МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
ХАРКІВСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

MAIN TYPES AND MECHANISMS OF THE REACTIONS IN ORGANIC CHEMISTRY

Methodical instructions for 1st year students' self-work
in Biological and Bioorganic Chemistry
(module 1)

ОСНОВНІ ТИПИ ТА МЕХАНІЗМИ РЕАКЦІЙ В ОРГАНІЧНІЙ ХІМІЇ

Методичні вказівки для самостійної роботи студентів 1-го курсу
з біологічної та біоорганічної хімії
(модуль 1)

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Subject I. CLASSIFICATION OF CHEMICAL REACTIONS**.**
REACTIVITY OF ALKANES, ALKENES, ARENES, ALCOHOLS, PHENOLS, AMINES, ALDEHYDES, KETONES AND CARBOXYLIC ACIDS

Motivational characteristic of the subject

This subject is the basis for understanding some biochemical reactions taking place in living organisms during metabolism (lipid peroxide oxidation, formation of hydroxyacids from unsaturated acids in Krebs cycle and others). This subject is important for understanding the mechanism of similar reactions at the synthesis of drugs and analogues of natural compounds.

Objectives

To be able to predict ability of main classes of organic compounds to undergo hemolytic and heterolytic reactions accordance with their electronic structure and electronic effects of substituents.

1. Free radical and electrophilic reactions (reactivity of hydrocarbons)

Training questions

1. To be able to describe the mechanisms of the following reactions:
- radical substitution – S_R
- electrophilic addition - A_E
- electrophilic substitution - S_E

2. To be able to explain effects of substituents on reactivity at the electrophilic interactions using knowledge about their electronic effects.

Initial level

1. Structure of carbon atom. Types of hybridization and its electronic orbitals.
2. Structure, length and energy of σ- and π- bonds.
3. Conformation of cyclohexane.
4. Conjugation. Open and closed (aromatic) conjugated systems.
5. Electronic effects of substituents.
6. Transient state. Electronic structure of carbocation. Intermediators σ- and π - complexes.

Practical skills

1. To be able to determine possibility of covalent bond cleavage, type and mechanism of the reaction.
2. To be able to perform bromination reactions for compounds with double bonds and for aromatic compounds.

Test questions

1. Give the mechanism of ethylene hydrogenation.
2. Describe mechanism of propenoic acid hydration reaction. Explain role of acid catalyst.
3. Write the equation of toluene (methylbezene) nitration. What is the mechanism of this reaction?
4. Explain deactivating and orienting effect of nitrogroup in the molecule of nitrobenzene by the example of bromination reaction.

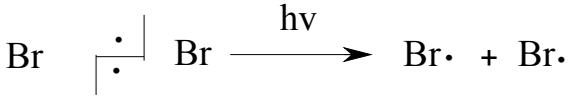
Teaching tasks

Task №1. Decribe the mechanism of isobutene and cyclopentane bromination reaction at exposure to UV light.

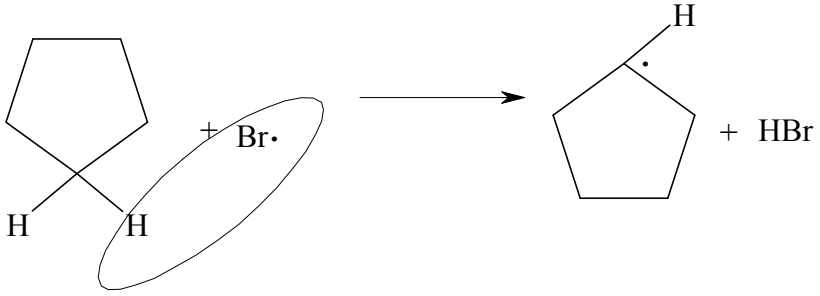
Solution. Molecules of isobutene and cyclopentane consist of sp^3- hybridized carbon atoms. C – C-bonds in their molecules are nonpolar, but C – H-bonds are low-polar. These bonds are undergone hemolytic fision readily that leads to the formation of free radicals – particles having unpaired electrons. Thus, radical substitution reactions - R_s – reaction or chain - should take place in the molecules of these substances.

The stages of any R_S –reaction are: chain initiation, chain propagation and chain termination.

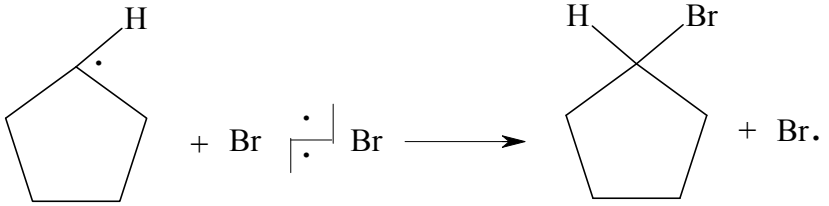
Chain initiation is a process of formation of free radicals at the high temperature and at exposure to UV light:



Chain propagation occurs at the expense of interaction of high-reactive free radical ·Br with low polar C – H-bond in the cyclopentane molecule that leads to the formation of new cyclopentyl-radical:

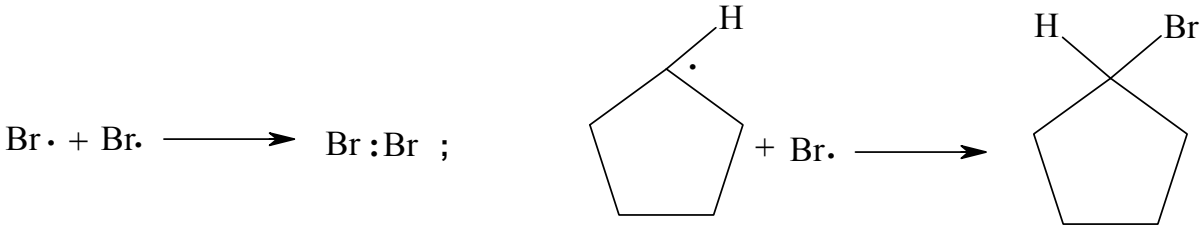


Cyclopentyl-radical reacts with new bromine molecule, resulting in it hemolytic fision of bond and forming bromocyclopentane and new bromine radical:



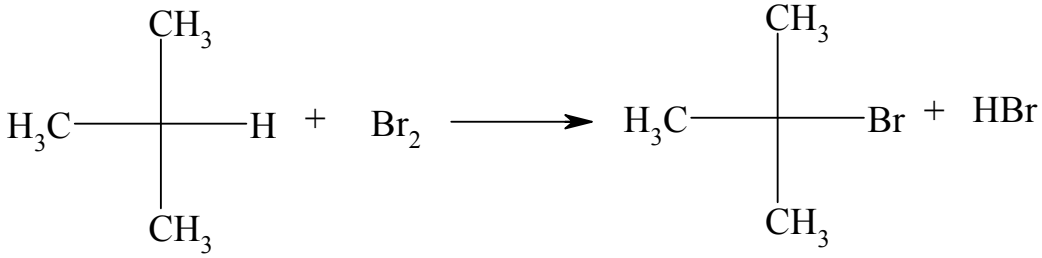
Free bromine radical attacks new cyclopentane molecule. Thus, chain propagation repeats many times, i.e., chain reaction takes place.

Chain termination completes chain reaction at the expense of combination of different radicals:



Whereas all carbon atoms in the cyclopentane molecule are equivalent, only monocyclobromopentane forms.

C – H-bonds are not equivalent in isobutane. They differ in the energy of hemolytic dissociation and stability of formed fre radicals. It is known that dissociation energy of C – H-bond increases from tertiary to primary carbon atom, stability of free radicals descreases in the same order. That is why in the molecule of isobutane bromination reaction proceeds regioselectively – using tertiary carbon atom:

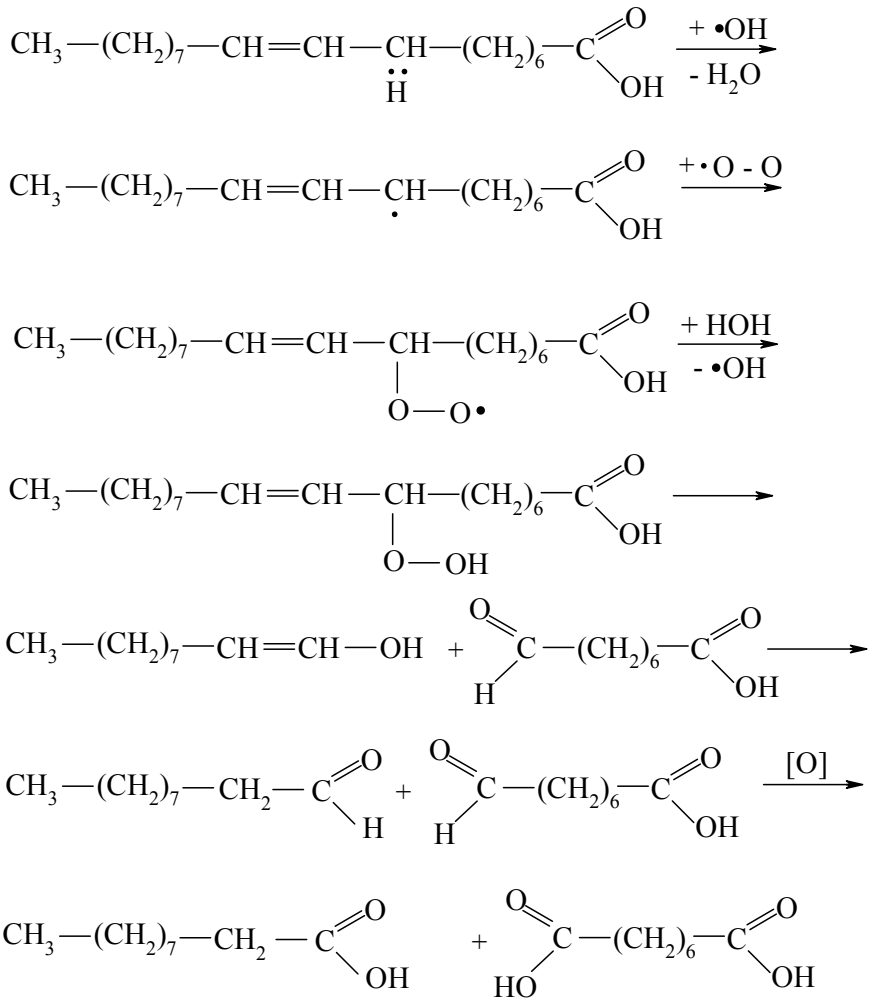


It should be pointed out that for more active chlorine radical regioselectivity is not kept to the full extent. Hydrogen atoms can be substituted at any carbon atoms under the chlorination, but quantity of substitution product at the tertiary carbon will be the greatest.

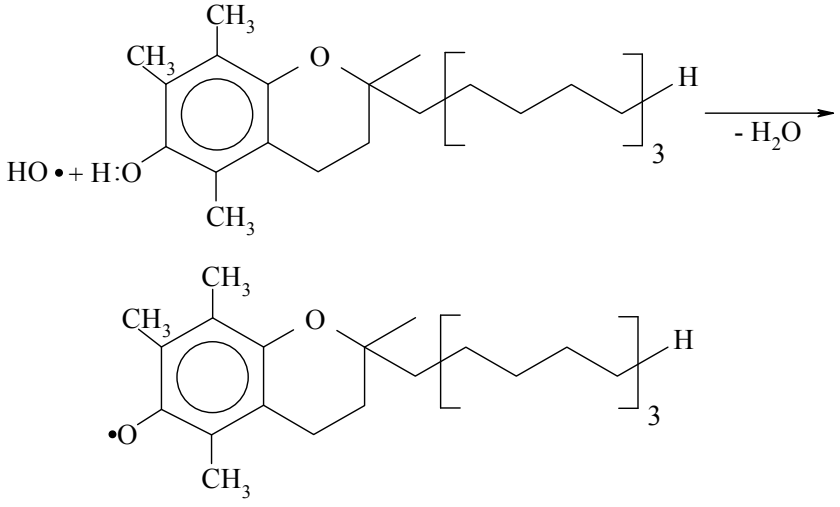
Task №2. Describe the mechanism of oleic acid peroxidation which takes place at radiation sickness as a result of damage of cellular membranes. What compounds do serve as antioxidants in our organism?

Solution. Example of radical reaction is peroxidation when unsaturated faty acids are undergone free radical effect. Unsaturated fatty acids are a part of cellular membranes. Breakage on radicals of water molecules is possible at radiation exposure. Hydroxyl radicals attack molecule of unsaturated acid in methylene group, neighboring with double bond, because free radical, stabilized at the expense of participation of unpaired electron in conjugation with electrons of π-cbonds, forms in

such a case. Further organic radical reacts with biradical oxygen molecule forming unstable hydroperoxides. These hydroperoxides dissociate forming aldehydes which are oxidized to acids – terminal products of the reaction. Damage of cellular membrame is a consequence of peroxidation:



Inhibiting effect of vitamin E (tocopherol) in the organism is conditioned with its ability to combine free radicals, forming in the cells:

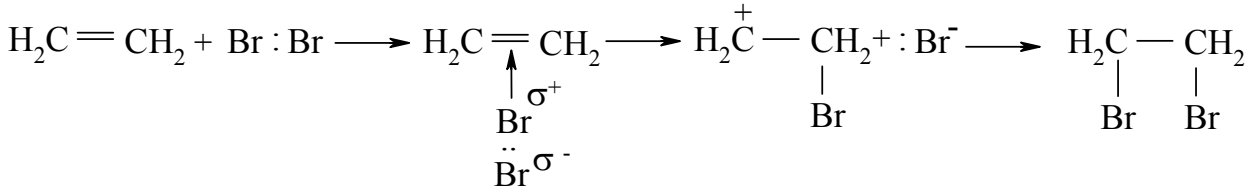


In the formed phenoxide radical unpaired electron is in the conjugation with π-electronic cloud of aromatic ring that reslts in its relative stability.

Task №3. Give the mechanism of ethylene bromination reaction.

Solution. Reactions which undergo π-bonds fision, i.e., addition reactions, are typical for compounds which consist of carbon atoms in the state of sp^2- or sp-hybridization. These reactions can pass on radical or onic mechanism depending on reagent nature, solvet polaity, temperature and others. Ionic reactions proceed under action of electrophilic reagents having electron affinity, or nucleophilic reagents, which donate their electrons. As electrophilic reagents can be catuins and compounds which have atoms with incomplete electron shells. Elementary electrophilic reagent is roton. Nucleophilic reagents are anions, or compounds with atoms having unshared electron pairs.

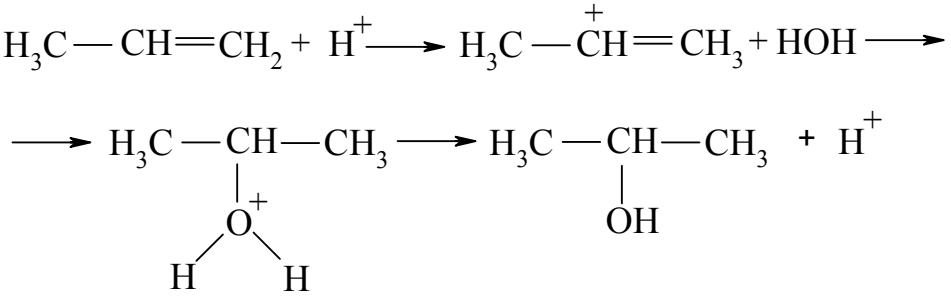
Reactions of electrophilic addition - A_E-reactions- are typical for alkenes – compounds having sp^2 - or sp-hybridized carbon atom. Halogenation reaction proceeds by ionic mechanism with the formation of carbocations in the polar solvents:



Bromine molecule is polarized under the action of π-bond of ethylene molecule causing the formation of unstable π-complex, which transforms into a carbocation. In this carbocation bromine is bound with carbon using π-bond. Process is terminated with interaction of bromine anion with this carbocation that results in the formation of final product of reaction - dibromoethane.

Task №4. Substantiate Markovnikov's rule by the example of propene hydration reaction.

Solution. As water molecule is nucleophilic reagent then its addition across the double bond without catalyst is impossible. Acids serve as catalyst in such reactions. Formation of carbocations occurs at the addition of proton of acid at the fission of π-bond:

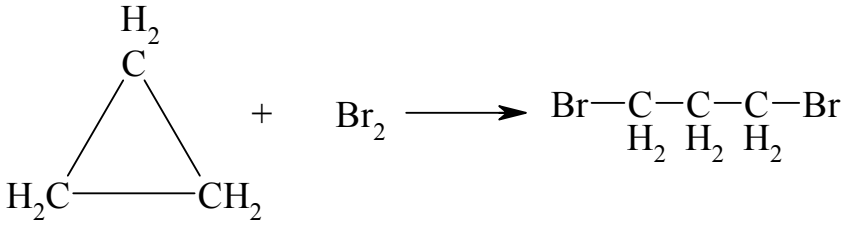


Water molecule attaches to the formed carbocation at the expense of paired electrons of oxygen atom. Stable alkyl derivative of oxonium stabilized with proton elimination is formed. Product of reaction is secondary propanol (propan-2-ol).

In hydration reaction proton attaches in accordance with Markovnikov's rule – to the carbon atom with more hydrogen atoms, as electron dencity shifts to this atom because of positive inductive effect of CH_3-group. Besides, formed after addition tertiary carbocation is more stable than primary (influence of two alkyl-groups).

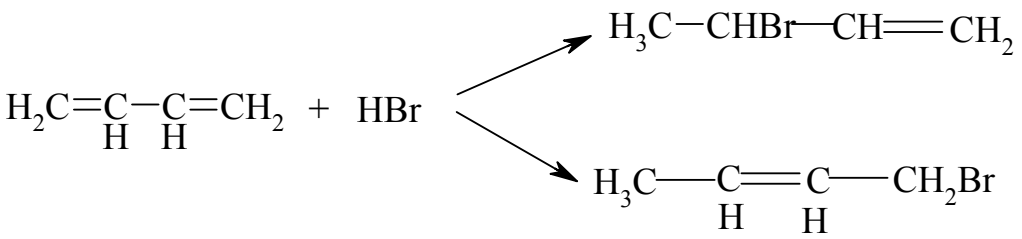
Task № 5. Substantiate ability to form 1,3-dibromopropane at the cyclopropane bromination.

Solution. Molecules which are three- or four-membered cycles (cyclopropane and cyclobutane) exhibit properties of unsaturated compounds, because electronic state of their "banana" bonds resemble π-bond. That's why they undergo addition reactions with cycle breakage like unsaturated compounds:

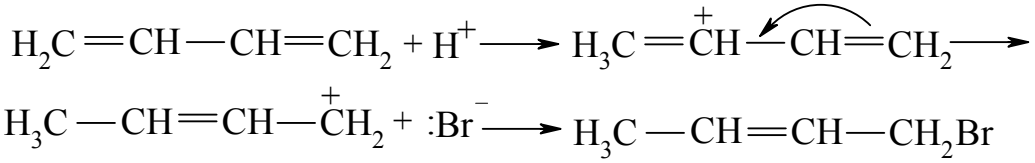


Task № 6. Describe reaction between hydrobromide and butadiene -1,3. What is the feature of this reaction?

Solution. 1,2 Adition products (1) and 1,4 addition products (2) form after interaction between hydrobromide and butadiene -1,3:



Formation of product (2) is stipulated with presence of common to whole molecule π-electron cloud in the conjugated system, hereupon it undergoes electrophilic addition reaction (A_E- reaction) as whole block:

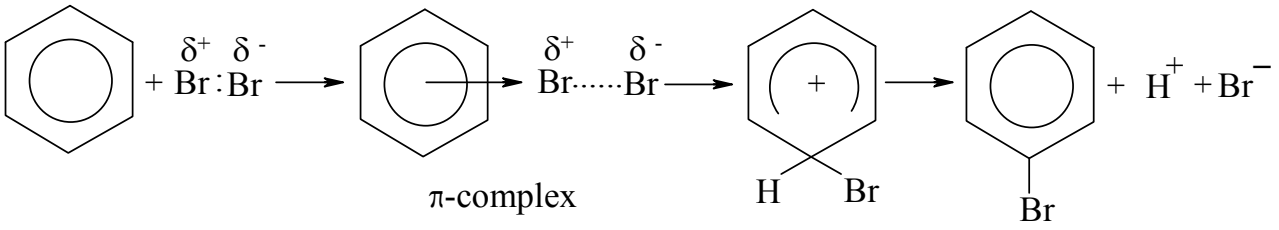


Task № 7. Describe mechanism of benzene bromination.

Solution. Electrophilic substitution reactions are typical for aromatic compounds having closed conjugate-electronic system and which because of it have significant stability. Presence of increased electron density on both sides of ring protects its from attack with nucleophilic reagents and vice versa it simplifies

capability of attack with nucleophilic reagents and vice versa - it simplifies capability of attack with cations and other electrophilic reagents.

Interaction between benzene and halogens proceeds in the presence of catalysts - $AlCl_3$, $FeCl_3$ (so called Lewis acid). They provoke polarization of halogen molecule, after which it attacks π-electrons of benzene ring:

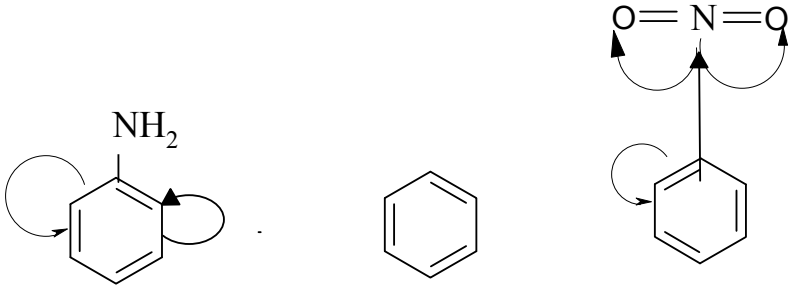


At first π-complex forms, which slowly transfers into σ - complex, where bromine forms covalent bond with one of the carbon atoms at the expense of two of six electrons of aromatic ring. Four retained π-electrons are dispensed between five atoms of carbon ring; σ-complex is less convenient structure because of disturbance of aromaticity, which restores by poton separation.

Sulphonation and nitration refer to electrophilic substitution reactions in aromatic compounds. Nitroyl-cation - NO^{2+}, formed under interaction between concentrated sujphuric acid and nitric acid (nitrated mixture), serves as nitrating agent; cation SO_3H^+, or sulfur oxide (IV) serves as sulphonating agent, if sulphonation is performed with oleum.

Task № 8. Evaluate reactivity of benzene, aniline, nitrobenzene, pyrrol and pyridine electrophilic substitution reactions (S_E-reactions).

Solution. Activity of compounds in S_E-reactions depends on value of electron demcity in aromatic ring (direct dependence). Depending on this reactivity of compounds should be considered with reference with electronic effects of substituents and heteroatoms.



Amino group in aninline exhibits + M-effect, that results in increasing of dencity in benzene ring and its greatest concentration is in orto- and para-positions. Reaction behavior is facilitated.

Nitro group has -I and –M-effects in nitrobenzen, that's why it desctivates benzene ring notably in orto- and para-positions. Since interaction of electrophile occurs in the place of highest electron dencity then meta-isomers form. Thus, electron-donating substituents – these orto- and para-orientants (orientants of I type and activators of S_E-reactions; electron withdrawing substituents – metha-orientants (orientants of II type) deactivators of S_E-reactions.

In five-membered heterocycles (pyrrole, furan, thiophen), which are π-excessive systems, S_E-reactions proceed easier then in benzene; in this case α-position is more reactive.

Heterocyclic systems with pyridine nitrogen are π –deficient, that's why they undergo electrophilic substitution reactions more difficult; in such a case electrophile occupies β-position in relation to nitrogen atom.

Revision exercises

№1

1. What is the name of the product obtained after 2-methylbutane bromination reaction at exposure to UV light? Describe mechanism of the reaction.
2. Describe mechanism of the reaction between butene-1 with hydrobromide. What is the type of this reaction?
3. Write the reaction equation for aniline (aminobenzene) bromination. Point out orienting effect of amino group. What is easier to brominate – benzene or aniline? Why?

№2

1. Describe mechanism of 2-methylpropane chlorination reaction at exposure to UV light.
2. Write the mechanisms of interaction reaction between butadiene-1,3 and hydrobromide.
3. Write the reaction equation of nitration of benzoic taking into account orienting influence of carboxyl group. What is easier to nitrate: benzene or benzoic acid? Why?

№3

1. Write mechanism of the cyclohexane chlorination reaction. Write predominant conformation of chlorocyclohexane.
2. Write the mechanism for HCl addition reaction to acrylic (propenoic) acid. Explain why this addition takes place against Markovnikov's rule.
3. Write the reaction equation for pyridine bromination taking into account orienting influence of heteroatom. What is easier to brominate: benzene or pyridine? Why?

№4

1. What is the name of the substance obtained at the toluene (methylbenzene) chlorination at exposure to UV light? Describe the mechanism of the reaction.
2. Write the mechanism of the butendioic acid chlorination reaction.
3. Write the reaction equation for phenol nitration taking into account orienting influence of hydroxyl. What is easier to nitrate: benzene or phenol? Why?

№5

1. Write the mechanism for propane bromination reaction. Explain where C-H-bond is and why in this case attacking place of free radical is bond.
2. Describe the mechanism of the interaction reaction between propen and water. What is the role of sulfuric acid in this process.
3. Write the reaction equation for benzaldehyde bromination. Compare this reaction with benzene bromination reaction.

№6

1. Write the mechanism of the cyclopentane bromination reaction.
2. Describe the mechanism of interaction reaction between isoprene (methylbutadiene) with 1 mol of bromine.
3. Write the reaction equation for toluene (methylbenzene) nitration taking into account orienting influence of methyl group. Does CH_3-group facilitate or trouble nitration reaction?

№7

1. Write the reaction equation for cyclopropane bromination. Explain direction of the reaction.
2. Justify Markovnikov's rule at the example of 2-methylpropen hydrochlorination reaction. Describe the mechanism of the reaction.
3. Write the reaction equation for pyrrol bromination. Point out orienting influence of heteroatom.

№8

1. What is the name of the substance obtained at the ethylbenzene chlorination at exposure to UV light? Describe the mechanism of this reaction.
2. Give the mechanism of transformation of fumaric acid (trans-butenedioic acid) into malic acid (2-hydroxybutanedioic acid) at metabolism in living organisms on one of the stage of Krebs cycle.
3. What products are formed at the chlorination of bromobenzene and benzoic acid? What compound will be active in the chlorination reaction?

№9

1. Give the mechanism of isobutene bromination at exposure to UV light.
2. Compare reactivity of vinyl chloride (chloroethene), ethylene and propene in the electrophilic addition reactions. Write hydrobromination reaction for one of the more active compound from them.
3. Describe the mechanism of the aniline bromination reaction with account of electronic effect of the amino group. Does presence amino-group in the benzene ring facilitate or trouble reaction?

№10

1. Give the mechanism of cyclohexane chlorination at exposure to UV light.
2. Give the mechanism of HBr addition reaction to the acrolein (propenal). Does reaction proceed in accordance with Markovnikov's rule? Substantiate answer.
3. Write the mechanism of the phenacetin (antipyretic) formation reaction using phenetole nitration reaction (ethoxy benzene).

№11

1. Write the reaction equation of cyclobutane with chlorine. Explain the direction of the reaction.
2. Give the mechanism of acrylic (propenoic) acid hydration reaction. What is the role of sulfuric acid in this reaction?
3. Write the reaction equation of toluene bromination. What is easier to nitrate – benzene or toluene and why?

№12

1. Give the mechanism of the 2-methylpentane chlorination reaction at exposure to UV light. Is regioselectivity observed in this case?
2. Give the mechanism of the pentene-1chlorination reaction.
3. Give the mechanism of the pyrrole bromination reaction. What is easier to brominate: pyrrole or pyridine and why?

№13

1. What is the product in 3-methylpentene bromination reaction at exposure to UV light? Give the mechanism of the reaction.
2. Give the mechanism of the reaction between butadiene-1,3 with 1 mol of HBr.
3. Write the mechanism of the methyl-phenyl ketone nitration reaction at the synthesis of mesatonum (adrenoceptor agonist).

№14

1. What is the product in the toluene bromination reaction at exposure to UV light? Write the mechanism of this reaction.
2. Give the mechanism of vinyl chloride (chloroethene) bromination reaction.
3. Write the reaction equation of nicotinic acid (β-pyridine carboxylic acid) nitration with account of electronic effect of heteroatom. Which compound is easier to brominate: pyridine or benzene? Why?

№15

1. Give the mechanism of cyclohexane bromination reaction.
2. Give the mechanism of the 2- butenoic acid in the presence of H_2SO_4.
3. Write the reaction equation of furfural (furan-2-aldehyde) nitration, on the base of which bactericides: furacilin, nitrofurantoin, furasolidone and others are synthesized.

Subject II. REACTIVITY OF ALCOHOLS, PHENOLS, AMINES, ALDEHYDE, KETONES AND CARBOXYLIC ACIDS.

Initial level

1. Electronegativity of elements.
2. Bond polarity and polarization.
3. Structure of the π-bond.
4. Electronic effect of substituents.
5. Type of reagents. Intermediate state. Structure of carbocation and carboanion. Factors that influence their stability.
6. Acidity and basicity of organic compounds.

Practical skills

1. To be able to predict the reactivity of different types of organic compounds in nucleophilic substitution, addition, and elimination reactions.
2. Learn how to obtain chloroethane, conduct alcohol dehydration reaction and perform qualitative reaction for acetone.

Test questions

1. Provide mechanisms of propanol bromination and dehydration. Justify a necessity of acid catalysis.
2. Obtain propionaldehyde ethyl hemiacetal, imine from methylamine and acetaldehyde; malonic acid mono- and diamide.

Teaching tasks

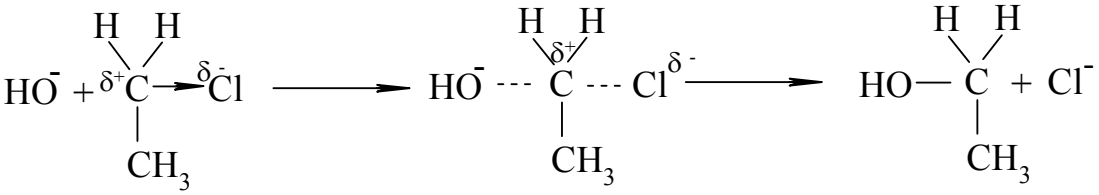
Task № 1. Obtain ethanol and ethylene from chloroethane.

Solution. There is a presence of the polar covalent bond in the molecule of chloroethane because of the difference in electronegativity between carbon $C^{\delta+}\rightarrow Cl^{\delta-}$ and chlorine. The reaction of chloroethane with nucleophile i.e. $OH^-; H_2\ddot{O}; H_2\ddot{S}; \ddot{N}H_3$ goes with the heterolytic cleavage and substitution of Cl^- for another nucleophile (OH^-). The haloalkane splits heterolytically to form a carbocation and a free halide ion.

Hence, it is the nucleophilic substitution reaction – S_N. Water solution of KOH is used as a source of OH^- ions.

This is an ionic reaction. In S_N reactions there is a loss of the leaving group, formation of an intermediate product (or activated complex) - carbocation, which is then, undergone a rapid reaction with an electron rich nucleophile.

In the reaction of haloalkane with alkali solutions, hydroxyl ion attacks positively charged carbon from the opposite side to the negatively charged halogen:

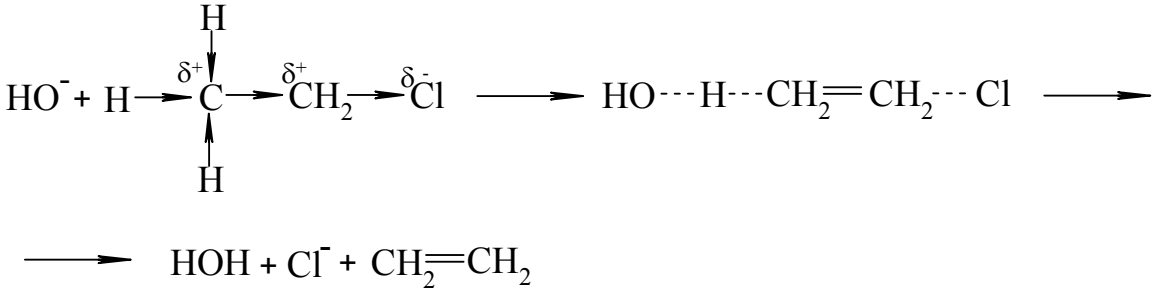


Intermidiate state

In the presence of a sufficient amount of energy OH^- ion moves in such distance that it forms bond with carbon but bond between carbon atom and halogen weakens.

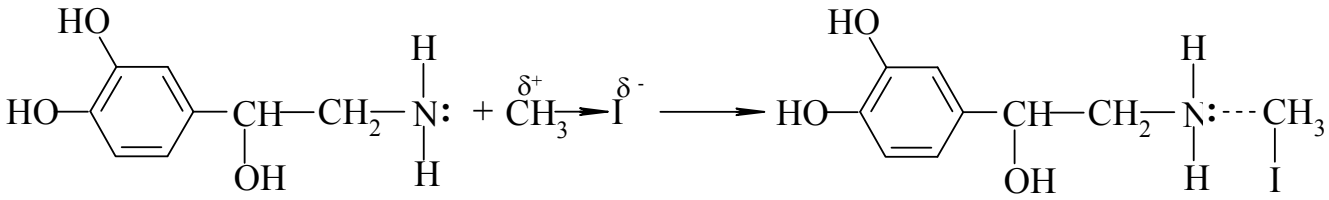
In the formed activated complex carbon atom is in sp^2-hybridization and this complex has planar structure. Then sequentially the bond with chlorine is broken and alcohol forms. Reaction proceeds in mild conditions taking into consideration that Cl^- is more stable then OH^--ion, which reacts, i.e., belongs to good leaving groups. Based on S_N reactions, with the aid of halogen derivatives, very important vital substances are synthesized such as hormone adrenaline, vasoconstrictive drug ephedrine, spasmodic agent tetranium, natural α-hydroxyacids ect.

Elimination reactions (E) compete with nucleophilic substitution (S_N) reactions. In the reaction of alkyl halides with an aqueous alcoholic solution of the alkali hydroxide unsaturated hydrocarbons forms. In this case, nucleophile, a strong base, attacks the hydrogen atom on a β-carbon having a partial positive charge because of -I-effect of the halogen (C-H acidity). The activated complex forms an intermediate product in this reaction.

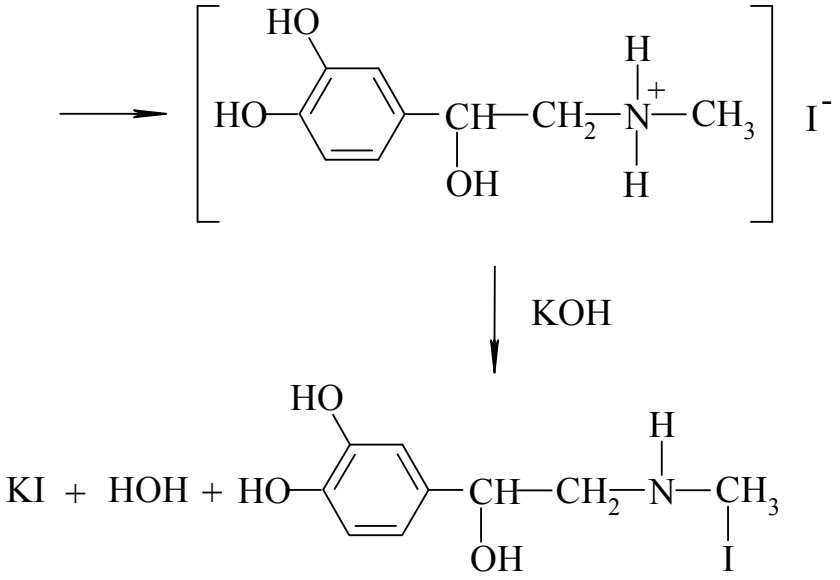


Task № 2. Obtain adrenaline from noradrenaline in vitro.

Solution. The alkylation reaction goes by S_N mechanism, where the product forms through a generation of an intermediate state. Alkylation means substituting an alkyl group into something – in this reaction into hydrogen. In other words, an alkylation is an addition of alkyl chain to another molecule. Alkyl halides are often used as alkylating agents. In our case the methyl iodide is used.



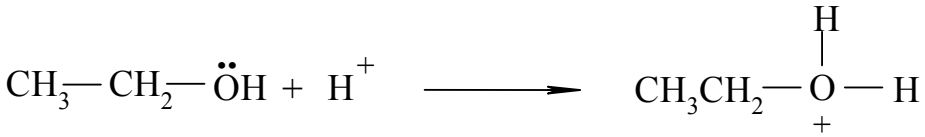
Noradrenaline



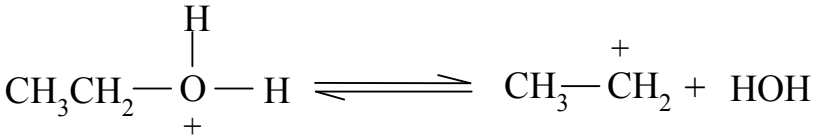
Adrenaline

Task № 3. Describe the mechanism of chloroethane (ethyl chloride) formation (a mild topical anaesthetic) and competitive to it the elimination reaction.

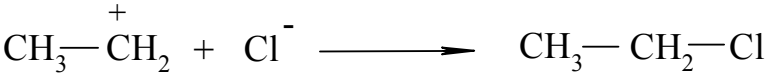
Solution. Hydroxyl group of alcohol in S_N reaction can be substituted by nucleophile such as halogen. The nucleophilic substitution reaction occurs when the leaving group is more stable than the incoming group. Whereas the OH^- ion is less stable than Cl^-, the reaction goes under acidic condition. When hydroxyl group is protonated, it is transformed into the better leaving group – H_2O. Hydrogen is attached to the alcoholic oxygen due to the lone pair on it:



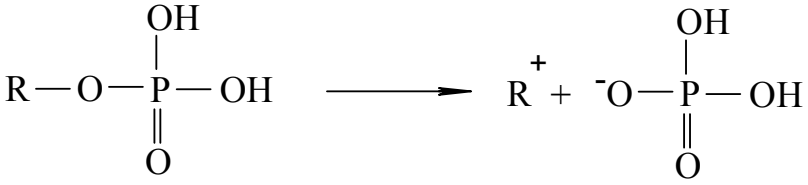
Oxonium (Lewis) base stays in equilibrium with a carbocation:



Carbocation is stabilized by the nucleophilic attack of Cl- ion:

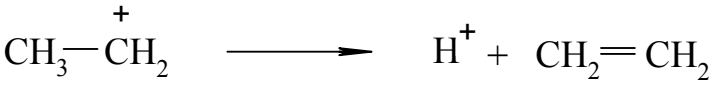


In the organism, the substitution of the alcoholic hydroxyl group proceeds by the transformation step into phosphoric, diphosphoric or triphosphoric acids because ethers formed from these acids are good leaving groups:



S_N reactions for alkyl halides and alcohols compete with elimination reactions. When alcohol is heated with concentrated H_2SO_4, dehydration of alcohol takes place and hydrocarbon of ethylene series form:

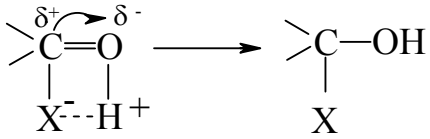
In this case carbocation is stabilized by the deprotonation:



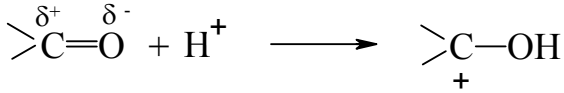
Task № 4. Give the mechanisms of acetic aldehyde and ethyl alcohol reaction in acidic medium.

Solution. Carbon atom in a carbonyl group  is sp^2-hybridyzed, which means it form three σ-bounds. The geometric arrangement of these three sp^2 hybrid orbitals is in a flat plane with 120-degree angles between them. Carbon and oxygen atoms are bonded by π-bond, which lies at 90^o angle to the hybrid σ-orbitals.

Since oxygen is more electronegative than carbon, the electron density attracted towards oxygen in a carbonyl group  (mostly π-electrons), so double bond is polarized in a way that there is high electron density on the oxygen atom and low on the carbon atom:  . Therefore the π-bond must be broken easily under the attack of polar agents; hence the nucleophilic addition reactions (A_N) are typical for carbonyl compounds:

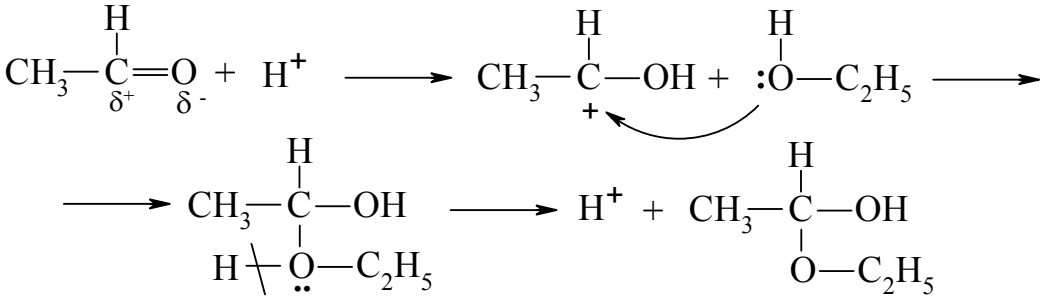


Usually the nucleophilic addition reactions catalyzed by acids, which convert a molecule into carbocation by addition of the proton:

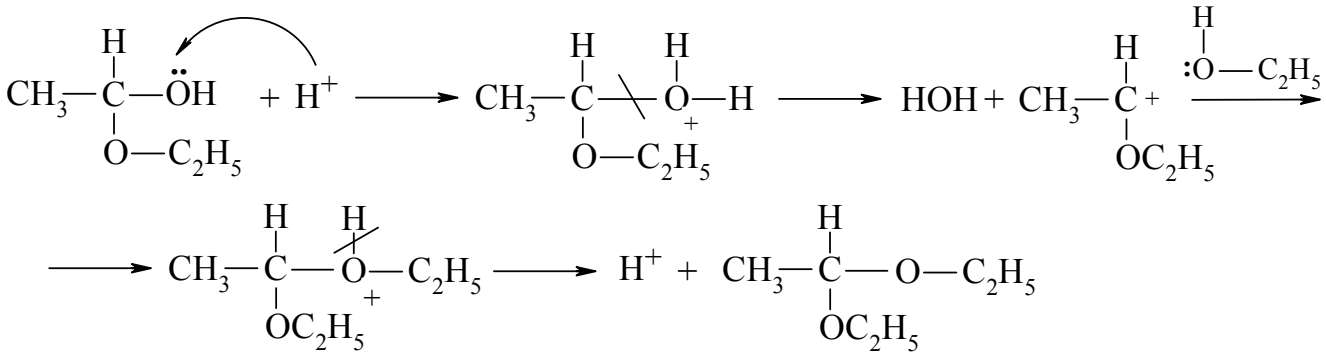


An addition of alcohols to aldehydes starts with initial protonation of the carbonyl group in acidic medium.

The carbocation forms a covalent bond with the alcohol molecule with a help of lone pair of electron from oxygen. The oxonium derivative that was formed is stabilised by deprotonation reaction:

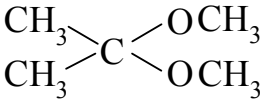


The product in this reaction is the hemiacetal in which an alcohol and ether attached to the same carbon. The acetal forms by the interaction of hemiacetal with a second alcohol molecule in acidic medium:



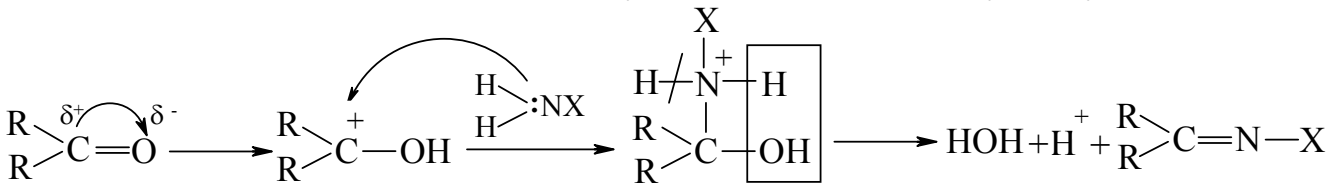
The presence of cyclic form of monosaccharaides can be explained by the formation of intramolecular hemiacetals.

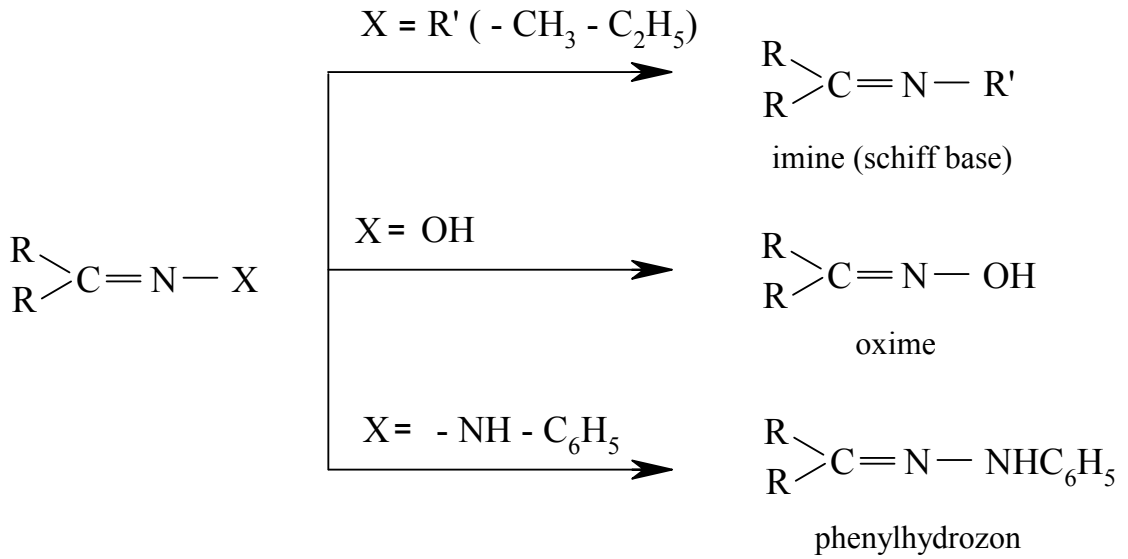
The addition of alcohol to ketones is more difficult than with aldehydes. Ketone derivatives are ketals:



Task № 5. Describe the mechanism of the carbonyl compounds reaction with amine and hydrazine.

Solution. Aldehydes and ketones react in substitution reactions, where oxygen of the carbonyl group can be substituted for another group. Reactions proceed by two steps: first it is an addition reaction based on a cleavage of the π-bond, second is elimination of a water molecule. Generally, the reactions are catalyzed by an acid:



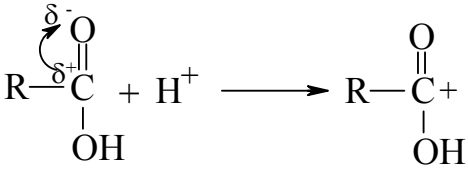


Imines (Schiff bases) formed in this reaction are intermediate products in enzymatic processes. Biosynthesis of amino acids in an organism goes through the formation of imine with pyridoxal-phosphate (vitamin B_6).

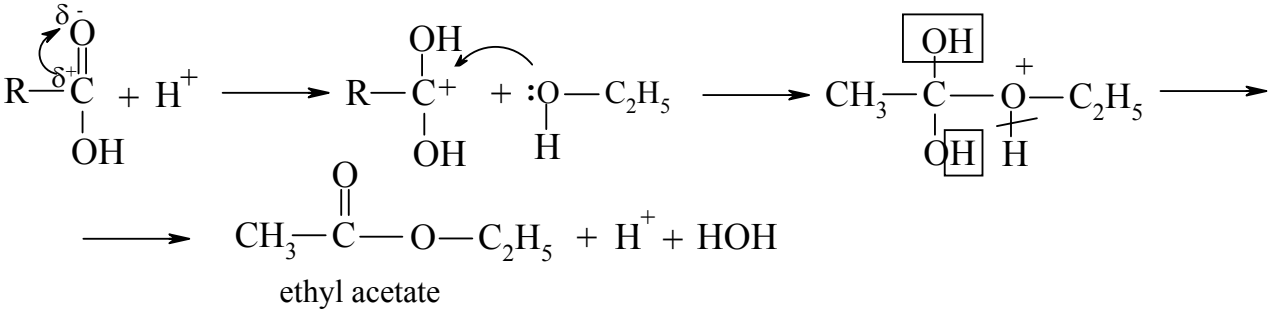
Oximes, phenylhydrazons are well crystallized and for this reason used for identification and isolation of aldehydes and ketones from a mixture with other substances.

Task № 6. Compare the properties of a carbonyl and hydroxyl of aldehydes, ketones, alcohols and carboxylic acids in nucleophilic reactions.

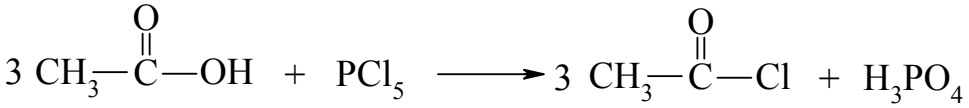
Solution. Carboxyl group conjugation complicates addition reactions by π-bond and a substitution of OH^- group. Nevertheless, carboxylic acids can be protonated and form carbocation in the presence of dehydrated mineral acids:



Carbocations are intermediates in different reactions such as ether formation:

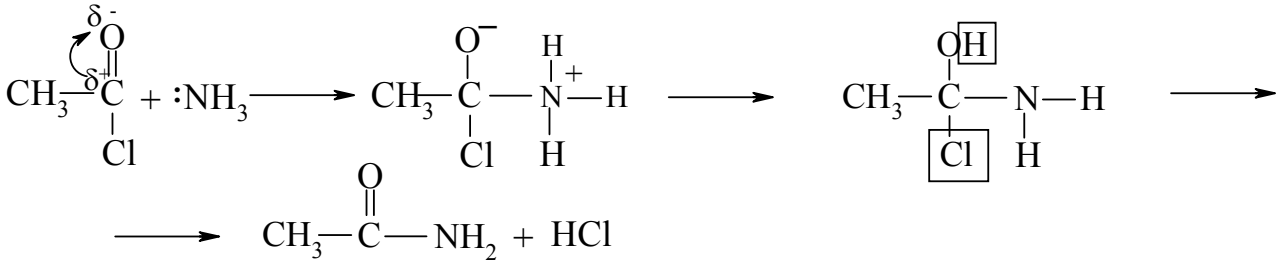


Phosphorous chloride (PCl_3, PCl_5) or thyonil chloride ($SOCl_2$) are strong chlorodehydrating agents which can be used to convert carboxylic acids to corresponding acid chlorides. The substitution of the hydroxyl group with a halogen takes place in this reaction:



acetyl chloride

An acyl halide is a product in this reaction. These compounds are not stable and very reactive. They are widely used acylating agents to incorporate an acyl radical into organic compounds. Acylation applies for protection of amino group during the peptide synthesis. Amine acylation yields an amide formation:



acetamide

Suject III. OXIDATION AND REDUCTION OF ORGANIC COMPOUNDS

Motivational characteristic of the subject

All processes in the organism require ongoing energy. Biological energy is released by oxidation-reduction reactions conducted in cells. Biologically important compounds released during redox reactions participate in biochemical processes. Thereby, this subject is a base for understanding multiple chemical reactions in the organisms.

Knowledge of this topic is necessary for the following chapters: hydroxyl acids and oxoacids, carbohydrate, lipids, nucleic acids, and such disciplines as biological chemistry, normal and pathological physiology, pharmacology etc.

Purpose

To study the oxidation-reduction properties of organic compounds as a basis for understanding the numerous chemical reactions in the organism.

Objectives:

1. To be able to write scheme and know conditions of oxidation reactions of saturated and unsaturated hydrocarbons, alcohols, aldehydes, and ketones.
2. To understand the electronic structure of quinones and mechanisms of its participation in redox processes.
3. To know features of oxidation of sulphur containing compounds.

Initial level

1. Electronegativity of elements.
2. Bond polarity and polarization.
3. Structure of the π-bond.
4. Electronic effects of substituents.
5. Covalent bond cleavage and its types, energy of the covalent bond.

Practical skills

1. To be able to predict reaction behaviour of different classes of organic compounds in redox reaction.
2. To learn how to perform oxidation reaction of unsaturated compounds, alcohols, and aldehydes.

Test questions

1. Write the scheme of redox reaction of glyoxylic acid (oxoethanoic acid) and acetone. Name the products.

2. What kind of reagents is used for oxidation of saturated hydrocarbons and alcohols? What are the products of these reactions?

3. Give the scheme of redox reaction of cysteine *in vivo*. What is the significance of this reaction?

Teaching tasks

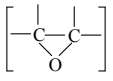
Task № 1. Describe oxidation capacity of alkane, alkene, and arenes.

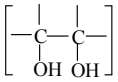
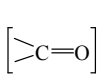
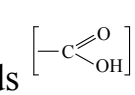
Solution. Oxidation of organic compounds is the process that involves increasing its oxygen in an organic substrate or decreasing its hydrogen content, accompanied by π-bond formation or a new bond between carbon and more electronegative atoms such as oxygen, nitrogen, sulphur etc. The transfer of electrons from a substrate to an oxidant determines the oxidation of a compound. Therefore, highly electronegative elements that easily accept electrons can be oxidizing agents. Examples of oxidizing agents include oxygen, peroxides, nitric acid, potassium permanganate, potassium dichromate and others.

Reduction of an organic compound usually involves increasing its hydrogen content accompanied by electrons transfer from reducing agent to organic substrate. Hydrogen is used as the reducing agent in the presence of heterogenic catalysts (Pt, Pd, Ni), metal hydride in acidic medium (NaH, $NaBH_4$, $ZiBH_4$).

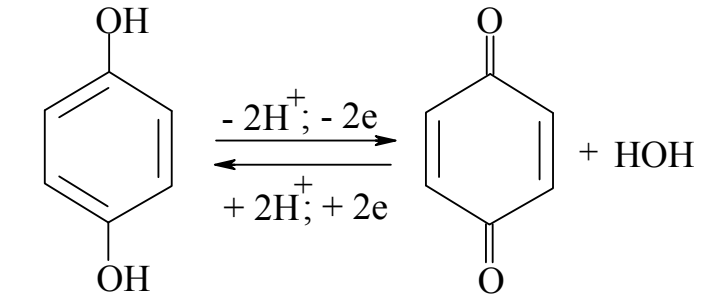
The capacity of organic compounds to oxidation depends on their ability to loose electrons. The easier the substrate looses electrons, the faster it oxidizes. Thereby, saturated hydrocarbons (alkanes) are the most difficult to oxidize. Strong conditions (chromic acid solution typically $K_2Cr_2O_7^{2-}{}_{(aq)}$) are required for their oxidation. Oxidation proceeds in a sequence: alkane oxidizes to alcohols, alcohols to aldehydes or ketones, which can be oxidized to carboxylic acids. The ability for oxidation increases in the following order:

$$-CH_3 \quad < \quad -CH_2- \quad < \quad -CH-$$

Homologous series of benzene and heterocyclic compounds oxidizes similar to alkanes. Compounds with double and triple bonds such as alkenes, alkynes oxidize much easier then alkanes. Alkenes oxidation products can be epoxides  ,

diols  , ketones  , and carboxylic acids  . Epoxides are formed from condensed aromatic systems in the organism and exhibit cancerogenic effects.

Benzene is extremely stable towards oxidation. It can react only in the presence of catalyst and require high activation energy. The presence of the electronegative substituents in benzene ring such as –OH increases its reactivity. The specificity of redox reaction with 1,4-dihydroxybenzene (hydroquinone) is its reversibility that has a significant biological role. This process represents the fundamental interaction in multiple chemical and biological processes:

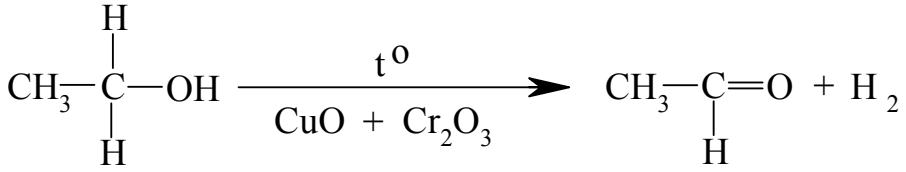


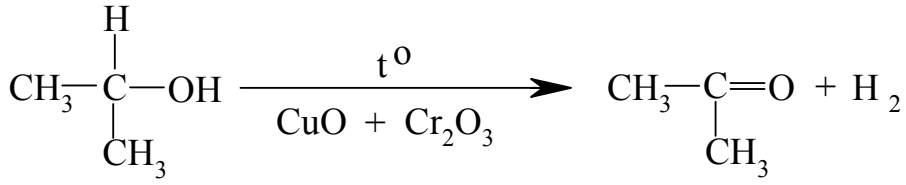
Hydroquinone Quinone

The electron transfer in mitochondrial respiration chain by coenzymes Q (ubiquinones) is a similar process.

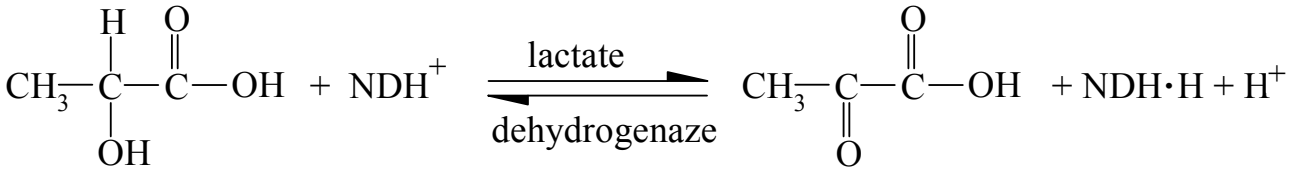
Task№2. Give the scheme of the lactic acid oxidation *in vivo*.

Solution. Primary and secondary alcohols are oxidized much easier to the corresponding alkanes. Oxidation of alcohols can be done under the high temperature and in the presence of catalyst:



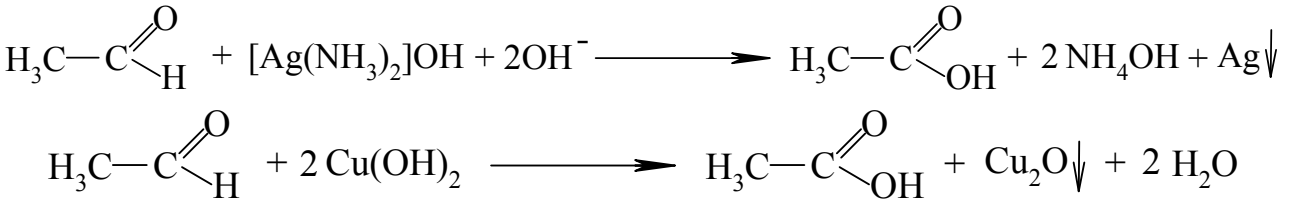


This is the dehydration reaction, which takes place in the organism upon the biological oxidation. This process is catalyzed by enzymes dehydrogenase, whose cofactor is NAD^+ (nicotinamide adenine dinucleotide). In the dehydration reaction the substrate looses 2 electrons and 2 protons or 1 proton and 1 hydride ion which is accepted by NAD^+:



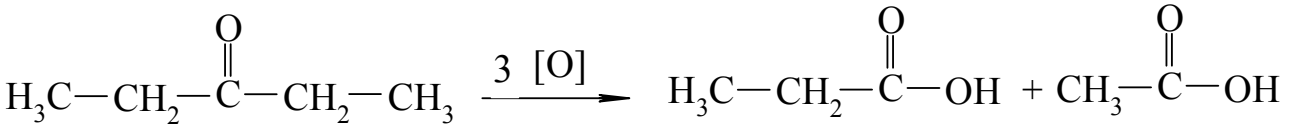
Task № 3. Compare aldehydes and ketones ability to oxidize.

Solution. Aldehydes can be easily oxidized to carboxylic acids by air oxygen or by mild oxidizing agents as ammonia solution of silver oxide or cupper hydroxide. These are qualitative reactions of aldehydes:



Carboxylic acids are products of aldehyde oxidation. The functional group of carboxylic acids represents a conjugated system with delocalization of electrons. Thus, oxidation of aldehydes leads to the more stable compound.

Ketones oxidize only by strong oxidant such as potassium permanganate. The carbon chain splits next to the carbonyl group with a formation of two molecules of acids:

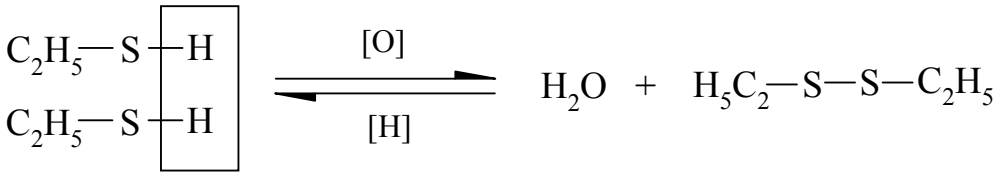


The difference in aldehydes and ketones oxidation explains by different bond oxidation. C-H bond oxidizes in aldehydes whereas C-C bond oxidizes in ketones. The structure of ketones can be determined by product of oxidation.

Task № 4. Give the scheme of ethyl mercaptan (ethylthiol) oxidation.

Solution. Unlike alcohols in thiols oxidation undergoes the sulphur atom instead of carbon, because the S-H bond is less stabile then the O-H bond. In the reaction with strong oxidant the сульсеновые, sulfinic acids and sulfonic acids are formed.

Disulphides are formed under mild condition of oxidation (peroxides):



Disulphide formation and reduction reactions tale an important place in vital processes, e.g. interconversion of lipoic and dihydrolipoic acids take place in lipid and carbohydrate metabolisms, cystein-cystine reaction in the formation of the protein space structure.

Revision exercises

№ 1

1. Describe the mechanism of 5-hydroxypentanal transformations in acidic medium.

2. Write the reaction equation of 1-chlorobutane with KOH(aq). Give the mechanism of this reaction.

3. What are products obtained by oxidation of n-propanol and isopropanol? Write scheme of these reactions.

№ 2

1. Give the mechanism of the acetaldehyde reaction with methylamine.

2. Write the reaction equation of 1-chloropropane with KOH (alcoholic). What is the mechanism of this reaction?

3. Give the mechanism of the reversible redox reaction of hydroquinone-quinone. What is the importance of such a reaction for biological processes?

№ 3

1. Give the mechanism of the tetamon synthesis, used in therapy of cerebral angiospasm. It can be obtain by the reaction of triethanolamine with ethyl iodide.

2. Write the mechanism of the prpanol-2 reaction with HBr. What is the mechanism of this reaction?

3. Provide the scheme of the malic acid enzymatic oxidation to oxaloacetic acid.

№ 4

1. Give the mechanism of the ephedrine formation in the reaction of 1-chloroethyl phenyl ketone $C_6H_5-\overset{\overset{O}{\|}}{C}CHCl-CH_3$ with methylamine.

2. Give the mechanism of the malic acid (2-hydroxybitandioic acid) dehydration in acidic medium.

3. Write the scheme of the ethanol oxidation reaction into corresponding acid. What is the intermediate product?

№ 5

1. Give the mechanism of the vitamin PP (nicotinic acid amide) formation from ammonia and nicotinic acid acyl chloride (pyridine-3-carbonyl chloride). The product is the anti-allergic medication.

2. Synthesize benzyl iodide from benzyl alcohol $C_6H_5CH_2OH$ and hydroiodic acid. Give the mechanism of this reaction.

3. Can the drug methaform (1,1-methylpropanol-2), having sedative и mild narcotic action oxidize? Justify your answer.

№ 6

1. Provide the mechanism of α-alanine (α-aminopropanoic acid) formation in the reaction of α-chloropropanoic acid with ammonia).
2. What kind of reagent you need to use with ethanol for the synthesis of chloroethane (a mild topical anaesthetic)? Provide the mechanism of this reaction. Give the mechanism of this reaction.
3. Write the reaction equation of the menthol (1-isopropyl-4-methylcyclohexanol) oxidation, is the ingredient of the drug named validol (1-isopropyl-4-methylcyclohexanol). Specify the class of organic compounds this product refers to.

№ 7

1. Give the mechanism of ethanolamine (2-aminoethanol-1) alkylation by methyl iodide, where the quaternary ammonium base is formed.
2. Give the mechanism of the malic (2-hydroxybutanedioic) acid dehydration under heating. How can you explain the easiness of this reaction?
3. Give the mechanism of the reversible redox reaction of cystein-cystine. What is the importance of such a reaction for biological processes?

№ 8

1. Give the scheme of the chloral hydrate (2,2,2-trichloroethane-1,1-diol, sedative and hypnotic drug) formation by trichloroacetaldehyde hydration. Explain the stability of the obtained compound.
2. Synthesize lactic acid (2-hydroxypropanoic acid) by the reaction of α-halogen carboxylic acid with alkali (aqueous solution). Provide the mechanism of this reaction.
3. Give the scheme of the pyruvic (2-oxopropanoic) acid transformation into lactic acid.

№ 9

1. Give the scheme of the reaction of propanal with ethylamine. Does this reaction take place in the organism? What is the significance of this reaction?
2. Write each step of the butanol-1 interaction with HCl. What is the mechanism of this reaction?
3. Give the scheme of the ethane thiol (ethyl mercaptan) oxidation reaction. Specify the condition of this reaction.

№ 10

1. Provide the mechanism of the acetone reduction with the aid of metal hydrides in acidic medium.
2. Obtain glycine (aminoacetic acid) from chloroacetic acid. Explain the mechanism of the reaction.
3. Write each step of the propanol-1 oxidation as the component of fusel oils that obtain by alcoholic fermentation to acid. Compare the ability to oxidation of propanol-1 and the intermediate product of this reaction.

№ 11

1. Provide the scheme of the intramolecular reaction of 5-hydroxypentanal in acidic medium.
2. Obtain acetic acid methylamide from acetyl chloride and methylamine. Provide the mechanism of this reaction.
3. Write the reaction equation of the butanal reduction.

№ 12

1. Give the mechanism of the acetone reaction with hydroxylamine NH_2-OH.
2. Give the mechanism of the malic acid (2-hydroxybitandioic acid) dehydration in acidic medium.
3. Give the mechanism of the reversible redox reaction of cystein-cystine. What is the importance of such a reaction for biological processes?

№ 13

1. Describe the mechanism of the acetal formation from acetaldehyde and propanol in the presence of catalyst.
2. Give the scheme of the acetylcholine formation from amino alcohol and acetic acid.
3. Write the reaction of menthol oxidation Menthol is the ingredient of the drug named validol (1-isopropyl-4-methylcyclohexanol). Specify the class of organic compounds this product refer.

№ 14

1. Give the mechanism of the reaction of pyridine with methyl iodine. What is the significance of this reaction?
2. What kind of reagent you need to use with ethanol for the synthesis of chloroethane (a mild topical anaesthetic)? Provide the mechanism of this reaction.
3. Write the reaction of acetic acid oxidation by cupper (II) hydroxide. What is observed? Provide the mechanism of this reaction.

№ 15

1. Describe the mechanism of the reaction of acrolein **or** acrylic aldehyde (prop-2-enal) with ethanol as one stage of the glyceraldehyde synthesis.
2. Synthesize benzyl iodide from benzyl alcohol $C_6H_5CH_2OH$ and hydroiodic acid. Provide the mechanism of this reaction.
3. Write the formaldehyde oxidation reaction by silver oxide in ammonia solution. What are the name and the significance of this reaction?

Test questions:

1. To be able to represent the more preferred conformation:
   cyclohexanol;
   cyclohexanediol;
   hexachlorocyclohexane;
   aminocyclohexane;
   1, 2-dimethylcyclohexane;
   ethylcyclohexane;
   bromocyclohexane.
2. To be able to represent in Newman projection:
   staggered conformation of chloroethane;
   eclipsed conformation of ethanolamine;
   staggered conformation of ethanolamine;
   staggered conformation of ethanol.
3. Know structures of:
   furan;
   thiophene;
   pyrrole;
   pyridine;
   naphthalene;
   phenanthrene.

To be able to explain criteria of aromaticity of these compounds.

4. Know how to determine the type and the sign of electronic effects of:
   chlorine atom in benzene and benzyl chloride;
   carboxyl group in acrylic acid and propionic acid;
   methyl and hydroxyl groups in o-cresol;
   carboxyl group in benzoic acid and acetic acid;
   carboxyl and amino groups in p-aminobenzoic acid;
   hydroxyl and amino groups in p-aminophenol;
   amino- and sulfo groups in sulfanilic acid;
   hydroxyl and carboxyl groups in salicylic acid.
5. Know the mechanisms of the following reactions:
   propane chlorination;
   ethylene bromination;
   propylene with hydrogen chloride;
   ethane bromination;
   butylene - 1,3 bromination;
   propylene hydration;
   isobutene bromination;
   butylene – 1 hydration;
   cyclohexane chlorination;
   benzene nitration;
   benzene chlorination.

6. To be able to provide the reaction equation with account of redirecting effect of substituent groups:
   phenol bromination;
   pyridine sulfonation;
   aniline sulfonation;
   toluene bromination;
   aniline bromination;
   benzoic acid bromination;
   pyrrole bromination;
   toluene nitration.
7. To be able to compare acidity and basicity of the following compounds:
   propanol and isopropanol;
   methanol and 1-propanol;
   1-propanol and glycerine;
   ethanol and 2- chloroethanol;
   phenol and 2,4,6-trinitrophenol;
   phenol and 2,4,6-tribromophenol;
   propanoic acid and 2-hydroxyprpanoic acid;
   2-chloropropionic acid and 3-chloropropionic acid;
   benzoic acid and salicylic acid;
   benzoic acid and phthalic acid;
   methyl-, dimethyl- and trimethylamine;
   methylamine and tribromaniline;
   aniline and tribromaniline;
   aniline and trinitroaniline;
   dimethylamine and dimethyl ether.
8. To be able to provide the mechanisms of the following reaction:
   1-chloropropane with alcoholic KOH;
   isopropanol with HBr;
   benzyl alcohol with hydroiodic acid (HI);
   1-chloropropane with KOH (aq);
   propanol dehydration in acidic medium;
   obtain successively hemiacetal and **di**acetal of acetaldehyde;
   propanal with ethanol;
   acetaldehyde with isopropanol;
   aldol condensation of acetaldehyde.

9. To be able to provide the oxidation reaction equation:
   propanol;
   isopropanol;
   hydroquinone;
   ethyl mercaptan (CH_3-CH_2-SH) **or** ethane thiol.

10. Know how to write the following reaction equations:
    disproportionation (Cannizzaro reaction) of benzaldehyde;

methyl ethyl keton reduction;
formaldehyde oxidation by silver salts in ammonia solution;
propionaldehyde oxidation by cupper (II) hydroxide;
iodoform test for acetone;
diacetal of acetaldehyde hydrolysis;
intramolecular reaction of 5-hydroxybutanal in acidic medium.

SUGGESTED READINGS

1. Biologically important classes of bioorganic connections. Biopolymers and their structural components: Theoretical course of biological and bioorganic chemistry, Module 1 / A. O. Syrovaya, E. R. Grabovetskaya, N. M. Tkachuk, L. G. Shapoval, V. N. Petiunina, S. A. Nakonechnaya. – X.: «Цифровая типография № 1». – 2013. – 183 p.

2. Zurabyn S. E. Fundamentals of Bioorganic Chemistry. – M.: GEOTAR-MED, 2003. – 320 p.

Навчальне видання

Основні типи та механізми реакцій в органічній хімії

Методичні вказівки для самостійної роботи студентів 1-го курсу з біологічної та біоорганічної хімії (Модуль 1)

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