‘Metabolic flux’ describes the rate of flow of intermediates through a metabolic pathway

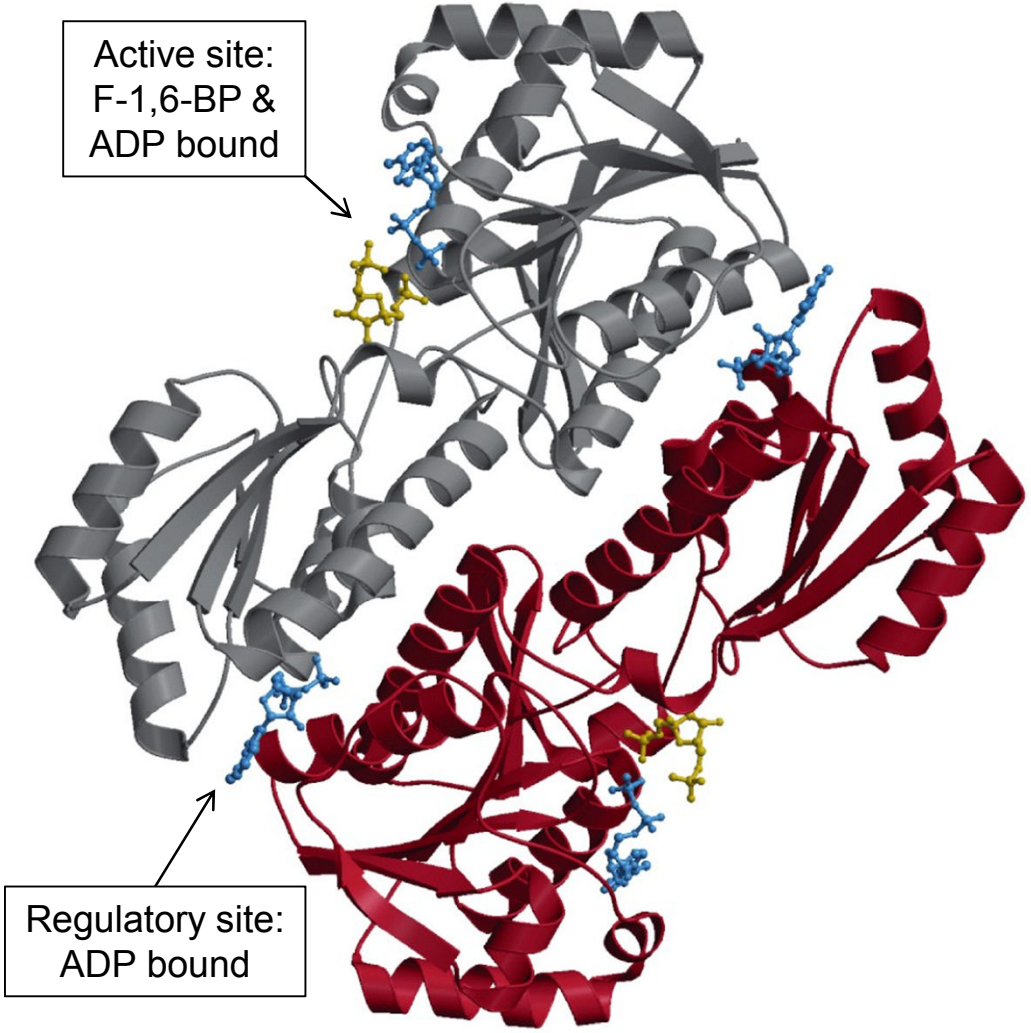
ΔG, determined by measuring [metabolites], reveals the rate-limiting steps of a pathway

Table 15-1 $\Delta G^{\circ\prime}$ and ΔG for the Reactions of Glycolysis in Heart Muscle[a]

Reaction	Enzyme	$\Delta G^{\circ\prime}$ ($kJ \cdot mol^{-1}$)	ΔG ($kJ \cdot mol^{-1}$)
1	Hexokinase	−20.9	−27.2
2	PGI	+2.2	−1.4
3	PFK	−17.2	−25.9
4	Aldolase	+22.8	−5.9
5	TIM	+7.9	~0
6 + 7	GAPDH + PGK	−16.7	−1.1
8	PGM	+4.7	−0.6
9	Enolase	−3.2	−2.4
10	PK	−23.0	−13.9

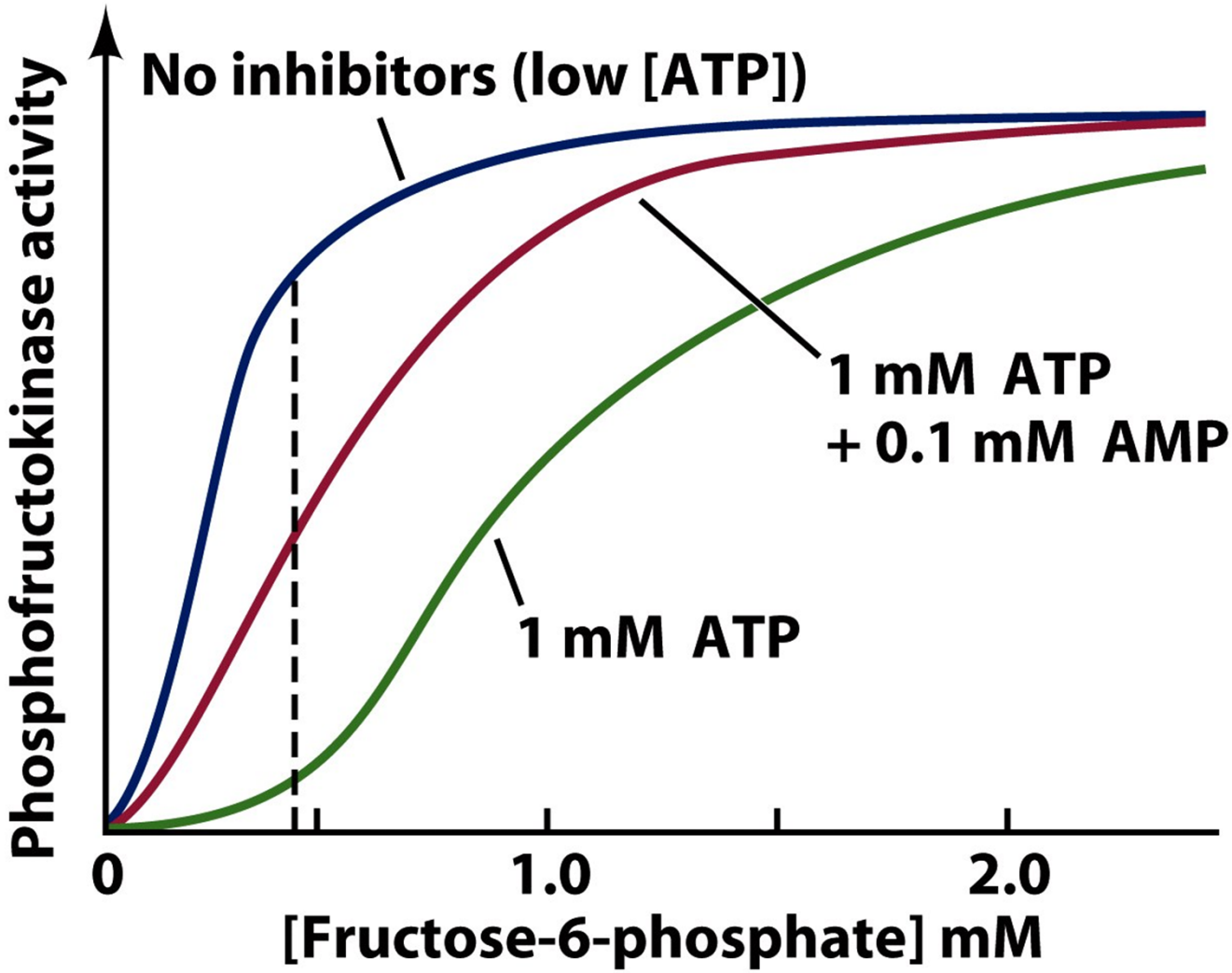
[a]Calculated from data in Newsholme, E.A. and Start, C., *Regulation in Metabolism*, p. 97, Wiley (1973).

PFK is the major regulatory enzyme of glycolysis in muscle (F6P + ATP $\rightarrow$ F-1,6-BP + ADP)

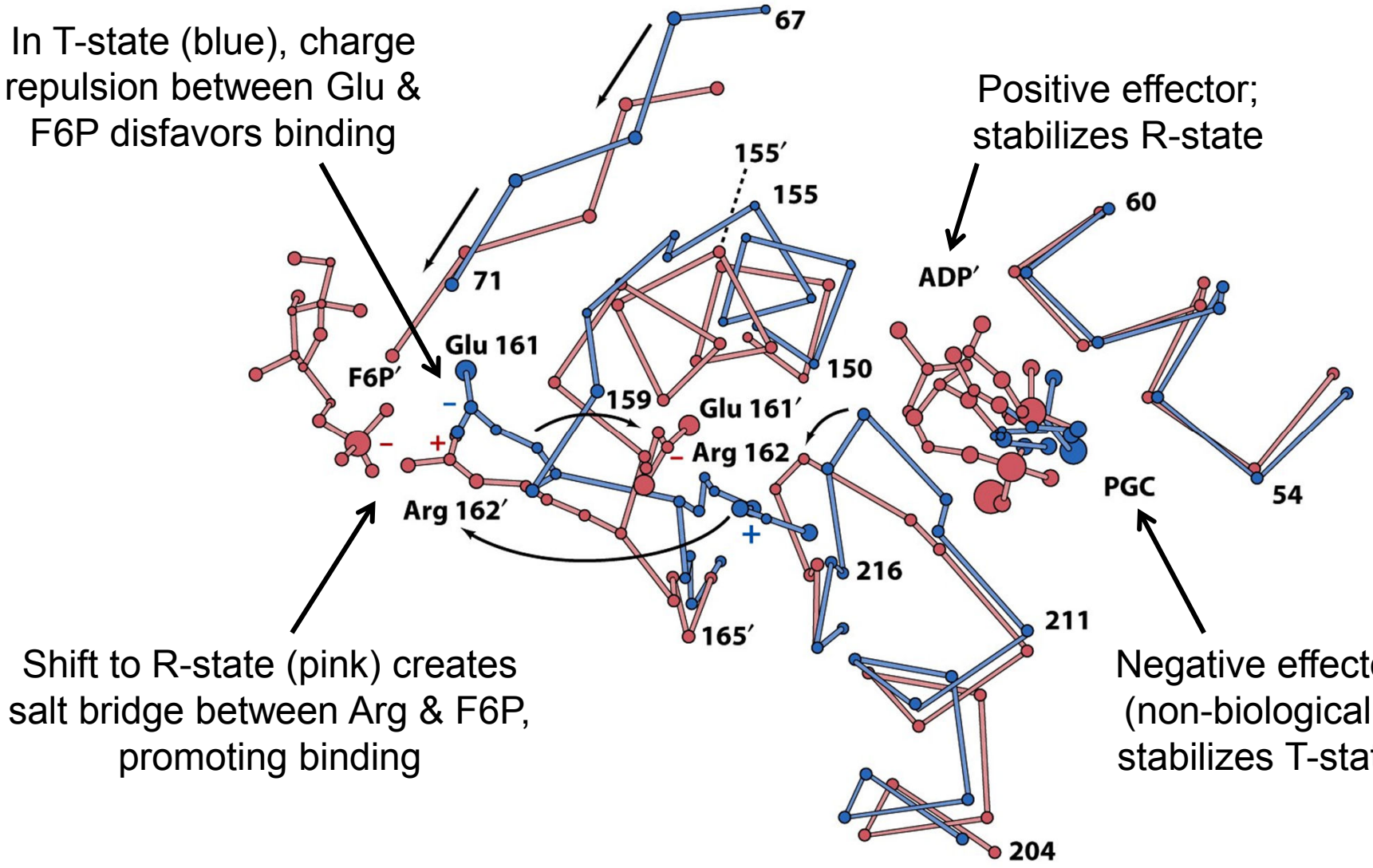


- Homotetramer (here, 2 subunits are shown)
- Each subunit has catalytic and regulatory sites
- Positive effectors:
  - F6P (substrate)
  - ADP, AMP
  - F-2,6-BP
- Negative effectors:
  - ATP
  - citrate

ATP, ADP, or AMP can bind at the same regulatory site and influence PFK activity

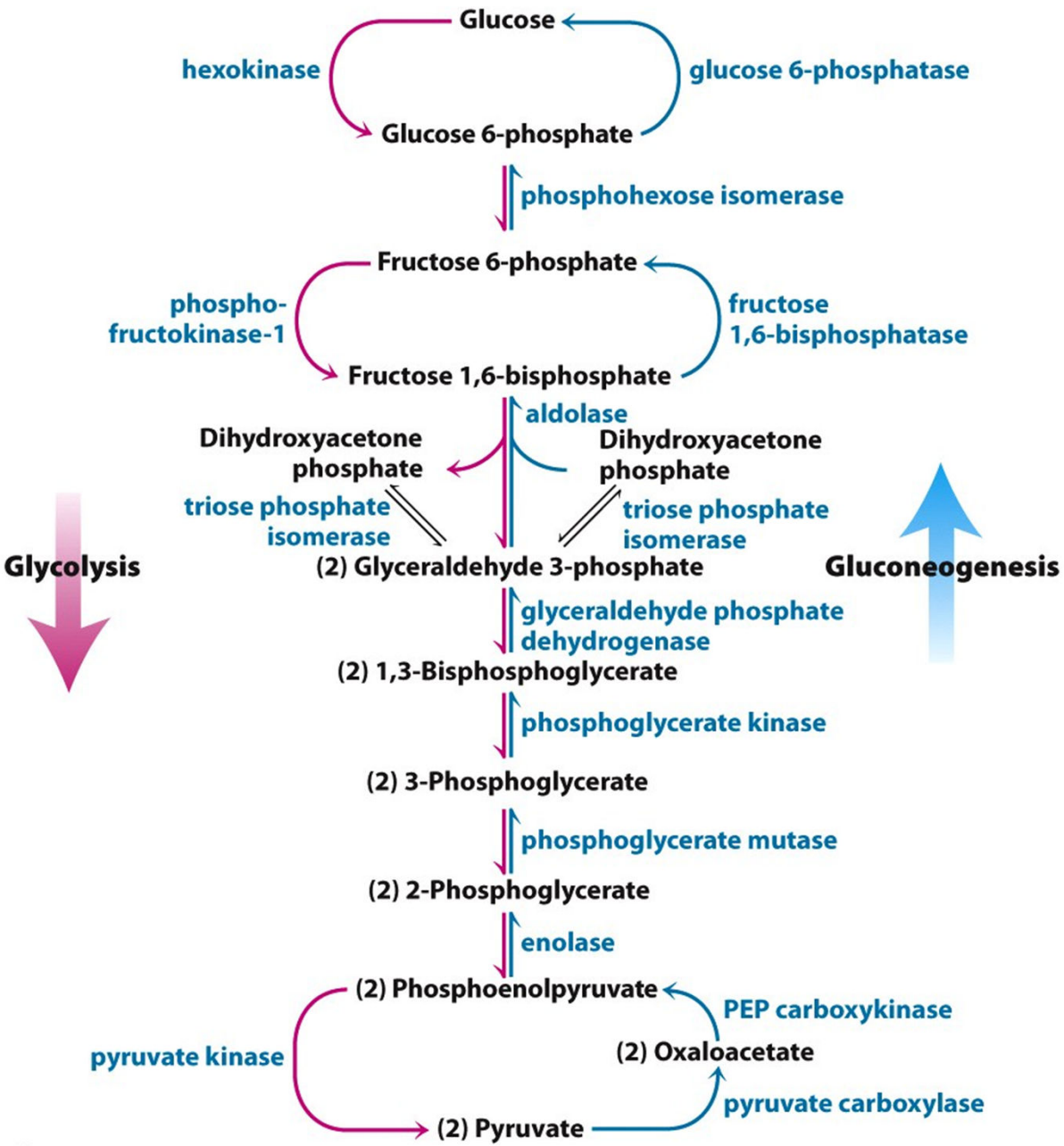


The R-state of PFK promotes binding of F6P; the T-state has low affinity for F6P

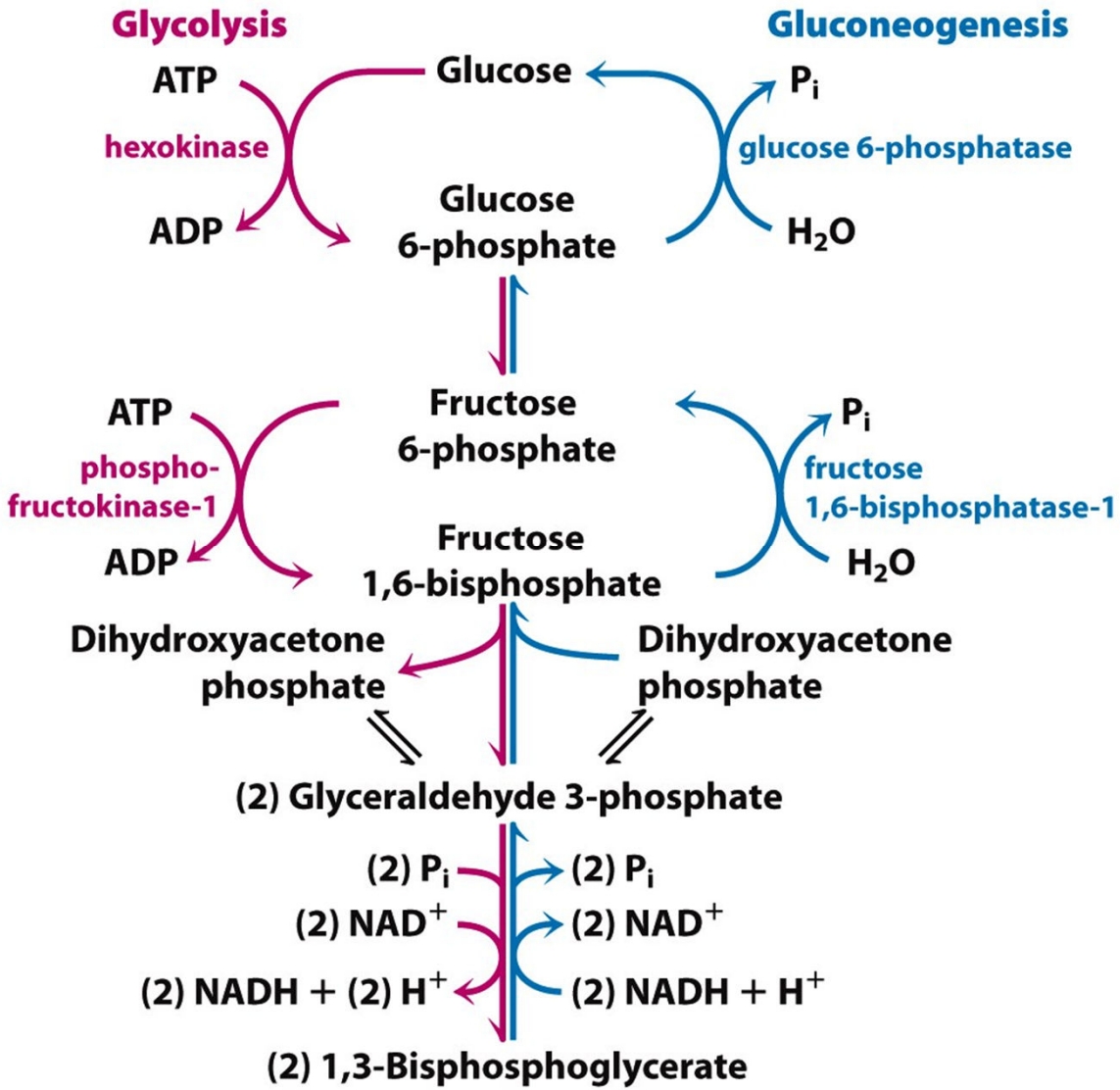


Gluconeogenesis is a pathway in which glucose is synthesized from 2-4C precursors

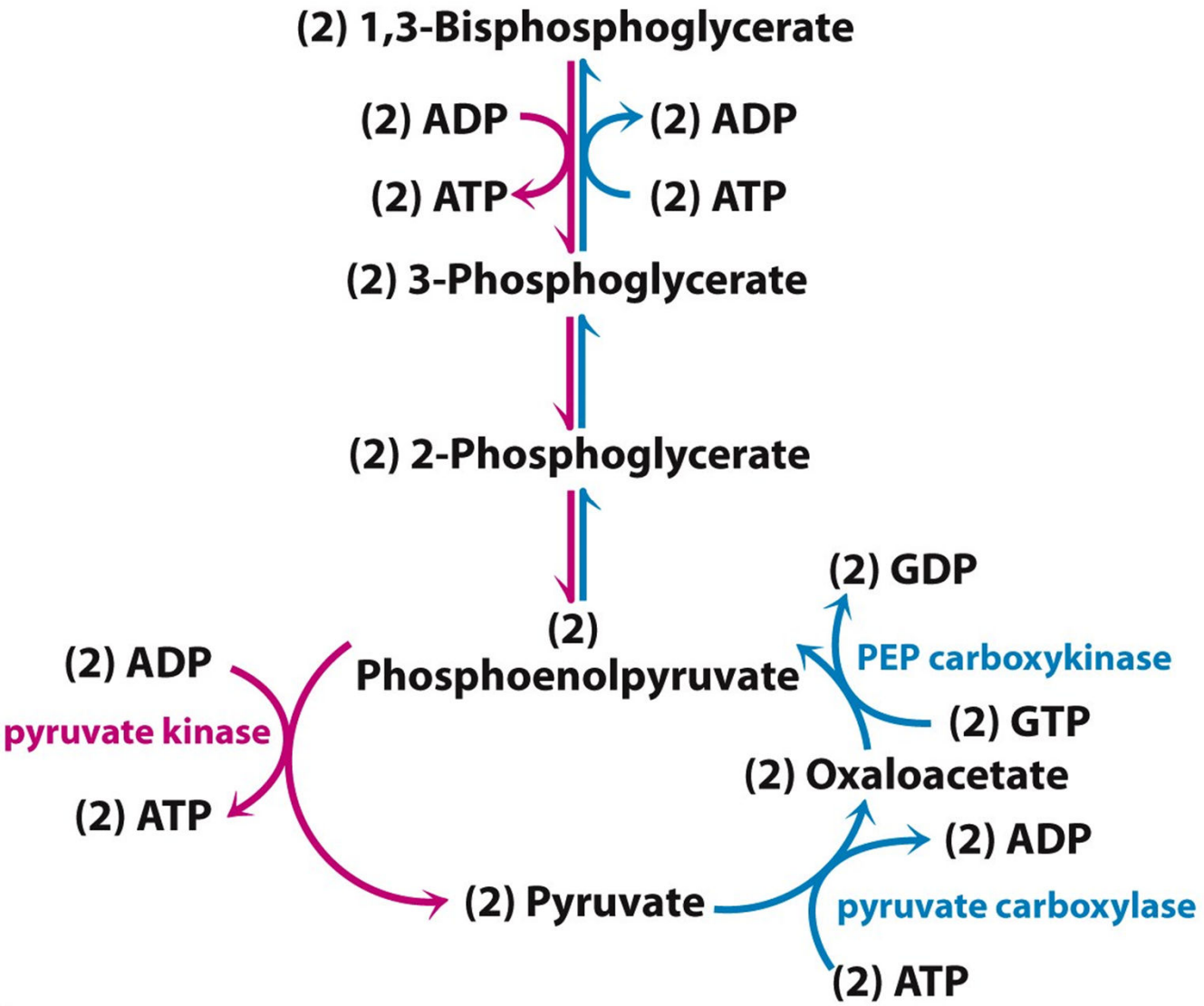
- Many organisms and many cell types require a constant supply of glucose (ex: neurons, red blood cells)
- In humans, glucose can be synthesized from pyruvate (or lactate, or oxaloacetate, or certain amino acids) through this pathway (mainly occurring in the liver)
- Uses many of the same enzymes as glycolysis – those that catalyze reversible reactions
- For irreversible steps of glycolysis, uses other reactions (and other enzymes)
- Opposite regulation vs. glycolysis


Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
Fructose 6-phosphate
phospho-
fructokinase-1
fructose
1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
Dihydroxyacetone
phosphate
Dihydroxyacetone
phosphate
triose phosphate
isomerase
triose phosphate
isomerase
Glycolysis
(2) Glyceraldehyde 3-phosphate
Gluconeogenesis
glyceraldehyde phosphate
dehydrogenase
(2) 1,3-Bisphosphoglycerate
phosphoglycerate kinase
(2) 3-Phosphoglycerate
phosphoglycerate mutase
(2) 2-Phosphoglycerate
enolase
(2) Phosphoenolpyruvate
PEP carboxykinase
(2) Oxaloacetate
pyruvate kinase
pyruvate carboxylase
(2) Pyruvate

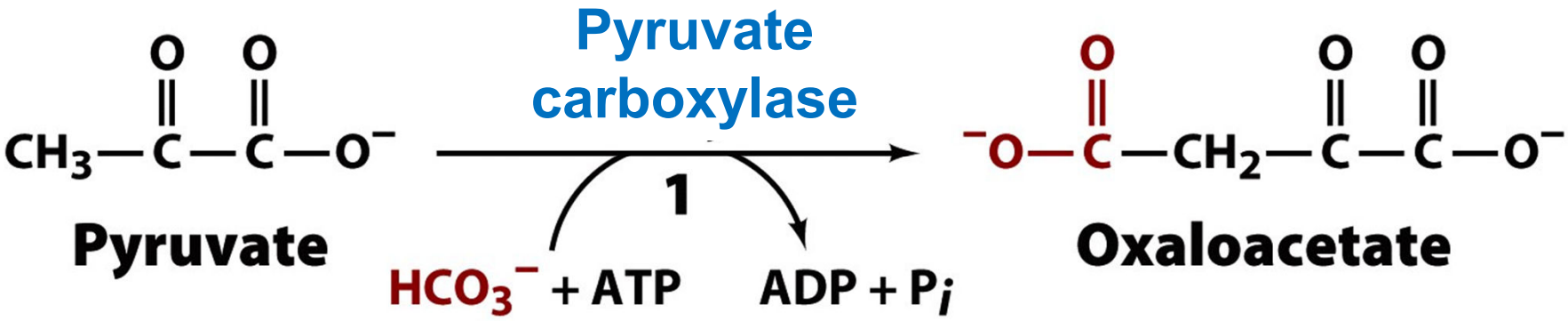
Phosphatases remove the phophoryl groups added by hexokinase and PFK



Two energy-requiring steps reverse the action of pyruvate kinase



Pyruvate carboxylase uses the energy of ATP hydrolysis to drive a carboxylation



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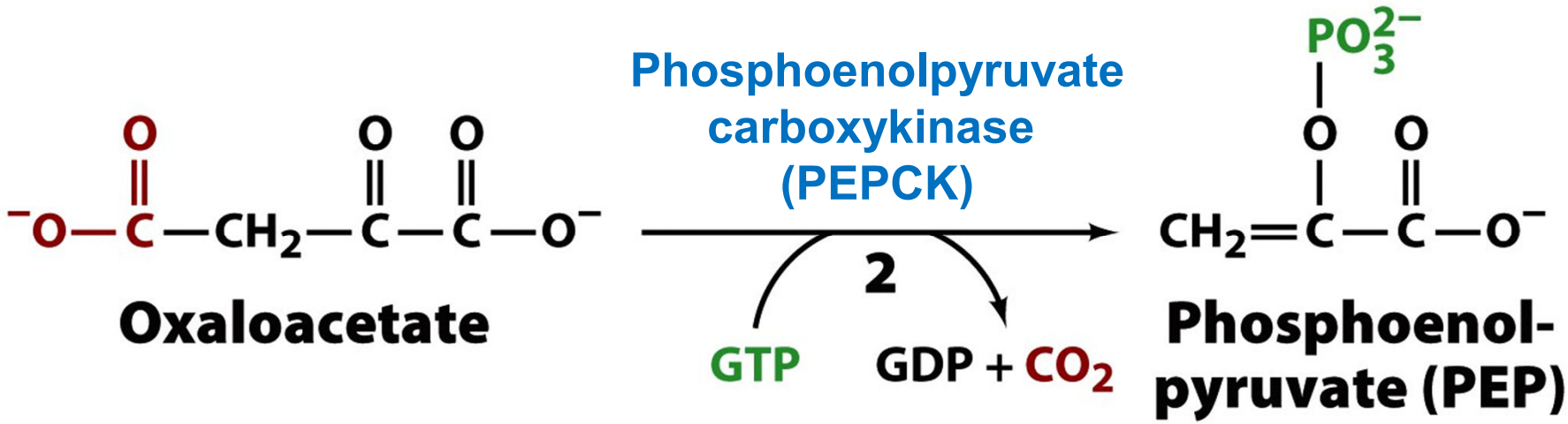
PEPCK couples decarboxylation and NTP hydrolysis to PEP formation



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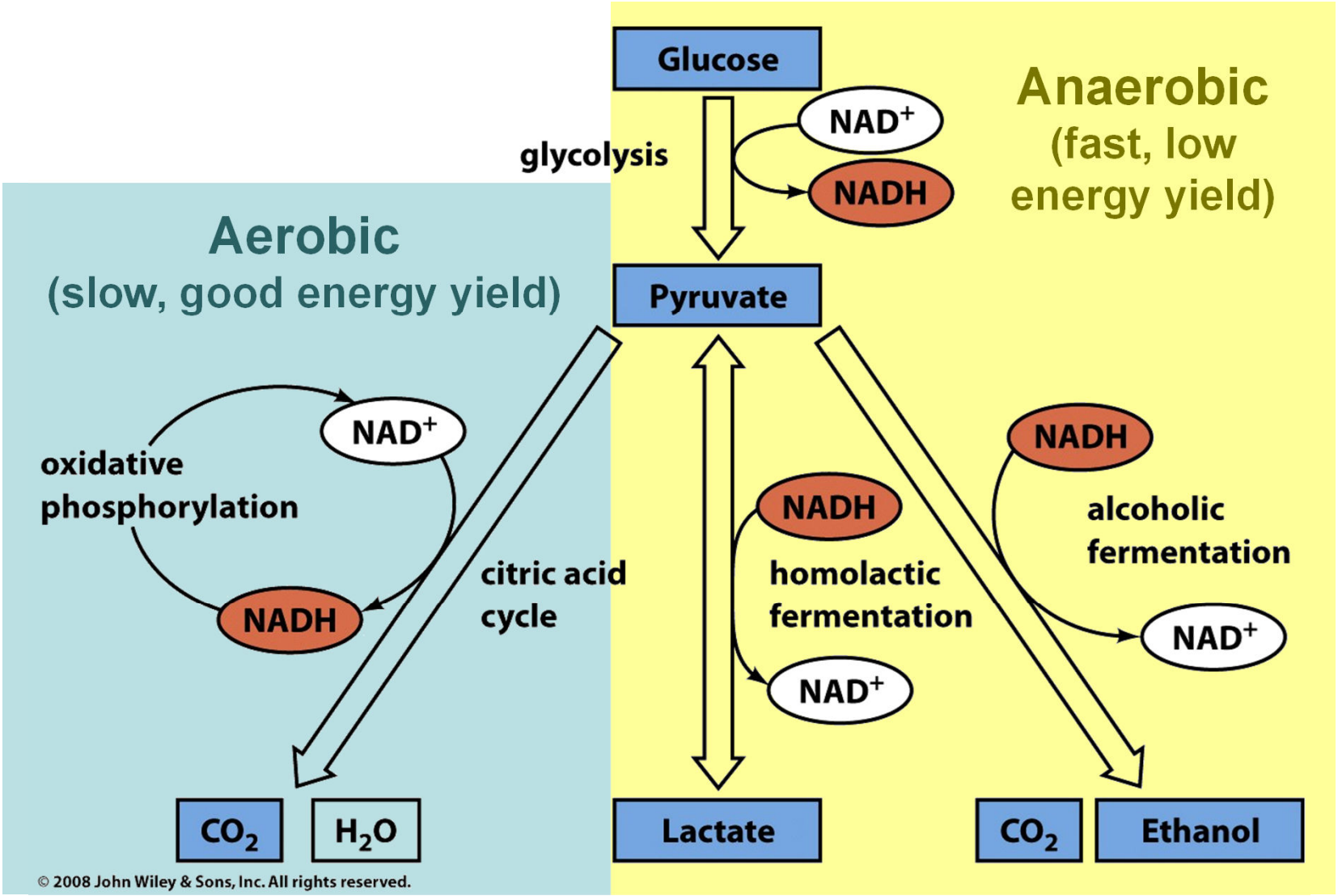
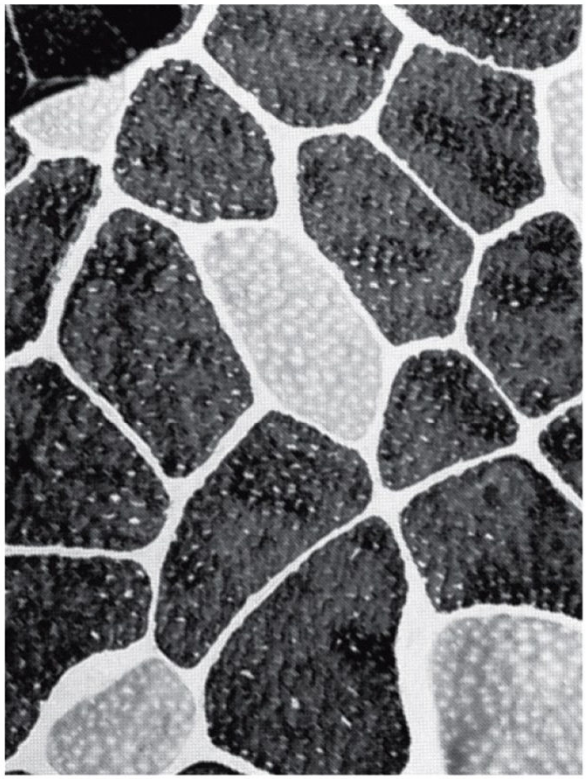
From glycolysis, pyruvate has multiple options for further metabolism

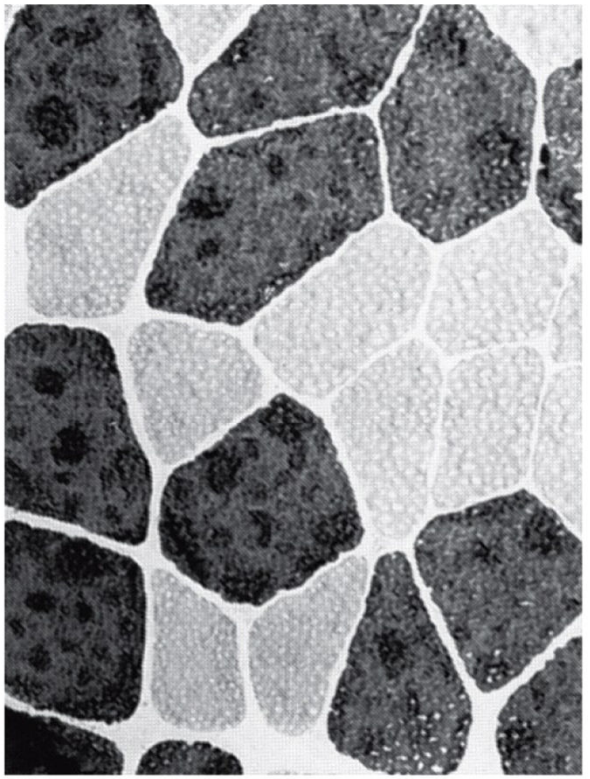


Different color in muscle can reflect different levels of aerobic vs. anaerobic metabolism



slow-twitch muscle fiber

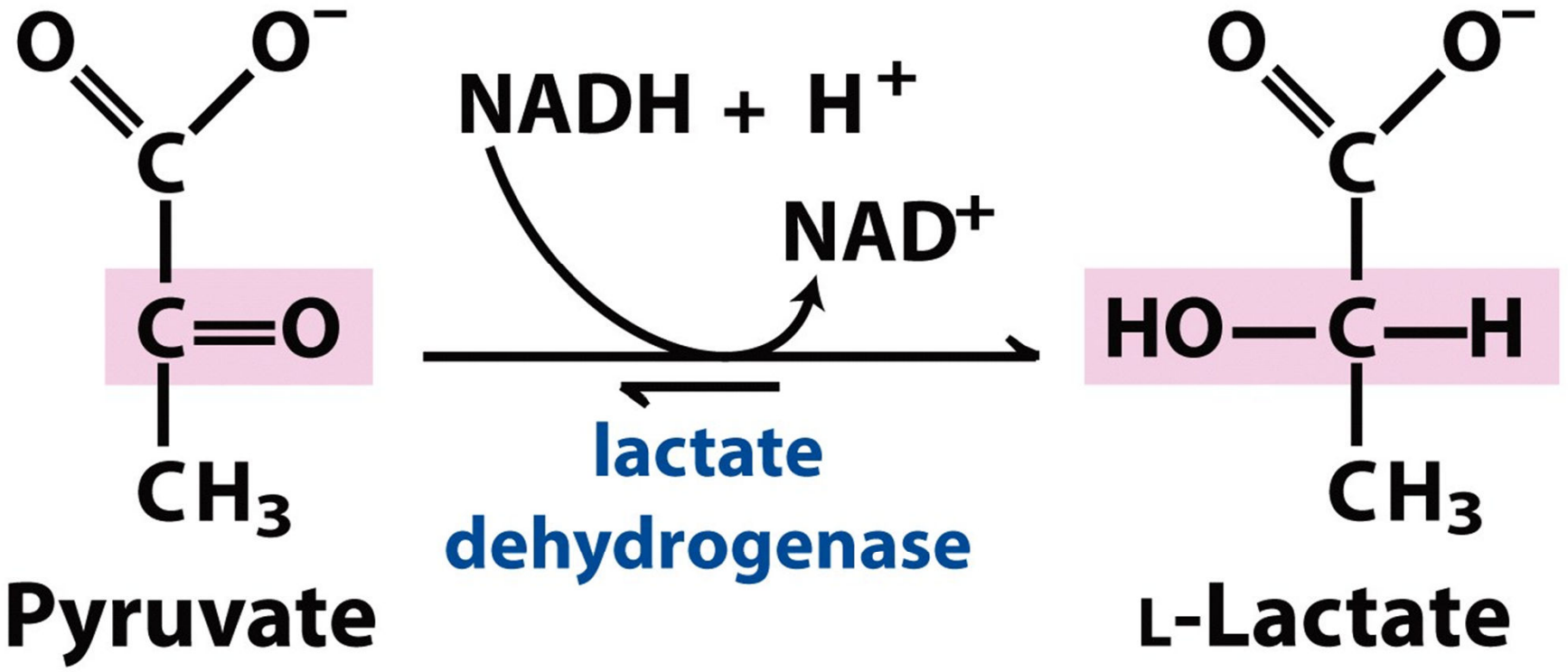
Lots of heme-containing mitochondria, used in aerobic metabolism



fast-twitch muscle fiber

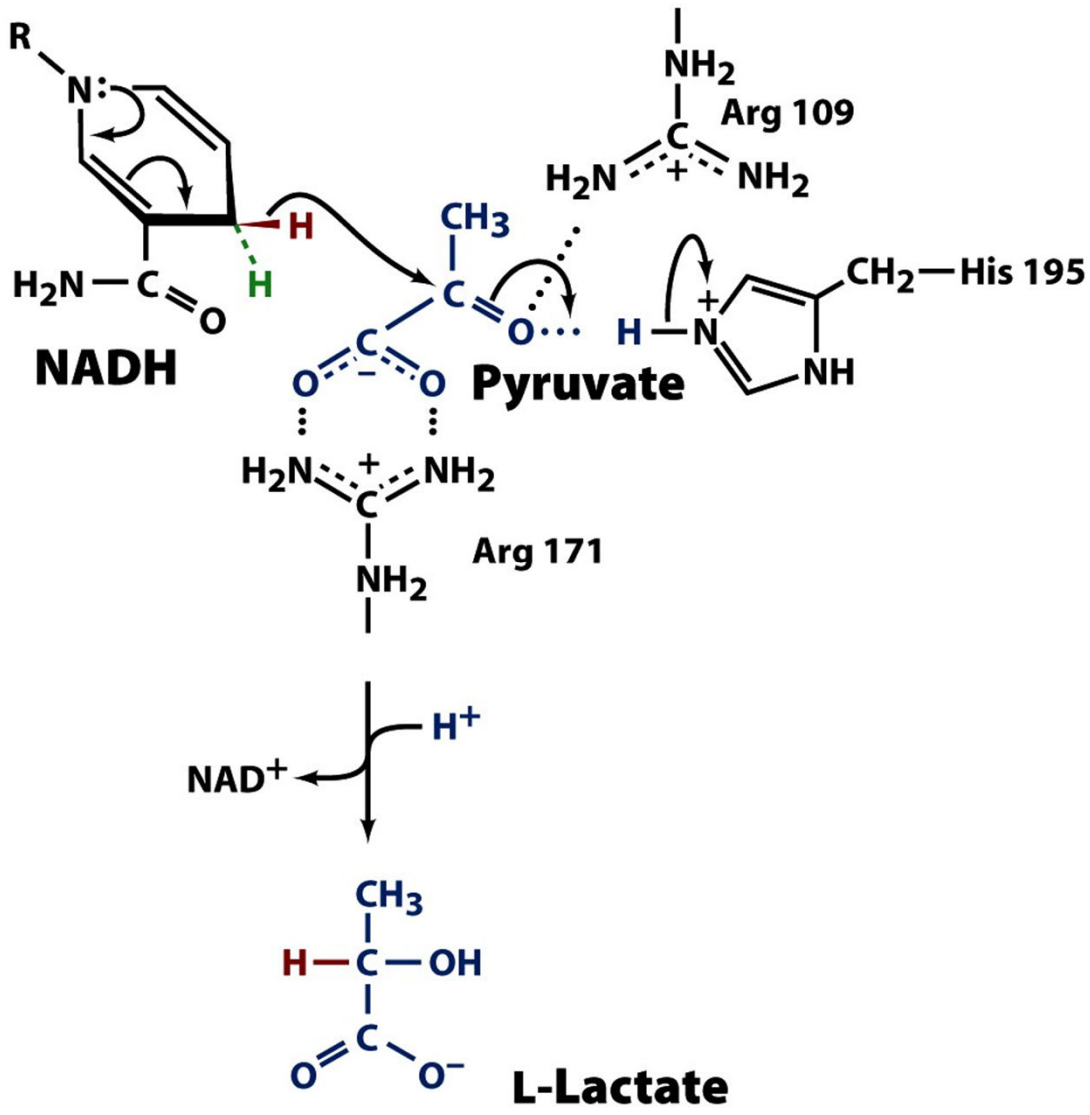
Fewer mitochondria; heavy reliance on anaerobic metabolism

In homolactic fermentation, lactate DH reduces pyruvate to regenerate NAD^+

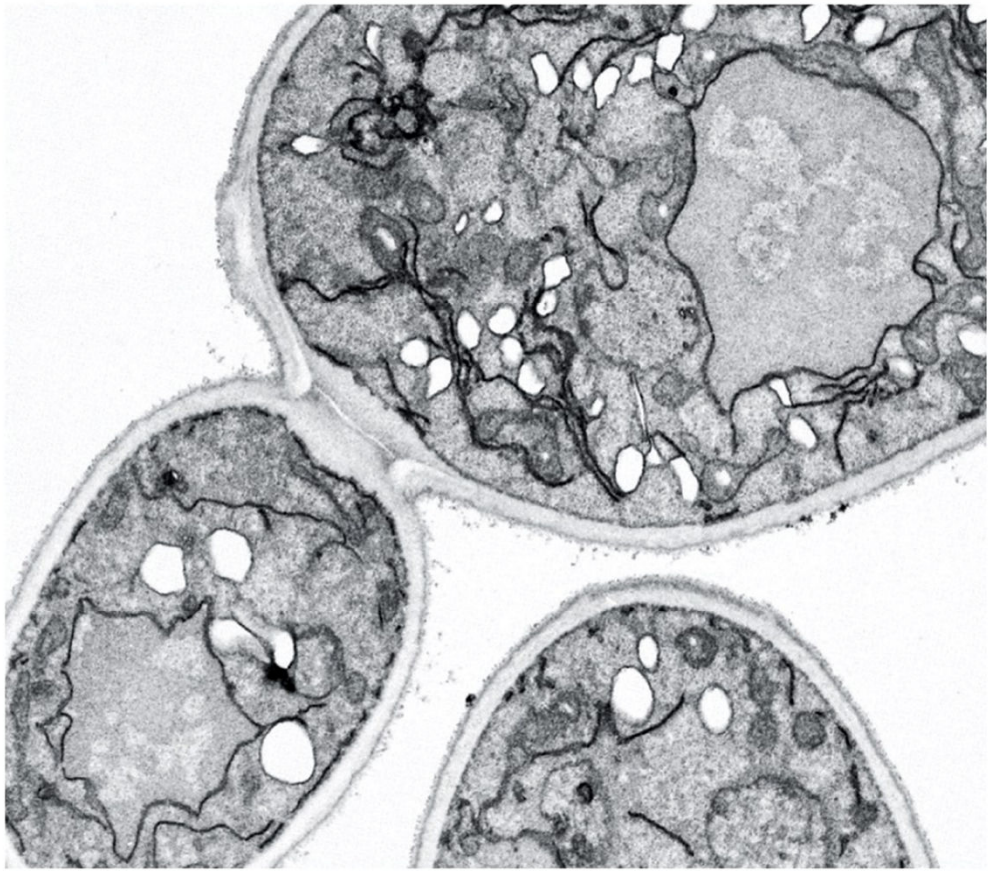


$\Delta G'° = -25.1$ kJ/mol

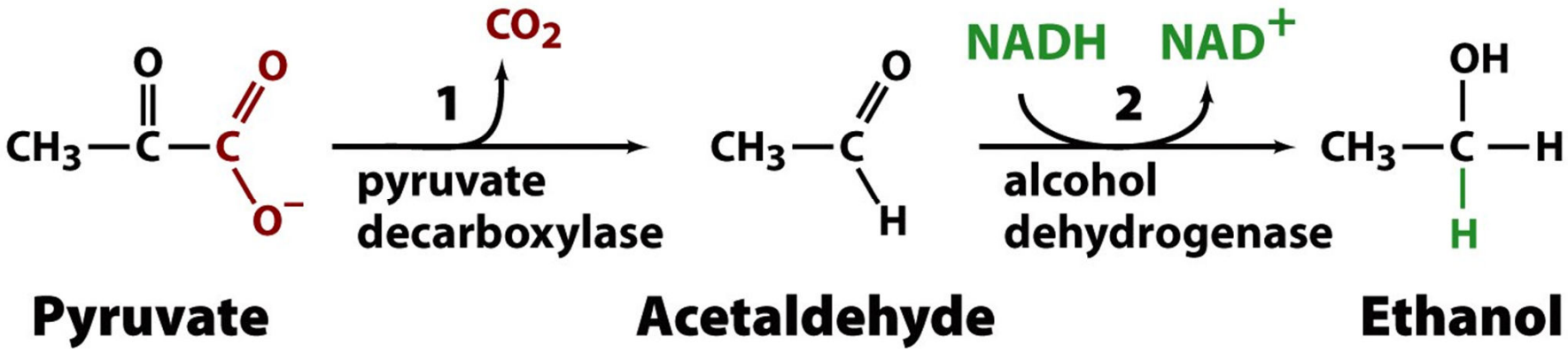
A hydride from NADH is transferred directly to pyruvate's carbonyl carbon



Yeast carry out alcoholic (ethanolic) fermentation, producing CO_2 and ethanol



Ethanolic fermentation converts pyruvate to ethanol in two steps



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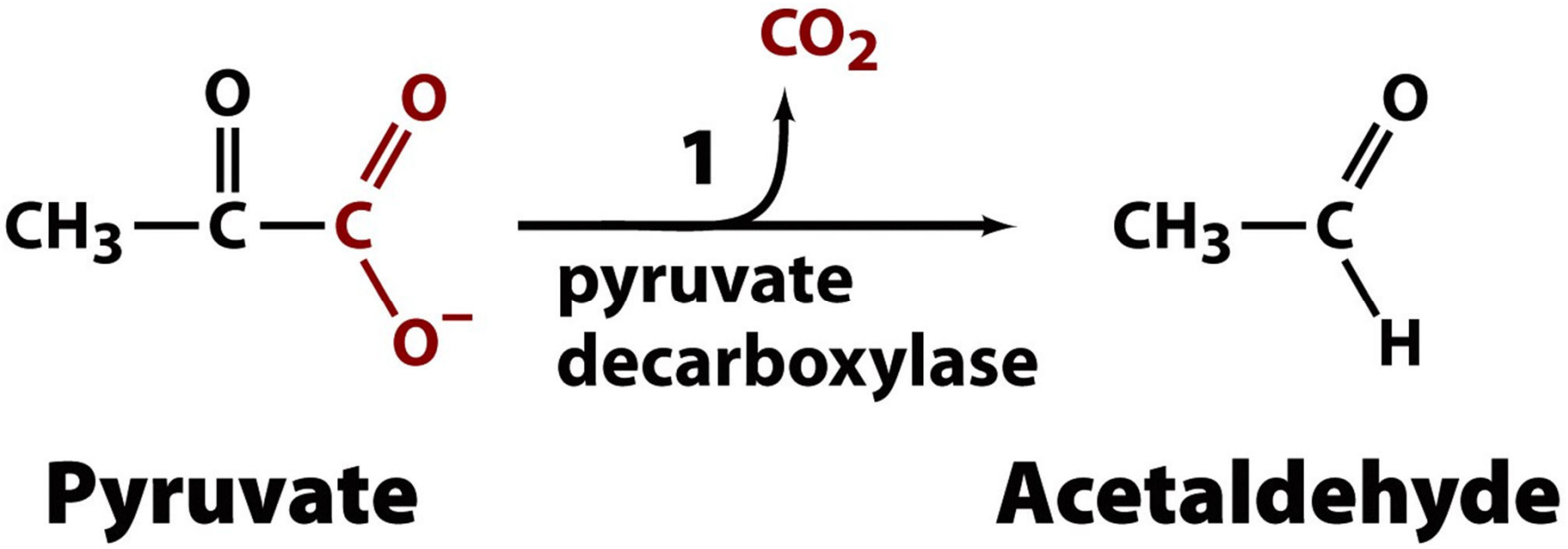
Pyruvate decarboxylase catalyzes the decarboxylation of pyruvate to acetaldehyde



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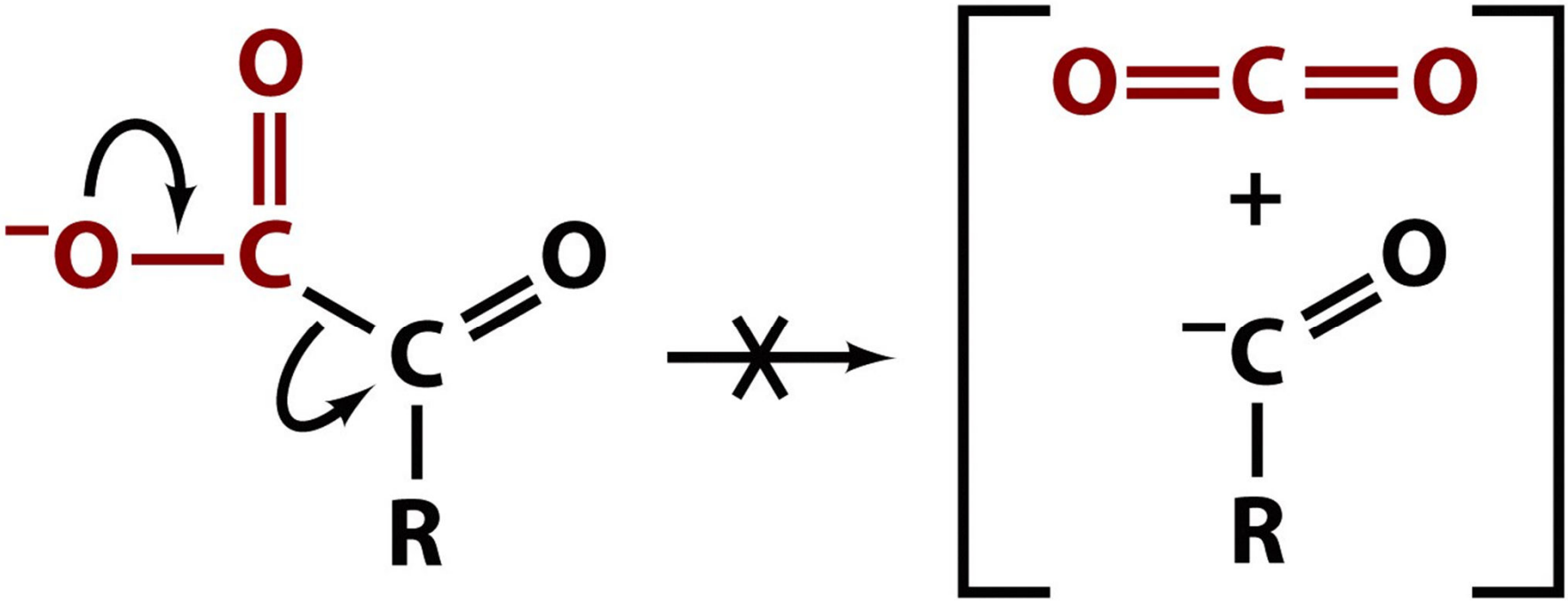
Decarboxylation does not happen without catalysis



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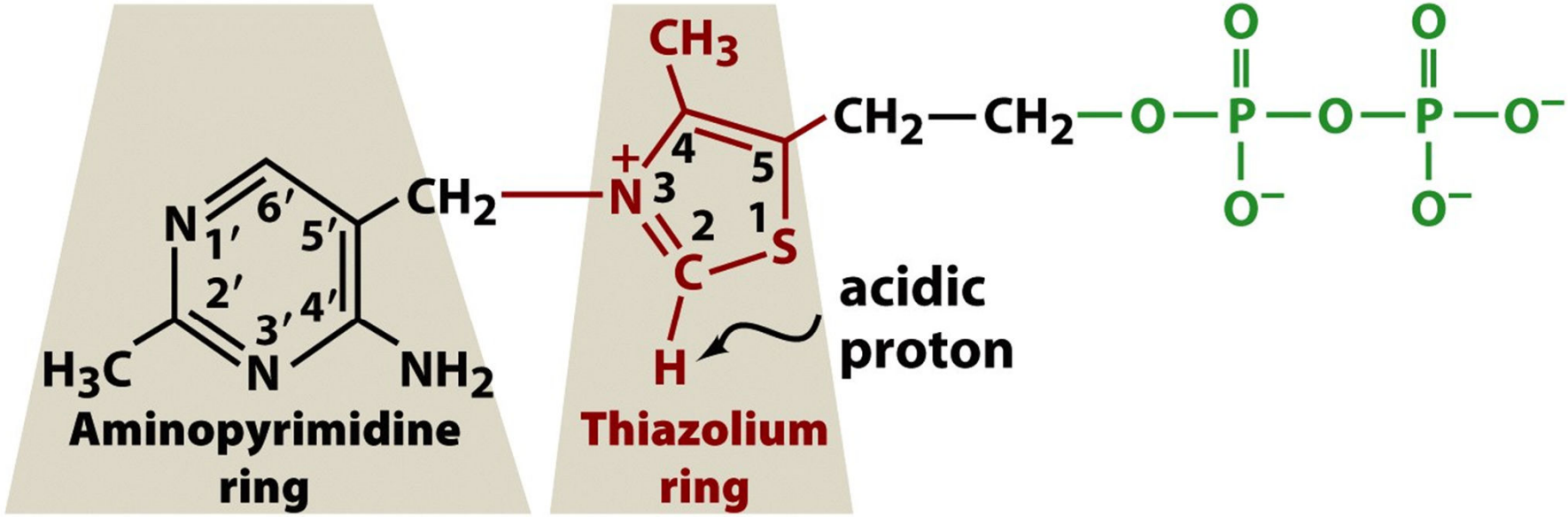
unstable
carbanion intermediate

The cofactor TPP functions as an electron sink to stabilize carbanion intermediates



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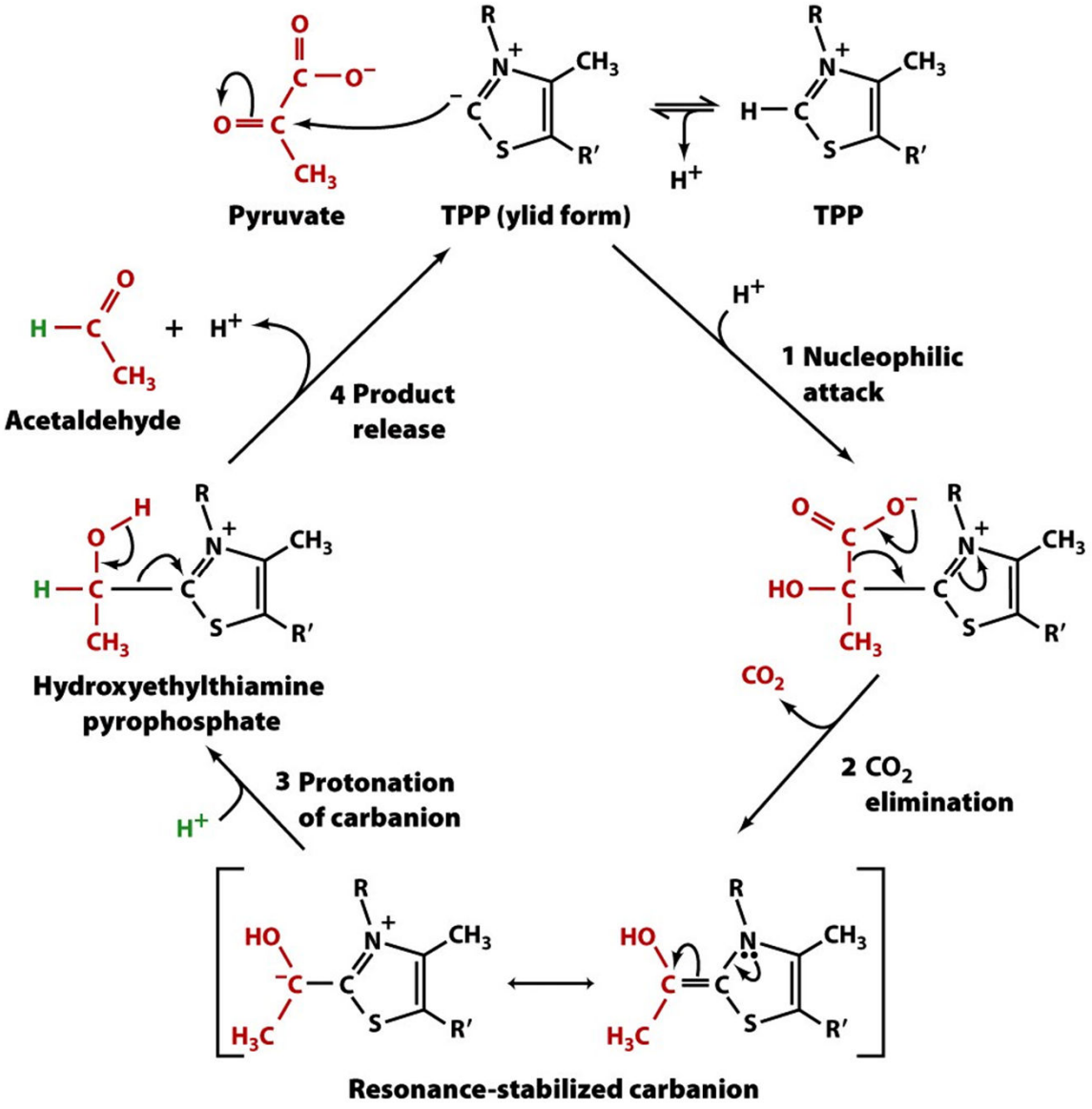
TPP catalyzes the decarboxylation of α-keto acids



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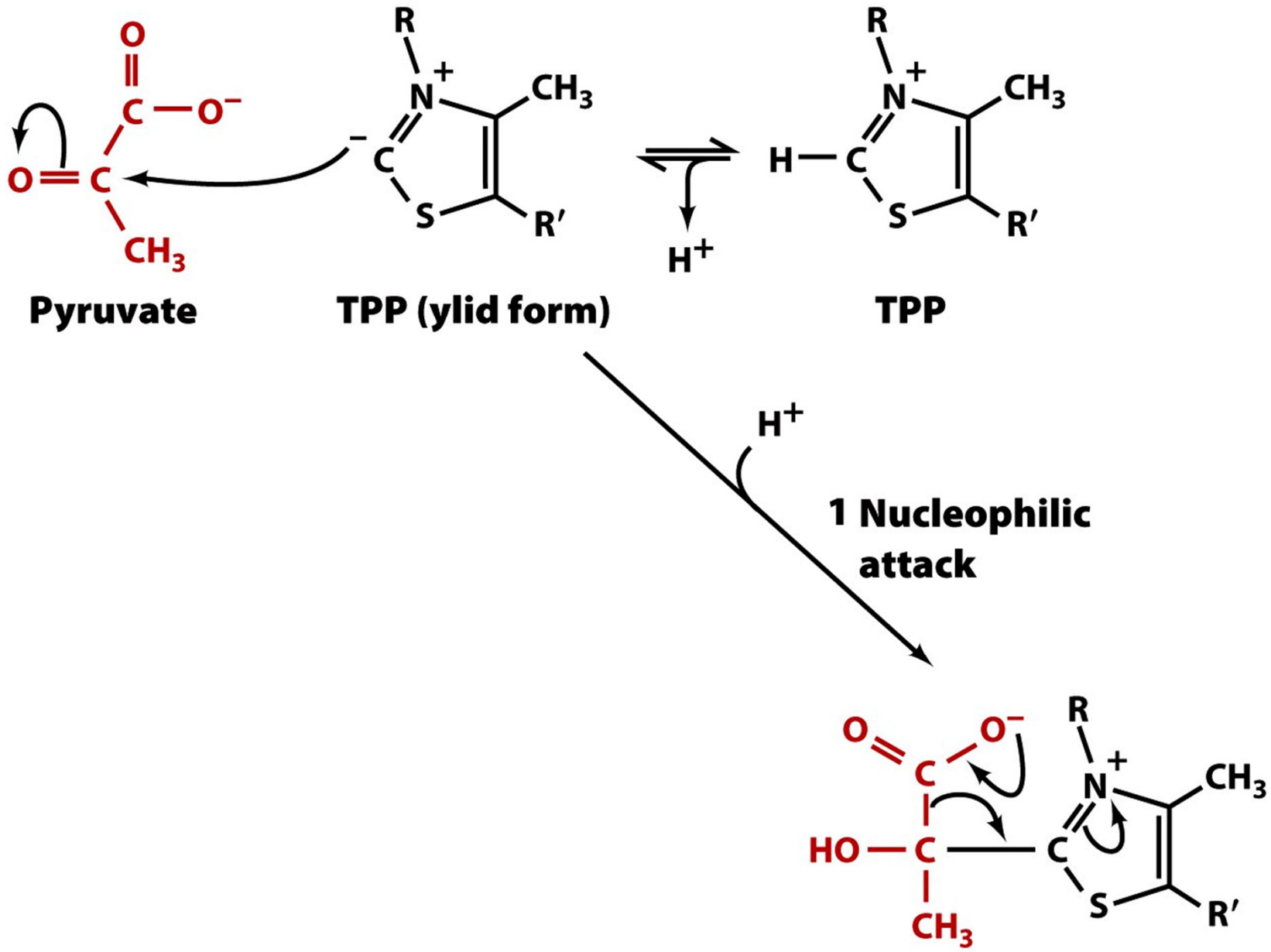

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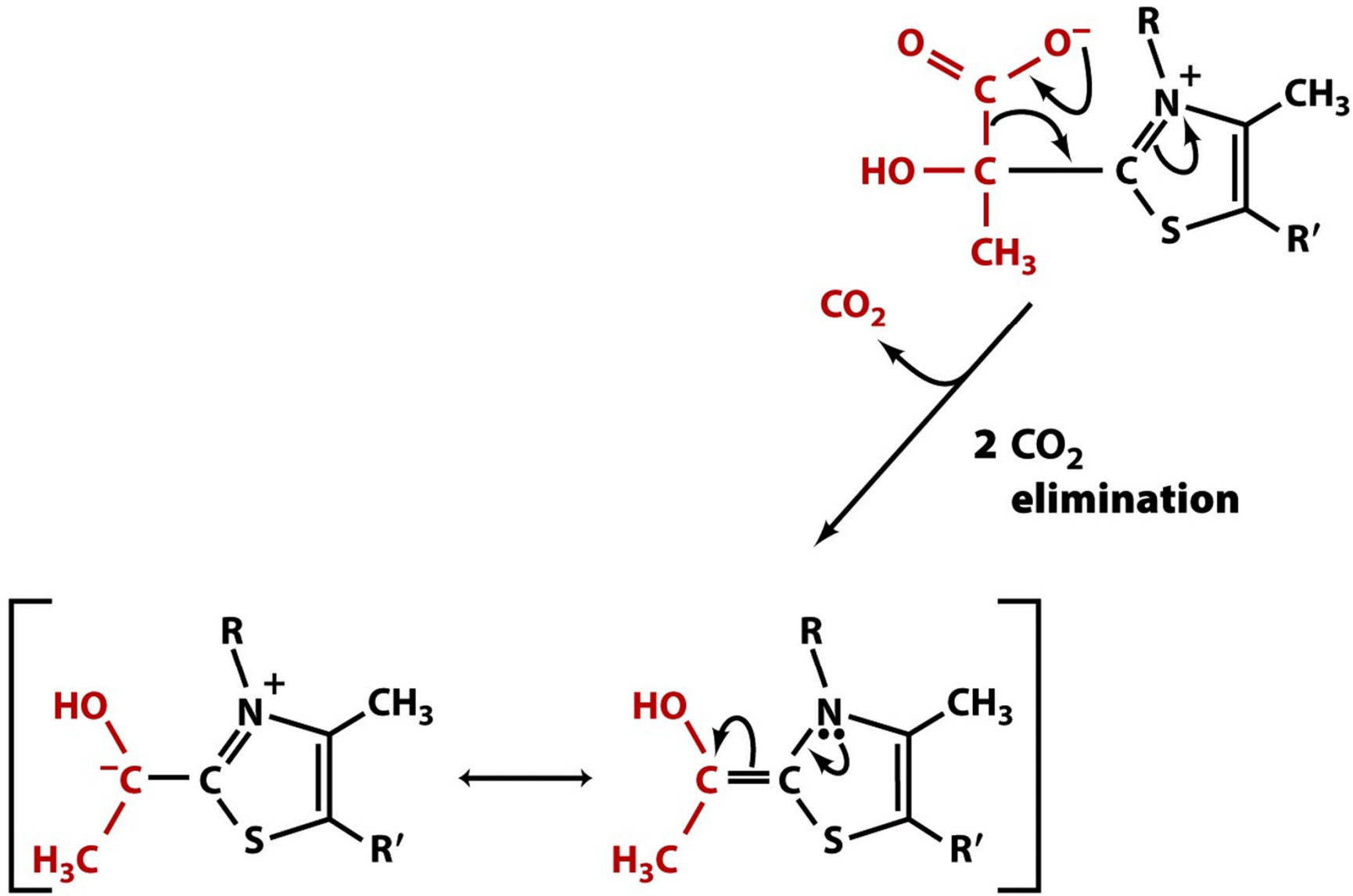

Resonance-stabilized carbanion

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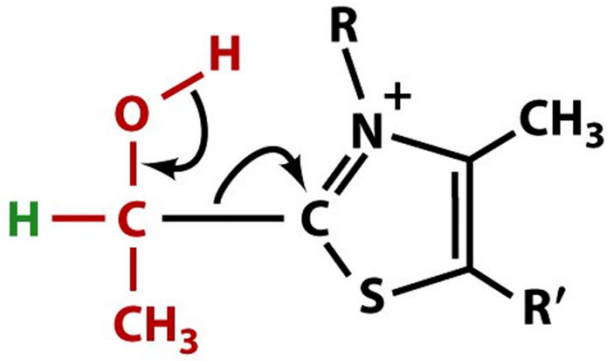
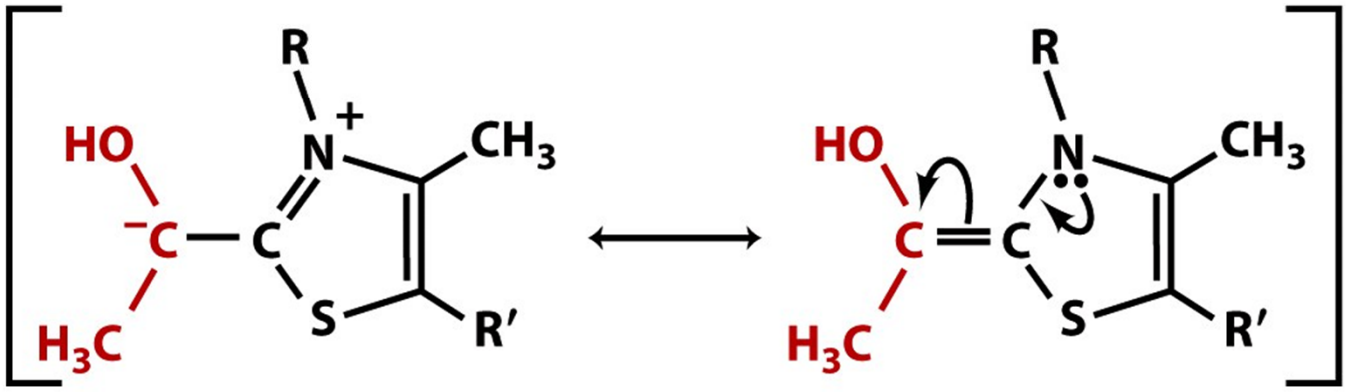


Hydroxyethylthiamine pyrophosphate

3 Protonation of carbanion

H^+



Resonance-stabilized carbanion

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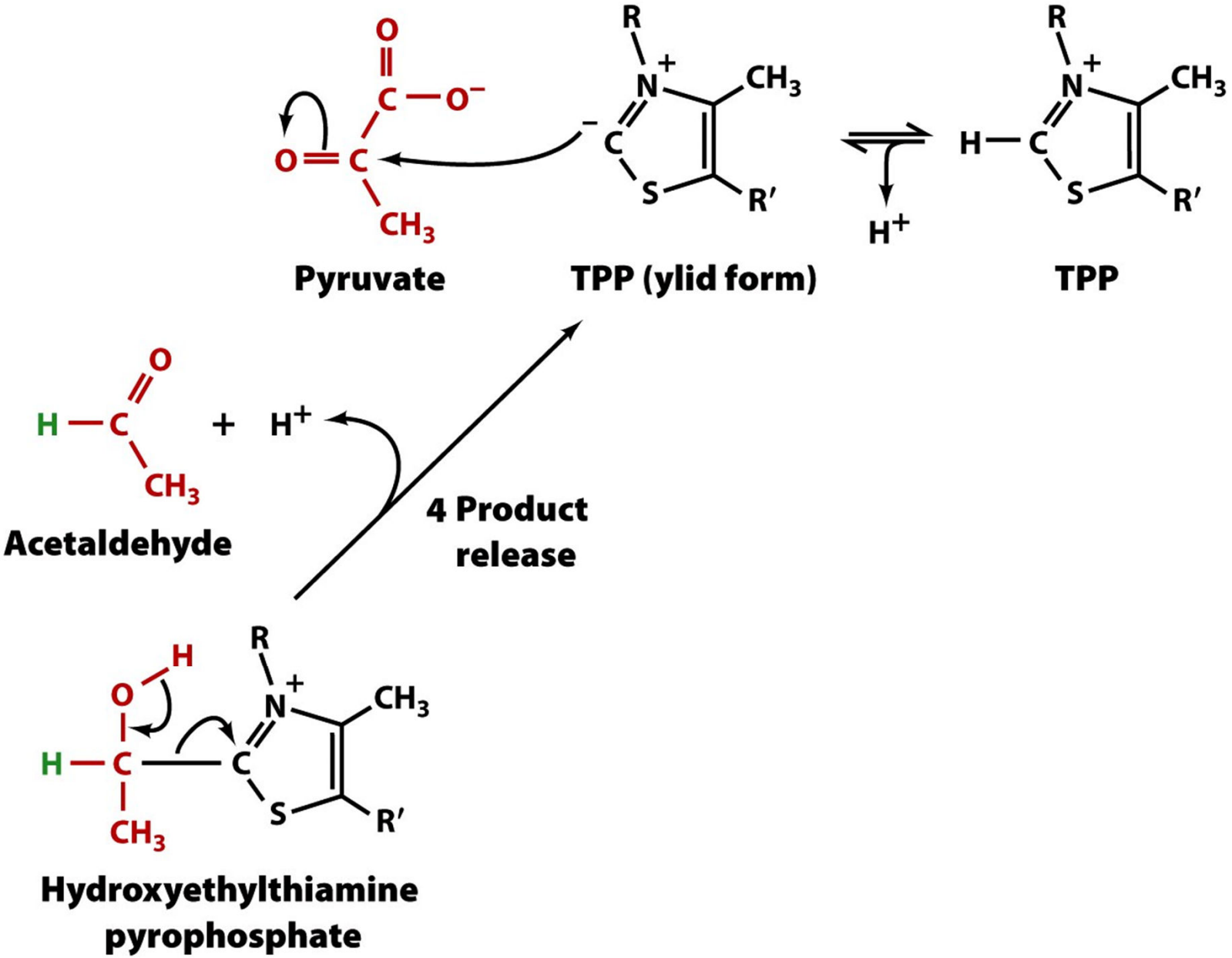

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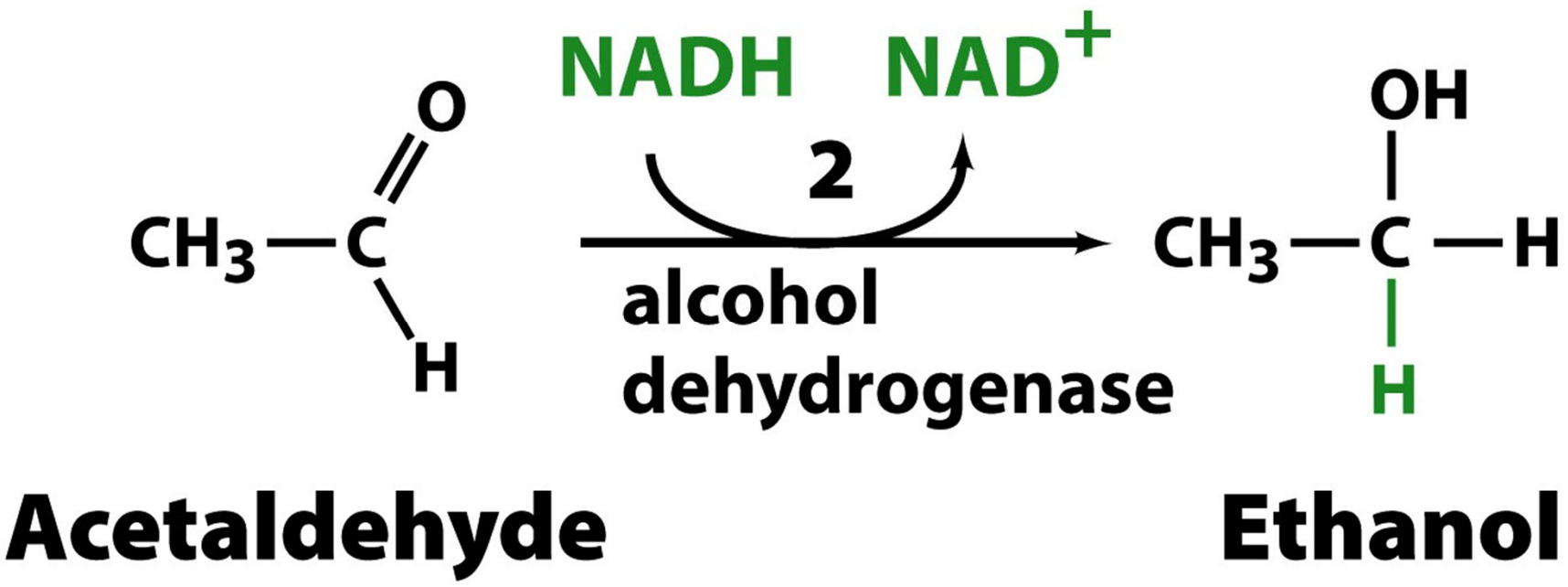
Alcohol DH regenerates NAD+ through the reduction of acetaldehyde to ethanol



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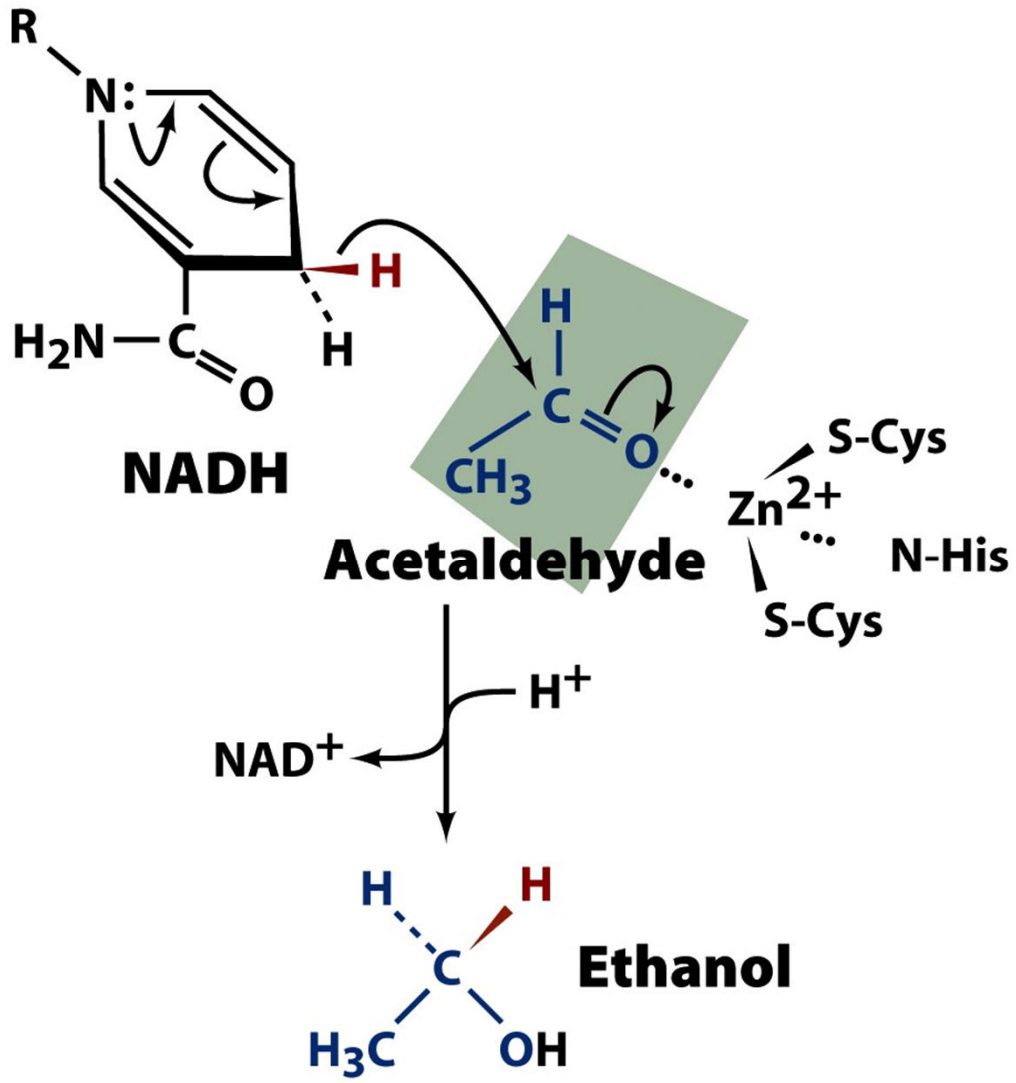
A hydride from NADH is transferred directly to acetaldehyde's carbonyl carbon



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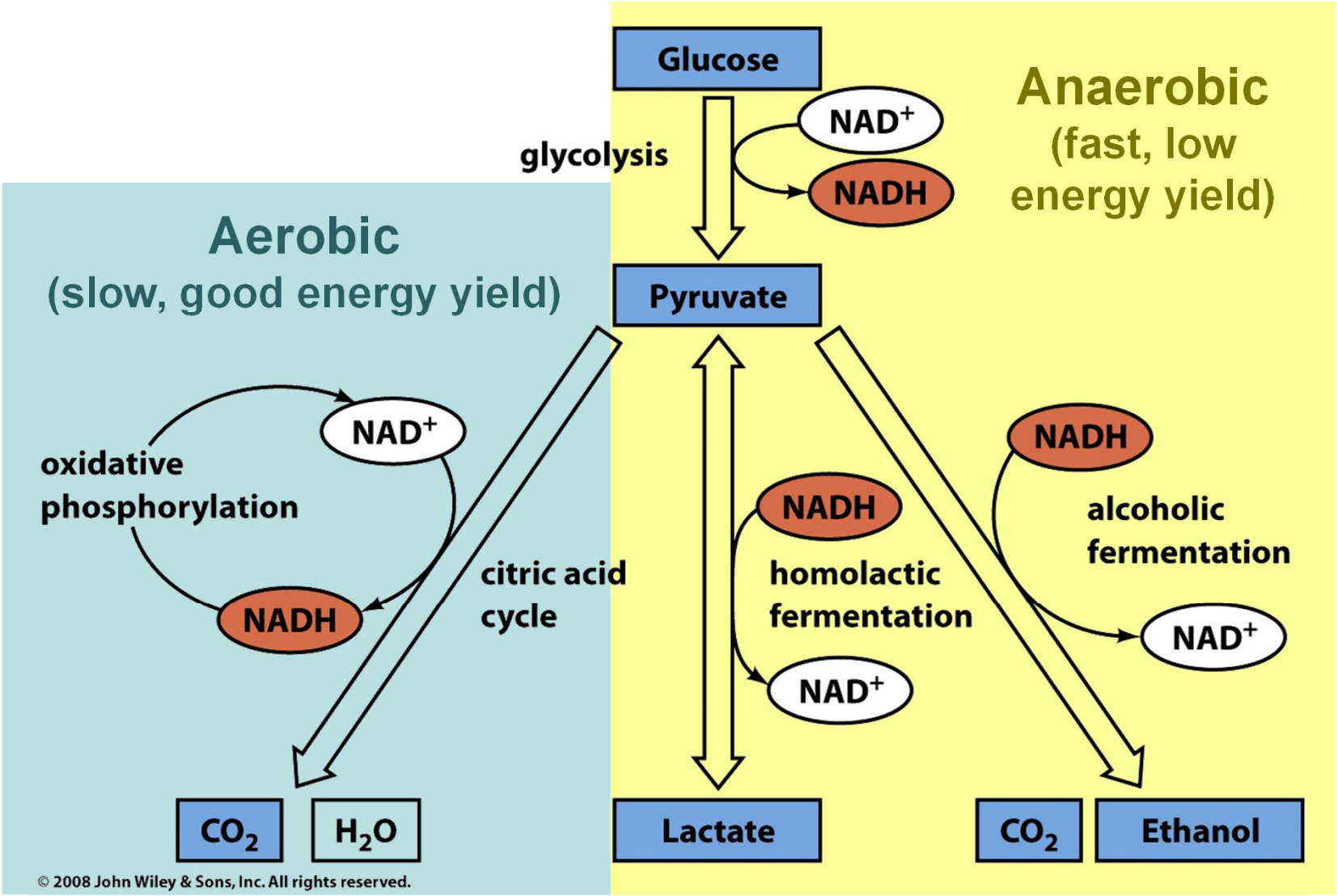
From glycolysis, pyruvate has multiple options for further metabolism



Oxidation of glucose releases more free energy & yields more ATP than fermentation

Fermentation: 2 ATP (per glucose)

glucose $\rightarrow$ 2 lactate + $2H^+$ $\quad \Delta G'^\circ = -196$ kJ/mol

glucose $\rightarrow$ $2CO_2$ + 2 ethanol $\quad \Delta G'^\circ = -235$ kJ/mol

Oxidation: up to 32 ATP (per glucose)

glucose + $6O_2 \rightarrow 6CO_2 + 6H_2O$ $\quad \Delta G'^\circ = -2850$ kJ/mol