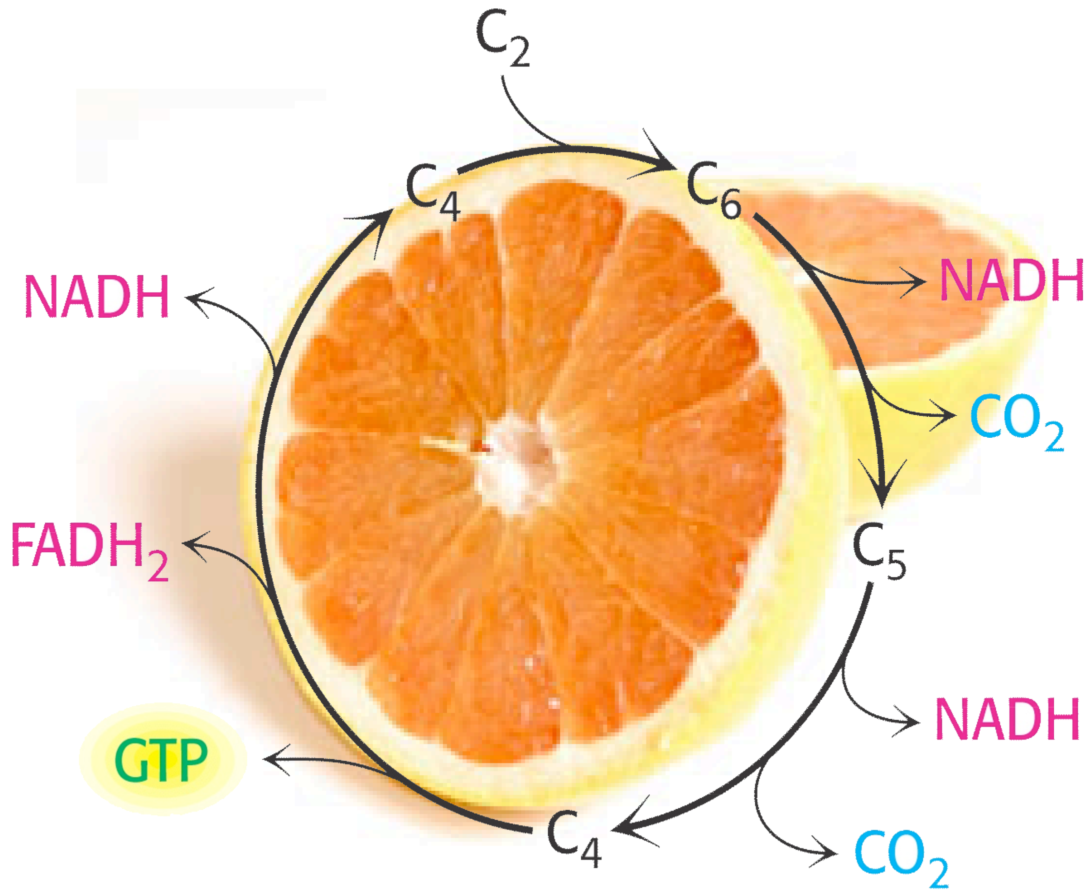
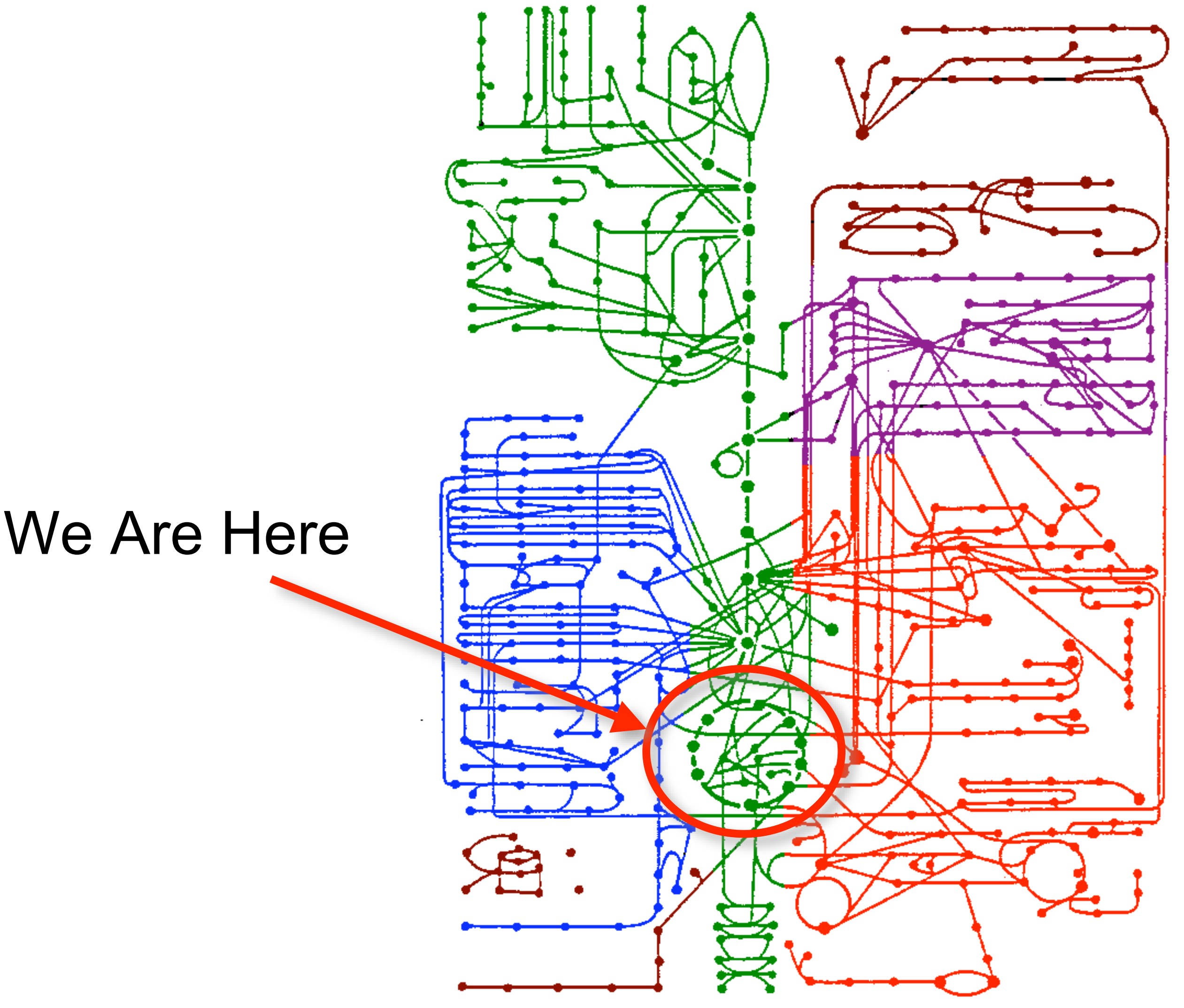
Chapter 17

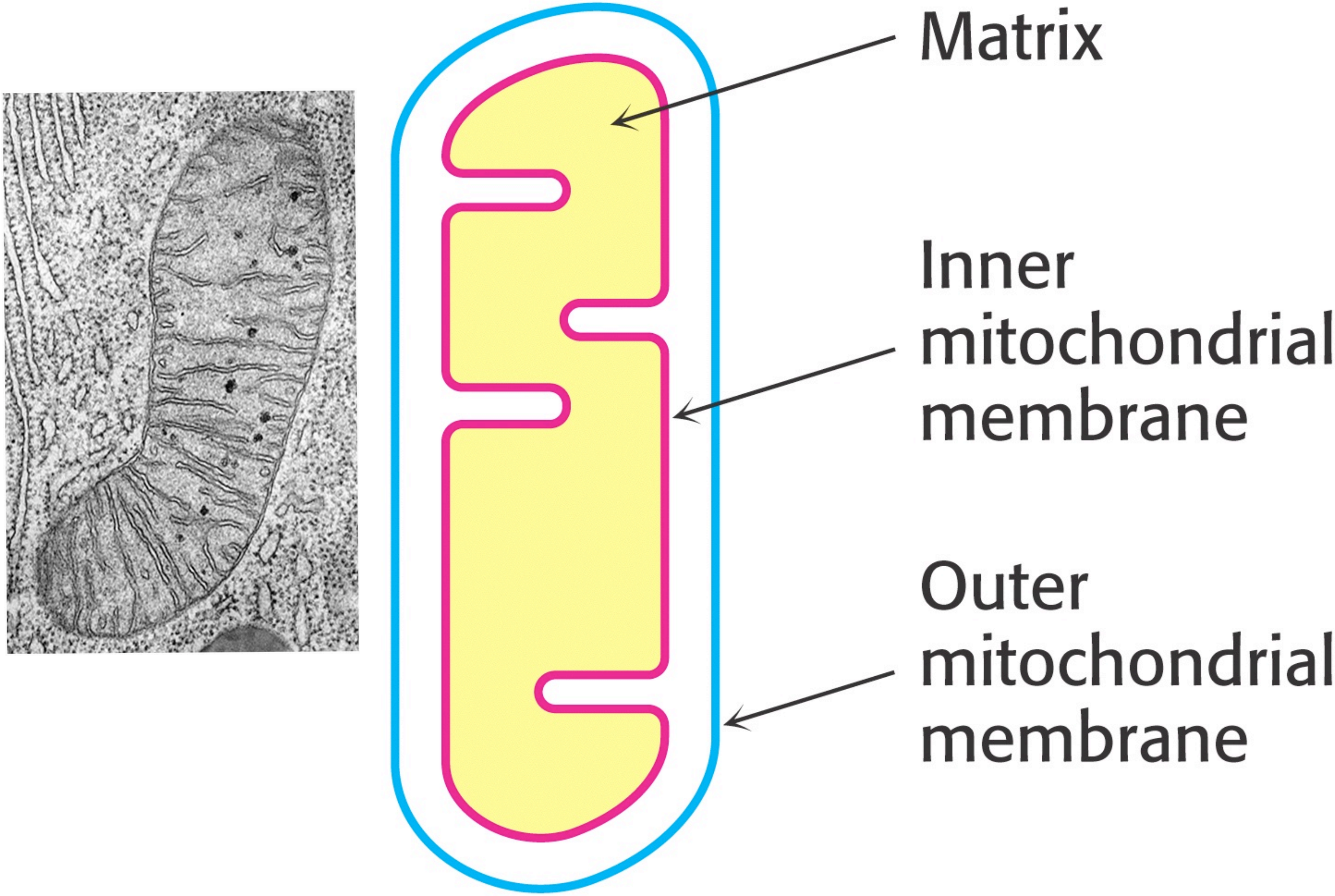
The Citric Acid Cycle

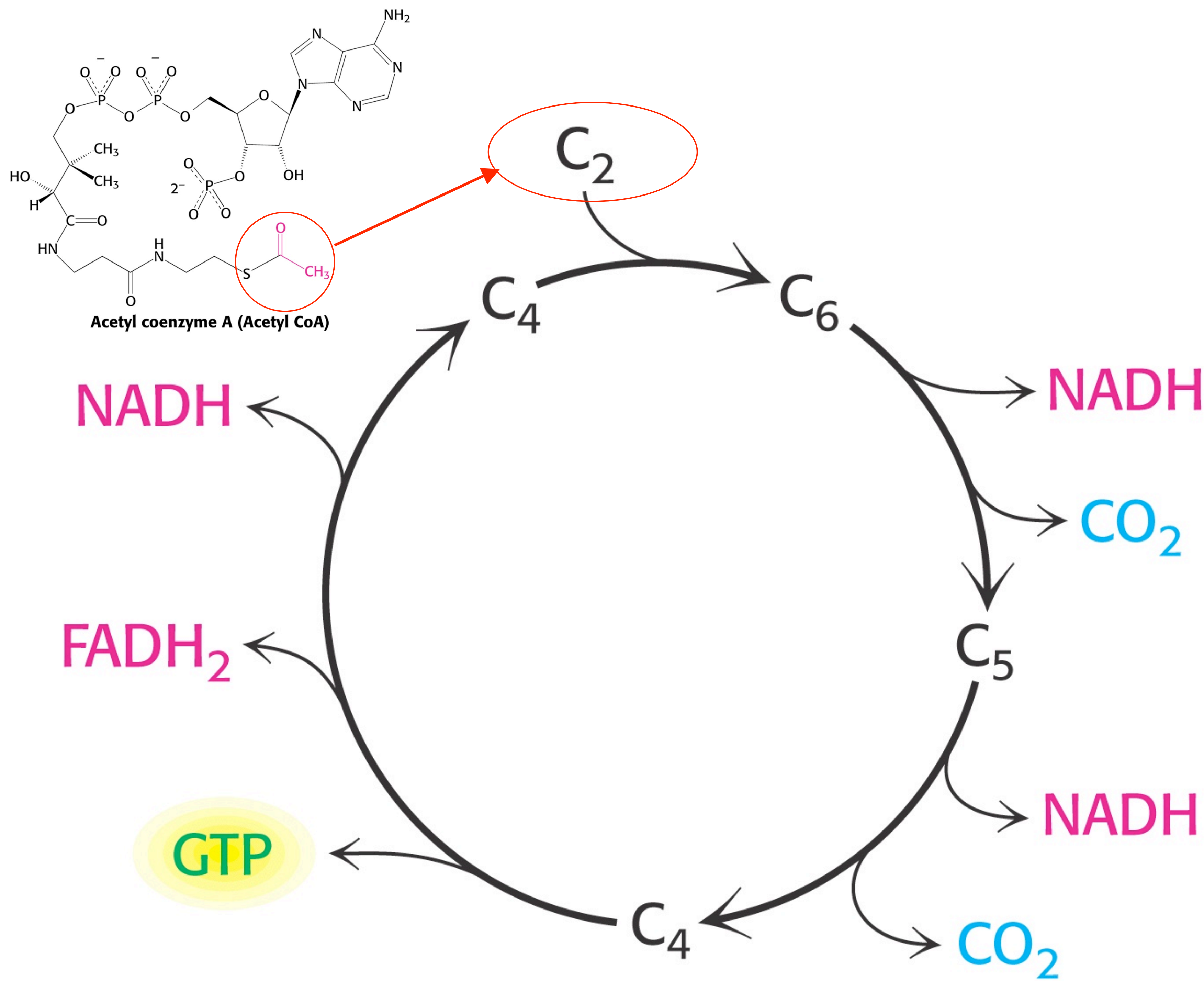


Chapter 17

The Citric Acid Cycle




Matrix
Inner mitochondrial membrane
Outer mitochondrial membrane



NH2
N
N
N
N
O
O
P
O
O
P
O
O
O
O
CH3
CH3
HO
H
C=O
HN
H
N
O
S
O
CH3
2−
P
O
O
O
OH
Acetyl coenzyme A (Acetyl CoA)
C2
C6
NADH
CO2
C5
NADH
CO2
C4
GTP
FADH2
NADH
C4

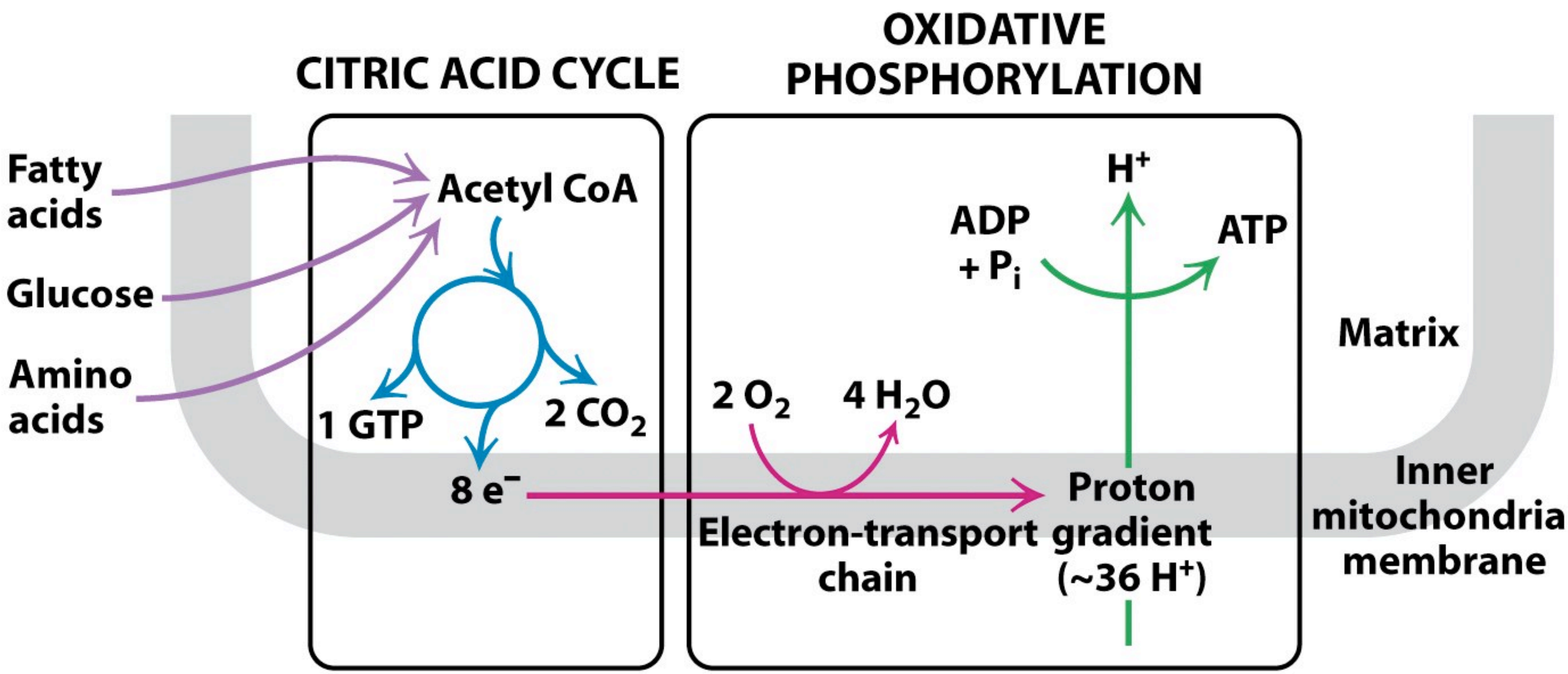


Figure 17-3
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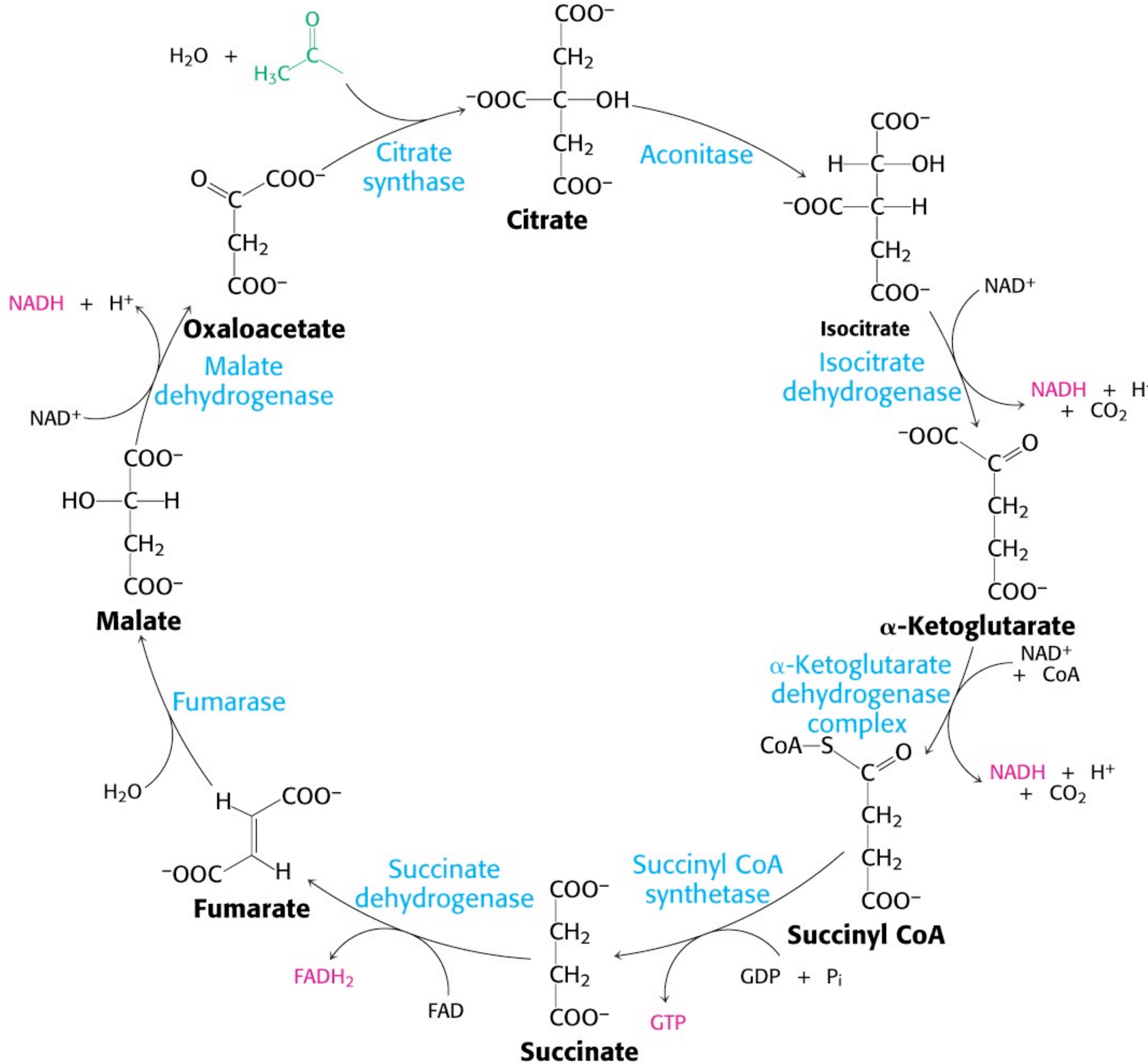


H2O +
Citrate
Citrate synthase
Aconitase
Isocitrate
NAD+
Isocitrate dehydrogenase
NADH + H+ + CO2
α-Ketoglutarate
NAD+ + CoA
α-Ketoglutarate dehydrogenase complex
NADH + H+ + CO2
Succinyl CoA
Succinyl CoA synthetase
GDP + Pi
GTP
Succinate
Succinate dehydrogenase
FAD
FADH2
Fumarate
Fumarase
H2O
Malate
Malate dehydrogenase
NAD+
NADH + H+
Oxaloacetate

TABLE 17.2 **Citric acid cycle**

Step	Reaction	Enzyme	Prosthetic group	Type*	$\Delta G^{\circ\prime}$ kcal mol^{-1}	$\Delta G^{\circ\prime}$ kJ mol^{-1}
1	Acetyl CoA + oxaloacetate + $H_2O \longrightarrow$ citrate + CoA + H^+	Citrate synthase		a	−7.5	−31.4
2a	Citrate $\rightleftharpoons$ *cis*-aconitate + H_2O	Aconitase	Fe–S	b	+2.0	+8.4
2b	*cis*-Aconitate + $H_2O \rightleftharpoons$ isocitrate	Aconitase	Fe–S	c	−0.5	−2.1
3	Isocitrate + $NAD^+ \rightleftharpoons$ α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase		d + e	−2.0	−8.4
4	α-Ketoglutarate + NAD^+ + CoA $\rightleftharpoons$ succinyl CoA + CO_2 + NADH	α-Ketoglutarate dehydrogenase complex	Lipoic acid, FAD, TPP	d + e	−7.2	−30.1
5	Succinyl CoA + P_i + GDP $\rightleftharpoons$ succinate + GTP + CoA	Succinyl CoA synthetase		f	−0.8	−3.3
6	Succinate + FAD (enzyme-bound) $\rightleftharpoons$ fumarate + $FADH_2$ (enzyme-bound)	Succinate dehydrogenase	FAD, Fe–S	e	~0	0
7	Fumarate + $H_2O \rightleftharpoons$ L-malate	Fumarase		c	−0.9	−3.8
8	L-Malate + $NAD^+ \rightleftharpoons$ oxaloacetate + NADH + H^+	Malate dehydrogenase		e	+7.1	+29.7

*Reaction type: (a) condensation; (b) dehydration; (c) hydration; (d) decarboxylation; (e) oxidation; (f) substrate-level phosphorylation.

The Lead-in to TCA

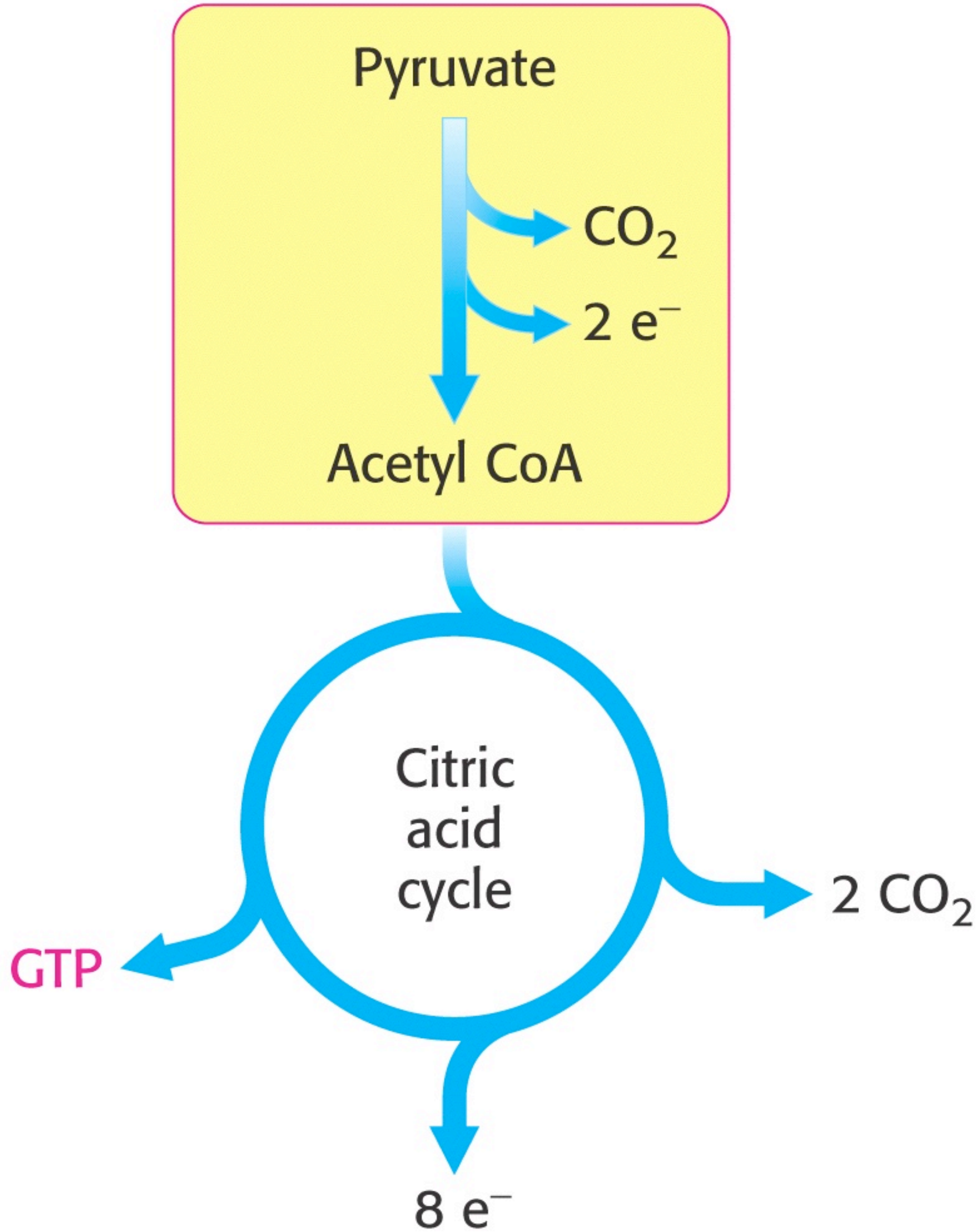
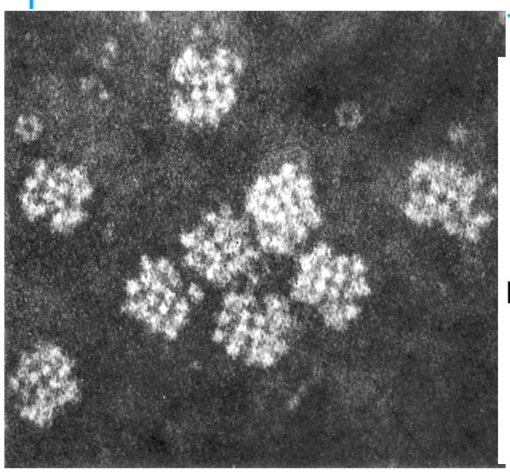
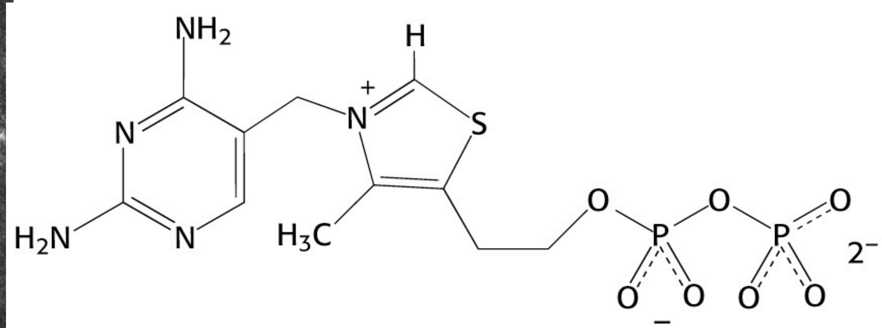


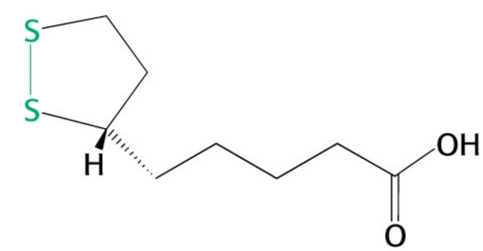
TABLE 17.1 **Pyruvate dehydrogenase complex of *E. coli***

Enzyme	Abbreviation	Number of chains	Prosthetic group	Reaction catalyzed
Pyruvate dehydrogenase component	E_1	24	TPP	Oxidative decarboxylation of pyruvate
Dihydrolipoyl transacetylase	E_2	24	Lipoamide	Transfer of the acetyl group to CoA
Dihydrolipoyl dehydrogenase	E_3	12	FAD	Regeneration of the oxidized form of lipoamide

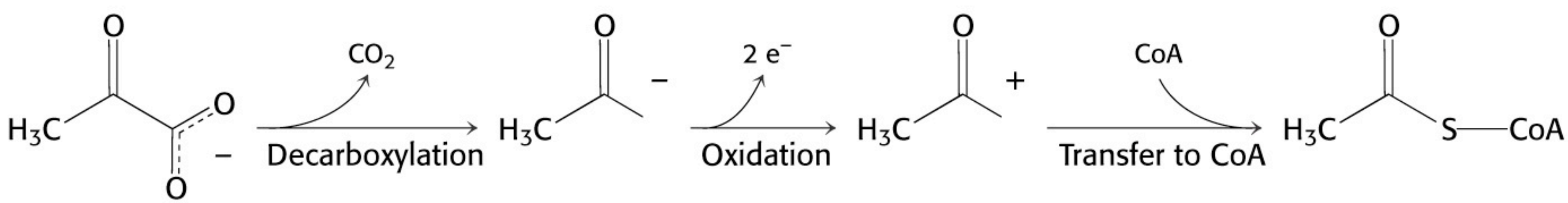




Thiamine pyrophosphate (TPP)

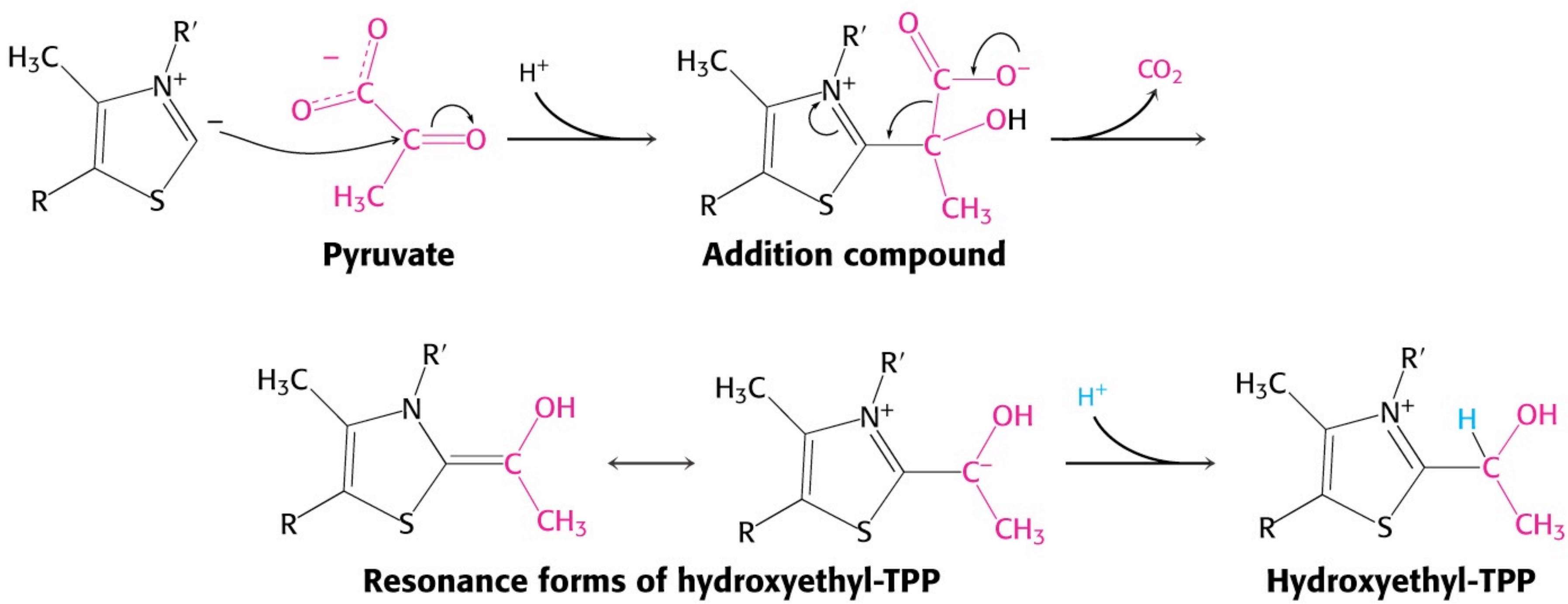


Lipoic acid

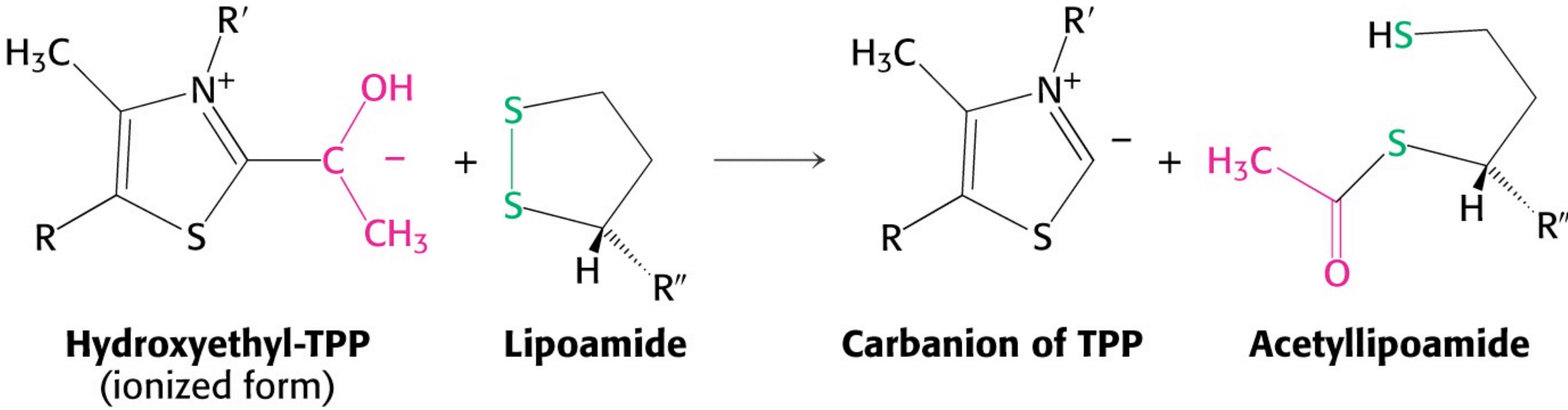


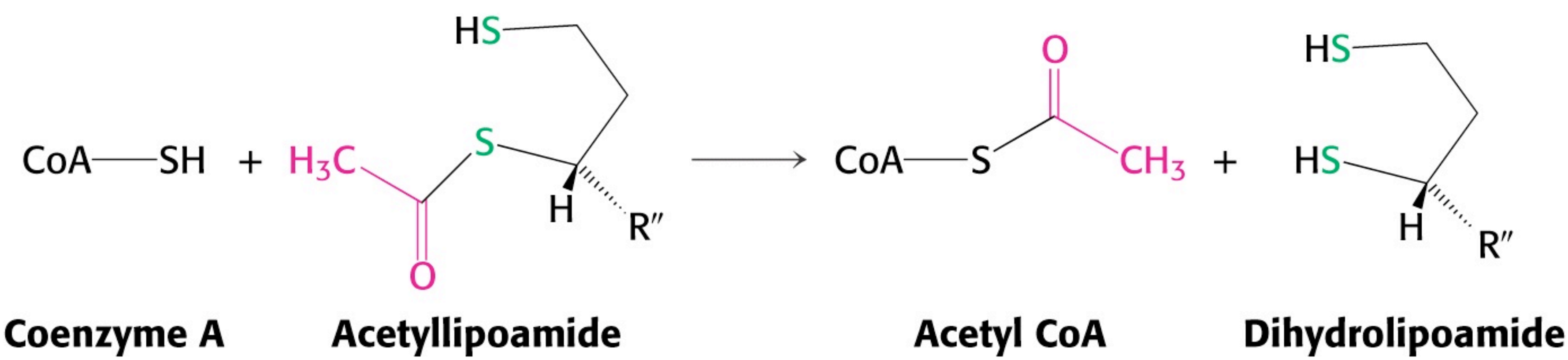
Pyruvate **Acetyl CoA**

PDH: the start

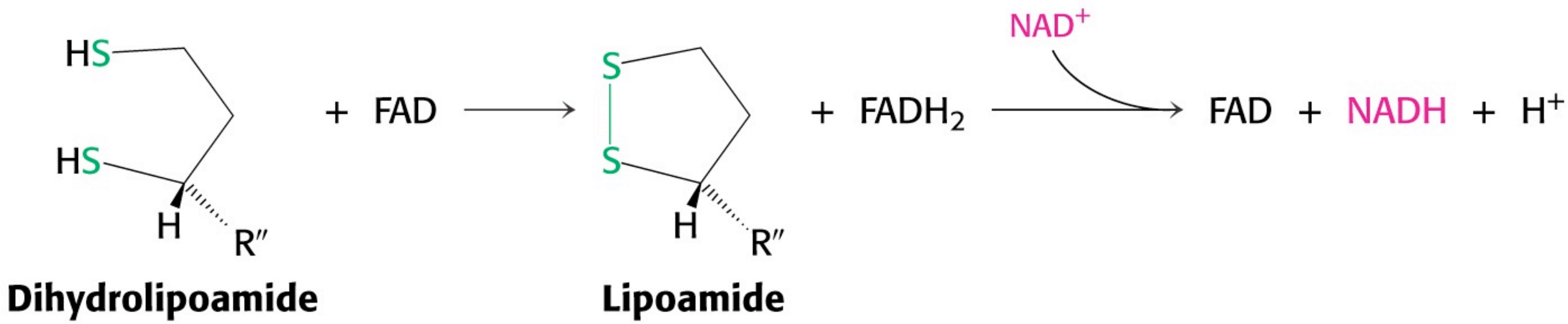


PDH: the oxidation phase

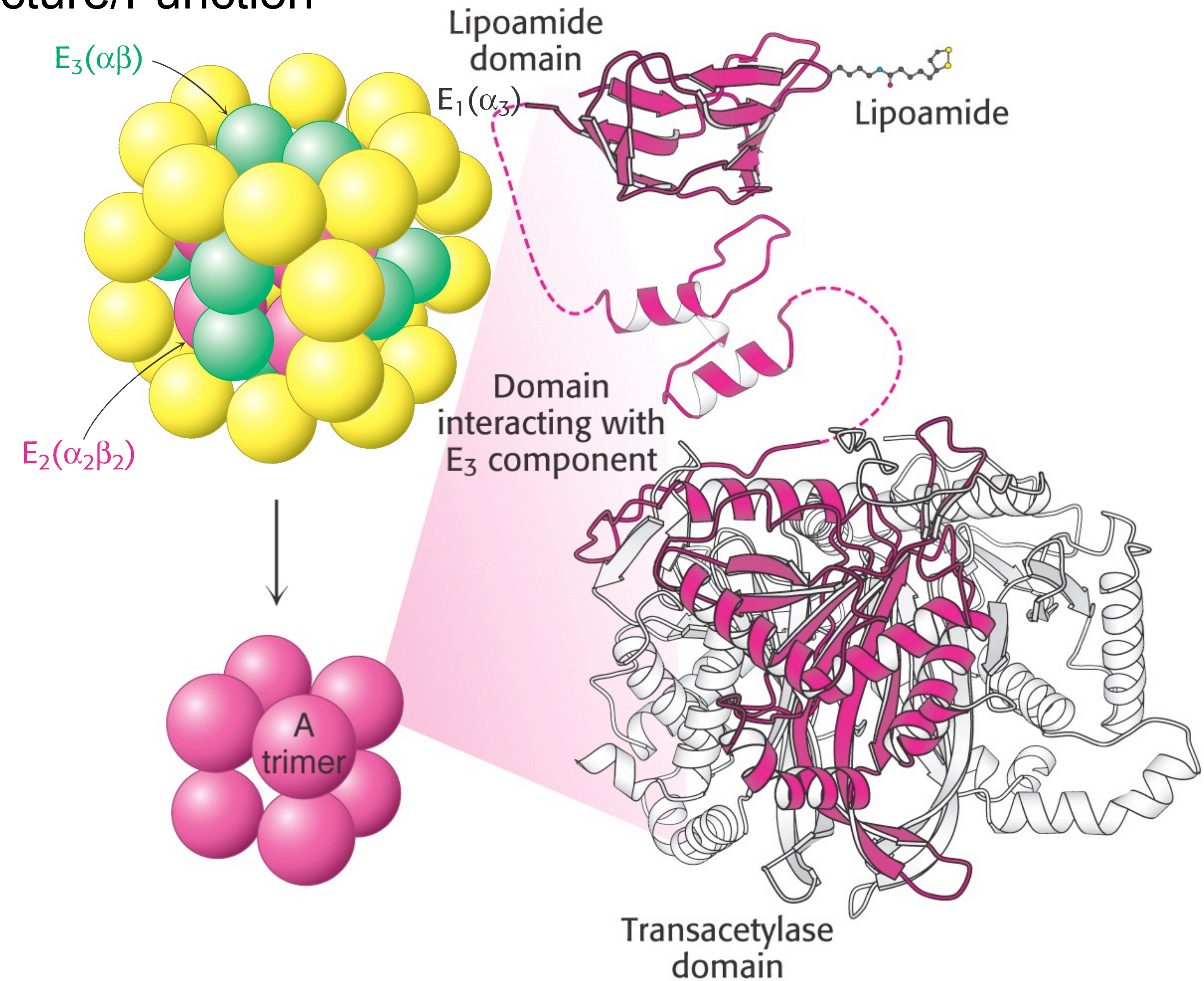




PDH:restoring lipoamide



PDH:Structure/Function



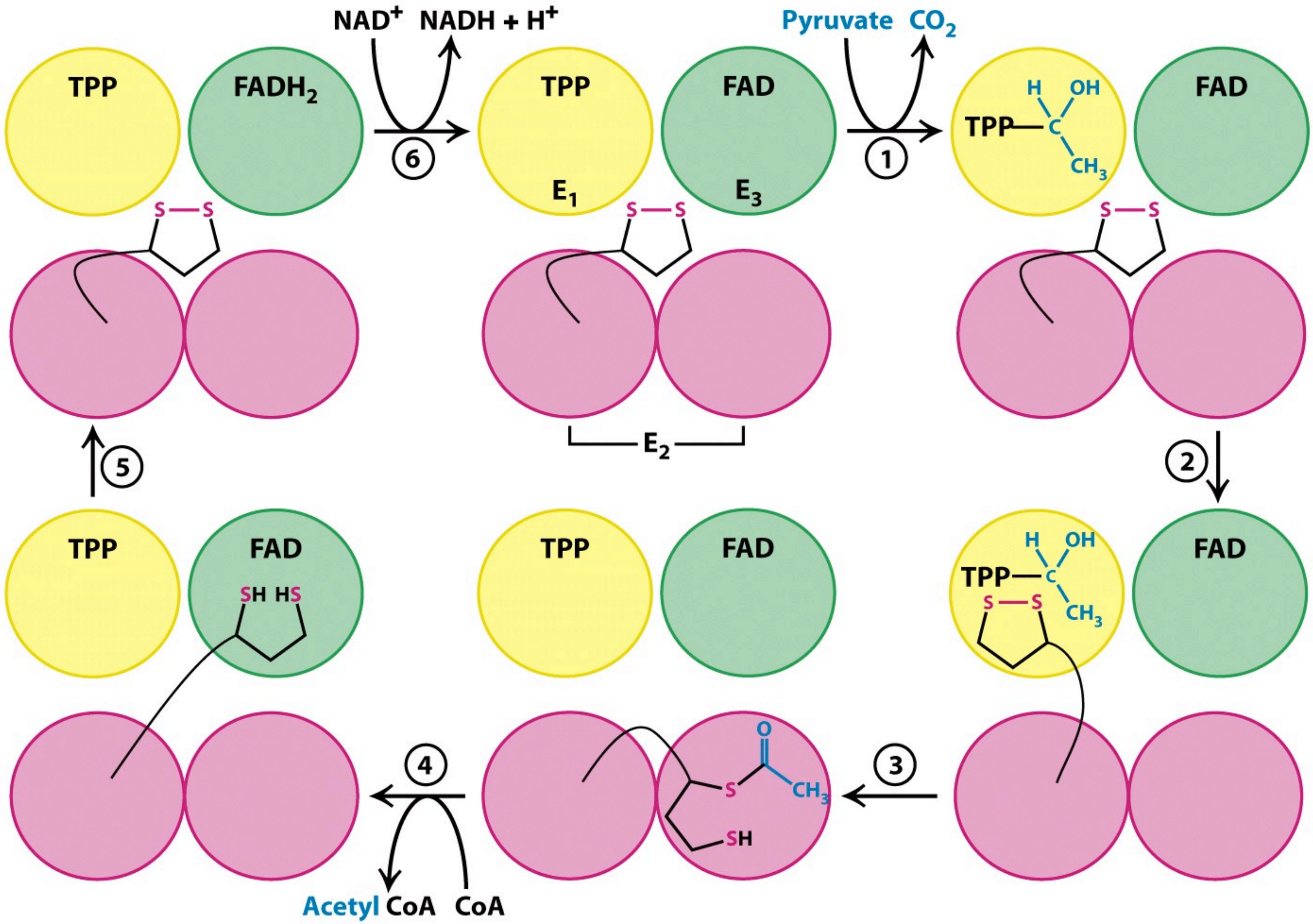


Figure 17-9
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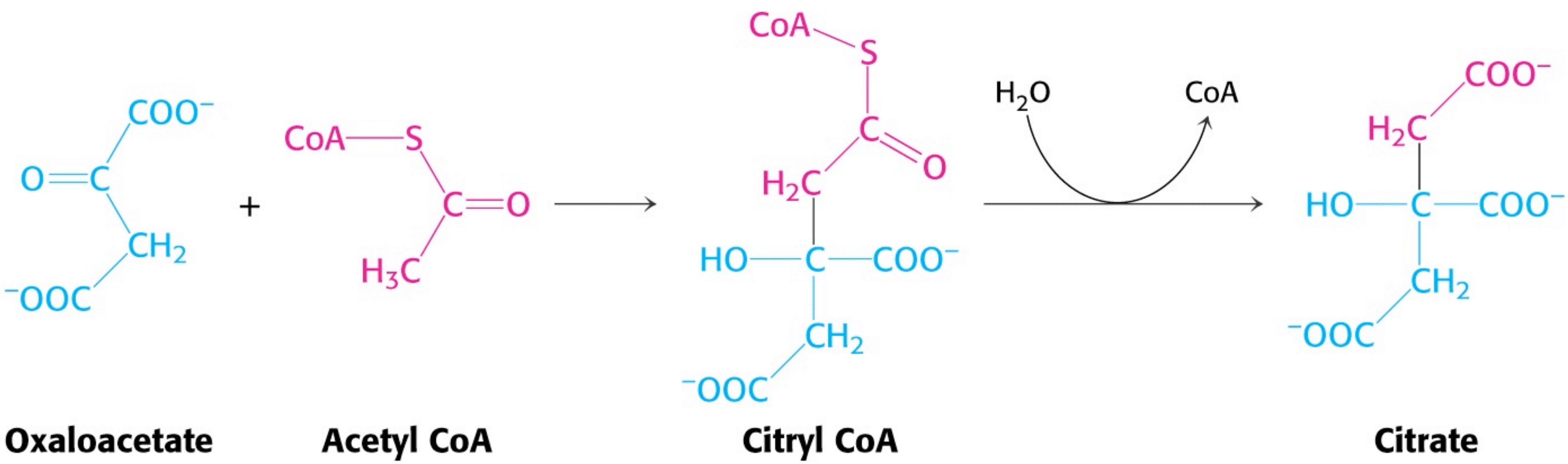
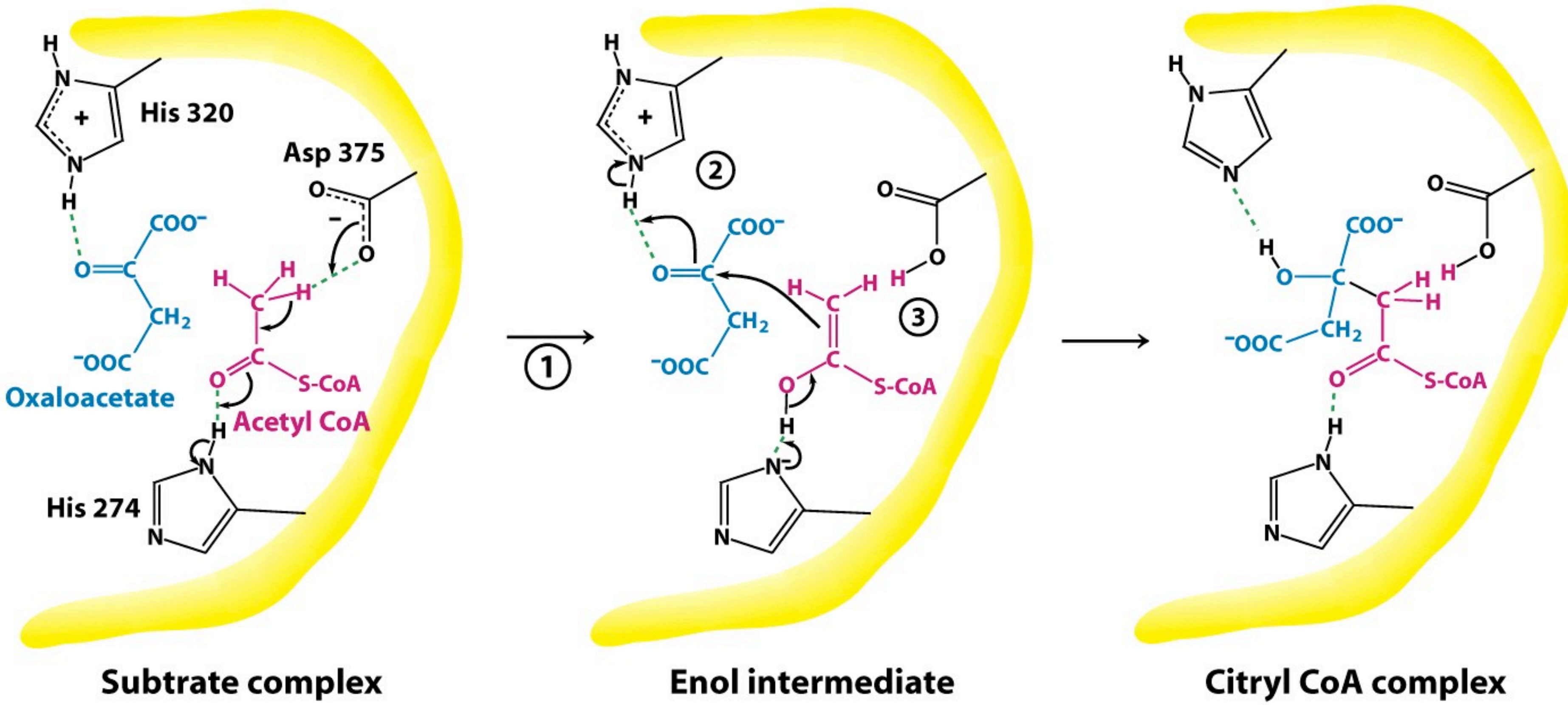
Citrate Synthase



Citrate Synthase



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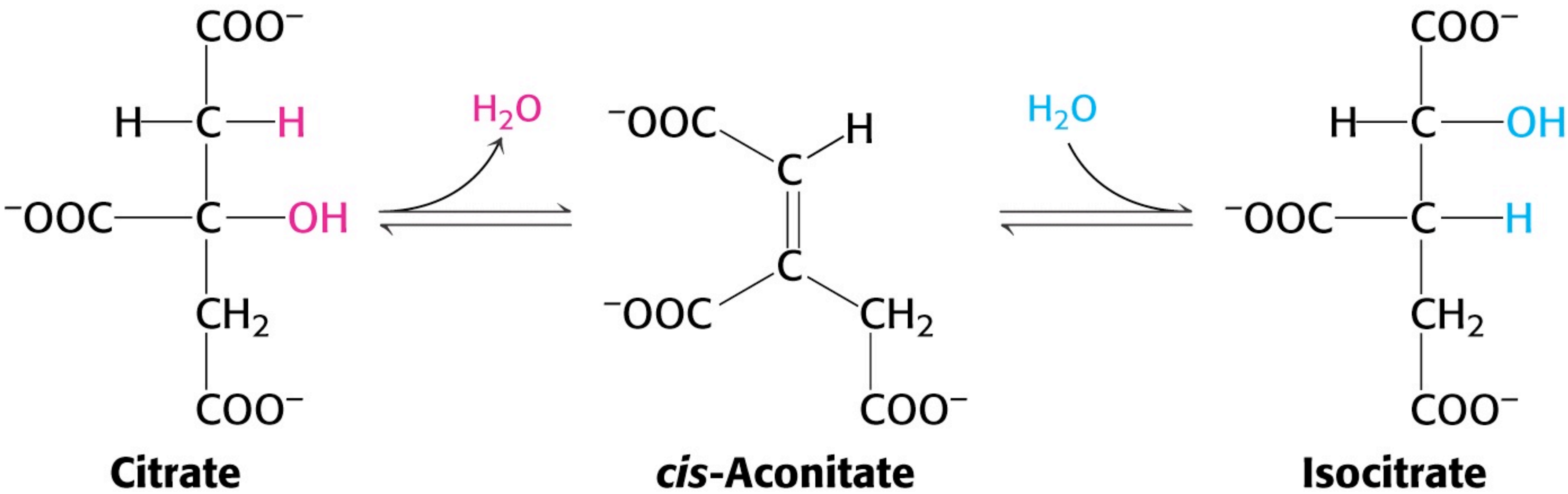
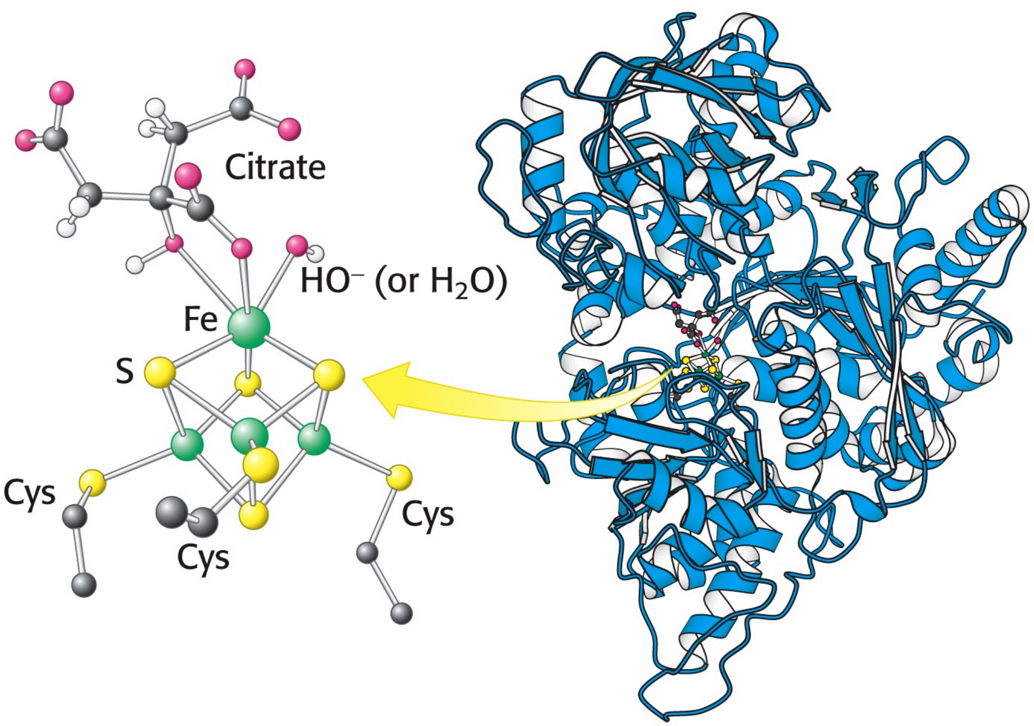
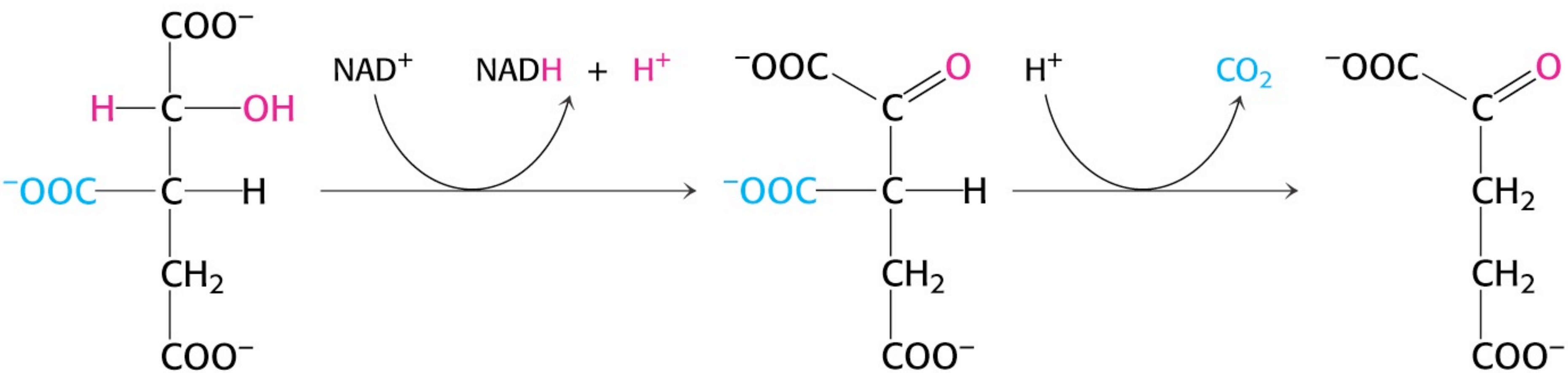
Aconitase

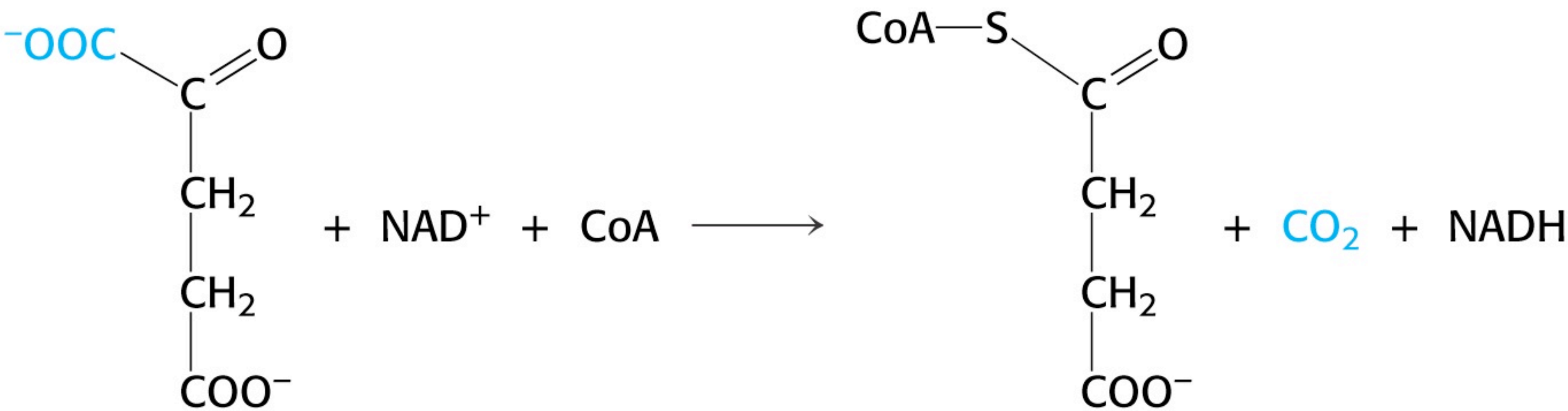

COO⁻
H—C—H
⁻OOC—C—OH
CH2
COO⁻
Citrate
H2O
⁻OOC
C—H
C
⁻OOC
CH2
COO⁻
cis-Aconitate
H2O
COO⁻
H—C—OH
⁻OOC—C—H
CH2
COO⁻
Isocitrate


Citrate
HO⁻ (or H2O)
Fe
S
Cys
Cys
Cys



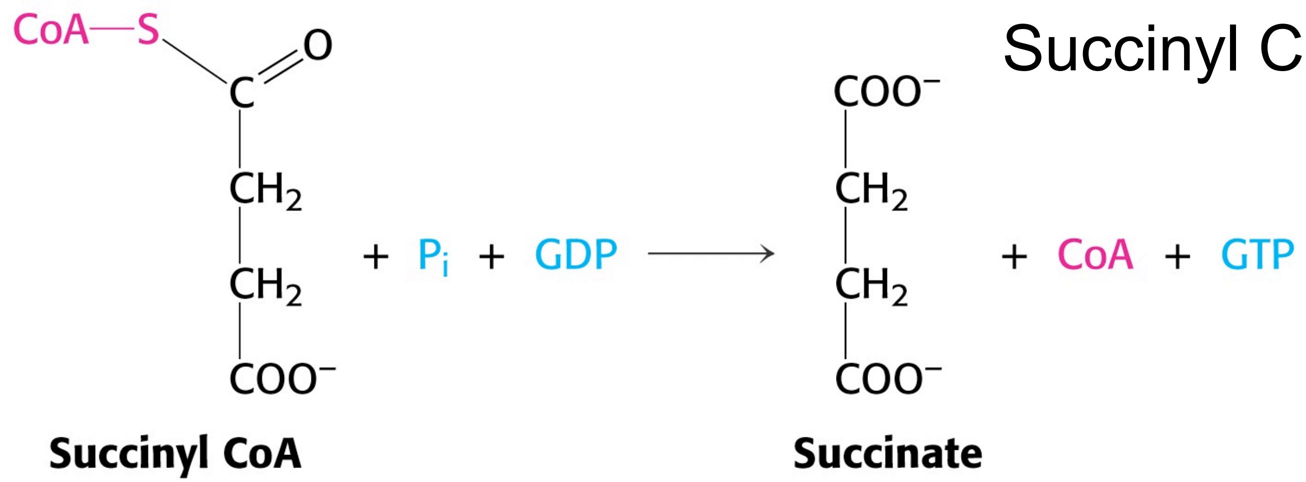
Isocitrate **Oxalosuccinate** **α-Ketoglutarate**

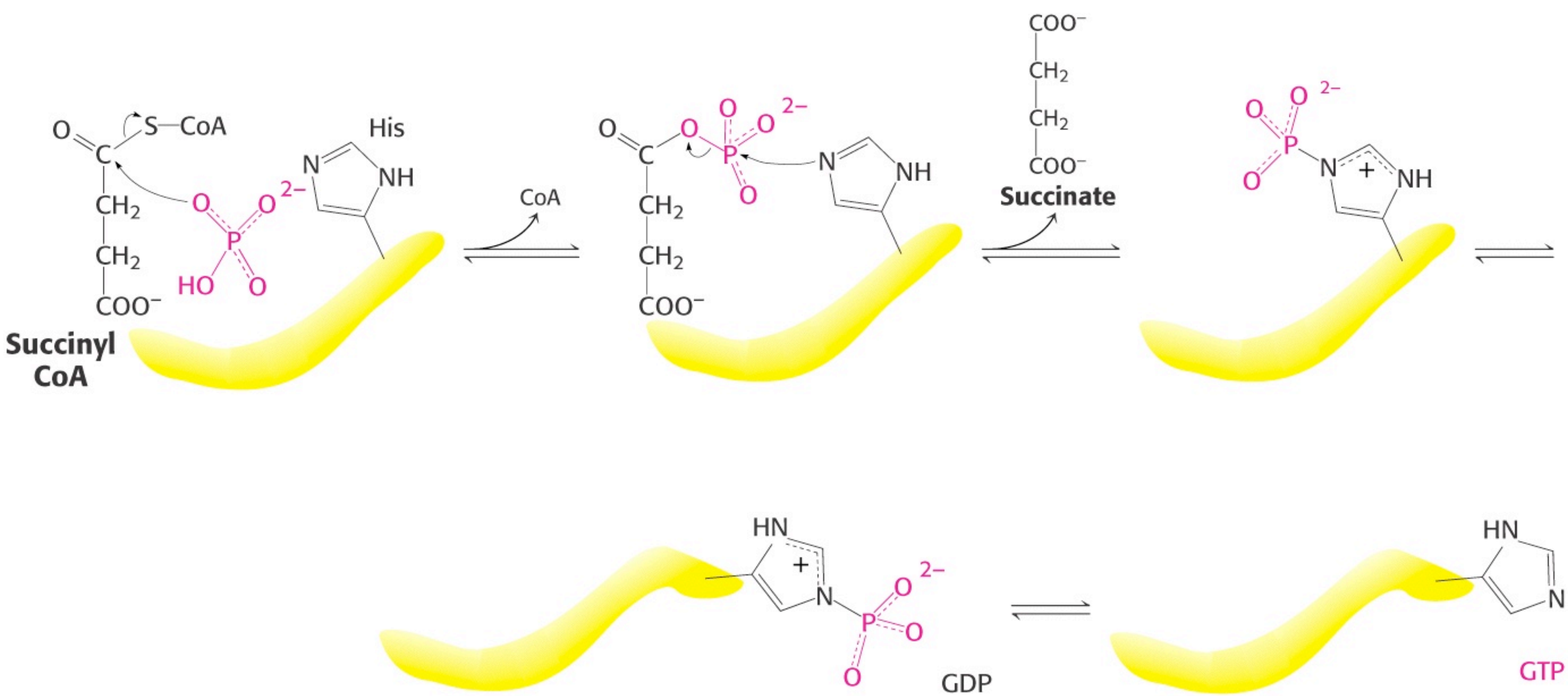
α–ketoglutarate dehydrogenase

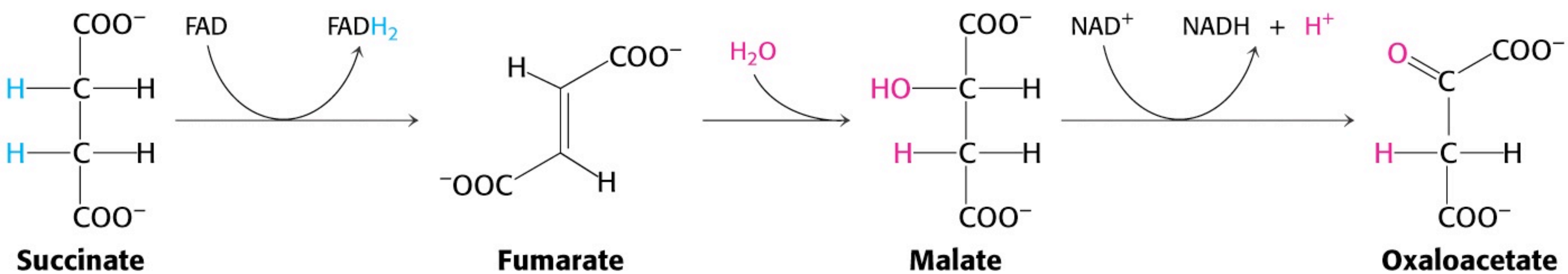


α-Ketoglutarate **Succinyl CoA**

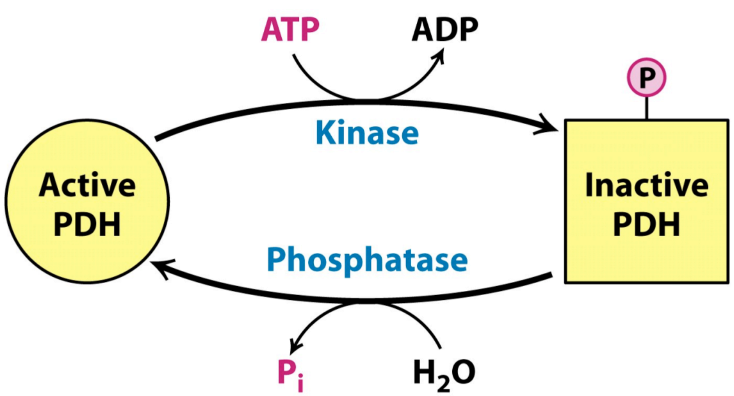
Succinyl CoA Synthase






COO⁻
FAD
FADH2
H
C
H
COO⁻
Succinate
Fumarate
H2O
HO
NAD+
NADH + H+
O
Malate
Oxaloacetate
OOC

REGULATION



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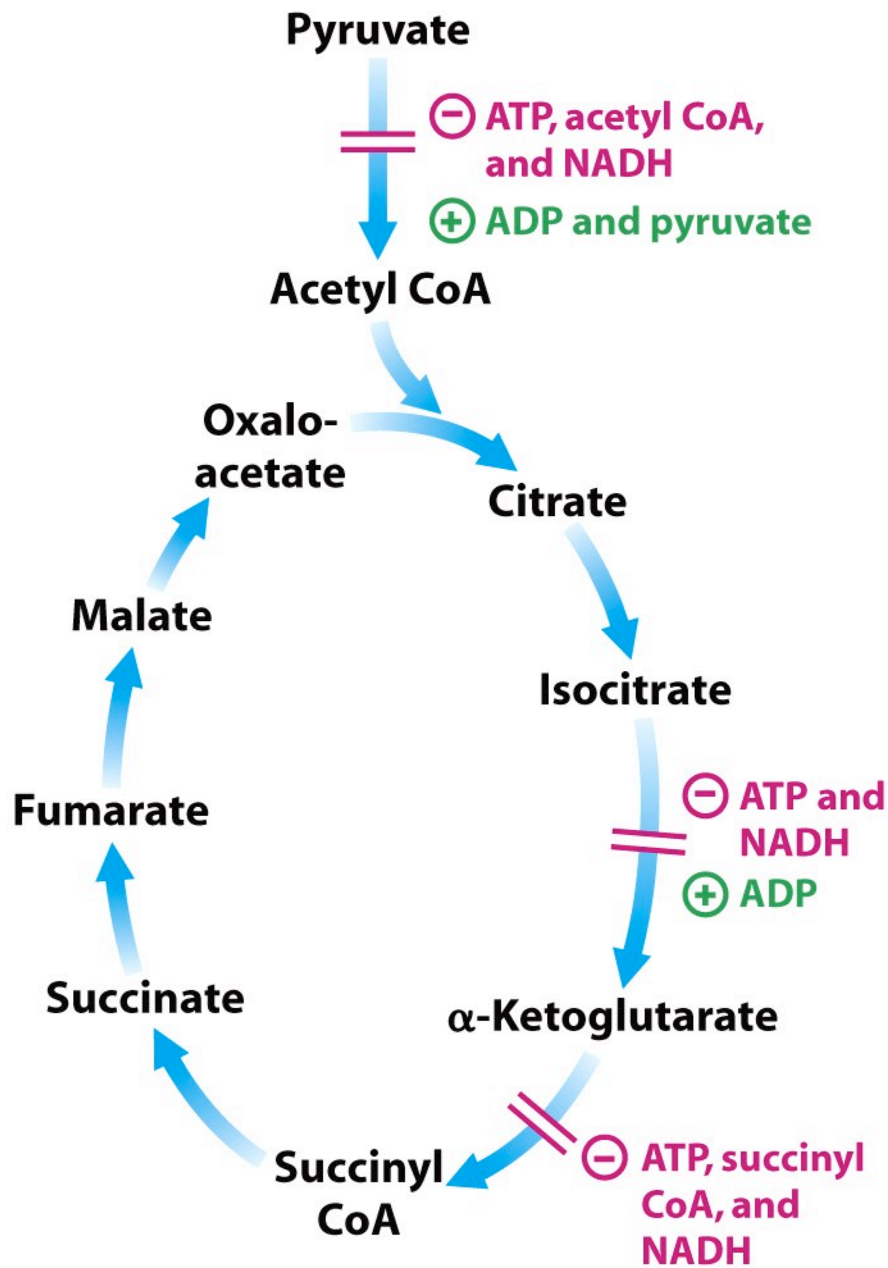

Figure 17-19
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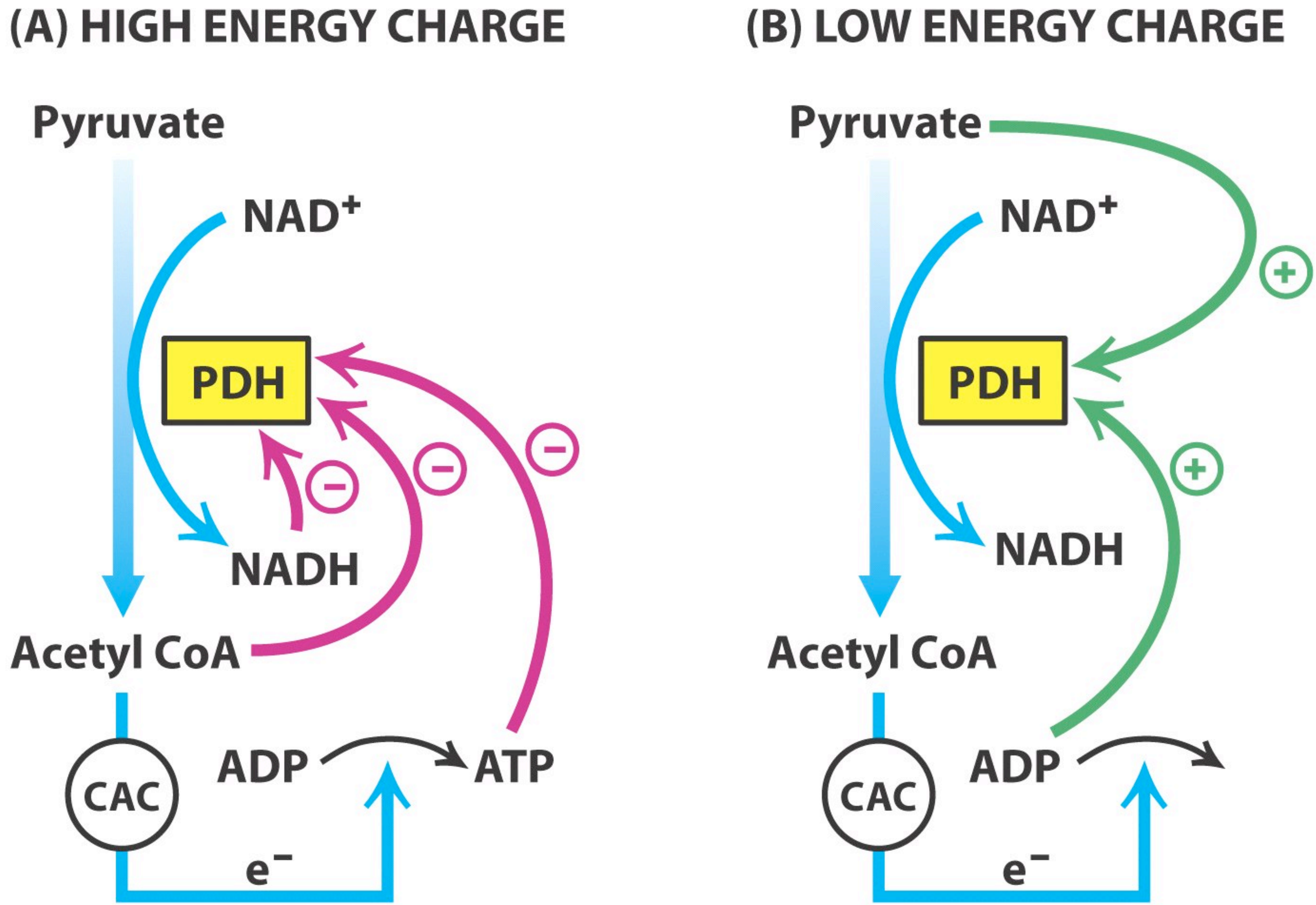

Figure 17-18
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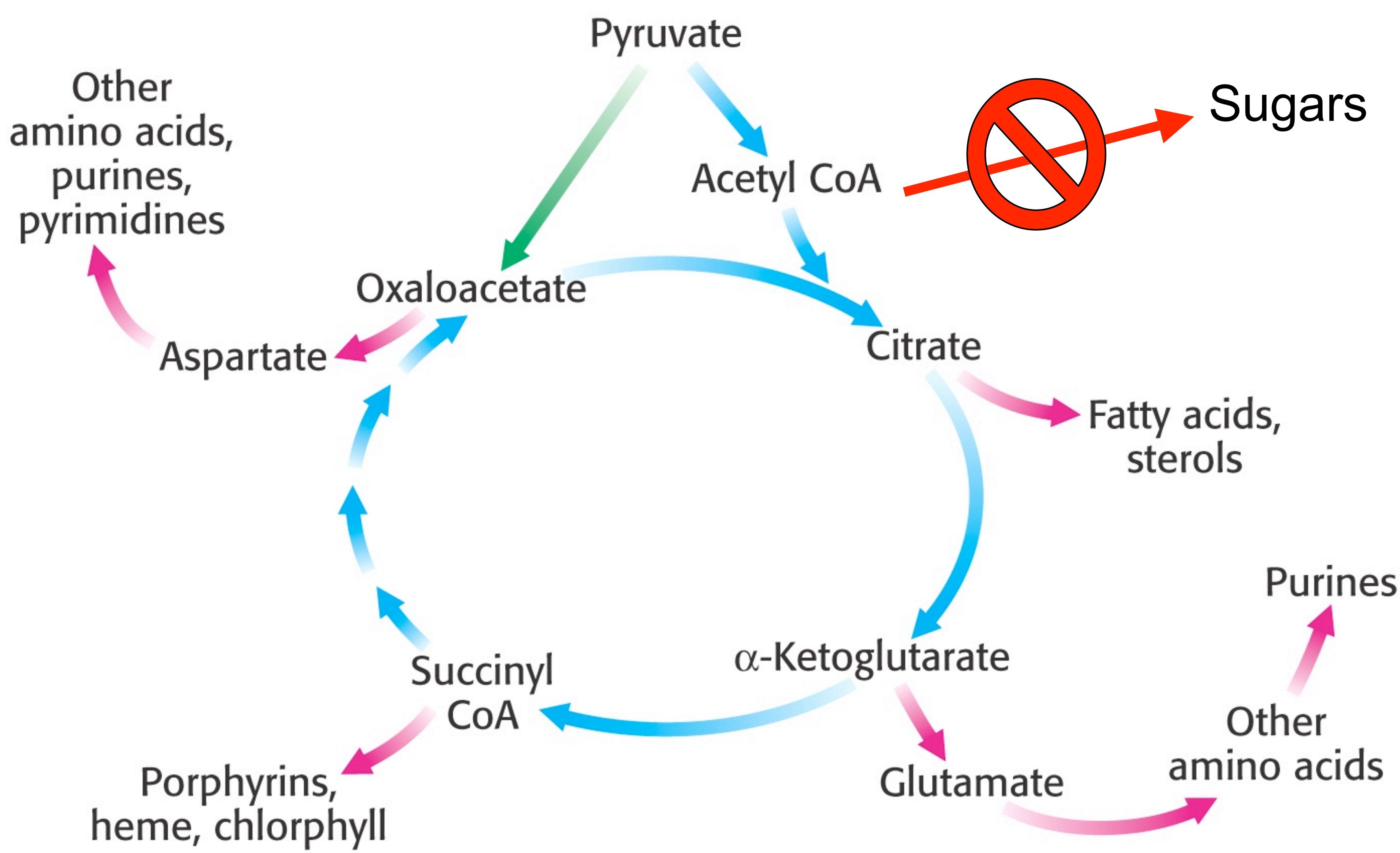
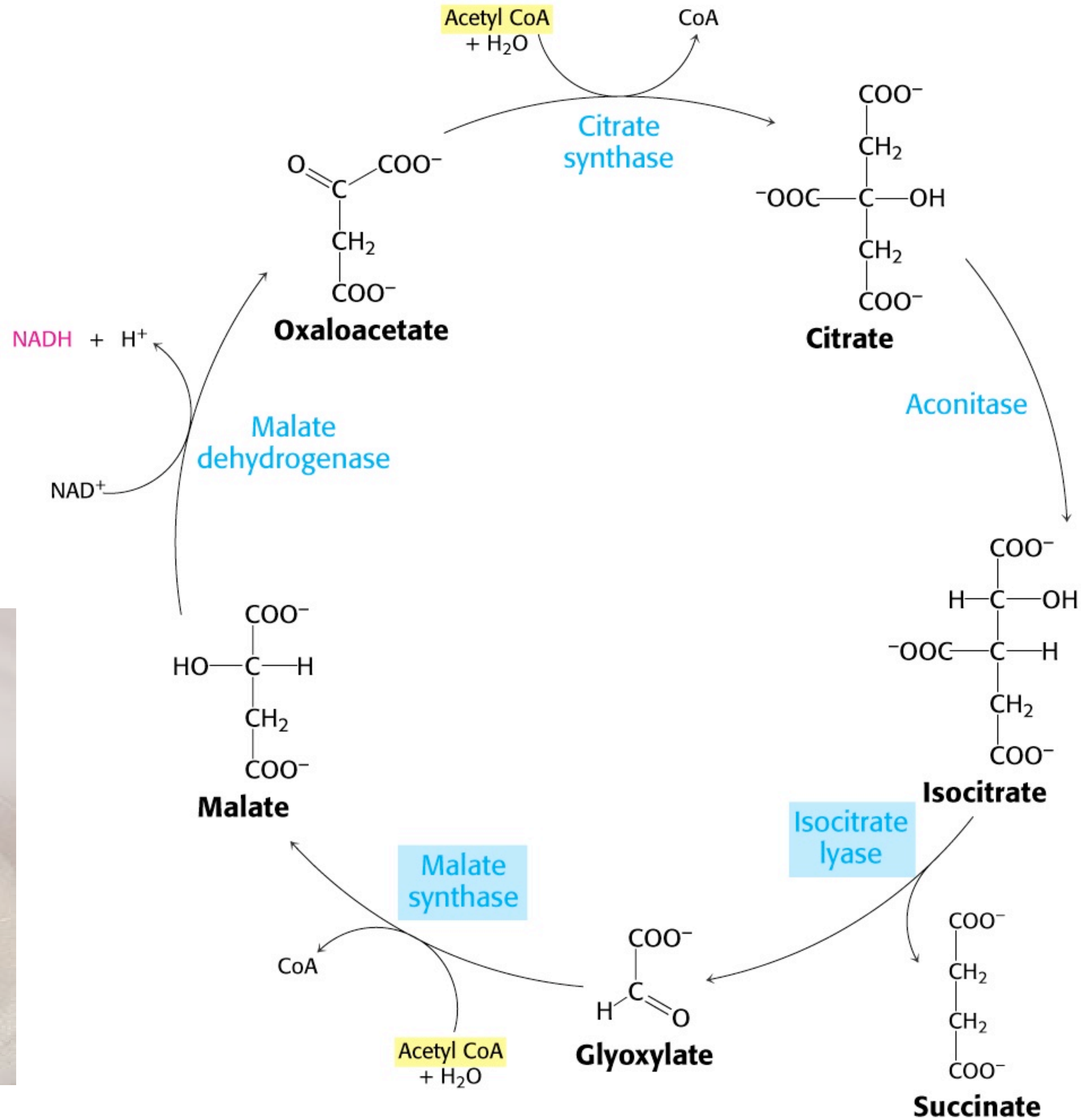

Pyruvate
Other amino acids, purines, pyrimidines
Acetyl CoA
Sugars
Oxaloacetate
Aspartate
Citrate
Fatty acids, sterols
Purines
Succinyl CoA
α-Ketoglutarate
Other amino acids
Porphyrins, heme, chlorphyll
Glutamate

The Glyoxalate Cycle:

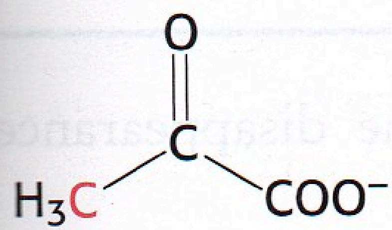
Making sugars from fats because we *know* you can make fat from sugar!



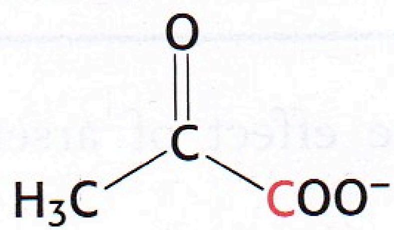
Thought Problem…..

1. *Flow of carbon atoms.* What is the fate of the radioactive label when each of the following compounds is added to a cell extract containing the enzymes and cofactors of the glycolytic pathway, the citric acid cycle, and the pyruvate dehydrogenase complex? (The ^{14}C label is printed in red.)

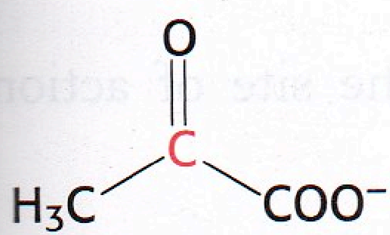
(a)



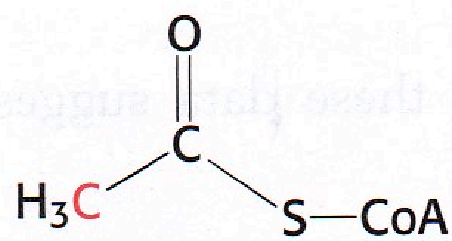
(b)



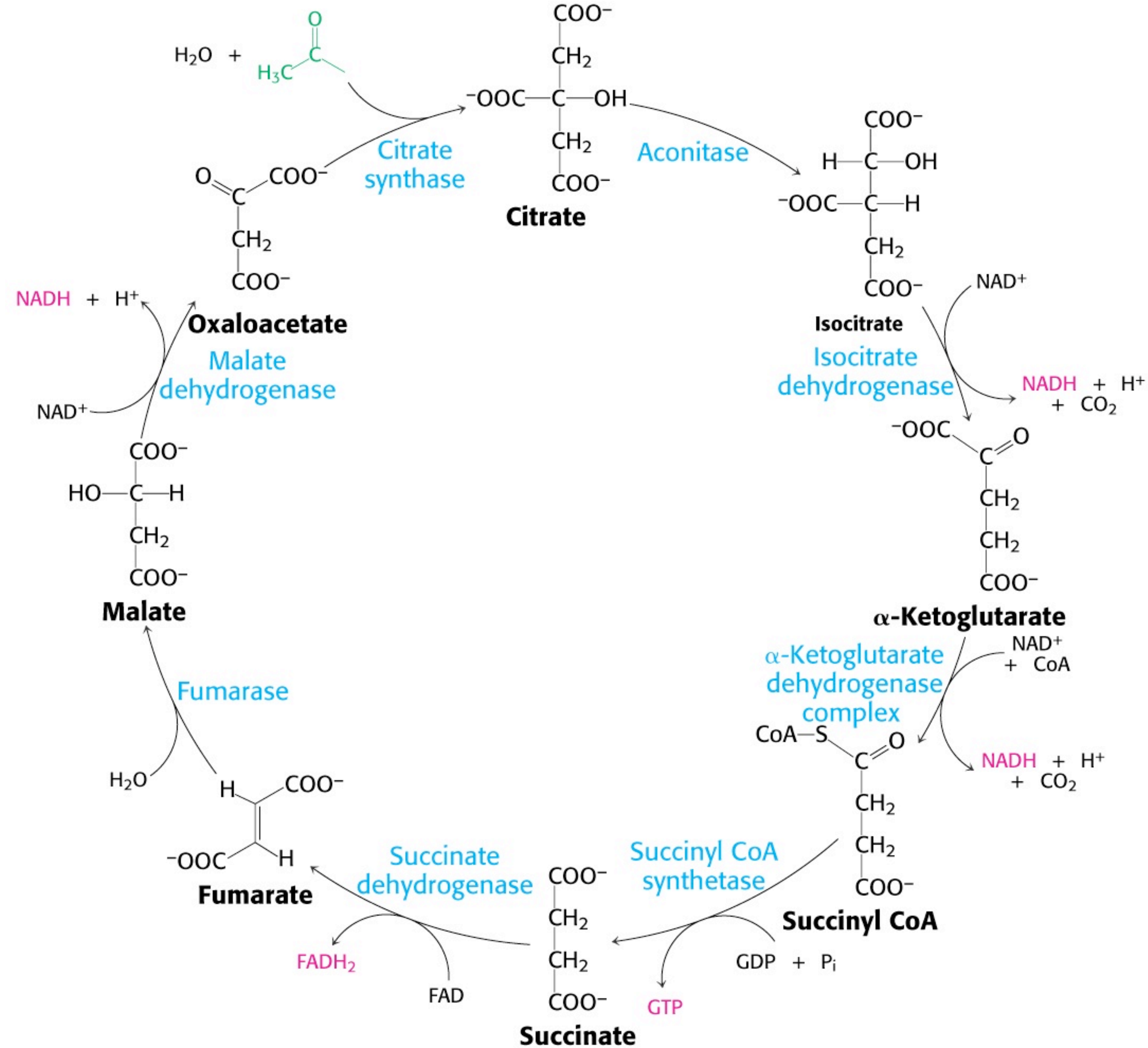
(c)



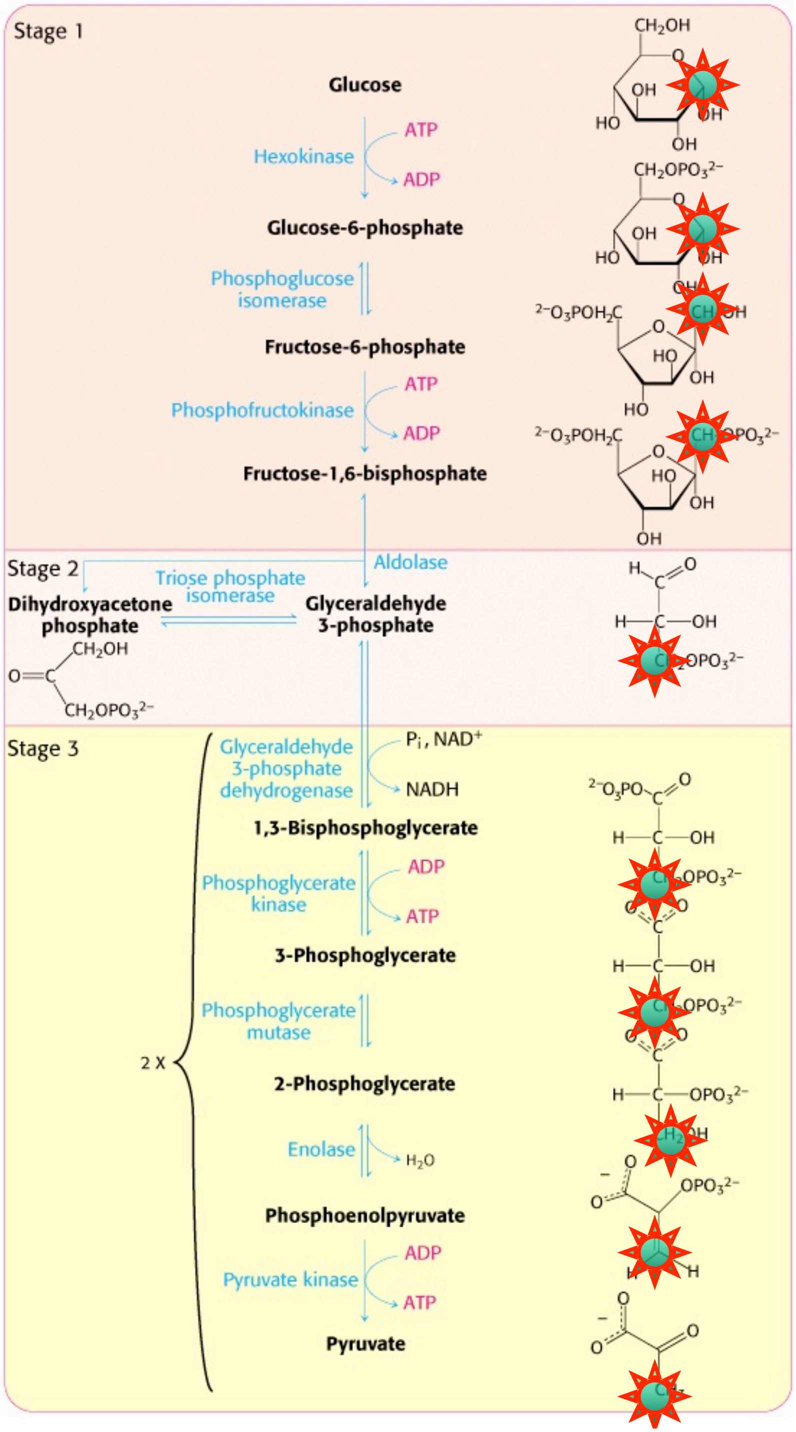
(d)



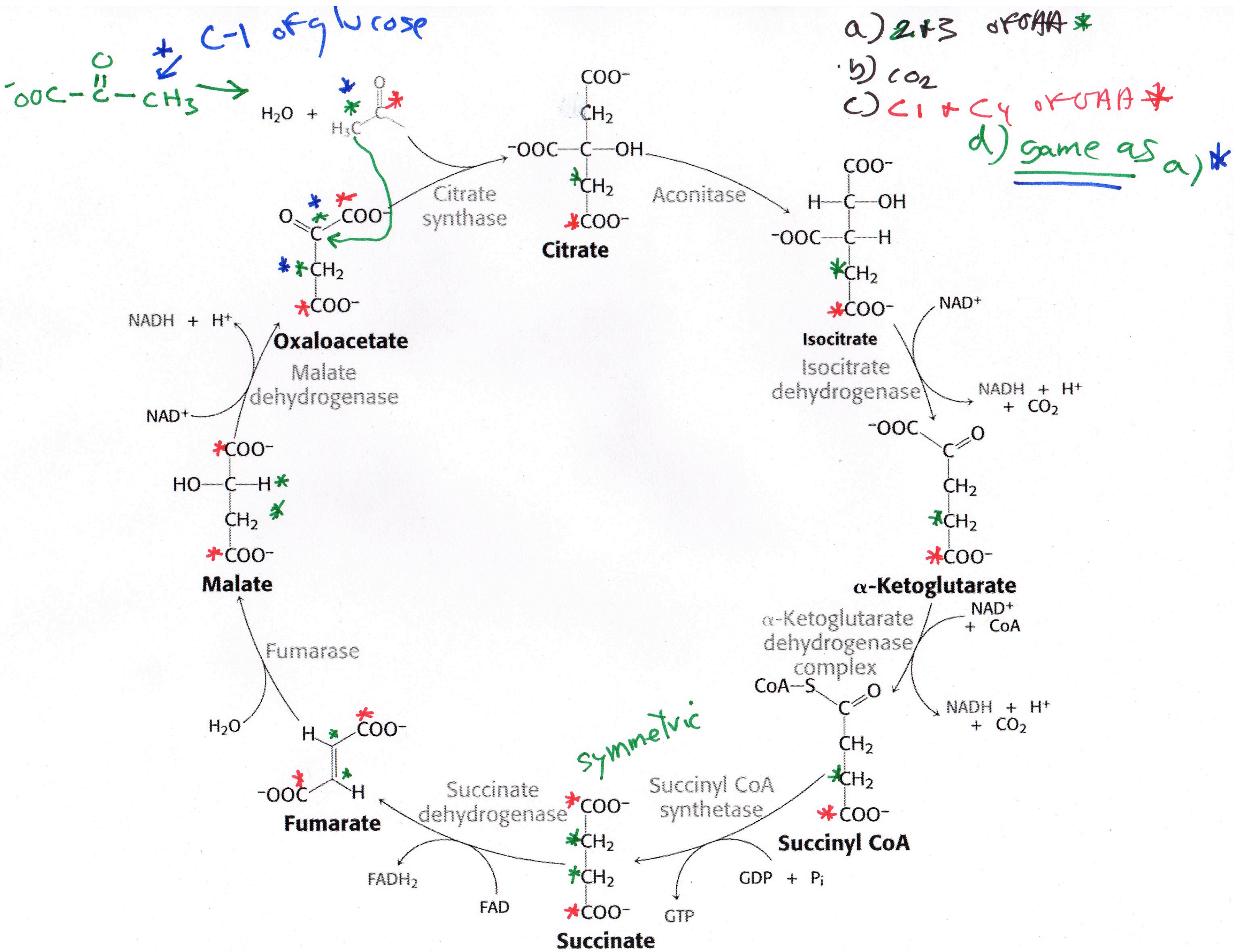
(e) Glucose 6-phosphate labeled at C-1.


Citrate
Aconitase
Isocitrate
Isocitrate dehydrogenase
α-Ketoglutarate
α-Ketoglutarate dehydrogenase complex
Succinyl CoA
Succinyl CoA synthetase
Succinate
Succinate dehydrogenase
Fumarate
Fumarase
Malate
Malate dehydrogenase
Oxaloacetate
Citrate synthase
NAD+
NADH + H+
CO2
CoA
GDP + Pi
GTP
FAD
FADH2
H2O

Thought F



Stage 1
Glucose
Hexokinase
ATP
ADP
Glucose-6-phosphate
Phosphoglucose isomerase
Fructose-6-phosphate
Phosphofructokinase
ATP
ADP
Fructose-1,6-bisphosphate
Stage 2
Aldolase
Triose phosphate isomerase
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
Stage 3
Glyceraldehyde 3-phosphate dehydrogenase
Pi, NAD+
NADH
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
ADP
ATP
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
H2O
Phosphoenolpyruvate
Pyruvate kinase
ADP
ATP
Pyruvate
2 X



C-1 of glucose
$^{-}OOC-C(=O)-CH_3$
H_2O +
Citrate synthase
Citrate
Aconitase
Isocitrate
Isocitrate dehydrogenase
NAD^+
$NADH + H^+ + CO_2$
α-Ketoglutarate
α-Ketoglutarate dehydrogenase complex
$NAD^+ + CoA$
$NADH + H^+ + CO_2$
Succinyl CoA
Succinyl CoA synthetase
GDP + P_i
GTP
Succinate
symmetric
Succinate dehydrogenase
FAD
$FADH_2$
Fumarate
Fumarase
H_2O
Malate
Malate dehydrogenase
NAD^+
$NADH + H^+$
Oxaloacetate
a) 2+3 of OAA *
b) CO_2
c) C1 + C4 of OAA *
d) same as a) *