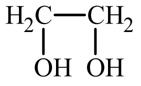
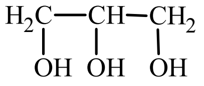
LECTURE 9
POLY– AND HETEROFUNCTIONALITY.

Polyfunctional compounds reactivity features. The most of the compounds participating in metabolic processes are poly– or heterofunctional compounds. Polyfunctional compounds are those containing several identical functional groups, for example polyhydric alcohols (and phenols) contain severeal hydroxyl groups:



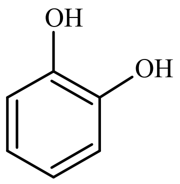
$HOCH_2-CH_2OH$

ethylene glycol

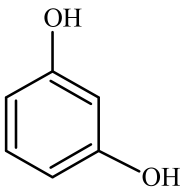


$HOCH_2-CH(OH)-CH_2OH$

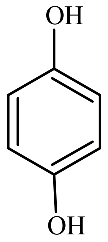
glycerol



pyrocatechol

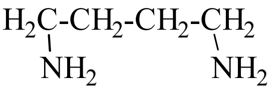


resorcinol



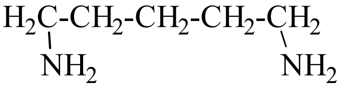
hydroquinone

Polyamines contain severe amino–groups:



$H_2N-CH_2-CH_2-CH_2-CH_2-NH_2$

butanediamine-1,4



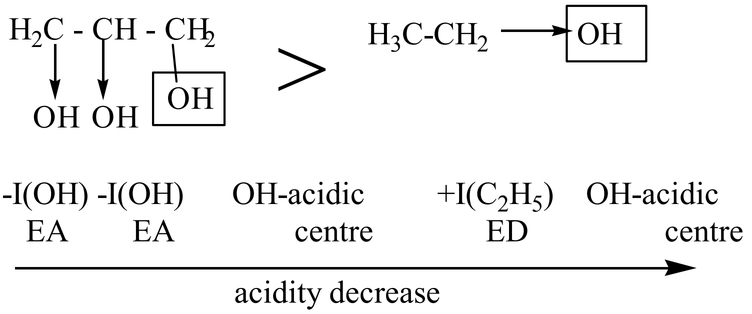
$H_2N-CH_2-CH_2-CH_2-CH_2-CH_2-NH_2$

pentanediamine-1,5

Their characteristics extensively depend on the characteristics of corresponding polyhydric alcohols (phenols) and amines.

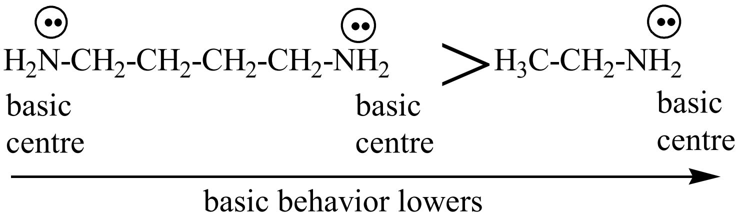
Simultaneous coexisting of severe functional groups in the compound leads to the appearance of specific features of chemical characteristics:

1. accumulation of carboxyl groups leads to acidity increase:



$HOCH_2-CH(OH)-CH_2\boxed{OH} > H_3C-CH_2\rightarrow\boxed{OH}$

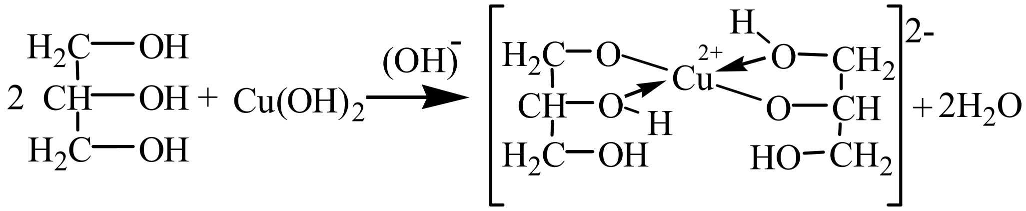
2. accumulation of basic groups on a certain distance increases the basic characteristics:



$H_2N-CH_2-CH_2-CH_2-CH_2-NH_2 > H_3C-CH_2-NH_2$

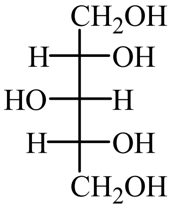
3. the tendency to chelates formation appears:

$$CuSO_4 + 2NaOH \rightarrow Cu(OH)_2 + Na_2SO_4$$

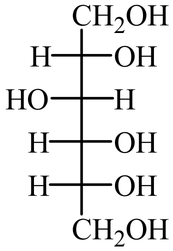


copper glycerate
(blue colored)

Biologic importance possess the alcohols with high hydroxyl content xylitol (contain 5 hydroxyl groups) and sorbitol (contain 6 hydroxyl groups). They are often used as sweeteners by patients with diabetes mellitus, since the accumulation of hydroxyl groups increases sweetness.

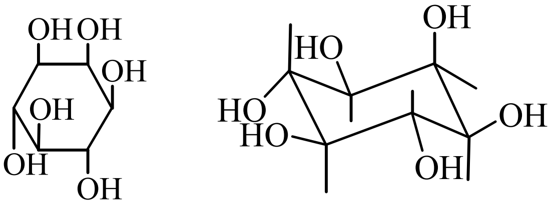


xylitol



sorbitol

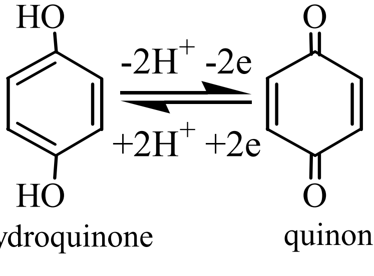
Concerning the cyclohexane family alcohols, the myoinositol can be found in human organism:



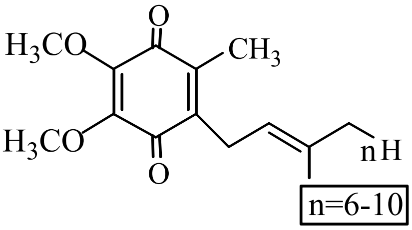
$^4C_1$ (e,e,e,e,e,a)

myoinositol

Myoinositol is a vitamin–like compound, it's hexaphosphate in the form of calcium salt participates in haemopoiesis process. The oxidation-reduction characteristics of dihydric phenol hydroquinone are of big importance in human organism. The redox activity of substituted hydroquinone fragment provides the electron transport chain function in biological oxidation (ubiquinone, coenzyme Q):

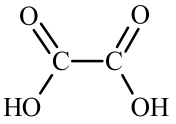


hydroquinone quinone

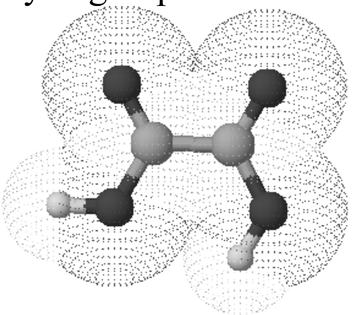


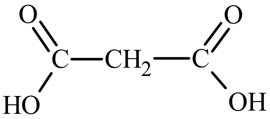
ubiquinone, coenzyme Q

Dicarboxylic acids possess two carboxylic groups:

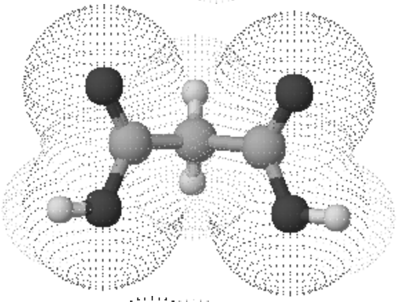


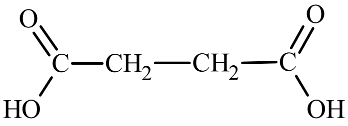
oxalic acid



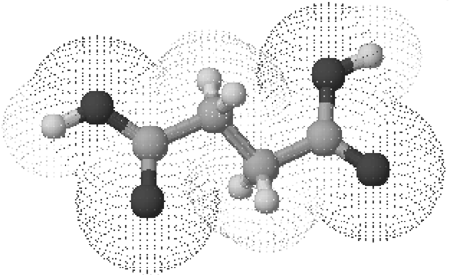


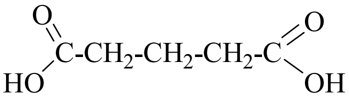
malonic acid



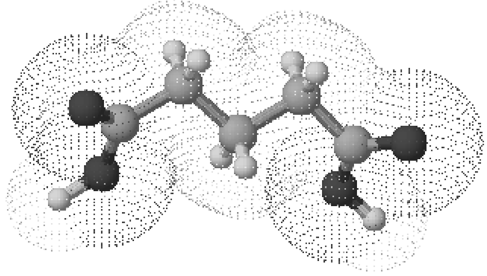


succinic acid



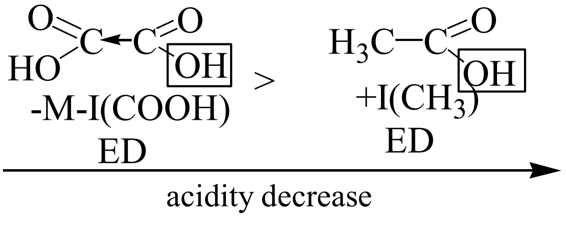


glutaric acid

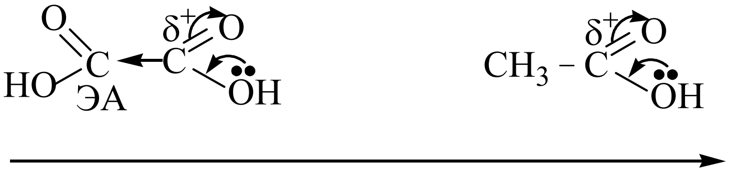


Their chemical characteristics are similar to one of monocarboxylic acids, but interference of carboxylic groups leads to some peculiarities of their chemical characteristics:

1. acidity increased in carboxylic acids with close carboxylic groups location:

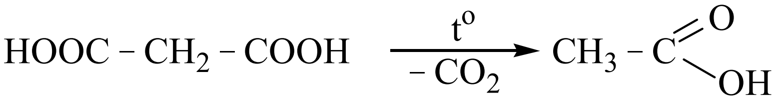


2. reactivity in S_N reactions increases in case of α–location of carboxylic groups:

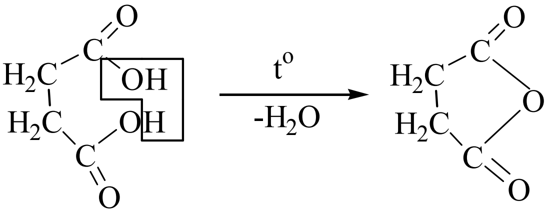


δ+ decrease on electrophyle center

3. decarboxylation reactions occurs easily in two first compounds of homologous series (oxalic and malonic acids):



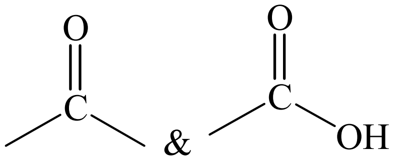
4. as carbon atoms chain elongates, the opportunity of formation internal cyclic anhydrides, as the chain takes the claw-shaped conformation.



succinic acid (cyclic anhydride of succinic acid)

Classification of heterofunctional compounds

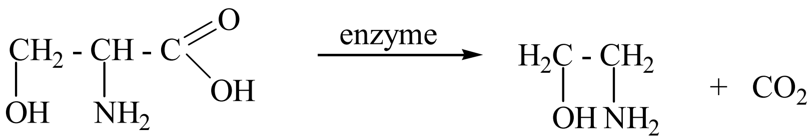
Heterofunctional are the compounds containing two or more different functional groups. Among the compounds containing two different functional groups, the most common are the following families:

United groups	Types of compounds
$–OH$ & $–NH_2$	Amino-alcohols (amino-phenols)
$–OH$ & $–COOH$	Hydroxy-acids
$–NH_2$ & $–COOH$	Amino-acids
	Oxo-acids

Amino–alcohols and amino–phenols

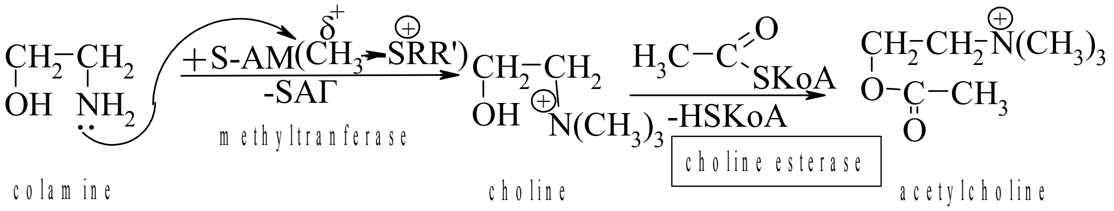
Amino–alcohols and amino–phenols are the compounds containing simultaneously alcohol or phenol hydroxyl and amino–group.

The simplest example of amino–alcohols is colamine forming in human organism from serine in decarboxylation reaction:



2-amino-3-hydroxypropanoic acid (serine) 2-aminoethanol (colamine)

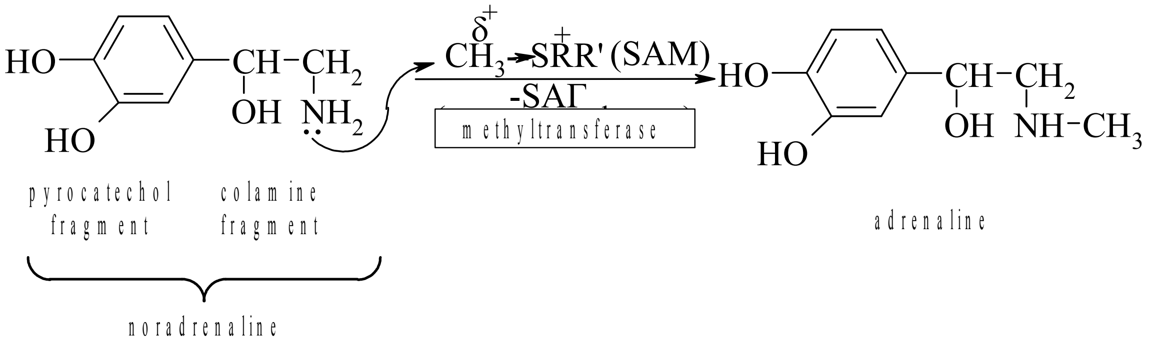
Colamine has the reaction centre of alcohols and amines, that's why it participates in alkylation and acylation reactions. One of the products of such a transformation is acetylcholine (neurotransmitter):



S-adenosyl–methionine (S-AM) provides colamine alkylation, acetyl coenzyme A (HSCoA) provides acylation.

Colamine and choline are the parts of cell membranes phospholipids, choline is physiologically active substance. Choline reduces blood pressure, regulates lipid metabolism (vitamin–like substance). Acetylcholine participates in nervous impulse conduction.

Pyrocatechol and colamin fragments containing phenols play an important role in humal organism. They are more commonly named as catecholamines and include norepinephrine (noradrenaline) and epinephrine (adrenaline). Noradrenaline are being transforming to adrenaline in methylation reaction with S-adenosyl–methionine presence:

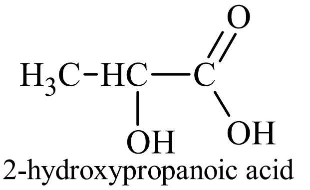


Noradrenaline is adrenergic synapses mediator. Adrenaline is the hormone of adrenal glands medulla (stress hormone), it participates in cardiac activity regulation, changes carbohydrates metabolism, raises the blood pressure.

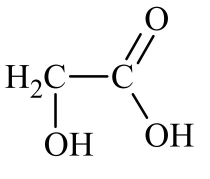
Hydroxy and amino acids.

Hydroxy acids contain in the molecule hydroxyl and carboxylic group simultaneously, amino acids — amino and carboxylic group. According to carboxylic group number attached to the chain, they are classified on monocarboxylic, dicarboxylic, tricarboxylic acids:

monocarboxylic acids

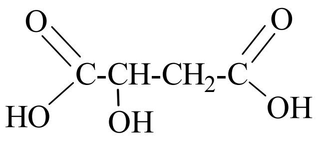


2-hydroxypropanoic acid
(lactatic acid)

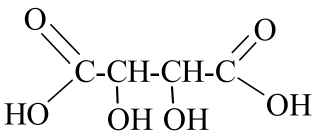


hydroxyacetic acid

dicarboxylic acids

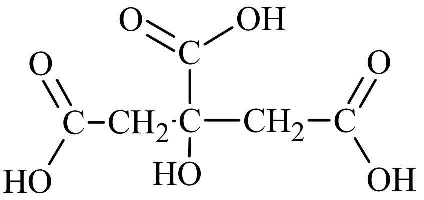


2-hydroxybutanedioic acid

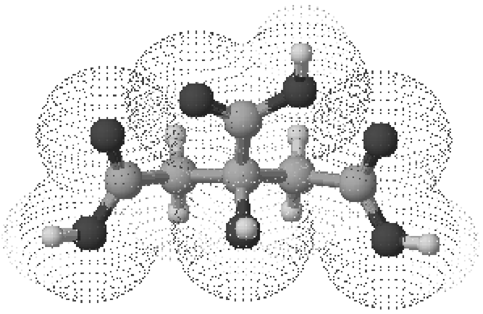


2,3-dihydroxybutanedioic acid

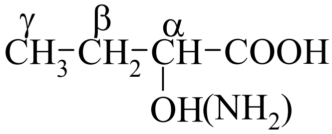
tricarboxylic acid



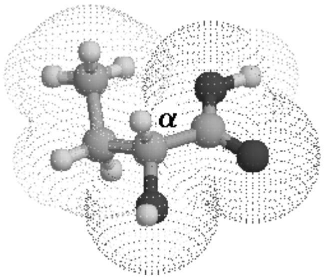
2-hydroxypropane-1,2,3-tricarboxylic acid
(citric acid)



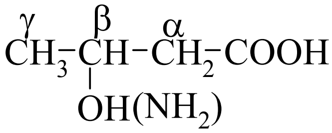
According to positional relationship between functional groups, they can be classified on α, β, γ etc. hydroxy and amino acids:



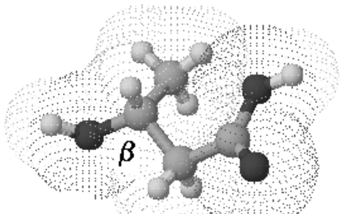
$\overset{\gamma}{C}H_3-\overset{\beta}{C}H_2-\underset{OH(NH_2)}{\overset{\alpha}{C}H}-COOH$



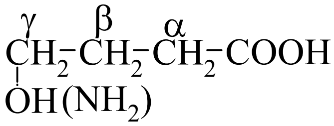
α–hydroxyl (or amino) butyric acid



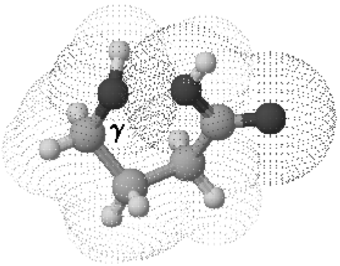
$\overset{\gamma}{C}H_3-\underset{OH(NH_2)}{\overset{\beta}{C}H}-\overset{\alpha}{C}H_2-COOH$



β–hydroxyl (or amino) butyric acid

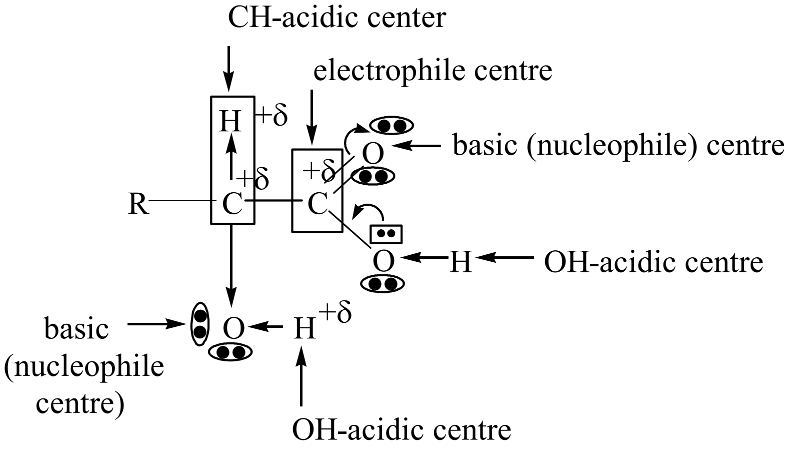


$\underset{OH(NH_2)}{\overset{\gamma}{C}H_2}-\overset{\beta}{C}H_2-\overset{\alpha}{C}H_2-COOH$

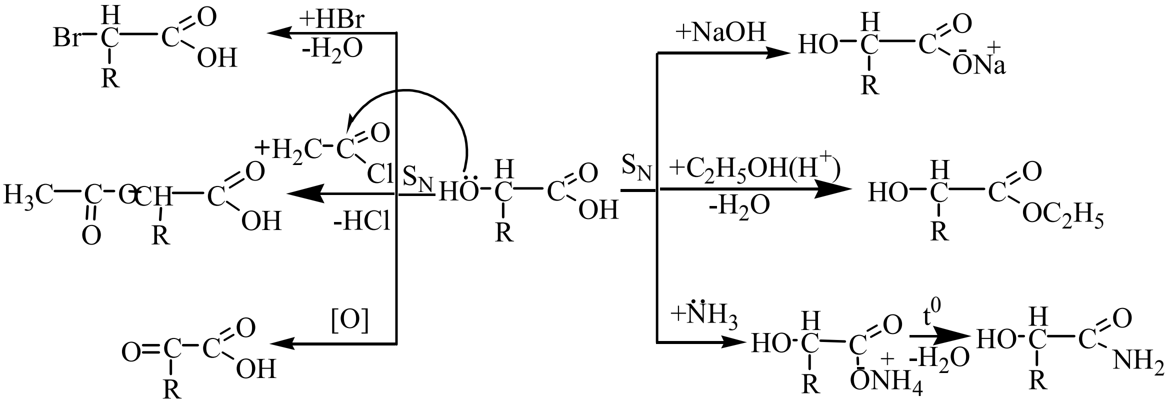


γ–hydroxyl (or amino) butyric acid

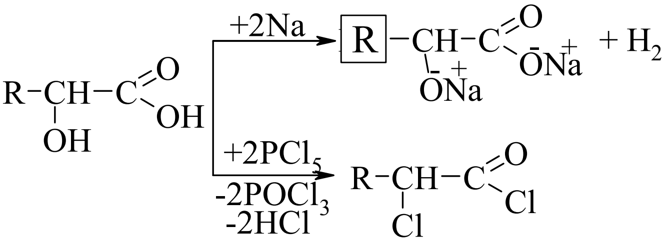
Hydroxy acids have all reaction centre and develop the characteristics of corresponding alcohols and carboxylic acids.



Reactions roadmap:



Some reactions involve concurrently two acidic or two electrophile centre:

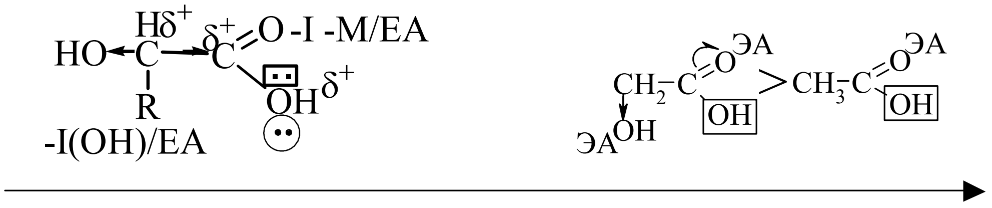


Specific chemical properties caused by interference of functional groups.

1. Chiral centers appears in hydroxy and amino acids

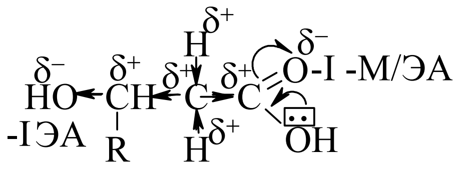
$D^{(-)}$lactic acid $L^{(+)}$lactic acid

2. In case of α–location of heterofunctional groups, the inclination to SN reactions increases and OH–acidic centre strength increases also because of electron-seeking interference of the groups.

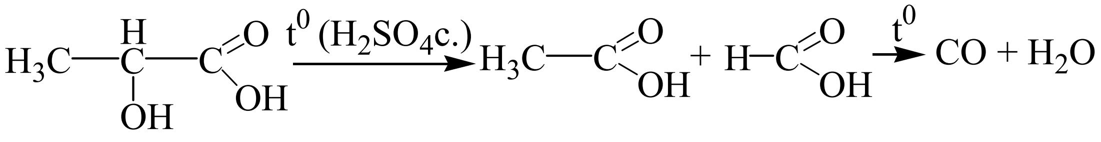


acids strength decrease

3. In case of β–location of heterofunctional groups the reactivity of CH–acidic center increases:



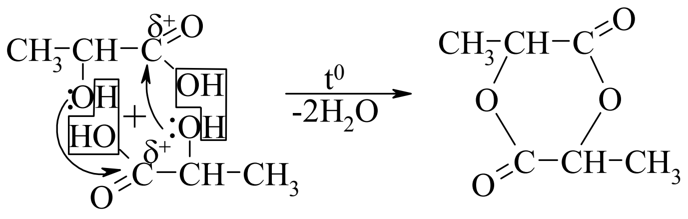
4. A range of specific reactions appears. Heating of α–hydroxy acids with strong mineral acids leads to decomposition and formation of formic acid and carbonyl compound.



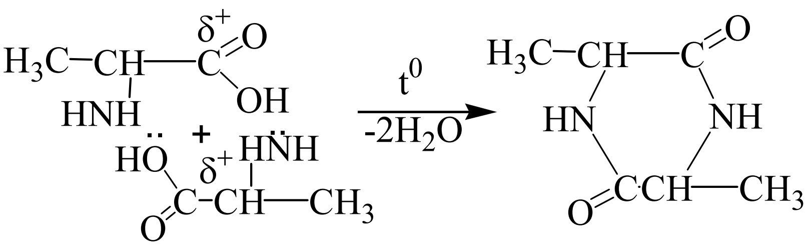
$$H_3C-CH(OH)-C(=O)OH \xrightarrow{t^0\,(H_2SO_4c.)} H_3C-C(=O)OH + H-C(=O)OH \xrightarrow{t^0} CO + H_2O$$

lactic acid formic acid

In heating but absence of mineral acids α–hydroxy and α–amino acids undergo intermolecular dehydratation leadind to 6–membered ring heterocycles formation. These heterocycles are nemed lactides and diketopiperasines.

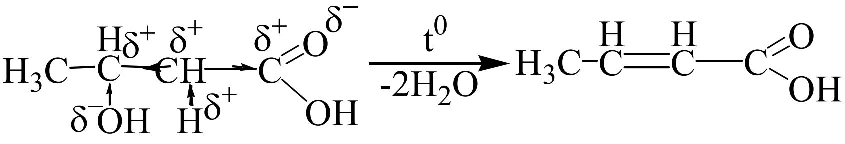


lactic acid lactide

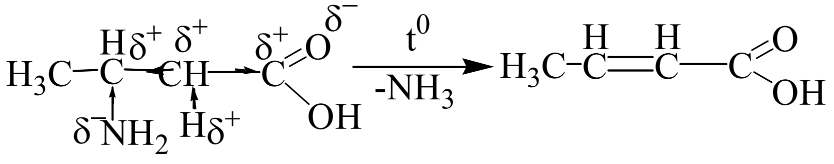


alanine diketopiperasine

Heating of β–hydroxy and β–amino acids leads to reactions of elimination:

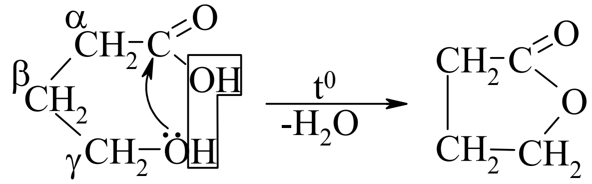


β-hydroxybutyric acid crotonic acid



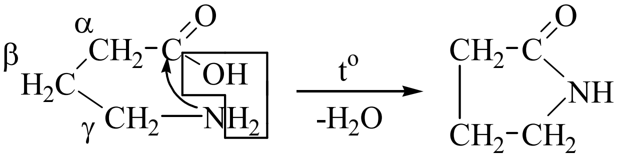
β-aminobutyric acid crotonic acid

Heating of γ–hydroxy and γ–amino acids leads to intramolecular dehydratation and corresponding heterocycles formation (lactones and lactams):



γ–hydroxybutyric acid
(claw-shaped conformation)

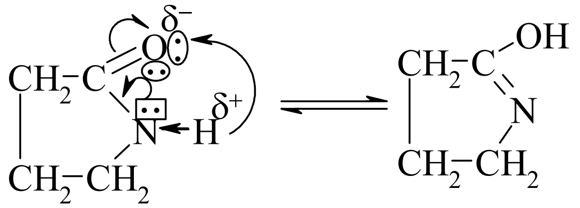
γ-lactone



γ–aminobutyric acid
(claw-shaped conformation)

γ–lactam

Non–substituted lactams are the simplest compounds possessing the ability of lactam–lactim tautomerism. This is a special type of isomerism supposing dynamic equilibrium of two interconvertible forms (lactam and lactim).



lactam lactim

The most of above-listed hydroxy acids have a biologic significance.

Lactic acid (L$^{(+)}$–isomer) is a product of glucose metabolism in glycolysis process. Lactic acid accumulates in muscles during hard physical exertion.

β–hydroxybutyric acid is the intermediate product of β–oxidation of fatty acids, the precursor of acetoacetic acid, it accumulates in organisms of patients with diabetes mellitus.

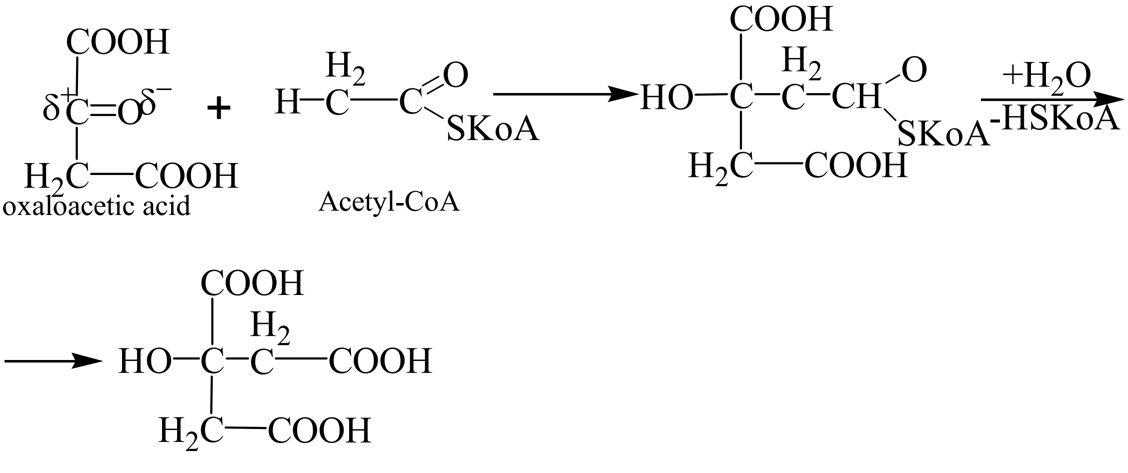
β–aminopropionic acid is a part of coenzyme A.

γ–hydroxybutyric acid has the narcotic effect, it is used as soporific in form of sodium salt.

γ–aminobutyric acid plays an important role in brain metabolism, behave itself as neurotransmitter.

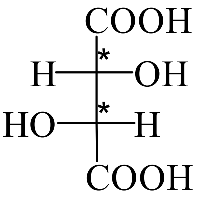
Malic acid and citric acid are the components of universal stage of carbohydrates, lipids and other substances catabolism called Krebbs cycle.

Citric acid biosynthesis in Krebbs cycle occurs according to aldol condensation reaction of oxaloacetic acid and acetyl coenzyme A.

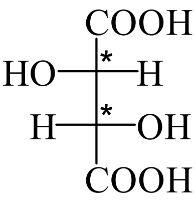


citric acid

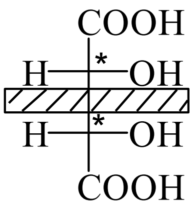
D$^{(+)}$ tartaric acid is found in many plants. L$^{(-)}$ tartaric acid is the enantiomere of D$^{(+)}$ tartaric acid. Meso tartaric acid is achiral, because it possess one plane of symmetry.



D(+) tartaric acid



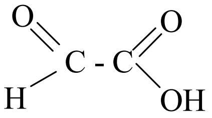
L(-) tartaric acid



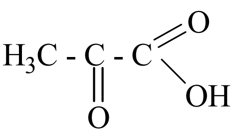
meso tartaric acid

Oxo acids

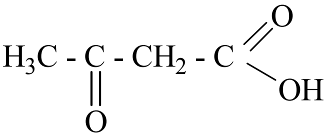
Oxo acids (aldehyde acids and keto acids) are the organic compounds possessing simultaneously carboxylic group and aldehyde group or ketone group. The most important natural oxo acids are the following:



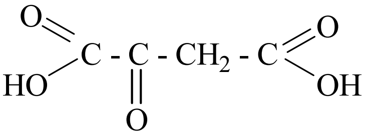
2-oxoethanoic
(glyoxyl)



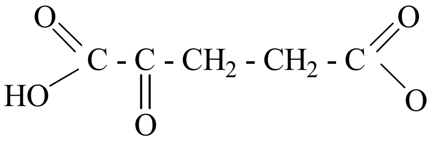
2-oxopropanoic acid
(pyruvic acid)



3-oxobutanoic acid
(acetoacetic acid)

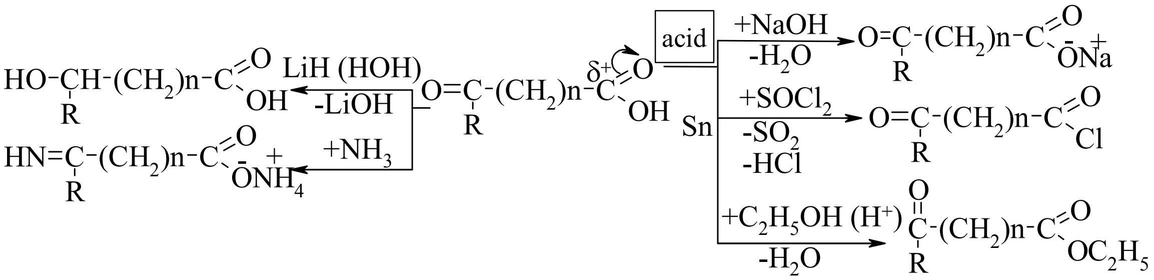


2-oxobutanoic



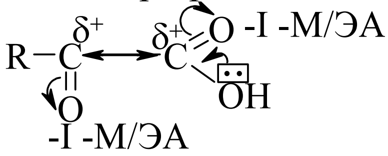
2-oxopentanedioic acid
(α–oxoglutaric acid)

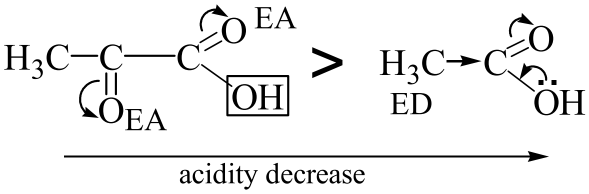
In case of significant distance between functional groups, each of them retain reactivity typical to corresponding monofunctional compounds.



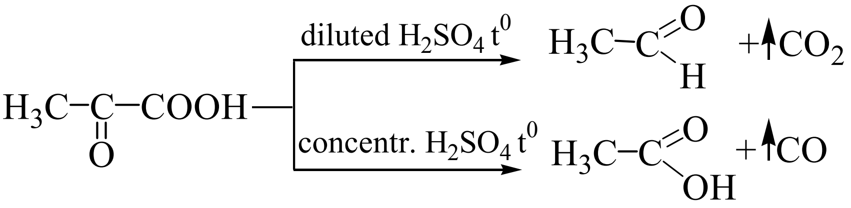
Specific features are conditioned by interference and arrangement of functional groups.

1. In case of α–location of functional groups, the reactivity in A_N reactions for oxo and S_N reactions for carboxylic groups increases due to electron seeking interaction of the groups. Acidic properties of oxo acids increase too.

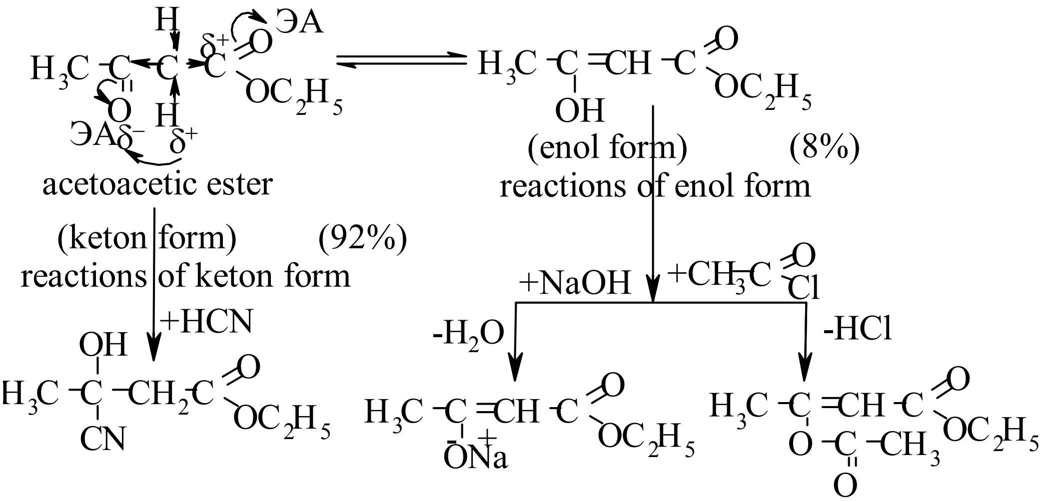




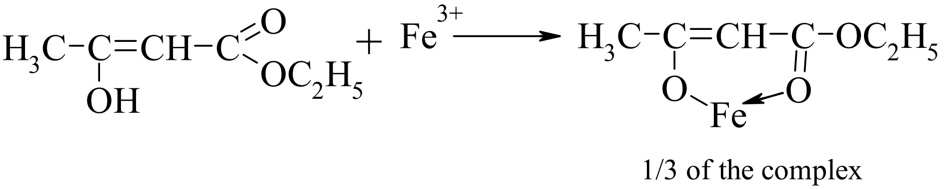
2. Typical reactions for α–oxo acids are decarboxylation reaction in diluted sulphuric acid and decarbonylation in heating with concentrated sulphuric acid.



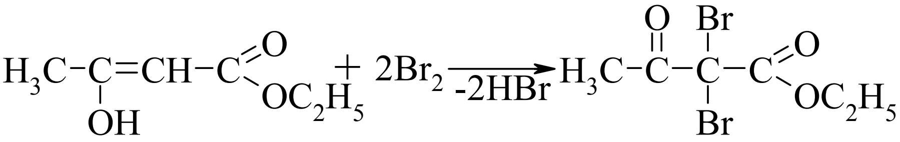
3. In case of β–location of functional groups the strength of CH–acidic center increases and the phenomenon of keto–enol tautomerism appears. Keto–enol tautomerism is a kind of isomerism leading to dynamic equilibrium between two simultaneously coexisting forms – keton and enol (example: acetoacetic ester). While acting upon the ester any reagent one tautomeric form participate in the reaction, and it's leakage is compensated by equilibrium shift.



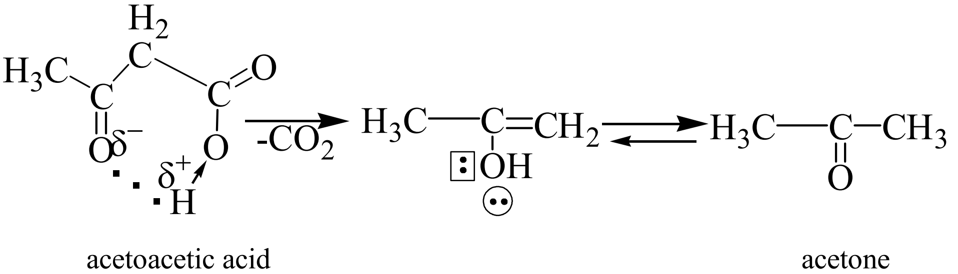
Acetoacetic ester forms a violet colored complex compound with iron chloride.



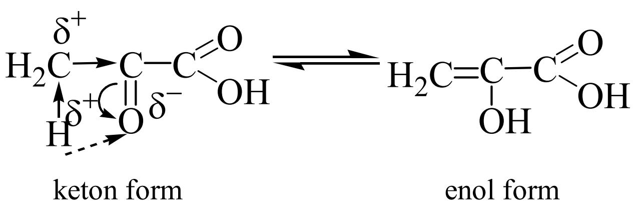
If than add to the obtained solution drop by drop bromine, than enol tautomer will add bromine and the solution will fade, but than in some time appears again as keton tautomer will turn into enol form. Reaction with bromine occurs as S_N and leads to keton form of product formation.



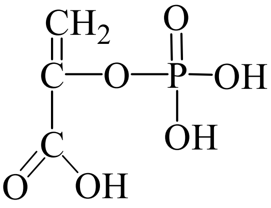
4. β–oxo acids are being decarboxylating even in room temperature, forming before the enol form.



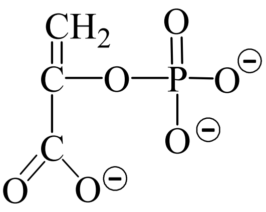
All the oxo acids listed above are the participants of metabolism. Pyruvic acid, oxaloacetic acid and α-oxoglutaric acid are the participants of Krebbs cycle. Pyruvic acid is capable of enolisation:



Phosphoenolpyruvic acid (in anion form — phosphoenolpyruvate) is very important biological metabolite of pyruvic acid.



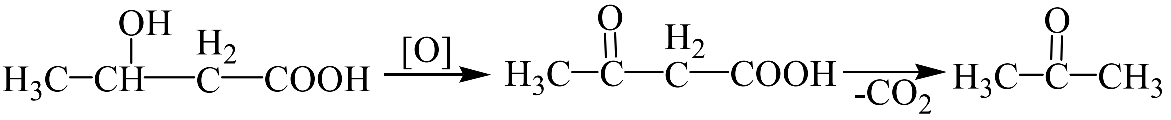
phosphoenolpyruvic acid



phosphoenolpyruvate

Phosphoenolpiruvate (as a precursor of pyruvate) is being forming in glycolysis process.

Acetoacetic acid is being forming in vivo in higher fatty acids metabolism. As it is a product of β–hydroxybutyric acid oxidation, it accumulates in organism of patients with diabetes mellitus.

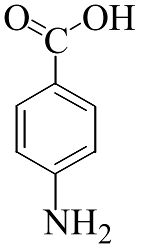


$$H_3C-\overset{OH}{\overset{|}{CH}}-\overset{H_2}{C}-COOH \xrightarrow{[O]} H_3C-\overset{O}{\overset{\|}{C}}-\overset{H_2}{C}-COOH \xrightarrow[-CO_2]{} H_3C-\overset{O}{\overset{\|}{C}}-CH_3$$

β–hydroxybutyric acid acetoacetic acid acetone

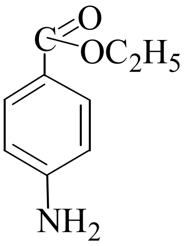
Heterefunctional benzene derivates as pharmaceutical substances. Para–aminobenzoic acid and it's derivates.

Para–aminobenzoic acid is essential for microorganisms growth. The absence of para–aminobenzoic acid in microorganism's environment causes death of the microorganism.

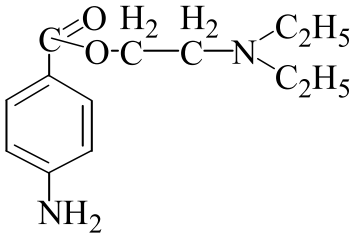


4-aminobenzoic acid
(para-aminobenzoic acid)

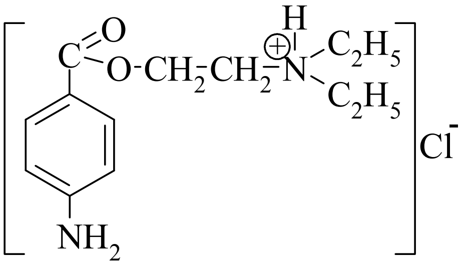
Esters of para–aminobenzoic acid (anesthesine, novocaine) are widely used in medicine as anesthetics (substances capable to cause local anesthesia, or loss of sensation). For water solubility increase novocaine is used as a salt – novocaini hydrochloride.



anesthesine



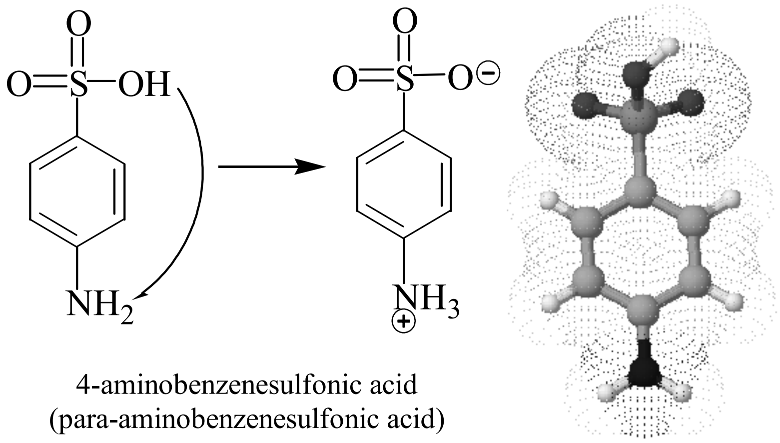
novocaine



novocaini hydrochloride

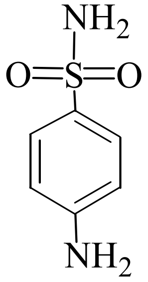
Sulfanilic acid and it's derivates.

Sulfanilic acid — para–aminobenzenesulfonic acid (4-aminobenzenesulfonic acid) exists as bipolar ion.

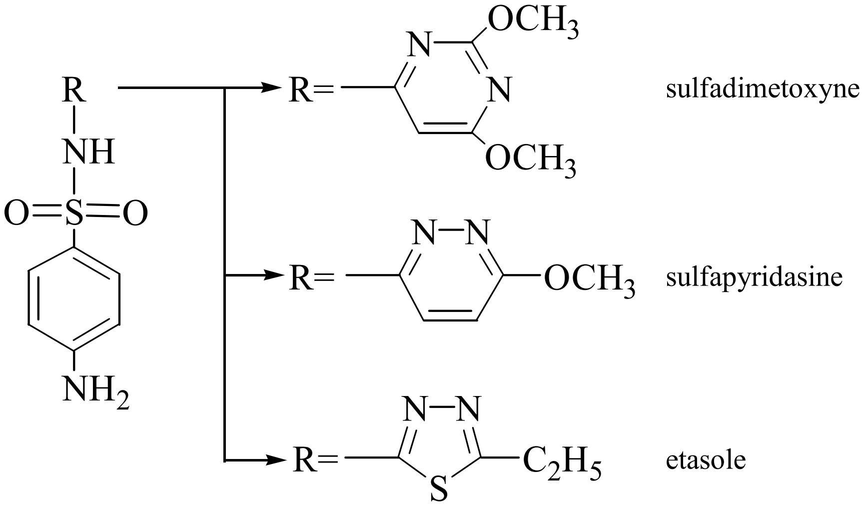


4-aminobenzenesulfonic acid
(para-aminobenzenesulfonic acid)

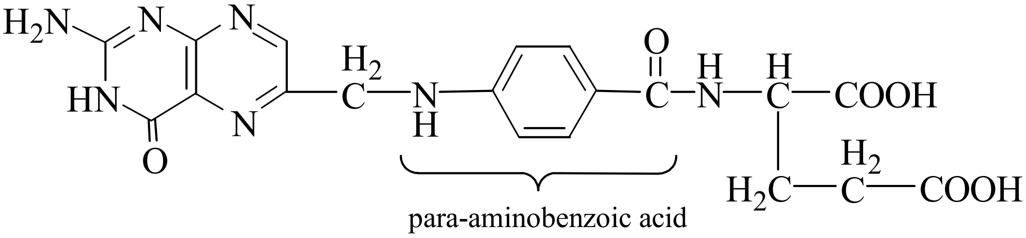
Its amide – streptocid – is the founder of a range of pharmaceutical substances possessing anti-bacterial acticity called sulfanilamides. They are formed by hydrogen atom substitution on the radical in the sulfamide group.

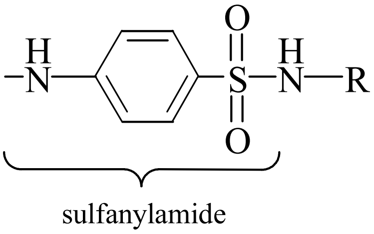


streptocid



Anti-bacterial effect of sulfanylamides is based on the antimetabolic effect against para–aminobenzoic acid, participating in folic acid synthesis in microorganisms. Folic acid contains the fragment of para–aminobenzoic acid and is essential for nucleic acids synthesis:

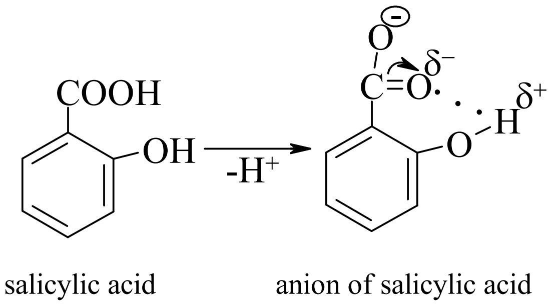


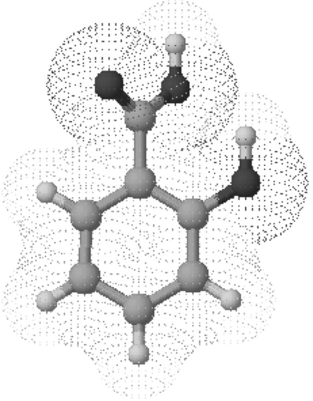


Sulfanylamides compete with para–aminobenzoic acid and block the synthesis of folic acid. Selectivity of sulfanylamides is conditioned by peculiarities of human metabolism (humans do not synthesize folic acid, that's why sulfanylamides do not affect humans).

Salicylic acid and its derivates.

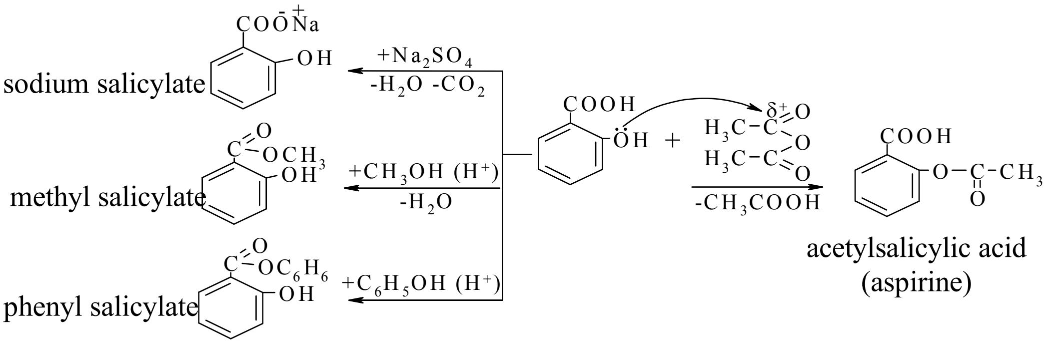
Salicylic acid – ortho–hydroxybenzoic acid – shows quite strong acidic characteristics as its anion is stabled by intramolecular hydrogen bond:





Salicylic acid is used as antirheumatic and antimycotic medicine (for external use only).

Derivates of salicylic acid can be formed on two functional groups: carboxyl and phenol hydroxyl:



All the derivates (except phenyl salicylate) have analgetic, antipyretic and antiinflammatory activity. Phenyl salicylate (salol) is used as desinfection agent in intestinal diseases.