

Energy Currency of the Cell

Objective:

In this module, we have discussed the different energy currency of the cell. Energy currencies of the cell are ATP, GTP, UTP or any other NTP. We have discussed why these NTPs are energy currency. We will also discuss other high-energy compounds such as phospho-anhydride, phosphor-esters, acyl phosphates and thioesters. This module is divided into following sections

1. Basics of Energy Currency
2. NTPs as energy currency of cell
3. Why NTP gives energy
4. Other High-energy currency of the cell
5. Summary
6. Questions
7. Suggested Book

Introduction:

1. Basic of Energy Currency

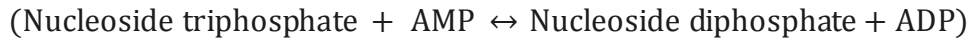
When simple precursors are assembled into high molecular weight polymers with defined sequences (DNA, RNA, proteins), energy is required both for the condensation of monomeric units and for the creation of ordered sequences. The precursors for DNA and RNA synthesis are nucleoside triphosphates, and polymerization is accompanied by cleavage of the phosphoanhydride linkage between the α and β phosphates, with the release of PPI. The moieties transferred to the growing polymer in these reactions are adenylate (AMP), guanylate (GMP), cytidylate (CMP), or uridylate (UMP) for RNA synthesis, and their deoxy analogs (with TMP in place of UMP) for DNA synthesis. Not only that, the activation of amino acids for protein synthesis involves the donation of adenylate groups from ATP. In all cases, the exergonic breakdown of a nucleoside triphosphate is coupled to the endergonic process of synthesizing a polymer of a specific sequence. There are other molecules that also act as storage of the energy in the cell and known as high-energy compound which consists of phospho-anhydride, phosphor-esters, acyl phosphates and thioesters etc. We will also discuss the mechanism of favorable energy change of these high-energy compounds. We will also discuss why different enzyme required different energy equivalents.

2. NTPS AS ENERGY CURRENCY

Although we have focused on ATP as the cell's energy currency and donor of phosphoryl groups but all other nucleoside triphosphates (GTP, UTP, and CTP) and all the deoxynucleoside triphosphates (dATP, dGTP, dTTP, and dCTP) are energetically equivalent to ATP. The free energy changes associated with hydrolysis of their phosphoanhydride linkages for ATP is same for the all the NTPs and dNTPs as they have same constrains which is responsible for the ATP production or breakdown. During various biological functions, these other nucleotides are generated and maintained as the nucleoside triphosphate (NTP) forms by phosphoryl group transfer to the corresponding nucleoside diphosphates (NDPs) and monophosphates (NMPs).

ATP is the primary high-energy phosphate compound produced by catabolism, in the processes of glycolysis, oxidative phosphorylation, and, in photosynthetic cells, photophosphorylation. Several enzymes then carry phosphoryl groups from ATP to the other nucleotides. The ΔG changes for the hydrolysis of the other NTPS are

same as ATP therefore conversions of one NTP to other, have ΔG of zero hence they can be interconverted into other NTPs. The enzymes involved in the reaction are nucleoside-triphosphate-adenylate kinase that converts nucleoside into nucleotide.



Similarly, nucleoside-diphosphate kinase catalyzes exchange of phosphate groups between different nucleoside diphosphates. NDK activities maintain equilibrium between the concentrations of different nucleoside triphosphates such as, for example, when GTP produced in the TCA converted to ATP ($\text{GTP + ADP} \leftrightarrow \text{GDP + ATP}$).

ATP (adenosine triphosphate) is the “most widely distributed high-energy compound within the human body. This ubiquitous molecule is “used to build complex molecules, contract muscles, generate electricity in nerves, and light fireflies. All fuel sources of Nature, all foodstuffs of living things, produce ATP, which in turn powers virtually every activity of the cell and organism. Imagine the metabolic confusion if this were not so: Each of the diverse foodstuffs would generate different energy currencies and each of the great variety of cellular functions would have to trade in its unique currency”. ATP contains the nucleoside adenosine and a tail consisting of three phosphates. As far as known, all organisms from the simplest bacteria to humans use ATP as their primary energy currency. The energy level it carries is just the right amount for most biological reactions. Nutrients contain energy in low-energy covalent bonds that are not very useful to do most of kinds of work in the cells. These low energy bonds must be translated to high-energy bonds, and this is a role of ATP. A steady supply of ATP is so critical that a poison that attacks any of the proteins used in ATP production kills the organism in minutes. Certain cyanide compounds, for example, are poisonous because they bind to the copper atom in cytochrome oxidase. This binding blocks the electron transport system in the mitochondria where ATP manufacture occurs.

3. Why NTP gives energy

Conversion of ATP to ADP and Pi (or in some cases, of ATP to AMP and pyrophosphate, P₂i). ATP-dependent reaction is “driven by the hydrolysis of ATP.” These reactions of ATP appear to be simple hydrolysis reactions in which water displaces Pi. ATP hydrolysis per se usually accomplishes nothing but the liberation of heat, which cannot drive a chemical process in an isothermal system. It represents a two-step process in which part of the ATP molecule, a phosphoryl or pyrophosphoryl group or the adenylate moiety (AMP), is first transferred to a substrate molecule or to an amino acid residue in an enzyme, becoming covalently attached to the substrate or the enzyme and raising its free-energy content. Then, in a second step, the phosphate-containing moiety transferred in the first step is displaced, generating Pi, P₂i, or AMP. Thus ATP participates covalently in the enzyme-catalyzed reaction to which it contributes free energy. ATP hydrolysis is favored by the following reasons show below

1. The charge separation that results from hydrolysis relieves electrostatic repulsion among the four negative charges on ATP⁴⁻.
2. The product inorganic phosphate (P_i) is stabilized by formation of a resonance hybrid, in which each of the four phosphorus-oxygen bonds has the same degree of double-bond character and the hydrogen ion is not permanently associated with any one of the oxygen.
3. The product ADP²⁻ immediately ionizes, releasing a proton into a medium of very low [H⁺] (at physiological i.e. pH 7) and converted into ADP³⁻, which is favorable according to Le Chatelier’s principle.
4. A fourth factor that favors ATP hydrolysis is the greater degree of solvation (hydration) of the products P_i and ADP relative to ATP, which further stabilizes the products relative to the reactants.
5. Because the concentrations of the direct products of ATP hydrolysis are, in the cell, far below the concentrations at equilibrium (figure 1), mass action favors the hydrolysis reaction in the cell.

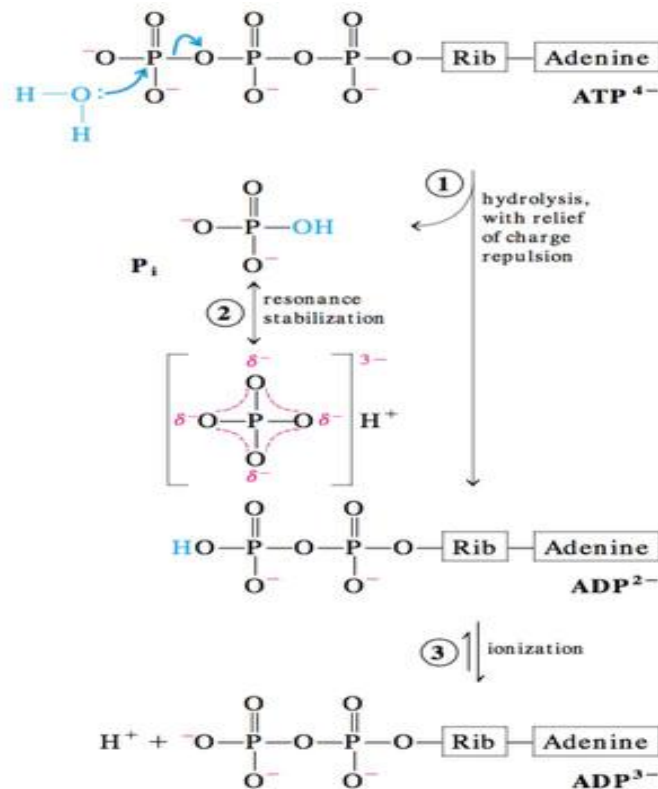


Figure 1: ATP hydrolysis

Although the hydrolysis of ATP is highly exergonic (ΔG -30.5 kJ/mol), the molecule is kinetically stable at pH 7 because the activation energy for ATP hydrolysis is relatively high. Rapid cleavage of the phosphoanhydride bonds occurs only when catalyzed by an enzyme. The free-energy change for ATP hydrolysis is -30.5 kJ/mol under standard conditions, but the actual free energy of hydrolysis (ΔG) of ATP in living cells is very different: the cellular concentrations of ATP, ADP, and P_i are not identical and are much lower than the 1.0M of standard conditions. Furthermore, Mg²⁺ in the cytosol binds to ATP and ADP, and for most enzymatic reactions that involve ATP as phosphoryl group donor, the true substrate is Mg-ATP²⁻. The relevant ΔG is therefore that for Mg-ATP²⁻ hydrolysis. In intact cells, ΔG for ATP hydrolysis, usually designated G_p , is much more negative than ΔG , ranging from -50 to -65 kJ/mol. G_p is often called the phosphorylation potential.

Some processes do involve direct hydrolysis of ATP (or GTP). For example, non-covalent binding of ATP (or of GTP), followed by its hydrolysis to ADP (or GDP) and P_i, can provide the energy to cycle some proteins between two conformations, producing mechanical motion. This occurs in muscle contraction and in the

movement of enzymes along DNA or of ribosomes along messenger RNA. The energy-dependent reactions catalyzed by helicases, RecA protein, and some topoisomerases also involve direct hydrolysis of phospho-anhydride bonds. GTP-binding proteins that act in signaling pathways directly hydrolyze GTP to drive conformational changes that terminate signals triggered by hormones or by other extracellular factors. The phosphate compounds found in living organisms can be divided somewhat arbitrarily into two groups, based on their standard free energies of hydrolysis. "High-energy" compounds have a ΔG of hydrolysis more negative than -25 kJ/mol; "low-energy" compounds have a less negative ΔG . The breaking of all chemical bonds requires an input of energy. The free energy released by hydrolysis of phosphate compounds does not come from the specific bond that is broken; it results from the products of the reaction having a lower free-energy content than the reactants. For simplicity, we will sometimes use the term "high-energy phosphate compound" when referring to ATP or other phosphate compounds with a large, negative, standard free energy of hydrolysis. As is evident from the additivity of free-energy changes of sequential reactions, any phosphorylated compound can be synthesized by coupling the synthesis to the breakdown of another phosphorylated compound with a more negative free energy of hydrolysis. Although, all the NTP has its ΔG same but different enzyme required different NTPs because of difference in the NTP binding pockets.

4. Other energy currency of the cell

Along with phospho-anhydride (eg. ATP), there are other high-energy compounds such as phospho-ester linkages (eg. phosphoenolpyruvate), acyl phosphates (eg. 1,3-bisphospho-glycerate) and thioesters (eg. acetyl-CoA). In all these phosphate-releasing reactions (ATP, 1,3-bisphospho-glycerate, phosphoenolpyruvate and phosphocreatine), the several resonance forms available to P_i stabilize this product relative to the reactant, contributing to an already negative free-energy change.

4.1.) Phosphocreatine

In phosphocreatine, the P-O-N bond can be hydrolyzed to generate free creatine and P_i . The release of P_i and the resonance stabilization of creatine favor the forward reaction. The standard free-energy change of phosphocreatine hydrolysis is again large, -43.0 kJ/mol.

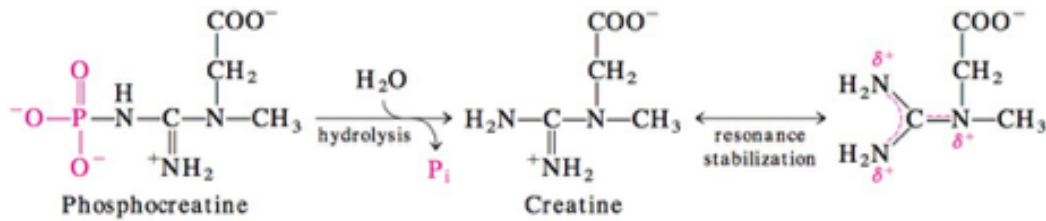


Figure 2: Hydrolysis of phosphocreatine.

The muscles of the body function through the use of ATP, or adenosine triphosphate, to power contractions. When one molecule of ATP is used in the contraction process, it is hydrolyzed to ADP, adenosine diphosphate, and an inorganic phosphate. The muscles limited ATP supply is used very quickly in muscle activity, so the need to regenerate ATP is essential. One of the ways that this ATP supply is regenerated is through the molecule creatine phosphate (or phosphocreatine). Phosphocreatine is formed from parts of three amino acids: arginine, glycine, and methionine. It can be synthesized by formation of guanidinoacetate from Arg and Gly (in kidney) followed by methylation (S-adenosyl methionine is required) to creatine (in liver), and phosphorylation by creatine kinase (ATP is required) to phosphocreatine (in muscle). Phosphocreatine is synthesized in the liver and transported to the muscle cells, via the bloodstream, for storage. The creatine phosphate shuttle facilitates transport of high-energy phosphate from mitochondria.

It can anaerobically donate a phosphate group to ADP to form ATP during the first 2 to 7 seconds following an intense muscular or neuronal effort. Conversely, excess ATP can be used during a period of low effort to convert creatine to phosphocreatine. The reversible phosphorylation of creatine (i.e., both the forward and backward reaction) is catalyzed by several creatine kinases. The presence of creatine kinase (CK-MB, MB for muscle/brain) in blood plasma is indicative of tissue damage and is used in the diagnosis of myocardial infarction. The cell's ability to generate phosphocreatine from excess ATP during rest, as well as its use of phosphocreatine for quick regeneration of ATP during intense activity provides a spatial and temporal buffer of ATP concentration. In other words, phosphocreatine acts as high-energy reserve in a coupled reaction; the energy given off from donating the phosphate group is used to regenerate the other compound- in this case, ATP.

Phosphocreatine plays a particularly important role in tissues that have high, fluctuating energy demands such as muscle and brain.

4.2.) Phosphoenolpyruvate

Phosphoenolpyruvate contains a phosphate ester bond that undergoes hydrolysis to yield the enol form of pyruvate, and this direct product can immediately tautomerize to the more stable keto form of pyruvate. Because the reactant (phosphoenolpyruvate) has only one form (enol) and the product (pyruvate) has two possible forms, the product is stabilized relative to the reactant. This is the greatest contributing factor to the high standard free energy of hydrolysis of phosphoenolpyruvate: $\Delta G^{\circ} -61.9 \text{ kJ/mol}$.

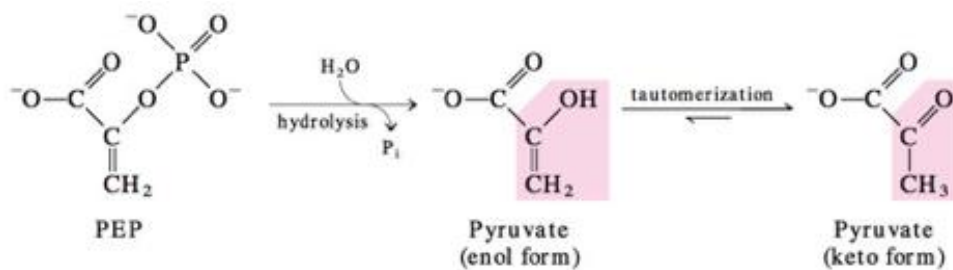


Figure 3: Hydrolysis of Phospho-enol-pyruvate

4.3). 1,3-bisphospho-glycerate

1,3-bisphospho-glycerate contains an anhydride bond between the carboxyl group at C-1 and phosphoric acid. Hydrolysis of this acyl phosphate is accompanied by a large, negative, standard free-energy change ($\Delta G^{\circ} -49.3 \text{ kJ/mol}$), which can, again, be explained in terms of the structure of reactant and products. When H₂O is added across the anhydride bond of 1,3-bisphospho-glycerate, one of the direct products, 3-phosphoglyceric acid, can immediately lose a proton to give the carboxylate ion, 3-phosphoglycerate, which has two equally probable resonance forms. Removal of the direct product (3-phosphoglyceric acid) and formation of the resonance-stabilized ion favor the forward reaction.

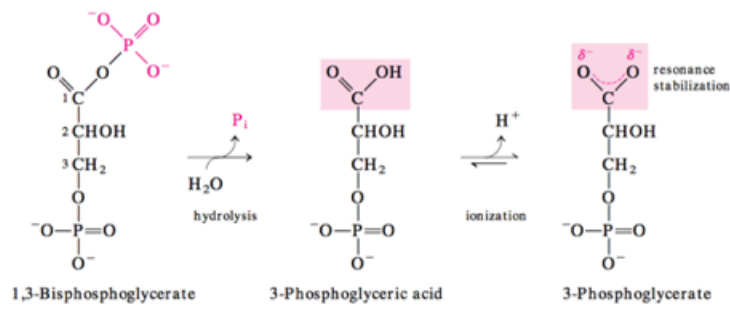


Figure 4: Hydrolysis of 1,3-bisphospho-glycerate

4.4) Thioesters

Thioesters, in which a sulfur atom replaces the usual oxygen in the ester bond, also have large, negative, standard free energies of hydrolysis. Acetyl-coenzyme A, or acetyl-CoA, is one of many thioesters important in metabolism. The acyl group in these compounds is activated for transacylation, condensation, or oxidation-reduction reactions. Thioesters undergo much less resonance stabilization than do oxygen esters; consequently, the difference in free energy between the reactant and its hydrolysis products, which are resonance-stabilized, is greater for thioesters than for comparable oxygen esters. In both cases, hydrolysis of the ester generates a carboxylic acid, which can ionize and assume several resonance forms. Together, these factors result in the large, negative ΔG° (-31 kJ/mol) for acetyl-CoA hydrolysis.

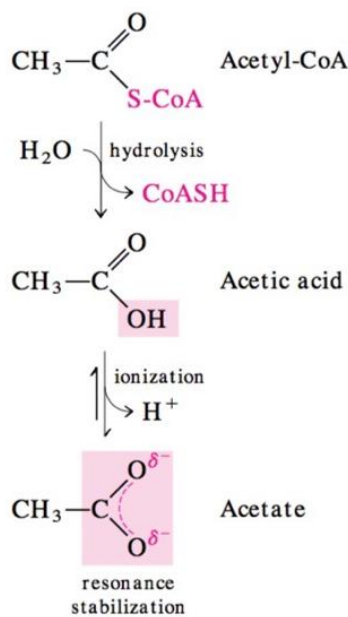


Figure 5: Hydrolysis of acetyl-coenzyme A

5. Summary

In the present module, we have discussed the different form of NTP and their energy contributions. Although, all the NTP has its ΔG same but different enzyme required different NTPs because of difference in the NTP binding pockets. We have also discussed high-energy compound such as phosphor-ester linkages (eg. phosphoenolpyruvate), acyl phosphates (eg. 1,3-bisphospho-glycerate) and thioesters (eg. acetyl-CoA) and their energy production mechanism. Similarly, we have also discussed hydrolysis reactions with large, negative, standard free-energy changes; the products are more stable than the reactants for one or more of the following reasons:

- The bond strain in reactants due to electrostatic repulsion is relieved by charge separation, as for ATP.
- The products are stabilized by ionization, as for ATP, acyl phosphates, and thioesters.
- The products are stabilized by isomerization (tauto-merization), as for phosphoenolpyruvate.
- The products are stabilized by resonance, as for creatine released from phosphocreatine, carboxylate ion released from acyl phosphates and thioesters, and phosphate (P_i) released from anhydride or ester linkages.

Therefore, this module explains the different high-energy compounds in the body.