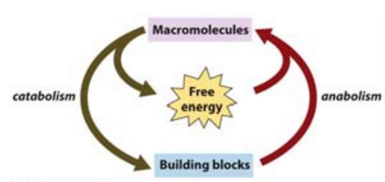
Metabolism and Bioenergetics

Pratt and Cornely, Chapter 12

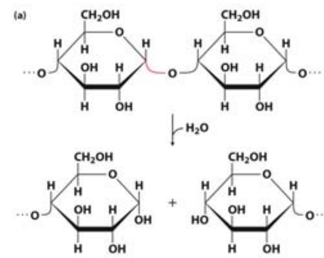
Fuel and Digestion

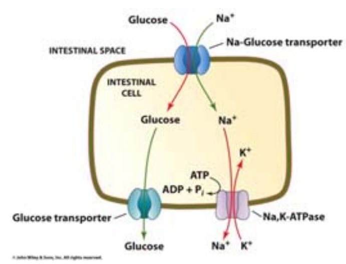
- Breakdown of food biomolecules to monomers
- Absorption of monomers
  - Storage
  - metabolism



Carbohydrates

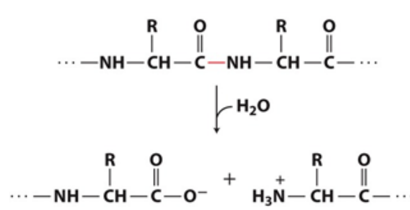
- Amylase in mouth, intestine
  - Amylose
  - Amylopectin
- Transported through intestine to portal vein
  - liver/bloodstream
- Storage
  - Muscle
  - Liver
  - Converted to fat





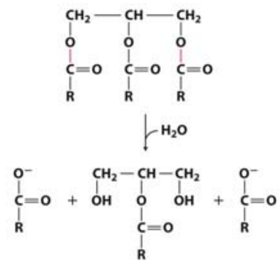
Proteins

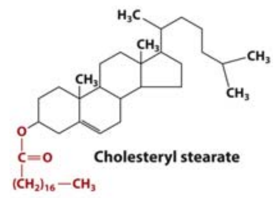
- Breakdown of peptide bond
  - Gastric proteases
  - Pancreatic proteases
- Amino acids transported through intestine to blood/liver
  - Incorporated into proteins (if needed)
  - Broken down to carbs and fats (storage)



Lipids

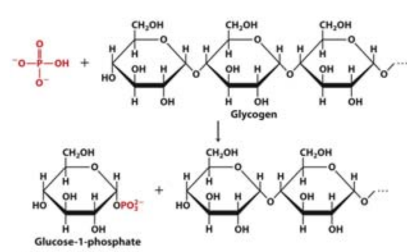
- Digestion
  - Pancreatic lipases
  - Bile salts
- Transported through intestinal cell (diffusion or transport)
- Re-packaged
- Circulated as chylomicrons and lipoproteins
- Stored in adipose





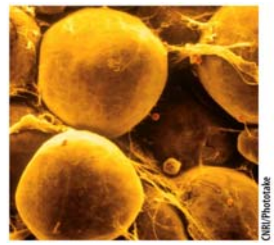
Mobilization of Glycogen

- Required for brain
- Highly branched; release of energy
- Phosphorolysis
- Muscle: Energy conservation
- Liver: phosphate hydrolysis before entering blood



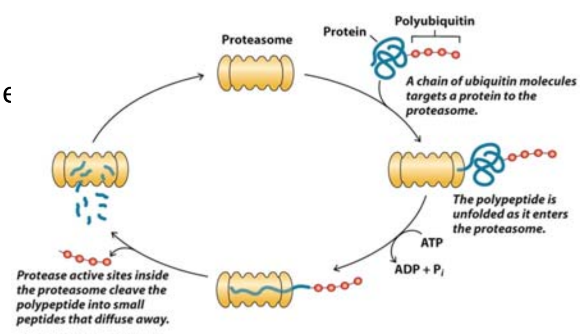
Mobilization of Lipids

- Primary energy for heart
- Compact energy form
- Lipases release from adipose
- Circulate as protein complexes
- Major basal energy source

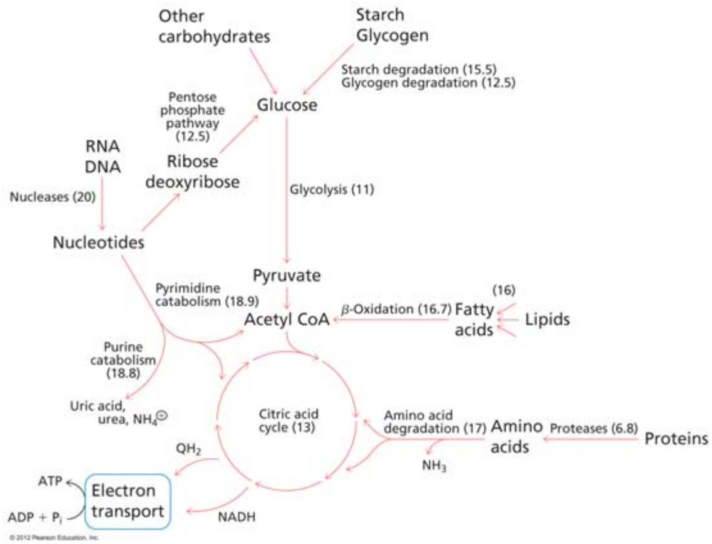


Protein Processing

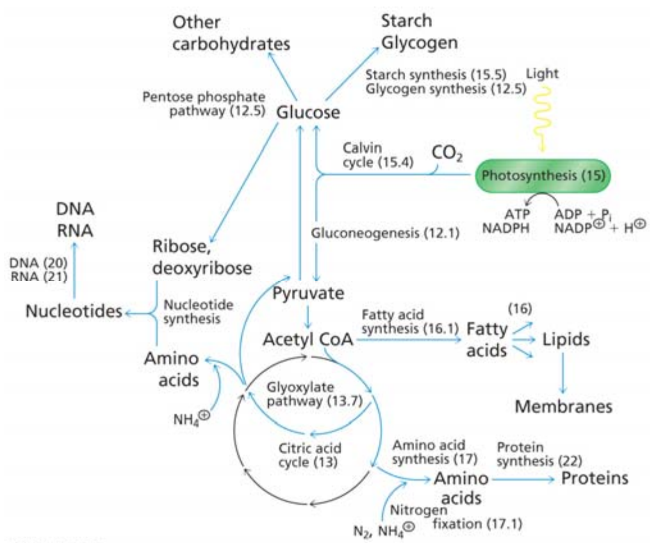
- Proteins not a storage form
- But do need constantly degrade (diet or outside source)
- Lysozome
  - Membrane and extracellular
  - pH 5 optimum
- Proteasome
  - Barrel shaped
  - Ubiquitin tag



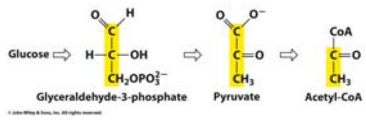
Catabolism

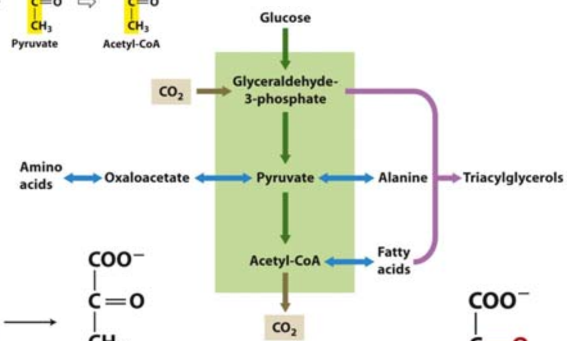


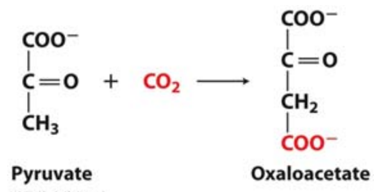
Anabolism

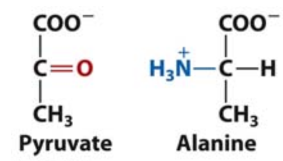


Key intermediates









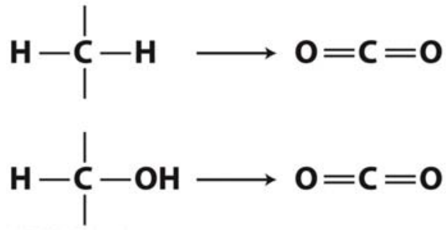
Problem 25

- Check the box of each pathway in which this intermediate is a reactant or product

	Glycolysis	Citric Acid Cycle	Fatty Acid metabolism	TAG synthesis	Trans-amination
Acetyl-CoA					
Glyceraldehyde-3-P					
Pyruvate					

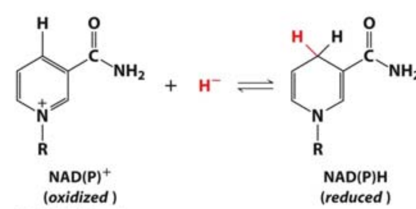
Redox Reactions

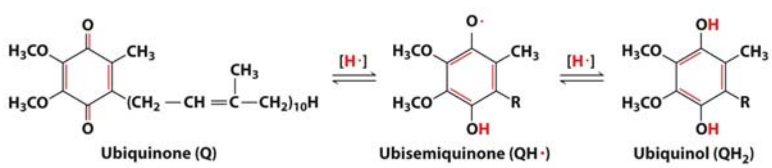
- Catabolism
  - Oxidation
- Anabolism
  - Reduction



Redox Cofactors

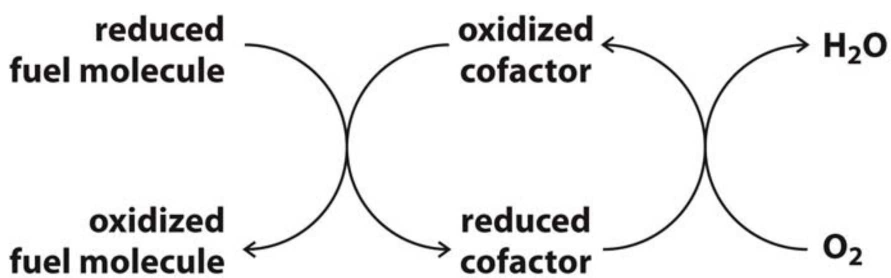
- 2 electron transfer
  - NAD^+/NADH (catabolism)
  - $NADP^+$/NADPH (anabolism)
- 1 or 2 electron transfer
  - FAD/$FADH_2$
- 1 electron transfer
  - Ubiquinone, metals
  - membrane





Catalytic Cofactors

- Electron transport chain
- Purpose of breathing oxygen



Essential Nutrients

TABLE 12-1 Some Essential Substances for Humans

Amino Acids	Fatty Acids		Other	
Isoleucine	Linoleate	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COO^-$	Choline	$(CH_3)_3N^+ CH_2CH_2OH$
Leucine	Linolenate	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO^-$		
Lysine				
Methionine				
Phenylalanine				
Threonine				
Tryptophan				
Valine				

Vitamins

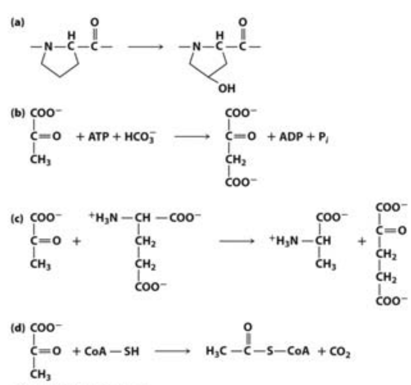
TABLE 12-2 Vitamins and Their Roles

Vitamin	Coenzyme Product	Biochemical Function	Human Deficiency Disease	Text Reference
Water-Soluble				
Ascorbic acid (C)	Ascorbate	Cofactor for hydroxylation of collagen	Scurvy	Box 5-D
Biotin (B_7)	Biocytin	Cofactor for carboxylation reactions	*	Section 13-1
Cobalamin (B_{12})	Cobalamin coenzymes	Cofactor for alkylation reactions	Anemia	Section 17-1
Folic acid	Tetrahydrofolate	Cofactor for one-carbon transfer reactions	Anemia	Section 18-2
Lipoic acid	Lipoamide	Cofactor for acyl transfer reactions	*	Section 14-1
Nicotinamide (niacin, B_3)	Nicotinamide coenzymes (NAD^+, $NADP^+$)	Cofactor for oxidation–reduction reactions	Pellagra	Fig. 3-3, Section 12-2
Pantothenic acid (B_5)	Coenzyme A	Cofactor for acyl transfer reactions	*	Fig. 3-3, Section 12-3
Pyridoxine (B_6)	Pyridoxal phosphate	Cofactor for amino-group transfer reactions	*	Section 18-1
Riboflavin (B_2)	Flavin coenzymes (FAD, FMN)	Cofactor for oxidation–reduction reactions	*	Fig. 3-3
Thiamine (B_1)	Thiamine pyrophosphate	Cofactor for aldehyde transfer reactions	Beriberi	Sections 12-2, 14-1
Fat-Soluble				
Vitamin A (retinol)		Light-absorbing pigment	Blindness	Box 8-B
Vitamin D		Hormone that promotes Ca^{2+} absorption	Rickets	Box 8-B
Vitamin E (tocopherol)		Antioxidant	*	Box 8-B
Vitamin K (phylloquinone)		Cofactor for carboxylation of blood coagulation proteins	Bleeding	Box 8-B

*Deficiency in humans is rare or unobserved.

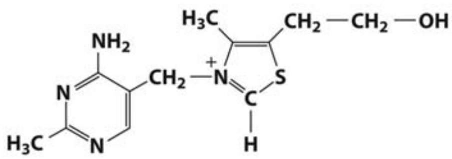
Problem 33

- Refer to table 12.2 to identify the vitamin necessary for these reactions:

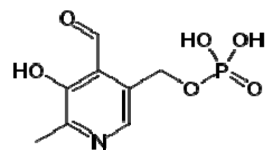


Vitamin Chemistry

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

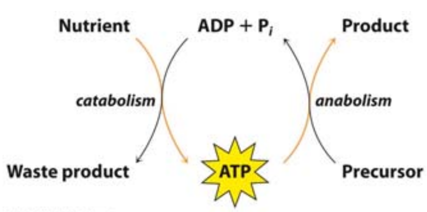


Thiamine (vitamin B_1)



Pyridoxyl Phosphate (PLP)
Vitamin B_6

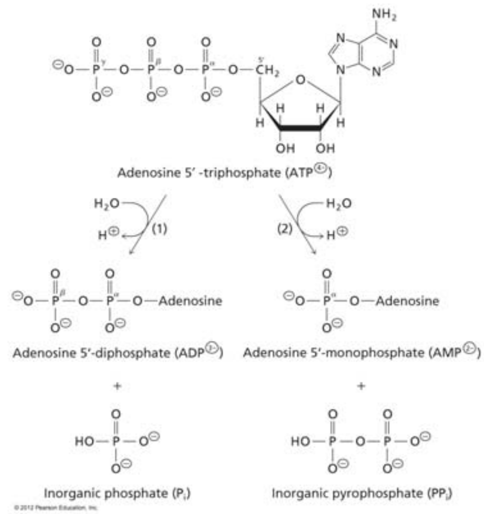
Formal Metabolism

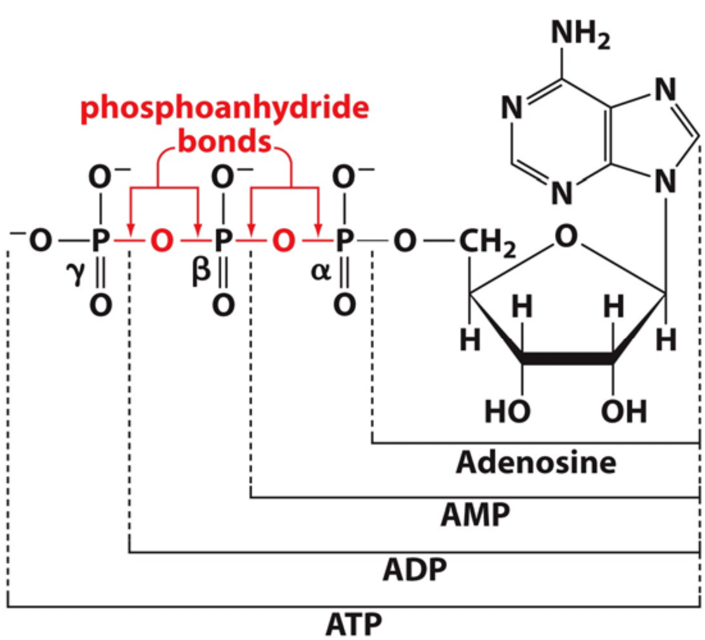


- Spontaneity
  - Oxidation of carbon
  - Hydrolysis
    - Especially of high energy bonds

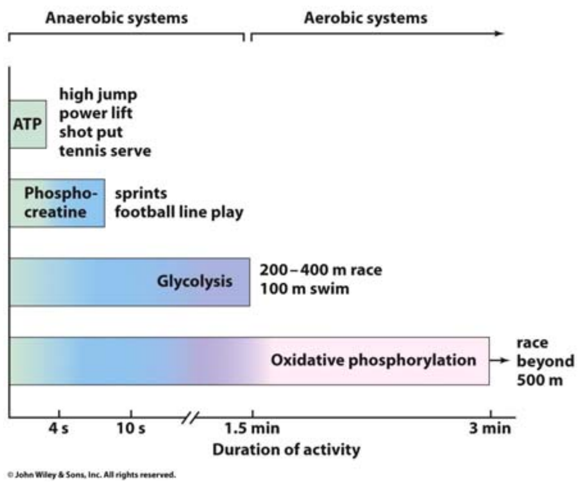
Qualitative Energetics

- ATP: High energy bonds—inherent chemistry
  - Electrostatic repulsion
  - Solvation of products
  - Resonance
- Rxn goes to "completion"

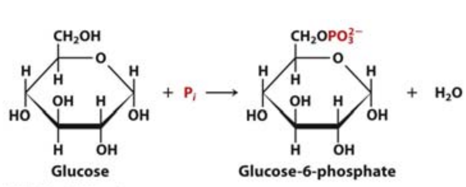


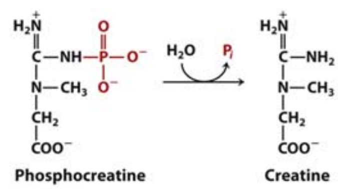


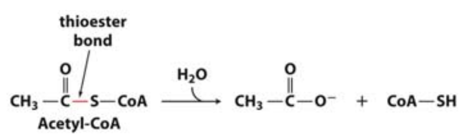
Energy Currency

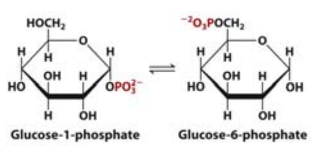


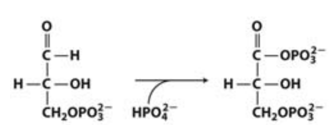
Uphill or Downhill?











Qualitative Predictions

- Inherently favorable, unfavorable, or near equilibrium?

$$GMP + ATP \rightleftharpoons GDP + ADP$$

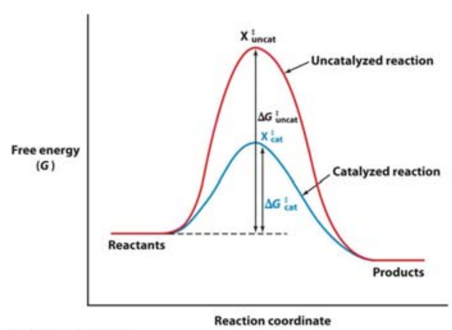
$$GDP + ATP \rightleftharpoons GTP + ADP$$

$$AMP + ATP \rightleftharpoons 2\,ADP$$

$$AMP + ATP + 2\,P_i \rightleftharpoons 2\,ATP + 2\,H_2O$$

Thermodynamics vs Kinetics

- Gibbs Free Energy
  - Spontaneous
  - Favorable
  - exergonic
- $\Delta G = G_{pdt} - G_{rxt}$
  - Path independent
  - Doesn't tell us about kinetics



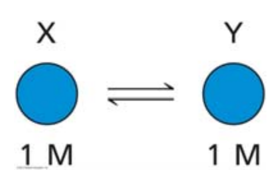
Free Energy

- The free energy of a PARTICULAR reaction depends on two terms
  - The nature of the bonds in the reaction
    - The position of equilibrium
  - The concentration of the compounds
    - How far from equilibrium
- A reaction with a $-\Delta G^{o\prime}$ can be spontaneous or nonspontaneous under cellular conditions.

$$\Delta G = \Delta G^{0\prime} + RT \ln\frac{[pdts]}{[rxts]}$$

Standard Free Energy

- Every reaction moves spontaneously toward **equilibrium—but that could be either direction**
- There is a relationship between equilibrium constant and free energy of the reaction
- If we start with 1M reactants and products, the free energy change of that reaction is called the "standard" free energy
- $\Delta G^{o\prime}$ is a reflection of the chemical potential (stability of bonds)
  - Negative $\Delta G^{o\prime}$ means equilibrium favors pdts
  - Larger $\Delta G^{o\prime}$ means it is favored to a greater degree



- **$\Delta G^{0\prime} = -RT \ln K_{eq}$**
- The ^{0} means "standard"
  - 1 M, 1 atm, 298 K
- The ' means "biological standard"
  - pH 7, 55M water

Standard Free Energy

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

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

TABLE 12-4

Standard Free Energy Change for Phosphate Hydrolysis

Compound	$\Delta G^{\circ\prime}$ (kJ · mol^{-1})
Phosphoenolpyruvate	−61.9
1,3-Bisphosphoglycerate	−49.4
ATP → AMP + PP_i	−45.6
Phosphocreatine	−43.1
ATP → ADP + P_i	−30.5
Glucose-1-phosphate	−20.9
PP_i → 2 P_i	−19.2
Glucose-6-phosphate	−13.8
Glycerol-3-phosphate	−9.2

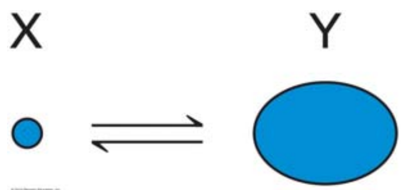
- What do these examples mean?
  - Under standard conditions, glutamine will spontaneously turn into glutamate.
  - Hydrolysis of ATP is more favorable than hydrolysis of glucose-6-phosphate

Quantitative Problems

- What is [product]/[rxt] ratio of ATP hydrolysis to ADP at equilibrium?
  - **$\Delta G^{0\prime}$ = -RT ln K_{eq}**
  - R = 8.314 J/mol K, T in Kelvin
  - [ADP][Pi]/[ATP] = 4.1 x 10^5 = K_{eq}
- What is the free energy of ATP hydrolysis when it reaches equilibrium?
  - Equilibrium = DEAD!

Equilibrium

- You can't understand thermodynamics until we clear up some common misconceptions about equilibrium…



- Is this reaction at equilibrium or not?
- If not, in which direction does the equilibrium lie?

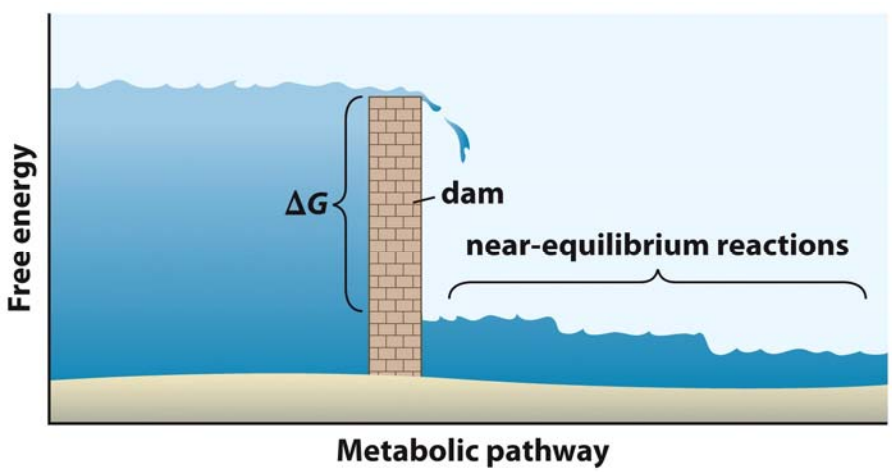
Free Energy of ATP hydrolysis

- Actual cellular concentrations don't vary much from $[P_i]$=[ATP] = 5 mmol and [ADP]= 1 mmol
- **Problem 43**: What is the actual free energy of ATP hydrolysis in the cell? More or less than -32 kJ? What does this mean, physiologically?

$$\Delta G_{\text{reaction}} = \Delta G^{\circ\prime}_{\text{reaction}} + RT \ln \frac{[\text{products}]}{[\text{reactants}]}$$

Two Types of Reactions

- Near-equilibrium reactions
  - Actual [pdt] /[rxt] ratio near the equilibrium concentrations
  - ΔG close to zero (regardless of $\Delta G^{o\prime}$)
  - Not regulated—part of overall flux of metabolism
- Metabolically irreversible reactions
  - ΔG far from zero
  - Can only be overcome by energy input
  - regulated



ATP in Metabolism

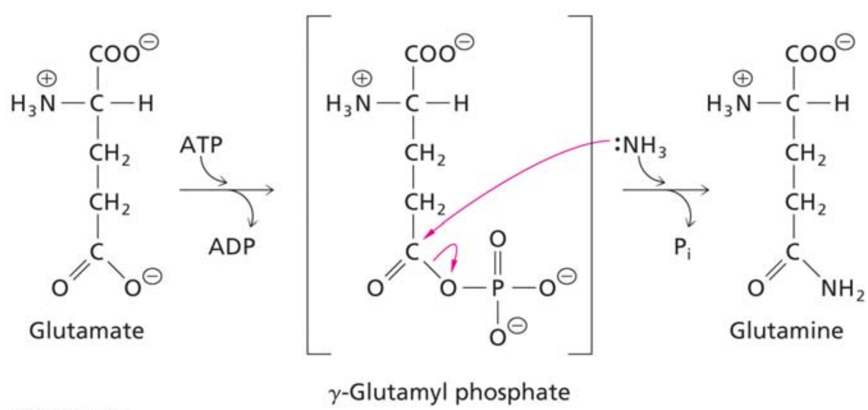
- Overcoming a barrier...
  - Can't change concentrations (ammonia is toxic!)
  - Couple the reaction to a spontaneous reaction!

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

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

  - **Problem 59**: Write an equation to couple this reaction to ATP hydrolysis.

Mechanism of Coupling



Another Type of Coupling

- Problem 50: 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

Phosphoryl Transfer in Energetic Intermediates

[TABLE 12-4]

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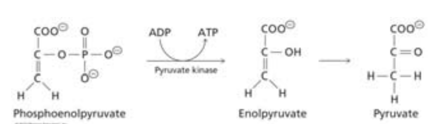
Phosphoryl group transfer potential



PPi → 2 Pi = -29 kJ/mol

Problem 42

TABLE 12-4

Standard Free Energy Change for Phosphate Hydrolysis

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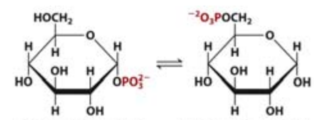
ATP → ADP + P_i	−30.5
Glucose-1-phosphate	−20.9
PP_i → 2 P_i	−19.2
Glucose-6-phosphate	−13.8
Glycerol-3-phosphate	−9.2

- 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?



Glucose-1-phosphate Glucose-6-phosphate