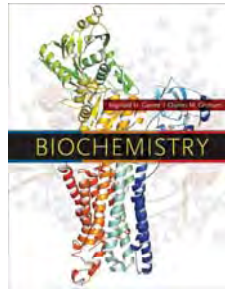


# Chapter 19



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## The Tricarboxylic Acid Cycle

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## Before the class...

- Do you know...
  - What is respiration? What is cellular respiration?
  - What is TCA cycle? Where does it take place?
  - How many coenzymes have you learned yet?
  - How many dehydrogenase have you learned?

## Outline

- Part 1
  - Introduction: the Chemical Logic of the TCA Cycle.
  - Pyruvate Oxidatively Decarboxylated to Acetyl-CoA
  - TCA cycle part I: Two CO<sub>2</sub> Molecules Produced from Acetyl-CoA.
- Part 2
  - TCA cycle part II: Oxaloacetate Regenerated
  - Energetic Consequences of the TCA Cycle
  - How Is the TCA Cycle Regulated?
- Part 3
  - TCA Cycle Provides Intermediates for Biosynthesis.
  - Anaplerotic, or "Filling Up," Reactions
  - Glyoxylate cycle

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## What is TCA cycle?

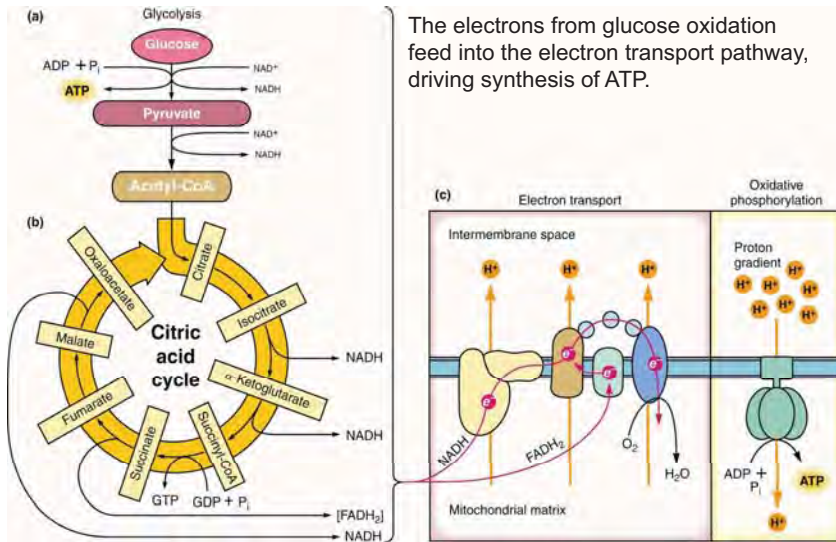
- **Tricarboxylic Acid Cycle**
- **Kreb cycle**
- **Citric acid cycle**
- **1953 Nobel prize**
- **Takes place in mitochondria**
- Pyruvate (actually acetate) from glycolysis is degraded to CO<sub>2</sub>



Hans Krebs

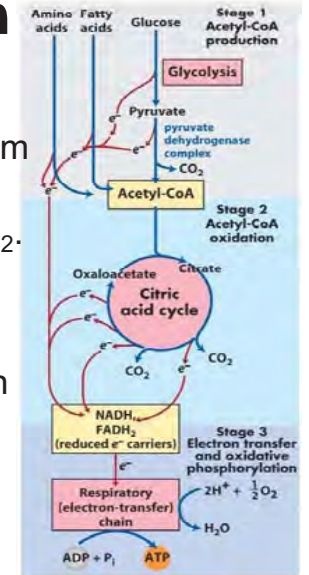
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# Oxidation of glucose to CO<sub>2</sub> is a 24-electron oxidation



# Respiration

- General meaning:
  - The aerobic phase of catabolism in the multicellular organism's uptake of O<sub>2</sub> and release of CO<sub>2</sub>.
- Cellular respiration:
  - cells consume O<sub>2</sub> and produce CO<sub>2</sub>-processes, which occurs in three major stages.
- TCA cycle is a hub in metabolism



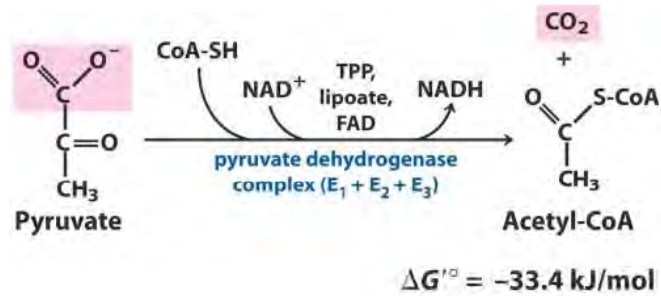
The tricarboxylic acid cycle.



## 19.2 How Is Pyruvate Oxidatively Decarboxylated to Acetyl-CoA?

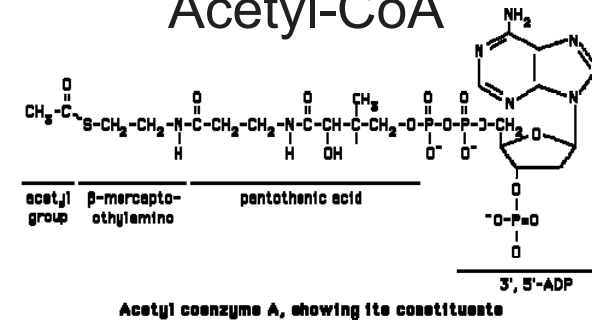
- Pyruvate must **enter the mitochondria** to enter the TCA cycle
- Oxidative decarboxylation of pyruvate is catalyzed by the **pyruvate dehydrogenase complex (PDC): irreversible reaction!**
- Pyruvate dehydrogenase is a noncovalent assembly of **three enzymes**
- **Five coenzymes** are required

## Overall reaction catalyzed by PDC



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## Acetyl-CoA

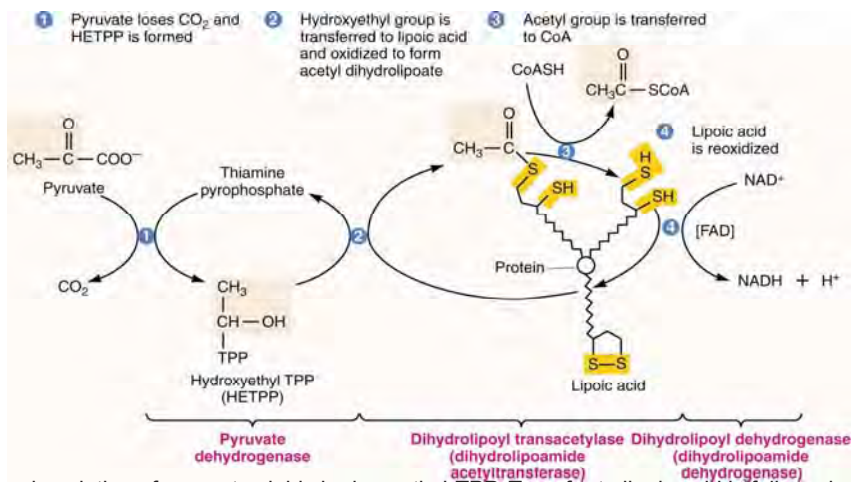


Acetyl coenzyme A, showing its constituents

- Activation form of acetate!
- Common metabolite of many catabolic pathways: amino acid, lipid and carbohydrate catabolism...

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## Figure 19.4 The Reaction Mechanism of the Pyruvate Dehydrogenase Complex



Decarboxylation of pyruvate yields hydroxyethyl-TPP. Transfer to lipoic acid is followed by formation of acetyl-CoA.

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## Pyruvate Dehydrogenase is a Multi-Subunit Complex of Three Enzymes

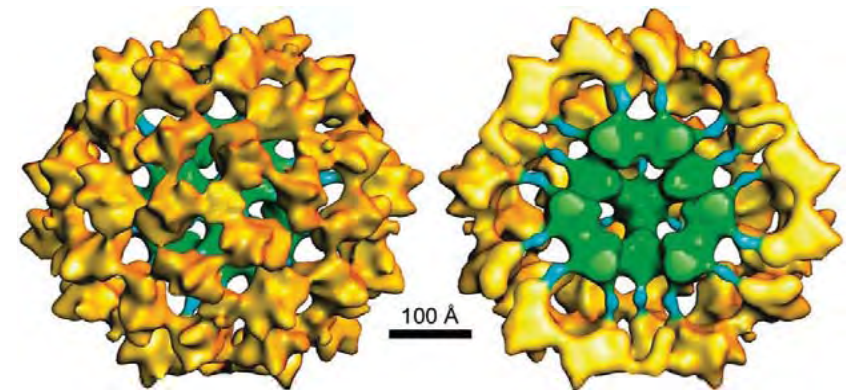


Figure 19.3 Icosahedral model of the pyruvate dehydrogenase complex (PDC) core structure. E1 subunits are yellow; E2 subunits are green. Linkers in blue; E3 not shown.

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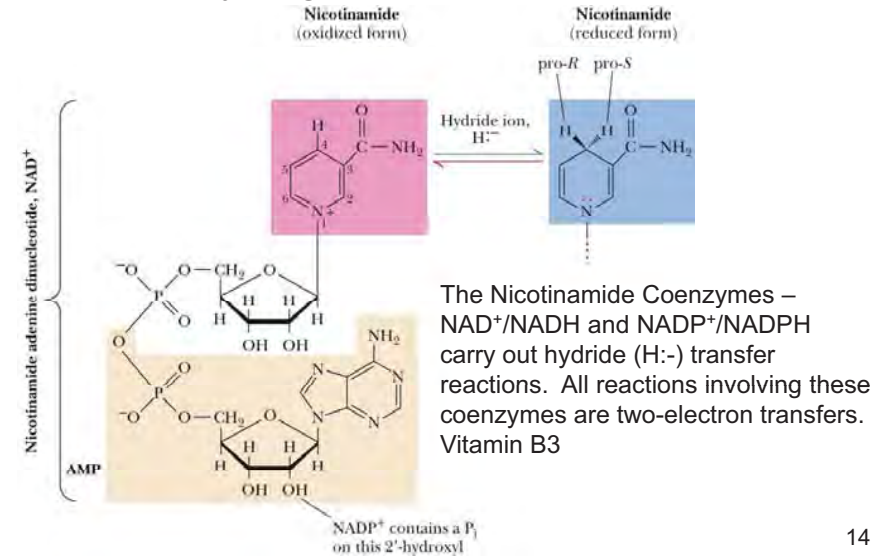
## The Coenzymes of the Pyruvate Dehydrogenase Complex: 1/5



Thiamine pyrophosphate (Vitamin B1)  
 TPP assists in the decarboxylation of  $\alpha$ -keto acids (here) and in the formation and cleavage of  $\alpha$ -hydroxy ketones (as in the transketolase reaction; see Chapter 22).

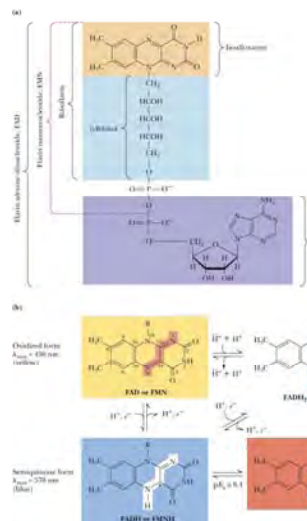
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## The Coenzymes of the Pyruvate Dehydrogenase Complex: 2/5



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## The Coenzymes of the Pyruvate Dehydrogenase Complex: 3/5



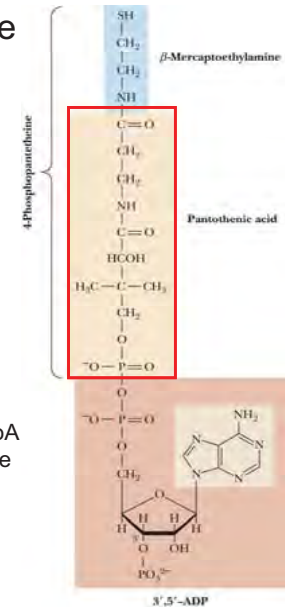
The Flavin Coenzymes – FAD/FADH<sub>2</sub> (Vitamin B2)  
 Flavin coenzymes can exist in any of three oxidation states, and this allows flavin coenzymes to participate in one-electron and two-electron transfer reactions. Partly because of this, flavoproteins catalyze many reactions in biological systems and work with many electron donors and acceptors.

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## The Coenzymes of the Pyruvate Dehydrogenase Complex: 4/5

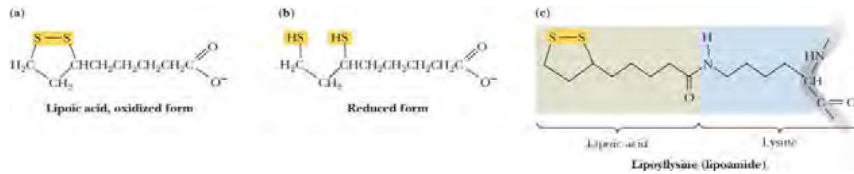
Coenzyme A (from Vitamin B5)  
 The two main functions of Co A are:  
 1) Activation of acyl groups for transfer by nucleophilic attack  
 2) Activation of the  $\alpha$ -hydrogen of the acyl group for abstraction as a proton

The reactive sulfhydryl group on CoA mediates both of these functions. The sulfhydryl group forms **thioester** linkages with acyl groups. The two main functions of CoA are illustrated in the citrate synthase reaction (see Figure 19.6).



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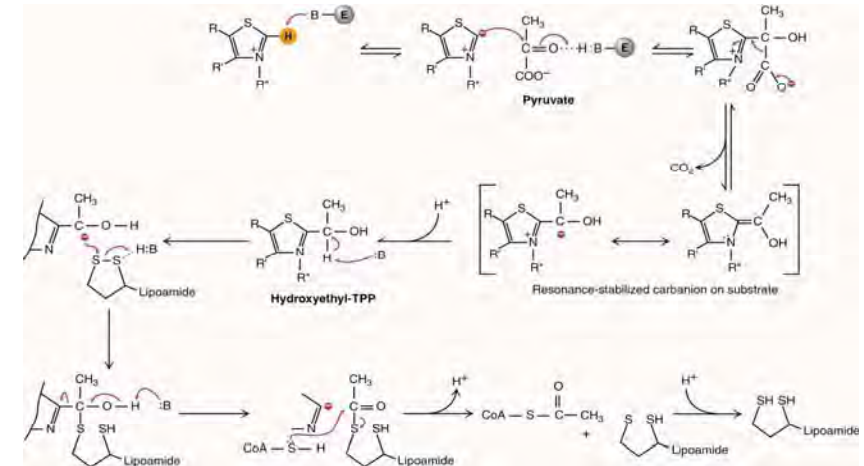
## The Coenzymes of the Pyruvate Dehydrogenase Complex: 5/5



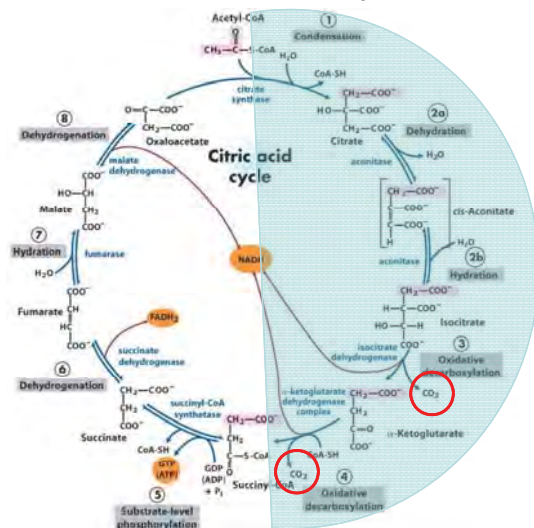
Lipoic Acid functions to couple acyl-group transfer and electron transfer during oxidation and decarboxylation of  $\alpha$ -keto acids. It is found in pyruvate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase. Lipoic acid is covalently bound to relevant enzymes through amide bond formation with the  $\epsilon$ -NH<sub>2</sub> group of a lysine side chain.

Alpha lipoic acid (APA) is not a vitamin (we can make it by ourselves)!

## Figure 19.5 The mechanism of the first three steps of the pyruvate dehydrogenase complex reaction



## TCA cycle first phase : Two CO<sub>2</sub> Molecules Produced from Acetyl-CoA.



## The citrate synthase reaction initiates the TCA cycle

Reaction	Enzyme	$\Delta G^{\circ\prime}$ (kJ/mol)	$\Delta G$ (kJ/mol)
1. Acetyl-CoA + oxaloacetate + H <sub>2</sub> O $\rightleftharpoons$ CoASH + citrate	Citrate synthase	-31.4	-53.9
2. Citrate $\rightleftharpoons$ isocitrate	Aconitase	+6.7	+0.8
3. Isocitrate + NAD <sup>+</sup> $\rightleftharpoons$ $\alpha$ -ketoglutarate + NADH + CO <sub>2</sub>	Isocitrate dehydrogenase	-8.4	-17.5
4. $\alpha$ -Ketoglutarate + CoASH + NAD <sup>+</sup> $\rightleftharpoons$ succinyl-CoA + NADH + CO <sub>2</sub>	$\alpha$ -Ketoglutarate dehydrogenase complex	-30	-43.9
5. Succinyl-CoA + GDP + P <sub>i</sub> $\rightleftharpoons$ succinate + GTP + CoASH	Succinyl-CoA synthetase	-3.3	$\approx$ 0
6. Succinate + [FAD] $\rightleftharpoons$ fumarate + [FADH <sub>2</sub> ]	Succinate dehydrogenase	+0.4	$\neq$ 0
7. Fumarate + H <sub>2</sub> O $\rightleftharpoons$ L-malate	Fumarase	-3.8	$\approx$ 0
8. L-Malate + NAD <sup>+</sup> $\rightleftharpoons$ oxaloacetate + NADH + H <sup>+</sup>	Malate dehydrogenase	+29.7	$\approx$ 0

## Rx1: The citrate synthase reaction initiates the TCA cycle

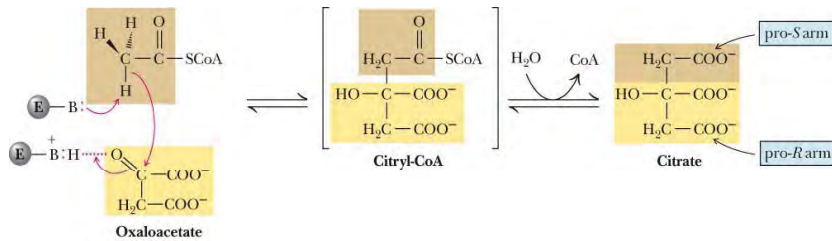
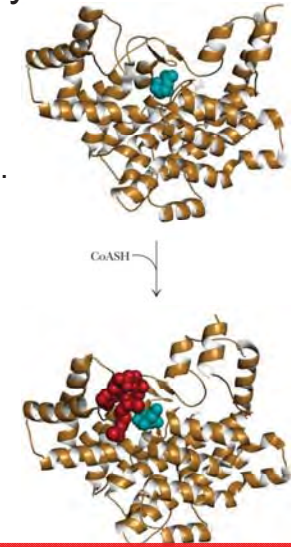


Figure 19.6 Citrate is formed in the citrate synthase reaction from oxaloacetate and acetyl-CoA. The mechanism involves nucleophilic attack by the carbanion of acetyl-CoA on the carbonyl carbon of oxaloacetate, followed by thioester hydrolysis.

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## The citrate synthase reaction initiates the TCA cycle

Figure 19.7 Citrate synthase in mammals is a dimer of 49-kD subunits. In the monomer shown here, citrate (blue) and CoA (red) bind to the active site, which lies in a cleft between two domains and is surrounded mainly by  $\alpha$ -helical segments.



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## Rx2: Citrate Is Isomerized by Aconitase to Form Isocitrate

- Isomerization of Citrate to Isocitrate
- Citrate is a poor substrate for oxidation
- So aconitase isomerizes citrate to yield isocitrate which has a secondary -OH, which can be oxidized
- Note the stereochemistry of the Rxn: aconitase removes the pro-R H of the pro-R arm of citrate!
- Aconitase uses an iron-sulfur cluster - see Fig. 19.9

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## Citrate Is Isomerized by Aconitase to Form Isocitrate

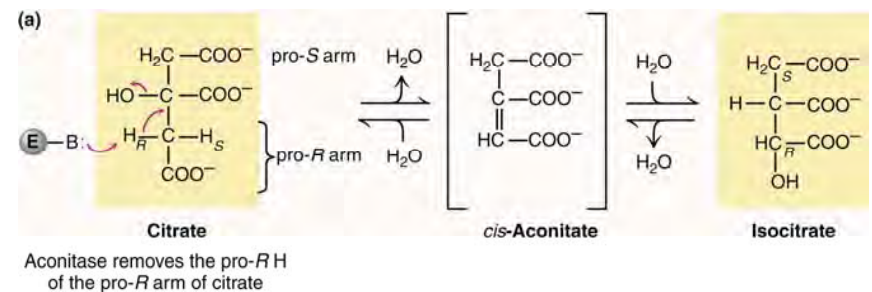
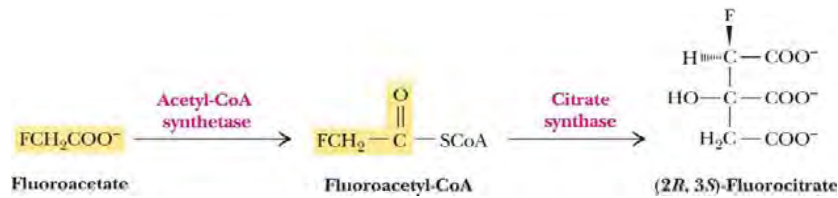


Figure 19.8 The aconitase reaction converts citrate to *cis*-aconitate and then to isocitrate. Aconitase is stereospecific and removes the pro-R hydrogen from the pro-R arm of citrate.

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## Fluoroacetate Blocks the TCA Cycle



- **Suicide inhibitor**
- Fluoroacetate is an extremely poisonous agent that blocks the TCA cycle in vivo, although it has no apparent effect on any of the isolated TCA cycle enzymes.
- The action of aconitase has been traced to aconitase
- Aconitase is inhibited by fluorocitrate, which is formed from fluoracetate in two steps, as shown here.

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## Citrate Is Isomerized by Aconitase to Form Isocitrate

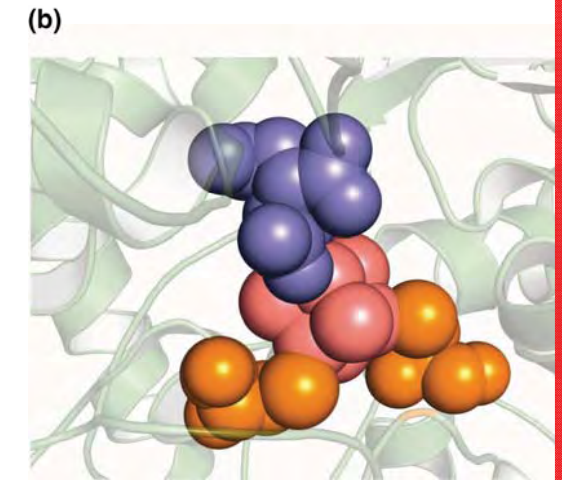


Figure 19.8 The active site of aconitase. The iron-sulfur cluster (pink) is coordinated by cysteines (orange) and isocitrate (purple).

## Aconitase Utilizes an Iron-Sulfur Cluster

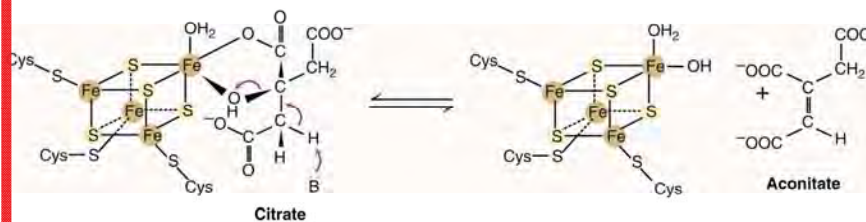


Figure 19.9 The iron-sulfur cluster of aconitase. Binding of  $\text{Fe}^{2+}$  to the vacant position of the cluster activates aconitase. The added iron atom coordinates the C-3 carboxyl and hydroxyl groups of citrate and acts as a Lewis acid, accepting an electron pair from the hydroxyl group and making it a better leaving group.

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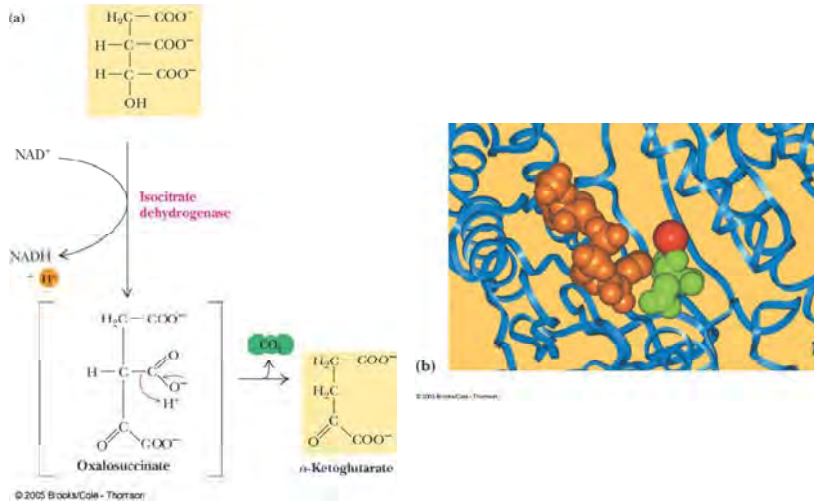
## Rx3: Isocitrate Dehydrogenase Catalyzes the First Oxidative Decarboxylation in the Cycle

- *Oxidative decarboxylation of isocitrate to yield  $\alpha$ -ketoglutarate*
- Classic  $\text{NAD}^+$  chemistry (hydride removal) **followed by a decarboxylation**
- Isocitrate dehydrogenase is a link to the electron transport pathway because it makes NADH

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Figure 19.10

(a) The isocitrate dehydrogenase reaction. (b) The active site of isocitrate dehydrogenase. Isocitrate is shown in green, NAD<sup>+</sup> is shown in gold, with Ca<sup>2+</sup> in red.



## Rx4: $\alpha$ -Ketoglutarate Dehydrogenase Catalyzes the Second Oxidative Decarboxylation of the TCA Cycle

- A second oxidative decarboxylation
- This enzyme is nearly identical to pyruvate dehydrogenase - structurally and mechanistically
- Five coenzymes used - TPP, CoASH, Lipoic acid, NAD<sup>+</sup>, FAD
- You know the mechanism if you remember pyruvate dehydrogenase

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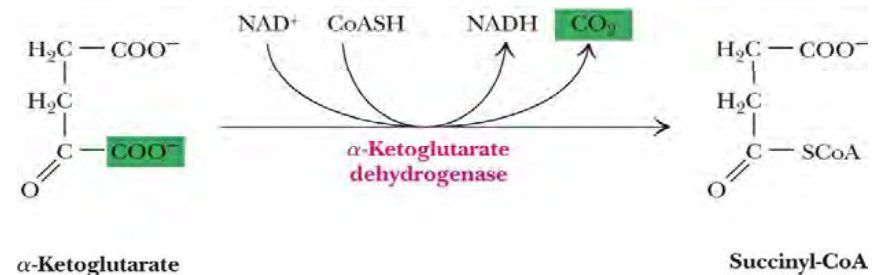
## The Subunits of $\alpha$ -Ketoglutarate Dehydrogenase are Similar to Those of Pyruvate Dehydrogenase

**TABLE 19.2** Composition of the  $\alpha$ -Ketoglutarate Dehydrogenase Complex from *Escherichia coli*

Enzyme	Coenzyme	Enzyme M <sub>r</sub>	Number of Subunits	Subunit M <sub>r</sub>	Number of Subunits per Complex
$\alpha$ -Ketoglutarate dehydrogenase	Thiamine pyrophosphate	192,000	2	96,000	24
Dihydrolipoil transsuccinylase	Lipoic acid, CoASH	1,700,000	24	70,000	24
Dihydrolipoil dehydrogenase	FAD, NAD <sup>+</sup>	112,000	2	56,000	12

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## $\alpha$ -Ketoglutarate Dehydrogenase Catalyzes the Second Oxidative Decarboxylation of the TCA Cycle



Like pyruvate dehydrogenase,  $\alpha$ -ketoglutarate dehydrogenase is a multienzyme complex – consisting of  $\alpha$ -ketoglutarate dehydrogenase, dihydrolipoil transsuccinylase, and dihydrolipoil dehydrogenase. The complex uses five different coenzymes.

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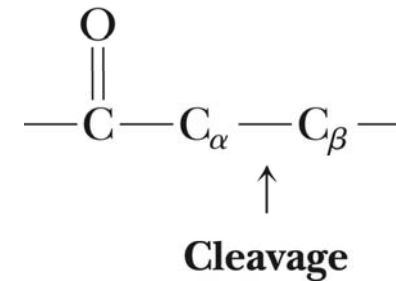


## 19.1 – What Is the Chemical Logic of the TCA Cycle?

- TCA seems like a complicated way to oxidize **acetate units** to CO<sub>2</sub>
- To condense acetate with oxaloacetate and carry out a **β-cleavage**.
- TCA combines this with oxidation to form CO<sub>2</sub>, regenerate oxaloacetate and capture all the energy as NADH and ATP!

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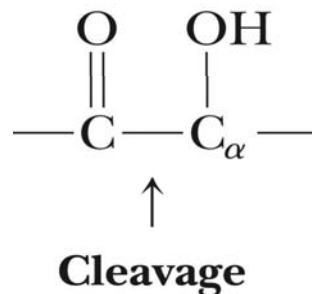
### Cleavage Between Carbon Atoms α and β to a Carbonyl



- This type of cleavage occurs in the fructose bisphosphate aldolase reaction in glycolysis
- But it can't be used for acetate, which does not have a β carbon

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### α-Cleavage of an α-Hydroxyketone



- This type of cleavage occurs in the transaldolase reaction (described in Chapter 22).
- But it would require hydroxylation of acetate, which is not a favorable or facile reaction for acetate

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## End of Part 1

- You should know...
  - 5 coenzymes involved in pyruvate dehydrogenase complex
  - What are the 3 decarboxylation reactions?
  - How many dehydrogenase in TCA cycle?
  - How many high-energy electrons released in TCA cycle?

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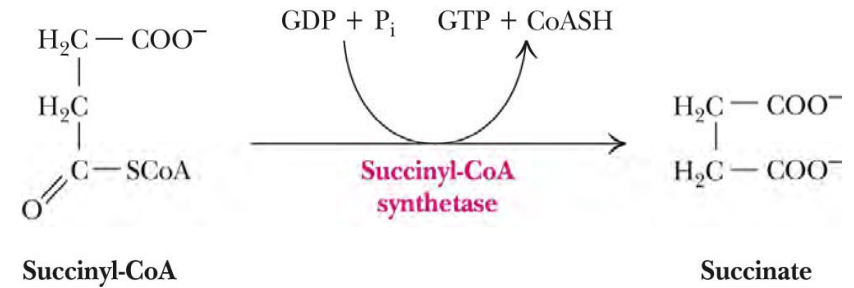
## TCA cycle Second Phase

### 19.5 – How Is Oxaloacetate Regenerated to Complete the TCA Cycle?

- Rx 5: Succinyl-CoA Synthetase
- A substrate-level phosphorylation**
- A nucleoside triphosphate is made
- Its synthesis is driven by **hydrolysis of a CoA ester**
- The mechanism involves a phosphohistidine

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### Rx 5: Succinyl-CoA Synthetase

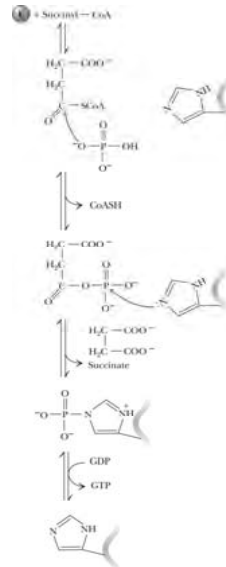


Hydrolysis of succinyl-CoA (a CoA ester) drives the phosphorylation of GDP to produce GTP

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### The mechanism of the succinyl-CoA synthetase reaction

- Phosphate anion carries out a nucleophilic attack on the carbonyl C of succinyl-CoA, forming succinyl phosphate
- Subsequent phosphoryl transfer to an active-site His forms a phosphohistidine intermediate, releasing the product succinate
- The phosphoryl group is then transferred to GDP to produce GTP



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### Completion of the TCA Cycle – Oxidation of Succinate to Oxaloacetate

- These reactions include:
  - Rx 6: Oxidation of a single bond to a double bond
  - Rx 7: Hydration across the double bond
  - Rx 8: Oxidation of the resulting alcohol to a ketone
- This trio of reactions will be seen again (you will see it 5 times in text book) in:
  - Fatty acid breakdown and synthesis
  - Amino acid breakdown and synthesis

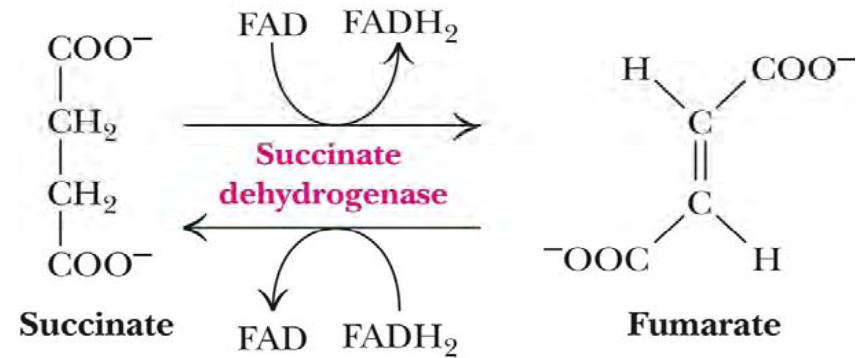
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## Rx6: Succinate Dehydrogenase Is FAD-Dependent

- An oxidation involving FAD
- Mechanism involves hydride removal by FAD and a deprotonation
- This enzyme is actually **part of the electron transport pathway** in the inner mitochondrial membrane
- The electrons transferred from succinate to FAD (to form FADH<sub>2</sub>) are passed directly to ubiquinone (UQ) in the electron transport pathway

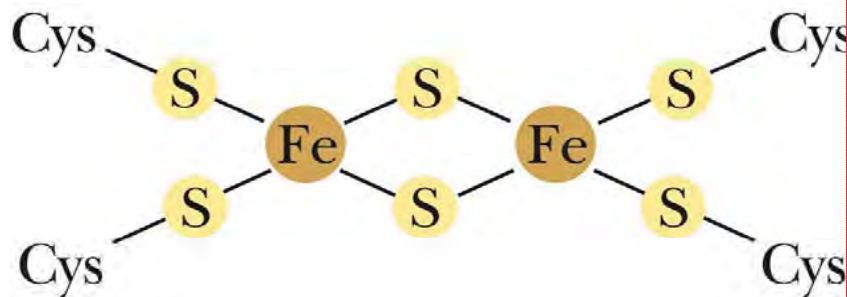
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## The Succinate Dehydrogenase Reaction



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## Succinate Dehydrogenase Uses Iron-Sulfur Clusters



Succinate Dehydrogenase contains three types of Fe-S centers – a 4Fe-4S center, a 3Fe-4S center, and a 2Fe-2S center, as shown here.

4

## FAD is Covalently Bound to Succinate Dehydrogenase

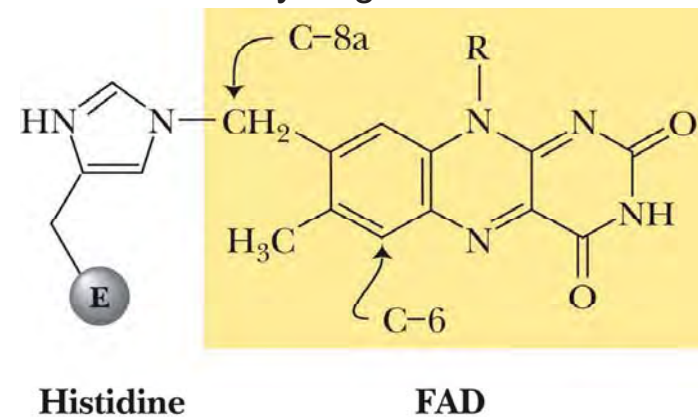
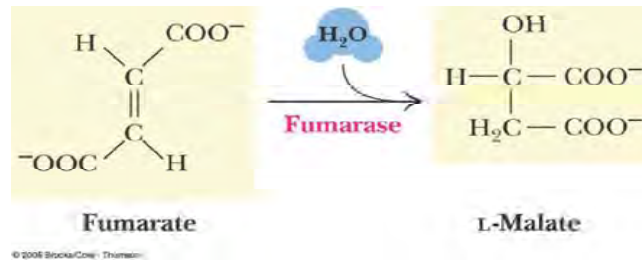


Figure 19.12 The covalent bond between FAD and succinate dehydrogenase links the C-8a carbon of FAD and the N-3 of a His residue of the enzyme.

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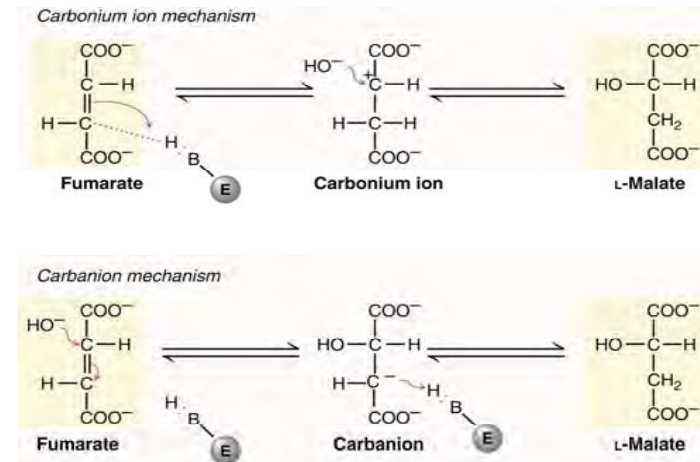
## Rx 7: Fumarase Catalyzes the Trans-Hydration of Fumarate to Form L-Malate

- Hydration across the double bond
- trans-addition of the elements of water across the double bond



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## Possible Mechanisms For the Fumarase Reaction



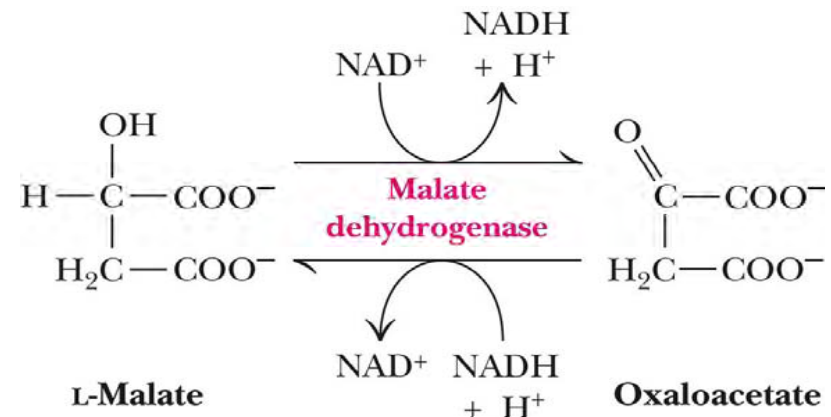
## Rx8: Malate Dehydrogenase Completes the Cycle by Oxidizing Malate to Oxaloacetate

*An NAD<sup>+</sup>-dependent oxidation*

- The carbon that gets oxidized is the one that received the -OH in the previous reaction
- This reaction is energetically expensive  
 $\Delta G^{\circ}$  of +30 kJ/mol
- Thus the concentration of oxaloacetate in the mitochondrial matrix is quite low
- However, the malate dehydrogenase reaction is pulled forward by the favorable citrate synthase reaction

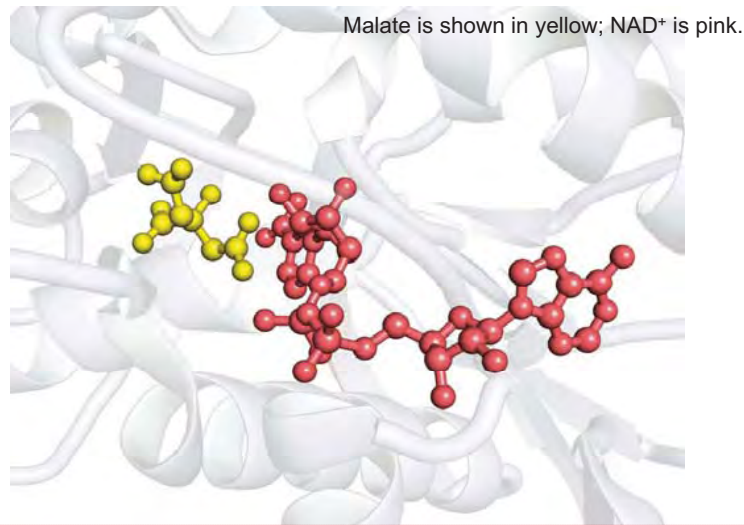
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## The Malate Dehydrogenase Reaction



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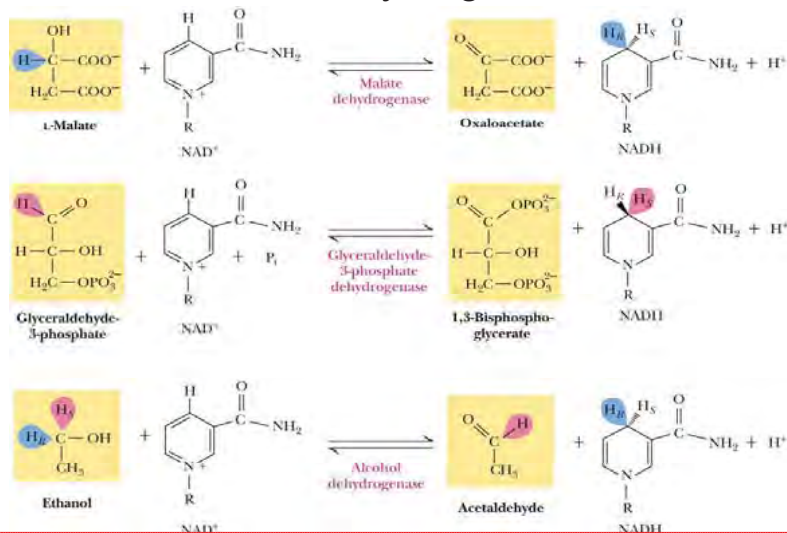
Figure 19.14 The Active Site of Malate Dehydrogenase



## Steric Preferences in NAD<sup>+</sup>-Dependent Dehydrogenases

- The dehydrogenases that require nicotinamide coenzymes are stereospecific, and they transfer hydride to either the pro-*R* or the pro-*S* positions selectively
- What accounts for this specificity? The **enzymes** involved are asymmetric structures.
- The nicotinamide coenzyme (and substrate) fit into the active site in only one way
- The hydride transfers can only be accomplished to or from one side or the other of the NAD<sup>+</sup> molecule
- Dehydrogenases (and other enzymes too) are also stereospecific with respect to the substrates as well

## The Preferred Stereospecificities of Several Dehydrogenases



## 19.6 – What Are the Energetic Consequences of the TCA Cycle?

- One acetate through the cycle produces two CO<sub>2</sub>, one ATP, four reduced coenzymes
- Try also to account for the overall energetics of this pathway
- The TCA cycle is exergonic, with a net ΔG<sup>o'</sup> for one pass around the cycle of -40 kJ/mol
- The combination of glycolysis and TCA produce 12 reduced coenzymes, which can eventually produce as much as 34 molecules of ATP

## The Carbon Atoms of Acetyl-CoA Have Different Fates in the TCA Cycle

- The carbonyl C of acetyl-CoA turns to CO<sub>2</sub> only in the second turn of the cycle (following entry of acetyl-CoA)
- The methyl C of acetyl-CoA survives two cycles completely, but half of what's left exits the cycle on each turn after that
- The C-C bond cleaved in a given TCA cycle actually entered as an acetate in the previous turn
- Thus the oxidative decarboxylations that cleave this bond are just a disguised acetate C-C cleavage and oxidation

## The carbonyl C of acetyl-CoA turns to CO<sub>2</sub> only in the second turn of the cycle

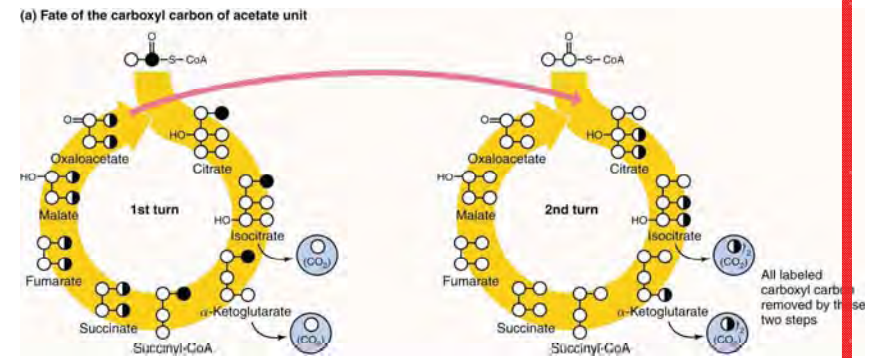


Figure 19.15 The fate of the carbon atoms of acetate in successive TCA cycles.

## The methyl C of acetyl-CoA survives two cycles completely

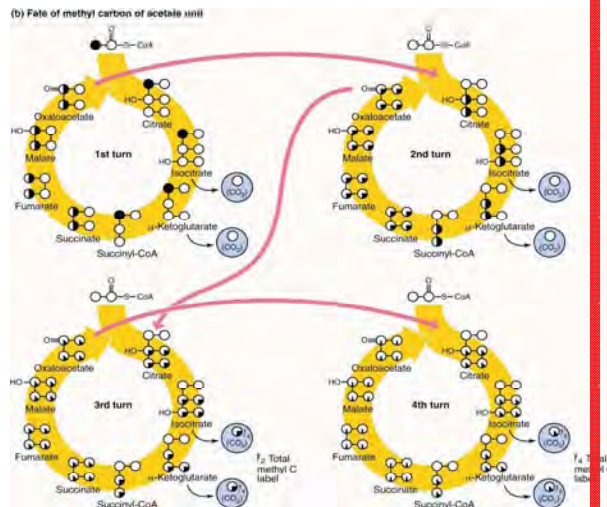


Figure 19.15 The fate of the carbon atoms of acetate in successive TCA cycles.

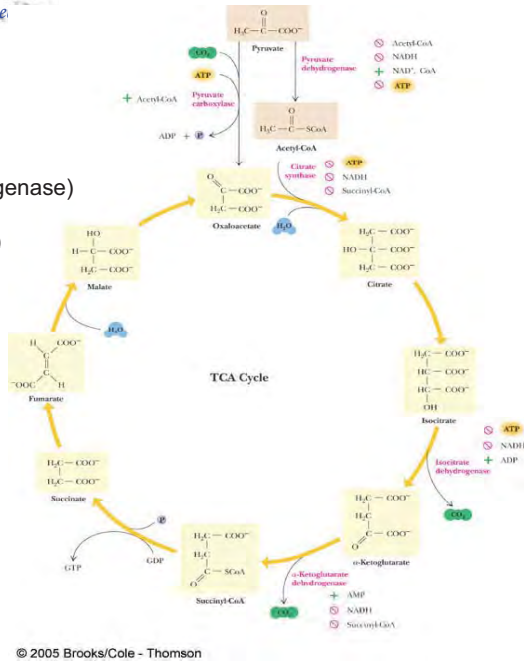
## 19.9 – How Is the TCA Cycle Regulated?

Again, 3 reactions are the key sites

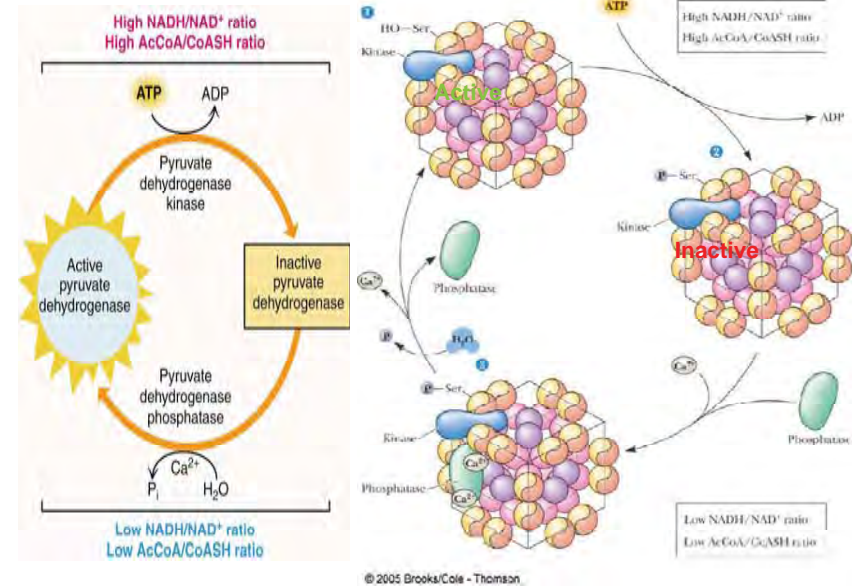
- Citrate synthase - ATP, NADH and succinyl-CoA inhibit
- Isocitrate dehydrogenase - ATP inhibits, ADP and NAD<sup>+</sup> activate
- $\alpha$ -Ketoglutarate dehydrogenase - NADH and succinyl-CoA inhibit, AMP activates
- Also note pyruvate dehydrogenase: ATP, NADH, acetyl-CoA inhibit, NAD<sup>+</sup>, CoA activate

Figure 19.18  
Regulation of the TCA cycle.

- 4 enzymes and 3 hints:
1. Energy state  
(ex. Isocitrate dehydrogenase)
  2. Redox state  
(ex. NAD<sup>+</sup>/NADH ratio)
  3. Energy compounds  
(ex. Succinyl-CoA or Acetyl-CoA)



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## End of Part 2

- You should know...
  - How many substrate level phosphorylation reactions in glucose catabolism?
  - Trio reactions to reproduce oxaloacetate
  - How to release the carbon of acetyl-CoA in TCA cycle?
  - Which enzymes are regulation enzymes in TCA cycle?

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## 19.7 – Can the TCA Cycle Provide Intermediates for Biosynthesis?

The TCA cycle provides several of these

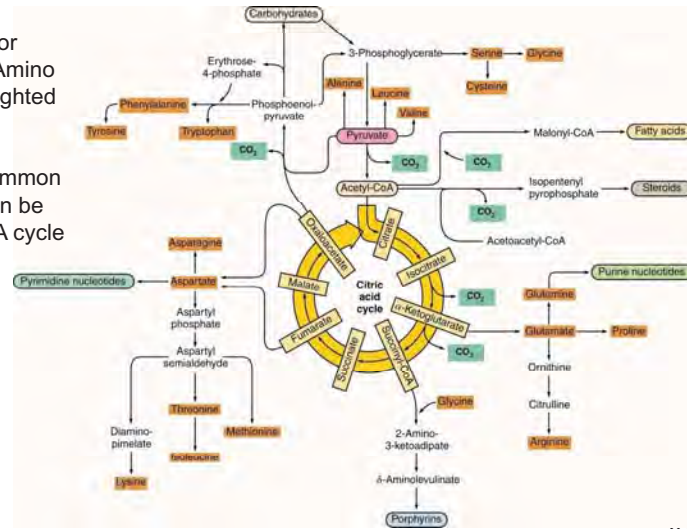
- **α-Ketoglutarate** is transaminated to make glutamate, which can be used to make purine nucleotides, Arg and Pro
- **Succinyl-CoA** can be used to make porphyrins
- **Fumarate** and **oxaloacetate** can be used to make several amino acids and also pyrimidine nucleotides
- Note that mitochondrial citrate can be exported to be a cytoplasmic source of acetyl-CoA and oxaloacetate

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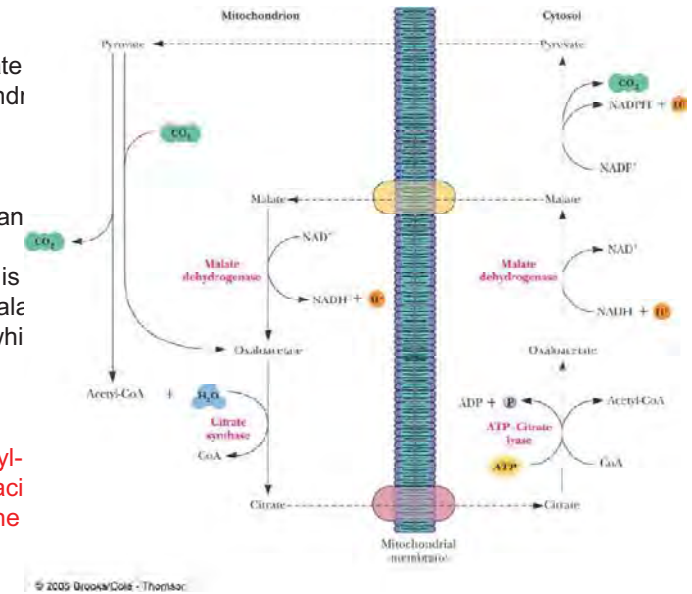
# The TCA Cycle Can Provide Intermediates For Biosynthesis

Figure 19.16 The TCA cycle provides intermediates for biosynthesis. Amino acids are highlighted in orange.

All 20 of the common amino acids can be made from TCA cycle intermediates.



Export of citrate from mitochondria and cytosolic breakdown produces oxaloacetate and acetyl-CoA. Oxaloacetate is recycled to malate or pyruvate, which reenters the mitochondria. This cycle provides acetyl-CoA for fatty acid synthesis in the cytosol.



## 19.8 – What Are the Anaplerotic, or “Filling Up,” Reactions?

- PEP carboxylase - converts PEP to oxaloacetate
- Pyruvate carboxylase - converts pyruvate to oxaloacetate
- Malic enzyme converts pyruvate into malate

There are 4 major reactions classed as anaplerotic, yet the production of oxaloacetate from pyruvate has probably the most physiologic importance.

From	To	Reaction	Notes
Pyruvate	oxaloacetate	$\text{pyruvate} + \text{HCO}_3^- + \text{ATP} \longrightarrow \text{oxaloacetate} + \text{ADP} + \text{P}_i + \text{H}_2\text{O}$	This reaction is catalysed by <b>pyruvate carboxylase</b> , an enzyme activated by Acetyl-CoA, indicating a lack of oxaloacetate. It occurs in animal mitochondria. Pyruvate can also be converted to L-malate, another intermediate, in a similar way.
Aspartate	oxaloacetate	-	This is a reversible reaction forming oxaloacetate from aspartate in a transamination reaction, via <b>aspartate transaminase</b> .
Glutamate	α-ketoglutarate	$\text{glutamate} + \text{NAD}^+ + \text{H}_2\text{O} \longrightarrow \text{NH}_4^+ + \alpha\text{-ketoglutarate} + \text{NADH} + \text{H}^+$	This reaction is catalysed by <b>glutamate-dehydrogenase</b> .
β-oxidation of fatty acids	succinyl-CoA	-	When odd-chain <b>fatty acids</b> are oxidized, one molecule of succinyl-CoA is formed per fatty acid. The final enzyme is <b>methylmalonyl-CoA mutase</b> .

### Anaplerotic Reaction #1: Pyruvate carboxylase

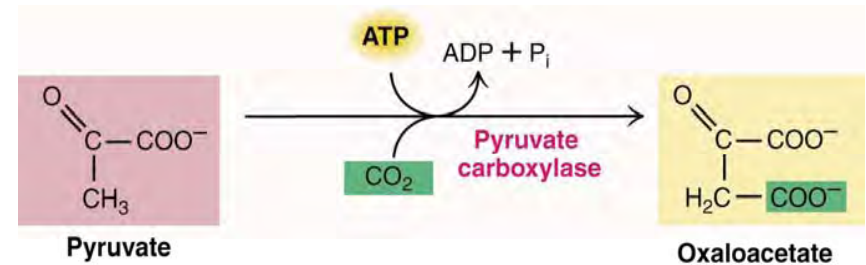


Figure 19.17 Pyruvate carboxylase (shown here), and also phosphoenolpyruvate (PEP) carboxylase, and malic enzyme catalyze anaplerotic reactions, replenishing TCA cycle intermediates.



## Anaplerotic Reaction #2: PEP carboxylase?

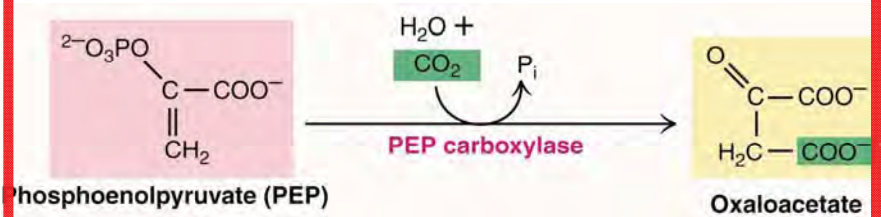


Figure 19.17 Pyruvate carboxylase, phosphoenolpyruvate (PEP) carboxylase (shown here), and malic enzyme catalyze anaplerotic reactions, replenishing TCA cycle intermediates.

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## Anaplerotic Reaction #3: Malic enzyme?

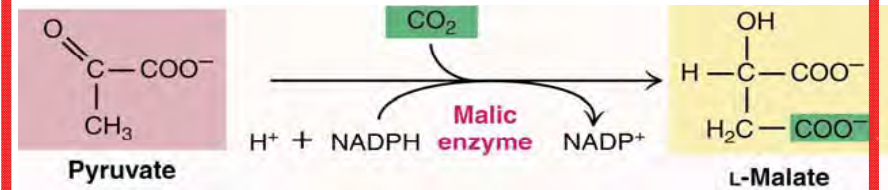
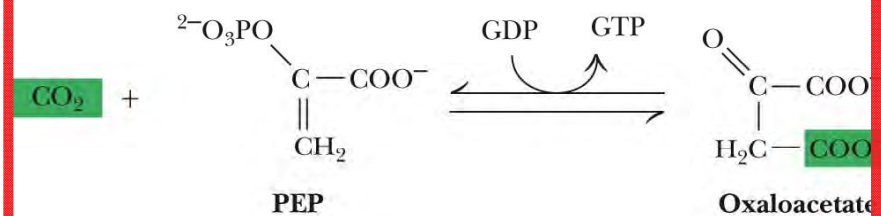


Figure 19.17 Pyruvate carboxylase, and also phosphoenolpyruvate (PEP) carboxylase and malic enzyme (shown here) catalyze anaplerotic reactions, replenishing TCA cycle intermediates.

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## Is PEP Carboxykinase an Anaplerotic Reaction?

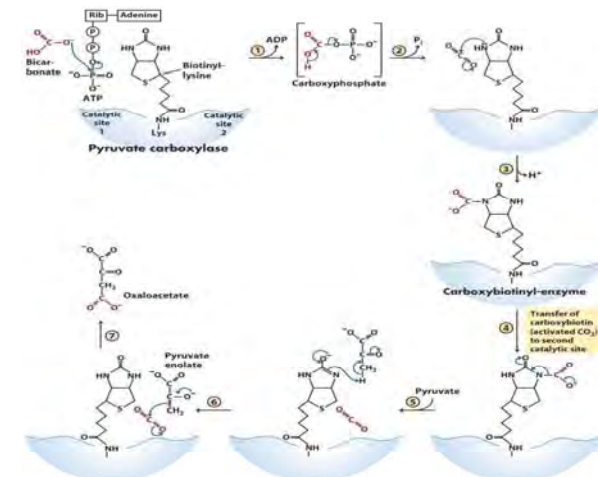


This reaction *might* be an anaplerotic reaction, except for the fact that  $\text{CO}_2$  binds weakly to PEP carboxykinase, and oxaloacetate binds very tightly. As a result, the enzyme favors formation of PEP from oxaloacetate.

Thus the reaction operates in the wrong direction to be an anaplerotic reaction.

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## Biotin in pyruvate carboxylase carries $\text{CO}_2$ groups

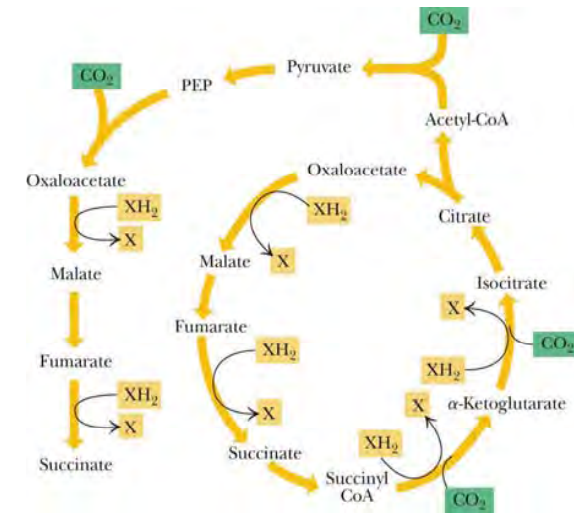


## The Reductive TCA Cycle

- The TCA cycle running backward could assimilate CO<sub>2</sub>
- This may have been the first metabolic pathway
- Energy to drive it? Maybe reaction of FeS with H<sub>2</sub>S to form FeS<sub>2</sub> (iron pyrite)
- Iron pyrite, which was plentiful in ancient times, and which is an ancient version of 'iron-sulfur clusters'!

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The rTCA cycle is a carbon dioxide fixation pathway found in autotrophic eubacteria and archaea



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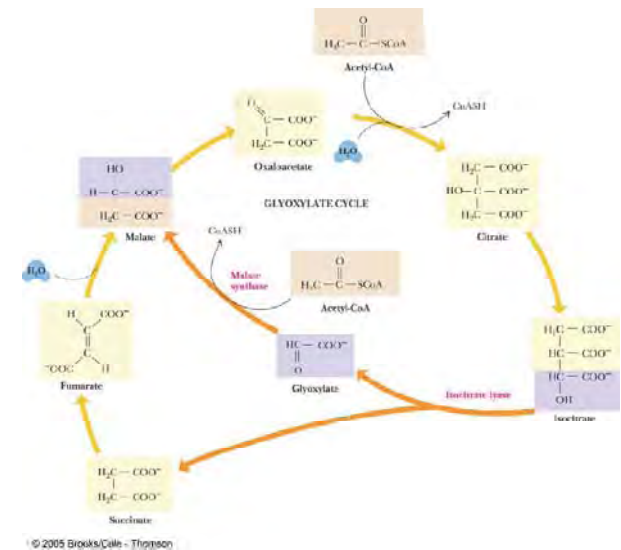
## 19.10 – Can Any Organisms Use Acetate as Their Sole Carbon Source?

### The Glyoxylate (乙醛酸) Cycle

- Acetate-based growth - net synthesis of carbohydrates and other intermediates from acetate - is not possible with TCA
- Glyoxylate cycle offers a solution for plants and some bacteria and algae
- **The CO<sub>2</sub>-evolving steps are bypassed and an extra acetate is utilized**
- Isocitrate lyase and malate synthase are the short-circuiting enzymes

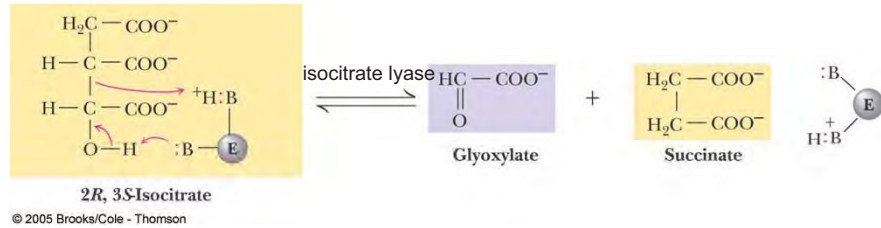
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Figure 19.20  
The glyoxylate cycle. The first two steps are identical to TCA cycle reactions. The third step bypasses the CO<sub>2</sub>-evolving steps of the TCA cycle to produce succinate and glyoxylate. The malate synthase reaction forms malate from glyoxylate and another acetyl-CoA. The result is that one turn of the cycle consumes one oxaloacetate and two acetyl-CoA molecules but produces two molecules of oxaloacetate. The net for this cycle is one oxaloacetate from two acetyl-CoA molecules.



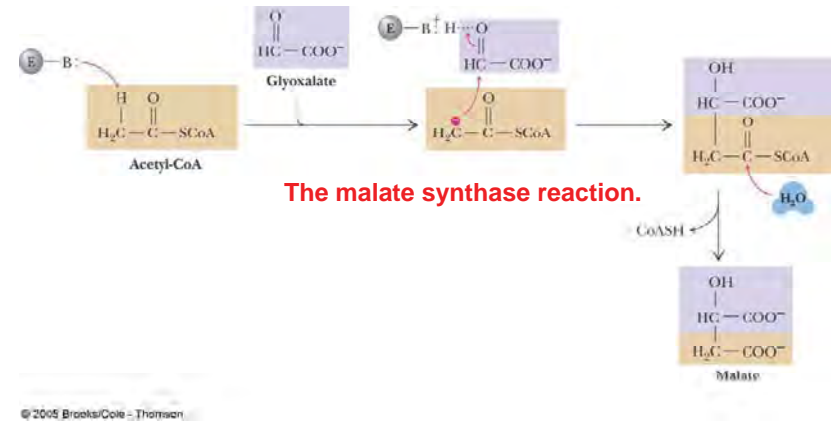
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## Rx1: Isocitrate lyase produces glyoxylate and succinate



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## Rx2: Malate synthase does a **Claisen condensation** of acetyl-CoA and the aldehyde group of glyoxylate



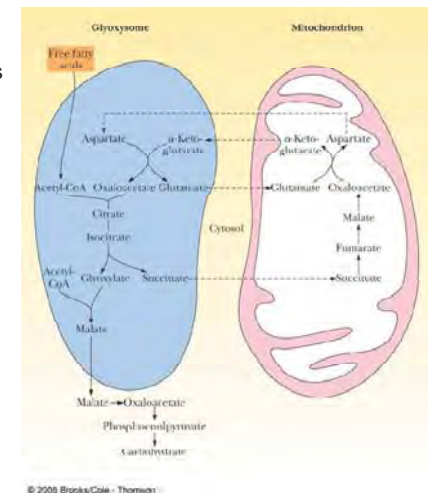
## Glyoxysomes Must Borrow Three Reactions from Mitochondria

- Glyoxysomes do not contain all the enzymes needed to run the glyoxylate cycle
- Succinate dehydrogenase, fumarase, and malate dehydrogenase are absent
- Glyoxysomes borrow these three reactions from mitochondria, so that they can convert succinate to oxaloacetate

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## Glyoxysomes Must Borrow Three Reactions from Mitochondria

- The glyoxylate cycle helps plants grow in the dark!
- Glyoxysomes borrow three reactions from mitochondria: succinate to oxaloacetate



## End of Part 3

- You should know...
  - Which TCA cycle intermediates could be used for biosynthesis?
  - What Are the Anaplerotic, or “Filling Up,” Reactions?
  - What is the reversed TCA cycle?
  - What is glyoxylate cycle?

## End of the class

- You should have learned...
  - All reactions from pyruvate through TCA cycle
  - 5 coenzymes involved in these reactions
  - Regulation of TCA cycle
  - TCA cycle as a hub for metabolism
  - How to fill-up TCA cycle
  - Glyoxylate cycle