STATE UNIVERSITY OF MEDICINE AND PHARMACY
«NICOLAE TESTEMITANU»

## Department of Biochemistry

Svetlana BOBKOVA
Leonid LYSYI
Constantin CHEPTANARU

# BIOORGANIC CHEMISTRY

*Course of lectures*

CHIȘINĂU 2002

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Authors: **Svetlana BOBKOVA**, Dr., assoc.prof., Department of Biochemistry;
**Leonid LYSYI**, Dr. Hab., Univer.prof., Chief of Department of Biochemistry;
**Constantin CHEPTANARU**, Dr., assoc.prof., Department of Biochemistry

Reviews were given by:

1. Constantin TURTA, Dr.Hab., Corresponding Member of Moldavian Academy of Science;
2. Ion SANTEVOI, Dr., Assoc.prof., Department of General Chemistry;
3. Liubovi REVENKO, Director of International organization of Migration.

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# INTRODUCTION

Carbon has the unusual ability of bonding strongly to itself to form long chains or rings of carbon atoms. In addition, carbon forms strong bonds to other nonmetals such as hydrogen, nitrogen, oxygen, sulfur, and the halogens. Because of these bonding properties, there is myriad of carbon compounds, several million are now known, and the number continues to grow rapidly. Among these many compounds are **biomolecules**, those responsible for maintaining and reproducing life.

The study of carbon-containing compounds and their properties is called **organic chemistry.** Vast majorities are organic compounds that typically contain chains or rings of carbon atoms.

The synthetic fibers, plastics, artificial sweeteners, and drugs that are such accepted part of modern life are products of industrial organic chemistry. Beyond that **organic chemistry** plays a vital role in our quest to understand living systems. Life is possible only because each cell, when it divides, can transmit the vital information about how it works to the next generation. The substance that stores and transmits the genetic information is polymer called **nucleic acid**, those processes are studied by **bioorganic chemistry**. Another class of biologically important molecules is the **carbohydrates**, which serve as a food source for most organisms and a structural material for plants.

**Bioorganic chemistry** is studied a class of natural polymers, the **protein,** which make up about 15% of our bodies and have many important functions in the human body.

Another class of organic substance is **lipids,** important constituents of all plant and animal. **Bioorganic chemistry** is studied substances, tissues, that lie on basis of living processes, in connection with understanding of their biological functions. **Bioorganic chemistry** is a subject that touches the lives of every one.

# CLASSIFICATION, NOMENCLATURE, AND STRUCTURE OF ORGANIC COMPOUNDS
## NOTION OF CONFORMATION AND CONFIGURATION

The analysis of any plants or animals product reveals that it always contains carbon, hydrogen and usually also oxygen and/or nitrogen. In many organic compounds sulfur, phosphorus, and the halogens are also to be found. In some cases even a metallic element makes up part of a naturally occurring organic structure (iron is present in the hemoglobin of blood to the extent of 0,34% ). How is it possible for such a small number of elements to account for over two million organic compounds? To obtain the answer to this question we need to examine the manner in which the atoms in compounds are held together. We must be able to translate each molecular formula into a structure. When we have done this, we will see that carbon is nearly unique among the elements. Every organic compound have three notions: the structure, the configuration and conformation. Chemical reactions involving organic compounds center, for the most part, known as _functional group_. This group not only bestows a characteristic behavior upon the molecule, but also identifies it as belonging to a certain family of compounds a _homologous_ series.

$CH_3$ –$O$
|
$H$

$C_2H_5$ –$O$
|
$H$

$C_3H_7$ –$O$
|
$H$
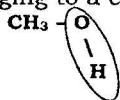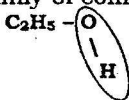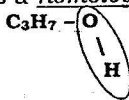
**Methanol**         **Ethanol**         **Propanol**

From this example we see that hydroxyl group – OH is functional group that characterizes the alcohol family. Table 1. lists the principal families, or classes of compounds, the corresponding functional groups and a common example within each class.

Another frequently used classification of organic compounds is that based on the molecular framework of the molecules, i.e. that part of the molecular other than the functional group.
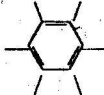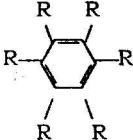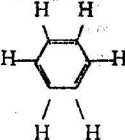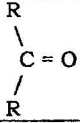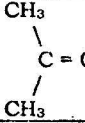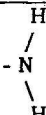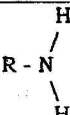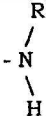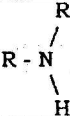
**Figure I:.**

*Classification of Organic Compounds Based on Molecular Framework.*
**Organic Compounds**
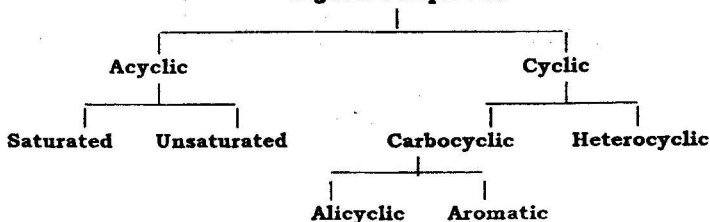
## Table 1:

### Classes of Compounds and Their Functional Groups.

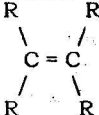| Class Names | Functional Group | General Formula | Common Examples | Example Name |
|---|---|---|---|---|
| Alkanes | None | R-H | $CH_3 - CH_3$ | Ethane |
| Alkenes | $\begin{array}{c}\backslash\qquad/\\ C = C\\ /\qquad\backslash\end{array}$ | $\begin{array}{c}R\qquad R\\ \backslash\quad/\\ C = C\\ /\quad\backslash\\ R\qquad R\end{array}$ | $CH_2 = CH_2$ | Ethylene |
| Alkynes | $- C \equiv C -$ | $R - C \equiv C - R$ | $H\text{-}C \equiv C\text{-}H$ | Acetylene |
| Axenes | | $R-\hexagon-R$ | $H-\hexagon-H$ | Benzene |
| Alkyl Halides | -F, -Cl, -Br, -J | $R - X$ | $CH_3 - J$ | Methyl Iodide |
| Alcohol's | - O-H | R- OH | $CH_3\text{-}CH_2\text{-}OH$ | Ethanol |
| Ethers | - O - | R-O-R | $C_2H_5\text{-}O\text{-}C_2H_5$ | Diethyl Ether |
| Aldehydes | $\begin{array}{c}- C = O\\ \backslash\\ H\end{array}$ | $\begin{array}{c}R - C = O\\ \backslash\\ H\end{array}$ | $\begin{array}{c}CH_3 - C = O\\ \backslash\\ H\end{array}$ | Acetaldehyde |
| Ketones | $\begin{array}{c}\backslash\\ C = O\\ /\end{array}$ | $\begin{array}{c}R\\ \backslash\\ C = O\\ /\\ R\end{array}$ | $\begin{array}{c}CH_3\\ \backslash\\ C = O\\ /\\ CH_3\end{array}$ | Acetone |
| Carboxylic Acids | $\begin{array}{c}- C = O\\ \backslash\\ O\text{-}H\end{array}$ | $\begin{array}{c}R\text{-} C = O\\ \backslash\\ O\text{-}H\end{array}$ | $\begin{array}{c}CH_3\text{-} C = O\\ \backslash\\ O\text{-}H\end{array}$ | Acetic Acid |
| Primary Amines | $\begin{array}{c}H\\ /\\ - N\\ \backslash\\ H\end{array}$ | $\begin{array}{c}H\\ /\\ R - N\\ \backslash\\ H\end{array}$ | $\begin{array}{c}H\\ /\\ CH_3 - N\\ \backslash\\ H\end{array}$ | Methylamine |
| Secondary Amines | $\begin{array}{c}R\\ /\\ - N\\ \backslash\\ H\end{array}$ | $\begin{array}{c}R\\ /\\ R - N\\ \backslash\\ H\end{array}$ | $\begin{array}{c}CH_3\\ /\\ C_2H_5 - N\\ \backslash\\ H\end{array}$ | Methylethylamine |

3

*Nomenclature* is a system of naming substances. In organic chemistry, the nomenclature of compounds is exceedingly important. Without a system of names, the science of organic chemistry with its millions of compounds would be difficult to comprehend. The phenomenon of isomerism easily illustrates this important point. In 1892, at meeting in Geneva, Switzerland, chemists systematized the nomenclature of all compounds, including organic compounds. The system continues as part of the activities of the International Union f Pure and Applied Chemistry (IUPAC). The rules result in a clear and definitive name for compound.

In the IUPAC system, a chemical name has three parts: prefix, parent, and suffix. The parent name specifies the overall size of the molecule by identifying the number of carbon atoms in it main chain; the suffix identifies the family that the molecule belongs to; and the prefix specifies the location of various substituents on the main chain:

**prefix - parent - suffix**

where are          how          what family?
substituents ?    many carbons?
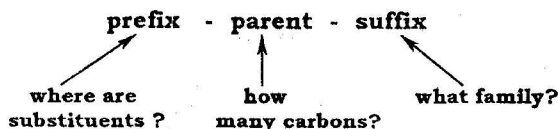
All but the most complex branched-chain alkanes can be named by following four steps:

1. Find the parent hydrocarbon
a. Find the longest continuous carbon chain in the molecule and use the name. The longest chain may not always be obvious; you may have to "turn corners"

**CH₂CH₃**
$$|$$
**CH₃CH₂CH₂CH – CH₃**
**named as a substituted hexane**
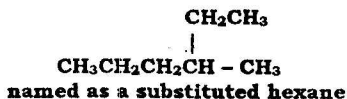
b. If two different chains of equal length are present, choose the one with the lager number of branch points as the parent:

**CH₃**
$$|$$
**CH₃CHCHCH₂CH₂CH₃**
$$|$$
**CH₂CH₃**
**named as a hexane with two substituents**
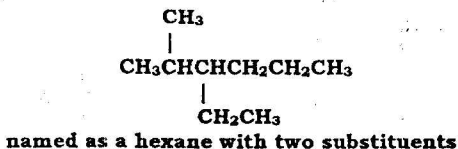
2. Beginning at the end nearer the first branch point, number each carbon atom in the parent chain:

$$\underset{3}{\overset{2}{CH_2}}\overset{1}{CH_3}$$

$$CH_3 - \underset{3}{CH}\underset{4}{CH} - \underset{}{CH_2CH_3}$$

$$\underset{5\ \ 6\ \ 7}{CH_2CH_2CH_3}$$
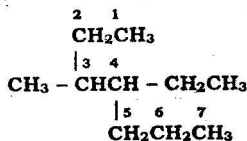
3. Assign a number to each substituent according to its point of attachment on the parent chain. If there are two substituents on the same carbon, assign them both the same number. There must always be as many numbers in the name as there are substituents.

$$\overset{CH_3}{|}\qquad\overset{CH_3}{|}$$

$$\underset{6}{CH_3}\underset{5}{CH_2} - \underset{4}{C} - \underset{3}{CH_2}\underset{2}{CH}\underset{1}{CH_3}$$
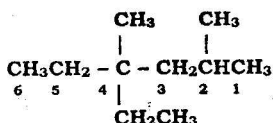
$$\underset{}{\overset{|}{CH_2CH_3}}$$

Substituents: On C2, - CH₃    (2-methyl)
              On C4, - CH₃    (4-methyl)
              On C4, - CH₂CH₃  (4-ethyl)

4. Write the name as a single word, using hyphens to separate the various prefixes and commas to separate numbers. If two or more different side chains are present, cite them in alphabetical order. If two or more identical side chains are present, use one of the prefixes di-, tri-, tetra-, and so forth. Don't use prefixes for alphabetizing, though.

$$\overset{CH_3}{|}\qquad\overset{CH_3}{|}$$

$$\underset{6}{CH_3}\underset{5}{CH_2} - \underset{4}{C} - \underset{3}{CH_2}\underset{2}{CH}\underset{1}{CH_3}$$

$$\underset{}{\overset{|}{CH_2CH_3}}$$
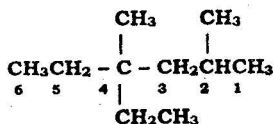
4-ethyl-2,4-dimethylhexane

**Structure** – present the successive bonds of atoms in molecular formula.

$C_2H_6O$

$$H - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - O - H$$

Ethanol

$$H - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - O - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - H$$

Diethyl ether

5

$C_6H_{12}O_6$

```
        CH = O                      CH2-OH
         |                            |
    H – C – OH                      C = O
         |                            |
   HO – C · H                    H – C · OH
         |                            |
    H – C – OH                    H – C – OH
         |                            |
    H – C – OH                    H – C – OH
         |                            |
        CH2OH                       CH2OH
       Glucose                     Fructose
```
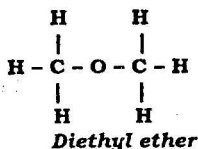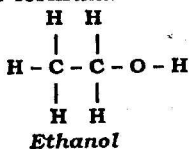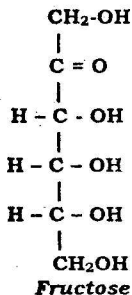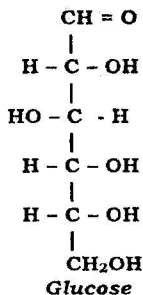
The structure proposed that all bonds are in the same plane. When we write structure on the paper, we lose idea (notion) of really arrangement atoms in space. For example sp³-hibridization's atom of carbon has tetrahedral structure and all it's substitutions dispose (arrange) from angle 109°28'. If compound consists from such atoms of carbon, the molecular hasn't planar structure, it has definite configuration.

### Projection Formulas and Relative Configurations

Relative configuration – the space arrangement of atoms or groups.

When we write Relative configurations of Ethane molecule, two bonds that lie in the same plane mean by straight line.

```
    H   H                        H       H
    |   |                         \     /       configuration
H – C – C – H                Hᴵᴵᴵ·C – C·ᴵᴵᴵH
    |   |                         ▲     ▲
    H   H                         H     H
```
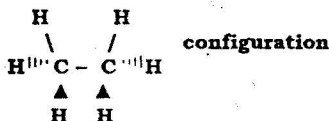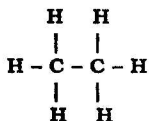
▲ - this means that the bond is in front of the paper's plane
·ᴵᴵ· - this means that the bond is behind the paper's plane

```
    H   H                        H       H
    |   |                         \     /
H – C – C – H                Hᴵᴵᴵ C – C ᴵᴵᴵ H
    |   |                         ▲     ▲
   H2N  OH                       H2N    OH
                            2-amino-ethanol (colamin)
```

6
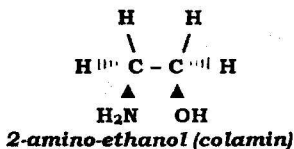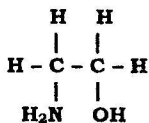
## Structural formulas and isomerism

We have learned that in methane the four hydrogen's are bonded to a central carbon atom. Now the gaseous hydrocarbon butane has the formula $C_4H_{10}$. We discover that there are two structures:

$$CH_2 \qquad CH_3$$
$$/ \quad \backslash \quad /$$
$$H_3C \qquad CH_2$$

$$CH_3$$
$$|$$
$$CH$$
$$/ \quad \backslash$$
$$H_3C \quad CH_3$$
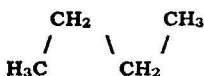
**Normal butane, b.p. 0,5⁰C** ("straight" chain structure)
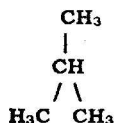
**Izobutane, b.p. 11,7⁰C** (a branched chain structure)

In order to draw these two structures, we have allowed the **sp³** hybrid orbitals of carbon atoms to overlap those of other carbons, as well as with **s** orbitals of hydrogen atoms, to form the four sigma bonds.

Although both compounds have the same molecular formula, they have different structures and are called _isomers_. Another pair of gaseous hydrocarbons has molecular formula: $C_4H_8$. In a continuos cyclic arrangement we are able to draw two different $C_4H_8$ structures.

$$\begin{array}{cc} H & H \\ | & | \\ H - C - C - H \\ | & | \\ H - C - C - H \\ | & | \\ H & H \end{array} \qquad I$$
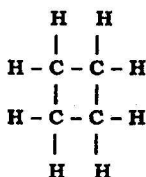
$$\begin{array}{cc} & H \quad H \\ & \backslash \; / \\ H & C - H \\ \backslash & / \\ & C \\ / & \backslash \\ H - C - C - H \\ | & | \\ H & H \end{array} \qquad II$$

_**Cyclobutane**_  b.p. 13,0⁰C
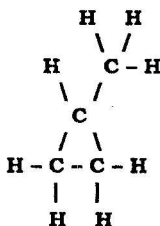
_**Methylcyclopropane**_ b.p.4,0⁰C

The same molecular formula will permit four additional structures:

$$\begin{array}{cc} H & H \\ | & | \\ C & = C - CH_2 - CH_3 \\ | \\ H \end{array} \quad III$$

_**1-butene**_

$$\begin{array}{cc} H & H \\ | & | \\ CH_3 - C & = C - CH_3 \end{array} \quad IV$$

_**cis – 2 – butene**_

$$CH_3 \quad H$$
$$\diagdown \quad |$$
$$C = C - H \quad \textbf{V}$$
$$\diagup$$
$$CH_3$$
**2 – methylpropene**
**(izobutylene)**

$$H \quad CH_3$$
$$| \quad |$$
$$C = C \qquad \textbf{VI}$$
$$| \quad |$$
$$CH_3 \quad H$$
**Trans–2–butene**
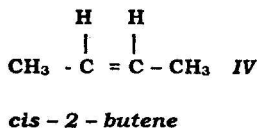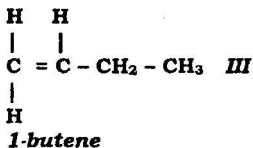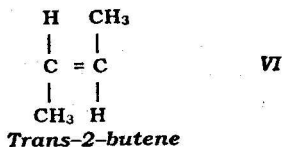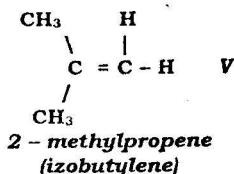
If the number of carbon atoms is increased from four to ten as in compounds $C_{10}H_{22}$ we could draw seventy –five different structures.

## Chirality and optical isomerism

The chiral molecules bear to each other as the right hand bears to the left. The enantiomers are nondentical mirror images, or nonsuperimposable mirror images. The most common feature of chiral molecules is the presence of an asymmetric carbon atom (sometimes called a chiral carbon atom). For example, in the formula for sec.butyl.chloride the number two carbon atom is asymmetric

$$H \quad H \quad H \quad H$$
$$| \quad | \quad | \quad |$$
$$H \cdot C \cdot C - C^* - C \cdot H$$
$$| \quad | \quad | \quad |$$
$$H \quad H \quad Cl \quad H$$
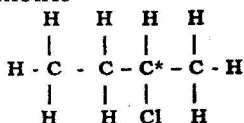
Mirrow-image, optically active isomers are called *enantiomers*.

Because the absolute (or true) structures of optical isomers were unknown to the early chemists working with optically active compounds, Fischer decided to relate as many configuration as possible to that of standard structure, one whose absolute structure was unknown but was to be arbitrarily defined by Fischer. His choise for the standard structure was that of glyceraldehyde.

$$CHO$$
$$|$$
$$H - C - OH$$
$$|$$
$$CH_2OH$$
**D-configuration**

$$CHO$$
$$|$$
$$HO - C - H$$
$$|$$
$$CH_2OH$$
**L-configuration**
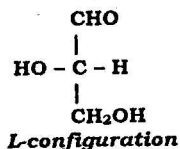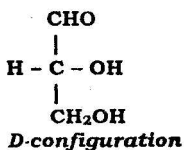
If the X group (– OH, - NH₂, or halogen usually) is on the right, the relative configuration is D-(dee); it is on the left, the configuration is L-(ell).

The designation "D" and "L" refer to configuration only and are not to be interpreted as "dexter" and "levo". The latter terms refer to the direction of rotation. If the direction of rotation is specified in the name of an enantiomer (either with or without the "D" or "L", the designations (+) – for dextrotatory isomers and (-) – for the levorotatory isomers should be used (occasionally the abbreviations D and L are used for dextro and levo, respectively.

The examples of opticall isomers are:

Lactic acid

COOH
|
H – C – OH
|
CH₃
*D-configuration*

COOH
|
HO – C – H
|
CH₃
*L-configuration*

α - aminoacid

COOH
|
H – C – NH₂
|
R
*D-form*

COOH
|
NH₂ – C – H
|
R
*L-form*
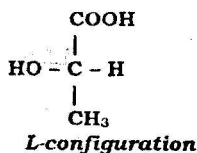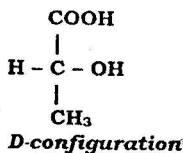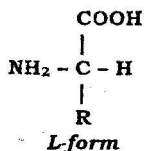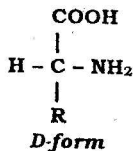
The acids with two centers assymetric – acid tartaric.

H
|
HO — C* — COOH
|
HO — C* — COOH
|
H
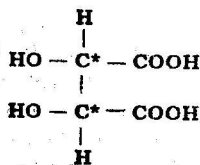
The crotonic acid was prepear from β - hydroxy acids – (β - hydroxybutiric) on high temperature:

H
|
CH₃ – CH – C – COOH   →(heat)   H₂O +   CH₃ – C = C – COOH
|        |                                         |   |
OH      H                                        H   H
                                              *2- butenoic*
                                              *(crotonic acid)*

```
    COOH                      COOH
     |                         |
    CH                        CH
    ‖                         ‖
    HC                        CH
     |                         |
    COOH                      COOH
```
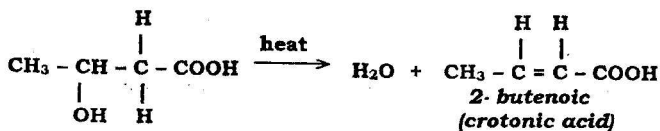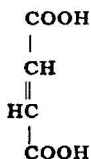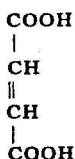
*trans – fumaric acid*          *cis – maleic  acid*


## Conformational isomeria

The single (σ) bond between carbon atoms in a molecule permits rotation of these atoms as if the shared pair of electrons were a pivot between two tetrahedrons.

Frequently, this ability to revolve around the line joining two carbons is called *free rotation*.

How free or easy it is dependents upon the nature of atoms or groups occupying the other three corners of each tetrahedron. If these groups are large or bulky, free rotation may be not only inhibited, but prevented entirely. Again, if groups on adjacent carbons are of high electron density such as chlorine or bromine, they will tend to repel each of other and will occup positions as far from each other as possible.

The different spatial arrangements made possible by rotation about a single bond are called *conformations*, and a small energy barrier must be overcome in order for adjacent carbon atoms to rotate from one conformation to another. The conformational isomers possible for ethane and the potential energy changes required when carbon atom 2 is rotated through successive 60⁰ angles may be shown more clearly by using the representations first devised by Pr. M. S. Newman of Ohio State University. In the Newman projections of the ethane molecule, the viewer is looking along the axis connecting the two carbon atoms. The conformational isomers or conformers of 1,2 dicloroethane are shown.
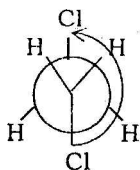
**Anti**
*θ-dihedral angle*
θ=180°
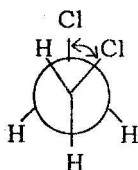
**Gauche**
θ=60°
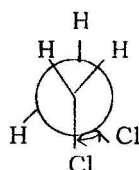
**eclipsed**
θ=0°

**The Newman projections for the three conformations of ethane**



3Kcal/mol

60°          120°          180°
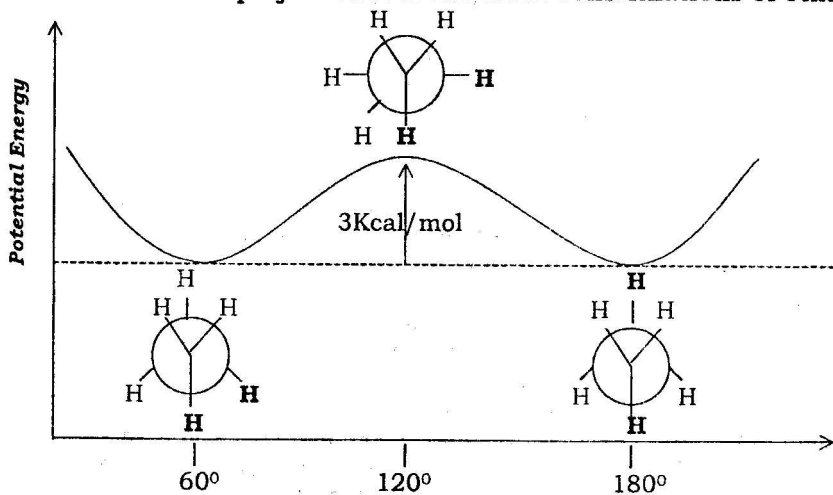
**Potential Energy Changes Required to Rotate Carbon Atoms of Ethane Troughs Successive 60°C Angles.**

Free rotation about singly-bonded carbons permits hydrocarbons in continuous chain to be anything but not "straight". They may zigzag, turn corners, spiral. And e ven cyclize, in a head-to-tail arrangement.

# CONJUGATED SYSTEMS AND ELECTRON'S EFFECT OF SUBSTITUENTS

## DIENES

Dienes in which the two double bonds are separated by one or more carbon atoms behave very much like the simple alkenes and such double bonds are called (separated) _izolated_ double bonds.

Dienes, or polyenes, wich have a sistem of alternating double and single bonds, may show reactions not caracteristic of izolated double bonds, and such sistem called _conjugated._

One important characteristic of conjugated dienes is their greater stability than isolated dienes with the same carbon skeleton. For example, when we show butadiene as

$CH_2 = CH - CH = CH_2$   or
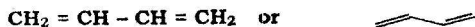
We are showing its structure as if the two $\pi$ bonds were independent of each other.

If we redraw 1,3 – butadiene as shown below
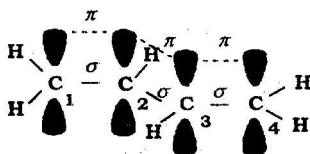


We can see that the 2p orbitals comprising the basis of the $\pi$ system can overlap between carbons 2 and 3 as well as between 1 or 3 and 4. Thus the $\pi$ - electrons can move to a limited extent over the whole system and are said to be delocalized. The delocalization of the $\pi$ - electrons not only adds somewhat to the stability of the butadiene molecule but also alters its chemical behavior.

To illustrate the reactivity of butadiene, we will examine possible reactions of the compound with bromine

$$\underset{\substack{| \quad |\\ \text{(III)}}}{\overset{\substack{Br \quad Br\\ | \quad |}}{CH_2 = CH - CH - CH_2}}$$

**3,4 dibromo-1-butene**

$$\underset{\text{(IV)}}{\overset{Br - CH_2}{\diagdown}} \overset{CH = CH}{\diagup} \underset{CH_2Br}{\diagdown}$$

**trans-1,4-dibromo-2-butene**
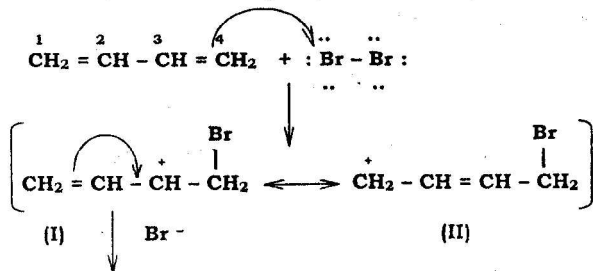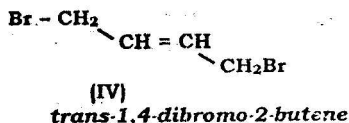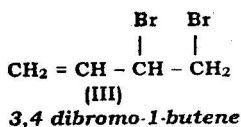
The way of the addition leading to structure III is called 1,2-addition; and the one leading to structure IV is called 1,4-addition.

Conjugated dienes also give both 1,2 – and 1,4-addition products in free radical chain addition reactions such as polymerization and halogenation.

For example, the current industrial process for the preparation of the important diene, 2-chloro -1,3-butadiene, "chloroprene" is based on the free radical addition of chlorine to butadiene in the vapor phase, followed by alkaline dehydrochlorination. CuCl – catalyst izomerization 1,4- to 3,4-izomer of the intermediate dihalide

$$CH_2 = CH - CH = CH_2$$

$$300°C \downarrow Cl_2$$

$$\underset{\substack{| \quad |}}{\overset{Cl \quad Cl}{CH_2 = CH - CH - CH_2}}$$
**3,4 – dichloro – 1 butene**

$$\xleftarrow{\quad CuCl \quad} \quad \underset{\substack{cis - trans\ 1,4 -\\ dichloro - 2,butene}}{Cl - CH_2 - CH = CH - CH_2 - Cl}$$

*dilute*
*alcals*

$$\underset{CH_2 = CH - \overset{|}{C} = CH_2}{\overset{Cl}{|}}$$
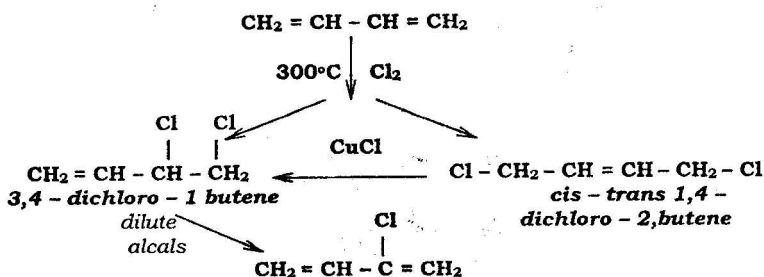
## POLYENES AND TERPENES

A large number of natural products appear to be built from *izoprene units*.

One important class of these natural products is the *terpenes*, which are sometimes called *isoprenoid* compounds because there carbons skeletons are multiples of the $C_5$ isopren units.

The diterpene vitamin A is apparently formed in the body by oxidation of the central double bond of the tetraterpene β - carotene, the yellow coloring substance of carrots.

Tetraterpenes (four terpene units)
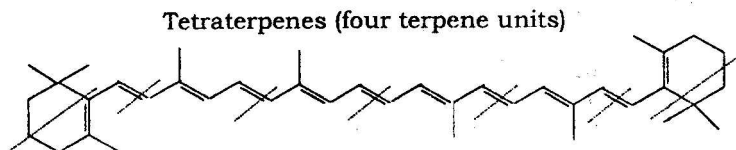
β · *carotene (carrot)*

↓

Diterpenes (two terpene units)
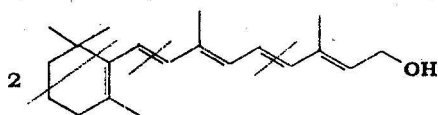


*vitamin A (retinol)*

## AROMATIC COMPOUNDS (ARENES)

Kekule proposed a cyclic hexagonal planar structure of six carbon atoms with alternate double and single bonds. Each carbon atom was bonded to only one hydrogen atom

The Kekule structure for benzene (shown below) is still used today.
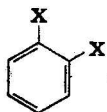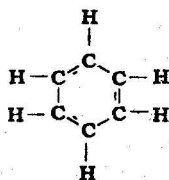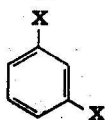




*ortho position*          *meta pozition*          *para pozition*
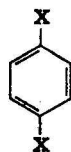
Today we consider the structure of benzene to be that of a resonance hybrid intermediate between structures (a) and (b)



(a)                    (b)

14
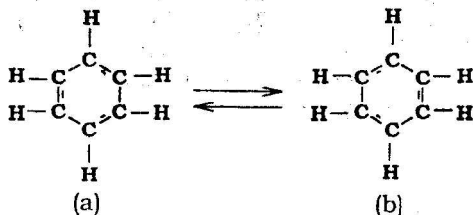
In formulating a molecular orbitals representation of the benzen molecule we form planar, hexagonal framework by the overlap of sp$^2$ orbitals of the six carbon atoms

There are three bonding molecular orbitals, each occupied by two electrons (still called $\pi$-electrons), and three empty antibonding orbitals. The lowest energy orbital could be shown below.
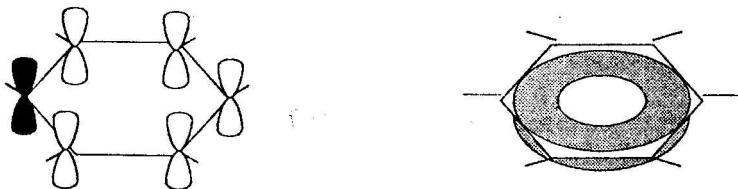


Thus the $\pi$ - electrons are delocalized over the whole ring system. They appear as a cloud above and below the plane of the ring much like two hexagonal doughnuts with six carbon and hydrogen atoms sandwiched in between

## THE AROMATIC SEXTET. AROMATIC CHARACTER

To be classified as aromatic, a compound must have the following requirements. It must be a cyclic structure in order for the delocalized $\pi$ electrons to be in orbital ring. It must be a planar structure in order to permit a maximum overlap of p orbitals.

If the ring is monocyclic, the member of p electrons must be equal to $4n + 2$ where n is an integer. The latter requirement is refferred to as the Hückel Rule. If n=1, we have the sextet of $\pi$ electrons, possessed by benzene. For other values of n the 4n+2 rule gives the necessary number of $\pi$ electrons required for stability. The rule is a mathematical way of stating that monocyclic polyenes having 2, 6, 10, 14, 18, 22 ... $\pi$ electrons are likely to be aromatic, wheres, those with 4, 8 , 12, 16, 20 ... are likely to be nonaromatic.

Aromatically implies a high degree of stability. The $\pi$ electrons above and below the plane of molecule are able to participate in the formation of more than one bond. _The results are strong bonds and a stable molecule._ The additional stability possessed by benzene is called _stabilization or resonance energy_ and the benzene structure is said to be _stabilized by resonance._
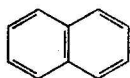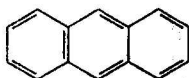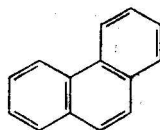
**Naphtalene**        **Anthrathene**        **Phenantrene**

The rich chemistry of the heteroatomic compounds may appear to be quiete different from that of aromatic compounds containing only carbon in the ring, however, the differences consists in degree, not in kind. Thus heteromatic compounds may be more or less aromatic than benzene, and their reactions will reflect this difference.

Consider the two heterociclic systems, pyridine and pyrrole. Both have one nitrogen atom in the ring, but pyridin is a 6 – ring and pyrrole is a 5 – ring system.

In pyridine the nitrogen atom is sp² hybridized, as are all the carbon atoms. Each carbon atom and the nitrogen contribute one electron to the six electron π system, and we predict that the molecules is likely to be aromatic. Its resonance energy has been estimated to be about 32 kcal/mole not greatly different from that of benzen itself .

## Pyridine
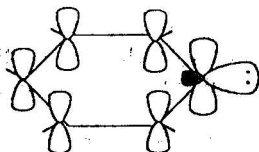


Pyridine enters in composition of biologically activ compounds such as asid nicotinamide – adenine – dinucleotide (NAD), vit B₆ and so on. The nitrogen atom having more electron's density shifts π-electron cloud that decrease the electron density of aromatic ring, called insufficient system.

## Pyrrole



The molecular structure of pyrrole is quite different from the aromatic structures that we have previosly discusses. Let as consider

the result of sp² hybridization of the nitrogen atom. The bond pair to the hydrogen atom will be in an sp² – 1 s sigma orbitals lying in the plane of the ring, whereas the unshared pair will be in 2p orbital that cap overlap easily with four 2p orbitals on the four carbon atoms.

Thus the six electrons required for an aromatic sextet may be derived from two 2p electrons from the nitrogen atom and four 2p electrons from the four carbon atoms.
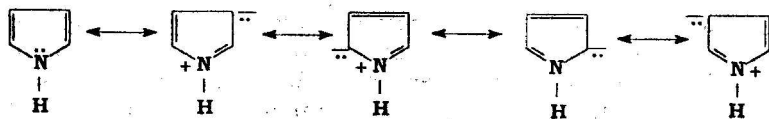


## Pyrrole
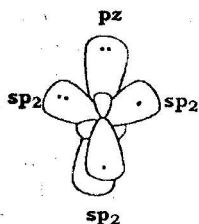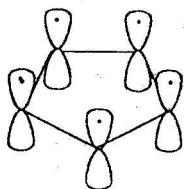


The cloud of 6 ē in pyrrole belongs to the systeme of 5 centers, such a system is $\pi$ - abundance or superaromatic system.

The pyrrole cycle often meet in different biological systems, such as porphyrin structure of hemoglobin.

### 26$\pi$-electrons
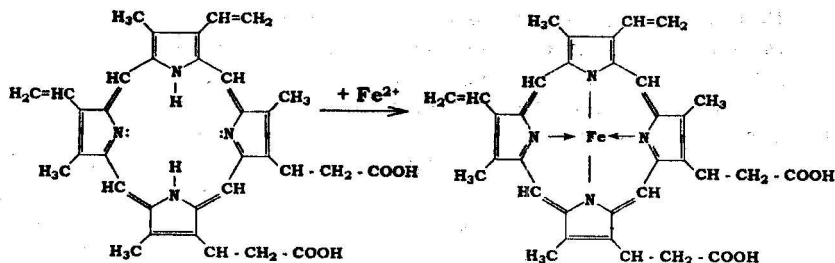


*Protoporphyrin IX*

$$O_2$$

globin
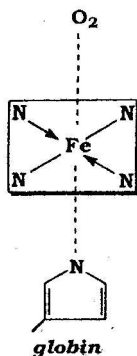
The aromatic compounds are
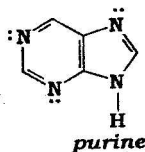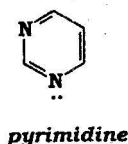


*pyrimidine*          *purine*

Pyrimidine and purine are heterocyclic aromatic compounds, there are thermodinamic stability and enter in the structure of nucleic acids.

## THE ELECTRON'S EFFECTS

Chemistry reactions are the process, in which the electron's density redistributes in the reactant molecules. The electron density in the molecule (Shifts) displacements in direction of more electronegative atom.

$$C^{\delta+} \longrightarrow C^{\delta+} \longrightarrow C^{\delta+} \longrightarrow X^{\delta-}$$
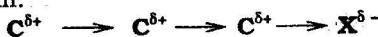
Polarization does not limit only one δ - bond, but spreads along the chain and the substituent X translates influence on the neighbouring δ - bonds. Such kind of electron influence is called *inductive effect* ( I )

**The inductive effect – the transfer of electron's influence of substituent along a chain of δ - bonds in dependence of electronegativity of the atoms, which form this bonds.**

The standart serve non polar covalent bond  C – H

18

$$R^{\delta'+} \longrightarrow CH_2^{\delta} \longrightarrow X^{\delta}_{-}$$
$$\delta'+ \; < \; \delta+ \qquad - I$$

$$R - CH_2 - H$$
$$I = 0$$

$$R^{\delta'-} \longleftarrow CH_2^{\delta} - \longleftarrow X$$
$$\delta'- \; < \; \delta- \qquad + I$$
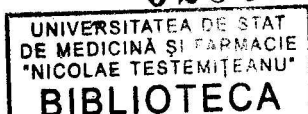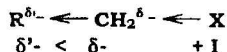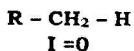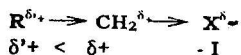
The substituent X, which attracted electron's density of $\sigma$ - bond is stronger, than hydrogen atom, has the negative inductive effect (- I).

But if the substituent increases the electron density in a chain, the inductive effect is pozitiv (+ I effect).

+ I possesses the alkyle groups, the atoms of metals, aniones:

$$+ I$$
$$- CH_3 \longrightarrow - CH = CH_2$$
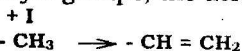
- I for all other substituents:

$$- CH_3 \longrightarrow - CH_2 \longrightarrow - OH ; \qquad - CH_3 \longrightarrow - CH_2 \longrightarrow - Cl \; (I, Br)$$
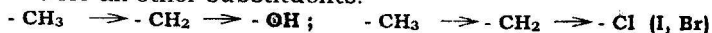
The inductive effect includ 2 – 3 bonds on the reason of weak polarity of $\sigma$ - bond.

It is important to mention, that inductive effect influences property and direction of organic's reactions.

## MEZO – EFFECT

For mezo – effect it is necessary the conjugate part in the molecule (M $\longrightarrow$ ). Mezo – effect is takes place in this case, when the substituent X (which has $\pi$ - bond or p – orbital with unshare pair of electrons) bonds with $sp^2$ or sp hybridized carbon atom.

**Mezo – effect – transference the electron influence of substituents along the conjugate system.**



$$CH_2 = CH - C \overset{O}{\underset{H}{\diagup}}$$
$$sp_2$$
$$\pi\pi \cdot conjugation$$
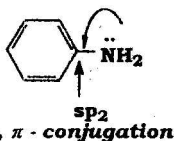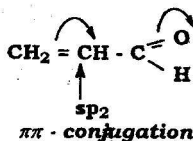
$$p, \pi \cdot conjugation$$
$$sp_2$$

In the both cases $\pi$ or p – orbitals of substituent overlap the with $\pi$ - orbitals of conjugate systems, realises $\pi\pi$ - or p,$\pi$ - conjugation. Formed $\pi$ - electron's cloud displacement to electronegative atom.

The substituent, which attractes the electron's cloud from conjugate system, has a negativ mezo – effect (-M). Such substituents are unsaturated groups, pozitiv charge atoms:

$$>C=O, \quad C \equiv N, \quad NO_2, \quad SO_3H$$
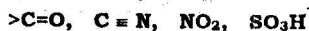
**The substituent, which increases electron density in conjugated system, has a pozitiv mezo–effect (+M).** Such

substituents are heteroatoms with unshare pair of electrons or with negative charge:

$$\overset{..}{N}H_2, \overset{..}{O}H, OR, O^-$$

$$CH_2 = CH - \overset{..}{N}\overset{CH_3}{\underset{CH_3}{}}$$    $$CH_2 = CH - C\overset{O}{\underset{H}{}}$$
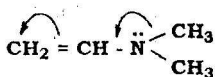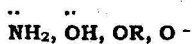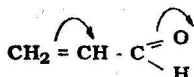
+ M                    -M

Mezo-effect always actions with an inductiv effect. They can be direct in the same, or in oppose directions. The influence of substituent at electron density of molecule is determine by the summary between action of inductiv – and mezo – effects.

The substituents which increased the electron density of systems called donor(D), but decreases acceptor (A).

For example:

$$\longrightarrow \overset{..}{N}H_2$$          $$\longrightarrow C\overset{O}{\underset{H}{}}$$          $$CH_3 - CH_2 \longrightarrow NH_2$$

+M >> - I          -M, -I          -I
ED                 EA
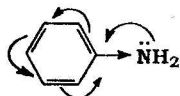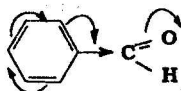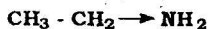
# ACIDS AND BASES ELECTROPHILES AND NUCLEOPHILES

Examination of the presently mecanisms of organic reactions shows that many of them are best described as acids-bases reactions.

As defined by Bronsted and Lowry, an acid is a substance that supplies protons (to a base), and a base is a substance that accepts protons (from an acid).

Examples of Brensted – Lowry

acids: $HCl$, $H_2SO_4$ (strong), $CH_3COOH$ – (weak),

bases: $NaOH$ ($OH^-$)(strong bases), $NH_3$ – (weak base ammonia)

The strengths of Brensted–Lowry acids and bases are measured by the position of equilibrium:

$$HA \;+\; B: \;\overset{K}{\rightleftharpoons}\; A: \;+\; BH^+$$

| HA | B: | A: | BH+ |
|---|---|---|---|
| *acid* | *base* | *conjugate base of HA* | *conjugate acid of B:* |
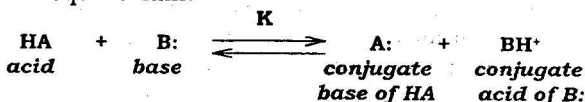
Where the conjugate acid and conjugate base are defined as the products resulting from the proton exchange, and K is the equilibrium constant

for the equation:  $A^+H \;\rightleftharpoons\; A^- + H^+$

$$Ka = \frac{[A^-][H^+]}{[AH]}$$ ,pKa = - lg Ka,  pKa $\downarrow$ acidity $\uparrow$
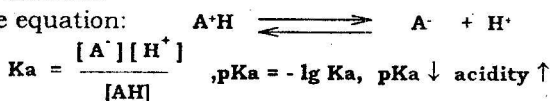
The most general and most useful definition of acids and bases is that of Lewis, which is based on the sharing of electron pair between acid and base. A Lewis acid is a species that accepts an electron pair, and a Lewis base is a species that donates an electron pair.

Typical Lewis acids are the proton ($H^+$), silver ion ($Ag^+$), boron trifluoride ($BF_3$), aluminium chloride ($AlCl_3$), and carbocations (such as $CH_3^+$) – that is, positive ions and species containing atoms with unfilled octets or electron-deficient atoms.

Lewis bases are the same as Bronsted – Lowry bases, and typical are: hydroxide ion ($OH^-$), ammonia (:$NH_3$), chloride ion ($Cl^-$), water ($H_2O$) and carbanions (such as $CH_3$:$^-$) – that is negative ions.

In organic chemistry reagents that are electron – seeking (Lewis acids) and can form a covalent bond by accepting the electron pair *from a carbon atom* are called *electrophiles* (electron–loving). Reagents that are electron – donating  (Lewis bases) and can form a covalent bond to carbon by donating a pair of electrons to a carbon atom are called nucleophiles (nucleus-loving).

Nucleophility is the affinity of a base for a carbon atom is measured by the rate of reaction in which the nucleophile forms a bond to a carbon atom in a standard substrate.

phenol
pKa = 10

carboxilic acids
pKa = 4 – 8
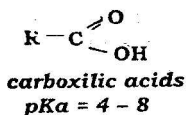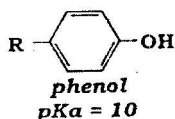
More stable from organic anions – carboxilate ion (anione) $R - COO^-$. In carboxilate ions negativ charge dictated by $p,\pi$ - conjugation distribuites among two atoms of oxygen.



### CH < NH < SH< OH
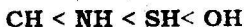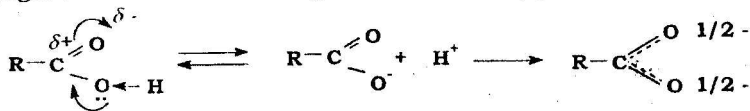
This sequence shows the increase of the acidity.

When we compare acidity of amine, alcohols, thiols, phenols we can say that the most acid properties have alcohols and phenols, that is explained by a bigger electronegativity of oxigen (the ability of keeping back electrons pair after the proton had left):

### R – N < R – O⁻

Thioalcohols are stronger acids than alcohols. But the electronegativity of O is bigger than of S, pseudominancing is polarization of sulf atom and negative charge delocalizes in bigger volume.

### R – S⁻ > R – O⁻

For phenol thanks to $p,\pi$ - conjugate negative charge in phenol the ion delocalisates on ring and stabilates the anion, increasing the acidity.
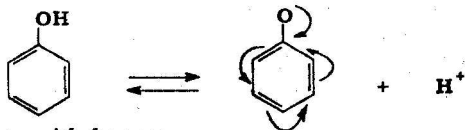


Phenol reacts with bases:

$C_6H_5 - OH + NaOH \longrightarrow C_6H_5ONa + HOH$
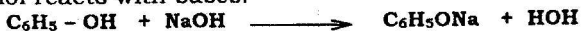
Influence of substituents:

There are four main classes of substituents:

O – H acids (alcohols, phenol, carboxilic acids)

S – H acids (thiols and thioalcohols)

N – H acids (amine, amide and imine)

C – H acids (carbohydrates and their derivatives)

If we compare different classes of organic compounds the strongest are OH and SH, for example:

| R – CH₂ – H | R – NH – H | R – OH | R – SH |
|---|---|---|---|
| alkanes | amine | alcohols | thiols |
| pKa = 50 | pKa = 30 | pKa = 18 | pKa = 11 |
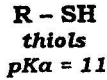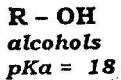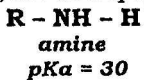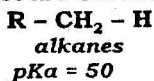
The power of acids depends of the stable state of anion, formed after the proton had left.

As we get the stable anion, (conjugated base), as the stronger is acid.

The anione stable depends of following facts:

1 The nature of atom in acids centre:
   a) electronegativity (EN) of atoms (EN↑ AC↓)
   b) dimention (DM) of atom (polarization) (DM↑ AC↑)

2 The posibility of atoms to delocalization on others atoms (Influence of conjugation on anion stable)
3 The electron's effects of substituents
4 The solvatation effect



**p – nitrophenol**     **phenol**     **p – methyl phenol**
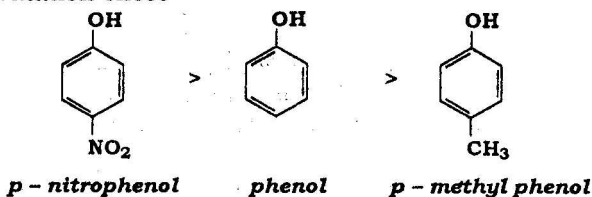
*EA – electronic addition; ED – electronic donation.*

EA – delocalization o phenol – ion, ED – destable phenole – ion
    Acidity is higher   AC↑          Acidity is lower AC↓
    Among alcohols the acidity changes as shown

$$CH_3 - OH > (CH_3)_2 - CH - OH > (CH_3)_3C - OH$$

Alkiles radicals, thanks to +I, – effect unstable anions, decrease the acidity of second and third alcohols.

With increasing the hidroxo – groups increasing acidity, too.



**glycerol**     **ethyleneglicol**     **methanol**
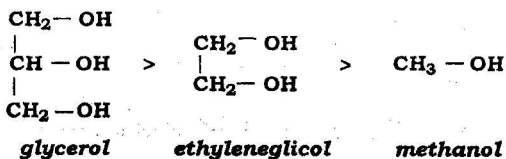
Glycerol and ethyleneglycol react with hydroxid of hard metals, such as $Cu(OH)_2$



*chelates*

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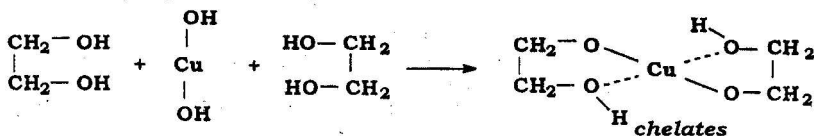
# BASES PROPERTY OF ORGANICS COMPOUNDS

For adding proton, wich has free orbital, the substance must contain element, having undivisioned pair of electrons or $\pi$ - bond. In the composition of such bases more often we meat heteroatoms $\ddot{o}, \ddot{s}, \ddot{N}$

Basity determines by access of undivisioned electrons pair and depends of :

1. the electronegativity o atoms (EN↑ BS↓)
2. the demention of atom (DM↑ BS↓)
3. the posibility to delocalization on others atoms
4. the electron's effects of substituents

There are following classes of bases:

1. Ammonium with N in the centre

$$R - \ddot{N}H_2, \quad R_2\ddot{N}H, \quad R_3 \ddot{N}, \quad R - CH = \ddot{N}H$$

2. Oxonium O in the centre

$$R - OH, \quad R - O - R, \quad R-C\underset{H}{\overset{\ddot{O}:}{{<}}}, \quad R-\overset{\overset{O}{\|}}{C}-R, \quad R-C\underset{OH}{\overset{\ddot{O}}{{<}}}$$
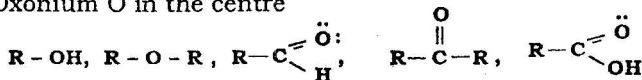
3. Sulfonium S in the centre

$$R - \ddot{S}H, \quad R - \ddot{S} - R$$

4. $\pi$ - bases

$$R - CH = CH_2 \text{ and s. on}$$

From all discussed classes of organic compounds the strongest bases are amine. Electronegativity of nitrogen atoms is smaller than oxygen, electron's pair is more accesible and proton adding lighier.

ED – group wich increased basity

EA – group wich decreased basity

Aliphatic amines are the stronger bases than ammine.

$$R-\ddot{N}\overset{-H}{\underset{H}{{\Big<}}} \quad + \quad H^+ \quad \rightleftarrows \quad R \rightarrow \overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N}} - H^+$$
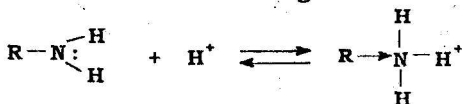
+I – electron's density increased on nitrogen, basity increases

Second amines are smaller bases than aliphatic one's



$$\left. \begin{array}{c} . + M \\ - I \end{array} \right\} \quad ED \qquad p, \pi \text{ - conjugation}$$

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## Bases and Acids Properties of Heterocycls.
### Pyridine

Free pair of electrons of nitrogen don't enter in aromatic sextet and is responsible for bases ability.



*pyridine*     *pyridine chlorine*

### Imidazole



Imidazole has the property of base (nitrogen n1) and property of acid (nitrogen n3). Existence in imidazol's molecular NH – acid group, and one's – N = bases group can form polymers, which bonds are hydrogen



Influence of substituents in ring.



### Pyrrol

Undivisioned pair of electrons of nitrogen is the part of aromatic sextet and has possibility of additioning proton and shows bases property. NH – group on the contrary shows an acid property; pyrrol reacts with metalic natriu of amidous:

$$\underset{\underset{H}{|}}{\overset{\ddots}{N}} \xrightarrow[- NH_3]{NaNH_2} \underset{\underset{Na}{|}}{N} \xrightarrow{H_2O} \underset{\underset{H}{|}}{N} + NaOH$$

## CLASSIFICATION OF ORGANIC REACTIONS AND REAGENTS

Reaction possibility, direction of chemical reactions and mechanisms depends of electrons structures of carbon atoms and their bonds.

A chemical reaction – is the process in which the system changes its chemistry composition:

$$AB + C \longrightarrow [A ... B ... C] \longrightarrow A + BC$$

substrate          activ complex        final products
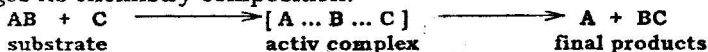
The general principles of mechanisms of chemical reactions were shown in the part of chemical kinetics:

### Ordinary classification of reactions:

Classification on directions of reactions and resulted compounds:

1. the substitution reactions (S);
2. the addition reactions (A);
3. the elimination reactions (E);
4. the regrouption reactions (R);
5. the oxido – reductiv reactions (OR).

### Classification of reactions by mechanisms:

1. radical (homolitic mechanism)

$$R \overset{|}{\underset{|}{\text{ᴸ}}} X \longrightarrow R\bullet + X\bullet$$

Free radicals are the atom or group of atoms, which have one free electron.

2. Ion's mechanism with formation of electrophiles and nucleophiles
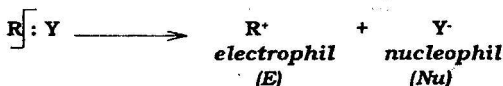
$$R \overset{\lceil}{\rvert} : Y \longrightarrow R^+ + Y^-$$

electrophil    nucleophil

(E)        (Nu)

In organic chemistry reagents that are electron – seeking (Lewis acids) and can form a covalent bond by accepting of electron pair from carbon atom are called electrophiles (electron – loving). Reagents that are electron – donating (Lewis bases) and can form a covalent

bond by donating a pair of electrons to a carbon atom are called nucleophiles (nucleus – loving).

It is important not to confuse the terms basicity and nucleophilicity. As stated above, *basicity* is measured by position of an equilibrium and is the affinity of base for a proton. *Nucleophilicity* is the affinity of a base for a carbon atom and it is measured by the rate of a reaction in which the nucleophile forms a bond to a carbon atom in a standard substrate.

*Electrophile* – is a particle with electron's deficit, which can interact with electrons pair, such as:

a) particles with positiv charge
   $H^+$ proton, (source HCl, $H_2SO_4$)
   $NO_2^+$ nitrogroup (source $HNO_3 + H_2SO_4$)

b) neutrons molecular with electrodeficit centers
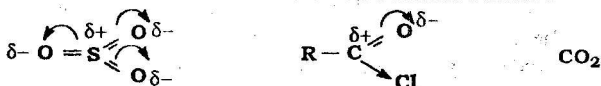


*Nucleophile* – is a particle which is the donor of electrons pair and can interact with charged positive carbon.

a) negativ ions such as
   $HO^-$ (source NaOH, KOH)
   $Cl^-$ (source HCl, NaCl)
   $H^-$ (source MeH)

b) neutrous molecules which have undivisioned pair of electrons

$$H\ddot{O}H, \quad R - \ddot{O}H, \quad \ddot{N}H_3, \quad R - \ddot{N}H_2 \text{ and s.on}$$

## REACTIONS OF ELECTROPHILE ADDITION (AE)

Reactions of electrophile addition is caracteristic for unsaturated compounds. The most important "in vivo" is double bond saturation. Formation of double bond is characteristic for a lot of biochemic process which takes place in organism. Alkenes have a region with increasing electron density, they are nucleophyle and are attacked by electrophile reagents



$$\pi \cdot complex \qquad \sigma \cdot complex \qquad 2\ chlorpropane$$
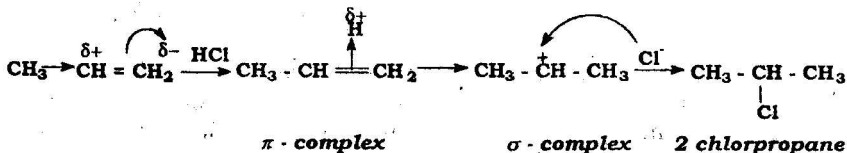
Reaction is taking in such way thanks to the statistic fact; in molecule of propene methyl group possessions +I effects increases electron density and $=CH_2$ group appears partial negativ charge ($\delta$-)

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## General scheme:

$$\text{C} = \text{C} + \overset{\delta+}{\text{E}} - \overset{\delta-}{\text{Nu}} \longrightarrow \overset{|}{\underset{\text{E}}{\text{C}}} - \overset{|}{\underset{|}{\text{C}}} \underset{\text{Nu}}{}$$
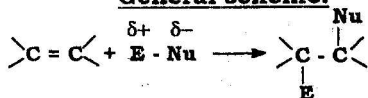
## Mecanism:

a) formation $E^+$: $E - Nu \longrightarrow E^+ + Nu$

b) electrophyl attack:

$$\text{C} = \text{C} + \overset{\delta+}{\text{E}} \longrightarrow \underset{\sigma\text{-complex}}{E - \overset{|}{\underset{|}{\text{C}}} - \overset{|}{\underset{|}{\text{C}}}^+}$$

*π- complex*
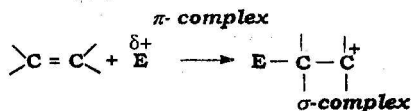
c) nucleophyl attack:

$$E - \overset{|}{\underset{|}{\text{C}}} - \overset{|}{\underset{|}{\text{C}}}^+ + N\bar{u} \xrightarrow{\text{fast}} E - \overset{|}{\underset{|}{\text{C}}} - \overset{|}{\underset{|}{\text{C}}} - Nu$$
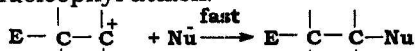
Typical reactions of addition to alkene are:

1. Addition of water (hydratation)

$$\text{C} = \text{C} + H_2O \xrightarrow{H^+} \overset{|}{\underset{H}{\text{C}}} - \overset{|}{\underset{OH}{\text{C}}}$$
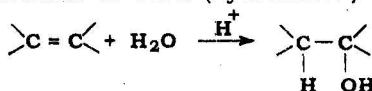
2. Addition of hydrogen (hydrogenation)

$$\text{C} = \text{C} + H_2 \longrightarrow \overset{|}{\underset{H}{\text{C}}} - \overset{|}{\underset{H}{\text{C}}}$$
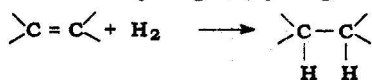
3. Addition of HCl (hydrohalogenation)

$$\text{C} = \text{C} + HCl \longrightarrow \overset{|}{\underset{H}{\text{C}}} - \overset{|}{\underset{Cl}{\text{C}}}$$
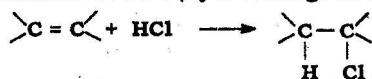
4. Addition of halogens:

$$\text{C} = \text{C} + Cl_2 \longrightarrow \overset{|}{\underset{Cl}{\text{C}}} - \overset{|}{\underset{Cl}{\text{C}}}$$
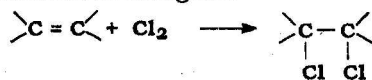
Relative stability of formation carbcation is determin   by +I effect of two methyl groups, wich has possibility to decrease positive charge on the neighboring carbon atom, it is a dynamic fact.

That is why tertiary carbcations are more stable than secondary, that are more stable than primary.

$$\underset{R}{\overset{R}{R \rightarrow \overset{|}{C}^+}} > \underset{R}{\overset{R}{H - \overset{|}{C}^+}} > \underset{H}{\overset{H}{R - \overset{|}{C}^+}} > \underset{H}{\overset{H}{H - \overset{|}{C}^+}}$$

*increasing of stability*
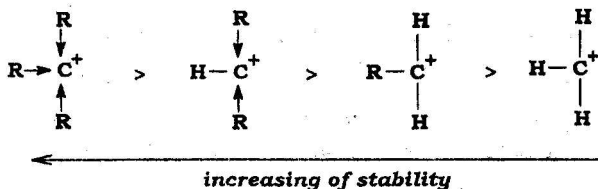
The russian chemist Markovnikov in 1871 formulated an empirical rule regarding this mode of addition. The rule simply states: " In addition of acids to unsymmetrical alkenes, the negative portion of the species added will seek the carbon atom holding the fewer hydrogen atoms"

Since the relative stabilities of free radicals parallel those of carbocations, namely

<center>tertiary > secondary > primary</center>

## Contemporain rulls of Markovnikov:

Addition of proton to alkene formes more stable cation.

Addition of water:

Addition takes place easily in the prezence of acids.

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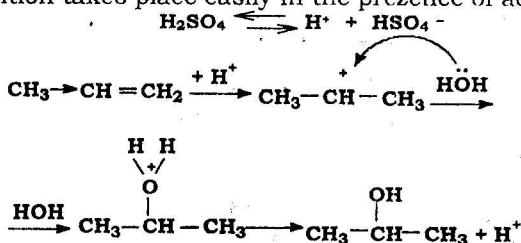




The role of acids catalyze consists in formation of carboxoanione (Markovnikov rull is observing).

In the case of unsaturated $\alpha$-$\beta$-carbonylic compounds Markovnikov's rule is not observing which can be explain by statistic and dynamic facts:



*β- hydroxipropionic acid*
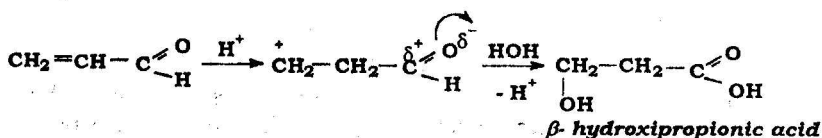
"in vivo" we have such reactions: cycle Krebs:



*cytric acid*          *cis – aconitic acid*          *izocitric acid*
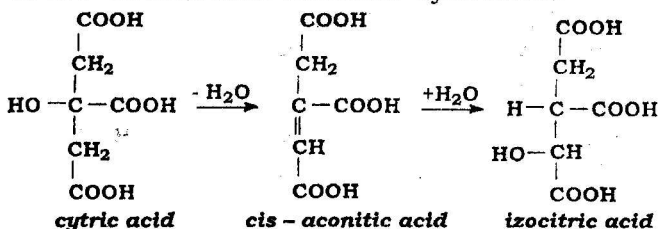
*The Baeyer Te*st on the double bond

Alkenes are oxidized with cold potassium permanganate to form glycols. This reaction serves as an easily recognizable test for alkenes because as the oxidant is consumed, its bright purple color disappears, and a brown precipitate of manganese dioxide forms. The reaction is the basis for Baeyer Test for unsaturation, as shown in the second example:

$$3\ CH_2 = CH_2\ +\ 2KMnO_4\ +\ 4\ H_2O\ \longrightarrow\ 3\ \underset{\underset{HO}{|}}{CH_2} - \underset{\underset{OH}{|}}{CH_2}\ +\ 2MnO_2\ +\ 2KOH$$
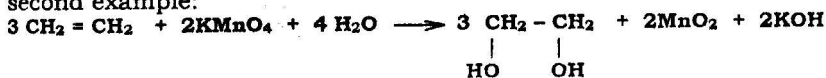
## *Additions to dienes*

Carbcation can participates in $A_E$ reaction in the capacity electrophyle reagent. This process meets in the synthasis of terpenes and steroids.

## Reactions of the aromatic hydrocarbons

The reactions of benzene and other aromatic hydrocarbons are mainly reactions of substitution in the aromatic ring. Substitution reactions involving the aromatic ring, unlike those of the alkanes, are controllable and much more useful.

The benzene ring is attacked in nearly every case by an electrophilic reagent that may be either a cation or a neutral but polarized molecule. The electron-dificent group, by sharing in an electron pair supplied at one of the ring carbons, first forms with the benzene ring a cationic intermediate, called sigma complex, in which the positive charge is distributed among the remaining carbon atoms. In the second step a proton is lost to regenerate the more stable aromic ring.

Catalysts are often necessary to generate the electrophile. Such catalysts, as you will see undermentioned, are often Lewis acids, each of which lacks an electron pair.

The result of attracting a pair of electrons from the substituting reagent by the catalyst is the formation of either a positive ion or a polarized molecule. The mechanism of electrophilic aromatic substitution may be illustrated by the following.

$$E^{\delta+} - Y^{\delta-} \ldots\ldots \overset{..}{\underset{..}{C}} : \text{ the catalyst}$$

Sigma complex

$$H+ + Y - C \longrightarrow H - Y + C$$
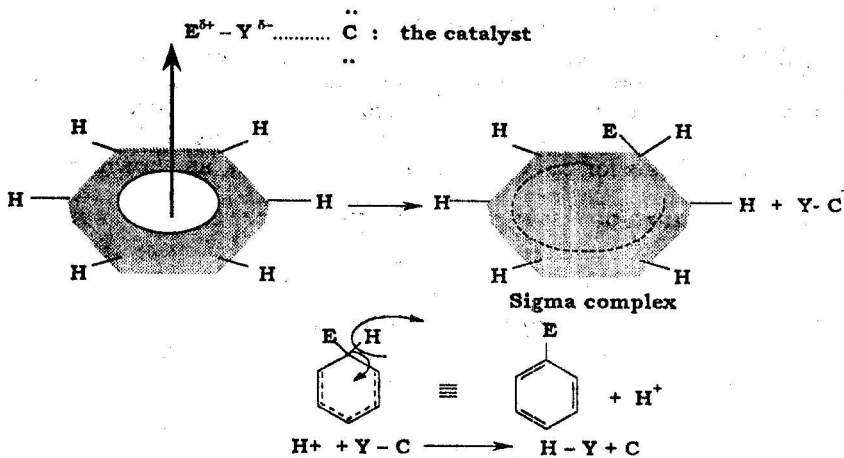
## 1. Halogenation of benzene.

Halogenation of the aromatic ring may be illustrated by bromination. Ferric bromide, $FeBr_3$, is actual catalyst.
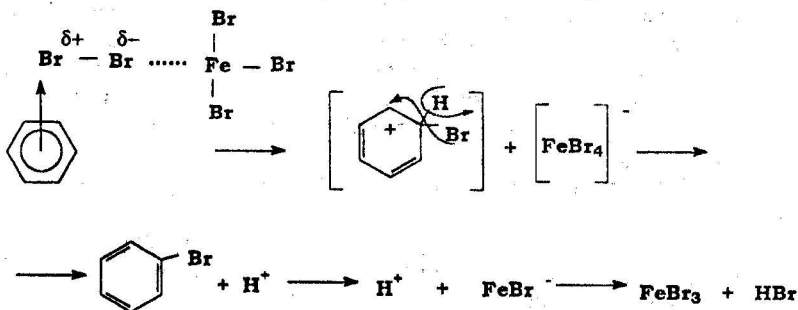


Substitution of benzene by chlorine also can be accomplished in a manier similar to that shown for the bromination reaction.

## 2. Nitration of benzene.

Nitration of the aromatic ring is a very important reaction and produces a number of useful compunds unobtained in any other way. Nitration is usually accomplished by treating benzene with a mixture of concentrated nitric and sulfuric acids.

$$HO-\overset{O}{\underset{O}{N}} + 2\ H_2SO_4 \longrightarrow 2\ HSO_4^- + H_3O^+ + \overset{+}{\underset{O}{N}}\overset{O}{}$$



*Nitrobenzene*
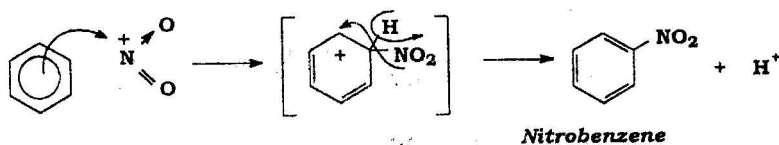
### 3. Alkylation of benzene.

The simple alkyl benzenes such as toluene (methylbenzene) and xylenes (dimethylbenzenes) are readily available from pertroleum. On occasion, however, it may be necessary or desirable to introduce an alkyl group into the benzene ring. One method for accomplishing this substitution is a reaction known as the Friedel-Crafts reaction. In the Friedel-Krafts reaction an alkyl group is attached to the ring by treating benzene with an alkyl halide in the presence of anhydrous aluminum chloride, $AlCl_3$.



$$R-\ddot{C}\ddot{l}: + AlCl_3 \rightleftharpoons \overset{\delta+}{R} \overset{+}{\to} Cl-\underset{Cl}{\overset{Cl}{Al}}-Cl \rightleftharpoons R^+ + AlCl_4^-$$



*toluene*          *xylene*
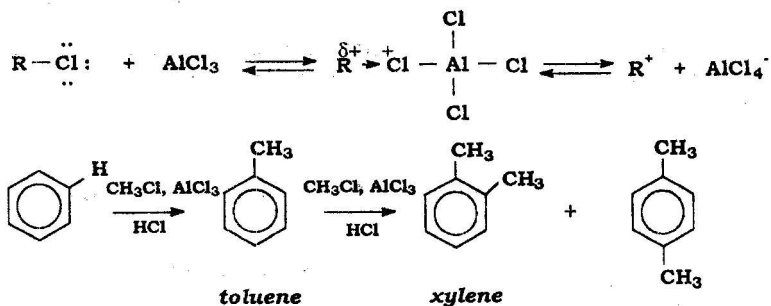
If benzene is treated with n-propyl chloride and aluminum chloride, the product obtained is largely isopropylbenzene, or cumene.

Only small amounts of normal isomer are obtained. Formation of the more highly branched secondary carbocation, which may be accomplished by rearrangement of a hydrogen atom and a pair of electrons, appear to be favored because it represents a more stable intermediate than the primary carbcation.
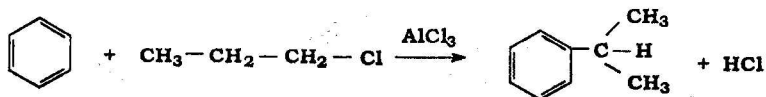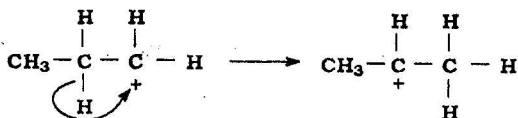
## 4. Sulfonation of benzene

Benzenesulfonic acid is produced when benzene is heated with concentrated sulfuric acid. The ring – attacking group in the sulfonation reaction is not a pozitive ion as was the case in the previous reactions. Instead, it appears to be the electron – deficient sulfur trioxide molecule produced by the reaction of two molecules of sulfuric acid.
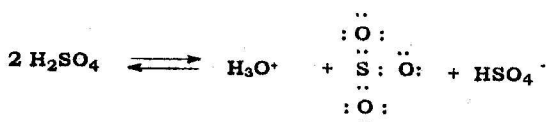


The sulfonation of aromatic compounds is a very important reaction, especially in the preparation of dyestuffs.



benzenesulfonic acid



sodium benzenesulfonate
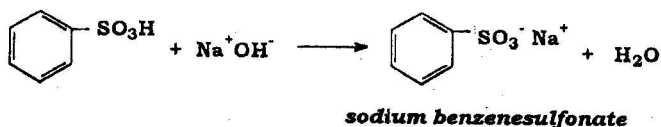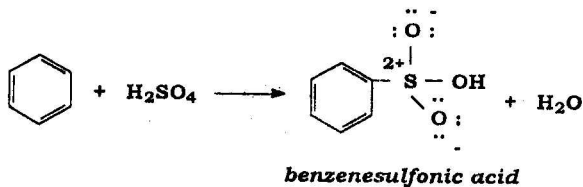
We can obtain phenols following reaction:

$$Ar - SO_3H \xrightarrow[- H_2O, - Na_2SO_3]{NaOH, 350°C} Ar - ONa \xrightarrow{H_2O/H^+} A - OH$$

The examples of biological reaction Se are iodization of tyrozine (Tyr) with formation of hormonous tyronine and tyroxine. Active form of iod forms on oxidation I- by action of iodite – peroxidase:



$$2I^- \longrightarrow I_2 \longrightarrow \overset{\delta+\ \delta-}{I:I} \longrightarrow I^+ + I^-$$

**3'3'5' – three iodtironine**

**3, 5, 3', 5' tetraiodtyronine**

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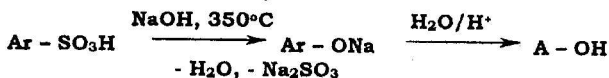
# REACTIONS OF NUCLEOPHILIC SUBSTITUTION ON THE SATURATE CARBON ATOM ($S_N$-REACTIONS). REACTIONS OF ELIMINATION (E- REACTIONS)

Reactions of nucleophilic substitutions are characterize for saturate organic compounds, which contain such functional groups as halogen, hydroxile, thiol and amino (R-Hal, R-OH, R-SH, R-NH$_2$).

In such compounds the bond carbon – heteroatom is strong polarized thanks to J effect of heteroatom:

$$\backslash \overset{\delta+}{\phantom{x}} \quad \overset{\delta-}{\phantom{x}}$$
$$- C \rightarrow X$$
$$/$$
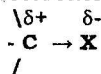
The appearance of electrophilic center gives the posibility of nucleophilic attack. Therefore this compounds are the substrates of nucleophilic substitution:

$$\backslash \overset{\delta+}{\phantom{x}} \quad \overset{\delta-}{\phantom{x}} \qquad\qquad \backslash$$
$$- C \rightarrow X + Nu \cdot \xrightarrow{\phantom{xxxxx}} - C - Nu + X^-$$
$$/ \qquad\qquad\qquad\qquad /$$
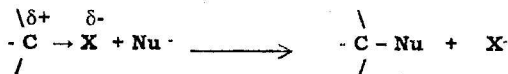
From the other side inductive influence of the mention group increases agility of hydrogen in β-position of carbon.

$$H$$
$$|\beta \qquad\qquad \delta-$$
$$R - C \rightarrow CH_2 \rightarrow X$$
$$\downarrow$$
$$H$$
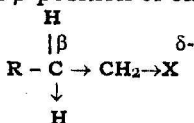
The appearance of the posibility to loss proton with X group: elimination reaction - E.

$$H$$
$$|$$
$$R - C - CH_2 - X \xrightarrow{\phantom{xxxxxxx}} R - CH=CH_2 + HX$$
$$|$$
$$H$$

The reactions of alkyl halides are principally of two types – substitution and elimination.

The halogen atom in substitution reaction is displaced by an electron – rich nucleophilic reagents. Such a nucleophilic reagents are Lewis Bases and often are negative ions. Substitution reactions may take place by two different mechanisms. In one of these, the rate of reaction depends upon the concentration of one reacting species and is called a substitution, nucleophilic, unimolecular $S_N1$.

In the other substitution mechanism, the rate of reaction usually depends upon the concentration of two reacting species and is called substitution, nucleophilic, bimolecular or $S_N2$.

The rate at which a reaction proceeds is never greater that the slowest step and this phase is called rate – determined step.

In $S_N1$ the rate – determining step is formation of a carbocation. Any factors such as spheric, resonance stabilization, or inductive effects that help to promote the formation of the carbcation will increase the rate of reaction. The reaction rate may be increased further through the assistance of a polar solvent, which can solvate both cation and anion.

An example of a $S_N1$ reactions is hydrolysis of tert – butyl chloride in 80% aqueous-alcoholic solutions.

**Route 1:**



*tert - butyl alcohol 83%*
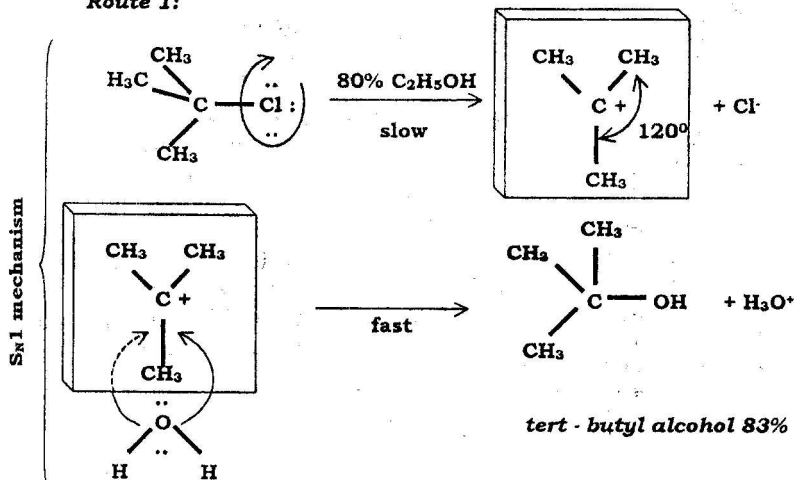
For tert alkyl halides (and secondary with capacious substitution) appears steric effects and nucleophile can not approach electrophyl carbon. In our example you will note that the attaching nucleophile (water) may approach the positive carbon from either front or back. The end result in the hydrolysis of tert – butyl chloride is the same, but the choice in the direction of combination may lead to racemization if optically active halides are hydrolyzed in this manner. Let us illustrate this point using an optically active form of α-phenyl-ethyl chloride.
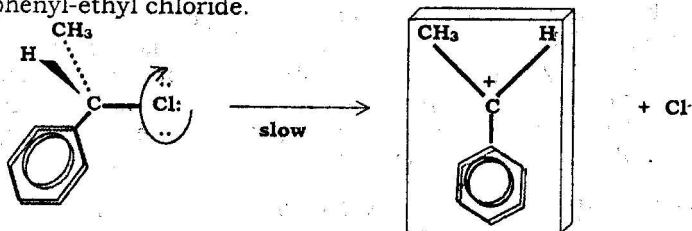


(+) or (-) Phenyl-ethyl chloride

**(±) - α - phenylethyl alcohols**
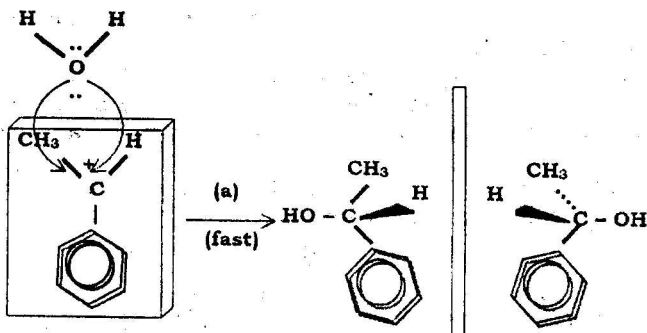
Regard less of which optical isomers of α-phenyl-ethyl chloride is hydrolyzed, the product is always a partially racemized mixture. However, racemization is characteristic for all $S_N1$ reactions.

Let us now return to the tert-butyl chloride hydrolysis reaction and see what has happened to the remainder of our starting materials. In order to account for the other 17% we must consider another possible reaction route. If, instead of combineing with the nucleophilic reagent, the carbocation loses a proton (Route II).

*Route II (E1- mechanism)*
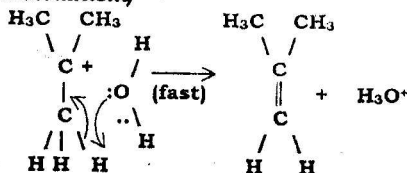


In the second (fast) step, when the product of reaction is an alkene, and the reaction mechanism is referred to as E1. As in the $S_N1$ mechanism, the number in the abbreviation refers to unimolecular. The E1 in such cases, indicates elimination. Because of the competition between substitution and elimination, more than one product often results.

$S_N1$ mechanism is characterizes for nucleophylic substitution in alcohols, amines, thiols and their derivatives. But this compounds contains hard leaving groups $OH^-$, $NH_2^-$, $SH^-$. Therefore the straight nucleophilic substituence is impossible. In this cases is used the mechanism of transformation hardly leaving group into easily leaving group. For example for the alcohols we can uses acids catalizator.

$$CH_3 - CH_2 - OH + NaBr \xrightarrow{H_2SO_4} CH_3 - CH_2 - Br + H_2O + NaHSO_3$$

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The temperature of reaction is high and the most posible mechanism is $S_N1$:

$$CH_3\text{-}CH_2\text{-}OH + H^+ \xrightarrow{\text{fast}} CH_3\text{-}CH_2\text{-}\overset{\overset{H}{+/}}{\underset{\underset{H}{\backslash}}{O}} \xrightarrow[\text{slow}]{-H_2O} CH_3 - CH_2^+ \xrightarrow[\text{fast}]{+Br^-} CH_3\text{-}CH_2\text{-} Br$$

The nucleophilic substituence amine – group in amine on hydroxo – group is realized by the influence of $HNO_3$.

$$R - NH_2 + HONO \xrightarrow{-H_2O} R - NH - N - N{=}O \underset{H}{\rightleftharpoons} R - N {=} N - OH \xrightarrow{+H^+}$$

$$\longrightarrow R - N {=} N - \overset{\overset{H}{+/}}{\underset{\underset{H}{\backslash}}{O}} \xrightarrow{+/- H_2O} R{\rightarrow}N \equiv N \xrightarrow{+ HOH} R - \overset{}{\underset{\underset{H}{\backslash}}{O}} + N_2$$

$$R - \overset{\overset{H}{+/}}{\underset{\underset{H}{\backslash}}{O}} \longrightarrow R{-}OH + H^+$$

The examples of biological processes which are realized by nucleophilic substituence are synthesis of S–adenozilmethionine (I) and methylation of noradrenaline (II). May be illustrated by alkaline hydrolysis of primary – ethyl chloride to primary – ethyl alcohol. In this case in the slow step of reaction sequence both ethyl chloride ion are involved.

**Formation of S- adenozilmethionine(I)**

**Formation of adrenaline from noradrenaline (II)**

$$CH_3 - CH_2 - Br \quad + \quad NaOH \longrightarrow C_2H_5OH + NaBr$$

HO $-\langle\rangle-$ CH $-$ CH$_2$ $-$ NH$_2$ + H$_3$C $\rightarrow$ S $-$ CH$_2$ (A) NH$_2^+$

with HO, HO on the ring and OH below the CH; side chain CH$_2$ $-$ CH$_2$ $-$ CH $-$ COO$^-$ with NH$_2$; ribose ring with HO OH.

HO $-\langle\rangle-$ CH $-$ CH$_2$ $-$ NH $-$ CH$_3$ + S $-$ CH$_2$ (A) NH$_2$

with HO, HO on the ring and OH below the CH; side chain CH$_2$ $-$ CH$_2$ $-$ CH $-$ COOH; ribose ring with HO OH.

*adenozilhomocisteine*
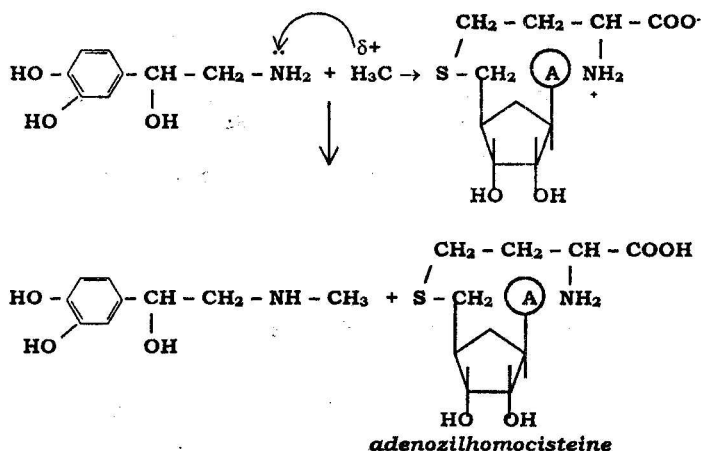
## THE S$_N$2 REACTION MECHANISM

May be illustrated by alkaline hydrolysis of primary – ethyl chloride to primary – ethyl alcohol. In this case in of the slow step of reaction sequence, both ethyl chloride ion are involved. The hydroxide ion displaced the chloride ion, not by a head – on approach to the face of the carbon atom bonded to the chlorine atom, but by an attack from the rear. In making this backside approach, a new bond forms between the carbon atom and the hydroxil group as the bond between the carbon atom and chlorine atom is broken. Thus the reaction proceeds through a transition state in which the carbon atom is partially bonded to both the hydroxil group and the chlorine atom. Transition states are often shown in brackets to emphasize that they are a transitory, high energy species.

$$CH_3 - CH_2 - Br \quad + \quad NaOH \longrightarrow C_2H_5OH + NaBr$$
$$V = k \cdot C\,[C_2H_5Br] \cdot C\,[NaOH]$$

HO $\cdot$ + H $\overset{CH_3}{\underset{H}{\overset{|\delta+ \ \delta-}{C \rightarrow Br}}}$ $\longrightarrow$ $\left[ HO \underset{\overset{H \ H}{/\backslash}}{\overset{\overset{CH_3}{|}}{\underset{\delta-}{\cdots\cdots}} C \underset{\delta-}{\cdots\cdots} Br} \right]$ $\longrightarrow$ HO $-$ $\overset{CH_3}{\underset{H}{C}}$ H + Br$^-$
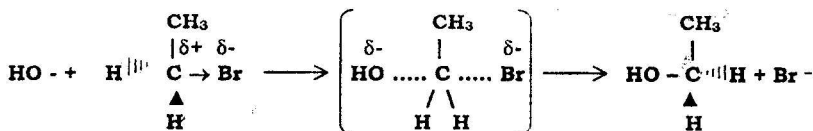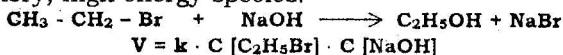
At the transition state collapses to form the products, the groups bonded to the carbon atom change their relative positions as it

is shown. And the configuration becomes exactly opposite than the oneof the starting material. Such a reversal configuration is referred to as a _Walden inversion_ and invariably occurs in an $S_N2$ reaction.

Primary – alkyle halogen reacts on $S_N2$ mechanism with alkooxides, thiols, phooxides, amines and others nucleophyles.

Alkylation of alcohols:

$$R – Hal + C_2H_5\overset{-}{O}\overset{+}{N}a \longrightarrow R-O-C_2H_5 + Na – Hal$$

Alkylation of phenols:

$$R – Hal + Ar – \overset{-}{O} – \overset{+}{N}a \longrightarrow R – O – Ar + Na – Hal$$

Alkylation of thiols and thioethers:

$$R – Hal + C_2H_5- \overset{-}{S}\overset{+}{N}a \longrightarrow R-S-C_2H_5 + Na – Hal$$

$$R – Hal + C_2H_5- \overset{..}{S} - R \longrightarrow R-\overset{\overset{R}{|}}{\underset{+}{S}}-C_2H_5 + Hal^-$$

Alkylation of $NH_3$:

$$R –Hal + :NH_3 \longrightarrow R – NH_2 + HHal$$
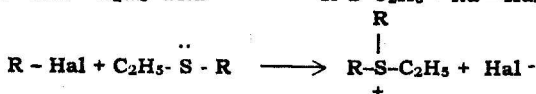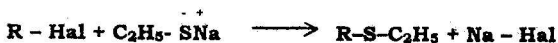
Alkylation of amine:

$$R –Hal + R' - :NH_2 \longrightarrow R – NH – R^1 + HHal$$
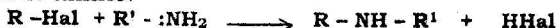
## ELIMINATION REACTIONS (E)

Reactions β- elimination are called the reactions, in which from the molecule pass two atoms or groups from neighboring atoms of carbons with formation of unsaturated bond

$$-\overset{|}{\underset{\underset{H}{|}}{C}} - \overset{|}{\underset{\underset{Y}{|}}{C}} - \longrightarrow \overset{\backslash}{\underset{/}{C}} = \overset{/}{\underset{\backslash}{C}} + HY$$
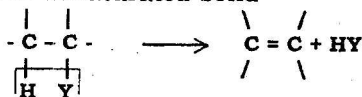
The typical E- reactions are elimination of HX (halogens) from alkyl halides and $H_2O$ from alcohols.

$$CH_3 – \underset{\underset{H}{|}}{CH} – \underset{\underset{Br}{|}}{CH_2} \xrightarrow{\text{KOH (alcohol) t}^{\circ}\text{C}} CH_3 – CH = CH_2 + KBr + H_2O$$
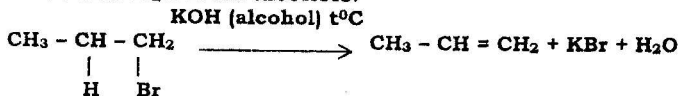
Primary halids reacts to E2 mechanism:

$$CH_3 \overset{\overset{H}{\downarrow}}{\rightarrow}\overset{\overset{H}{\downarrow}}{C}\rightarrow\overset{\delta-}{C}\rightarrow Br + OH^- + \left[CH_3 – CH\underset{\underset{H ... OH}{\overset{\uparrow\delta+}{\quad}}}{\rightarrow} CH_2 – \overset{\delta-}{Br}\right] \longrightarrow CH_3–CH = CH_2 + H_2O + Br$$
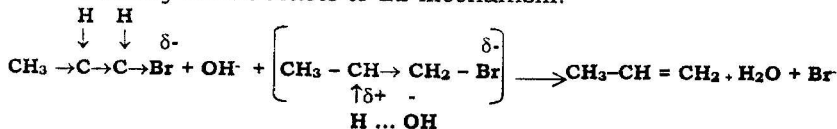
For the tert halids is realized the E1 mechanism with the formation of a carbcation.

$$H_3C - \underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}} - Br \xrightarrow[- Br^-]{t^oC} CH_2 \rightarrow \underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|+}}{C}} - \overset{OH^-}{} \longrightarrow CH_2 = \underset{\underset{CH_3}{\diagdown}}{\overset{\overset{CH_3}{\diagup}}{C}} + H_2O$$

Dehydratation of alcohols always needs acids ($H_2SO_4$, $t^oC$), by mechanism S1.

$$CH_3 - \underset{\underset{H}{|}}{CH} - \underset{\underset{OH}{|}}{CH_2} \xrightarrow{H_2SO_4,\ t^oC} CH_3 - CH=CH_2 + H_2O$$

**S1**

$$CH_3 - CH \rightarrow CH_2 + H^+ \longrightarrow CH_3 - \underset{\underset{O^+}{\overset{|}{}}}{CH} - \underset{H}{CH_2} \xrightarrow[slow]{t^oC} CH_3 - \underset{\overset{\uparrow}{H}}{CH} \rightarrow CH_2 \longrightarrow CH_3 - CH = CH_2 + H^+$$

carbcation          propene

## Lightly of unhydratations:

primary < secondary < tertiary

This reaction often meats in Biochemistry (cycle Krebs)

$$HOOC - \underset{\underset{OH}{|}}{CH} - CH_2 - COOH \xrightarrow{fumaraze} \underset{\underset{H \quad COOH}{\diagup \quad \diagdown}}{\overset{\overset{HOOC \quad H}{\diagdown \quad \diagup}}{C = C}}$$

**Fumaric acid**

$$HOOC - CH_2 - \underset{\underset{OH}{\overset{\overset{COOH}{|}}{|}}}{C} - CH_2 - COOH \xrightarrow[- H_2O]{aconitaze} HOOC - CH_2 - \underset{\overset{COOH}{|}}{C} = CH - COOH$$

**cis – aconitic acid**

# REACTIONS OF NUCLEOPHILIC ADDITION IN ALDEHYDES AND KETONES.

Organic compounds, which contains functional group carbonilic one >C=O, are called carbonilic or oxo – compounds.

The main biological activ natural compounds (proteins, lipids, steroic hormonous) contain carbonilic group.

We shell speak about chemical properties of aldehydes and ketones.

Compared with double bond in alkenes double bond in aldehydes are stronger polarizated because of the difference between the electronegativity of carbon and oxygen atoms.

## The structure of carbonilic group
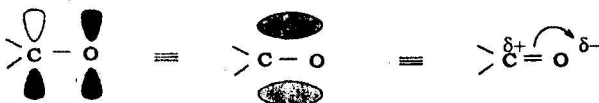


As a result on the carbon atom appears partial positiv charge, but on the oxygen atom negativ charge. Therefore carbon atom is convinable centre for nucleophilic attack. Power of nucleophilic attack depends of following facts.

1. The value of effective $\delta+$ charge on carbon atom.
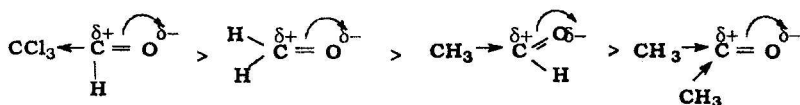


Aldehydes are more active in comparison with ketones

2. The acidity and basidity of reaction's evironment. In acid environment the activity increased.
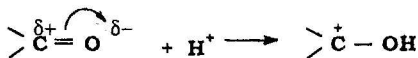


## The general scheme of $A_N$ – reaction



42
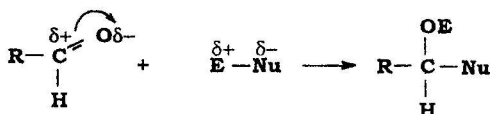
# Mechanism of $A_N$ - reaction
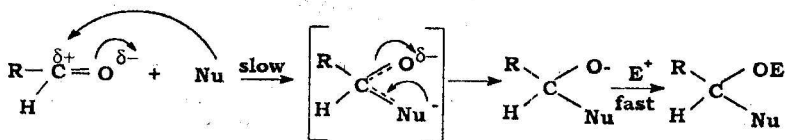


The process is the same as in $S_N2$ reaction, with one's difference additioned electron pair oxygen atom isn't a lossing group, but remains in substrat's molecula.

This mechanism is applicaited in different reactions

## 1. Addition of water

Addition of water ⟶ formate the hydrate

$$> C = O \; + \; HOH \rightleftarrows \; -\overset{|}{\underset{|}{C}} - OH$$
$$\hphantom{xxxxxxxxxxxxxxxxxxxx} OH$$
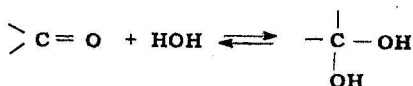
The aldehydes and ketones show a smaller tendency for generateing stable hydrates. In a few compounds, in which the carbonyl group is attached to other strong electron – attracting groups, a hydrate sufficiently stable to be isolated is formed. One of the best examples of such a compound is trichloracetaldehyde, or chloral, which forms a stable hydrate used medicinally as a sopofiric.



*chloral*                           *chloral hydrate*
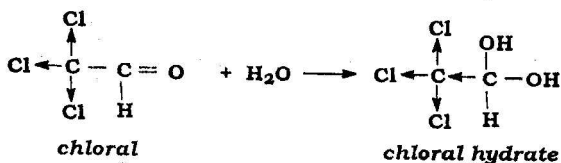
Formic aldehyde formic also forms a stable hydrate:
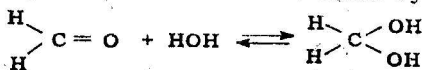


Ninhydrin – reagent of determination amino-acids. Amino-acids react with ninhydrin solution to produce purple compounds – formes also hydrate:

43
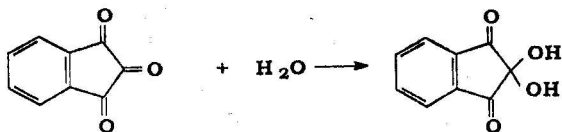
## 2. Additions of alcohols

On the other hand, alcohols will add at aldehydes in the presence of acid catalysts. An unstable addition product called hemiacetal, formed in the first stage of the reaction, reacts with a second molecule of alcohol to yield a stable compound called acetal.



*hemiacetal (unstable)*



*acetaldehyde diethyl acetal*
*(stable)*
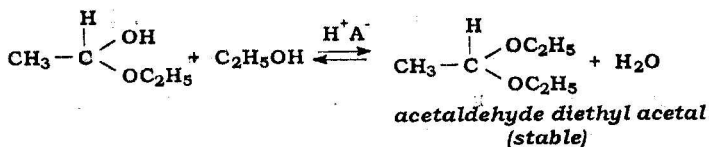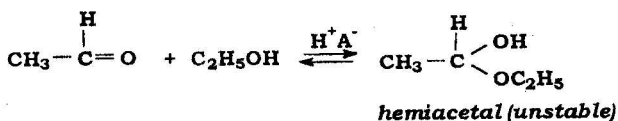
Mechanism $A_N$ reaction efficient in acid environment:



*carbcation I*          *ion of oxonium I*          *hemiacetal*



*carbcation II*



*ion of oxonium II*          *acetal*

44
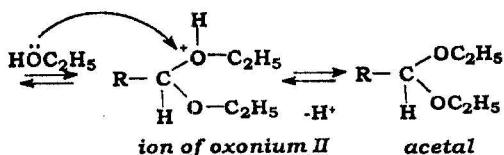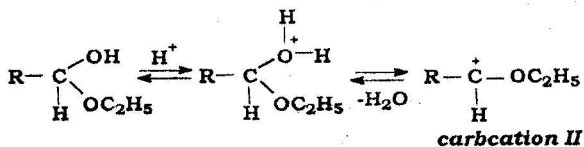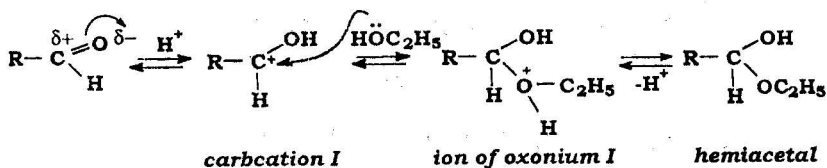
In the case when hydroxile and aldehide groups are in the same molecule, it is possible formation intermoleculas cyclice hemiacetal.

$$
\begin{array}{cc}
\underset{H}{\diagdown}\underset{\displaystyle C}{\phantom{}}\overset{\displaystyle O}{\diagup} & \underset{H}{\diagdown}\underset{\displaystyle C}{\phantom{}}\underset{OH}{\diagup} \\
CH_2 & CH_2 \\
CH_2 \quad \xrightarrow{H^+} & CH_2 \quad O \\
CH_2 & CH_2 \\
CH_2OH & CH_2
\end{array}
$$
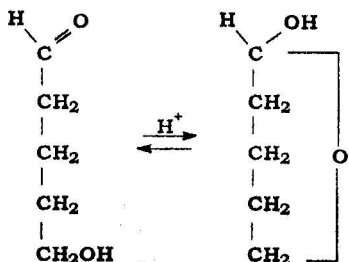
The reaction is reversible:

$$
\underset{\textbf{5-hydroxipentanal}}{H_2C\underset{CH_2-CH_2}{\overset{CH_2-OH}{}}\overset{\delta+}{C}\underset{H}{\overset{O\,\delta-}{}}}
\;\xrightleftharpoons{H^+}\;
\underset{\textbf{cyclic form (piranozic cycle)}}{H_2C\underset{CH_2-CH_2}{\overset{CH_2-O}{}}C\underset{H}{\overset{OH}{}}}
$$
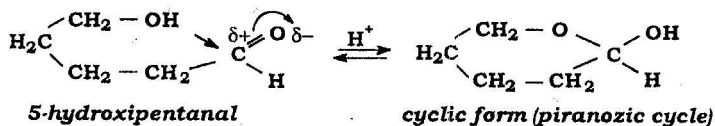
Acetal and hemiacetal are hydrolize in acid solution, but in base environment are stable.

The importance of acelatylation reactions:
1. In the acetal forms stranged for organism substances (phenoles) are leaded out;
2. The reaction is used to protect the aldehyde group;
3. In the hemiacetal forms existence monosaccharides and in acetal forms – polysaccharides.

## 3. Reaction of thiole with formation of thioacetals

By analogic mechanism thiole reacts with formation of hemiacetals and thioacetals

$$
R-C\overset{O}{\underset{H}{\diagup}} \;+\; R'-SH \longrightarrow R-\underset{H}{\overset{OH}{\underset{|}{C}}}-SR' \;\xrightarrow{+R'-SH}\; R-\underset{H}{\overset{SR'}{\underset{|}{C}}}-SR' \;+\; H_2O
$$
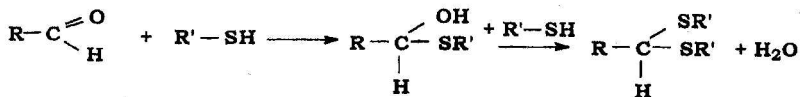
## 4.Condensation with ammonia derivatives

Certain derivatives of ammonia that contain the primary aminogroup, - $NH_2$, add to aldehydes and ketones to form unstable intermediates. The initial addition product loses the elements of water (condensation) to form a carbon – nitrogen double bond.

$$\underset{R}{\overset{R}{>}}C=O \ + \ H_2NR' \ \rightleftharpoons \ \underset{R}{\overset{R}{>}}C\underset{\underset{R'}{N}}{\overset{OH}{\diagup}}H \ \longrightarrow \ \underset{R}{\overset{R}{>}}C=N\diagdown_{R'} \ + \ H_2O$$

### *Mechanism:*

$$R-C\underset{R}{\overset{O}{\diagdown}} \ + \ \overset{H}{\underset{H}{:N-R'}} \ \xrightarrow{addition} \ \left[ R-\overset{\overset{\overset{\ominus}{O}}{|}}{\underset{\underset{H}{|}}{C}}-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N^{\oplus}}}-R' \right] \ \longrightarrow \ R-\overset{\overset{HO}{|}}{\underset{\underset{R}{|}}{C}}-\overset{\overset{H}{|}}{N}-R' \longrightarrow$$

$$\xrightarrow{loss \ H_2O} \ \underset{R}{\overset{R}{>}}C=N-R'$$

**Shiff base**
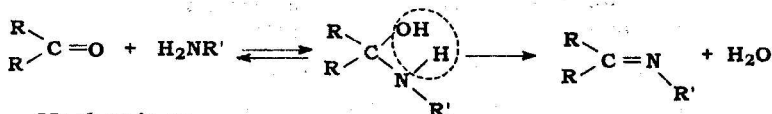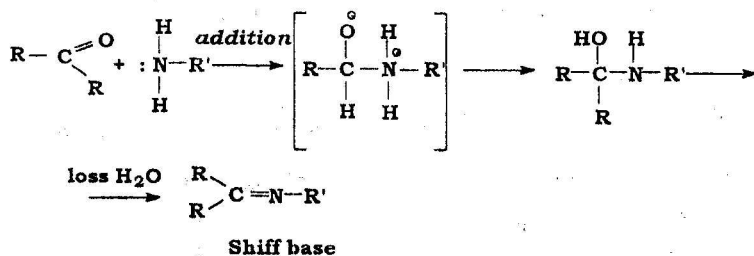
Formation and hydrolise of immine has importance for such a main processes as transamination and sinteses of new aminoacids.

$$R-\overset{\overset{H}{|}}{\underset{\underset{NH_2}{|}}{C}}-COOH \ + \ R'-\overset{\overset{O}{||}}{C}-COOH \ \xrightarrow{\underset{phosphate}{piridoxal}} \ R-\overset{\overset{O}{||}}{C}-COOH \ + \ R'-\overset{\overset{H}{|}}{\underset{\underset{NH_2}{|}}{C}}-COOH$$

$$R-\overset{\overset{H}{|}}{\underset{\underset{NH_2}{|}}{C}}-COOH \ + \ [\text{pyridoxal phosphate aldehyde}] \ \longrightarrow \ [\text{imine intermediate}] \ \longrightarrow$$

$$\longrightarrow \ R-\overset{\overset{O}{||}}{C}-COOH \ + \ [\text{pyridoxamine phosphate}]$$
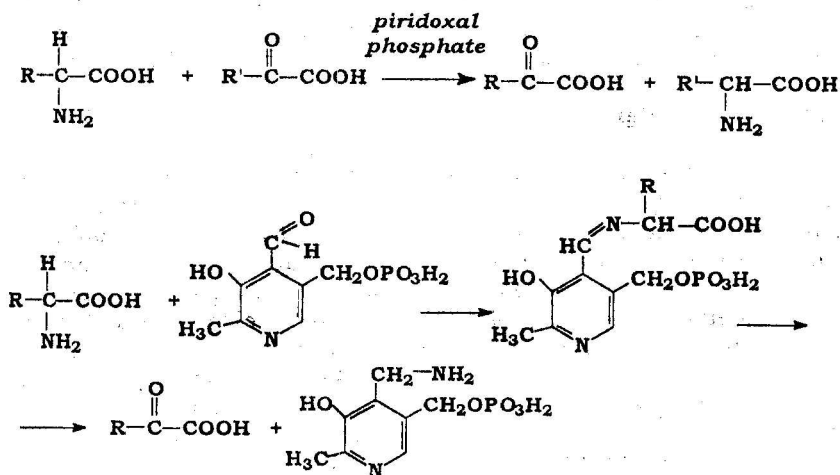
Many of these condensation generate a crystalline solids with sharp melting point. For this reason they frequently are employed for the preparation of aldehyde and ketone derivatives needed in identification work. Ammonia derivatives commonly used and their condensation products follow.

| carbonil compound | ammonia derivate | condensation product |
|---|---|---|

$$R-\overset{\overset{\textstyle R}{|}}{C}=O \;+\; \overset{\overset{\textstyle H}{\diagdown}}{\underset{\underset{\textstyle H}{\diagup}}{N}}-OH \;\xrightarrow{H^+}\; R-\overset{\overset{\textstyle R}{|}}{C}=N-OH \;+\; H_2O$$

*ketone*   *hydroxilamine*   *an oxime*

$$R-\overset{\overset{\textstyle R}{|}}{C}=O \;+\; \overset{\overset{\textstyle H}{\diagdown}}{\underset{\underset{\textstyle H}{\diagup}}{N}}-\overset{\overset{\textstyle H}{|}}{N}-C_6H_5 \;\xrightarrow{H^+}\; R-\overset{\overset{\textstyle R}{|}}{C}=N-\overset{\overset{\textstyle H}{|}}{N}-C_6H_5 \;+\; H_2O$$

*phenylhydrazine*   *phenylhydrazone*

$$R-\overset{\overset{\textstyle R}{|}}{C}=O+ \overset{\overset{\textstyle H}{\diagdown}}{\underset{\underset{\textstyle H}{\diagup}}{N}}-\overset{\overset{\textstyle H}{|}}{N}-\overset{\overset{\textstyle O}{\|}}{C}-NH_2 \;\xrightarrow{H+}\; R-\overset{\overset{\textstyle R}{|}}{C}=N-\overset{\overset{\textstyle H}{|}}{N}-\overset{\overset{\textstyle O}{\|}}{C}-NH_2 + H_2O$$

*semicarbazide*   *semicarbazone*
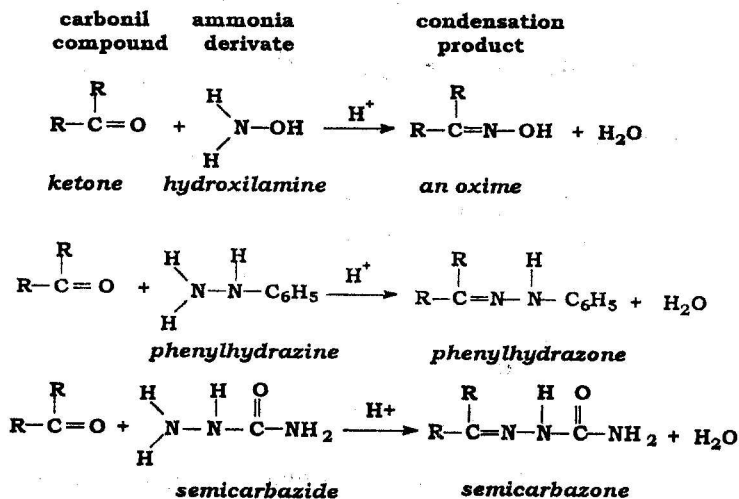
The carbonil derivatives formed in each case simply is designated as the aldoxime, the ketoxime, the phenylhydrazone or semicarbazone of the carbonyl compound from which it wasprepared.

## 5. The aldol condensation

In enolate ion the negative charge is largely on the more electronegtive oxygen atom, as is indicate by name, enolate. Thus enolate ion can and do behave as carbanions (carbons nucleophiles) in many reactions. When an enolate ion adds (as it were a carbanion) to another molecular of aldehyde or ketone, the reaction is called an aldol condensation. An aldol condensation involves aceltaldehyde reacting with it self in presence of a basic catalyst.

The reversibility of the aldol condensation is important in biological processes for it is involved in both the biosynthesis (anabolism) and degradation (catabolism) of carbohydrates, with enzymes called aldolases serving as the catalysts

**I** 

$$H-\overset{\underset{\displaystyle H}{|}}{\underset{\displaystyle H}{C}}-C=O \quad \rightleftharpoons \quad \left[ H-\overset{\underset{\displaystyle H}{|}}{\underset{\displaystyle \cdot\cdot}{C}}-C=O \quad \longleftrightarrow \quad H-C=C-\overset{..}{\underset{..}{O}}^{-} \right] + H_2O$$

$(:\overset{..}{O}H)^-$ **base**

**II** 

$$H-\overset{\underset{\displaystyle H}{|}}{\underset{\displaystyle H}{C}}-\overset{\delta-}{\underset{\delta+}{C}}=O \quad + \quad \left[ H-\overset{\underset{\displaystyle H}{|}}{\underset{\displaystyle \cdot\cdot}{C}}-C=O \right] \quad \rightleftharpoons \quad H_3C-\overset{H}{\underset{:\overset{..}{\underset{..}{O}}:}{C}}-CH_2-\overset{H}{C}=O$$

**III** 

$$H_3C-\overset{H}{\underset{:\overset{..}{\underset{..}{O}}:}{C}}-CH_2-\overset{H}{C}=O \quad + \quad H_2O \quad \rightleftharpoons \quad H_3C-\overset{H}{\underset{OH}{C}}-CH_2-\overset{H}{C}=O \quad + \quad OH^-$$

*aldol*
*(3 – hydroxibutanal)*
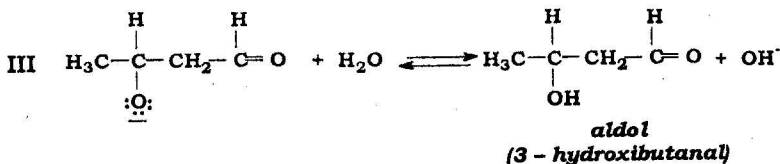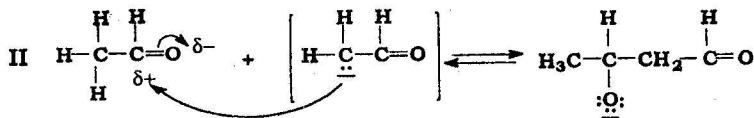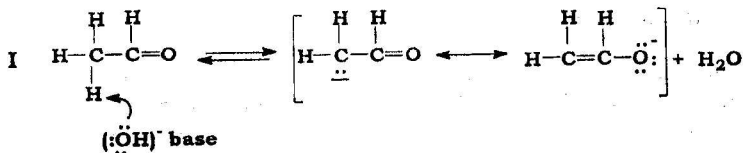
These reactions have biological importance. For example formation of citric acid in the cycle of threecarbonic acids:



*product of aldol*
*addition*

*acid citric*

An other example:



*gliceraldehyde*
*3·phosphate*

*dioxyacetone*
*3·phosphate*
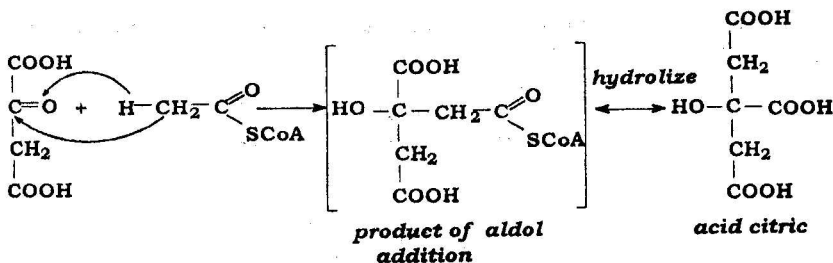
*fructozo-1,6*
*-diphosphate*
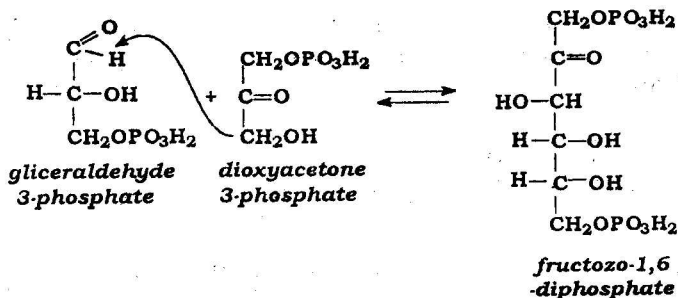
# 6.Oxidation and reduction

Aldehydes are so easy oxidized that even the mildest of oxidizing reagents will serve to bring about their conversing to acids.

Tollens' reagent (an ammoniacal solution of silver oxide)

$$R-\overset{\overset{\displaystyle H}{|}}{C}=O \ + \ 2 Ag(NH_3)_2OH \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-O-NH_4^+ + 2Ag^+ + H_2O + 3NH_3$$
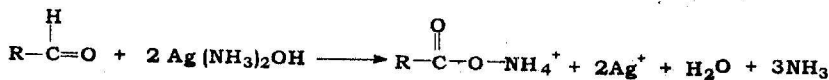
Fehling's solution, an alkaline solution of cupric ion complexed with sodium potassium tartrate (Rochelle salt).

$$R-\overset{\overset{\displaystyle H}{|}}{C}=O \ + \ 2Cu(OH)_2 \ + \ NaOH \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-ONa^+ + Cu_2O + 3H_2O$$

The oxidation of ketones, when forced by the use of strong oxidizing reagents and heat, results in rupture of carbon-carbon bonds to produce acids.

$$CH_3-\overset{\overset{\displaystyle}{\underset{\underset{\displaystyle O}{\|}}{C}}}{}-C_3H_7 \ \xrightarrow{[O]} HCOOH \ + C_3H_7COOH \ + CH_3COOH \ + C_2H_5COOH$$
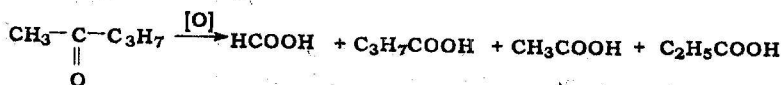
The carbonil group of aldehydes and ketones may be reduced to primary and secondary alcohols, respectively.

$$R-\overset{\overset{\displaystyle H}{|}}{C}=O \ + \ 2H_2 \xrightarrow[\text{pressure}]{\text{Pt or Ni}} R-CH_2-OH$$

$$R-\overset{\overset{\displaystyle R}{|}}{C}=O \xrightarrow{LiAlH_4} R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-OH$$
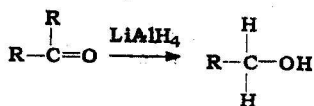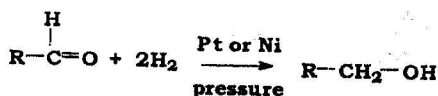
This transformation can be accomplished either catalytically with hydrogen or by means of a chemical-reducing agent such as lithium hydride:

$$4 CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-H \ + \ LiAlH_4 \longrightarrow \left( CH_3-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-H \right)_4 AlLi \xrightarrow{H_2O}$$

$$\longrightarrow 4 CH_3-CH_2-OH \ + \ LiOH \ + \ Al(OH)_3$$

## Mechanism:

$$CH_3-C\overset{O}{\underset{H}{\big\backslash}} + H^-\ Li^+ \longrightarrow CH_3-C\overset{O^-\ Li^+}{\underset{H}{\big\langle}}H \xrightarrow{HOH} CH_3-CH_2-OH + LiOH$$
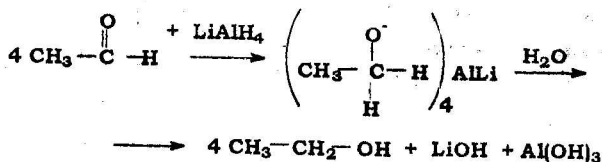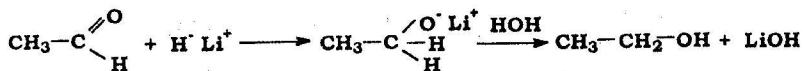
One of examples of oxido – reduction systems is NAD$^+$/NADH+H$^+$ abbr. For nicotinamide-adenine dinucleotide which is known in oxidate we and reduce forms.

# REACTIONS OF NUCLEOPHILIC SUBSTITUTIONS
## OF SP² – HYBRIDIZED CARBON ATOM
### (CARBOXILIC ACIDS AND THEIR DERIVATIVES)

Previosly was discussed, that carboxylic acids have high acidity. Suppleness of hydrogen atom of hydroxyl group increased because of – M effect of carbonil group. In the same time electrophility of carbonyl carbon decreased because of +M effect of hydroxyl group:

$$R-C\overset{\delta-}{\underset{\underset{\cdot\cdot}{OH}}{\overset{\delta+}{O}}} + H_2O \longrightarrow R-C\overset{\delta-}{\underset{O^-}{\overset{\delta+}{O}}} + H_3O^+$$

Carboxylic acids differ from alcohols with a higher acidity, but from aldehydes and ketones differ with a lawer ability to add substitutents at carbonilyc group.

## Examples of such carboxilic acids

1. Monocarbonic acids:

saturated:  $HC\overset{O}{\underset{OH}{}}$   $H_3C-C\overset{O}{\underset{OH}{}}$   $H_3C-CH_2-C\overset{O}{\underset{OH}{}}$ **and s.on**

unsaturated: $CH_2 = CH – COOH$, $CH_3 – CH = CH – COOH$ **and s.on**
        *acrilyc acid*

2. Dicarboxilic acids:
saturated:   $HOOC – COOH$, $HOOC – CH_2 – COOH$, $HOOC – (CH_2)_2 – COOH$
        *oxalic acid      malonic acid       succinic acid*
unsaturated:   $HOOC – CH = CH – COOH$
        *fumaric acid (trans form)  and  maleic (cis form)*

3. Aromatic acids:

—COOH

4. Heterocyclic acids:

—COOH

One of the main property is formation of salts:

$$CH_3-C\overset{O}{\underset{OH}{}} + NaOH \longrightarrow CH_3-C\overset{O}{\underset{ONa}{}} + H_2O$$

$Na^+$, $K^+$, $NH_4^+$ $\longrightarrow$   soluble salts;  $Cu^{2+}$, $Pb^{2+}$ $\longrightarrow$ unsoluble salts

## Functional derivatives of carboxylic acids

$$R-C\overset{O}{\underset{Cl}{\big\langle}}$$  **chloranhydrate**

$$R-C\overset{O}{\underset{O}{\big\langle}}\overset{O}{\underset{}{\big\rangle}}C-R$$  **anhydrate**

$$R-C\overset{O}{\underset{O-R'}{\big\langle}}$$  **esthers**

$$R-C\overset{O}{\underset{NH_2}{\big\langle}}$$  **amides**
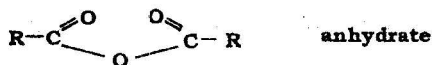
All this compounds containe acylic group $R-C\overset{O}{\diagup}$ and are obtained in the results of nucleophilic substitution -OH group on $Cl^-$ ,$R-COO^-$, $NH_2^-$, or $OR$ therefore such reactions are called reaction of acylation.

## Mechanism:

$$R-C\overset{O}{\underset{X}{\big\langle}} + Nu^- \rightleftharpoons R-\overset{O^-}{\underset{X}{\overset{\mid}{C}}}\to Nu \rightleftharpoons R-C\overset{O}{\underset{Nu}{\big\langle}} + X^-$$
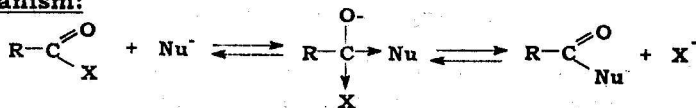
Reaction takes place in the presence of strong nucleophilic and fast lossing group X or in condition of acide catalyze. Lust increased electrophility of carbonil group.

$$R-C\overset{O}{\underset{X}{\big\langle}} \overset{H^+}{\rightleftharpoons} R-\overset{+}{C}\overset{OH}{\underset{X}{\big\langle}} \overset{Nu^-}{\rightleftharpoons} R-\overset{OH}{\underset{X}{\overset{\uparrow}{C}}}\to Nu \rightleftharpoons R-C\overset{O}{\underset{Nu}{\big\langle}} + X^- + H^+$$
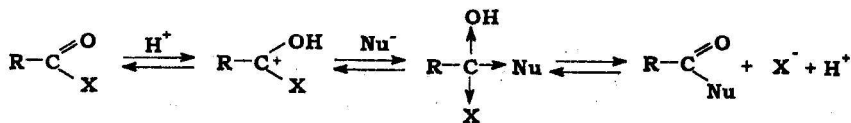
Reaction ability of functional group decreased in follow order:

$$R-C\overset{O}{\underset{Cl}{\big\langle}} > R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R > R-C\overset{O}{\underset{OH}{\big\langle}} > R-C\overset{O}{\underset{O-R'}{\big\langle}} > R-C\overset{O}{\underset{NH_2}{\big\langle}}$$

$$Cl^- \qquad R-\overset{O}{\overset{\|}{C}}-\overset{-}{O} \qquad \underset{\substack{fast\ lossing \\ of\ group\ in \\ acid\ solution}}{OH^-} \qquad \underset{\substack{slow\ leaving \\ of\ group}}{^-OR} \overset{}{\longleftarrow} NH_2^-$$
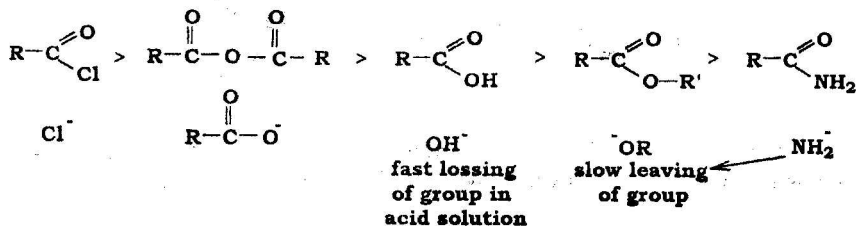
Reaction of obtain and hydrolyze of functional derivatives of carbonic acids are the reactions of nucleophylic substitutions and acylation.

## Halogen anhydrate (acetyl chloride).

It was obtained by the action of halogenides on carbonic acids, for example:

$$CH_3-C\overset{O}{\underset{OH}{}} + PCl_3 \longrightarrow 3\ CH_3-C\overset{O}{\underset{Cl}{}} + H_3PO_3$$
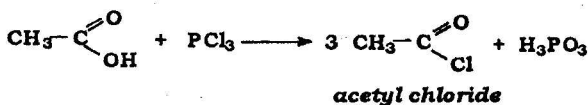
*acetyl chloride*

Acetyl chloride easy hydrolised with formation of acids:

$$CH_3-C\overset{O}{\underset{Cl}{}} + HOH \longrightarrow CH_3-C\overset{O}{\underset{OH}{}} + HCl$$
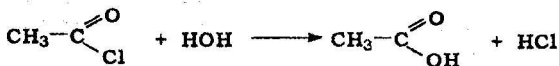
## Anhydrides of carbonic acids

The preparation of an acid anhydride is a reaction that has the net effect of removing a molecule of water from between two molecules of the acid.

$$CH_3-C\overset{O}{\underset{\boxed{OH}}{}} + \overset{O}{\underset{\boxed{HO}}{}}C-CH_3 \longrightarrow \begin{matrix} CH_3-C\overset{O}{\underset{O}{}} \\ CH_3-C\overset{}{\underset{O}{}} \end{matrix} + H_2O$$
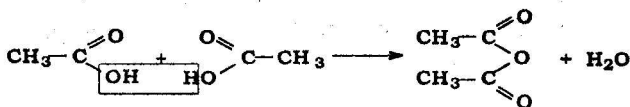
Direct dehydratation, howerer, is seldom practiced dehydratation usually is accomplished indirectly by reaction between the sodium salt of the acid with its acid chloride:

$$CH_3-C\overset{O}{\underset{\boxed{Cl}}{}} + \overset{O}{\underset{\boxed{Na}}{}}O-C-CH_3 \longrightarrow \begin{matrix} CH_3-C\overset{O}{\underset{O}{}} \\ CH_3-C\overset{}{\underset{O}{}} \end{matrix} + NaCl$$
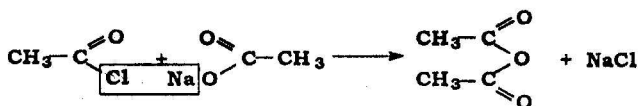
One's of anhydrides obtained by heating of carbonic acids. Especially easy were obtained cyclic anhydrides.

**succinic acid**        **succinic anhydride**
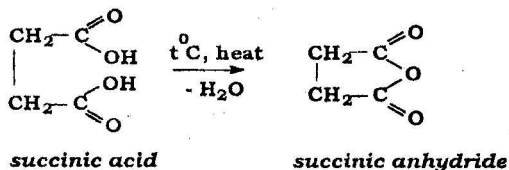
Oxalic acid, when strongly heated, undergoes decomposition accordind to the following equation



$$\text{HCOOH} + CO_2 \longrightarrow H_2O + CO + CO_2$$
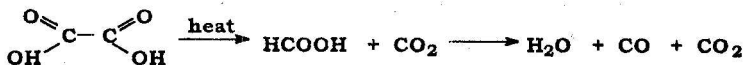
Malonic acid is so easily decomposed by heat that it is decarboxylated at the melting point (137°C)



$$\longrightarrow CH_3-COOH + CO_2$$
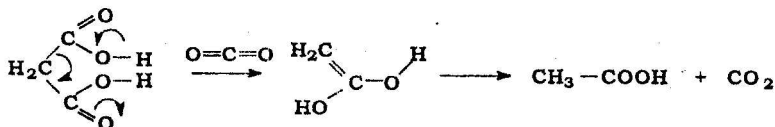
The important meaning have mixed anhydrides of carbonic and mineral acids.
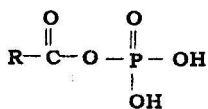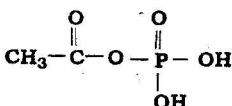


**acylphosphate**     **acetylphosphate**     **substitutional acylphosphate**
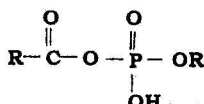
Acylphosphates are the natural metabolits that participate in the reactions of acylation alcohols, thiols, amines:
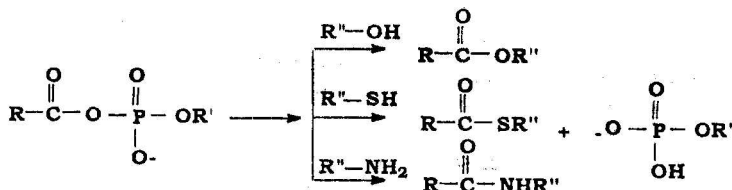
# Preparation of esters

The reaction of an acid with an alcohol in the presence of a mineral acid catalyst produces an ester. A direct esterification of alcohols and acids in this manner is known as a Fischer esterification.

$$R-\overset{\displaystyle O}{\underset{\displaystyle OH}{C}} + R'-OH \underset{}{\overset{H^+}{\rightleftharpoons}} R-\overset{\displaystyle O}{\underset{\displaystyle \parallel}{C}}-OR' + H_2O$$

$$CH_3-\overset{\displaystyle O}{\underset{\displaystyle OH}{C}} + C_2H_5-OH \underset{}{\overset{H^+}{\rightleftharpoons}} CH_3-\overset{\displaystyle O}{\underset{\displaystyle \parallel}{C}}-OC_2H_5 + H_2O$$
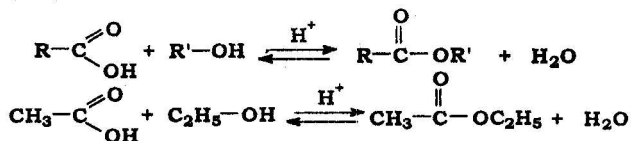
Mechanism presents the tipical reaction of nucleophylic acylation substitution - $S_N$
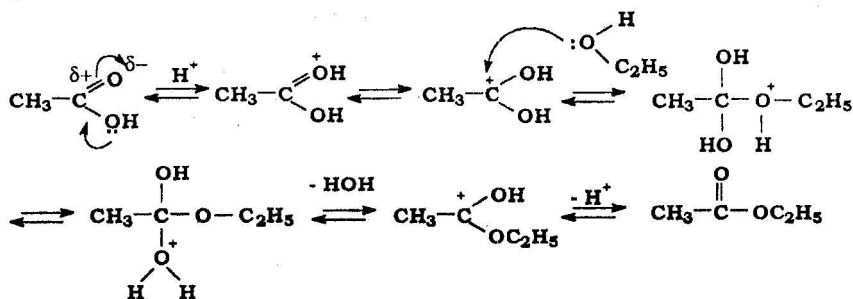


Reaction in acid medium is irreversible, hydrolyse of ethylacetate in acid medium:
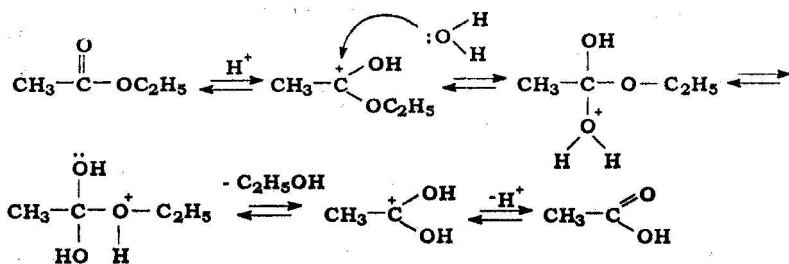


Reaction of hidrolisation base-medium is unreversible.

$$CH_3-\overset{\displaystyle O}{\underset{\displaystyle OC_2H_5}{C}} + NaOH \longrightarrow CH_3-\overset{\displaystyle O}{\underset{\displaystyle ONa}{C}} + C_2H_5OH$$

The important meaning has thioesters of carbonic acids. For example:

acetyl CoA ( $CH_3-C\overset{O}{\underset{SCoA}{\diagup}}$ ), which is formed in result of splitting acetylphosphate.

$$CH_3-\overset{O}{\overset{\|}{C}}-O-\underset{\underset{OH}{|}}{\overset{O}{\overset{\|}{P}}}-OR' + HSCoA \longrightarrow CH_3-C\overset{O}{\underset{SCoA}{\diagup}} + HO-\underset{\underset{O-}{|}}{\overset{O}{\overset{\|}{P}}}-OR'$$
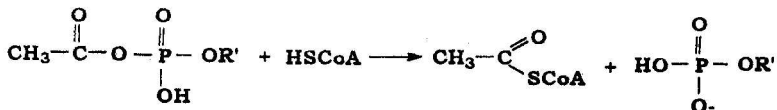
With helping of this reaction choline transferes in acetyl choline, the important nervos mediator

## Formation and hydrolysation of amides.

Amides of carbonic acids are formed by acylation of ammonias or amines with helping acyl halides, anhydrides, esters or carbonic acids:

1.  $R-C\overset{O}{\underset{Cl}{\diagup}} + 2NH_3 \longrightarrow R-C\overset{O}{\underset{NH_2}{\diagup}} + NH_4Cl$

2.  $R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R + NH_3 \longrightarrow R-C\overset{O}{\underset{NH_2}{\diagup}} + R-COOH$

3.  $R-C\overset{O}{\underset{O-R'}{\diagup}} + NH_3 \longrightarrow R-C\overset{O}{\underset{NH_2}{\diagup}} + R-OH$

4.  $R-C\overset{O}{\underset{OH}{\diagup}} + NH_3 \longrightarrow R-C\overset{O}{\underset{ONH_4}{\diagup}} \overset{t^o}{\longrightarrow} R-C\overset{O}{\underset{NH_2}{\diagup}} + H_2O$

All reactions possess mechanism of nucleophylic substitution

$$R-C\overset{O}{\underset{Cl}{\diagup}} + :N\overset{H}{\underset{H}{\diagdown}}-H \longrightarrow R-\underset{\underset{Cl}{\downarrow}}{\overset{\overset{O^-}{|}}{C}}\overset{+}{\underset{H}{\overset{H}{-}}}N-H \overset{NH_3}{\longrightarrow} R-C\overset{O}{\underset{NH_2}{\diagup}} + NH_4Cl$$
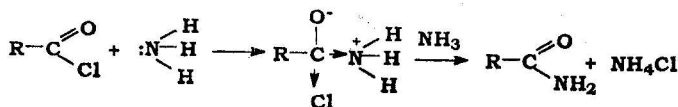
The amides can be hydrolysed in acid or in alcaline solution. Hydrolysis carried out in an acid solution produces the free organic acid and an ammonium salt. Hydrolysis carried out in a basic solution produces the free base (NH₃) and salt of the organic acid. Both types of procedures are illustrated by the following reaction equations.
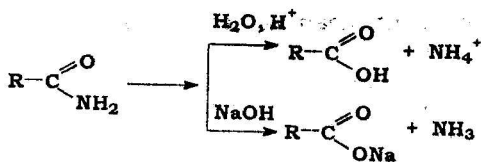
Mechanism of nucleophylic substitutions are shown below:

1. Acid hydrolysis
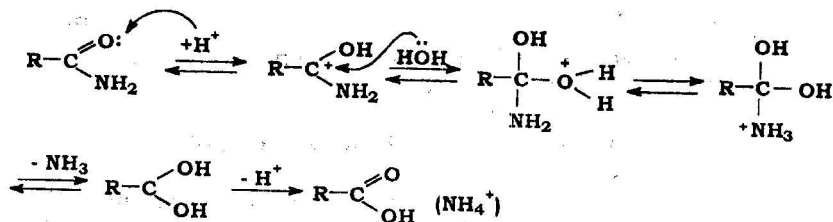


2. Alcaline hydrolysis
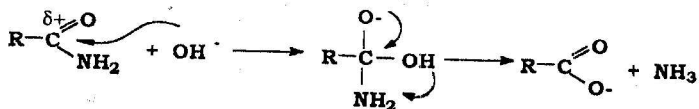


## The **Claisen** condensation

The $\alpha$ - hydrogen atoms of an ester such as ethyl acetate are sufficiently acidic to react with a strong base such as sodium ethoxide to produce the ester enolite anion. The ester anion is strong nucleophile, which then may attack the carbonyl carbon atom of a second ester molecule. Elimination of ethoxide ion results in the formation of $\beta$ - keto ester, ethyl acetoacetate in the case of ethyl acetate. The reaction, illustrated in the following sequence, is called Claisen condensation.

$$C_2H_5O^- + H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-C\overset{\displaystyle O}{\underset{\displaystyle OC_2H_5}{\big\langle}} \; \rightleftharpoons \; C_2H_5OH + \left[ :CH_2-C\overset{\displaystyle O}{\underset{\displaystyle OC_2H_5}{\big\langle}} \;\longleftrightarrow\; CH_2=C\overset{\displaystyle \ddot{O}:^-}{\underset{\displaystyle OC_2H_5}{\big\langle}} \right]$$

**ester enolate anion**

$$CH_3-\overset{\overset{\displaystyle \delta+\;\ddot{O}:\;\;\delta-}{}}{C}\overset{}{\underset{\displaystyle OC_2H_5}{\big\langle}} \;+\; \Big|\; :CH_2-C\overset{\displaystyle O}{\underset{\displaystyle OC_2H_5}{\big\langle}} \;\rightleftharpoons\; CH_3-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OC_2H_5}{|}}{C}}-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle OC_2H_5}{\big\langle}}$$

$$CH_3-\overset{\overset{\displaystyle :\ddot{O}:^-}{|}}{\underset{\underset{\displaystyle OC_2H_5}{|}}{C}}-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle OC_2H_5}{\big\langle}} \;\rightleftharpoons\; C_2H_5O^- \;+\; CH_3\overset{\displaystyle O}{\overset{\|}{C}}-CH_2\overset{\displaystyle O}{\overset{\|}{C}}-OC_2H_5$$
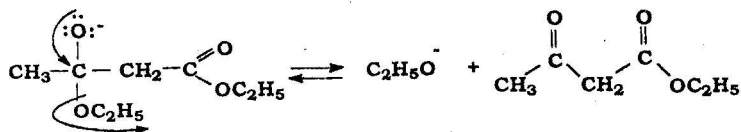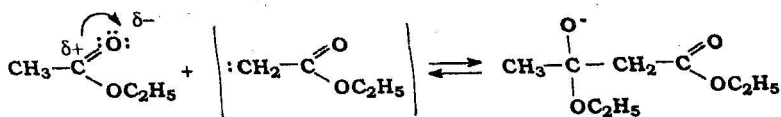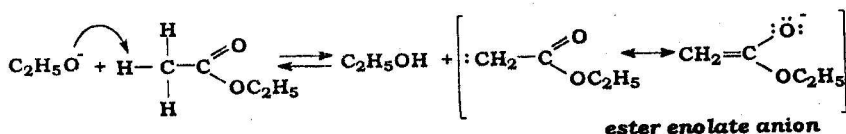
Such is the mechanism of citric acid formation:

$$\begin{array}{c} COOH \\ | \\ C=O \\ | \\ CH_2 \\ | \\ COOH \end{array} \;+\; CH_3-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}} \;+\; H_2O \;\longrightarrow\; \begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ HO-C-COOH \\ | \\ CH_2 \\ | \\ COOH \end{array} \;+\; HSCoA$$
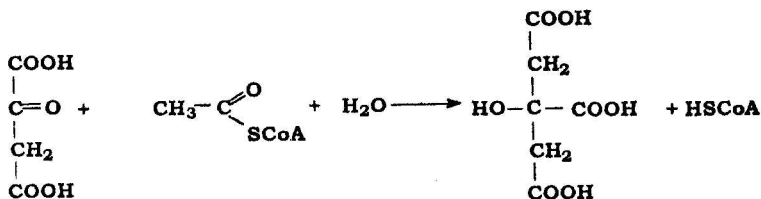
Another example of biological important reactions are the following:

$$CH_3-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}} \;+\; CH_3-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}} \;\longrightarrow\; CH_3-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle SCoA}{|}}{C}}-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}} \;\longrightarrow$$

$$\longrightarrow\; CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}} \;+\; HSCoA$$
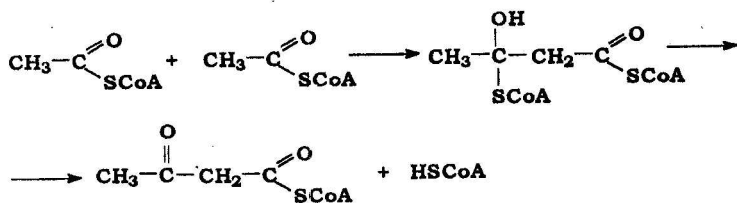
Formation of malonil CoA

$$O=C=O \;+\; CH_3-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}} \;\longrightarrow\; HOOC-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{\big\langle}}$$

Thioesters used for extention of carbon's chain. Splitting of β - keto esters by attack of alkaline (or acids).

1.

$$CH_3-\overset{O}{\underset{\|}{C}}-CH_2-C\overset{O}{\underset{OC_2H_5}{\diagup}} + H_2O \longrightarrow CH_3-\overset{O}{\underset{\|}{C}}-CH_2-C\overset{O}{\underset{OH}{\diagup}} + C_2H_5OH$$

$$\Big\downarrow - CO_2$$

$$CH_3-\overset{O}{\underset{\|}{C}}-CH_3$$

2. On heat with alcaline carried out an acid's splitting

$$CH_3-\overset{O}{\underset{\|}{C}}-CH_2-C\overset{O}{\underset{OC_2H_5}{\diagup}} \xrightarrow{+ 2 \text{ KOH}} CH_3-\overset{O}{\underset{\|}{C}}-OK + CH_3-\overset{O}{\underset{\|}{C}}-OK + C_2H_5OH$$
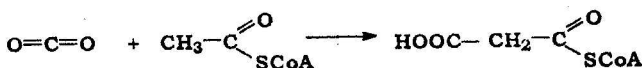
# STRUCTURE, CLASSIFICATION AND PROPERTIES OF LIPIDS

Natural products that are soluble in ether, chloroform, carbon tetrachloride and other and insoluble water, are known as *lipids*. The lipids are important constituents of all plant and animal tissue. About 40 – 50% of most membranes is composed of lipids of various types. The saponifiable lipids derived from the fatty acids: the fats, oils and waxes.

The important biochemical regulators, the prostaglandin's, as well as the phospholipids, are also derived from the fatty acids and are included in our discussion. In addition to the fats and oils (complex lipids) there are other water insoluble natural substances – the steroids, hormones, and fat – soluble vitamins.

Simples lipids consist from two components. Compose lipids consist more than two components on hydrolyses.

Waxes – simple lipids, are esters of long – chain "fatty" alcohol's. Both the acid and the alcohol's that combine to form wax may be sixteen to thirty carbons in length. The general formula of a wax is essentially that of a simple ester,

$$R-C\underset{O-R'}{\overset{O}{\diagdown}}$$
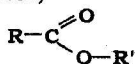
Both, plants and animals produce natural waxes. The waxes melt over a wide range of temperature (35 – 100°C), have a satiny "waxy" feel, and are very insoluble in water. Wax solution generally are used as protective coatings. They are often protective coatings in nature, too.

## STRUCTURE AND COMPOSITION OF FATS AND OILS

Fats differ from waxes in that they are glycerides, or esters of glycerol, trihydroxy alcohol.

$$R-\overset{O}{\overset{\|}{C}}-O-\begin{array}{l} CH_2-O-\overset{O}{\overset{\|}{C}}-R \\ CH \\ CH_2-O-\overset{O}{\overset{\|}{C}}-R \end{array}$$
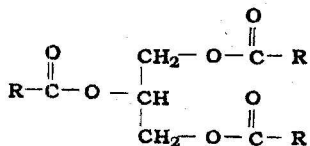
A simple glyceride is one in which all R groups in the previous general formula are identical. If R represents an aliphatic group $C_nH_{2n+1}$, such chains are saturated. It R is an unsaturated alkyl group $C_nH_{2n-1}$, $C_nH_{2n-3}$ or $C_nH_{2n-5}$, then n usually is 17.

The natural fats and oils usually are not simple glycerides. The three acid residues produced on hydrolyse usually vary not only in length, but also in degree of unsaturation.

The fats are glyceryl esters in which longchain saturated acid components predominate. They are animal products.

$C_{11}H_{23}COOH$ - lauric acid
$C_{13}H_{27}COOH$ - myristic acid
$C_{15}H_{31}COOH$ - palmitic acid
$C_{17}H_{35}COOH$ - stearic acid
$C_{19}H_{39}COOH$ - arachidic acid

The formulas of unsaturated acids
$C_{15}H_{29}COOH$ - palmitooleic acid
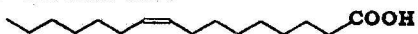


$C_{17}H_{33}COOH$ - oleic acid
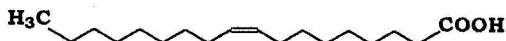


$C_{17}H_{31}COOH$ - linoleic acid
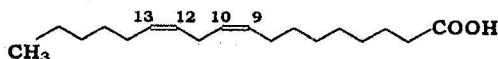


$C_{17}H_{29}COOH$ - lanolenic acid
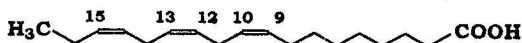


$C_{19}H_{31}COOH$ - arachidonic acid
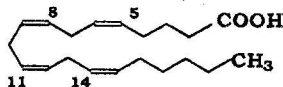


It is well known the process of biosynthesis of fatty acids, which takes place in the citozole of the cell from acetyl CoA. Acetyl CoA enters in reaction with malonil CoA by following the successive reactions:

NADPH$_2$ NADP$^+$    OH

$$CH_3-\underset{\underset{}{|}}{CH}-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{}} \xrightarrow{- H_2O} CH_3-CH=CH-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{}} \longrightarrow$$

NADPH$_2$ NADP$^+$

$$CH_3-CH_2-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{}}$$

*butiril CoA*
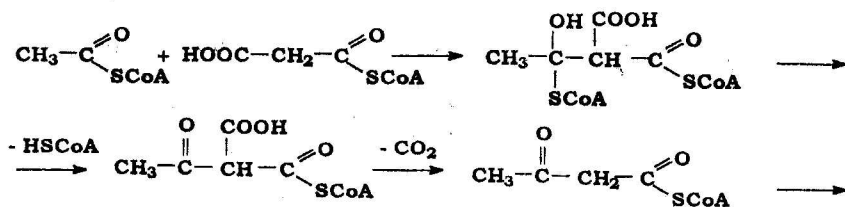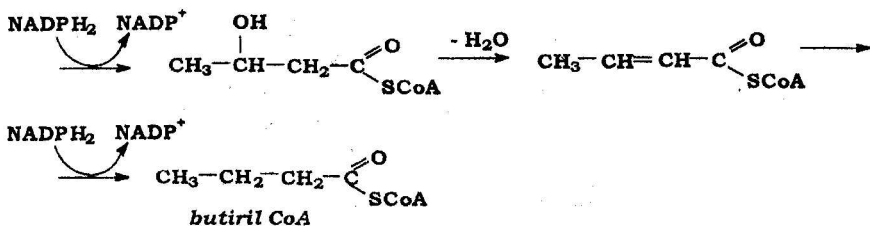
Then the reactions repet. The summary reaction of synthesis of palmitic acid:

$$CH_3-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{}} + 7\ HOOC-CH_2-C\overset{\displaystyle O}{\underset{\displaystyle SCoA}{}} + 14\ NADPH_2 \longrightarrow$$

$$\longrightarrow C_{15}H_{31}COOH + 7\ CO_2 + 8\ HSCoA + 14\ NADP^+ + 6\ H_2O$$
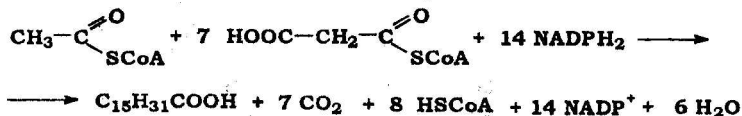
## β-Oxidation of fatty acids

β-Oxidation of fatty acids takes place in mitocondrial matrix the gell-like material, with considerable fine structure, that lies in the matrix space of a mitochondrion. It contains the enzymes concerned with fatty-acid oxidation and enzymes of tricarboxilic acid cycle.

Inspection of the acyl-CoA molecule and consideration of the biochemical reaction types available shows that the only reasonable mode of further attack is oxidation by a flavoprotein to remove hydrogens from α and β positions (Eq.a). One of the few possible reactions of the unsaturated compound so formed is nucleophilic addition at the β-position. Water is added (Eq.b) and the resulting alcohol is oxidized to a ketone by NAD$^+$ (Eq.c). This series of three reactions is the well-known β-oxidation sequence. Figure 1 also shows another β-oxidation sequence that converts succinic acid to oxaloacetic acid within the citric acid cycle.
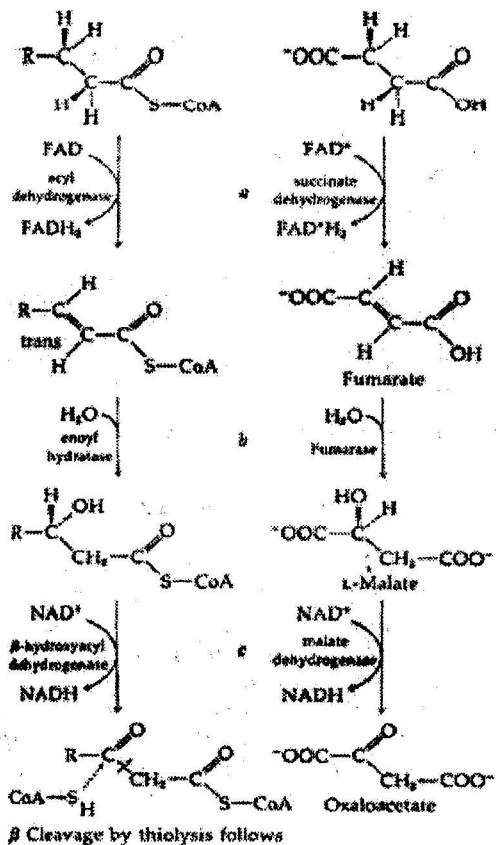
**Figure 1:** Reactions of the β-oxidation sequence. Left: oxidation of CoA derivatives of fatty acids; right: oxidation of succinate in cycle of tricarboxilic acids.

## Oxidation of fatty acids in peroxisomes

Fatty acids can be oxidation not only in mitochondrion, but in peroxisomes, too. Peroxisomes are a type of microbody that is rich in enzymes that act or generate hydrogen peroxide.

Peroxisomal oxidation differs from mitochondrial oxidation by reaction of oxidation acyl- CoA in enoilCoA. This reaction in peroxisomes is catalyses by acyl CoA oxidase:

$$R - (CH_2)n - CH_2 - CH_2 - CO \sim S - CoA$$
*acyl CoA*

*acyl CoA oxidaza* $\qquad$ $O_2$

$\qquad$ $H_2O_2$

$$R - (CH_2)n - CH = CH - CO \sim S - CoA$$
*enoil-CoA*
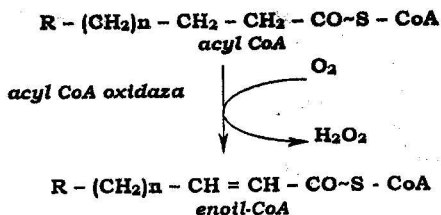
Then hydrogen peroxide disintegrates by catalase:

$$2\ H_2O_2 \xrightarrow{catalase} 2\ H_2O\ +\ O_2$$
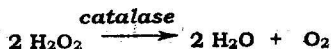
Peroxisomal fatty-acids oxidation increases by influences of different facts: dietics, hormonous, drugs.

## Phospholipids

Phospholipids are glycerides in wich two of the hydroxil groups are esterified

$$
\begin{array}{l}
\quad\quad O \\
\quad\quad \| \\
R - C - O - CH_2 \\
\quad\quad O \\
\quad\quad \| \\
R - C - O - CH \\
\\
\quad\quad\quad\quad\quad\quad O \\
\quad\quad\quad\quad\quad\quad \| \\
\quad\quad CH_2 - O - P - OH \\
\quad\quad\quad\quad\quad\quad | \\
\quad\quad\quad\quad\quad\quad OH
\end{array}
$$
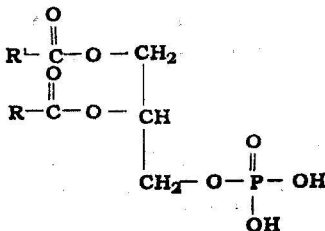
The free phosphatidic acid is seldom found in nature because the phosphoric acid portion still functions as an acid and usually is esterified to another alcohol.
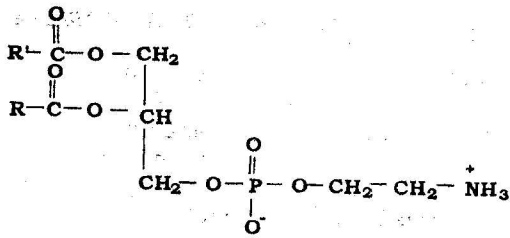
**phosphatidyl ethanolamine**
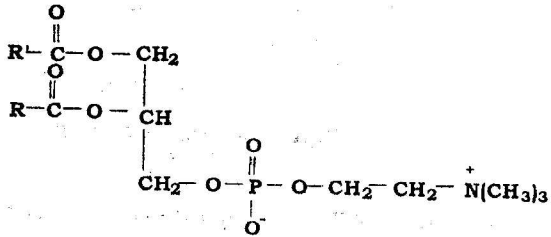
**phosphatidyl choline (a lecithin)**
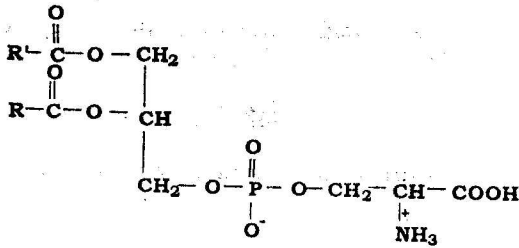
**phosphatidyl serine**

water

water

**Figure 2:** Phosfolipids in compozition of celular's membranes

65
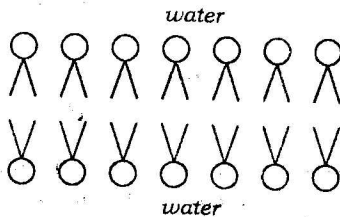
As can be seen from their structures, the ethanolamine and choline esters are salts and not unlike some of the detergent and soap molecules, also have a long hydrocarbon nonpolar taie and a polar head. In contact with water the phosphatidic acid esters, like soaps, arrange themselves with the polar head seeking the aqueons environment and the nonpolar tails aligning themselves to form a bilayer (see Figure 2). The bilayers of phospholipids make up the framework of cell membranes and play important roles in the chemistry of living systems.

Phospholipids form a significant portion of cell membranes. (Figure 3)



protein loosely attached to membrane surface

proteins embedded in membrane
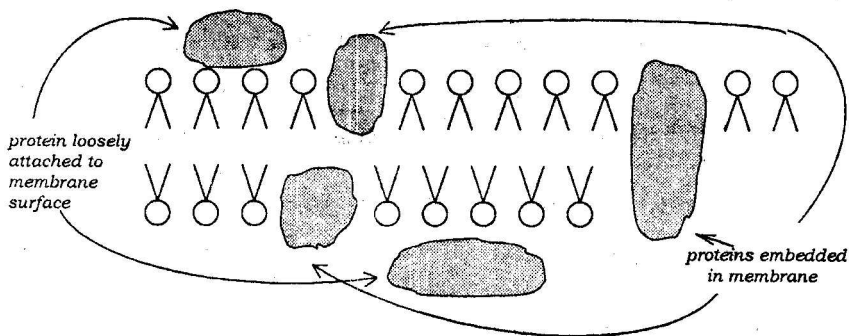
**Figure 3** A reprezentation of a cell membrane consisting of proteins imbeded in a bilayer of phospholipids that are oriented with their polar heads outward

Figure 3 shows a cell membrane in the form of a phospholipid bilayer with proteines distribuited in it. The cell membrane must first protect the workings of the cell from the extracelular fluid's that bathe in it. Its second function is to allow nutrients and other necessary chemicals to enter the cell while allowing waste products to leave the cell. The detailed operation of the membrane is very complex and not well understood; however, according to the most widely accepted model, called the fluid mosaic model, same small uncharged molecules such as water, oxygen, and carbon dioxide diffuse freely through the lipid bilayer, white other substances pass through.

"Gates and passages" provided by specific proteins imbedded in the membrane. The proteins in the membrane also provide the means for communication between cells, with hormones and other messenger molecules.

## Sphingolipids

Like phosphoglycerides, sphingophospholipids contain a phosphate group and coline. However, there is a substantial difference because sphingophospholipids contain a long-chain unsaturated amino alcohols called sphinosine rather than glycerol.

$$CH_3 - (CH_2)_{12} - \overset{\overset{\displaystyle H}{|}}{C} = \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle H}{|}}{C}} - \overset{\displaystyle C}{\underset{\underset{\displaystyle H_2N - \overset{\displaystyle C}{\underset{\underset{\displaystyle CH_2 - OH}{|}}{|}} - H}{|}}} - H$$

*sphingosine*

$$CH_3 - (CH_2)_{12} - \overset{\overset{\displaystyle H}{|}}{C} = \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle H}{|}}{C}} - C - H$$

$$CH_3 - (CH_2)_{16} - \underset{\underset{\displaystyle O}{\|}}{C} - \underset{\underset{\displaystyle H}{|}}{N} - \overset{\displaystyle C}{\underset{\underset{\displaystyle CH_2 - OH}{|}}{|}} - H$$

_____
*fatty acid*   *a ceramide*

$$CH_3 - (CH_2)_{12} - \overset{\overset{\displaystyle H}{|}}{C} = \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle H}{|}}{C}} - C - H$$

$$CH_3 - (CH_2)_{16} - \underset{\underset{\displaystyle O}{\|}}{C} - \underset{\underset{\displaystyle H}{|}}{N} - \overset{\displaystyle C}{\underset{\underset{\displaystyle CH_2 - O}{|}}{|}} - H \quad \underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}} - O - CH_2 - CH_2 - N^+(CH_3)_3$$

_____       _____
*fatty acid*         *choline*

*a sphingophospholipid*
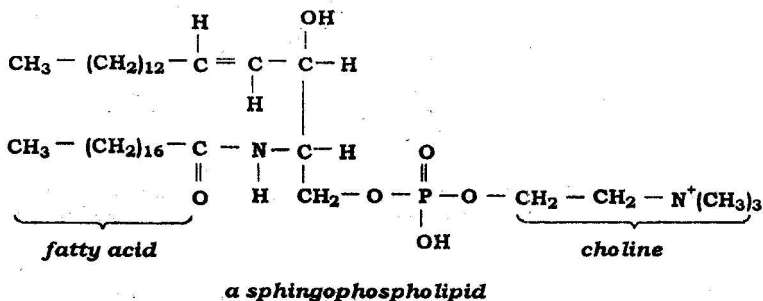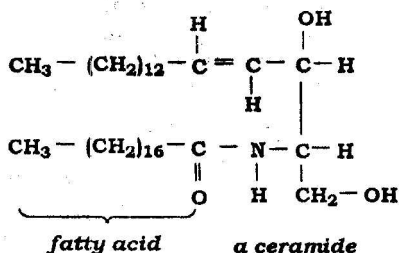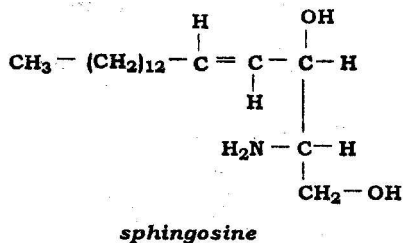
Conversion of amine of sphingosine into an amide with a fatty acid yields a ceramide. Esterification of the primary alcohol of ceramide with phosphoric acid and choline results in sphingolipid.

By comparing the structure of sphingophospholipid to phosphoglyceride we see that dispiteing the components are different, the overall structures are similar. Both compounds consist of a polar head and two nonpolar tails. However, chemically there are significant differences between the two types of compounds. Sphingophospholipids, which have a single amide group, are more stable to hydrolysis than phosphoglycerides, which have two carboxylic esters.

Sphingomyelins, compounds found in the myelin sheath surrounding nerve fibers, are sphingophospholipids. Sphingomyelins have acid residues that are 20-26 carbon atoms long. These long chains interwine and wrap around each other to form a very stable

coat for the sensitive nerve fibers. In individuals with some genetic diseases, the carbon chains are shoter and defect result in the myelin sheath. Gaucher's disease, Nimann-Pick disease, multiple sclerosis, and leukodystrophy are all the result of unstable myelin membranes.

## Glycosphingolipids

Glycosphingolipids are similar to sphingophospholipids since they contain sphingosine and fatty acid residue bonded as an amide in a ceramide. However, glycosphingolipids contain no phosphate. A carbonhydrate is bonded via a glycosilic linkage to the primary alcohol oxygen atom of the ceramide.



_Cerebrosides_ and gangliosides are two of the several types of glycosphingolipids. Cerebrosides usually contain only glucose or galactose, whereas gangliosides contain an oligosaccharide. Both are found in the myeline sheath. In addition, cerebrosides are in the white matter of brain, whereas gangliosides occur in the gray matter.

_Gangliosides_ are synthesized or degraded by sequential addition or removal of monosaccharide units. Tay-Sachs disease is a genetic disease that results from the abnormal accumulation of gangliosides in the brain. Tay-Sachs disease occurs in American Jews an incidence 100 times higher than for other Americans.

# AMINOACIDS, PEPTIDES, AND PROTEINS

The name protein has its origin in the Greek world proteios, meaning "of first importance". The name is well chosen, because proteins are the basis of protoplasm and comprise the underlying structure of all living organisms proteins, in the form of muscle. Skin, hair, and other tissue, make up the bulk of the body's non bony structure.

Proteins have biochemical importance:

    1. catalyze biochemical reactions

    2. as hormones, they regulate metabolic processes

    3. as antibodies, they resist and rullify the effects of toxic substances.

Such specialized functions illustrate the great importance of proteins.

Proteins have high molecular weight, longchain polymers made up largely of varions amino acids linked together. The constituent amino acids are obtained when a protein is hydrolyzed by dilute acids, by dilute alkalis, or by protein digesting enzymes. It would be difficult to consider the properties of molecules as complex as the proteins without first examining the propeties of the α-amino acids from which they are made of.

## Structure of Amino Acids

Nearly all amino acids obtained from plant and animal proteins have an amino group on the carbon atom alpha (α) to the carboxyl function. An α-amino acid has the following general formula.

$$R - \underset{\underset{NH_2}{|}}{\overset{\overset{H}{|}}{C}} - C \overset{\displaystyle O}{\underset{\displaystyle OH}{\diagdown}}$$
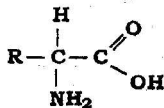
The R in the general formula for an α-amino acid may be a hydrogen, a straight or branched chain aliphatic group, an aromatic ring, or a heterocyclic nitrogen-containing ring.

Most amino acids have one amino group and one carboxyl group and usually are classified as neutral aminoacids.

A few have a second aminogroup joined to other carbon atoms in the molecule and show basic properties.

Others contain a second carboxyl group and behave as acids.
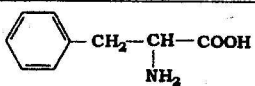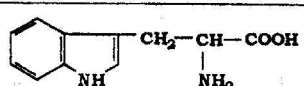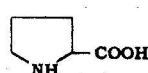
All amino acids (with the exception of glycine) contain at least one center of asymmetry and are optical active. Amino acids of protein origin all possess the L-configuration. With a few exceptions,

the body is able to utilize competely only the L-izomers of those aminoacids that is able to synthesize itself.

## Nomenclature and Clasification by Structure.

Of the known α-amino acids, about twenty have been found to be constituents of the most common plant and animal proteins.

**Table.1** Amino Acids Derived from Proteins

| №  | Name (Abbreviation) | Formula |
|----|---------------------|---------|
| | *Neutral amino acids with nonpolar R group* | |
| 1. | Glycine (Gly) <br><br> (aminoacetic acid) | $H_2N-CH-COOH$ <br> $\quad\quad\ \ |$ <br> $\quad\quad\ \ H$ |
| 2. | Alanine (Ala) <br><br> (α-aminopropionic acid) | $H_2N-CH-COOH$ <br> $\quad\quad\ \ |$ <br> $\quad\quad\ CH_3$ |
| 3. | Valine (Val) <br><br> (α-aminoisovaleric acid) | $H_3C-CH-CH-COOH$ <br> $\quad\quad\ |\quad\ \ |$ <br> $\quad\ CH_3\ NH_2$ |
| 4. | Leucine (Leu) <br><br> (α-aminoisocapronic acid) | $H_3C-CH-CH_2-CH-COOH$ <br> $\quad\quad\ |\quad\quad\quad\ |$ <br> $\quad\ CH_3\quad\quad\quad NH_2$ |
| 5. | Izoleucine (Ile) <br><br> (α-amino-β-methylvaleric acid) | $H_3C-CH_2-CH-CH-COOH$ <br> $\quad\quad\quad\quad\ |\quad\ |$ <br> $\quad\quad\quad\ CH_3\ NH_2$ |
| 6. | Phenylalanine (phe) <br><br> (α-amino-β-phenylpropionic acid) | $CH_2-CH-COOH$ <br> $\quad\quad\quad\ |$ <br> $\quad\quad\quad NH_2$ |
| 7. | Tryptophan (Trp) <br><br> (α-amino-β-(3-indolylpropionic acid) | $CH_2-CH-COOH$ <br> $\quad\quad\quad\ |$ <br> $\quad\quad\quad NH_2$ |
| 8. | Proline (Pro) <br><br> (2-pyrrolidine carboxylic acid | $-COOH$ |

| 9. | Methionine (Met)<br><br>(α-amino-γ-methylthiobutiric acid) | $CH_3-S-CH_2-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
|---|---|---|
| | **Neutral amino acids with polar R group** | |
| 10. | Serine (Ser)<br><br>(α-amino-β-hydroxypropionic acid) | $HO-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 11. | Threonine (Thr)<br><br>(α-amino-β-hydroxybutiric acid) | $H_3C-\underset{\underset{HO}{\displaystyle\vert}}{CH}-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 12. | Cysteine (Cys)<br><br>(α-amino-β-mercaptopropionic acid) | $HS-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 13. | Tyrosine (Tyr)<br><br>(α-amino-β-hydrocinnamic acid) | $HO-\langle C_6H_4\rangle-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 14. | Asparagine (Asn)<br><br>(β-carbomoyl-αaminopropionic acid) | $\underset{H_2N}{\overset{\displaystyle O}{\diagup}}C-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 15. | Glutamine (Gln)<br><br>(γ-carbomoyl-α-aminobutiric acid) | $\underset{H_2N}{\overset{\displaystyle O}{\diagup}}C-CH_2-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| | **Basic amino acids** | |
| 16. | Histidina (His)<br><br>(α-amino-β-4-imidasolpropionic acid) | $\underset{N\quad NH}{\text{(imidazole)}}-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 17. | Lysine (Lys)<br><br>(α,ε-diaminocapronic acid) | $H_2N-CH_2-(CH_2)_3-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| 18. | Arginine (Arg)<br><br>(α-amino-δ-guanidinvaleric acid) | $H_2N-\overset{\overset{\displaystyle NH}{\|}}{C}-NH-(CH_2)_3-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |
| | **Acidic amino acids** | |
| 19. | Aspartic acid (Asp)<br><br>(aminosuccinic acid) | $\underset{HO}{\overset{\displaystyle O}{\diagup}}C-CH_2-\underset{\underset{NH_2}{\displaystyle\vert}}{CH}-COOH$ |

| 20. | Glutamic acid (Glu) (α-aminoglutaric acid) | $\underset{HO}{\overset{O}{\diagdown}} C - CH_2 - CH_2 - \underset{\underset{NH_2}{\mid}}{CH} - COOH$ |

## Nutritive classification of amino acids

A nutritive classification of α-amino acids has resulted from nutritional experiments carried out on laboratory animals. The animals organism either is incapable of synthesizing certain aminoacids. On basis of such stadies, the α-aminoacids are divided into categoies as essential or nonesential.

**Tabel 2.** The amino acids according to nutritional requirements

| Essential (indispensable) | Nonesential (dispensable) |
|---|---|
| Arginine * | Alanine |
| Glycine + | Aspagine |
| Histidine + | Aspartic acid |
| Isoleucine ^ | Cysteine |
| Leucine ^ | Glutamic acid |
| Lysine ^ | Glutamine |
| Methionine ^ | Proline |
| Phenylalanine ^ | Serine |
| Threonine ^ | Tyrosine |
| Tryptophan ^ | |
| Valine ^ | |

\* required for optimum growth in the rat and chick
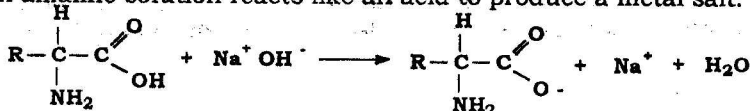+ required for optimum growth in the chick
+ required by all subhuman species tested and by infants, but not adult human
^ required by all species tested, including adult human.

## Properties of amino acids. Isoelectric point

The amino acids are colorless crystalline solids and have melting points (with decomposition) in excess of 200°C. Most amino acids are soluble in water but sparingly soluble in organic solvents.

A neutral amino acid possesses an amino group and a carboxyl group and thus can behave either as a base or an acid. An aminoacid in an alkaline solution reacts like an acid to produce a metal salt:

$$R - \underset{\underset{NH_2}{\mid}}{\overset{\overset{H}{\mid}}{C}} - C \underset{\diagdown OH}{\overset{\diagup O}{}} + Na^+ OH^- \longrightarrow R - \underset{\underset{NH_2}{\mid}}{\overset{\overset{H}{\mid}}{C}} - C \underset{\diagdown O^-}{\overset{\diagup O}{}} + Na^+ + H_2O$$

If an alkaline solution of an amino acids is electrolyzed, the anion of the aminoacid salt migrates toward to the anode or possitive electrode.

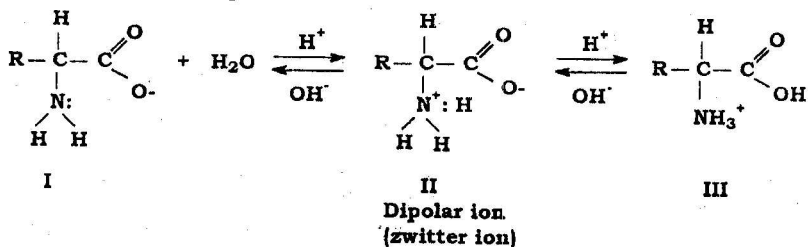An amino acid in an acidic solution behaves like a base to form an amine salt:

$$R-\underset{\underset{\underset{H}{N:}}{|}}{\overset{\overset{H}{|}}{C}}-C\underset{OH}{\overset{O}{<}} \quad + \quad H^+Cl^- \quad \longrightarrow \quad R-\underset{\underset{\underset{H}{N:H}}{|}}{\overset{\overset{H}{|}}{C}}-C\underset{OH}{\overset{O}{<}} \quad + \quad Cl^-$$
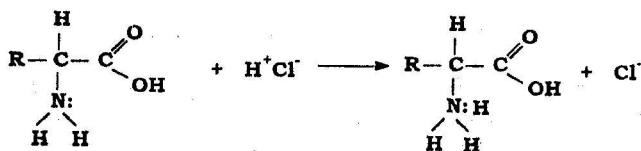
If an acid solution of an amino acid is electrolyzed, the cation of the amine salt migrates to the cathode or negative electrode.

The hydrogen ion concentration at which the amino acid shows no net migration to either electrode is called the _isoelectric point_. Isoelectric points are given in pH values and vary from low values for acidic amino acids (pH 3 for aspartic acid) to high values for basic amino acids (pH 10,8 for arginine). Neutral amino acids do not have izoelectric points at the neutral figure (pH 7,0), as might be expected, but slightly on the acid side.

At its izoelectric point, a "neutral" aminoacid is completely ionized and forms dipolar ion:

$$R-\underset{\underset{\underset{H}{N:}}{|}}{\overset{\overset{H}{|}}{C}}-C\underset{O^-}{\overset{O}{<}} + H_2O \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} R-\underset{\underset{\underset{H}{N^+:H}}{|}}{\overset{\overset{H}{|}}{C}}-C\underset{O^-}{\overset{O}{<}} \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} R-\underset{\underset{NH_3^+}{|}}{\overset{\overset{H}{|}}{C}}-C\underset{OH}{\overset{O}{<}}$$

I           II          III

**Dipolar ion.**
**(zwitter ion)**

Dipolar ions are amphoteric and can act either as acids or bases.

For an acidic amino acid the isoelectric point is in the acid range, whereas for a basic amino acid the isoelectric point is in the basic range.

The isoelectric point of an amino acid is easily measured. If a charged molecule is placed in an electric field, it will migrate to the electrode of opposite charge. At low pH an amino acid has a net positive charge and will migrate toward the negative electrode. At high pH an amino acid has a net negative charge and will migrate toward the positive electrode. At the isoelectric point the zwitterion, which