Chem 352 - Lecture 9
Chemical Logic of Metabolism

Question for the Day: *How is metabolism like a flowing river?*

Or as Heraclitus (c. 535 - 475 BCE) said

"Πάντα χωρεῖ καὶ οὐδὲν μένει" καὶ "δὶς ἐς τὸν αὐτὸν ποταμὸν οὐκ ἂν ἐμβαίης"

"*Everything changes and nothing remains still ... and ... you cannot step twice into the same stream*"

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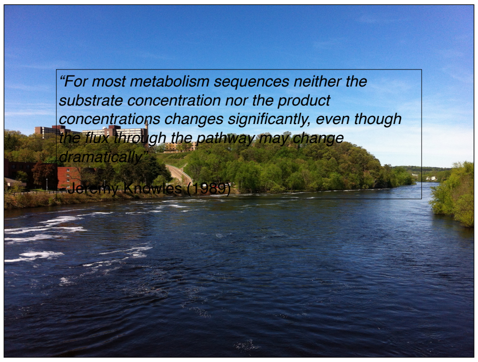

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11.1 A First Look at Metabolism

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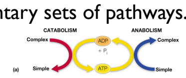
Metabolism

Metabolism is divided into two complimentary sets of pathways.



- ***Anabolic pathways*** (anabolism)
  - The synthetic reactions, which usually require an input in free energy.
- ***Catabolic pathways*** (catabolism)
  - The degradative reactions, which usually lead to a release of free energy.
- Some pathways can do both
  - These are called ***amphibolic pathways***.

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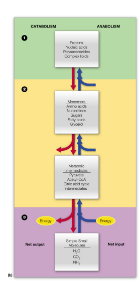
Metabolism

Both catabolic and anabolic pathways can be subdivided into three states

- Stage 1: Interconversion of polymers and complex lipids with monomeric intermediates
- Stage 2: Interconversion of monomeric sugars, amino acids, and lipids with still simpler organic compounds.
- Stage 3: Ultimate degradation to, synthesis from, inorganic compounds, include CO_2, H_2O, and NH_3.



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Metabolism

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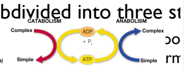

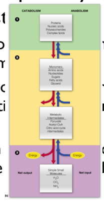

- St… …po… …mplex lip… …rm…
- Stage 2: Interconversion of mo… …s, amino acids, and lipids with sti… …nic compounds.
- Stage 3: Ultimate degradation … …om, inorganic compounds, include … …l NH_3.

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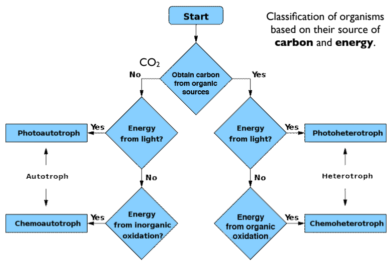
Autotrophs *vs.* Heterotrophs



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11.2 Freeways on the Metabolic Road Map

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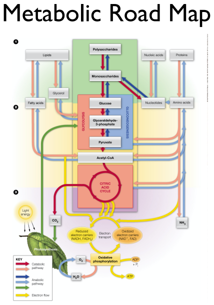
Metabolic Road Map



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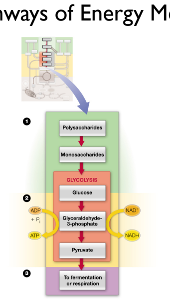
Central Pathways of Energy Metabolism

Glycolysis:



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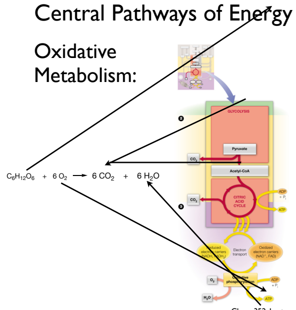
Central Pathways of Energy Metabolism

Oxidative Metabolism:



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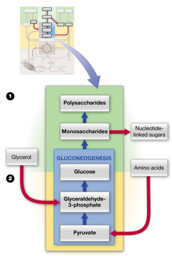
Central Pathways of Energy Metabolism

Gluconeogenesis:



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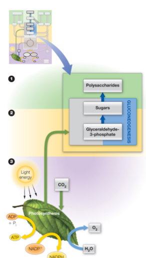
Central Pathways of Energy Metabolism

Photosynthesis:



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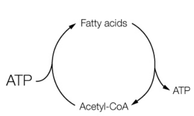
Central Pathways of Energy Metabolism

While the catabolic and anabolic pathways may share some reactions, their overall pathways are distinct from one another.

- This is necessary in order to prevent what is known as futile cycling.



Futile cycle

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11.3 Biochemical Reaction Types

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Biochemical Reaction Types

Five types of chemical transformations are commonly found in living systems (cells):

1. Nucleophilic substitutions
2. Nucleophilic additions
3. Carbonyl condensations
4. Eliminations
5. Oxidations/reductions

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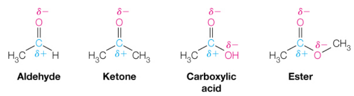
Nucleophilic Substitutions

The chemistry of the carbonyl group is predominant because so many biological molecules contain this group.



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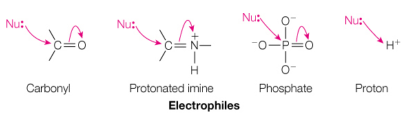
Nucleophilic Substitutions

The carbonyl group along with other groups can serve as an electrophiles in nucleophilic reactions.



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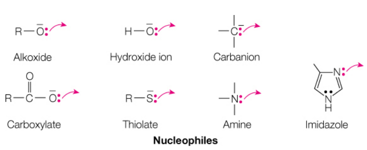
Nucleophilic Substitutions

Some common nucleophiles include,



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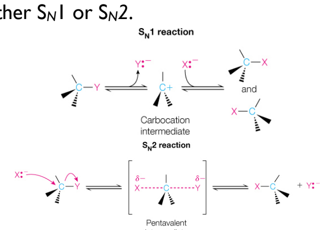
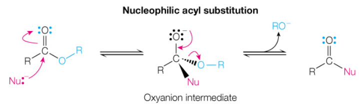
Nucleophilic Substitutions

Nucleophilic substitution reactions can be either S_N1 or S_N2.



Nucleophilic Substitutions

For example, the acyl substitution involves an S_N2 reaction.



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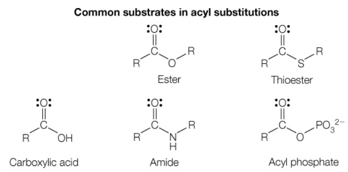
Nucleophilic Substitutions

Some common substrates for acyl substitutions include,



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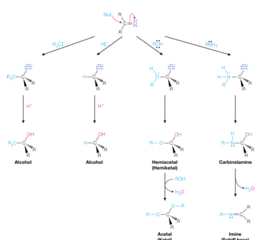
Nucleophilic Additions

Carbonyl carbons are well suited for addition reactions because the adjacent C or H is not a good leaving group.



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Carbonyl Condensations

Carbonyl condensations involving the condensation between two carbonyl-containing compounds can be used to make C—C bonds.

- ***Aldol Condensations*** involve the addition of an aldehyde or ketone to an aldehyde to produce a β-hydroxy aldehyde or ketone.
- ***Claisen Condensations*** involve the addition of an aldehyde or ketone to an ester to produce a β-keto aldehyde or ketone.

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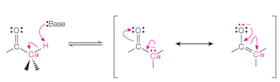
Carbonyl Condensations

Carbonyl condensations involving the condensation between two carbonyl-containing compounds can be used to make C—C bonds.

- For both, an enolate stabilized carbanion nucleophile is produced from the aldehyde or ketone.



Resonance-stabilized enolate ion

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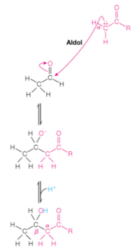
Carbonyl Condensations

Aldol Condensations: involve the addition of an aldehyde or ketone to an aldehyde to produce a β-hydroxy aldehyde or ketone



β-hydroxy product

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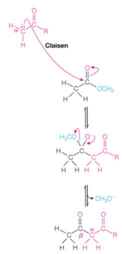
Carbonyl Condensations

Claisen Condensations: involve the addition of an aldehyde or ketone to an ester to produce a β-keto aldehyde or ketone.



β-keto product

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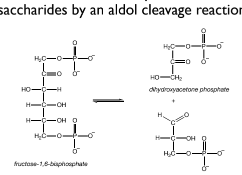
Carbonyl Condensations

Aldol and Claisen condensations are reversible as retro-also and retro-Claisen reactions.

- In glycolysis we will see an example when the 6-carbon monosaccharide is split into two 3-carbon monosaccharides by an aldol cleavage reaction.



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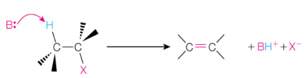
Eliminations

Elimination reactions lead to the formation of a double bond.

Elimination reaction



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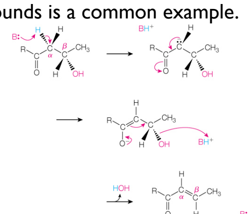
Eliminations

The dehydration of β-hydroxy carbonyl compounds is a common example.



α,β-elimination reaction

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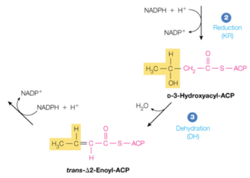
Eliminations

In fatty acid biosynthesis there is an example of a dehydration of β-hydroxy carbonyl compound.



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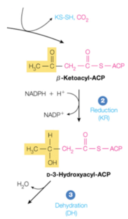
Oxidation and Reduction

Most often we will see these as the addition (hydrogenation) or removal (dehydrogenation) of H_2.

- The H_2 is transferred as $H^+ + :H^-$
- A common redox reagent in these reactions is NAD^+ or $NADP^+$



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11.4 Bioenergetics of Metabolic Pathways

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Oxidation as a Metabolic Energy Source

Concomitant with the ready supply of oxygen in our atmosphere, oxidation reactions have become a major source of energy for many organisms.

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Oxidation as a Metabolic Energy Source

The oxidation of glucose for energy, will be a major focus for our discussions.

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O \qquad \Delta G^{\circ\prime} = -2870 \text{ kJ/mol}$$

- When burned, most of this free energy is released as heat, which can be measured using a calorimeter.
- When metabolized, about 40% of the free energy is coupled to the phosphorylation of ADP to produce ATP.
  - This will involve carrying out this overall reaction a number of tiny steps.

Oxidation as a Metabolic Energy Source

The oxidation of glucose for energy, will be a major focus for our discussions.

- When metabolized, the electrons from the intermediates are not transferred directly to O_2 to produce H_2O, but rather, are transferred to the intermediate carriers, NAD^+ and FAD^+.
- These carriers are deoxidized in the electron transport chain, where O_2 will be the terminal electron acceptor.

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Oxidation as a Metabolic Energy Source

The oxidation of glucose for energy, will be a major focus for our discussions.

- For anaerobic organisms that cannot utilize O_2, we will see that fermentation pathways can lead to a small production of ATP from the breakdown of glucose.

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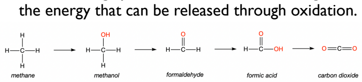
Oxidation as a Metabolic Energy Source

Other substrates, such as fatty acids, can also be oxidized as a metabolic energy source.

- The more highly reduced a substrate is, the greater the energy that can be released through oxidation.



- Palmitic acid ($C_{16}H_{32}O_2$) $\Delta G^{\circ\prime} = -38.9\ \frac{\text{kJ}}{\text{g}}$

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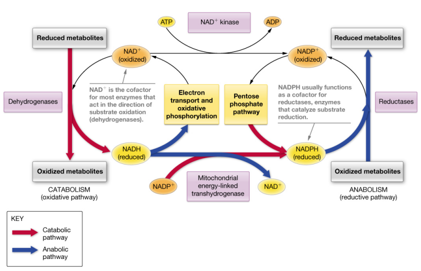
Oxidation as a Metabolic Energy Source



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Oxidation as a Metabolic Energy Source

ATP is commonly referred to as the "free energy currency", as it provides a means of exchanging free energy from reactions and processes the release free energy to those that require it.

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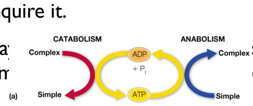

- A quantity approximately equal to their body weight.

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ATP

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TABLE 10.1 Standard Gibbs free energies of hydrolysis for ATP, AMP, and pyrophosphate.

Reactants and products	Hydrolysis of	$\Delta G^{\circ\prime}_{hydrolysis}$ ($kJ\ mol^{-1}$)
$ATP + H_2O \rightarrow ADP + P_i + H^{\oplus}$	Phosphate Anhydride	−32
$ATP + H_2O \rightarrow AMP + PP_i + H^{\oplus}$	Phosphate Anhydride	−45
$AMP + H_2O \rightarrow Adenosine + P_i$	Phosphate Ester	−13
$PP_i + H_2O \rightarrow 2\ P_i$	Phosphate Anhydride	−29

P_i (inorganic phosphate) = HPO_4^{2-}

PP_i (pyrophosphate) = $HP_2O_7^{3-}$

Inorganic phosphate (P_i) Inorganic pyrophosphate (PP_i)

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ATP

Adenosine Triphosphate (ATP) is just one of the molecules used by a cell to store chemical energy.

- The other ribonucleotide triphosphates are also used for this same purpose.
  - Guanosine triphosphate (GTP)
  - Cytidine triphosphate (CTP)
  - Uridine triphosphate (UTP)

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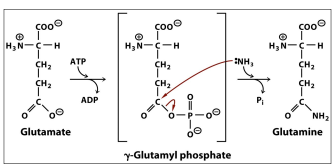
ATP

The energy released by the hydrolysis of ATP can be used to drive unfavorable reactions.

- For example, the conversion of the amino acid glutamate to glutamine.



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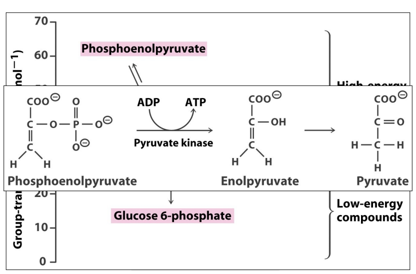
ATP



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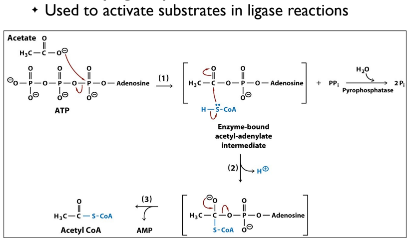
ATP

Nucleotidyl group transfer

- Used to activate substrates in ligase reactions



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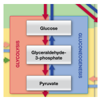
Kinetic Control of Metabolic Pathways

In glycolysis and gluconeogenesis, there is substrate cycling between fructose-6-phosphate and fructose-1,6-bisphoshate.



Both of these reactions are favorable at both standard state and under physiological conditions

	Reaction	$\Delta G°'$	K	ATP coupling coefficient
glycolysis	Fructose-6-phosphate + ATP ⟶ fructose-1,6-bisphosphate + ADP (PFK)	−14.2	308	−1
gluconeogenesis	Fructose-1,6-bisphosphate + H_2O ⟶ fructose-6-phosphate + P_i (FBPase)	−16.3	719	0
	Net: ATP + H_2O → ADP + P_i			

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Kinetic Control of Metabolic Pathways

In [illegible] pre[illegible] tha[illegible] equ[illegible]e.

Reaction	$\Delta G°'$	K	ATP coupling coefficient
Fructose-6-phosphate + ATP ⟶ fructose-1,6-bisphosphate + ADP (PFK)	−14.2	308	−1
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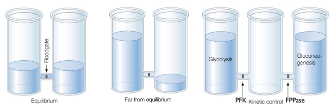
Net: ATP + H_2O → ADP + P_i			



For a reaction at equilibrium, turning off or on an enzyme will have little effect

For a reaction far from equilibrium, turning off or on an enzyme has a much greater effect

By coordinately controlling the enzymes PFK and FBPase, the glycolytic and gluconeogenic pathways are coordinately regulated.

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11.5 Major Metabolic Control Mechanisms

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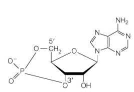
Metabolic Control Mechanisms

There are an array of regulatory strategies in controlling metabolism

- Control of enzyme levels (genetic regulation)
- Control of enzyme activity: substrate-level, allosteric, covalent modification
- Signal transduction (hormones, growth factors): intercellular control often exercised through action of a second messenger such as cyclic-AMP (the hormone is the first messenger)



Adenosine-3′,5′-cyclic monophosphate (cyclic AMP)

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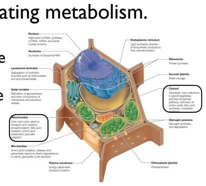
Metabolic Control Mechanisms

Compartmentalizing metabolic pathways to particular locations in a cell is another strategy used for regulating metabolism.

- For example, fatty acid biosynthesis occurs in the cytosol, while fatty acid degradation occurs in the mitochondria



Next Up

Lecture 10, Part I - Carbohydrate Metabolism:

- Glycolysis
- Gluconeogenesis
- Glycogen Metabolism
- Pentose Phosphate Pathway