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БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ОБЩЕЙ ХИМИИ

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ОРГАНИЧЕСКАЯ ХИМИЯ. ЛАБОРАТОРНЫЙ ПРАКТИКУМ

ORGANIC CHEMISTRY. LABORATORY HANDBOOK

Допущено Министерством образования Республики Беларусь
в качестве учебного пособия для иностранных студентов
учреждений высшего образования по специальности «Фармация»

В двух частях

Часть 1

Минск БГМУ 2025

УДК 547(076.5)(075.8)-111
ББК 24.2я73
Л29

Р е ц е н з е н т ы: канд. хим. наук, доц., зав. каф. органической химии Белорусского государственного технологического университета С. Г. Михалёнок; каф. химии и методики преподавания химии Белорусского государственного педагогического университета имени Максима Танка

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Л29 Органическая химия. Лабораторный практикум = Organic chemistry. Laboratory handbook : учебное пособие. В 2 ч. Ч. 1 / Ф. Ф. Лахвич, О. Н. Ринейская, Г. П. Фандо. – Минск : БГМУ, 2025. – 183 с.

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Содержит методические рекомендации для подготовки к лабораторным занятиям по органической химии на английском языке. К каждой теме даны цель занятия, вопросы для обсуждения, письменные задания, а также указана литература для подготовки. Приведены описания и протоколы лабораторных опытов.

Предназначено для студентов фармацевтических специальностей, обучающихся на английском языке.

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REGISTRATION FORM

Student's name _____ Group Number _____

PART 1

№	Theme	Date	Mark	Signature
1.	Classification and nomenclature of organic compounds			
2.	Chemical bonding			
3.	Stereoisomerism and stereochemistry			
4.	Chemical reactivity			
5.	Instrumental methods of structure determination. Infrared spectroscopy			
6.	Nuclear magnetic resonance spectroscopy			
7.	**Continuous assessment № 1.** Structure and nomenclature of the organic compounds. **Academic research № 1**			
8, 9.	Nonaromatic hydrocarbons and alkyl fragments			
10.	Aromatic hydrocarbons and aryl fragments			
11.	Organic halides. Nucleophilic substitution vs elimination			
12.	Hydroxy- and thioderivatives, ethers, sulfides			
13.	Amino-derivatives; azo and diazo compounds			
14.	**Continuous assessment № 2.** Structure, reactivity and identification of hydrocarbons, halides, hydroxy-, thio- and aminoderivatives, ethers, sulfides. **Academic research № 2**			
15.	Oxo compounds			
16.	Carboxylic acids and their functional derivatives			
17.	Functional derivatives of carbonic acid. Sulfonic acids and their functional derivatives			
18.	**Continuous assessment № 3.** Structure, reactivity and identification of carbonyl compounds, carbonic and sulfonic acids and their functional derivatives. **Academic research № 3**			
CREDIT				

LABORATORY SAFETY RULES

1. Dress appropriately for the lab. Wear a white lab coat. Tie back long hair.
2. Get to know what safety equipment is available and how to use it. This includes an eyewash place, a fire blanket, fire extinguisher and sand.
3. Get to know the dangers of the chemicals in use, and read the labels carefully. Do not taste or sniff the chemicals.
4. Dispose of the chemicals according to the instruction. Use the designated disposal sites, and follow the rules. Never return used chemicals to the original containers.
5. Always add acids and bases to water slowly to avoid splattering. This is especially important when using strong acids and bases that can generate significant heat, form steam, and splash out of the container.
6. Never point test tubes at yourself or others. Be aware of the reactions that are occurring so that you can remove them from the heat if necessary.
7. Do not eat or drink in the lab! It is too easy to take in some dangerous substance accidentally.
8. Follow all directions. Never occasionally mix the chemicals. Pay attention to the order in which the chemicals are to be added to each other, and do not deviate!
9. After the end of the experiment each student should submit an account of the work that have been done, then wash up the chemical crockery, clean a workplace and ask the student on duty to check it.

Responsibilities of the student on duty:

– to get all the necessary equipment from the laboratory assistant;

– to keep an order in the laboratory room;

– the student on duty should leave the laboratory the last, after receiving permition from the lab assistant.

I agree _____ 202__ year _____
(date) (signature)

PRECAUTIONS

Work with alcohol lamps

Careless work with an alcohol lamp can result in a fire, that is why it is necessary to follow the below requirements:

– the wick of an alcohol lamp should tightly enter the aperture of a metal bush; the topping should be put forward for 1 cm and fluffed up;

– the bush should close the aperture of a alcohol lamp tightly; the alcohol lamp should be filled with alcohol no more than 2/3 of the volume;

– the lighting of an alcohol lamp should be carried only by matches, it is strictly forbidden to light an alcohol lamp from another alcohol lamp, because the bush can stoop and coming out steams of alcohol can be fired;

– to blow out an alcohol lamp only by covering it with a bell-glass;

– when heating up substances in a chemical glassware it is necessary to heat them at the top or mid-range flame, not touching a wick, because a wick is always cool, and when a hot glass contacts with it, the glass may burst.

Work with a chemical glassware

Heating substances in glassware should be performed gradually, slightly rotating it and cautiously shaking from time to time. When heating a test tube with a liquid in the open fire, splasing of a liquid is possible. Because of this fact, the aperture of a test tube should be directed aside from you and from your neighbors. Especially it is necessary to avoid injuring the eyes with hot splashes, that it is why it is forbidden to bend forward to the test tube and look inside. When heating the test tube, it should be kept at the angle of the inclined position (45°), so that splashes will hit the walls of a glassware and will not be thrown outside. If the liquid starts to rise in an exhaust tube, it is necessary to let down a test tube immediately, so that the fluid level in it will become lower than the end of an exhaust tube.

Work with inflammable liquids (IL)

IL (diethyl ether, alcohol, toluene, acetone, acetoacetic ether) are always kept in a fume hood. Experiments with these substances are carried out under draught, far from open fire and the turned on small stoves. If an ignition of the IL happened in a vessel, it is necessary to cover it quickly with a fire-prevention blanket. If the burning liquid has been spilt, it must be extinguished by sand. If the clothes begin to fire, it is necessary to wrap up quickly and densely in a fire-prevention blanket.

Work with acids and alkalis

Concentrated solutions of nitric, sulfuric, hydrochloric acids are kept in a fume hood. All experiments with concentrated acids and alkalis are carried out only in the fume hood. It is necessary to cover carelessly spilt on the floor acids and alkalis by sand and after that to clean up.

Work with toxicants

Toxic organic substances — aniline, methyl amine, toluene, picric acid are kept in a fume hood. It is necessary to be cautious with these substances, not to inhale their steams, to avoid injuring the hands as they can penetrate through the skin. In case of emergency when these substances got on hands, it is necessary to wash up quickly the hands with warm water and soap. If inhaled the steams — immediately to go out in the fresh air.

First-aid treatment in case of accidents:

– in case the hands are cut with glass, first of all it is necessary to remove all the splinters out of the wound, then to treat the wound with an alcohol solution of iodine and to put a bandage;

– in case the thermal burns happen it is necessary to treat the burnt place with the 70 % solution of ethanol;

– in case burns are caused by solutions of acids or alkalis it is necessary to wash up the burnt site with water quickly and to put an aseptic bandage;

– in case acids or alkalis hit the eyes, it is necessary wash them with water carefully and to refer the victim to the outpatient clinic;

– in case skin burns are caused by bromine, it is necessary to quickly wash the injured place off with ethanol and to put anti-burn emulsion;

– in case burns are caused by hot organic liquids, it is necessary to wash out the injured place with ethanol;

– in case burns are caused by liquid phenol it is necessary to massage the emerged sites of the white skin with a glycerin until a normal skin color is restored, then to wash with water and to put the gauze bandage moistened with a glycerin solution;

– after providing the first-aid treatment it is necessary to address to the health center of the university or to the outpatient clinic.

LABWORK № 1
CLASSIFICATION AND NOMENCLATURE OF ORGANIC COMPOUNDS

Objective: to promote safety awareness and encourage safe working practices in the chemical laboratory; to study structure, classification and nomenclature of the organic compounds.

Recommended literature

Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for a discussion:

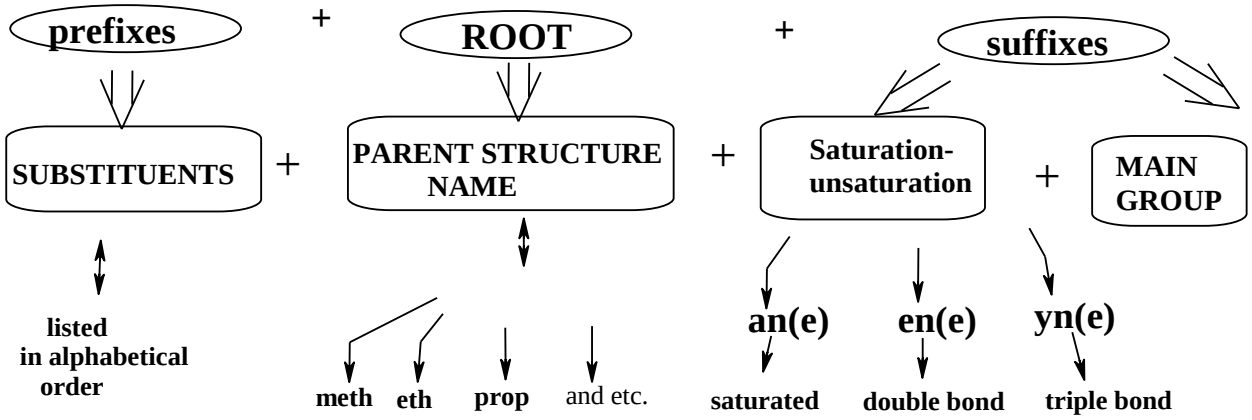
1. Organic chemistry laboratory: equipment, glassware and reagents.
2. Personal, equipment, glassware and reagents safety in the organic chemistry laboratory.
3. Constitution and isomerism of the organic compounds.
4. Classification of the organic compounds.
5. IUPAC nomenclature of the organic chemistry.

NAMING OF ORGANIC COMPOUNDS

Names of the organic compounds can be generated in different ways. Now it is known more than 50 million organic compounds. So the use of trivial (historic, common) names is limited and various types of systematic nomenclatures have been developed.

IUPAC (International Union of Pure and Applied Chemistry) has proposed the substitutive approach for the naming of the organic substances. To generate names according to this approach, one should choose the **PARENT STRUCTURE**, followed by the substitution of its hydrogen atoms by structural fragments (represented by suffixes and prefixes) as shown below:

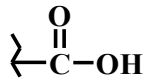
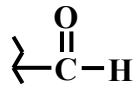
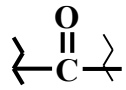
prefixes [substituents] + **parent structure** [carbon chain] + **suffixes** [(un)saturation and main functional group]

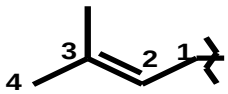


The root of the compound name is determined by a number of carbon atoms in a parent structure.

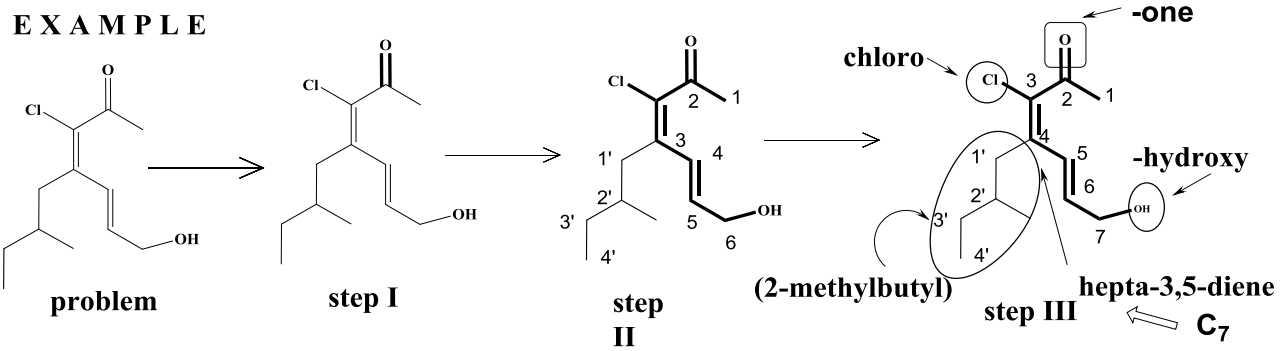
C_n	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{18}	C_{20}
Name	Meth	Eth	Prop	But	Pent	Hex	Hept	Oct	Non	Dec	Undec	Octadec	Icos

Groups with heteroatoms can be regarded either as functional groups or substituents depending of their priority. Only the main functional group will be named as a functional one and will be placed in the final position of the word. 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).

FUNCTIONAL GROUPS AND SUBSTITUENTS				
GROUP IN FORMULA		**WRITING IN NAME**		PRIORITY ORDER DOWN
Grafics	**Name (in text)**	**Functional group**	**Substituent**	
	Carboxyl group	-oic acid (carboxylic acid)	carboxy-	
	Aldehyde group	-al	formyl-	
	Keto group	-one	oxo-	
-OH	Hydroxyl group	-ol	hydroxy-	
-NH_2	Amino group	-amine	amino-	

GROUPS WHICH ARE EXCLUSIVELY SUBSTITUENTS			
NO_2	**Nitro group**	**nitro-**	
Cl (Br, I, F)	**Halide group**	**chloro- (bromo-; iodo, fluoro)**	
Hydrocarbon fragments		**core structure name + yl**	
		**(3-methylbut-2-enyl)-**	

To name the structure one should find the parent structure, then number it and finally, indicate saturation-unsaturation and functional groups with suffixes and substituents with prefixes.



7-Hydroxy-4-(2-methylbutyl)-3-chlorohepta-3,5-diene-2-one

I step

To determine the parent structure we should follow a hierarchical system of rules (the rule placed above has the priority).

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

1) carries the main functional group;
2) carries the maximum number of double (triple) bonds;
3) the longest;
4) carries the minimum number to chains attaches.

II step

One should indicate with a number the position of C-atoms in a parent structure, using the lowest possible number for main functional group (if it is absent — for double bonds). For alkanes number the parent chain, starting at the end to result the set with the lowest numbers; thus, the numbers 2, **3**, 5, 6 is to be chosen rather than 2, **4**, 4, 5.

III step

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

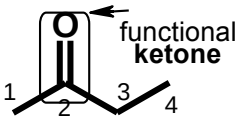
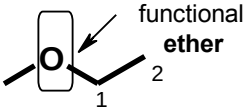
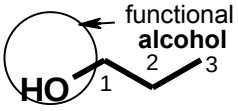
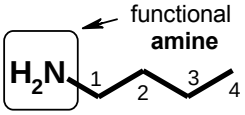
We name the functional groups and substituents using the table above. The name of hydrocarbon groups can be constructed according to the rules regarded above, followed by the addition of –yl suffix. For these indicate the position of the carbon attached to the parent structure using the lowest possible number.

IV step

Finally we give the name to the structure.

The first we list prefixes (which are the names of the substituents) in an alphabetical order; next, we name the parent structure (C_n) indicating by suffixes saturation/unsaturation character, followed by the naming of the main functional group in a final position.

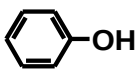
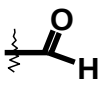
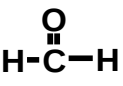
In a **radico-functional** approach the characteristic group in the compound is expressed as one word (called the "functional class name"). The remainder of the molecule attached to that group is expressed in its radical form as another word which precedes the functional class name.

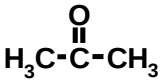
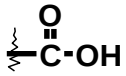
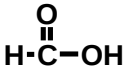
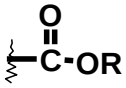
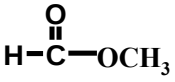
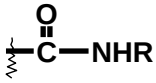
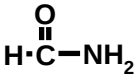
Approach				
Substitutive	Butan-2-one	Methoxyethane	Ethanol	Butanamine
Radico-Functional	Ethyl methyl ketone	Ethyl methyl ether	Ethyl alcohol	Buthylamine

The presence of functional group(s) in the structure gives rise to the classification of the organic compounds.

Hydrocarbons have no functional groups. They can be aliphatic or cyclic, saturated or unsaturated. Monofunctional compounds carry the only functional groups.

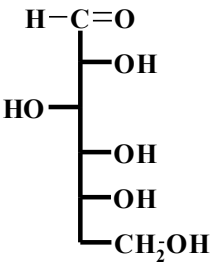
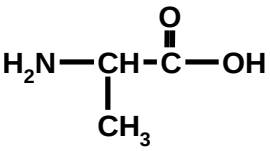
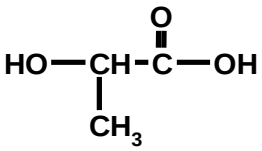
MONOFUNCTIONAL COMPOUNDS

Class name	**Functional group**		**Example**	
	Formula	**Name**	**Formula**	**Name**
ALCOHOLS	**–OH**	Hydroxyl	**CH_3OH**	methanol
PHENOLS	**–OH**	Hydroxyl		phenol
ALDEHYDES		Aldehyde		Methanal (formaldehyde)

Class name	Functional group		Example	
	Formula	Name	Formula	Name
KETONES		Keto		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≡N**	Nitrile	**$CH_3C{\equiv}N$**	Acetonitrile

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

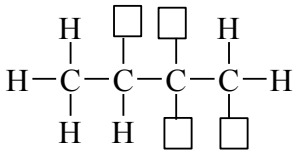
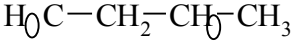
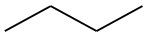
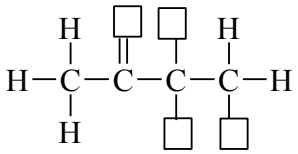
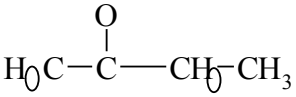
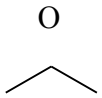
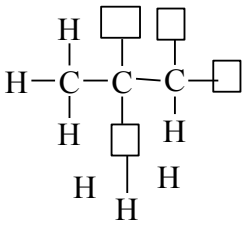
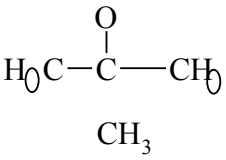
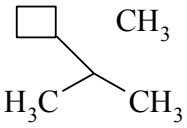
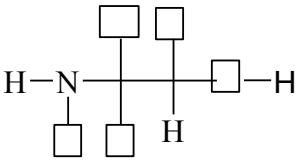
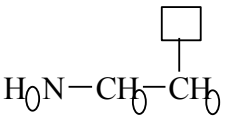
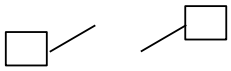
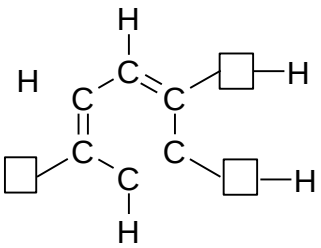
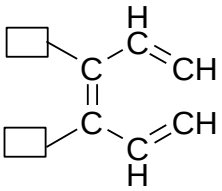
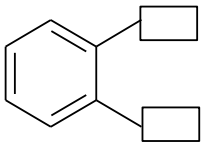
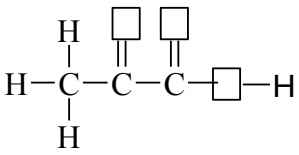
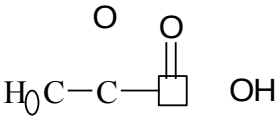
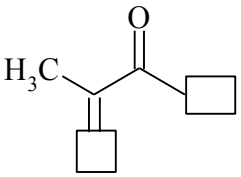
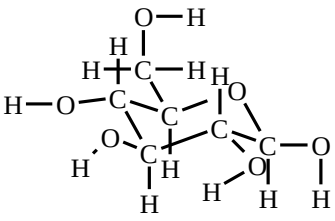
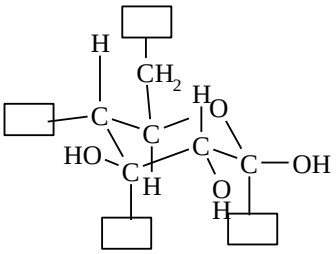
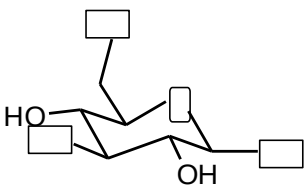
HETEROFUNCTIONAL COMPOUNDS

Class name	Functional group		Example	
	Formula	Name	Formula	Name
CARBOHYDRATES (SUGARS)	**-OH** **-C=O**	Hydroxyl Aldehyde or Keto		Glucose
AMINO ACIDS	**-NH_2** **-COOH**	Amino Carboxyl		Alanine (2-amino-propanoic acid)
HYDROXY ACIDS	**-OH** **-COOH**	Hydroxyl Carboxyl		Lactic acid (2-hydroxy propanoic acid)

The structure of the course is based on this classification and every new lab session you will meet a new class of compounds. First classes start from basic principles. Therefore the naming of organic compounds gives us the set of practice problems for the first laboratory session.

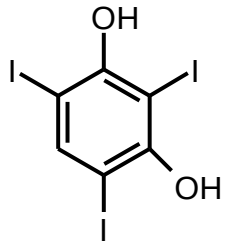
PRACTICE PROBLEMS

1. Complete the formulas of the following compounds.

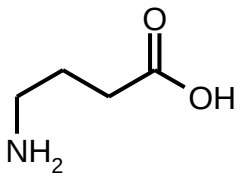
The name	*Kekule*	Condensed	Stick (line)*
Butane			
Butan-2-one			
2-Methyl-propan-2-ol			
2-Amino-ethan-1-ol			
Benzene-1,2-diol			
Pyruvic acid (2-oxopro-panoic)			
β-D-Gluco-pyranose			

* In stick (line) formulas any carbon atom can be indicated in condensed form.

2. Find functional groups and other structural fragments in formulas of the pharmaceutical drugs presented.



Riodoxolum



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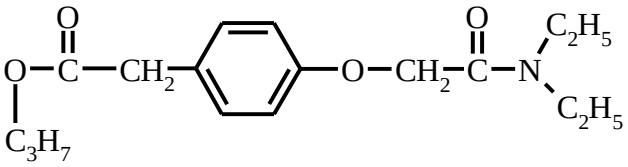

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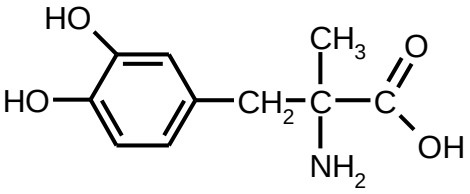
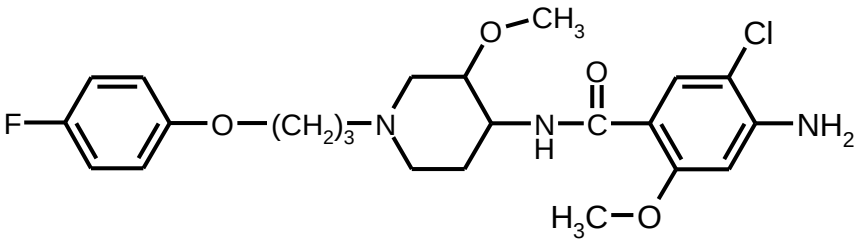


Metyldopa



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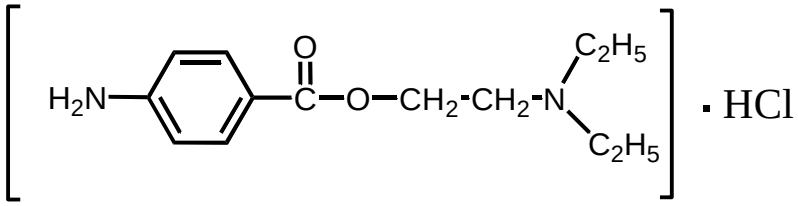
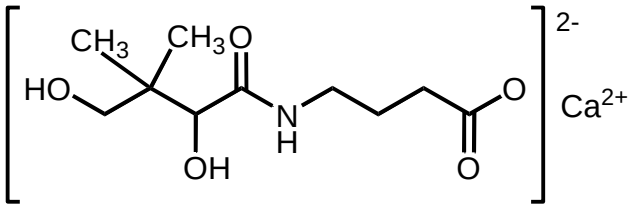
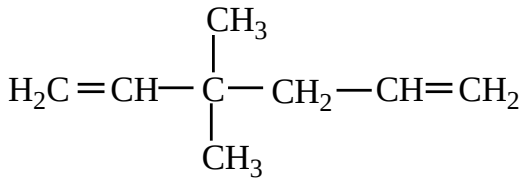
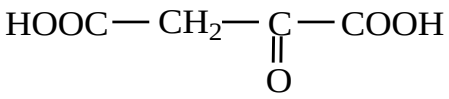
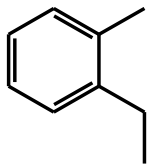
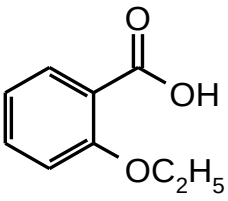
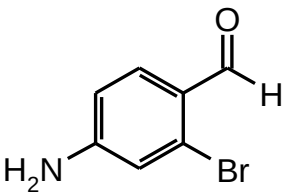
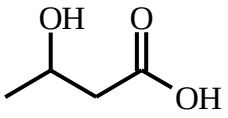
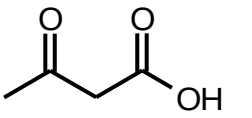
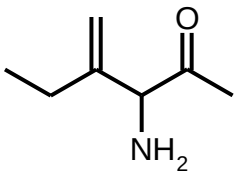
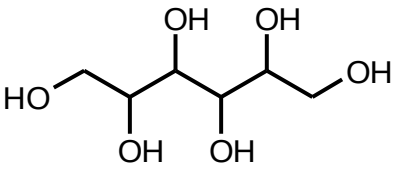
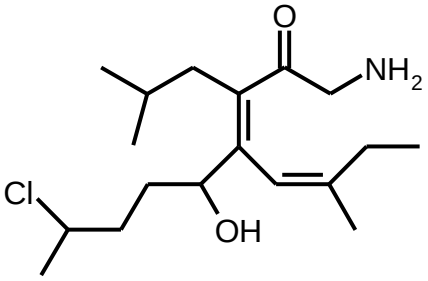
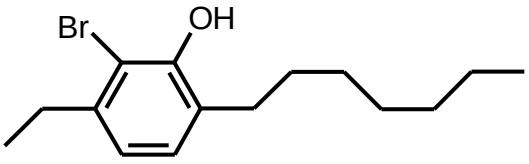
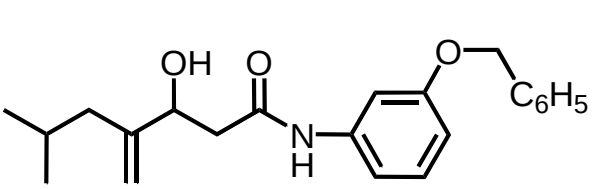
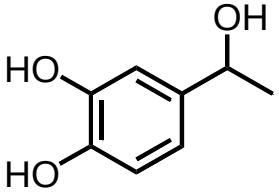


Procaine



Hopaten

3. Give the names of following compounds (IUPAC nomenclature).

4. Write the formulas of the following compounds.

2,3-Dimethylpentane	4,4-Diethyl-3-methylheptane
Cyclopentane	Propane-1,2,3-triol
3-Hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridine (vitamin B_6)	
Sodium 2-ethylpentanoate (sodium valproate, the active substance of *Depakene*, with antiepileptic action)	

5. Draw and name all the isomers of the compound with the formula C_4H_6.

6. Draw and name all the isomers of the compound with the formula C_8H_8O. Find functional groups and fragments.

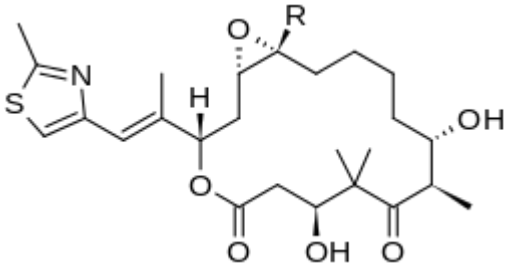
7. Draw and name all the isomers of the compound with the formula C_3H_6O.

8. Write the formulas of the following compounds. Give IUPAC names (substitutive approach).

Benzyldiethylamine	Diethyl ether	Ethane dicarbonic acid
Methyl ethyl ketone	*tert.*-Butyl alcohol	Nitroglycerine
γ-Oxybutyric acid	Phenyl acetone	Vinyl acetylene

9. Draw 3 bicyclic isomeric compounds with the formula $C_8H_{12}O_2$: the acid, the hydroxy ketone, the diol. Give their IUPAC names.

10. The *Epothilones* are a class of potential cancer drug, preventing cancer cells from dividing by interfering with tubulin. Analyze the formula of *Epothilones* A (R = H) and B (R = CH_3) and indicate functional groups and structural fragments.



Signature of the instructor:

LABWORK № 2
CHEMICAL BONDING

Objective: to study the electronic configuration of the organogenic elements and the process of the covalent bond formation; to discuss the process of a charge distribution in molecules.

Recommended literature

Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

1. Chemical bonding in the organic compounds.
2. Charge distribution in the organic compounds. Induction and mesomerism. Electron donating and electron withdrawing substituents.
3. Conjugated systems. Conjugation energy.
4. Aromaticity. *Huckel*'s rule. Aromaticity of benzoic and non-benzoic systems.

CHEMICAL BOND CONCEPT MODELLING IN ORGANIC COMPOUNDS

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

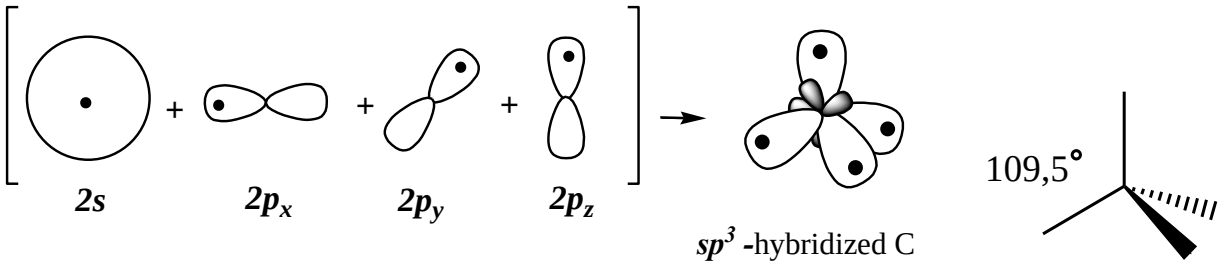
Carbon is in the second row of the periodic table and it has the following electronic configuration at the ground state: $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^0$. However, carbon is present in an excited state in the organic compounds. Promotion of one 2*s* electron to the 2*p* orbital forms the configuration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

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: $1s^2 \mathbf{2s^1 2p_x^1 2p_y^1 2p_z^1}$.

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



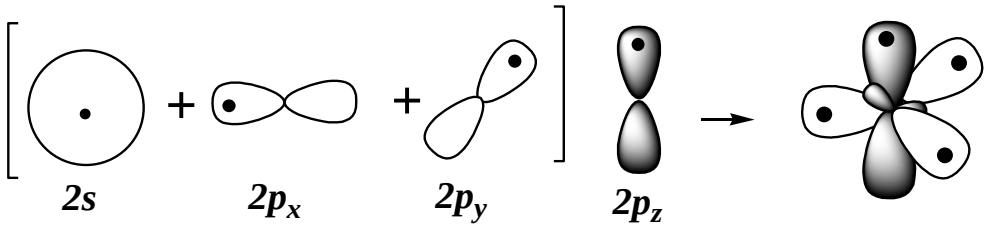
sp^3 **-**hybridized C

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: $1s^2 \mathbf{2s^1 2p_x^1 2p_y^1} 2p_z^1$.

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

and one unhybridized *p* orbital left



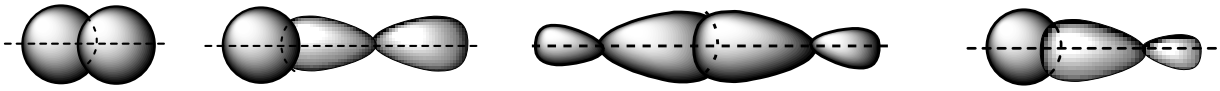
sp^2 hybridized C

The valency angles between the hybrid orbitals are 120 degrees.

Although ionic bonds a 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.

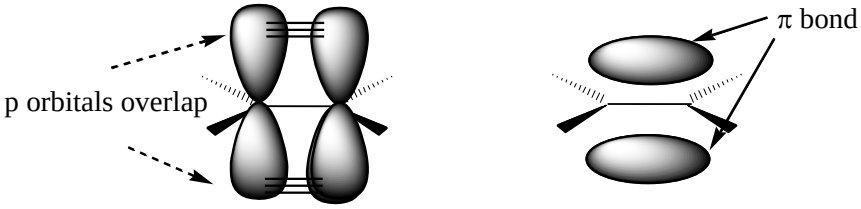
There are σ and π covalent bonds depending on the overlap type.

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.



s-s *s-p* overlap of hybrid orbitals overlap of hybrid and *s* orbitals

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.

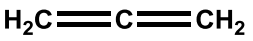
A double bond can be considered as a combination of one σ bond and one π bond. Double bonds are present in alkenes, carbonyl compounds, etc.

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.

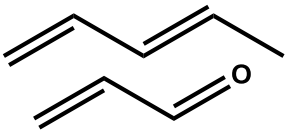
CONJUGATION

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



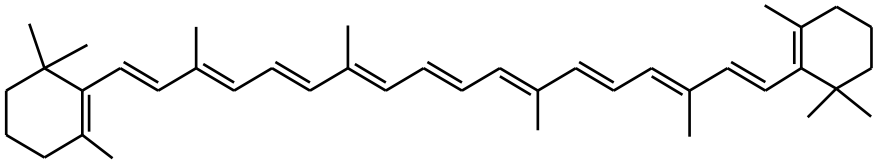
cumulated π bonds

isolated 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 biological processes. For example, β-carotene, the yellow-orange pigment in carrots, contains eleven conjugated double bonds.



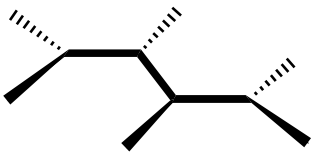
β-carotene

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

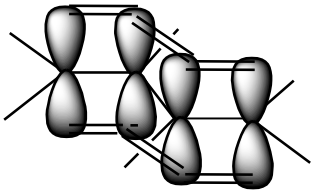
Buta-1,3-diene (formerly 1,3-butadiene) is a typical example of a conjugated system.

$$CH_2 = CH - CH = CH_2$$

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-skeleton of buta-1,3-diene

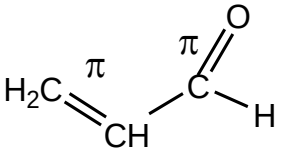


overlapping of p orbitals of buta-1,3-diene

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 orbitals and increased stability of the molecule.

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

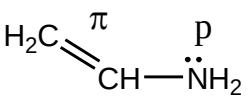
π,π Conjugation is the delocalization of *p* orbitals over an entire *π* system. This type is characterized by alternating double and single bonds. Buta-1,3-diene is an example of ***π,π*** conjugation. A π,π-conjugated system may also include heteroatoms, for example, acrolein (propenal is the systematic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



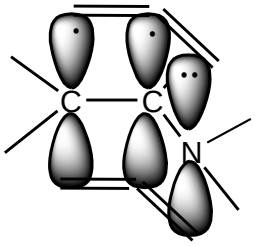
π,π conjugation

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 **>C=CH–X**, where

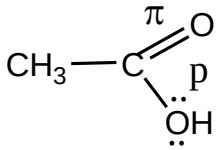
X is an atom possessing a lone pair of electrons. In this case three orbitals are delocalized: two *p* orbitals of the double bond and one *p* orbital of the X atom.



π,p conjugation



ethenamine

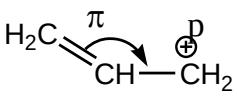


π,p conjugation

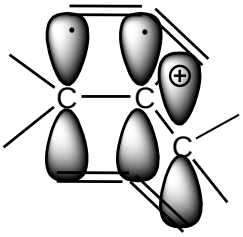
ethanoic acid

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

For example *p*,π conjugation is typical of compounds with a fragment **>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.

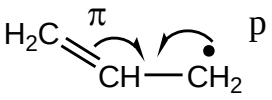


π,p conjugation

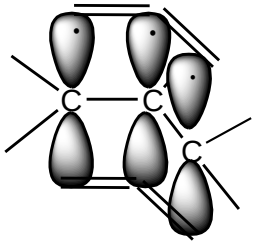


allyl cation

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



π,p conjugation

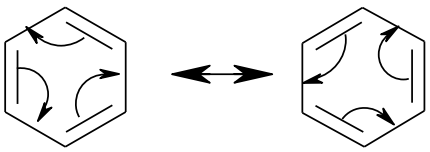


allyl radical

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

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 “cyclohexantriene” structure.

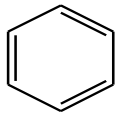


The formula was accepted and soon was complemented with the concept of cyclic conjugation between all three bonds. Since then, aromaticity has been associated with the presence of a benzene ring and fused benzene ring compounds.

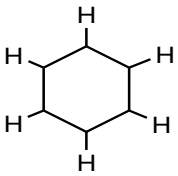
In 1931, Erich Hückel was the first to separate bonding electrons into σ- and π-type electrons. He proposed a quantum mechanical theory of aromaticity. This concept is valid for a larger range of compounds and has been widely used till today.

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

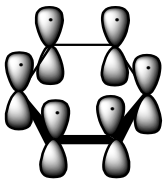
A typical example of an aromatic system is a *benzene*. It is a highly unsaturated compound. It has been found experimentally (i.e. by means of X-ray diffraction) that benzene consists of flat symmetrical molecules shaped like regular hexagons. All six carbon-carbon bonds in benzene are of the same length, 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.



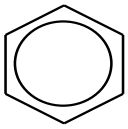
benzene



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:

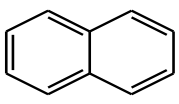
1) all atoms are sp^2-hybridized, therefore, a molecule has a coplanar structure;

2) a molecule has a cyclic system of conjugation;

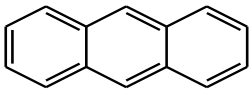
3) a cyclic system of conjugation contains $(4n + 2)$ π electrons (N), where n is an integer (0, 1, 2, 3, etc.), which means that N = 2, 6, 10, 14, 18, 22, etc.

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

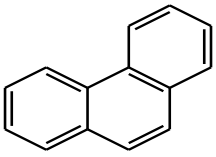
Benzene corresponds to the Hückel rule for N = 6 (n = 1) that is involved in the conjugation of six *p* electrons. Such molecules as naphthalene, anthracene, phenanthrene satisfy all the requirements of aromaticity.



naphthaline
N=10
n=2



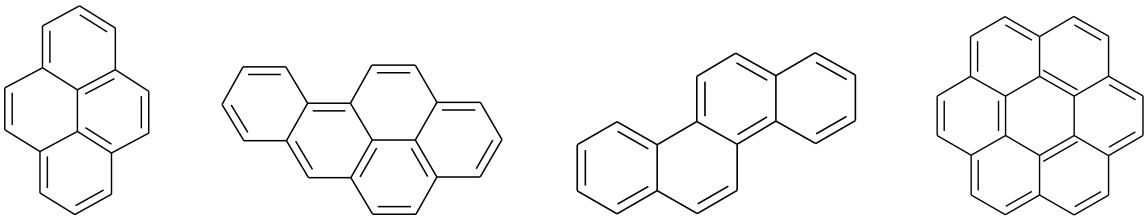
anthracene
N=14
n=3



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.



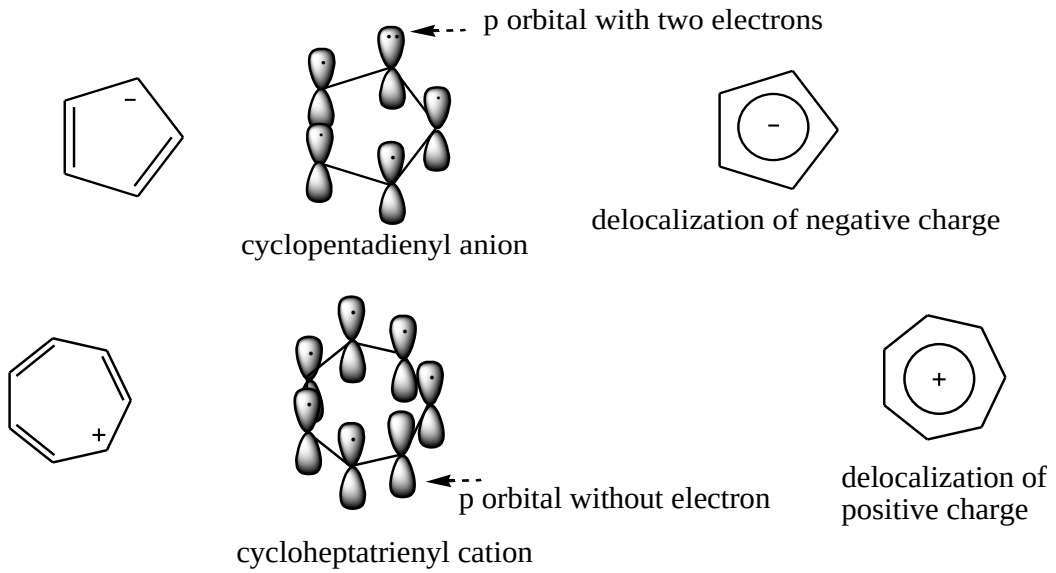
Pyrene **Benzo[*a*]pyrene** **Chrysene** **Coronene**

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.

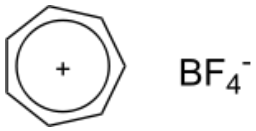
Though PAHs is considered highly toxic for mammals, these compounds may also be abundant in the universe. According to some theories, more than 20 % of the carbon in the universe is presumably associated with PAHs. They were formed shortly after the Big Bang and later on were widely spread throughout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

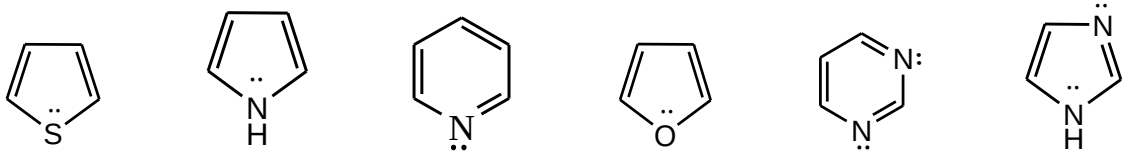


In both cases a cyclic conjugation system involves six *p* electrons. This corresponds to the Hückel rule. Since the conjugation is delocalization of the electron density, the correct images of the cyclopentadienyl anion and cycloheptatrienyl cation are the ones in which the charge belongs to the entire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

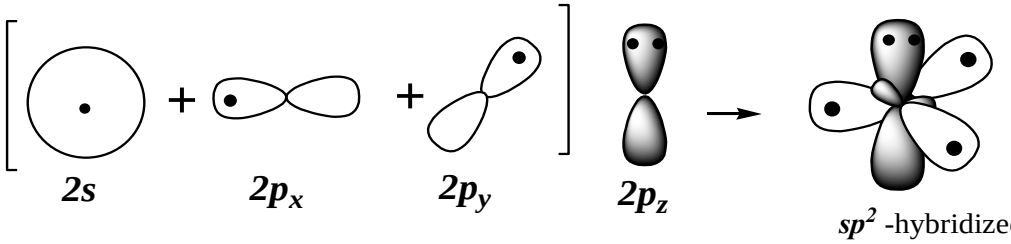


In heterocyclic molecules, a delocalized *p* electron system is formed with the participation of the *p* orbitals of carbon atoms and the *p* orbitals of heteroatoms.



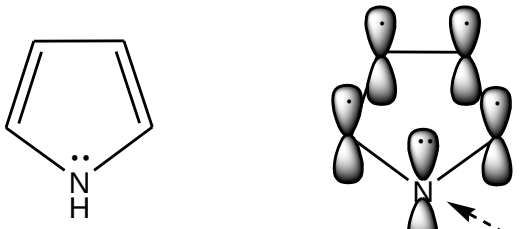
Thiophene **Pyrrole** **Pyridine** **Furane** **Pyrimidine** **Imidazole**

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



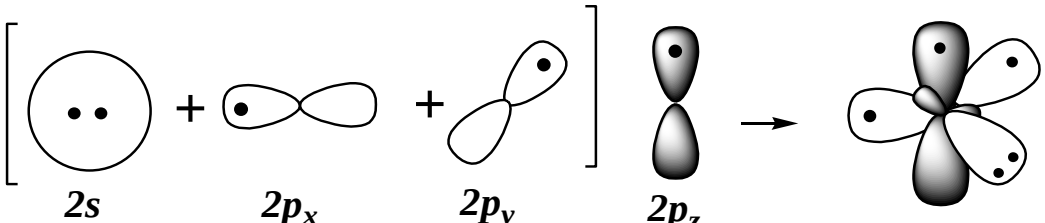
sp² -hybridized pyrrole N

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.



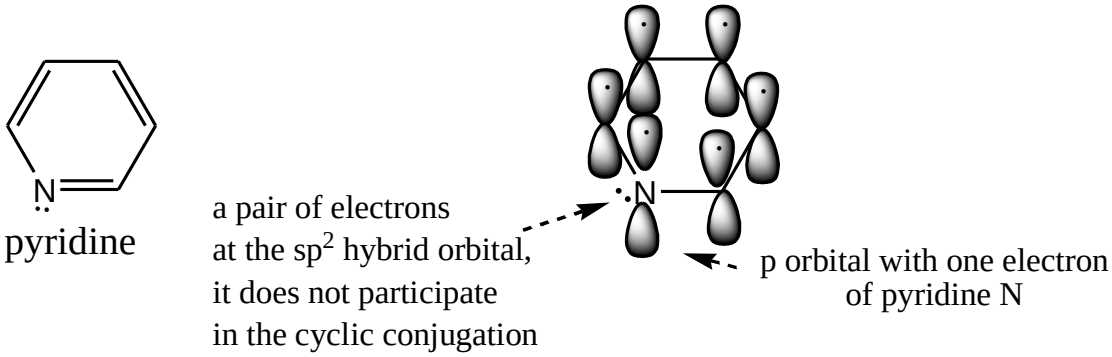
pyrrole p orbital with two electrons of pyrrole N

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.



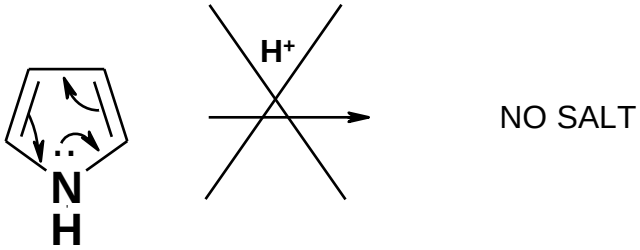
sp² -hybridized pyridine N

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.

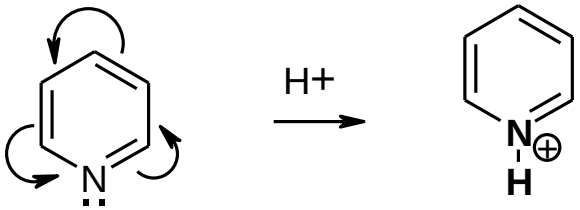


The unhybridized *p* orbital of the nitrogen atom (with one electron) is perpendicular to the plane of the ring and overlaps the *p* orbitals of the carbon atoms to form an aromatic conjugated system containing six *p* electrons. Thus, pyridine satisfies all criteria of aromaticity.

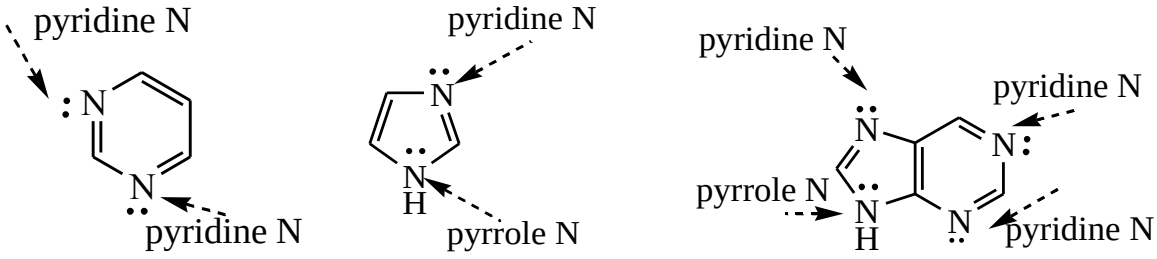
It is interesting to compare the availability of the electrons from nitrogen in pyrrole and pyridine. Pyrrole shares its electrons to form the aromatic system. As a result, it has no lone electrons and cannot form a new bond, in particular, in base/acid interactions.



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.



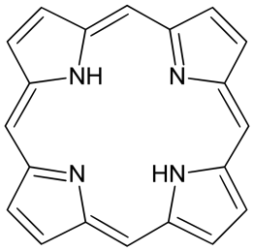
Pyrrole and pyridine nitrogen atoms are found in many biologically important compounds. In these compounds the basic atom is called pyridine nitrogen and the non-basic one (sharing electrons to form aromatic structure) is called pyrrole nitrogen.



pyrimidine **imidazole** **purine**

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 porphine structure.

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

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.

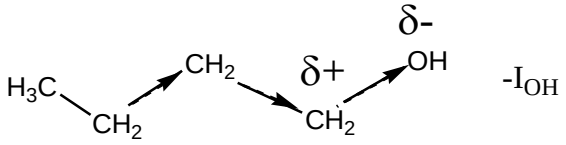
The presence of a polar σ or π bond in an organic molecule results in polarization of neighboring atoms. The electron density of chemical bonds is not evenly distributed in the molecules containing atoms different from carbon and hydrogen. That leads to polarization of a covalent bond and the appearance 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.

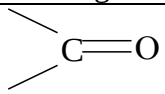
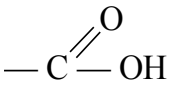
Alkyl groups, by contrast to the above, are less electron-withdrawing than hydrogen and are therefore considered to be electron-releasing. The electron donating (i.e. positive) inductive effect is designated as *+I effect*. In the case of the –I effect the electron density at the nearby atom is decreased, 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.



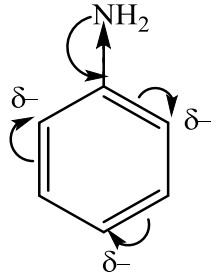
A more significant electronic effect is observed in molecules with conjugated fragments. In such cases the polarization effect of a substituent extends through the entire conjugation system.

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 adjacent benzene ring or a π bond. The mesomeric effect can be transmitted along any number of carbon atoms in a conjugated system.

Group	**I effect**	**M Effect**	**Correlation**	**Integrated influence**
alkyls	+I	no M	–	D
NH_2	–I	+M	+M > –I	D
–OH, –SH	–I	+M	+M > –I	D
– O – R	–I	+M	+M > –I	D
Halogens	–I	+M	–I > +M	A
	–I	–M	–I, –M	A
	–I	–M	–I, –M	A
– SO_3H	–I	–M	–I, –M	A
– NO_2	–I	–M	–I, –M	A

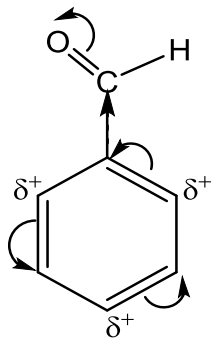
Consider the distribution of the electron density in a molecule of phenylamine (aniline). The amine group produces the negative inductive effect. As phenylamine represents a conjugated system, the amine group has the mesomeric effect. And since the nitrogen atom has a lone pair of electrons, the amine group shows the positive mesomeric effect. Thus, the amine group donates the electrons to the adjacent benzene ring.



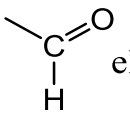
-I +M +M > -I

NH_2 - is 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



elecron 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.

PRACTICE PROBLEMS

1. Draw the model of the bond formation in methane and ethane using the concept of hybridization.

2. Draw the model of the bond (σ and π) formation in ethene and ethyne using the concept of hybridization.

3. Draw the formulas and discuss spatial structure of the buta-2,3-diene, hexa-2,4-diene and penta-1,4-diene. Use the concept of hybridization.

4. Convert the name to the structure and identify the type of the conjugation.

Name	Formula	Conjugation type
Buta-1,3-diene		
Vinyl chloride (chloroethene)		
Propanoic acid		
Methyl propenoate		

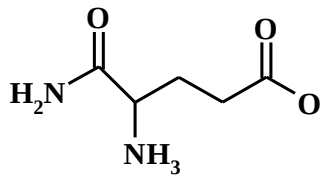
Name	Formula	Conjugation type
Phenol		
Aniline (aminobenzene)		
2-(3,4-Dihydroxyphenyl)ethyl amine (*Dopamine*)		
Pyrrole		
Propenal		
Nitrosourea		
2-Ethyl 3-hydroxy-6-methyl-pyridine succinate (acting principle of *Emoxypine*, is an antioxidant)		

5. Fill the blank cells in the table.

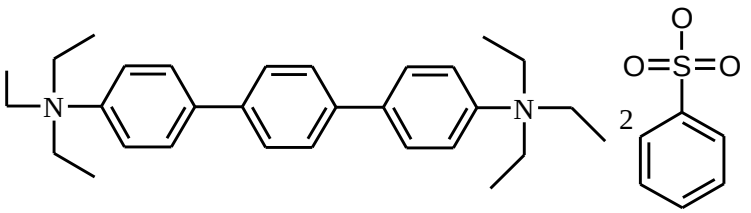
Compound	Formula	Factors required for aromaticity
Naphthalene		
Phenanthrene		

Compound	Formula	Factors required for aromaticity
Pyridine		
Pyrrole		
Pyridine		
Tropylium (cyclohepta-1,3,5-trienium) cation		
Thiophene		
Indole		

6. Indicate the charges on atoms of glutamine (proteinogenic amino acid) and *Tercuronium* (quaternary ammonium muscle relaxant).

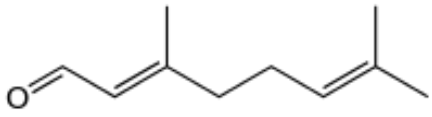
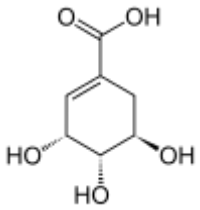


Glutamine



Tercuronium

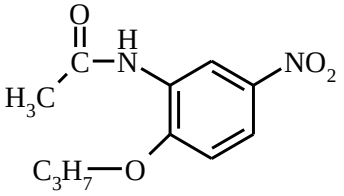
7. Show graphically the influence of the substituents on the distribution of the electrons in a double bond. Indicate the effects (induction/mesomerism) and a cumulative action of the substituents (donor/acceptor).

2-Methylbut-2-ene	3,3,4-Trifluoropropene	Phenyl acetylene
2- Methoxypropene	Cyclopent-2-enone (C=C bond)	*trans*-1-Nitrobut-1-ene
Dimethyl sulfoxide	*cis*- Hept-2-enoic acid (C=C bond)	Ethyl cinnamate (C=O bond)
N-Ethenyl piperidine	*trans*-Oct-5-enoic acid (C=O bond)	Hexa-2,4-dienoic acid
Geranial 	Shikimic acid 	

8. Show graphically the influence of each of the functional groups on the distribution of the electrons in benzene ring of the molecule of vanillin (4-hydroxy-3-methoxybenzaldehyde).

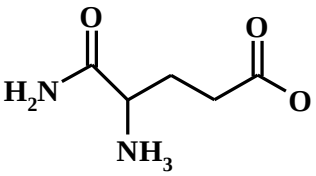
9. Show graphically the influence of substituents on the distribution of the electrons in aromatic system. Indicate the effects (induction/mesomerism) and a cumulative action of the substituents (donor/acceptor).

Phenol	N-Methylaniline	Methyl benzoate

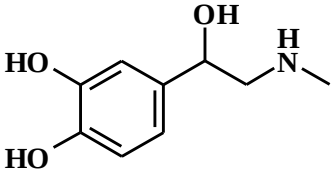
Salicylic acid	p-Aminophenol	p-Nitroaniline
p-Aminobenzenesulfonic acid	Cinnamic acid (3-(phenylpropenoic acid)	*Falimintum* 

10. Compare the distribution of electrons in benzene rings of tyrosine (2-amino-3-(4-hydroxyphenyl) propanoic acid) and phenylalanine (2-amino-3-phenylpropanoic acid).

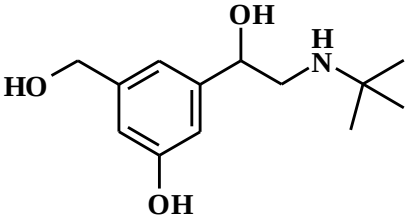
11. Assign charges to all appropriate atoms and formal charges to atoms forming the double bonds for glutamine (one of the proteinogenic* amino acids).



12. Show graphically the influence of functional groups on the distribution of the electrons in benzene ring of the molecules of *Epinephrine* (hormone and neurotransmitter, also used as medication) and *Salbutamo*l (a bronchodilator, which is a substance that dilates the bronchi and bronchioles, decreasing resistance in the respiratory airway and increasing airflow to the lungs. They are both in the List of Essential Medicines† proposed by World Health Organization).



Epinephrine

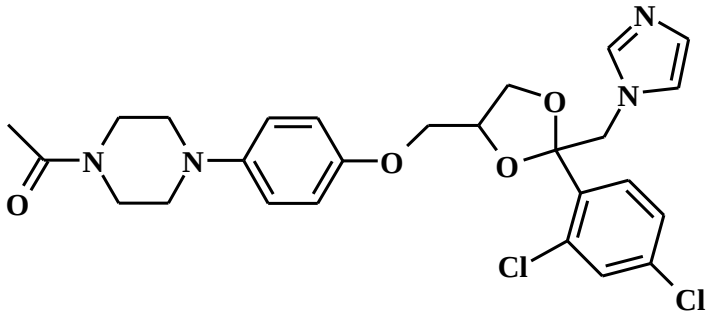


Salbutamol

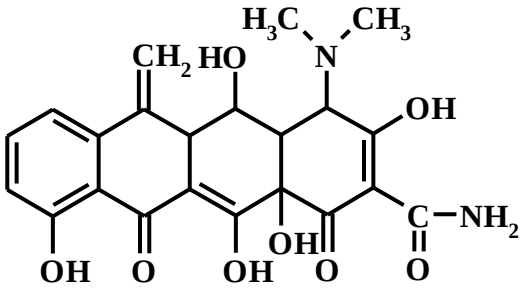
* Proteinogenic amino acids are incorporated biosynthetically into proteins during translation.
† The list of the most effective and safe drugs covering the most important needs in a healthcare system.

13. Range following substances (phenol, 3-nitrobenzenesulfonic acid, benzene, 1,3-dinitrobenzene, anisole, benzyl alcohol) according to the increase of a charge in benzene ring. Explain your choice.

14. Find the aromatic fragments and indicate the conjugation types in *Ketoconazole* (a synthetic imidazole antifungal drug). Show graphically the influence of the substituents on the distribution of the electrons in aromatic fragments and double bond.



15. Find the aromatic fragments and indicate the conjugation types in *Doxycycline* (tetracycline antibiotic). Show graphically the influence of the substituents on the distribution of the electrons in aromatic fragments and double bond.



Signature of the instructor:

LABWORK № 3
STEREOISOMERISM AND STEREOCHEMISTRY

Objective: to study spatial arrangement of atoms that form the structure of molecules and their manipulation.

Recommended literature

Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

1. Configuration and conformations.
2. Spatial molecular models and formulas.
3. Chirality and symmetry of molecules.
4. Diastereomers and enantiomers.
5. Conformational analysis of aliphatic and cyclic compounds.
6. Stereochemistry in life systems.

SPATIAL STRUCTURE OF ORGANIC MOLECULES

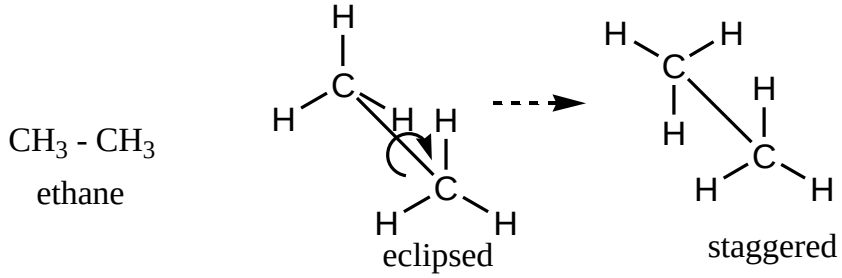
Stereochemistry is a science which studies spatial structure of organic compounds.

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

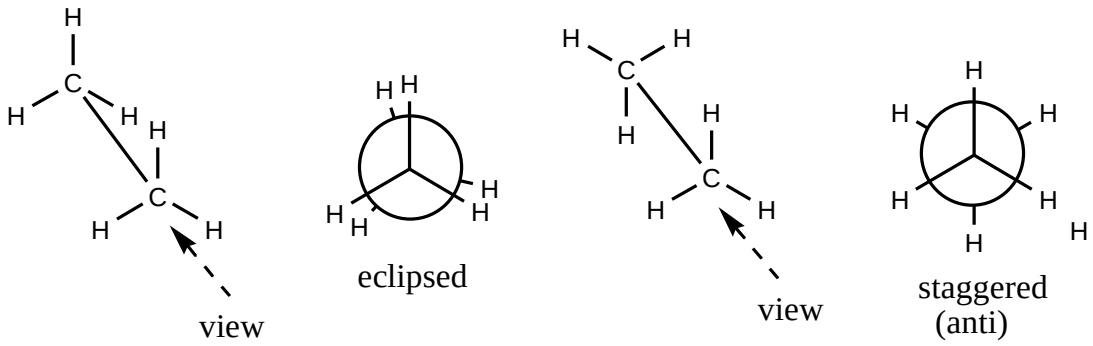
CONFORMATIONAL ISOMERS

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

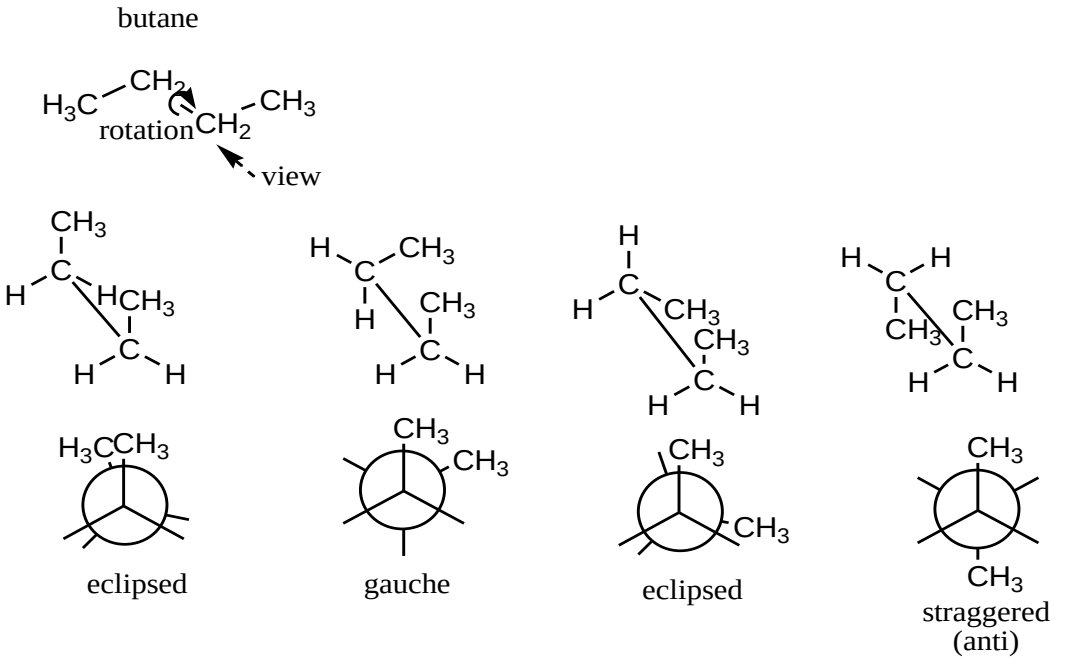
Conformations are interconverted without breaking σ bonds. A rotation angle about a σ bond is called the torsion angle. We take into account only six conformations that can be obtained from the rotation about a single bond for the minimal torsion angle of 60°; the rest forms are neglected. Conformations 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.



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.

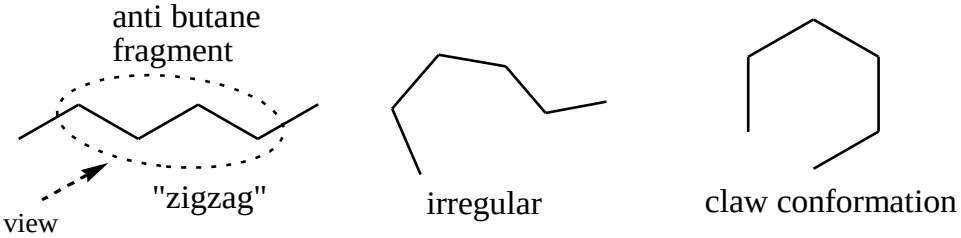


More complex molecules have a greater number of conformations that differ by their energy. Consider butane conformations resulting from rotations about the C_2–C_3 bond.

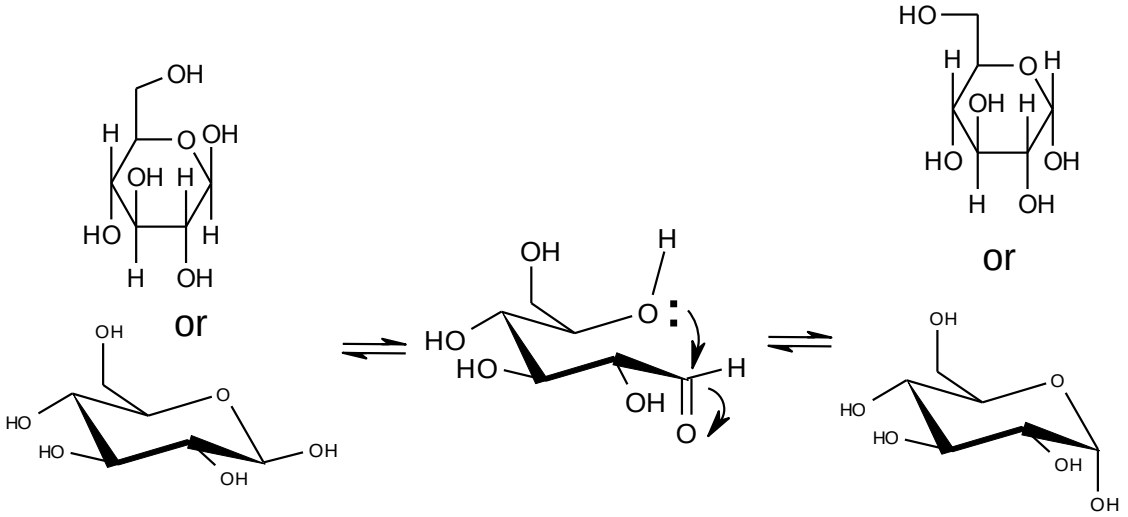


The eclipsed conformations are formed with the torsion (dihedral) angles of 0° and 120°. The gauche and anti-conformations are formed with the torsion angles of 60° and 180°, respectively. The stability of conformations depends on several factors: the torsional strain and *van der Waals* strains. **Torsional 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).

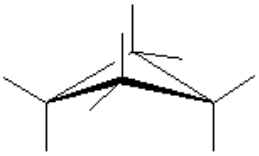


β-D glucopyranose D glucopyranose oxo-form α-D glucopyranose

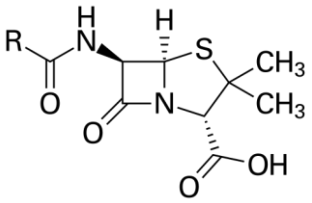
Angle strain is an increase in potential energy of a molecule, due to bond angles deviating from the ideal.

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.

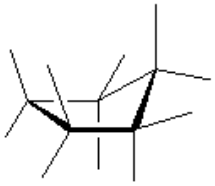


"butterfly" cyclobutane conformation

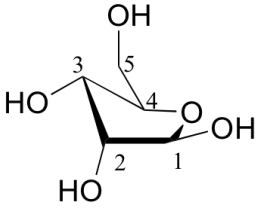


core structure of penicillin

In cyclopentane presents in the envelope non-planar conformation in which one of the carbon atoms is off the plane where the rest four atoms are located.



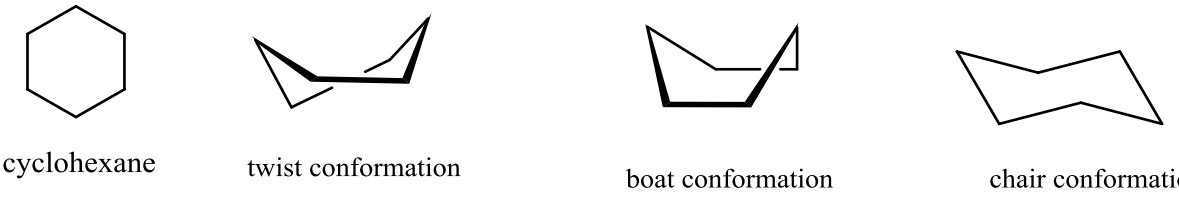
cyclopentane
envelope conformation



C_3-endo conformation (as in RNA)

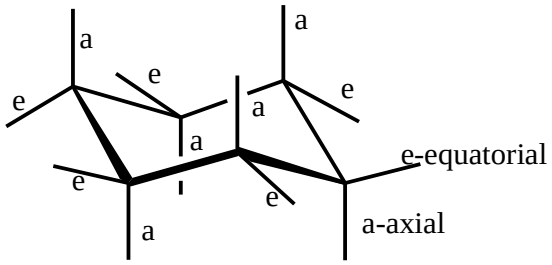
This conformation of a five-membered ring is stable. Such conformation is observed of ribose and deoxyribose in RNA and DNA (a C_3-endo form is subtype of the envelope conformation).

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.



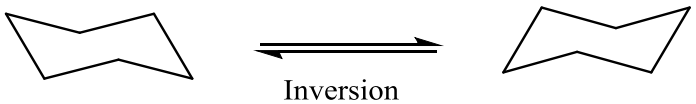
cyclohexane twist conformation boat conformation chair conformation

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



chair conformation

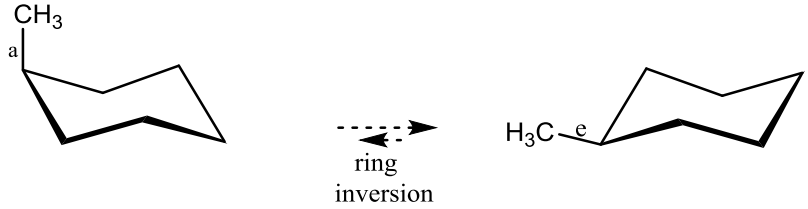
The six C–H bonds posed perpendicular to the mean plane and directed alternately upwards and downwards, are called ***axial*** (denoted by *a*). The other six C–H bonds are angled 109° and lie almost parallel to the mean plane; they are called ***equatorial*** (designated by *e*). This leads to the fact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



Inversion

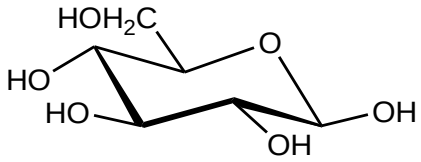
All axial substituents during their transition are converted to equatorial substituents, while all equatorial substituents become axial. This process is called the *ring inversion* (commonly referred to as the “ring flipping” or the chair inversion). The inversion is a rapid process, hence cyclohexane 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.

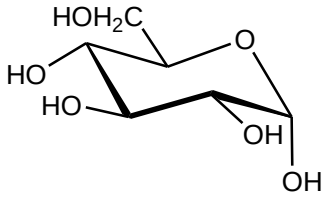


less stable chair conformation more stable chair conformation

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)

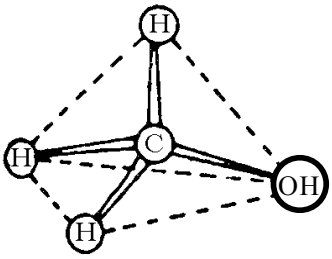
The most stable conformation of glucose is the chair conformation of β-D-glucopyranose in which all bulky substituents (OH, CH_2OH) are in the equatorial positions. This form is widespread in nature.

CONFIGURATIONAL ISOMERS

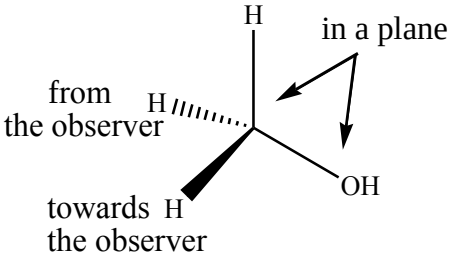
A **configuration** is a specific spatial arrangement of atoms in a molecule that excludes differences resulting from rotations about single bonds.

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).

CH_3OH (methanol)



tetrahedral configuration of carbon atom

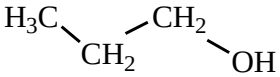


stereochemical formula of methanol

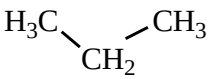
THE CONCEPT OF CHIRALITY. CHIRAL MOLECULES

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, propanol-1, propane (represented in the figure right below).

benzene



propan-1-ol



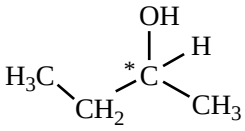
propane

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

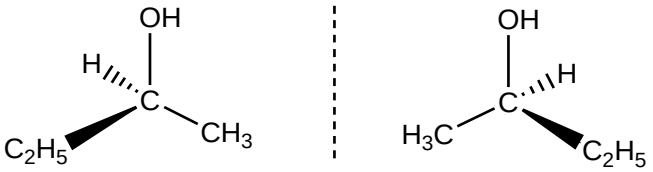
Chirality is the property of an object to be non-superimposable with its mirror image. Objects that have such property are ***chiral***. If an object can be superimposed on its mirror image, it is

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 (*).

Chiral molecules are represented by two stereoisomers that are related to each other as a subject and non-superimposable on their mirror images.



butan-2-ol



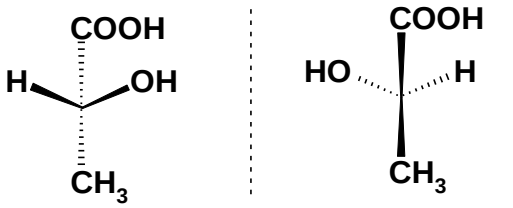
two stereoisomers of butan-2-ol

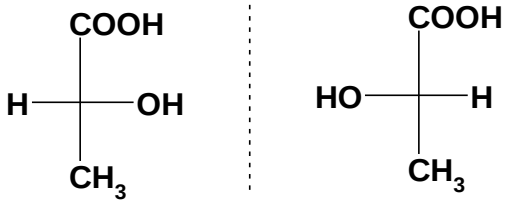
Enantiomers are stereoisomers which are mirror images of each other.

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 (counter-clockwise) and are called laevorotatory (–).

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 20th century *Fischer* projection formulas were widely used to represent the structures of enantiomers.



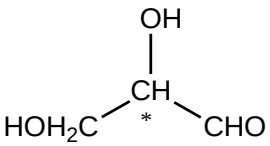


In writing Fischer projections, the following rules are to be followed:

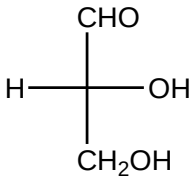
1) a carbon chain is arranged vertically;
2) the “top” and “bottom” groups are oriented backward, away from the plane;
3) the highest priority group is placed in the “top” position;
4) the “right” and “left” groups are placed in front of the plane;
5) all bonds are drawn as simple lines;
6) the central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

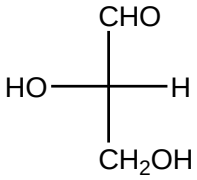
Generally, D/L nomenclature is used mostly in biochemistry and originates from the d/l system, which came from the proposals made in 1906 by professor *Rosanoff*. The configuration of a molecule was compared with the configuration of glyceraldehyde (2,3-dihydroxy propanal). Glyceraldehyde contains a 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



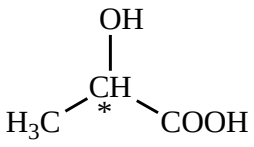
D-(+)-glyceraldehyde

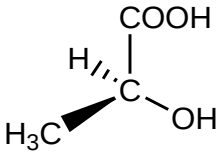


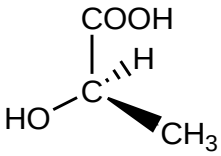
L-(-)-glyceraldehyde

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.

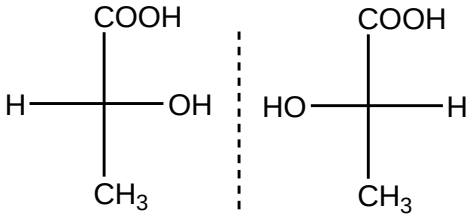






lactic acid

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.



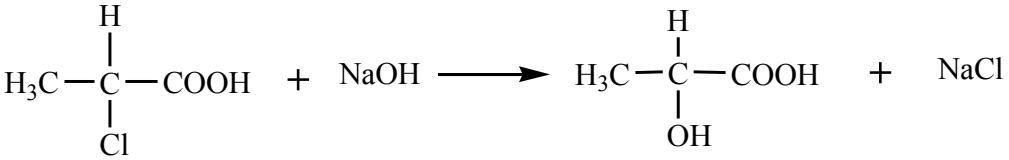
D-lactic acid L-lactic acid

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-chloro-propanoic acid with aqueous NaOH.

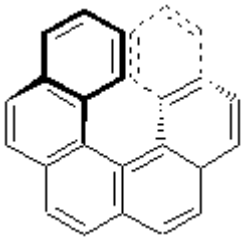


(+,-) lactic acid

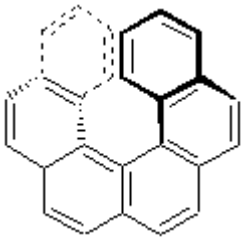
The final stage of laboratory synthesis of drugs often requires separation of a racemic mixture into its constituent enantiomers, in order to select only one biologically important stereoisomer. Mechanical, microbiological (enzyme-assisted), chemical, chromatographic and other methods are applicable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



P-Hexahelicene
(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.

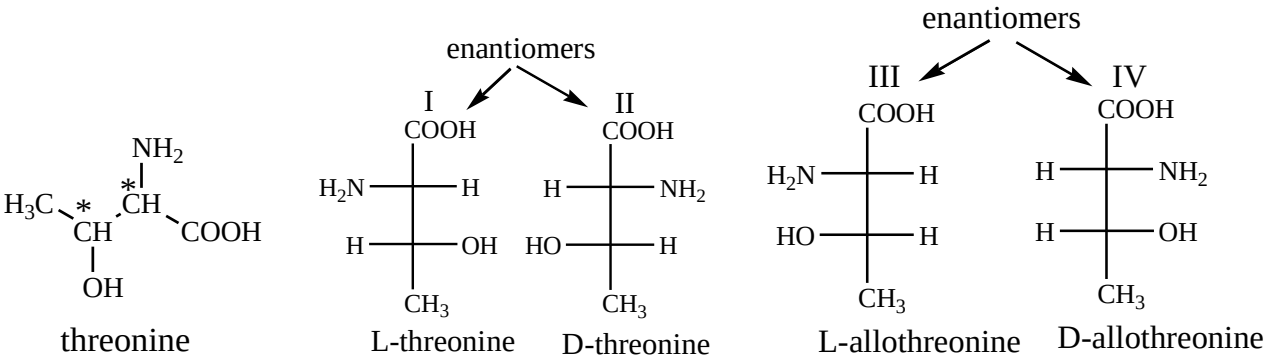
Microbiological method. If the nutrient medium for microorganisms is a cultivated racemic mixture, then the microorganisms, while growing, absorb from it only one of the enantiomers. The other enantiomer remains in the nutrient medium.

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 conventional methods such as crystallization, distillation, chromatography, etc.

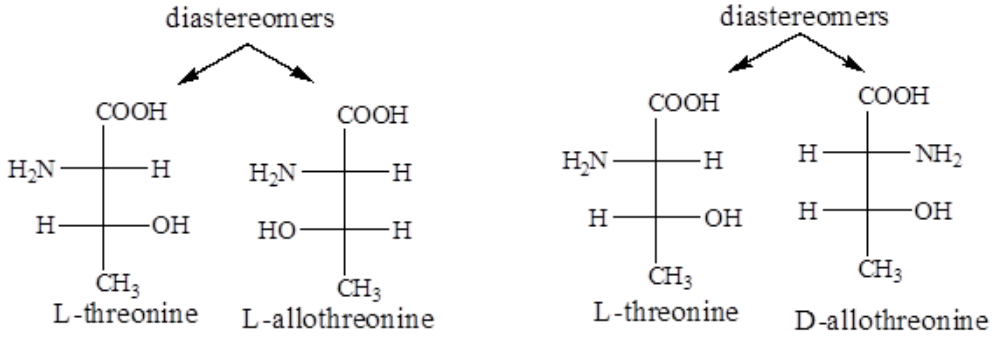
Affinity chromatography is a modern method. It is based on the selective interaction of biologically active compounds only with specific substance mixtures and form noncovalent complexes with them. Thus in the biochemical practice, a racemic mixture passes through a chromatographic column with secrete 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.

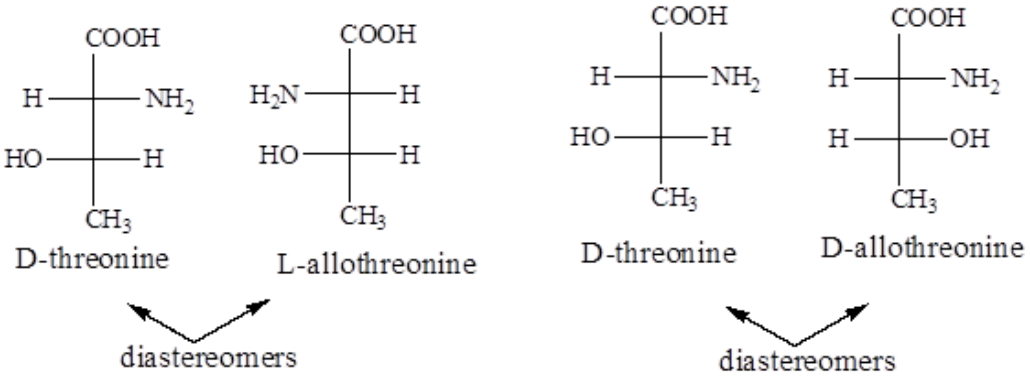
The presence of two centres of chirality in a molecule presupposes the existence of four stereoisomers. Consider 2-amino-3-hydroxybutanoic acid (proteinogenic acid threonine) as an example of such substance. For amino and hydroxy acids with more than one chiral centre the D/L configuration is determined 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.



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

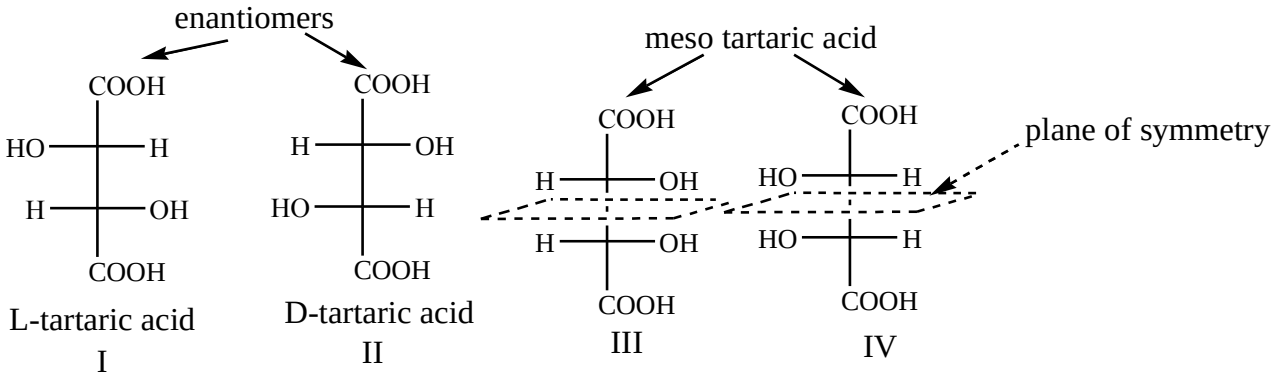


Diastereomers are stereoisomers which are not the mirror images of each other.



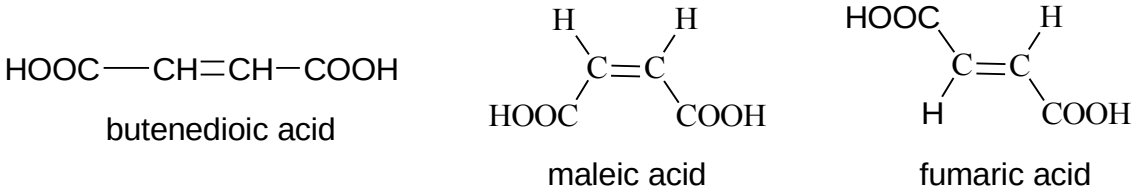
These diastereomers are called *σ-diastereomers*. Diastereomers, unlike enantiomers, have different physical scalar properties (e.g. the melting and boiling points, solubility, etc.). They show a different reactivity even in achiral environments.

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 I and III, II and III 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.

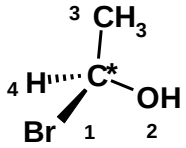


Unsaturated octadeca-9-enoic acid exists as the *cis* isomer (oleic acid, the point of melting at 14°) and the *trans* isomer (elaidic acid, the point of melting at 52°). Oleic acid is a part of biological membrane lipids.

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.

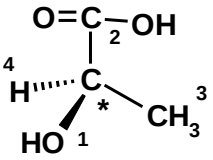
1. Rank the priority of the substituents attached to chiral centre.

1.1. The higher is the atomic number of the immediate substituent atom, the higher is the priority of the substituent. For example,



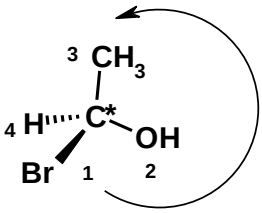
$_{35}Br– > _{8}O– > _{6}C– > _{1}H–$. The substituents in 2-bromoethanol shall be ranked as follows: Br– (1st); HO– (2nd); H_3C– (3rd); H– (4th).

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).

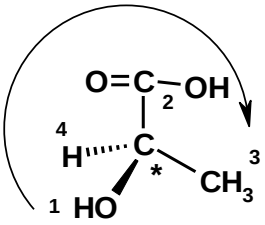


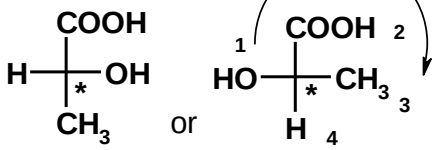
2. After ranking the priority of the substituents we are to look at the molecule from the side opposite to the substituent with the lowest priority 4 (in other words, we must place the molecule in space so that the lowest priority group is pointing backward). In the two examples above (2-bromoethanol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

PRACTICE PROBLEMS

1. Give definitions:

Stereoisomers are _____

_____

_____

Enantiomers are _____

_____

_____

Diastereomers are _____

_____

_____

Chirality is _____

_____

_____

Asymmetric carbon is _____

_____

_____

2. Write the formulas of the following compounds. In chiral molecules define asymmetric carbon atoms. In achiral molecules find the symmetry elements, excluding chirality.

Butane

3-Methylhexane

Propane-1,2-diol

Glycerol

Glycine (2-aminoethanoic acid)

Alanine (2-aminopropanoic acid)

Cyclohexanol

Cyclohex-2-en-1-ol

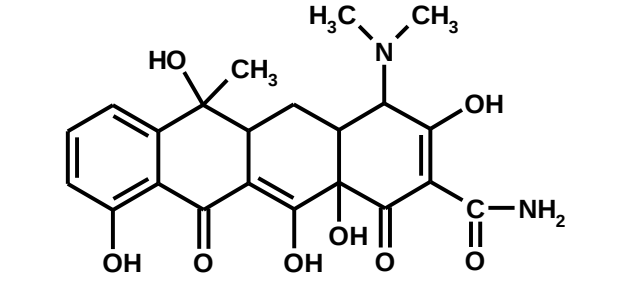
cis-Cyclohexane-1,2-diol

trans-Cyclohexane-1,2-diol

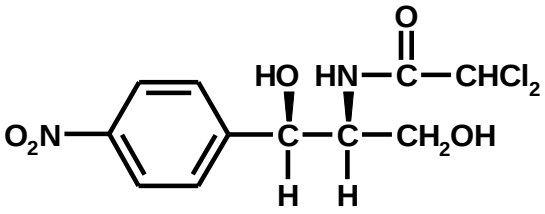
Carvone
(2-methyl-5-(1-methylethenyl)cyclohex-2-enone)

Menthol
(2-isopropyl-5-methylcyclohexanol)

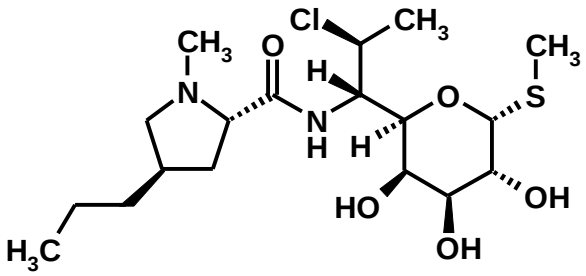
3. Find functional groups, structural fragments and chiral centers in pharmaceutical drugs



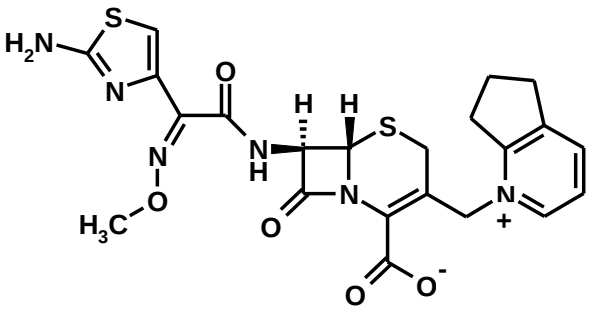
Sumycin (the first representative of *tetracycline* antibiotics)



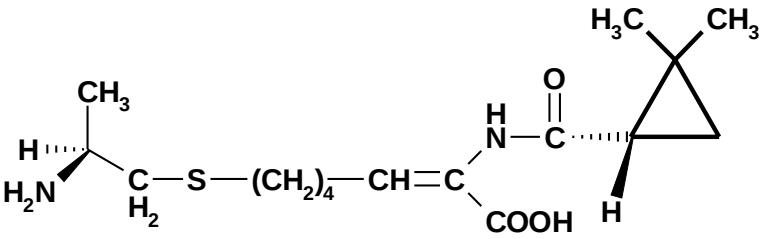
Chloramphenicol (antibiotic)



Clindamycin
(antibiotic with a primarily bacteriostatic effect; it is a bacteria protein synthesis inhibitor by inhibiting ribosomal translocation, in a similar way to macrolides)

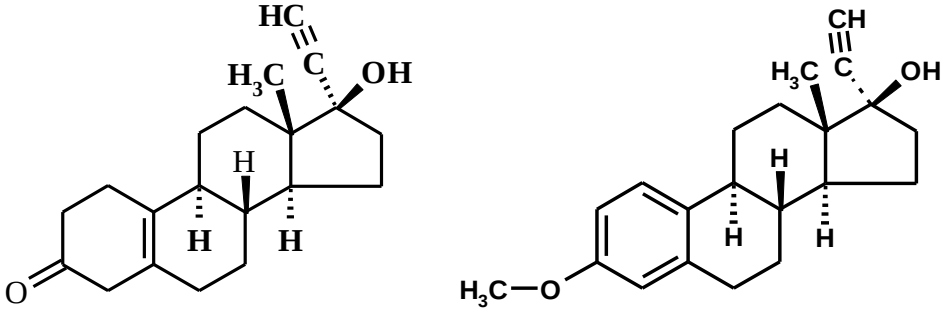


Cefpirome
(a fourth-generation c*ephalosporin*, which is a class of β-lactam antibiotics originally derived from the fungus *Acremonium*, which was previously known as *Cephalosporium*)



Cilastatin

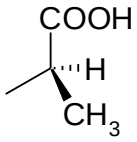
(a chemical compound which inhibits the human enzyme dehydropeptidase and can therefore be combined in *Primaxin* with β-lactam antibiotic *Imipenem* in order to protect it from degradation)



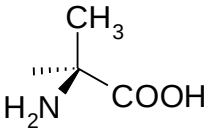
Norethynodrel and *Mestranol*

(components of the combined oral contraceptive *Enovid*)

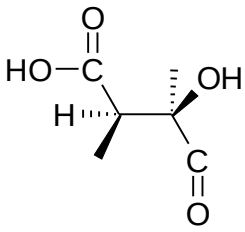
4. Complete the formula drawing by adding the missed fragments. For chiral compounds draw the second enantiomer.



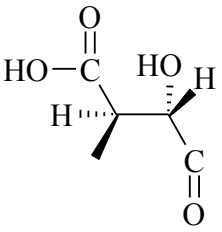
D-Lactic acid



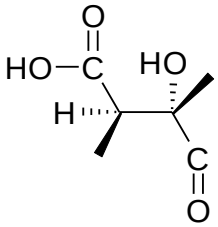
L-Alanine



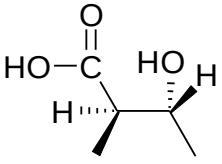
dextro-Tartaric acid



meso-Tartaric acid



levo-Malic acid



Methyl *meso*-tartrate

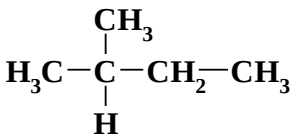
5. Give the definition: **racemate** is _____

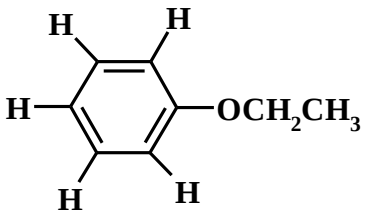
_____

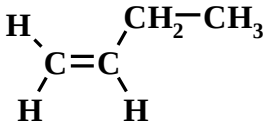
6. Draw the examples of π- and σ-diastereomers (2 for each type). Give the names.

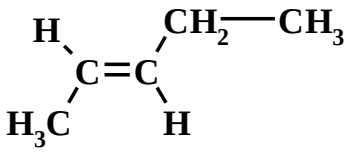
7. Write down the formulas of the isomeric pentanedienes and consider their spatial structure. Indicate which of these are diastereomers and enantiomers.

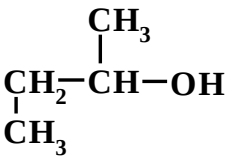
8. Define the various structural types of protons in the following compounds. If there are two or more protons of the same type indicate which of them are homotopic (H), enantiotopic (E) and diastereotopic (D).

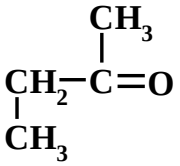


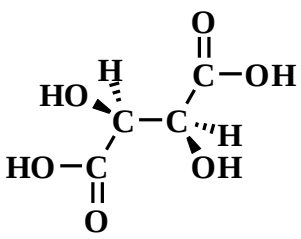


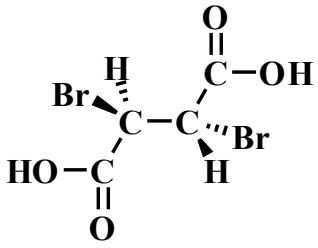






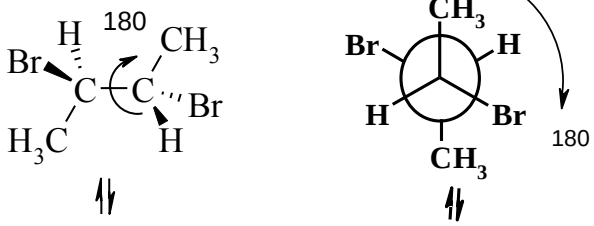




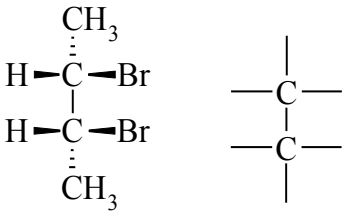


9. Transform perspective formula of *meso*-2,3-dibromobutane successively in *Newman* projection, and then in *Fischer* projection.

Staggered conformation

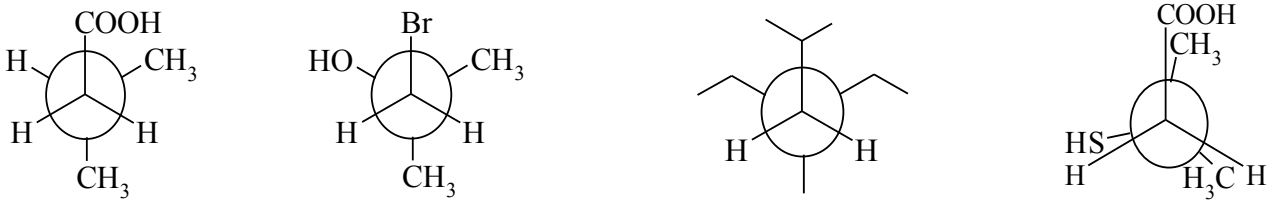


Eclipsed conformation



Newman projection *Fischer* projection

10. Draw the perspective formulas of the substances, presented in *Newman* projections.



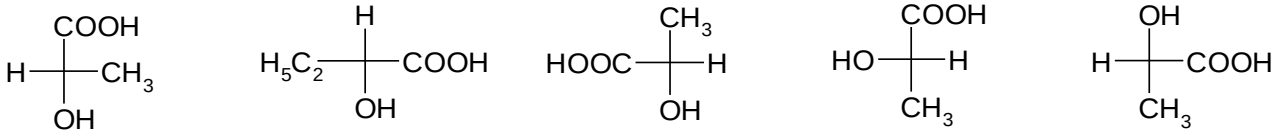
11. Write *Newman* projections for all staggered conformations (looking along the C_1-C_2 bond) of *Halothane* (trademarked as *Fluothane*, 2-bromo-1,1,1-trifluoro-2-chloroethane) which is inhaled as a general anesthetic.

12. Write *Newman* projections for all staggered and eclipsed conformations of γ-aminobutyric acid, looking down the C_2-C_3 bond.

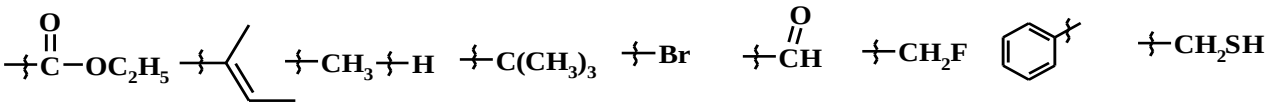
13. Write *Newman* projections for all conformations of butane, looking along the C_2-C_3 bond. Select the most stable and explain your choice.

14. Write and name *Newman* projections for all conformations of ethylene glycol, looking along the C_1-C_2 bond. Select the most stable and explain your choice taking in account the formation of intramolecular hydrogen bonds.

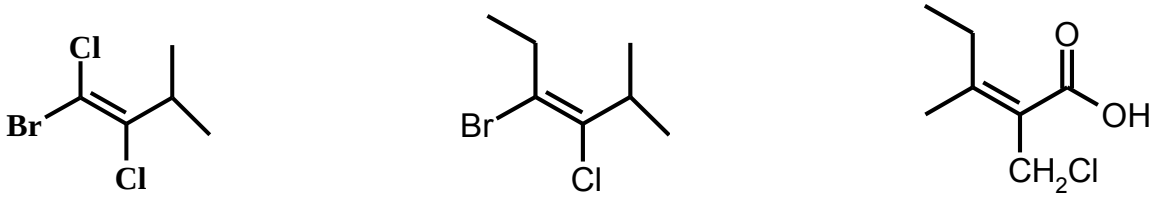
15. Find enantiomers from the compounds presented below.



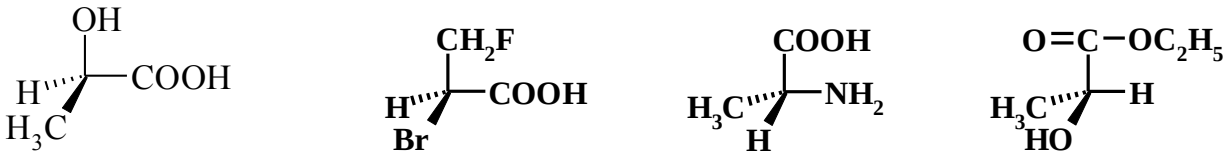
16. Rank the priority of the groups (*Cahn–Ingold–Prelog* priority rules).

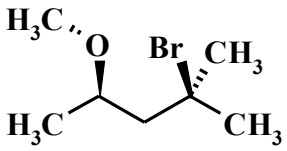
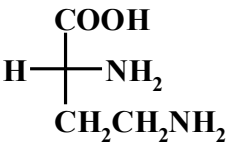
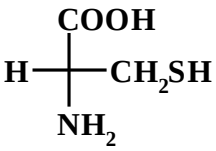
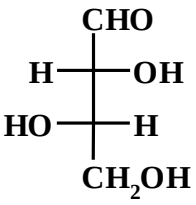
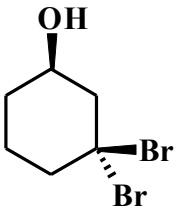


17. Name the substances (IUPAC names; E/Z and, if applicable, *cis*/*trans* discriptors).

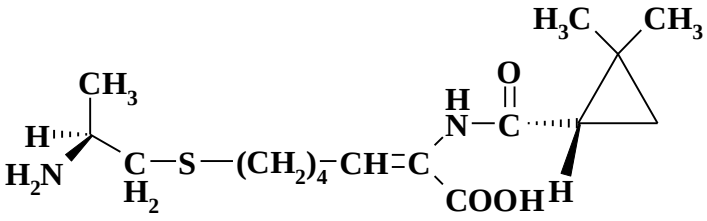


18. Determine the configuration (R/S) of the chiral centers. Indicate the priority of substituents. Assign, if applicable, L- and D-series.

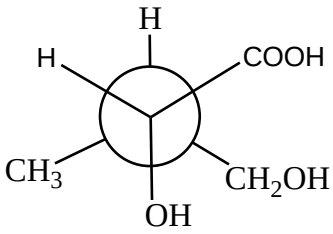
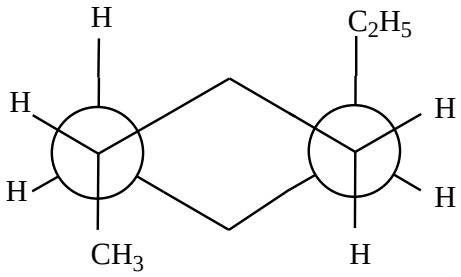


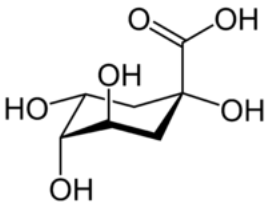

19. Assign the configuration (R/S) of chiral centers in *Cylastine* (*Thyenam* component).

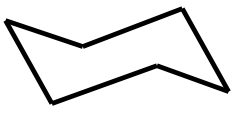
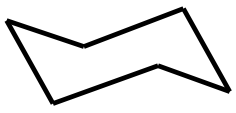
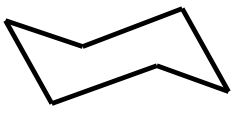
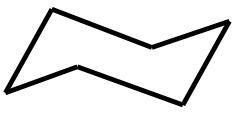


20. Give the names to the substances (IUPAC names and stereochemical nomenclatures). Find (if it is possible) the plane(s) of the symmetry.

21. Natural quinic acid is a versatile chiral starting material for the synthesis of new pharmaceuticals. A medication *Tamiflu* for the treatment of influenza A and B strains has been successfully developed and launched into the market.
Complete consecutively templates presented below:



Draw only axial substituents

Draw only equatorial substituents

Draw all the substituents

Draw all the substituents in inverted form

22. Write both chair conformations for *cis*- 4-*tert*-butyl cyclohexanol and rank their relative stability. Identify axial groups by circling them.

23. Write all chair conformations for both *cis* and *trans* isomers of 1,2-dichlorocyclohexane. Rank all four conformations in terms of their expected relative stability. Assign the configuration of the chiral centers.

24. Write chair conformation of *cis* cyclohexane-1,3-diol, which allows the formation of the intramolecular hydrogen bond.

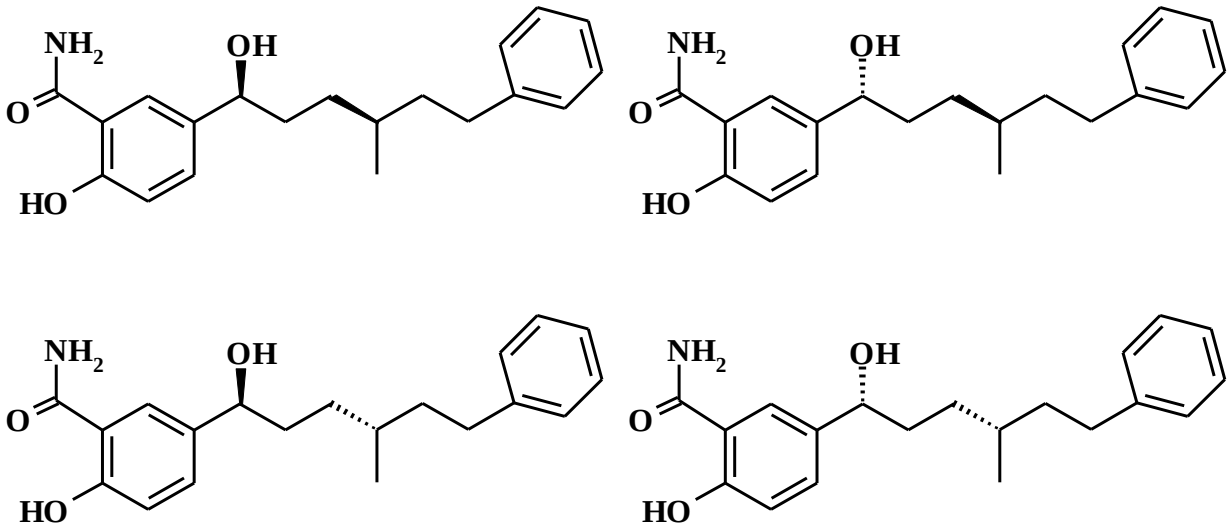
25. Write conformation of piperidin-4-ol, which allows the formation of the intramolecular hydrogen bond.

26. Write the plane and chair conformations for both *trans*- and *cis*-decalins. Rank all isomers in terms of their expected relative stability.

27. There are some general principles of a drug action that are applicable to many drugs. The *Nobel* prize winner *Paul Ehrlich* develops the idea of the receptor blockade concept. Binding is orthosteric in most cases, which means that the drug binds to the receptor within the same site as the receptor's physiological ligand. A drug that activates its receptor is referred to as an agonist, whereas an inhibitory drug is also called an antagonist. Therefore, only one or the other may have a vtherapeutic value; for example, with histamine receptors, only antagonists are clinically useful.

Labetalol, an α- and β-adrenergic agent, is a mixture of four stereoisomers. The R,R-isomer carries most of the β-adrenergic (β-antagonist), whereas the S,R-isomer carries most of the α-blocking activity (α-antagonist). The R,S- and S,S-isomers are not active (or inert).

Find and indicate the corresponding structures from formulas shown below.



Signature of the instructor:

LABWORK № 4
CHEMICAL REACTIVITY

Objective: to study classification and mechanisms of organic reactions. Reactants. Solvents.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Problems for discussion:

1. Organic reactions: basic principles and approaches.
2. Organic reactions classification:
2.1. by a mechanism;
2.2. by changes in the structure of a targeted substance (“(bio)synthetic classification”)
2.2. by change of oxidation state.
3. Acidity and basicity.
4. Reactants and reagents.
5. Nucleophiles and electrophiles.
6. The main principles of *Brønsted* and *Lewis* theories, examples of *Brønsted* and *Lewis* acids and bases.
7. Reaction characteristics and factors that influence reactions (enegertics, electronic, steric, stereoelectronic and solvent effects.
8. Basic concepts about the mechanisms of organic reactions.
9. Steps of chemical reaction and intermediates, the arrow notation and writing of reaction mechanisms.

PRACTICE PROBLEMS

1. Write the examples of pharmaceuticals possessing the properties of –OH, –SH, –NH и –CH acids (you can use [2] for substance search). Explain your choice.

–OH acids (4 examples)

–SH acids (2 examples)

–NH acids (3 examples)

–CH acids (2 examples)

2. Write examples of pharmaceuticals possessing the properties of bases (you can use [2] for substance search). Explain your choice.

π Bases (3 examples)

p Bases (4 examples)

3. Write the following compounds and rank their acidity, from 1 (most) to 4 (least). Write corresponding conjugated bases and rank their basic properties.

Acetic, lactic, β-hydroxybutyric and γ-hydroxybutyric acids

Methyl, ethyl, trifluoromethyl and *tert.*-butyl alcohols

Phenol, picric acid, 4-nitrophenol, 3,4-dimethoxyphenol

Butylamine, ammonia, pyrrole, pyridine

Ethanol, ethanethiol, ethylamine

Glycerol, ethylene glycol, resorcinol, 2-ethoxyethanol

4. Write 3 pharmaceuticals [2], possessing the properties of amphoteric substances.

5. Write 3 pharmaceuticals [2], possessing the properties of *Lewis* acids.

6. Give definition.

Free radical is _____

_____

Write 4 unstable and two stabilized radicals.

7. Give definition.

Nucleophile is _____

_____

Give 2 examples (for each problem) of reagents possessing the properties of nucleophiles:

ions with lone electron pair;

neutral molecules with lone electron pair;

neutral molecules which get lone electron pair in heterolysis.

8. Give definition.

Electophile is_____

_____

Give 2 examples (for each problem) of reagents possessing the properties of electophile:

ions with free (vacant) orbital;

neutral molecules with free (vacant) orbital;

neutral molecules which gets vacant orbital in heterolysis.

9. Write chemical reactions and classify each as by structural change type (addition, elimination or substitution) and reagent type (nucleophilic, electrophilic or radical):

a) reaction of cyclohexane with chlorine under UV irradiation

b) reaction of 2-methylpent-2-ene with bromine in tetrachloromethane as solvent

c) reaction of pent-1-yne with chlorine

d) reaction of chlorocyclohexane with butyllithium

e) reaction of chlorocyclohexane with aqueous sodium hydroxide

f) reaction of 1-bromo-1-methylcyclohexane with alcoholic sodium hydroxide

g) cyclopentanone hydrogenation in presence of palladium

i) acid catalyzed reaction of isobutiric acid with ethanol

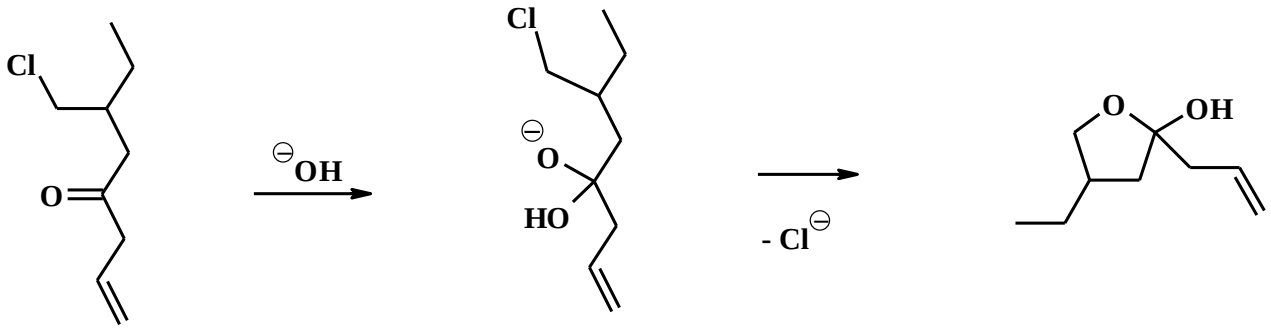
j) reaction of ethyl lactate with isoamyl alcohol

k) iron catalyzed reaction of benzene with bromine

l) the acid-base reactions of lactic acid with sodium hydroxide and methylamine

m) the acid-base reactions of 4-aminobutanoic acid with ammonium carbonate, benzyl amine, acetic acid.

9. Draw arrows to show electron transfer in the following two steps. Draw a circle around the nucleophilic atom in step 1 and in step 2.



10. Write pharmaceuticals [2]. Find reactivity centers. Write reaction of hydrochloride formation.

Diphenhydramine (antihistamine)

Chloramphenicol (antibiotic)

Quinidine (antiarrhythmic agent)

EXPERIMENTAL SECTION

CHEMICAL PROPERTIES AND QUALITATIVE FUNCTIONAL ANALYSIS

The methods available for the identification of the functional groups involve chemical reactions that are characteristic of the individual groups. However within the past few years numerous instruments have become available that provide considerable information regarding many functional groups. Most of these instrumental methods make use of some type of spectroscopy. The instrumental methods which are most useful for the qualitative analysis of organic compounds are ultraviolet and visible absorption spectroscopy, infrared spectroscopy, nuclear magnetic spectroscopy, and mass spectroscopy. Therefore, chemical methods of identification are still in use. Organic compounds are generally recognized by the detection of the functional group that is present in the molecule. For example, detection of the carbonyl group indicates an aldehyde or a ketone; the presence of nitrogen with basic properties indicates the presence of amine; detection of hydroxyl groups indicates either alcohols or phenols.

In this lab section we're beginning to study of functional group detection and will pursue the tradition in next Lab sessions. You will use in your educational problems both chemical methods and instrumental methods to detect the structure of organic compounds.

Experiment 1. Preparation of sodium ethoxide and its hydrolysis.

Place 10 drops of ethanol*[*] in a dry test tube, and add a small piece of sodium metal* with a tweezers (You must previously remove kerosene from the Sodium surface by placing it between sheets of filter paper). Close the tube with a stopper and gather the hydrogen formed. Bring the tube to the burner and remove the plug. A mixture of hydrogen and air burns with a characteristic "barking" sound.

Dissolve the white precipitate of sodium ethoxide in 3–4 drops of ethanol* and add 1 drop of 1 % phenolphthalein*. The indicator remains colorless. After adding 1–2 drops of water in tube magenta coloration appears.

Write a reaction scheme of sodium ethoxide formation, followed by its hydrolysis. Why does water dissolves sodium ethoxide?

Whether you can detect acidic properties of isoamyl alcohol using common acid base (pH-) indicators?

Experiment 2. Preparation of sodium phenoxide and its acidic hydrolysis

Place 10 drops of phenol-water* emulsion in a test tube and shake the mixture. Add dropwise 10 % solution of sodium hydroxide (21) to emulsion till the solution become clear. After adding of a few drops of 10 % sulfuric acid (23) you will observe the formation of opaque emulsion.

Write a reaction scheme for formation and hydrolysis of sodium phenoxide. Why does phenol react quantitatively with sodium hydroxide in contrary to ethanol?

* Notice: reagents marked with asterisk (*) are in the fume hood.

Why does the addition of sulfuric acid lead to formation of turbid emulsion? Write a reaction scheme.

Experiment 3. Detection of acidic properties of stearic acid.

The redox reaction between iodide and iodate slightly acidic medium leads to free iodine formation, and is used to detect weak organic acids (in particular fatty acids, such as palmitic, stearic, etc.). These acids are not detected by acid-base indicators.

In each of the two test tubes add 2 drops of 10 % potassium iodide (20) solution and 2 drops of 4 % potassium iodate (1) solution. Then, add 2 drops of 10 % alcoholic solution of stearic acid* to one of them. Heat both tubes for 1 minute in a boiling water bath. After cooling, add to each tube 2 drops of starch emulsion*. Compare coloring in both tubes.

Write a scheme of redox reaction between iodide (NaI) and iodate ($NaIO_3$). Explain the role of steric acid in this reaction.

Experiment 4. Basic properties of aliphatic and aromatic amines.

Place 2 drops of water in the two test tubes. Add to the first tube 1 drop of aniline*, and to the second — 1 drop of diethyl amine*. Agitate both tubes. Use universal indicator or *red litmus* to detect approximately pH of both solutions.

Add 1 drop of 10 % hydrochloric acid (9) to aniline emulsion in first tube. You can observe the formation of transparent solution. Then add 3 drops of saturated aqueous picric acid solution (5) to a solution of diethyl amine* in the second tube, agitate the mixture and cool the tube in a glass with a cold water, in few minute diethyl amine picrate precipitate is formed.

Compare basicity and solubility in water of diethyl amine and aniline.

Explain the formation of transparent solution after the addition of hydrochloric acid to aniline emulsion. Write the scheme of the reaction.

Write the scheme of the reaction between diethylamine and picric acid (2,4,6-trinitrophenol).

Signature of teacher:

LABWORK № 5
INSTRUMENTAL METHODS OF STRUCTURE DETERMINATION. INFRARED SPECTROSCOPY

Objective: to study the algorithm for instrumental analysis of organic compounds and basic concepts as well as IR spectroscopy techniques.

Recommended further reading

1. *Chernykh, V. P.* A. Applied infrared spectroscopy : a manual for students of higher schools / V. P. Chernykh, ed. by V. P. Chernykh. – Kharkiv : NUPh, 2014. – 152 p.

2. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

1. Instrumental methods of organic compounds analysis.
2. Basic concepts of optical spectroscopy.
3. Spectrum of electromagnetic waves.
4. Ultraviolet spectroscopy and spectroscopy in the visible region. Types of electronic transitions.
5. The chromophore group. The displacement of the absorption bands.
6. Infrared spectroscopy
7. Molecular vibrations (stretching, bending). Interpretation of major absorption frequencies of functional groups.
8. The use of characteristic bands and lines from "fingerprints" for identification of organic compounds.

INSTRUMENTAL METHODS OF STRUCTURE DETERMINATION

We can apply many techniques to differentiate few compounds. Differentiation includes two procedures separation and identification.

Separation includes methods that convert a mixture into two or more distinct products. These are distillation, crystallization, extraction, chromatography, electrophoresis, etc. Purification can be regarded in terms of separation of the main (targeted) product from impurities, which are not important for the further application and utilized in a mixture after the experiment.

Identification includes methods that differentiate two or more substances from each other based on the values the scientist obtained in an analytical experiment. One may suggest that typical identification is a variant of the virtual separation when we distinguish substances from each other because of different characteristics. Some methods of identification are of the part of the general procedure of separation (e.g. chromatography, distillation, etc.), the other are based on the characteristics, which are not suitable for separation (e.g. spectral methods, X-Ray diffraction, etc.)

Generally, all the differentiation methods can be divided into two groups: scalar and chiral.

The first group includes the methods, which distinguish the substances because of different scalar properties. Thus, we can list such scalar values as melting and boiling points, solubility, distribution constant, relative retention. The latter gives rise to a plenty traditional methods of separation, including distillation, crystallization, extraction and chromatography, respectively.

Now we will study few spectral methods, which are based on the differentiation of scalar properties. Thereby, most of optical methods are based on different absorptions of unpolarized light (IR and UV spectroscopy), NMR-spectroscopy detects the electromagnetic signal with a frequency

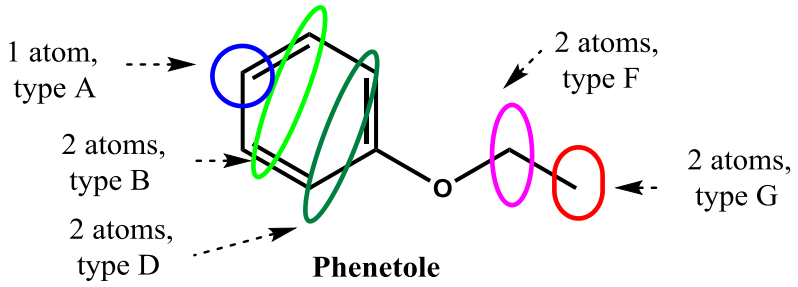
characteristic of the magnetic field at the nucleus, X-Ray diffraction distinguishes atoms because of reflection of X-Ray from the atoms of a compound.

Scalar methods can differentiate substances with different molecular formulas, structural isomers and diastereoisomers. This can be used for both separation and identification. However, enantiomers are not different in scalar properties. Analogously, different scalar values gives rise to identification of structurally inequivalent and diastereotopic atoms in one molecule. Conversely, enantiotopic atoms possess the same characteristics in scalar methods. That is why they cannot be differentiated by such methods similar to identical atoms.

Chiral methods are applied for separation and identification of two enantiomers, as well as for identification of enantiotopic atoms in one molecule. Quantitative separation of a racemic mixture can be provided by the chiral chromatography (Chiral phase provides the chiral differentiation). Identification of the absolute configuration of two enantiomers can be achieved also by means of chiroptical methods (polarimetry, circular dichroism, etc.).

In IR- and UV spectroscopy we will study the identification of atoms and groups of atoms, functional groups in particular, to determine the structure of examined molecule. Evidently, the structurally non-identical atoms and groups are non-equivalent when examined by a scalar method.

In the molecule of Phenetol we can distinguish six groups of structurally non-equivalent Hydrogens: 3 Hydrogens are circled in red, 2 alkyl Hydrogens are circled in magenta, two pairs of equivalent Hydrogens (*ortho*- and *metha*-positions) in the benzene ring are circled in green and dark green, and finally, benzene Hydrogen in *para*-position is circled in dark blue.

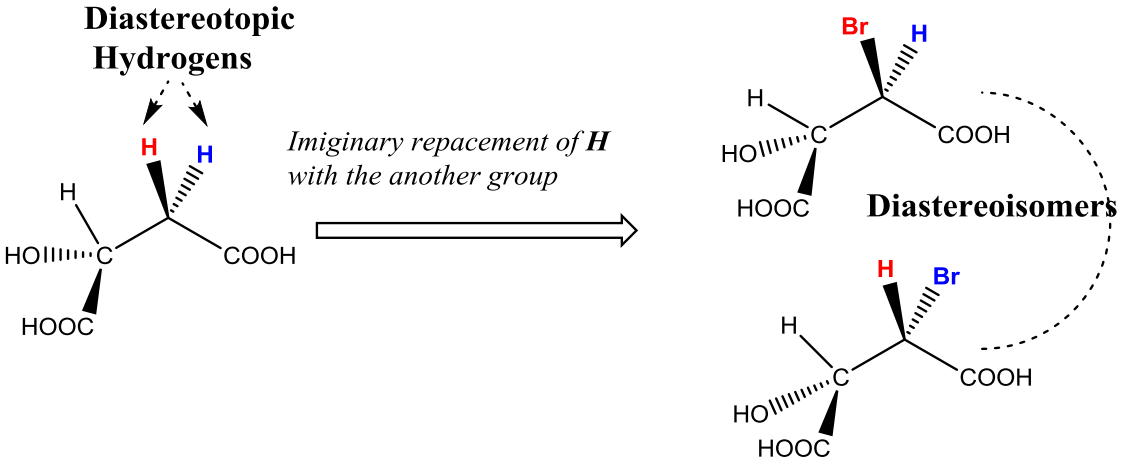


Phenetole

In the next topic we will discuss how such a differentiation affords different values in NMR-spectrum and can be used for structure differentiation.

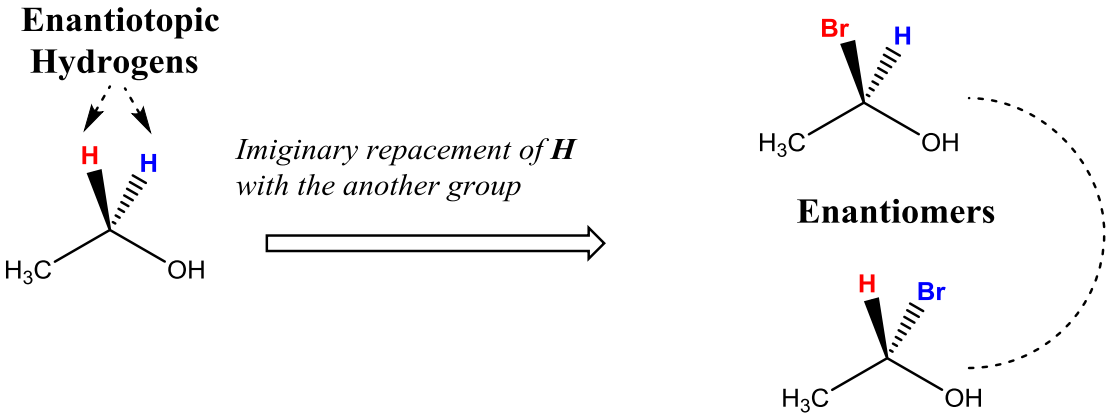
Diastereotopic atoms can be differentiated by scalar methods similar to structurally non-equivalent.

In the formula of Malic acid two methylene Hydrogens belong to the same carbon atom. Some students mistakenly consider these Hydrogens are identical. To challenge how much different are structurally identical atoms we can apply the test for diastereotopicity or enantiostereotopicity.



Two Hydrogen atoms will be diastereotopic if their consequent replacement with another atom (Bromine in the example given) will produce two diastereoisomers. The test proves diastereotopicity for methylene protons in Malic acid. Generally, these atoms may have different signals in scalar methods.

Analogously we can prove enantiotopicity for methylene Hydrogens in Ethanol, as the consequent replacement of any of two methylene Hydrogens with the another atom (Bromine in the example given) will produce two enantiomers.



Based on the test we conclude that methylene Hydrogens in Ethanol are enantiotopic. It means that in achiral methods these Hydrogens will **ALWAYS** have the same signals. They are not fully equivalent, chiral methods differentiate them; coenzyme NAD^+ in the process of Ethanol oxidation by Alcohol dehydrogenase abstracts only one of two Hydrogens. But in NMR-spectrum, that is based on achiral physical phenomenon, these Hydrogens have the same characteristics. That is why we qualify them as magnetically equivalent (equivalent in the magnetic field).

Analogously, the challenged atoms are considered as homotopic if the exchange test will produce identical molecules. Homotopic atoms are identical in all the methods of identification, both scalar and properties. Homotopic atoms are identical in all methods of identification, including both scalar and vector property-based methods

BASICS OF OPTICAL SPECTROSCOPY

Organic spectroscopy uses electromagnetic energy, or irradiation, as the physical stimulus.

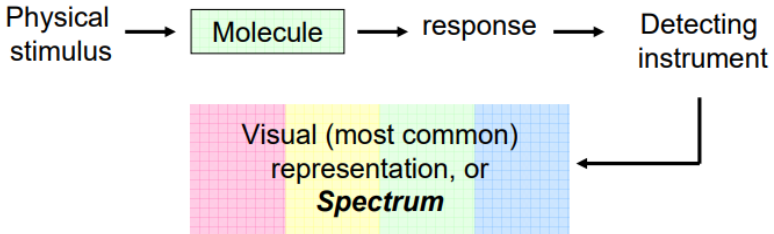
The important parameters associated with electromagnetic radiation are: Energy (E), Frequency (μ) and Wavelength (λ). Energy is directly proportional to frequency, and inversely proportional to wavelength, as indicated by the equation below.

$$\mathbf{E = h\mu}$$

In applied spectroscopy we use few special terms.

Band (absorption band) is the area of intense radiation uptake. Bands together give **absorption spectrum.**

Upon irradiation with the light, certain fragments respond in such a way to produce the more absorption. This response can be detected and translated into a visual representation called a spectrum.



The analytical experiment includes few steps as it presented in scheme above. The first, we need to stimulate some changes in the structure of the sample. After the specific response we are ready to recognize a pattern. Finally, we associate patterns with the physical parameters, and the spectrum will be interpreted based on some special correlations which are based on the work with databases and/or some general rules and equations.

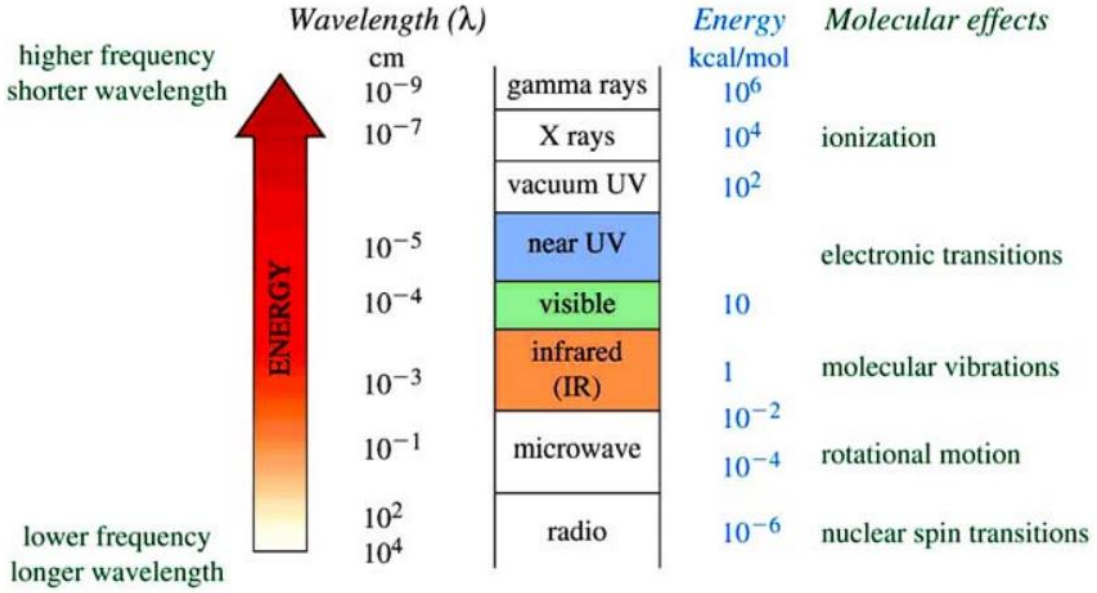
Each type of the change in the energetic levels of a molecule occurs depending on the region of a specific for every method frequency.

The highest energy is required to excite electrons. This energy corresponds to radiation in the ultraviolet and visible region (electron spectroscopy), or UV-spectroscopy.

The lower energy is required to change bond lengths (stretching) and angles between atoms (bending) in the infrared region to give IR-spectrum.

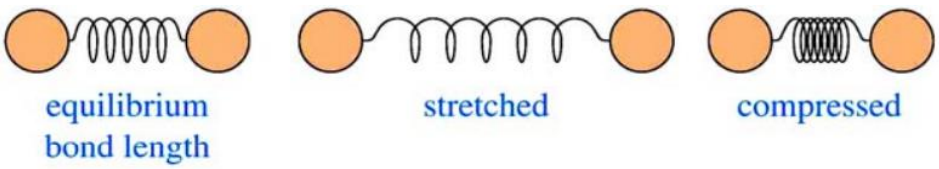
The lowest energy is needed to refocus the spins of nuclei nuclear magnetic resonance spectroscopy to give NMR-spectrum.

EFFECT OF ELECTROMAGNETIC RADIATION ON MOLECULES

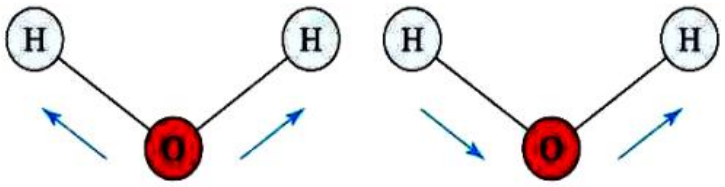


Infrared radiation is largely thermal energy. It induces stronger molecular vibrations in covalent bonds, which can be viewed as springs holding together two masses, or atoms.

Specific bonds respond to (absorb) specific frequencies. The changes in the structure of the molecule duty for the specific absorption can be divided into two types. The first type is characterized with the change of the bond length: the molecule from the equilibrium bond length can be either stretched or compressed.

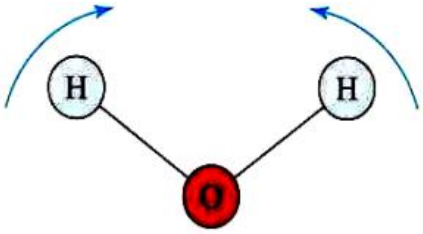


The change of the bond length is associated with STRETCHING bands in the spectrum. The stretching can be directed both in symmetrical and asymmetrical way.



symmetric stretching antisymmetric stretching

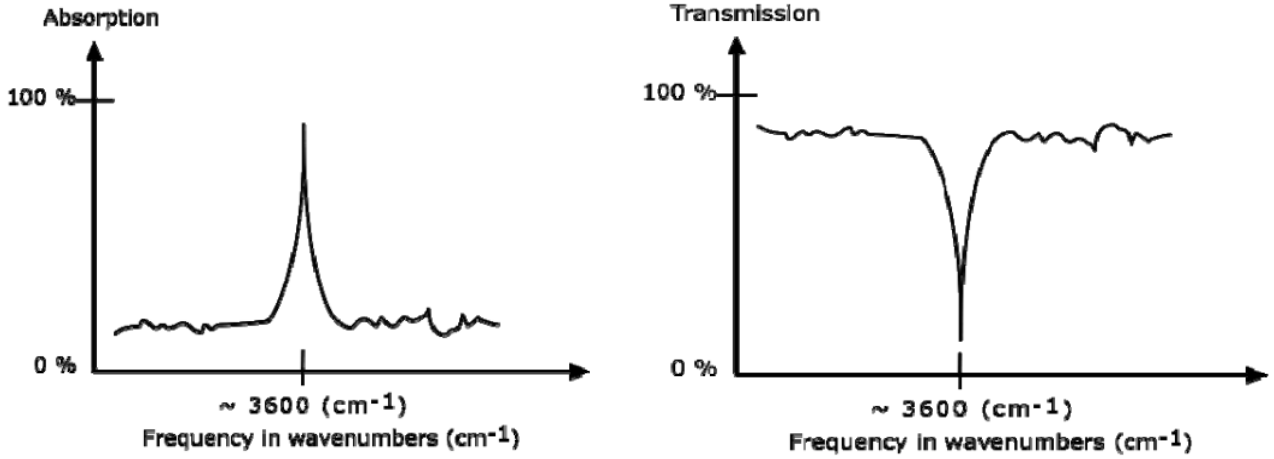
Another type of vibrations includes the change between bond angles, corresponding for a few types of BENDING bands.



bending (scissoring)

When a chemical sample is exposed to the action of IR light, it can absorb some frequencies and transmit the rest. Some of the light can also be reflected back to the source.

The IR spectrum is basically a plot of transmitted (or absorbed) frequencies vs. intensity of the transmission (or absorption). Frequencies appear in the x-axis in units of inverse centimeters (wavenumbers), and intensities are plotted on the y-axis in percentage units. The graph below shows a spectrum in absorption mode.



The transmission mode which graph is presented above is the most commonly used representation and the one found in most chemistry and spectroscopy books. Therefore we will use this mode of representation.

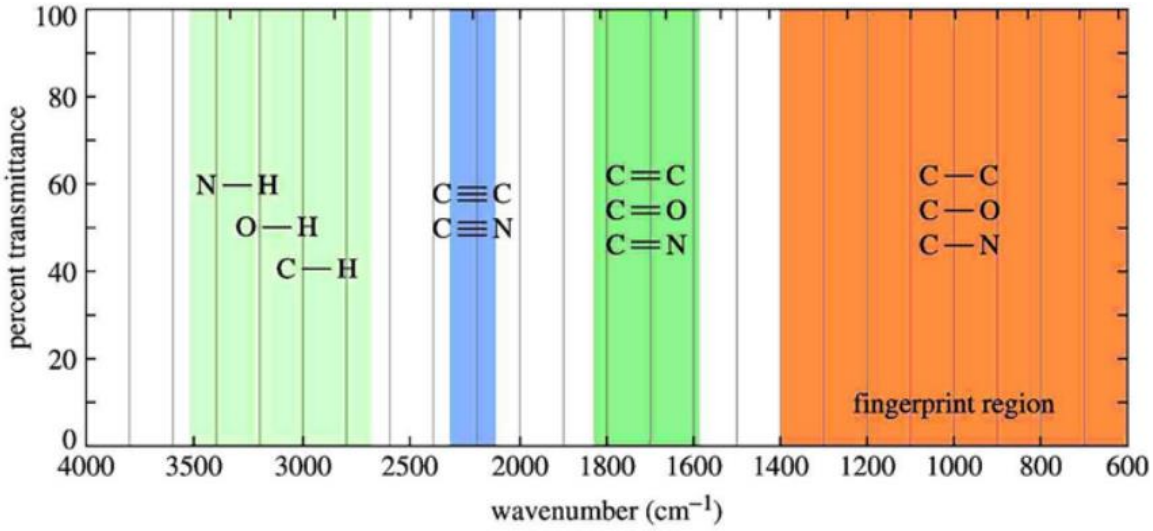
IR spectrum characterizes the structure of the whole molecule. However, it was found experimentally that some groups of atoms absorb a certain frequency of light independently from the rest fragments of the molecule.

Not all covalent bonds display bands in the IR spectrum. Only polar bonds do so. These are referred to as IR active. The intensity of the bands depends on the magnitude of the dipole moment associated with the bond type:

- Strongly polar bonds such as carbonyl groups (C=O) produce **strong** bands.
- Medium polarity bonds and asymmetric bonds produce **medium** bands.
- Weakly polar bond and symmetric bonds produce **weak** or non-observable bands.

Infrared band shapes come in various forms. Two of the most common are narrow and broad. Narrow bands are thin and pointed, like a dagger. Broad bands are wide and smoother. A typical example of a broad band is that displayed by O-H bonds, which form intramolecular Hydrogen bonds. Such bands are typical for crystalline and concentrated solution samples containing alcohols and carboxylic acids.

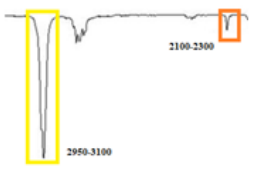
The typical IR absorption range for covalent bonds is 600–4000 cm^{-1}. The graph shows the regions of the spectrum where the following types of bonds normally absorb. For example a sharp band around 2200–2400 cm^{-1} would indicate the possible presence of a C≡N or a C≡C triple bond.



IR-spectroscopy provides the information about the presence or absence of specific functional groups. Usually they are present in the middle to right part of spectrum and corresponding to stretching of functional group. The typical stretchings are widely used for primary determination of the molecule structure. IR does not provide detailed information or proof of molecular formula and structure. It provides information on molecular fragments, specifically functional groups. Therefore, it is very limited in scope, and must be used in conjunction with other techniques to provide a more complete picture of the molecular structure.

Fingerprint region for most of organic molecules contain an integrated graph, which includes stretchings and bendings from different groups. This region is barely can be used for structural analysis. But it is widely used for identification of samples based on the comparison with the spectra in databases. Because of the uniqueness of the spectrum and simplicity of the experiment, identification by IR-spectroscopy is widely used in pharmacy for identification of the pharmaceutical substances and impurities.

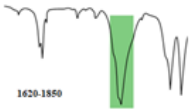
Correlation tables are used in structural functional analysis (page 58). Different band characteristics can be used to interpret the spectra, including wavenumber, band shape and strength. In most cases, IR-spectroscopy for structural functional analysis operates with typical stretching which are not overlapped with the other bands. Simplified graph presenting the main typical stretching is presented below.



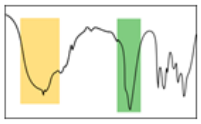
v C≡C-H

v C≡N *v* C≡C (asymmetric)

v OH *v* N-H



v C=O Aldehydes, Ketones, Esters, Acyl halides, Anhydrides

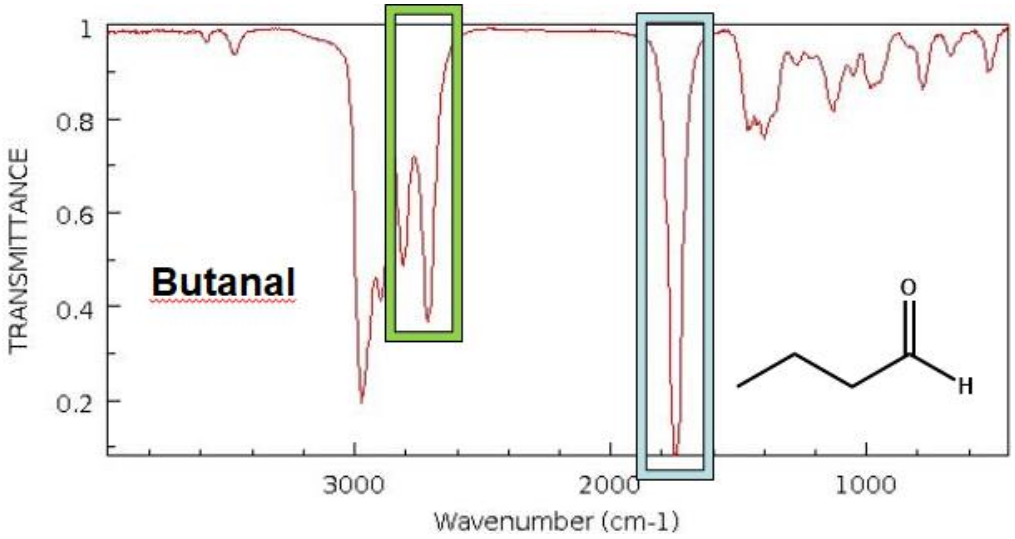


v OH

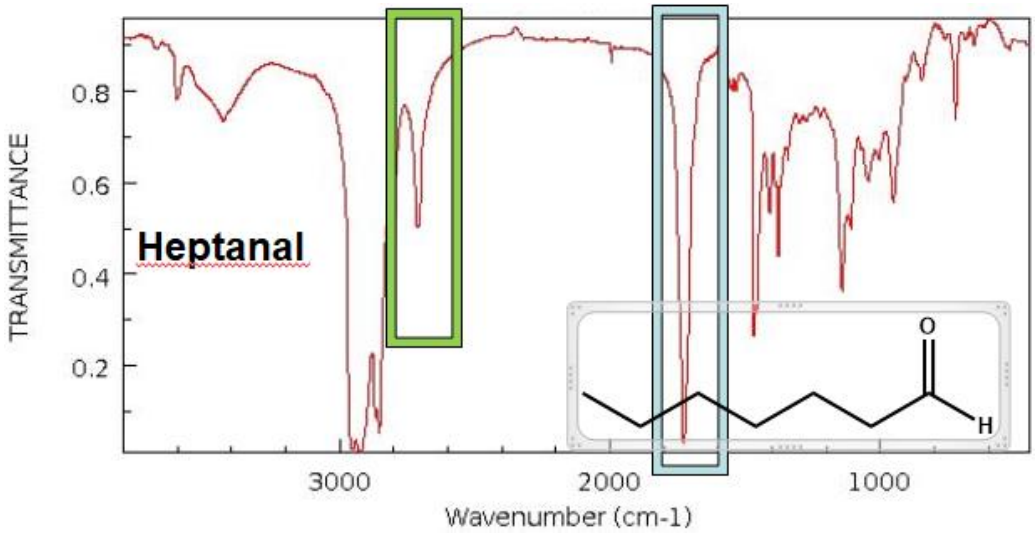
v C=O

Carboxylic acids

For example, in the spectrum of Butanal we can easily identify aldehyde carbonyl group with wavenumber around 1700 cm^{-1}, as well as the band for Aldehyde Hydrogen with wavenumber around 2950 cm^{-1}.



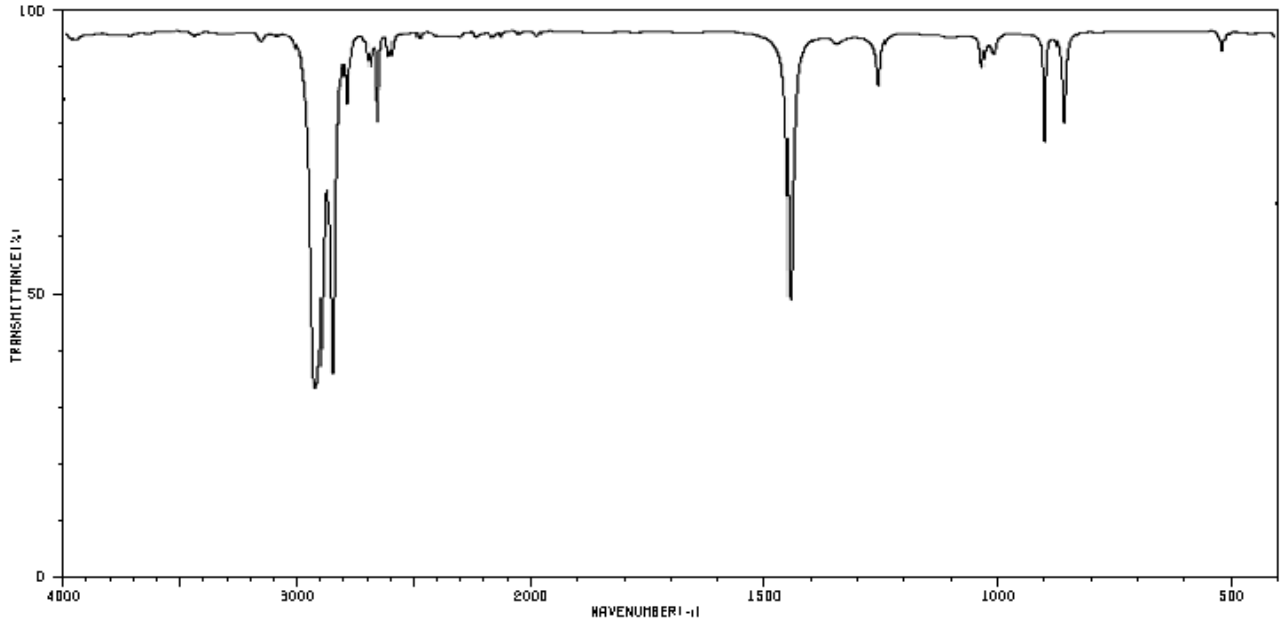
Not coincidentally, the analogous spectrum was recorded for Heptanal.



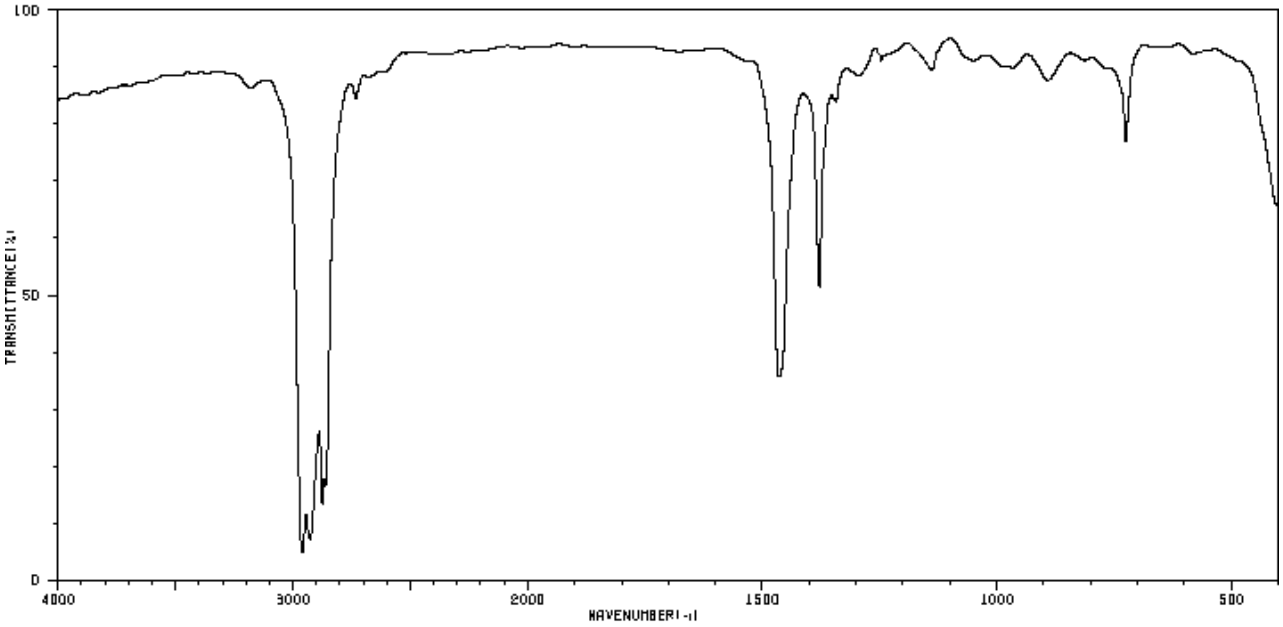
PRACTICE PROBLEMS

1. Analyze the stretching vibrations of C-H in spectra of following compounds. Explain the difference. Explain why in the spectra of hexane and methylcyclohexane bands of medium intensity at 1379 cm^{-1} and 1376 cm^{-1} are observed, and why these bands are absent in the spectrum of cyclohexane.

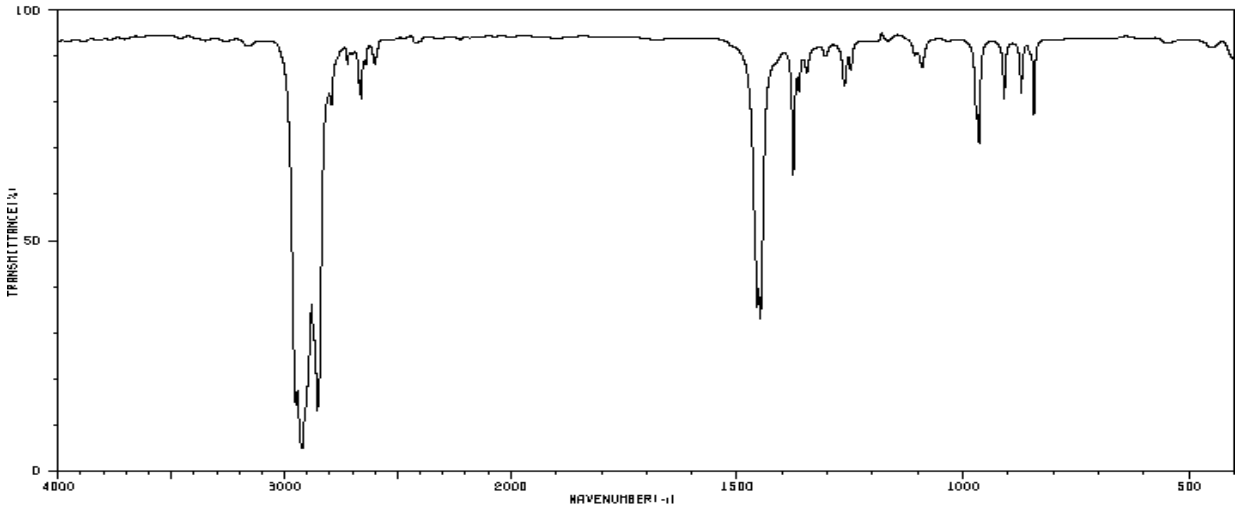
IR spectrum of cyclohexane 2953, 2875, 1450 cm^{-1}.



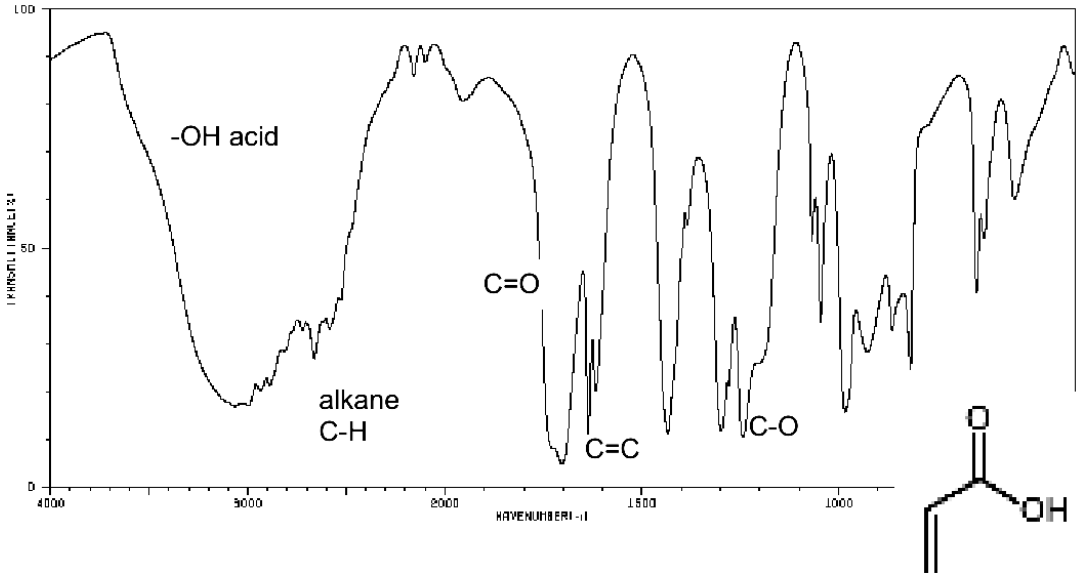
IR spectrum of hexane 2962, 2872, 2852, 2848, 1451, 1379 cm^{-1}.

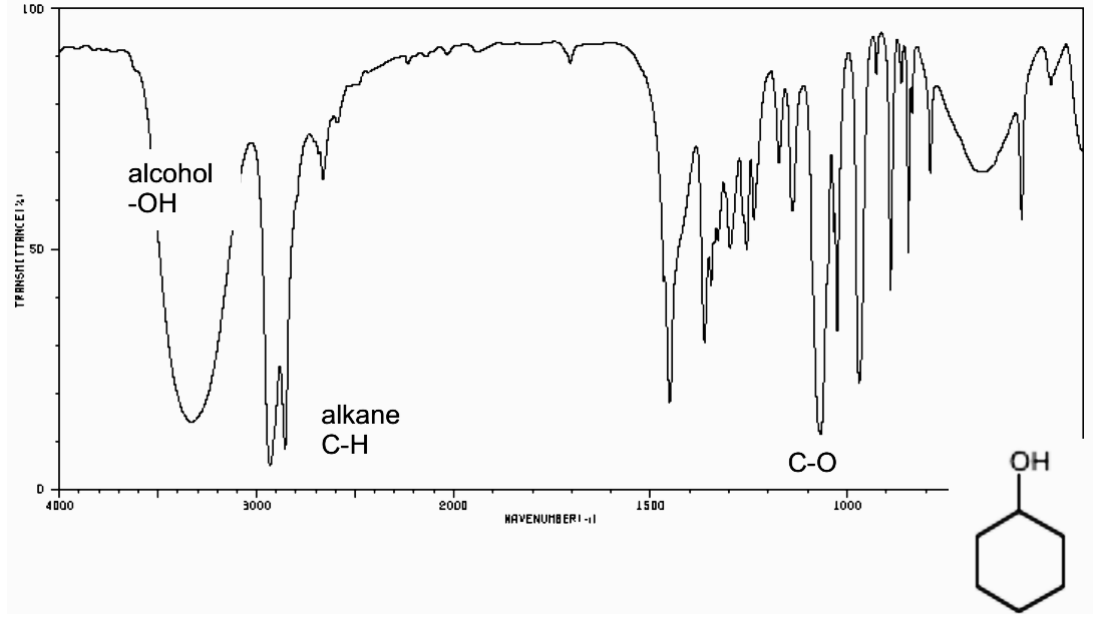


IR spectrum of methylcyclohexane 2922, 2883, 1449, 1376 cm^{-1}.



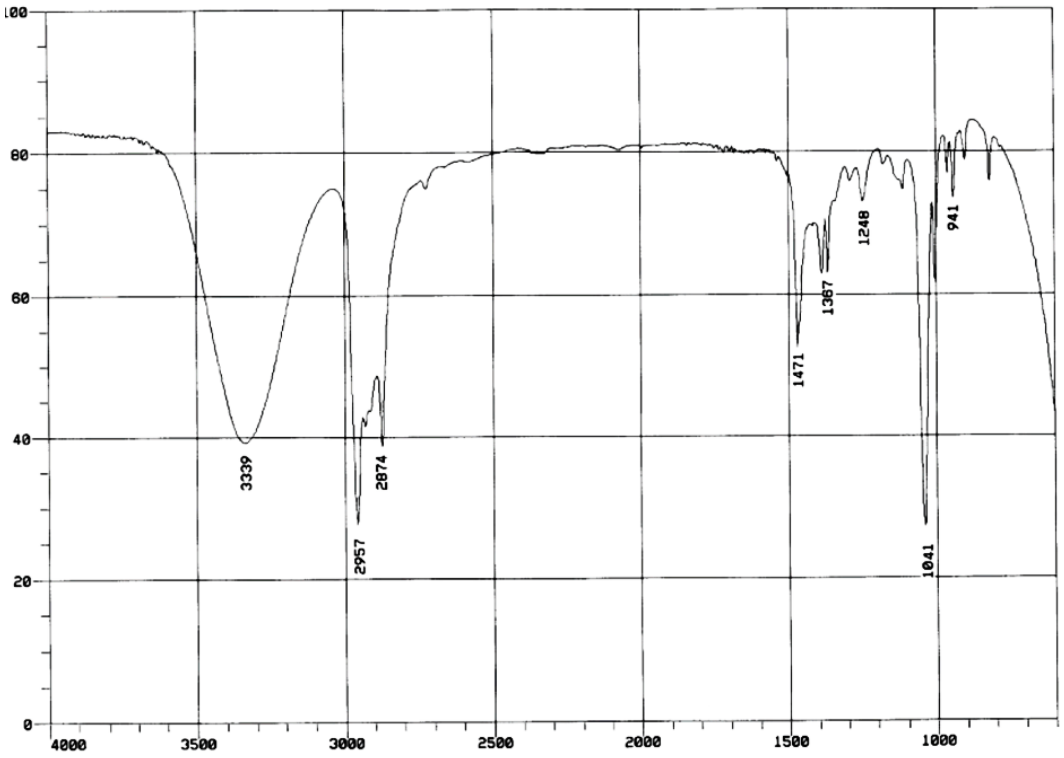
2. For each of the following IR spectra, select three IR peaks and label the functional groups to which they correspond.



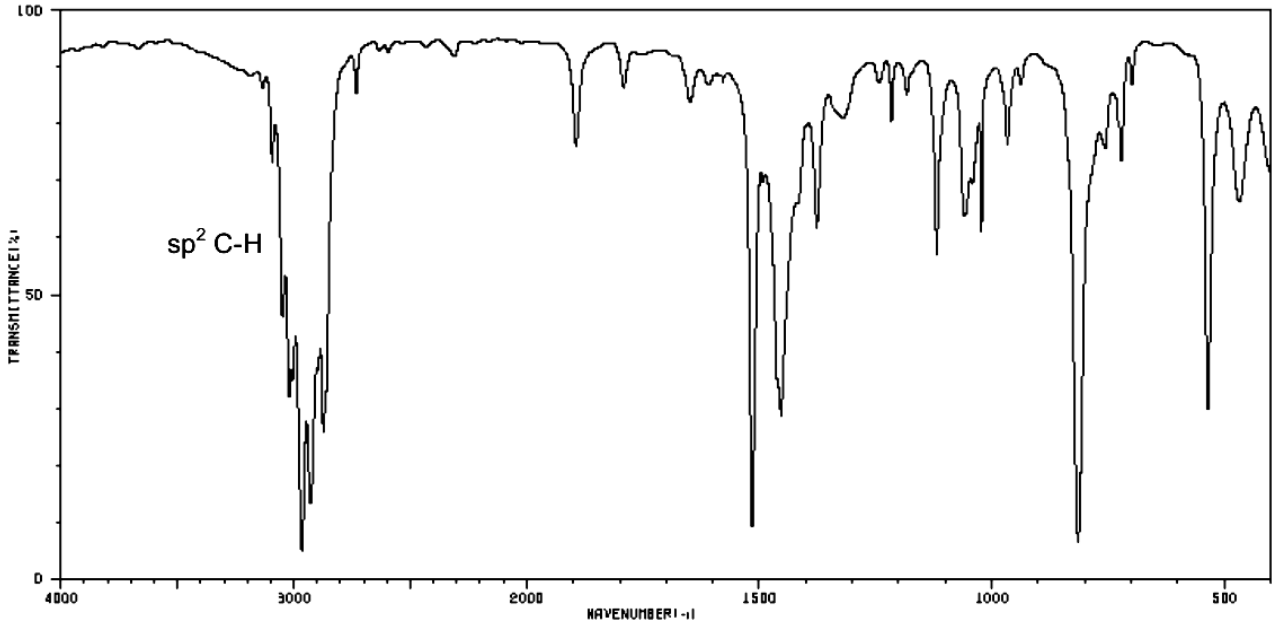


3. You find a bottle on the shelf only labeled C_3H_6O. You take an IR spectrum of the compound and find major peaks at 2950, 1720, and 1400 cm^{-1}. Draw a structural formula of the substance that was found in the bottle.

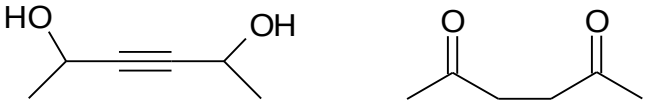
4. Find the structure for the following molecules $C_4H_{10}O$.

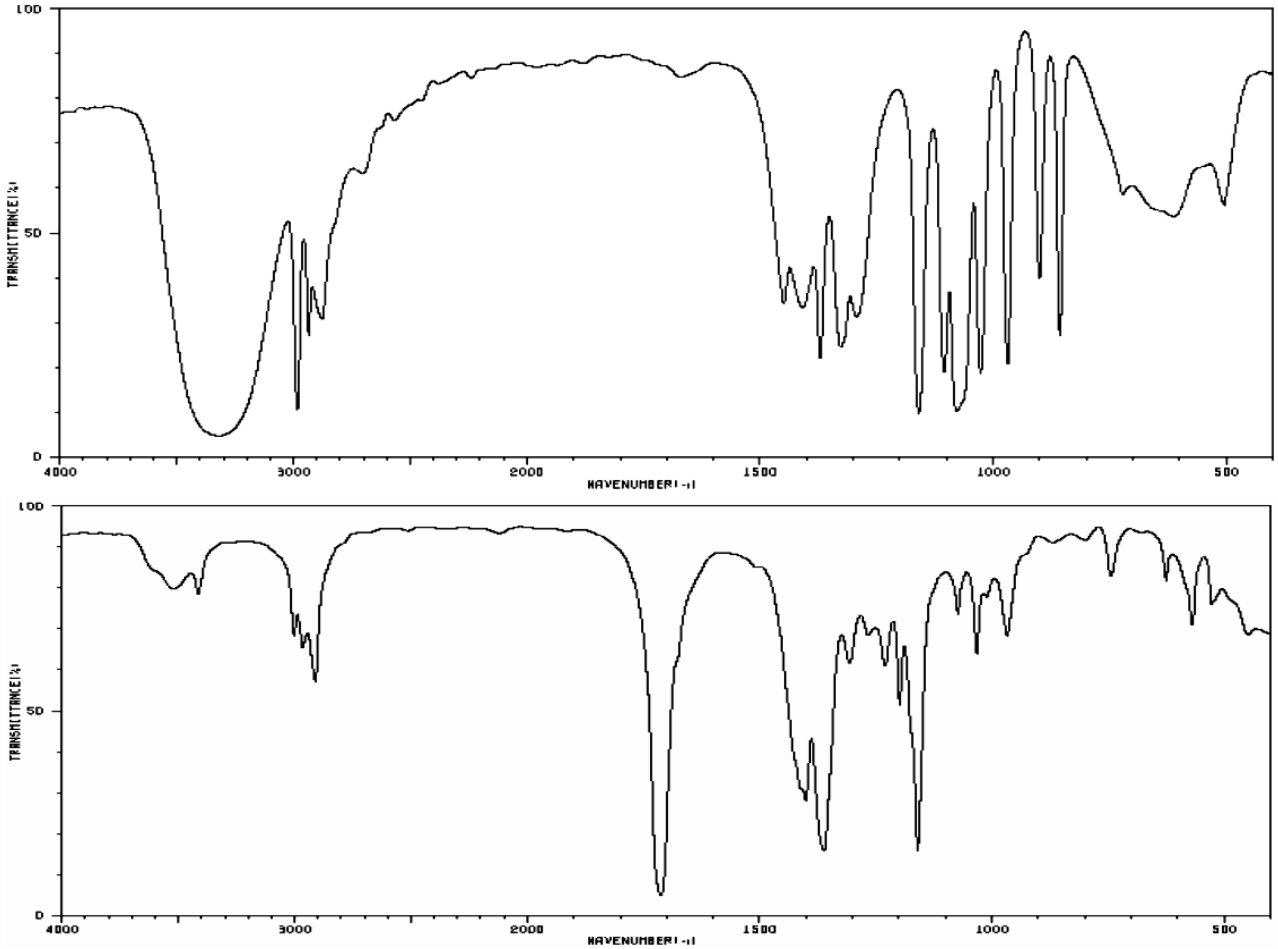


5. Use the IR data to determine the structure of the molecule C_9H_{12}.



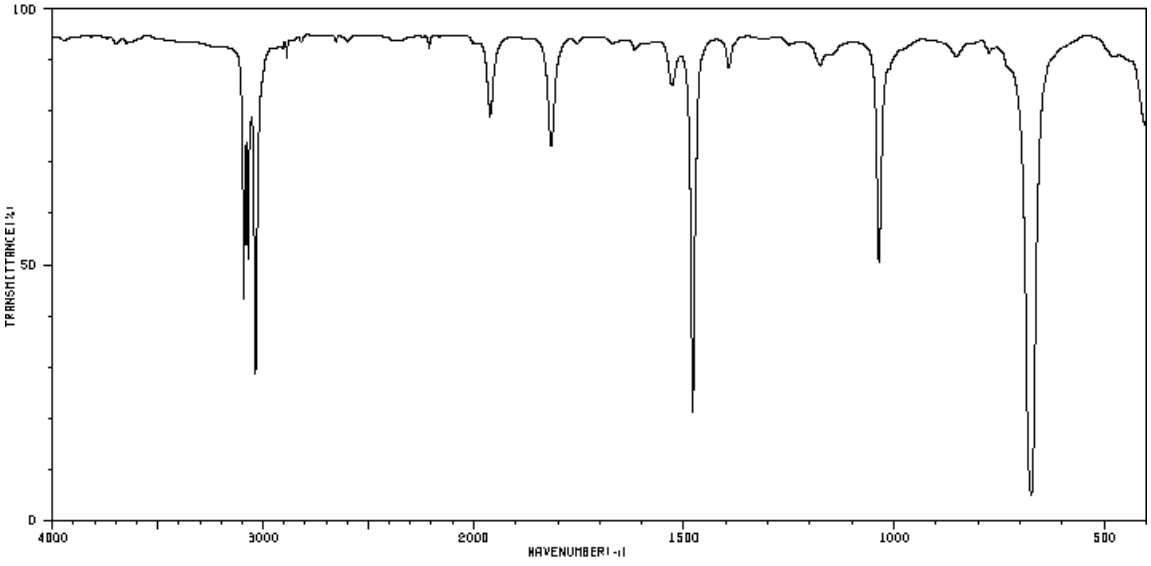
6. Both of the following molecules have the formula $C_6H_{10}O_2$. Match each compound to its corresponding spectrum, and give an evidence for your choice.



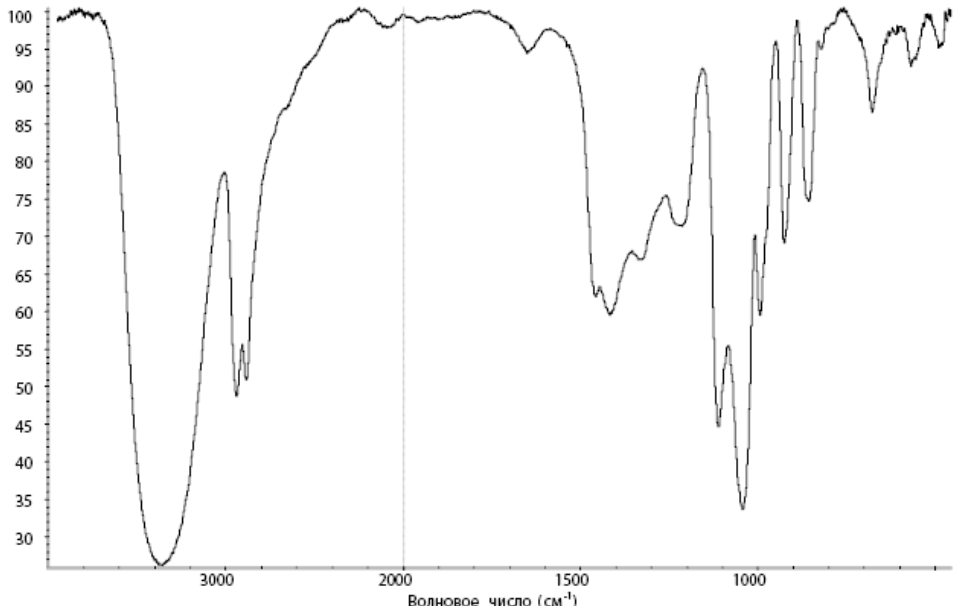


7. Analyze the following IR spectra given bellow and explain the origin of the absorption bands.

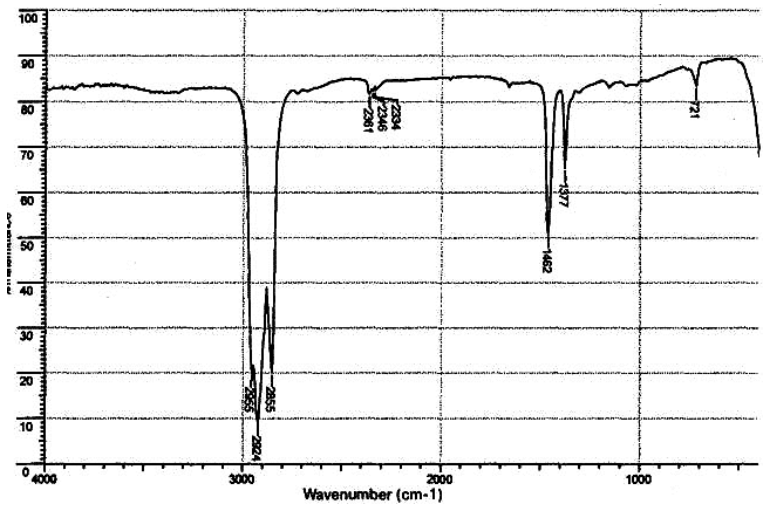
Benzene



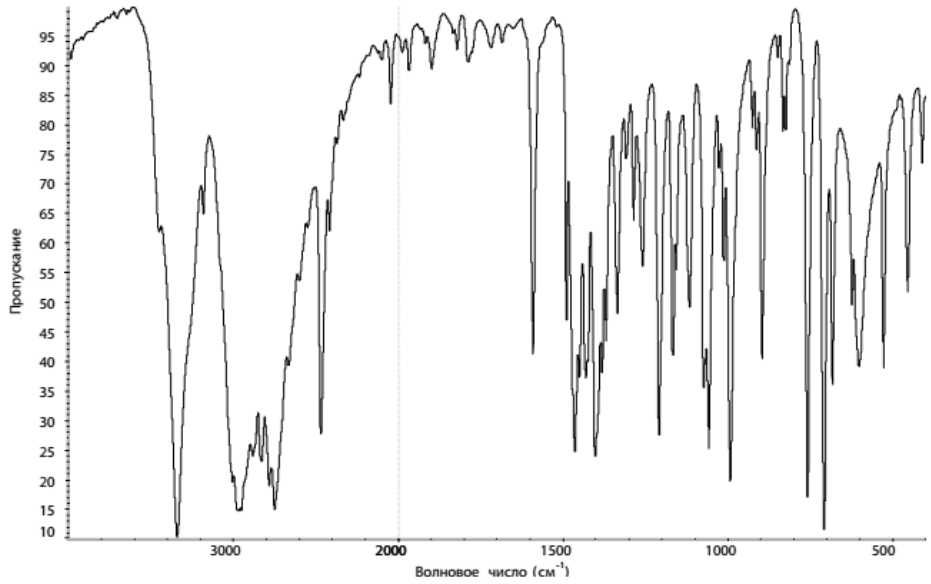
Glycerol

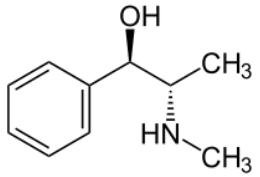


Vaseline oil



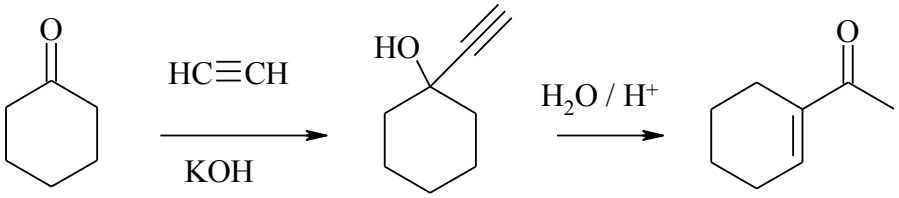
Component of pharmaceutical drug *Ephedrine.*



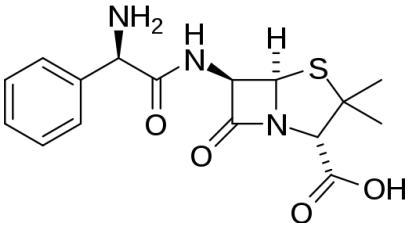


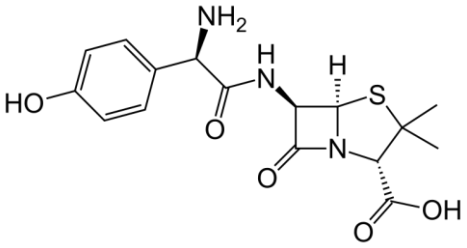
8. Cyclohexene and hex-1-yne both have the molecular formula C_6H_{10}. How would you use infrared spectroscopy to distinguish between the two compounds?

9. What characteristic frequencies in the IR spectrum can be used to monitor the progress of two step reaction which include *Favorsky* reaction (nucleophilic attack of a terminal alkyne) followed by the arrangement of *Kucherov* type?



10. Propose characteristic frequencies which can be used to distinguish IR spectra of *Ampicillin* and *Amoxicillin*?





Signature of the instructor:

LABWORK № 6
NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Objective: to study basic concepts and techniques of ^{1}H NMR and ^{13}C NMR spectroscopy.

Recommended further reading

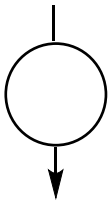
Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

1. The basic concepts of nuclear magnetic resonance spectroscopy.
2. ^{1}H NMR spectroscopy.
3. Chemical shift.
4. Spin-spin interactions and coupling constants.
5. Integration.
6. ^{13}C NMR spectroscopy.
7. Solvents for NMR spectroscopy.

BASIC PRINCIPLES

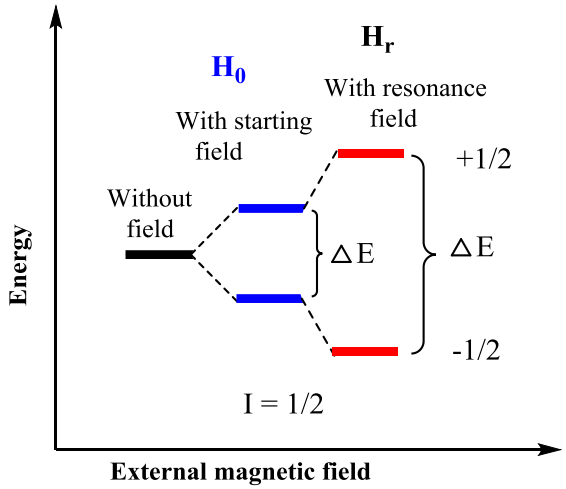
The nuclei of certain atoms are characterized with the definite proton number (n_b, that is equal to atomic number Z) and neutron number (N). Atoms with the even Mass number M=N+Z (it is possible when both N and Z are even) have not spinning charges; hence such nuclei do not generate the magnetic moment. In addition, their **μ=0**. The nuclei with odd Mass number behave as spinning charges and possess non-zero magnetic moment. Spinning charge of the nucleus generates a tiny magnetic field, indicated as a vector with a magnitude and direction.



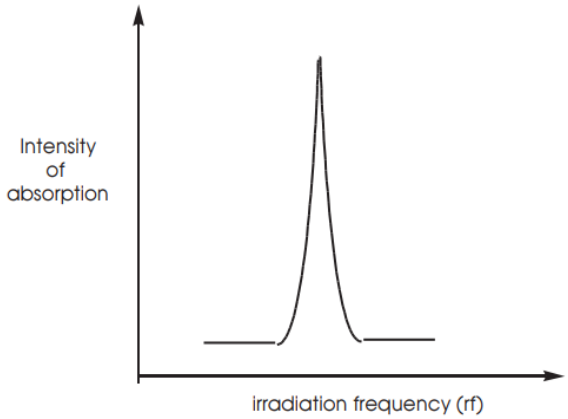
If the chemical substance with the odd Mass number is placed inside an external magnetic field (also referred to as applied field), the nuclear magnetic moment can only acquire a finite number of orientations, according to the principles of quantum mechanics.

The spin of atom depends of few characteristics. Generously, we can mention that the nucleus with even Mass number have no nucleus spin; hence their nucleus spin I=0. Nuclei with even Z and odd N possess half-integer spin, such as 1/2, 3/2, 5/2. For proton (^{1}H), Carbon-13 (^{13}C). Fluorine-19 (^{19}F) and Phosphorus-31 (^{31}P) I =1/2, hence the number of possible orientations is two: aligned with or against the field. When the nucleus is aligned with the field it is said to be in the α-state. When it is aligned against the field it is said to be in the β-state. The atoms with odd Mass and Neutron numbers possess integer spin, such as 1, 2, etc. For Deuterium (^{2}H) and Nitrogen-14 (^{14}N) I=1, hence their spin have three orientations. Atoms of half-integer and integer nucleus spins are both referred to as magnetically active, and hence can be examined in the experiments based on the Nuclear magnetic resonance phenomenon (NMR-spectroscopy).

The potential energies of the α- and β-states for atoms with I = 1/2 are different. The α-state has the lower potential energy than the β-state. Furthermore, the energy gap between the two states increases as the strength (intensity) of the external field increases.



It is possible to excite, or "flip" the nuclear magnetic vector from the α-state to the β-state by bridging the energy gap between the two. This is accomplished by irradiating the sample with electromagnetic radiation of the correct frequency (which is proportional to its energy) in the radiofrequency region. The absorption of energy occurs, and radiofrequency signal is induced in a detector coil located in the sample probe (housing).



The instrument records this frequency absorption as a resonance signal, or peak.

The nuclear spin is a nucleus-specific property. Different elements have different absorption ranges. They usually do not interfere with each other unless their absorption ranges are very close, which is rare. For example, at a magnetic field strength of 1 Tesla, the absorption frequency for the H-1 nucleus is approximately 43 MHz (megahertz). At the same field strength, C-13 absorbs at 10.7 MHz, F-19 at 40 MHz, and P-31 at 17.2 MHz. Since ΔE depends on the external magnetic field strength, the signal occurs at different rf values for different magnets. In NMR experiments equipment with a different power of external magnetic is used. To resolve the problem the relative value has been proposed.

The **chemical shift** is the resonant frequency of an atom relative to a standard in a magnetic field. The position and number of chemical shifts are diagnostic of the structure of a substance.

In structural analysis chemical shift δ is expressed in parts per million (ppm) by frequency, because it is calculated from

$$\delta = \frac{\nu_{sample} - \nu_{ref}}{\nu_{ref}},$$

where ν_{sample} is the absolute resonance frequency of the sample and ν_{ref} is the absolute resonance frequency of a standard reference compound, measured in the same applied magnetic field. Since the numerator is usually expressed in hertz, and the denominator in megahertz, δ is expressed in ppm.

The detected frequencies (in Hz) for ^{1}H and ^{13}Cnuclei are usually referenced against TMS (Tetramethylsilane), which chemical shift by the definition is equal to zero, as it was chosen as the reference. Few more standards can be used in the experiments on other atoms.

Consider the experiment detect the NMR signal for some atom at a frequency 750 Hz higher than the signal from TMS, where the TMS resonance frequency is 500 MHz. Based on formula above we can calculate the chemical shift ppm:

$$\delta = \frac{750\ \text{Hz}}{500\ \text{MHz}} = 0{,}0000015 = \mathbf{1{,}5\ ppm}$$

The absorption signal in NMR experiment is atom-nature dependent. There are special techniques providing the detection of absorption signal in heteronuclear NMR. However, in the most cases homonuclear procedure is applied.

Hydrogen ^{1}H, or proton, is the most extensively studied nucleus due to its high natural abundance (99 % relative to other isotopes) and widespread presence in organic molecules. In a given molecule, different types of protons are surrounded by different degrees of electron density, and therefore experience different degrees of electron "shielding" in an NMR experiment. The ^{13}C nuclei are also widely included in NMR experiments in spite of the minor abundance (1 % relative to other isotopes). However, the differences in energy arisen from the irradiation are much higher than for ^{1}H, hence the differences between ^{13}C signals in a molecule are higher. Taking into account the low abundance of ^{13}C isotope in nature, the higher concentration of sample is required for the experiment.

Generally, NMR spectrum provides the information that is fall into four categories:

– number of signals present;

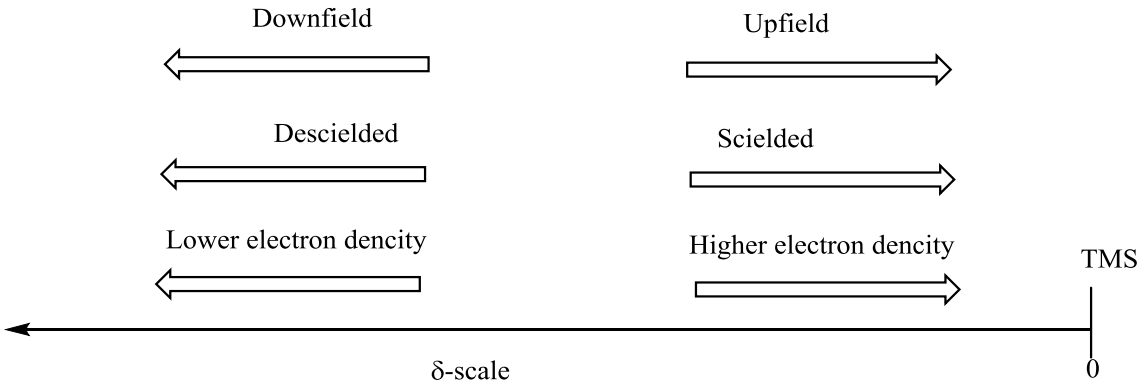
– chemical shift (position of the signals in the frequency axis);

– relative signal intensities;

– signal multiplicities.

CHEMICAL SHIFT

The proton and Carbon-13 absorptions for TMS today are always assigned according to δ-scale where an arbitrary value of zero ppm. All other protons (or carbons) in the spectrum are then referenced to the TMS peak. The δ-scale increases from right to left and have a typical range in ^{1}H spectra about 0–15 ppm for most common organic compounds. The y-axis in the δ-scale represents the intensity of the absorption. The typical range in ^{13}C spectra is of about 0–300 ppm for most common organic compounds.

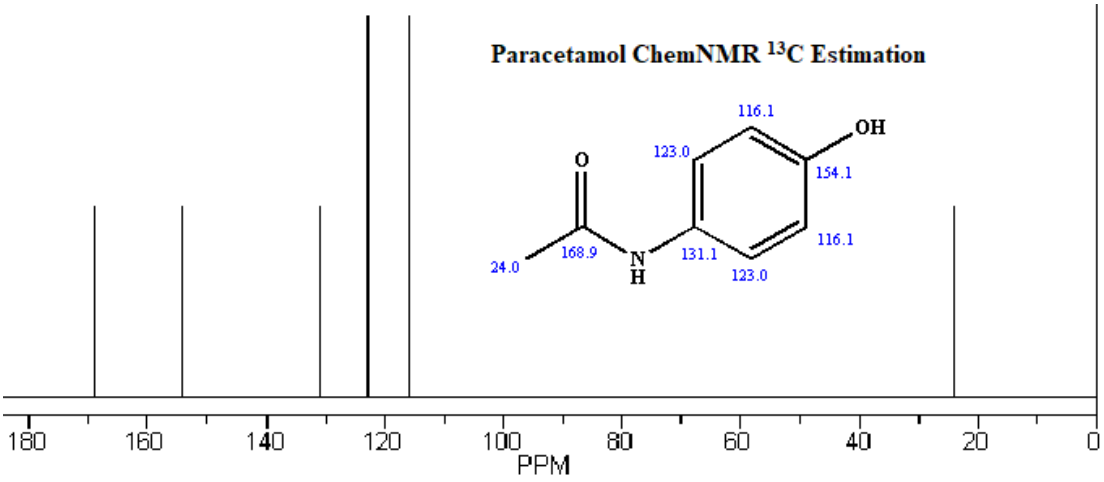


In homonuclear spectrum, the position of signals from non-equivalent protons or Carbons depends on surrounding charge cloud due to adjacent bonds and atoms. Important factors

influencing chemical shift are electron density, electronegativity of neighboring groups and anisotropic induced magnetic field effects through a space. In the most general approach, electronegative atoms and double bonds deshielded the signal left (the range of the lower field).

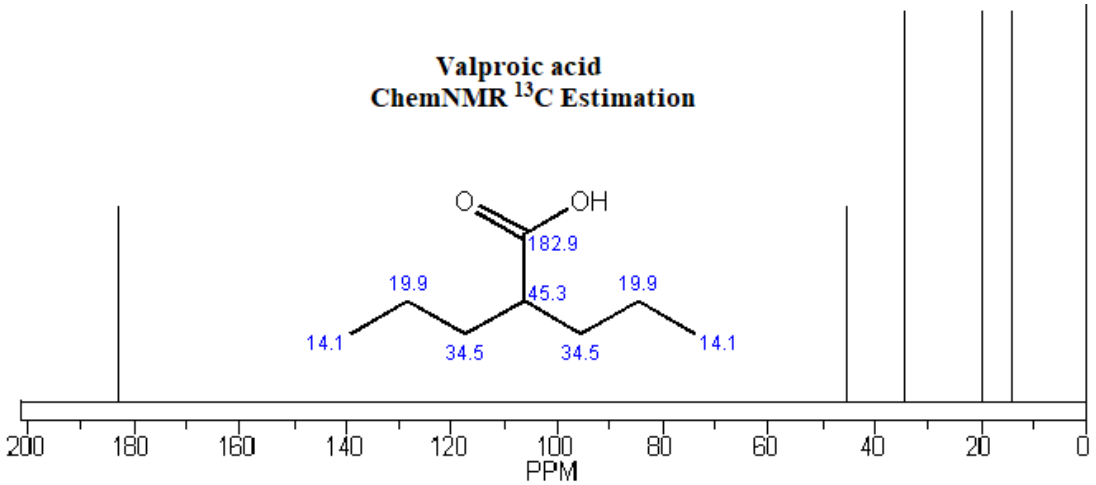
The longer distance between the detected and electronegative atom, the less the electronegativity of the latter the less deshielding effect.

Consider the estimated ^{13}C spectrum for *Paracetamol, which* is widely used as non-opioid analgesic and antipyretic agent.



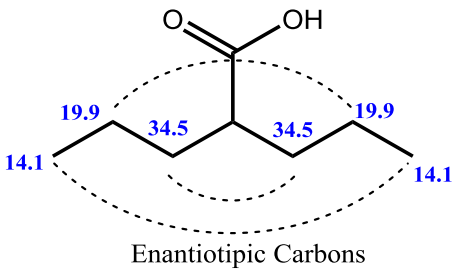
The most downfield is observed for Carbon belonging to amide group: the Carbon connected directly to two electronegative atoms (Oxygen and Nitrogen); carbonyl group contains the double bond. All the atoms belonging to benzene ring are rather downfielded due to the deshielding influence of aromatic system. However, the aromatic Carbon connected to Oxygen has the higher value of the chemical shift, followed by the atom connected to Nitrogen.

The next example, the spectrum of the *Valproic acid*, that is used to treat epilepsy and bipolar disorder, demonstrates how the distance between the detected and the electronegative atom correlates with the chemical shift.

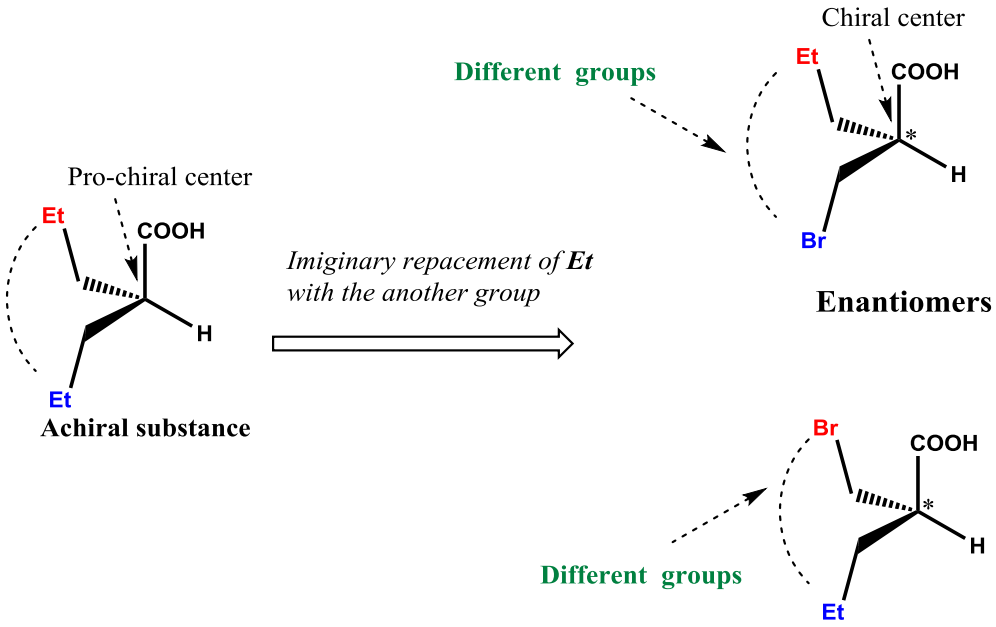


The Carboxylic carbon connected to two oxygens (and with one of them is double bounded!) has the highest value of the chemical shift, followed by the carbon atom connected next to the previous. Evidently, the longer distance between oxygen and carbons, the lower values are observed.

Interestingly, that we have the same chemical shifts to three pairs of magnetically equivalent carbons.

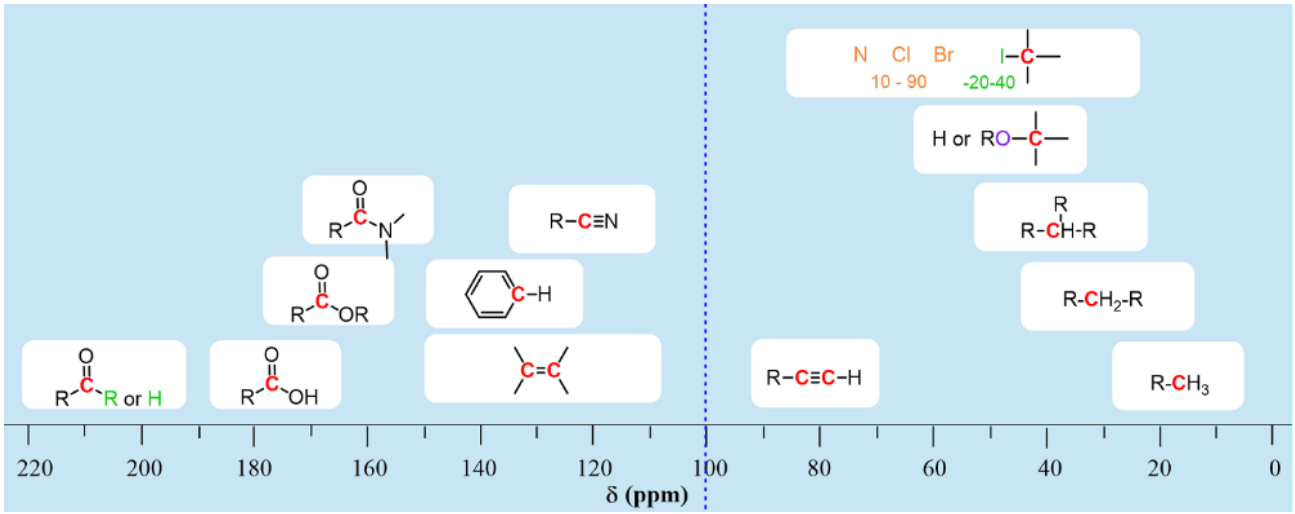


Evidently, it can be easily explained applying the topicity test we discussed in the previous chapter.



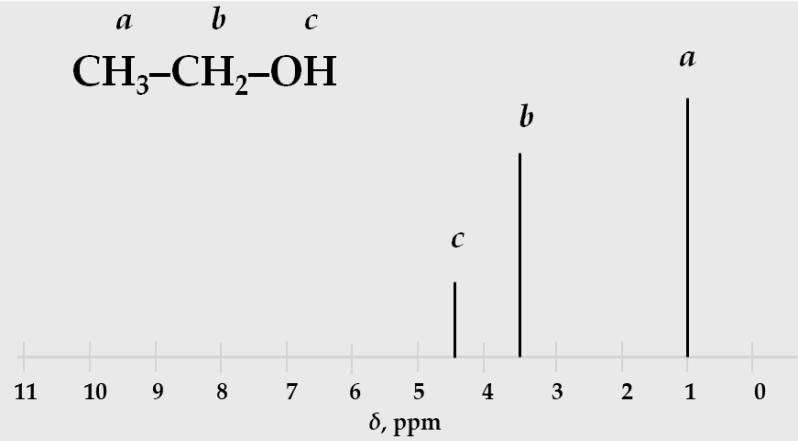
In the picture above the topicity test proves the enantiotopic relations between two carbons, which are closest to the branching point of the molecule. Analogously, the enantiotopic relations can be proved for the rest of pairs of carbon. Because the signal in NMR referred to achiral scalar values, the standard NMR spectrum does not differentiate enantiotopic Carbons. Hence they are magnetically equivalent and have the same chemical shifts.

Commonly, the chemical shifts obtained in the experiment are interpreted based on the correlation tables and graphs, which include the approximate (sometimes very rough) chemical shifts ranges for typical structural fragments according to their chemical environment. Such a graph for ^{13}C spectrum is presented below.



Analogically, correlation between chemical shifts and molecule structure can be used in ^{1}H and NMR spectra. The graph below presents Ethanol spectrum in deuterated Dimethylsulfoxide (DMSO-d6):

As one would expect, three different signals have been detected. (a), (b) and (c) atoms are structurally different; two protons from the (b) pair are enantiotopic and three protons from the (a) trio are homotopic. Due to the achirality of the standard NMR both homotopic and enantiotopic protons are magnetically equivalent, and hence, "pair" and "trio" protons have the sane chemical shift in their sub-groups.



In this spectrum you can notice the distinct difference between the intensity of the three signals which corresponds to the number of protons in every sub-group. Resulting intensities are as follows **3 : 2 : 1** corresponding to the **number of protons** in groups (a), (b) and (c).

Contrary to ^{13}C spectroscopy in ^{1}H spectroscopy the intensities of the signals of equivalent protons are widely used for structure analysis.

May be you noticed that the solvent was specified for example discussed. DMSO-d6 is the ***deuterated aprotic*** solvent. Only ***deuterated*** solvents are used in routine ^{1}H spectroscopy. The application of proton (^{1}H) containing solvents hinders the detection of signals of the substance examined due to the much higher amount of the solvent molecules. Moreover, the modern NMR apparatus reference additionally the scale to Deuterium chemical shift.

The aprotic (as we discuss the inability of Deuterium donation, it would be better to say "adeuteriumic", but nobody saying in such a way) nature of the solvent was also specified because it is crucially influence the spectrum appearance. If we used a protic deuterated solvent, e.g. deuterated methanol (CD_3OD), the latter would donate Deuterium to Ethanol molecule in the Proton-Deuterium exchange process. Hence, the Ethanol spectrum in CD_3OD would have only two signals referred to Methylene (b) and Methyl (a) protons. In such experiment the signal of Hydroxy group Hydrogen is disappeared because the Hydrogen is substituted with a Deuterium. The phenomenon discussed can be used to prove the presence of acidic protons in molecule based on spectra recorded in aprotic solvents: the signal of equivocal proton (from O-H, N-H fragments) can be additionally challenged by the addition of few drops of Deuterated water D_2O. The signal disappearance after the D_2O addition substantiates the presence of mobile Hydrogen in the molecule.

You may notice that the range of the scale for ^{1}H NMR spectroscopy is much smaller than those in ^{13}C NMR spectroscopy. Hence, the potential of chemical shifts interpretation is not enough to determine the structure of the compound. Nevertheless, ^{1}H NMR spectroscopy is still one of the most widely used methods for structure identification. This is attributed by the correlation analysis based on multiplicity of signals in NMR spectrum.

MULTIPLICITY

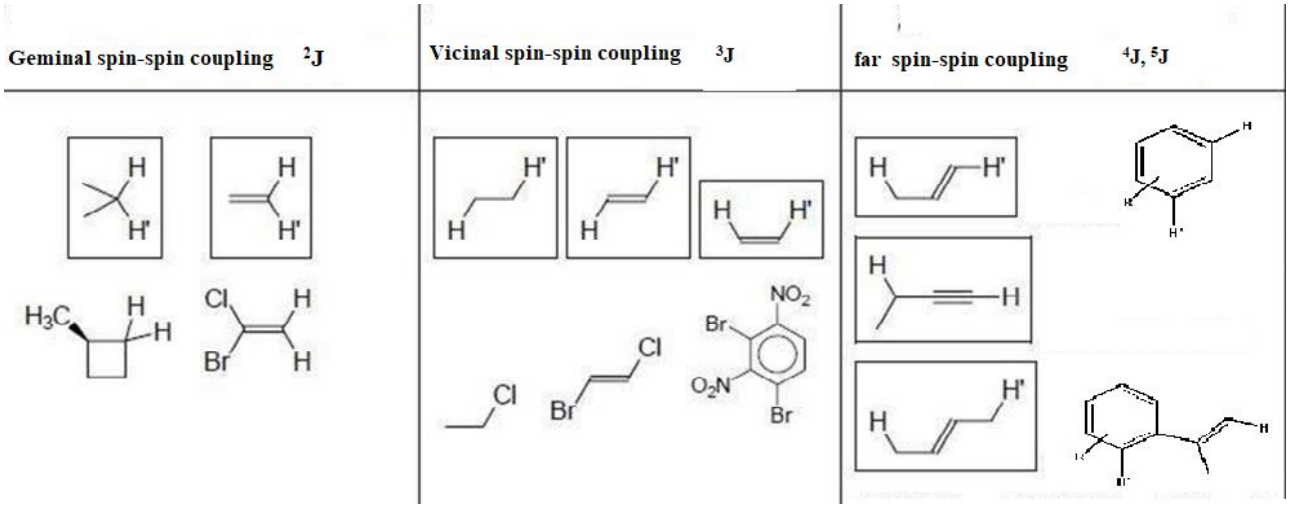
Signal multiplicity is characterized by a specific splitting of the signal due to the interaction with neighboring atoms.

In homonuclear NMR spectroscopy we discuss only the interaction between atoms belonging to one element. In ^{1}H NMR spectroscopy, we will consider proton-proton interactions, which are visualized in the signal multiplicities and are digitalized in spin-spin coupling constants.

Spin-spin coupling, a term that describes the magnetic interactions between neighboring, non-equivalent NMR-active nuclei, is the source of signal splitting. The terms "splitting" and "coupling" are often used interchangeably when discussing NMR. Now we will omit the complex reasons for spin-spin coupling. In contrast, we will postulate some simple rules for interpretation of signal splitting.

1. Only interaction of non-equivalent nuclei generates spin-spin coupling resulting in the signal split.

2. When the routine NMR technique is applied (apparatus up to 500 MHz), spin-spin interactions between **geminal (constant ^{2}J)** and **vicinal (constant ^{3}J)** Hydrogen are mostly observed. The term geminal refers to two Hydrogens that are attached to the same Carbon. Vicinal Hydrogens are bonded to two adjacent Carbon atoms.

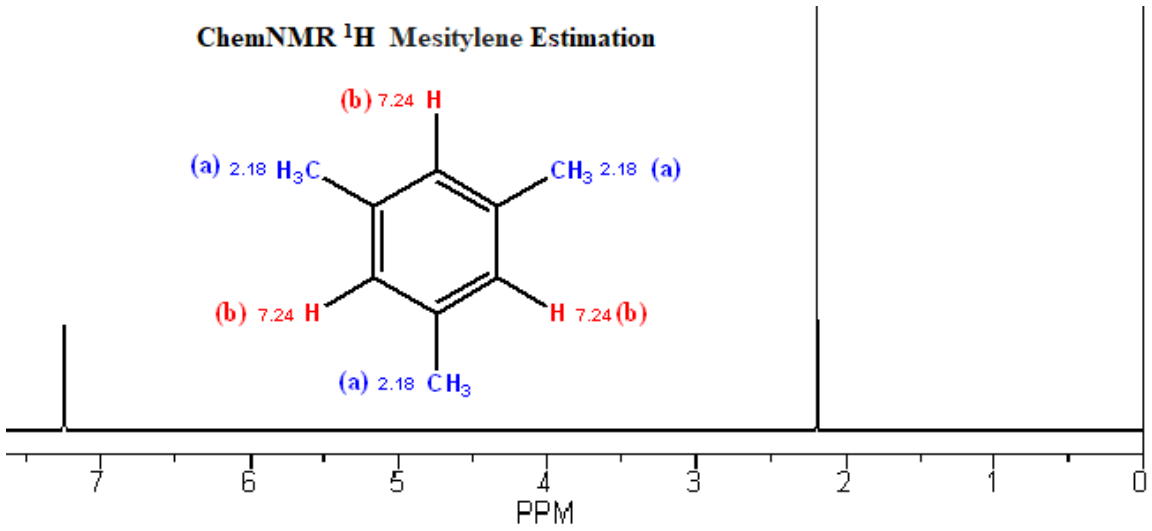


Conjugation gives rise to the far distant interactions (**constants ^{4}J, ^{5}J**). However, in our course we will consider mostly geminal and vicinal interactions. The cases we will discuss the far interactions will specially denoted.

3. The multiplicity of a signal depends on number of atoms the detected Hydrogen is coupled with and the interrelation in which the splitting atoms exist (equivalent or non-equivalent).

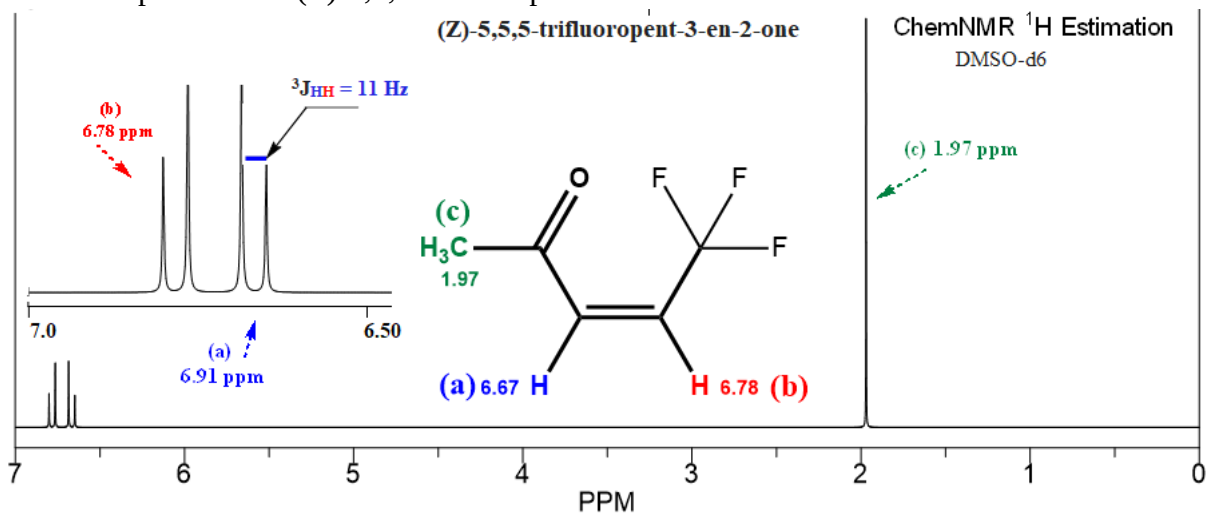
The first, we consider the signals from the Hydrogens that have no "neighboring" to couple.

Mesitylene, or 1,3,5-trimethylbenzene, has only two sets of non-equivalent protons, types (a) and (b). All the protons of one type are homotopic: 9 trimethyl protons of type (a) and 3 lone Hydrogens of type (b). Once the homotopic protons are magnetically equivalent, they give one signal. Moreover, any of the protons in the molecule has no geminal or vicinal neighbor; hence, they are not coupled and signals are not splitted. Such signals are presented in the form of singlets (abbreviation: s = singlet).



Coupling with non-equivalent protons

Now we consider the protons that have only one non-equivalent neighbor. The graph below presents the spectrum for (Z)-5,5,5-trifluoropent-3-en-2-one in DMSO-d6.

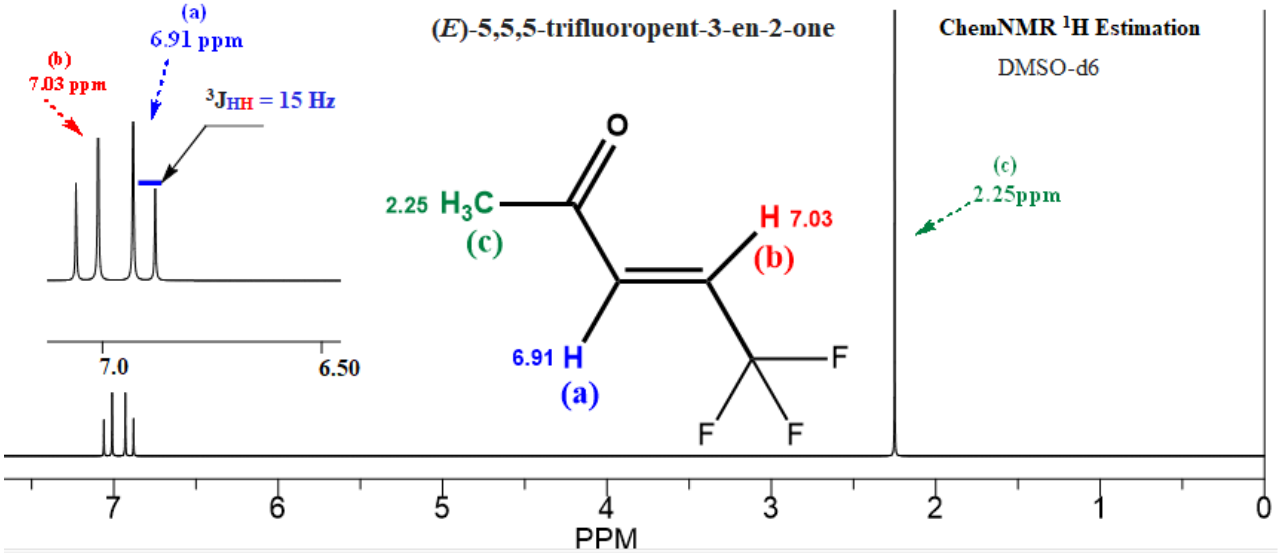


The molecule contains three types of non-equivalent protons: two vinylic protons, types (a) and (b), which are highly downfielded due to the influence of double bond, and three methyl protons, type (c). All three methyl protons are homotopic and have no non-equivalent neighbors; hence, their signal is presented graphically as a singlet with the relative (to one Hydrogen) intensity 3. Vinylic Hydrogens are vicinal and non-equivalent; hence their signals are splitted with spin-spin constant $^3J_{HH}$ **= 11 Hz.** Because the proton nucleus spin I = 1/2, the coupling with one neighboring non-equivalent proton generates the split into two lines; the latter we define as a doublet (abbreviation: d = s doublet). Naturally both vinylic protons couple with each other to induce the same split; hence the spin-spin constant will be the same for both doublets ($^3J_{HH}$ **= 11 Hz**).

Information from NMR can be recorded conveniently in a condensed form without having to reproduce the actual spectrum. For example, the information from spectrum above can be presented both in tabular and text format, listing the chemical shift, the peak splitting pattern, and the relative area under peaks (usually, the smallest peak is set to 1). For example discussed the text format will be presented as follows:

1.97 ppm, 3H, s; 6.67 ppm, 1H, d ($^2J_{HH}$ = 11 Hz); 6.78 ppm, 1H, d ($^3J_{HH}$ = 11 Hz).

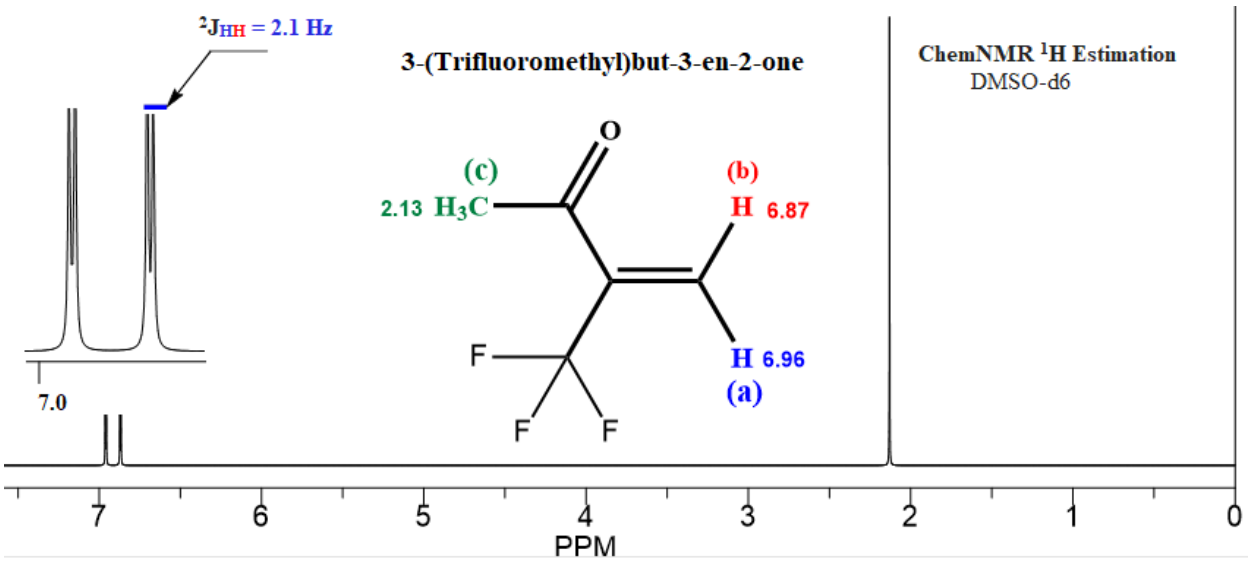
Next, it will be interesting to compare the spectra of (Z)-5,5,5-trifluoropent-3-en-2-one discussed previously with its diastereoisomer (*E*)-5,5,5-trifluoropent-3-en-2-one. Diastereoisomers are different in scalar properties; hence, they will have different spectra. It is not a great surprise that spectra of the two diastereoisomers are characterized with different parameters. All chemical shifts for structurally identical (but spatially scalarly different!) groups will be different. Hence, the method can be used for detection and identification of two diastereoisomers.



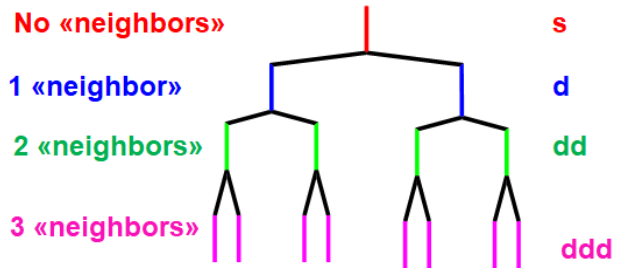
Moreover, we can try to interpret the spectra parameters in intention to determine the configuration of stereoisomers with unknown stereochemistry (the issue for newly synthesized substances). May be the first idea that comes to mind it is to speculate the values of chemical shifts in both spectra. No doubt, the mutual orientation in space of groups in the molecule influences the signal position. Thus, we can explain the downfield of type (b) proton by the unshielding effect of the carbonyl group, the latter being in cis position to a proton in (*E*) isomer. However, you must be very cautious with such speculations, because the shielding effects depend on many factors. That is why in the case it would be more convincing to compare the spin-spin constants for proton coupling. It is known that for cis-vicinal vinylic Hydrogens the more value of the spin-spin constant is typical. Therefore, if we did not know the stereochemistry of substances discussed we could identify (*E*) configuration for isomer with the higher $^3\mathbf{J_{HH}}$ **= 15 Hz,** and (*Z*) configuration for isomer with the smaller $^3\mathbf{J_{HH}}$ **= 11 Hz**.

Next example will demonstrate the diastereotopicity, and that is why non-equivalency, of the geminal vinylic protons. One may suppose the vinylic protons in the fragment $=CH_2$ are equivalent. But this would be a fatal mistake to a great inaccuracy in spectrum analysis. Let's consider a spectrum of the 3-(trifluoromethyl)but-3-en-2-one which spectrum is presented below.

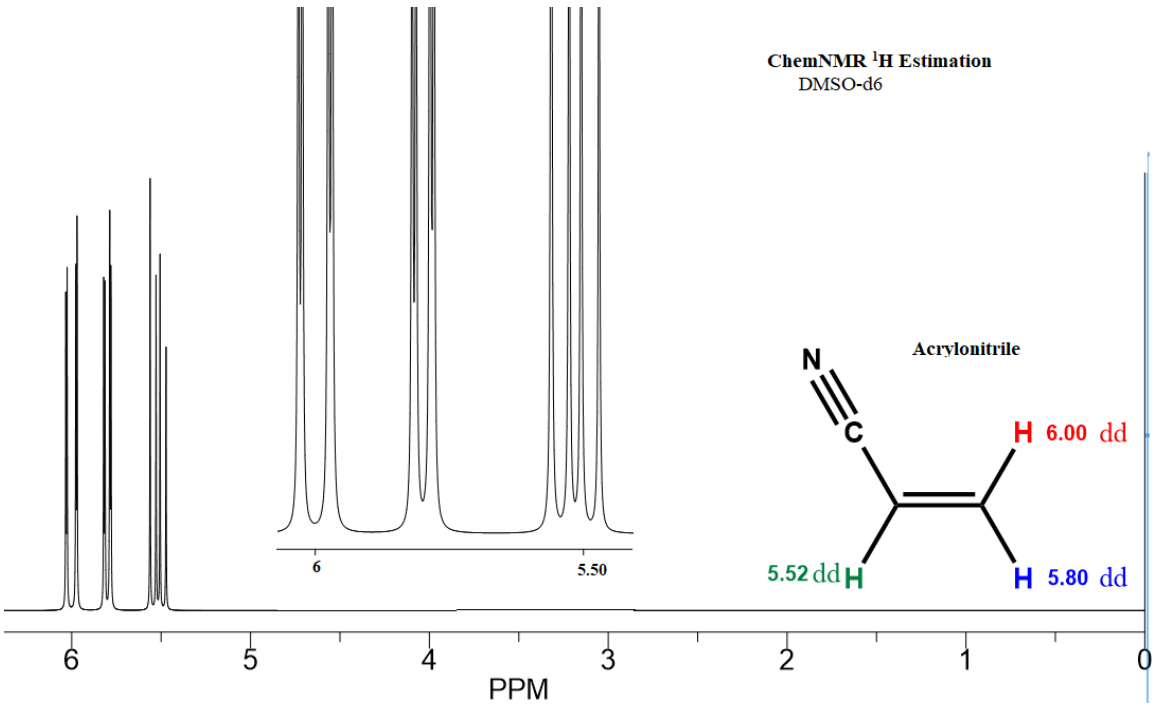
You can see that the signals of the vinylic protons have different chemical shifts (6.87 ppm and 6.96 ppm); it follows that these protons are non-equivalent. This is in line with what we discussed about the diastereotopicity of atoms and groups. Replacing Hydrogens with the Bromine, we will get two diastereoisomers. It does mean the Hydrogens discussed are diastereotopic, therefore they are magnetically non-equivalent in NMR experiment. Clearly, the "weak" device (with the low power of the external field) may have no enough resolution to distinguish to atoms. But the more powerful apparatus will resolve two signals. At first, when one analyze the general plot in the spectrum it looks that there is no splitting for protons discussed. In a very rare case, the coupling constant can be zero. However, in our example after enlarging the spectral region with geminal protons we can clearly distinguish the splitting with a very small spin-spin coupling constant ($^2\mathbf{J_{HH}}$ **= 2.1 Hz)**.



When the Hydrogen couples with the more non-equivalent Hydrogens, the signal splitting will provide the more complex multiplicity. Moreover, every new coupling appears to give the new doubling of the previously splitted signal. The graph below presents logically the correlation between the number of the non-equivalent neighboring Hydrogen and the multiplicity of a signal.



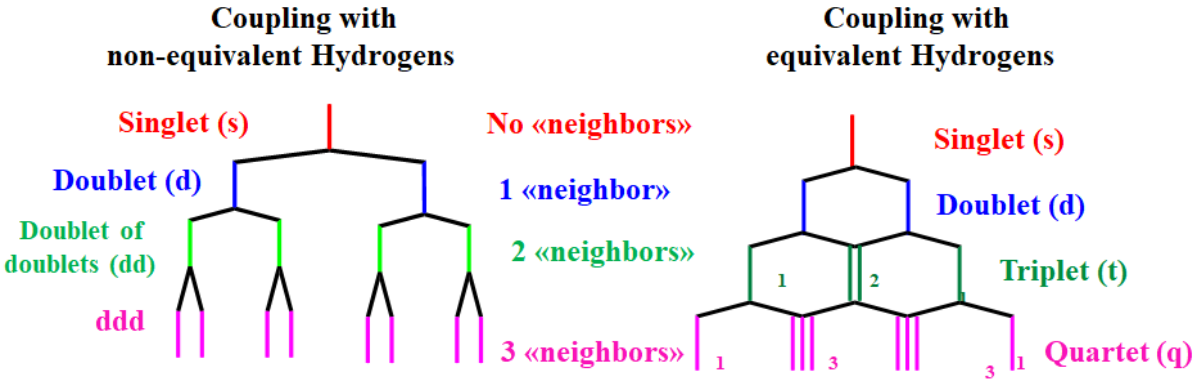
In the molecule of the Acrylonitrile, all Hydrogens are non-equivalent and neighboring to each other. That is why each of them couples twice to produce doublet of doublets (dd) in the spectrum. Geminal constant will be low similar to previous sample and two different vicinal constants will be not much close by value to each other.



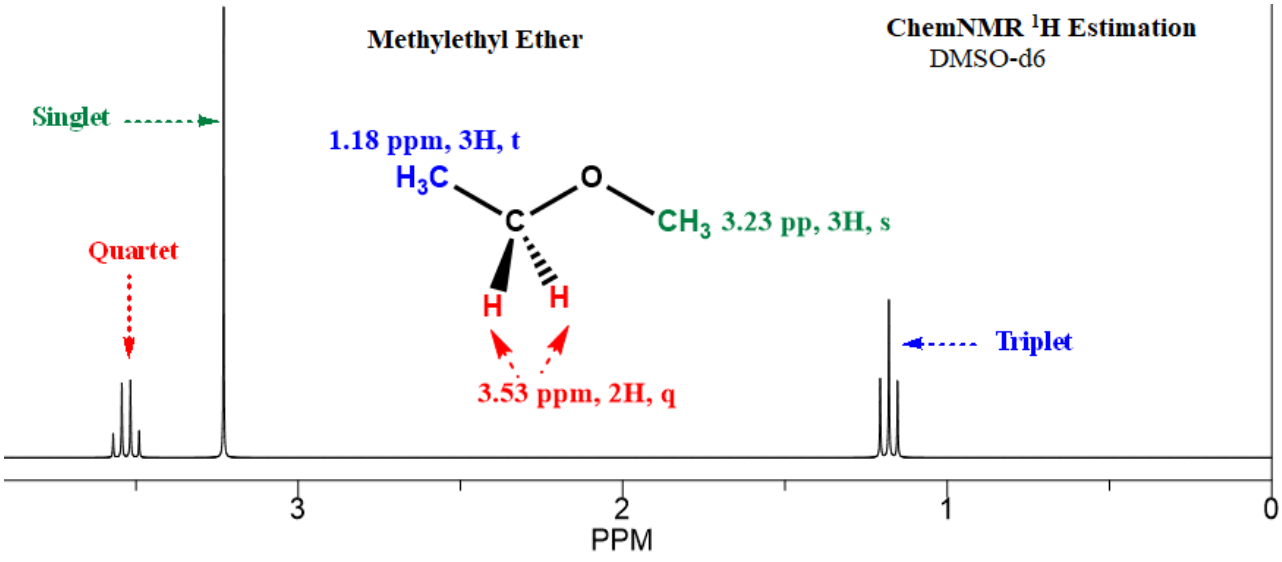
Coupling with equivalent protons

Finally, we will consider the coupling with a group of equivalent protons. Let us to remind you that equivalent protons do not couple with each other, in other words they are all the same with the multiplying intensity of the signal. Metaphorically speaking, one can say that equivalent protons are not able to "see" each other. However, the number of equivalent protons influences the multiplicity of the proton coupling with them. In general, the coupling logically might have been similar to those we had for coupling with non-equivalent protons. Yet there is a change of the multiplicity because spin-spin coupling constants will the same in relation to all equivalent protons in the group. The graph below presents logically the correlation between the number of the equivalent and non-equivalent neighboring Hydrogen and the multiplicity of a signal.

In the case of the interaction with three non-equivalent Hydrogens instead of double of doublets we obtain the signal with a three lines due to the identical spin-spin coupling constants leading to the coincidence of the middle lines of the dd-signal; we name such a signal as triplet (t). Analogously, the coupling with four non-equivalent Hydrogens gives the signal with four lines instead of ddd-signal; we name such a signal as quartet (q). It is worthy to mention, that "degenerated" signals are characterized with different relative line intensities. Thus in the triplet the middle line is twice as intense as the side ones (due to coincidence of the middle lines in the "degenerated" dd-signal). Analogously, in the quartet two middle lines are three times more intense than the lateral ones. The relative intensities are visualized in graph above for interaction with equivalent Hydrogens.



Now we will consider the spectrum of the Methyl Ethyl Ether, possessing few sets of protons with a different multiplicity.



Three homotopic Hydrogens belonging to the methoxy group have no neighbors, hence they are presented as a singlet with tripled intensity. Two enantiotopic (it does mean magnetically equivalent!) methylene Hydrogens have 3 equivalent neighbors, hence they are presented as a quartet with the doubled intensity. Finally, three homotopic Hydrogens belonging to the ethoxy group have 2 equivalent neighbors; hence they are presented as a triplet with the tripled intensity.

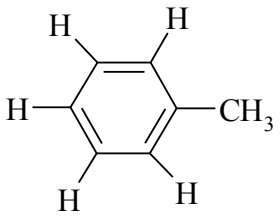
The multiplicity of signal of a proton that interacts with magnetically equivalent neighbors can be derived from the formula

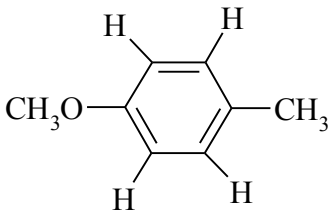
$$N = n + 1,$$

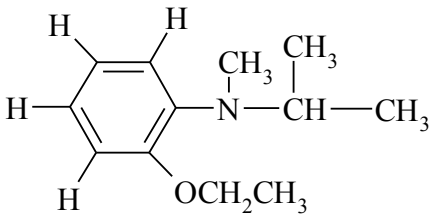
where ***N*** is the number of lines in the splitted signal and ***n*** the number of equivalent neighboring Hydrogens. Therefore, for four equivalent neighbors we have a signal with five lines (Pentet) and for four equivalent neighbors we have a signal with seven lines (Septet).

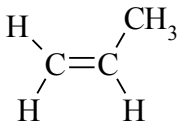
PRACTICE PROBLEMS

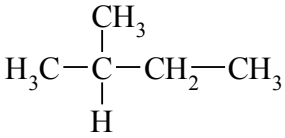
1. Define various structural types of protons in the following compounds. If there are two or more protons of the same type to indicate which of them are homotopic (H), enatiotopic (E) and diastereotopic (D). Which of them are magnetically equivalent.

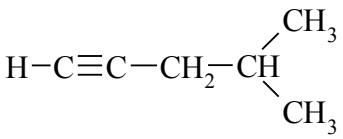


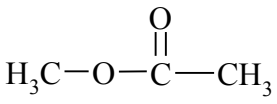


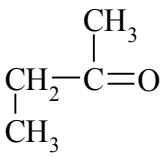


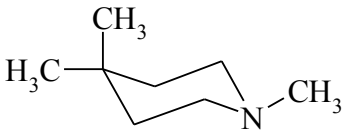


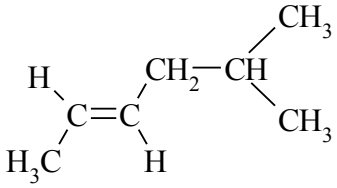


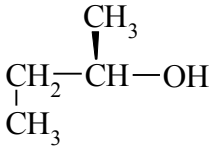


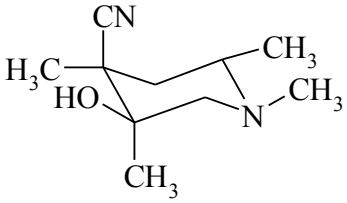












2. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of 3,5-dimethoxyacetophenone* (consider only the spin-spin interaction of geminal and vicinal proton — ^{2}J and ^{3}J). Explain the coupling.

3. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of *para*-methylaniline*.

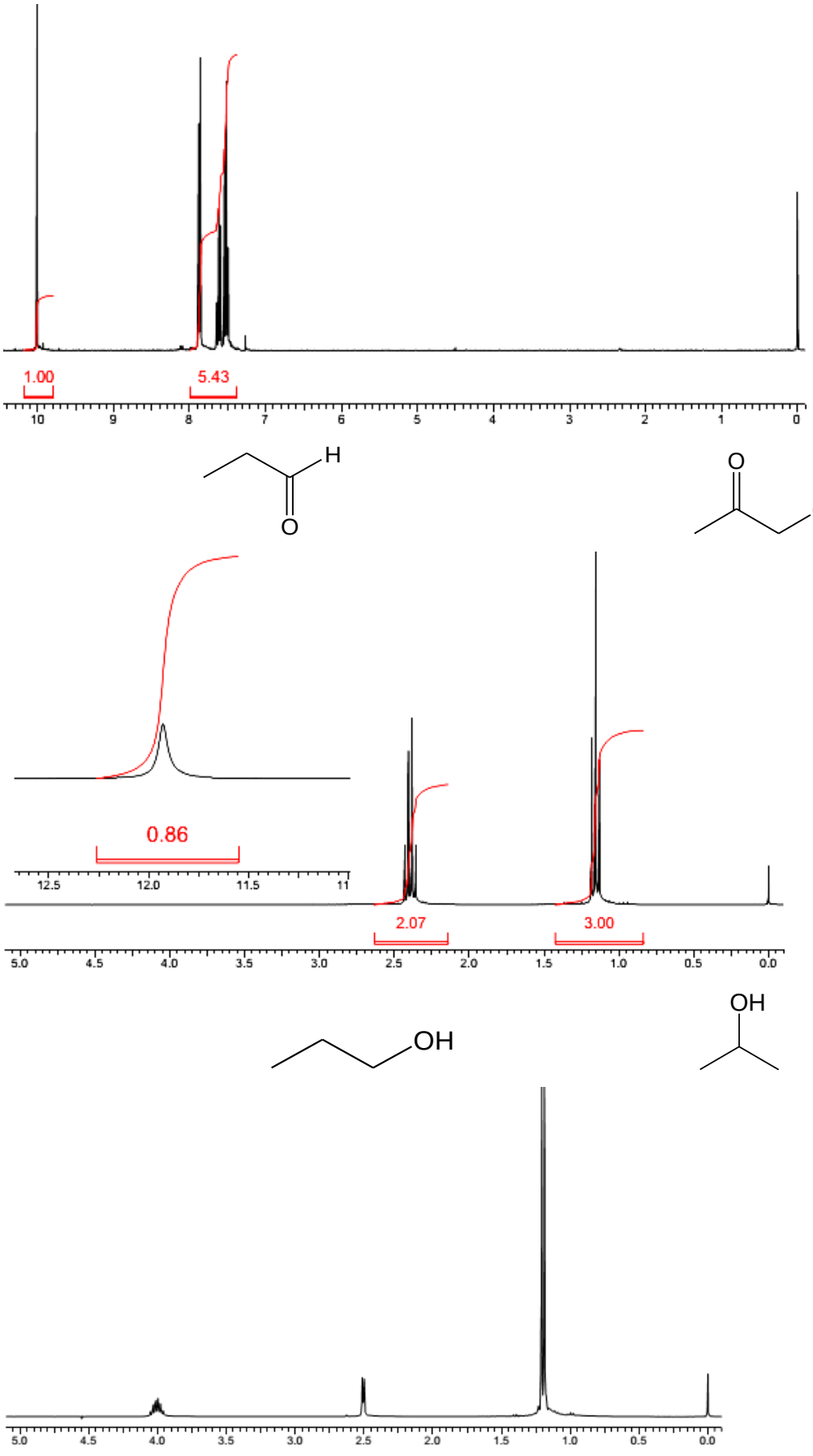
4. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of methoxybenzene*. Explain the coupling.

5. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of isopropyl ethyl ether*. Explain the coupling.

* Consider only the spin-spin interaction of geminal and vicinal proton — ^{2}J and ^{3}J.

6. Find the compound corresponding the spectrum proposed. Explain your choice.

Phenol or benzaldehyde



7. Based on chemical shifts, integrity and coupling distinguish the substances proposed by means of NMR ^{1}H spectroscopy.

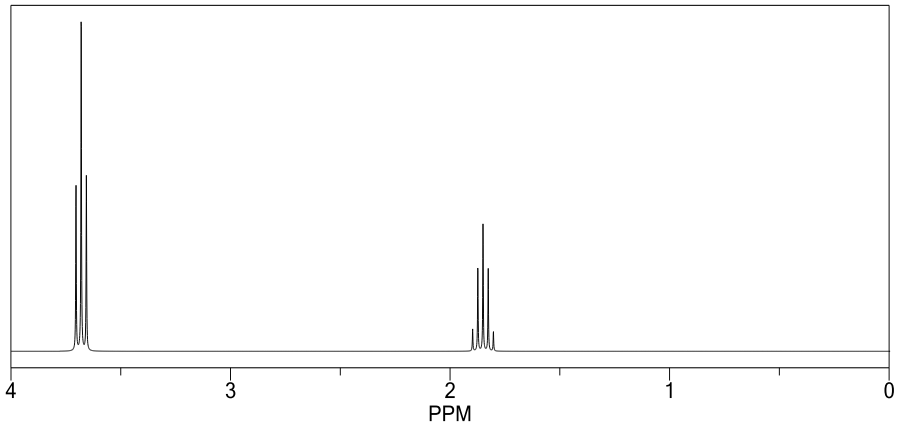
Diethyl ether and methyl ethyl ether

Methanal and acetone

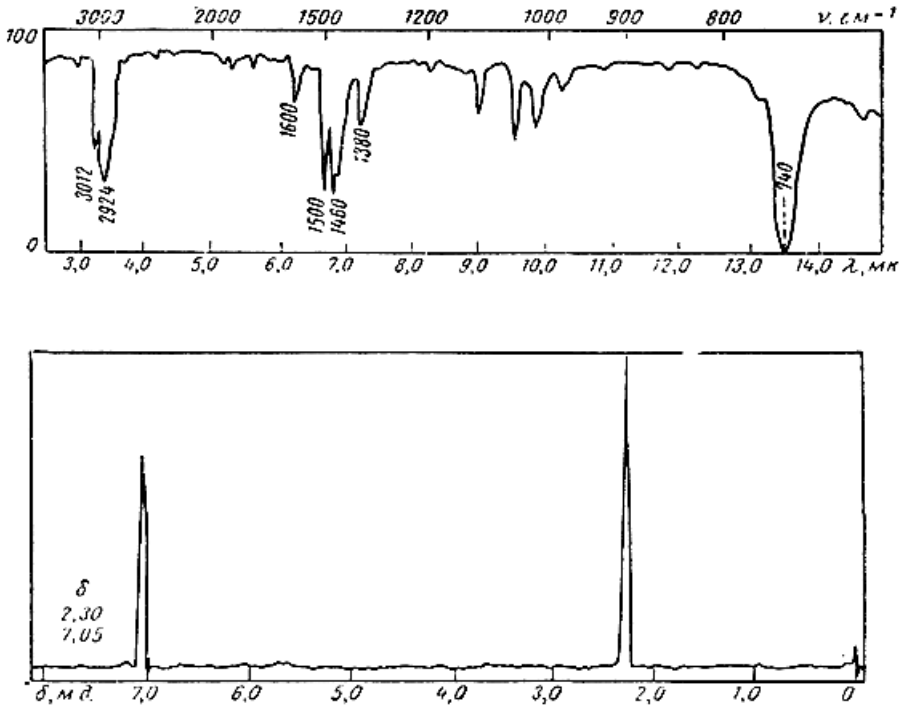
Benzene, toluene, *para*-xylene

Salicylic and acetylsalicylic acids

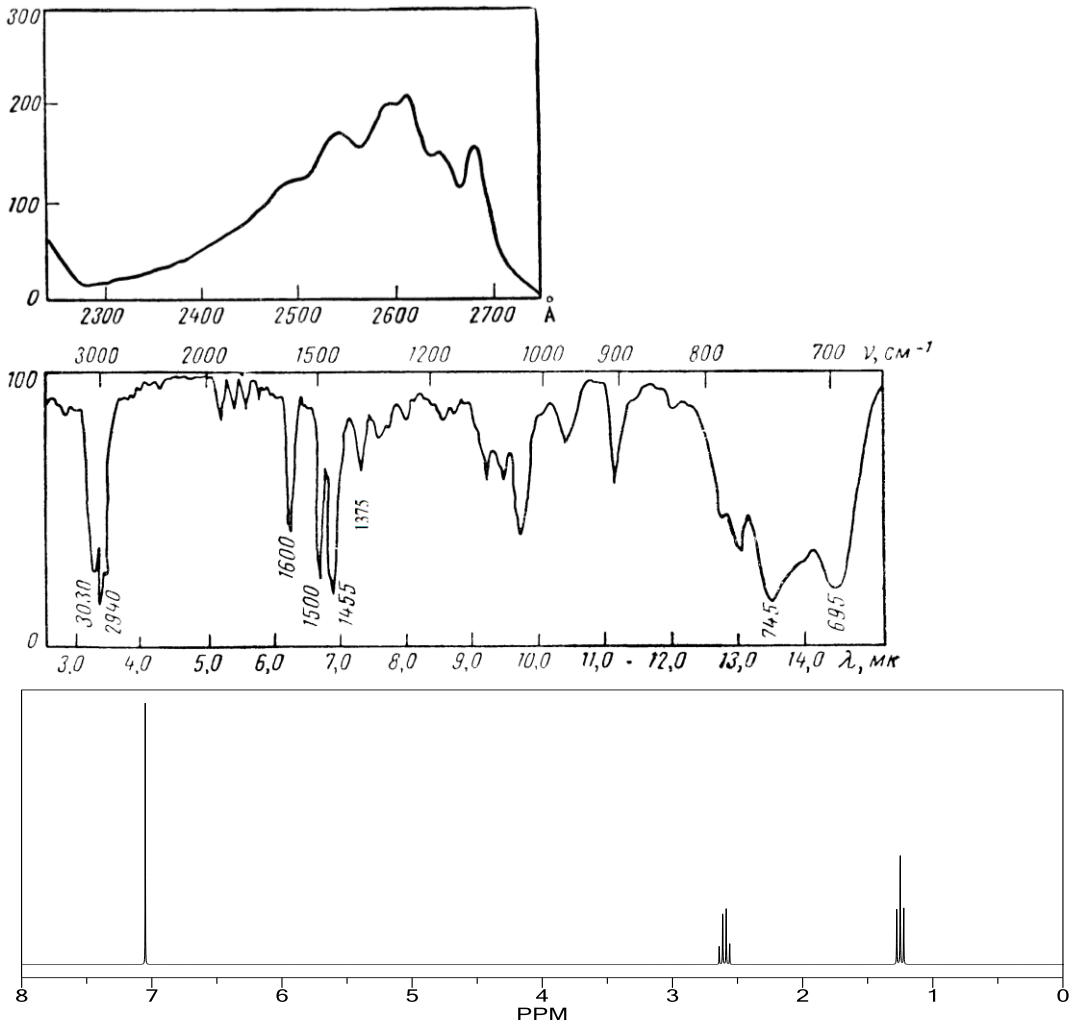
8. Which of isomeric dichloropropanes correspond NMR ^{1}H spectrum proposed. Explain your choice.



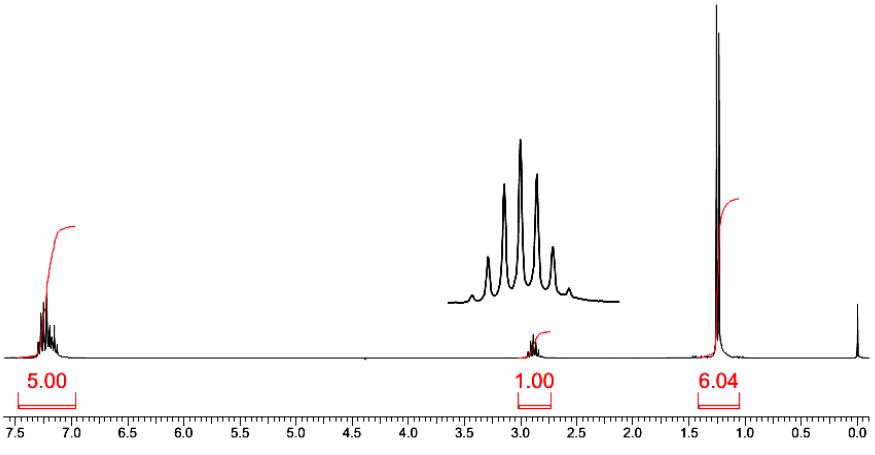
9. Determine the structure of the compound C_8H_{10} based on IR and NMR ^1H spectra.



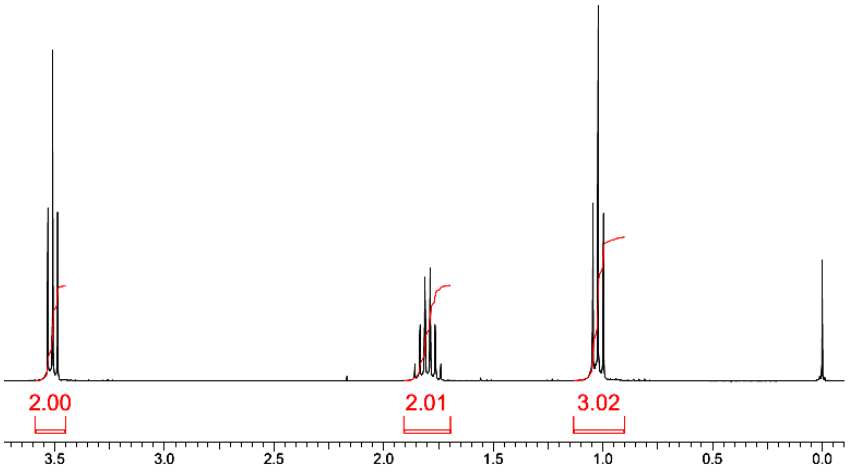
10. Determine the structure of the compound C_8H_{10} based on UV, IR and NMR ^1H spectra.



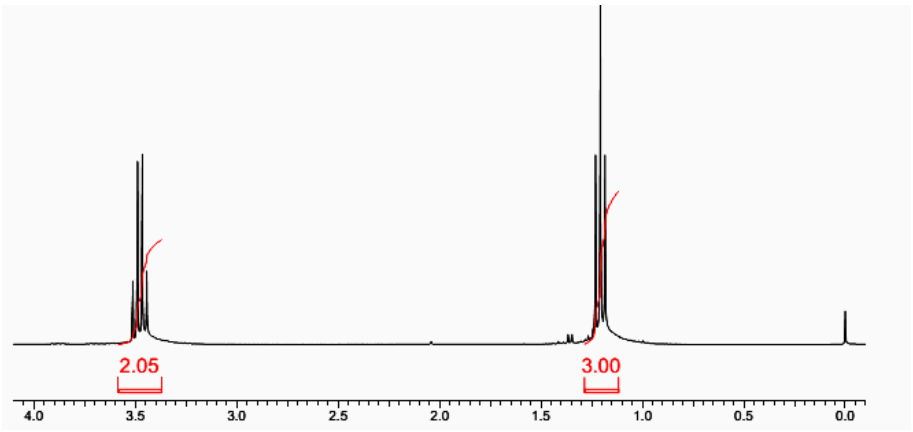
11. Determine the structure based on NMR ^{1}H spectra and molecular formula.



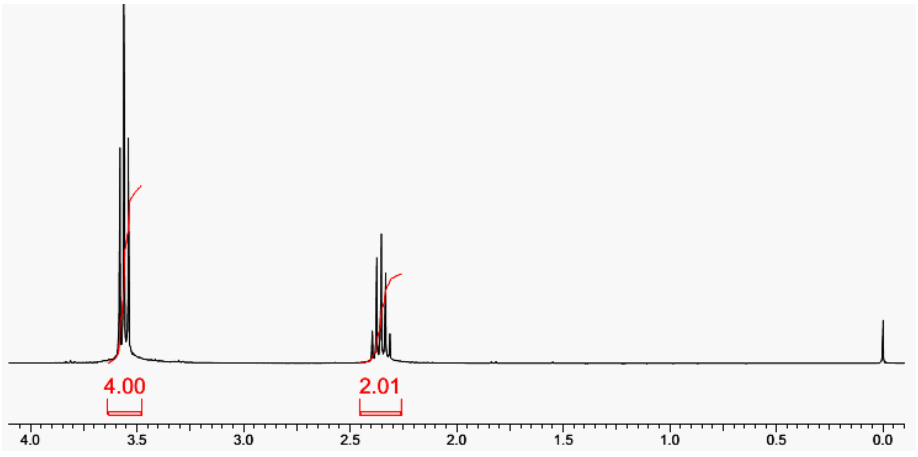
C_9H_{12}



C_3H_7Cl

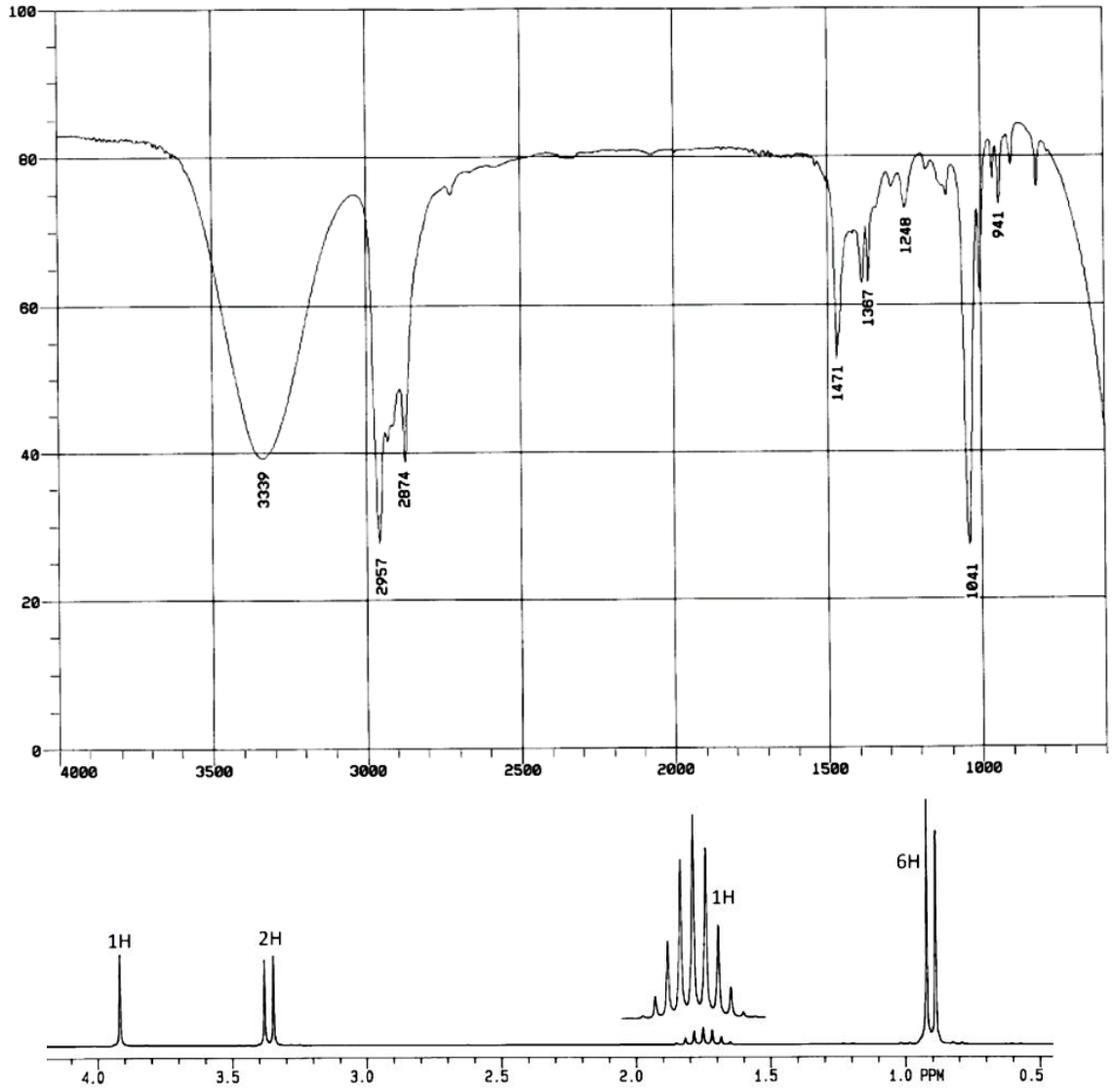


$C_4H_{10}O$

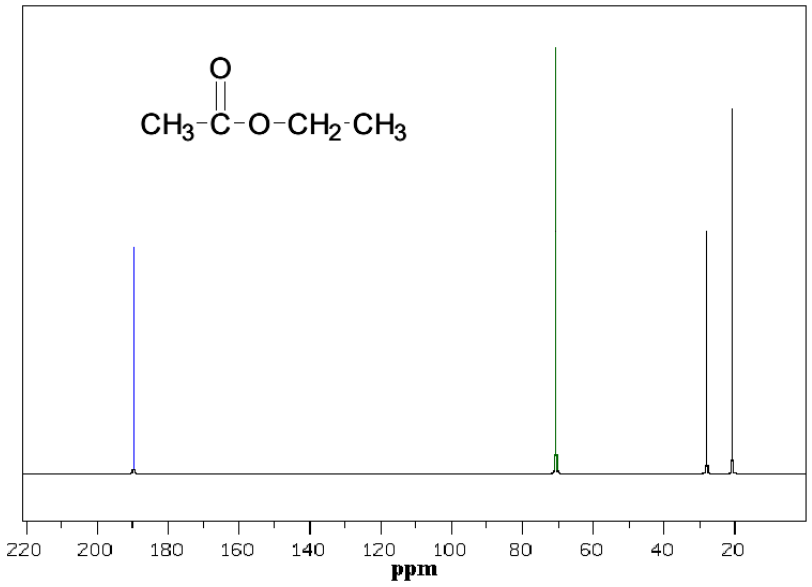


$C_3H_6Br_2$

12. Determine the structure of compound $C_4H_{10}O$ based on spectra proposed.



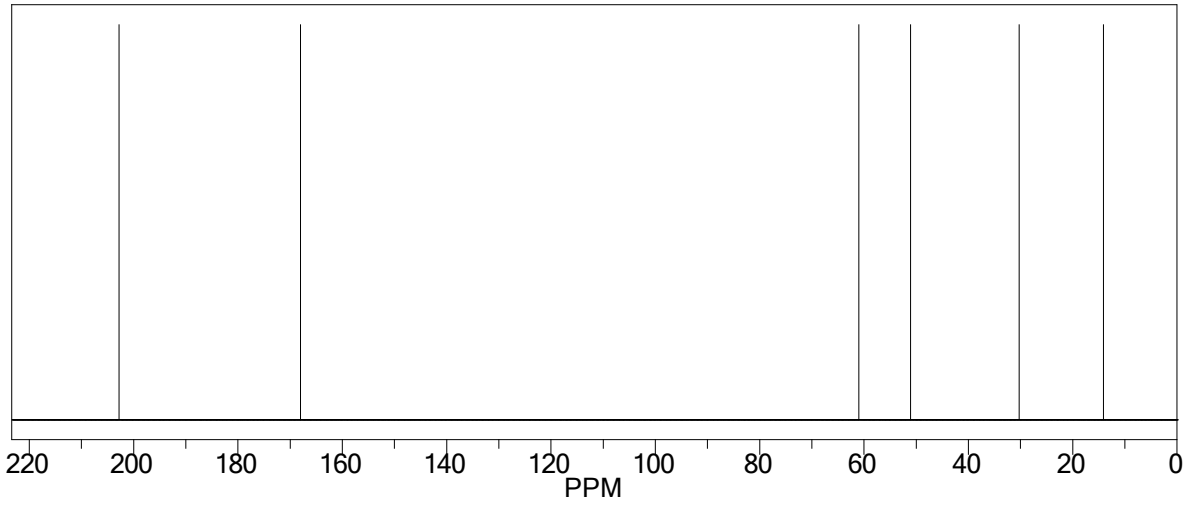
13. Explain the shifts in NMR ^{13}C spectrum*.



* Spectrum both carbon and proton decoupled.

14. Predict chemical shifts in NMR ^{13}C and ^{1}H spectra of 3-methoxy-1-methylbenzene.

15. Explain the shifts in decoupled NMR ^{13}C spectrum of acetoacetic ester. Predict the coupling $^{1}J_{CC}$, $^{2}J_{CC}$, $^{3}J_{CC.}$



Signature of the instructor:

LABWORK № 7
CONTINUOUS ASSESSMENT № 1. STRUCTURE AND NOMENCLATURE OF THE ORGANIC COMPOUNDS. ACADEMIC RESEARCH № 1

Remind the program material from topics 1 to 5.

Recommended literature: study the literature from topics 1 to 5.

Questions to the concluding test:

1. Constitution and isomerism of the organic compounds.
2. Classification of the organic compounds.
3. IUPAC nomenclature of the organic chemistry.
4. Organic chemistry laboratory: equipment, glassware and reagents.
5. Chemical bonding in the organic compounds.
6. Charge distribution in the organic compounds. Induction and mesomerism. Electron donating and electron withdrawing substituents.
7. Conjugated systems. Conjugation energy.
8. Aromaticity. *Huckel's* rule. Aromaticity of benzoic and non-benzoic systems.
9. Configuration and conformations.
10. Spatial molecular models and formulas.
11. Chirality and symmetry of molecules.
12. Diastereomers and enantiomers.
13. Conformational analysis of aliphatic and cyclic compounds.
14. Stereochemistry in life systems.
15. Classification of the organic reactions (by reaction change and reaction type).
16. Variables of the organic reactions Acidity and basicity (the main principles of *Brønsted* and *Lewis* theories, examples of *Brønsted* and *Lewis* acids and bases).
17. Reactant and reagents.
18. Nucleophiles and electrophiles.
19. Reaction characteristics and factors that influence reactions (energetics, electronic, steric, stereoelectronic and solvent effects.
20. Mechanisms of the organic reactions (basic concepts, steps of chemical reaction and intermediates, the arrow notation and writing of reaction mechanisms).
21. The main classes of biologically active substances from natural raw materials. Their acidic and basic properties.
22. Methods of separation and purification of substances from natural raw materials.
23. Solubility and use of solvents in organic chemistry.

LABWORK № 8, 9
NONAROMATIC HYDROCARBONS AND ALKYL FRAGMENTS

Objective: to study the structure and properties of nonaromatic hydrocarbons.

Recommended literature

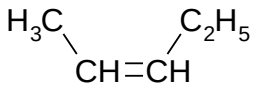
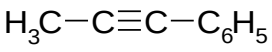
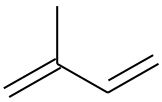
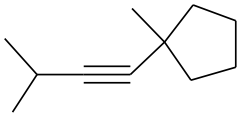
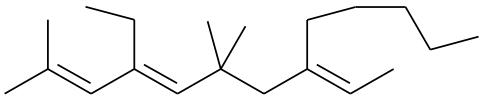
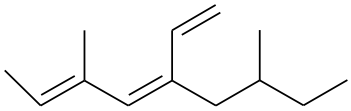
Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

1. Structure and nomenclature of hydrocarbons.
2. Addition reaction to multiple bond.
3. Allylic substitution in alkenes.
4. Substitution of acetylenic hydrogen.
5. Addition reactions to dienes.
6. Redox reactions of hydrocarbons.
7. Polymerization of unsaturated hydrocarbons.
8. Hydrocarbon identification.

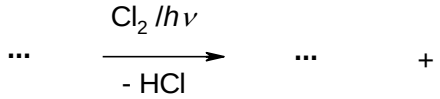
PRACTICE PROBLEMS

1. Give IUPAC names to following compounds.

2. Discuss and write all steps of the mechanism of methane chlorination under irradiation.

3. Write and name all of the structural isomers which are formed in monochlorination of 2-methylbutane during irradiation. Calculate the ratio of isomers (rates of substitution for primary / secondary / tertiary hydrogens correspond as 1/3/8). Indicate chiral centers in halides. For chiral halides draw stereoformulas of enantiomeric pairs and designate the configuration (R-/S-) of chiral centers.



2-Methylbutane

4. Draw examples of cumulated, conjugates and unconjugated dienes C_6H_{10}. Give them the names.

5. Draw a pair of diastereomers for:

3,5-Dimethylhex-3-ene

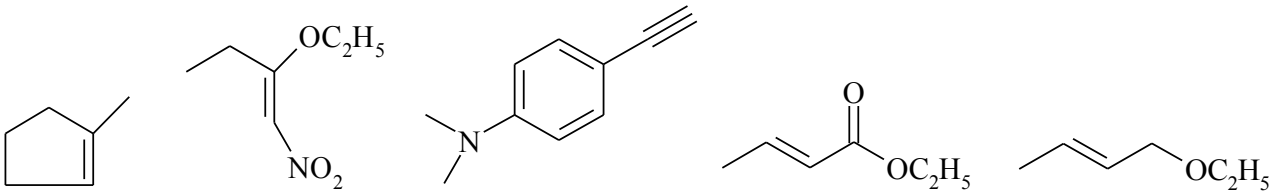
Penta-2,4-diene

6. Draw a pair of enantiomers for:

3-Methylcycloxene

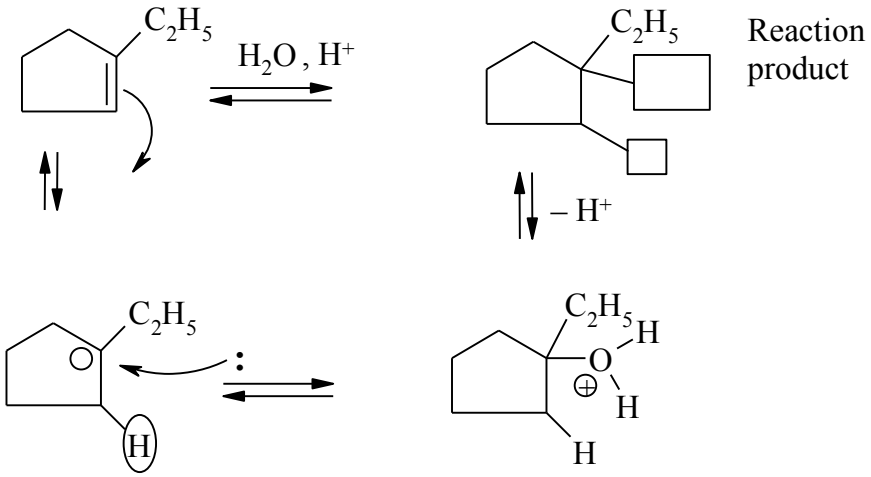
Penta-2,3-diene

7. Show graphically the influence of substituents on distribution of electrons in double bond. Indicate the effects (induction/mesomerism) and a cumulative action of the substituents (donor/acceptor).

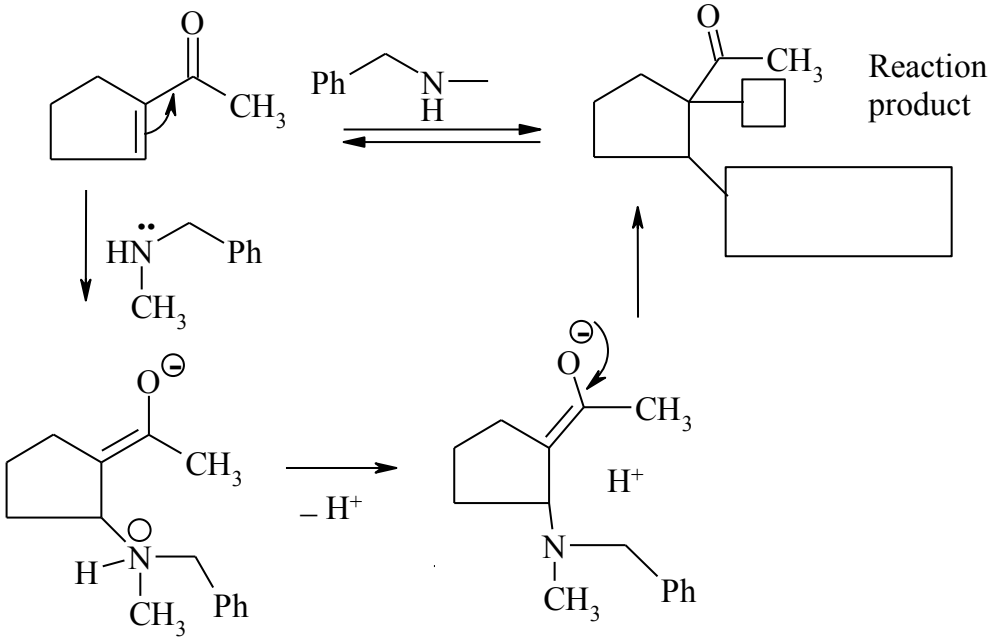


8. Complete the following schemes (add atoms, arrows, charges). Discuss the mechanism and predict the selectivity. Explain why amination is possible only to double bond substituted with acceptor.

Hydration



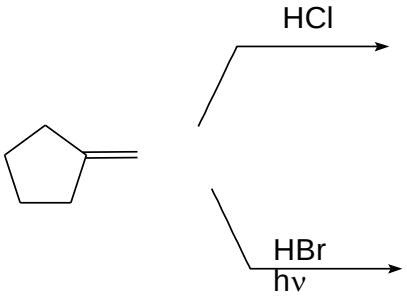
Amination



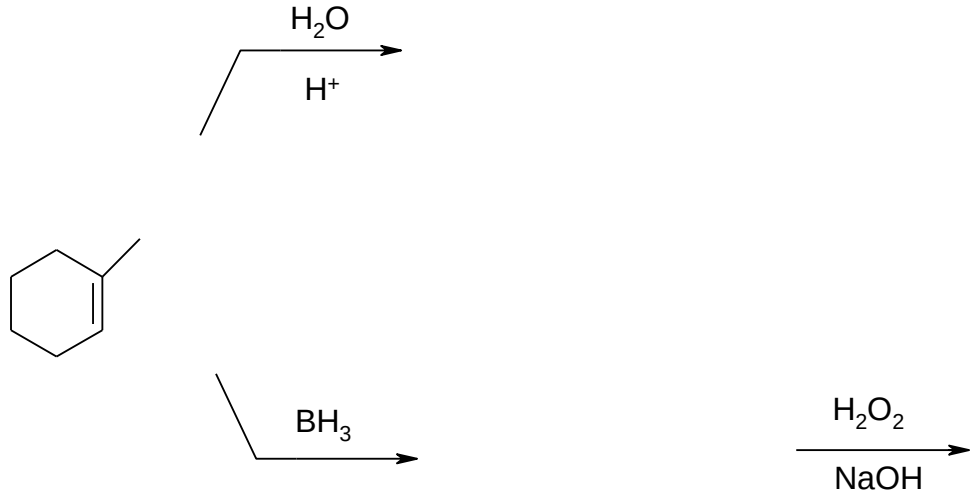
9. Write constitutional formulas of substrates and products of addition reactions.

Hydrocarbon	Reagent	Product formula and name
Pent-1-ene	$\xrightarrow{Br_2}$	
But-2-ene	$\xrightarrow{HCl}$	
Propyne	$\xrightarrow{HCl(equim.)}$	
But-2-yne	$\xrightarrow{HCl(ex.)}$	
2-Methylbut-1-ene	$\xrightarrow{H_2O/\,H^+}$	
1-Methylcyclohexene	$\xrightarrow{C_2H_5OH/H^+}$	
But-1-yne	$\xrightarrow{H_2O/\,H^+,\ Hg_2^{+}}$	
But-2-yne	$\xrightarrow{C_2H_5OH/H^+}$	
hex-3-yne	$\xrightarrow[t]{C_6H_5CH_2NHCH_3}$	
But-2-ene	$\xrightarrow{KMnO_4/\,H^+,\ 0^oC}$	
1-Ethylcyclohexene	$\xrightarrow[(ROOR)]{HBr}$	
Cyclopentene	$\xrightarrow{C_6H_5COOOH}$	

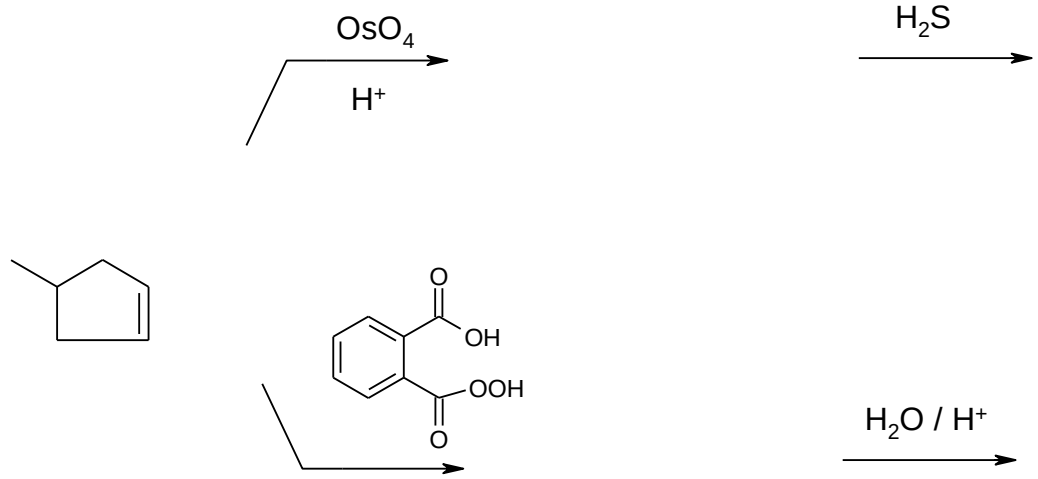
10. Write reaction schemes of hydrohalogenation. Describe the mechanisms and explain the regioselectivity (preference for the formation of one constitutional isomer over another).



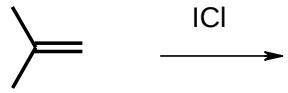
11. Write reaction schemes of alcohol formation. Using diagrams, mechanisms with curly arrows, and/or short paragraphs, explain the regioselectivity of both processes.

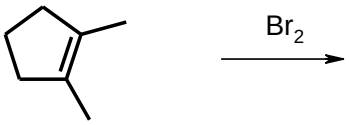


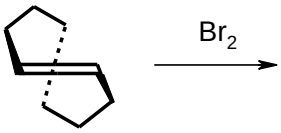
12. Write reaction schemes of diol hydroxylation. Using diagrams, mechanisms with curly arrows, and / or short paragraphs, explain the selectivity of both processes.



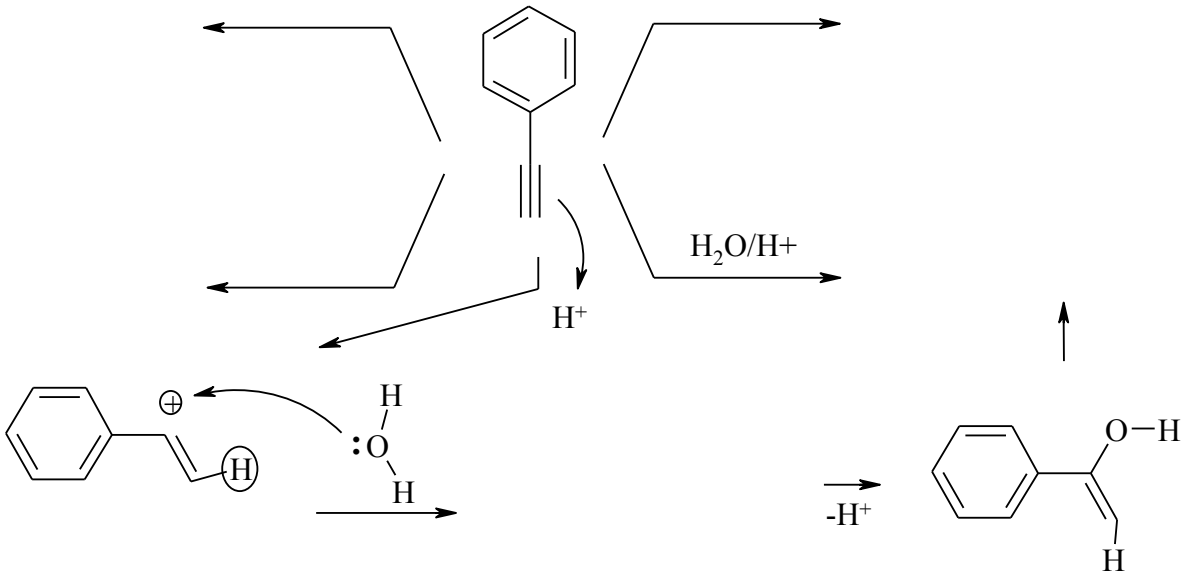
13. Write reaction schemes of halogenations. Describe the mechanisms and explain the selectivity.







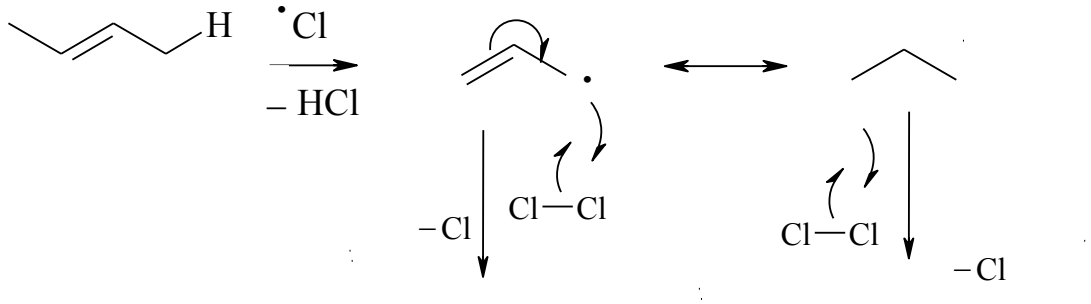
14. Finish the schemes of acid catalyzed reactions of phenyl acetylene with water, ethanol, acetic acid and isopropylamine. Complete the mechanism for *Kucherov* reaction.



15. Write reaction schemes of nucleophilic addition of sodium phenoxide, diisopropylamine, phenyl mercaptane to ethinylcyclohexane.

16. Explain the mechanism of the reaction between cyclopentylacetylene and morpholine.

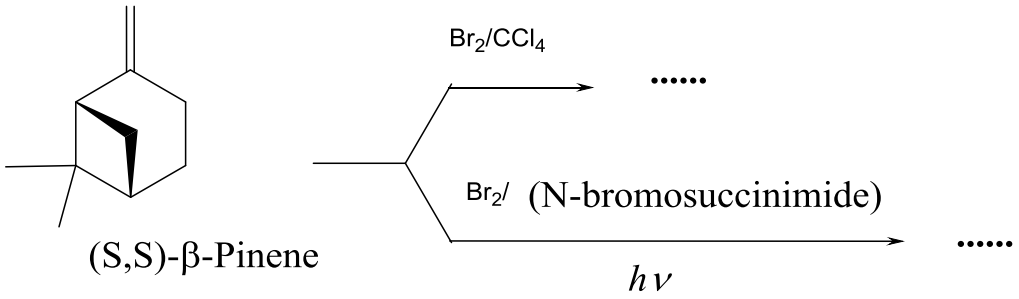
17. Complete the scheme of allylic substitution of but-2-ene. Explain the stability of intermediate allylic radical and formation of isomeric halides.



Product 1 Product 2

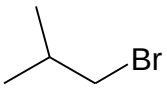
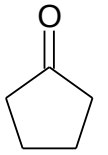
18. Write reaction schemes for allylic hydroxylation (SeO_2) and bromination (N-bromosuccinimide) of hex-1-ene. Explain the mechanism and factors facilitating the substitution of allylic hydrogen.

19. Write reaction schemes of bromination of β-pinene. Explain chemoselectivity.



(S,S)-β-Pinene

20. Write constitutional formulas of substrates and products of the acetylenic hydrogen substitution.

Alkyne	Acetylenide anion	Product
Propyne	$NaOCH_3$	C_2H_5Br
Ethyl acetylene	$NaNH_2$	
Ethyne	NaOH	
Acetylene	$Ag(NH_3)_2OH$	

21. Write reaction schemes for 1,2- and 1,4-additions (bromination and hydrogenation) to cyclohexa-1,3-diene. Explain the regioselectivity of the process.

22. Draw *s-cis* and *s-trans* forms of 2,3-dimethylpenta-1,3-diene. Write *Diels-Alder* reaction of this substance with methoxyethene

23. Write *Diels-Alder* reaction for next reactants:

2,3-Dimethylbuta-1,3-diene and nitroethene

2,3-Dimethoxybuta-1,3-diene and acrylonitrile

Cyclohexa-1,3-diene and methyl acrylate

24. Write reaction schemes and give the names of the polymerization products from next monomers:

Vinyl chloride $\longrightarrow$

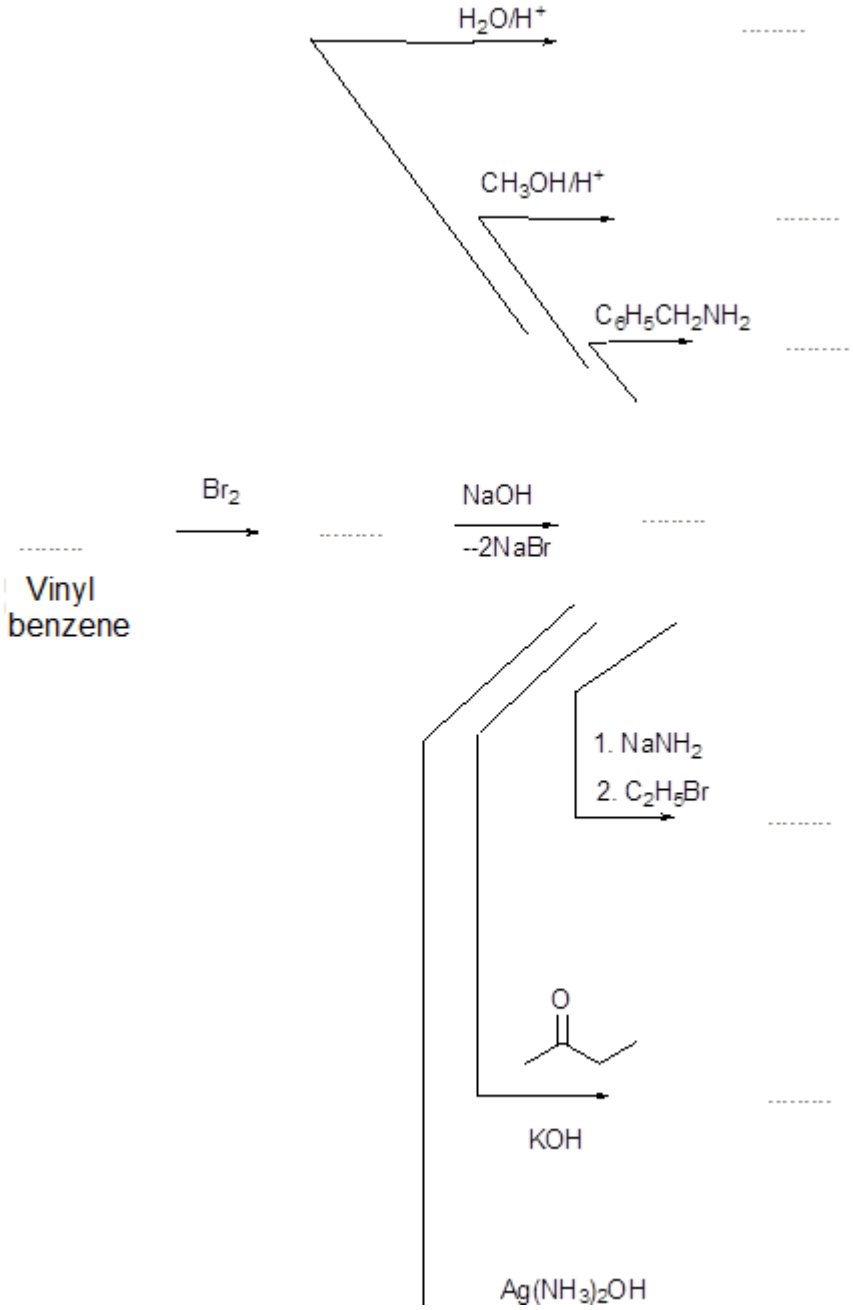
2-Methylbut-2-ene $\longrightarrow$

25. Explain radical mechanism for propene polymerization.

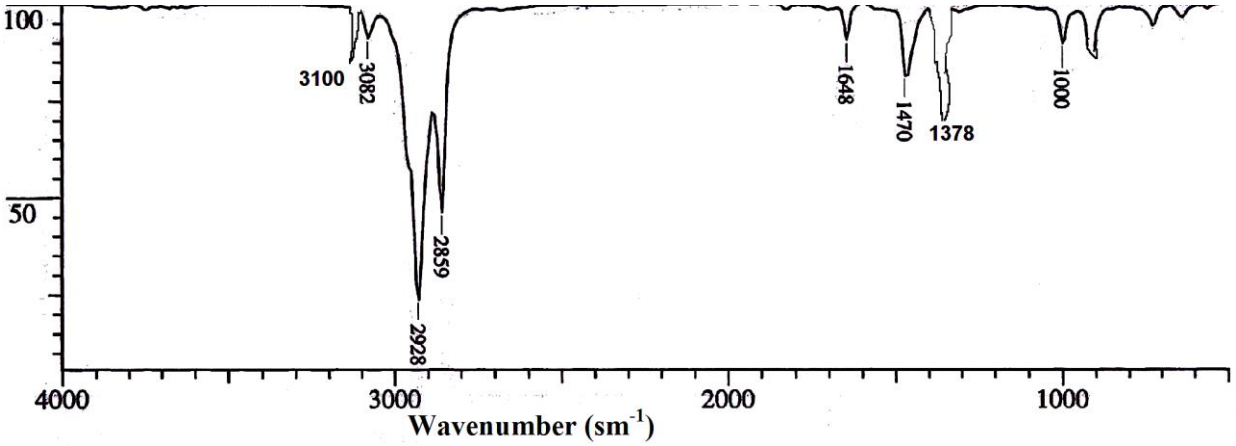
26. Write reaction schemes for 1,2- and 1,4-addition polymerization of isoprene.

27. Write reaction scheme for copolymerization of buta-1,3-diene and styrene (head-tail).

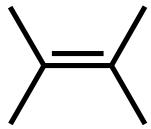
28. Fill the blanks in scheme.



29. Draw the constitutional formular of the substance which IR-spectrum is shown below. Explain the position of bands.



30. Predict chemical shifts (approximately), coupling and integrity of NMR ^{1}H spectra for substances shown. Explain your answer.



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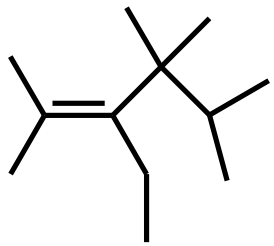
0 ppm.



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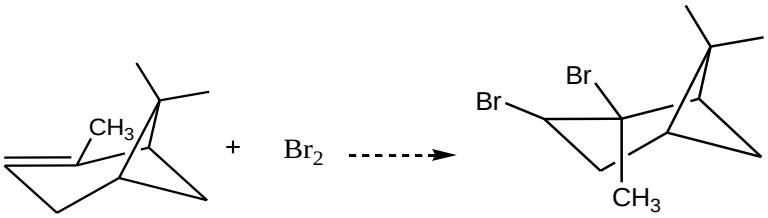
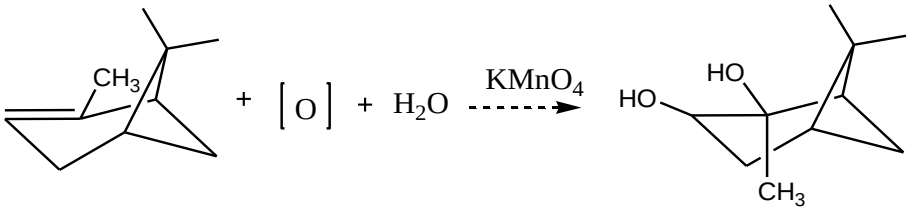
0 ppm.

Experiment 1. Chemical test on double bond with bromine water.



Place 2 drops of α-pinene* in a dry test tube followed by addition of few drops of bromine water*. Shake the mixture. Fix the change of bromine water color.

Experiment 2. Chemical test on double bond with potassium permanganate.



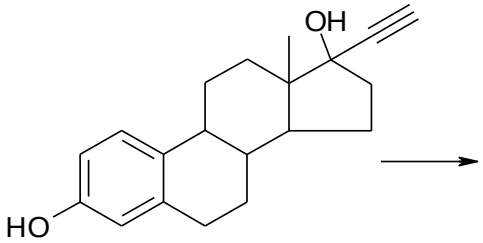
α-pinene α-pinene glycol

Place 2 drops of α-pinene* in a dry test tube followed by addition of few drops of potassium permanganate (14) solution. Shake the mixture. Fix the change of potassium permanganate solution color.

Explain why both solutions became colourless.

Explain why potassium permanganate oxidation for diol syntheses is limite.

Complete the scheme of the reaction between ethynylestradiol with an ammonia solution of copper (I) chloride.



Signature of the instructor:

LABWORK № 10
AROMATIC HYDROCARBONS AND ARYL FRAGMENTS

Objective: to study the structure and properties of aromatic hydrocarbons.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

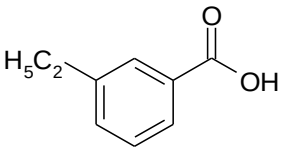
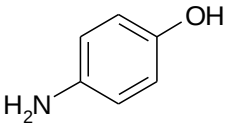
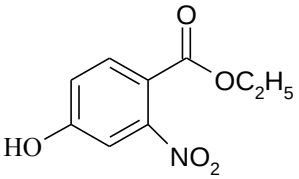
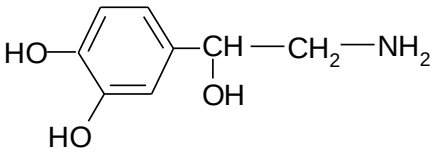
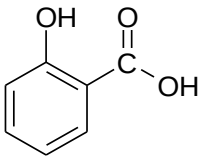
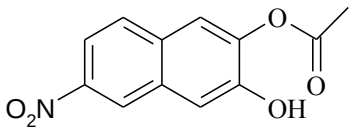
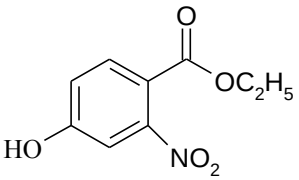
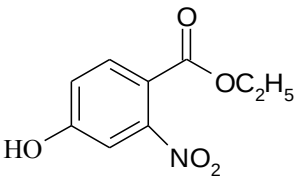
2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of aromatic hydrocarbons.
2. Aromaticity of arenes.
3. Reactivity of arenes: reactions on a benzene ring vs reactions on a side chain.
4. Radical substitution in a side chain.
5. Addition and oxidation of a ring fragment.
6. Mechanism S_EA: general scheme, the influence of substituent and nature of electropjile.
7. Examples of aromatic halogenation, nitration, sulfonation, alkylation and acylation.
8. Chemical and instrumental detection of arenes.

PRACTICE PROBLEMS

1. Give IUPAC names to following compounds.

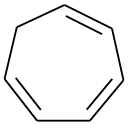
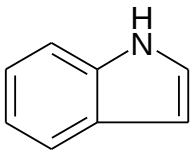
	
	
	
	

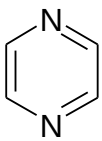
2. Convert the name to structure. Give IUPAC names (substitutive approach).

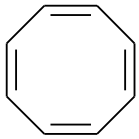
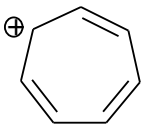
Benzyl chloride	*p*-Sulfobenzoic acid
2,3-Dihydrophenanthrene	Phthalic acid
Anthracene	Anthraquinone
1,4-Dibromo-1,4-dihydronaphthalene	α-Naphthylamine

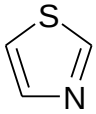
3. Draw the formulae of all the isomers (including stereoisomers) of monosubstituted benzene ($C_{10}H_{14}$). Give the names.

4. Determine which of the following compounds contain aromatic fragments. Discuss their aromaticity in terms of the *Hückel* concept.

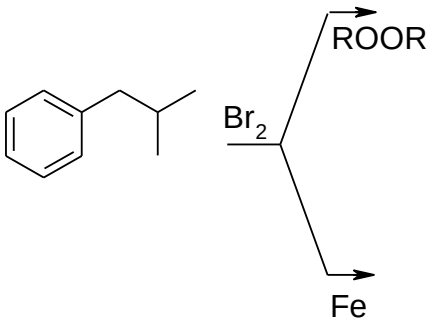








5. Write the reaction of isobutyl benzene with bromine in different conditions. Explain the regioselectivity and indicate the type of the reagent and reaction.

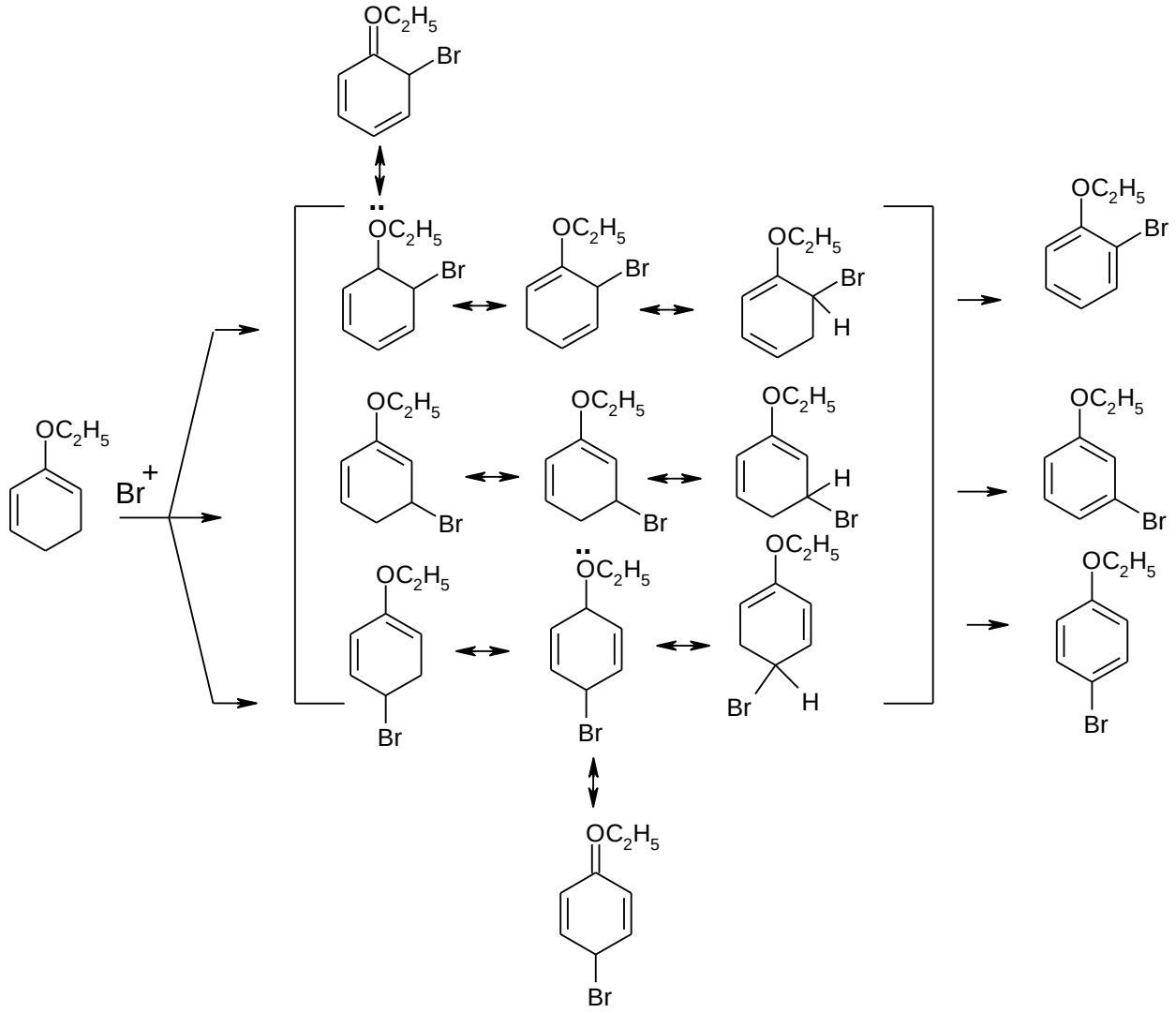


6. Write the products of toluene oxidation by SeO_2, MnO_2 and $KMnO_4$. Explain why toluene is less toxic compare to benzene under enzymatic oxidation *in vivo.*

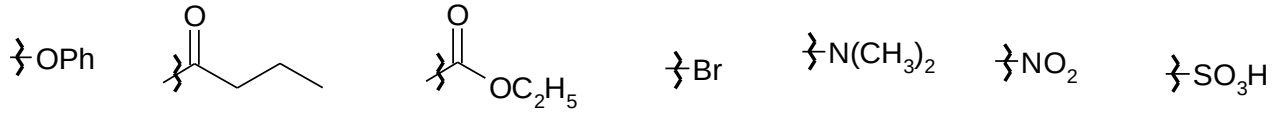
7. Write the reactions schemes of oxidation and reduction of naphthalene in drastic and mild conditions.

8. Write the reactions schemes of bromination, oxidation and *Diels-Alder* addition to anthracene. Explain the mechanism.

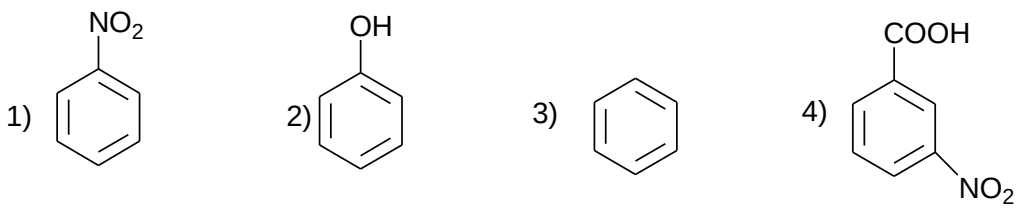
9. Draw arrows and charges to show electron-movement in the following two steps (draw arrows for each step and for all the resonance hybrids). Detect electrophile, rate limiting step and explain the formation of major products.



10. For the following substituents, classify each as electron-donating or electron-withdrawing ("D" or "W"); as activating or deactivating ("act" or "dea"); and as *ortho-para* directing or *meta* directing ("*o/p*" or "*m*").

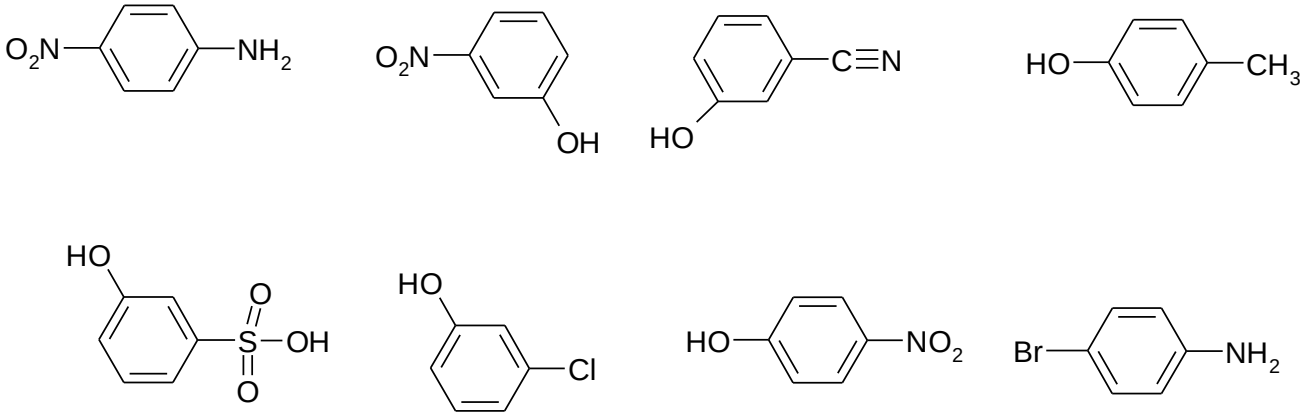


11. Rank substances in context of their reactivity in electrophilic substitution.



12. Explain why ester (-OCOR) and amide groups (-NHCOR) are less activating than ether (-OR) and amino ($-NH_2$) groups; and why amino ($-NH_2$) is better activator than alcohol (-OH) group.

13. Predict the regioselectivity for further substitution of disubstituted benzenes by looking at the cumulative effects of both substituents. As a suggested method, look at each of the substituents, label their directing effects, then indicate the sites where they would promote reactivity with small arrows.



14. Design a synthetic scheme leading to pure 2-bromobenzoic acid from toluene based on protection group strategy.

15. Design a synthetic scheme to obtain 1-bromo-2-isoamyl-4-nitrobenzene starting from benzene.

16. Discuss the mechanisms of alkylation reactions. Propose catalysts to generate electrophiles.

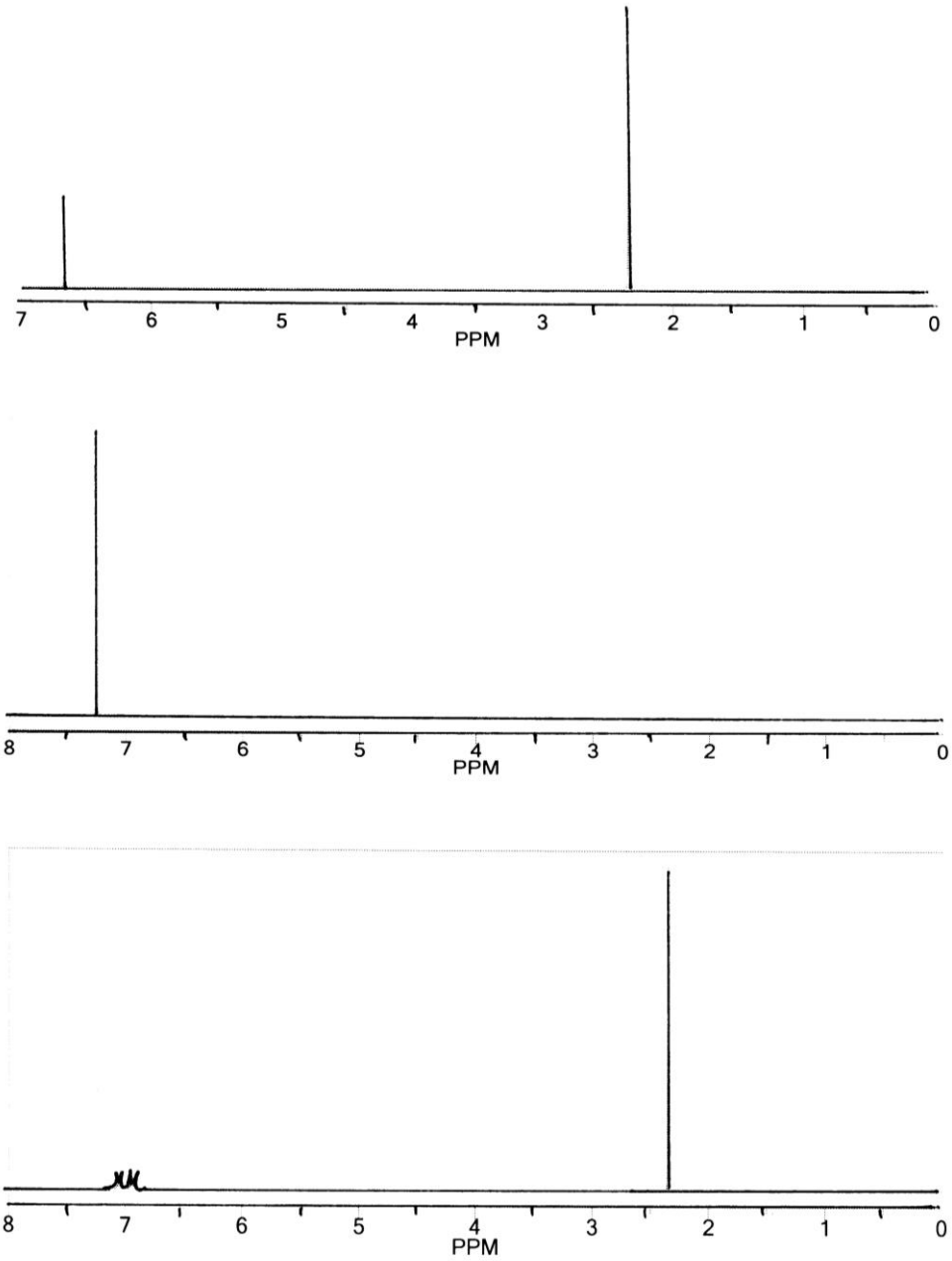
Benzene with propene

Methoxybenzene with *tert.*-butyl alcohol

Intramolecular cyclization of (5-bromohexyl)benzene

Explain why alkylation is not applicable to synthesize 7-methyloctylbenzene from benzene. Propose the synthetic scheme *via* acylation reaction.

17. Distinguish spectra for benzene, 1,2-dimethylbenzene and 1,3,5-trimethylbenzene. Explain your choice.



18. Predict for *para*-diacetoxybenzene frequency bands in IR spectrum as well as chemical shifts, J-coupling and integrity in the ^{1}H NMR spectrum.

EXPERIMENTAL SECTION

Experiment 1. Ignition test for high degrees of unsaturation.

Heat a small samples benzoic acid (44) on a spatula. First, hold the sample near the side of a *Bunsen* burner to see if it melts normally and then burns. Heat it in the flame. Do the same with samples of α-pinene*, and hexane*. Give your observations. Aromatic compounds often burn with a smoky flame.

A sooty yellow flame is an indication of an aromatic ring or other centers of unsaturation.

Experiment 2. Bromination test on arenes.

Place 3 drops of bromine water* in 3 test tubes, then add to the first tube 2 drops of benzene*, and to the second — 2 drops of toluene*, and to the third 2 drops of or aniline*. Shake both tubes vigorously.

The disappearance of the yellow coloring means the positive test.

How to promote the bromination of benzene?

Experiment 3. Permanganate test on arenes.

Place in two tubes 2 drops of 2 % aq. $KMnO_4$ (14) and 2 drops of H_2O followed by the addition 2 drops of benzene to the first and 2 drops of toluene to the second tube. The disappearance of the pink-violet coloring means the positive test. Explain why we see no positive test for both tubes. Add to each tune 2 drops of 10 % sulfuric acid and heat the mixtures. Fix the change of the coloring in one of the tubes. Explain your observation.

Signature of the instructor:

LABWORK № 11
ORGANIC HALIDES. NUCLEOPHILIC SUBSTITUTION VS ELIMINATION

Objective: to study the structure and properties of halogenated hydrocarbons.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

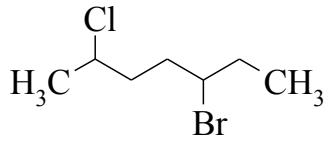
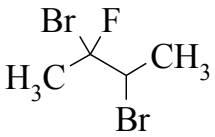
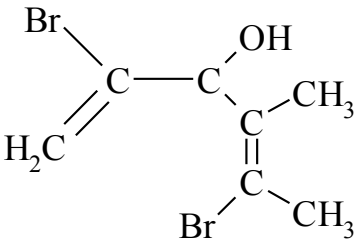
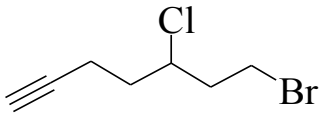
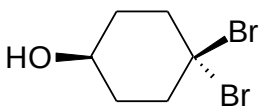
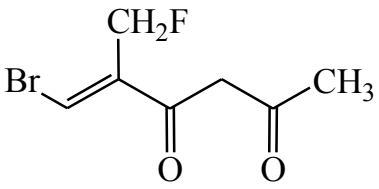
2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of halogenated hydrocarbons
2. Competitive mechanisms of nucleophilic substitution and elimination.
3. S_N1, S_N2 mechanisms.
4. Allyl and benzyl halides. Reasons for higher reactivity in nucleophilic substitution reactions.
5. Reactivity of vinyl and aryl halides.
6. Chemical and instrumental detection of organic halides.

PRACTICE PROBLEMS

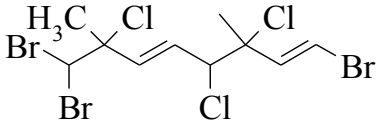
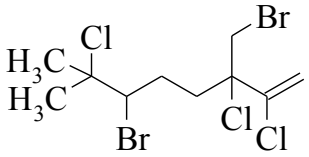
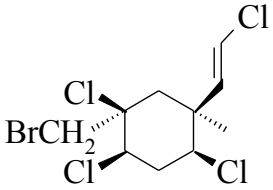
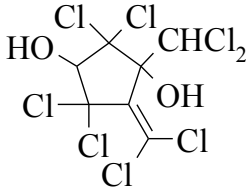
1. Give IUPAC names to following compounds.

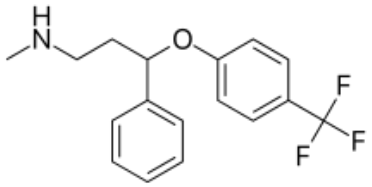
2. Write the structures of the following compounds. Give IUPAC names (substitutive approach). Identify which of the compounds are primary, secondary or tertiary halides. Indicate the reaction centers.

Allyl chloride	Isoamyl chloride
Tert.-butyl bromide	Chloroprene
Benzyl chloride	Methylene chloride
Chloroform	Vinyl chloride

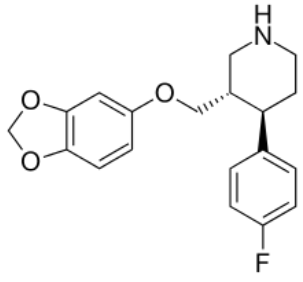
3. Give IUPAC names to following natural compounds:

 It was isolated from the digestive gland of the bearded seal	 *Halomon* is halogenated monoterpene which was first isolated from the marine red algae and being potential anticancer drug
 Violacene (isolated from algae)	 It was isolated from fungi

4. A relatively small size of the fluorine is convenient as fluorine acts as an approximate bioisostere of the hydroxyl group. Chemists using organofluorine strategy try to introduce carbon-fluorine bond to increases the probability of having a successful drug. An estimated 20 % of pharmaceuticals, and 30–40 % of agrichemicals are organofluorines, including several of the top drugs. *Fluoxetine* and *Paroxetine* are selective serotonin re-uptake inhibitors and used as antidepressants.
Find the reactivity centers in both substances. Show graphically the influence of the functional groups on the distribution of charge in benzene ring. Predict solubility of both substances in physiological pH.



Fluoxetine



Paroxetine

5. Write the structural formulas of substances and rank the set of compounds in terms of relative reactivity in S_N2 reactions.

Methyliodide, bromoethane, 2-bromobutane, *tert.*-butyl chloride

Benzyl chloride, bromobenzene, chloromethane, chlorodiphenylmethane

6. Write structural formulas of substances and rank the set of compounds in terms of relative reactivity in S_N1 reactions

Bromoethane, 2-chlorobutane, 1-chloro-1-methylcyclohexane

Benzyl chloride, bromobenzene, chloromethane, chlorodiphenylmethane

7. Complete the reaction schemes. Give systematic names to products. Identify a reaction type.

Halide	Reagent	Product and type of reaction
Chlorocyclohexane	$\xrightarrow{NaI}$	
3-Bromohexane	$\xrightarrow{NaOH/H_2O}$	
3-Bromo-2,4-dimethylpentane	$\xrightarrow{NaOH/C_2H_5OH}$	
1-Bromo-2-methylcyclopentane	$\xrightarrow{KOH/C_2H_5OH}$	
3-Chloro-2-methylbutane	$\xrightarrow{C_6H_5ONa}$	
Benzyl chloride	$\xrightarrow{NH(CH_3)_2}$	
3-Bromo-2-methylpentane	$\xrightarrow{KCN}$	
2-Bromo-3-methylbutane	$\xrightarrow{HC\equiv CNa}$	

8. Write the reactions of (S-) iodo-1-phenylpropane with potassium cyanide in methanol and acetone respectively. Explain the stereochemistry of both reactions and why is allyl and benzyl chlorides exhibit increased activity in the nucleophilic substitution.

9. Write the schemes and discuss the mechanisms of the reactions between:

tert.-Butyl bromide and water (t = 100 °C)

Isoamyl bromide and aq. sodium hydroxide

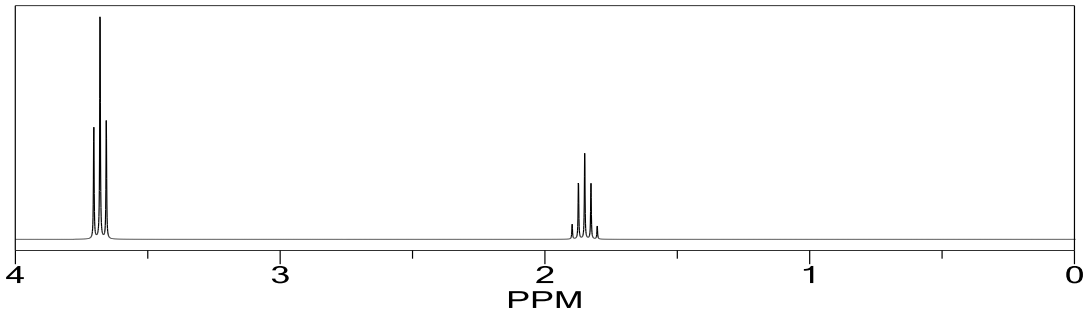
Chlorocyclopentane and alcoholic sodium hydroxide

10. Write an alkylation reaction of the biologically active compounds: *Norepinephrine* (R)-4-(2-amino-1-hydroxyethyl)benzene-1,2-diol), ethanolamine and *Nicotinamide* with methyl iodide. Name the products (including trivial biochemical names). Explain why alkylation with alkylhalides is impossible in living cell and name the group of substances that generate methylation *in vivo.*

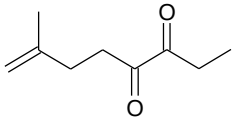
11. Design regioselective synthesis of less (*Hofmann*) and more substituted (*Zaitsev*) alkenes starting from 1-chloro-2-methylcyclohexane and using elimination reactions.

12. Hydrolysis of compound ($C_5H_{11}Br$) gives tertiary alcohol and its dehydrobromination leads to 2-methylbut-2-ene. Find the structure of substrate and write the corresponding reactions.

13. Correlate the NMR ^1H spectrum with the structure of dibromopropane.



14. Predict for substance shown below frequency bands in IR spectrum as well as chemical shifts, J-coupling and integrity in the ^1H NMR spectrum.



EXPERIMENTAL SECTION

All tests presented below can be used for detecting of chloroform, benzyl chloride, bromobenzene, bromobutanes, and any other halogenated hydrocarbons.

Experiment 1. *Beilstein* test.

Any halogenated compound as a positive standard, such as, 1-bromobutane, and any non-halogenated compound, such as butan-1-ol, as a negative standard.

Heat the tip of a copper wire in a burner flame until there is no further coloration of the flame. Let the wire cool slightly, then dip it into the unknown (solid or liquid, e.g. chloroform) and again, heat it in the flame. A green flash is indicative of chlorine, bromine, and iodine; fluorine is not detected because copper fluoride is not volatile. The *Beilstein* test is very sensitive, thus halogen-containing impurities may give false results.

A green flash is indicative of chlorine, bromine, and iodine, but NOT fluorine

Do the same procedure with butan-1-ol. Fix the false test result for assay.

Is Beilstein test applicable for detecting chlorine in nitrogen mustard derivatives of the general formula $RN(CH_2CH_2CI)_2$*, which are used as antitumor agents?*

Experiment 2. Silver nitrate test on chloroform.

Place in tube 3 drops of chloroform and 5 drops of 10 % NaOH (21). Heat the reaction mixture to start boiling. Cool at room temperature. Acidify (indicator) with concentrated Nitric acid. Add 2 drops of 1 % silver nitrate. Record the time required for precipitate to form. If no precipitates are seen after 5 minutes, heat the solution on the steam bath for approximately 5 minutes. Note whether a precipitate forms in the test tube.

Experiment 3. Silver nitrate test on benzyl and aryl halides.

Place in two tubes 2 drops of chlorobenzene and 2 drops of benzyl chloride and add to each 6–8 drops of water. Heat to boiling and add to both tubes 1–2 drops of 1 % silver nitrate solution. Observe the formation of precipitate only in one tube. Which reagent was hydrolyzed?
Write the reaction scheme of hydrolysis.

Explain the reason for the ease of hydrolysis of one of the reagents and resistance to hydrolysis of the other.

Signature of the instructor:

LABWORK № 12
HYDROXY- AND THIODERIVATIVES, ETHERS, SULFIDES

Objective: to study the structure and properties of hydroxy- and thio-derivatives, ethers, sulfides.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

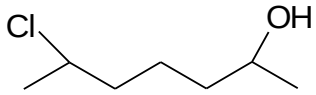
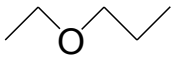
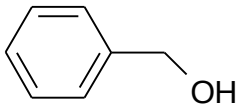
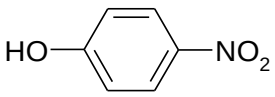
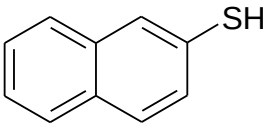
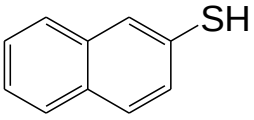
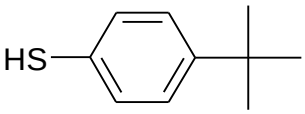
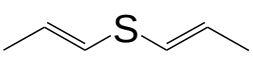
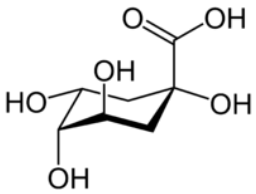
2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of alcohols, phenols, thiols, ethers and sulfides.
2. Acidic/basic and nucleophilic properties of alcohols, phenols, thiols and their conjugated bases.
3. Reactivity of alcohols and phenols.
4. Alcohols as substrates in nucleophilic substitution and elimination reactions.
5. Oxidation of alcohols, phenols and thiols *in vitro* and *in vivo.*
6. Special properties of polyols as polyfunctional compounds.
7. Ethers and esters in synthesis and life processes. Ethers as solvents.
8. Chemical and instrumental detection of amines and azo compounds.

PRACTICE PROBLEMS

1. Give IUPAC names to the following compounds.

	
	
	
	
 Quinic acid	This acid is a versatile chiral starting material for the synthesis of new pharmaceuticals. A medication for the treatment of influenza A and B strains called *Tamiflu* has been successfully developed and launched into the market.

2. Write the structures of the following compounds. Give IUPAC names (substitutive approach). Indicate reaction centers.

Phenetole (phenyl ethyl ether)	*p*-Cresol
Divinyl ether	Benzyl mercaptane
Anisole	Hydroquinone
Benzyl 2,4-dinitrophenyl sulfide	Butan-1-thiol

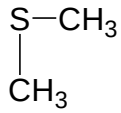
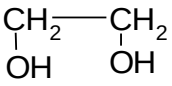
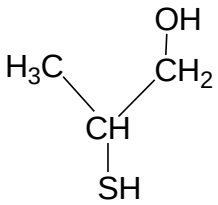
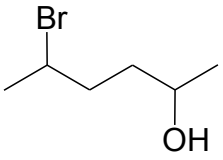
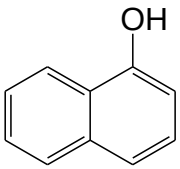
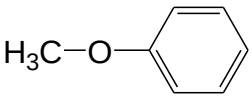
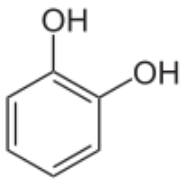
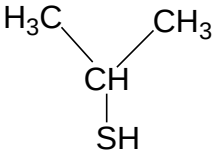
3. Write constitutional formulas of substance and rank the set of compounds in terms of relative acidity.

Methanol, phenol, glycerol, methanthiol

Methanol, 2-methylpropan-2-ol, trifluoromethanol

2,4,6-Trinitrophenol, 1-amino-3-hydroxybenzene, hydroquinone, catechol

4. Indicate reaction centers:

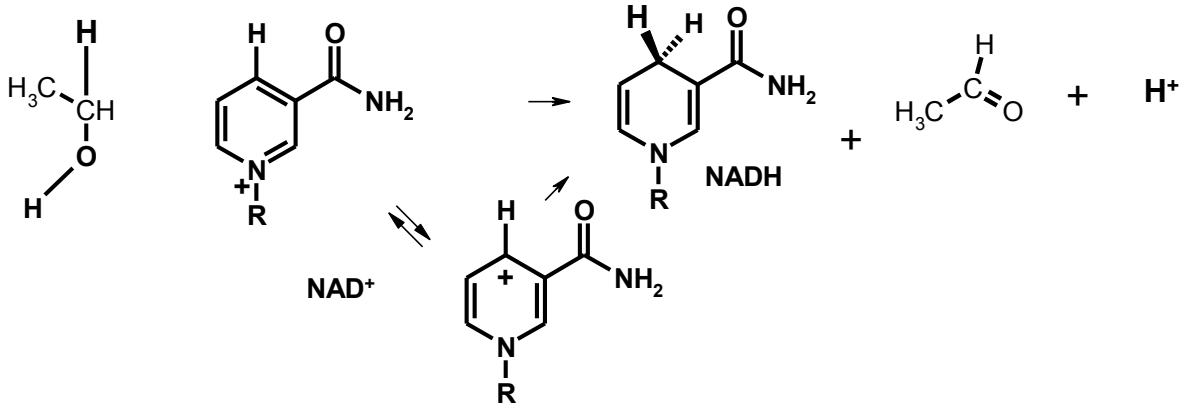
			
			

5. Write the scheme of a multi-step reaction between 2-methylbutan-2-ol and 15 % H_2SO_4 (draw arrows for each step to show electron-movement. Indicate the mechanism of the reaction).

6. Write the scheme of a multi-step reaction between cyclohexylmethanol and concentrated phosphoric acid (draw arrows for each step to show electron-movement and indicate the type of each step-reaction).

7. Write the scheme of a multi-step reaction between (R,R-) 2-methylcyclohexanole and hydrogen bromide (draw arrows for each step to show an electron-movement). Explain the stereoselectivity.

8. Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme found in all living cells. In metabolism NAD^+ is involved in redox reactions, carrying hydride anion (electrons) from one substance to another. The coenzyme is, therefore, found in two forms in the cells: NAD^+ is an oxidizing agent — it accepts hydride anion from other molecules and becomes reduced. The reaction forms NADH, which is a reducing agent to donate hydride anion. It is also used in other cellular processes. Because of the importance of these functions, the enzymes involved in NAD metabolism are targets for a drug discovery.
Draw arrows to show electron-movement in oxidation of ethanol *in vivo*. Draw a circle around the atom that functions as nucleophile, and a square around the electrophilic center.

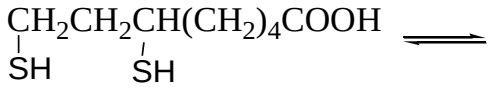


9. Write a reaction scheme for oxidation of methanol with NAD^+. Draw arrows to show an electron movement. Explain why methanol is much more toxic than ethanol.

10. Write reaction schemes that can be used to distinguish *n*-butyl and *tert.*-butyl alcohols.

11. Write reaction schemes that can be used to distinguish propan-2-ol and propan-1,2,3-triol.

12. Write a reaction scheme for *in vivo* oxidation of dihydrolipoic acid, which participate in a variety of biochemical transformations, in particular in redox processes.



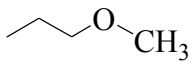
Dihydrolipoic acid is optically and only the R-enantiomer is biochemically significant. Write it is Newman projection for C_6–C_7 bond.

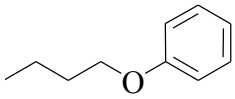
Antioxidants are _____

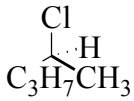
_____

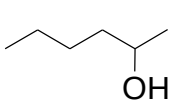
13. Write the scheme of reversible two-electron, two-proton redox system for cathechol/*ortho*-benzoquinone pair.

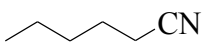
14. Based on nucleophilic substitution design synthetic schemes for substances shown below:

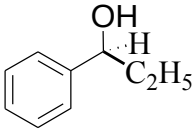
a) 

b) 

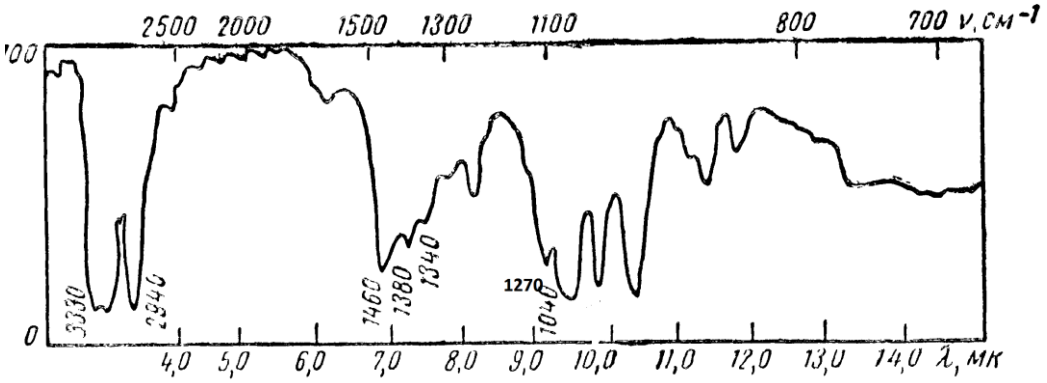
c) 

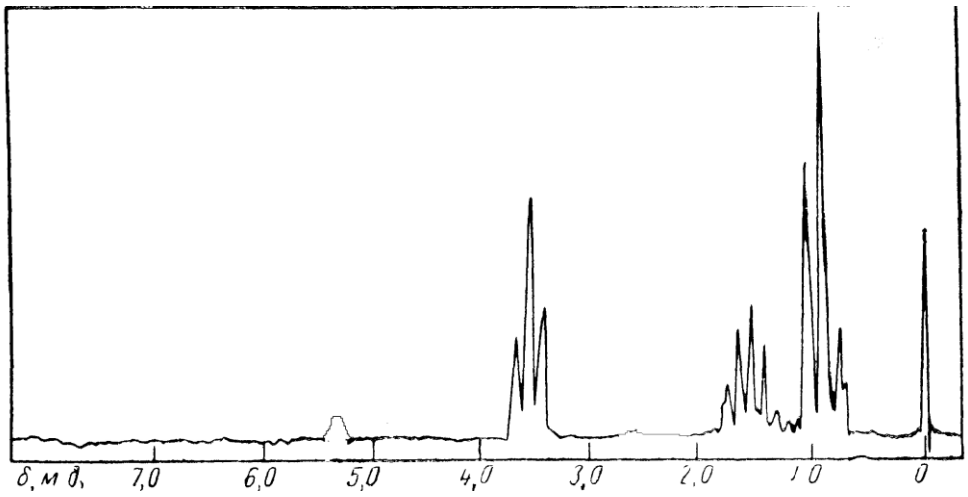
d) 

e) 

f) 

15. The compound C_3H_8O has now absorbtion in UV absorption in the UV region. By using IR and NMR spectra identify its structure. NMR ^1H: 0.92 ppm. – t, 1.57 ppm. – m, 3.8 ppm. – t, 5.2 ppm. – broad s.





16. Find drugs which contain in their structure two or more hydroxyl groups [2]. Indicate reaction centers and structural fragments.

EXPERIMENTAL SECTION

Experiment 1. Detection of primary, secondary and tertiary alcohols (*Lucas* test).

To 3–4 drops of unknown alcohol (primary, secondary and tertiary alcohols, e.g. butan-1-ol*, butan-2-ol*, *t-butyl* alcohol*) in test tubes add 6 drops of the *Lucas* reagent (18) at room temperature. Stopper the tube and shake vigorously, then let the mixture stand. Note the time required for the formation of the alkyl chloride, which appears as an insoluble layer or emulsion.

A positive test is an appearance of a cloudy second layer or emulsion:
tertiary alcohols: immediate to 2–3 minutes;
secondary alcohols: 5–10 minutes;
primary alcohols: no reaction.

Explain the role of zinc chloride in the reaction.

Explain why alcohols with more than six carbon atoms cannot be tested in Lucas test.

Experiment 2. *Jones* oxidation for primary and secondary alcohols.

To 2 drops of the unknown (primary, secondary or tertiary alcohols, e.g. ethanol*) in the tube add *Jones* reagent: 1 drop of 10 % sulfuric acid (23) and 2 drops of 10 % potassium dichromate (24). Heat the tube. A positive test is marked by the formation of a green color within 15 seconds upon addition of the orange-yellow reagent to a primary or secondary alcohol. Ethanol oxidation gives ethanol with an apple scent.

Add 1 drop of the resulting solution to a second tube containing 3 drops of fuchsine sulfurous acid (33). It appears a pink-violet color (*Shiff* test on the aldehyde group).

Aldehydes also give a positive test, but tertiary alcohols do not. A positive test for aldehydes and primary or secondary alcohols consists in the production of an opaque suspension with a green to blue color. Tertiary alcohols give no visible reaction within 2 seconds, the solution remaining orange in color. Disregard any changes after 15 seconds.

Explain why phenols and enols can give a positive test.

Experiment 3. Iodoform test on ethanol.

To 4 drops of ethanol* in two test tubes add 5 drops of the iodine solution, I_2 in KI solution (47), and 3 drops of 10 % sodium hydroxide (21). Stopper the test tube and shake vigorously. A positive test will result in the brown color of the reagent disappearing and the yellow iodoform solid precipitating out of the solution.

Which alcohols form iodoform?

Iron (III) Chloride test for phenols

Place 3 drops of phenol emulsion* in the tube. Add 1 drop of 1 % aqueous iron (III) chloride solution (8). Observe the pink coloring.

Proceed analogously with 1 % solutions of catechol (19), resorcinol (17), hydroquinone (22). For α-naphthol we need % alcoholic solution.

A red, blue, green, or purple coloring is a positive test.

Explain why we need alcoholic solution of α-naphthol.

Signature of the instructor:

LABWORK № 13
AMINO-DERIVATIVES, AZO AND DIAZO COMPOUNDS

Objective: to study the structure and properties of amino-derivatives, azo and diazo compounds.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of amines, azo and diazo compounds.
2. Basic and nucleophilic properties of amines.
3. Reactivity of amines.
4. Alkylation and acylation of amines.
5. Nitrosation and diazotization of amines.
6. Formation of diazonium salts and their substitution and coupling reactions.
7. Chemical and instrumental detection of amines and azo compounds.
8. Diazomethane in organic synthesis and analysis.

PRACTICE PROBLEMS

1. Write the structures. Identify which of them are primary, secondary or tertiary amines. Indicate reaction centers. Give substitutive IUPAC nomenclature names.

Ethylamine	Methylethylamine
Dimethylamine	Triethylamine
Isoamylamine	Ethanolamine
2,4,6-Tribromaniline	N,N-Dimethylaniline
Phenylenediamine	*p*-Aminosalicylic acid
Triethylbenzylammonium chloride	(R-) Amylmethylphenylbenzylammonium chloride

2. Write constitutional formulas of substances and rank the set of compounds in terms of relative basicity.

Aniline, *p*-nitroaniline, *p*-methoxyaniline, *p*-toluidine.

Dimethylamine, trimethylamine, benzylamine, phenylethylamine.

Acetanilide, diphenylamine, aniline.

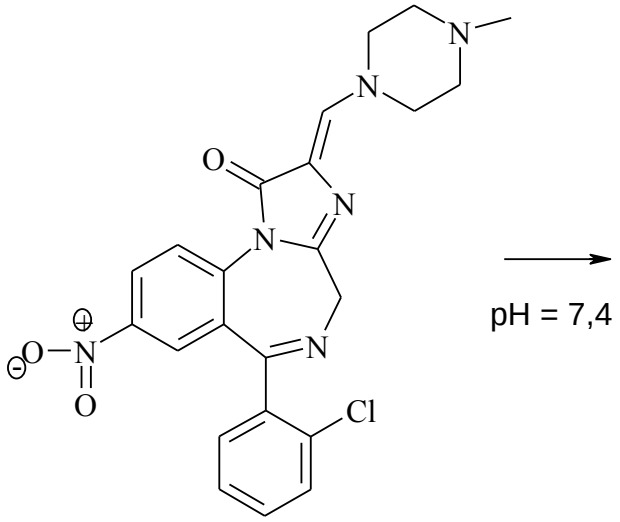
3. Give the structural formulas of local anesthetics [2]. Detect the basic centers and indicate the strongest. Write the reaction with hydrochloric acid.

Procaine

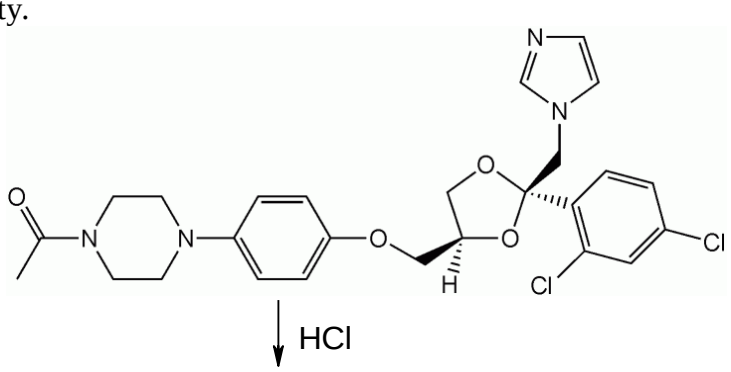
Lidocaine

Articaine

4. *Loprazolam* is a short-acting benzodiazepine possessing anxiolytic, sedative, anticonvulsant and skeletal muscle relaxant properties. Show the structure of the predominate form of the following molecules at physiological pH 7.4.



5. The systemic antifungal agent *Ketoconazole* is administered orally as the free base. The oral bioavailability of this drug is dependent upon solubility in the gastric contents and solubility is promoted by the acidic pH of the digestive tract. Using the structures show how acidity enhances ketoconazole solubility.



6. Write the schemes and name of the products of the following reactions of aniline and benzyl ethyl amine.

Acylation with propionyl chloride

Acylation with acetic anhydride

Alkylation with 2-bromopropane

7. Write the scheme of a multi-step diazotization reaction between *p*-methoxyaniline and nitric acid (draw arrows for each step to show an electron-movement).

8. Write and name the products of the reaction between the resulting diazonium salt from previous problem and with compounds listed below. Indicate the mechanism and specify the conditions of each reaction.

Water

Sodium iodide

Sodium bromide

Potassium cyanide

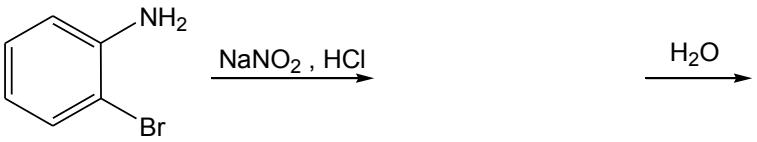
Tetrafluoroboric acid

Metaphosphoric acid

β-Naphthol

9. Write the reaction schemes and name the products:

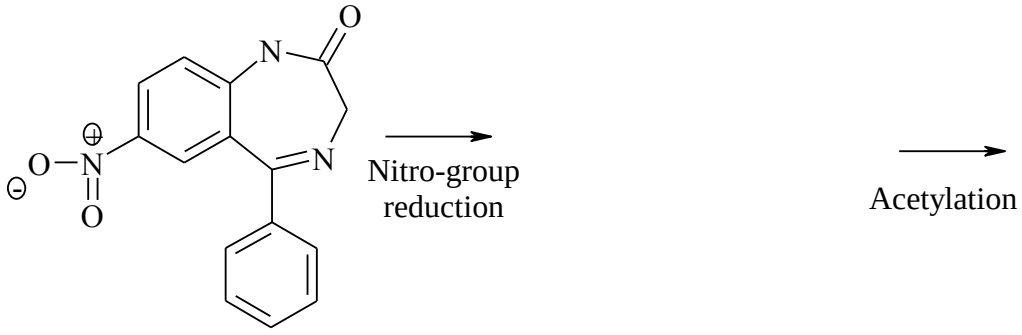
10. Complete the scheme and name the products.



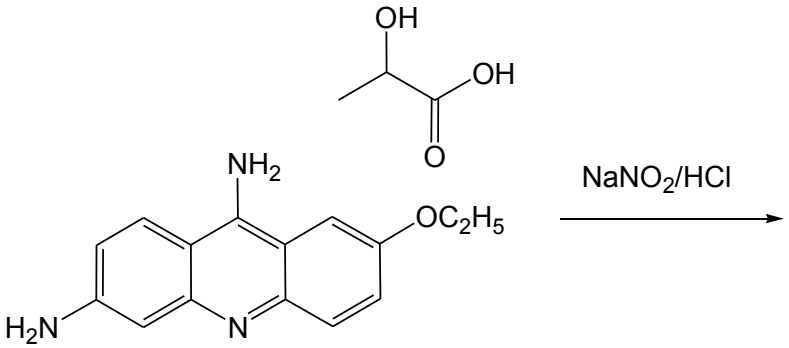
11. Design the synthesis of 1,3,5-tribromoaniline from benzene using the nitration/diazotization strategy.

12. Write the reactions of diazomethane with hydrogen bromide, resorcinol, isoamyl alcohol, isobutyric acid, *p*-toluenesulfonic acid, pent-2-ene.

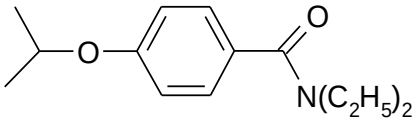
13. *Nitrazepam* is a psychoactive drug possessing mostly hypnotic and sedative action. Show the end product of *Nitrazepam* metabolism resulting from nitro group reduction followed by conjugation of the intermediate aniline derivative by acetylation.

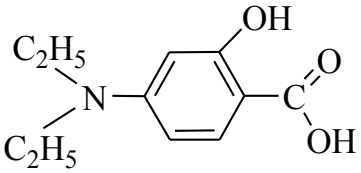


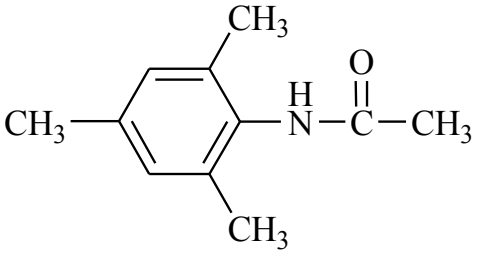
14. Explain the color change from yellow to crimson for *Ethacridine Lactate* (antiseptic medication) reacting with sodium nitrite in acidic conditions. Discuss the possibility of spectral detection of the compound.

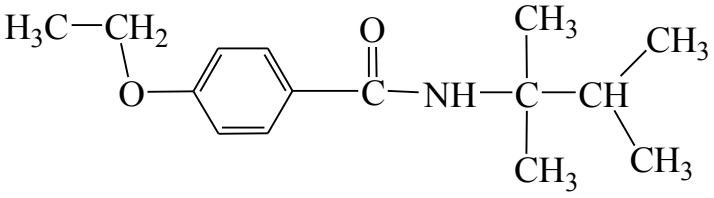


15. Predict frequency bands in IR spectrum as well as chemical shifts, J-coupling and intensity in the ^{1}H NMR spectrum. Explain the answer.









EXPERIMENTAL SECTION

Experiment 1. Aniline synthesis.

Add 5 drops of concentrated hydrochloric acid* and a small granule of zinc metal* to a tube with 2 drops nitrobenzene*. Shake the tube vigorously and carry out the reaction till zinc will be dissolved completely (you may need to heat the tube and/or to add few more drops of hydrochloric acid*). As the result you will see the upper layer of nitrobenzene will disappear to give the aniline hydrochloride which is well soluble in water. The solution obtained you should use exp. 2.

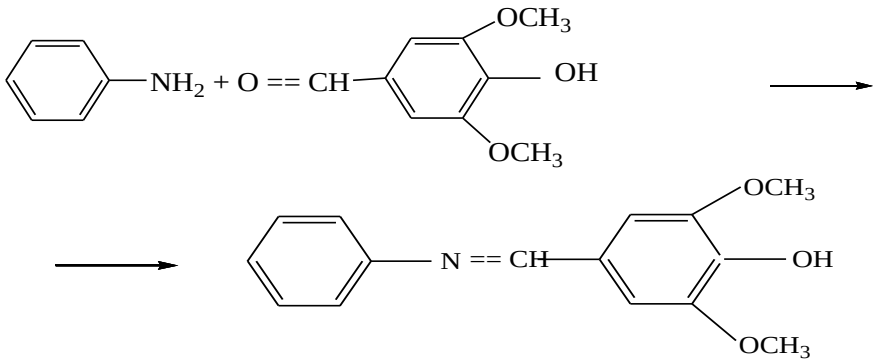
Add sodium hydroxide solution and fix the changes.

Write the reaction of an aniline formation.

Write the reaction which is taking place after the addition of sodium hydroxide to aniline hydrochloride *solution. On what grounds can the formation of free aniline be judged?*

Experiment 2. Aniline detection.

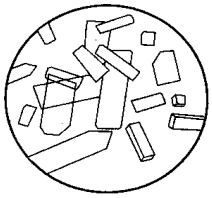
Webster has proposed a very simple test for primary and secondary aryl amines. The test depends on the action of lignin in a newsprint paper. Ethanolic solution of amines applied on newsprint paper and treated with hydrochloric acid (approx. 6M HCl,). Primary and secondary aryl amines produce immediate yellow or orange color, while alkyl and alicyclic amine require a hot solution for color development. The test is based on the reaction of the substances containing amino-group with aromatic aldehydes forming under acidic hydrolysis of lignin, e.g. syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde).



Place a few drops of the hydrochloric solution from the previous experiment on newsprint and filter the paper. It will produce on newsprint paper immediate yellow or orange coloring in contrary to a filter paper.

Explain the difference between lignin probe for a newsprint and filter paper.

Experiment 3. Aniline acetylation.



Many of the acetylated derivatives of aromatic amines (or anilines) are pharmacologically important compounds. Some of these exhibit distinct analgesic activity (e.g. N-acetyl-4-hydroxyaniline, or acetaminophen).

Place 2 drops of aniline* in the test tube and add 4 drops of acetic anhydride* (you can observe warming of the tube). Heat the mixture over the burner flame. After cooling add 10 drops of water and shake vigorously the tube. The well-shaped crystals are formed. With a glass rod place a few crystals on a microscope slide. Examine the crystals under the microscope. They have the form of prismatic plates.

Write the reaction of the aniline acetylation. Discuss the mechanism of the reaction.

Which functional derivatives of acetic acid are better to use for aniline acetylation*?*

Experiment 4. Basic properties of aliphatic and aromatic amines.

Place one drop of diethylamine* and aniline* in two different tubes followed by addition of 3 drops of water to each. Shake vigorously. With a glass rod place a bit of both mixtures to pH indicator and determine the approximate value of pH. Compare the solubility in water and the basic properties of both amines.

Divide aniline emulsion into two portions followed by adding 1 drops of 10 % hydrochloric (9) and 10 % sulfuric (23) acids.

Explain the higher solubility of diethylamine.

Explain the higher bacisity of diethylamine.

Experiment 5. Amine nitrosation.

Place 6–7 drops of glycine (6) (analogue of primary amine), N,N-dimethylaniline and aniline in three different tubes and cool tubes in an ice water bath. Add dropwise (aprox. 5 drops) add successively concentrated HC* and 5 % aq. sodium nitrite (34)

Fix the changes in both tubes.

Write the reaction schemes and show the mechanisms of the reactions.

Experiment 6. Diazotization of aniline and diazo coupling.

Place in the first tube 5 drops of aniline, 5 drops of concentrated HCl* and a piece of ice followed by addition of 5 drops of 5 % aq. sodium nitrite (34). Shake the tube vigorously after adding of each drop. To check the end of the reaction, place a bit of mixture onto a strip of iodine-starch paper — the blue coloring indicates the end of the reaction.

Place in the second tube a few crystals of β-naphthol followed by addition of 10 % aq. NaOH (21) till the solid comes to the solution. Add a drop of the solution from the second tube into the first tube.

Divide azo dye into two tubes followed by addition of 10 % aq. HCl (9) 10 % aq. NaOH (21) in different tubes.

Write the schemes and mechanisms of reactions.

Design schemes of detection (using azo-coupling reactions) for
α-naphthol *para-phenetidine*

Signature of the instructor:

LABWORK № 14
CONTINUOUS ASSESSMENT № 2. STRUCTURE, REACTIVITY AND IDENTIFICATION OF HYDROCARBONS, HALIDES, HYDROXY-, THIO- AND AMINODERIVATIVES, ETHERS, SULFIDES. ACADEMIC RESEARCH № 2

Objective: to systematize the knowledge of the structure, reactivity and identification of hydrocarbons, organic halides, hydroxy, thio- and aminoderivatives, ethers, sulfides

Remind the program material from the topic 6–13.

Recommended literature: study the literature from the topic 6–13.

EXPERIMENTAL SECTION

An example for experimental problem:

1. Propose and carry out chemical tests, which let us distinguish catechol and ethylene glycol; pinene and heptane; menthol, penene, aniline and benzylchloride.
2. Identify chemically the proposed substance.
3. Predict spectral characteristics (UV, IR, NMR-spectra) of the proposed substance.

ACADEMIC RESEARCH № 2

Signature of the instructor:

LABWORK № 15
OXO COMPOUNDS

Objective: to study the structure and properties of oxo compounds (aldehydes and ketones).

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of aldehydes and ketones.
2. Structure of carbonyl group. Reaction sites and reactivity of oxo conpounds.
3. Reactions of nucleophilic addition at the carbonyl group: the general scheme, the role catalysis.
4. Reactions with O-, C-, S-, N-nucleophiles: the general scheme, examples.
5. Reactions with C-nucleophiles: mechanism and application.
6. Hydrogenation: mechanism of hydrogen and hydride addition, and application.
7. Condensation reactions: the general scheme, the role catalysis.
8. Reactions with alcohols and thiols: mechanism and application.
9. Reactions with nitrogen nucleophiles: mechanism and application.
10. Keto-enol balance and formation of an enolate anion.
11. α-Substitution in aldehydes and ketones.
12. Oxidation/reduction of aldehydes and ketones *in vitro* and *in vivo*.
13. Some representatives of aldehydes and ketones (formaldehyde, acetaldehyde, acryl aldehyde, benzaldehyde, acetone, cyclohexanone, and etc.), their application in medicine and pharmacy.
14. Chemical and instrumental detection of oxo compounds.

PRACTICE PROBLEMS

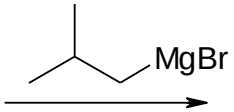
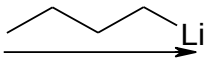
1. Write the structures, convert trivial names. Determine the electronic effects and indicate the reaction sites.

2,3-Dimethylpentanal	4-Ethylhex-1-en-3-one
Butyraldehyde	Vanillin

2. Show graphically the distribution of charge in the molecules of formaldehyde, ethanal, benzaldehyde and butanone. Indicate the reaction centers and discuss the influence of the substituents on electrophility of carbon in carbonyl group.

3. Rank formaldehyde, acetaldehyde, acetone and chloroacetic aldehyde according to their ability to nucleophilic addition.

4. Write the structural formulas and addition reactions of oxo compounds. Give the name of the reaction products.

Oxo compound	Reagent	Product
3,5-Dimethylcyclohexanone	H_2/Pd	
2-Methylhexanal	$NaCN/H^+$	
2-Methylpentan-3-one		
Methyl ethyl ketone		
Cyclopentanone	$HC\equiv CNa$	
Benzaldehyde	CH_3OH / H^+ (Equimolar)	
Trichloroethanal	H_2O	

5. Write the scheme of the multi-step condensation reaction between cyclohexanone and the excess of methanol in acidic conditions. Draw arrows for each step to show an electron-movement.

6. Write the scheme of the multi-step intermolecular cyclization of γ-hydroxybutyraldehyde in ether as a solvent. Draw arrows for each step to show an electron-movement.

7. Write the scheme of the multi-step intermolecular cyclization of 5-hydroxy hexan-2-one in a methanol solution under the acid catalysis with the formation of mixed acetal. Draw arrows for each step to show an electron-movement.

8. Write the scheme of a multi-step condensation reaction between cyclopentanone and benzylamine: imine formation. Draw arrows for each step to show an electron-movement.

9. Write the scheme of a multi-step condensation reaction between cyclopentanone and diethylamine: enamine formation. Draw arrows for each step to show an electron-movement.

10. Hexamethylenetetramine (*Urotropin*) was discovered by *Alexander Butlerov* in 1859 and widely used in organic synthesis. As the mandelic salt (*Methenamine mandelate*) it has been used from the end of 19^{th} century for the treatment of an urinary tract infection. It decomposes at an acidic pH to form formaldehyde and ammonia, and the formaldehyde is bactericidal; the mandelic acid adds to this effect, along with aspirin *Urotropin* being one of the first pro-drug. Though its use had temporarily been reduced in the late 1990s, due to adverse effects, now its application been reapproved because of the prevalence of antibiotic resistance to more commonly used drugs.
Write the scheme of a multi-step formation of hexamethylenetetramine. Draw arrows for each step to show an electron-movement.

11. Write the reaction scheme (draw arrows for each step to show electron-movement) for syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde) reduction in interaction with:

Hydrogen (Pt-catalyzed)

Lithium aluminum hydride (followed by alcoholate hydrolysis)

Formaldehyde (*Cannizzaro* dismutation in presence of KOH)

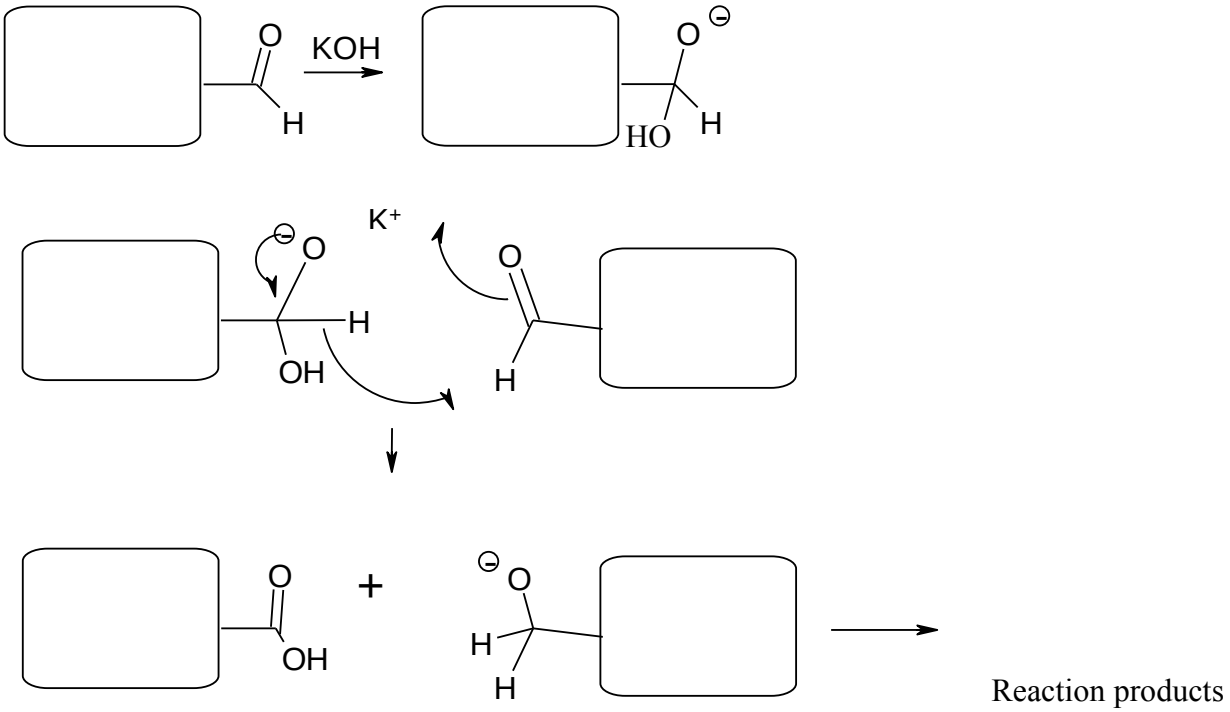
NADH *in vivo*

Zinc amalgam and HCl (*Clemmensen* reduction)

in *Wolff-Kishner* reduction (hydrazone denitrogenation)

12. Write the scheme of benzaldehyde dismutation (*Cannizzaro* reaction).

13. Complete the scheme of the cross *Cannizzaro* reaction between formaldehyde and 1-acetylcyclohexene by adding the missing elements (taking in account the electrophility of carbonyl carbon).



Explain why the transition state is energetically stable.

14. Write the reaction scheme for aldol condensation of hexan-3-one with equimolar formaldehyde in acidic conditions (aldol formation).

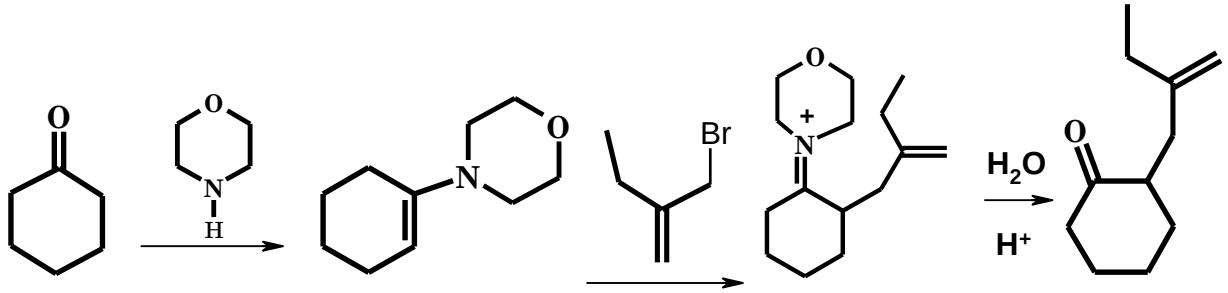
15. Write the reaction scheme for aldol condensation of nicotinic aldehyde with acetophenone in basic conditions (unsaturated ketone formation). Draw arrows for each step to show an electron-movement.

16. Write the reaction schemes of acetaldehyde and cyclohexanone oxidations in mild and drastic conditions (CrO_3, $KMnO_4$/40ºC, $KMnO_4$/120ºC, C_6H_5COOOH)

17. Write the reaction schemes of cyclohexane alkylation with ethylbromide in presence of LDA (lithium diisopropylamide).

Based on *Brønsted* concept explain why LDA behaves as one of the strongest bases and widely used in synthesis for deprotonation.

18. *Storch* enamine strategy is used for alkylation of oxo compounds in mild conditions. Draw arrows to show an electron-movement in the following multi-step reaction (draw arrows for each step).

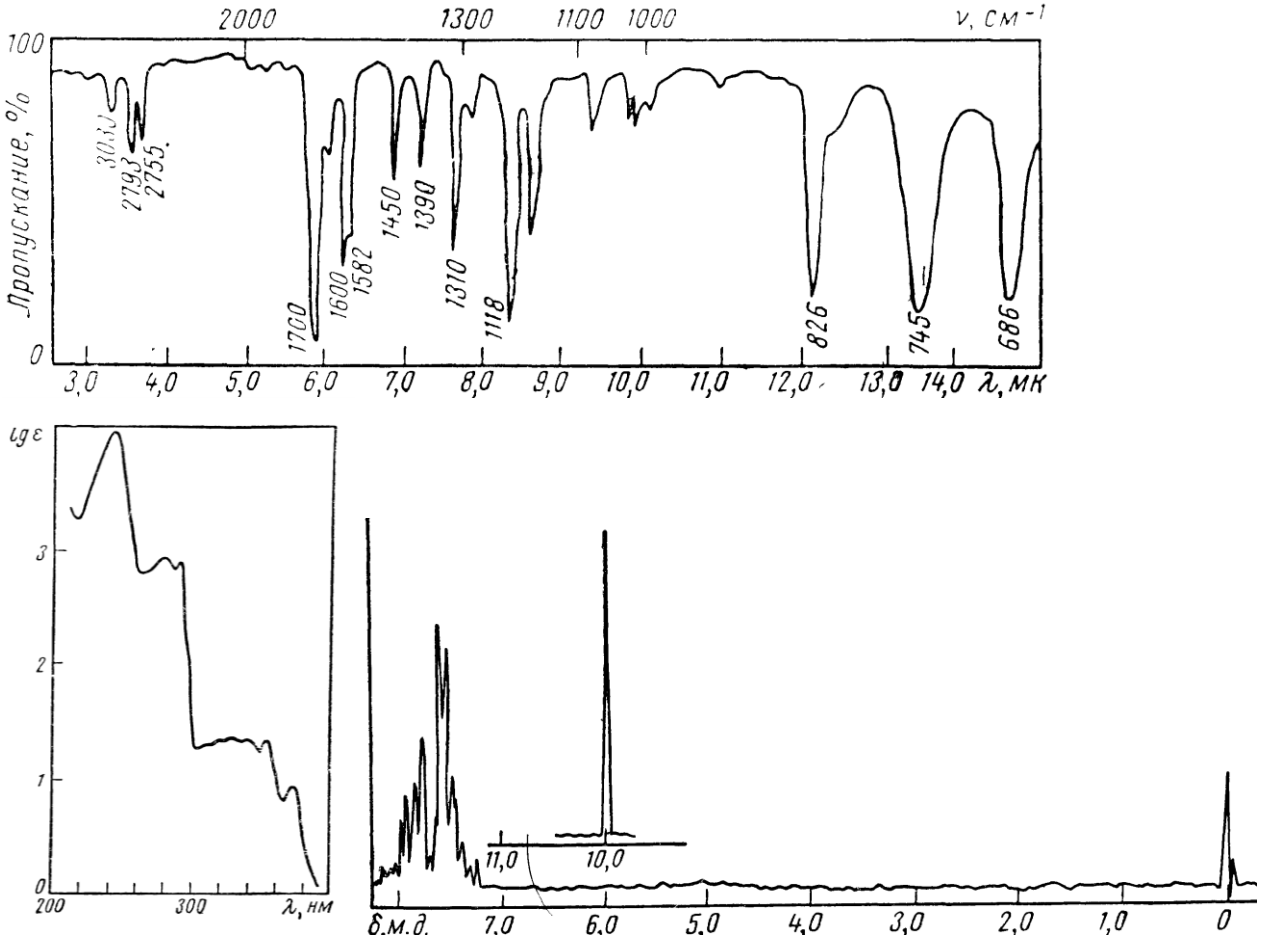


19. Design the synthesis of *Nylon* 6, or polycaprolactam, (which is widely used in polymer industry, in particular for surgical sutures production) based on the benzene structure and acid catalyzed *Beckmann* rearrangement of cyclohexanone oxime).

20. Design the synthesis of N-methyldihydroxyphenylalanine based on 3,4-dihydroxyphenylacetic aldehyde structure and aminocyanation strategy (hydrocyanation of imino group).

21. Design the synthesis of acetylcyclohexane from acetylbenzene, using the procedure of the carbonyl group acetal protection in the reduction reaction.

22. Compound (C_7H_6O) has an absorption in the UV region. By using IR and NMR spectra identify its structure.



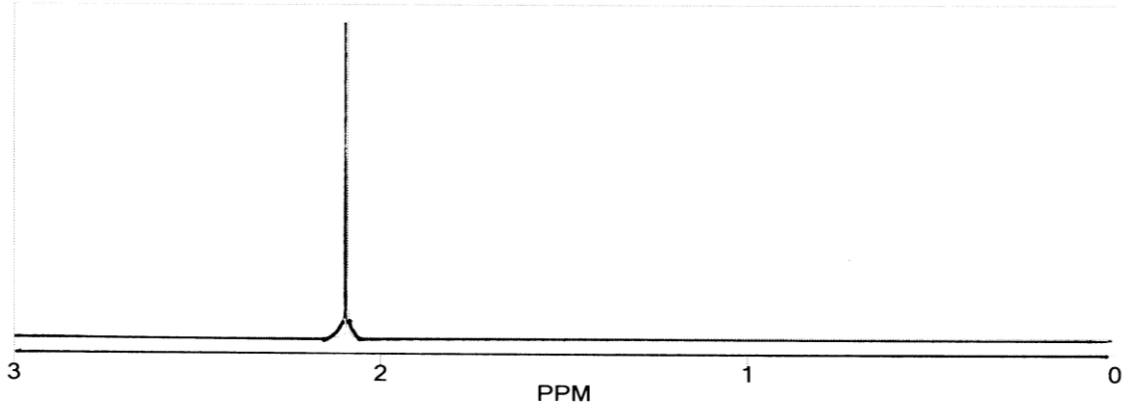
23. Detect substances based on chemical shifts and spin coupling in NMR ^1H spectra:

Dimethyl ketone and diethyl ketone

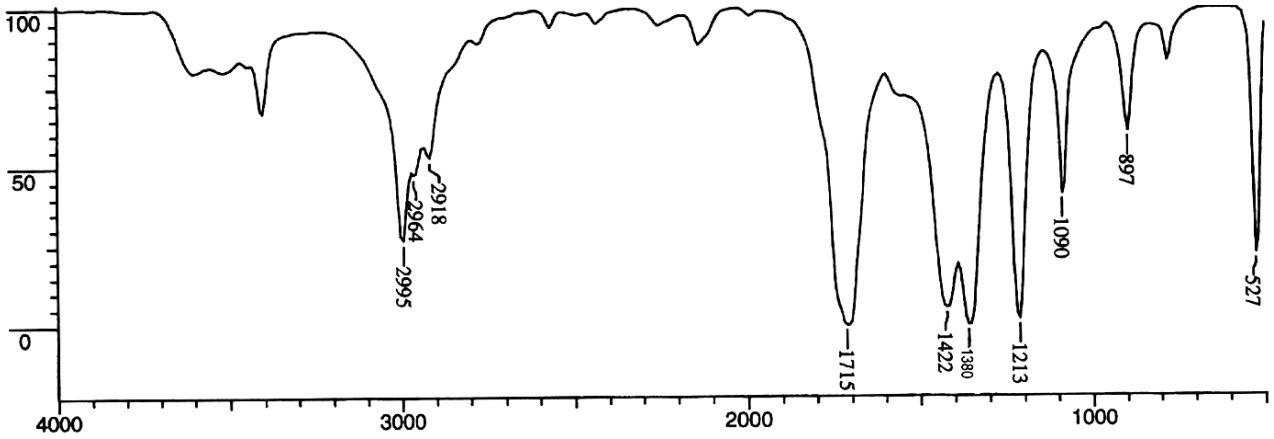
para-Methoxybenzaldehyde and acetophenone

Methyl isobutyrate and 2,2-dimethylpropanal

24. The oxidation of hydrocarbon C_6H_{12} with potassium dichromate gives a compound which ^1H NMR spectrum has the only singlet at 2.04 ppm. Detect substrate and product of the oxidation.



25. Define the structure based on IR spectrum of compound (C_3H_6O).



EXPERIMENTAL SECTION

Experiment 1. Synthesis of acetone oxime.

200 mg of hydroxylamine hydrochloride (13) and 200 mg of sodium carbonate (15) is dissolved in 2.5 ml of water. After the end of the carbon dioxide formation, cool the mixture (ice water bath) and add drop wise (so that the temperature does not rise above 15 °C). Add to the mixture 1 mL of acetone with stirring (or shaking). The acetone oxime usually starts to crystallize when about half the acetone has been added. When the addition is complete, the mixture is allowed to stand in ice-water for additional 15 minutes. The solution is filtered and the crude acetone oxime is collected, yielding approximately 1 g of crystalline product. The acetone oxime so obtained contains the small amount of sodium chloride, but is otherwise almost pure for the most synthesis purposes. Crude acetone oxime is purified by crystallization from petroleum ether (with boiling point 60–80 °C) or other hydrocarbons. The acetone oxime is freely soluble in water and in most organic liquids.

Write a step-by-step reaction scheme for acetone oxime *formation.*

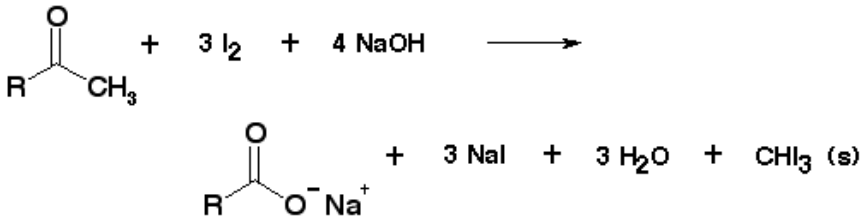
Explain why the reaction depends much on pH of solution.

Experiment 2. 2,4-DNP test for benzaldehyde (cyclohexanone, benzophenone).

Add a solution of 1 or 2 drops of benzaldehyde* in 2 mL of 95 % ethanol* to 3 mL of 2,4-dinitrophenylhydrazine reagent*. Shake vigorously, and, if no precipitate forms immediately, let the solution stand for 15 minutes.
The formation of a precipitate is a positive test.
Write the scheme of the reaction showing all arrow drawings for a multistep mechanism.

Why do some allylic alcohols give a positive 2,-4-DNP test?

Experiment 3. Iodoform test for acetone.



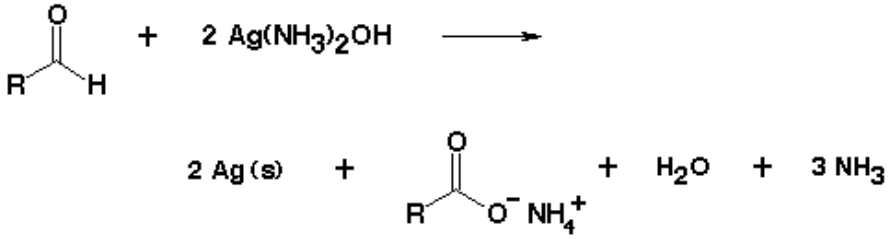
Place in a tube 3 drops of the iodine solution, I_2 in KI solution, (47). Add dropwise 10 % sodium hydroxide (21) till the solution come colorless. Add to the obtained mixture 1 drop of acetone. Stopper the test tube and shake vigorously. A positive test will result in the brown color of the reagent disappearing and the yellow iodoform solid precipitating out of the solution.

The formation of solid iodoform (yellow) is a positive test. Iodoform can be recognized by its odor and yellow color and, more securely, from the melting point 119–123 °C.

Write the scheme of the reaction showing all arrow drawings for a multi-step mechanism.

Which oxo compounds do not work in iodoform test?

Experiment 4. Tollen's test for aldehydes.



To prepare *Tollens* reagent place into each of three test tubes 2 drops of 1 % silver nitrate and 2 drops of 10 % sodium hydroxide (21). Then add 10 % ammonia solution, drop by drop, with constant shaking, until almost all of the precipitate of silver oxide dissolves.

Add in three test tubes with freshly prepared *Tollens* reagent 1–2 drops of formalin (32), benzaldehyde* and acetone* to 1 mL of the. Gentle heating can be employed if no reaction is immediately observed.

The formation of silver mirror or a black precipitate is a positive test.

Why do aromatic amine and some phenols give positive Tollen's Test?

Experiment 5. Formaldehyde dismutation.

Place the tube in 2–3 drops of 40 % formaldehyde (32) solution. Add 1 drop of methyl red indicator* (the range of color change which is within pH of 4.8–6.0).

Explain the change of the color observed.

Signature of the instructor:

LABWORK № 16
CARBOXYLIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES

Objective: to study the structure and properties of carboxylic acids and their functional derivatives.

Recommended literature

Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

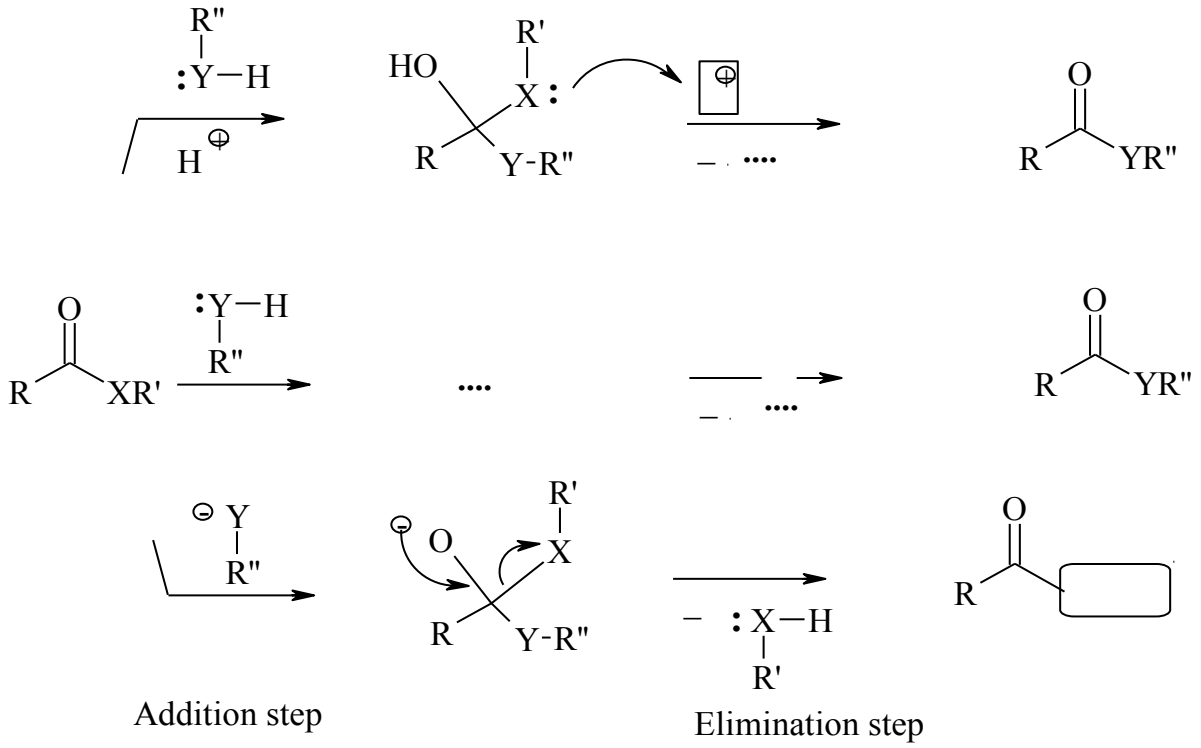
1. Structure and nomenclature of carboxylic acids and their functional derivatives.
2. Structure of functional groups and reactivity of carboxylic acids and their functional derivatives.
3. Reactions of nucleophilic substitution of carboxylic acids and their functional derivatives: the general scheme, the role catalysis. Reactions of derivative interconversion (hydrolysis, aminonolysis, alcoholysis, interaction with C-Nucleophiles).
4. Hydrogenation: mechanism of hydrogen and hydride addition, and application.
5. Specific reactions of acids.
6. Specific reactions of esters.
7. Specific reactions of amides and nitriles.
8. Specific reactions of acyl halides and anhydrides. Acylation *in vitro* and *in vivo*.
9. α-Substitution in carboxylic acids and their functional derivatives. CH-Acidic properties of malonic ester. Synthesis of carboxylic acid derivatives based on malonic ester.
10. Keto-enol balance and formation of an enolate anion.
11. Hydrazides of carboxylic acids. Hydroxamic acids.
12. Application of carboxylic acids and their functional derivatives in medicine and pharmacy.

PRACTICE PROBLEMS

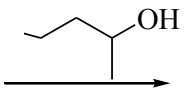
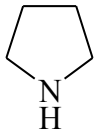
1. Write the structures, convert trivial to systematic names. Determine electronic effects and indicate reaction sites.

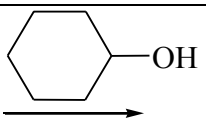
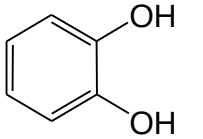
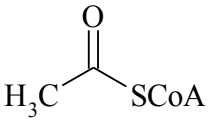
Valeric acid	Methyl formate	Ethyl methacrylate
Acetic anhydride	Acetyl chloride	Isovaleric acid chloride
N, N-Dimethylformamide	Acetonitrile	Isobutyl caproate

2. Complete the general scheme of the nucleophilic substitution reaction of carboxylic acids and their derivatives under different conditions (add atoms, arrows, charges, connections).

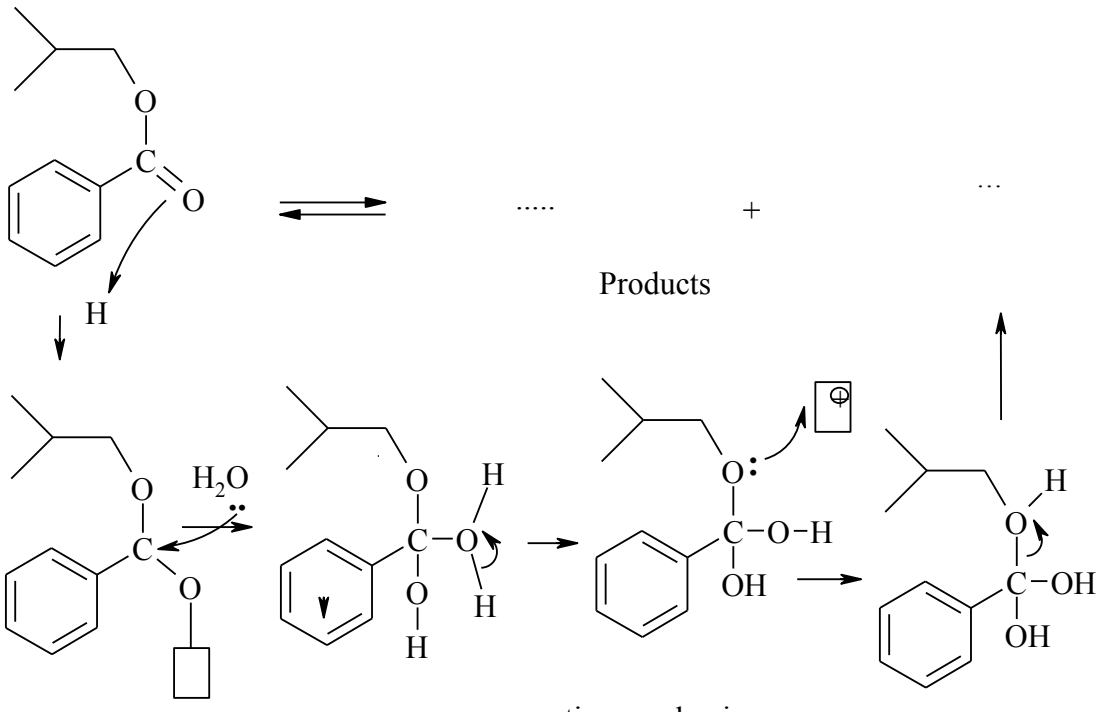


3. Write the structural formulas and addition reactions of carboxylic acids and their derivatives. Give the name of the reaction products.

Acetic acid	C_2H_5OH/H^+ →
Ethyl benzoate	
Methyl butyrate	C_2H_5MgBr →
Methyl benzoate	$C_6H_5CH_2NH_2$ →
Propionyl chloride	

Butyric acid	$SOCl_2$ →
Acrylamide	KOH/t →
Acetic anhydride	 →
Oxalic acid dichloride	 →
	→ choline

4. Complete the scheme of the mechanism of isobutyl benzoate acidic hydrolysis (add atoms, arrows, charges, connections).



reaction mechanism

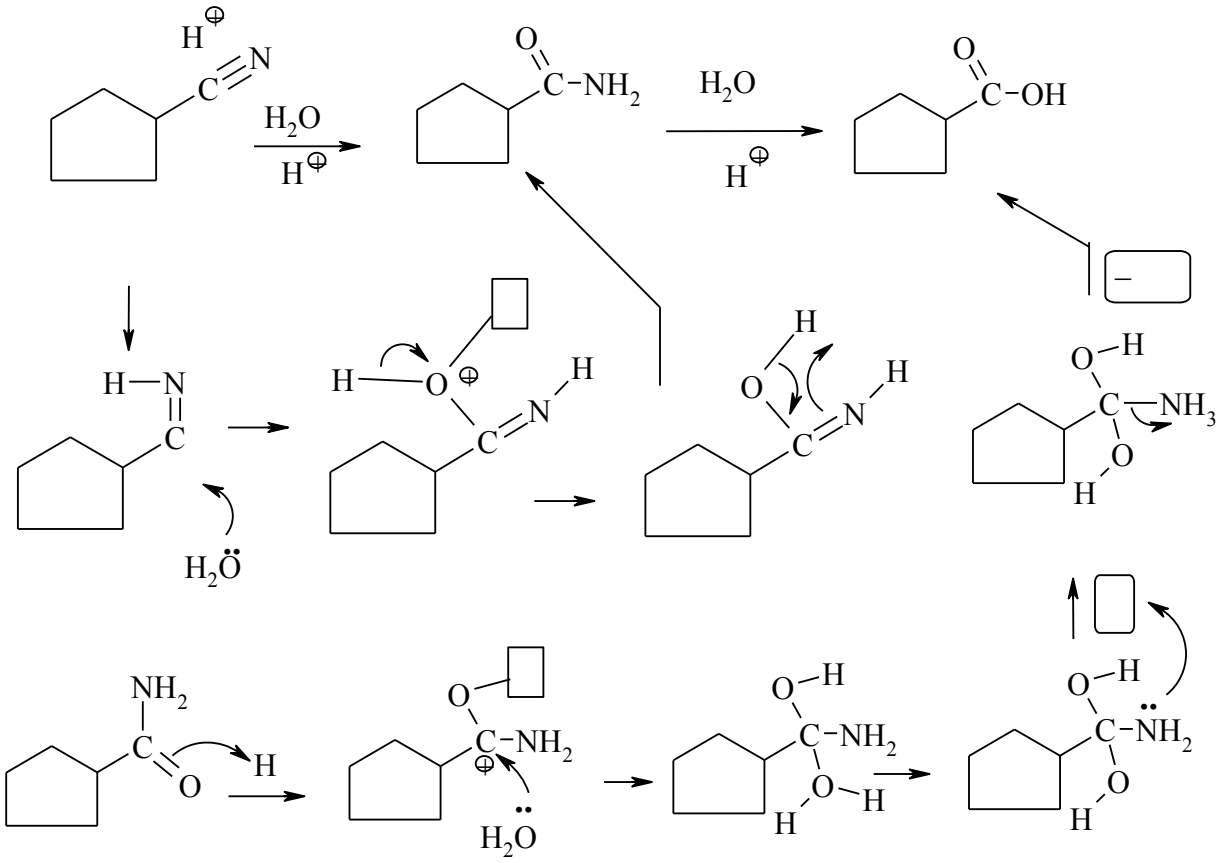
5. Discuss the mechanism of the alcoholysis (esterification) on the example of the interaction between isobutyric acid and ethanol.

6. Discuss the mechanism of the alcoholysis (esterification) on the example of the interaction between ethyl butyrate and isoamyl alcohol.

7. Discuss the mechanism of the aminolysis (amide formation) the example of the interaction between ethyl butyrate and benzyl amine.

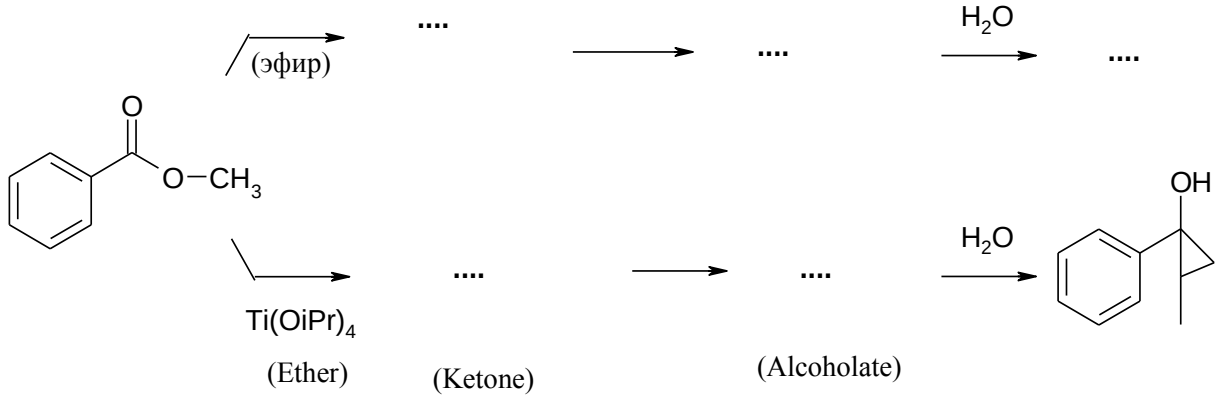
8. Write the schemes of hydrolysis of *Novocaine and Lidocaine*. Explain different rates of their hydrolysis and predict the possibility of application of these drugs for a short-term (urgent) and a prolonged action.

9. Complete the scheme of two-step cyclopentane carbonitrile acidic hydrolysis (add atoms, arrows, charges, connections).



Explain why in concentrated acids (sulfuric, phosphoric) the reaction usually stops on the amide formation, while full hydrolysis to carboxylic acid requires the reflux (heating) in dilute acids.

10. Complete the schemes of reactions of methyl benzoate with Propylmagnesium Bromide under different conditions.



11. Compare the acylating ability of acetic acids and its functional derivatives — methyl ester, N-benzylamide, anhydride and acid chloride. Explain your choice.

In vivo acylation is carried out with _____

12. Write acylation reactions of

Cyclopentanol with propionic acid chloride

Hexane-2-amine with acetic anhydride

Phenol by acetyl chloride (O-acylation)

Phenol by acetyl chloride (C-acylation)

Choline *in vivo* to acetylcholine

13. Rank the acidity of the compounds in series:

Acetic, isobutyric and trifluoroacetic acids

Formic, acetic and oxalic acids

Benzoic, o-hydroxybenzoic and p-hydroxybenzoic acids

Phthalic, terephthalic, 4-methoxybenzoic acid

14. Name the products and write the schemes of the reactions that occur when the oxalic, benzoic and malonic acids are heated. Specify the type of the reaction. Give examples of biologically important reactions of this type.

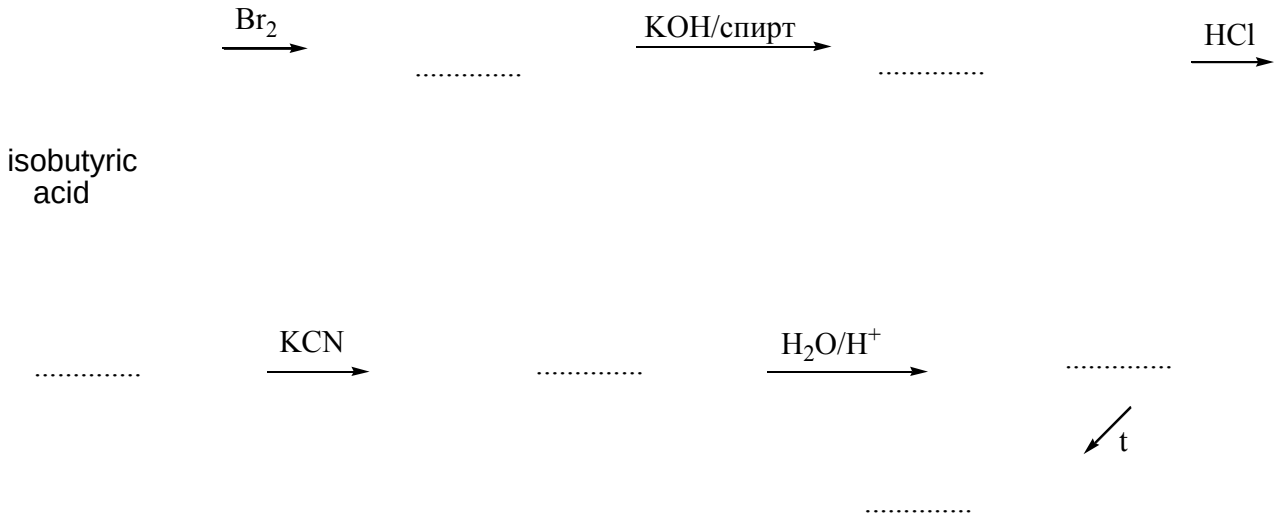
15. Name the products and write the schemes of the reactions that occur when the succonic, fumaric and maleic acids are heated. Specify the type of the reaction.

16. Discuss the mechanism of halogenation of ethyl propionate with bromine in the presence of phosphorus.

17. Discuss the mechanism of Hoffman degradation of isovaleric amide to the primary amine.

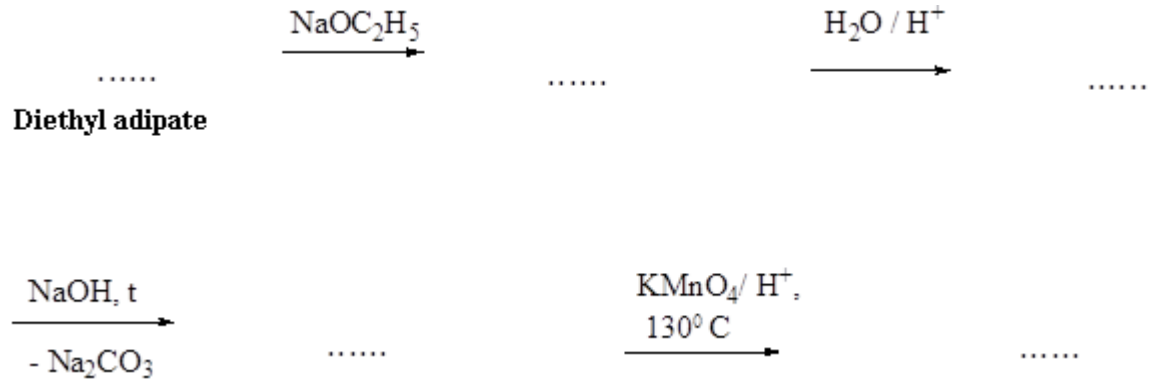
18. Design synthesis of 4-methylpentanamine based on 3-methylbut-1-ene *via* intermediate isocaproic amide.

19. Complete the scheme. Name the products and indicate the mechanism type.



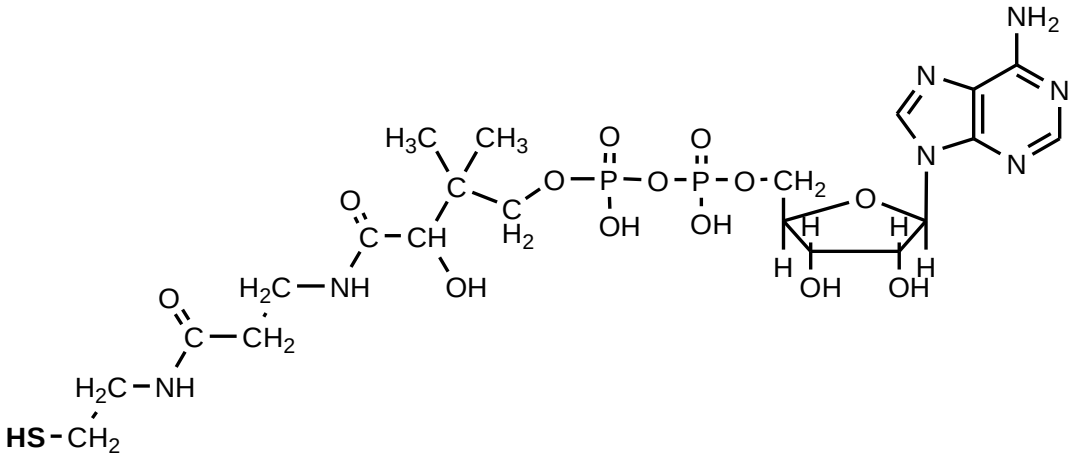
20. Discuss the scheme of Claisen condensation of methyl butyrate.

21. Complete the scheme and name the products.

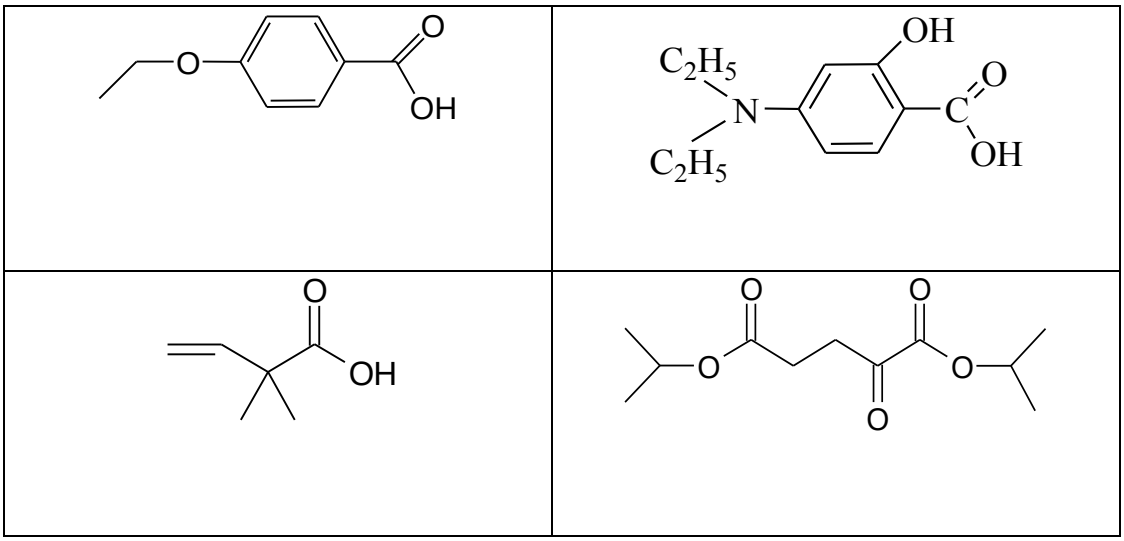


22. Design malonic ester synthesis of 2-methyl-3-phenylpropanoic acid.

23. Identify in the formula of coenzyme A esteric, amide, anhydride fragments. Give the scheme for the formation of acetylcoenzyme A (denote coenzyme A in abbreviated form CoA-SH).



24. Predict for substances shown below typical frequency bands in IR spectrum as well as chemical shifts, J-coupling (approximately) and intensity in the ^{1}H NMR spectrum.



EXPERIMENTAL SECTION

Experiment 1. Acidic properties of carboxylic acids.

Place 3 drops of acetic acid (36) in three test tubes. Add 1 drop of blue litmus* to the first test tube (the pH range of the color transition is 8–5), to the second tube — methyl orange* (pH interval 3.1–4.4), in the third tube — 1 % alc. solution of phenolphthalein* (pH range 8.2–10.0). Fix in which test tubes the color of the inductor changes, and determine the approximate pH of the acetic acid solution.

Write a scheme for the dissociation of acetic acid in an aqueous solution. How can you confirm this process experimentally?

Experiment 2. Synthesis of sodium benzoate.

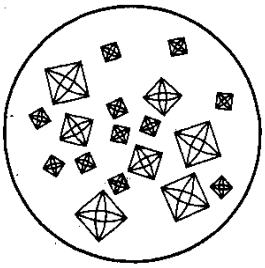
Place a few crystals of benzoic acid (44) and 2 drops of water in a tube. Then, with shaking, add 2–3 drops of 10 % aq. sodium hydroxide solution (21) until the crystals dissolve completely. To the clear solution obtained, add 2–3 drops of 10 % hydrochloric acid (9). Fix the changes you observed in the test tube.

Write the reaction schemes for sodium benzoate synthesis and its interaction with hydrochloric acid. Explain why hydrochloric acid decomposes sodium benzoate.

Based on the experience, draw a conclusion about the solubility of benzoic acid and its sodium salt in water.

Experiment 3. Detection of oxalic acid.

Put a few crystals (on spatula) of oxalic acid in the tube (25) and add 3–4 drops of water until it completely dissolved.



Take with a pipette 1 drop of the solution obtained and apply on a slide. Add to it 1 drop of 5 % aq. calcium chloride solution (41). Soon you will see the formation of the crystals of calcium oxalate. Place the slide under the microscope and consider the shape of the crystals: they look like envelopes.

Using a glass rod, divide the crystals on a slide into two portions. Add to the first one 1 drop of acetic acid (36), and to the second one — 1 drop of 10 % hydrochloric acid (9). Fix in which case calcium oxalate crystals are observed.

Write the reaction of calcium oxalate formation.

Explain the difference between the action of acetic and hydrochloric acid on calcium oxalate and write the possible reaction.

Experiment 4. Formic acid oxidation.

Oxidation with potassium permanganate.

Place in the first tube 3 drops of formic acid*, 2 drops of a 10 % aq. solution of sulfuric acid (23) and 5 drops of a 2 % aq. solution of potassium permanganate (14). Close the test tube tightly with a gas outlet tube, the end of which is poured into a second test tube with 4–5 drops of barite water*. Heat gently the first tube until a precipitate appears in the second tube.

Oxidation with Tollens' reagent (diammine silver). Place 1 drop of a 1 % aq. solution of silver nitrate* and 1 drop of 10 % aq. sodium hydroxide solution (21) into the tube. To dissolve the resulting precipitate of silver oxide add 2 drops of 10 % aq. ammonia solution (38) and 2 drops of water followed by addition of 3 drops of formic acid*, and gently heat the tube. Fix the changes you can observe in the tube.

Write a scheme of formic acid oxidation. Which product is detected by the oxidation of formic acid? Write the schemes of the reactions.

Experiment 5. Oxalic acid decarboxylation.

Put a few crystals (on a spatula) of oxalic acid (25) in a dry tube, Close the test tube tightly with a gas outlet tube, the end of which is placed into a second test tube with 2–3 drops of calcareous water (2). Heat the first tube until a precipitate appears in the second test tube. Remove the end of the gas-outlet tube from the liquid and, continuing the heating of the first tube, set fire to the emerging gas at the opening of the tube. It burns with a characteristic blue flame.
Write the scheme of oxalic acid decarboxylation.

Experiment 6. *Hoffman* amide degradation.

Degradation of amides with bromine in the presence of sodium hydroxide, aka sodium hypobromide, is called the *Hoffmann* rearrangement and to be used to produce primary amines and to reduce the length of the carbon chain.

Place 2 spatulas of acetamide* in the first tube and dissolve it in 5 drops of water. Add 5 drops of bromine water* and 5 drops of concentrated aq. sodium hydroxide to the solution (30) and plug the tube with a gas outlet tube. The gas outlet tube is placed into a second tube containing 10 drops of distilled water. Heat the first test tube over the flame of the burner for 5 minutes. Cool the tube and add 2 drops of a 2 % aq. solution of copper sulfate (26) to the solution in the second tube. Intense blue-violet coloring is the positive test for primary amine formation.
Write the scheme of Hoffman degradation for acetamide.

Consider whether N-methylacetamide and N, N-dimethylacetamide will be degraded by bromine in the presence of sodium hydroxide?

Experiment 7. Hydroxamic test on esters, acid amides and anhydrides.

Place 2 drops of ethyl acetate, acetic anhydride and acetamide in three test tubes. Add to each of them 2 drops 5 % aq. hydroxylamine chloride solution* and 2 drops 10 % aq. sodium hydroxyde (21). Heat to boiling and cool. Add to each tube a few drops of 10 % hydrochloric acid (9) to reach acidic pH (by the indicator) and then 1–2 drops of 1 % aq. $FeCl_3$ (8) into each tube. Fix the change of the color in each tube.
Write schemes of the mechanism of the reactions. Discuss the mechanism.

Signature of the instructor:

LABWORK № 17
FUNCTIONAL DERIVATIVES OF CARBONIC ACID. SULFONIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES

Objective: to study the structure and properties of functional derivatives of carbonic acid; sulfonic acids and their functional derivatives.

Recommended literature

Chernykh, V. P. Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

Problems for discussion:

1. Structure, nomenclature and chemical properties of functional derivatives of carbonic acid.

a) Phosgene, chloroformates; organocarbonates.

b) Carbamic acid and its esters (urethanes).

c) Carbamide (urea): hydrolysis, basic and nucleophilic properties; cyclisation; biuret test; nitrozation of the urea and its interaction with hypobromites.

d) Acyl ureas (ureides).

e) Guanidine, its basic properties.

2. Biogenic and pharmaceutic functional derivatives of carbonic acid.

3. Structure and nomenclature of sulfonic acids and their functional derivatives.

4. Chemical properties of organic sulfonic acids and their salts, their use in industry and pharmacy.

5. Chemical properties and application of sulfonic acid functional derivatives (esters, halides amides).

6. Sulfanilic acid. Sulfa drugs (antibacterial sulfonamides) as competitive of the enzyme dihydropteroate synthase.

PRACTICE PROBLEMS

1. Write structural formulas of carbonic acid and its mono- and full amides and halides. Determine electronic effects and indicate reaction sites.

2. Write the structures, convert trivial to IUPAC names. Determine the electronic effects and indicate the reaction sites.

Ethyl chloroformate	Ethyl propyl carbonate
Diethyl carbonate	Di-*tert*-butyl dicarbonate

Ethyl carbamate	N, N-dimethyl ethyl carbamate
Butyric acid ureide	Ethyl isocyanate
Guanidine	Nitrosourea

3. Write the reactions of phosgene with the next reagents:

with an excess of isopropyl alcohol

successively with equimolar amounts of ethanol and cyclohexanol

with anisole (methoxybenzene) in the presence of aluminum chloride

with an equimolar amount of aniline in the presence of pyridine

with an equimolar amount of pyrocatechol

with an equimolar amount of ethanolamine

with an excess of benzene

4. A protecting (protective) group is introduced into a molecule of heterofunctional compound by chemical modification of a functional group to obtain in a subsequent chemical reaction. The first step of the scheme includes protection of the functional group a chemist wants to keep unchanged. The second step, the main reaction, changes functionality of the other (unprotected) groups; the protected group must be stable within the conditions. And finally, in the third step a chemist removes protection giving back the original functional group. Protecting groups plays an important role in multistep synthesis.

Write the schemes of protection and deprotection for the functional groups of the heterofunctional compounds.

L-Phenylalanine (BOC protection with **di-*tert*-butyl dicarbonate)**

D-Lactic acid (benzyloxy protection with benzyl bromoformate)

5. Consider the basic acid properties of:

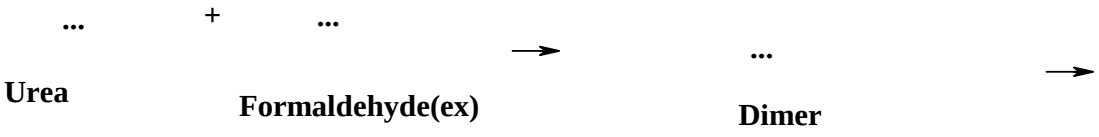
urea

guanidine

arginine

6. Write the reaction schemes of the formation of urea nitrates and oxalates. Explain the shift of equilibrium to salt formation.

7. Complete the scheme and give product names.

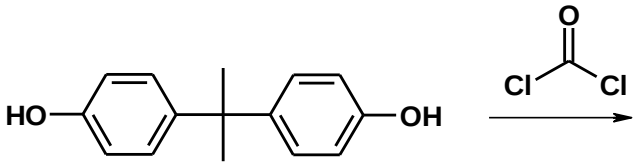


Urea **Formaldehyde(ex)** **Dimer**

Leniar polymer

Spacial (2D) polymer

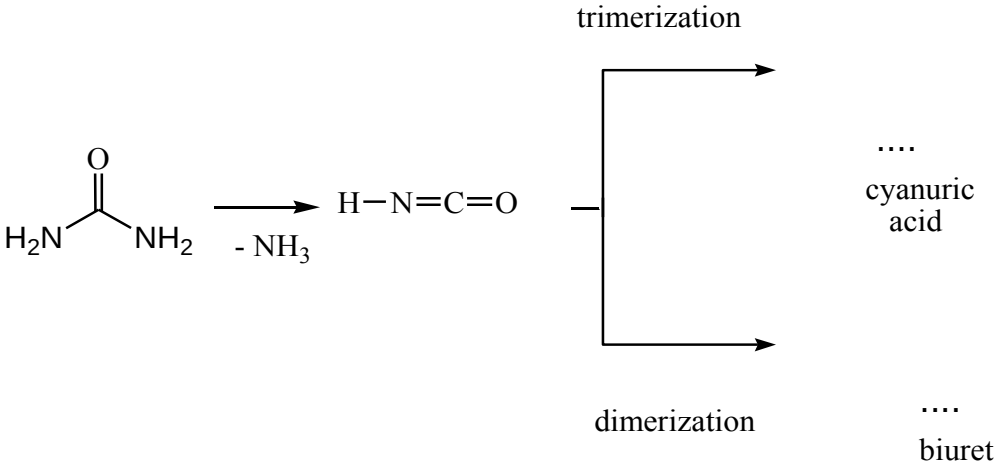
8. Complete the scheme and give product names.



Dimer

Polymer

9. Complete the schemes the urea oligomerization.

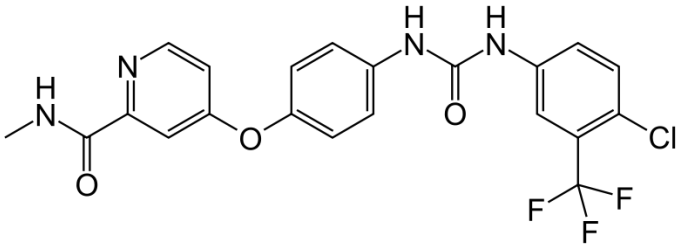


Write the chelate complex of dimer with copper (II) hydroxide.

10. ***Clathrates are*** _____

_____

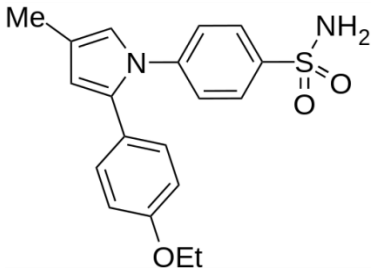
11. Analyze the structure of *Sorafenib*, the active principle of *Nexavar*, which possess antitumor activity. Select the known structural fragments, specify the functional groups and reaction cites.



12. Give the formulas of pharmaceutical drugs [4] and find the structural fragments.

Sulgin	*Chlorhexidine*
Metformin	*Proguanil*
N-Nitroso-N-methylurea	*Carmustine*

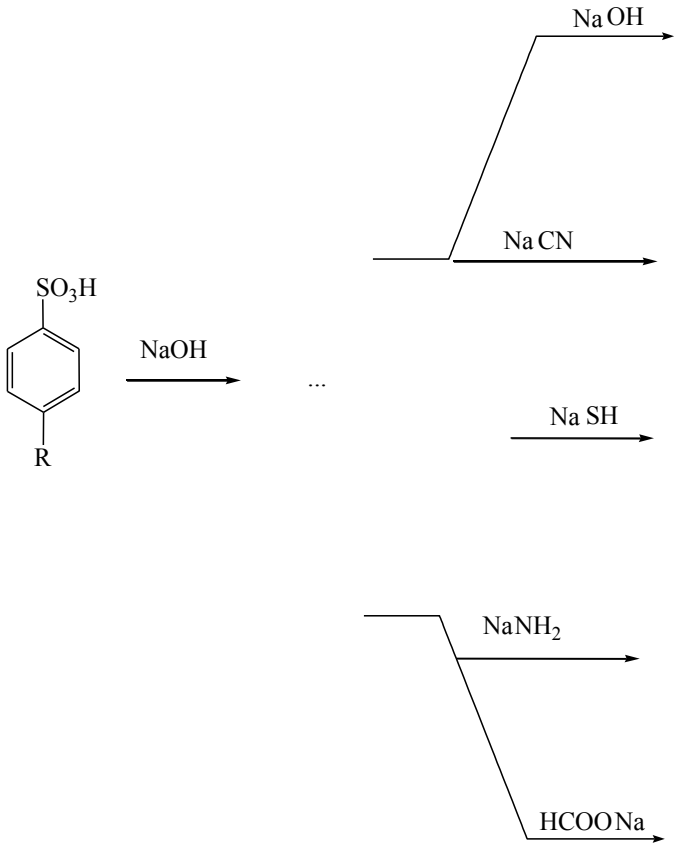
13. Analyze the structure of *Apricoxib*. Select structural fragments that are similar to those in drugs of other groups.



14. Write structures, convert trivial to IUPAC names. Determine electronic effects and indicate reaction sites.

Toluenesulfonic acid	Cyclohexyl tosylate
Ammonium ethylsulfonate	4,4'-Dichlorodiphenylsulfone
N, N-dimethyl toluene sulfonamide	Saccharin

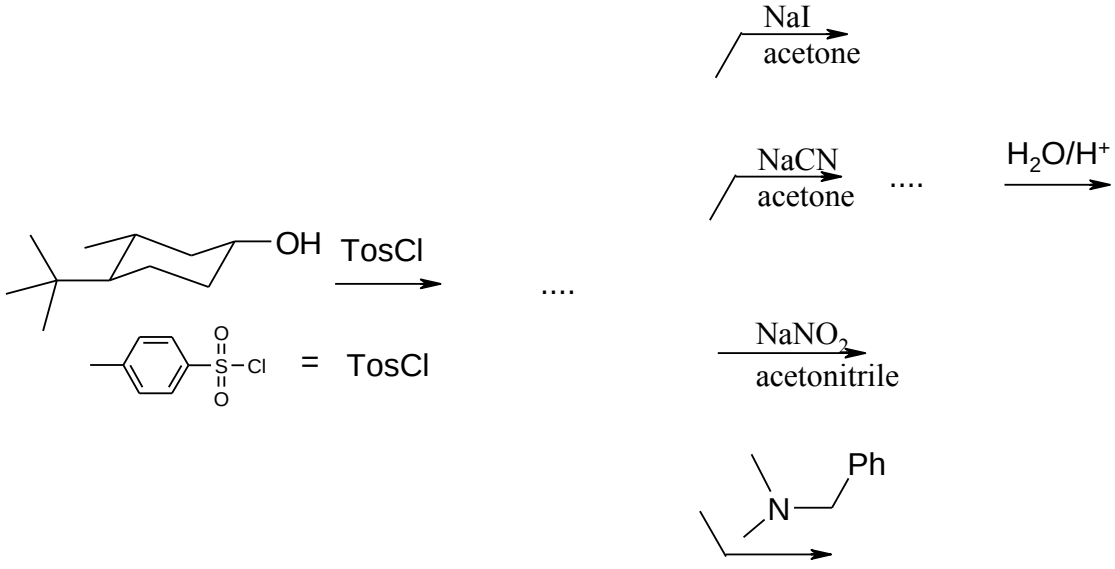
15. Complete the scheme. Name the products.



16. Design regioselective synthesis of pure (without isomeric products) 1-bromo-2-methylbenzene from toluene using a sulfonation as an protecting group approach.

17. Write both products of nucleophilic substitution in the reaction of 3a-methyl-4e-tert-butylcyclohexane-1e-ol with hydrogen chloride as a protic solvent. Explain the result.

Write the reaction of the same substrate with tosyl chloride and predict the products of its interaction with various reagents in aprotic solvents.

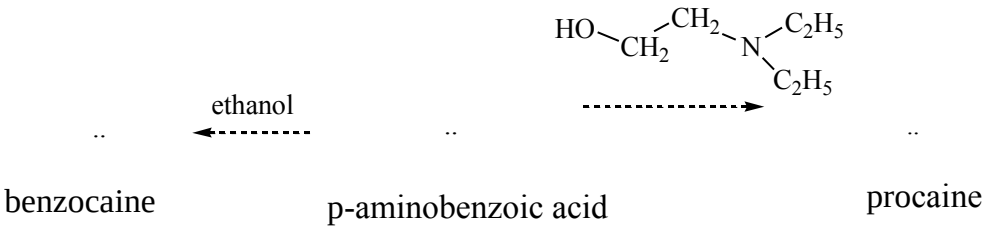


Explain why sulfonates are substrates with good leaving groups.

18. Analyze the structure of the active principles of pharmaceutical drugs [4]. Select the known structural fragments, specify the functional groups and reaction cites.

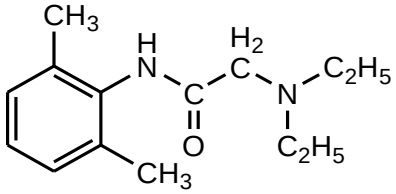
Sulfacetamide	*Sulfadimethoxine*
Amprenavir	*Celecoxib*
Zonisamide	*Chlorpropamide*
Furosemide	*Mafenide*
Sotalol	*Tamsulosin*
Taurine	*Glyburide*

19. Complete reaction scheme of *p*-aminobenzoic acid synthesis. Indicate the type of mechanisms.



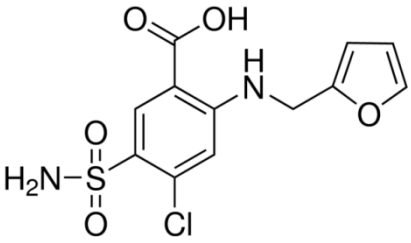
benzocaine p-aminobenzoic acid procaine

Explain the longer anesthetic action of *Lidocaine* compared to *Procaine (Procainamide)*



lidocaine

20. Predict frequency bands in IR spectrum as well as chemical shifts, J-coupling and intensity in the ^{1}H NMR spectrum of *Furosemide*. Explain the answer.



EXPERIMENTAL SECTION

Experiment 1. Basic properties of urea.

Place in each two test tubes one spatula of urea (60) and 2 drops of water. In the first tube add 2 drops of concentrated nitric acid*. In the second tube add 2 drops of a saturated solution of oxalic acid, prepared previously in other tube by dissolving 1 spatula of oxalic acid (25) in 1–2 drops of water. After a few seconds, the precipitation of urea nitrate and urea oxalate begins, which are less soluble in water compared to urea.

Explain why urea form salt with only one equivalent of oxalic acid.

Experiment 2. Urea hydrolysis.

Place in a test tube 1 spatula of urea (60) and add 4–5 drops of barite water (59) so as not to wet the top of the tube. Heat the mixture to a boil and, continuing heating, bring a strip of red litmus paper moistened with water to the upper edge of the tube. Fix the change in the color of the litmus paper, a white feculence appears in the test tube.

Which of the products of urea hydrolysis is identified with a litmus indicator?

Which of the products of urea hydrolysis is detected in the test with barite water?

Experiment 3. Interaction of urea with nitrous acid.

Place 1 spatula of urea (60) and 2–3 drops of water in a test tube. To the solution obtained add 2 drops of a 5 % aq. solution of sodium nitrite (34) and 1 drop of concentrated sulfuric acid*. Shake the contents of the tube, a vigorous release of gas bubbles begins.

Write the reaction scheme.

Experiment 4. Thermal decomposition of urea.

Place 1 spatula of urea (60) in a dry test tube and heat the tube gently. The release of gas bubbles is observed. Bring a strip of red litmus paper* moistened with water to the test tube. Note the discoloration of the litmus. Heat the tube until the melting solidifies. After cooling add 5–6 drops of water to the tube and boil for 2–3 minutes. Allow the contents of the tube to sediment, decant the solution carefully in another tube and add 2 drops of 10 % aq. sodium hydroxide solution (21) and 1 drop of 2 % aq. copper (II) sulfate solution (26) to it. Fix the coloring of the biuret complex salt with copper (II) ions.

Which of the reaction products is detected with a litmus indicator?

Signature of the instructor:

LABWORK № 18
CONTINUOUS ASSESSMENT № 3. STRUCTURE, REACTIVITY AND IDENTIFICATION OF CARBONYL COMPOUNDS, CARBONIC AND SULFONIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES. ACADEMIC RESEARCH № 3

Objective: to systematize the knowledge of the structure, reactivity and identification of oxo compounds.

Remind the program material from the topics 15–17.

Recommended literature: study the literature from the topics 15–17.

EXPERIMENTAL SECTION

An example for experimental problem:

1. Propose and proceed chemical tests, which permit us to distinguish formaldehyde, acetone, acetic acid, acyl acetate and urea (solutions).
2. Identify chemically the proposed substance.
3. Predict spectral characteristics (UV, IR, NMR-spectra) of the proposed substance.

Signature of the instructor:

RECOMMENDED FURTHER READING

Basic

1. *Lakhvich, T. T.* Organic chemistry : handbook. Part I / T. T. Lakhvich, O. N. Ryneyskaya, G. P. Fando. – Minsk : BSMU, 2017. – 132 p.

2. *Lakhvich, T. T.* Organic chemistry : handbook. Part II / T. T. Lakhvich, O. N. Ryneyskaya, G. P. Fando. – Minsk : BSMU, 2017. – 152 p.

3. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – 4 ed., rev. and enl. – Kharkiv : NUPh, Original, 2011. – 440 p.

4. *Chernykh, V. P.* A. Applied infrared spectroscopy : a manual for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. – Kharkiv : NUPh, 2014. – 152 p.

5. *Zurabian, S.* Fundamentals of bioorganic chemistry: textbook for medical students / S. Zurabian. – M. : ГЭОТАР-Медиа, 2012. – 304 p.

Additional

6. *Organic* chemistry. Tests with explanations : the study manual for students of higher schools. – Kharkiv : NUPh, 2015. – Scientific publication.

7. *Loudon, M.* Organic Chemistry / M. Loudon, J. Parise. – 6th ed. – New York : W. H. Freeman and Company, 2015. – 1648 p.

8. *Klein, D. R.* Organic Chemistry / D. R. Klein. – New York : Wiley, 2015. – 1648 p.

9. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. – 16-е изд., перераб., испр. и доп. – М. : Новая волна, 2012.

Normative regulatory acts

10. European Pharmacopoeia. In 3 vol. – 9th ed. – Council of Europe, Strasbourg, 2016.

TABLE OF IR ABSORPTIONS

Groups	Vibration type	Frequency range (cm^{-1})	Intensity*
Alyl, cycloalkyl	Stretching C–H:		
	Asymmetric	2999–2926	s – m
	Symmetric	2872–2853	s – m
	Bending C–H:		
	Asymmetric	1485–1430	m
	Symmetric	1380–1340	s
Double bond	Stretching C=C	1680–1600	m
	Stretching =C–H	3100–3000	m
	Terminal vinyl group $=CH_2$:		
	Asymmetric	3100	m
	Symmetric	3000	m
	Bending =C–H	1000–800	s
***Z*-diastereomers**	Bending =C–H	730–650	s
***E*-diastereomers**	Bending =C–H	980–900	s
Triple bond	Stretching C≡C	2300–2100	m
	Stretching ≡C–H	3333–3267	s
	Bending ≡C–H	700–610	
Benzene fragment	Stretching $C_{ar}\overset{\cdots}{—}C_{ar}$	~ 1600	
		~ 1580	m
		~ 1500	
		~ 1450	
	Stretching C_{ar}–H	3100–3000	m
	Bending C_{ar}–H	900–675	m
monosubstituted	Bending C_{ar}–H	710–690; 770–730	m; m
***o*-disubstituted**	Bending C_{ar}–H	770–735	m
***м*-disubstituted**	Bending C_{ar}–H	710–690	m
		810–750	m
***n*-disubstituted**	Bending C_{ar}–H	840–810	m
Hydroxyl group	Stretching O–H	3650–3200	s, board
primary	Stretching C–O	~ 1050	s
	Bending O–H	1350–1260	s
secondary	Stretching C–O	~ 1100	s
	Bending O–H	1350–1260	s
tertiary	Stretching C–O	~ 1150	s
	Bending O–H	1410–1310	s
Hydroxyl group (phenols)	Stretching O–H	3650–3200	s
	Stretching C–O	1200	s
	Bending O–H	1410–1310	s

* s — strong; m — medium; w — weak.

Groups	Vibration type	Frequency range (cm^{-1})	Intensity*
Etheric	Stretching C–O–C:		
alkyl	Asymmetric	1150–1085	s
aryl	Asymmetric	1275–1200	s
	Symmetric	1075–1020	s
vinyl	Asymmetric	1225–1200	s
	Symmetric	1075–1020	s
Mercapto group	Stretching S–H	2600–2550	w
Sulfoxides	Stretching S=O	1070–1030	s
Sulfones	Stretching SO_2		
	Asymmetric	1350–1300	s
	Symmetric	1160–1140	s
Sulfonic acids	Stretching SO_2		
	Asymmetric	1260–1150	s
	Symmetric	1080–1010	s
Amines	Free stretching N–H:		
primary	Asymmetric	~ 3500	m
	Symmetric	~ 3400	m
	Bonded	3400–3250	s
secondary	Free stretching N–H	3450–3300	m
	bonded	3350–3200	s
	Bending N–H	1650–1550	m
aliphatic	Stretching C–N	1220–1020	w
aromatic	Stretching C–N	1360–1280	s
Amine salts	$+$ Stretching NH in RNH_3	~ 3000	s
	$+$ Stretching NH		
	in R_2NH_2	2700–2250	s
	in R_3NH	2700–2250	s
Azo compounds	Stretching N=N	1630–1575	m
Diazo compounds	$+$ Stretching –N≡N	2300–2000	m
Nitro compounds	Stretching NO_2:		
aromatic	asymmetric	1570–1500	s
	symmetric	1370–1300	s
aliphatic	asymmetric	1570–1550	s
	symmetric	1380–1370	s
***C*-Nitro compounds**	Stretching NO	1600–1500	s
***N*-Nitro compounds**	Stretching NO	1500–1430	s
***O*-Nitro compounds**			
trance	Stretching NO	1680–1650	s
cis	Stretching NO	1625–1610	s
Nitriles	Stretching C≡N	2260–2220	m

Groups	Vibration type	Frequency range (cm^{-1})	Intensity*
Imines, oximes	Stretching C=N	1690–1630	m
Aldehydes	Stretching C=O		
aliphatic		1740–1720	s
α, β-unsaturated		1705–1680	s
aromatic		1715–1695	s
Ketones	Stretching C=O		
aliphatic		1725–1705	s
alkyl aryl		1700–1680	s
diaryl		1670–1660	s
1,4-quinones		1690–1660	s
	Bending C=O	~1100	s
Carboxylic acids	Stretching OH	2700–2500	w
	Stretching C=O		
aliphatic		1725–1700	s
α, β-unsaturated		1715–1690	s
aromatic		1700–1680	s
Carboxylates	Stretching C=O		
	Asymmetric	1650–1610	s
	Symmetric	1450–1400	s
Esters			
aliphatic	Stretching C=O	1750–1735	s
α, β-unsaturated, aromatic	Stretching C=O	1730–1717	s
Amides	Stretching C=O		
	(I amide band)	1700–1630	c
	Free stretching N–H	3500–3400	m
	Bonded stretching N–H	3350–3140	m
	Bending N–H (II amide band)	1620–1510	s
Anhydrides	Stretching C=O:		
	asymmetric	1870–1800	s
	symmetric	1790–1740	s
	Stretching C–O	1130–900	s
Acyl halides	Stretching C=O	1810–1750	s
Halides	Stretching: C–F	1400–1000	s
	C–CI	800–600	s
	C–Br	600–500	s
	C–I	~ 500	s

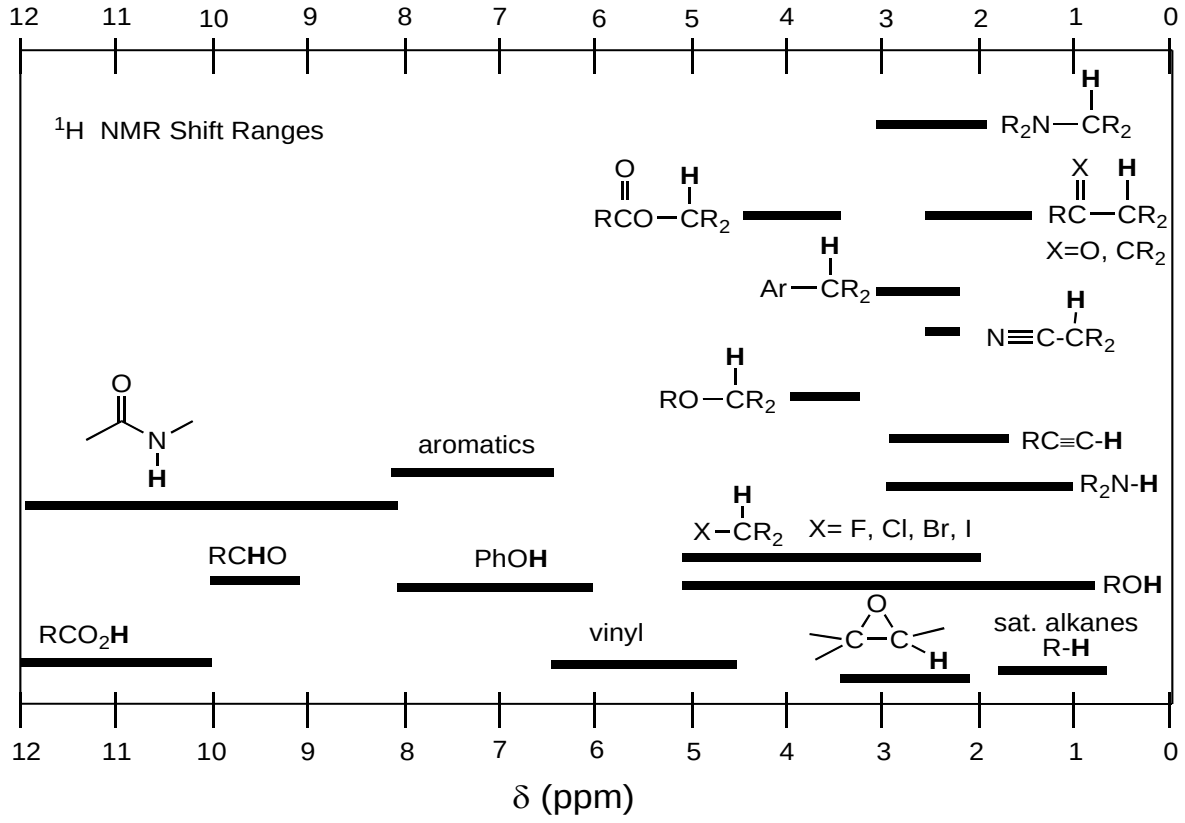
Supplement 2

TYPICAL VIBRATIONAL FREQUENCIES OF FUNCTIONAL GROUPS

Bond	Molecule	Wavenumber (cm^{-1})
C–O	Alcohols, ethers, esters, carboxylic acids, etc.	1300 – 1000
C=O	Aldehydes, ketones, esters, carboxylic acids	1750 – 1680
C=O	Amides	1680 – 1630
N–H (Stretching)	Amines and amides	3500 – 3100
–N–H (Bending)	Amines and amides	1640 – 1550
O–H	Alcohols	3650 – 3200
C–N	Amines	1350 – 1000
S–H	Mercaptans	2550

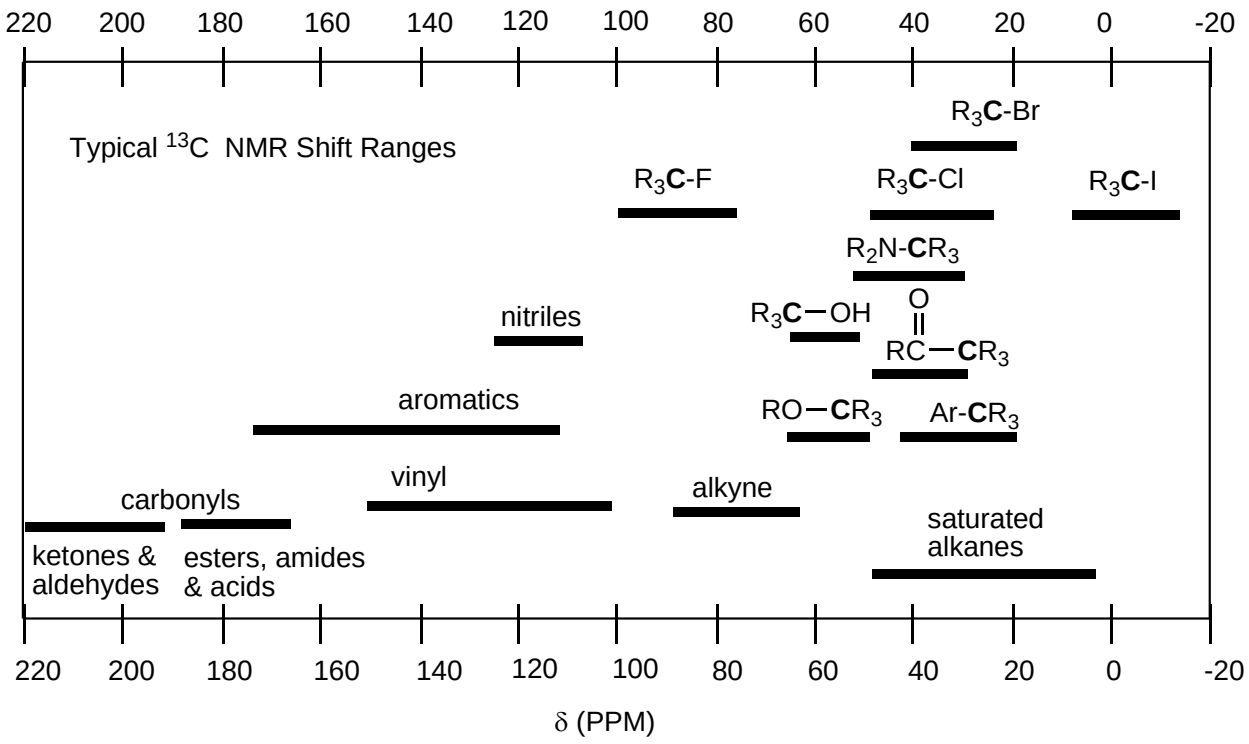
Supplement 3

TYPICAL ^{1}H NMR CHEMICAL SHIFTS RANGES; ADDITIONAL SUBSTITUTION*



* Can move the resonances out of the range.

TYPICAL ^{13}C NMR CHEMICAL SHIFTS RANGES



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ORGANIC CHEMISTRY. LABORATORY HANDBOOK

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На английском языке

В двух частях

Часть 1

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