Metabolism

Introduction to Metabolism

Metabolism, the overall process through which living systems acquire and use free energy to carry out their various functions, is traditionally divided into two parts:

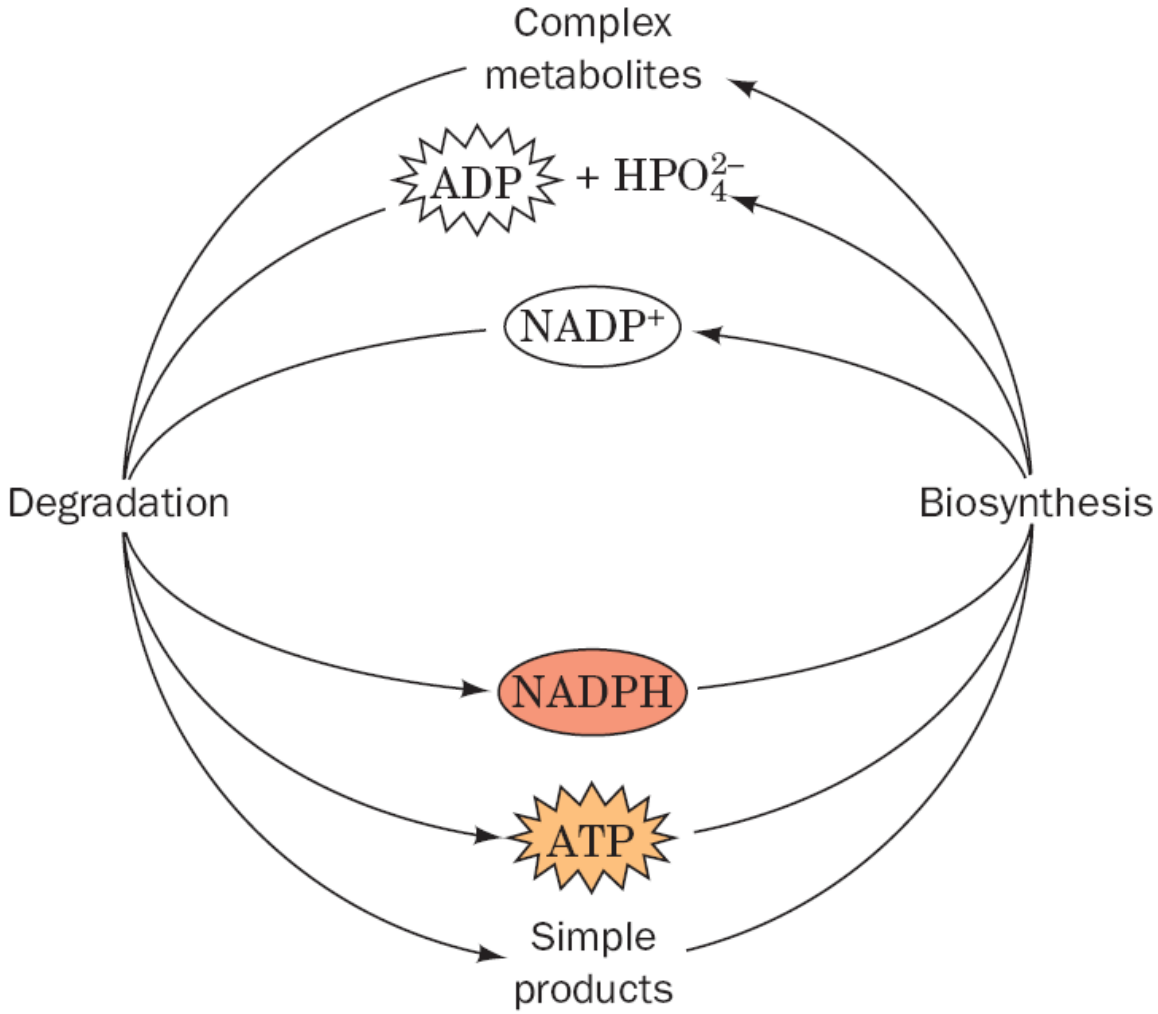
1. Catabolism, or degradation, in which nutrients and cell constituents are broken down to salvage their components and/or to generate energy.

2. Anabolism, or biosynthesis, in which biomolecules are synthesized from simpler components.

Metabolic pathways are series of connected enzymatic reactions that produce specific products.

- There are around 4000 known metabolic reactions, each catalyzed by a distinct enzyme.
- Many metabolic pathways are branched and interconnected, so delineating a pathway from a network of thousands of reactions is somewhat arbitrary and is driven by tradition as much as by chemical logic.

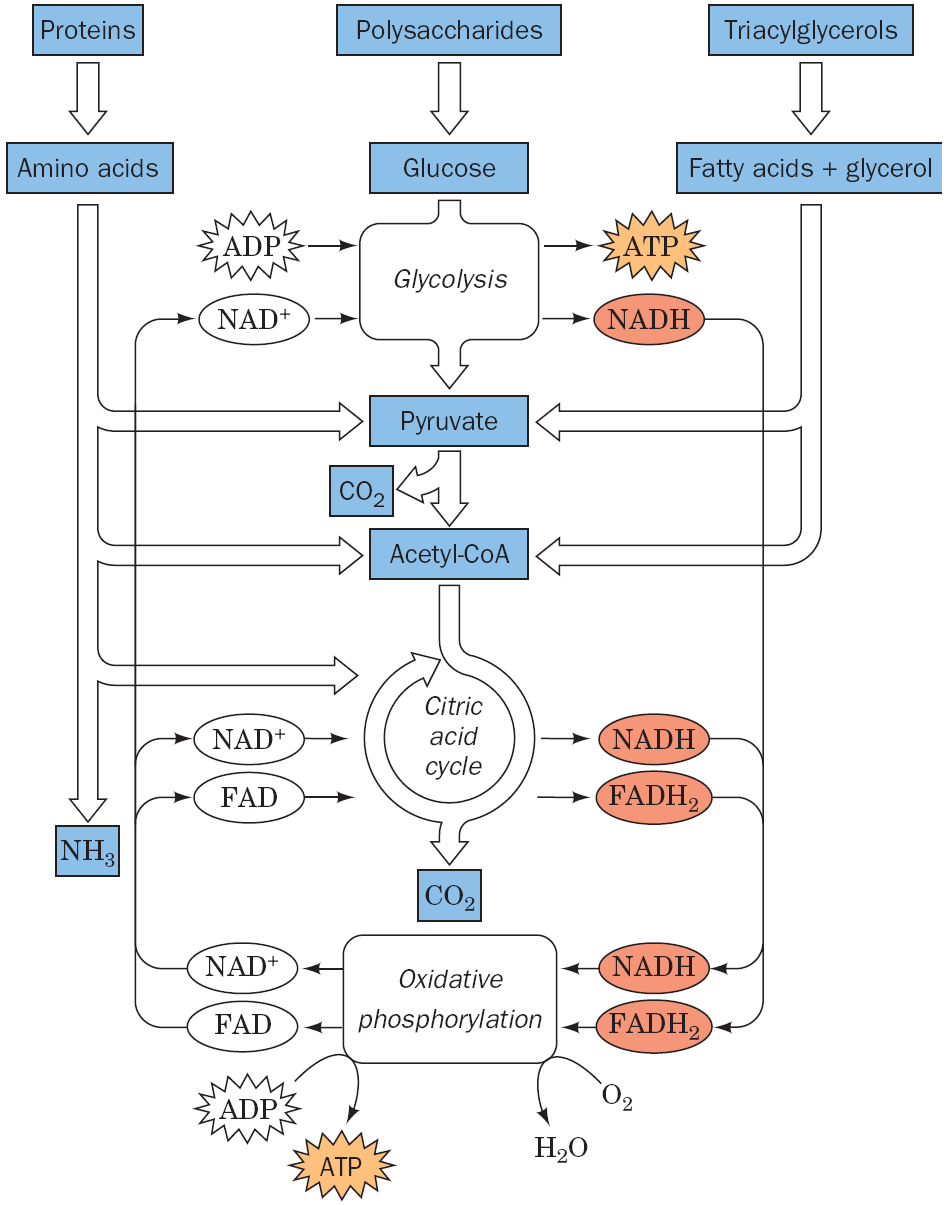
In general, degradative and biosynthetic pathways are related as follows



- In degradative pathways, the major nutrients, referred to as complex metabolites, are exergonically broken down into simpler products. The free energy released in the degradative process is conserved by the synthesis of ATP from ADP P*i* or by the reduction of the coenzyme NADP to NADPH. ATP and NADPH are the major free energy sources for biosynthetic reactions.

Overview of catabolism.

Complex metabolites such as carbohydrates, proteins, and lipids are degraded first to their monomeric units, chiefly glucose, amino acids, fatty acids, and glycerol, and then to the common intermediate, acetyl-CoA. The acetyl group is oxidized to CO2 via the citric acid cycle with concomitant reduction of NAD and FAD. Reoxidation of NADH and FADH2 by O2 during electron transport and oxidative phosphorylation yields H2O and ATP.



Metabolic Pathways Occur in Specific Cellular Locations.

- The compartmentation of the eukaryotic cytoplasm allows different metabolic pathways to operate in different locations. For example, electron transport and oxidative phosphorylation occur in the mitochondria, whereas **glycolysis** (a carbohydrate degradation pathway) and fatty acid biosynthesis occur in the cytosol.
- Metabolic processes in prokaryotes, which lack organelles, may be localized to particular areas of the cytosol.

Thermodynamics Dictates the Direction and Regulatory Capacity of Metabolic Pathways

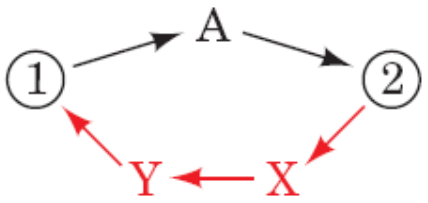
- When the reactants are present at values close to their equilibrium values, and This is the case for many metabolic reactions, which are said to be **near-equilibrium reactions.** Because their ΔG values are close to zero, they can be relatively easily reversed by changing the ratio of products to reactants. When the reactants are in excess of their equilibrium concentrations, the net reaction proceeds in the forward direction until the excess reactants have been converted to products and equilibrium is attained. Conversely, when products are in excess, the net reaction proceeds in the reverse direction so as to convert products to reactants until the equilibrium concentration ratio is again achieved.
- *Enzymes that catalyze near-equilibrium reactions tend to act quickly to restore equilibrium concentrations, and the net rates of such reactions are effectively controlled by the relative concentrations of substrates and products*.

Other metabolic reactions function far from equilibrium

- Other metabolic reactions function far from equilibrium; that is, they are irreversible. This is because an enzyme catalyzing such a reaction has insufficient catalytic activity (the rate of the reaction it catalyzes is too slow) to allow the reaction to come to equilibrium under physiological conditions. Reactants therefore accumulate in large excess of their equilibrium amounts, making Changes in substrate concentrations therefore have relatively little effect on the rate of an irreversible reaction; the enzyme is essentially saturated. Only changes in the activity of the enzyme, through allosteric interactions, for example, can significantly alter the rate.

Metabolic Flux

- Understanding the **flux** (rate of flow) of metabolites through a metabolic pathway requires knowledge of which reactions are functioning near equilibrium and which are far from it.
- **1. *Metabolic pathways are irreversible.***
- ***2. Every metabolic pathway has a first committed step.***
- **3. *Catabolic and anabolic pathways differ.***



Metabolic Flux Must Be Controlled

- Living organisms are thermodynamically open systems that tend to maintain a steady state rather than reaching equilibrium.

The flux of intermediates through a metabolic pathway in a steady state is more or less constant; that is, the rates of synthesis and breakdown of each pathway intermediate maintain it at a constant concentration.

- A steady state far from equilibrium is thermodynamically efficient, because only a nonequilibrium process ($\Delta G \neq 0$) can perform useful work.

- **Indeed, living systems that have reached equilibrium are dead.**

The flux of metabolites

- The flux of metabolites, *J*, through each reaction step is the rate of the forward reaction, *vf*, less that of the reverse reaction, *vr*:

$$J = v_f - v_r$$

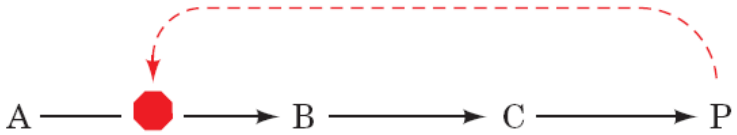
- At equilibrium, by definition, there is no flux (J = 0) although *vf* and *vr* may be quite large.
- In reactions that are far from equilibrium, *vf* >> *vr* the flux is essentially equal to the rate of the forward reaction ($J \approx vf$).

- For the pathway as a whole, flux is set by the rate-determining step of the pathway.
- By definition, this step is the pathway's slowest step, which is often the first committed step of the pathway.
- Because a rate-determining step is slow relative to other steps in the pathway, its product is removed by succeeding steps in the pathway before it can equilibrate with reactant.
- Thus, *the rate-determining step functions far from equilibrium and has a large negative free energy change*.

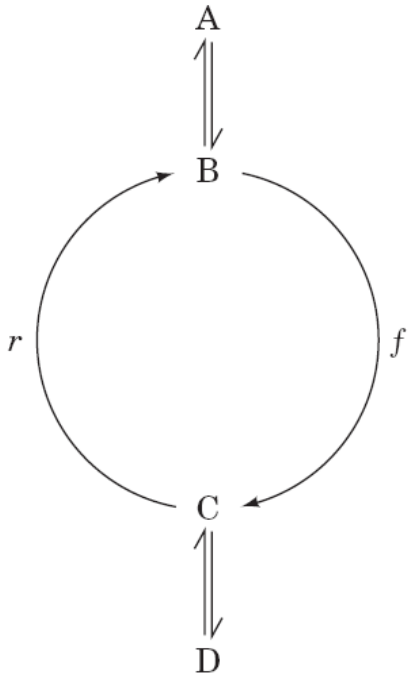
- Reactions that function near equilibrium respond rapidly to changes in substrate concentration.
- For example, upon a sudden increase in the concentration of a reactant for a near-equilibrium reaction, the enzyme catalyzing it would increase the net reaction rate so as to rapidly achieve the new equilibrium level.
- In practice, it is often possible to identify flux control points for a pathway by identifying reactions that have large negative free energy changes.
- The relative insensitivity of the rates of these nonequilibrium reactions to variations in the concentrations of their substrates permits establishment of a steady state flux of metabolites through the pathway.

Cells use several mechanisms to control flux through the rate-determining steps of metabolic pathways:

- **1. *Allosteric control.***



- **2. *Covalent modification.***
- **3. *Substrate cycles.***
- For example, flux can be increased not just by accelerating the forward reaction but by slowing the reverse reaction.



- **4. *Genetic control.***

“High-Energy” Compounds

The complete oxidation of a metabolic fuel such as glucose

$$C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O$$

releases considerable energy ($\Delta G^{\circ\prime} = -2850\ \text{kJ} \cdot \text{mol}^{-1}$). The complete oxidation of palmitate, a typical fatty acid,

$$C_{16}H_{32}O_2 + 23\,O_2 \longrightarrow 16\,CO_2 + 16\,H_2O$$

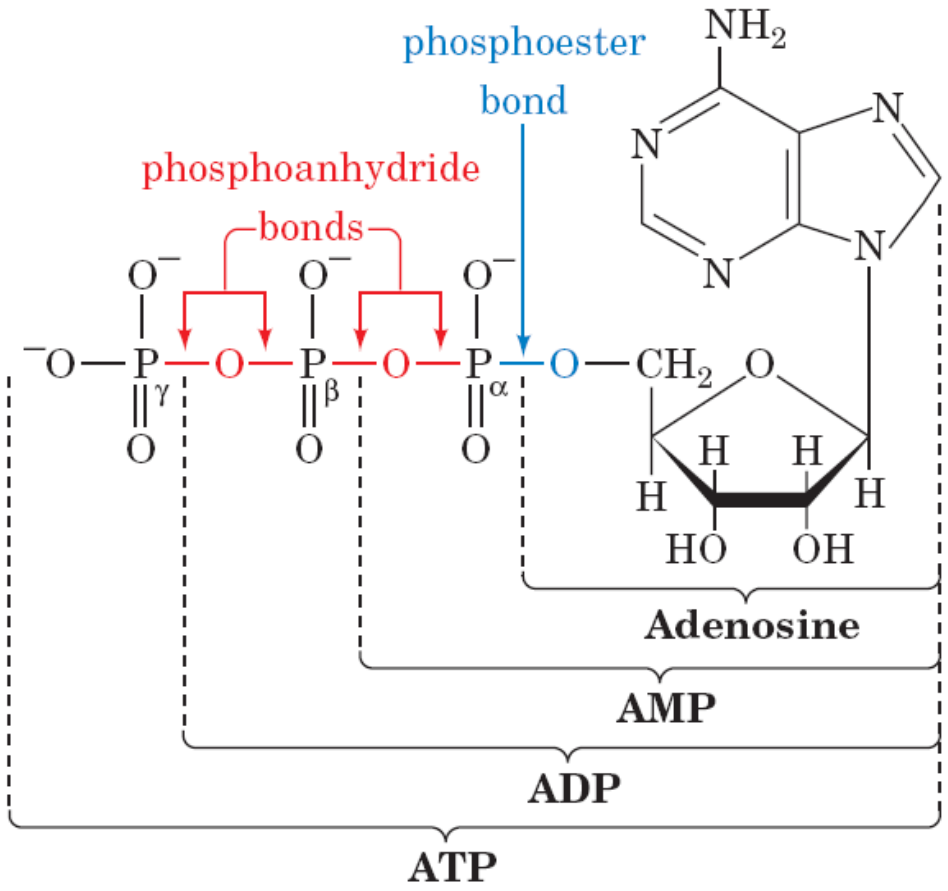
is even more exergonic ($\Delta G^{\circ\prime} = -9781\ \text{kJ} \cdot \text{mol}^{-1}$).

These “packets” of energy are conserved by the synthesis of a few types of ***“high-energy” intermediates*** *whose subsequent exergonic breakdown drives endergonic processes.*

ATP Has a High Phosphoryl Group-Transfer Potential

- The “high-energy” intermediate adenosine triphosphate occurs in all known life-forms.

- The biological importance of ATP rests in the large free energy change that accompanies cleavage of its phosphoanhydride bonds.



Energy Currency

- The negatives of these values are often referred to as **phosphoryl group-transfer potentials;** they are a measure of the tendency of phosphorylated compounds to transfer their phosphoryl groups to water.
- Under standard conditions, the compounds above ATP in Table 14-4 can spontaneously transfer a phosphoryl group to ADP to form ATP, which can, in turn, spontaneously transfer a phosphoryl group to the appropriate groups to form the compounds listed below it. Note that a favorable free energy change for a reaction does not indicate how quickly the reaction occurs. Despite their high group-transfer potentials, ATP and related phosphoryl compounds are **kinetically stable** and do not react at a significant rate unless acted upon by an appropriate enzyme.

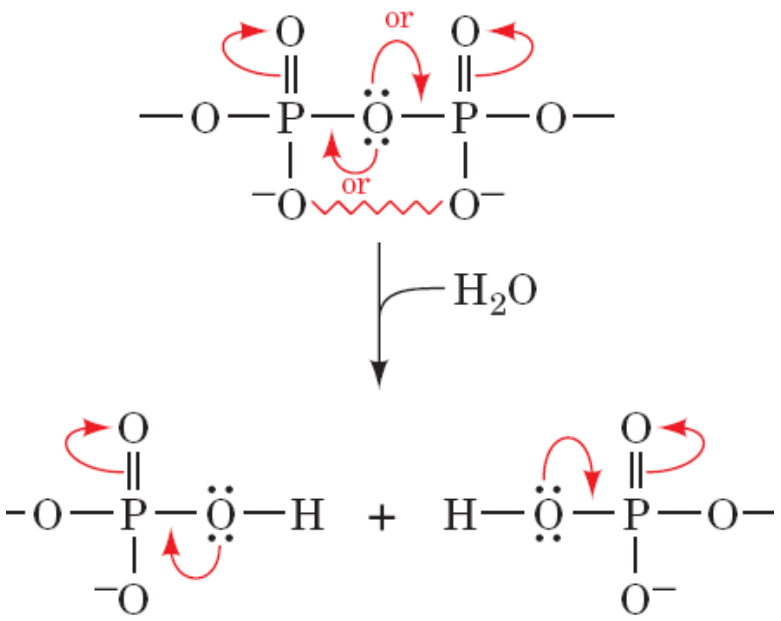
Table 14-4 Standard Free Energies of Phosphate Hydrolysis of Some Compounds of Biological Interest

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

What Is the Nature of the “Energy” in “High-Energy” Compounds?

- Bonds whose hydrolysis proceeds with large negative values of (customarily more than -25 kJ mol^{-1} are often referred to as **“high-energy” bonds** or **“energy-rich” bonds** and are frequently symbolized by the squiggle (~).
- **High-energy” bonds** should not be confused with the term **“bond energy,”** energy required to break, not hydrolyze, a covalent bond).

Several factors appear to be responsible for the “high-energy” character of phosphoanhydride bonds such as those in ATP



- The competing resonances (*curved arrows* from the central O) and charge–charge repulsions (*zigzag lines*) between phosphoryl groups decrease the stability of a phosphoanhydride relative to its hydrolysis products.
- Another destabilizing influence, which is difficult to assess, is the smaller solvation energy of a phosphoanhydride compared to that of its hydrolysis products. Some estimates suggest that this factor provides the dominant thermodynamic driving force for the hydrolysis of phosphoanhydrides.

In the physiological pH range,ATP has three to four negative charges whose mutual electrostatic repulsions are partially relieved by ATP hydrolysis.

Coupled Reactions Drive Endergonic Processes

- The exergonic reactions of "high-energy" compounds can be coupled to endergonic processes to drive them to completion.

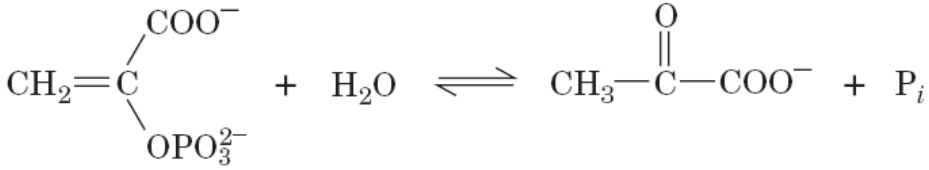
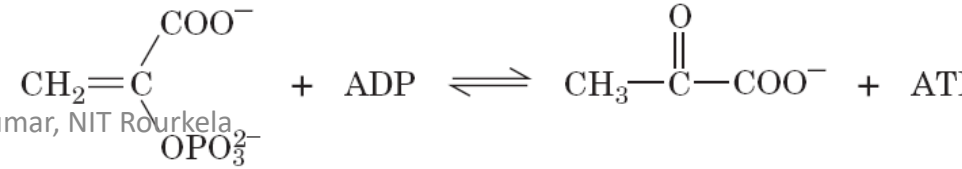
(1) $A + B \rightleftharpoons C + D \qquad \Delta G_1$

(2) $D + E \rightleftharpoons F + G \qquad \Delta G_2$

(a)

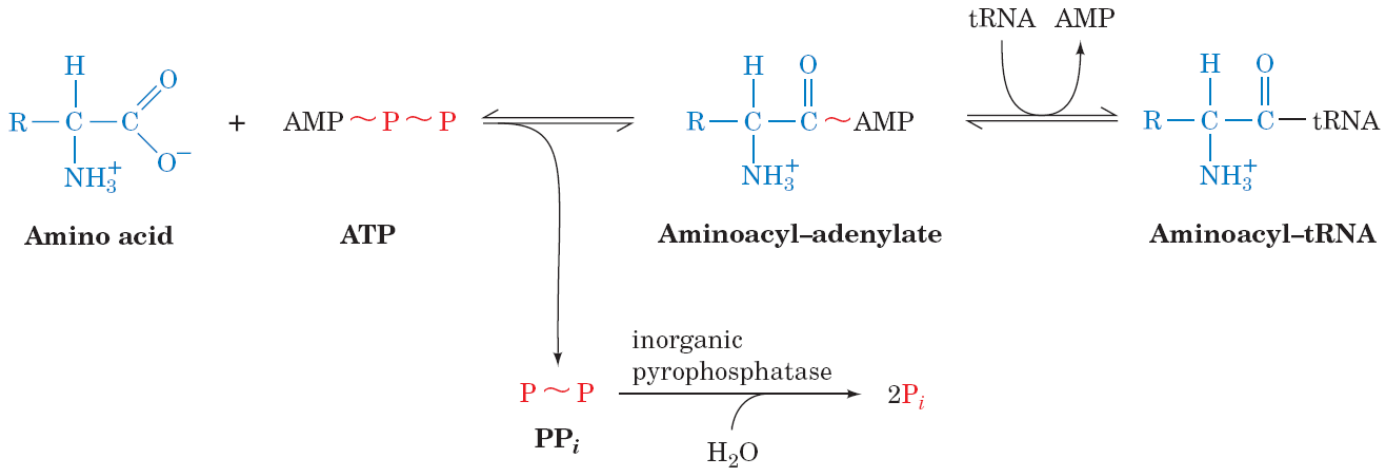
		$\Delta G^{\circ\prime}$ (kJ·mol^{-1})
Endergonic half-reaction 1	P_i + glucose $\rightleftharpoons$ glucose-6-P + H_2O	+13.8
Exergonic half-reaction 2	ATP + H_2O $\rightleftharpoons$ ADP + P_i	–30.5
Overall coupled reaction	ATP + glucose $\rightleftharpoons$ ADP + glucose-6-P	–16.7

(b)

		$\Delta G^{\circ\prime}$ (kJ·mol^{-1})
Exergonic half-reaction 1		–61.9
	Phosphoenolpyruvate **Pyruvate**	
Endergonic half-reaction 2	ADP + P_i $\rightleftharpoons$ ATP + H_2O	+30.5
Overall coupled reaction		–31.4

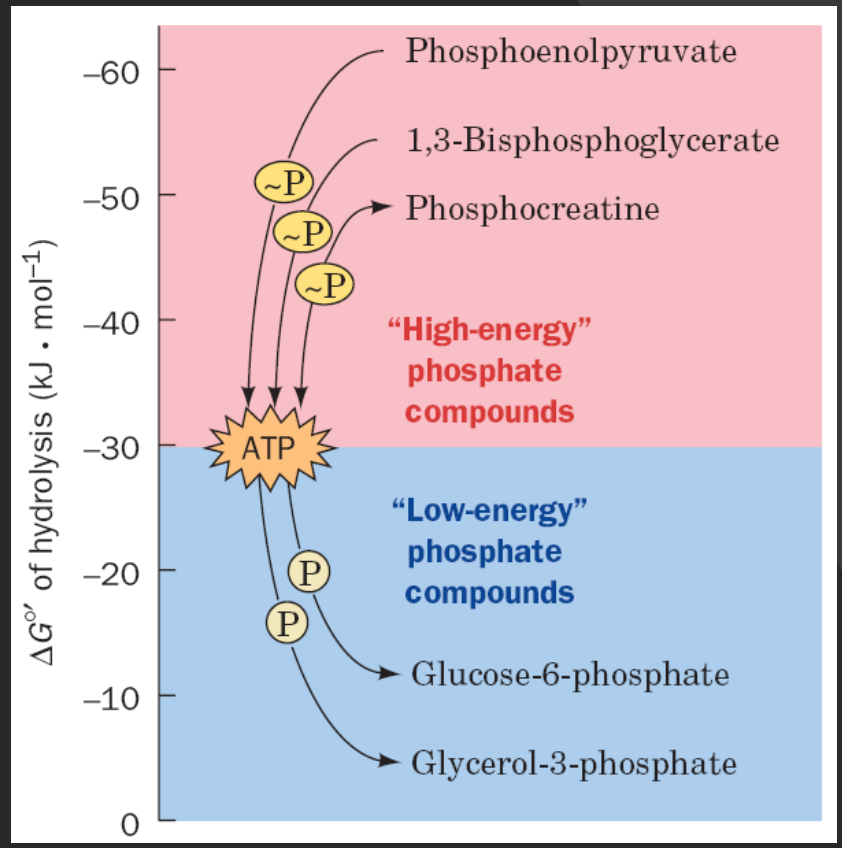
Inorganic Pyrophosphatase Catalyzes Additional Phosphoanhydride Bond Cleavage.

- Although many reactions involving ATP yield ADP and P*i* **(orthophosphate cleavage),** others yield AMP and Pp*i* **(pyrophosphate cleavage).** In these latter cases, the PP*i* is rapidly hydrolyzed to 2 P*i* by **inorganic pyrophosphatase (ΔG =**19.2 kJ mol^{-1})



Some Other Phosphorylated Compounds Have High Phosphoryl Group-Transfer Potentials

- *ATP is continually being hydrolyzed and regenerated*.
- An average person at rest consumes and regenerates ATP at a rate of ~3 mol (1.5 kg) per hour and as much as an order of magnitude faster during strenuous activity.
- *ATP itself can be regenerated by coupling its formation to a more highly exergonic metabolic process*.



ATP regeneration

ATP can therefore be formed from ADP by direct transfer of a phosphoryl group from a “high-energy” compound, referred to as a **substrate-level phosphorylation.**

Other mechanisms generate ATP indirectly, using the energy supplied by transmembrane proton concentration gradients.

In oxidative metabolism, this process is called **oxidative phosphorylation** whereas in photosynthesis, it is termed **photophosphorylation**