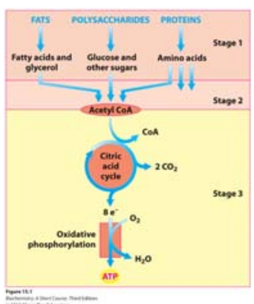
Basic Concepts of Metabolism

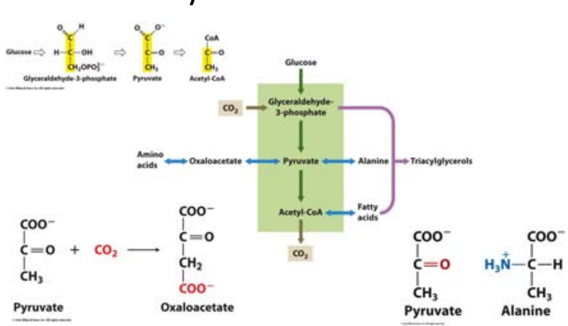
Chapter 15, Stryer Short Course

Stages of Catabolism

- Digestion
- Formation of key intermediate small molecules
- Formation of ATP

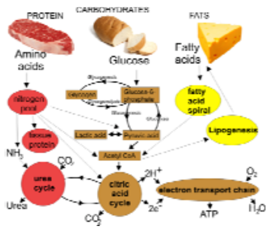


Key intermediates



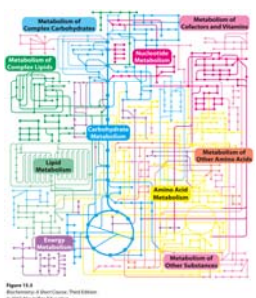
Fundamental Needs for Energy

- Three needs
  - Movement
  - Active transport of molecules and ions
  - Biosynthesis
- Complex, but understood in terms of key principles



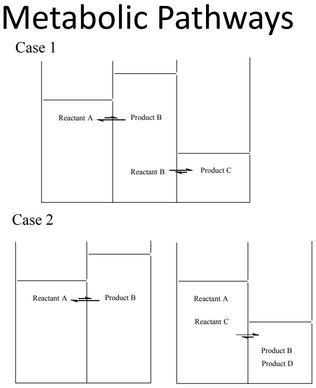
Metabolism

- Interlocking reactions in a pathway
- Catabolism
- Anabolism



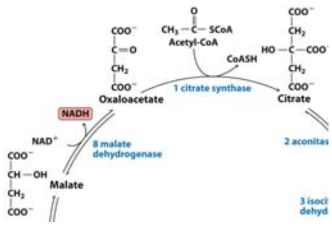
Energetics of Metabolic Pathways

- Unfavorable reactions can be driven by
  - 1. Coupling to subsequent spontaneous reaction
  - 2. Energy input (change reaction)



Case 1: Conceptual Understanding

- Basically, this is LeChatlier’s Principle
- Control of flux—change concentrations



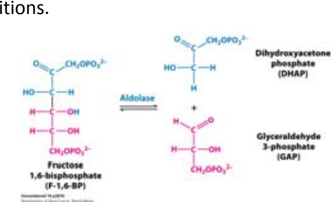
Common Motif: Link to pyrophosphate

- The standard free energy of formation of UDP-glucose from G-1-P and UTP is about zero. Yet the production of UDP-glucose is highly favorable. Explain.

Glucose-1-phosphate + UTP ←→ UDP-glucose + PP_i

Case 1: Quantitative Understanding

(Problem 30) The enzyme aldolase catalyzes the reaction below, with a standard free energy of +23.8 kJ/mol. The free energy of the reaction under cellular conditions is -1.3 kJ/mol. Calculate the ratio of reactants to products under equilibrium and cellular conditions. Explain how the reaction can be endergonic under standard conditions, but exergonic under cellular conditions.



Problem 14

The formation of acetyl CoA from acetate is an ATP-driven process:

Acetate + ATP + CoA → acetyl CoA + AMP + PP_i

If the standard free energy of ATP hydrolysis to AMP is -45.6 kJ/mol, and hydrolysis of acetylCoA is -31.4 kJ/mol, what is the standard free energy for this reaction? This reaction is coupled to the hydrolysis of Ppi, with a standard free energy of -19.3 kJ/mol. What is the standard free energy of the coupled reaction? How does the fact that pyrophosphate is constantly hydrolyzed in the cell affect the energetics of formation of acetyl CoA?

Case 2: ATP in Metabolism

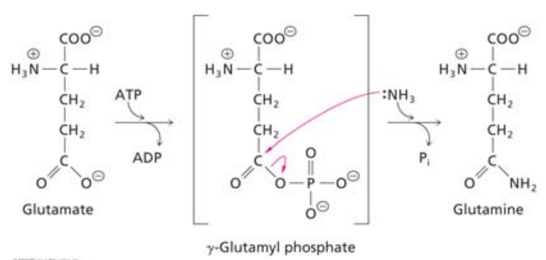
- Overcoming a barrier...
  - Can't change concentrations (ammonia is toxic!)

$$\text{Glutamate} + NH_4^{\oplus} \rightleftharpoons \text{glutamine} + H_2O$$

$$\Delta G^{\circ\prime}_{\text{reaction}} = +14 \text{ kJ mol}^{-1}$$

  - Change the whole reaction by directly coupling it to a spontaneous reaction: ATP hydrolysis
  - Chemical coupling through an enzyme

Mechanism of Coupling



Quantitative

- Why is this reaction spontaneous?

ATP + Glutamate + ammonia → ADP + P_i + glutamine

$\Delta G^{o\prime}$ = _______

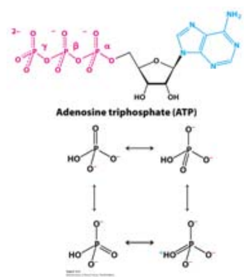
- This reaction is a formal combination of these two reactions:

Glutamate + ammonia → glutamine $\Delta G^{o\prime}$ = +14 kJ/mol

ATP → ADP + P_i $\Delta G^{o\prime}$ = -31 kJ/mol

ATP: Chemical Potential

- High energy bonds
  - Charge repulsion
  - Resonance
  - Entropy
  - Hydration
  - (acid/base equilibrium)



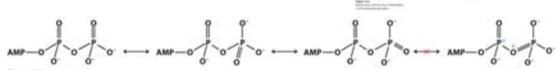


Figure 15.6
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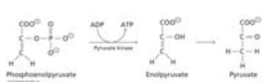
Phosphoryl Transfer in Energetic Intermediates

Table 15.1 Standard free energies of hydrolysis ($\Delta G^{o\prime}$) of s[ome] compounds

Compound	kJ mol⁻¹
Phosphoenolpyruvate (PEP)	−61.9
1,3-Bisphosphoglycerate (1,3-BPG)	−49.4
Creatine phosphate	−43.1
ATP (to ADP)	−30.5
Glucose 1-phosphate	−20.9
Pyrophosphate (PP_i)	−19.3
Glucose 6-phosphate	−13.8
Glycerol 3-phosphate	−9.2

Phosphoryl group transfer potential



Reactions using formal hydrolysis

Table 15.1 Standard free energies of hydrolysis ($\Delta G^{\circ\prime}$) of s[ome] compounds

Compound	kJ mol^{-1}
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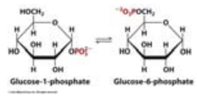
Glycerol 3-phosphate	−9.2

- Calculate the biological standard free energy for the isomerization of G-1-P to G-6-P. Is it spontaneous under standard conditions? Is it spontaneous when [G-6-P] is 5 mM and [G-1-P] = 0.1 mM?



(a) glucose + P*i* → glucose-6-phosphate + H2O $\Delta G^{o\prime}$ = + 13.8 kJ/mol
glucose-1-phosphate + H2O → glucose + P*i* $\Delta G^{o\prime}$ = - 20.9 kJ/mol

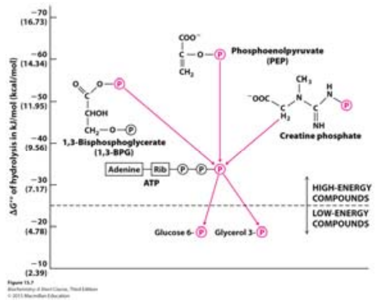
glucose-1-phosphate → glucose-6-phosphate $\Delta G^{o\prime}$ = - 7.1 kJ/mol

The reaction is spontaneous under standard conditions.

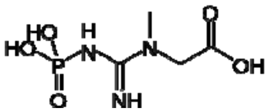
(b) $\Delta G = \Delta G^{o\prime} + RT \ln [G6P]/[G1P]$
ΔG = -7.1 kJ/mol + 8.314 x 10^{-3} (310K) ln (5 x 10^{-3} / 0.1 x 10^{-3})
ΔG = + 3.0 kJ/mol

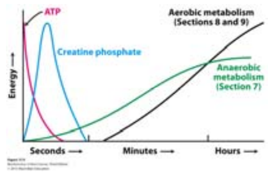
The reaction is not spontaneous under these conditions.

ATP: Middle of High Energy Bonds

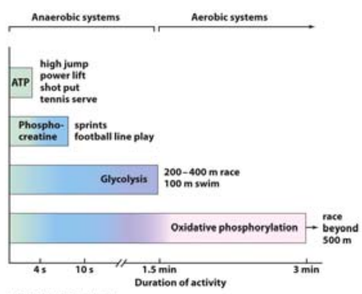


Phosphocreatine



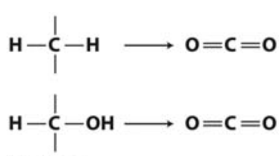


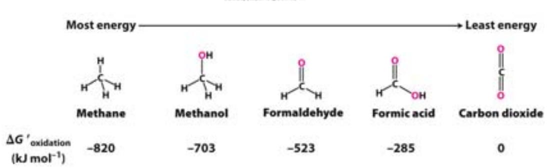
Energy Currency



Redox Reactions

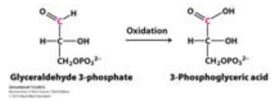
- Catabolism
  - Oxidation
- Anabolism
  - Reduction

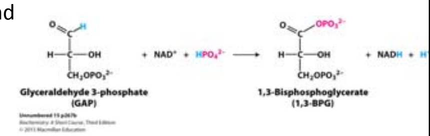




Capturing Chemical Potential

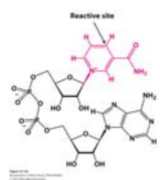
- Reduced carbons have much potential
- Oxidation releases potential
- Can be coupled to formation of high energy bond

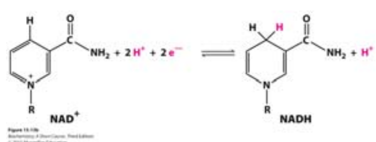


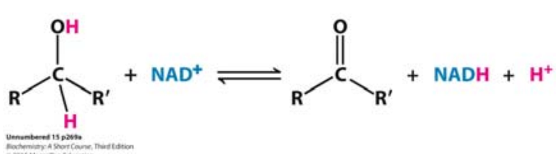


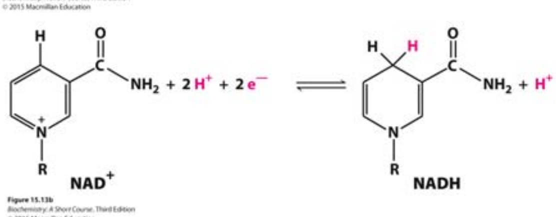
Recurring Motif: Activated Carrier

- Capturing chemical potential in **activated carriers**
- A. NAD^+/NADH



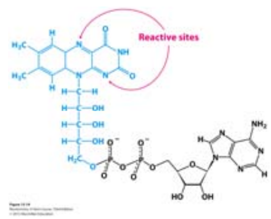


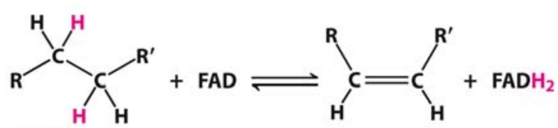




Activated Carriers

- B. $FAD/FADH_2$
- Can transfer one electron or two electrons
- Different redox reactions than NADH





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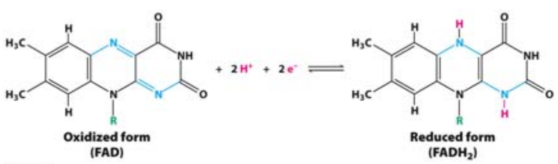

Figure 15.15
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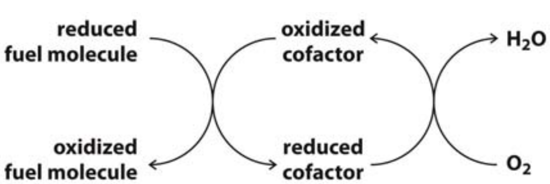
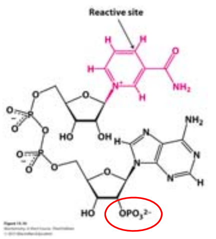
Catalytic Redox Cofactors

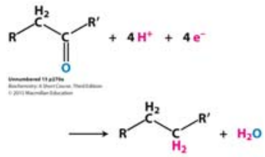
- Electron transport chain
- Purpose of breathing oxygen



Activated Carriers

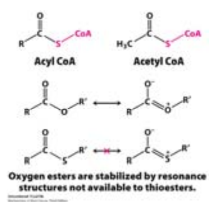
- C. NADP+/NADH
- For biosynthesis

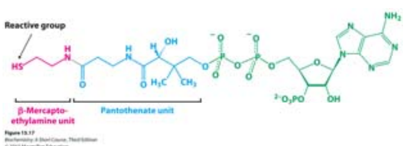




Activated Carriers

- D. Acyl group carriers
- Coenzyme A
- Thioesters
  - Unstable resonance
- High energy bonds





Activated Carriers

Table 15.2 Some activated carriers in metabolism

Carrier molecule in activated form	Group carried	Vitamin precursor
ATP	Phosphoryl	
NADH and NADPH	Electrons	Nicotinate (niacin) (vitamin B_3)
$FADH_2$	Electrons	Riboflavin (vitamin B_2)
$FMNH_2$	Electrons	Riboflavin (vitamin B_2)
Coenzyme A	Acyl	Pantothenate (vitamin B_5)
Lipoamide	Acyl	
Thiamine pyrophosphate	Aldehyde	Thiamine (vitamin B_1)
Biotin	CO_2	Biotin (vitamin B_7)
Tetrahydrofolate	One-carbon units	Folate (vitamin B_9)
S-Adenosylmethionine	Methyl	
Uridine diphosphate glucose	Glucose	
Cytidine diphosphate diacylglycerol	Phosphatidate	
Nucleoside triphosphates	Nucleotides	

Note: Many of the activated carriers are coenzymes that are derived from water-soluble vitamins.

Table 15.2
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B Vitamins

Table 15.3 The B vitamins

Vitamin	Coenzyme	Typical reaction type	Consequences of deficiency
Thiamine (B_1)	Thiamine pyrophosphate	Aldehyde transfer	Beriberi (weight loss, heart problems, neurological dysfunction)
Riboflavin (B_2)	Flavin adenine dinucleotide (FAD)	Oxidation–reduction	Cheliosis and angular stomatitis (lesions of the mouth), dermatitis
Pyridoxine (B_6)	Pyridoxal phosphate	Group transfer to or from amino acids	Depression, confusion, convulsions
Nicotinic acid (niacin, B_3)	Nicotinamide adenine dinucleotide (NAD^+)	Oxidation–reduction	Pellagra (dermatitis, depression, diarrhea)
Pantothenic acid (B_5)	Coenzyme A	Acyl-group transfer	Hypertension
Biotin (B_7)	Biotin–lysine adducts (biocytin)	ATP-dependent carboxylation and carboxyl-group transfer	Rash about the eyebrows, muscle pain, fatigue (rare)
Folic acid (B_9)	Tetrahydrofolate	Transfer of one-carbon components; thymine synthesis	Anemia, neural-tube defects in development
Cobalamin (B_{12})	5'-Deoxyadenosyl cobalamin	Transfer of methyl groups; intramolecular rearrangements	Anemia, pernicious anemia, methylmalonic acidosis

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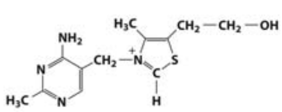
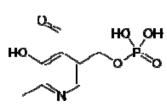
Vitamin Chemistry

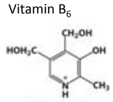
- We will build throughout semester
- Introduction to fundamental chemistry of decarboxylation



Thiamine (vitamin B_1)

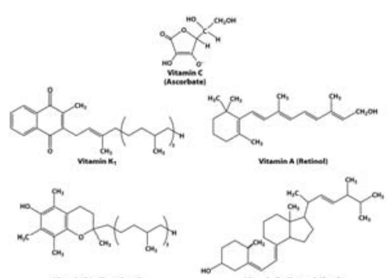


Pyridoxyl Phosphate (PLP)
Vitamin B_6



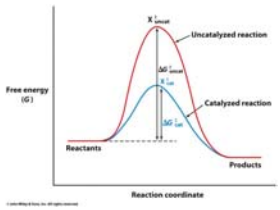
Vitamin B_6
(Pyridoxine)

Other Vitamins



Thermodynamics vs Kinetics

- Characteristics of an energy currency or activated carrier:
- Kinetically stable
- Thermodynamically unstable



Qualitative Predictions

- Inherently favorable, unfavorable, or near equilibrium?

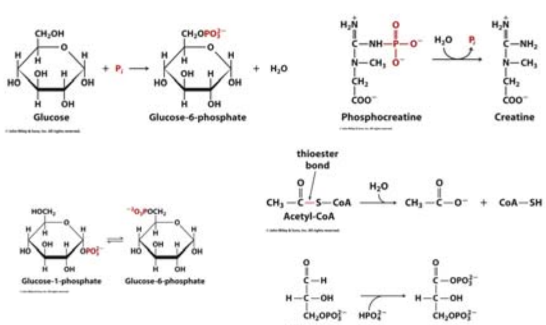
$$\text{GMP} + \text{ATP} \rightleftharpoons \text{GDP} + \text{ADP}$$

$$\text{GDP} + \text{ATP} \rightleftharpoons \text{GTP} + \text{ADP}$$

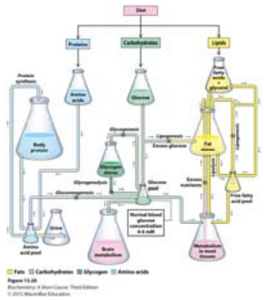
$$\text{AMP} + \text{ATP} \rightleftharpoons 2\ \text{ADP}$$

$$\text{AMP} + \text{ATP} + 2\ \text{P}_i \rightleftharpoons 2\ \text{ATP} + 2\ \text{H}_2\text{O}$$

Uphill or Downhill?

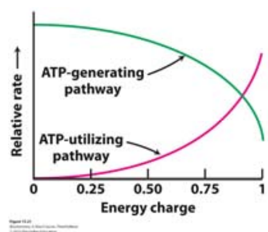


Regulation



Regulation

- Control amount of enzyme
- Control activity of enzyme
  - Energy charge
- Compartmentalization



$$Energy\ charge = \frac{[ATP] + \frac{1}{2}[ADP]}{[ATP] + [ADP] + [AMP]}$$