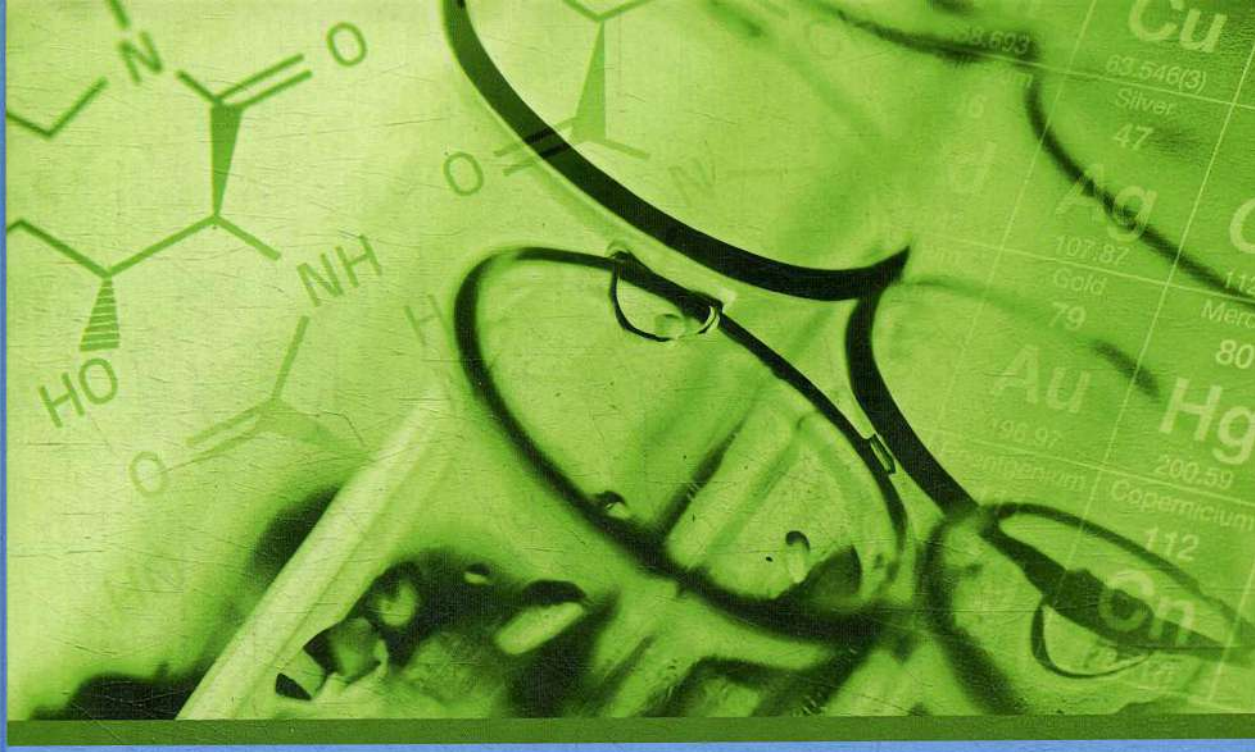


# BIOORGANIC CHEMISTRY

# БИООРГАНИЧЕСКАЯ ХИМИЯ

# BIOORGANIC CHEMISTRY

*Допущено*
*Министерством образования Республики Беларусь*
*в качестве учебного пособия для иностранных студентов*
*учреждений высшего образования*
*по специальностям «Лечебное дело», «Стоматология»*

МИНСК
«НОВОЕ ЗНАНИЕ»
2018

УДК 577.1(075.8)-054.6
ББК 28.072я73
Б63

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**Биоорганическая** химия = Bioorganic Chemistry : учеб. пособие для иностранных студентов / О.Н. Ринейская [и др.]. — Минск : Новое знание, 2018. — 174 с. : ил.
Б63
ISBN 978-985-475-976-0.

Изложены основы дисциплины «Биоорганическая химия» с учетом современных представлений о структуре и химических превращениях органических соединений, участвующих в процессах жизнедеятельности.

Для студентов медицинских университетов, обучающихся на английском языке по специальностям «Лечебное дело» и «Стоматология». Может быть полезно магистрантам и аспирантам при подготовке к кандидатскому экзамену по английскому языку.

**УДК 577.1(075.8)-054.6**
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**ISBN 978-985-475-976-0**

# Contents

# Introduction

Bioorganic chemistry studies the structure and properties of biologically important substances. It is a young science. Its present form was shaped in the 1950s. Bioorganic chemistry is a branch of science that studies biological processes by the methodology and techniques of organic chemistry. It studies the structure and properties of organic compounds that participate in biological processes in special environment of living cells. Bioorganic chemistry is in close relationship to biochemistry, molecular biology, physiology, pharmacology, and other disciplines that have their common and overlapping research fields: 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 between the structure, chemical properties and functions of a biologically important classes of natural and synthetic organic compounds. A physician needs to know the physicochemical properties and structure of compounds and the mechanism of the action of drugs, most of which are organic compounds. Drugs are mostly specific chemical substances which are able to interact with specific receptors and alter the ways of biochemical and physiological processes in a body, and this can be explained in terms of structure and chemical properties of organic compounds.

# 1. CLASSIFICATION AND NOMENCLATURE OF ORGANIC COMPOUNDS

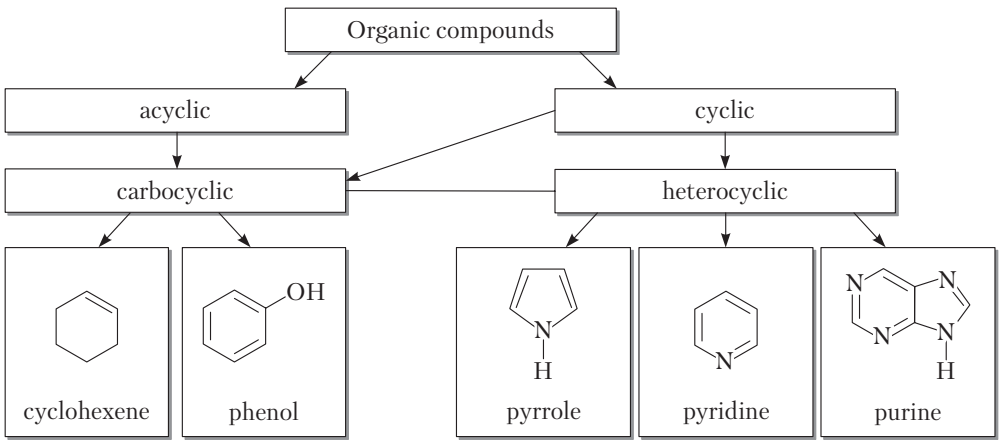
Of the almost 90 million or so compounds known today, about 85 million are carbon-containing compounds. Prior to studying so many substances, it is necessary to classify and name them. Adequate classification helps to structure the theoretical course. Correct naming of organic compounds helps scientists, teachers, and those who work in industry and medicine to understand each other whenever they take up scientific issues and read texts.

## 1.1. Classification of organic compounds

The classification can be based on the following principles:

- the structure of the carbon chain;
- the presence of functional groups.

**Classification of organic compounds by the structure of the carbon chain**




**Classification of organic compounds by functional groups**

The concept of functional groups is very important in organic chemistry. It helps not only to classify substances but also to predict their properties.

**Functional group** is an atom or a group of atoms of a non-hydrocarbon character (contain heteroatoms, i.e. atoms other than carbon and hydrogen) which determine the chemical properties of a particular class of compounds.

The reactivity of a functional group is assumed to be typical in different compounds. Therefore, the presence of a certain functional group determines the main chemical and physical properties of substances. For example, all substances that

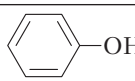
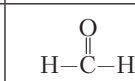
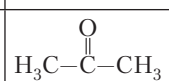
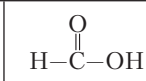
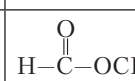
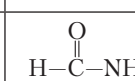
contain the carboxylic functional group possess some hydrophilic properties and tend to form esters.

Presence of functional group(s) in the structure of organic compounds presents the ground for the classification thereof.

***Hydrocarbons*** have no functional groups. They can be aliphatic or cyclic, saturated (alkanes) or unsaturated (alkenes, alkynes and polyenes).

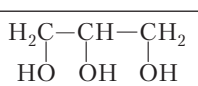
***Monofunctional compounds*** carry the only functional group which gives the name to the respective class of compounds: e.g., haloalkan, alcohol, carbonyl compound, carboxylic acid, amine, etc.

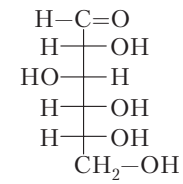
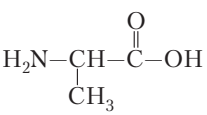
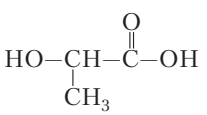
**Monofunctional compounds**

| Class name | Functional group | | Example | |
|---|---|---|---|---|
| | Formula | Name | Formula | Name |
| alcohols | –OH | hydroxyl | $CH_3OH$ | methanol |
| phenols | –OH | hydroxyl |  | phenol |
| aldehydes |  | aldehyde |  | methanal (formaldehyde) |
| ketones |  | ketone |  | propanone (acetone) |
| amines | $-NH_2$ | amino | $CH_3NH_2$ | methanamine |
| carboxylic acids |  | carboxyl |  | methanoic (formic) acid |
| esters |  | ester |  | methyl formiate |
| amides |  | amide |  | formamide |
| nitriles | $-C\equiv N$ | nitrile | $CH_3C\equiv N$ | acetonitrile |

***Polyfunctional compounds*** have a few identical functional groups and heterofunctional compounds have a few different functional groups.

**Poly and heterofunctional compounds**

| Class name | Functional group | | Example | |
|---|---|---|---|---|
| | Formula | Name | Formula | Name |
| polyols | –OH | hydroxyl |  | glycerol |

| Class name | Functional group | | Example | |
|---|---|---|---|---|
| | Formula | Name | Formula | Name |
| carbohydrates (sugars) | –OH<br>–C=O | hydroxyl<br>aldehyde or carbonyl |  | glucose |
| amino acids | $-NH_2$<br>–COOH | amino<br>carboxyl |  | alanine (2-aminopropanoic acid) |
| hydroxy acids | –OH<br>–COOH | hydroxyl<br>carboxyl |  | lactic acid (2-hydroxypropanoic acid) |

The structure of the course is based on this classification and you will be presented a new class of compounds every lecture and laboratory session. The introductory topics start with the basic principles. Therefore, the naming of organic compounds gives us the set of practical problems for the first laboratory session.

## 1.2. Nomenclature of organic compounds

Names of organic compounds can be generated in different ways.

Conditional ***"trivial"*** (***historic***, ***common***) ***names*** of substances are still widely used in bioorganic chemistry. The origin of these names is accidental and not related to the structure of matter. Some compounds are named for the natural sources from which they are isolated or on the basis of which they have been synthesized, e.g. lactic acid, pyruvic acid.

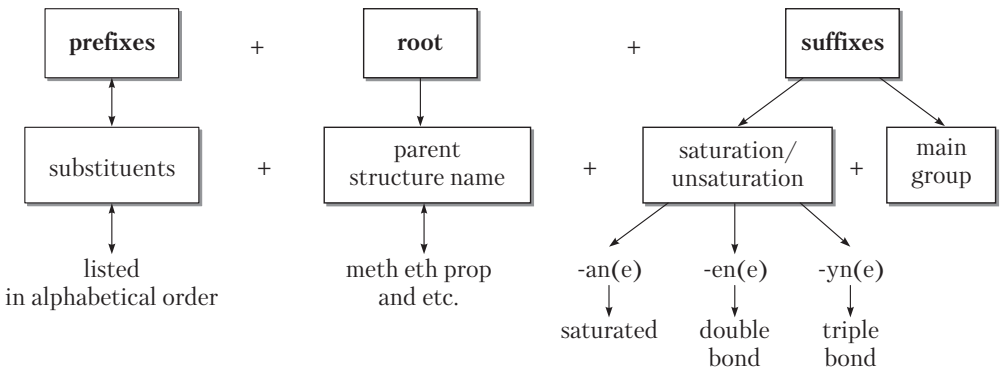
Now more than 80 million organic compounds are known in the world. So, the use of common names is limited; therefore, various types of systematic nomenclatures have been developed.

***IUPAC*** (***The International Union of Pure and Applied Chemistry***) has proposed a substitutive approach for naming organic substances.

To generate names according to this approach, one should find the *parent structure*, to be followed by substitution of its hydrogen atoms with structural fragments (represented by suffixes and prefixes) as follows:

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

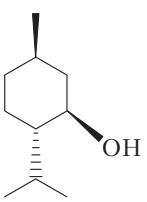
Thus a compound name may be represented by the basic pattern below:



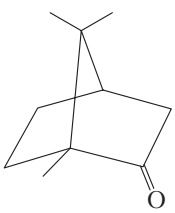

The *root* indicates the number of carbon atoms in the parent structure. The parent structure is the main carbon chain that includes a maximum number of functional groups, radicals, and multiple bonds. A cycle can be chosen as the parent structure in most of carbo- and heterocyclic compounds. Roots indicate the number of carbon atoms in the parent structures, as shown in the table below.

| Number of carbon atoms in carbon chain | Root | Number of carbon atoms in carbon chain | Root | Number of carbon atoms in carbon chain | Root |
|---|---|---|---|---|---|
| 1 | meth | 6 | hex | 11 | undec |
| 2 | eth | 7 | hept | 12 | dodec |
| 3 | prop | 8 | oct | 16 | hexadec |
| 4 | but | 9 | non | 18 | octadec |
| 5 | pent | 10 | dec | 20 | icos |

The *infix* is used to denote the cycle: for example, cyclohexane (the parent structure for menthol) or bicyclo[2,2,1]heptane (the parent structure for camphor).




(–)-menthol
(2-isopropyl-5-methylcyclohexanol)

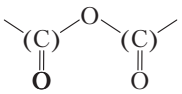
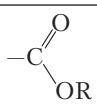
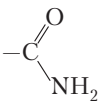
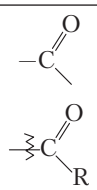



camphor
(1,7,7-trimethylbicyclo[2.2.1]heptan-2-one)

The *primary suffix* indicates the degree of saturation or unsaturation:

- ❒ saturated compound *-an(e)*
- ❒ unsaturated compound with one C=C *-en(e)*
- ❒ unsaturated compound with two C=C *-dien(e)*
- ❒ unsaturated compound with three C=C *-trien(e)*
- ❒ unsaturated compound with one C≡C *-yn(e)*

**Groups and their names**

| Class of compound | Formula | Name in the prefix | Name in the suffix |
|---|---|---|---|
| carboxylic acids |  | carboxy- | -oic acid*<br>-carboxylic acid |
| sulfonic acids | $-SO_3H$ | sulfo- | -sulfonic acid |
| acid anhydrides |  | — | -oic anhydride* |
| esters |  | R-oxycarbonyl- | -oate*<br>-carboxylate |
| amides |  | carbamoyl- | -amide<br>-carboxamide |
| nitriles | $-C\equiv N$ | cyano- | -nitrile*<br>-carbonitrile |
| aldehydes |  | oxo-<br>formyl- | -al*<br>-carbaldehyde |
| ketones |  | oxo-<br>alkanoyl- | -one* |
| alcohols, phenols | $-OH$ | hydroxy- | -ol |
| thiols | $-SH$ | mercapto- | -thiol |
| amines | $-NH_2$ | amino- | -amine |
| imines | $=NH$ | imino- | -imine |
| ethers | R—O— | alkyloxy- (alkoxy-)<br>R-oxy | — |

| Class of compound | Formula | Name in the prefix | Name in the suffix |
|---|---|---|---|
| sulfides | —S— | alkylthio- | — |
| nitro compounds | $-NO_2$ | nitro- | — |
| halogen derivatives | —Cl | chloro- | — |

* The carbon atom in the group belongs to the parent structure.

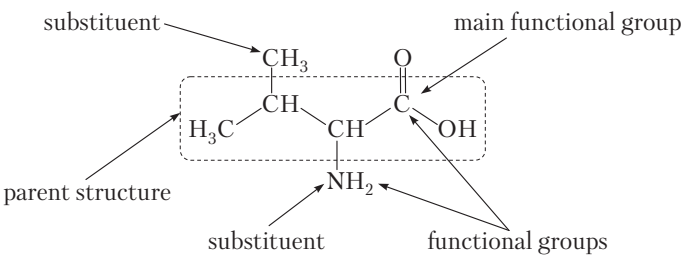
Groups with heteroatoms can be regarded either as functional groups or as substituents, depending on their priority. The main functional group will be solely named the functional group.

The *secondary suffix* indicates the main (older) functional group in a compound. The main functional group has the top position in the table of functional groups.

All the other groups will be substituents, in addition to hydrocarbon substituents and a few groups never to be functional (e.g. nitro or chloro groups).

The *prefix* is used to indicate the side chains, substituents and low-priority functional groups (which are considered as substituents).

**A substituent** is any atom or group of atoms that replaces (substitutes) a hydrogen atom of the parent structure.




Thus, to name the structure, one should find the parent structure, then number it and finally, indicate saturation/unsaturation and the functional group with suffixes and the substituents with prefixes.

**Step I.** To determine the parent structure, we should follow a hierarchical system of the rules (a rule listed above has priority over any of the below listed one(s)).

*The parent structure* is a continuous hydrocarbon chain (or a cycle) that

1) carries the maximum number of the main functional groups;
2) carries the maximum number of double (triple) bonds;
3) is the longest;
4) carries the minimum number of chains attached.

**Step II.** One should indicate the position of the carbon atoms in the parent structure by using the lowest possible number for the main functional group (or for the double bonds, in the absence of such group). For alkanes, number the parent

chain by starting from the end to result the set with the lowest numbers; thus, the set of numbers 2, **3**, 5, 6 is to be chosen rather than 2, **4**, 4, 5.

**Step III.** To name the parent structure, we use the root for $C_n$ taking into account the number of the atoms. Then, we indicate whether the parent structure is saturated or unsaturated, by using suffixes *-an*(*e*), *-en*(*e*), *-yn*(*e*).

We name the functional groups and the substituents with reference to the table above. The name for the hydrocarbon groups can be constructed according to the rules mentioned above, followed by the addition of -yl suffix. For these indicate the position of the carbon atoms attached to the parent structure by choosing the lowest number possible.

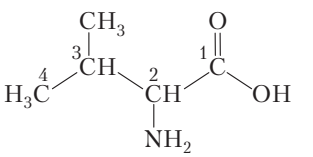
**Step IV.** Finally we give the name to the structure.

First, we arrange the prefixes (which are the names of the substituents) in the alphabetical order; next, we name the parent structure ($C_n$) by indicating the saturation/unsaturation character with suffixes, followed by naming the main functional group in the final position. We denote the substituents by indicating their positions with numbers (1, 2, 3, etc.) and, if necessary, by using the multiplying morphemes (di-, tri-, tetra-, penta-, etc.) in the prefixes (for the substituents) and by adding suffixes (for the multiple bond(s) and the main functional group(s).

Senior group: carboxylic group -oic acid

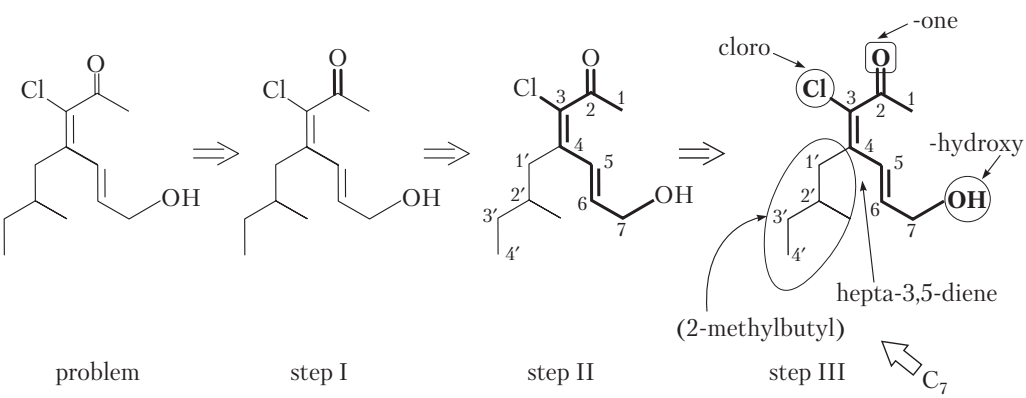
Parent structure: butan

Substituents: methyl- and amino- groups




2-amino-3-methylbutanoic acid

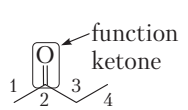
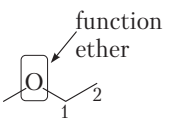
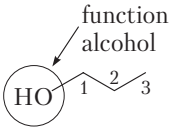
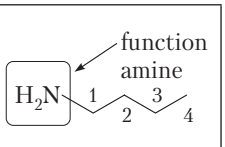
The more difficult example requires the use of the all mentioned rules.




3-chloro-7-hydroxy-4-(2-methylbutyl)hepta-3,5-diene-2-one

Formerly, ***a radico-functional approach*** was widely used. Currently the approach is used to name some simple structures. The characteristic group in the

compound is expressed as one word (called the "functional class name"). The remainder of the molecule attached to that group is expressed in its radical form as another word which precedes the functional class name.

| Approach |  |  |  |  |
|---|---|---|---|---|
| substitutive | butanone | methoxy-ethane | propan-1-ol | butanamine |
| radico-functional | ethyl methyl ketone | ethyl methyl ether | propyl alcohol | butylamine |

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

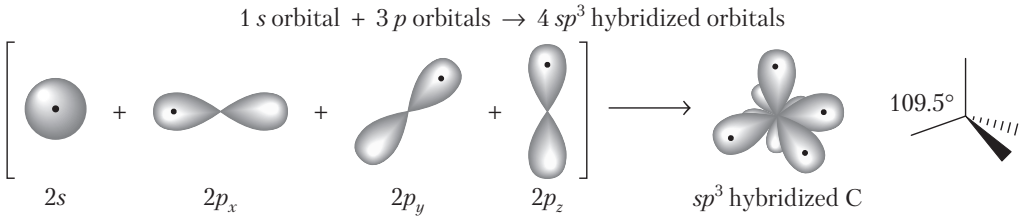
The main chemical elements in the organic compounds are carbon (C), hydrogen (H) and oxygen (O).

Carbon is in the second row of the periodic table and it has the following electronic configuration at the ground state: $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^0$. However, carbon is present in an excited state in the organic compounds. Promotion of one 2*s* electron to the 2*p* orbital forms the configuration $1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1$. The orbitals can be mixed in context of hybridization model.

## 2.1. Concept of hybridization in organic compounds

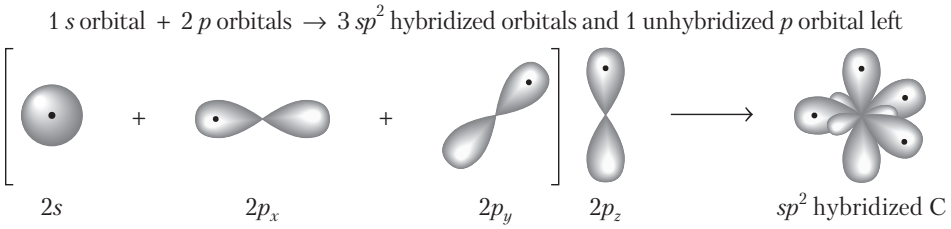
**Hybridization** is a mathematical model, according to which it is aligned on the energy and shapes of atomic orbitals. There are a few types of hybridization: $sp^3$, $sp^2$, *sp*, etc.

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




Orbitals are oriented in space to make the longest distances between each other. All of the angles between any two of the orbitals are approximately 109.5 degrees. As a result, the configuration of a $sp^3$ hybridized carbon atom is tetrahedral.

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



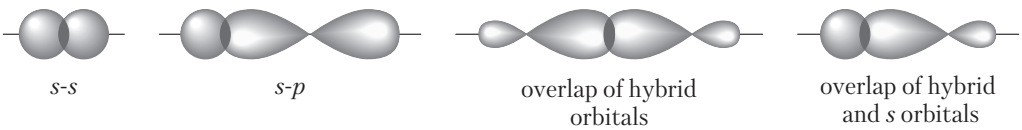

The valency angles between the hybrid orbitals are 120 degrees.

Although ionic bonds are present in organic compounds, the main type of chemical bonding for organic compounds is covalent; it is formed by the sharing

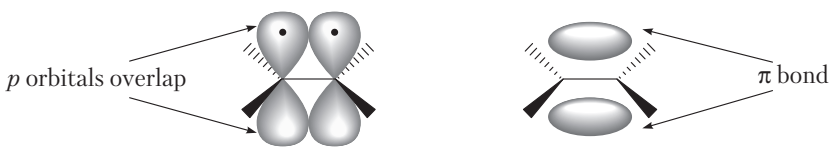
of electrons between atoms. The hydrogen bonds are also important as a form of intermolecular interaction.

There are σ and π covalent bonds depending on the overlap type.

**A *σ bond*** is a single covalent bond which is formed by overlapping hybrid $sp^n$ (or unhybridized *s*) atomic orbitals in a straight line connecting the nuclei of atoms with a high electron density along this line.




***π Bonds*** are formed by lateral overlapping of unhybridized *p* orbitals of a carbon, with the maximum electron density above and below the plane of the σ bonds.




A π bond is weaker, than a σ bond and potentiates unsaturated compounds for proceeding in addition reactions. The rotation around a π bond is impossible (the transfer of *cis* isomers into *trans* isomers while heating can be attributed to isomerization).

Saturated organic compounds contain only σ bonds. Unsaturated compounds may contain double or triple bonds.

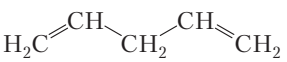
A double bond can be considered as a combination of one σ bond and one π bond. Double bonds are present in alkenes, carbonyl compounds, etc.

A triple bond can be considered as a combination of one σ bond and two π bonds. Triple bonds are present in alkynes, nitriles, etc.

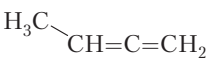
The structure of many compounds can be explained in terms of localized bonds. Localized bonds are formed by two electrons shared between two atoms. The molecular orbitals of a delocalized bond is distributed between more than two atoms.

## 2.2. Conjugation

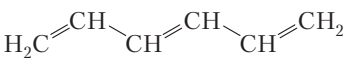
There are many organic compounds formed of molecules that contain more than one multiple (double or triple) bonds. There are separated, cumulated and conjugated types of multiple bonds.



separated π bonds

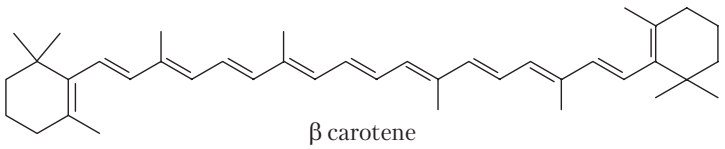


cumulated π bonds



conjugated π bonds

Conjugated double bonds, where double and single bonds alternate in the chain, are of most interest. There are numerous unsaturated and polyunsaturated compounds with conjugated double bonds. Many of such compounds play important roles in biological processes. For example, β carotene, the yellow-orange pigment in carrots, contains eleven conjugated double bonds.



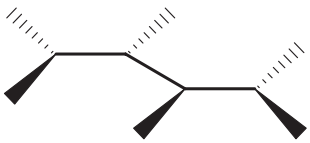
β carotene

**Conjugation** is the formation of a single system in a delocalized electron cloud as a result of an overlap of nonhybridized *p* orbitals.

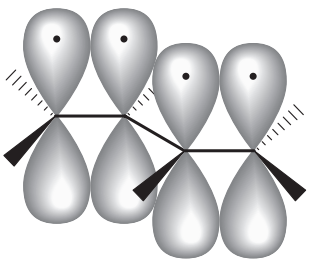
Buta-1,3-diene (formerly 1,3-butadiene) is a typical example of a conjugated system.

$$CH_2{=}CH{-}CH{=}CH_2$$

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



σ sceleton of buta-1,3-diene

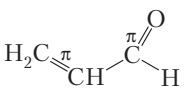


overlapping of *p* orbitals of buta-1,3-diene

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

There are two types of conjugation: π,π conjugation and π,*p* conjugation.

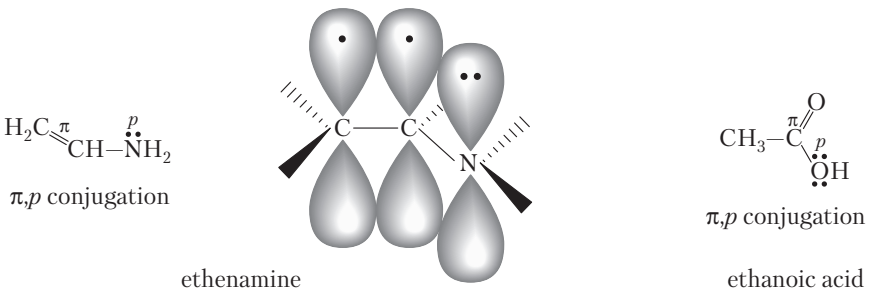
***π,π Conjugation*** is the delocalization of *p* orbitals over an entire π system. This type is characterized by alternating double and single bonds. Buta-1,3-diene is an example of π,π conjugation. A π,π conjugated system may also include heteroatoms, for example, acrolein (propenal is the systematic name).



π,π conjugation

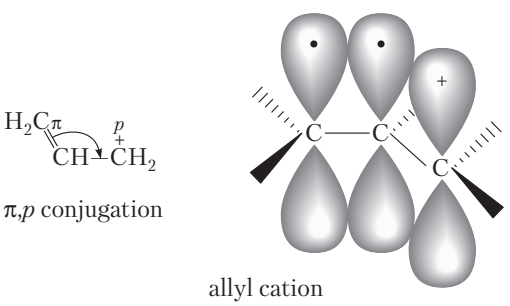
Another type of conjugation, ***p,π conjugation***, refers to the interaction between π bond orbitals and the *p* orbital of an adjacent atom. It is typical of compounds with a fragment $\diagdown$C–CH–X, where X is an atom possessing a lone pair of electrons.

In this case three orbitals are delocalized: two *p* orbitals of the double bond and one *p* orbital of the X atom.

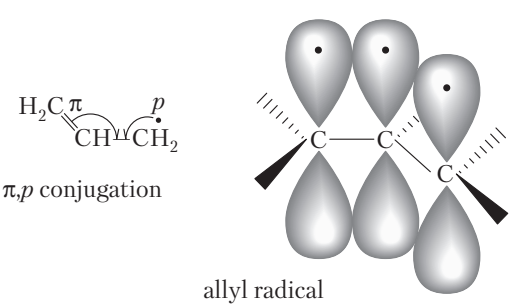



Intermediates such as ions and free radicals may also contain conjugated systems.

For example *p*,π conjugation is typical of compounds with a fragment $\diagdown C{=}CH{-}C^{+}$, where $C^{+}$ is the carbon atom with a free (vacant) orbital. In this case three orbitals are delocalized, i.e. the two *p* orbitals of the double bond and the *p* orbital of the adjacent carbon atom.

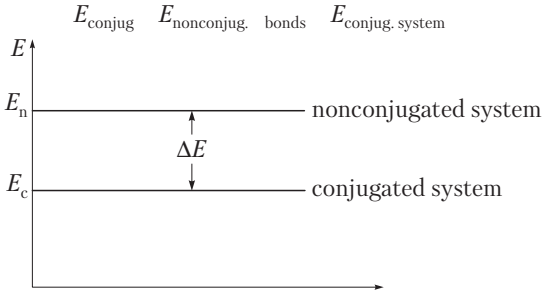



Conjugation is the phenomenon which explains the higher stability and specific chemical properties of conjugated molecules, ions, and radicals.



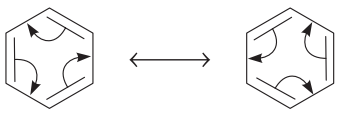

The concept of conjugation is of use for better understanding of chemical and biochemical processes.

**Conjugation energy** is a value of thermodynamic stability; it is expressed as the difference between the complete π electron energy of a nonconjugated system (with localized double bonds) and the π electron energy of the corresponding conjugated system.




## 2.3. Aromaticity of carbo- and heterocyclic compounds

In 1855 August von Hofmann used the term "aromatic" for a class of benzene compounds for the first time. Many of those substances had odor (aromas), unlike pure saturated hydrocarbons. According to a quantitative analysis, the substances had formally high level of unsaturation but exhibited more stability and were unable to be saturated under the "normal" conditions, as contrasted to "normal" unsaturated compounds. The first concept which tried to explain the structure and behavior of those compounds was elaborated by August Kekulé who proposed the famous "cyclohexatriene" structure.



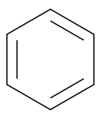
The formula was accepted and soon was complemented with the concept of cyclic conjugation between all three bonds. Since then, aromaticity has been associated with the presence of a benzene ring and fused benzene ring compounds.

In 1931, Erich Hückel was the first to separate bonding electrons into σ and π type electrons. He proposed a quantum mechanical theory of aromaticity. This concept is valid for a larger range of compounds and has been widely used till today.

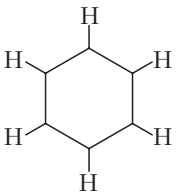
**Aromaticity** explains the ability of planar cyclic fragments with a locked system of conjugation to enter into substitution reactions rather than addition and oxidation.

A typical example of an aromatic system is a *benzene*. It is a highly unsaturated compound. It has been found experimentally (i.e. by means of X-ray diffraction) that benzene consists of flat symmetrical molecules shaped like regular hexagons.

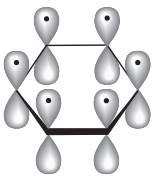
All six carbon-carbon bonds in benzene are of the same length, 140 pm, and are $sp^2$ hybridized. Two $sp^2$ orbitals form σ bonds with the adjacent carbons. The third $sp^2$ orbital of each carbon forms a C—H bond. In addition, each carbon has a *p* orbital with one electron.



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 the both vicinal orbitals to form a cloud of six *p* electrons completely delocalized around the ring. Thus, a benzene molecule represents a circular π,π conjugated system with two doughnut-shaped electron clouds — one above and one below the ring. For this reason, a more adequate representation of a benzene molecule might be a hexagon with an inscribed circle.

The electron delocalization results in increased stability of benzene. For example, conjugation energy for benzene is 151 kJ/mol. Benzene has aromatic properties.

According to Erich Hückel, a molecule has aromatic properties if it meets the following criteria:

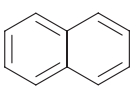
1) all atoms are $sp^2$ hybridized, therefore, a molecule has a coplanar structure;

2) a molecule has a cyclic system of conjugation;

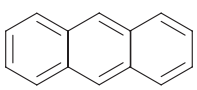
3) a cyclic system of conjugation contains $(4n + 2)$ π electrons ($N$), where $n$ is an integer (0, 1, 2, 3, etc.), which means that $N$ = 2, 6, 10, 14, 18, 22, etc.

This is known as the ***Hückel's rule***: $(4n + 2)$.

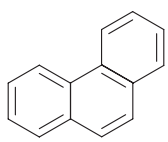
Benzene corresponds to the Hückel's rule for $N$ = 6 ($n$ = 1) that is involved in the conjugation of six *p* electrons. Such molecules as naphthalene, anthracene, phenanthrene satisfy all the requirements of aromaticity.



naphthalene
$N = 10, n = 2$



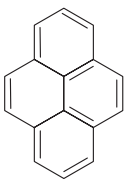
anthracene
$N = 14, n = 3$



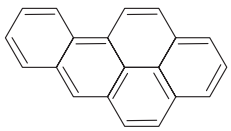
phenanthrene
$N = 14, n = 3$

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

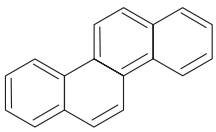
Napthtalene, antracene and phenathrene are the simplest representatives of polycyclic aromatic hydrocarbons (PAHs). Fusion with more unsaturated cycles gives pyrenes and other PAHs.



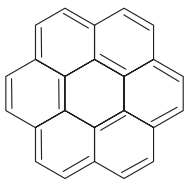
pyrene



benzo[*a*]pyrene



chrysene



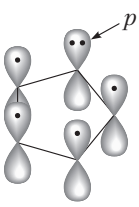
coronene

PAHs are non-polar hydrophobic (viz., insoluble in water) and lipophilic (viz., able to be dissolved in fats and oils) molecules found in coal and tar deposits. They are also produced by incomplete combustion of organic compounds and are found in cigarette smoke, burnt food and traffic fumes.

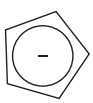
The degree of aromaticity is different for each ring. Generally, PAHs show less aromaticity if compared to benzene. Therefore some fragments in PAHs tend to participate in addition reactions, in particular enzymatic oxidation, to produce genotoxic substances. The latter interact with nucleic acids and damage the genetic information within a cell, thereby causing mutations. This may lead to cancer.

Though PAHs are considered highly toxic for mammals, these compounds may also be abundant in the universe. According to some theories, more than 20 % of the carbon in the universe is presumably associated with PAHs. They were formed shortly after the Big Bang and later on were widely spread throughout the universe to transfer the matter to new stars and the interstellar medium. According to the PAH World hypothesis, such compounds may be also the primary starting matter for abiologic synthesis of substances required in the formation of life.

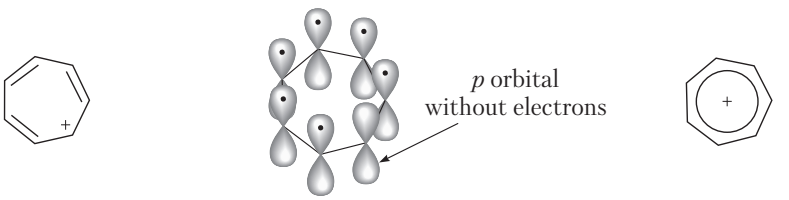
Not only neutral molecules but also ions have aromatic properties, e.g. cyclopentadienyl anions and cycloheptatrienyl (tropylium) cations.




cyclopentadienyl anion



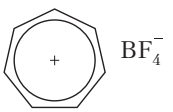
delocalization of negative charge



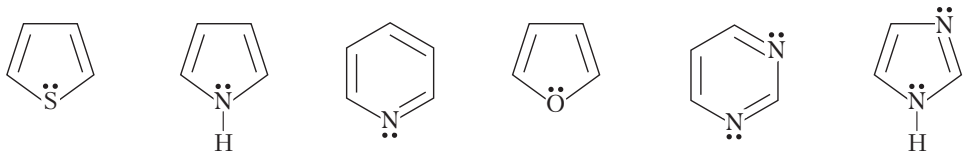

cycloheptatrienyl cation — delocalization of positive charge

In both cases a cyclic conjugation system involves six *p* electrons. This corresponds to the Hückel rule. Since the conjugation is delocalization of the electron density, the correct images of the cyclopentadienyl anion and cycloheptatrienyl cation are the ones in which the charge belongs to the entire system.

Salts of tropylium cation are unexpectedly stable. For example, tropylium tetrafluoroborate is a stable organic compound formed of the tropilium cation and the non-coordinating tetrafluoroborate counteranion. It is commercially available.

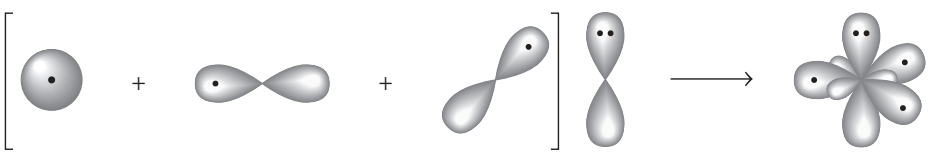



In heterocyclic molecules, a delocalized *p* electron system is formed with the participation of the *p* orbitals of carbon atoms and the *p* orbitals of heteroatoms.



thiophene — pyrrole — pyridine — furan — pyrimidine — imidazole

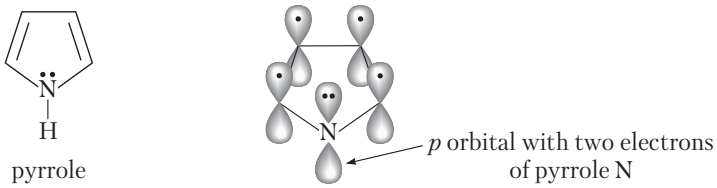
All the carbons and the nitrogen atom in *pyrrole* are $sp^2$-hybridized. The pyrrole nitrogen atom has the following electronic configuration: $1s^2\mathbf{2s^1 2p_x^1 2p_y^1} 2p_z^2$.



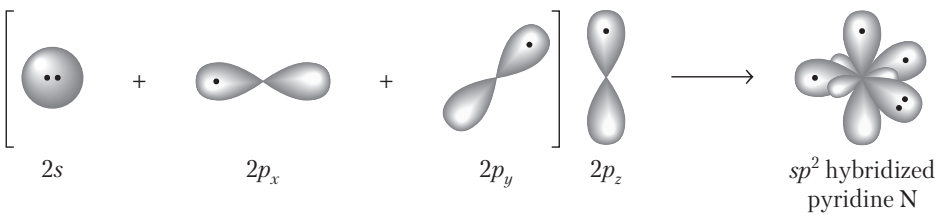
2*s* — 2$p_x$ — 2$p_y$ — 2$p_z$ — $sp^2$ hybridized pyrrole N

The aromatic system in pyrrole (as well as in thiophene and furan) is formed by five *p* orbitals: the four *p* orbitals of the carbon atoms and the *p* orbital of the heteroatom on which there is a lone pair of electrons. The six *p* electrons form a locked conjugation system. The hybrid orbitals of the nitrogen atom form three

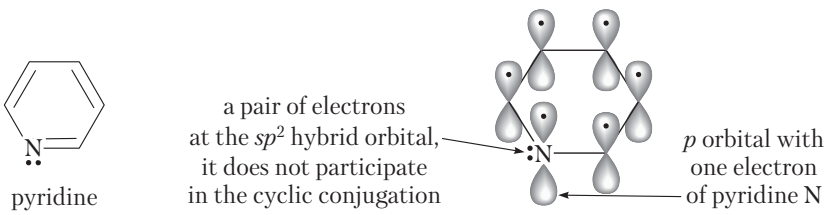
σ bonds: two orbitals with the carbon atoms and the third orbital with the hydrogen. The nitrogen's lone pair of electrons interacts with the unhybridized *p* orbitals of carbon atoms and participates in the formation of a delocalized electron cloud. Therefore, pyrrole is an aromatic compound.




*Pyridine* is an example of six-membered heterocyclic compounds. An aromatic system in pyridine is formed with the participation of the five *p* orbitals of the carbon atoms and one *p* orbital of the nitrogen atom containing one electron. A 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.

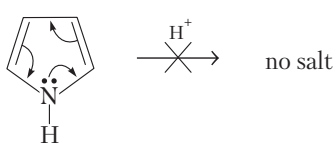



The two hybrid orbitals of the nitrogen atom form two σ bonds. The remaining hybrid orbital of the nitrogen atom possesses a lone (unshared) electron pair and does not form a bond.

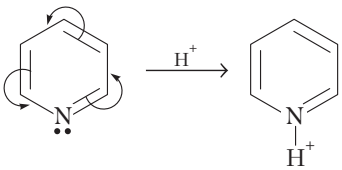



The unhybridized *p* orbital of the nitrogen atom (with one electron) is perpendicular to the plane of the ring and overlaps the *p* orbitals of the carbon atoms to form an aromatic conjugated system containing six *p* electrons. Thus, pyridine satisfies all criteria of aromaticity.

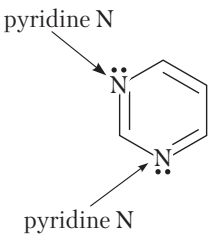
It is interesting to compare the availability of the electrons from nitrogen in pyrrole and pyridine. Pyrrole shares its electrons to form the aromatic system. As a result, it has no lone electrons and cannot form a new bond, in particular, in base/acid interactions.

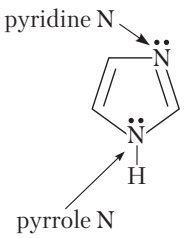


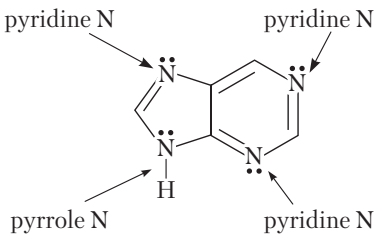
In contrast to pyrrole, pyridine forms an aromatic system without sharing the nitrogen electrons. The latter are available to form a new bond. It explains the formation of pyridinium salts.



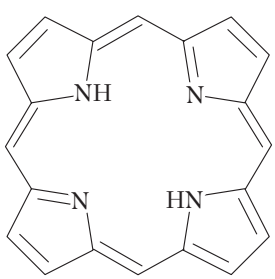

Pyrrole and pyridine nitrogen atoms are found in many biologically important compounds. In these compounds the basic atom is called pyridine nitrogen and the nonbasic one (sharing electrons to form aromatic structure) is called pyrrole nitrogen.




An *imidazole* cycle is a fragment of the amino acid histidine, biogenic amines histamine, an important part of many pharmaceuticals and other compounds. A stable aromatic ring of pyrimidine is a part of nucleic acid bases: uracil, thymine and cytosine. Purine is a part of the purine nucleic acid bases: adenine and guanine. A purine system consists of a fused ring pyrimidine and imidazole and contains three pyridine nitrogen atoms and one pyrrole nitrogen atom and a pyrrole. They form a π,π,π,π,*p* conjugated system which includes ten *p* electrons and satisfies Hückel's rule for $N = 10$ ($n = 2$).




Four pyrrole fragments formally form porphin structure.

This is a planar aromatic system (26 *p* electrons are involved in the conjugation); it is characterized by a very high stability. Porphin structure is a part of hemoglobin and chlorophyll, which constitute the complex ions $Fe^{2+}$ and $Mg^{2+}$, respectively.

## 2.4. Electronic effects

A polar covalent bond is formed by two atoms of different electronegativity. Two atoms with the same electronegativity can form a nonpolar covalent bond. But the carbon-carbon covalent bond can be polarized by the action of adjacent substituents via electronic effects.

The presence of a polar σ or π bond in an organic molecule results in polarization of neighboring atoms. The electron density of chemical bonds is not evenly

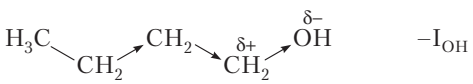
distributed in the molecules containing atoms different from carbon and hydrogen. That leads to polarization of a covalent bond and the appearance of partial charges, designated δ.

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

There are the electron withdrawing inductive effect and the electron donating (electron releasing) inductive effect. The inductive effect of hydrogen is equal to zero.

If an electronegative atom is joined to a chain of atoms, the positive charge is relayed to other atoms in the chain. This is the electron-withdrawing, or negative inductive effect, (designated as –I effect). All groups containing atoms which are more electronegative than carbon manifest the negative (–I) effect.

Alkyl groups, by contrast to the above, are less electron-withdrawing than hydrogen and are therefore considered to be electron-releasing. The electron donating (i.e. positive) inductive effect is designated as +I effect. In the case of the –I effect the electron density at the nearby atom is decreased, and in the case of the +I effect the electron density is increased. The effect of a substituent is the strongest on the neighboring atom and decreases along the carbon chain. Usually it does not extend for more than three or four sequent bonds. Thus, the inductive effect is fading. Graphically, the inductive effect is represented with an arrow that coincides with the σ bond and its head is directed at the more electronegative atom. For example, the oxygen of the hydroxyl group in butan-1-ol has a negative inductive effect, so 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 cases the polarization effect of a substituent extends through the entire conjugation system.

The **mesomeric (or resonance) effect** is a shift of electron density caused by a substituent in conjugated system.

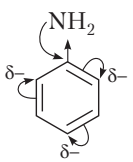
The mesomeric effect is symbolized by M. There exist the electron donating (designated +M) and the electron-withdrawing (designated –M) effect. The –M effect of a functional group leads to a decreased electron density on all carbons in the remaining part of the molecule (as compared with unsubstituted compounds, such as ethene and benzene). The positive mesomeric effect is observed in most of *p*,π conjugated systems. In such cases a substituent with a lone pair of electrons donates electrons to the ajacent benzene ring or a π bond.

The mesomeric effect can be transmitted along any number of carbon atoms in a conjugated system.

**Electronic effects of the sustituents**

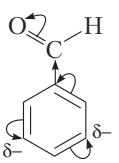
| Substituent | I Effect | M Effect | Correlation | Character |
|---|---|---|---|---|
| alkyls | +I | no M | — | electron donor |
| $NH_2$ | –I | +M | +M > –I | electron donor |
| –OH, –SH | –I | +M | +M > –I | electron donor |
| –O–R | –I | +M | +M > –I | electron donor |
| halogens | –I | +M | –I > +M | withdrawer (in neutral substrate) |
|  | –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 a molecule of phenylamine (aniline). The amine group produces the negative inductive effect. As phenylamine represents a conjugated system, the amine group has the mesomeric effect. And since the nitrogen atom has a lone pair of electrons, the amine group shows the positive mesomeric effect. Thus, the amine group donates the electrons to the adjacent benzene ring.

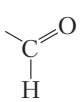



–I +M +M > –I
$NH_2$ is the electron donor

Conversely, the aldehyde group in a benzaldehyde molecule withdraws the electron density from the benzene ring to itself. The $C_3$ and $C_5$ carbon atoms acquire partial negative charges.




–I –M




is the electron withdrawer

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

Distribution of the electron density determines the reactivity of a compound and its reaction centres.

# 3. SPATIAL STRUCTURE OF ORGANIC MOLECULES

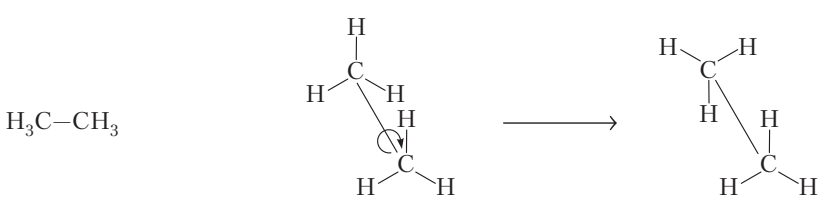
Stereochemistry is a science which studies spatial structure of organic compounds.

**Stereoisomers** are isomers that differ in the arrangement of their atoms in space. Stereoisomers are divided into ***conformational*** and ***configurational*** ones.

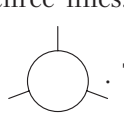
## 3.1. Conformational isomers

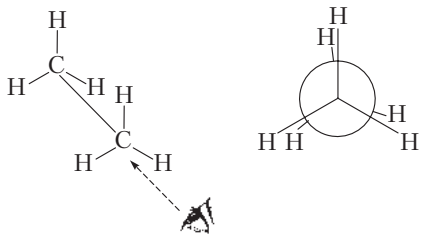
Different spatial forms of a molecule that result from rotation about single bonds are called **conformations**. Conformations differ by their potential energy.

Conformations are interconverted without breaking σ bonds. A rotation angle about a σ bond is called the *torsion angle*. We take into account only six conformations that can be obtained from the rotation about a single bond for the minimal torsion angle of 60°; the rest forms are neglected. Conformations with substituents eclipsing each other have a higher internal energy. They are called ***eclipsed*** conformations. Conformations in which the substituents are most remote from each other have a relatively lower internal energy; they are called ***staggered*** conformations.

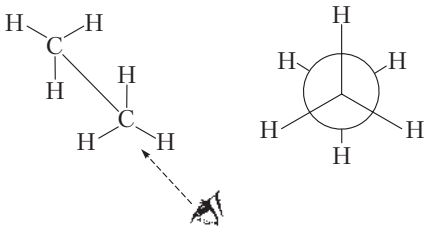



ethane eclipsed staggered

The Newman projection is a convenient approach in representation of conformational transitions and it is widely used in conformation analysis. A molecule is arranged so that an observer's view coincides with the σ bond around which the rotation is performed. The carbon atom closest to the observer is designated with a dot and three lines:  . The next rear carbon atom is represented by a circle and dashes:  . The hydrogen atoms may be omitted.

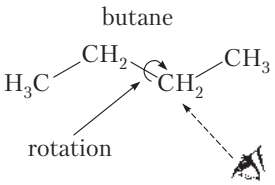


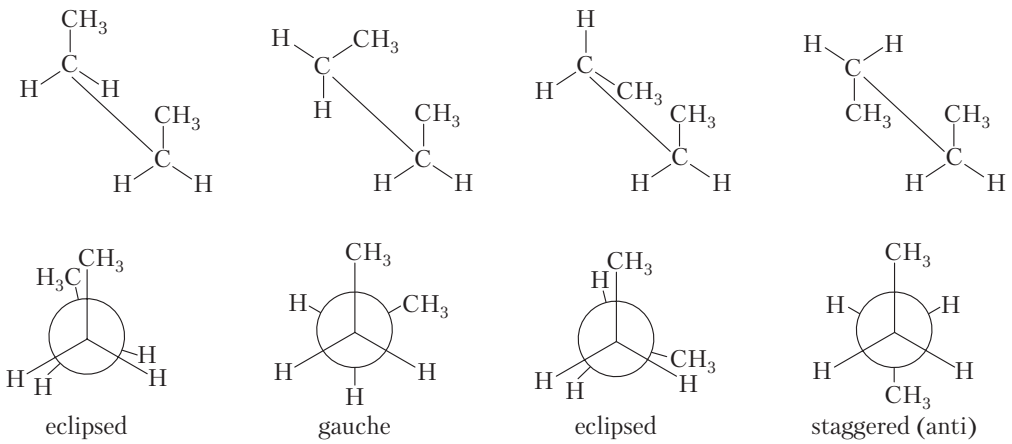
eclipsed



staggered (anti)

More complex molecules have a greater number of conformations that differ by their energy. Consider butane conformations resulting from rotations about the $C_2—C_3$ bond.

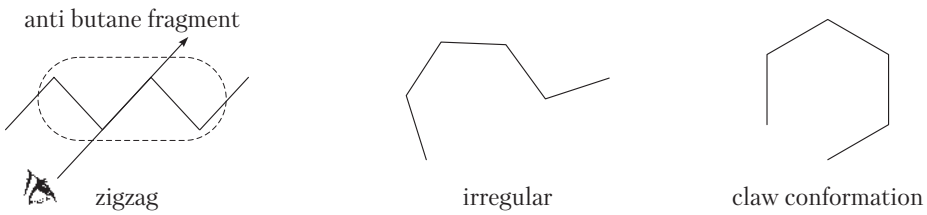


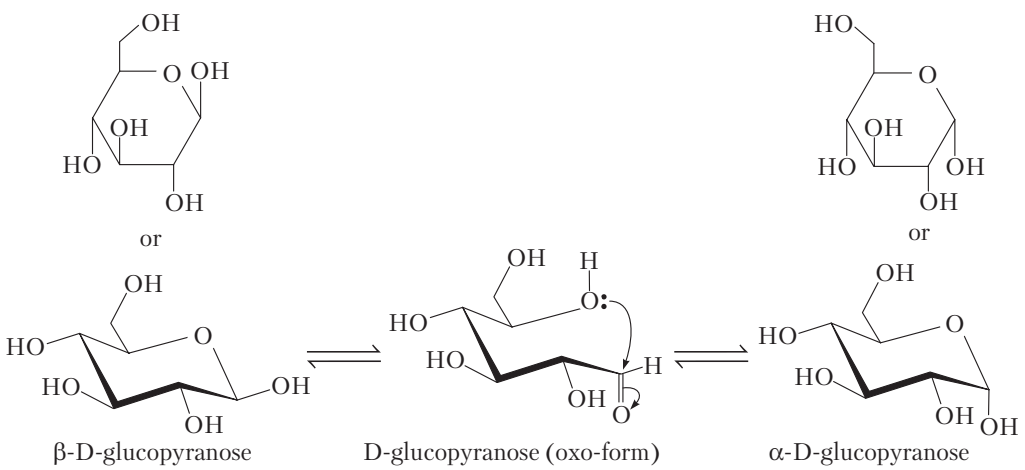

The eclipsed conformations are formed with the torsion (dihedral) angles of 0° and 120°. The gauche and anti-conformations are formed with the torsion angles of 60° and 180°, respectively. The stability of conformations depends on several factors: the torsional strain and van der Waals strains. ***Torsional strain*** is caused by the repulsion of the electron clouds of nearby σ bonds. ***Van der Waals strain*** is caused by the repulsion of the electron clouds of large atomic groups. The anti-conformation is characterized by a minimal torsional strain and van der Waals strain, therefore it is stable. Most compounds exist mainly as the anti-conformations.

The eclipsed type of conformations are characterized by high torsional strains, so they are unstable.

We can also analyze rotations about a few C—C bonds in longer carbon chains. Therefore, the entire chain can take a variety of geometric shapes. Because the anti-conformation is lowest in energy (and also simply for ease of drawing), it is conventional to draw open-chain alkanes in a zigzag form, which implies anti-conformation at all carbon-carbon bonds.



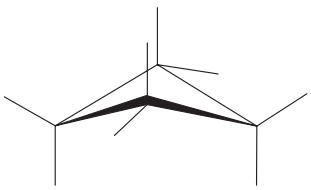

Distant carbon atoms are approaching each other in the claw conformation, which makes it possible for them to interact. For example, in the acyclic form of glucose the aldehyde and the hydroxyl group at the $C_4$ or $C_5$ atom interact with each other (the process will be considered in detail in Chapter 12).



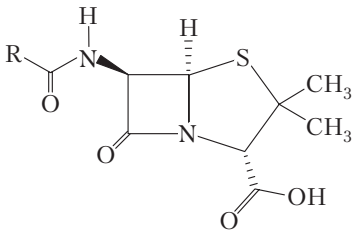

***Angle strain*** is an increase in potential energy of a molecule, due to bond angles deviating from the ideal.

Due to the rigidity of the cyclopropane ring it is the only monocyclic compound with planar conformation. Each carbon atom in the cyclopropane ring is tetracoordinate. 109.5° should be the ideal bond angle at a tetracoordinate carbon atom. In the planar cyclopropane ring (actually, an equilateral triangle) the internal bond angle at each carbon atom is 60°. As the result, the cyclopropane ring gets a high amount of angle strain.

The conformation of cyclobutane is not planar. The ring adopts a folded (commonly known as the "puckered" or "butterfly") conformation. The four-membered ring with the nitrogen atom is found in the penicillin class of antibiotics.

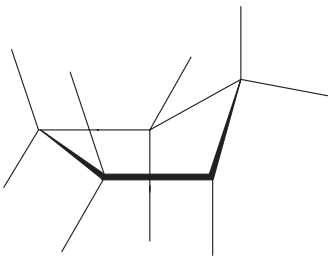


cyclobutane "butterfly" conformation

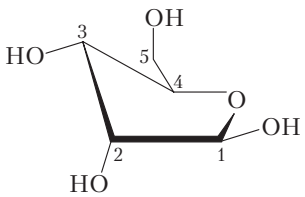



penicillin core structure

With cyclopentane, the so-called envelope non-planar conformation is observed. In this conformation one of the carbon atoms is off the plane in which the remaining four atoms are located.



cyclopentane envelope conformation



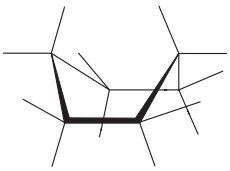

$C_3$-endo conformation (as in RNA)

This conformation of a five-membered ring is stable. Such conformation is observed in ribose and deoxyribose in RNA and DNA (a $C_3$-endo form is subtype of the envelope conformation).

Different conformations are possible for a six-membered ring: their shape options are called "twist", "boat" and "chair". The chair and boat conformations are both free from angle strain. The boat conformation is eclipsed and also gets strong repulsion from 1, 4 hydrogen atoms (bowsprit hydrogens). It is less stable and is a transition state between the "twist" conformations.

cyclohexane

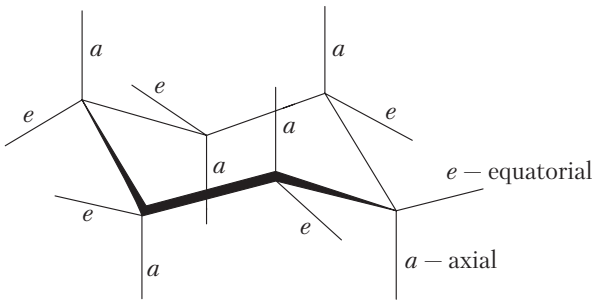
twist conformation



boat conformation

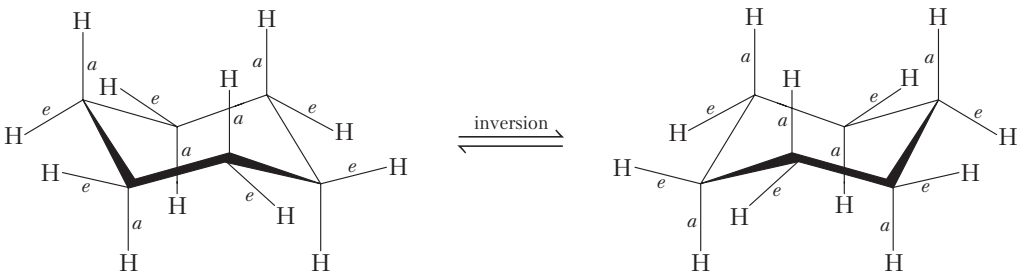
chair conformation

The chair conformation is the most thermodynamically stable, as it has no torsional and van der Waals strain.




chair conformation

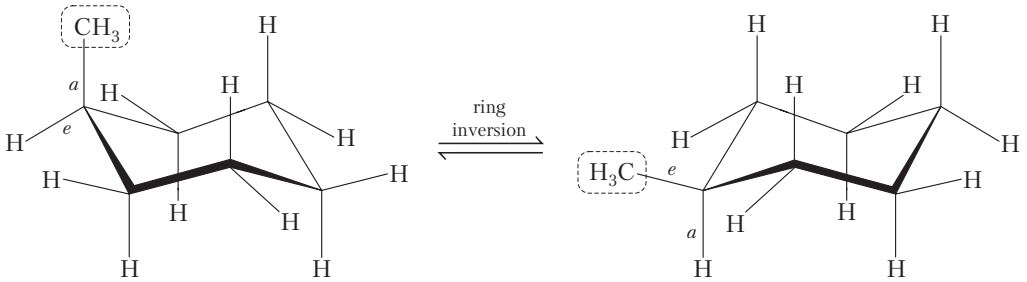
The six C—H bonds posed perpendicular to the mean plane and directed alternately upwards and downwards, are called ***axial*** (denoted by *a*). The other six C—H bonds are angled 109° and lie almost parallel to the mean plane; they are called ***equatorial*** (designated by *e*). This leads to the fact that ethane fragments are the anti-conformation and butane fragments are the gauche conformation. Cyclohexane is represented by two energetically equal chair conformations.




chair conformation chair conformation

All axial substituents during their transition are converted to equatorial substituents, while all equatorial substituents become axial. This process is called the *ring inversion* (commonly referred to as the "ring flipping" or the chair inversion). The inversion is a rapid process, hence cyclohexane is usually a mixture of the two chair conformations, equal in their energy.

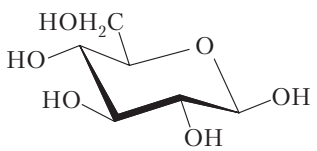
Axial hydrogens hardly ever interact with each other. More bulky groups in 1, 3 positions, however, can interact strongly with other axial substituents, thereby making the occupation of axial positions energetically unfavorable for these groups. This is why in the substituted cyclohexane bulky groups tend to occupy the equatorial positions. For example, a chair conformation with the equatorial arrangement of the methyl group is a more stable conformation of methylcyclohexane.



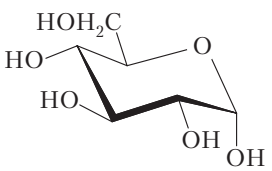

chair conformation of methylcyclohexane

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 (more stable)



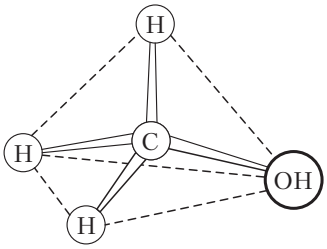

α-D-glucopyranose (less stable)

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

## 3.2. Configurational isomers

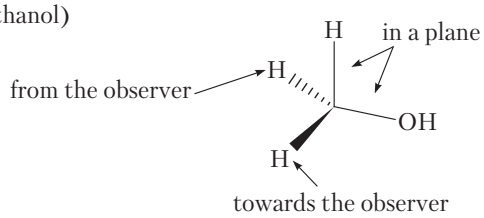
A **configuration** is a specific spatial arrangement of atoms in a molecule that excludes differences resulting from rotations about single bonds.

The fundamentals of stereoisomerism have been set forth by Jacobus Henricus van't Hoff. In 1874, van't Hoff formulated the idea that the carbon atom in substituted fragments has the tetrahedral configuration. Stereochemical formulas are used to show the tetrahedral configuration of a carbon atom on the plane. For this purpose, the tetrahedral model is oriented in a special way: the carbon atom with two of its bonds is arranged in the plane and the third bond is arranged "in front" of the projection plane, and the fourth one is represented "behind" the plane. The hydrogens are then located as follows: one in the plain (at the end of the bond dash), and the other two in the surrounding "space", viz., one in front of the plane, at the basis of the wedge pointed at the central carbon in the plane, and one at the basis of the hatched wedge pointed at the central carbon (depicting the bond behind the plane).




tetrahedral configuration of carbon atom

$CH_3OH$ (methanol)

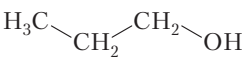



stereochemical formula of methanol

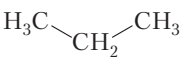
## 3.3. The concept of chirality. Chiral molecules

Any molecule can be characterized from the perspective of presence or absence of symmetry elements. A large number of molecules are highly symmetrical: e.g., benzene, propan-1-ol, propane (represented in the figure right below).

benzene



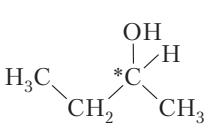

propan-1-ol



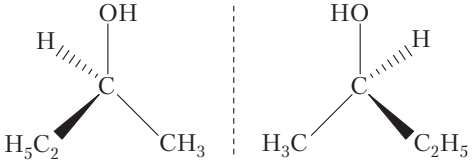

propane

However, many biologically important compounds have no elements of symmetry and are asymmetric. This can lead to chiral molecules.

**Chirality** is the property of an object to be non-superimposable with its mirror image. Objects that have such property are ***chiral***. If an object can be superposed on its mirror image, it is ***achiral***. Chiral molecules have at least one chiral carbon atom (a $sp^3$ hybrid carbon atom that is bonded to four different substituents). An asymmetric (or chiral) carbon is marked with the asterisk sign (*).




butan-2-ol




two stereoisomers of the butan-2-ol

Chiral molecules are represented by two stereoisomers that are related to each other as a subject and its nonidentical mirror image.

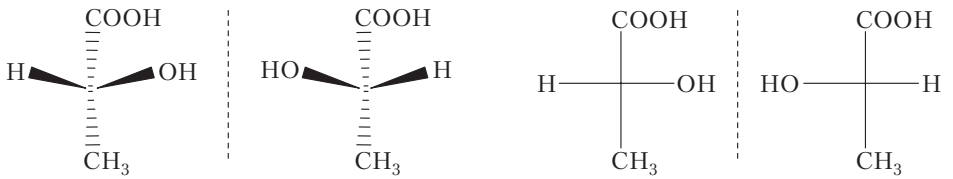
**Enantiomers** are stereoisomers which are mirror images of each other.

Chiral molecules exhibit the effect of rotating the plane of polarised light when it is passed through a solution containing the substance. This property is called **optical activity**. The rotation angle is measured with a device known as polarimeter. Some chiral substances rotate the plane of polarisation to the right (clockwise); they

are *dextrorotatory* (+). The rest of chiral substances rotate the plane to the left (counterclockwise) and are called *levorotatory* (–).

Enantiomers have identical physical scalar properties (melting and boiling points, solubility, etc.) and show the same reactivity in achiral surroundings. Optical rotation is a chiral method, so one enantiomer rotates the plane of polarized light clockwise, and the second type the same angle counterclockwise (scalar property). Enantiomers can also be differentiated when interacting with biological systems, e.g. in contacts with receptor in organisms or while being digested by fungi.

From the beginning of 20$^{th}$ century Fischer projection formulas were widely used to represent the structures of enantiomers.

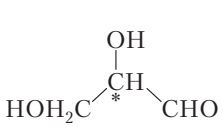



In writing Fischer projections, the following rules are to be followed:

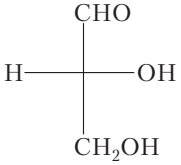
1) a carbon chain is arranged vertically;
2) the "top" and "bottom" groups are oriented backward, away from the plane;
3) the highest priority group is placed in the "top" position;
4) the "right" and "left" groups are placed in front of the plane;
5) all bonds are drawn as simple lines;
6) the central carbon is usually omitted.

**Relative D/L nomenclature** is used in naming of stereoisomeric hydroxy and amino acids as well as sugars. Compounds with hydroxyl or amino groups on the right of the standard Fischer projection (aldehyde or carboxylic group in top position) are D-stereoisomers, and those with hydroxyl or amino groups on the left are L-stereoisomers.

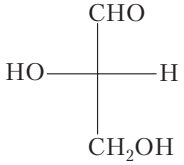
Generally, D/L nomenclature is used mostly in biochemistry and originates from the d/l system, which came from the proposals made in 1906 by professor Rosanoff. The configuration of a molecule was compared with the configuration of glyceraldehyde (2,3-dihydroxypropanal). Glyceraldehyde contains a chiral centre and exists in the forms of two stereoisomers, each having a different optical activity. Rosanoff attributed dextrorotatory glyceraldehyde to the d-configuration. Similarly glyceraldehyde was attributed to the l-configuration. For glyceraldehyde d/l convention corresponds D/L convention.




glyceraldehyde



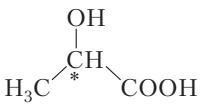

D-(+)-glyceraldehyde



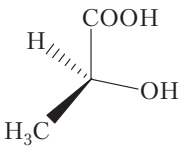

L-(–)-glyceraldehyde

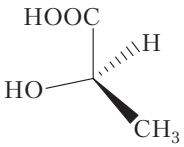
The D/L labeling does not indicate which enantiomer is dextrorotatory and which is levorotatory. Both dextrorotatory and levorotatory substances can be referred to D and L series. The main criterion is based on position of hydroxyl and amino groups in Fischer projection. To avoid misunderstanding, nowadays optical rotation is indicated by (–) and (+) instead of "d" and "l" descriptors.

Lactic acid has a chiral carbon atom. This is why there are two stereoisomers of it.

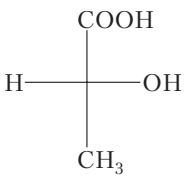



lactic acid

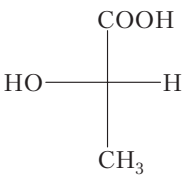



Thus, one stereoisomer of lactic acid is called D-lactic acid, the other L-lactic acid. Natural L-lactic acid is dextrorotatory and natural D-lactic acid is levorotatory. A mixture of equal amounts of the enantiomers of lactic acid exhibits no optical activity.




D-lactic acid



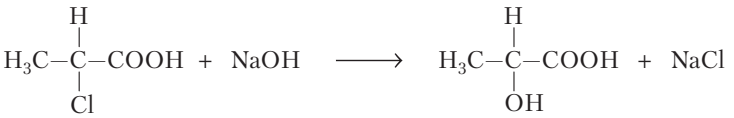

L-lactic acid

During the anaerobic glycolysis in the body, only L-lactic acid is produced from D-glucose, as the process involves enzymes. Some bacteria species produce D-lactic acid, in particular some gram-negative enteric aerobes, e.g. *Escherichia coli*. Being aware of the ability of the intestine microflora to produce D-lactic acid, we can explain why the patients with small intestine (or small bowel) after an intestinal resection or anastomosis may suffer from D-lactic acidosis.

The third form of natural lactic acids is produced in fermentation of glucose and other six-membered sugars; the resulting form is optically inactive. Louis Pasteur was the first to describe the fermentation as a method of production of this lactic acid, but evidently people had been using microbial lactic acid fermentation for food production well before Pasteur's study. In 2006, the global production of lactic acid reached 275,000 tones with an average annual growth by 10 %. Optically inactive lactic acid is an ***equimolar mixture*** of the both enantiomers, levorotatory and dextrorotatory. Both of the enantiomers compensate the optical rotation of each other (the same angle, but the opposite directions). As a result, no optical activity is observed.

**A racemic mixture (or a racemate)** is an equimolar mixture of enantiomers (means equal concentrations of both enantiomers).

Racemic mixtures do not show optical activity and are formed, generally in chemical syntheses in special conditions of achiral surroundings. For example, racemic D,L-lactic acid is produced from 2-chloropropanoic acid with aqueous NaOH.

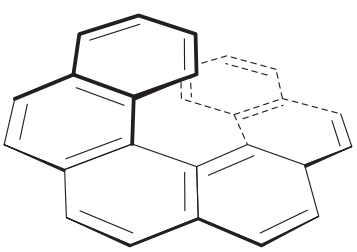



(+,–)-lactic acid

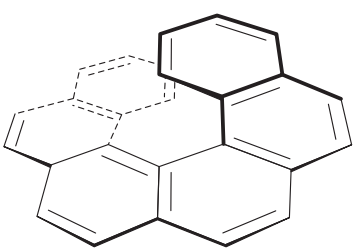
The final stage of laboratory synthesis of drugs often requires separation of a racemic mixture into its constituent enantiomers, in order to select only one biologically important stereoisomer. Mechanical, microbiological (enzyme-assisted), chemical, chromatographic and other methods are applicable for the resolution of racemic mixtures.

**Mechanical method.** This method was applied in 1848 by Louis Pasteur. He separated the sodium-ammonium salt of optically inactive tartaric acid into optically active components. He got a chance to resolve the mixture to optically active components due to the ability of racemic tartaric acid to form enantiomorphic crystals. The crystals were different to each other as mirror images, so Louis Pasteur separated them mechanically from each other by using a magnifying glass or a microscope. Subsequently, he dissolved the two isolated types of crystals separately in two different glasses and found that both solutions possessed optical activity. In one solution the plane of polarized light was rotated clockwise, and in the second counterclockwise, yet the same angle (the scalar property). Certainly, crystals of the both enantiomers had the same melting points and showed the same chemical reactivity.

Nowadays, this method is used sometimes for resolution of some compounds, e.g. helicenes. The helical molecular shape in these polycyclic aromatic compounds is forced by the steric interaction of the overlapping terminal aromatic rings. Helicenes have no chiral centres, but their chirality is generated from the helix structure (the “minus” and “plus” helixes).



M hexahelecene
(left, or minus helix)



P hexahelecene
(right, or plus helix)

The same type of chirality is typical for some conformations of biological macromolecules, i.e. the helix forms of nucleic acids and proteins.

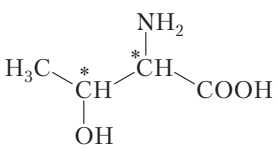
**Microbiological method.** If the nutrient medium for microorganisms is a cultivated racemic mixture, then the microorganisms, while growing, absorb from it only one of the enantiomers. The other enantiomer remains in the nutrient medium.

**Chemical method** of racemate separation based on the conversion of enantiomers to diastereomers. The latter differ in physical properties (the solubility, boiling points, melting points, etc.) and can be separated by conventional methods such as crystallization, distillation, chromatography, etc.

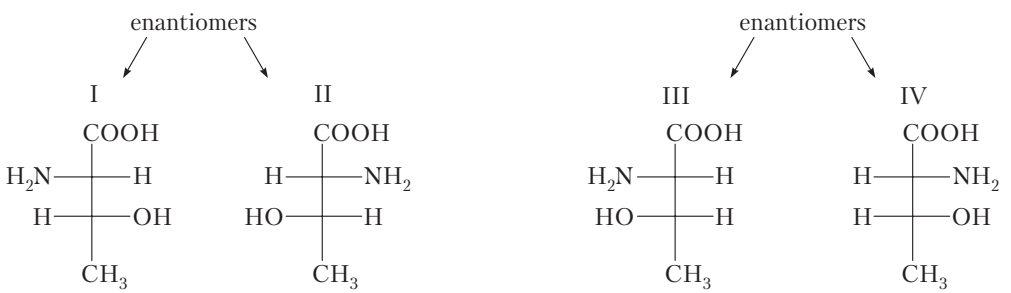
**Affinity chromatography** is a modern method. It is based on the selective interaction of biologically active compounds only with specific substance mixtures to form noncovalent complexes with them. Thus in the biochemical practice, a racemic mixture passes through a chromatographic column with secrete proteins (enzymes, immunoglobulins, receptor proteins) that serve as the chiral sorbent.

Substances with the more chiral centres have the more stereoisomers. The maximum number of stereoisomers depends on the number of chiral centres and is determined by the formula: $N = 2^n$, where $N$ stands for the number of stereoisomers, $n$ denotes the number of the chiral centres.

The presence of two centres of chirality in a molecule presupposes the existence of four stereoisomers. Consider 2-amino-3-hydroxybutanoic acid (proteinogenic acid threonine) as an example of such substance. For amino and hydroxy acids with more than one chiral centre the D/L configuration is determined by the position of the hydroxyl group attached to the uppermost chiral centre (in a Fisher projection). L-threonine and D-threonine, as well as L-allothreonine and D-allothreonine form two pairs of enantiomers. Of these four stereoisomers, only L-threonine is a part of proteins of the human body.



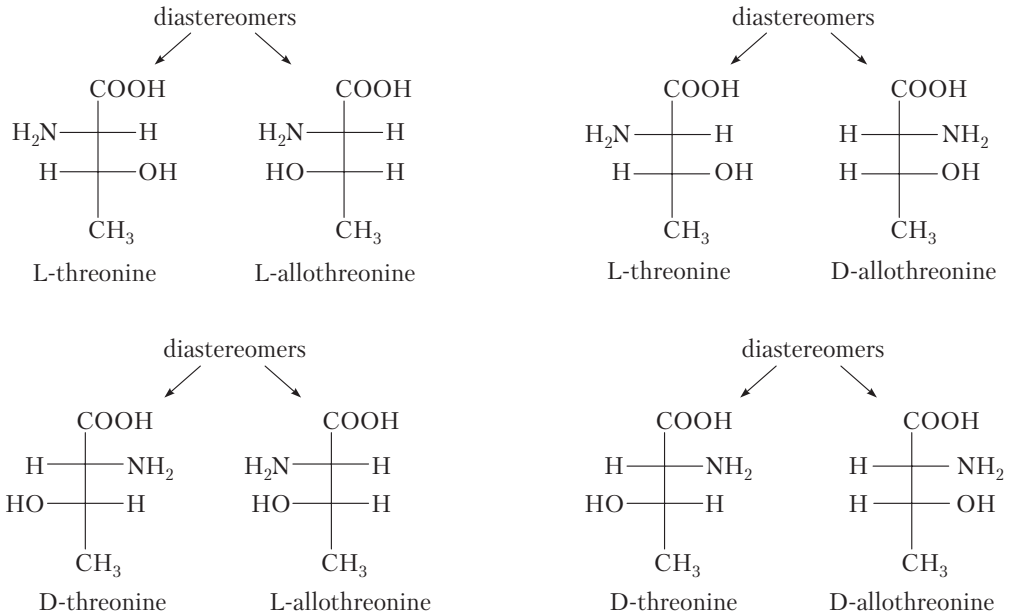

threonine




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

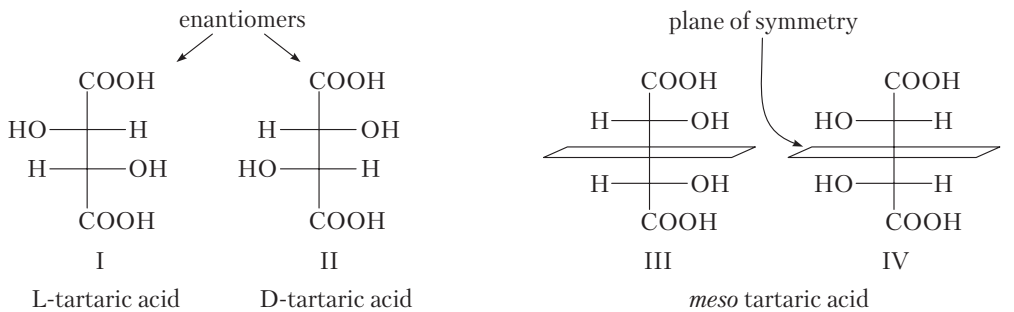
At the same time, the pairs L-threonine and L-allothreonine, L-threonine and D-allothreonine, D-threonine and L-allothreonine, D-threonine and D-allothreonine are structurally not the mirror images of each other. They are diastereomers.

**Diastereomers** are stereoisomers which are not the mirror images of each other.




These diastereomers are called *σ diastereomers*. Diastereomers, unlike enantiomers, have different physical scalar properties (e.g. the melting and boiling points, solubility, etc.). They show a different reactivity even in achiral environments.

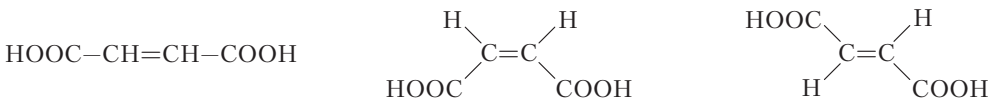
Tartaric (2,3-dihydroxybutanedioic) acid contains two chiral centres and should have four stereoisomers.




In fact, tartaric acid has three stereoisomers: L-tartaric acid, D-tartaric acid and achiral *meso* tartaric acid. *Meso* tartaric acid corresponds both to the third and

fourth projections which are identical, as they have a plane of symmetry. Therefore, *meso* tartaric acid exhibits no optical activity. Pairs of isomers are σ diastereomers.

π (*cis/trans*) diastereomers represent another type of stereoisomers. Butenedioic acid has two stereoisomers. Only the *trans* isomer, fumaric acid, is involved in biological processes.



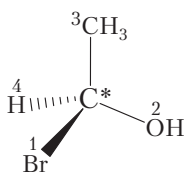

butenedioic acid maleic acid fumaric acid

Unsaturated octadeca-9-enoic acid exists as the *cis* isomer (oleic acid, the point of melting at 14°) and the *trans* isomer (elaidic acid, the point of melting at 52°). Oleic acid is a part of biological membrane lipids.

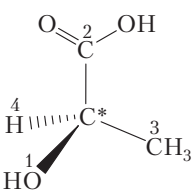
Currently **R/S convention** is widely used to describe the structures of stereoisomers of amino acids, hydroxyl acids, etc. To assign the R or S descriptor for a certain chiral centre, one must follow the set of rules.

1. Rank the priority of the substituents attached to chiral centre.

1.1. The higher is the atomic number of the immediate substituent atom, the higher is the priority of the substituent. For example, $_{35}Br- > _{8}O- > _{6}C- > _{1}H-$. The substituents in 2-bromoethanol shall be ranked as follows: −Br (1st); −OH (2nd); $-CH_3$ (3rd); −H (4th).



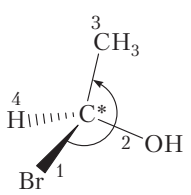

1.2. If two substituents have the same immediate substituent atom, the priority of atoms must be ranked progressively farther away from the chiral centre, until a difference is found. For example, a carboxyl group (−COOH) in which the central carbon is connected directly with oxygens takes priority over a methyl group ($-CH_3$) in which the central carbon is connected directly with hydrogens. In combination with the previous rule, this one ranks the substituents in (−)-lactic acid as follows: −OH (1st); −COOH (2nd); $-CH_3$ (3rd); −H (4th).

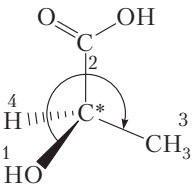



2. After ranking the priority of the substituents we are to look at the molecule from the side opposite to the substituent with the lowest priority 4 (in other words, we must place the molecule in space so that the lowest priority group is pointing backward). In the two examples above (2-bromoethanol and (−)-lactic acid) the youngest substituent is hydrogen, as shown in the pictures.

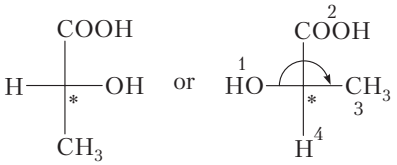
3. When looking at the molecule from the side opposite to substituent 4, the observer must draw a curved arrow from the 1st position to the 2nd location and then to the 3rd. The arrow may turn clockwise or counterclockwise. If the turn is clockwise, as in 2-bromoethanol, the configuration is classified R. If the turn

is counterclockwise, the configuration is S. The symbol letter R originates from the Latin *rectus* for right, and S from the Latin *sinister* for left.




S 2-bromoethanol

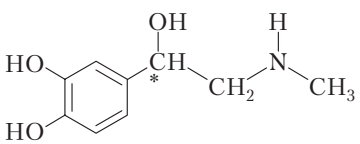



R lactic acid

There are two projections provided above for lactic acid. To assign correctly the configuration of the chiral centre in a Fisher projection, one must remember that substituents on horizontal lines (bonds) in it are placed in front of the plane. It means that in a standard Fisher projection a hydrogen is placed above the plane. To place the hydrogen above the plane, we can use operations that do not change the configuration of the chiral centre. In the first approach, we do an even amount of rearrangements (e.g. two) between the substituents attached to the chiral centre. The same result can be obtained from rotation of any three substituents of the chiral centre in any direction when the last is keeping its fixed position. For the presentations above the right Fischer projection was obtained after the rotation of $-H$, $-CH_3$ and $-OH$ with the $-COOH$ fixed at the top of the molecule.

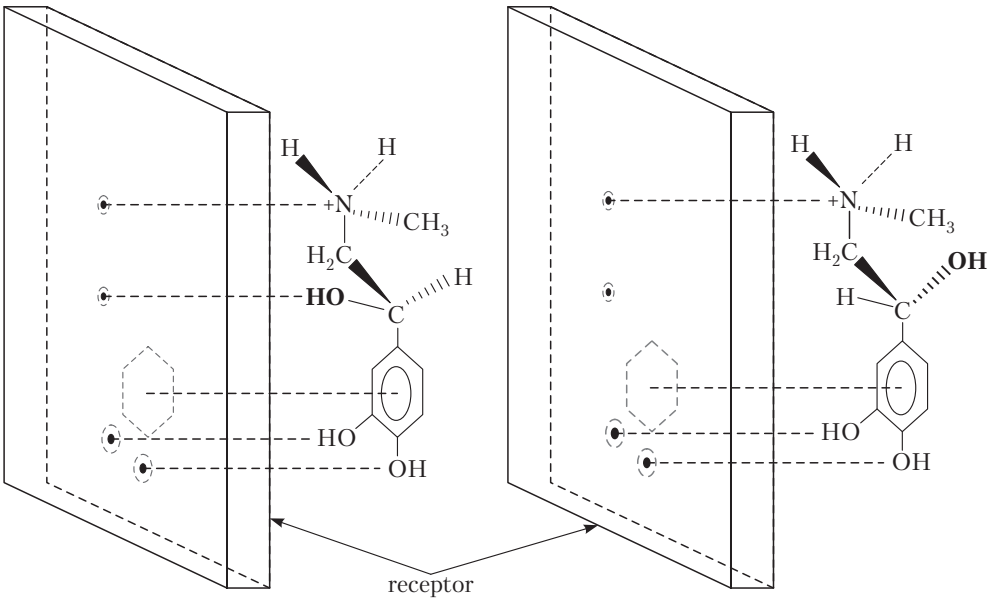
## 3.4. Stereochemistry and biological activity

Most metabolites are chiral molecules. L-Hydroxy acids, L-amino acids, D-monosaccharides are involved in metabolic processes in a cell. Proteins are constructed from L-amino acids, phospholipids, vitamins, hormones, nucleic acids and are also chiral molecules. Spatial structure of stereoisomers defines the specificity of such interactions as substrate-enzyme, hormone-receptor, antibody-antigen, etc. Pharmacological action of pharmaceuticals is provided by their interaction with cell receptors. Physiological action of pharmaceutical preparations is provided by their interaction with cell receptors. For example, the greater pharmacological activity is manifested by levorotatory epinephrine (adrenaline) than the dextrorotatory form of epinephrine.




epinephrine

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




(—)-epinephrine has effective interaction with the receptor due to complementarity

(+)-epinephrine does not bind to the receptor completely

# 4. ORGANIC REACTIONS

Biologically important reactions in living cells (*in vivo*) proceed on the similar mechanisms as reactions in a chemical laboratory (*in vitro*).

The reaction mechanism is a consistent description of all changes in reacting compounds that occur at the molecular level, as the reactants become products.

## 4.1. Classification of organic reactions

Organic reactions can be classified in different way.

First of all consider the classification of organic reactions by the direction and the overall results of the reactions:

1) addition reactions (designated by A or Ad);
2) elimination reactions (E);
3) substitution reactions (S);
4) isomerization reactions (I);
5) redox reactions;
6) acid-base interactions.

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

Radical reactions are accompanied by ***homolysis*** (homolytic cleavage, or fission) of a bond and the formation of radicals.

***Radicals*** are neutral species, that contain an atom with an unpaired electron in its outer shell.

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

Nonpolar and low polar covalent bonds in organic compounds predispose to homolysis. Radical reactions usually occur in the gas phase or in nonpolar solvents. They are initiated by physical (ultraviolet radiation, heat), as well as chemical factors (presence of R—O—O—R, $Fe^{2+}$). Radical reactions are sensitive to electron acceptors. They are usually self-accelerating chain reactions which go through the following steps:

1) initiating radicals;
2) propagation of the chain;
3) termination of the chain.

Ionic reactions are accompanied by ***heterolysis*** (heterolytic cleavage, or fission) of the covalent bond that leads in many cases to the formation of ions, named anions (with negative charge) and cations (with positive charge).

Heterolysis: $A\bullet\bullet|K \rightarrow :A^- + K^+$

A polar covalent bond in organic compounds predisposes to heterolysis. Usually ionic reactions occur in polar solvents and can be catalyzed by acids or bases.

There are two types of reagents involved in ionic reactions: electrophiles and nucleophiles.

***Electrophilic reagents*** are aceptors of electrons in the formation of a new bond.

Electrophiles have a vacant orbital or tend to break the bond to form such orbital (full or partial positive charge on the reaction site). They are designated by E. Proton $H^+$ is a typical electrophile.

***Nucleophilic reagents*** are donors of electrons in the formation of a new bond.

Nucleophiles have negative charges, a pair of lone electrons or tend to break the bond to form an orbital with a lone electron pair. They are designated by Nu. The most important nucleophiles are hydride ion $H^-$, water HOH, alcohols R—OH, amines $R—NH_2$, thiols R—SH, etc.

The other classification discusses the acidic and basic properties of substances.

## 4.2. Acidity and basicity of organic compounds

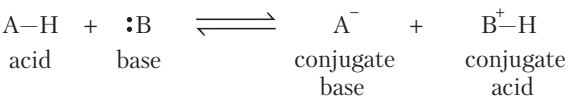
Many fundamental physicochemical and biochemical properties of organic compounds are determined by their acidity and basicity. First of all, acid and basic catalyses are the most widespread enzymatic reactions.

At present, there are two main concepts of acids and bases in organic chemistry.

According to the Brønsted theory, an acid is a proton donor, and a base is a proton acceptor.

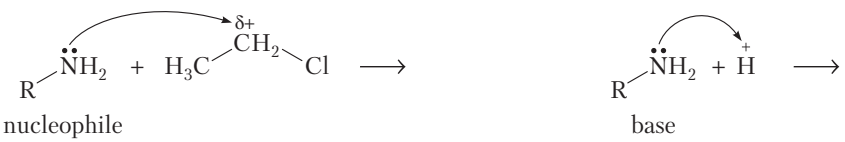
According to the Lewis theory, an acid is an electron pair acceptor, and a base is an electron pair donor.

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




When a Brønsted acid loses a proton, its conjugate base is formed. When a Brønsted base accepts a proton, its conjugate acid is formed.

A molecule or an intermediate particle behaves both as an electrophile/nucleophile and acid/base, depending on the reaction.



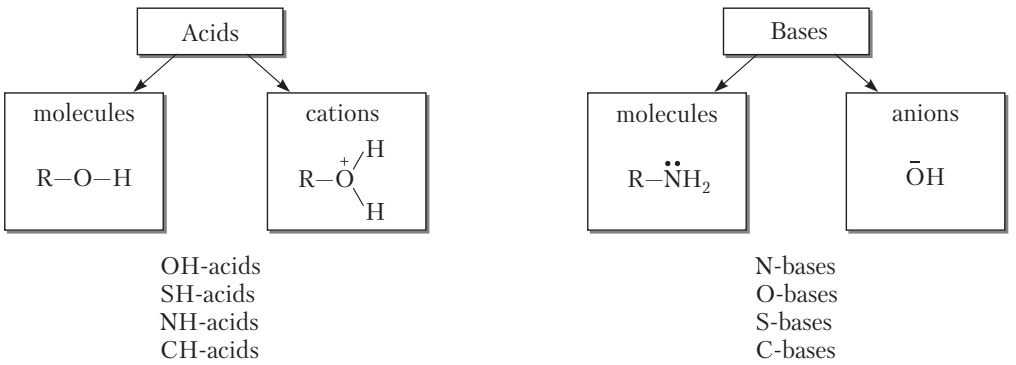
The strength of an acid is determined by how well it donates a proton to a base. In order to indicate it quantitatively, the dissociation constant is calculated. Thus, the acid strength is measured by the magnitude of its dissociation constant $K_a$. The latter covers a range of many powers of 10. So it is easier to express acid strength in logarithmic form. Negative logarithm can be abbreviated to p giving the final value p$K_a$.

$$pK_a = -\lg K_a$$

A stronger acid has a lower p$K_a$, and a weaker acid has a higher p$K_a$.

Base strength is expressed as logarithmic basicity constant p$K_{BH^+}$. A stronger base has a higher p$K_{BH^+}$, a weaker base has a lower p$K_{BH^+}$.

**Classification of Brønsted acids and bases**




However, p$K_a$ and p$K_{BH^+}$ are barely measurable in cases of real biochemical processes. Instead we can correlate the acid/base strength with their structure qualitatively.

The stability of an acid anion depends on the nature of the acidic atom (its electronegativity and radius), the degree of delocalization of the electron density and the ability to solvate.

The ***element effect*** explains the correlation between the acidity and the position of elements in the periodic table of chemical elements. Thus, the acidity of acids H—A increases toward higher atomic numbers of the A atom within a group (column) and a period (row) in the periodic table. Within a row, it can be discussed in terms of the H—A bond strength which depends on A. The higher is the electronegativity, the more pronounced are the acidic properties. For example, ethanol $CH_3CH_2OH$ is a stronger acid than ethylamine $CH_3CH_2NH_2$.

The ***polar effect*** explains the correlation between the acidity and the stability of conjugate bases. The more stable is a conjugate base the bigger is the shift in the equilibrium towards proton formation, and hence, the stronger is the acid.

$$R{-}X{-}H \rightleftharpoons R{-}X^- + H^+$$

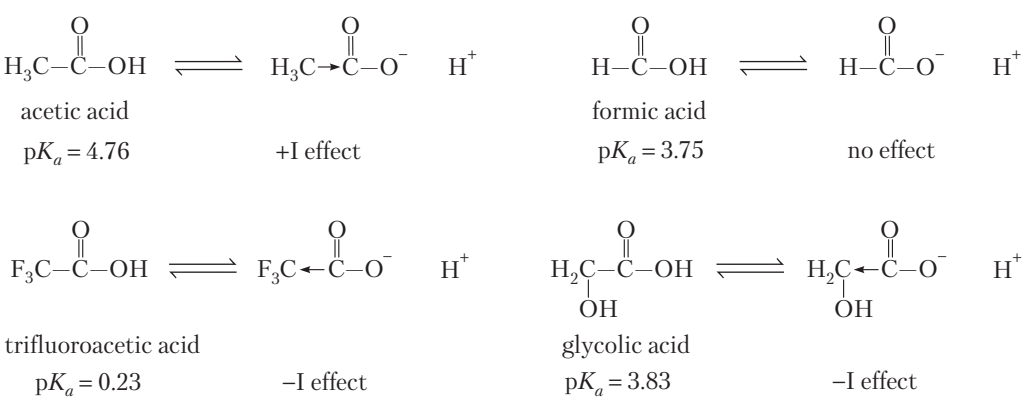
For example, methanthiol $CH_3SH$ is a stronger acid than methanol $CH_3OH$, methanol is a stronger acid than ethanol. Not only the element effect but alsothepolar effectisinaccordancewiththistendency.Thus,thehigherpolarizabilityof the sulfur atom in the conjugated base $CH_3S^-$ correlates with the strongeracidic properties of methanthiol $CH_3SH$. It can be explained in view the fact thata larger atom delocalizes a negative charge more effectively than a smaller atom.

Ifacidshavethe sameatomintheacidicsite,thedelocalizationofthenegativecharge in the anion as well as the acid strength depends on conjugation and the substituent electron effects.

Methanoic acid (formic acid) is a much stronger Brønsted acid than methanol.


It can be explained easily taking in account the structure of the carboxylate anion (conjugate base) which is effectively stabilized due to the sharing of the double bonds (and therefore the negative charge) between the two oxygen atoms.

The presence of acceptors increases the acid strength within a series of compounds with the same acidic centre. In contrary, the presence of donors decreases the acid strength. For example, trifluoroacetic acid ($CF_3$ is the acceptor) is stronger than formic acid (no substituents), and in turn, the latter is stronger than acetic acid ($CH_3$ is donor).




The same trend is observed in series of hydroxy acids which are stronger than unsubstituted acids.

One more factor, the hydrogen bond effect, also plays a very important role in the stabilization of conjugate bases, thereby increasing the strength of acids.

The strength of Lewis bases correlates with the ability of their atoms to donate the lone electron pair to acids.

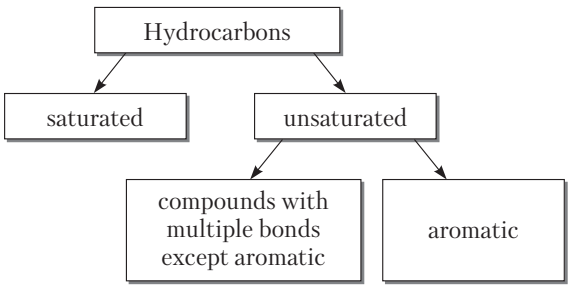
Taking into account the element effect we can predict that within the same row of the periodic table electron donation is increased with the atomic number. Thus, amines are much stronger bases than alcohols and alkanes have no basic properties at all.

In view of the polar effect, we can predict that donor substituents increase and acceptor substituents decrease the basicity. Thus dimethyl amine is a stronger base than methylamine ($CH_3$ is the donor), and the latter is a stronger base than trifluoromethyl amine ($CF_3$ is the acceptor).

In some cases solvation of the lone electron pair can influence the strength of a base.

# 5. REACTIVITY OF HYDROCARBONS

There are two main types of hydrocarbons: saturated and unsaturated.




Unsaturated hydrocarbons contain one or more multiple bonds (alkenes, alkynes, dienes and polyenes, arenes. Dienes (and polyenes) can be divided into three classes, depending on the relative location of their double bonds:

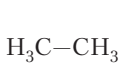
- ***cumulated dienes*** have the double bonds sharing a common carbon atom;
- in ***conjugated dienes*** alternating double bonds are separated by one single bond;
- in ***unconjugated*** **(*isolated*)** ***dienes*** the double bonds are separated by more than one single bonds.

Hydrocarbons are hydrophobic. They are toxic for mammals, because they can easily penetrate into the body through the skin and mucous membranes.

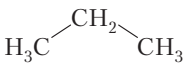
## 5.1. Saturated hydrocarbons

Saturated hydrocarbons contain only σ bonds.

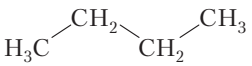
methane



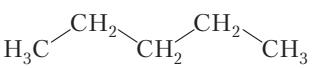
ethane



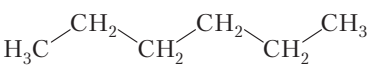
propane



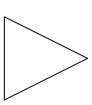
butane



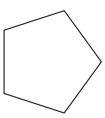
pentane

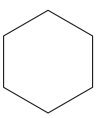


hexane

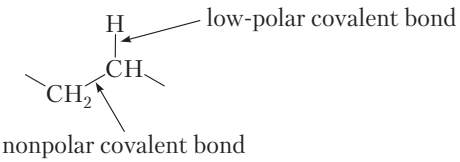

cyclopropane


cyclobutane


cyclopentane

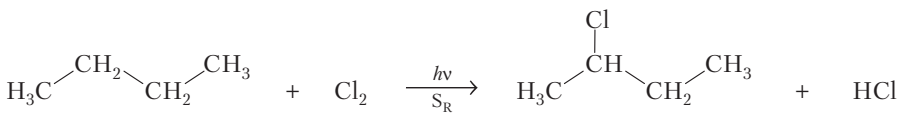

cyclohexane

Saturated hydrocarbons contain nonpolar and low-polar covalent bonds, which predispose to homolytic bond breaking.



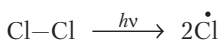

Reactions of radical substitution ($S_R$) and radical oxidation are typical of alkanes, cycloalkanes (except cyclopropane, cyclobutane), saturated fragments of other classes of organic compounds.

The halogenation of alkanes proceeds by radical substitution. It requires ultraviolet lightening and proceeds through a series of stages.

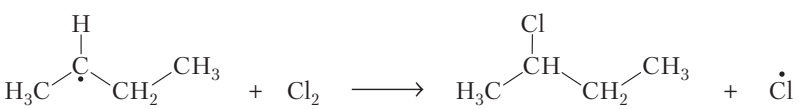



butane 2-chlorbutane

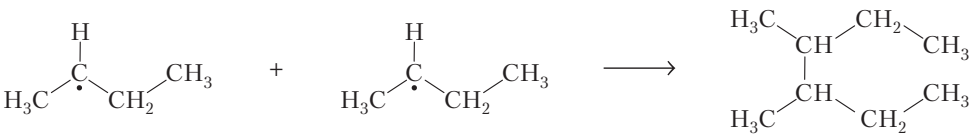
First, the ***initiating*** stage takes place, i.e. in the splitting of the chlorine molecule into two halogen atoms (free radicals).

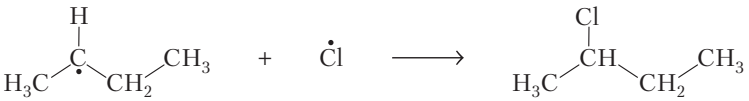



In the second, ***chain-propagating*** stage, a very reactive chlorine atom collides with a butane molecule, to abstract a hydrogen atom and produce a HCl molecule and a highly reactive alkyl radical.


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

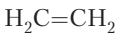




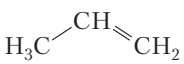
While there is no evidence for radical halogenation *in vivo*, oxidation reactions proceeding on alkyl fragments are widely spread in biochemical processes. For example, alkanes as xenobiotics are removed from living organism *via* oxidation reactions (the process of detoxification).

## 5.2. Unsaturated hydrocarbons

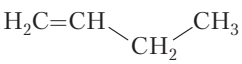
Electrophilic addition reactions ($A_E$) are typical for alkenes, alkadienes, arenes (in special conditions).



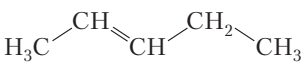
ethene



propene

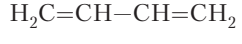


but-1-ene



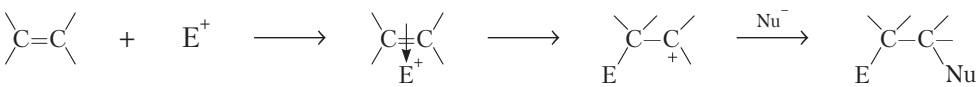
pent-2-ene

cyclopenta-1,3-diene



buta-1,3-diene

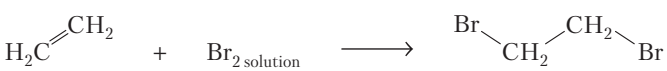
Electrophilic addition reactions proceed in a series of stages. This type of reactions can be represented in a general form as shown below.



π complex σ complex product

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

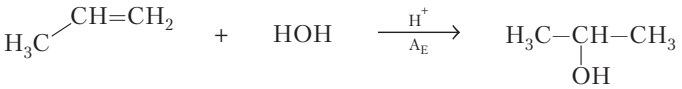
Synthesis *in vitro* may involve the reactions of halogenation, hydrohalogenation, hydration, alkylation, etc. The reaction with bromine water is used as a chemical test for presence of double bonds.



brown colorless

Bromine water is coloured reddish-brown-yellow (depends on the concentration). When passing the gaseous alkene through bromine water, one can observe decoloration. A solution of an unknown substance may also be added to a solution of bromine in an organic solvent. Similar to the above technique, decoloration proves the presence of double or triple bond in the added substance.

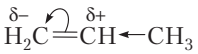
Hydration is the water addition reaction. This reaction *in vitro* requires a strong acidic catalyst. Acid as a catalyst generates a proton (electrophile) that is capable of reacting with a π bond. Hydration of propene and other unsymmetrical alkenes goes according to the Markovnikov's rule.



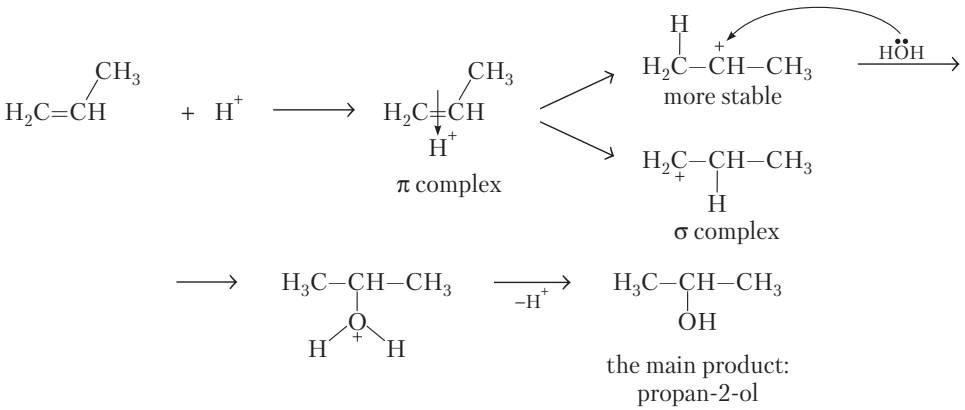

propene propan-2-ol

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

The Markovnikov's rule can be explained in two ways. The first approach is based on the analysis of the charge distribution in a substrate alkene molecule. In propene the π bond is polarized under the influence of the methyl group. It is obvious that with such distribution of the electron density in the molecule, the electrophile should join the less substituted carbon atom and the nucleophile will attack the more substituted atom of the double bond.

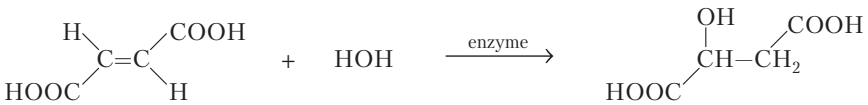



The second approach is based on the analysis of carbocation stability: the addition reaction proceeds in the direction of the formation of the more stable intermediate.



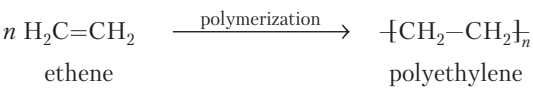
In the case of propene, the secondary carbocation is more stable due to the positive induction from the two methyl groups, which decrease the positive charge on carbon.


Many biologically important reactions proceed against the Markovnikov's rule or this rule is insignificant for them. The hydration reaction of butenedioic (fumaric) acid proceeds towards the formation of hydroxybutanedioic (malic) acid.

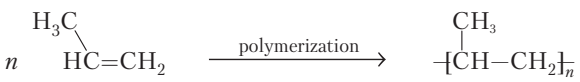



fumaric acid malic acid

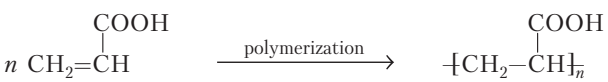
Alkenes can be polymerized easily.



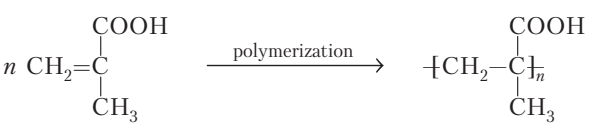

ethene polyethylene




propene polypropylene




acrylic acid polyacrylate




methacrylic acid polymethacrylate

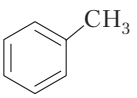
The reaction is widely used in industry in the synthesis of polymers. An overview of the application of polymers in medicine is presented in Chapter 11.

## 5.3. Aromatic hydrocarbons

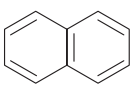
Aromatic hydrocarbons, or arenes, are cycle hydrocarbons which contain a framework built from carbons connected with σ bonds and delocalized π electrons forming a circle. The number of delocalized electrons corresponds to the Hückel's rule (see Chapter 2). Contrastingly, aliphatic hydrocarbons (also known as non-aromatic compounds) lack this delocalization.

Benzene is the simplest representative of aromatic hydrocarbons; its structure is based on a six-membered ring. Aromatic hydrocarbons can be monocyclic (MAH) or polycyclic (PAH). Examples of benzene-based arenes are shown below.

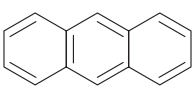
benzene



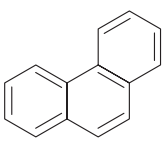

toluene



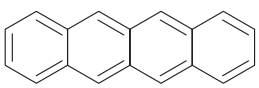
naphthalene



anthracene



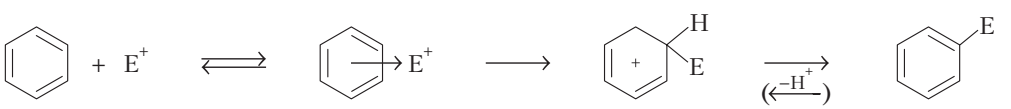
phenantrene



tetracene

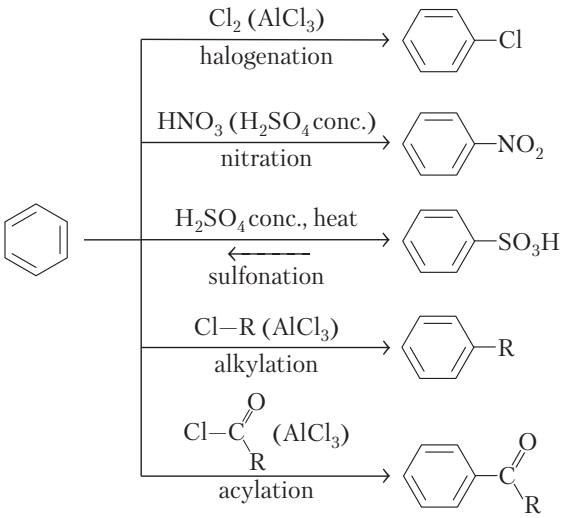
Electrophilic substitution reactions ($S_E$) are typical of arenes.

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

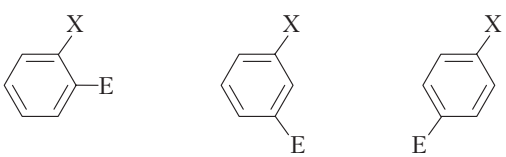



π complex σ complex end product

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




In benzene all positions are equivalent, but in its substituted derivatives the electrophile (E) may be introduced selectively. In monosubstituted benzenes the electrophile can be directed to *ortho*, *meta* or *para* positions to the original substituent in the substrate (X).



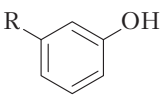

Electrophilic directing groups are divided into two types. Type I substituents direct the electrophile in the *ortho* and *para* position of the benzene ring. Most of type I directors are electron-donating groups such as $-NH_2$, $-OH$, etc. The $S_E$ reactions proceed the faster with compounds that carry electron-donating substituents. The higher the electron density in the aromatic ring, the more the electrophile tends to form a bond. Type II substituents (*meta* directors) are electron acceptors and thus they put the electrophile in the *meta* position of the benzene ring. They decrease the reactivity of the benzene ring.

Detoxication reactions of arenes in the body include the introduction of the hydrophilic groups into the ring by hydroxylation (hydroxyl group) or acylation (acyl fragment $\overset{R}{\underset{}{}}C(=O)$) and other reactions. The detoxication reactions are facilitated by the presence of electron-donating substituents. For example, toluene has the donating methyl group and thus reacts faster than benzene. As a result, it is less toxic.

# 6. REACTIVITY OF MONOFUNCTIONAL DERIVATIVES OF HYDROCARBONS

Monofunctional derivatives of hydrocarbons contain various functional groups in their structure. But in this section we will discuss 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 |

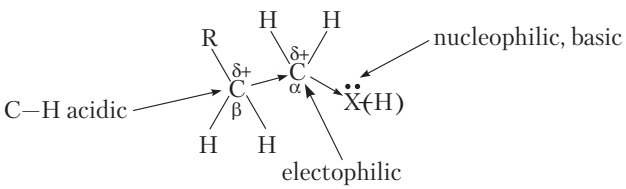



phenols

R—Hal

halogenated hydrocarbons

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




reaction sites of monofunctional derivatives of hydrocarbons

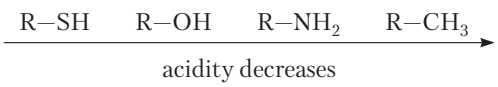
Nucleophilic substitution reactions ($S_N$) proceed at the electrophilic centre. Under certain reaction conditions, the C—H acidic centre attacked by a base; the latter withdraw a proton, and the elimination reaction takes place. Elimination reactions and nucleophilic substitution are competitive processes.

Thus, monofunctional hydrocarbon derivatives possess acid-base properties, properties of an electrophilic centre ($S_N$) and a C—H acidic centre (E), and can take part in redox reactions.

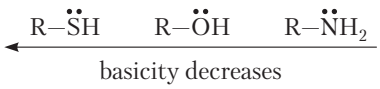
# 6.1. Acid-base properties of monofuntional derivatives of hydrocarbons

It should be reminded that the qualitative characteristics of acids and those of bases are most essential for biologically important compounds. The stability of the anion formed by an acid dissociation is a qualitative characteristic of acidity: the more stable is an anion, the stronger is the acid. The value of the electron density in the basic centre is a qualitative characteristic of basicity: the higher is the electron density at a basic site, the stronger is the base.

In the row of acids with the same radicals thiols are strongest acids.

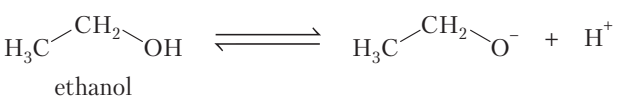



The dependence correlates with the stability of anions. Thiolate anion is the most stable in the series because of the greater delocalization of the negative charge of the sulfur atom having a larger radius, compared with the oxygen atom. Alcohols are stronger acids than amines and hydrocarbons, as the oxygen atom in the former has a higher electronegativity than nitrogen and carbon atoms. Consequently, the oxygen holds a pair of electrons better, and so the alkoxide anion is more stable.

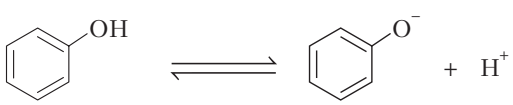



Basic properties change in the reverse order. Amines are strongest bases. Thiols show tenuous basic properties. Hydrocarbons are not bases, because the carbon atom has no lone pair of electrons and is not able to attach a proton.

The change of a fragment attached to the functional group drastically influence acidic and basic properties. It depends on the electronic effect of the substituent and conjugation. Thus, the electron-withdrawing substituents and conjugation increase the stability of the acid anion and hence the acidity, but reduce the basicity. And the electron donating substituents reduce the acidity, but increase the basicity.



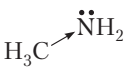

ethanol



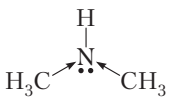

phenol

To compare the acidity of phenol and ethanol, it is necessary to write their dissociation reaction and discuss the stability of the resulting anions. The phenoxide anion is more stable since the negative charge is delocalized by the conjugation. Consequently, phenol is a stronger acid than ethanol. Phenol water solutions have slightly acidic properties (carbolic acid) and therefore have been once widely used as antiseptics.

Dimethylamine possesses more pronounced basic properties than methylamine, because its two methyl groups have a positive inductive effect, which is expressed in a more pronounced electron density at the basic site.

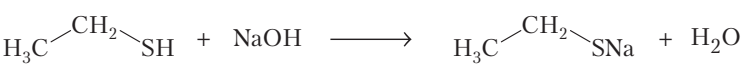


methylamine



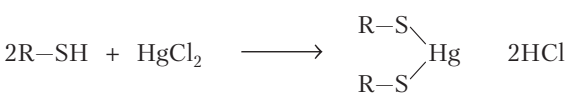
dimethylamine

The substitution of a proton is the manifestation of acidic properties. Alcohols react only with metallic sodium or potassium, and thiols as stronger acids can react with alkalies.

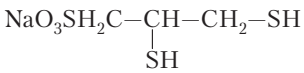


Basic properties of conjugated bases decrease from amide to thiolate. It correlates with a general trend: the stronger is an acid, the weaker is the conjugated base (the weaker is an acid, the stronger is the conjugated base). Thus, methoxide is a stronger base then phenolate.

Thiols and thiolates also react with transition metal hydroxides and ions, to form stable complexes. The term *mercaptan* (the older name of thiols) is derived from the Latin *mercurium captans* (capturing mercury), because the thiolate group bonds strongly with mercury derivatives. According to the theory of hard and soft acids and bases (HSAB), sulfur is a relatively soft (polarizable) atom. This explains the tendency of thiols to bind to soft elements/ions such as mercury, lead, or cadmium. Such reactions are of great medical importance because they help to transfer highly toxic metal cations into non-toxic derivatives.

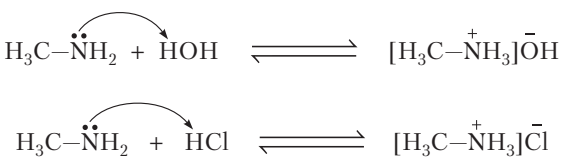


Thiols (e.g. Unitiol) are used as antidotes for poisoning arsenic, mercury, chromium, bismuth, etc.

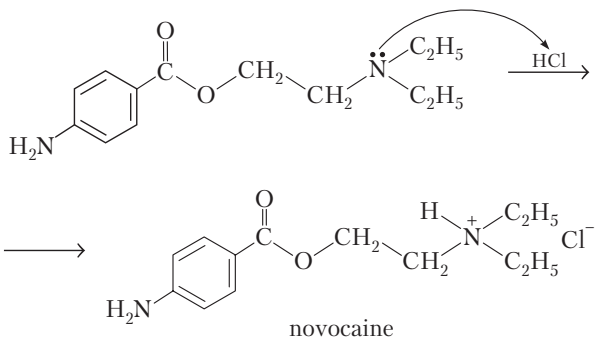


2,3-dimercaptopropane-1-sulphonate sodium, or Unitiol

In the acid-base interaction the base attaches a proton.



Many medicines are applied in the salt form. For example, Procaine (Novocaine) is a hydrochloride salt of the corresponding free base. It is prescribed as a local anesthetic agent.



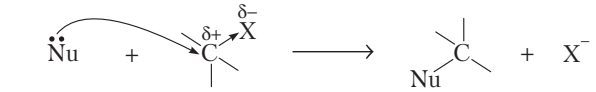
novocaine

Most of biologically important compounds (hydroxy acids, phenolic acids, amino acids, purine and pyrimidine base, etc.) have amphoteric properties. As the conditions may be, either the acidic or the basic centres are activated. Intra- and intermolecular hydrogen bonds are also a consequence of the amphoteric properties of the compounds.

## 6.2. Nucleophilic substitution and elimination reactions

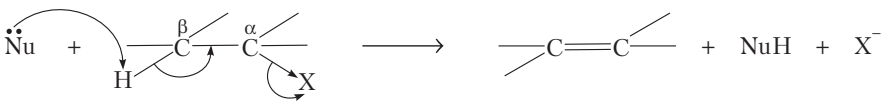
Nucleophilic substitution at saturated carbon is at once formally one of the simplest and the most important type of organic reactions. Different compounds with an electrophilic site undergo nucleophilic substitution reactions. It may also be characterized as an alkylation reaction with reference to the nucleophile.

Nucleophilic substitution occurs in many biologically important processes. In this reaction, one covalent bond is broken and a new bond is formed. The reaction can be represented by the following general scheme.



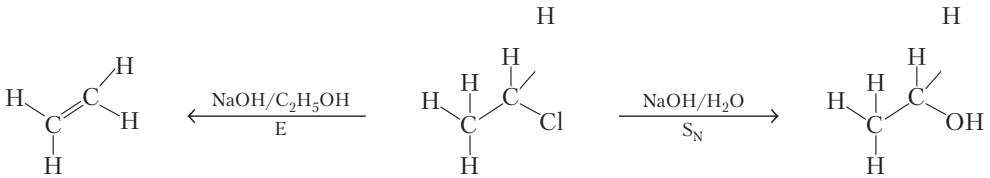

nucleophile substrate product

Compounds of different classes may be considered as nucleophiles. Both neutral molecules and anions can serve as nucleophilic reagents. Under certain conditions, a base withdraws a proton from the C—H acidic centre of the β-carbon atom in a substrate to give rise to the elimination reaction.




nucleophile with strong basic properties | substrate | product

*In vitro*, the nature of reactants and the reaction conditions set the reaction either to the substitution or the elimination pathway. For example, haloalkanes, when reacting with aqueous NaOH solutions, tend to produce alcohols ($S_N$). By contrast to the above, the interaction of the same substrate with an alcoholic NaOH yields alkene as the major product (E).



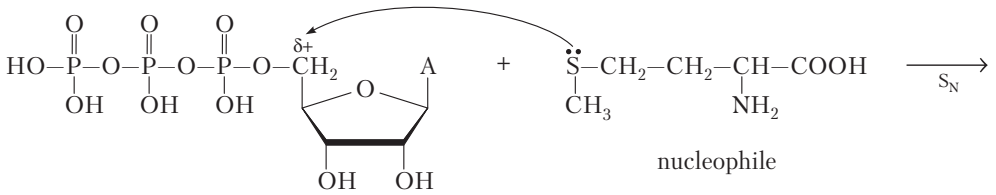

ethene chloroethane ethanol

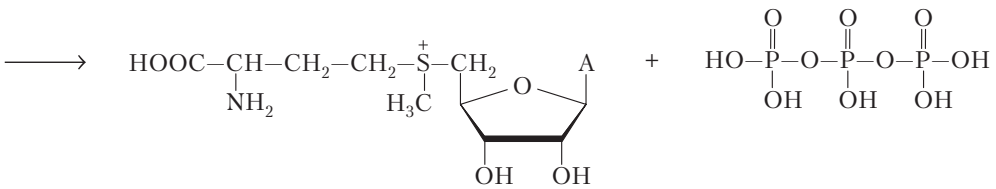
Substrates with bulky branched substituents also tend to produce elimination products.

The nucleophilic substitution mechanism is also typical of biochemical reactions in the cell.

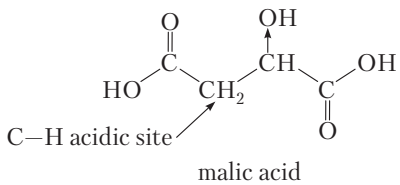
Biochemical alkylation (methylation) prevails among all substitution reactions *in vivo*. S-adenosylmethionine is an important methylating agent; it is formed in the reaction of the ATP and amino acid methionine (by the same $S_N$ mechanism). Adenosine triphosphate has an electrophilic centre attacked by the sulfur atom

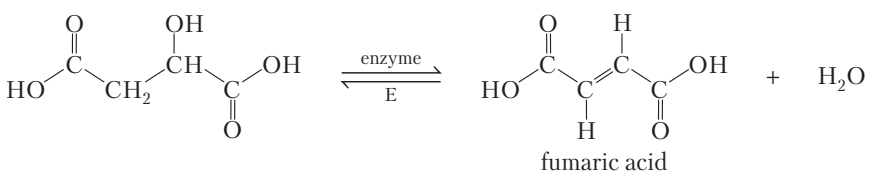
which is the nucleophilic centre. The resulting product is further able to act as a substrate in the $S_N$ reactions.




Malic acid has a hydroxyl group which is an electron acceptor. The shift of the electron density increase the C—H acidity in the β carbon atom, which promotes the elimination reaction.




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

## 6.3. Oxidation

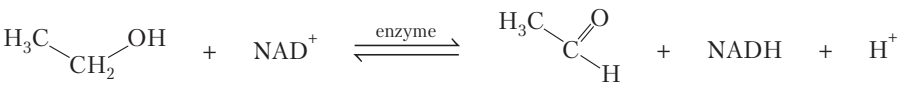
Oxidation of many biologically active substances in the living cell often proceeds by the dehydrogenation mechanism.

Coenzyme $NAD^+$ (the oxidized form of nicotinamide adenine dinucleotide) participates in enzymatic reactions. Its role is to join a hydride anion, which is

released from the α carbon atom of a substrate. NADH (nicotinamide adenine dinucleotide reduced) is formed during the reaction. The substrate also releases a proton into the solution. In many cases the reaction is reversible.

$$\text{H—substrate—H} + \text{NAD}^+ \overset{\text{enzyme}}{\rightleftharpoons} \text{substrate} + \text{NADH} + \text{H}^+$$

Lactic acid, malic acid, exogenous and endogenous ethanol are oxidized in such way *in vivo*.




ethanol ethanal

Oxidation of thiols occurs easily under mild conditions to form disulfides.

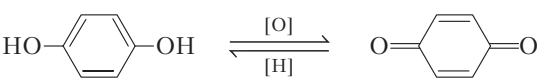
$$2\text{R—SH} \xrightarrow{[O]} \text{R—S—S—R} + \text{HOH}$$

dialkyldisulfide

Disulfide bonds are formed by oxidation of the thiol groups of amino acids in the formation of the tertiary structure of proteins. Due to easy oxidizability thiols may behave as antioxidants in living cells.

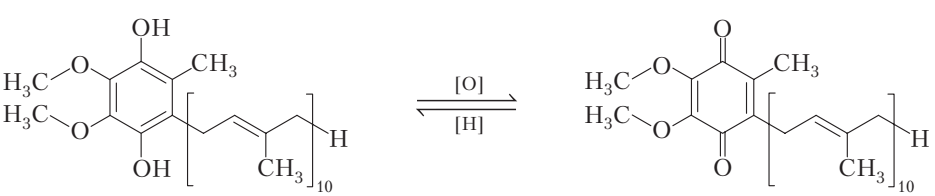
**Antioxidants** are the substances that prevent oxidation of biologically important compounds.

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




hydroquinone quinone

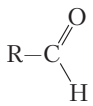
This reaction underlies the application of polyphenols as inhibitors and the functioning of respiratory chain ubiquinones (coenzyme Q).

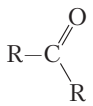


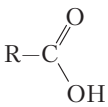

coenzyme QH coenzyme Q

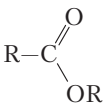
# 7. CARBONYL COMPOUNDS. ALDEHYDES AND KETONES

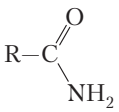
Carbonyl compounds are a very important class of organic compounds; they play a special role in biological processes. These compounds contain a carbonyl, or an oxo group  .

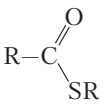

aldehydes

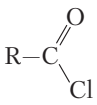

ketones

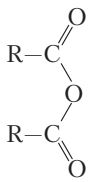

carboxylic acids


esters

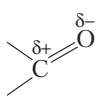

amides

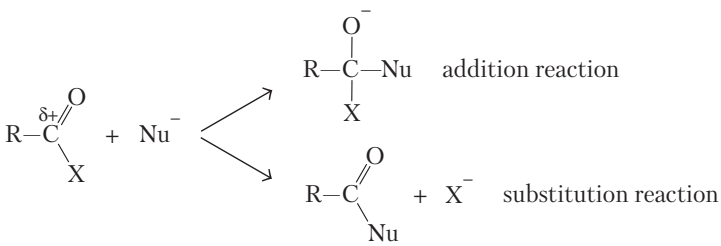

thioesters


acyl chlorides


anhydrides

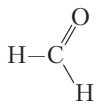
The electrons of the C=O bond are shifted to the oxygen atom, so the carbon atom forms a partial positive charge (an electrophilic centre); and thus, nucleophilic reagents attack the electrophilic carbon of the carbonyl group. This attack may produce both addition and substitution products. Addition is more typical of aldehydes and ketones. Carboxylic acids tend to form substitution products.

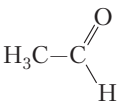


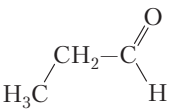


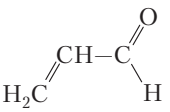

## 7.1. Nomenclature of aldehydes and ketones

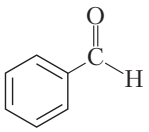
The presence of the aldehyde group in the structure of a compound is indicated by the suffix *-al*, and the presence of the ketone group is denoted by the suffix *-one*. Some of the compounds representing the group are widely used in biology and medicine and are mentioned by their trivial names.

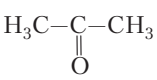

methanal
(formaldehyde)

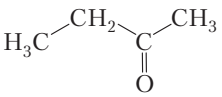

ethanal
(acetaldehyde)


propanal


propenal

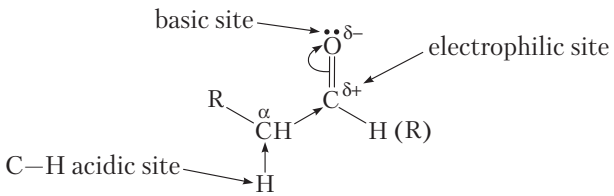

benzaldehyde


propanone
(acetone)


butanone

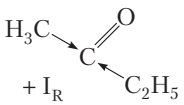
## 7.2. Structure of carbonyl group

The carbon atom and the oxygen atom in a carbonyl group are both $sp^2$ hybridized, so the structure of this fragment is planar. The bond between the carbon and oxygen atoms is highly polarized. The electron density is shifted towards the more electronegative oxygen atom. The carbonyl carbon atom acquires a partial positive charge and becomes an electrophilic centre.




The oxygen atom has a pair of electrons. Hence it is able to attach a proton, so it is a basic centre. A carbonyl group has a negative inductive effect, whereby the $C_1—C_2$ bond is also polarized and the C—H acidic site appears in the α position. The mechanism of nucleophilic addition is realized by the electrophilic centre.

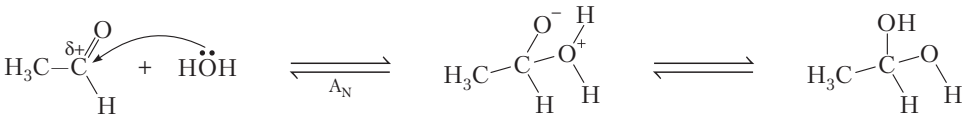
The rate of nucleophilic addition ($A_N$) depends on the electrophility of the carbon atom in a carbonyl group and the spatial accessibility of the electrophilic centre. Ketones are less reactive in $A_N$ reactions because the positive inductive effect of hydrocarbon substituents reduces the electrophility of the carbonyl carbon atom.



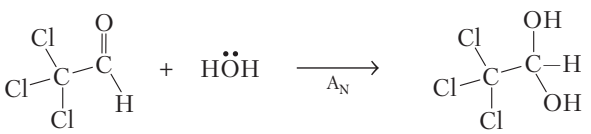

Moreover, hydrophobic radicals create a steric hindrance for a nucleophile to attack the electrophilic centre.

## 7.3. Nucleophilic addition reactions

Aldehydes and ketones react with water. In most cases, the reaction is reversible. The geminal diol of trichloroethanal (chloral hydrate) is stable. It is used as a sedative-hypnotic in medicine.

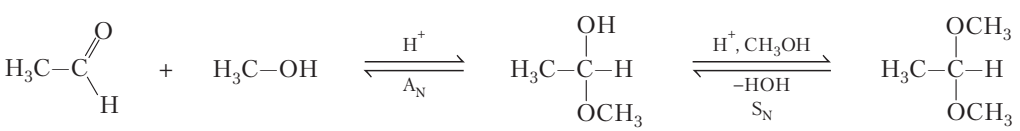


gem-diol



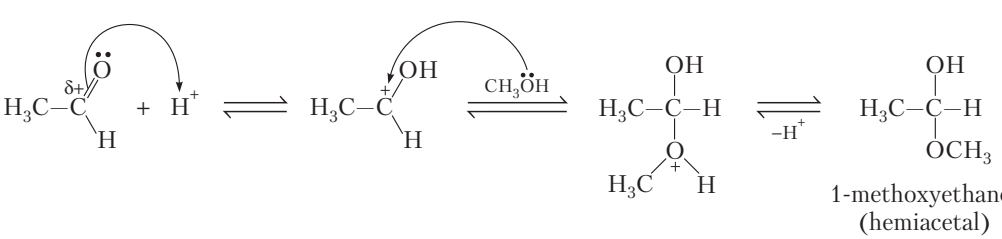
chloral hydrate

The reaction of aldehydes and ketones with alcohols is called **acetalization**. The reaction proceeds through a series of stages, each of them reversible. One mole of aldehyde or ketone is capable to react either with one or two moles of alcohol. An addition product of one molecule of alcohol is called ***hemiacetal***. The interaction of the carbonyl compound with two moles of alcohol results in the formation of an ***acetal***.



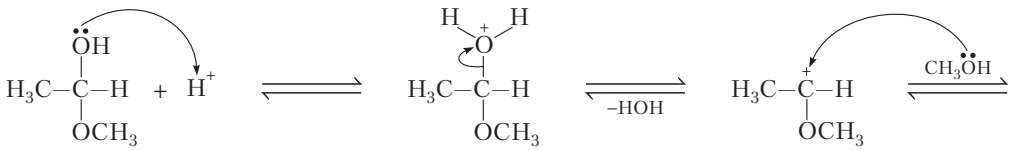
ethanal hemiacetal acetal

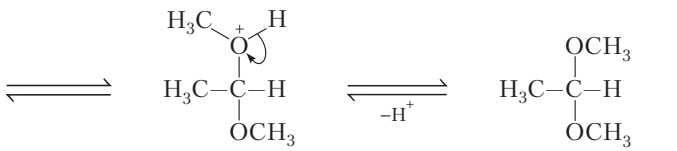
The reaction starts with the addition of a proton to the oxygen atom of the carbonyl group (basic centre). As a result, a partial positive charge on the electrophilic centre turns into the full charge. Then, the alcohol being a nucleophile, attacks the carbonyl carbon atom.



1-methoxyethanol (hemiacetal)

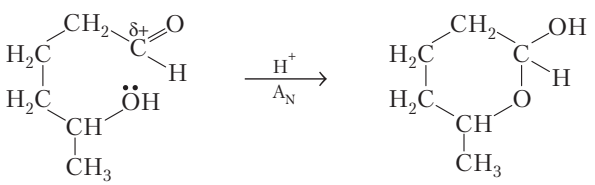
The hemiacetal formed contains a hydroxyl group. The latter can be eliminated easily in the form of water under acidic catalysis. The carbocation formed adds another molecule of alcohol, to eventually form an acetal.




1,1-dimethoxyethane
(acetal)

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

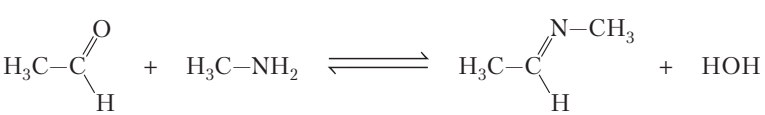



5-hydroxyhexanal

cyclic hemiacetal
of 5-hydroxyhexanal

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

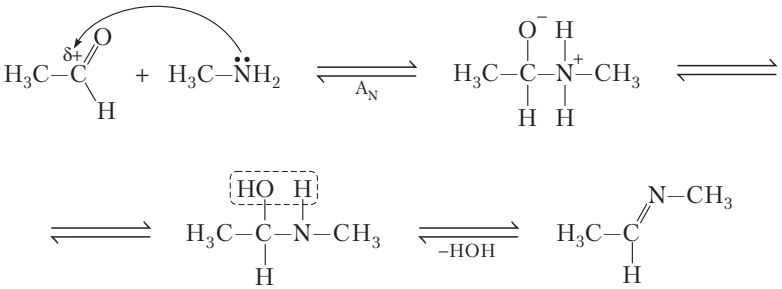
Aldehydes and ketones react with amines to form imines (Schiff bases).



imine

The reaction is impossible in the presence of acids because amines are strong bases and form salts and hence lose their nucleophilic properties. However, amines being strong nucleophiles can attack the carbon in the carbonyl group (electro-

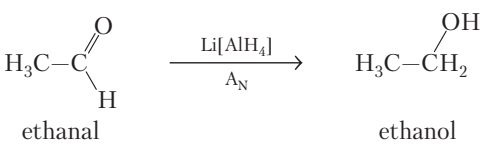
philic centre) directly to break the π bond and to form an amino alcohol. The latter eliminate the water to form an imine.



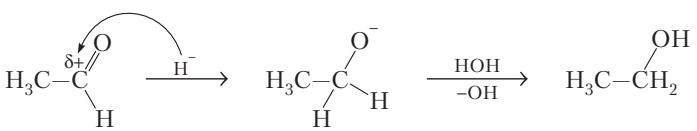
The reaction of carbonyl compounds with amines underlies many physiological and pathological processes. For example, the disinfecting action of such aldehydes as formaldehyde and glutaraldehyde can be explained by their reaction with amino groups of proteins. This process leads to denaturation, and destruction of microorganisms.

Reduction of carbonyl compounds can also occur by the mechanism of nucleophilic addition. The reaction takes place with the participation of the hydride ion $H^-$, which is a nucleophile.

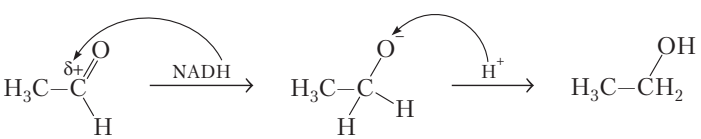
$LiAlH_4$ and $NaBH_4$ are the reagents which are the sources of the hydride ion in the laboratory.



ethanal ethanol

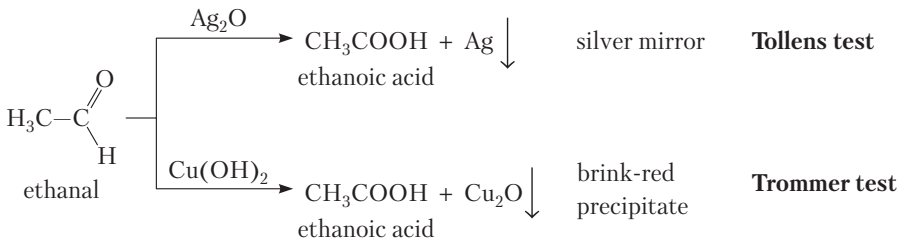


Coenzyme NADH · $H^+$ takes part in the reduction of the oxo group *in vivo*.



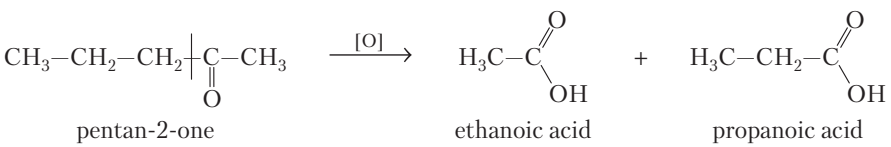
## 7.4. Oxidation of aldehydes and ketones

Aldehydes are easily oxidized to carboxylic acids by strong (potassium permanganate) and mild oxidizing agents ($Ag_2O$/heat, $Cu(OH)_2$/heat). The reactions with the latter two agents are chemical tests for aldehyde group.

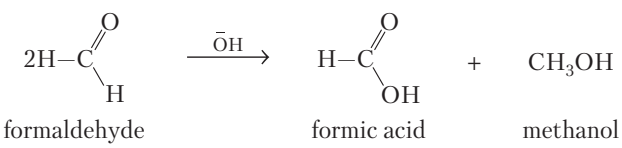



In humans, the aldehyde group can also be enzymatically oxidized to a carboxylic group.

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



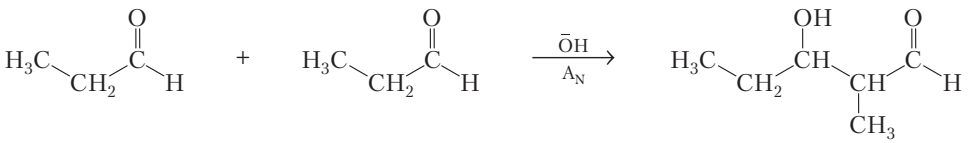

***The dismutation reaction*** (Cannizzaro reaction) is accompanied by the oxidation of one molecule of an aldehyde to a carboxylic acid and the reduction of another aldehyde molecule to an alcohol. It is typical of aldehydes which do not have a C—H acidic centre at the α position. The reaction requires alkaline conditions. Aromatic aldehydes and formaldehyde are good substrates for the Cannizzaro reactions.



## 7.5. Reactions of C—H acidic centre

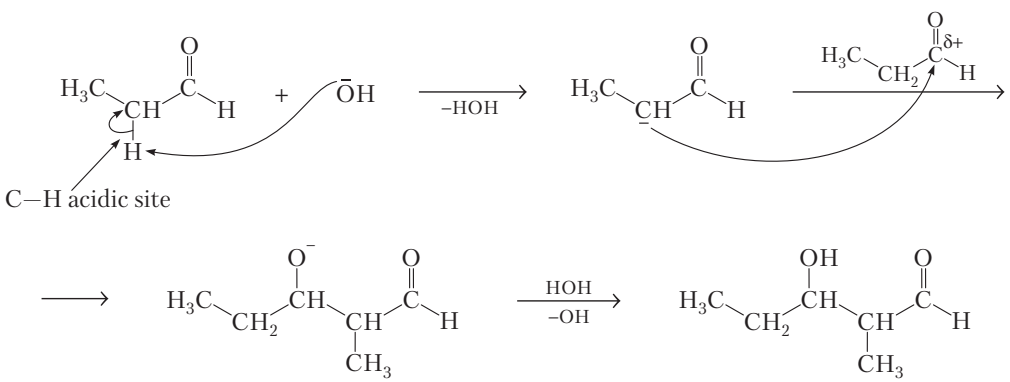
***Aldol addition*** take place when two compounds react with each other. It is typical of carbonyl compounds that have a C—H acidic centre in the α position. Aldol condensation leads to the formation of hydroxyl aldehyde, or aldol, (the name consists of *ald-* and *-ol*).

Aldol addition can be carried out under alkaline conditions *in vitro*.



propanal propanal 3-hydroxy-2-methylpentanal

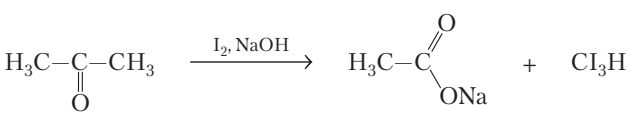
In presence of alkali one aldehyde molecule is transformed into a carbanion which is a nucleophile. The latter then reacts with another aldehyde molecule.




*In vivo*, the reaction goes in the presence of enzymes, for example in synthesis of citric acids, neuraminic acid, etc.

The retro-aldol cleavage reaction is also possible. For example, serine is an amino acid that is cleaved enzymatically to form glycine and formaldehyde.

The ***haloform reaction*** is typical of aldehydes and ketones that have hydrogen atoms at the α position. Such reaction may go in the presence of bases.



acetone iodoform

The iodoform reaction can be used for detection of acetone in biological fluids, which occurs during prolonged fasting, diabetes, etc.

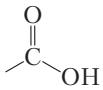
## 7.6. Important representatives

The aqueous 40 % formaldehyde solution is called ***formalin***. It is used in medicine as a disinfectant, a preservative of anatomical preparations since it has the protein denaturing properties.

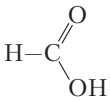
***Acetone*** is a colorless volatile flammable liquid. Acetone is miscible with water, ethanol, ether, etc., and it is a good solvent for organic compounds, for example, fats. In the human body acetone is produced and disposed of through normal metabolic processes. It is normally present in blood and urine. People with diabetes produce it in larger amounts as a result of the decompensation.

# 8. CARBOXYLIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES

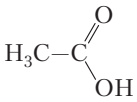
Carboxylic acids contain the carboxyl functional group —COOH.



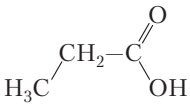
Some of them are presented below with their common (trivial) names.



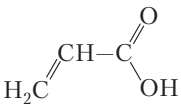
methanoic acid
(formic)



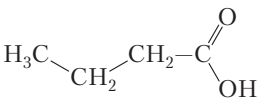
ethanoic acid
(acetic)



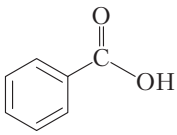
propanoic acid
(propionic)



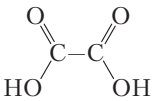
propenoic acid
(acrylic)



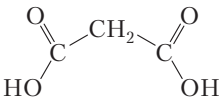
butanoic acid
(butyric)



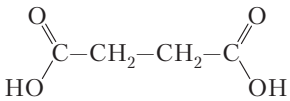
benzoic acid



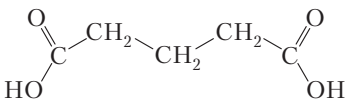
ethanedioic acid
(oxalic)



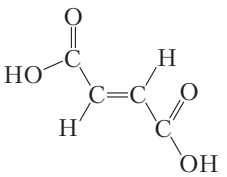
propanedioic acid
(malonic)



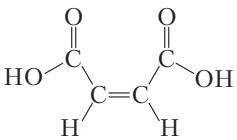
butanedioic acid
(succinic)



pentanedioic acid
(glutaric)



*trans*-butenedioic acid
(fumaric)

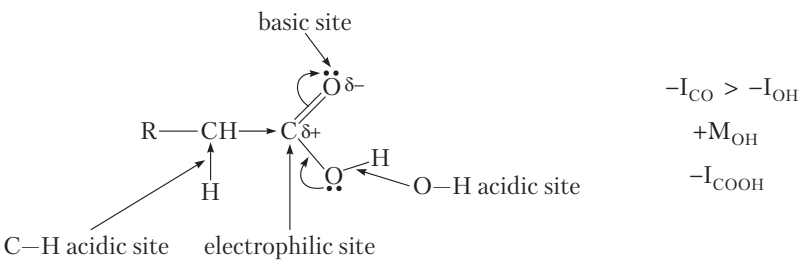


*cis*-butenedioic acid
(maleic)

Being a fragment of lipids, fatty acids with a long hydrocarbon chain are also biologically important. They will be considered in detail in Chapter 17.

## 8.1. Structure and reactivity of carboxylic acids

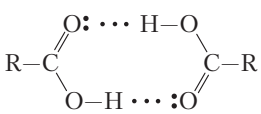
The carboxylic group is composed of the carbonyl group and the hydroxyl group. The interaction of the aforementioned groups through the inductive and mezomeric effects leads to the formation of a new functional group, the carboxylic group. The structure of the carboxylic group is planar due to the conjugation of a lone pair of electrons of the oxygen atom in the hydroxyl group and the π bond of the carbonyl group (the *p*,π conjugation). The carbonyl group has the more negative inductive effect, and so it polarizes the hydroxyl group. As a result, carboxylic acids are stronger acids than alcohols.



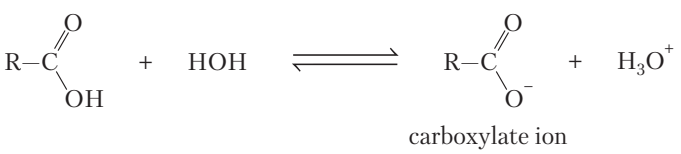

Carboxylic acids also take part in the nucleophilic substitution reaction ($S_N$) in which the hydroxyl group is replaced with a nucleophile. The *p*,π conjugation in the carboxylic group decreases the electrophility of the carbon in the carbonyl group, thus resulting in lower reactivity of acids to the attack of nucleophilic reagents.

## 8.2. Acid-base properties of carboxylic acids

Due to the co-presence of acidic and basic centres in carboxylic acids, these substances are capable of association by hydrogen bonds and normally exist in the form of dimers.

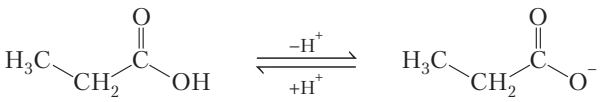



Acid ionization in a water solution leads to the formation of a carboxylate ion and a hydrated proton.

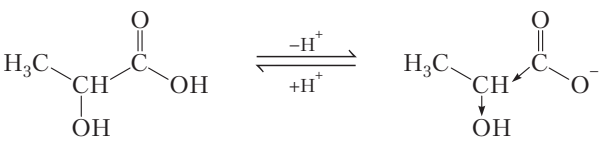


The acidity of carboxylic acid correlates with the stability of the conjugated carboxylate ion. It is stabilized due to its *p*,π conjugation; as a result, the negative charge is distributed equally between the two oxygen atoms (both the C—O bonds are equal in length).

Electron-withdrawing substituents and conjugation increase acidity. Thus, 2-hydroxypropanoic (lactic) acid is stronger than propionic acid.



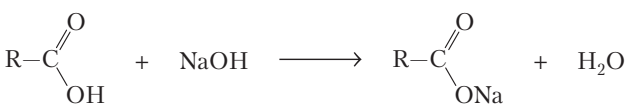
propionic acid



lactic acid

The hydroxyl group of lactic acid shifts the electronic density to itself, thereby delocalizing the negative charge and stabilizing the anion. Aromatic acids are stronger than aliphatic due to the conjugation of the former with the benzene ring.

Carboxylic acids react with bases to form salts.

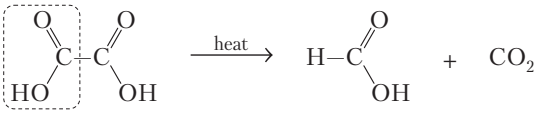


sodium carboxylate

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

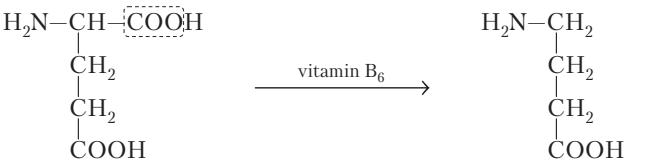
## 8.3. Decarboxylation reactions

Decarboxylation is the reaction of carbon dioxide elimination. It is typical of carboxylic acids in which the electron acceptor is in the α position to the carboxylic group. Oxalic acid and malonic acid are decarboxylated easily by heating.




oxalic acid formic acid

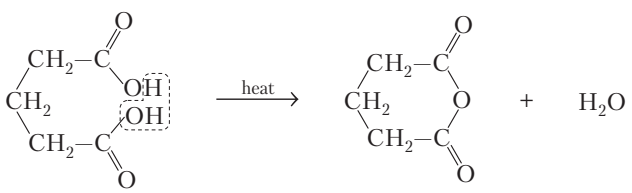
The decarboxylation reactions in biological systems proceed in the presence of decarboxylase enzymes. Products of the decarboxylation reactions of proteinogenic amino acids are called biogenic amines.




glutamic acid γ-aminobutyric acid (GABA)

## 8.4. Reaction of cyclic anhydride formation

The heating of dicarboxylic acids such as succinic and glutaric acids leads to cyclic anhydrides which form stable conformations.

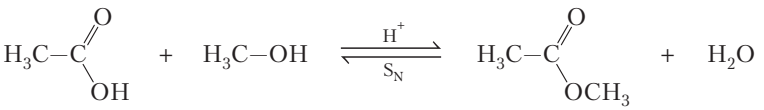



glutaric acid glutaric anhydride

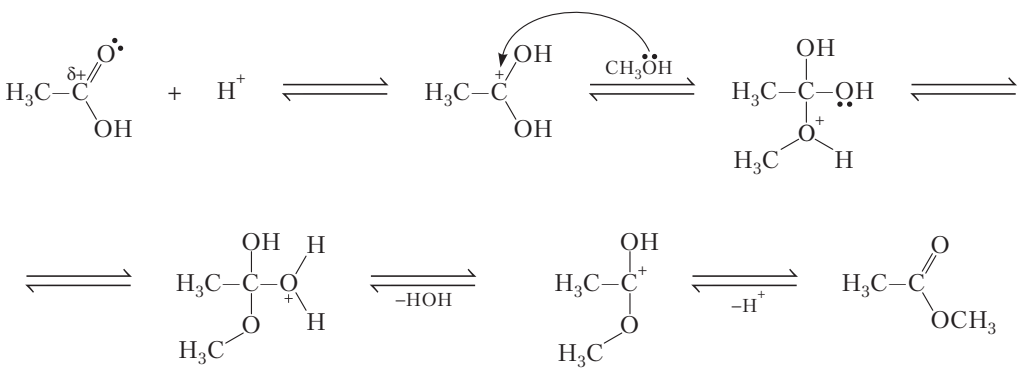
## 8.5. Nucleophilic substitution reactions

Carboxylic acids and their functional derivatives take part in the nucleophilic substitution reaction ($S_N$) in which the hydroxyl (alkoxy, amino, chloro, acyloxy) group is replaced with a nucleophile to form products with the acyl (R—C=O) fragment.

In ***acylation*** an acyl group is introduced in the compound. Therefore, carboxylic acids and their functional derivatives are ***acylating agents***. Esterification (i.e. the reaction of carboxylic acids with alcohols) is an example of acylation reactions.



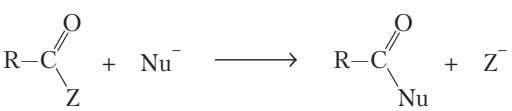

ethanoic acid — methyl ethanoate

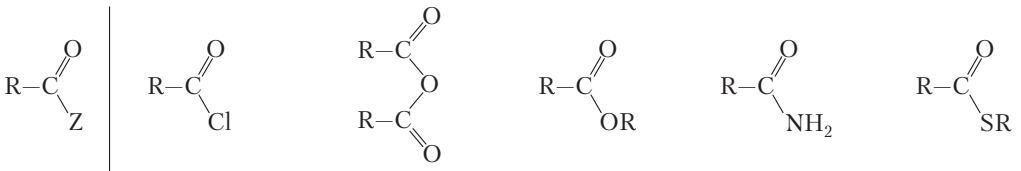



The esterification reaction is reversible. Esters easily undergo hydrolysis both in acidic and alkaline conditions. Alkaline hydrolysis is irreversible and is called saponification. This process is used to produce soaps (salts of long chain fatty acids) from fats.

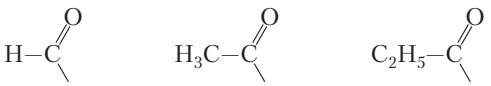

Many biologically important molecules and drugs are esters. Many of them are exposed to enzymatic hydrolysis. An ester bond is present in the neurotransmitter acetylcholine, lipids, nucleotides, coenzymes, etc.

Functional derivatives of carboxylic acids also pass acylation reactions. Acylation can be represented in general form as follows:

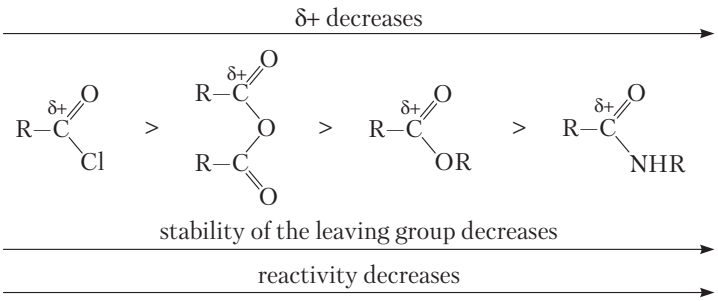




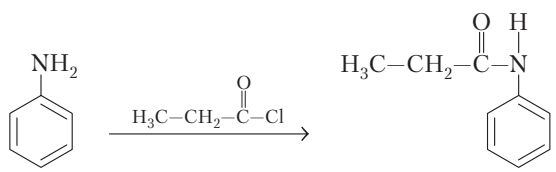

Thus, **acylation** is the transfer of an acyl residue (acetyl, formyl, etc.) to a nucleophile.




Reactivity of carboxylic acids and their derivatives in acylation reactions depends on the electrophility of the carbon in the carboxylic group and on the stability of the leaving group.



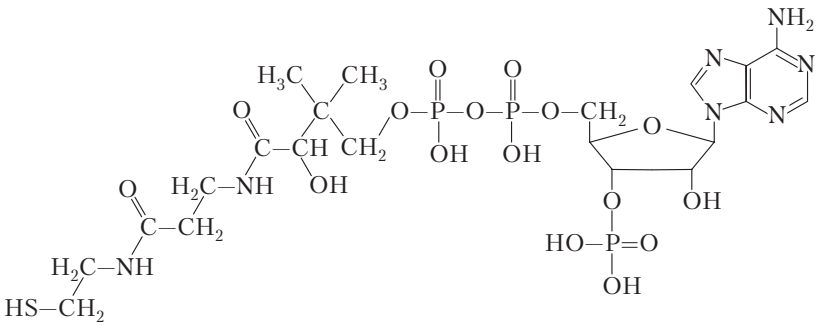

Thus, *in vitro*, acyl chlorides and anhydrides are the best acylating agents.




The acylation reactions *in vivo* mainly occur with the participation of mixed anhydrides and thioesters. Mixed anhydrides may contain fragments of carboxylic (acyl) and phosphoric acids. The acyl residue of acetic acid is called ***acetyl***.

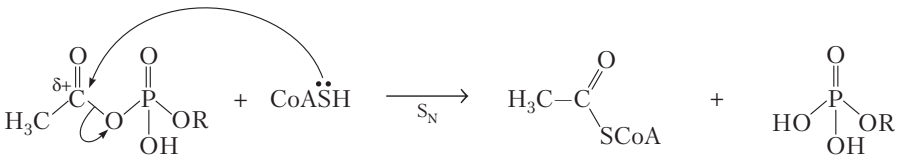

mixed anhydrides

*In vivo*, one of the most efficient acylating agents acetyl coenzyme A is formed from a mixed anhydride and coenzyme A.



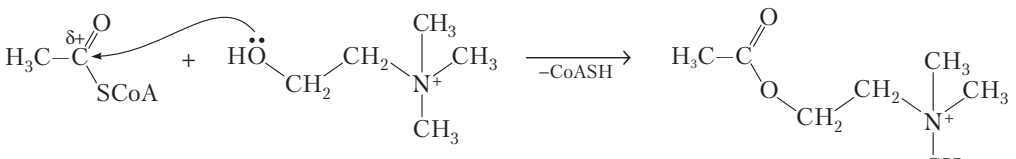
coenzyme A (CoASH)

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



coenzyme A acetyl coenzyme A

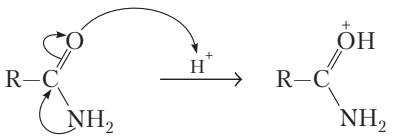
*In vivo* processes, thioesters are the most widely spread derivatives of carboxylic acid. Acetyl coenzyme is one of them. *In vivo*, acetyl coenzyme A serves as a carrier of the acetyl group (for example, in synthesis of acetylcholine).



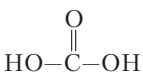
acetyl coenzyme A choline acetylcholine

Amides of carboxylic acids are the products of the substitution of the hydroxyl group in the carboxylic group with the amino or substituted amino group. Amides have very weak basic properties because of the *p*,π conjugation between lone electron pair on nitrogen and π bond of carbonyl group (positive mesomeric

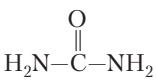
effect). Thus, amides may accept a proton only under highly acidic conditions, and mainly on their oxygen atom.




The amide bond is present in peptides and proteins. Urea is a full carbonic acid amide. It is a product of the nitrogen metabolism in humans.




carbonic acid




urea

# 9. POLY- AND HETEROFUNCTIONAL COMPOUNDS

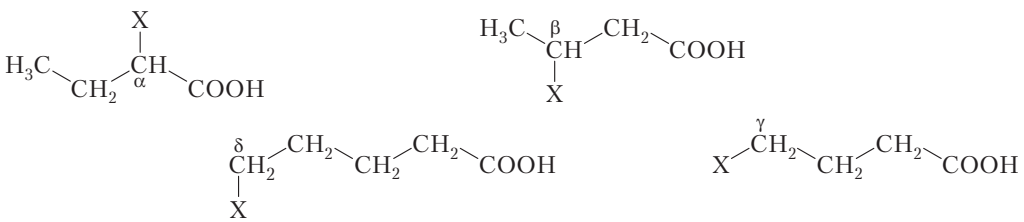
Very often biologically important organic compounds contain a few functional groups.

***Polyfunctional compounds*** contain several identical functional groups. Polyfunctional compounds include polyols, polyatomic phenols, dicarboxylic acids, etc.

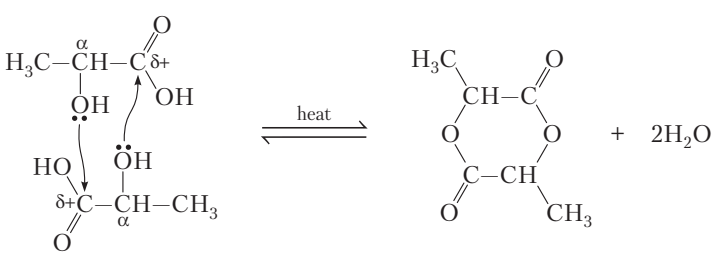
***Heterofunctional compounds*** have different functional groups in the same molecule and contain such groups as hydroxyl, amino, oxo and carboxyl and some other groups.

## 9.1. Reactivity of poly- and heterofunctional compounds

Poly- and heterofunctional compounds have their typical reactivity. Such compound may react typically of each of the groups present in it. The mutual influence of the 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 the functional groups, on the distance between them. The functional group X may be located in the α, β, γ, δ positions to the carboxyl group. When the functional groups are close to each other, their interaction influence more of their specific properties.

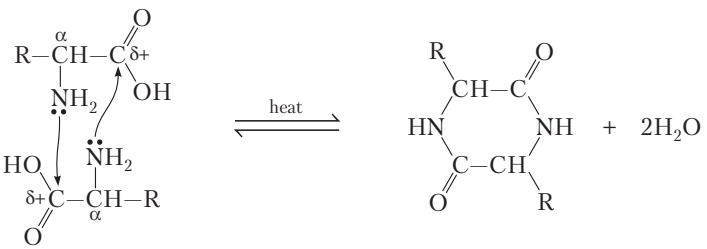


α-Hydroxy acids and α-amino acids can react intermolecularly. Lactic acid, for example, undergoes intermolecular esterification when heating. A six-membered cyclic diester (lactide) is formed.



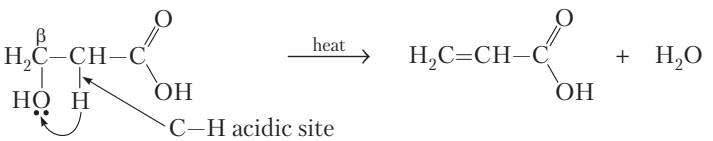

lactic acid lactide

A similar intermolecular cyclization is typical of α-amino acids. The reaction product is a cyclic diamide (diketopiperazine). Both these reactions proceed by the mechanism of nucleophilic substitution.

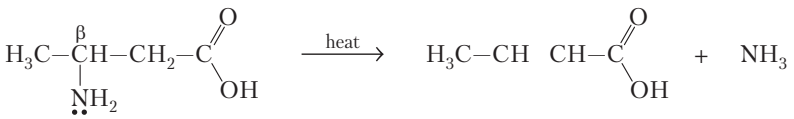



α-amino acid diketopiperazine

The elimination reactions are typical for β-hydroxy and β-amino acids to give α,β-unsaturated acids via elimination of water or ammonia, respectively.

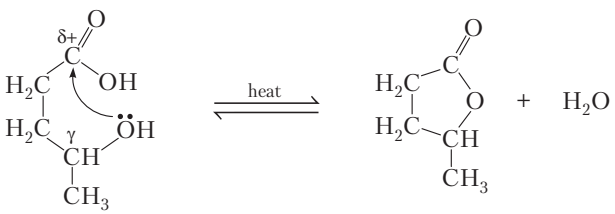



3-hydroxypropanoic acid propenoic acid




3-aminobutanoic acid but-2-enoic acid

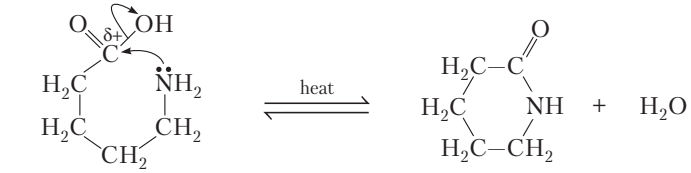
Intramolecular reactions proceed when two functional groups are spaced apart in the compound. The nucleophilic substitution reactions are typical of γ- and δ-hydroxy or amino acids. Such molecules form claw-shaped conformations to make a better contact of both functional groups. ***Lactones*** are cyclic esters which are formed in intermolecular esterification of γ- and δ-hydroxy acids.




4-hydroxypentanoic acid γ-lactone

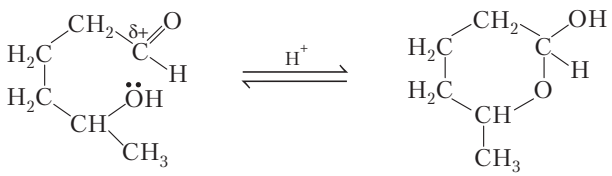
Cyclization occurs if a thermodynamically stable five- or six-membered cycle is formed.

By intermolecular cyclization of γ- and δ-amino acids ***lactams*** are formed.



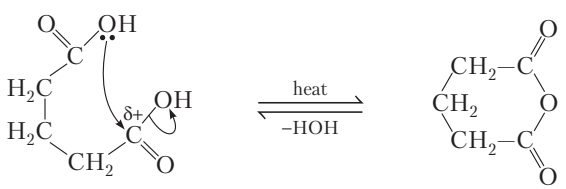

5-aminopentanoic acid δ-lactame

Hydroxylaldehydes are able to form cyclic hemiacetals by the nucleophilic addition reaction.




5-hydroxyhexanal cyclic hemiacetal of 5-hydroxyhexanal

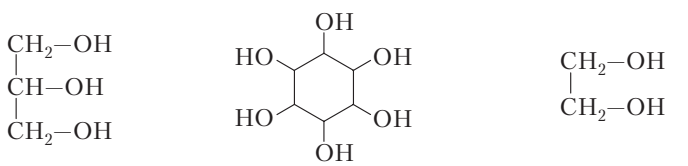
Dicarboxylic acids such as succinic and glutaric acids are also capable of forming cyclic anhydrides.




glutaric acid glutaric anhydride

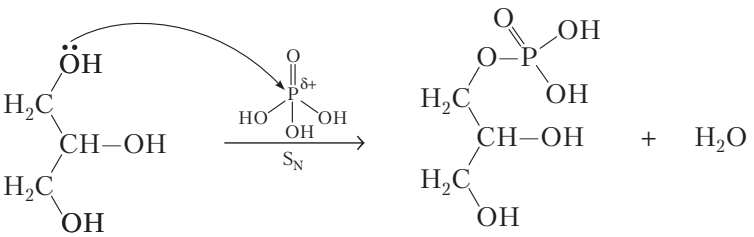
## 9.2. Representatives of biologically important classes of poly- and heterofunctional compounds

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



glycerol inositol ethylene glycol

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

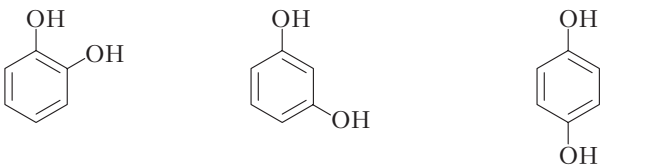



α-glycerophosphate

Ethylene glycol is highly toxic for humans. It is used in the production of antifreeze.

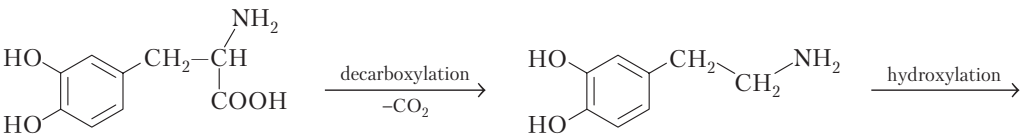
***Dicarboxylic acids***, such as oxalic, malonic, succinic, glutaric, fumaric, contain two carboxylic groups (their formulas are presented in Chapter 8). Oxalic acid and oxalates are abundant in plants. In humans, the insoluble calcium oxalate may be formed and deposited in kidneys in the form of nephroliths (kidney stones). Malonic, succinic, glutaric and fumaric acids participate in 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, epinephrine and norepinephrine) which are synthesized from tyrosine by decarboxylation, hydroxylation and methylation. These substances are also known as remedies stimulating adrenoreceptors.

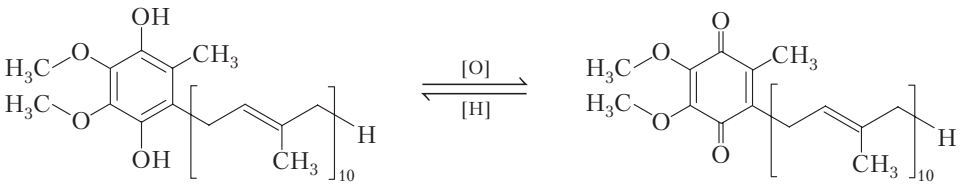



3,4-dihydroxyphenylalanine (DOPA) dopamine


noradrenaline, or norepinephrine adrenaline, or epinephrine

Resorcinol shows an antiseptic effect, and is used as a component of hygiene products.

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

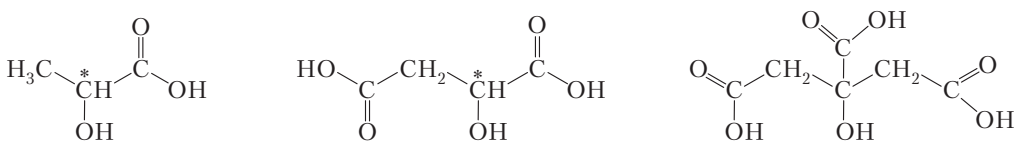



coenzyme QH coenzyme Q

Ethanolamine and choline represent the group of ***amino alcohols***. They are involved in the construction of lipids.


ethanolamine choline

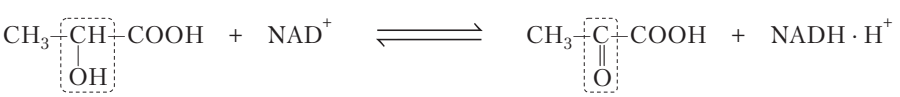
Lactic, malic and citric acids are biologically important ***hydroxy acids***. Their trivial names are widely used in medicine and biology. Their carboxyl group has an ionized form at physiological pH levels, and various compounds having a carboxyl group are often referred to in relation with the name of their salts.



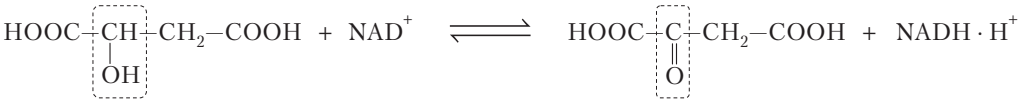

lactic acid, or lactate malic acid, or malate citric acid, or citrate

Lactic acid and malic acid are chiral compounds. They are found in humans only in the form of L-enantiomers. In humans L-lactate is produced from pyruvate via the process of enzymatic fermentation during normal metabolism. Industrially, lactic acid fermentation is performed by *Lactobacillus bacteria*. These bacteria can operate in the mouth; the acid they produce is the cause of dental caries. Citric and L-malic acids are participants of the citric acid cycle (known as the Krebs cycle).

In human cells, lactic and malic acids are oxidized with the coenzyme $NAD^+$ to form the respective oxo acids (enzymatically).

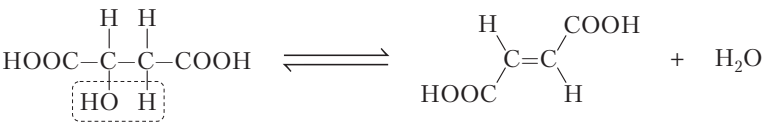



lactate pyruvate



malate oxaloacetate

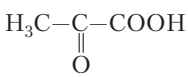
Malic acid is able to proceed dehydration. This reaction takes place in the Krebs cycle.



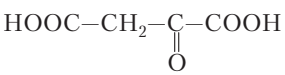
malic acid fumaric acid

Citric acid has three carboxyl groups. It is capable of binding multivalent ions, e.g. calcium. That is why sodium citrate is used for blood conservation. This compound binds calcium ions of blood plasma, so blood does not clot.

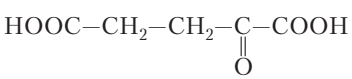
Pyruvic acid, oxaloacetic acid, α-ketoglutaric acid, acetoacetic acid are biologically important ***oxo acids***.



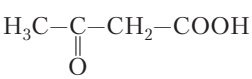
pyruvic acid, or pyruvate



oxaloacetic acid, or oxaloacetate

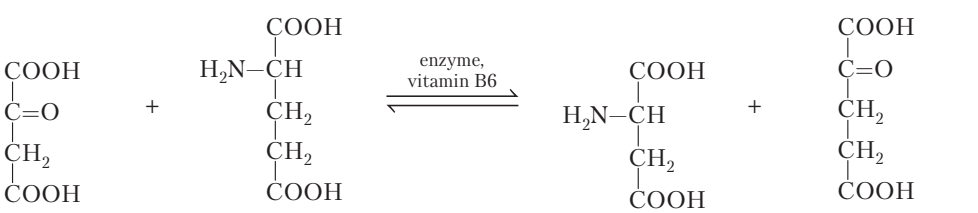


α-ketoglutaric acid



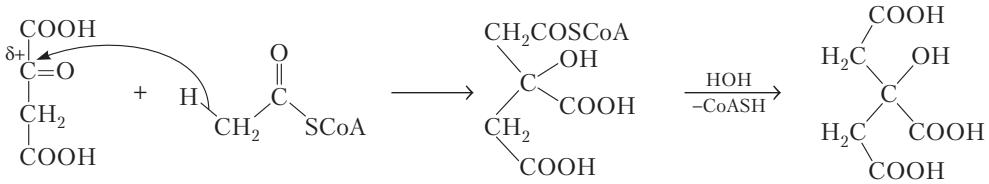
acetoacetic acid

The **transamination** type of reactions is typical for oxo acids *in vivo*. These reversible reactions include the exchange of their functional groups on the α carbon atom between the oxo acid and the amino acid.



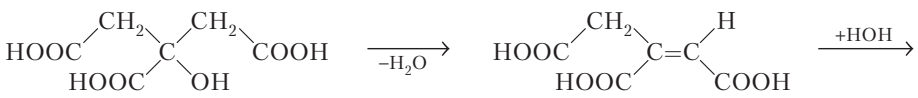

oxaloacetic acid L-glutamic acid L-aspartic acid α-ketoglutaric acid

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

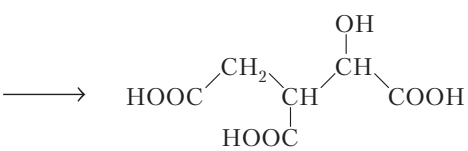



oxaloacetic acid acetylcoenzyme A citric acid

Citric acid can eliminate water to form *cis*-aconitic acid. Then the hydration reaction proceeds with the formation of the citric acid isomer. These reactions occur in the Krebs cycle.

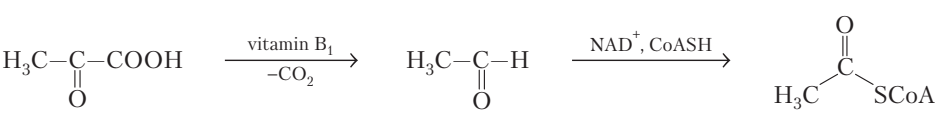



citric acid *cis*-aconitic acid




isocitric acid

Decarboxylation plays an essential role in metabolic processes. Oxo and amino acids are enzymatically decarboxylated *in vivo*. Oxidative decarboxylation of pyruvic acid leads to the formation of acetyl coenzyme A.




pyruvic acid acetaldehyde 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.


acetone acetoacetic acid β-hydroxybutyric acid

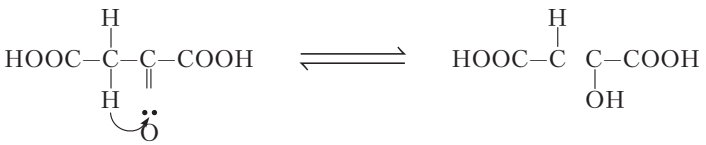
Ketone bodies are used as a source of energy in the heart and brain. In the brain, they are a vital source of energy during starvation.

***Amino acids*** will be discussed in Chapter 14.

## 9.3. Tautomerism

**Tautomerism** is a dynamic isomerism in which isomers can be transformed into each other, being present in a solution in a state of dynamic equilibrium. In many cases tautomerization is accompanied by migration of a proton. This is called prototropic tautomerism. There are several types of prototropic tautomerism. ***Keto-enol tautomerism*** is more typical of compounds that have a strong C—H acidic site and an 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 more stable tautomer is predominant. Tautomerism can play an important role in biochemistry.

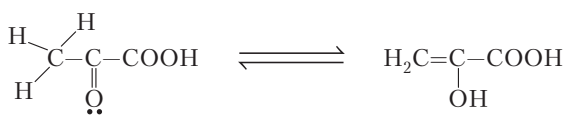
Oxaloacetic acid is one of the most important carboxylic acid in many biochemical processes. Despite its common name that corresponds to an oxo acid, this compound is a rather an unsaturated acid because of the predominance of the enol form in the tautomeric equilibrium (80 %).




keto form enol form

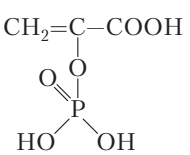
oxaloacetic acid

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 its 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

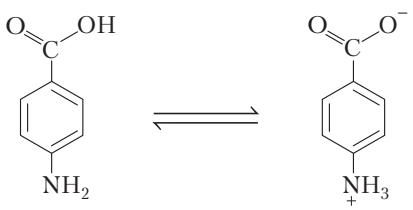
Cyclic amides known as lactams are also characterized by tautomerism, which is called ***lactam-lactim tautomerism***.

γ-lactam of 4-aminobutanoic acid

γ-lactim of 4-aminobutanoic acid

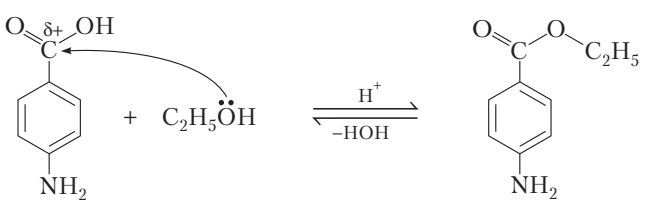
## 9.4. Heterofunctional compounds containing benzene ring

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



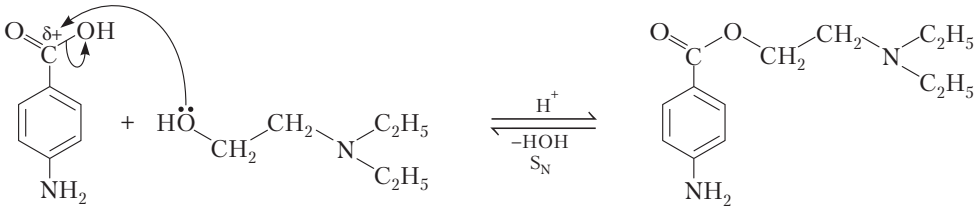
*p*-aminobenzoic acid

*p*-Aminobenzoic acid is also used in synthesis of local anesthetics. The first obtained synthetic anesthetic bensocaine (Anesthesine) has been used for more than a hundred years. Procaine (as a hydrochloric salt) is more effective and widely used nowadays.



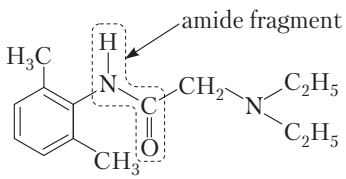
*p*-aminobenzoic acid

benzocaine



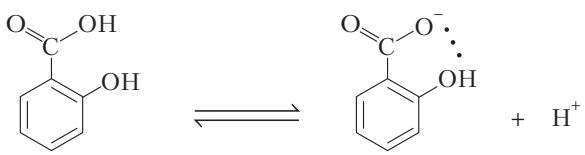
*p*-aminobenzoic acid procaine

Amide derivatives contain the amide bond which is more stable to hydrolysis and hence can be used for prolonged anesthetic action. Lidocain, Ultracain are widely used and are characterized by a rapid onset of action and medium- to long-time effects.



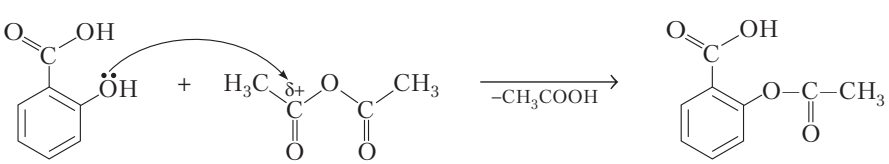

lidocaine

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



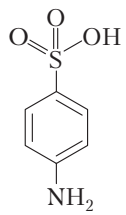
salicylic acid

Salicylic acid forms esters in 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 anti-inflammatory medication. It also shows the antiplatelet effect.

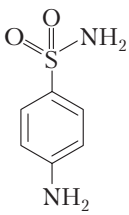


salicylic acid acetic anhydride acetylsalicylic acid

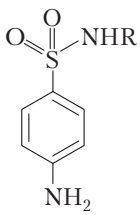
Sulfa drugs (sulfonamides) are derivatives of sulfanilic acid. They exhibit antibacterial activity.




sulfanilic acid




sulfanilamide




general formula of sulfa drugs

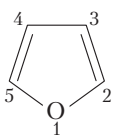
In bacteria, sulfonamides inhibit the synthesis of folate (vitamin $B_9$, or $B_c$) because the sulfonamide molecule is isosteric to the molecule of *p*-aminobenzoic acid, which is necessary for the synthesis of filate. Folate is necessary for the cell to synthesize nucleic acids, and in its absence cells are unable to divide. Hence, the sulfa drugs exhibit a bacteriostatic effect. Folate is not synthesized in mammalian cells. This explains the selective toxicity of these medications to bacterial cells.

# 10. BIOLOGICALLY IMPORTANT HETEROCYCLIC COMPOUNDS. ALKALOIDS

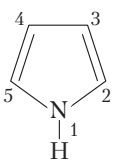
Heterocyclic compounds are cyclic organic compounds that have atoms of at least two different elements in their molecular ring (i.e. one element is other than carbon).

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

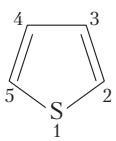
**Five-membered heterocycles**



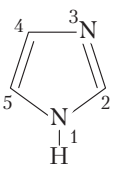

furan



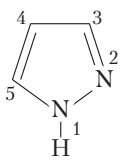

pyrrole



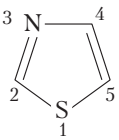

thiophene



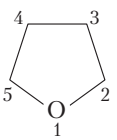

imidazole



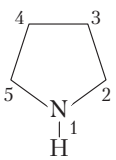

pyrazole




thiazole

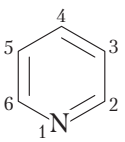



tetrahydrofuran

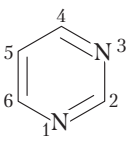



pyrrolidine

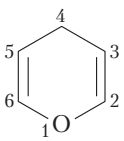
**Six-membered heterocycles**



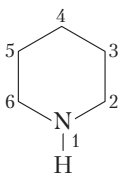

pyridine




pyrimidine



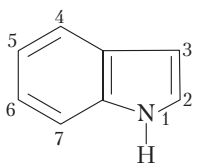

pyran



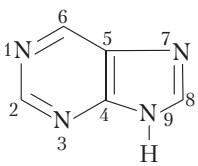

piperidine

This group of compounds, according to their electronic structure, is divided into saturated, unsaturated and aromatic heterocycles.

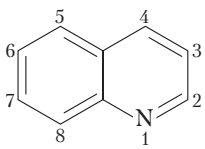
Fused heterocycles are often found in biologically important molecules.



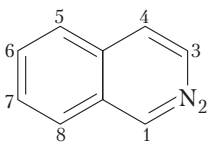

indole




purine



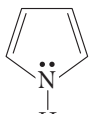

quinoline




isoquinoline

## 10.1. Representatives of heterocyclic compounds

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



pyrrole

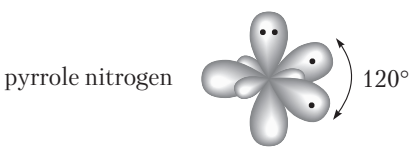
$_7$N $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^1$

electronic configuration of the ground state N

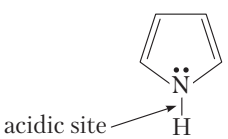
$1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1$

electronic configuration of the exited state N

The electron orbitals of the excited nitrogen atom undergo $sp^2$ hybridization. Three hybrid orbitals (of the same energy and form) bear 1 electron; they lie in one plane. The unhybridized $p_z$ orbital has a pair of electrons and it is perpendicular to the hybride orbital plane.

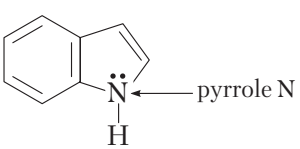



The electron pair of the nitrogen atom takes part in the formation of a cyclic conjugation. Pyrrole is an aromatic compound because all atoms in the cycle are $sp^2$-hybridized, so the molecule has a cyclic conjugated system (π,π,*p*) and six electrons participate in the conjugation ($4n + 2 = 6$, $n = 1$).



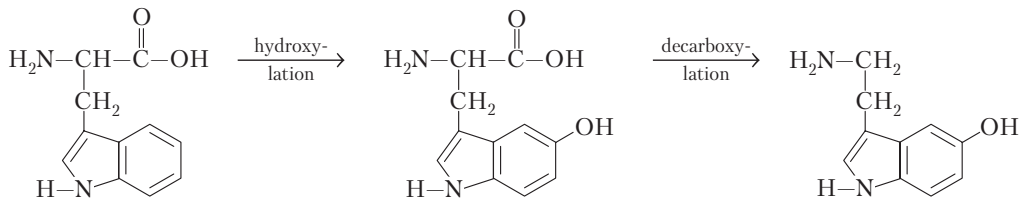

Pyrrole is a π-excessive system because six *p* electrons belong to its five-membered ring. Therefore, pyrrole comes into reactions of electrophilic substitution easier than benzene. Pyrrole does not exhibit the properties of a basic; rather, it is a weak N—H acid.

***Indole*** also contains a pyrrole nitrogen atom.

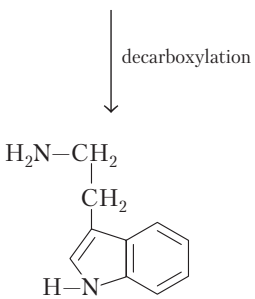


indole

Amino acid tryptophan and biogenic amines serotonin and tryptamine contain the indole ring structure. The indole fragment is also a part of some pharmaceutical drugs.

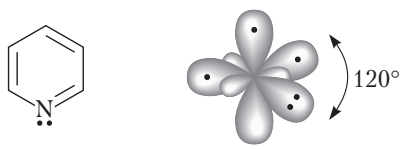



tryptophane 5-hydroxytryptophane serotonin




tryptamine

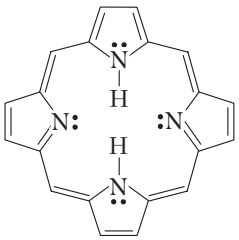
***Pyridine*** is a nitrogen-containing six-membered aromatic cycle. The structure of the pyridine nitrogen atom is different from the pyrrole nitrogen (see Chapter 2).



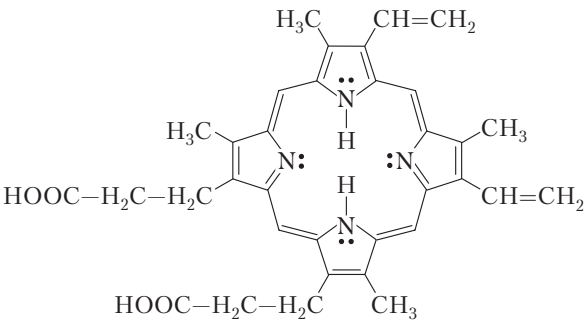

pyridine pyridine nitrogen

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

Compounds containing more than one pyrrole ring are widespread in nature (e.g., porphine). Porphines, if partially or completely substituted in the pyrrole ring, are called ***porphyrins***. Protoporphyrin, a representative of porphyrins, is shown in the figure below.



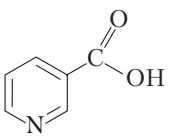
porphine



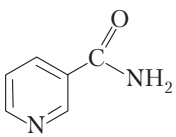
protoporphyrin

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

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

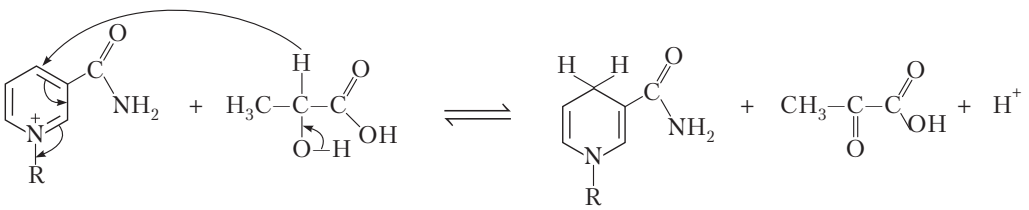


nicotinic acid



nicotinamide

*In vivo*, nicotinamide transfers a hydride ion (as a part of coenzyme $NAD^+$).

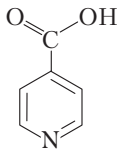


$NAD^+$ lactate NADH pyruvate

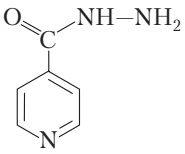
For example, coenzyme $NAD^+$ adds a hydride ion from nicotinamide at the γ position during oxidation of lactic acid. Coenzyme $NAD^+$ is converted to its reduced form NADH. The cycle of pyridine loses aromaticity. Lactic acid is converted into pyruvic acid. The reaction is reversible.

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 acid is the base

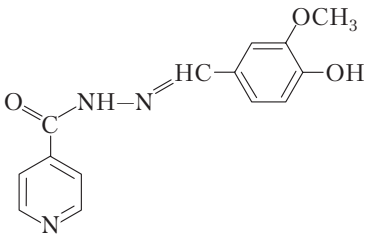
for the synthesis of antituberculosis medicines. Isoniazid and Phthivazid (Phthivazidum) are first-line antituberculous medications used in the prevention and treatment of tuberculosis.



Isonicotinic acid

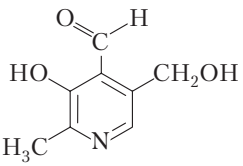


Isoniazid

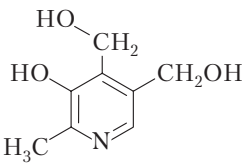


Phthivazid

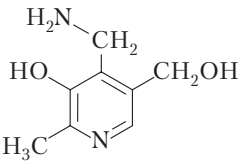
Pyridine is a part of vitamin $B_6$. There are several different forms of vitamin $B_6$. Pyridoxal phosphate is the metabolically active form.



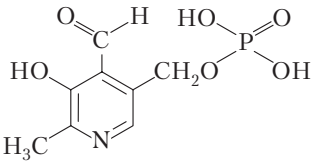
pyridoxal



pyridoxol



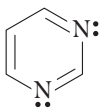
pyridoxamine



pyridoxal phosphate

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

***Pyrimidine*** has two pyridine nitrogen atoms, both of them being the basic centres. Since the nitrogen atoms produce the electron acceptor action on each other, the basic properties of pyrimidine are weaker than those of pyridine.

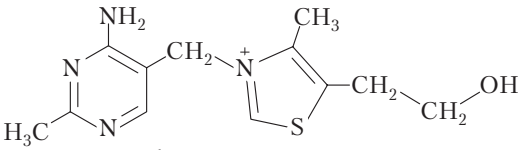


pyrimidine

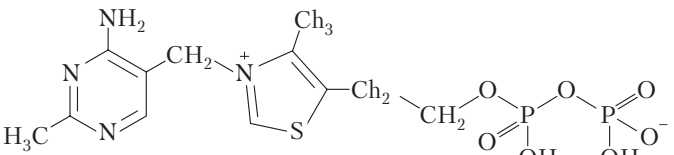
Pyrimidine underlies the nucleic bases, as it forms parts of the DNA and the RNAs (uracil, cytosine, thymine). They will be covered further, in Chapter 16.

Pyrimidine is part of thiamine (vitamin $B_1$). Thiamine is involved in decarboxylation of α-oxo acid. Thiamine diphosphate is the metabolically active

form of vitamin $B_1$. It is formed by the phosphorylation reaction of the alcohol group.

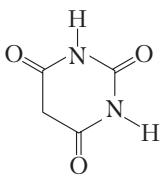


thiamine (vitamin $B_1$)



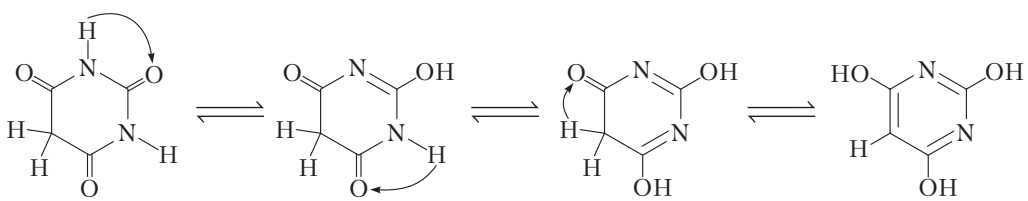
thiamine diphosphate

Barbituric acid is a pyrimidine derivative.

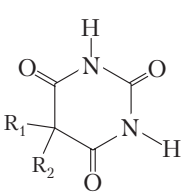


barbituric acid

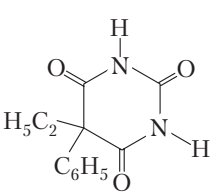
It exists in several tautomeric forms. Two types of tautomers are typical of barbituric acid: the lactime-lactam and the keto-enol. Mutual transformations from one form to another are shown by arrows.



Barbituric acid is the parent compound of a large class of barbiturates that show depressant properties on the central nervous system, although barbituric acid itself is pharmacologically inactive.

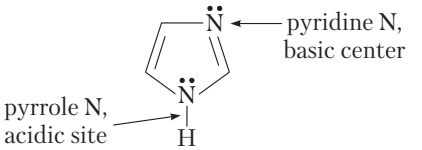


the general formula
of barbituric acid derivatives

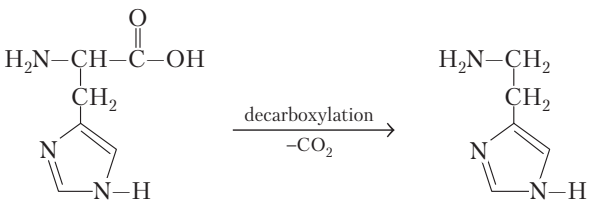


phenobarbital

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

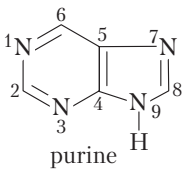



Due to its amphoteric properties, imidazole is involved in the transfer of a proton (the acid-base catalysis). It is part of many biologically important compounds. Histamine, for instance, is formed from histidine by decarboxylation reactions in eosinophils and basophils. In the body, histamine participates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



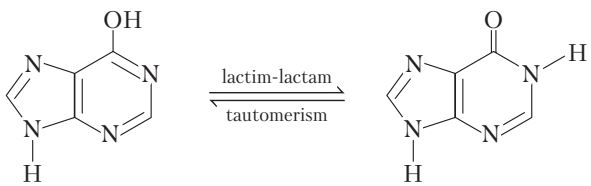

histidine histamine

***Purine*** consists of two fused rings: pyrimidine and imidazole. Purine is 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 the metabolism of purine bases.

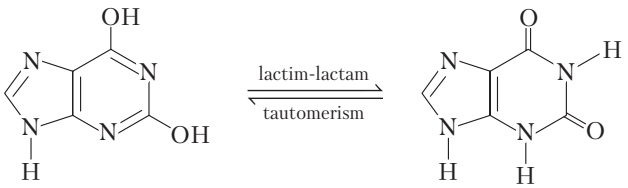


purine

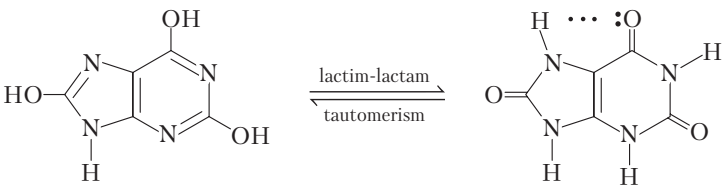
Adenine and guanine are purine bases; their roles will be discussed in the course of nucleotide chemistry, in Chapter 16. Hypoxanthine, xanthine and uric acid are products of purine base degradation *in vivo*. The lactam form is the most stable of all the tautomeric forms shown in the scheme below.




6-hydroxypurine (hypoxanthine)

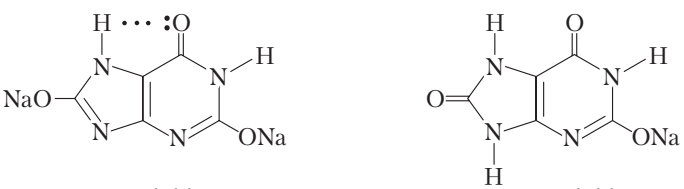



2,6-dihydroxypurine (xanthine)




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 of the antioxidant capacity of plasma comes from uric acid. Uric acid is a diprotic acid. It forms two series of salts (urates).




soluble unsoluble

In a strong alkali, at high pH, it forms a full urate diion, but at biological pH values, it forms the singly-charged hydrogen urate or an acid urate ion. The low solubility of urates is essential in the etiology of gout and some other diseases when insoluble urate stones are formed.

## 10.2. Alkaloids

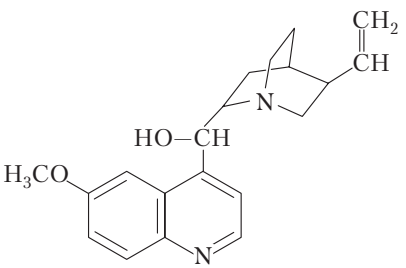
Alkaloids are natural chemical compounds containing basic nitrogen atoms. The name derives from the word *alkaline*. The latter name was introduced in 1819 by Carl Weisner, a German chemist (pharmaceutist), and it had derived from late Latin root *alkali* (which, in turn, comes from the Arabic *al-qalwī* ("ashes of plants"), and the greek suffix -οειδής meaning "like"). Alkaloids are produced by a wide variety of organisms, including plants, bacteria, fungi. They are part of natural products (also called secondary metabolites). Many alkaloids are toxic to other organisms. They often show pharmacological effects and are used as medications

and recreational drugs. The examples are cocaine (a local anesthetic and stimulant), caffeine and nicotine (stimulants), morphine (an analgesic), quinine (an antimalarial medication). Some alkaloids taste bitter.

There are several classifications of alkaloids, including the botanical and chemical approaches. The chemical classification of alkaloids is based on the names of parent heterocycles. There are the following groups of alcaloids: pyridine, pyrrolidine, tropane, isoquinoline, the indole group, the purine group, xanthine, etc.

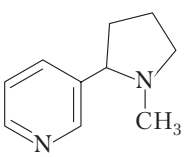
The basicity of alkaloids depends on the lone pairs of electrons on their nitrogen atoms. As organic bases, alkaloids form salts in reactions with mineral acids such as hydrochloric acid and sulfuric acid and organic acids such as tartaric acid or maleic acid. These salts are usually more water-soluble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

***Quinine*** has been isolated from the bark of the cinchona tree. This alkaloid has antipyretic properties, 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 of other plants of the nightshade (*Solanaceae* family). Nicotine refers to the group of pyridine and pyrrolidine.

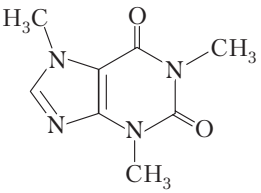


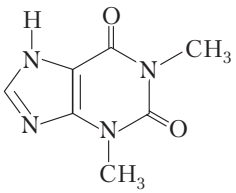

nicotine

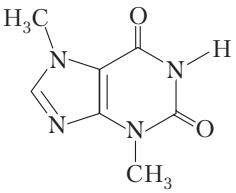
In low concentrations (e.g., an average cigarette yields about 1 mg of absorbed nicotine), the substance acts as a stimulant in mammals and is one of the main factors responsible for the dependence of tobacco. Nicotine acts on the nicotinic acetylcholine receptors.

***Caffeine*** is a bitter white crystalline xanthine alkaloid that acts as a psychoactive stimulant and a mild diuretic in humans. Caffeine is found in varying quantities in beans, leaves and fruit of more than 60 plant species. The most commonly used caffeine-containing plants are coffee, tea, and to a lesser extent cocoa. These plants also contain other alkaloids that belong to the xanthine group, viz.,

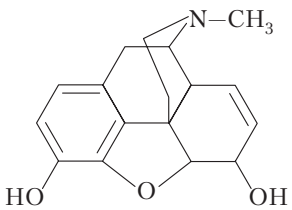
theophylline and theobromine. The xanthine alkaloids act on the purine receptors in humans.


caffeine


theophylline

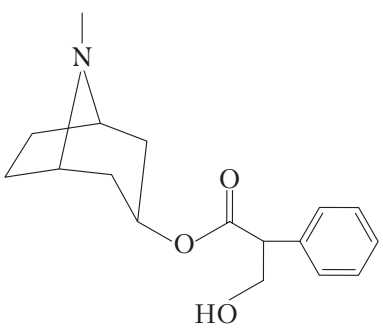

theobromine

***Morphine*** is an alkaloid of the opium poppy. It belongs to the phenanthrene and isoquinoline group. It has an analgesic effect and therefore, it is used in medicine. Morphine exerts a narcotic action and is referred to as 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 which is extracted from the deadly nightshade (*Atropa belladonna*) and other plants of the *Solanaceae* family.


atropine

It is a secondary metabolite of these plants and it 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 agent.

# 11. ORGANIC COMPOUNDS USED IN DENTISTRY

Organic compounds used in dentistry include primarily polymers. **Polymers** are substances that consist of large molecules called macromolecules that consist of many repeating units. **Monomers** are compounds with low molecular weight from which polymers are formed. Polymers are produced in polymerization reactions.

## 11.1. Classification of polymers

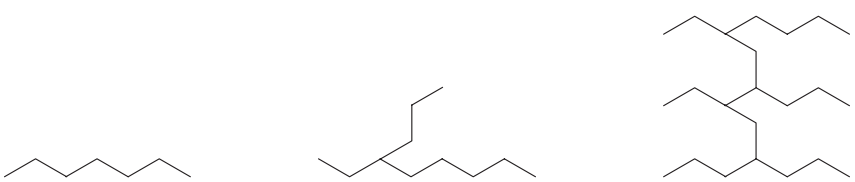
1. According to the origin: ***natural*** and ***synthetic*.**

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

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

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

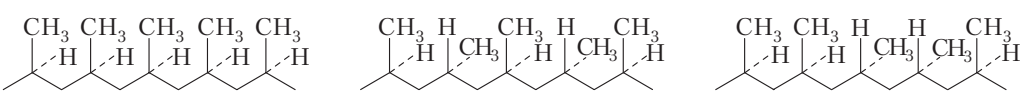
3. According to the structure of the macromolecule: ***linear***, ***branched*** and ***spatial*** (or ***cross-linked***, or ***3D***).



linear branched spatial

For example, polyethylene has a linear structure. Amylopectin as a component of starch is a branched polymer. Polymerization of certain monomers leads to the formation of two- or three-dimensional structures called spatial or cross-linked polymers.

4. According to tacticity (spatial regularity) of the macromolecule chain: ***isotactic***, ***syndiotactic*** and ***atactic***.



isotactic syndiotactic atactic

An isotactic polymer arranges all substituents on the same side of the polymer chain (the chain appears a zigzag). A syndiotactic polymer arranges substituents

regularly on the alternating sides of the zigzag chain. An atactic polymer has its substituents bonded arranged randomly on the chain.

5. In relation to heating, polymers are divided into ***thermoplastic*** and ***thermosetting*** types.

Thermoplastic materials can be repeatedly heated and cooled. Thus, they do not lose their properties and form. Most of 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 the shape previously taken. Most of thermosetting materials have a network structure. Thermosetting polymers are used in the production of household articles.

## 11.2. Types of polymerization reactions

There are two types of polymerization possible: chain polymerization and step polymerization.

***Chain polymerization*** is a sequential addition of each monomer unit to the active site located at the end of the growing chain. The monomer type of structure has a double bond.

$$\underset{\text{monomer}}{n\mathrm{CH_2{=}CH_2}} \longrightarrow \underset{\text{polymer}}{\text{-}[\mathrm{CH_2{-}CH_2}]_n\text{-}}$$

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 the reaction. The anionic and cationic types of 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 of the initiators. Compounds containing nonpolar bonds (peroxides, azo or diazo compounds) are prone to disintegration and formation of homolytic radicals.

The mechanism of polymerization involves several steps: initiation, propagation and termination.

*Initiation*:

$$\underset{\text{initiator}}{\mathrm{I}_n{-}\mathrm{I}_n} \xrightarrow{\text{heating, light or activator}} \underset{\text{free radicals}}{\mathrm{I}_n^{\bullet} + {}^{\bullet}\mathrm{I}_n}$$

$$\underset{\text{monomer}}{\mathrm{I}_n^{\bullet} + \mathrm{M}} \longrightarrow \mathrm{I}_n{-}\mathrm{M}^{\bullet}$$

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

*Propagation*:

$$I_n{-}M\bullet + M \longrightarrow I_n{-}M{-}M\bullet$$

$$I_n{-}M{-}M\bullet + M \longrightarrow I_n{-}M{-}M{-}M\bullet$$

up to $M_x$, where $x$ is the number of monomers

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

*Termination*:

$$I_n{-}M_x\bullet \quad M_x{-}I_n \longrightarrow I_n{-}M_x{-}M_x{-}I_n$$

$$I_n{-}M_x\bullet + HB \longrightarrow I_n{-}M_xH + \bullet B$$

inhibitor; stable radical

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

$$n\,\text{glucose} \longrightarrow \text{glycogen} + H_2O$$

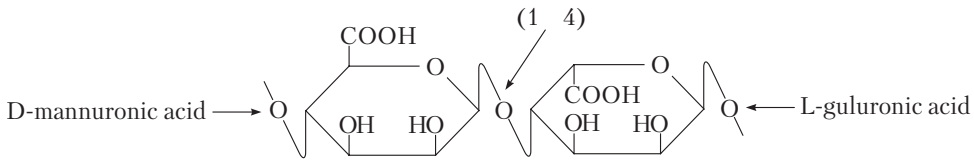
monomer; polymer

## 11.3. Polymers in medicine and dentistry

Natural and synthetic polymers are used in medicine and dentistry for:

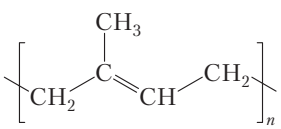
- ❒ equipment;
- ❒ filling materials (composites, adhesives);
- ❒ impression materials;
- ❒ obturation materials;
- ❒ dentures, etc.

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

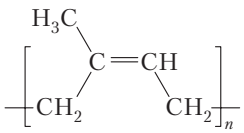



Agar-agar is a mixture of polysaccharides. One of them is agarose. Agarose is formed of alternating residues of β-D-galactopyranose and 3,6-anhydro-α-L-galactopyranose by means of the β(1-4) bond.

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




*trans*-polyisoprene (gutta-percha)

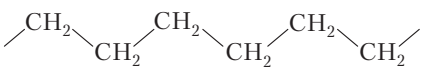
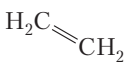
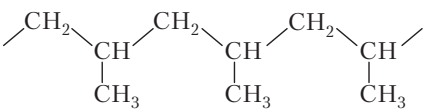
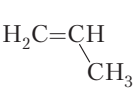
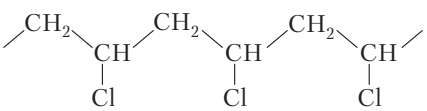
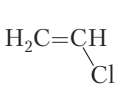


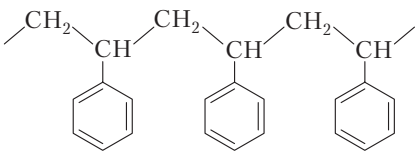
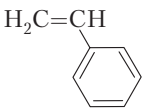
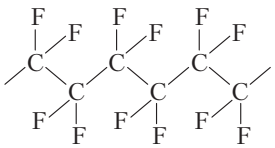
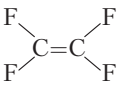
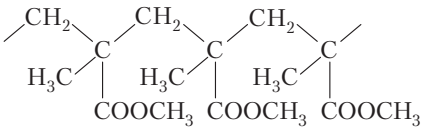
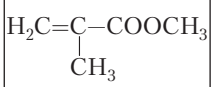

*cis*-polyisoprene (latex)

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

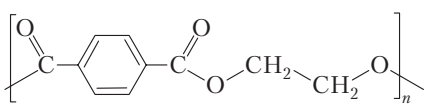
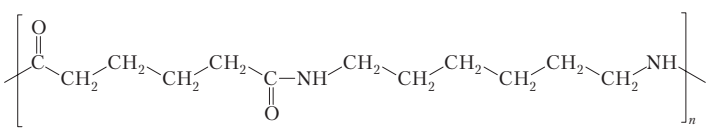
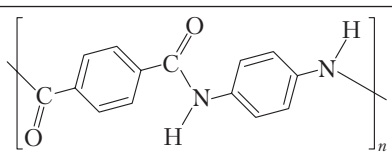
*Synthetic* polymers are found in reactions of step and chain polymerization. Examples of industrial polymers for medical purposes are presented in the Table below.

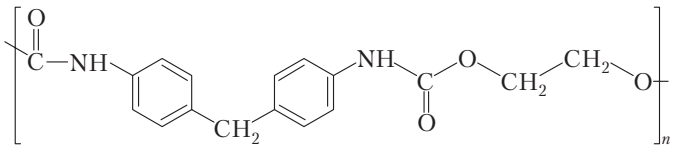
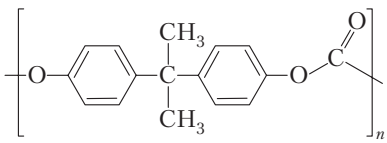
**Polymers obtained in chain polymerization reaction and used for production of medical devices**

| Name | Applying | Polymer | Monomer |
|---|---|---|---|
| Polyethylene | syringes, packaging |  |  |
| Polypropylene | syringes, surgical suture material |  |  |
| Polyvinyl chloride | packaging, backing material in dentistry |  |  |

| Name | Applying | Polymer | Monomer |
|---|---|---|---|
| Polysterene | containers for transportation and disinfection |  |  |
| Polytetrafluoroethylene | backing material in dentistry, peripheral catheters |  |  |
| Polymethyl methacrylate (PMMA) | organic glass, basis of most polymer materials in dentistry |  |  |

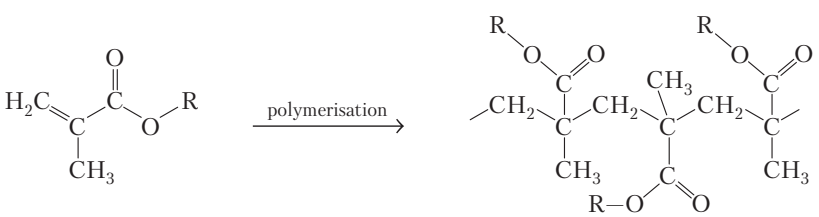
**Polymers obtained in step polymerization reaction and used for production of medical devices**

| Name | Application | 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 |  |

| Name | Application | Polymer |
|---|---|---|
| Poly-uretane | basises in prosthetic dentistry |  |
| Poly-cabonate | endotracheal tubes, mouthguards, protective glasses |  |

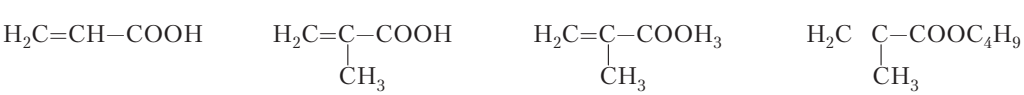
## 11.4. Acrylic acid based polymers in dentistry

Acrylic and methacrylic acid derivatives and the derivative-based polymers are of special importance for dentistry. They have been used in this field for many years. Methacrylate-based polymers have good mechanical properties, biocompatibility (they are flavourless, non-toxic) suitable optical properties, chemical resistance to oral liquids and disinfectants.




$R = CH_3,\ C_2H_5,\ n\text{-}C_3H_7,\ n\text{-}C_4H_9$

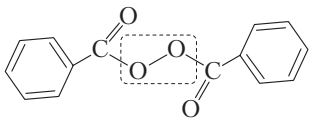
The presence of the double bond provides the ability to react in radical chain polymerization.



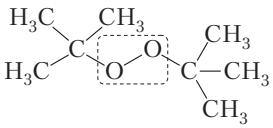
acrylic acid — methacrylic acid — methyl methacrylate — butyl methacrylate

The reaction starts with decomposition of the initiator. Substances with a non-polar covalent bond such as peroxides serve as the radical reaction initiators. The

nonpolar covalent bond between the oxygen atoms of peroxides easily decompose into radicals under the action of visible light, heat or activators.

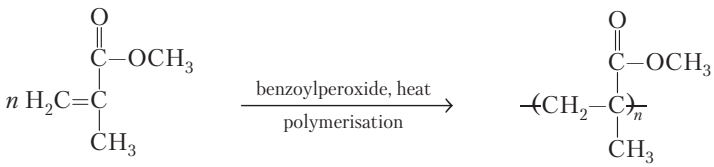


dibenzoyl peroxide



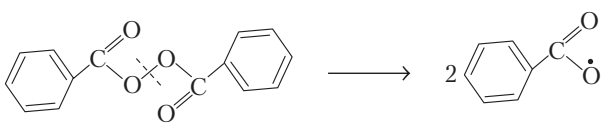
*tert*-butyl peroxide

Consider the reaction mechanism of radical polymerization of methyl methacrylate (MMA) upon the application of heat.

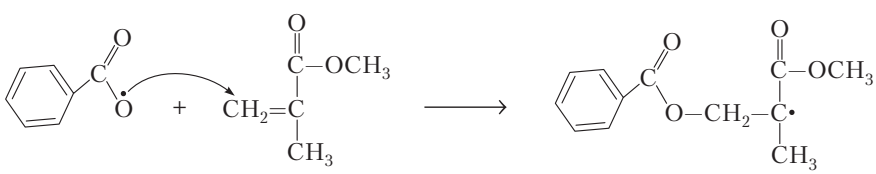



methyl methacrylate polymethyl methacrylate

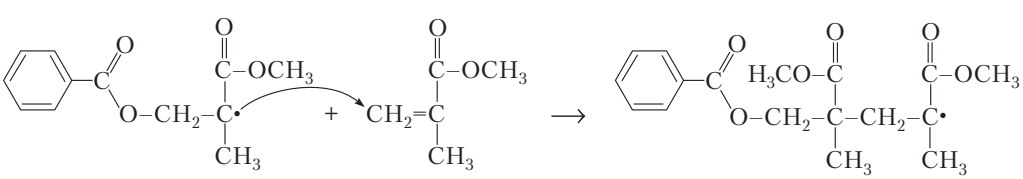
*Initiation*. At this stage, benzoyl peroxide breaks down into two radicals under the action of heat. Each radical reacts with the double bond of methyl methacrylate.



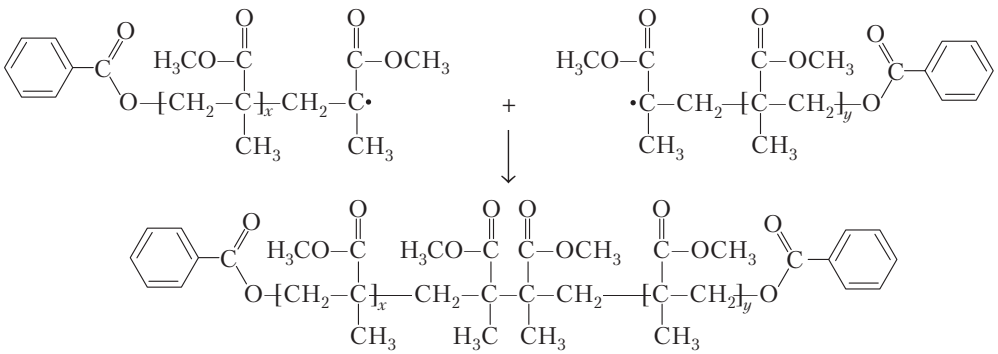
benzoyl peroxide benzoyloxy radical



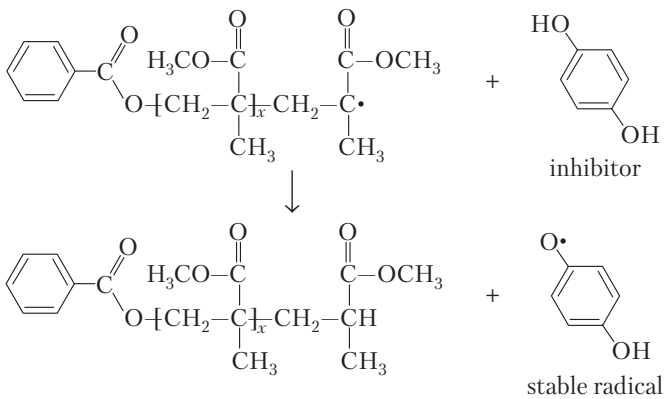
*Propagation*. The reaction goes on further until all of the monomer is consumed.



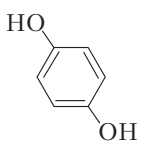
*Termination*. The chain termination occurs when two radicals react with each other.



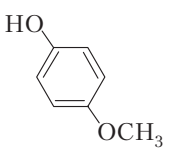
A big radical can interact with a compound (inhibitor), which breaks the chain growth. Polymethyl methacrylate (PMMA) is formed in this way.



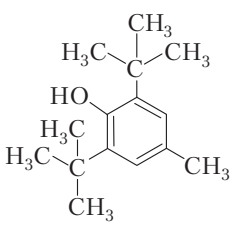

Inhibitors are capable of rapidly reacting with active radicals to form stable compounds which lose the ability to add further a monomer. That is why inhibitors completely stop polymerization. Compounds containing a phenolic hydroxyl group are generally used in dentistry as inhibitors. These chemical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



hydroquinone
HQ

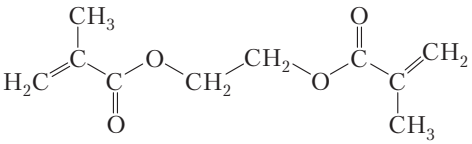


hydroquinone methyl ether
MEHQ



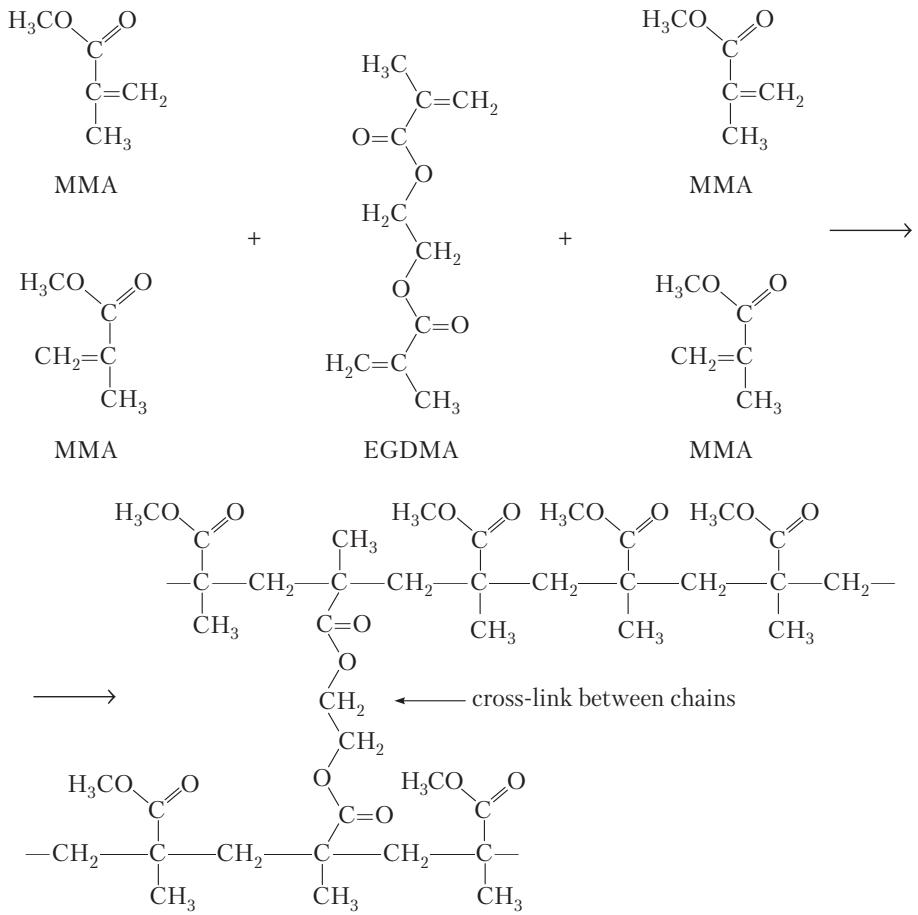
butylated hydroxytoluene
BHT

When used in dentistry, polymerization of the acrylic acid is accompanied by cross-linking with ethylene glycol dimethacrylate (EGDMA).



ethylene glycol dimethacrylate

The formation of cross-links between chains increases the strength of a material and its resistance to thermal and mechanical stresses, including grinding and polishing, so it reduces the formation of microcracks.




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

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

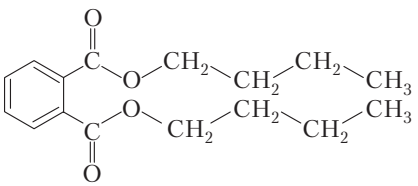
1) heat activated (heat-curing) resins, or polymers; they consist of two components;

2) chemically activated resins; they consist of two components;

3) light activated (light-curing) resins; they are one-component systems;

4) hybrid systems.

***Heat activated polymers*** are used for dentures. They consist of a powder and a liquid. The *powder* includes PMMA prepolymer, dibenzoyl peroxide as the initiator. The *liquid components* are MMA, a cross-linking agent (EGDMA), inhibitors, plasticizers.



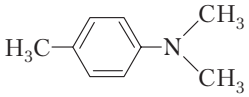
dibutyl phthalate

*Plasticizers* are compounds with low molecular weight that increase the plasticity of a polymer by reducing the interaction between the components' molecules in the polymer. Phthalates are usually used as plasticizers.

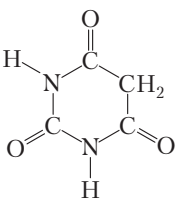
The powder is mixed with the liquid. Some form is created from the resulting viscous mass. The product is then heated, whereupon the polymerization reaction proceeds.

***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 of 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.



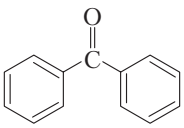
N,N-dimethyl-*p*-toluidine



barbituric acid

*UV absorbers* such as benzophenone are used to prevent discoloration of dental material.

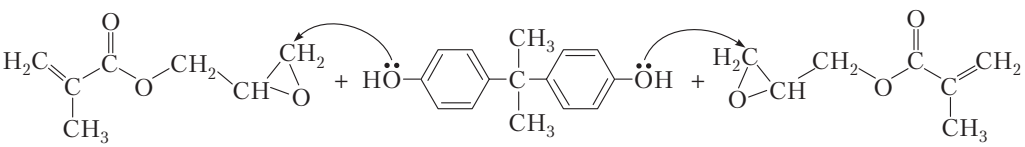
When mixed with the powder, the liquid activator promotes the decomposition of the initiator into free radicals that start the radical polymerization reaction. The copolymers then are linked together by monomers. The composite cures during the polymerization.



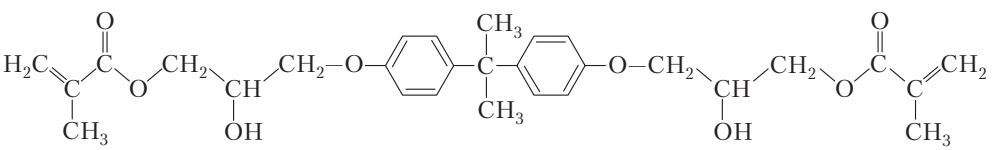
benzophenone

***Light-curing polymers*** are used as the bases of modern dental composite materials, adhesives, glass ionomer cements, etc. The composite materials generally consist of an organic resin matrix, an inorganic filler and a coupling agent that enhances the bond between the filler and the resin matrix. The organic resin matrix includes monomers, a photoinitiator system, inhibitors, UV absorbents.

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

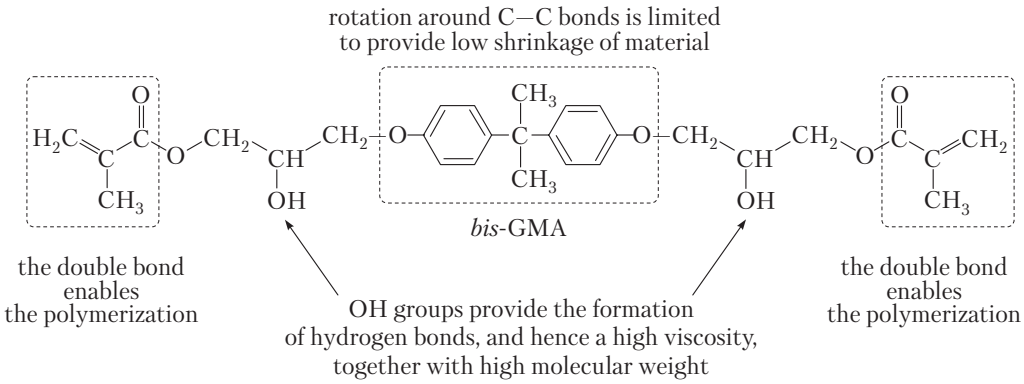


glycidyl methacrylate *bis*-phenol A glycidyl methacrylate

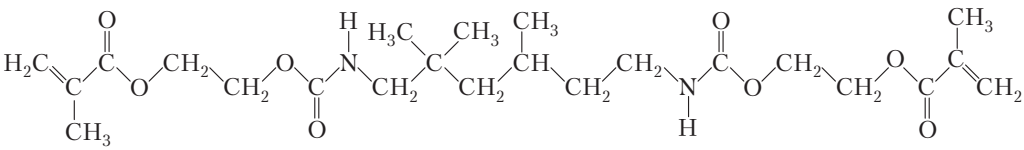


*bis*-GMA

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 the formation hydrogen bonds, which makes for the composit's 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 this defines the low shrinkage of material.

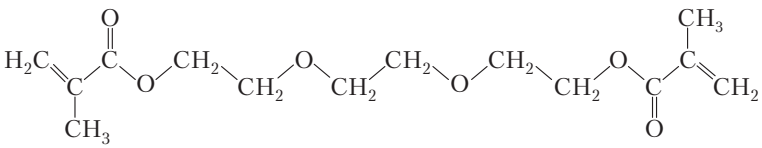



UDMA (urethane dimethacrylate) is another monomer of high molecular weight and high viscosity. It is often found in modern restorative materials. UDMA also contains methacrylic acid residues that are necessary for the polymerization.

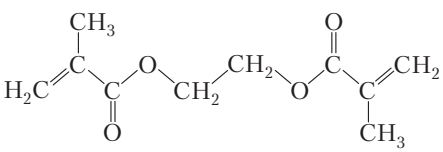


urethane dimethacrylate (UDMA)

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

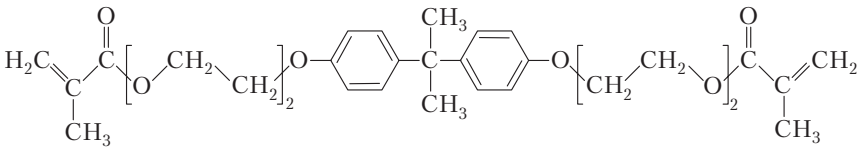


triethylene glycol dimethacrylate (TEGDMA)



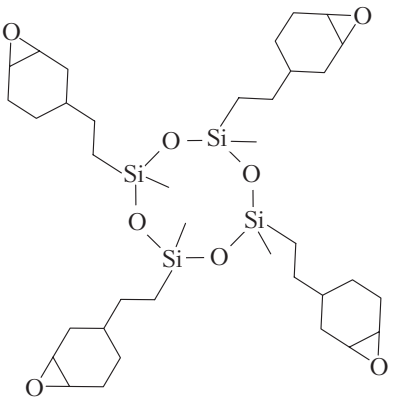
ethylene glycol dimethacrylate (EGDMA)

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

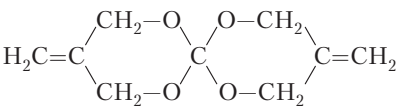


*bis*-phenol A tetraethoxylated dimethacrylate (*bis*-EMA)

Thus, modern dental materials contain mixtures of monomers that serve as their organic matrixes, which should provide lower shrinkage and a small amount of residual monomer. In order to reduce shrinkage, new monomers containing molecular rings (*expanding monomers*) are currently being studied and some of them have been introduced in the practical dentistry, e.g., epoxy-based resins, spiro-orthocarbonates (SOC).

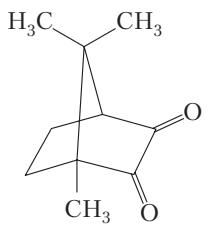


3,4-epoxycyclohexyl cyclopolymethylsiloxane

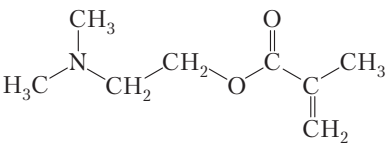


*bis*-methylene spiroorthocarbonate (BMSOC)

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

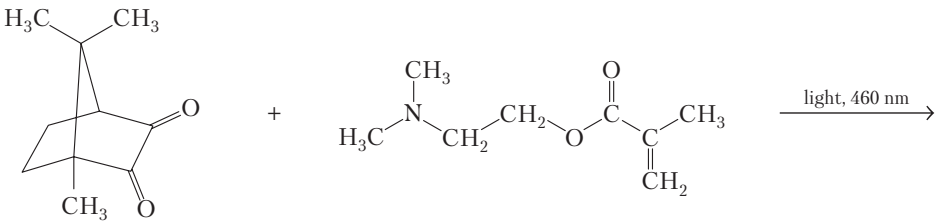


camphoroquinone (CQ)

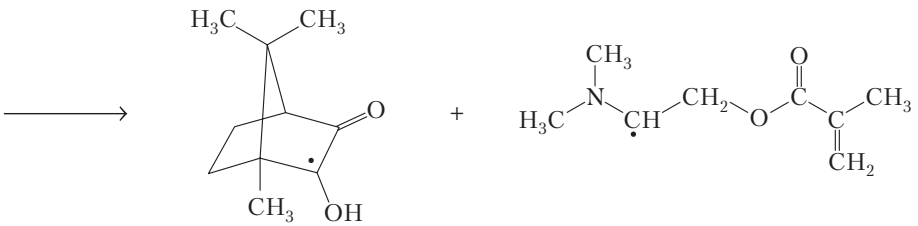


dimethylaminoethyl methacrylate (DMAEMA)

DMAEMA reacts with camphoroquinone, and it produces a free radical which is responsible for the polymerization reaction.




CQ DMAEMA

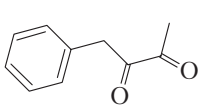


inactive radical

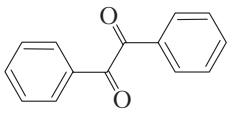
the radical responsible for the initiation of the polymerization reaction

Other amines can be also used as the co-initiators. However, there is an essential disadvantage in the use of a two-component photo-initiating system in the composite, discoloration of the material due to the oxidation of the amine.

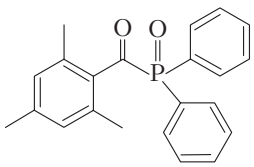
More recently an alternative one-component photo-initiating system has been used in resin-based composites such as phenyl propanedione (PPD), Benzil (BZ), Lucirin TPO, Irgacure 819, Ivocerin, etc. Their advantage is that they do not require the presence of a co-initiator.



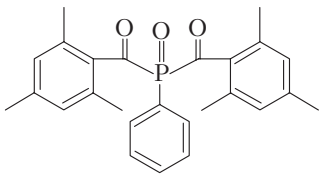
phenyl propanedione (PPD)



benzil (BZ)

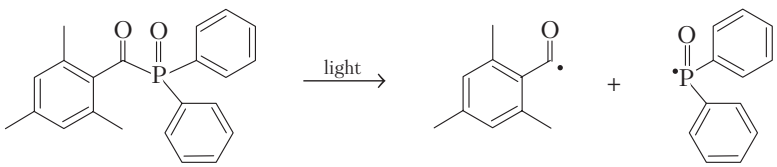


2,4,6-trimethylbenzoyl-diphenylphosphine oxide (Lucirin TPO)



*bis*(2,4,6-trimethylbenzoyl)-phenylphosphine oxide (Irgacure 819)

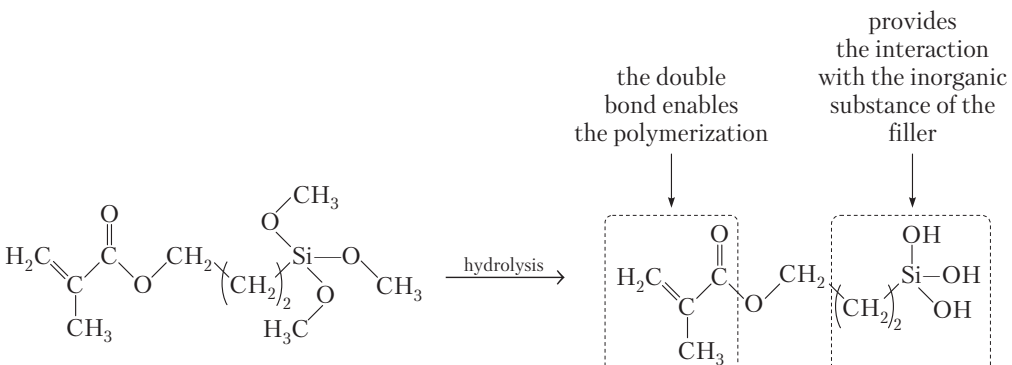
For example, Lucirin TPO produces free radicals by the photochemical cleavage of the carbon-phosphorus bond, which results in the formation of two initiating radicals ready to start the polimerization without a co-initiator.




Lucirin TPO

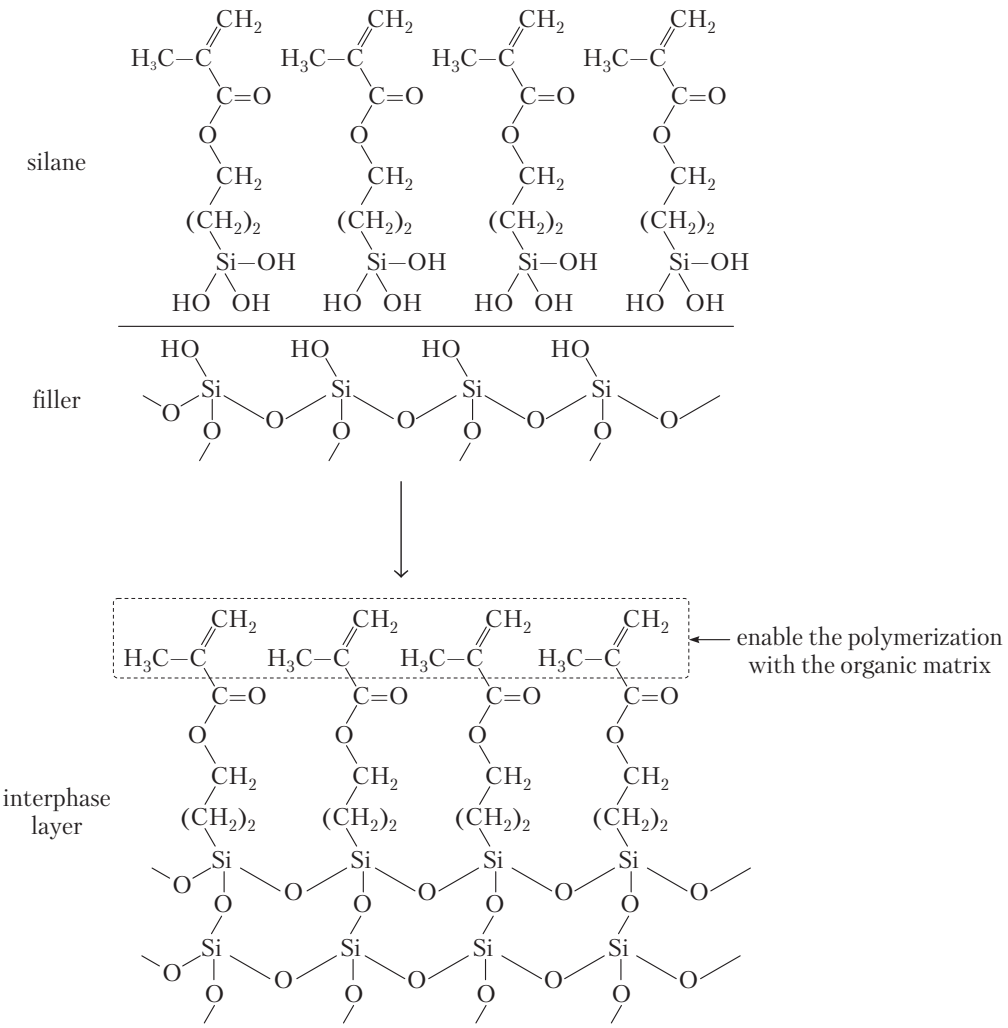
Restorative materials are mixtures of inorganic substances in an organic matrix. The ratio of the organic matrix and the *inorganic filler* predetermine the physical properties of the woud-be material. Fillers increase the hardness of materials, decrease their shrinkage, prevent matrix deformations, improve the esthetic properties of the materials and decrease their water absorption. Most of modern composites are filled with silicate particles based on Ba, Sr, Zn, Al. The size of the particles is more important than the composition.

The filler particles are bound organic matrixes with a *coupling agent*. The process of binding is based on refers to the organosilane branch of chemistry.



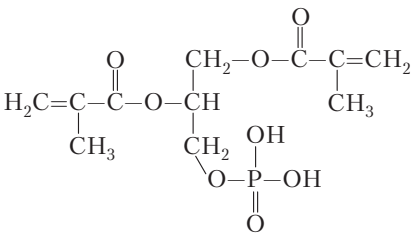

3-methacryloxypropyl
trimethoxysilane

In production-line conditions, silane is hydrolyzed. The bipolar structure of the molecule allows to bond both to the organic part *via* the double bond of methacrylic fragments and to the filler particles *via* the silanol groups.



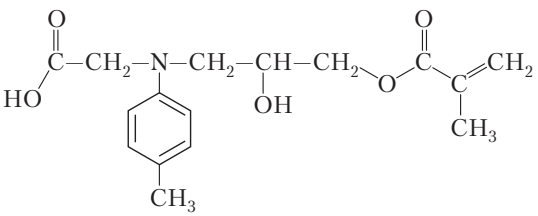

Currently, *adhesive systems* are used to improve the adhesion of the restorative material to the tooth tissues. A solution of phosphoric acid is used for this purpose. Phosphoric acid opens the pores of the enamel and promotes the penetration of the restorative material.

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

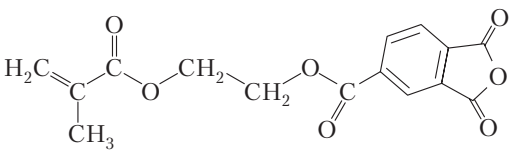


dimethacrylate of glycerophosphoric acid

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

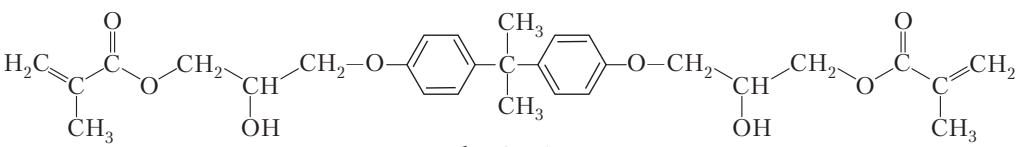


N-(*p*-tolyl)-glycine-glycidil methacrylate (NTG-GMA)

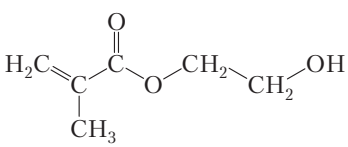


anhydride 4-methacrylhydroxyethyl of pyromellitic acid (4-META)

A mixture of *bis*-GMA and HEMA is often used.



*bis*-GMA

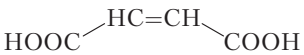


2-hydroxyethyl methacrylate (HEMA)

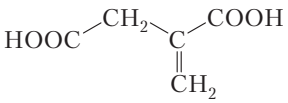
*Glass ionomer cements* (GICs) are a class of dental materials commonly used as filling materials and luting cements in prosthetic dentistry. GICs are two-component systems. Their powder is an acid-soluble calcium fluoroalumosilicate glass ($CaF_2$, $AlF_3$, $SiO_2$, $Al_2O_3$, NaF, $AlPO_4$, ZnO, etc.). The liquid fraction of GICs is a highly viscous solution of polyacrylic acid in the form of a co-polymer with itaconic acid and maleic acid. Tartaric acid is also present in the liquid part.



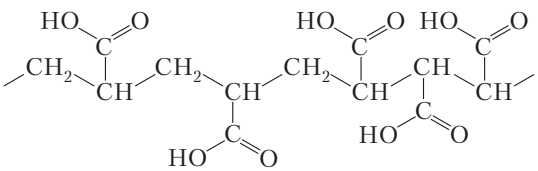
acrylic acid



maleic acid



itaconic acid

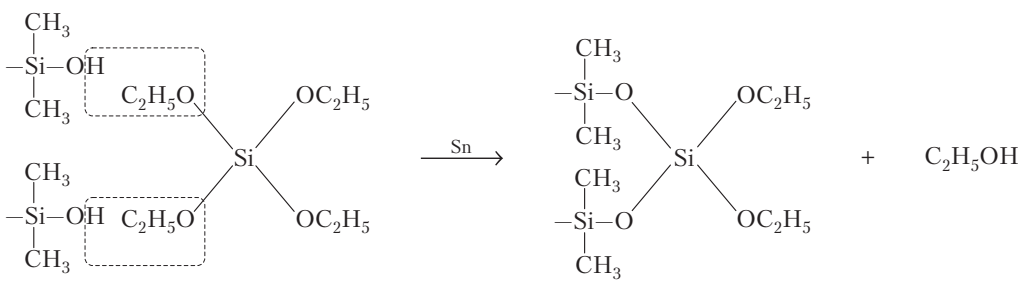


The setting reaction is an acid-base reaction between the acidic polyelectrolyte and the alumosilicate glass. Free carboxylic groups also interact with the tissues of the tooth by linking its calcium. Fluoride is released from the glass powder at the mixing and stays free within the matrix. Therefore,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

Modern dental materials are often combinations of glass ionomer cements and composites (resin-modified GICs).

## 11.5. Materials for use in prosthetic dentistry

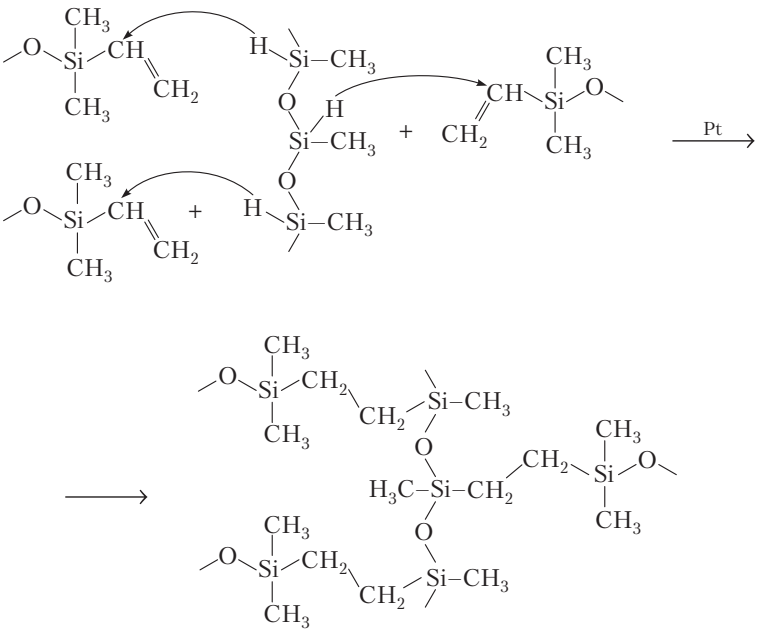
Organosilicon compounds have been widely used in medicine recently. Silicone materials are widely used as elastomeric impression materials. There are two types of silicone materials, the A type and the C type.



the curing mechanism of silicone materials of the polycondensation type

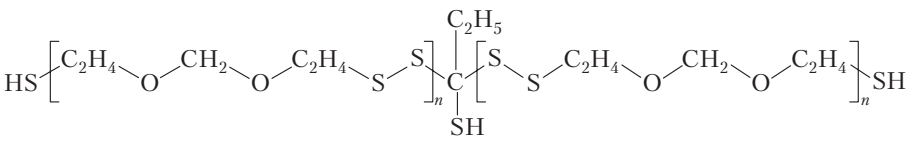
*Polycondensation silicone materials* (the type C) are formed in step polycondensation reactions. By-products with low molecular weights are formed during this reaction, which complicates the use of these materials.

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




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 elongation of chains and their cross-linking.



# 12. MONOSACCHARIDES: STRUCTURE, REACTIVITY, BIOLOGICAL ROLES

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

Carbohydrates are divided into three groups:

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

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

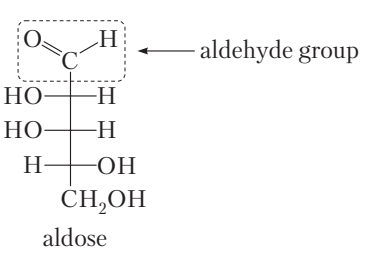
3) polysaccharides ($(C_6H_{10}O_5)_n$, where $n > 10$).

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

## 12.1. Classification of monosaccharides

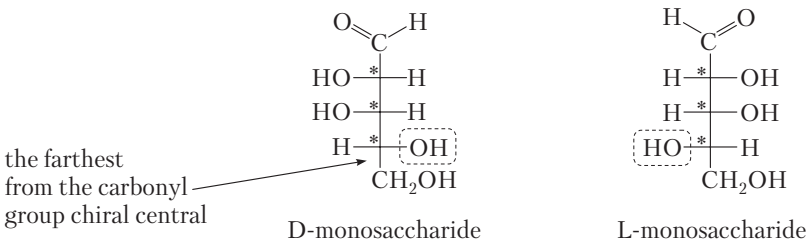
There are the following classifications of monosaccharides:

1) based on the presence of an aldehyde or a ketone group in their molecule (***aldoses*** contain an aldehyde group; ***ketoses*** contain a ketone group);




2) based on the number of carbon atoms in their molecule (***tetroses***, ***pentoses***, ***hexoses***, etc.);

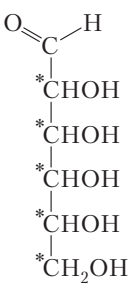
3) based on the configuration of the last chiral carbon atom (the D and L stereoisomers).



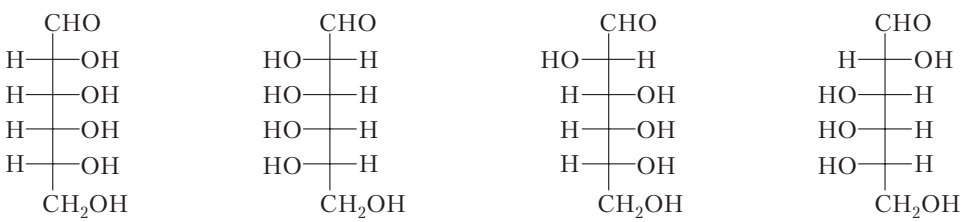

D-monosaccharide L-monosaccharide

## 12.2. Stereoisomerism of monosaccharides

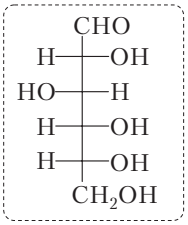
Aldohexoses are the most important monosaccharides for humans. They contain an aldehyde group and six carbon atoms. Aldohexoses have molecular formula $C_6H_{12}O_6$ and four chiral centres. According to formula, $N = 2^n$, there are 16 stereoisomers; 8 of them belong to the D series and eight to the L series. Natural monosaccharides involved in the process of vital activity refer to the D series.



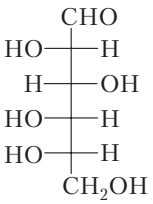
aldohexose



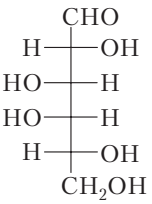
D-allose L-allose D-altrose L-altrose



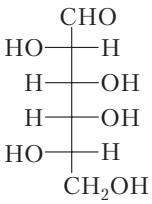
D-glucose



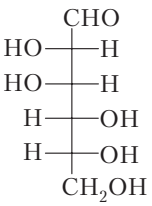
L-glucose



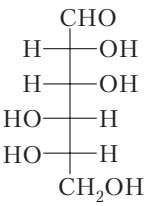
D-galactose



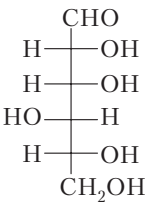
L-galactose



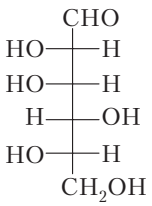
D-mannose



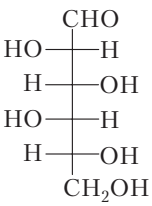
L-mannose



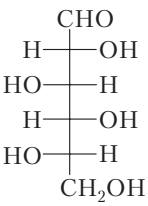
D-gulose



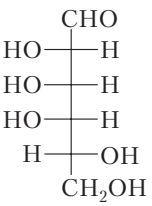
L-gulose



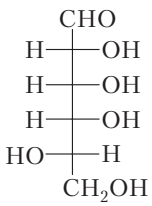
D-idose



L-idose



D-talose



L-talose

**Epimers** are stereoisomers that differ by the configuration at one of their chiral centres.

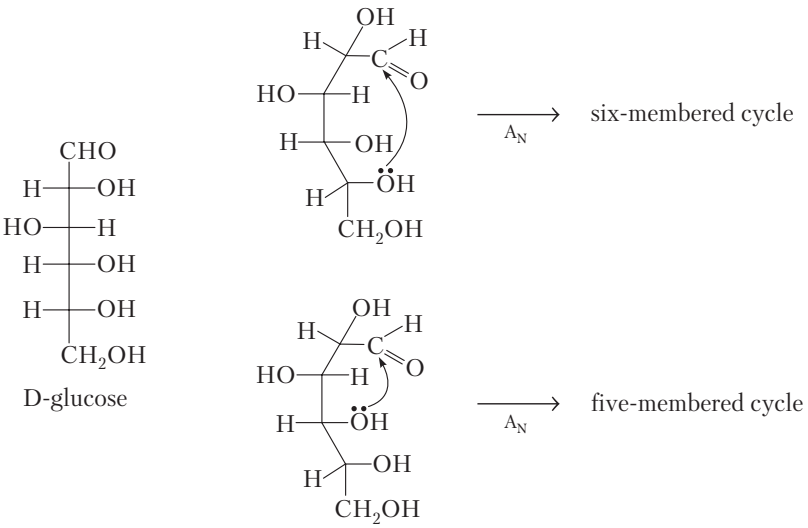
For example, D-galactose and D-glucose are the epimers on $C_4$. D-Mannose and D-glucose are the epimers on $C_2$. They also exist in the tautomeric forms.

## 12.3. Structure and tautomerism of glucose

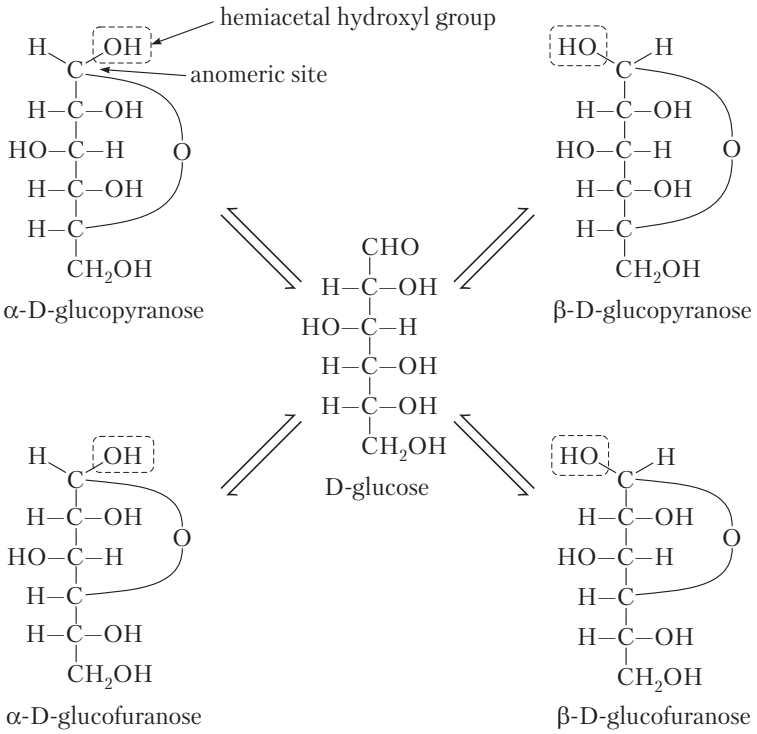
Glucose is the most important of aldohexoses to humans. Natural glucose involved in biochemical processes refers to the D row. Glucose is found in significant quantities in a free state in grapes (another name of glucose is grape sugar). Glucose is a monomer of oligosaccharides and polysaccharides such as starch, glycogen, cellulose, dextrane.

D-glucose has the right optical rotation (+52.5). Therefore another common name is often used for this substance, viz *dextrose*. Glucose, like the other monosaccharides, exists predominantly in the cyclic form, either as a solution or in the crystalline state.

The cyclic forms are derived through the nucleophilic addition reaction between the carbonyl group and one of the hydroxyls of the same molecule.



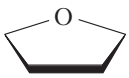

A six- or five-membered ring is formed at the same time.



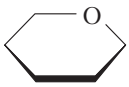
In these reactions the $C_1$ atom becomes chiral (the anomeric site). The hydroxyl group derived from an aldehyde group is called ***hemiacetal***, ***anomeric***, or ***glycosidic group***. It has specific chemical properties different from other hydroxyl groups. Additional chirality of the $C_1$ carbon enables the appearance of the two cyclic stereoisomeric (anomeric) forms, viz the α and β forms. In the α anomer, the hemiacetal hydroxyl group and the hydroxyl group attached to the last chiral centre are on the one side in a Fischer projection. Contrastiongly, in the β anomer, the hemiacetal hydroxyl group and the hydroxyl group attached to the last chiral centre are on the opposite sides in a Fischer projection.

Five forms of D-glucose (as well as any monosaccharide) exist in solutions. Formed cycles can be opened and then 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. The cyclic forms are more stable; therefore, they predominate in solutions (99.99 %).

Monosaccharides are cyclic hemiacetals of polyhydroxy carbonyl compounds.



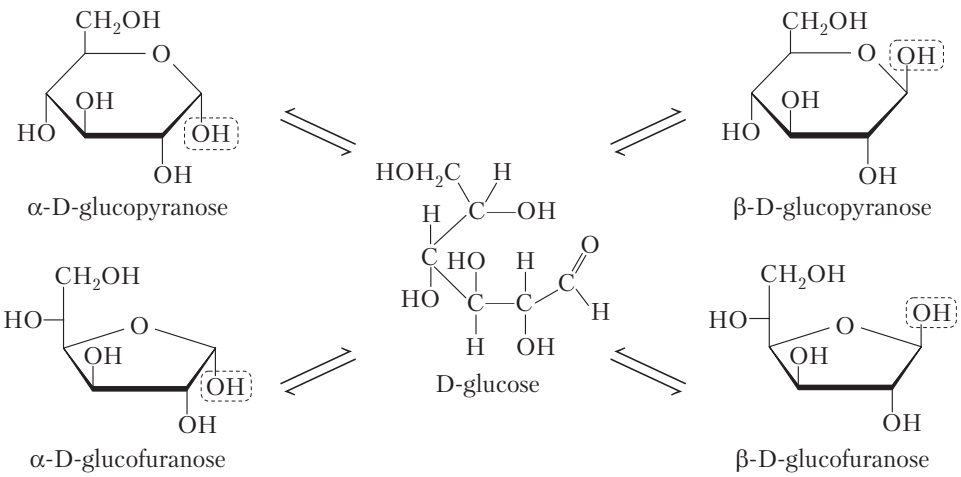
furanose



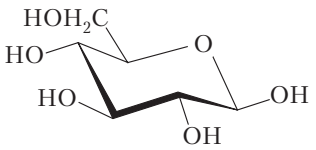
pyranose

Cyclic forms can be represented by the Fischer projection (shown above) and by the Haworth formulas (shown below). According to Haworth, the six-membered rings are depicted as hexagons with the oxygen atom in the upper right corner, and the five-membered rings as pentagons with the oxygen atom in the top corner.

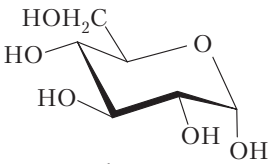
The tautomeric forms of glucose are shown below. The hydrogen atoms bonded to the chiral centres are omitted. The hemiacetal hydroxyl group in each tautomeric form is highlighted.




Monosaccharides exist mainly in their non-planar conformations. The chair conformation is the most favorable for the pyranose cycle and the envelope or the twist conformations are stable for the furanose cycle.




β-D-glucopyranose



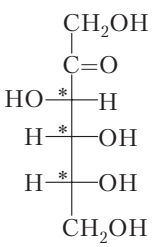

α-D-glucopyranose

The most stable conformation of glucose is the chair conformation of β-D-glucopyranose in which all of the bulky substituents (OH, $CH_2OH$) are in the equatorial positions. This form is widespread in nature. And it is α-D-glucopyranose which is involved in human biochemical reactions. Conformations of monosaccharides are very important for the space structures of polysaccharide chains.

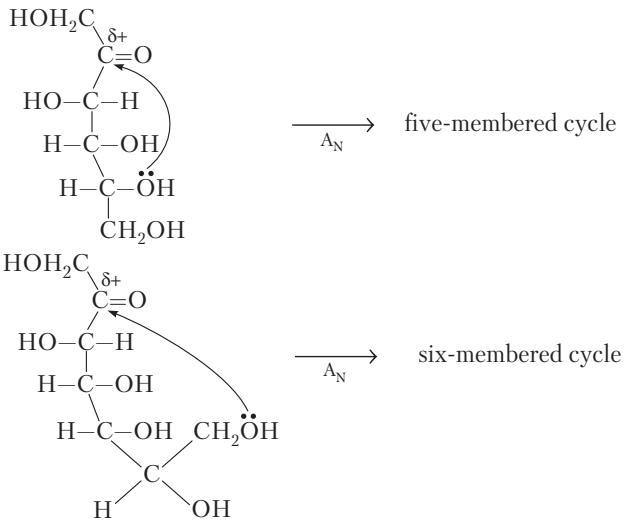
**Mutarotation** is a change of the rotation angle of the plane of polarized light in freshly prepared solutions of monosaccharides for a certain period of time. Anomeric α and β forms provide different angles of polarized light rotation. Thus, α-D-glucopyranose rotates polarized light +112.5°, and β-D-glucopyranose rotates it by +19.3°. When solved in water, the equilibrium between these forms is settled with the following proportion: 2/3 β-form ⇄ 1/3 α-form. The rotation angle of this equilibrium-state solution is +52.5°.

## 12.4. Structure and tautomerism of fructose

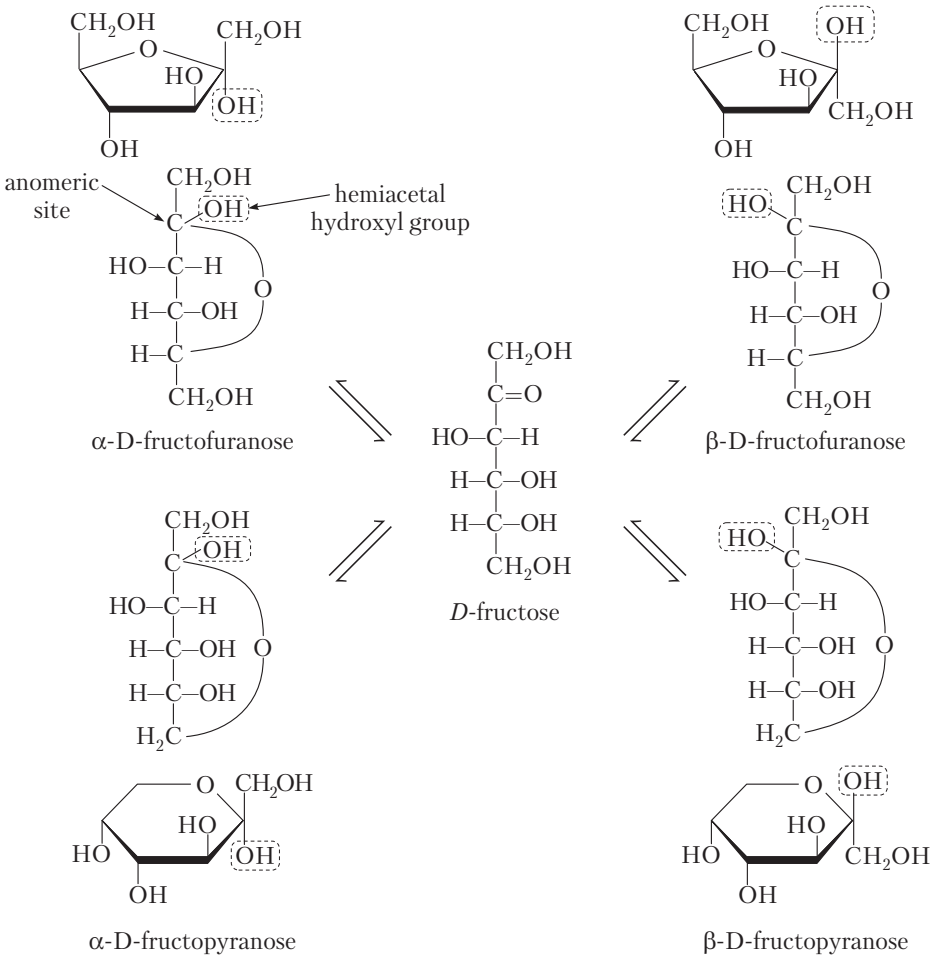
***Fructose*** (fruit sugar) is a functional isomer of glucose. Its molecular formula is the same as glucose ($C_6H_{12}O_6$). But in contrast to the aldohexose glucose, fructose is ketohexose. An acyclic form of fructose has three chiral centres. Natural D-fructose shows the left optical rotation (–82°). Fructose exists mainly in its cyclic forms. They are formed by the nucleophilic addition between the carbonyl group and one of the hydroxyls in the same molecule (at the 5$^{th}$ or 6$^{th}$ carbon).




D-fructose



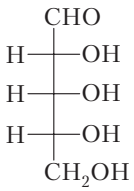
The tautomeric forms of fructose are shown in the picture below. The cyclic forms are shown both by the Fischer and the Haworth projections.

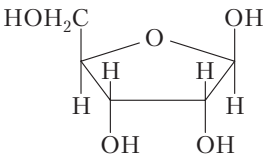


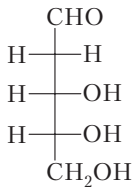

Glucose and fructose being the functional isomers are converted into each other *in vivo*. They are a source of energy in the body.

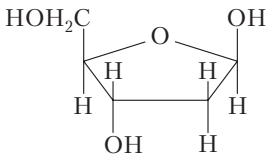
## 12.5. Biologically important aldopentoses

D-Ribose and 2-deoxy-D-ribose are essential in the living process. Unlike ribose, 2-deoxy-D-ribose, does not have a hydroxyl group at the second carbon atom. These pentoses exist in the tautomeric forms in solutions. They are parts of nucleic acids in the form of β-furanose.


D-ribose

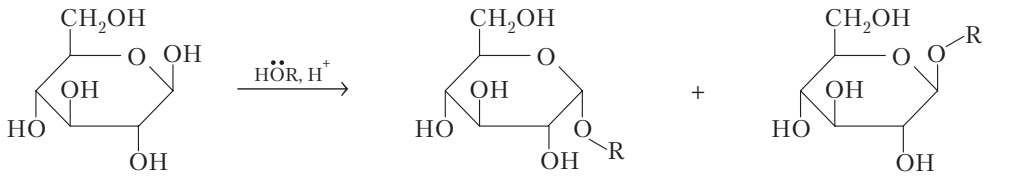

β-D-ribofuranose


2-deoxy-D-ribose


β-D-deoxyribofuranose

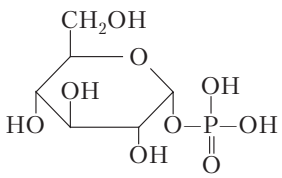
## 12.6. Chemical properties of monosaccharides

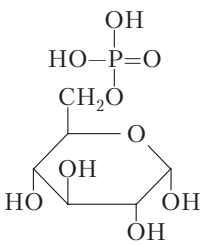
***Glycoside*** are formed in a reaction of nucleophilic substitution of a hemiacetal hydroxyl group. Chemically, glycosides are mixed acetals. Their names are derived from the names of the corresponding monosaccharides by replacing of suffix *-osa* to suffix *-oside*. Glycoside is composed of a carbohydrate and a non-carbohydrate part (aglycone) which are connected by a glycosidic bond. Glycosides are hydrolyzed in acidic conditions or enzymatically. *In vitro*, the reaction between monosaccharide and alcohol leads to the formation of two glycoside anomers.

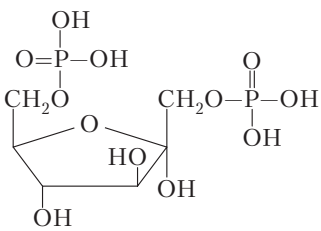

β-D-glucopyranose — alkyl-α-D-glucopyranoside — alkyl-β-D-glucopyranoside

Glycosides are divided into O-, N-, S-glycosides. Oligo/polysaccharides are O-glycosides.

***Ethers*** and ***esters*** of monosaccharides are widespread in nature. Phosphoric esters of glucose, fructose and other monosaccharides are essential for the metabolic processes in humans. They are the metabolically active forms of monosaccharides. The process of their formation is called phosphorylation.

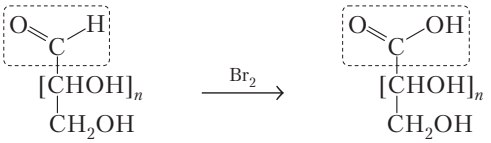

α-D-glucopyranose-1-phosphate


α-D-glucopyranose-6-phosphate


α-D-fructofuranose-1,6-diphosphate

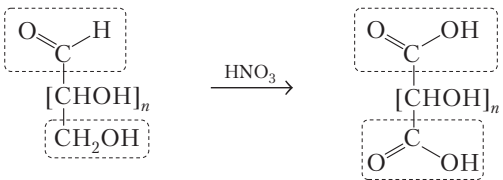
Monosaccharides are readily oxidized in an alkaline medium by the action of metal cations such as $Ag^+$ or $Cu^{2+}$. These reactions lead to reduction products of the metals and mixtures of oxidation products of the monosaccharide.

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



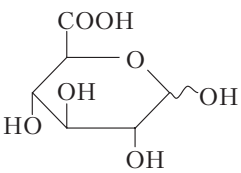

aldose aldonic acid

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*.

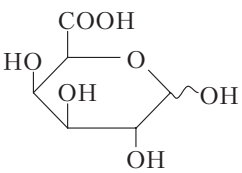



aldose aldaric acid

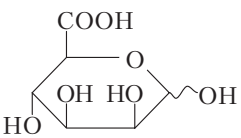
In the cases when only the primary alcoholic group is oxidized, *uronic acids* are formed.




D-glucuronic acid

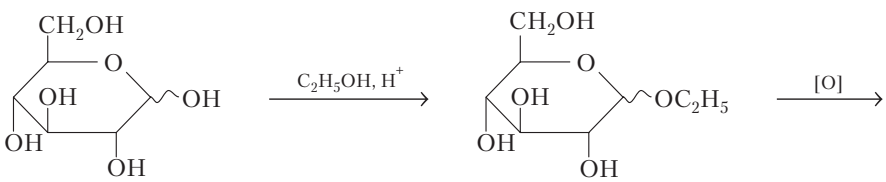



D-galacturonic acid

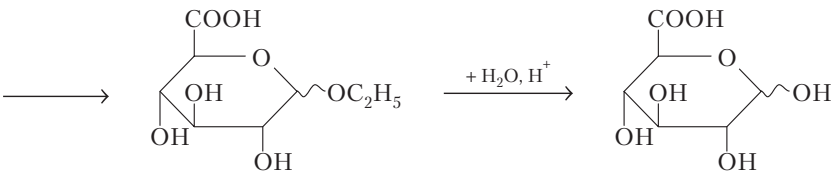



D-mannuronic acid

The synthesis of uronic acids is a complex of transformations, the first of which is the formation of the glycoside. Then the primary alcohol group is oxidized.



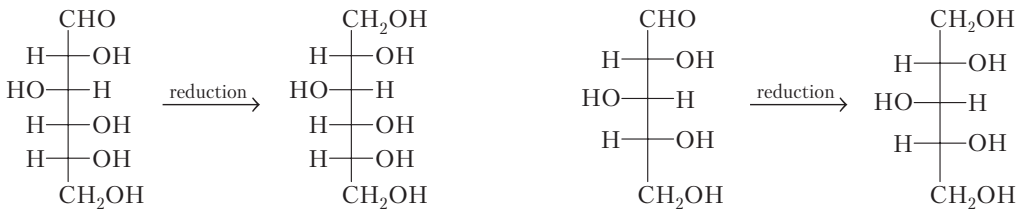

anomeric mixture
of D-glucopyranoses




D-glucuronic acid

Uronic acids such as glucuronic and galacturonic acids are parts of 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 monosaccharide carbonyl group into the $CH_2OH$ fragment produces sugar alcohols, also known as ***alditols***.

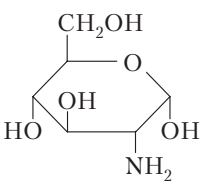



D-glucose D-sorbitol D-xylose xylitol

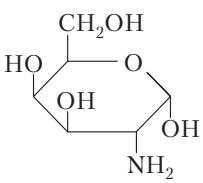
Alditols are crystalline substances; they are soluble in water and taste sweet. Alditols cannot be included in the glucose metabolism and are used as sugar substitutes for people with diabetes and for dietic purposes.

## 12.7. Monosaccharide derivatives

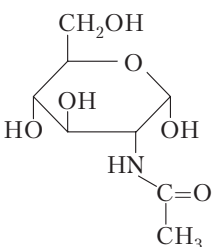
**Aminosugars** are monosaccharide derivatives in which the nonglycosidic hydroxyl is substituted by an amino group. They are part of the heteropolysaccharides in which the amino group is acetylated.




2-amino-2-deoxy-
α-D-glucopyranose
(D-glucosamine)

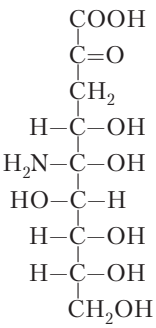



2-amino-2-deoxy-
α-D-galactopyranose
(D-galactosamine)

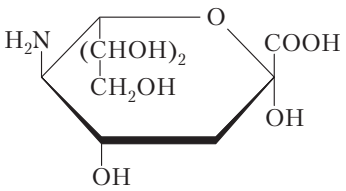



N-acetyl-
D-glucosamine

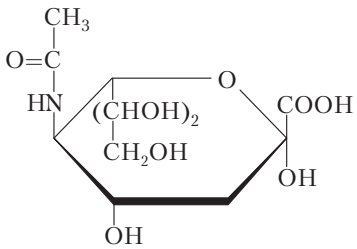
The carbon chain of ***neuraminic acid*** consists of nine carbon atoms and has a ketone group located next to a carboxyl group. In the cell, it is predominantly present in its cyclic form.



acyclic form of neuraminic acid



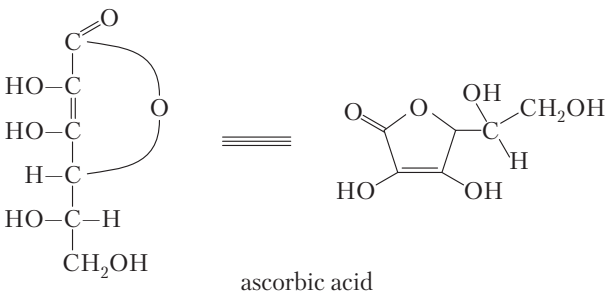
cyclic form of neuraminic acid



*N*-acetylneuraminic acid

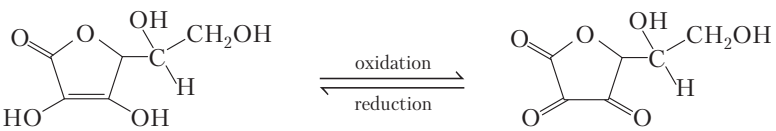
The N- and O-acylated derivatives of neuraminic acid are called sialic acids. Sialic acids determine the surface properties of living cells.

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



ascorbic acid

Ascorbic acid was found in plants and some animals but it is not produced in humans. Therefore, humans receive ascorbic acid from nutrients. Ascorbic acid is unstable and easily oxidized. It is a water soluble antioxidant.




ascorbic acid dehydroascorbic acid

Vitamin C takes part in hydroxylation of amino acids and other biologically important compounds. It is necessary for the production of collagen.

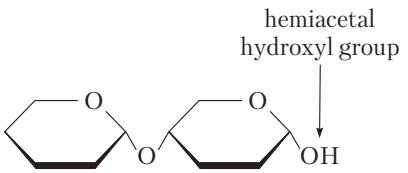
# 13. OLIGO- AND POLYSACCHARIDIES

Most of sugars are present in animals and plants in forms of short or long chains. According to their degree of polymerization sugars may be subdivided into two principal groups, oligosaccharides and polysaccharides.

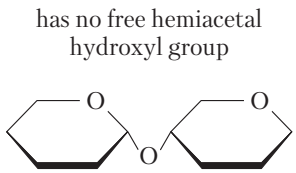
## 13.1. Oligosaccharides

Oligosaccharides consist of monosaccharides (2 to 10); they are subdivided into di-, tri-, tetra-, penta- and so on.

Disaccharides can be classified as reducing and nonreducing types. Reducing disaccharides contain a free hemiacetal group and therefore they are able to take acyclic forms, and are positive in the chemical test for an aldehyde group. Furthermore, they can form glycosides. Nonreducing disaccharides do not contain a free hemiacetal group and therefore they are not capable of conversion into acyclic forms. They neither show positive results in the chemical tests for an aldehyde group nor form glycosides.

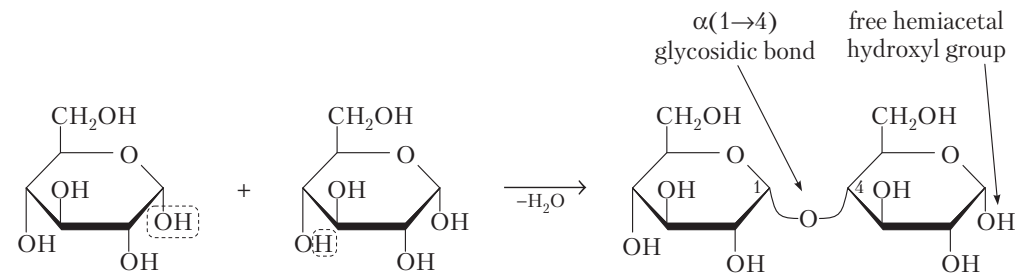



reducing disaccharide



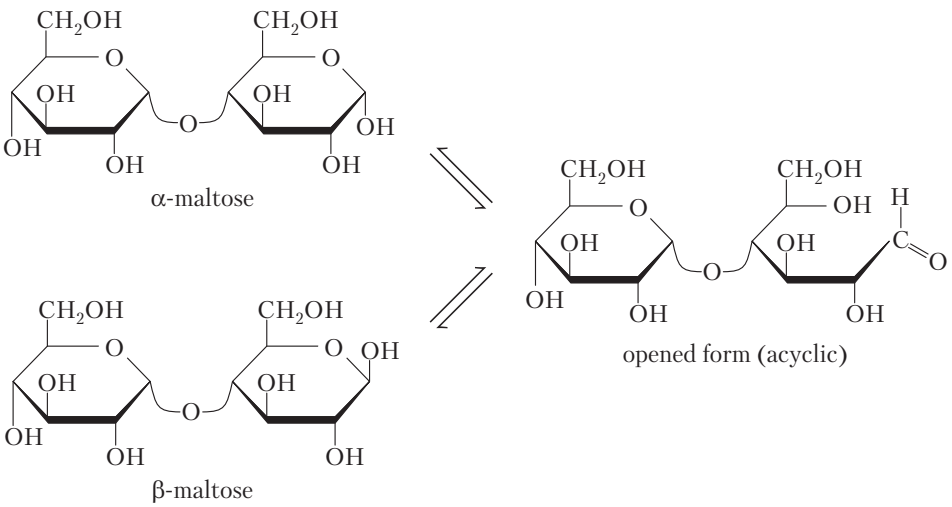

nonreducing disaccharide

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



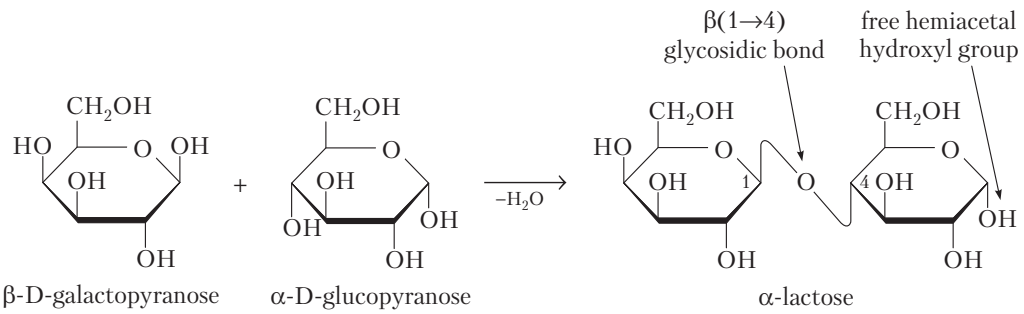

α-D-glucopyranose α-D-glucopyranose α-maltose

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 an acyclic form.



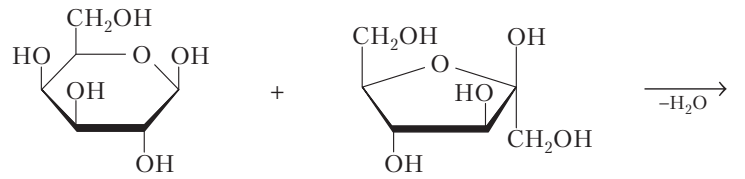

Maltose is a disaccharide unit of starch. It is produced from starch in the intestine and then hydrolyzed to glucose.

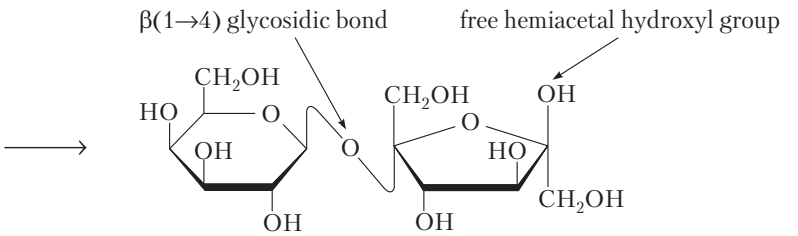
***Lactose*** is a disaccharide found in milk. Lactose is necessary for the formation of intestinal microflora in the newborn. It consists of D-galactose and D-glucose. Monosaccharides are connected by the β(1→4) glycosidic bond.



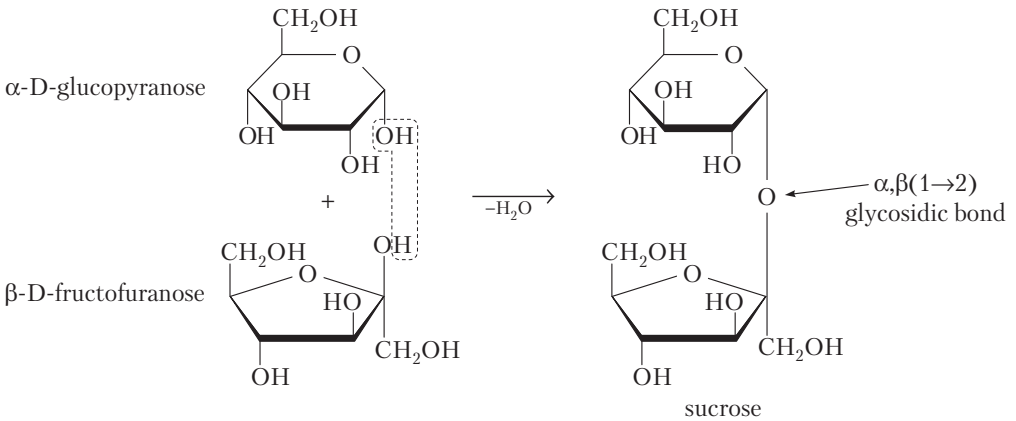

Lactose has reducing properties. It exists in few tautomeric forms: α-lastose, β-lastose and an acyclic form.

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




***Sucrose*** is the commonly known table sugar, the most widely used disaccharide. Annually, about 200 million tons of sugar is produced worldwide. It is found in all photosynthetic plants. Sucrose is a nonreducing disaccharide, because its glycosidic bond is formed by the two hemiacetal hydroxyl groups of α-D-glucopyranose and β-D-fructofuranose.

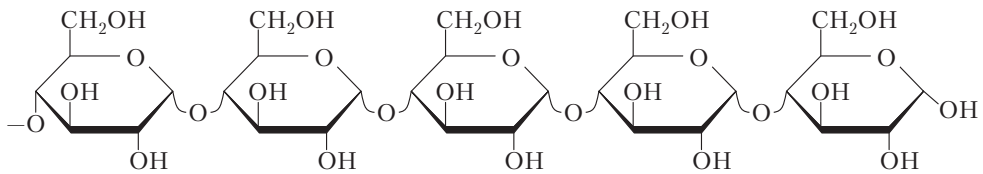



## 13.2. Polysaccharides

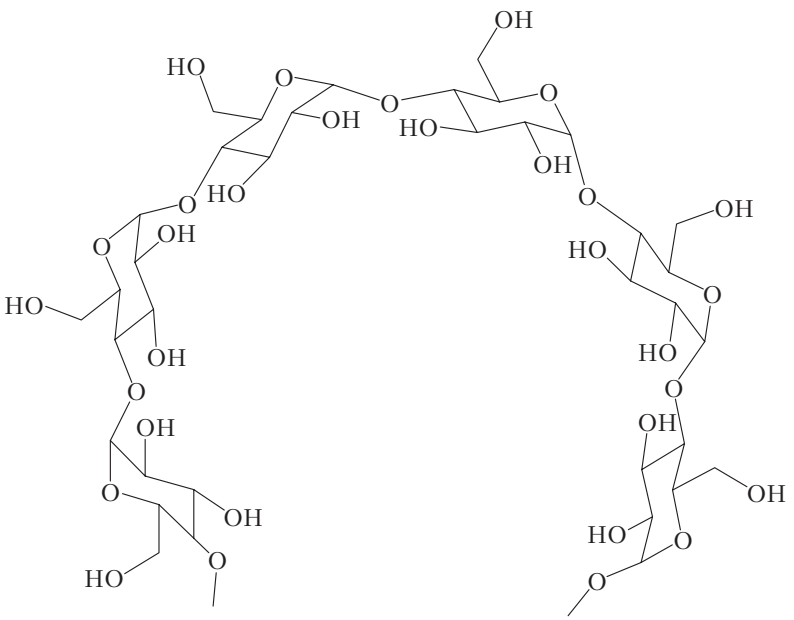
Polysaccharides (glycans) are complex carbohydrates. They are polymers that consist of several monosaccharides joined together by glycosidic bonds. When all monosaccharides in a polysaccharide are of the same type, the polysaccharide

is called a *homopolysaccharide*; and if more than one type of monosaccharide is present in a polysaccharide molecule, it is called a *heteropolysaccharide*. There are storage polysaccharides and structural polysaccharides.

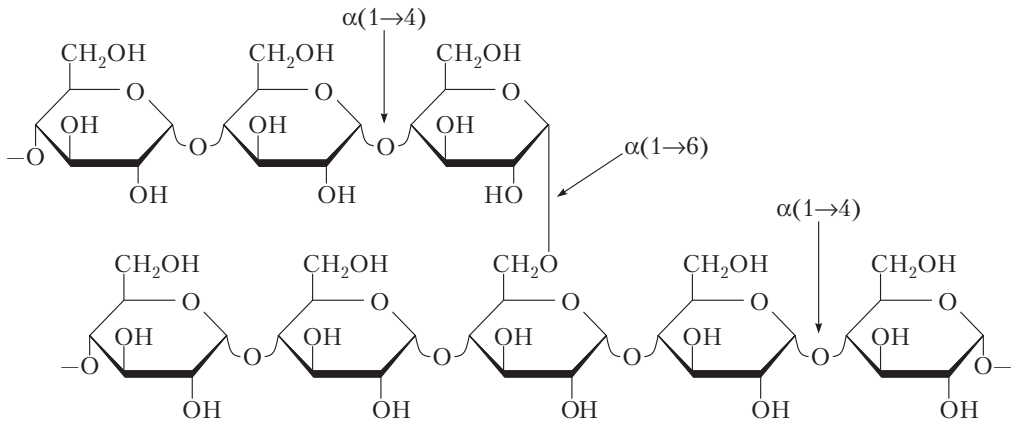
Components of ***starch*** are polymers of the vegetable origin. There are formed from glucose and accumulates in the roots, tubers, and seeds of plants. Corn, potatoes, wheat and rice are important sources of starch. Starch is composed of two fractions: 10–20 % *amylose* and 80–90 % *amylopectin*. Amylose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



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 tends to assume a helical arrangement. The peculiar spatial structure of amylose provides its positive test to starch with iodine.



The structure of amylopectin is branched. α-D-glucopyranose is its monomer. The main type of bond is α(1→4). Branches are formed by α(1→6) bonds.

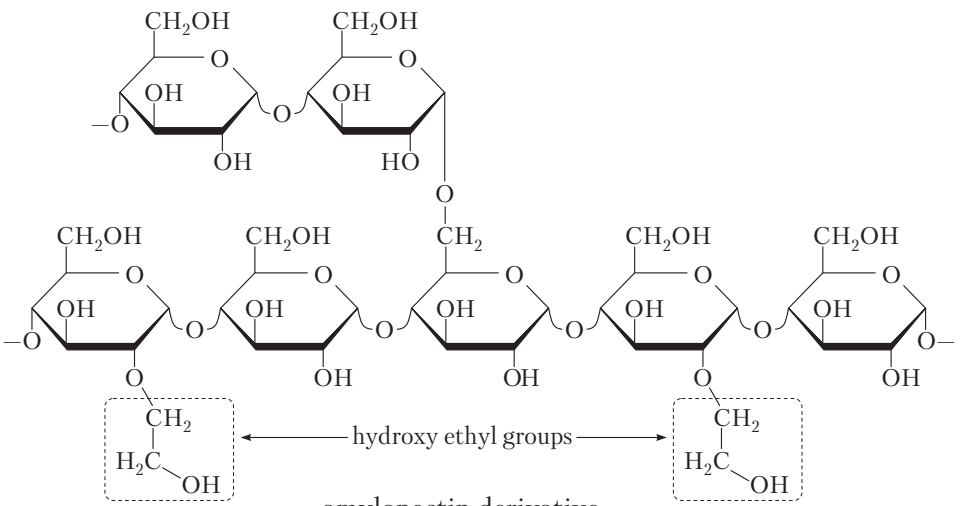



fragment of amylopectin

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

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

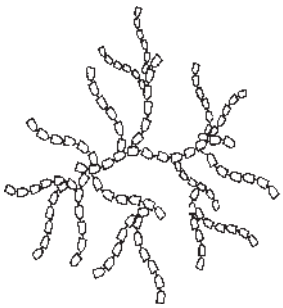
Usually, the hydroxyl groups of amylopectin are modified by introducing a hydroxyethyl group.



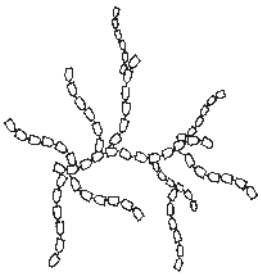

amylopectin derivative

***Glycogen*** is very similar to the amylopectin structure. Its macromolecules consist of α-D-glucopyranose. Glucose units are linked with a α(1→4) glycosidic

bonds. Branches are attached to the chains which are linked with α(1→6) glycosidic bonds. However, chains of glycogen are much more branched. It has a very high molecular weight.



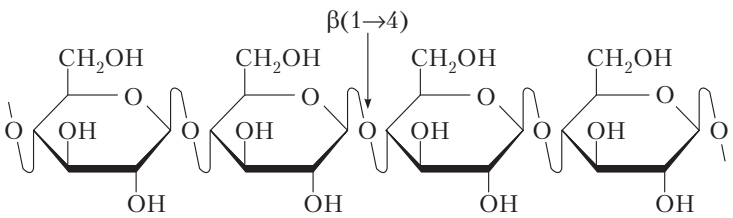
a granule of glycogen



a granule of amylopectin

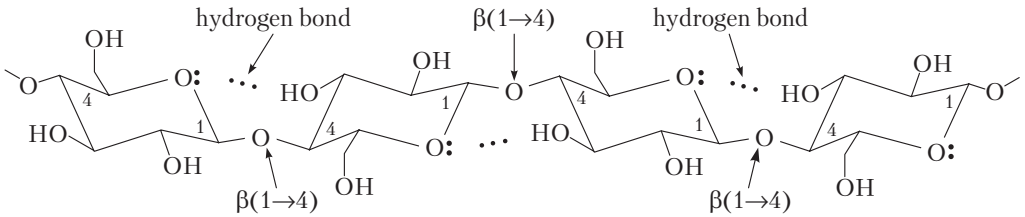
The size and the structure of glycogen molecules provide its function as a reserve carbohydrate for humans and animals. The large size of glycogen granules prevents it from passing through biological membranes, so it stays inside body cells. Since glycogen is so highly branched, a very large number of end groups are available for enzyme hydrolysis.

***Cellulose*** is a homopolysaccharide of the vegetable origin. Its structure is linear. Its chains consist of β-D-glucopyranose. The type of the glycosidic bonds is β(1→4).




fragment of cellulose

Each glucose unit in the chain of cellulose is rotated 180° degrees against the previous one. An intramolecular hydrogen bond is formed between each oxygen of the pyranose cycle and the hydroxyl group at the 3rd carbon atom.

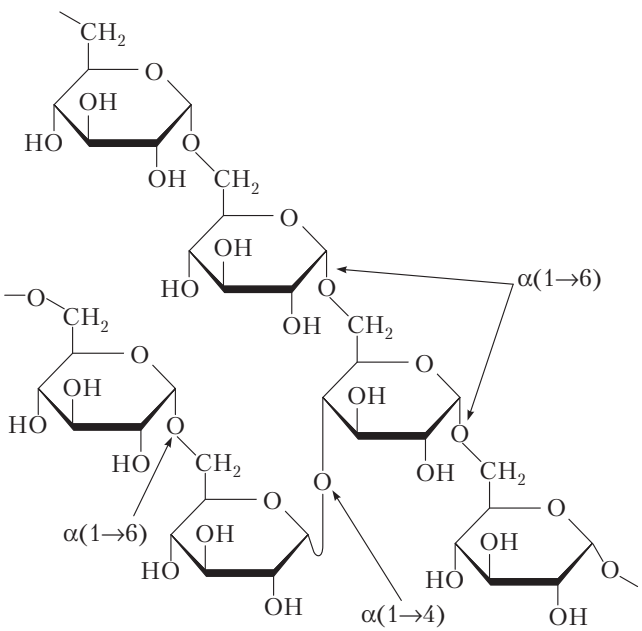



a fragment of cellulose

Furthermore, hydrogen bonds are also formed between the chains. Thus, cellulose is insoluble in water and chemically inert. It performs the structural function in plants. Humans cannot hydrolyze the β-glycosidic linkages of cellulose. Therefore, it is of no use to humans as a source of glucose. However, the fruits and vegetables containing cellulose are necessary in their diet. Cellulose is partially used to sustain the intestinal microflora; it also helps to create a feeling of satiety and stimulate the peristalsis of the gastrointestinal tract.

***Dextran*** is a branched polysaccharide of the bacterial origin; it is formed of many glucose molecules joined into chains of varying lengths.

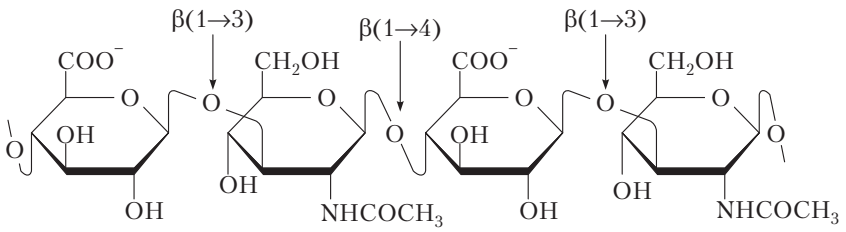
α-D-glucopyranose is its monomer. The main type of bond is α(1→6). Branches are formed by α(1→4), α(1→3) glycosidic bonds. Dextran is synthesized from sucrose by certain bacteria. Dental plaque is rich in dextrans. Dextrans can be used as plasma expanders (substitutes for whole blood) in cases of severe progressive shocks.




a fragment of dextran

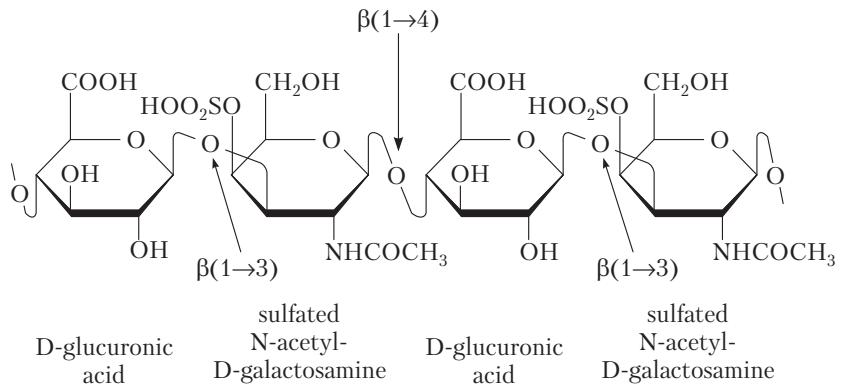
***Hyaluronic acid*** is a heteropolysaccharide. It is distributed widely in the connective, epithelial and neural tissues. It is one of the main components of the extracellular matrix, as it contributes significantly to the cell proliferation and migration. Hyaluronic acid is an important component of the articular cartilage, where it is present as a coat around each cell (chondrocyte). In the connective tissues, hyaluronic acid is associated to proteins, thereby forming aggregates. They imbibe water and are responsible for this tissues' resistance to compression. The molecular weight of hyaluronic acid in the cartilaginous tissues decreases with age,

while 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. It is 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 the cartilage tissues and notably contributes to their resistance to compression.

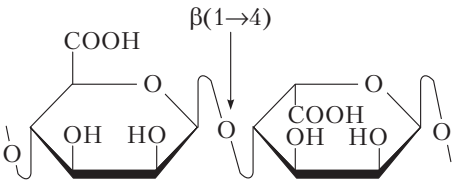



chondroitin sulfate

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

Alginic acid and agar-agar are of natural origin and are synthesized in algae. They are widely used in dentistry.

***Alginic acids*** (alginates) consist of disaccharide units constructed, in turn, 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 formed by crosslinking of macromolecules to the corresponding nearby —COOH groups. Therefore, alginic asids are used in orthopedic stomatology as impression materials.



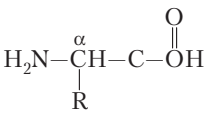

D-mannuronic acid L-guluronic acid

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 a β(1→4) bond. It has a clearly expressed feature in the formation of gels.

# 14. STRUCTURE AND REACTIVITY OF AMINO ACIDS

Amino acids are heterofunctional compounds which have carboxylic and amino groups. There have been about 300 amino acids found in nature (*biogenic* amino acids), but only 20 (precisely, 22, if some bacteria cells are taken into account) of them are found in protein structures; they are called *proteinogenic* amino acids. Proteinogenic amino acids are α-amino acids, because they contain an amino group in the α-position.



general formula of proteinogenic amino acid

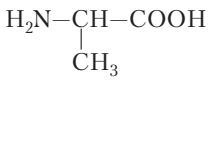
Trivial names and three-letter code are used to indicate amino acids. Trivial names are accepted by the IUPAC nomenclature.

Few systems are used to classify proteinogenic amino acids.

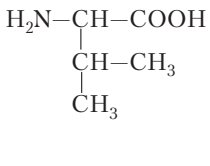
## 14.1. Classification of proteinogenic amino acids

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

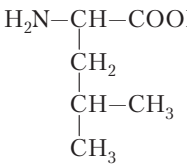
1. Amino acids with a hydrophobic radical.



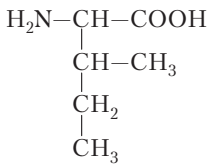
alanine
**Ala**



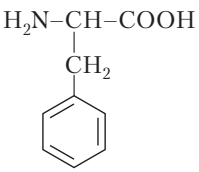
valine
**Val**



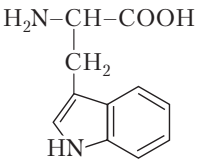
leucine
**Leu**



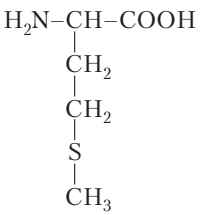
isoleucine
**Ile**



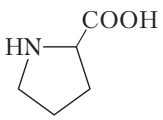
phenylalanine
**Phe**



tryptophane
**Trp**



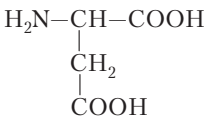
methionine
**Met**



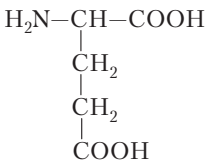
proline
**Pro**

2. Amino acids with a hydrophilic (ionized and unionized) radical.

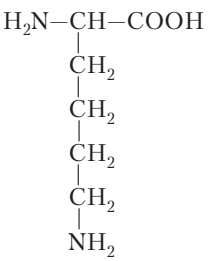
Amino acids containing an ionized (negative and positive) radical are presented below:



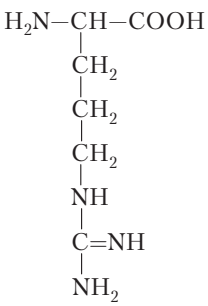
aspartic acid
**Asp**



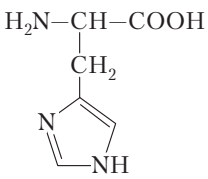
glutamic acid
**Glu**



lysine
**Lys**

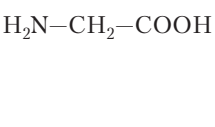


arginine
**Arg**

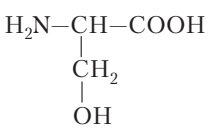


histidine
**His**

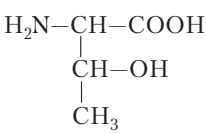
Amino acids, containing unionized radical:



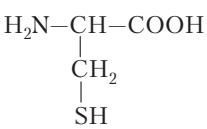
glycine
**Gly**



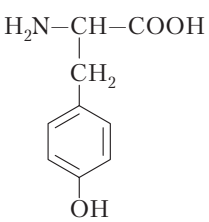
serine
**Ser**



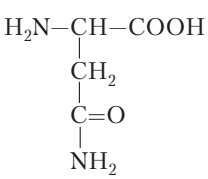
threonine
**Thr**



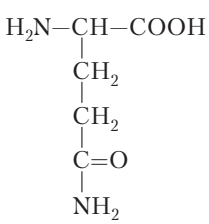
cycteine
**Cys**



tyrosine
**Tyr**



asparagine
**Asn**



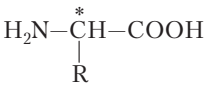
glutamine
**Gln**

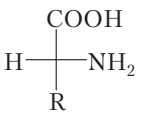
Amino acids, according to their acid-base properties, are divided into acidic (Glu, Asp), basic (Lys, Arg, His) and neutral (all the rest).

Some amino acids may be synthesized in the body. *Essential* amino acids are not formed in humans 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 infants under one year.

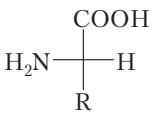
## 14.2. Stereochemistry of amino acids

Most of amino acids are chiral. Glycine is the only exception, as it has no chiral centre. Amino acids containing one chiral centre exist in the forms of their two enantiomers.





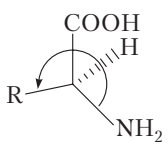
D-amino acid



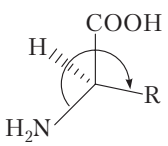
L-amino acid

Threonine and isoleucine have two chiral centres. Therefore, four stereoisomers are possible for their structure.

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



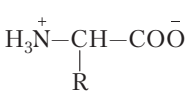
S-amino acid



R-amino acid

## 14.3. Chemical properties of amino acids

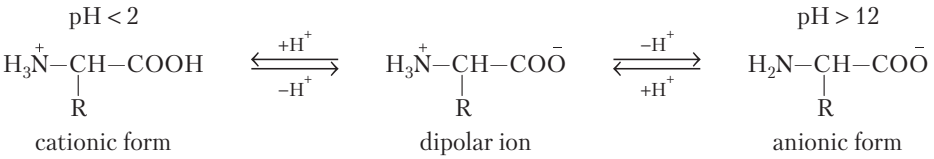
Amino acids react at the carboxyl and amino groups; thus they exhibit their *amphoteric properties*. Biologically important reactions of amino acids constitute a separate group.



dipolar structure of amino acid

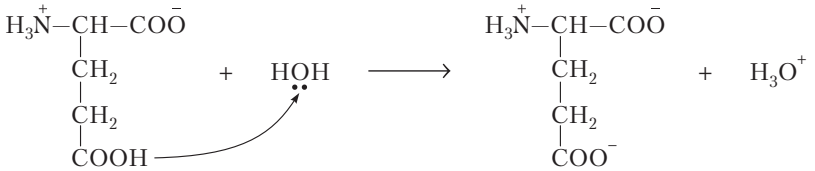
The carboxyl and amino groups of amino acids are ionized in aqueous solutions and in the crystalline state. That is why an amino acid forms a dipolar ion.

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

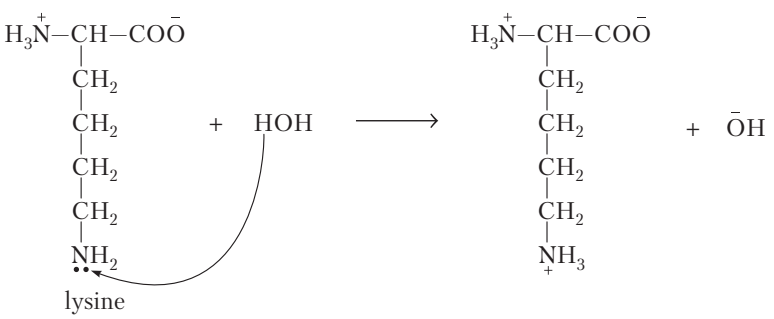


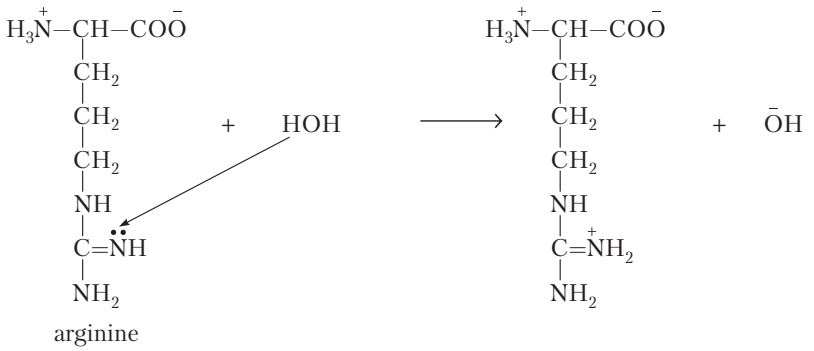

An **isoelectric point** is the pH value at which an amino acid exists in an electrically neutral form. The isoelectric point depends on the structure of the amino acid. Neutral amino acids have isoelectric points in the pH range of 5.0 to 6.3.

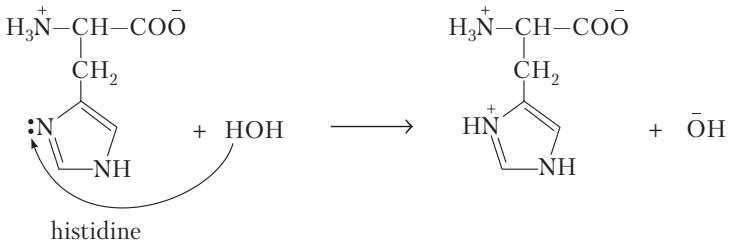
Aspartic acid and glutamic acid have an extra carboxyl group. Therefore, Asp and Glu are classified as acidic amino acids. Their isoelectric points are 3.2 and 2.7 respectively.



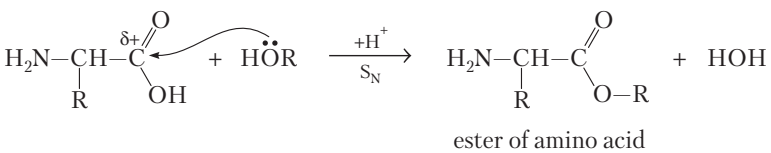

Lysine, arginine, histidine have an extra basic function in their side chains. Their isoelectric points are 9.8, 10.8 and 7.6 respectively.



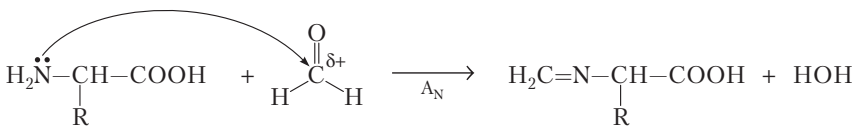



Amino acids are able to take part in the reactions of nucleophilic substitution at the carboxyl group, such as esterification, the formation of anhydrides, amides, and others. Amino acid esters are important intermediates in the synthesis of peptides.



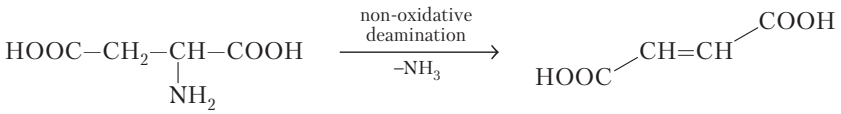

Most of carbonyl compounds react with the amino group of an amino acid, thereby producing Schiff bases.



## 14.4. Biologically important reactions

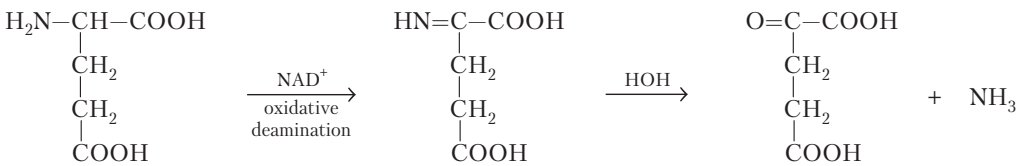
***Deamination*** is the removal of an amino group. There are two types of enzymatic deamination.

The first one is the non-oxidative type of deamination; it leads to the formation of α,β-unsaturated carboxylic acids.




Asp fumaric acid

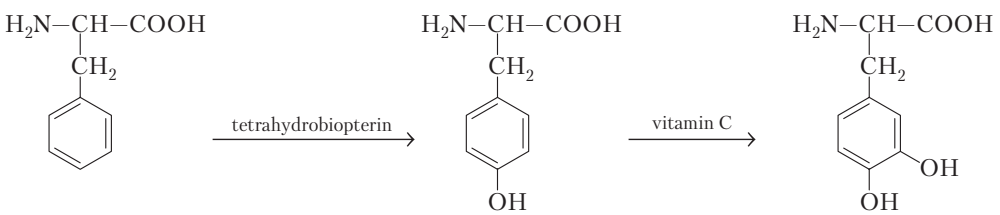
Another type is the oxidative type of deamination which is a two-step process. The first step represents the enzymatic oxidation of an amino acid into an intermediate α-imino acid in the presence of coenzyme $NAD^+$. The second step is hydrolysis.




Glu α-oxoglutaric acid

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

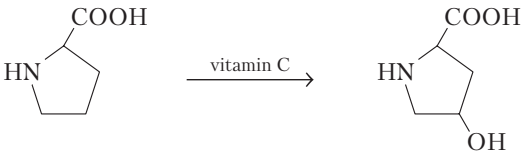
***Hydroxylation*** is the type of reactions accompanied by introducing hydroxyl groups into the skeletons of amino acids. Such reactions require the presence of ascorbic acid (vitamin C). Tyrosine is formed by hydroxylation of phenylalanine.



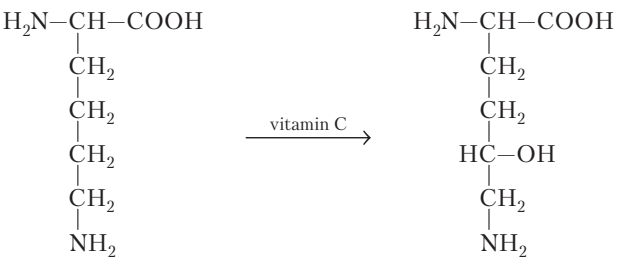

Phe Tyr DOPA (3,4-dioxyphenylalanine)

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

Hydroxylation of proline and lysine is necessary for the formation of specific spatial structures of collagen.

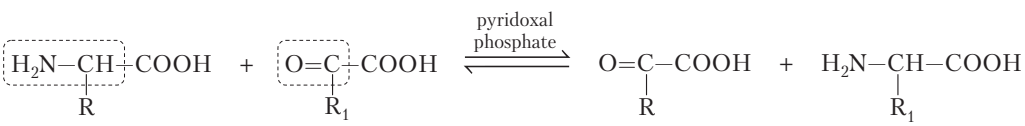



Pro 4-hydroxyproline

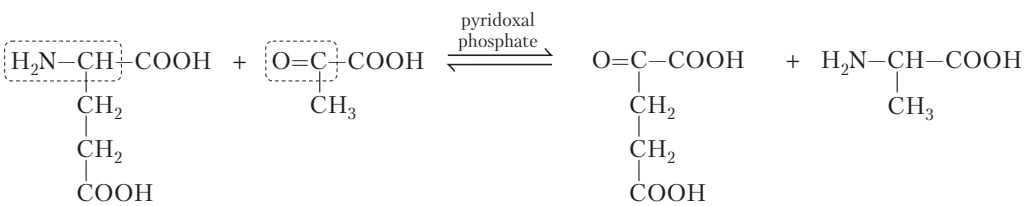



Lys 5-hydroxylysine

***Transamination*** is a reaction between oxo and amino acids. The exchange of their functional groups occurs at the same time. Such reaction proceed in the presence of pyridoxal phosphate (vitamin $B_6$).



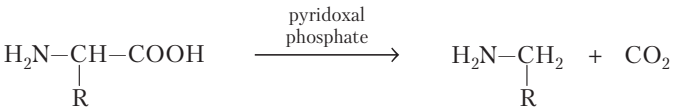

Transamination is used for the synthesis of amino acids, and oxo acids are required at this moment in the cell. Oxo acid such as pyruvic, oxaloacetic, α-ketoglutaric are the acceptors of the amino group in reactions of transamination.



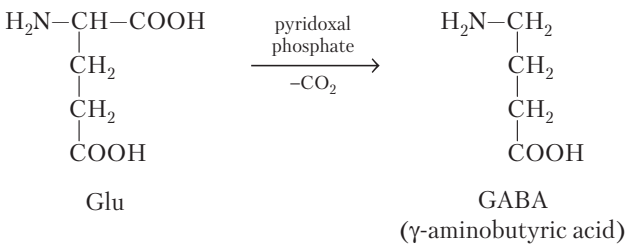

Glu pyruvic acid α-oxoglutaric acid Ala

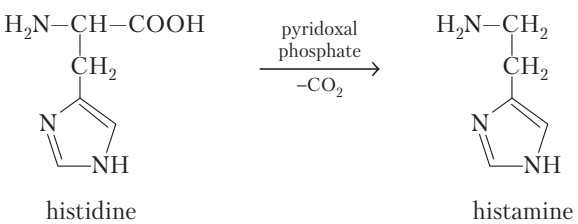
***Decarboxylation*** is the reaction that removes a carboxylic group and eliminates carbon dioxide. *In vivo*, this reaction proceeds in the presence of pyridoxal phosphate and leads to the formation of biogenic amines.

**Biogenic amines** are products of the decarboxylation reaction of amino acids that perform their specific functions in living cells.

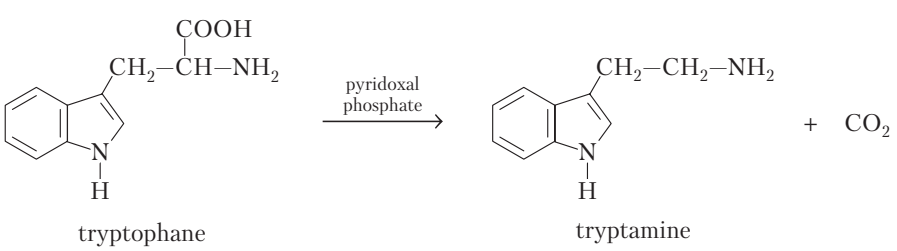



For example, decarboxylation of glutamic acid leads to the formation of the neurotransmitter GABA (γ-aminobutyric acid). A similar reaction with histidine gives ***histamine***. Histamine provides manifestations of inflammatory and allergic reactions.

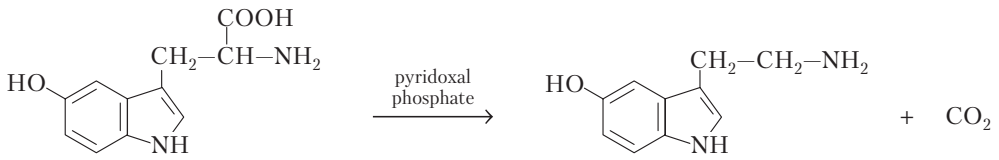



***Tryptophane*** is decarboxylated *in vivo* to tryptamine. Many compounds that contain the tryptamine skeleton produce their effect on the brain and nervous system.



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

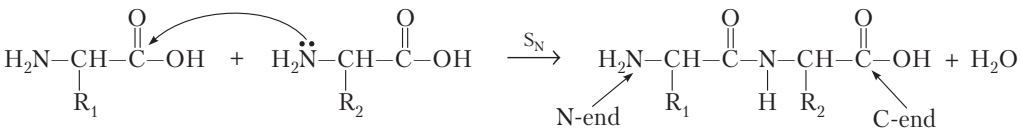



5-hydroxytryptophane serotonin

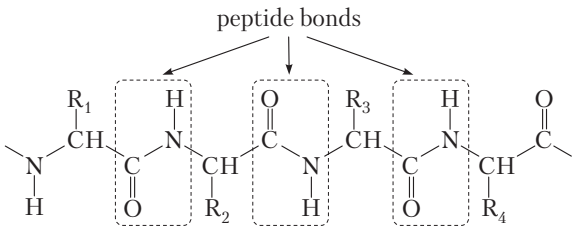
In the central nervous system, serotonin plays an important role as a neurotransmitter in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, appetite, and the metabolism.

# 15. PEPTIDES AND PROTEINS

Peptides and proteins are natural or synthetic substances consisting of residuals of α-amino acids connected to each other by means of amide or peptide bonds.

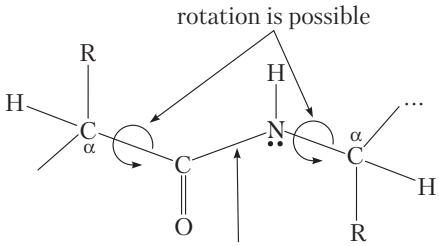



Peptides contain less than 100 amino acid residues. Proteins consist of more than 100 amino acid residues. They also have a more complex spatial organization. Amino acids are linked by ***peptide bonds*** in molecule of the peptide or protein.




general structure of peptide

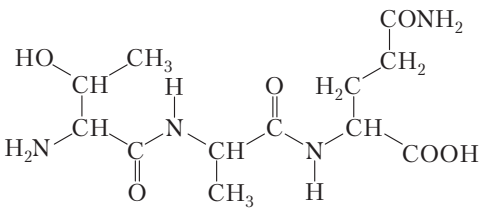
A peptide bond has a flat structure: its carbon, oxygen and nitrogen atoms are in the $sp^2$ hybridization. The nitrogen atom has a *p* orbital with an unshared pair of electrons. A *p*,π conjugated system is formed. A flat conjugated system complicates the rotation about the C—N bond. Thus, the electronic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




A polypeptide chain may be represented as a number of angularly located planes of peptide groups connected with α carbon atoms by using $C_\alpha$—N and $C_\alpha - C_{sp^2}$ bonds. Rotation about the $C_\alpha - C_{sp^2}$ and $C_\alpha$—N bonds is possible, but it is restricted due to the difficulties with the spatial placement of side radicals. Thus,

the electronic and spatial structure makes a contribute essentially to the determination of the structure of a polypeptide chain.

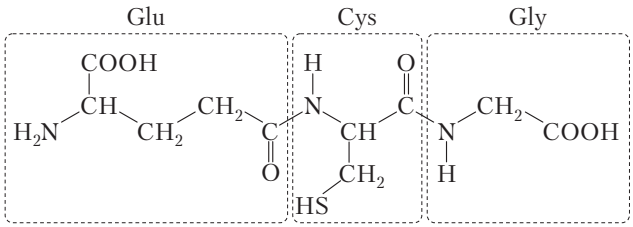
To build a peptide's name, one must name sequentially all its amino acid residuals, by starting from the N-end, and add the suffix *-yl*. The full name of only the last amino acid (at the C-end) is used.



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

## 15.1. Representatives of peptides

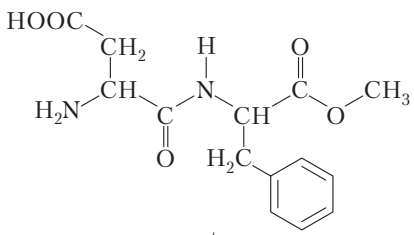
***Glutathione*** (γ-glutamylcysteinylglycine) is a tripeptide. It is found in all animal and plant cells, as well as in bacteria. The presence of cysteine means that glutathione can exist both in its reduced and oxidized forms.




glutathione

Glutathione takes part in redox processes. It performs the function of protein protector, i.e. 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

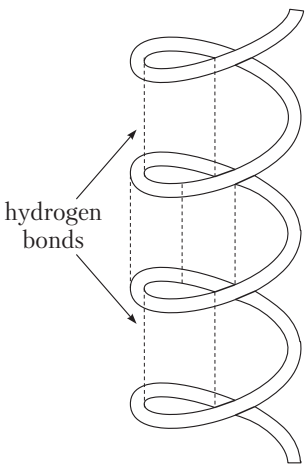
***Neuropeptides*** (opioid peptides) were first discovered in the brain. There are two groups of neuropeptides distinguished: enkephalins and endorphins. Their synthetic analogues which interact with the opiod receptors possess the analgetic action and are used as drugs.

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

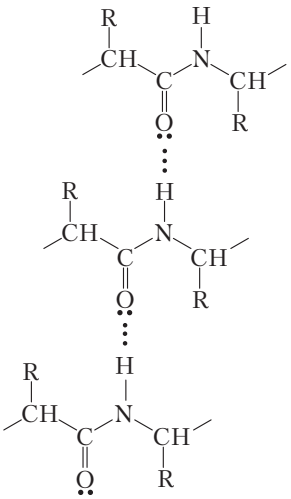
## 15.2. Levels of protein structure

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

**The secondary structure** is a local conformation of a certain part of a polypeptide chain as a result of the rotation about the σ bonds of α carbon atoms of the polypeptide chain, which leads to high order and stabilization. The most studied secondary structures are a the α-helix and the β-pleated sheet structure.



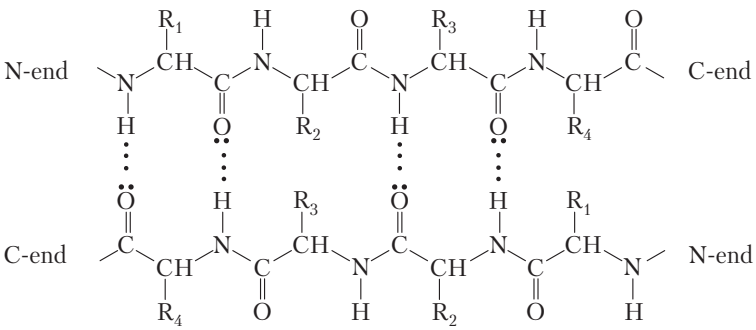

α-helix



hydrogen bonds

An α-*helix* is a right-handed helical structure which is stabilized by the hydrogen bonds between the —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 by the hydrogen bonds between the —NH and —CO groups of different polypeptide chains in fibrillary proteins or different parts of the same polypeptide chain in globular proteins.



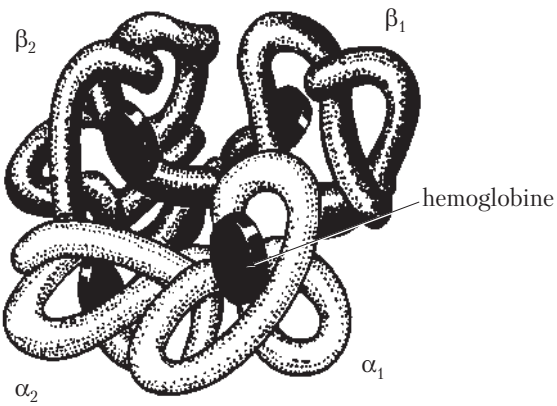

β-pleated sheet structure

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

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

Hydrogen bonds, dipolar and hydrophobic interactions are of great importance in the formation of a tertiary structure. These bonds are very weak, but due to a great number of individual weak interactions they define the spatial structure and stability of protein molecules. Nonpolar amino acid radicals are attracted to each other. In most cases they tend to limit their contact with water and hide themselves inside a protein molecule, thereby forming a hydrophobic core. Radicals of polar amino acids are capable of forming hydrogen bonds with each other or with water molecules on the surface of protein molecules. 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 protein molecules have a hydration shell on the surface, which is very important to maintain the natural spatial shape.

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




A single protomer usually shows no biological activity. Hemoglobin is an example of quaternary structure proteins. 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 a heme. The hemes are located in hollows ("heme pockets"), one in each subunit.

## 15.3. Denaturation of proteins

The initial spatial structure of proteins can be broken under the influence of different factors: a temperature rise, pH changes, exposure to ultraviolet light or X-rays, mechanical effects (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 proteins' structure, are broken. Denaturation of proteins results in their decreased solubility in water, a decrease of their biological activity. Denaturation may be reversible or irreversible. If it is reversible, an active (renaturated) protein may be obtained upon the removal of the denaturants.

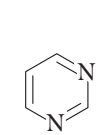
# 16. NUCLEIC ACIDS

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

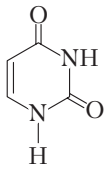
## 16.1. Nucleic acids

A nucleic acid consists of mononucleotides. A nucleotide is built of nucleoside and phosphoric acid. A nucleoside, in turn, consists of a heterocyclic base and a sugar (D-ribose or 2-deoxy-D-ribose). All nucleosides that can be obtained from DNA contain 2-deoxy-D-ribose and one of four heterocyclic bases (adenine, guanine, cytosine, thymine). All nucleosides that can be obtained from RNA contain D-ribose and either of four heterocyclic bases (adenine, guanine, cytosine, uracil).

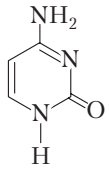
The aromatic compounds purine and pyrimidine underlie the heterocyclic base structures.



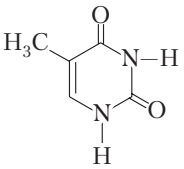
pyrimidine



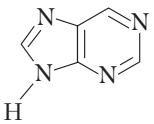
uracil



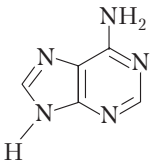
cytosine



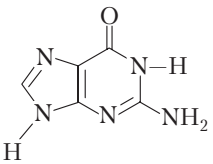
thymine



purine

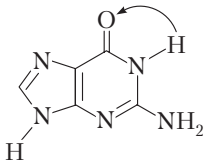


adenine

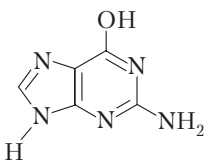


guanine

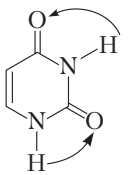
The heterocyclic bases are capable of taking tautomeric forms. Lactam forms are the predominant forms of the bases when they are present in nucleic acid.



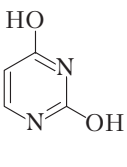
guanine
lactam form



lactim form



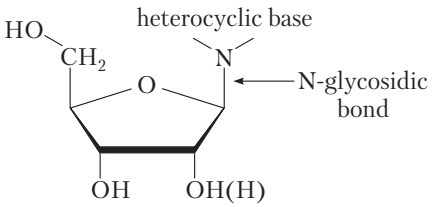
uracil
lactam form



lactim form

## 16.2. Nucleosides

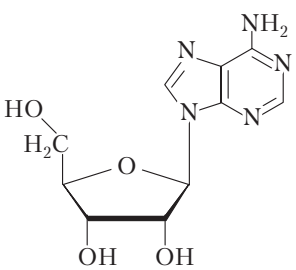
***Nucleosides*** are the "building blocks" of nucleic acids. Nucleosides are N-glycosides constructed from two components: a sugar and a heterocyclic base. D-Ribose and 2-deoxy-D-ribose are in their cyclic β-furanose form.



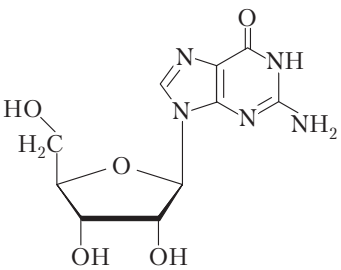

the general formula of nucleoside

| 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 |

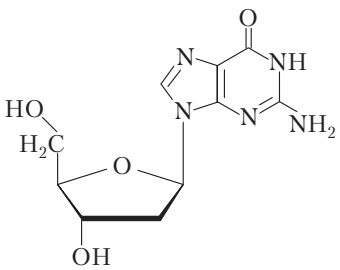
The names and the structures of the nucleosides are shown below.



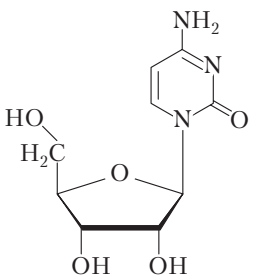

adenosine



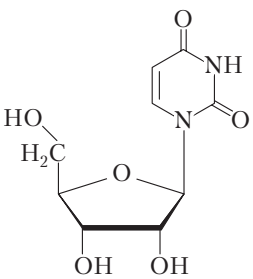

guanosine



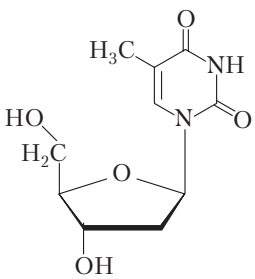

deoxyguanosine




cytidine




uridine

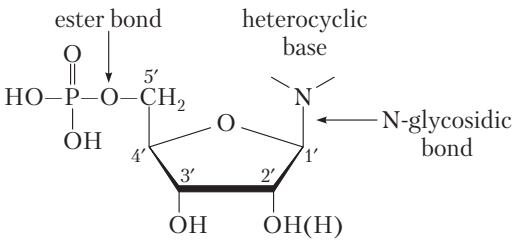



thymidine

## 16.3. Nucleotides

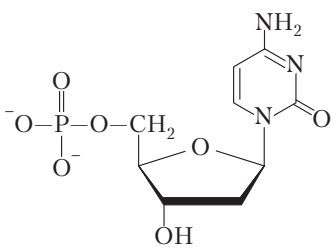
***Nucleotide*** is an ester of phosphoric acid and a nucleoside. The heterocyclic base and the ribose fragments are numbered separately. The carbon atoms of ribose or deoxyribose are numbered with a prime (′). Phosphate esterification usually occurs at the 5′ position of the pentoses. However, sometimes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

A general formula for nucleotides is shown in the figure below (esterification at the 5 position).




the general formula of nucleotide

Nucleotides show acid properties, because they contain a phosphate fragment. Under physiological conditions nucleotides exist in an ionized form.




deoxycytidine-5′-monophosphate (dCMP)

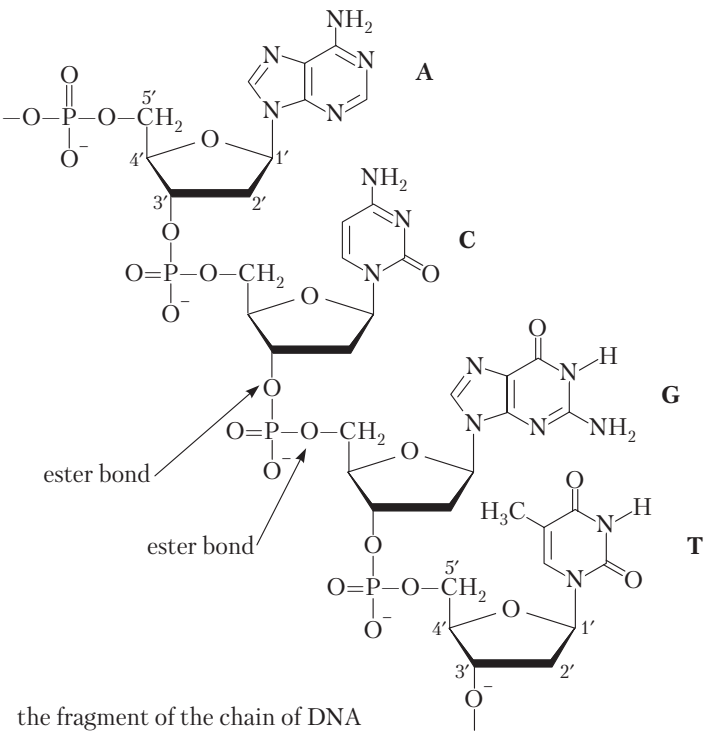
The complete hydrolysis of a nucleotide (acidic or enzymatic) yields a heterocyclic base (either a purine or a pyrimidine base), a five-carbon monosaccharide (either D-ribose or 2-deoxy-D-ribose) and a phosphate ion.

Nucleotides are the components of nucleic acids (DNA and RNAs). 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 the adjacent nucleotides. The end of the polymeric chain that has a free

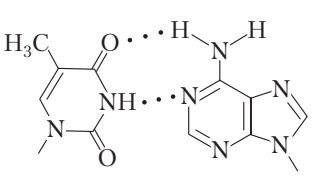
hydroxyl group at $C_{5'}$ is called the *5′-end* and the end with a free —OH group at $C_{3'}$ is called the *3′-end*. Each end can be phosphorylated.

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 a 3-dimensional organization of the macromolecule.

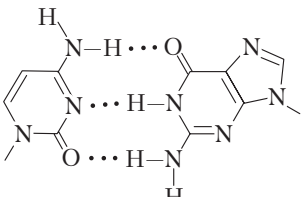



the fragment of the chain of DNA

Two factors are mainly responsible for the stability of the double helix of DNA: (1) the base pairing between the complementary heterocyclic bases by hydrogen bonds and (2) the stacking between the adjacent bases. Thus, the two polynucleotide chains are linked by hydrogen bonds. These hydrogen bonds form two types of pairs: adenine-thymine, guanine-cytosine.



thymine adenine



cytosine guanine

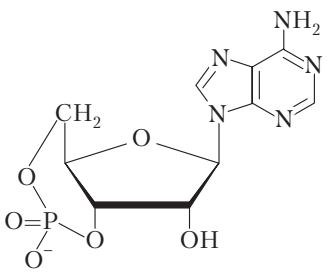
Stacking is a vertical interaction between the hydrophobic nucleobases located in the same chain over each other.

RNAs are structurally similar to DNA. Like the DNA, an RNA has a sugar-phosphate polymer backbone with attached heterocyclic bases. RNA molecules are smaller than DNA. RNA molecules exist mostly as single strands. There are four types of RNA:

- the ribosomal RNA (rRNA);
- the messenger RNA (mRNA);
- the transport RNA (tRNA);
- the small interfering RNA (si-RNA).

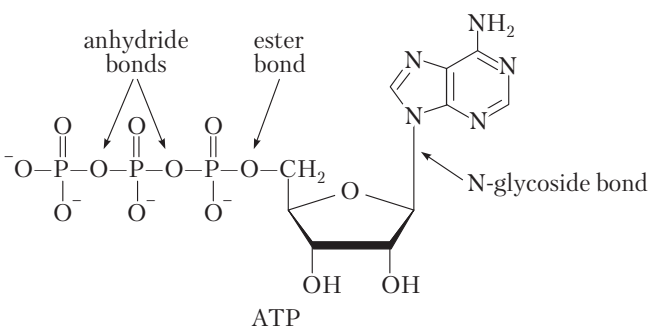
The messenger RNA is the RNA that carries information from the DNA to a ribosome, the sites of protein synthesis (translation) in the cell.

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

5′-Triphosphate of adenosine, or ATP is the energy source. This molecule contains two anhydride fragments; therefore, it has two high-energy bonds.



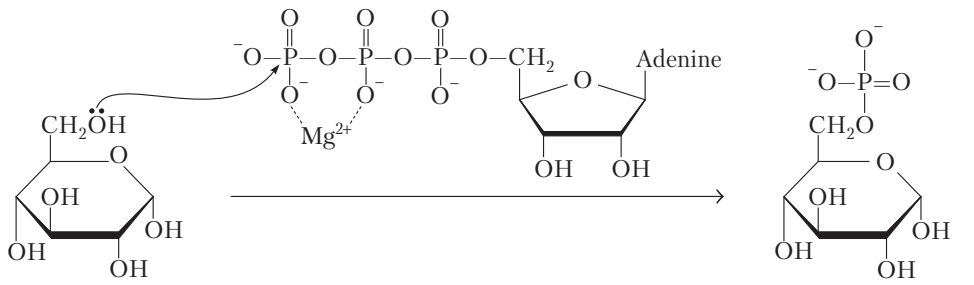

ATP

The break of an anhydride bond is accompanied by the release of large amounts of energy.

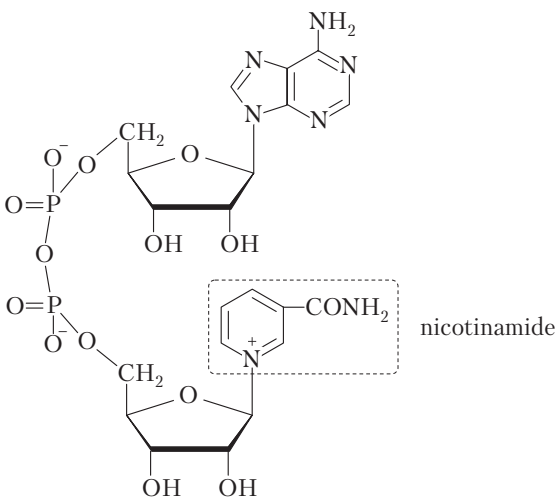
$$\text{ATP} \longrightarrow \text{ADP} + \text{energy} + \text{phosphate}$$

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

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

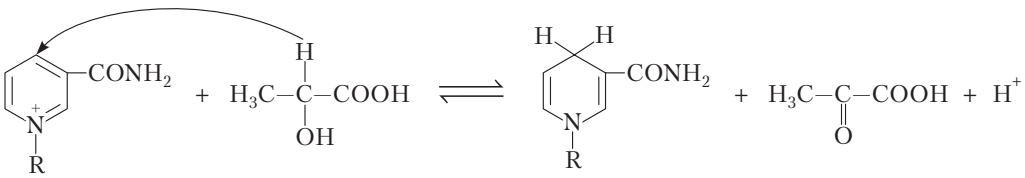



An adenosine unit is a part of the structure of coenzyme $NAD^+$ (nicotinamide dinucleotide).




Coenzyme $NAD^+$ participates in redox reactions. Coenzyme $NAD^+$ attaches the hydride anion, which splits off from a substrate. As a result, the nicotinamide

loses its aromaticity, and NADH (nicotinamide adenine dinucleotide reduced) is formed.




$NAD^+$ lactate NADH pyruvate

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 various structures and biological functions. They are united in a single category on the basis of the following three main criteria:

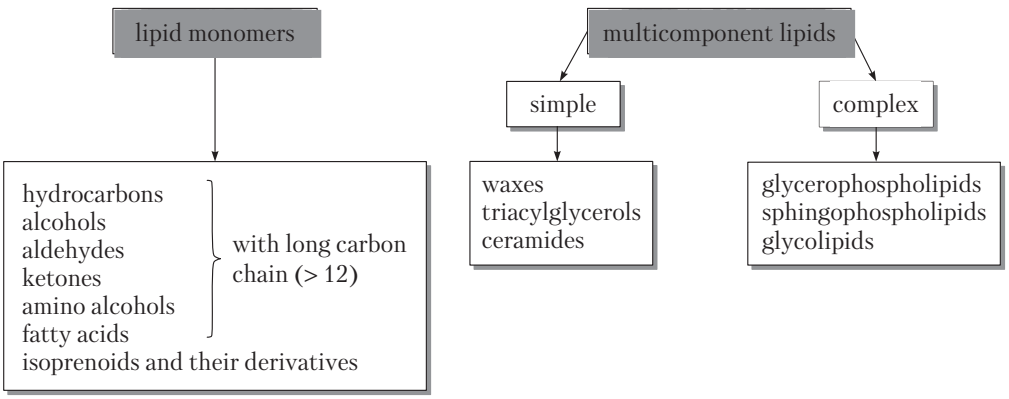
1) almost completely insoluble in water and soluble in nonpolar solvents;
2) present in nature in the form of esters of fatty acids;
3) present in all living organisms.

## 17.1. Classification and categories of lipids

Formerly lipids have been divided into hydrolysable and non-hydrolysable. Hydrolysable lipids contain a ester fragment and can be hydrolyzed. Non-hydrolysable lipids cannot undergo hydrolysis.

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

**Classification of lipids**



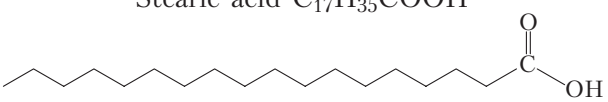

Lipids mainly perform energetic, structural, protective and regulatory functions. Reserve lipids (fats) perform energy storage function. The amount and structures of reserve lipids are changeable and depend on the diet and the physical state of an organism. The quantity and structure of structural lipids in an organism are constant, as they are genetically predefined and normally do not depend on the diet and the state of an organism. The protective function is performed mainly by lipids that constitute the subcutaneous fat. The regulatory function is performed by fat-soluble vitamins and lipids which have a hormone-like activity.

Different alcohols may be part of lipids: glycerol, inositol, propane-1,2-diol (see Chapter 9). Long-chain alcohols ($C_{12}$—$C_{30}$) are found in composition of lipids.

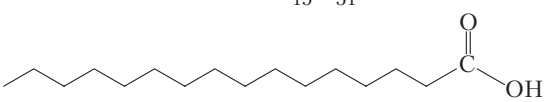
Fatty acids are often included in multicomponent lipids. Fatty acids are mono carboxylic acids with a long carbon chain containing usually an even number of carbon atoms (12 to 24). Fatty acids can be saturated and unsaturated. Trivial names are used to designate fatty acids. Additionally, unsaturated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

**Saturated fatty acids**

Stearic acid $C_{17}H_{35}COOH$

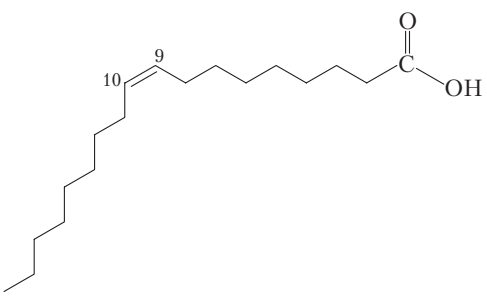



Palmitic acid $C_{15}H_{31}COOH$

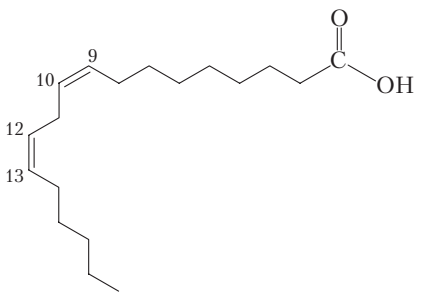



**Unsaturated fatty acids**

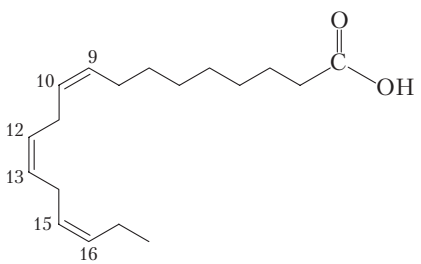
Oleic acid $C_{17}H_{33}COOH$ (18:1 ω9)



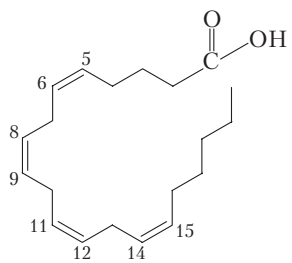

Linoleic acid $C_{17}H_{31}COOH$ (18:2 ω6)




Linolenic acid $C_{17}H_{29}COOH$ (18:3 ω3)




Arachidonic acid $C_{19}H_{31}COOH$ (20:4 ω6)



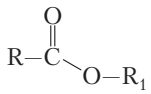

Natural fatty acids have unbranched carbon chains. Under physiologic pH conditions, the fatty acids are ionized. The melting points of unsaturated fatty acids are lower than of saturated acids with the same number of carbon atoms.

The chains of saturated fatty acids have a zigzag-shaped structure in which the carbon atoms are arranged in the *anti*-butane conformation. Natural unsaturated acids have the *cis*-configuration, which is less thermodynamically stable. They melt at lower temperatures than the corresponding *trans*-isomers. At somatic temperatures, unsaturated fatty acids are liquids. The double bonds in poly-unsaturated fatty acids are not conjugated. Unsaturated fatty acids except for oleic acid are essential because they are not synthesized *in vivo*. So they must be obtained from food (for example, vegetable oils).

## 17.2. Simple lipids

Simple lipids consist of two components: an alcohol and a fatty acid.

***Waxes*** are the esters formed by long-chain alcohols and fatty acids.

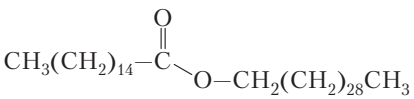


the general formula of waxes

R — the residual of a fatty acid

$R_1$ — the residual of an alcohol with a long chain

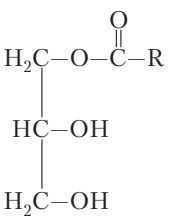
Natural waxes comprise an admixture of free fatty acids, alcohols, hydrocarbons. Myricyl palmitate is the main component of bee wax.



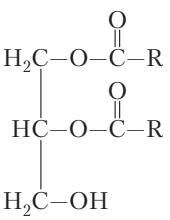
myricyl palmitate

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.

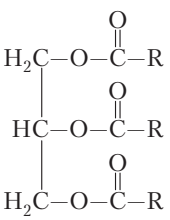
***Triacylglycerols*** are esters of fatty acids and glycerol. Triacylglycerol synthesis in the cell passes the stages of the formation of monoacylglycerole and diacylglycerole.



monoacylglycerol



diacylglycerol

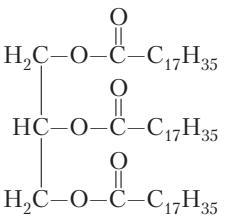


triacylglycerol

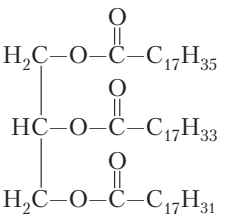
Triacylglycerols may contain the same or different fatty acid residues. According to the nature of the constituent fatty acid (saturated or unsaturated), triacylglycerols are either solids (fats) or liquids (oils).

Triacylglycerols of the human organism contain residues of different fatty acids, with the predominance of unsaturated ones.

According to the international nomenclature, names of triacylglycerols are formed by adding the suffix *-oyl* to the name of the corresponding acyl radical of the fatty acid.



tristearoylglycerol



1-stearoyl-2-oleoyl-
3-linoleoylglycerol

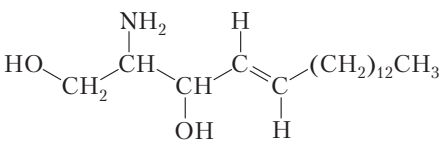
Triacylglycerols are hydrophobic substances. Their melting points depend on the degree of unsaturation of the corresponding constituent fatty acid. Vegetable fats (oils) containing mono- and polyunsaturated fatty acids melt at lower temperatures. The degree of unsaturation is characterized by the iodine number.

In animals and humans triacylglycerols have special functions:

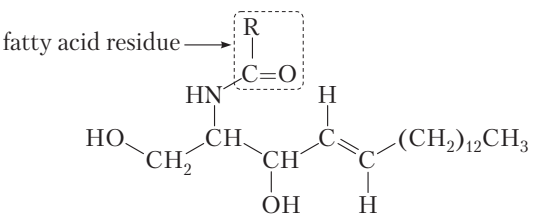
❒ in fatty tissues they form the so-called fatty deposits representing a form of energy storage;

❒ triacylglyceroles play the physical protection role and act as a temperature regulator of various body organs.

***Ceramides*** are also referred to as simple lipids. They are N-acylated sphingosine derivatives. Ceramides are found in tissues of the nervous system.



sphingosine

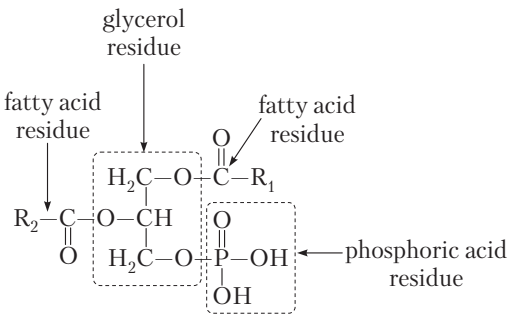



ceramide

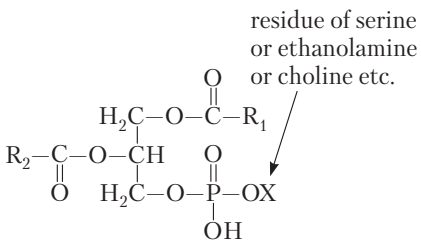
# 17.3. Complex lipids

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

***Glycerophospholipids*** are derivatives of phosphatidic acid. In the formation of glycerophospholipids a phosphoric acid residue reacts with a hydroxyl-containing compound by the nucleophilic substitution mechanism.

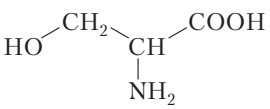



phosphatidic acid

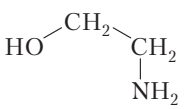



general formula of glycerophospholipids

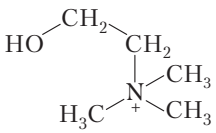
Substances such as ethanolamine, serine, choline, inositol often represent the complex lipids.



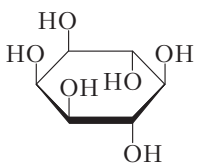
serine



ethanolamine

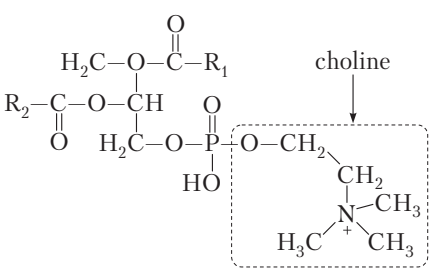


choline



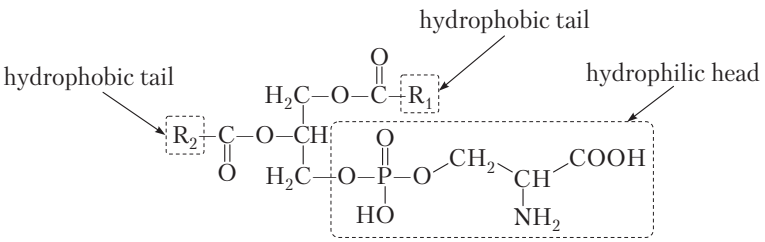
inositol

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

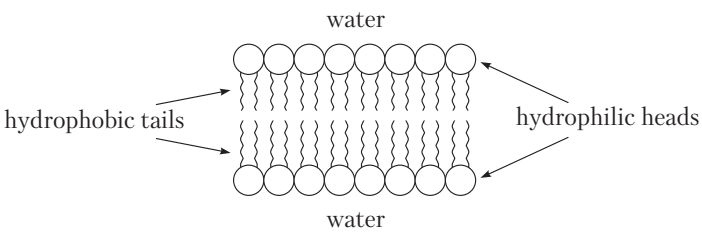



phosphatidylcholine

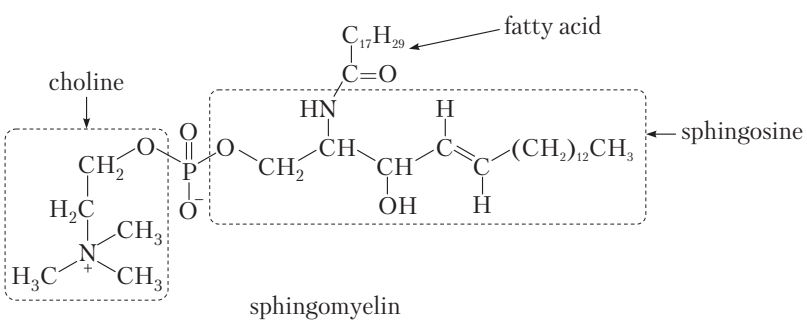
Every phospholipid incorporates a waterproof nonpolar part including radicals of fatty acids (*the hydrophobic tails*) and a polar part (*the hydrophilic head*) including the residuals of glycerol, phosphoric acid and amino alcohol.



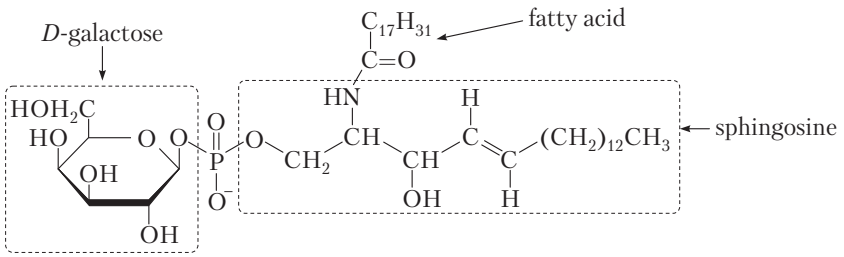

Molecules of glycerophospholipids are inherently amphiphilic and are able to settle down in an appropriate way on the boundary of two phases, thereby enabling the formation of lipid double-layer membranes. Biological membranes are cell structures which separate cytoplasm and the majority of intracellular organelles.




***Sphingolipids*** are a class of lipids containing a backbone of sphingoid bases, a set of aliphatic amino alcohols that includes sphingosine. They are often found as part of the myelin sheath of nerve fibers. Similar to glycerophospholipids, sphingolipids perform the structural function. Sphingomyelin is an example of sphingophospholipids.



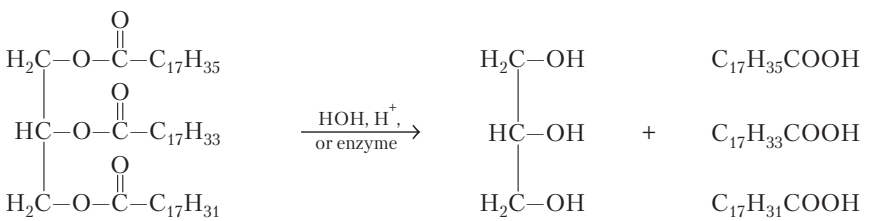
A molecule of ***glycolipids*** contain in its composition residues of mono- or polysaccharides. Glycolipids are also found as part of biological membranes.



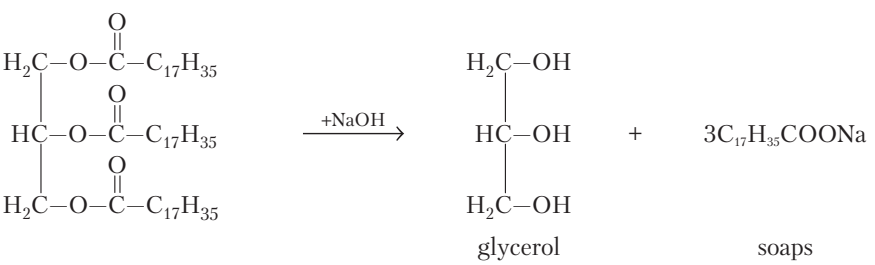

the example of glycolipids

## 17.4. Chemical properties of lipids

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

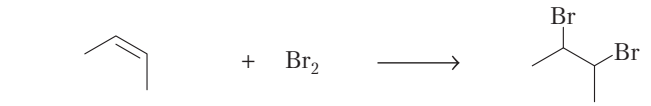



The alkaline hydrolysis results in the formation of glycerol and fatty acid salts (soaps).

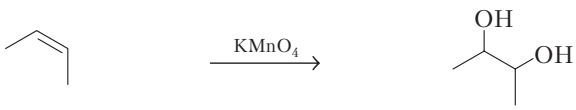



Soaps have detergent action because their molecules are amphiphilic.

Lipids containing unsaturated fatty acids give positive chemical tests with bromine water and potassium permanganate.



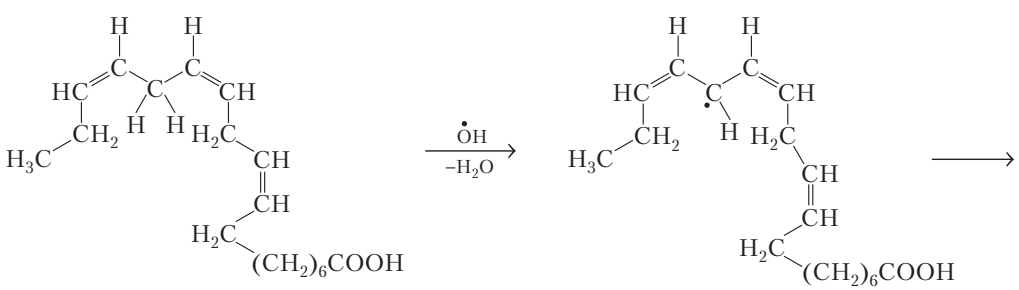

unsaturated fragment of fatty acid — product of addition reaction



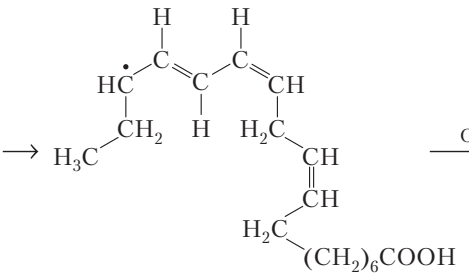

unsaturated fragment of fatty acid — product of oxidation reaction

***Lipid peroxidation*** refers to the oxidative degradation of lipids. Normally, peroxidation of lipids is supposed to update the biological membranes. However, this process can lead to damage of the membranes. It is a process whereby free radicals take electrons from the lipids in cell membranes, which results in cell damage. This process runs by the free radical chain reaction mechanism. Only unsaturated fatty acids in lipids undergo oxidation. The methylene groups between the double bonds are highly reactive due to the formation of stabilized radicals.

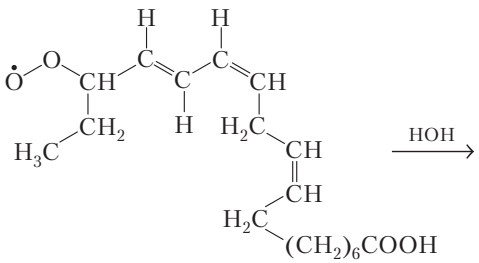
The initiation is the step, whereby a fatty acid radical is produced. The initiators in living cells are most notably reactive oxygen species (ROS), such as OH; they combine with a hydrogen atom to form water and a fatty acid radical.



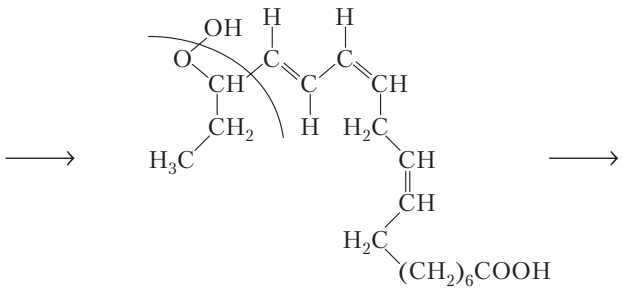

linolenic acid — radical of linolenic acid with ,*p*, conjugated system



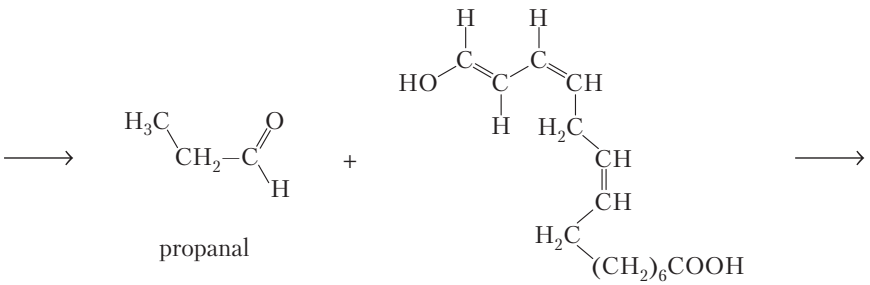
radical of linolenic acid
with *p*,π,π conjugated system



superoxide radical

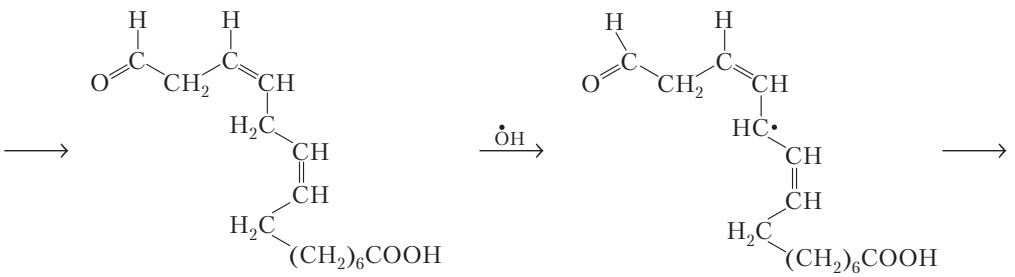


hydroperoxide of linolenic acid

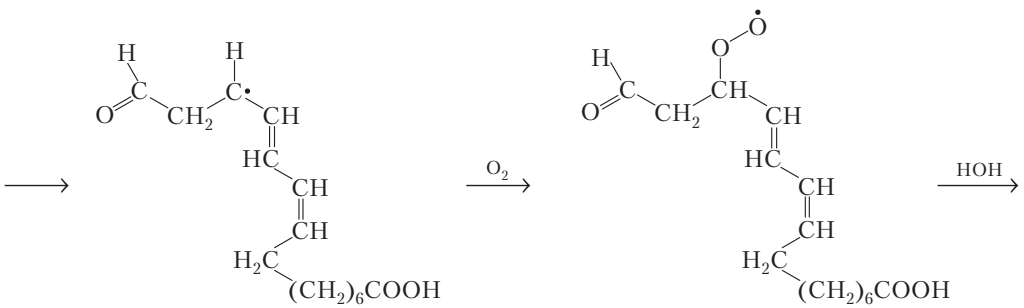


propanal

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

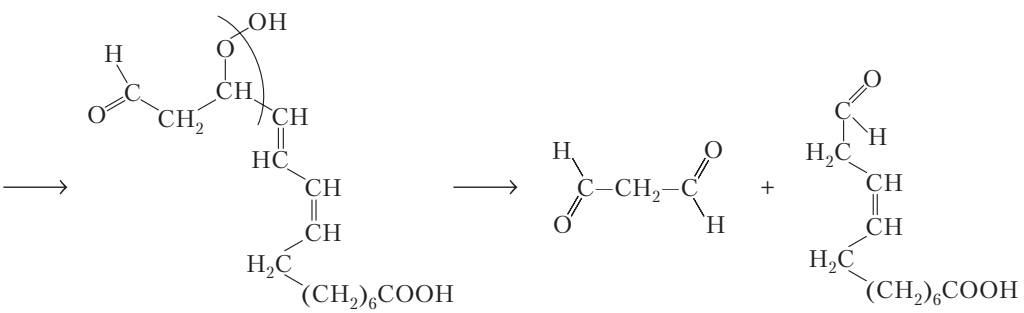


radical with ,*p*, conjugated system




radical with $p,\pi,\pi$ conjugated system

superoxide radical



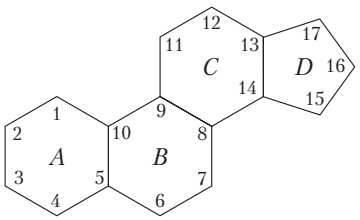
hydroperoxide

malonic aldehyde

Living cells usually contain antioxidant systems (e.g. vitamins E, A and C, and many other compounds) which serve to limit the process of lipid peroxidation. Synthetic antioxidants are produced in the pharmaceutical industry.

# 18. STEROIDS

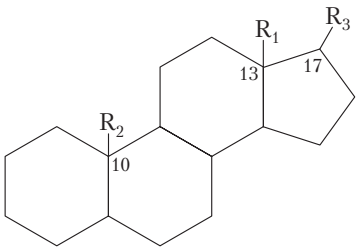
Steroids are important biological regulators that always show dramatic physiological effects. Among these important compounds there are male and female sex hormones, adrenocortical hormones, vitamins D, bile acids, etc. Steroids are derivatives of perhydrocyclopentanophenanthrene, or gonane. The carbon atoms of this ring system are numbered as shown below. The four rings are designated with letters.

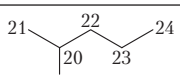
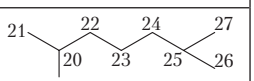


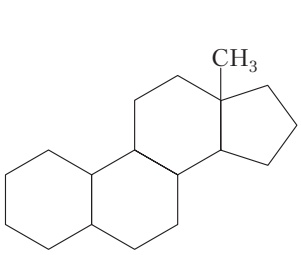

gonane

## 18.1. Classification of steroids

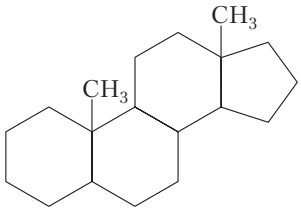
Steroids which are found in the human body can be divided into 5 groups. Representatives of these groups differ from each other in the presence or absence of radicals in positions 10, 13 and 17.



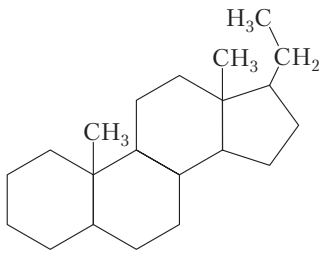

| Name | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| estrane | $-CH_3$ | H | H |
| androstane | $-CH_3$ | $-CH_3$ | H |
| pregnane | $-CH_3$ | $-CH_3$ | $-CH_2-CH_3$ |
| cholane | $-CH_3$ | $-CH_3$ |  |
| cholestane | $-CH_3$ | $-CH_3$ |  |



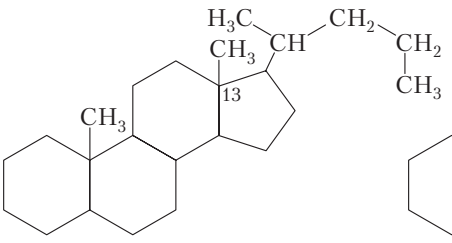

estrane



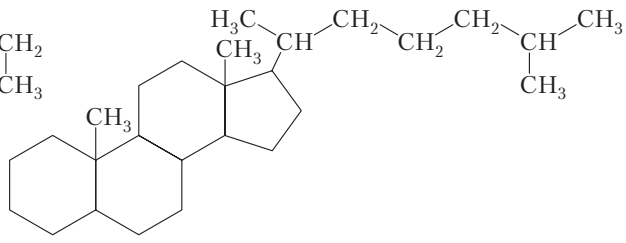

androstane




pregnane

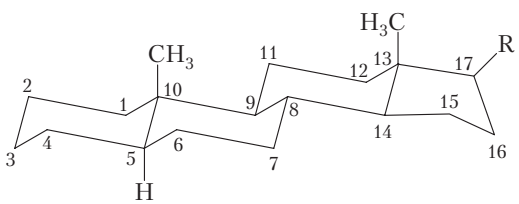



cholane

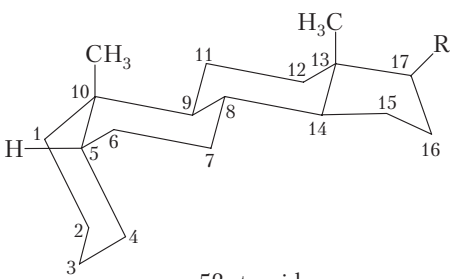



cholestane

Rings A and B may be connected either in the *cis* or the *trans* position and this possibility gives rise to two general groups of steroids with the three-dimensional structures shown below.




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

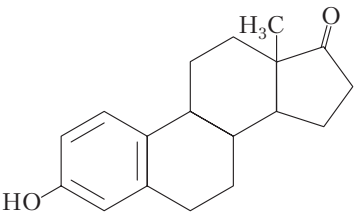



5β steroid
(A/B ring connection is *cis*)

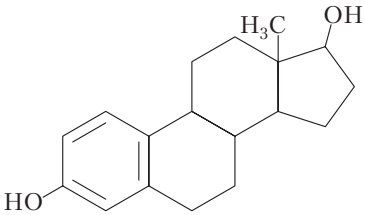
The methyl groups attached at the connection points of the rings (i.e., those numbered 18 and 19) are called angular methyl groups. The angular methyl groups protrude above the general plane of the ring system when it is represented in the manner shown in the figures above. By convention, other groups that are located on the same side the molecule as the angular methyl groups (on the top side) are designated as β-substituents. Groups that located on the bottom side are designated as α-substituents. When α- and β-descriptors are applied to the hydrogen atom at $C_5$, 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.

## 18.2. Representatives of steroids

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



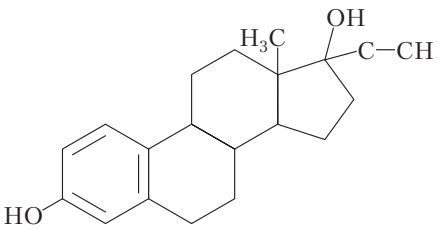

estrone




estradiol

Estradiol is secreted by the ovaries and promotes the development of secondary female characteristics.

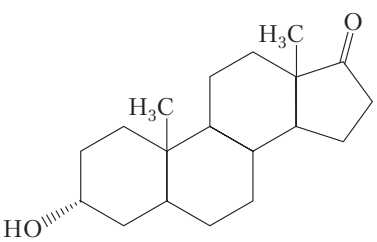
Synthetic estrogens have also been developed and these are often used in oral contraceptives in combination with synthetic progestins. The compound called ethynylestradiol is a very potent synthetic estrogen.



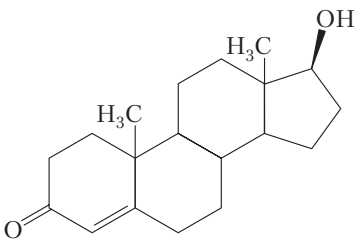

ethynylestradiol

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

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




androsterone

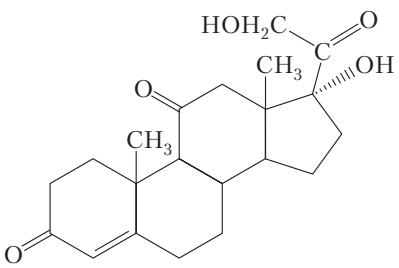



testosterone

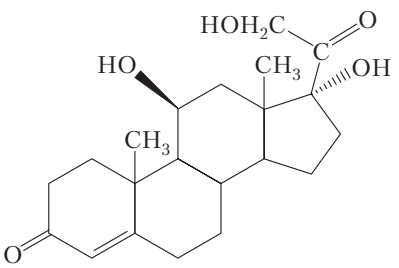
***Testosterone***, secreted by the testes, is the hormone that promotes the development of secondary male characteristics: the growth of facial and body hair, the deepening of the voice, the typical muscular development, the maturation of the male sex organs.

The structural formula of estradiol is very slightly different to that of testosterone. Testosterone has an angular methyl group at the A/B ring connection. The A ring in an estradiol molecule has aromatic properties and, as a result, estradiol is a 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.



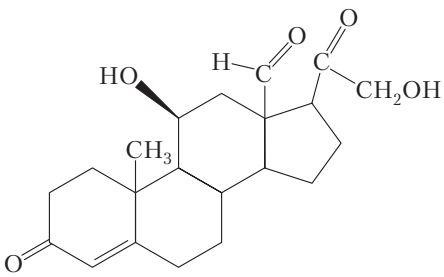
cortisone



cortisol

Most of adrenocortical steroids have an oxygen function at $C_{11}$. ***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 the carbohydrate, protein, and lipid metabolism, the maintenance of the 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 skin inflammations.

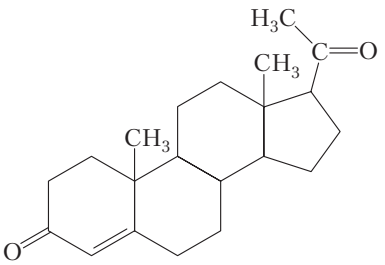
Adrenal hormones are divided into glucocorticoids and mineralocorticoids. Cortisone and cortisol are glucocorticoids. Aldosterone is a mineralocorticoid that participates in the regulation of the water and mineral metabolism.



aldosterone

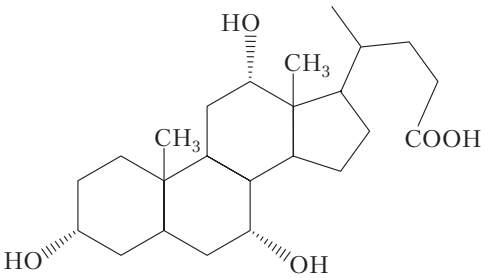
It regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions.

***Progesterone*** is the most important progestin (the pregnancy hormone). After an ovulation, the *corpora lutea* begin to secrete progesterone. This hormone prepares the cellular lining of the uterus for the implantation of fertilized ova. Continued secretion of progesterone is necessary for the completion of the pregnancy.

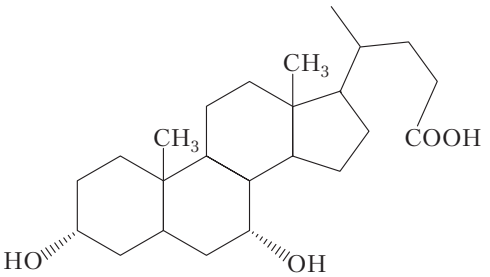



progesterone

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

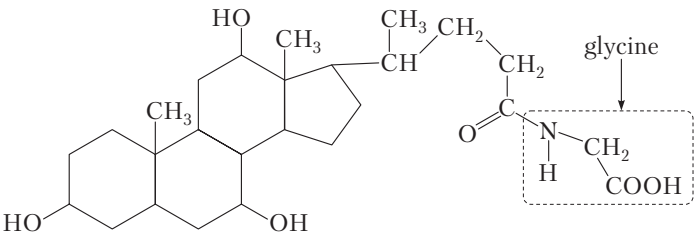



cholic acid




12-deoxycholic acid

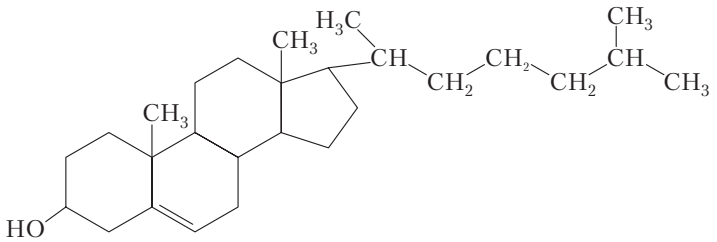
Bile acids can be conjugated (bonded) to taurine or glycine. The conjugation results in a lowered p$K_a$ and therefore, the compounds remain ionized.




glycocholic acid

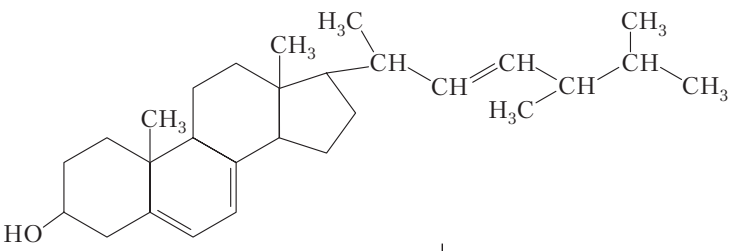
These ionized compounds stay in the gastrointestinal tract until they reach the ileum where they are reabsorbed. The purpose of this conjugation is to keep the bile acids in the tract until the end in order to facilitate the lipid digestion all the way to the ileum.

**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. Therefore, cholesterol is vitally important.



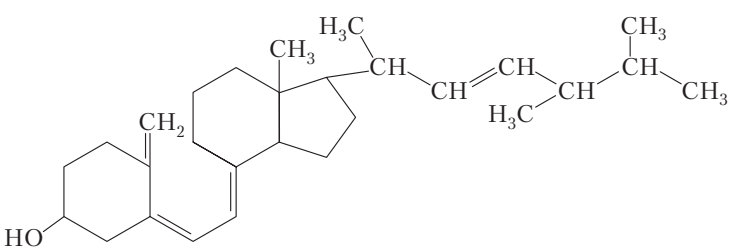

cholesterol

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



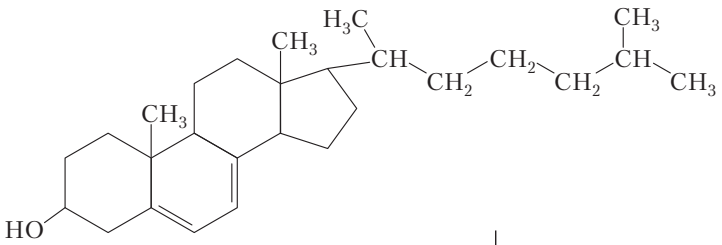

ergosterol

UV

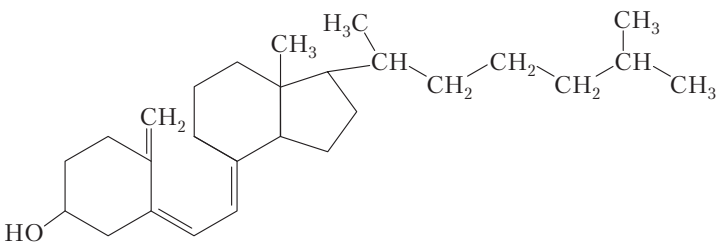



vitamin $D_2$

***Vitamin $D_3$*** is formed in the human body. It is synthesized from cholesterol, which first undergoes a dehydrogenation reaction. This reaction occurs in the skin. Thereupon the ring B is broken under the influence of ultraviolet.

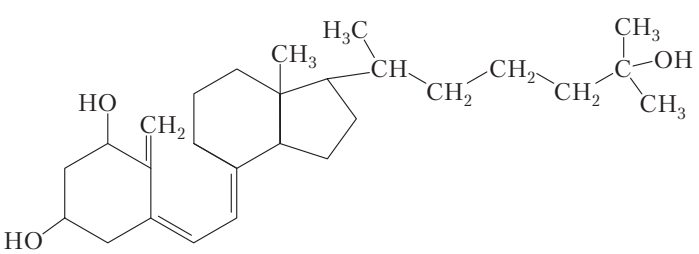



7-dehydrocholesterol UV




cholecalciferol

Cholecalciferol is hydroxylated in the liver and kidneys ($C_{25}$ and $C_1$).




activated form of vitamin $D_3$

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

# Notes

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*Учебное издание*

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# БИООРГАНИЧЕСКАЯ ХИМИЯ
# BIOORGANIC CHEMISTRY

Учебное пособие

Ответственный за выпуск — *С.В. Исаенко*

Подписано в печать 26.06.2018. Формат 70×100 $^{1}/_{16}$. Бумага офсетная. Печать офсетная.
Усл. печ. л. 14,65. Уч.-изд. л. 13,45. Тираж 500 экз. Заказ №

Общество с ограниченной ответственностью «Новое знание».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/276 от 23.12.2015.
Пр. Пушкина, д. 15а, Минск, Республика Беларусь.
Почтовый адрес: а/я 79, 220050, Минск, Республика Беларусь.
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http://wnk.biz

Отпечатано в ОАО «Можайский полиграфический комбинат».
143200, г. Можайск, ул. Мира, 93
www.oaompk.ru, www.oaompk.рф, тел.: 8-495-745-84-28, 8-49638-20-685