

Vinnitsia National Pirogov Memorial Medical University

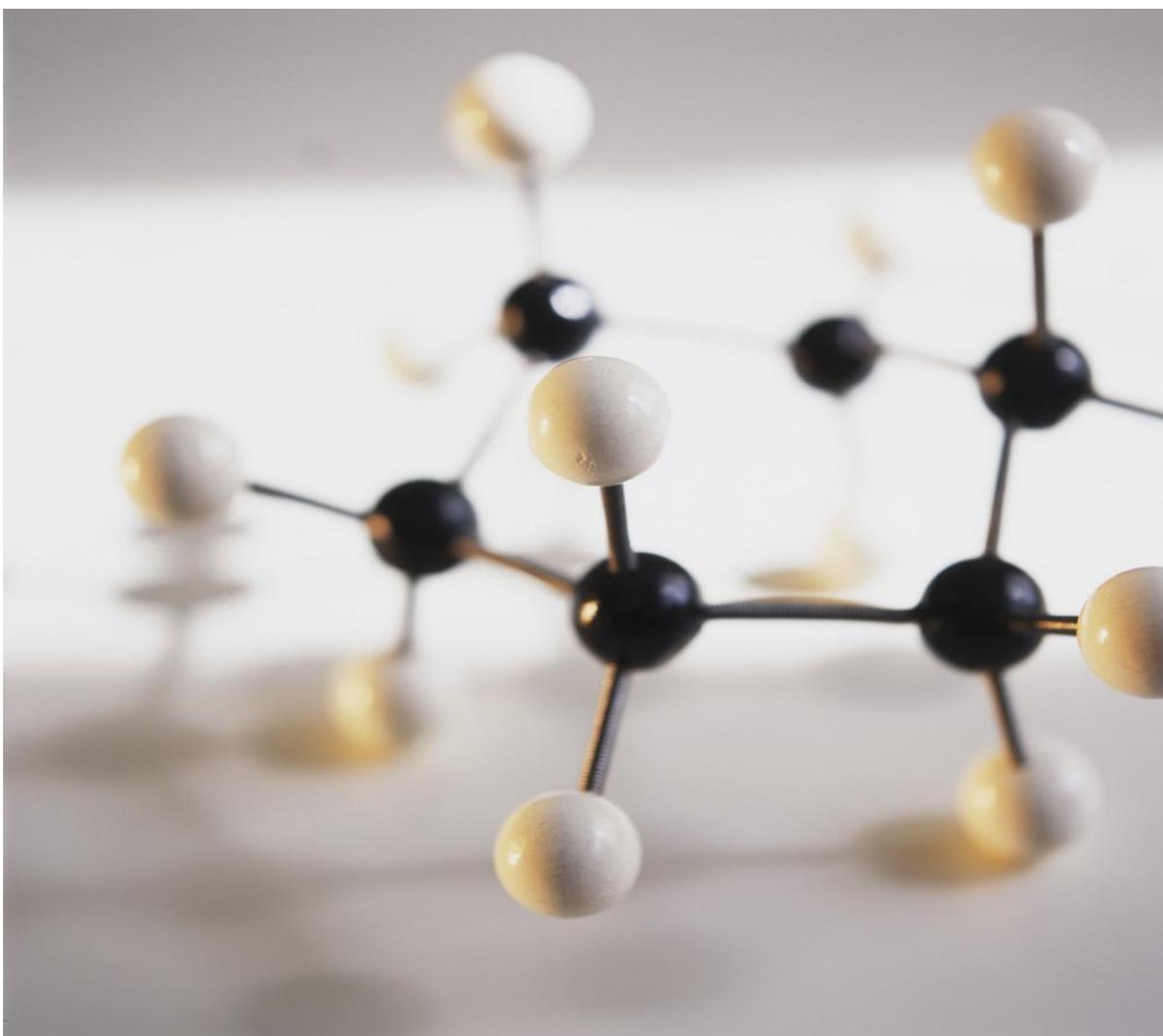
Biological and General Chemistry Department

Bioorganic chemistry course

Part I

THEORETICAL BASIS OF REACTIVITY

BIOLOGICALLY ACTIVE COMPOUNDS



Vinnitsia 2017

A work sheet and methodical developments (Methodical of recommendation for practical classes from Bioorganic chemistry for 1-st year foreign students) are made by the employees of department of biological and general chemistry of VNMMU Pirogov in accordance with a curriculum, worked out on principles of the European credit-transfer system (ECTS) for higher medical establishments of Ukraine III - IV levels of accreditation for specialities of “Medical Affairs” direction of the preparation “Medicine” is in accordance with education qualification descriptions (EQD) and scientific professional programs (SPP) of the preparation of specialists, approved by an order MES Ukraine from 16.04.03 № 239.

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Bioorganic chemistry studies the structure, physico-chemical properties and mechanisms of reactions, which involve the biologically active compounds.

Biologically active compounds are synthesized in the human body or enter the body and are involved in biochemical processes. They are:

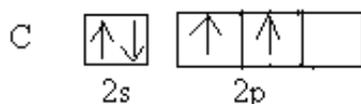
Biopolymers	low-molecular substances
↓	↓
proteins	vitamins
nucleic acids	hormones
polysaccharides	alkaloids
and their derivatives	drugs
containing lipids	and other

Although bioorganic chemistry emerged at the boundary of organic and biological chemistry, it uses the theoretical concepts and physical - chemical methods of classical organic chemistry. The scientific basis of bioorganic chemistry, is the theory of Butlerov, which explains the large number and variety of organic compound.

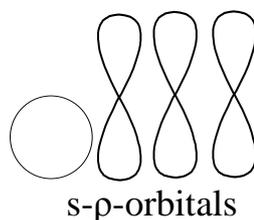
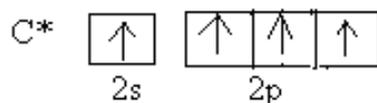
Electronic structure of atoms of carbon and its

CHEMICAL COMMUNICATIONS

One reason for the large number and variety of organic compounds lies in the peculiarities of the structure of the carbon atom. Electron - graphic formula of the carbon atom in the ground state is given by:

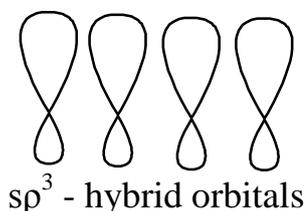


With its two unpaired electrons of carbon can form two covalent bonds. However, organic compounds, carbon atom in accordance with the theory of Butlerov always tetravalent, that is, he is excited and the electron - a graphic formula in this case is as follows:

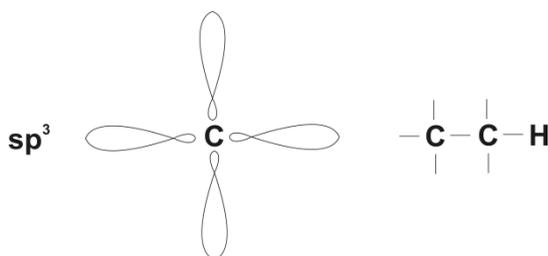


Such a carbon atom forms four covalent bonds, but they are unequal, as the s - and p-orbitals have different energy and shape. At the same alkane molecules all links are equal, which is achieved by hybridization. Hybridization - is the alignment of the orbitals in the energy and shape. Depending on the conditions in which there is formation of chemical bonds, carbon atom is in a different hybridization.

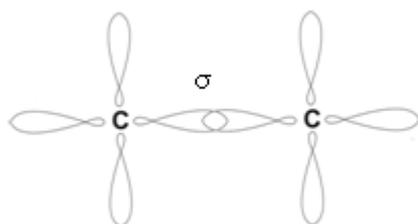
1) If the conditions of bond formation, such that a s - orbital and three p-orbitals are hybridized, the formation of four equivalent sp^3 - hybrid orbitals. They have the same energy and shape. In this case we say that a carbon atom is in sp^3 - hybridization.



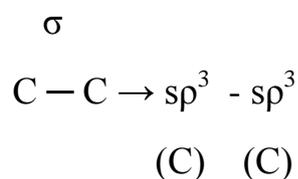
This gives the carbon atom to the formation of chemical bonds of four equivalent sp^3 - hybrid orbitals.



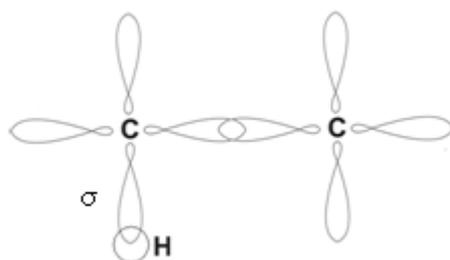
If sp^3 - a hybrid carbon atom forms a chemical bond with another sp^3 - a hybrid carbon atom, it is the overlap of hybrid orbitals formed and σ - bond.



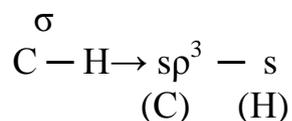
Schematically, this can be written as:



C-H bond in alkanes is σ - bond and is formed by the overlap sp^3 - hybrid orbitals of carbon and s-orbital of the hydrogen atom.

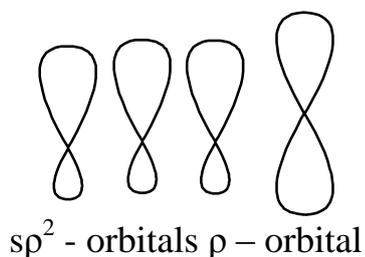


Schematically, this can be written as:

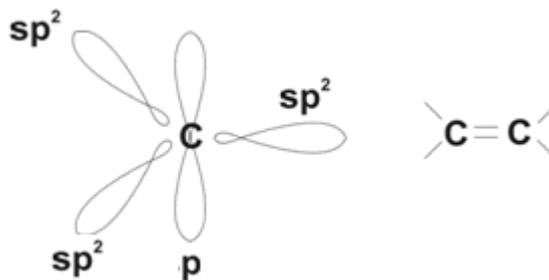


sp^3 - hybrid orbitals are directed at an angle of $109^\circ 28'$ and determine the spatial configuration of the molecule.

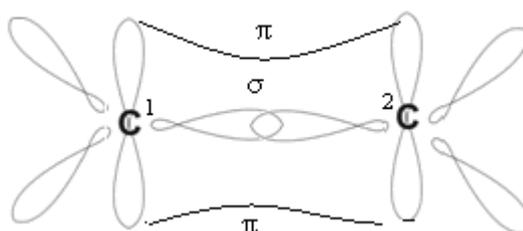
2) The other conditions of formation of the chemical bond is a carbon atom in sp^2 - hybridization. Such an atom has three sp^2 - hybrid orbitals and the one free ρ - orbital.



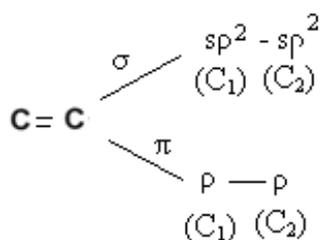
In the state of sp^2 - hybridization carbon atom is in alkenes:



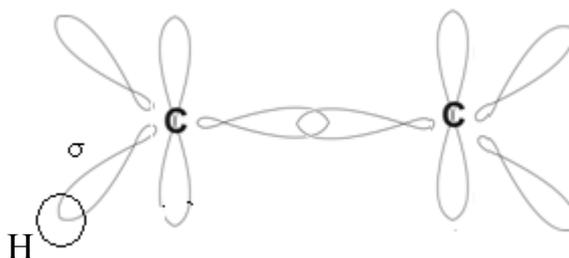
Double bond between carbon atoms in alkenes consists of σ - bond and π - bond. σ - bond is formed by overlapping sp^2 - orbitals and π - bond formed by the overlap of the free p - orbitals.



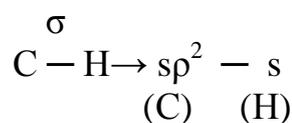
Schematically, this can be written as:



C-H bond in alkenes is σ - bond and is formed by the overlap sp^2 - hybrid orbitals of carbon and s-orbital of the hydrogen atom.

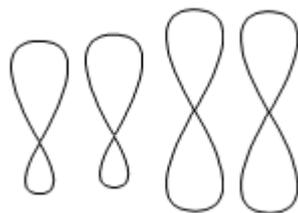


Schematically, this can be written as:



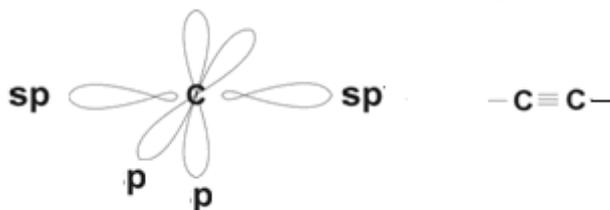
sp^2 - hybrid orbitals are directed at an angle of 120° , the molecule is located in the plane.

3) The conditions of formation of chemical bonds may be such that the carbon atom is in sp - hybridization. Such a carbon atom has two sp - hybrid orbitals and two free p - orbitals.

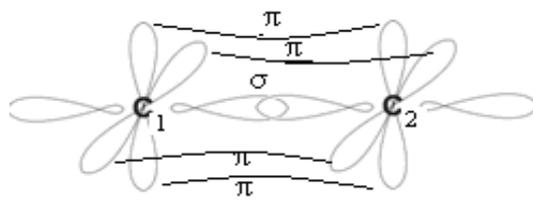


sp - p - orbitals

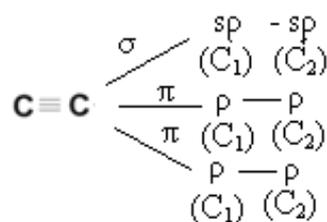
In the state of sp - hybridization carbon atom is in alkyne.



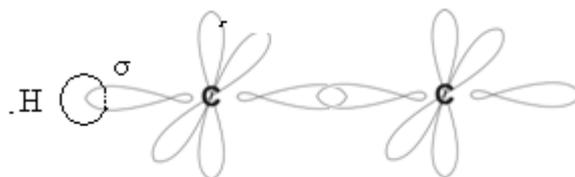
In the alkyne between the carbon atoms - a triple bond. One of them is σ - bond is formed by overlapping sp - hybrid orbitals. The remaining two bonds - is π - bonds which are formed by the overlap of the free p - orbitals.



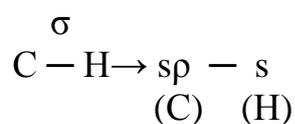
Schematically, this can be written as:



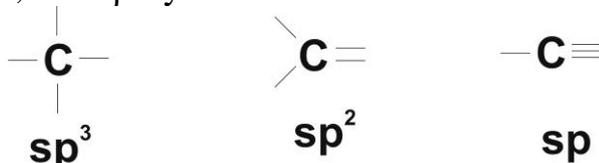
C-H bond in the alkyne - a σ - bond that is formed by the overlap sp - hybrid orbitals of carbon and s - orbitals of the hydrogen atom.



Schematically, this can be written as:



sp - hybrid orbitals are directed at an angle of 180° , i.e., the molecule has a linear configuration. Thus, if a carbon atom forms four simple σ -communication, it is in sp^3 - hybridization. If a carbon atom forms a double bond with another atom, it is in sp^2 - hybridization. If a carbon atom forms a triple bond with other atoms, it is sp -hybridization.



In biologically active compounds, carbon is mainly located in the sp^3 -hybridization and sp^2 - hybridization.

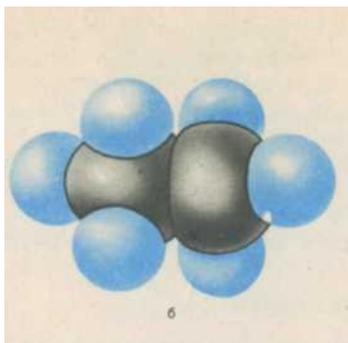
The spatial structure of biologically active compound

Another reason for the large number and variety of organic compounds are isomers. Isomerism - is the existence of organic compounds with the same qualitative and quantitative composition but different properties, due to different structure (structure) of organic compounds. For Bioorganic and Biological Chemistry isomerism is the cause of different biological activity. That is, only certain isomers exhibit biological activity, which may disappear in the process of isomerization, which causes pathological changes in the human body.

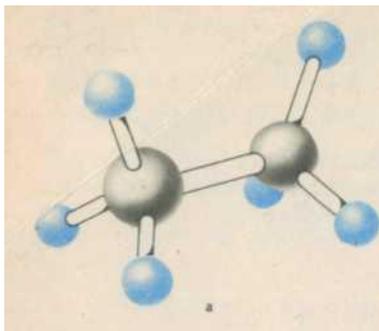
One type of isomerism is a spatial isomerism. The molecules of organic compounds can be arranged differently in space. The spatial arrangement of the molecules is called a configuration.

For the spatial images of molecules using:

- Stewart model, in which the atoms are represented in the form of a hemisphere

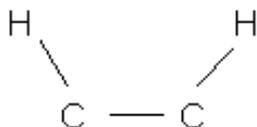


- ball-rod model in which the atoms are shown as spheres connected by rods - links:

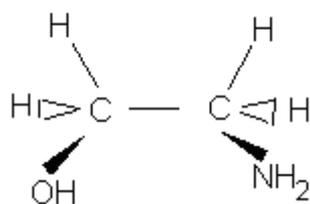


In the plane of the spatial arrangement of the molecules is written with the help of the formulas and stereo-chemical configurations.

For example, to write the configuration of the molecule coalmine $\text{HO-CH}_2\text{-CH}_2\text{-NH}_2$ (produced in the human body as a result of decarboxylation of the amino acid serine), you must create a model of the molecule and look at it so you can see two carbon atoms, two hydrogen atoms which are directed upwards and are coplanar with the carbon atoms, the relationship between them is written as usual in the structural formula, i.e. a single line:



The other two hydrogen atoms are directed away from the observer in space, they write to us. Functional groups HO-NH_2 and sent to the observer in space, they write to us

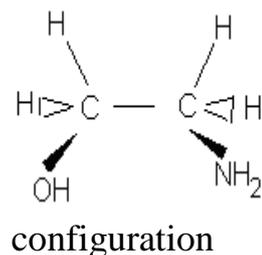


Configuration

Thus, to characterize coalmine can write the following formula:

$\text{C}_2\text{H}_7\text{ON}$
molecular
formula

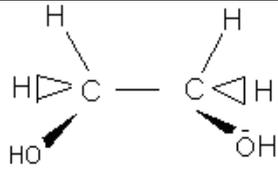
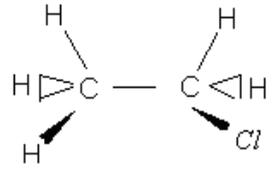
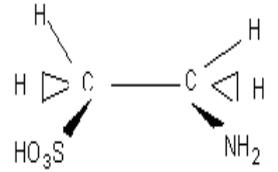
$\begin{array}{c} \text{H}_2\text{C} \text{ --- } \text{CH}_2 \\ | \qquad | \\ \text{OH} \quad \text{NH}_2 \end{array}$
structural
formula



Characteristics of some biologically active compounds are given in table number 1.

Table number 1

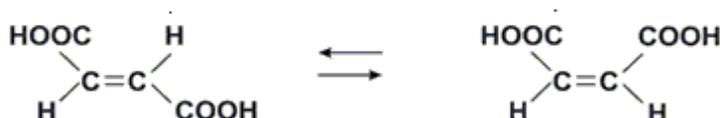
The biologically active agent	Molecular formula	Structural formula	Configuration
<i>Ehanol - antiseptic, a toxic effect on the human body</i>	$\text{C}_2\text{H}_6\text{O}$	$\text{CH}_3\text{-CH}_2\text{-OH}$	$\begin{array}{c} \text{H} \qquad \qquad \text{H} \\ \diagdown \qquad \diagup \\ \text{H} \triangleright \text{C} \text{ --- } \text{C} \triangleleft \text{H} \\ \blacktriangleright \text{H} \qquad \blacktriangleleft \text{OH} \end{array}$

<i>Ethylene glycol - antifreeze, toxic effects on the human body</i>	$C_2H_6O_2$	$\begin{array}{c} \text{CH}_2 - \text{CH}_2 \\ \quad \\ \text{HO} \quad \text{OH} \end{array}$	
<i>Chloroethane – anesthetic</i>	C_2H_5Cl	$CH_3 - CH_2 - Cl$	
<i>Taurine - an intermediate in the synthesis of bile acids:</i>	$C_2H_7O_3SN$	$\begin{array}{c} \text{CH}_2 - \text{CH}_2 \\ \quad \\ \text{HO}_3\text{S} \quad \text{NH}_2 \end{array}$	

Types of spatial isomerism. Cis - trans isomers

Cis-trans isomerism is due to different arrangement of atoms relative to the double bond.

A classic example of cis-trans isomerism is fumaric-maleic acid.

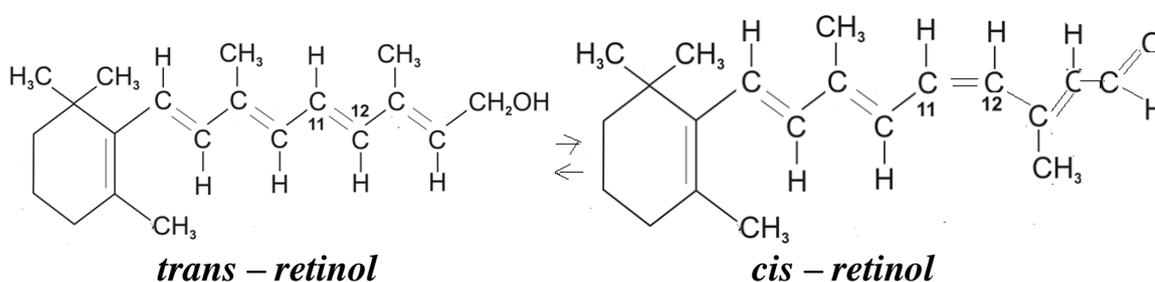


Isomerization is a gap in communications.

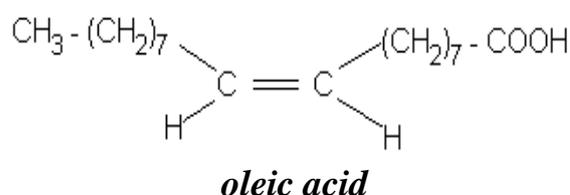
The biological significance of cis-trans isomerism.

1) Fumaric acid is formed in the body are normal. The formation of maleic acid is a skin disease - psoriasis.

2) Retinol (vitamin A) has a trans configuration. In humans, he gets isomerized and the cis-configuration, which takes participate in the process of vision.



3) High unsaturated fatty acids in the lipid composition have cis-configuration.



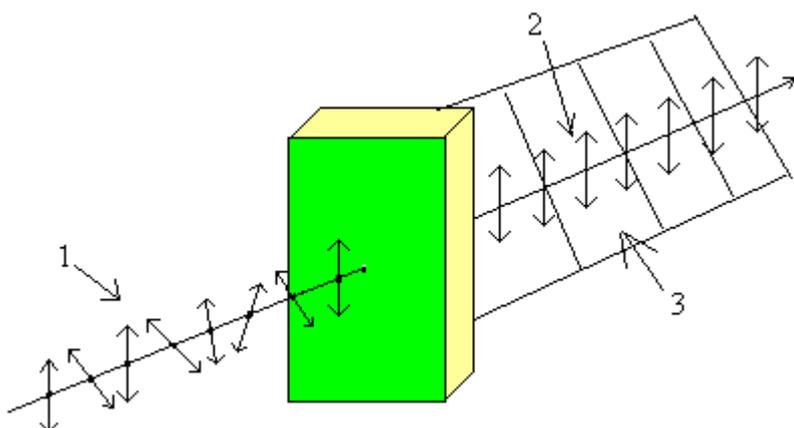
This makes them shortened and bent form, which is important for maintaining the structure of cell membranes.

4) Natural compounds polyprenols that transport carbohydrates in the human body, have a cis configuration.

Enantiomers

Enantiomers - the kind of isomerism due to the ability of substances to rotate the plane of polarization.

The plane of polarization is perpendicular to the plane of polarized beams. The polarized beam is produced by passing an ordinary light beam, in which the oscillations occur in different planes. (1), through the prism of spar. As a result of electromagnetic waves in a polarized beam occur in the same plane (2).



If the path of the polarized beam to put the tube with a solution of an organic compound, the plane of polarization (3) will rotate to the right or the left.

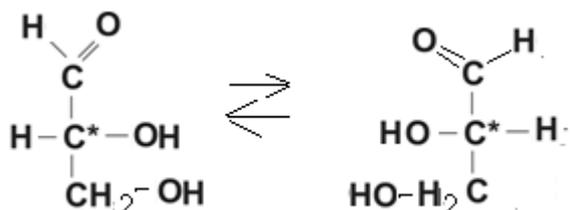
The ability of certain substances to rotate the plane of polarization is called optical activity.

Exhibit optical activity only asymmetric molecules. Asymmetry - one of the main signs of wild life: amino acids, monosaccharides, polysaccharides, DNA - it is asymmetrical molecules. By an asymmetrical body is the human hand. Hand in Greek - Hiroshi. Hence the term - surgery, palmistry, and the term in organic chemistry - chirality.

Chirality - a property of a substance to exist as a pair of incompatible specular reflections.

The formulas of chiral molecules is usually written in the Fischer projection, that is, have a carbon chain vertically, and at the top of the carbon atom is written senior functional group.

An example of a chiral molecule can be glyceraldehyde:



D – glyceraldehyde L – glyceraldehyde

These molecules are asymmetric, because they have an asymmetric carbon atom C* and chiral center.

Chiral center - a carbon atom, which is in sp^3 - hybridization and associated with four different substituents.

These two molecules have a different configuration of the chiral center. The first molecule is a functional group is located on the right, so the molecule has D - configuration. The second functional group of the molecule is located on the left, so the molecule is L - configuration. D- and L- is the relative configuration.

These two molecules they are an optical isomers. Optical isomers are known to rotate the plane of polarization on the same corner just in different directions.

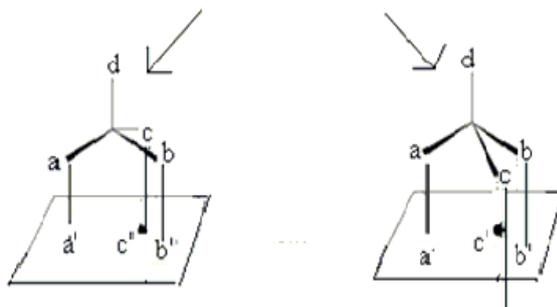
Rotation to the right indicate the sign - "+" denote the rotation of the left "-".

"+" and "-" is the absolute configuration of which is determined only by experiment using a polarimeter. Enantiomers - a isomers, which are related to each other as an object and its mirror image. A mixture of enantiomers is a racemate. The racemate of optically inactive. Diastereomers - a isomers, which do not relate to each other as an object and its mirror image.

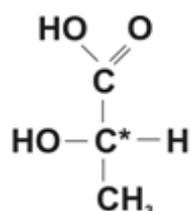
The biological significance of the enantiomers.

A) In humans, the substrate and the active sites of enzymes are optical antipodes, that is, they fit together like a lock and key. Only in this way they can interact.

Substratum

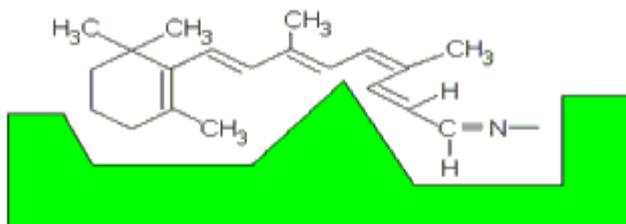


B) Lactic acid in the human body has a configuration of L (+).



L (+) - lactic acid

C) Cis-retinal and opsin protein are optical antipodes. In this case, they interact and form a complex of rhodopsin, which is involved in the process of vision.



D) Antigen and antibody interact with each other because they are optical antipodes, and fit together like a lock and key.

Conformational isomers

The conformational isomerism due to rotation of atomic groups with respect to carbon-carbon σ -communication.

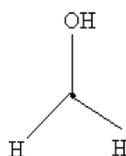
Isomers, which are formed at the same time, are called conformers. This is not different, and one molecule, but different geometric shapes it. Cause of rotation - it is the repulsion of the atoms when they are at a distance, which is approximately equal to the sum of the radii of the atoms.

The conformation of the compounds with an open carbon chain

During the rotation of the atoms with respect to σ - bonds may be two extreme positions:

- in which the atoms are too close to each other and obscure (obscure) one another;
- in which the atoms are located at maximum distance from each other.

To use the image conforms Newman projection. To do this, look at the model along the carbon - carbon σ - communication. The carbon atom that is closer to the observer, represent a point; from it at an angle of $109^{\circ}28'$ conduct communication and record the atoms and atomic groups, which are connected to this atom.



The carbon atom, which is located behind the first atom and is invisible to the observer. Depict a circle. Since his connection is also not visible, then the image of a little shift from the constraints of the first atom. This conformation is called eclipsed(Fig.1).

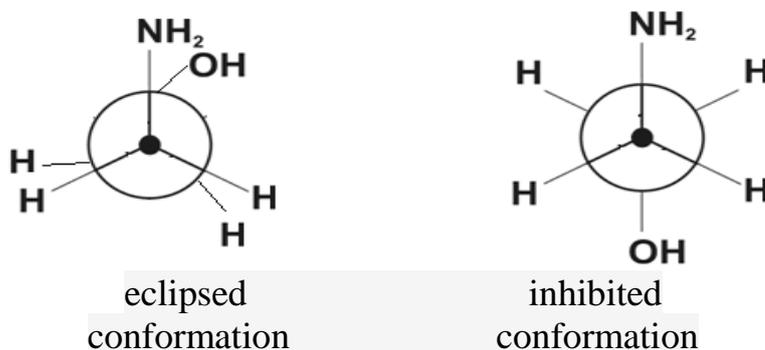
In the eclipsed conformation of the minimum distance between the atoms, their electron shells interact with each other, which creates additional energy in the system.

This is disadvantages for the system and it is thermodynamically unstable, since it raises torsional stress.

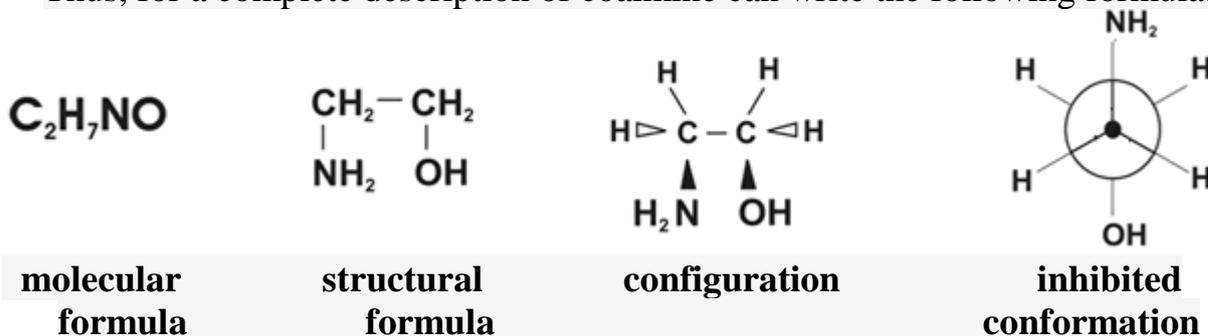
Torsional stress - is to increase the energy of the system due to the conformation of the shaded.

Therefore, the atoms repel each other and take more extreme position, which is inhibited conformation. In this case, the atoms are at maximum distance from each other, their electron shells do not interact with each other, and the energy of the system is minimal. In this conformation of the molecule is delayed or inhibited, so the conformation is inhibited (Fig. 2).

Occlusion and inhibited conformation in the Newman projection for coalmine can be written as:



Thus, for a complete description of coalmine can write the following formula:



Full characterization of some of some biologically active compounds are given in table

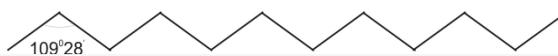
the biologically active substance	the molecular formula	structural formula	configuration	inhibited conformation
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Ethanol - antiseptic, a toxic effect on the human body	C_2H_6O	CH_3- CH_2-OH		
Ethylene glycol - antifreeze, toxic effects on the human body	$C_2H_6O_2$	CH_2-CH_2 $ \quad $ $HO \quad OH$		
Chloromethane anaesthetic tool, the body is decomposed with formation of free radicals	C_2H_5Cl	CH_3- CH_2-Cl		
Taurine - an intermediate in the synthesis of bile acids:	$C_2H_7O_3SN$	CH_2-CH_2 $ \quad $ $HO_3S \quad NH_2$		
Mercaptoethylamine - radioprotective agent	C_2H_7SN	CH_2-CH_2 $ \quad $ $HS \quad NH_2$		

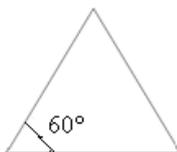
Closed conformation of the compounds with carbon chain

If the carbon atom form a long chain, the result of rotation of atomic groups with

respect to the C-C σ - communication, this chain is flexible with the size of the angle between σ -bonds $109^{\circ}28'$.



As a result, flexible carbon chain can form loops. The smallest loop is formed by three carbon atoms



This is - cyclopropane, in which the angle between the σ - bonds is 60° , which is significantly different from the normal value of $109^{\circ}28'$. As a result, the system generates surplus energy, which is called the angular strain.

The angular power - is the excess energy due to the deviation angle from the normal value.

Most importantly, the six-membered ring, as it contains many biologically active compounds.

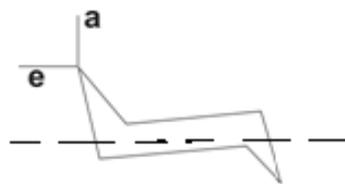


Cyclohexane

The angle of 120° in cyclohexane is also different from the normal value, so it appears the angular strain. Consequently, this cycle cannot be located in the plane. As a result, the rotation of atomic groups with respect to σ -connection, cyclohexane is located in space and forms the two extreme conformations.

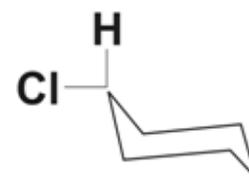
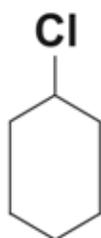
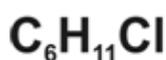


boat



chair

Chair conformation is energetically more favorable, since it not having any torsional and angular strain. Of great importance is an oriented carbon bond: equatorial and axial. Equatorial communications(e) is directed parallel to the equator. The axial bond (a) perpendicular to the equator. Bulky substituents are located on the equatorial regard as energetically more favorable. For example, a complete characterization of chlorocyclohexane can be written as:



molecular

structural

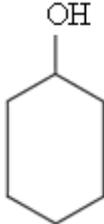
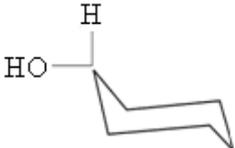
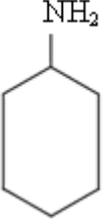
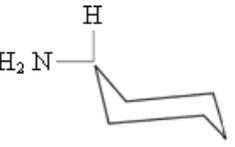
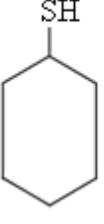
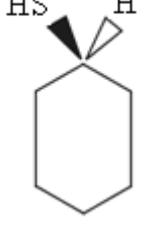
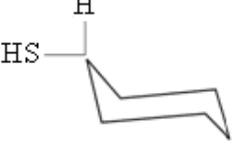
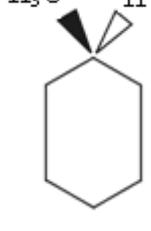
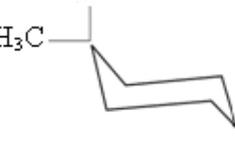
configuration

formula

formula

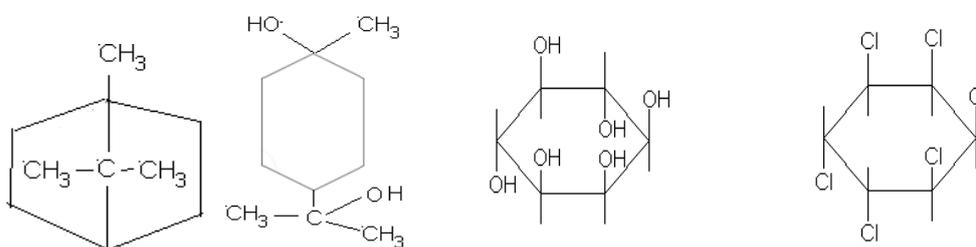
conformation

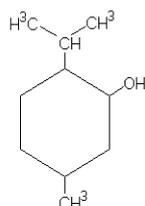
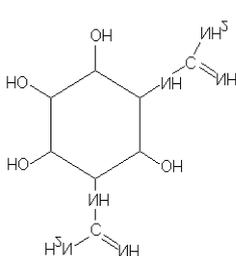
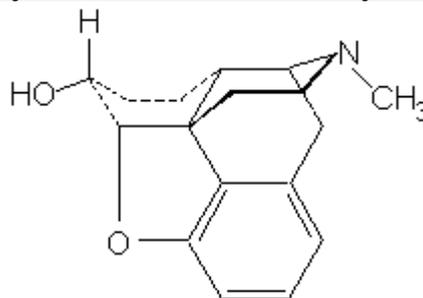
A complete characterization of some derivatives of cyclohexane is given table 3.

Substance	The molecular formula	Structural formula	Configuration	Conformation
Cyclohexane - solvent, starting material for the preparation of adipic acid for the synthesis of Dacron	$C_6H_{12}O$			
Aminocyclohexane	$C_6H_{13}N$			
Mercaptocyclohexane	$C_6H_{12}S$			
Methylcyclohexane	C_7H_{14}			

The biological significance of conformational isomerism

Drugs on the basis of cyclohexane:



Camphor**Terpin hydrate****Myoinositol****Chlorocyclohexane**

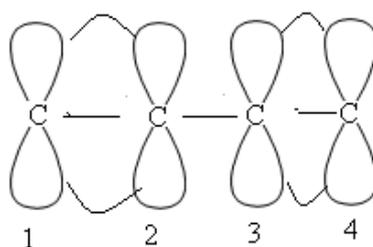
Methyl
(antiseptic calming
action sedative effect)

Streptidine
(an antibiotic)

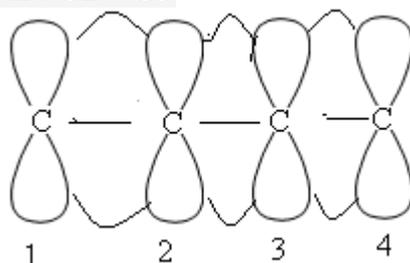
Morphine
an analgesic

Pairing and Aromaticity in biologically active compounds

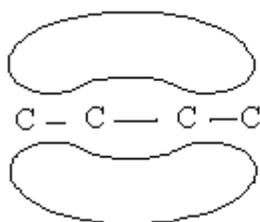
Another factor that affects the reactivity biologically active compounds are the phenomena of conjugation and aromaticity. Called conjugated systems in which the alternating double and simple communication. Conjugate systems with open-chain coupling A classic example of such systems is a butadiene-1, 3, or simply butadiene $\text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2$. The carbon atom in butadiene is in sp^2 - hybridization, the molecule is in the plane. A double bond consists of σ - bond that is formed by the overlap sp^2 - hybrid orbitals of carbon atoms, and π - bond formed with the free p - orbitals, which overlap between the C1 - C2 and C3 - C4 atoms, i.e. isolated double bonds:



p - orbitals, which form a π - bond is also called π - orbitals or π - electron density. π -electron density is located in space, so it is very mobile, and is overlapped between the C2 - C3



That is, the electron density is not centered between two adjacent carbon atoms and is delocalized over the whole system (i.e., molecule), and formed a single dual four central cloud that covers all carbon atoms:

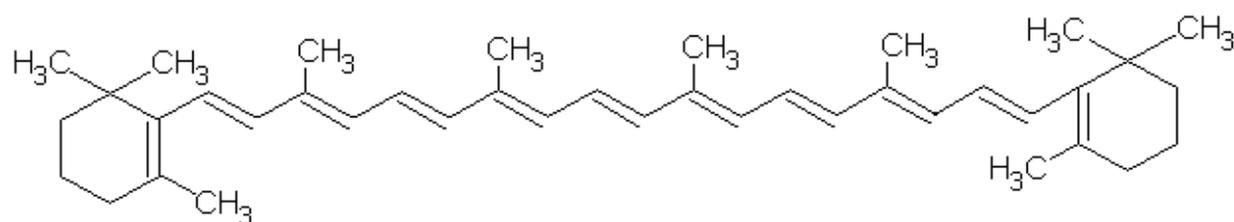


System with a continuous electron density is thermodynamically more stable than those with isolated bonds. This redistribution of electron density in the π - bonds, leading to stabilization of the molecule, called conjugation. Since the pair take only the π - orbital, then this type of interface is called π, π - conjugation. The degree of stability and stabilization of the system is characterized by the delocalization energy.

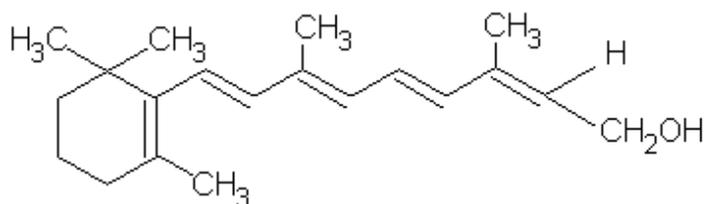
The energy of delocalization - the decrease of energy due to delocalization. For example, for butadiene the delocalization energy is 15 kJ mol^{-1} .

The biological significance of conjugate systems with open-chain coupling

Examples of biologically active compounds with open chain pairing are carotene and retinol:



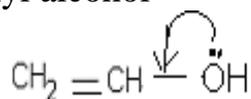
Carotene



Retinol (vitamin A)

The longer the chain of conjugation, the more stable the system, which has implications for the functioning of biological systems.

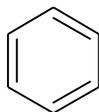
There is another kind of coupling in systems in which the alternating double bond - simple -electron pair, such as vinyl alcohol



Electron pair of the oxygen atom enters into conjugation with the π - electron density of the radical. Graphically this is shown by an arrow that starts from the electron pair and is aimed at the middle of the σ - communication. This kind of pairing is called p, π - conjugation, and has the greatest value in heterocyclic compounds.

Paired with a closed circuit system interface

A classic example of such a system is benzene.



The carbon atom in benzene is in the sp^2 - hybridization, the molecule is in the plane. A double bond consists of σ - bond that is formed by the overlap of sp^2 - hybrid orbitals of carbon atoms, and π - bond formed with the free p - orbitals, which, because of the high mobility of the overlap between all carbon atoms, that is delocalized over the whole system. The result is a continuous dual of the electron cloud that covers all carbon atoms. Graphically, it shows a circle inside the loop:



Continuous closed electron density results in a high energy delocalization - 227.8 kJ/mol. This high stability of the system with a high degree of unsaturation is a key criterion for aromaticity. Aromaticity - is unusually low energy of the unexcited state, which is due to delocalization of π - electrons.

There are three signs of aromaticity:

- planar skeleton of the molecule (due to sp^2 - hybridization of the atom carbon);
- a continuous circuit (due to the presence of π , π -, or ρ , π - conjugation);
- the number of delocalized electrons must comply with the rule

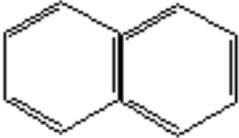
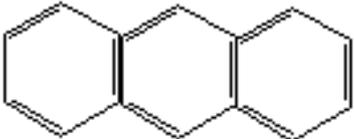
Huckel (the number of delocalized electrons = $4n + 2$, where n must be an integer).

We find these three characteristics of aromaticity in the benzene molecule:

- The benzene molecule has a planar skeleton, since the carbon atoms in sp^2 - hybridization;
- in the benzene molecule as a result of a continuous chain of conjugation π , π - conjugation;
- the number of delocalized electrons in benzene is 6, i.e. Each carbon atom gives a pair of one π electron. Hence, $6 = 4n + 2$, hence $n = 1$. Consequently, the Huckel's rule confirmed. Consequently benzene is an aromatic system.

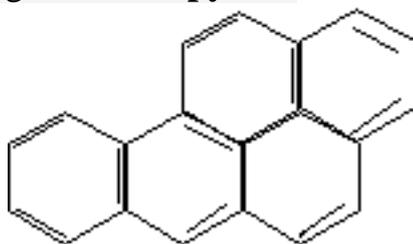
We find signs of aromaticity in the benzene derivatives.

Connection	Signs of aromaticity
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 <p>Naphthalene (used for the synthesis of drugs, solvents)</p>	<p>a) The skeleton of a planar molecule, since the carbon atoms in sp^2 - hybridization;</p> <p>b) an unbroken chain of conjugation due to π, π - conjugation;</p> <p>c) the number of delocalized electrons in the molecule of naphthalene is equal 10. Means that, $10 = 4n + 2$, hence the $n = 2$. Consequently, the Huckel's rule of confirmed.</p>
 <p>Anthracene (used for the synthesis of dyes, part of the medical substances)</p>	<p>a) The skeleton of a planar molecule, since the carbon atoms in sp^2 - hybridization;</p> <p>b) an unbroken chain of conjugation due to π, π - conjugation;</p> <p>c) the number of delocalized electrons in a molecule is equal to 14 Means that anthracene, $14 = 4n + 2$, hence the $n = 3$. Consequently, the rule of Huckel confirmed.</p>

The biological significance of conjugate systems of the benzene series.

Benzene and its derivatives - a carcinogenic substance. Compound carcinogens benzene rings or polycyclic aromatic hydrocarbons are the result of a variety of industries: metallurgy, petrochemical, coking, thermal power plants. With exhaust gases in the air gets a lot of carcinogens. But even in cities where there are no enterprises in these industries, the air contains high concentrations of these substances. And they are the primary source of vehicle exhaust, buy out contain one of the strongest carcinogens – **benzpyrene**

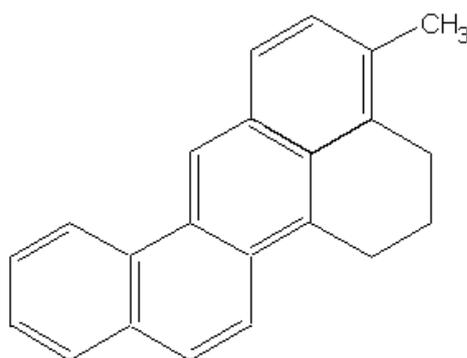


Its maximum allowable concentration of 10^{-9}g m^{-3} in the air. In some cities, this concentration is greater in 3 - 8 times.

High concentrations of benzopyrene in tobacco smoke.

Every smoker receives a portion of this carcinogen.

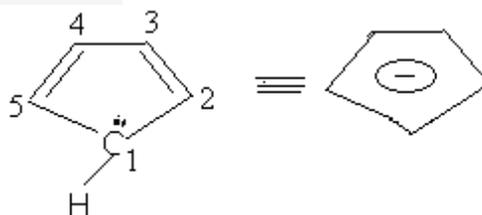
In humans with metabolic disorders of cholesterol can form a very powerful carcinogen –methylcholanthrene?



RELATED NON BENZOIC SYSTEMS

it is now known a large number of compounds that do not contain a benzene nucleus, but possess aromaticity.

a) these include cyclopentadienyl - anion, which is formed by deprotonation (cleavage of H^+) cyclopentadiene



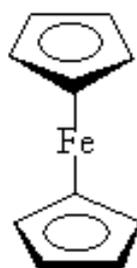
cyclopentadienyl – anion

This anion is aromatic because:

- the skeleton of the molecule due to the flat sp^2 - hybridization of carbon atoms;
- an unbroken chain of conjugation by p, π - conjugation (electron pair of carbon C1 overlaps with the π - electrons of the carbon atoms C2 and C5);
- in conjunction participate electron 6 (2, 3, 4, 5 carbon atoms give a conjugated system of 1 electron and the first carbon gives two electron).

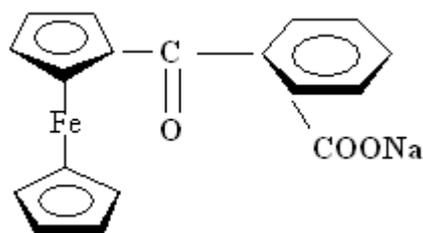
Hence, $6 = 4n + 2$, hence $n = 1$.

Cyclopentadienyl - anion with cations of heavy metals makes the connection with the so-called "sandwich" structure - metallocenes. If the complex contains an iron atom, it is called ferrocene



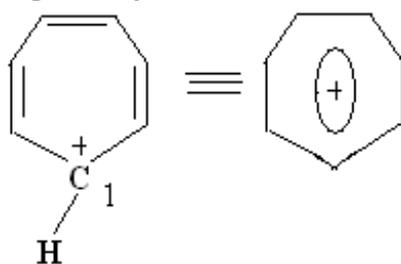
The biological significance of ferrocene derivatives:

- organic iron medication used to treat iron deficiency anemia



b) ferrocene derivatives are used as intermediates for synthesis of biologically active substances, such as simple acid.

c) another system is non benzoic cyclopentadienyl - or tropylium cation - cation which is formed by the cleavage of hydride - anion H from cycloheptatriene:



Cycloheptatriene – cation

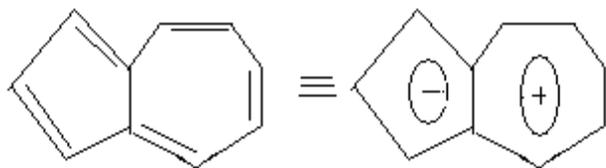
This cation is aromatic because:

- the skeleton of the molecule due to the flat sp^2 - hybridization of carbon atoms;
- an unbroken chain of conjugation by π, π - conjugation (π - electron density is redistributed to the free orbital of C1);
- in conjunction participate electron 6 (all carbon atoms except the first, sent to a dual system of 1 electron). Hence, $6 = 4n + 2$, hence $n = 1$.

The biological significance of tropylium derivatives are - the cation:

- antibiotics that inhibit rotting wood, for example: tuaplisine;
- coal mine used to treat skin cancer;
- colchicine causes the division of chromosomes, so it is used to study the genetics of plants.

b) Condensed core, consisting of cyclopentadienyl - anion and tropylium – called azulene cation



Which is also an aromatic system, as:

- the skeleton of the molecule due to the flat sp^2 - hybridization of carbon atoms;
- an unbroken chain of conjugation by π, π - conjugation;
- take part in the conjugation of 10 electron. Hence, $10 = 4n + 2$, hence $n = 2$.

In nature, there is no azulene, he obtained synthetically.

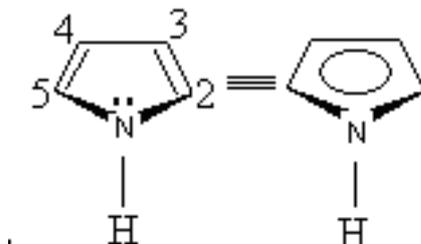
The biological significance are alkyl-substituted azulene contained in essential oils of medicinal plants - Roman chamomile, eucalyptus, worm wood - which explains their anti-inflammatory effect.

AROMATIC HETEROCYCLIC COMPOUNDS

Aromatic characteristic of heterocyclic compounds. They are basis of many biologically active compounds, their stability is due to aromaticity.

Aromaticity of five-membered cycles

an example of five-membered pyrrole cycle is



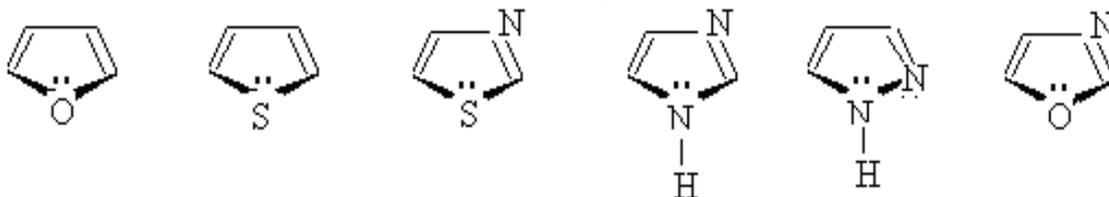
In the pyrrole molecule has three features of aromaticity:

- the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms;
- an unbroken chain of conjugation by p, π - conjugation (nitrogen gives a pair electron pair);
- in conjunction participate electron 6 (2, 3, 4, 5 carbon atoms give a conjugated system of 1 electron and the nitrogen atom gives unshared electron pair).

Hence, $6 = 4n + 2$, hence $n = 1$.

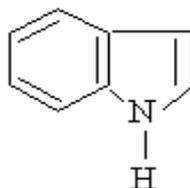
Consequently, the pyrrole is aromatic ring. The nitrogen atom, which commends to the lone pair electron pair is called the pyrrole nitrogen.

By the five-membered aromatic heterocyclic cores include



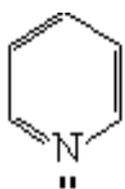
Furan Thiophene Imidazole Pyrazol Thiazole Oxazole

and heterocyclic fused with benzene:



Indol

Aromaticity of six-membered rings an example of a six-membered aromatic heterocycle is pyridine



In the molecule of pyridine aromaticity are three features:

a) the skeleton of the molecule due to the flat sp^2 - hybridization of carbon atoms and nitrogen;

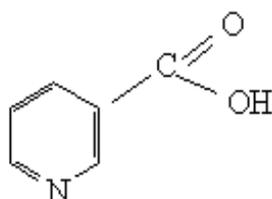
b) an unbroken chain of conjugation by π, π - conjugation;

c) in conjunction participate electron 6 (each of the five carbon atoms in the conjugated system gives to the nitrogen atom and 1 electron gives a electron).

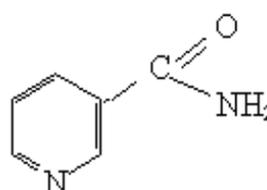
Hence, $6 = 4n + 2$, hence $n = 1$. Consequently, the pyridine this aromatic rings.

The nitrogen atom, which does not give an unshared electron pair to pair, called the pyridine nitrogen.

Examples of biologically active compounds based on pyridine nucleus are vitamins PP, B6, niacin, folic acid, barbiturates, etc.

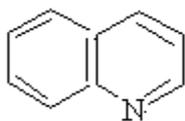


Nicotinic acid

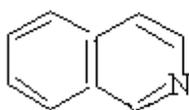


Vitamin PP

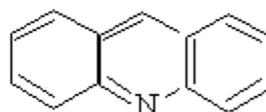
By the six-membered aromatic nuclei with pyridine nitrogen atom are condensed heterocyclic with one nitrogen atom:



Quinoline

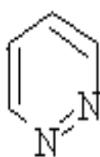


Isoquinoline

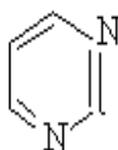


Acridine

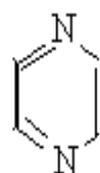
With two nitrogen atoms:



Pyridazine

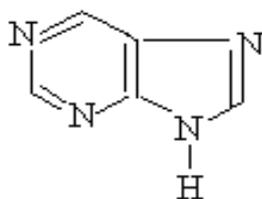


Pyrimidine



Pyrazine

And condensed systems with pyrrole and pyridine nitrogen atoms, the most important of which is a purine:

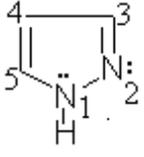
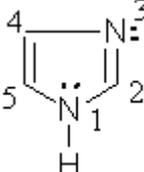
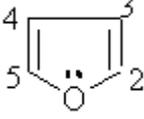
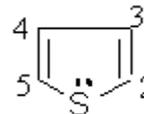


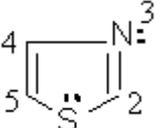
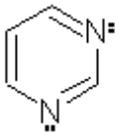
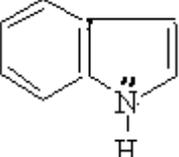
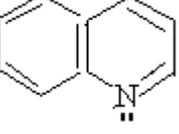
Purine

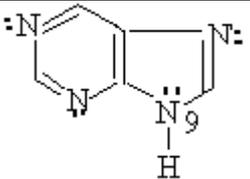
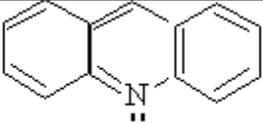
It is very important biologically active compounds containing heterocycles

with pyrrole and pyridine nitrogen atoms are chlorophyll, hemoglobin, vitamin B12. A long chain of conjugation in these compounds results in high stability of these molecules, which is of great importance to carry out important functions in the human body.

We find signs of aromaticity of heterocyclic compounds

 <p>Pyrrole (the basis of drugs: aminopyrine, analgine, phenylbutazone)</p>	<p>a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms;</p> <p>b) an unbroken chain of conjugation by ρ, π - conjugation (nitrogen gives an electron pair in the pair);</p> <p>c) in conjunction participate 6 electron (3, 4, 5 atoms of carbon and nitrogen in the two give the conjugated system of 1electron and the nitrogen atom gives an unshared electron pair). Hence, $6 = 4n + 2$, hence $n = 1$.</p>
 <p>Imidazole (In purines, histidine, alkaloids)</p>	<p>a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms;</p> <p>b) an unbroken chain of conjugation by ρ, π - conjugation (nitrogen gives an electron pair in the pair);</p> <p>c) in conjunction participate 6 electron (2, 4, 5 atoms of carbon and nitrogen in the three give the conjugated system of 1 electron, and the nitrogen atom gives an unshared electron pair). Hence, $6 = 4n + 2$, hence $n = 1$.</p>
 <p>Furan (consisting of furfural, furacilinum)</p>	<p>a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms;</p> <p>b) an unbroken chain of conjugation by ρ, π - conjugation (oxygen gives a pair electron pair);</p> <p>c) in conjunction participate 6electron (2, 3, 4, 5 carbon atoms give a conjugated system of 1electron, and an oxygen atom gives an unshared electron pair). Hence, $6 = 4n+2$; hence $n = 1$.</p>
	<p>a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms;</p> <p>b) an unbroken chain of conjugation by ρ, π -</p>

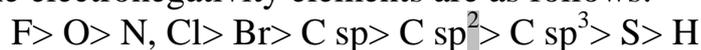
Thiophene (in the ichthyolum)	conjugation (sulfur gives a pair electron pair); c) in conjunction participate electron 6 (2, 3, 4, 5 carbon atoms give a conjugated system of 1 electron, and a sulfur atom gives an unshared electron pair). Hence, $6 = 4n + 2$, hence $n = 1$.
 Thiazole (in the norsulfazole, penicillin)	a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms; b) an unbroken chain of conjugation by ρ, π - conjugation (sulfur gives a pair electron pair); c) in conjunction participate 6 electron (2, 4, 5 atoms of carbon and nitrogen in the three give the conjugated system of 1 electron, and a sulfur atom gives an unshared electron pair). Hence, $6 = 4n + 2$, hence $n = 1$.
 Pyrimidine (the basis of nitrogenous bases: uracil, thymine, cytosine)	a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms; b) an unbroken chain of conjugation by π, π - conjugation; c) in conjunction participate electron 6 (all carbon and nitrogen atoms to give the conjugated system of an electron). Hence, $6 = 4n + 2$, hence $n = 1$.
 Indole (consisting of tryptophan, serotonin, indigo)	a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms; b) an unbroken chain of conjugation by ρ, π - conjugation (nitrogen gives a pair electron pair); c) in conjunction participate 10 electron (all the carbon atoms to give the conjugated system of 1 electron, and the nitrogen atom gives an unshared electron pair). Hence, $10 = 4n + 2$, hence $n = 2$.
 Quinoline (consisting of alkaloids, drugs - cinhofen - for the treatment of gout)	a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms; b) an unbroken chain of conjugation by π, π - conjugation; c) in conjunction participate electron 10 (all the atoms of carbon and nitrogen to give a conjugated system of an electron). Hence, $10 = 4n + 2$, hence $n = 2$.

 <p>Purine (composed of nitrogenous bases – adenine, guanine, alkaloids - theophylline, theobromine, caffeine, uric acid)</p>	<p>a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms; b) an unbroken chain of conjugation by ρ, π - conjugation (nitrogen gives an electron pair in the pair); c) in conjunction participate 10 electron (9 gives the nitrogen atom lone electron pair, all other carbon and nitrogen atoms give a conjugated system of 1 electron). Hence, $10 = 4n + 2$, hence $n = 2$.</p>
 <p>Acridine (consisting of quinacrine - an antimalarial drugs)</p>	<p>a) the skeleton of the molecule due to the flat sp^2 - hybridization of the atoms; b) an unbroken chain of conjugation by π, π - conjugation; c) in conjunction participate electron 14 (all the atoms of carbon and nitrogen to give a conjugated system of an electron). Hence, $14 = 4n + 2$, hence $n = 3$.</p>

ELECTRONIC EFFECTS IN BIOLOGICALLY ACTIVE COMPOUNDS

The electronic effect - a shift of electron density in the system (molecule). This shift occurs when the molecule is different in electronegativity of the atoms.

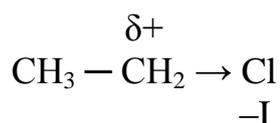
Among the electronegativity elements are as follows:



There are two types of electronic effects: inductive and mesomeric.

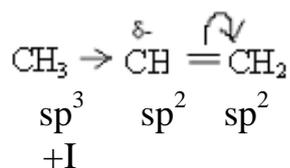
a) Inductive effect (I) - is the offset of the electron density to the more electronegative atom of σ - communication. The inductive effect is manifested in any system (molecule), where there are different electro-negativities of the atoms. For example:

a) in the molecule of chloroethane more electronegative element is chlorine, so he pulls over the electron density from the carbon; graphically shown by the arrow, which goes to σ - communications:



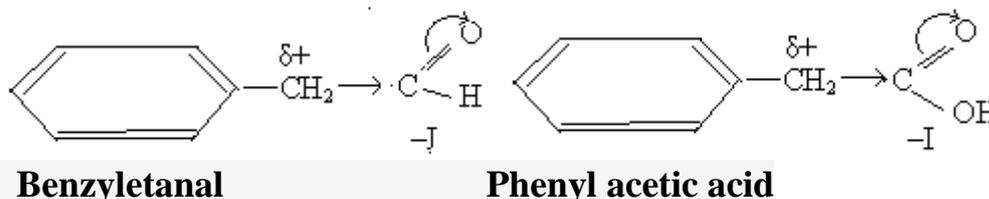
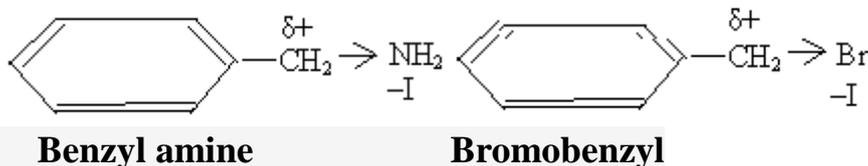
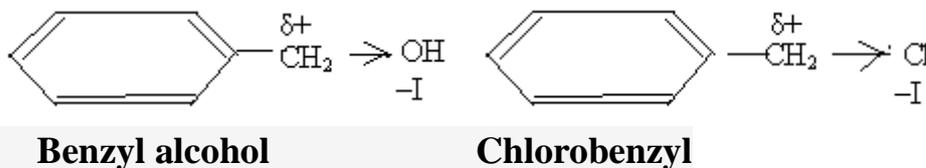
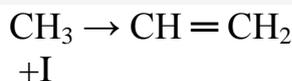
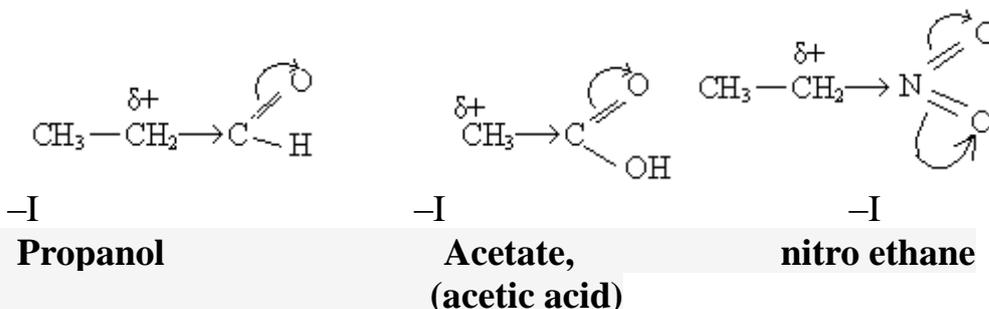
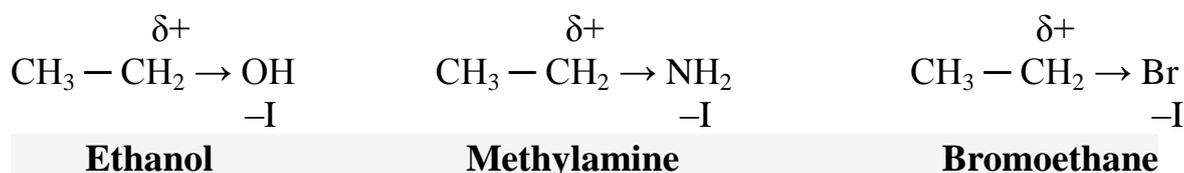
On the carbon atom a partial positive charge arises, that is in the (radical) decreases the electron density. In this case, we say that the inductive effect is manifested negative-I.

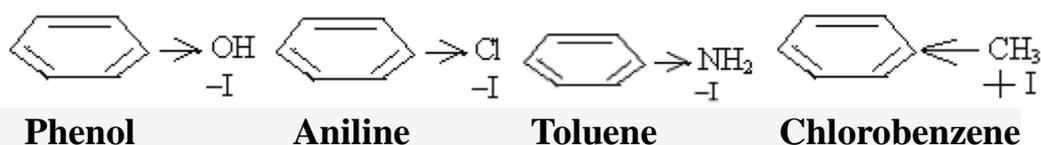
b) In the propene molecule is more electronegative atom of carbon in the sp^2 - hybridization, so he pulls over the electron density from the carbon in the sp^3 - hybridization:



On the carbon atom occurs a partial negative charge, i.e. in the (radical with a double bond) increases electron density. In this case we say that shows a positive inductive effect + I. (It should be noted that the methyl group is always pushes himself to the electron density as well as carbon in the sp^3 -hybridization has low electronegativity). A characteristic feature of the inductive effect is the rapid decrease in its chain of σ -bonds.

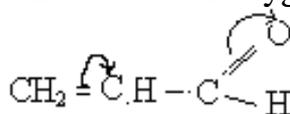
Examples of manifestations of the inductive effect.





2) Mesomeric effect (M) or the effect of conjugation - the shift of electron density on the conjugated system.

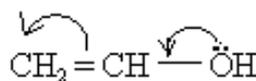
In conjugated systems can alternate double and single bonds: = — = (for example: $\text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2$), i.e. π, π - conjugation or a double bond - a simple communication - e-pair: = —: (e.g., $\text{CH}_2 = \text{CH} - \ddot{\text{O}}\text{N}$), i.e. ρ, π - conjugation. For example, acrylic aldehyde in the molecule, which is observed π, π - conjugation to an electronegative oxygen atom, the electron density is shifted from the carbon π - communication, because it is more mobile than the electron density σ - communications, graphically shown by a curved arrow that starts from the middle of the double bond and directed to an oxygen atom .



-M

Acrylic aldehyde

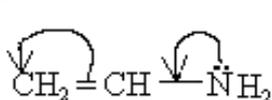
But in the dual system is the shift of the entire system of π - bonds, graphically shown by a curved arrow that starts from the middle of the double bond between carbon atoms and is directed to the adjacent carbon atom toward the oxygen. As a result, the influence of the aldehyde group of the electron density in the system, i.e. in the radical is reduced, and then the negative mesomeric effect is manifested -M. In a system with ρ, π - conjugation, such as vinyl alcohol



+M

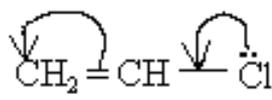
Electron pair of the oxygen atom is at the interface with π - orbitals of carbon atoms. Graphically, it shows a curved arrow that starts from the electron pair and is aimed at the middle of the C - O. Since the dual system is the shift of electron density throughout the molecule, then the next shift of π - electron density of the double bond shows a curved arrow from the middle of the double bond in the carbon atom. As a result, the system increases the electron density, that is, they say that shows a positive mesomeric effect + M.

Examples of manifestations of mesomeric effect.



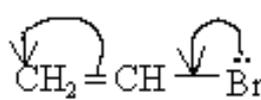
+M

Vinyl amine



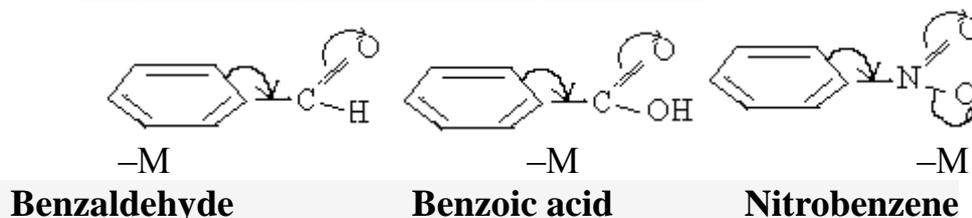
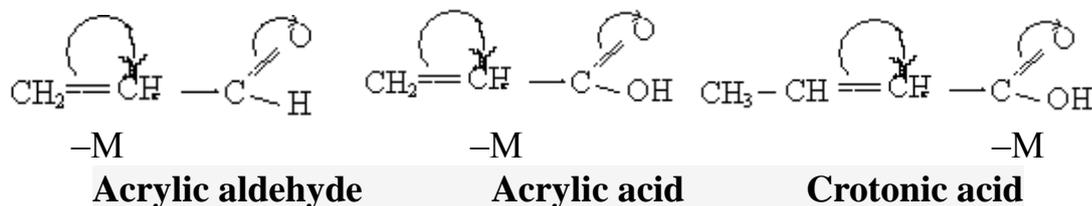
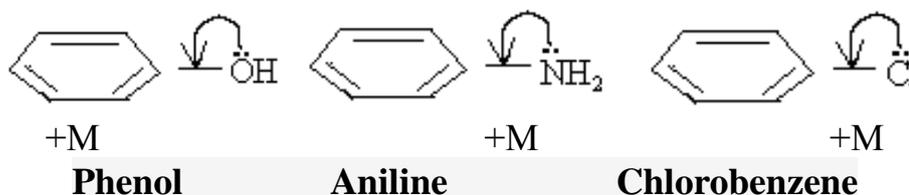
+M

Chlorovinyl

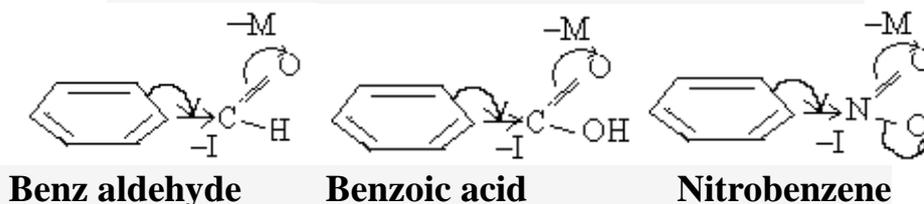
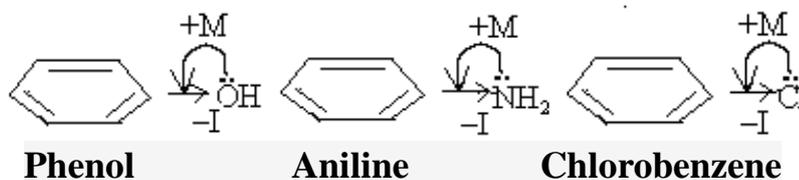
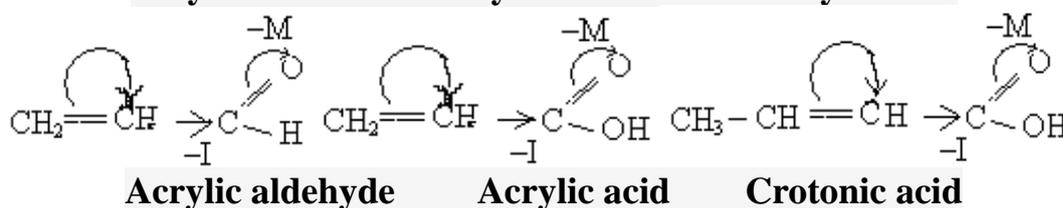
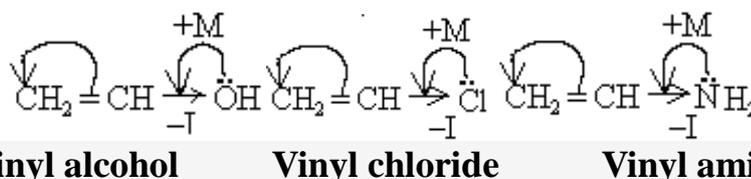


+M

Bromovinyl



Examples of simultaneous manifestation of the inductive and mesomeric effects



Mesomeric effect of conjugated chain extends without attenuation. Substituents that increase the electron density in the system, called the electron donor. Substituents, which reduce the electron density in the system, called an electron acceptor. The same substituent may be in a single molecule electron donor,

and in the other - an electron acceptor. Electronic effects are very important for the reactivity of organic compounds.

Acidic and basic biologically active compounds

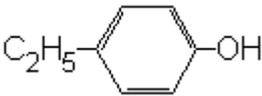
In inorganic chemistry of acid - base properties explains the theory of electrolytic dissociation Arrhenius, according to which the acid dissociation of the proton yield of H^+ and reason - OH^- OH^- anion. But the organic compounds do not dissociate, so to explain their acid - base properties of the two theories are used - Bronsted and Lewis.

1. According to the theory of proton Bronsted acid - a donor protons and the foundation - is the proton acceptors.

That is any substance that contains hydrogen, may cleave it in the form of a proton, thus exhibiting acidic properties (Table 4).

The acidity of different classes of organic compounds

Table 4

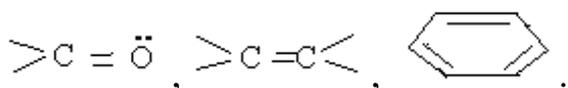
Acid	pKa
$C_2H_5CH_3$	48 - 60
$C_2H_5NH_2$	30
C_2H_5OH	18
H_2O	14
	12
CH_3COOH	4,7
HCl	1

1. According to the electron theory of Lewis acids - are acceptors electron pair, and the reason - is an electron pair donor.

Acids have a free orbital, which they accept electron pair from the base.

Examples of Lewis acids: $AlCl_3$, $AlBr_3$, $FeCl_3$, $ZnCl_2$ and others, in which metal atoms are free orbital.

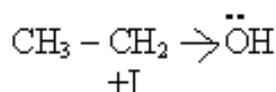
Examples of Lewis bases H^- , Cl^- , OH^- , Cl^- , $H\ddot{O}H$, $\ddot{N}H_3$, $R-\ddot{O}H$, $R-\ddot{N}H_2$



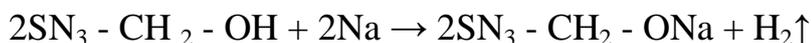
Consider the acid - base properties of some classes of compounds.

1. The acidity of alcohols.

Acidic properties of alcohols depends on the strength of the attraction of a proton to an oxygen atom, this in turn depends on the electron density on the oxygen atom, which is due to the presence of an unshared electron pair of oxygen and the electronic effect of the radical. Alcohols exhibit acidic properties of the resulting hydroxyl proton separation. But this weak acid, since the oxygen atom creates a high electron density due to the presence of an unshared electron pair and the positive inductive effect of the radical. Such oxygen is strongly attracted to the positively charged proton

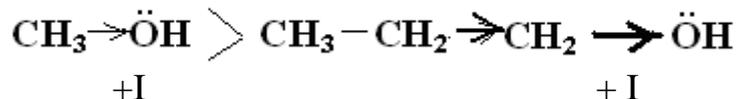


Therefore, alcohols give alcoholates salts only with strong bases, for example, with alkali metals:



The presence of structural fragments and substituents in the radical influence on the acidic properties of alcohols:

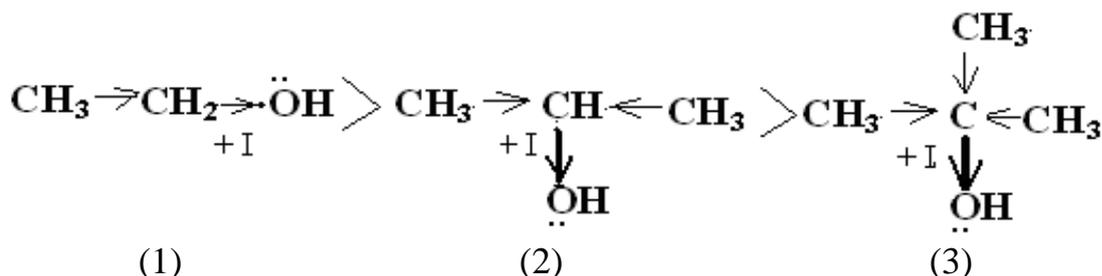
a) in a homologous series the acidity decreases, as it increases the positive inductive effect of the longer radical, electron density on the oxygen becomes more and more attracted to a proton to such oxygen



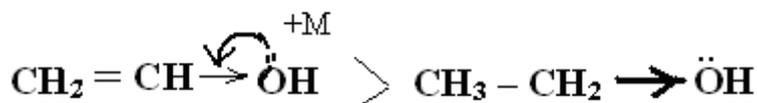
(\rightarrow) Stronger than the inductive electronic effect)

($\xrightarrow{+}$) Weaker than the inductive electronic effect)

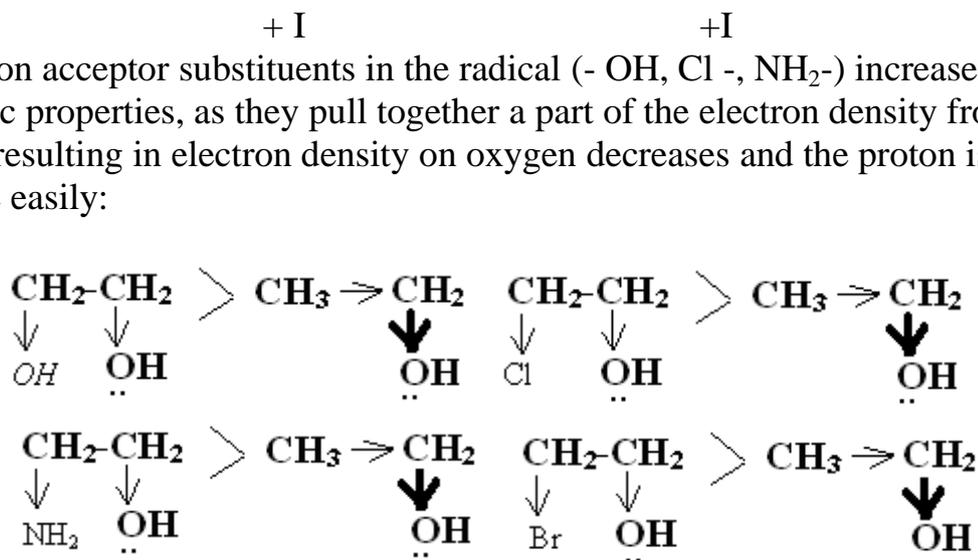
b) primary alcohols (1) acidic than secondary (2) and tertiary (3), as it increases the positive inductive effect of neighboring radicals, the electron density at the oxygen becomes more and more attracted to a proton to this oxygen



c) unsaturated alcohols acidic than the rich, as a positive inductive effect of the radical with sp^2 - carbon hybrid is less than radical with sp^3 - a hybrid of carbon and the lone electron pair of oxygen goes to the ρ , π - conjugation, resulting in electron density on oxygen decreases and the proton is split off easily



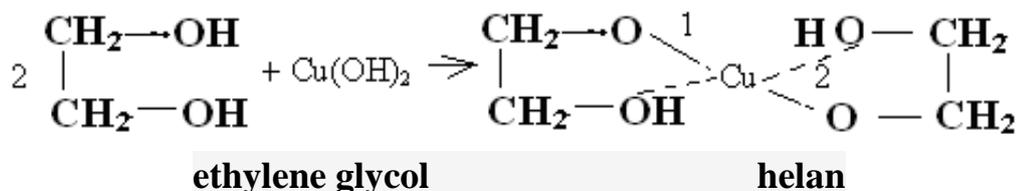
d) electron acceptor substituents in the radical (- OH, Cl -, NH₂-) increases the acidic properties, as they pull together a part of the electron density from the radical, resulting in electron density on oxygen decreases and the proton is split off more easily:



(\Downarrow Electronic effect is stronger)

(\Downarrow Electronic effect is weaker)

As a result of increased acidity of the polyols may interact with cuprum (II) hydroxide. The products of this reaction are chelates - a blue solution.

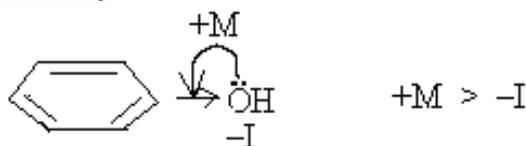


In chelates are two types of communication - ion (1) and by covalent donor - acceptor mechanism (2).

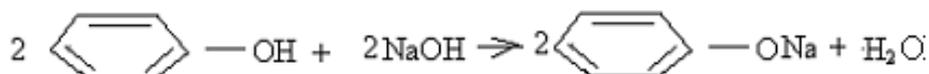
The formation of chelates used as a qualitative response to the polyhydric alcohols, and in clinical analysis for the detection of sugars in biological fluids.

2. Acidity phenols.

Phenols exhibit stronger acidic properties than alcohols because hydroxyl group shows a strong positive mesomeric effect (an unshared electron pair of oxygen goes to the ρ , π -conjugation), resulting in electron density on oxygen decreases and the proton is split off easily



Phenols give a salt phenolates in the interaction with metals, metal oxides, bases:



The biological significance of the acidity of phenol is that due to the high acidic

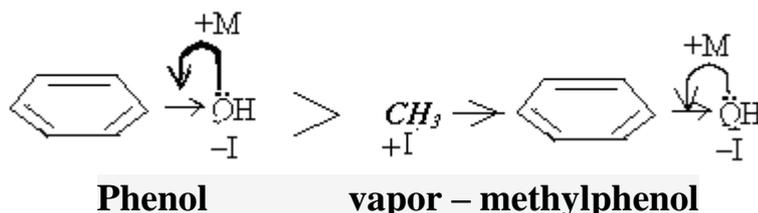
properties of phenol, or carbolic acid is used as an antiseptic.

The presence of substituents in the benzene ring affects the acidic properties of phenols (Table number 5).

Formula of compound	<i>pKa</i>
o-CH₃-C₆H₄-OH	10,28
π-CH₃-C₆H₄-OH	10,19
m-CH₃-C₆H₄-OH	10,08
C₆H₄-OH	9,95
m-NO₂-C₆H₄-OH	8,35
o-NO₂-C₆H₄-OH	7,20
π-NO₂-C₆H₄-OH	7,14
2,4-(NO₂)₂-C₆H₃-OH	4,01
2,4,6-(NO₂)₃-C₆H₂-OH	1,02

Electron substituents decrease the acidity of phenols:

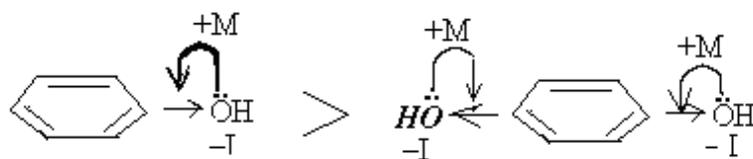
a) radical - in a pair of methyl - methyl phenol increases the electron density in the benzene ring, so the electron pair of oxygen slightly shifted to the pair (M + decreases), resulting in the oxygen atom remains relatively high electron density and the proton more strongly attracted to him. Therefore, phenol is a stronger acid than steam - methylphenol ::



mesomeric effect is stronger	mesomeric effect is weaker
------------------------------	----------------------------

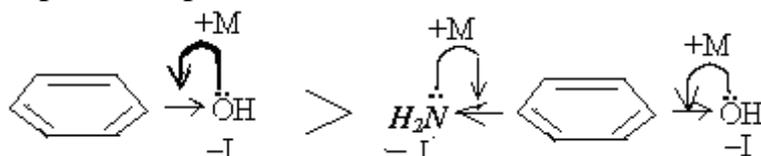
b) in the molecule pair - because dioxybenzene + M effect of the second hydroxyl groups decreased + M first hydroxyl group, resulting in an atom oxygen remains relatively high electron density and the proton strongly attracted to him.

Therefore, phenol is more stronger acid than steam – dioxyphenol



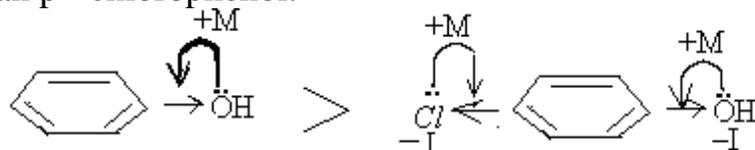
Phenol **vapor – dioxybenzenes**

c) in the molecule pair - + M aminophenol due to the effect of amino decreases + M hydroxyl, resulting in an atom of oxygen maintained a fairly high electron density and the proton strongly attracted to him. Therefore, phenol is more stronger acid than p - aminophenol ::



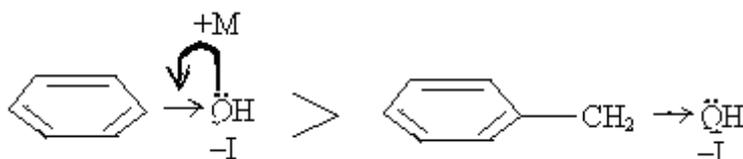
Phenol **vapor – aminophenol**

d) in the molecule pair - chlorophenol by + M effect of the chlorine atom decreases +M hydroxyl, resulting in an atom of oxygen maintained a fairly high electron density and the proton strongly attracted to him. Therefore, phenol is more stronger acid than p - chlorophenol:



Phenol **vapor – chlorophenol**

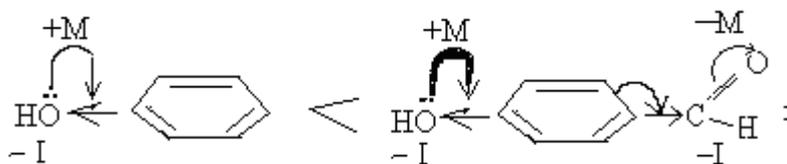
e) in a molecule of benzyl alcohol is manifested only - I (as in alcohols fatty), resulting in the oxygen atom remains quite high electron density and the proton more strongly attracted to him. Therefore, phenol is a stronger acid than the benzyl alcohol:



phenol, **benzyl alcohol**

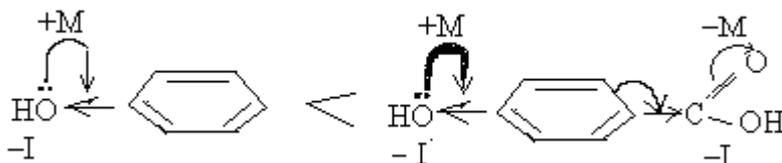
Electron substituents increase the acidity of phenols.

a) in the molecule of p – hydroxybenzaldehyde, aldehyde – group by a negative inductive and mesomeric effects reduces the electron density in the benzene ring, resulting in increased hydroxyl + M, and decreases the density at the oxygen electronic hydroxyl groups, therefore, the proton is easily cleaved, hence, the pair – hydroxybenzaldehyde is a stronger acid than phenol:



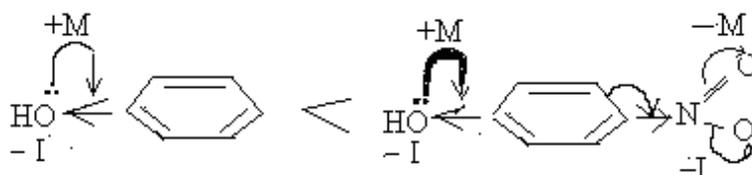
phenol, p - hydroxybenzaldehyde

b) in the molecule of p - hydroxybenzoic acid, carboxyl – a group of negative inductive and mesomeric effects reduces the electron density in the benzene ring, resulting in increased M + and hydroxyl groups decreases the electron density at the hydroxy oxygen, so it is easy to split off a proton, then p -hydroxybenzoic acid is a stronger acid than phenol:



Phenol, p - hydroxybenzoic acid

c) in the molecule pair – nitrophenol, nitro - a group of negative inductive and mesomeric effects reduces the electron density in the benzene ring, resulting in increased hydroxyl + M, and decreases the density at the oxygen electronic hydroxyl groups, so it is easy to split off a proton, then p - nitrophenol is a stronger acid than phenol:



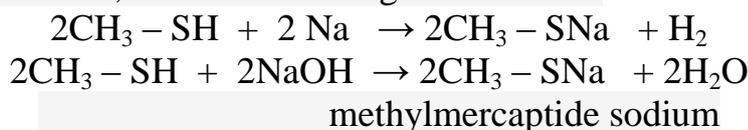
phenol, p - nitrophenol

3) The acidity of thiols

Thiols exhibit stronger acidic properties than alcohols because the sulfur atom less electronegative than oxygen, and smaller contracts over the electron density from the radical. Therefore, the sulfur atom is created is not very high electron density, and the proton is not strongly associated with it



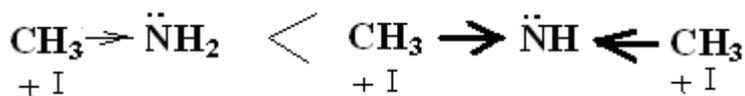
Thiols react with metals, alkalis and salts give a thiolate:



Thiols form salts with heavy metals, which is of great biological significance:

a) heavy metals (Pb, Hg, Bi), which are called thiol poisons, bind SH - groups of proteins -enzymes and destroy their catalytic activity;

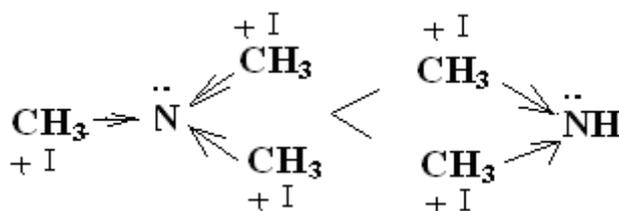
becomes more and more active secondary amine reacts with the proton acid



Methylamine
(primary)

dimethyl amine
(secondary)

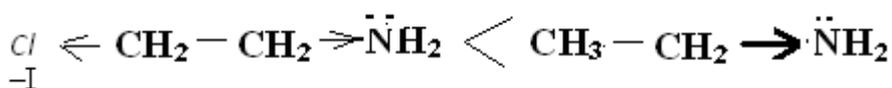
Tertiary amines are less basic than the secondary as well as the three methyl groups hinder the approach of the proton (spatial factor):



trimethyl amine
(tertiary)

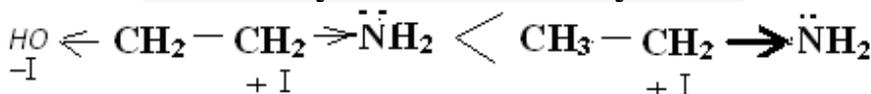
dimethyl amine
(secondary)

c) electron acceptor substituents (OH-, Cl-) reduces the basicity of amines, as part of the electron density from the radical tightening on itself, resulting in the nitrogen atom decreases the electron density and the proton is not actively attacking it:



2 - hlorethylamine

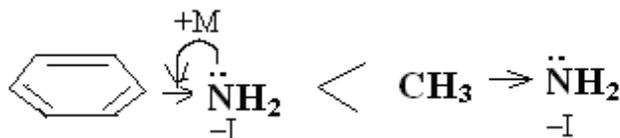
ethylamine



oxymethylamine (coalmine)

ethylamine

d) aromatic amines (aniline) exhibit weak basic properties, because the electron pair of the nitrogen atom is in the ρ , π - conjugation (a lone electron pair of nitrogen in the aliphatic amines is free, there is no mesomeric effect) and is easily attacked by a proton:



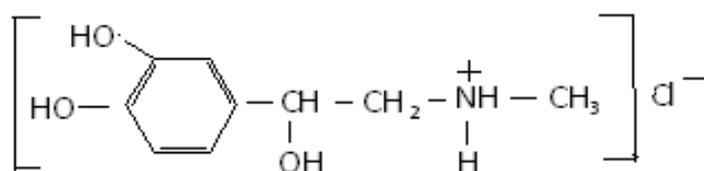
Aniline

Methylamine

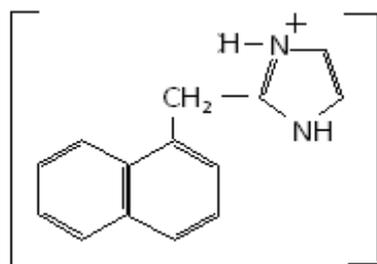
The biological significance of the basicity of amines

Basity amines is of great importance for the absorption of pharmaceutical substances - amines. They are used in the form of salts of inorganic and organic acids. This increases their solubility in water and the rate of absorption.

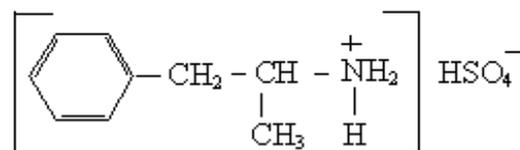
Two amina – drugs



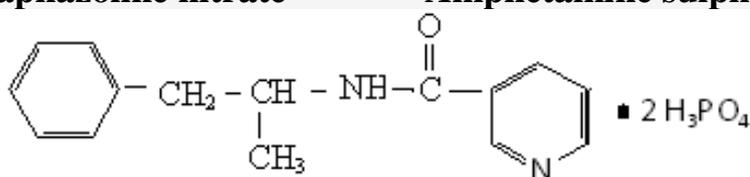
Adrenaline hydrochloride



Naphazoline nitrate



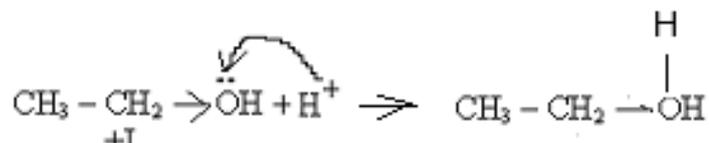
Amphetamine sulphate



Phenatine diphosphate

The basicity of the individual atoms in a variety of organic compounds:

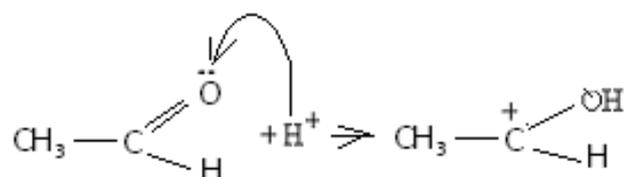
a) alcohols may be due to the basic properties of the lone pair of electrons of the oxygen atom, oxygen atom. This can be attacked by a proton, that is to protonate:



This process can go in the reactions of nucleophilic substitution or elimination (removal) oxy - group.

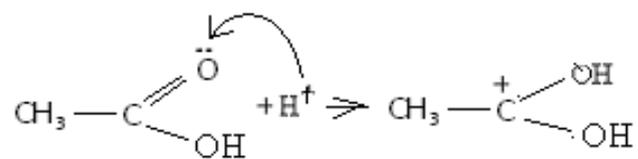
b) in the protonated aldehydes attacks may occur in the process of nucleophilic substitution or elimination (removal) oxy - group.

b) aldehydes protonated oxygen atom of the aldehyde group, which shows basic properties due to the unshared electron pair and the oxygen of the aldehyde group, which shows basic properties due to the unshared electron pair:



This process occurs in the reactions of nucleophilic addition to aldehydes.

c) in carboxylic acids protonated oxygen atom - oxo group:



This process occurs in the reactions of nucleophilic substitution in carboxylic acids and their derivatives.

Thus, the above described theoretical concepts used to explain the mechanisms of reactions involving biologically active substances.

