Jelena Dodonova

Bioorganic chemistry

(Set of lectures)

Vilnius
2016

Set of lectures was approved and recommended for publishing as e-edition
by Council of the Faculty of Chemistry of Vilnius University on
April 8, 2016
(Protocol Nr. 7)

Reviewer: prof. habil. dr. Sigitas Tumkevičius

Introduction

This set of lectures on bioorganic chemistry intend for non-chemistry students, mainly those entering health sciences and related fields, such as medicine, dentistry. It also can be useful for students in environmental studies.

Most students who take such courses consider bioorganic chemistry to be the most relevant part of the course of study. However, an understanding of bioorganic chemistry depends upon a sound background in organic chemistry. These lectures present organic chemistry in sufficient depth and breadth to make the bioorganic chemistry understandable.

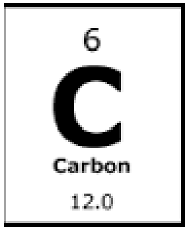
The organic part of the set starts with basics of organic chemistry, such as classification of organic compounds, representation of organic molecules, nomenclature and hybridization, then moves to all classes of organic compounds, covering their physical and chemical properties, application and the most important examples. The bioorganic part allows students immediately apply the organic knowledge to carbohydrates and other biologically important compounds. This part ends with a chapter on DNA and RNA and a discussion of the chemistry of life.

Content

Bioorganic chemistry is a chemistry which integrates organic chemistry and biochemistry.

Bioorganic chemistry involves the study of biological processes using chemical methods. Organic chemistry methods are used to synthesize biological molecules and to examine their structure, to investigate biochemical reactions.

Organic chemistry is the study of *the compounds of carbon*.



The compounds of carbon are the central substances of which all living things on this planet are made.

Food

clothes

Pharmaceuticals

DNA: the giant molecules that contain all genetic information for a given species.

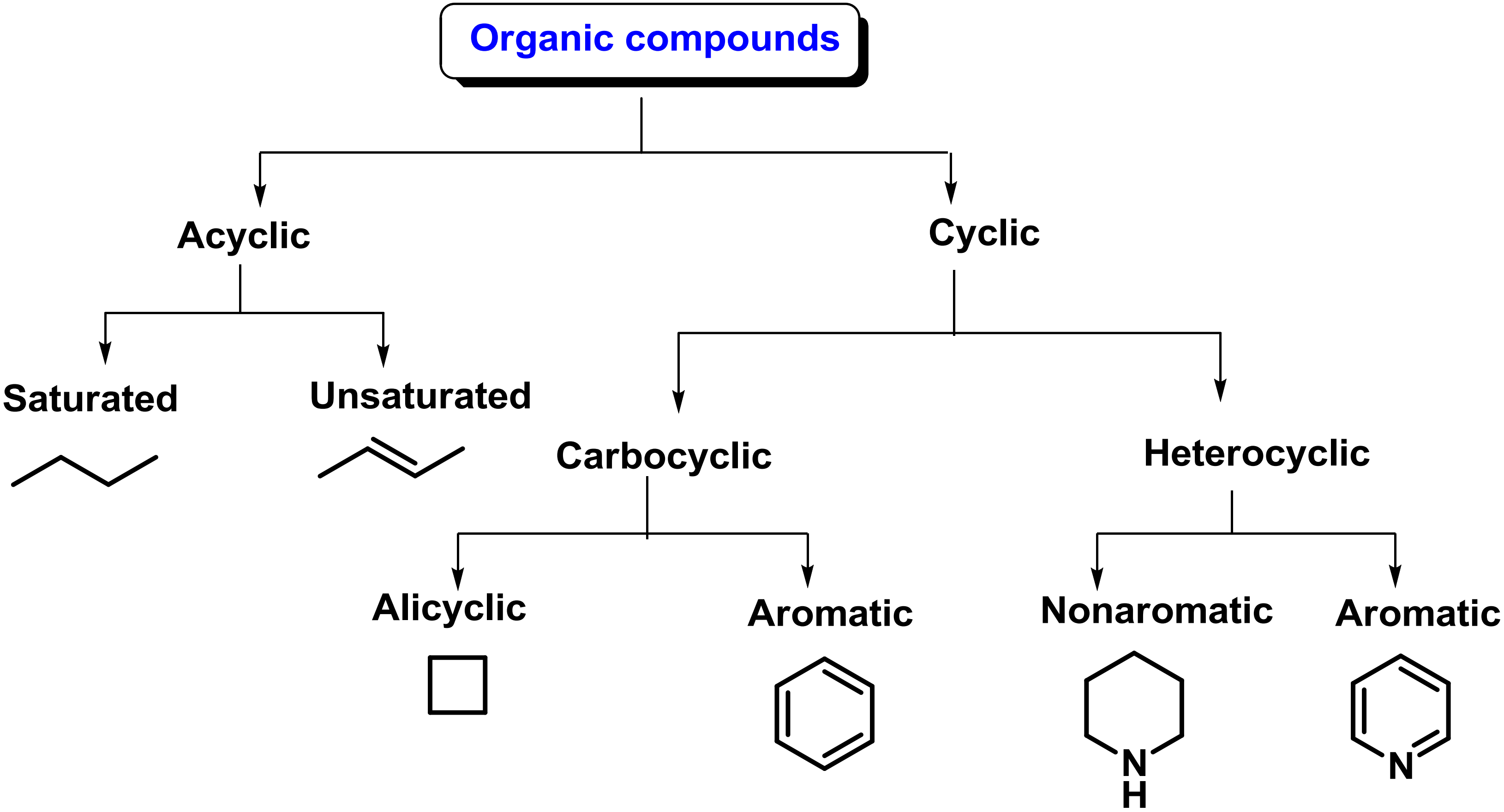
proteins: blood, muscle, and skin.

enzymes: catalyze the reactions that occur in our bodies.

Compounds which furnish the energy that sustains life.

Classification of organic compounds

1. According to the character of chain of carbon atoms:



Organic compounds

Acyclic

Saturated

Unsaturated

Cyclic

Carbocyclic

Heterocyclic

Alicyclic

Aromatic

Nonaromatic

Aromatic

2. According to the functional group:

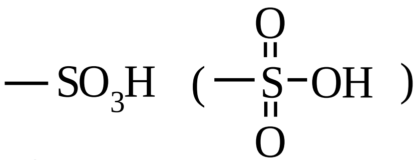
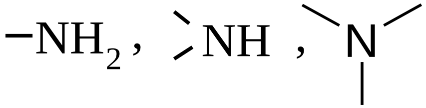
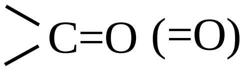
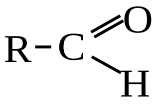
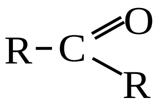
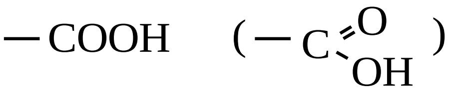
All organic compounds are grouped into classes based on characteristic features called *functional groups*.

A functional group is an atom or a group of atoms within a molecule that serves as a site of chemical reactivity.

The most important functional groups with the key structural elements and a simple example.

Functional group and its name	**General structure and name**	**Example**
-F, -Cl, -Br, -I (-Hal) **Halogeno**	R-Hal Halogenides	CH_3CH_2-Cl
-OH **Hydroxy group**	R-OH alcohols Ar-OH Phenols	CH_3-OH C_6H_5-OH
-OR **Alkoxy group**	R-O-R Ethers	C_2H_5-O-C_2H_5
-SH **Mercapto group**	R-SH Thiols	CH_3-SH
-SR **Alkylthio group**	R-S-R Sulfides	CH_3-S-CH_3

Table Continued

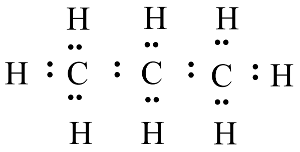
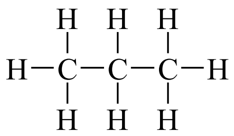
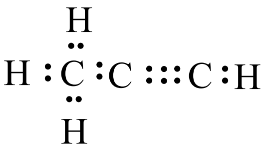
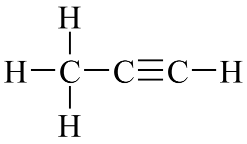
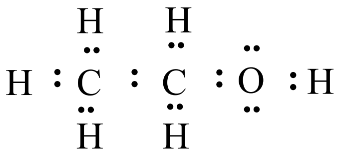
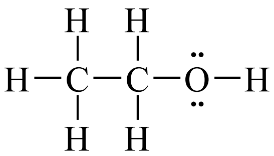
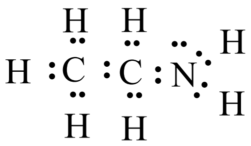
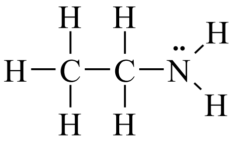
Functional group and its name	General structure and name	Example
 $-SO_3H \; (-S(=O)(=O)-OH)$ **Sulfo group**	$R\text{-}SO_3H$ Sulfonic acids	$C_6H_5\text{-}SO_3H$
 $-NH_2$, $>NH$, $>N-$ **Amino group**	RNH_2, R_2NH, R_3N Amines	CH_3NH_2, $(CH_3)_2NH$, $(CH_3)_3N$
$-NO_2$ **Nitro group**	$R\text{-}NO_2$ Nitro compounds	$CH_3CH_2\text{-}NO_2$
 $>C=O$ (=O) **Carbonyl group (oxo group)**	 (RCHO) Aldehydes  (RCOR) Ketones	$CH_3\text{-}CHO$ CH_3COCH_3
 $-COOH \; (-C(=O)OH)$ **Carboxylic group**	$R\text{-}COOH$ Carboxylic Acids	$CH_3\text{-}COOH$

Representation of Structural Formulas

Show the bonding between atoms of a molecule and the lone pairs of electrons that may exist in the molecule

Shared pairs of electrons are shown by line, not by dots

Uses grouping of atoms in which central atoms and the atoms connected to them are written as a group to convey molecular structural information

Compound	Molecular formula (Brutto)	Dot formula (Lewis)	Dash formula	Condensed formula
Propane	C_3H_8			$CH_3CH_2CH_3$
Propyne	C_3H_4			$CH_3C{\equiv}CH$
Ethanol	C_2H_6O			CH_3CH_2OH or C_2H_5OH
Ethanamine (ethylamine)	C_2H_7N			$CH_3CH_2NH_2$

Bond-Line Formulas (shorthand structure)

Rules for shorthand structure:

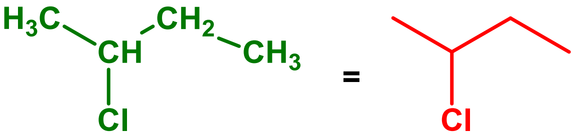
1) Carbon atoms are not usually shown ⇒ intersections, end of each line

2) Hydrogen atoms bonded to C are not shown. They are shown in cases when they are attached to heteroatom

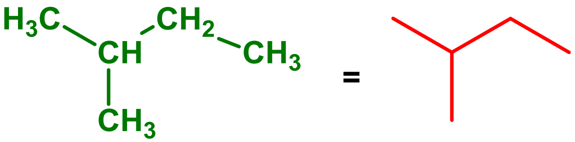
3) All atoms other than C and H are indicated.

condensed **semi-dash** **Bond-line formulas**

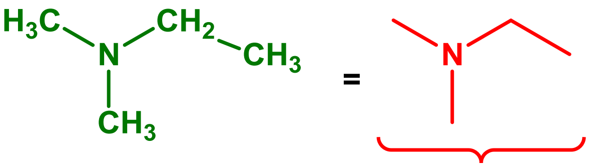
$CH_3CHClCH_2CH_3$ =

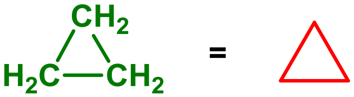


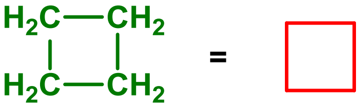
$CH_3CH(CH_3)CH_2CH_3$ =

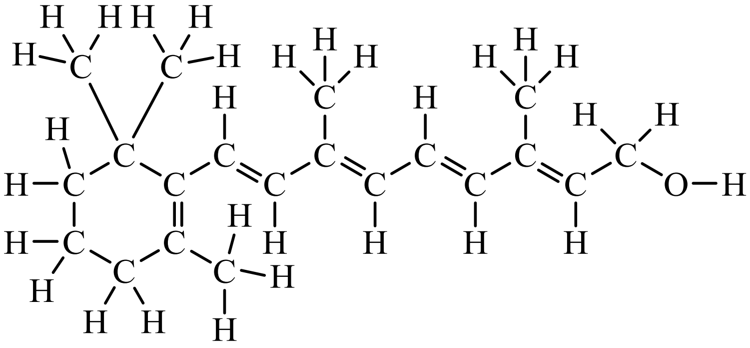


$(CH_3)_2NCH_2CH_3$ =

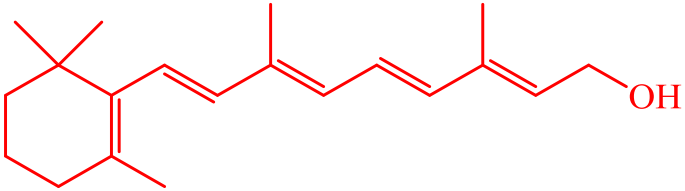




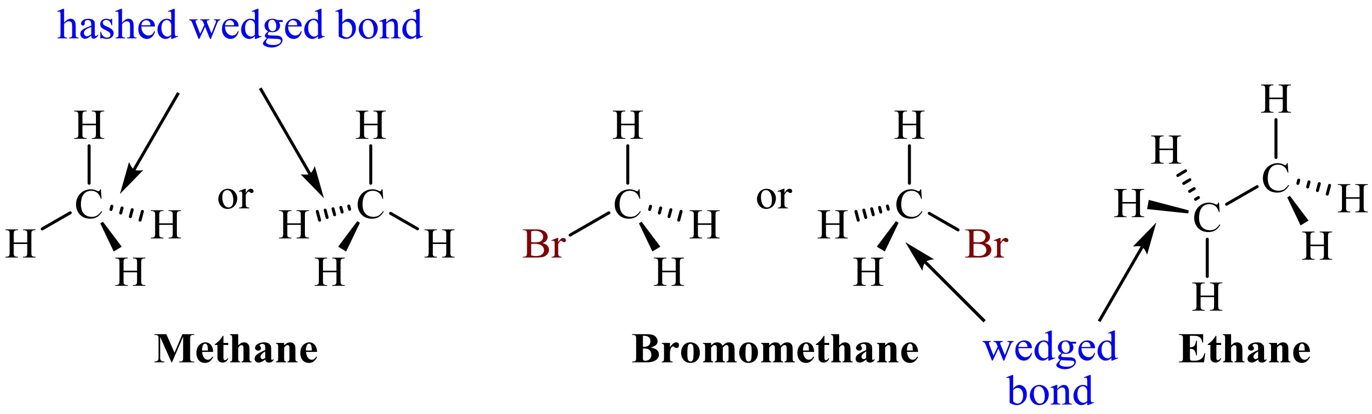


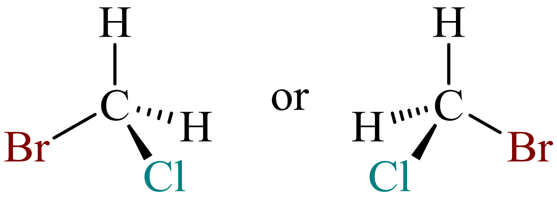


Vitamin A (retinol), $C_{20}H_{30}O$

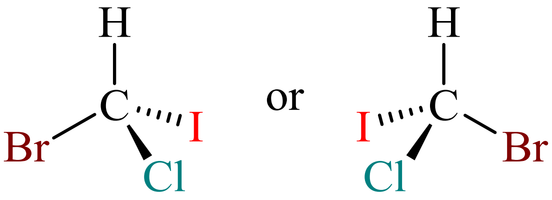


Three-Dimensional Formulas





Bromochloromethane



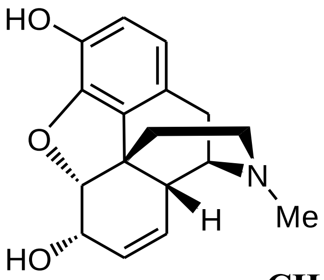
Bromochloroiodomethane

Three-dimensional formulas are represented using hashed wedged and wedged bonds.

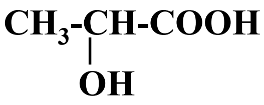
Nomenclature of Organic Compounds

Examples of non-systematic (trivial) names

In chemistry trivial name is a *common name* or *vernacular name.* It is not scientific name.

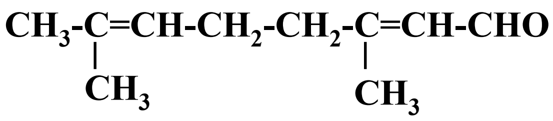


Morphine (named after Morpheus, the Greek god of dreams)



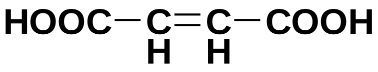
$CH_3-\underset{\substack{|\\ OH}}{CH}-COOH$

lactic acid



$CH_3-\underset{\substack{|\\ CH_3}}{C}=CH-CH_2-CH_2-\underset{\substack{|\\ CH_3}}{C}=CH-CHO$

citral

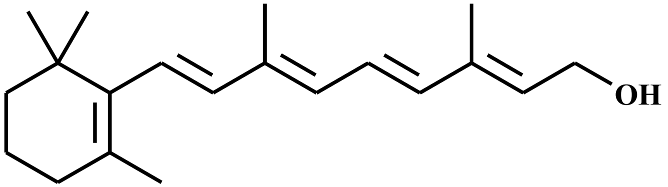


$HOOC-\underset{H}{C}=\underset{H}{C}-COOH$

maleic acid

$CH_3-CO-CH_3$

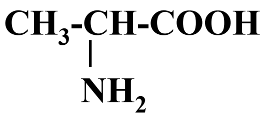
acetone



retinol

CH_3-COOH

acetic acid



$CH_3-\underset{\substack{|\\ NH_2}}{CH}-COOH$

alanine

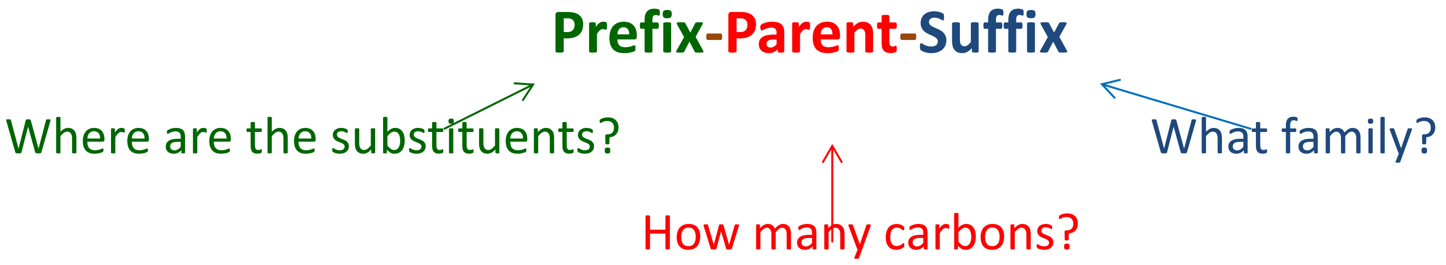
$HOOC-COOH$

oxalic acid

IUPAC rules

A set of rules that is used to name organic compounds has been devised by International Union of Pure and Applied Chemistry (IUPAC)

- **A chemical name has three parts in the IUPAC system:**



Prefix-Parent-Suffix

Where are the substituents?

What family?

How many carbons?

Step 1. Find the longest continuous chain of carbon atoms. This chain determines the **parent name** for the compound.

Criteria of determining the longest chain for acyclic compounds:

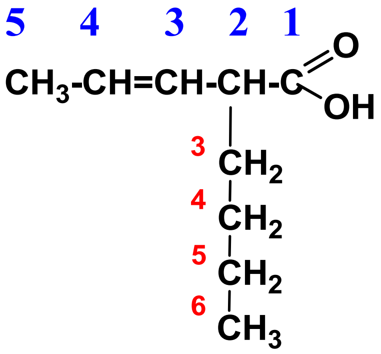
✓ **Longest chain with the functional group of the highest priority (principal functional group)**

-COOH, $-SO_3H$, -COOM, -COOR, $-CONR_2$, -CN, -CHO, -CO-, -OH, -SH, NH_2,

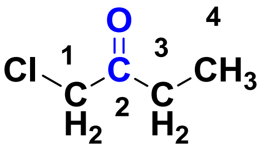
Decreasing priority of functional groups

NR_2, alkenes, alkynes.

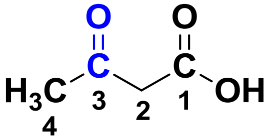
✓ **Chain containing maximum double or triple bonds**



2-butyl-3-pentenoic acid



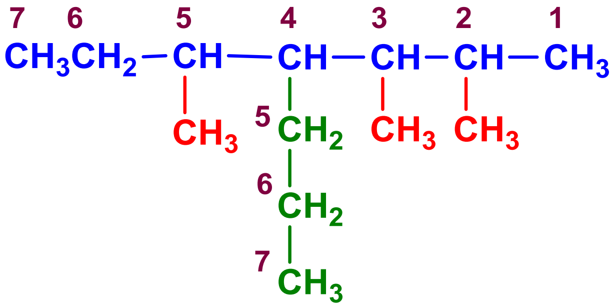
1-chloro-2-butanone



3-oxobutanoic acid

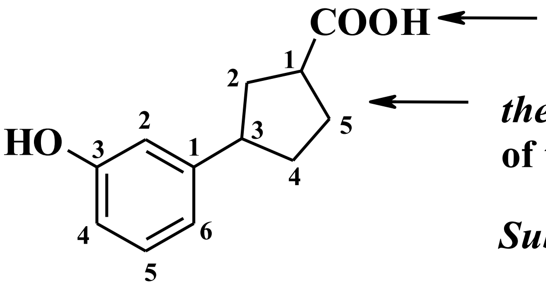
Functional group depending on its priority in a concrete compound can appear in the name as prefix or suffix.

✓ **When two chains of equal length compete for selection as the parent chain, choose the chain with the greater number of substituents.**



2,3,5-Trimethyl-4-propylheptane

If compound is cyclic, aromatic or heterocyclic, ring to which a group of highest priority is attached is considered as the main ring.



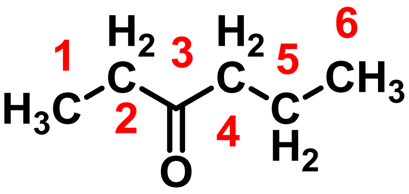
Group of the highest priority

the main cycle **with group of the highest priority: -cyclopentan-**

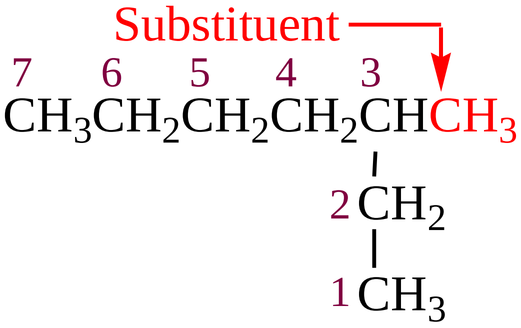
Substituent: **3-hydroxyphenyl-**

3-(3-Hydroxyphenyl)cyclopentane carboxylic acid

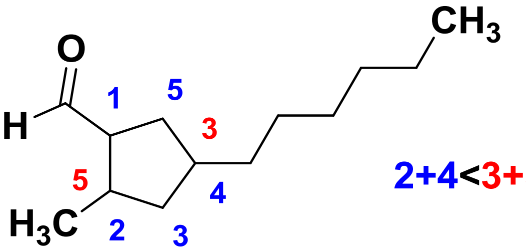
Step 2. Number the longest chain beginning with the end of the chain nearer the highest priority group or substituent.



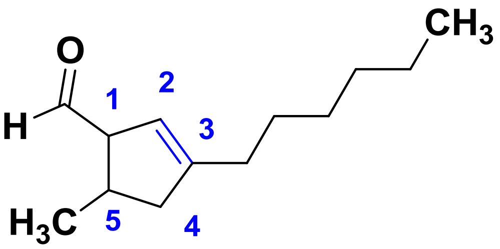
3-hexanone,
not 4-hexanone


$$\mathrm{\overset{7}{C}H_3\overset{6}{C}H_2\overset{5}{C}H_2\overset{4}{C}H_2\overset{3}{C}H\,CH_3}$$
$$\mathrm{{}^{2}CH_2 \;|\; {}^{1}CH_3}$$

Cyclic compounds:



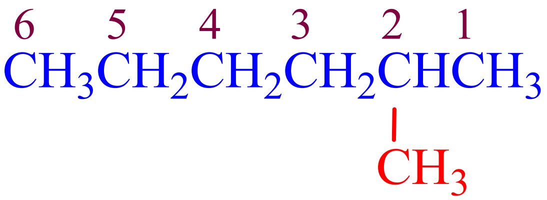
2+4<3+5



4-hexyl-2-methylcyclopentane carbaldehyde
not 3-hexyl-5-methylcyclopentane carbaldehyde

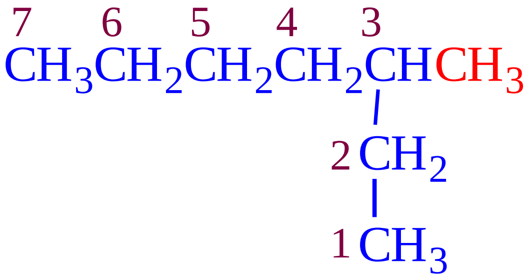
3-hexyl-5-methyl-2-cyclopentene carbaldehyde
not 4-hexyl-2-methyl-4-cyclopentene carbaldehyde

Step 3. Use the numbers obtained by application of rule 2 to **designate the location of the substituent group**.



$$\overset{6}{CH_3}\overset{5}{CH_2}\overset{4}{CH_2}\overset{3}{CH_2}\underset{\substack{|\\ CH_3}}{\overset{2}{CH}}\overset{1}{CH_3}$$

2-Methylhexane

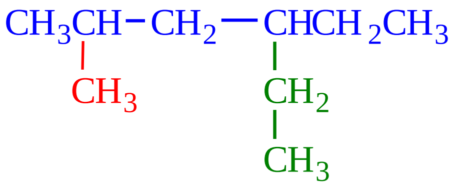


$$\overset{7}{CH_3}\overset{6}{CH_2}\overset{5}{CH_2}\overset{4}{CH_2}\underset{\substack{|\\ {}^{2}CH_2\\ |\\ {}^{1}CH_3}}{\overset{3}{CH}}CH_3$$

3-Methylheptane

The **parent name** is placed **last**; the **substituent group**, preceded by the **number** indicating its **location** on the chain, is placed **first**.

- ✓ When two or more substituents are present, **give each substituent a number corresponding to its location** on the longest chain.

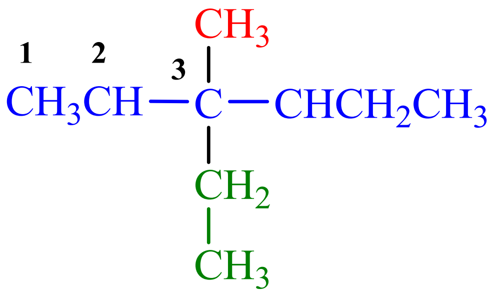


$$\mathrm{CH_3\underset{\underset{\textstyle CH_3}{|}}{CH}-CH_2-\underset{\underset{\underset{\underset{\textstyle CH_3}{|}}{CH_2}}{|}}{CH}CH_2CH_3}$$

4-Ethyl-2-methylhexane

The **substituent groups** are listed **alphabetically**.

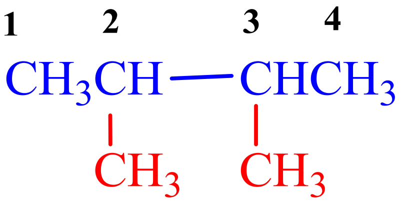
- ✓ When two substituents are present on the same carbon, use the number twice.



$$\mathrm{\overset{1}{CH_3}\overset{2}{CH}-\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\underset{\underset{\textstyle CH_3}{|}}{CH_2}}{|}}{\overset{3}{C}}}-CHCH_2CH_3}$$

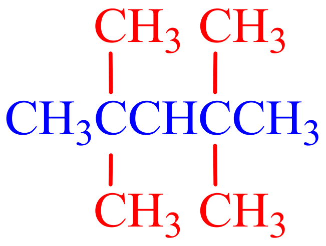
3-Ethyl-3-methylhexane

- ✓ When two or more substituents are identical, indicate this by the use of the prefixes **di-**, **tri-**, **tetra-**, and so on.



$$\mathrm{\overset{1}{CH_3}\underset{\underset{\textstyle CH_3}{|}}{\overset{2}{CH}}-\underset{\underset{\textstyle CH_3}{|}}{\overset{3}{CH}}\overset{4}{CH_3}}$$

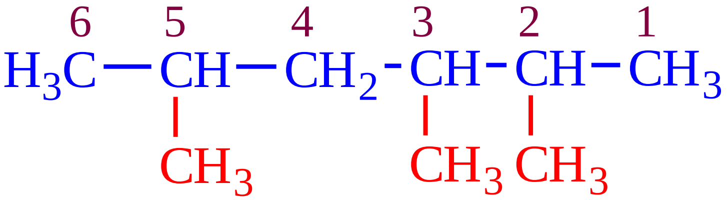
2,3-Dimethylbutane



$$\mathrm{CH_3\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}CH\overset{\overset{\textstyle CH_3}{|}}{\underset{\underset{\textstyle CH_3}{|}}{C}}CH_3}$$

2,2,4,4-Tetramethylpentane

✓ When branching first occurs at an equal distance from either end of the longest chain, **choose the name that gives the lower number at the first point of difference**.

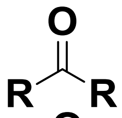
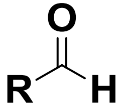


$$\begin{array}{cccccc} 6 & 5 & 4 & 3 & 2 & 1 \\ H_3C- & CH- & CH_2- & CH- & CH- & CH_3 \\ & | & & | & | & \\ & CH_3 & & CH_3 & CH_3 & \end{array}$$

2,3,5-Trimethylhexane

(*not* 2,4,5-Trimethylhexane)

Suffixes of some classes of organic compounds

principle group	class of compound	suffix
-	Alkane	-ane
-COOH	carboxylic acid	-oic
	ketone	-one
	aldehyde	-al
-OH	alcohol	-ol
SH	thiols	-thiol
NH_2	amine	-amine
=	alkene	-ene
≡	alkyne	-yne

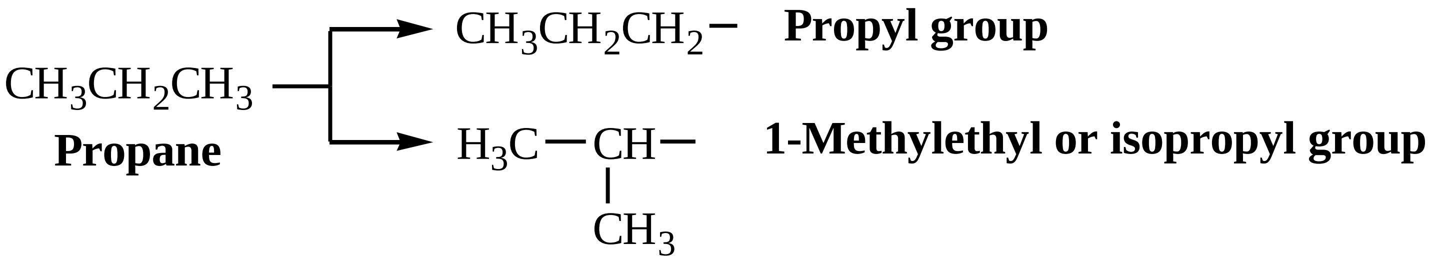
Nomenclature of Unbranched Alkyl Groups

Alkyl groups: **-ane ⇒ -yl** **(alkane ⇒** alkyl)

Alkane		Alkyl Group	Abbreviation
$CH_3—H$ **Methane**	becomes	$CH_3—$ **Methyl**	Me–
$CH_3CH_2—H$ **Ethane**	becomes	$CH_3CH_2—$ **Ethyl**	Et–
$CH_3CH_2CH_2—H$ **Propane**	becomes	$CH_3CH_2CH_2—$ **Propyl**	Pr–
$CH_3CH_2CH_2CH_2—H$ **Butane**	becomes	$CH_3CH_2CH_2CH_2—$ **Butyl**	Bu–

Nomenclature of Branched Alkyl Groups

Three-Carbon Groups



$CH_3CH_2CH_3$ **Propane**

$CH_3CH_2CH_2-$ **Propyl group**

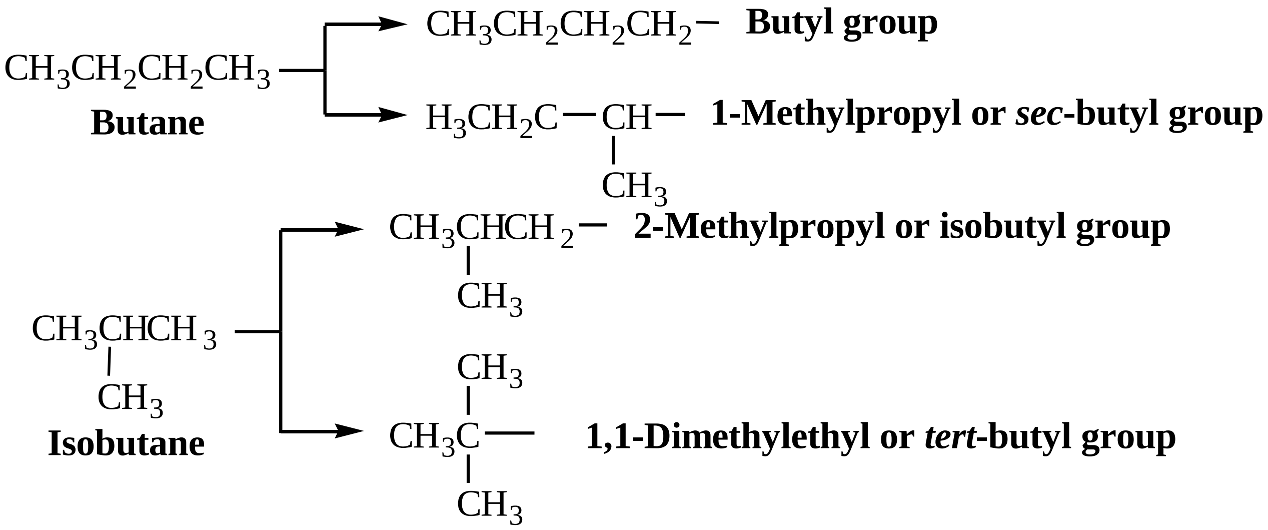
$H_3C-\underset{\displaystyle CH_3}{CH}-$ **1-Methylethyl or isopropyl group**

1-Methylethyl is the **systematic name**; **isopropyl** is a **common name**.

Numbering always begins at the point where the group is attached to the main chain.

Four-Carbon Groups

4 alkyl groups: 2 derived from **butane**; 2 derived from **isobutane**.



$CH_3CH_2CH_2CH_3$ **Butane**

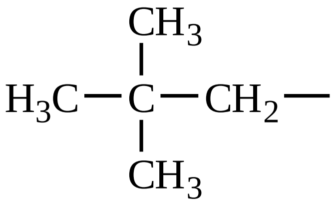
$CH_3CH_2CH_2CH_2-$ **Butyl group**

$H_3CH_2C-\underset{\displaystyle CH_3}{CH}-$ **1-Methylpropyl or *sec*-butyl group**

$CH_3\underset{\displaystyle CH_3}{CH}CH_3$ **Isobutane**

$CH_3\underset{\displaystyle CH_3}{CH}CH_2-$ **2-Methylpropyl or isobutyl group**

$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-$ **1,1-Dimethylethyl or *tert*-butyl group**



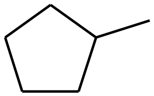
$$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH_2-$$

2,2-Dimethylpropyl or neopentyl group

Some other substituent names

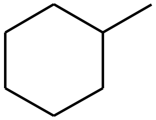
CH_2=CH- **CH_2=CH-CH_2-**

vinyl **allyl**



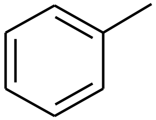
C_5H_9

cyclopentyl



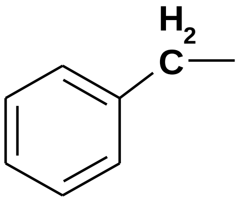
C_6H_{11}

cyclohexyl



C_6H_5

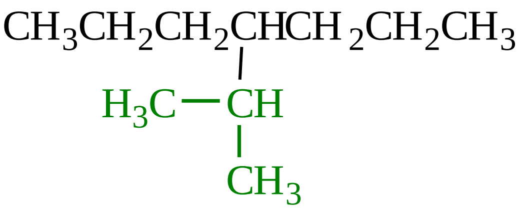
phenyl



$C_6H_5CH_2$

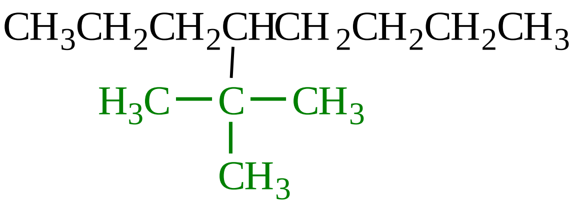
benzyl

Examples:



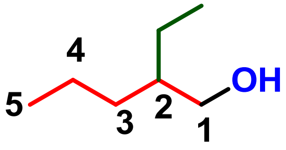
$$CH_3CH_2CH_2\underset{\displaystyle H_3C-\underset{\displaystyle CH_3}{CH}}{CH}CH_2CH_2CH_3$$

4-(1-Methylethyl)heptane or 4-isopropylheptane

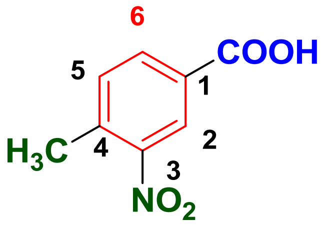


$$CH_3CH_2CH_2\underset{\displaystyle H_3C-\underset{\displaystyle CH_3}{C}-CH_3}{CH}CH_2CH_2CH_2CH_3$$

4-(1,1-Dimethylethyl)octane or 4-*tert*-butyloctane



2-ethylpentanol

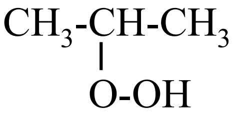
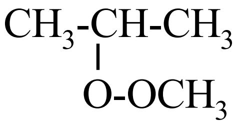


4-methyl-3-nitrobenzoic acid

Functional groups the names of which are used only as prefixes

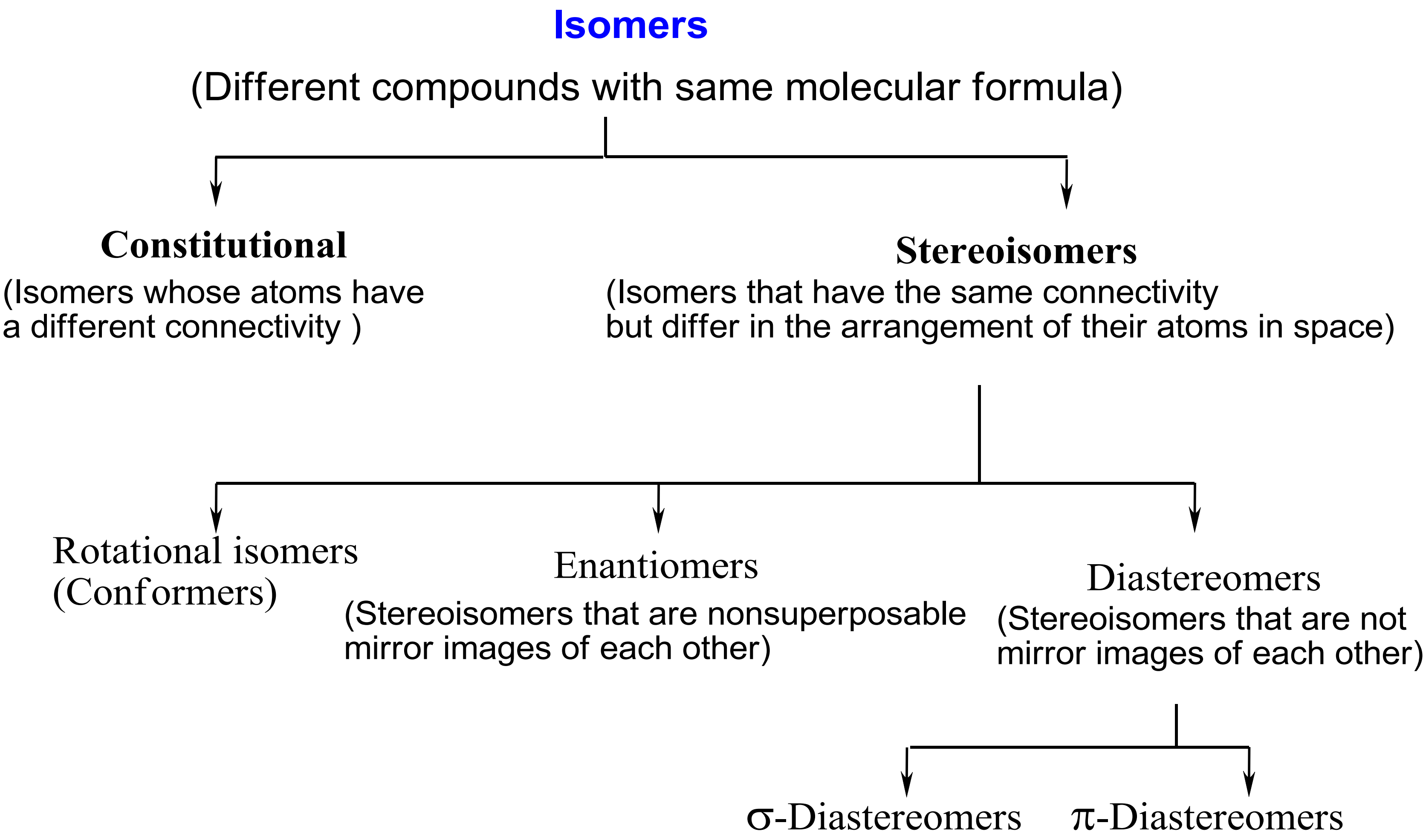
Organic compound class and general f-la	Functional group	Prefix	Examples
Halogenides R-Hal	-F, -Cl, Br, -I (-Hal)	fluoro-, chloro-, bromo-, iodo- (halogeno-)	CH_3CH_2Cl chloroethane $BrCH_2COOH$ 2-bromoethanoic acid
Nitro derivatives $R-NO_2$	$-NO_2$	nitro-	CH_3NO_2 nitromethane
Ethers R-O-R	-OR	(R)oxy-	$CH_3OCH_2CH_3$ methoxyethane $C_2H_5OCH_2CH_2SH$ 2-ethoxyethanethiol
Sulfides R-S-R	-SR	(R)thio-	$CH_3SCH_2CH_3$ methylthioethane

Continued

Organic compound class and general f-la	Functional group	Prefix	Example
Disulfides R-S-S-R	-S-SR	R(dithio)-	$CH_3SSC_6H_5$ methyldithiobenzene $C_2H_5SSCH_2CHO$ 2-ethyldithioethanal
Hydroperoxides R-O-OH	-O-OH	hydroperoxy-	 $CH_3\text{-}\underset{\text{O-OH}}{\underset{\vert}{CH}}\text{-}CH_3$ **2-hydroperoxypropane**
Alkylperoxides R-O-O-R	-O-OR	R(peroxy)-	 $CH_3\text{-}\underset{\text{O-}OCH_3}{\underset{\vert}{CH}}\text{-}CH_3$ **2-methylperoxypropane**

Isomerism

SUBDIVISION OF ISOMERS



Isomers

(Different compounds with same molecular formula)

Constitutional

(Isomers whose atoms have a different connectivity)

Stereoisomers

(Isomers that have the same connectivity but differ in the arrangement of their atoms in space)

Rotational isomers (Conformers)

Enantiomers

(Stereoisomers that are nonsuperposable mirror images of each other)

Diastereomers

(Stereoisomers that are not mirror images of each other)

σ-Diastereomers

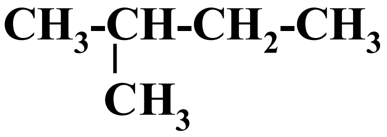
π-Diastereomers

- *Isomers of different carbon atom chains (different connectivity of atoms)*

Constitutional

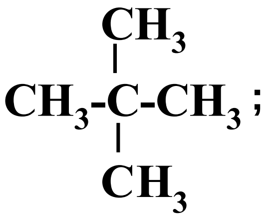
$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3$

pentane



$CH_3\text{-}\underset{CH_3}{CH}\text{-}CH_2\text{-}CH_3$

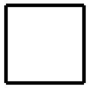
2-methylbutane (isopentane)



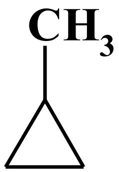
$CH_3\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}CH_3$;

2,2-dimethylpropane (neopentane)

C_6H_{12}



cyclobutane



methylcyclopropane

C_4H_8

- *Regioisomers*

of multiple bond

$CH_3\text{-}CH{=}CH\text{-}CH_3$

2-butene

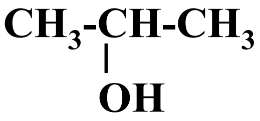
$CH_2{=}CH\text{-}CH_2\text{-}CH_3$;

1-butene

of functional group

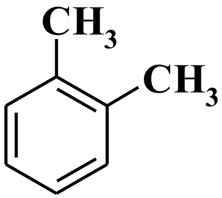
$CH_3\text{-}CH_2\text{-}CH_2\text{-}OH$

1-propanol

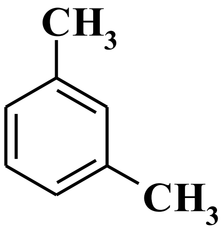


$CH_3\text{-}\underset{OH}{CH}\text{-}CH_3$

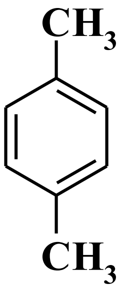
2-propanol



1,2-dimethylbenzene



1,3-dimethylbenzene

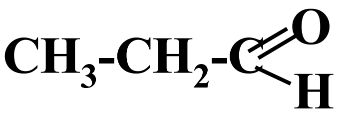


1,4-dimethylbenzene

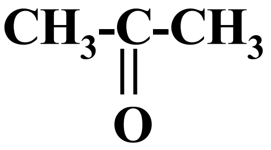
of substituent

Constitutional

- ## *Functional isomers*



$CH_3\text{-}CH_2\text{-}C\overset{O}{\underset{H}{<}}$

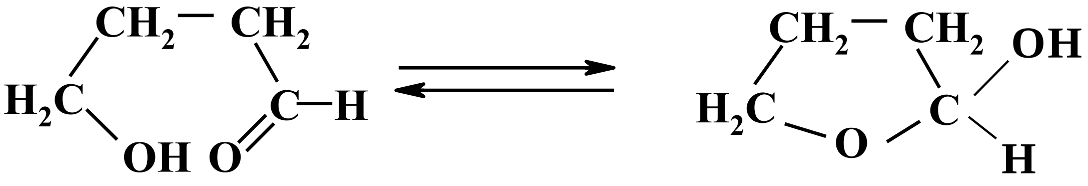


$CH_3\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_3$;

$CH_3\text{-}CH_2\text{-}OH$ $CH_3\text{-}O\text{-}CH_3$

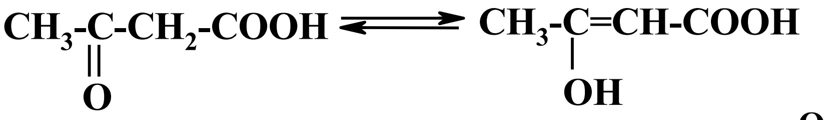
propanal **propanone (acetone)** **ethanol** **methoxymethane (dimethyl ether)**

Open chain-cyclic forms of molecules



open chain isomer **cyclic isomer**

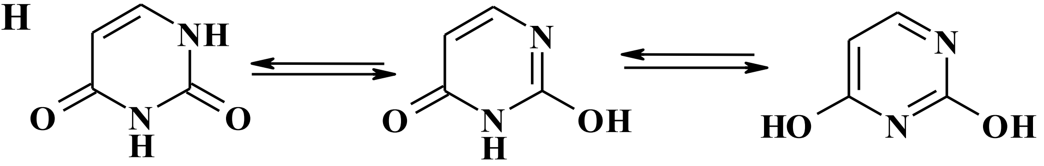
Keto-enolic tautomerism



$CH_3\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2\text{-}COOH \rightleftarrows CH_3\text{-}\underset{\underset{OH}{|}}{C}{=}CH\text{-}COOH$

keto-form **enol-form**

Lactam-lactimic tautomerism



lactam **hemilactam** **lactim**

Stereoisomerism

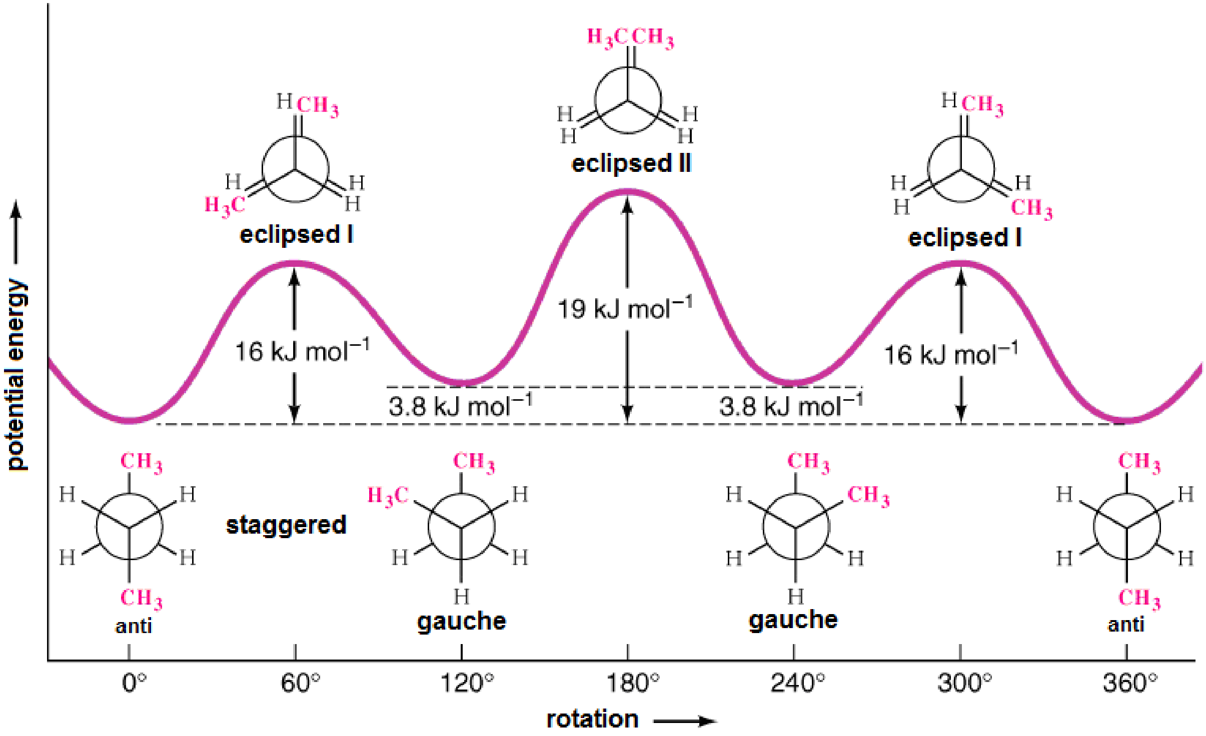
Conformations. Conformers

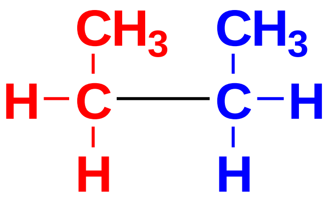
There is, in fact, free rotation about a single carbon–carbon bond in molecules. As a result, a molecule has an infinite number of possible three- dimensional shapes, or **conformations.**

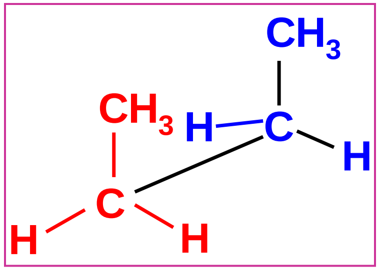
The different arrangements of atoms that result from rotation about a single bond are called *Conformations.*

Conformers – **stereoisomers in different conformations.**

Conformations of butane





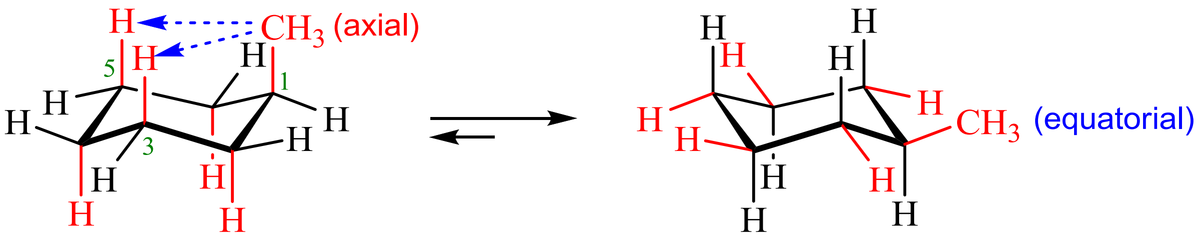


Eclipsed conformation – a temporary orientation of groups around two atoms joined by a single bond such that the groups directly oppose each other.

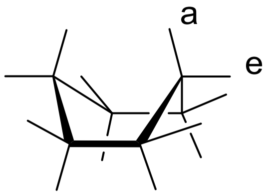
Gauche conformation - a temporary orientation of groups which are close enough to each other that the van der Waals forces between them are repulsive. (the electron clouds of the two groups are so close that they repel each other).

Anti conformation – does not have torsional strain because the groups are staggered and are far apart (usually angle between them is 180^o).

Cyclohexane conformations:



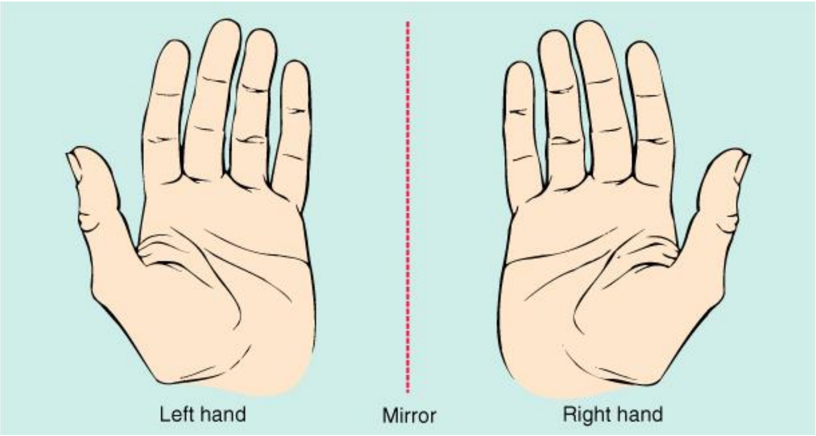
(less stable) **Chair conformations** (more stable 7.5 kJ mol^{-1})



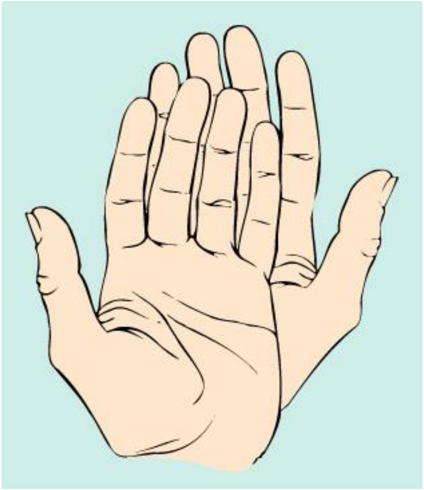
Boat conformation

ENANTIOMERS AND CHIRAL MOLECULES

A **chiral** molecule is one that is *not* ***identical with its mirror image***.

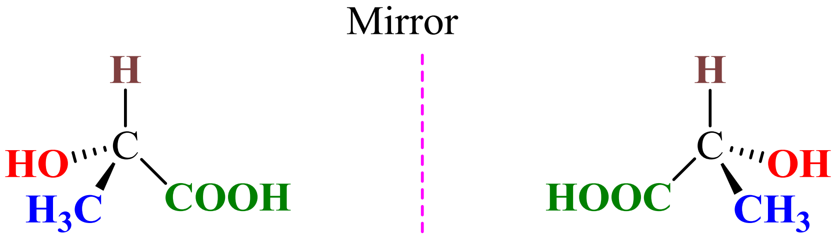


The mirror image of a left hand is a right hand.



Left and right hands are not superimposable.

Enantiomers are mirror-image molecules that are not superimposable with each other.



(+)-Lactic acid, $[\alpha]_D = +3.82$ (-)-Lactic acid, $[\alpha]_D = -3.82$

Configuration of a molecule – three-dimentional arrangement of atoms in the molecule. The ability to form two or more molecules with different configuration is called stereoisomerism.

Stereocenter is defined as an atom bearing groups such that an interchanging of any two groups leads to a **stereoisomer.**

A tetrahedral atom with four different groups attached to it is a ***stereocenter*** (***chiral center***, ***stereogenic center, asymmetric atom***)

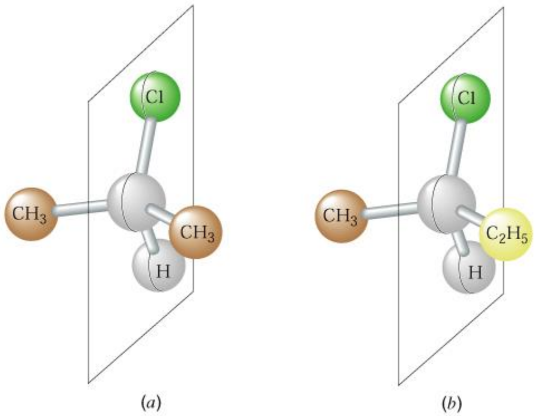
A molecule with stereocenter has no symmetrical elements (plane of symmetry, center of symmetry) is called a **chiral molecule**.

TESTS FOR CHIRALITY

1. The **presence** of **a *single* tetrahedral stereocenter** ⇒ **chiral molecule**.
2. The **presence** of **a plane of symmetry** ⇒ **achiral molecule**

A **plane of symmetry** (also called a **mirror plane**) is ***an imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other***.

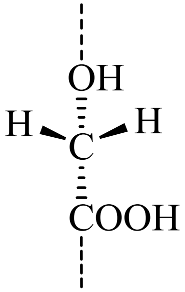
The plane may pass through atoms, between atoms, or both.



(a) 2-Chloropropane has a plane of symmetry and is achiral.

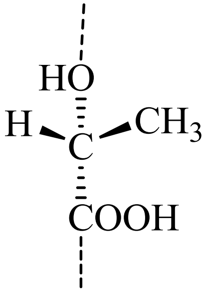
(b) 2-Chlorobutane does not possess a plane of symmetry and is chiral.

Symmetry plane



$HO–CH_2COOH$
Hydroxyacetic acid
(achiral)

NO symmetry plane



$CH_3CH(OH)COOH$
Lactic acid
(chiral)

NOMENCLATURE OF ENANTIOMERS

THE (*R*-*S*) SYSTEM (CAHN-INGOLD-PRELOG SYSTEM)

(*R*) and (*S*) are from the Latin words *rectus* and *sinister.*

R configuration: clockwise (*rectus*, “**right**”)

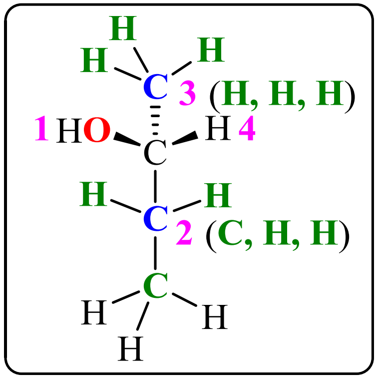
S configuration: counterclockwise (*sinister*, “**left**”)

1. **Each of the four groups attached to the stereocenter is assigned a priority.**

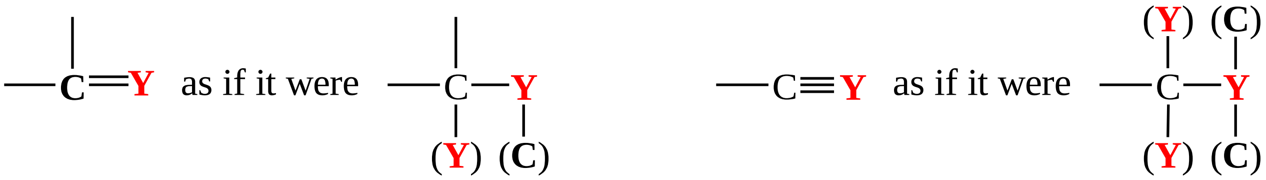
- ✓ Priority is first assigned on the basis of the **atomic number** of the atom that is directly attached to the stereocenter. The group with the **lowest atomic number** is given the **lowest priority**, **4**; the group with **next higher atomic number** is given the **next higher priority**, **3**; and so on.
- ✓ In the case of isotopes, the isotope of greatest atomic mass has highest priority.

2. Assign a priority at the **first point of difference**.

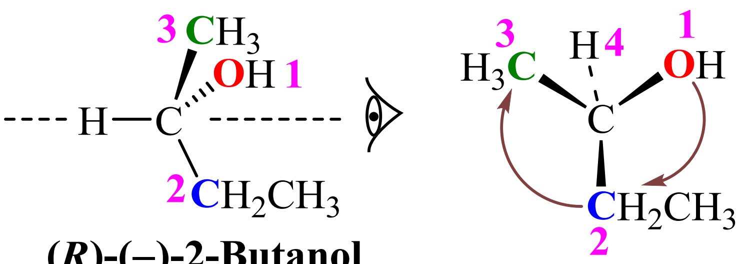
- ✓ When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the stereocenter, then the next set of atoms in the unassigned groups are examined.



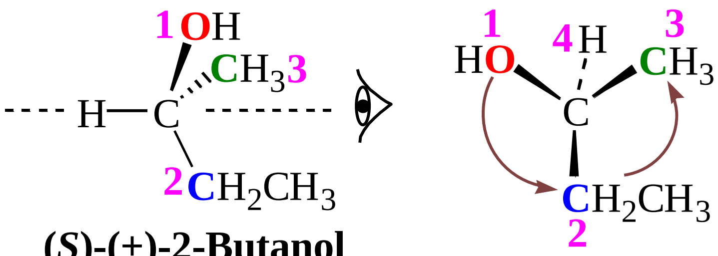
Groups containing double or triple bonds are assigned priority as if both atoms were duplicated or triplicated.



3. View the molecule with the group of lowest priority pointing away from us.



(*R*)-(–)-2-Butanol

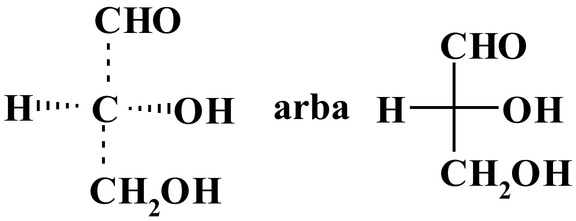


(*S*)-(+)-2-Butanol

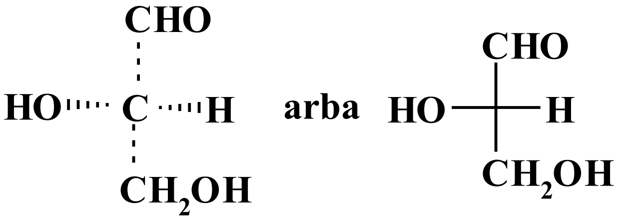
- ✓ If the direction from highest priority (1) to the next highest (2) to the next (3) is **clockwise**, the enantiomer is designated *R*.
- ✓ If the direction is **counterclockwise**, the enantiomer is designated *S*.

Some classes of chiral compounds (α-amino acids, carbohydrates) are named using Fisher system (**D ir L system**)

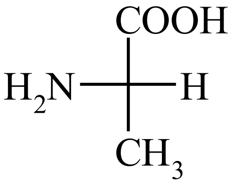
D symbol means that stereocenter of compound has the same configuration as (+)-glyceral, L symbol designates that configuration of stereocenter is such as of (-)-glyceral



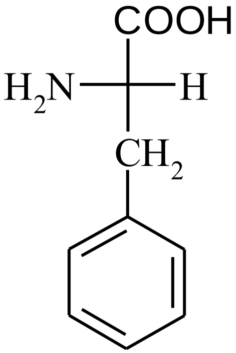
D(+)-glyceral



L(-)-glyceral



L-alanine



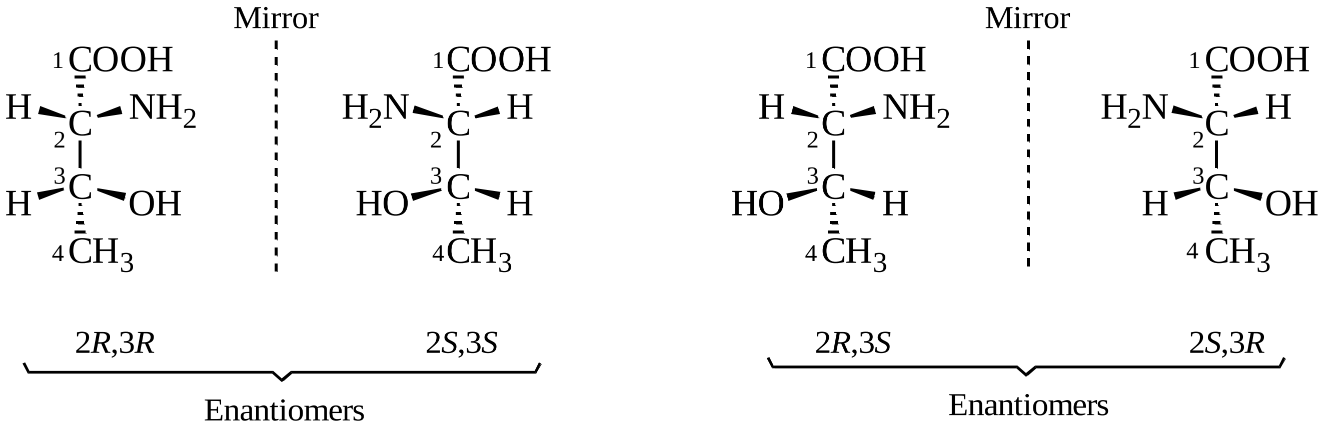
L-phenylalanine

Molecules with More than One Stereocenter

Many organic molecules, especially those important for biology, contain more than one stereocenter.
For instance, *cholesterol has 8 stereocenters*.

A useful rule gives maximum number of stereoisomers: In compounds with tetrahedral stereocenter, **the total number of stereoisomers will not exceed 2^n, where n is equal to the number of tetrahedral stereocenters**.

Amino acid - *threonine*



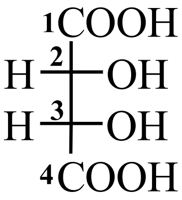
Enatiomers must have opposite (mirror-image) configurations at *all* stereogenic centers.

Diastereomers must have opposite configurations at *some* (one or more) stereogenic centers, but the same configurations at other stereogenic centers

Diastereomers

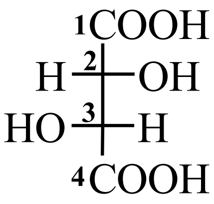
Diastereomers – stereoisomers that are not mirror images.

σ-Diastereomers – diastereomers with different configuration of some chiral centers.



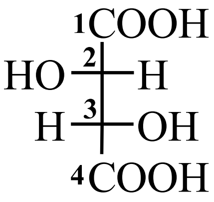
2R, 3S-tartaric acid

A



2R, 3R-tartaric acid

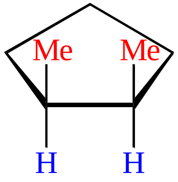
B



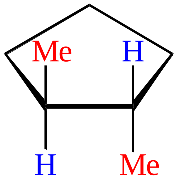
2S, 3S-tartaric acid

C

B and C are enantiomers; A and B, A and C are σ-diastereomers

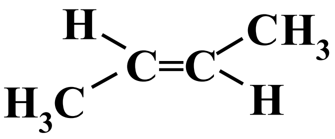


cis-1,2-Dimethylcyclopentane
(C_7H_{14})

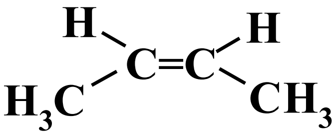


trans-1,2-Dimethylcyclopentane
(C_7H_{14})

π-Diastereomers – stereoisomers of alkenes

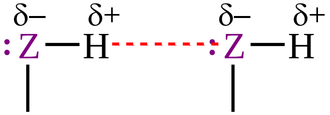


E-2-butene
trans-2-butene



Z-2-butene
cis-2-butene

Hydrogen bond

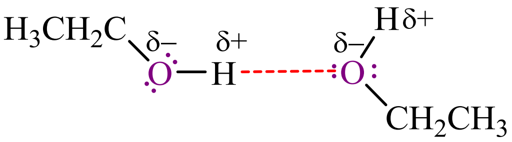


A **hydrogen bond** is the electrostatic attraction between polar molecules that occurs when a hydrogen (H) atom bound to a highly electronegative atom such as nitrogen (N), oxygen (O) or fluorine (F) experiences attraction to some other nearby highly electronegative atom.

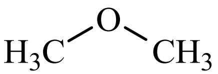
A *hydrogen bond* is not a true bond, but a particularly strong dipole-dipole attraction, and should not be confused with a covalent bond.

These hydrogen-bond attractions can occur between molecules (***intermolecular***) or within different parts of a single molecule (***intramolecular***).

intermolecular

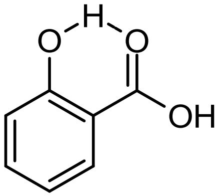


EtOH bp 78.5 °C



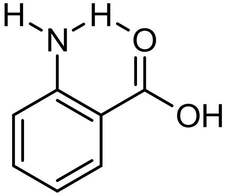
Dimethylether bp -24.9 °C

intramolecular



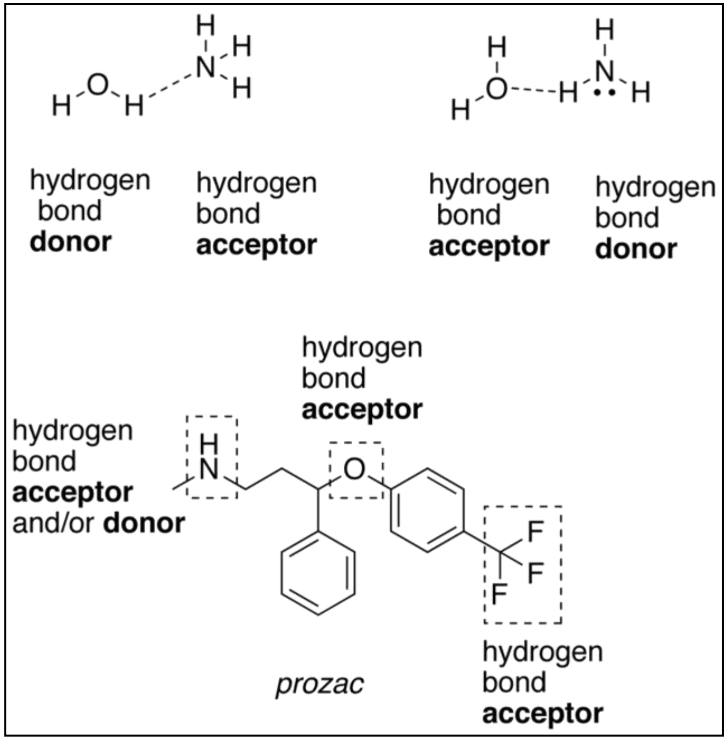
Salicylic acid

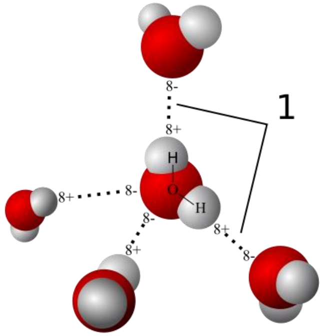
mp 159 °C



Anthranilic acid

mp 146-148 °C



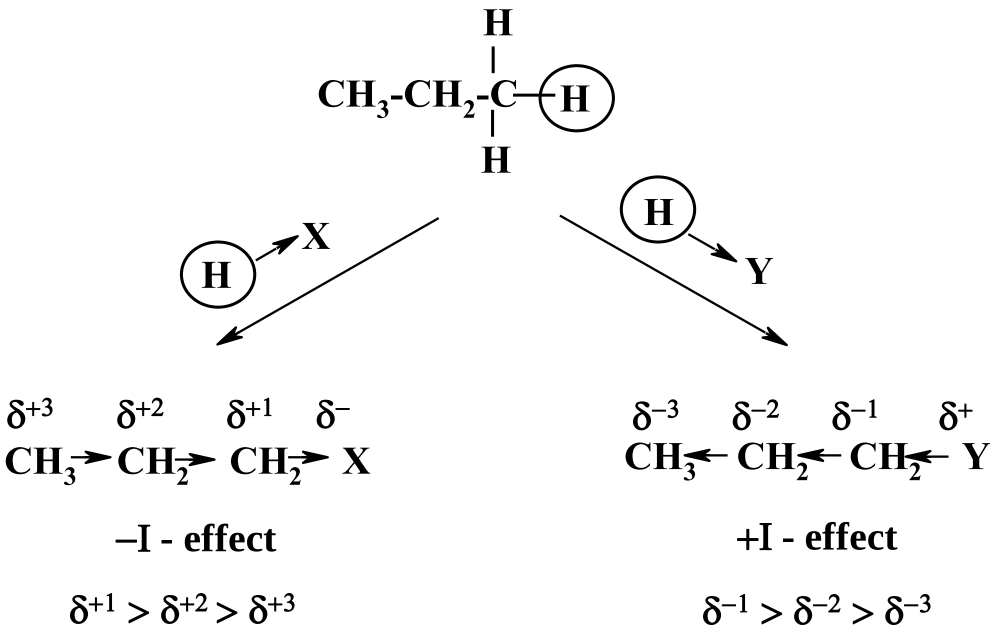


Intermolecular hydrogen bonding is responsible for the high boiling point of **water** (100 °C). Intramolecular hydrogen bonding is partly responsible for the secondary and tertiary structures of proteins and nucleic acids. It also plays an important role in the structure of polymers.

Interaction of atoms in a molecule

Inductive and mesomeric electronic efects

Electronic efects in a σ bond system. Inductive efect.



$CH_3\text{-}CH_2\text{-}CH_2\text{-}H$

$$\overset{\delta^{+3}}{CH_3} \rightarrow \overset{\delta^{+2}}{CH_2} \rightarrow \overset{\delta^{+1}}{CH_2} \rightarrow \overset{\delta^{-}}{X}$$

–I - effect

$\delta^{+1} > \delta^{+2} > \delta^{+3}$

$$\overset{\delta^{-3}}{CH_3} \leftarrow \overset{\delta^{-2}}{CH_2} \leftarrow \overset{\delta^{-1}}{CH_2} \leftarrow \overset{\delta^{+}}{Y}$$

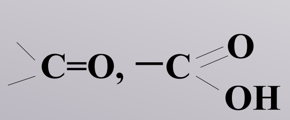
+I - effect

$\delta^{-1} > \delta^{-2} > \delta^{-3}$

Polarization of σ-bond which results from electron accepting or electron donating group or atom is called inductive effect.

Electron withdrawing groups (-I):

X = -F, -Cl, -Br, -I, -OR, -NH$_2$, -NHR, -NR$_2$, -$\overset{+}{N}R_3$,



$>C{=}O$, $-C\begin{smallmatrix}{=}O\\ OH\end{smallmatrix}$, **-NO$_2$, -SO$_3$H.**

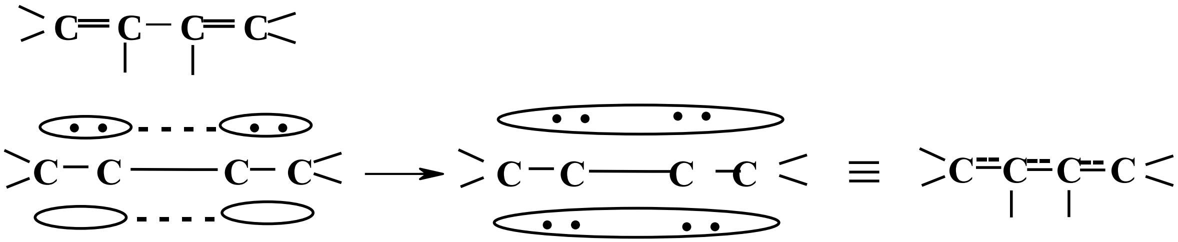
Electron donating groups (+I):

Y = -CH$_3$, -CH$_2$CH$_3$, -CH(CH$_3$)$_2$, -(CH$_3$)$_3$, anions -O$^-$, -S$^-$,
metal atoms –M.

Electronic effects in conjugated systems.

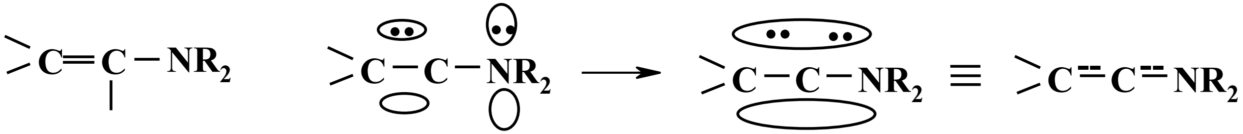
Resonance effect

Linear conjugated systems



π-MO π-MO

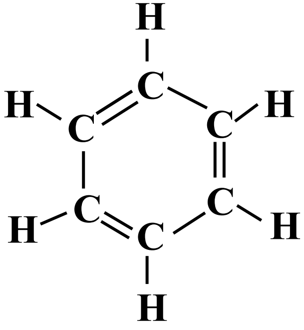
π, π-conjugation



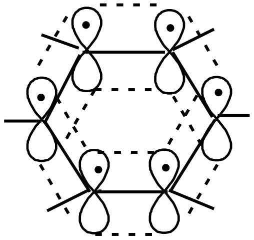
π–MO p-MO

p, π-conjugation

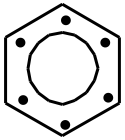
Cyclic conjugated systems

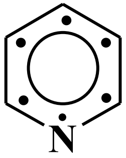


benzene

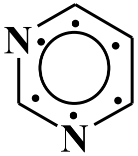


π-MO

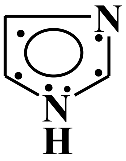




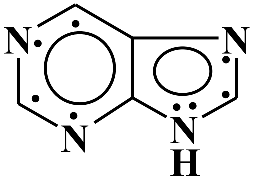
pyridine



pyrimidine

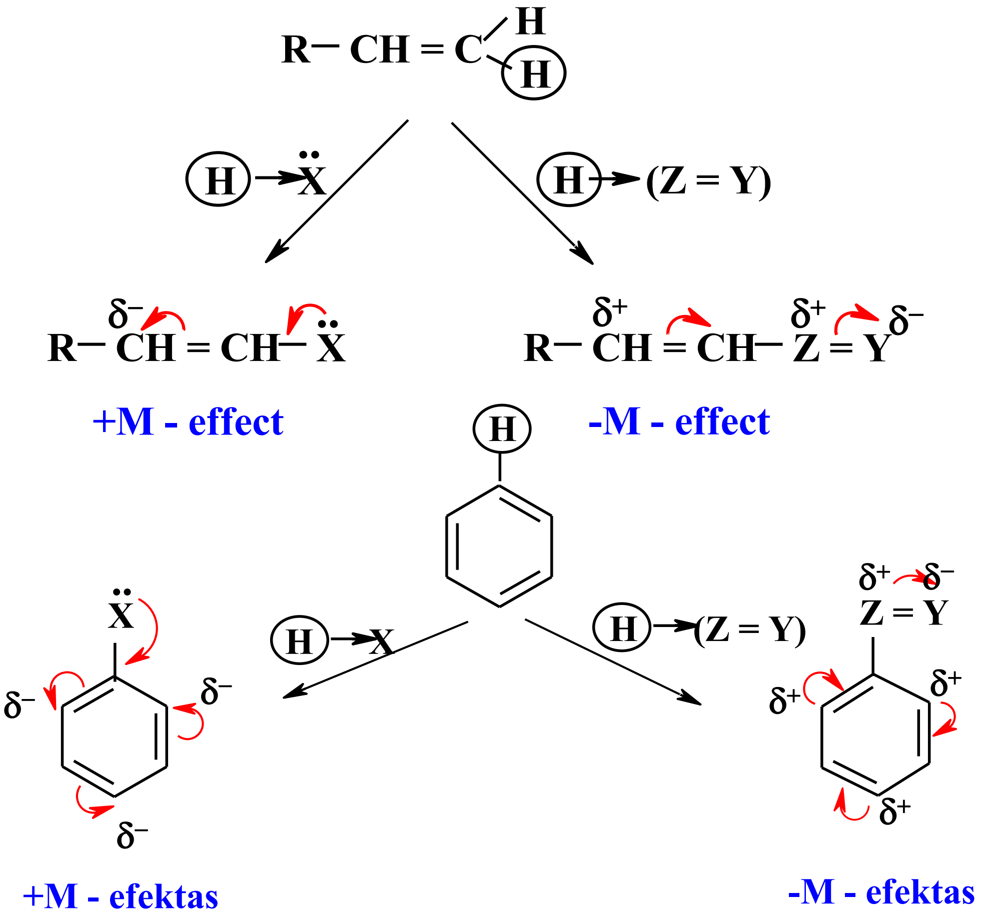


imidazole



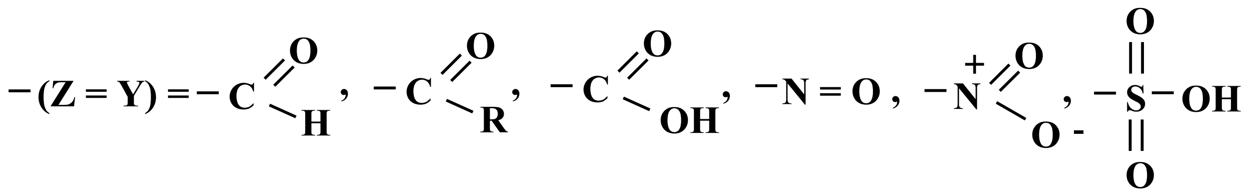
purin

Resonance (mesomeric) effect



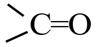
Electron donors: $X = -\ddot{O}H, -\ddot{O}R, -\ddot{O}:^{-}, -\ddot{N}H_2, -\ddot{N}HR, -\ddot{N}R_2, -\ddot{F}, -\ddot{Cl}, -\ddot{Br}, -\ddot{I}$

Electron acceptors:



$-(Z=Y) = -C(=O)H,\ -C(=O)R,\ -C(=O)OH,\ -N=O,\ -\overset{+}{N}(=O)O^{-},\ -S(=O)_2-OH$

Substituent electronic effects (summary)

Substituent	Electronic effects		Influence of substituent
	inductive	mesomeric	
Alkyl: $-CH_3$, $-C_2H_5$, … $-R$	+I	–	Electron donor
$-NH_2$, $-NHR$, $-NR_2$	–I	+M	+M >> –I Electron donor
–OH	–I	+M	+M > –I electron donor
Alkoksi: $-OCH_3$, $-OC_2H_5$, …–OR	–I	+M	+M > –I Electron donor
–Hal: –F, –Cl, –Br, –I	–I	+M	–I > +M Electron acceptor
 C=O	–I	–M	Electron acceptor
–COOH	–I	–M	Electron acceptor
$-SO_3H$	–I	–M	Electron acceptor
$-NO_2$	–I	–M	Electron acceptor

Classification of organic reactions. Types of reagents.

Heterolytic reactions. Electrophiles ir nucleofpiles

$$A:B \rightleftharpoons \overset{\delta-}{A}:\overset{\delta+}{B} \xrightleftharpoons{\text{heterolysis of covalent bond}} \underset{\text{nucleophile}}{[A:]^-} + \underset{\text{electrophile}}{[B]^+}$$

Electrophiles **– positively charged ions or fragments of molecules,** having an ability to accept electron pair of nucleophile.

C-electrophiles : carbene ions R_3C^+, compounds with polar bond $R_3\overset{\delta+}{C}-\overset{\delta-}{X}$, $R_2\overset{\delta+}{C}=\overset{\delta-}{Y}$, $R\overset{\delta+}{C} = \overset{\delta-}{Z}$;

O-electrophiles : $R-\overset{\delta+}{O}-\overset{\delta-}{X}$;

S-electrophiles : $R-\overset{\delta+}{S}-\overset{\delta-}{X}$;

N-electrophiles : $R_2\overset{\delta+}{N}-\overset{\delta-}{X}$, $\overset{\delta-}{X}-\overset{\delta+}{N}O_2$;

Hal-electrophiles : $\overset{\delta+}{Hal}-\overset{\delta-}{Hal}$ (exmp., $\overset{\delta+}{Cl}-\overset{\delta-}{Cl}$).

Nucleophiles – negatively charged ions or fragments of molecules, having an electron pair and able to donate it to electrophiles.

C-nucleophiles : R_2C^-, $R_3\overset{\delta-}{C}—\overset{\delta+}{M}$, $R_2C = CR_2$, $RC = CR$;

N-nucleophiles : $\ddot{N}H_3$, $R\ddot{N}H_2$, $R_2\ddot{N}H$, $R_3\ddot{N}$;

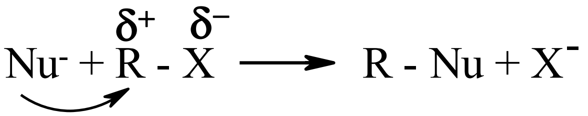
O-nucleophiles : $H_2\ddot{O}$, $R\text{-}\ddot{O}\text{-}R$, $H\ddot{O}\text{-}$, $R\overset{\delta-}{\ddot{O}}\text{-}\overset{\delta+}{M}$;

S-nucleophiles : $H_2\ddot{S}$, $R\text{-}\ddot{S}\text{-}R$, $H\ddot{S}\text{-}$, $R\overset{\delta-}{\ddot{S}}\text{-}\overset{\delta+}{M}$;

Hal-anions : F^-, Cl^-, Br^-, I^-.

During electrophilic-nucleophilic reaction nucleophiles used to be **electron donors**.

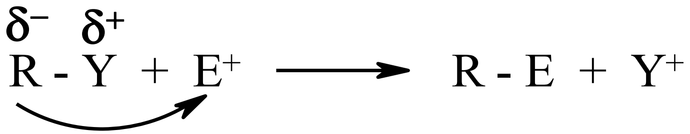
Nucleophilic reactions



$Nu^- + \overset{\delta+}{R} - \overset{\delta-}{X} \longrightarrow R - Nu + X^-$

S_N

Electrophilic reactions

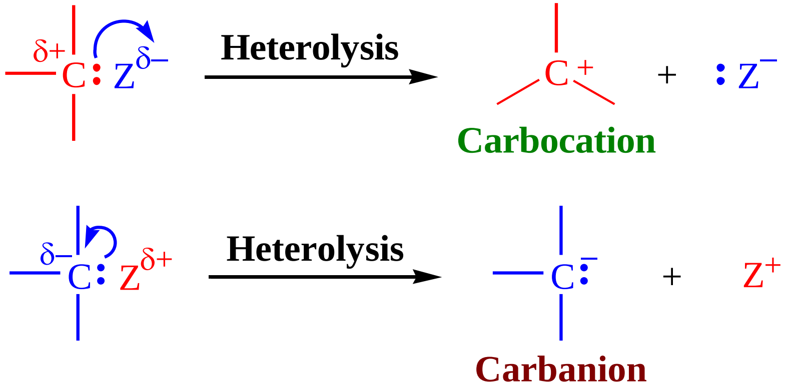


$\overset{\delta-}{R} - \overset{\delta+}{Y} + E^+ \longrightarrow R - E + Y^+$

S_E

Heterolysis of Bonds to Carbon:

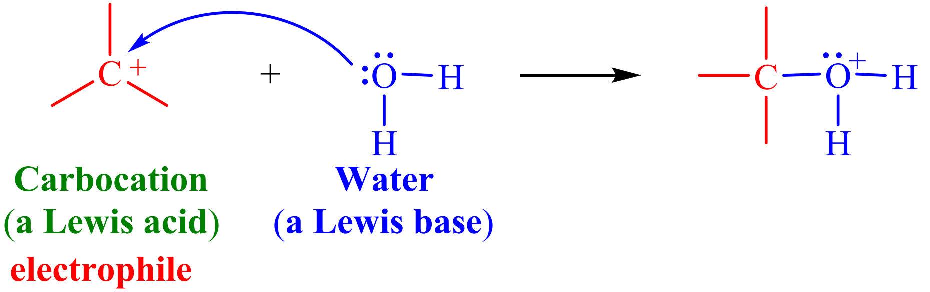
Carbocations and Carbanions



Carbocations have six electrons in their valence shell, and are electron deficient. ⇒ Carbocations are Lewis acids.

1) **Most carbocations are short-lived** and **highly reactive**.

2) **Carbocations react rapidly with *Lewis bases* (molecules or ions that can donate electron pair) to achieve a stable octet of electrons.**



Electrophile: “electron-loving” reagent

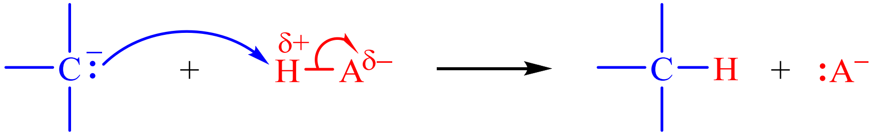
1) Electrophiles seek the extra electrons that will give them a stable valence shell of electrons.

2) A proton achieves the valence shell configuration of helium; carbocations achieve the valence shell configuration of neon.

Carbanions are Lewis bases.

1) Carbanions donate their electron pair to a proton or some other positive center to neutralize their negative charge.

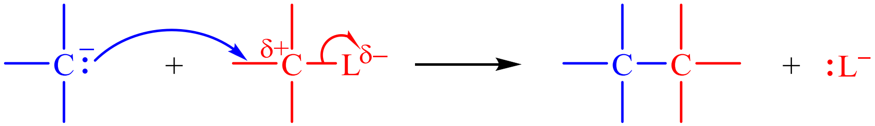
Carbanions are Nucleophiles: “nucleus-loving” reagent



Carbanion

(nucleophile)

Bronsted acid

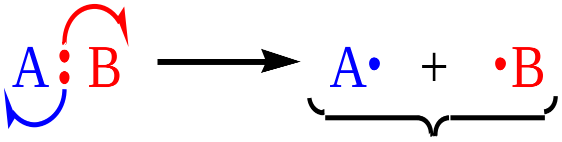


Carbanion
(nucleophile)

Lewis acid
(elektrophile)

leaving group

Homolytic bond dissociation (**homolysis**): electronically *symmetrical* bond breaking ⇒ produces **radicals**.



Homolytic bond cleavage

Radicals

Reactions and Their Mechanisms

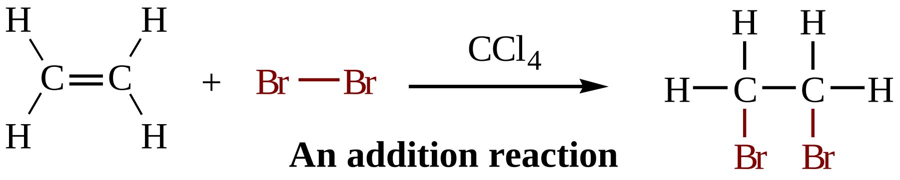
Categories of Reactions

1. **Substitution Reactions:**

$$H_3C-Cl + Na^+ OH^- \xrightarrow{H_2O} H_3C-OH + Na^+ Cl^-$$

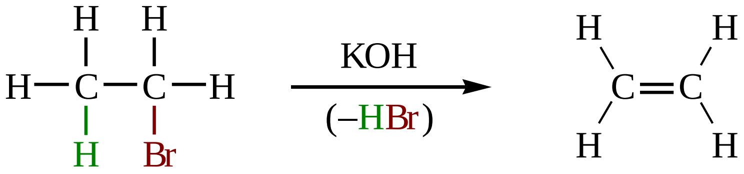
A substitution reaction

2. **Addition Reactions:**



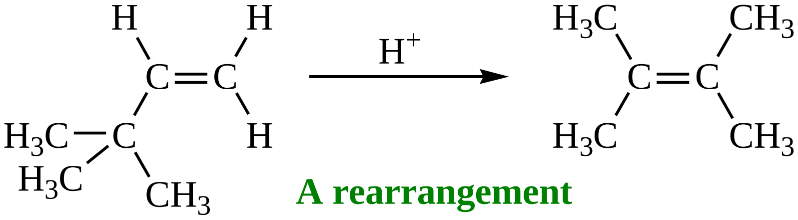
An addition reaction

3. **Elimination Reactions:**



An elimination reaction (Dehydrohalogenation)

4. **Rearrangement Reactions:**

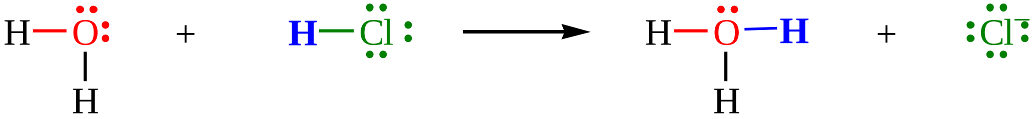


A rearrangement

Acidity-Basicity of Organic Compounds

The Brønsted-Lowry Definition of Acids and Bases

Acid is a substance that can donate (or lose) a **proton**;
Base is a substance that can accept (or remove) a **proton**.

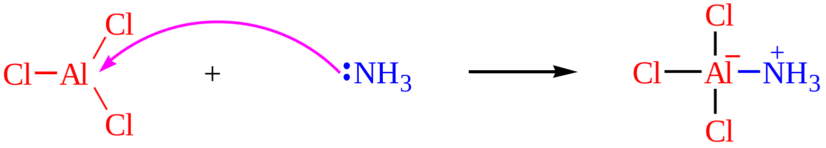


Base **(proton acceptor)** · **Acid** **(proton donor)** · **Conjugate acid of H_2O** · **Conjugate base of HCl**

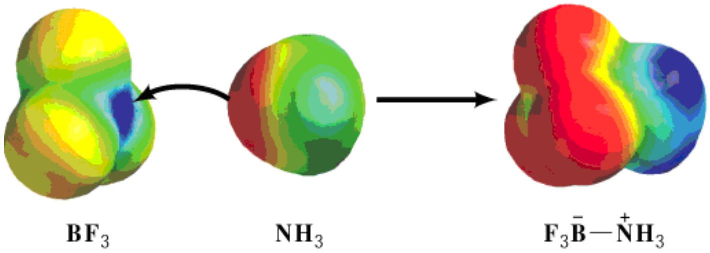
Conjugate acid: the molecule or ion that forms when a base accepts a proton.
Conjugate base: the molecule or ion that forms when an acid loses its proton.

The Lewis Definition of Acids and Bases

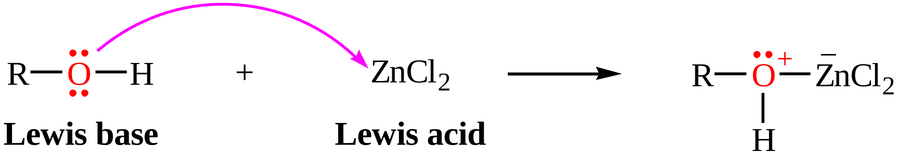
Acid: electron-pair acceptor
Base: electron-pair donor



Lewis acid (electron-pair acceptor) · **Lewis base (electron-pair donor)**



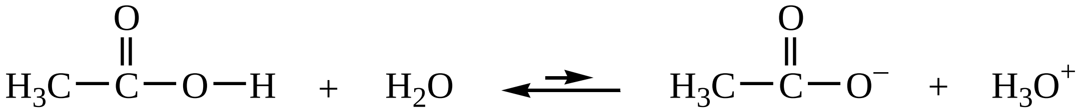
curved arrow shows the donation of the electron-pair



Lewis base (electron-pair donor) · **Lewis acid (electron-pair acceptor)**

The Strength of Acids and Bases: K_a and pK_a

In a 0.1 *M* solution of acetic acid at 25 ºC only 1% of the acetic acid molecules ionize by transferring their protons to water.



$$H_3C{-}\overset{\overset{\Large O}{\|}}{C}{-}O{-}H + H_2O \rightleftharpoons H_3C{-}\overset{\overset{\Large O}{\|}}{C}{-}O^- + H_3O^+$$

The Acidity Constant, K_a

An aqueous solution of acetic acid is an equilibrium:

$$Keq = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3CO_2H][H_2O]}$$

The acidity constant:

For dilute aqueous solution: water concentration is essentially constant (~ 55.5 *M*)

$$Ka = Keq\,[H_2O] = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3CO_2H]}$$

A **large value of Ka** means the acid is a **strong acid**, and a **smaller value of Ka** means the acid is a **weak acid**.

If the **Ka** is greater than 10, the acid will be completely dissociated in water.

Acidity and pK_a

$$pK_a = -\log K_a$$
$$pH = -\log [H_3O^+]$$

The **pK_a** for acetic acid is 4.75:
$pK_a = -\log(1.76 \times 10^{-5}) = -(-4.75) = 4.75$

The **larger the value of the pK_a, the weaker is the acid**.

CH_3CO_2H	**CF_3CO_2H**	**HCl**
pK_a = 4.75	**pK_a = 0.18**	**pK_a = −7**

Acidity increases

Predicting the Strength of Bases

1. **The stronger the acid, the weaker will be its conjugate base.**

2. **The larger the p*K*a of the conjugate acid, the stronger is the base.**

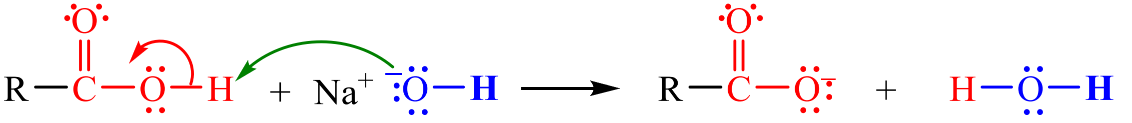
Increasing base strength

Cl^-	**$CH_3CO_2^-$**	**HO^-**
Very weak base		**Strong base**
pKa of conjugate acid (HCl) = -7	**pKa of conjugate acid (CH_3CO_2H) = 4.7**	**pKa of conjugate acid (H_2O) = 15.7**

Predicting The Outcome of Acid-Base Reactions

Acid-base reactions always favor the formation of the weaker acid and the weaker base.

Equilibrium control: the outcome of an acid-base reaction is determined by the position of an equilibrium.



Stronger acid $pK_a = 3\text{-}5$

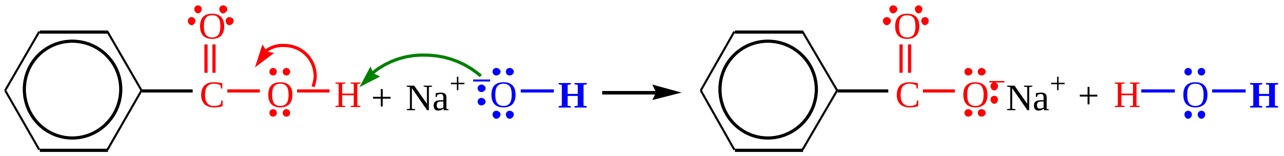
Stronger base

Weaker base

Weaker acid $pK_a = 15.7$

Large difference in pK_a value ⇒ the position of equilibrium will greatly favor the formation of the products (one-way arrow is used)

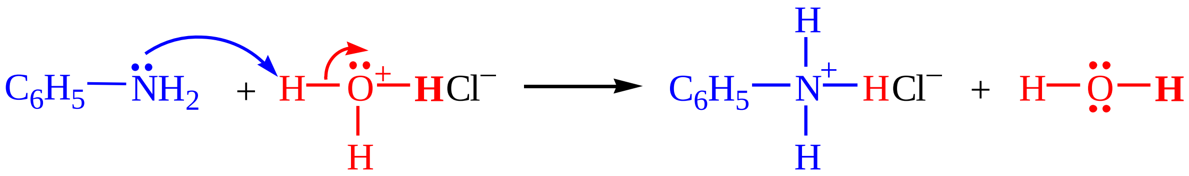
Water-insoluble carboxylic acids dissolve in aqueous sodium hydroxide:



Insoluble in water

Soluble in water
(Due to its polarity as a salt)

Water-insoluble amines dissolve readily in hydrochloric acid:



Water-insoluble

Water-soluble salt

Hydrocarbons

Alkanes

Alkenes

Alkynes

Aromatic hydrocarbons

Alkanes and Cycloalkanes

C_nH_{2n+2} C_nH_{2n}

Sources of alkanes are **natural gas and petroleum**.

Natural gas consists of approximately 90 to 95% methane, 5 to 10% ethane, and a mixture of other relatively low-boiling alkanes—mainly propane, butane, and 2-methylpropane.

Petroleum is a viscous liquid mixture of thousands of compounds, most of them hydrocarbons, formed from the decomposition of marine plants and animals.

Nomenclature

Names of Unbranched alkanes

(C_nH_{2n+2})

Formula	Number of Isomers	Name
CH_4	1	Methane
C_2H_6	1	Ethane
C_3H_8	1	Propane
C_4H_{10}	2	Butane
C_5H_{12}	3	Pentane
C_6H_{14}	5	Hexane
C_7H_{16}	9	Heptane
C_8H_{18}	18	Octane
C_9H_{20}	35	Nonane
$C_{10}H_{22}$	75	Decane

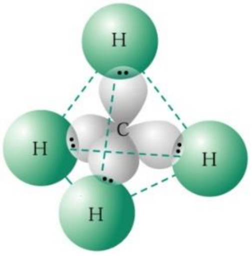
Hybridization

The concept of mixing atomic orbitals into new *hybrid orbitals* (with different energies, shapes, etc., than the component atomic orbitals) suitable for the pairing of electrons to form **chemical bonds**.

sp^3 hybrids

Carbon's **ground state** configuration is:

	1s	2s	$2p_x$	$2p_y$	$2p_z$
C	↑↓	↑↓	↑	↑	



CH_4

The carbon atom can bond to four hydrogen atoms by an **excitation of an electron from the doubly occupied 2s orbital to the empty 2p orbital**, so that there are four singly occupied orbitals:

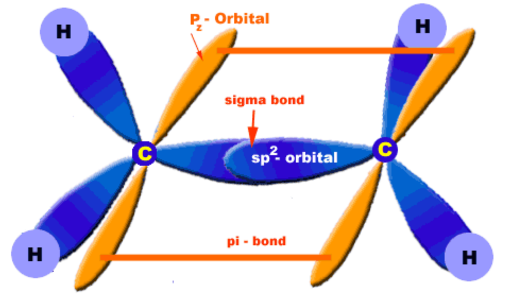
	1s	2s	$2p_x$	$2p_y$	$2p_z$
C*	↑↓	↑	↑	↑	↑

Quantum mechanically, **the lowest energy is obtained if the four bonds are equivalent** which requires that they be formed from equivalent orbitals on the carbon.

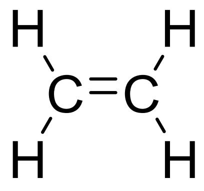
	1s	sp^3	sp^3	sp^3	sp^3
C*	↑↓	↑	↑	↑	↑

sp^2 hybrids

Carbon will sp^2 hybridize, because **one π (pi) bond is required for the double bond between the carbons, and only three σ bonds are formed per carbon atom**. In **sp^2 hybridization** the 2s orbital is mixed with only two of the three available 2p orbitals:



Orbital structure of ethene



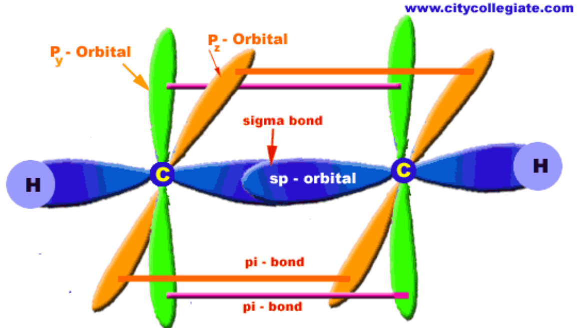
Ethene

C*	↑↓	↑	↑	↑	↑
	1s	sp^2	sp^2	sp^2	2p

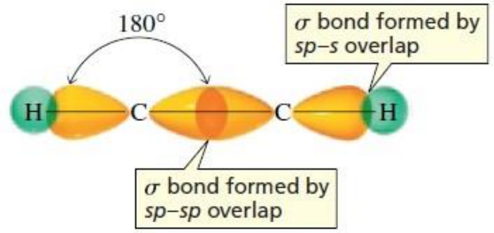
sp hybrids

The 2s orbital mixes with only one of the three p orbitals resulting in two sp orbitals and two remaining unchanged p orbitals.

The chemical bonding in acetylene (ethyne) (C_2H_2) consists of sp–sp overlap between the two carbon atoms forming a σ bond and two additional π bonds formed by p–p overlap. Each carbon also bonds to hydrogen in a σ s–sp overlap at 180° angles



Orbital structure of ethyne



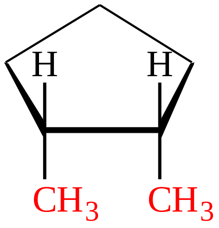
C*	↑↓	↑	↑	↑	↑
	1s	sp	sp	2p	2p

H−C≡C−H

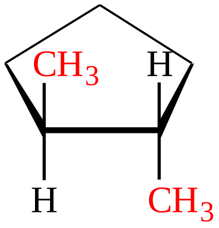
Ethyne

Cis-trans isomerism in cycloalkanes

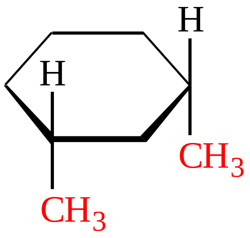
Cis-trans isomers - Isomers that have the same connectivity of their atoms but a different arrangement of their atoms in space due to the presence of either a ring or a carbon–carbon double bond. Such isomers are **stereoisomers**.



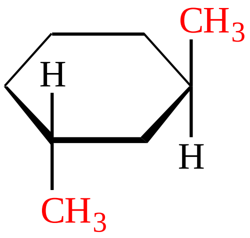
Cis-1,2-dimethylcyclopentane
(b.p. 99.5 ^{o}C)



Trans-1,2-dimethylcyclopentane
(b.p. 91.5 ^{o}C)



Cis-1,3-dimethyl
cyclohexane
(b.p. 120 ^{o}C)



Trans-1,3-dimethyl
cyclohexane
(b.p. 123.5 ^{o}C)

Characteristic reactions of alkanes

The most important chemical property of alkanes and cycloalkanes is their **inertness**. **C—C** and **C—H** bonds are quite strong: alkanes are generally inert to many chemical reagents.

1) C—H bonds of alkanes are only **slightly polarized** ⇒ alkanes are generally unaffected by most bases.

2) Alkane molecules have no unshared electrons to offer sites for attack by acids.

Reactivity of alkanes:

1) Alkanes react vigorously with oxygen when an appropriate mixture is ignited —— combustion.

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O + 212\ \text{kcal/mol}$$

heat of combustion

$$CH_3CH_2CH_3 + 5O_2 \longrightarrow 3CO_2 + 4H_2O + 530\ \text{kcal/mol}$$

2) Alkanes react with chlorine and **bromine** when **heated**, and they react explosively with **fluorine**.

$$CH_4 \xrightarrow[\text{light}]{Cl_2} CH_3Cl \xrightarrow[\text{light}]{Cl_2} CH_2Cl_2 \xrightarrow[\text{light}]{Cl_2} CHCl_3 \xrightarrow[\text{light}]{Cl_2} CCl_4$$

Mechanism (S_R):

$$Cl\text{-}Cl \xrightarrow[\text{light}]{Cl_2} 2\ Cl^{\bullet}$$

$$CH_4 + Cl^{\bullet} \longrightarrow {}^{\bullet}CH_3 + HCl$$

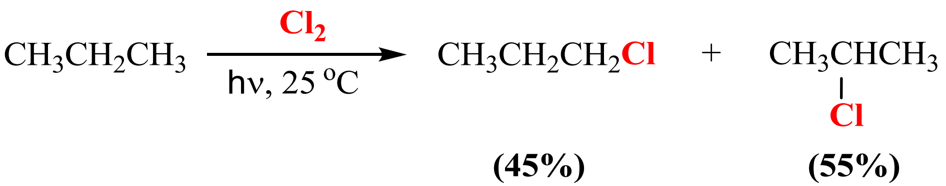
$$^{\bullet}CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl^{\bullet}$$

$$CH_3Cl + Cl^{\bullet} \longrightarrow {}^{\bullet}CH_2Cl + HCl$$

$$^{\bullet}CH_2Cl + Cl_2 \longrightarrow CH_2Cl_2 + Cl^{\bullet}$$

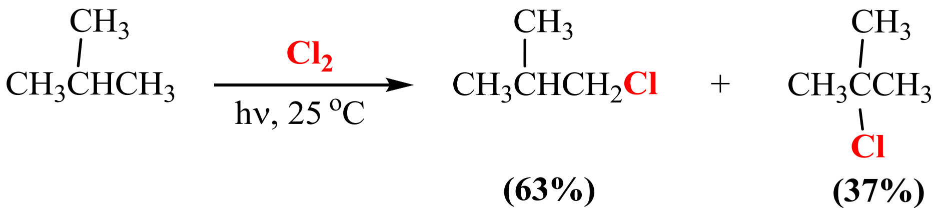
and so on till CCl_4 is formed

Halogenation of higher alkanes



$$CH_3CH_2CH_3 \xrightarrow[h\nu,\ 25\ ^{o}C]{Cl_2} CH_3CH_2CH_2Cl + CH_3\underset{\underset{\displaystyle Cl}{|}}{C}HCH_3$$

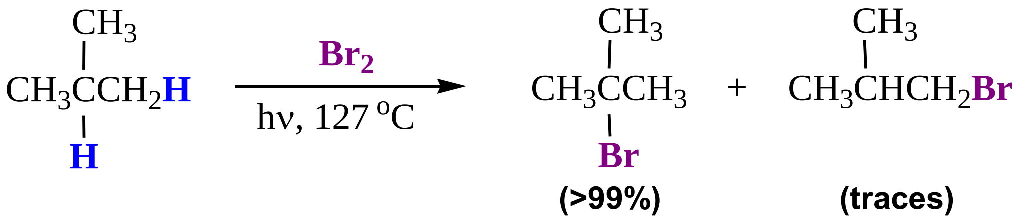
(45%) **(55%)**



$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_3 \xrightarrow[h\nu,\ 25\ ^{o}C]{Cl_2} CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2Cl + CH_3\underset{\underset{\displaystyle Cl}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_3$$

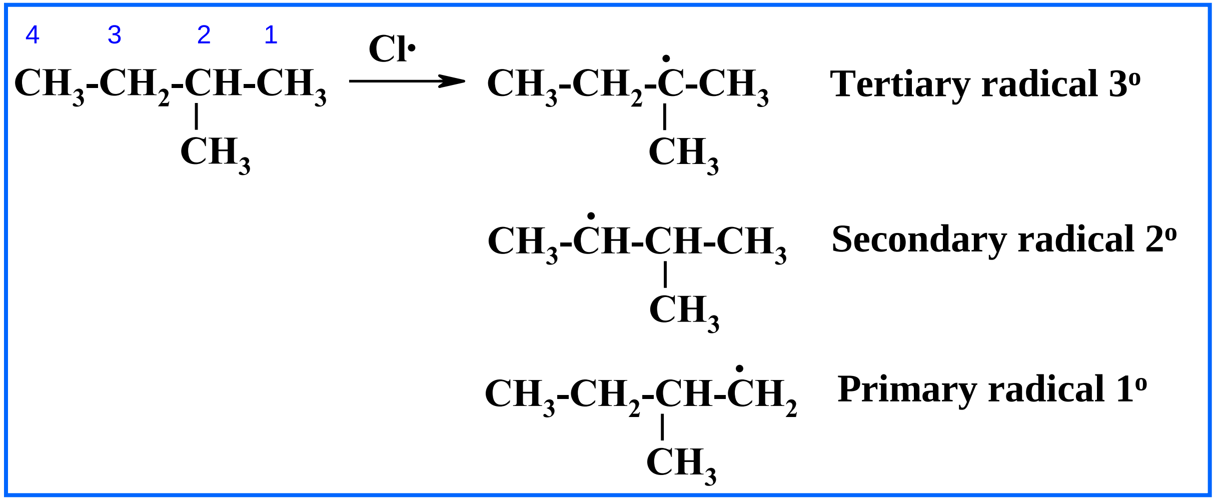
(63%) **(37%)**

Bromination is more selective than chlorination



$$CH_3\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_2H \xrightarrow[h\nu,\ 127\ ^{o}C]{Br_2} CH_3\underset{\underset{\displaystyle Br}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_3 + CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2Br$$

(>99%) **(traces)**



$$\overset{4}{CH_3}\text{-}\overset{3}{CH_2}\text{-}\underset{\underset{\displaystyle CH_3}{|}}{\overset{2}{CH}}\text{-}\overset{1}{CH_3} \xrightarrow{Cl\cdot} CH_3\text{-}CH_2\text{-}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\bullet}{C}}\text{-}CH_3$$

Tertiary radical 3^o

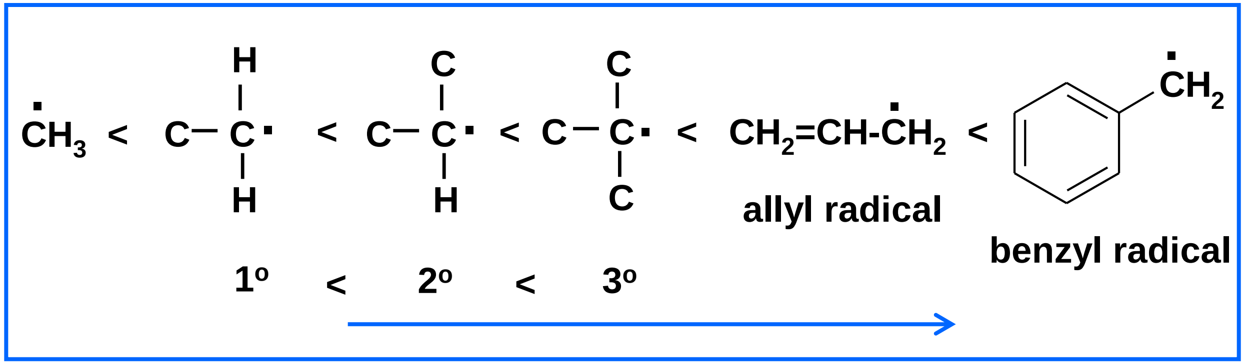
$$CH_3\text{-}\overset{\bullet}{C}H\text{-}\underset{\underset{\displaystyle CH_3}{|}}{CH}\text{-}CH_3$$

Secondary radical 2^o

$$CH_3\text{-}CH_2\text{-}\underset{\underset{\displaystyle CH_3}{|}}{CH}\text{-}\overset{\bullet}{C}H_2$$

Primary radical 1^o

Stability of radicals increases:



$$\dot{C}H_3 < C-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}\cdot < C-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle C}{|}}{C}}\cdot < C-\underset{\underset{\displaystyle C}{|}}{\overset{\overset{\displaystyle C}{|}}{C}}\cdot < CH_2\text{=}CH\text{-}\dot{C}H_2 <$$

allyl radical

benzyl radical

1^o < 2^o < 3^o

Reactivity of halogens:

$F_2 > Cl_2 > Br_2 >> I_2$

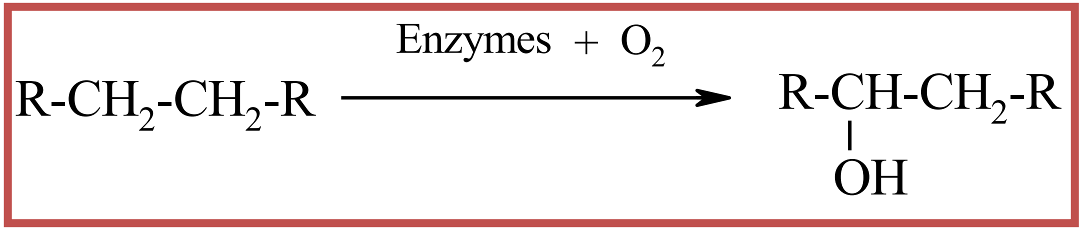
Oxidation of alkanes in biological systems

- **Dehydrogenolysis of Alkanes**

$$\mathrm{R\text{-}CH_2\text{-}CH_2\text{-}R} \xrightarrow[]{\substack{\mathrm{NAD^+} \\ \text{dehydrogenase}}} \mathrm{R\text{-}CH{=}CH\text{-}R} + \mathrm{NADH} + \mathrm{H^+}$$

* NAD – nicotinamide adenosine dinucleotide

- **Hydroxylation**



$$\mathrm{R\text{-}CH_2\text{-}CH_2\text{-}R} \xrightarrow{\text{Enzymes} + \mathrm{O_2}} \underset{\mathrm{OH}}{\underset{|}{\mathrm{R\text{-}CH}}}\mathrm{\text{-}CH_2\text{-}R}$$

By this reaction alkane is transformed to more water soluble alcohol that is easier excreted from the body.

Radical oxidation

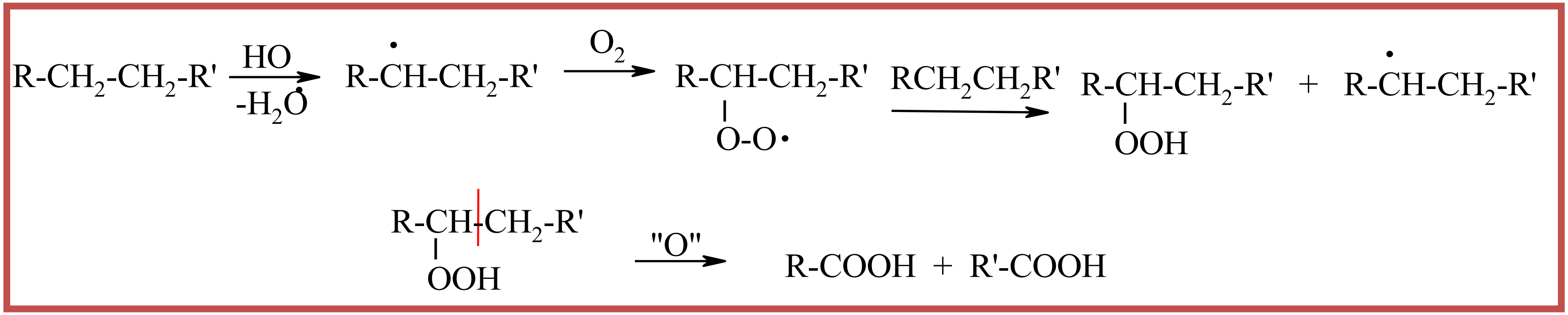
The main source of radicals in a body is O_2. Accepting some amount of electrons and protons it form various oxidants.

$O_2 + e^- \longrightarrow \dot{O}_2^-$ **anion radical of superoxide**

$O_2 + e^- + H^+ \longrightarrow H\dot{O}_2$ **hydroperoxy radical**

$O_2 + 2e^- + 2H^+ \longrightarrow H_2O_2$ **hydrogen peroxide**

$O_2 + 3e^- + 3H^+ \longrightarrow H_2O + HO\bullet$ **hydroxyl radicals**

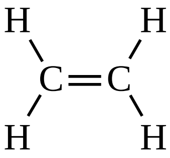


$$R\text{-}CH_2\text{-}CH_2\text{-}R' \xrightarrow[-H_2\dot{O}]{HO} R\text{-}\dot{C}H\text{-}CH_2\text{-}R' \xrightarrow{O_2} R\text{-}\underset{O\text{-}O\bullet}{CH}\text{-}CH_2\text{-}R' \xrightarrow{RCH_2CH_2R'} R\text{-}\underset{OOH}{CH}\text{-}CH_2\text{-}R' + R\text{-}\dot{C}H\text{-}CH_2\text{-}R'$$

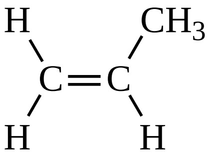
$$R\text{-}\underset{OOH}{CH}\text{-}CH_2\text{-}R' \xrightarrow{"O"} R\text{-}COOH + R'\text{-}COOH$$

Alkenes and Alkynes

Alkenes are hydrocarbons whose molecules contain the C–C double bond.



Ethene



Propene

$H-C\equiv C-H$

Ethyne (acetylene)

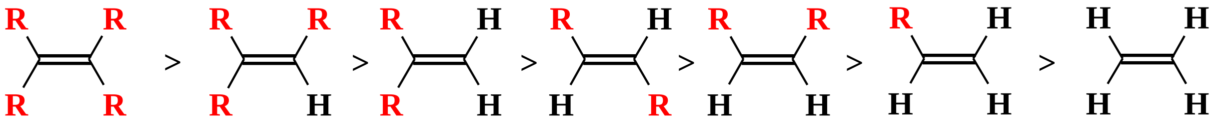
Alkynes are hydrocarbons whose molecules contain the C–C triple bond.

Physical Properties of Alkenes and Alkynes

- ✓ Alkenes and alkynes up to four carbons are gases at room temperature (except 2-butyne).
- ✓ Alkenes and alkynes dissolve in nonpolar solvents or in solvents of low polarity.
- ✓ Alkenes and alkynes are only ***very slightly soluble*** in water.
- ✓ Alkenes and alkynes have densities lower than that of water.

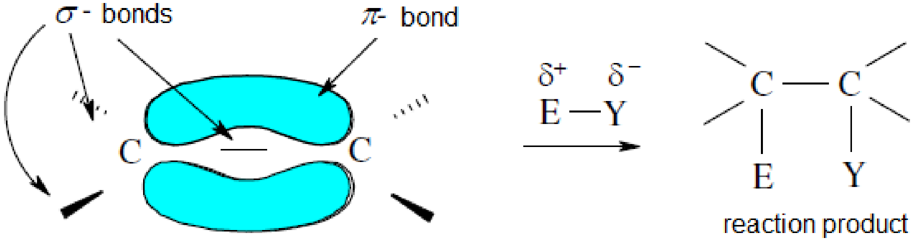
Relative Stabilities of Alkenes

The greater the number of attached alkyl groups (i.e., the more substituted the carbon atoms of the double bond), the greater is the alkene's stability.

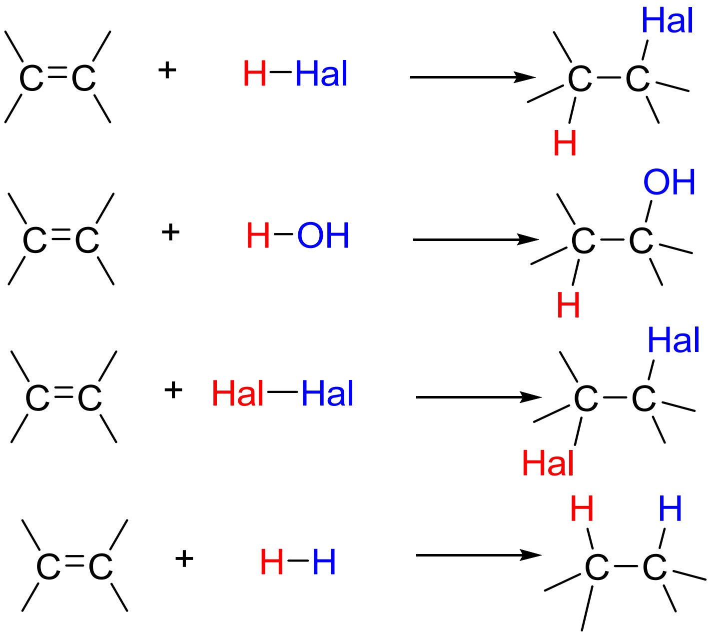


Tetrasubstituted Trisubstituted ← Disubstituted → Monosubstituted Unsubstituted

The most characteristic reaction of alkenes is addition to the carbon-carbon double bond. Usually only p-bond takes part in the reaction. It is broken and in its place two single s-bonds form to two new atoms. As the p- bond has a nucleophilic nature, addition reaction proceeds with electrophiles (A_E) or radicals (A_R).



Characteristic addition reactions of alkenes



Hydrohalogenation

Hydration

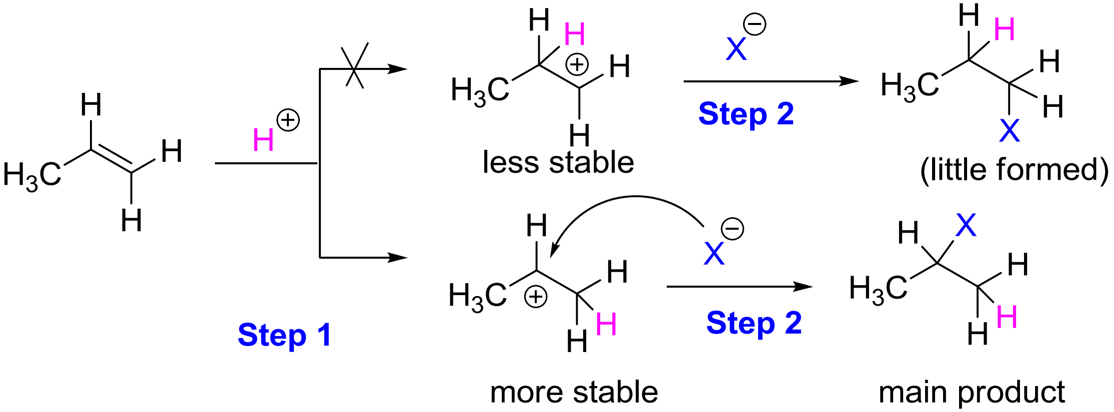
Halogenation

hydrogenation
(reduction)

Reactions of Electrophilic Addition (A_E) to Double or Triple Bond

Addition H-X to Alkenes

Addition of hydrohalogenides is very regioselective.



Step 1 is slower than step 2, therefore **rate-determining step – is step 1**.

The more stable cation predominates because its formation is a faster process.

Addition occurs according to the Markovnikov's rule (was fist formulated in 1870 by Russian scientist Vladimir Markovnikov):

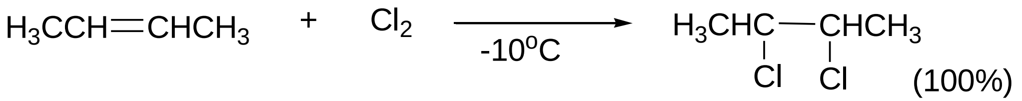
Markovnikov's rule: In the addition of HX to an alkene, the hydrogen atom adds to the carbon of the double bond that already has the greater number of hydrogen atoms.

Reactivity of hydrohalogenides: H-F < H-Cl < H-Br < H-I.

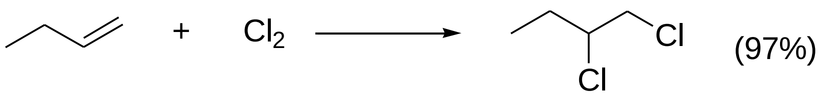
Addition of halogens to a double bond

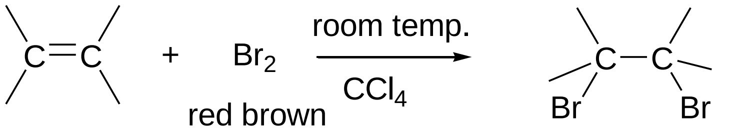
Alkenes react rapidly with chlorine and bromine in nonnucleophilic solvents to form vicinal dihalides.

Examples:



$$H_3CCH{=}CHCH_3 + Cl_2 \xrightarrow[-10^oC]{} H_3CHC(Cl){-}CHCH_3(Cl) \quad (100\%)$$





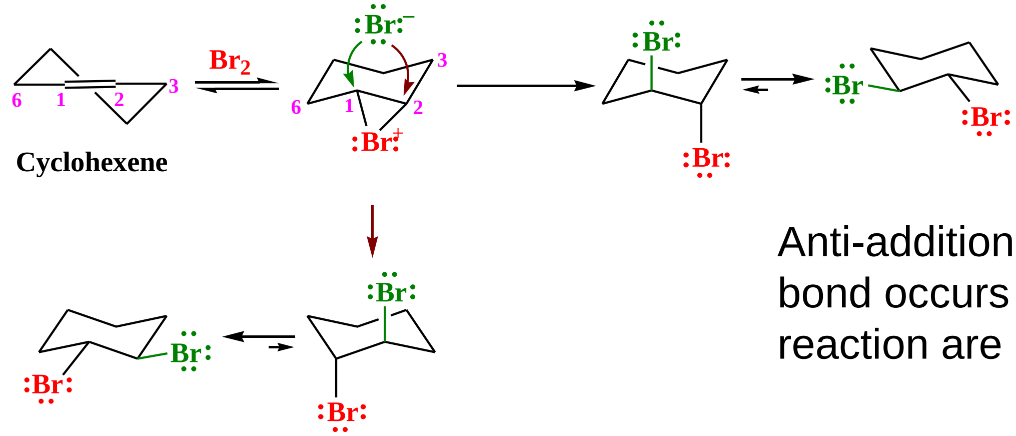
(vicinal dibromide
(a colorless compound)

Rapid decolorization of Br_2/CCl_4 solution is a test for alkenes and alkynes

This behavior contrasts with that of alkanes which do not react appreaciably with bromine or chlorine at room temp.

$$R{-}H + Br_2 \xrightarrow{r.t./\ CCl_4} \text{no reaction}$$

Mechanism of Halogen Addition

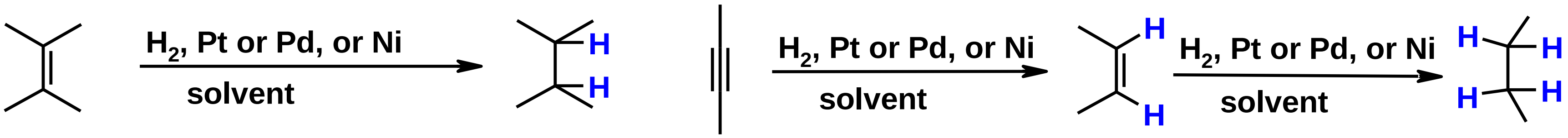


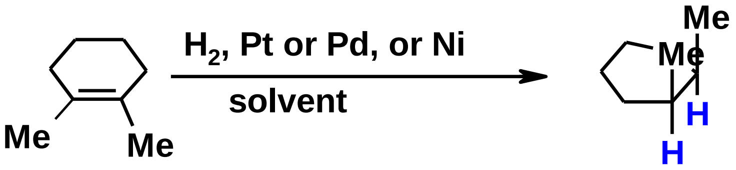
Anti-addition of halogens to a double bond occurs and the products of the reaction are *trans*-1,2-dihalocycloalkanes

Hydrogenation of a double and triple bond

Alkenes and alkynes react with hydrogen in the presence of metal catalysts to produce alkanes or alkenes, respectively. One molar equivalent of hydrogen is required to reduce an alkene to an alkane. Two molar equivalents of hydrogen are required to reduce an alkyne.

Examples:





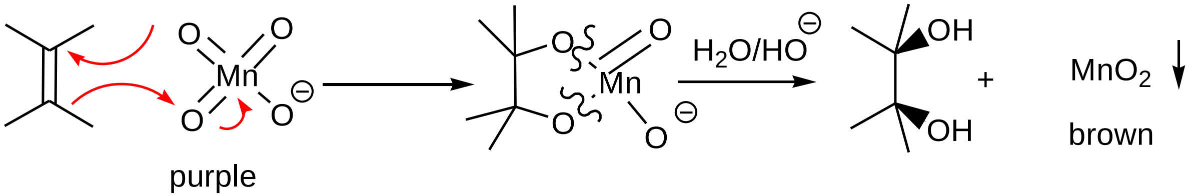
cis-1,2-dimethylcyclohexane

The both hydrogen atoms adds to a double or triple bond from ***one side***. ***Syn*****-addition of hydrogen is always observed**. Because of such a stereochemistry, hydrogenation of substituted cycloalkenes gives *cis*-substituted cycloalkanes.

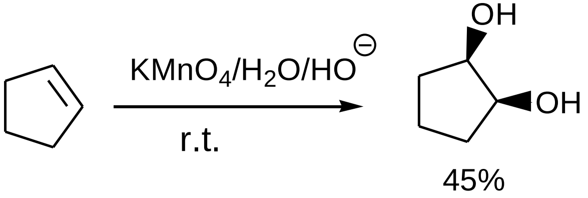
Oxidations of Alkenes

syn-1,2-dihydroxylation. Formation of 1,2-diols.

With $KMnO_4$



Reaction with potassium permanganate is used as chemical test for the presence of unsaturation in an unknown compound.

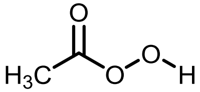


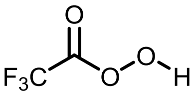
cis-1,2-cyclopentandiol

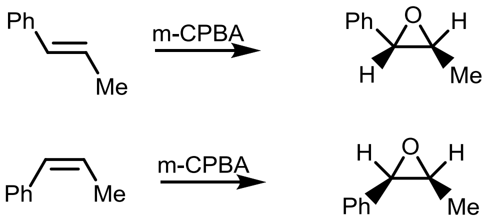
Oxidation with peroxyacids to oxiranes (alkene oxides, epoxides)

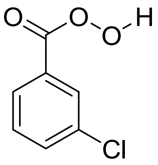
Reaction proceeds with retenion of configuration of an alkene.

Various peroxyacids or hydrogen peroxide are used as oxidants in the reaction.

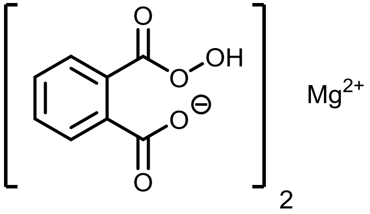






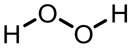


m-CPBA



magnesium monoperoxyphtalate
(MMPP)

Hydrogen peroxide

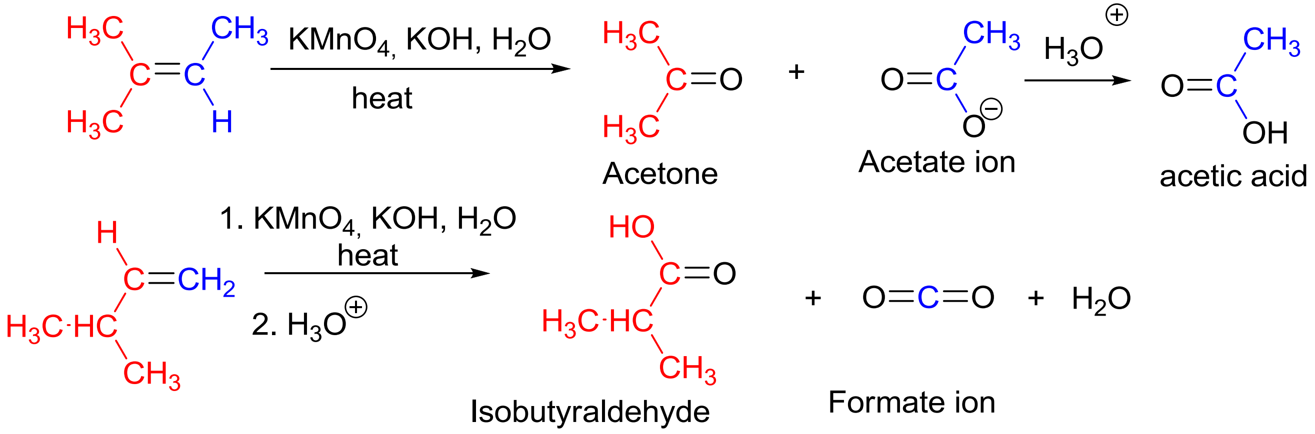


Oxidative Cleavage of Alkenes

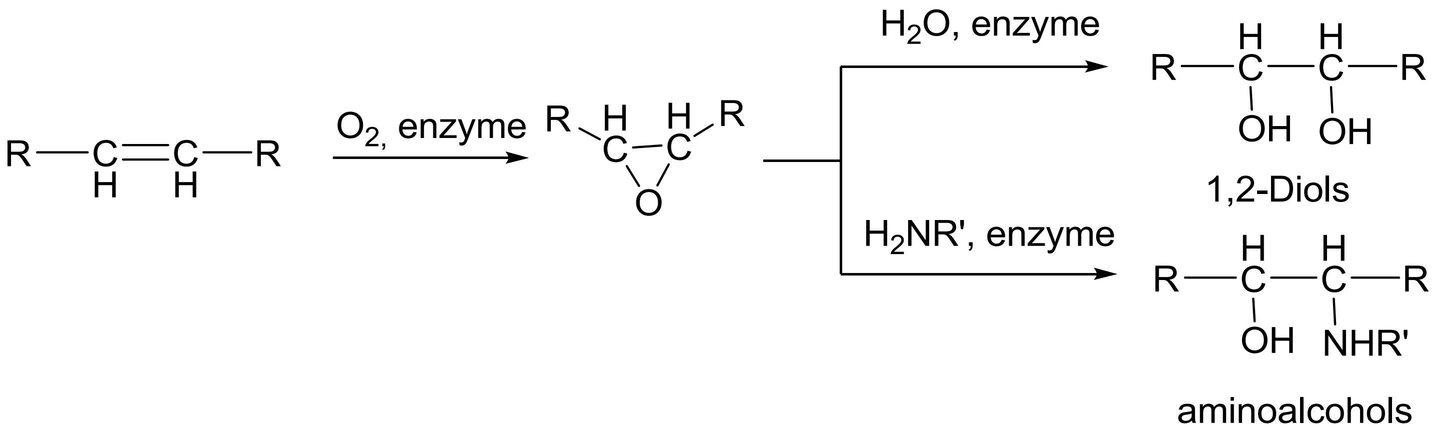
Cleavage with Hot Basic Potassium Permanganate

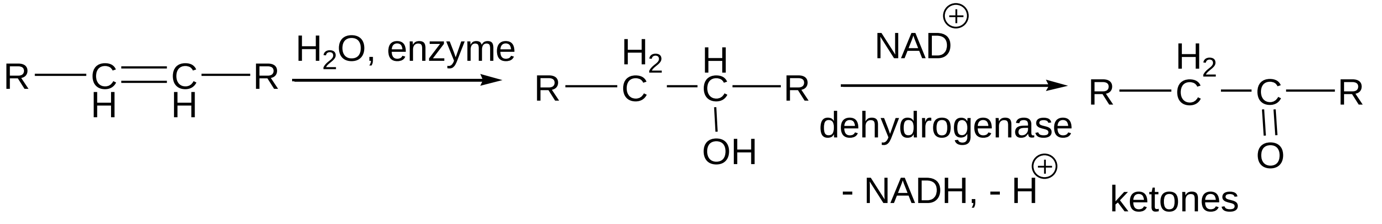
Treatment with hot basic $KMnO_4$ oxidatively cleaves the double bond of an alkene.

Alkenes with monosubstituted carbon atoms are oxidatively cleaved to salts of carboxylic acids. Disubstituted alkene carbons are cleaved to ketones.

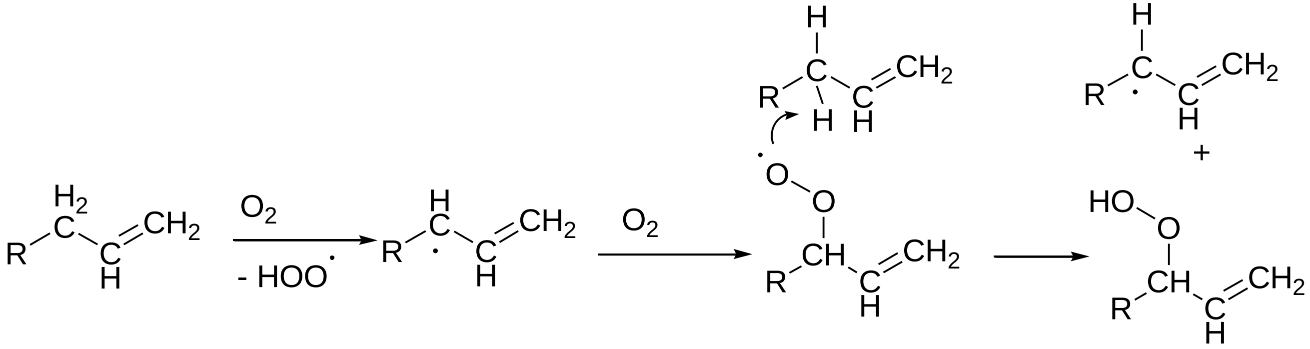


Oxidation of alkenes in living organisms





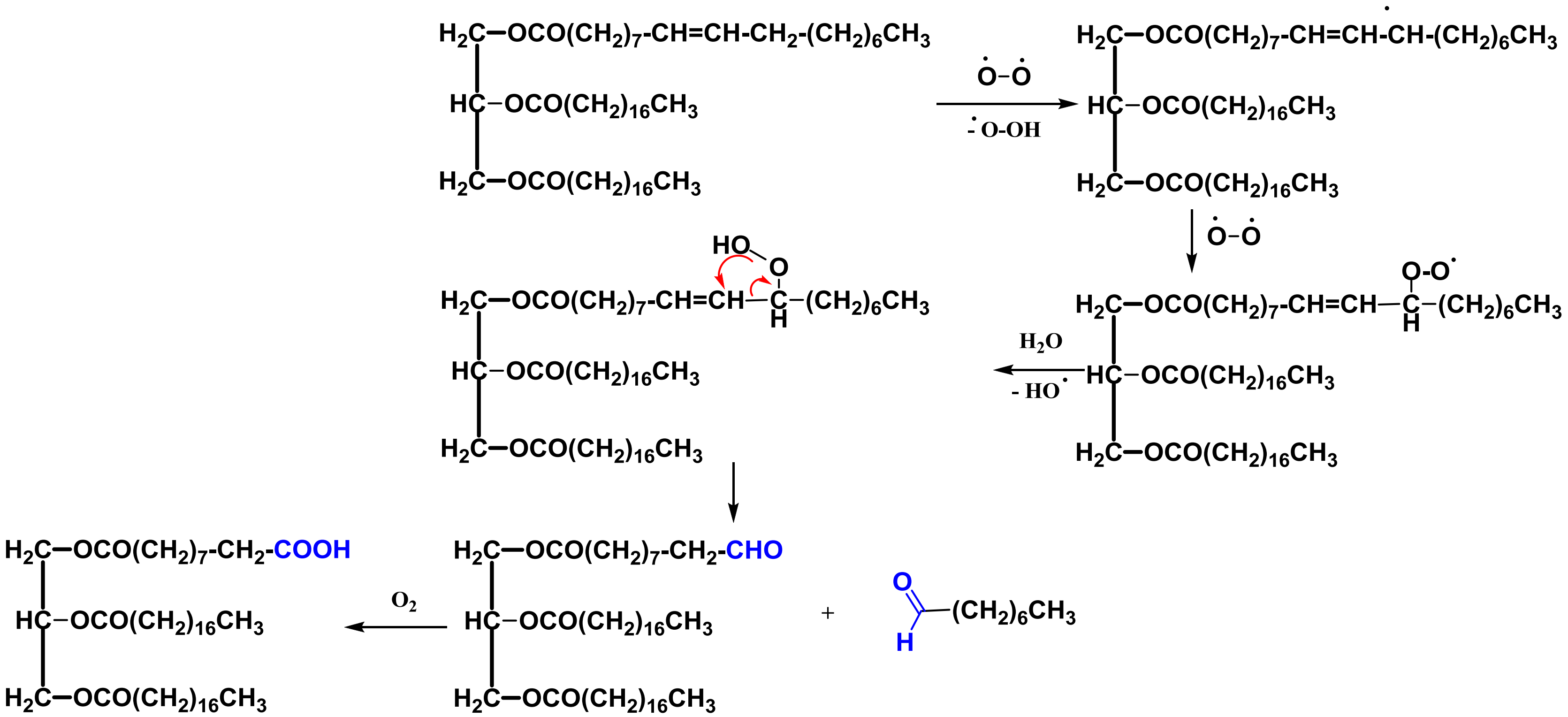
* NAD – nicotinamide adenosine dinucleotide



If such an oxidation is caused by atmospheric oxygen, it is called as autooxidation

Autooxidation of fats (cooking oils)

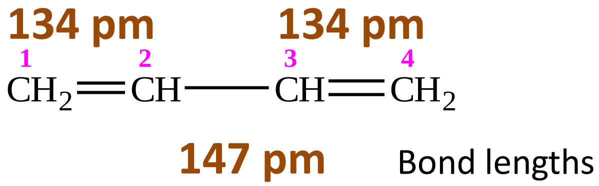
Autoxidation is a radical-chain process that converts an R-H group to an R-O-O-H group, called a hydroperoxide. Hydroperoxides themselves are unstable and, under biological conditions, degrade to short-chain aldehydes and carboxylic acids with unpleasant smells.



Conjugated dienes and polyenes

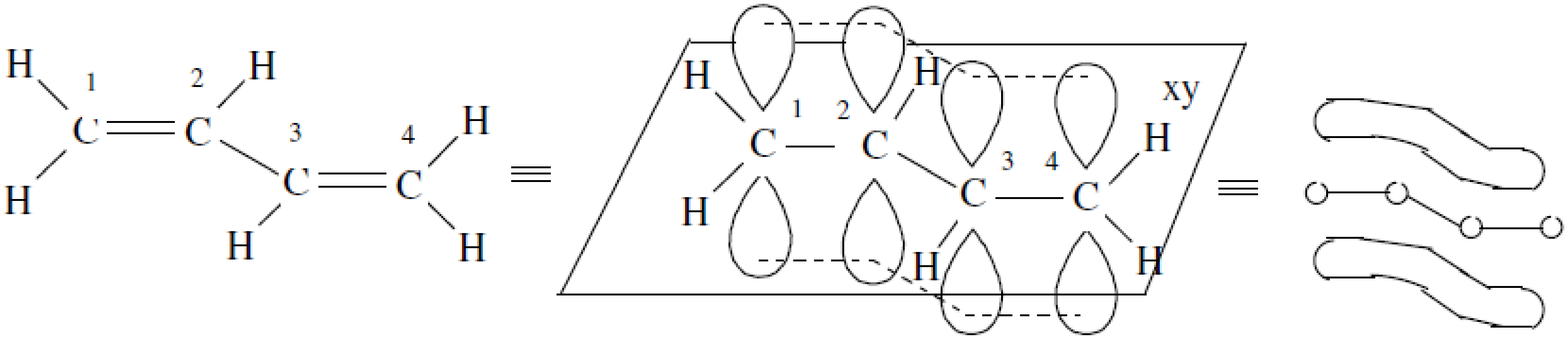
Structure and properties

In conjugated dienes and polyenes the double and single bonds *alternate* along the chain.



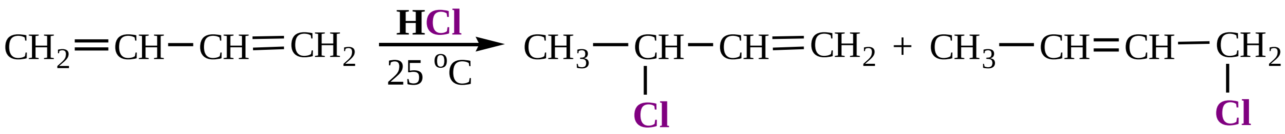
$\overset{1}{C}H_2=\overset{2}{C}H-\overset{3}{C}H=\overset{4}{C}H_2$

Bond lengths



1,3-butadiene

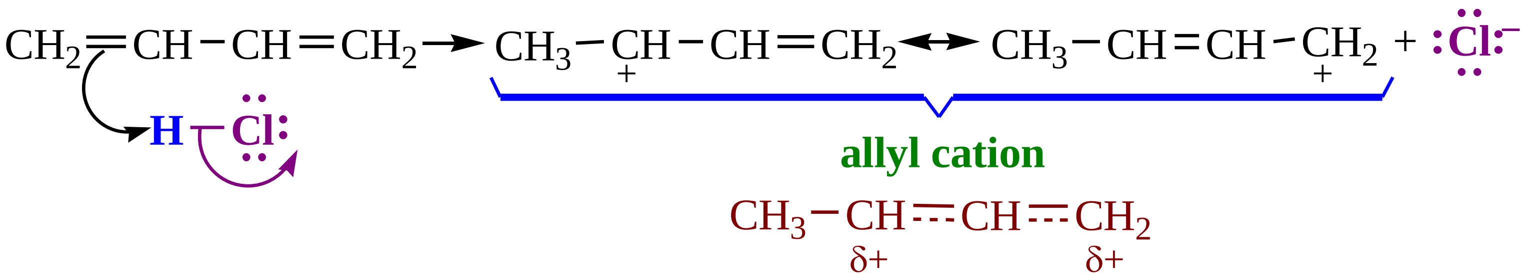
1,3-butadiene reacts with one molar equivalent of HCl to produce two products: 3-chloro-1-butene and 1-chloro-2-butene.

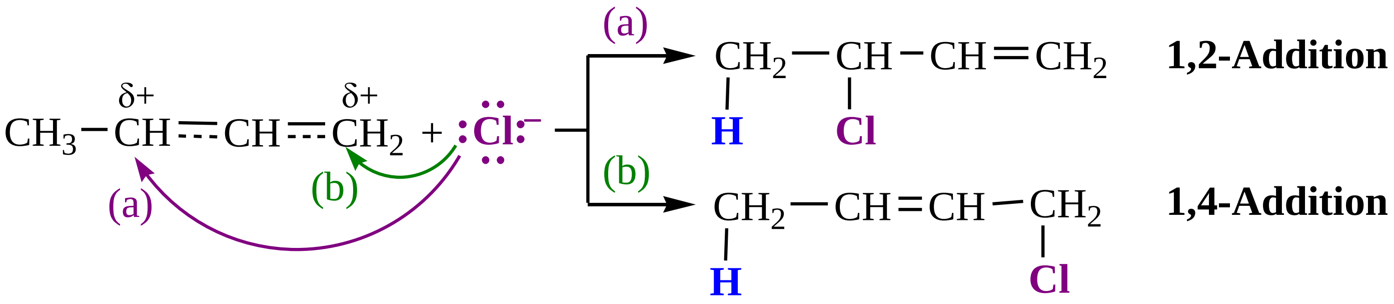


$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[25\ ^{o}C]{HCl} CH_3{-}\underset{Cl}{CH}{-}CH{=}CH_2 + CH_3{-}CH{=}CH{-}\underset{Cl}{CH_2}$$

1,3-Butadiene **3-Chloro-1-butene** **1-Chloro-2-butene**

1,2- ir 1,4-Addition

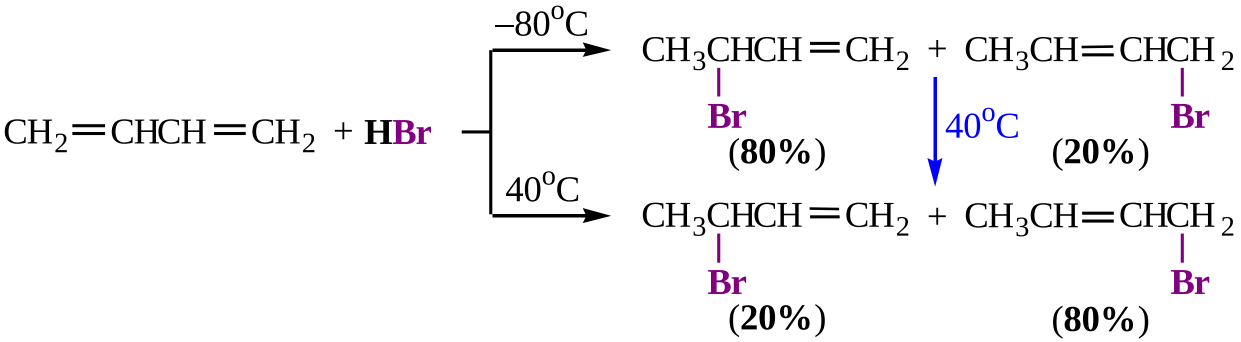




1,2-Addition

1,4-Addition

The relative amounts of 1,2- and 1,4-addition products are dependent on the reaction temperature. For example:



$$CH_2{=}CHCH{=}CH_2 + HBr \xrightarrow{-80^{o}C} CH_3\underset{\substack{|\\ Br}}{CH}CH{=}CH_2 + CH_3CH{=}CH\underset{\substack{|\\ Br}}{CH_2}$$

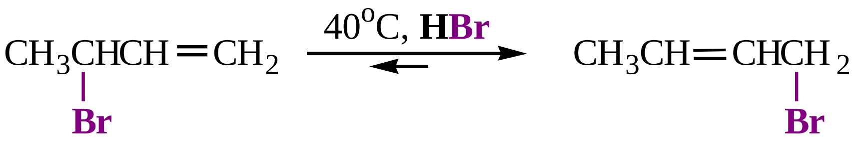
(80%) (20%)

$$\downarrow 40^{o}C$$

$$CH_2{=}CHCH{=}CH_2 + HBr \xrightarrow{40^{o}C} CH_3\underset{\substack{|\\ Br}}{CH}CH{=}CH_2 + CH_3CH{=}CH\underset{\substack{|\\ Br}}{CH_2}$$

(20%) (80%)

At the higher temperature and in the presence of HBr, the 1,2-adduct rearranges to 1,4-product and that an equilibrium exists between them. The equilibrium favors the 1,4-addition product. **Therefore, *1,4-adduct must be more stable*.**



$$CH_3\underset{\substack{|\\ Br}}{CH}CH{=}CH_2 \underset{}{\overset{40^{o}C,\ HBr}{\rightleftharpoons}} CH_3CH{=}CH\underset{\substack{|\\ Br}}{CH_2}$$

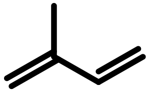
1,2-Addition product **1,4-Addition product**

$$CH_2{=}CHCH{=}CH_2 \xrightarrow[-15^{o}C]{Br_2} CH_2BrCHBrCH{=}CH_2 + CH_2BrCH{=}CHCH_2Br$$

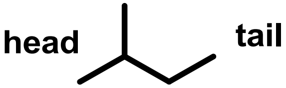
(54%) (46%)

Terpenes and terpenoids

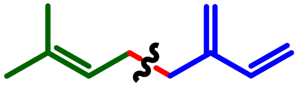
Terpenes – compounds whose carbon skeleton can be devided into two or more units of isoprene (C_5H_8). Terpenes according to carbon chain structure can be acyclic and cyclic. Terpenes with oxygen containing functional group are called **terpenoids.** Terpenes are components of the so-called essential oils extracted from various parts of plants. Essential oils contain low molecular weight substances that are largely responsible for characteristic plant fragrances. Many essential oils, but particularly those from flowers, are used in perfumes.



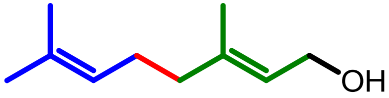
Isoprene
(2-methyl-1,3-butadiene)



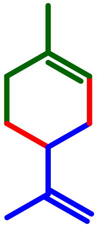
isoprene structural unit



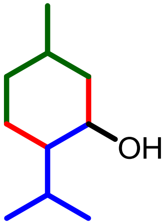
Myrcene
(bay oil)



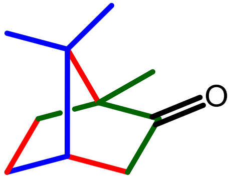
geraniol
(rose)



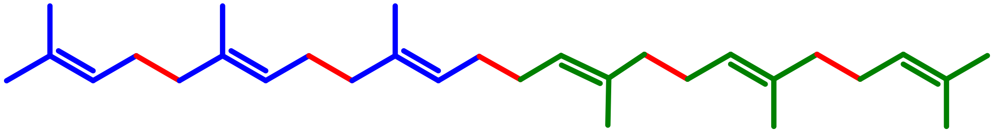
limonene
(lemon and orange)



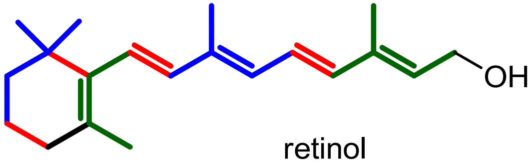
menthol
(pepper mint)



camphor
(camphor tree)



squalene
(shark liver oil,
wheat germ, and olives)



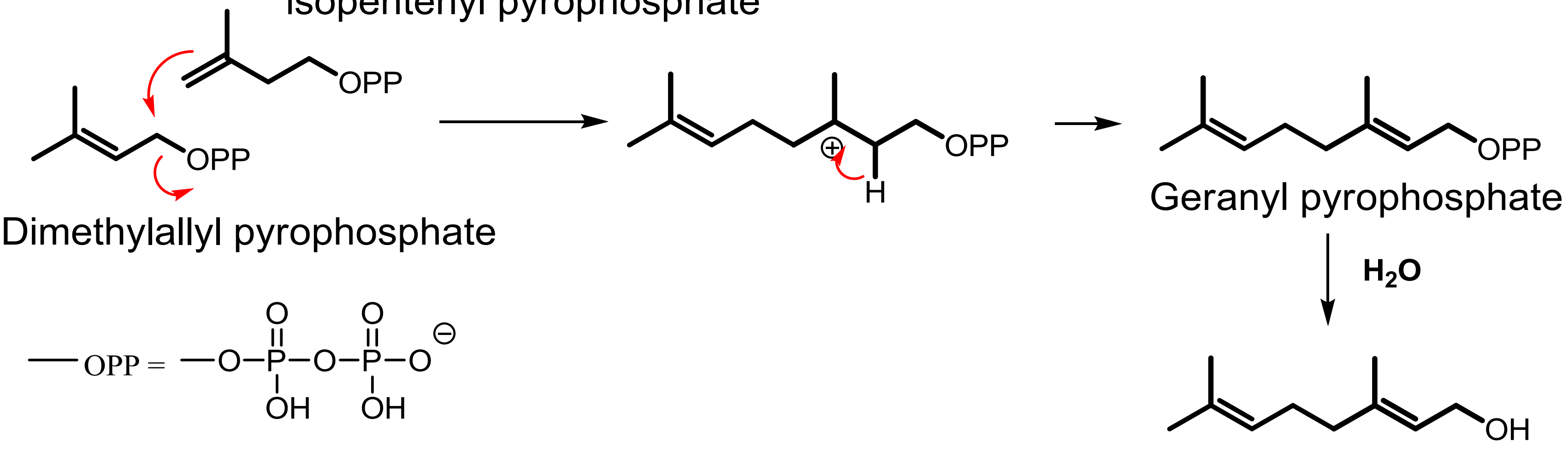
retinol
(Vitamin A)
essentional for vision

Classified according to the number of isoprene units they contain.

Class	# C atoms	# isoprene units
Monoterpene	10	2
Sesquiterpene	15	3
Diterpene	20	4
Sesterpene	25	5
Triterpene	30	6
Tetraterpene	40	8

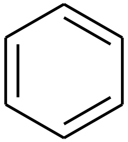
Mono- ir sesquiterpenes are mainly found in plants, higher terpenes – in plants and in animals.

In nature all terpenes are synthesised by the reaction of isopentenyl pyrophosphate and dimethylallyl pyrophosphate.



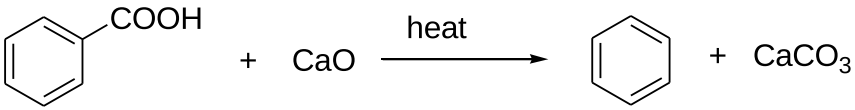
$$—\text{OPP} = —\text{O}—\overset{\text{O}}{\underset{\text{OH}}{\overset{\|}{\underset{|}{\text{P}}}}}—\text{O}—\overset{\text{O}}{\underset{\text{OH}}{\overset{\|}{\underset{|}{\text{P}}}}}—\text{O}^{\ominus}$$

Aromatic compounds (Arenes)



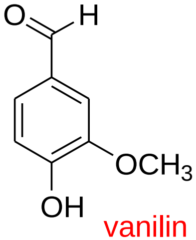
Benzene
(C_6H_6)

First synthesized in 1834 by German chemist Eilhardt Mitscherlich (University of Berlin). He also showed that benzene has a molecular formula C_6H_6. The formula itself was surprising. *Benzene has only as many hydrogen atoms as it has carbon atoms*.

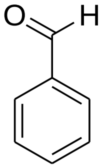


Benzoic acid

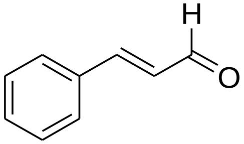
In the second part of 19th century organic compounds were classified into two broad categories: aliphatic and aromatic. Most of the early aromatic compounds were isolated from plants, balsams, resins and essential oils. Many of them were fragrant.



vanilin



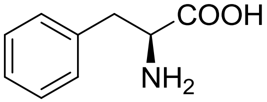
benzaldehyde
(from oil of bitter almonds)



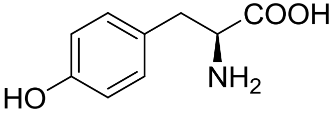
cinamic aldehyde

Kekule was the first who recognized that these early aromatic compounds all contain a six-membered unit and that this is retained through most chemical reactions.

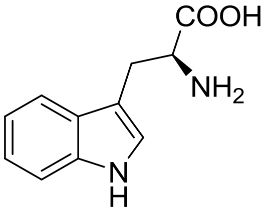
Examples of well-known organic compounds containing aromatic fragment.



phenylalanine

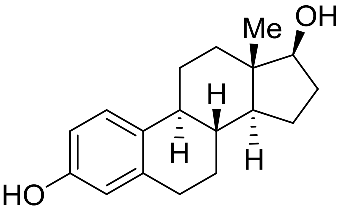


Tyrosine

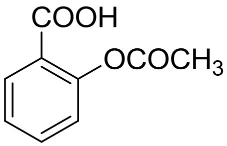


Tryptophan

α- Amino acids

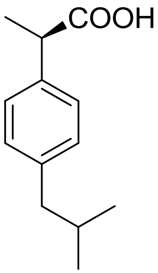


Estradiol
(female sex hormone)



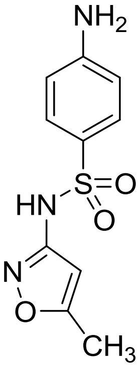
Aspirin

(analgesic and
antipyretic activity)



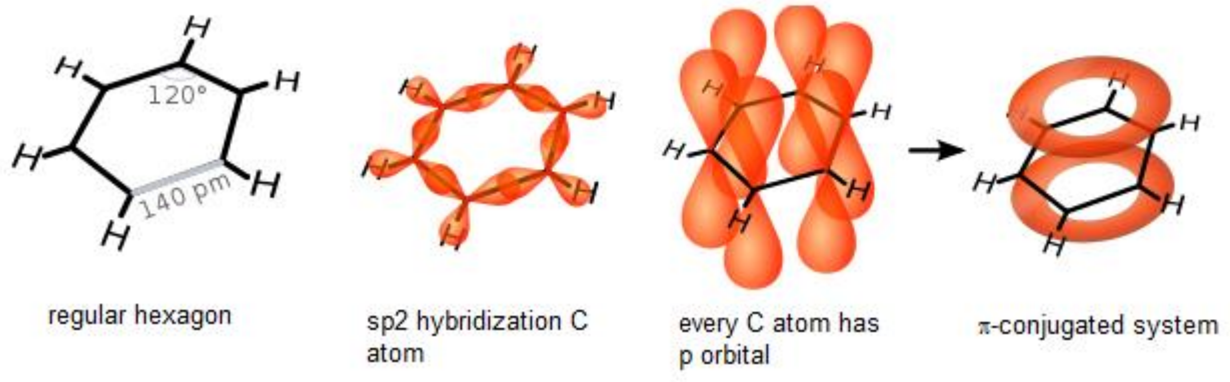
Ibuprofen

(anti-inflammatory activity)

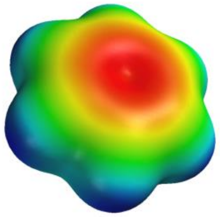


Sulphamethoxazole
(antimicrobal activity)

Structure of benzene



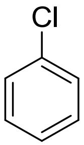
Red – negative charge



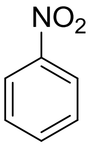
Delocalization of electron density in benzene .

Nomenclature of aromatic compounds

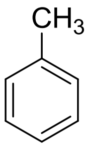
Benzene derivatives are named by prefixing the name of the substituent to the word benzene, e.g. chlorobenzene and nitrobenzene. Many benzene derivatives have trivial names, which may show no resemblance to the name of the attached substituent group, e.g. phenol, toluene and aniline.



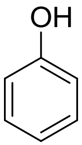
Chlorobenzene



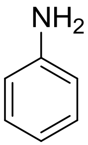
Nitrobenzene



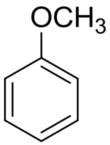
Toluene



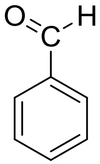
Phenol



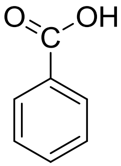
Aniline



Anisol

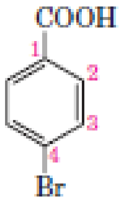


Benzaldehyde

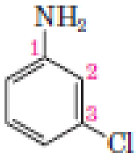


Benzoic acid

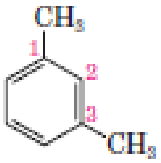
When two groups are attached to the benzene ring, their relative positions have to be identified. The three possible isomers of a disubstituted benzene are differentiated by the use of the names ***ortho- (1,2-positions), meta- (1,3-positions and para- (1,4-positions)***, abbreviated as **o-, m- and p-**, respectively.



4-Bromobenzoic acid
(p-Bromobenzoic acid



3-Chloroaniline
(m-Chloroaniline)

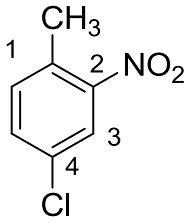


1,3-Dimethylbenzene
(m-Xylene)

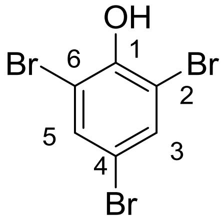
When more than two groups are attached to the benzene ring, numbers are used to indicate their relative positions.

If one of the groups that give a trivial name is present, then the compound is named as having the special group in position 1.

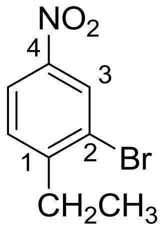
If the groups are the same, each is given a number, the sequence being the one that gives the lowest combination of numbers;



4-Chloro-2-nitrotoluene

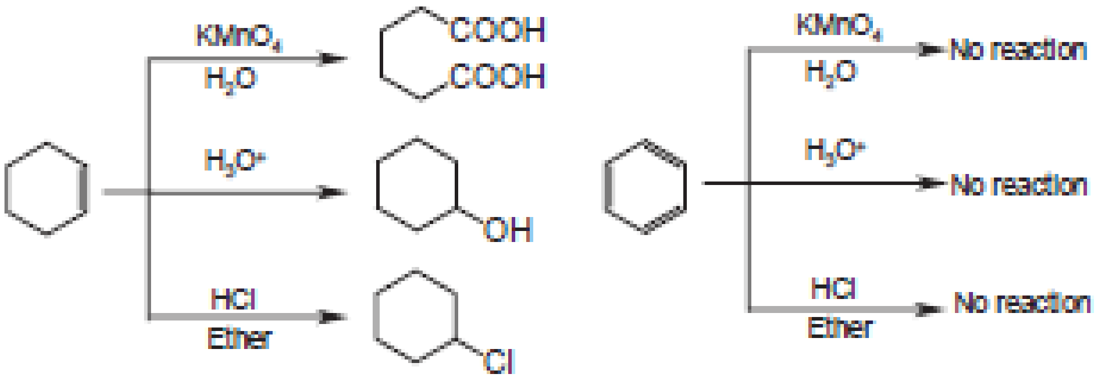


2,4,6-tribromophenol



2-bromo-1-ethyl-4-nitrobenzene

Comparison of cyclohexene with benzene

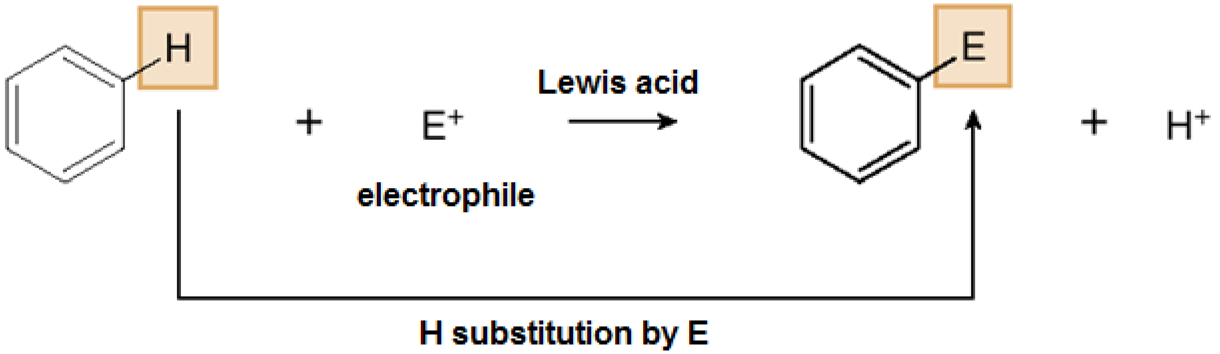


Cyclohexene vs benzene

Benzene does not take part in addition reactions. Benzene is susceptible to electrophilic atack primarily because of its exposed π electrons.

Reactions of electrophilic substitution in arenes (S_E)

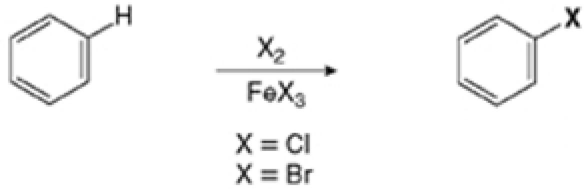
Electrophilic aromatic substitution reactions



Aromaticity is retained when substitution of hydrogen atom in arene occurs.

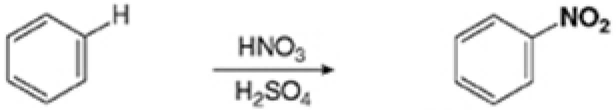
Reaction	Electrophile

[1] **Halogenation: H substitution by X (X = Cl or Br**



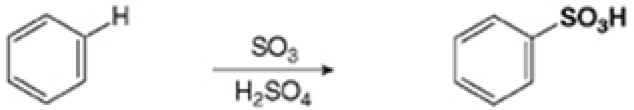
$E^+ = Cl^+$ or Br^+

[2] **Nitration**



$E^+ = \overset{+}{N}O_2$

[3] **Sulfonation**

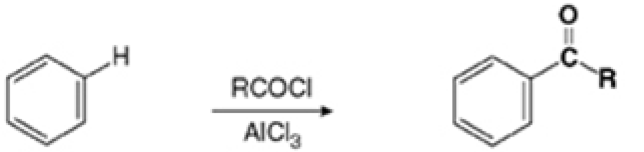


$E^+ = \overset{+}{S}O_3H$

[4] **Friedel - Crafts alkylation: H substitution by alkyl**

$E^+ = R^+$

[5] **Friedel - Crafts acylation: H substitution by acyl**



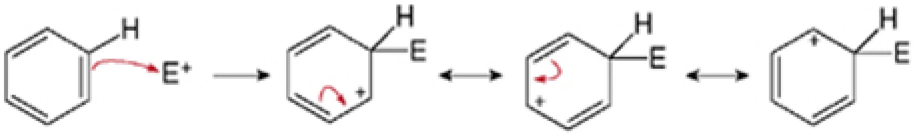
$E^+ = R\overset{+}{C}O$

http://science.jbpub.com/organic/movies/

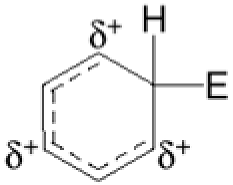
Mechanism of S_EAr reactions

Step 1. The electrophile takes two electrons of the six-electron π system to form a σ bond to one of the carbon atoms of the benzene ring. In an arenium ion 4 π electrons are delocalized through 5 p orbitals.

Step 1

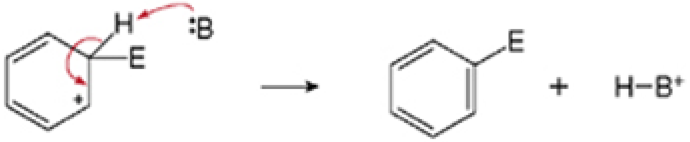


stabilized arenium ion



Hybride structure

Step 2



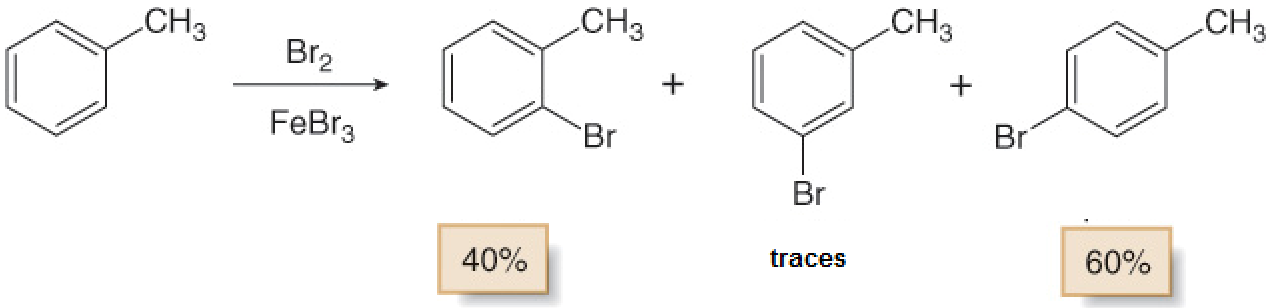
In step 2 a proton is removed from the carbon atom of arenium ion that bears an electrophile. The two electrons that bound this proton with carbon become a part of the π system. The proton is removed by any of the bases present. For example, by the anion derived from the electrophile.

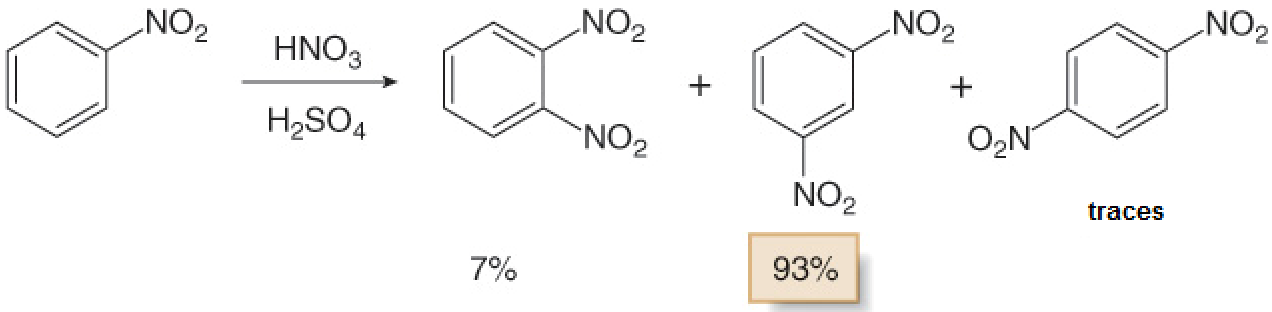
S$_E$Ar reactions of monosbstituted benzenes

What would happen if we were to carry out a reaction on a aromatic ring that already has a substituent? A substituent already present on the ring has two effects:

- **A substituent affect the reactivity of the aromatic ring. Some substituents activate the ring, making it more reactive than benzene. Electron donoric substituents, such as alkyl, alkoxy, amino, substituted amino, hydroxy, make the ring more reactive**

- **Substituents affect the orientation of the reaction.** The three possible disubstituted products – *ortho-, meta- or para-* are usually not formed in equal amounts. Instead **the nature of the substituent already present on the benzene ring determines the position of the second substituent.**

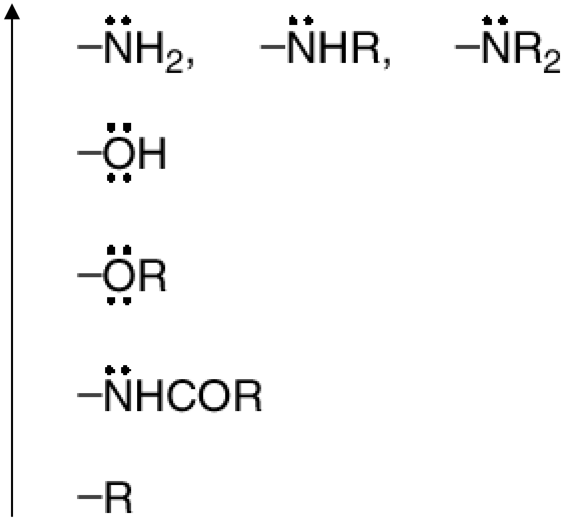




Substituents are classified into three groups:

1. *ortho- ir para-directing activators*.

2. *ortho- ir para-directing deactivators*.



$-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$

$-\underset{..}{\ddot{O}}H$

$-\underset{..}{\ddot{O}}R$

$-\ddot{N}HCOR$

$-R$

$-\underset{..}{\ddot{F}}\colon$ $-\underset{..}{\ddot{Cl}}\colon$ $-\underset{..}{\ddot{Br}}\colon$ $-\underset{..}{\ddot{I}}\colon$

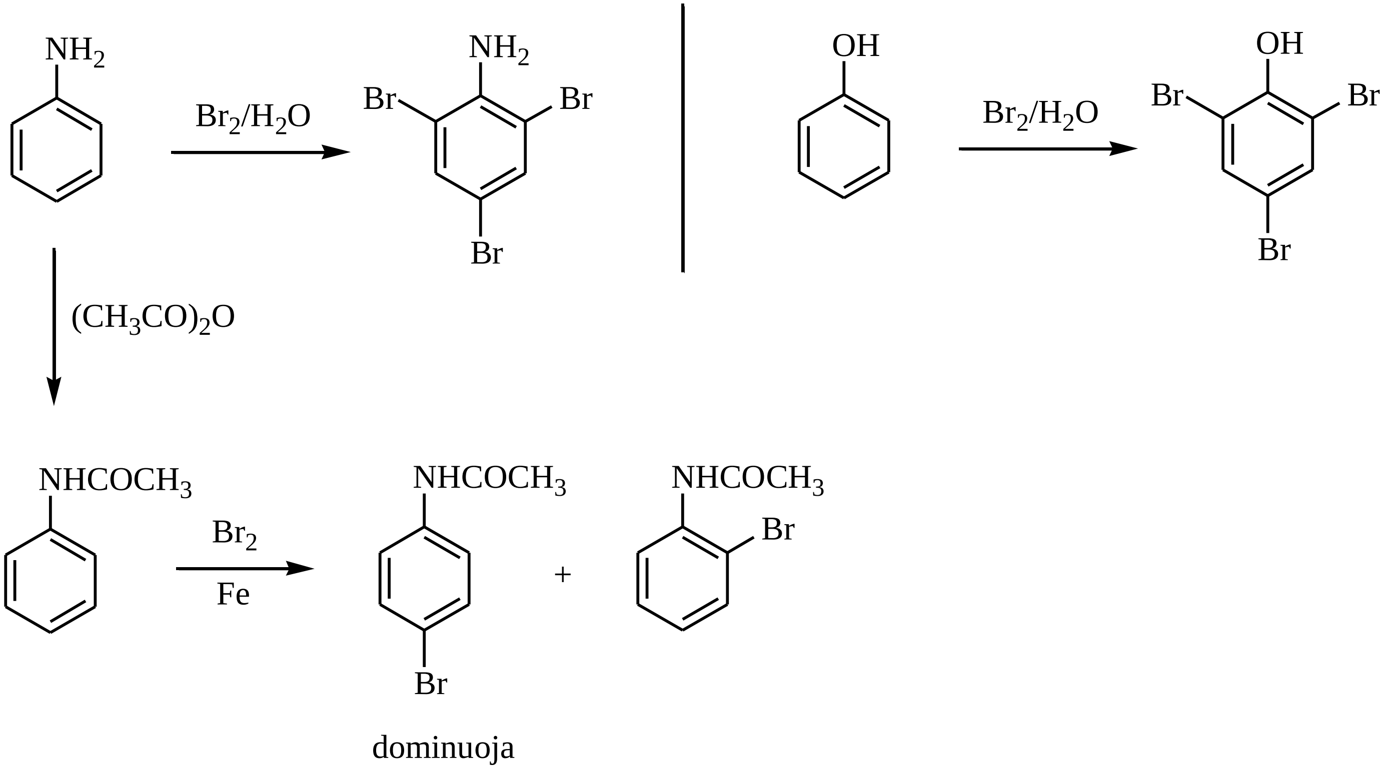
3. *meta-directing deactivators*.

$-CHO$, $-COR$, $-COOR$, $-COOH$, $-CN$, $-SO_3H$, $-NO_2$, $-\overset{+}{N}R_3$

$$\xrightarrow{\hspace{10cm}}$$

Examples:

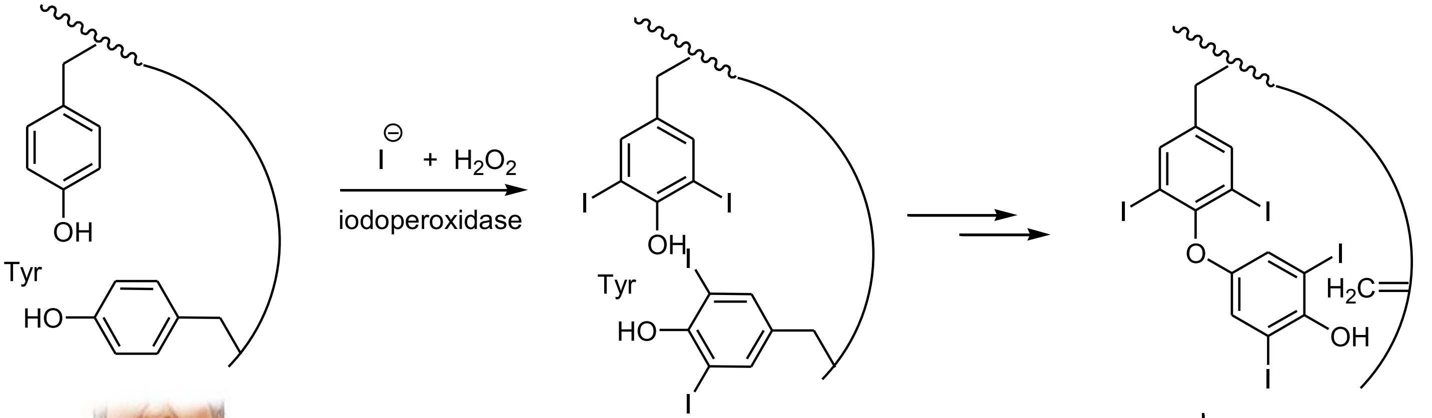
Amino and hydroxy groups are strong electron donors, therefore, aniline and phenol are very reactive in electrophilic substitution reactions (bromination occurs even at room temperature without use of catalyst – Lewis acid.)

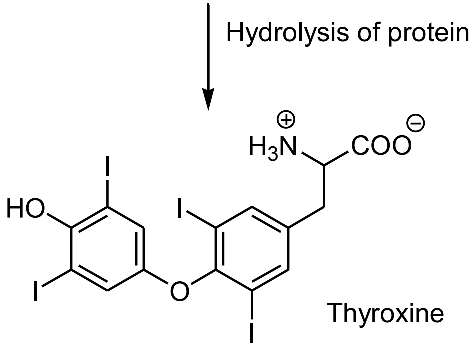


Acetyl group in acetanilide weakens electron donor properties of amino group. Therefore, the reaction is more slow, but it is possible to perfom monobromination reaction.

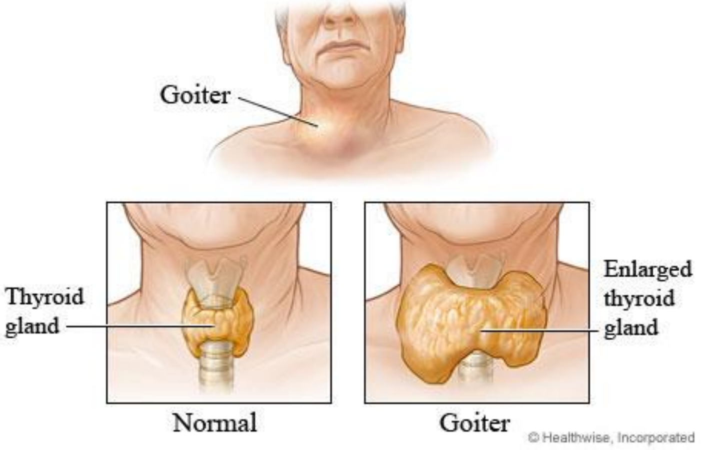
Iodide Ion and Goiter. Biosynthesis of Hormone - Thyroxine

Goiter - an enlargement of the thyroid gland caused by iodine deficiency. This disease results from underproduction of thyroxine, a hormone synthesized in the thyroid gland. Young mammals require this hormone for normal growth and development. Low levels of thyroxine in adults result in hypothyroidism, commonly called goiter, the symptoms of which are lethargy, obesity, and dry skin.



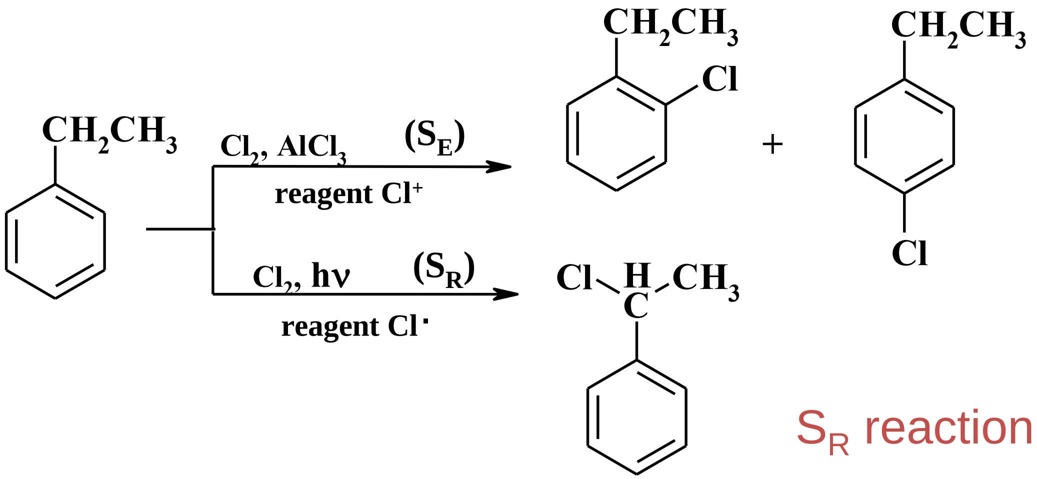


Thyroxine



© Healthwise, Incorporated

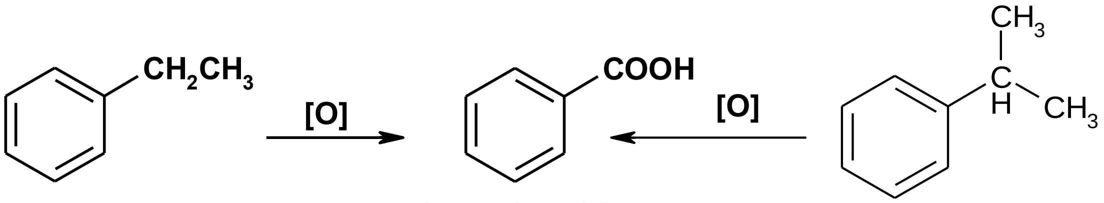
For alkyl derivatives of benzene S_E ir S_R reactions are characteristic.



S_E reaction

S_R reaction

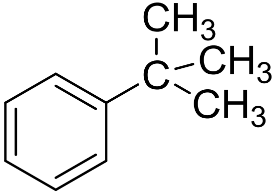
Oxidation reaction of alkylbenzenes starts with benzylic C atoms. As a result, benzoic acid is formed from different alkylbenzenes.



benzoic acid

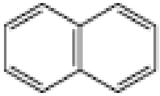
[O] = O_2, $KMnO_4$, $K_2Cr_2O_7$, biological oxidation.

However,

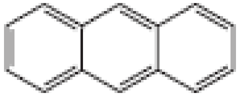


stable under various oxidation conditions

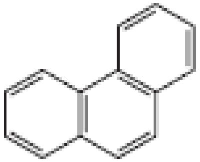
Polynuclear Aromatic Hydrocarbons (PAHs)



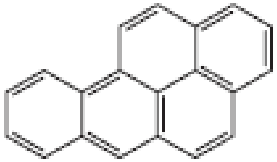
Naphthalene



Anthracene

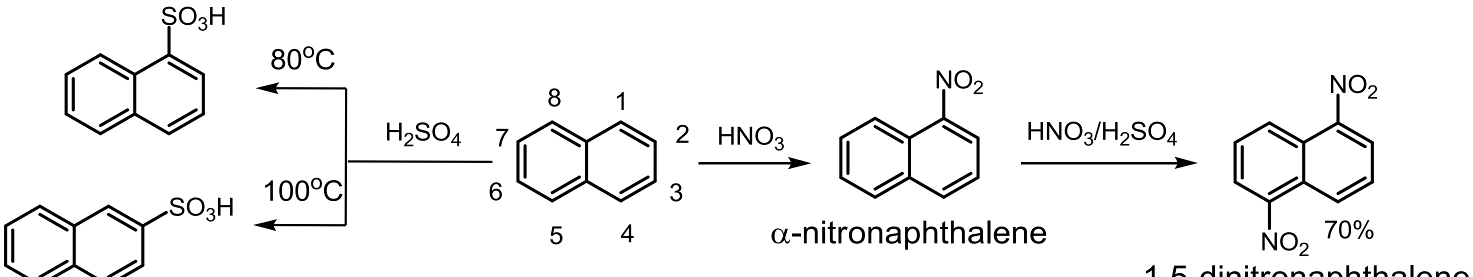


Phenanthrene

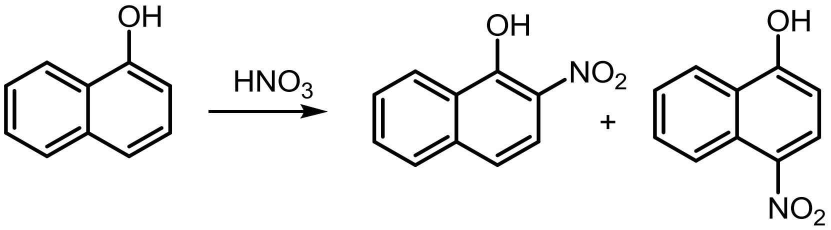


Benz[a]pyrene

Napthalene

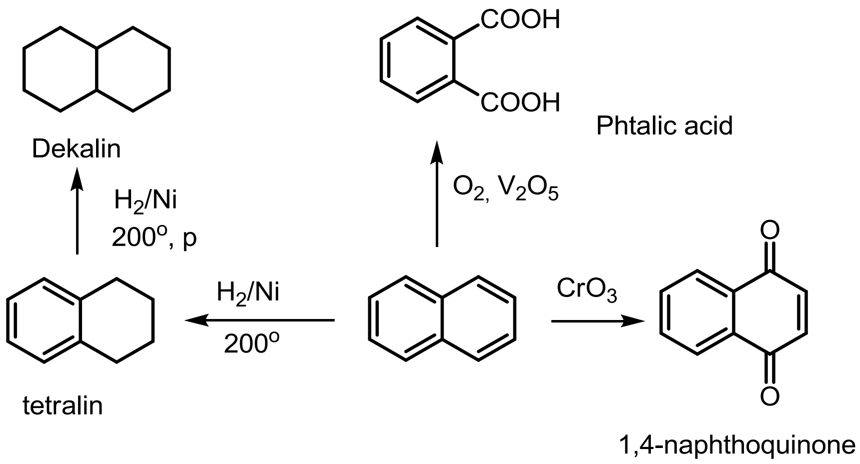


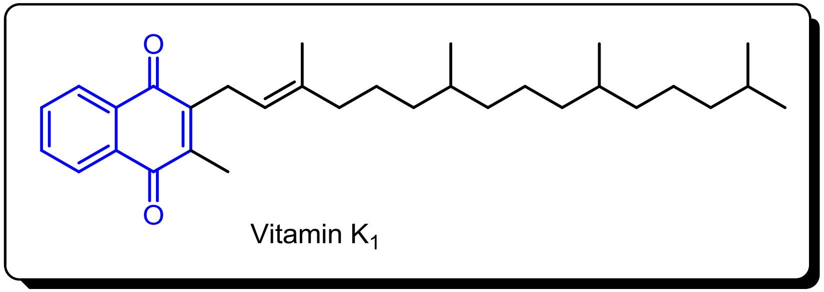
1st position is α-position
2nd position is β-position



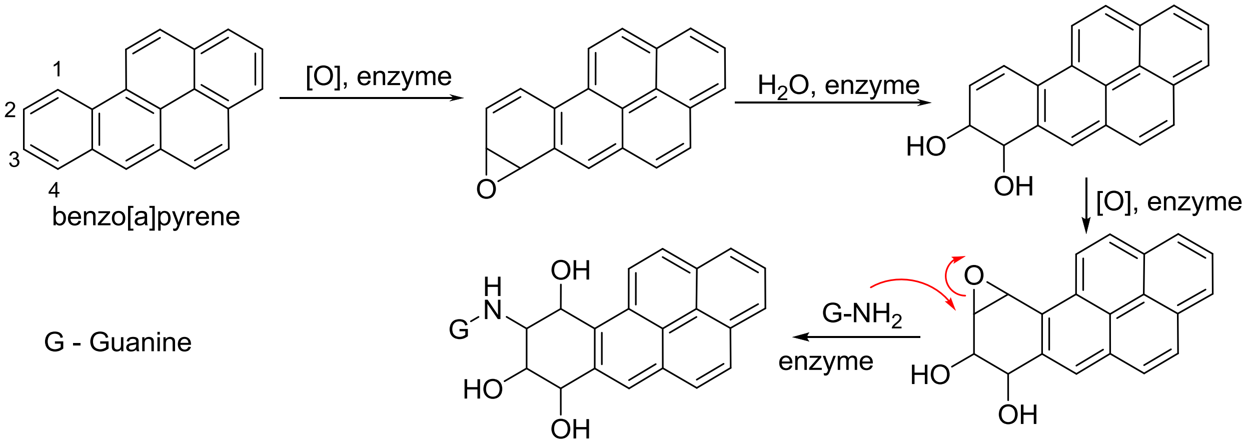
Substituent – activator directs an electrophilic reagent to the same ring.
Substituent – deactivator directs an electrophilic reagent to another ring.

Naphthalene undergoes oxidation and hydrogenation reactions more easily than benzene





Polyaromatic hydrocarbons consisting of more than four aromatic rings are carcinogens. High carcinogenic activity is shown by benzo[a]pyrene. Its action is following: Once it is absorbed or ingested, the body attempts to convert it to more water soluble compound that can be excreted easily. By a series of enzyme catalyzed reactions benzopyrene is transformed into a diole-epoxide. This compound can bind to DNA by reacting with one of its amino groups, thereby altering the structure of DNA and producing a cancer-causing mutations.



HO-, HS-, -O- and –S- groups containing compounds

Alcohols

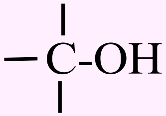
Phenols

Thiols

Ethers and Sulfides

Alcohols

Compounds that contain one or several hydroxy groups attached to sp³ carbon atoms are named as alcohols.


$-\overset{|}{\underset{|}{C}}-OH$ R-OH , $C_nH_{2n+1}OH$

Primary alcohols

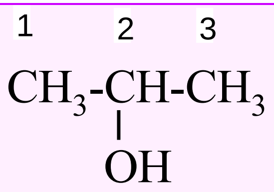
CH_3OH

CH_3CH_2OH

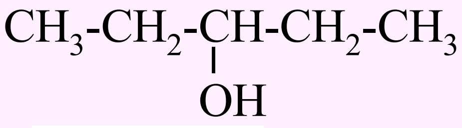
$CH_3CH_2CH_2OH$

$CH_3CH_2CH_2CH_2OH$

Secondary alcohols

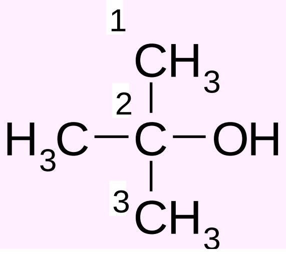

$\overset{1}{CH_3}-\overset{2}{\underset{OH}{\underset{|}{CH}}}-\overset{3}{CH_3}$

2-propanol
(isopropanol)


$CH_3-CH_2-\underset{OH}{\underset{|}{CH}}-CH_2-CH_3$

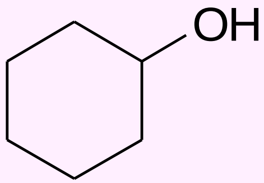
3-pentanol

Tertiary alcohols


$H_3C-\overset{\overset{1}{CH_3}}{\underset{\underset{3}{CH_3}}{\overset{2}{C}}}-OH$

2-methyl-2-propanol

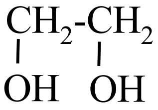
Cyclic alcohols



Cyclohexanol

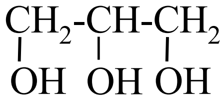
Diols, triols, and polyhydroxylic alcohols

Molecule can contain several HO groups. Alcohols bearing hydroxy groups at different carbon atoms are called diols (2 HO groups), triols (3 HO groups) and so on.



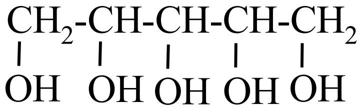
$\underset{OH}{CH_2}-\underset{OH}{CH_2}$

1,2-ethanediol
(ethylenglycol)



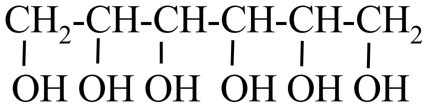
$\underset{OH}{CH_2}-\underset{OH}{CH}-\underset{OH}{CH_2}$

propane-1,2,3-triol
(glycerol)



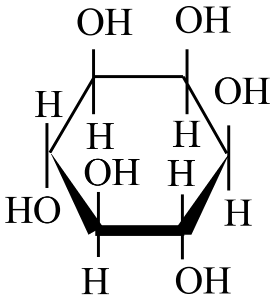
$\underset{OH}{CH_2}-\underset{OH}{CH}-\underset{OH}{CH}-\underset{OH}{CH}-\underset{OH}{CH_2}$

pentane-1,2,3,4,5-pentaol
(xylitol)



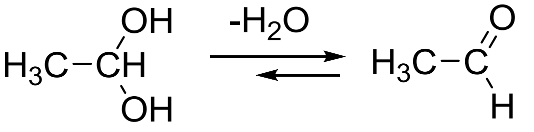
$\underset{OH}{CH_2}-\underset{OH}{CH}-\underset{OH}{CH}-\underset{OH}{CH}-\underset{OH}{CH}-\underset{OH}{CH_2}$

hexane-1,2,3,4,5,6-heksaol
(sorbitol)

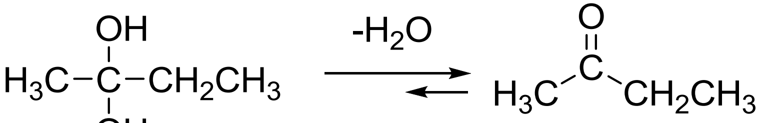


myo-inositol

However, compounds in which two hydroxy groups are connected with the same C atom, are unstable and do not exist. If they are forming in the reaction they immediately loose water and aldehydes or ketones are obtained.



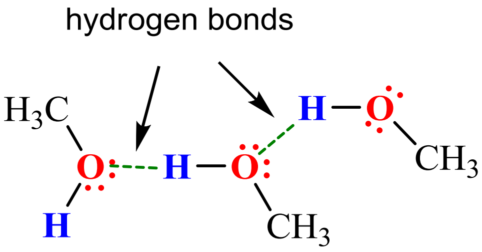
ethanal
(acetic aldehyde)

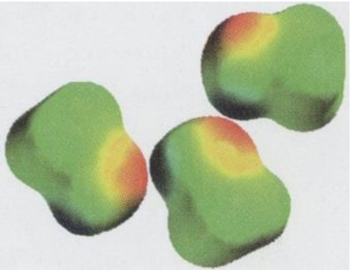


2-butanone

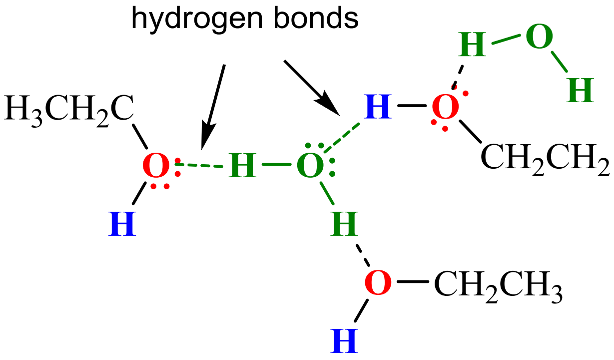
Physical properties of alcohols

Alcohols have higher boiling points than do alkanes, alkenes, and alkynes of similar molecular weight, because alcohol molecules associate with one another in the liquid state by **hydrogen bonding**.





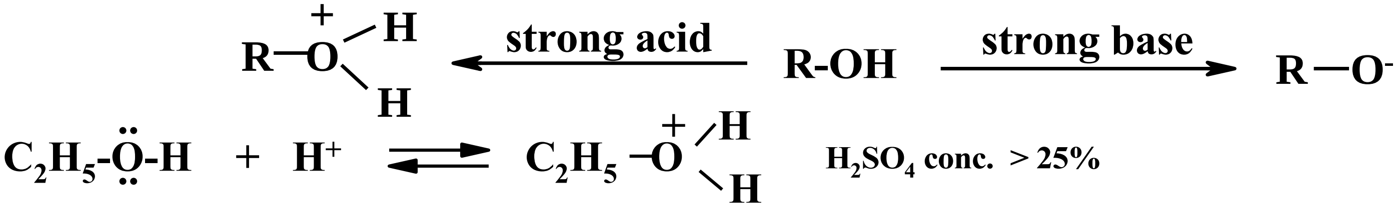
Alcohols are much more soluble in water than are hydrocarbons of similar molecular weight, because alcohol molecules interact by hydrogen bonding with water molecules.



The solubility of alcohols in water gradually decreases as the hydrocarbon portion of the molecule lengthens. Methanol, ethanol, both propanols, and *tert*-butyl alcohol , ethylene glycol, glycerol are completely miscible with water. The remaining butyl alcohols and higher alcohols are partially soluble in water.

Acid-base properties of alcohols

Alcohols have about the same p*Ka* values as water, what means that aqueous solutions of alcohols have approximately the same pH as that of pure water.



$$R{-}\overset{+}{O}H_2 \xleftarrow{\text{strong acid}} R\text{-}OH \xrightarrow{\text{strong base}} R{-}O^-$$

$$C_2H_5\text{-}\ddot{O}\text{-}H + H^+ \rightleftharpoons C_2H_5{-}\overset{+}{O}H_2 \quad H_2SO_4\ \text{conc.} > 25\%$$

ethyloxonium cation

$$C_2H_5OH + NaH \rightleftharpoons C_2H_5ONa + H_2$$

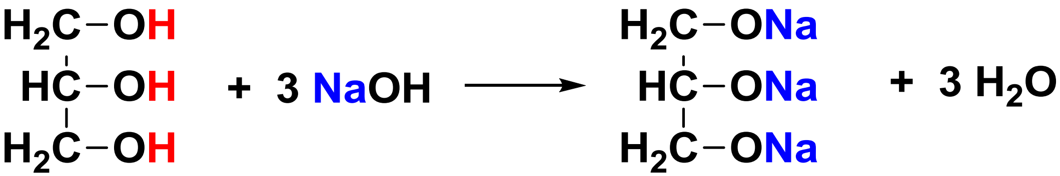
	$(CH_3)_3C\text{-}OH$	$CH_3CH_2\text{-}OH$	$\underset{OH}{CH_2}\text{-}\underset{OH}{CH_2}$	$\underset{OH}{CH_2}\text{-}\underset{OH}{CH}\text{-}\underset{OH}{CH_2}$	CF_3CH_2OH
pKa	18.0	16.0	15.1	14.0	11.4

→ acidic properties increases

Electron-withdrawing substituents increases the acidity of alcohols. Electron-donating substituents increases basicity of alcohols.

$$C_2H_5OH + NaOH \cancel{\rightleftharpoons} C_2H_5ONa + H_2O$$

Therefore:



$$\begin{array}{l} H_2C{-}OH \\ \ \ HC{-}OH \\ H_2C{-}OH \end{array} + 3\,NaOH \longrightarrow \begin{array}{l} H_2C{-}ONa \\ \ \ HC{-}ONa \\ H_2C{-}ONa \end{array} + 3\,H_2O$$

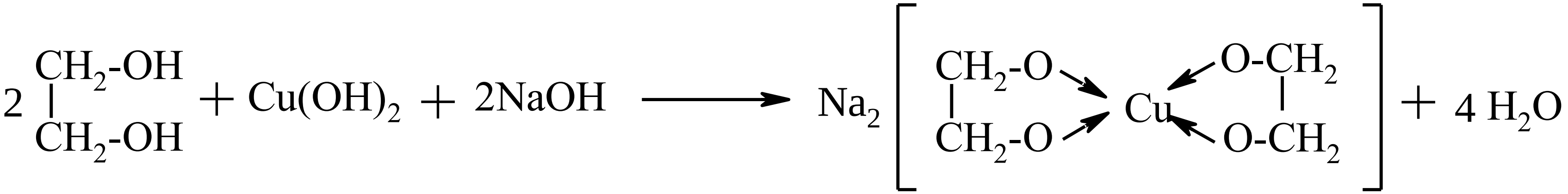
Characteristic Reactions of Alcohols

- **Reaction with strong bases (alkali metals and hydrides)**

$$RO\text{-}H + Na \longrightarrow RONa + H_2$$

$$C_2H_5OH + NaH \rightleftharpoons C_2H_5\overset{-}{O}Na + H_2$$

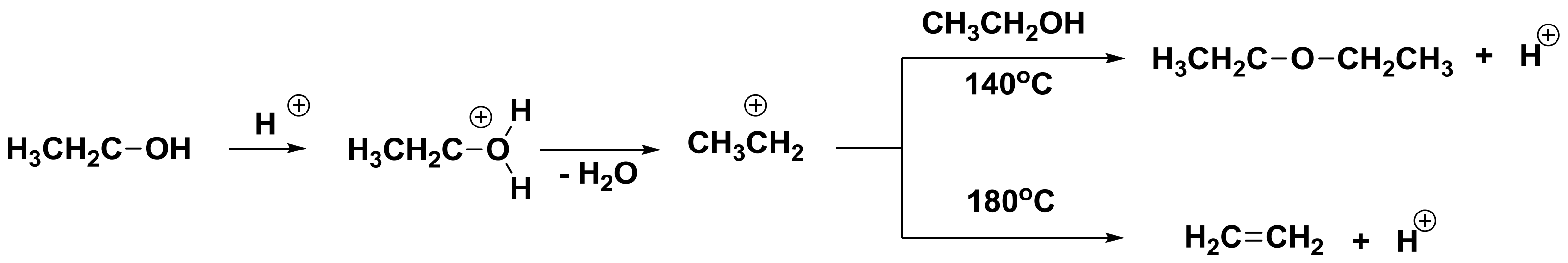
Under basic conditions diols react with salts or hydroxides of d-metals to form chelates. Chelates with copper(II) ions are blue colored and this reaction is used for the detection of diols.



$$2\,\begin{array}{l}CH_2\text{-}OH\\ |\\ CH_2\text{-}OH\end{array} + Cu(OH)_2 + 2NaOH \longrightarrow Na_2\left[\begin{array}{l}CH_2\text{-}O\\ |\\ CH_2\text{-}O\end{array}\begin{array}{c}\searrow\\ \nearrow\end{array} Cu \begin{array}{c}\swarrow\\ \nwarrow\end{array}\begin{array}{l}O\text{-}CH_2\\ |\\ O\text{-}CH_2\end{array}\right] + 4\,H_2O$$

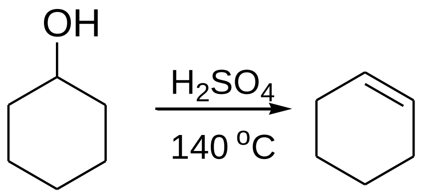
Acid-Catalyzed Dehydration of Alcohols

Dehydration - elimination of a molecule of water from an alcohol. In the dehydration of an alcohol, **OH** is removed from one carbon and **H** is removed from an adjacent carbon atom and alkenes are formed. Dehydration reaction is catalyzed by mineral acids.

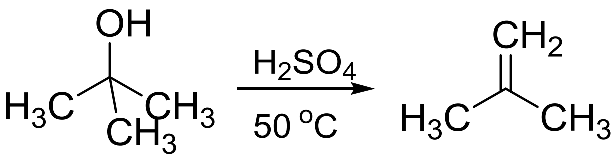


The ease of acid-catalyzed dehydration of alcohols follows this order:

1° alcohols < 2° alcohols < 3° alcohols

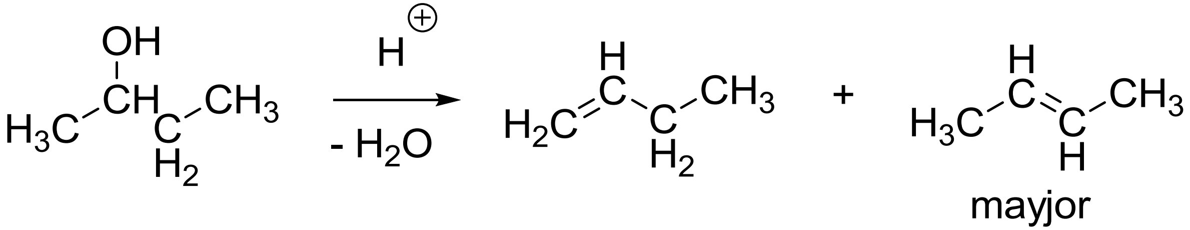


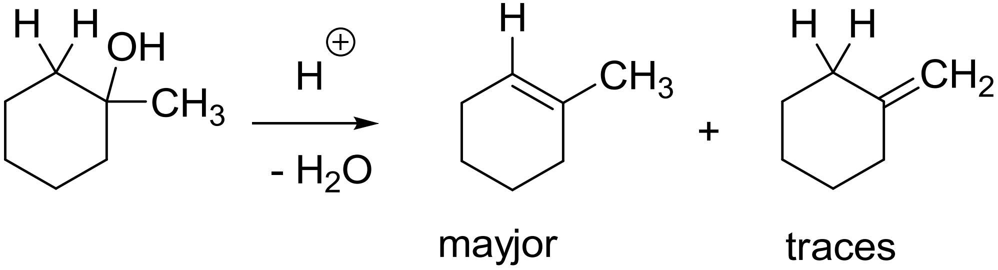
Cyclohexanol Cyclohexene



tert-butanol isobutene

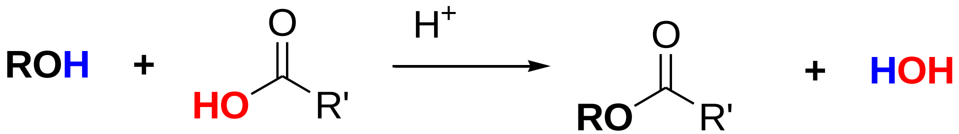
Dehydration of 2^o ir 3^o alcohols proceeds with the formation of isomeric alkenes. However, **the main reaction product is the most stable alkene – more substituted alkene.**



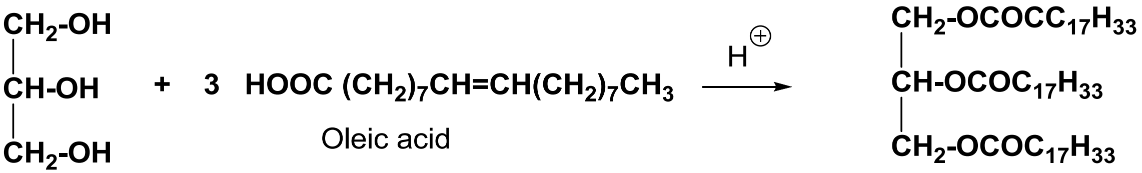


Ester Formation Reactions

Alcohols react with organic and inorganic acids to yield esters.



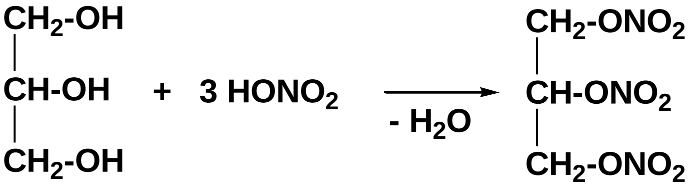
alcohol carboxylic acid ester



$$\begin{array}{l} CH_2\text{-}OH \\ | \\ CH\text{-}OH \\ | \\ CH_2\text{-}OH \end{array} + 3\ HOOC\ (CH_2)_7CH{=}CH(CH_2)_7CH_3 \xrightarrow{H^{\oplus}} \begin{array}{l} CH_2\text{-}OCOCC_{17}H_{33} \\ | \\ CH\text{-}OCOC_{17}H_{33} \\ | \\ CH_2\text{-}OCOC_{17}H_{33} \end{array}$$

Oleic acid

Glyceryl trioleate
(fats)



$$\begin{array}{l} CH_2\text{-}OH \\ | \\ CH\text{-}OH \\ | \\ CH_2\text{-}OH \end{array} + 3\ HONO_2 \xrightarrow[-\ H_2O]{} \begin{array}{l} CH_2\text{-}ONO_2 \\ | \\ CH\text{-}ONO_2 \\ | \\ CH_2\text{-}ONO_2 \end{array}$$

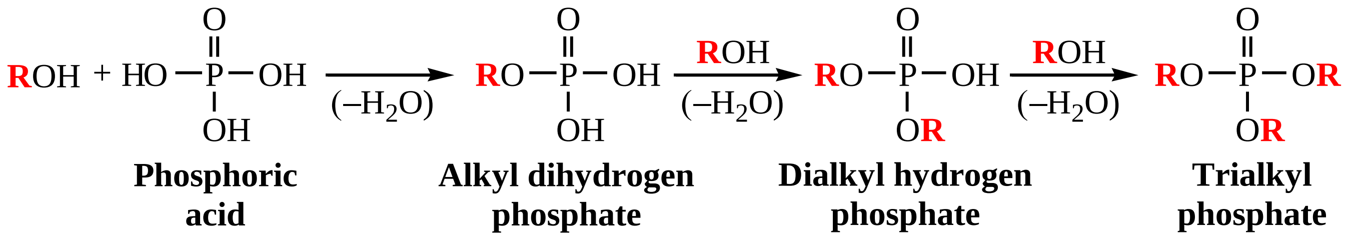
1,2,3-propanetriol
(Glycerol)

Trinitroglycerol

Nitrogycerol is explosive; when heated, it explodes! Nitroglycerol is more stable when absorbed onto an inert solid, a combination called dynamite. **Alfred Nobel** (1833–1896), built on the manufacture of dynamite. Now funds the Nobel Prizes.

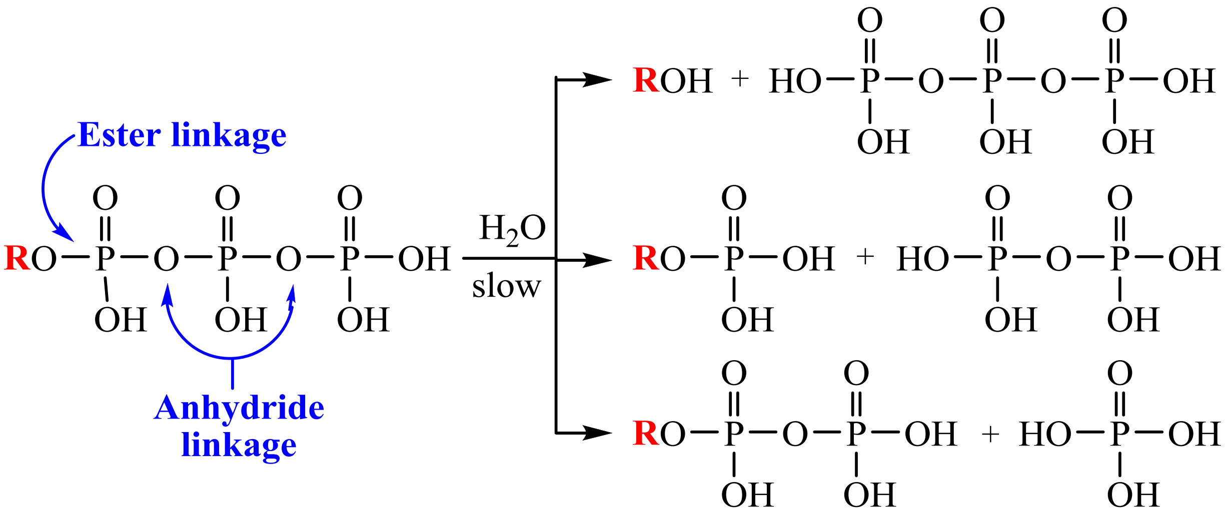
Nitroglycerol is also used in medicine to treat *angina pectoris*. Nitroglycerol, which is available in liquid form (diluted with alcohol to render it nonexplosive), tablet form, and paste form, relaxes the smooth muscles of blood vessels, causing dilation of the coronary artery. This dilation, in turn, allows more blood to reach the heart.

Reaction with phosphoric acid. Formation of alkyl phosphates



Esters of phosphoric acids are important in biochemical reactions (triphosphate esters are especially important). Near pH 7, these phosphates exist as negatively charged ions and hence are much less susceptible to nucleophilic attack ⇒ Alkyl triphosphates are relatively stable compounds in the aqueous medium of a living cell.

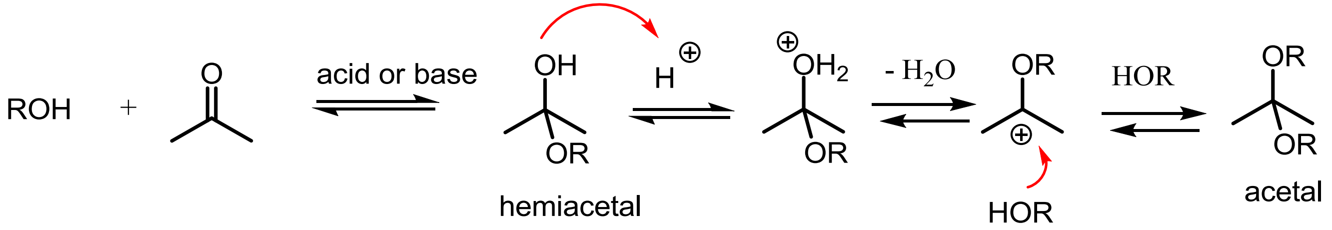
Enzymes are able to catalyze reactions of these triphosphates in which the energy - made available when their anhydride linkages break - helps the cell make other chemical bonds.



Formation of hemiacetals and acetals

Hemiacetal - a molecule containing a carbon bonded to one -**OH** group and one –**OR** (*alcoxy-*) group; the product of adding one molecule of alcohol to the carbonyl group of an aldehyde or ketone.

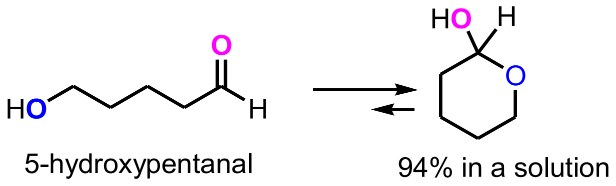
Acetal - a molecule containing two -**OR** groups bonded to the same carbon.

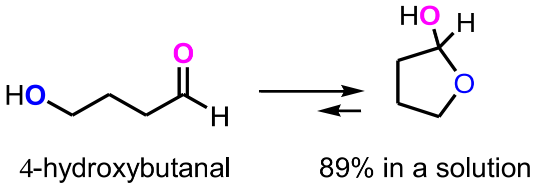


Hemiacetals are generally unstable and are only minor components of an equilibrium mixture, except in one very important type of molecule.

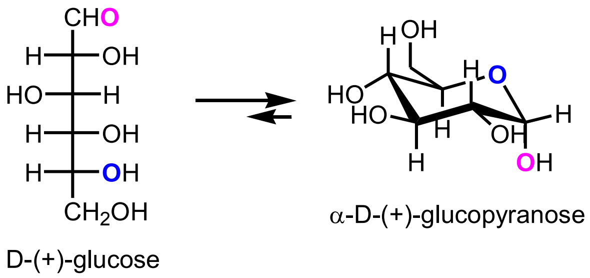
Acetals are stable under basic and neutral conditions. They are unstable in acidic media: they undergo hydrolysis to the initial alcohol and carbonyl compound

5-member and 6-membered cyclic hemiacetals are stable in a solution. For example:





However, **monosaccharides mostly exist in a cyclic hemiacetal form:**



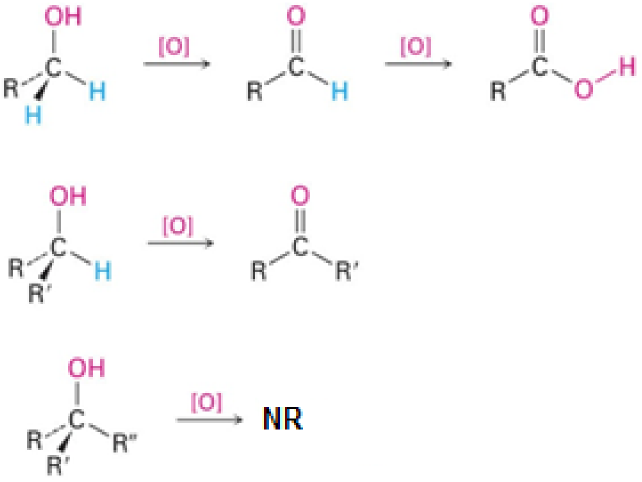
Oxidation of Alcohols

Oxidants: $KMnO_4$, CrO_3, K_2CrO_4, $K_2Cr_2O_7$. They are strong oxidants. Therefore, to obtain aldehydes from the primary alcohols using these oxidants is practically impossible, because aldehydes undergo oxidation more easily than the primary alcohols.

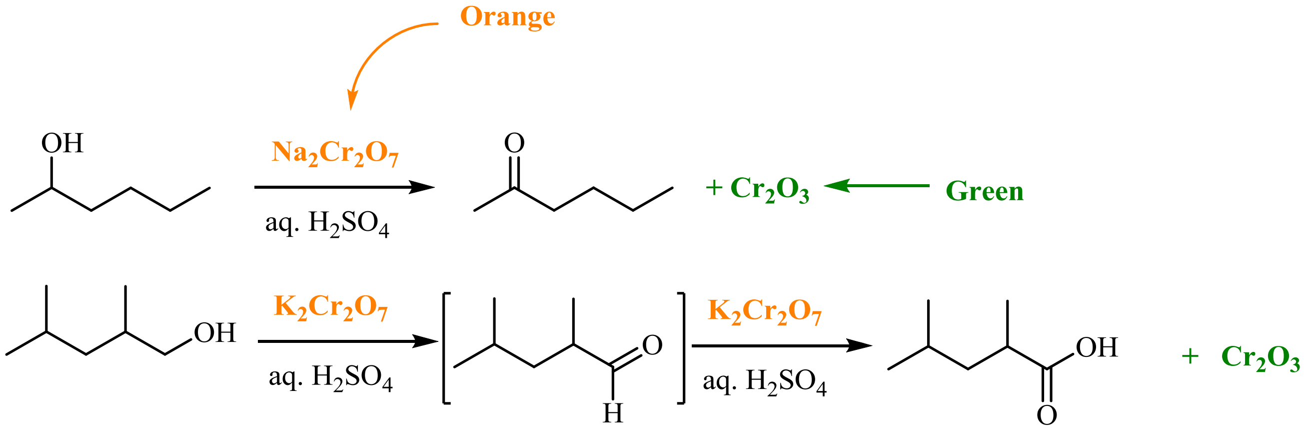
1° alcohol

2° alcohol

3° alcohol

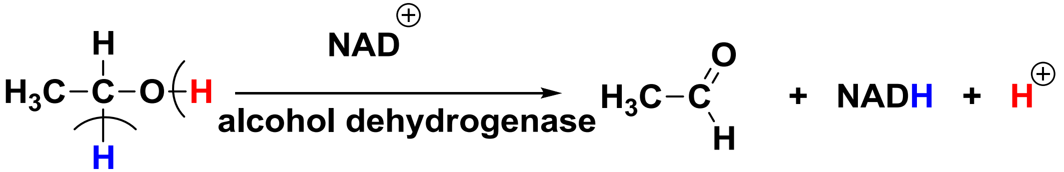


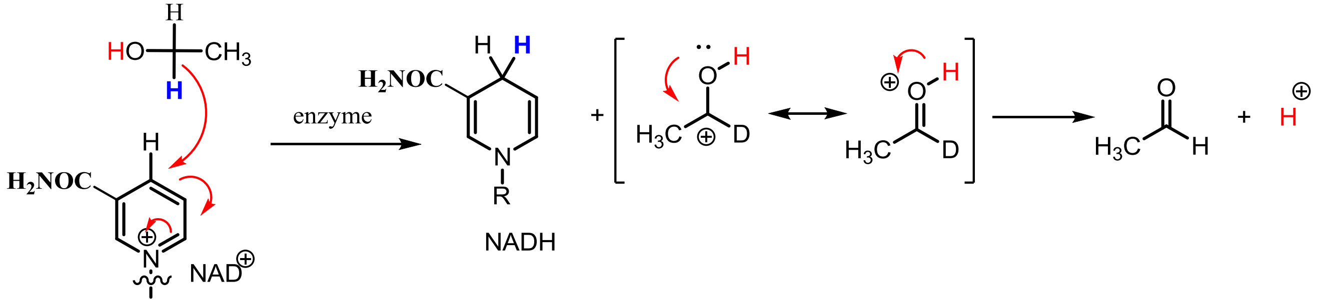
Oxidation with chromates and bichromates is usually carried out in an acidic media. Bichromate is reduced and green Cr_2O_3 is formed. **This color change, associated with the reduction of $Cr_2O_7^{2-}$ to Cr^{3+}, forms the basis for “Breathalyzer tubes” used to detect intoxicated motorists.**

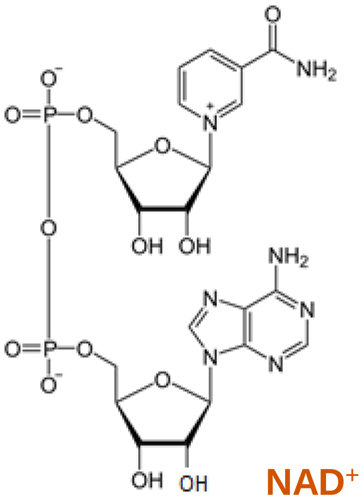


○ Oxidation of alcohols *in vivo*

In vivo alcohols are oxidized with help of enzyme - alcohol dehydrogenase, in the presence of co-enzyme - **nicotinamide adenine dinucleotide (NAD^+).** The products of the reaction are aldehydes and ketones.

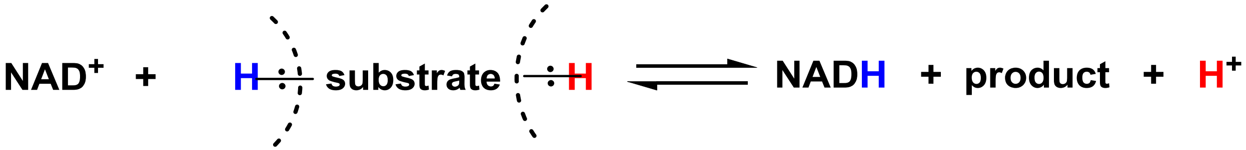






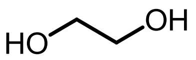
NAD^+

General scheme of dehydrogenolysis of various substrates:



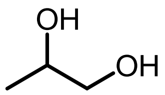
$$NAD^+ + H : substrate : H \rightleftharpoons NADH + product + H^+$$

Ethylene Glycol, Glycerol and Polyhydroxylic Alcohols



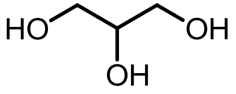
1,2- ethanediol
(Ethylene glycol)

pKa = 14.22



1,2-propanediol
(propylene glycol)

1,3-propanediol
(Trimethylene glycol)



1,2,3-propanetriol
(glycerol)

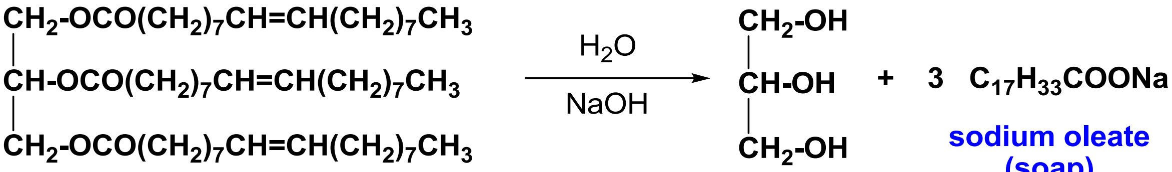
pKa = 14.15

Ethylene glycol has a high boiling point, it is miscible with water in all proportions.

Mixtures of ethylene glycol with water are used as good antifreeze for cars.

EG (%)	Freezing point (° C)
40	-23
50	-34
60	-48
70	-51
80	-45
90	-29
100	-12

Their Only Visual Difference Is Viscosity
They have many similar properties & uses, yet **Ethylene Glycol** ($C_2H_6O_2$, L), or antifreeze, is Toxic while **Glycerol** ($C_3H_8O_3$, R) is used as a sweetener for liqueurs & confectioneries.



$$\begin{array}{l} CH_2\text{-}OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3 \\ | \\ CH\text{-}OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3 \\ | \\ CH_2\text{-}OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3 \end{array} \xrightarrow[NaOH]{H_2O} \begin{array}{l} CH_2\text{-}OH \\ | \\ CH\text{-}OH \\ | \\ CH_2\text{-}OH \end{array} + 3\ C_{17}H_{33}COONa$$

natural fat

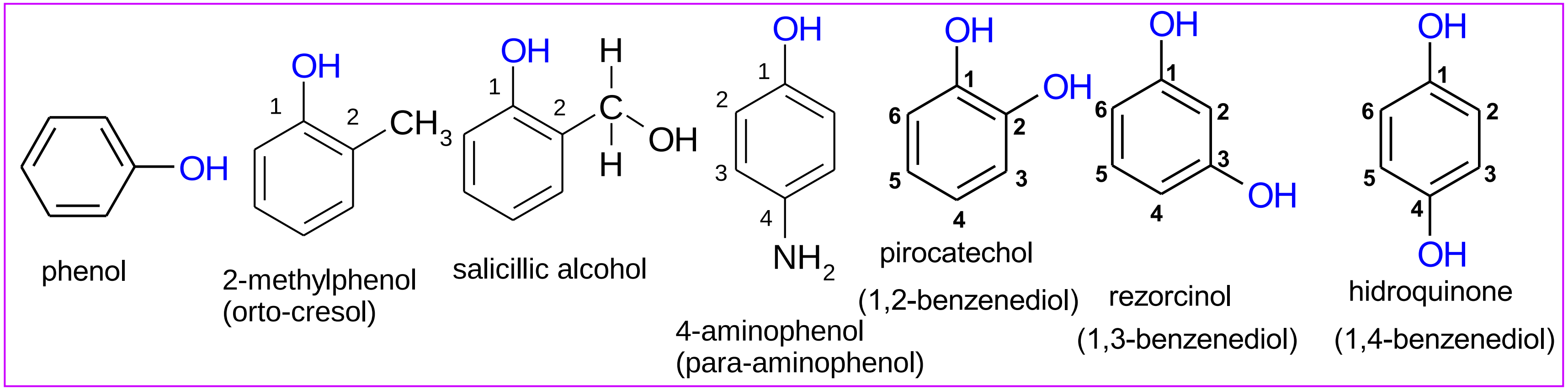
Glycerol

sodium oleate (soap)

Glycerol is the main structural unit of natural fats and oils, phosphoglycerides

Phenols

Phenols are compounds in which hydroxy group is bonded to benzene ring. Substituted phenols are called as derivatives of phenols or by common (trivial) names.



phenol

2-methylphenol
(orto-cresol)

salicillic alcohol

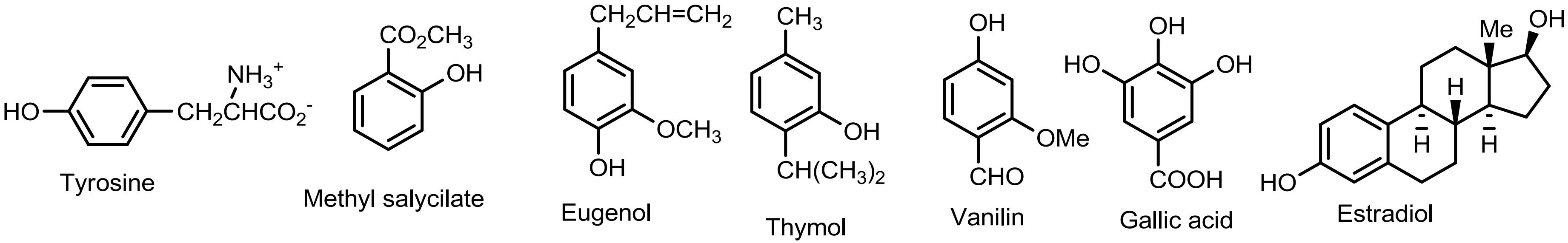
4-aminophenol
(para-aminophenol)

pirocatechol
(1,2-benzenediol)

rezorcinol
(1,3-benzenediol)

hidroquinone
(1,4-benzenediol)

Phenols are widespread in nature:



Tyrosine

Methyl salycilate

Eugenol

Thymol

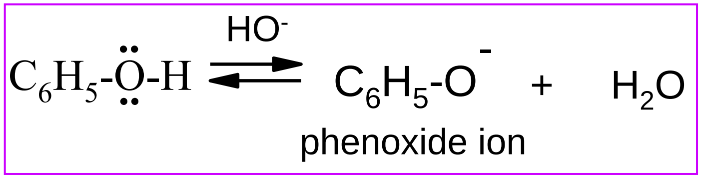
Vanilin

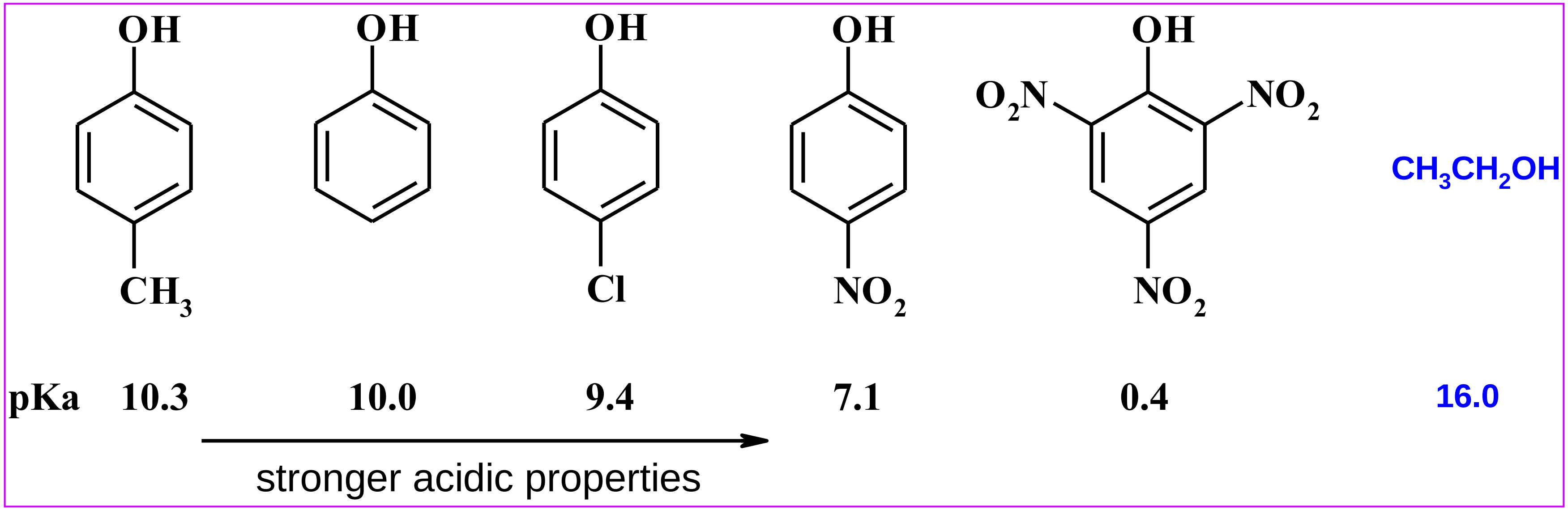
Gallic acid

Estradiol

Acid-base properties

Phenols are stronger acids than alcohols. Their pKa ~ 10.

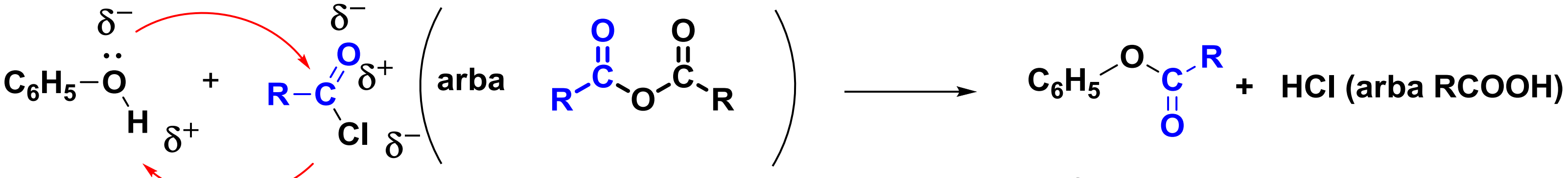




Electron-withdrawing substituents and groups increase the acidity of phenols, Electron-donating groups decrease the acidity of phenols.

Properties of Phenols

○ *O-Acylation reaction*

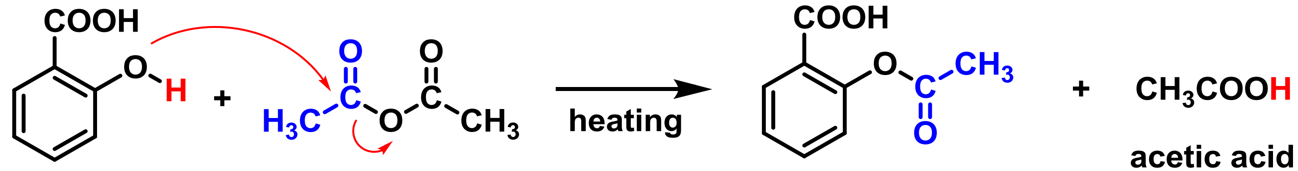


acid anhydride

ester of carboxylic acid

Acid
chloranhydride

Exmpl.:



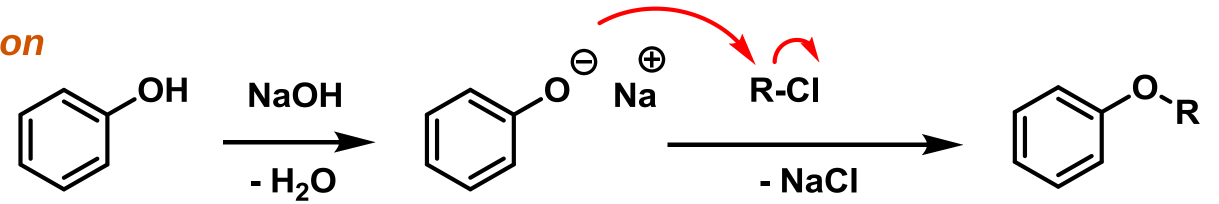
acetic acid

salicylic acid

acetic acid anhydride

acetylsalicylic acid
(aspirin)

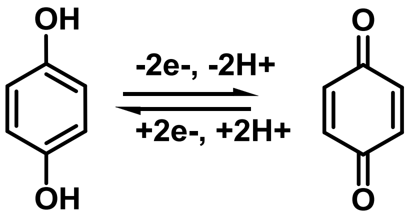
○ *O-Alkylation reaction*



alkoxybenzenes

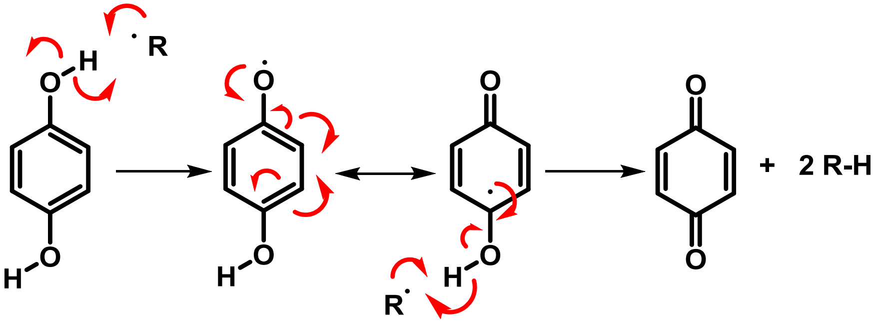
○ *Oxidation-reduction reactions*

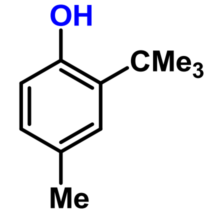
Phenols and their anions easily oxidize. Especially facile oxidation reaction proceeds with the dihydroxybenzenes. They can easily lose electrons and protons converting to benzoquinones – an oxidized form of phenols.



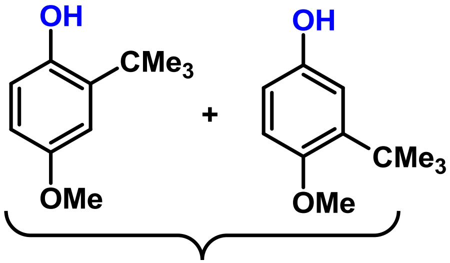
hydroquinone (reductant) **1,4-benzoquinone (oxidant)**

Phenols are good antioxidants. Formation of active radicals in a body causes the deposition of low-density lipoproteins (LDL) on the walls of arteries leading to cardiovascular disease in humans and causes many effects of aging . Strong natural antioxidants are vitamin E and vitamin C.





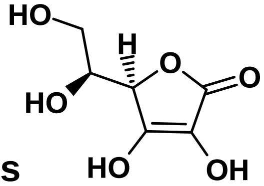
BHT (E321)



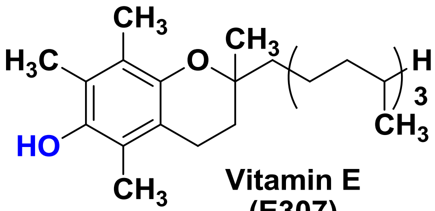
BHA (E320)

Food preservatives

Natural antioxidants



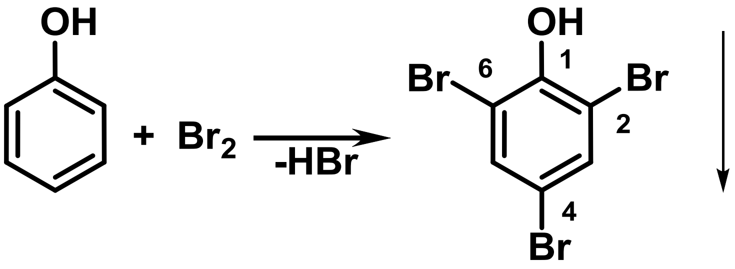
Vitamin C (E206)



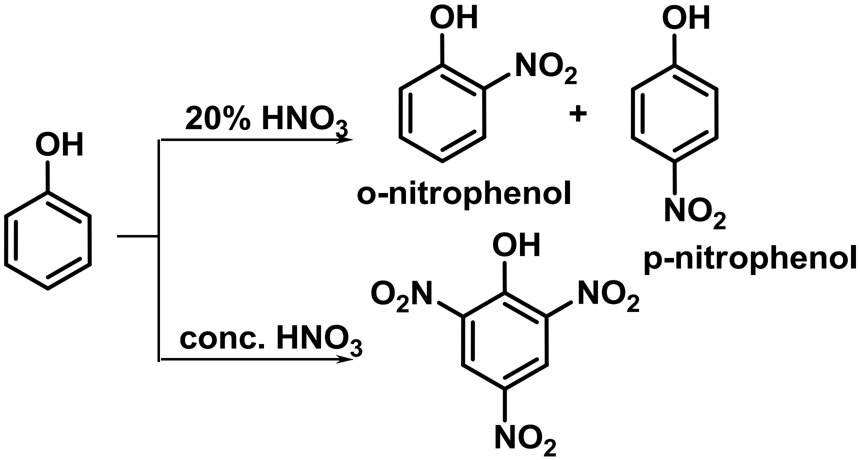
Vitamin E (E307)

○ *Electrophilic substitution reactions (S_EAr)*

Phenols due to electron-donating property of HO group are more active in S_EAr reactions than benzene. For example, with bromine in water solution phenol reacts already at room temp. to give trisubstitution product - 2,4,6-tribromophenol, which is insoluble in water and deposits as precipitate. This property is used for the identification of phenols.



2,4,6-tribromophenol

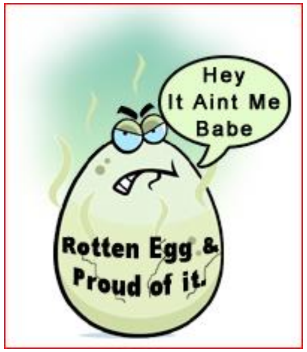


2,4,6-trinitrophenol
(picric acid)

Reaction with nitric acid depending on its concentration leads to the formation of *o*- and *p*-nitrophenols or picric acid.

Thiols and Sulfides

R-SH **R-S-R**



The functional group of a **thiol** is an -SH **(sulfhydryl) group** bonded to a carbon atom.

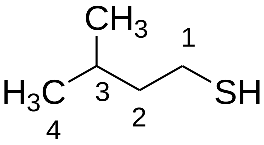
Nomenclature

The sulfur analog of an alcohol is called a thiol (*thi*- from the Greek: *theion*, sulfur) or, in the older literature, a **mercaptan,** which literally means “mercury capturing.” Thiols react with Hg^{2+} in aqueous solution to give sulfide salts as insoluble precipitates. Thiophenol, C_6H_5SH, for example, gives $(C_6H_5S)_2Hg$.

In the IUPAC system, thiols are named by selecting the longest carbon chain that contains the -SH group as the parent alkane. To show that the compound is a thiol, we add the suffix ***-thiol*** to the name of the parent alkane. The parent chain is numbered in the direction that gives the -SH group the lower number.

$CH_3CH_2CH_2SH$

1-Propanethiol
(n-propyl mercaptan)



3-Methyl-1-butanethiol

Physical Properties

Because of the small difference in electronegativity between sulfur and hydrogen (2.5 - 2.1) = 0.4, we classify the S-H bond as nonpolar covalent. Because of this lack of polarity, *thiols show little association by hydrogen bonding*. They have **lower boiling points** and **are less soluble in water and other polar solvents than are alcohols** of similar molecular weight.

Acidic properties of thiols

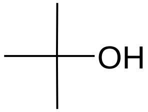
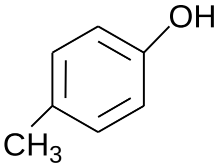
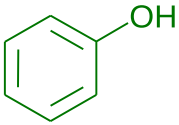
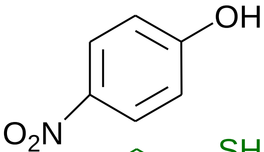
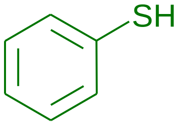
Thiols are weak acids (p*Ka* ~ 10) that are comparable in strength to phenols. Thiols react with strong bases such as NaOH to form thiolate salts:

$$CH_3CH_2S\text{-}H \quad + \quad NaOH \xrightarrow{H_2O} CH_3CH_2\overset{\ominus}{S}\ \overset{\oplus}{Na} \quad + \quad H_2O$$

pKa = 10 pKa = 15.7

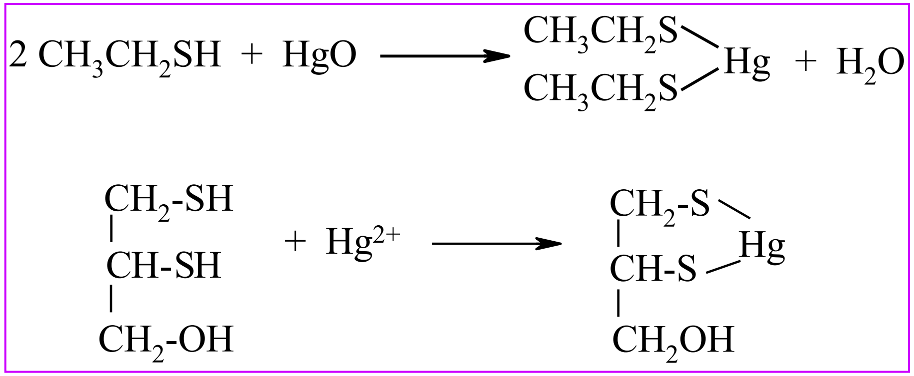
$$CH_3CH_2O\text{-}H \quad + \quad NaOH \cancel{\xrightarrow{H_2O}} CH_3CH_2\overset{\ominus}{O}\ \overset{\oplus}{Na} \quad + \quad H_2O$$

pKa = 16 pKa = 15.7

	pKa = 18
CH_3CH_2OH	pKa = 16
H_2O	pKa = 15.7
CH_3OH	pKa = 15.5
CH_3SH	pKa = 10.3
	pKa = 10.2
	pKa = 9.9
	pKa = 7.2
	pKa = 6.0

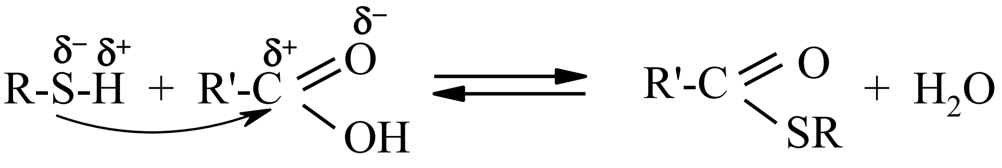
↑ Decreasing acidity

○ Reactions with heavy metals

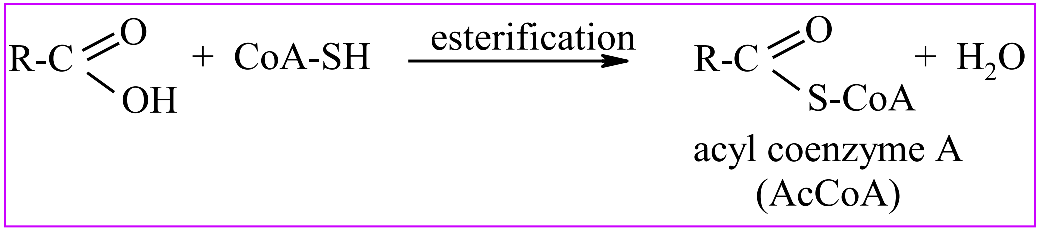


This is an explanation why **Pb, Cd, Hg, As** salts are toxic. (They react with sulfhydryl groups present in proteins. The result is loss of protein activity and denaturation).

○ Ester formation reaction (esterification reaction)



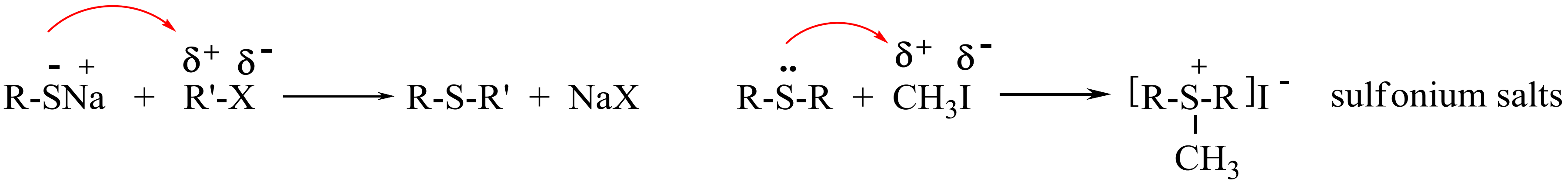
Thioester



acyl coenzyme A (AcCoA)

This is the main reaction of the biosynthesis of acetyl-coenzyme A. AcCoA is responsible for many biochemical reactions including the transfer of acyl groups from one molecule to another.

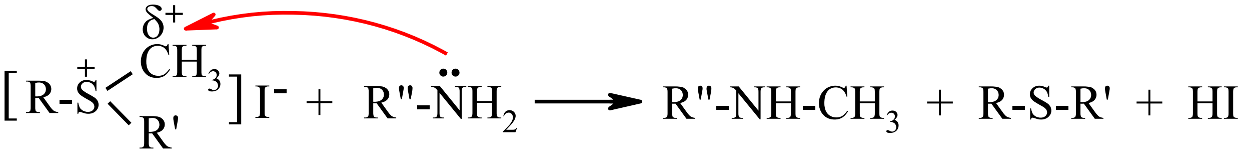
○ Alkylation reactions



$$R\text{-}S^{-}Na^{+} + \overset{\delta+}{R'}\text{-}\overset{\delta-}{X} \longrightarrow R\text{-}S\text{-}R' + NaX \qquad R\text{-}\ddot{S}\text{-}R + \overset{\delta+}{CH_3}\overset{\delta-}{I} \longrightarrow [R\text{-}\underset{\large CH_3}{\overset{+}{S}}\text{-}R]I^{-}$$

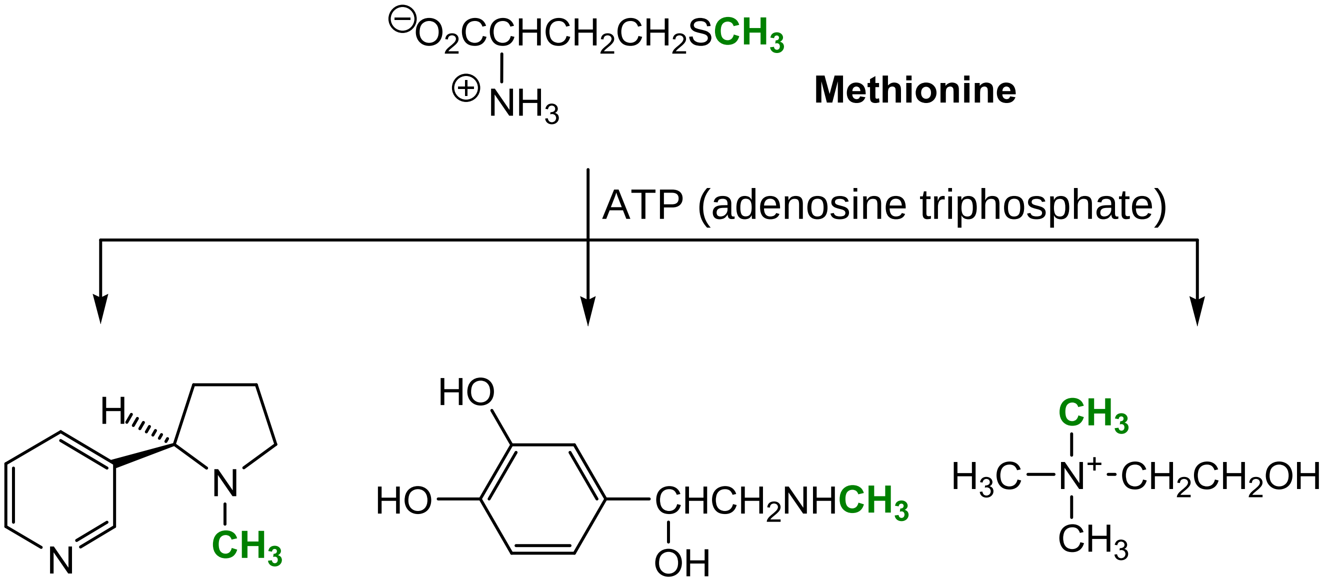
sulfonium salts

Sulfonium salts are powerful alkylating agents. They react very easily with various nucleophiles to give alkylated products.



$$[R\text{-}\overset{+}{S}\begin{smallmatrix}\overset{\delta+}{CH_3}\\ R'\end{smallmatrix}]I^{-} + R''\text{-}\ddot{N}H_2 \longrightarrow R''\text{-}NH\text{-}CH_3 + R\text{-}S\text{-}R' + HI$$

This reaction is employed in transfer of methyl group to various important biomolecules. Amino acid – methionine - is the initial source of methyl group in biochemical reactions.



$$^{\ominus}O_2C\underset{\oplus NH_3}{CH}CH_2CH_2S\mathbf{CH_3}$$

Methionine

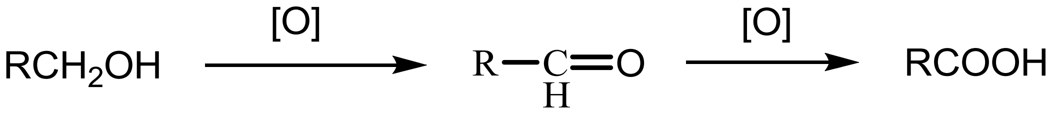
Nicotine

Epinephrine (Adrenalin)

Choline

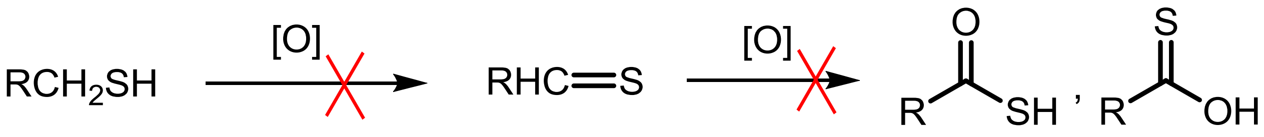
Oxidation of thiols. Comparison with alcohol oxidation.

Products of oxidation of alcohols

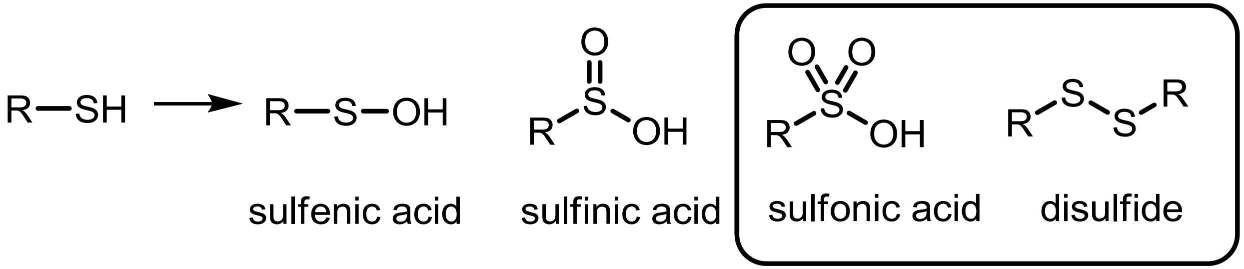


$$RCH_2OH \xrightarrow{[O]} R-\underset{H}{C}=O \xrightarrow{[O]} RCOOH$$

C atom undergoes oxidation



Products of oxidation of thiols

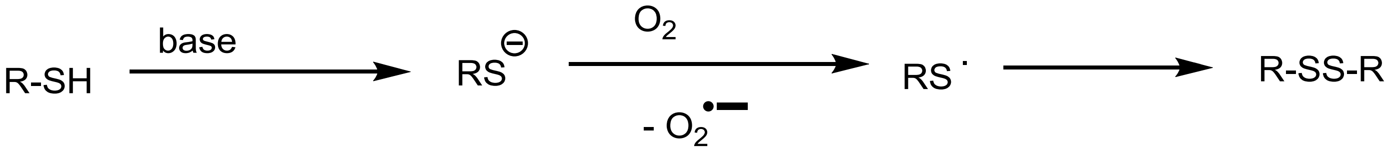


S atom undergoes oxidation

The main oxidation products of thiols

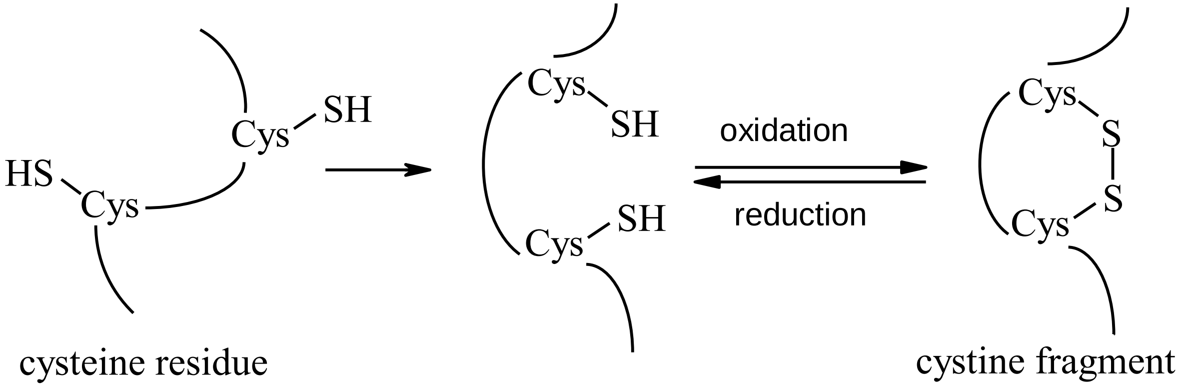
The most common reaction of thiols in biological systems is their oxidation to disulfides, the functional group of which is a disulfide (-S-S-) bond.

Thiols are readily oxidized to disulfides by molecular oxygen. In fact, they are so susceptible to oxidation that they must be protected from contact with air during their storage.



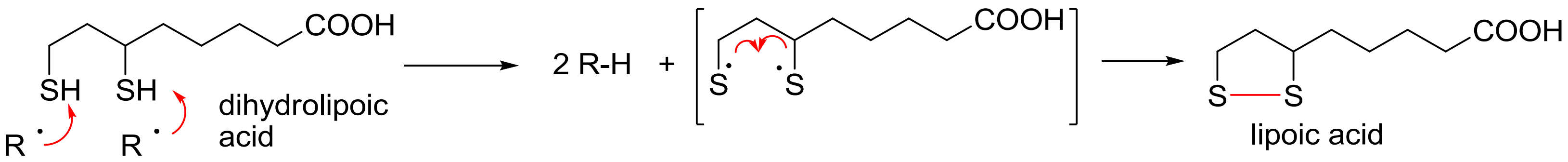
$$R\text{-}SH \xrightarrow{\text{base}} RS^{\ominus} \xrightarrow[-\,O_2^{\bullet -}]{O_2} RS^{\cdot} \longrightarrow R\text{-}SS\text{-}R$$

Disulfides, in turn, are easily reduced to thiols by several reducing agents. This easy interconversion between thiols and disulfides is very important in protein chemistry and determines the overall shapes of proteins.



Conversion of thiols to disulfides and *vise versa* protects the body against oxidants and radicals.

In a body there are some compounds that catch radicals which are formed during the oxidation reaction The main of them are dihydrolipoic acid, glutathione , 2-aminoethanethiol.

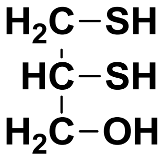


$$2\ H_2N\text{-}CH_2\text{-}CH_2\text{-}SH + 2R^{\bullet} \longrightarrow 2RH + 2\ H_2N\text{-}CH_2\text{-}CH_2\text{-}\dot{S} \longrightarrow H_2N\text{-}CH_2\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}CH_2\text{-}NH_2$$

2-aminoethanethiol

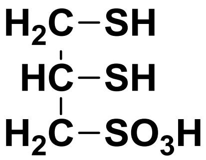
cystamine

Radioprotectors and antidotes for heavy metals are also compounds containing several mercapto groups.



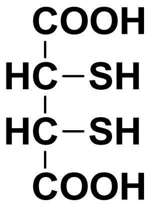
$$\begin{array}{c} H_2C-SH \\ | \\ HC-SH \\ | \\ H_2C-OH \end{array}$$

dimercaprol (dithioglycerol)



$$\begin{array}{c} H_2C-SH \\ | \\ HC-SH \\ | \\ H_2C-SO_3H \end{array}$$

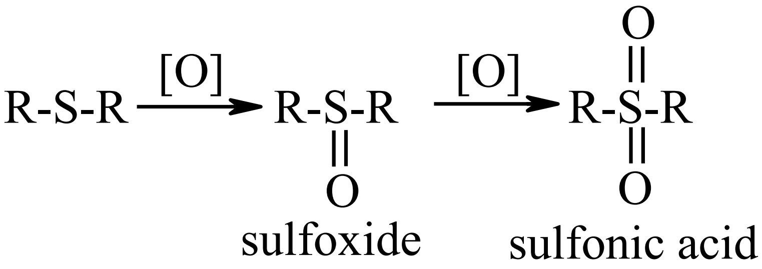
unithiol



$$\begin{array}{c} COOH \\ | \\ HC-SH \\ | \\ HC-SH \\ | \\ COOH \end{array}$$

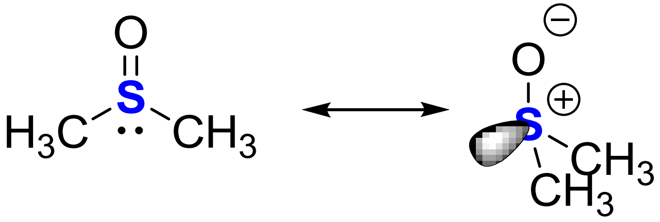
dimercaptosuccinic acid

Oxidation of sulfides



Oxidants: H_2O_2, peroxyacids (RCOOOH), $KMnO_4$

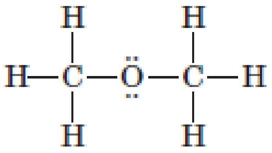
$(CH_3)_2SO$ (dimethyl sulfoxide) was found to be able penetrate the skin and other membranes without damaging them and could carry other compounds into a biological system.

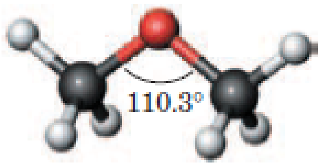


Dimethyl sulfpoxide is used in some transdermal drug delivery systems. It is also shows anti-inflammatory and antioxidant properties.

Ethers

The functional group of an ether is an atom of oxygen bonded to two carbon atoms.



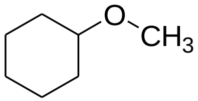


Nomenclature

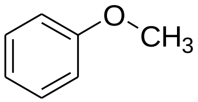
Common names are derived by listing the alkyl groups bonded to oxygen in alphabetical order and adding the word *ether*. Alternatively, one of the groups on oxygen is named as an alkoxy group. The -OCH_3 group, for example, is named “methoxy” to indicate a methyl group bonded to oxygen.

CH_3CH_2-O-CH_2CH_3

Diethyl ether

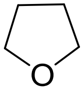


Cyclohexyl methyl ether
(methoxycyclohexane



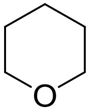
Phenyl methyl ether
(methoxybenzene)

In **cyclic ethers**, one of the atoms in a ring is oxygen.



tetrahydrofuran

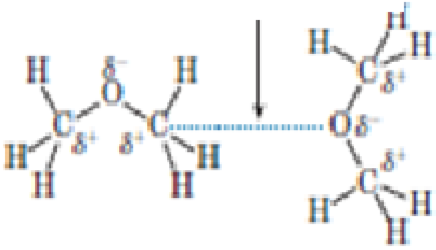
ethylene
oxide



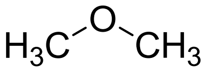
tetrahydropyran

Physical Properties

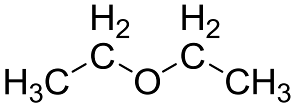
Ethers are polar compounds in which oxygen bears a partial negative charge and each attached carbon bears a partial positive charge. However, only weak forces of attraction exist between ether molecules in the pure liquid. Molecules of ethers do not take part in the formation of hydrogen bonds between each other. However, with water molecules they form hydrogen bonds. Therefore solubility of ethers in water depends on number of oxygen atoms in a molecule and on size of hydrofobic hydrocarbon part. Boiling points of ethers are close to those of hydrocarbons of similar molecular weight.



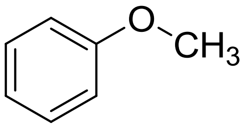
Only very week dipole-dipole interaction



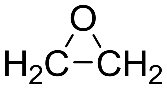
Dimethyl ether
(methoxymethane)
b.p. -24°C



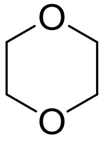
Diethyl ether
(ethoxyethane)
b.p. 34.6°C



Anisole
(methoxybenzene)

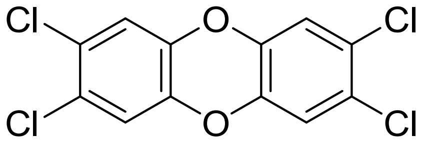


ethylene oxide
(oxirane)
b.p. 10.7°C



1,4-dioxane

b.p. 101°C
Soluble
in water



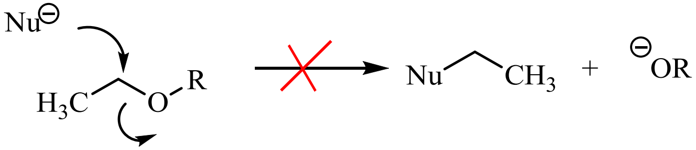
Dioxin

Nonsoluble in water, soluble in fats and nonpolar solvents

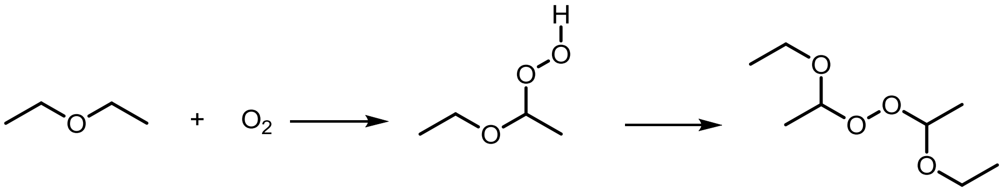
Ethers are excellent solvents for nonpolar organic substances.

Chemical properties of ethers

Ethers resemble hydrocarbons in their resistance to chemical reaction. They are stable and rather inert compounds. The only reactive sites of dialkyl ethers are **O** atom and **C-H** near the oxygen.



✓ Ethers resist attack by nucleophiles and by bases.
✓ They are inert toward hydrochloric acid.
✓ The ethers that contain the 1^o an 2^o C atoms bonded with oxygen are slowly oxidized by air oxygen to form explosive peroxides.

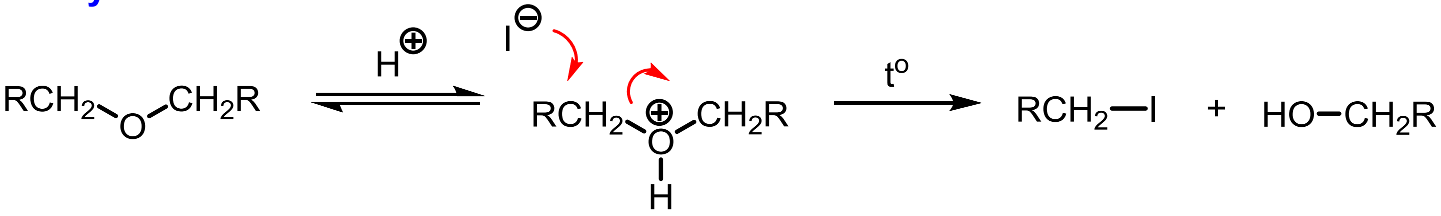


Diethyl ether peroxide

Cleavage of ethers

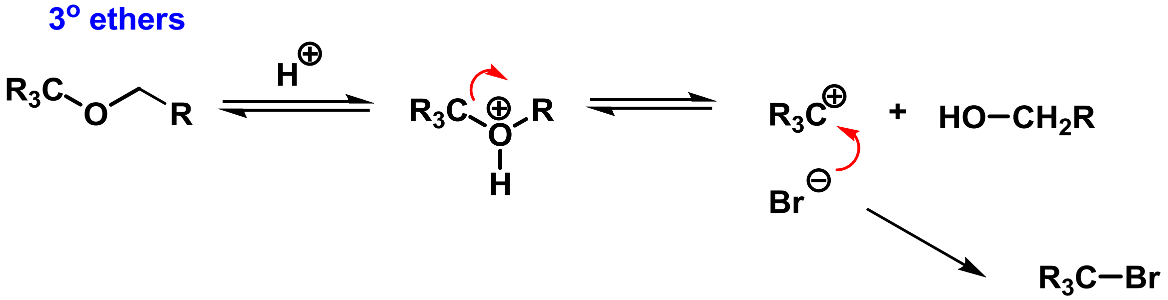
Ethers react with strong acids such as HBr, HI, and H_2SO_4 to form oxonium salts. Heating of ethers with HBr and HI causes cleavage of C-O bond and alcohols and alkyl halogenides are formed.

methyl- ir 1^o ethers



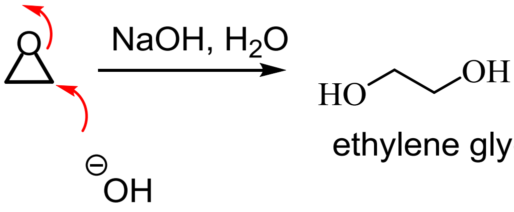
Dialkyl oxonium salt

The reaction of 3° ethers with H-I or H-Br proceeds more easily (sometimes at room temp.) to give *tert*-alkyl halogenides and alcohols.

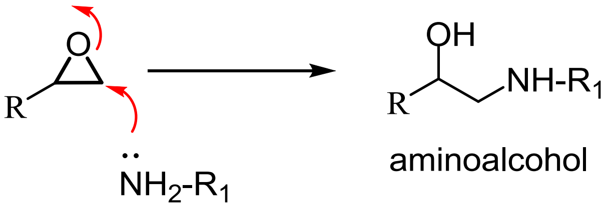


Epoxide cleavage

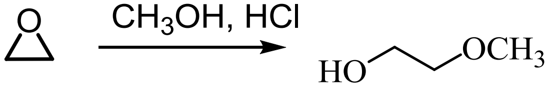
The highly strained 3-membered ring in epoxides makes them much more reactive toward nucleophiles than other ethers. During the reaction the ring opening occurs and acyclic alcohols are formed.



ethylene glycol



aminoalcohol



2-methoxyethanol

Important Alcohols and Ethers

Methanol CH_3OH

At one time, most methanol was produced by the destructive distillation of wood (i.e., heating wood to a high temperature in the absence of air) ⇒ "wood alcohol".
Today, most methanol is prepared by the catalytic hydrogenation of carbon monoxide.

$$CO + H_2 \xrightarrow[\substack{200\text{-}300\text{ atm} \\ ZnO\text{-}CrO_3}]{300\text{-}400^{o}C} CH_3OH$$

Methanol is highly toxic ⇒ ingestion of small quantities of methanol can cause blindness; large quantities cause death. Methanol poisoning can also occur by inhalation of the vapors or by prolonged exposure to the skin.

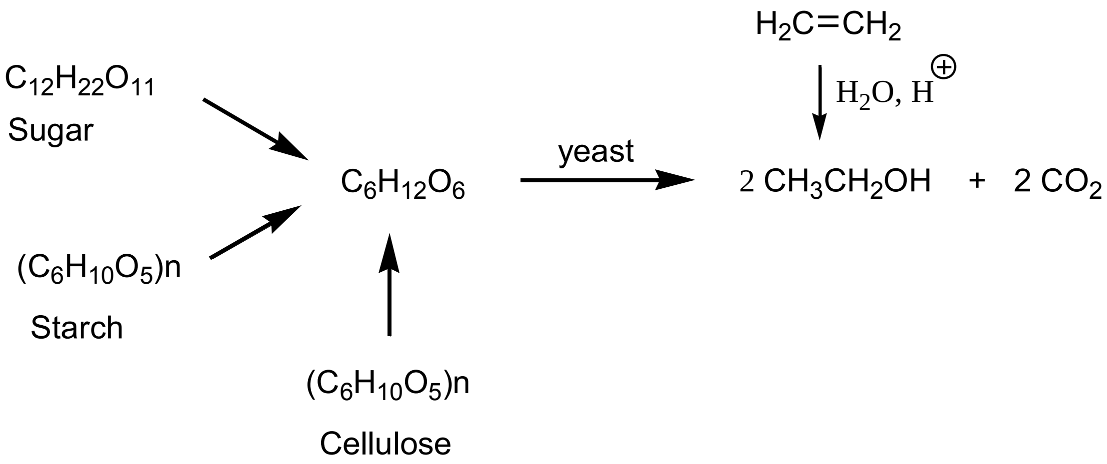
Ethanol CH_3CH_2OH

Ethanol can be made by fermentation of sugars, and it is the alcohol of all alcoholic beverages. Sugars from a wide variety of sources can be used in the preparation of alcoholic beverages.
Often, these sugars are from grains ⇒ "grain alcohol"

Fermentation is usually carried out by adding yeast to a mixture of sugars and water.

Yeast contains enzymes that promote a long series of reactions that ultimately convert a simple sugar ($C_6H_{12}O_6$) to ethanol and carbon dioxide.

Methods of ethanol production



Enzymes of the yeast are deactivated at higher ethanol concentrations ⇒ fermentation alone does not produce beverages with an ethanol content greater than 12-15%.
To produce beverages of higher alcohol content (brandy, whiskey, and vodka) the aqueous solution must be distilled.

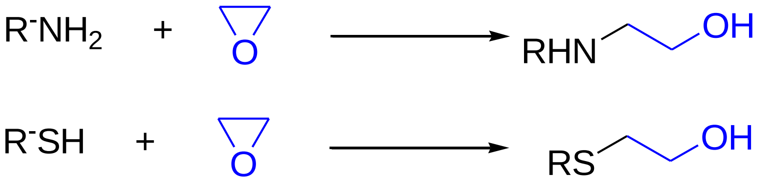
Ethanol is a ***hypnotic*** (sleep producer).

1) Ethanol depresses activity in the upper brain even though it gives the illusion of being a stimulant.

2) Ethanol is toxic. for human **LD_{50} = 5.5 g/kg**

Ethylene Oxide: A Chemical Sterilant

Ethylene oxide is a colorless, flammable gas with a boiling point of 11°C. Ethylene oxide reacts with the amino -NH_2 and sulfhydryl -SH groups present in biological materials.



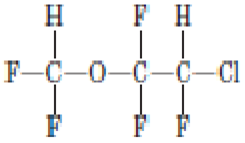
At sufficiently high concentrations, it reacts with enough molecules in cells to cause the death of microorganisms. This toxic property is the basis for ethylene oxide's use in hospitals to sterilize surgical instruments.

Diethyl ether as anesthetic

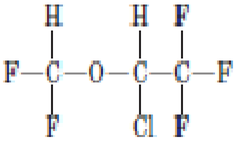
$CH_3CH_2OCH_2CH_3$

Diethyl ether causes excellent muscle relaxation. Blood pressure, pulse rate, and respiration are usually only slightly affected. Diethyl ether's chief drawbacks are its irritating effect on the respiratory passages and its after effect of nausea.

Among the inhalation anesthetics used today are several halogenated ethers, the most important of which are enflurane and isoflurane.



Enflurane
(Ethrane)



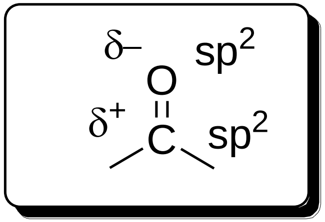
Isoflurane
(Forane)

Carbonyl compounds

Aldehydes

Ketones

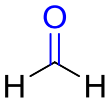
Carbohydrates

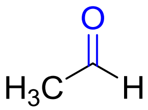


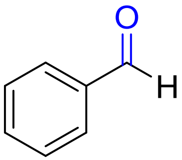
Carbonyl group C=O is present in aldehydes, ketones, and carboxylic acids and their derivatives, as well as in carbohydrates, it is one of the most important functional groups in organic chemistry.

The functional group of an aldehyde is a carbonyl group bonded to a hydrogen atom.

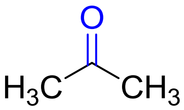
Aldehydes

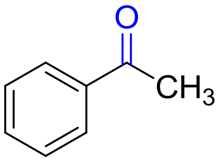

methanal
(formaldehyde)

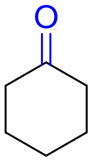

ethanal
(acetaldehyde)


benzene carbaldehyde
(benzaldehyde)

Ketones


propanone
(acetone)


methyl ethyl ketone
(acetophenone ir acetylbenzene)


Cyclohexanone

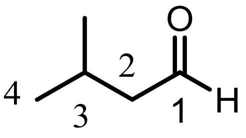
The functional group of a ketone is a carbonyl group bonded to two carbon atoms.

Because aldehydes always contain at least one hydrogen bonded to the C=O group, they are often written RCH=O or RCHO. Similarly, ketones are often written RCOR’.

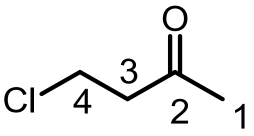
Nomenclature of Aldehydes and Ketones

To name an aldehyde, we change the suffix ***-e*** of the parent alkane to ***-al***. Because the carbonyl group of an aldehyde can appear only at the end of a parent chain and numbering must start with it as carbon 1, there is no need to use a number to locate the aldehyde group.

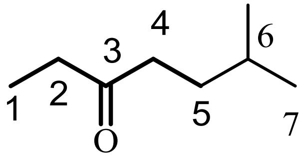
For **unsaturated aldehydes,** we show the presence of the carbon–carbon double bond and the aldehyde by changing the ending of the parent alkane from *-ane* to *-enal:* "-en-" to show the C–C double bond, and "-al" to show the aldehyde. We show the location of the C–C double bond by the number of its first carbon.



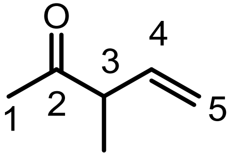
3-methylbutanal



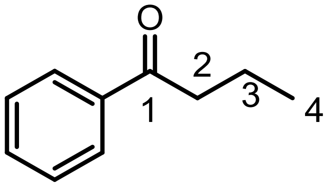
4-chloro-2-butanone



6-methyl-3-heptanone



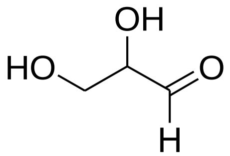
3-Methylpent-4-en-2-one



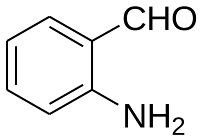
1-Phenylbutanone

Ketones are named by selecting as the parent alkane the longest chain that contains the carbonyl group and then indicating the presence of this group by changing the ***-e*** of the parent alkane to ***-one***. The parent chain is numbered from the direction that gives the smaller number to the carbonyl carbon.

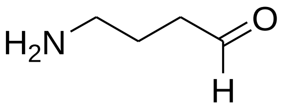
In naming aldehydes or ketones that also contain an -OH or -NH_2 group elsewhere in the molecule, the parent chain is numbered to give the carbonyl group the lower number. An -OH substituent is indicated by *hydroxy*, and an -NH_2 substituent is indicated by *amino*-. Hydroxy and amino substituents are numbered and alphabetized along with any other substituents that might be present.



2,3-dihydroxypropanal
(glyceral)

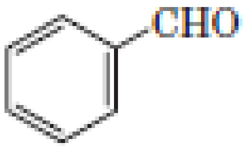


2-Aminobenzaldehyde

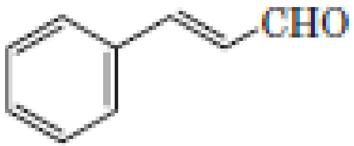


4-Aminobutanal

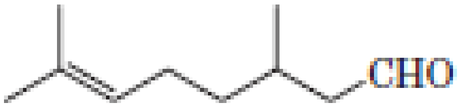
Some Naturally Occurring Aldehydes and Ketones



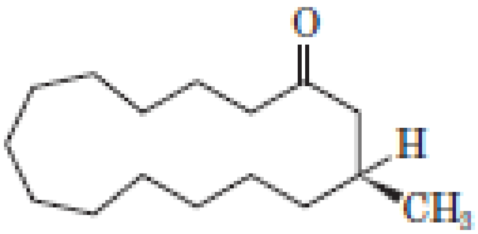
Benzaldehyde
(oil of almonds)



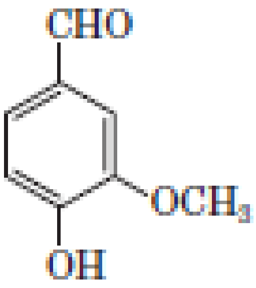
Cinnamaldehyde
(oil of cinnamon)



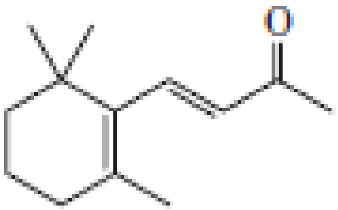
Citronellal
(citronella oils; also in
lemon and lemon grass oils)



Muscone
(from the musk deer;
used in perfumes)



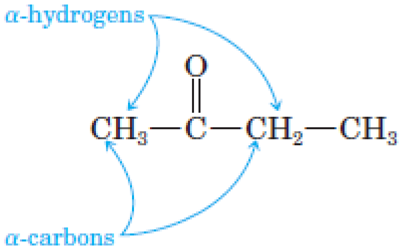
Vanillin
(vanilla bean)



β-Ionone
(from violets)

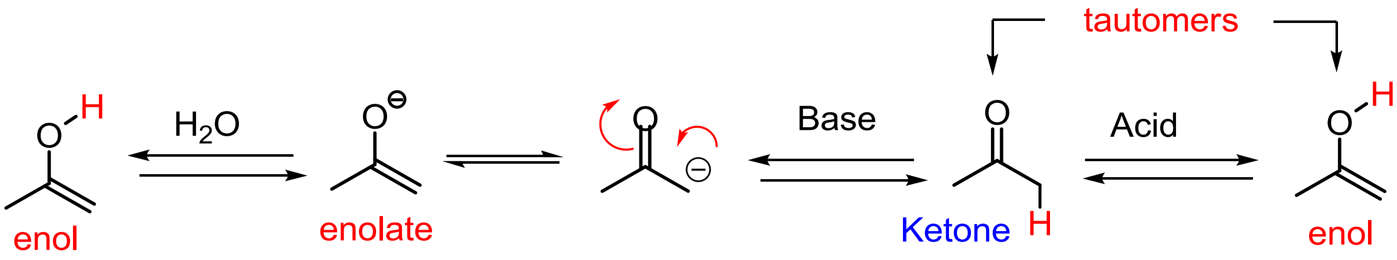
Keto-Enol Tautomerism

A carbon atom adjacent to a carbonyl group is called an α-carbon, and a hydrogen atom bonded to it is called an α-hydrogen.



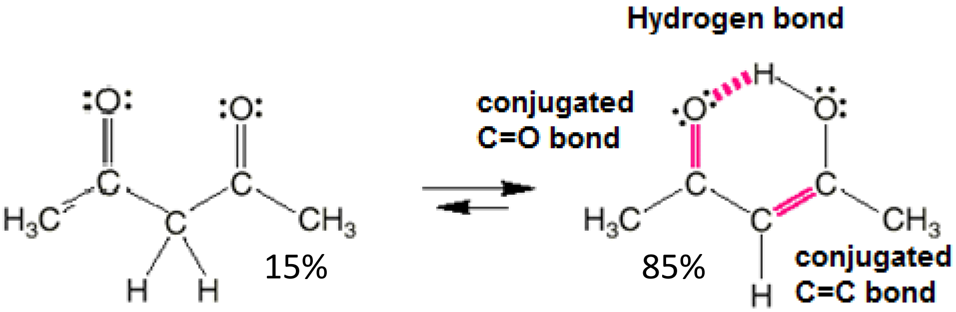
$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-CH_3$

A carbonyl compound that has a hydrogen on an α-carbon is in equilibrium with a constitutional isomer called an **enol.** The name "enol" is derived from designation of it as both an alkene (***-en-***) and an alcohol (***-ol***).



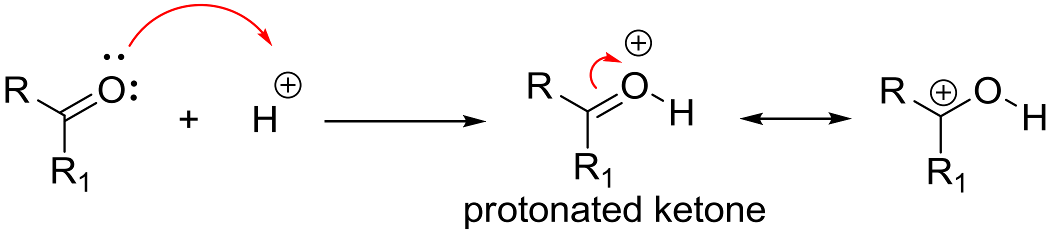
Keto and enol forms are examples of **tautomers,** constitutional isomers in equilibrium with each other that differ in the location of a hydrogen atom and a double bond. This type of isomerism is called **keto-enol tautomerism.** For aldehydes and ketones bearing one oxo group **the keto form generally predominates** at equilibrium.

However, in 1,3-diketones and related carbonyl compounds keto-enol equilibrium is shifted toward enol form. The reason is more stable enol form due to hydrogen bond and conjugated double bonds formed in an enol form.

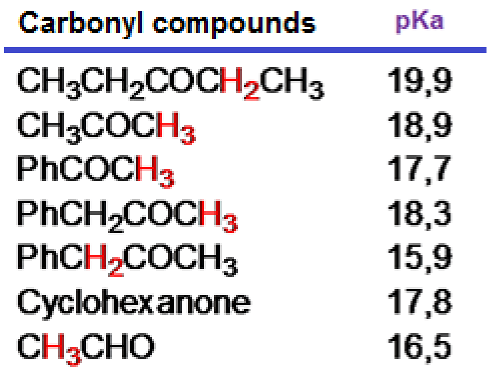


Acid-base properties of aldehydes and ketones

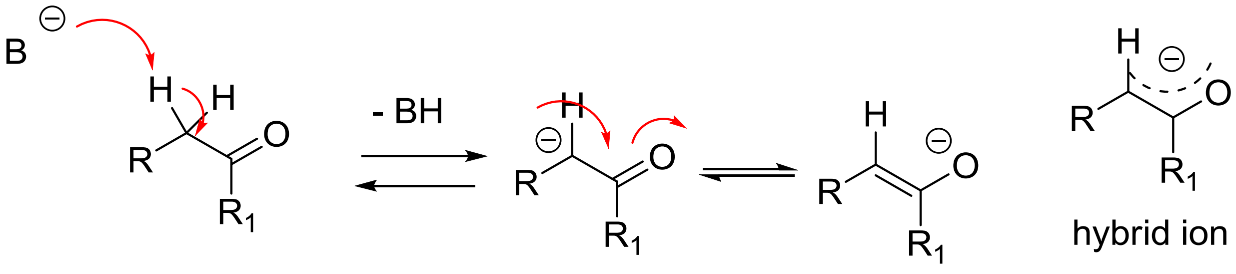
Due to lone pairs of electrons oxygen of carbonyl group is Lewis base. Strong mineral acids (HCl, H_2SO_4, HI) protonate carbonyl group and the corresponding oxonium ion is formed. Positive charge in such an ion is delocalized between **O** and **C**.



Aldehydes and ketones bearing C-H bonds in an α-position are weak C-H acids. Depending on a structure of carbonyl compounds **pKa** of a-CH groups are found in a range **17-20**. Strong bases (NaOH, NaH, NaOEt) abstract proton from a-position and carbanion is formed.

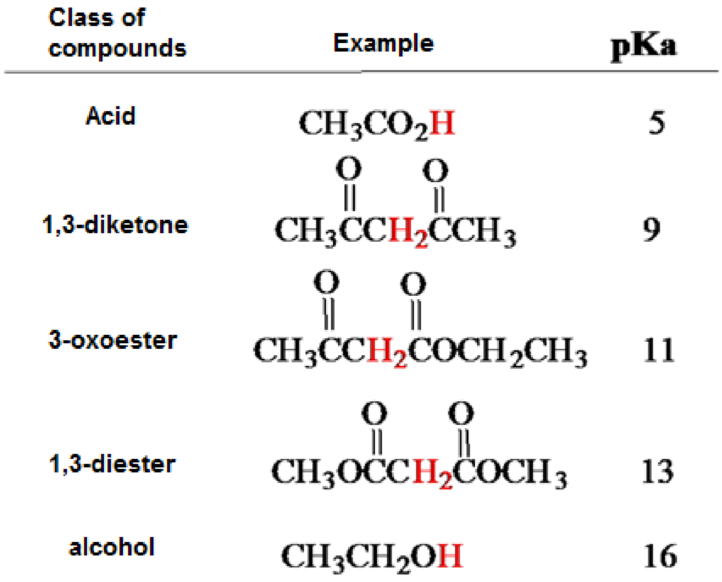


Carbonyl compounds	pKa
$CH_3CH_2COCH_2CH_3$	19,9
CH_3COCH_3	18,9
$PhCOCH_3$	17,7
$PhCH_2COCH_3$	18,3
$PhCH_2COCH_3$	15,9
Cyclohexanone	17,8
CH_3CHO	16,5



Acidity of 1,3-dicarbonyl compounds

Methylene group ($-CH_2-$) between two carbonyl groups is the most acidic in a molecule.

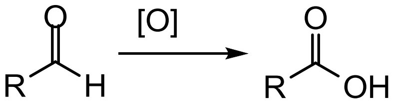


Class of compounds	Example	pKa
Acid	CH_3CO_2H	5
1,3-diketone	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	9
3-oxoester	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$	11
1,3-diester	$CH_3O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_3$	13
alcohol	CH_3CH_2OH	16

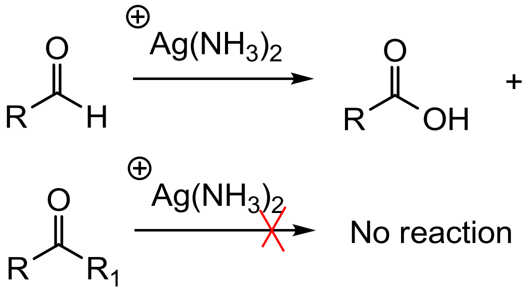
Characteristic Reactions of Aldehydes and Ketones

Oxidation

Aldehydes are oxidized to carboxylic acids by a variety of oxidizing agents,



$[O] = KMnO_4, HNO_3, CrO_3, K_2Cr_2O_7, K_2CrO_4, Ag(NH_3)_2NO_3$

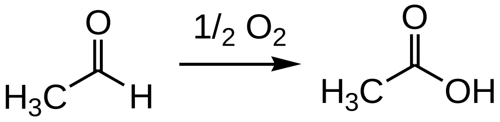


silver-mirror test

Ketones

If this reaction is carried out properly, the silver metal precipitates as a smooth, mirror-like deposit on the inner surface of the reaction vessel.

Ketones, in contrast, resist oxidation by most oxidizing agents, including potassium bichromate and molecular oxygen.

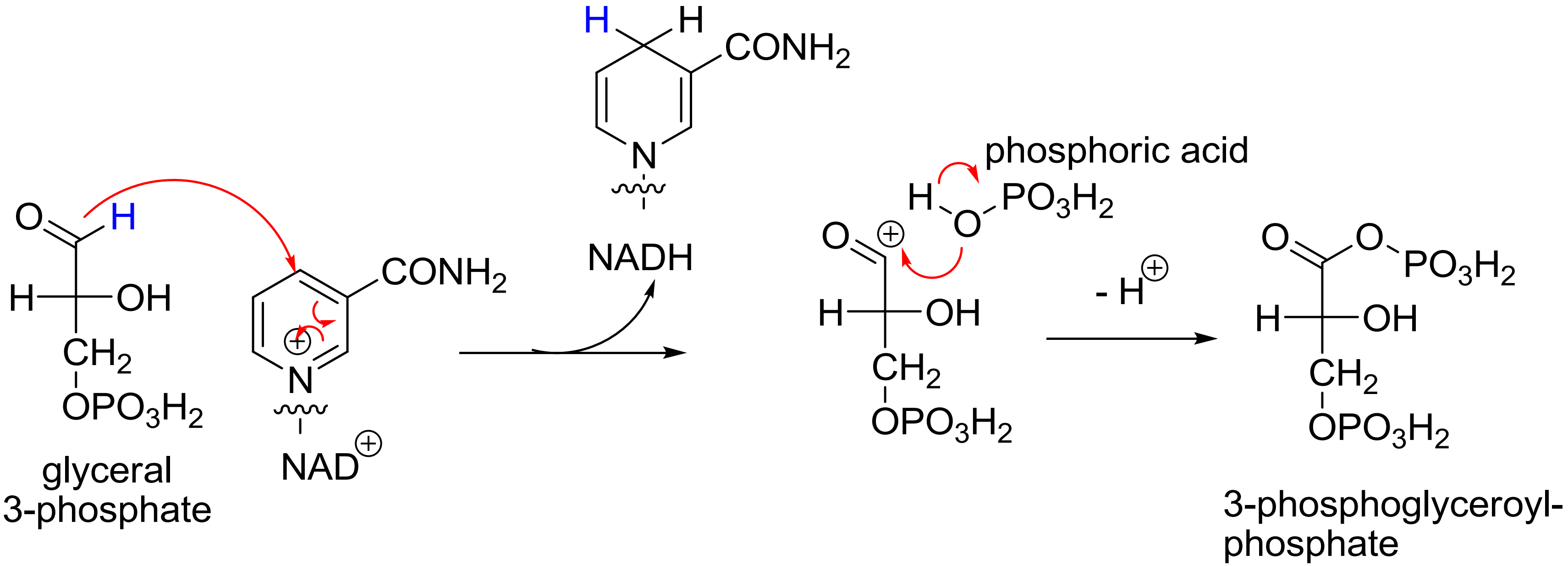


acetaldehyde acetic acid

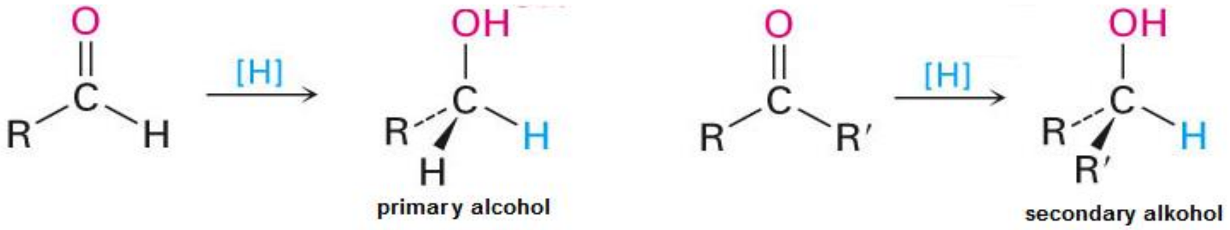
Some adehydes are oxidized even with the air oxygen.

Oxidation of aldehides *in vivo*

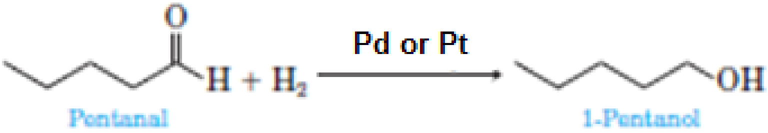
In a cell aldehydes are oxidized by enzymes and cofactor NAD^+. For example, during the oxidation of glyceral phosphate with NAD^+ phosphoglyceroyl phosphate is formed. NAD^+ is reduced to NADH during the reaction.



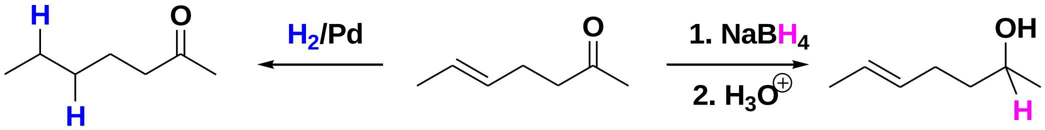
Reduction

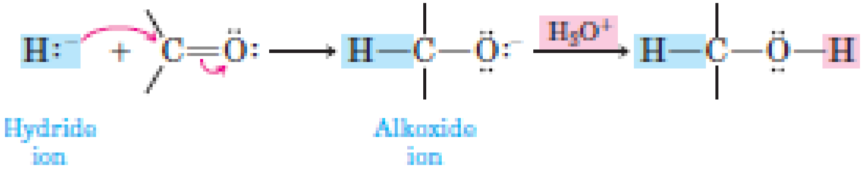


Aldehydes and ketones can be reduced by a variety of reagents.
The main are: H_2/Pd or Pt, $NaBH_4$, $LiAlH_4$.

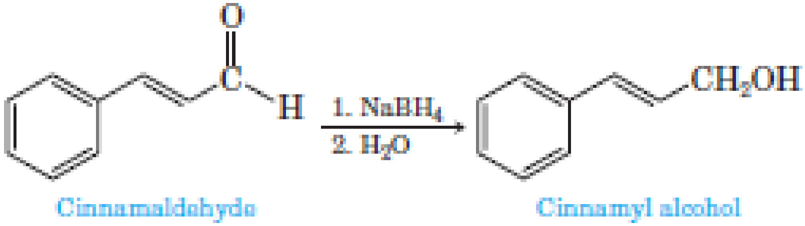


The reduction of a C=O double bond under these conditions is slower than the reduction of a C=C double bond. Thus, if the molecule contains both C=O and C=C double bonds, the C=C double bond is reduced first.



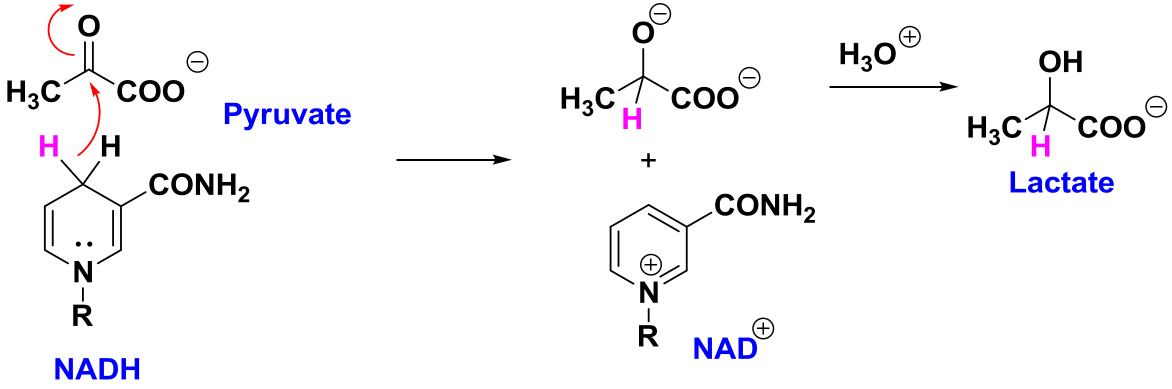


An advantage of using $NaBH_4$ over the H_2/metal reduction is that $NaBH_4$ does not reduce C=C bonds.

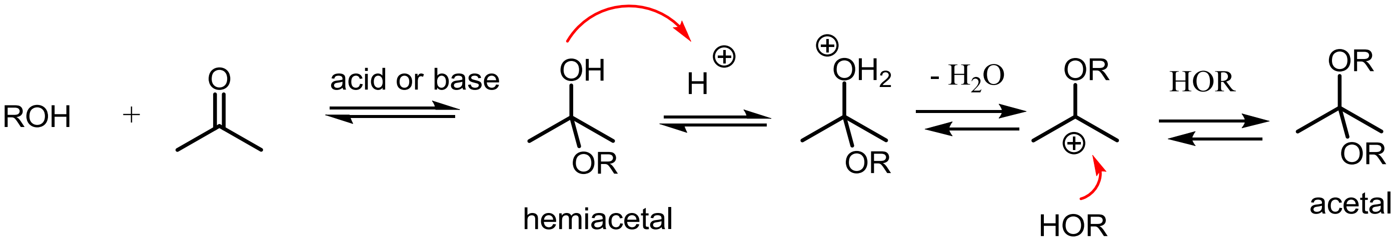


The reason for this selectivity: There is no partial positive or negative charges on a C=C bond. Therefore, a C=C double bond has no partially positive site for attract of the negatively charged hydride ion.

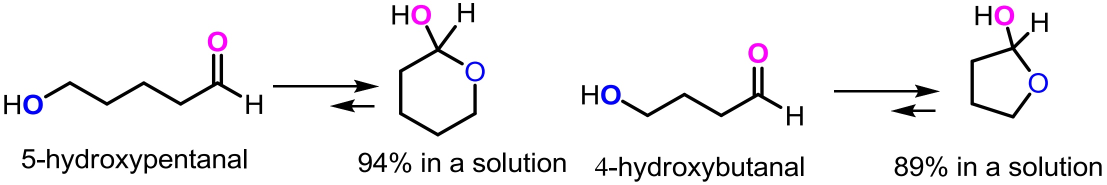
In biological systems, the agent for the reduction of aldehydes and ketones is the reduced form of the coenzyme **nicotinamide adenine dinucleotide, abbreviated NADH**. This reducing agent, like $NaBH_4$, delivers a hydride ion to the carbonyl carbon of the aldehyde or ketone.

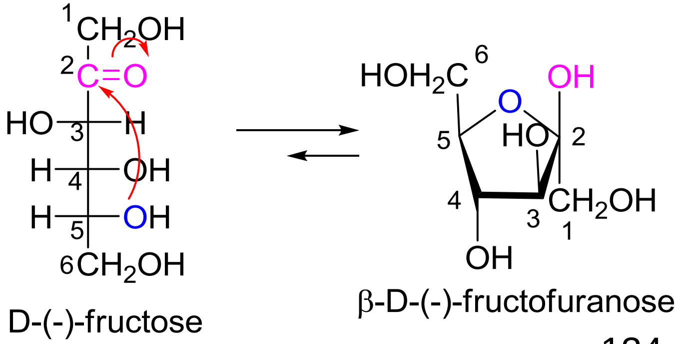


Addition of Alcohols



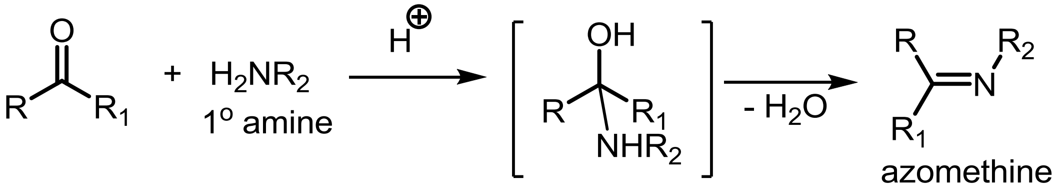
5-member and 6-membered cyclic hemiacetals are stable in a solution. For example:



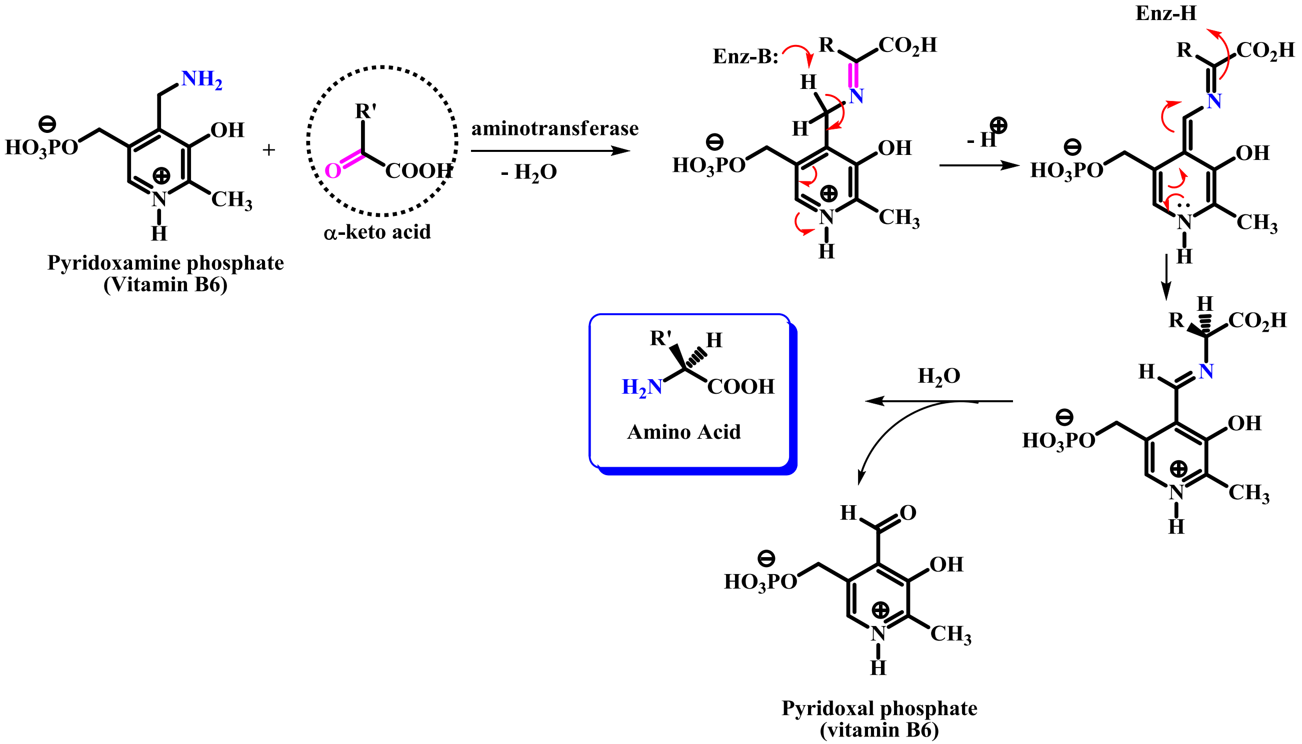


Reaction with amines

Aldehydes and ketones readily react with primary amines to form azomethines, called Shiff’s bases:



The reaction is important in the biosynthesis of amino acids from α-keto carboxylic acids in the presence of Vitamin B6 and enzyme aminotransferase.



Carbohydrates

Carbohydrates

Carbohydrates are the most abundant organic compounds in the plant world. Carbohydrates account for approximately three-fourths of the dry weight of plants. Animals (including humans) get their carbohydrates by eating plants, but they do not store much of what they consume. In fact, **less than 1% of the body weight of animals is made up of carbohydrates.**

The word *carbohydrate means “hydrate of carbon” and derives from the* formula $Cn(H_2O)m$.

Glucose: $C_6H_{12}O_6$, which can be written as $C_6(H_2O)_6$
Sucrose : $C_{12}H_{22}O_{11}$, which can be written as $C_{12}(H_2O)_{11}$

Most carbohydrates are polyhydroxyaldehydes, polyhydroxyketones, or compounds that yield them after hydrolysis. The simpler members of the carbohydrate family are often referred to as **saccharides because of their sweet taste (Latin: *saccharum, “sugar”).***

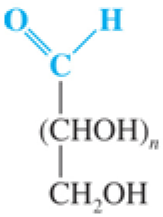
Carbohydrates are classified as **monosaccharides, oligosaccharides, or polysaccharides** depending on the number of simple sugars they contain.

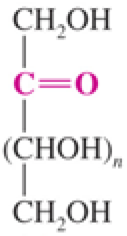
- ✓ **Monosaccharides – carbohydrates that can not be hydrolyzed to more simple carbohydrates;**
- ✓ **Oligosaccharides – carbohydrates that under the hydrolysis give from 2 to 10 molecules of monosaccharides;**
- ✓ **Polysaccharides – carbohydrates that consists of more then 10 units of monosaccharides**

- **Monosaccharides**
  - Classification of monosaccharides
    - They are classified according to:

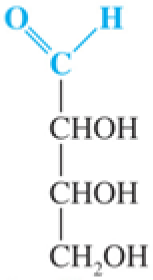
      (1) number of C atoms in the molecule

      (2) the presence of aldehyde or ketone group


Aldose


$CH_2OH-C(=O)-(CHOH)_n-CH_2OH$

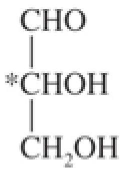
Ketose


Aldotetrose
4C atoms and
aldehyde group

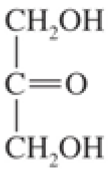

$CH_2OH-C(=O)-CHOH-CHOH-CH_2OH$

Ketopentose
5C atoms and
ketone group

- There are only two trioses:


$CHO-{}^{*}CHOH-CH_2OH$

Glyceraldehyde


$CH_2OH-C(=O)-CH_2OH$

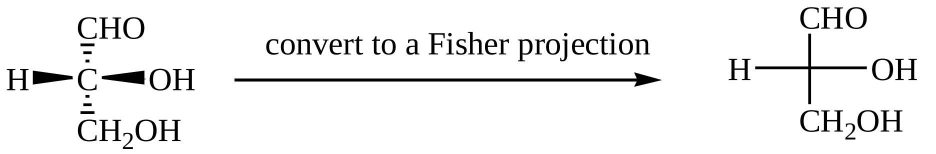
Dihydroxyacetone

Representation of saccharide molecules

Fischer Projection Formulas

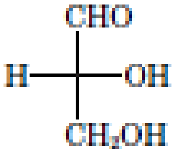
Two-dimensional representations called **Fischer projections** **to show the configuration of carbohydrates** are commonly used**.**

To draw a Fischer projection, draw a three-dimensional representation of the molecule oriented so that the vertical bonds from the stereocenter (atom bonded with 4 different groups) are directed away from you and the horizontal bonds from it are directed toward you (none of the bonds to stereocenter are in the plane of the paper). Then write the molecule as a cross, with the stereocenter indicated by the point at which the bonds cross.

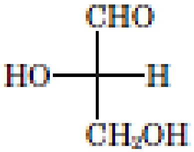


3D representation Fischer representation

Molecules, having a stereocenter can exist in the form of stereoisomers, called **enantiomers.** **Enantiomers are nonsuperimposable mirror images** . Their chemical and physical properties are the same with the exception that one enantiomer rotates plane of polarized light to the right, another – to the left by the same angle.



D-Glyceraldehyde
$[\alpha]_D^{25} = +13.5°$



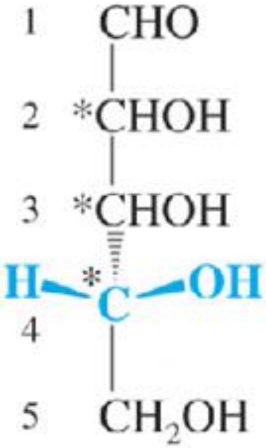
L-Glyceraldehyde
$[\alpha]_D^{25} = -13.5°$

Emil Fischer (*German chemist*) proposed that these enantiomers be designated **D and L**, but he had no experimental way to determine which enantiomer has which specific rotation. Only In 1952 it was proved that his assignment of the D,L-configuration to the enantiomers of glyceraldehyde is correct.

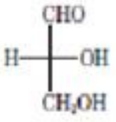
D-glyceraldehyde and L-glyceraldehyde serve as reference points for the assignment of relative configurations to all other aldoses and ketoses. The reference point is the **penultimate** carbon—that is, the **next-to-the-last** carbon on the chain.

D-monosaccharide has the same configuration at its penultimate carbon as D-glyceraldehyde (its -OH group is on the right) in a Fischer projection;

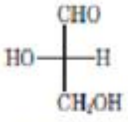
L-monosaccharide has the same configuration at its penultimate carbon as L-glyceraldehyde (its -OH group is on the left).



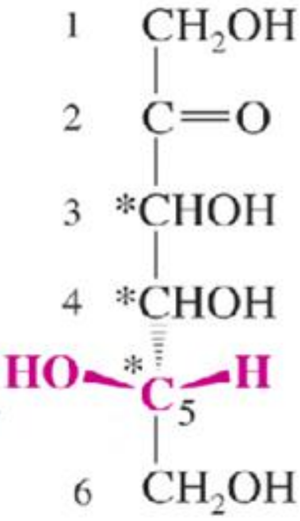
D-Aldopentose



D-Glyceraldehyde

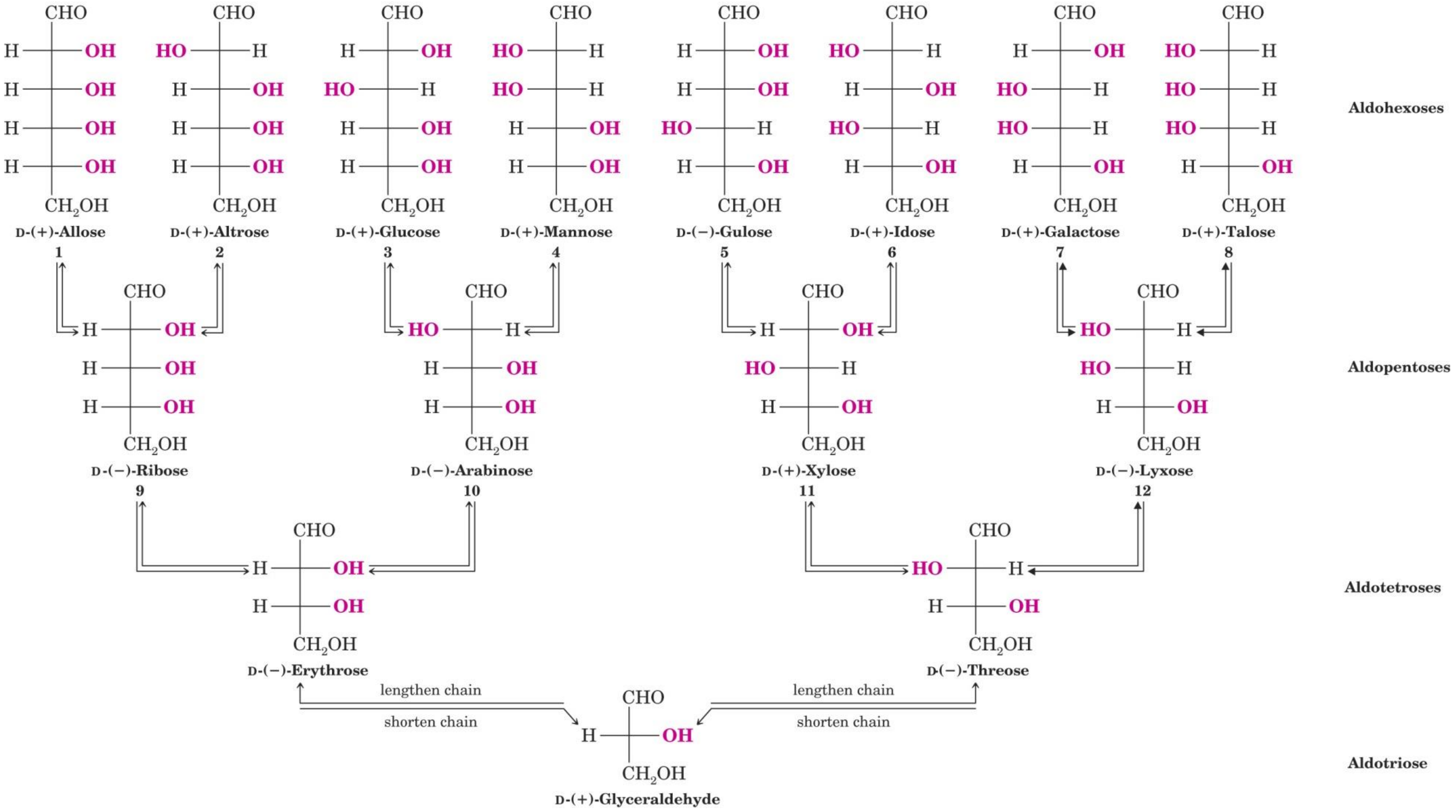


L-Glyceraldehyde

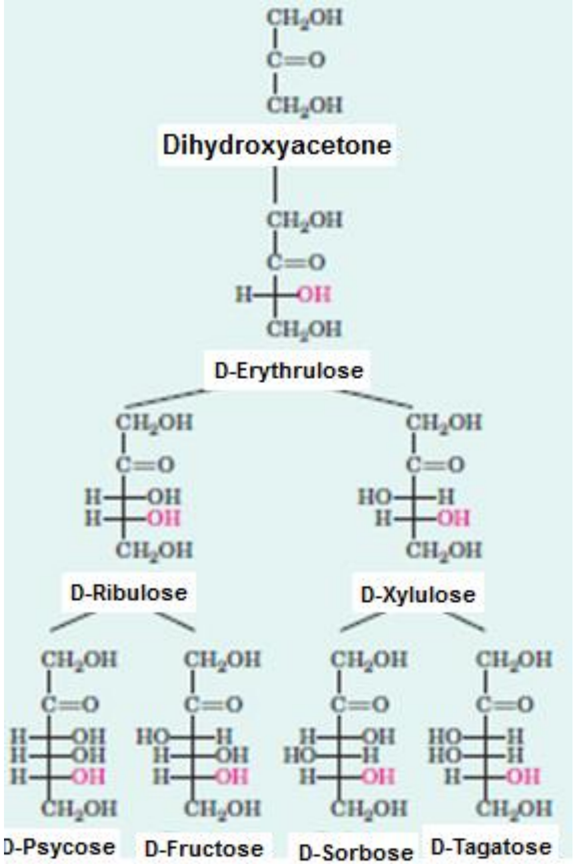


L-ketohexose

Configurational Relationships among the Isomeric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses

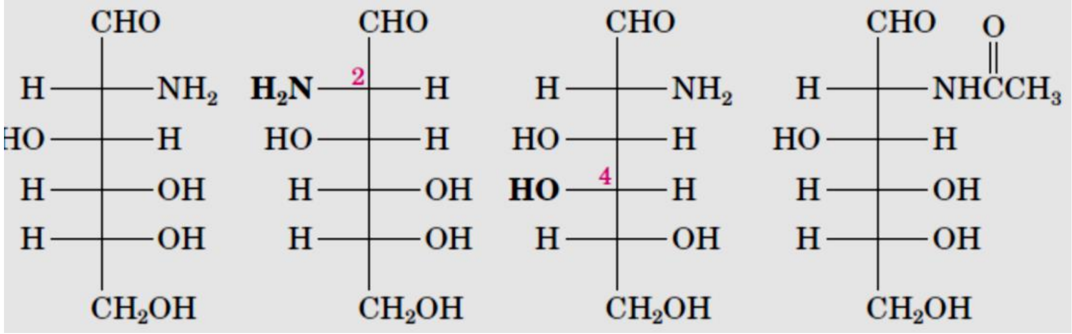


Configurational Relationships among the D-2-Ketoses



Amino Sugars

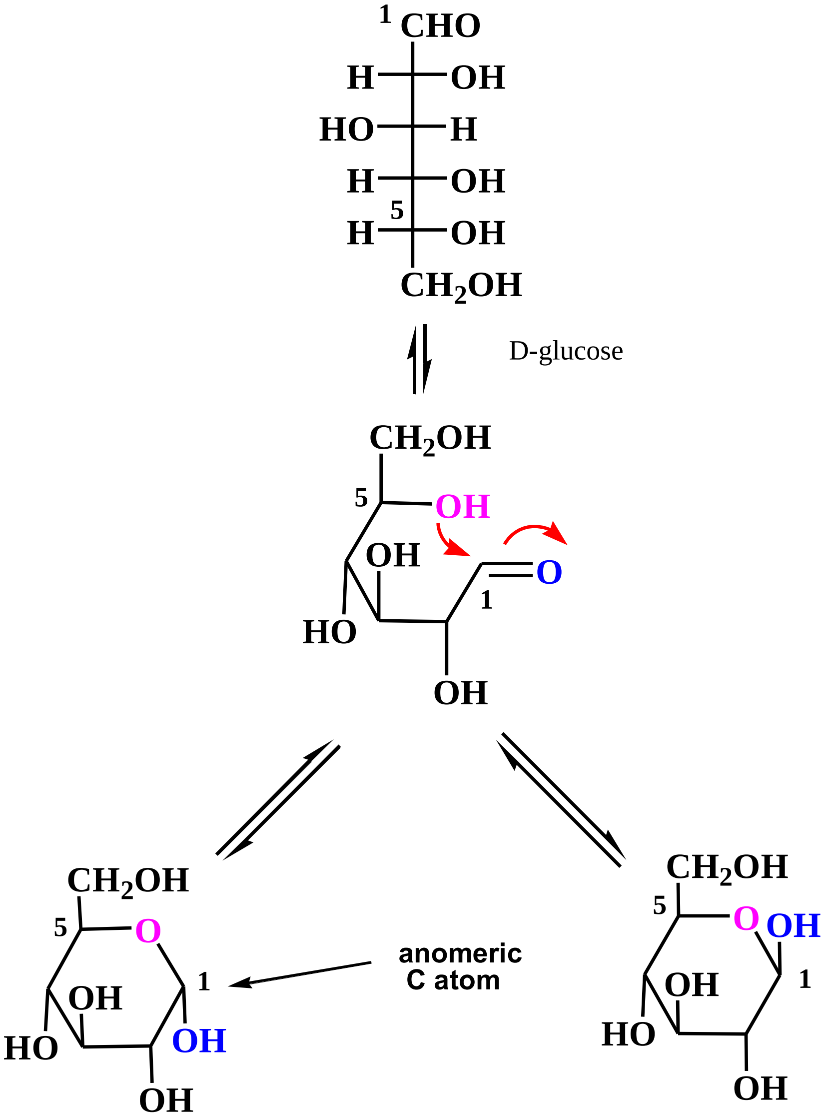
Amino sugars contain an $-NH_2$ group in place of an -OH group. **Only three amino sugars are common in nature: D-glucosamine, D-mannosamine, and D-galactosamine.**



D-glucosamine D-Mannosamine D-Galactosamine N-Acetyl-D-glucosamine

N- Acetyl-D-glucosamine, a derivative of D-glucosamine, is a component of many polysaccharides, including connective tissue such as cartilage. It is also a component of chitin, the hard, shell-like exoskeleton of lobsters, crabs, shrimp, and other shellfish.

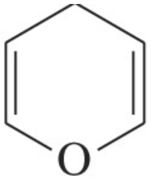
Cyclic form of monosaccharides



D-α-glucopyranose

D-β-glucopyranose

The names of cyclic form of sacharides come from the names of heterocycles



Pyran

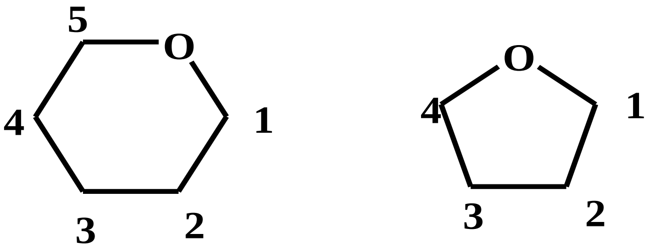
Furan

The new carbon stereocenter created in forming the cyclic structure is called an **anomeric carbon.**

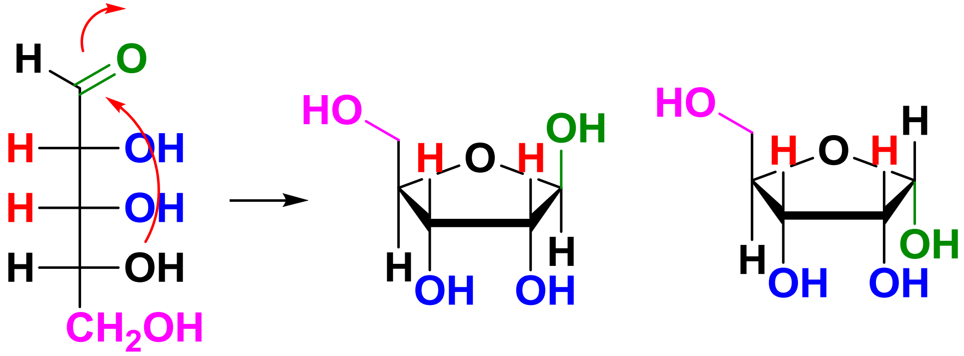
Stereoisomers that differ in configuration only at the anomeric carbon are called **anomers.**

Rules for drawing Haworth projections

- ✓ Draw either a 6- or 5-membered ring including oxygen as one atom and number the ring clockwise starting next to oxygen.



- ✓ If the substituent is to **the right** in the Fisher projection, it **will be drawn down** in the Haworth projection (Down-Right Rule)

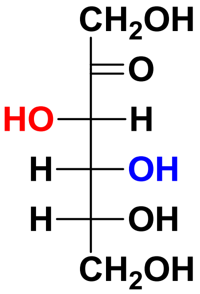


D-Ribose β-D-ribofuranose α-D-ribofuranose

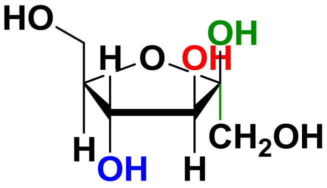
- ✓ For D-sugars the **highest numbered carbon** (furthest from the carbonyl) **is drawn up**. For L-sugars, it is drawn down
- ✓ for D-sugars, **the OH group at the anomeric** position is drawn **down for α** and **up for β**. For L-sugars α is up and β is down

Conformation Representations

A five-membered furanose ring is so close to being planar that Haworth projections provide adequate representations of furanoses.

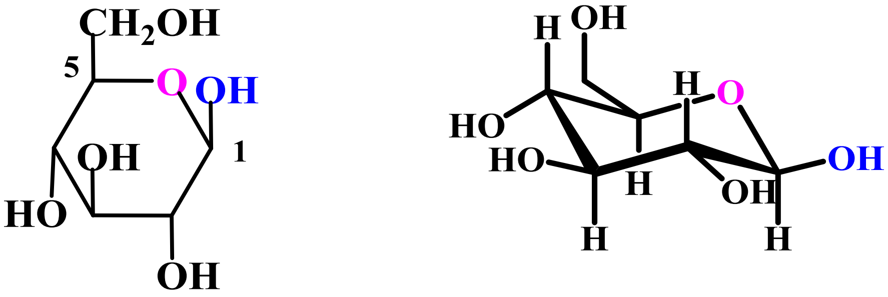


D-Fructose



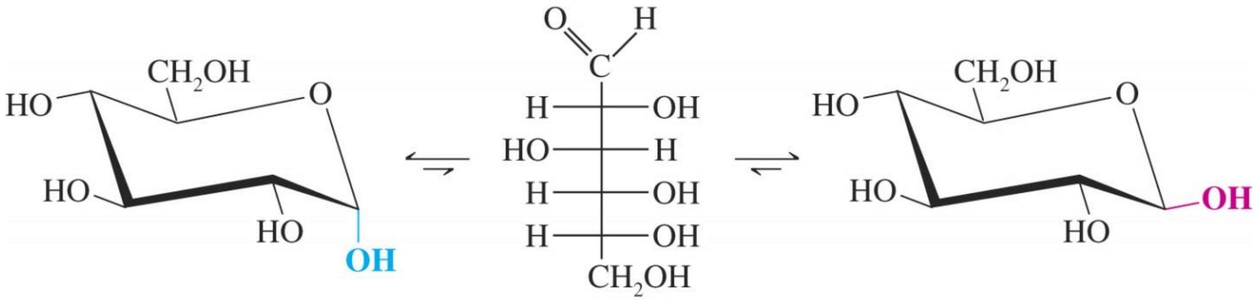
β-D-fructofuranose

For pyranoses, the six-membered ring is more accurately represented as a **chair conformation.**



D-β-glucopyranose

- Mutarotation
- The α- and β-forms of glucose can be isolated separately
  - Pure α-glucose has a specific rotation of +112^{o}
  - Pure β-glucose has a specific rotation of +18.7^{o}
- When either form of glucose is allowed to stand in aqueous solution, the specific rotation of the solution slowly changes to +52.7^{o}
  - It does not matter whether one starts with pure α- or β-glucose
- Mutarotation is the change in optical rotation as an equilibrium mixture of anomers forms



α-D-(+)-Glucopyranose
(mp 146°C; $[\alpha]_D^{25}$ = +112°)

Open-chain
form of
D-(+)-glucose

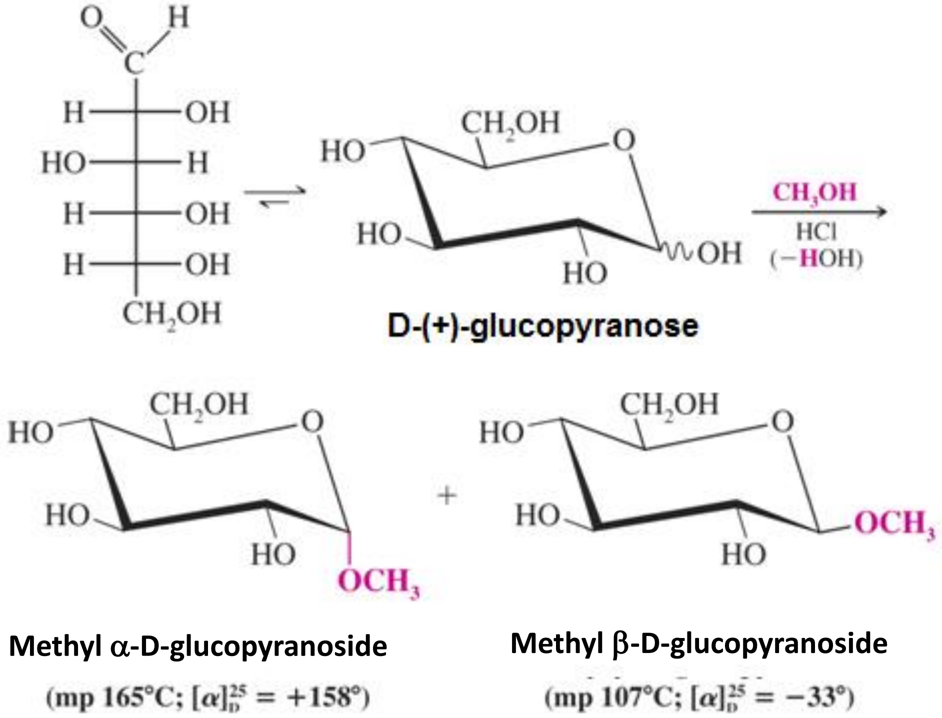
β-D-(+)-Glucopyranose
(mp 150°C; $[\alpha]_D^{25}$ = +18.7°)

- Mutarotation of glucose results in an equilibrium mixture of 36% α-glucose and 64% β-glucose.
  - The more stable β-glucose form predominates
  - A very small amount (0.003%) of the open-chain form exists in this equilibrium

Characteristic Reactions of Monosaccharides

Formation of Glycosides (Acetals)

Treatment of a monosaccharide with an alcohol yields an acetal, as illustrated by the reaction of β-D-glucopyranose with methanol.



D-(+)-glucopyranose

Methyl α-D-glucopyranoside

(mp 165°C; $[\alpha]_D^{25} = +158°$)

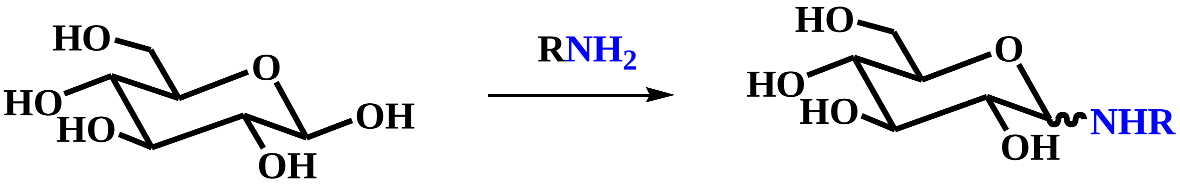
Methyl β-D-glucopyranoside

(mp 107°C; $[\alpha]_D^{25} = -33°$)

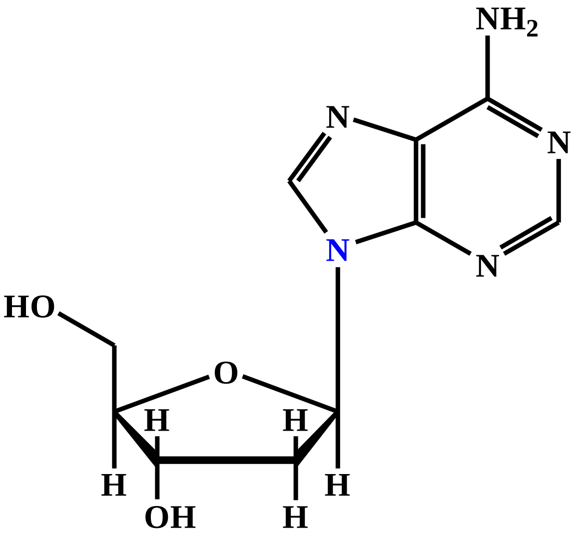
A cyclic acetal derived from a monosaccharide is called a **glycoside,** and the bond from the anomeric carbon to the -OR group is called a **glycosidic bond. Mutarotation is not possible in a glycoside** because an acetal—unlike a hemiacetal—is no longer in equilibrium with the open-chain carbonyl containing compound. **Glycosides are stable in water and aqueous base**; like other acetals. However, **they are hydrolyzed in aqueous acid** to an alcohol and a monosaccharide.

N-Glycosides

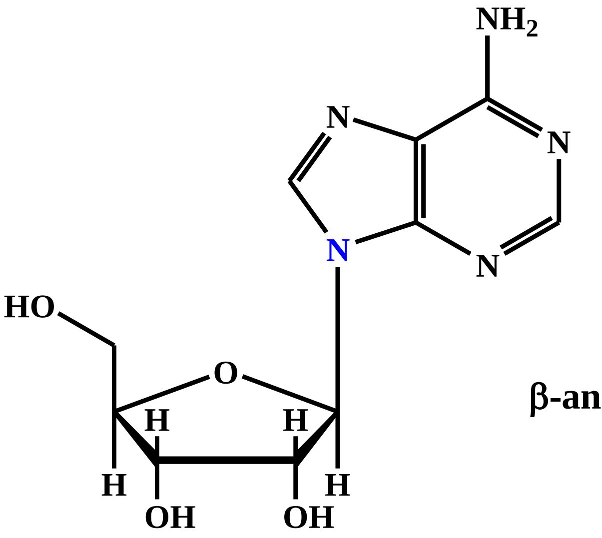
N-Glycosides – glycosides in which anomeric carbon atom is connected with nitrogen atom.



Among natural N-glycosides the most important are nucleosides (found in DNR and RNR). For example:



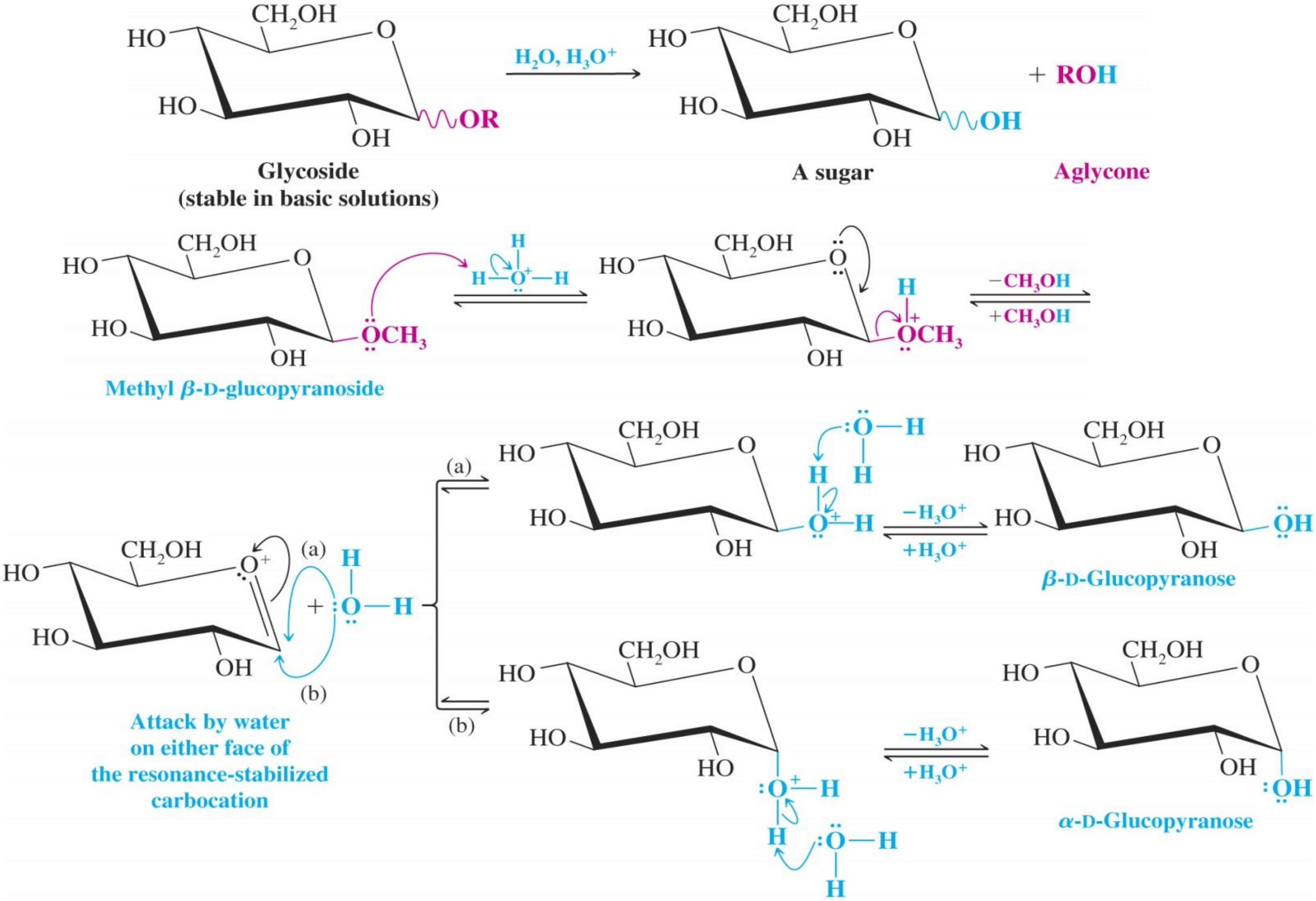
2'-Deoxyadenosine



Adenosine

β-anomers

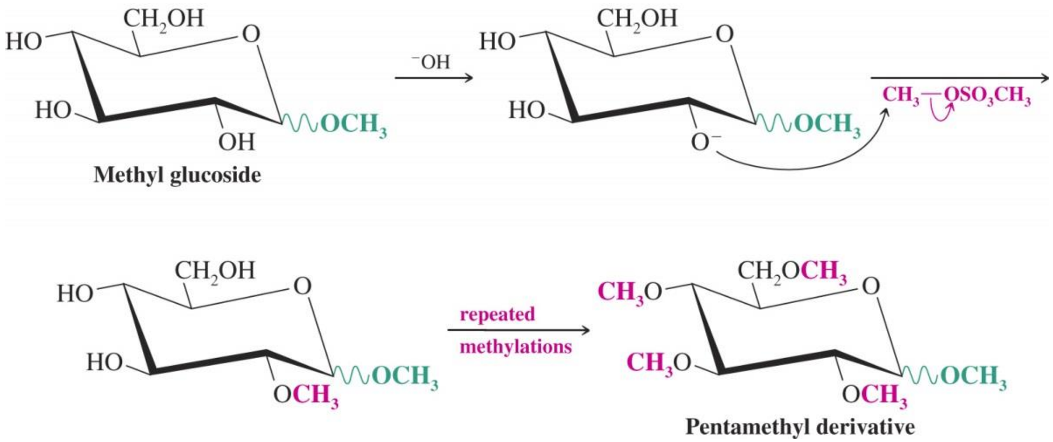
- Glycosides can be hydrolyzed in aqueous acid
  - The alcohol obtained after hydrolysis of a glycoside is called an aglycone



Formation of Ethers

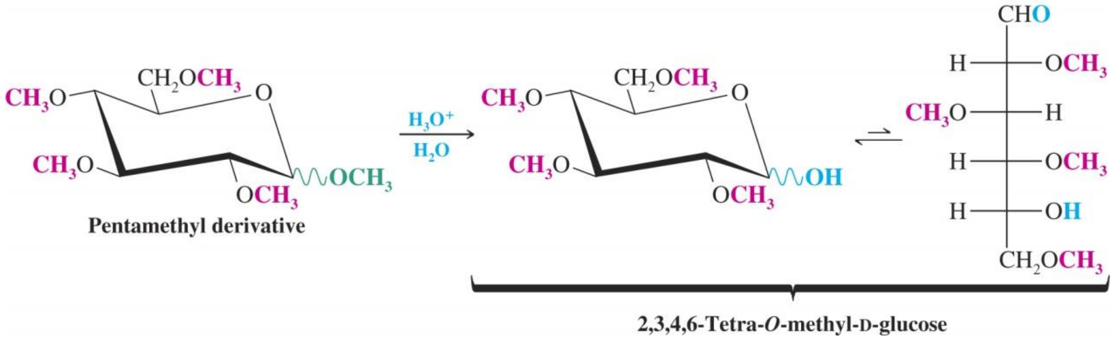
The hydroxyl groups of carbohydrates can be converted to ethers by the Williamson ether synthesis

Exhaustive methylation of methyl glucoside can be carried out using dimethylsulfate



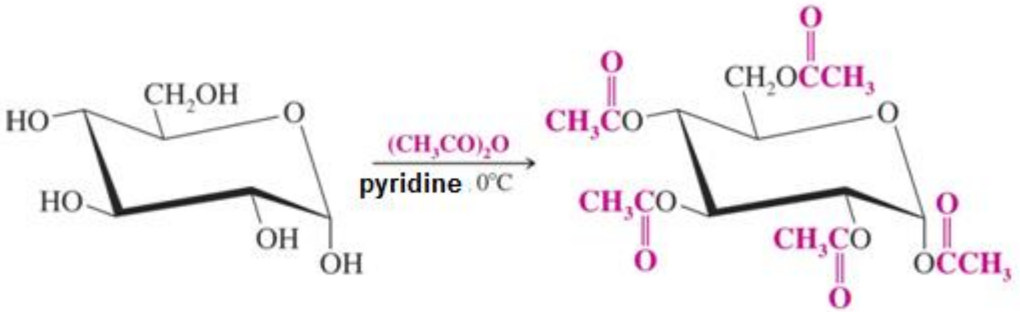
Exhaustive methylation can be used to prove that glucose exists in the pyranose (6-membered ring) form

- **Hydrolysis of the pentamethyl derivative results in a free C5 hydroxyl**



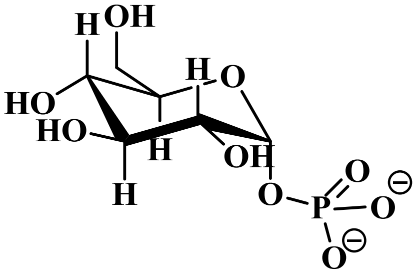
Formation of Esters

Carbohydrates as polyhydroxylic alcohols react easily with acids (organic and inorganic) or their anhydrides to give the corresponding esters.

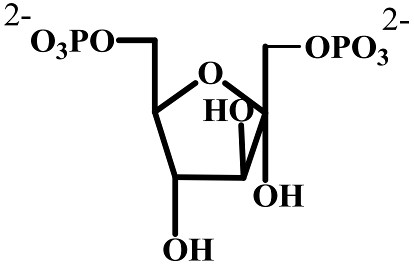


1,2,3,4,5,6-hexaacetyl-α-D-glucopyranose

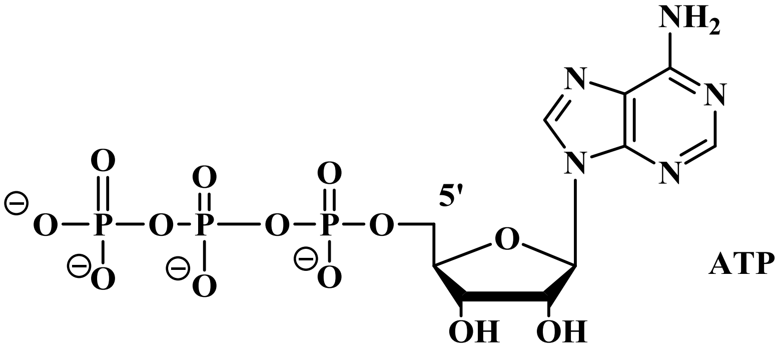
Mono- and diphosphoric esters are important intermediates in the metabolism of monosaccharides. Note, that phosphoric acid is a strong enough acid so that at the pH of cellular and intercellular fluids, both acidic protons of a phosphoric ester are ionized, giving the ester a charge of -2.



α-D-glucopyranose 1-phosphate

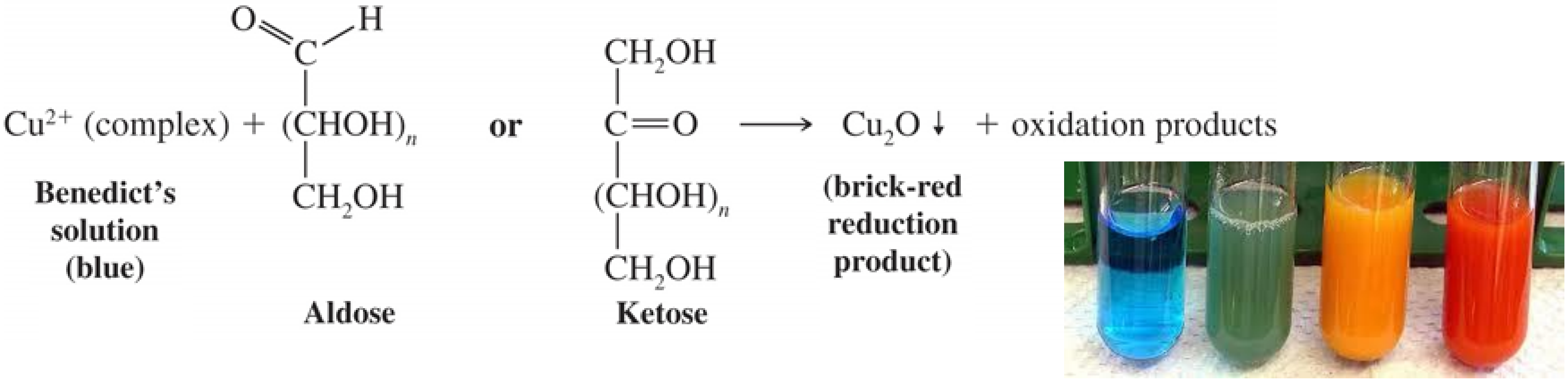


α-D-fructofuranose 1,6-diphosphate

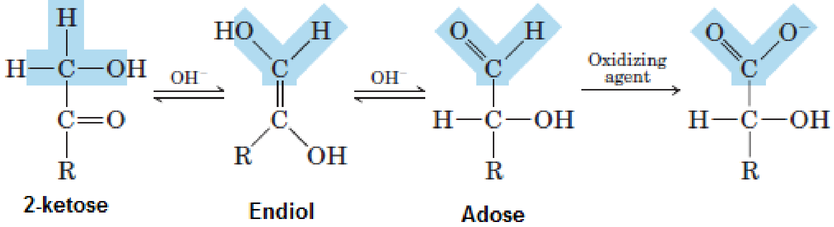


Adenosine 5'-triphosphate

- Oxidation Reactions of Monosaccharides
  - Benedict’s or Tollens’ Reagents: Reducing Sugars
    - Aldoses and ketoses give positive tests when treated with Tollens’ solution or Benedict’s reagent
      - Tollens’ reagent [$Ag(NH_3)_2OH$] gives a silver mirror when Ag^+ is reduced to Ag^0
      - Benedict’s reagent (an alkaline solution of cupric citrate complex) gives a brick red precipitate of Cu_2O
      - In basic solution a ketose can be converted to an aldose that can then react with Tollens’ or Benedicts’s reagent

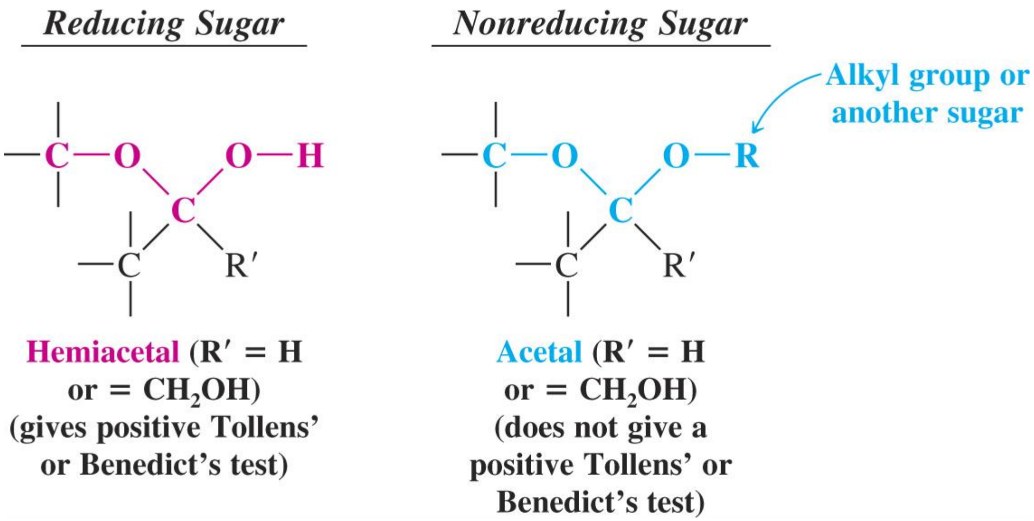


2-Ketoses are also reducing sugars. Carbon 1 of a ketose is not oxidized directly. Instead, under the basic conditions of this oxidation, a 2-ketose exists in equilibrium with an aldose by way of an enediol intermediate. The aldose is then oxidized by the mild oxidizing agent.



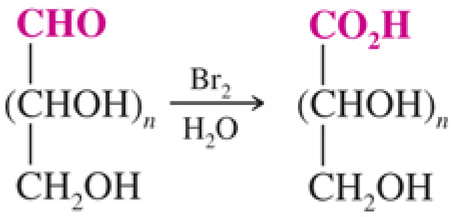
- Carbohydrates with hemiacetal linkages are *reducing sugars* because they react with Tollens' and Benedict's reagents
  - The hemiacetal form is in equilibrium with a small amount of the aldehyde or ketone form, which can react with Tollens' and Benedict's reagents

- Carbohydrates with only acetal groups (glycosidic linkages) do not react with these reagents and are called non-reducing sugars
  - Acetals are not in equilibrium with the aldehyde or ketone and so cannot react with these reagents



● Oxidation to Aldonic Acids

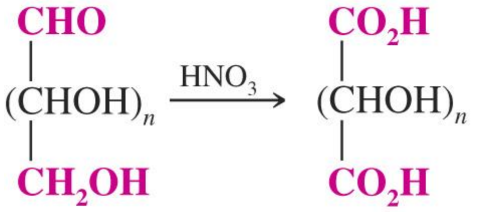
Bromine in water selectively oxidizes the aldehyde group of an aldose to the corresponding carboxylic acid. **An aldose becomes an aldonic acid:**



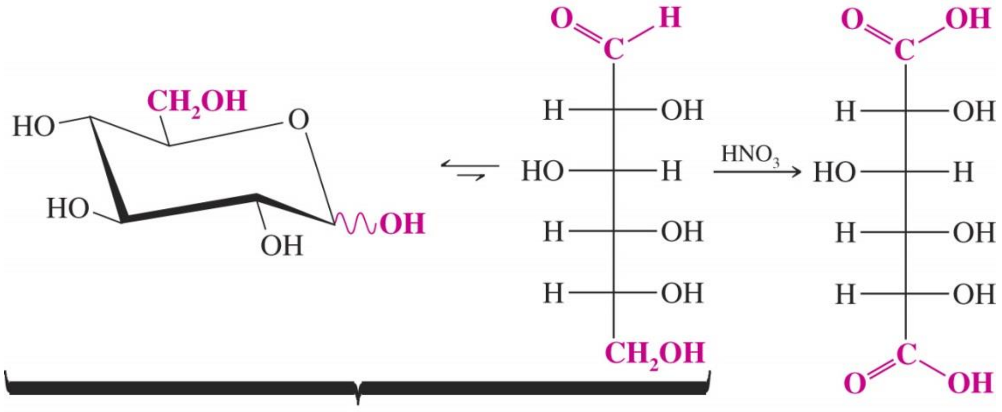
Aldose **Aldonic Acid**

– Nitric Acid Oxidation: Aldaric Acids

Dilute nitric acid oxidizes both the aldehyde and primary hydroxyl groups of an aldose to an aldaric acid:



Aldose **Aldaric acid**

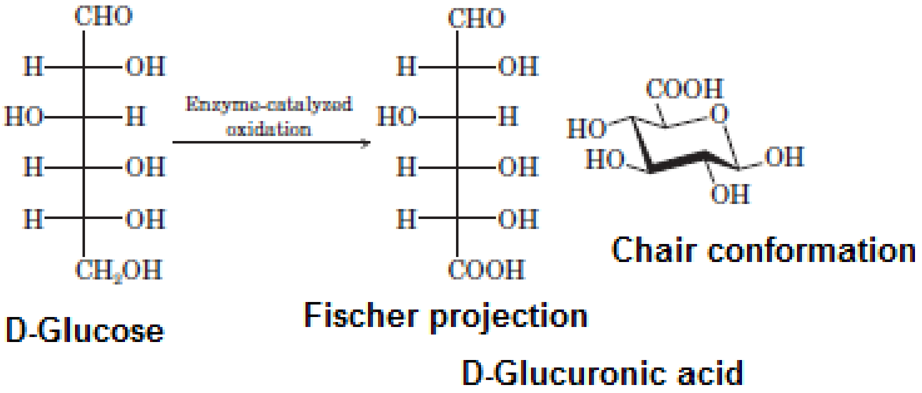


D-Glucose

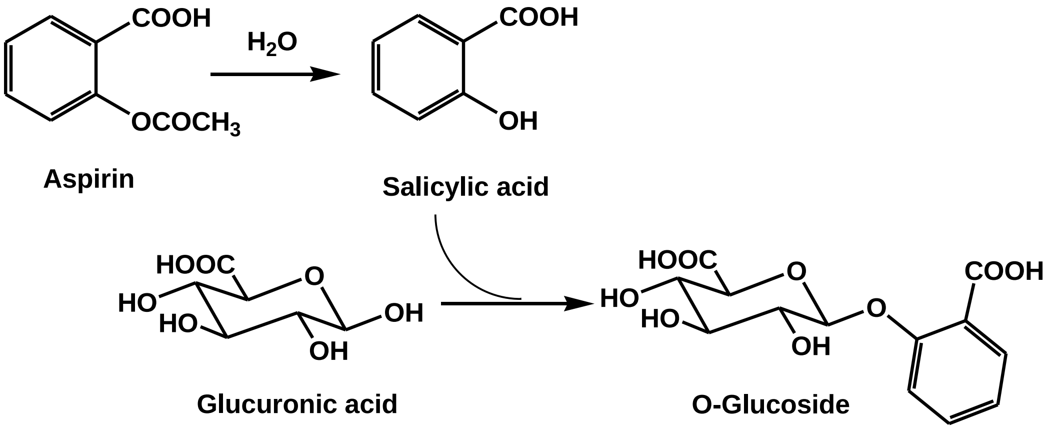
D-Glucaric acid

- **Oxidation to Uronic Acids**

Enzyme-catalyzed oxidation of the primary alcohol at carbon 6 of a hexose yields a uronic acid.

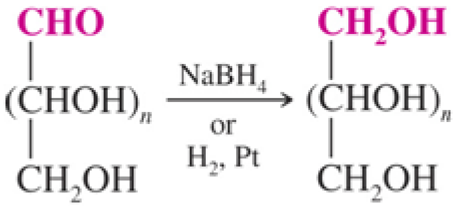


The body also uses D-glucuronic acid to detoxify foreign phenols and alcohols. In the liver, these compounds are converted to glycosides of glucuronic acid (glucuronides), usually more soluble in water, and excreted in the urine.

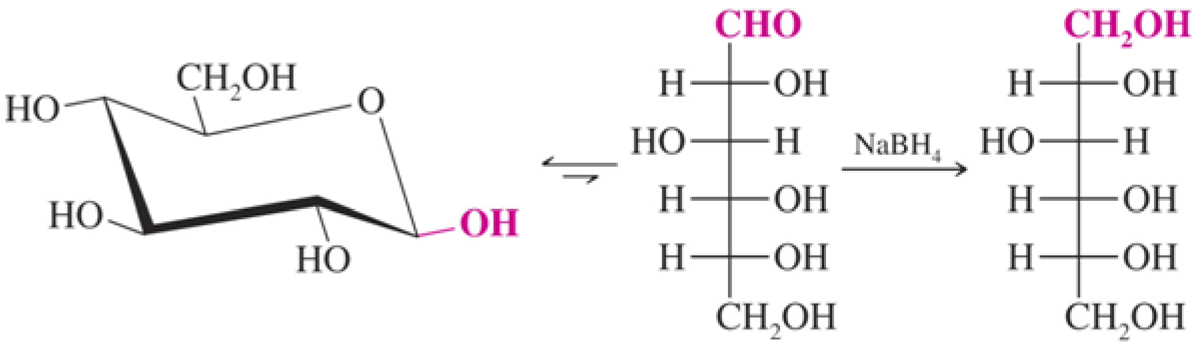


Reduction to Alditols

The carbonyl group of a monosaccharide can be reduced to a hydroxyl group by a variety of reducing agents, including H_2/Pt and sodium borohydride. The reduction products are known as **alditols.** The names of alditols are made by dropping the -**ose** from the name of the monosaccharide and adding -**itol.**



Aldose **Alditol**



D-glucose

D-glucitol (D-sorbitol)

In the reaction the open-chain form takes part. Only a small amount of this form is present in solution but, as it is reduced, the equilibrium between cyclic hemiacetal forms (only the β form is shown here) and the open-chain form shifts to replace it.

Disaccharides and Oligosaccharides

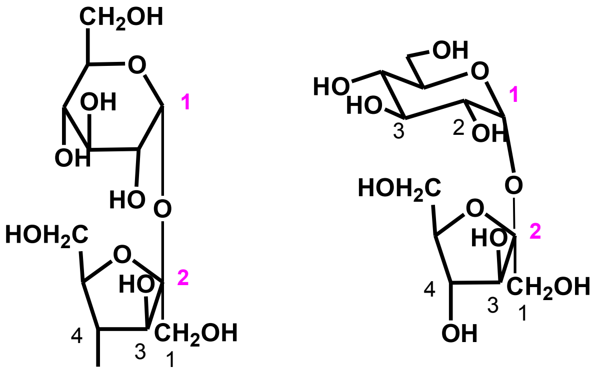
Disaccharide - a carbohydrate containing **two** monosaccharide units joined by a glycosidic bond.
Oligosaccharide - a carbohydrate containing from **six to ten** monosaccharide units, each joined to the next by a glycosidic bond.

In a disaccharide, two monosaccharide units are joined by a glycosidic bond between the anomeric carbon of one unit and an -OH group of the other unit.

Three important disaccharides are **sucrose, lactose, and maltose**.

Sucrose ($C_{12}H_{22}O_{11}$)

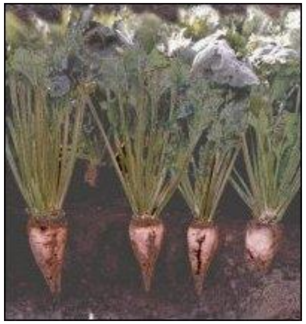
In sucrose, carbon 1 of a-D-glucopyranose bonds to carbon 2 of D-fructofuranose by an α-1,2-glycosidic bond. Because the anomeric carbons of both the glucopyranose and fructofuranose units are involved in formation of the glycosidic bond, neither monosaccharide unit is in equilibrium with its open-chain form. **Thus sucrose is a non-reducing sugar**.



Sucrose

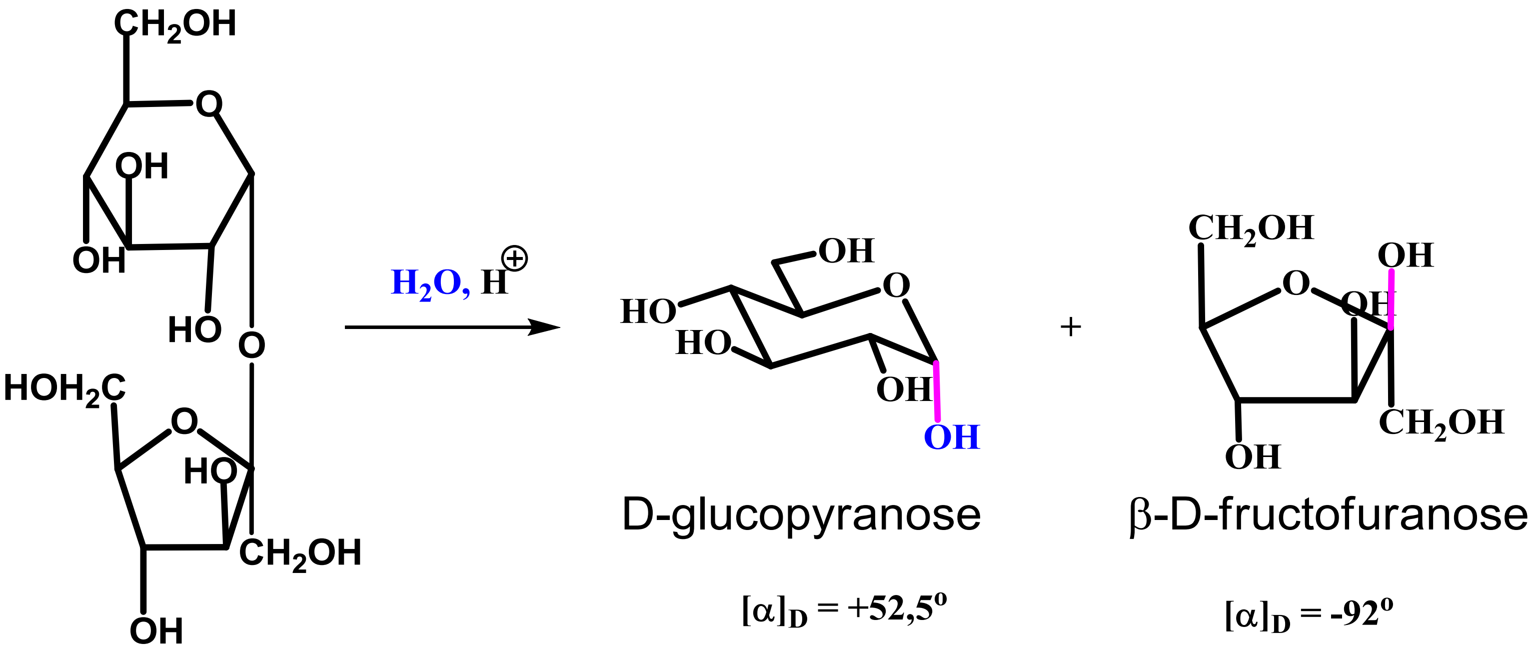
2-O-(a-D-glucopyranosyl)-b-D-fructofuranose

Sugar cane
(sucrose 15-20%)



Sugar beet
(sucrose 14-18%)

Sucrose undergoes hydrolysis in acidic media to give equimolar amount of glucose and fructose. The obtained mixture of two saccharides rotates the plane of polarized light to the left. So the rotation angle after the hydrolysis changes from the positive value (sucrose) to the negative value (mixture of glucose and fructose). For this reason, this mixture was called as an **inverted sugar**.



D-glucopyranose

β-D-fructofuranose

$[\alpha]_D = +66,5^o$

$[\alpha]_D = +52,5^o$

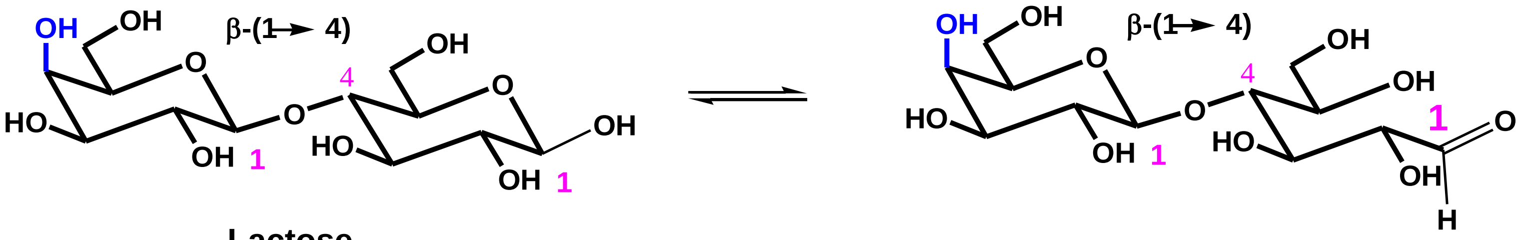
$[\alpha]_D = -92^o$

Sum = - 39.5°

Inverted sugar

Lactose

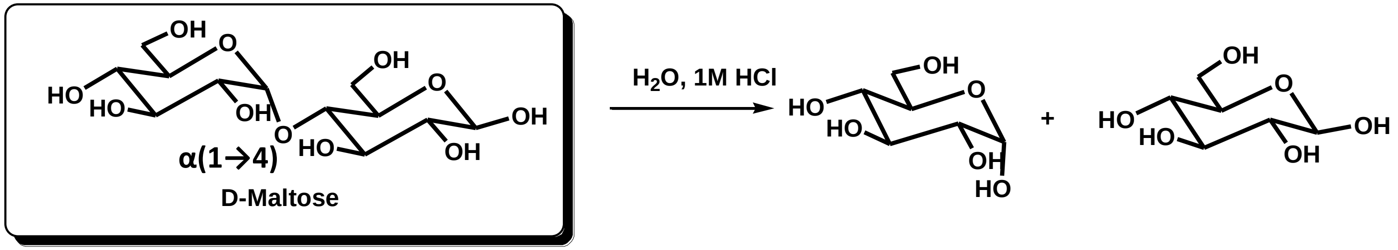
Lactose is the principal sugar present in milk (sometimes it is called milk sugar). It accounts for **5 to 8% of human milk** and **4 to 6% of cow's milk**. This disaccharide consists of D-galactopyranose bonded by a β-1,4-glycosidic bond to carbon 4 of D-glucopyranose. **Lactose is a reducing sugar**, because the cyclic hemiacetal of the D-glucopyranose unit is in equilibrium with its open-chain form and can be oxidized to a carboxyl group.



Lactose

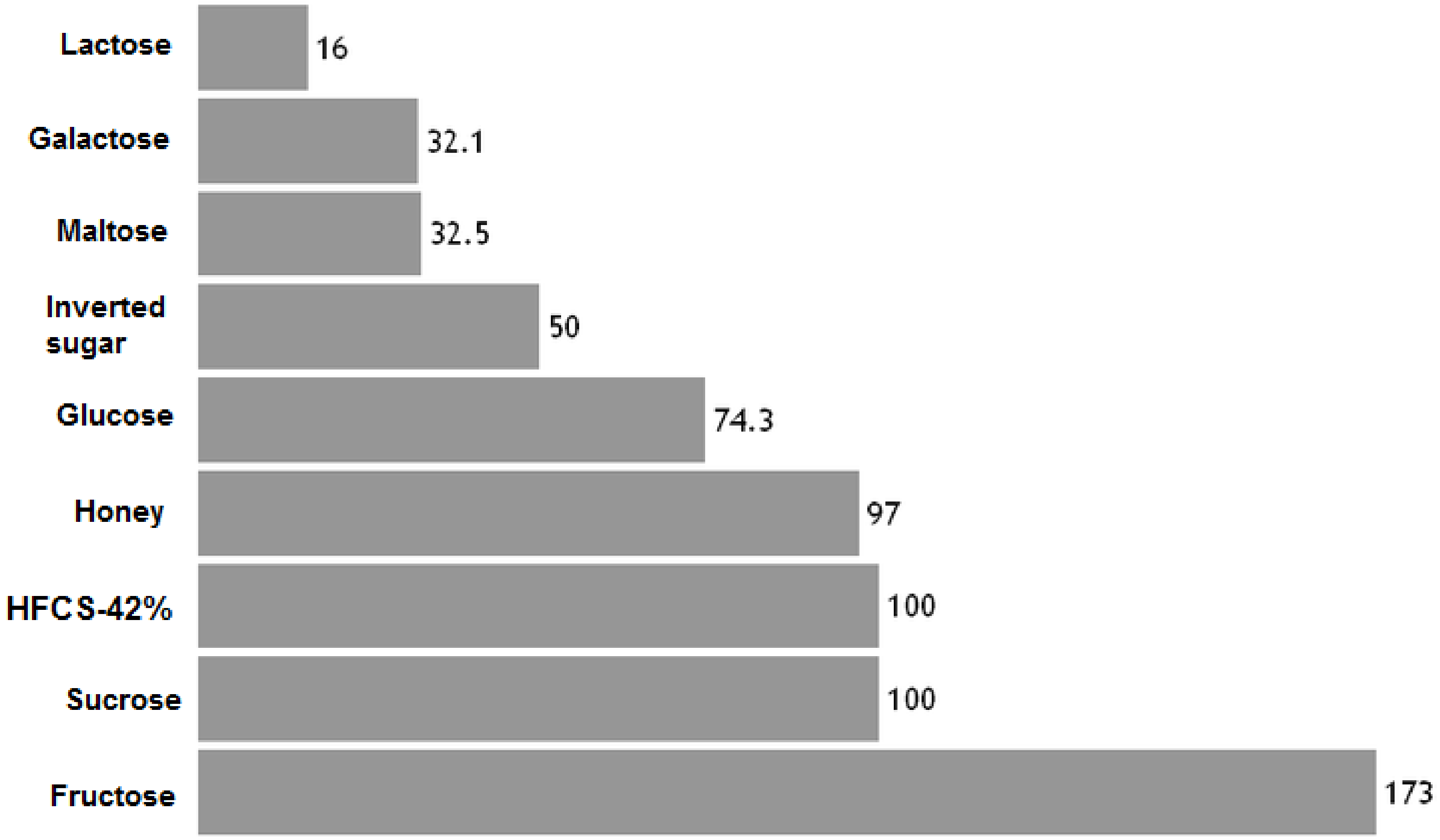
Maltose

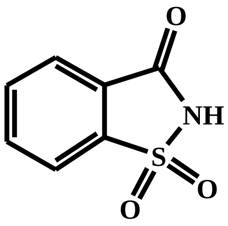
It consists of two units of D-glucopyranose joined by a glycosidic bond between carbon 1 (the anomeric carbon) of one unit and carbon 4 of the other unit.



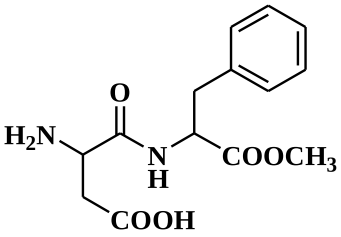
Maltose is a reducing sugar; the hemiacetal group on the right unit of D-glucopyranose is in equilibrium with the free aldehyde and can be oxidized to a carboxylic acid.

Relative Sweetness



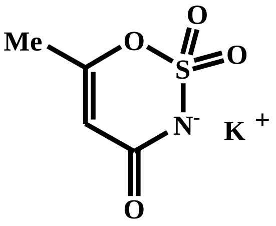


saccharine



Asp-Phe-OCH_3

aspartame



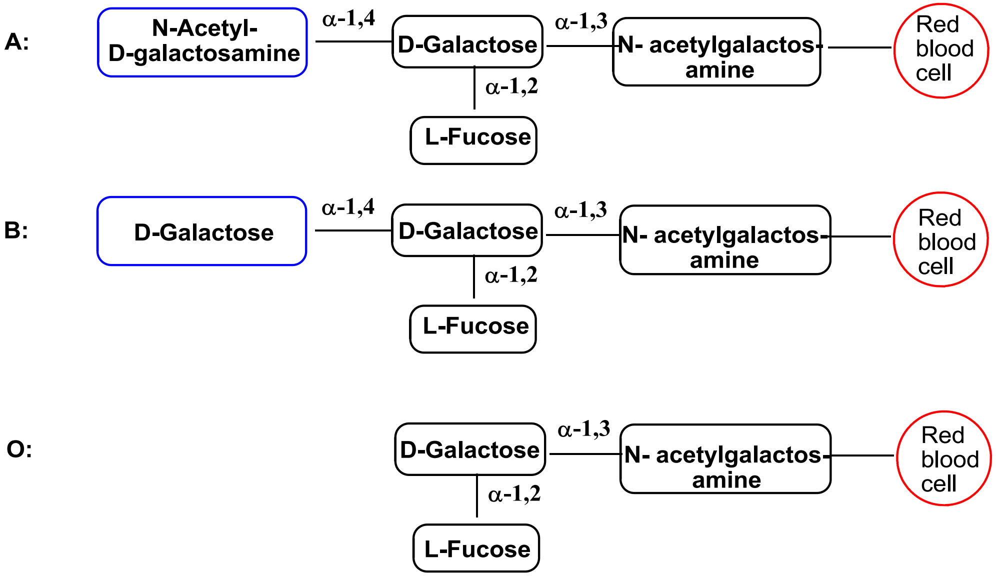
Acesulfame-K

Sweetener	Sweetness
Glucose	75
Sucrose	100
Aspartame	18000
Acesulfame-K	20000
Saccharine	45000

A, B, AB, and O Blood Types

Membranes of animal plasma cells have large numbers of relatively small carbohydrates bound to them. In fact, the outsides of most plasma cell membranes are literally “sugar-coated.” These **membrane-bound carbohydrates** are part of the mechanism by which cell types recognize one another and, in effect, **act as biochemical markers.** They contain relatively few monosaccharides, the most common of which are D-galactose, D-mannose, L-fucose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine.

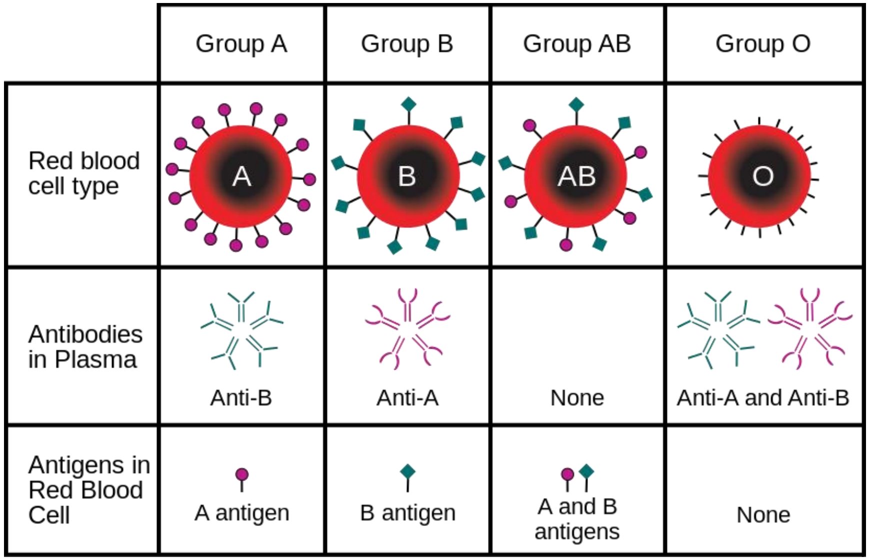
Whether an individual belongs to type A, B, AB, or O is genetically determined and depends on the type of trisaccharide or tetrasaccharide bound to the surface of the red blood cells. These surface-bound carbohydrates, designated as A, B, and O, act as antigens.



A: N-Acetyl-D-galactosamine —α-1,4— D-Galactose —α-1,3— N- acetylgalactosamine — Red blood cell
D-Galactose —α-1,2— L-Fucose

B: D-Galactose —α-1,4— D-Galactose —α-1,3— N- acetylgalactosamine — Red blood cell
D-Galactose —α-1,2— L-Fucose

O: D-Galactose —α-1,3— N- acetylgalactosamine — Red blood cell
D-Galactose —α-1,2— L-Fucose

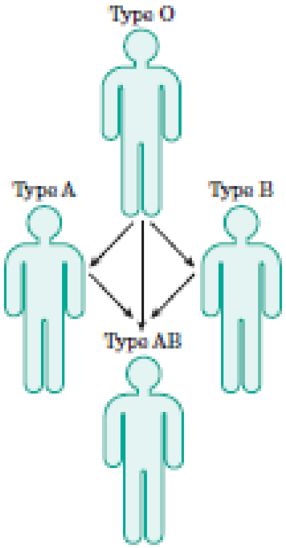


	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies in Plasma	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in Red Blood Cell	A antigen	B antigen	A and B antigens	None

The blood carries antibodies against foreign substances. When a person receives a blood transfusion, the antibodies clump together (aggregate) the foreign blood cells. Type A blood, for example, has A antigens (*N*-acetyl-D-galactosamine) on the surfaces of its red blood cells and carries anti-B antibodies (against B antigen). B-type blood carries B antigen (D-galactose) and has anti-A antibodies (against A antigens). **Transfusion of type A blood into a person with type B blood can be fatal, and vice versa**.

The relationships between blood type and donor–receiver interactions

Sugar on surface: O
Has antibodies against: A and B
Can receive blood from: O
Can donate blood to: O, A, B and AB



Sugar on surface: A
Has antibodies against: B
Can receive blood from: A and O
Can donate blood to: A and AB

Sugar on surface: B
Has antibodies against: A
Can receive blood from: B and O
Can donate blood to: B and AB

Sugar on surface: A and B
Has antibodies against: None
Can receive blood from: O, A, B, and AB
Can donate blood to: AB

People with type O blood are universal donors, and

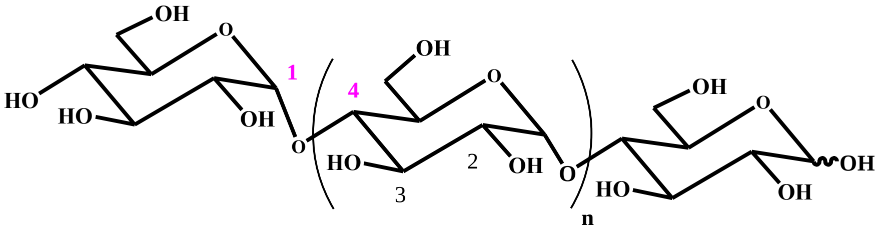
those with type AB blood are universal acceptors.

Polysaccharides

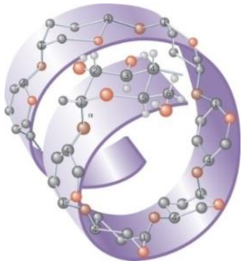
Polysaccharides consist of large numbers of monosaccharide units bonded together by glycosidic bonds. **Three important polysaccharides, all made up of glucose units, are starch, glycogen, and cellulose.**

Starch

Starch is used for energy storage in plants. It is found in all plant seeds and tubers and is the form in which glucose is stored for later use. **Starch** can be separated into two principal polysaccharides: **amylose and amylopectin**. Most starches contain 20 to 25% amylose and 75 to 80% amylopectin. Complete hydrolysis of both **amylose and amylopectin yields only D-glucose**. **Amylose is composed of continuous, unbranched chains of as many as 4000 D-glucose units joined by α-1,4-glycosidic bonds.**



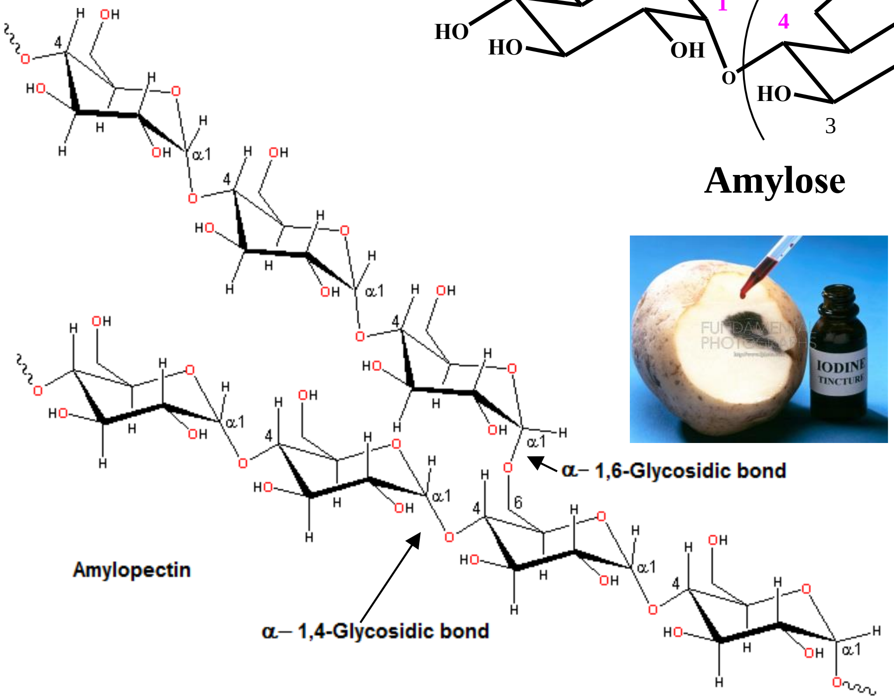
Amylose



Amylose tends to assume a shape of left handed helix.

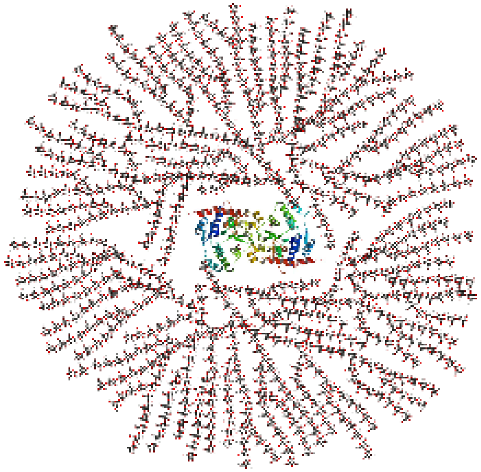
Iodine solution is used to test for starch; a dark blue color indicates the presence of starch.

Amylopectin contains chains of as many as 10,000 D-glucose units also joined by α-1,4-glycosidic bonds. In addition, **considerable branching from this linear network occurs. New chains of 24 to 30 units are started at branch points by α-1,6-glycosidic bonds**



Glycogen

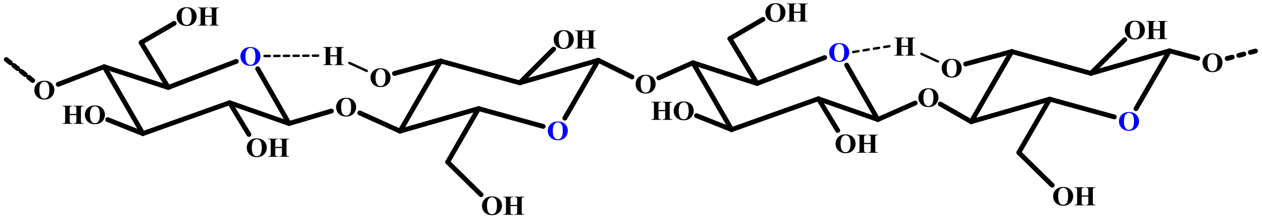
Glycogen acts as the energy-reserve carbohydrate for animals. Like amylopectin, it is a branched polysaccharide containing approximately 10^6 **glucose units joined by α-1,4- and α-1,6-glycosidic bonds.** The total amount of glycogen in the body of a well-nourished adult human is about 350 g, divided almost equally between liver and muscle.



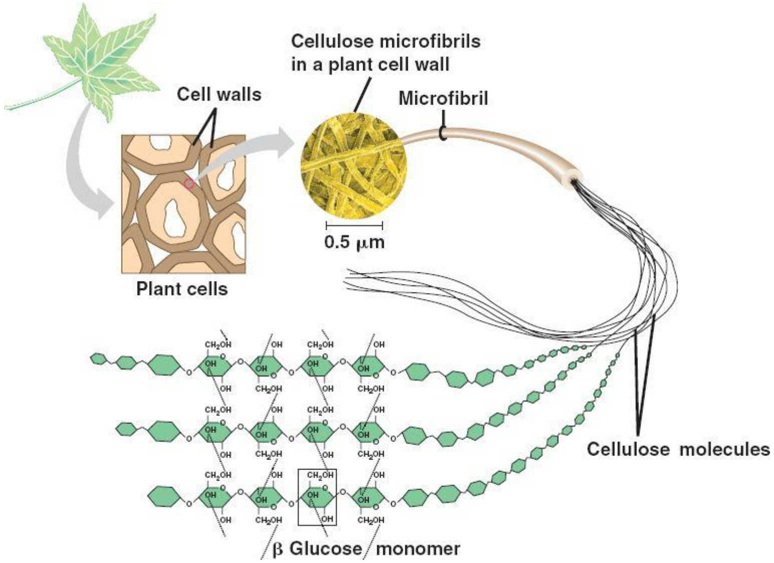
Schematic view of glycogen.
In the center, the molecule of protein - glycogenin that starts the biosynthesis of glycogen is represented

Cellulose

Cellulose, the most widely distributed **plant skeletal polysaccharide**, constitutes almost half of the cell-wall material of wood. **Cotton is almost pure cellulose.** Cellulose is a linear polysaccharide of D-glucose units joined by β-1,4-glycosidic bonds. It has an average molecular weight of 400,000 g/mol, corresponding to approximately 2200 glucose units per molecule.



Cellulose molecules align themselves side by side into well-organized, water-insoluble fibers in which the OH groups form numerous intermolecular hydrogen bonds. It explains why cellulose is insoluble in water. When a piece of cellulose-containing material is placed in water, there are not enough -OH groups on the surface of the fiber to pull individual cellulose molecules away from the strongly hydrogen-bonded fiber.



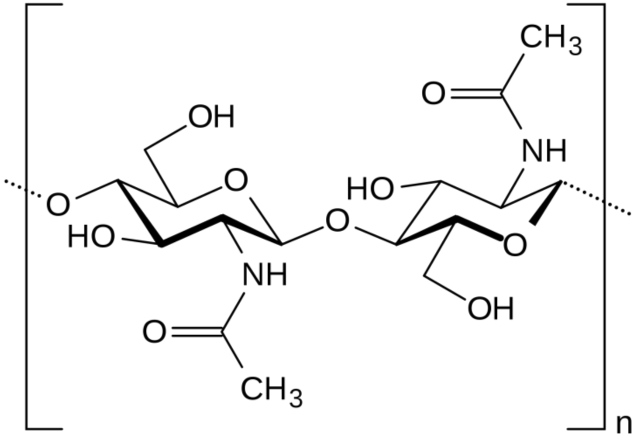
Humans and other animals cannot use cellulose as food because our digestive systems do not contain β-glucosidases, enzymes that catalyze the hydrolysis of β-glucosidic bonds. Instead, we have only α-glucosidases; hence, we use the polysaccharides starch and glycogen as sources of glucose.

In contrast, many bacteria and microorganisms do contain β-glucosidases and so can digest cellulose.

Chitin

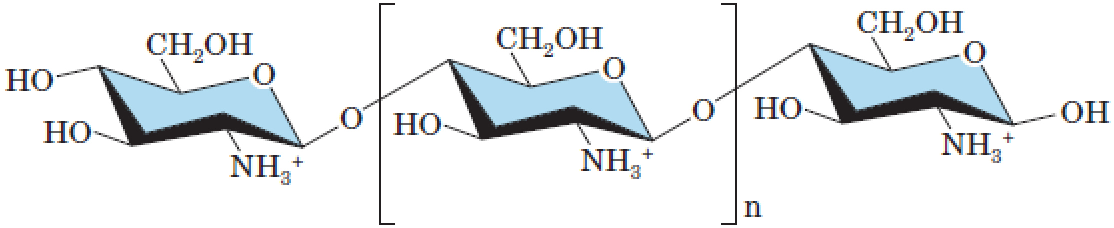
Chitin is a second most abundant polysaccharide (after cellulose) in the nature. **It is a long-chain polymer of a β-D-N-acetylglucosamine**. Chitin is the main component of cell walls of fungi, crustaceans (such as crabs, shrimps, lobsters) and insects.

In terms of structure, chitin may be compared to the polysaccharide cellulose. Chitin has proven useful for several medical and industrial purposes.



Chitin's properties as a flexible and strong material make it favorable **as surgical thread**. Its biodegradibility means it wears away with time as the wound heals. Also, **chitin** has some unusual properties that **accelerate healing of wounds in humans**.

Chitosan



When the acetyl groups are removed from chitin, the chitosan that remains is a polymer of glucosamine.

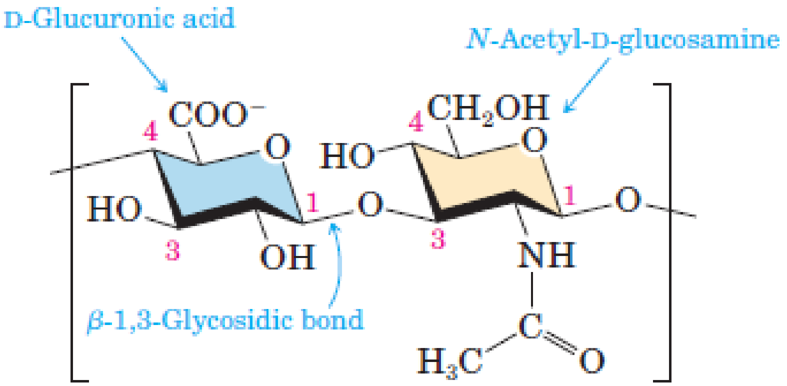
Chitosan differs from cellulose in that it has an amino group on each monomer unit. At physiological pH amino groups of chitosan are protonated. This forms the basis for the improved dressing. The outer membrane of red blood cell has a net negative charge. The opposite charges attract, producing a blood clot and stopping the bleeding.

Acidic Polysaccharides

Acidic polysaccharides are a group of polysaccharides that contain carboxyl groups and/or sulfuric acid groups. Acidic polysaccharides play important roles in the structure and function of connective tissues. Because they contain amino sugars, a more current name for these substances is **glucosaminoglycans**.

Hyaluronic acid

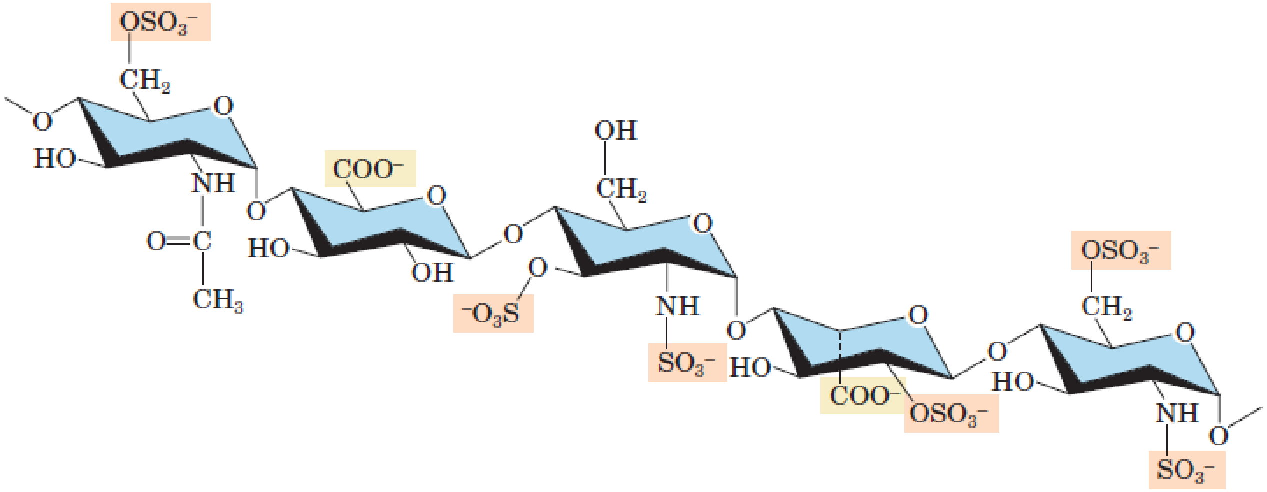
It is composed of D-glucuronic acid joined by a β-1,3-glycosidic bond to N-acetyl-D-glucosamine, which is in turn linked to D-glucuronic acid by a β-1,4-glycosidic bond.



The repeating unit of hyaluronic acid

Hyaluronic acid is the simplest acidic polysaccharide present in connective tissue. Its molecular weight is between 10^5 and 10^7 g/mol and it contains from 300 to 100,000 repeating units. **It is most abundant synovial fluid, the lubricant of joints in the body, and in the vitreous of the eye**, where it provides a clear, elastic gel that holds the retina in its proper position. Hyaluronic acid is also a common ingredient of lotions, moisturizers, and cosmetics.

Heparin



Heparin is a heterogeneous mixture of variably sulfonated polysaccharide chains, ranging in molecular weight from 6000 to 30000 g/mol. Heparin is synthesized and stored in mas cells (cells that are part of the immune system and that occur in liver, lung, and gut). **Heparin has many biological functions, the best known of which is its anticoagulant activity.** It binds strongly to antithrombin III, a plasma protein involved in terminating the clotting process. A heparin preparations with good anticoagulant activity contains a minimum of eight repeating units described in a picture. The larger molecule, the greater its anticoagulant activity.

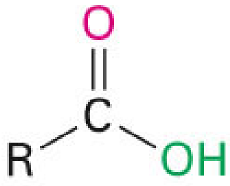
Carboxylic Acids and Their Derivatives

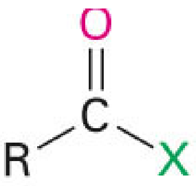
Functional group of a **carboxylic acid** is a **carboxyl group**, which can be represented in any one of three ways:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-OH \qquad -COOH \qquad -CO_2H$$

Carboxylic group

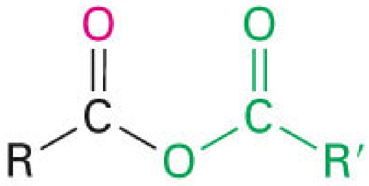
Derivatives of carboxylic acids:



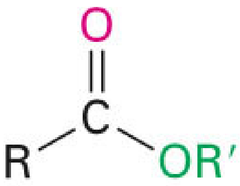


Halogenanhydrides of Carboxy Acids (Alkanoyl halogenides)

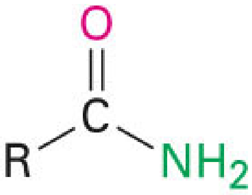
(X = Cl, Br)



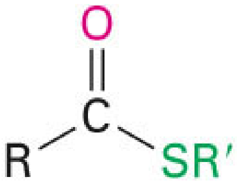
Anhydrides



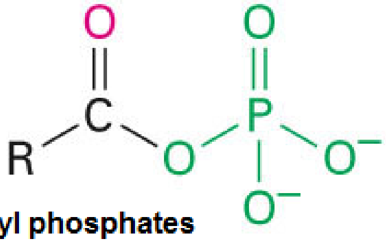
Esters



Amides

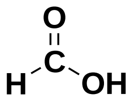


Thioesters

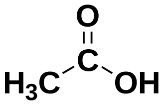


Acyl phosphates

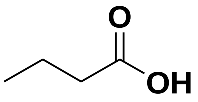
Monocarboxylic Acids



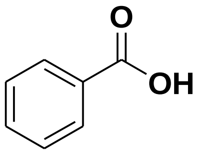
Methanoic acid
(Formic acid)



Ethanoic Acid
(Acetic acid)

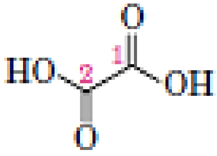


Butanoic Acid
(Butyric Acid)

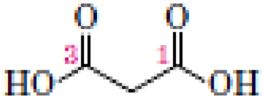


Benzoic Acid

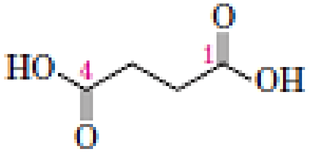
Dicarboxylic acids



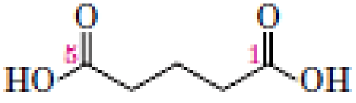
Ethanedioic acid
(Oxalic acid)



Propanedioic acid
(Malonic acid)

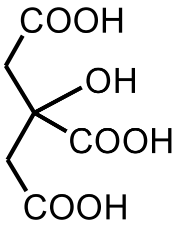


Butanedioic acid
(Succinic acid)



Pentanedioic acid
(Glutaric acid)

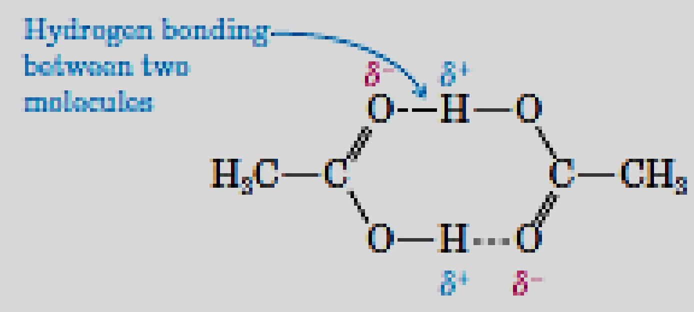
Hexanedioic acid
(Adipic acid)



Citric acid

Tricarboxylic acid

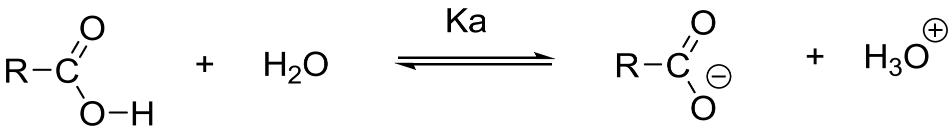
A major feature of carboxylic acids is the **polarity of the carboxyl group**. This group contains three polar covalent bonds: **C=O, C-O, and O-H**. The polarity of these bonds determines the major physical properties of carboxylic acids. **Carboxylic acids have significantly higher boiling points** than other types of organic compounds of comparable molecular weight. Their higher boiling points result from their polarity and the fact that hydrogen bonding between two carboxyl groups creates **a dimer** that behaves as a higher-molecular-weight compound.



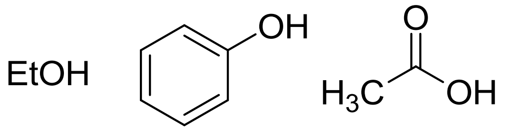
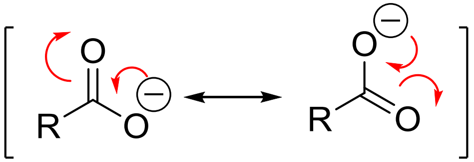
A hydrogen-bonded dimer of acetic acid

Acid-Base Properties of Carboxylic Acids

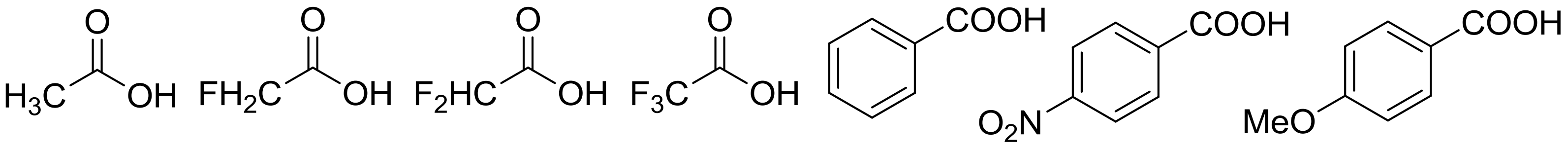
Carboxylic acids are **the most acidic** in comparison with other organic O-H acids (alcohols, phenols). Values of p*K*a for most unsubstituted aliphatic and aromatic carboxylic acids fall within the range **4.0 - 5.0**.



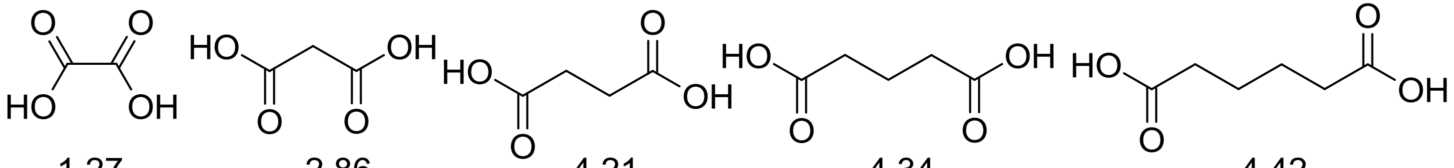
Acidity depends on the nature of substituent in the molecule of carboxylic acid. **Aromatic acids are stronger than aliphatic. Dicarboxylic acids are stronger than monocarboxylic ones.**

pKa	16	9.9	4.76

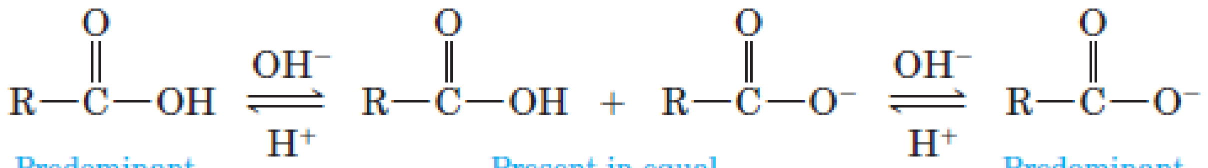


pKa	4.76	2.66	1.24	0.23	4.18	3.43	4.47



pKa (1)	1.27	2.86	4.21	4.34	4.42
pKa (2)	4.27	5.70	5.64	5.27	5.28

Reaction with bases



$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} \underset{\mathrm{H^+}}{\overset{\mathrm{OH^-}}{\rightleftharpoons}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} + \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^-} \underset{\mathrm{H^+}}{\overset{\mathrm{OH^-}}{\rightleftharpoons}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^-}$$

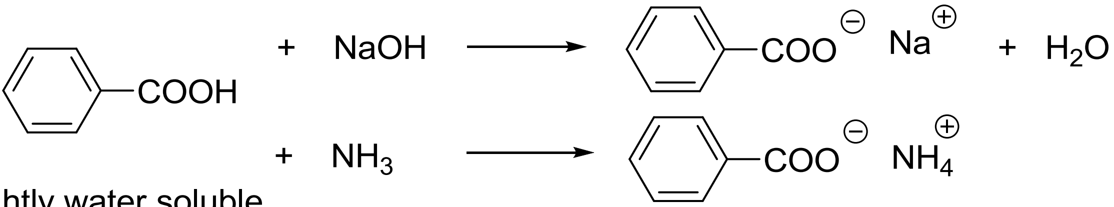
Predominant species when pH of the solution is ≤2.0

Present in equal concentrations when pH of the solution = pK_a of the acid

Predominant species when pH of the solution is ≥7.0

If the pH of the solution is adjusted **lower than 2.0** by the addition of strong mineral acid the carboxylic acid is present almost entirely as **RCOOH**. In the solutions with **pH>7.0** the carboxylic acids is present entirely **as anion**. Even in **neutral** solutions a carboxylic acid is present **predominately as its anion**.

All carboxylic acids react with NaOH or KOH or NH_3 to form **water soluble salts**.

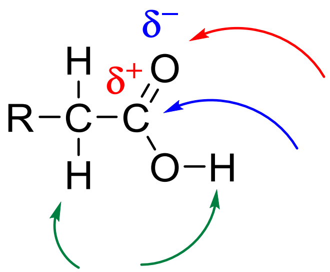


slightly water soluble

water soluble salts

Other Chemical properties of carboxylic acids

Reactive atoms of carboxylic acids:

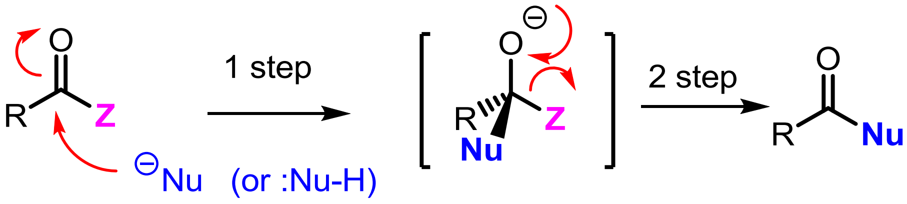


attack of electrophiles or acids

atack of nucleophiles

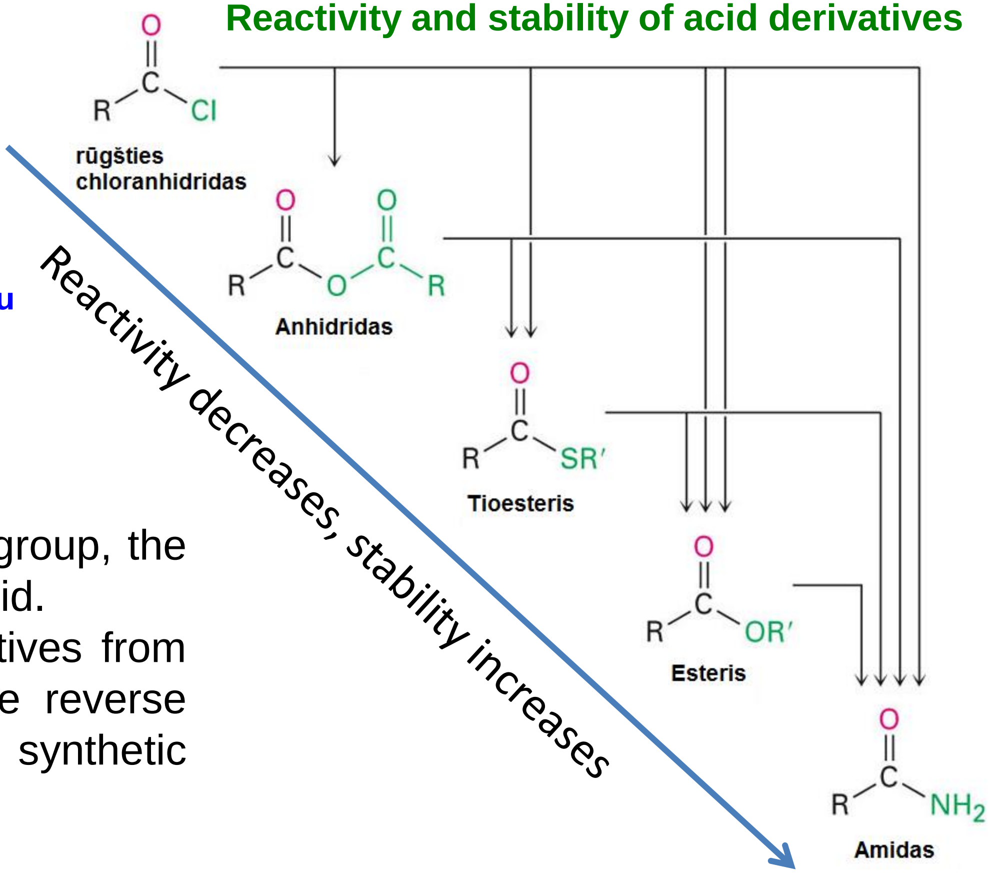
attack of bases

Nucleophilic substitution at acyl group



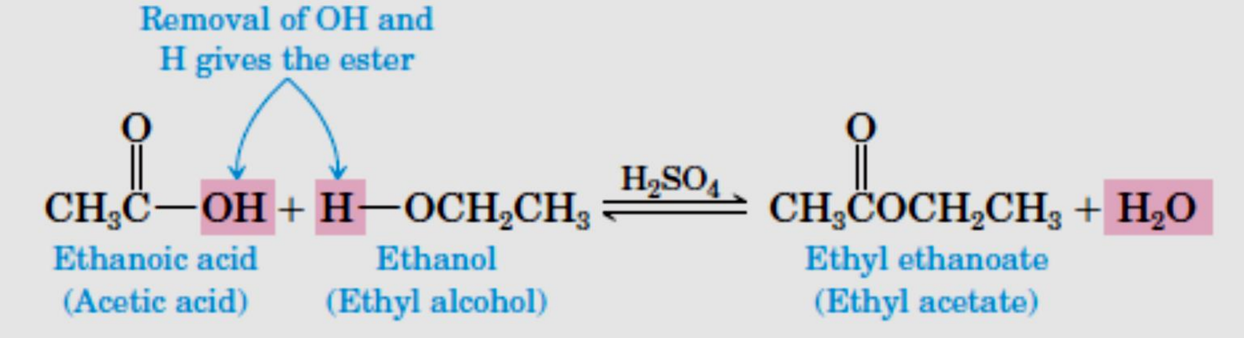
- The more electrophilic C atom in C=O group, the more reactive derivative of carboxylic acid.
- It is easy to obtain more stable derivatives from more reactive ones. But to realize the reverse synthetic path it is difficult or other synthetic routes have to be developed.

Reactivity and stability of acid derivatives



Reaction of Acids with alcohols. Formation of Esters.

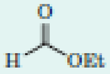
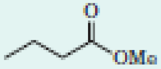
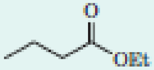
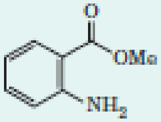
Treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst—most commonly, concentrated sulfuric acid—gives an **ester.**



$$CH_3\overset{O}{\overset{\|}{C}}-OH + H-OCH_2CH_3 \xrightleftharpoons{H_2SO_4} CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 + H_2O$$

A number of esters have pleasant flavor. Many have flavors very close to the target flavor, and so adding only one or a few of them is sufficient to make ice cream, soft drinks, or candies taste natural. The table shows the structures of a few of the esters used as flavoring agents.

Esters as flavoring agents:

Structure	Name	Flavor
	Ethyl formate	Rum
	Isopentyl acetate	Banana
	Octyl acetate	Orange
	Methyl butanoate	Apple
	Ethyl butanoate	Pineapple
	Methyl 2-aminobenzoate (Methyl anthranilate)	Grape

Esters

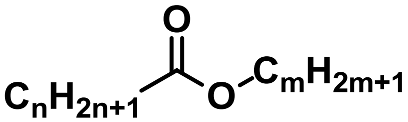
Table of esters and their smells

from the alcohol (first word)

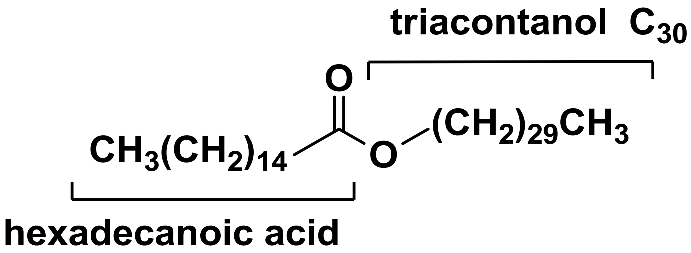
from the carboxylic acid (second word)

	methyl 1 carbon	**ethyl** 2 carbons	**propyl** 3 carbons	2-methyl propyl-	**butyl** 4 carbons	**pentyl** 5 carbons	**hexyl** 6 carbons	benzyl benzene ring	**heptyl** 7 carbons	**octyl** 8 carbons	**nonyl** 9 carbons
methanoate 1 carbon	ETHEREAL	BACARDÍ		ETHEREAL							?
ethanoate 2 carbons											
propanoate 3 carbons											?
2-methyl propanoate 4 carbons, branched		ETHEREAL	BACARDÍ								?
butanoate 4 carbons											?
pentanoate 5 carbons					ETHEREAL					?	?
hexanoate 6 carbons											
benzanoate benzene ring										?	
heptanoate 7 carbons						?					?
salicylate from salicylic acid					 STRONG			DIFFERENT PEOPLE PERCEIVE DIFFERENT AROMAS!	?		?
octanoate 8 carbons											
nonanoate 9 carbons										?	
cinnamate											?
decanoate 10 carbons					JACK DANIEL'S OLD TIME Old No.7 BRAND		?	?	?	?	?

Waxes are esters of long-chain fatty acids and long-chain alcohols. Waxes are found as protective coatings on the skins, fur or feathers of animals and on the leaves and fruits of plants.

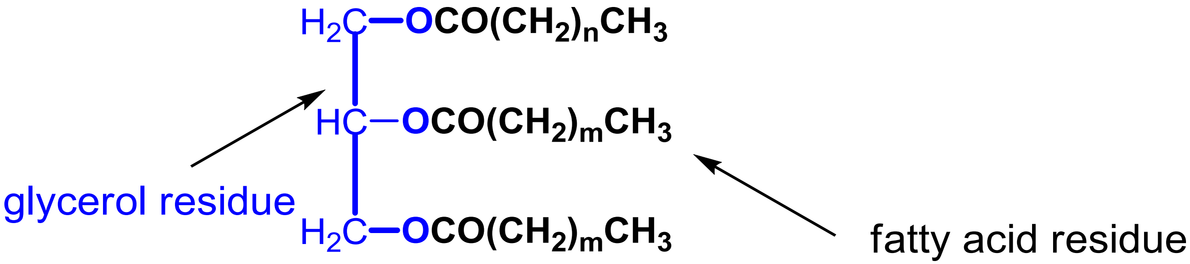


n = even 16 - 36
m = even 24 - 36



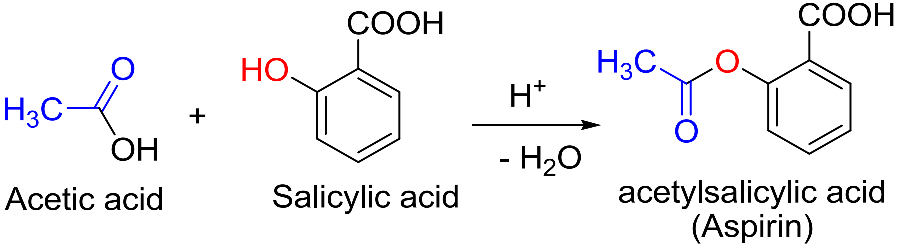
The main constituent of beeswax

Fats (triglycerides) are esters of long-chain fatty acids and trihydroxylic alcohol - glycerol.

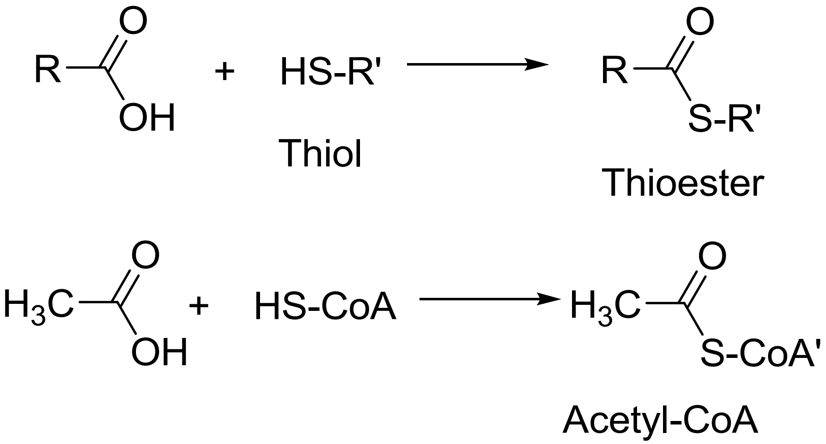


n, m - 14-18

Aspirin synthesis

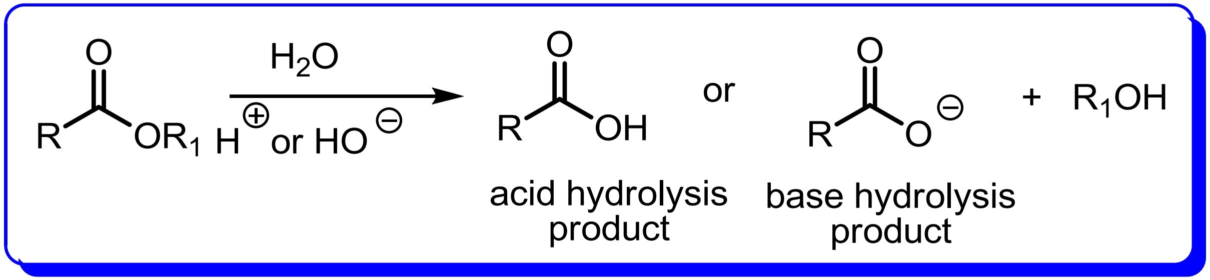


Thioesters are esters obtained from *carboxylic acid and thiols*.

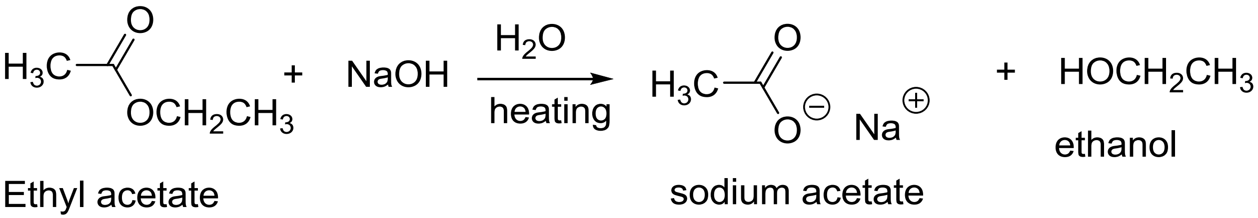


Reactions of esters and thioesters.

Reaction with water (hydrolysis). Esters and thioesters are hydrolysed only very slowly even in boilng water. However, hydrolysis becomes more rapid when esters are heated in aqueous acid or base.



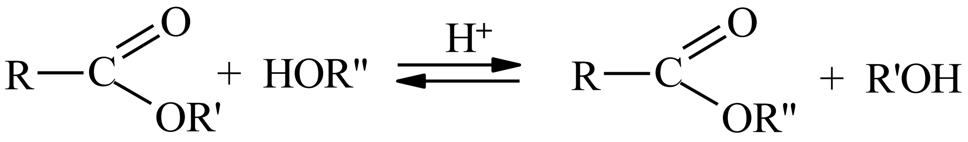
When hydrolysis is carried out in the presence of base, the reaction is called **saponification (from the production soaps)**.

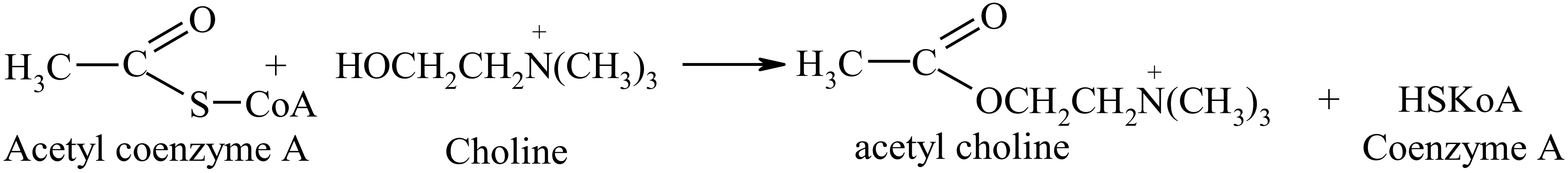


Each mole of ester in order to be hydrolyzed requires one mole of base, as shown in the balanced equation.

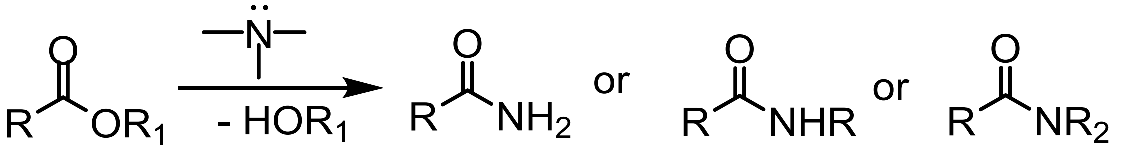
Reaction with alcohols and amides.

The reaction with alcohols is called **transesterification** reaction. It leads to the formation of another ester. *Transesterification reaction is catalyzed by acids and is reversible.* So, an excess of an alcohol is required to shift the equilibrium to the formation of product.



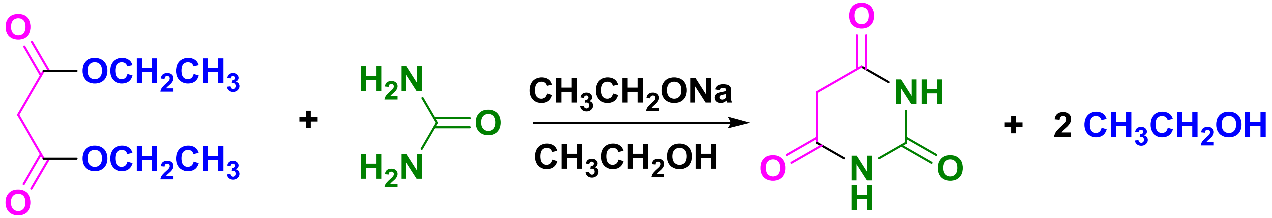


Treatment **esters with amines gives amides**. Depending on the amine structure *primary, secondary and tertiary* amides can be obtained.



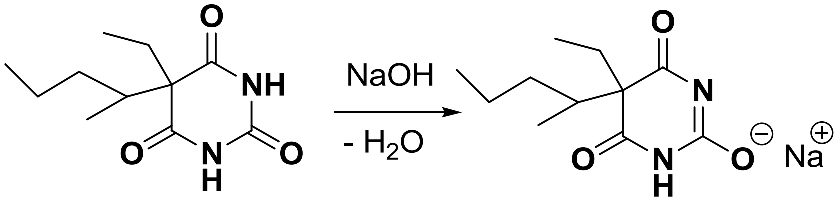
(with NH_3) (with RNH_2) (with R_2NH)

Amide linkage is very important in nature. All proteins and enzymes are based on that linkage (amino acids are connected with each other by amide linkage). Many medicines also contain amide linkage.



Diethyl malonate **carbamide** **barbituric acid**

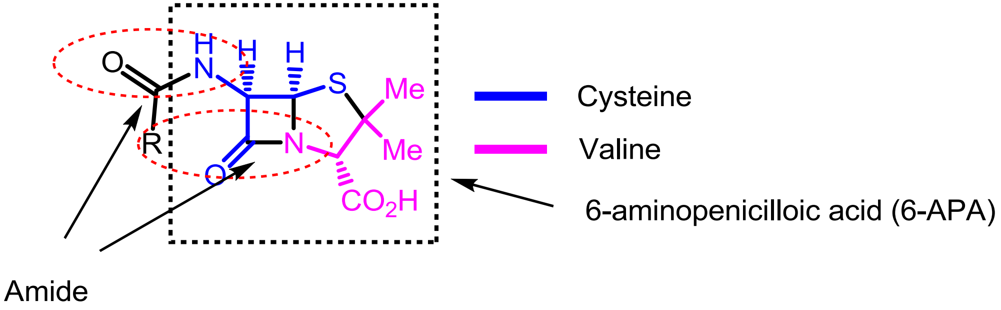
A number of derivatives of barbituric acid have powerful sedative and hypnotic effects. These derivatives are called **barbiturates**. For example, pentobarbital. To increase its solubility in water usually sodium salt is prepared. The sodium salt is given the name Nembutal.



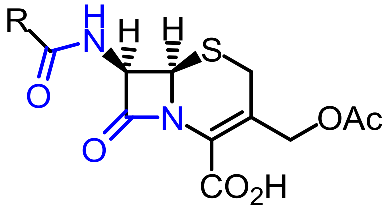
Pentobarbital

Sodium pentobarbital
(Nembutal)

Penicillins

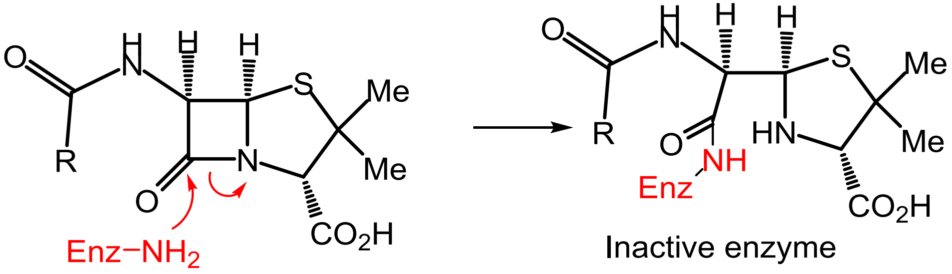


Cephalosporins



Penicillins and cephalosporins are β-lactam antibiotics and are used in treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.

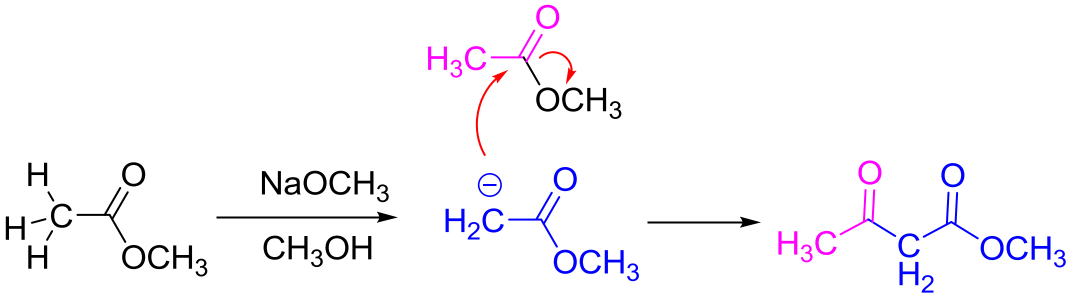
Penicillins act by interfering with the synthesis of bacterial cell walls. They do that by reacting with an amino group of an essential enzyme of the cell wall by biosynthetic pathway. This reaction involves ring opening of the β-lactam and acylation of the enzyme, inactivating it.



Reaction at α-carbon atom of carboxylic acids.

Claisen ester condensation reaction.

α-hydrogens of carboxylic acids are weakly acidic. Treatment of esters containing α-hydrogens with strong bases results in the formation of carbanions, that react with ester group of the other molecule to form ester of β-oxo carboxylic acid.



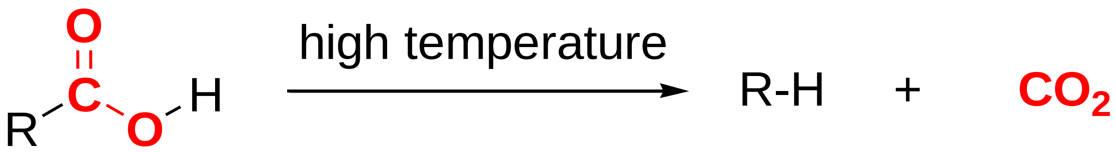
Methyl acetate

Methyl β-oxobutanoic acid
(methyl acetoacetate)

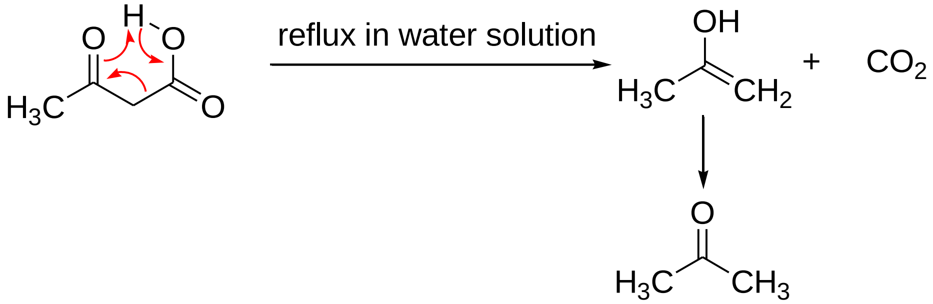
This reaction is one of main reactions in the biosynthetic pathway of fatty acids in a body.

Decarboxylation

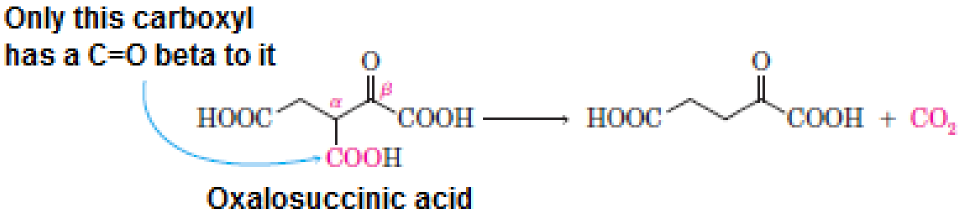
Decarboxylation is the loss of CO_2 from a carboxyl group. Almost any carboxylic acid, when heated to a very high temperature, undergoes thermal decarboxylation:



Most carboxylic acids, however, are quite resistant to moderate heat and melt or even boil without decarboxylation. Exceptions are **carboxylic acids that have a carbonyl group β to the carboxyl group**. This type of carboxylic acid undergoes decarboxylation quite readily on mild heating.



Oxalosuccinic acid, one of the intermediates in citric cycle of biological world, undergoes spontaneous decarboxylation to produce α-ketoglutaric acid. Only one of the three carboxyl groups of oxalosuccinic acid has a carbonyl group in the position β to it, and this carboxyl group is lost as CO_2:



Fatty Acids are long, unbranched chain carboxylic acids, most commonly consisting of 12 to 20 carbons. They are derived from the hydrolysis of animal fats, vegetable oils, and the phospholipids of biological membranes. More than 500 different **fatty acids** have been isolated from various cells and tissues, but only about 40 are the most popular.

Fatty acids are **saturated and unsaturated.**

The Most Abundant Fatty Acids in Animal Fats, Vegetable Oils, and Biological Membranes

Saturated fatty acids			**Unsaturated fatty acids**		
Lauric	12C	$CH_3(CH_2)_{10}COOH$	Palmitoleic	16C:1	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$ *cis*
Myristic	14C	$CH_3(CH_2)_{12}COOH$	Oleic	18C:1	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ *cis*
Palmitic	16C	$CH_3(CH_2)_{14}COOH$	Linoleic	18C:2	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$ **ω-6** *cis* *cis*
Stearic	18C	$CH_3(CH_2)_{16}COOH$	Linolenic	18C:3	$CH_3(CH_2CH{=}CH)_3(CH_2)_7COOH$ **ω-3** all *cis*
Arachidic	20C	$CH_3(CH_2)_{18}COOH$	Arachidonic	20C:4	$CH_3(CH_2)_4(CH{=}CHCH_2)_4CH_2CH_2COOH$ **ω-6** all *cis*

Following are several characteristics of the most abundant fatty acids in higher plants and animals:

1. Nearly all fatty acids **have an even number of carbon atoms**, most between 12 and 20, in an unbranched chain.
2. The three most abundant fatty acids in nature are palmitic acid (16:0), stearic acid (18:0), and oleic acid (18:1).
3. In most unsaturated fatty acids, **the *cis* isomer predominates**; the *trans* isomer is rare.

High amount of saturated fatty acids or *trans* fatty acids in the diet substantially increases the risk of cardiovascular disease.

The oils used for frying in fast-food restaurants are usually **partially hydrogenated** plant oils and, therefore, they contain substantial amounts of *trans* fatty acids that are transferred to the foods cooked in them.

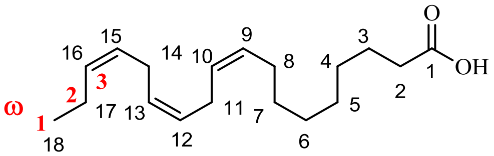
4. Unsaturated fatty acids **have lower melting points** than their saturated counterparts. The greater the degree of unsaturation, the lower the melting point.

Saturated fatty acids are solids at room temperature, because the regular nature of their hydrocarbon chains allows their molecules to pack together in close parallel alignment. When packed in this manner, the attractive interactions between adjacent hydrocarbon chains (London dispersion forces) are maximized.

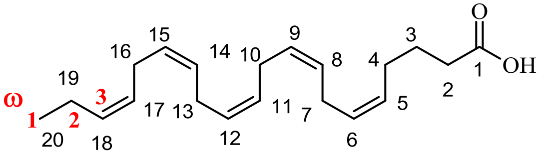
Omega-3 fatty acids

Some polyunsaturated (*cis*) fatty acids, such as those found in certain types of fish, have been shown to have beneficial effects in some studies. **These are the so-called omega-3 fatty acids**. The last carbon of the hydrocarbon chain is called the omega carbon (the last letter of the Greek alphabet). *Omega-3s are considered essential fatty acids,* meaning that they cannot be synthesized by the human body -except that mammals have a limited ability.

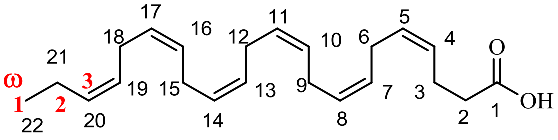
The two most commonly found in health food supplements are **eicosapentaenoic acid and docosahexaenoic acid.**



Linolenic acid (ALA)
(α-linolenic acid)



Eicosapentaenoic acid (EPA)



Dokosahexaenoic acid (DHA)

Eicosapentaenoic acid is an important fatty acid in the marine food chain and **serves as a precursor in humans of several members of the prostacyclin and thromboxane** families.

Docosahexaenoic acid is found in marine fish oils and many phospholipids. It is a major structural component of membranes in the retina and brain, and is synthesized in the liver from linolenic acid.

Lipids

(Greek lipos – fats)

Lipids are family of substances that are soluble in nonpolar solvents but insoluble in water. So, lipids are defined in terms of a property and not in terms of their structure. Lipids can be isolated from every cells by extraction.

Lipids major roles in human biochemistry are:

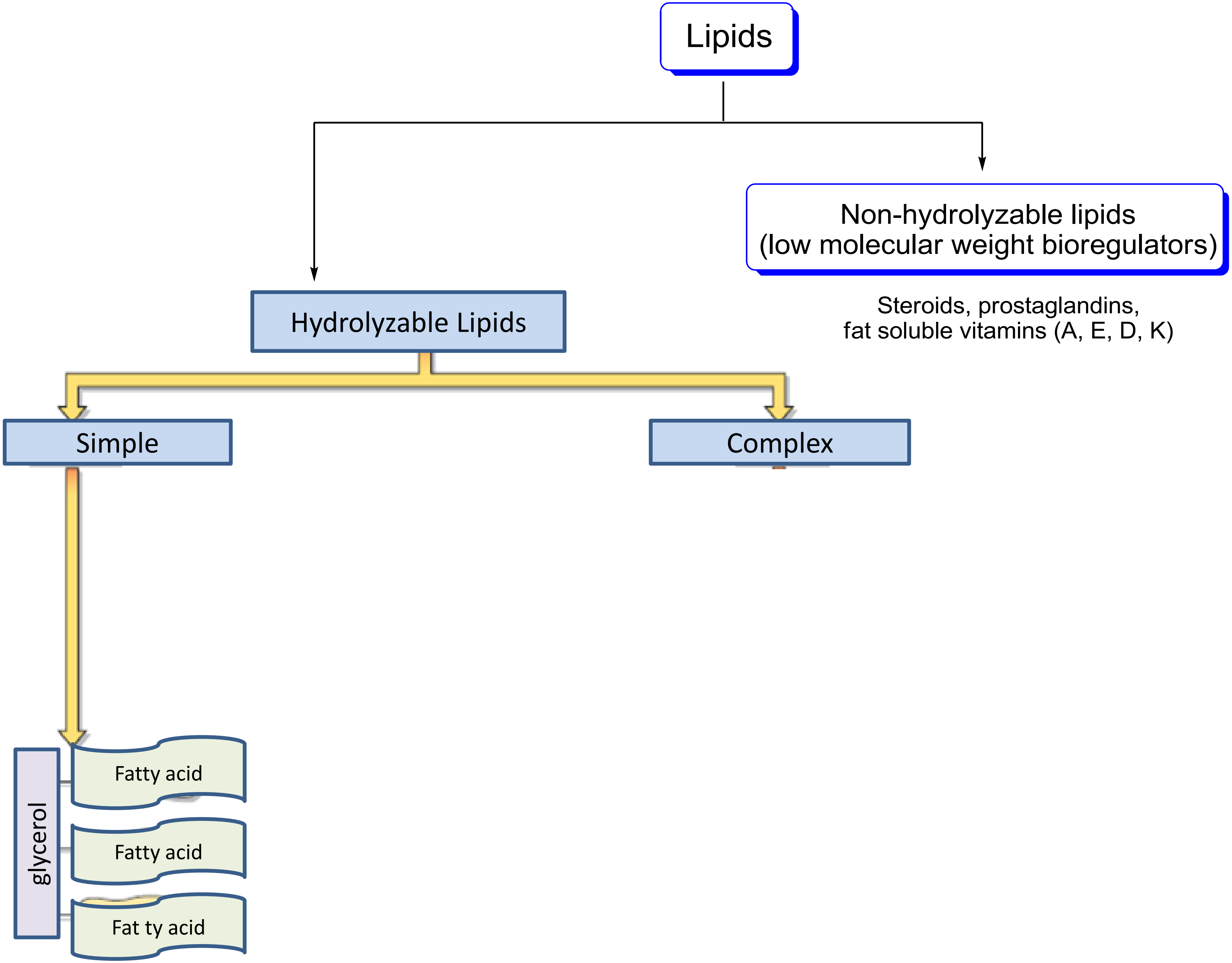
1. **They store energy within fat cells**

Energy is stored in the form of glycogen for quick energy when we need it. However, the burning of fats gives more than twice as much energy as the burning of the equal weight of carbohydrates.

2. They are parts of membranes that separate compartments from each other.

Most body constituents, for example carbohydrates and proteins are soluble in water. For membranes that separate compartments containing aqueous solutions the body needs insoluble compounds. Lipids provide these membranes.

3. They serve as chemical messengers. Primary messengers such as steroid hormones, deliver signals from one part of the body to another part. Secondary messengers, such as prostaglandins and thromboxanes, mediate the hormonal response.



Lipids

Non-hydrolyzable lipids
(low molecular weight bioregulators)

Steroids, prostaglandins,
fat soluble vitamins (A, E, D, K)

Hydrolyzable Lipids

Simple

Complex

glycerol

Fatty acid

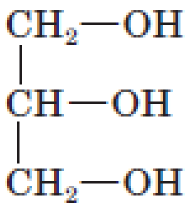
Fatty acid

Fatty acid

Hydrolyzable lipids

Simple lipids

Triglycerides are triesters of **glycerol and long-chain carboxylic acids** called **fatty acids.**
Animal fats and plant oils are triglycerides.

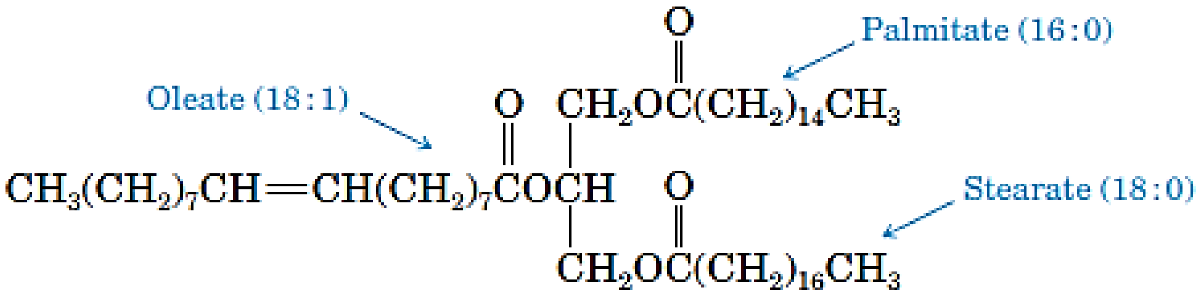


$$\begin{array}{l} CH_2-OH \\ | \\ CH-OH \\ | \\ CH_2-OH \end{array}$$

Glycerol

In triglycerides all hydroxy groups of glycerol are **esterified**.

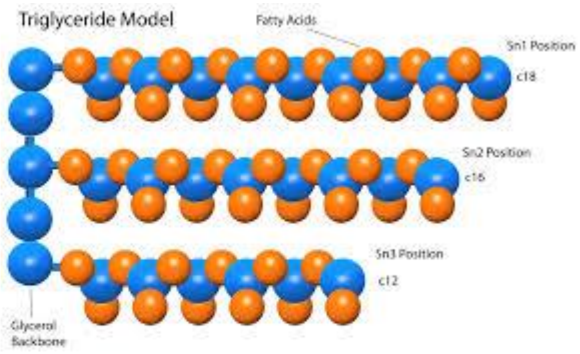
Although some of the molecules contain three identical fatty acids, in most cases two or three different acids are present. For example,



$$\begin{array}{l} \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad\; O \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad\;\; \| \\ \qquad\qquad\qquad\qquad\qquad\quad O \;\; CH_2OC(CH_2)_{14}CH_3 \\ \qquad\qquad\qquad\qquad\qquad\quad\; \| \quad\;\; | \\ CH_3(CH_2)_7CH{=}CH(CH_2)_7COCH \quad O \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad | \quad\;\; \| \\ \qquad\qquad\qquad\qquad\qquad\qquad\;\; CH_2OC(CH_2)_{16}CH_3 \end{array}$$

A triglyceride

The hydrophobic character of triglycerides is caused by the long hydrocarbon chains. This makes the triglycerides insoluble in water.



Animal fats are solids at room temperature, and **those from plants and fish are usually liquids.** Liquid fats are often called **oils**.

Solid animal fats contain saturated fatty acids, whereas vegetable oils contain high amounts of unsaturated fatty acids.

In human fats unsaturated fatty acids predominate. Their ratio with saturated fatty acids is approx. 3:2.

In natural triglycerides the 2nd position of glycerol usually is occupied by unsaturated fatty acid.

Average percentage of fatty acids of some common fats and oils

	Saturated fatty acids			Unsaturated fatty acids			
	Myristic (C14)	Palmitic (C16)	Stearic (C18)	Oleic (C18)	Linoleic* (C18)	Linolenic* (C18)	Other
Animal fats							
Beef tallow	6.3	**27.4**	14.1	49.6	2.5	-	0.1
Butter	11	**29**	9.2	26.7	3.6	-	17.9
Lard	1.3	28.3	11.9	**47.5**	6.0	-	5.0
Vegetable oils							
Linseed	-	6.3	2.5	19.0	24.1	**47.4**	0.7
Olive	-	6.9	2.3	**84.4**	4.6	-	1.8
Soybean	0,1	9.8	2.4	28.9	**52.3**	3.6	2.7
Sunflower	-	6.1	2.6	**25.1**	**66.2**	-	-

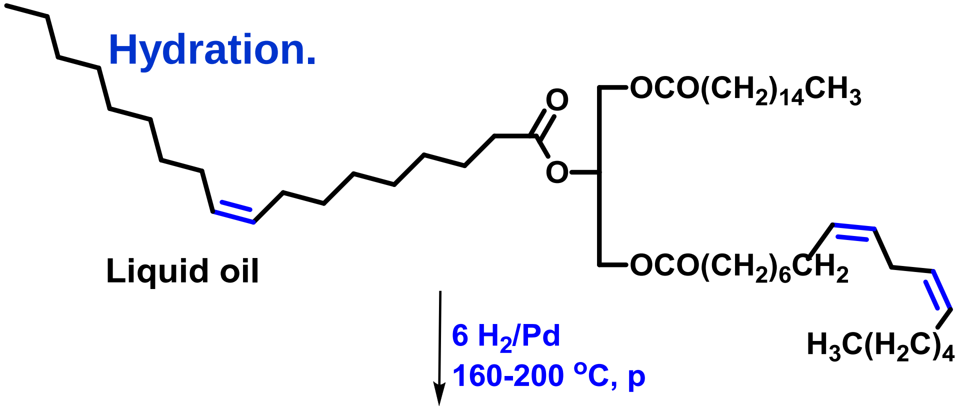
*Linoleic and linolenic acids are essential (they must be consumed as part of the diet).

Chemical properties of fats

Hydrolysis (saponification) was discussed at ester properties.

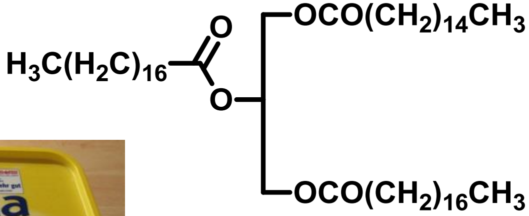
Addition reactions. Unsaturated residues of fatty acids undergo addition reactions with halogens, ammonia, water and other.

Hydration.

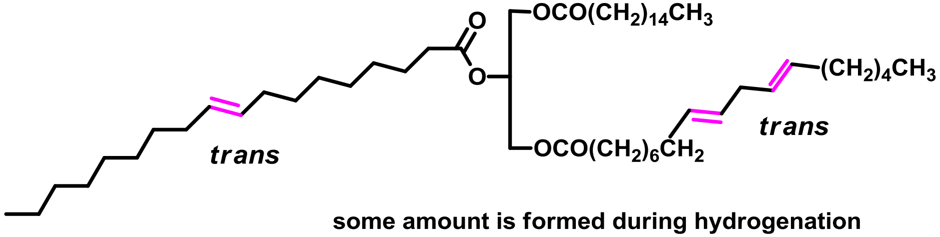


Liquid oil

The reaction is used for the production of solid fats from liquid ones.



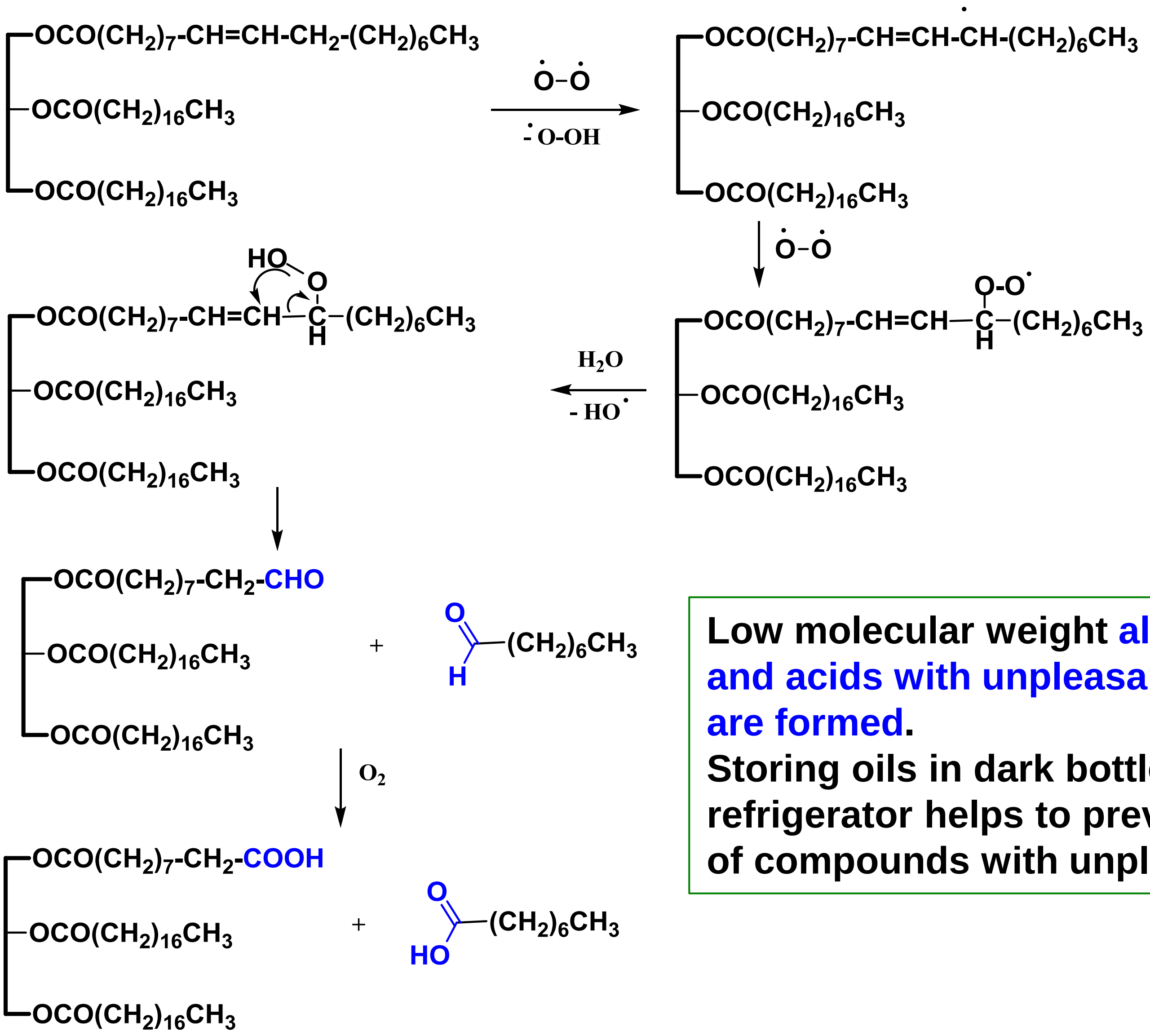
solid fats



some amount is formed during hydrogenation

Margarine is also made by partial hydrogenation of vegetable oils. Because less hydrogen is used margarine contains more unsaturation than fully hydrogenated fats. **The hydrogenation process is the source of trans fatty acids.** For example, margarine contains ~ 35% *cis*-acids and 12% *trans*- acids. For comparison, butter contains > 50% *cis*-acids and 3-4% *trans*-acids. **Triglycerides containing *trans*-acids increase level of low density lipoproteins (bad cholesterol) in blood (negative effect).**

Autooxidation

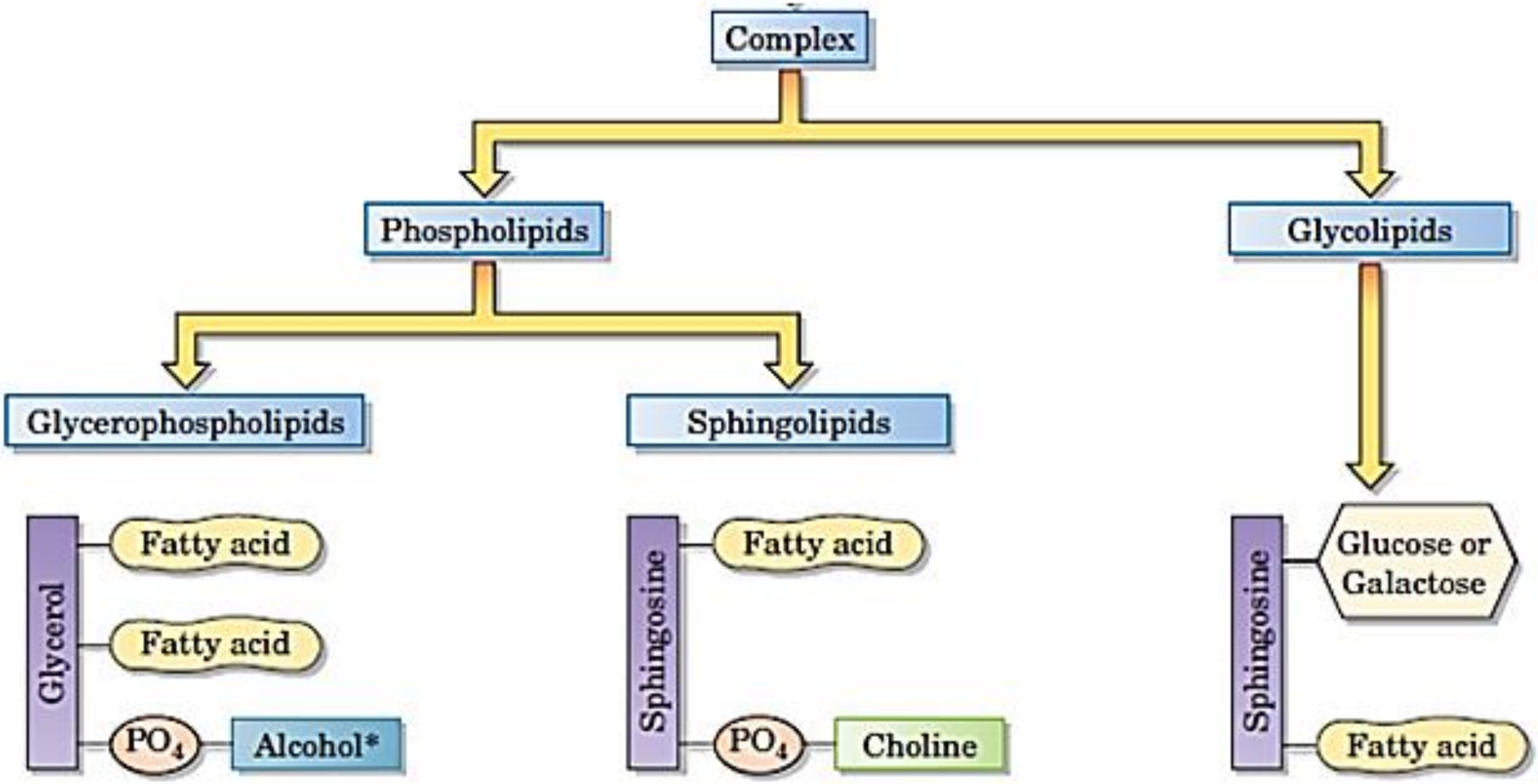


Low molecular weight **aldehydes, ketones, and acids with unpleasant tastes and odors are formed**.
Storing oils in dark bottles and in refrigerator helps to prevent the formation of compounds with unpleasant tastes.

Hydrolyzable lipids

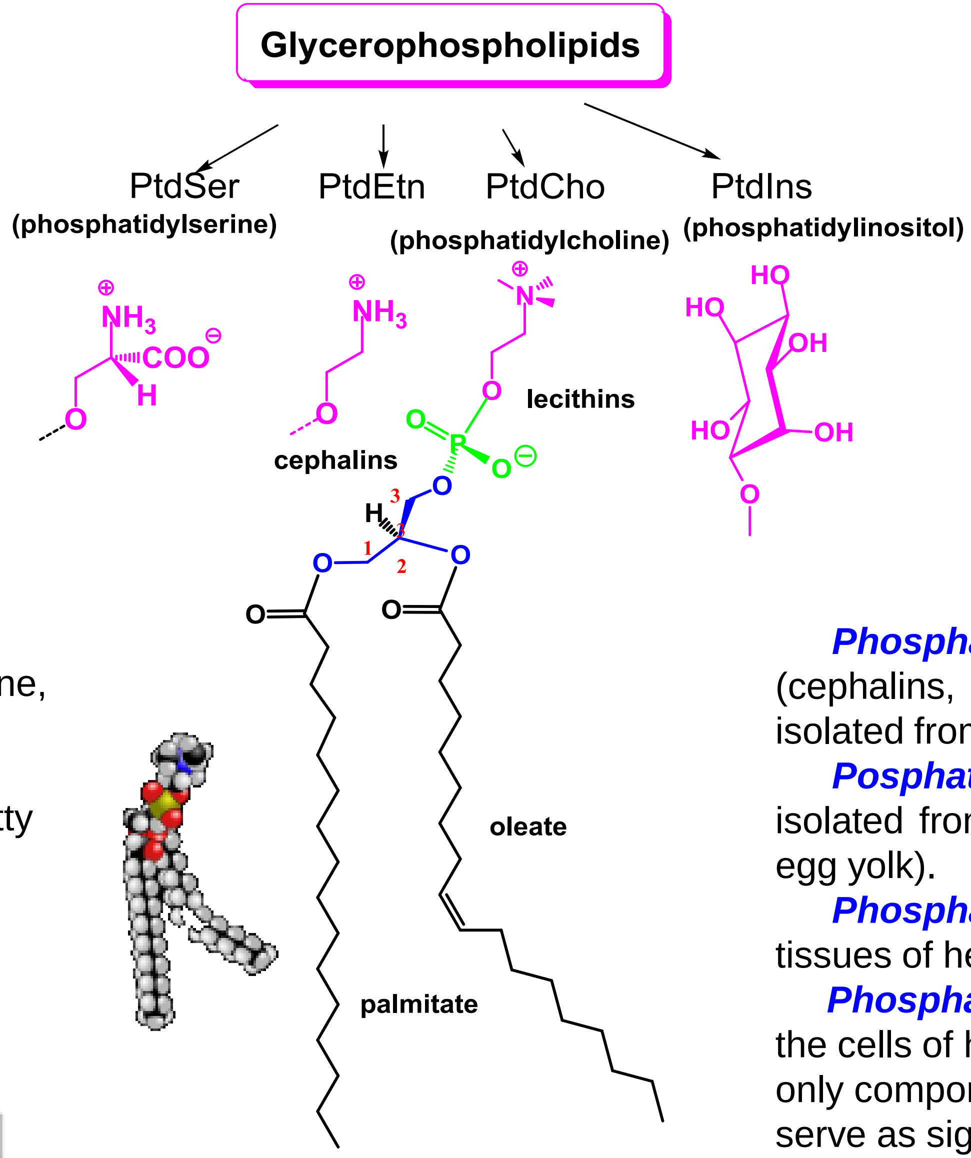
Complex lipids

Complex lipids constitute the main components of membranes.



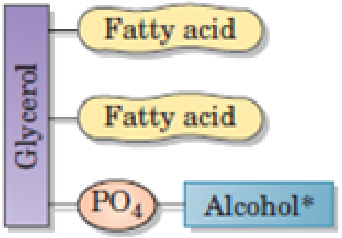
Phospholipids

Glycerophospholipids are membrane components throughout the body. The alcohol is glycerol. Glycerophospholipid structure includes both polar and nonpolar parts within one molecule.



At the 1st C – saturated fatty acid;
At the 2nd C – unsaturated fatty acid
At the 3rd C – phosphate residue.

Polar part – phosphate group and ionized amino group of serine, aminoethanol or choline.
Nonpolar part – fatty acid residues



Phosphatidylethanolamines (cephalins, greek *kephale - head)* isolated from brain tissues.

Posphatidylcholines (lecithins) isolated from egg yolk (greek *lekithos* – egg yolk).

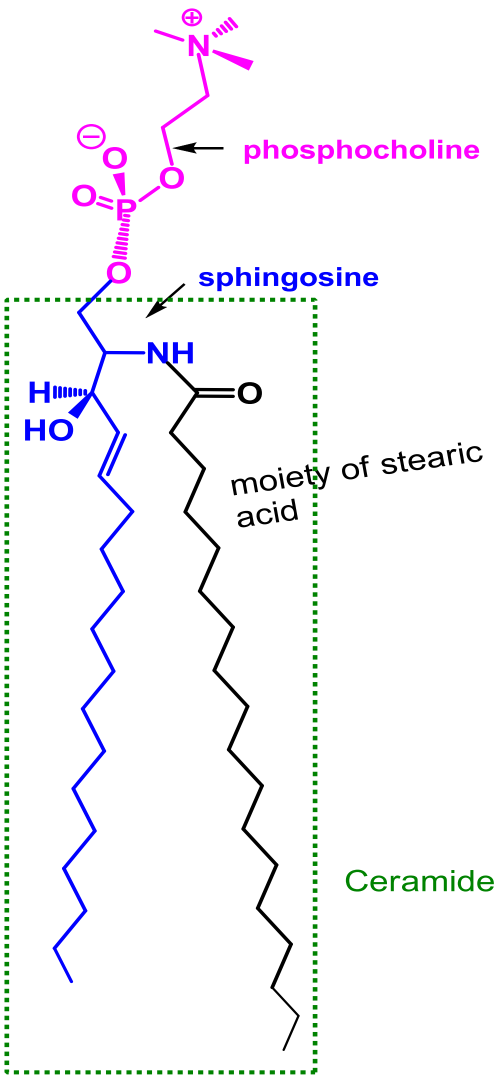
Phosphatidylserines isolated from tissues of heart, brain and liver.

Phosphatidylinosotols isolated from the cells of heart and liver. They are not only components of membranes but serve as signaling molecules, as well.

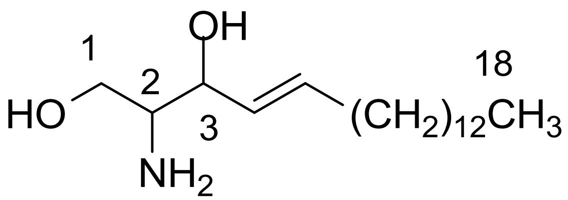
Phospholipids

Sphingolipids

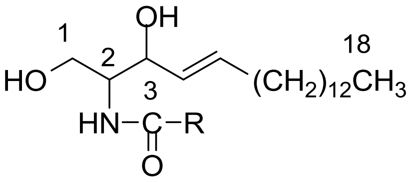
Sphingomyelin



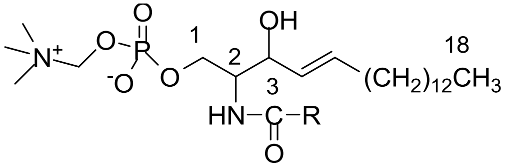
Ceramide portion



Sphingosine

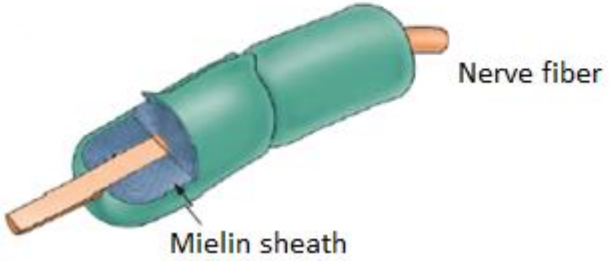


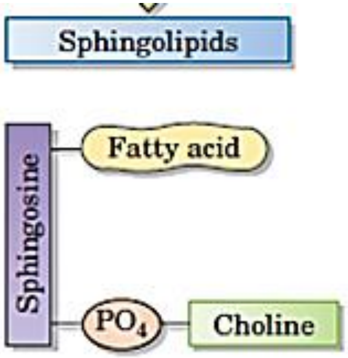
Ceramide



Sphingomyelin

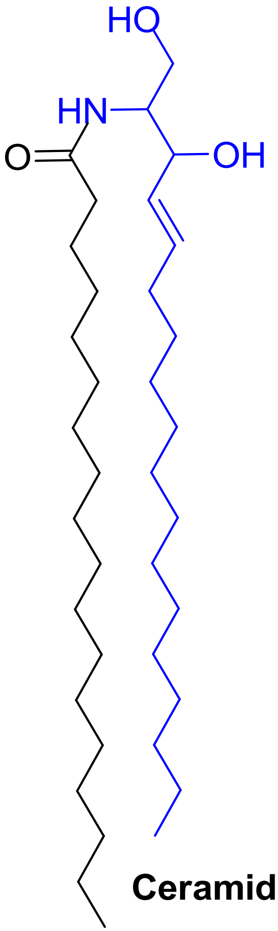
Sphingomyelins are the main components of coating of nerve axons, called the myelin sheath, which provides insulation and allows conduction of electrical signals. The myelin sheath consists of 70% lipids and 30% proteins in the lipid bilayer structure.





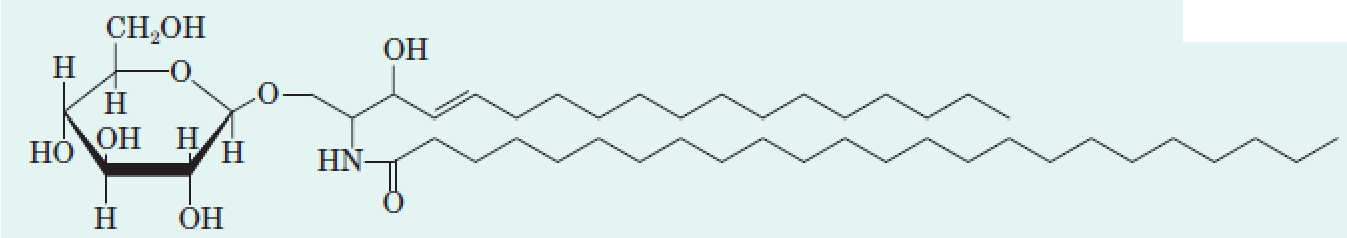
Glycolipids

Glycolipids are complex lipids that contain carbohydrates and ceramides. One group– cerebrosides, consists of ceramide mono- or oligosacharides. Other groups, such as gangliosides, contain a more complex carbohydrate structure.

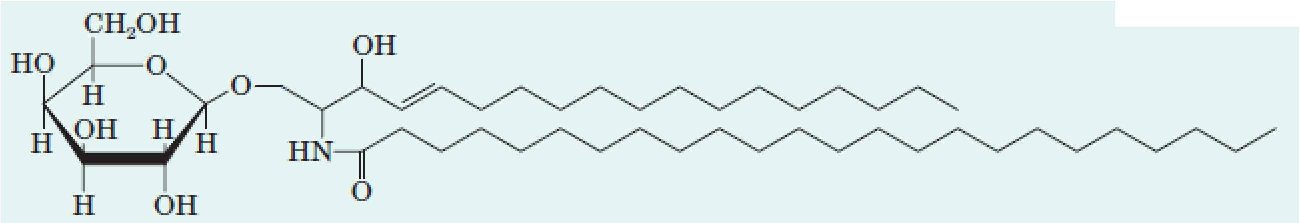


Ceramide

Glucocerebroside



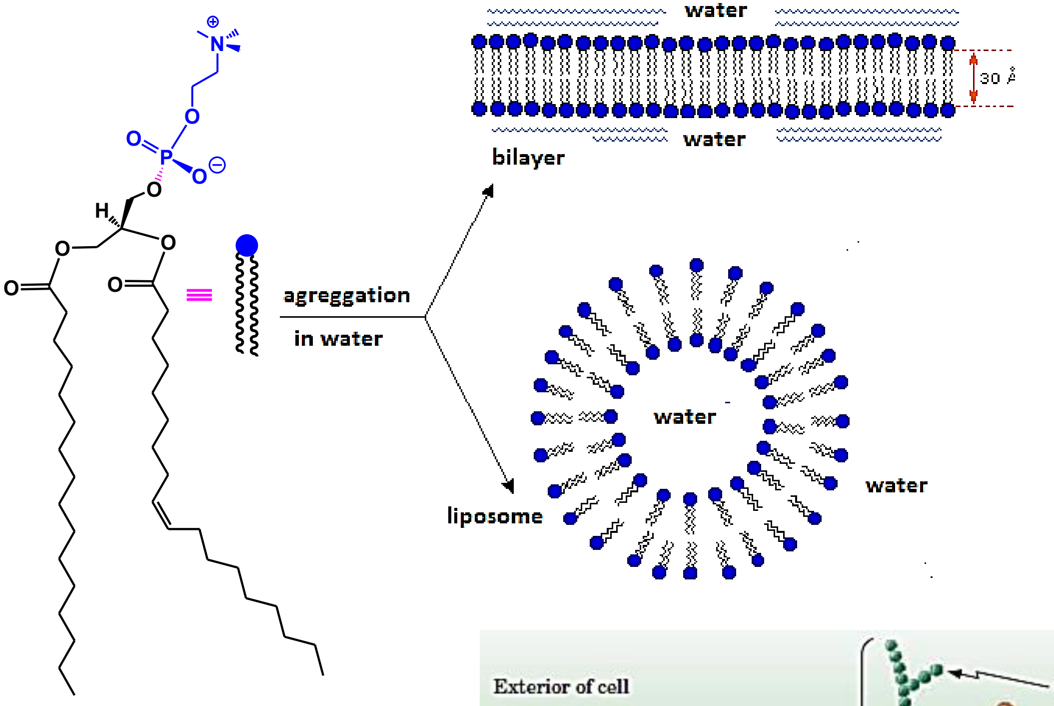
Galactocerebroside

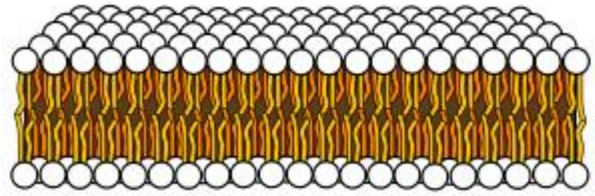


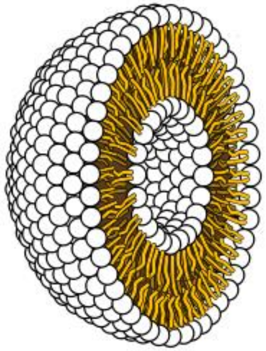
In cerebrosides, the fatty acid of the ceramide part may contain either C18 or C24 chains. Glucose or galactose are connected with ceramide by β-glycosidic bond.

Cerebrosides occur primarily in the brain (7% of the brain dry weight).

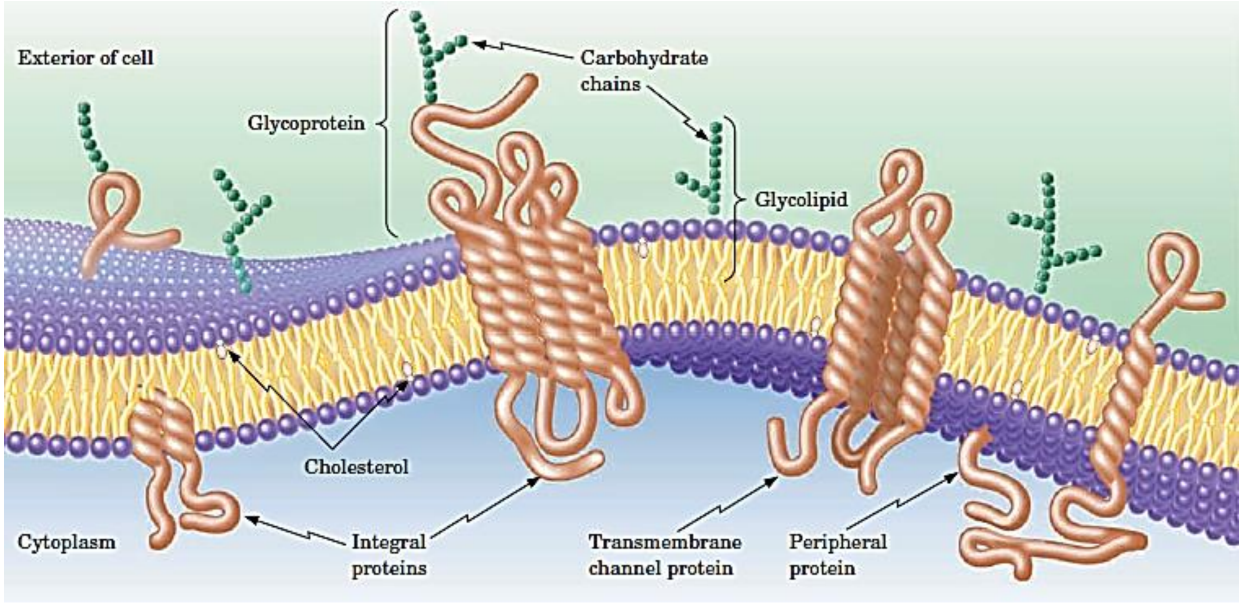
Phosphatidylcholine







Liposome



The fluid mosaic model of membrane. Proteins are embedded in the lipid matrix

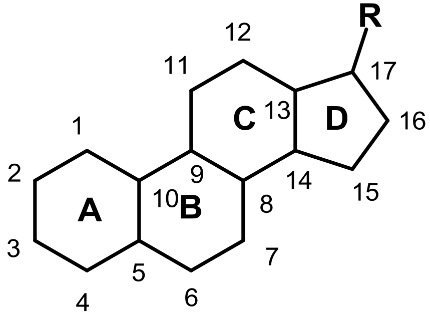
Non-hydrolyzable lipids

Steroids

Steroids are **non-hydrolyzable lipids**. Steroids are compounds containing four fused carbocyclic rings. Steroids are completely different in structure from the discussed lipids. They are normally not esters, although some of them are. Steroids are closely related in structure but are highly diverse in function.

This group of lipids involves:

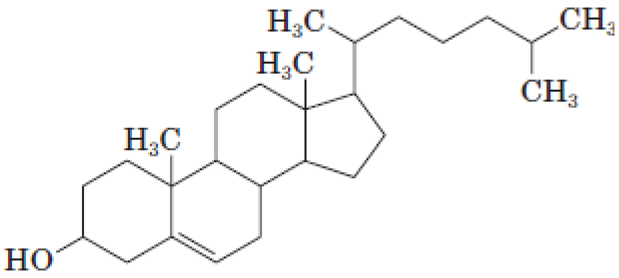
- **Cholesterol**
- **Sex and adrenocorticoid hormones**
- **Bile acids**
- **Vitamins D**



Cholesterol

Cholesterol is the most abundant steroid in human body (200-300 g in adult) and the most important.

Cholesterol

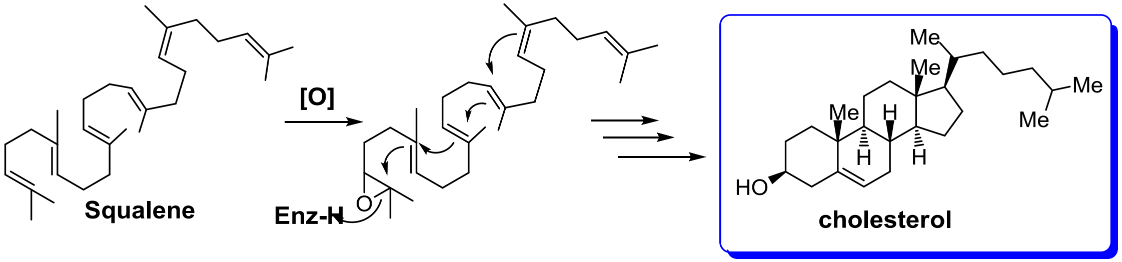


Cholesterol functions:

- **A membrane component in all animal cells**
- **Initial compound for the biosynthesis of such bioactive substances as sex and adrenocorticoid hormones and bile acids**

A human gallstone is almost pure cholesterol (∅ 5 mm)

Cholesterol is synthesized in a human liver from terpene - squalene.

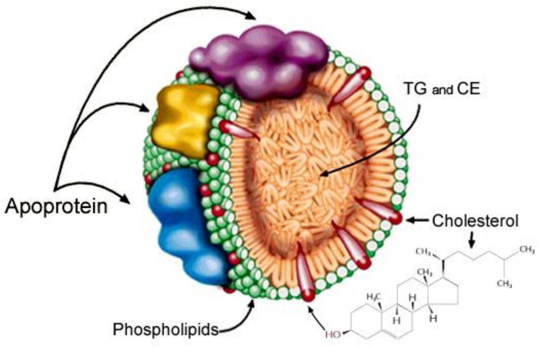


Cholesterol in the body is in a dynamic state. It constantly circulates in the blood. Cholesterol and esters of cholesterol, being hydrophobic, need a water-soluble carrier to circulate in the aqueous medium of blood.

Carriers of cholesterol are lipoproteins (Spherically shaped clusters containing both protein and lipid molecules). Most lipoproteins contain a core of hydrophobic lipid molecules surrounded by a shell of hydrophilic protein and phospholipid molecules.

There are four kinds of lipoproteins

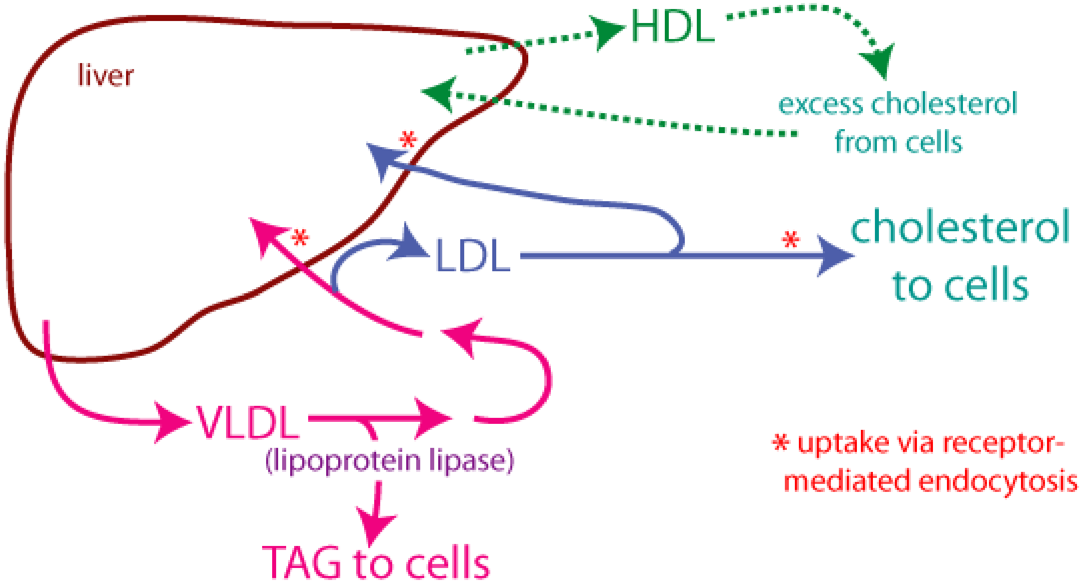
- **High density lipoprotein (HDL)** ('good cholesterol'). It consists of 33% protein and 30% cholesterol.
- **Low density lipoproteins (LDL)** ('bad cholesterol'). Constitution of LDL approx. 25% protein and 50% cholesterol.
- **Very low density lipoprotein (VLDL).** Mostly carries triglycerides synthesized by the liver.
- **Chylomicrons,** which carry dietary lipids synthesized in the intestines.



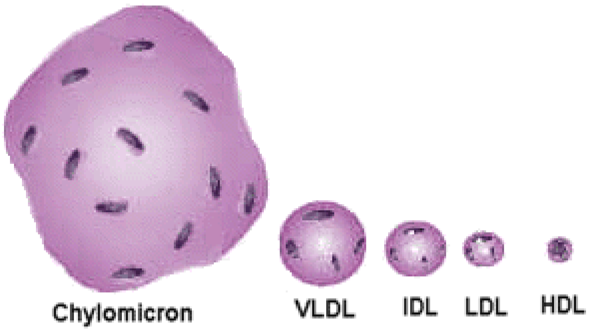
Schematic view of lipoprotein

The LDL carries cholesterol to the cells. In the cells enzyme break down lipoprotein and liberate free cholesterol. In this manner, the cell can use cholesterol as a component of membrane. This is the normal fate of LDL and the normal course of cholesterol transport. If the cell contains enough cholesterol, LDL does not enter the cell and cholesterol accumulates in the blood. **This accumulation can happen even with low intake of dietary cholesterol.** So, both genetics and diet play a role in determining cholesterol levels in the blood.

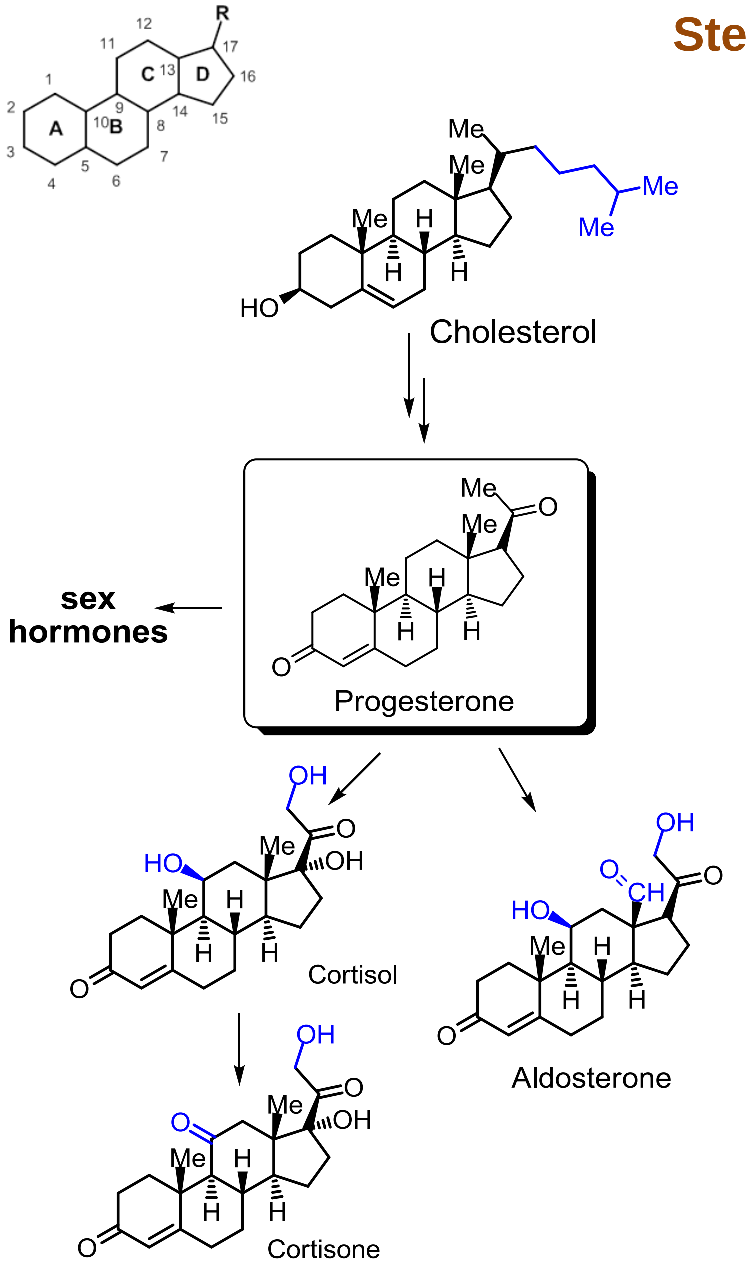
HDL transports cholesterol from peripheral tissues to the liver for the synthesis of bile acids and steroid hormones. It is desirable to have high level of HDL in the blood because it removes cholesterol from bloodstream.



Relative Sizes of Lipoproteins



Steroid hormones



Adrenocorticoid hormones

Cholesterol is a starting material for the synthesis of steroid hormones. In this process, cholesterol is oxidized and the side chain at D ring is shortened to two C atoms. The 3-HO group is oxidized to ketone group to give **progesterone**. Progesterone serves as starting compound for both sex hormones and adrenocorticoid hormones.

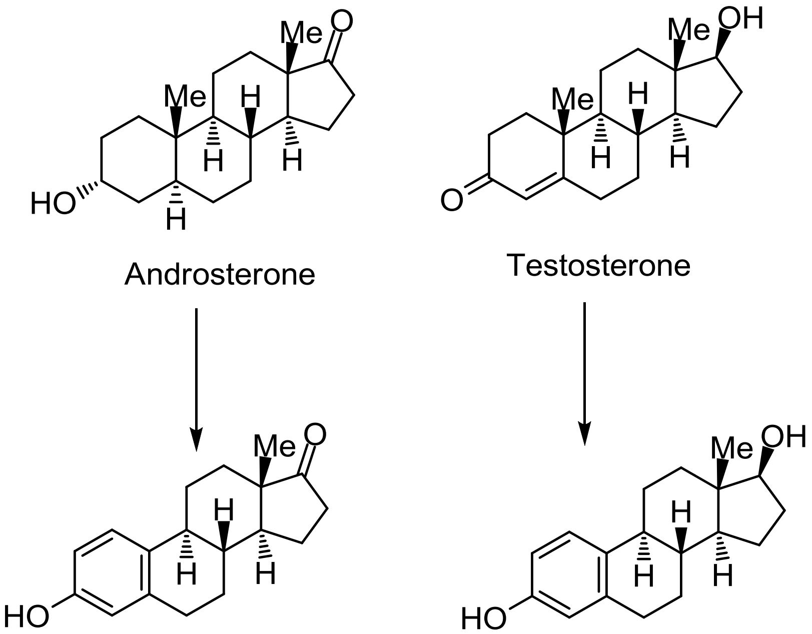
Adrenocorticoid hormones are products of the adrenal glands. They are classified into two groups according to function: **Mineralocorticoids** regulate the concentration of ions (mainly Na$^+$ and K$^+$) and **glucocorticoids** that control carbohydrate metabolism. ***Aldosterone*** is one of the most important mineralocorticoids. Increased secretion of aldosterone enhances the reabsorption of Na$^+$ and Cl$^-$ ions in the kidney and increases the loss of K$^+$.

The function of ***Cortisol*** is to increase the glucose and glycogen concentration in the body. Fatty acids and amino acids from body proteins are transported to the liver, which under the influence of cortisol produces glucose and glycogen from these sources.

Cortisol and cortisone possess anti-inflammatory effects. They or similar synthetic derivatives (e.g. prednisone) are used to treat such diseases as rheumatoid arthritis, and bronchial asthma.

Sex hormones

They are classified into **1) male sex hormones (androgens); 2) female sex hormones (estrogens); 3) pregnancy hormones (progestins)**. Some of them are synthesized in genital glands, some - in adrenal cortex.



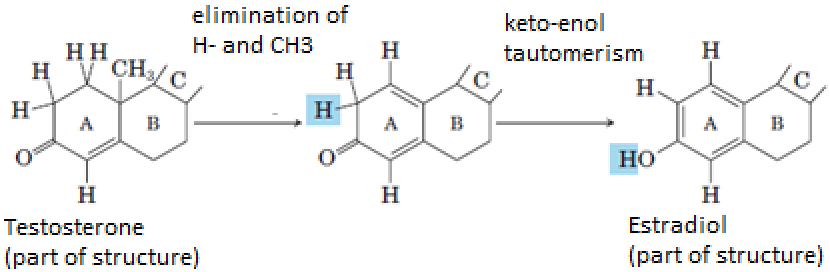
Androsterone

Testosterone

Estrone

Estradiol

Estradiol is synthesized from testosterone



Testosterone is secreted primarily in the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands.

In men, testosterone plays a key role in the development of male reproductive tissues such as the testis and prostate as well as promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair. In addition, testosterone is essential for health and well-being as well as the prevention of osteoporosis.

Estradiol *in vivo* is interconvertible with estrone; estradiol to estrone conversion being favored. Estradiol has not only a critical impact on reproductive and sexual functioning, but also affects other organs, including the bones. Estradiol is also present in males, being produced as an active metabolic product of testosterone. The serum levels of estradiol in males (14 - 55 pg/mL) are roughly comparable to those of postmenopausal women (< 35 pg/mL).

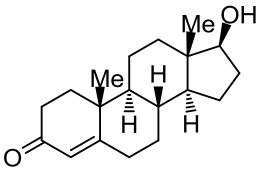
Anabolic steroids

Testosterone as male hormone is responsible for the buildup of muscles in men. For this reason many athletes have taken this drug in an effort to increase their muscular development.

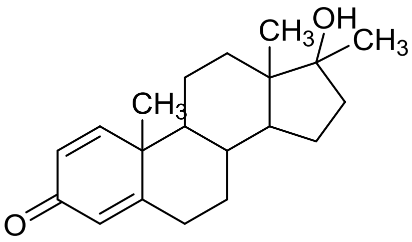
However, testosterone has two disadvantages:

1. Besides the effect on muscles it affects secondary sexual characteristics and can result in undesired side effects.
2. It is not very effective when taken orally and must be injected to achieve the best result.

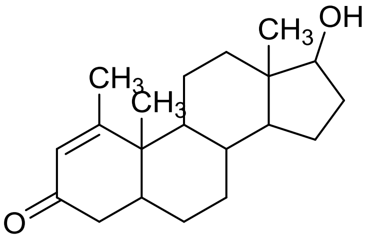
For this reason, a large number of synthetic anabolic steroids have been developed. For example:



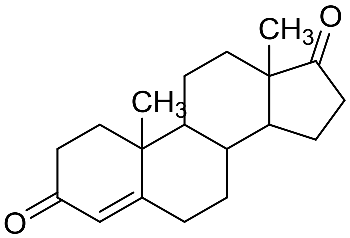
Testosterone



Methandienone



Methenolone



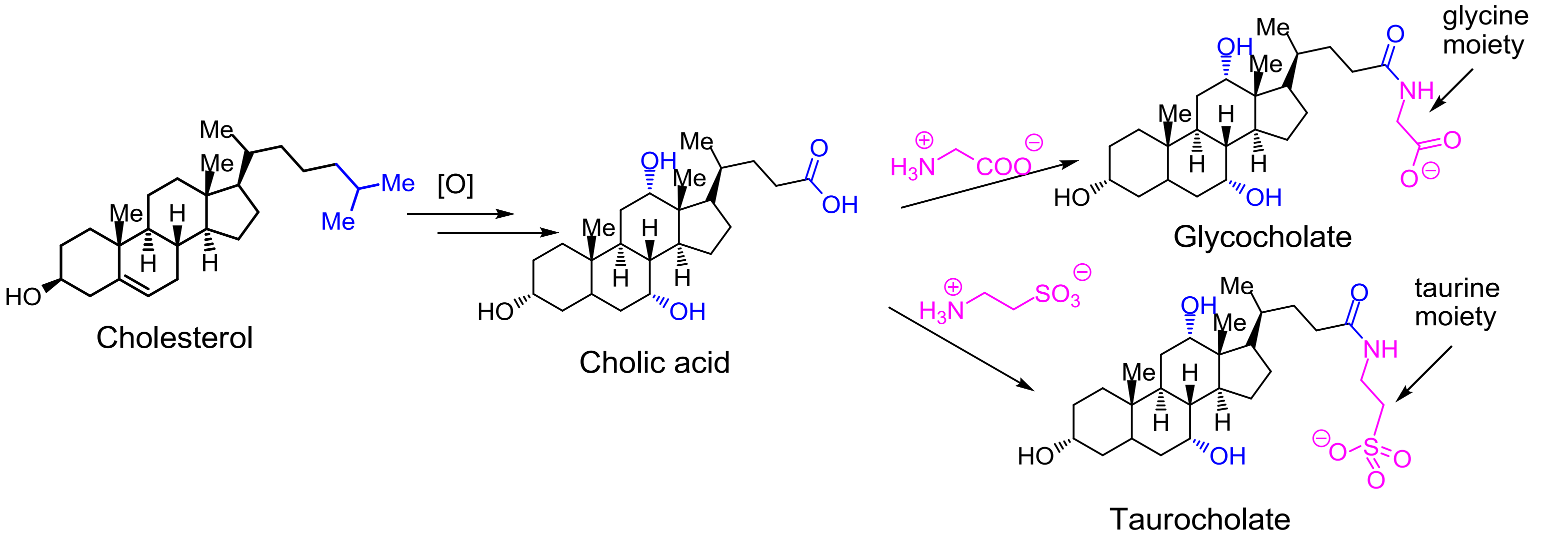
4-Androstene-3,17-dione
(prohormone)

Some women athletes use anabolic steroids, as well. Because their bodies produce only small amount of testosterone, women have much more to gain from anabolic steroids than men.

Another way to increase concentration is to use prohormones, which the body converts to testosterone. An example of prohormone is 4-androstenedione.

Bile acids

Bile acids are oxidation products of cholesterol. First the cholesterol is oxidized to the trihydroxy derivative, and the aliphatic chain is oxidized to the carboxylic acid. The latter, in turn, forms an amide bond with an amino acid, either glycine or taurine.



Bile salts are very good detergents. One end of the molecule is strongly hydrophylic because of the negative charge. Hydroxy groups are also directed to one side of the molecule. The rest of the molecule is largely hydrophobic. Thus, bile salts can disperse dietary lipids in the small intestine into the emulsions and thus, facilitate digestion. The dispersion of dietary lipids by bile salts is similar to the action of soap on dirt.

Because bile salts are eliminated in the feces, they remove excess cholesterol in two ways: (1) they are themselves breakdown products of cholesterol (cholesterol is eliminated via bile salts); (2) they solubilize deposited cholesterol in the form of bile-salts-cholesterol particles.

Amino Acids and Proteins

Amino Acids and Proteins

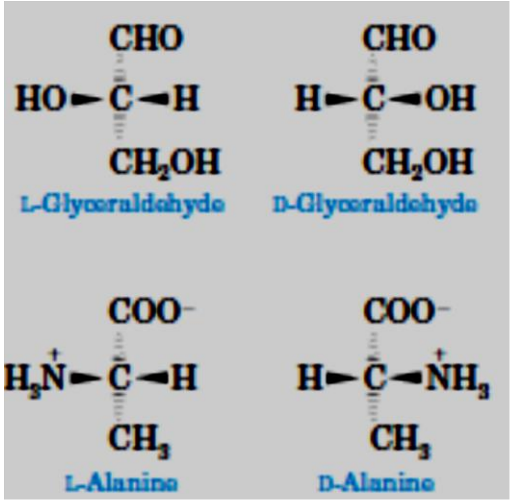
Although a wide variety of proteins exist, they all have basically the same structure: **They are chains of amino acids.** **Amino acid** is an organic compound containing **an amino group and a carboxylic group**.

Fisher projection

L-α-amino acids

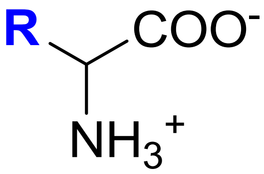
The **20** amino acids commonly found in proteins are called **alpha amino acids**.

The most important aspect of the R groups is their polarity. On that basis amino acids are classified into four groups: **nonpolar, polar but neutral, acidic, and basic**.
The nonpolar side chains are ***hydrophobic*** (they repel water), whereas polar but neutral, acidic, and basic side chains are ***hydrophilic*** (attracted to water).

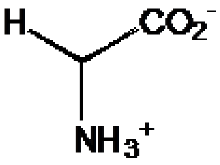


Except for glycine, which is achiral, **all the amino acids in all the proteins in your body are the L-isomers.**

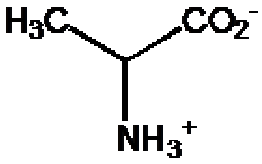
D-amino acids are extremely rare in nature; some are found, for example, in the cell walls of a few types of bacteria.



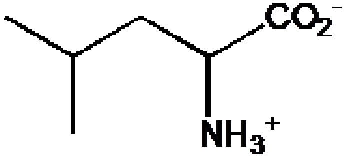
Neutral amino acids with nonpolar side chain (9)



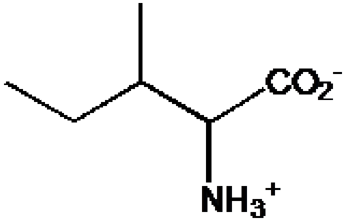
Glycine
(Gly; G)



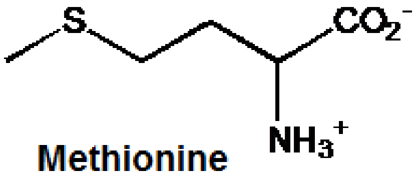
Alanine
(Ala, A)



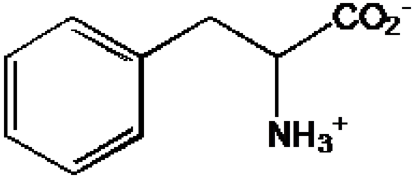
Leucine
(Leu; L)



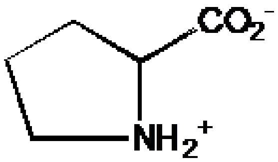
Isoleucine
(Ile; I)



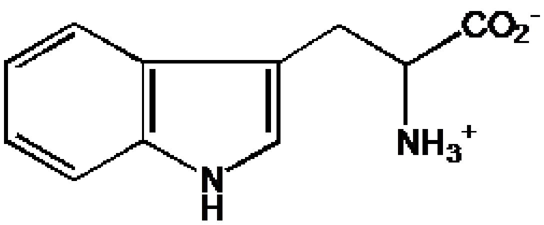
Methionine
(Met; M)



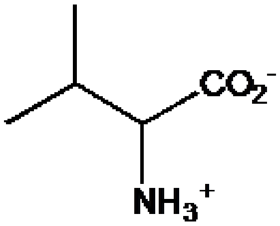
Phenylalanine
(Phe; F)



Proline
(Pro; P)

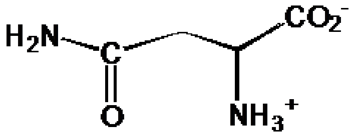


Tryptophan
(Trp; W)

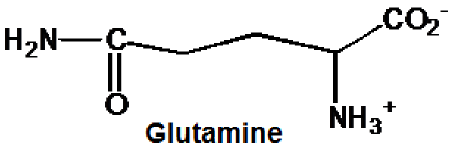


Valine
(Val; V)

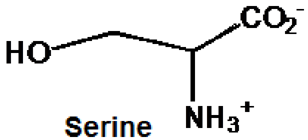
Neutral amino acids with polar side chain (4)



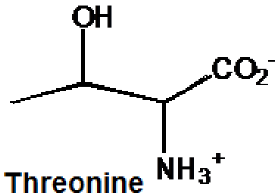
Asparagine
(Asn; N)



Glutamine
(Gln; Q)

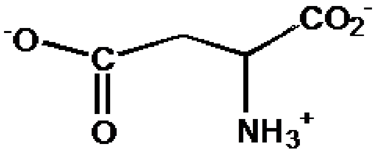


Serine
(Ser; S)

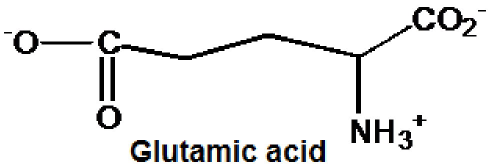


Threonine
(Thr; T)

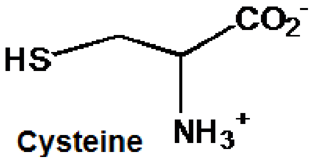
Acidic Amino Acids (4)



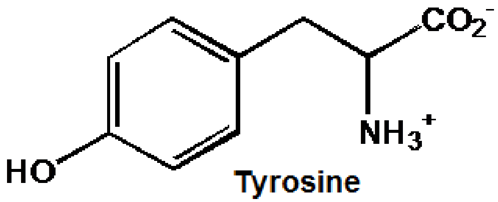
Aspartic acid
(Asp; D)



Glutamic acid
(Glu; E)

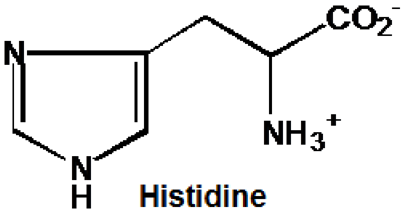


Cysteine
(Cys; C)

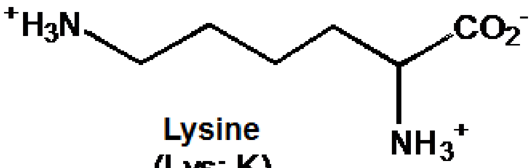


Tyrosine
(Tyr; Y)

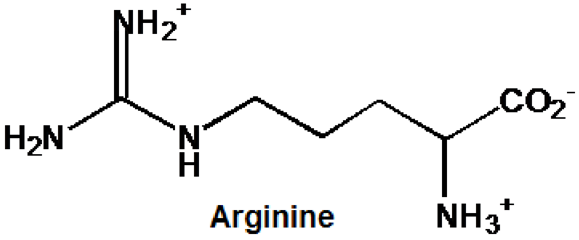
Basic Amino Acids (3)



Histidine
(His; H)



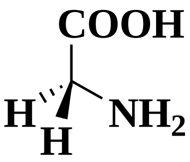
Lysine
(Lys; K)



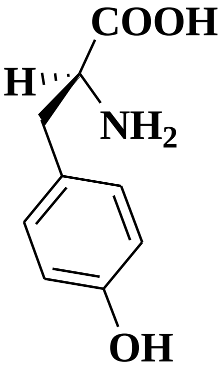
Arginine
(Arg; R)

Properties of Amino Acids

✓ Amino acids are insoluble in aprotic organic solvents.
✓Amino acids have very high melting point.



Glycine (Gly) m.p. 262^{o}C (dec.)

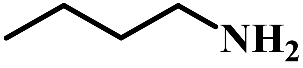


Tyrozine (Tyr) m.p. 310^{o}C (dec.)

✓ Amino acids have very high dipole moment. Such value of dipole moment is usually characteristic for compounds with the separated charges

$\mu = 14$

$\mu = 1,7\ D$

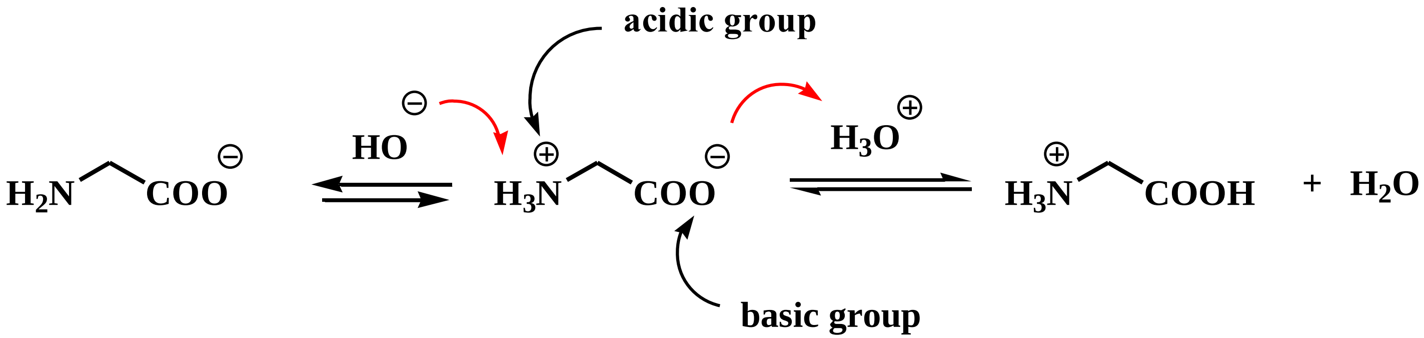


$\mu = 1,4\ D$

These and some other properties of amino acids are explained by zwitterionic character of amino acid molecules.

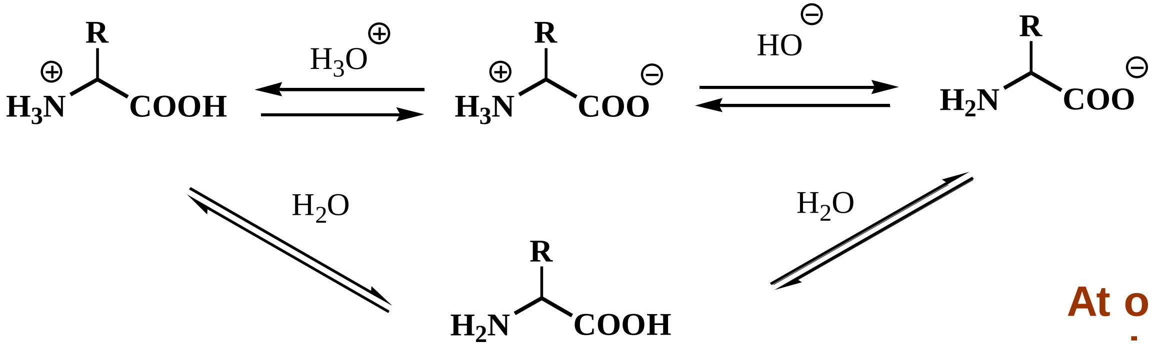
An amino acid has -COOH and $-NH_2$ groups in the same molecule. Therefore, in water solution, the **-COOH donates a proton to the $-NH_2$** so that an amino acid actually has the structure of the internal salt.

Compounds that have a positive charge on one atom and a negative charge on another are called **zwitterions,** from the German word ***zwitter,* meaning "hybrid**." Amino acids are zwitterions, not only in water solution but also in the solid state.



In basic solutions up with pH 14 amino acids exist as anions, in acidic solutions (pH < 7) – in cationic form.

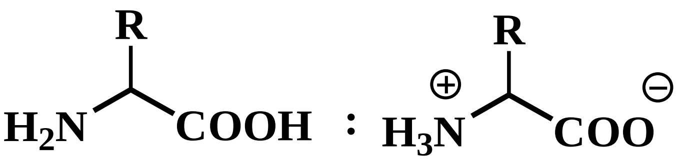
In aqueous solutions amino acids depending on the pH of a solution exist in different forms:



A pH at which an amino acids has an equal number of positive and negative charges is called isoelectric point (pI) of amino acid

At or near the isoelectric point, amino acids exist in aqueous solution largely or entirely as zwitterions.

From two neutral forms of amino acid the **zwitterionic form is predominant**.



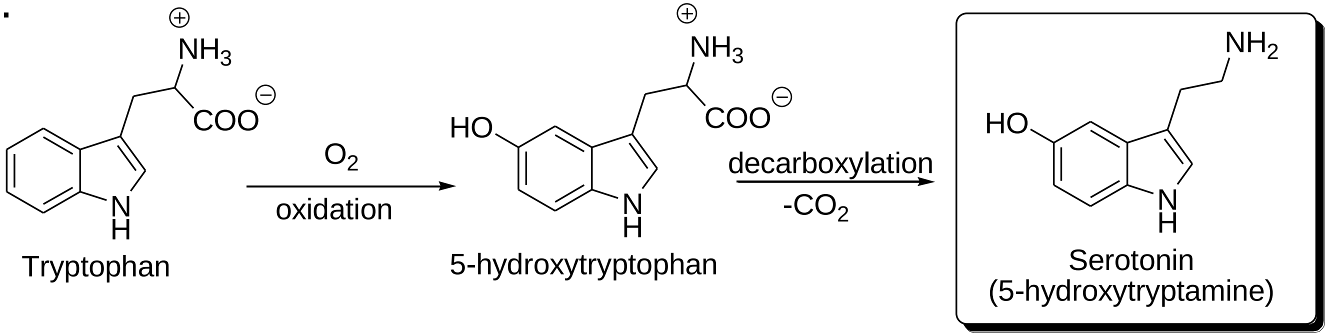
$= 1 : 10^5$

Every amino acid has a different isoelectric point. Fifteen of the 20 amino acids have isoelectric points near 6. However, the three basic amino acids have higher isoelectric points, and the two acidic amino acids have lower values. **At physiological pH ~ 7.3 all amino acids are ionized.**

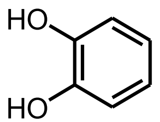
Some Characteristic Amino Acids

Phenylalanine, tryptophan, and tyrosine have aromatic rings in their side chains. These amino acids are very important physiologically because they **are** key **precursors to neurotransmitters** (substances involved in the transmission of nerve impulses).

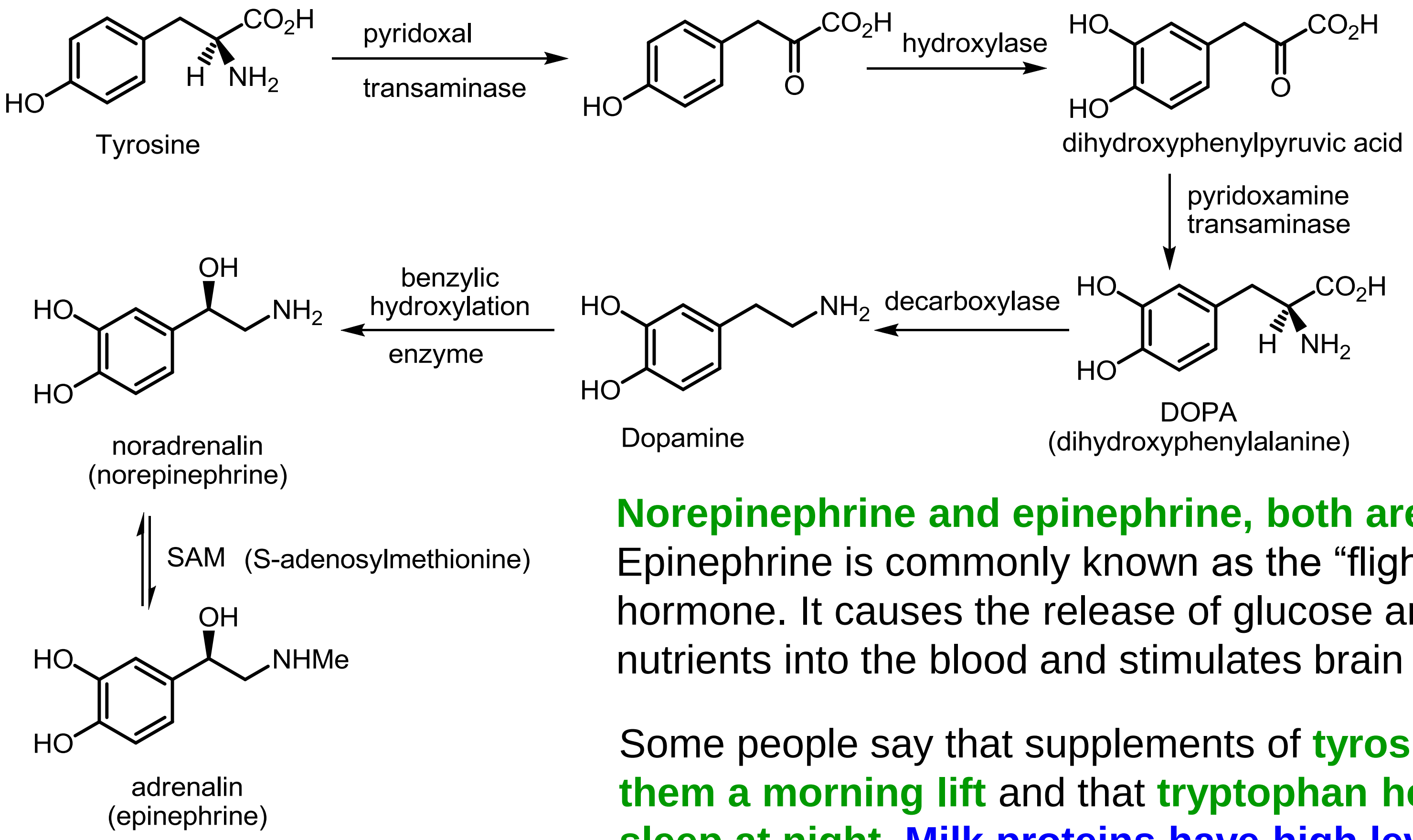
Tryptophan is converted to serotonin, more properly called **5-hydroxytryptamine**, which has a calming effect. Very low levels of serotonin are associated with depression, whereas extremely high levels produce a manic state. Thus, manic-depressive schizophrenia (also called bipolar disorder) can be managed by controlling the levels of serotonin and its further metabolites.



Amino acids **phenylalanine and tyrosine** are converted to the neurotransmitter class called **catecholamines**, which includes epinephrine, commonly known by the name, **adrenalin**. Lower than normal levels of **L-DOPA are involved in Parkinson’s disease**. **Tyrosine or phenylalanine supplements might increase the levels of dopamine**, although L-DOPA, the immediate precursor, is usually prescribed because it passes into the brain quickly through the blood–brain barrier.



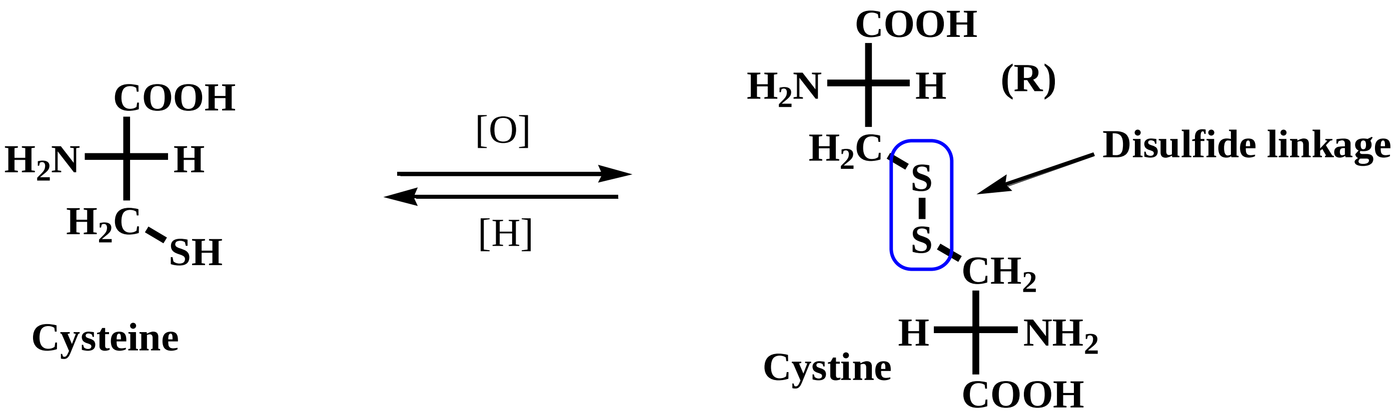
catechol



Norepinephrine and epinephrine, both are stimulators. Epinephrine is commonly known as the “flight or fight” hormone. It causes the release of glucose and other nutrients into the blood and stimulates brain function.

Some people say that supplements of **tyrosine give them a morning lift** and that **tryptophan helps them sleep at night. Milk proteins have high levels of tryptophan**; a glass of warm milk before bed is widely believed to be an aid in inducing sleep.

Since the side chains are the only differences between the amino acids, ultimately the functions of amino acids and their polymers, proteins, are determined by these side chains. One of the 20 amino acids has a chemical property not shared by any of the others. **This amino acid, cysteine, can easily be dimerized by many mild oxidizing agents:**

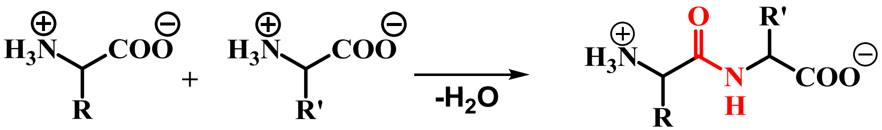


The presence of cystine has important consequences for the chemical structure and shape of the protein molecules of which it is part. The –S-S- bond is called a **disulfide bond.**

Polypeptides and Proteins

Amino acids are polymerized in living systems by enzymes that **form amide linkage from the amino group of one amino acid to the carboxyl group of another**.

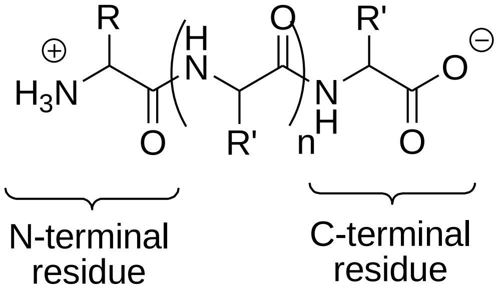
A molecules formed by joining amino acids together are called **peptides**, and amide linkages are called **peptide bonds or peptide linkages.** Each amino acid in the peptide is called **amino acid residue**.



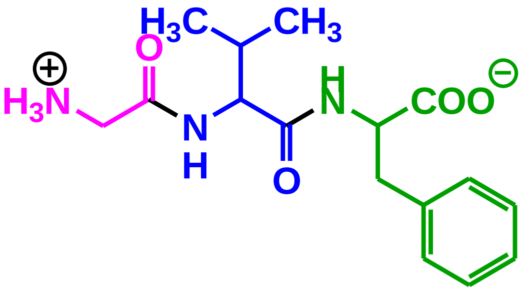
a dipeptide

Peptides that contain 2, 3, a few (3-10), or many amino acids are called **dipeptides**, **tripeptides**, **oligopeptides** and **polypeptides**, respectively.

Peptides are **linear polymers**. One end of a polypeptide chain terminates in an amino acid residue that has a free $–NH_3^+$ group; the other terminates in an amino acid residues with a free $–CO_2^-$ group. These two groups are called the **N-terminal** and **C-terminal** residues, respectively.



By convention, we write peptide and protein structures with the **N-terminal amino acid residue on the left and the C-terminal residue on the right**.



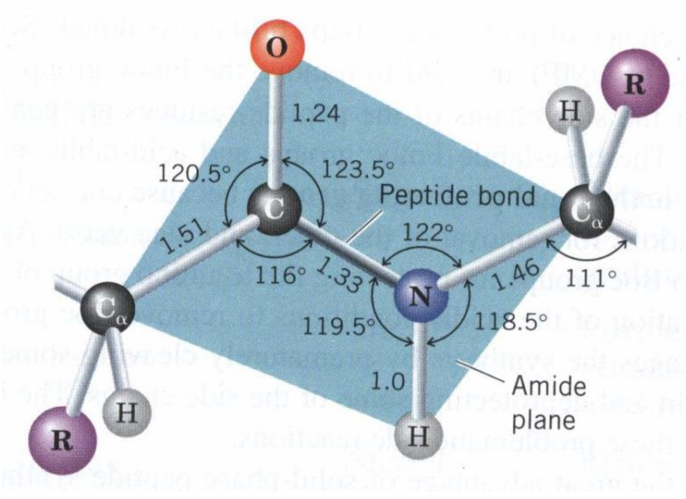
Glycylvalylphenylalanine
(Gly-Val-Phe or G-V-F)

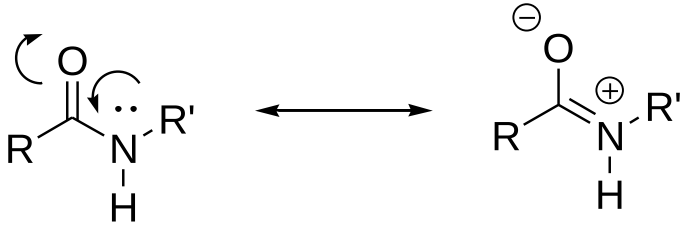
It becomes a significant task to write a full structural formula for a polypeptide that contains any more than a few amino acid residues. Therefore, **use of the three letter or one letter abbreviations is the norm** for showing the sequence of amino acids.

Properties of Proteins

The properties of proteins are based on properties of the peptide backbone and properties of the side chains.

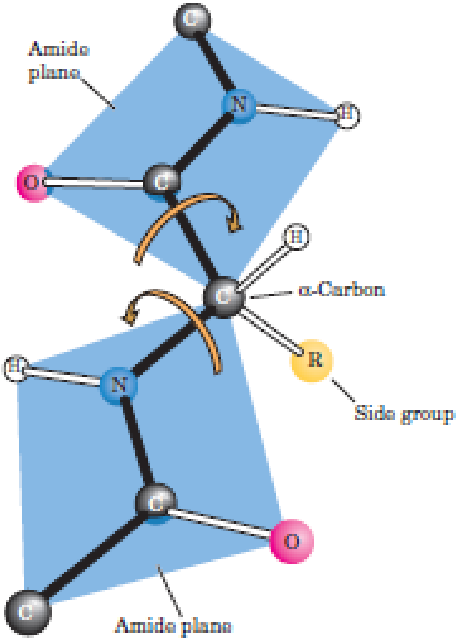
Although the peptide bond is typically written as a carbonyl group bonded to an N-H group, such bonds can exhibit keto-enol tautomerism. **The carbon–nitrogen bond actually has around 40% double bond character**, and therefore there is no free rotation around this bond. As a result, **the peptide group that forms the link between the two amino acids is actually planar**.





Resonance formulas of a peptide bond

There is freedom of rotation about the two bonds from the alpha carbon, but there is no rotation of the carbon–nitrogen bonds. **The rigidity of the amide plane limits the possible orientation of the peptide.**

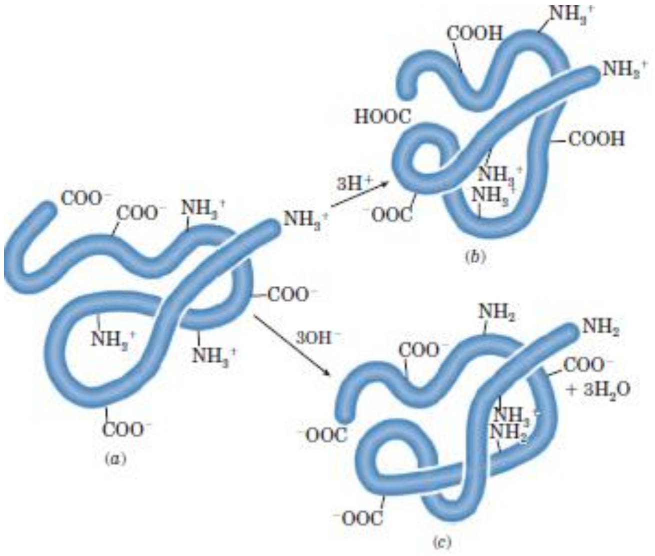


The isoelectric point of a protein occurs at the pH at which there **are an equal number of positive and negative charges.** ***Proteins are least soluble in water at their isoelectric points and can be precipitated from their solutions.***

At any pH above the isoelectric point, the protein molecules have a net negative charge; at any pH below the isoelectric point, they have a net positive charge.

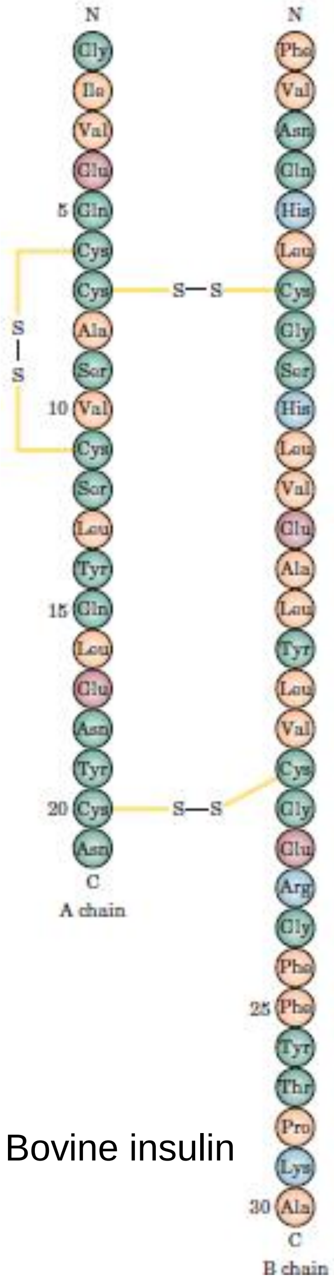
To understand functions of proteins, four levels of organization in their structures must be taken into account. They are:

- **Primary structure;**
- **Secondary structure;**
- **Tertiary structure;**
- **Quaternary structure.**



Primary Structure of a Protein

The structure of bovine insulin
was discovered by Senger in 1953 (it took 10 years).
In 1958 he was awarded with Nobel prize for this.



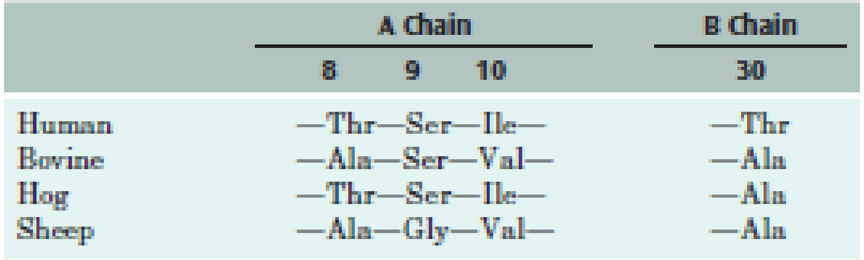
Bovine insulin

Primary structure: The sequence of amino acids in a protein.

Each of the very large number of peptide and protein molecules in biological organisms has a different sequence of amino acids—and that sequence allows the protein to carry out its function. The primary structure of a protein determines to a large extent the native (most frequently occurring) secondary and tertiary structures.

Each peptide or protein in the body has its own unique sequence of amino acids. As with naming of peptides, the ***assignment of positions of the amino acids in the sequence starts at the N-terminal end.***

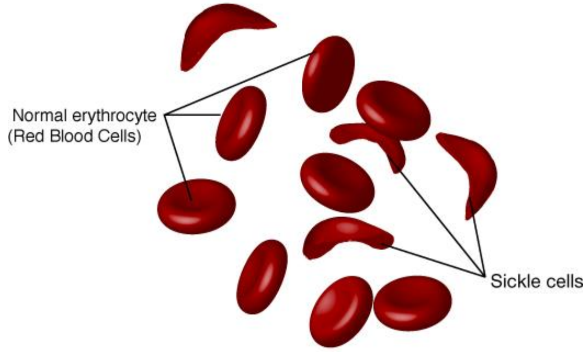
For example, **Human insulin consists of two chains having a total of 51 amino acids.** The two chains are connected by disulfide bonds. **Insulin is necessary for proper utilization of carbohydrates**, and people with severe diabetes must take insulin injections. The amount of human insulin available is far too small to meet the need for it, so bovine insulin (from cattle) or insulin from hogs or sheep is used instead. Insulin from these sources is similar, but not identical, to human insulin.



	A Chain			B Chain
	8	9	10	30
Human	—Thr—	Ser—	Ile—	—Thr
Bovine	—Ala—	Ser—	Val—	—Ala
Hog	—Thr—	Ser—	Ile—	—Ala
Sheep	—Ala—	Gly—	Val—	—Ala

Amino acid sequence differences for human, bovine, hog and sheep insulins

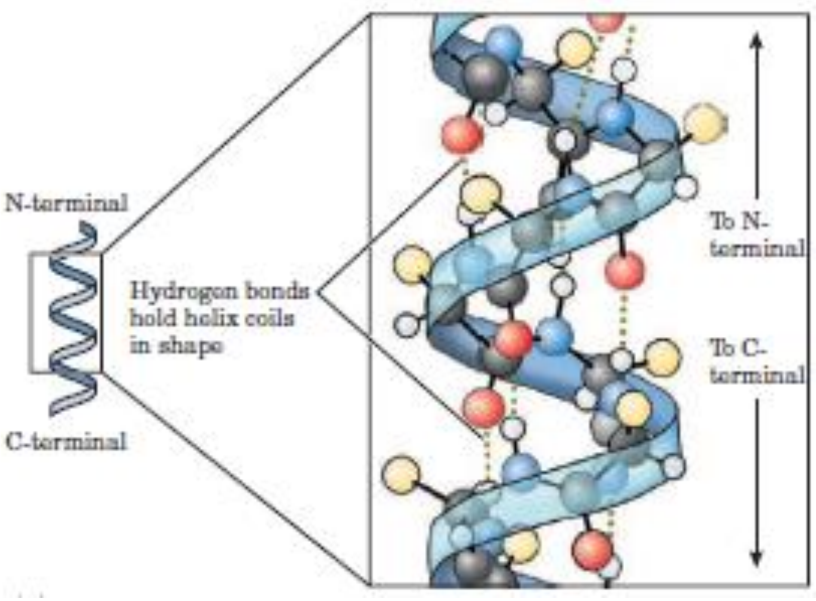
In some cases, a minor change makes a major difference. For example, in the blood protein hemoglobin. **A change in only one amino acid in a chain of 146 is enough to cause a fatal disease - sickle cell anemia.**



Secondary Structure of a Protein

Secondary structure - a repetitive conformation of the protein backbone.

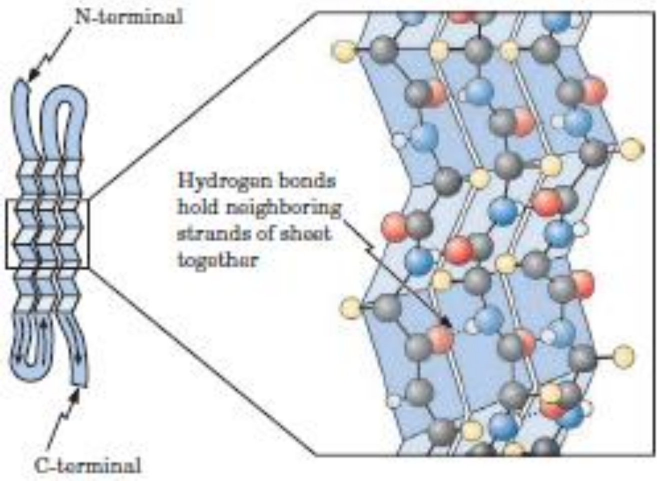
The two most common secondary structures encountered in proteins are the **α-helix and the β-pleated sheet**. Those protein conformations that do not exhibit a repeated pattern are called **random coils**.



In the **α-helix** form, a single protein chain twists in such a manner that its shape **resembles a right-handed coiled spring**—that is, a helix. The shape of the helix is maintained by numerous **intramolecular hydrogen bonds** that exist between the backbone **–C=O and H-N-** groups.

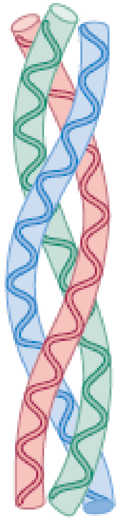
Each –N-H points upward and each C=O points downward, roughly parallel to the axis of the helix. **All the amino acid side chains point outward from the helix**.

The other important orderly structure in proteins is the **β-pleated sheet.** In this case, the orderly alignment of protein chains is maintained by **intermolecular** or **intramolecular hydrogen bonds.**



The β-sheet structure can occur between molecules when polypeptide chains run parallel (all N-terminal ends on one side) **or antiparallel** (neighboring N-terminal ends on opposite sides). β-Pleated sheets can also occur intramolecularly, when the polypeptide chain makes a U-turn, forming a hairpin structure, and the pleated sheet is antiparallel.

In all secondary structures, the hydrogen bonding is between backbone –C=O and H-N- groups.

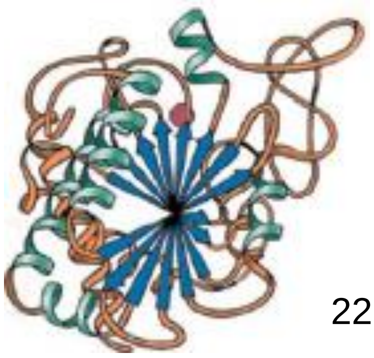


The triple helix of collagen

Another repeating pattern classified as a secondary structure is the **extended helix** of collagen. It is quite different from the α-helix. Collagen is the structural protein of connective tissues (bone, cartilage, tendon, blood vessels, skin), where it provides strength and elasticity. It makes up about 30% by weight of all the body’s protein. The extended helix structure is made possible by the primary structure of collagen. Each strand of collagen consists of repetitive units that can be symbolized as Gly—X—Y; that is, every third amino acid in the chain is glycine. About one-third of the X amino acid is proline, and the Y is often hydroxyproline.

Few proteins have predominantly α-helix or β-sheet structures. **Most proteins, especially globular ones, have only certain portions of their molecules in these conformations. The rest of the molecule consists of random coil.**

Enzyme carboxypeptidase. The **β-pleated sheet** portions are shown **in blue**, the **green** structures are the **α-helix p**ortions, and **the orange strings** are the **random coil** areas.

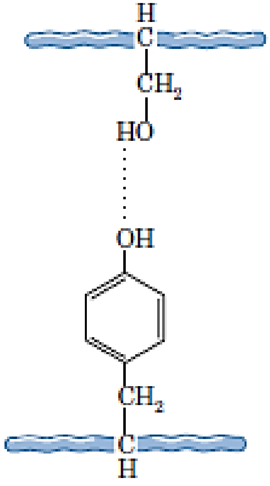


Tertiary Structure of a Protein

The tertiary structure of a protein is the 3D-arrangement of every atom in the molecule. Unlike the secondary structure, it includes interactions of the side chains, and not just the peptide backbone. In general, **tertiary structures are stabilized by five ways**:

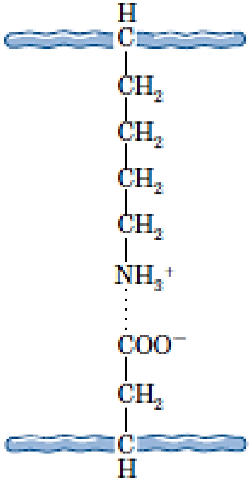
Covalent bonds

The covalent bond most often involved in stabilization of the tertiary structure of proteins is the **disulfide** bond.



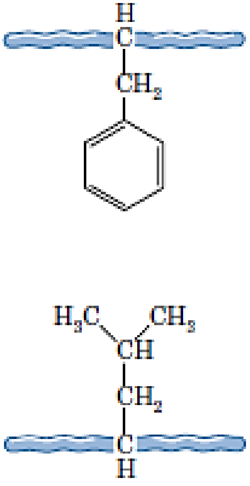
Hydrogen bonding

Tertiary structures are stabilized by hydrogen bonding between **polar groups on side chains or between side chains and the peptide backbone**



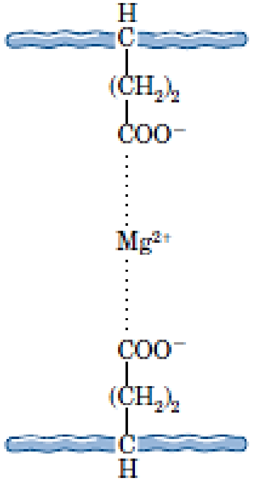
Salt bridge (electrostatic interaction)

Salt bridges, also called electrostatic attractions, occur between two amino acids with ionized side chains



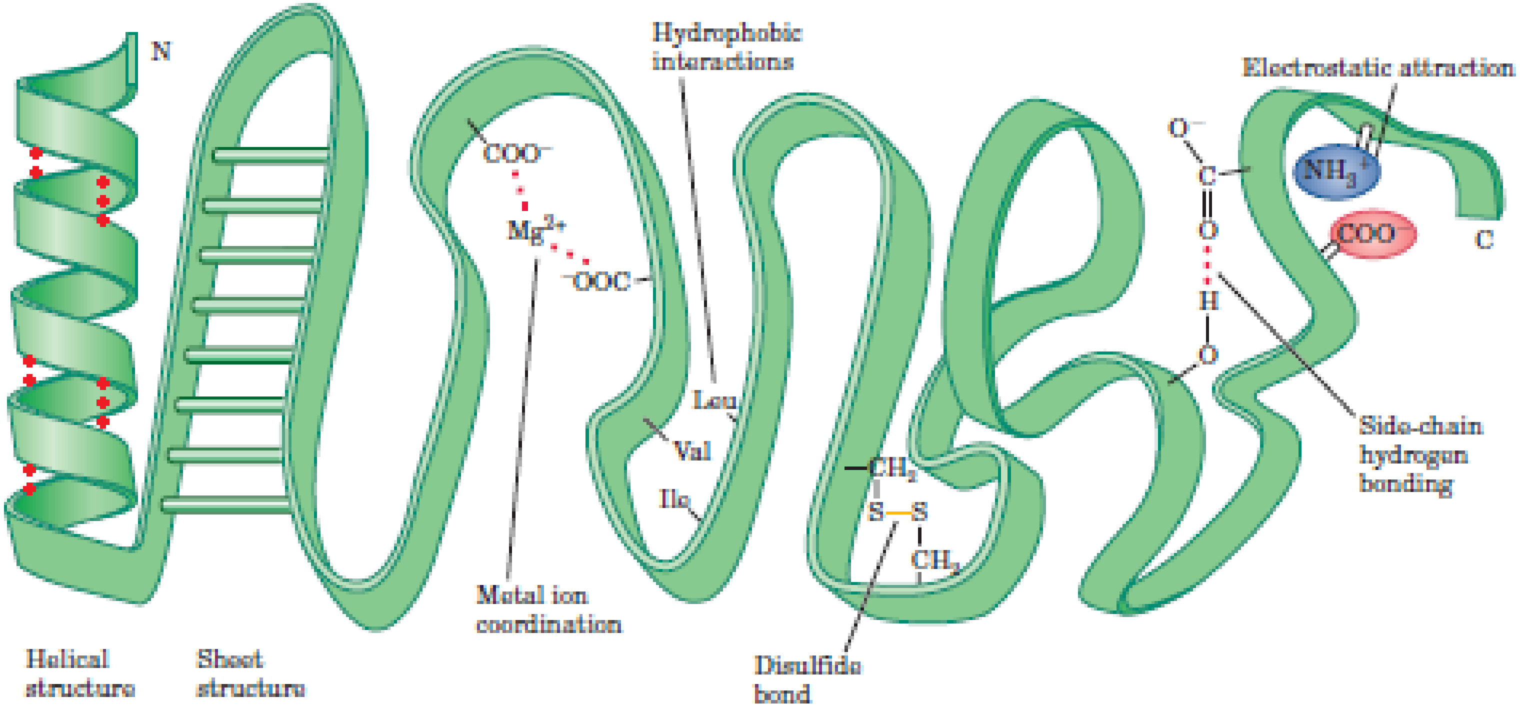
Hydrophobic interaction

The nonpolar groups prefer to interact with each other, excluding water from inward regions.



Metal ion coordination

Two side chains with the same charge would normally repel each other, but they can also be linked via a metal ion.



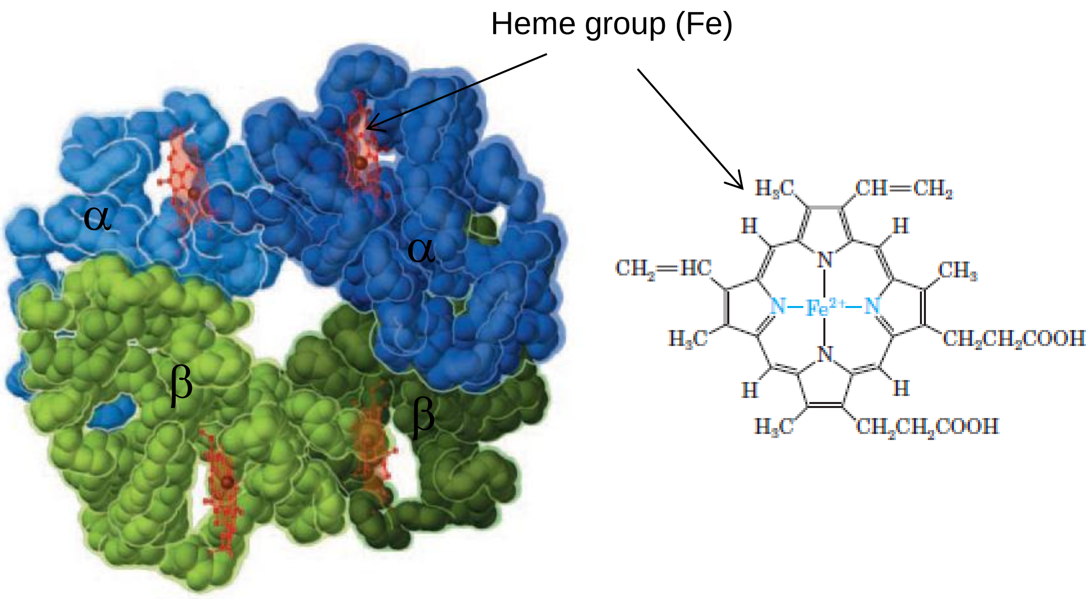
Forces that stabilize the tertiary structures of proteins. The helical structure and the sheet structure are two kinds of backbone hydrogen bonding. Although the backbone hydrogen bonding is part of the secondary structure, the conformation of the backbone puts constraints on the possible arrangement of the side chains.

The Quaternary Structure of a Protein?

The highest level of protein organization is the **quaternary structure**, **which applies to proteins with more than one polypeptide chain.**

The subunits are packed and held together by hydrogen bonds, salt bridges, and hydrophobic interactions—the same forces that operate within tertiary structures.

Hemoglobin in adult humans is made of four chains (called globins): **two identical α chains of 141 amino acid residues each and two identical β chains of 146 residues each**.

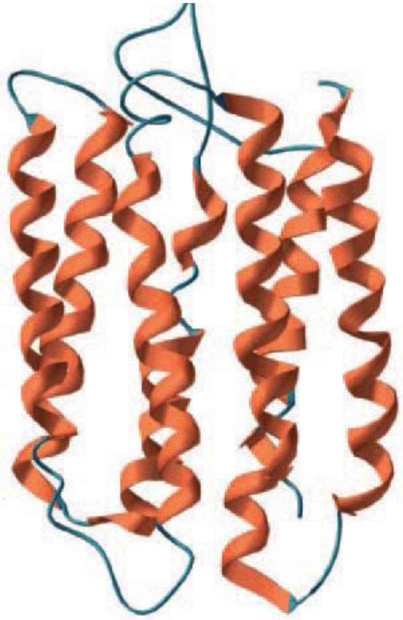


The quaternary structure of hemoglobin.

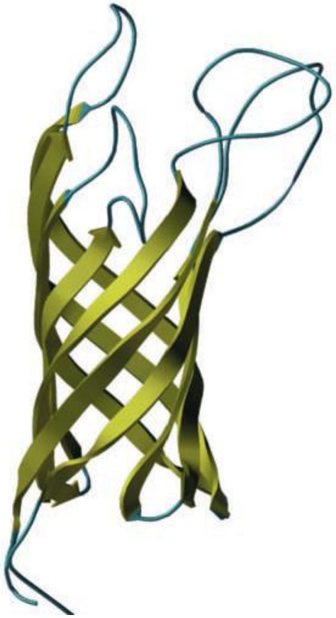
In hemoglobin, each globin chain surrounds an iron-containing heme unit. Proteins that contain non-amino acid portions are called **conjugated proteins. The non-amino acid portion** of a conjugated protein is called a **prosthetic group.** In hemoglobin, the globins are the amino acid portions and the heme units are the prosthetic groups.

Integral membrane proteins traverse partly or completely a membrane bilayer.

An estimated one-third of all proteins are integral membrane proteins. To keep the protein stable in the nonpolar environment of a lipid bilayer, it must form quaternary structures in which the outer surface is largely nonpolar and interacts with the lipid bilayer. Thus **most of the polar groups of the protein must turn inward.** **Two such quaternary structures exist in integral membrane proteins: (1) often 6 to 10 α-helices crossing the membrane and (2) β-barrels made of 8, 12, 16, or 18 antiparallel β-sheets.**



Integral membrane protein of rhodopsin, made of α-helices.



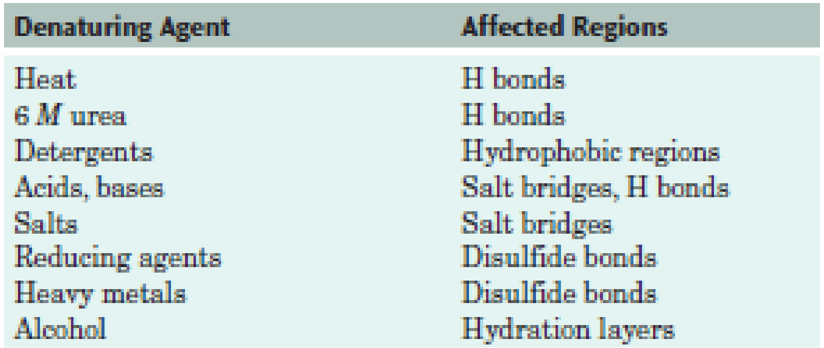
An integral membrane protein from the outer mitochondrial membrane forming a β-barrel from eight β-pleated sheets.

Denaturation of Proteins

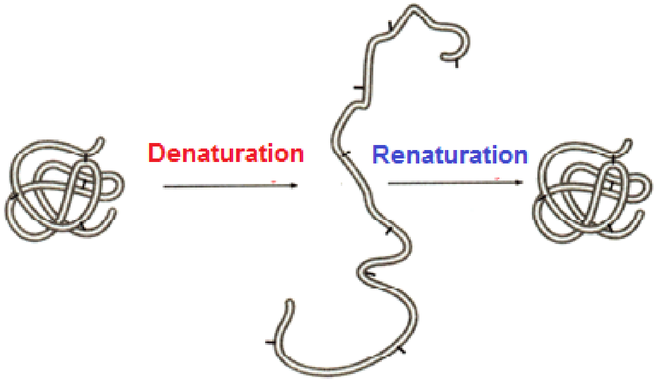
Denaturation - the loss of the secondary, tertiary, and quaternary structures of a protein by a chemical or physical agent that leaves the primary structure intact.

For example, heat cleaves hydrogen bonds, so boiling a protein solution destroys the α-helical and β-pleated sheet structure. **In globular proteins heat causes the unfolding of the polypeptide chains**; because of subsequent intermolecular protein–protein interactions, precipitation or coagulation then takes place. That is what happens when we boil an egg.

Destruction of Secondary and Higher Structures



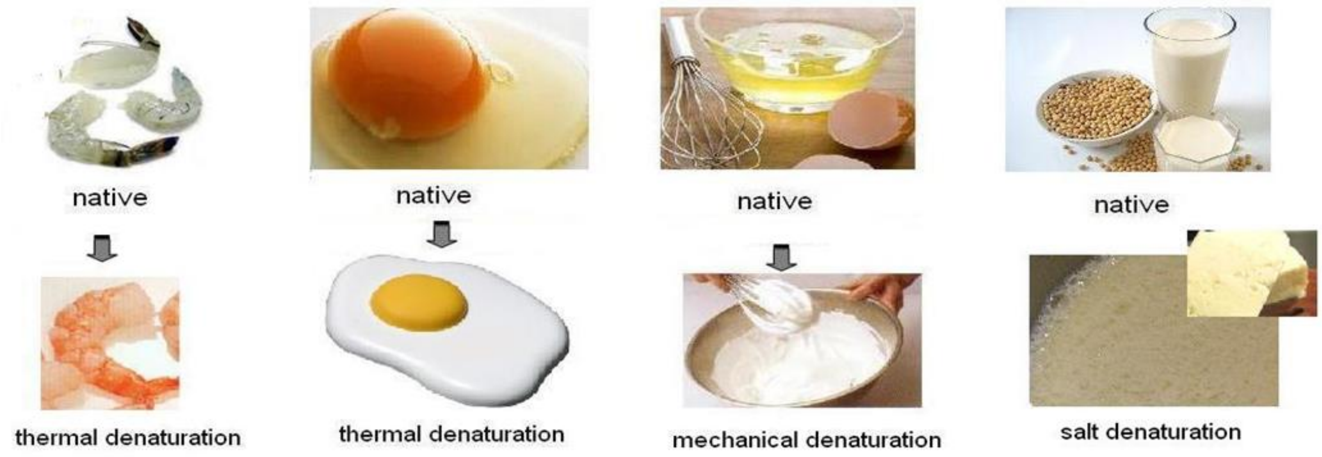
Denaturing Agent	Affected Regions
Heat	H bonds
6 *M* urea	H bonds
Detergents	Hydrophobic regions
Acids, bases	Salt bridges, H bonds
Salts	Salt bridges
Reducing agents	Disulfide bonds
Heavy metals	Disulfide bonds
Alcohol	Hydration layers



Denaturation changes secondary, tertiary, and quaternary structures. It does not affect primary structures (that is, the sequence of amino acids that make up the chain). **If these changes occur to a small extent, denaturation can be reversed.** For example, when we remove a denatured protein from a urea solution and put it back into water, it often reassumes its secondary and tertiary structures. **This process is called reversible denaturation.** In living cells, some denaturation caused by heat can be reversed by **chaperones.** These proteins help a partially heat-denatured protein to regain its native secondary, tertiary, and quaternary structures. Some denaturation, however, is irreversible. We cannot unboil a hard-boiled egg.

Heavy metal ions (for example, Pb^{2+}, Hg^{2+}, and Cd^{2+}) also denature protein by attacking the -SH groups. They **form salt bridges, as in –S- Hg^{2+} -S-**. This feature is taken in advance in the antidote for heavy metal poisoning: raw egg whites and milk. The egg and milk proteins are denatured by the metal ions, forming insoluble precipitates in the stomach. These must be pumped out or removed by inducing vomiting.

Other chemical agents such as **alcohol also denature proteins, coagulating them**. This process is used in sterilizing the skin before injections. **At a concentration of 70%, ethanol penetrates bacteria and kills them by coagulating their proteins,** whereas 95% alcohol denatures only surface proteins.



Nucleosides and Nucleotides. Nucleic Acids.

Two kinds of nucleic acids are found in cells: **ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Each has its own role in the transmission of hereditary information.**

DNA is present in the chromosomes of the nuclei of eukaryotic cells. RNA is not found in the chromosomes, but rather is located elsewhere in the nucleus and even outside the nucleus, in the cytoplasm.

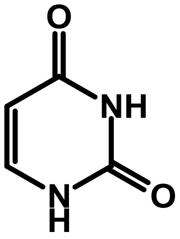
Both DNA and RNA are polymers. Just as proteins consist of chains of amino acids, and polysaccharides consist of chains of monosaccharides, nucleic acids are also chains. **The building blocks (monomers) of nucleic acid chains are *nucleotides. Nucleotides themselves, however, are composed of* three simpler units:**

- **a base,**
- **a monosaccharide**
- **a phosphate**

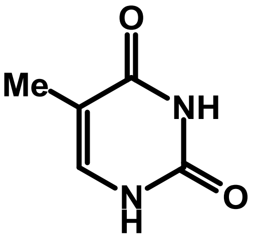
Bases

The **bases found in DNA and RNA are: adenine (A) and guanine (G)**—are derivatives of purine; the other three—**cytosine (C), thymine (T), and uracil (U)**—are derivatives of pyrimidine. All of them are basic because they are heterocyclic aromatic amines.

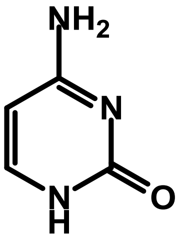
Thus both DNA and RNA contain four bases: two pyrimidines and two purines. **For DNA, the bases are A, G, C, and T; for RNA, the bases are A, G, C, and U.**



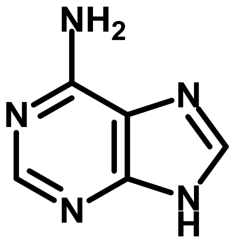
Uracil (U)
(RNA only)



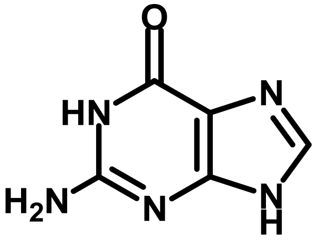
Thymine (T)
(DNA only)



Cytosine (C)
(DNA and RNA)



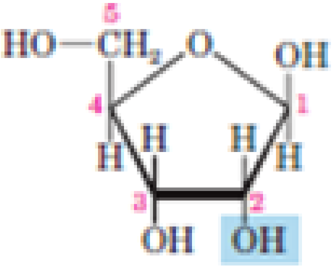
Adenine (A)
(DNA and RNA)



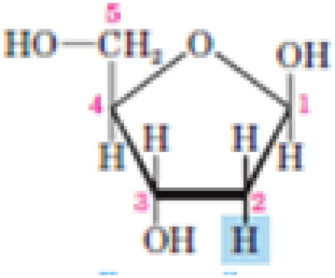
Guanine (G)
(DNA and RNA)

Sugars

The sugar component of **RNA is D-ribose**. In **DNA**, the sugar component is **2-deoxy-D-ribose** (hence the name deoxyribonucleic acid).



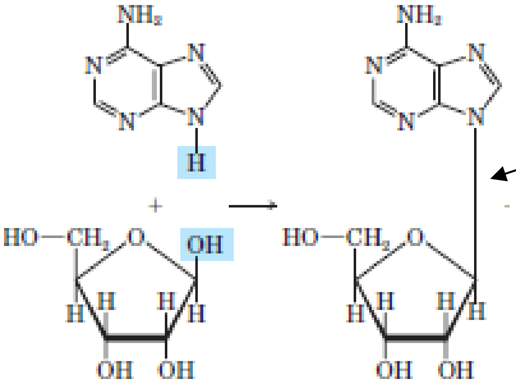
β-D-ribose



β-D-2-deoxyribose

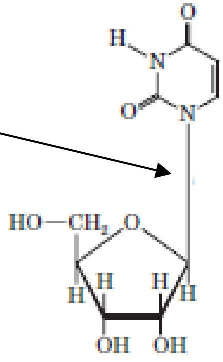
The combination of sugar and base is known as a **nucleoside. The purine** bases are linked to **C-1 of the monosaccharide through N-9 (the nitrogen at position 9)** by a ***β-N-glycosidic bond.***

The pyrimidine bases are linked to **C-1 of the monosaccharide through their N-1 by a *β-N-glycosidic bond.***



Adenosine

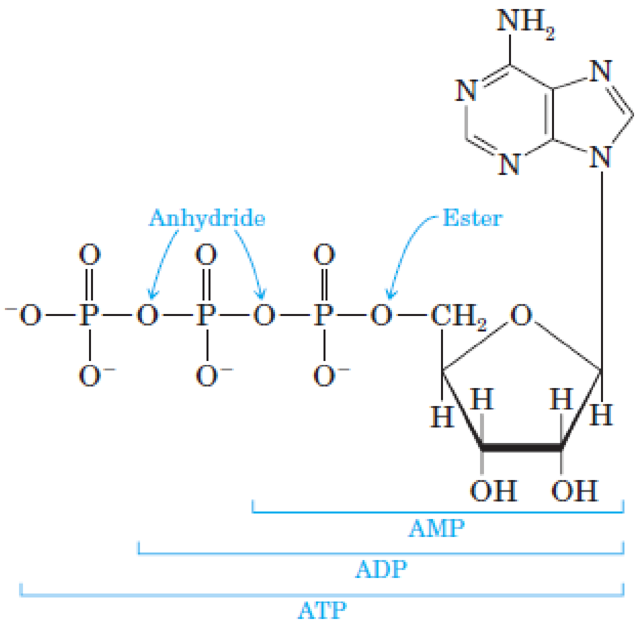
β-N-glycosidic bond

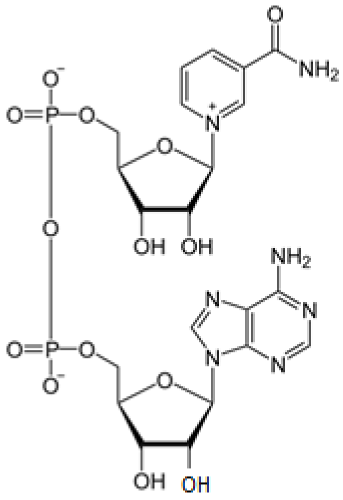


Uridine

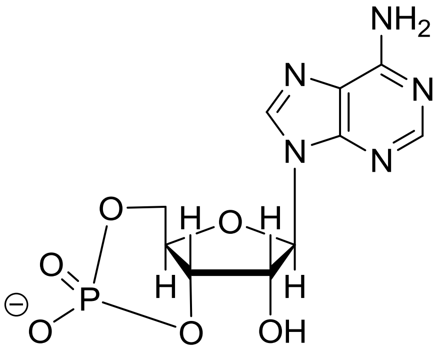
Phosphate

The third component of nucleic acids is phosphoric acid. When this group forms a phosphate ester bond with nucleoside, the result is a compound known as a **nucleotide.** For example,



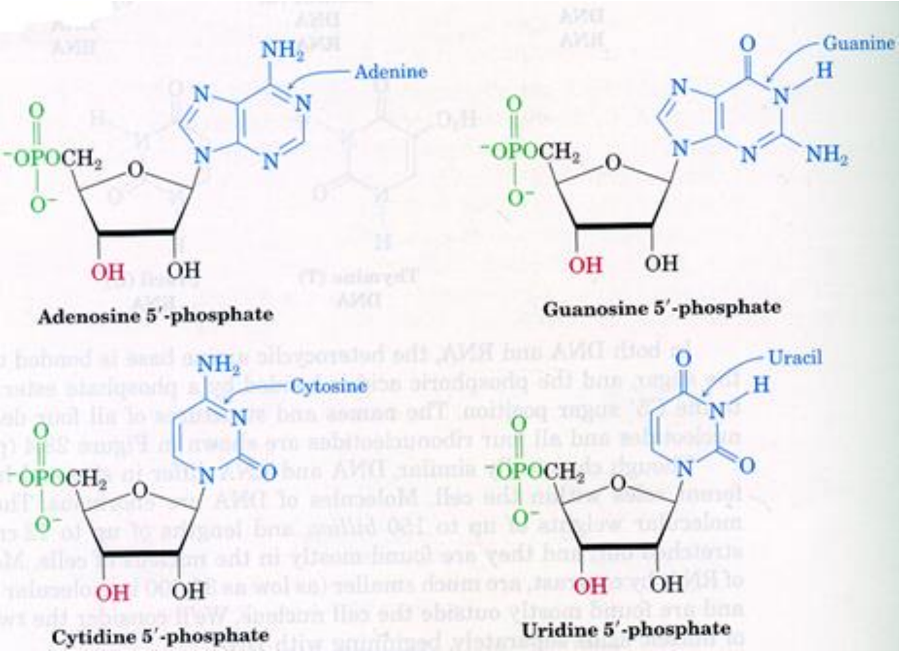


Nicotinamide adenosine dinucleotide (NAD^+)



cAMP
(cyclic adenosine
monophosphate)

Ribonucleotides



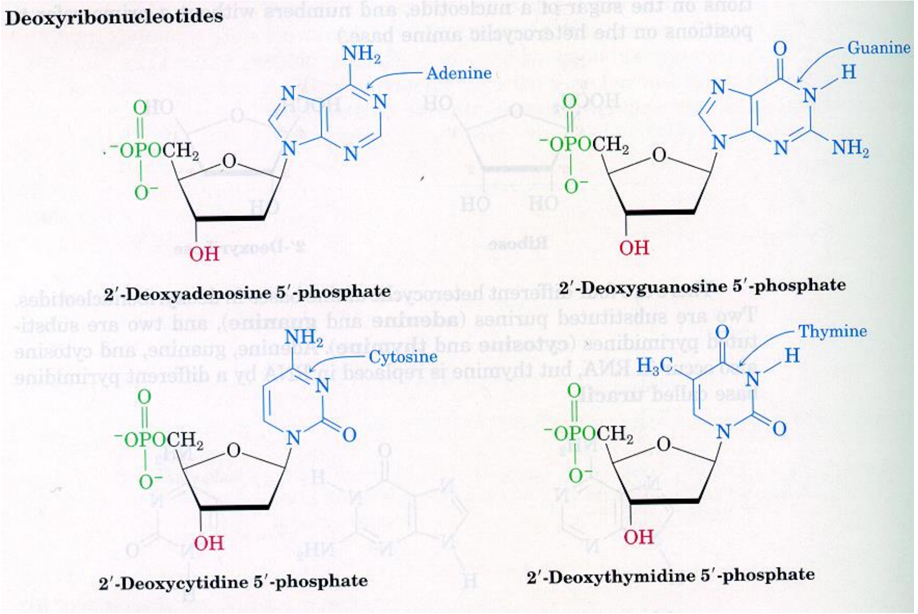
Adenosine 5′-phosphate

Guanosine 5′-phosphate

Cytidine 5′-phosphate

Uridine 5′-phosphate

Deoxyribonucleotides


Deoxyribonucleotides

2′-Deoxyadenosine 5′-phosphate

2′-Deoxyguanosine 5′-phosphate

2′-Deoxycytidine 5′-phosphate

2′-Deoxythymidine 5′-phosphate

In summary:

Nucleoside = Base + Sugar

Nucleotide = Base + Sugar + Phosphate

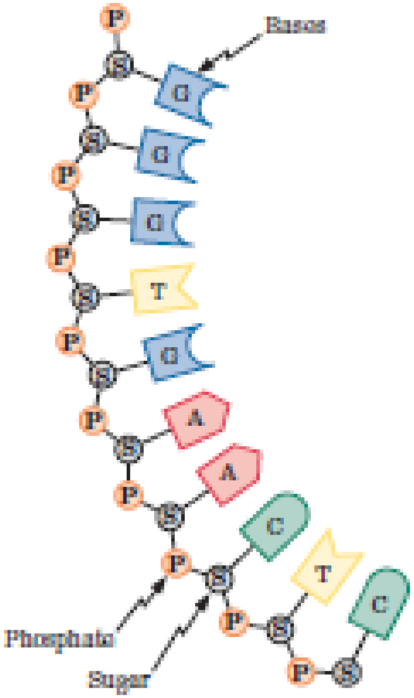
Nucleic acid = A chain of nucleotides

Nucleic acids

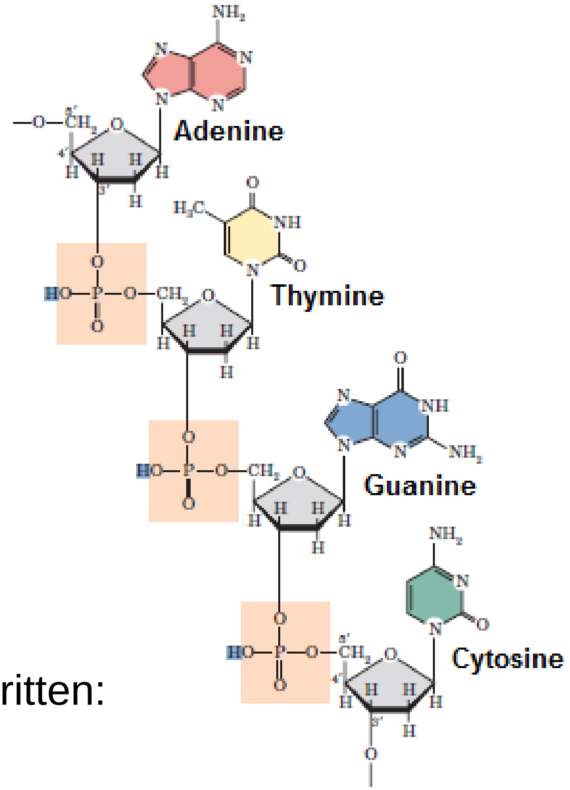
Nucleic acids, which are chains of monomers, also have primary, secondary, and higher-order structures.

Nucleic acids are polymers of nucleotides. **Their primary structure is the sequence of nucleotides**. It can be divided into two parts: **(1) the backbone of the molecule and (2) the bases that are the side-chain groups**.

The backbone of the DNA and RNA chains has two ends: a 3’-OH end and a 5’-OH end. These two ends have roles similar to those of the C-terminal and N-terminal ends in proteins. The backbone provides structural stability for the DNA and RNA molecules.



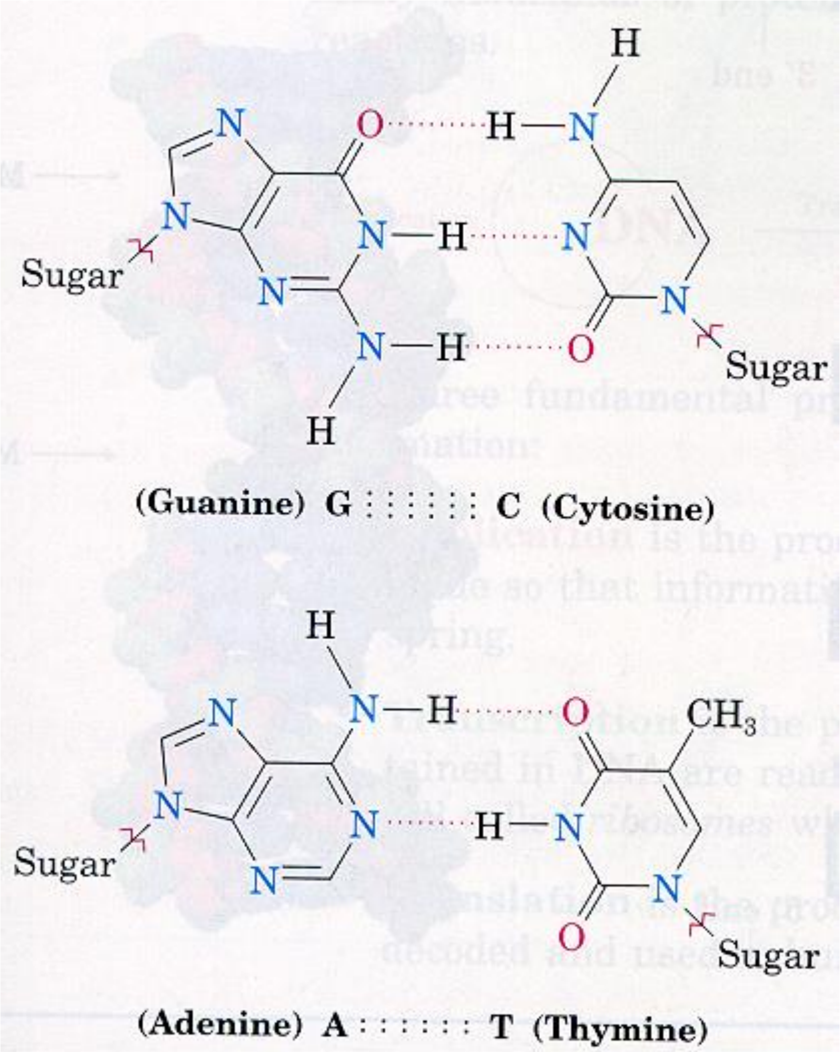
The bases that are linked, one to each sugar unit, are the side chains. They carry all of the information necessary for protein synthesis.



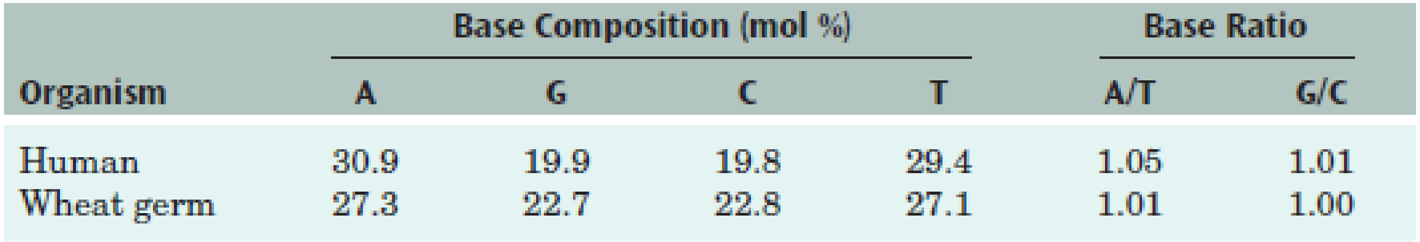
Primary structure can be written:
5’-ATGC-3’

The analysis of the base composition of DNA molecules from many different species showed that **the quantity of adenine (in moles) is always approximately equal to the quantity of thymine**, and **the quantity of guanine is always approximately equal to the quantity of cytosine (Chargaff rule).**

However, the adenine/guanine ratio varies widely from spiecies to spieces.



Base composition and Base Ratio in two species

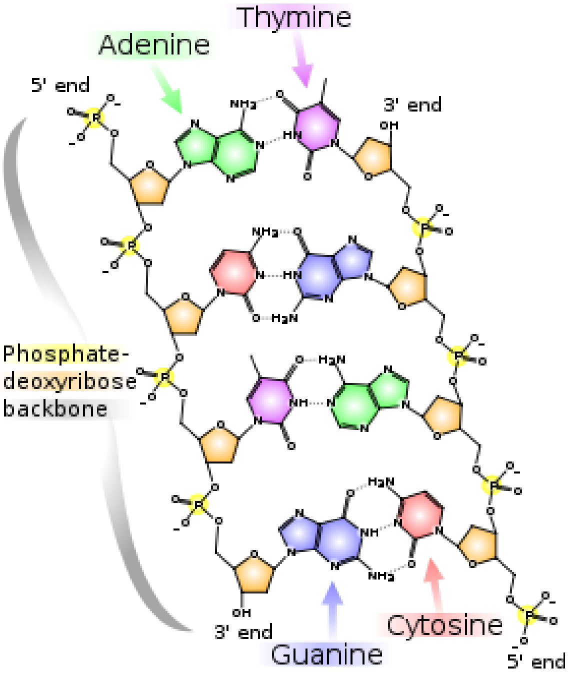


Organism	Base Composition (mol %)				Base Ratio	
	A	G	C	T	A/T	G/C
Human	30.9	19.9	19.8	29.4	1.05	1.01
Wheat germ	27.3	22.7	22.8	27.1	1.01	1.00

Secondary structure of DNA

In 1953, James Watson and Francis Crick established the three-dimensional structure of DNA. **DNA is composed of two strands entwined around each other in a double helix. In the DNA double helix, the two polynucleotide chains run in opposite directions** (which is called antiparallel). Thus, at each end of the double helix, there is one 5'-OH and one 3'-OH terminus. The sugar–phosphate backbone is on the outside, exposed to the aqueous environment, and the bases point inward. The bases are paired according to Chargaff's rule: For each adenine on one chain, a thymine is aligned opposite it on the other chain; each guanine on one chain has a cytosine aligned with it on the other chain. ***The bases so paired form hydrogen bonds with each other, two for A-T and three for G-C, thereby stabilizing the double helix). A-T and G-C are called complementary base pairs.***

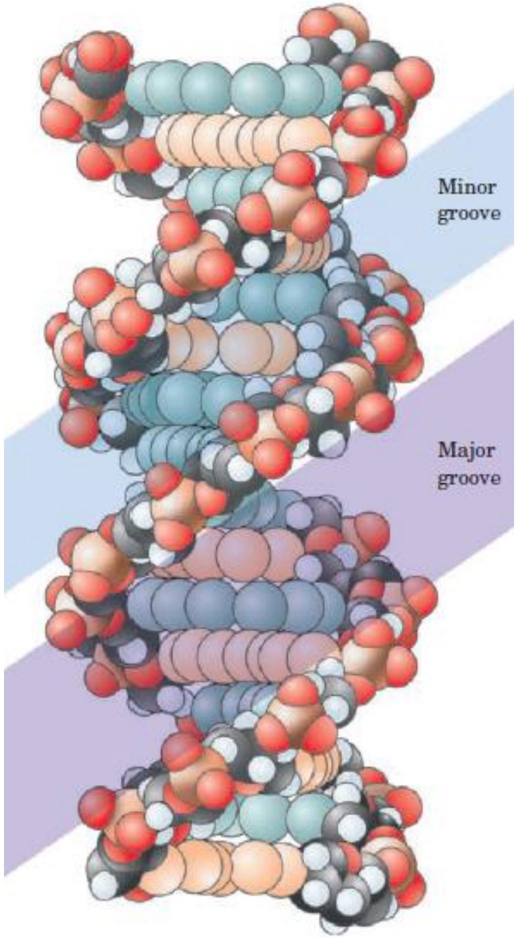
James Watson and Francis Crick



A distinguishing feature is the presence of a **major groove and a minor groove, which arise because the two strands are** not equally spaced around the helix. Interactions of proteins and drugs with the major and minor grooves of DNA serve as an active area of research.

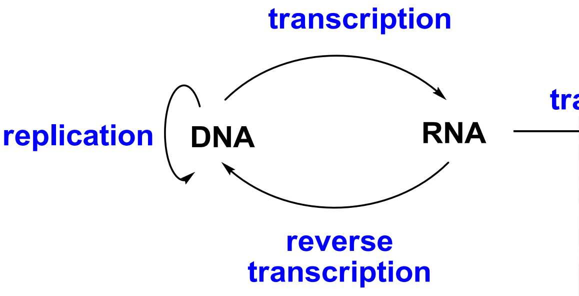
The entire action of DNA depends on the fact that, ***wherever there is an adenine on one strand of the helix, there must be a thymine on the other strand because that is the only base that fits and forms strong hydrogen bonds with adenine, and similarly for G and C.***

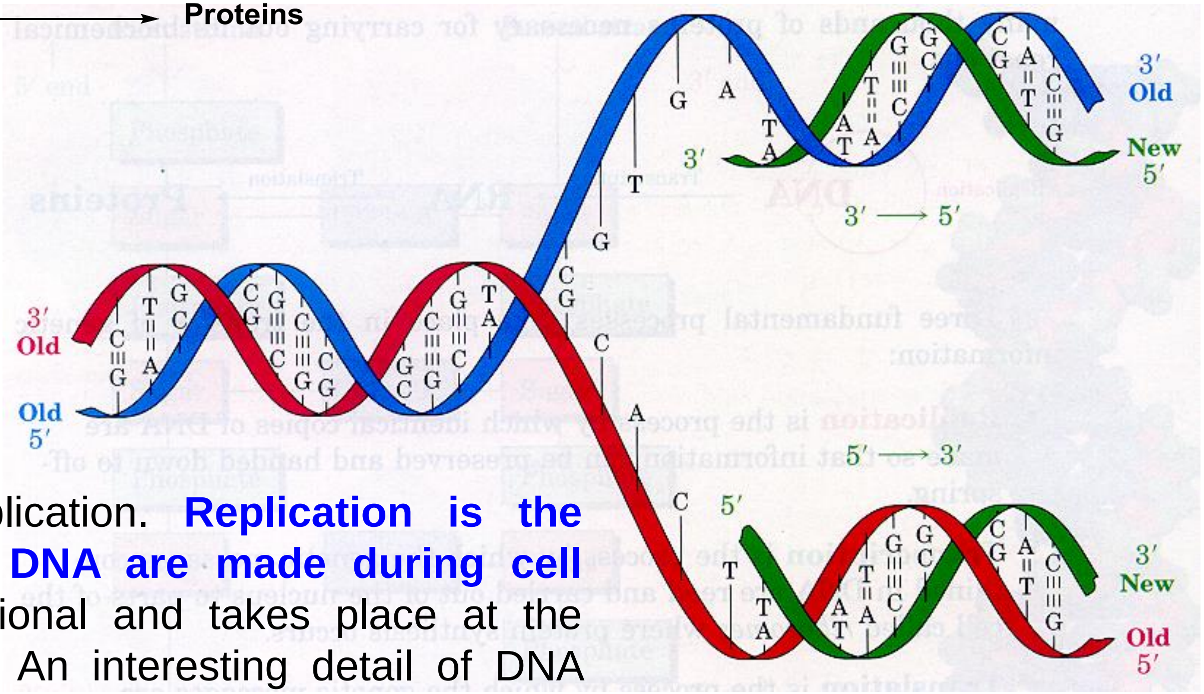
The entire heredity mechanism rests on these aligned hydrogen bonds.



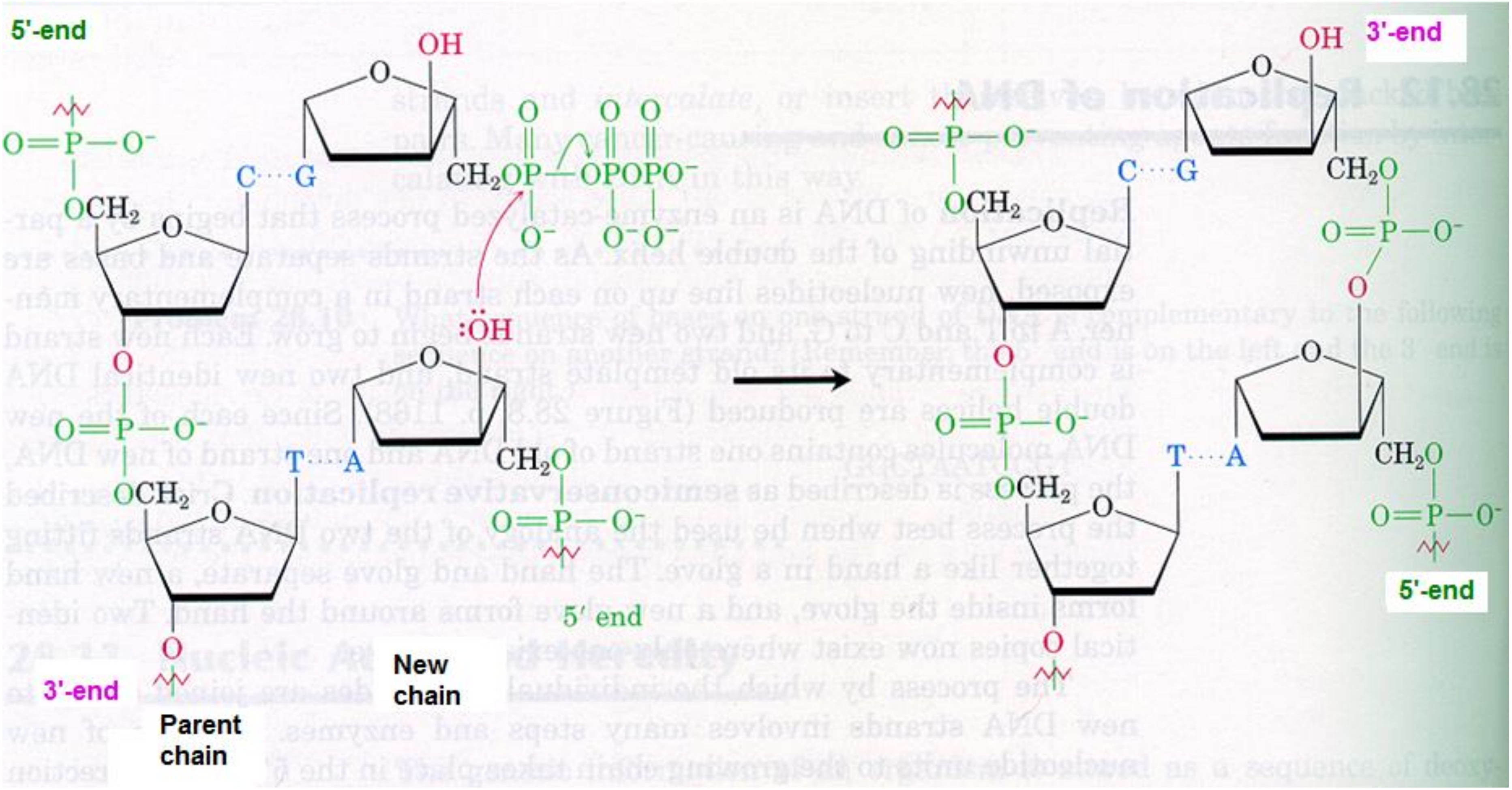
3D view of double helix of DNA

The DNA in the chromosomes carries out two functions: (1) It reproduces itself and (2) it supplies the information necessary to make all the RNA and proteins in the body, including enzymes.



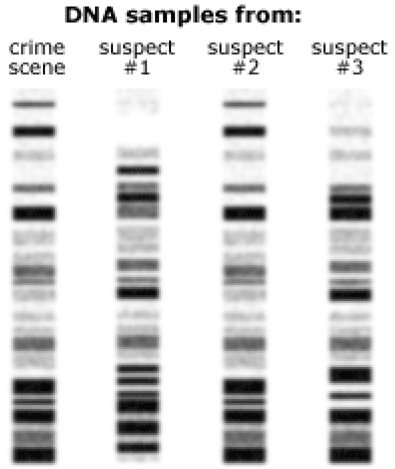


DNA reproduces itself by replication. **Replication is the process by which copies of DNA are made during cell division.** Replication is bidirectional and takes place at the same speed in both directions. An interesting detail of DNA replication is that the two daughter strands are synthesized in different ways. One of the syntheses is continuous along the 3’ to 5’ strand. It is called the **leading strand. The other strand that runs in the 5’ to 3’ direction** is called the **lagging strand.** The replication process is called **semiconservative because each daughter** molecule has one parental strand (conserved) and one newly synthesized one.

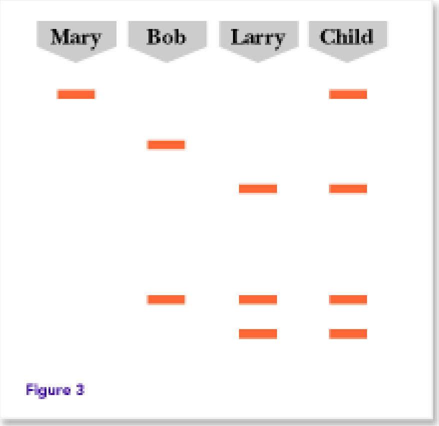


Scheme of the formation of the complementary strand of DNA.

The base sequence in the nucleus of every of our cell is identical. However, except for identical twins, the base sequence in the total DNA of one person is different from that of every other person. This makes it possible to identify suspects in criminal cases and to prove the identity of a child’s father in paternity cases.



For this purpose the nuclei of the cells are extracted. Their DNA is amplified by PCR (Polymerase Chain Reaction) techniques. Then, using the restriction enzymes the DNA molecules are cut at specific points. **The resulting DNA fragments are subjected to electrophoresis.** In this process, the DNA fragments move with different velocities; the smaller fragments move faster and the larger fragments move slower. After the sufficient amount of time, the fragments separate. The obtained sequence is called a DNA fingerprint.



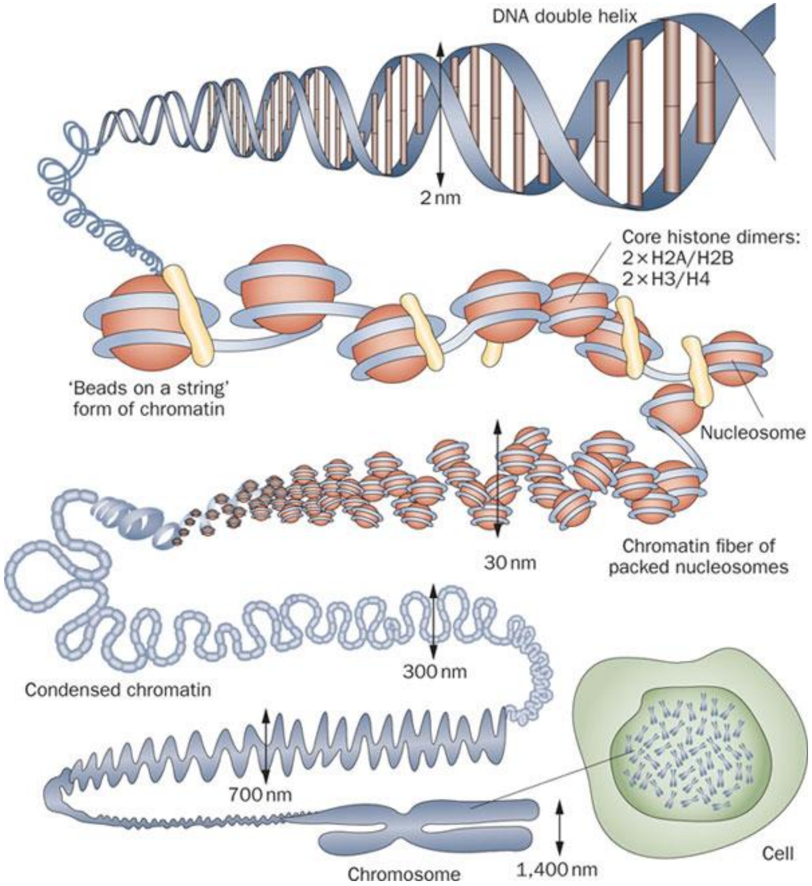
Higher order structures of DNA

If a human DNA molecule was fully stretched out, its length would be aprox. 1 m.

However, the DNA molecules in the nuclei are not stretched out, but coiled around basic proteins called **histones** to form units called **nucleosomes**. In a nucleosome, 8 histones form a core, around which DNA double helix is wound.

Nucleosomes are further condensed into **chromatin** when a 30 nm wide fiber forms with six nucleosomes forming a repeating unit.

Chromatin fibers are then organized into **loops**, and loops are arranged into **bands** to provide the superstructure of chromosomes.



Chromatin – the DNA complexed with histone and nonhistone proteins that exist in cells between cells divisions.

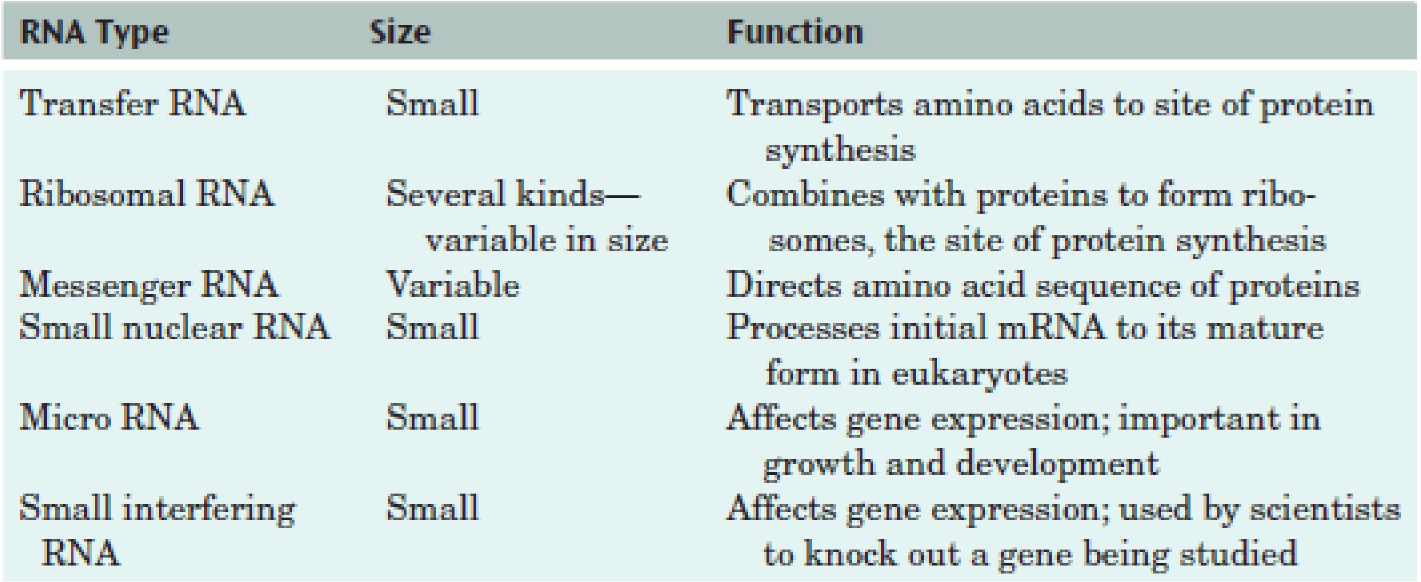
Selenoid – a coil wound in the form of helix.

Ribonucleic Acids (RNRs)

There are several kinds of RNA. **None of them has a repetitive double – stranded structure** like DNA, although base-pairing can occur within a chain. **When it does adenine pairs with uracil because thymine is not present.** Other combinations of H-bonded bases are also possible outside the confines of a double helix, and **Chargaff's roule does not apply.**

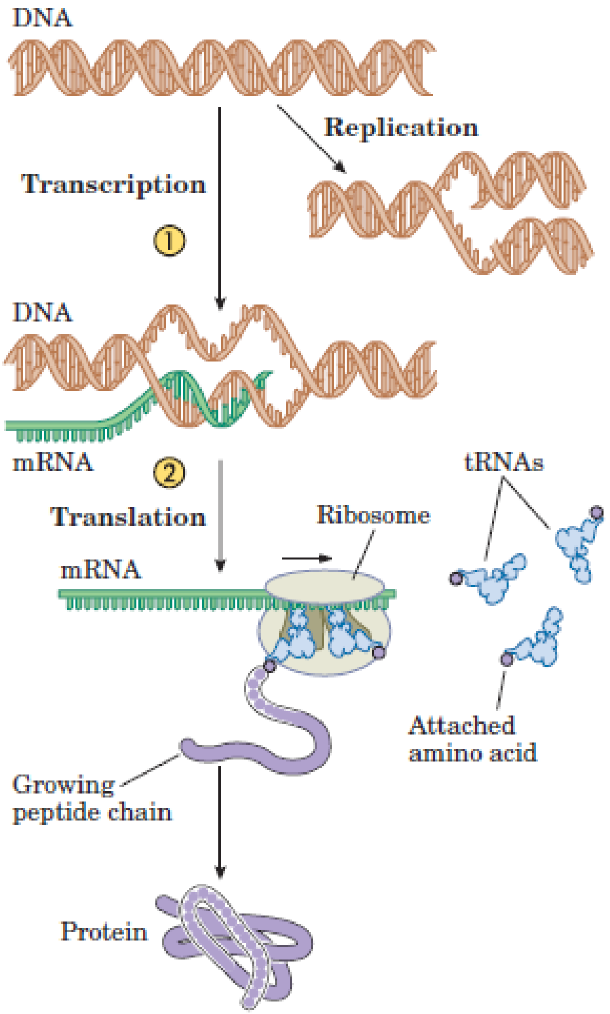
There are six types of RNA.

The roles of different kinds of RNA.



RNA Type	Size	Function
Transfer RNA	Small	Transports amino acids to site of protein synthesis
Ribosomal RNA	Several kinds—variable in size	Combines with proteins to form ribosomes, the site of protein synthesis
Messenger RNA	Variable	Directs amino acid sequence of proteins
Small nuclear RNA	Small	Processes initial mRNA to its mature form in eukaryotes
Micro RNA	Small	Affects gene expression; important in growth and development
Small interfering RNA	Small	Affects gene expression; used by scientists to knock out a gene being studied

Messenger RNA (mRNA) molecules are produced in the process called transcription and they carry the genetic information from the DNA to the cytoplasm where most of the proteins are synthesized. mRNA consists of a chain of nucleotides whose sequence is exactly complementary to that of one of the strands of the DNA. The size of mRNA varies widely, with the average unit contair

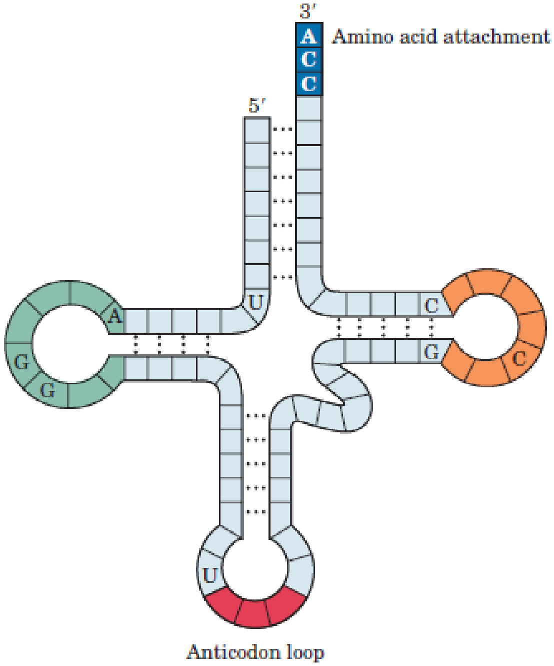


Replication
DNA replication yields two DNA molecules identical to the original one, ensuring transmission of genetic information to daughter cells with exceptional fidelity.

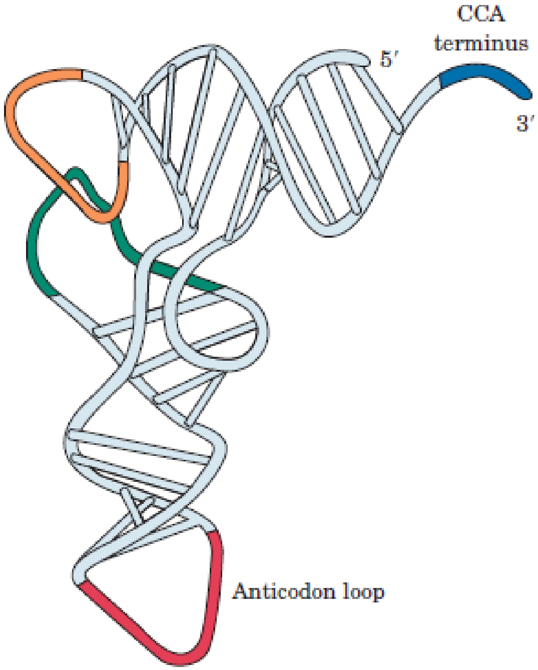
Transcription
The sequence of bases in DNA is recorded as a sequence of complementary bases in a single-stranded mRNA molecule.

Translation
Three-base codons on the mRNA corresponding to specific amino acids direct the sequence of building a protein. These codons are recognized by tRNAs (transfer RNAs) carrying the appropriate amino acids. Ribosomes are the “machinery” for protein synthesis.

Transfer RNA (tRNA) – the RNA that transports amino acids to the site of protein synthesis in ribosomes. tRNAs are relatively small molecules and contain from 73 to 93 nucleotides per chain. **There is at least one different tRNA molecule for each of the 20 amino acids.** The 3D tRNA molecule is L-shaped, but they can be represented as cloverleaf.

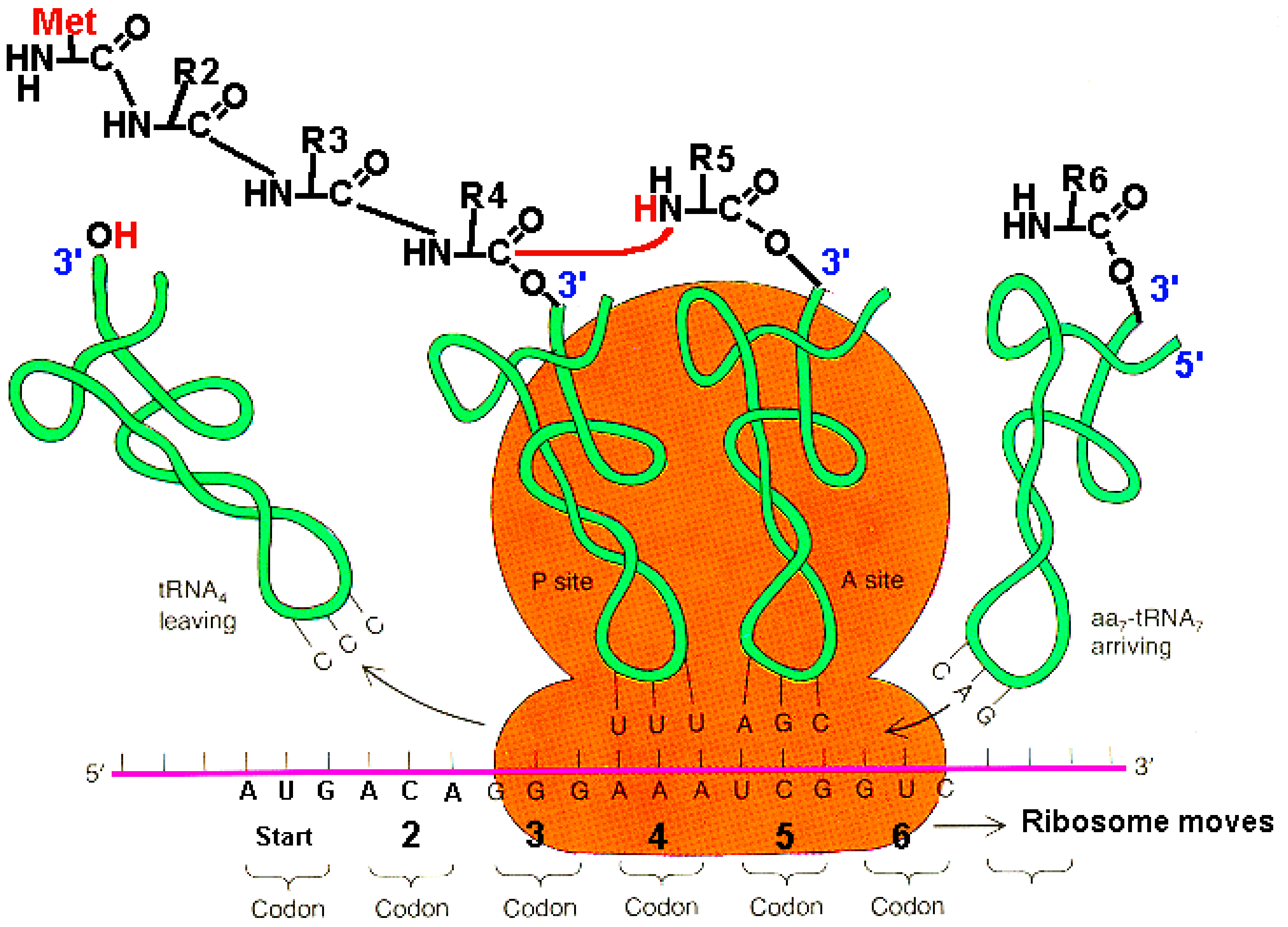


Two dimensional simplified structure of tRNA



Three dimensional structure of tRNA

Ribosomal RNA (rRNA) – the RNA complexed with proteins in ribosomes. Ribosomes consists of about 35% proteins and 65% rRNA. These molecules have molecular weights up to 1 million.



Schematic view of protein synthesis in ribosomes.

Used and Recommended Textbooks:

- **Frederick A. Bettelheim, William H. Brown, Mary K. Campbell, Shawn O. Farrell**. ***Introduction to general, organic and biochemistry***. - Cengage Learning: Belmont, 614 p.

- **Morris Hein, Leo R. Best, Scott Pattison, Susan Arena. Introduction to general, organic, and biochemistry.** – Thompson Leraning: Australia, Canada, Singapore, Spain, United Kingdom, United States, 999 p.

- **T.W. Graham Solomons, Craig B. Fryhle. *Organic Chemistry***. - Wiley: New York, 1258 p.

- **John McMurry. *Organic Chemistry***. - Thompson Learning: New York, 1284 p.