O. N. RYNEISKAYA, I. V. RAMANOUSKI

BIOORGANIC CHEMISTRY

Course of lectures

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БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА БИООРГАНИЧЕСКОЙ ХИМИИ

О. Н. РИНЕЙСКАЯ, И. В. РОМАНОВСКИЙ

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BIOORGANIC CHEMISTRY

Курс лекций

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INTRODUCTION

Bioorganic chemistry studies the structure and properties of biologically important substances. It is a young science. It appeared in its present form approximately in 1950 (nineteen fifty). This science studies the structure and properties of organic compounds which participate in the biological processes. Bioorganic chemistry is in close relationship to the biochemistry, molecular biology, physiology, pharmacology, and other disciplines. Unifying these research directions — heterofunctional natural organic matter, the underlying processes of life or influence on these processes. Therefore the aim of the study of bioorganic chemistry as an academic discipline is to develop systematic knowledge about the relationship of the structure, chemical properties and functions of biologically important class of natural and synthetic organic compounds. The physician needs to know the physicochemical properties and structure of the compounds and on their basis, especially in the distribution body and the mechanism of action of drugs, most of which are organic compounds. Most drugs are a specific chemical substance to the features of their spatial organization and chemical properties that they are able to specifically interact with specific receptors and alter the course of biochemical and physiological processes in the body.

1. CLASSIFICATION AND NOMENCLATURE OF ORGANIC COMPOUNDS

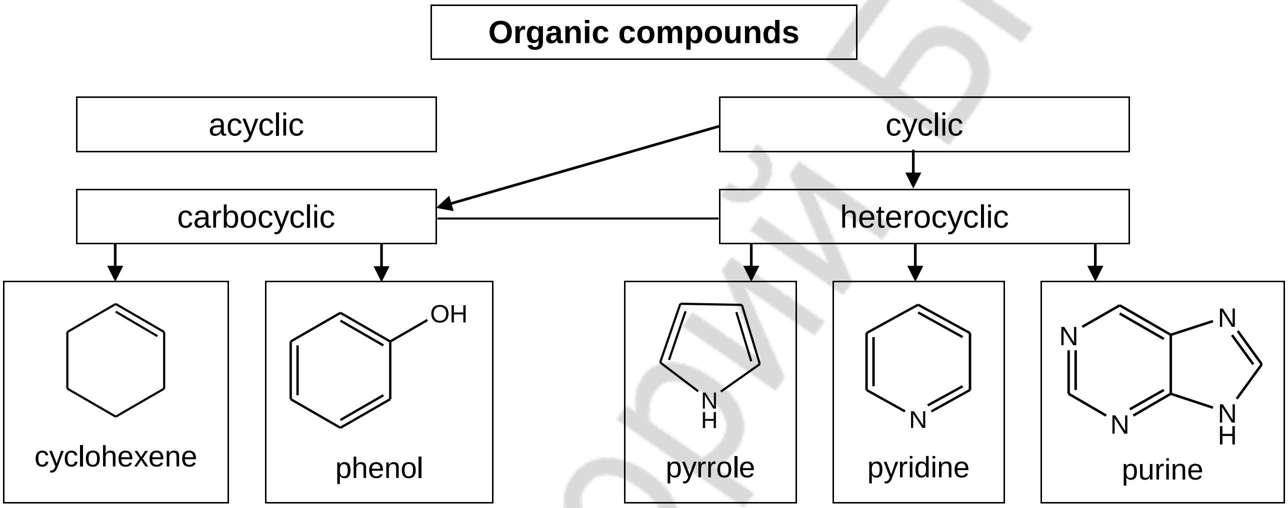
CLASSIFICATION OF ORGANIC COMPOUNDS

Currently there are more than 10 million of organic compounds. For such an amount of organic matter could be studied, it is necessary to classify them. The classification can be based on the following principles:

– the structure of the carbon chain;

– the presence of functional groups.

Classification of organic compounds according to the structure of the carbon chain:



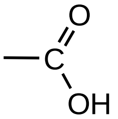
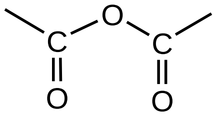
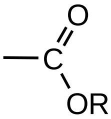
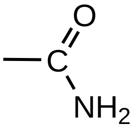
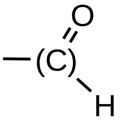
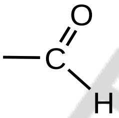
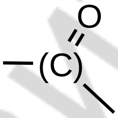
CLASSIFICATION OF ORGANIC COMPOUNDS BY FUNCTIONAL GROUPS

Functional group is atom or group of atoms, nonhydrocarbon character, which determine the chemical properties of a particular class of compounds. Organic compounds containing two or more different functional groups, called heterofunctional.

NOMENCLATURE OF ORGANIC COMPOUNDS

Nomenclature is a collection of the names of individual chemical substances, their groups and classes, as well as rules for the preparation of these names. In bioorganic chemistry still uses conditional «trivial» names of substances. The origin of these names is accidental and not related to the structure of matter. Some compounds named for the natural sources from which they are allocated, or on the basis of which the synthesized, for example, lactic acid, pyruvic acid. Trivial names do not determine the structure of matter, but they are used as a tradition, and because of what is strictly constructed systematic names are too bulky for frequent practical use.

FUNCTIONAL GROUPS AND THEIR NAMES

Class of compounds	Formula	Name in the prefix	Name in the suffix
Carboxylic acids	–(C)OOH*	–	-oic acid
		carboxy-	- carboxylic acid
Sulfonic acids	$–SO_3H$	sulfo-	-sulfonic acid
Acid anhydrides		–	-oic anhydride
Esters		R-oxycarbonyl-	-carboxylate
Amides		carbamoyl-	-carboxamide
Nitriles	–(C) ≡ N	–	-nitrile
	–C ≡ N	cyano-	-carbonitrile
Aldehydes		oxo-	-al
		formyl-	-carbaldehyde
Ketones		oxo-	-one
Alcohols, phenols	–OH	hydroxy-	-ol
Thiols	–SH	mercapto-	-thiol
Amines	$–NH_2$	amino-	-amine
Imines	=NH	imino-	-imine
Ethers	–O–	-oxy-	–
Sulfides	–S–	-thio-	–
Nitro compounds	$–NO_2$	nitro-	–
Halogen derivatives	–Cl	chloro-	–

* The carbon atom in brackets is a part of the parent structure.

Currently, the standard is the international or systematic nomenclature IUPAC (IUPAC — International Union of Pure and Applied Chemistry). In compiling the names of organic compounds by a systematic IUPAC nomenclature is used in some general concepts. Compound name may be represented as:

prefix (-es) + infix + root + primary suffix+ secondary suffix.

Root indicates the number of carbon atoms in the parent chain. The parent structure is the main carbon chain, which includes maximum number of the functional groups, radicals, and multiple bonds. The parent structure in the carbo- and heterocyclic compounds is a cycle. The roots used for the different length of carbon chain are shown in table below.

Number of carbon atoms in chain	**Root**
1	meth
2	eth
3	prop
4	but
5	pent
6	hex
7	hept
8	oct
9	non
10	dec

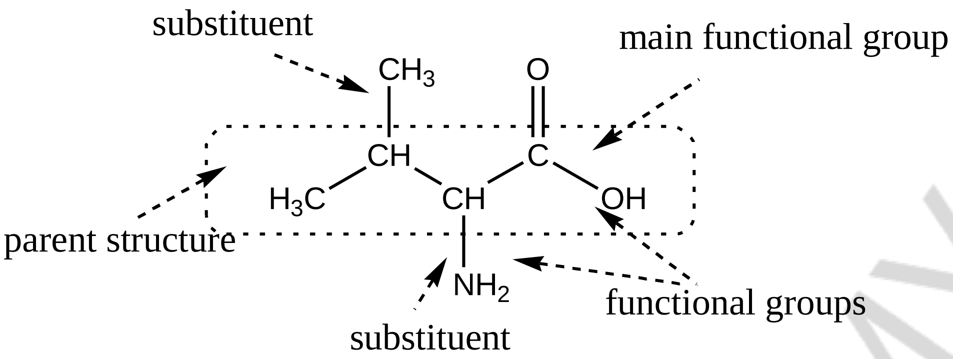
Infix is used to denote the cycle.

Primary suffix indicates the degree of unsaturation.

Saturated compound	-ane
Unsaturated compound with one C = C	-ene
Unsaturated compound with two C = C	-diene
Unsaturated compound with three C = C	-triene
Unsaturated compound with one C ≡ C	-yne

Secondary suffix indicates the main (older) functional group in the compound. Main functional group has the highest position in the table of functional groups. Since the carbon atom of this group numbering of the carbon chain begins.

Prefix is used to indicate the side chains, substituents and low priority functional groups (which are considered as substituents). **Substituent** is any atom or group of atoms that replaces a hydrogen atom of the starting compound.



Thus, it is necessary to call the compound:

1. Determine the main functional group.

2. Select a main hydrocarbon chain. For aliphatic compounds main hydrocarbon chain is selected by the following criteria: the maximum number of characteristic groups; the maximum number of double bonds; the maximum length of a chain of carbon atoms; the maximum number of substituents.

3. Numbering the parent structure so that the main functional group received the lowest number.

4. In the prefix denote substituents indicating their positions (2, 3 ...) and the number (di-, three- ...). Substituents are listed in alphabetical order.

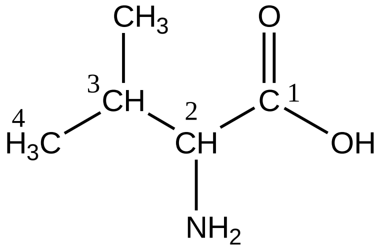
5. Name the parent structure.

6. The main functional group is designated by suffix.

Senior group - carboxylic group - **oic acid**

Parent structure - **butane**

Substituents - methyl- and amino- groups



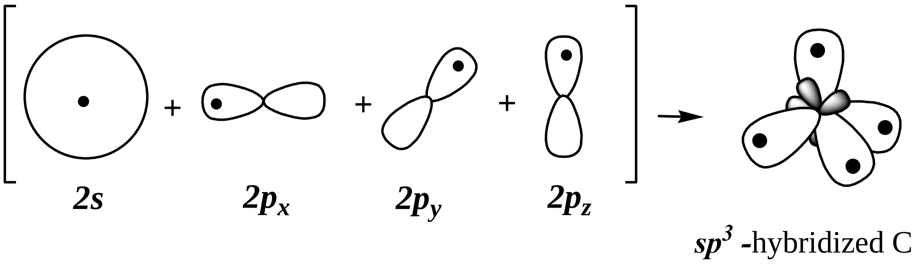
2-amino-3-methylbutanoic acid

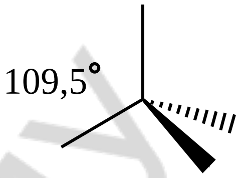
2. CHEMICAL BONDS AND MUTUAL INFLUENCE OF ATOMS IN ORGANIC COMPOUNDS

The main chemical elements of organic compounds are C, H, O. Carbon is in the second row of the periodic table and it has the following electronic configuration at the base state: $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^0$. But in the organic compounds carbon has excitated state. Excitation of one electron is the first step to hybridization. **Hybridization** is mathematical model, according to which it is aligned on the energy and shape of the atomic orbitals. Electronic configuration at the excited state: $1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1$. There are some type of hybridization: sp^3, sp^2, sp etc.

In sp^3 hybridization marked orbitals undergo equalization: $1s^2\mathbf{2s^1 2p_x^1 2p_y^1 2p_z^1}$.

1s orbital + 3p orbitals → $4sp^3$ hybridized orbitals

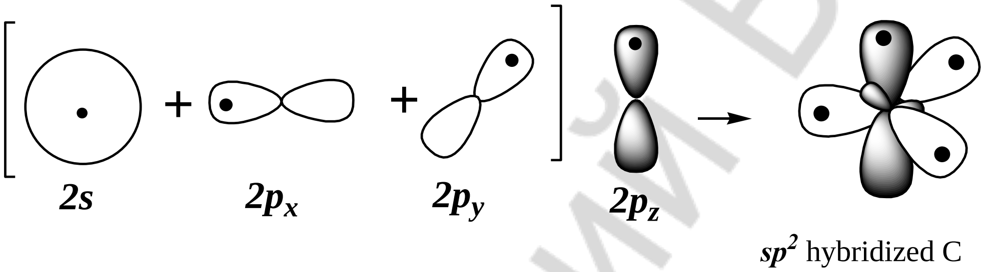




All of the angles between any two orbitals are approximately 109.5° degrees. Sp^3 hybridized carbon atom has a tetrahedral structure.

In the sp^2 hybridization marked orbitals undergo equalization: $1s^2\mathbf{2s^1 2p_x^1 2p_y^1}2p_z^1$.

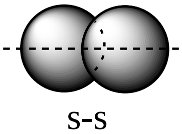
1s orbital + 2p orbitals → $3sp^2$ hybridized orbitals

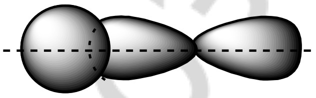


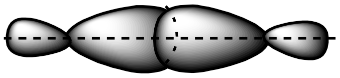
Bond angles between the hybrid orbitals are 120° degrees.

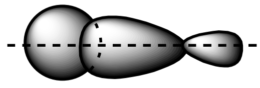
The main type of chemical bonding for organic compounds is a covalent bond, which is formed by the sharing of electrons between atoms. Although there are ionic bonds in the organic compounds. The hydrogen bonds are also important as a form of intermolecular interaction.

There are σ and π covalent bonds. **σ Bond** is a single covalent bond is formed by overlapping of atomic orbitals in a straight line connecting the nuclei of atoms with high electron density on this line.

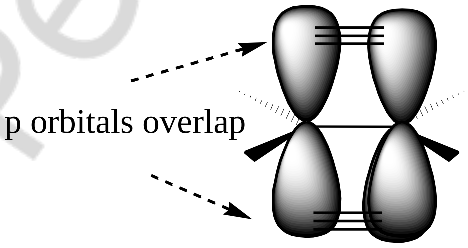

s-s

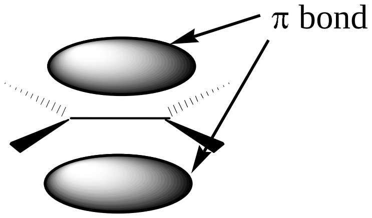

s-p


overlap of hybrid orbitals


overlap of hybrid and s orbitals

π Bonds are formed by lateral overlapping of p orbitals of sp^2 hybrid carbom with a maximum electron density above and below the plane of the σ-bonds.



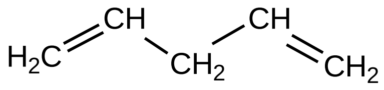


π Bond is less strong, than a σ bond and gives unsaturated compounds the possibility to enter the additition reactions. The rotation around the π bond is impossible. The combination of σ and one π bonds is a double bond, which is found in alkenes, carbonyl compounds, etc. Saturated organic compounds contain only σ bonds. Unsaturated ones may contain double or triple bonds.

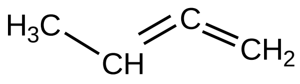
There are localized and delocalized links. Molecular orbitals of the localized bond belong to only two atoms. Molecular orbitals of delocalized bond cover more than two atoms.

CONJUGATION

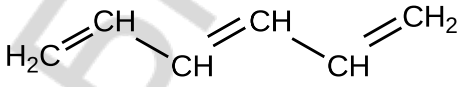
There are many organic compounds, which molecules contain more than one multiple (double or triple) bond. There are isolated, cumulated and conjugated multiple bonds.



isolated π bonds

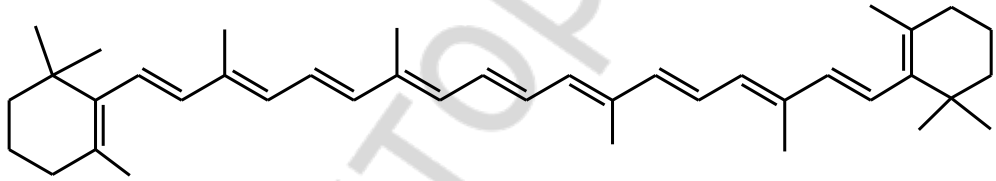


cumulated π bonds



conjugated π bonds

The most interesting are conjugated double bonds, where double and single bonds alternate in the chain. There are many unsaturated and polyunsaturated compounds with conjugated double bonds, which play an important role in nature and biology. For example, β-carotene. It is a yellow-orange pigment in carrots that contains eleven conjugated double bonds.

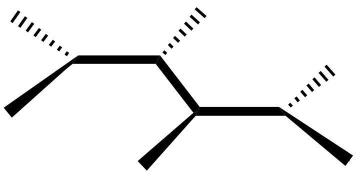


β-carotene

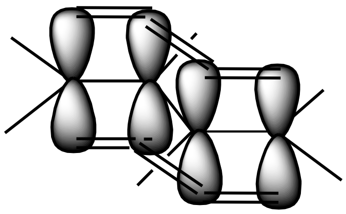
Conjugation is the formation of a single molecule in a delocalized electron cloud as a result of overlap of the nonhybridized *p* orbitals. A typical example of the conjugated system is but-1,3-diene (or 1,3-butadiene).

$$CH_2 = CH – CH = CH_2$$

All carbons in the molecule are sp^2 hybridized. It means that this molecule (σ skeleton) has a flat structure. Therefore, all *p* orbitals are parallel to each other and perpendicular to σ skeleton.



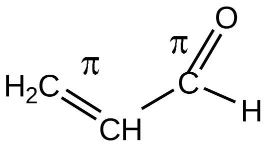
σ-skeleton of but-1,3-diene



overlapping of p orbitals of but-1,3-diene

Parallel arrangement of the *p* orbitals provides the effective orbital overlap and the delocalization of electrons. *P* orbitals of the central carbon atoms are also overlapped. Delocalization of the electron cloud leads to decreasing of orbitals energy and increased stability of the molecule.

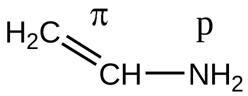
There are two types of conjugation: ***π***, ***π*** and ***π***, ***p*** conjugation. But-1,3-diene is an example of a ***π***, ***π*** conjugation. This type is characterized by alternating double and single bonds. π, π Conjugated system may include heteroatoms.



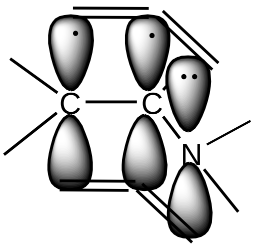
π,π conjugation

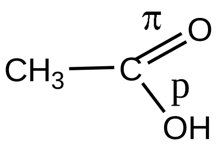
π, ***π*** **Conjugation** is the delocalization of *p* orbitals over the entire *π* system.

Another type of conjugation exists in compounds with a fragment > C = CH – X, where X is an atom possessing a lone pair of electrons. In this case three orbitals are delocalized: two *p* orbitals of the double bond and one *p* orbital of the atom X. The interaction between π bond orbitals and *p* orbital of an adjacent atom is ***p***, ***π*** **conjugation**.



π,p conjugation





π,p conjugation

ethenamine

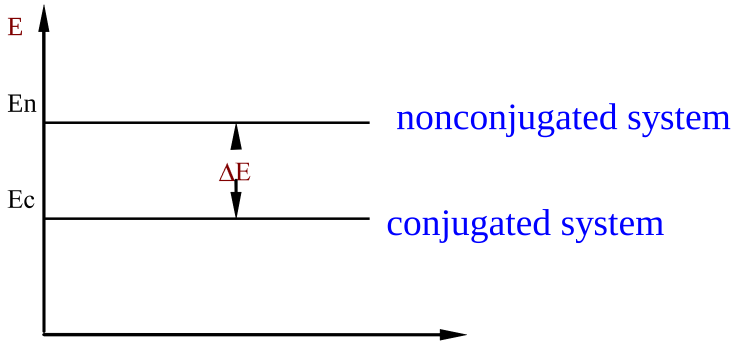
ethanoic acid

Not only molecules, but also free radicals and ions can be a conjugated system.

The conjugation is the phenomenon, which explains high stability and specific chemical properties of conjugated molecules, ions, or radicals. The concept of conjugation is useful for understanding chemical and biochemical processes.

Energy of conjugation is the value of thermodynamic stability is expressed as the difference between the complete π electron energy of the nonconjugated system (with localized double bonds) and the π electron energy of the conjugated system.

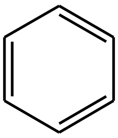
$$\mathbf{E_{conjug} = E_{nonconjug.\ \pi\ bonds} - E_{conjug.\ system}}$$



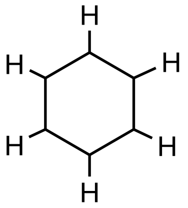
AROMATICITY OF CARBO- AND HETEROCYCLIC COMPOUNDS

Some molecules have a cyclic conjugated system and special aromatic properties. **Aromaticity** is the ability of planar ring systems with a closed system of conjugation to enter in the substitution reaction rather than addition and has a high resistance to rupture and cycle oxidation.

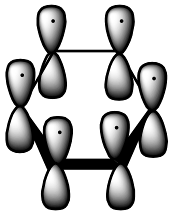
A typical example of an aromatic system is a benzene. It is a highly unsaturated compound. Physical measurements show that benzene is flat. It is symmetrical molecule with a shape of regular hexagon. Its all carbon-carbon bond lengths are 140 pm. All carbon atoms are sp^2-hybridized. Two sp^2-orbitals form σ bonds with adjacent carbons. The third sp^2-orbital of each carbon forms the C-H bond. In addition, each carbon has a *p* orbital with one electron.



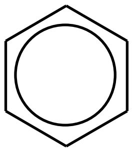
benzene



σ skeleton



p orbitals



benzene

All six *p* orbitals are perpendicular to the plane of the six-membered carbon framework. Each *p* orbital overlaps equally well with both neighboring orbitals to form a cloud of six p electrons completely delocalized around the ring. Thus, the benzene molecule represents a circular π-π-conjugated system with two doughnut-shaped clouds of electrons, one above and one below the ring. For this reason, a more satisfactory representation of the benzene molecule might be a hexagon with the inscribed circle.

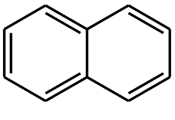
Electron delocalization results in enhanced stability of benzene. For example, conjugation energy for benzene is 151 kJ/mol. Benzene has an aromatic properties. A molecule has aromatic properties if it satisfies the following criteria:

1) all atoms are sp^2 hybridized, therefore a molecule has a planer structure;

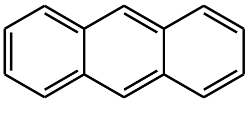
2) a molecule has a cyclic system of conjugation;

3) a cyclic system of conjugation contains $(4n + 2)$ π electrons, where *n* is an integer (0, 1, 2, 3, etc.) This is known as the Huckel’s $(4n + 2)$ rule.

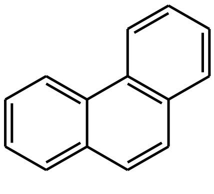
Benzene corresponds Huckel's rule for $n = 1$, that is involved in the conjugation of 6 p-electrons. Such molecules as naphthalene, anthracene, phenanthrene satisfy all the reguirements of aromaticity.



naphthaline
n=2



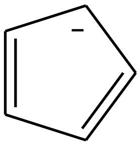
anthracene
n=3

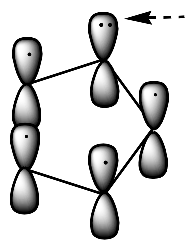


phenanthrene
n=3

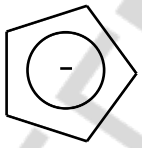
In these systems all the carbon atoms are sp^2 hybridized, hence σ skeleton has a plane structure and *p* orbitals are arranged in parallel. In the cyclic conjugation involved, respectively 10 and 14 p-electrons. Therefore, these systems, like benzene, exhibit aromatic properties.

Aromatic properties may have not only molecules but also ions, for example, a cyclopentadienyl anion and cycloheptatrienyl cation.

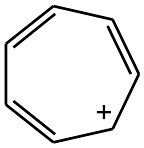


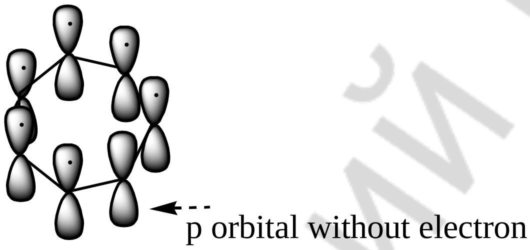


cyclopentadienyl anion

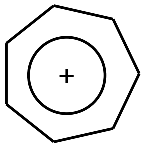


delocalization of negative charge





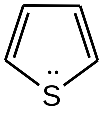
cycloheptatrienyl cation



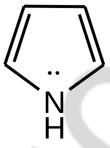
delocalization of positive charge

In the cyclic conjugation system of these ions involved 6 *p* electrons, which corresponds to the Huckel's formula. Since the conjugation is delocalization of the electron density, the correct image of the cyclopentadienyl anion and cycloheptatrienyl cation cation is one in which the charge belongs to the entire system.

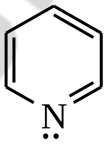
In heterocyclic molecules common *p* electron system is formed with the participation of *p* orbitals of carbon atoms and *p* orbitals of the heteroatoms.



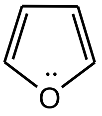
thiophene



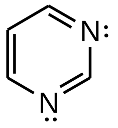
pyrrole



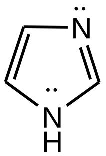
pyridine



furan

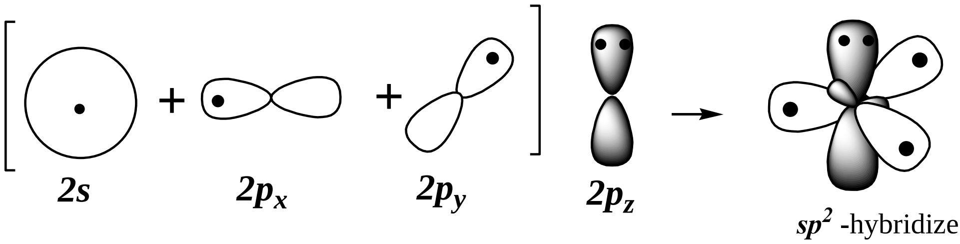


pyrimidine



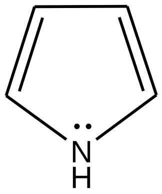
imidazole

One of the most important is the heterocycles pyrrole. All the carbons and the nitrogen atom of pyrrole are sp^2-hybridized. Pyrrole nitrogen atom has the following electronic configuration: $1s^2\mathbf{2s^1 2p_x^1 2p_y^1}2p_z^2$.

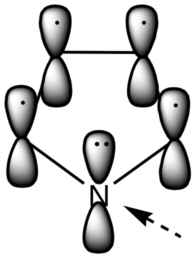


***sp*²** -hybridized pyrrole N

Aromatic system in pyrrole (as well as in thiophene and furan) is formed by five *p* orbitals: four *p* orbitals of the carbon atoms and one *p* orbital of the heteroatom on which the lone pair of electrons. Six *p* electrons form a closed system of conjugation. Hybrid orbitals of nitrogen form three σ bonds: two orbitals — with the carbon atoms and the third orbital — with hydrogen. The nitrogen lone pair of electrons interacts with unhybridized *p* orbital of carbon atoms and participaties in the formation of a delocalized electron cloud. Therefore pyrrole is an aromatic compound.

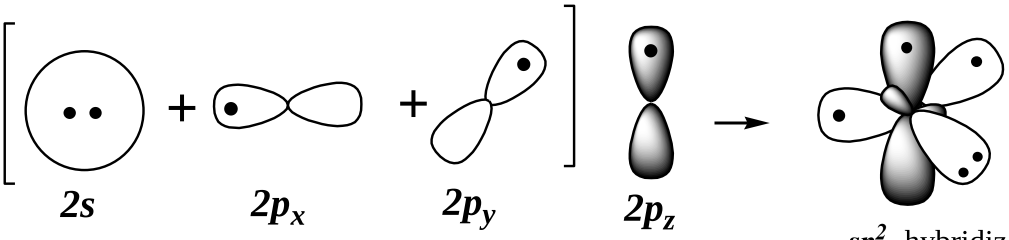


pyrrole



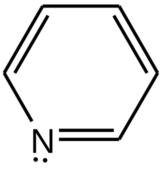
p orbital with two electrons
of pyrrole N

An example of a six-membered heterocyclic compounds are pyridine. Aromatic system in pyridine is formed with the participation of five *p* orbitals of carbon atoms and one *p* orbital of the nitrogen atom containing one electron. Pyridine nitrogen atom has the following electronic configuration: $1s^2\mathbf{2s^2 2p_x^1 2p_y^1}2p_z^1$. Nitrogen is sp^2 hybridized.

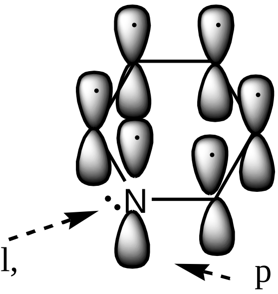


sp^2 -hybridized
pyridine N

The two hybrid orbitals of nitrogen form two σ bonds. The remaining hybrid orbital of nitrogen possesses an unshared electron pair and does not form a bond.



pyridine

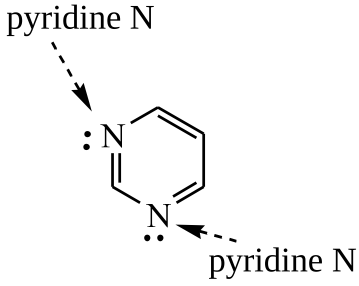


a pair of electrons
at the sp^2 hybrid orbital,
it does not participate
in the cyclic conjugation

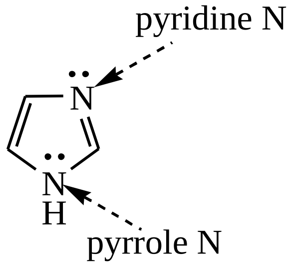
p orbital with one electron
of pyridine N

The unhybridised *p* orbital of nitrogen (with one electron) is perpendicular to the plane of the ring and overlaps the p orbitals of carbons to form an aromatic cloud, containing six *p* electrons. Thus, pyridine satisfies all criteria of aromaticity.

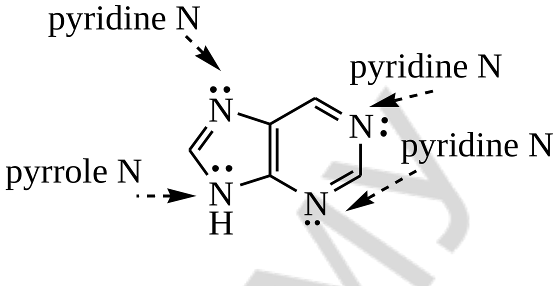
Pyrrole and pyridine nitrogens are found in the structure of many biologically important compounds.



pyrimidine

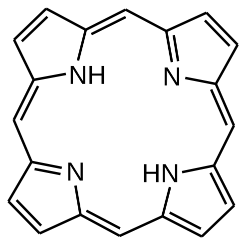


imidazole



purine

Stable aromatic ring of the pyrimidine is the part of the nucleic acid bases — uracil, thymine and cytosine. Imidazole cycle is contained in the amino acid histidine, biogenic amines histamine and other compounds. The most important heterocyclic system is the purine. It is part of the purine nucleic acid bases — adenine and guanine. Purine nucleus consists of fused ring pyrimidine and imidazole and contains three pyridine nitrogen atom and a pyrrole. They form π-π-π-π-p conjugated system, which includes 10 *p* electrons and satisfies Hückel rule for n = 2.



porphine

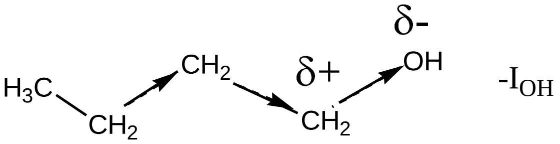
Four pyrrole nuclei form porphine. This is a planar aromatic system (26 p electrons involves in conjugation), charactarized by highly stablity. Porphine structure is part of hemoglobin and chlorophyll, which constitutes, respectively, the complex ions Fe^{2+} and Mg^{2+}.

ELECTRONIC EFFECTS

A nonpolar covalent bond is formed by atoms of the same electronegativity. A polar covalent bond is formed by two atoms of different electronegativity. The presence of a polar σ or π bond in an organic molecule results in polarization of neighbouring atoms. In the molecules containing atoms of more high electronegativity the electron density of the chemical bonds is not evenly distributed, that leads to polarization of covalent bond and the appearance of partial charges, designated δ.

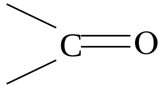
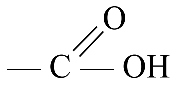
The inductive effect is the shifting of electrons in a bond in response to electronegativity of nearby atoms. Inductive effect is designated by the letter I.

There are an electron withdrawing and electron donating (electron releasing) inductive effect. An electron withdrawing or negative inductive effect is designated as –I. An electron donating or positive inductive effect is designated as +I. In the first case electron density at the nearby atom is decreased, in the second case it is increased. Inductive effect of hydrogen is equal to zero. The effect of a substituent is the strongest on the neighbouring atom and decreasing along the carbon chain. As a rule, it does not act within three or four links. Thus, the inductive effect is fading. Graphically, the inductive effect is represented with an arrow, which coincides with the σ bond and its tip is directed to the more electronegative atom. For example, the oxygen of the hydroxyl group of butan-1-ol has a negative inductive effect, it shifts the electron density to itself, acquires a partial negative charge. An adjacent carbon atom acquires a partial positive charge.

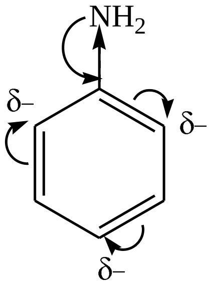


A more significant electronic effect is observed in molecules with conjugated fragments. In such case the polarization effect of a substituent extends through the entire system of conjugation. **Mesomeric (or resonance) effect** is the shifting of electron density caused by a substituent in conjugated system. The mesomeric effect is symbolized by the letter *M*. There are an electron donating (designated +*M*) and electron-withdrawing (designated –*M*) effect. The –*M* effect of the functional group leads to decreased electron density on the all carbons of the remaining part of the molecule (as compare with unsubstituted compounds such as ethene and benzene). The positive mesomeric effect is observed in the most of p, π conjugated systems. In such a case a substituent with a lone pair of electrons donates electrons to the neighbouring benzene ring or a π bond.

ELECTRONIC EFFECTS OF THE SUBSTITUENTS

Substituent	I-effect	M-effect	Correlation	Character
Alkyls	+I	no M	–	electron donor
NH_2	–I	+M	+M > –I	electron donor
–OH, –SH	–I	+M	+M > –I	electron donor
– O – R	–I	+M	+M > –I	electron donor
Halogens	–I	+M	–I > +M	withdrawer
	–I	–M	–I, –M	withdrawer
	–I	–M	–I, –M	withdrawer
– SO_3H	–I	–M	–I, –M	withdrawer
– NO_2	–I	–M	–I, –M	withdrawer

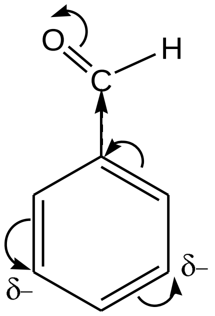
Consider the distribution of the electron density in the molecule in the phenylamine molecule. An amine group has a negative inductive effect. Since phenylamine represents a conjugated system an amine group possesses mesomeric effect. And since a nitrogen atom has a lone pair of electrons, an amine group possesses a positive mesomeric effect. Thus an amine group donates electrons to the neighbouring benzene ring.



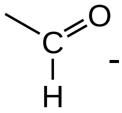
-I +M +M > -I

NH_2 - electron donor

In contrast an aldehyde group in the benzaldehyde withdraws the electron density from the benzene ring to itself. The third and the fifth carbon atoms aquire a partial negative charge.



-I -M



- elecron withdrawer

Thus, the mesomeric effect of a substituent can only be observed in the conjugated systems.

The electron density distribution determines the reactivity of the compound and its reaction centers.

3. SPATIAL STRUCTURE OF THE ORGANIC MOLECULES

The science that studies the spatial structure of organic compounds called stereochemistry. **Stereoisomers** is the isomers that differ arrangement of their atoms in space. Stereoisomers are divided into **conformational** and **configurational** ones.

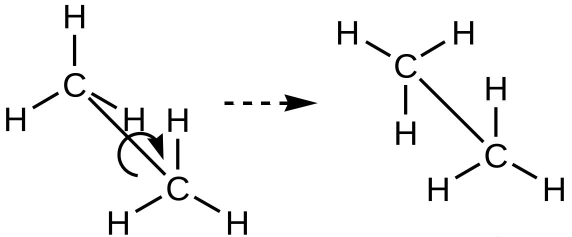
CONFORMATIONAL ISOMERS

The different spatial orientations of the atoms of a molecule that result from rotation about single bonds are called **conformations**. The conformations have different potential energy.

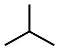
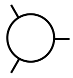
Interconversion of conformations are carried out without breaking σ bonds. Rotation angle σ bond is called torsion angle. For the minimum reading of torsion angle take 60°, therefore arise from a variety of conformations is taken into account only six. Relatively high internal energy usually have a conformation in which the substituents are in the most close to each other. Thise is called the **eclipsed** conformation. Conformation, in which the substituents are farthest from each other in space, have a relatively lower internal energy, called **staggered** or **anti**.

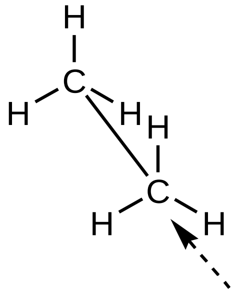
CH_3 - CH_3

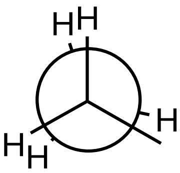
ethane



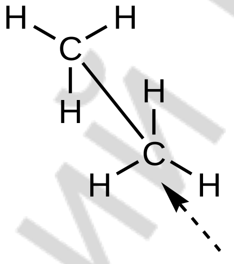
eclipsed anti

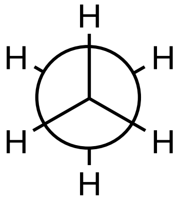
A Newman projection can be used to represent the conformation of the plane with clarity and detail. Molecule is arranged so that the observer view coincides with a σ bond around which rotation is performed. The closest to the observer carbon atom designated with point and three lines — . Rear carbon atom is designated with circle and dashes — . The hydrogen atoms may be omitted.





eclipsed

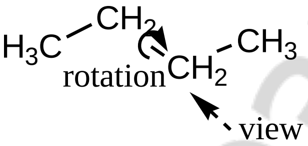


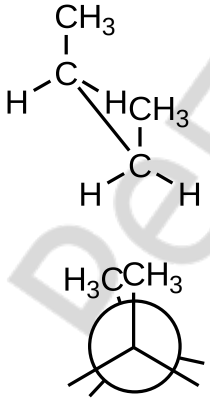


anti

More complex molecules have a greater number of conformations that differ in energy. For example, butane. Consider butane conformation resulting in rotation about the C2–C3 bond.

butane





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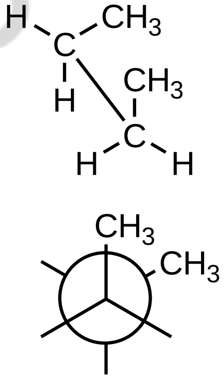
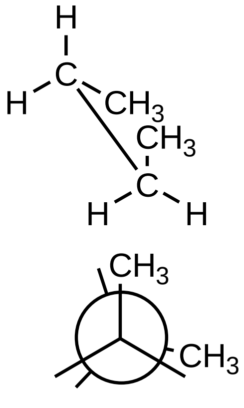
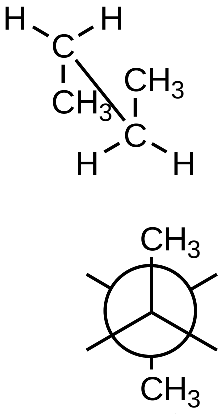


gauche



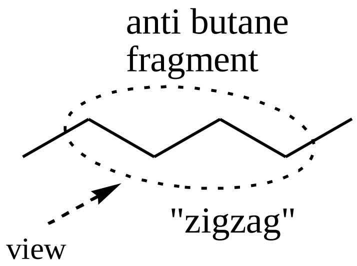
eclipsed



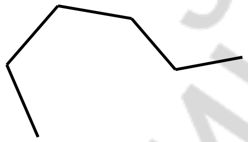
anti

Eclipsed conformations are formed by the torsion angles of 0° and 120°. Gauche and anti conformations are respectively by the torsion angles of 60° and 180°. Stability of conformations depends on several factors: the torsion and van der Waals strains. **Torsional strain** is caused by the repulsion of the electron clouds of nearby σ bonds. **van der Waals strain** is caused by the repulse of the electron clouds of large atomic groups. Anti conformation is characterized by minimal torsional strain and van der Waals minimum strain, it is stable. Most of the compounds exist mainly in the anti conformation. Eclipsed conformation is characterized by high torsional strain, it is unstable.

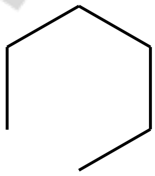
In the long carbon chains may rotate around a few C–C bonds. Therefore, the entire chain can take a variety of geometric shapes. Long-chain of saturated hydrocarbons are mainly in «zigzag» conformation in which the carbon atoms in each butane fragment are relative to each other in the staggered (anti) conformation.



"zigzag"



irregular

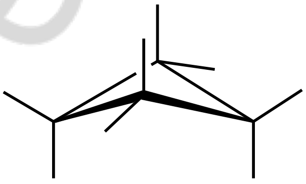


claw conformation

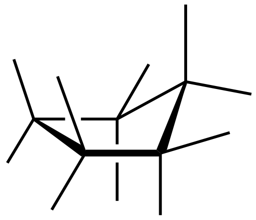
In the claw conformation carbon atoms distant from each other approach each other in space and may interact. For example, in the acyclic form of glucose aldehyde and the hydroxyl group of the 4th or 5th carbon atom interact with each other.

In the cyclic compounds may be present **angular strain.** Strain caused by the deviation of the normal value of bond angles between carbon atoms in the cycle called the **angular**.

Cyclopropane is a unique flat cycle. Large angular strain explains its instability. The chemical conformation of cyclobutane is not planar. It is also known as a «butterfly». Tense four-membered ring with the nitrogen found in the antibiotics of penicillin group. Cyclopentane has a non-planar conformation of the «envelope». In this conformation one of the carbon atoms moves off the plane in which are located the remaining four atoms. In such a conformation of five-membered ring is stable. Ribose and deoxyribose in RNA and DNA have such conformation.

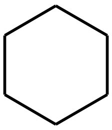


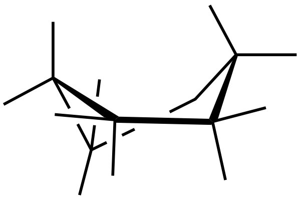
cyclobutane
butterfly conformation

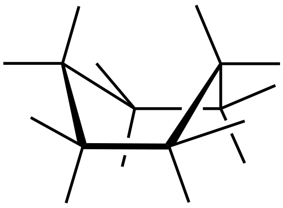


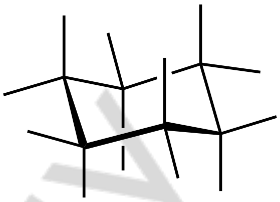
cyclopentane
envelope conformation

Different conformations are possible for the six-membered ring: twist, boat and chair. Boat conformation and chair conformation are free from angular strain.

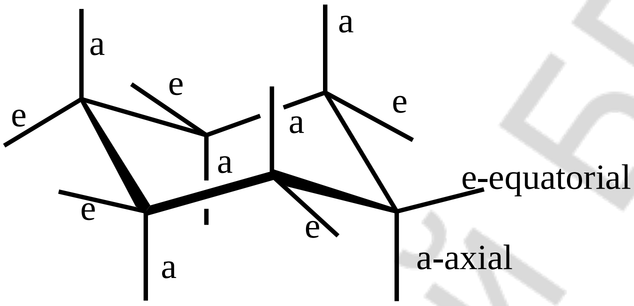

cyclohexane


twist conformation


boat conformation

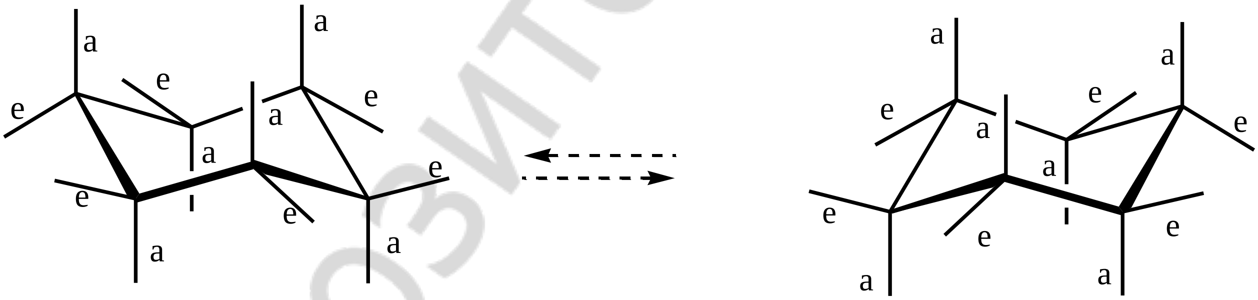

chair conformation

More thermodynamically favorable conformation is the chair, as it has no torsion and Van der Waals strain.



chair conformation

Six C-H bonds are located parallel to the axis of symmetry of the conformation and directed alternately upwards and downwards, called **axial** (a). The remaining six C–H bonds are angled 109°, they are called **equatorial** (e). This leads to the fact that ethane fragments have anti conformation and butane fragments have gauche one. Cyclohexane can have two energetically equally chair conformation.

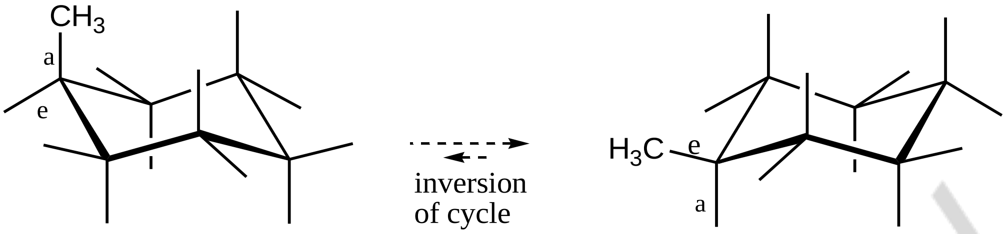


chair conformation

chair conformation

During their transition all axial substituents are converted to equatorial substituents, and all equatorial substituents become axial. This process is called **inversion of cycle**. Inversion is carried out quickly and cyclohexane is usually a mixture of the two conformations of the chair with the same energy.

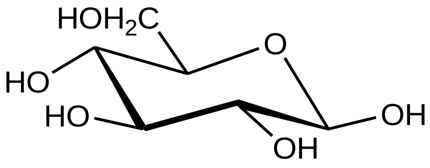
Axial hydrogens almost do not interact with each other. More bulky groups, however, can interact strongly with other axial substituents, making it energetically unfavorable for these groups to occupy axial positions. That is why in the substituted cyclohexane large groups tend to occupy the equatorial position. For example, more stable conformation of methylcyclohexane is a chair conformation with an equatorial arrangement of the methyl group.



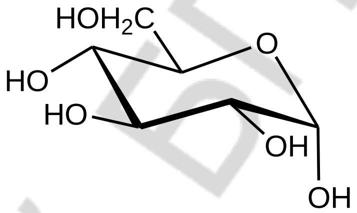
chair conformation
of methylcyclohexane

more stable
chair conformation
of methylcyclohexane

Six-membered rings are part of the monosaccharides, cholesterol, steroid hormones and other biologically active compounds.



β-D-glucopyranose



α-D-glucopyranose

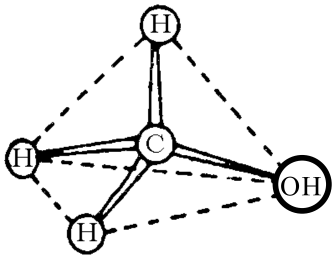
The most stable conformation of glucose is the chair conformation of the β-D-glucopyranose in which all the bulky substituents (OH, CH_2OH) are in the equatorial position. This form is widely represented in nature.

CONFIGURATIONAL ISOMERS

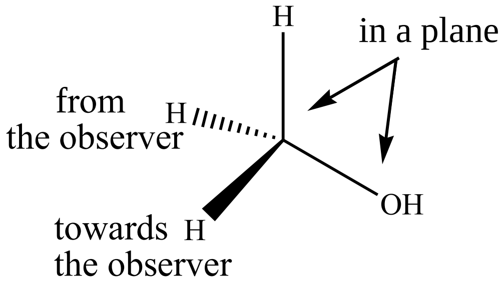
Configuration is a specific spatial arrangement of atoms in the molecule, excluding differences resulting due to rotation about single bonds.

Fundamentals of stereoisomerism laid by van't Hoff, who in 1874 formulated the idea that the carbon atom in the sp^3 hybridized state has a tetrahedral configuration. To show a tetrahedral configuration of carbon atom on the plane the stereochemical formulas are used. For their illustration the tetrahedral model is oriented in the special way: the carbon atom with its two bonds is arranged in the plane, and then the 3rd bond is arranged in the front of the projection plane, and the 4th is behind the plane. The hydrogens are then located in the surrounding space by wedge with its basis directed towards the viewer (in front of the plane) and hatched (behind the plane) bonds.

CH_3OH methanol



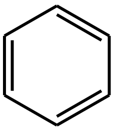
tetrahedral configuration
of carbon atom

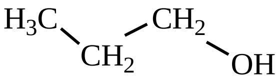


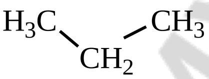
stereochemical formula of methanol

THE CONCEPT OF CHIRALITY. CHIRAL MOLECULES

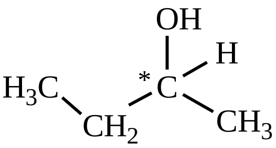
Any molecule can be characterized in terms of presence or absence of symmetry elements. A large number of molecules are highly symmetrical: for example, represented in figure benzene, propanol-1, propane.

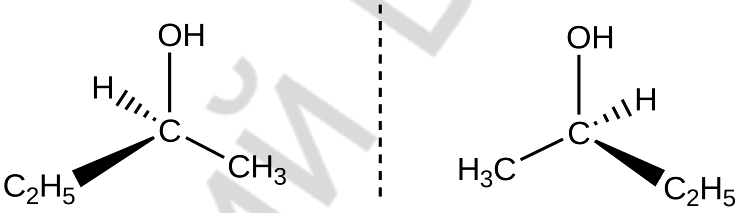

benzene


propan-1-ol


propane

However, many biologically important compounds do not have elements of symmetry and are **asymmetric**. Such molecules are called **chiral**. They have at least one **chiral** carbon atom is sp^3 hybrid carbon atom that is bonded to four different substituents. Asymetric (or chiral) carbon is designated with asterisk (*).


butan-2-ol

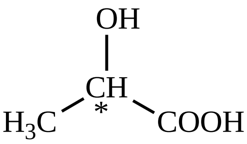

two stereoisomers of the butan-2-ol

Chiral molecules exist in the form of two stereoisomers that are related to each other as a subject and incompatible with it the mirror image. Any object which cannot be superimposed on its mirror image is **chiral**. If it can be superimposed on its mirror image it is **achiral**.

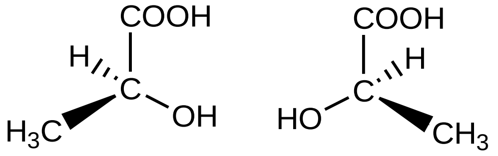
Chiral molecules possess the property of rotating the plane of polarised light when it is passed through a solution containing the substance. This property is called **optical activity**. The angle of rotation is measured in a device known as a polarimeter. Some chiral substances rotate the plane of polarisation to the right (clockwise), that is they are dextrorotatory (+). Others rotate the plane to the left (anticlockwise), and are called levorotatory (–).

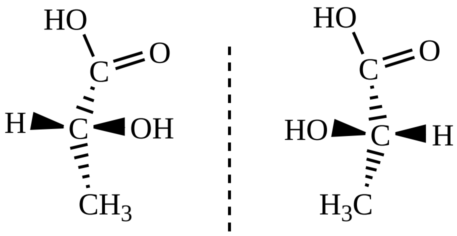
Stereoisomers which are related to each other as mirror images are called **enantiomers**. They possess identical chemical and physical properties in achiral surroundings, except for a sign of optical rotation. One enantiomer rotates the plane of polarized light clockwise, and the second type — anti-clockwise by the same angle.

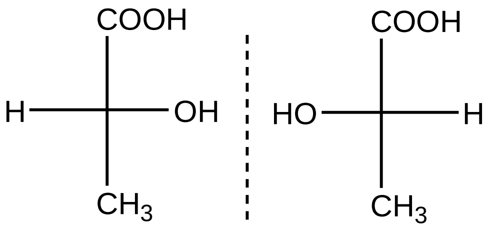
There are three forms of lactic acid in nature: dextrorotatory, levorotatory and optical inactivity. Lactic acid has chiral carbon atom. That is why, it has two stereoisomers.



lactic acid







Fischer formulas of lactic acid

To represent the structure of various enantiomers Fisher formulas are used. To write Fisher projections it's necessary to conform the following rules:

1) carbon chain is arranged vertically;

2) the «top» and «bottom» groups are oriented back, away from the plane;

3) the highest priority group is placed in the «top» position;

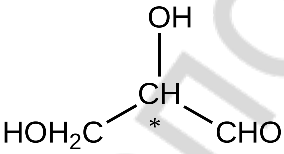
4) the «right» and «left» groups are placed in front of the plane;

5) all bonds are drawn as simple lines;

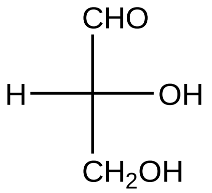
6) the central carbon is always omitted.

The number of stereoisomers depending on the number of chiral centers and is determined by the formula: $N = 2^n$, where N — number of stereoisomers, n — the number of chiral centers.

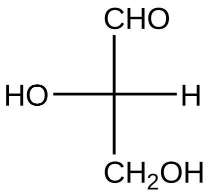
Relative D, L nomenclature is used for the name of the stereoisomers. Configuration of the molecule is compared with the configuration of glutaraldehyde (2,3-dihydroxypropanal). Glyceraldehyde contains a chiral center, it exists as two stereoisomers having different optical activity. Dextrorotatory (+) glyceraldehyde was attributed to D-configuration, that is the OH group in the projection formula at the chiral center is located on the right (dextra) side, levorotatory — L-configuration (laevus).



glyceraldehyde

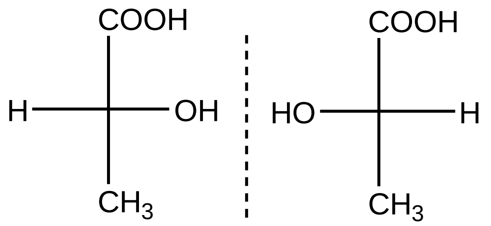


D-(+)-glyceraldehyde



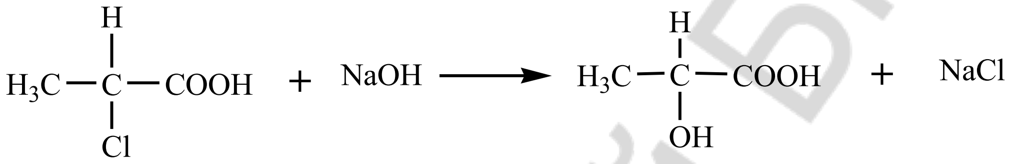
L-(+)-glyceraldehyde

Thus one stereoisomer of lactic acid is called D-lactic acid, other — L-lactic acid. Natural L-lactic acid is dextrorotatory and natural D-lactic acid is levorotatory. A mixture of equal amounts of enantiomers of lactic acid has no an optical activity.



D-lactic acid L-lactic acid

An equimolar mixture of enantiomers (means equal concentrations of both enantiomers) is known as a **racemic mixture** which doesn’t possess optical activity. Racemic mixtures are formed, generally in chemical syntheses without special conditions. For example, a racemic D, L-lactic acid is produced from 2-chloro-propanoic acid with aqueous NaOH.



$$\mathrm{H_3C-\underset{Cl}{\overset{H}{C}}-COOH} + \mathrm{NaOH} \longrightarrow \mathrm{H_3C-\underset{OH}{\overset{H}{C}}-COOH} + \mathrm{NaCl}$$

(+,-) lactic acid

During the anaerobic glycolysis in the body only L-lactic acid is produced from D-glucose, as the process goes involving enzymes.

Chemical synthesis of drugs often ends stage separation of a racemic mixture into its enantiomers to select only one of the possible biologically important stereoisomer. Mechanical, microbiological, enzyme, chemical and other methods can be used for the separation of racemic mixtures.

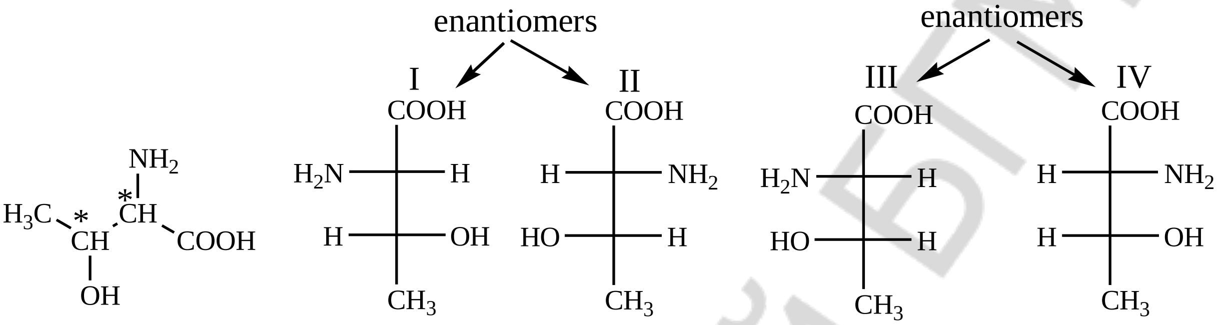
Mechanical method. This method was used in 1848 by Louis Pasteur separated into optically active components of the sodium-ammonium salt of tartaric acid. The essence of this method lies in the fact that at a certain temperature components of a racemic mixture crystallize in the form of crystals, mirror distinguished by their structure. Using a magnifying glass or microscope, they can be mechanically separated from each other. Then the crystals were dissolved separately and determine their optical activity. Currently, this method is not used and it has a historical importance.

Microbiological method. If the nutrient medium for microorganisms is cultivated racemic mixture, then growing the microorganisms absorb from it only one of the enantiomers. Second enantiomer remains in the nutrient medium.

Chemical method is the separation of racemic mixtures is based on the conversion of the enantiomers to diastereomers, which differ not only in the sign of optical rotation, but also other physical properties (solubility, boiling point, melting point, and so on). Using differences in these properties they are separated.

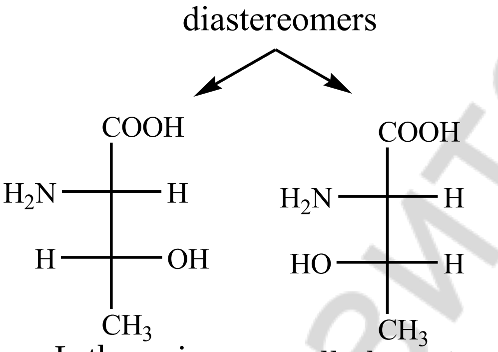
Other modern methods should allocate **affinity chromatography**. Affinity chromatography is based on the ability of biologically active compounds to interact only with specific substance mixture and form noncovalent complexes with them. Thus, in the biochemical practice when passing the racemic mixture through a chromatographic column with a chiral sorbent secrete proteins (enzymes, immunoglobulins, receptor proteins).

The presence in the molecule of two centers of chirality presupposes the existence four stereoisomers. Consider as an example 2-amino-3-hydroxybutanoic acid (proteinogenic acid threonine). Stereochemical attitude to at the hydroxy number of amino acids and is estimated on the configuration of the uppermost chiral center. L-Threonine, D-threonine, and L-allothreonine and D-allothreonine are enantiomers. From these stereoisomers, only L-threonine is a part of the proteins of the human body.

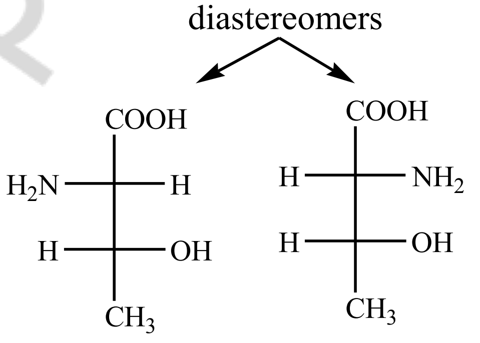


threonine L-threonine D-threonine L-allothreonine D-allothreonine

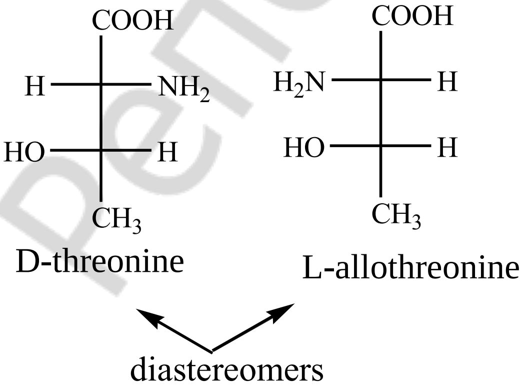
At the same time, the pairs L-threonine and D-allothreonine, L-threonine and L-allothreonine, D-threonine and D-allothreonine, D-threonine and L-allothreonine are not mirror images of each other and are **diastereomers**.



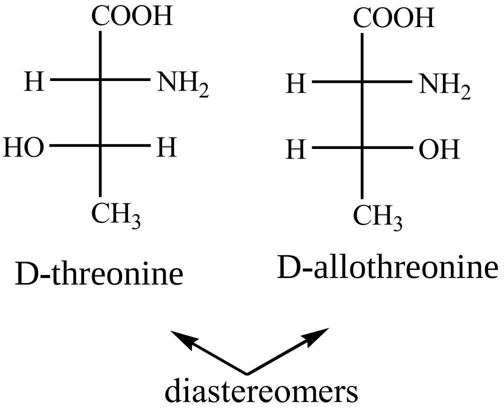
L-threonine L-allothreonine



L-threonine D-allothreonine



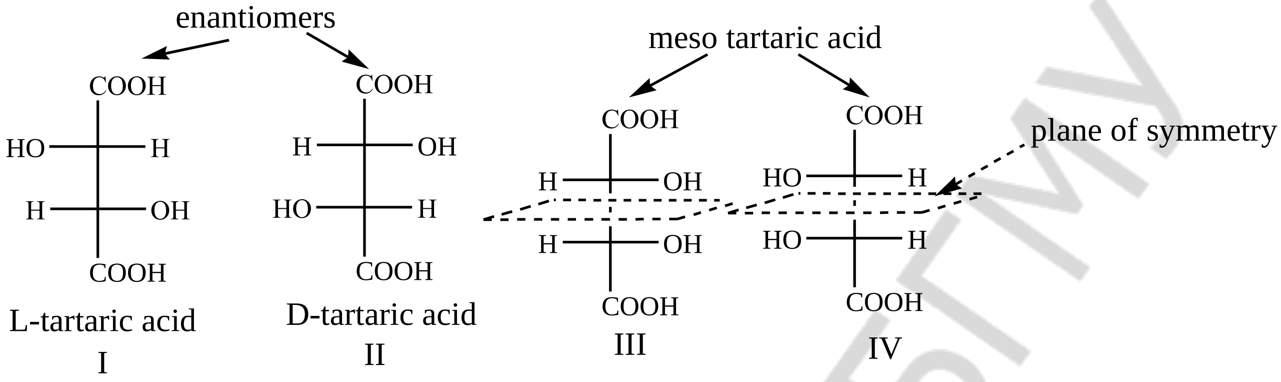
D-threonine L-allothreonine



D-threonine D-allothreonine

These diastereomers called σ diastereomers. Diastereomers, unlike enantiomers, have different physical and chemical properties.

Tartaric acid (2,3-dihydroxybutanedioic) contains two chiral centers and should have four stereoisomers.



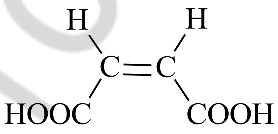
L-tartaric acid I D-tartaric acid II III IV

In fact, tartaric acid has three stereoisomers: L-tartaric acid, D-tartaric acid and achiral meso tartaric acid. The third and fourth structures are identical, as they have a plane of symmetry. They coincide with the projection of formula permitted rotation of one of them on the plane of the paper in 180° and correspond to the same compound — meso tartaric acid. Therefore, meso tartaric acid is an achiral and it has no optical activity. Pairs of isomers I and III, II and III are σ diastereomers.

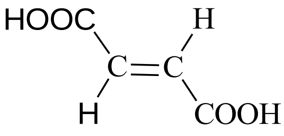
There are σ and π (*cis-trans*) diastereomers. Butenedioic acid has two stereoisomers. Only the *trans* isomer, fumaric acid, is involved in the biological processes.

$HOOC{-}CH{=}CH{-}COOH$

butenedioic acid



maleic acid



fumaric acid

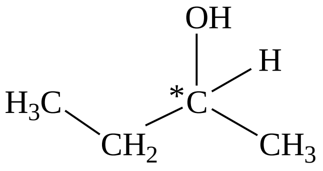
Unsaturated 9-octadecenic acid exists as *cis*-isomer (oleic acid, point of melting at 14°) and *tran*s-isomer (elaidic acid, point of melting at 52°). Oleic acid is a part of biological memdrane lipids.

Currently **R,S convention** is widely used to describe the structure of stereoisomers of amino acids, hydroxyl acids etc. To depict stereoisomer according to the system is necessary to perform certain rules. The rules are the following:

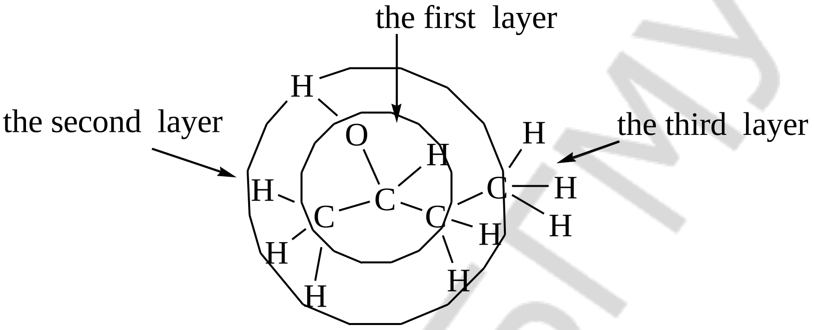
1. To refer to the configuration at the asymmetric carbon atom substituents are considered the sequence of decrease of seniority determing by atomic number in the periodic system. In case, when substituents are the same, compare the atomic numbers of the second atoms in each substituent, then the third, etc., until a difference is found. Multiple bonds count twice (or three times) when examining substituents.
2. Once the priorities have been assigned, rotate the molecule in space so that the lowest priority group is pointing back.

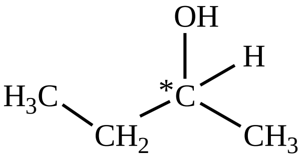
3. Connect the three remaining groups in order of decreasing priority and examine the direction of the resulting rotation. Rotation, which is clockwise, is termed R (rectus; right) and rotation, which is counterclockwise, is termed S (sinister; left).

For example, butanol-2 has the following sequence of seniority decreasing of substituents: OH > C_2H_5 > CH_3 > H.

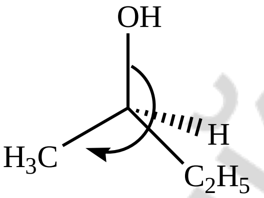


butanol-2

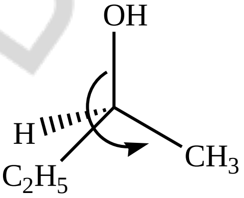




butanol-2



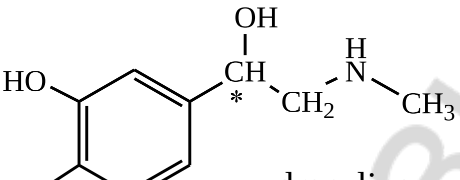
R-isomer



S-isomer

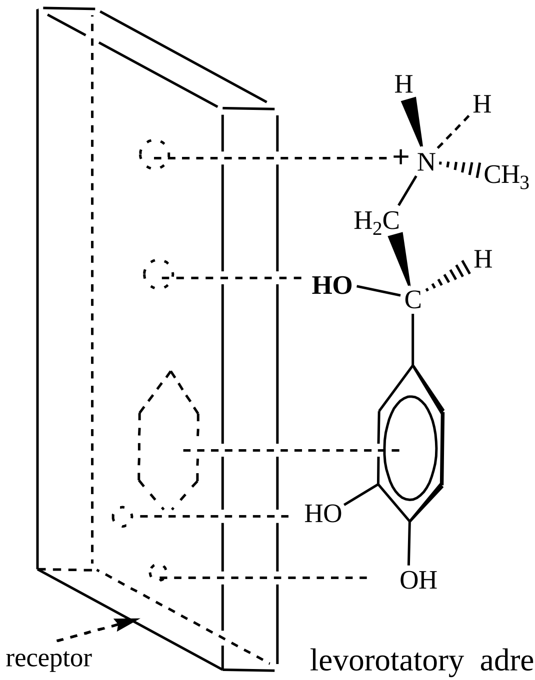
IMPORTANCE OF THE STEREOCHEMICAL STRUCTURE FOR BIOLOGICAL ACTIVITY

Most metabolites are chiral molecules. L-Hydroxy acids, L-amino acids, D-monosaccharides are involved in the metabolic processes in a cell. Chiral molecules are proteins, constructed from L-amino acids, phospholipids, vitamins, hormones, nucleic acids. Stereoisomers is the basis of specificity of the interaction of substrate-enzyme, hormone-receptor, antibody-antigen, etc. Pharmacological action of some drugs is provided by their interaction with cell receptors. For example, the greatest pharmacological activity manifests levorotatory adrenaline than dextrorotatory one.

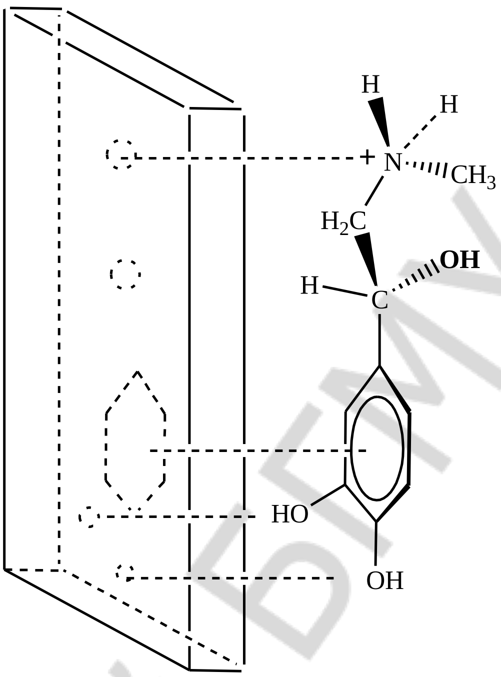


adrenaline

In dextrorotatory adrenaline OH group at the chiral center is oriented differently and does not interact with the receptor. The reason for this specificity of interactions is mutual correspondence of of complementary structures. Thus, the biological effects of biologically active substances and drugs is closely related with their spatial structure.



levorotatory adrenaline has effective interaction with the receptor due to complementarity



dextrorotatory adrenaline does not bind to the receptor completely

4. ORGANIC REACTIONS

Biologically important reactions proceed on the same mechanisms as ordinary chemical reactions. The reaction mechanism is a consistent description of all changes in reacting compounds that occur at the molecular level, as the reactants become products. Organic reactions can be classified according to several criteria. First of all consider the classification of organic reaction by the direction and the overall result of the reaction:

1) addition reactions (designated by the letter **A**);
2) elimination reactions (**E**);
3) substitution reactions (**S**);
4) isomerization reactions (**I**);
5) oxidation and reduction reactions;
6) acid-base interactions.

Another classification is based on the nature of changes in the substrate and the reactant. According to this classification, the reactions are divided into radical, ionic and coordinated.

Radical reactions are accompanied by homolytic cleavage of the bond and the formation of radicals. Radicals are the neutral species, containing an atom with an unpaired electron in its outer shell.

Homolysis: $A\cdot|\cdot B \rightarrow A\cdot + \cdot B$

Nonpolar and low polar covalent bonds in organic compounds predispose to homolysis. Usually radical reactions occur in the gas phase or in nonpolar solvents. They are initiated by physical (radiation, heat), as well as chemical factors (R-O-O-R, Fe^{2+}). Radical reactions are sensitive to electron acceptors. They are self-accelerating chain reactions and go through the following steps: 1) initiating radicals; 2) propagation of chain; 3) termination of chain.

Ionic reactions are accompanied by heterolytic cleavage of the covalent bond that leads to the formation of ions – anions (with negative charge) and cations (with positive charge).

$$\text{Heterolysis: } A{\cdot\cdot}|K \rightarrow {:}A^{-} + K^{+}$$

Polar covalent bond in organic compounds predisposes to heterolysis. Usually ionic reactions occur in polar solvents and catalyzed by acids or bases. There are two types of reagents involved in ionic reactions: electrophiles and nucleophiles. **Electrophilic reagents** have a full or partial positive charge. They are designated by **E**. Typical electrophile is proton H^+. **Nucleophilic reagents** have a full or partial negative charge. They are designated by **Nu**. The most important nucleophiles are water HOH, hydride ion H^-, alcohols R–OH, amines $R–NH_2$, thiols R–SH etc.

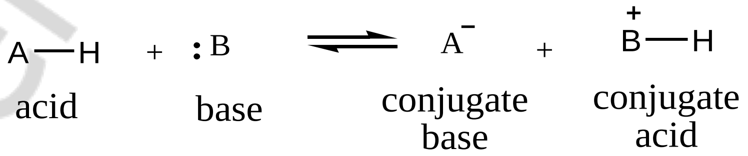
Reagents may also be acidic and basic.

ACIDITY AND BASICITY OF ORGANIC COMPOUNDS

Acidity and basicity of organic compounds are the main notions determining many fundamental physico-chemical and biochemical properties of organic compounds. First of all, acid and basic catalyses are the most widespread enzymic reactions. Besides, acid-base behaviour of organic compounds helps explain much of their biological properties.

At present, there are two main concepts of acids and bases in organic chemistry. According to the Bronsted theory, **an acid is a proton donor, and a base is a proton acceptor**. According to the Lewis theory, **an acid is an electron pair acceptor, and a base is an electron pair donor**.

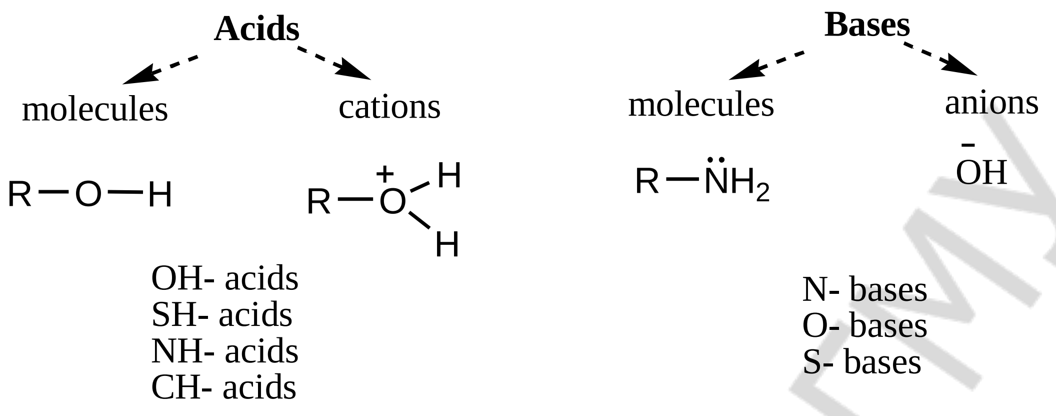
An acid and a base can be neutral molecules or ions. In a general sense, an acid-base reaction can be expressed in the following way.



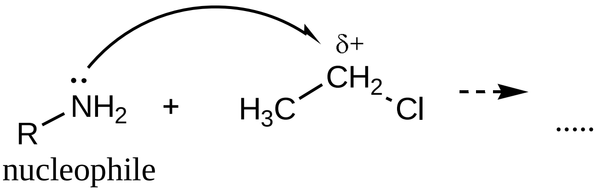
$$A{-}H + {:}B \rightleftharpoons A^{-} + \overset{+}{B}{-}H$$

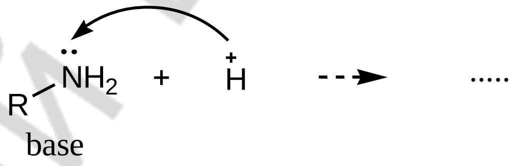
Acid strength is often expressed as pK_a, which is equal to the negative logarithm of the acidity constant. A stronger acid has a lower pK_a, and a weaker acid has a higher pK_a. Base strength is expressed as pK_{BH^+}. A stronger base has a higher pK_{BH^+}, a weaker base has a lower pK_{BH^+}.

Classification of Bronsted acids and bases



Molecule or particle can be an electrophile and acid or a nucleophile and a base depending on condition.



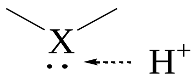


Quantitative characteristic of the acidic properties is a pK_a. The lower pKa, the stronger acid. Quantitative characteristic of the basic properties is a pK_{BH}^{+}. The higher pK_{BH}^{+}, the stronger base. But the constants of acid and base can not be calculated for the most complex of biologically important compounds. Therefore, the qualitative characteristics of acidity and basicity of compounds is important.

Qualitative characteristic of acidity is the stability of the anion formed by the acid dissociation. The more stable an anion, the stronger acid.

$$RH \leftrightarrow R^{-} + H^{+}$$

Qualitative characteristic of the basicity is the value of the electron density in the basic center. The higher electron density at the basic site, the greater base.



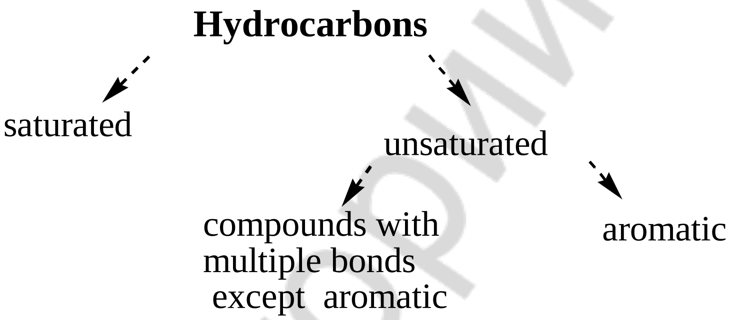
Stability of the acid anion and the value of the electron density at the basic center depend on the nature of atom in the acidic or basic center (electronegativity and radius), the degree of delocalization of the electron density and the ability to solvate.

Element electronegativity of acid or base centers can be taken into account when acids or bases are identical radicals and elements are arranged in the one period of the periodic table (for example, N, O, C). At the same time, the higher the electronegativity, the more pronounced acidic properties and below — the basic ones. Relative polarizability increases within one group of the periodic table from top to bottom. Polarizability of atoms of acid or base centers can be taken into account when acids or bases are identical radicals and elements are arranged in the one group of the periodic table (for example, O and S). A larger atom has more possibility for delocalization of a negative charge, than a smaller atom. The higher polarizability, the more pronounced acidic properties and lower — the basic properties.

The degree of delocalization of the negative charge in the anion is taken into account if the acids have the same acidic sites. The presence of conjugation, electron withdrawing substituents increase the acidity and decrease basicity; the presence of electron-donating substituents reduces acidity and increases the basicity.

5. REACTIVITY OF HYDROCARBONS

There are two main types of hydrocarbons: saturated and unsaturated. Unsaturated hydrocarbons are divided into organic compounds with isolated or conjugated multiple bonds and aromatic compounds.



Hydrocarbons are toxic because of its hydrophobic properties, they can easily penetrate into the body through the skin and mucous membranes.

SATURATED HYDROCARBONS

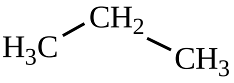
Saturated hydrocarbons contain only σ bonds.

CH_4

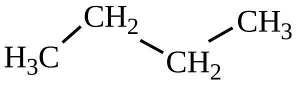
methane

H_3C-CH_3

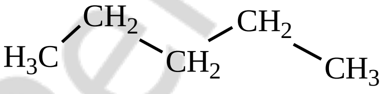
ethane



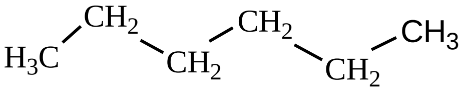
propane



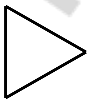
butane



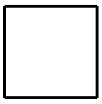
pentane



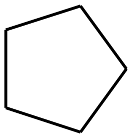
hexane



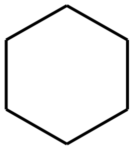
cyclopropane



cyclobutane

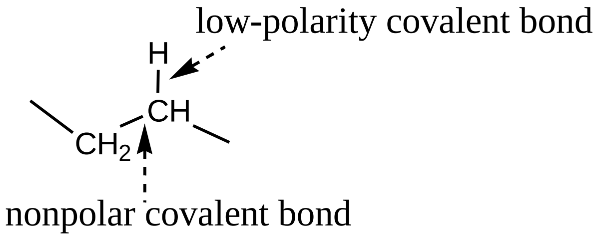


cyclopentane

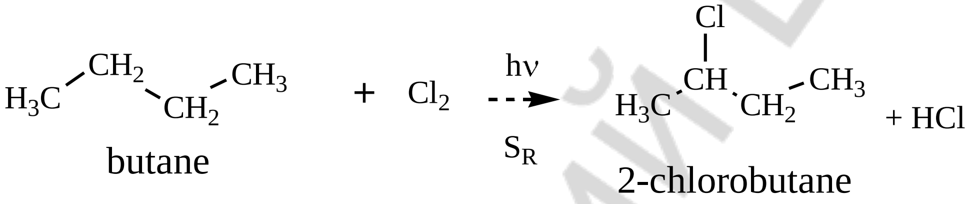


cyclohexane

Saturated hydrocarbons are characterized by the presence of nonpolar and low-polarity covalent bonds, which predispose to homolytic bond breaking.



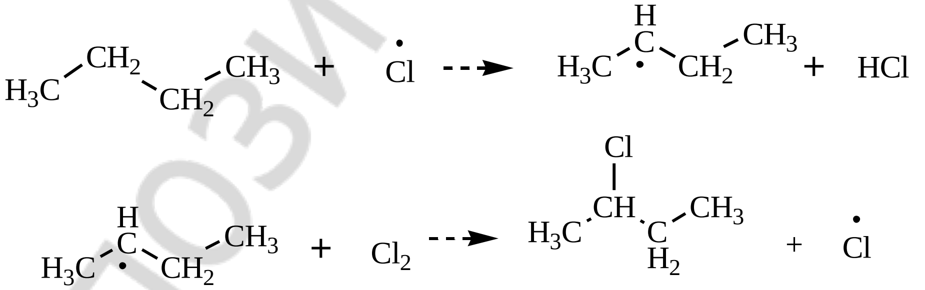
For alkanes, cycloalkanes (except cyclopropane, cyclobutane), saturated fragments of the other classes organic compounds are typical reactions of radical substitution (S_R) and radical oxidation. The halogenation reaction of alkanes proceeds according to a radical substitution, it requires the ultraviolent light and passes through a series of stages.



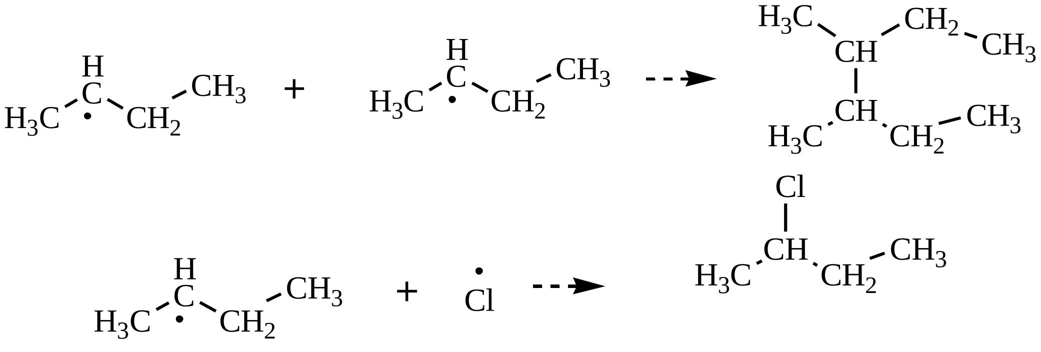
The first stage is the **initiating** that is in the breaking of the chlorine molecule into two halogen atoms (free radicals).

$$Cl - Cl \xrightarrow{h\nu} 2\dot{Cl}$$

In the second **chain-propagating** stage, a very reactive chlorine atom can collide with a butane molecule, abstracting a hydrogen atom and producing a molecule of HCl and a highly reactive carboradicals.



A chain reaction may be terminated if any two radicals combine (**termination** stage).



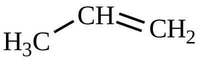
In vivo S_R are not detected, but it is possibly radical oxidation reactions. In case of contact with alkanes in the body reactions of the radical oxidation go as detoxification of xenobiotics.

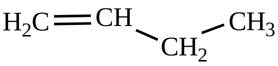
UNSATURATED HYDROCARBONS

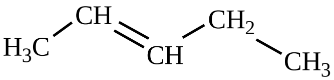
Electrophilic addition reactions (A_E) are typical for alkenes, alkadienes, arenes (in special circumstances).

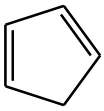
$H_2C{=}CH_2$

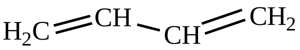
ethene


propene

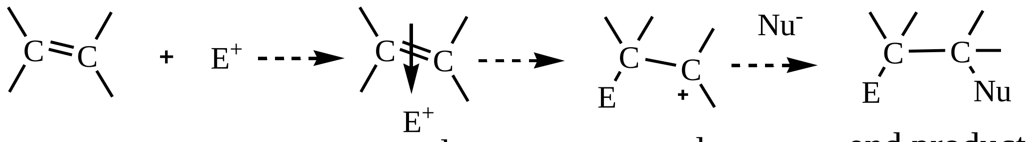

but-1-ene


pent-2-ene


cyclopent-1,3-diene

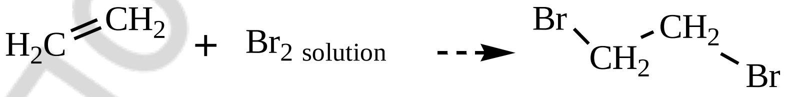

but-1,3-diene

Electrophilic addition reaction proceeds through a series of stages. The reaction can be represented in general form as as shown below.

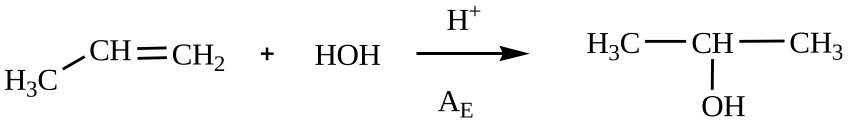

π complex σ complex end product

At first an electrophile interacts with electrons of π bond forming a π complex. Then electrophile forms a new bond with one of the carbon atoms using both electrons of π bond and the other carbon atom becomes positively charged. An obtained carbocation is called σ complex. The last stage is the nucleophilic attack and the end product is formed.

In vitro may involve the reactions of halogenations, hydrohalogenation, hydration, alkylation etc. The reaction with bromine water is used as test for presence of a double bonds.

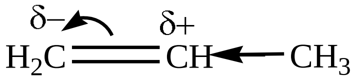

brown colorless

Hydration is the reaction of addition of water. This reaction *in vitro* requires a strong acidic catalyst. Acid as a catalyst generates a proton (electrophile) that is capable of reacting with π bond. Hydration of propene and other unsymmetrical alkenes goes according to Markovnikov's rule.


propene propanol

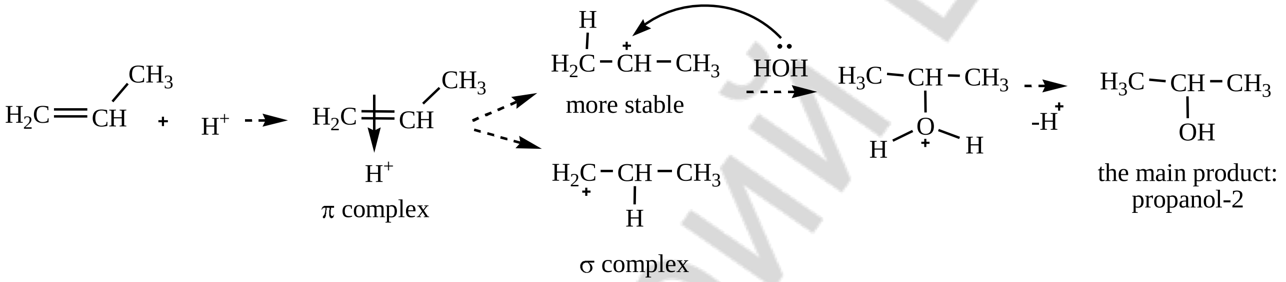
Markovnikov rule is formulated as follows: **when joining the HX type reagents to asymmetric alkenes hydrogen atom is always attached to a carbon atom with the greater number of hydrogens**.

There are two approaches for the explanation of the Markovnikov's rule. The first approach consists in the distribution of partial charges in a non-reacting alkene molecule. In propene under the influence of the methyl group π bond is polarized. It is obvious that with such distribution of the electron density in the molecule electrophile should join the first carbon atom as a nucleophile— second.



$$\overset{\delta-}{H_2C}{=}\overset{\delta+}{CH}\leftarrow CH_3$$

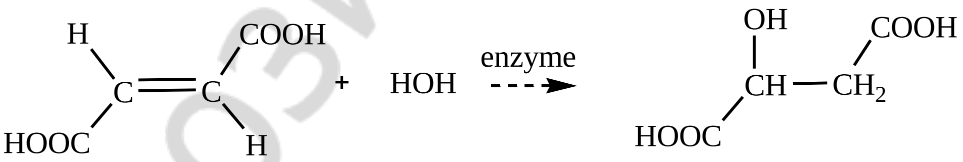
The second approach to explain Markovnikov's rule involves carbocation stability: the addition reaction proceeds in the direction of the formation of the more stable intermediate.



The more stable carbocation is the secondary one due to partial neutralization of the positive charge by electron donor influence of methyl groups.

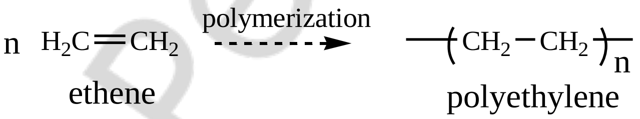
$$H_3C\rightarrow\overset{+}{CH}\leftarrow CH_3 \qquad +I\ CH_3$$

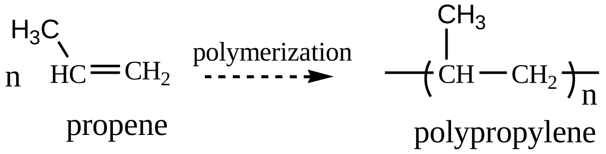
Many of biologically important reactions involving the double bond are against Markovnikov's rule or Markovnikov rule for them is insignificant. Hydration reaction of butenedioic (fumaric acid) goes with the formation of hydroxybutanedioic (malic) acid.

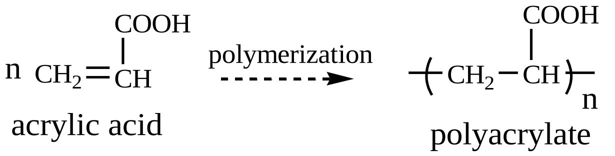


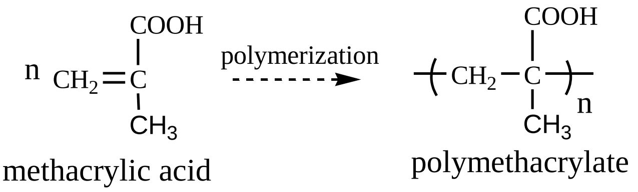
fumaric acid malic acid

Polymerization reaction are very important for alkenes.



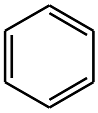


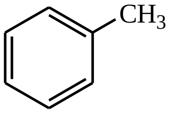




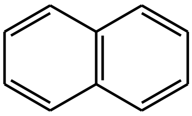
AROMATIC HYDROCARBONS

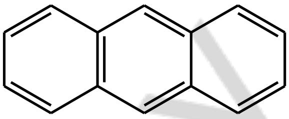
Electrophilic substitution reactions (S_E) are typical for arenes. Examples of aromatic compounds are shown below.

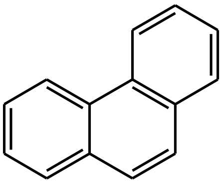

benzene

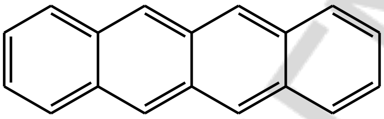


toluene

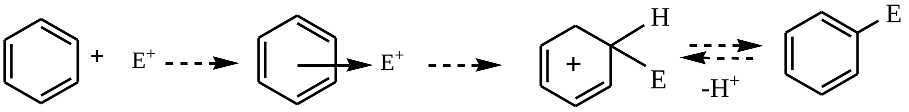

naphthalene


anthracene


phenantrene

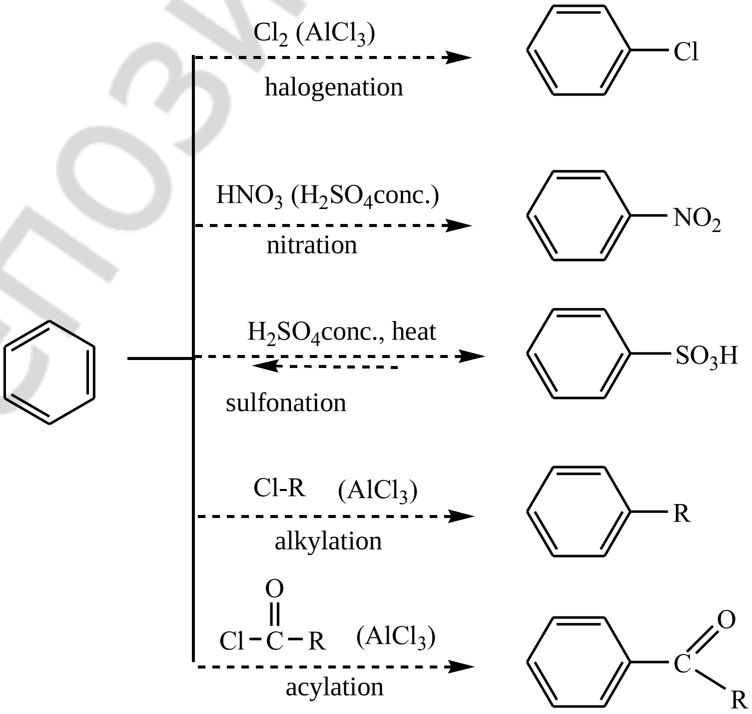

tetracene

Electrophilic substitution reaction proceeds through a series of stages. At first an electrophile interacts with *p* electrons of conjugation system forming a π complex. Then electrophile forms a new bond with one of the carbon atoms using two electrons of conjugation system and compound loses aromaticity (σ complex). The last stage is accompanied by loss of the proton, the stabilization of the σ complex and the formation of the end product. The reaction can be represented in general form as shown below.

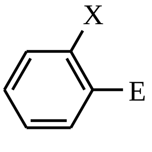


π complex σ complex end product

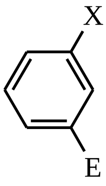
In vitro may involve the reactions of halogenation, nitration, sulfonation, alkylation, acylation.



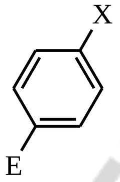
If the S_E reaction shall enter benzene itself, the place of the orientation of the electrophile does not matter, because the electron density of the benzene ring is evenly distributed. However, if such reactions shall enter homologues or substituted benzene derivatives, the symmetry of the *p* electron cloud are broken and the electrophile (E) may be oriented *ortho*, *meta* or *par*a position to the substituent (X).



ortho

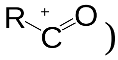


metha



para

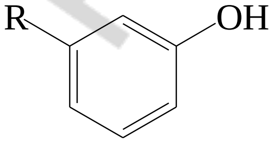
By the nature of the orientation of electrophilic particle all of the substituents in the benzene ring are divided into 2 groups. Substituents of type I are *ortho*, *para* orientants which direct the electrophile in the ortho and para position of the benzene ring. Most of type I orientants are electron-donating groups such as $-NH_2$, $-OH$ etc. The reactions S_E occur easier for compounds with electron-donating substituents. The higher electron density in the aromatic ring, the more electrophile tends to form a bond. Substituents of type II — *meta* orientants — are electron acceptors and direct the electrophile in the *meta* position of the benzene ring. They reduce the reactivity of the benzene ring.

Detoxication reactions of arenes in the body are the introduction of hydrophilic groups into the ring by hydroxylation (hydroxyl group) or acylation (carboxylic acid residue  $R-\overset{+}{C}=O$) and other reactions. Detoxication reactions are facilitated by the presence of electron-donating substituents. For example, benzene is more toxic than toluene.

6. REACTIVITY OF MONOFUNCTIONAL DERIVATIVES OF HYDROCARBONS

Monofunctional derivatives of hydrocarbons may contain in their structure a different functional group. But in this section we will discuss the alcohols, thiols, ethers, sulfides, amines, phenols, halogenated hydrocarbons.

$R-OH$	$R-SH$	$R-NH_2$	$R-O-R$	$R-S-R$
alcohols	thiols	amines	ethers	sulfides

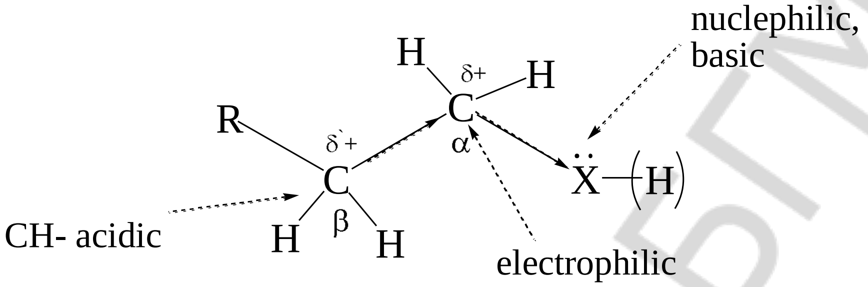


phenols

$R-Hal$

halogenated hydrocarbons

Each functional group incorporates the atom with higher electronegativity than carbon, and thus it has electron acceptor properties, shifts electron density to itself. This leads to a partial positive charge on the adjacent carbon atom, and the appearance of the electrophilic center. σ Bond between the first and second carbon atoms is also polarized, which explains the presence of CH-acidic site in the β carbon atom. The heteroatom (O, S or N) has a pair of electrons, so that it is a basic or nucleophilic center.



Reaction sites of monofunctional
derivatives of hydrocarbons

Nucleophilic substitution reactions (S_N) proceed by an electrophilic center. Under certain circumstances, an acidic CH center attacked simultaneously with an electrophilic center, and the elimination reaction takes place. Elimination reactions and nucleophilic substitution are competitive.

Thus, monofunctional hydrocarbon derivatives show acid-base properties, properties of electrophilic center (S_N) and CH-acidic center (E), oxidation reactions.

ACID-BASE PROPERTIES OF MONOFUNTIONAL DERIVATIVES OF HYDROCARBONS

Recall that the qualitative characteristics of acid and base is the most important for biologically important compounds. Qualitative characteristic of acidity is the stability of the anion formed by the acid dissociation. The more stable an anion, the stronger acid. Qualitative characteristic of the basicity is the value of the electron density in the basic center. The higher electron density at the basic site, the greater base.

In the row of acids with the same radicals thiols are the most strong acids.

$$R\text{-}SH \quad R\text{-}OH \quad R\text{-}NH_2 \quad R\text{-}CH_3$$

$$\xrightarrow{\hspace{6cm}}$$

acidity decreases

This is explained by the most stable thiolate anion from the greater delocalization of the negative charge of sulfur atom having a larger radius compared with the oxygen atom. Alcohols are stronger acids than amines and hydrocarbons as the oxygen atom has a higher electronegativity than nitrogen and carbon.

Consequently, the oxygen holds a pair of electrons more strongly and alkoxide anion is a more stable.

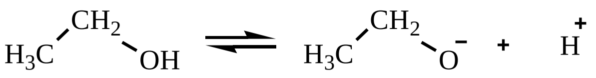
$$R\text{-}\ddot{S}H \quad R\text{-}\ddot{O}H \quad R\text{-}\ddot{N}H_2$$

$$\xleftarrow{\hspace{4cm}}$$

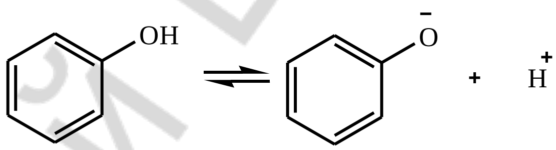
basicity decreases

Basic properties change in the reverse order. Amines are the strongest bases. Thiols almost do not show the basic properties. Hydrocarbons are not the base, because the carbon atom has no a pair of electrons and is not able to attach a proton.

Comparing the acid or base is necessary to consider the influence of the radical on the electron distribution in the molecule. Thus, electron-withdrawing substituents and conjygation increase the stability of the acid anion and hence the acidity, but reduce basicity. And the electron donating substituents reduce the acidity, but increase the basicity.

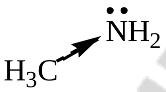


ethanol

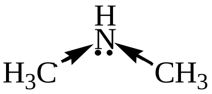


phenol

To compare the acidity of the phenol and ethanol is necessary to write the dissociation reaction of acids and obtain anions. Phenoxide anion is more stable since the negative charge is delocalized by conjugation. Consequently, phenol is a stronger acid than ethanol.



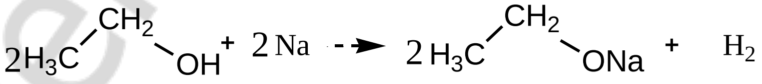
methylamine

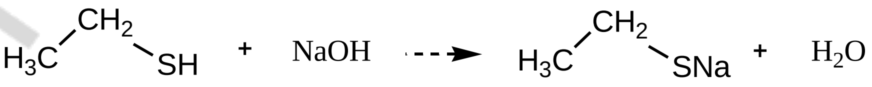


dimethylamine

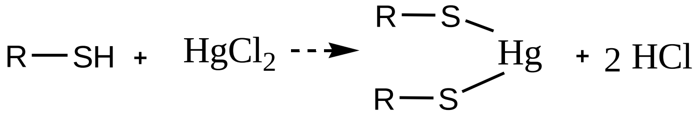
Dimethylamine possesses more pronounced basic properties than methylamine because two methyl groups, having a positive inductive effect, lead to a more pronounced electron density at the basic site.

Manifestation of the acidic properties is the substitution reactions. Alcohols react only with metallic sodium or potassium, and thiols as stronger acids can react with alkalis.



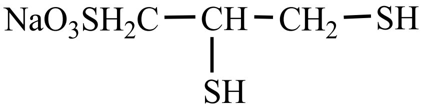


Thiols are able to react with salts of heavy metals. The result of these reactions are non-toxic derivatives. Such reactions are of great medical significance.



$$2\,R{-}SH + HgCl_2 \dashrightarrow (R{-}S)_2Hg + 2\,HCl$$

Thiols (for example unitiol) are used as antidotes for poisoning of arsenic, mercury, chromium, bismuth, etc.

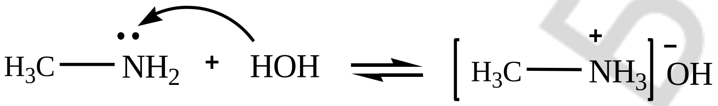


$$NaO_3SH_2C{-}\underset{\displaystyle SH}{\underset{|}{CH}}{-}CH_2{-}SH$$

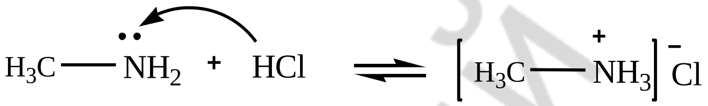
2,3-dimercaptopropane-1-sulphonate sodium or

unitiol

In the acid-base interaction the base attach proton.

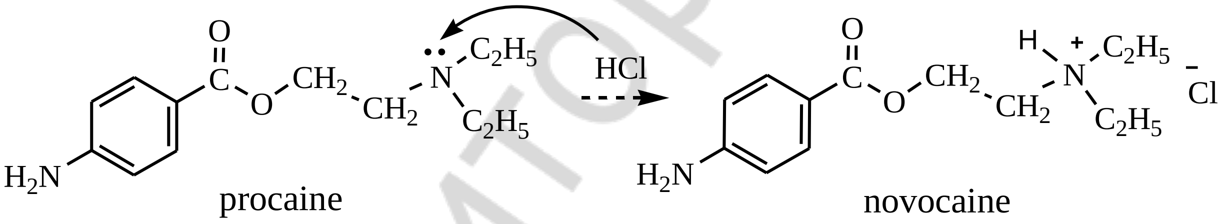


$$H_3C{-}\ddot{N}H_2 + HOH \rightleftharpoons [H_3C{-}\overset{+}{N}H_3]\overset{-}{O}H$$



$$H_3C{-}\ddot{N}H_2 + HCl \rightleftharpoons [H_3C{-}\overset{+}{N}H_3]\overset{-}{Cl}$$

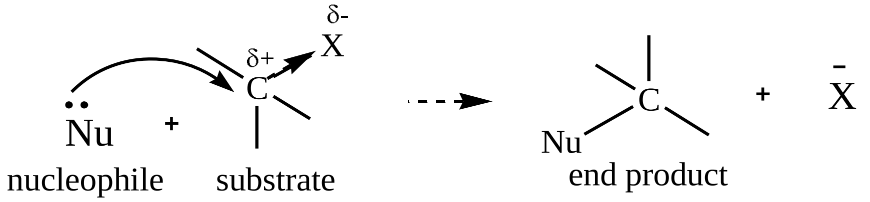
Many medicines (usually bases) are used as mineral acid salts. For example, procaine is a hydrochloride salt of procaine. Novocaine is prescribed as local anesthetics agent.



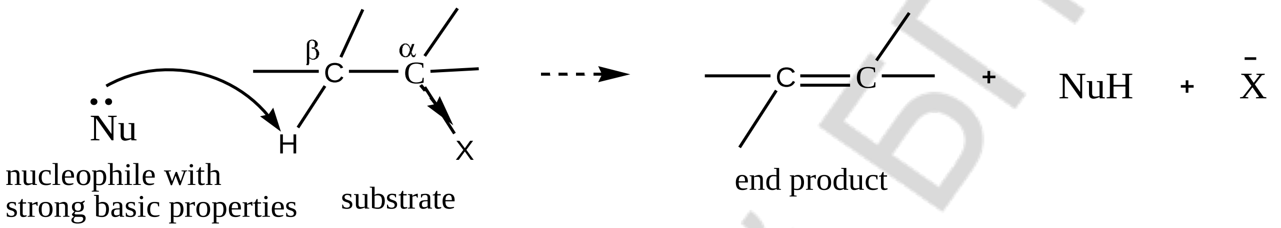
The most of the biologically important compounds have amphoteric properties: hydroxy acids, phenolic acids, amino acids, purine and pyrimidine base, etc. Depending on conditions acidic or basic centers are activated. Intra- and intermolecular hydrogen bonds are also a consequence of the amphoteric properties of the compounds.

NUCLEOPHILIC SUBSTITUTION AND ELIMINATION REACTIONS

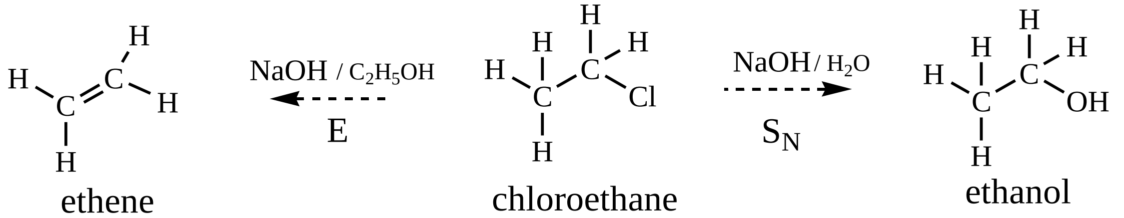
Nucleophilic substitution at saturated carbon is one of the simplest and, at the same time, the most important type of organic reactions. The different compounds with an electrophilic site undergo to the nucleophilic substitution reactions. It may also be characterized as the alkylation reaction with reference to the nucleophile. Many reactions of biological importance represent nucleophilic substitution. In this reaction, one covalent bond is broken, and a new bond is formed. The reaction can be expressed in the following general equation.



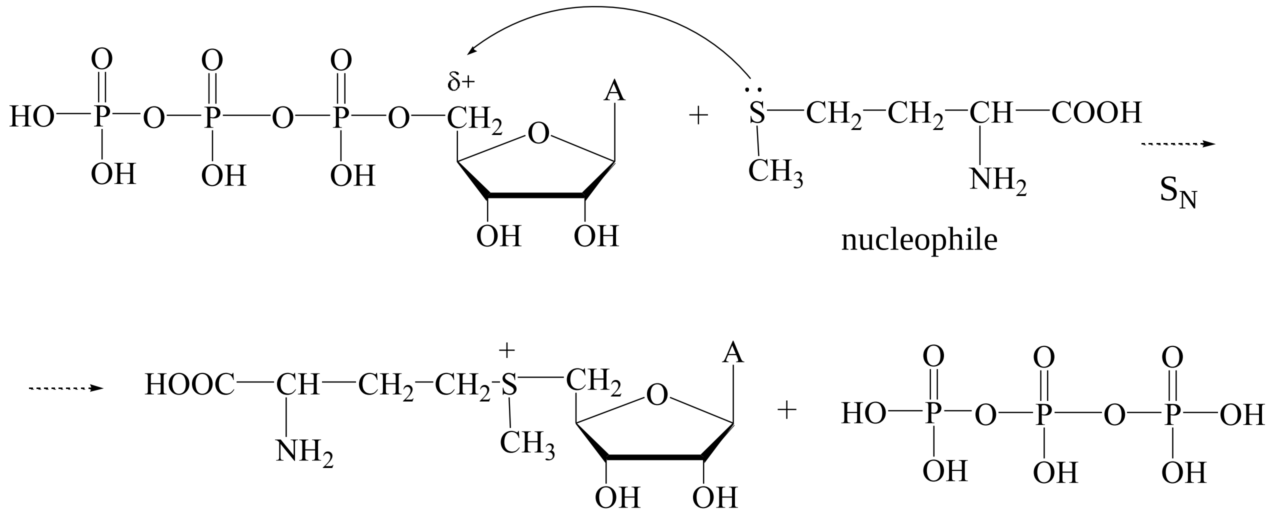
Compounds of different classes may be considered as nucleophiles. Both neutral molecules and anions can serve as nucleophilic reagents. Under certain conditions, the compound can not only be subjected to substitution by the electrophilic center, but also donates a proton from the C–H acidic center of β carbon atom. In this case the elimination reaction proceeds.



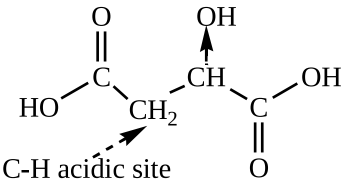
In vitro, depending on the reaction conditions and the structure of the substrate or reagent go substitution or elimination.



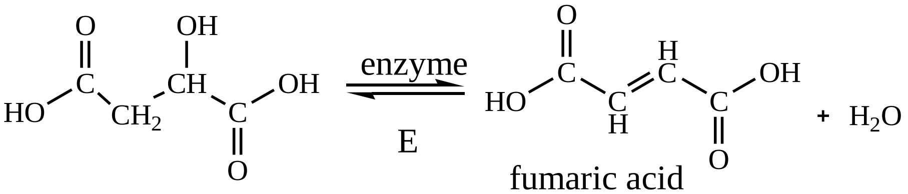
Nucleophilic substitution reactions often take place in the cell. Biochemical alkylation (methylation) is the most common of all substitution reaction *in vivo*. An important methylating agent is S-adenosylmethionine, which is also formed in the S_N reaction of ATP and the amino acid methionine. Adenosine triphosphate has an electrophilic center, which is attacked by a sulfur atom, which is a nucleophilic center. The resulting product was further able to be a substrate in the S_N reactions.



Malic acid has a hydroxyl group which is an electron acceptor. Shift of the electron density leads to a C-H acidic site in β carbon atom, which promotes the elimination reaction.



malic acid



fumaric acid

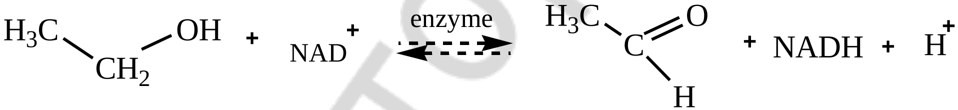
The reaction product (fumaric acid) is *trans* isomer of butenedioic acid.

OXIDATION REACTION

Oxidation of many biologically active substances in cell is the dehydrogenation reaction. Coenzyme NAD$^+$ (nicotinamide adenine dinucleotide oxidized) participates in the enzymatic reaction. Its role is to join a hydride anion, which is cleaved from the α carbon atom of the substrate. Nicotinamide adenine dinucleotide reduced (NADH) formed during the reaction. The substrate also cleaves a proton into solution. Usually the reaction is reversible.

$$\text{H-substrate-H} + \text{NAD}^+ \xrightleftharpoons{\text{enzyme}} \text{substrate} + \text{NADH} + \text{H}^+$$

Such a way lactic acid, malic acid, exogenous and endogenous ethanol are oxidized *in vivo*.



ethanol

etanal

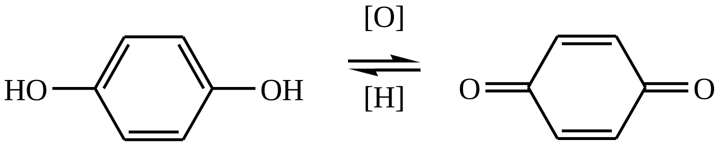
Oxidation of thiols occurs easily under mild conditions. The reaction products are disulfides.

$$2\,\text{R-SH} \xrightarrow{[\text{O}]} \text{R-S-S-R} + \text{HOH}$$

dialkyldisulfide

Disulfide bonds are formed by oxidation of the thiol groups of amino acids in the formation of the tertiary structure of the protein. Due to easy oxidizability thiols can act as antioxidants in the cell. **Antioxidants** are the substances that prevent oxidation of biologically important compounds.

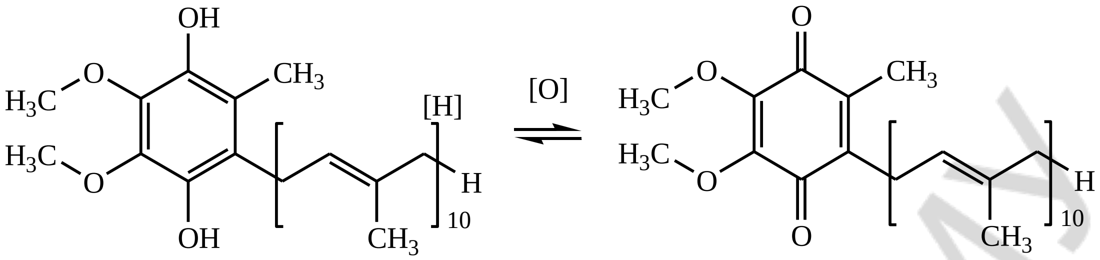
The oxidation of diatomic phenols, also occurs easily and leads to the formation of quinones. Free radicals are formed as intermediates in oxidation reaction.



hydroquinone

quinone

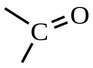
This reaction underlies the using of polyphenols as inhibitors and functioning of the respiratory chain ubiquinones (coenzyme Q).

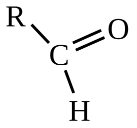


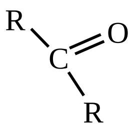
coenzyme QH

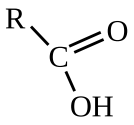
coenzyme Q

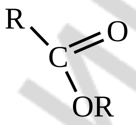
7. CARBONYL COMPOUNDS. ALDEHYDES AND KETONES

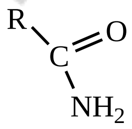
Carbonyl compounds are the most important of all organic compounds, especially, in biological processes. They contain in its structure a carbonyl or oxo group  .

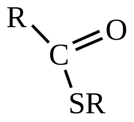

aldehydes

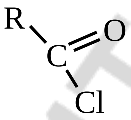

ketones

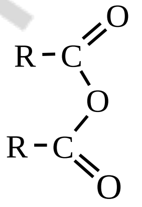

carboxylic acids


esters

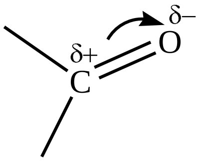

amides

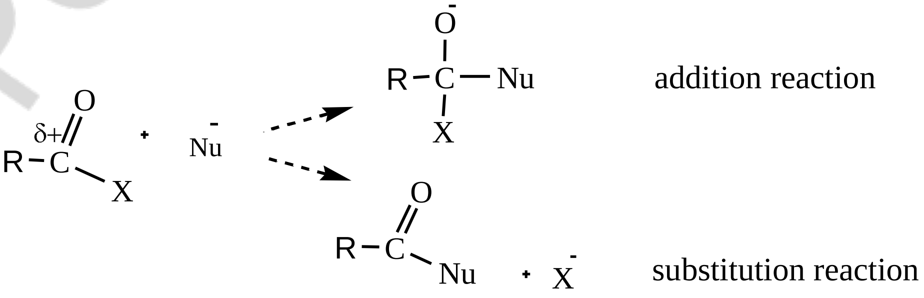

thioesters


acyl chlorides


anhydrides

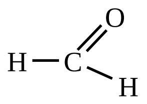
The electron density of the C=O bond is shifted to oxygen, so the carbon atom forms a partial positive charge (electrophilic center). Nucleophilic reagents tend to electrophilic center. Reacting the nucleophile and the electrophilic site can lead to the formation of addition product or substitution product. Aldehydes and ketones are characterized by their ability to enter into an addition reaction. Carboxylic acids and their derivatives are inclined to nucleophilic substitution reaction.



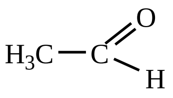


REACTIVITY OF ALDEHYDES AND KETONES

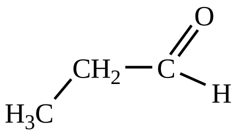
The presence of the aldehyde group in the structure of the compound is indicated by the suffix **-al**, ketone group — by the suffix **-one**. Some representatives are given with trivial names, which are widely used in biology and medicine.



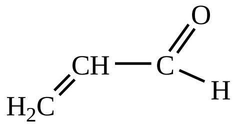
methanal
(formaldehyde)



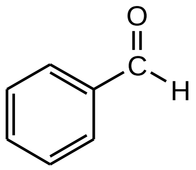
ethanal
(acetaldehyde)



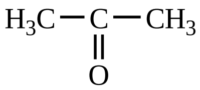
propanal



propenal

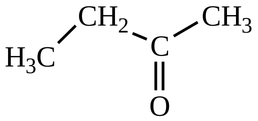


benzaldehyde



$H_3C-\underset{\overset{\|}{O}}{C}-CH_3$

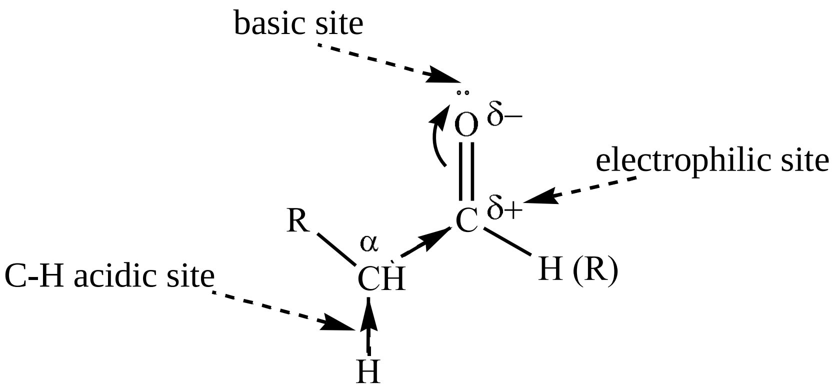
propanone
(acetone)



butanone

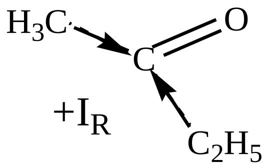
STRUCTURE OF THE CARBONYL GROUP

Both carbon and oxygen atoms are sp^2 hybridized in the carbonyl group, so it has a planar structure. Bond between the carbon and oxygen is polarized. Electron density is shifted to the more electronegative oxygen atom. Carbonyl carbon atom acquires a partial positive charge and becomes an electrophilic center.



Oxygen atom has a pair of electrons, it is able to attach a proton, so it is a basic center. Carbonyl group has a negative inductive effect, whereby bond $C_1 - C_2$ are also polarized and C–H acidic site appears in the α position. Mechanism reaction of nucleophilic addition is realized by the electrophilic center.

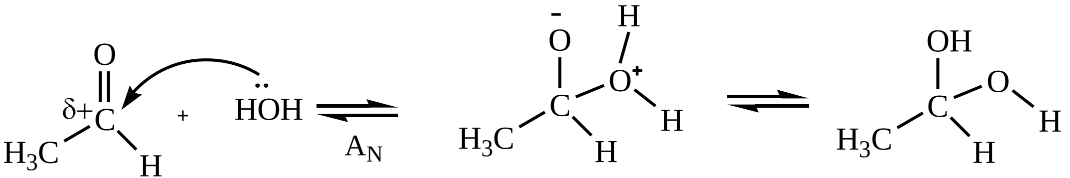
Nucleophilic addition (A_N) reaction rate depends on the magnitude of the positive charge on the carbon atom of the carbonyl group and the spatial accessibility of the electrophilic center. Ketones are less reactive in A_N reactions because positive inductive effect of radicals reduces the electrophilicity of the carbonyl atom C.



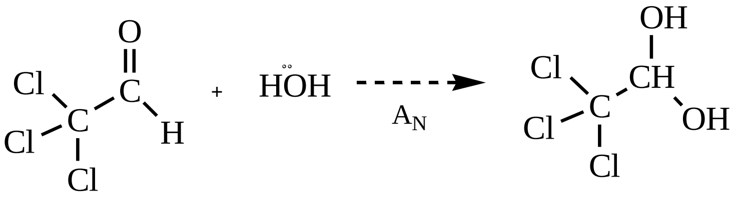
Moreover hydrophobic radicals create steric hindrance to attack the electrophilic center with nucleophile.

NUCLEOPHILIC ADDITION REACTIONS

Some aldehydes and ketones react with water. For most of them, the reaction is reversible. Gem-diol of trichloroethanal is stable. It is used as a sedative in medicine.

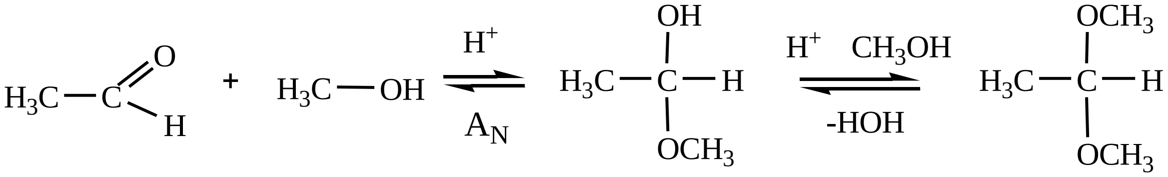


gem-diol



chloral hydrate

The reaction of aldehydes and ketones with alcohols is called **acetalization**. The reaction proceeds through a series of stages, each of them is reversible. The aldehyde or ketone is capable attach two moles of alcohol. Addition product of one molecule of alcohol is called **hemiacetal**. Result of the interaction of the carbonyl compound and two moles of alcohol is an acetal.

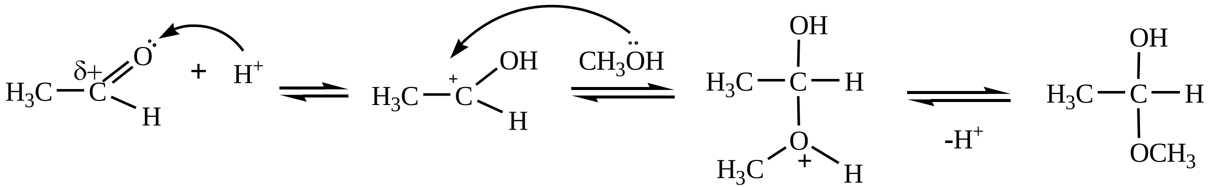


ethanal

hemiacetal

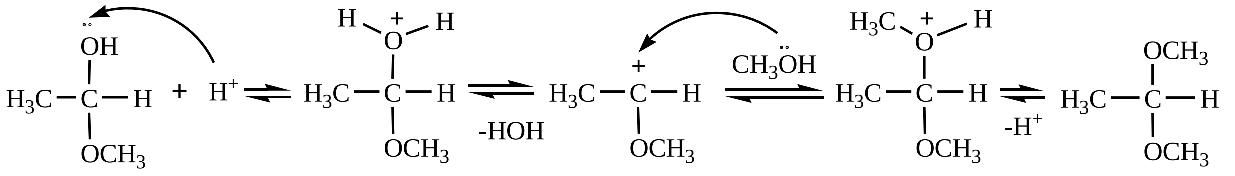
acetal

The reaction starts from the reacting an aldehyde with a catalyst. Proton reacts with the basic center. As a result a partial positive charge on the electrophilic center turns into a full. Further, the alcohol being a nucleophile attacks the carbonyl carbon atom.



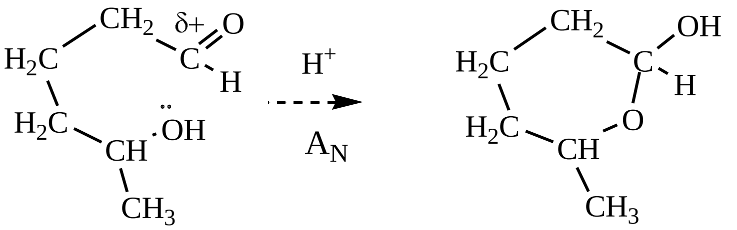
1-methoxyethanol
hemiacetal

Formed hemiacetal may again interact with the catalyst and then with another molecule of alcohol.



1,1-dimethoxyethane
acetal

If the oxo and hydroxyl groups are in the same molecule and they are relatively far apart, reaction of the cyclic hemiacetal formation is possible. This reaction is typical for heterofunctional compounds, in which the hydroxyl group is located at the fourth or fifth carbon atom relative to the oxo group.

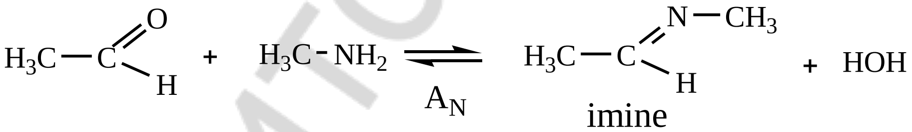


5-hydroxyhexanal

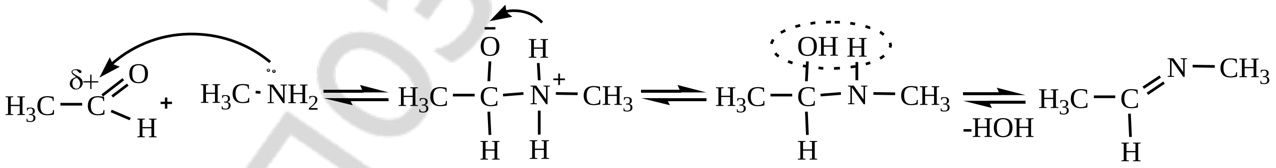
cyclic hemiacetal of
5-hydroxyhexanal

Acetalization reaction underlies the formation of cyclic forms of monosaccharides, since they contain carbonyl and hydroxyl groups.

Aldehydes and ketones react with amines to form imines (Schiff's bases).

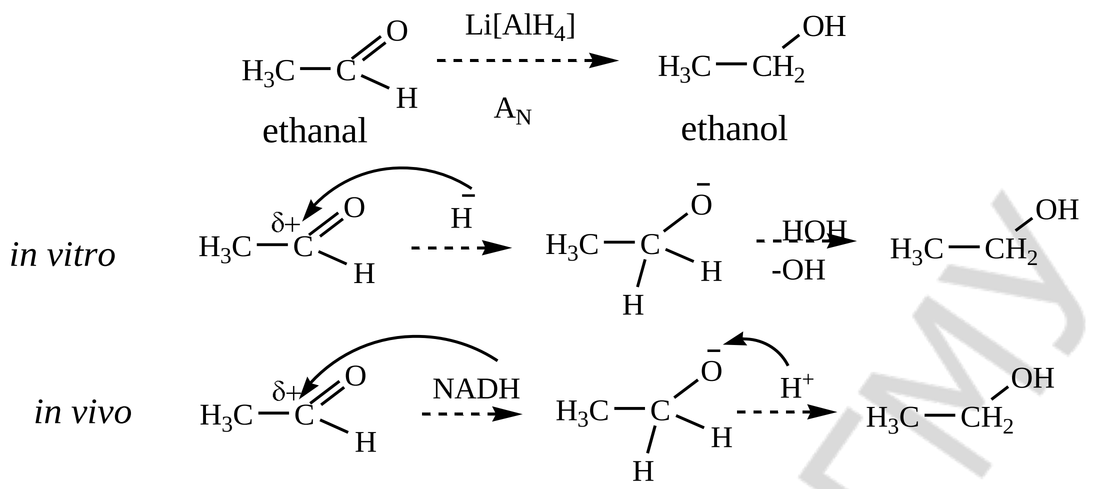


The reaction does not require an acid catalyst so as amines are strong nucleophiles and they are able to break π bond.



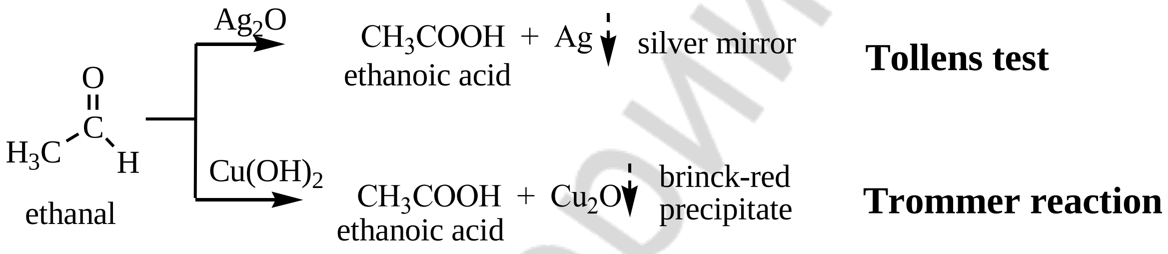
The reaction of carbonyl compounds with amines is the basis of many physiological and pathological processes. For example, the disinfectant action of such aldehydes as formaldehyde, glutaraldehyde is explained by reacting the aldehyde group with amino groups of proteins, which leads to denaturation, and destruction of microorganisms.

Reduction of carbonyl compounds also occurs by a mechanism A_N. The reaction takes place with the participation of the hydride ion H^-, which is a nucleophile. The source of the hydride ion is $Li[AlH_4]$, ($NaBH_4$) *in vitro* and coenzyme $NADH{\cdot}H^+$ *in vivo*.



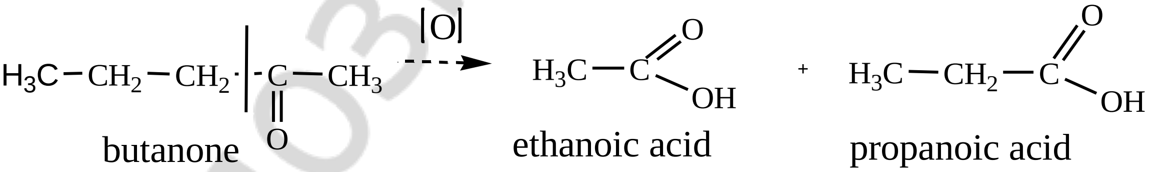
OXIDATION OF ALDEHYDES AND KETONS

Aldehydes are easily oxidized to carboxylic acids by strong (potassium permanganate) and mild oxidizing agents (Ag_2O/t, $Cu(OH)_2$/t). The last two reactions are qualitative on an aldehyde group.

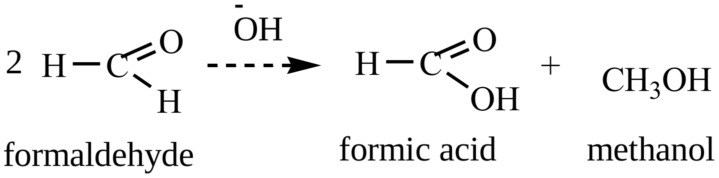


In humans, the aldehyde group can also be enzymatically oxidized to carboxyl.

Ketones are hard oxidized with breaking of the C–C bonds. Reaction requires stronger oxidizing agents such as HNO_3, $K_2Cr_2O_7/H_2SO_4$. The mixture of carboxylic acids is formed as a result of the reaction. Bond breaking occurs so that oxo group is mainly with the smallest radical.

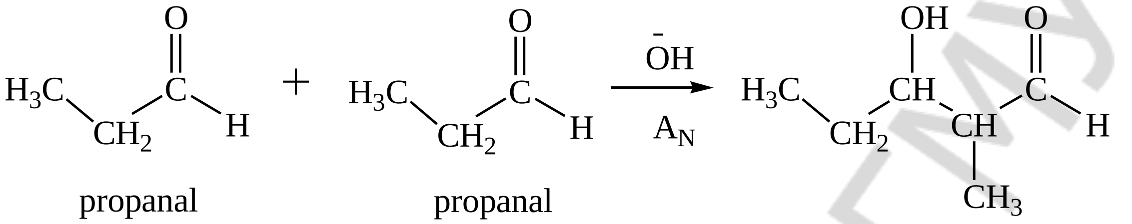


Dismutation reaction is accompanied by the oxidation of one molecule of aldehyde to the carboxylic acid and reduction of another aldehyde molecule to the alcohol. It is typical for aldehydes that do not have C–H-acid at α position. Reaction requires alkaline conditions. Examples of aldehydes that can undergo a Cannizaro reaction are aromatic aldehydes and formaldehyde.



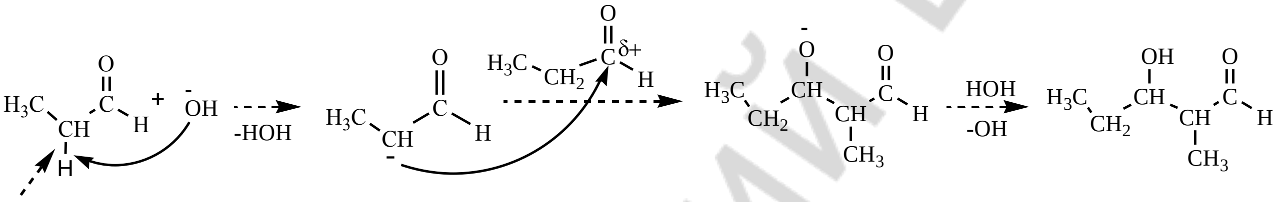
REACTIONS WITH PARTICIPATION OF C–H ACIDIC CENTER

Aldol condensation reactions are reffered to a nucleophilic addition mechanism and occur when two aldehydes react with each other. They are typical for carbonyl compounds that have a C–H acidic center in α position. Reactions are carried out under alkaline conditions *in vitro*; in the cell they go with the participation of enzymes.



propanal propanal 3-hydroxy-2-methylpentanal

In presence of alkali one aldehyde molecule turnes into carbanion which is nucleophyl and reacts with another aldehyde molecule.

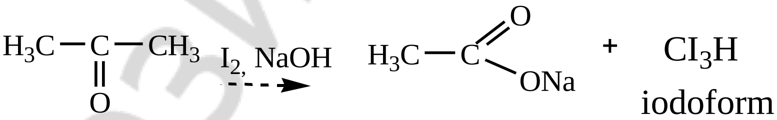


C-H acidic site

Aldol condensation leads to the formation of **aldol** (from ald- and -ol), since the product contains an aldehyde and an alcohol group.

In the cell aldol condensation proceeds during the synthesis of citric acids, neuraminic acid, etc. It is also possible aldol cleavage. For example the amino acid serine is cleaved enzymatically to glycine and formaldehyde.

The haloform reactions are typical for aldehydes and ketones that have hydrogen atoms at α position. Reactions go in the presence of bases.



$+ \quad CI_3H$

iodoform

acetone

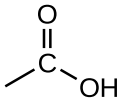
Iodoform reaction can be used for detection of acetone in biological fluids which is appearing during prolonged fasting, diabetes.

IMPORTANT REPRESENTATIVES

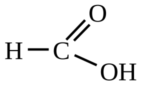
Aqueous 40 % formaldehyde solution is called **formalin**. It is used in medicine as a disinfectant, a preservative of anatomical preparations since it possesses protein denaturing action.

Acetone is a colorless, volatile, flammable liquid. Acetone is mixed with water, ethanol, ether, etc., and itself serves as a solvent of organic compounds, for example, fats. Acetone may be formed in the body in significant quantities as a result of diabetes decompensation.

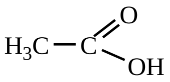
8. CARBOXYLIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES



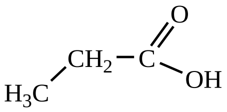
Carboxylic acids are characterized by the carboxyl functional group COOH. First consider the representatives of carboxylic acids. Some of them are presented with their trivial names.



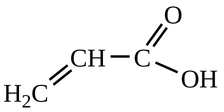
methanoic acid
(formic)



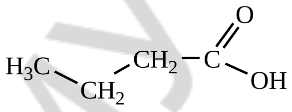
ethanoic acid
(acetic)



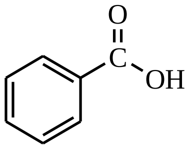
propanoic acid
(propionic)



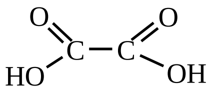
propenoic acid
(acrylic)



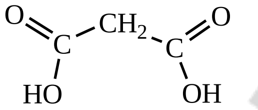
butanoic acid
(butyric)



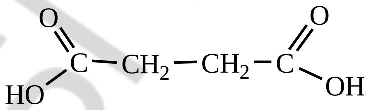
benzoic acid



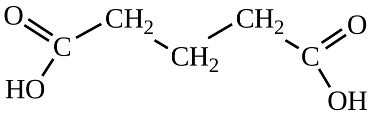
ethanedioic acid
(oxalic)



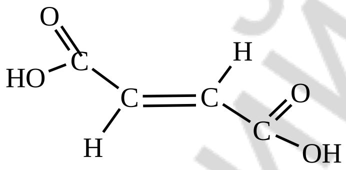
propanedioic acid
(malonic)



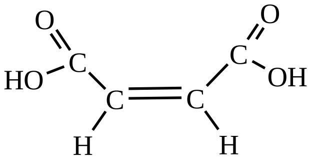
butanedioic acid
(succinic)



pentanedioic acid
(glutaric)



trans- butenedioic acid
(fumaric)

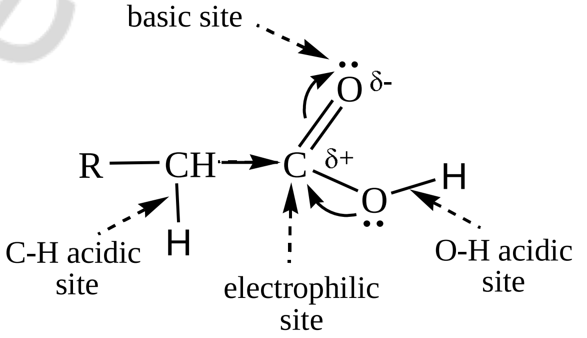


cys- butenedioic acid
(maleic)

Biologically important are also the fatty acids that have a long hydrocarbon chain and are part of lipids. They will be discussed in the topic «Lipids».

THE STRUCTURE AND REACTIVITY OF CARBOXYLIC ACIDS

The carboxylic group is composed of carbonyl and hydroxyl groups. Interaction of hydroxyl and carbonyl group through inductive and mezomeric effects leads to the formation of a qualitatively new functional group — carboxyl. The carboxylic group is a flat conjugated system, where an unshared pair of the oxygen atom OH-group combines with π bond (*p*, π conjugation). The negative inductive effect of a CO group is more than an OH group, and that is why electronic density of the bond between the oxygen and hydrogen is more displaced to oxygen; it increases the acidity as compared with alcohols.



$-I_{CO} > -I_{OH}$

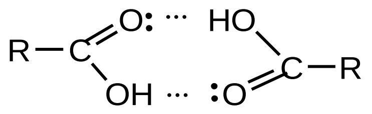
$+M_{OH}$

$-I_{COOH}$

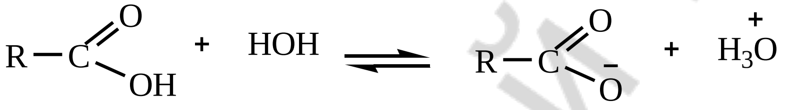
The forming of general *p*-π conjugation system result in loss of carbonyl and hydroxyl groups individuality. As a result, carboxylic acids come into nucleophilic substitution reaction (S_N) and does not addition. The carbonyl acids have a partial positive charge of carbonyl group carbon atom which is less than in oxo compounds; it decreases the carbonyl acids activity to perception of nucleophilic reagent attack.

ACID-BASE PROPERTIES OF CARBOXYLIC ACIDS

Due to simultaneous presence of acidic and basic centers, carboxylic acids are capable of association by hydrogen bonds and, as a rule, exist in the form of dimmers.

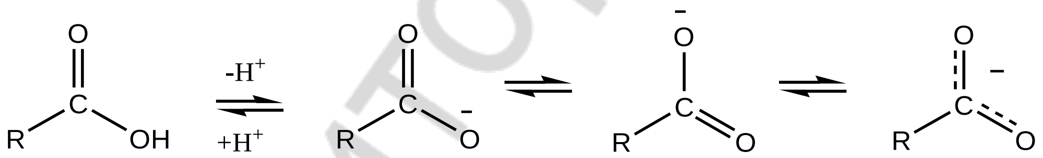


Acid ionization in water solution leads to the formation of carboxylate ion and hydrated proton.

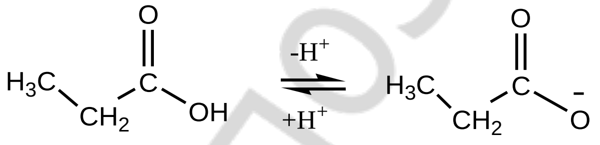


carboxylate ion

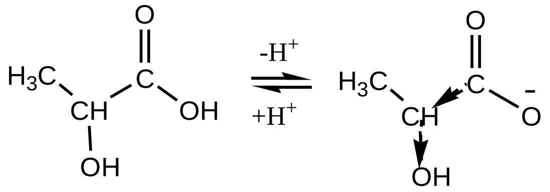
The strength of carboxylic acid properties is determined by the stability of the generated carboxylate ion. It's stabilization is realized due to *p*-π conjugation, as a result, negative charge proportionate equally among oxygen atoms (both length of bonds C – O are equal).



Electron-withdrawing substituents and conjugation increase acidity. Thus, the acidity of 2-hydroxypropanoic (lactic) acid greater than propanic acid.



propionic acid

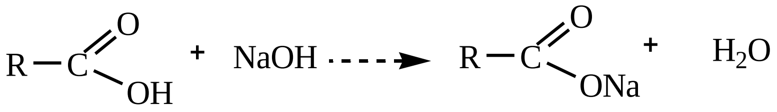


lactic acid

Hydroxyl group of lactic acid shifts the electronic density to itself delocalizing the negative charge and stabilizing anion.

Aromatic acids stronger than aliphatic due to formation of a strong conjugation system with the benzene ring.

Carboxylic acids react with bases to form salts. Salt formation is based on OH-acidic properties.

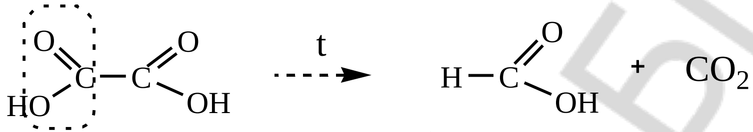


sodium carboxylate

Salts of long-chain fatty acids are called soaps (for example, sodium stearate $C_{17}H_{35}COONa$).

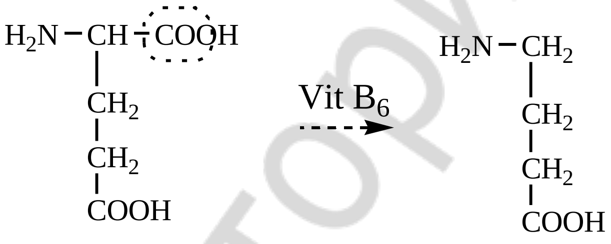
DECARBOXYLATION REACTIONS

Decarboxylation reaction is elimination reaction of CO_2. They are typical of the carboxylic acids in which the electron acceptor is in the alpha position to the carboxylic group. Oxalic and malonic acid are decarboxylated by heating.



oxalic acid formic acid

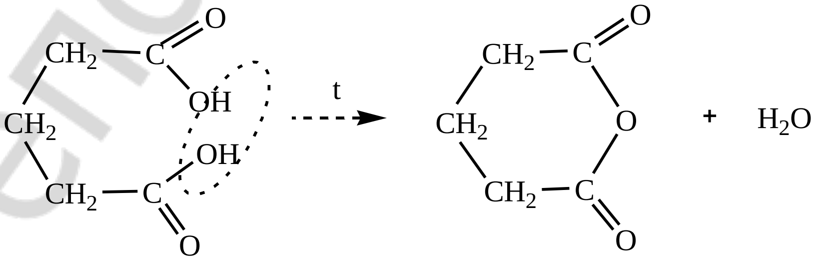
The decarboxylation reactions in biological systems are proceed with a participation of decarboxylase enzymes. Products of decarboxylation reaction of the proteinogenic amino acids are called biogenic amines.



glutamic acid γ-aminobutyric acid GABA

THE REACTION OF CYCLIC ANHYDRIDE FORMATION

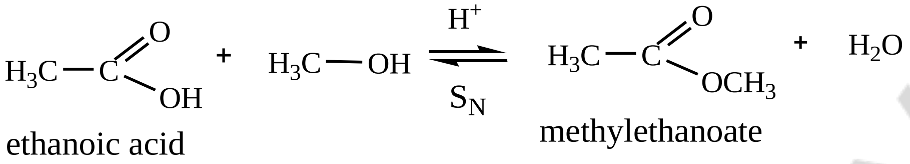
The heating of succinic and glutaric acids leads to cyclic anhydride formation which have the stable conformations.

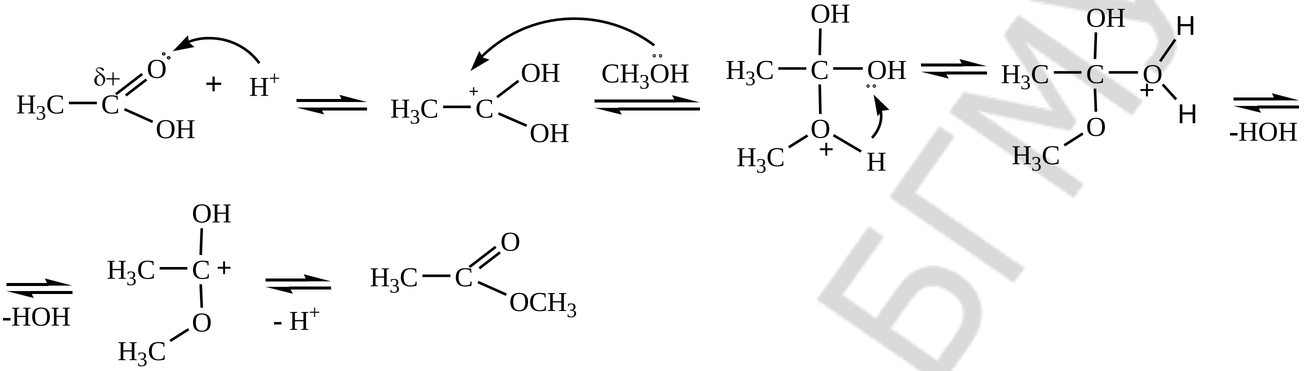


glutaric acid glutaric anhydride

NUCLEOPHILIC SUBSTITUTION REACTIONS

Nucleophilic substitution reactions on an electrophilic center of the carboxylic acid or its derivative are called **acylation** reactions. An example of the acylation reaction is esterification which represents the reaction of carboxylic acids and alcohols.



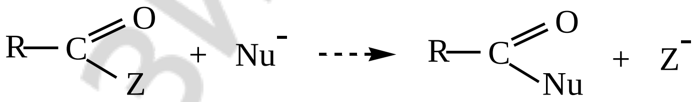


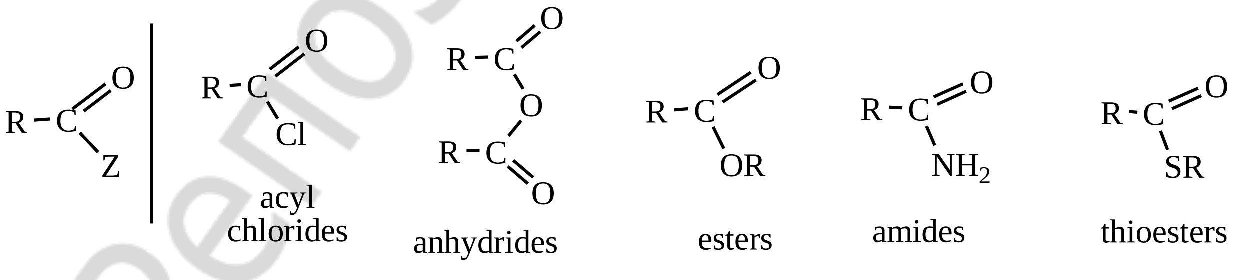
The esterification reaction is reversible. Esters readily undergo hydrolysis in acidic and alkaline conditions. Alkaline hydrolysis is called saponification because this type of reaction is used to make soaps (salts of long chain fatty acids) from fats. Saponification is an irreversible reaction.

$$R_1COOR_2 + NaOH \rightarrow R_1COO^{-}Na^{+} + R_2OH$$

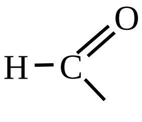
Many biologically important molecules and drugs are esters. A number of them are exposed to enzymatic hydrolysis. An ester bond is present in neurotransmitter acetylcholine, lipids, nucleotides, coenzymes, atc.

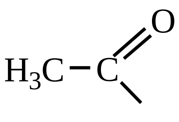
Functional derivatives of carboxylic acids can also enter into acylation reactions. The acylation reaction can be represented in general form as follows:

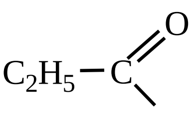




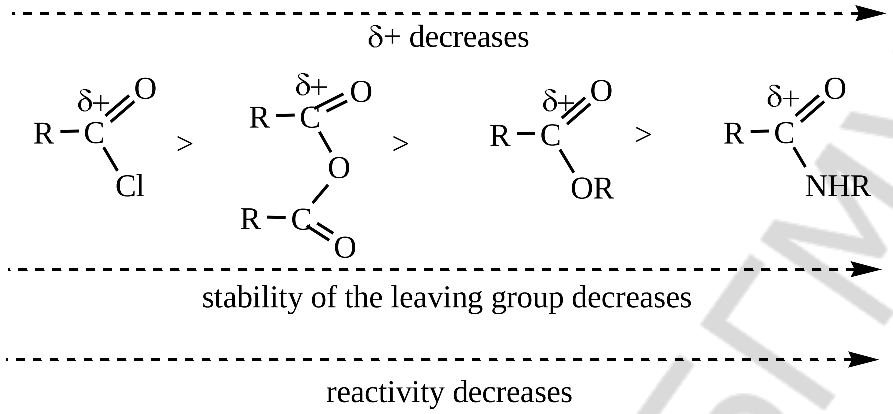
Acylation reaction is the transfer of an acyl residue (acetyl, formyl, etc.) on the nucleophile.


formyl

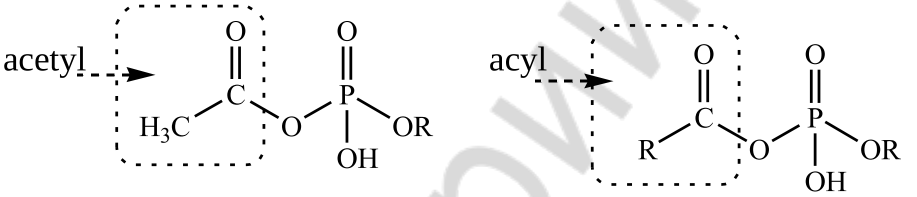

acetyl


propionyl

Reactivity of carboxylic acids in acylation reactions depends on the magnitude of the partial positive charge on the electrophilic center and stability of the leaving group. Thus, halogen anhydrides have the greatest acylating ability *in vitro*.

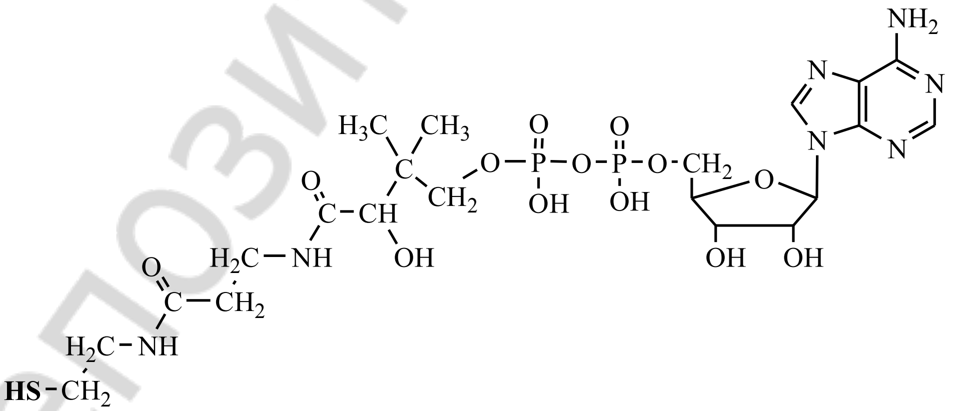


Acylation reactions *in vivo* mainly occur with participation mixed anhydrides and thioester. Mixed anhydrides may be formed by residues of the carboxylic acid (acyl) and phosphoric acid.



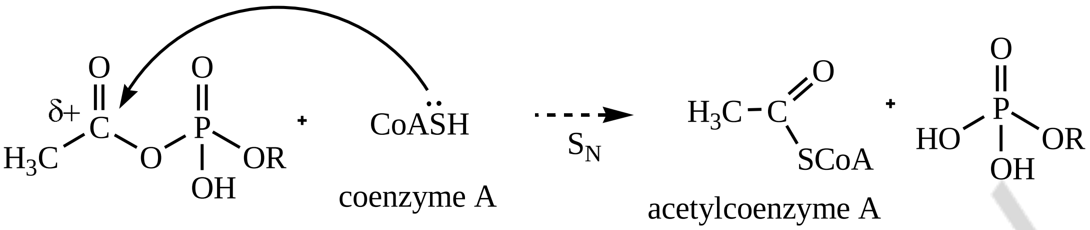
mixed anhydrides

One of the best acylating reagents (acetyl coenzyme A) is formed from a mixed anhydride and coenzyme A.

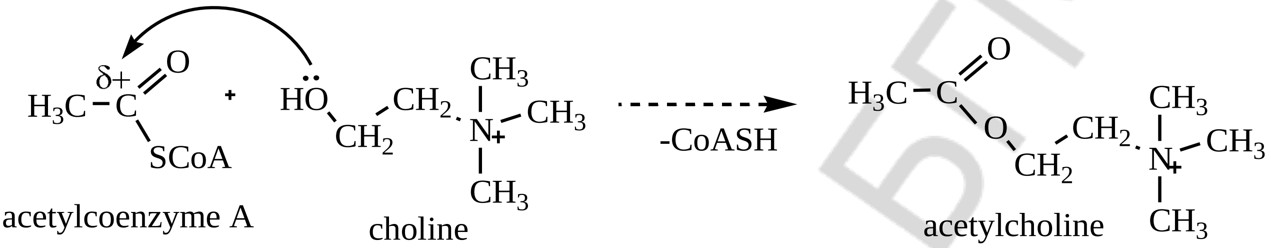


coenzyme A (CoA-SH)

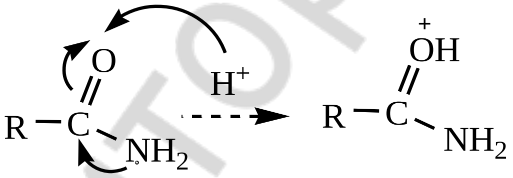
The mixed anhydride provides an electrophilic center. Coenzyme A is a nucleophile because of thiol group.The result is the synthesis of **acetyl coenzyme A**, which also is a good acylating agent.



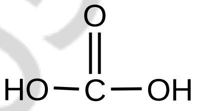
Thioesters are more widely spread in nature of carboxylic acid derivatives. Such representative of thioesters is acetyl coenzyme A. Acetyl coenzyme A *in vivo* serves as a carrier of the acetyl group (for example, at synthesis of acetylcholine).



Amides of carboxylic acids are the substitution products of a hydroxyl group at the -COOH on the amino group or substituted amino group. Amides have very weak basic properties as the *p* orbital of the nitrogen atom enters the conjugation with the π bond and shifts to the oxygen atom according to the positive mesomeric effect. Thus, amides attach proton only under highly acidic conditions, the ionization takes place mainly on the oxygen atom.

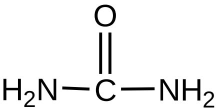


The amide bond is present in peptides and proteins. Full carbonic acid amide is urea which is a product of nitrogen metabolism in humans.



$\mathrm{HO-\overset{\overset{O}{\|}}{C}-OH}$

carbonic acid



$\mathrm{H_2N-\overset{\overset{O}{\|}}{C}-NH_2}$

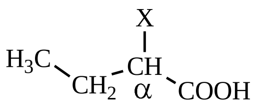
urea

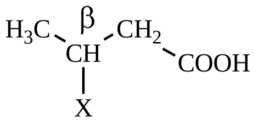
9. POLY- AND HETEROFUNCTIONAL COMPOUNDS

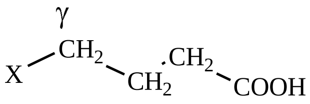
Very often biologically important organic compounds contain several functional groups. **Polyfunctional compounds** contain several identical functional groups. Polyfunctional compounds include polyols, diatomic phenols, dicarboxylic acids, and others. **Heterofunctional** compounds involve different functional groups in the same molecule. A significant importance in living systems belongs to this compounds.

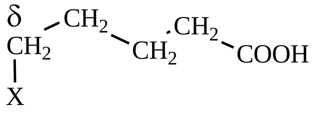
A hydroxyl, amino, oxo and carboxyl groups are most widely found in heterofunctional compounds.

Poly-and heterofunctional compounds have typical reactivity. The compound may react typical for each of the groups present in the compound. Mutual influence of functional groups leads to the appearance of specific properties. In various combinations of functional groups new properties appear. Mutual influence depends strongly on the relative position of functional groups, on their distance. For example, the functional group X may be located in the α, β, γ, δ positions relative to the carboxyl group. When the functional groups are close to each other their interaction is more sharply expressed.

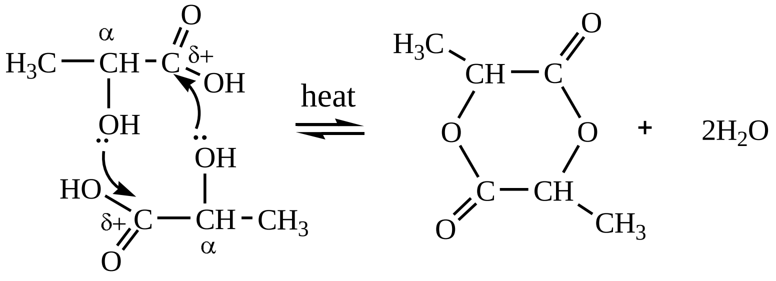






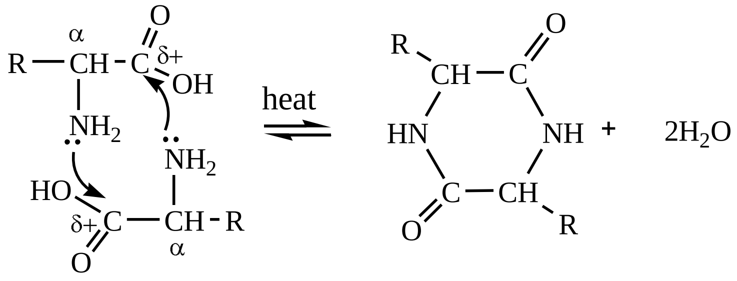


α-Hydroxy acids and α -amino acids can react intermolecularly. Lactic acid, for example, undergo to intermolecular esterification on heating. A six-membered cyclic diester (dilactide) is formed.



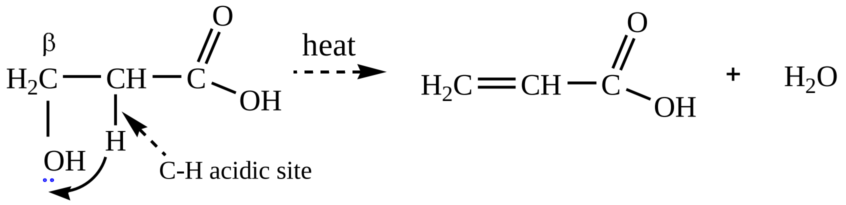
lactic acid dilactide

A similar intermolecular cyclization is characteristic for α amino acids. The reaction product is a cyclic diamide (diketopiperazine). The reaction proceeds according to the mechanism of nucleophilic substitution.

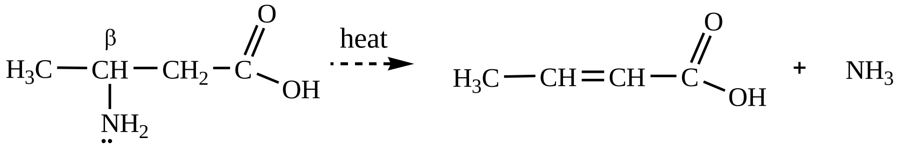


α–amino acid diketopiperazine

Elimination reactions are typical for β hydroxyl and β amino acids. Both types of the acids form α, β unsaturated acid releasing water or ammonia, respectively.

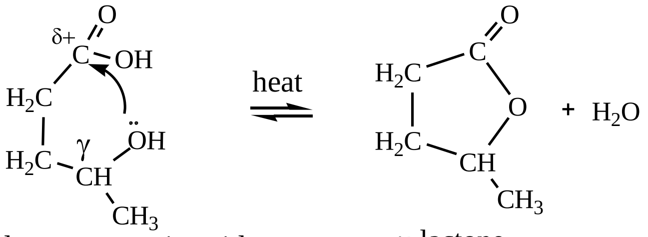


3-hydroxypropanoic acid propenoic acid



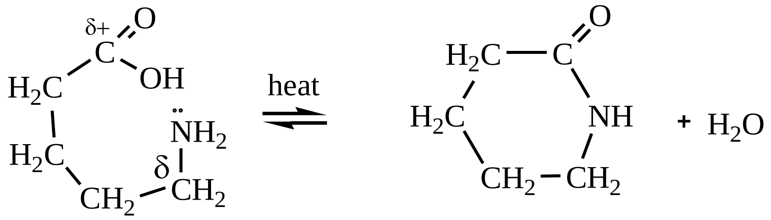
3-aminobutanoic acid but-2-enoic acid

The intramolecular interaction occurs when two functional groups occupy favourable positions for such a reaction. These reactions are possible for compounds having spaced apart functional groups. Nucleophilic substitution reactions are typical for γ and δ hydroxy or amino acids. Such molecules take claw-shaped conformation to make a better contact of both functional groups. The esterification reaction product of γ- and δ-hydroxyacid is lactone. The esterification reaction product of γ and δ amino acid is lactam.



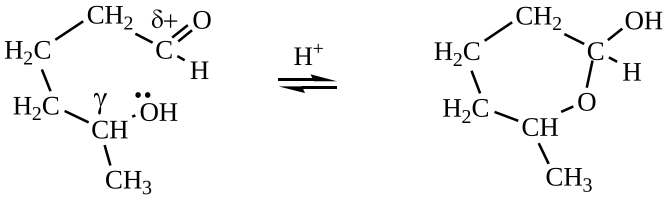
4-hydroxypentanoic acid γ-lactone

Cyclization occurs if a thermodynamically stable five- or six-membered cycle is formed.



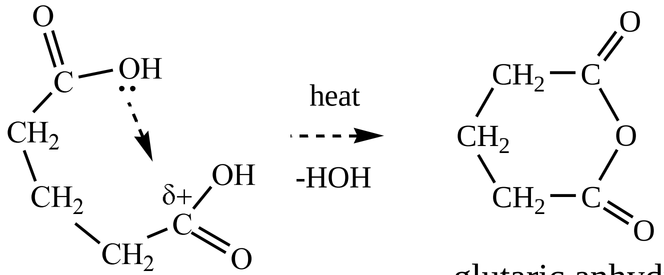
5-aminopentanoic acid δ-lactame

Aldehyde alcohols may form cyclic hemiacetals according to nucleophilic addition reaction.



5-hydroxyhexanal cyclic hemiacetal of 5-hydroxyhexanal

Dicarboxylic acids such as succinic and glutaric acids are also capable to cyclize.

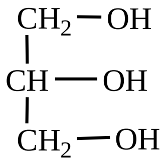


glutaric acid

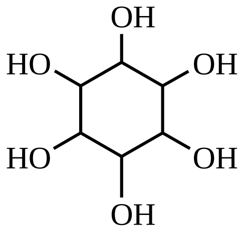
glutaric anhydride

REPRESENTATIVES OF BIOLOGICALLY IMPORTANT CLASSES OF POLY- AND HETEROFUNCTIONAL COMPOUNDS

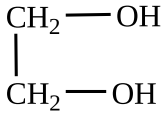
Polyols contain two or more hydroxyl groups. Glycerol and inositol are involved in constructing of lipids.



glycerol

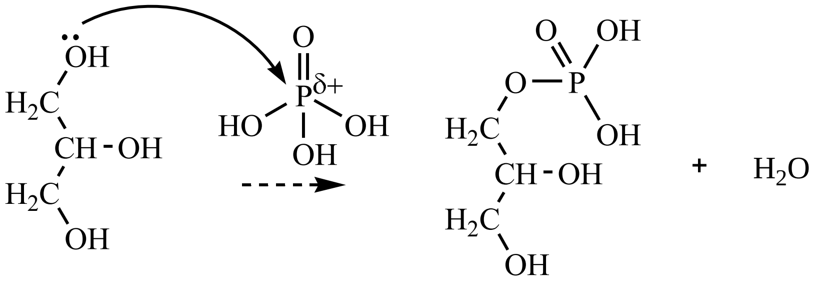


inositol



ethylene glycol

Glycerol and inositol may interact with different acylating reagents. α-Glycerophosphate is formed during the synthesis of phospholipids and triacylglycerols.

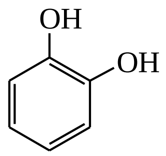


α-glycerophosphate

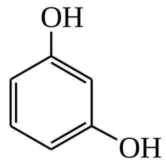
Ethylene glycol is toxic substance for human body. It is used in the technique for the preparation of antifreeze

Dicarboxylic acids, such as oxalic, malonic, succinic, glutaric, fumaric contain two carboxylic groups (their formulas are presented in chapter 8). Oxalic acid and oxalates are abundantly present in many plants. In humans, the insoluble calcium oxalate may be formed and deposited in the form of kidney stones. Malonic, succinic, glutaric and fumaric acids are the participants of the human metabolism.

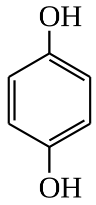
Catechol, resorcinol and hydroquinone refer to the group of **diatomic phenols**.



catechol

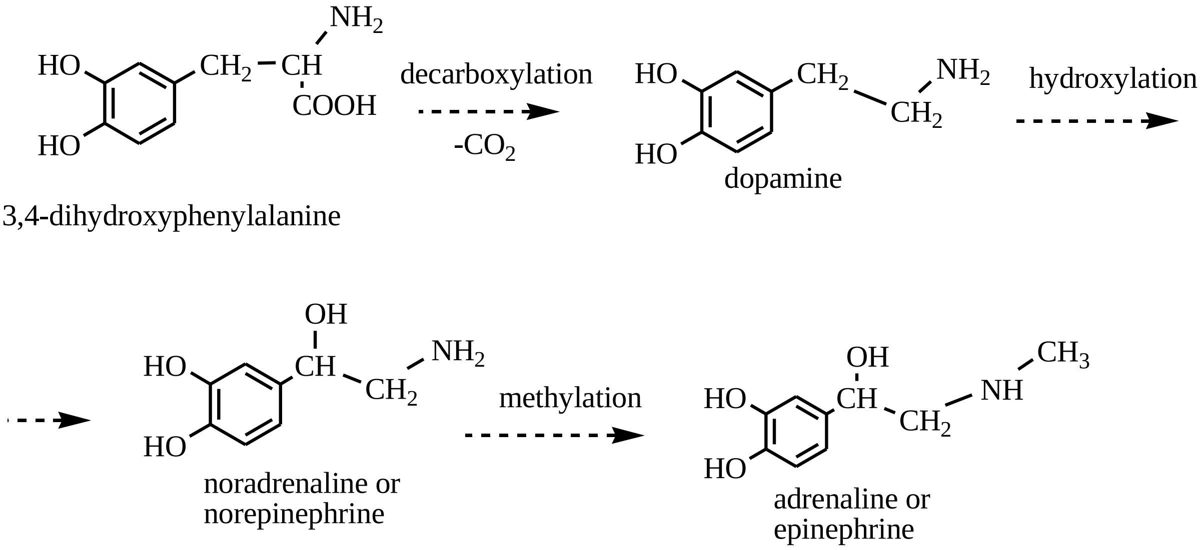


resorcinol



hydroquinone

Catechol is a part of the amino acid tyrosine, and catecholamines (dopamine, adrenaline and noradrenaline) which are synthesized from tyrosine with decarboxylation, hydroxylation and methylation reactions. These substances are also known as remedies stimulating adrenoreceptors.



3,4-dihydroxyphenylalanine

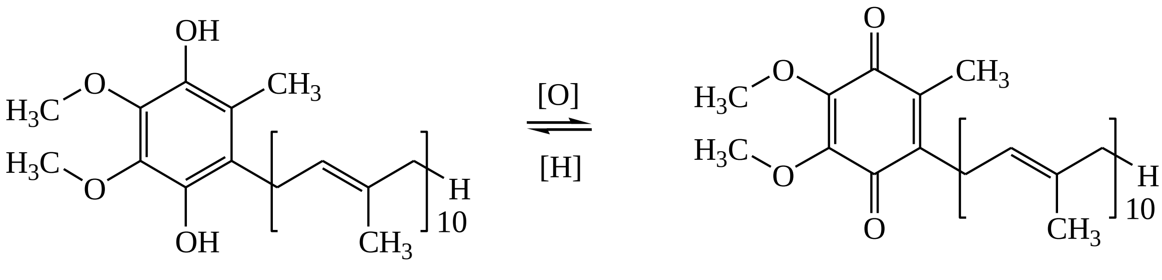
dopamine

noradrenaline or norepinephrine

adrenaline or epinephrine

Resorcinol has an antiseptic effect, used as a component of hygiene products.

Hydroquinone is a part of coenzyme Q, which involved in the transfer of electrons and protons in the respiratory chain.



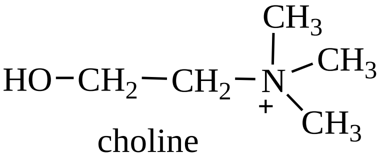
coenzyme QH

coenzyme Q

Representatives of **aminoalcohols** are ethanolamine and choline. They are involved in the construction of lipids.

$HO-CH_2-CH_2-NH_2$

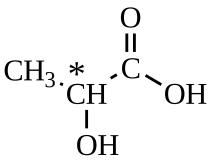
ethanolamine



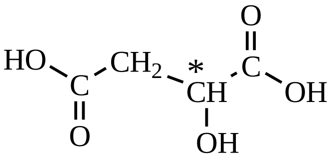
$HO-CH_2-CH_2-\overset{+}{N}(CH_3)_3$

choline

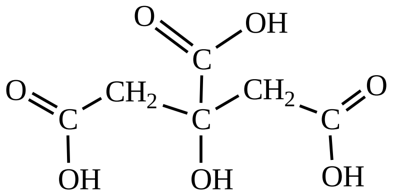
Biologically important **hydroxy acids** are lactic, malic and citric. Their trivial names are widely used in medicine and biology. Carboxyl group has ionized form at physiological pH value, various compounds having a carboxyl group is often referred to in accordance with the name of their salts.



lactic acid or lactate



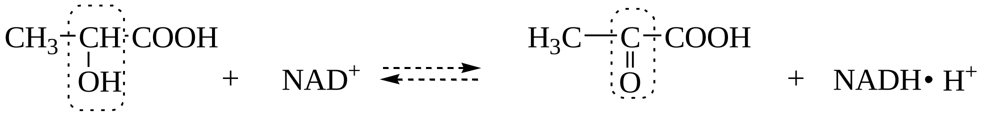
malic acid or malate



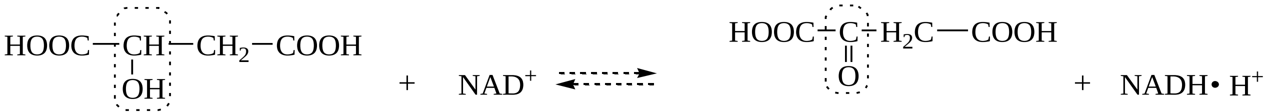
citric acid or citrate

Lactic acid and malic acid are chiral compounds. They are found in the human body only in the form of L-enantiomers. In humans L-lactate is produced from pyruvate via the enzyme in a process of fermentation during normal metabolism. Industrially, lactic acid fermentation is performed by *Lactobacillus bacteria*, among others. These bacteria can operate in the mouth; the acid they produce is responsible for the caries. Citric and L-malic acids are participants of Krebs cycle.

In the cell lactic and malic acids are oxidized with the coenzyme NAD$^+$ to the corresponding oxo acid (enzymatically).

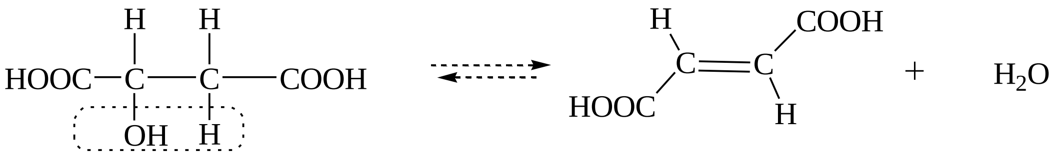


lactate pyruvate



malate oxaloacetate

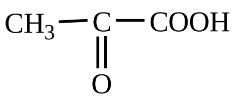
Malic acid is able to dehydration. This reaction proceeds in the Krebs cycle.



malic acid fumaric acid

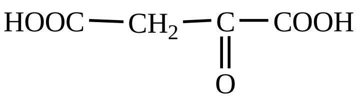
Citric acid has three carboxyl group. It is capable of binding multivalent ions, for example calcium. That is why sodium citrate is used for blood conservation. Citrate binds calcium ions of blood plasma and blood does not clot.

Biologically important **oxo acids** are pyruvic acid, oxaloacetic acid, α-ketoglutaric acid, acetoacetic acid.



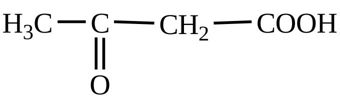
$$CH_3-\underset{\underset{O}{\|}}{C}-COOH$$

pyruvic acid or pyruvate



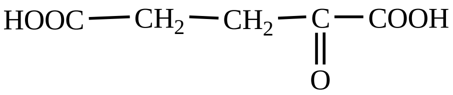
$$HOOC-CH_2-\underset{\underset{O}{\|}}{C}-COOH$$

oxaloacetic acid or oxaloacetate



$$H_3C-\underset{\underset{O}{\|}}{C}-CH_2-COOH$$

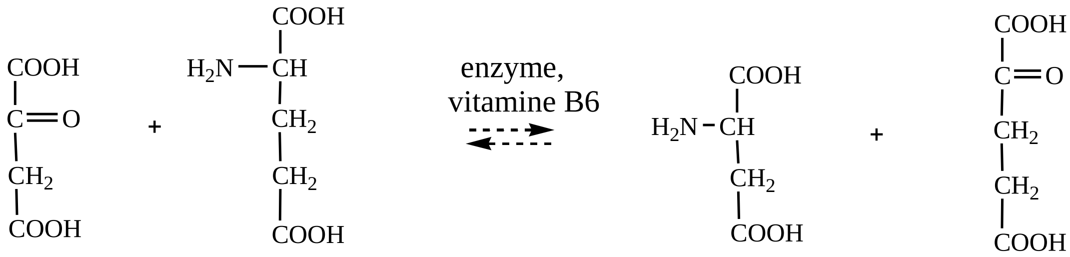
acetoacetic acid



$$HOOC-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-COOH$$

α-ketoglutaric acid

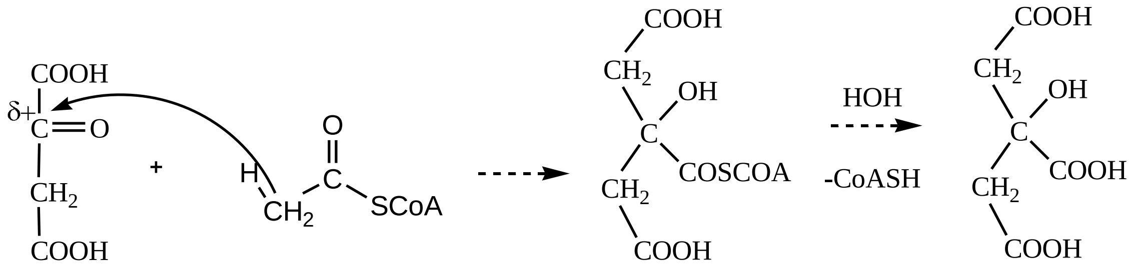
Transamination reaction is typical for oxo acids in cell. This reaction is the exchange of functional groups on the α carbon atom between the oxo acid and amino acid.



oxaloacetic acid L-glutamic acid L-aspartic acid α-ketoglutaric acid

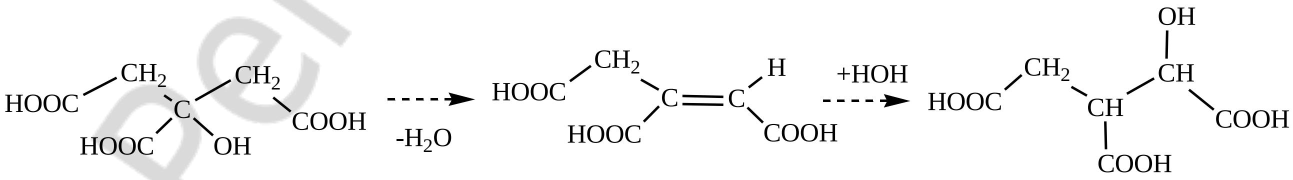
Substrates for the transamination reaction can be other oxo acid. The reaction is reversible.

Oxaloacetic acid is reacted by aldol condensation with acetyl coenzyme A to form citric acid *in vivo*.



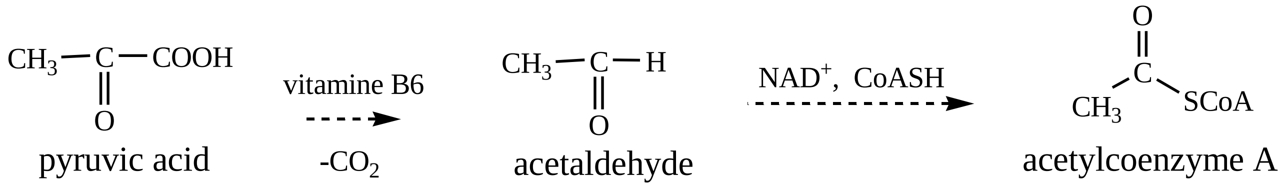
oxaloacetic acid acetylcoenzyme A citric acid

Citric acid which can undergo elimination of water. Then hydration reaction proceeds with the formation of citric acid isomer. These reactions occur in the Krebs cycle.

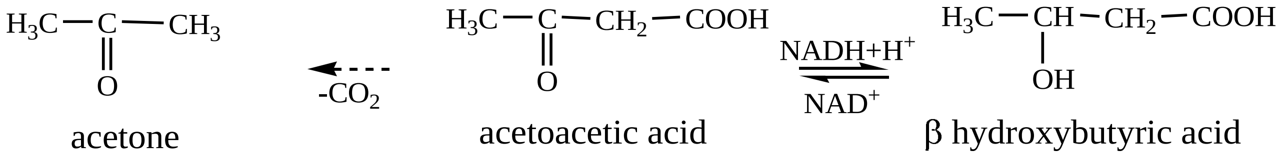


citric acid *cys*-acontic acid isocitric acid

Decarboxylation plays an essential role in metabolic processes. Oxo and amino acids are enzymatically decarboxylated in a cell. Pyruvic acid is subjected to **oxidative decarboxylation** which leads to the formation of acetyl coenzyme A.



Ketone bodies are three water-soluble compounds (acetone, acetoacetic acid, and β hydroxybutyric acid. They are produced in significant quantities at decompensated diabetes and during prolonged starvation.



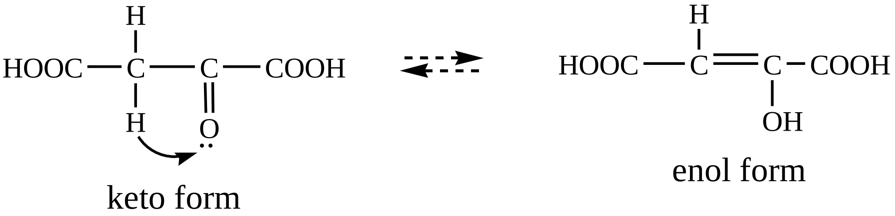
Ketone bodies are used as a source of energy in the heart and brain. In the brain, they are a vital source of energy during fasting.

Amino acids will be discussed in a special section.

TAUTOMERISM

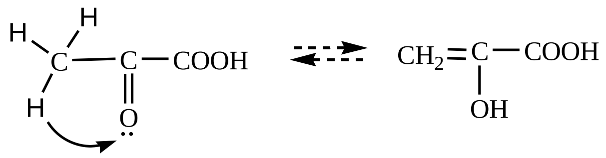
Tautomerism is a dynamic isomerism in which isomers can transform into each other, being in solution in a state of dynamic equilibrium. Usually tautomerization is accompanied by migration of a proton. This is prototropic tautomerism. There are several types of prototropic tautomerism. **Keto-enol tautomerism** is more pronounced for compounds that have a strong CH-acidic site and adjacent oxo group. This is observed in β-oxo carboxylic acids and their derivatives. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The ratio of the tautomers depends on several factors. The predominant form will be more stable. Tautomerism can play an important role in biochemistry.

Oxalacetic acid is one of the most important carboxylic acids in many biochemical processes. Despite its common name that corresponds to an oxo acid, this compound is a rather unsaturated acid because of the predominance of the enol form in the tautomeric equilibrium (80 %).



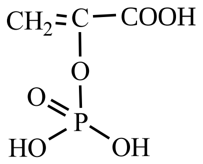
oxaloacetic acid

Phosphoenolpyruvic acid is an example of an enolic compound in living systems. It is produced in the glycolysis process and represents a phosphate of pyruvic acid in the enol form. Phosphoenolpyruvic acid is an energy-rich compound that eliminates energy for its transformation to pyruvic acid.



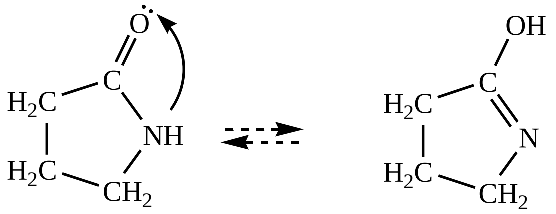
keto-form enol-form

pyruvic acid



phosphoenolpyruvic acid

Cyclic amides – lactams – are also characterized by tautomerism, which is called lactam-lactim tautomerism.

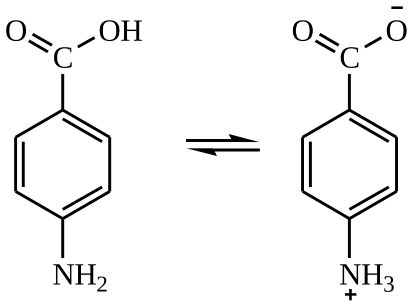


γ lactam of 4-aminobutanoic acid

γ lactim of 4-aminobutanoic acid

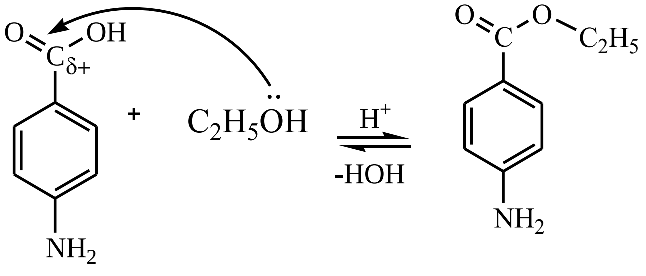
HETEROFUNCTIONAL COMPOUNDS CONTAINING BENZENE RING

p-Aminobenzoic acid is a metabolite. It is part of folic acid, it has amphoteric properties.



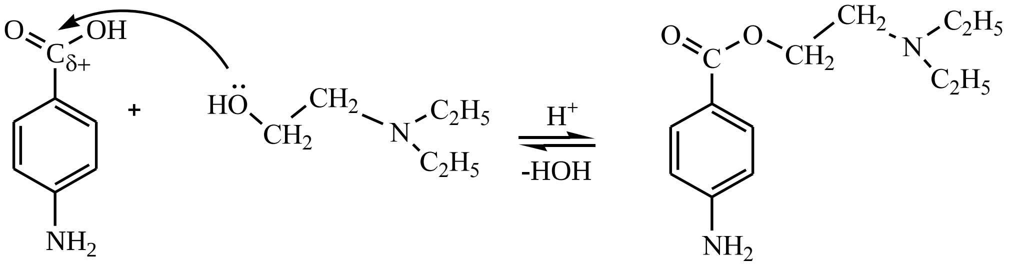
p-aminobenzoic acid

p-Aminobenzoic acid is also the basis for the synthesis of local anesthetics. The oldest of them is the ethyl ester or bensocaine (anesthesine) which is used for more than a hundred years. But more effective are procaine and its soluble salt novocaine.



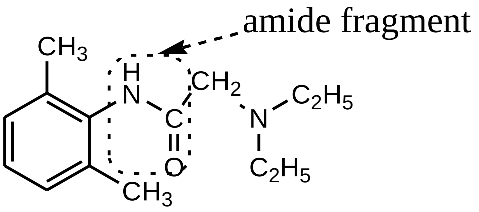
p-aminobenzoic acid

benzocaine



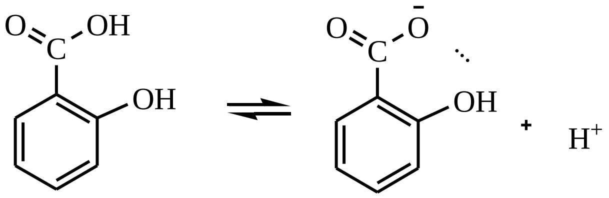
p-aminobenzoic acid procaine

Currently the most effective remedies are compounds with more steady amide bond such as lidocain, ultracain.



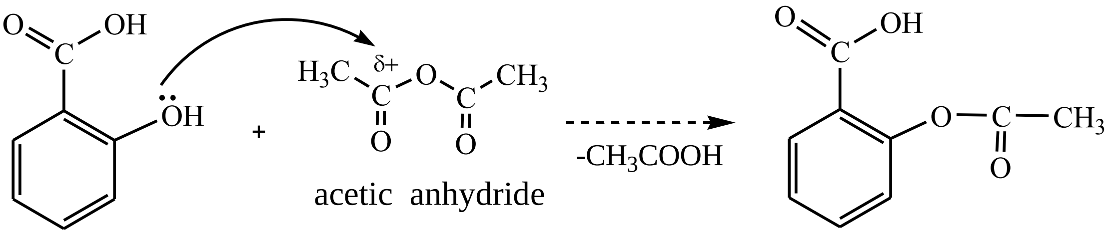
lidocaine

Representative of phenolic acids is salicylic acid. It is a relatively strong acid, as its anion is stabilized by an intramolecular hydrogen bond



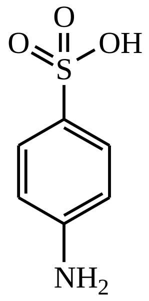
salicylic acid

Salicylic acid forms esters in the reactions with alcohols. Esterification of acid with methanol results in the formation of methyl salicylate. The reaction of salicylic acid with acetic anhydride is used to synthesize aspirin (acetylsalicylic acid). Aspirin is a salicylate drug, often used as an analgesic, an antipyretic and an antiinflammatory medication. It also has an antiplatelet effect.

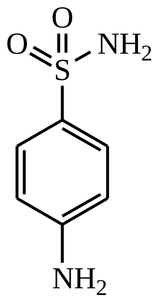


salicylic acid acetylsalicylic acid

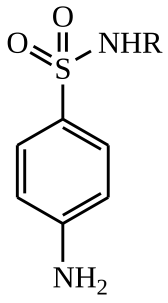
Sulfa drugs are derivatives of sulfanilic acid. They exhibit antibacterial properties.



sulfanilic acid



sulfanilamide



general formula
of sulfa drugs

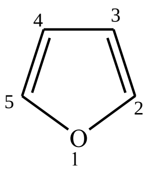
In bacteria, antibacterial sulfonamides inhibits synthesis of folate (vitamine B_c) because of sulfonamide molecule is similar to molecule of *p*-aminobenzoic acid which is necessary for synthesis of folate. Folate is necessary for the cell to synthesize nucleic acids, and in its absence cells will be unable to divide. Hence the sulfonamide antibacterials exhibit a bacteriostatic effect. Folate is not synthesized in mammalian cells. This explains the selective toxicity to bacterial cells of these drugs.

10. BIOLOGICALLY IMPORTANT HETEROCYCLIC COMPOUNDS. ALKALOIDS

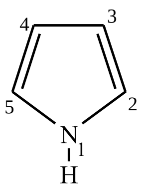
Heterocyclic compounds are cyclic organic compounds which contains one or more atoms of other elements, besides carbon atoms (N, O, S).

According to the ring size heterocycles are divided into five- and six-membered.

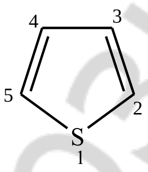
FIVE-MEMBERED CYCLES



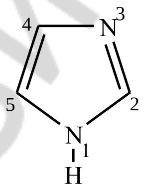
furan



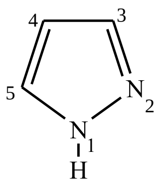
pyrrole



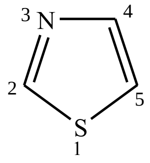
thiophene



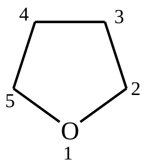
imidazole



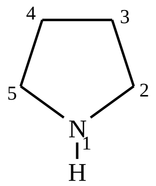
pyrazole



thiazole

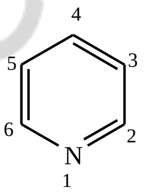


tetrahydro-
furan

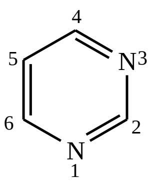


pyrrolidine

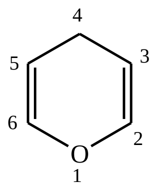
SIX-MEMBERED CYCLES



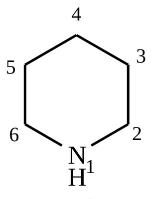
pyridine



pyrimidine



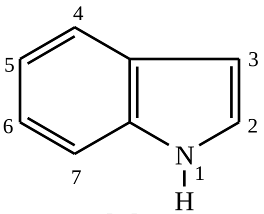
pyran



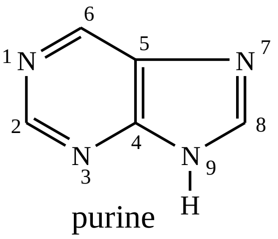
piperidine

According to the degree of saturation heterocycles are divided into saturated, unsaturated and aromatic.

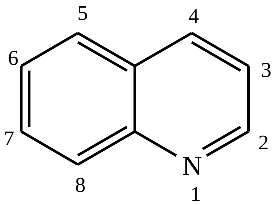
Fused heterocycles are often found in biologically important molecules.



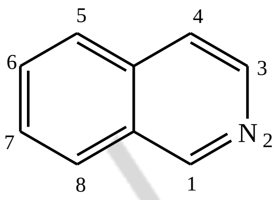
indole



purine



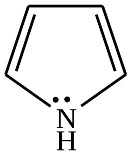
quinoline



isoquinoline

REPRESENTATIVES OF THE HETEROCYCLIC COMPOUNDS

Pyrrole is nitrogen-containing five-membered aromatic cycle. Pyrrole nitrogen has a special structure.



pyrrole

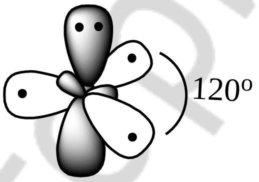
$_7$N $1s^22s^22p_x^12p_y^12p_z^1$

electronic configuration
of the ground state N

$1s^22s^12p_x^12p_y^12p_z^2$

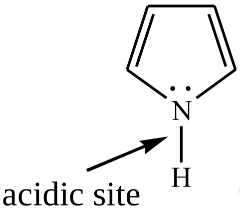
electronic configuration
of the exited state N

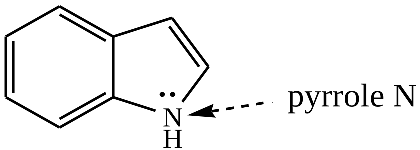
Electron orbitals of the excited nitrogen atoms undergo sp^2 hybridization. Three hybrid orbitals (same energy and form) bear 1 electron, they lie in one planeand. Unhybridized p_z orbital has a pair of electrons and it is perpendicular to the hybride orbital plane.



pyrrole nitrogen

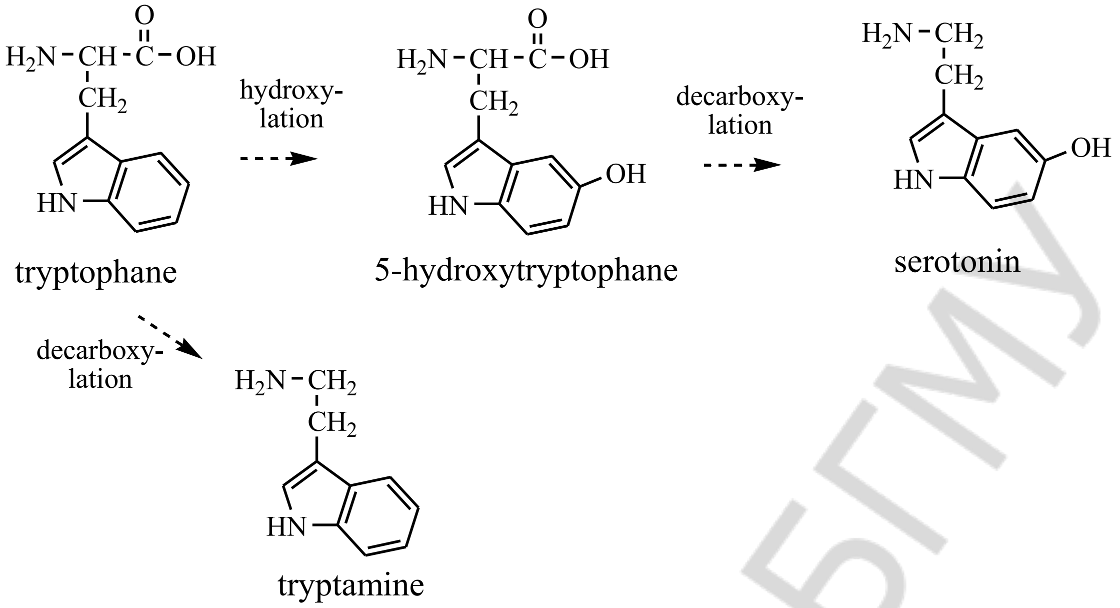
Electron pair of nitrogen takes part in the formation of cyclic conjugation. Pyrrole is aromatic compound because all atoms in the cycle are in sp^2 hybridization, molecule has cyclic conjugated system (π-π-p) and 6 electrons participate in the conjugation (4n +2 = 6, n = 1). Pyrrole is π-excessive system because six *p* electrons belong to five-membered ring. Therefore, pyrrole comes into reactions of electrophilic substitution easier than benzene. Pyrrole does not exhibit the basic properties, but it is a weak N-H acid. Pyrrole nitrogen atom is a part of the **indole**.



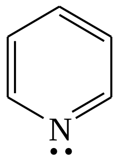


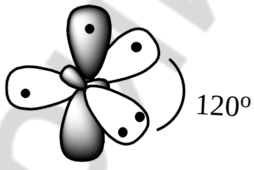
indole

Indole is a part of the amino acid tryptophan and biogenic amines — serotonin and tryptamine. Indole is also part of some drugs.



Pyridine is nitrogen-containing six-membered aromatic cycle. The structure of the pyridine nitrogen atom has its own characteristics. A nitrogen atom in the ground state is subjected hybridization.

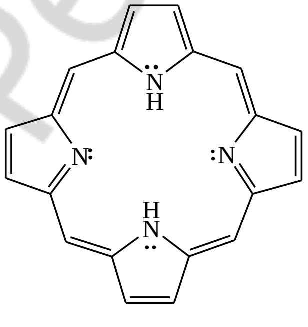

pyridine

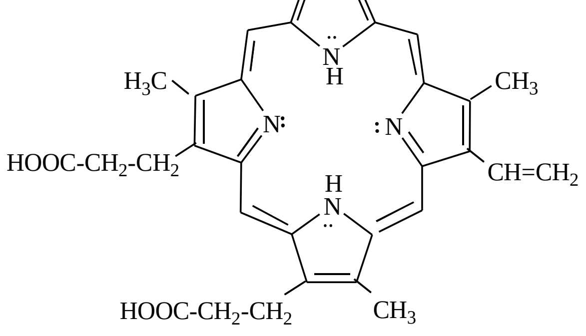


pyridine nitrogen

Pyridine is aromatic compound because all atoms in the cycle are in sp^2 hybridization, molecule has cyclic conjugated system (π-π-π) and 6 electrons participate in the conjugation (4n +2 = 6, n = 1). Pyridine is π insufficient system due to electron acceptor action of the nitrogen. A lone pair of electrons of the nitrogen atom provides basic properties.

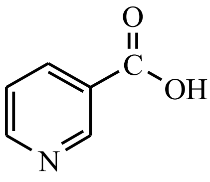
Compounds containing more than one pyrrole rings are widespread in nature. For example, **porphine**. Porphines, partially or completely substituted in the pyrrole ring, called porphyrins. The representative of the porphyrins, protoporphyrin, is shown in figure.


porphine

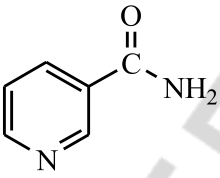

protoporphyrin

Porphine has aromatic properties. Circular conjugation includes 18 *p* electrons: $4n + 2 = 18$ ($n = 4$). The total number of electrons in the conjugated system is 26. Porphyrin complex with ferrum ion is the basis of the heme. Heme is prosthetic group of hemoglobin. Heme oxidation in our organism is accompanied by the formation of an orange pigment — bilirubin.

Pyridine underlies the structure vitamine PP. It comprises two compounds: nicotinic acid and its amide.

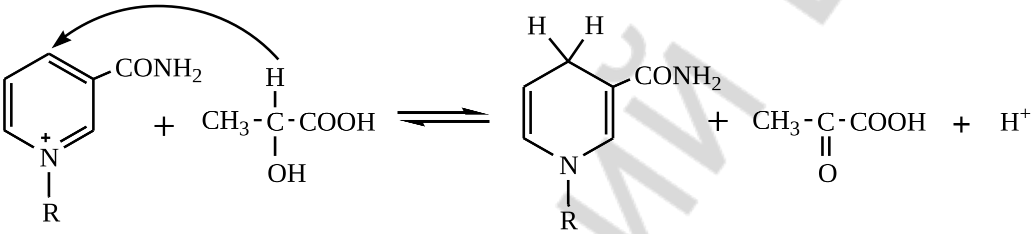


nicotinic acid



nicotinamide

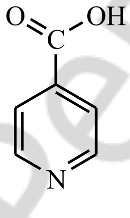
Nicotinamide role is to transfer a hydride ion (as part of the coenzyme NAD^+).



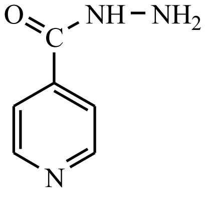
NAD^+ lactate NADH pyruvate

For example, the coenzyme NAD^+ adds a hydride ion at γ position of nicotinamide during oxidation of lactic acid. Coenzyme NAD^+ is converted to its reduced form NADH. The cycle of pyridine loses aromaticity. Lactic acid is converted into pyruvic acid. The reaction is reversible.

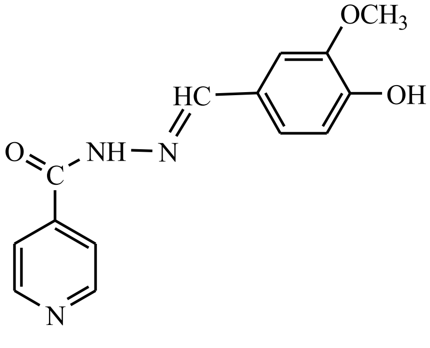
Isonicotinic acid is an isomer of nicotinic acid: the carboxyl group is on the 4-position instead of the 3-position for nicotinic acid. Isonicotinic acids is a term loosely used for derivatives of isonicotinic acid. Isoniazid and phthivazid are a first-line antituberculous medications used in the prevention and treatment of tuberculosis.



isonicotinic acid

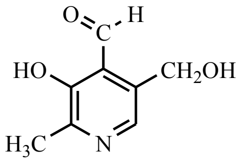


isoniazid

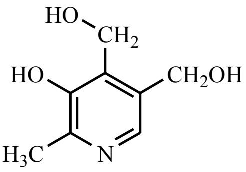


phthivazid

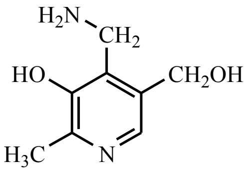
Pyridine is a part of the vitamin B_6. Several forms of vitamin B_6 exist. Pyridoxal phosphate is the metabolically active form.



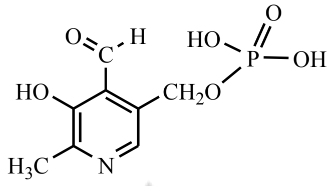
pyridoxal



pyridoxol



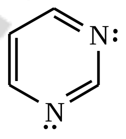
pyridoxamine



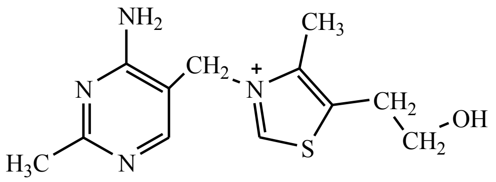
pyridoxal phosphate

Vitamin B_6 is involved in decarboxylation reactions of amino acids and transamination reactions as a coenzyme.

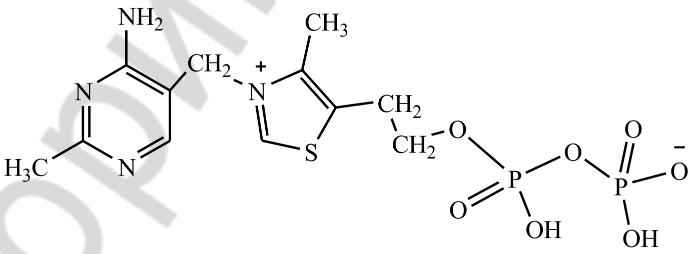
Pyrimidine has two atoms of pyridine nitrogen, which are the basic centers. Since the nitrogen atoms are an electron acceptor action on each other, the basic properties of the pyrimidine weaker than pyridine. Pyrimidine underlies nucleic bases forming part of DNA and RNA (uracil, cytosine, thymine). They will be examined further in the relevant section. Pyrimidine is a part of thiamine (vitamin B_1). Thiamine is involved in the decarboxylation reactions of α oxo acid. Thiamine diphosphate is a metabolically active form of vitamin B_1. It is formed by the phosphorylation reaction of alcohol group.



pyrimidine

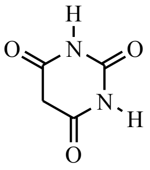


thiamine (vitamin B_1)

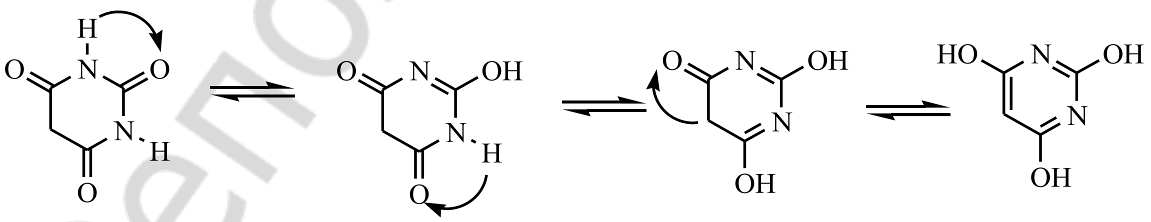


thiamine diphosphate

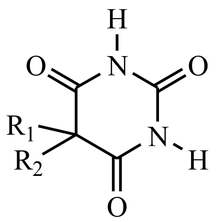
Barbituric acid is pyrimidine derivative. It exist in several tautomeric forms. Two types of tautomerism are typical for barbituric acid: lactime-lactam and keto-enol. Mutual transitions from one form to another are shown by arrows.



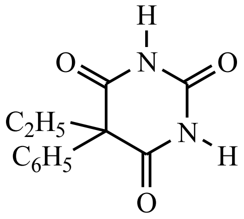
barbituric acid



Barbituric acid is the parent compound of a large class of barbiturates that have central nervous system depressant properties although barbituric acid itself is not pharmacologically active.

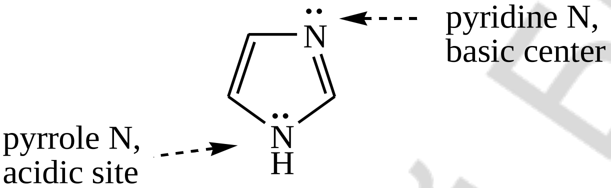


the general formula of
barbituric acid derivatives

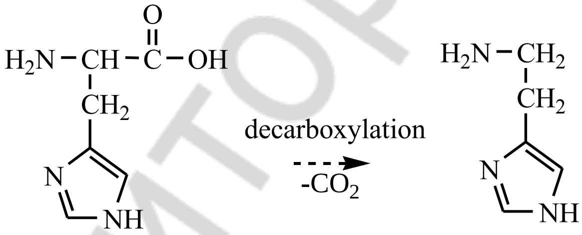


phenobarbital

Imidazole is five-membered aromatic cycle. It contains two nitrogen atoms. One of them is a nitrogen atom of the pyrrole type. It has a property of weak acid. Other nitrogen — pyridine type. It has basic properties.

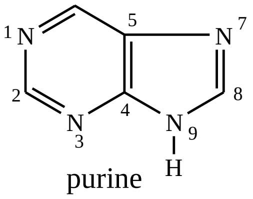


Thanks to amphoteric properties of imidazole is involved in the transfer of a proton (the acid-base catalysis). It is a part of many biologically important compounds. Histamine, for instance, is formed from histidine by decarboxylation reactions in eosinophils and basophils. Histamine participates in inflammatory and allergic responses.



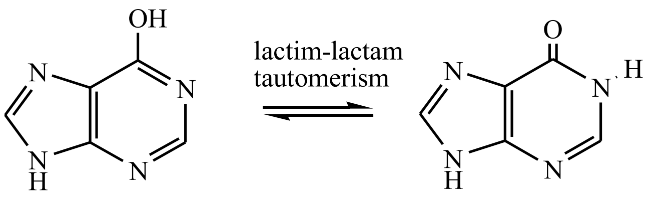
histidine histamine

Purine is a fused ring consisting of pyrimidine and imidazole. Purine is a part of purine nucleic bases (adenine, guanine). It is also present in the structure of hypoxanthine, xanthine and uric acid which are the end products of metabolism of purine bases.

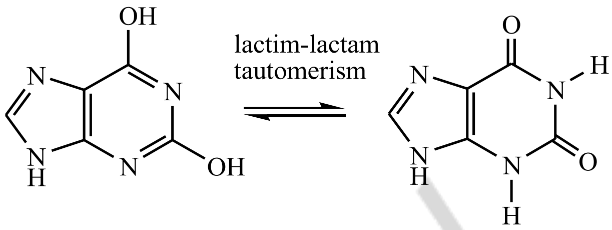


purine

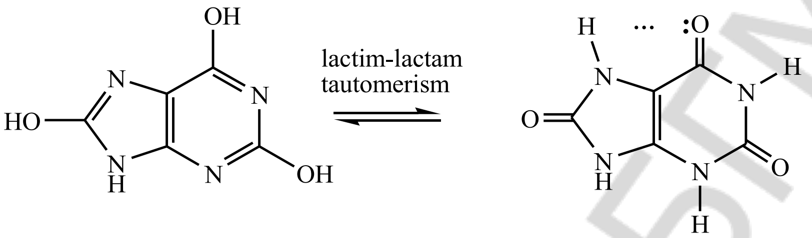
Adenine and guanine are discussed later in the section dedicated to the nucleic acid. This section will examine the degradation products of purine bases in cell: hypoxanthine, xanthine and uric acid. Figure shows the tautomeric forms of these compounds. Lactam form is more stable.



6-hydroxypurine
(hypoxanthine)

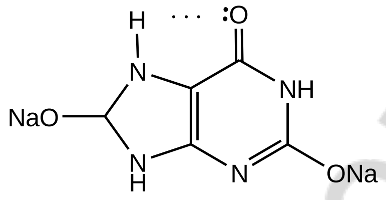


2,6-dihydroxypurine
(xanthine)

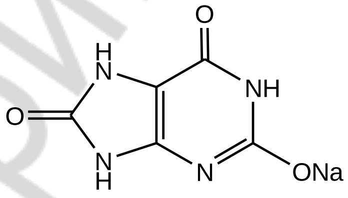


2,6,8-trihydroxypurine
(uric acid)

In humans and higher primates, uric acid is the final oxidation product of purine catabolism. In humans, about half the antioxidant capacity of plasma comes from uric acid. Uric acid is a dibasic acid. It forms two series of salts (urates).



soluble



unsoluble

Unsoluble urates can be placed in the joints as stones in some diseases.

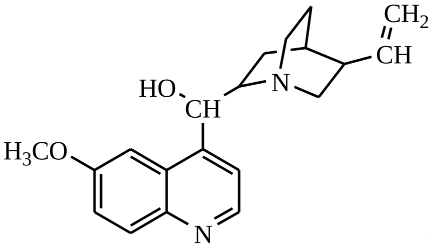
ALKALOIDS

Alkaloids are natural chemical compounds containing nitrogen atoms. The name derives from the word *alkaline*. Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants. They are the part of the natural products (also called secondary metabolites). Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications and recreational drugs. Examples are the local anesthetic and stimulant cocaine, the stimulant caffeine, nicotine, the analgesic morphine, or the antimalarial drug quinine. Some alkaloids have a bitter taste.

There are several classifications of alkaloids, including botanical and chemical. The chemical classification is based on the name of the heterocycle, which is part of alkaloid. There are the following groups: pyridine, pyrrolidine, tropane, isoquinoline, indole group, purine group, xanthine, and others.

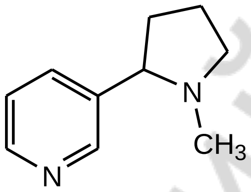
Basicity of alkaloids depends on the lone pairs of electrons on their nitrogen atoms. As organic bases, alkaloids form salts with mineral acids such as hydrochloric acid and sulfuric acid and organic acids such as tartaric acid or maleic acid. These salts are usually more water-soluble than their free base form.

Quinine has been isolated from the bark of the cinchona tree. This alkaloid has antipyretic effect, and is also used in the treatment of malaria. It contains quinoline and quinuclidine.



quinine

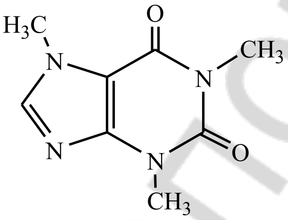
Nicotine is the most studied alkaloid of tobacco, as well as other plants of the nightshade family. Nicotine refers to the group of pyridine, and pyrrolidine.



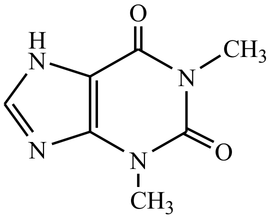
nicotine

In low concentrations (an average cigarette yields about 1 mg of absorbed nicotine), the substance acts as a stimulant in mammals and is one of the main factors responsible for the forming of dependence of tobacco smoking. Nicotine acts on the nicotinic acetylcholine receptors.

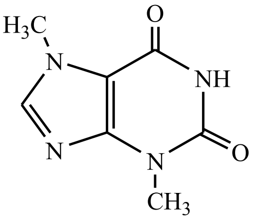
Caffeine is a bitter white crystalline xanthine alkaloid that acts as a psychoactive stimulant drug and a mild diuretic in humans. Caffeine is found in varying quantities in the beans, leaves, and fruit of over 60 plants. The most commonly used caffeine containing plants are coffee, tea, and to a lesser extent cocoa.



caffeine



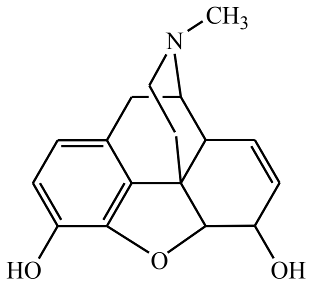
theophylline



theobromine

These plants also contain other alkaloids group of xanthine – theophylline and telbromin. Xanthine alkaloids act on the purine receptors in humans.

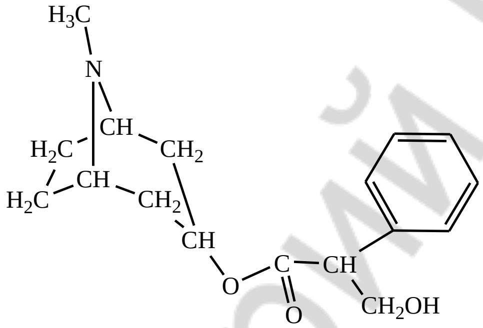
Morphine is an alkaloid of opium poppy. It belongs to the phenanthrene and isoquinoline group. It has an analgesic effect and therefore used in medicine. Morphine is the narcotic drug and is the standard against which all other opioids are tested.



morphine

Morphine interacts predominantly with the opioid receptors. Activation of the opioid receptors is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression.

Atropine is a tropane alkaloid extracted from the deadly nightshade (Atropa belladonna) and other plants of the family Solanaceae.



atropine

It is a secondary metabolite of these plants and serves as a drug with a wide variety of effects. It is a competitive antagonist for the muscarinic acetylcholine receptor. It is classified as an anticholinergic drug.

11. ORGANIC COMPOUNDS USING IN DENTISTRY

Organic compounds used in dentistry include primarily polymers. **Polymers** are substances that consist of large molecules called macromolecules that are made up of many repeating units. **Monomers** is a low molecular weight compounds from which the polymers are formed. The polymers are produced in a polymerization reaction.

CLASSIFICATION OF POLYMERS

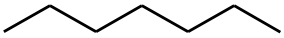
1. According to origin: **natural** and **synthetic.**

Macromolecules such as DNA, RNA, proteins, cellulose, starch are natural polymers. Representatives of synthetic polymers are polyethylene, polypropylene, phenol-formaldehyde resins, nylon and others.

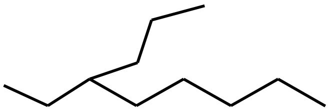
2. According to the number of monomer: **homopolymers** and **copolymers**.

Macromolecules are derived by polymerization of a single monomer are known as homopolymers. Polymers derived from two or more monomers are known as copolymers. For example, starch is a homopolymer composed of molecules of glucose. Protein is formed by different amino acid residues.

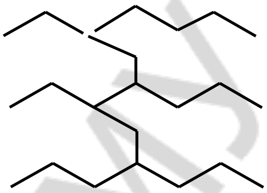
3. According to the structure of macromolecule: **linear, branched** and **spatial (or cross-linked).**



linear



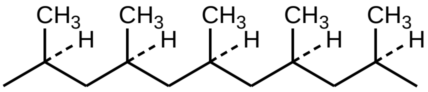
branched



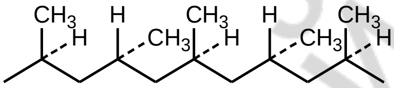
spatial

For example, polyethylene has a linear structure. Starch is a branched polymer. Polymerization of certain monomers leads to the formation of a two- or three-dimensional structures (networks), which are called spatial or cross-linked polymers.

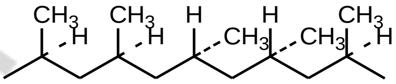
3. According to the spatial isomerism chain: **isotactic, syndiotactic** and **atactic**.



isotactic



syndiotactic



atactic

Isotactic polymer arranges all substituents on the same side of the polymer chain (chain see as a zig-zag). Syndiotactic polymer arranges substituents on the alternating sides of the zig-zag chain. Atactic polymer has its substituents arranged randomly on the chain.

4. In relation to heating polymers are divided into **thermoplastic** and **thermosetting**. Thermoplastic materials can be repeatedly heated and cooled. Thus they do not lose their properties and form. Most thermoplastic materials have a linear structure. They are often used in traumatology, orthopedics, dental surgery in the treatment of injuries. Thermosetting materials may be shaped by heating only once. And upon further heating they retain it. Most thermosetting materials have a network structure. Thermosetting polymers are used for producing household articles.

TYPES OF POLYMERIZATION REACTIONS

Two types of polymerization are possible: **chain** and **step** polymerization.

Chain polymerization is accompanied sequential addition of each monomer unit to the active site, located at the end of the growing chain. Monomer has double bond.

$$\underset{monomer}{n\,CH_2 = CH_2} \quad \rightarrow \quad \underset{polymer}{-[CH_2 - CH_2]_n-}$$

The reaction requires an initiator. **Initiators** are substances that trigger the chain polymerization. There are three types of chain polymerization depending upon the nature of the initiator: **cationic**, **anionic** and **radical**. Acids are used as initiators of cationic polymerization. Anionic initiation requires a base to start reaction. Anionic and cationic polymerization are not used in dentistry. Radical reaction initiators are substances which easily decompose into radicals under the action of light, heat or activators. **Activators** contribute to the decay the initiators.Compounds containing nonpolar bonds (peroxides, azo-, diazo- compounds) prone to disintegration and formation of homolytic radicals.

Polymerization reaction mechanism involves several steps: **initiation, propagation and termination.**

Initiation:

$$\underset{\text{initiator}}{\mathrm{In - In}} \xrightarrow{\text{heating, light or activator}} \underset{\text{free radicals}}{\mathrm{In}\cdot + \cdot\mathrm{In}}$$

$$\mathrm{In}\cdot + \underset{\text{mononer}}{\mathrm{M}} \longrightarrow \mathrm{In - M}\cdot$$

The next stage is accompanied by the growth of the chain.

Propagation:

$$\mathrm{In - M}\cdot + \mathrm{M} \longrightarrow \mathrm{In - M - M}\cdot$$

$$\mathrm{In - M - M}\cdot + \mathrm{M} \longrightarrow \underset{\text{up to Mx, where x is the number of monomers}}{\mathrm{In - M - M - M}\cdot}$$

Radicals with the high molecular weight encounter each other and recombine. Another variant of chain termination is the interaction with **inhibitor**, which breaks chain growth.

Termination:

$$\mathrm{In - Mx}\cdot + \cdot\mathrm{Mx - In} \longrightarrow \mathrm{In - Mx - Mx - In}$$

$$\mathrm{In - Mx}\cdot + \underset{\text{inhibitor}}{\mathrm{HB}} \longrightarrow \mathrm{In - MxH} + \underset{\text{stable radical}}{\cdot\mathrm{B}}$$

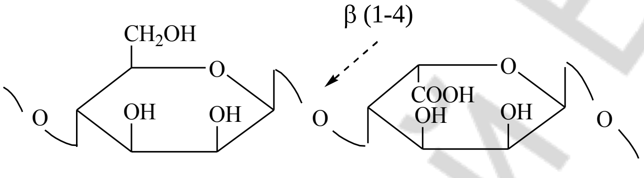
Step polymerisation occurs in the monomer mixture that have a different functional group, which react with each other. There are two type of step polymerization: polycondensation and polyaddition. Polycondensation is accompanied by elimination of small molecules such as water. Polyaddition is not accompanied by the release of by-products. Biopolymers such as starch, glycogen, DNA, RNA, formed by step polymerization.

n glucose → glycogen + H_2O
monomer *polymer*

POLYMERS IN MEDICINE AND DENTISTRY

Natural and **synthetic** polymers are used in medicine and dentistry for:
- equipment;
- filling materials (composites, adhesives);
- impression materials;
- obturation materials;
- dentures, etc.

Such polysaccharides of natural origin as alginate and agar-agar are widely used in dentistry. They are synthesized by the brown seaweed. Alginic acids (alginates) consist of disaccharide unit constructed from mannuronic acid and guluronic acid. Alginic acids are able to absorb water and swell. Therefore, they are used in orthopedic stomatology as impression materials.

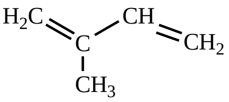


D-mannuronic acid L-guluronic acid

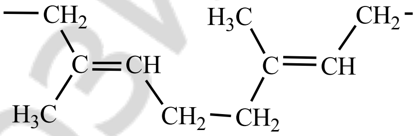
alginic acid

Agar-agar is a mixture of polysaccharides. One of them is agarose. Agarose is formed of alternating residues of β-D-galactopyranose and 3,6-anhydro-α-L-galactopyranose with β (1-4) bond. It has a clearly expressed feature in the formation of gels.

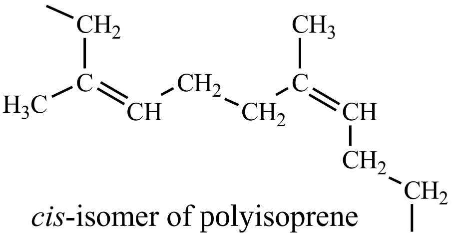
There are two natural isomers of polyisoprene. *Trans* isomer is the base of gutta-percha. It is rigid material and used in dentistry for filling of root canal.



isoprene



trans-isomer of polyisoprene
(gutta-percha)

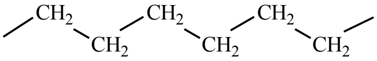
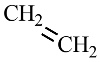
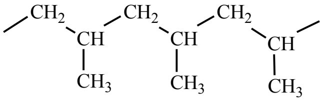
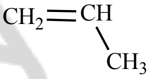
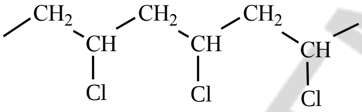
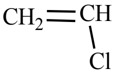
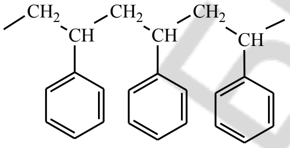
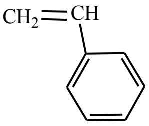
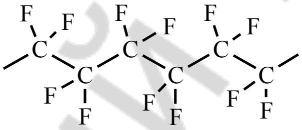
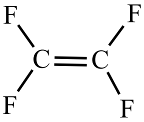
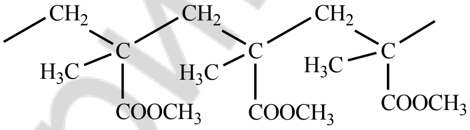
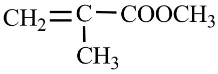


cis-isomer of polyisoprene
(natural rubber)

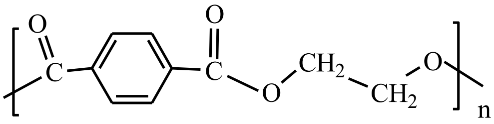
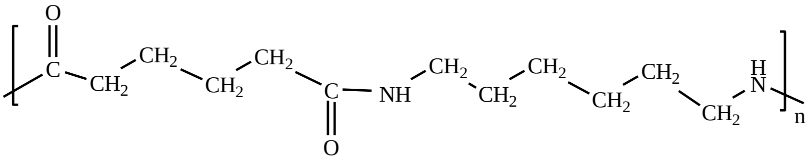
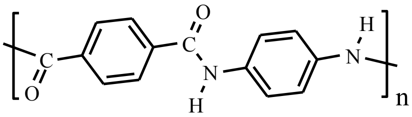
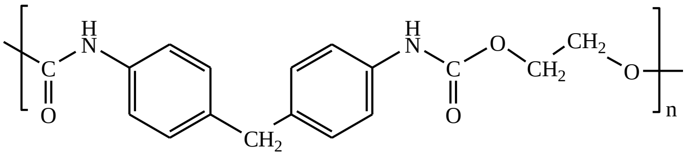
Natural rubber is used by many manufacturing companies for the production of rubber products. Currently, rubber is harvested mainly in the form of the latex from the rubber tree. Natural rubber is used extensively in many applications, either alone or in combination with other materials. It has a large stretch ratio and high resilience, and is extremely waterproof. Medical gloves are made of latex.

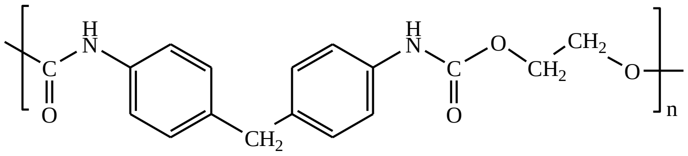
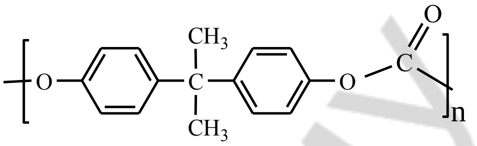
Synthetic polymeric materials are obtained in the reaction of step and chain polymerization. Examples of industrially produced polymers for medical purposes are presented in the tables below.

Polymers used for the production of medical devices and obtained in the chain polymerization reaction

Name	Applying	Polymer	Monomer
Polyethylene	syringes, packaging		
Poly-propylene	syringes, surgical suture material		
Polyvinyl chloride	packaging, backing material in dentistry		
Polysterene	containers for transporting and disinfection		
Polytetra-ftorethylene	backing material in dentistry, peripheral catheters		
Polymethyl-methacrylate (PMMA)	organic glass, basis of most polymer materials in dentistry		 $CH_2{=}C(CH_3){-}COOCH_3$

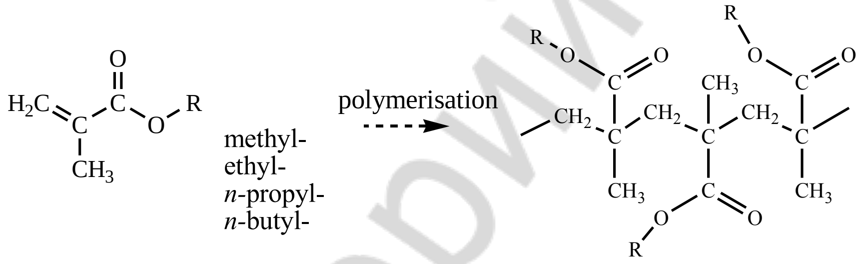
Polymers used for the production of medical and dentistry devices and obtained in the step polymerization reaction

Name	Applying	Formula of polymer
Mylar	surgical suture material, teeth aligners matrices in dentistry	
Nylon 66 **Nylon 6**	surgical suture material, dental floss, basises in prosthetic dentistry	
Kevlar	mouthguards, splints	
Polyure-tane	basises in prosthetic dentistry	

Polyuretane	basises in prosthetic dentistry	
Polycarbonate	endotracheal tubes, mouthguards, protective glasses	

THE USE OF POLYMERS BASED ON ACRYLIC ACID IN DENTISTRY

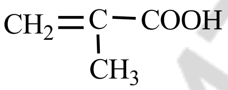
The special place in the dental materials sciences is occupied acrylic acid derivatives and polymers based on them. Polymers based on acrylic acid and methacrylic acid have long been used in dentistry. Methacrylate based polymers have good mechanical properties, biocompatibility (have no taste, odorless, non-toxic) suitable optical properties, chemical resistance to oral liquid and disinfectants.



The presence of the double bond provides the ability to react the radical chain polymerization.

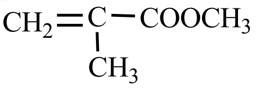
$CH_2{=}CH{-}COOH$

acrylic acid



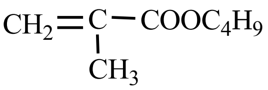
$CH_2{=}\underset{CH_3}{\underset{|}{C}}{-}COOH$

methacrylic acid



$CH_2{=}\underset{CH_3}{\underset{|}{C}}{-}COOCH_3$

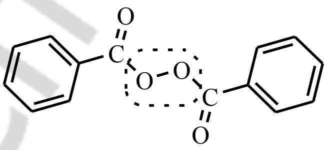
methylmethacrylate



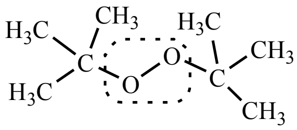
$CH_2{=}\underset{CH_3}{\underset{|}{C}}{-}COOC_4H_9$

butylmethacrylate

The reaction starts at the initiator decomposition. Radical reaction initiators are substances with nonpolar covalent bond such as peroxides. Nonpolar covalent bond between oxygen atoms of peroxides easily decompose into radicals under the action of visible light, heat or activators.

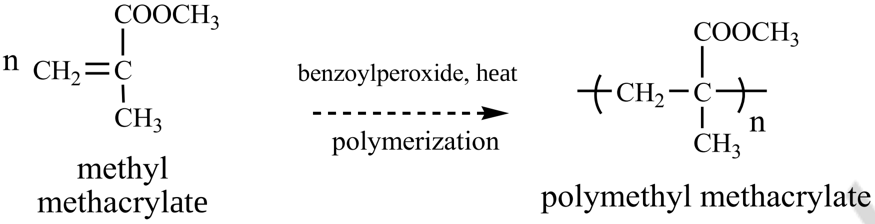


dibenzoyl peroxide

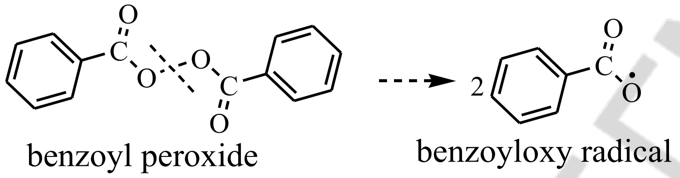


tert-butyl peroxide

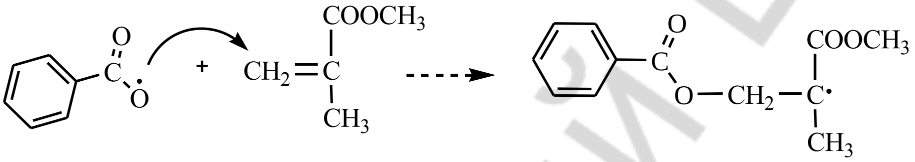
Consider the reaction mechanism of radical polymerization of methyl methacrylate (MMA) under heating.



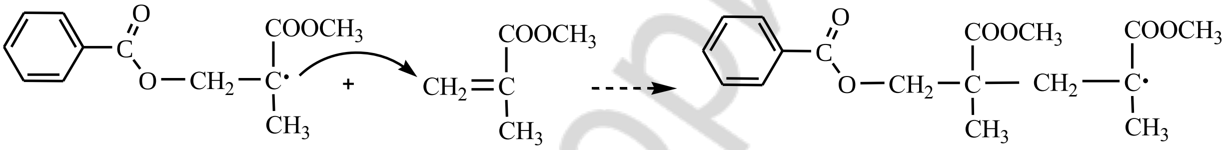
Initiation. At this stage, benzoyl peroxide breaks down into two radicals under the action of heat.



Each radical reacts with the double bond of methyl methacrylate.

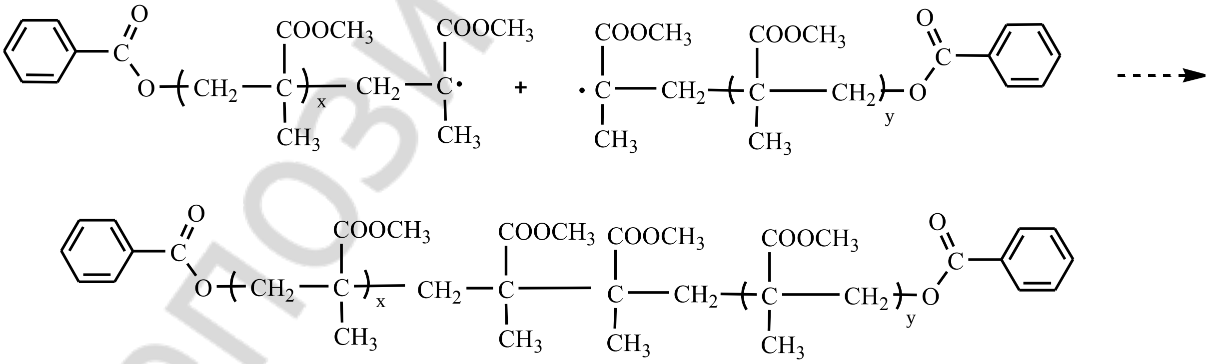


Propagation.

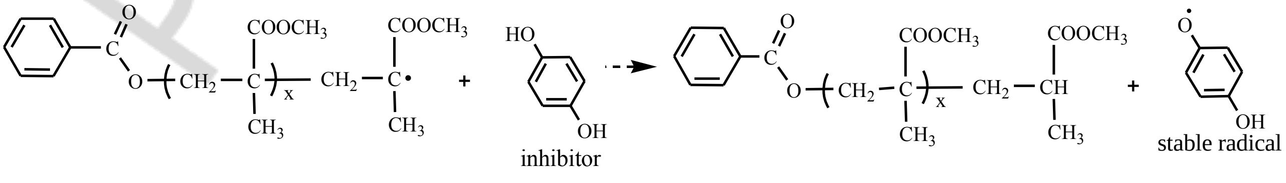


The reaction is continued further until all the monomers are used.

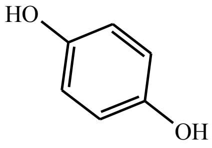
Termination. Chain termination occurs when two radicals react with each other.



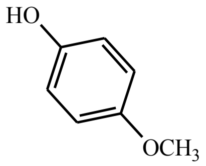
A big radical can interact with compound (inhibitor), which breaks chain growth. Polymethyl methacrylate (PMMA) is formed in this way.



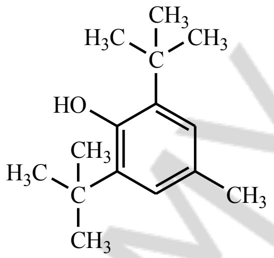
Inhibitors are capable of rapidly reacting with active radicals to form stable compounds which unable to bond to monomer. That is why inhibitors completely stop polymerization. Compounds containing a phenolic hydroxyl group are generally used in dentistry as inhibitors. These chemical species are also used to prevent premature polymerization.



hydroquinone
HQ

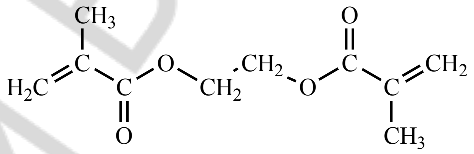


hydroquinone methyl ether
MEHQ

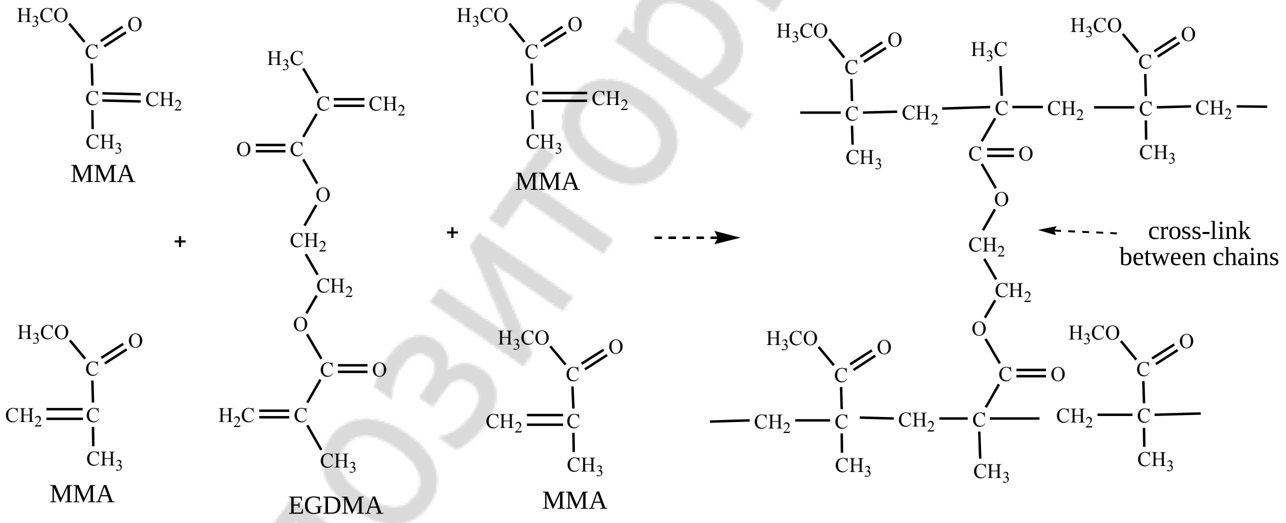


butylated hydroxytoluene
BHT

When using in dentistry polymers of the acrylic acid polymerization process is accompanied by cross-linking with ethylene glycol dimethacrylate (EGDMA). The formation of cross-links between chains increases the strength of the material, increases resistance to thermal and mechanical stress, including grinding and polishing, reduces the probability of formation of microcracks.



ethylene glycol dimethacrylate

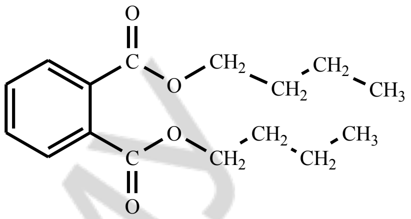


The basis of the composite is typically a mixture of copolymers of acrylic and methacrylic acid, their esters, and polyvinyl chloride, butadiene. Mixing of the different polymer is necessary to achieve the required quality of the composite.

There are four types of polymers (composites) of according to the of activation of polymerization reaction or curing:

1) heat activated (heat-curing) resins; they consist of two components;
2) chemically activated resins; they consist of two components;
3) light activated (light-curing) resins; one component systems;
4) hybrid systems.

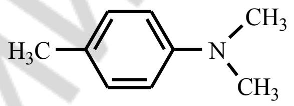
Activated by temperature polymers are used to make dentures. They consist of powder and liquid. A **powder** includes PMMA prepolymer, dibenzoyl peroxide as initiator. A f**luid** includes MMA, cross-linking agent (EGDMA), inhibitors, plasticizers. **Plasticizers** are low molecular weight compounds that increases the plasticity of the polymer by reducing the intermolecular interaction of polymer molecules components. Phthalates are usually used as plasticizers.



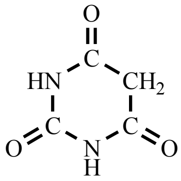
dibutyl phthalate

Powder and liquid are mixed. Some form is created from the resulting viscous mass. The product is then heated, while the polymerization reaction proceeds.

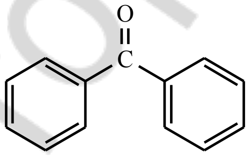
Chemically activated resins are used for filling materials, dentures reparations, relining. They also consist of powder and liquid. A **powder** includes PMMA prepolymer or copolymer and dibenzoyl peroxide as initiator. A **fluid** includes MMA, cross-linking agent (EGDMA), inhibitors, activators, ultraviolet (UV) absorbers, and various additives. **Activators** contribute to the decay the initiators. The compounds, which are electron donors, can be activators. For example, tertiary amines such as dimethyl-*p*-toluidine and derivatives of barbituric acid are used as activators. **UV absorbers** such as benzophenone are used to prevent discolouration of dental material.



N,N-dimethyl-*p*-toluidine



barbituric acid

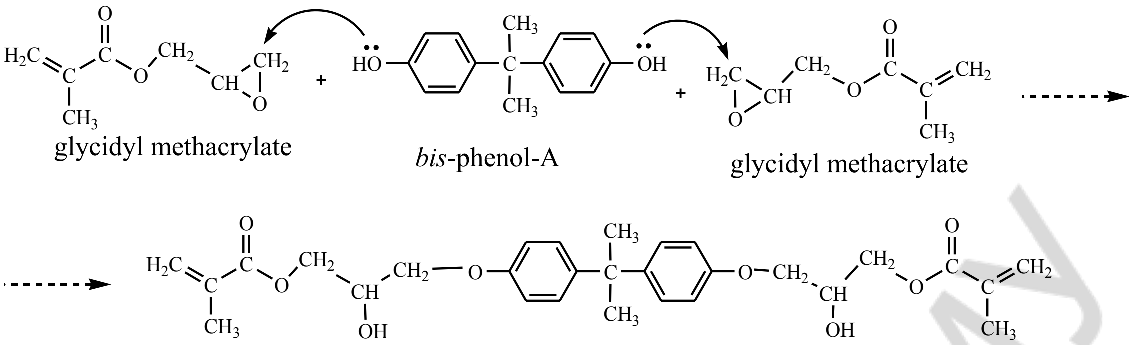


benzophenone

When mixing the powder and liquid activator promotes decomposition of the initiator into free radicals, which start a radical polymerization reaction. The copolymers are linked together by monomers. Material cures during polymerization.

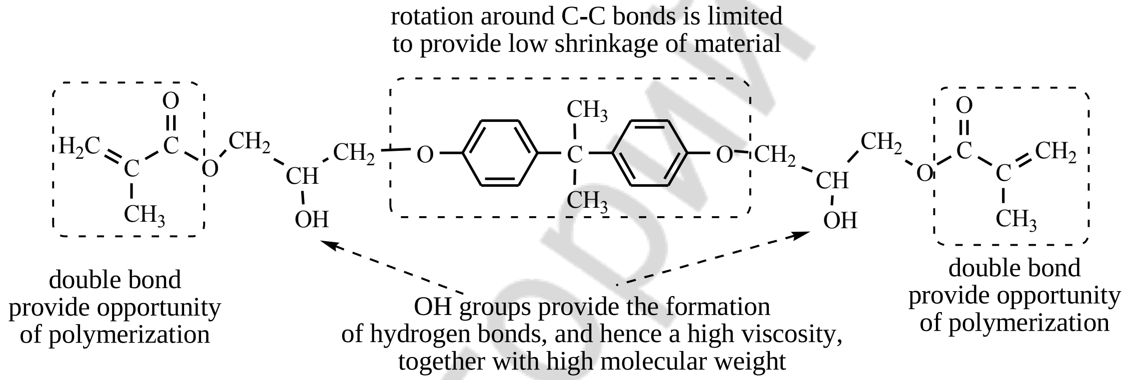
Light-curing polymers are the basis of modern dental composite materials, adhesives, glass ionomer cements, and others. Composite materials generally consist of an organic resin matrix, an inorganic filler and coupling agent, which enhances the bond between the filler and the resin matrix. Organic resin matrix includes monomers, photoinitiator system, inhibitors, UV absorbents.

Light-curing dental materials are a viscous tar-like liquid. The viscosity of the material is determined by a combination of specific monomers. The main component of organic matrix of typical modern restorative composite is *bis*-phenol-A-glycidyl methacrylate (Bis-GMA).

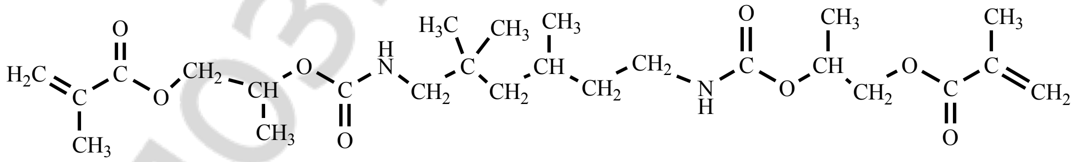


Bis-GMA

It is formed from *bis*-phenol A and glycidyl methacrylate. Bis-GMA has a higher molecular weight, than MMA. Consequently, it has a lower polymerization shrinkage. Furthermore, hydroxyl groups provide hydrogen bonds formation and therefore higher viscosity. Methacrylic acid residues allow the polymerization reaction. The central part of the molecule is a rigid fragment, along with the high molecular weight defines a low shrinkage of material.

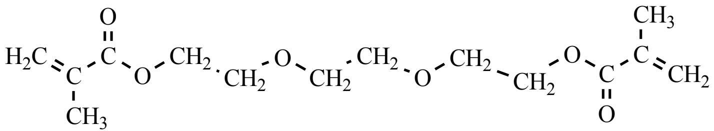


UDMA (urethane dimethacrylate) is another monomer with high molecular weight and high viscosity. It is often found in modern restorative materials. UDMA also contains methacrylic acid residues, that is necessary for polymerization.

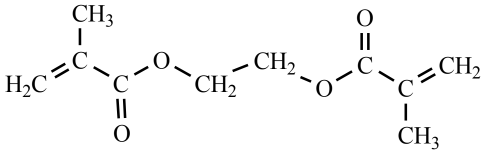


urethane dimethacrylate
UDMA

On the other hand, the high viscosity of the monomer determines the low degree of conversion, and hence high residual monomer content in the final product. That is why such monomers as triethylene glycol dimethacrylate (TEGDMA), ethylene glycol dimethacrylate (EGDMA), which have low molecular weight are added to reduce the viscosity.

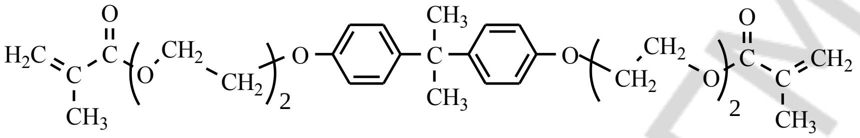


triethylene glycoldimethacrylate
TEGDMA



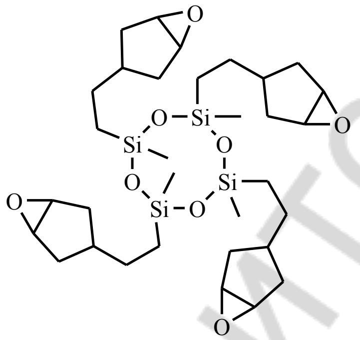
ethylene glycol dimethacrylate
EGDMA

Bis-EMA has a high molecular weight, however it has no hydroxyl groups and it does not form hydrogen bonds. Therefore, it does not possess high viscosity.

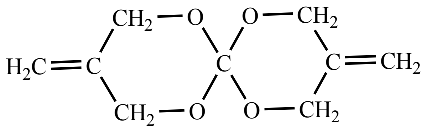


bis-phenolA tetraethoxylated dimethacrylate
Bis-EMA

Thus, modern dental materials contain, as organic matrix, mixture of monomers, which should provide low shrinkage and a small amount of residual monomer. In order to reduce shrinkage are currently being studied and begin to use the new monomers containing rings, which are opened in the polymerization, the so-called **expanding monomers**. For example, epoxy-based resins, spiro-orthocarbonates (SOC).

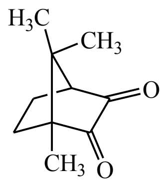


3,4-epoxycyclohexyl cyclopolymethylsiloxane

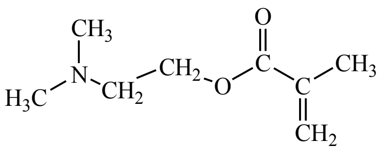


bis-imethylenespiro-orthocarbonate
BMSOC

Photo-initiation polymerization involves the use of a light to produce free radicals to start the polymerization process. **Photo-initiating system** within modern composites generally consist of two components: photo-initiator and co-initiator. Camphoroquinone is the most commonly used as photo-initiator for visible light free radical polymerization of dental resins. The co-initiator is a tertiary aliphatic amine as reducing agent, for example, dimethylamino ethylmethacrylate (DMAEMA).

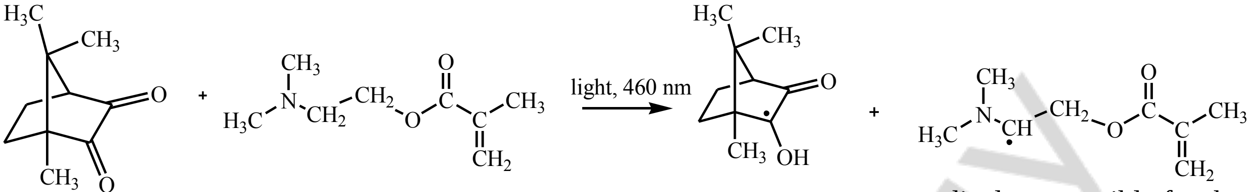


camphoroquinone
CQ



dimethylamino ethylmethacrylate
DMAEMA

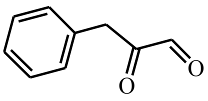
DMAEMA reacts with camphoroquinone, and it gives, which is responsible for polymerization reaction.



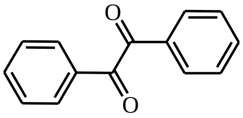
CQ DMAEMA inactive radical radical, responsible for the initiation of the polymerization reaction

Other amines can be also used as the co-initiator. However, the use of two-component photo-initiating system in the composite has an important disadvantage: discoloration of the material due to the oxidation of the amine.

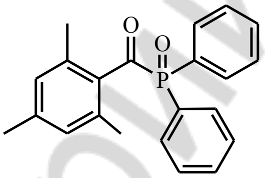
More recently alternative one-component photo-initiating system have been used in resin based composites such as phenyl propanedione (PPD), Benzil (BZ), Lucirin TPO, Irgacure 819, Ivocerin, etc. Their advantage is that they do not require the presence of a co-initiator.



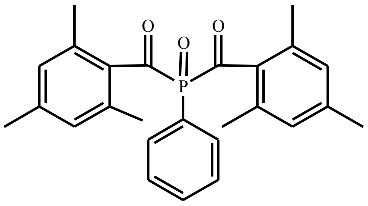
propanedione
PPD



Benzil
BZ

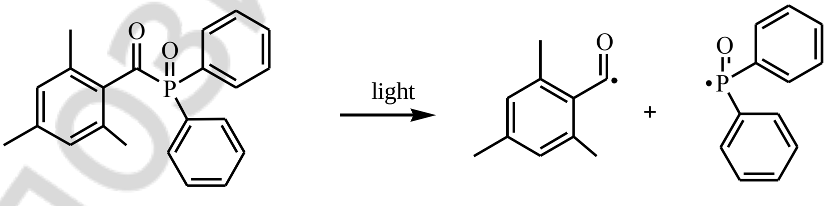


2,4,6-trimethylbenzoyl
diphenylphosphine oxide
Lucirin TPO



bis(2,6-dichlorobenzoyl)-(4-phenyl)phosphine oxide
Irgacure 819

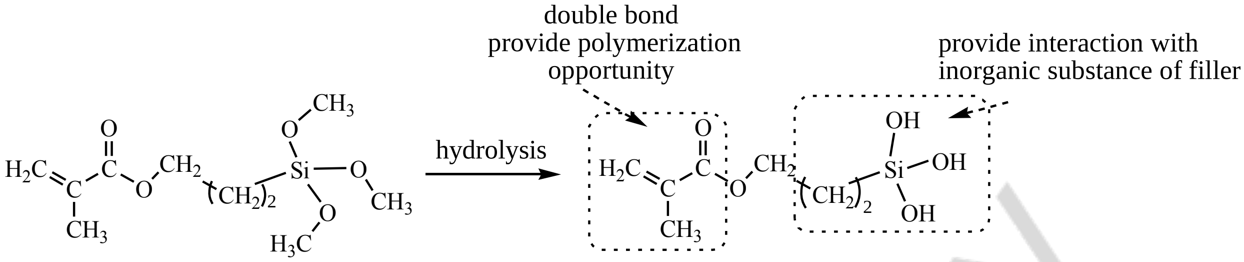
For example, Lucirin TPO produces free radicals by photochemical cleavage of carbon-phosphorus bond resulting in two initiating radicals without the need for a co-initiator.



Lucirin TPO

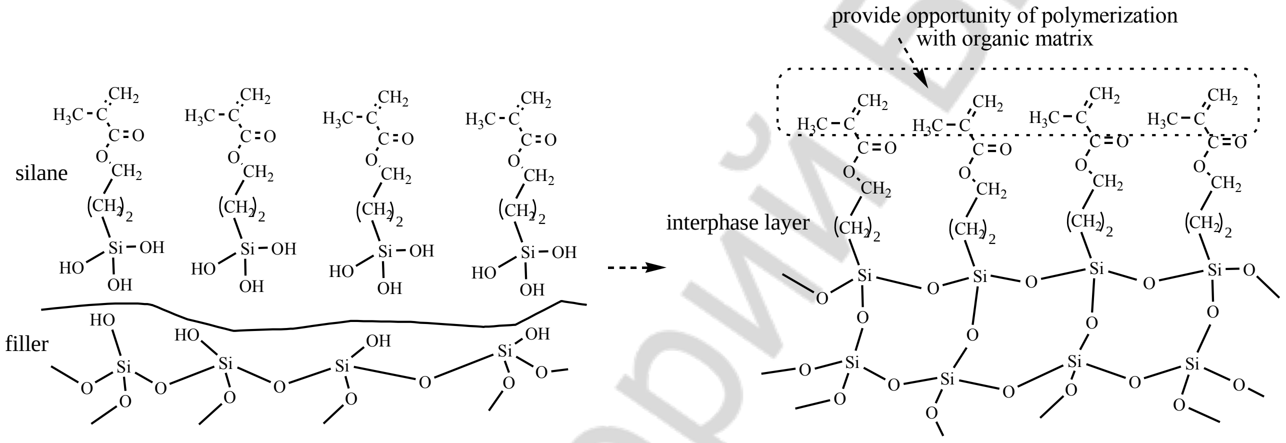
Restorative materials are a mixture of **inorganic substances**, which are in an organic matrix. Ratio of organic matrix and inorganic filler affect the physical properties of the material. Fillers increase hardness of materials, decrease shrinkage, prevent matrix deformation, improve esthetic properties of materials and decrease water absorption. Most modern composites are filled with silicate particles based on Ba, Sr, Zn, Al. The size of particles are more important then composition.

Filler particles are bound organic matrix with **coupling agent.** The process of binding is based on the organosilane chemistry.



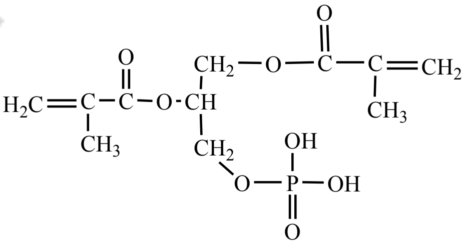
3-methacryloxypropyl trimethoxysilane

In the conditions of manufacture the silane is hydrolyzed. Bipolar structure of the molecule allows to bond to both the organic part via double bond of methacrylic fragments and to the filer particles via silanol groups.



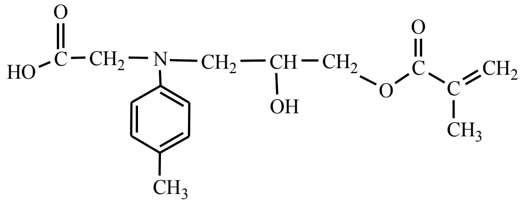
Currently, the **adhesive systems** are used to improve the adhesion of the restorative material to the tooth. For this purpose, a solution of phosphoric acid is used. Phosphoric acid opens the pores of the enamel and promotes the penetration of the restorative material.

Adhesive systems of the first generation contained dimethacrylate of glycerophosphoric acid. It is an amphiphilic compound. Hydrophilic part binds calcium and contributes to secondary dentin formation in dental tissues. The hydrophobic part of the molecule binds to the restorative material.

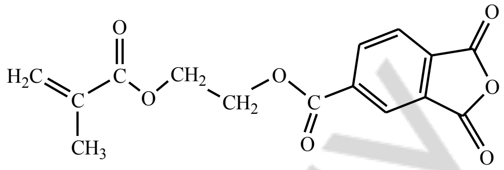


dimethacrylate of glycerophosphoric acid

All modern adhesive systems are solutions of multifunctional methacrylates with -OH, -COOH and $-NH_2$ groups, or monomers and fillers with different functionality in a water compatible and volatile solvents. Each compound has a part that interacts with the tooth and an unsaturated fragment that polymerizes.

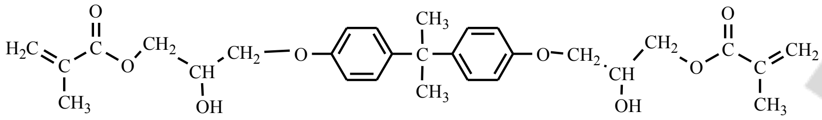


N-(p-tolyl)-glycine-2-hydroxyproryl methacrylate
NTG-GMA

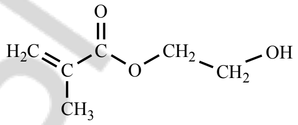


anhydride 4-methacrylhydroxyethyl
of pyromellitic acid
4-META

A mixture of Bis-GMA and HEMA is often used.



Bis-GMA

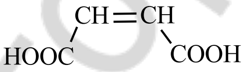


2-hydroxyethyl methacrylate
HEMA

Glass ionomer cements (GIC) are class of dental materials commonly used as filling materials and luting cements in prosthetic dentistry. GIC is two-component system. Powder is an acid-soluble calcium fluoroalumosilicate glass (CaF_2, AlF_3, SiO_2, Al_2O_3,NaF, $AlPO_4$, ZnO, etc.). GIC liquid is quite viscous solution of polyacrylic acid in the form of co-polymer with itaconic and maleic acids. Tartaric acid is also present in the liquid.

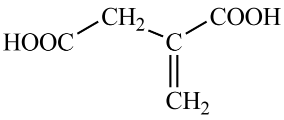
$CH_2{=}CH{-}COOH$

acrylic acid



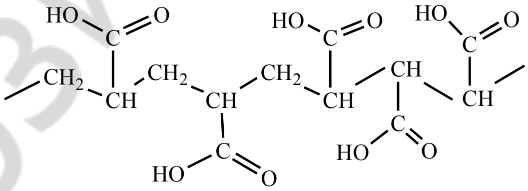
$HOOC{-}CH{=}CH{-}COOH$

maleic acid



$HOOC{-}CH_2{-}C({=}CH_2){-}COOH$

ataconic acid

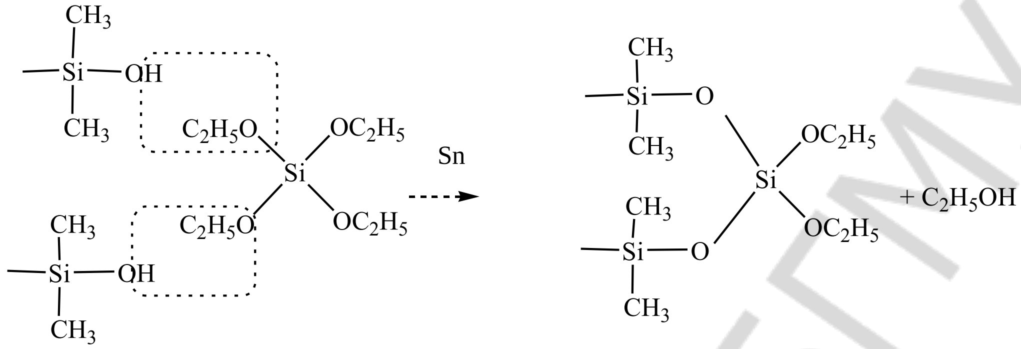


The setting reaction is an acid-base reaction between the acidic polyelectrolyte and alumosilicate glass. Free carboxylic groups also interact with tissues of the tooth by linking calcium. Fluoride is released from glass powder at the time of mixing and stay free within the matrix. As a result, it has been suggested, that GICs have anticariogenic properties.

Modern dental materials are often a combination of glass ionomer cements and composites (resin-modified GIC).

MATERIALS FOR USE IN PROSTHETIC DENTISTRY

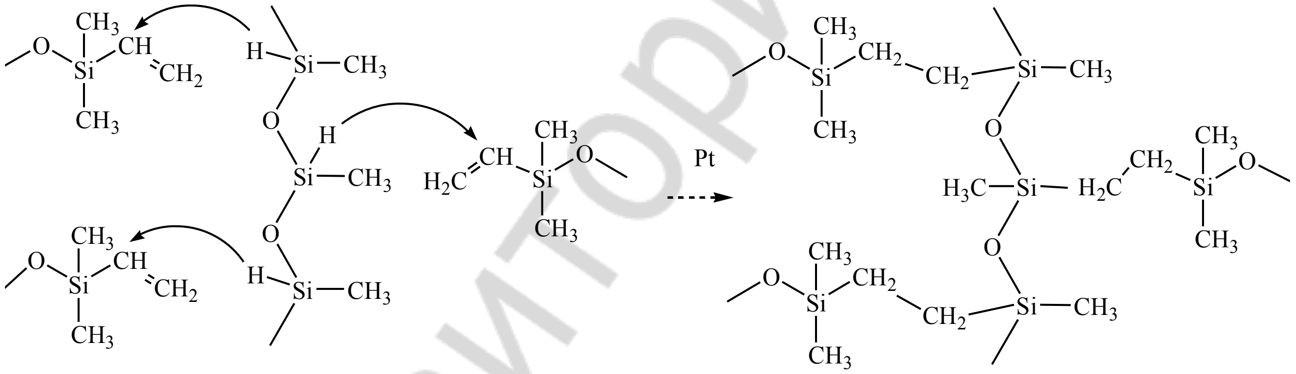
Organosilicon compounds have wide application in medicine recently. **Silicone materials** are widely used as elastomeric impression materials. There are two types of silicone materials: A and C types.



the curing mechanism of silicone materials of polycondensation type

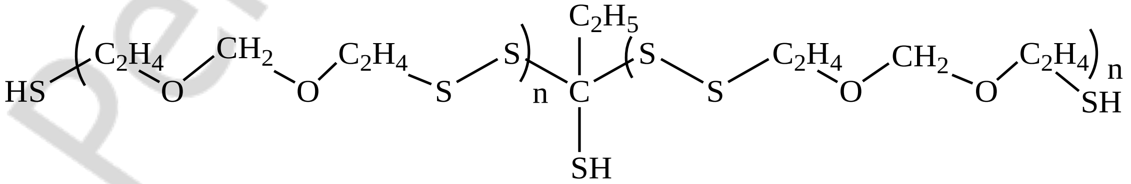
Polycondensation silicone materials (type C) are formed in the reaction of step polypolycondensation. The low molecular weight by-products are allocated during this reaction, which complicate the use of these materials.

Additive materials (type A) are formed during the reaction step polyaddition.



the curing mechanism of additive silicone materials

Polysulfide materials are formed from molecules containing thiol groups, which can be oxidized. Water is released during the reaction. This leads to the elongation of chains and cross-linking.



12. MONOSACCHARIDES. STRUCTURE, REACTIVITY, BIOLOGICAL ROLE

Carbohydrates are synthesized in green plants by photosynthesis formed from carbon dioxide and water. They perform numerous roles in cell, such as the storage of energy and structural components. Carbohydrates are also used in medicine.

Carbohydrates are divided into three groups:

1) monosaccharides, general formula is $C_nH_{2n}O_n$, where n = 3–10;

2) oligosaccharides, $(C_6H_{10}O_5)_n$, where n < 10;

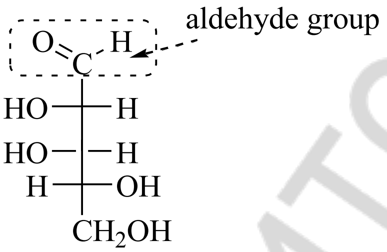
3) polysaccharides $(C_6H_{10}O_5)_n$, where n >10.

Monosaccharides are monomers polysaccharides. Monosaccharides cannot be hydrolyzed. They are usually colorless, water-soluble, crystalline solids. Some monosaccharides have a sweet taste.

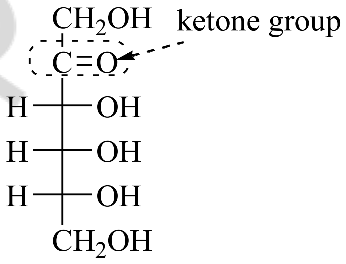
CLASSIFICATION OF MONOSACCHARIDES

There are the following classifications of monosaccharides:

1) based on the aldehyde or ketone group presence (**aldoses** contain aldehyde group, **ketoses** contain ketone group);

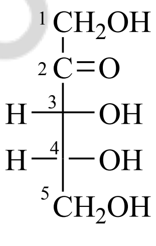


aldose

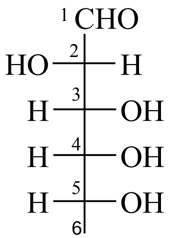


ketose

2) based on the number of carbon atoms (**tetroses**, **pentoses**, **hexose** and so on);

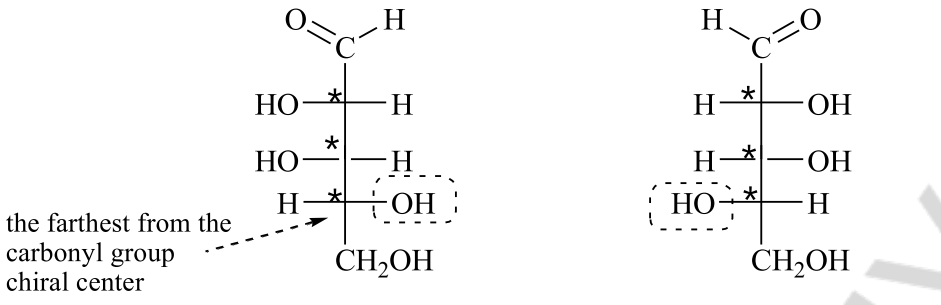


pentose



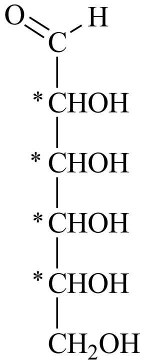
hexose

3) based on the configuration of the last chiral carbon atom (D- and L-stereoisomers).



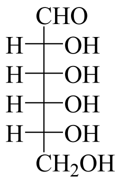
D-monosaccharide L-monosaccharide

STEREOISOMERISM OF MONOSACCHARIDES

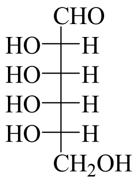


aldohexose

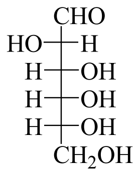
The most important for the human body monosaccharides are aldohexoses. Their formulas contain an aldehyde group and six carbon atoms. Aldohexoses have the following molecular formula — $C_6H_{12}O_6$. They have four chiral centers. In accordance with the formula $N = 2^n$ to calculate the number of possible stereoisomers aldohexoses. It turns sixteen, 8 of them belong to D-row and eight — to L-row. Natural monosaccharides involved in the process vital activity refer to D-row.



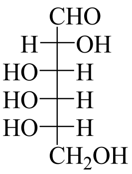
D-allose



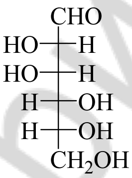
L-allose



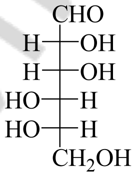
D-altrose



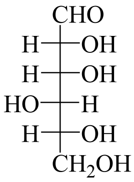
L-altrose



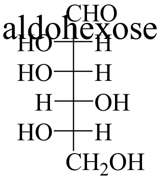
D-mannose



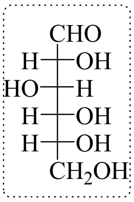
L-mannose



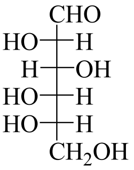
D-gulose



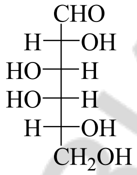
L-gulose



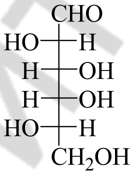
D-glucose



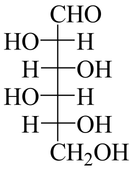
L-glucose



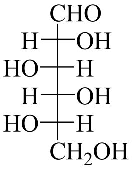
D-galactose



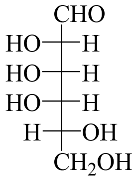
L-galactose



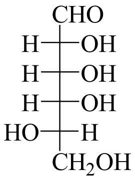
D-idose



L-idose



D-talose



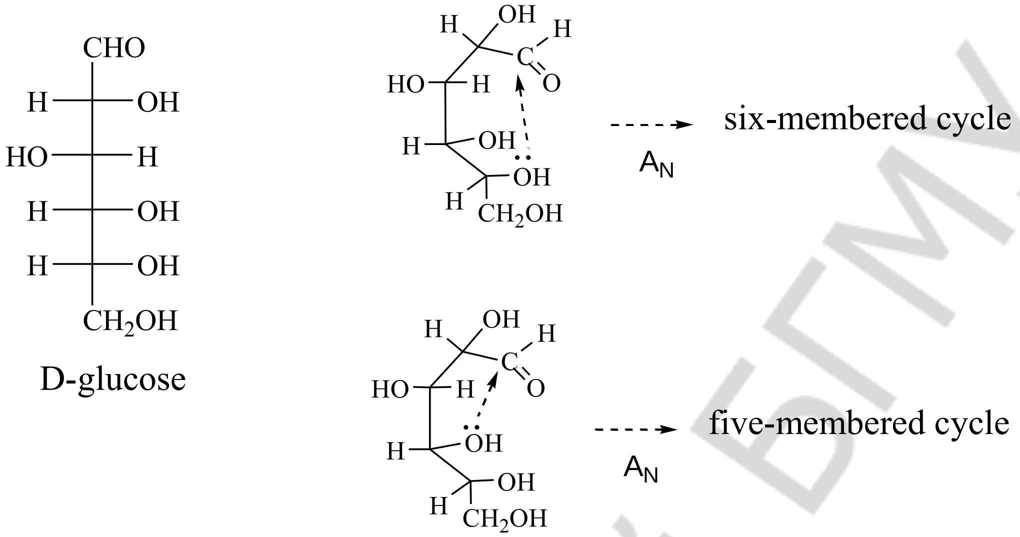
L-talose

Some of the aldohexoses are epimers. **Epimers** are stereoisomers that differ in configuration at one of the chiral centres (besides anomeric centre). For example, D-galactose and D-glucose are epimers on the C_4. D-mannose and D-glucose are epimers on the C_2. They also exist in the tautomeric forms.

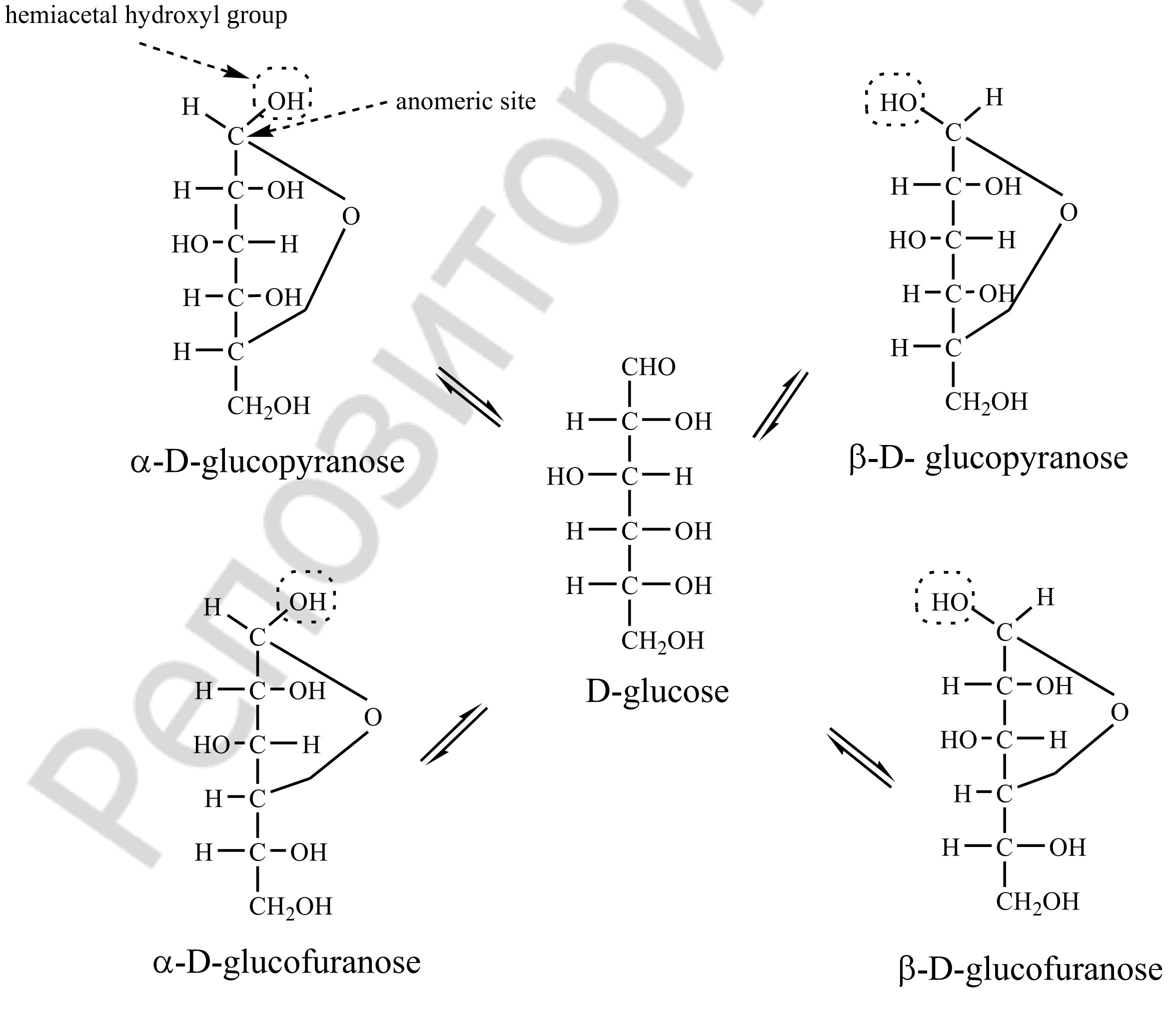
STRUCTURE AND TAUTOMERISM OF GLUCOSE

The most important for the human body aldohexose is glucose. Natural glucose involved in the process vital activity is the only one of the 16 stereoisomers and refers to D-row. Glucose is found in significant quantities in a free state in grapes (another name of glucose is grape sugar). Glucose is a monomer of certain oligosaccharides and polysaccharides such as starch, glycogen, cellulose, dextrane.

D-glucose has the right optical rotation (+52.5). Therefore another name often is used for this substance — dextrose. All monosaccharides, including glucose, are predominantly in the cyclic form in solution and in crystalline state.



Cyclic forms are produced during the reaction of nucleophilic addition by reacting of aldehyde (ketone) groups and one of the hydroxyl group. Six- or five-membered ring is formed at the same time.

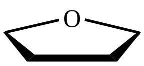


In these reactions C_1 atom becomes assymetryc (anomeric site). OH group formed from aldehyde group is called **hemiacetal** or **glycosidic** group. It differs from other OH groups of monosaccharide according to the chemical properties. Additional chiral centre formation leads to new stereoisomeric (anomeric) α- and β-forms. In the α anomeric form the hemiacetal OH-group is on the same side as the at the last chiral center. In the β-form the hemiacetal OH-group is on the opposite side of at the last hydroxyl chiral center. Hemiacetal hydroxyl groups are isolated in each of the cyclic forms.

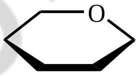
Thus, five forms of D-glucose (as well as any monosaccharide) exist in solution. Formed cycles can be opened and be formed again. These reactions underlie **ring-chain tautomerism** of monosaccharides. From a chemical point of view, the cyclic form of a monosaccharide is a hemiacetal. Cyclic forms are more stable therefore they predominate in solution (99.99 %).

Thus, monosaccharides are cyclic hemiacetals of polyhydroxy carbonyl compounds.

Cyclic forms can be represented by the formulas Fischer (represented above) and by using Haworth formulas. By Haworth six-membered rings depicted as hexagons with oxygen in the upper right corner, and five-membered — as pentagons with oxygen in the upper corner.

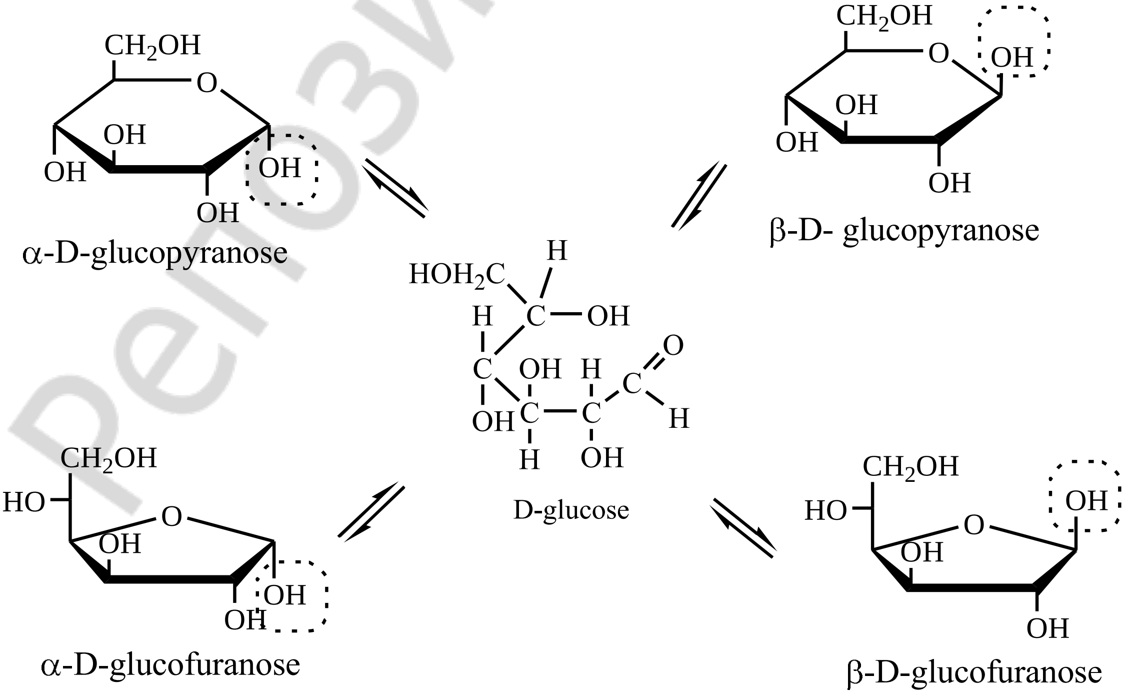


furanose

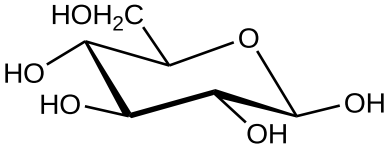


pyranose

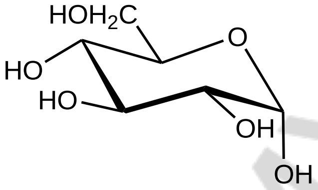
The following figure shows the tautomeric forms of glucose, and the cyclic forms are represented by Haworth. Hydrogen atoms bonded with the chiral centers are omitted. Hemiacetal hydroxyl group of each tautomeric form is highlighted.



The most real structures for monosaccharides are non-planar conformations. The chair confarmation is the most favorable for pyranose cycle and envelope or twist conformations are for furanose cycle.



β-D-glucopyranose



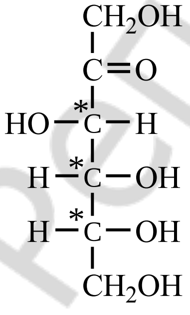
α-D-glucopyranose

The most stable conformation of glucose is the chair conformation of the β-D-glucopyranose in which all the bulky substituents (OH, CH_2OH) are in the equatorial position. This form is widely represented in nature. But α-D-glucopyranose is involved in human biochemical reactions. Conformation of monosaccharides is very important for the space structure of polysaccharide chains.

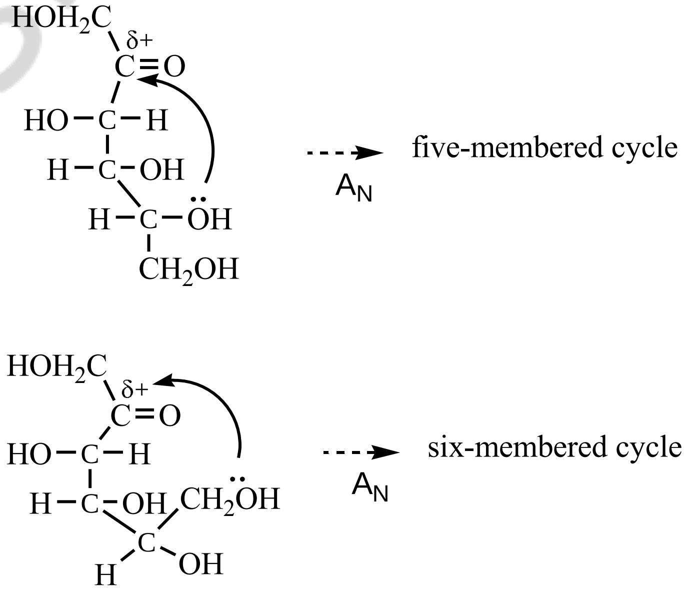
Mutarotation is a change of the rotation angle of plane of polarized light in freshly prepared solutions of monosaccharides for some time. Anomeric α- and β-forms have a different angle of polarized light rotation. So, α-D-glucopyranose rotates on the +112.5°, and β-D-glucopyranose rotates on the +19.3°. When solved in water equilibrium between these forms is settled: 2/3 β-form ⇄ 1/3 α-form. Rotation angle of this equilibrium equals to +52.5°.

STRUCTURE AND TAUTOMERISM OF FRUCTOSE

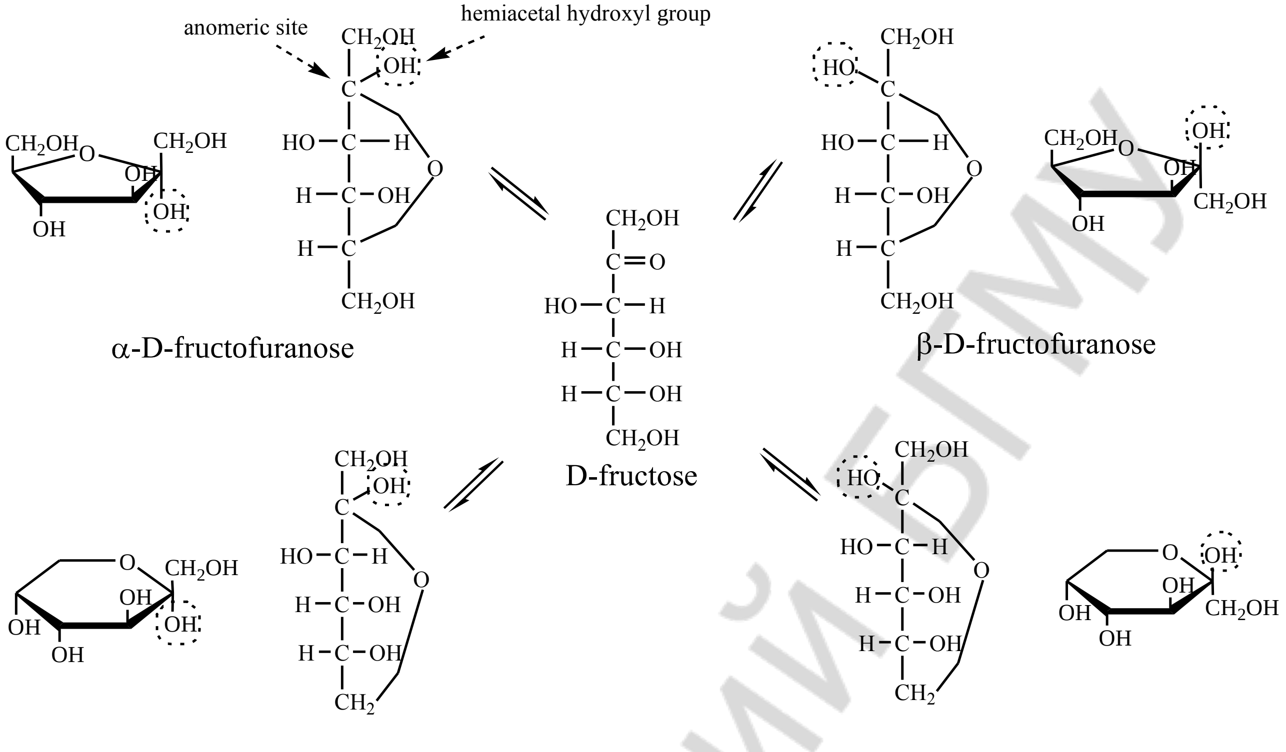
Fructose (fruit-sugar) is functional isomer of glucose. It has the same molecular formula as glucose ($C_6H_{12}O_6$). Fructose is ketohexose. Acyclic form of fructose has three chiral centers. Natural D-fructose possesses the left rotation (–82°). Fructose exists mainly in cyclic forms. They are formed by reacting an electrophilic center (the second carbon atom) with hydroxyl group at the 5th or 6th carbons.



D-fructose



Fructose tautomeric forms are shown on the figure below. Cyclic forms are shown by Fischer and Haworth.



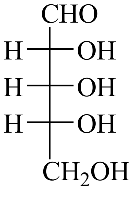
α-D-fructofuranose β-D-fructofuranose

α-D-fructopyranose β-D-fructopyranose

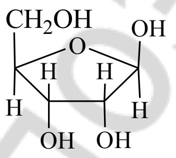
Glucose and fructose being the functional isomers are converted into each other in cell. They are a source of energy in the body.

BIOLOGICALLY IMPORTANT ALDOPENTOSES

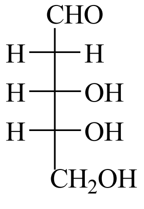
D-ribose and 2-deoxy-D-ribose are the most important in the metabolism. 2-Deoxy-D-ribose, unlike ribose, doesn't have OH-group at the second carbon atom. These pentoses exist in the tautomeric forms in the solution. They are part of nucleic acids in the form of β- furanose forms.



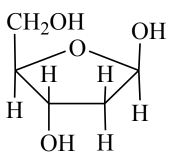
D-ribose



β–D-ribofuranose



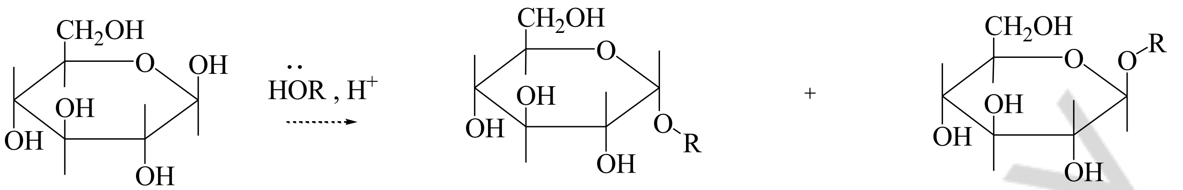
2-deoxy-D-ribose



β-D-deoxyribofuranose

CHEMICAL PROPERTIES OF MONOSACCHARIDES

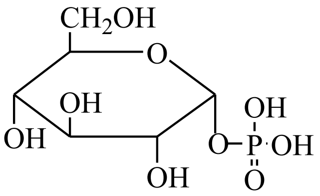
Glycoside formation reaction is a nucleophilic substitution reaction on hemiacetal hydroxyl group. From chemical point of view glycosides are acetals. They are named from the respective monosaccharides using suffix *-oside*. Glycoside is composed of carbohydrate and non-carbohydrate part of the (aglycone). The connection between them is called a glycosidic bond. It is hydrolyzed in acidic conditions or enzymatically. *In vitro* reaction to form glycosides leads to the formation of two anomers.



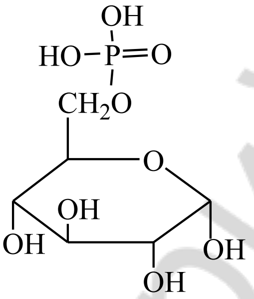
β-D-glucopyranose alkyl-α-D-glucopyranoside alkyl- β-D-glucopyranoside

Glycosides are divided into O-, N-, S-glycosides. Polysaccharides are O-glycosides.

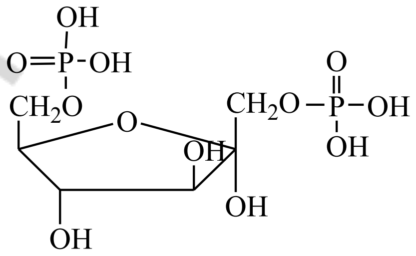
Ethers and esters of monosaccharides are widespread in nature. Phosphoric esters of glucose, fructose and other monosaccharides are important for the occurrence of the metabolic processes of the human body. They are metabolically active forms of monosaccharides. The reaction of their formation is called phosphorylation.



1-phosphate-
α-D-glucopyranose



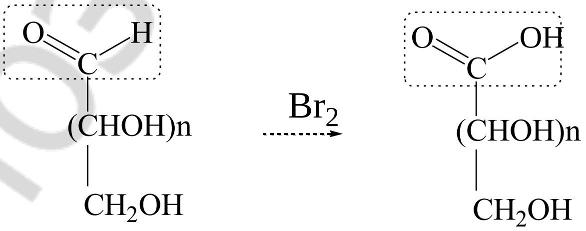
6-phosphate-
α–D-glucopyranose



1,6- diphosphate-
α-D-fructofuranose

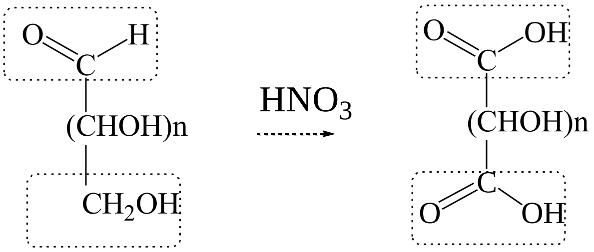
Monosaccharides are readily oxidized in an alkaline medium by the action of metal cations such as Ag^+ or Cu^{2+}. These reactions lead to the formation of reduction products of metals and mixtures of oxidation products monosaccharide.

Oxidant such as bromine water is a reagent that selectively oxidized the aldehyde group to carboxylic one. It converts an aldose to an **aldonic** acid.



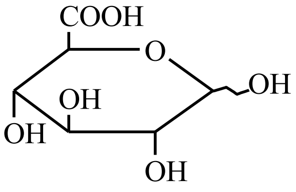
aldose aldonic acid

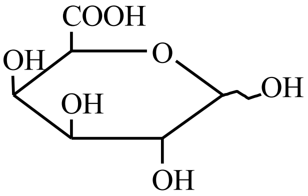
Stronger oxidants such as dilute nitric acid attack both the aldehyde group and the primary alcoholic group to form dicarboxylic acids known as **aldaric** acids.

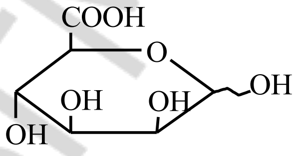


aldose aldaric acid

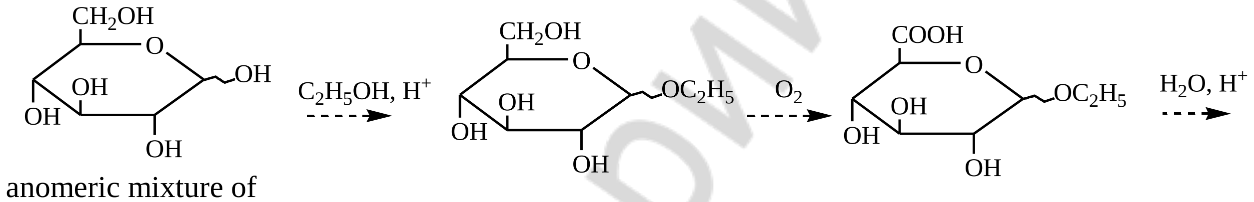
In case when only the primary alcoholic group is oxidized **uronic acids** are formed.


D-glucuronic acid

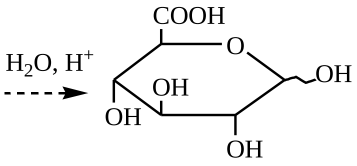

D-galacturonic acid


D-mannuronic acid

Preparation of uronic acids in vitro is a complex of transformations, the first of which is the formation of a glycoside. Then the primary alcohol group is oxidized.



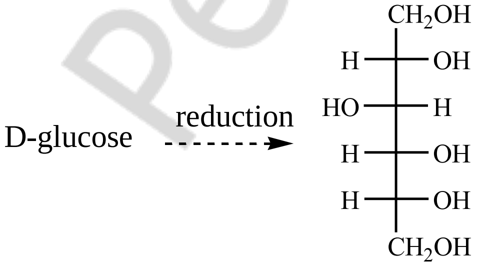
anomeric mixture of
D-glucopyranoses



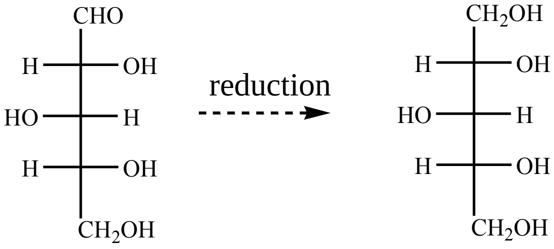
D-glucuronic acid

Uronic acids such as glucuronic and galacturonic acids are part of the heteropolysaccharides and participate in detoxication of some toxic compounds. Uronic acids are inclined to decarboxylation and as a result the corresponding pentoses are formed.

Reduction of the carbonyl group into the CH$_2$OH fragment of the monosaccharides gives sugar alcohols called **alditols**.



D-sorbitol

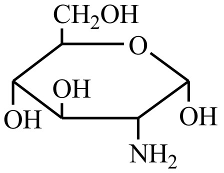


D-xylose D-xylitol

Alditols are crystal, soluble and have sweet taste. Alditols are used as a sugar substitute for diabetics.

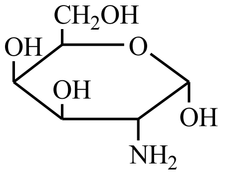
MONOSACCHARIDES DERIVATIVES

Such monosaccharides derivatives as **aminosugars** contain an amino group instead of the hydroxyl group at C_2. They are the part of the heteropolysaccharides in which the amino group is acetylated with acetic acid.



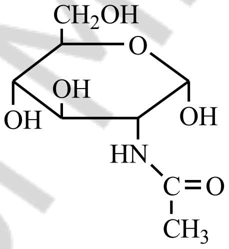
2-amino-2-deoxy-
α-D-glucopyranose

(D-glucosamine)



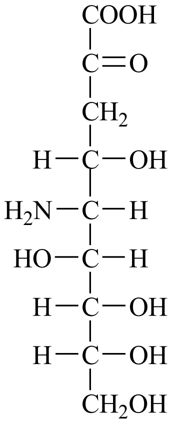
2-amino-2-deoxy-
α-D-galactopyranose

(D-galactosamine)

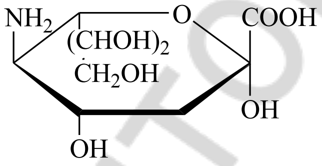


N-acetyl-D-glucosamine

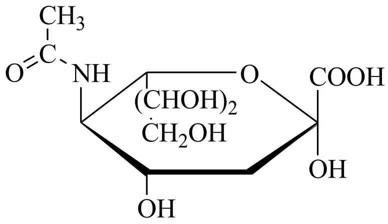
Carbon chain of **neuraminic acid** consists of nine carbon atoms and contains a ketone group next to carboxyl group. In the cell, it is preferably in a cyclic form.



acyclic form of
neuraminic acid



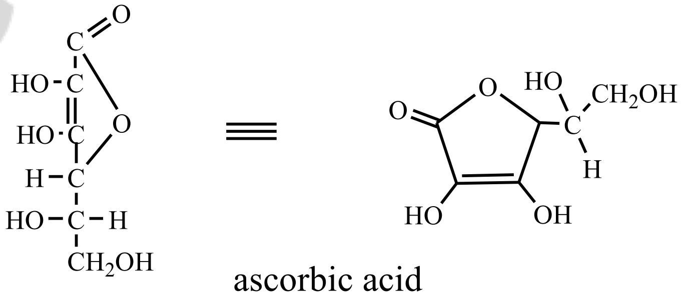
cyclic form of
neuraminic acid



N-acetylneuraminic acid

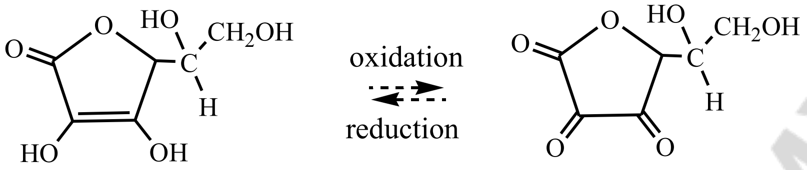
N- and O-acylated derivates of neuraminic acid are called sialic acids. Sialic acids determine cell surface properties.

Ascorbic acid or vitamin C is similar to a monosaccharide structure and represents γ-lacton of 2-oxo-L-gulonic acid. It shows quite strong acidic properties provided with by endiol fragment OH-groups.



ascorbic acid

Ascorbic acid is produced by plants, some animals and it isn't produced by humans. Therefore ascorbic acid must be received with nutrients. Ascorbic acid is unstable and easily oxidized. It is water soluble antioxidant.



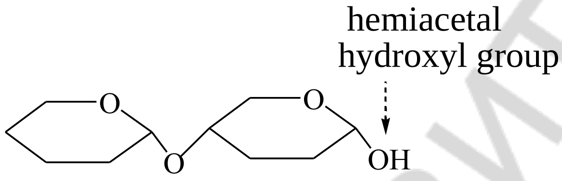
ascorbic acid dehydroascorbic acid

Vitamine C takes part in hydroxylation reactions of amino acids and other biologically important compounds. It is necessary to produce collagen.

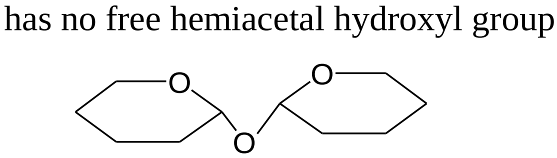
13. OLIGO- AND POLYSACCHARIDIES

OLIGOSACCHARIDES

Oligosaccharides consist of some monosaccharides (from 2 to 10) and they are divided into di-, tri-, tetra-, penta- and so on. Disaccharides are also reducing and nonreducing. Reducing disaccharides contain free hemiacetal group and because they are able to turn into an acyclic form, give qualitative reaction to an aldehyde group. They can also form glycosides. Nonreducing disaccharides don't contain free hemiacetal group and therefore they are not capable of conversion into an acyclic form. They don't give qualitative reaction to an aldehyde group and don't form a glycoside.

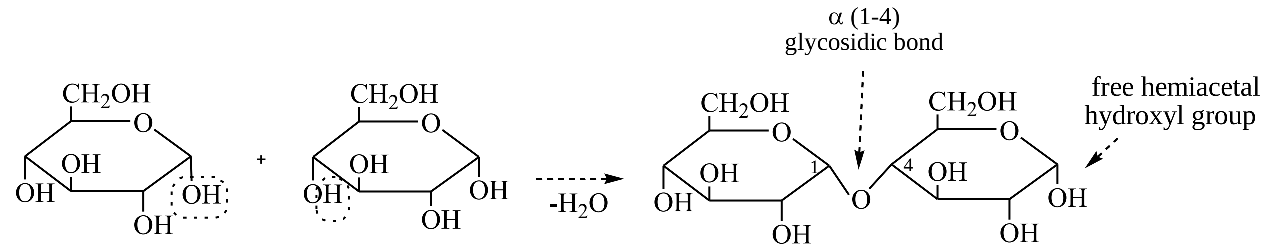


reducing disaccharide



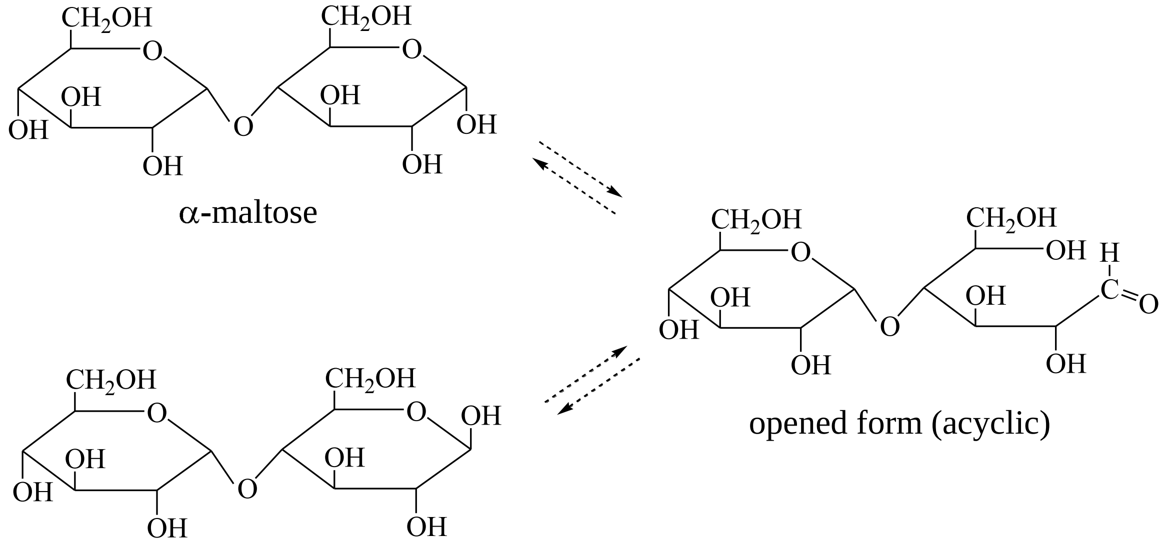
nonreducing disaccharide

Maltose is disaccharide, composed of two residues of α-D-glucopyranose. Monosaccharides are joined by α (1-4) glycosidic bond.



α-D-glucopyranose α-D-glucopyranose α-maltose

Maltose is a reducing sugar; it gives positive tests with Fehling's, and Tollens' solutions. Maltose exists in some tautomeric forms: α-maltose, β-maltose and acyclic form.



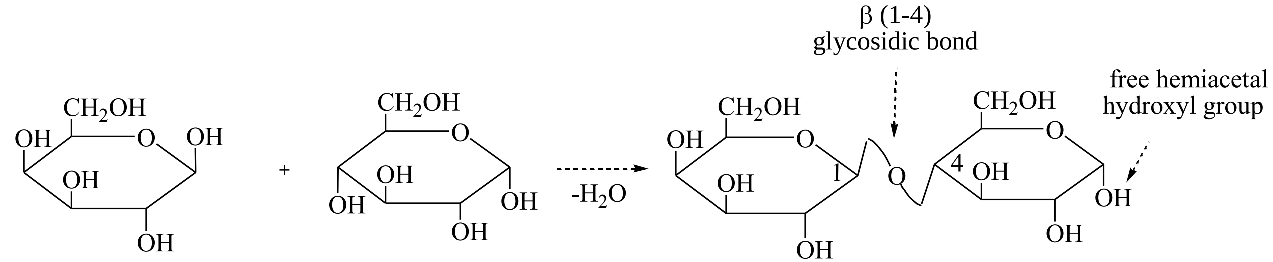
α-maltose

opened form (acyclic)

β-maltose

Maltose is a disaccharide unit starch. It is produced from starch in the intestine and then it is hydrolyzed to glucose.

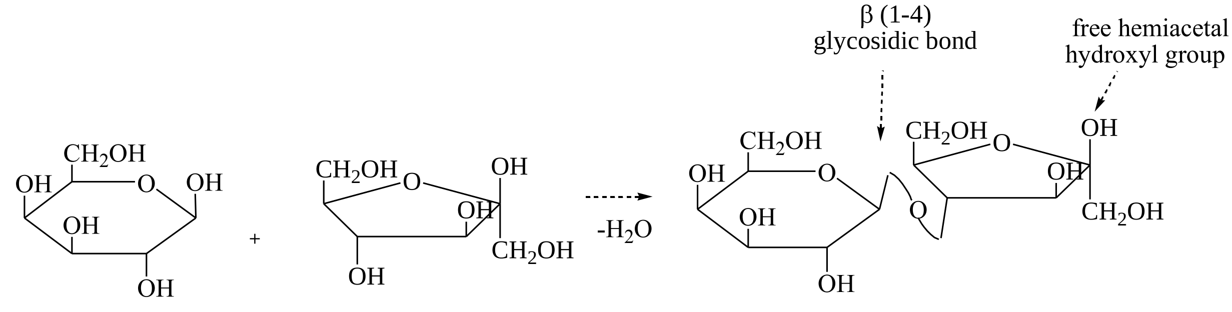
Lactose is a disaccharide of milk. Lactose is necessary for the formation of intestinal microflora in the newborn. It consists of D-galactose and D-glucose. The type of bond between monosaccharides is β (1-4).



β-D-galactopyranose α-D-glucopyranose α-lactose

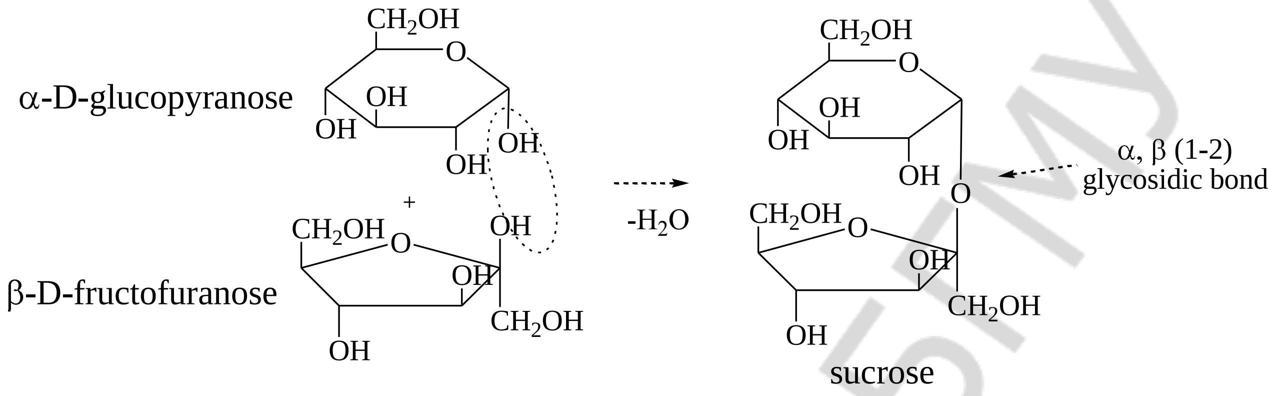
Lactose has reducing properties. It exists in the following tautomeric forms: α-lastose, β-lastose and acyclic form.

Lactulose is a synthetic sugar. It is produced commercially by isomerization of lactose. Lactlose is used as a food additive in milk products to sustain *Lactobacillus bifidum* as well as a medicament. Lactulose is reducing disaccharide. It is formed by galactose and fructose.



β-D-galactopyranose β-D-fructofuranose β-lactulose

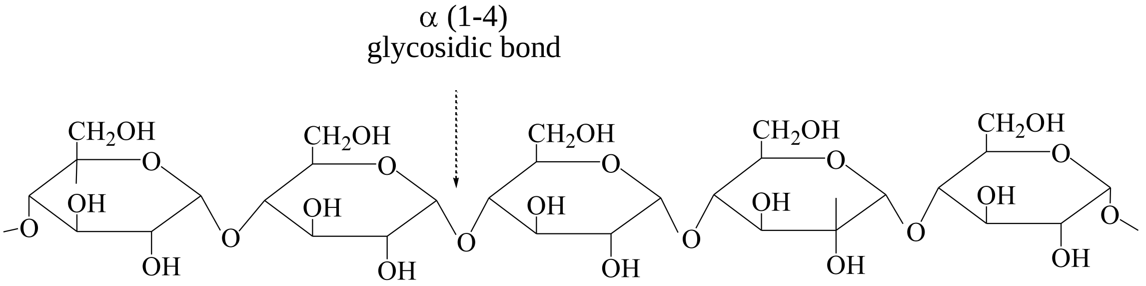
Sucrose, the most widely occurring disaccharide, is found in all photosynthetic plants. Ordinary table sugar is sucrose. Sucrose is nonreducing disaccharide, because its glycosidic bond is formed by two hemiacetal hydroxyl groups of α-D-glucopyranose and β-D-fructofuranose.



POLYSACCHARIDES

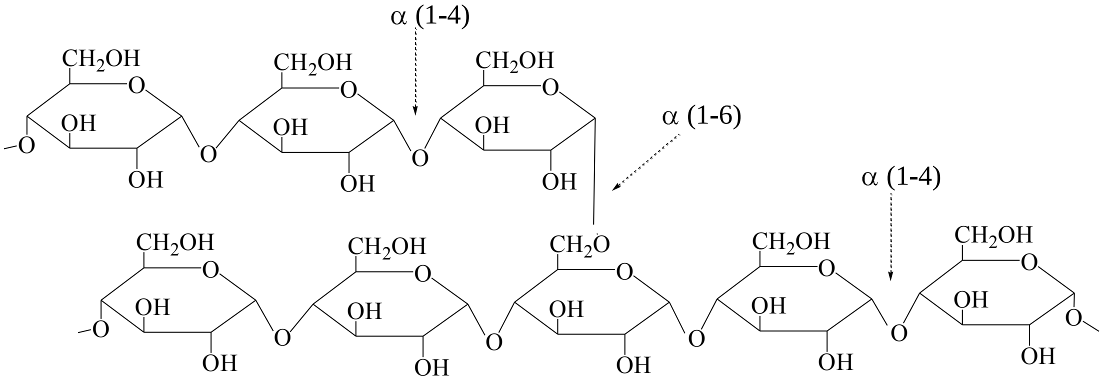
Polysaccharides (glycans) are complex carbohydrates. They are polymers made up of many monosaccharides joined together by glycosidic bonds. When all the monosaccharides in a polysaccharide are the same type the polysaccharide is called a **homopolysaccharide**, but when more than one type of monosaccharide is present they are called **heteropolysaccharides**. There are storage polysaccharides and structural polysaccharides.

Starch is a polymer of vegetable origin. It is formed from glucose and accumulates in the roots, tubers, and seeds of plants. Corn, potatoes, wheat and rice are important sources of starch. Starch is composed of two fractions: 10–20 % **amylose** and 80–90 % **amylopectin**. Amylose is unbranched structure. It consists of more than 1000 α-D-glucopyranose units connected by α (1-4) glycosidic bonds.



fragment of the amylose

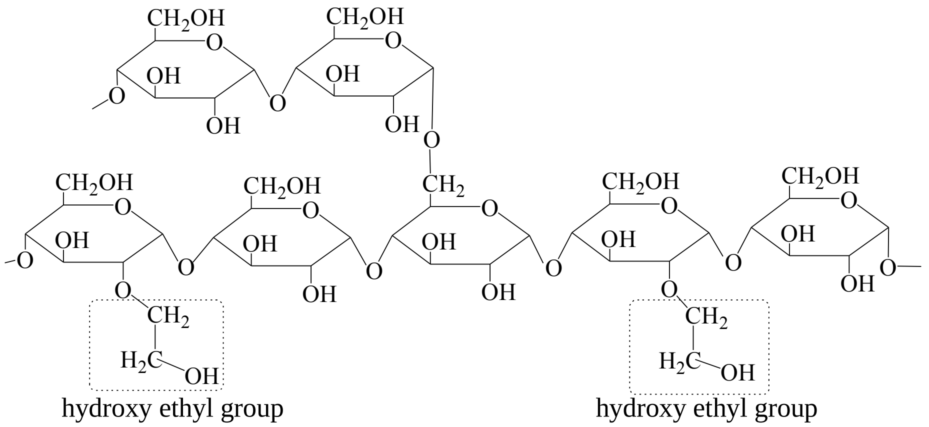
Each glucose residue in the chain of amylose is rotated by an angle of 60° degrees with respect to the previous one. That is why amylose chain of tend to assume a helical arrangement. Peculiar spatial structure of amylose provides the ability qualitative reaction to starch with iodine. Amylopectin has a branched structure. Its monomer is α-D-glucopyranose. The main type of bond is α (1-4). Branches are formed through connections of α (1-6) bonds.



fragment of the amylopectin

Starch is by far the most consumed polysaccharide in the human diet. Traditional foods such as cereals, roots and tubers are the main source of starch. Starch is a glucose source for humans. Its hydrolysis occurs in the gastrointestinal tract by enzymes.

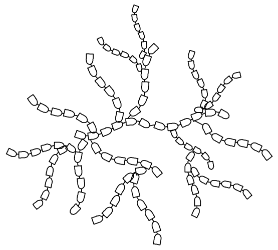
Currently, starch derivatives are widely used as a plasma substitute preparations.



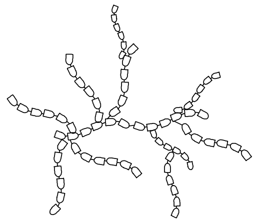
amylopectin derivative

Usually hydroxyl groups of amylopectin are modified by introducing a hydroxy ethyl group.

Glycogen is very similar to the structure of amilopestin. It also consists of α-D-glucopyranose. The bond types between glucose molecules are α (1-4), α (1-6). However, chains of glycogen are much more highly branched. Glycogen has a very high molecular weight.



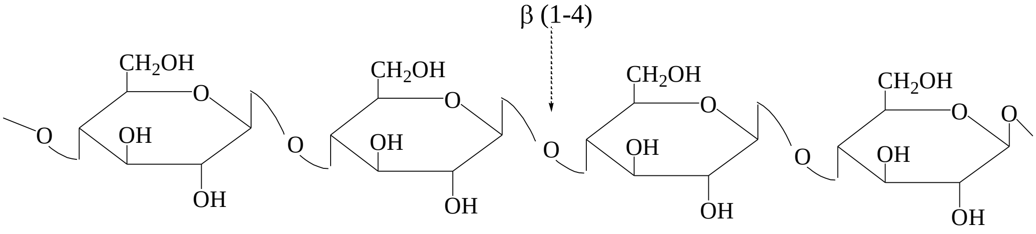
granule of the glycogen



granule of the amylopectin

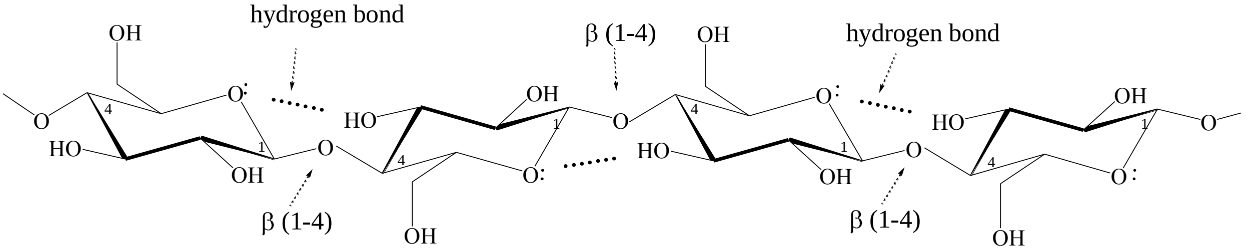
The size and the structure of glycogen provide its function as reserve carbohydrate for humans and animals. The large size of glycogen granules prevents it to pass through a biological membrane, and it is inside the cell. Because glycogen is so highly branched, a very large number of end groups are available to enzyme hydrolysis.

Cellulose is a homopolysaccharide of vegetable origin. It has a linear structure. Chains consist of β-D-glucopyranose. The type of glycosidic bonds is β (1-4).



fragment of the cellulose

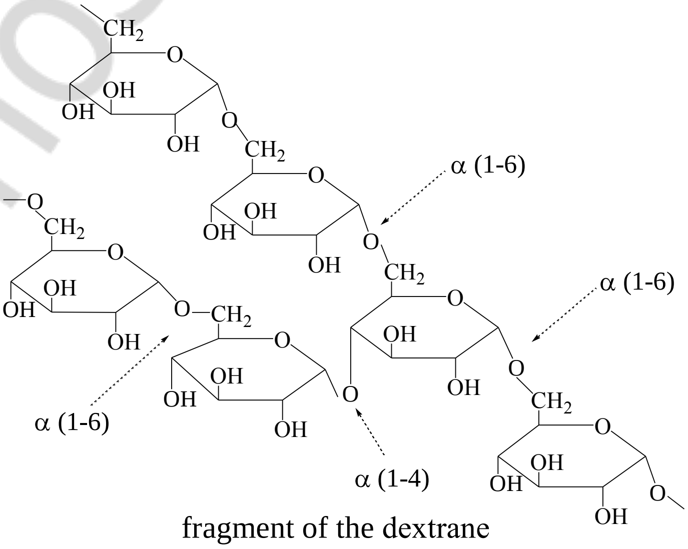
Each glucose unit in the chain of the cellulose is rotated by an angle of 180° degrees with respect to the previous one. Intramolecular hydrogen bond is formed between each oxygen of pyranose cycle and hydroxyl group of the 3rd carbon atom.



fragment of the cellulose

Hydrogen bonds are formed between the chains. Thus, cellulose is insoluble in water, chemically inert. It performs a structural function in plants. The human body cannot hydrolyze β glycosidic linkages of cellulose. Therefore, it does not matter to human as a source of glucose. However the use of in the diet fruits and vegetables containing cellulose is necessary. Cellulose is partially used for the life of the intestinal microflora; it is necessary to create a feeling of satiety and stimulation of peristalsis of the gastrointestinal tract.

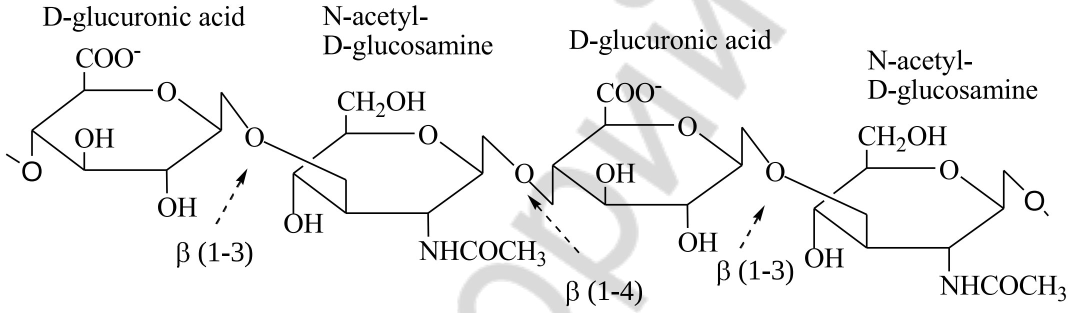
Dextran is a branched polysaccharide of bacterial origin made up of many



fragment of the dextrane

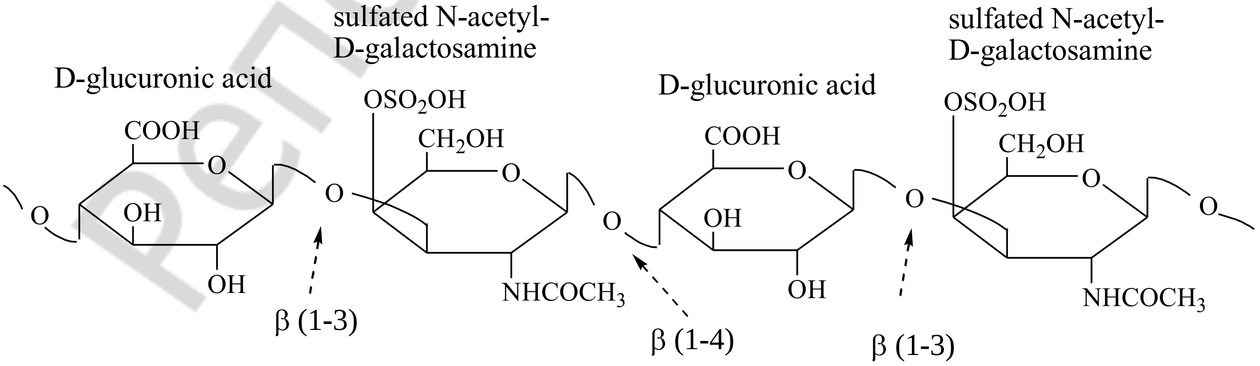
glucose molecules joined into chains of varying lengths. Its monomer is α-D-glucopyranose. The main type of bond is α (1-6). Branches are formed through connections of α (1-4), α (1-3) bonds. Dextran is synthesized from sucrose by certain bacteria. Dental plaque is rich in dextrans. Dextrans can be used as plasma expanders (substitutes for whole blood) in cases of severe shock.

Hyaluronic acid is heteropolysaccharide distributed widely in connective, epithelial and neural tissues. It is one of the chief components of the extracellular matrix, contributes significantly to cell proliferation and migration. Hyaluronic acid is an important component of articular cartilage, where it is present as a coat around each cell (chondrocyte). In the connective tissue hyaluronic acid is associated to proteins, forming aggregates. They imbibe water and are responsible for its resistance to compression. The molecular weight of hyaluronic acid in cartilage decreases with age, but the amount increases. Hyaluronic acid is a polymer of disaccharides which are composed of D-glucuronic acid and N-acetyl-D-glucosamine linked together via alternating β (1-4) and β (1-3) glycosidic bonds.



hyaluronic acid

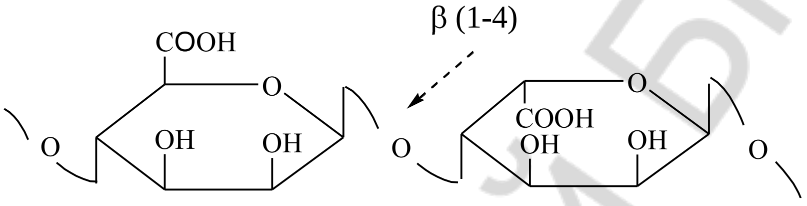
Chondroitin sulfate is a sulfated heteropolysaccharide composed of a chain of alternating monosaccharide derivatives: D-glucuronic acid and N-acetyl-D-galactosamine. It is usually found attached to proteins as part of a proteoglycan. Usually galactosamine residues are sulfated in different positions. Chondroitin sulfate is an important structural component of cartilage and provides much of its resistance to compression.



chondroitin sulfate

Chondroitin sulfate is a major component of extracellular matrix, and is important in maintaining the structural integrity of the tissue. This function is typical of the large aggregating proteoglycans: aggrecan, versican, brevican, and neurocan, collectively termed the lecticans.

Such polysaccharides of natural origin as alginic acid and agar-agar are widely used in dentistry. They are synthesized the algae. Alginic acids (alginates) consist of a disaccharide unit constructed from mannuronic acid and guluronic acid. Alginic acids are able to absorb water and swell. In the reaction of alginate with polyvalent cations, there is a network structure by crosslinking formation macromolecules according to -COOH groups. Therefore, they are used in orthopedic stomatology as impression materials.



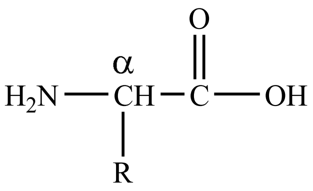
D-mannuronic acid L-guluronic acid

alginic acid

Agar-agar is a mixture of polysaccharides. One of them is agarose. Agarose is formed of alternating residues of β-D-galactopyranose and 3,6-anhydro-α-L-galactopyranose with β (1-4) bond. It has a clearly expressed feature in the formation of gels.

14. STRUCTURE AND REACTIVITY OF AMINO ACIDS

Amino acids (abbr. AA) are heterofunctional compounds which have carboxylic and amino groups. There are about 300 amino acids in nature (**biogenic** amino acids), but only 20 of them are found in the protein structure. They are called **proteinogenic** amino acids. Proteinogenic amino acids are α amino acids, because they contain an amino group in the α position.



$$H_2N-\underset{R}{\underset{|}{\overset{\alpha}{CH}}}-\overset{O}{\overset{\|}{C}}-OH$$

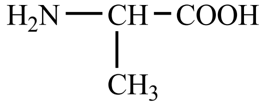
general formula of
proteinogenic amino acid

Trivial names and three-letter code are used to indicate amino acids. Trivial names are accepted by the IU nomenclature. There are several classifications of proteinogenic amino acids.

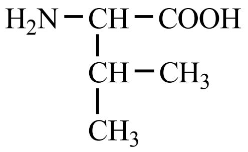
CLASSIFICATION OF THE PROTEINOGENIC AMINO ACIDS

There are two groups of proteinogenic amino acids according to classification based on polarity and ionization ability: AA with hydrophobic radical and AA with hydrophilic radical.

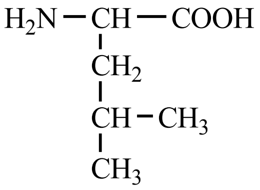
1. Amino acids with hydrophobic radical.


$H_2N-CH(CH_3)-COOH$

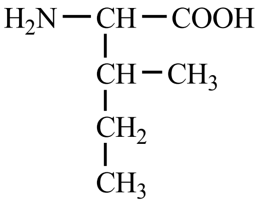
alanine
Ala


$H_2N-CH(CH(CH_3)-CH_3)-COOH$

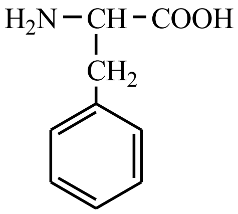
valine
Val


$H_2N-CH(CH_2-CH(CH_3)-CH_3)-COOH$

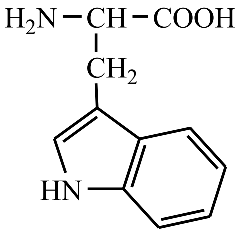
leucine
Leu


$H_2N-CH(CH(CH_3)-CH_2-CH_3)-COOH$

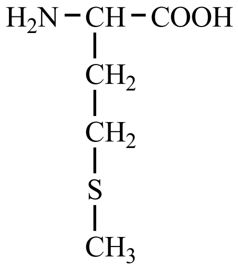
isoleucine
Ile



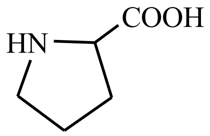
phenylalanine
Phe



tryptophane
Trp


$H_2N-CH(CH_2-CH_2-S-CH_3)-COOH$

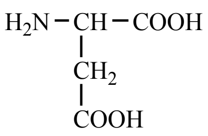
methionine
Met



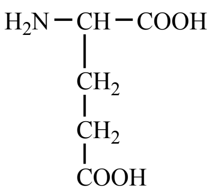
proline
Pro

2. Amino acids with hydrophilic (ionized and inionized) radical.

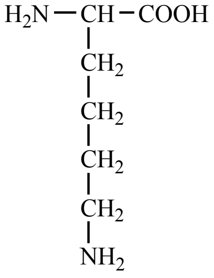
Amino acids, containing ionized (negative and positive) radical:


$H_2N-CH(CH_2-COOH)-COOH$

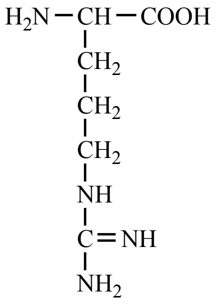
aspartic acid
Asp


$H_2N-CH(CH_2-CH_2-COOH)-COOH$

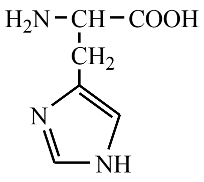
glutamic acid
Glu


$H_2N-CH(CH_2-CH_2-CH_2-CH_2-NH_2)-COOH$

lysine
Lys


$H_2N-CH(CH_2-CH_2-CH_2-NH-C(=NH)-NH_2)-COOH$

arginine
Arg

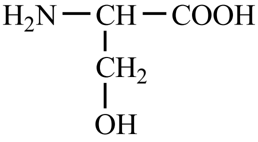


histidine
His

Amino acids, containing inionized radical:

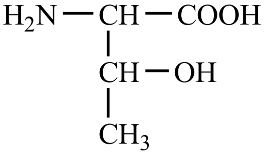
H_2N-CH_2-COOH

glycine
Gly



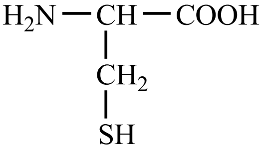
$H_2N-\underset{\substack{|\\CH_2\\|\\OH}}{CH}-COOH$

serine
Ser



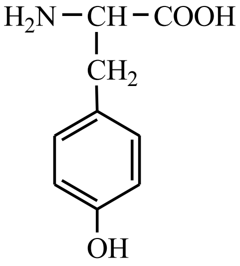
$H_2N-\underset{\substack{|\\CH-OH\\|\\CH_3}}{CH}-COOH$

threonine
Thr

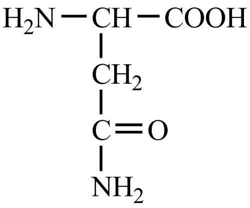


$H_2N-\underset{\substack{|\\CH_2\\|\\SH}}{CH}-COOH$

cycteine
Cys

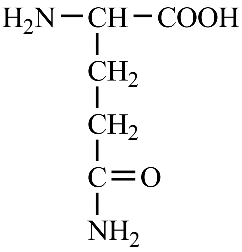


tyrosine
Tyr



$H_2N-\underset{\substack{|\\CH_2\\|\\C=O\\|\\NH_2}}{CH}-COOH$

asparagine
Asn



$H_2N-\underset{\substack{|\\CH_2\\|\\CH_2\\|\\C=O\\|\\NH_2}}{CH}-COOH$

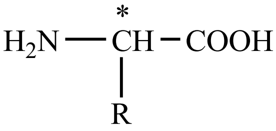
glutamine
Gln

According to acid-base properties of amino acids they are divided into acidic (Glu, Asp), basic (Lys, Arg, His) and neutral (all the other).

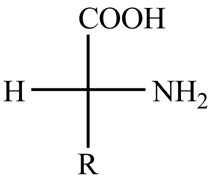
Certain amino acids may be synthesized in the body. Some of amino acids are not formed in the body (essential) and must be obtained with food. Essential amino acids are the following: Arg, Val, His, Ile, Leu, Lys, Met, Thr, Trp, Phe. Arginine and histidine are essential only for a child up to a year.

STEREOCHEMISTRY OF AMINO ACIDS

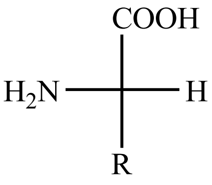
Most of amino acids are chiral. Just glycine has no chiral center. Two enantiomers exist for amino acids containing one chiral center.



$H_2N-\underset{\substack{|\\R}}{\overset{*}{CH}}-COOH$



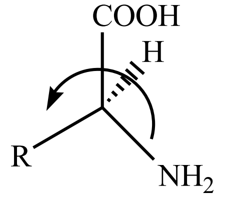
D-amino acid



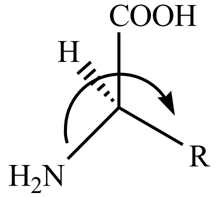
L-amino acid

Threonine and isoleucine have two chiral centers. Therefore, four enantiomers exist for them.

L-amino acids are found in the proteins of the human body, D-amino acids are in the microorganism proteins and peptides. D-amino acids aren’t assimilated by human organism. Due to the R, S- nomenclature the most of natural amino acids have S configuration (except Cys).



S-amino acid

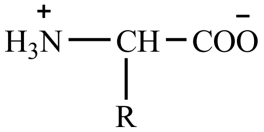


R-amino acid

CHEMICAL PROPERTIES

Amino acids react at the carboxyl and amino groups, exhibit **amphoteric properties**. Biologically important reactions of amino acids constitute a separate group.

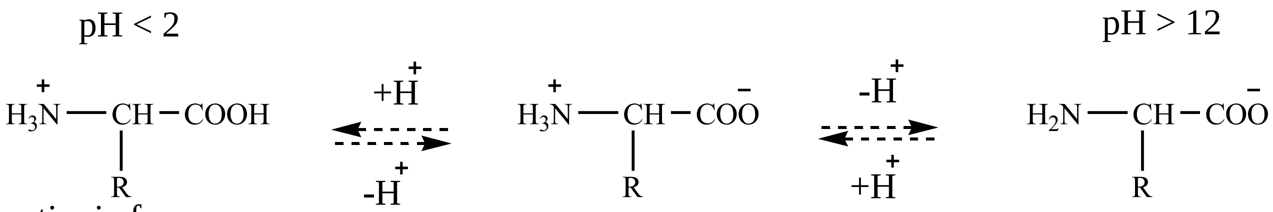
Carboxyl and amino groups of AA are ionized in aqueous solution and in the crystalline state. That is why amino acid is a dipolar ion.



$$\overset{+}{H_3N}-\underset{\displaystyle R}{\underset{|}{CH}}-CO\overset{-}{O}$$

dipolar structure of
amino acid

Most of amino acids have the neutral radicals. And at physiological pH, these amino acids have no charge. In an acidic medium ionized carboxyl groups are protonated and the amino acid acquires a positive charge. In an alkaline medium charged amino groups are deprotonated and anionic form of AA is formed. Cationic and anionic forms are transformed into each other. The predominant form of an amino acid in the solution depends on the solution pH and on the amino acid nature. In strongly acidic solutions (pH < 2) all amino acids exist mainly as cations, in strongly basic solutions (pH > 12) they are presented as anions.



$$\underset{\text{pH} < 2}{\overset{+}{H_3N}-\underset{\displaystyle R}{\underset{|}{CH}}-COOH} \underset{-\overset{+}{H}}{\overset{+\overset{+}{H}}{\rightleftarrows}} \overset{+}{H_3N}-\underset{\displaystyle R}{\underset{|}{CH}}-CO\overset{-}{O} \underset{+\overset{+}{H}}{\overset{-\overset{+}{H}}{\rightleftarrows}} \underset{\text{pH} > 12}{H_2N-\underset{\displaystyle R}{\underset{|}{CH}}-CO\overset{-}{O}}$$

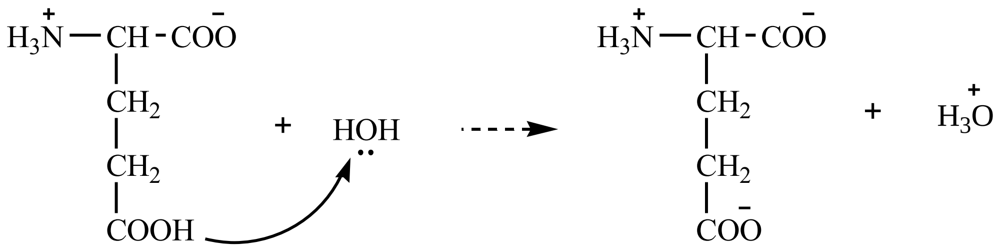
cationic form

dipolar ion

anionic form

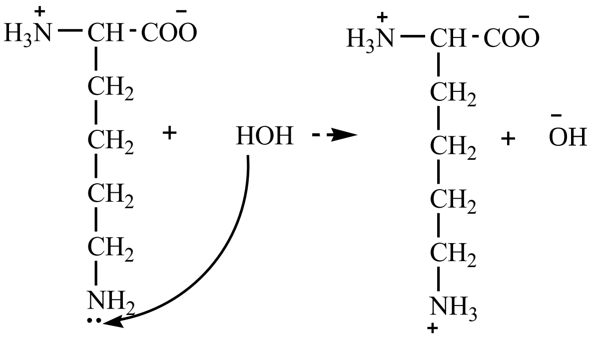
Isoelectric point is the pH value at which an amino acid exist in an electrically neutral form. The isoelectric point depends on the structure of an amino acid. Neutral amino acids have isoelectric points in the pH range of 5.0–6.3.

Aspartic and glutamic acids have the extra carboxyl group. Therefore Asp and Glu are related to acidic AA. Their isoelectric points are 3.2 and 2.7 respectively.

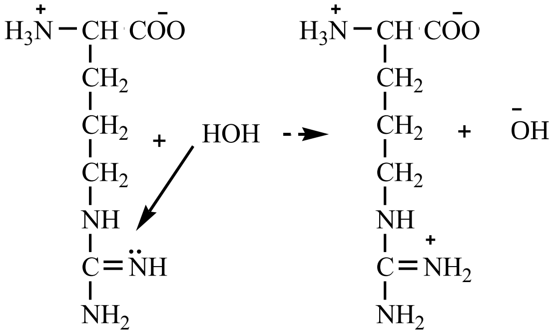


glutamic acid

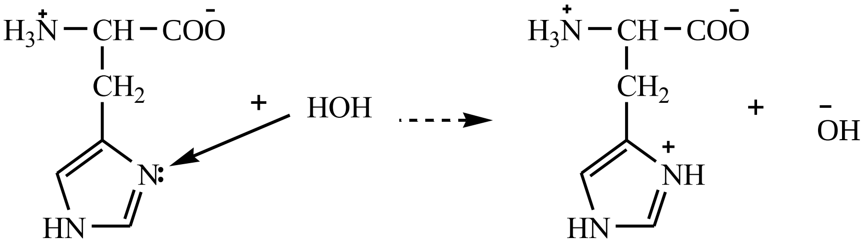
Lysine, arginine, histidine have an extra basic function in the side chains. Their isoelectric points are 9.8, 10.8 and 7.6 respectively.



lysine

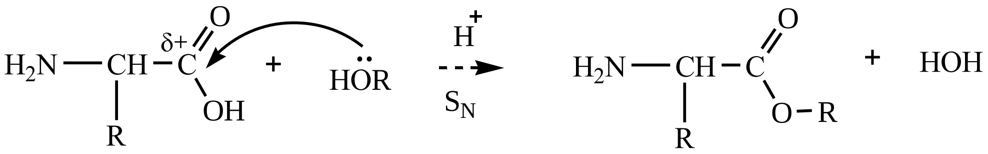


arginine



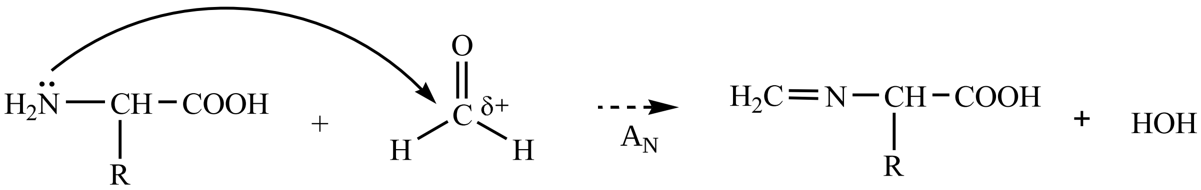
histigine

Amino acids are able to enter into reactions of nucleophilic substitution at the carboxyl group, such as esterification, the formation of anhydrides, amides, and other. Amino acid esters are important intermediates in peptides synthesis.



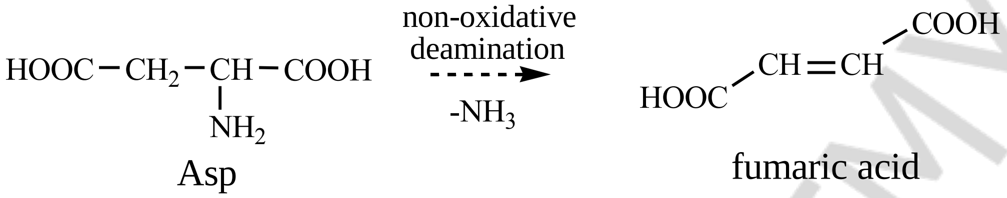
ester of amino acid

Most of carbonyl compounds react with the amino group of an amino acid giving the Schiff's bases.

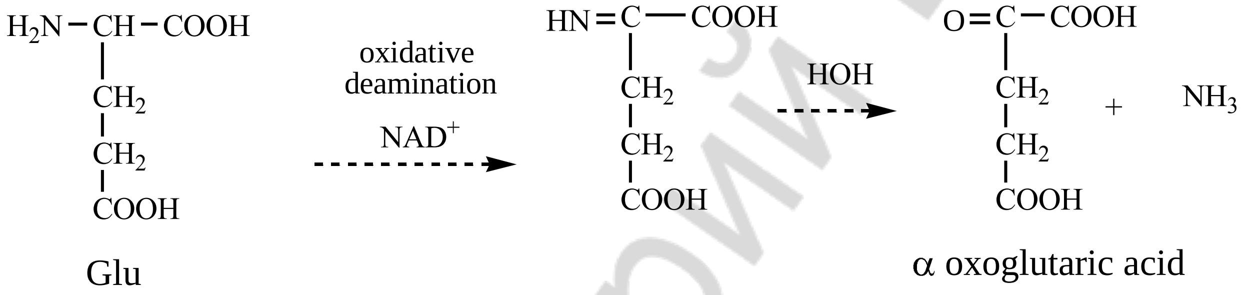


BIOLOGICALLY IMPORTANT REACTIONS

Deamination is removal of an amino group. There are two types of the enzymic deamination. The first one is the non-oxidative deamination that takes place without oxygen and leads to the α, β unsaturated carboxylic acids formation.

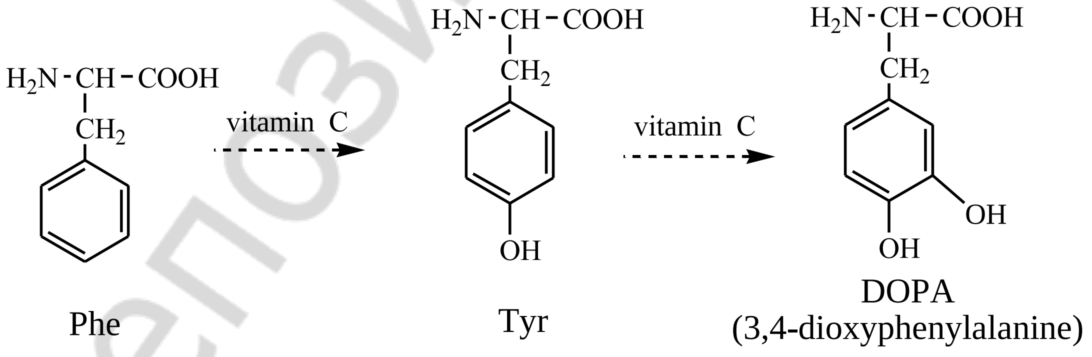


Another type of the reaction is the oxidative deamination which is a two step process. The first step represents the enzymic oxidation of an amino acid into an intermediate α imino acid in the presence of a coenzyme NAD^+. The second step is hydrolysis.



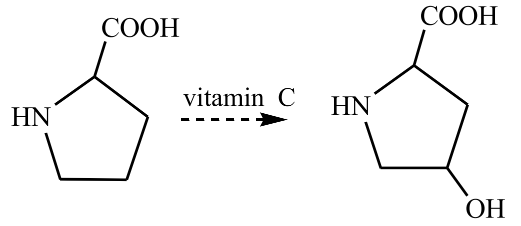
Oxidative deamination is an important way of disintegration of amino acids in the cell with the formation of oxo acid and ammonia.

Hydroxylation reactions are accompanied by introducing hydroxyl groups into the skeleton of amino acids. The reaction requires the presence of ascorbic acid (vitamin C). Tyrosine is formed by hydroxylation of phenylalanine.

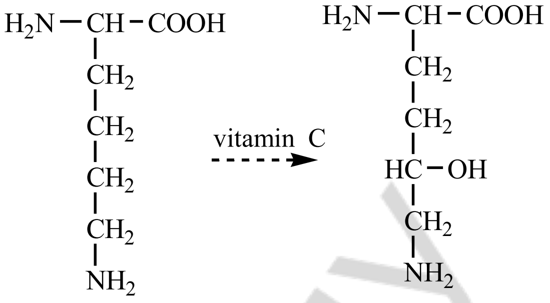


Tyrosine may also be hydroxylated and give DOPA which is the predecessor of catecholamines.

Hydroxylation reactions of proline and lysine are necessary for the formation of a specific spatial structure of collagen.



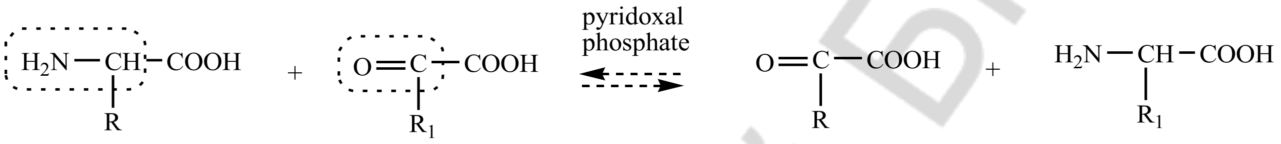
Pro 4-hydroxyproline



$H_2N-CH(COOH)-CH_2-CH_2-CH_2-CH_2-NH_2 \xrightarrow{\text{vitamin C}} H_2N-CH(COOH)-CH_2-CH_2-CH(OH)-CH_2-NH_2$

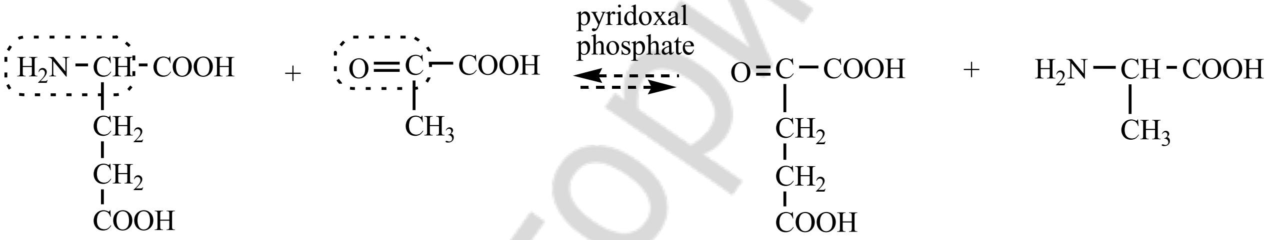
Lys 5-hydroxylysine

Transamination is reaction between oxo and amino acids. Exchange of functional groups occurs at the same time. The reaction proceeds in the presence of pyridoxal phosphate (vitamin B_6).



$H_2N-CH(R)-COOH + O=C(R_1)-COOH \underset{}{\overset{\text{pyridoxal phosphate}}{\rightleftarrows}} O=C(R)-COOH + H_2N-CH(R_1)-COOH$

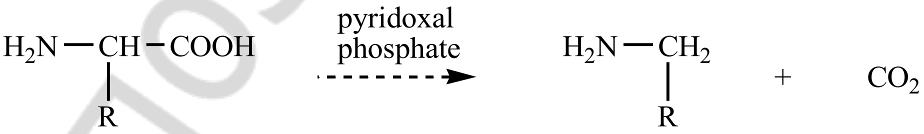
Transamination is used for the synthesis of amino acids and oxo acids required at that moment in the cell. Oxo acid such as pyruvic, oxaloacetic, α ketoglutaric are acceptors of the amino group in the reaction of transamination.



$H_2N-CH(CH_2-CH_2-COOH)-COOH + O=C(CH_3)-COOH \overset{\text{pyridoxal phosphate}}{\rightleftarrows} O=C(CH_2-CH_2-COOH)-COOH + H_2N-CH(CH_3)-COOH$

Glu pyruvic acid α oxoglutaric acid Ala

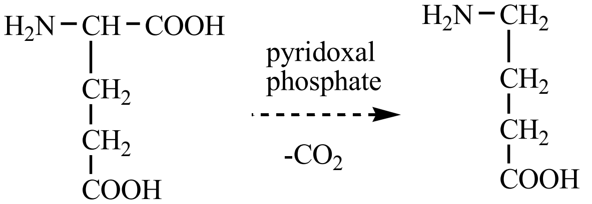
Decarboxylation reaction is isolation of CO_2. This reaction also proceeds with the participation of pyridoxal phosphate and leads to the formation of biogenic amines. Biogenic amines are products of the decarboxylation reaction of amino acids that perform specific functions in a cell.



$H_2N-CH(R)-COOH \xrightarrow{\text{pyridoxal phosphate}} H_2N-CH_2-R + CO_2$

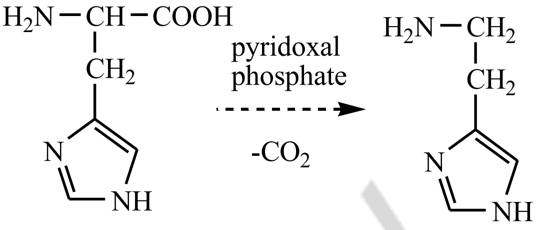
amino acid biogenic amine

For example, decarboxylation of glutamic acid leads to the formation of the neurotransmitter GABA (γ-aminobutyric acid). A similar reaction with histidine gives the histamine. Histamine provides manifestations of inflammatory and allergic reactions.



Glu

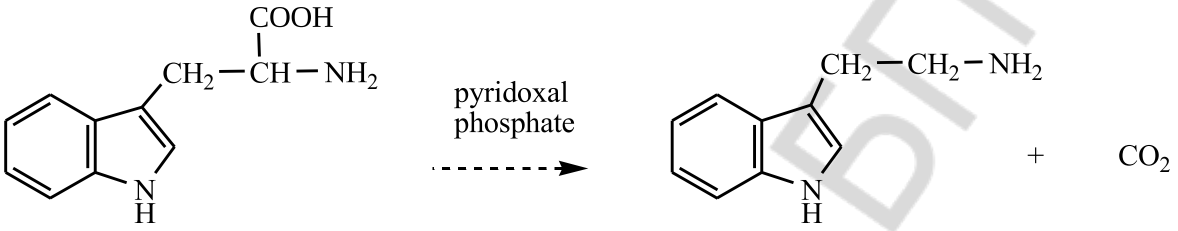
GABA
(γ aminobutyric acid)



histidine

histamine

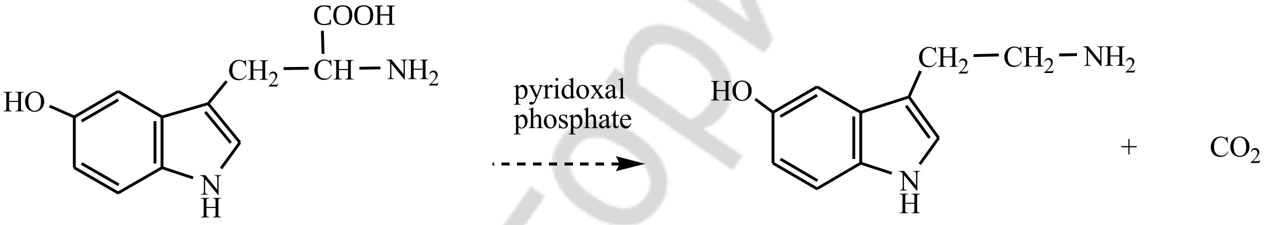
Tryptophan is decarboxylated *in vivo* to give tryptoamine. Many compounds that contain the tryptoamine skeleton have an effect on the brain and nervous system.



tryptophane

tryptamine

Serotonin is formed by decarboxylation of 5-hydroxytryptophane. Serotonin has broad activities in the brain.



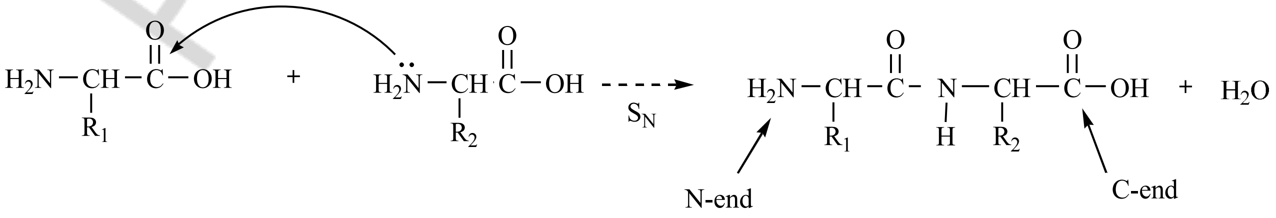
5-hydroxytryptophane

serotonin

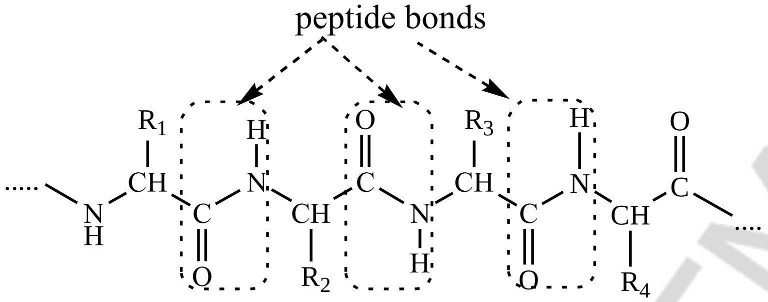
In the central nervous system, serotonin plays an important role as a neurotransmitter in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, appetite, and metabolism.

15. PEPTIDES AND PROTEINS

Peptides and proteins are natural or artificial substances that consist of residuals of α-amino acids connected with amide or peptide bonds.

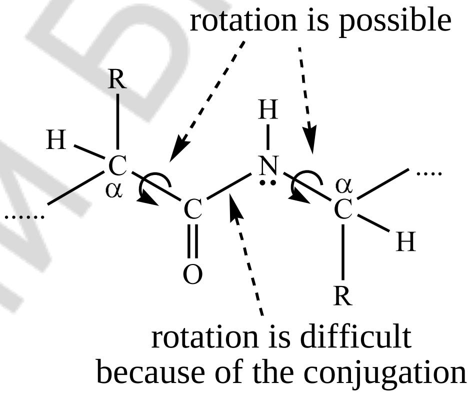


The peptides contain less than 100 amino acid residues. Proteins are made up of more than 100 amino acid residues. They have a more complex spatial organization. Amino acids are linked by **peptide bond** in the molecule of the peptide or protein.



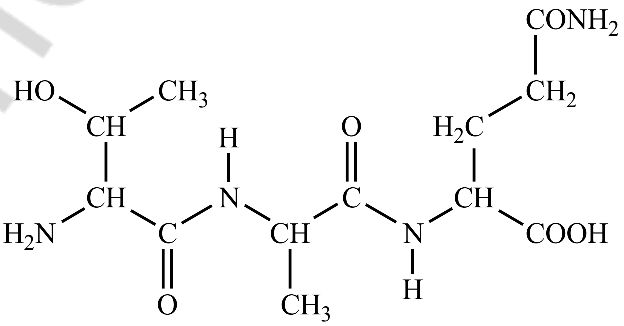
general structure of peptide

The peptide bond has a flat structure: carbon, oxygen and nitrogen atoms are in the sp^2 hybridization. Nitrogen atom has a *p* orbital with an unshared pair of electrons. A *p*-π conjugated system is formed. A flat conjugated system complicates the rotation about the C – N bond. Thus, the electronic structure predetermines a rather strict flat structure of peptide group. α Carbon atoms are situated on the opposite sides of the C – N bond.



A polypeptide chain may be presented as a number of angularly located planes of peptide groups connected with alpha-carbonic atoms using C2 – N and α-C – Csp^2 bonds. The rotation about Cα – Csp^2, Cα – N bonds is possible, but it is restricted because of the difficulties with the spatial placement of side radicals. Thus, the electronic and spatial structure makes a great contribution to the determination of the structure of a polypeptide chain.

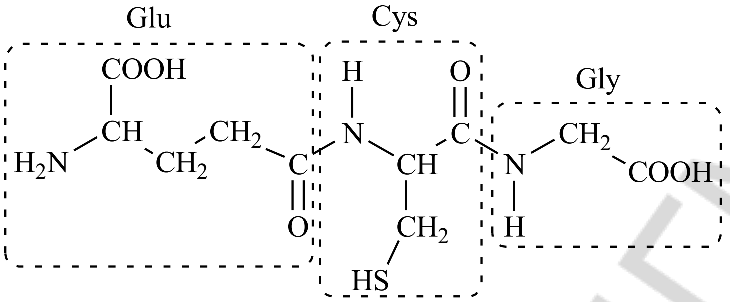
To build a peptide's name one must enumerate sequentially it's amino acid residuals beginning with the N-end and adding the suffix *yl*. Only for the last (C-end) amino acid its full name is remained.



threonyl-alanyl-glutamine
(Thr-Ala-Gln)

REPRESENTATIVES OF THE PEPTIDES

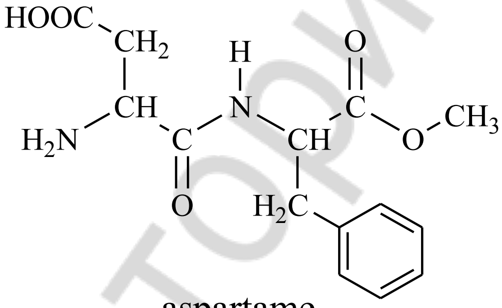
Glutathione (γ-glutamylcysteinylglycine) is tripeptide. All animal and vegetable cells, bacteria contain it. The presence of cysteine means that glutathione can exist both in a reduced and in an oxidized form.



glutathione

Glutathione takes part some oxidation-reduction processes. It performs the function of protein protector (prevents proteins with free SH-groups from oxidation and forming disulfide bonds -S-S-).

Aspartame consists of residuals of L-aspartic acid and the methyl ester of L-phenylalanine. It is used as a sugar substitute.



aspartame

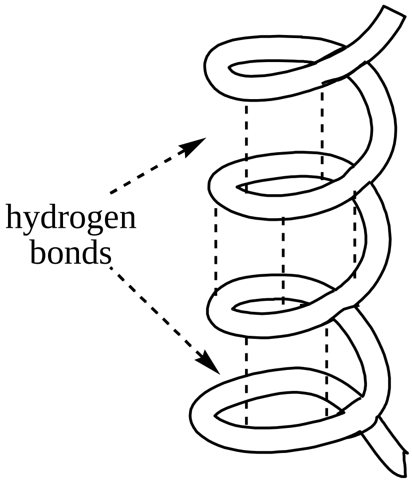
Neuropeptides (opiate peptides) were first discovered in the brain. Two groups of neuropeptides are distinguished: enkephalins and endorphins. These peptides render analgetic action and are used as drugs.

Insulin is a hormone responsible for the control of the metabolism of carbohydrates, fats and proteins. It's produced by the *beta* cells of the pancreas. Serious disturbances of carbohydrate metabolism such as diabetes are connected with insulin deficiency. Insulin consists of two peptide chains (A and B) connected with 2 disulfide bonds. A-chain has 21 amino acid residuals; B-chain has 30 ones.

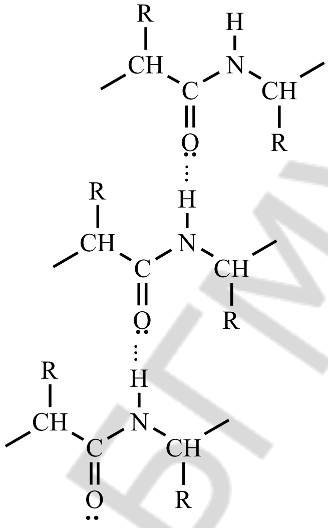
ORGANIZATION LEVELS OF MOLECULES OF PEPTIDES AND PROTEINS

The primary structure of the peptide or protein is a sequence of amino acids in the chain. It is determined by a nucleotide sequence in DNA encoding this protein. Proteins of the human body are made up of amino acids L stereochemical series

Secondary structure is a local conformation of a definite part of a polypeptide chain which appears as a result of rotation about σ bonds of α carbon atoms of a polypeptide chain and leading to a high order and stabilization. The most examined secondary structures are an α helix and a β pleated sheet structure.



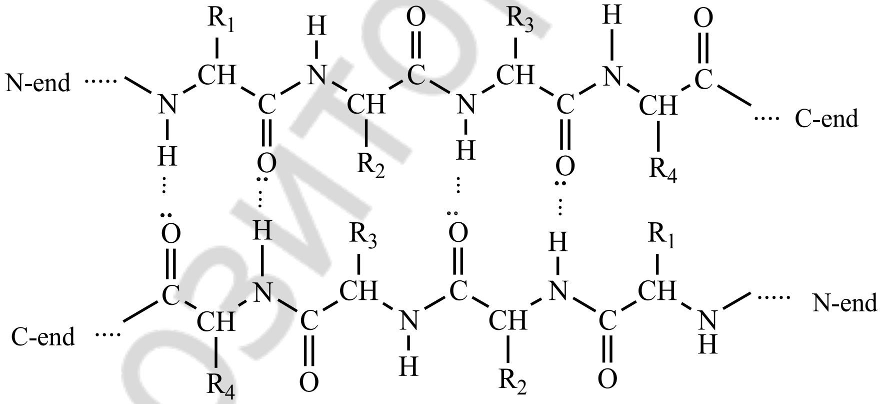
α helix



hydrogen bonds

An α helix is a right handed helical structure which is stabilized with hydrogen bonds between NH- and CO-groups of the main chain.

A β pleated sheet structure is formed from elongated polypeptide chains. This type of conformation is stabilized with hydrogen bonds between NH- and CO-groups of different polypeptide chains in fibrillar proteins or different parts of the same polypeptide chain in globular proteins.



β pleated sheet structure

The tertiary structure is the spatial form of the protein, which is formed by the interaction of the amino acid radicals with each other. Amino acid side groups, distant from each other, can occur in the space due to chain bends and interact. Tertial structure is stabilized with different types of bonds and interactions: disulfide bond, hydrogen bonds, hydrophobic and dipolar interactions.

A covalent disulfide bond is formed between cysteine residuals of the same protein chain or different ones.

Hydrogen bonds, dipolar and hydrophobic interactions are of great importance for forming a tertiary structure. These bonds are very weak but due to a great number of individual weak interactions define the spatial structure and stability of a protein molecule. Nonpolar amino acid radicals are attracted to each other. In most cases, they tend to limit their contact with the water and hide themselves inside the protein molecule, forming a hydrophobic core. Radicals of polar amino acids are capable of forming hydrogen bonds with each other or with the water molecules on the surface of the protein. Amino acids such as lysine, arginine, histidine on the one hand and aspartic, glutamic acid on the other hand may form bipolar connections. Most of the protein molecules have hydration shell on the surface, which is very important to maintain the natural spatial shape.

Some proteins consisting of several polypeptide chains have **quaternary structure**. Quaternary structure is a way of location in the space of separate polypeptide chains (identical or different) with tertiary structure that leads to forming of an integrated (structurally and functionally) macromolecular formation. Each polypeptide chain is named a protomer. Protomers are complementary and are bound to an integrated supramolecular structure by noncovalent bonds.

hemoglobine

A single protomer usually has no biological activity. Hemoglobin is an example of a protein with quaternary structure. Its main function as the principal component of erythrocytes is the transport of oxygen from lungs to tissues. Its quaternary structure is a formation of four polypeptide chains (subunits); each of them contains heme. Heme is located in a hollow («heme pocket») that each subunit has.

DENATURATION OF PROTEINS

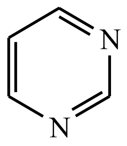
Spatial structure of proteins can be broken under the influence of different factors: rise of the temperature, pH changes, ultraviolet light or X-ray emission, mechanical effect (for example, mixing of solutions), chemical agents (urea, mercaptoethanol, sodium dodecyl sulfate, salts). Breaking of the native macrostructure of proteins is named **denaturation**. As a rule, noncovalent interactions, which stabilize protein’s structure, are broken. Denaturation results in decreased solubility in water, a decrease of biological activity. Denaturation may be reversible or irreversible. If it’s reversible, an active (renaturated) protein may be got after removing denaturants agents.

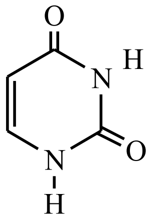
16. NUCLEIC ACIDS

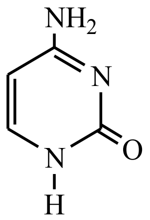
Nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are molecules which are involved in the storage and translation of genetic information. These biological polymers are sometimes found associated with proteins and in this form they are known as **nucleoproteins.**

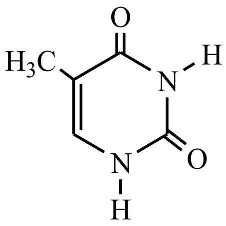
A nucleic acid consists of mononucleotides. Nucleotide is built of nucleoside and phosphoric acid. Nucleoside consists of the heterocyclic base and the sugar (D-ribose or 2-deoxy-D-ribose). The nucleosides that can be obtained from DNA all contain 2-deoxy-D-ribose and one of four heterocyclic bases (adenine, guanine, cytosine, thymine). The nucleosides that can be obtained from RNA all contain D-ribose and one of four heterocyclic bases (adenine, guanine, cytosine, uracil).

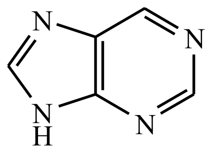
The aromatic compounds, purine and pyrimidine, lie on the base of the heterocyclic base structures.

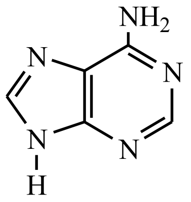

pyrimidine

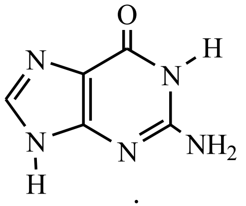

uracil


cytosine

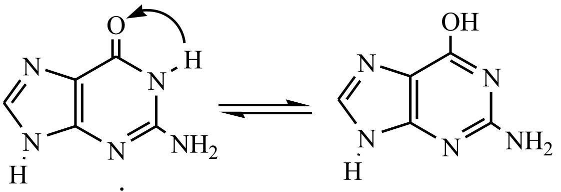

thymine


purine

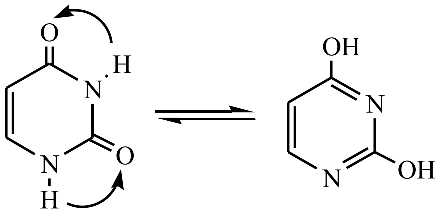

adenine


guanine

The heterocyclic bases are capable of existing in tautomeric forms. Lactam forms are the predominant forms that the bases assume when they are present in nucleic acid.

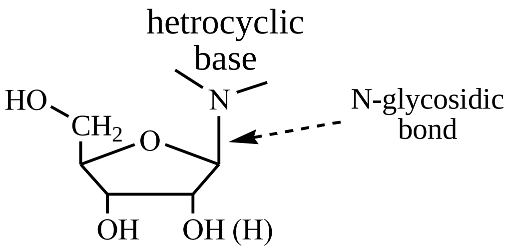

guanine lactam form

lactim form


uracil lactam form

lactim form

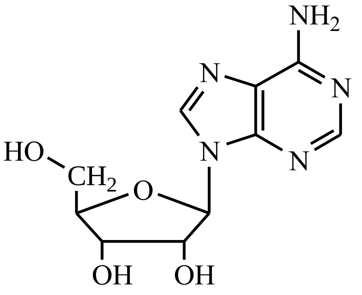
Nucleosides are the building blocks of nucleic acids. Nucleosides are N-glycosides constructed from two components: a sugar and a heterocyclic base. D-ribose and 2-deoxy-D-ribose are in the cyclic β-furanose form.



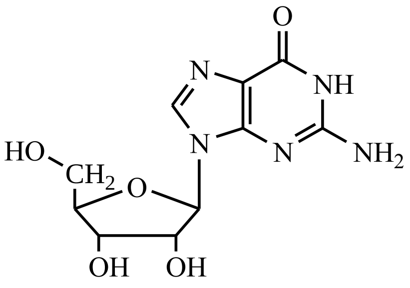
the general formula
of nucleoside

The nucleosides, which are constituents of RNA	The nucleosides, which are constituents of DNA
adenosine	2-deoxyadenosine
guanosine	2-deoxyguanosine
cytidine	2-deoxycytidine
uridine	thymidine

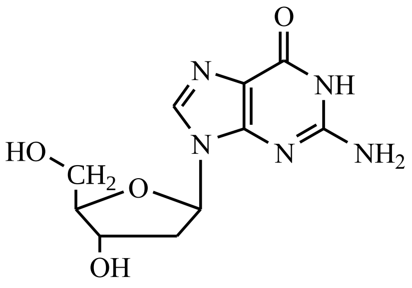
The names and the structures of the nucleosides are shown below.



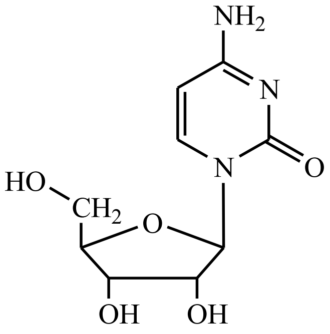
adenosine



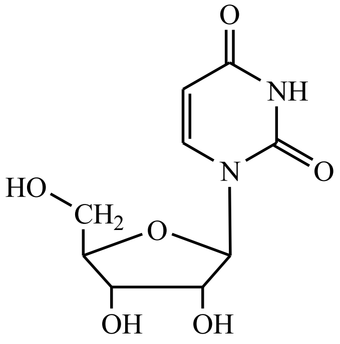
guanosine



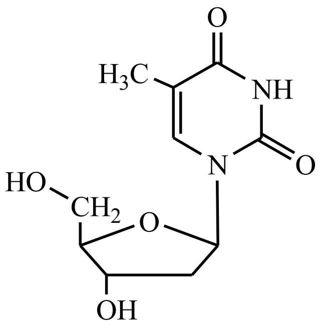
deoxyguanosine



cytidine



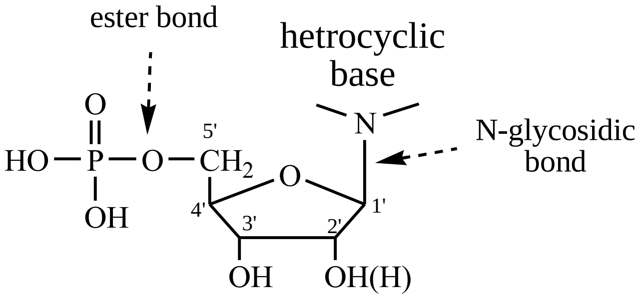
uridine



thymidine

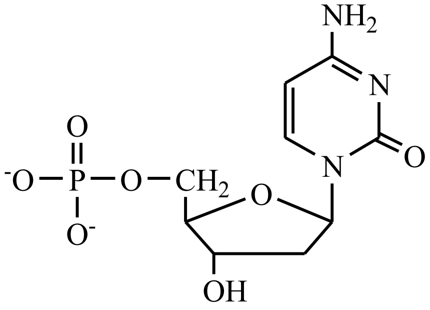
Nucleotide is an ester of phosphoric acid and nucleotide. The heterocyclic base and the ribose fragments are numbered separately. The carbon atoms of ribose or deoxyribose are numbered with a prime ('). Phosphate esterification usually occurs at the 5' position of the pentoses. Although it does occur at the 2' and 3' positions.

A general formula for a nucleotide is shown in the following figure (esterification at the 5' position).



the general formula
of nucleotide

Nucleotides possess acid properties, because they contain phosphate. And under physiological conditions nucleotides exist at the ionized form.



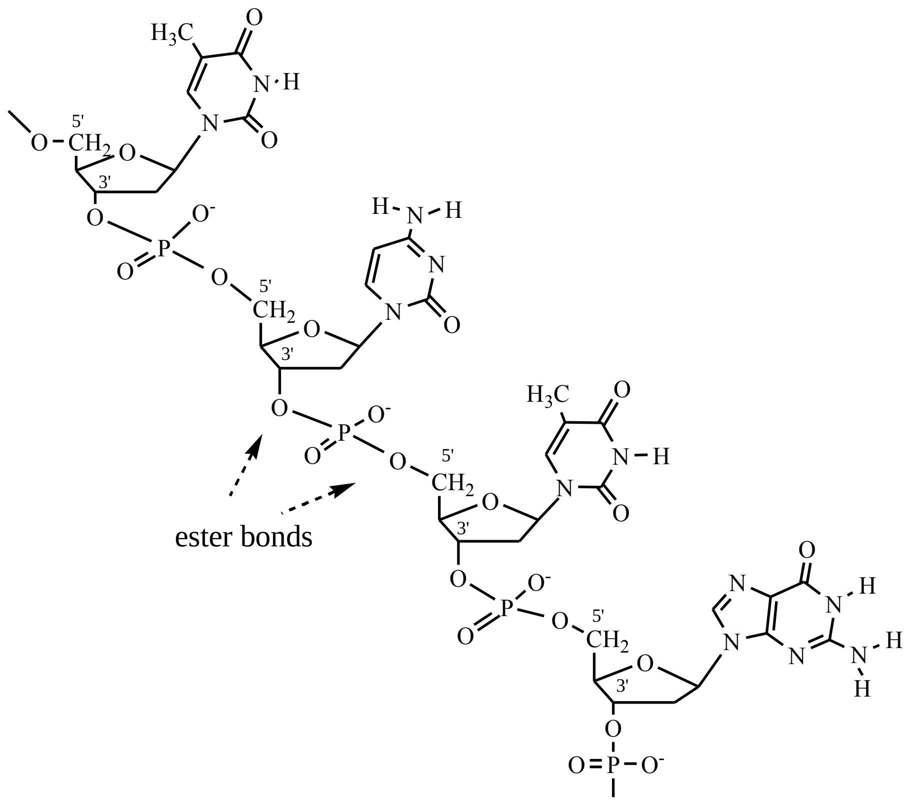
deoxycytidine-5'- monophosphate (dCMP)

Complete hydrolysis of a nucleotide (acidic or enzymatic) gives a heterocyclic base, either a purine or pyrimidine, a five-carbon monosaccharide, either D-ribose or 2-deoxy-D-ribose and a phosphate ion.

Nucleotides are the components of nucleic acids (DNA and RNA). DNA is found in the cell nucleus. RNA molecules are generally much smaller and are found outside the nucleus of the cell. In 1953 James Watson and Francis Crick suggested a double helix structure for DNA.

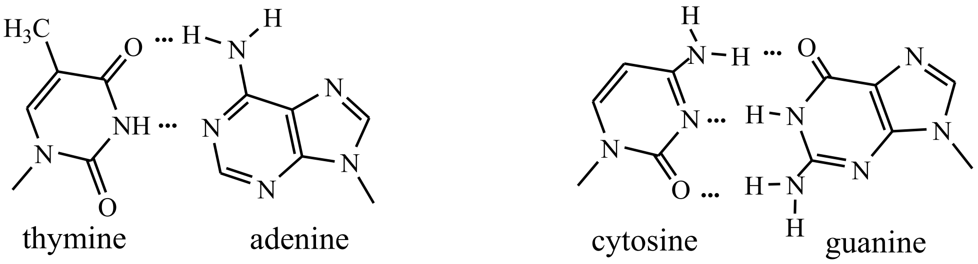
The structure of DNA contains two long antiparallel chains of deoxyribose nucleotides connected with a phosphate ester bond. Nucleotides are connected to each other by means of phosphoric acid, which forms two ester bonds between $C_{5'}$ and $C_{3'}$ of adjacent nucleotides. The end of polymeric chain that has a free hydroxyl group at $C_{5'}$ is called the 5' end and the end with a free OH at $C_{3'}$ is called the 3' end. Each end can be phosphorylated.

The primary structure of the nucleic acid is a sequence in which nucleotides are bound in a chain. The secondary structure of the nucleic acid is dimensional organization of a macromolecule.



the fragment of one chain of DNA

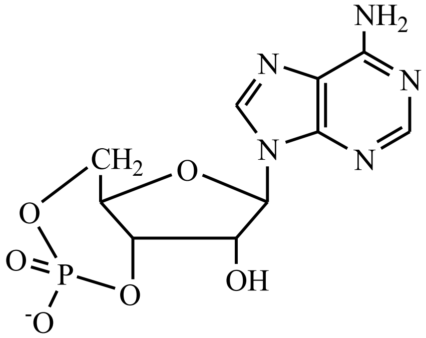
Two factors are mainly responsible for the stability of the DNA double helix: base pairing between complementary heterocyclic bases by hydrogen bonds and stacking between adjacent bases. Thus, the two polynucleotide chains are linked by hydrogen bonds. These hydrogen bonds form two pairs: adenine-thymine, guanine-cytosine.



Stacking is vertical interaction between the hydrophobic nucleobases, located in the same chain over each other.

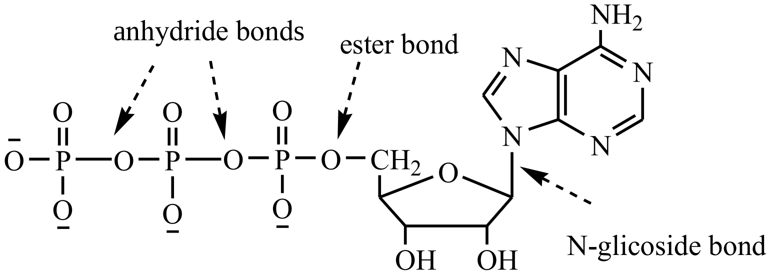
RNA is structurally similar to DNA. Like DNA, RNA has a sugar-phosphate polymer backbone with attached heterocyclic bases. RNA molecules are smaller than DNA. The most RNA molecules exist as single strands. There are four types of RNA: ribosomal RNA (rRNA), messenger RNA (mRNA), transport RNA (tRNA) and small interfering RNA (si-RNA). Messenger RNA is the RNA that carries information from DNA to the ribosome, the sites of protein synthesis (translation) in the cell.

Some nucleotides serve as co-enzymes and regulators of biochemical processes. The compound called cyclic adenosine-3',5'-phosphate (cAMP) is an important regulator of hormone activities.



cyclic adenosine-3',5'-phosphate

The 5'-triphosphate of adenosine or ATP is the energy source. This molecule contains two anhydride fragments, therefore it has two high energy bonds.



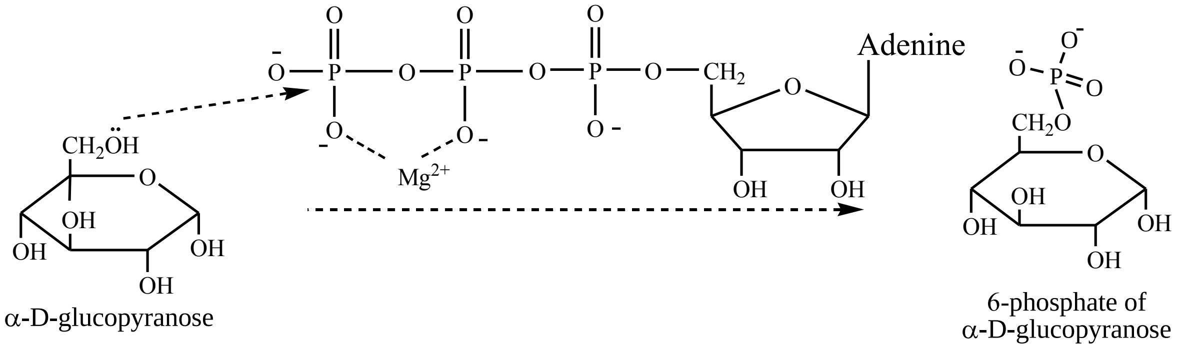
ATP

Break of anhydride bond is accompanied by the release of large amounts of energy.

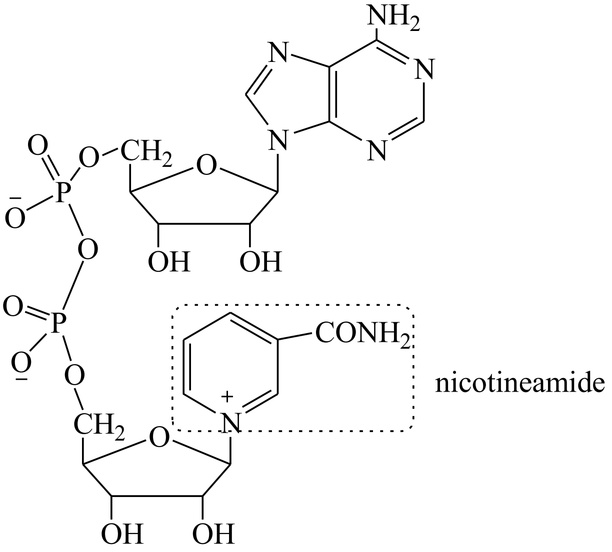
$$\text{ATP} \dashrightarrow \text{ADP} + \text{energy} + \text{phosphate}$$

$$\text{ADP} \dashrightarrow \text{AMP} + \text{energy} + \text{phosphate}$$

ATP participates in the phosphorylation (esterification by phosphoric acid) reactions. For example, the first step of glycolysis is a reaction of the glucose phosphorylation. The phosphate ester is formed via a nucleophilic substitution reaction involving the C_6 hydroxyl group of glucose. The reaction requires the presence of a magnesium ion to help the nucleophilic attack.

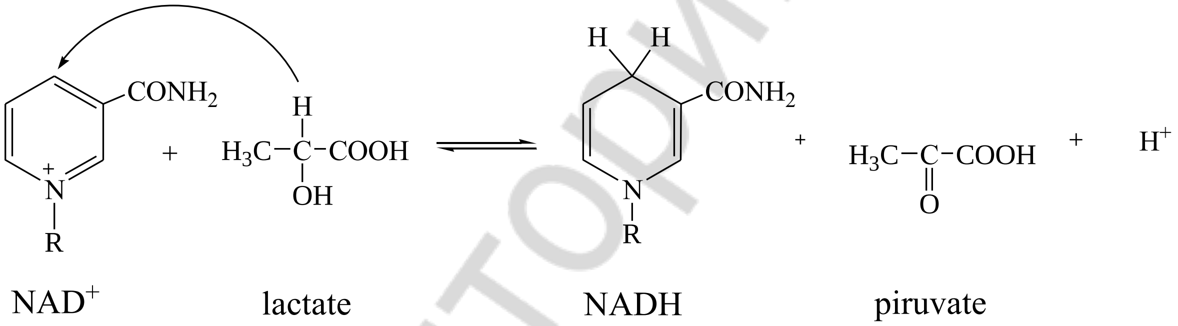


Adenosine unit is part of the structure of coenzyme NAD$^+$ (nicotinamide dinucleotide).



nicotineamide adenine dinucleitide

Coenzyme NAD$^+$ participates in oxidation-reduction reactions. Coenzyme NAD$^+$ attaches hydride anion, which split off from the substrate. As a result nicotinamide losses aromaticity. It is formed NADH (nicotinamide adenine dinucleotide reduced).



Coenzyme NAD$^+$ is involved in the oxidation of ethanol, lactic acid, malic acid, and many others.

17. LIPIDS, CLASSIFICATION, PROPERTIES

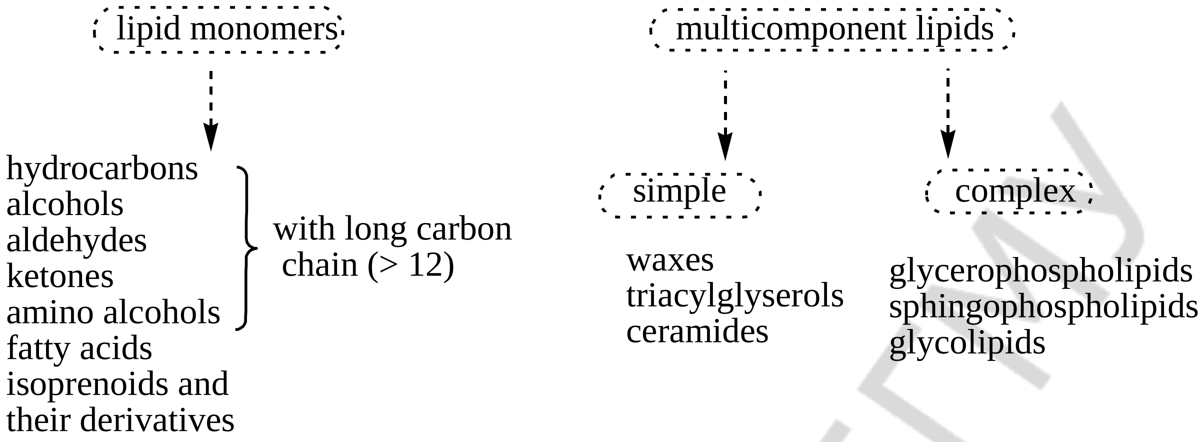
Lipids represent a large group of natural hydrophobic compounds with a various structure and biological functions. They are united in a single category on the basis of the following three main criteria:

1) almost completely insoluble in water and soluble in nonpolar solvents;
2) presented in nature in the form of the esters of the fatty acids;
3) presented in all living organisms.

Earlier the lipids were divided into hydrolyzable and non-hydrolyzable. Hydrolyzable lipids contain ester fragment and can be hydrolyzed. Non-hydrolyzable lipids can not undergo hydrolysis.

In accordance with modern classification are subdivided into multicomponent lipids and their components.

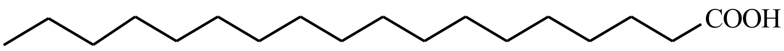
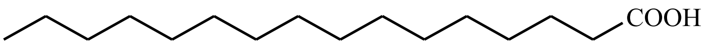
Classification of lipids

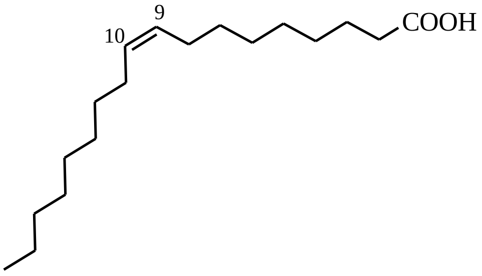
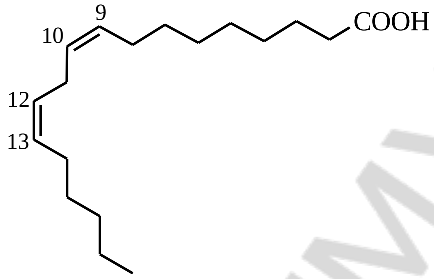
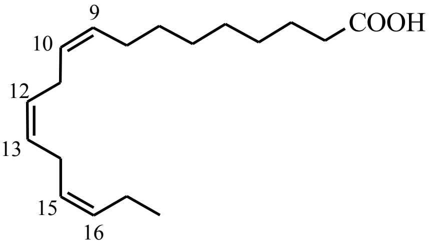
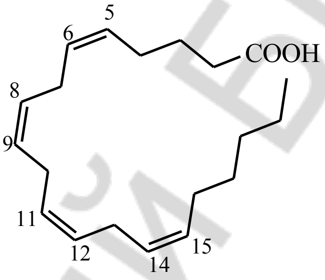


Lipids mainly perform energetic, structural, protective and regulatory functions. Reserve lipids (fats) perform energy function. Quantity and structure of reserve lipids are changeable and depend on the diet and the physical state of the organism. Quantity and structure of structural lipids in an organism are constant, genetically caused and normally do not depend on a diet and the state of an organism. The protective function is performed mainly lipids constituting the subcutaneous fat. Regulatory function is performed by fat-soluble vitamins and lipids, which have hormonal activity.

Different alcohols may be part of lipids: glycerol, inositol, propane-1,2-diol (see the section № 9). Long chain alcohols (C_{12}–C_{30}) are found in composition of lipids.

Fatty acids are often included in the multicomponent lipids. Fatty acids are mono carboxylic acids with a long carbon chain, containing usually even number of carbon atoms (from 12 to 24). The fatty acids can be saturated and unsaturated. Trivial names are used to designate fatty acids. Furthermore, unsaturated fatty acids are called by means ω-nomenclature, which includes the total number of carbon atoms, the number of double bonds and the number of carbon atoms between the double bond and the methyl group (ω-carbon).

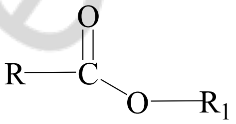
Saturated fatty acids
Stearic acid $C_{17}H_{35}COOH$ 
Palmitic acid $C_{15}H_{31}COOH$ 

Unsaturated fatty acids	
Oleic acid $C_{17}H_{33}COOH$  18:1 ω 9	Linoleic acid $C_{17}H_{31}COOH$  18:2 ω 6
Linolenic acid $C_{17}H_{29}COOH$  18:3 ω 3	Arachidonic acid $C_{19}H_{31}COOH$  20:4 ω 6

The natural fatty acids have the unbranched carbon chains. Under conditions of physiologic pH the fatty acids are ionized. The melting points of unsaturated fatty acids are lower than in saturated acids with the similar number of carbon atoms. The chains of saturated fatty acids have a zigzag shape in which the carbon atoms are arranged in *anti* butane conformation. The naturally unsaturated acids have the *cis* configuration, which is less thermodynamically stable. They have lower melting temperature than the *trans* isomers. At body temperature unsaturated fatty acids are liquids. The double bonds in poly-unsaturated fatty acids are not conjugated. The unsaturated fatty acids except oleic acid are essential because they are not synthesized *in vivo*. So they must be taken with food (for example, vegetable oil).

SIMPLE LIPIDS

Simple lipids are the bicomponent. They consist of an alcohol and a fatty acid. **Waxes** are the esters formed by alcohols with a long chain and fatty acids.

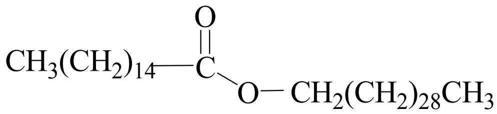


$$R-\overset{\displaystyle O}{\overset{\|}{C}}-O-R_1$$

R - the residual of fatty acid
R_1 - the residual of alcohol with a long chain

the general formula of waxes

Natural waxes comprise an admixture of free fatty acids, alcohols, hydrocarbons. Myricyl palmitate is the main component of bee wax.

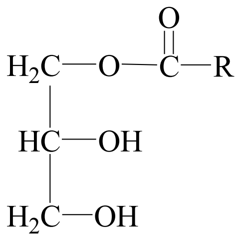


$$CH_3(CH_2)_{14}-\overset{O}{\overset{\|}{C}}-O-CH_2(CH_2)_{28}CH_3$$

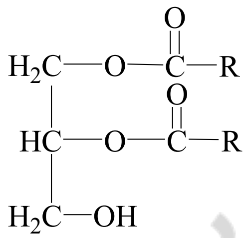
myricyl palmitate

Waxes are hydrophobic, so they perform a protective function in nature. Synthetic and natural waxes are widely applied in medicine and pharmacy for the preparation of ointments, and in orthopedic dentistry.

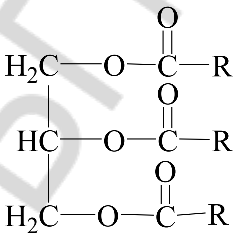
Triacylglycerols are esters of fatty acids and glycerol. Triacylglycerol synthesis in the cell passes through the stages formation monoacylglycerole and diacylglycerole.



monoacylglycerol



diacylglycerol

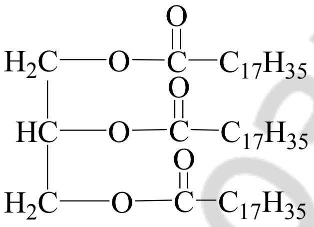


triacylglycerol

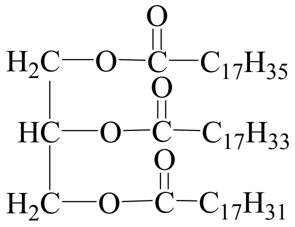
Triacylglycerols may contain the same or different fatty acid residues. According to the character of the fatty acid (saturated or unsaturated) there are solids (fats) and liquids (oils).

Triacylglycerols of human organism contain different fatty acid residues with predominance of unsaturated.

According to the international nomenclature the names of the triacylglyceroles are formed by the addition of a suffix *oyl* to the name of the corresponding acyl radical of the fatty acid.



tristearoylglycerol



1-stearoyl-2-oleoyl-3-linoleoylglycerol

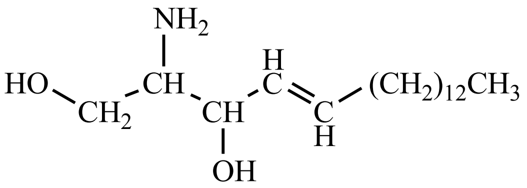
Triacylglyceroles are hydrophobic substances, the melting temperature depends on the fatty acid degree of unsaturation. The vegetative fats (oils) containing mono- and polynonsaturated fatty acid, have lower melting temperature. The degree of unsaturation is characterized by iodic number.

In animal and human tissues triacylglycerols have special functions:

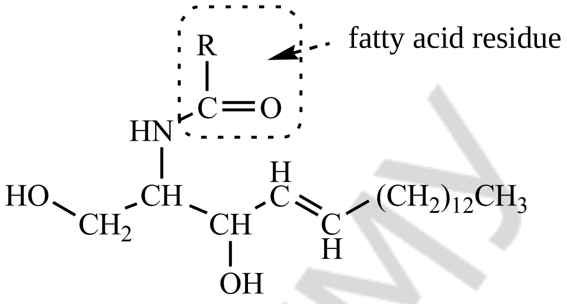
– in fatty tissue they form the so-called fatty deposits, representing the form of energy storage;

– triacylglycerols play the role of physical protection and a temperature regulator of various body organs.

Ceramides also refers to simple lipids. They are N-acylated sphingosine derivatives.



sphingosine



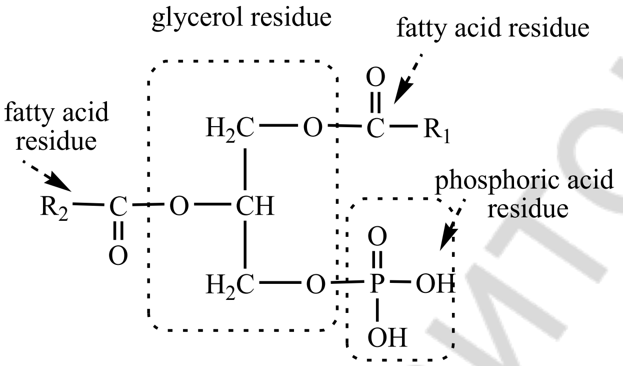
ceramide

Ceramides are found in the tissues of the nervous system.

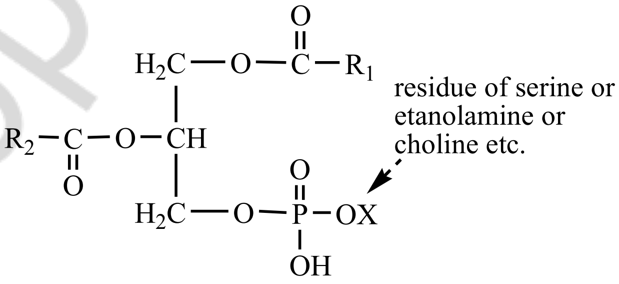
COMPLEX LIPIDS

There are three basic classes of complex lipids: glycerophospholipids, glycolipids, glycerosphingolipids.

Glycerophospholipids are derivatives of phosphatidic acid. In the formation of glycerophospholipids phosphoric acid residue is reacted with a hydroxy containing compound according to the mechanism of the nucleophilic substitution.

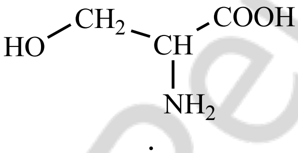


phosphatidic acid

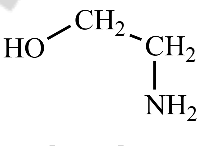


general formula of glycerophospholipids

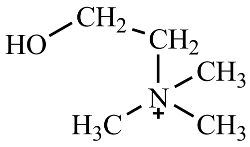
Substances such as ethanolamine, serine, choline, inositol often represent the complex lipids.



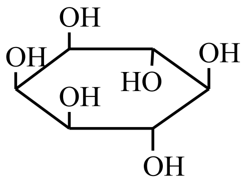
serine



ethanolamine

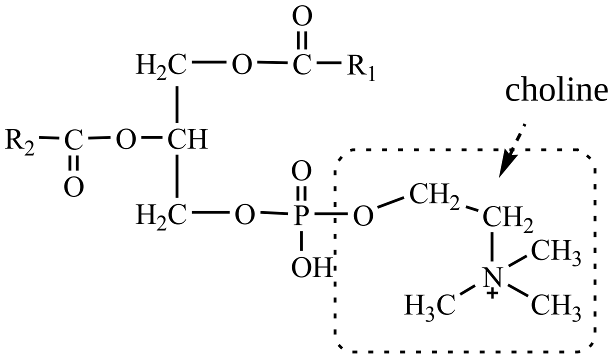


choline



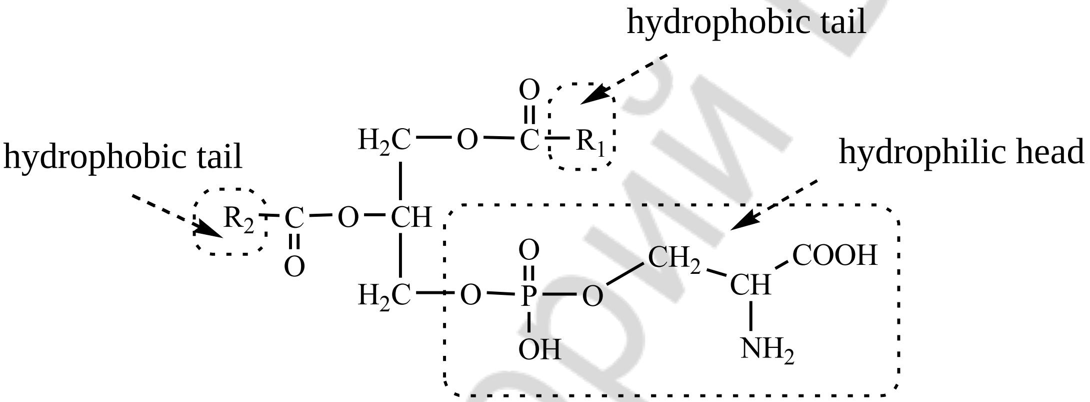
inositol

There are some groups of glycerophospholipids: phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylinositols, etc.



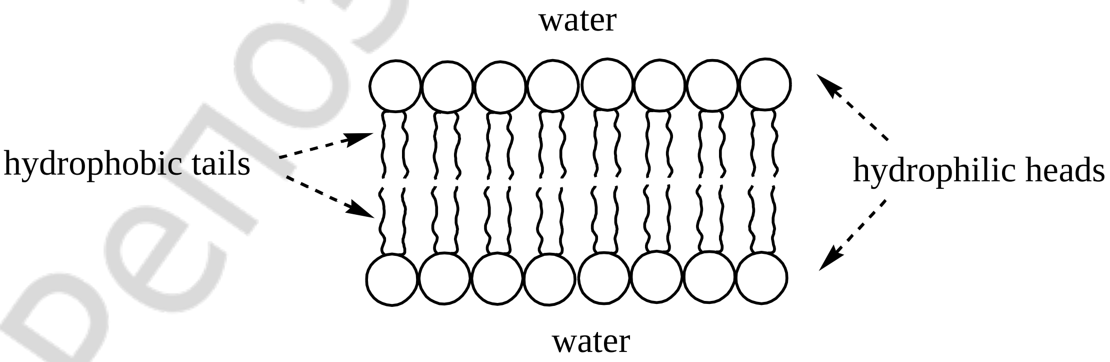
phosphatidylcholine

All phospholipids incorporate waterproof nonpolar part including radicals of fatty acids (*hydrophobic tails*) and a polar part (*hydrophilic head*), including the residuals of glycerol, phosphoric acid and amino alcohol.

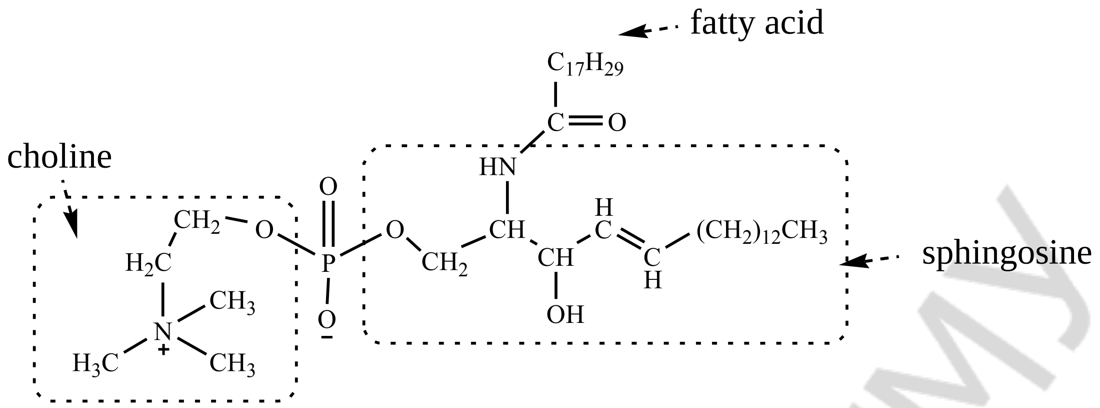


phosphatidylserine

The molecules of glycerophospholipids have amphiphilic nature and are capable to settle down in appropriate way on the border of two phases, thus which providing the formation of lipid double layer membranes. Biological membranes are cell structures, which separate cytoplasm and the majority of intracellular organelles.

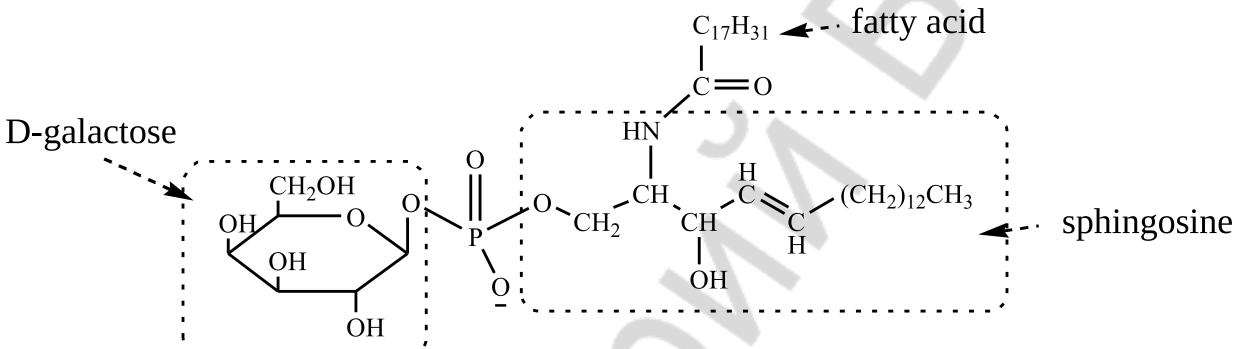


Similar to glycerophospholipids, other complex lipids perform structural function. Sphingomyelin is an example of sphingophospholipids. They are often found as part of the myelin sheath of nerve fibers.



sphingomyelin

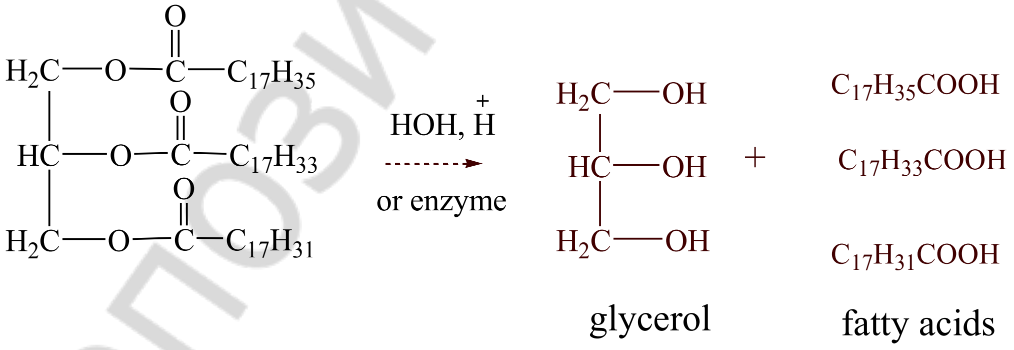
Glycolipids contain in its composition residues of mono- or polysaccharides. They are also found as part of of biological membranes.



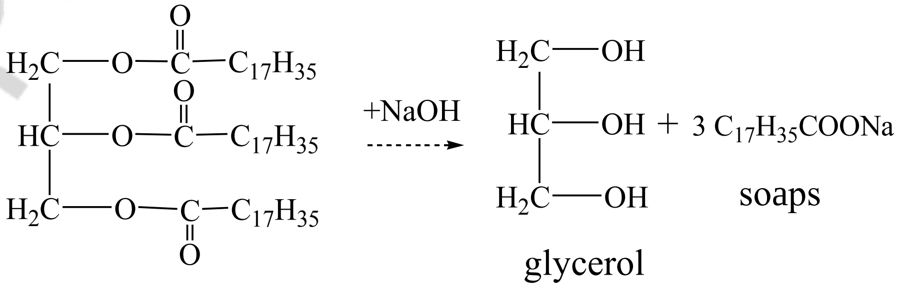
the example of glycolipids

CHEMICAL PROPERTIES OF LIPIDS

Lipids, which are esters, are capable of hydrolysis. It is their main chemical property. Hydrolysis may occur in an acidic, alkaline medium and by enzymes.

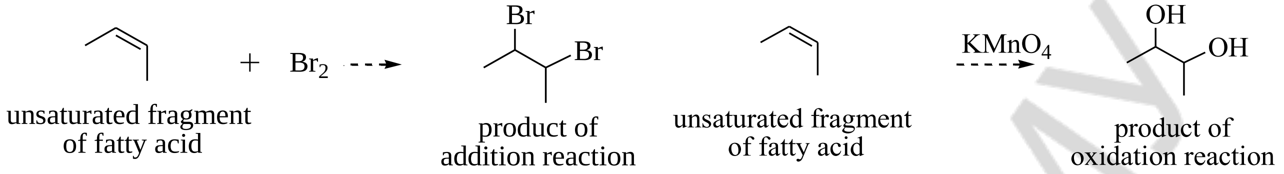


Alkaline hydrolysis results in the formation of glycerol and fatty acid salts (soaps).



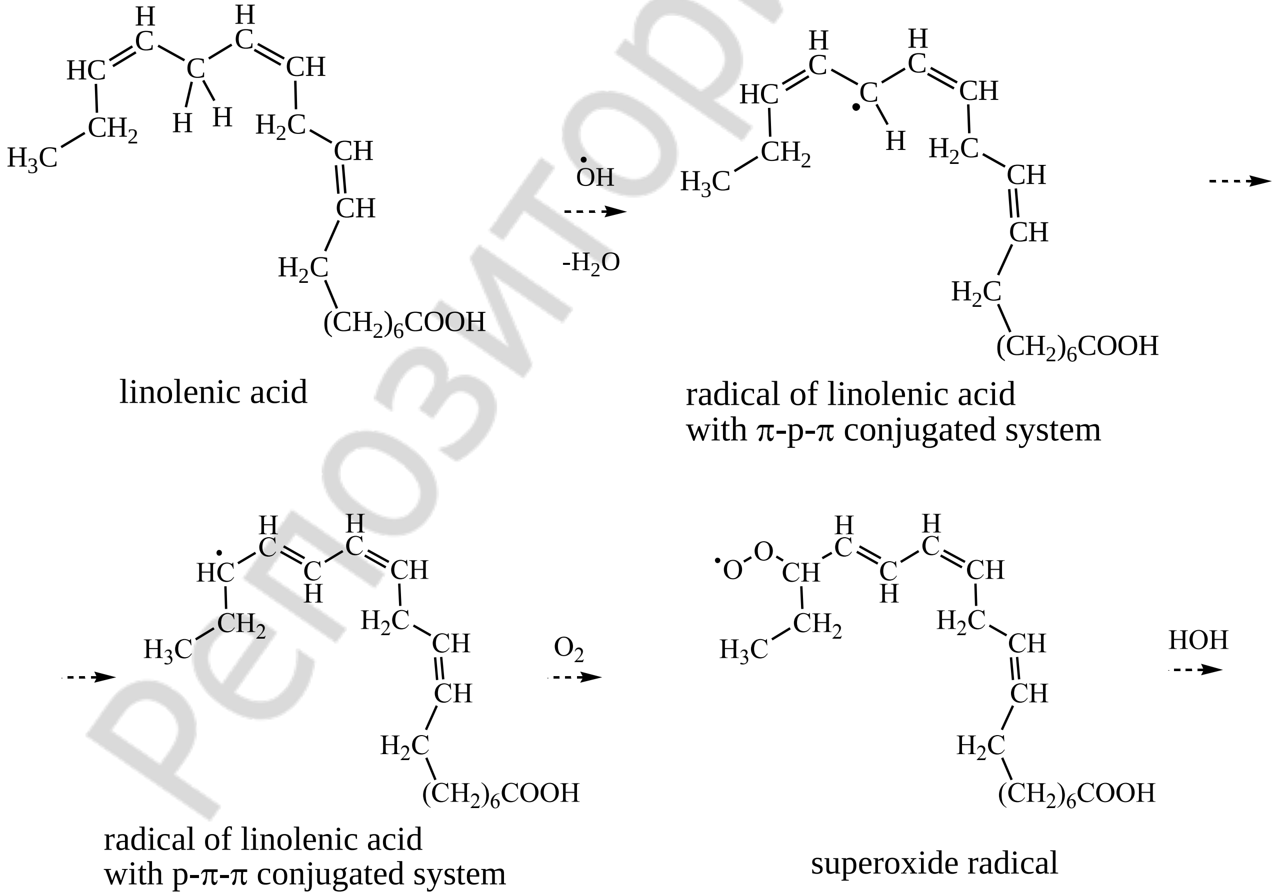
Soaps have detergent action because their molecules possess an amphiphilic character.

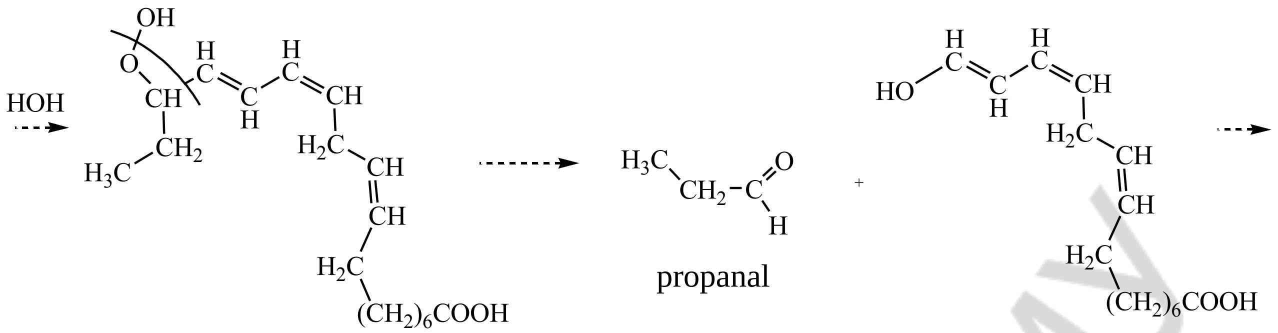
Lipids containing unsaturated fatty acids give qualitative positive reaction with bromine water and potassium permanganate.



Lipid peroxidation refers to the oxidative degradation of lipids. Normally, peroxidation of lipids is used to update the biological membranes. However, this process can lead to damage to the membranes. It is the process whereby free radicals take electrons from the lipids in cell membranes resulting in cell damage. This process proceeds by a free radical chain reaction mechanism. Only the unsaturated fatty acids in the lipid undergo oxidation. Methylene groups between the double bonds possess especially reactivity.

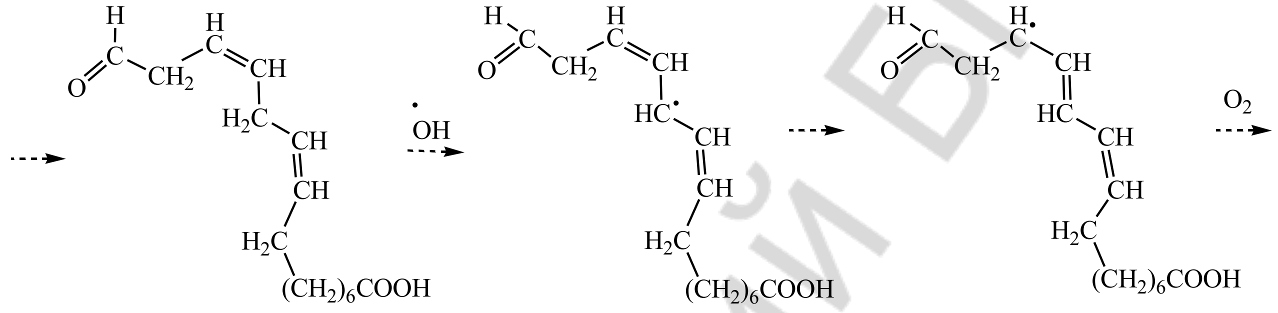
Initiation is the step, whereby a fatty acid radical is produced. The initiators in living cells are most notably reactive oxygen species (ROS), such as $OH^{\cdot}$, which combines with a hydrogen atom to make water and a fatty acid radical.





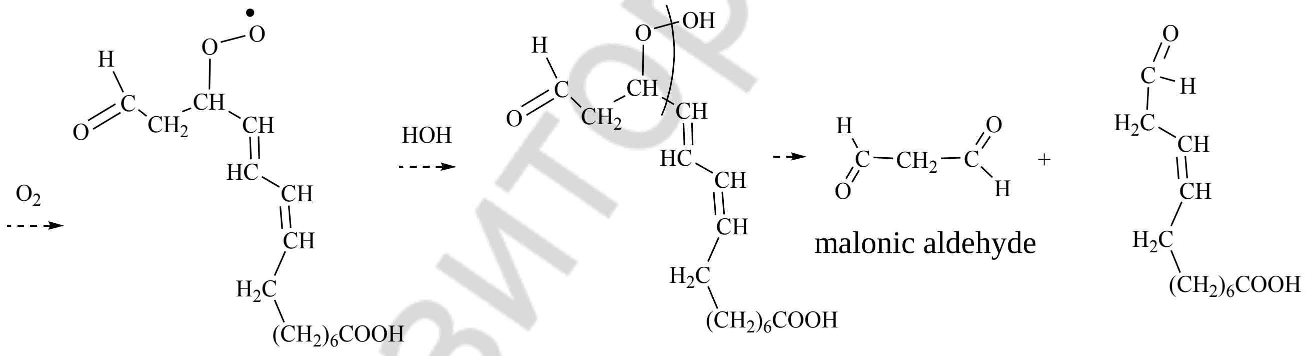
hydroperoxide of linolenic acid

Next, the resulting unsaturated alcohol is transformed into aldehyde. And the reaction cycle is repeated.



radical with π-p-π conjugated system

radical with p-π-π conjugated system



superoxide radical

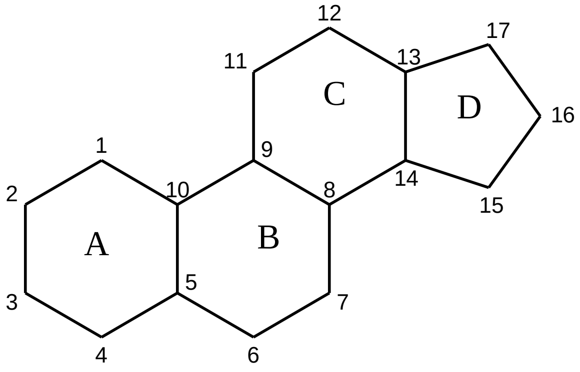
hydroperoxide

Living cells usually contain antioxidant systems, which serve to limit the process of lipid peroxidation. For example, vitamin E, vitamin A and C, and many other compounds. Synthetic antioxidants are also created in the pharmaceutical industry.

18. STEROIDS

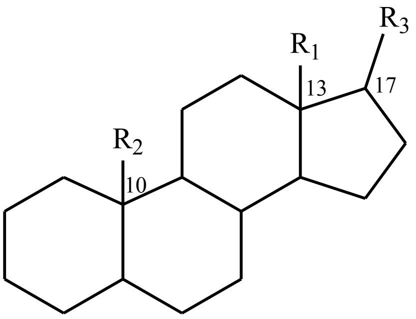
Steroids are important biological regulators that nearly always show dramatic physiological effects. Among these important compounds there are male and female sex hormones, adrenocortical hormones, vitamins D, the bile acids and others. Steroids are derivatives of the perhydrocyclopentanophenanthrene or gonane.

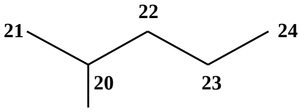
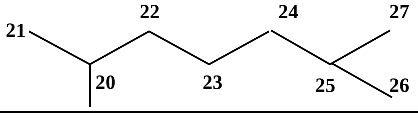
The carbon atoms of this ring system are numbered as shown below. The four rings are designated with letters.

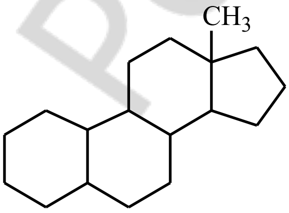


gonane

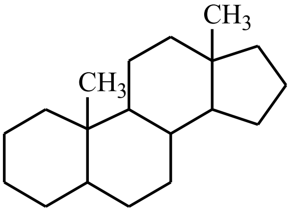
Steroids which are found in the human body can be divided into 5 groups. Representatives of these groups are different from each other by the presence or absence of the radicals in positions 10, 13 and 17.



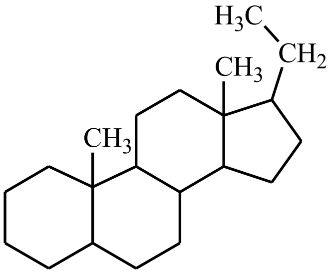
Name	R_1	R_2	R_3
Estrane	-CH_3	H	H
Androstane	-CH_3	-CH_3	H
Pregnane	-CH_3	-CH_3	— CH_2 — CH_3
Cholane	-CH_3	-CH_3	
Cholestane	-CH_3	-CH_3	



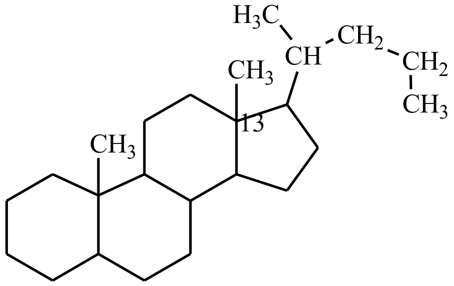
estrane



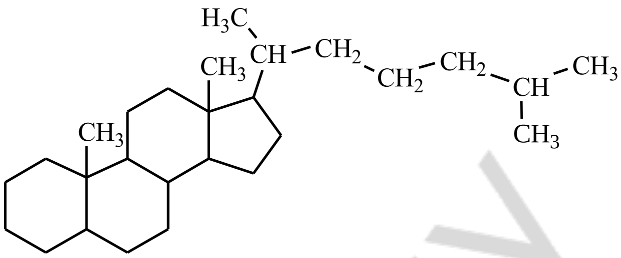
androstane



pregnane

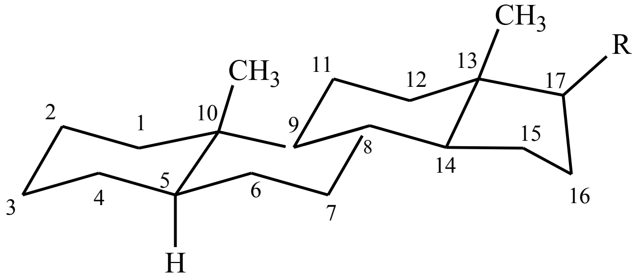


cholane

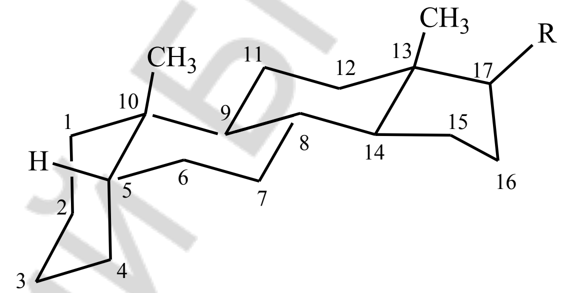


cholestane

Rings A and B may be connected by the type of *cis* or *trans* and this possibility gives rise to two general groups of steroids having the three-dimensional structures shown in the following figures.



5α-steroid (all ring connections are *trans*)

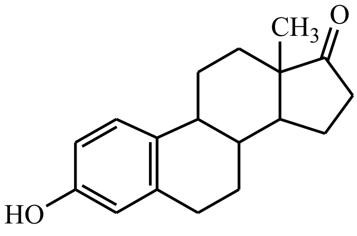


5β-steroid (A/B ring connection is *cis*)

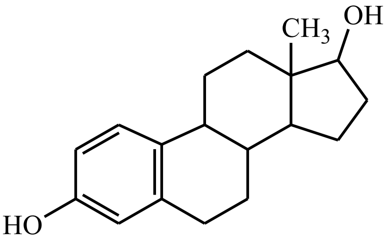
The methyl groups attached at points of ring connection (i. e., those numbered 18 and 19) are called angular methyl groups. The angular methyl groups protrude above the general plane of the ring system when it is written in the manner shown in figures above. By convention, other groups that lie on the same side the molecule as the angular methyl groups (i. e., on the top side) are designated as β substituents. Groups that lie on the bottom (i. e., are *trans* to the angular methyl groups) are designated as α substituents. When α and β designations are applied to the hydrogen atom at position 5, the ring system in which the A/B ring connection is *trans* becomes the 5α series; and the ring system in which the A/B ring junction is *cis* becomes the 5β series.

REPRESENTATIVES OF STEROIDS

Derivatives of estrane. The parent structure estrane underlies the female sex hormones — estrogens. Estrone is the first isolated sex hormone. Later a much more potent estrogen, called estradiol, was isolated.

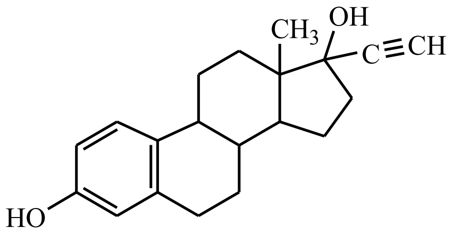


estrone



estradiol

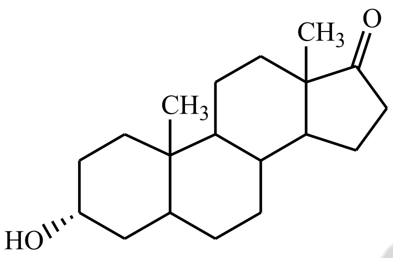
Estradiol is secreted by the ovaries and promotes the development of the secondary female characteristics. Synthetic estrogens have also been developed and these are often used in oral contraceptives in combination with synthetic progestins. A very potent synthetic estrogen is the compound called ethynylestradiol.



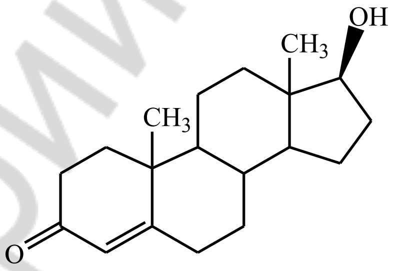
ethynylestradiol

The steroid hormones are hydrophobic compounds. All the steroid hormones exert their action by passing through the plasma membrane and binding to intracellular receptors.

Derivatives of androstrane. Representatives of male sex hormones (testosterone, androsterone) are derivatives of the androstane.



androsterone

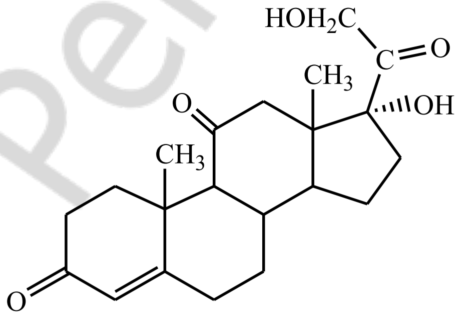


testosterone

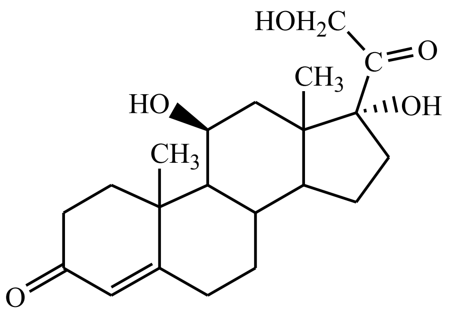
Testosterone, secreted by the testes, is the hormone that promotes the development of secondary male characteristics: the growth of facial and body hair; the deepening of the voice; muscular development; and the maturation of the male sex organs.

Structural formulas of estradiol and testosterone differ only a slight degree. Testosterone has an angular methyl group at the A/B ring connection. Ring A of estradiol has aromatic properties and, as a result, estradiol is phenol.

Derivatives of pregnane. Pregnane underlies two groups of steroid hormones: corticosteroids and progestins. At least 28 different hormones have been isolated from the adrenal cortex.



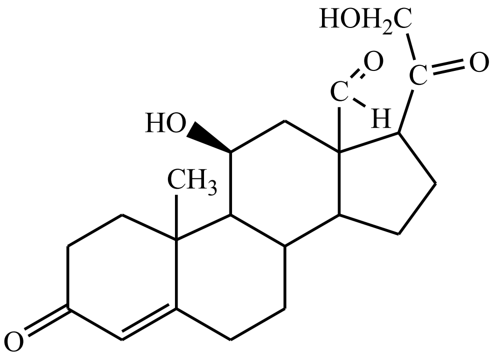
cortisone



cortisol

Most of the adrenocortical steroids have an oxygen function at position 11. Cortisol is the major hormone synthesized by the human adrenal cortex. The adrenocortical steroids are apparently involved in the regulation of a large number of biological activities including carbohydrate, protein, and lipid metabolism, water and electrolyte balance, and reactions to allergic and inflammatory phenomena. Most of 11-oxygenated steroids are now used in the treatment of a variety of disorders ranging from Addison's disease, to asthma, and to skin inflammations.

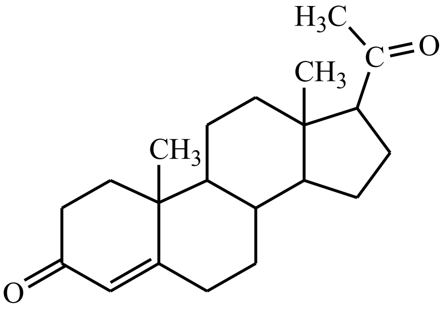
Adrenal hormones are divided into glucocorticoids and mineralocorticoids. Cortisone and cortisol are glucocorticoids. Aldosterone is a mineralocorticoid that participates in the regulation of water and mineral metabolism.



aldosterone

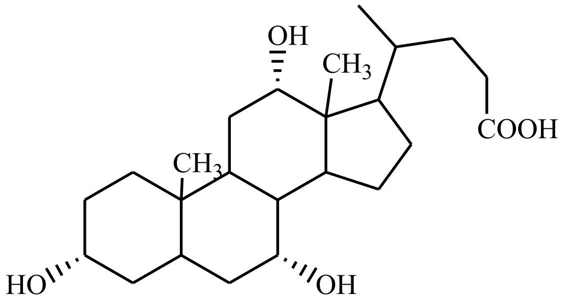
It regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions.

Progesterone is the most important progestin (pregnancy hormone). After ovulation occurs, the corpus luteum begins to secrete progesterone. This hormone prepares the lining of the uterus for implantation of the fertilized ovum, and continued progesterone secretion is necessary for the completion of pregnancy.

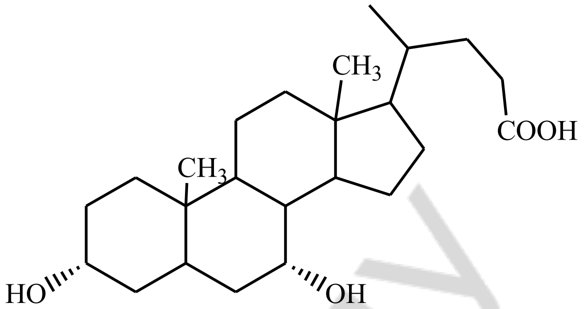


progesterone

Derivatives of cholane. Cholic acid and deoxycholic acids (7-deoxy-, 12-deoxy- or 7,12-dideoxy-) are the most important human bile acids. Salts of cholic acid are called cholates. Bile acids fulfill the function of emulsification of fats in the intestine. This function is performed due to the presence of hydrophobic and hydrophilic parts of these molecules.

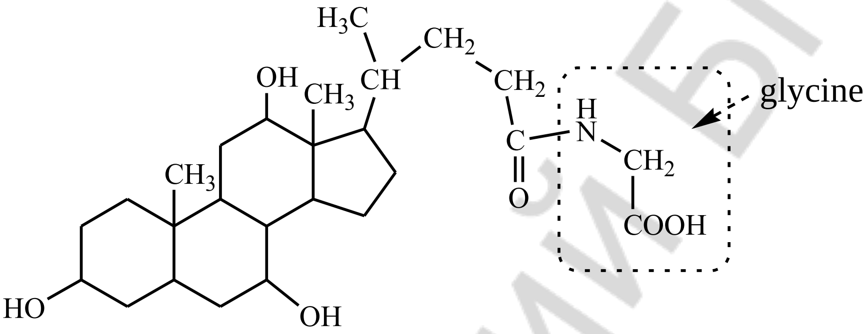


cholic acid



12-deoxycholic acid

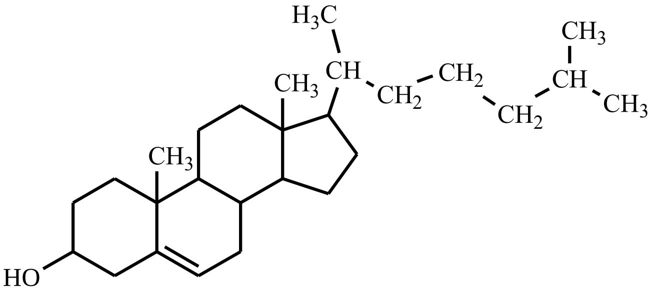
Bile acids can be conjugated (bonded) to taurine or glycine. Conjugation results in a lowered pKa and therefore, the compounds remain ionized.



glycocholic acid

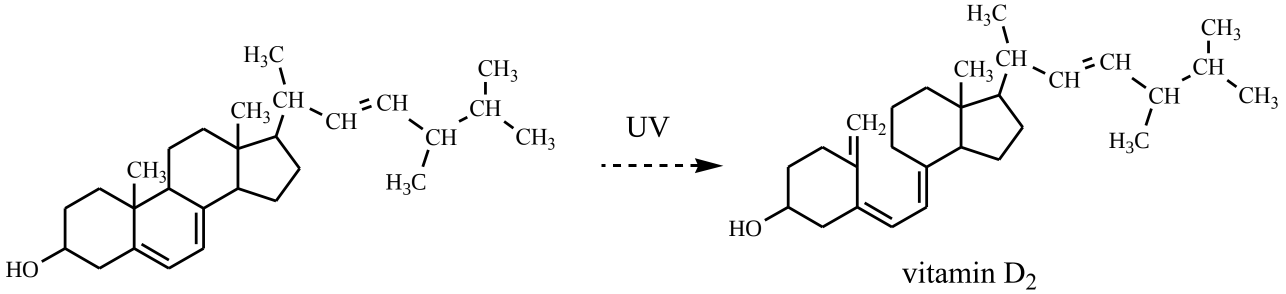
These ionized compounds will stay in the gastrointestinal tract until reaching the ileum where they will be reabsorbed. The purpose of this conjugation is to keep the bile acids in the tract until the end to facilitate lipid digestion all the way to the ileum.

Derivatives of cholestane. Cholesterol is widely spread in the human body. It is synthesized in all tissues of the body. Cholesterol is a structural component of biological membranes. Many steroids, such as bile acids, hormones, vitamins are synthesized from cholesterol in the human body. Cholesterol, therefore, is essential to life.



cholesterol

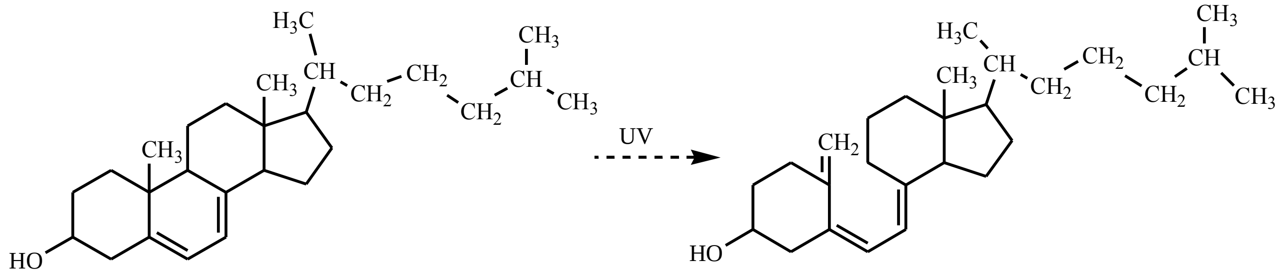
Vitamin D_2 and D_3 are also derivatives of cholestane. Vitamin D_2 is formed in plants and bacteria from ergosterol. Conjugation system in the ring B absorbs UV photon, which leads to a breakdown in ring B and the formation of vitamin.



ergosterol

vitamin D_2

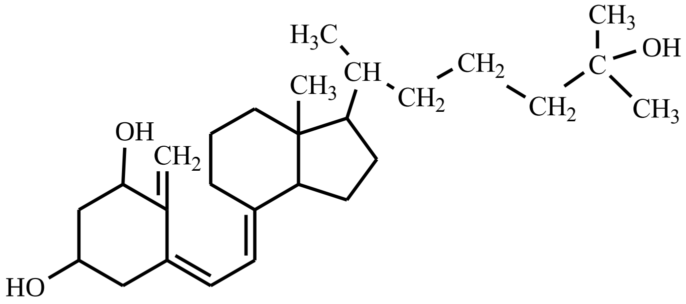
In humans vitamin D_3 is formed. It is synthesized from cholesterol, which first undergoes dehydrogenation reaction. This reaction occurs in the skin. And then ring B is broken under the influence of ultraviolet.



7-dehydrocholesterol

cholecalciferol

Cholecalciferol is hydroxylated in liver and kidney (C_{25} and C_1).



activated form of vitamin D_3

Vitamins D are involved in the regulation of metabolism of calcium and phosphorus.

CONTENTS