Vinnytsia National Pirogov Memorial Medical University

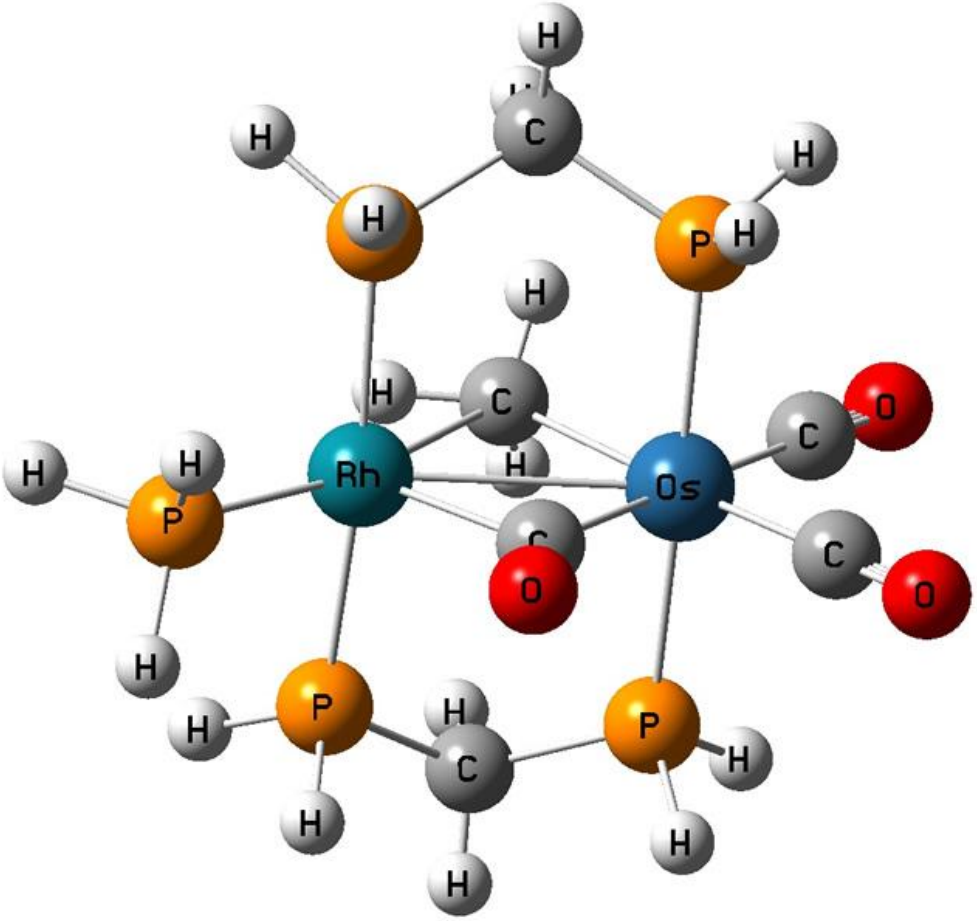
Biological and General Chemistry Department

Bioorganic chemistry course

Part II

THEORETICAL BASIS OF REACTIVITY

BIOLOGICALLY ACTIVE COMPOUNDS



Vinnytsia 2017

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

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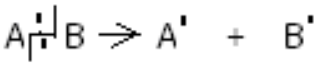
Content:

WAYS TO BREAK THE CHEMICAL BONDS

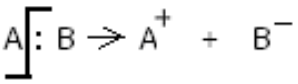
Organic reactions occur with the rupture of chemical bonds that can go different ways.

1) homolytic bond breaking, in which the particles are formed on the same electronic structure:



Particles with one or more unpaired electrons called free radicals.

2) heterolytic rupture bond at which the particles are formed in different electronic structure:



particle is called the A **+ electrophile (El) - a particle with a lack of electron density.**

Examples of electrophiles are such particles:

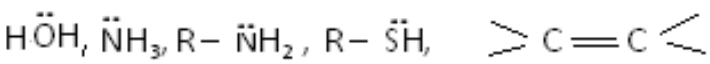
H^+, Cl^+, NO_2^+, SO_3^+, C^+ (carbocation).

"+" Sign means a free orbital, which electrophile may accept electron pair of the nucleophile. Particle B -called nucleophile (Nu) - a particle with an excess of electron density.

Examples of nucleophiles such particles are:

H –, OH–, Cl– , RO–, RCOO–, C– (carbocation).

It may also be a neutral molecule, in which an atom of oxygen, nitrogen or sulfur is the lone pair of electrons, alkenes, arenas, which have an excess of electron density due to electron π - due, for example:



The particles that we examined - free radicals, electrophiles, nucleophiles - have a simple structure and are called agents, they interact or attack the more complex molecules, called *substrates*.

RADICAL SUBSTITUTION REACTIONS S_R IN ALKANES

Alkanes - is saturated hydrocarbons with a simple σ bond between carbon atoms. Carbon in the alkanes is in the sp^3-hybridization.

For example: $CH_3 - CH_2 - CH_3$

propane.

Why in the alkanes are the substitution reaction and why the radical substitution?

1) In the alkanes all the bonds are saturated, so the only possible replacement (not joining).

2) In the alkanes all the carbon atoms are in a state sp^3-hybridization. Electronegativity of the same, so the molecule can be no displacement of the electron density, ie, electronic effects do not occur. This means that centers can not occur with an excess or a deficiency of electron density, so the only possible attack by free radicals.

The mechanism of radical substitution by the example of bromination of butane:

1) The stage of initiation: the action of ultraviolet homolytic bromine molecule is split into two free radicals

$$Br_2 \xrightarrow{h\nu} Br^{\bullet} + Br^{\bullet};$$

2) A free radical reacts with bromine molecule of butane and butane formed by free radical and formed a secondary radical, because it is more evenly distributed electron density and it is thermodynamically more stable than the primary radical

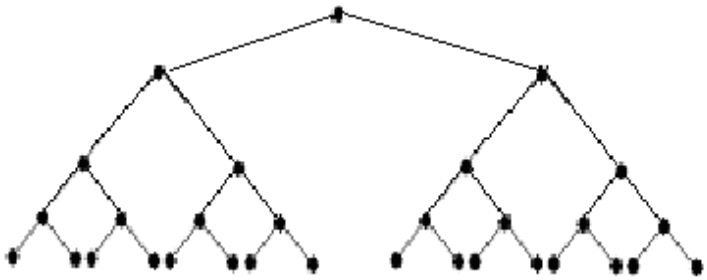
$$CH_3 - CH_2 - CH_2 - CH_3 + Br^{\bullet} \rightarrow CH_3 - CH_2 - C^{\bullet}N - CH_3 + NBr$$

3) A secondary radical of butane reacts with a molecule of bromine and radical substitution product is formed and a new free radical bromine

$$CH_3 - CH_2 - C^{\bullet}H - CH_3 + Br_2 \rightarrow CH_3 - CH_2 - \underset{\displaystyle Br}{\underset{|}{C}}H - CH_3 + Br^{\bullet}$$

Free radical reactions are very fast. If the third stage of free radical butane reacted with a second free radical bromine (see the first stage), the radical reaction to this would be broken. But often such reactions go in the chain process. The theory of the chain process has developed a russian scientist, academic Nikolay Nikolayevich Semyonov, for which he was awarded the Nobel Prize in 1956.

The scheme of the chain process



The biological significance of free radicals.

In humans, free radicals are formed as a result of radiation, ultraviolet radiation, ozone, oxides of nitrogen. They are the products of biochemical reactions, for example, the participation of iron in free radical reactions in the human body:

$$Fe^{2+} + \dot{O}\text{-}\dot{O} + H^{+} \rightarrow Fe^{3+} + HO\text{-}\dot{O}$$

In humans, these free radicals are formed:

$$H^{\bullet}, OH^{\bullet}, HO_2^{\bullet}, O_2^{\bullet}, CH_3^{\bullet}, RO^{\bullet}.$$

Normally, free radicals are involved in these processes:

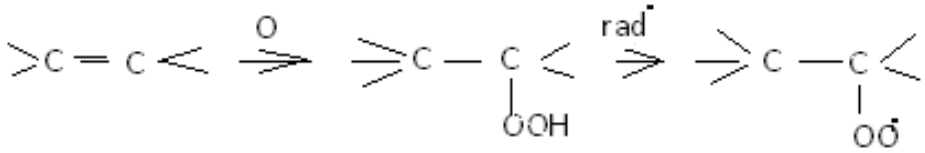
1) lipid peroxidation of membranes, which promotes cell growth;

2) the synthesis of prostaglandins - biologically active substances with a broad spectrum of activity in the human body.

But if the free radicals formed by a lot, they exhibit toxic effects:

1) Increased lipid peroxidation of membranes, which leads to their destruction.

The scheme of this process can be shown as follows



hydroperoxide peroxide

1) reduced levels of amino acids, methionine and tryptophan, which leads to a slowing down of protein synthesis;

2) break the disulfide bonds - S - S - in proteins;

3) is very sensitive to radiation is the process of oxidative phosphorylation, ie, impaired synthesis of ATP;

4) disrupted the structure of DNA and proteins by alkylation of the nitrogen bases of DNA and proteins of benzene rings (alkylation - is the reaction of the introduction of alkyl, ie, the balance of alkane).

The body is protected from free radicals with antioxidants - substances that bind free radicals. In humans, this is the role of enzymes - catalase, glutathione peroxidase, superoxide dismutase. Outside the body it is the role of certain vitamins such as retinol (vitamin), ascorbic acid (vitamin C), α - tocopherol (vitamin E), which is currently the most powerful antioxidant. The composition of vitamin E is a phenolic hydroxyl group, which binds free radicals.

Scheme of the binding of free radicals:

$$ArOH + RCOO^{\bullet} \rightarrow ArO^{\bullet} + RCOOH$$
$$ArO^{\bullet} + GSH \rightarrow ArOH + GS^{\bullet}$$
$$GS^{\bullet} + SG^{\bullet} \rightarrow GS - SG$$
$$GS - SG + HADH_2 \rightarrow 2GSH + HAD$$

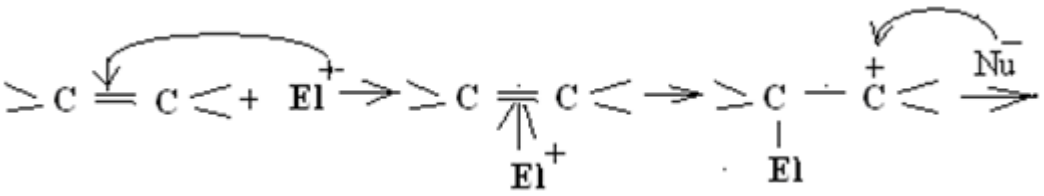
At the present time is the search for new antioxidants such as dibunol, derivatives oxypyridine, dextramine etc.

ELECTROPHILIC ADDITION REACTION A_E IN ALKENES

Alkenes - is unsaturated hydrocarbons with a double bond between carbon atoms. The simplest representative - ethene $CH_2 = CH_2$. Why in the alkenes are addition reactions, and why is electrophile attack:

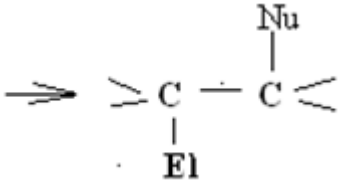
1) An unsaturated double bond, so go addition reactions;
2) Due to π - electron density of the double bond of alkenes are electrosaturation so attacked by electrophiles, i.e. particles with a lack of electron density.

The scheme of the mechanism of electrophilic addition:



π - a set σ - complex or carb - cation

(1) (2) (3)



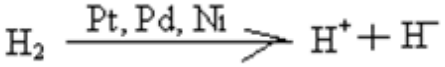
(4)

(Arrows must have the exact start and end)

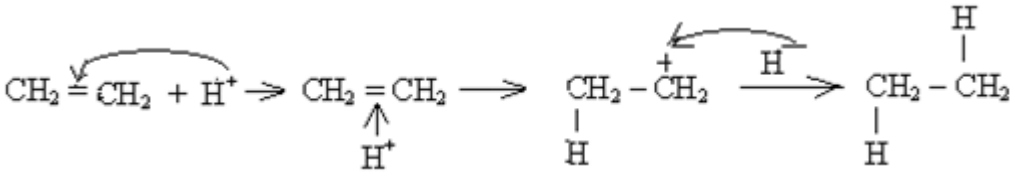
In step (1) The electrophile attacks the double bond, is coming to an alkene double bond and forms a π - complex (2). Further, the double bond is broken, electrophile attached at the other carbon atom occurs a full positive charge (ie free orbital) and formed σ - complex (3). The positive charge on the carbon atom is neutralized by a nucleophile - a particle with an excess of electron density - and the final product is formed electrophilic addition (4). Consider the specific reactions that occur with alkenes, and indicate their biological significance.

1) The hydrogenation of alkenes (addition of hydrogen).

In vitro reaction proceeds in the presence of a catalyst Pt, Pd or Ni, which splits the molecule of hydrogen electorophile H^+ and H-nucleophile:



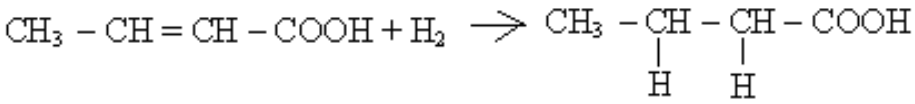
In the case of hydrogenation ethene reaction mechanism can be written graphically as follows:



π - a set σ – complex

The biological significance of the hydrogenation of alkenes:

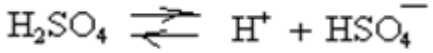
a) in the synthesis of fat hydrogenation of crotonic acid is:



crotonic acid, butyric acid

The hydration of alkenes (addition of water).

Water - a weak electrolyte. It does not provide a sufficient number of protons as the electrophile, so the reaction proceeds in vitro in the presence of a catalyst for H^+, which is formed by the dissociation of H_2SO_4 conc.:



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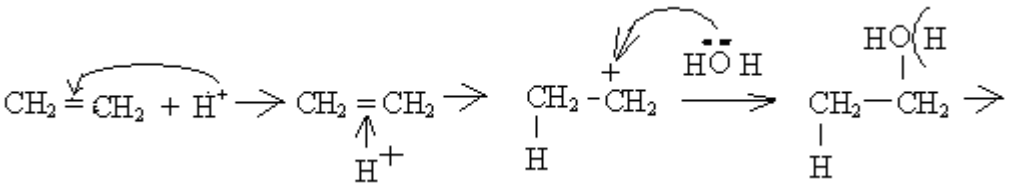
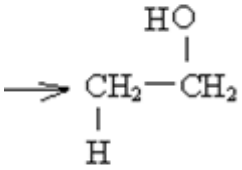
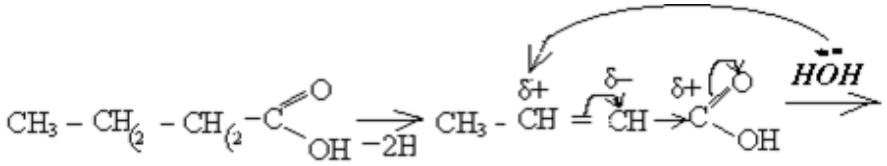


π-complex σ-complex

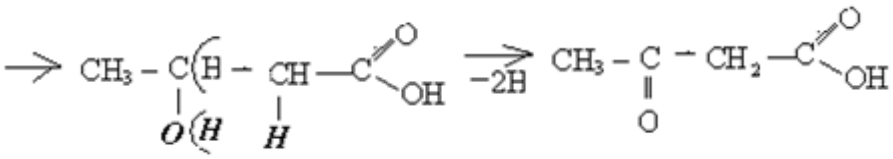


2) The biological significance of hydration of alkenes:

a) In the human body hydration of alkenes - one of the main reactions of the process of tissue respiration and biological oxidation. An example would be a chain of reaction

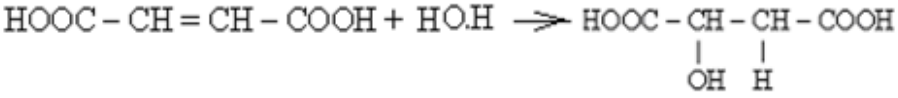


Butyric acid, Crotonic acid



β - hydroxybutyric acid β - ketobutyric acid

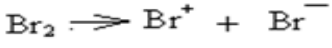
b) In the Krebs cycle is the hydration of fumaric acid to malic:



Fumaric acid Malic acid

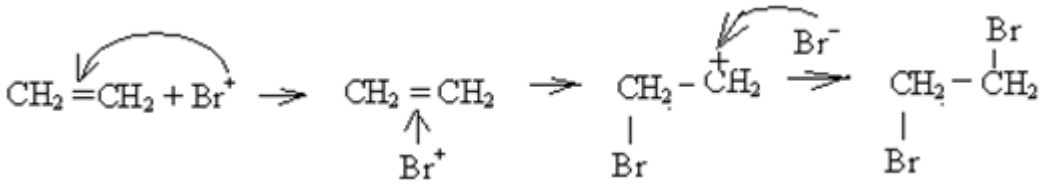
3) Halogenation of alkenes (addition of halogens).

Under the action of π - electron density of the double bond of the molecule splits into heterolytically bromine electrophile and nucleophile Br + Br $^{-}$:



In the example with ethane, bromination reaction mechanism can be written graphically as

follows:



π - a set σ – complex

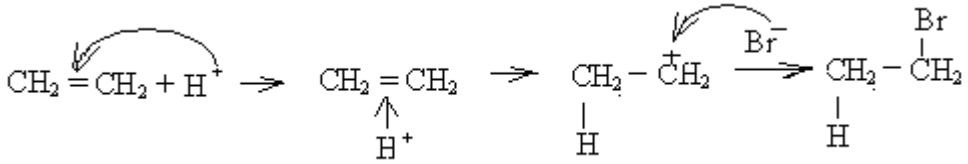
The reaction is discoloration of bromine water. Therefore, this reaction is used as a quality to the unsaturation.Halogenation of alkenes used for the synthesis of drugs. Since the halo is easily split off, it can be replaced by other functional groups.

4) Hydro halogenization alkenes (addition of hydrogen halides).

Under the action of π - electron density of the double bond of the molecule breaks down into hydrogen bromide heterolytically electrophile nucleophile H^+ and Br^-:

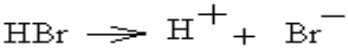
$$HBr \rightarrow H^+ + Br^-$$

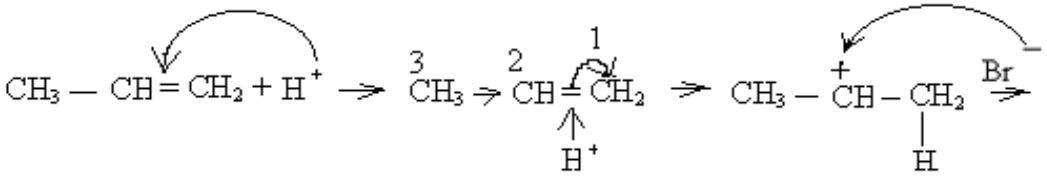
In the example hydrobromination ethene reaction mechanism can be written graphically as follows:



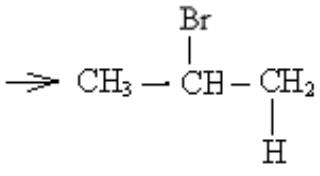
π - a set σ – complex

The reaction of alkenes hydrohalogenation used in the synthesis of drugs. Hydrohalogenation asymmetric hydration of alkenes and goes on to Markovnikov's rule, that is, hydrogen is added to a hydrogenated carbon atom. This can be explained by δ electron effects. For example:
a) the mechanism hydrobromination of propene, can be written as follows:





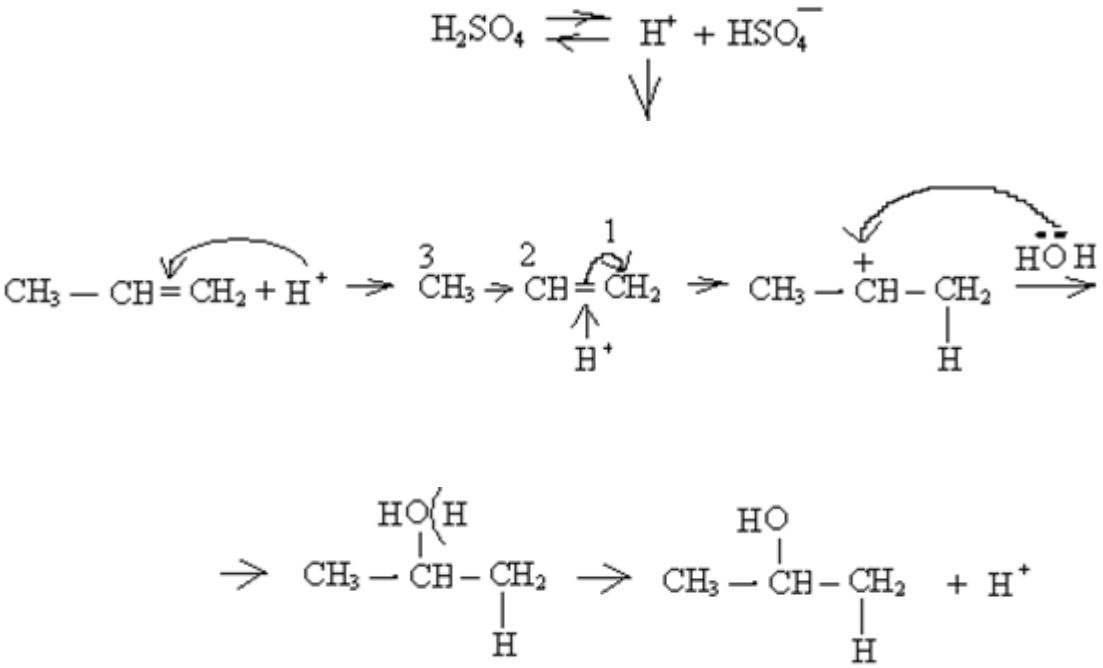
π - a set σ - complex
(1) (2)



(3)

In the π - complex (1) is the redistribution of electron density in this way: the inductive effect of electron density from C_3 (sp^3 - a hybrid carbon) is shifted to the more electronegative carbon C2 (sp^2 - a hybrid of carbon), from which it repels π - electron density of the double bond at C1. In the first carbon atom creates an excess of electron density, so the proton as a particle with a lack of electron density attached to it (2). In the second carbon atom occurs positively charged, and he attacked bromide - anion as a nucleophile. The result is a finished product (3).

b) The mechanism of hydration of propene can be written as follows:



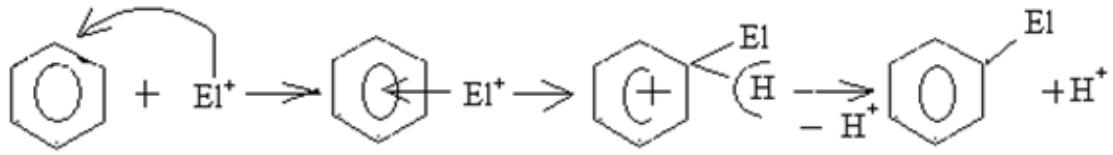
(See explanation in paragraph A)

ELECTROPHILIC SUBSTITUTION REACTIONS IN THE ARENES S_E

Arenes – this is benzene and its derivatives. In the arenes are reactions on the mechanism of electrophilic substitution as:

a) Due to the electronic structure of benzene as the aromatic compound is only possible substitution reaction, as to break a single dual clouds need more power;

b) Benzene has a surplus of electron density due to the presence of π - conjugated electron cloud, so the attack is only possible electrophile. The scheme of the mechanism of electrophilic substitution:



π -complex σ - complex

(1) (2) (3) (4)

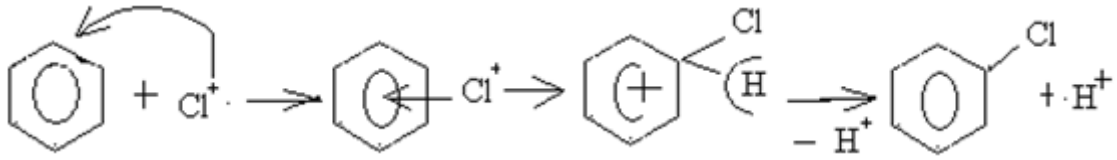
In (1) step the electrophile attacks the benzene ring. Then coming to an electronic system and the conjugate formed π-complex (2). Further, the dual cloud bursts, electrophile attached to one carbon atom and forms a σ - complex (3). It is unstable, since broken aromaticity. To get rid of the positive charge in the core of the system pushes the proton, and the reaction product formed by substitution of (4).Consider the specific reactions that occur with arenes, and indicate their biological significance.

1) Halogenation of arenes.

Because of aromaticity is halogenation in the presence of a catalyst, by which is formed electrophile. Lewis acid catalysts are:

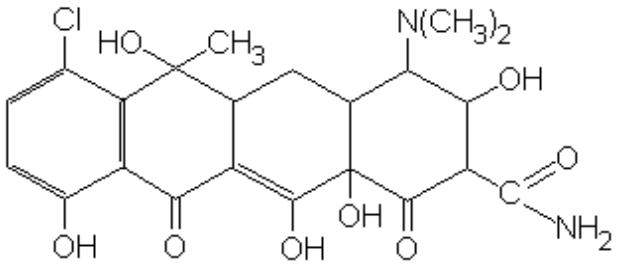
$$Cl_2 + FeCl_3 \rightarrow Cl + + FeCl_4\text{-}.$$

The mechanism of halogenation can be written graphically as follows:

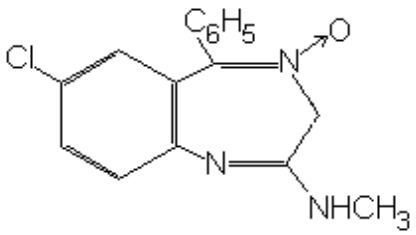


π-complex σ – complex

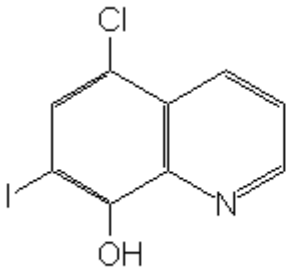
Halogenation of arenes used for the synthesis of drugs:

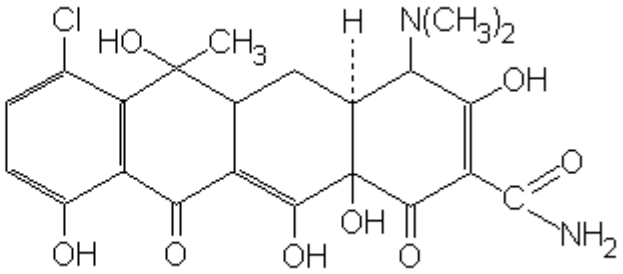


Biomycin (antibiotic)



Elenium (sleeping pill)

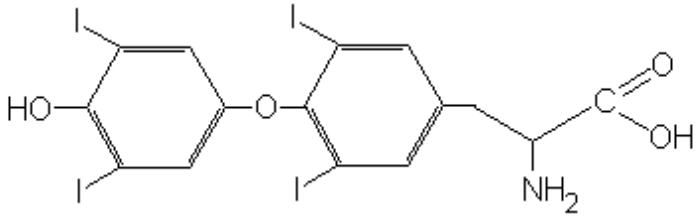




Enteroseptol **Chlortetracycline (antibiotic)**

(Intestinal diseases)

The human body is the product of the halogenation of arenes thyroid hormone - **thyroxine:**



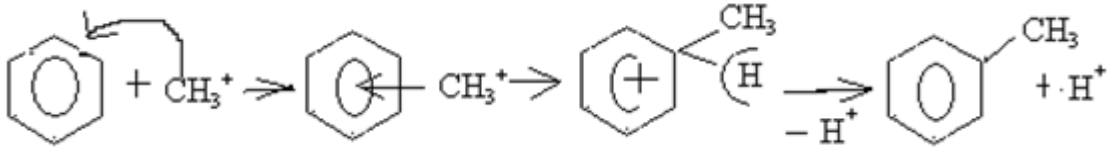
Thyroxine

2) Alkylation of arenes (the introduction of alkyl):

The reaction proceeds in the presence of a catalyst - a Lewis acid.

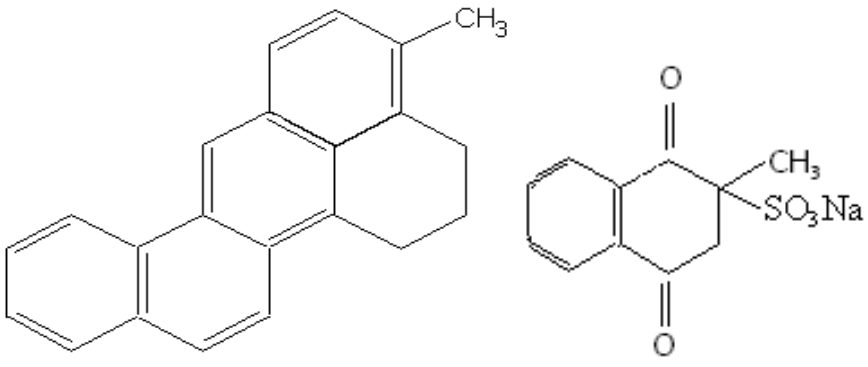
The mechanism of alkylation can be written graphically as follows:

$CH_3I + AlI_3 \rightarrow CH_3 + + AlI_4$-



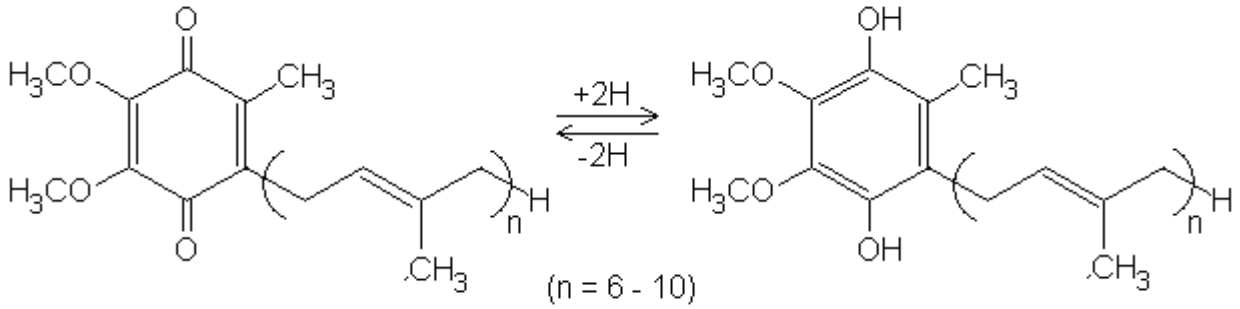
π-complex σ – complex

Alkyl part of the biologically active substances:

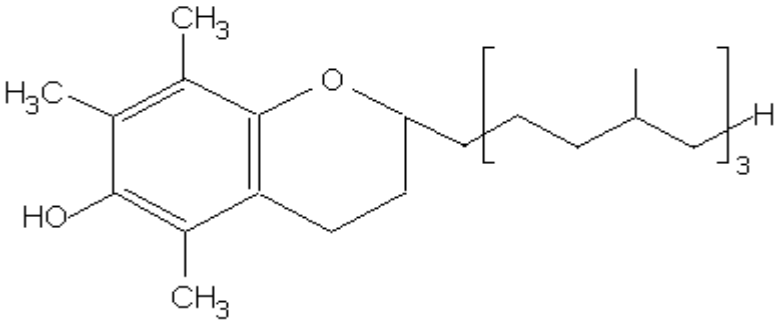


Methylcholanthrene **Menadione (increases blood clotting)**

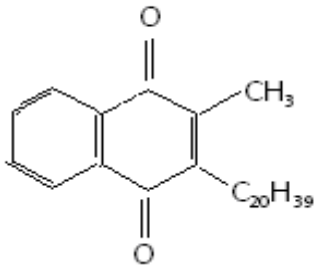
(Formed in the body from cholesterol)

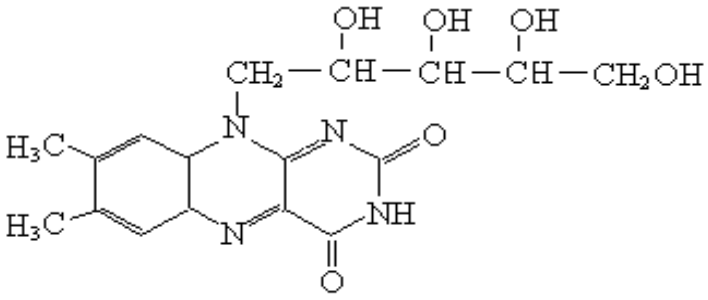


Ubiquinone (coenzyme Q, hydrogen transfer in the human body)



Vitamin E (α - tocopherol, an antioxidant)





Vitamin K, (antihemorrhagic action)

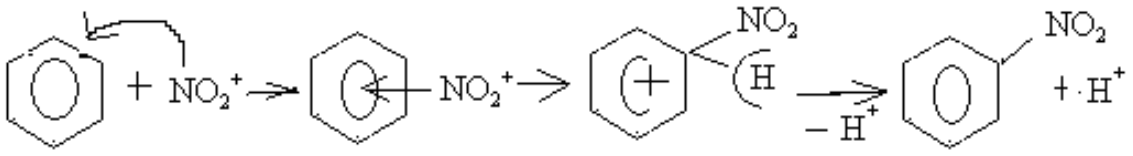
Riboflavin (vitamin B2, the lack of it causes growth retardation)

3) Nitration of arenes (the introduction of nitro-NO_2).

Nitration is carried out using nitrating mixture. It is a mixture of concentrated acids, nitrate and sulfate. In the presence of acid sulphate nitrate acid dissociates to form a nitronium ion, NO_2 +, which is the electrophile:

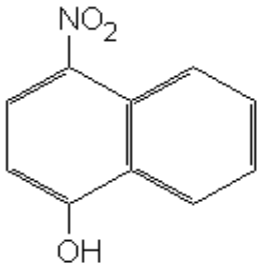
$$HNO_3 + H_2SO_4 \rightarrow NO_2 + + HSO_4^- + H_2O.$$

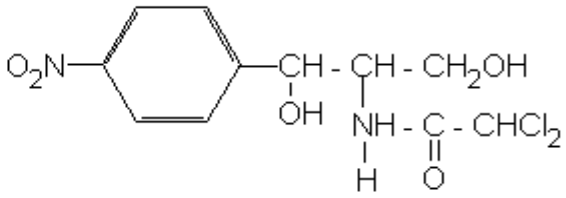
The mechanism of nitration can be written graphically as follows:



π-complex σ – complex

Nitration of arenes used for the synthesis of drugs:

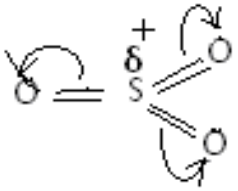




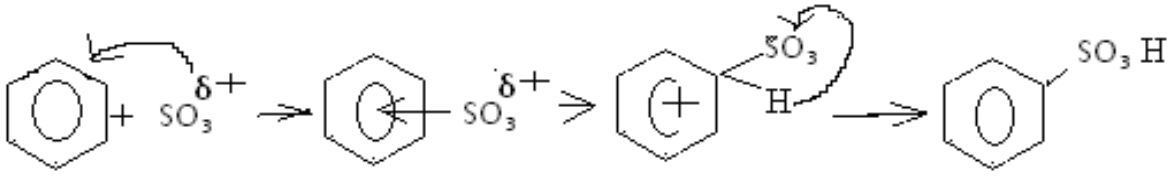
Nitroxoline (5 - NOC, germicide) **Chloramphenicol (synthetic antibiotic)**

4) Sulfonation of arenes (the introduction of sulfonic-SO_3H).

Sulfonation is carried out with the help of sulphur (VI) oxide, which as a result of the displacement electronic density electronegative to more oxygen to the sulfur atom arises up excess positive charge. This particle will electrophile and attacks the benzene ring.

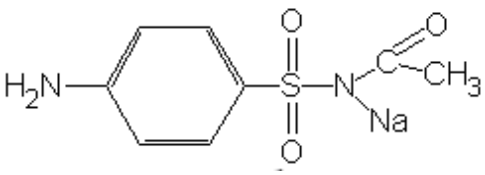


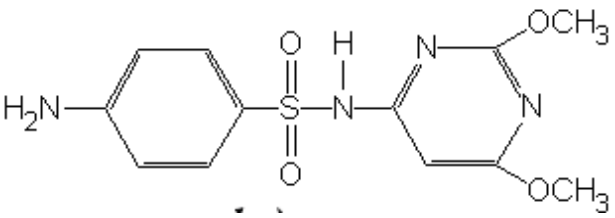
The mechanism of sulfonation can be written graphically as follows:



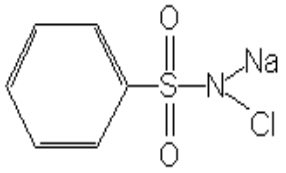
π-complex **σ - complex**

Sulfonation of arenes used for the synthesis of drugs:

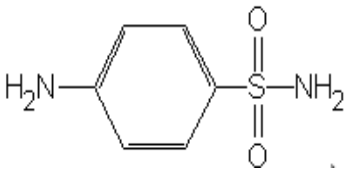




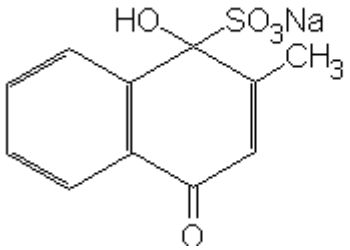
Sulfacyl sodium **Sulfadimethoxinum**



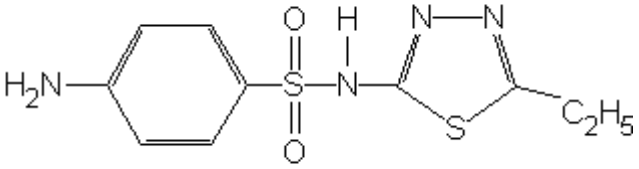
Chloramine



Streptocid



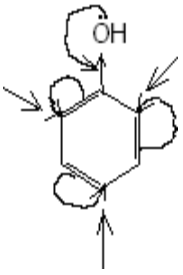
Vicasol



Etazol

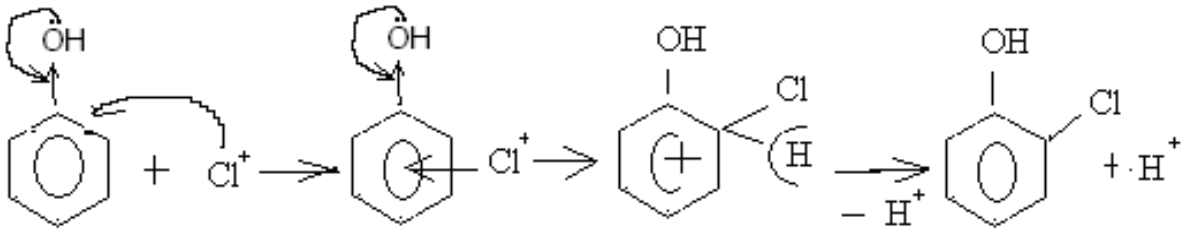
The electron and electron-substituents

Electron-donating substituents known to increase the electron density in the system. Electron-with drawing substituents known to reduce the electron density in the system. If the benzene ring has substituents - electron donor and electron acceptor, they sent another substituent (halogen, alkyl, nitro or sulfo) in a certain position. Electron substituents:-OH,-NH_2,-SH, alkyl - send another deputy in the ortho or para position.



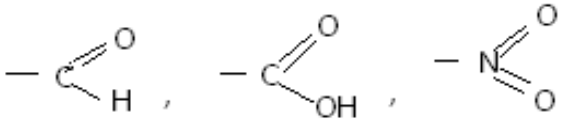
para

For example:

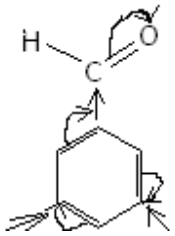


π-complex ***σ - complex***

Electron alternates:

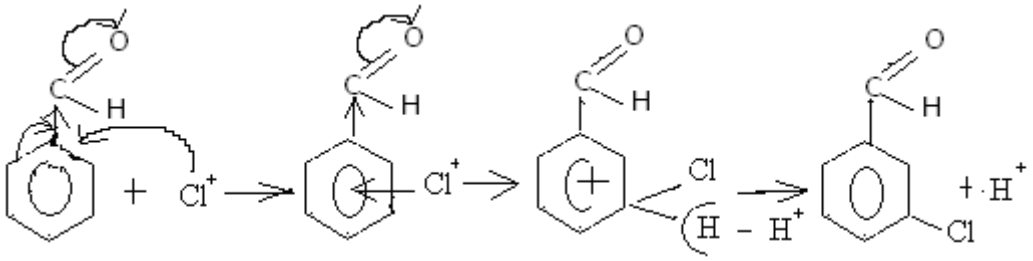


Send another deputy in the meta - position.



meta meta

For example:



π-complex ***σ – complex***

NUCLEOPHILIC SUBSTITUTION REACTIONS S_N IN HALOGENATION

Halogenalkane - is derived alkanes in which one or more hydrogen atoms substituted by halogen atoms.

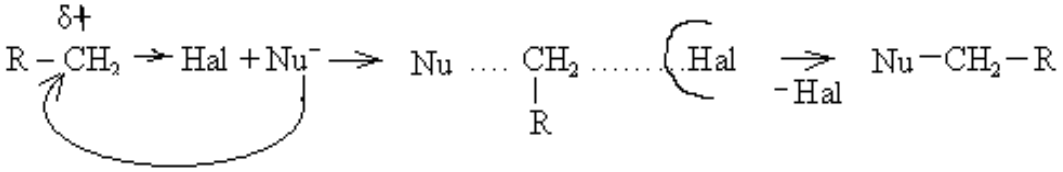
Presence of strongly electronegative halogen atom leads to a redistribution of electron density in the system (molecule). In halogenation goes nucleophilic substitution at sp^3 - hybrid carbon atom, because that:

a) All links *are* saturated, so the only possible replacement;

b) As a result of displacement of the electron density to the atom of halogen, that is a result of the negative inductive effect of halogen on the carbon atom there is a partial *positive* charge. This carbon atom is attacked by a nucleophile, i.e. the particle with an excess of electron density:

$$\overset{\delta +}{R - CH_2} \rightarrow Hal$$

Scheme mechanism of nucleophilic substitution S_N in halogenation:



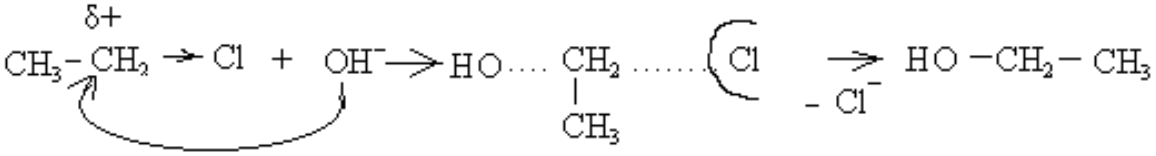
(1) ***(2) active complex or the transition state*** ***(3)***

For the formation of active complex nucleophile approaches from the side opposite halogen (1), that is saying that the attack comes from the rear. Next nucleophile begins to form relationship with carbon, and communication with halogen weakens and forms *an active complex or transition state* (2). Halogen is easy leaving group is cleaved from the active complex is formed and the replacement of the product (3).

Halogenation are used as intermediates in the synthesis of many organic substances, since halogen is easily replaced by other functional groups.
Consider the specific reactions that occur with halogenation, and indicate their biological significance.

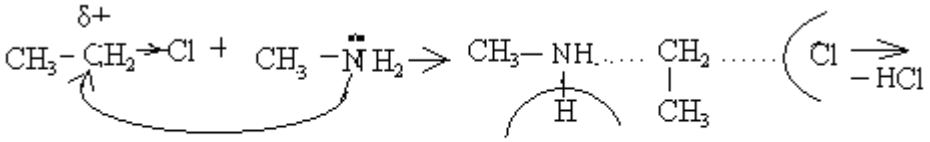
1) Interaction with alkali:
Dissociation of the alkali hydroxide is formed - the anion OH, which is the nucleophile. Mechanism can be written graphically as follows:

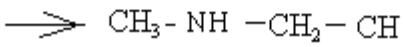
$$NaOH \rightarrow Na^{+} + OH^{-};$$



This reaction is used in the synthesis of drugs for the introduction of oxy - group.

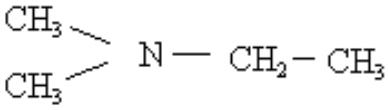
The interaction with *ammonia and* amines:
Ammonia and amines by nucleophile lone pair of electrons of the nitrogen atom.
Mechanism can be written graphically as follows:





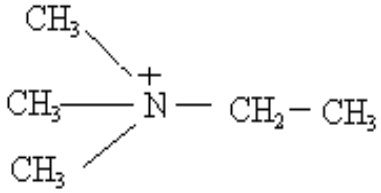
Ethylmethylamin

The result is alkylation of nitrogen. If you take even one molecule of amine is replaced by hydrogen and formed ethyldimethyliamin:



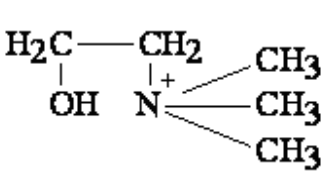
Ethyldimethylamin

By the nitrogen lone pair can attach another alkyl group and formation of the quaternary base:



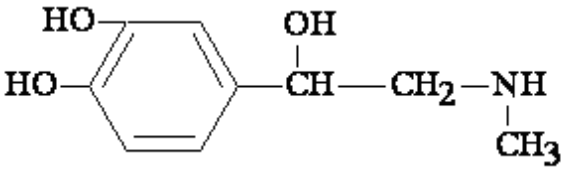
Ethyltrimethylamin

In humans, synthesized by *choline is methylation, epinephrine, carnitine,* creatine, etc.



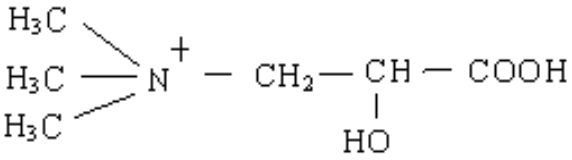
Choline

(Regulates fat metabolism)



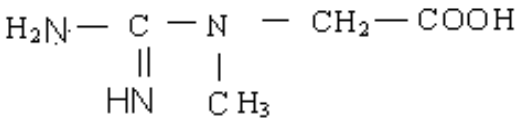
Adrenaline

(Constricts blood vessels)



Carnitine

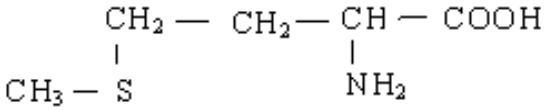
(Transports fatty acids)



Creatine

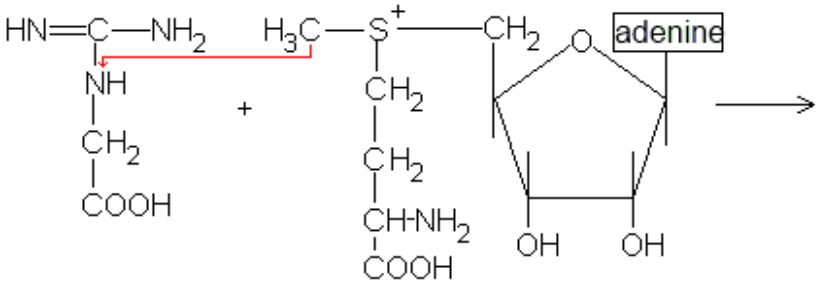
(Involved in muscle contraction)

The main methylating agent in the human body is an amino acid - methionine:

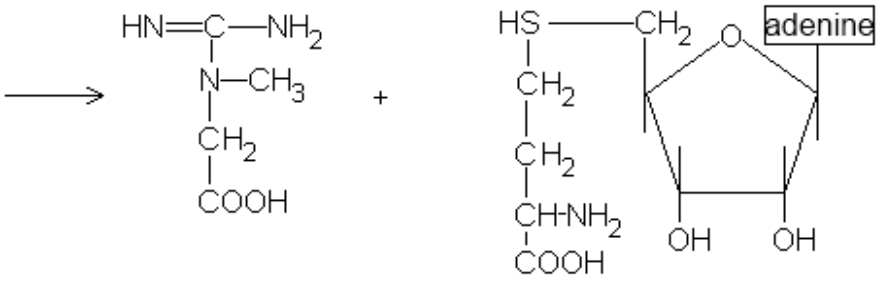


Methionine

The scheme of methylation in the human body



Glyco cyanine ***S - adenosylmethionine***



Creatine ***Adenosylhomocysteine***

NUCLEOPHILIC SUBSTITUTION S_N IN ALCOHOL

Alcohols - are derivatives of alkanes, in which one or more hydrogen atoms substituted by hydroxyl - groups.

Presence of strongly electronegative oxygen atom leads to a redistribution of electron density in the system (molecule).

In alcohols are *nucleophilic substitutions* at sp^3 - hybrid carbon atom, because:

a) All links *are* saturated, so the only possible replacement;

b) As a result of displacement of the electron density to the oxygen atom, that is, the negative inductive effect of oxygen on the carbon atom there is a partial *positive* charge. This carbon atom is attacked by a nucleophile, i.e. the particle with an excess of electron density:

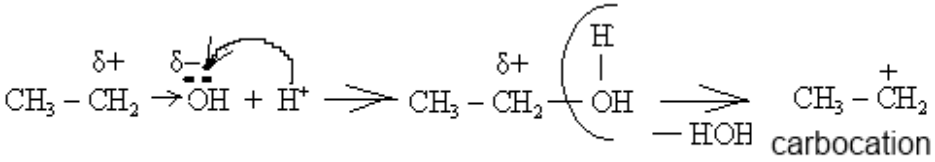
$$\overset{\delta +}{R - CH_2 OH} \rightarrow$$

Hydroxyl - a group difficult to split off as a strong base in the free state cannot exist. To split a OH - group, you should use a catalyst - a proton H^+, which gives the H_2SO_4 conc. The alcohol in this case reacts as a base, since the oxygen atom has an unshared electron pair.

Mechanism can be written graphically as follows:

Step 1:

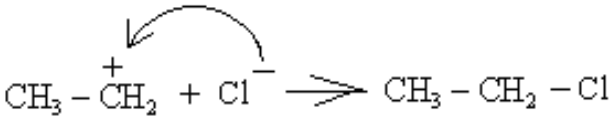
$$H_2SO_4 \rightarrow H^+ + HSO_4^-;$$



(1) (2) (3)

In step (1) the proton attacks the oxygen of hydroxyl group. Further, the proton attached to oxygen, forms the intermediate particle (2), in which oxygen was trivalent, so the water molecule is split off and formed carbocation (3).

Step 2:



Chloromethane

In the second step carb-cation is attacked by a nucleophile Cl^- and formed the final reaction product - chloromethane.

Humans, *in* substitution of OH - groups go through a stage of formation of phosphorus - esters, since it is easy to split off the phosphate residues:

$$R\text{-}OH + H_3PO_4 \rightarrow R - O - PO_3H_2 \rightarrow R^+ + OPO_3H_2.$$

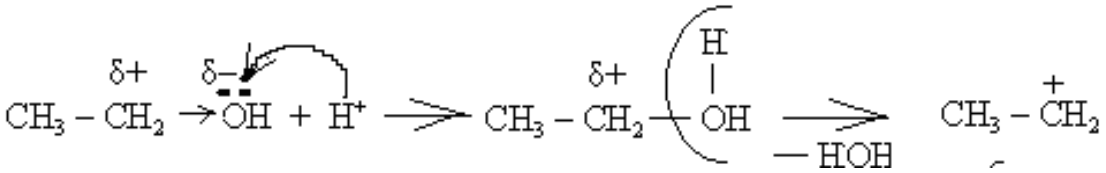
ELIMINATION REACTION IN ALCOHOL

Many reactions between organic compounds are accompanied by competing reactions. Such a reaction for nucleophilic substitution in alcohols is the reaction *of elimination E* (cleavage). In this case, from alcohol is split off the water molecule, that is *dehydration.*

Since oxy - the group is split off is difficult, it requires a catalyst for H^{+}.

Mechanism can be written graphically as follows:

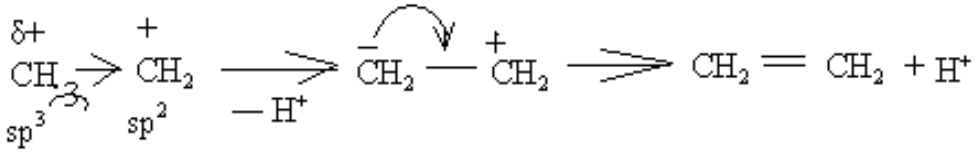
$$H_2SO_4 \rightarrow H^+ + HSO_4^-;$$



In (1) step the proton attacks the oxygen of hydroxyl group. Further, the proton attached to oxygen, forms the intermediate particle (2), in which oxygen was trivalent, so the water molecule is split off and formed carbo-cation (3). That is, the first step of the reaction proceeds as a nucleophilic substitution reaction. Next, the reaction proceeds in a different way.

Step 2:

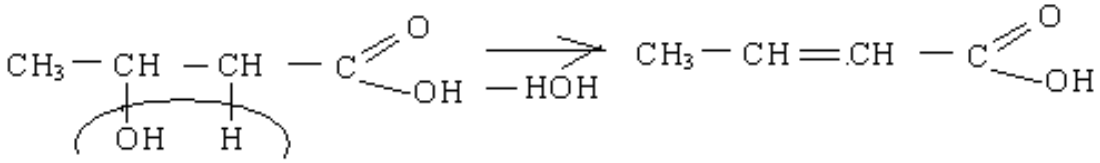
In the formed carb - cation (3) is the redistribution of electron density:



sp^2 - a hybrid carbon atom in the cation-carb (3) contracts over the electron density of the sp^3 - hybrid carbon. In the sp^3 - hybrid carbon occurs a partial positive charge (δ +), and from it can repel the proton $H^{+,}$ that is, at this carbon arises CH^- acidic center. After removal of the proton forms a particle with positive and negative charges on different atoms of carbon (4). As a result of redistribution of electron density between the carbon atoms of the double bond occurs, and the formed product elimination - the unsaturated hydrocarbon (5).

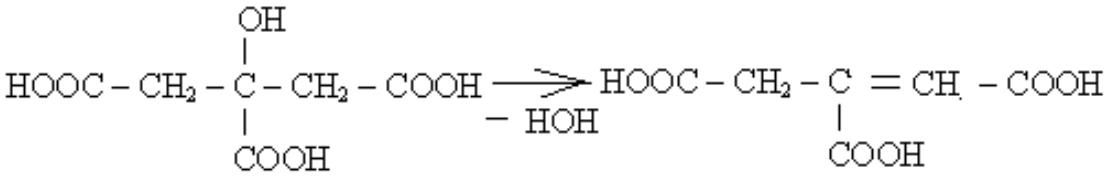
Biological significance of the reactions of dehydration of hydroxyl compounds:

a) The formation of crotonic acid:



β - hydroxybutyric acid ***Crotonic acid***

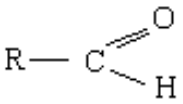
b) The formation of cis-aconitic acid:

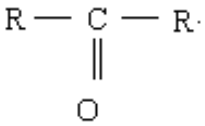


Citric acid ***cis - aconitic acid***

NUCLEOPHILIC ADDITION IN OXOCOMPOUND

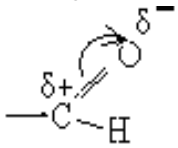
Oxo - compounds are those organic compounds, which contain oxo - group> C = O. If the oxo - group is connected to a hydrogen atom, these compounds belong to a class of aldehydes. If oxo - group is connected with the radical, these compounds belong to a class of ketones:





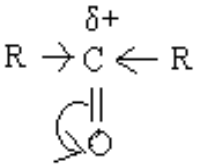
Aldehyde Ketone

Aldehydes are very reactive, since there is a high carbon atom a partial positive charge due to the shift π - electron density of the double bond to an oxygen atom:



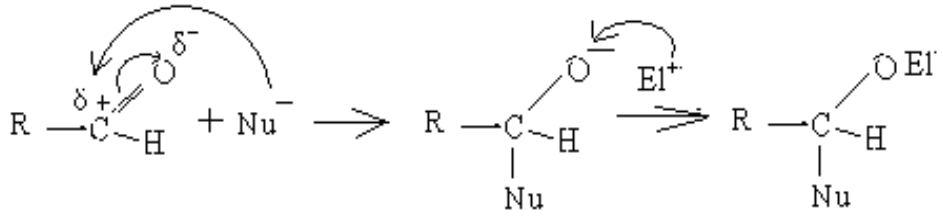
This carbon atom is attacked by a nucleophile.

Ketones are less reactive, as the second radical is a result of the positive inductive effect reduces the partial positive charge on the carbon atom of an oxo group.



Therefore, the mechanism of nucleophilic addition by the example of aldehydes.

Scheme of the mechanism of nucleophilic addition:



(1) (2) (3)

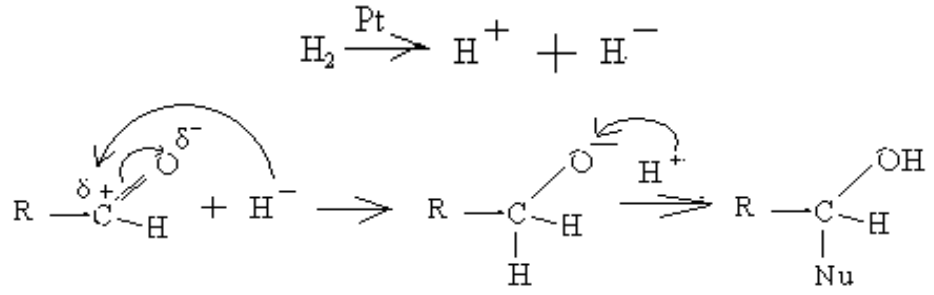
In step (1) the nucleophile attacks the carbon atom to the lack of electron density. As a result of the attack breaks the double bond, nucleophile attached to the carbon and forms the intermediate particle (2). The negative charge on oxygen in the particle (2) neutralize the electrophile (usually a proton $H^{+),}$ and produced the final product of the reaction (3).

If the nucleophile is weak, then the use of catalysis by acid or alkaline.

Consider the specific reactions that go with aldehydes in vitro as well as in the human body.

1. Hydrogenation of aldehydes (recovery).

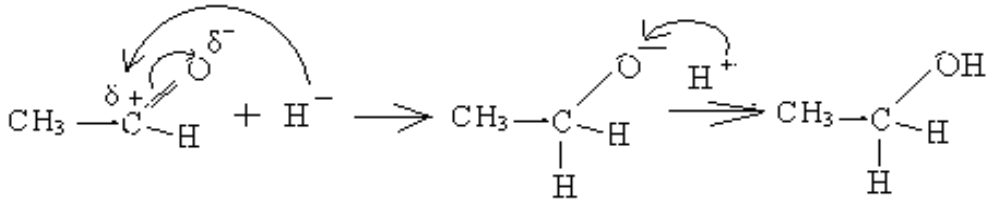
Hydrogenation of aldehydes in vitro in the presence of a catalyst is platinum or nickel, with which the hydrogen molecule heterolytically decays into a proton and a hydride anion, which is the nucleophile. Graphically, the mechanism can be written as follows:



(1) (2) (3)

In step (1) hydride - anion, which was formed in the heterolytic decomposition of the hydrogen molecule, attacks the carbon of the aldehyde group. Double bond C = O is broken and the hydrogen atom attached to carbon and oxygen occurs on the negative charge (2). Then, a proton, which was formed in the heterolytic decomposition of the hydrogen molecule, neutralizes the negative charge of oxygen, and the final product is obtained (3).

For example, the mechanism of hydrogenation of acetaldehyde can be shown graphically such a scheme:

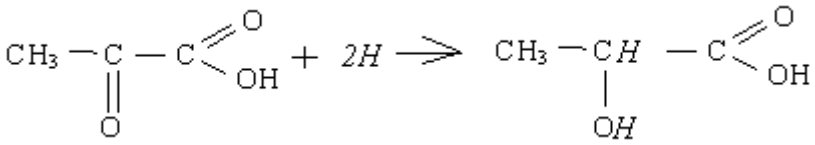


Acetaldehyde ***Ethanol***

The biological significance of hydrogenation of Oxo compounds:

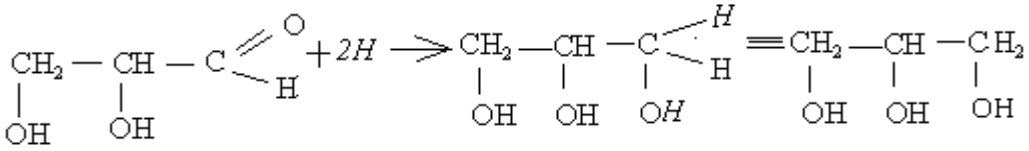
a) in the process of anaerobic glycolysis is the reduction reaction

Of pyruvate (pyruvic acid - PVC) to lactate (lactic acid):



STC ***milk***

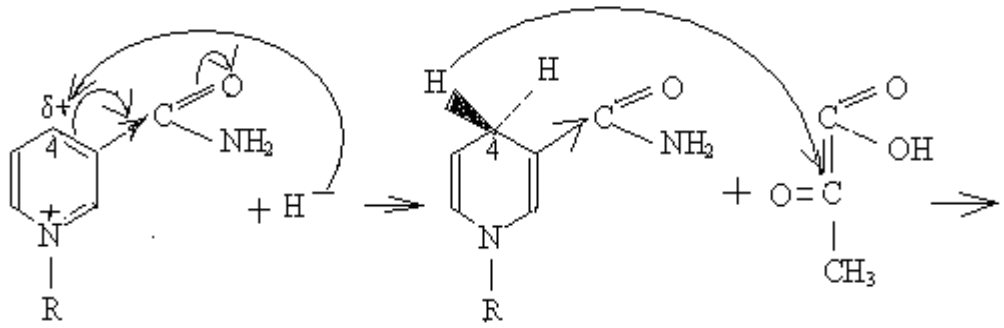
b) in the process of fat synthesis is the reduction reaction of glyceraldehyde to glycerol:



Glyceraldehydes ***Glycerin***

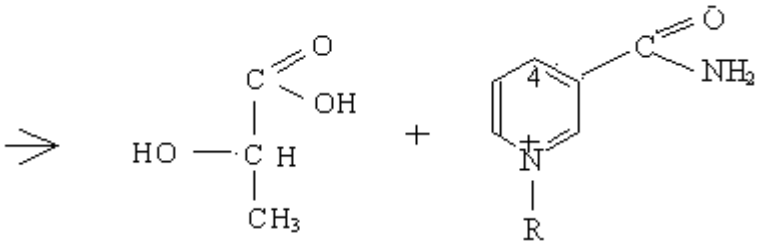
Hydrogen and electrons are transferred into the body coenzymes NAD, NADP, Ubiquinone.

The chemistry of the NAD:



NAD ***NADH*** ***STC***

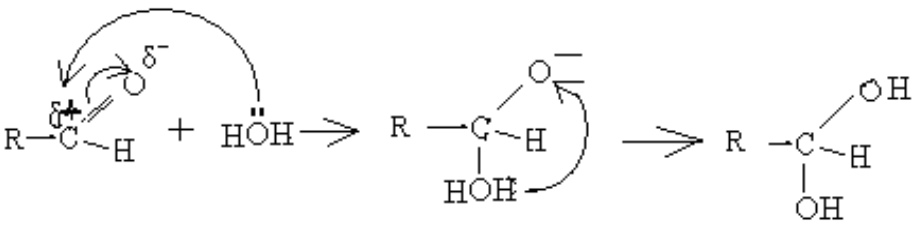
($SubH_2 \rightarrow Sub + H^-H^+ \rightarrow$ is dehydrogenation of the substrate, resulting in N^- is a molecule of NAD and H^+ into solution, which then goes into oxygen STC).



Lactic acid ***NAD***

2. Hydration of aldehydes (can go without a *catalyst).*

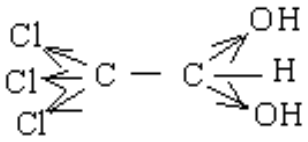
Graphically, the reaction mechanism can be written as follows:



(1) (2) (3)

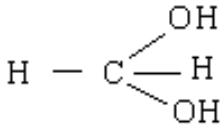
The first is the attack of a water molecule as the nucleophile (1), and form an intermediate compound (2), in which the oxygen in the aldehyde of the negative charge arises, and in the water molecule appears trivalent oxygen, which is impossible. Therefore, water molecules are split off from the proton and moves to the negatively charged oxygen (2). The result is a finished product (3).

However, compounds with two hydroxyl groups at one carbon atom unstable, because each oxygen atom pulls the electron density itself. As a result of the uneven distribution of electron density in the system there is an excess of energy, and she splits the water molecule. But if the radical is electron-substituents, which tightens a part of the electron density, in this case, the electron density is distributed uniformly, and the system becomes stable. An example would be *chloral* hydrate, which is used as a hypnotic



Chloral hydrate

and the presence of hydroxyl groups reduces the toxic effects of chlorine atoms. Formaldehyde in solution is always hydrated



40% solution of formaldehyde is called ***formalin,*** which is used for the storage of anatomical specimens. The action of formaldehyde due to irreversible denaturation of proteins. But when the concentration of an aqueous solution of formaldehyde, 0.75 - 1% of the observed reversible denaturation. It is used to store tissue and organ transplantation, followed by their patients, and in this case decreases graft rejection.

3. Co-operation with alcohols.

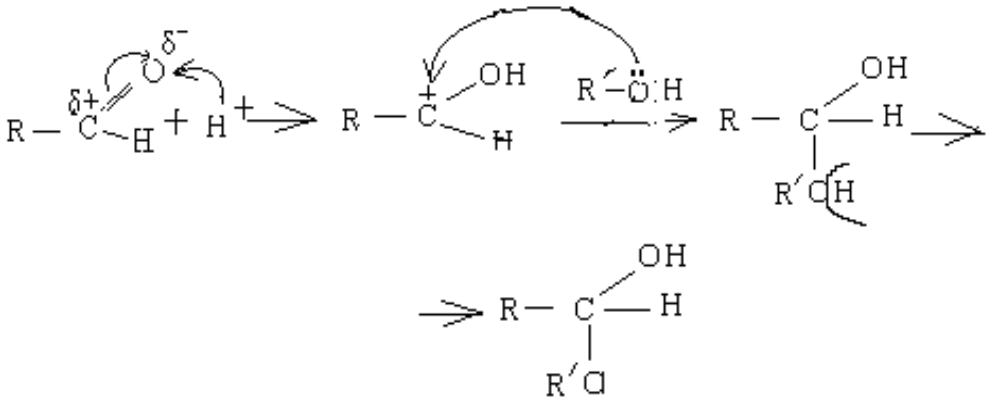
Alcohols by nucleophilic lone electron pairs of oxygen. But it is weak nucleophiles as oxygen, due to the high electronegativity strongly attracts an unshared electron

pair, and this molecule cannot attack the carbon with a *partial* positive charge, so you need a catalyst.

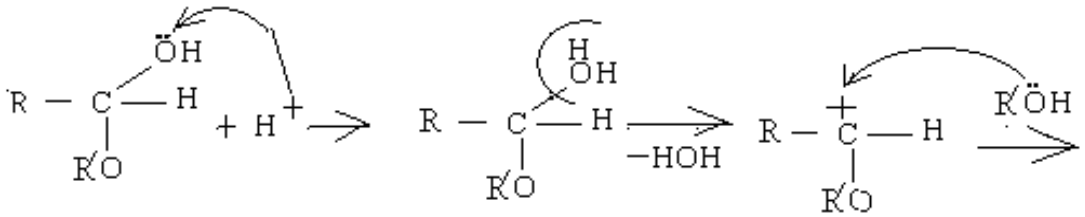
The catalyst used proton, which gives the H_2SO_4.

Mechanism of the reaction graph can be written as:

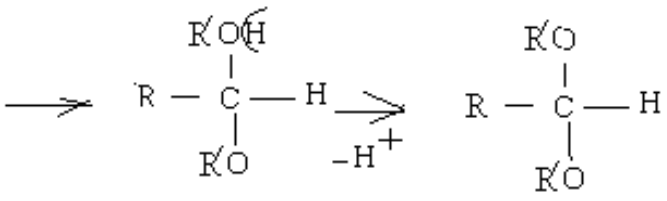
$$H_2SO_4 \rightarrow H^+ + HSO_4^-$$



In step (1) the proton attacks the oxygen (protonation process) in which there is partial negative charge due to the inductive effect. Formed intermediate (2) with a positive charge on the carbon atom, ie carbocation. This compound was attacked by a molecule of alcohol as a nucleophile, alcohol, joins, and forms an intermediate compound (3), in which oxygen is trivalent, so the proton is split off from him, and produced the final product (4). The final product is called a ***hemiacetal.*** These compounds are unstable, since the carbon atom bonded to two oxygen atoms, each of which pulls the electron density itself. Therefore, it is easy to split off from the hemiacetal molecule of water. Hemiacetal interaction with a second molecule of alcohol, is ***acetal*** formed, but the reaction proceeds by the mechanism of nucleophilic substitution S_N from sp^3 - hybrid carbon atom. Catalyst also serves as a proton. Graphically acetal formation mechanism can be described as follows:



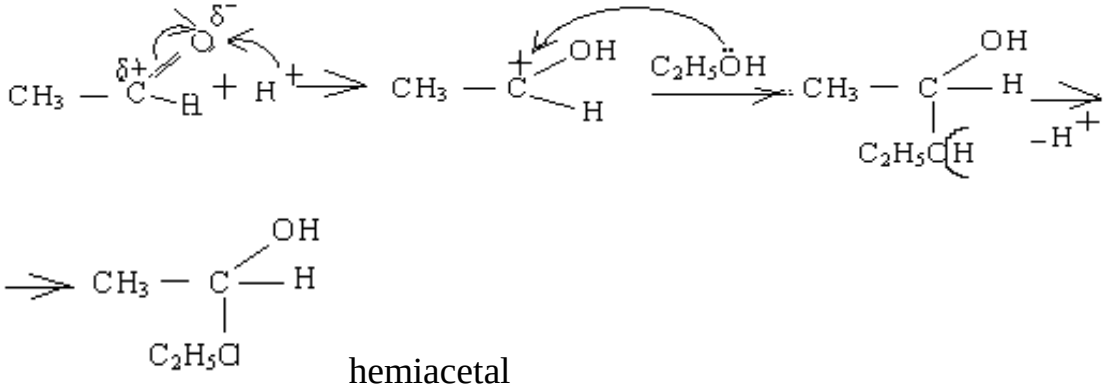
(1) (2) (3)



(4) (5)

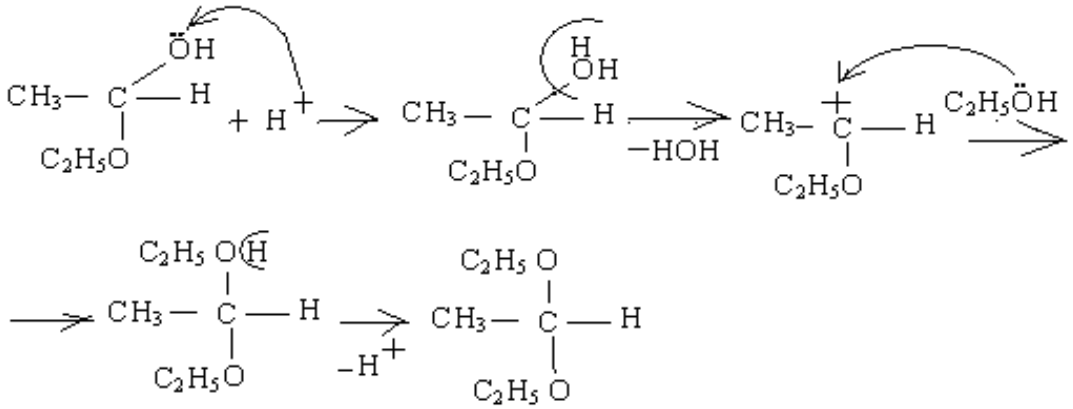
In step (1) is protonated hydroxyl oxygen. Proton joins and forms an intermediate compound (2), in which oxygen is trivalent, which is not typical for him. Therefore, the water molecule is split off and formed carbocation (3). He was attacked by a second molecule of alcohol. Formed intermediate (4) with trivalent oxygen, from which the proton is split off. The final product (5) is an ***acetal.***

For example, the interaction of acetaldehyde and 1st ethanol: stage - the formation of hemiacetal:



hemiacetal

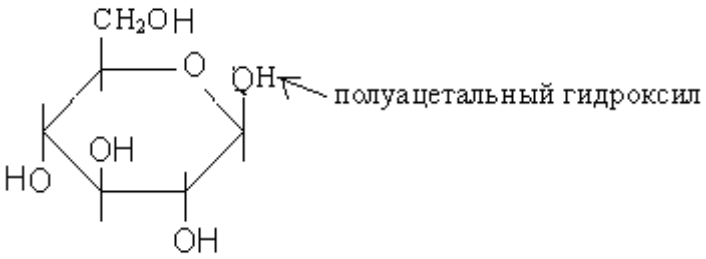
Step 2 - Acetal Formation:



Acetal

The biological significance of hemiacetal and acetal:

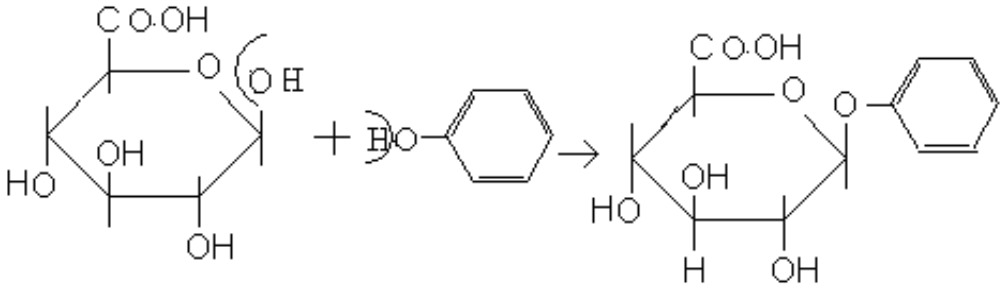
a.) in the human body monosaccharaides are cyclic hemiacetal



Glucose

b) disaccharides and polysaccharides – a acetals

c)in the form of acetals derived from toxins:



Glucuronic ***Phenol***

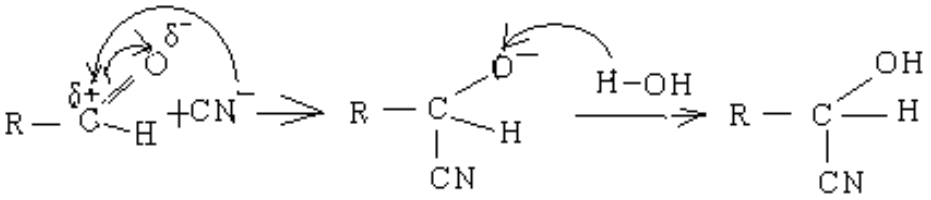
4. Interactions with acid hydrogen cyanide HCN.

Prussic acid -- weak acid, so it is necessary to create the dissociation of the alkaline medium (catalyst):

$$HCN + OH^- \rightarrow HOH + CN^-$$

Cyanide - anion CN^- is the nucleophile.

Graphically, the reaction mechanism can be written as follows:



(1) (2) (3)

Cyanohydrin ***Oroxinitril***

In step (1) cyanide - anion as the nucleophile attacks the carbon of the aldehyde group. As a result, breaks the double bond carbon - oxygen, and cyanide - ion associates (2), with the formation of an intermediate particle with negative charge on oxygen, which is neutralized by a proton from a water molecule (water easily dissociates under the action of the negative charge of oxygen, that is, water is the protonation. Produced the final product - a **cyanohydrin.**

Biological significance of cyanohydrins:

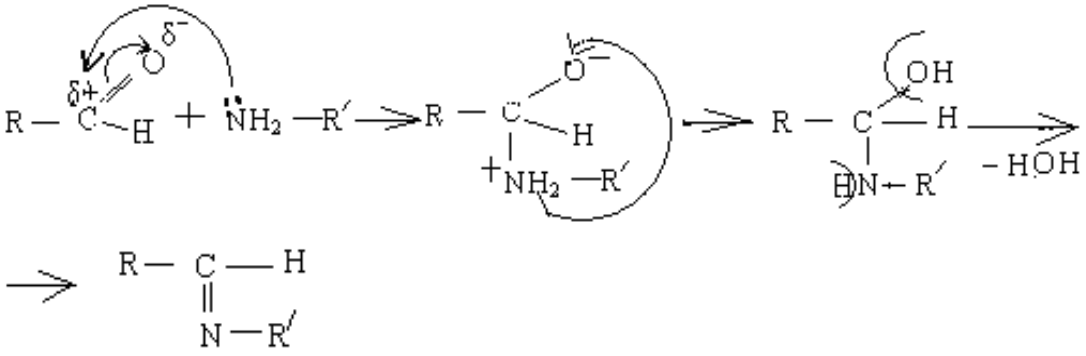
a) They are intermediates in the synthesis of amino acids in vitro;

b) Some cyanohydrins, such as ***amygdalin,*** located in the nuclei of stone plants (cherry, plum, almond). When injected into the human body, they decompose to form hydrogen cyanide (prussic) acid, which can lead to poisoning.

5. Interaction with ammonia and amines (the reaction of accession - cleavage).

Amines strong nucleophiles due to the unshared electron pair of the nitrogen atom, so they directly attack carbon of the aldehyde group.

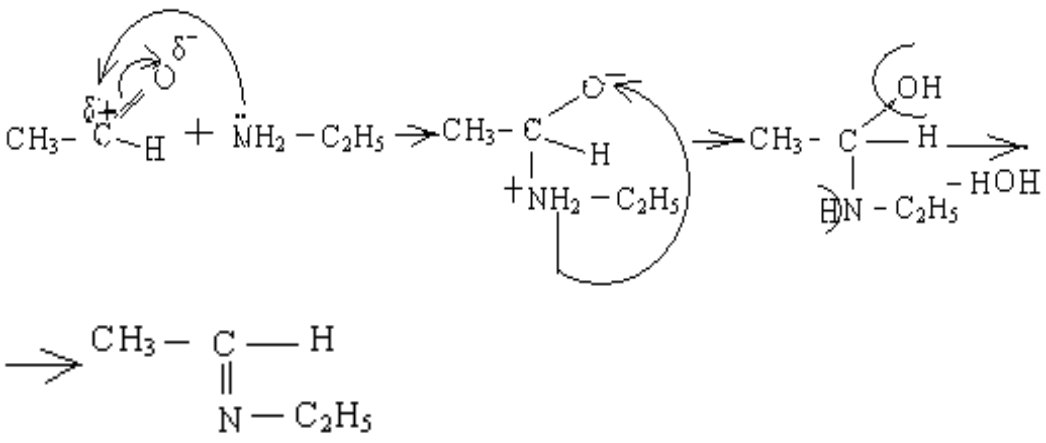
Graphically, the reaction mechanism can be written as:



Amine or Schiff base

At the first stage (1) amine as a strong nucleophile attacks the carbon of the aldehyde group. As a result, breaks the double bond carbon - oxygen, and amine attached. Formed an intermediate particle (2) with a negative charge on oxygen and nitrogen occurs in the positive charge (because it gave undivided electron pair in contact with carbon). From nitrogen cleaved the proton and neutralizes the negative charge on oxygen (particle 3). These carbon particles associated with two electronegative atoms - oxygen and nitrogen, each of which pulls the electron density itself. That is, in the electron density is unevenly distributed, making the system unstable. Therefore, it is cleaved by a water molecule, and the final product is formed ***imine or Schiff base*** (4).

For example, the interaction of acetaldehyde with ethylamine:

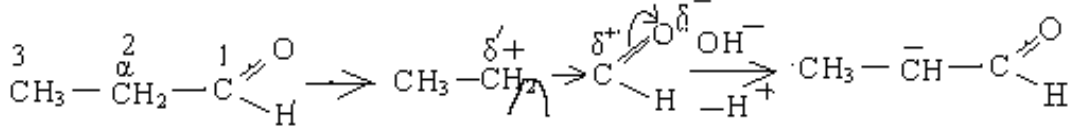


The biological significance of imines:

a) Imines or Schiff bases are of great biological importance because they are intermediates in the synthesis of proteins in the human body, which is called transamination. **Transamination -** this enzymatic reaction is reversible amino group transfer between the amino and keto acids without releasing ammonia.
b) Imines are intermediates in the synthesis of proteins compound in vitro.

Reactions caused by the mobility of α - hydrogen atom.

a - hydrogen is a hydrogen atom at the carbon atom bound to the aldehyde group (1):



(1) (2) (3)

Carb-anion

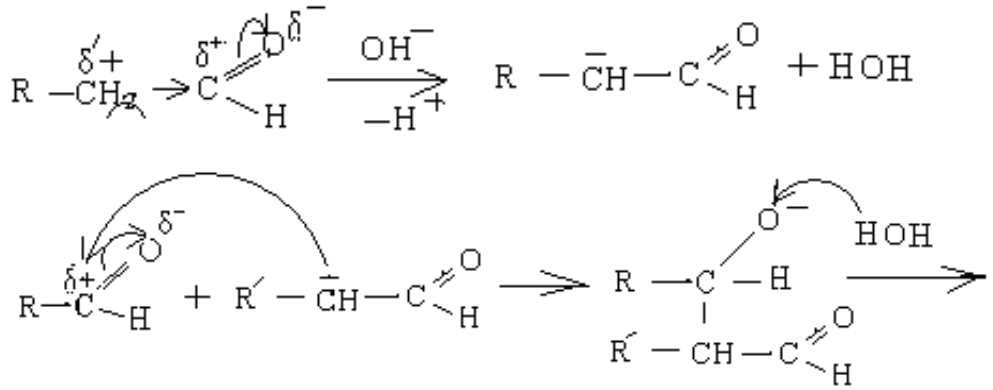
In result of the polarization due to the aldehyde group on carbon occurs a partial positive charge $\delta^{+,}$ which from the α - carbon atom, the electron density is shifted to σ - bond (inductive effect). At this carbon occurs a partial positive charge $\delta' +$ (2). In the alkaline environment of the carbon is cleaved from the proton, i.e., from on the$_2$ there CH- acid center. In the presence of alkali, which is the catalyst, the proton is split off easily. The end product is a carb - anion (3), which as a nucleophile attacks the carbonyl carbon of a second molecule of aldehyde.

To reactions caused by the mobility of α - hydrogen-atom reactions include aldol condensation reaction galoformic.

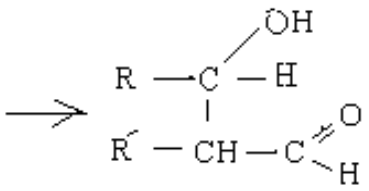
A). **Aldol condensation** reaction of a compound of two molecules of aldehyde.

Graphically, the mechanism of aldol condensation can be shown as:

$NaOH \rightarrow Na^{+} + OH^{-;}$



(1) (2)



(3) aldol

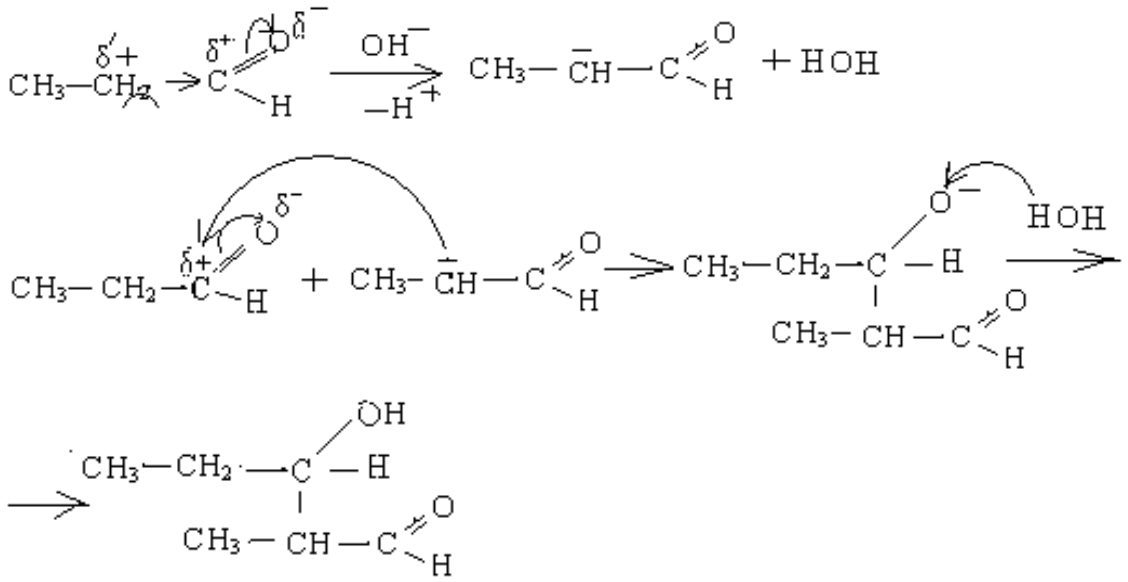
In the step (1) carbanion as a nucleophile attacks the carbonyl carbon.

As a result, breaks the double bond carbon - oxygen and the carbanion attached to carbon. Formed an intermediate particle (2) with a

Negative charge on oxygen. To neutralize this charge is the protonation of water (water under the influence of the negative charge of oxygen dissociates more easily), and the final product is formed ***aldol***(3).It is so called because it contains an aldehyde group, which gives the end of *Aldol*, and alcoholic hydroxyl group, which gives ending *ol.*

Example aldol condensation may be an interaction of two molecules of propanol.

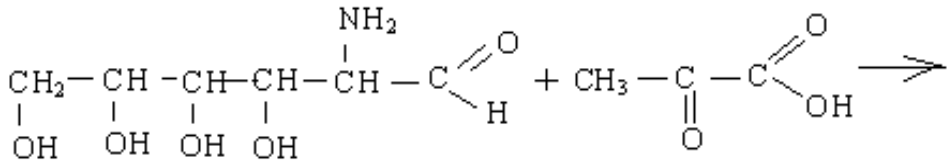
$NaOH \rightarrow Na^+ + OH^-$;



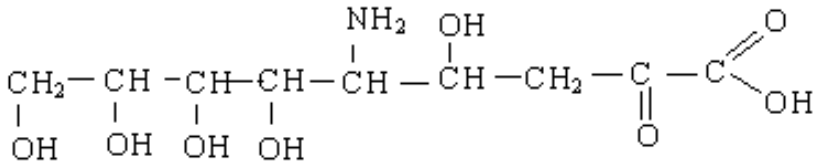
The biological significance of the aldol condensation.

a) The mechanism of aldol condensation in nature is the formation of glucose in the process of photosynthesis

b) In the human body is synthesized neuraminic acid, a scheme of formation which can be written as:



Mannosamin ***STC***



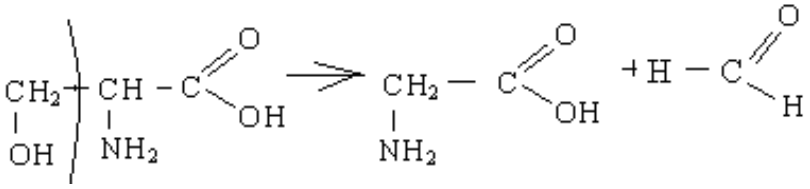
Neuraminic acid

Synthesis of citric acid in the Krebs cycle (see "carboxylic acids"),

c) The synthesis of steroid hormones.

Reverse aldol condensation reaction is called **aldol** cleavage:

a) In the human body is exposed to such a splitting of the amino acid *serine*. The scheme of this process is as follows:



Serin ***Glycine*** ***Formaldehyde***

b) In animal organisms is the splitting of fructose - 1,6 - phosphate, and in the plant, on the contrary, the synthesis of it.

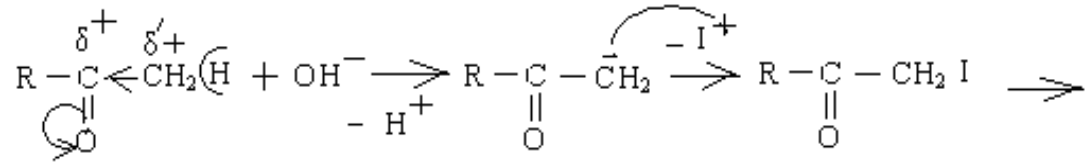
c) **Aloform reaction -** is getting halo form, i.e. chloroform, bromoform and iodoform.

Graphically, the reaction mechanism can be written as:

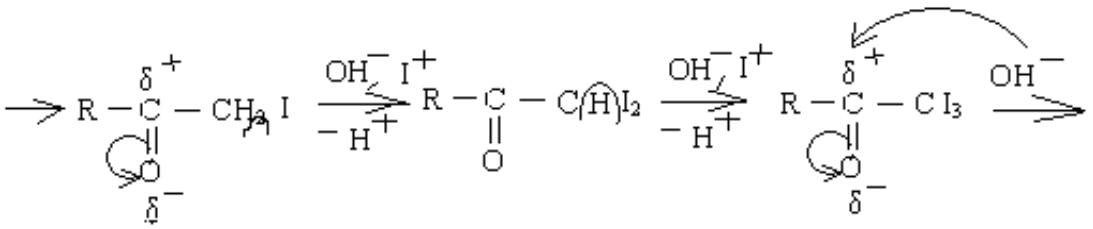
$I_2 + NaOH \rightarrow NaI + NaIO$; (1)

$NaIO + HOH \rightarrow HOI + NaOH$; (2)

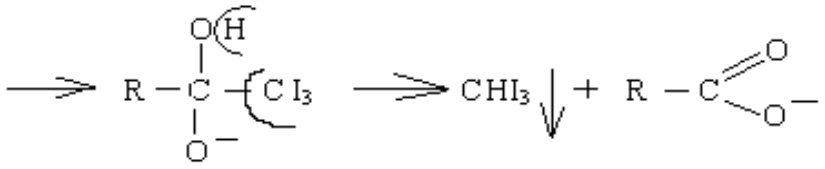
$HIO \rightarrow I^+ + OH^-$; ($OH^-$ is a nucleophile) (3)



(4) (5) (6)



(7) (8) (9)



(10) (11)

I_2 in alkaline solution disproportionate (1). The salt is hydrolyzed by NaIO (2). The acid in these conditions HOI dissociates to form OH^-, which is the nucleophile (3). In step (4) splits off a proton from carbon to δ '+ is formed and the carb - anion (5), which is attacked by an ion $I^{+.}$ The result is an intermediate (6), in which one hydrogen atom is replaced by an iodine atom. Next comes the gradual detachment of the proton and its replacement by iodine atom (stage 7, 8.9). At the intermediate (9) is a nucleophile attack of OH^- who joins the carbon atom (10) and pushes the molecule CH_3I (11). This is - **iodoform,** a substance pale - yellow color with a characteristic odor. By-product (12) - is an anion, which gives the sodium cation with the salt.

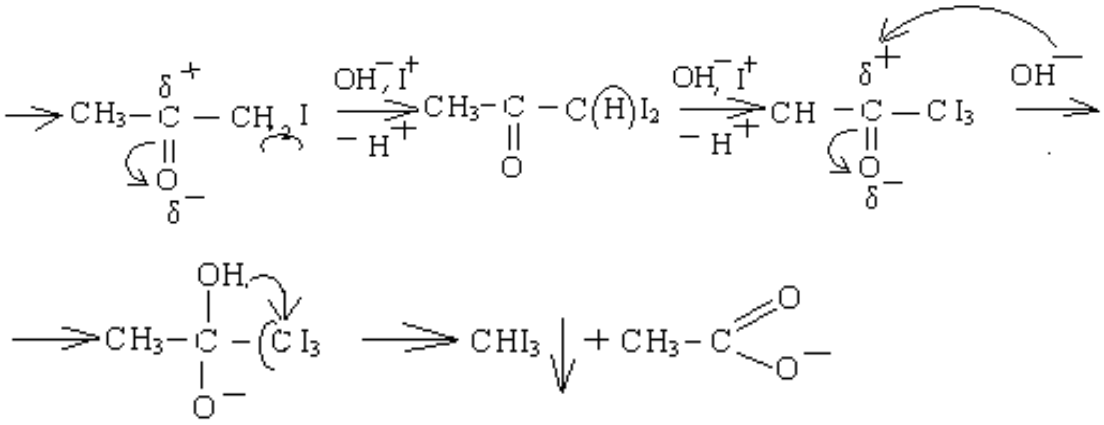
Halo form example of the reaction may be the interaction of acetone with iodine in alkaline medium:

$I_2 + NaOH \rightarrow NaI + NaIO;$

$NaIO + HOH \rightarrow HOI + NaOH;$

$HIO \rightarrow I^+ + OH^-;$

acetone

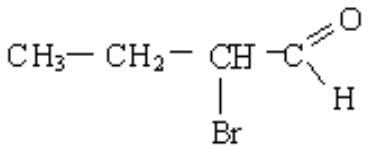


Biodoform

The biological significance of halo form.

a) Chloroform $SNCl_3^-$ Means for *anesthesia* (not recently used, as in the decomposition yields free radicals).

b) If α - hydrogen atom is replaced by Br, is obtained *lachrymatory* (tear gas), for example, the brom butanoic aldehyde:

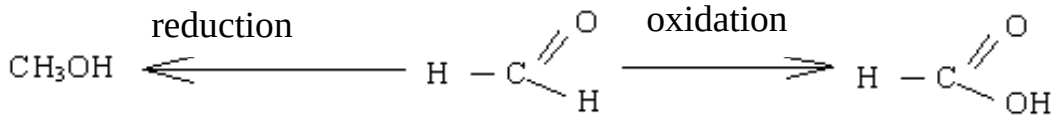


c) The formation of iodoform CHI_{3s} used as a *simple test for acetone in the urine of* patients with diabetes. In addition, the iodoform is used as an *antiseptic.*

Reactions due to the absence of α - hydrogen atom

*(*Reaction *disproportionation*).

In a series of oxidation - reduction processes aldehydes are intermediate between alcohols and carboxylic acids, i.e. aldehydes reduced to alcohols and oxidized to carboxylic acids.



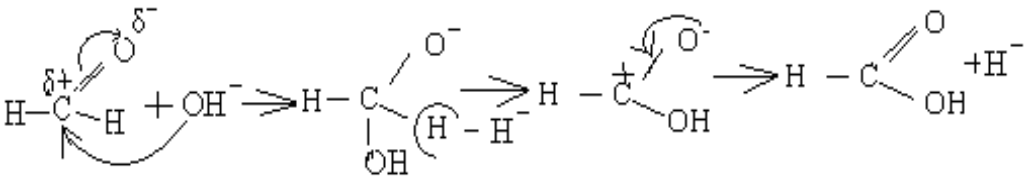
Alcohol ***Aldehyde*** ***Acid***

Disproportionation reactions are in the presence of a catalyst - alkali water in the presence and absence of α - hydrogen atom.

Graphically, the reaction mechanism can be written as

1step:

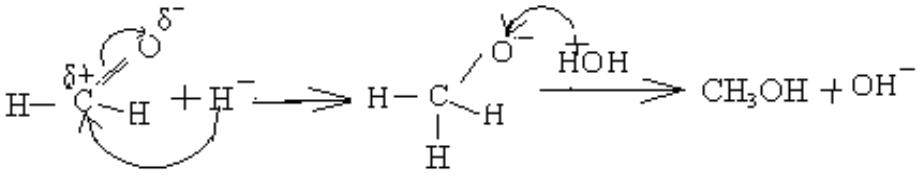
$$NaOH \rightarrow Na^{+} + OH^{-};$$



(1) (2) (3) (4)

As a result of dissociation of sodium hydroxide catalyst is formed, while the nucleophile OH^{-}, which attacks the carbon of the aldehyde group (1). Hydroxyl groups attached to carbon as a result of rupture of the double bond carbon - oxygen, and oxygen occurs a negative charge (2). To get rid of the negative charge, the system pushes hydride - anion H^{-} and forms the intermediate particle (3), in which there is a redistribution of electron density, closed the double bond carbon - oxygen, and forms the final product - acid (4).

2 step:



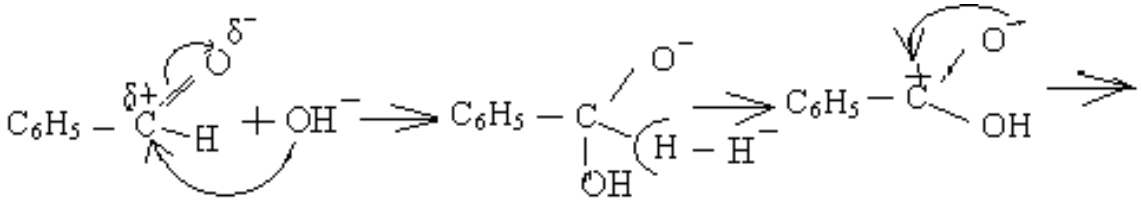
(5) (6) (7)

In the second phase hydride - anion attacks the second molecule of aldehyde (5).

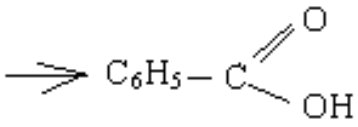
As a result of rupture of the double bond carbon - oxygen, hydrogen atom attached to carbon and oxygen, there is a negative charge (6). To neutralize the negative charge is the protonation of water (6). Formed one more final product - alcohol and

the catalyst is released - OH^- is an example of a disproportionation (oxidation - reduction) benzaldehyde:

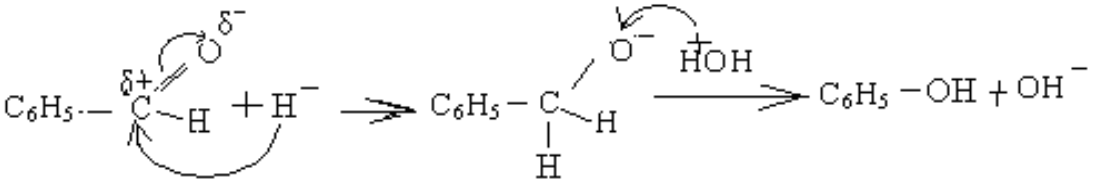
$NaOH \rightarrow Na^+ + OH^-$;



Benzaldehyde



Benzoic acid



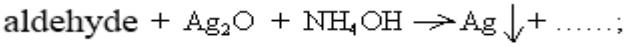
Benzyl ***Alcohol***

Aldehyde disproportionation occurs during alcoholic fermentation of glucose.

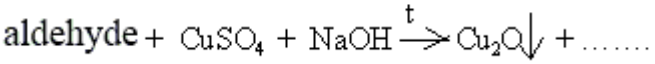
Oxidation of aldehydes and ketones,

Aldehydes and ketones are oxidized. Aldehydes are oxidized more easily than ketones. They even oxidize atmospheric oxygen. Consider the oxidation of aldehydes, which are of practical importance.

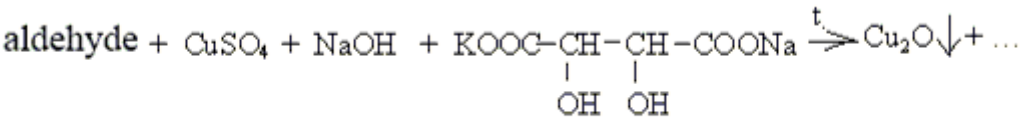
1) The reaction of Tollens (silver mirror reaction) - the interaction of aldehydes with ammonia solution of silver:



2) The reaction of Trommer - the interaction of aldehydes with cuprum (II) hydroxide in alkaline medium:



3) The reaction of Fehling - the interaction of aldehydes with cuprum (II) hydroxide in alkaline medium in the presence of Rochelle salt:



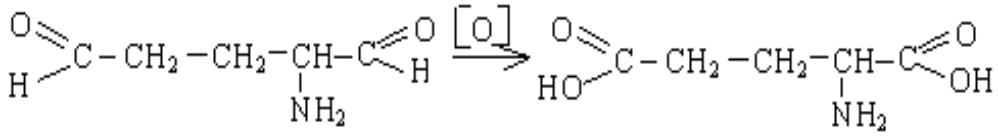
All these reactions are accompanied by an external effect, i.e. precipitation and staining. Therefore used as the aldehyde group on the quality, and clinical analysis - for the determination of monosaccharaides in biological fluids. The most common used *Trommer test.*

Oxidation of ketones is accompanied by rupture of the carbon chain.

Biological significance of the oxidation of aldehydes and ketones.

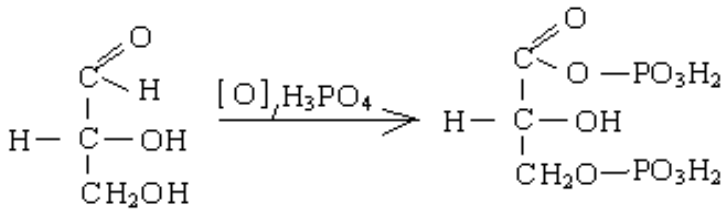
a) Due to its high reactivity, aldehydes are toxic to the human body, so they are oxidized to harmless carboxylic acids. For example:

b) the oxidative deamination of amino acids, glutaraldehyde is oxidized to glutaric acid



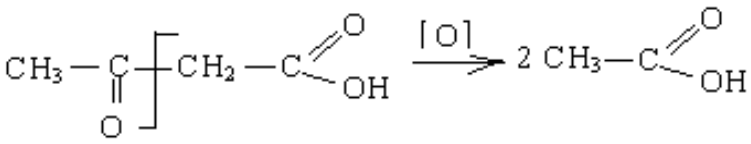
Glutaral ***Dihydro glutaric acid***

b) Glyceraldehyde is oxidized to glyceric acid and phosphorylated at the same time:



Glyceraldehydes ***1,3 - difosfo glyceric acid***

acetoacetic acid (acetoacetate) as the keto acid is oxidized with rupture of the carbon skeleton:



Acetoacetate *(β-ketobutanoic acid)* ***Acetate***

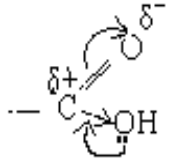
NUCLEOPHILIC SUBSTITUTION IN CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Carboxylic acids are derivatives of alkanes, in which one or

more carbon atoms substituted karbocroup — 

carboxyl consists of oxo - and hydroxyl groups, which mutually influence each other, so these groups change their properties compared with the oxo and the hydroxyl group in aldehydes in alcohols.

Electronic structure of carboxyl:

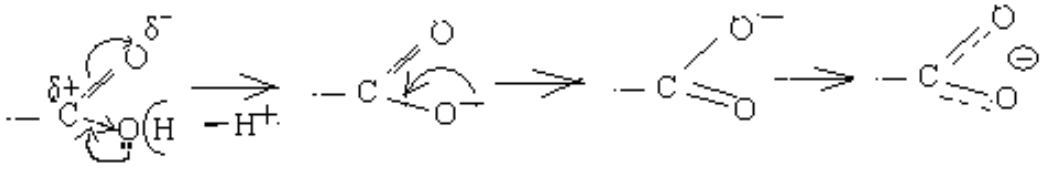


Oxo oxygen atom as the more electronegative pulls over π - electron density of the double bond, resulting in carbon occurs a partial positive charge, as in aldehydes. Hydroxyl oxygen atom as a more electronegative pulls itself from the electron density on the carbon σ - bond, but its lone electron pair is a pairing of π - electron density of the double bond. As a result of decreases in carbon a partial positive charge in comparison with aldehydes, carboxylic acids, so are the substitution reactions (rather than joining in aldehydes). This reflects the influence of the hydroxyl group at the oxo group.

On the other hand the shift unshared electron pair of oxygen to carbon with a partial positive charge increases the ease of removal of a proton. That is, acidity of carboxylic acids is higher than that of alcohols. This demonstrates the effect of oxo - hydroxyl group at the - group.

Acidic properties of carboxylic acids.

Carboxylic acids exhibit acidic properties due to removal of a proton (Bronsted). But it is much stronger acid than alcohols, which also contain a hydroxyl group. Elevated carboxy acid properties of the `plained as follows:



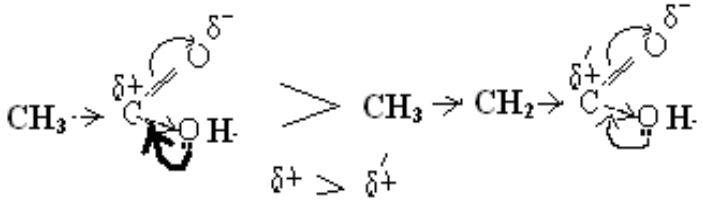
(1) (2) (3) (4)

(4) Carboxyl (1) is the redistribution of electron density in such a way that the resulting displacement of the oxygen lone pair to pair it easy to split off from the proton and the anion is formed (2). This anion is a redistribution of electron density and there is an anion (3). Eventually, the electron density is distributed evenly between the two oxygen atoms and the carbon atom and forms a *three-center*

delocalized conjugated system. In this system, the electron density is distributed evenly, which makes its thermodynamic stability and ease of removal of a proton.
Acidity of carboxylic acids depends on the structure of the radical and the presence substituents:

a) **H-COOH> CH_3-COOH>CH_3-CH_2-COOH**

3,77 ***4,46*** ***4,88***

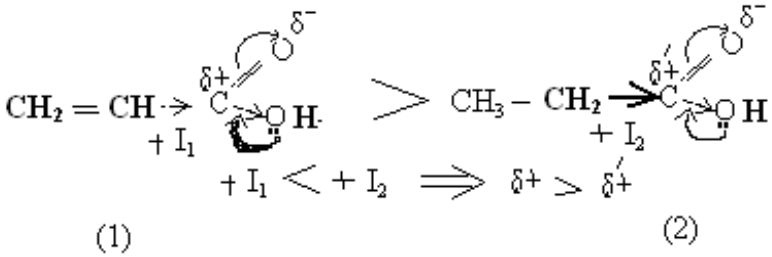


Electronic effect is stronger, the electronic effect is weaker.

In homologous series the acidity decreases as a result of the positive inductive effect of the long radical decreases the partial positive charge on carbon, thereby decreasing the displacement of the unshared electron pair of oxygen to carbon, ie on the oxygen atom remains high electron density, and the proton is split off more difficult.

b) **CH_2= CH-COOH > CH_3-CH2-COOH**

4,25 4,88.



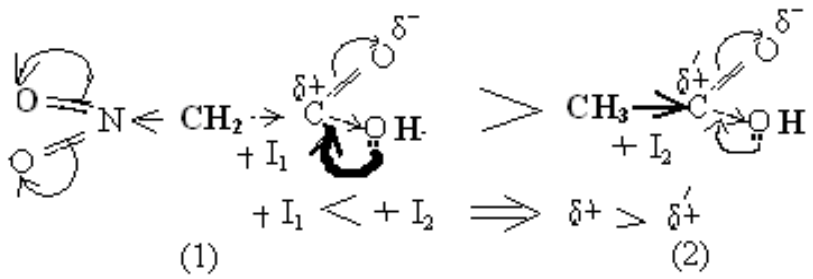
Unsaturated acid is stronger than saturated, as a positive inductive effect $s\rho^2$ - hybrid carbon atom (+ I_1) is less than the positive inductive effect $s\rho^3$ - a hybrid of a carbon atom (+ I_2),so δ+>'δ+; thereby increasing the displacement of the unshared electron pair of oxygen to carbon (1), ie on the oxygen atom decreases the electron density and the proton is split off more easily.

c) **CF_3-COOH>CH_2F-COOH> CH_3-COOH**

0,7 ***2,9*** ***4,76***

$O_2NC_6H_4$-COOH>HOOC-C_6H_4-COOH>C_6H_5COOH> CH_3COOH

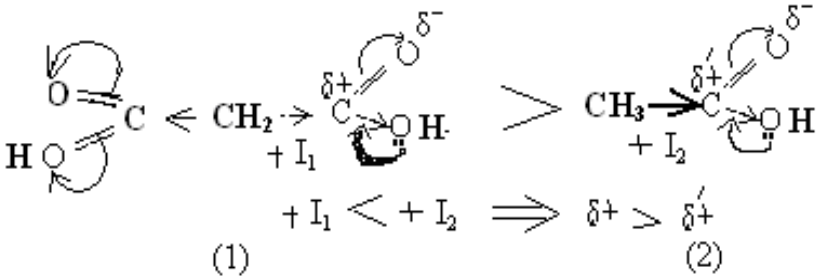
2,17 ***2,98*** ***4,2*** ***4,76***



The presence of electron withdrawing substituents in the radical, such as F or NO_2 increases the acidity, since F or NO_2 pulls itself from the radical electron density and its inductive effect (I_1) becomes smaller, so why δ+>'δ+; therefore increasing displacement of unshared electron pairs from oxygen to carbon (1), ie on the oxygen atom decreases the electron density and the proton is split off more easily.

d) **HOOC-COOH> HOOC-CH_2-COOH>HOOC-CH_2-CH_2-COOH> CH_3-COOH**

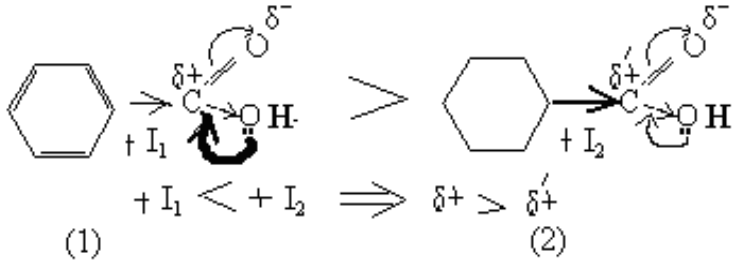
1,23 2,83 4,19 4.76



Dibasic acid is stronger than monobasic, since the second carboxyl group pulls itself from the radical electron density and its inductive effect (I_1) becomes smaller, so that $\delta^+ > {}' \delta^+$ thereby increasing the displacement of the unshared electron pair of oxygen to carbon (1), i.e. on the oxygen atom decreases the electron density and the proton is split off more easily.

d) C_6H_5COOH> $C_6H_{11}COOH$

4,2



A omatic acids are stronger than acid - derived cycloalkanes, as a positive inductive effect $s\rho^2$ - hybrid carbon benzene ring (+ I_1) is less than the positive inductive effect $s\rho^3$ - hybrid carbon atoms of cyclohexane (+ I_2), so $\delta^+ > {}' \delta^+$; herefore increases displacement of unshared electron pairs from oxygen to carbon (1), i.e. on the oxygen atom decreases the electron density and the proton is split off more

easily. By being acidic properties of carboxylic acids react with metals, oxides, bases and salts give, for example:

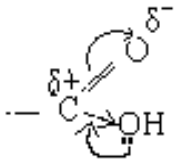
$$CH_3COOH + NaOH \rightarrow CH_3 + H\ SOONa_2O.$$

In the human body formed of many salts organic acids:

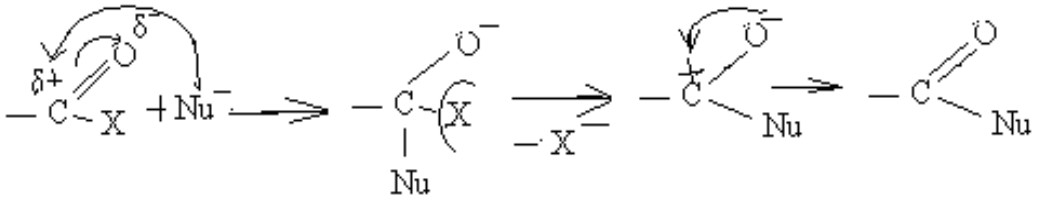
lactic acid	gives salt	lactates
pyruvic acid	<<	pyruvate
citric acid	<<	citrate
oxalate (oxalic acid)	<<	oxalate
succinate (succinic acid)	<<	succinate,
malic acid	<<	malate.

NUCLEOPHILIC SUBSTITUTION IN CARBOXYLIC ACID AND ITS DERIVATIVES

In the carboxyl-group shows a positive mesomeric effect (shear lone electron pair to the carbon atom), which reduces the partial positive charge on carbon in comparison with aldehydes, carboxylic acids, so go for the reaction mechanism of nucleophilic substitution instead of joining in aldehydes. In this case, an effect of the hydroxyl group in the oxo-group.



The scheme of the mechanism of nucleophilic substitution:



(1) (2) (3) (4)

Where X is -OH, -NH_2,OR-,RCOO-,halogen.

Nucleophile attacks the carbon atom with a partial positive charge (1), followed by a double bond is broken, and the nucleophile attached (2), and the system pushes the particle X, which carries with it a negative charge (who brought Nu) and the particle is formed (3). As a result of redistribution of electron density of the final product formed by nucleophilic substitution (4).

If the nucleophile is weak, then apply the acid catalysis or base.

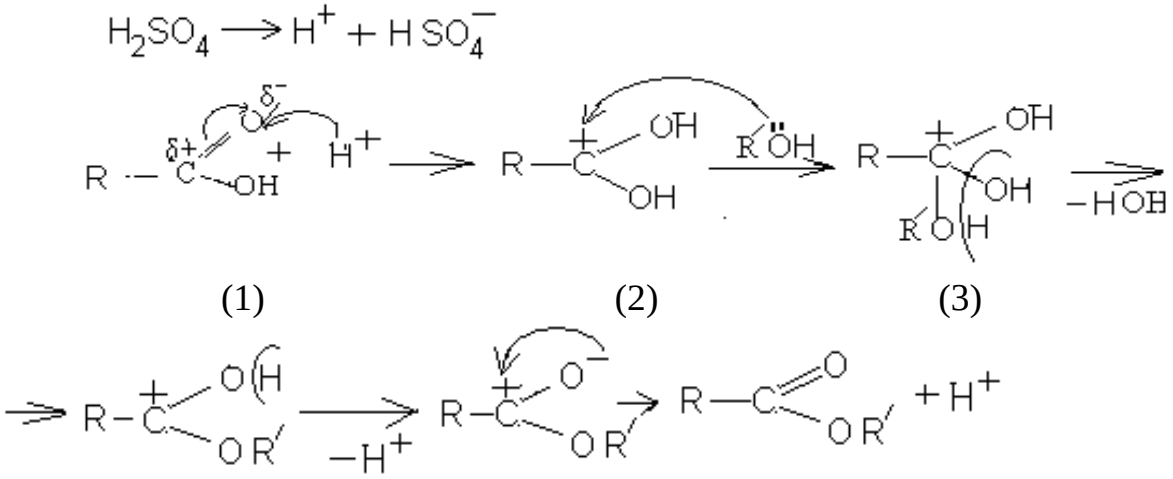
Consider the specific reactions that go with carboxylic acids and their derivatives in vitro, as well as in the human body.

1. The formation of esters.

Most common and most studied derivatives of carboxylic acids include esters (esters). The formation of esters called the reaction ***esterification.***

Esterification reaction takes place between carboxylic acids and alcohols on the mechanism of nucleophilic substitution. Since alcohols are weak nucleophiles (see "Aldehydes" - the formation of hemiacetal), then use an acid catalysis.

Graphically, the scheme of the reaction mechanism of esterification can be shown as follows:



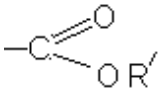
(1) (2) (3)

(4) (5) (6)

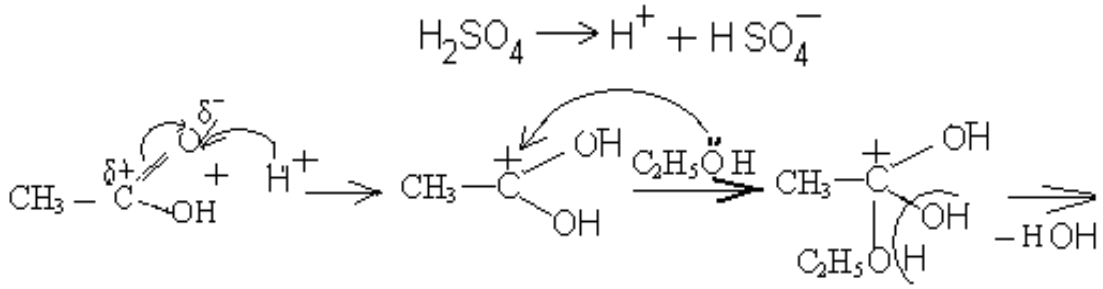
Sulfated acid dissociates and gives catalyst - proton H^{+}.

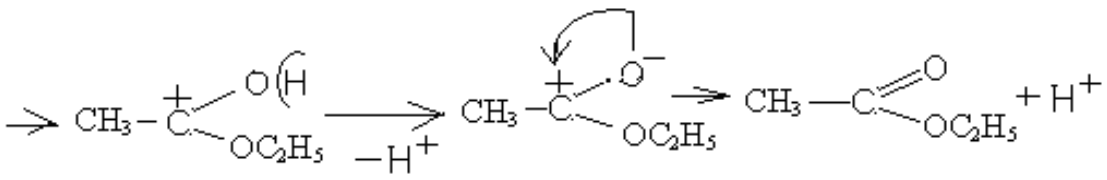
Proton attacks the (protonated) oxygen oxo (1), which accumulates excess negative charge due to mesomeric effect. Formed carb-cation (2), which is attacked as an alcohol nucleophile. Alcohol is attached at carbon occurs a positive charge, while oxygen is a trivalent alcohol (3). Therefore, the proton is split off from oxygen, and carbon is cleaved from the hydroxyl group (this is confirmed by the method of labeled atoms), which pushes the alcohol, and forms the intermediate carb-cation (4), from which the proton is split off. The result is an intermediate particle (5), in which there is a redistribution of electron density are obtained final product - ester (6) and dismissed the catalyst - a proton.

Group of atoms

 - It is difficult - the ether bond, which is found in many medicinal substances.

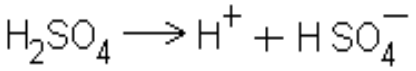
An example of the esterification reaction may be the interaction of acetate (acetic acid) with ethanol. Graphically, this can be written as:

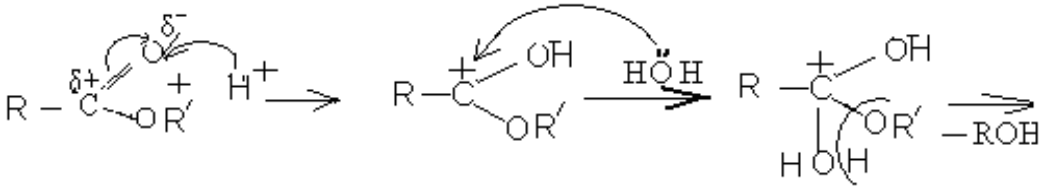


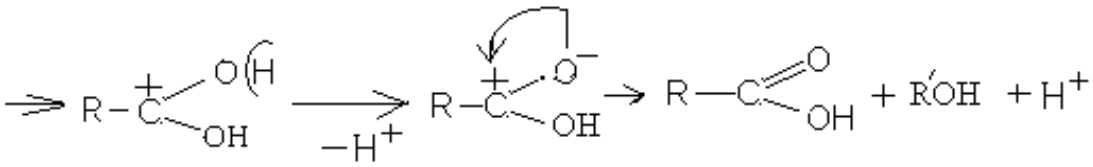


Reverse reaction of esterification is called *hydrolysis*, which is also on the mechanism of nucleophilic substitution. Hydrolysis can proceed in acidic and alkaline media.

Graphically, the mechanism of *acid hydrolysis* can be shown as follows:

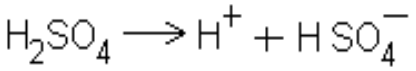


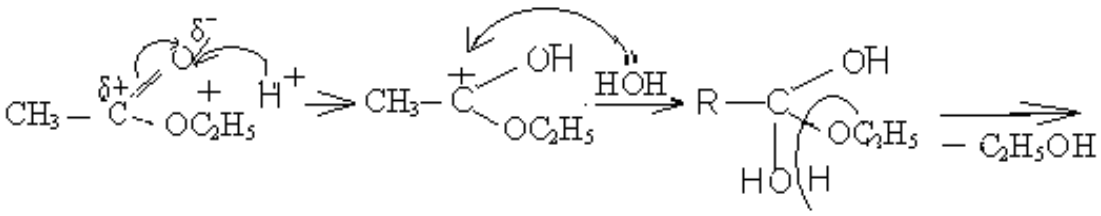




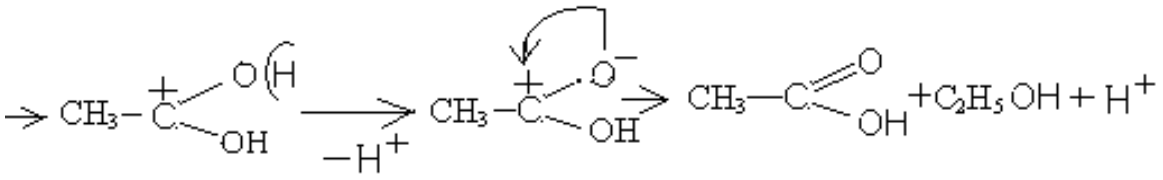
Concentrated sulfuric acid dissociates, gives a proton, which is a catalyst and oxygen attacks the oxo group in the molecule of the ester (1). Formed carb-cation (2), which is attacked by a water molecule as a nucleophile to neutralize the positive charge on carbon. Water is attached to carbon, oxygen, water is trivalent, and the proton is split off from it, and simultaneously cleaved alkoxy group OR 'on carbon (3). Formed back carb - cation, from which the proton is split off (4). In the particle (5) is the redistribution of electron density, and form the final products - acid (6) and alcohol (7), as well as the proton is released as a catalyst. Thus, the *products of hydrolysis of esters in an acidic environment are a carboxylic acid and alcohol.*

Example of hydrolysis of esters in an acidic environment may be the hydrolysis of ethyl acetate:



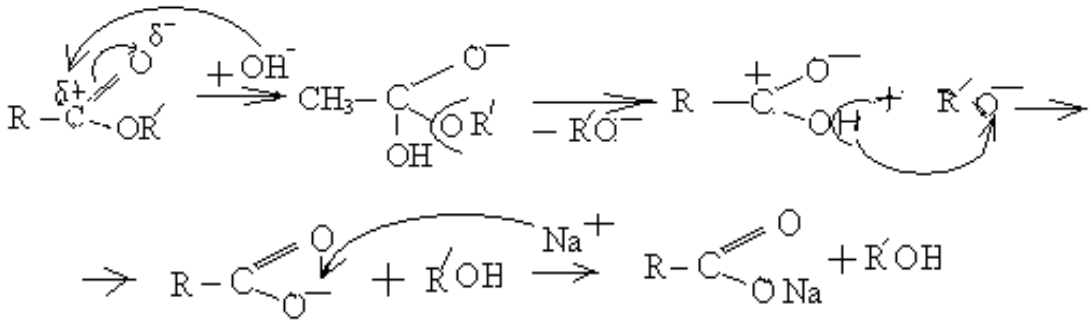


Ethyl acetate



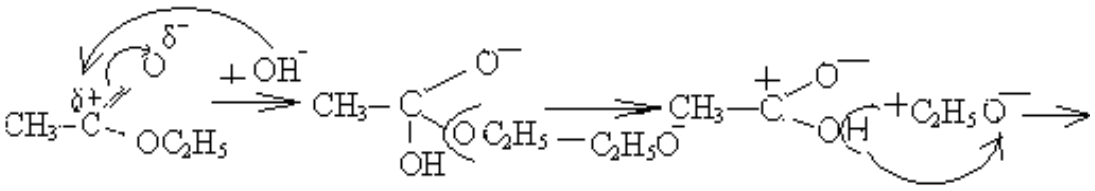
Acetate **Ethanol**

Graphically, the mechanism of *alkaline hydrolysis* can be shown as:

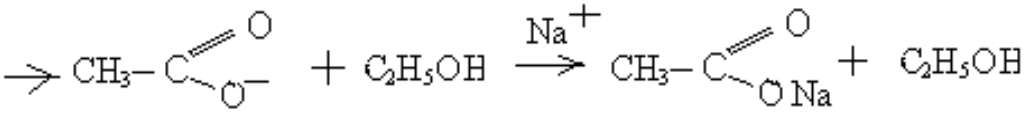


Hydroxide ion, which is the catalyst that attacks the carbon atom of the carboxyl group (1). As a result, the intermediate particle (2), in which the hydroxyl group of associates and pushes alkoxy RO^-. Formed particle (3), from which the proton is split off and goes to the alkoxy group. As a result of redistribution of electron density occurs carboxylate anion (5), which gives a sodium salt of the cation (6).*Thus, the products of alkaline hydrolysis of esters are the salt of a carboxylic acid and alcohol.*

Example of hydrolysis of esters in alkaline hydrolysis of ethyl acetate can be:



Ethyl acetate



Sodium acetate ***Ethanol***

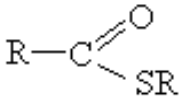
Esters and their hydrolysis in the human body.

1) In humans, esters are ***fat***. This is the esters of higher fatty acids and glycerol triatomic. Hydrolysis of fats takes place in the intestine in an alkaline medium under the action of the enzyme ***lipase*** to glycerol and salts of higher carboxylic acids, i.e. soap.

2) Ester bond is formed between the amino acids and transfer RNA.

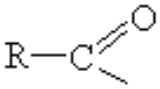
3) Series of biologically active compounds contains ester bond to the phosphate acid (RNA molecules, DNA, ATP), with sulfuric acid (in the molecules of heparin, chondroitin sulfate).

4) Many biological importance tioanalogi complexes efires - ***thioethers***

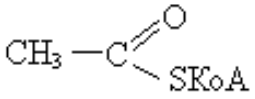


Thioethers more reactive than the esters, since the group - SR cleaved easier than -OH. The group - SR is more stable due to the low electronegativity of the sulfur atom. In addition, the carbonyl carbon, there is a higher positive charge than the esters.

The human body forms a coenzyme thioesters of CoA-SH (coenzyme A). He is an activator of carboxylic acids, ie carries the remnants of carboxylic acids, which are called ***acyl (ie, the remnants of carboxylic acids without hydroxyl group):***

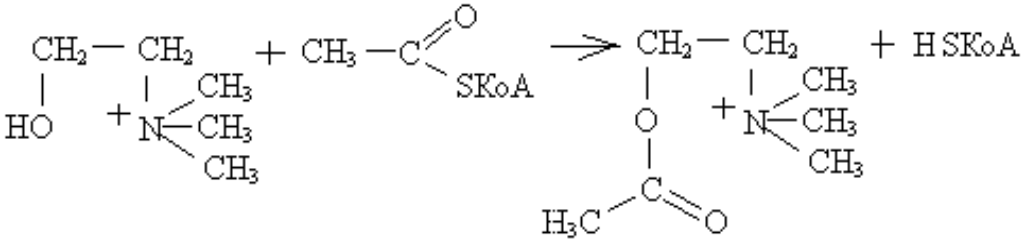


Because of this, he takes part in the reactions, ***acylation i.e. the introduction of*** acyl, resulting in synthesized biologically active substances with a long chain. Most importantly, the ***acetyl-CoA***



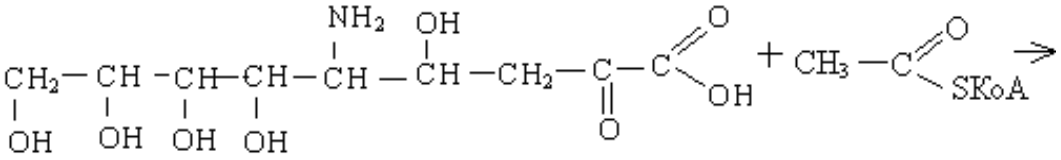
The biological significance of acylation:

a.) Synthesis of acetylcholine:

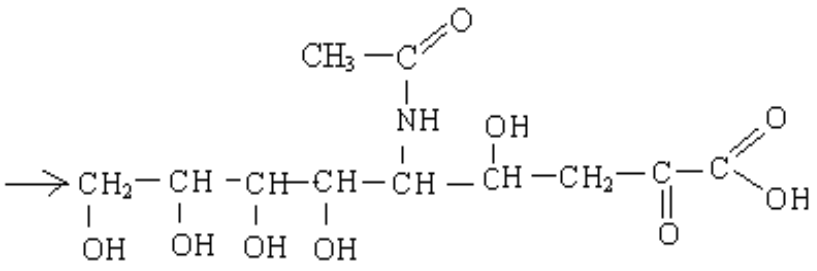


Choline ***Acetylcholine***

b) By acylation of neuraminic acid formed sialic acid

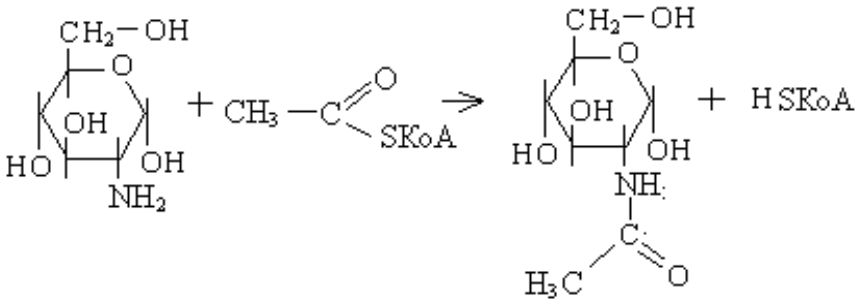


Acetyl-neuraminic acid ***SKoA***



Sialic acid

Synthesis of N - acetyl glucosamine



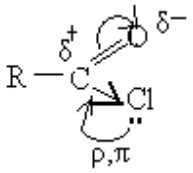
Glucose ***N-acetylglucosamine***

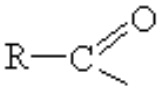
d) synthesis of citric acid in the Krebs cycle

e) the synthesis of succinate (succinic acid) from α-ketoglutaric

f) synthesis of the higher carboxylic (fatty) acids, which have an even number of carbon atoms by gradually joining the two carbon atoms.

2. Halides of carboxylic acids.



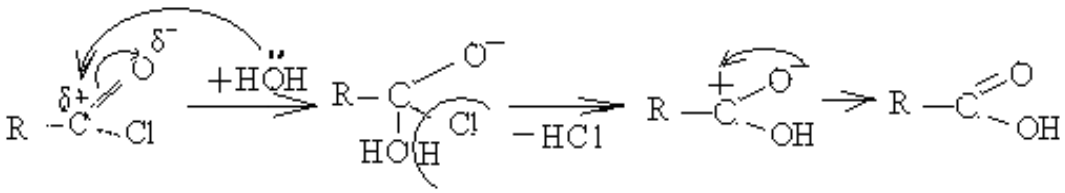
Halides more reactive than carboxylic acids. This is explained by the fact that ρ, π - conjugation in the halide is less efficient than in carboxylic acids, as an unshared electron pair of chlorine is to pair with the third energy level to the π-orbital of the carbon second energy level (in acid pair electrons of oxygen and π- orbitals of carbon are on the second energy level). Therefore, bond - Cl less robust and more easily detached halo than the OH-group. As a result of cleavage of the halogens ***acylformed, is,*** that without a hydroxyl acid  residue, so halides used for the acylation reactions.

Chemical properties of halides.

Reactions with halides are the mechanism of nucleophilic substitution, and without the catalyst, due to their high reactivity:

1) The hydrolysis of halides.

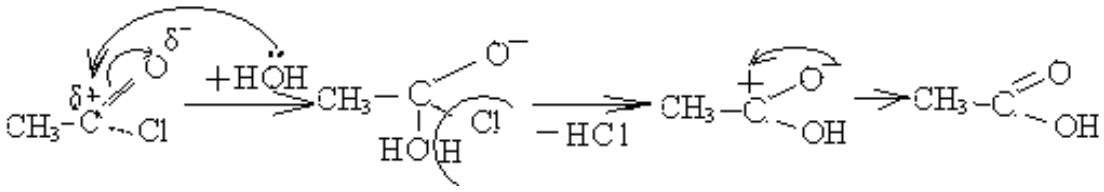
Graphically, the hydrolysis can be show as follows:



(1) (2) (3) (4)

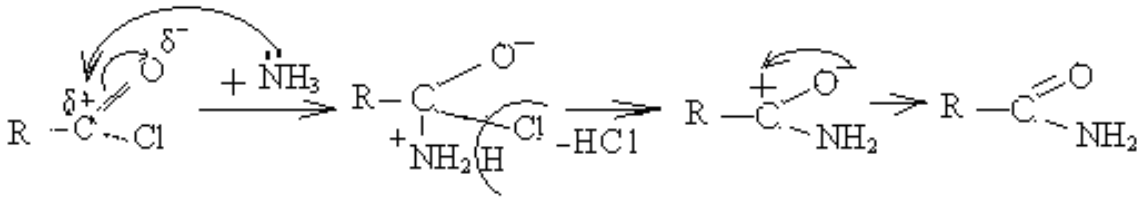
In (1) step attack is a water molecule as a nucleophile on the carbonyl carbon. Dual carbon-oxygen bond is broken and the water joins (2). Water is pushed out of the particle (2) chloride - anion and a proton simultaneously cleaved from the molecule of water, as water becomes trivalent oxygen as a result of accession. Formed an intermediate particle (3), in which there is a redistribution of electron density, and form the final product (4) - carboxylic acid.

An example would be the hydrolysis of acetate acid chloride:



Acetyl chloride

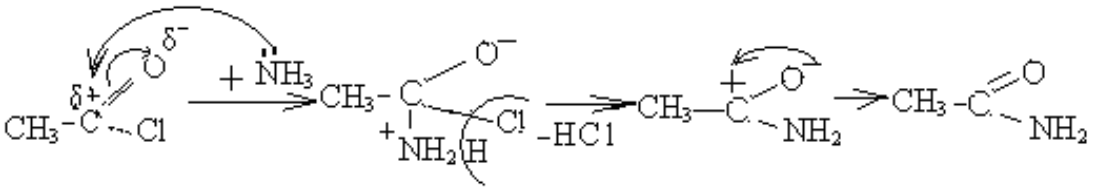
2) The interaction with ammonia.



(1) (2) (3) (4)

In (1) step attack is a molecule of ammonia as a nucleophile on the carbonyl carbon. Dual carbon-oxygen bond is broken and ammonia joins (2). Ammonia is pushed out of the particles (2) chloride - anion and a proton simultaneously cleaved from the molecule of ammonia, as nitrogen is tetravalent with the accession (from the positive nitrogen is easily split off a proton). Formed an intermediate particle (3), in which there is a redistribution of electron density, and form the final product (4) - amide.

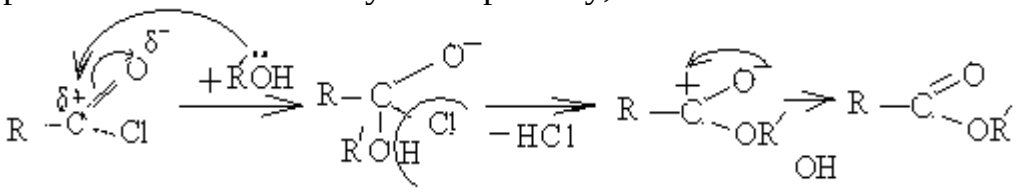
An example might be the interaction of acetyl chloride (chloride acetate acid) with ammonia:



Acetyl chloride

3)Interaction of with alcohols.

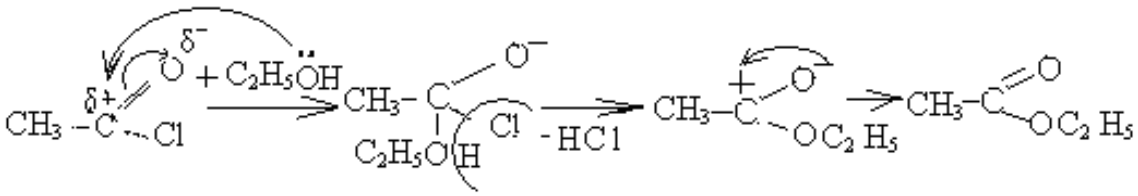
Alcohols - weak nucleophiles. But as a highly halides, reactive the reaction proceeds without a catalyst. Graphically, it can be shown as follows:



(1) (2) (3) (4)

In (1) step attack is a molecule of alcohol as a nucleophile on the carbonyl carbon. Dual carbon-oxygen bond is broken and alcohol joins (2). Alcohol pops out of the particle (2) chloride - anion and a proton simultaneously cleaved from the molecule of alcohol, as oxygen becomes trivalent in the result of a merger. Formed an intermediate particle (3), in which there is a redistribution of electron density, and form the final product (4) - ester.

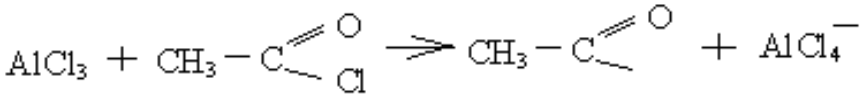
An example might be the interaction of acetyl chloride (chloride acetate acid) with ethanol:



Acetyl chloride

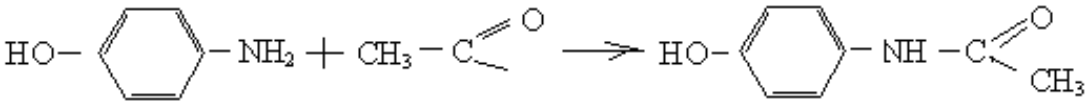
Biological significance of the reactions with halides.

As acylating agent halogen anhydride used for the synthesis of drugs such as ***paracetamol:***



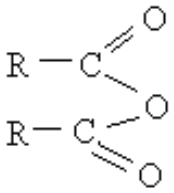
Acid Acyl

Lewis

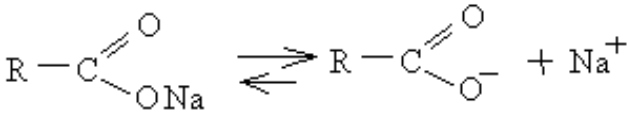


Pair - aminophenol ***Paracetamol***

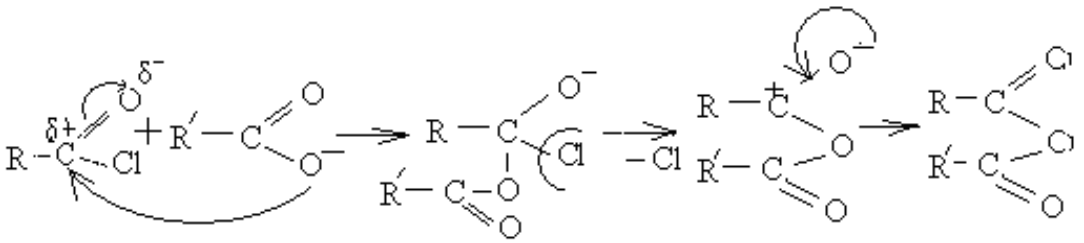
3) Anhydrides of carboxylic acids



Anhydrides of carboxylic acids are formed when water molecules are split off from the acid. Since the water molecule split off hard, then easily obtained from the anhydrides halides by the reaction of nucleophilic substitution in which the nucleophile is a carboxylate - anion. Graphically, it can be shown as follows:

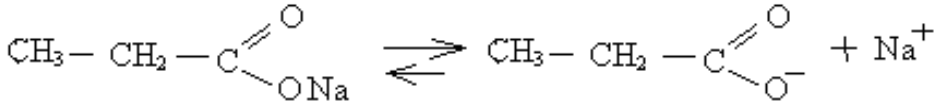


(1) (2)

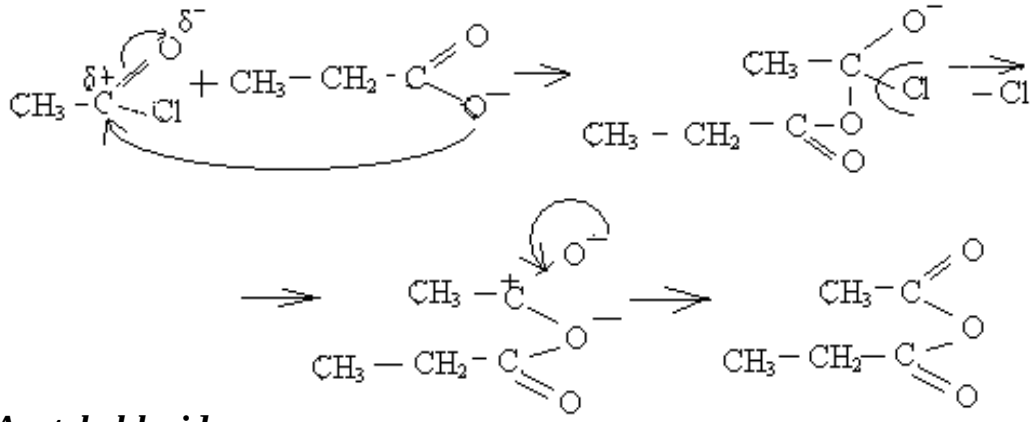


(3) (4) (5) (6)

Salt of the carboxylic acid (1) dissociates and forms carboxylate - anion (2), which is the nucleophile. Further, the carbon halide (3) is attacked by a nucleophile (2). As a result of this attack breaks the double bond C = O, and the nucleophile associates (5). Then cleaved from the carbon chloride - anion formed by the intermediate particle (6), which is the redistribution of electron density, resulting in a final product - anhydride (7).
An example might be the interaction of acetyl chloride (chloride acetate acid) and sodium propionate:



Sodium propionate

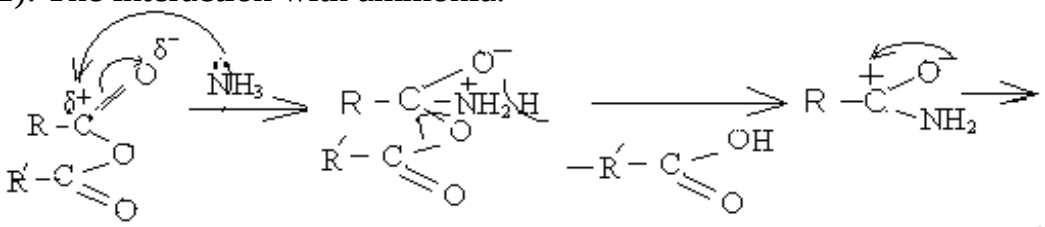


Acetyl chloride

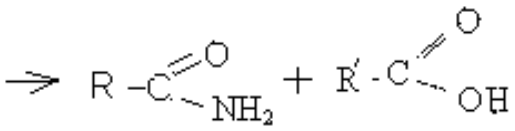
Chemical properties of anhydrides.

Reactions with anhydrides are the mechanism of nucleophilic substitution, and without the catalyst, due to their high reactionary ability

1). The interaction with ammonia.



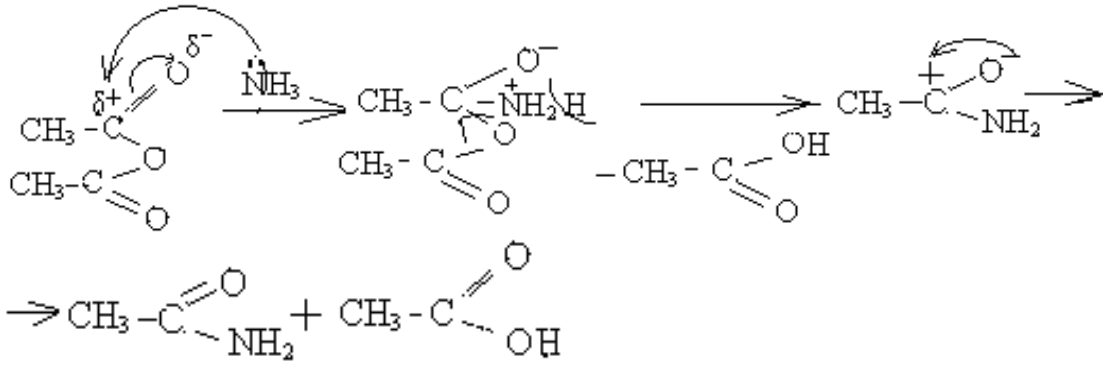
(1) (2) (3)



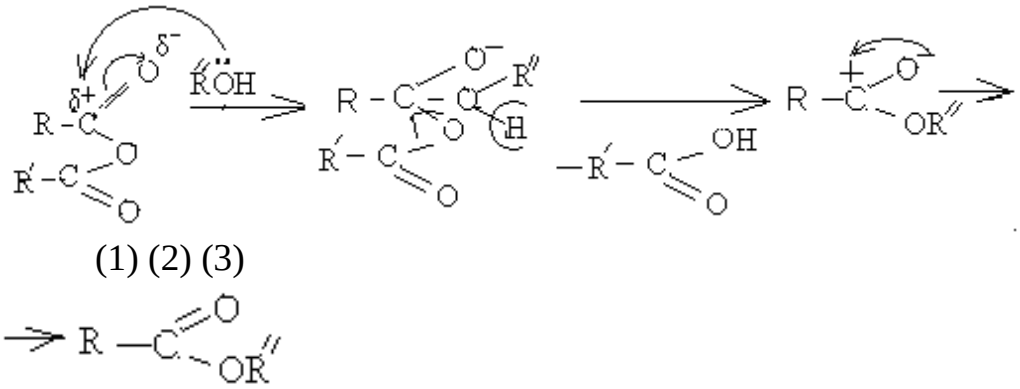
(4) (5)

In (1) step attack is a molecule of ammonia as a nucleophile on the carbonyl carbon dioxide. Dual carbon-oxygen bond is broken and ammonia joins (2). Ammonia is pushed out of the particle (2) carboxylate - anion and a proton simultaneously cleaved from the molecule of ammonia, as nitrogen is tetravalent

with the accession (from the positive nitrogen is easily split off a proton). Formed an intermediate particle (3), in which there is a redistribution of electron density, and form the final product (4) - amide, and a by-product - Acid (5).
An example might be the interaction of acetate acid anhydride with ammonia:

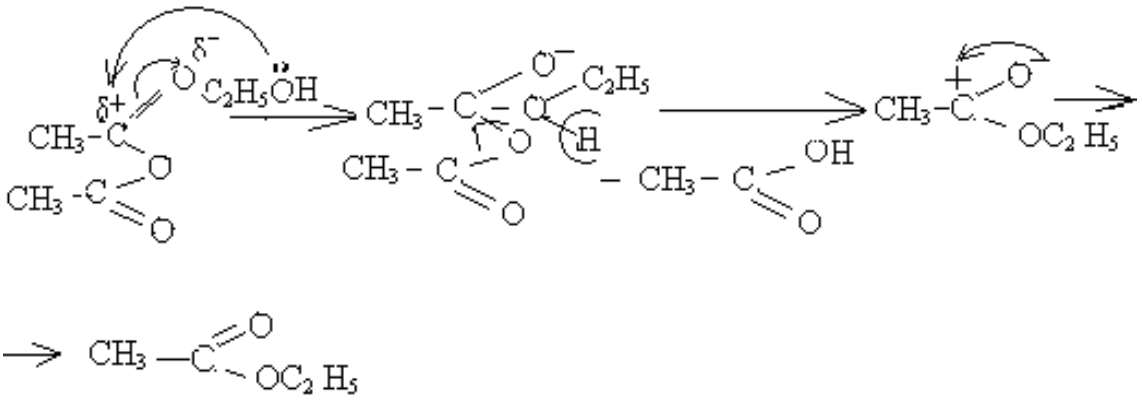


2) Interaction with alcohols. Alcohols - weak nucleophiles. But as a highly reactive anhydrides, the reaction proceeds without a catalyst. Graphically, it can be shown as follows:



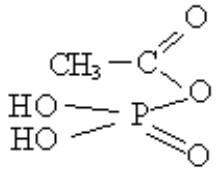
(1) (2) (3)

(4) In step (1) attack is a molecule of alcohol as a nucleophile on the carbonyl carbon. Dual carbon-oxygen bond is broken and alcohol joins (2). Alcohol pushes the particles of (2) of the carboxylate anion and a proton simultaneously cleaved from the molecule of alcohol, as oxygen becomes trivalent in the result of a merger. In the intermediate particle (3), is the redistribution of electron density, and form the final product (4) - ester.
An example might be the interaction of acetate acid anhydride with ethanol:



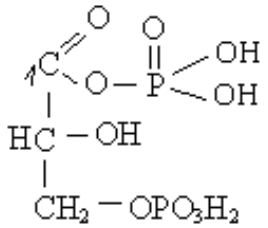
The biological significance of anhydrides

a) In the process of protein synthesis are involved derivatives ***Acetylphosfate.*** This anhydride acetate and phosphate acid:

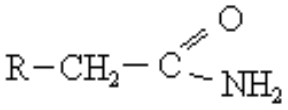


b) macroergic system in the human body is

1.3 - diphosfoglyceric acid, in which anhydrite bond is formed on the first ***carbon:***



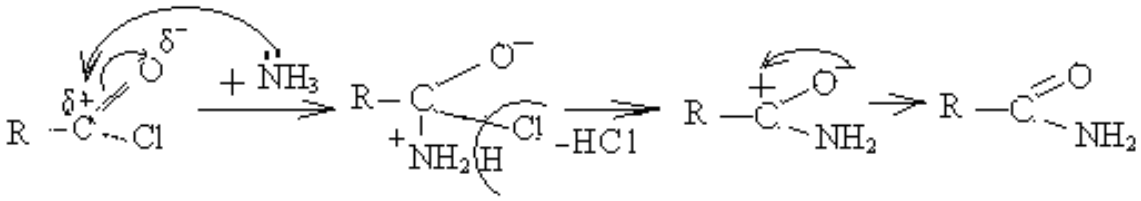
4) Amides of carboxylic acids - are derivatives of carboxylic acids, which the hydroxyl group is substituted with the amino group



Amides are the mechanism of nucleophilic substitution of halides and anhydrides in the interaction with ammonia.

a) The formation of amides from halides.

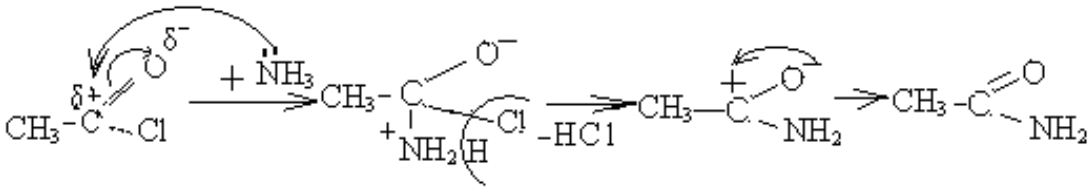
Since ammonia is a strong nucleophile, the reaction proceeds without a catalyst. Graphically, it can be shown as follows:



(1) (2) (3) (4)

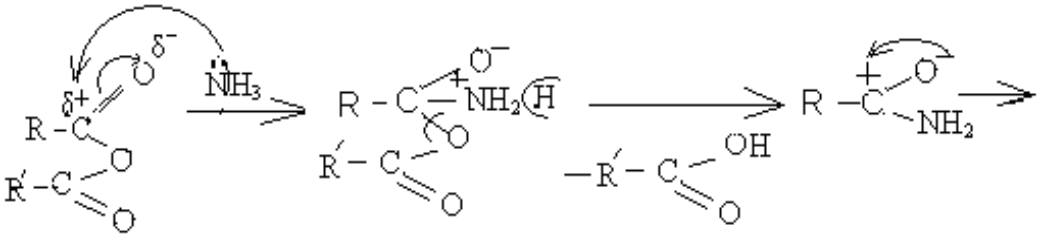
In (1) step attack is a molecule of ammonia as a nucleophile on the carbonyl carbon. Dual carbon-oxygen bond is broken and ammonia joins (2). Ammonia is pushed out of the particles (2) chloride - anion and a proton simultaneously cleaved from the molecule of ammonia, as nitrogen is tetravalent with the accession (from the positive nitrogen is easily split off a proton). Formed an intermediate particle (3), in which there is a redistribution of electron density, and form the final product (4) - amide.

An example might be the interaction of acetate acid chloride with ammonia:

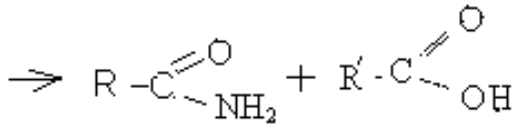


b) The formation of amides from anhydrides

Since ammonia is a strong nucleophile, the reaction proceeds without catalyst. Graphically, it can be shown as follows:

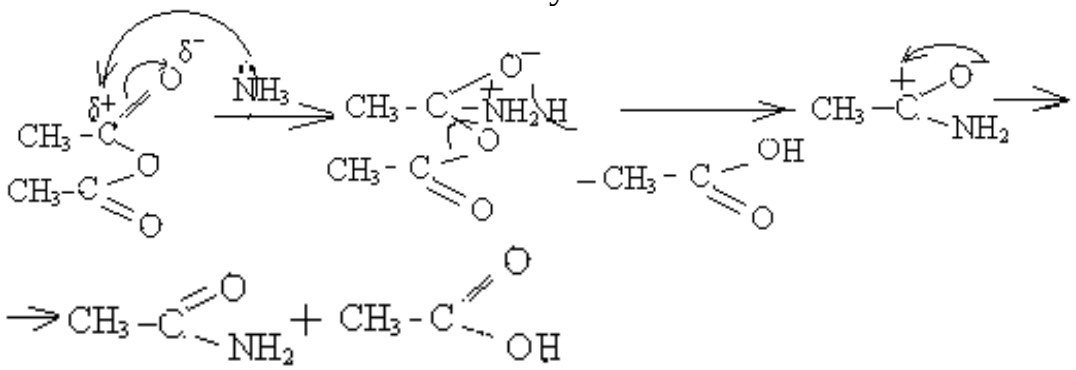


(1) (2) (3)



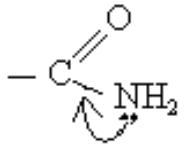
(4) (5)

In (1) step attack is a molecule of ammonia as a nucleophile on the carbonyl carbon dioxide. Dual carbon-oxygen bond is broken and ammonia joins (2). Ammonia is pushed out of the particle (2) carboxylate - anion and a proton simultaneously cleaved from the molecule of ammonia, as nitrogen is tetravalent with the accession (from the positive nitrogen is easily split off a proton). Formed an intermediate particle (3), in which there is a redistribution of electron density, and form the final product (4) - amide, and a by-product - acid. An example might be the interaction of acetate acid anhydride with ammonia:



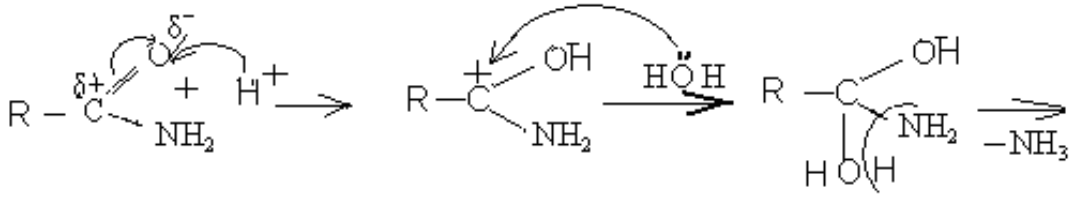
The chemical properties of amides

a) Base properties of amides are mild, as the lone electron pair of nitrogen is in the pairing and less available to the proton:

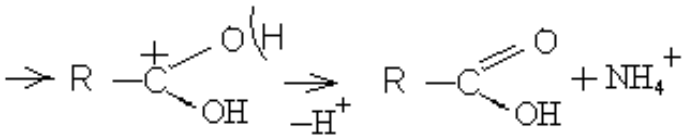


b) Hydrolysis in acidic medium is the mechanism of nucleophilic substitution:

$H_2SO_4 \rightarrow H^+ + HSO_4^-$



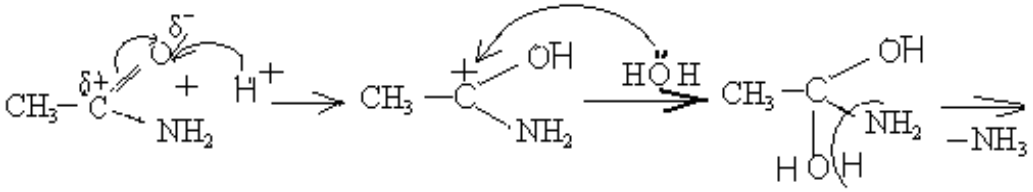
(1) (2) (3)



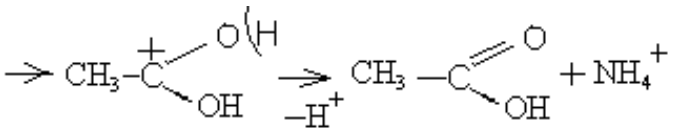
(4) (5) (6)

In (1) step is an attack by a proton as a catalyst for oxygen oxo - group. Dual carbon-oxygen bond is broken and formed carb - cation (2), which is attacked by water as the nucleophile. Formed an intermediate particle (3), which split off from both the amino group and a proton, forming a molecule of ammonia. From carb-cation (4) the proton is split off and formed the final products - acid (5) and the ammonium ion (6).

An example would be the hydrolysis of acetamide:

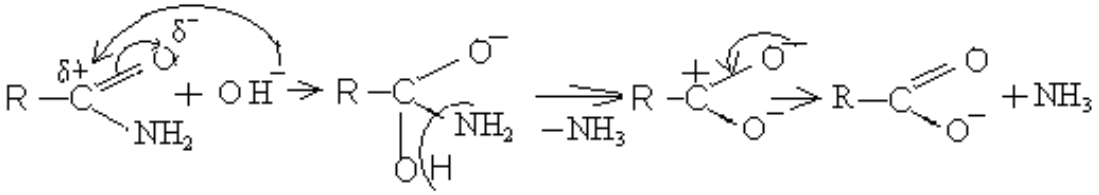


Acetamide



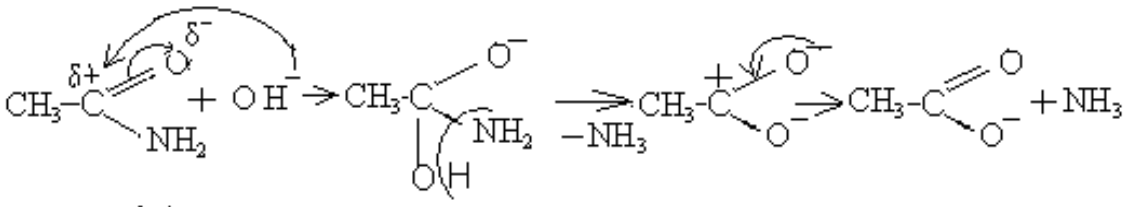
c) hydrolysis in alkaline medium is also on the mechanism of nucleophilic substitution.

$$NaOH \rightarrow Na^+ + OH^-$$



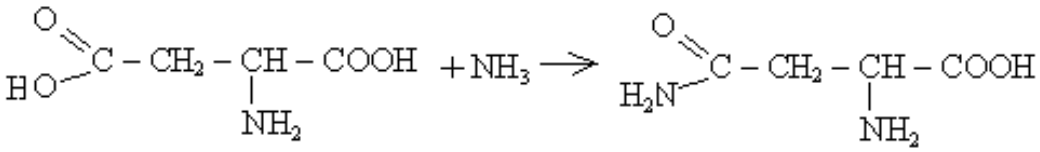
(1) (2) (3) (4) (5)

In (1) step is an attack OH - anion as the nucleophile on carbon oxo - group. Dual carbon-oxygen bond is broken and formed anion (2), which split off from both the amino group and a proton, forming a molecule of ammonia. In the intermediate particle (3) are the redistribution of electron density and the formation of end products - the carboxylate anion (4) and the ammonia molecule (5).
An example would be the hydrolysis of acetamide:



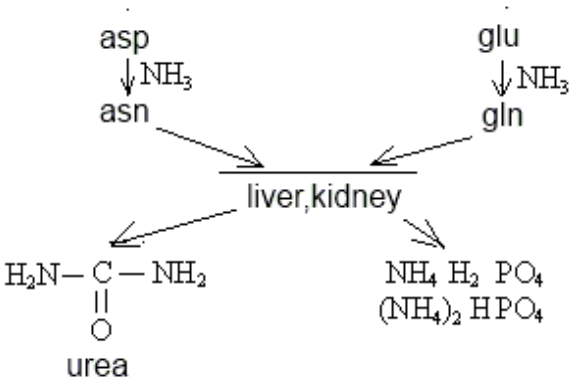
The biological significance of amide

Formation of amides in the human body - a way of neutralizing the ammonia, which is a product of metabolism of amino acids and proteins. Ammonia is a negative effect on the central nervous system. Therefore, it binds to the amino acids - aspartic acid and glutamic with the formation of amides. For example:



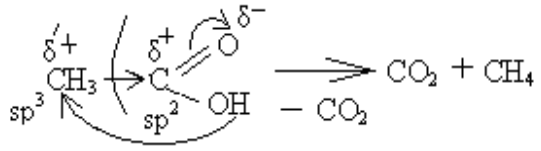
Aspartic acid ***Amide of aspartic acid (asp) or asparagine (ASN)***

Scheme of the binding and excretion of ammonia as follows:



Decarboxylation of carboxylic acids,

Carboxylic acids feature is decarboxilation reaction. ie cleavage of carbon dioxide. This can be exlain as follows:

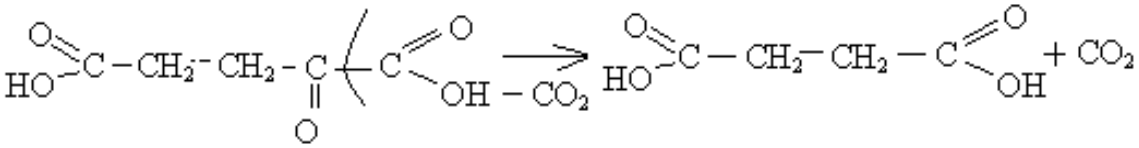


As a result of displacement of the electron density to the oxygen atom on carbon-carboxyl group occurs a partial positive charge δ^+.This carbon in sp^2 -hybridization

of the radical, in which the carbon in sp^3 hybridization shifts the electron density and the carbon radical occurs a partial positive δ^+ charge. So close are two carbon a partial positive charge, so they repel each other and split off carbon dioxide and hydrogen from the carboxyl group is connected to the carbon radical and the alkane is formed

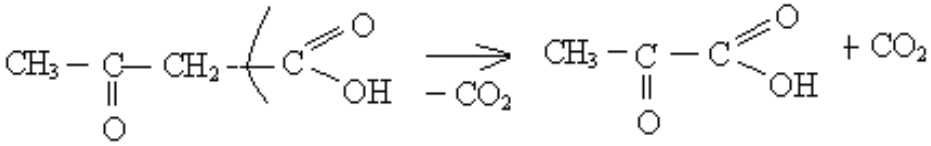
The biological significance of the decarboxylation reaction

a) As a result of decarboxylation of α- ketoglutaric acid, succinic acid is formed (the reaction proceeds in the presence of CoA-SH).



α-ketoglutaric acid ***Succinic acid***

b) The decarboxylation of β-ketobutyric acid forms acetone.



β-ketobutyric acid ***Acetone***

Acetone, β-ketobutyric acid and β-hydroxybutyric acid are a group of *ketone* bodies, which are found in the urine of patients with *diabetes.*

The above mechanisms are used to explain the reactivity of heterocyclic and heterofunctional, and biologically active compounds of different classes of organic compounds.