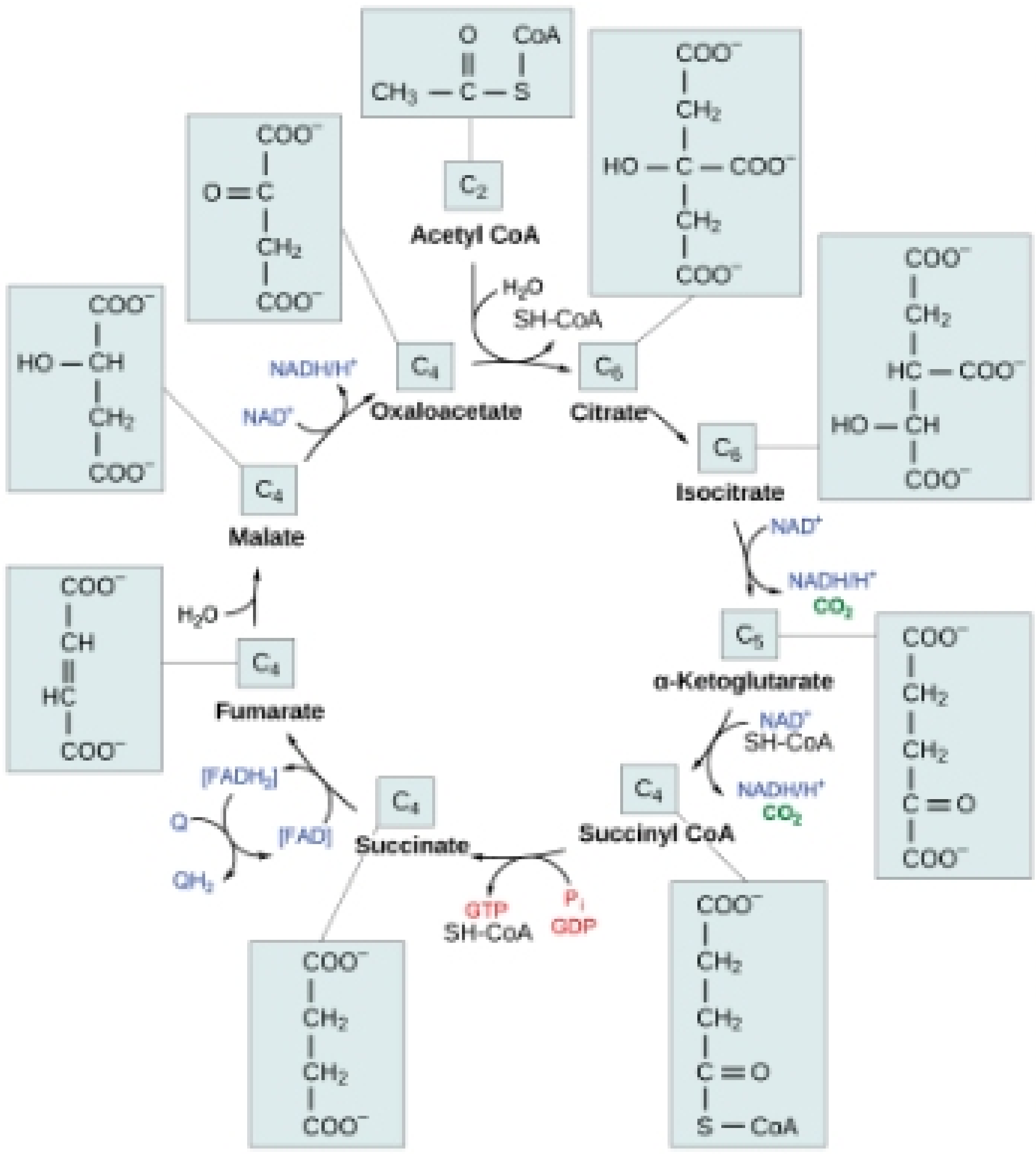
CMB311 Fall 2017
Friday, October 20
Lecture 17 Notes
The TCA Cycle (Krebs cycle, citric acid cycle)

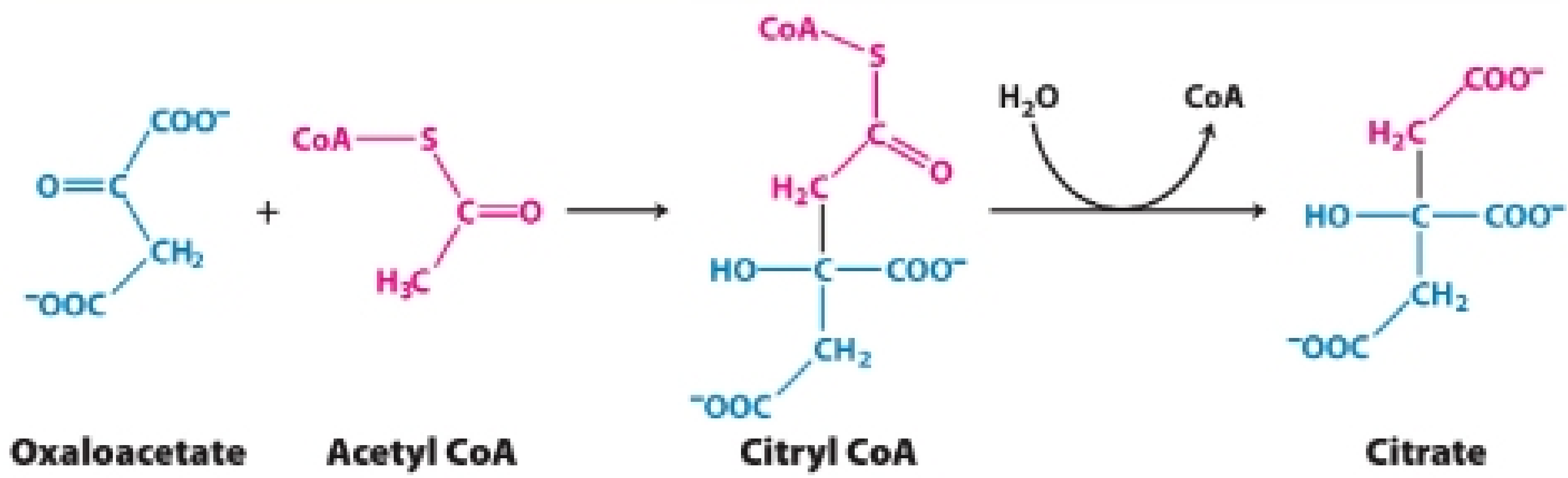
Today we discussed the TCA cycle, also known as the Krebs cycle or the citric acid cycle. This is the central hub of intermediary metabolism, as many catabolic pathways lead to it while many anabolic pathways emerge from it. The cycle consists of 8 steps. Overall, the process takes the two carbons of acetyl-CoA and converts them to CO_2. This produces one GTP molecule (ATP in some species), 3 NADH and 1 $FADH_2$ along with 2 CO_2. The pathway forms a cycle, with the starting molecule, oxaloacetate, regenerated with each turn of the cycle. It's this regeneration of oxaloacetate that makes it a cycle. The TCA cycle is carried out by enzymes found in the mitochondrion, the organelle present in eukaryotic cells or it takes place in the cytoplasm in bacteria and archaea.



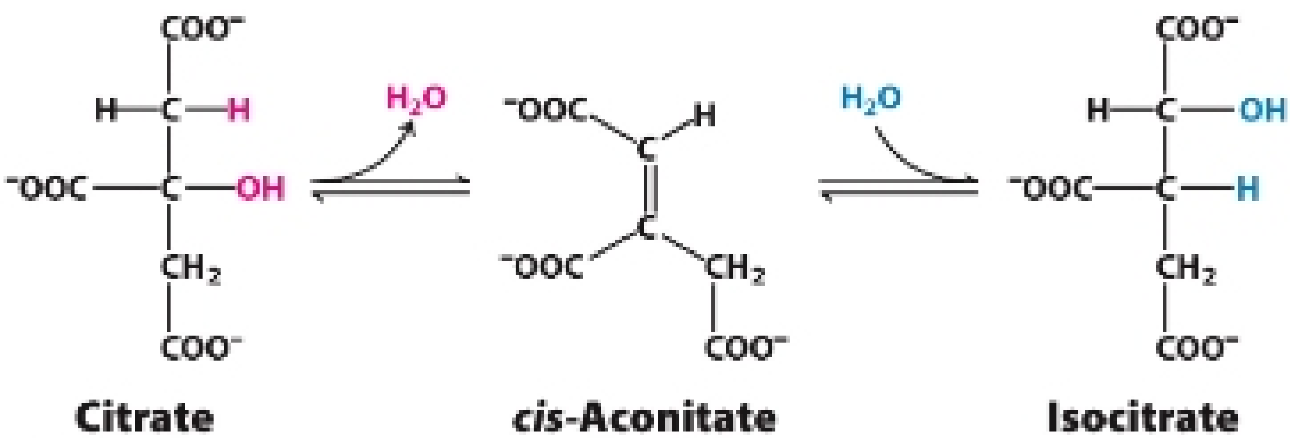
The figure on the left shows the structures of the intermediates. Note the number of carbon atoms in each molecule. Note also at which steps CO_2 is released, and at which steps NADH, $FADH_2$ and GTP are produced. There is also a step in which a water molecule is used to add a hydroxyl group. Along with glycolysis, this is the most important series of reactions we will discuss in this course. It is worth committing this cycle to memory, but along the way understanding the logic behind it. A number of the reactions are identical to those taking place during oxidation of fatty acids and the breakdown of some amino acids. Also keep track of the energetics of the individual steps of the cycle.

The Krebs cycle also contributes intermediates for the biosynthesis of amino acids and gluconeogenesis, so it is **amphibolic**, meaning it is involved in both catabolism and anabolism. It is a central metabolic cycle.

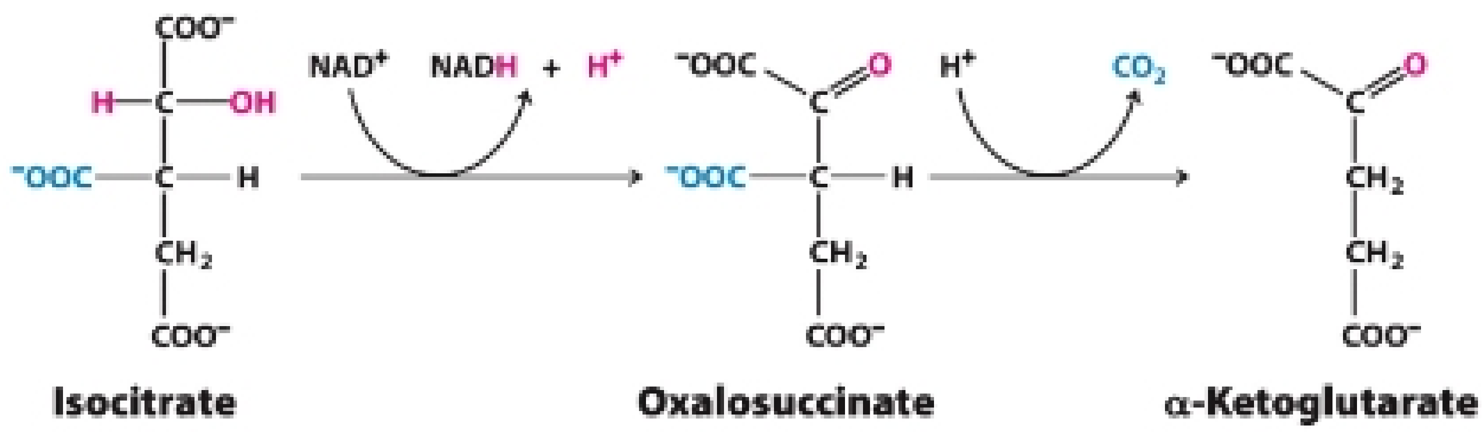
Step 1. Formation of citrate. The two carbon acetyl group from acetyl-CoA is added in a condensation reaction to the four-carbon molecule oxaloacetate to form the six-carbon molecule citrate. This reaction is carried out by the enzyme citrate synthase and releases CoA-SH. The reaction is very exergonic, due to the energy released by hydrolysis of the acetyl-CoA thioester bond and the resonance stabilization of the carboxyl group from acetate. **$\Delta G^{\circ\prime}$ = -31.4 kJ/mol**.



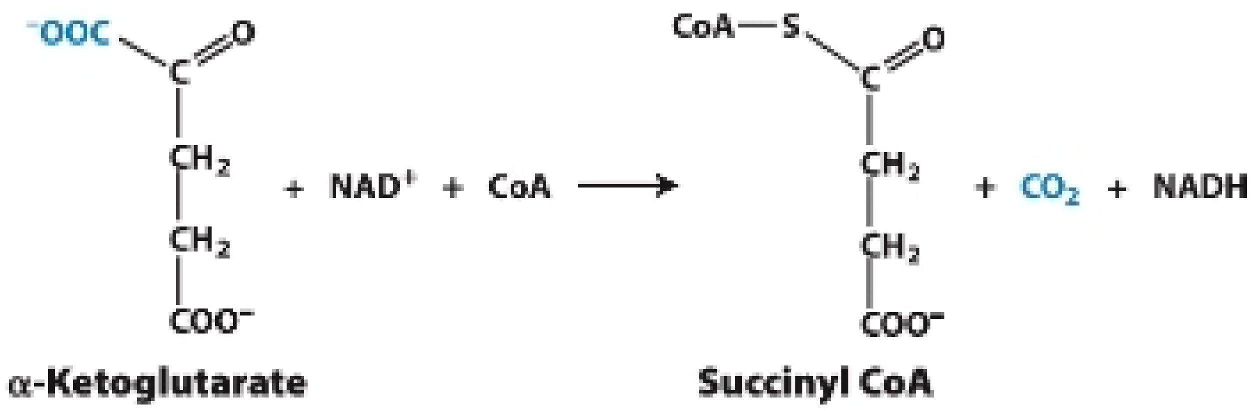
Step 2. Isocitrate formation. The six-carbon citrate molecule is then converted to the six-carbon isocitrate. This actually occurs through two steps and involves a dehydration reaction to produce the intermediate *cis*-aconitate and a rehydration reaction to produce isocitrate. The reaction is catalyzed by the enzyme aconitase. **$\Delta G^{\circ\prime}$ = +6.3 kJ/mol**.



Step 3. Oxidation of isocitrate to α-ketoglutarate. The next reaction sees the release of the first CO_2 with decarboxylation of isocitrate in its conversion to α-ketoglutarate. This reaction is catalyzed by the enzyme isocitrate dehydrogenase. In this reaction, we also see the reduction of NAD^+ or $NADP^+$ to NADH or NADPH. This oxidizes the hydroxyl group of isocitrate and generates a ketone to produce α-ketoglutarate. This oxidation also favors decarboxylation. **$\Delta G^{\circ\prime}$ = -8.4 kJ/mol**.



Step 4. Oxidative decarboxylation of α-ketoglutarate to succinyl-CoA. In this step, α-ketoglutarate is decarboxylated by the **α-ketoglutarate dehydrogenase** complex. This utilizes CoA-SH and NAD^+ and releases the second CO_2 molecule. **$\Delta G^{\circ\prime}$ = -30.1 kJ/mol**.



Step 5. Substrate-level phosphorylation. Here, energy of the thioester bond of succinyl-CoA is transferred to the phosphodiester bond formed in conversion of GDP to GTP. Bacteria use ADP and ATP instead of GDP and GTP. The reaction, catalyzed by **succinyl-CoA synthetase**, also produces free CoA-SH and succinate. $\Delta G^{\circ\prime}$ = -3.3 kJ/mol. Why is the release of CoA-SH here not as exergonic as in Step 1?