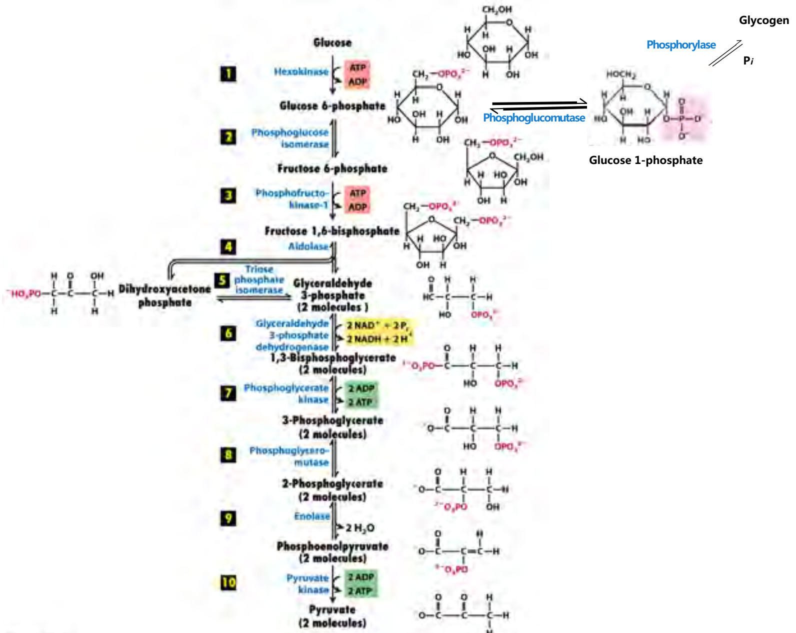
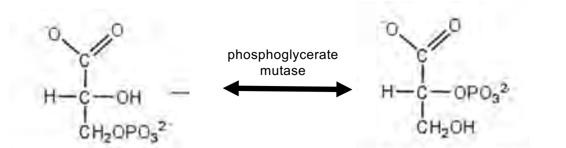
Glycolysis: Summary



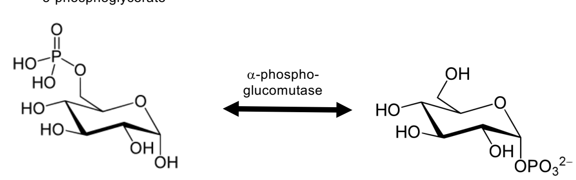
The Mutases

Accomplishing Phosphomutase Activity



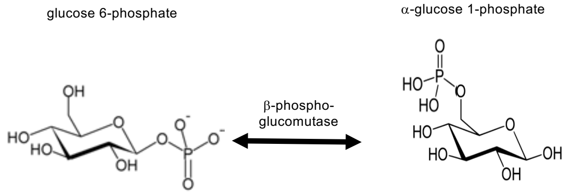
3-phosphoglycerate — 2-phosphoglycerate

- One binding step
  - No reorientation required



glucose 6-phosphate — α-glucose 1-phosphate

- Two binding steps
  - Glycogen metabolism
  - Bis-phosphorylated intermediate flips in "vestibule"
  - No glucose exchange



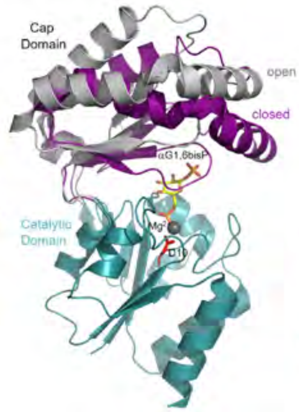
β-glucose 1-phosphate — glucose 6-phosphate

- Two binding steps
  - Free bis-phosphorylated intermediate flips outside active site
  - HAD
  - Exchange glucose
  - Micro-organisms

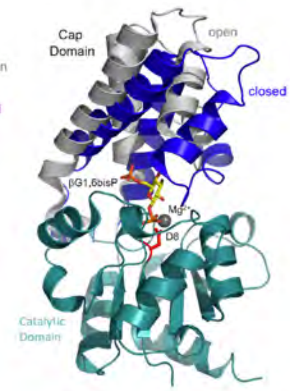
The Mutases

HAD family

Hs α-phosphoglucomutase
…....and also
phosphomannomutase



Hs α-phosphomannomutase



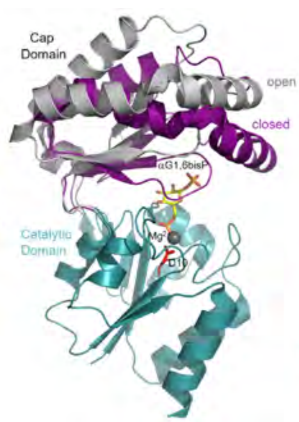
Ll β-phosphoglucomutase

Glycogen metabolism

microbes

The Mutases

Hs α-phosphoglucomutase
…....and also
phosphomannomutase



Hs α-phosphomannomutase

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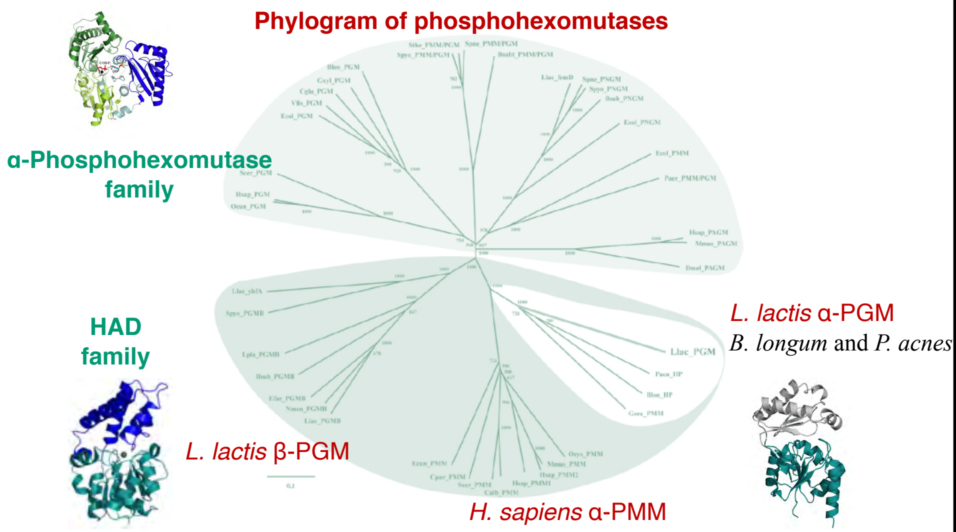
Glycogen metabolism

microbes

The Mutases

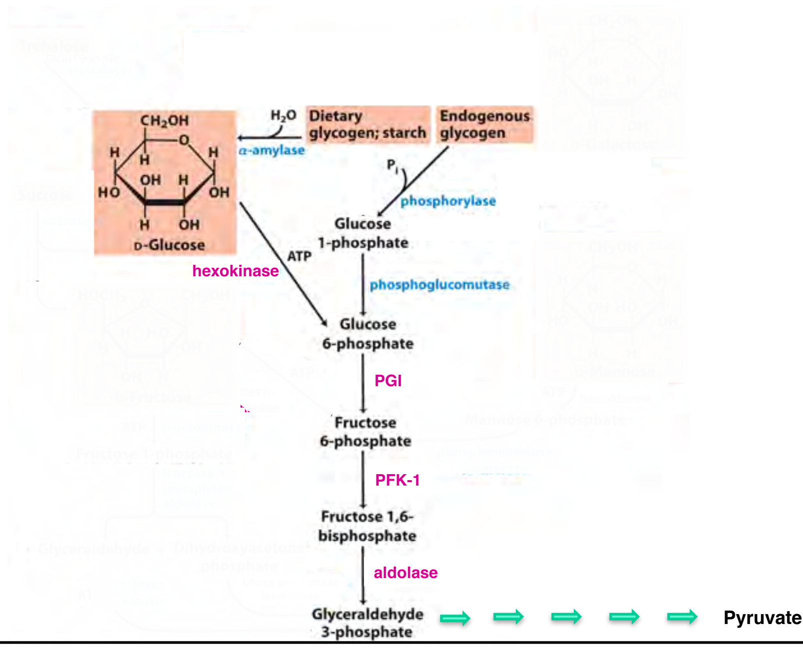


Neves et al. (2006) J. Biol Chem. 281, 36864

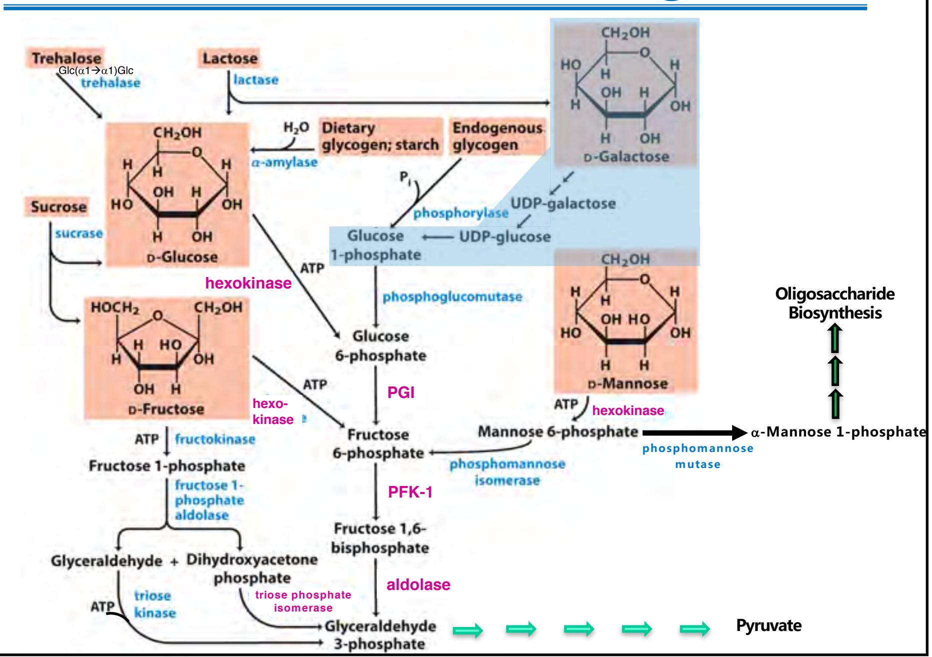
Catabolism of Other Sugars

- Ingestion yields free glucose from glycogen and starch by α–amylase, maltase, and isomaltase
- In the cell, glucose molecules are cleaved from glycogen and starch by glycogen phosphorylase.
  - yielding glucose 1-phosphate
  - uses inorganic phosphate for lysis (phosphoro-lysis)
- Disaccharides are hydrolyzed.
  - lactose: glucose and galactose
  - sucrose: glucose and fructose
  - trehalose: glucose
  - Monosaccharides fructose, galactose, and mannose enter glycolysis at different points.

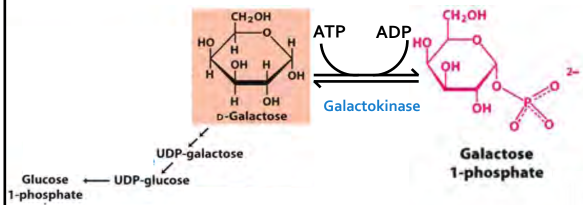
Catabolism of Other Sugars



Catabolism of Other Sugars

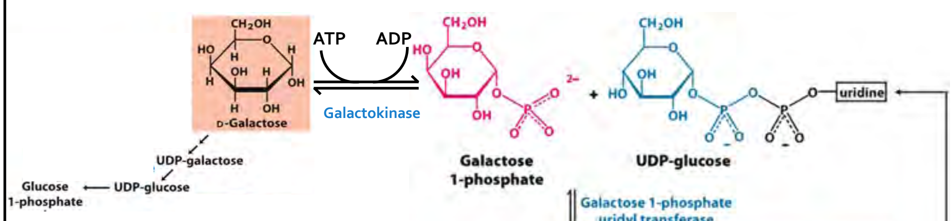


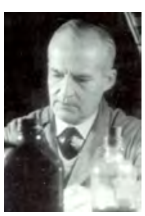
Catabolism of Other Sugars

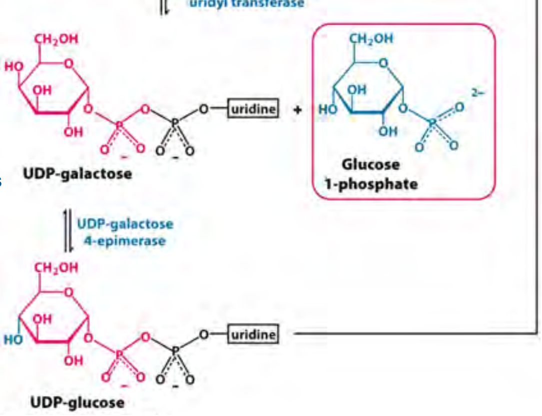


- Use of nucleotide sugars discovered by Argentinian biochemist Luis Leloir in 1940 for which he received the Nobel Prize.
- Defects in the human genes for these enzymes causes what are called inborn errors in metabolism.
- The cause of one of these due to galactose ingestion was one of the first discovered in 1956 by Herman Kalckar.
- Galacotsemia causes enlarged liver, cirrhosis, kidney failure, cataracts, hypoglycemia, lethargy, and brain damage. Without treatment, mortality is about 75%.
- Defects in transferase are the underlying cause, with incidence of about 1:60,000 births.

Catabolism of Other Sugars







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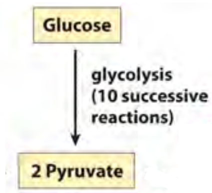
Fates of Pyruvate

Pasteur effect

$+O_2 \rightarrow$ growth ↑ & fermentation ↓



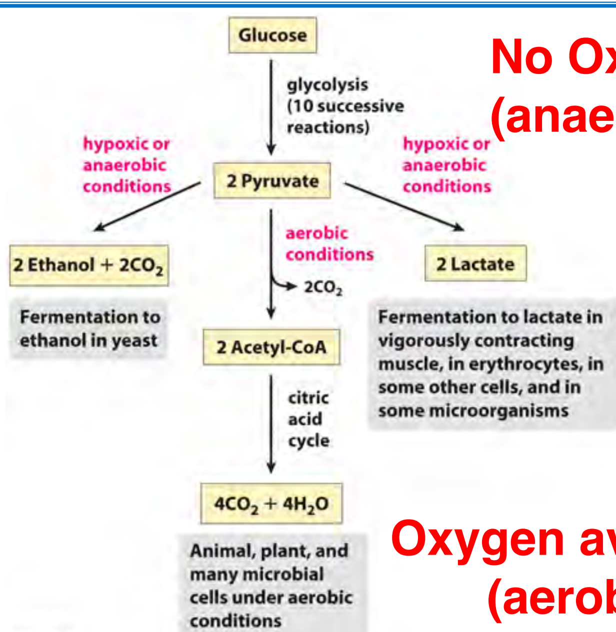
No Oxygen (anaerobic)

Oxygen available (aerobic)

In 1857, Louis Pasteur was studying fermentation by yeast, which are facultative anaerobes. They can produce energy with or without oxygen. When oxygen is low, the product of glycolysis, pyruvate, is turned into ethanol and carbon dioxide. When oxygen is high, pyruvate is converted to acetyl CoA and completely oxidized. More ATP is made aerobically than anaerobically. Therefore, about 15 times more glucose is consumed anaerobically as aerobically.

Fates of Pyruvate

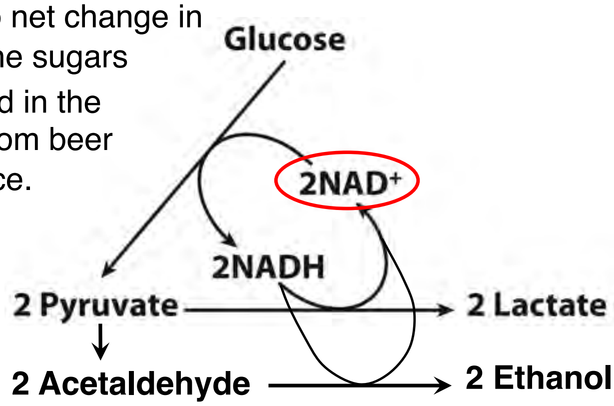
No Oxygen (anaerobic)



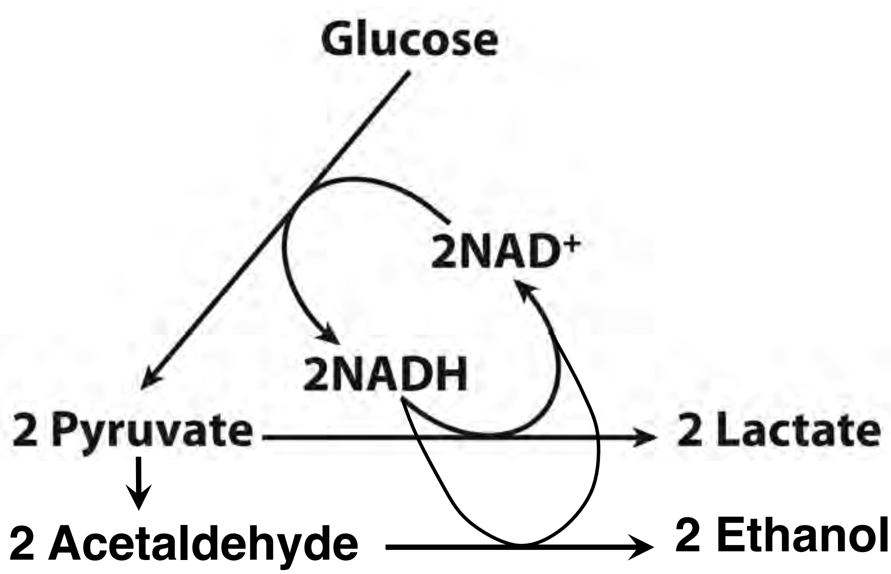
Oxygen available (aerobic)

Fermentation

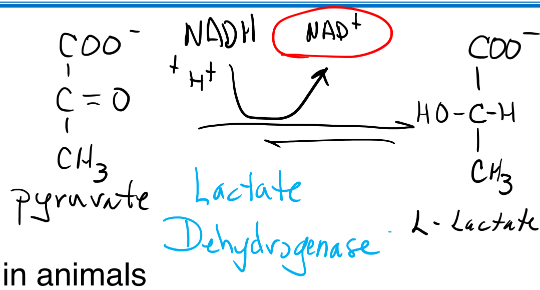
- **Regenerates NAD+ for further glycolysis under anaerobic conditions**
- Generation of energy (ATP) without consuming oxygen
- Reduction of pyruvate to another product, there is no net change in oxidation state of the sugars
- The process is used in the production of food from beer to yogurt to soy sauce.



Fermentation



Fermentation: Lactic acid

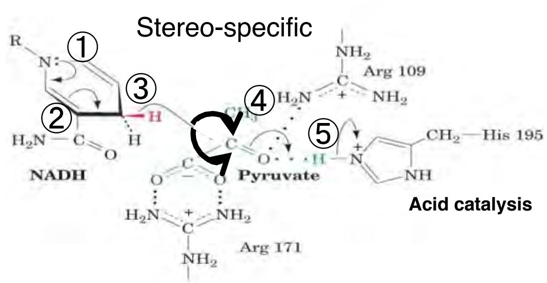


- Pathway in animals
- Reduction of pyruvate to lactate, reversible
- Highly thermodynamically favorable/reversible ($\Delta G^{o\prime}$ = –6 kcal/mol)
- During strenuous exercise, lactate builds up in the muscle.
  - generally less than 1 minute
- The lactate can be transported to the liver and converted to glucose there. Called the Cori cycle.
  - Requires a recovery time
  - high amount of oxygen consumption to fuel gluconeogenesis
  - restores muscle glycogen stores

Fermentation: Lactic acid

Mechanism

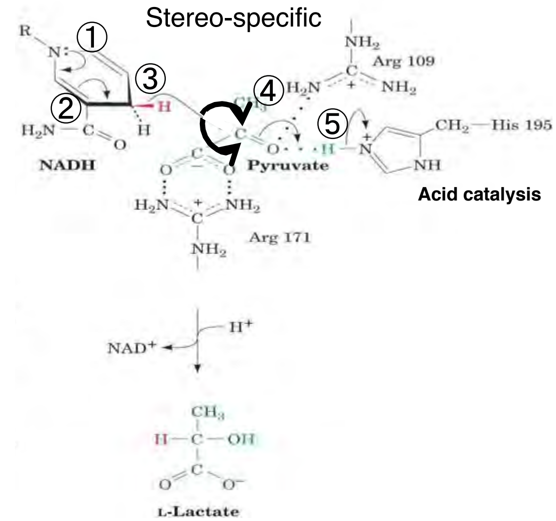
Lactate dehydrogenase



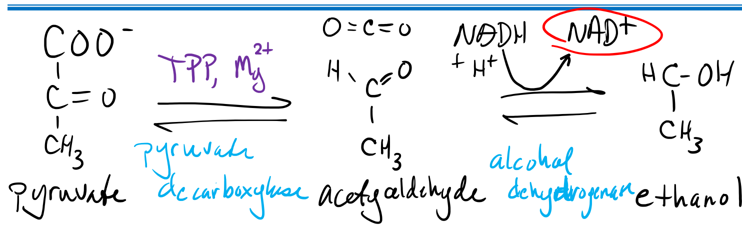
Fermentation: Lactic acid

Mechanism

Lactate dehydrogenase

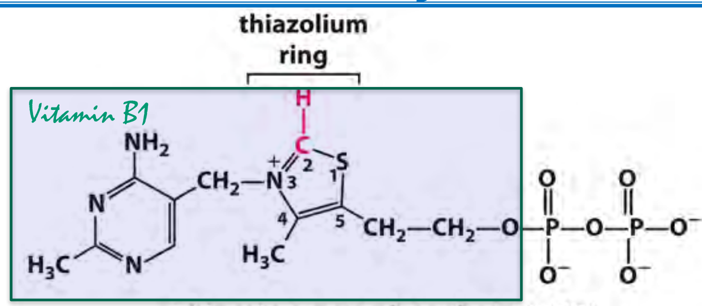


Fermentation: Ethanol



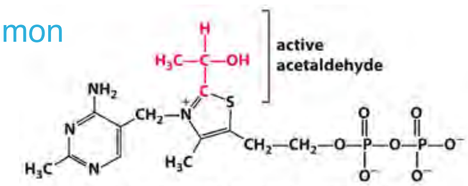
- Two-step reduction of pyruvate to ethanol
- Humans do not have pyruvate decarboxylase.
- Humans express alcohol dehydrogenase for ethanol metabolism, but is largely used in the reverse reaction, then aldehyde dehydrogenase (recall the different forms with different K_m values for why some people get flush).
- Both steps require cofactors.
  - pyruvate decarboxylase: Mg^{++} and thiamine pyrophosphate (TPP)
  - alcohol dehydrogenase: Zn^{++} and NAD^+
- CO_2 produced in the first step is responsible for:
  - carbonation in beer
  - dough rising when baking bread

Fermentation: Pyruvate decarboxylase



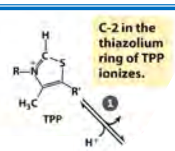
Thiamine pyrophosphate (TPP)

TPP Is a Common Acetaldehyde Carrier



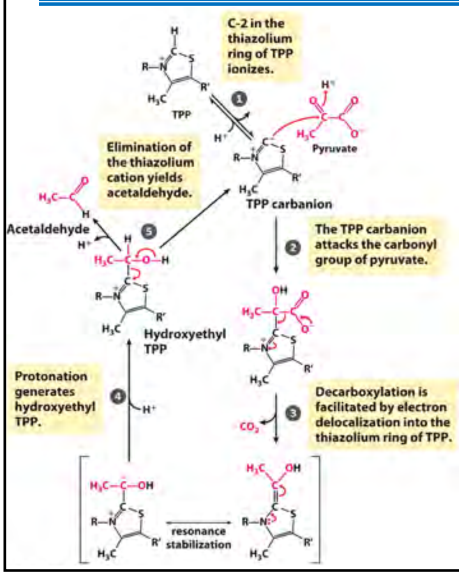
Hydroxyethyl thiamine pyrophosphate

Fermentation: Pyruvate decarboxylase



- TPP forms a covalent bond with carbonyl carbon, forming an alcohol, and resulting in release of CO_2.
- TPP then allows rearrangement of and protonation of carbonyl carbon to release from complex.

Fermentation: Pyruvate decarboxylase



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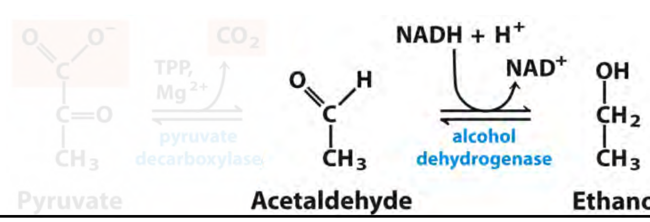
Fermentation: Pyruvate decarboxylase

TABLE 14-1 Some TPP-Dependent Reactions

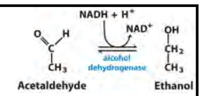
Enzyme	Pathway(s)	Bond cleaved	Bond formed
Pyruvate decarboxylase	Ethanol fermentation	$R^1-C(=O)-C(=O)O^-$	$R^1-C(=O)-H$
Pyruvate dehydrogenase α-Ketoglutarate dehydrogenase	Synthesis of acetyl-CoA Citric acid cycle	$R^2-C(=O)-C(=O)O^-$	$R^2-C(=O)-S\text{-CoA}$
Transketolase	Carbon-assimilation reactions Pentose phosphate pathway	$R^3-C(=O)-C(OH)(H)-R^4$	$R^3-C(=O)-C(OH)(H)-R^5$

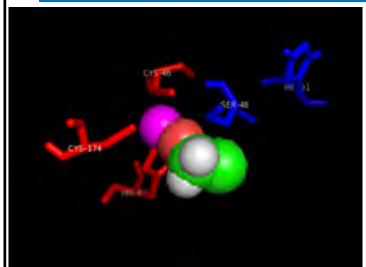


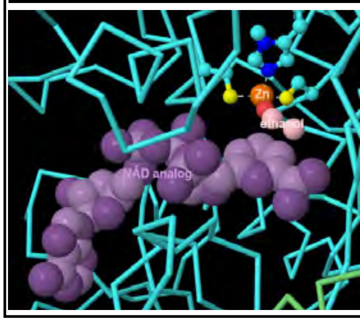
Like LDH, highly thermodynamically favorable ($\Delta G^{\circ\prime}$ = –6 kcal/mol)

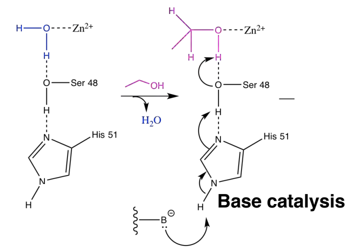
This reaction pulls the entire fermentation pathway.

Fermentation: Alcohol Dehydrogenase (ADH)









Fermentation: Alcohol Dehydrogenase (ADH)