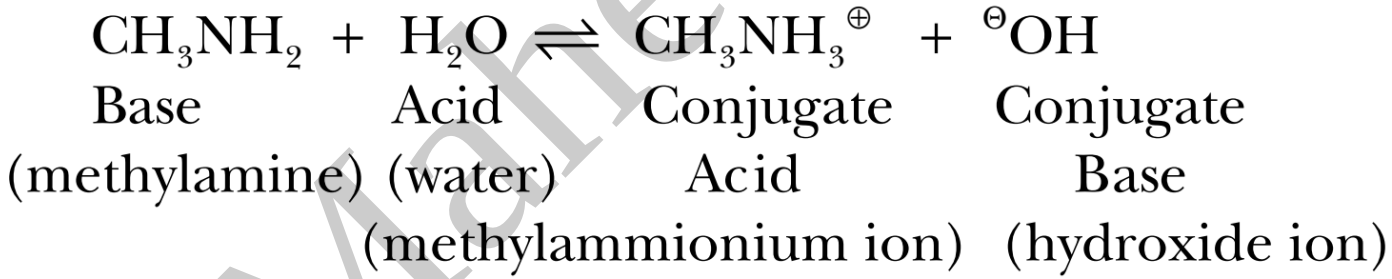
- This is a very important concept in medicinal chemistry, ***because the acid–base properties of drug molecules have a direct effect on absorption, excretion, and compatibility with other drugs in solution.***

- When an **acidic functional group** loses its proton (often referred to as having undergone "dissociation"), it is left with an extra electron and becomes negatively charged. This is the "ionized" form of the acid.

- When a **basic functional group** is converted to the corresponding conjugate acid, it too becomes ionized. The functional group becomes positively charged due to the extra proton.

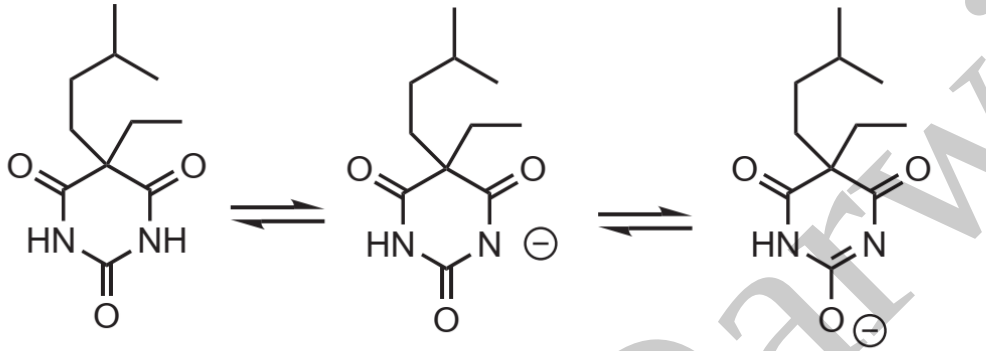
- Functional groups that cannot give up or accept a proton are considered to be "**neutral**"





An example

Calculation of percent ionization of **amobarbital**.



Acid form
pK_a 8.0

Conjugate base

Question: At a pH of 7.4, what is the percent ionization of amobarbital?

Answer: $8.0 = 7.4 + \log \frac{[acid]}{[base]}$

$0.6 = \log \frac{[acid]}{[base]}$

$10^{0.6} = \frac{[acid]}{[base]} = \frac{3.98}{1}$

$\%\ acid\ form = \frac{3.98 \times 100}{4.98} = 79.9\%$

2 WATER SOLUBILITY OF DRUGS

➢ Given that we are ~75% water, the solubility of a drug in water directly affects the route of administration, as well as its absorption, distribution, and elimination (ADME).

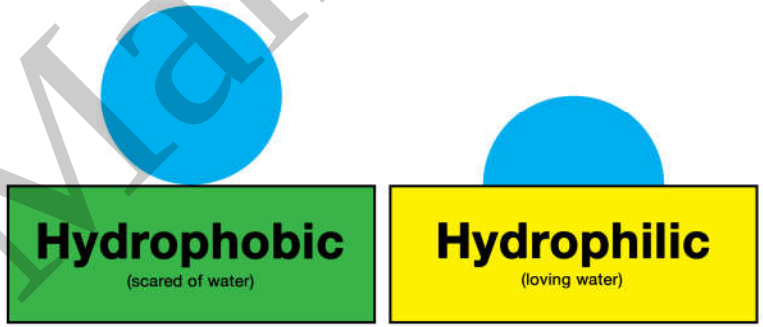
➢ The most important two key factors that influence this are:

- Hydrogen bonding: more H-bonds => ↑ solubility
- Ionization: dissociable ions => ↑ solubility

1- Hydrogen Bonds

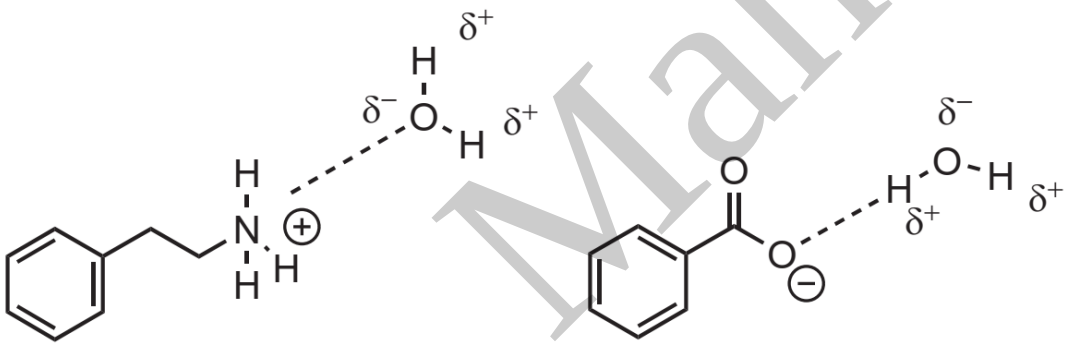
- Each functional group capable of **donating** or **accepting** a hydrogen bond contributes to the overall water solubility of the compound and increases the hydrophilic (water-loving) nature of the molecule.

- Conversely, functional groups that cannot form hydrogen bonds do not enhance hydrophilicity and will contribute to the hydrophobic (water-fearing) nature of the molecule.



2- Ionization

- In addition to the hydrogen-bonding capacity of a molecule, another type of interaction plays an important role in determining water solubility: the **ion–dipole interaction**.
- This type of interaction can occur with organic salts.
- Ion–dipole interactions occur between either a **cation** and the partially negatively charged atom found in a permanent dipole (e.g., the oxygen atom in water) or an **anion** and the partially positively charged atom found in a permanent dipole (e.g., the hydrogen atoms in

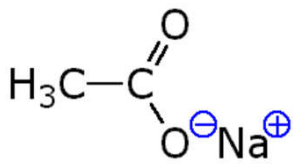


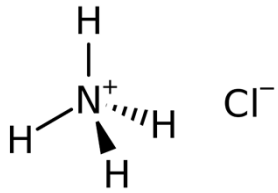
Examples of ion–dipole interactions.

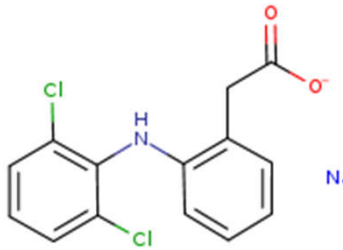
2- Ionization

Drugs and their salt forms

- **Organic salts** are composed of a drug molecule in its ionized form and an oppositely charged counterion.
- For example, the salt of a carboxylic acid is composed of the carboxylate anion (ionized form of the functional group) and a positively charged ion (e.g., Na+)
- The salt of a secondary amine is composed of the ammonium cation (ionized form of the functional group and a negatively charged ion; e.g., Cl−).





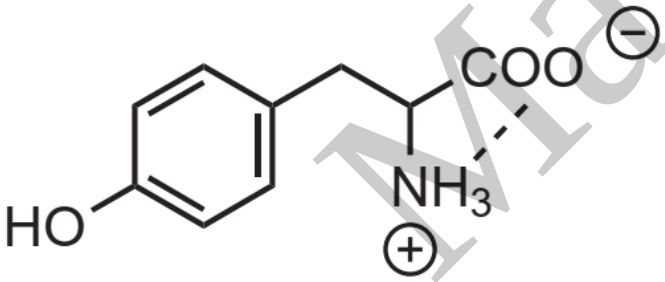


diclofenac sodium

Another example

Tyrosine

- Because of the presence of three very polar functional groups (two of them being ionizable), one would expect tyrosine to be very soluble in water, yet its solubility is only 0.45 g/1,000 mL.
- The basic alkylamine (pKa 9.1 for the conjugate acid) and the carboxylic acid (pKa 2.2) are both ionized at physiologic pH, and a zwitterionic molecule results.
- These two charged groups are **sufficiently close** that a strong ion–ion interaction occurs, thereby keeping each group from participating in ~~ion–dipole interactions~~ with surrounding water molecules.
- This lack of interaction between the ions and the dipoles found in water results in a molecule that is very water insoluble



Zwitterionic form of tyrosine showing ion–ion bond

Predicting Water Solubility

- Empirical Approach
- Analytical Approach

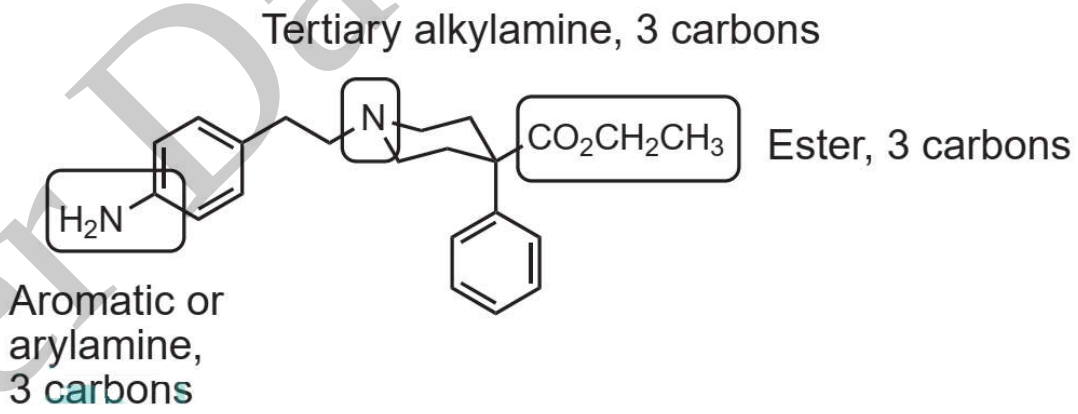
1- Empirical Approach النهج التجريبي

- Based on carbon-solubilizing potential of several organic functional groups.
- If solubilizing potential of the functional groups **exceeds** the total number of carbon atoms present, then the molecule is considered to be **water soluble**. Otherwise, its **water insoluble**.

  - Functional groups that can interact either through ***intramolecular hydrogen*** or ***ion-ion interactions*** will decrease the solubilizing potential of each group.

Examples

- Anileridine (أنيليريدين) is an opioid analgesic that contains three functional groups that contribute to water solubility:
  - *A. an aromatic amine (very weak base)*
  - *B. a tertiary alkylamine (weak base)*
  - *C. an ester (neutral).*
- There are a total of **22 carbon** atoms in the molecule and a solubilizing potential from the three functional groups of **nine carbon atoms**.
- Since the solubilizing potential of the functional groups is less than the total number of carbons that are present, it is predicted that anileridine is insoluble in water.
- **Practically:** The solubility of anileridine is reported in the U.S. Pharmacopeia (USP) as 1 g/10,000 mL, or 0.01%.
- **To solve the problem:** consider the **hydrochloride salt of anileridine**.



Predicting Water Solubility

Analytical Approach النهج التحليلي

- The alternative approach for predicting water solubility utilizes the "logP" of molecules
- logP is a measure of lipophilicity (hydrophobic) properties of a molecule
- It is determined by measuring the "**PARTITION COEFFICIENT (P)**" between water and octanol for a given molecule (***i.e. the solubility of the compound in octanol versus the solubility of the compound in water)***

$$P = C_{oct} / C_{water}$$

Predicting Water Solubility

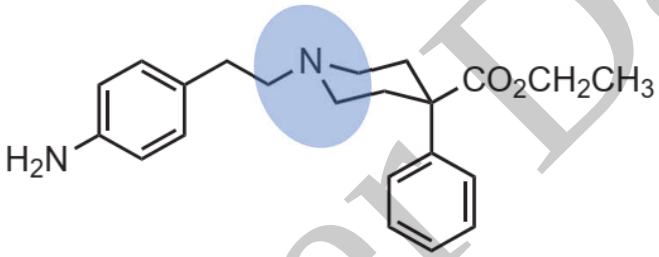
Analytical Approach

- Log of the partition coefficient for a molecule predicts **Water Solubility**
- LogP is the sum of the hydrophobic and hydrophilic characteristics of the organic functional groups making up the structure of the molecule
- It is calculated by adding the contributions from each functional group in the molecule
- A hydrophobic substituent constant π has been assigned to most organic functional groups, such that LogP = ∑ π (fragments)
- *Water solubility as defined by the USP is solubility greater than 3.3%, which equates to an approximate logP of +0.5*
- LogP values < than +0.5 are considered to be water soluble
- LogP values > than +0.5 are considered to be water insoluble

Examples

Anileridine

- This compound has a total of 22 carbon atoms, some aliphatic and some aromatic.
- We need to distinguish between the **aliphatic** and **aromatic** carbon atoms because the delocalized p orbitals for the sp2 hybridized aromatic carbon atoms make them **more polar** than aliphatic carbons.
- The compound also contains one tertiary alkylamine, one aromatic or aryl amine, and one ester.
- Evaluation of esters and amides requires that the oxygen, nitrogen, and ester/amide carbon atoms are counted in this p value.
- The remaining aliphatic carbons are then counted.



Fragments	π
1 primary alkylamine	-1.23
1 teriary alkylamine	-0.30
9 aliphatic carbons	+4.5
2 phenyl rings	+4.30
1 ester	-0.27
logP	+7.0

TABLE 2.6 Hydrophilic-lipophilic Values (πV) for Organic Fragments (10)

Functional Group	π value (aliphatic)	π value (aromatic)
H		0.00
Alkane	0.50	0.56 (CH_3); 1.02 (CH_2CH_3)
Alkene		0.82
C_6H_5 (phenyl)	2.15	1.96
Br, Cl, F, I	0.60; 0.39; −0.17; 1.00	0.86; 0.71; 0.14; 1.12
NO_2	−0.85	−0.28
NH_2 (primary amine)	−1.19	−1.23
NHR (secondary amine)	−0.67	0.47
NR_2 (tertiary amine)	−0.30	0.18
-NHC=OR (amide)	−0.97	
SC_6H_5	2.32	
OH	−1.12	−0.67
OCH_3		−0.02
-OC=OR (ester)	−0.27	−0.64
CHO (aldehyde)		−0.65
C=OCH_3 (ketone)		−0.55
CO_2H		−0.32
SO_2NH_2 (sulfonamide)		−1.82

STEREOCHEMISTRY AND DRUG ACTION

3 STEREOCHEMISTRY AND DRUG ACTION

➢ The physicochemical properties of a drug are not only influenced by which functional groups are present, but also by the spatial arrangement of groups.

➢The spatial arrangement of groups is especially important when dealing with biological systems, since receptors are susceptible to the shape of a molecule.

➢If the crucial functional groups do not occupy the proper spatial region, so the desired pharmacological effect will not be possible

➢However, if these functional groups are in the proper three dimensional orientation the drug can produce a strong interaction with the receptor

1- Optical isomerism التصاوغ البصري

- Approximately one in every four drugs currently on the market is some type of isomeric mixture
- For many of these drugs, the biologic activity may only reside in one isomer (or at least predominate in one isomer)

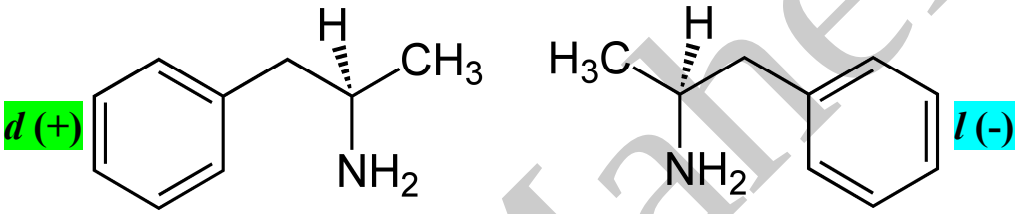
- The majority of these isomeric mixtures are termed "racemic mixtures" (or "racemates") المزيج الراسيمي
- A racemic mixture is comprised of equal amounts of both possible drug enantiomers

- When enantiomers are introduced into an asymmetric, or chiral, environment, such as the human body, ***they display different physicochemical properties***

- This can lead to significant differences in their pharmacokinetic and pharmacodynamic behavior, resulting in adverse side effects or toxicity

Enantiomers التصاوغ المرآتي

- Enantiomers were distinguished by their ability to rotate the plane of polarized light.
- Isomers that rotate the plane of polarized light to the right, or in a clockwise direction, were designated as dextrorotatory, indicated by a (+)- sign before the chemical name [e.g., (+)-amphetamine or dextroamphetamine].
- The opposite designation, levorotatory or (−)-, was assigned to molecules that rotate the plane of polarized light to the left, or in a counterclockwise direction.



- The letters *d*- and *l* were formerly used to indicate (+)- and (−)-, respectively.
- A racemate (racemic mixture)—that is, a 1:1 mixture of enantiomers—is indicated by placement of a (±)- before the compound name.

Stereochemistry and Biologic Activity

- Whilst enantiomers have identical physical properties, they can have very different biological properties (e.g. (+)-asparagine is sweet, whilst (–)-aspargine is tasteless).
- This was one of the earliest observation by in 1886

Easson-Stedman hypothesis

- Easson-Stedman hypothesis states that the more potent enantiomer must be involved in a minimum of three interactions with the receptor and that the less potent enantiomer only interacts with two sites.
- This difference is due to the **asymmetry** of receptor – ligand interactions

Selective Reactivity

The differences in vasopressor activity of R-(−)-epinephrine, S-(+)-epinephrine, and the achiral N-methyldopamine

- With **R-(−)-epinephrine**, the three points of interaction with the receptor site are the substituted aromatic ring, b-hydroxyl group, and the protonated secondary ammonium group. All three functional groups interact with their complementary sites on the receptor surface, resulting in receptor stimulation (in this case).
- With **S-(+)-epinephrine**, only two interactions are possible (the protonated secondary ammonium and the substituted aromatic ring). The b-hydroxyl group is located in the wrong place in space and, therefore, cannot interact properly with the receptor.
- **N-methyldopamine** can achieve the same interactions with the receptor as S-(+)-epinephrine; therefore, it is not surprising that its vasopressor response is the same as that of S-(+)-epinephrine and less than that of R-(−)-epinephrine.

Diastereomer التصاوغ الفراغي

- Molecules that are nonsuperimposable غير قابلة للتراكب , non–mirror images.
- This type of isomer can result from the presence of more than one chiral center in the molecule, double bonds, or ring systems.
- These isomers have different physicochemical properties, and as a result, it is possible that they can have differences in biologic activity.
- Prioritize atoms around a chiral center, based upon the atomic weight of the atom
- Once you have assigned priority from 1 (= highest) to 4 (= lowest), then "look from the chiral center towards the lowest priority and count from 1 to 3
  - If you count clockwise it is "*R*" ("Rectus" → Latin= "right")
  - If you count anticlockwise it is "*S*" ("Sinister" → Latin= "left")

Diastereomers & Biological Activity

- Molecules that contain more than one chiral center probably are the most common type of drug-based diastereoisomers.
- When a molecule contains two chiral centers, there can be as many as four possible stereoisomers consisting of two sets of enantiomeric pairs.
- When considering an enantiomeric pair of molecules, there is inversion of both chiral centers.
- In diastereomers, there is inversion of only one chiral center.

2- Geometric isomers التصاوغ الهندسي

➢Geometrical isomerism (= restricted rotation)

➢Restricted bond rotation caused by carbon–carbon double bonds (alkenes or olefins) and similar systems, such as imines (C =N), can produce stereoisomers.

➢In this situation, substituents can be oriented on the same side or on opposite sides of the double bond.

Z- comes from German "Zusammen" (= together)

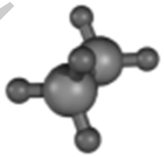
E- comes from German "Entgegen" (= opposite)

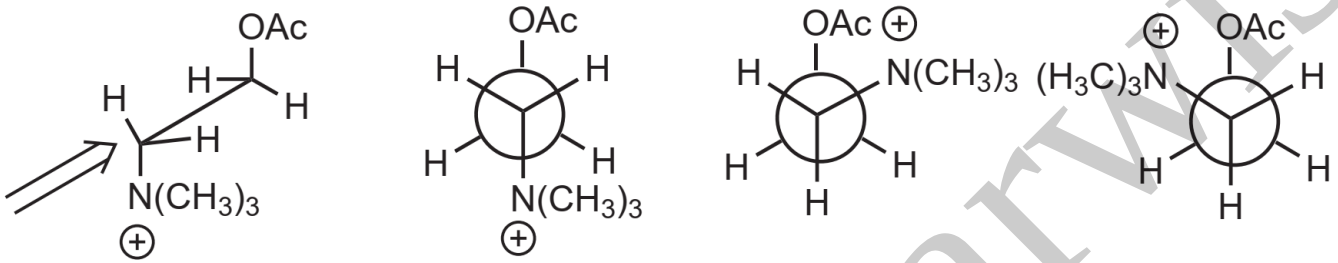
- Sometimes *E*- and *Z*- becomes difficult to determine when it is less obvious which substituents are the highest priority

▯ The key here is to assign the two groups on each side of the double bond, and then "simply" see if the two highest priority groups are on the same side or opposite sides

3- Conformational isomers التصاوغ الشكلي

- Conformational isomerism takes place via rotation about one or more single bonds.
- Such bond rotation results in nonidentical spatial arrangement of atoms in a molecule.
- This type of isomerism does not require much energy because no bonds are broken.
- In the conversion of one enantiomer into another (or diastereomer) bonds are broken, which requires significantly more energy.
- The neurotransmitter acetylcholine can be used to demonstrate the concept of conformational isomers.





anti or staggered conformer

gauche or skew conformers

للاطلاع

•Each single bond within the acetylcholine molecule is capable of undergoing rotation, and at room temperature, such rotations readily occur.

•Rotation around single bonds Cα–Cβ of acetylcholine produces the greatest spatial rearrangement of atoms compared to rotation around any other bond.

•Since the atoms at the end of some of the bonds within acetylcholine are identical, rotation about several of these bonds produces redundant structures when viewed along the Cα–Cβ bond, and acetylcholine can be depicted in the sawhorse or Newman projections

•When the ester and trimethylammonium groups are 180° apart, the molecule is said to be in the anti, or staggered, conformation (or conformer or rotamer). This conformation allows maximum separation of the functional groups and is the most stable conformation energetically.

•It is possible that other conformations are more stable if factors other than steric interactions are considered (e.g., intramolecular hydrogen bonds).

•Rotation of one end of the Cα–Cβ bond by 120° or 240° results in the two gauche, or skew, conformations.

•These are less stable than the anti conformer, although some studies suggest that an electrostatic attraction between the electron-poor trimethylammonium and electron-rich ester oxygen atom stabilizes this conformation.

•Rotation by 60°, 180°, and 240° produces the least stable conformations in which all of the atoms overlap, what are referred to as eclipsed conformations.

Drugs & Drug Targets

Interactions

Drugs & Drug Targets

- Some drugs react with the binding site and become permanently attached via a Covalent Bond that has a bond strength of 200–400 kJ/mol.
- Most drugs interact through weaker forms of interaction known as Intermolecular Bonds.
- Intermolecular Bonds include:

1. Ionic Bonds
2. Hydrogen Bonds
3. Van Der Waals Interactions
4. Dipole–dipole Interactions
5. Ion-dipole interaction
6. Hydrophobic Interactions

Drugs & Drug Targets

- ✓ The Functional groups of the drug which can be important in forming intermolecular bonds with the target binding site, are called Binding Groups.
- ✓ The specific regions of the target binding site where the binding takes place are known as Binding Regions.
- ✓ The study of how drugs interact with their targets through binding interactions and produce a pharmacological effect is known as Pharmacodynamics.

Intermolecular bonding interactions

1. Electrostatic or Ionic bonds:

An ionic or electrostatic bond is the strongest of the intermolecular bonds (20–40 kJ mol^{-1}) and takes place between groups that have opposite charges, such as a carboxylate ion and an aminium ion

Intermolecular bonding interactions

2. Hydrogen bond:

A hydrogen bond takes place between an electron-rich heteroatom (O or N) and an electron-deficient hydrogen.

- ✓ The strength of a hydrogen bond can vary widely varying from 16 to 60 kJ mol^{-1}
- ✓ The functional group that provides the hydrogen for the hydrogen bond known as a Hydrogen Bond Donor HBD.
- ✓ The functional group that provides the electron-rich atom to receive the hydrogen bond is known as a Hydrogen Bond Acceptor HBA.

Intermolecular bonding interactions

3. Van der Waals interactions

Van der Waals interactions involve interactions between hydrophobic regions of different molecules, such as aliphatic substituents or the overall carbon skeleton.

Intermolecular bonding interactions

4. Dipole-dipole interactions

- ✓ Many molecules have a permanent dipole moment resulting from the different electronegativities of the atoms and functional groups present
- ✓ For example, a ketone has a dipole moment due to the different electronegativities of the carbon and oxygen making up the carbonyl bond.
- ✓ The binding site also contains functional groups, so it is inevitable that it too will have various local dipole moments

5. Ion-dipole interactions

- ✓ An ion-dipole interaction is where a charged or ionic group in one molecule interacts with a dipole in a second molecule.

Intermolecular bonding interactions

6. Hydrophobic interactions

- ✓ It is not possible for water to solvate the non-polar or hydrophobic regions of a drug or its target binding site.
- ✓ Instead, the surrounding water molecules form stronger than-usual interactions with each other, resulting in a more ordered layer of water next to the non-polar surface

لتقليل مساحة الاتصال بين الماء والجزيئات غير القطبية

- ✓ When the hydrophobic region of a drug interacts with a hydrophobic region of a binding site, these water molecules are freed and become less ordered
- ✓ This leads to gain in binding energy