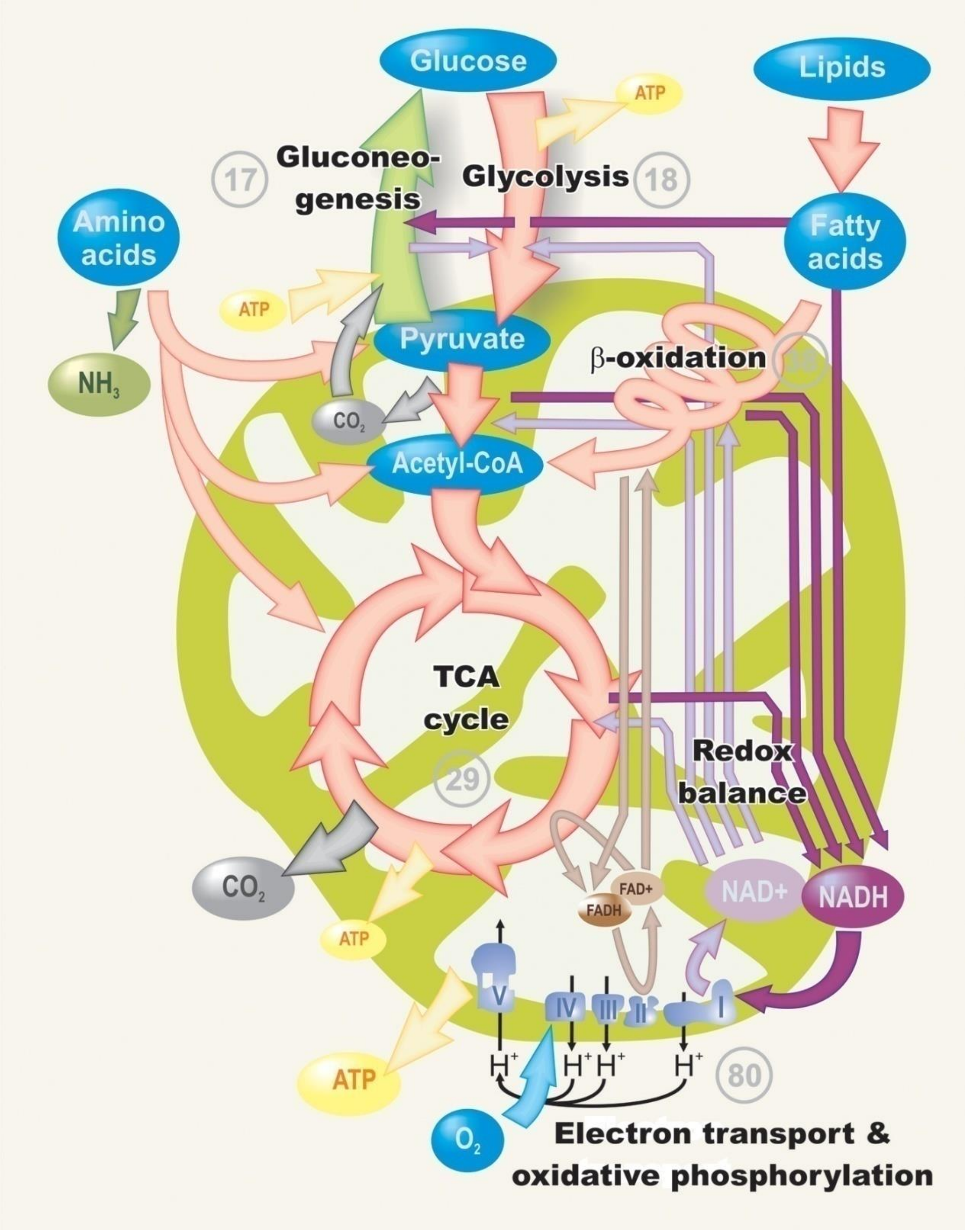


BIOENERGETICS AND METABOLISM

PRINCIPLES OF BIOENERGETICS

❖Living cells and organisms must perform work to stay alive, to grow, and to reproduce.

❖The ability to harness energy and to channel it into biological work is a fundamental property of all living organisms.

❖Modern organisms use the chemical energy in fuels to bring about the synthesis of complex, highly ordered macromolecules from simple precursors.

❖They also convert the chemical energy of fuels into concentration gradients and electrical gradients, into motion and heat, and, in a few organisms such as fireflies and some deep-sea fish, into light.

❖Photosynthetic organisms transduce light energy into all these other forms of energy.

- Many quantitative observations made by physicists and chemists on the interconversion of different forms of energy led, in the nineteenth century, to the formulation of two fundamental laws of thermodynamics.

- The first law is the principle of the conservation of energy: for any physical or chemical change, the total amount of energy in the universe remains constant; energy may change form or it may be transported from one region to another, but it cannot be created or destroyed.

- The second law of thermodynamics, which can be stated in several forms, says that the universe always tends toward increasing disorder: in all natural processes, the entropy of the universe increases.

- Three thermodynamic quantities that describe the energy changes occurring in a chemical reaction could be defined as;

- **Gibbs free energy, G**, expresses the amount of energy capable of doing work during a reactionat constant temperature and pressure.

- **Enthalpy, H**, is the heat content of the reacting system. It reflects the number and kinds of chemical bonds in the reactants and products.

- **Entropy, S**, is a quantitative expression for the randomness or disorder in a system (see Box 1–3). When the products of a reaction are less complex and more disordered than the reactants, the reaction is said to proceed with a gain in entropy.

- Under the conditions existing in biological systems (including constant temperature and pressure), changes in free energy, enthalpy, and entropy are related to each other quantitatively by the equation;

$$\Delta G = \Delta H - T\Delta S$$

- in which ΔG is the change in Gibbs free energy of the reacting system, ΔH is the change in enthalpy of the system, T is the absolute temperature, and ΔS is the change in entropy of the system.

- The composition of a reacting system (a mixture of chemical reactants and products) tends to continue changing until equilibrium is reached.

- At the equilibrium concentration of reactants and products, the rates of the forward and reverse reactions are exactly equal and no further net change occurs in the system.

- The concentrations of reactants and products at equilibrium define the equilibrium constant, Keq.

$$aA + bB \rightleftharpoons cC + dD$$

$$K_{eq} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

- Under standard conditions (298 °K or 25 °C), when reactants and products are initially present at 1 M concentrations or, for gases, at partial pressures of 101.3 kilopascals (kPa), or 1 atm, the force driving the system toward equilibrium is defined as the standard free-energy change, ΔG^0.

- By this definition, the standard state for reactions that involve hydrogen ions is $[H^+]$ 1 M, or pH 0.

- Most biochemical reactions, however, occur in well-buffered aqueous solutions near pH 7; both the pH and the concentration of water (55.5 M) are essentially constant.

- For convenience of calculations, biochemists therefore define a different standard state, in which the concentration of H^+ is 10^{-7} M (pH 7) and that of water is 55.5 M.

- Physical constants based on this biochemical standard state are called standard transformed constants and are written with a prime (such as $\Delta G'^\circ$ and K'_{eq}) to distinguish them from the untransformed constants used by chemists and physicists.

- ΔG’° is the difference between the free-energy content of the products and the free-energy content of the reactants, under standard conditions.

- When ΔG’° is negative, the products contain less free energy than the reactants and the reaction will proceed spontaneously under standard conditions.

- A positive value of ΔG’° means that the products of the reaction contain more free energy than the reactants, and this reaction will tend to go in the reverse direction.

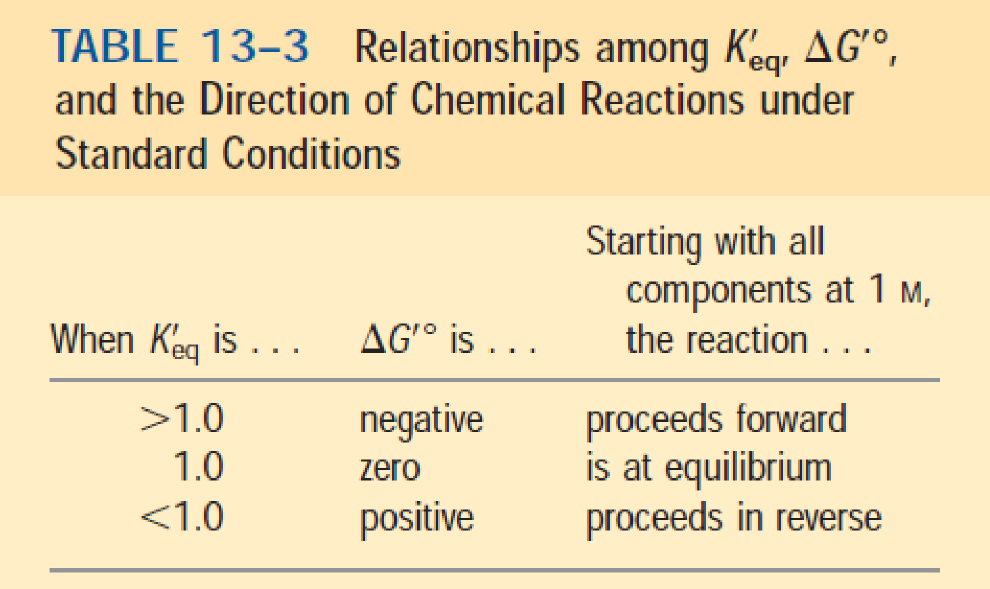


TABLE 13–3 Relationships among K'_{eq}, $\Delta G'^{\circ}$, and the Direction of Chemical Reactions under Standard Conditions

When K'_{eq} is . . .	$\Delta G'^{\circ}$ is . . .	Starting with all components at 1 M, the reaction . . .
>1.0	negative	proceeds forward
1.0	zero	is at equilibrium
<1.0	positive	proceeds in reverse

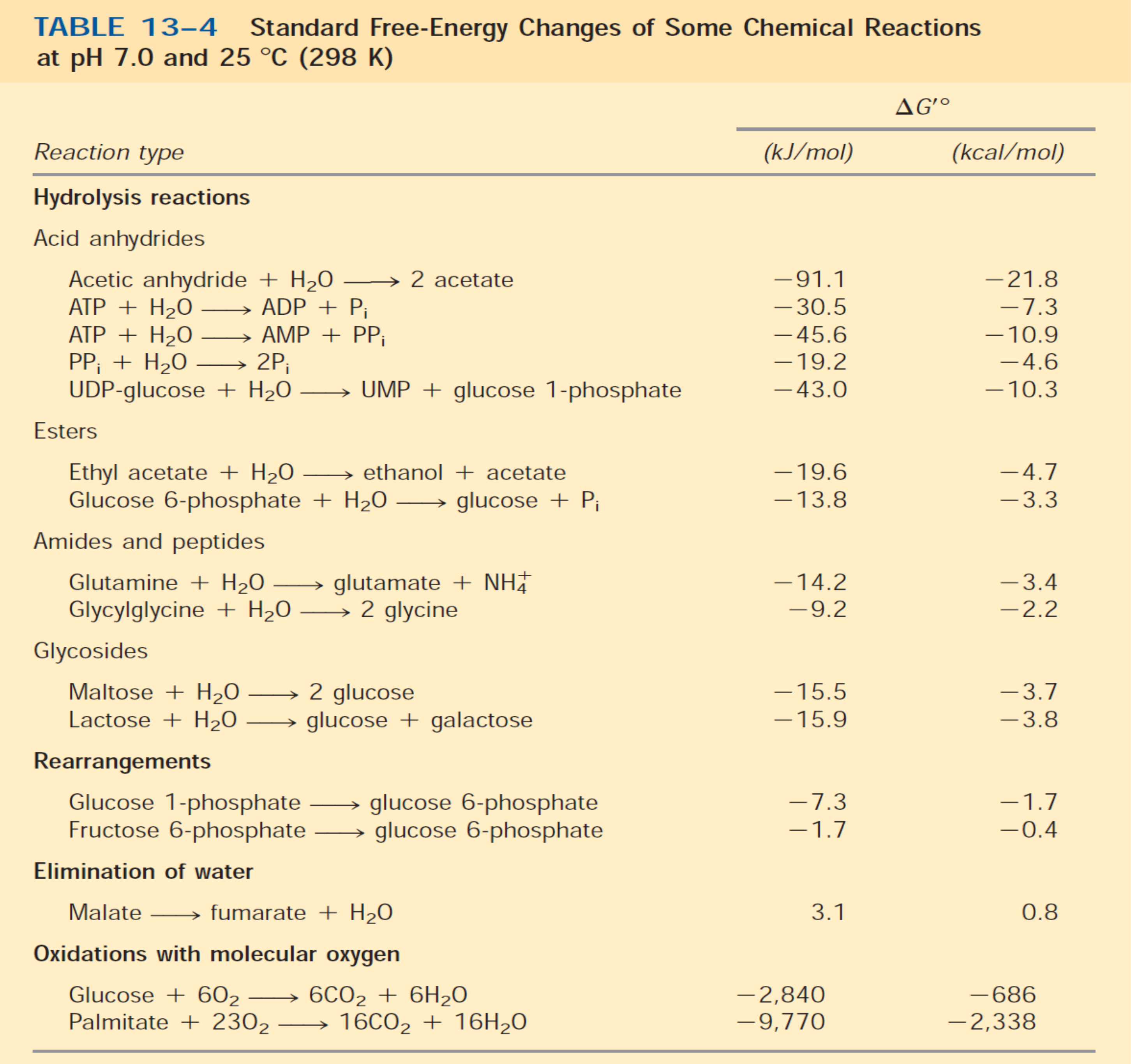
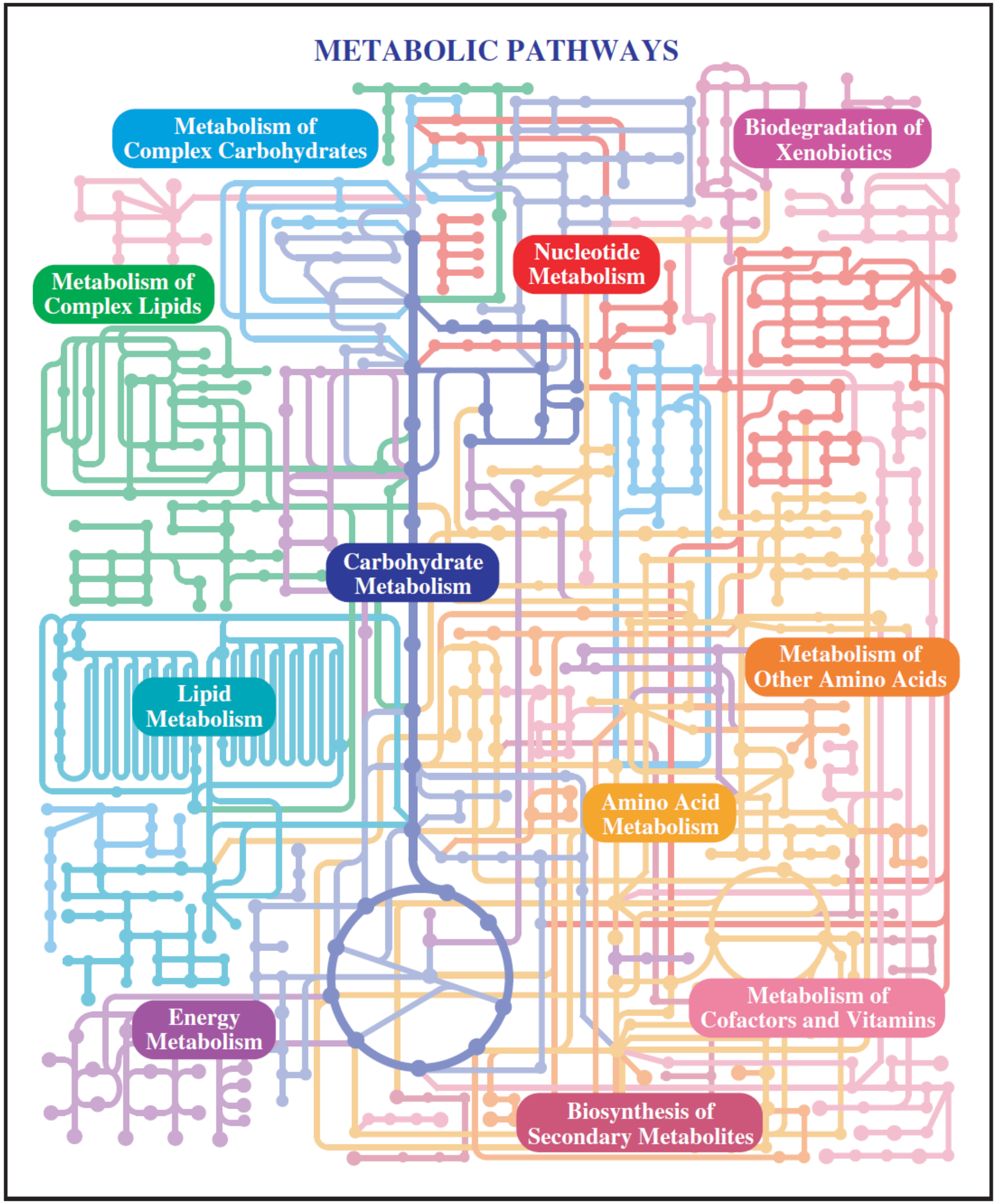


TABLE 13–4 **Standard Free-Energy Changes of Some Chemical Reactions at pH 7.0 and 25 °C (298 K)**

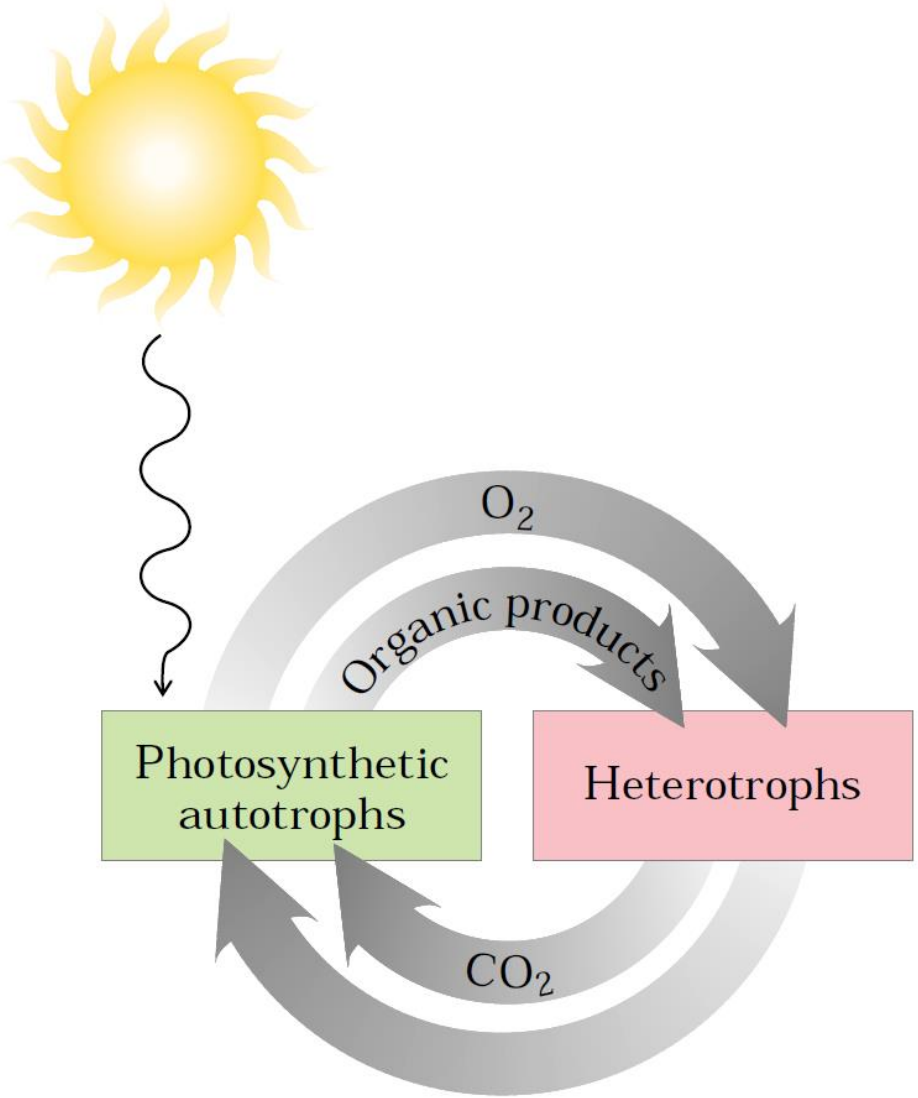
	$\Delta G'^\circ$	
Reaction type	*(kJ/mol)*	*(kcal/mol)*
Hydrolysis reactions		
Acid anhydrides		
Acetic anhydride + $H_2O \longrightarrow$ 2 acetate	−91.1	−21.8
ATP + $H_2O \longrightarrow$ ADP + P_i	−30.5	−7.3
ATP + $H_2O \longrightarrow$ AMP + PP_i	−45.6	−10.9
PP_i + $H_2O \longrightarrow 2P_i$	−19.2	−4.6
UDP-glucose + $H_2O \longrightarrow$ UMP + glucose 1-phosphate	−43.0	−10.3
Esters		
Ethyl acetate + $H_2O \longrightarrow$ ethanol + acetate	−19.6	−4.7
Glucose 6-phosphate + $H_2O \longrightarrow$ glucose + P_i	−13.8	−3.3
Amides and peptides		
Glutamine + $H_2O \longrightarrow$ glutamate + NH_4^+	−14.2	−3.4
Glycylglycine + $H_2O \longrightarrow$ 2 glycine	−9.2	−2.2
Glycosides		
Maltose + $H_2O \longrightarrow$ 2 glucose	−15.5	−3.7
Lactose + $H_2O \longrightarrow$ glucose + galactose	−15.9	−3.8
Rearrangements		
Glucose 1-phosphate $\longrightarrow$ glucose 6-phosphate	−7.3	−1.7
Fructose 6-phosphate $\longrightarrow$ glucose 6-phosphate	−1.7	−0.4
Elimination of water		
Malate $\longrightarrow$ fumarate + H_2O	3.1	0.8
Oxidations with molecular oxygen		
Glucose + $6O_2 \longrightarrow 6CO_2 + 6H_2O$	−2,840	−686
Palmitate + $23O_2 \longrightarrow 16CO_2 + 16H_2O$	−9,770	−2,338

❖Metabolism is a highly coordinated cellular activity in which many multienzyme systems (metabolic pathways) cooperate to;

- ❖(1)obtain chemical energy by capturing solar energy or degrading energy-rich nutrients from the environment;
- ❖(2)convert nutrient molecules into the cell’s own characteristic molecules, including precursors of macromolecules;
- ❖(3)polymerize monomeric precursors into macromolecules: proteins, nucleic acids, and polysaccharides; and
- ❖(4)synthesize and degrade biomolecules required for specialized cellular functions, such as membrane lipids, intracellular messengers, and pigments.


METABOLIC PATHWAYS
Metabolism of Complex Carbohydrates
Biodegradation of Xenobiotics
Nucleotide Metabolism
Metabolism of Complex Lipids
Carbohydrate Metabolism
Metabolism of Other Amino Acids
Lipid Metabolism
Amino Acid Metabolism
Energy Metabolism
Metabolism of Cofactors and Vitamins
Biosynthesis of Secondary Metabolites

- Living organisms can be divided into two large groups according to the chemical form in which they obtain carbon from the environment.
  - **Autotrophs** (such as photosynthetic bacteria, green algae, and vascular plants) can use carbon dioxide from the atmosphere as their sole source of carbon, from which they construct all their carbon-containing biomolecules.
  - **Heterotrophs** cannot use atmospheric carbon dioxide and must obtain carbon from their environment in the form of relatively complex organic molecules such as glucose. Multicellular animals and most microorganisms are heterotrophic.
- Autotrophic cells and organisms are relatively self-sufficient, whereas heterotrophic cells and organisms, with their requirements for carbon in more complex forms, must subsist on the products of other organisms.



- The flow of mass through this cycle is enormous; about $4x10^{11}$ metric tons of carbon are turned over in the biosphere annually.

- In our biosphere, autotrophs and heterotrophs live together in a vast, interdependent cycle.

- Autotrophic organisms use atmospheric carbon dioxide to build their organic biomolecules, some of them generating oxygen from water in the process.

- Heterotrophs in turn use the organic products of autotrophs as nutrients and return carbon dioxide to the atmosphere.

- Some of the oxidation reactions that produce carbon dioxide also consume oxygen, converting it to water.

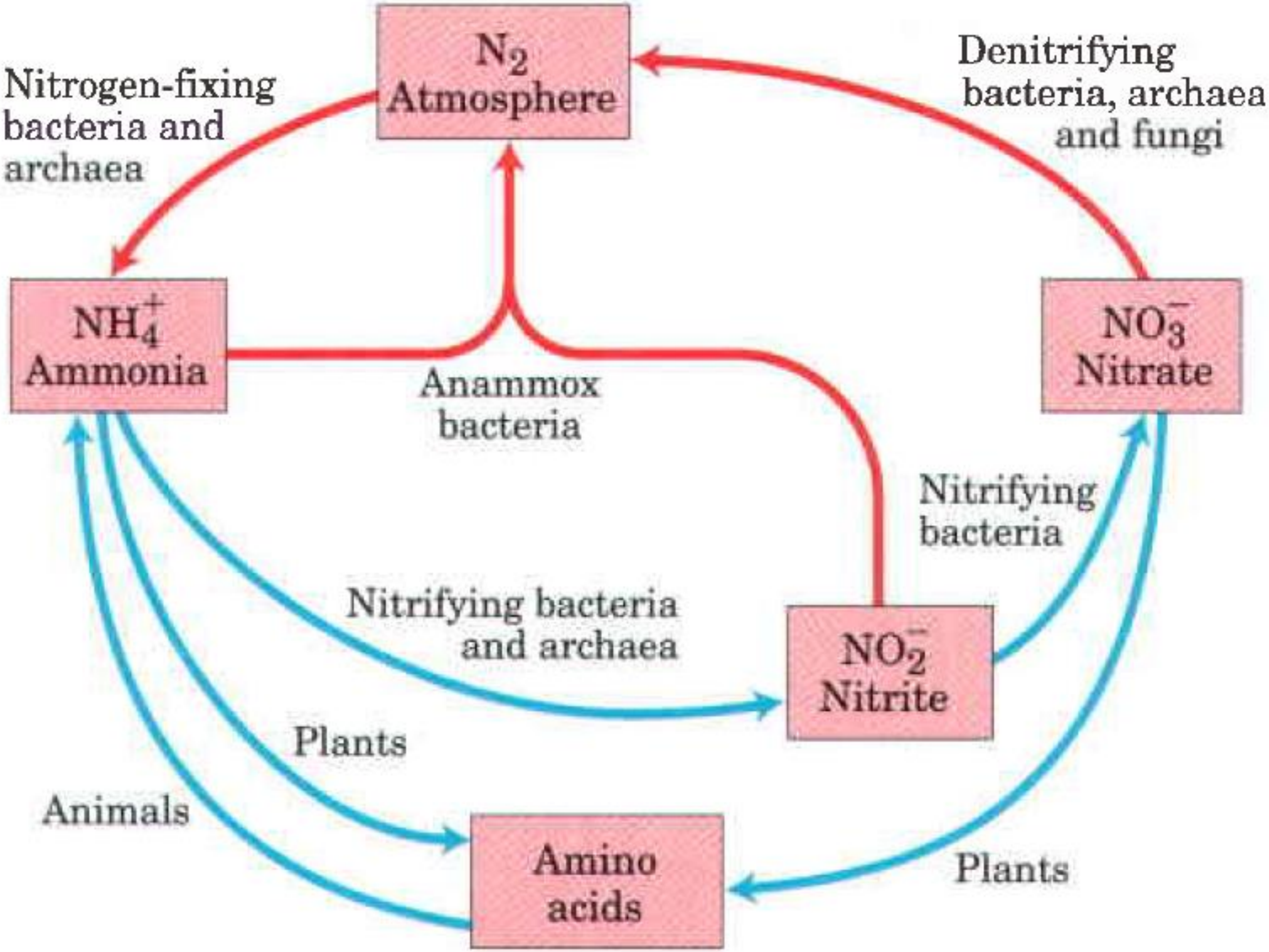
- Thus carbon, oxygen, and water are constantly cycled between the heterotrophic and autotrophic worlds, with solar energy as the driving force for this global process.

❖All living organisms also require a source of nitrogen, which is necessary for the synthesis of amino acids, nucleotides, and other compounds.

❖Bacteria and plants can generally use either ammonia or nitrate as their sole source of nitrogen, but vertebrates must obtain nitrogen in the form of amino acids or other organic compounds.

❖Only a few organisms—the cyanobacteria and many species of soil bacteria that live symbiotically on the roots of some plants—are capable of converting (“fixing”) atmospheric nitrogen (N_2) into ammonia.

❖Therefore there is a cycle of nitrogen in the nature.



N_2
Atmosphere

Nitrogen-fixing bacteria and archaea

Denitrifying bacteria, archaea and fungi

NH_4^+
Ammonia

Anammox bacteria

NO_3^-
Nitrate

Nitrifying bacteria

Nitrifying bacteria and archaea

NO_2^-
Nitrite

Plants

Animals

Amino acids

Plants

- These cycles of matter are driven by an enormous flow of energy into and through the biosphere, beginning with the capture of solar energy by photosynthetic organisms and use of this energy to generate energy-rich carbohydrates and other organic nutrients; These nutrients are then used as energy sources by heterotrophic organisms.

- In metabolic processes, and in all energy transformations, there is a loss of useful energy (free energy) and an inevitable increase in the amount of unusable energy (heat and entropy).

- In contrast to the cycling of matter, therefore, energy flows one way through the biosphere; organisms cannot regenerate useful energy from energy dissipated as heat and entropy.

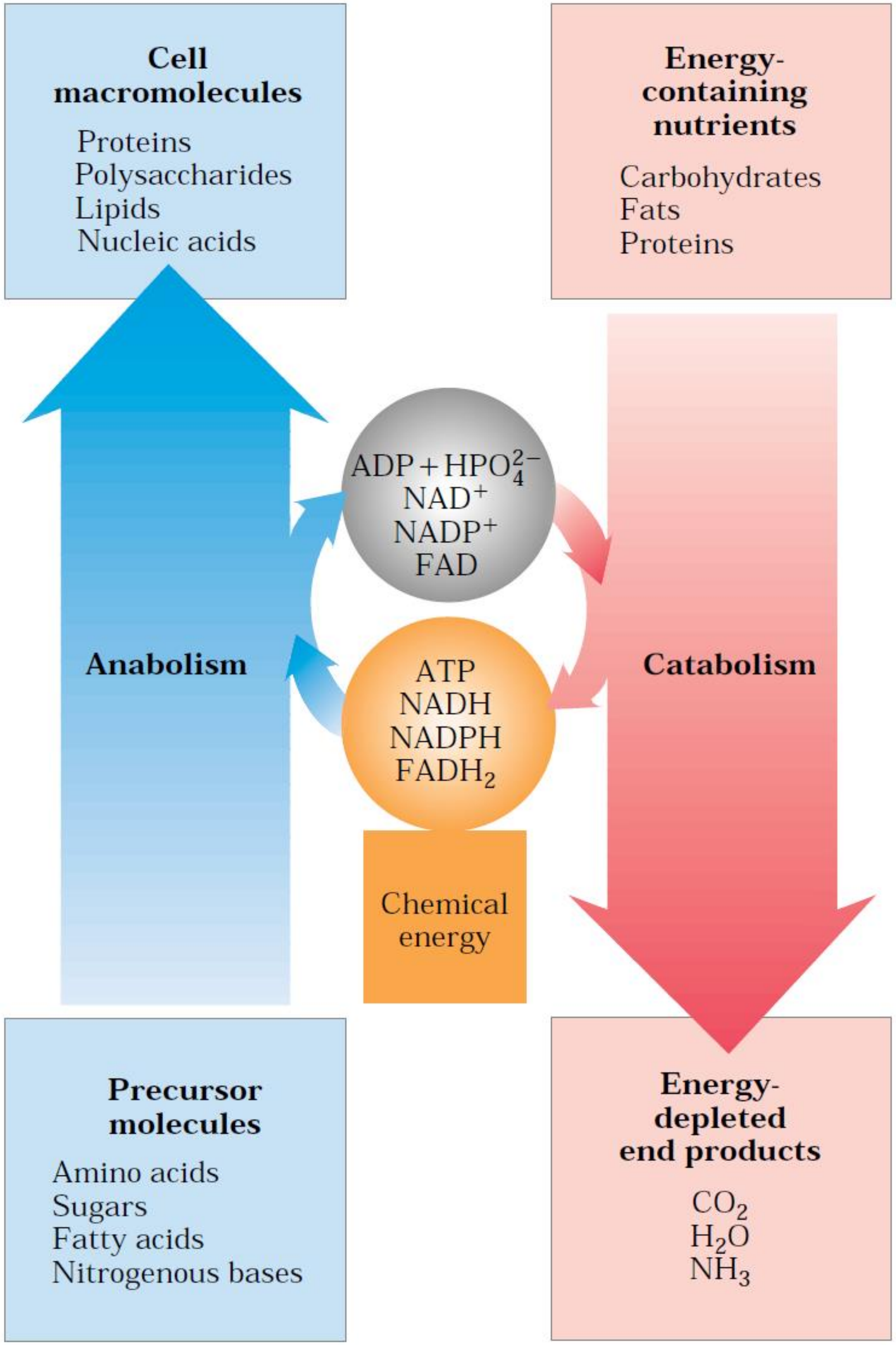
- Carbon, oxygen, and nitrogen recycle continuously, but energy is constantly transformed into unusable forms such as heat.

❖**Metabolism**, the sum of all the chemical transformations taking place in a cell or organism, occurs through a series of enzyme-catalyzed reactions that constitute **metabolic pathways**.

❖Each of the consecutive steps in a metabolic pathway brings about a specific, small chemical change, usually the removal, transfer, or addition of a particular atom or functional group.

❖The precursor is converted into a product through a series of metabolic intermediates called **metabolites**.

❖The term **intermediary metabolism** is often applied to the combined activities of all the metabolic pathways that interconvert precursors, metabolites, and products of low molecular weight (generally, Mr , 1,000).

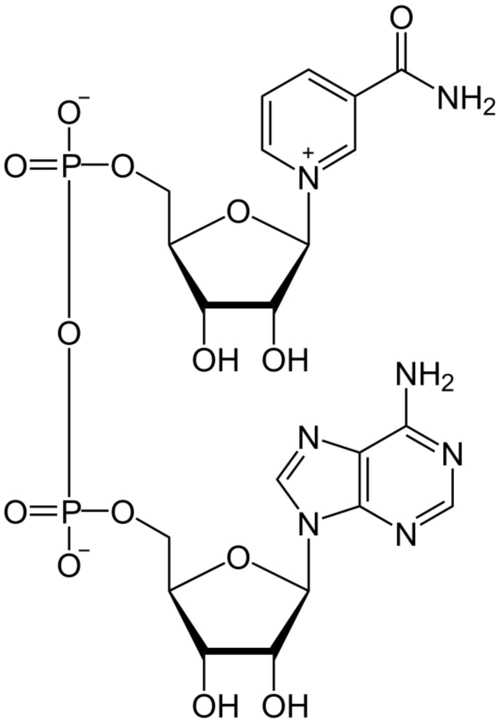


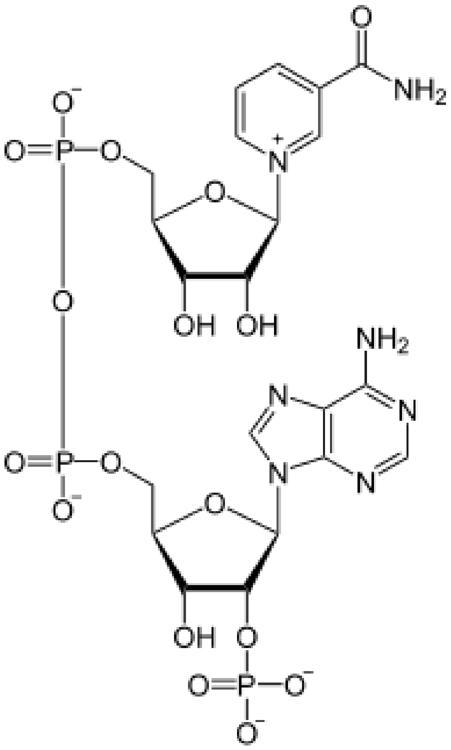
- ❖**Catabolism** is the degradative phase of metabolism in which organic nutrient molecules (carbohydrates, fats, and proteins) are converted into smaller, simpler end products (such as lactic acid, CO_2, and NH_3).

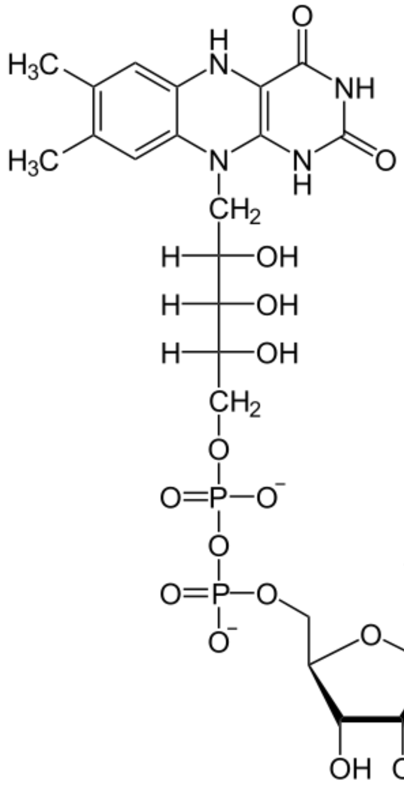
- ❖In **anabolism**, also called biosynthesis, small, simple precursors are built up into larger and more complex molecules, including lipids, polysaccharides, proteins, and nucleic acids.

- Catabolic pathways release energy, some of which is conserved in the formation of ATP and reduced electron carriers (NADH, NADPH, and $FADH_2$); the rest is lost as heat.

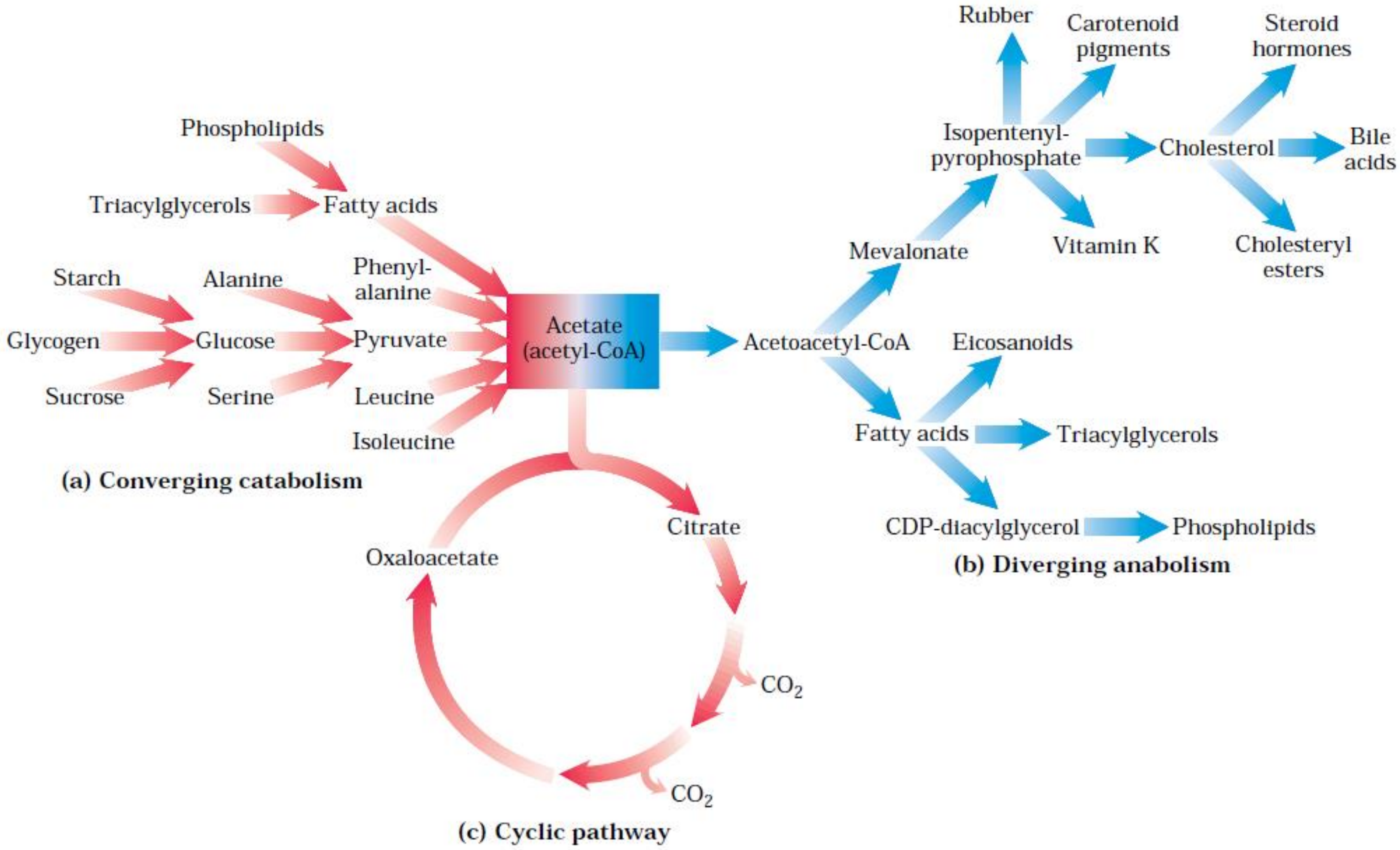
- Anabolic reactions require an input of energy, generally in the form of the phosphoryl group transfer potential of ATP and the reducing power of NADH, NADPH, and $FADH_2$.







❖Some metabolic pathways are linear, and some are branched, yielding multiple useful end products from a single precursor or converting several starting materials into a single product.



(a) Converging catabolism

(b) Diverging anabolism

(c) Cyclic pathway

❖Some pathways are cyclic: one starting component of the pathway is regenerated in a series of reactions that converts another starting component into a product.

Regulation of Metabolism

- Most cells have the enzymes to carry out both the degradation and the synthesis of the important categories of biomolecules—fatty acids, for example.

- The simultaneous synthesis and degradation of fatty acids would be wasteful, however, and this is prevented by reciprocally regulating the anabolic and catabolic reaction sequences: when one sequence is active, the other is suppressed.

- Such regulation could not occur if anabolic and catabolic pathways were catalyzed by exactly the same set of enzymes, operating in one direction for anabolism, the opposite direction for catabolism.

- Catabolic and anabolic pathways that connect the same two end points may employ many of the same enzymes, but invariably at least one of the steps is catalyzed by different enzymes in the catabolic and anabolic directions.

❖Moreover, for both anabolic and catabolic pathways to be essentially irreversible, the reactions unique to each direction must include at least one that is thermodynamically very favorable—in other words, a reaction for which the reverse reaction is very unfavorable.

❖As a further contribution to the separate regulation of catabolic and anabolic reaction sequences, paired catabolic and anabolic pathways commonly take place in different cellular compartments: for example, fatty acid catabolism in mitochondria, fatty acid synthesis in the cytosol.

❖Metabolic pathways are regulated at several levels, from within the cell and from outside. The most immediate regulation is by the availability of substrate, a second type of rapid control from within is allosteric regulation by a modulator.

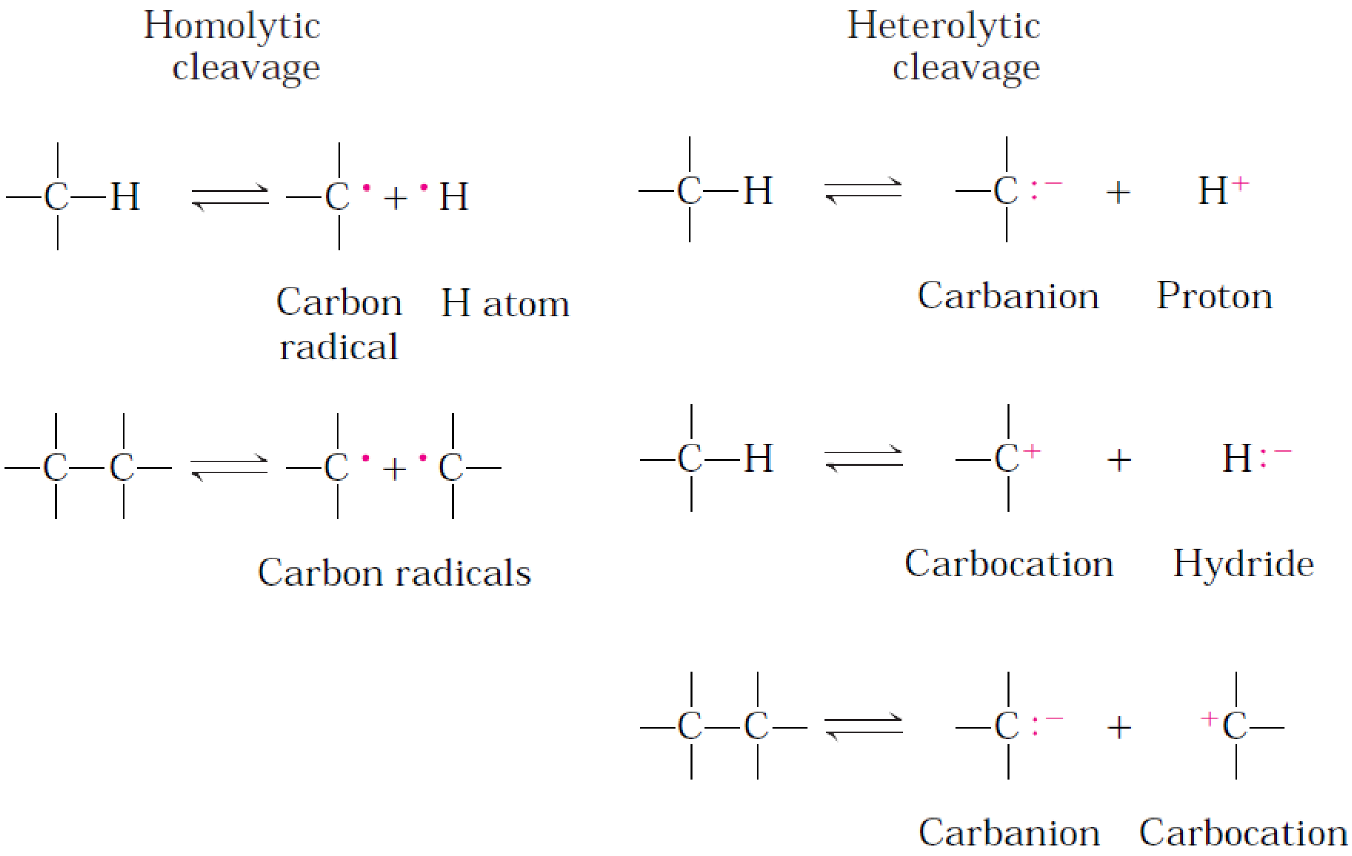
❖In multicellular organisms, the metabolic activities of different tissues are regulated and integrated by growth factors and hormones that act from outside the cell.

Classification of Metabolic Reactions

- Most of the reactions in living cells fall into one of five general categories:
- (1) reactions that make or break carbon–carbon bonds;
- (2) internal rearrangements, isomerizations, and eliminations;
- (3) free-radical reactions;
- (4) group transfers; and
- (5) oxidation-reductions.

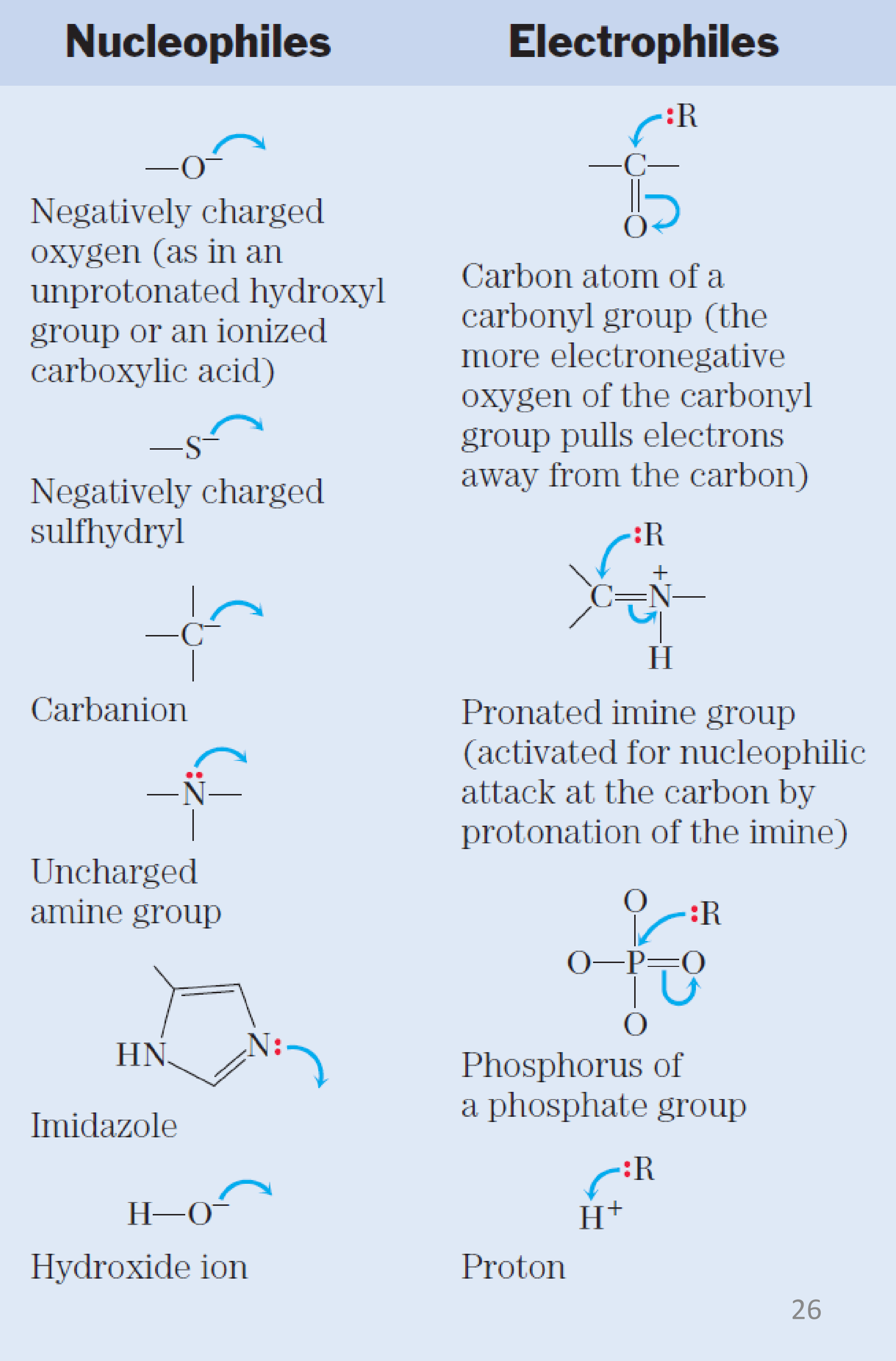
- Before proceeding, however, we should review two basic chemical principles.

- First, a covalent bond consists of a shared pair of electrons, and the bond can be broken in two general ways.



❖The second basic principle is that many biochemical reactions involve interactions between nucleophiles (functional groups rich in and capable of donating electrons) and electrophiles (electron-deficient functional groups that seek electrons).

❖Nucleophiles combine with and give up electrons to electrophiles.



Nucleophiles

- Negatively charged oxygen (as in an unprotonated hydroxyl group or an ionized carboxylic acid)
- Negatively charged sulfhydryl
- Carbanion
- Uncharged amine group
- Imidazole
- Hydroxide ion

Electrophiles

- Carbon atom of a carbonyl group (the more electronegative oxygen of the carbonyl group pulls electrons away from the carbon)
- Pronated imine group (activated for nucleophilic attack at the carbon by protonation of the imine)
- Phosphorus of a phosphate group
- Proton

1- Reactions That Make or Break Carbon–Carbon Bonds

- Heterolytic cleavage of a C-C bond yields a carbanion and a carbocation.

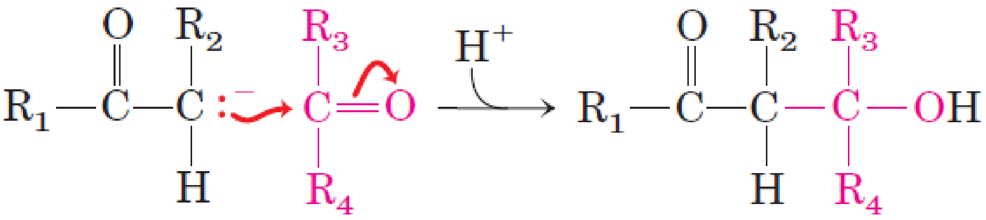
- Conversely, the formation of a C-C bond involves the combination of a nucleophilic carbanion and an electrophilic carbocation.

- Carbanions and carbocations are generally so unstable that their formation as reaction intermediates can be energetically inaccessible even with enzyme catalysts.

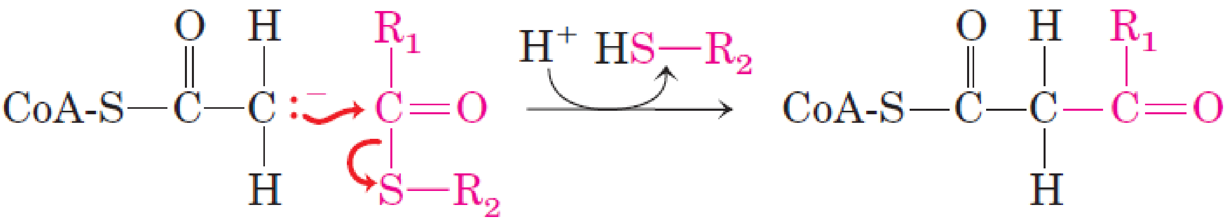
- Carbonyl groups are particularly important in the chemical transformations of metabolic pathways.

- The carbon of a carbonyl group has a partial positive charge due to the electron-withdrawing property of the carbonyl oxygen, and thus is an electrophilic carbon.

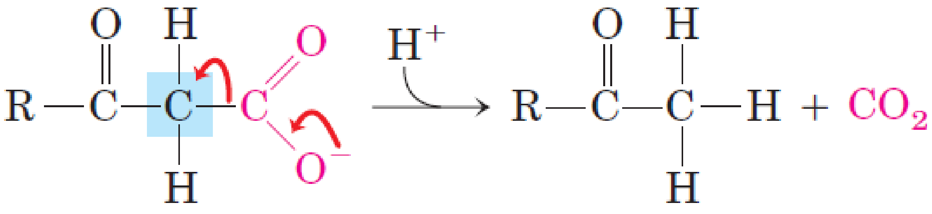
❖The importance of a carbonyl group is evident in three major classes of reactions in which C-C bonds are formed or broken (Fig. 13–4): aldol condensations, Claisen ester condensations, and decarboxylations.



Aldol condensation



Claisen ester condensation

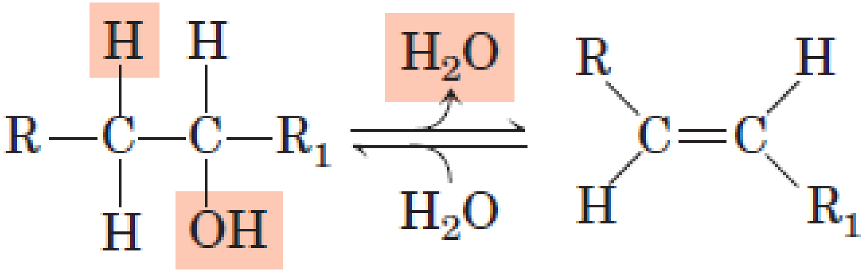


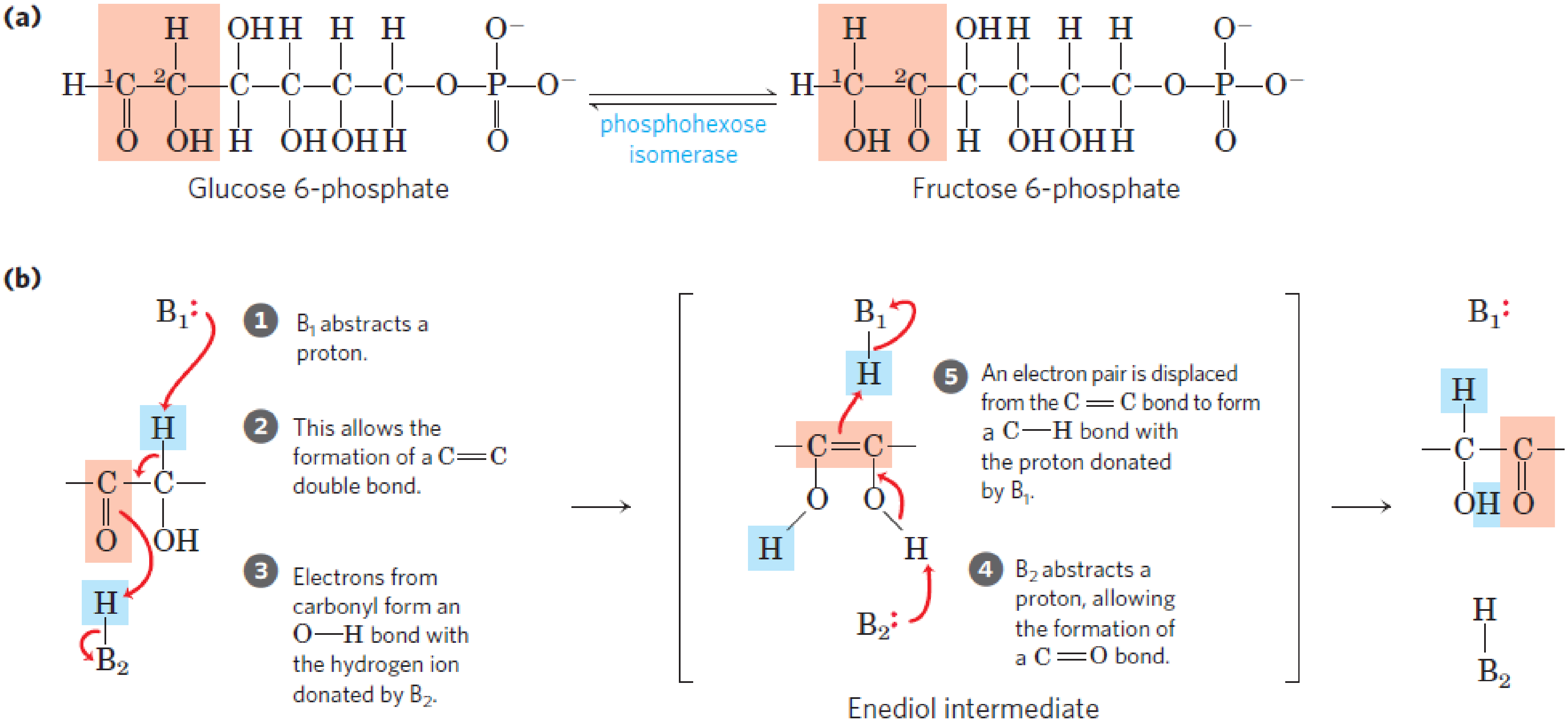
Decarboxylation of a β-keto acid

2- Internal Rearrangements, Isomerizations, and Eliminations

- Another common type of cellular reaction is an intramolecular rearrangement in which redistribution of electrons results in alterations of many different types without a change in the overall oxidation state of the molecule.

- For example, different groups in a molecule may undergo oxidation-reduction, with no net change in oxidation state of the molecule; groups at a double bond may undergo a cis-trans rearrangement; or the positions of double bonds may be transposed.





❶ B_1 abstracts a proton.

❷ This allows the formation of a C═C double bond.

❸ Electrons from carbonyl form an O—H bond with the hydrogen ion donated by B_2.

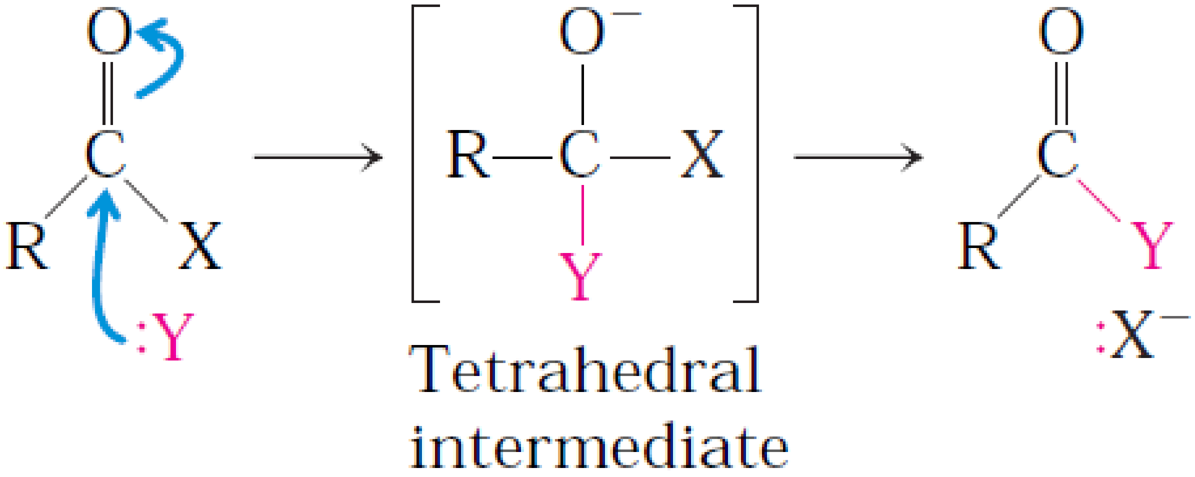
❹ B_2 abstracts a proton, allowing the formation of a C═O bond.

❺ An electron pair is displaced from the C═C bond to form a C—H bond with the proton donated by B_1.

3- *Group Transfer Reactions*

- The transfer of acyl, glycosyl, and phosphoryl groups from one nucleophile to another is common in living cells.

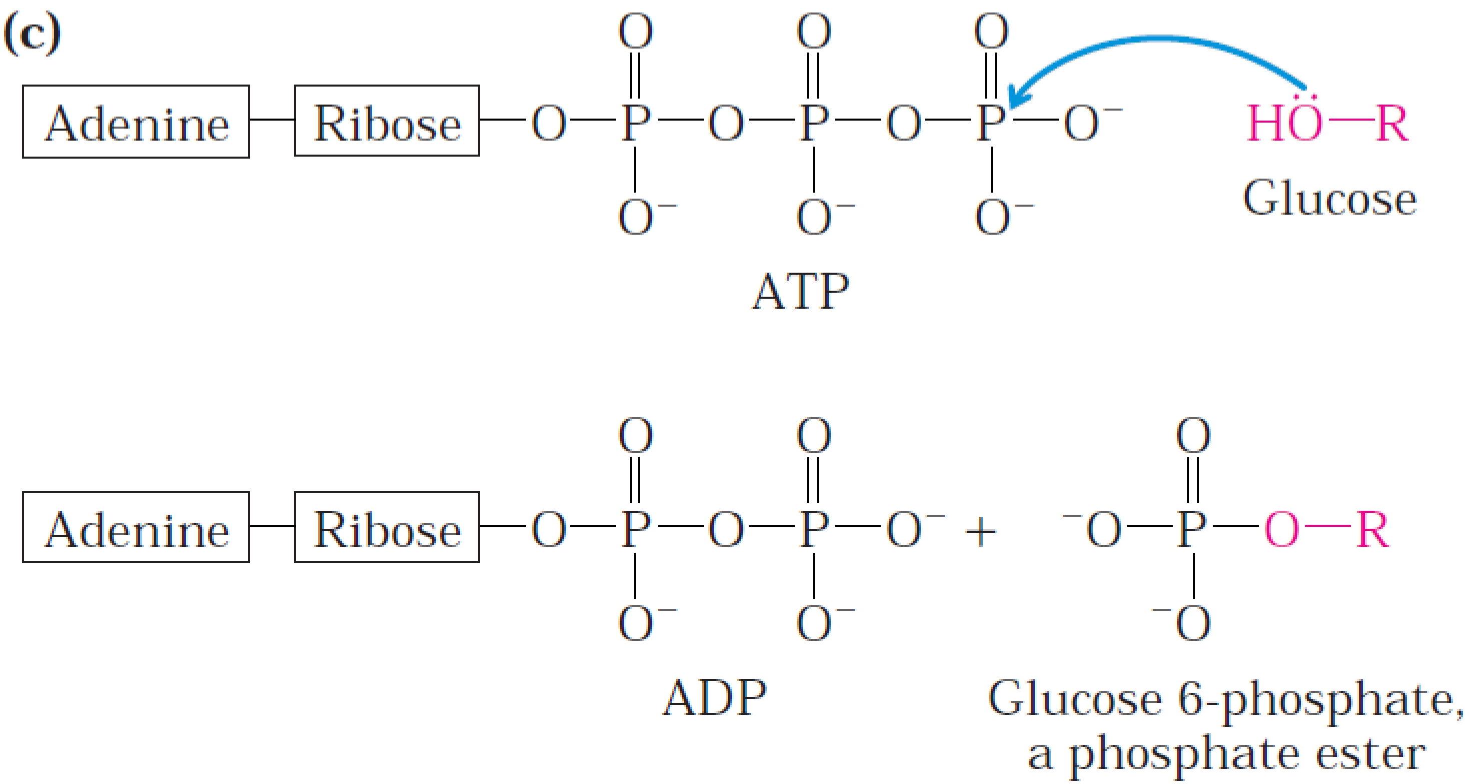
- Acyl group transfer generally involves the addition of a nucleophile to the carbonyl carbon of an acyl group to form a tetrahedral intermediate:



- Phosphoryl group transfers play a special role in metabolic pathways.

- A general theme in metabolism is the attachment of a good leaving group to a metabolic intermediate to “activate” the intermediate for subsequent reaction.

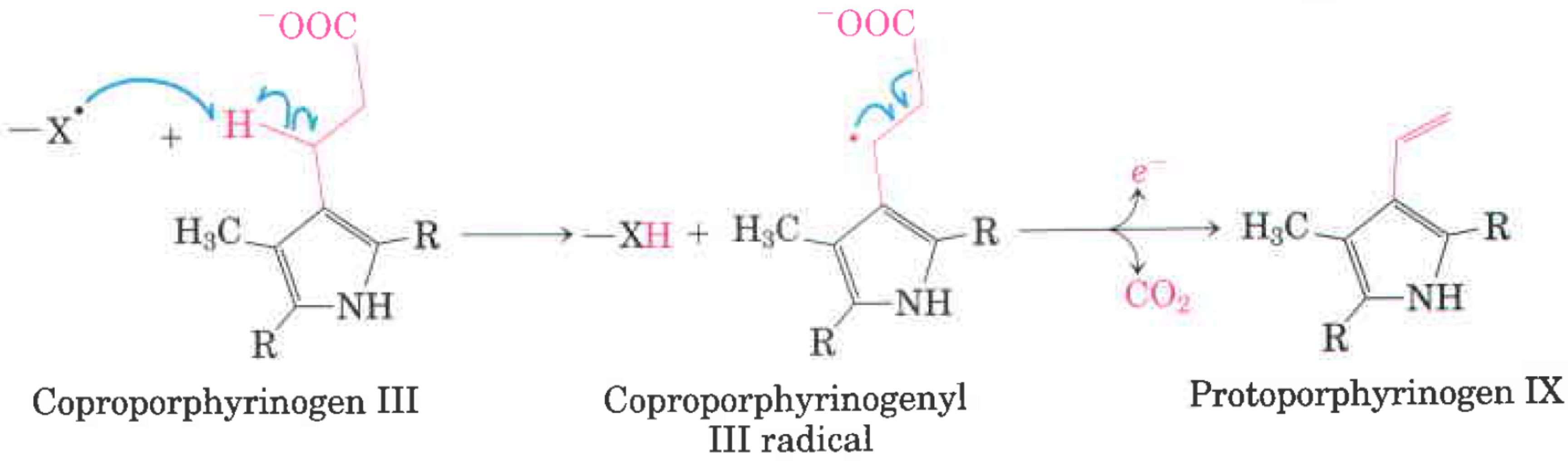
(c)



4- *Free-Radical Reactions*

- Once thought to be rare, the homolytic cleavage of covalent bonds to generate free radicals has now been found in a wide range of biochemical processes.

- These include: isomerizations that make use of adenosylcobalamin (vitamin B12) or S-adenosylmethionine, which are initiated with a 5’- deoxyadenosyl radical



5- *Oxidation-Reduction Reactions*

- Carbon atoms can exist in five oxidation states, depending on the elements with which they share electrons, and transitions between these states are of crucial importance in metabolism.

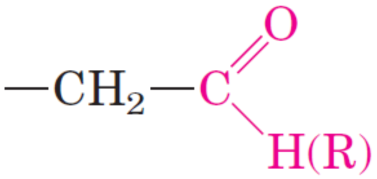
- In many biological oxidations, a compound loses two electrons and two hydrogen ions (that is, two hydrogen atoms); these reactions are commonly called dehydrogenations and the enzymes that catalyze them are called dehydrogenases.

- In some, but not all, biological oxidations, a carbon atom becomes covalently bonded to an oxygen atom. The enzymes that catalyze these oxidations are generally called oxidases or, if the oxygen atom is derived directly from molecular oxygen (O_2) oxygenases.

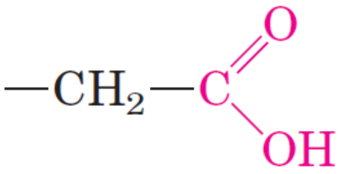
- Every oxidation must be accompanied by a reduction, in which an electron acceptor acquires the electrons removed by oxidation.

$-CH_2-CH_3$ Alkane

$-CH_2-CH_2OH$ Alcohol

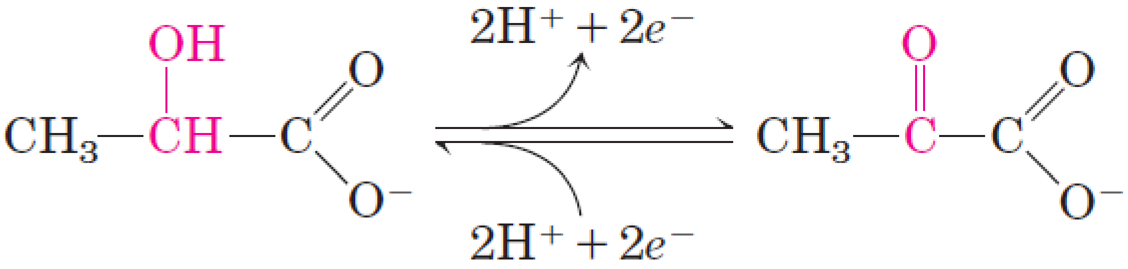


Aldehyde (ketone)



Carboxylic acid

$O=C=O$ Carbon dioxide



Lactate

lactate dehydrogenase

Pyruvate

❖Oxidation reactions generally release energy (think of camp fires: the compounds in wood are oxidized by oxygen molecules in the air).

❖Most living cells obtain the energy needed for cellular work by oxidizing metabolic fuels such as carbohydrates or fat (photosynthetic organisms can also trap and use the energy of sunlight).

❖The catabolic (energy-yielding) pathways are oxidative reaction sequences that result in the transfer of electrons from fuel molecules, through a series of electron carriers, to oxygen.

❖The high affinity of O_2 for electrons makes the overall electron-transfer process highly exergonic, providing the energy that drives ATP synthesis— the central goal of catabolism.

- Many of the reactions within these five classes are facilitated by cofactors, in the form of coenzymes and metals (vitamin B12, S-adenosylmethionine, folate, nicotinamide, and iron are some examples).

- Cofactors bind to enzymes—in some cases reversibly, in other cases almost irreversibly—and confer on them the capacity to promote a particular kind of chemistry.

- Most cofactors participate in a narrow range of closely related reactions.