

CELLULAR METABOLISM

What is metabolism?

- How cells acquire, transform, store and use energy
- Study reactions in a cell and how these processes are coordinated and regulated

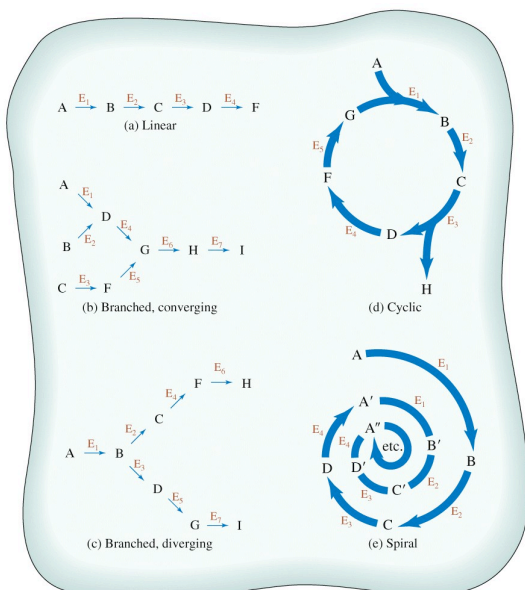


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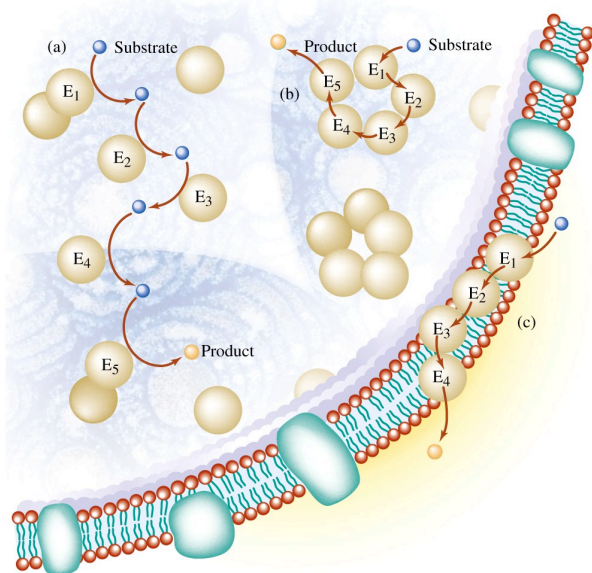


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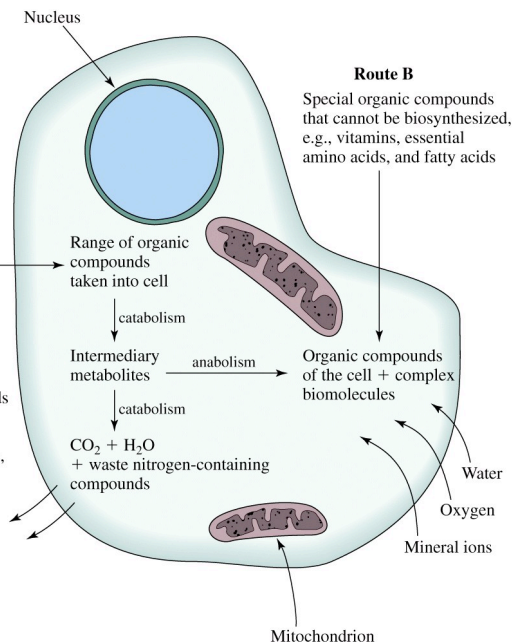


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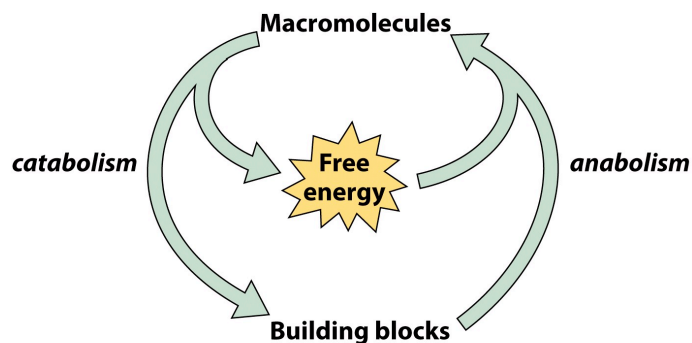
Metabolic pathways can be linear, branched, cyclic or spiral

Multienzyme systems arranged into different metabolic pathways:

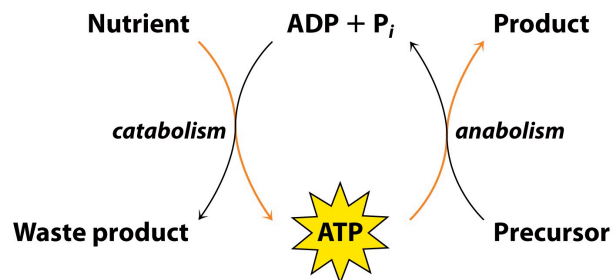
- Enzymes loosely held together. Diffusion of intermediates to other enzyme.
- Multienzyme complex tightly associated. Intermediates channeled from one active site to the other.
- Multienzyme system in a membrane

TWO PARTS:

- **CATABOLISM:** Degradative Pathway
 - Generating energy from macronutrients
 - Formation of NADH, FADH₂ and ATP
 - NADH and FADH₂ are used to make ATP
- **ANABOLISM:** Biosynthesis
 - Synthesizing molecules and polymers that make up the cell
 - Uses NADPH, FADH₂ and ATP



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Table 14.1**Contrasting characteristics of catabolism and anabolism****Catabolism**

Leads to degradation of biomolecules

Overall process of chemical oxidation and formation of reduced cofactors of NADH, NADPH, FADH₂

Release of chemical energy (exergonic) and production of ATP from ADP

Convergence of pathways

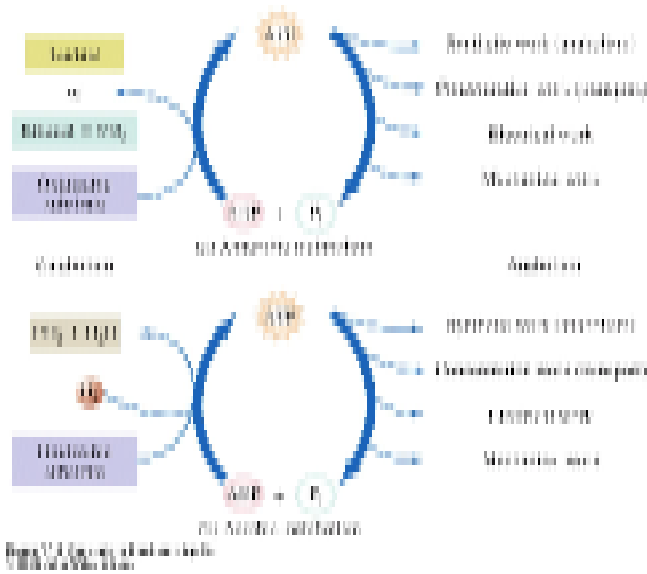
Anabolism

Synthesis of biomolecules

Overall process of chemical reduction and formation of oxidized cofactors NAD⁺, NADP⁺, FAD

Requirement for energy input (endergonic) and use of ATP

Divergence of pathways

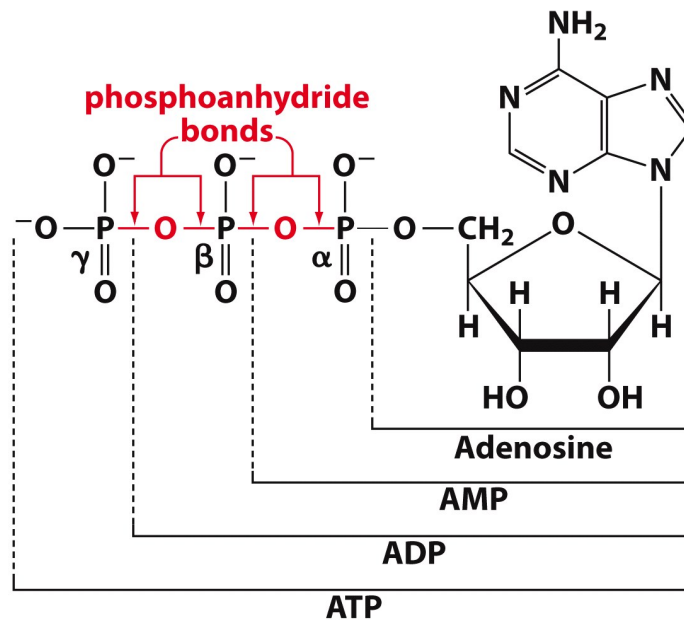


Metabolic Pathways Are Sequences of Reactions

- Metabolism includes all enzyme reactions
- Metabolism can be subdivided into branches
- The metabolism of two of the four major groups of biomolecules will be considered:
 - Carbohydrates
 - Lipids
 - Amino Acids and Nucleotides not in this course

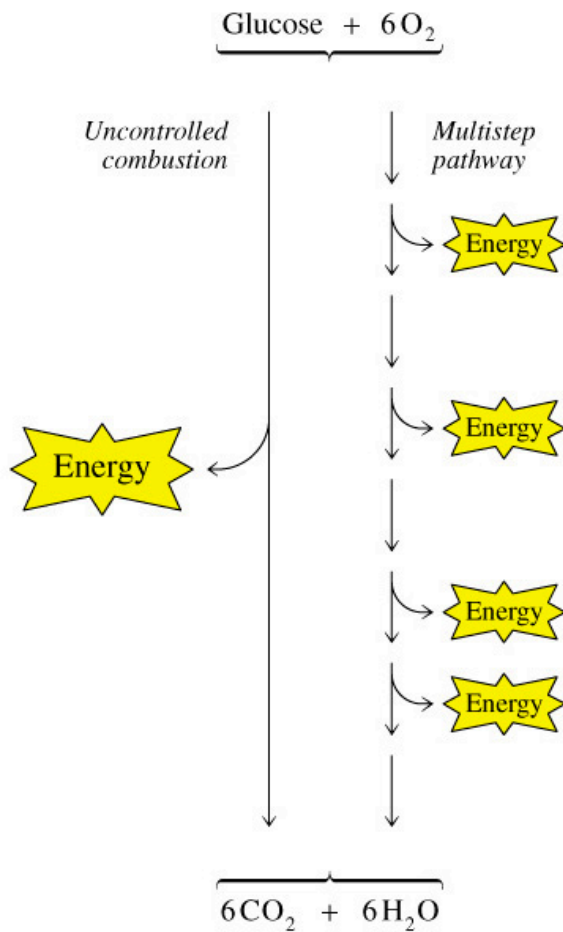
THE ATP ENERGY CYCLE

- Energy derived from metabolic fuels is largely recovered in the form of **ATP**
- Pathways of catabolism release free energy that is captured as ATP
- **ATP – adenosine triphosphate**
 - Main source of energy for the body
 - Not stored but used up rapidly and resynthesized
 - Common to both **aerobic** (with oxygen) and **anaerobic** (without oxygen) organisms
 - **Phosphoanhydride** bonds are energy rich – release energy when broken



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Metabolism Proceeds by Discrete Steps



- Multiple-step pathways permit control of energy input and output
- Catabolic multi-step pathways provide energy in smaller stepwise amounts
- Each enzyme in a multi-step pathway usually catalyzes only one single step in the pathway
- Control points occur in multi-step pathways: Regulation!

- For example: Regulation by reversible phosphorylation

- **Protein kinases** phosphorylate enzymes (+ ATP)

- **Protein phosphatases** remove phosphoryl groups

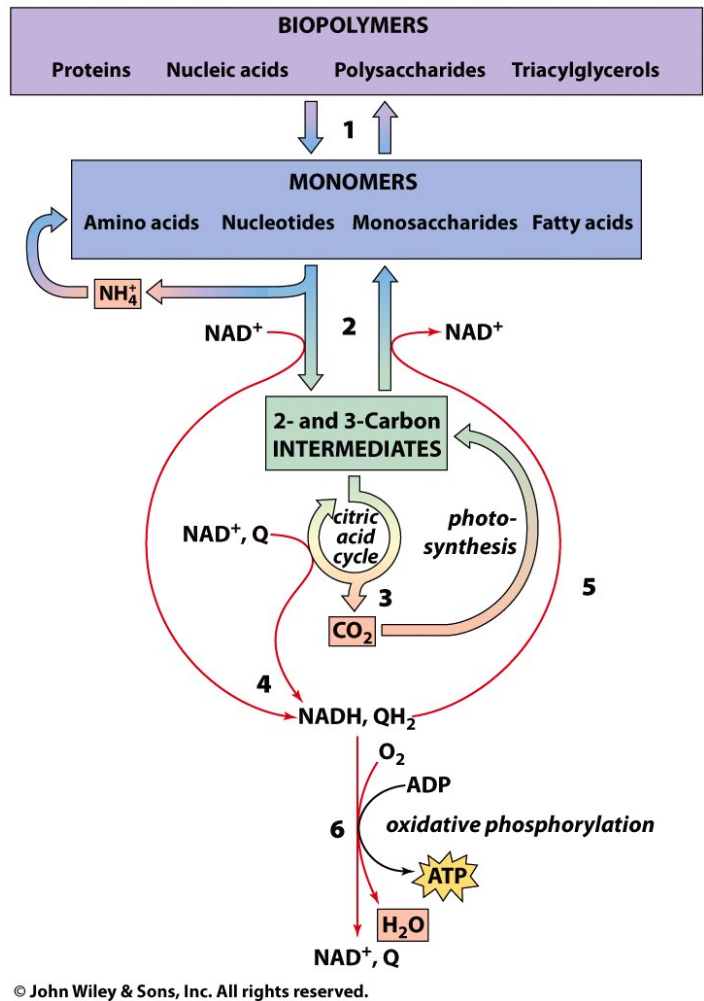
Metabolism is **highly regulated** to permit organisms to respond to changing conditions and most pathways are **irreversible**

- Single-step vs multi-step pathways
- A multistep enzyme pathway releases energy in smaller amounts that can be used by the cell

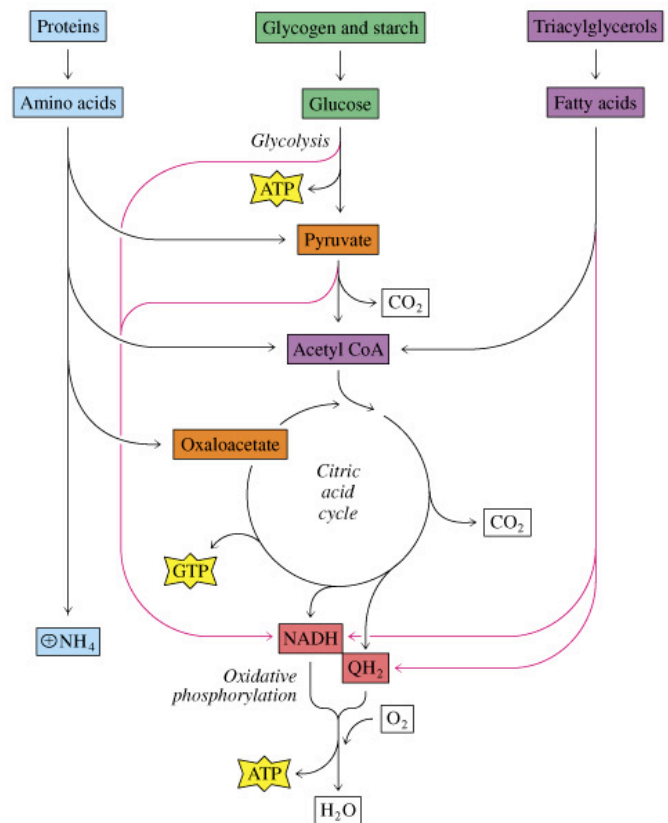
Metabolic fuels

Three major nutrients consumed by mammals:

- (1) **Carbohydrates** - provide energy
- (2) **Proteins** - provide amino acids for protein synthesis and some energy
- (3) **Fats** - triacylglycerols provide energy and also lipids for membrane synthesis



Three Stages of Metabolism (for now concentrate on Catabolism)



I. Breakdown of Macromolecules into Building Blocks

- Virtually no useful energy is released
- Preparing substrates for next stage

II. Amino acids, Fatty acids and monosaccharides are OXIDIZED to a common intermediate

- Common intermediate = **ACETYL-CoA (acetyl coenzyme A)**
- All building blocks converge to same pathway
- Some energy is released also small amount of energy is used

III. Acetyl-CoA enters the TCA CYCLE

- Oxidized further to CO₂ – the end product of aerobic carbon metabolism
- Reduced NADH and FADH₂ formed give up their electrons (are oxidized!) and the electrons are transported through proteins and other molecules to O₂ which is reduced to water
- This produces a proton flow and a transmembrane potential
- The energy potential across the membrane is is coupled DIRECTLY to ATP synthesis from ADP and Pi. $ADP + Pi \leftrightarrow ATP$

- **Processes called: ELECTRON TRANSPORT AND OXIDATIVE PHOSPHORYLATION**

Anabolism:

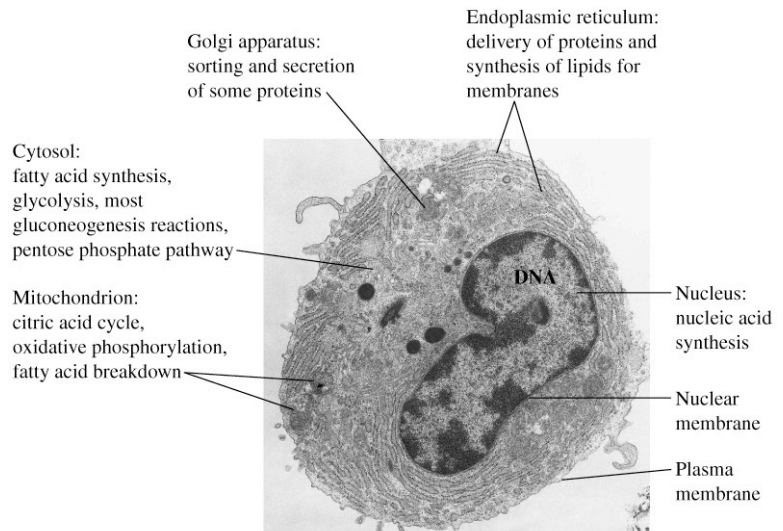
- Also has three stages
- Characterized by divergence not convergence
- NOT simply the reverse of catabolism

COMPARTMENTALIZATION OF METABOLISM

Compartmentalization of metabolic processes permits:

1. separate pools of metabolites in a cell
2. simultaneous operation of opposing metabolic paths
3. high local concentrations of metabolites
4. coordinated regulation of enzymes

Example: fatty acid synthesis enzymes (cytosol), fatty acid breakdown enzymes (mitochondria)



CELLULAR COMPARTMENTS

CHEMISTRY OF METABOLISM:

Table 14.2 – 6 MAIN TYPES OF CHEMICAL REACTIONS

- No need to memorize details
- Be able to recognize the type of reaction if shown an example

Table 14.2

Types of chemical reactions in metabolism correlated to enzyme classes

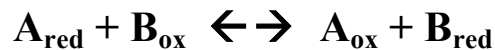
Type of Reaction	Enzyme Class	Description of Reaction
1. Oxidation–reduction	Oxidoreductases (dehydrogenases)	Transfer of electrons
2. Group transfer	Transferases	Transfer of a functional group from one molecule to another or within a single molecule
3. Hydrolytic cleavage (hydrolysis)	Hydrolases	Cleavage of bonds by water (transfer of functional groups to water)
4. Nonhydrolytic cleavage	Lyases	Splitting a molecule by nonhydrolytic processes
5. Isomerization and rearrangement	Isomerases	Rearrangement of functional groups to form isomers
6. Bond formation using energy from ATP	Ligases	Formation of carbon–carbon and other bonds with energy from ATP

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1. Oxidation-Reduction Reactions:

REACTIONS OF CATABOLISM ARE OXIDATIVE! (Oxidation/Reduction Reactions)

- Also known as REDOX reactions
- Amino acids, monosaccharides and lipids are oxidized in the catabolic pathways
- These substrates are relatively reduced substrates (sugars, fats)
- **Oxidizing agent** - accepts electrons, is reduced
- **Reducing agent** - loses electrons, is oxidized
- Oxidation of one molecule must be coupled with the reduction of another molecule



O
I
L
R
I
G

Oxidation

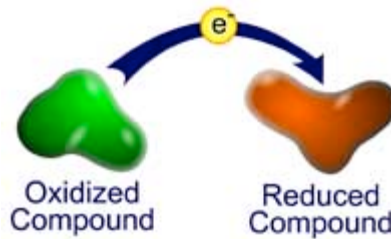
Is

Loss of electrons

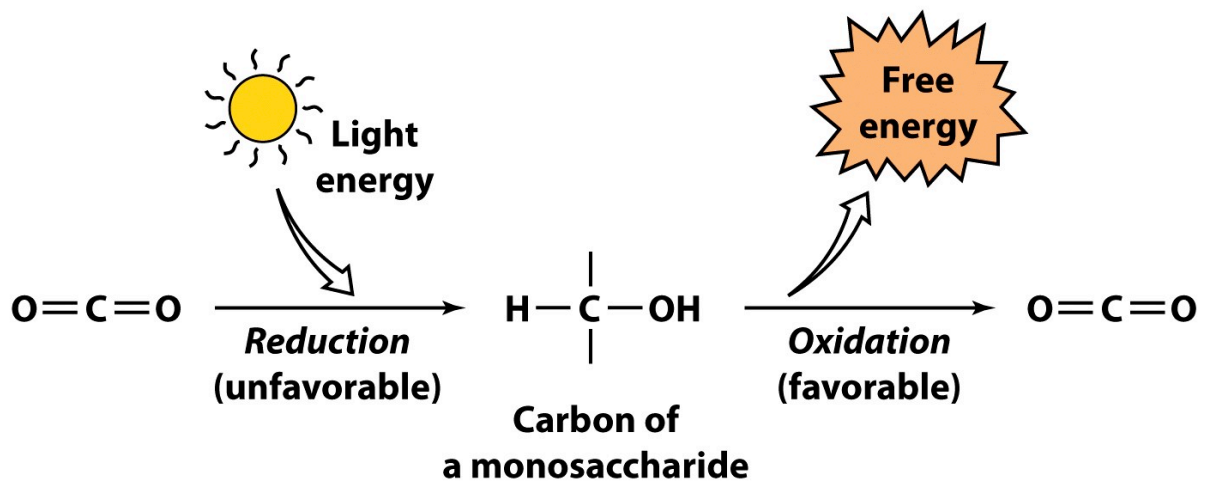
Reduction

Is

Gain of electrons



"OIL RIG"



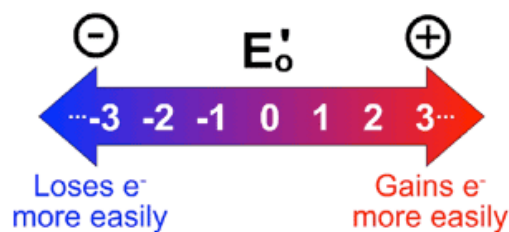
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Oxidation and reduction reactions always occur together, because the electrons that are donated from one compound must be received by another compound. This is why redox reactions are said to be the product of two half reactions, the oxidation half reaction and the reduction half reaction.

Each half reaction has a measurable reduction potential E_0 , which is a measure in volts of how easily the compound is reduced (how easily it gains electrons).

Remember, the **reduction potential is how much a species "wants" to get reduced**, and the higher the number, the greater the potential.

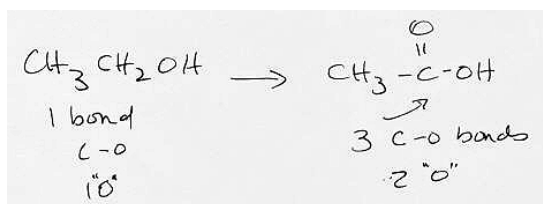
- Transfer of electrons from reducing agent (that which is oxidized) to an oxidizing agent (that which is reduced)
- **Two simple rules identify the players in carbon compounds:**



- A. **OXIDATION** has occurred if molecule has **LOST HYDROGEN** from carbon



- B. **OXIDATION** has occurred if molecule **GAINS** an **OXYGEN** or if the **NUMBER OF CARBON BONDS TO OXYGEN** increases.



Reduction: Molecule has fewer bonds to O or gains hydrogen to carbon

TABLE 1-3 | Oxidation States of Carbon

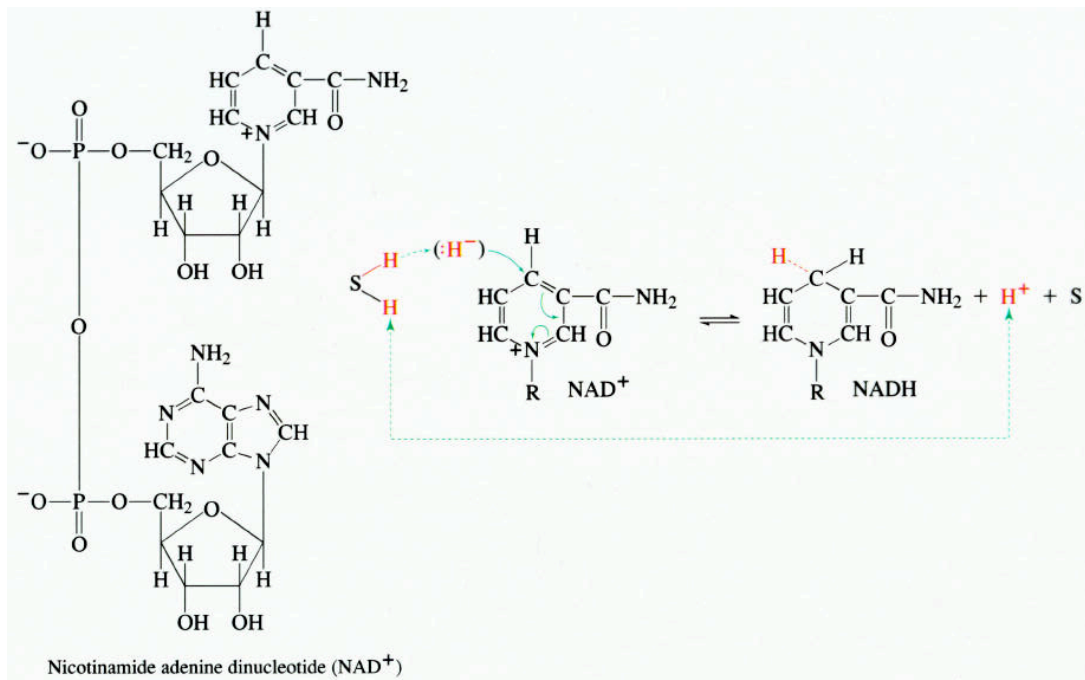
Compound ^a	Formula	Compound ^a	Formula
Carbon dioxide <i>most oxidized</i> <i>(least reduced)</i>	O=C=O	Formaldehyde	
Acetic acid		Acetylene	H-C≡C-H
Carbon monoxid	C≡O	Ethanol	
Formic acid		Ethene	
Acetone		Ethane	
Acetaldehyde		Methane <i>least oxidized</i> <i>(most reduced)</i>	

^aCompounds are listed in order of decreasing oxidation state of the red carbon atom.

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COENZYMES INVOLVED IN DEHYDROGENASE REACTIONS

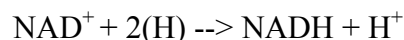
- Redox reactions transfer large amounts of energy. Much of the energy liberated in an oxidation is captured in the reduction of the oxidizing agent, such as NAD^+ or FAD .
 - Reducing equivalents are released from substrates, often as hydride ions (proton + $2e^-$)
- H^-**
- Hydride ion is transferred in enzymatic **DEHYDROGENASE** reactions from substrates to the coenzymes NAD^+ and FAD (2 H^+ accompanies the reaction)
 - $\text{NAD}^+ \leftrightarrow \text{NADH} + \text{H}^+$ (Vitamin precursor NAD^+ of is Niacin)
 - $\text{FAD} \leftrightarrow \text{FADH}_2$
 - NAD^+ and FAD COLLECT THE ELECTRONS FROM THE REACTION!
 - NAD^+ and FAD accept electrons and therefore are REDUCED
 - NADH and FADH_2 will ultimately pass their electrons on to other molecules (get oxidized)
 - Electrons of reduced coenzymes (NADH and FADH_2) flow toward O_2
 - End result is formation of ATP

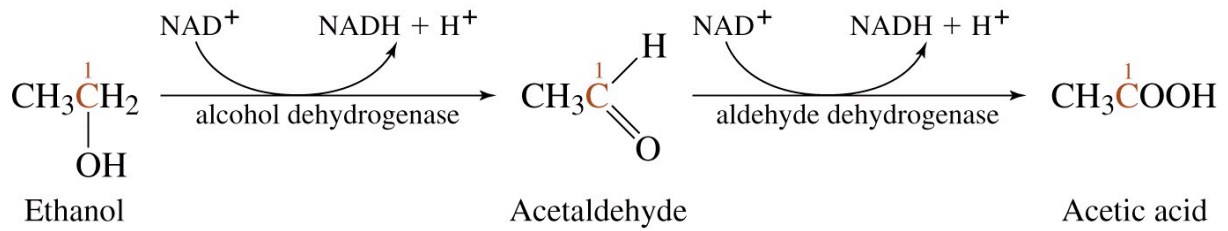


Derived from the vitamin nicotinamide

The NAD^+ coenzyme is involved with many types of oxidation reactions at **oxygen – carbon centers** (e.g. alcohols converted to ketones or aldehydes).

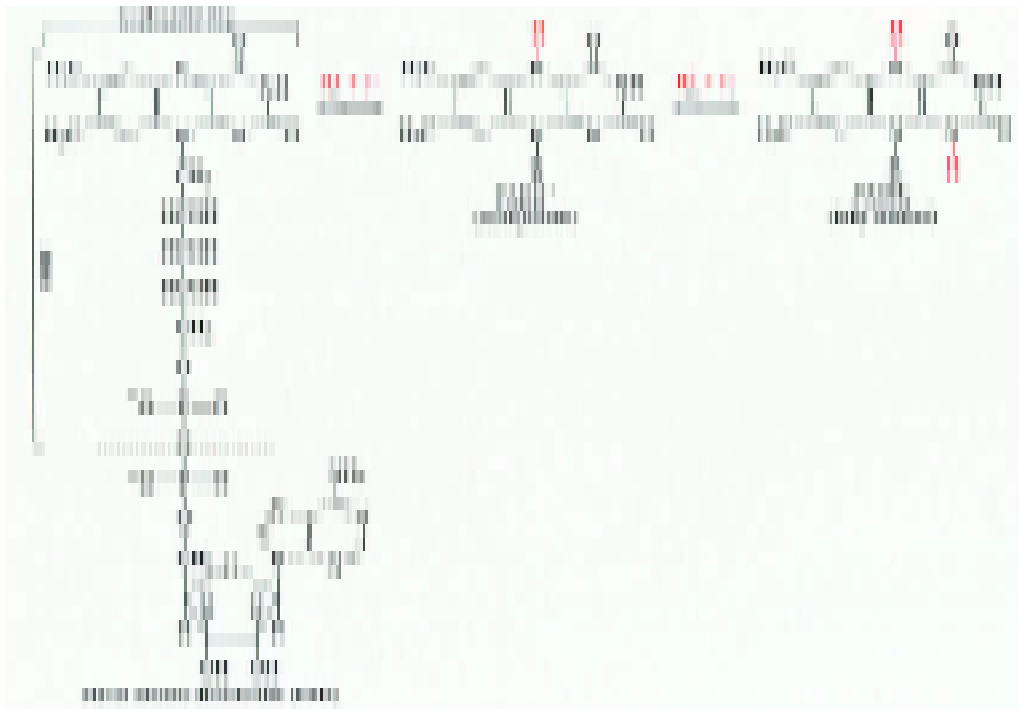
NAD^+ accepts two electrons and one proton when it is reduced. Although NAD carries two reducing equivalents, only one hydrogen atom attaches to the nicotinamide ring. The second hydrogen atom becomes a hydrogen ion in solution.





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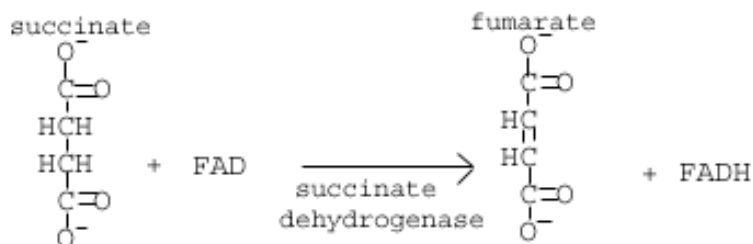
FAD



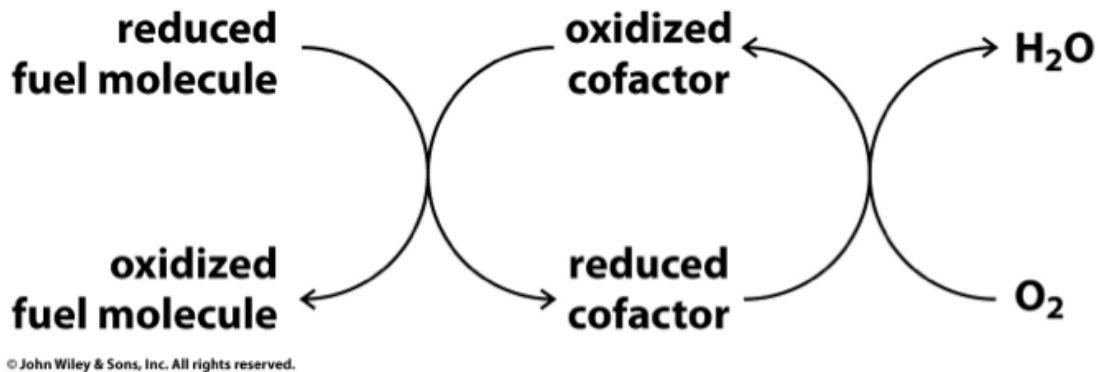
Derived from the vitamin riboflavin (B₂)

Both hydrogens derived from a redox reaction become attached to the flavin ring.

The FAD coenzyme is involved with many types of oxidation reactions at **carbon – carbon centers** to form **double bonds**



- Remember, in complete chemical reactions, oxidation and reduction complement each other; Use corollaries of above rules to figure out when REDUCTION occurs



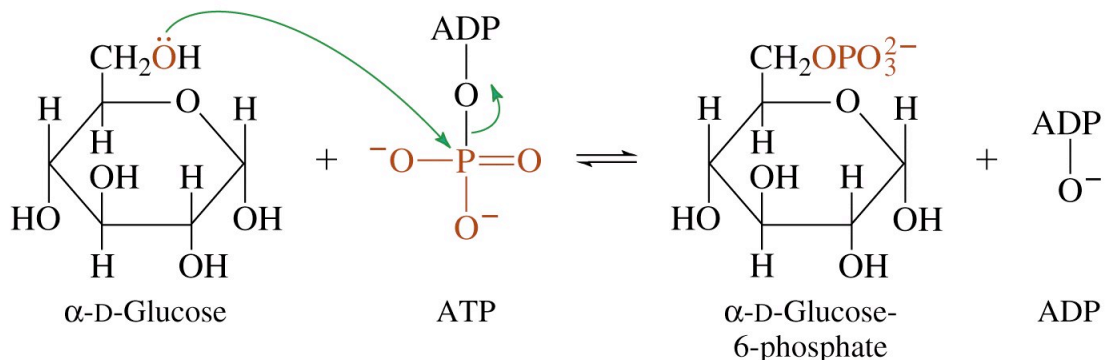
2. Group Transfer Reaction:

- **Phosphorylation** is one of the most common group transfers
 - o Usually the first step in nutrient entering metabolism
 - o Glucose gets into cells via glucose transport proteins in the cell membrane
 - o Phosphorylation of glucose inside cells adds charge and prevents glucose from exiting
 - o Kinases are the subclass of transferases that catalyze phosphorylation

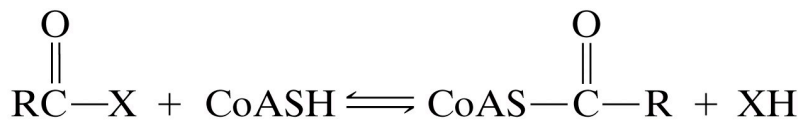
Table 14.4
Groups transferred in metabolic reactions

Name	Structure
Phosphoryl	$\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{P}- \\ \\ \text{O}^- \end{array}$
Acyl	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}- \end{array}$
Glycosyl	

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Carboxylic acid
derivative

Coenzyme A

Thioester

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3. Isomerization and Rearrangement Reactions

- Two kinds of chemical transformations:

1. Intramolecular hydrogen atom shifts

a. Results in changing location of double bonds

2. Intramolecular rearrangement of functional groups (b)

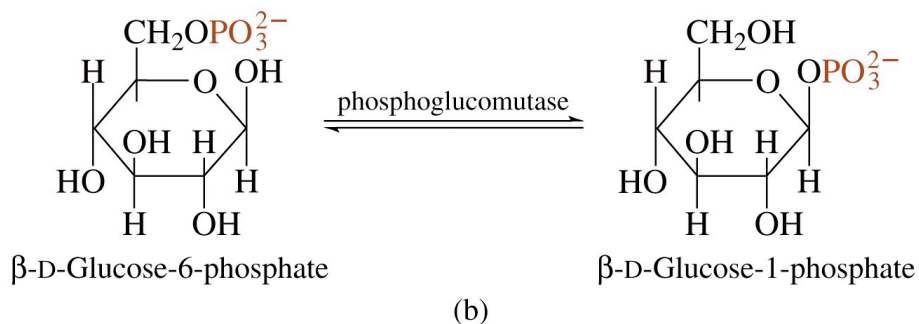
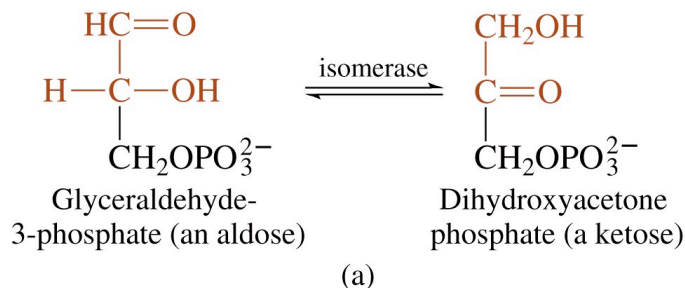
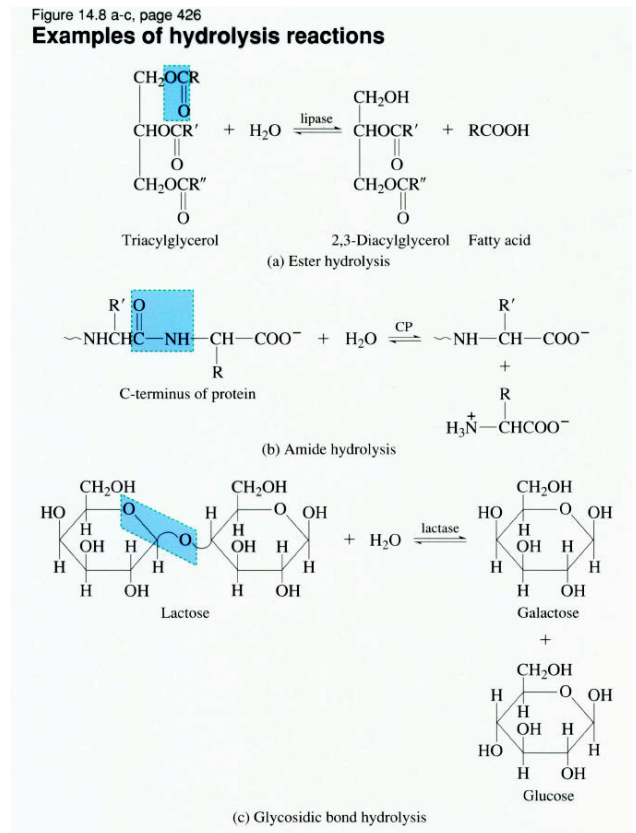


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4. Hydrolysis Reactions:

- Water is used to split a molecule into TWO distinct molecules
- All three nutrient types are shown in Figure below:
- **ESTER HYDROLYSIS:** Hydrolytic release of FA from TAG
- **AMIDE HYDROLYSIS:** Peptidase reaction; Cleaving peptides into amino acids
- **GLYCOSIDIC BOND HYDROLYSIS:** Glycosidic bonds in sugars hydrolyzed by glucosidases
- Opposite of nutrient formation which releases water via dehydration reactions
- Recall lipid and disaccharide formation - Lost water in those reactions



5. Non-hydrolytic Cleavage Reactions:

- Molecules split WITHOUT use of water
- Most prevalent are carbon-carbon cleavages
- Enzymes called LYASES
- May also include:
 - o Addition of functional groups to double bonds
 - o **Enolase:** water removed to form the double bond (b)
 - o Reverse of **aldolase**: Addition of Dihydroxyacetone phosphate to carbonyl of glyceraldehydes 3-phosphate to make fructose 1,6-bisphosphate (a)

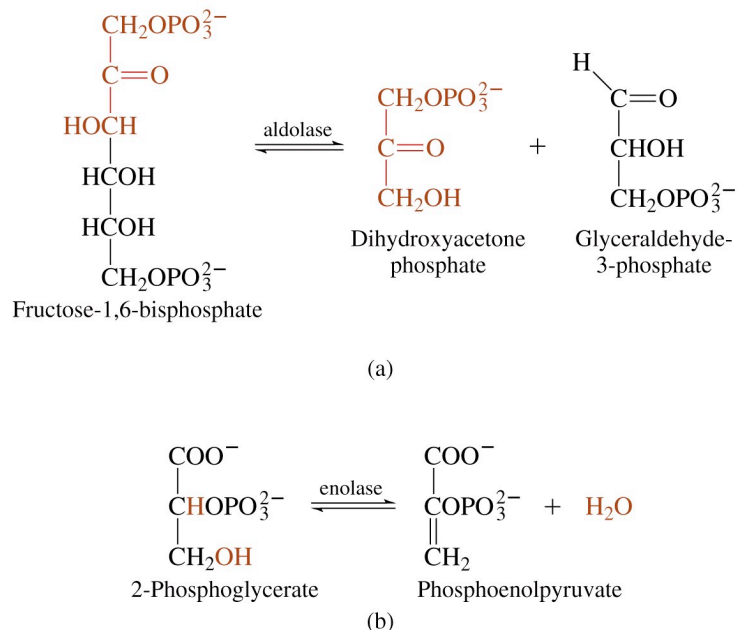
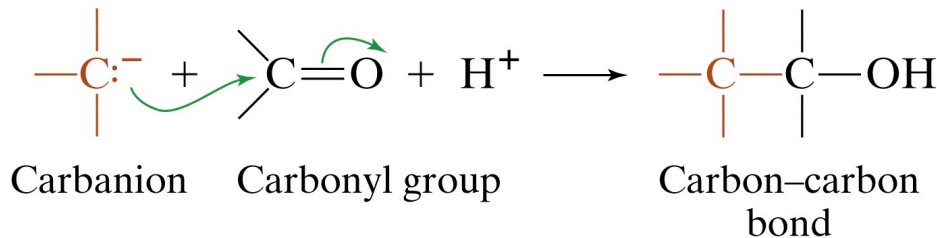


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6. Bond Formation Using Energy of ATP

- Enzymes that catalyze the joining of two separate molecules using the energy from ATP hydrolysis
- For example, **ligases** and **synthetases**
- Carbon – carbon bonds formed by reaction of **stabilized carbanion** with the **carbonyl** groups of ketones, esters or CO₂
- Carbanions are stabilized by the presence of electron-withdrawing groups such as acyl groups. Inductive withdrawal of electrons or resonance stabilization of the negative charge.



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REACTION EXAMPLES:

Carboxylation of pyruvate to make oxaloacetate

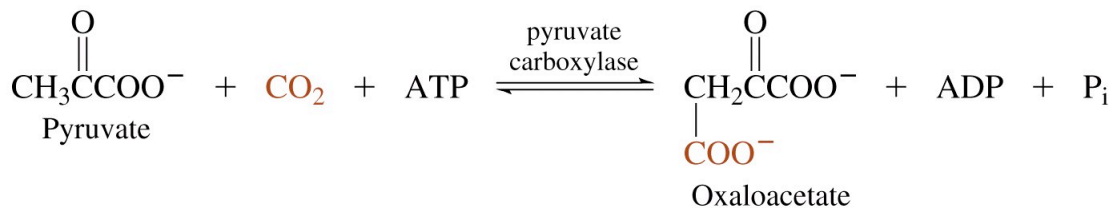


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Combination of acetyl-CoA and OAA to make citryl-CoA

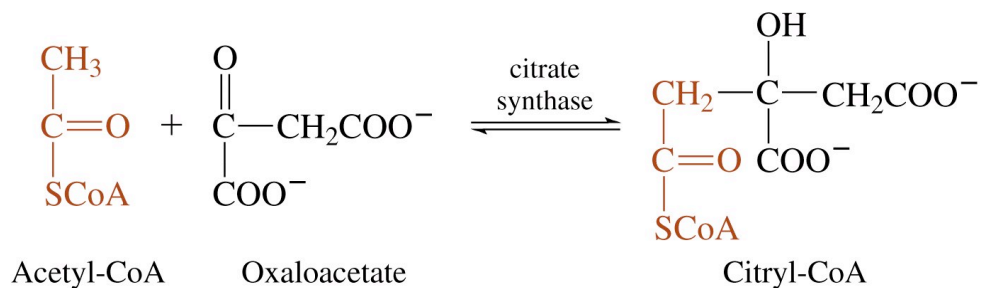


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Resonance stabilized carbanion generated on methyl group of substrate: Pyruvate or acetyl-CoA

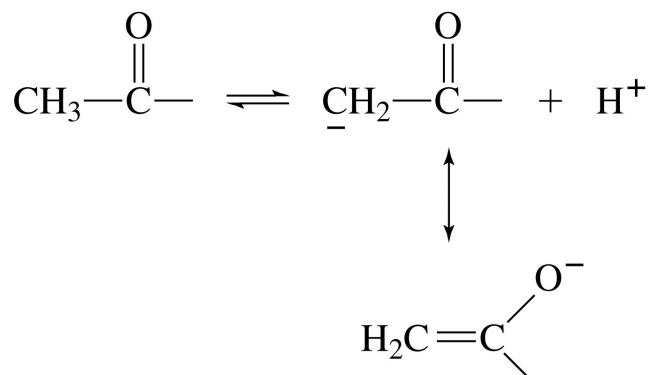
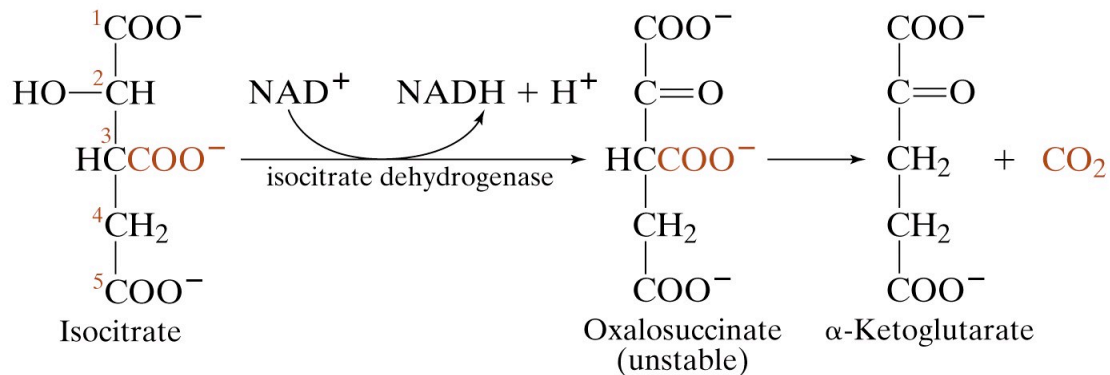


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Reactions types can be combined in a single metabolic step:

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

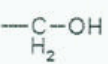
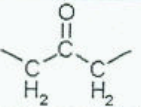
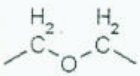
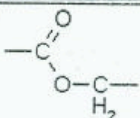
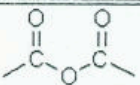


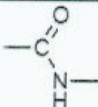
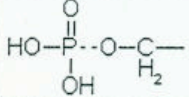
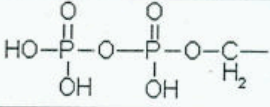
Oxidative decarboxylation of isocitrate:

1. Alcohol on C2 on isocitrate oxidized to a keto group. Coupled to reduction of NAD^+ to NADH
 2. Intermediate formed is oxalosuccinate – unstable and spontaneously loses CO_2 (decarboxylation)
- So, two reactions: Oxidation – reduction & Non-hydrolytic cleavage of a C-C bond

TYPES OF FUNCTIONAL GROUPS INVOLVED IN BIOCHEMICAL REACTIONS

Fundamental structural components of biomolecules

Functional Groups

Structure	Name	Structure	Name
	Acid		Aldehyde
	Alcohol		Ketone
	Ether (alcohol + alcohol)		ester (acid + alcohol)
	Anhydride (acid + acid)		Mercaptan
	Amine		Amide (acid + amine)
	Phosphoester		Phosphoanhydride