Disciplina: SLC0673

Ciclos energéticos vitais

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The citric acid cycle,

The tricarboxylic acid (TCA) cycle

or

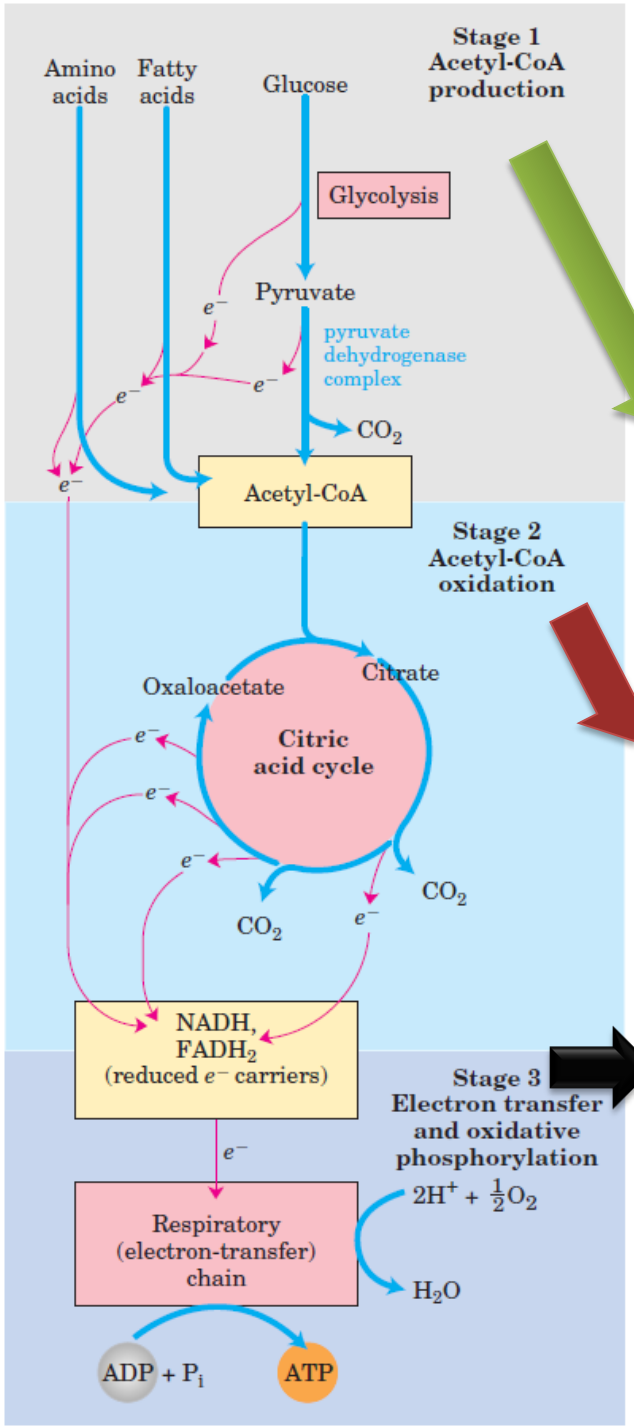
The Krebs cycle

Cellular Respiration

Rather than being reduced to lactate, ethanol, or some other fermentation product, the pyruvate produced by glycolysis is further oxidized to H_2O and CO_2. This aerobic phase of catabolism is called (cellular) respiration.

In the broader physiological or macroscopic sense, respiration refers to a multicellular organism's uptake of O_2 and release of CO_2.

Cellular Respiration



Cellular respiration occurs in three major stages:

Organic fuel molecules-glucose, fatty acids, and some amino acids-are oxidized to yield two-carbon fragments in the form of the acetyl group of acetyl-coenzyme A (acetyl-CoA).

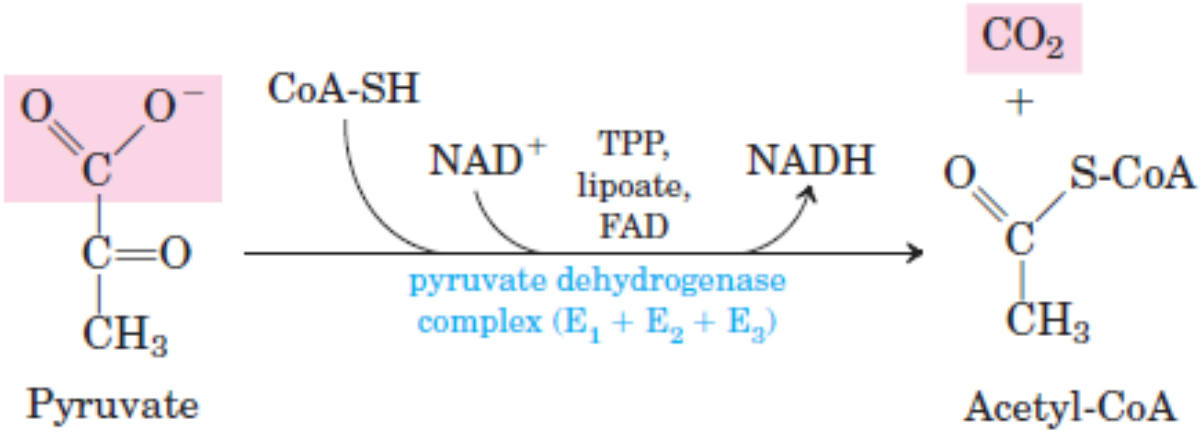
The acetyl groups are fed into the citric acid cycle, which enzymatically oxidizes them to CO_2; the energy released is conserved in the reduced electron carriers NADH and $FADH_2$.

Reduced coenzymes are oxidized, giving up protons and electrons. The electrons are transferred to O_2 via a chain of electron-carrying molecules known as the respiratory chain. The large amount of energy released is conserved in the form of ATP, by a process called oxidative phosphorylation.

Acetyl-CoA production

Before entering the citric acid cycle, the carbon skeletons of sugars and fatty acids are degraded to the acetyl group of acetyl-CoA.

Pyruvate, derived from glucose and other sugars by glycolysis, is oxidized to acetyl-CoA and CO_2 by the **pyruvate dehydrogenase (PDH) complex,** a cluster of enzymes—multiple copies of each of three enzymes—located in the mitochondria of eukaryotic cells and in the cytosol of prokaryotes.

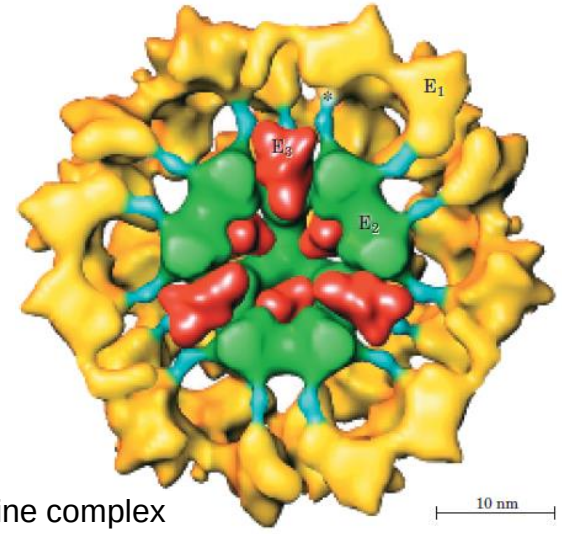


$\Delta G'^{\circ} = -33.4$ kJ/mol

Acetyl-CoA production

It is necessary to use **three different enzymes** (pyruvate dehydrogenase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3)) and **five different coenzymes or prosthetic groups**—thiamine pyrophosphate (TPP), flavin adenine dinucleotide (FAD), coenzyme A (CoA, sometimes denoted CoA-SH, to emphasize the role of the OSH group), nicotinamide adenine dinucleotide (NAD), and lipoate.

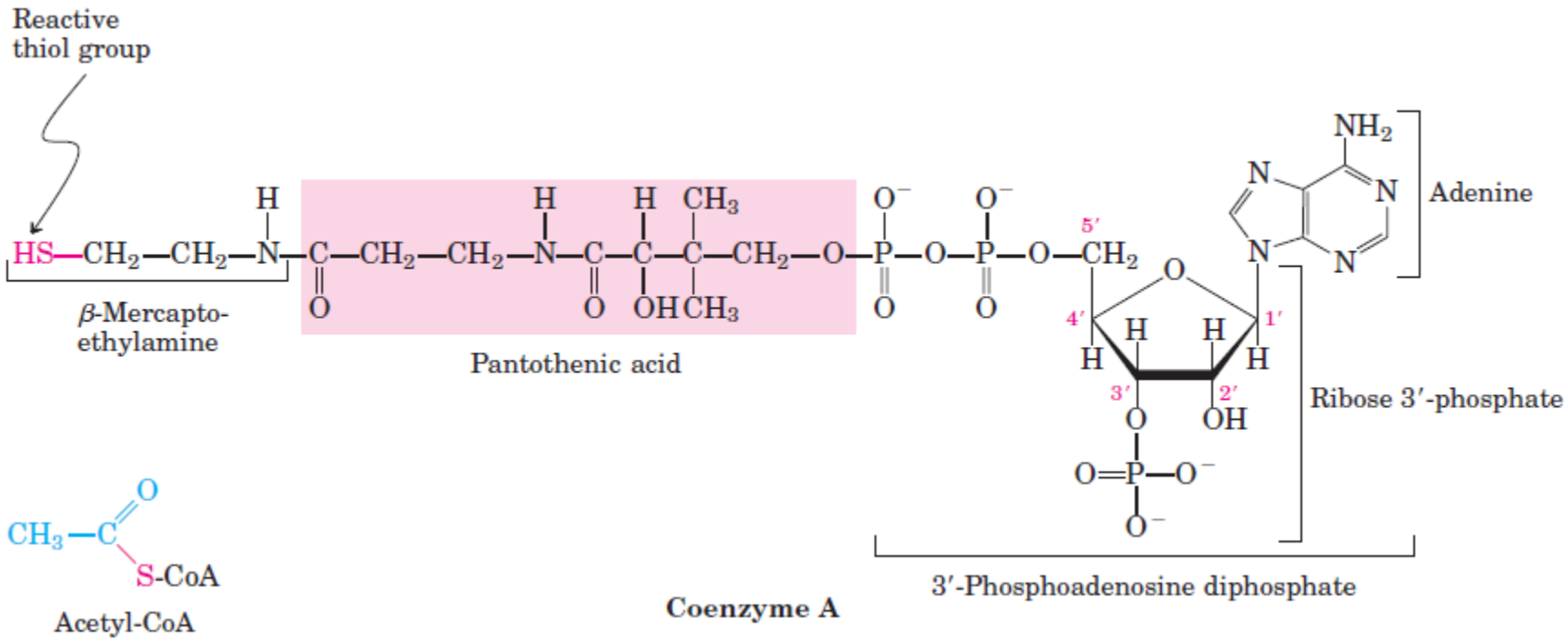
Four different vitamins are required in human nutrition are vital components of this system: thiamine (in TPP), riboflavin (in FAD), niacin (in NAD), and pantothenate (in CoA).



Bovine complex with 3 enzymes

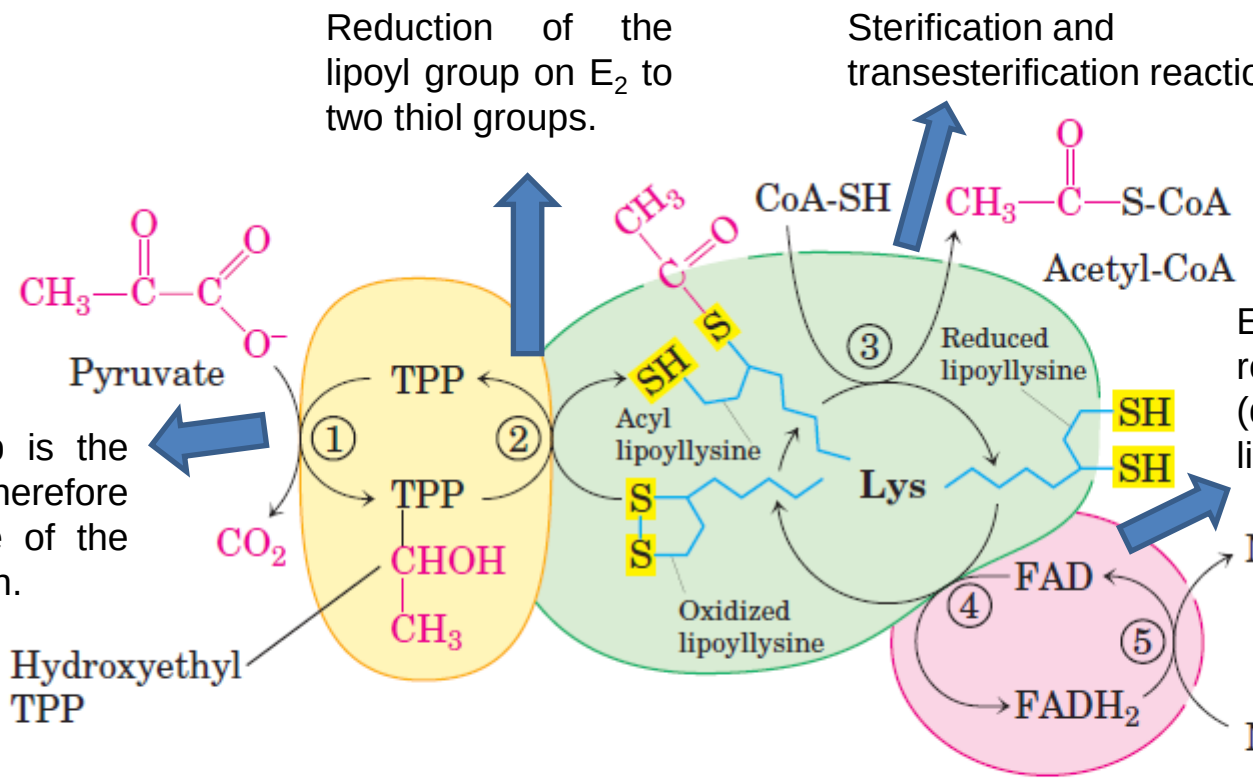
Acetyl-CoA production

The transfer of electrons from NADH to oxygen ultimately generates 2.5 molecules of ATP per pair of electrons.



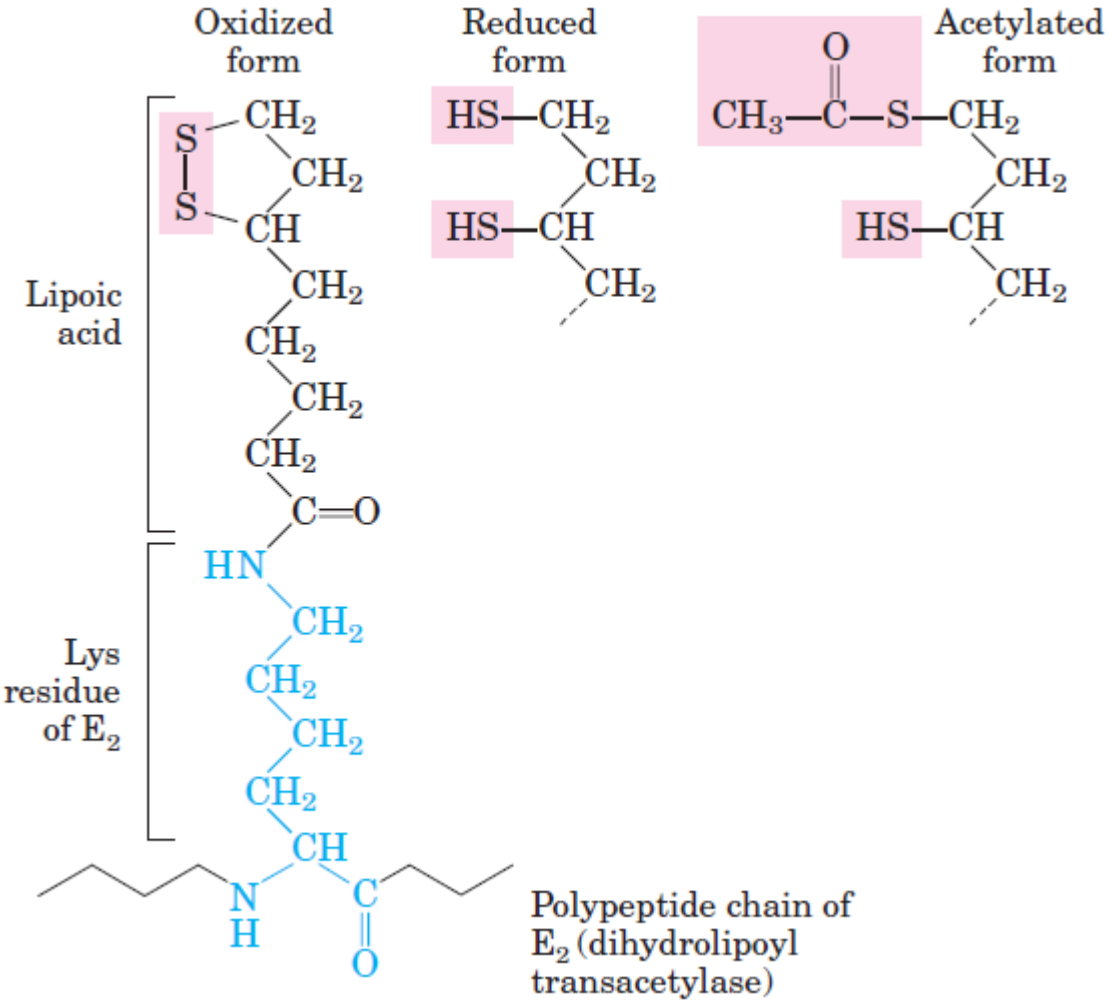
Substrate channeling

Oxidative decarboxylation of pyruvate to acetyl-CoA by the PDH complex.



Importance of the lipoate

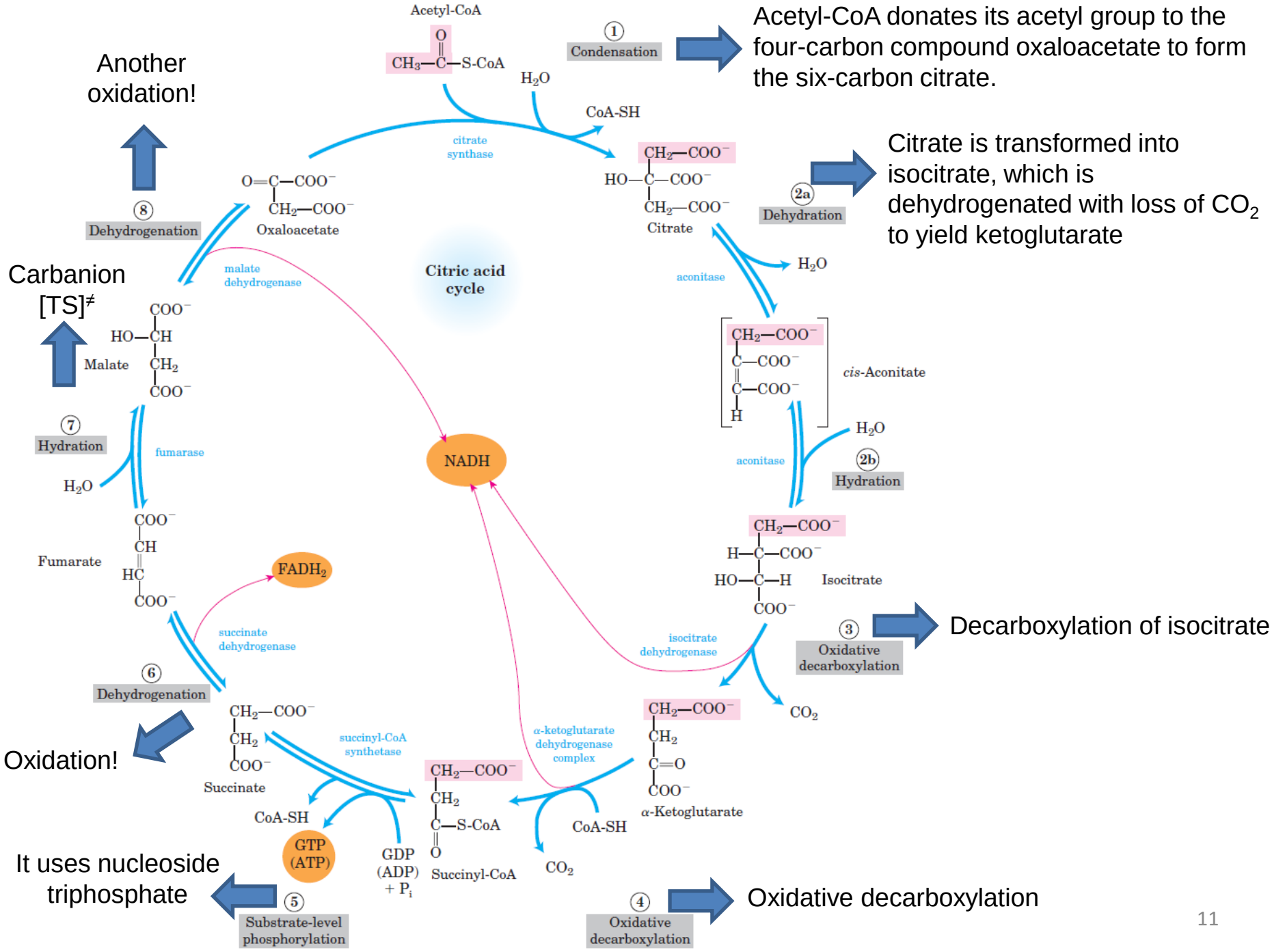
Lipoate has two thiol groups that can undergo reversible oxidation to a disulfide bond (OSOSO), similar to that between two Cys residues in a protein. Because of its capacity to undergo oxidation-reduction reactions, lipoate can serve both as an electron hydrogen carrier and as an acyl carrier.



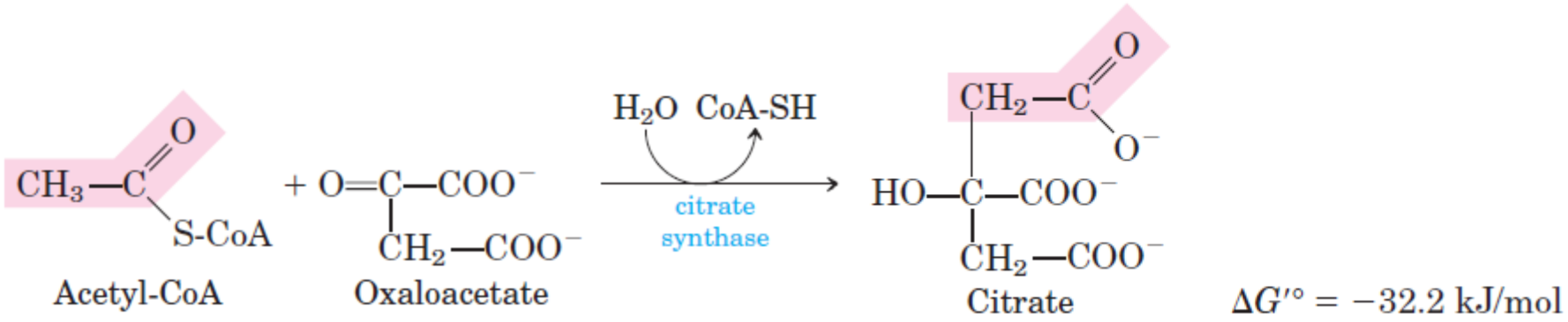
Reactions of the Citric Acid Cycle

Acetyl-CoA undergoes oxidation by the citric acid cycle.

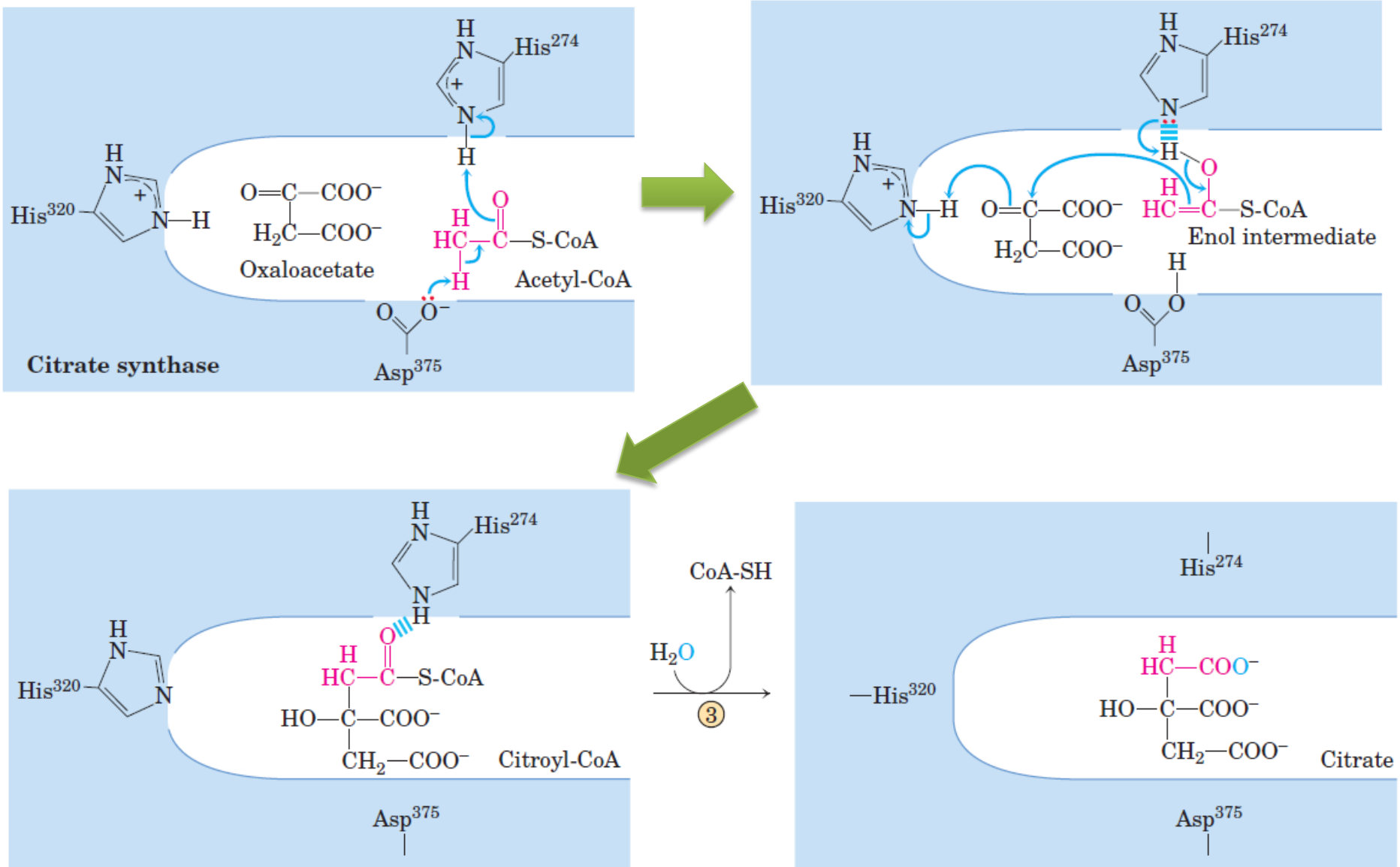
Many steps are involved in this cycle, shown in the next slide.


Acetyl-CoA donates its acetyl group to the four-carbon compound oxaloacetate to form the six-carbon citrate.
Citrate is transformed into isocitrate, which is dehydrogenated with loss of CO_2 to yield ketoglutarate
Decarboxylation of isocitrate
Oxidative decarboxylation
It uses nucleoside triphosphate
Oxidation!
Carbanion [TS]≠
Another oxidation!
Acetyl-CoA
1 Condensation
citrate synthase
CoA-SH
H_2O
Citrate
2a Dehydration
aconitase
H_2O
cis-Aconitate
aconitase
2b Hydration
H_2O
Isocitrate
3 Oxidative decarboxylation
CO_2
isocitrate dehydrogenase
NADH
α-ketoglutarate dehydrogenase complex
α-Ketoglutarate
CO_2
CoA-SH
Succinyl-CoA
4 Oxidative decarboxylation
GDP (ADP) + P_i
GTP (ATP)
5 Substrate-level phosphorylation
succinyl-CoA synthetase
CoA-SH
Succinate
6 Dehydrogenation
succinate dehydrogenase
$FADH_2$
Fumarate
7 Hydration
fumarase
H_2O
Malate
8 Dehydrogenation
malate dehydrogenase
Oxaloacetate
Citric acid cycle

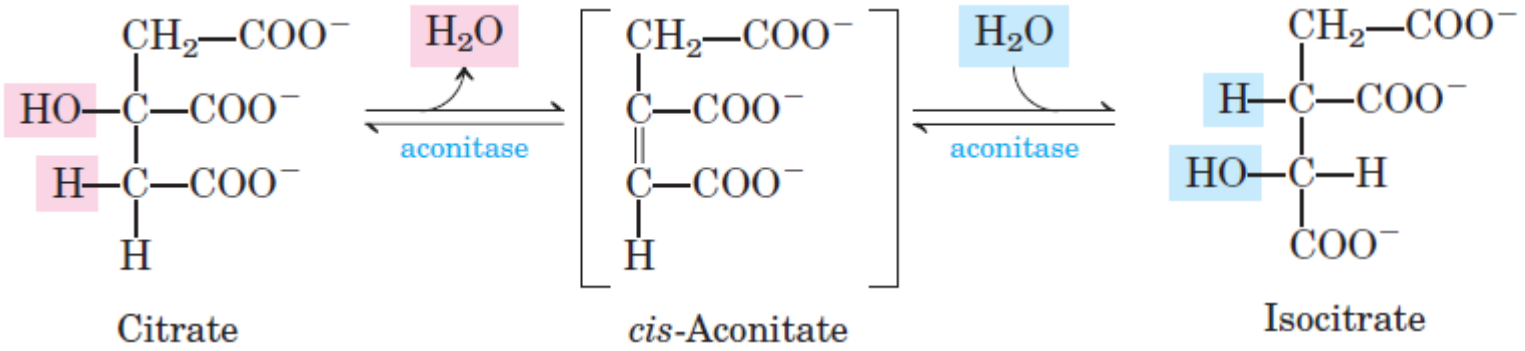
Citrate synthase



Citrate synthase

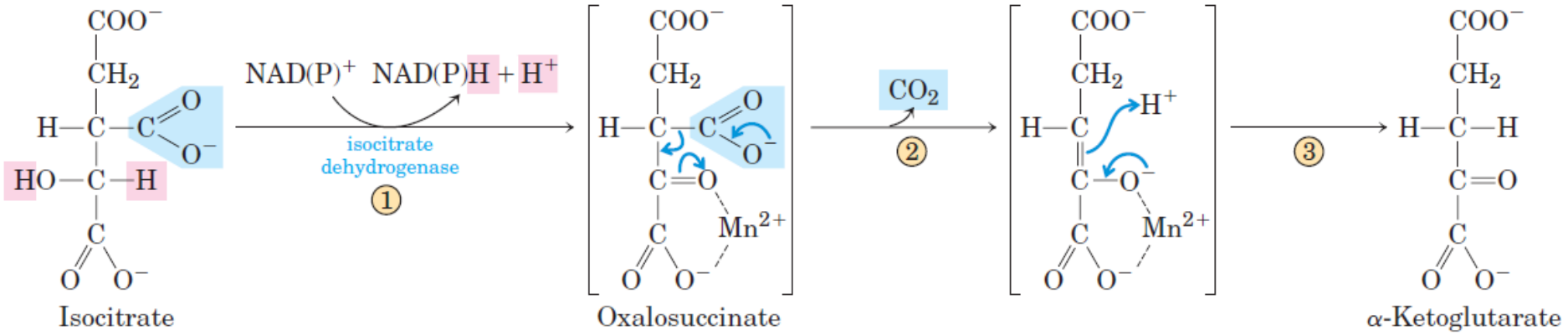


Aconitase

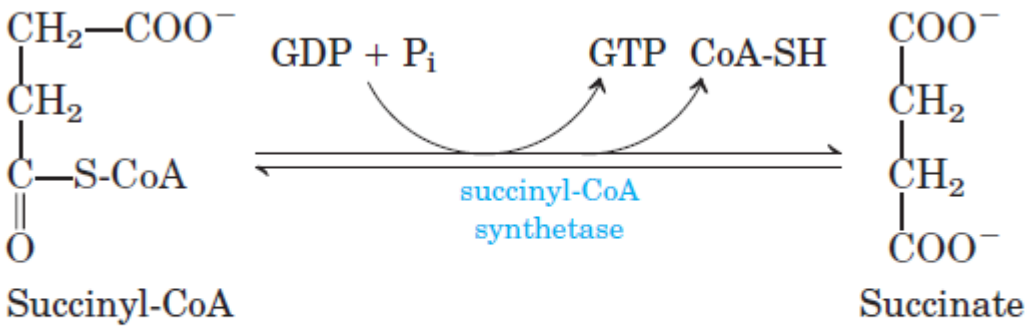


$\Delta G'^{\circ} = 13.3$ kJ/mol

Isocitrate dehydrogenase

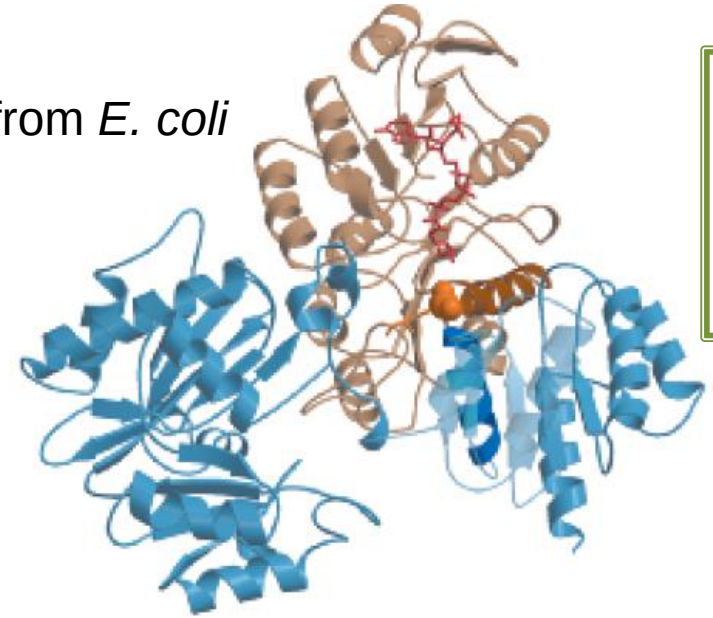


Succinyl-CoA synthetase



$$\Delta G'^{\circ} = -2.9 \text{ kJ/mol}$$

Enzyme from *E. coli*

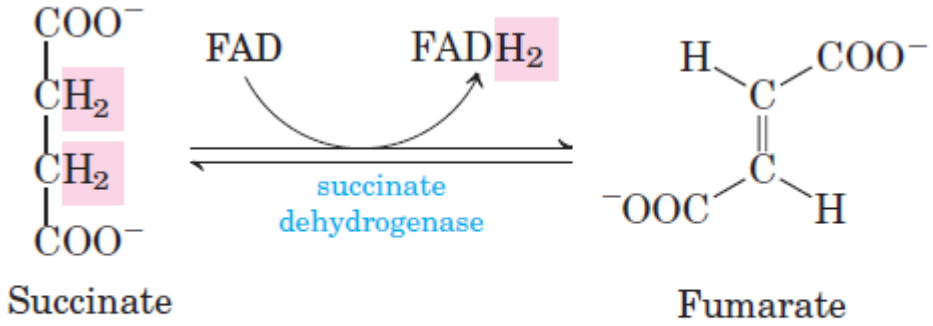


Reaction catalyzed by nucleoside diphosphate kinase

$$\text{GTP} + \text{ADP} \longrightarrow \text{GDP} + \text{ATP} \qquad \Delta G'^{\circ} = 0 \text{ kJ/mol}$$

Succinate dehydrogenase

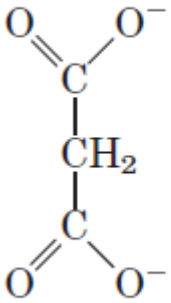
In eukaryotes, succinate dehydrogenase is tightly bound to the inner mitochondrial membrane; in prokaryotes, to the plasma membrane.



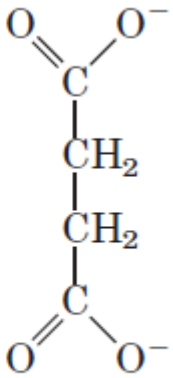
Succinate

Fumarate

$\Delta G'^{\circ} = 0$ kJ/mol



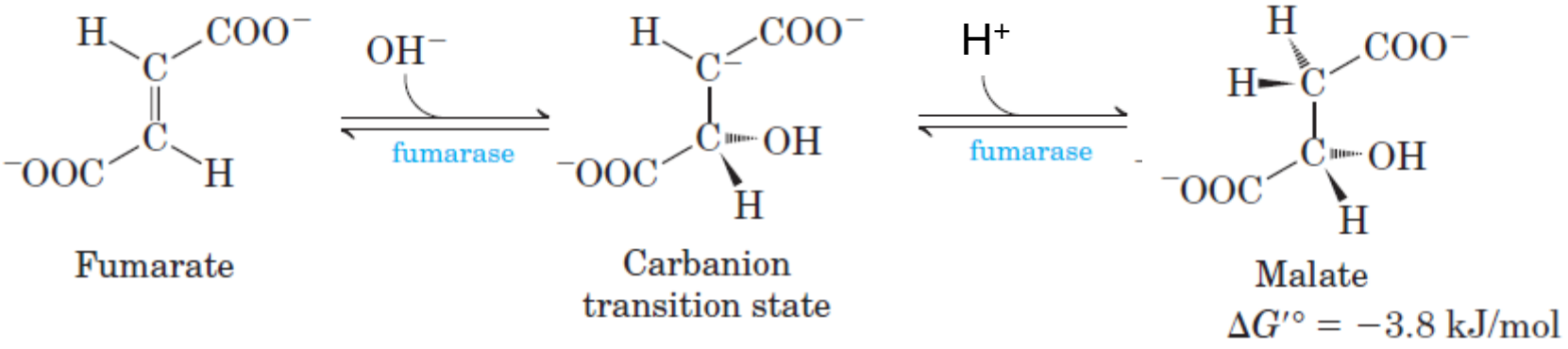
Malonate



Succinate

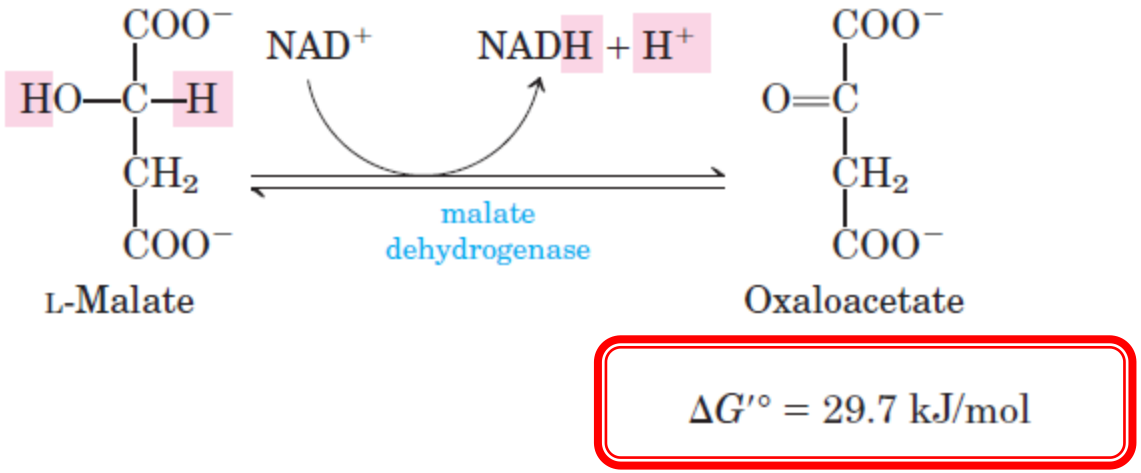
Malonate is a succinate competitor, but it is not present inside the cell

Fumarase



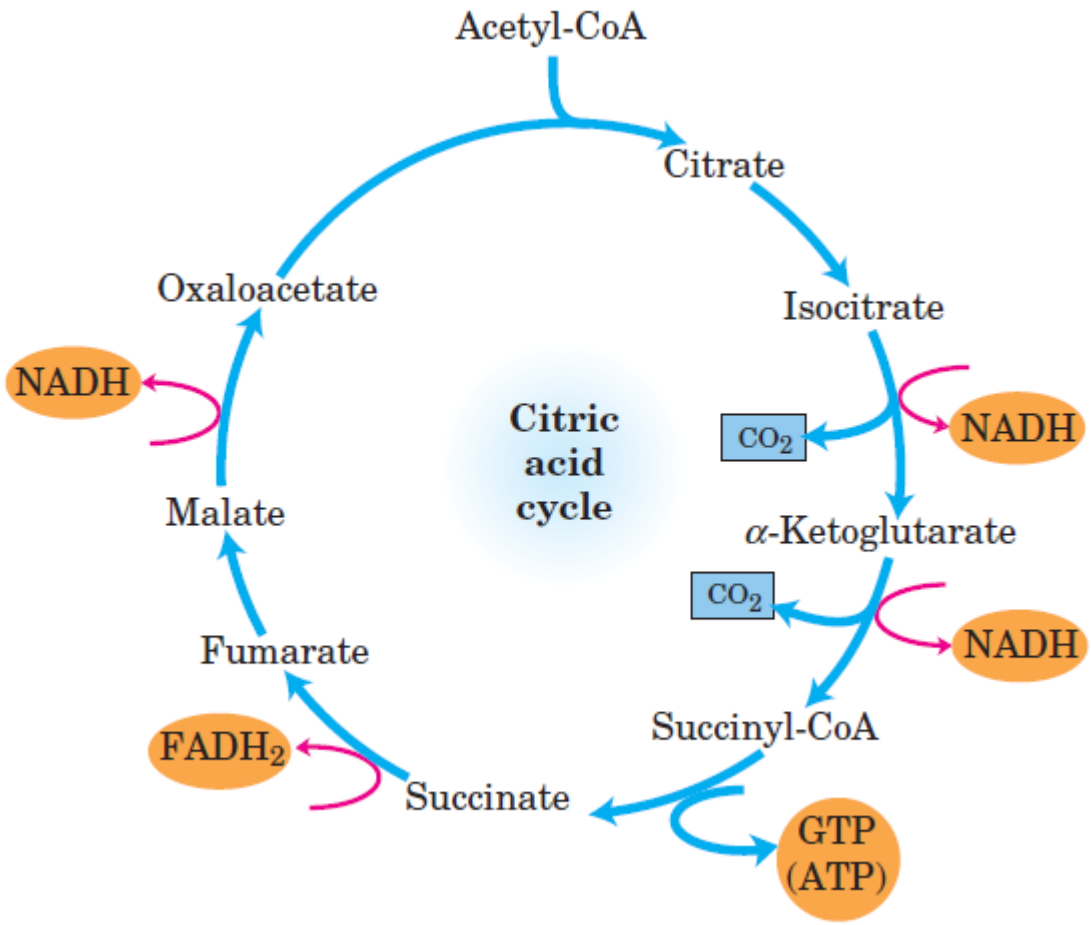
Stereospecificity!!!

Malate dehydrogenase

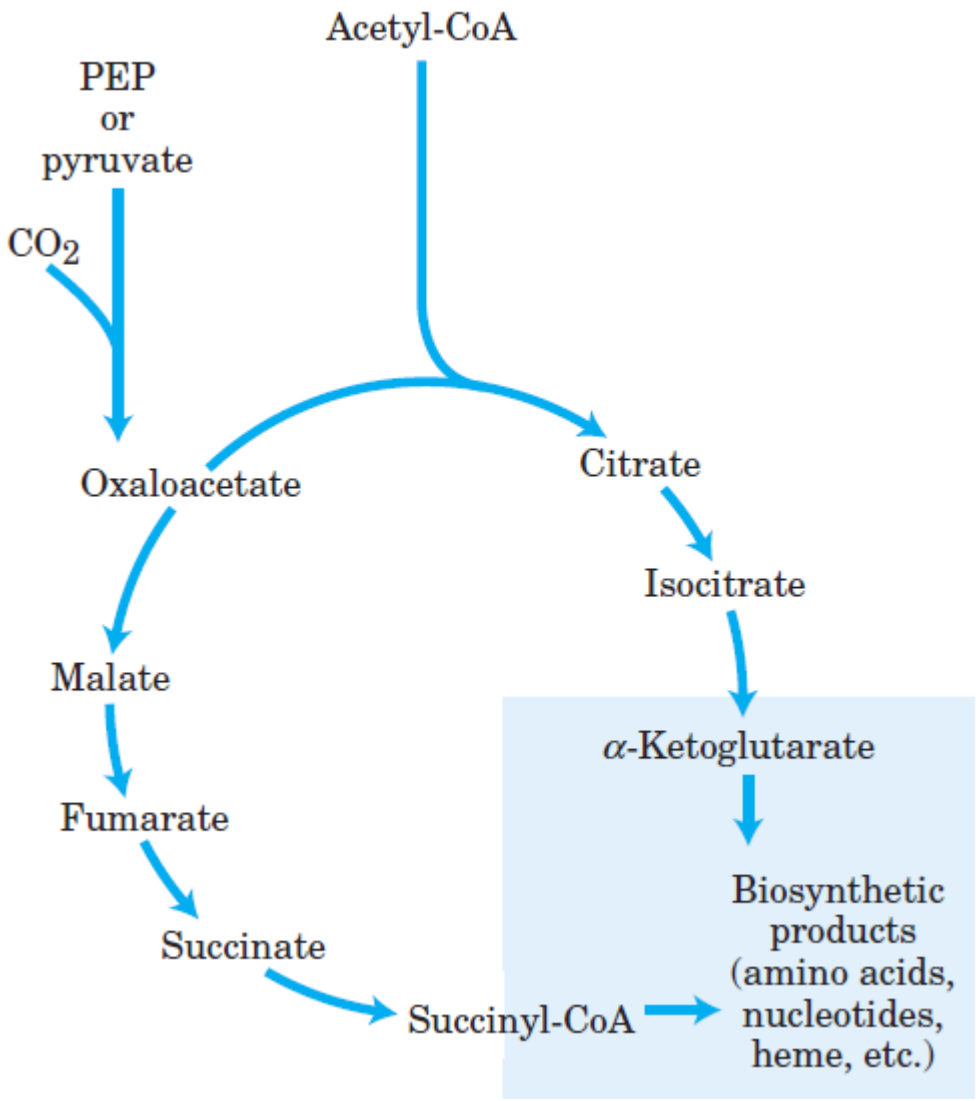


Oxaloacetate is continually removed from the cell

Products of the citric acid cycle



Incomplete citric acid cycle in anaerobic bacteria



Role of the citric acid cycle in anabolism