KREB'S CYCLE

CC-12
UNIT-4

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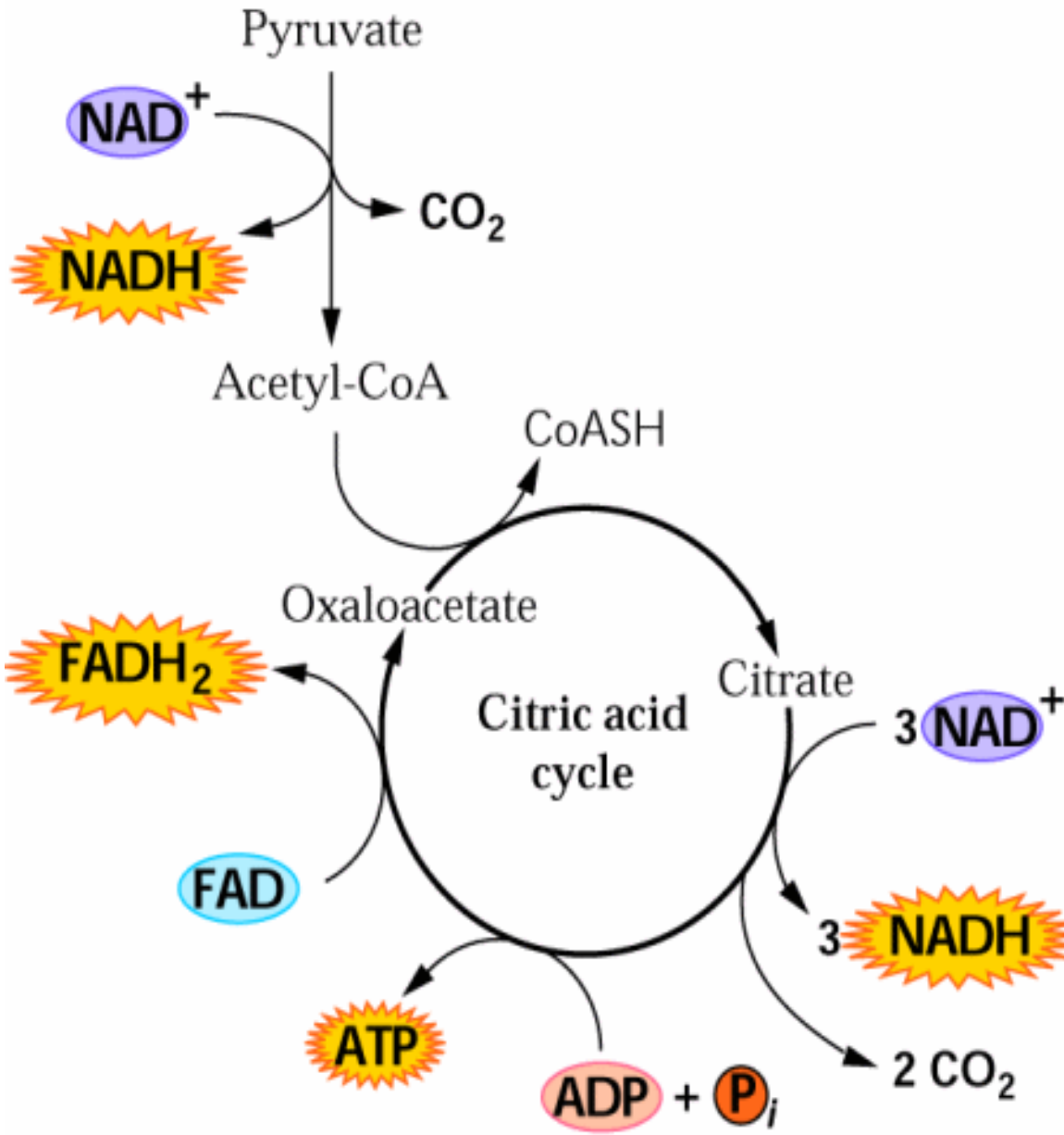
Kreb's cycle

Series of reactions that oxidize acetyl CoA to $2CO_2$ in a manner that conserves the liberated free energy for ATP production.

Breakdown products of glc, fats and amino acids are all oxidized via the cycle.

Intermediates also a source for many biosynthetic pathways -"amphibolic" which means serves in both catabolic and anabolic processes

Also called "TCA cycle" - tricarboxylic acid cycle or "Krebs cycle"



Discovery

- Several of the components and reactions of the citric acid cycle were established in the 1930s by the research of Albert Szent-Györgyi, who received the Nobel Prize in Physiology or Medicine in 1937
- The citric acid cycle itself was finally identified in 1937 by Hans Adolf Krebs and William Arthur Johnson while at the University of Sheffield, for which the former received the Nobel Prize for Physiology or Medicine in 1953, and for whom the cycle is sometimes named (Krebs cycle).

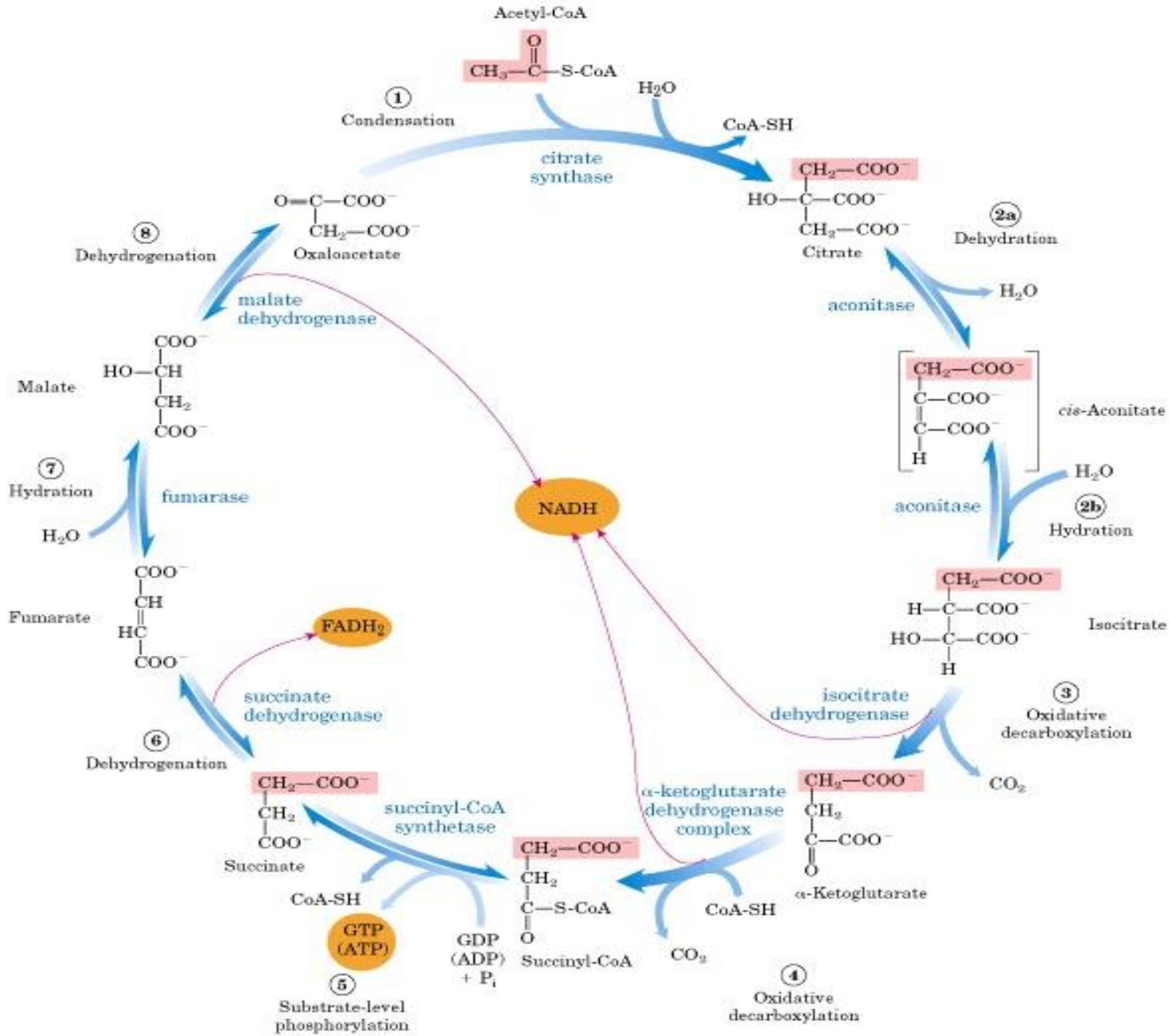
Overview

- The citric acid cycle is a key metabolic pathway that connects carbohydrate, fat, and protein metabolism.
- The reactions of the cycle are carried out by eight enzymes that completely oxidize acetate, in the form of acetyl-CoA, into two molecules each of carbon dioxide and water. Through catabolism of sugars, fats, and proteins, the two-carbon organic product acetyl-CoA (a form of acetate) is produced which enters the citric acid cycle.

Overview

- The reactions of the cycle also convert three equivalents of nicotinamide adenine dinucleotide (NAD+) into three equivalents of reduced NAD+ (NADH), one equivalent of flavin adenine dinucleotide (FAD) into one equivalent of $FADH_2$, and one equivalent each of guanosine diphosphate(GDP) and inorganic phosphate (P_i) into one equivalent of guanosine triphosphate (GTP).
- The NADH and $FADH_2$ generated by the citric acid cycle are, in turn, used by the oxidative phosphorylation pathway to generate energy rich ATP.
- One of the primary sources of acetyl-CoA is from the breakdown of sugars by glycolysis which yield pyruvate that in turn is decarboxylated by the enzyme pyruvate dehydrogenase generating acetyl-CoA

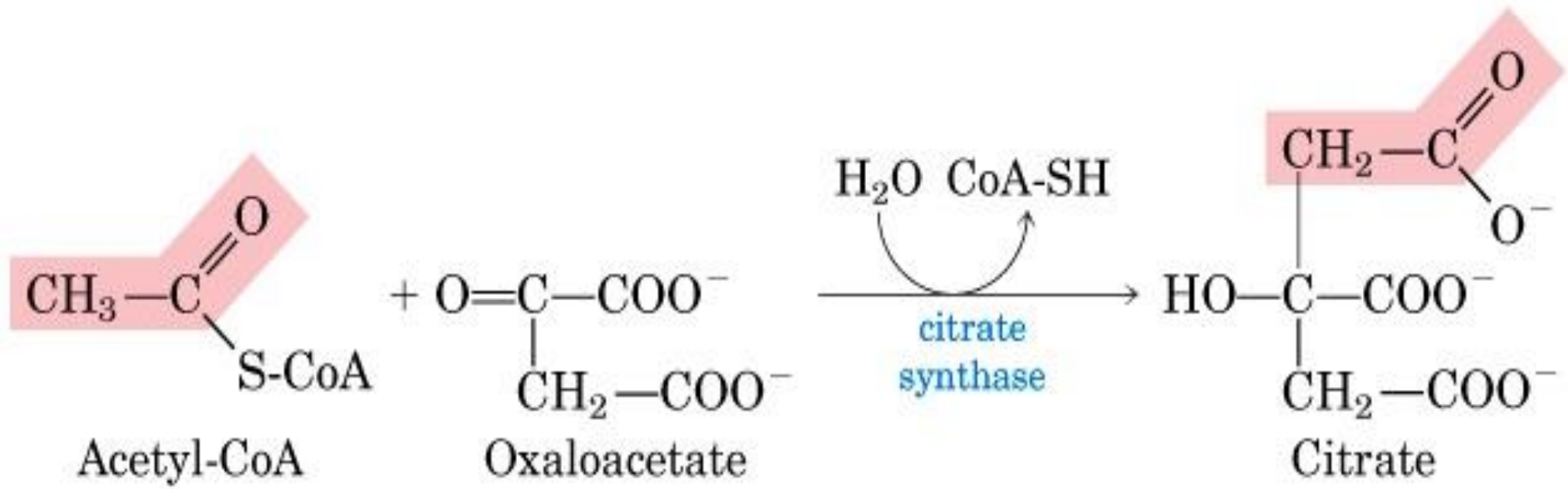
Citric Acid Cycle



[STEP 1] Citrate Synthase

The first reaction is a synthase reaction, called such since a new molecule is made but ATP is not used.

Oxaloacetate + Acetyl-CoA + H2O → Citrate + CoA



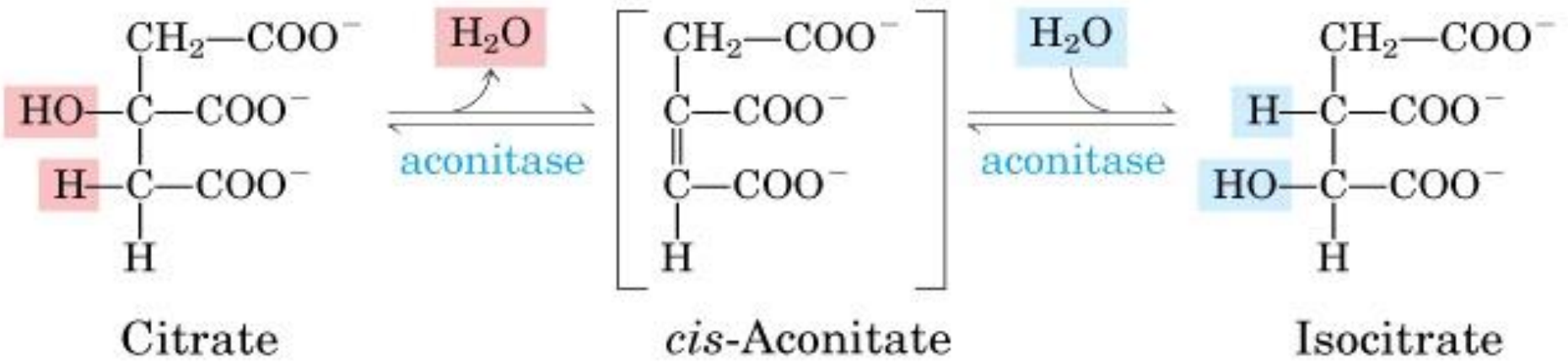
$\Delta G'^{\circ} = -32.2$ kJ/mol

[STEP 2] Aconitase.

Citrate ↔[H2O + cis-Aconitate] ↔ Isocitrate

This is a dehydration reaction followed by ahydration.

Aconitase uses an iron-sulfur cluster cofactor; Three Cys residues and multiple Fe atoms make the cluster.

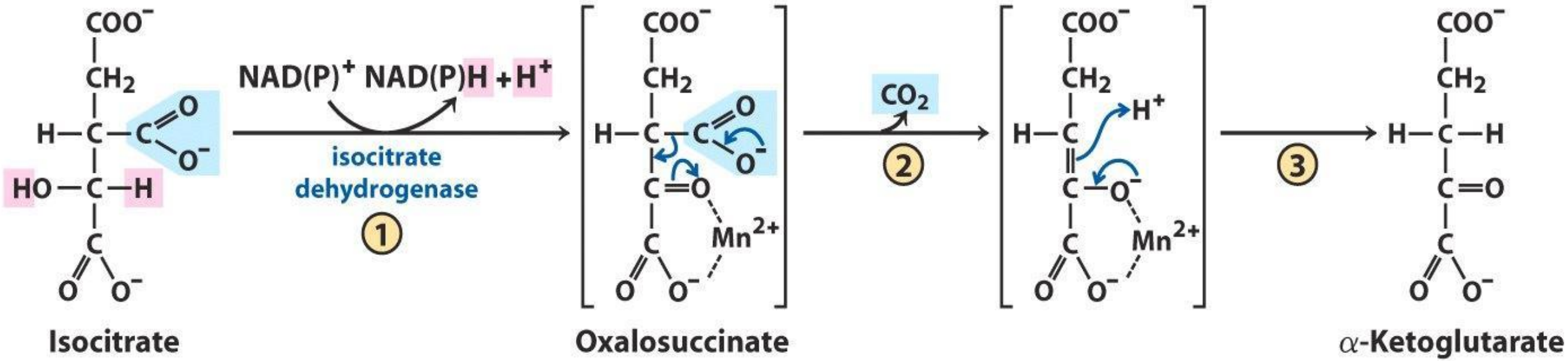


[STEP 3] Isocitrate Dehydrogenase.

Isocitrate →α-keto glutarate + CO2

This is an oxidation coupled to a hydride transfer to NAD+.

After hydride transfer, the enzyme uses a Mn2+-ion cofactor. The metal further enhances the electron withdrawing power of the carbonyl, facilitating decarboxylation.



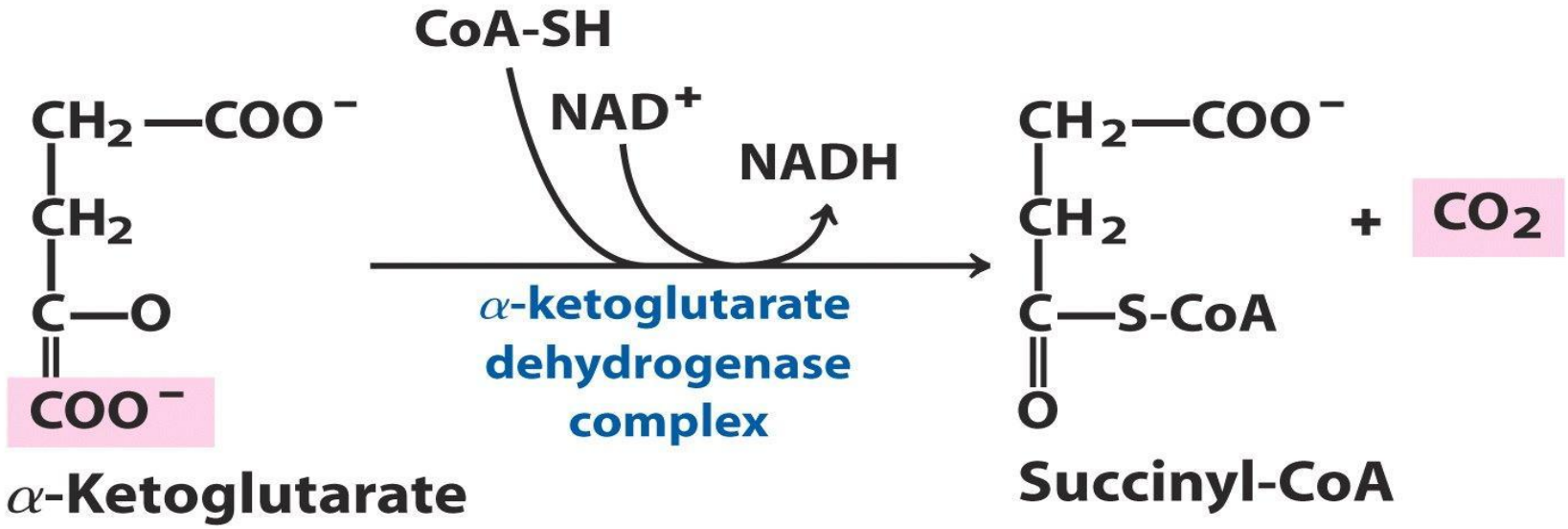
[STEP 4] α-Keto Glutarate Dehydrogenase.

α-keto glutarate + CoA → Succinyl-CoA

This enzyme splits the carbon-carbon bond;

It have five coenzymes: TPP, lipoyllysine, CoA,FAD and NAD^+. These are all used, and oxidation takes place.

The decarboxylated product, succinyl-CoA, occurs as a thioester.

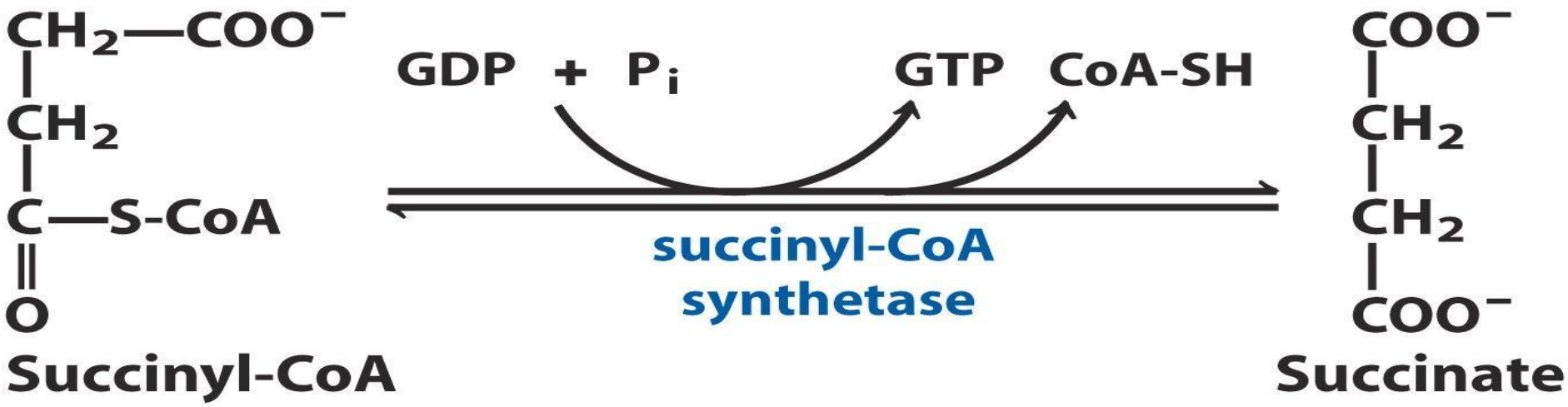


$\Delta G'^{\circ} = -33.5$ kJ/mol

[STEP 5] Succinyl-CoA Synthetase.

Succinyl-CoA + GDP + Pi →Succinate + GTP

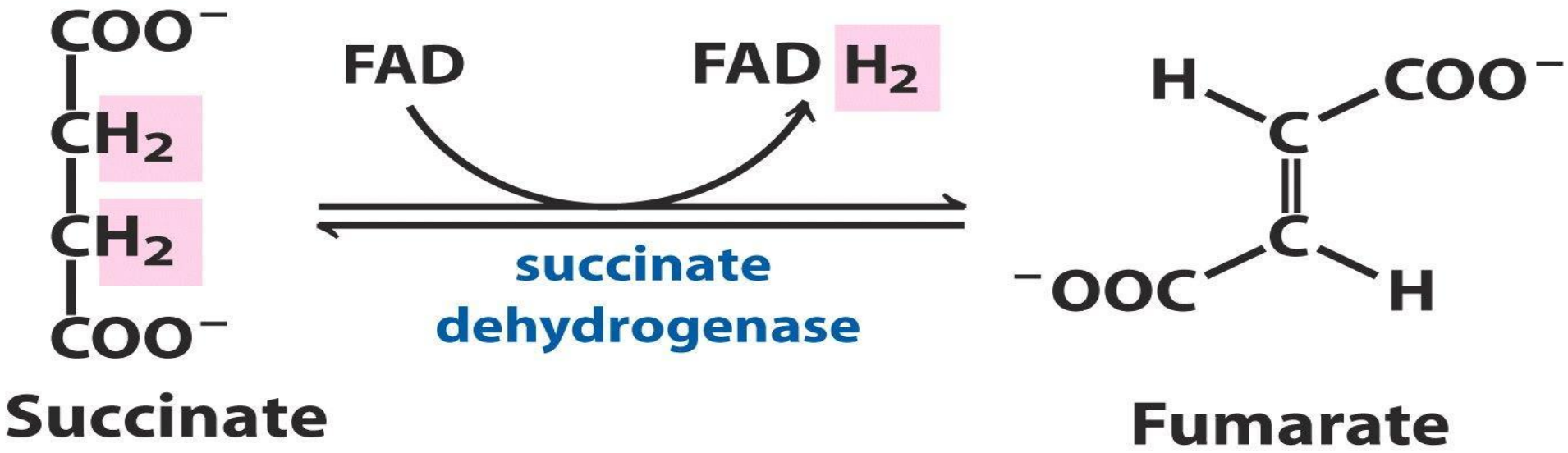
Phosphorylysis reaction is followed by phosphoryl transfer to GDP, producing succinate plus GTP.



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

[STEP 6] Succinate Dehydrogenase

The next step is succinate dehydrogenase. Starting from succinate and take away two hydrogen atoms to make fumerate. FAD is reduced to form FADH2.

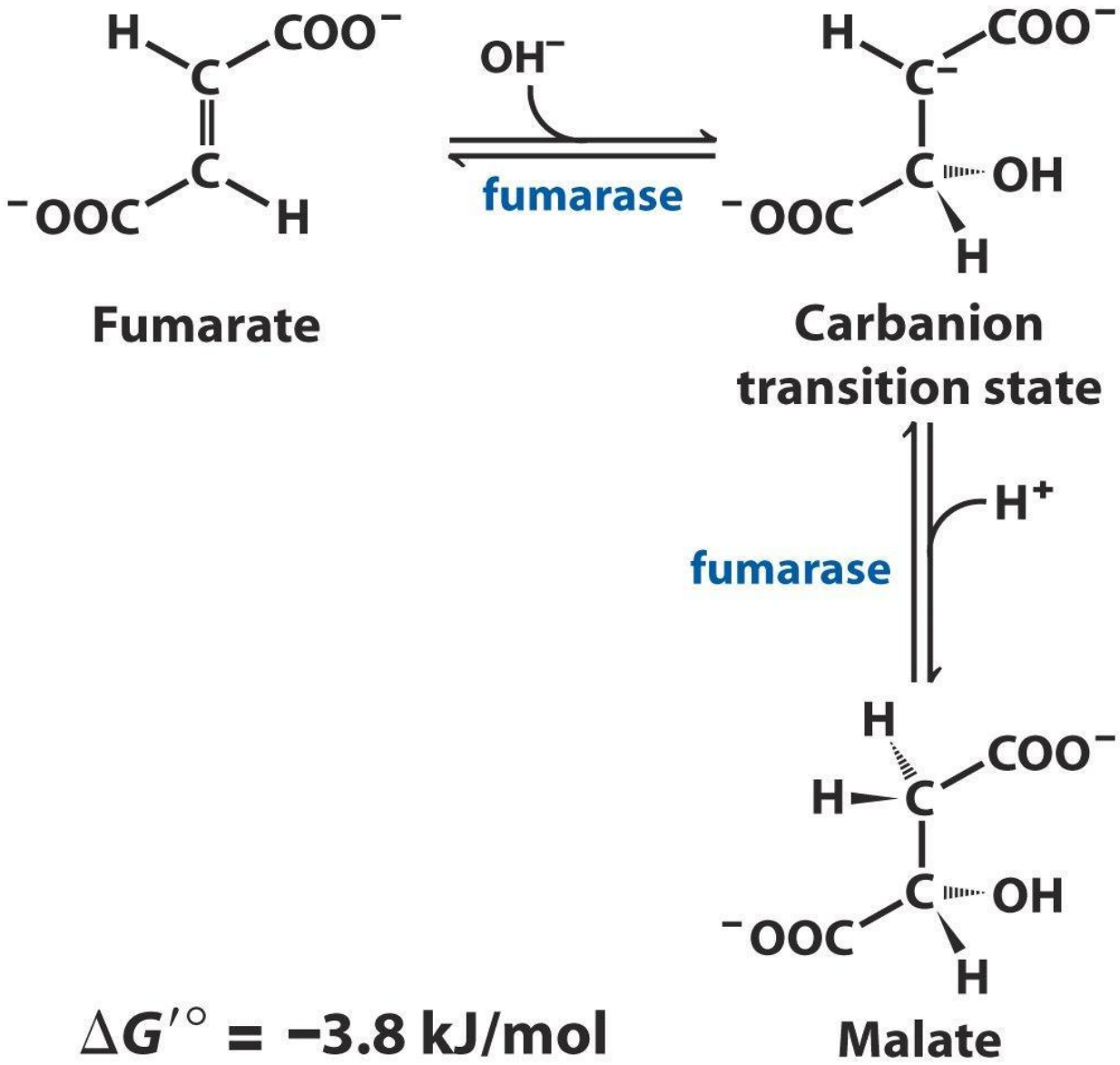


$\Delta G'^{\circ} = 0$ kJ/mol

[STEP 7] Fumarase

The next reaction converts fumarate into a hydroxy-dicarboxylic acid called malate.

This is an addition of water across the double bond.

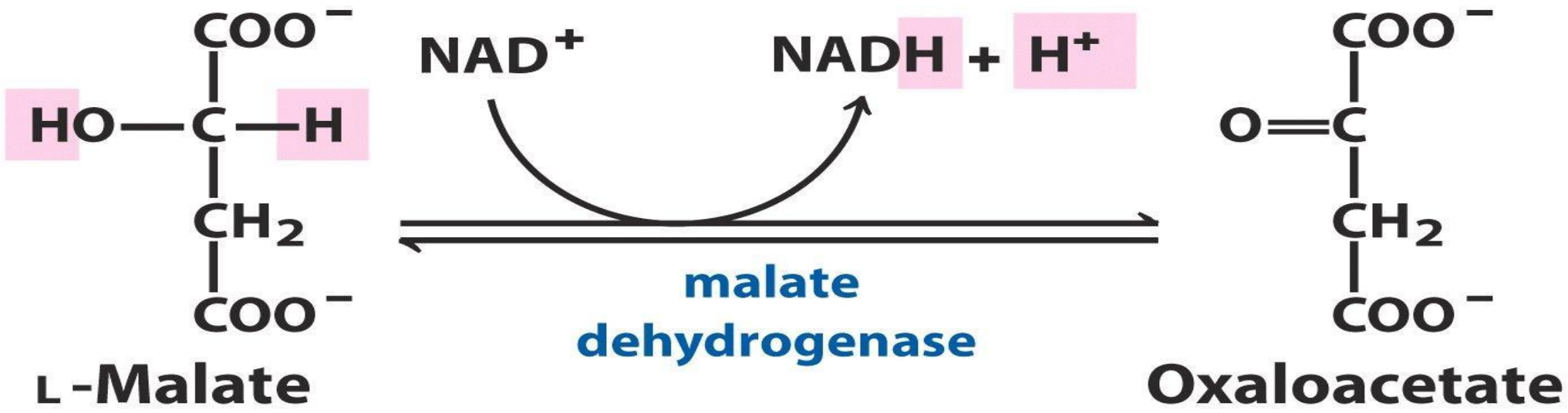


[STEP 8] Malate Dehydrogenase

Finally, malate dehydrogenase, uses NAD+ to oxidize this product malate to oxaloacetate.

This process yields NADH.

Here the reaction completes the TCA Cycle, remaking oxaloacetate.



$$\Delta G'^{\circ} = 29.7 \text{ kJ/mol}$$

Net reaction

$$Acetyl\ CoA + 3NAD^+ + FAD + GDP + Pi + 2H_2O \rightarrow 2CO_2 + CoA + 3NADH + FADH_2 + GTP + 2H^+$$

Energy Yield in Kreb's Cycle

- Per Cycle

3 NADH/H+

1 FADH2

1 GTP (ATP equivalents)

- Per Glucose = 2 Cycles (2 Acetyl-CoA molecules)

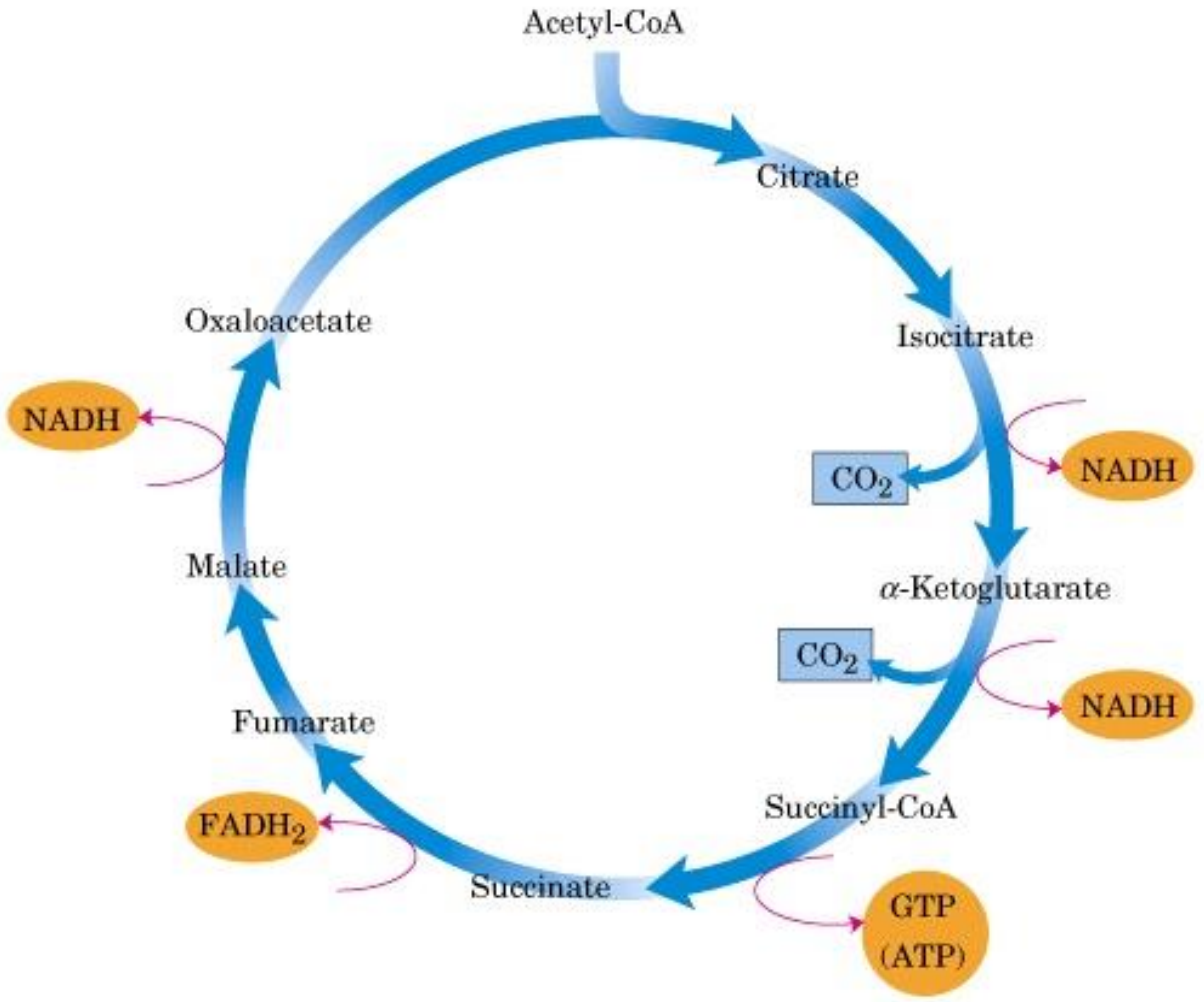
6 NADH/H+

2 FADH2

2 GTP (ATP equivalents)

Significance of TCA Cycle

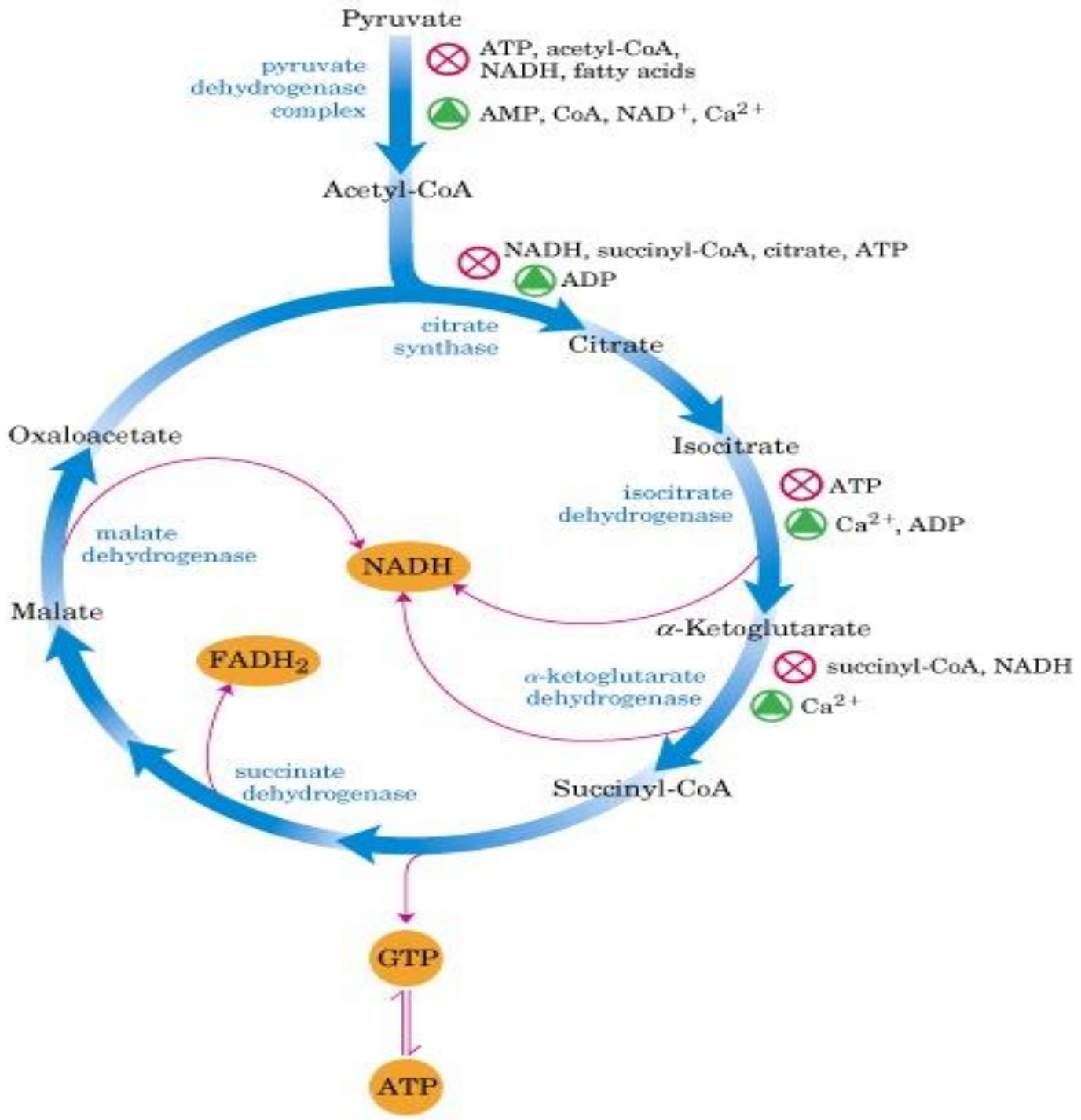
1. Complete oxidation of Acetyl-CoA
2. As provider of energy
3. Final common oxidative pathway
4. Integration of major metabolic pathways
5. Fat is burned on the wick of carbohydrates
6. Amino acids enters TCA cycle
7. Amphibolic pathway
8. Anaplerotic role



Regulation

Rate of cycle is determined by:

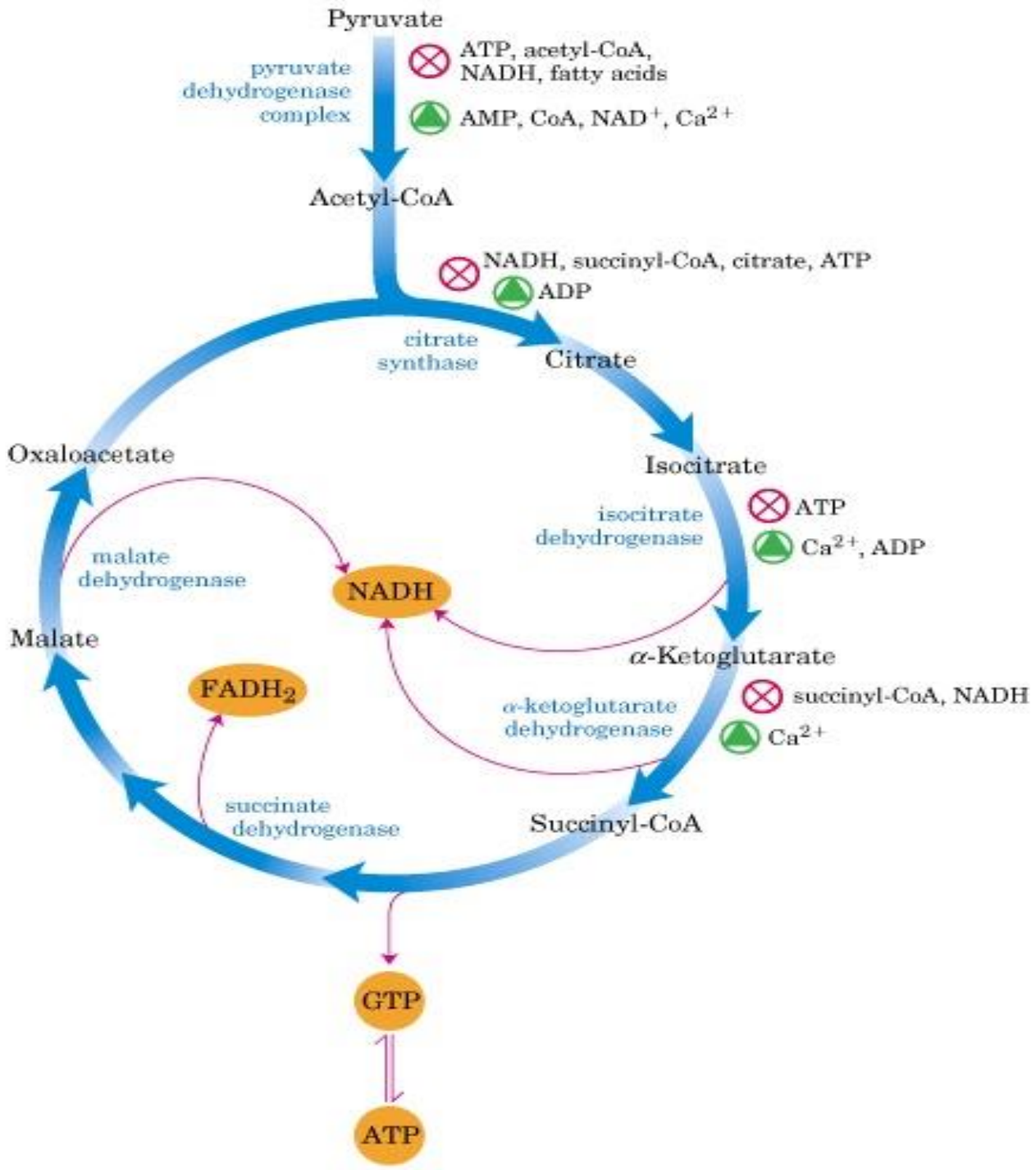
1. Availability of substrates (acetyl CoA, NAD+, FAD).
2. Inhibition by accumulating products.
3. Allosteric feedback inhibition of enzymes.



Regulation

Three nonequilibrium reactions:

1. Citrate synthase
2. Isocitrate dehydrogenase
3. α-ketoglutarate dehydrogenase



Regulation

Table 16.4

The important regulatory enzymes of pyruvate and acetyl-CoA metabolism

Enzyme Name	⊕ Modulators	⊖ Modulators	Comments
Pyruvate dehydrogenase complex	AMP, NAD^+, CoA	ATP, acetyl-CoA, NADH	Also regulated by covalent modification
Citrate synthase	ADP	NADH, succinyl-CoA, citrate, ATP	Activity depends on metabolite concentrations
Isocitrate dehydrogenase	ADP	ATP	Activity depends on metabolite concentrations
α-Ketoglutarate dehydrogenase complex	—	Succinyl-CoA, NADH	Activity depends on metabolite concentrations

Table 16-4 Concepts in Biochemistry, 3/e

Amphibolic nature of the cycle

Intermediates of respiration branch off:

- amino acids biosynthesis
- pentoses for cell wall structure
- nucleotides
- porphyrin biosynthesis
- fatty acid synthesis
- lignin precursors
- precursors for carotenoid synthesis, hormones biosynthesis