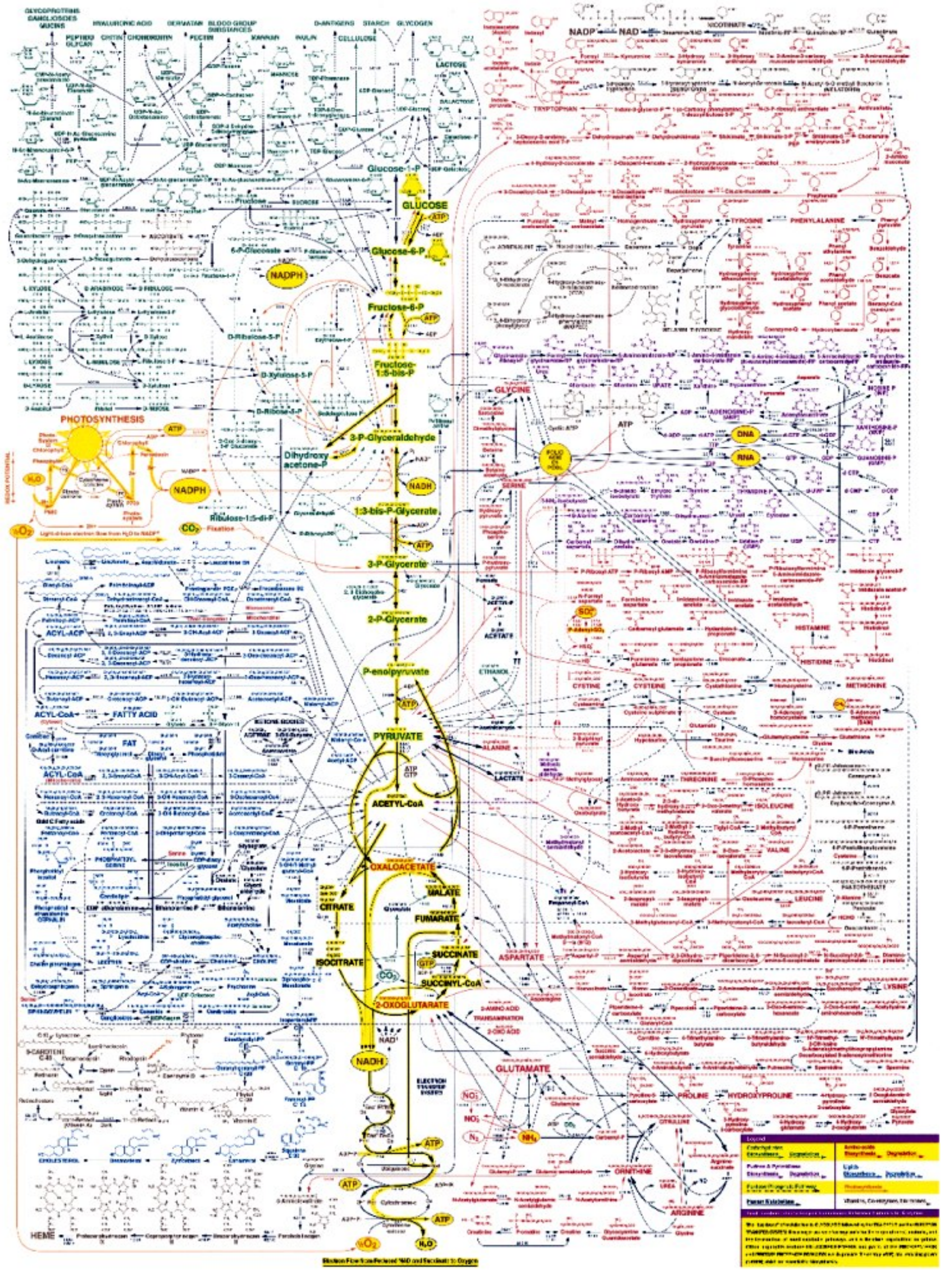
Chapter 1:
Introduction to Metabolism



Chapter 13 Opener Fundamentals of Biochemistry, 2/e

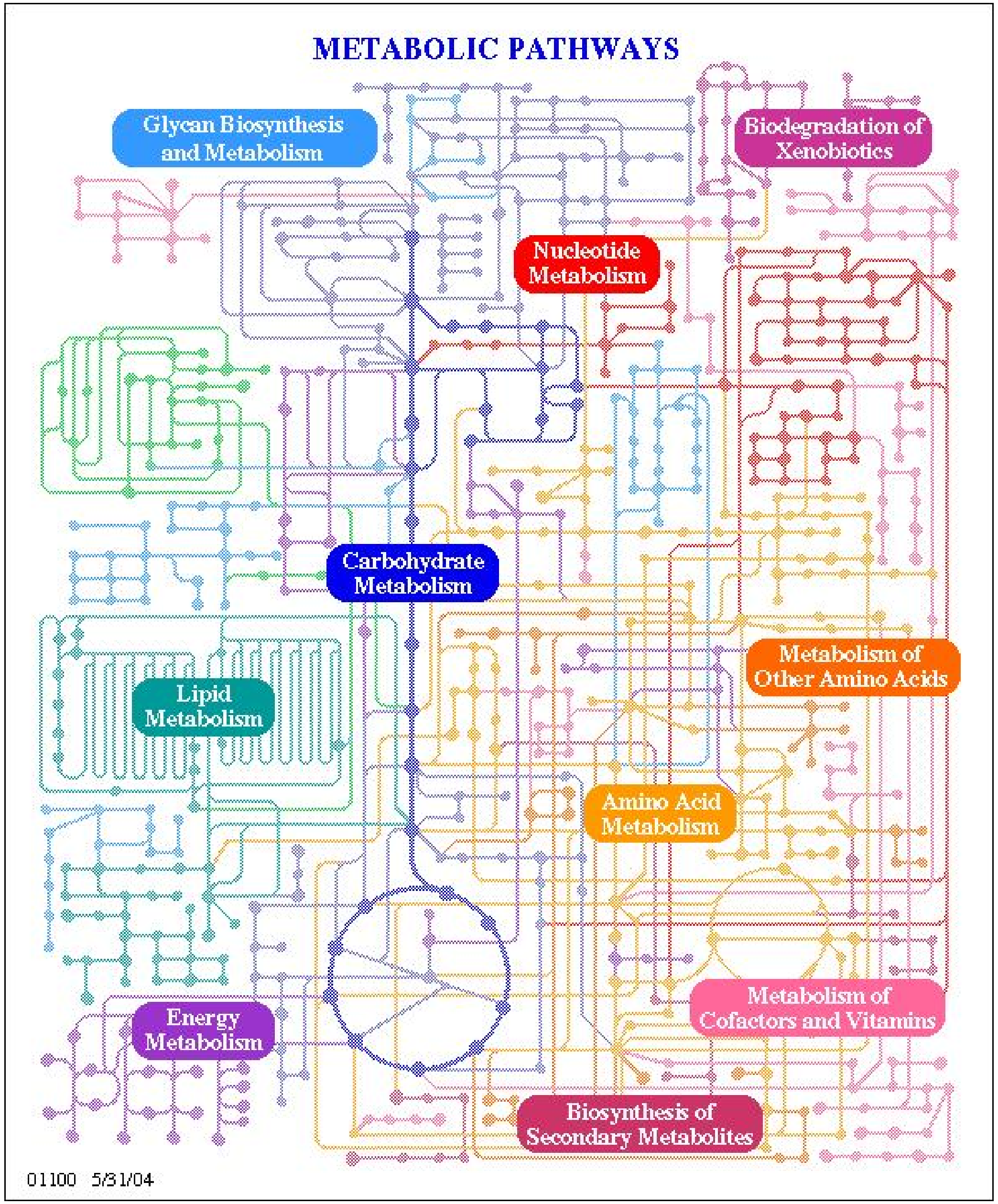
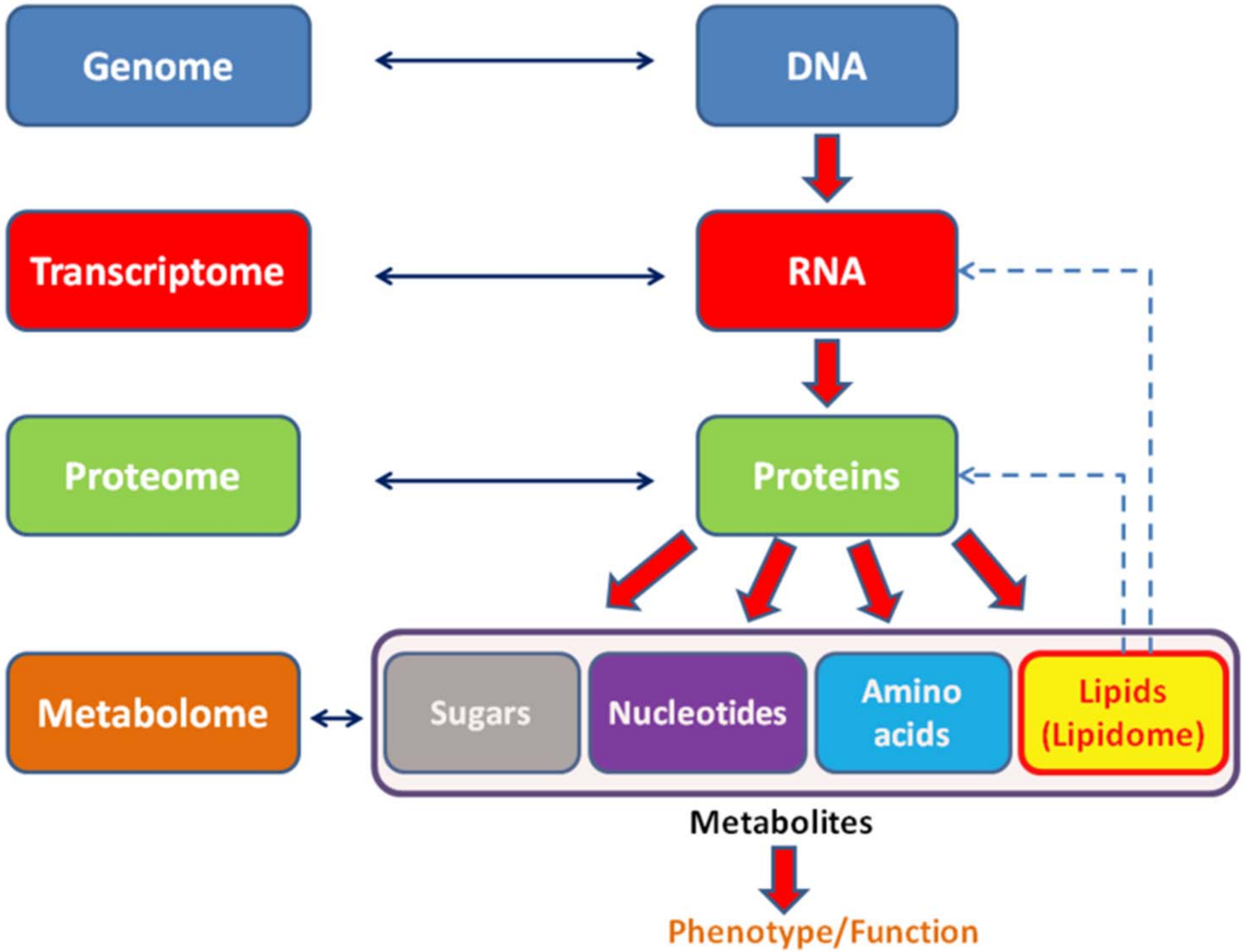
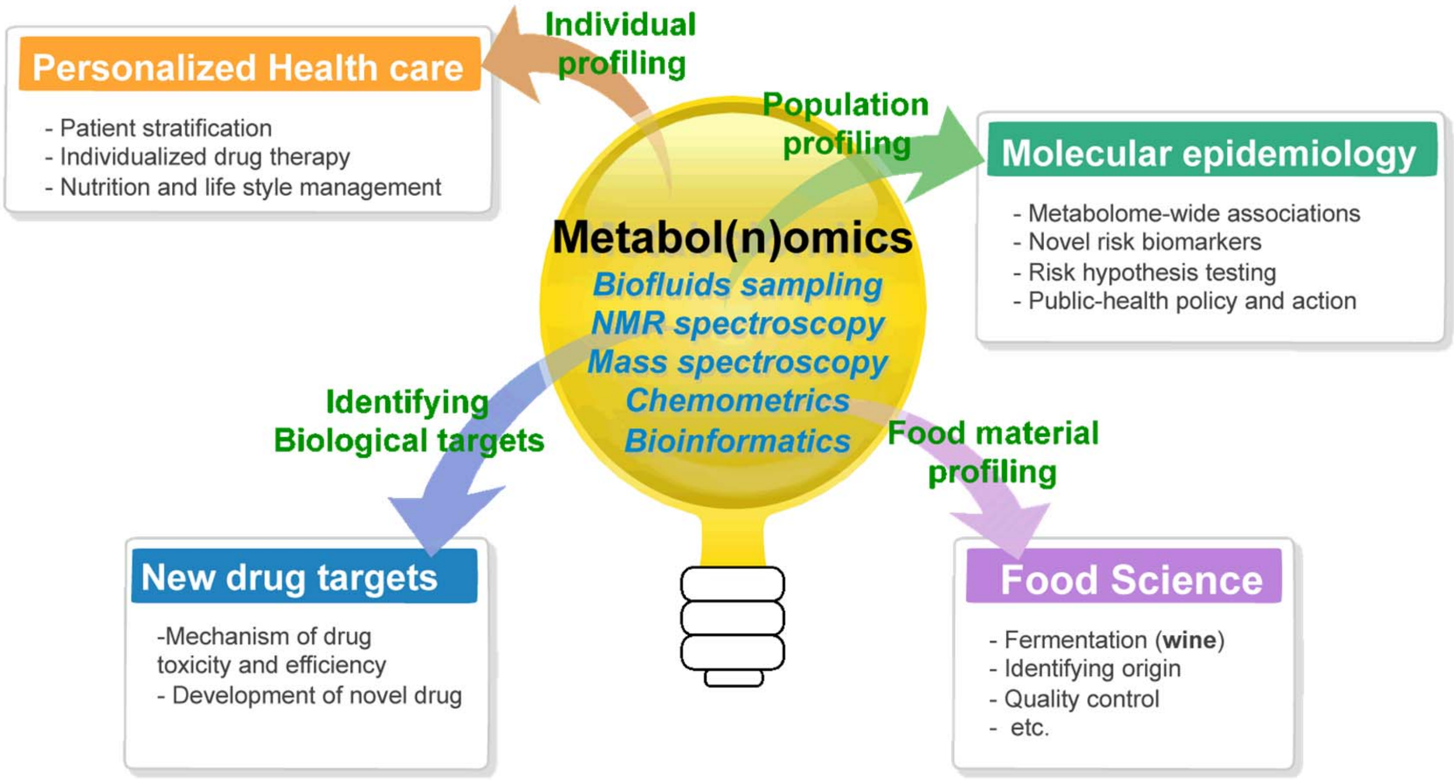


Diagram taken from the [SYSFYS project]() carried out by the University of Helinski Computer Department.
http://labrat.fieldofscience.com/2010/02/metabolomics.html

Metabolomics





modified from Nature 2008, 455,1054-1056

5년내 사망위험 예측 혈액검사법 개발

http://www.e-healthnews.com/news/article_view.php?art_id=106705

Trophic strategies: nutritional requirements

Autotrophs
- chemolithotrophs
- photoautotrophs

Heterotrophs

Energy

Obligate aerobes

Anaerobes
- facultative anaerobic
- obligate anaerobic

Electron acceptor (oxidizing agent)

Metabolic pathway

Catabolic & anabolic

Enzymes & metabolites

Roles of ATP and NADP+ in metabolism

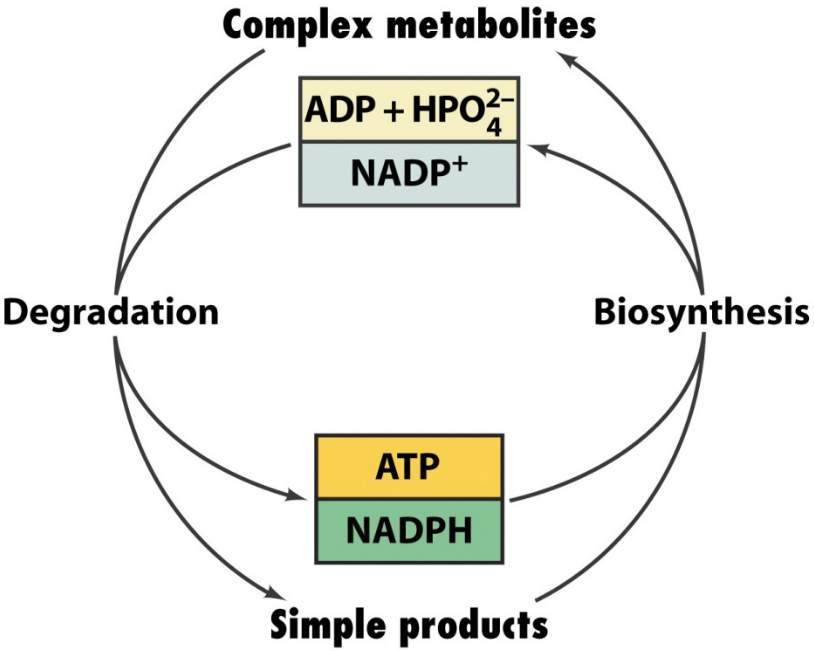


Figure 13-1 Fundamentals of Biochemistry, 2/e

Overview of catabolism

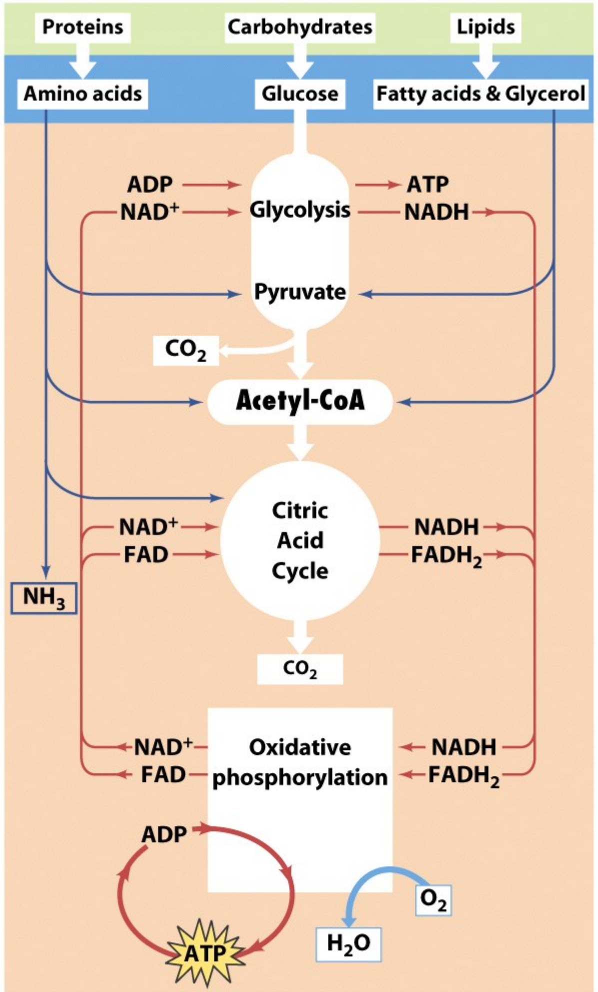


Figure 13-2 Fundamentals of Biochemistry, 2/e

Converge to common intermediates

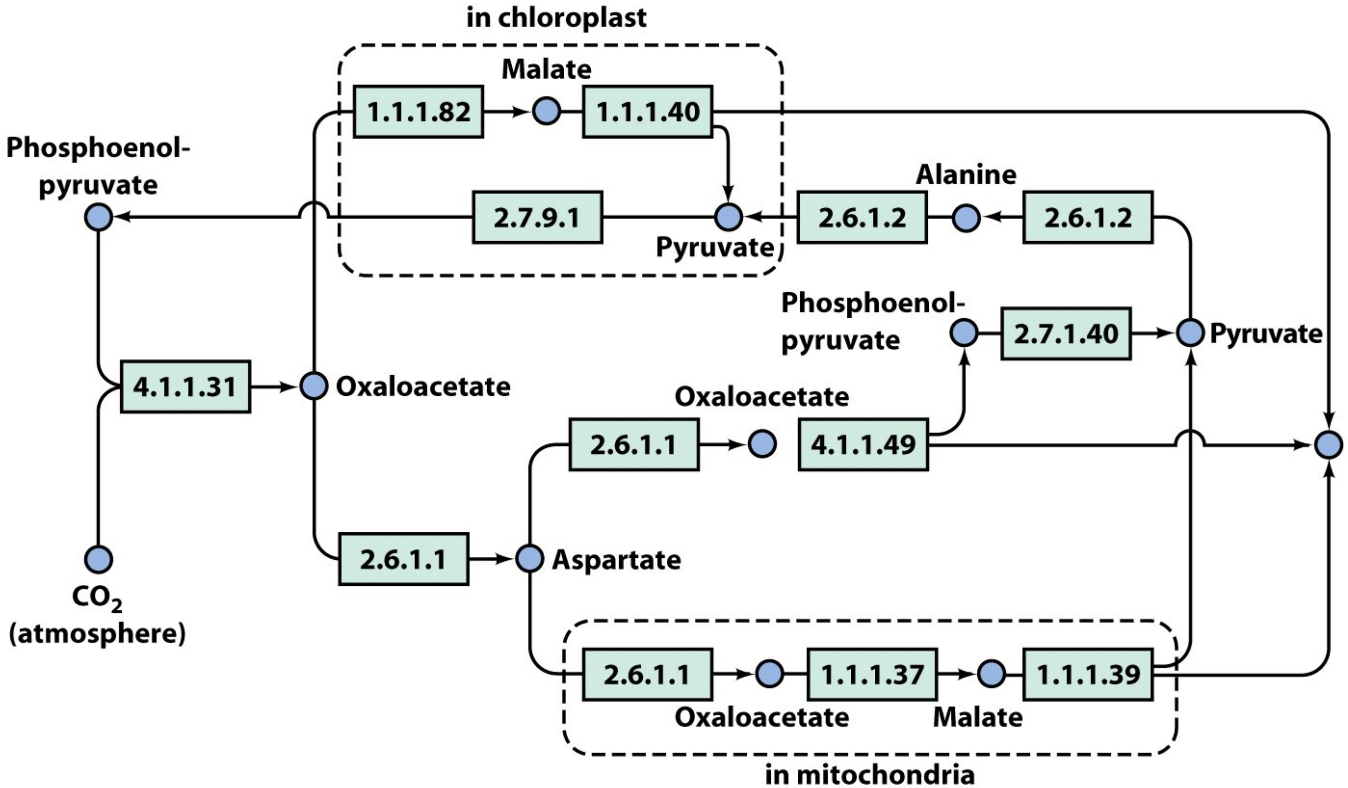
Oxidation states of carbon

C-O	+1
C-H	- 1
C-C	0

Compound	Formula	Oxidation Number
Carbon dioxide	$O{=}C{=}O$	4 (most oxidized)
Acetic acid	$H_3C{-}C(=O){-}OH$	3
Carbon monoxide	$:C{\equiv}O:$	2
Formic acid	$H{-}C(=O){-}OH$	2
Acetone	$H_3C{-}C(=O){-}CH_3$	2
Acetaldehyde	$H_3C{-}C(=O){-}H$	1
Formaldehyde	$H{-}C(=O){-}H$	0
Acetylene	$HC{\equiv}CH$	−1
Ethanol	$H_3C{-}CH_2{-}OH$	−1
Ethene	$H_2C{=}CH_2$	−2
Ethane	$H_3C{-}CH_3$	−3
Methane	CH_4	−4 (least oxidized)

Box 13-1 table 1 Fundamentals of Biochemistry, 2/e

Mapping metabolic pathways catalyzed by enzymes



Box 13-2 Fundamentals of Biochemistry, 2/e

Enzyme reactions
fall into 4 major types

Oxidations and reductions (oxidoreductases)
Group-transfer reactions (transferases and hydrolases)
Eliminations, isomerizations, and rearrangements (isomerases and mutases)
Reactions that make or break C-C bonds (hydrolases, lyases, and ligases)

CLASSIFICATION OF ENZYMES		
Group of Enzyme	**Reaction Catalysed**	**Examples**
1. Oxldoreductases	Transfer of hydrogen and oxygen atoms or electrons from one substrate to another.	Dehydrogenases Oxidases
2. Transferases	Transfer of a specific group (a phosphate or methyl etc.) from one substrate to another.	Transaminase Kinases
3. Hydrolases	Hydrolysis of a substrate.	Estrases Digestive enzymes
4. Isomerases	Change of the molecular form of the substrate.	Phospho hexo isomerase, Fumarase
5. Lyases	Nonhydrolytic removal of a group or addition of a group to a substrate.	Decarboxylases Aldolases
6. Ligases (Synthetases)	Joining of two molecules by the formation of new bonds.	Citric acid synthetase

Compartmentation

Metabolic pathways occur in specific cellular locations

Table 13-1 Metabolic Functions of Eukaryotic Organelles

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

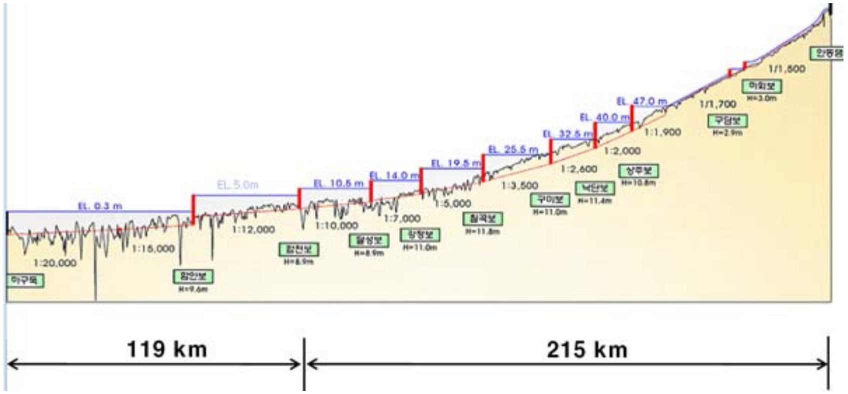
Table 13-1 Fundamentals of Biochemistry, 2/e

Metabolic pathways depends on tissues and organs

liver, muscle, adipocyte

isozymes: LDH

Thermodynamic considerations



$$\Delta G = \Delta G^{o} + RT\ln\frac{[C]^{c}[D]^{d}}{[A]^{a}[B]^{b}}$$

near-equilibrium reaction (reversible): $\Delta G \approx 0$

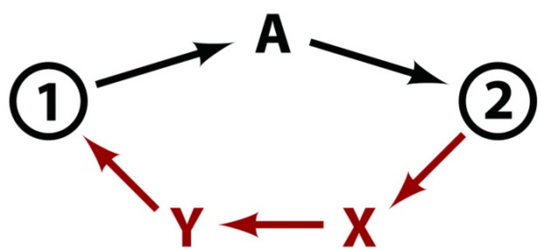
depends on the relative concentrations of substrates and products

far-equilibrium reaction (irreversible): $\Delta G << 0$

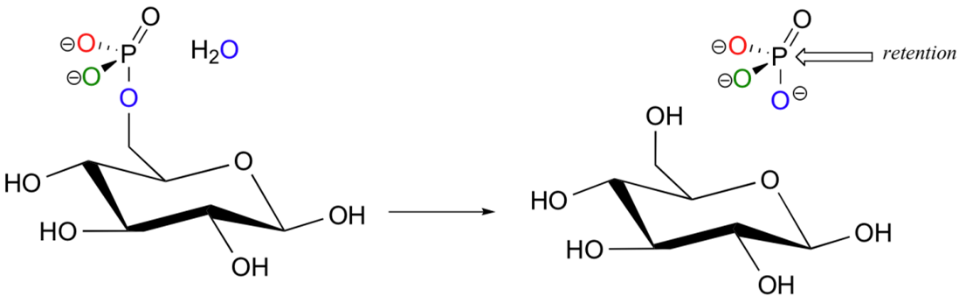
accumulation of substrate (insufficient catalytic efficiency)

controlled by allosteric effector

1. Metabolic pathways are irreversible: confers directionality
2. Every metabolic pathway has a first committed step
3. Catabolic and anabolic pathways differ



Unnumbered figure pg 402 Fundamentals of Biochemistry, 2/e



glucose-6-phosphate glucose

Calculate the equilibrium constant for the hydrolysis of glucose-6-phosphate at 37℃

$\Delta G^{o'}$ for the reaction is -20.9 kJ・mol-1

At equilibrium, $\Delta G = 0$ and $\Delta G^{o'} = -RT\ln K$

Therefore,

$K = e^{-\Delta G^{o'}/RT}$

$= e^{-(-20900\ \text{kJ}\cdot\text{mol-1})/(8.3145\ \text{J}\cdot\text{K-1}\cdot\text{mol-1})(310\text{K})}$

$= 3.3 \times 10^3$

$$\Delta G = \Delta G^{o} + RT\ln\frac{[C]^c[D]^d}{[A]^a[B]^b}$$

Control of metabolic flux

Steady state & equilibrium

The flux of metabolites J = v(f) – v(r)

At equilibrium, J=0, although v(f) and v(r) may be quite large

In reactions that are far from equilibrium, v(f)>>v(r), so the flux is essentially equal to the rate of the forward reaction (J ≈ v(f))

Flux is determined by the slowest step (rate-determining step) *** committed step

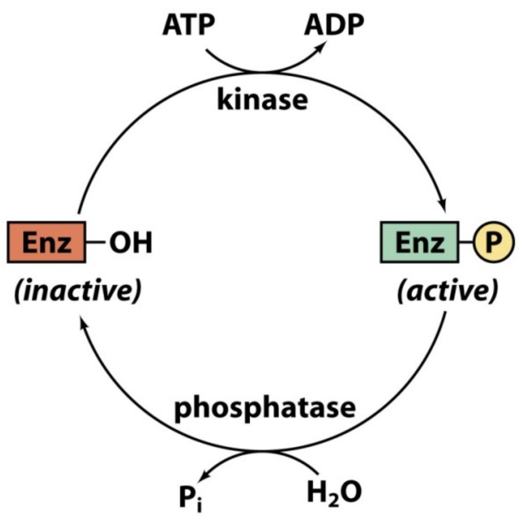
Allosteric control

Covalent modification

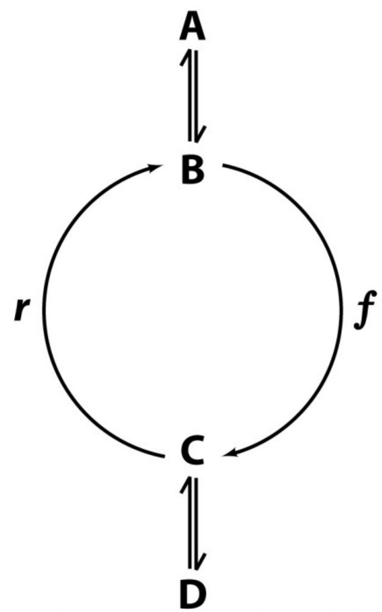
Substrate cycles

Genetic control

Unnumbered figure pg 403a Fundamentals of Biochemistry, 2/e



Unnumbered figure pg 403b Fundamentals of Biochemistry, 2/e



Unnumbered figure pg 404 Fundamentals of Biochemistry, 2/e

High-energy compounds

High-energy intermediates: phosphorylated compounds, NADH
A sort of free energy currency

ATP and phosphoryl group transfer:
thermodynamically favored
but kinetically disfavored

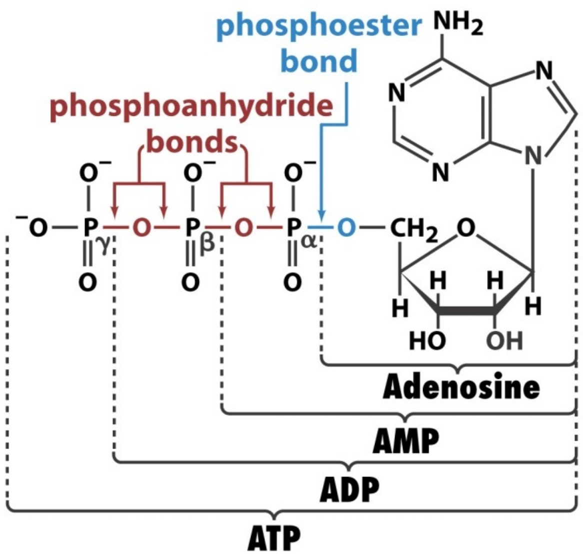


Figure 13-3 Fundamentals of Biochemistry, 2/e

Table 13-2 Standard Free Energies of Phosphate Hydrolysis of Some Compounds of Biological Interest

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

Source: Mostly from Jencks, W.P., *in* Fasman, G.D. (Ed.), *Handbook of Biochemistry and Molecular Biology* (3rd ed.), Physical and Chemical Data, Vol. I, pp. 296–304, CRC Press (1976).

Table 13-2 Fundamentals of Biochemistry, 2/e

What are high energy bonds (energy rich bonds)?

Resonance stabilization
Electrostatic repulsion
Solvation energy

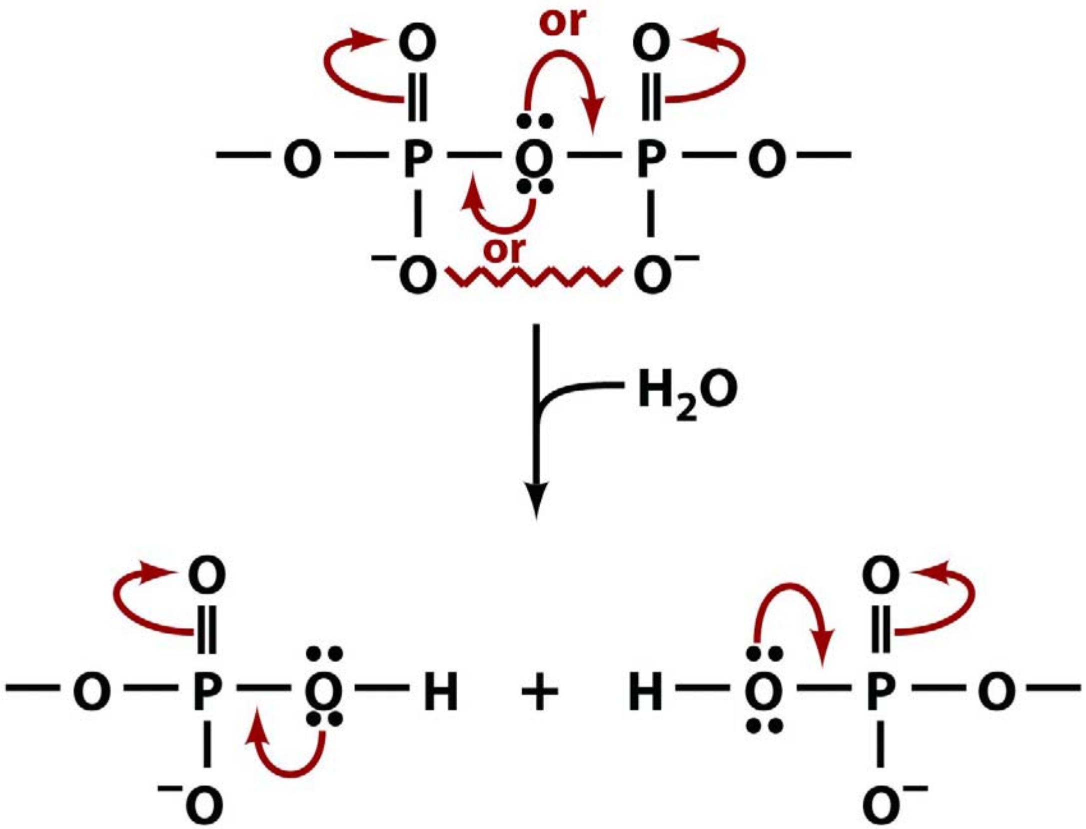


Figure 13-4 Fundamentals of Biochemistry, 2/e

Coupled reactions

coupling of exergonic and endergonic process
Not actual process in the catalyzing enzyme
ATP coupling to conformational changes

(a)

	Reaction	G' ($kJ\cdot mol^{-1}$)
Endergonic half-reaction 1	P_i + glucose $\rightleftharpoons$ glucose-6-P + H_2O	+13.8
Exergonic half-reaction 2	ATP + H_2O $\rightleftharpoons$ ADP + P_i	–30.5
Overall coupled reaction	ATP + glucose $\rightleftharpoons$ ADP + glucose-6-P	–16.7

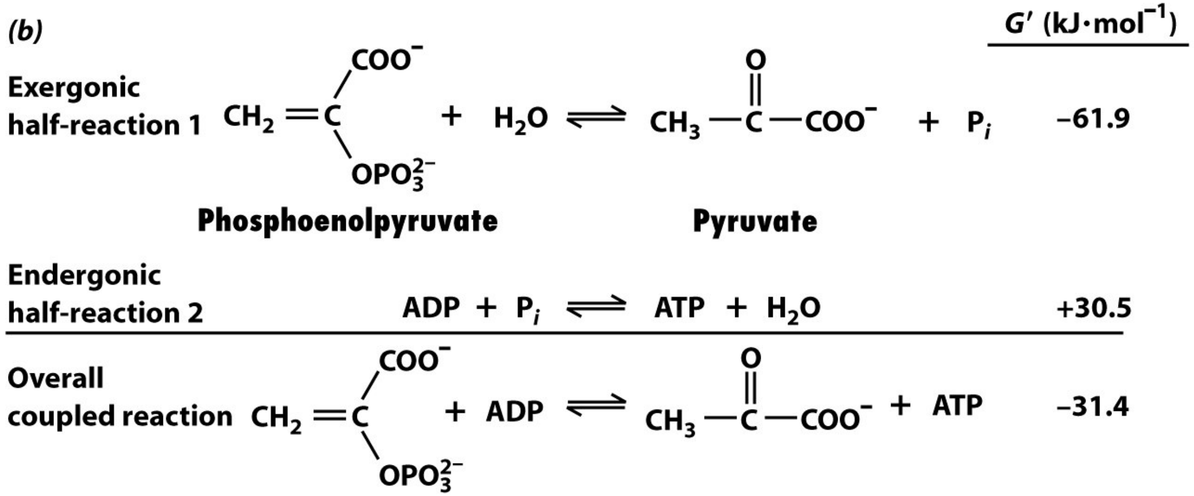


Figure 13-5 Fundamentals of Biochemistry, 2/e

Pyrophosphate cleavage

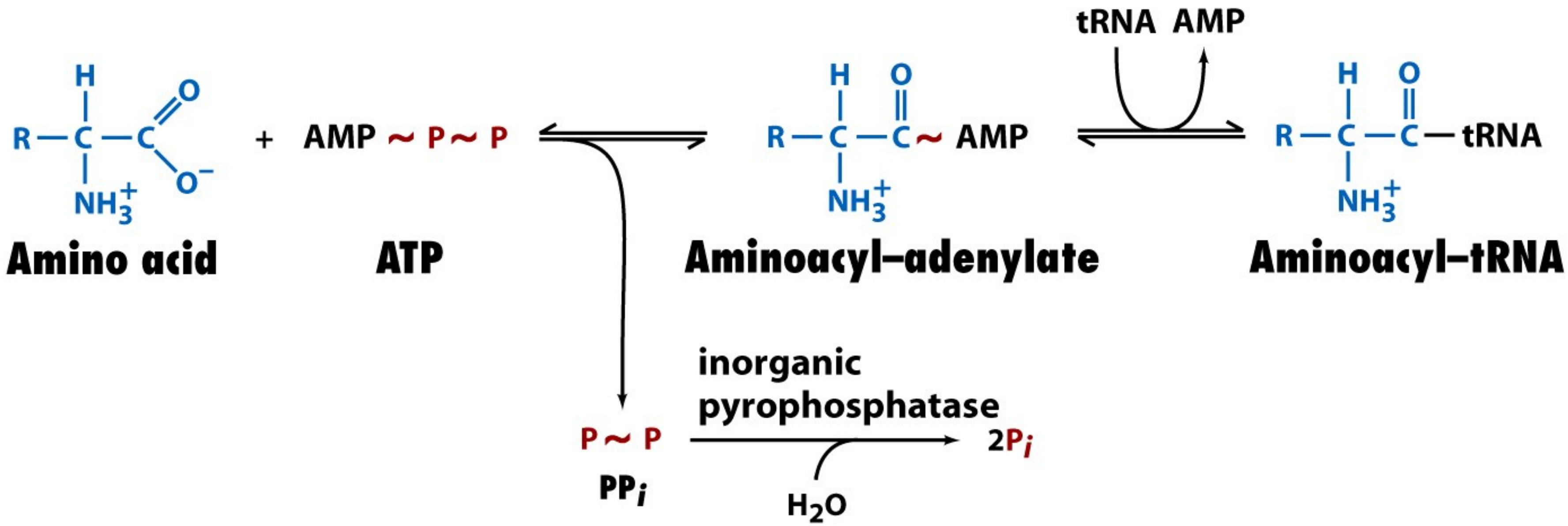


Figure 13-6 Fundamentals of Biochemistry, 2/e

Other phosphorylated compounds

ATP is continually being hydrolyzed and regenerated
metabolic half-life: from seconds to minutes

Substrate level phosphorylation
Oxidative phosphorylation
Photophosphorylation

Interconversion of nucleoside triphosphates
Kinases & phosphatases

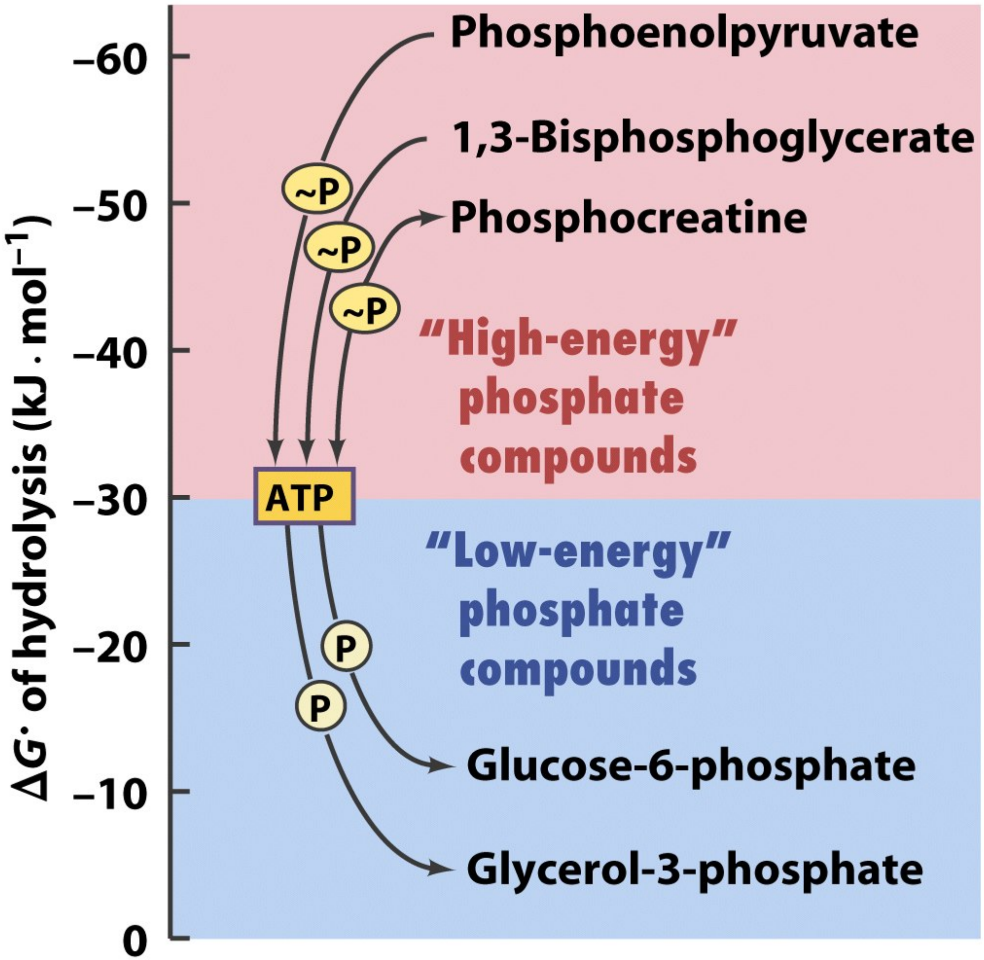
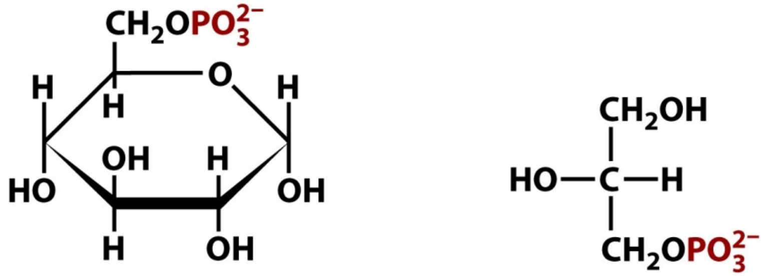


Figure 13-7 Fundamentals of Biochemistry, 2/e

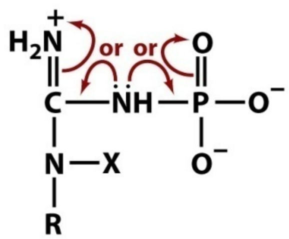
Acetyl phosphate **1,3-Bisphosphoglycerate**

Unnumbered figure pg 411a Fundamentals of Biochemistry, 2/e

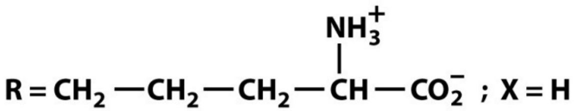


α-D-Glucose-6-phosphate **L-Glycerol-3-phosphate**

Unnumbered figure pg 411b Fundamentals of Biochemistry, 2/e



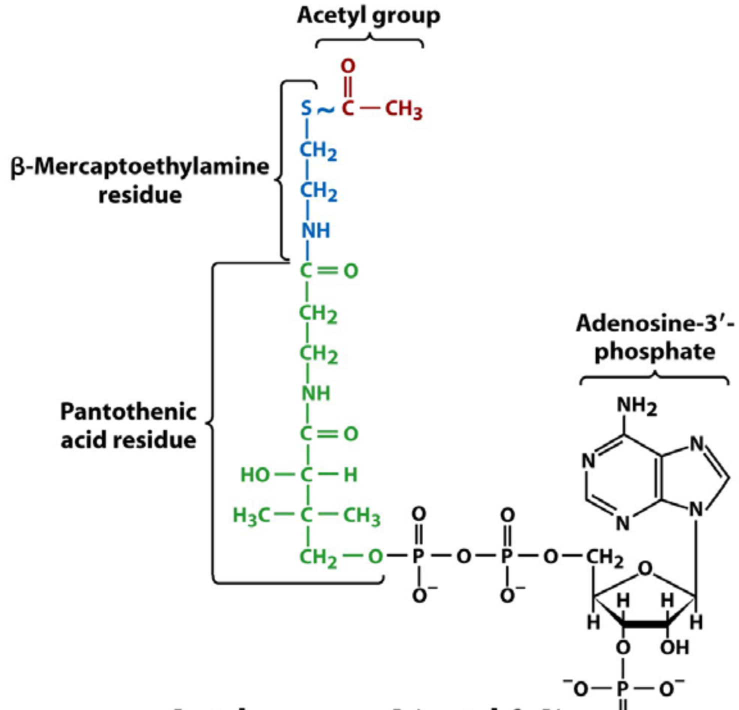
$R = CH_2-CO_2^-$; $X = CH_3$ **Phosphocreatine**



Phosphoarginine

Unnumbered figure pg 411c Fundamentals of Biochemistry, 2/e

Thioester: primitive compound



Acetyl-coenzyme A (acetyl-CoA)

Figure 13-9 Fundamentals of Biochemistry, 2/e

Oxidation-reduction reactions

- One electron transfer
- Two electron transfer
- Reversible reaction

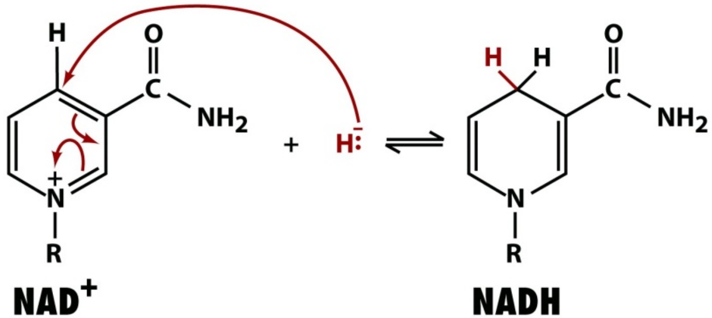


Figure 13-10 Fundamentals of Biochemistry, 2/e

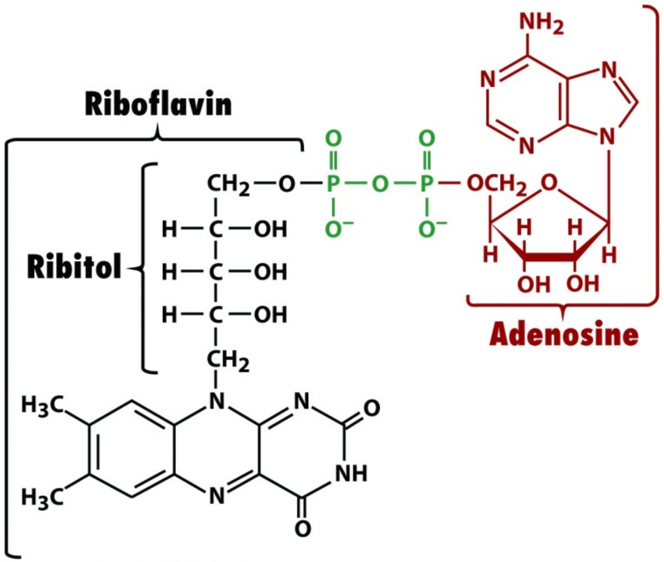


Figure 13-11 Fundamentals of Biochemistry, 2/e

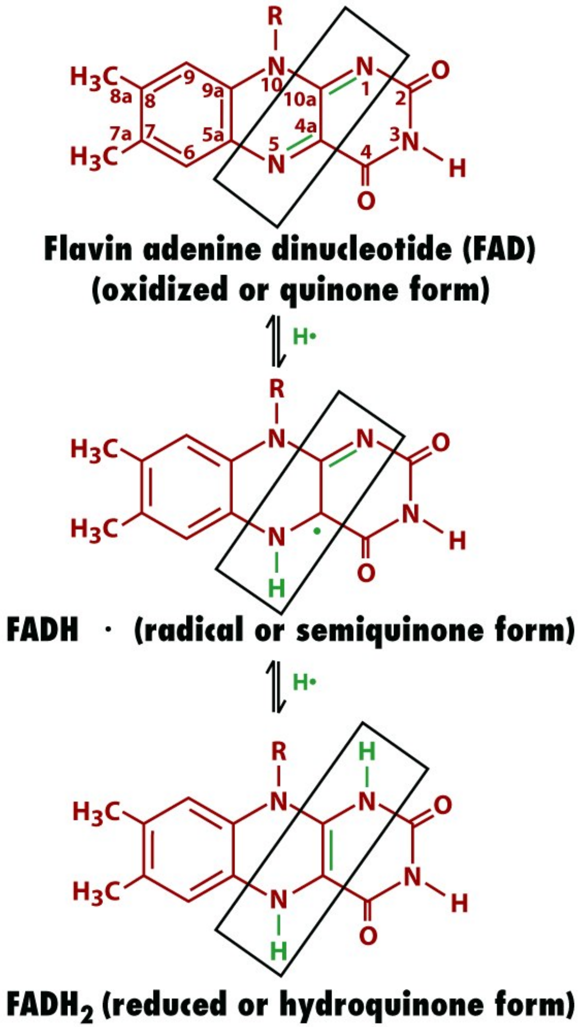


Figure 13-12 Fundamentals of Biochemistry, 2/e

The Nernst equation

Oxidation-reduction reactions: electron transfer reaction
Electron donor & acceptor
Electrochemical cells:

- redox pair (analogous to acid-base pair)
- a half-reactions: electron donor and its conjugate electron acceptor

$$E = E_0 - \left(\frac{RT}{zF}\right) \ln\left(\frac{[red]}{[ox]}\right)$$

$$\Delta G^{o\prime} = -\, nF\Delta E^{o\prime}$$

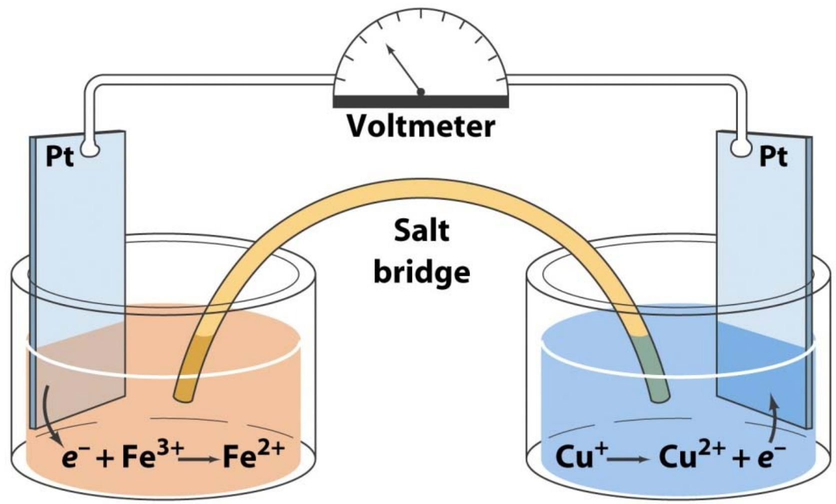


Figure 13-13 Fundamentals of Biochemistry, 2/e

Table 13-3 Standard Reduction Potentials of Some Biochemically Important Half-Reactions

Half-Reaction	$\mathscr{E}°'$ (V)
$\frac{1}{2}O_2 + 2H^+ + 2e^- \rightleftharpoons H_2O$	0.815
$SO_4^{2-} + 2H^+ + 2e^- \rightleftharpoons SO_3^{2-} + H_2O$	0.48
$NO_3^- + 2H^+ + 2e^- \rightleftharpoons NO_2^- + H_2O$	0.42
Cytochrome a_3 (Fe^{3+}) + e^- $\rightleftharpoons$ cytochrome a_3 (Fe^{2+})	0.385
$O_2(g) + 2H^+ + 2e^- \rightleftharpoons H_2O_2$	0.295
Cytochrome *a* (Fe^{3+}) + e^- $\rightleftharpoons$ cytochrome *a* (Fe^{2+})	0.29
Cytochrome *c* (Fe^{3+}) + e^- $\rightleftharpoons$ cytochrome *c* (Fe^{2+})	0.235
Cytochrome c_1 (Fe^{3+}) + e^- $\rightleftharpoons$ cytochrome c_1 (Fe^{2+})	0.22
Cytochrome *b* (Fe^{3+}) + e^- $\rightleftharpoons$ cytochrome *b* (Fe^{2+}) (*mitochondrial*)	0.077
Ubiquinone + $2H^+ + 2e^-$ $\rightleftharpoons$ ubiquinol	0.045
Fumarate$^-$ + $2H^+ + 2e^-$ $\rightleftharpoons$ succinate$^-$	0.031
FAD + $2H^+ + 2e^-$ $\rightleftharpoons$ $FADH_2$ (*in flavoproteins*)	~0.
Oxaloacetate$^-$ + $2H^+ + 2e^-$ $\rightleftharpoons$ malate$^-$	−0.166
Pyruvate$^-$ + $2H^+ + 2e^-$ $\rightleftharpoons$ lactate$^-$	−0.185
Acetaldehyde + $2H^+ + 2e^-$ $\rightleftharpoons$ ethanol	−0.197
FAD + $2H^+ + 2e^-$ $\rightleftharpoons$ $FADH_2$ (*free coenzyme*)	−0.219
$S + 2H^+ + 2e^- \rightleftharpoons H_2S$	−0.23
Lipoic acid + $2H^+ + 2e^-$ $\rightleftharpoons$ dihydrolipoic acid	−0.29
$NAD^+ + H^+ + 2e^-$ $\rightleftharpoons$ NADH	−0.315
$NADP^+ + H^+ + 2e^-$ $\rightleftharpoons$ NADPH	−0.320
Cystine + $2H^+ + 2e^-$ $\rightleftharpoons$ 2 cysteine	−0.340
Acetoacetate$^-$ + $2H^+ + 2e^-$ $\rightleftharpoons$ β-hydroxybutyrate$^-$	−0.346
$H^+ + e^- \rightleftharpoons \frac{1}{2}H_2$	−0.421
Acetate$^-$ + $3H^+ + 2e^-$ $\rightleftharpoons$ acetaldehyde + H_2O	−0.581

Source: Mostly from Loach, P.A., *In* Fasman, G.D. (Ed.), *Handbook of Biochemistry and Molecular Biology* (3rd ed.), Physical and Chemical Data, Vol. I, pp. 123–130, CRC Press (1976).

Table 13-3 Fundamentals of Biochemistry, 2/e

$$\frac{1}{2}O_2 + 2H^+ + 2e^- \longrightarrow H_2O \qquad E^{o\prime} = +0.82\text{ V}$$

$$NADH \longrightarrow NAD^+ + H^+ + 2e^- \qquad E^{o\prime} = +0.32\text{ V}$$

$$\frac{1}{2}O_2 + 2H^+ + NADH \longrightarrow H_2O + NAD^+ + H^+ \qquad \Delta E^{o\prime} = +1.14\text{ V}$$

$$\Delta G^{o\prime} = -(2)(23.06)(1.14) = -52.6\text{ kcal/mol}$$

Experimental approaches to the study of metabolism

Understanding the sequence, mechanism, and regulation

Approaches

- tracing metabolic fates
- perturbing the system
  - metabolic inhibitors, genetic defects, genetic manipulation
- DNA microarrays (DNA chips): transcriptomics
- proteomics

13C NMR spectrum of rat liver

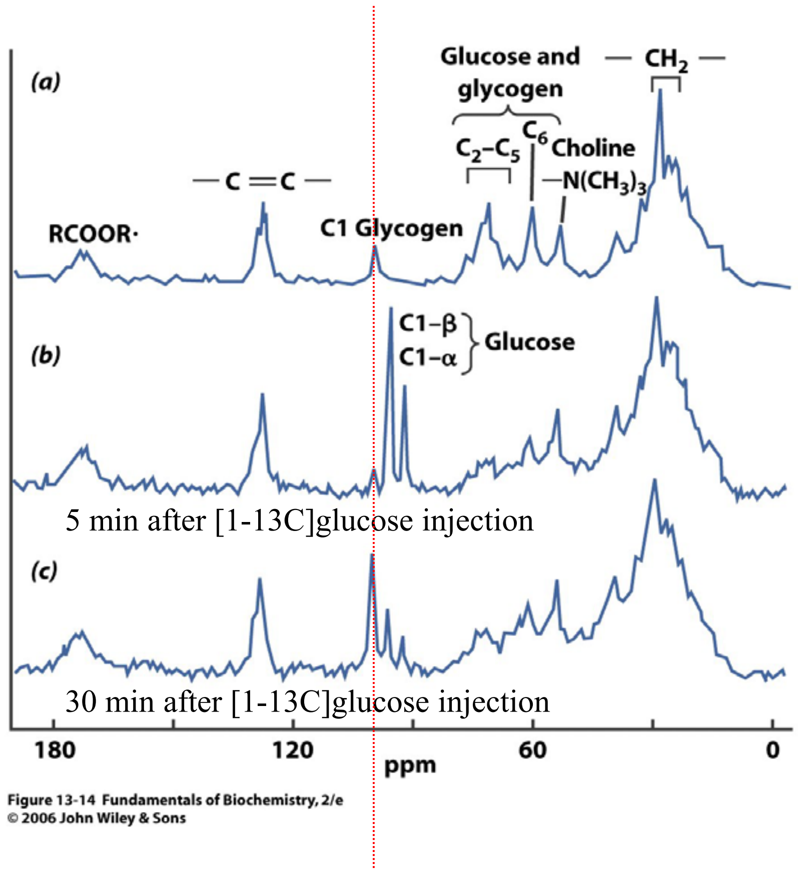


Figure 13-14 Fundamentals of Biochemistry, 2/e

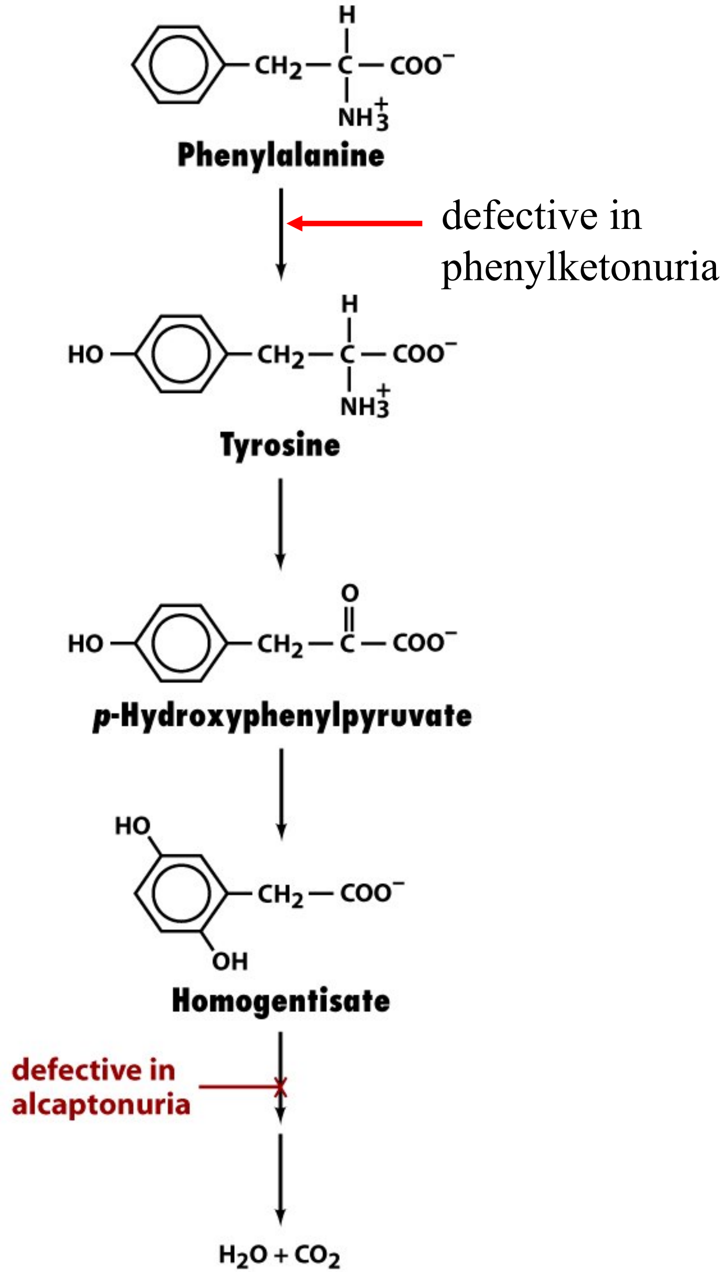


Figure 13-15 Fundamentals of Biochemistry, 2/e

PCR amplified yeast cDNAs

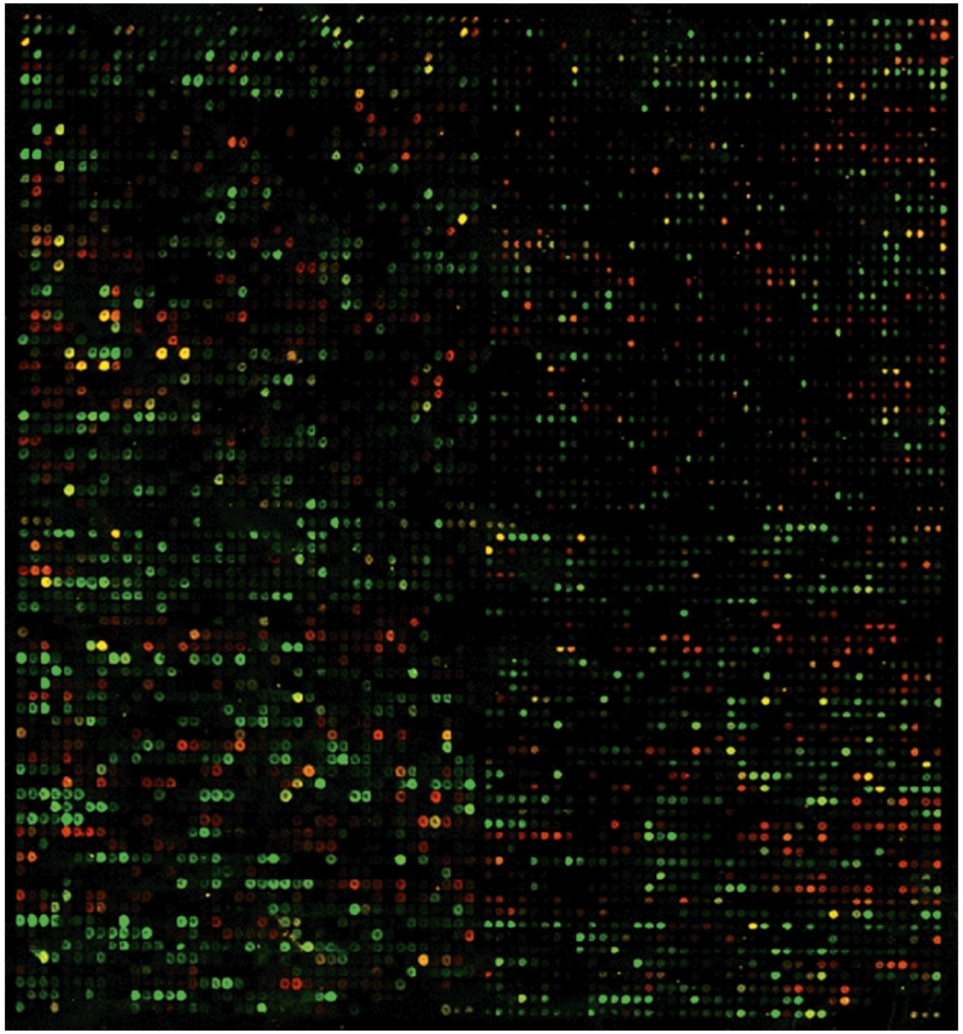


Figure 13-16 Fundamentals of Biochemistry, 2/e

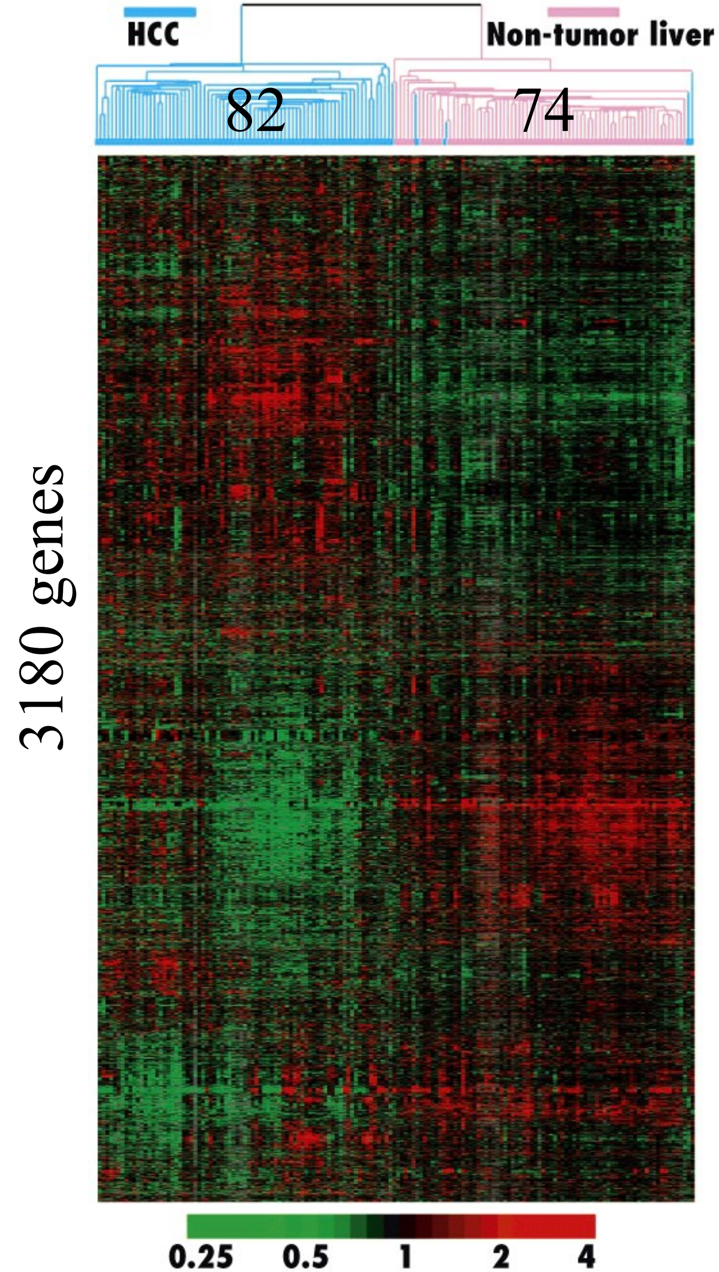


Figure 13-17 Fundamentals of Biochemistry, 2/e