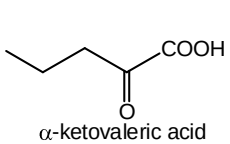
№ 32. OXOACIDS - ALDEHYDE AND KETO ACIDS. CHARACTERISTICS, ISOMERISM, PROPERTIES REPRESENTATIVES

I. Characteristics and isomerism.

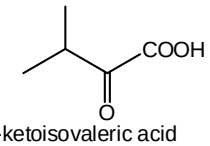
The class of bifunctional organic compounds containing carboxylic acid group and containing also an aldehyde (CHO) or keto (CO) group is called oxoacids. If the COOH and CO groups are far removed from each other, the compound exhibits properties of the individual classes - acids and ketones or aldehydes. Compounds with 1,2- and 1,3- located functional groups exhibit characteristic properties due to interaction of the functional groups. 1,3-Dicarbonyl containing compounds are named also β-dicarbonyl compounds.

For aldehyde and ketoacids are typical chain isomerism, position isomerism and tautomerism. Carbonyl compounds with one or more hydrogen atoms on their α-carbons rapidly interconvert with their corresponding **enols**. This rapid interconversion between two substances, differing in the position of a hydrogen and a double bond is a special kind of isomerism known as **tautomerism**. Individual isomers are called **tautomers**. Especially in 1,3-dicarbonyl compounds, including β-ketoacids, the keto-enol tautomerism is of major importance – in organic synthesis, in biochemical metabolic pathways, and, of particular importance, base pairing in DNA.

Chain isomerism is referred to identically located functional groups but different chains, e.g.:

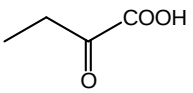


α-ketovaleric acid

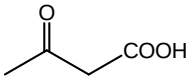


α-ketoisovaleric acid
3-methyl-2-oxobutanoic acid

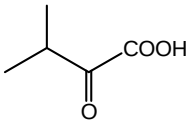
Position isomerism refers to different mutual locations of the functional groups in an aldehyde- or ketoacid, e.g. α-, β-, γ-ketocarboxylic acids and 2-, 3-, 4-formylcarboxylic acids, like 2-, 3-, 4-formylbenzoic acids:



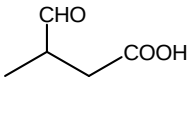
α-ketobutyric acid
(2-ketobutanoic acid)



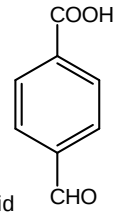
β-ketobutyric acid
(acetoacetic acid)



α-ketoisovaleric acid
3-methyl-2-oxobutanoic acid

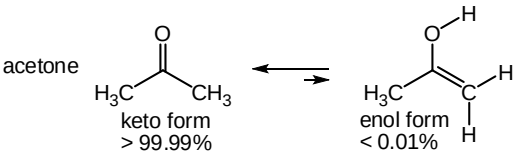


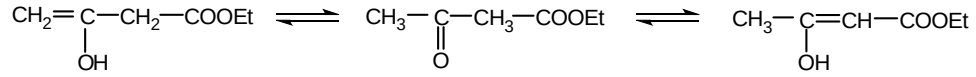
β-formylbutyric acid
3-methyl-4-oxobutanoic acid



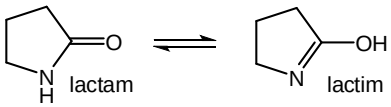
4-formylbenzoic acid

Keto-enol tautomerism. Monocarbonyl compounds exist almost exclusively in keto form but even the very small amount of enol form is important in much of the chemistry of these compounds. For example, acetone contains much less than 0.01% enol, and the percent enol is even less for carboxylic acids and esters. Keto-enol tautomerism is more pronounced and significant when second carbonyl group is present at β-position to a carbonyl group in ketones, carboxylic acids, esters. The tautomerism is possible with the participation of this second keto group, as in β-ketoacids or β-ketoesters, e.g. in ethyl acetoacetate:





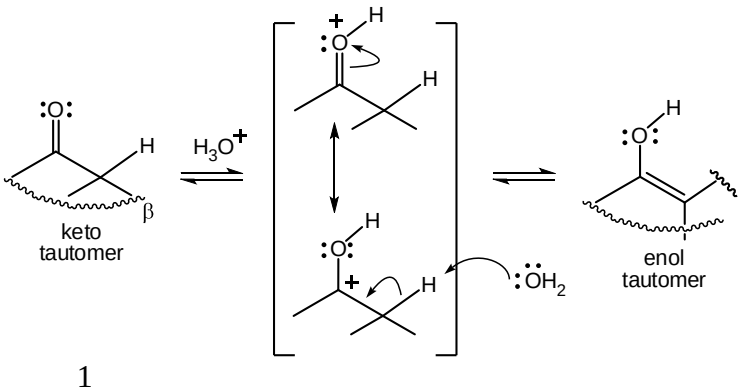
Lactam-lactim tautomerism. This kind of tautomerism involves heterocyclic N and carbonyl group, as shown. Lactam-lactim tautomerism has importance in base pairing of DNA and RNA.



The keto-enol tautomerism of carbonyl compounds is catalyzed by acids and bases.

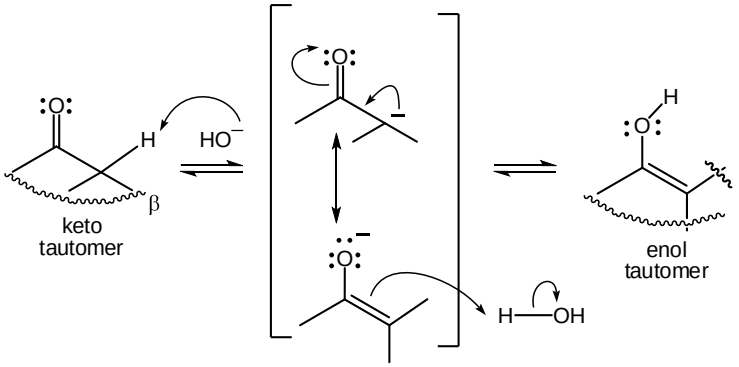
The mechanism of formal proton transfer from an α-carbon to carbonyl oxygen, catalyzed by an acid is shown in general in the keto-enol equilibrium.

(The possible "border structures" are in square brackets.)



Acid catalyzed keto-enol tautomerism.

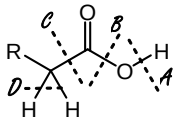
Base catalyzed keto-enol tautomerism.



The amount of enol tautomer in pure liquid 2,4-pentanedione is 76% and in hexane solution reaches 92%, whereas in pure ethyl acetoacetate the enol is 8% and in hexane solution - 46%.

II. Properties. The variation of properties in the diverse group of oxoacids is considered together because their chemistry is dominated by the interaction of two carbonyl groups in each case. The 1,2-compounds such as α-ketoacids, α-ketoesters, α-formyl esters are rare. The most important group of dicarbonyl compounds is comprised by 1,3-dicarbonyl compounds (β-dicarbonyl compounds). Other dicarbonyl compounds show chemical behavior that is combination of the reactivity of their monofunctional counterparts, except for cases where the two functional groups allow for intramolecular reactions.

The reactions characteristic for a carboxylic group can be systematized:



A Breaking the chemical bond between oxygen and hydrogen in a carboxylic group results in dissociation and formation of salts;

B Breaking the chemical bond between carbonyl carbon and OH accounts for various nucleophilic substitution reactions leading to esters, amides, acid anhydrides, acyl halides;

C Breaking the bond between carbonyl carbon and C(2) leads to decarboxylation

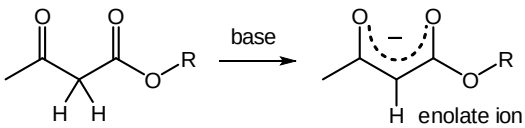
D Reactions after deprotonation of an α-hydrogen due to its acidity. The acidity is much higher in β-keto acids.

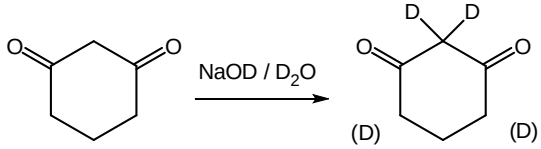
When the acid (ester, amide, etc.) has additional aldehyde and keto group, it accounts for reactions of nucleophilic addition to it and redox processes that are with great biochemical importance.

The **acidity of α-hydrogens** (the indicated methylene group next to various functional, activating, groups is shown in the Table:

Monoactivation	R**CH$_2$**-NO$_2$	R**CH$_2$**-COR	R**CH$_2$**-CO$_2$CH$_3$	R**CH$_2$**-C≡N	R**CH$_2$**-SO$_2$R′
Compound **pK$_a$**	9	20	25	25	25
Diactivation	**CH$_2$**(NO$_2$)$_2$	(CH$_3$CO)$_2$**CH$_2$**	CH$_3$CO**CH$_2$**CO$_2$C$_2$H$_5$	**CH$_2$**(C≡N)$_2$	**CH$_2$**(CO$_2$C$_2$H$_5$)$_2$
Compound **pK$_a$**	4	9	11	11	13

For comparison: H_2O has pK_a=15.75 and diisopropylamine (for LDA) - pK_a=36. With acidity of α-hydrogens in the range pK_a 16-20, aldehydes and ketones are about as acidic as water and alcohols but it is C-H acidity. Thus, hydroxide ion and alkoxide ions are sufficiently strong bases to produce solutions containing significant concentrations of enolate ions at equilibrium. The deprotonated product is a carbanion, it contains negatively charged carbon. More frequently, chemists refer to it as an **enolate ion**, since it is at the same time the conjugate base of an enol. When the methylene group is activated by two neighboring groups, as in 1,3-dicarbonyl compounds, the acidity increases enormously. Even in water solution, ethyl acetoacetate can act as an acid and transfer proton to a water molecule serving as a base. The increased acidity (by factor of 10^{14}!) of a β-keto ester in respect to an ester is due to the ability of carbonyl group to accept the generated negative charge. Notice that it is the methylene group flanked by the two carbonyl groups that is deprotonated, or more acidic. Both carbonyl groups participate in stabilizing enolate by delocalizing its negative charge which as a result is highly delocalized charge, as shown.

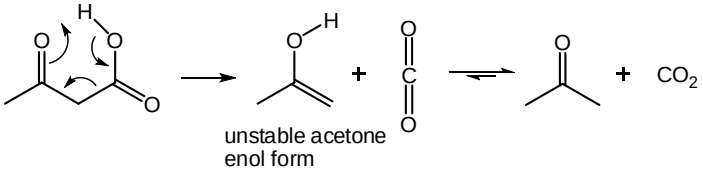




Experimental evidence for the increased acidity of a β-dicarbonyl compound is the replacement of the α-hydrogens in cyclohexane-1,3-dione with deuterium atoms when treated in solution of NaOD in heavy water (D_2O).

Decarboxylation is a typical reaction of β-keto acids and β-keto carboxylates, whereas carboxylic acids and their salts are usually thermally stable. Examples for β-dicarbonyl compounds that decarboxylate easily are: malonic acid ($HOOCCH_2COOH$) and acetoacetic acid (CH_3COCH_2COOH, 3-oxobutanoic acid). The presence

of carbonyl group beta to the carboxylic acid is essential for the cyclic mechanism of decarboxylation. It involves rearrangement of six electrons in a cyclic six-membered transition state (an example of concerted mechanism).

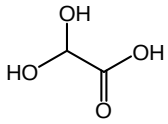


Acetoacetic acid decomposes easily at a moderate rate to acetone and carbon dioxide:
The basic form (the anion) reacts more slowly in water (a half-life of 130 hours at 37°C) than the acid form (half-life of 140 minutes).

II. Representatives. A) Formyl carboxylic acids.

OHC—COOH
glyoxylic acid

1. Glyoxylic acid. Glyoxylic acid or oxoacetic acid (oxoethanoic or formylformic acid) is the simplest aldehyde carboxylic acid. The compound is found in sour green fruits.
The conjugate base (anion) of glyoxylic acid is known as glyoxylate. This compound is an intermediate of the glyoxylate cycle, which enables bacteria, fungi, and plants to convert fatty acids into carbohydrates. The stable form of glyoxylic acid is its monohydrate.

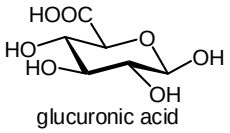


$OHC-CH_2-COOH$
formylacetic acid

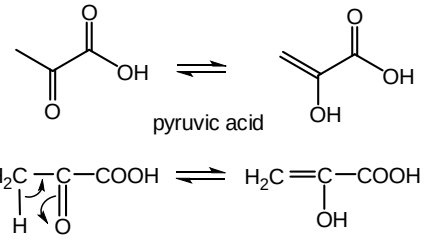
2. Formylacetic acid does not occur in Nature and its esters are unstable but can be formed *in situ*, e.g. from decarbonylation of malic acid and used in organic synthesis.

$OHC-(CHOH)_n-COOH$
uronic acid (class name)

3. Uronic acid is a hydroxyaldehyde carboxylic acid (sugar acid). It is best thought of as a sugar in which the terminal carbon's hydroxyl function has been oxidized to a carboxylic acid. (Oxidation of the terminal aldehyde instead yields an aldonic acid while oxidation of both the terminal hydroxyl group and the aldehyde yields an aldaric acid.) The names of uronic acids are generally based on their parent sugars, e.g **glucuronic acid**.
Many waste products of metabolism and other non-useful materials are excreted (eliminated) from human body in the urine as glucuronate salts or esters.



B) Keto carboxylic acids.

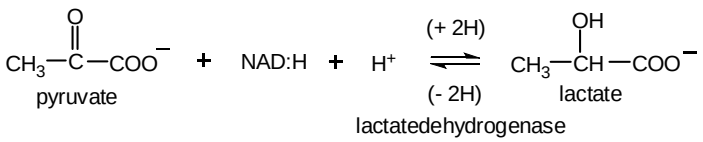


1. Pyruvic acid (*ac. Pyruvicum*). Pyruvic acid (α-ketopropionic acid) is the simplest α-keto acid. Its carboxylate ion and its esters are called, pyruvate. They are known to show keto-enol tautomerism. The keto-form is monoprotic acid, enol – diprotic (with two mobile, acidic H). The last form is stronger acid than propionic or lactic acids.

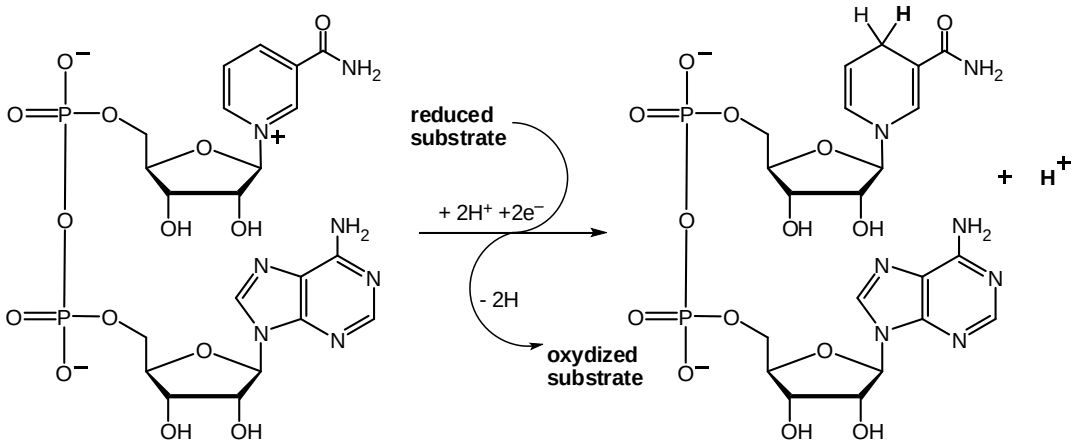
Pyruvate is a key intersection in several metabolic pathways. Metabolically it is produced from glucose through glycolysis (both aerobic and anaerobic); supplies energy to living cells in the citric acid cycle, and can also be converted to carbohydrates, to fatty acids or to energy through acetyl-CoA, to the amino acid alanine and to ethanol.

Pyruvate is intermediate in aerobic cell respiration. In aerobic organisms, a complex mechanism has evolved to use the oxygen in air as the final electron acceptor of respiration. Glycolysis is a metabolic pathway that converts one molecule of glucose into two molecules of pyruvate. The process does not require oxygen (it is anaerobic). Then the pyruvate enters the mitochondrion in order to be fully oxidized by the Krebs cycle:

- Pyruvate is converted to acetyl-CoA and CO_2 within the mitochondria in a process called pyruvate decarboxylation.
- The acetyl-CoA enters the citric acid cycle, where it is fully oxidized to carbon dioxide and water, producing yet more NADH.
- NADH is oxidized to NAD^+ by the electron transport chain, using oxygen as the final electron acceptor. This process creates a "hydrogen ion gradient" across the inner membrane of the mitochondria.
- This proton gradient is used to produce a large amount of ATP in a process called oxidative phosphorylation.



One of the many examples of redox processes in cells is the conversion of the keto group in pyruvate ion into secondary alcohol of the lactate ion. **Pyruvic acid is reduced to lactic acid** when the demand for energy is high and oxygen supply is relatively low. This reduction is accompanied with transfer of hydride ion (from NAD:H) and a proton, or as a sum, of two hydrogen atoms to pyruvate.

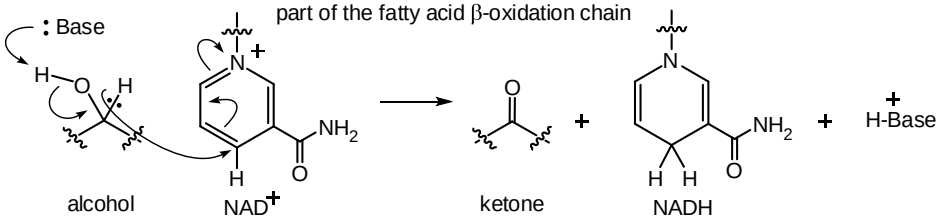


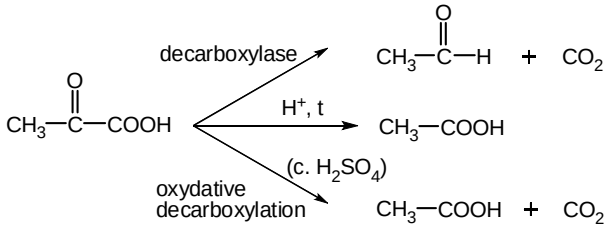
NAD+, Nicotinamide adenine dinucleotide

NADH, Reduced nicotinamide adenine dinucleotide

Lactate production is associated with rising NAD^+ level. The main role of NAD^+ in metabolism is the transfer of electrons from one molecule to another. Reactions of this type are catalyzed by a large group of enzymes called oxidoreductases, e.g. alcohol dehydrogenase.

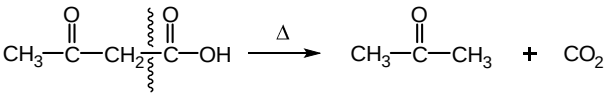
Enzyme-catalyzed reductions of carbonyl groups are completely stereoselective, that is only one of two (or more) stereoisomers is produced. Pyruvic acid is converted exclusively to (*S*)-(+)-lactic acid by the lactatedehydrogenase-NADH system. The enantiomer (*R*)-(**–**)-lactic acid is not formed. In this reaction, the enzyme (a chiral molecule) binds the coenzyme and substrate in such a way that hydrogen is transferred only to one face of the flat carbonyl group. The reversed, oxidation reaction proceeds also with preferential stereo orientation. The abbreviated equation involving hydride ion transfer from an alcohol to NAD^+ is shown:





Depending on the conditions pyruvic acid can decarboxylate, or undergo oxidative decarboxylation.

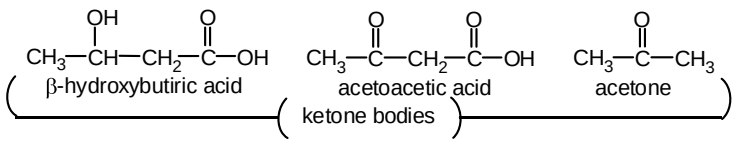
2. Acetoacetic acid (3-ketobutanoic acid). Its salts are acetoacetates. The free acid is unstable and decarboxylates – the process is ketone cleavage.



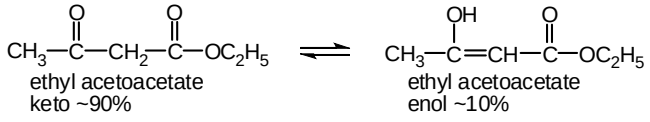
β-Keto acids are less stable than α-keto acids where conjugation of both carbonyl groups stabilizes the molecule.

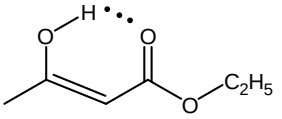
Ketone cleavage is responsible for rancidity of fats. Rancidity is due to the chemical decomposition of fats, oils and other lipids. When these processes occur in food, undesirable odors and flavors can result. Oxidative rancidity is associated with the degradation by oxygen in the air. Via a free radical process, the double bonds of an unsaturated fatty acid can undergo cleavage, releasing volatile aldehydes and ketones with unpleasant and noxious odors and flavors.

Acetoacetic acid is product of β-hydroxybutyric acid oxidation. β-Hydroxybutyric acid, acetoacetic acid and acetone are collectively called **ketone bodies**. An improper metabolism, as in diabetes, leads to accumulation of ketone bodies. Both acetoacetic acid and β-hydroxy-butyric acid are acidic, and, if levels of these ketone bodies are too high, the pH of the blood drops, resulting in ketoacidosis.

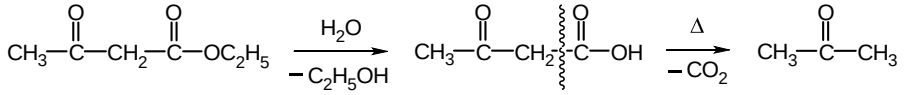


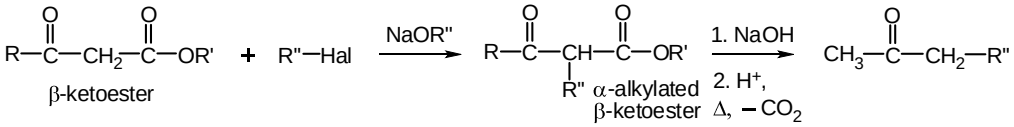
Esters and salts of β-keto carboxylic acids are more stable than the free acids. Ethyl acetoacetate exists as a mixture of keto and enol forms. Ethyl acetoacetate is a classical example for keto-enol tautomerism. The keto-form is proven by reactions with bisulfite (HSO_3^-), hydrogen cyanide (HCN), hydrazine (NH_2NH_2), and the enol form – by complex formation with $FeCl_3$. The enol double bond reacts with Br_2. The enol form is stabilized to a certain extent by intramolecular hydrogen bond and conjugation of a double bond with the carbonyl, resulting in electron delocalization, thus increased stability.

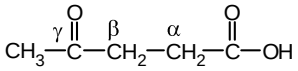




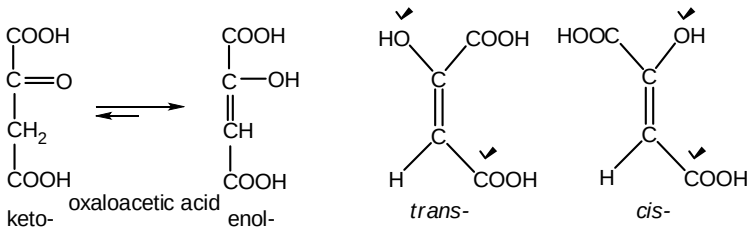
After hydrolysis of ethyl acetoacetate occurs cleavage of the bond between COOH and C(α), leading to decarboxylation. This seemingly simple reaction has principle importance in organic synthesis. Because of the high acidity of α-hydrogens, this position of a starting β-keto ester can be alkylated using alkyl halide (R"-Hal). Base hydrolysis of the product, followed by acidification and brief treatment at elevated temperature gives a ketone.



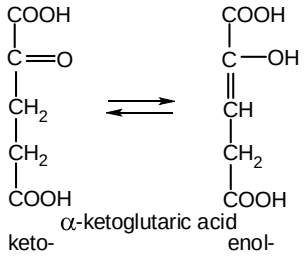




3. Levulinic acid (γ-ketovaleric acid) behaves chemically as monofunctional compounds – a ketone and carboxylic acid. Levulinic acid is obtained by heating of hexoses or starch with conc. HCl. This acid is stable acid, does not decarboxylate easily. The amino substituted derivative, δ-aminolevulinic acid is the biogenetic precursor of pyrrole ring in synthesis of hem.



4. Oxaloacetic acid (oxaloacetate) is product of oxidation of malic acid (in living cells using the enzyme – malate dehydrogenase). Participates in the malate-oxaloacetate redox pair in the cycle of citric acid (Krebs' cycle). Oxaloacetic acid is converted into citric acid by addition of acetyl CoA. Oxaloacetic acid exists as keto-enol tautomeric mixture. The enol form is more stable due to π-π conjugation. The enol form can be separated into *cis*- and *trans*- geometrical isomers. Free oxaloacetate is unstable in solution, decomposing to pyruvate by decarboxylation of the γ-COOH (room temperature).



5. α-Ketoglutaric acid (α-ketoglutarate) is obtained in the citric acid cycle by oxidation of isocitric acid followed by decarboxylation of the β-COOH. α-Ketoglutaric acid exists as keto and enol forms.