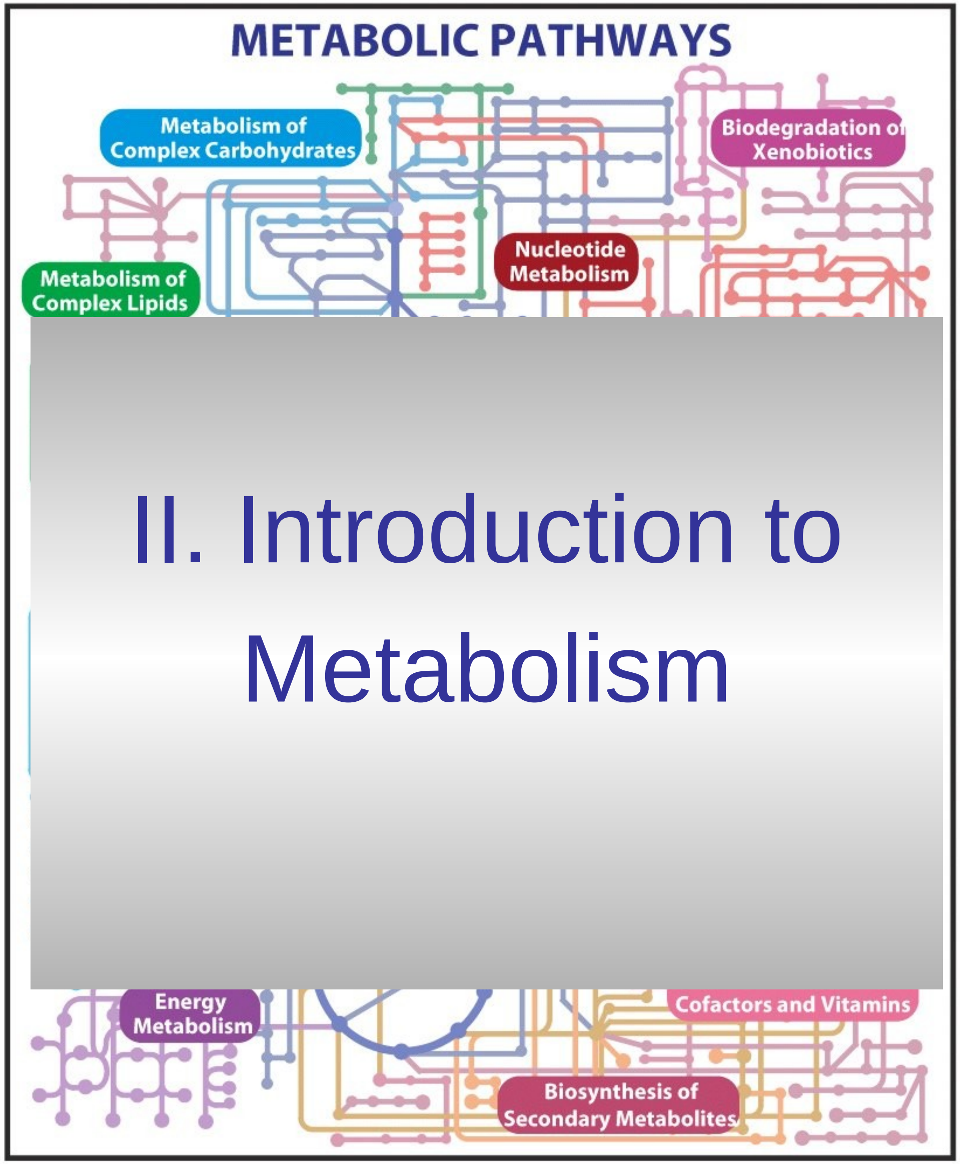
Department of Chemistry and Biochemistry
University of Lethbridge



II. Introduction to Metabolism

Metabolism

Metabolism is the overall process through which living systems acquire and utilize the free energy they need to carry out various functions.

Living organisms are not at equilibrium

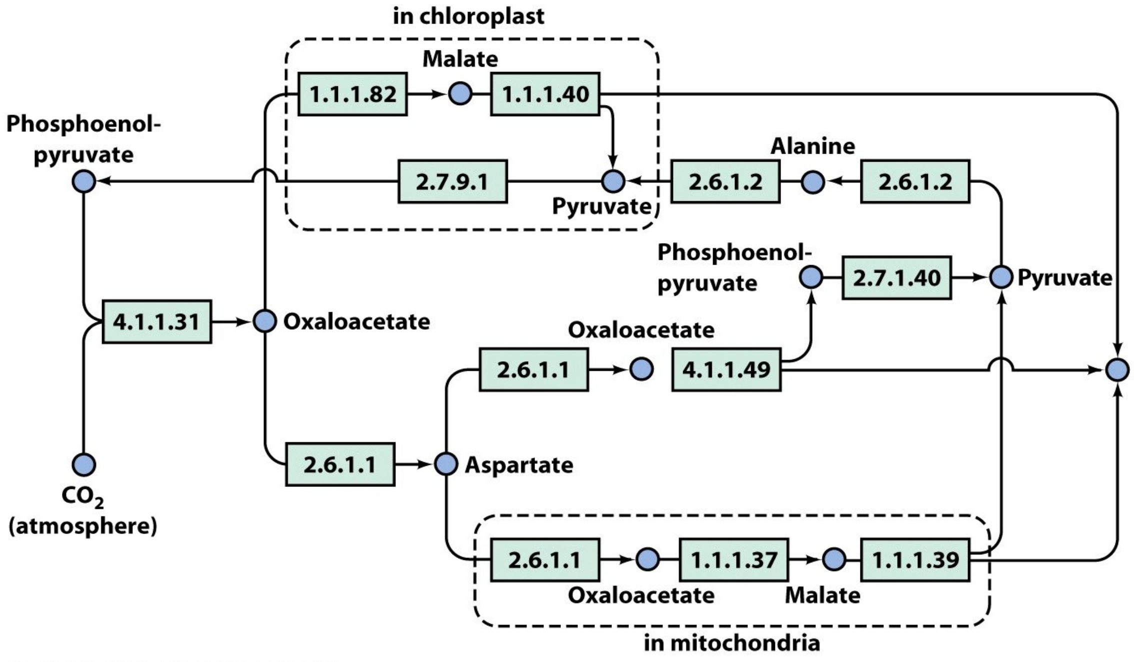
How do living organisms acquire the necessary free energy?

Phototrophs : plants and certain bacteria utilize 'light energy'
Chemotrophs: use organic compounds from other organisms

Living organisms are at a steady state

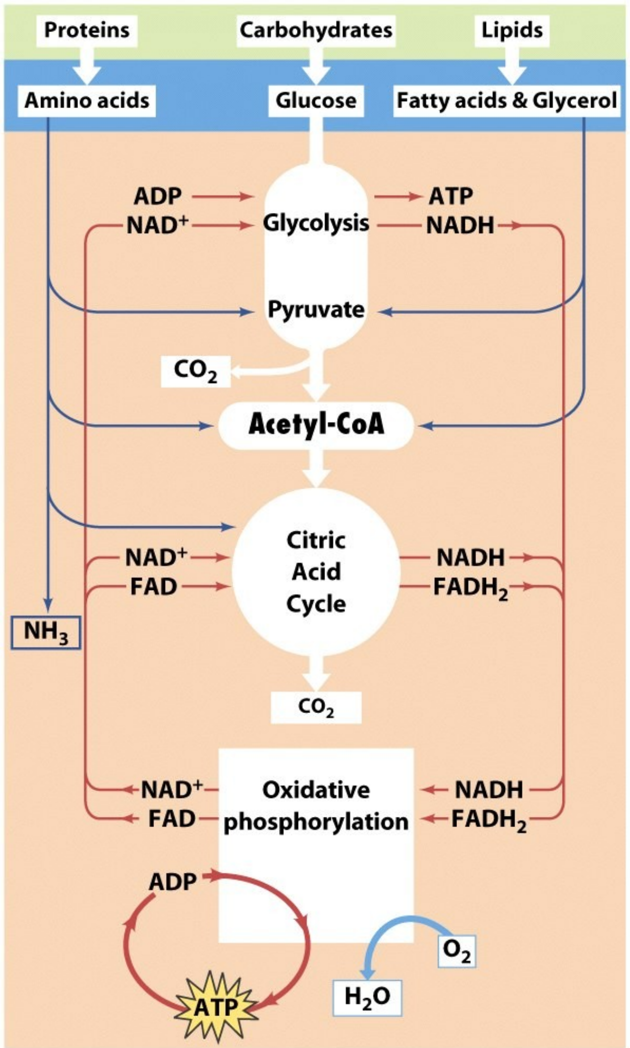
Metabolic Pathways

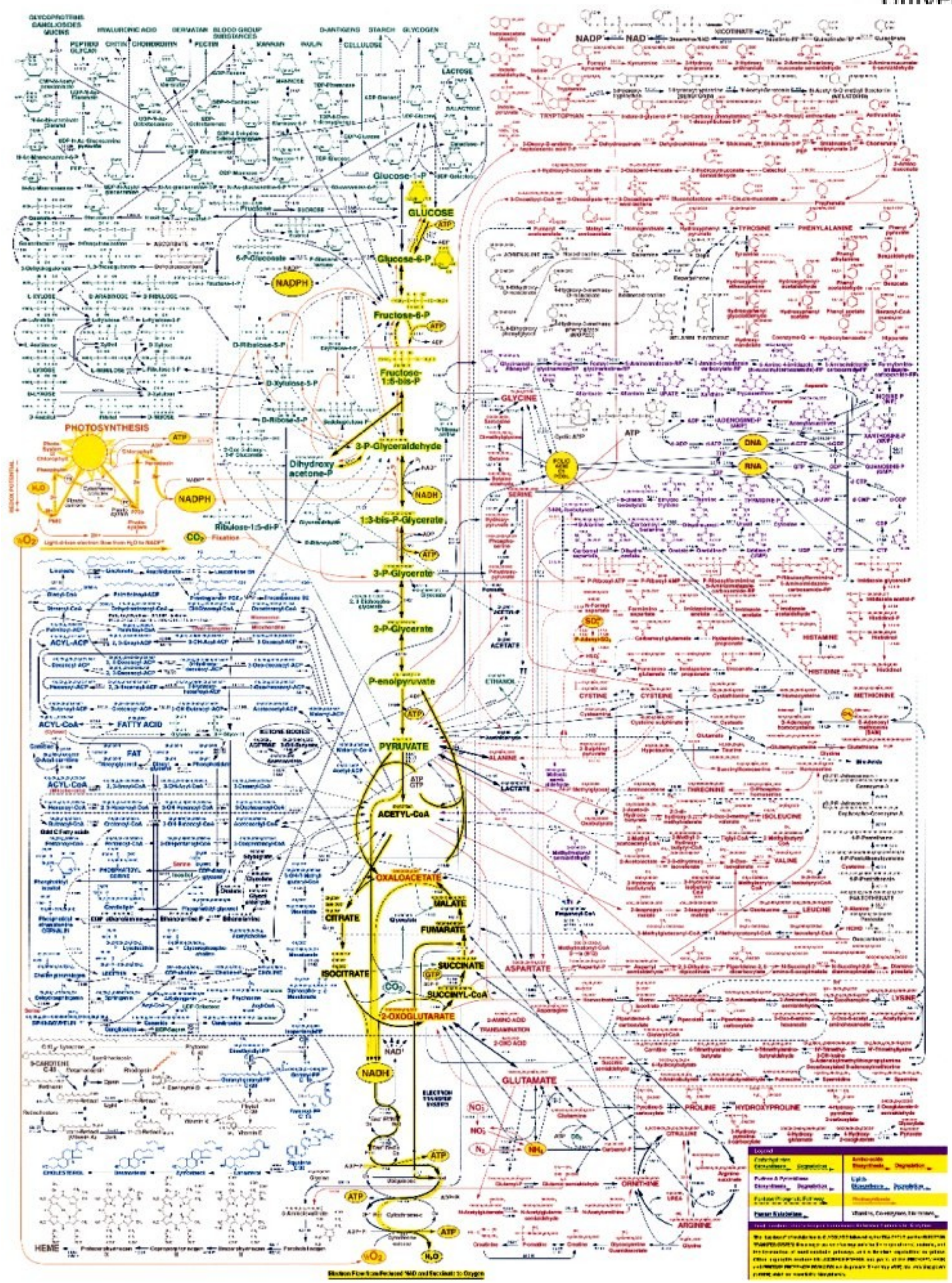
Metabolic pathways are series of consecutive enzymatic reactions that produce specific products.



Reactants, intermediates and products are referred to as metabolites.

And they can be pretty complex ….



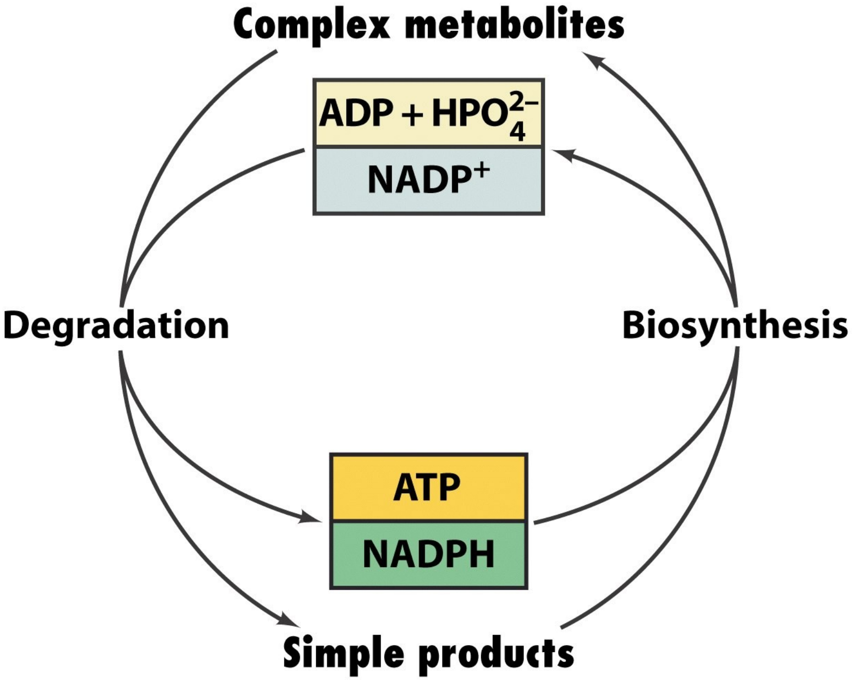


Reaction Pathways

Reaction Pathways that comprise metabolism are often divided in:

1. Catabolism – the degradation of nutrients and cell constituents to salvage components and/or generate free energy.

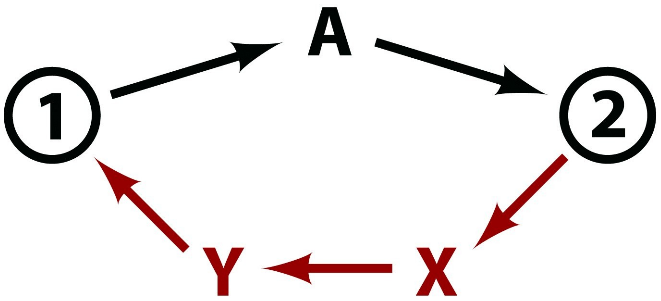
2. Anabolism - biosynthesis of biomolecules from simpler components.



Metabolic Pathways

Four principal characteristics of metabolic pathways:

1) Metabolic pathways are **irreversible**
2) Catabolic and anabolic pathways **must differ**



3) Every metabolic pathway has a **first committing step**
4) All metabolic pathways are **regulated**

Additional characteristic of eucaryotic metabolic pathways:

Occur in **specific cellular locations**

Eucaryotic Metabolic Pathways

Organelle	Major functions
Mitochondrion	Citric acid cycle, oxidative phosphorylation, fatty acid oxidation, amino acid breakdown
Cytosol	Glycolysis, pentose phosphate pathway, fatty acid biosynthesis, many reactions of gluconeogenesis
Lysosomes	Enzymatic digestion of cell components and ingested matter
Nucleus	DNA replication and transcription, RNA processing
Golgi apparatus	Posttranslational processing of membrane and secretory proteins; formation of plasma membrane and secretory vesicles
Rough endoplasmic reticulum	Synthesis of membrane-bound and secretory proteins
Smooth endoplasmic reticulum	Lipid and steroid biosynthesis
Peroxisomes (glyoxysomes in plants)	Oxidative reactions catalyzed by amino acid oxidases and catalase; glyoxylate cycle reactions in plants

Pathways on the Web

http://www.genome.ad.jp/kegg/pathway.html

KEGG PATHWAY Database

Wiring diagrams of molecular interactions, reactions

KEGG2 KID PATHWAY BRITE GENES SSDB LIGAND

Pathway Maps

KEGG PATHWAY is a collection of manually drawn pathway maps representin
the molecular interaction and reaction networks for:

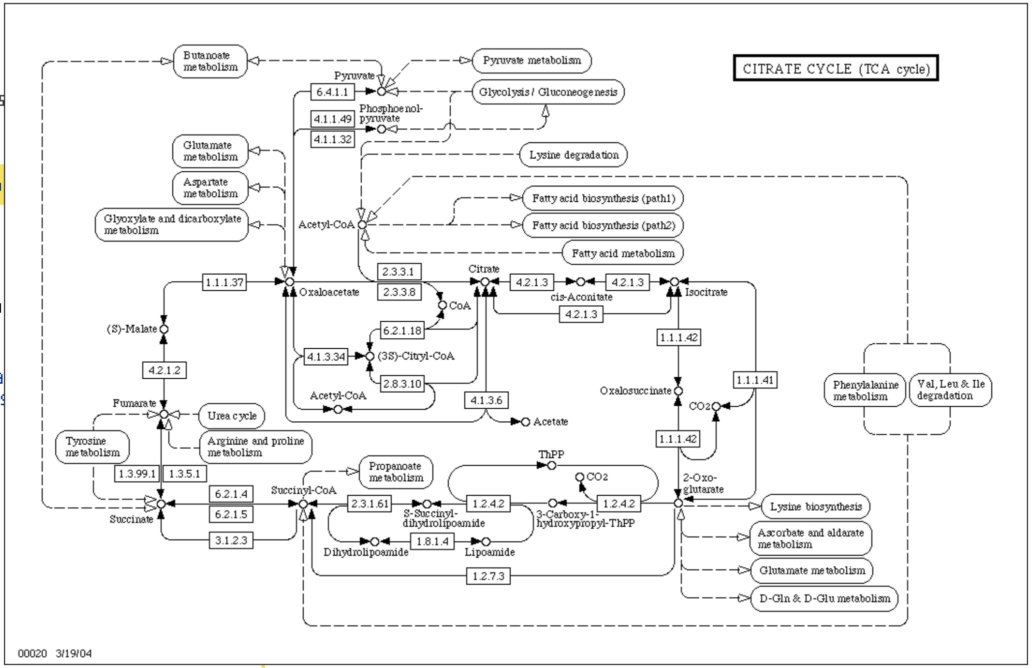
1. **Metabolism**
   Carbohydrate Energy Lipid Nucleotide Amino acid Other amino a
   Glycan PK/NRP Cofactor/vitamin Secondary metabolite Xenobiotics
2. **Genetic Information Processing**
3. **Environmental Information Processing**
4. **Cellular Processes**
5. **Human Diseases**

and also on the structure relationships (KEGG drug structure maps) in:

6. **Drug Development**

Search PATHWAY **for** Go Clear

bfind mode bget mode



1. Metabolism

1.1 Carbohydrate Metabolism

Glycolysis / Gluconeogenesis
Citrate cycle (TCA cycle)
Pentose phosphate pathway
Pentose and glucuronate interconversions
Fructose and mannose metabolism
Galactose metabolism

KEGG Orthology (KO)

KEGG pathway modules
Overview of biosynthetic pathways

Enzymes (+diseases)

Organic Reaction Mechanisms

Almost all reactions (in metabolism) are enzyme catalyzed organic reactions.

ie. same chemical mechanism as non-enzyme catalyzed reaction

Knowledge of organic reaction mechanism aids understanding of biochemical reactions

Note: some enzymes do alter the chemical mechanism of reactions so there is a limit to what can be learned from non-enzymatic model reactions

Classification of biochemical reactions*:

(1) group-transfer reactions (including hydrolysis)
(2) oxidation and reductions
(3) eliminations (eg. lyases and isomerases)
(4) reactions that make or break carbon-carbon bonds

*** Christopher Walsh (similar but not identical to the EC numbering of enzymes)**

Basic Chemistry (review)

CHEMICAL LOGIC

Covalent bonds involve the sharing of an electron pair between two atoms

Breaking a covalent bond can be accomplished in two basic ways:

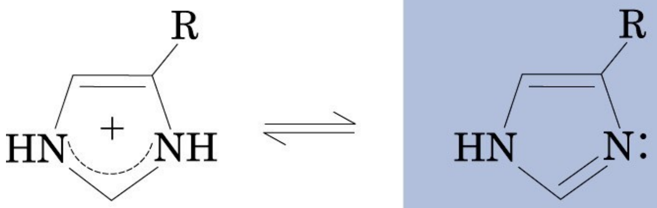
1) heterolytic bond cleavage (electron pair remains with one of the two atoms)
   - normal case
2) homolytic bond cleavage (electron pair separates with one electron per atom)
   - primarily oxidation:reduction reactions

Heterolytic bond cleavage reactions always involve a nucleophile (electron rich) and an electrophile (electron deficient)

Basic Chemistry (review)

Nucleophilic groups important in enzyme catalyzed reactions

ie. groups participating in heterolytic bond cleavage and formation

Amino acid residue			Nucleophilic form		
S, T, Y	$R\ddot{O}H$	$\rightleftharpoons$	$R\bar{O}:$	$+ H^+$	**Hydroxyl group**
C	$R\ddot{S}H$	$\rightleftharpoons$	$R\bar{S}:$	$+ H^+$	**Sulfhydryl group**
K, R	RNH_3^+	$\rightleftharpoons$	$R\ddot{N}H_2$	$+ H^+$	**Amino group**
H				$+ H^+$	**Imidazole group**

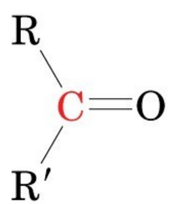
Basic Chemistry (review)

Electrophilic groups important in enzyme catalyzed reactions

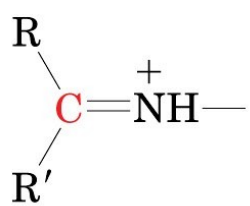
ie. groups participating in heterolytic bond cleavage and formation

H^{+} **Protons**

M^{n+} **Metal ions**



Carbonyl carbon atom



Cationic imine (Schiff base)

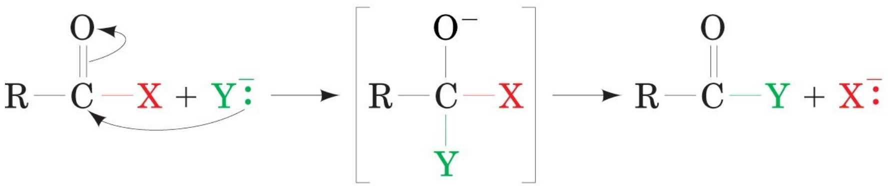
Classes of Biochemical Reactions

1) Group-transfer Reactions

Group transfer and hydrolysis reactions in biological systems transfer an electrophile from one nucleophile to another.

Note: combines both transferase and hydrolase groups of EC system

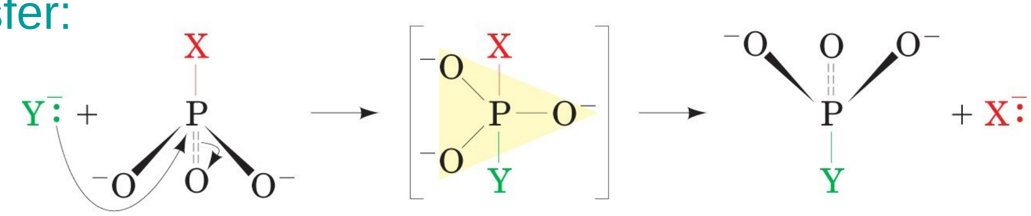
eg. A) Acyl group transfer:



Tetrahedral intermediate

X, Y nucleophiles
Black electrophile

eg. B) Phosphoryl group transfer:

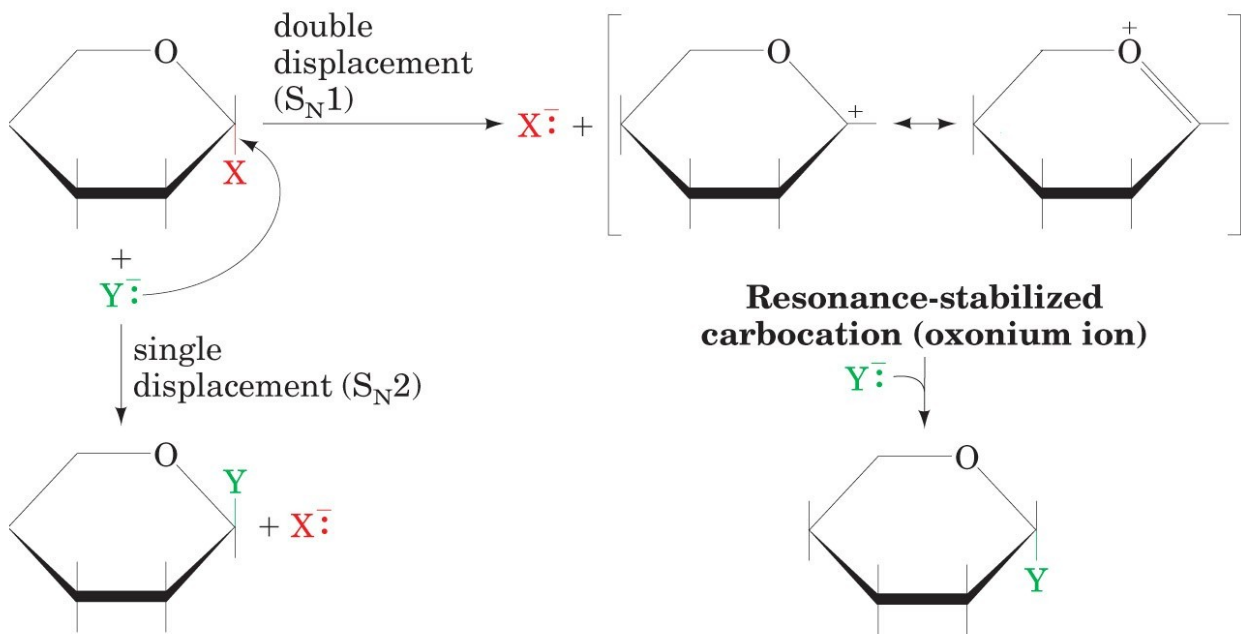


Trigonal bipyramid intermediate

Classes of Biochemical Reactions

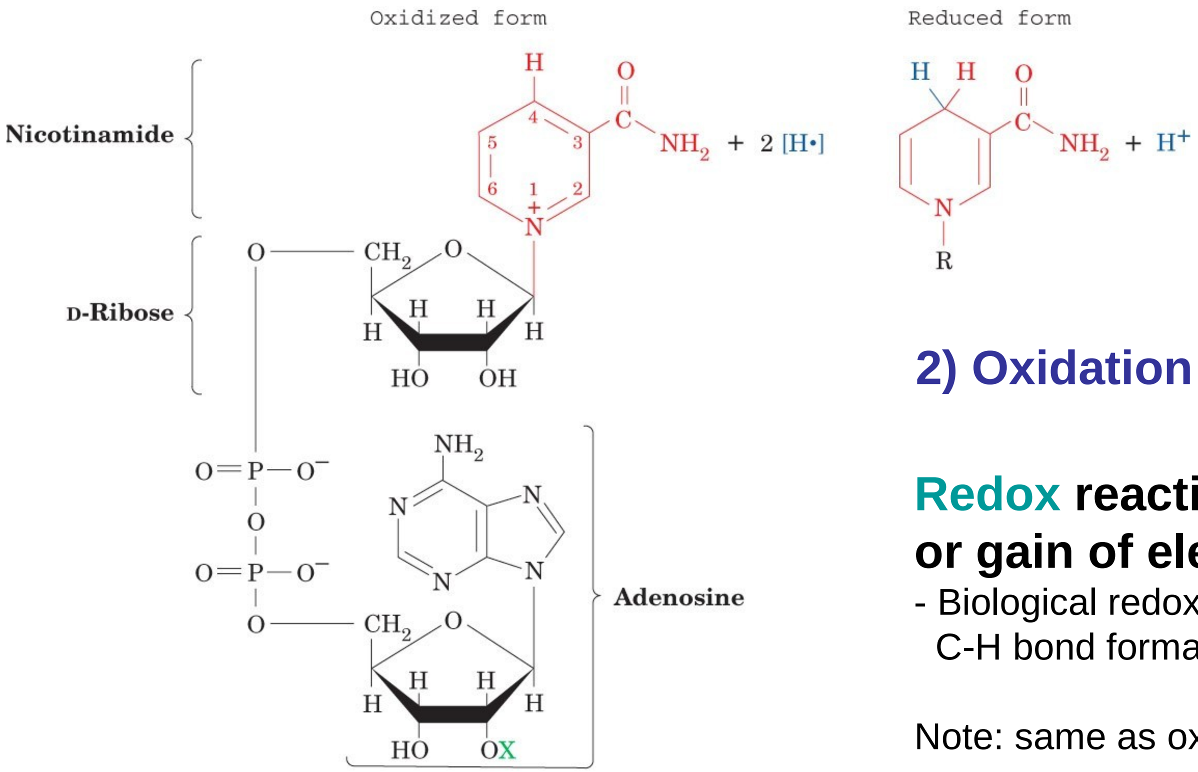
Group-transfer Reaction (cont.)

eg. 3) Glycosyl group transfer:



X, Y nucleophiles
Black electrophile

Classes of Biochemical Reactions



X = H Nicotinamide adenine dinucleotide (NAD^+)
X = PO_3^{2-} Nicotinamide adenine dinucleotide phosphate ($NADP^+$)

2) Oxidation and Reductions:

Redox reactions involve the loss or gain of electrons

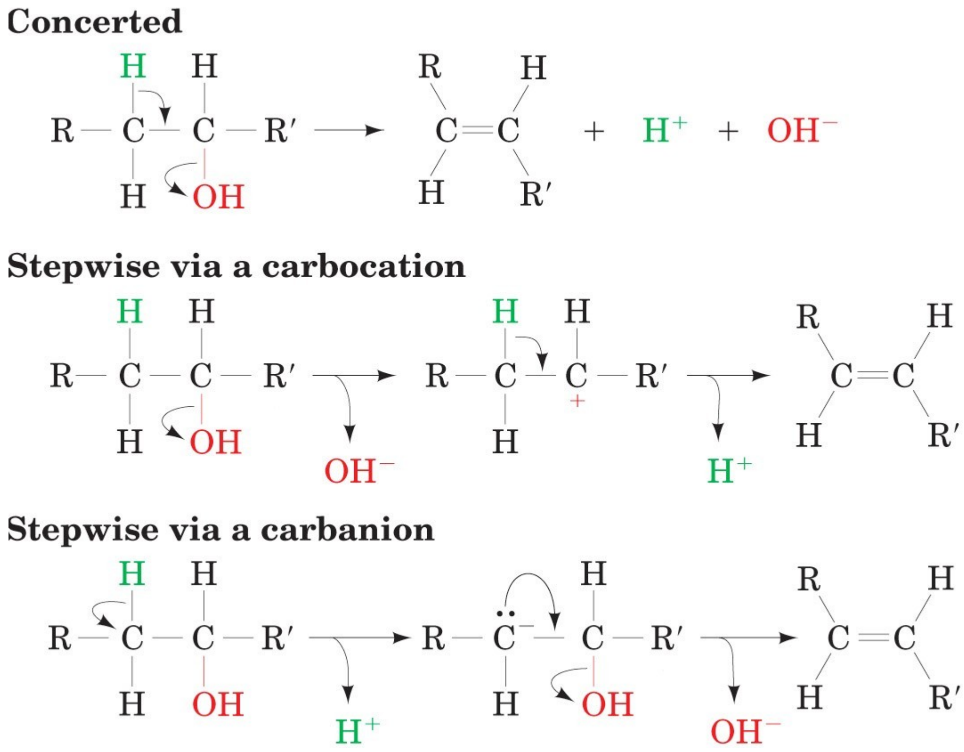
- Biological redox reactions often involve C-H bond formation/cleavage

Note: same as oxidoreductases in EC system

Classes of Biochemical Reactions

3) Eliminations, Isomerizations, and Rearrangements:

Elimination Reactions form double bonds



Virtually all biochemical elimination reaction mechanisms proceed via

1) acid catalysis
   (carbocation intermediate)

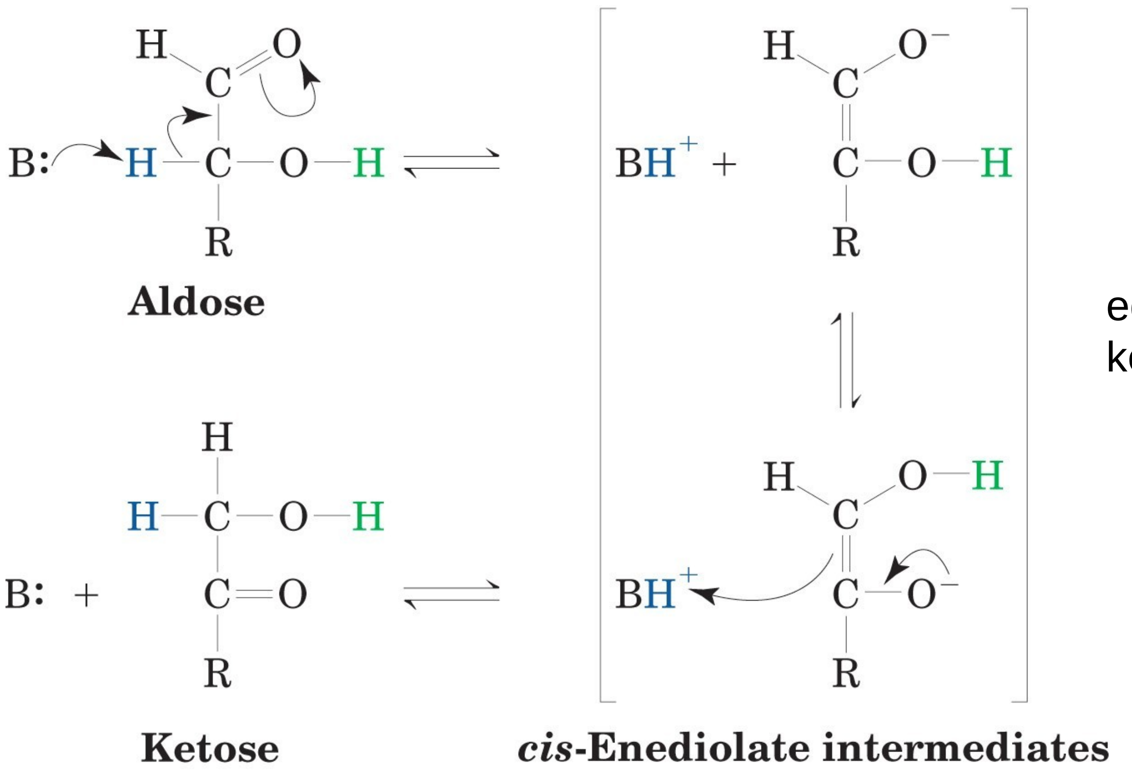
2) base catalysis
   (carbanion intermediate)

(or acid-base catalysis)

Classes of Biochemical Reactions

3) Eliminations, Isomerizations, and Rearrangements:

Isomerizations involve intramolecular hydrogen atom shifts

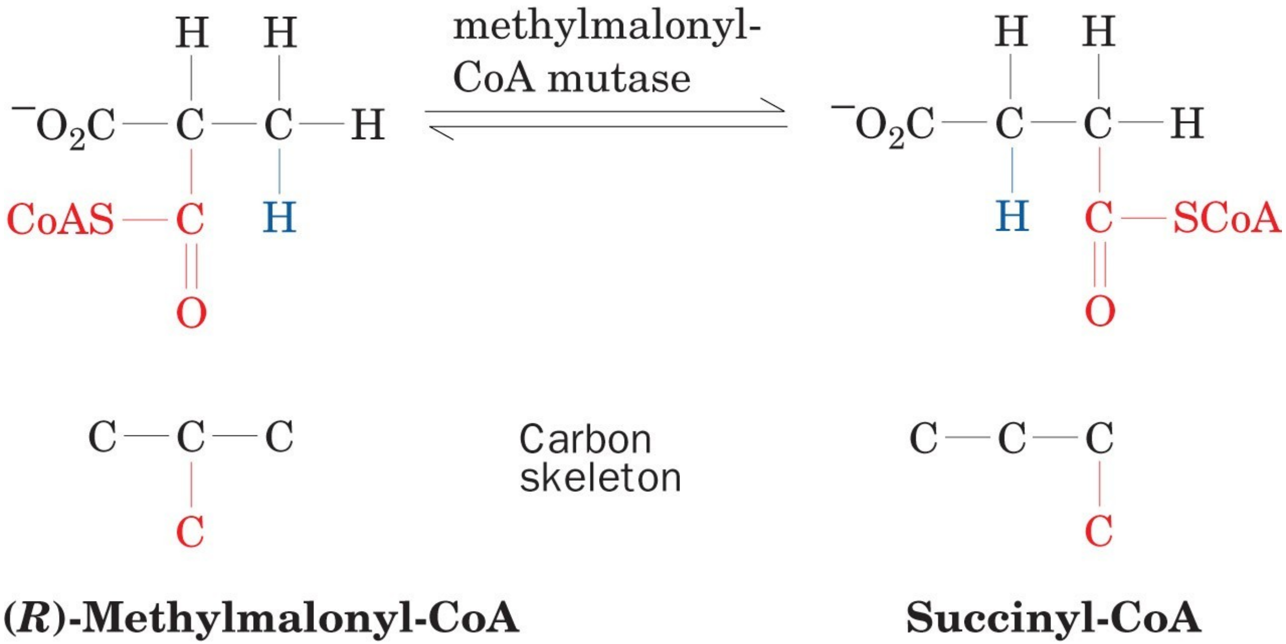


eg. Base catalyzed aldose to ketose isomerization

Classes of Biochemical Reactions

3) Eliminations, Isomerizations, and Rearrangements:

Rearrangements produce altered carbon Skeletons

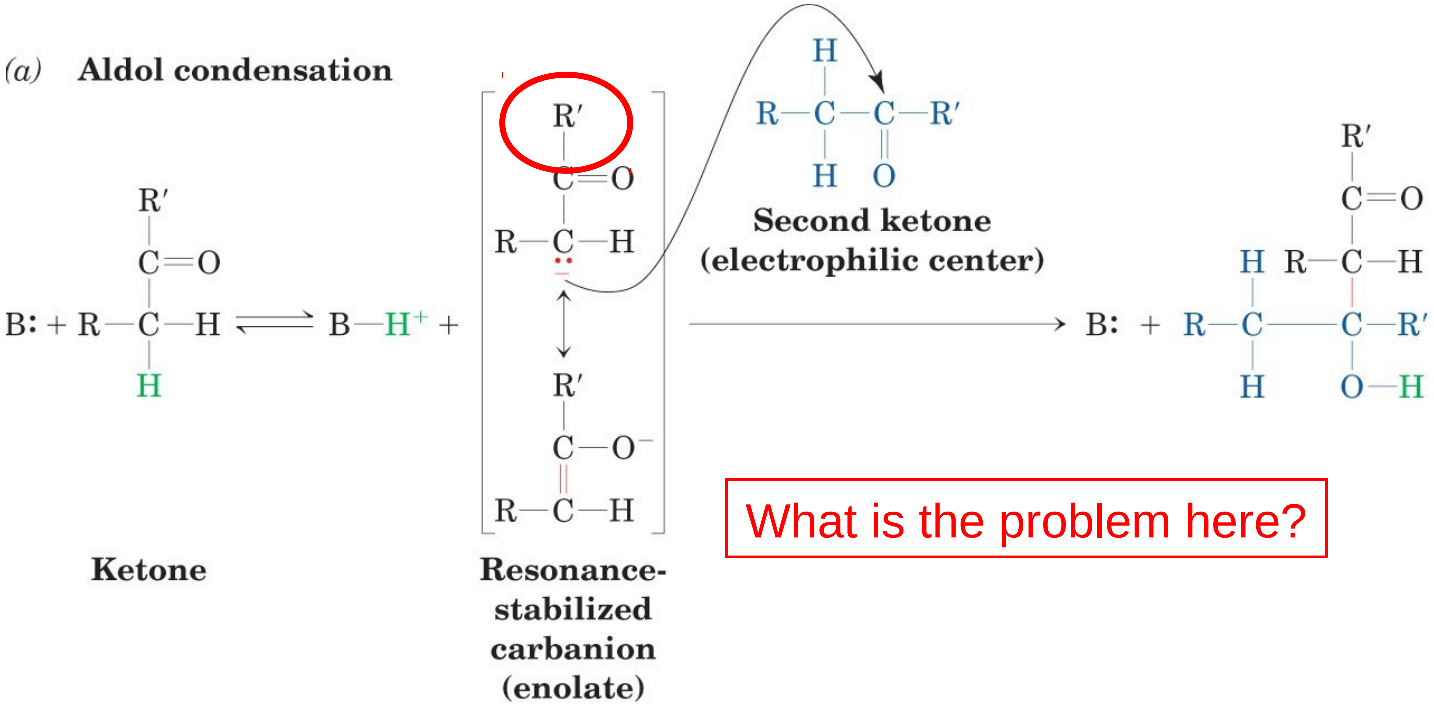


Classes of Biochemical Reactions

4) Reaction making and breaking C-C bonds:

These reactions form the basis of both degradative and biosynthetic metabolism.

Example:



What is the problem here?

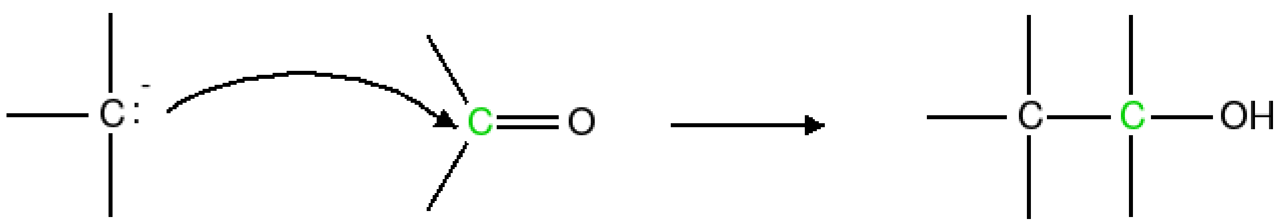
Classes of Biochemical Reactions

4) Reaction making and breaking C-C bonds:

These reactions form the basis of both degradative and biosynthetic metabolism.

Reactions that make C-C bonds involve the addition of a nucleophilic carbanion to an electrophilic C atom (breaking C-C bonds is simply the reverse)

In almost all cases, the electrophilic C is an *sp*^{2}-hybridized carbonyl carbon of aldehydes, ketones, esters and CO_2



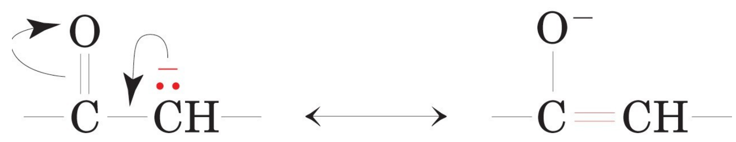
Stabilization of the nucleophilic carbanion is an essential component of these reaction types

Classes of Biochemical Reactions

4) Reaction making and breaking C-C bonds:

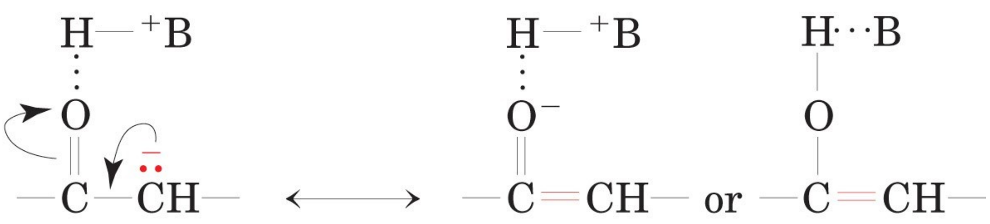
eg. formation of enolates → charge delocalization

Carbanion intermediate must be stabilized to enhance reaction rates



Carbanion **Enolate**

eg. H bond from a general acid (electrostatic stabilization)



Hydrogen-bonded carbonyl

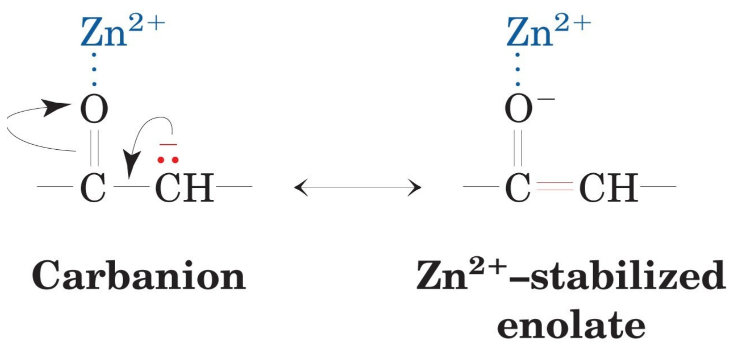
Hydrogen-bonded enolate or enol

Note:
Stabilizing enolate

Classes of Biochemical Reactions

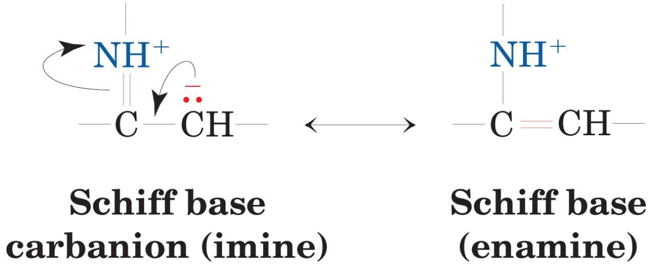
More stabilization of carbanions:

eg. metal ion interaction (electrostatic stabilization)



Equivalent to H bond
from general acid

eg. formation of enamines
→ charge delocalization



Equivalent to
'formation of enolates'