Energy in Biology: Demand and Use

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A coupled energy source is a prerequisite of sustained dynamics in thermodynamically open systems.

Abstract

From the point of view of energy management in biological systems, a fundamental requirement is to ensure spontaneity. **Process spontaneity** is necessary since in a thermodynamically open system—such as the living cell—only spontaneous reactions can be catalyzed by enzymes. Note that enzymes do not, by themselves, contribute additional energy. Spontaneity of biological processes may be expressed by the following correlation, $\Delta G = \Delta H - T\Delta S$, where ΔG means the change of free energy; ΔH, change of enthalpy; ΔS, change of entropy; and T, temperature. Desirable processes which do not occur on their own must be coupled to other highly spontaneous mechanisms serving as energy sources. In biology, the fundamental sources of energy involve synthesis of water and photosynthesis. Since both processes are rather complex and cannot be exploited directly, they are used to synthesize ATP which acts as an energy carrier. Approaching biology from the point of view of elementary physics and chemistry reveals important mechanisms and enhances our understanding of various phenomena.

Keywords

Spontaneity · Source of energy · Entropy-driven processes · Enthalpy-driven processes · Direct and indirect use of energy

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1. Process spontaneity is denoted by ΔG. What does ΔG_0 stand for?
2. How can non-spontaneous processes be imbued with spontaneity?
3. How does the ΔG parameter relate to cell life and cell death?
4. How does water synthesis drive the synthesis of phosphoanhydride bonds in ATP?
5. What is the role of intermembrane space in mitochondria?
6. What are the direct and indirect products of photosynthesis?
7. Energy carriers—their role and importance.
8. Why aren't biological processes 100% efficient?
9. Processes dominated by entropy—examples.
10. How do organisms solve the problem of limited availability of oxygen during muscle contractions?
11. The kinetics of muscle activity.

2.1 General Principles of Thermodynamics

Physical and chemical processes may only occur spontaneously if they generate energy or non-spontaneously if they consume it. However, all processes occurring in a cell must have a spontaneous character because only these processes may be catalyzed by enzymes. Enzymes merely accelerate reactions; they do not provide energy.

In the inanimate world, non-spontaneous (endergonic) reactions, including most synthesis processes, consume thermal energy. In a cell, chemical energy can be derived from exergonic (energy-producing) processes. An important source of energy in living organisms is sunlight—the driving force in photosynthesis.

Due to high susceptibility of living organisms to heat damage, thermal energy is inconvenient.

Catalysis of inherently non-spontaneous processes becomes possible only when they are thermodynamically coupled to other spontaneous processes in such a way that the resulting complex process dissipates energy.

Examples of inherently non-spontaneous processes which acquire spontaneity by relying on exergonic reactions include:

1. Synthesis
2. Structural rearrangement of proteins (e.g., in muscle contraction)

Processes related to degradation are usually spontaneous by nature, and most of their stages do not require additional exergonic processes as a source of energy.

In physical terms, spontaneity is subject to Gibb's definition, where ΔG (change in free energy) corresponds to ΔH (change in enthalpy) and ΔS (change in entropy), according to the following equation:

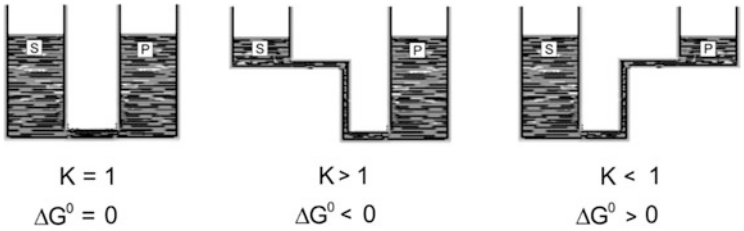

Fig. 2.1 The relationship between ΔG^0 and the equilibrium constant K in a model system

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

(T—temperature in °K)

The change in enthalpy associated with a chemical process may be calculated as a net difference in the sum of molecular binding energies prior to and following the reaction.

Entropy is a measure of the likelihood that a physical system will enter a given state. Since chaotic distribution of elements is considered the most probable, physical systems exhibit a general tendency to gravitate toward chaos. Any form of ordering is thermodynamically disadvantageous.

According to the presented formula, energy loss and the corresponding increase in entropy (ΔH and ΔS) are the hallmarks of a spontaneous process.

For specific processes, the change in free energy may be determined without referring to the presented mechanism and instead relying on reaction dynamics; specifically, on the ratio of product and substrate concentrations:

$$\Delta G = \Delta G^0 + RT^* \, ln\{([C] * [D])/([A] * [B])\}$$

R, gas constant; T, absolute temperature.

The ΔG^0 parameter is a measure of spontaneity. It depends on the properties of process elements and is therefore a function of the state of equilibrium. It may be derived from the ratio of product and substrate concentrations once a state of equilibrium has been reached.

If the process is in equilibrium, ΔG becomes equal to 0, and thus, according to the formula, ΔG^0 is given as

$$\Delta G^0 = -RT\{\, ln\ (K)\}$$

where K is the equilibrium constant (Fig. 2.1 and Table 2.1).

The figure depicts three types of communicating vessels in which the liquid has reached a state of equilibrium corresponding to various ratios of "products" (right vessel) and "substrates" (left vessel). The table (in Fig. 2.1) presents some numerical examples of the relation between K and ΔG^0.

The true measure of spontaneity is therefore not ΔG^0 but ΔG, which expresses the capability to perform work for a reaction which is not in a state of equilibrium. In

Table 2.1 An integral part of Fig. 2.1

K	ΔG^0 (kJ/mol)—temp. 25 °C
10^4	−22.8
10^1	−5.7
10^0	0.0
10^{-1}	5.7
10^{-4}	22.8

contrast, ΔG^0 merely indicates the reactivity of substrates as a consequence of their physical and chemical nature.

A reaction which is in a state of equilibrium cannot perform useful work. Energy can only be extracted from processes which have not yet reached equilibrium.

Maintaining a steady state of nonequilibrium is possible only in a thermodynamically open environment where energy and reaction components may flow through the system. This, in turn, calls for an external source of energy as well as a means of automatic control (see Fig. 1, Introduction).

Any spontaneous reaction can be treated as a source of energy as long as its spontaneity is sufficient for the thermodynamically disadvantageous reaction to occur and provided that both processes are thermodynamically coupled. In practice, synthesis reactions may only draw energy from highly spontaneous processes due to the need to form covalent bonds.

The chemical reactions which power biological processes are characterized by varying degrees of efficiency. In general, they tend to be on the lower end of the efficiency spectrum, compared to energy sources which drive matter transformation processes in our universe.

In search for a common criterion to describe the efficiency of various energy sources, we can refer to the net loss of mass associated with a release of energy, according to Einstein's formula:

$$E = m\,c^2$$

The $\Delta M/M$ coefficient (relative loss of mass, given, e.g., in %) allows us to compare the efficiency of energy sources. The most efficient processes are those involved in the gravitational collapse of stars. Their efficiency may reach 40%, which means that 40% of the stationary mass of the system is converted into energy. In comparison, nuclear reactions have an approximate efficiency of 0.8%.

The efficiency of chemical energy sources available to biological systems is incomparably lower and amounts to approximately 10^{-7}% (Fig. 2.2).

Among chemical reactions, the most potent sources of energy are found in oxidation processes, commonly exploited by biological systems. Oxidation tends to result in the largest net release of energy per unit of mass, although the efficiency of specific types of oxidation varies. For instance, the efficiency of hydrogen-halogen reactions (expressed in kcal/mol), calculated as the balance of binding energies, is as follows:

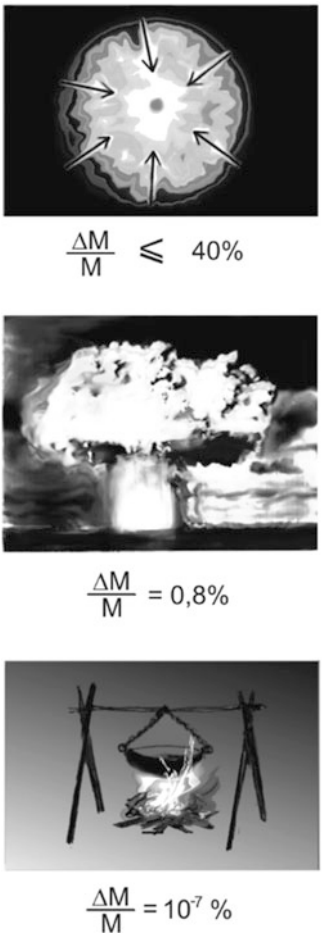

Fig. 2.2 Pictorial representation of the efficiency of selected energy sources, including stellar collapse, nuclear reactions, and chemical processes

$$H_2 + F_2 = 2HF \quad 104 + 37 = 2^*135(\text{kcal/mol}) \quad \Delta H = 129(\text{kcal/mol})$$

$$H_2 + Cl_2 = 2HCl \quad 104 + 58 = 2^*103(\text{kcal/mol}) \quad \Delta H = 44(\text{kcal/mol})$$

$$H_2 + Br_2 = 2HBr \quad 104 + 46 = 2^*87.5(\text{kcal/mol}) \quad \Delta H = 25(\text{kcal/mol})$$

Under similar conditions the reaction between hydrogen and oxygen yields an average of 56.7 kcal/mol. It should come as no surprise that—given unrestricted access to atmospheric oxygen and to hydrogen atoms derived from hydrocarbons—the combustion of hydrogen (i.e., the synthesis of water; $H_2 + 1/2O_2 = H_2O$) has become a principal source of energy in nature, next to photosynthesis, which exploits the energy of solar radiation.

2.2 Biological Energy Sources: Synthesis of Water

Hydrogen is combined with oxygen on inner mitochondrial membrane, while the conversion of hydrogen carriers (lipids, sugars, and proteins) into forms appropriate for water synthesis occurs in the cytoplasm and the mitochondrial matrix. Major energy-generating metabolic pathways include glycolysis, β-oxidation, and degradation of amino acids.

The basic process associated with the release of hydrogen and its subsequent oxidation (called the Krebs cycle) is augmented by processes which transfer electrons onto oxygen atoms (Fig. 2.3).

Oxidation occurs in stages, enabling optimal use of the released energy. An important byproduct of water synthesis is the universal energy carrier known as ATP (synthesized separately).

As water synthesis is a highly spontaneous process, it can be exploited to cover the energy debt incurred by endergonic synthesis of ATP, as long as both processes are thermodynamically coupled, enabling spontaneous catalysis of anhydride bonds in ATP.

Water synthesis is a universal source of energy in heterotrophic systems. In contrast, autotrophic organisms rely on the energy of light which is exploited in

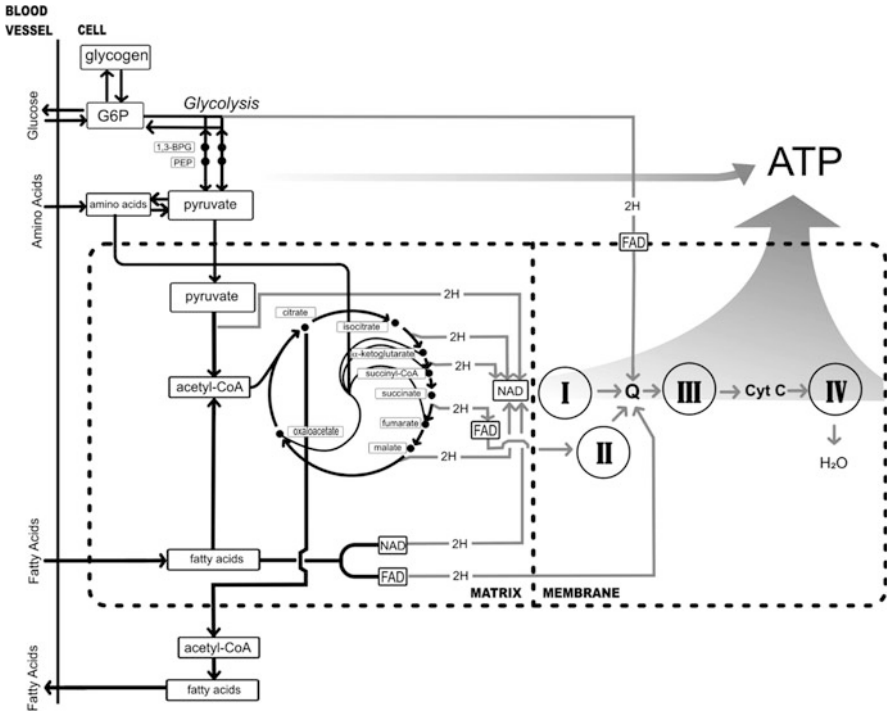

Fig. 2.3 A schematic depiction of energy conversion processes in living cells

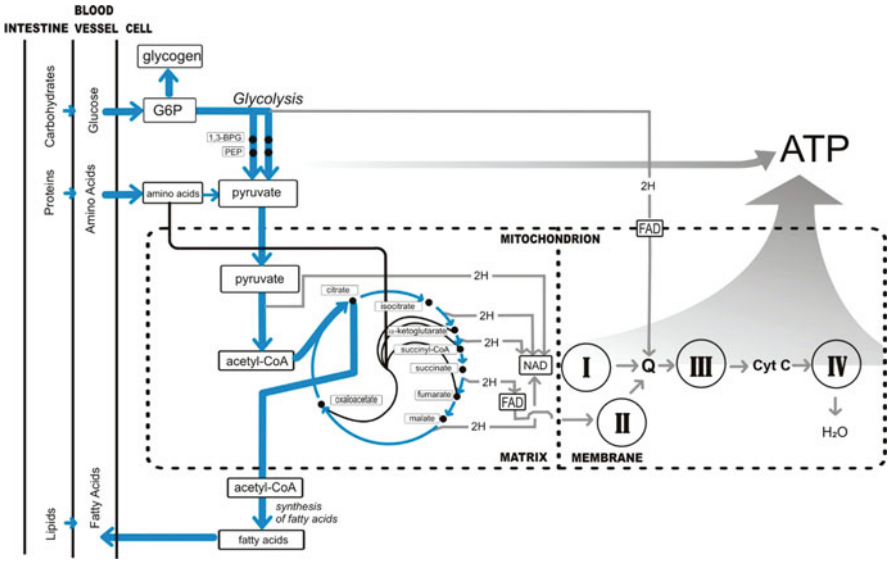

Fig. 2.4 Directed energy transfer occurring in a living cell when nutrients (hydrogen carriers) are freely available (fed state)

the process of photosynthesis. Both processes yield ATP along with reduced pyridine nucleotides.

As mentioned above, linking the spontaneous process of water synthesis with non-spontaneous creation of anhydride bonds in ATP is a prerequisite for achieving a thermodynamically unified system. This is done by introducing a hydrogen ion gradient which affects both processes, although in different ways:

A. The respiratory chain—by carrier proteins which transfer hydrogen atoms and electrons and must therefore be able to dissociate or attach hydrogen ions, enabling their transduction across the mitochondrial membrane and giving rise to an ion gradient
B. ATP synthesis—by exploiting the energy released in the spontaneous discharge of the hydrogen ion gradient

The hydrogen atoms used to synthesize water in the respiratory chain are derived from nutrients and can directly participate in the chain by way of the Krebs cycle (TCA). Nutrients include sugars (mostly glucose), amino acids, and lipids, which reach hepatocytes following absorption from the small intestine. The energy they carry is exploited in sequestration processes (mainly fatty acid synthesis and lipogenesis) (Fig. 2.4).

During periods of starvation, hydrogen carriers can be retrieved from storage: glucose comes from glycogen, while fatty acids are extracted from adipose tissue.

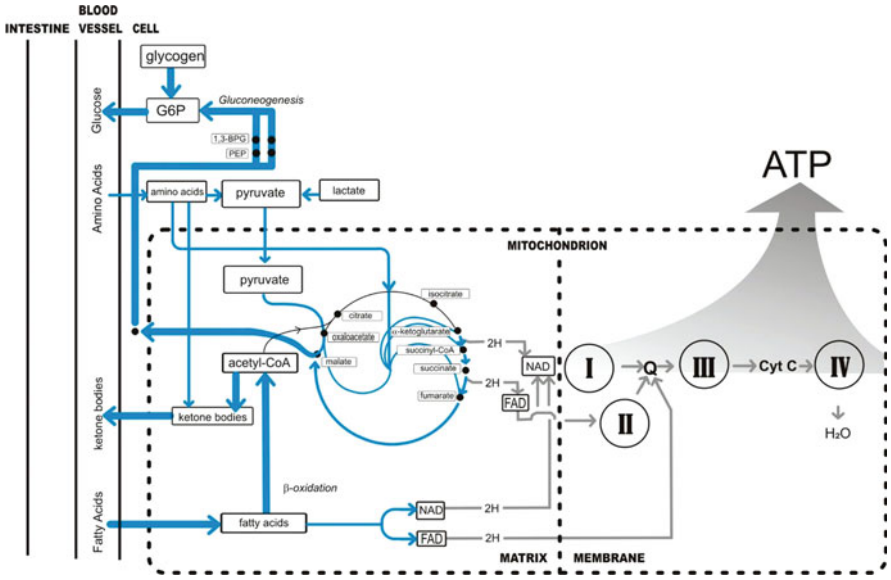

Fig. 2.5 Directed energy transfer occurring in a living cell whenever stored resources must be expended to maintain appropriate levels of glucose in blood (fasted state)

Under conditions of high physical exertion or inadequate food intake, the extraction of lipids increases, and most of the released energy is used to resynthesize glucose from amino acids (Fig. 2.5).

Dehydrogenation of substrates is catalyzed by pyridine- and flavin-linked dehydrogenases. Respiratory chain proteins are integrated in the mitochondrial membrane transport hydrogen atoms and electrons onto oxygen (O_2) molecules across the potential gradient, via complexes I, III, and IV, namely, NADH dehydrogenase (complex I) and coenzyme Q, cytochrome bc_1 complex reductase (complex III), cytochrome c, and finally cytochrome c oxidase (complex IV). Hydrogen atoms released by dehydrogenation of succinate are introduced to the respiratory chain via complex II (succinate dehydrogenase) and coenzyme Q, skipping complex I (Figs. 2.3, 2.4, and 2.5).

Complexes I, III, and IV are integrated in the membrane. In contrast, coenzyme Q (mediating capture of electrons by complex III) and cytochrome c are mobile, although the former is located within the membrane, while the latter is found in the intermembrane space. The double-electron NAD dehydrogenase initiator changes to a conduit for univalent electron carriers (iron-sulfur proteins, cytochromes) and a four-electron channel in the last phase of oxygen reduction.

Water synthesis ultimately results in phosphorylation, which (in this case) converts ADP to ATP. Since an anhydride bond must be created, there is a need of energy. ATP synthesis must therefore be coupled to the synthesis of water if spontaneity is to be maintained. The link is effected by introducing a hydrogen ion gradient between the mitochondrial matrix and the intermembrane space, which

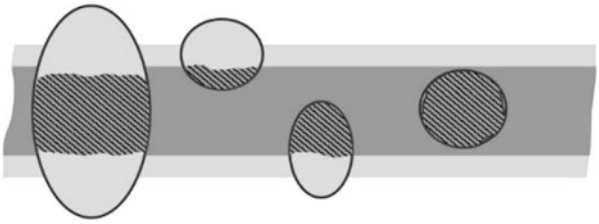

Fig. 2.6 Various forms of protein-membrane integration (gray zones indicate hydrophobic surfaces)

requires ejecting of hydrogen ions into the intermembrane space in the course of electron transportation for synthesis of water. The structures responsible for transporting ions must do so in a predetermined direction and maintain functional specificity. This task, like many others, is performed by dedicated proteins.

Ion transport is usually effected by a protein-specific change in pK of selected proton-binding groups, similar to the Bohr effect which occurs in hemoglobin. Transduction of hydrogen ions from the mitochondrial matrix to the intermembrane space works against the emerging ion gradient. Thus, protein ion channels must also fulfill the role of a sluice gate. Electron carriers participating in the highly spontaneous process of water synthesis in the membrane also act as transverse carriers of hydrogen ions. Thus owing to the mutual dependence of both ways of transport, the non-spontaneous formation of an ion gradient may draw energy from the oxidation process.

A suitable direction of transduction is ensured by maintaining proper alignment and integration of hydrogen and electron carrier proteins in the membrane so that protons are captured and released on specific sides (either within the mitochondrial matrix or in the intermembrane space). The structure of membrane proteins and their localization in the membrane is well suited to this task. Their apolar amino acids and their shape enforce the correct alignment and integration of protein molecules in the membrane (Fig. 2.6).

The ability to transport hydrogen ions is a property of proteins forming complexes I and IV. In complex III a similar function is most likely performed by coenzyme Q. Its specific structure and integration with the membrane, as well as its interaction with proteins, ensure unidirectional ion transfer. Coenzyme Q is an apolar, non-protein mobile molecule, consisting of a quinone derivative ring and a polyisoprenyl chain which, in humans, contains ten elements. The carbonyl groups of the quinone ring may undergo reduction by a hydrogen ion or by an electron (Fig. 2.7).

A proton may also dissociate from the hydroxyl group, leaving behind an anionic residue.

According to the most widely accepted hypotheses, the ubiquinone molecule (coenzyme Q) is able to rotate in the hydrophobic area of the membrane, coming into contact with integrated respiratory chain proteins and mediating the transduction of electrons and hydrogen ions. Through reduction (with an electron), the carboxyl group assumes a polar form and migrates from the membrane to the aqueous environment where it immediately attracts a proton (as its pK precludes the existence

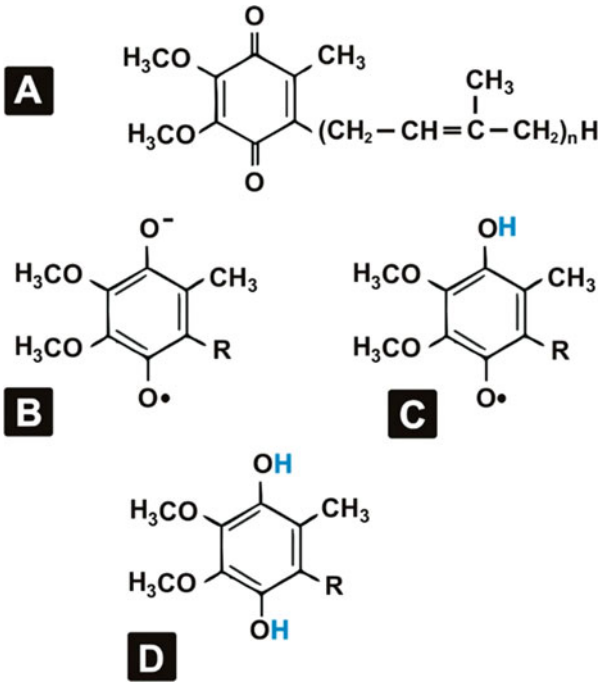

Fig. 2.7 Ubiquinone oxidation and reduction products: (**a**) ubiquinone, (**b**) semiquinone intermediate, (**c**) ubiquinol, and (**d**) dissociated ubiquinol

of a dissociated form in a non-alkaline environment). Subsequently, the ubiquinone again becomes apolar and returns to the hydrophobic zone of the membrane. While rotating it encounters cytochrome b and releases an electron, converting to semiquinone or quinone.

The presence of iron-sulfur proteins within the mitochondrial matrix, and of cytochrome b in the intermembrane space, results in a situation where the shortest proton transport route across the membrane is the one provided by ubiquinone. The source of energy powering this process is the electron transport carried by the respiratory chain (Fig. 2.8). A suitable arrangement of respiratory chain proteins is therefore crucial for coupling ATP synthesis to the synthesis of water.

The process depends on respiratory chain proteins being integrated and properly aligned in the membrane (either on the side of the matrix or in the intermembrane space) as well as on the presence of mobile ubiquinone molecules.

The arrangement of proteins which participate in binding hydrogen ions and transporting electrons across the membrane is such that electron transduction follows changes in the oxidation-reduction potential. A proof of structural ordering can be found in the stability of complexes I, II, III, and IV, even in their isolated forms. All enzymes connected with hydrogen and electron transportation are permanently integrated in the membrane with exception of few TCA cycle dehydrogenases and cytochrome c. For obvious reasons, this does not apply to NADH dehydrogenases which participate in the Krebs cycle in the mitochondrial matrix. Also the loose bond between the membrane and cytochrome c, facilitating its mobility and ability to bind

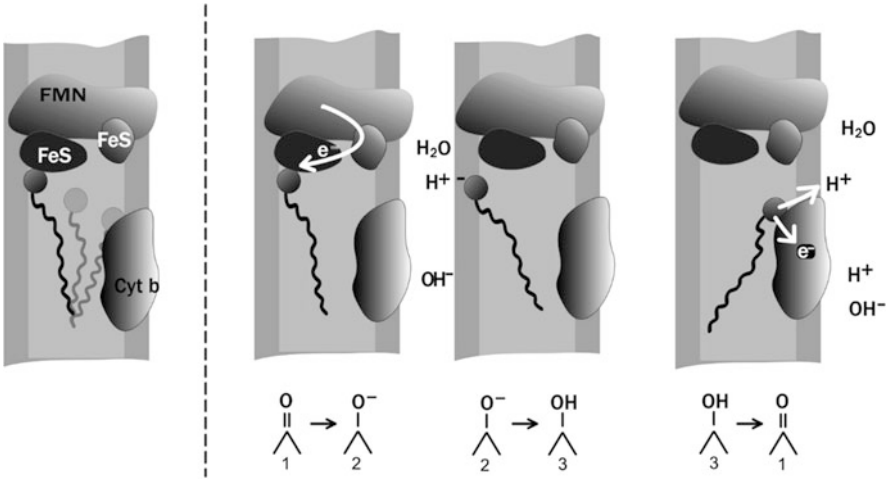

Fig. 2.8 Hypothetical hydrogen ion transduction mechanism between the mitochondrial matrix and the intermembrane space with the participation of ubiquinone

electrons, is most likely maintained in order to mask variations in the availability of oxygen while simultaneously enabling the transfer of concerted transfer of four electrons onto an oxygen molecule with the aid of cytochrome c oxidase:

$$4 \text{ cyt c red} + 4H^+ + O_2 = > 4 \text{ cyt.c ox} + 2H_2O$$

Cytochrome c molecules, loosely integrated with the membrane on its dorsal surface (i.e., within the intermembrane space), may therefore act as an electron reservoir, maintaining the consistency of the respiratory chain.

2.3 ATP Synthesis

The structure responsible for creating a high-energy anhydride bond in the process of converting ADP to ATP is a dedicated protein complex called ATP synthase—a mushroom-shaped structure anchored in the inner mitochondrial membrane. It is a very efficient machine, drawing power from the hydrogen ion gradient which itself emerges as a result of water synthesis. In order to achieve spontaneous synthesis of an anhydride bond, discharge of the ion gradient must release significantly more energy than the ATP synthesis process consumes. The synthase complex undergoes rotation which results in reordering of its structural components. It is capable of synthesizing approximately 100 ATP molecules per second, discharging three protons per molecule, although its specific mechanism of action remains still unclear.

It seems valid to assume that changes in the structure of the synthase effected by the ion gradient should result in shifting the ADP substrate (bound to the active site)

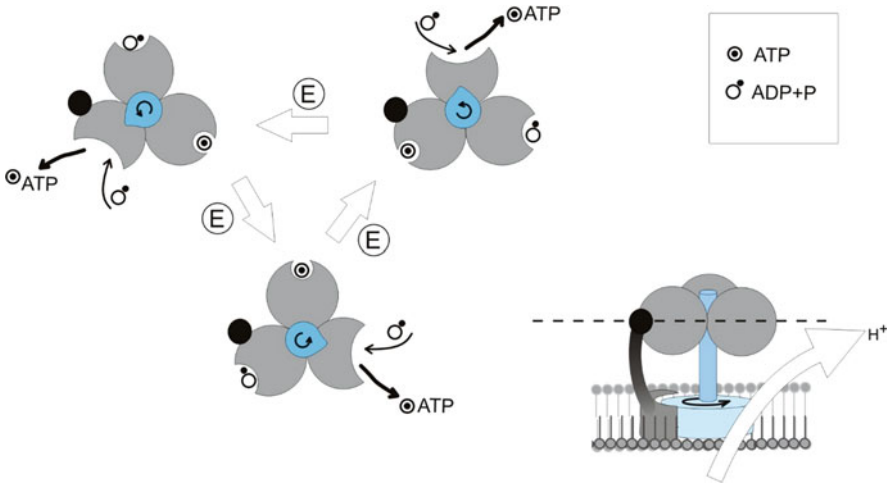

Fig. 2.9 Simplified diagram of ATP synthesis

and the phosphate group to an environment characterized by low polarity. According to this theory, the ATP molecule, which is less polar than the substrates used in its synthesis (ADP and P) and which tends to undergo spontaneous hydrolysis in the presence of water, becomes now easier to synthesize following a change in environmental conditions. Thus, a change in polarity driven by synthesis of water may reverse the direction of spontaneity making the process of ATP synthesis spontaneous.

An alternative hypothesis assumes that the reversal in the spontaneity of ATP hydrolysis is a result of local acidification. It can be observed that the rate of ATP hydrolysis decreases rapidly in low-pH environments. The high susceptibility of ATP to pH changes in the neutral space is a consequence of changes in pK of the -OH moiety, which migrates from an alkaline area (in a free phosphate group) to an area with pH = 6.95 (in ATP).

It is also likely that both mechanisms (reversal in polarity and acidification) come into play simultaneously. Observational evidence seems to propose even more convincing theory suggesting that the structural rearrangement of synthase components results in the creation of a binding site with high affinity for ATP, far exceeding its corresponding affinity for ADP. This effect negates the spontaneity of ATP hydrolysis; however it also introduces a very strong bond between the enzyme and the ATP molecule, making it difficult to release the product. This is why the process requires a source of motive power (the aforementioned ion gradient discharge), driving structural changes in the synthase complex. Once the gradient is restored, the synthesis process may repeat itself (Fig. 2.9).

The central rotating element (subunit γ, marked in color) forces a realignment of non-rotating catalytic subunits. Rotation is powered by the hydrogen ion gradient discharge. Side view and cross-section are presented.

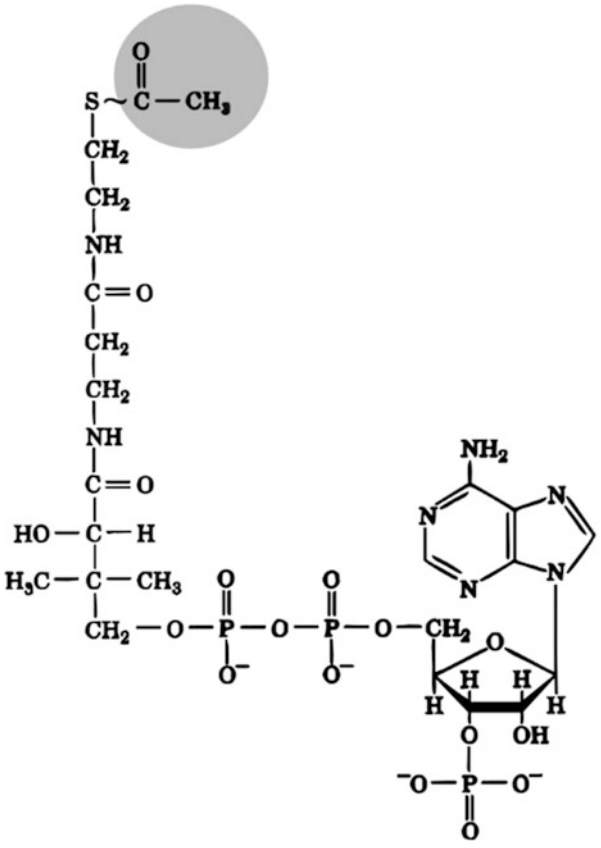

Fig. 2.10 Coenzyme A—the grayed-out area indicates the acetyl residue

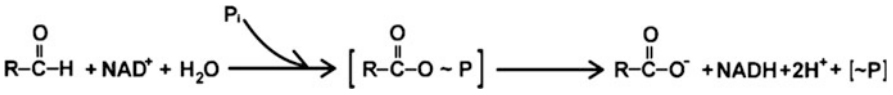

Fig. 2.11 Creation of a high-energy bond (mixed anhydride) through carbon oxidation (glyceraldehyde 3-phosphate oxidation)

Preparing nutrients (hydrogen carriers) for participation in water synthesis follows different paths for sugars, lipids, and proteins. This is perhaps obvious given their relative structural differences; however, in all cases the final form, which acts as a substrate for dehydrogenases, is acetyl-CoA (Fig. 2.10).

Sugars are converted into acetyl-CoA in the glycolysis process, following oxidative pyruvate decarboxylation; fatty acids undergo β-oxidation, while proteins are subject to hydrolysis, deamination, and some changes in their hydrocarbon core.

Aside from water synthesis, part of the energy required to form high-energy bonds comes from oxygenation of carbon atoms. The glycolysis process affords two molecules of ATP as a result of glyceraldehyde 3-phosphate oxidation (Fig. 2.11).

This process is an example of substrate-level phosphorylation and occurs in the cell cytoplasm. As a result, high-energy anhydride (1,3-biphosphoglycerate) and ester bonds (phosphoenolpyruvate acid) are created directly within the substrate, through dehydrogenation and dehydration, respectively.

Oxidation of carbon atoms yields acetyl-CoA as a product of the thiolysis process involved in β-oxidative degradation of fatty acids. The energy gain resulting from carbon oxidation covers the cost of synthesis of acetyl-CoA and succinyl-CoA in the course of oxidative decarboxylation of α-keto acids.

2.4 Photosynthesis

Photosynthesis is a process which—from the point of view of electron transfer—can be treated as a counterpart of the respiratory chain. In heterotrophic organisms, mitochondria transport electrons from hydrogenated compounds (sugars, lipids, proteins) onto oxygen molecules, synthesizing water in the process, whereas in the course of photosynthesis, electrons released by breaking down water molecules are used as a means of reducing oxidized carbon compounds (Fig. 2.12).

In heterotrophic organisms the respiratory chain has a spontaneous quality (owing to its oxidative properties); however any reverse process requires energy to occur. In the case of photosynthesis, this energy is provided by sunlight (Fig. 2.13).

The reduction process consumes solar energy by way of dedicated protein "antennae" which contain chlorophyll and carotenoids, each capable of capturing photons and transferring their energy to electrons. The system resembles the macroscopic model of a pumped-storage hydroelectric power plant (Fig. 2.14) which uses excess energy to pump downstream water back to its upper reservoir during nighttime. When the demand for energy increases (during daylight hours), water can flow back to the lower reservoir, generating power. Clearly, this direction of flow is spontaneous, while pumping water back to the upper reservoir consumes energy. A direct counterpart of this process in the scope of synthesis of $NADPH^+ + H^+$ reductors is its reliance on light energy, used to excite electrons extracted from water molecules.

Photosystems P680 and P700 perform the role of "electron pumps," imparting electrons with additional energy.

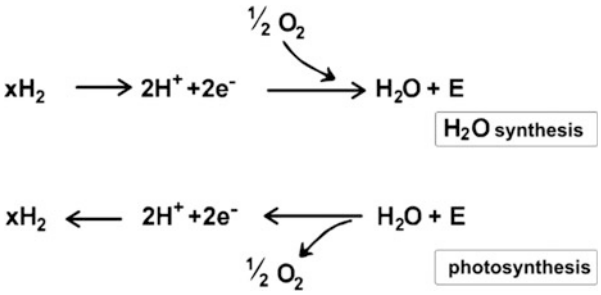

Fig. 2.12 Synthesis of water using the hydrogen atoms released by hydrogenated compounds (xH_2) within the respiratory chain, compared to synthesis of hydrogenated compounds from water in the presence of solar energy (photosynthesis)

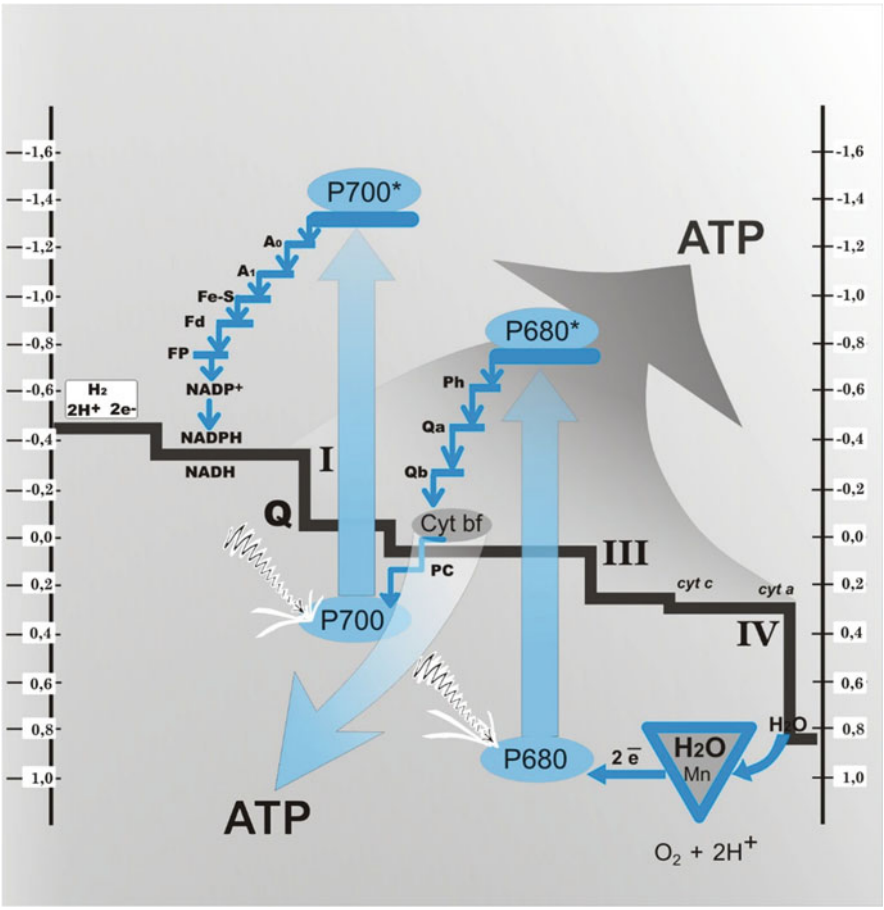

Fig. 2.13 Stage-by-stage electron flow comparison between the respiratory chain (black descending path) and photosynthesis (gray pathway), with energy changes indicated. Ph, pheophytin; Qa and Qb, quinone carriers; cyt bf, cytochrome bf complex; Pc, plastocyanin; A_0 and A_1, electron acceptors; Fe-S, iron-sulfur center; Fd, ferredoxin; Fp, NADP reductase

Assimilation and reduction of carbon dioxide (dark stage) are facilitated by reduced NADPH nucleotides which are produced in the light-dependent stage.

Hydrogen combustion and photosynthesis are the basic sources of energy in the living world. As they are subject to common laws of physics, their operating principles resemble those observed in many macroscopic systems (Fig. 2.15).

2.5 Direct and Indirect Exploitation of Energy Sources

Direct exploitation (direct coupling of spontaneous and non-spontaneous processes to an energy source)

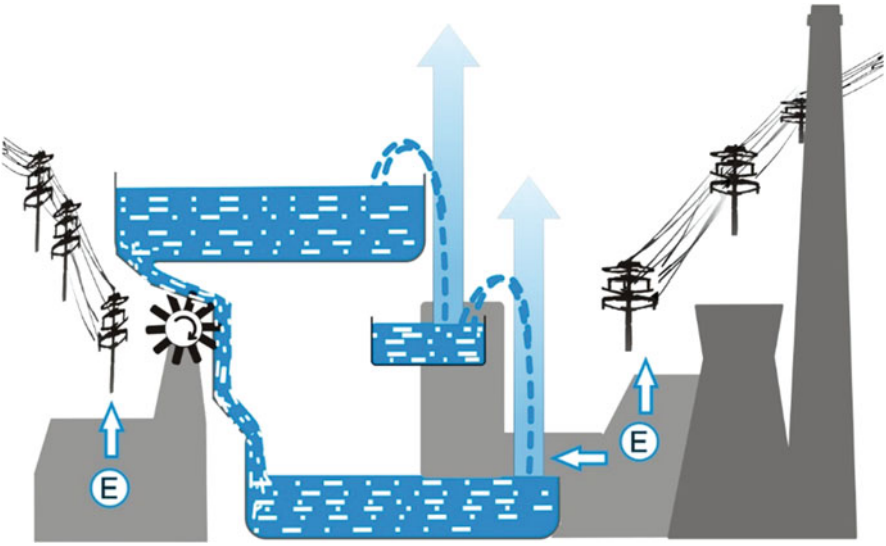

Fig. 2.14 Water circulation in a pumped-storage hydroelectric power plant as a model for the circulation of electrons in natural energy storage systems (synthesizing and breaking down water molecules in the course of photosynthesis)

The ability to exploit an energy source enables processes to maintain a state of nonequilibrium. As mentioned above, only these types of processes may occur spontaneously and be of use to biological entities. For an energy source to become useful, non-spontaneous reactions must be coupled to its operation, resulting in a thermodynamically unified system. Such coupling can be achieved by creating a coherent framework in which the spontaneous and non-spontaneous processes are linked, either physically or chemically, using a bridging component which affects them both. If the properties of both reactions are different, the bridging component must also enable suitable adaptation and mediation. In a water mill, the millstone shaft couples water flow (which acts as an energy source) to the work performed by quern-stones. A car engine combusts gasoline, using the released energy to impart motive force to the wheels. In some situations both processes (the spontaneous one and the non-spontaneous one) may share similar characteristics—for instance, skiers may propel themselves down a slope in order to effortlessly ski up the opposite slope. In this case, both processes involve skiing and are therefore similar; however a prerequisite of coupling is that both slopes need to be in a close proximity to each other (otherwise the energy gained in the descent would be lost).

Direct exploitation of the energy released via the hydrolysis of ATP is possible usually by introducing an active binding carrier mediating the energy transfer.

Carriers are considered active as long as their concentration ensures a sufficient release of energy to synthesize a new chemical bond by way of a non-spontaneous process. Active carriers are relatively short-lived and exist either in the active site of an enzyme or as independent substrates. In the latter case, they can be treated as

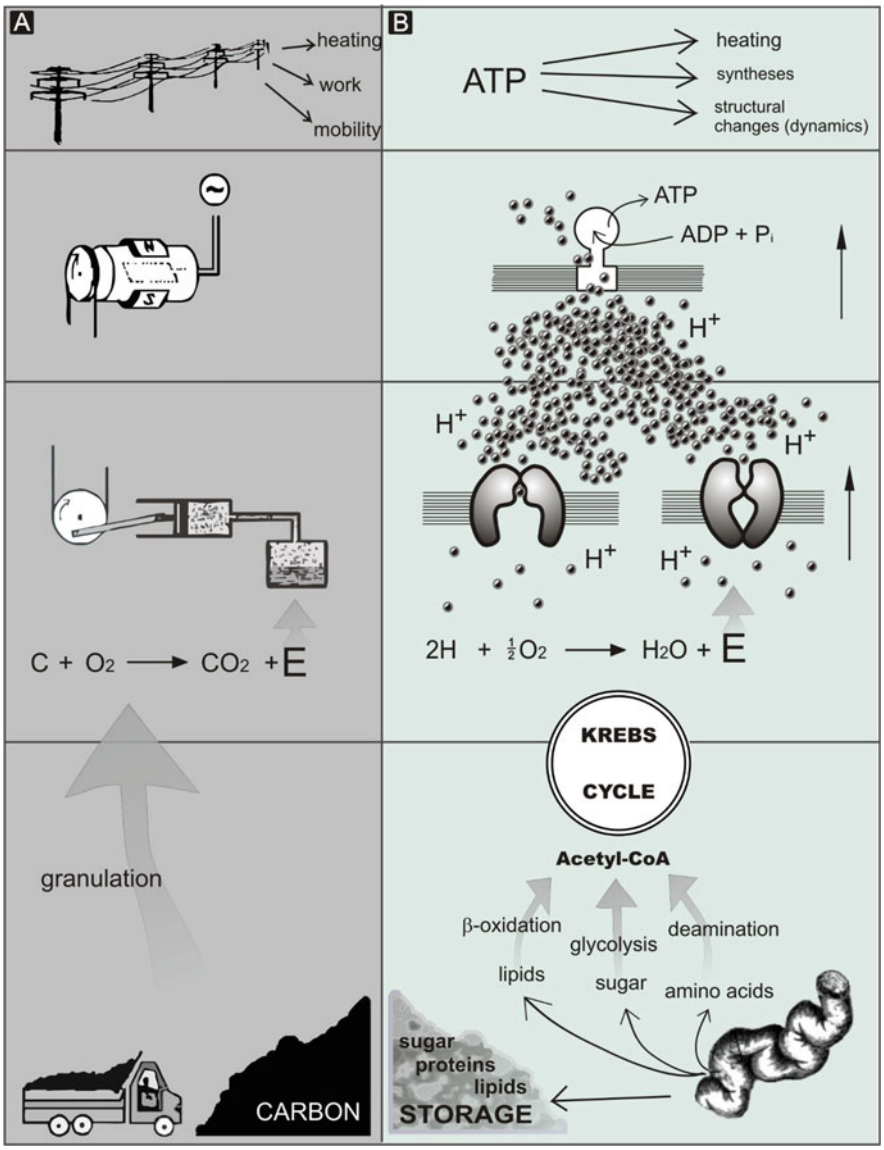

Fig. 2.15 Comparison of corresponding stages in the synthesis of universal energy carriers: (**a**) physical processes (involving electricity) and (**b**) chemical processes (ATP synthesis), showing analogies between both approaches

distinct components of cellular metabolic pathways. Examples include PRPP, UDPG, active mediators of cholesterol synthesis, and others. If the phosphorylation resulting from ATP hydrolysis yields a low-energy compound (such as glucose-6-phosphate), the reaction may consist of a single stage, and its product is not an active

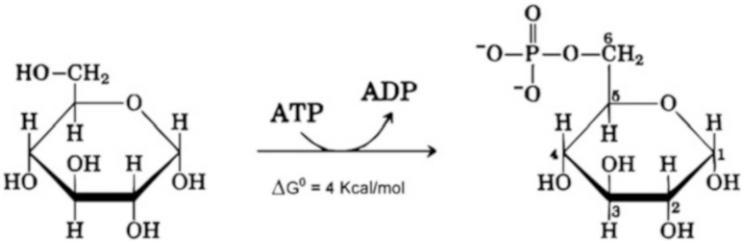

Fig. 2.16 Spontaneous synthesis of glucose-6-phosphate

carrier. The energy released via hydrolysis of ester bonds in glucose-6-phosphate is insufficient to cover the cost of creating a new chemical bond. The net change in free energy (ΔG^0) associated with hydrolysis of glucose-6-phosphate is approximately 3.3 kcal/mol, whereas synthesis costs 4.0 kcal/mol [$-7.3 - (-3.3) = -4.0$ kcal/mol]. Since the binding energy for a typical chemical bond is on the order of 3 kcal/mol, the energy stored in the ester bond of glucose-6-phosphate cannot cover the cost of synthesizing additional compounds. On the other hand, synthesis of glucose-6-phosphate is a spontaneous process, and the cell has no problem deriving this compound (Fig. 2.16).

In most synthesis reactions, ATP is only involved at an intermediate stage, where its energy covers the cost of creating a new ester, amide, thioester, or similar bond.

Any active carrier which performs its function outside of the active site must be sufficiently stable to avoid breaking up prior to participating in the synthesis reaction. Such mobile carriers are usually produced when the required synthesis consists of several stages or cannot be conducted in the active site of the enzyme for sterical reasons. Contrary to ATP, active energy carriers are usually reaction-specific.

Examples of active carriers include acid anhydrides and other types of compounds (especially thioesters and esters). Mobile energy carriers are usually formed as a result of hydrolysis of two high-energy ATP bonds. In many cases this is the minimum amount of energy required to power a reaction which synthesizes a single chemical bond. The adenosine residue often generates an active carrier in addition to a reaction product, while the dissociated pyrophosphate group undergoes hydrolysis, contributing to the spontaneity of the process and limiting its reversibility (Fig. 2.17).

Expelling a mobile or unstable reaction component in order to increase the spontaneity of active energy carrier synthesis is a process which occurs in many biological mechanisms, including decarboxylation of malonyl-CoA at the initial stage of fatty acid synthesis and decarboxylation of oxaloacetate acid at the initial stage gluconeogenesis, where an easily diffunding carbon dioxide molecule is ejected from the reaction site (Fig. 2.18).

The action of active energy carriers may be compared to a snowball rolling down a hill. The descending snowball gains sufficient energy to traverse another, smaller

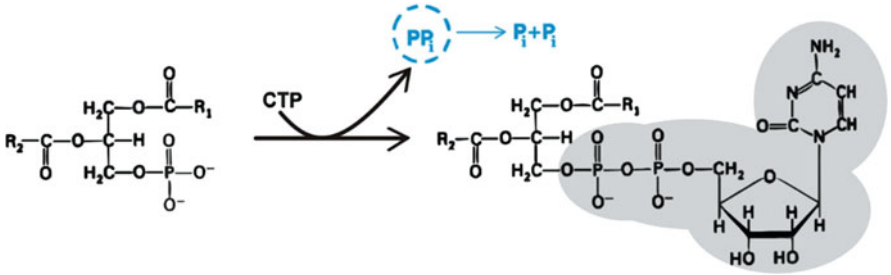

Fig. 2.17 Promoting the irreversibility of active energy carrier synthesis via releasing and hydrolysis of pyrophosphates. Creation of an activated diacylglycerol molecule

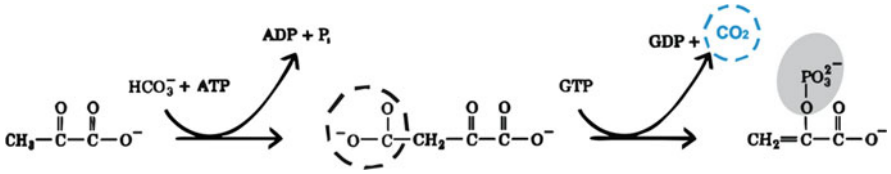

Fig. 2.18 Ensuring irreversibility of a chemical process by dissociating easily diffunding carbon dioxide molecules: synthesis of phosphoenolpyruvate

mound, adjacent to its starting point. In our case, the smaller hill represents the final synthesis reaction (Fig. 2.19).

Common energy carriers include pyrophosphate containing compounds (cholesterol synthesis intermediates, UDP-glucose PRPP), carboxybiotin (active carbon dioxide), S-adenosyl methionine (active methyl group), and many others (Fig. 2.20).

If an active energy carrier is created and subsequently consumed to form a new bond within the active site of the enzyme, synthesis of that enzyme's product may become energetically advantageous. What is more, correct alignment of substrates in the active pocket increases their likelihood of coming into contact with each other and therefore contributes to the spontaneity of the synthesis reaction. To illustrate this process, let us consider the formation of an amide bond in glutamine. This reaction involves an active carrier (mixed acyl-phosphate anhydride), synthesized at the cost of one high-energy ATP bond (Fig. 2.21). In this case, the energy of the carrier is comparable to that of the source. A similar situation occurs in the synthesis of phosphocreatine.

Proper alignment of substrates in the active pocket ensures direct contact, mimicking increased concentrations of both substances.

$$\text{ATP} + \text{creatine} <=> \text{ADP} + \text{phosphocreatine}$$

The process is not inherently spontaneous ($\Delta G^0 = 3$ kcal/mol); however its direction can be determined by changes in the concentration of ATP in myocytes between work and rest periods. Thus, phosphocreatine acts as a reservoir of

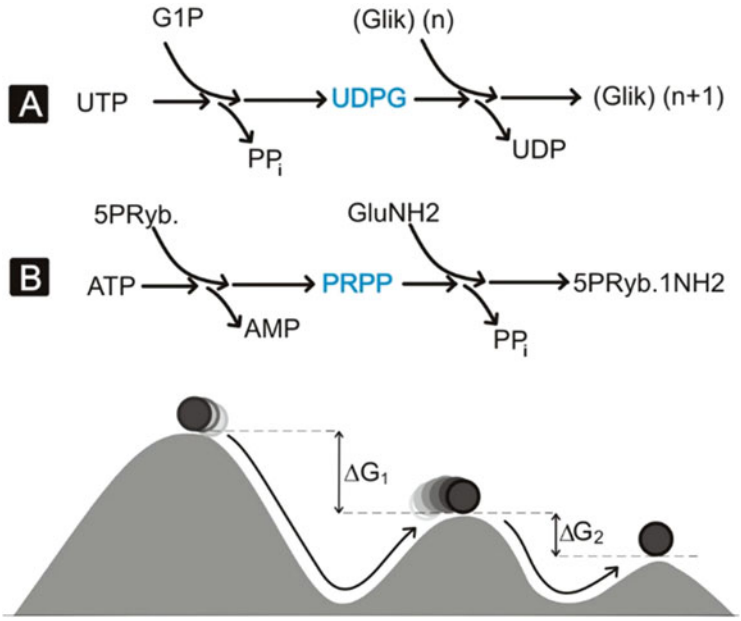

Fig. 2.19 Schematic depiction of the synthesis of active energy carriers and their role as coupling factors, linking energy sources to product synthesis processes: (**a**) synthesis of glycogen $(Glyc)_{n+1}$ from $(Glyc)_n$ and (**b**) synthesis of 5-phosphorybosylamine

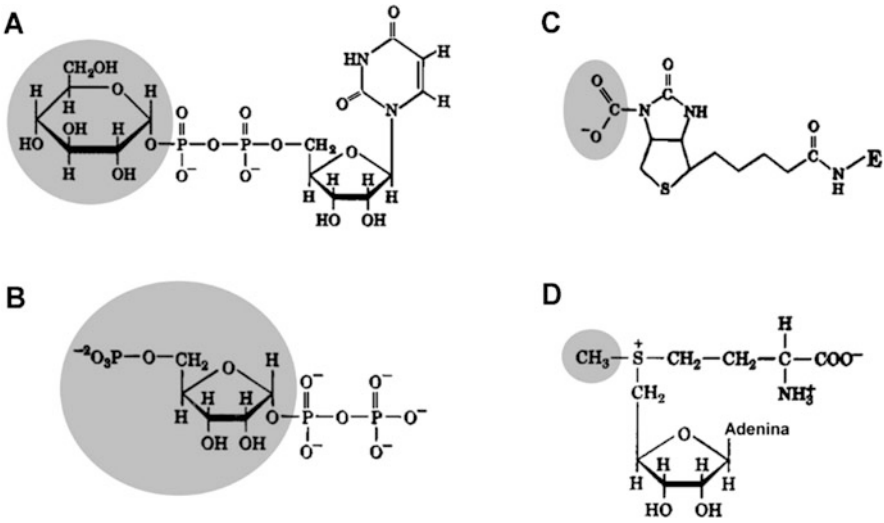

Fig. 2.20 Examples of active energy carriers: (**a**) active glucose (UDPG), (**b**) active ribose (PRPP), (**c**) active carbon dioxide (carboxybiotin), and (**d**) active methyl group (S-adenosyl methionine)

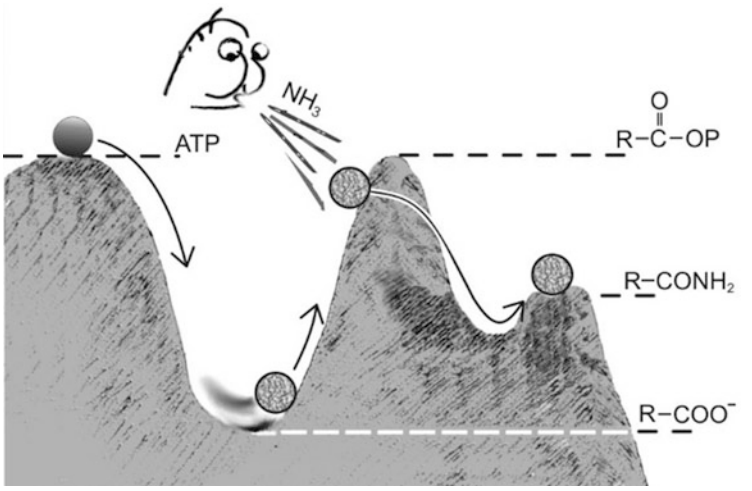

Fig. 2.21 Synthesis of a glutamine amide bond in the active site as an example of using a carrier whose energy is comparable to that of the source

high-energy bonds, accumulating while the muscle is at rest and resynthesizing ATP when physical effort is required.

Understanding the role of active carriers is essential for the study of metabolic processes.

The second category of processes, directly dependent on energy sources, involves structural reconfiguration of proteins, which can be further differentiated into low- and high-energy reconfiguration. Low-energy reconfiguration occurs in proteins which form weak, easily reversible bonds with ligands. In such cases, structural changes are powered by the energy released in the creation of the complex. The scope of reconfiguration depends on the packing of the protein and on its stability. Packing a folded, single-chain native protein results in a relatively stable structure, immune to significant changes which may result from the creation of a noncovalent protein-ligand bond. As a rule, the protein assumes the structural configuration corresponding to its global energy minimum. However, it may also temporarily stabilize in a local minimum (if the associated energy is not significantly greater than that of the global minimum). In most cases, such an intermediate structure is inherently unstable, and the protein spontaneously refolds to its most stable configuration.

Important low-energy reconfiguration processes may occur in proteins which consist of subunits. Structural changes resulting from relative motion of subunits typically do not involve significant expenditures of energy. Of particular note are the so-called allosteric proteins—for instance, hemoglobin (hemoglobin T (tens) $\leftrightarrow$ hemoglobin R (relaxed)), whose rearrangement is driven by a weak and reversible bond between the protein and an oxygen molecule. Allosteric proteins are genetically conditioned to possess two stable structural configurations, easily swapped as a result of binding or releasing ligands. Thus, they tend to have two comparable

energy minima (separated by a low threshold), each of which may be treated as a global minimum corresponding to the native form of the protein. Given such properties, even a weakly interacting ligand may trigger significant structural reconfiguration. This phenomenon is of critical importance to a variety of regulatory proteins.

In many cases, however, the second potential minimum in which the protein may achieve relative stability is separated from the global minimum by a high threshold requiring a significant expenditure of energy to overcome. For proteins associated with motor functions or other difficult structural changes, the ligand must be a high-energy compound which "pays" for the thermodynamically disadvantageous structural change by forming an active complex with the protein. Contrary to low-energy reconfigurations, the relative difference in ligand concentrations is insufficient to cover the cost of a difficult structural change. Such processes are therefore coupled to highly exergonic reactions such as ATP hydrolysis. Figure 2.22 depicts this type of situation.

In the case of myosin, the following structural configurations can be distinguished: relaxed structure with no ligand present (protein molecule without ATP) (Fig. 2.22c1), ATP-bound structure (Fig. 2.22c2), and contracted structure resulting from hydrolysis of a high-energy bond (Fig. 2.22c3) prior to releasing the products of this reaction. Relaxation of myosin (Fig. 2.22c3 and c1) is a highly spontaneous process, capable of performing useful work (Figs. 2.22c4, 2.23, and 2.24). Phases 1–4 are depicted in Figs. 2.23, 2.24, and 2.25. Catalysis of structural changes by high-energy bonds is not limited to motor proteins—it can also be observed in ribosomes, microtubule synthesis, protein G functions, and many other biological processes.

Indirect Method (Indirect Coupling Between Non-spontaneous Processes and Sources of Energy)

The link between a biological process and an energy source does not have to be immediate. Indirect coupling occurs when the process is driven by relative changes in the concentration of reaction components. The cell—a thermodynamically open system—may take advantage of external energy sources by acquiring substrates and expelling reaction products. This model is similar to an apartment block where tenants may utilize power, water, and natural gas supplied ready to use to their building.

The equation

$$\Delta G = \Delta G^0 + RT^* Ln\{[C]^*[D])/([A]^*[B])\}$$

indicates that reactions may acquire spontaneity if substrate concentrations increase and/or product concentrations decrease (since these are the only variables in the equation). However, an exogenous process is needed to supply substrates and absorb products so that the cell can maintain a state of balanced nonequilibrium purely through regulation.

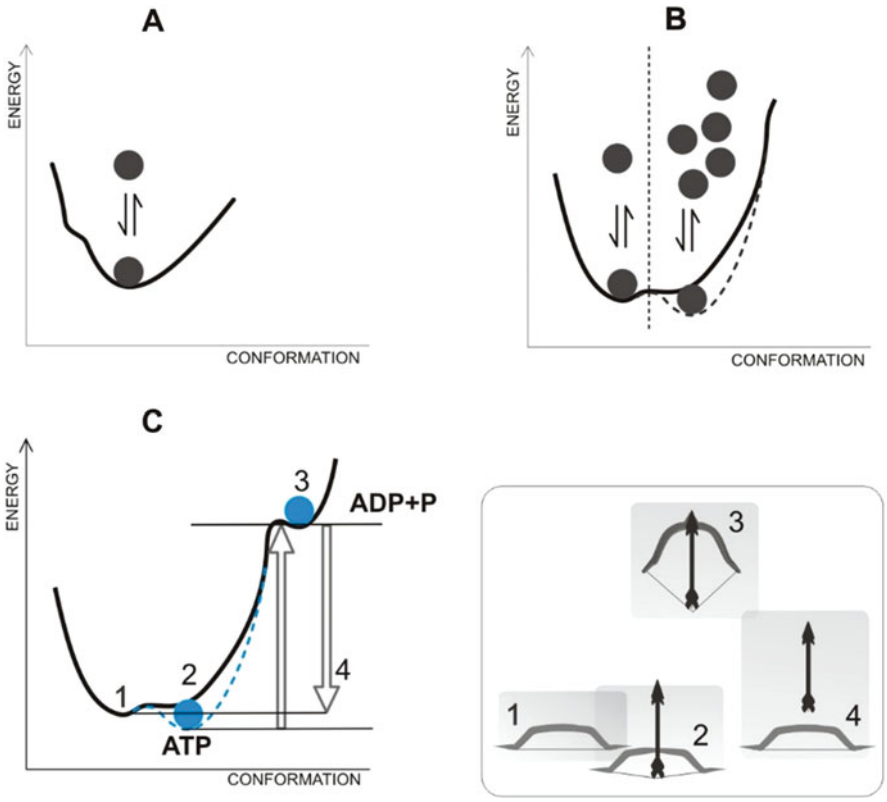

Fig. 2.22 Structural rearrangement of proteins as a result of energy expenditure: (**a**) non-allosteric protein (one energy minimum), (**b**) allosteric protein (two overlapping energy minima), and (**c**) motor protein (two distinct energy minima) (symbolic presentation). Muscle contraction phases and their associated energy levels are indicated. Spheres mark the role of ligands in stabilizing protein configurations. The bow diagram represents the phase-like properties of muscle contraction

Being part of an organism, the cell is usually provided with reaction substrates and may expel unneeded products. The energy debt incurred in this process is covered by other types of cells. For instance, high levels of glucose required for its spontaneous absorption by muscle cells (where it can power glycolysis) are maintained by hepatic metabolism. Figure 2.26 depicts the spontaneity of glycolysis as a function of ΔG^0, compared with observed values of ΔG in blood cells.

As can be seen, many stages of glycolysis are not inherently spontaneous (in terms of ΔG^0). Empirically determined ΔG values indicate that cells maintain their spontaneity by exploiting both direct (phosphorylation) and indirect links to energy sources. Limiting major changes in ΔG to stages where direct coupling comes into play (Fig. 2.26 a–c) means that these stages are effective in control of the entire process. ΔG^0 values observed at each stage indicate that the process can

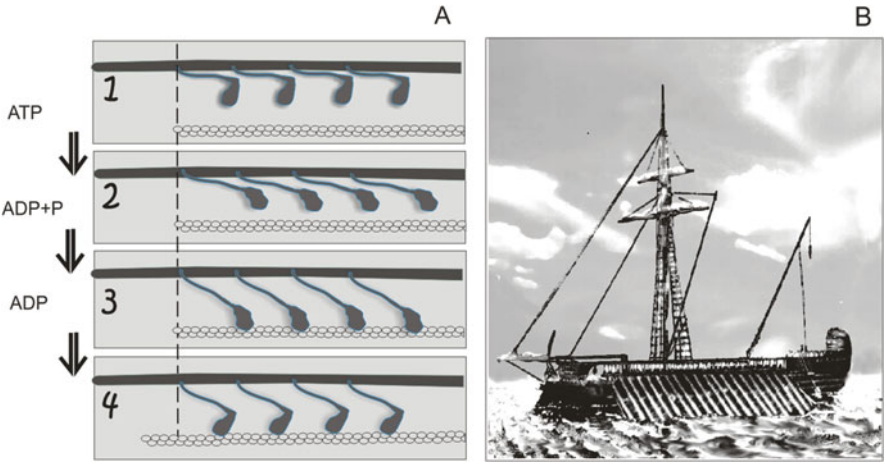

Fig. 2.23 Motor proteins: (**a**) action of motor proteins in muscle and (**b**) analogies between motor proteins and an oar-powered vessel (Roman galley)

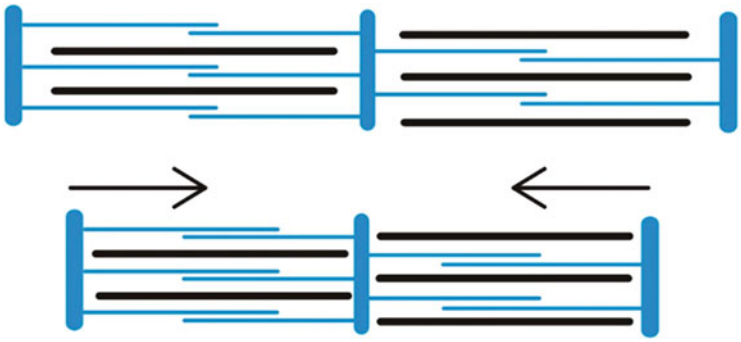

Fig. 2.24 Telescopic motion as the principle of contraction in motor proteins

easily be reversed (phosphoenolpyruvate synthesis) provided that ATP molecules are not resynthesized and only it is the threshold to be crossed.

Indirect coupling may also benefit processes associated with low-energy structural reconfiguration of proteins (mostly allosteric ones). Such processes are usually powered by changes in ligand concentrations and not by direct links to exergonic reactions. Examples include hemoglobin, receptors, regulatory enzymes, etc.

In general, high-energy reconfigurations exploit direct coupling mechanisms, while indirect coupling is more typical of low-energy processes (however, an important exception to this rule is the coupling of water synthesis to ATP synthesis effected by the hydrogen ion gradient).

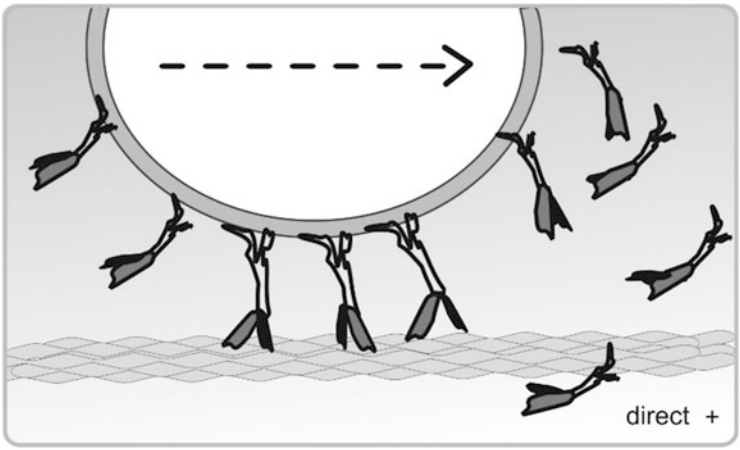

Fig. 2.25 Kinesin in motion

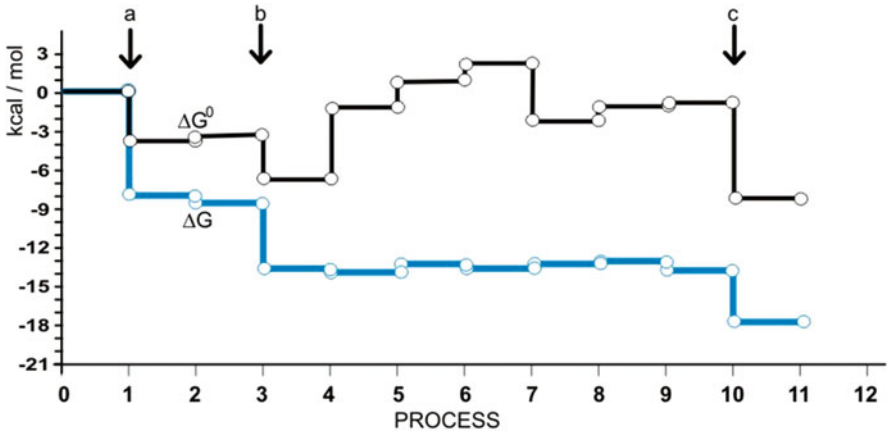

Fig. 2.26 Spontaneity of glycolysis as a function of ΔG^0 and ΔG. Arrows indicate stages directly coupled to energy sources (stages a, b, and c catalyzed, respectively, by hexokinase, phosphofructokinase-1, and pyruvate kinase)

2.6 Energy Conversion Efficiency in Biological Processes

It is impossible to exploit all the energy released by a source. Any system characterized by 100% efficiency would effectively become a *perpetuum mobile*.

We may therefore ask why lossless exploitation of energy is undesirable. The answer lies in the fundamental contradiction between high conversion efficiency and the quantity of conserved energy. Let us again refer to the example of a skier going downhill except this time there are many skiers and the aim is to propel oneself as far

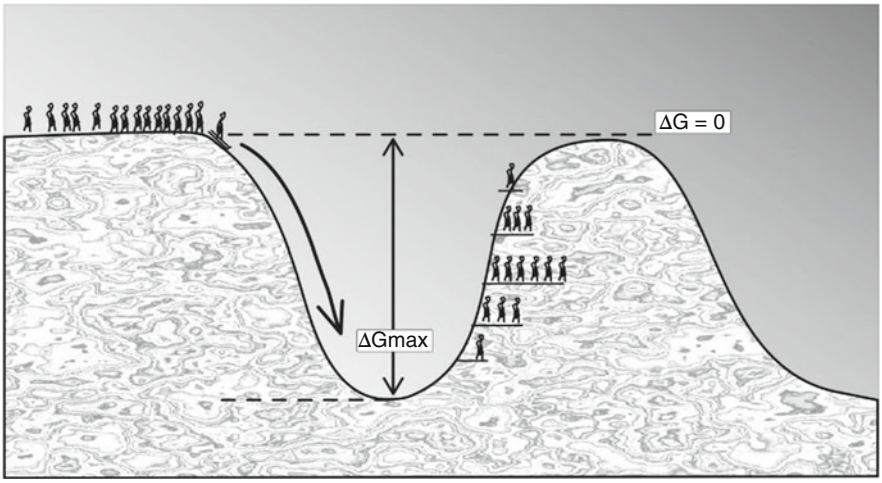

Fig. 2.27 Reaction efficiency depicted as the distribution of skiers reaching various points on a slope and quantified by the number of skiers multiplied by the elevations they reach

up the opposite slope as possible. While analyzing the outcome of the competition, we will note that the relative density of skiers increases up until a certain elevation and begins to drop off beyond that point. Peak efficiency (the number of skiers multiplied by the attained elevation) occurs at approximately 30–40% of the total elevation of the slope. This value corresponds to the peak fraction of energy which may be exploited in a spontaneous process.

Once the competition is over, each skier is again in possession of stored energy which can pay for further, spontaneous downhill descent. The total number of skiers positioned behind the starting line on the initial slope (at a certain elevation) is equivalent to the total potential energy of the process, while the final distribution of skiers on the opposite slope can be treated as a measure of conserved energy. The difference between both values (potential and conserved energy) is the free energy (ΔG) dissipated during the process while ensuring its spontaneity. Assuming a statistical distribution of skier skill, we can predict that the amount of conserved energy will increase up until a certain elevation (which can be reached by moderately skilled skiers) and then begin to drop off, becoming equal to 0 at an elevation which no skier is able to reach. The elevation reached by the best skier is still lower than that of the starting line; otherwise we would be dealing with a *perpetuum mobile*, i.e., a process which can generate energy despite its ΔG being 0 (Fig. 2.27).

The efficiency of biological processes is usually below 40%. Synthesizing 1 mol of water yields 56.7 kcal of energy yet can only generate 3.0 mol (2.5 according to some studies) of ATP yielding 7.3 kcal/mol each upon hydrolysis. Thus, the total amount of conserved energy is not higher than 21.9 kcal/mol, which corresponds to an efficiency of 37.4%. It should, however, be remembered that this low efficiency is the price paid for spontaneity, as more than 60% of the energy released by the source is dissipated. A typical human transforms 3 mol (approximately 1.5 kg) of ATP

(ATP ↔ ADP) in 1 h. Strenuous physical exertion may increase this demand by a factor of 10, though the process itself is dynamic and, on average, no more than 0.1 mol of ATP exists in the organism at any given time.

2.7 Entropic Effects

The spontaneity of biological processes is a consequence of enthalpic and entropic changes:

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

In most cases both phenomena have a measurable effect on spontaneity; however in some situations one clearly dominates the other. In processes where covalent bonds are formed or broken, enthalpy is usually more important than entropy, whereas synthesis of protein complexes and many other noncovalently stabilized structures (such as cellular membranes) relies primarily on entropic effects and is often powered by thermodynamically disadvantageous rearrangement of water molecules, emerging as a result of contact with water-repellent hydrophobic surfaces of compounds introduced into the aqueous environment. Such compounds include polymer chains or particulate organic structures which contain apolar and polar moieties and are therefore water-soluble. In the latter case, aggregation occurs as a result of hydrophobic interactions.

Hydrophobic interaction is not, strictly speaking, a chemical bond—instead, it can be treated as a physical phenomenon related to the thermodynamically disadvantageous interaction between hydrophobic structures and water. Such interaction introduces an entropic force which tries to destroy any structural ordering of water resulting from contact with hydrophobic residues (Fig. 2.28). Aggregation is a means by which such thermodynamically undesirable changes (caused by hydrophobic compounds intruding into the aqueous environment) are reversed. Coupling hydrophobic surfaces to each other, and stabilizing this aggregation with hydrophobic bonds (usually van der Waals bonds) lessens their exposure to water and is therefore thermodynamically preferable.

Synthesis applies to structures which are partly apolar but also contain polar elements. It is necessary for such polar elements to be sufficiently large to dissolve, thus pulling and exposing its apolar groups to water and—as a consequence—forcing aggregation. This mechanism is one of the most basic forms of self-organization.

A classic example of self-association at work is the clustering of phospholipids in the cellular membrane, which determines its tertiary structure (Fig. 2.29). Polypeptide chain folding is considered to be of fundamental importance to this process, although our knowledge of its mechanisms is still somewhat limited. We do know that in order for a tertiary structure to emerge, the polypeptide chain immersed in the aqueous environment must exhibit a noneven distribution of polarity, corresponding to nonrandom ordering of hydrophobic amino acids. The apolar fragments of the

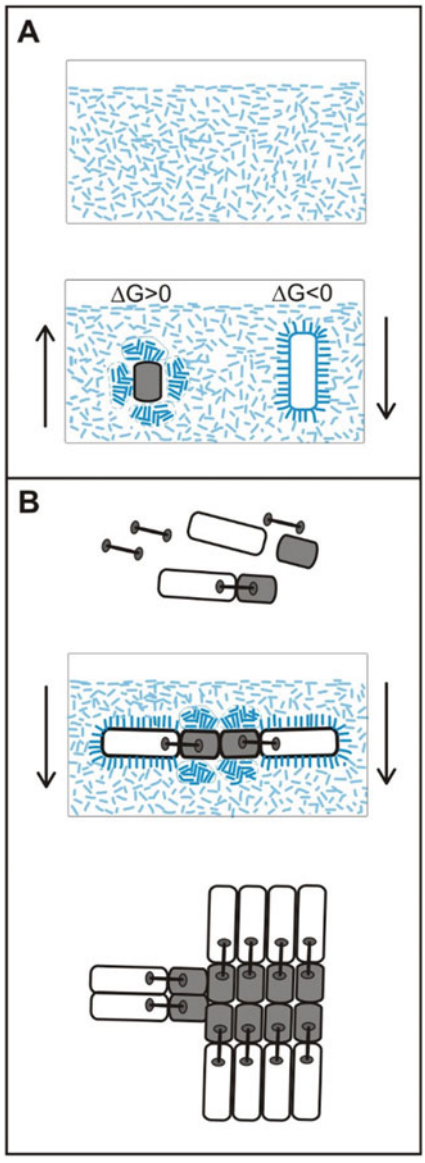

Fig. 2.28 Self-organization powered by hydrophobic interactions (aggregates of apolar structures in an aqueous environment). (**a**) The thermodynamically disadvantageous effect of introducing a hydrophobic compound ($\Delta G > 0.0$) into an aqueous environment and the corresponding effect observed for a polar compound ($\Delta G < 0.0$). (**b**) Covalent (permanent) binding of both compounds results in their selective, nonrandom aggregation and ordering in the presence of water. Arrows indicate salvation tendency

chain undergo aggregation, forming a hydrophobic core which, in turn, is encapsulated by polar fragments. Such thermodynamically optimal folding of the polypeptide chain determines the so-called native structure of the protein. The process is assisted by a special class of proteins called chaperones, and its nature constitutes one of the most important unresolved problems in modern biology. A fully folded globular protein resembles a tightly packed solid, although it usually includes an active pocket, which can be interpreted as a point of access to its apolar

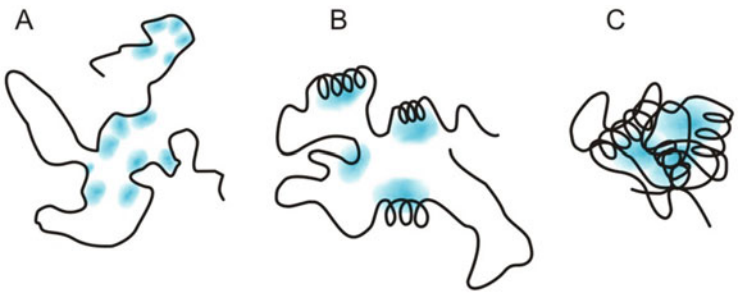

Fig. 2.29 Globular protein synthesis divided into phases: (**a**) Synthesis of an unraveled polypeptide chain, (**b**) creation of subdomains, and (**c**) structural collapse. Hydrophobic areas marked in color (schematic view)

core. The existence of an active pocket is a prerequisite of forming protein-ligand complexes in aqueous environments.

2.8 Energy Requirements of Organisms

Maintaining baseline biological processes requires a supply of energy. In humans, the so-called basal metabolic rate (BMR) is approximately 1500–2000 kcal/day. Normal activity introduces additional demands; thus most humans burn approximately 2000–2500 kcal/day, although strenuous physical exercise may increase this amount to 5000–10,000 kcal/day or even more. Energy demands are normally met through consumption of food. Among nutrients the highest calorie content is found in lipids (9.4 kcal/g). Sugars and proteins are somewhat less energetic, yielding 4.2 kcal/g and 4.3 kcal/g, respectively.

The following list illustrates the approximate calorie content of common foodstuffs:

Vegetables (100 g serving)	20–30 kcal
Potatoes (80 g serving)	60–80 kcal
Sugar (1 teaspoon)	30–40 kcal
Egg (domestic chicken)	100 kcal
Veal cutlet	200–250 kcal
Sausage (100 g serving)	250–300 kcal
Butter (100 g)	750 kcal
Vegetable oil (100 g)	900 kcal

The average daily intake of carbohydrates (a major component of human diet) is approximately 250 g, which corresponds to 1000 kcal. If we assume that 1 mole of glucose (180 g) affords 38 mol of ATP, 250 g of glucose can cover the cost of synthesizing 52.8 mol of ATP, i.e., 385.3 kcal at an efficiency of 38.5%. This value matches stoichiometric studies of ATP/water synthesis, where 56.7 kcal of energy

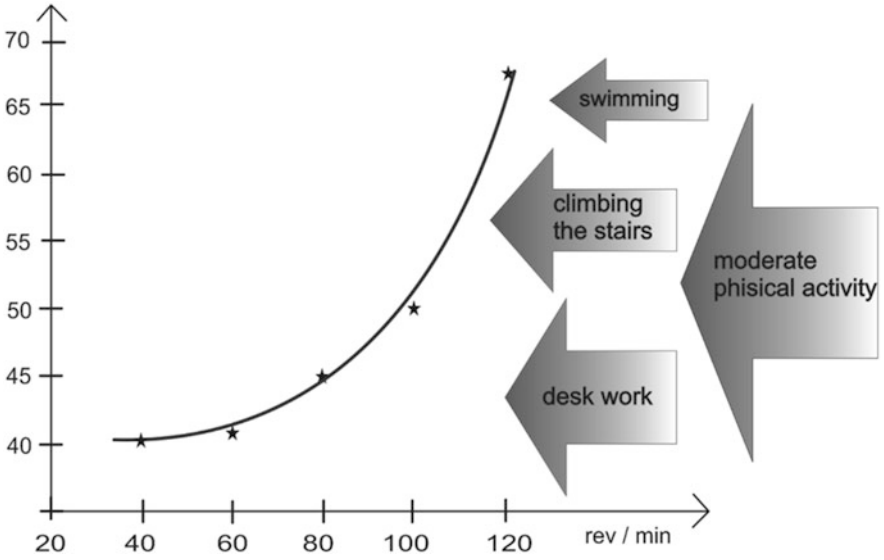

Fig. 2.30 Relationship between energy expenditure and physical exertion. The diagram illustrates the energy cost incurred by a cyclist pedaling at a rate of 40, 60, 80, 100, and 120 revolutions/min over a period of 6 min against a constant drag force. Measurements are based on the intake of oxygen required for the synthesis of water (Zoladz et al. 1998). Arrows indicate average energy requirements for specific types of activity, while their width denotes the possible range of values

released in the oxidation of hydrogen covers the cost of synthesizing three anhydrous ATP bonds which can subsequently be hydrolyzed for an energy gain of 21.9 kcal. Our calculation therefore assumes that synthesis of 1 mole of water affords 3 mol of ATP.

The energy of anhydrous bonds may be tapped to power endoergic processes. Muscle action requires a major expenditure of energy. There is a nonlinear dependence between the degree of physical exertion and the corresponding energy requirements. Figure 2.30 presents the energy expenditure associated with physical exertion as a function of cyclist pedaling at different rates.

Training may improve the power and endurance of the muscle tissue. Muscle fibers subjected to regular exertion may improve their glycogen storage capacity, ATP production rate, oxidative metabolism, and the use of fatty acids as fuel.

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