

PART III

FREE ENERGY

CHAPTER 9

Free Energy

How do we know when a chemical or biological process is at equilibrium? Various macroscopic properties of the system, such as the total energy, the temperature, or the entropy, are stable and unchanging at equilibrium (Figure 9.1). But molecular systems are always far from being static at a microscopic level, with each of the molecules moving along chaotic trajectories and exchanging energy as they collide. Nevertheless, for systems with large numbers of molecules, there is no net change in the global properties of the system at equilibrium.

If we perturb a system that is at equilibrium, perhaps by changing the temperature or by adding more molecules, then the system will no longer be at equilibrium. The macroscopic variables of the system will respond to the changes until the system reaches a new equilibrium, defined by the new set of environmental conditions (Figure 9.2). As the system moves towards a new equilibrium, what is the direction of spontaneous change? Will the temperature rise or fall? Will the concentrations of particular molecules increase or decrease? What will the values of these parameters be after equilibrium has been reestablished?

The first and second laws of thermodynamics provide powerful guiding principles that help answer these questions. We will find it helpful to define a new property of the system, known as the **free energy**, which incorporates both the energy of the system (which is constrained by the first law) and its entropy (constrained

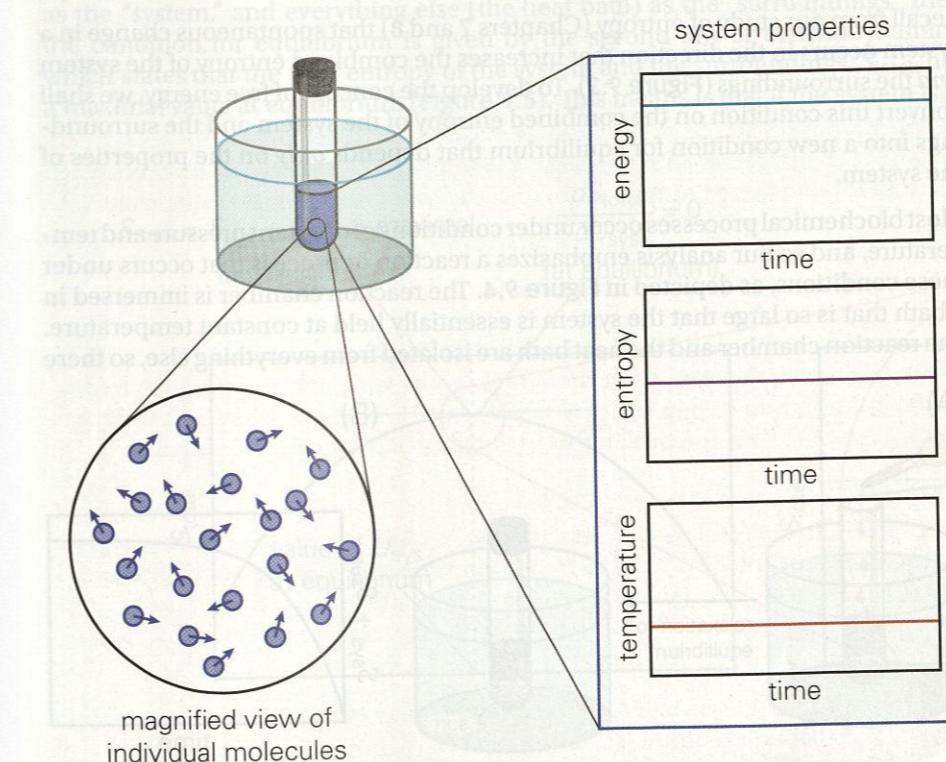
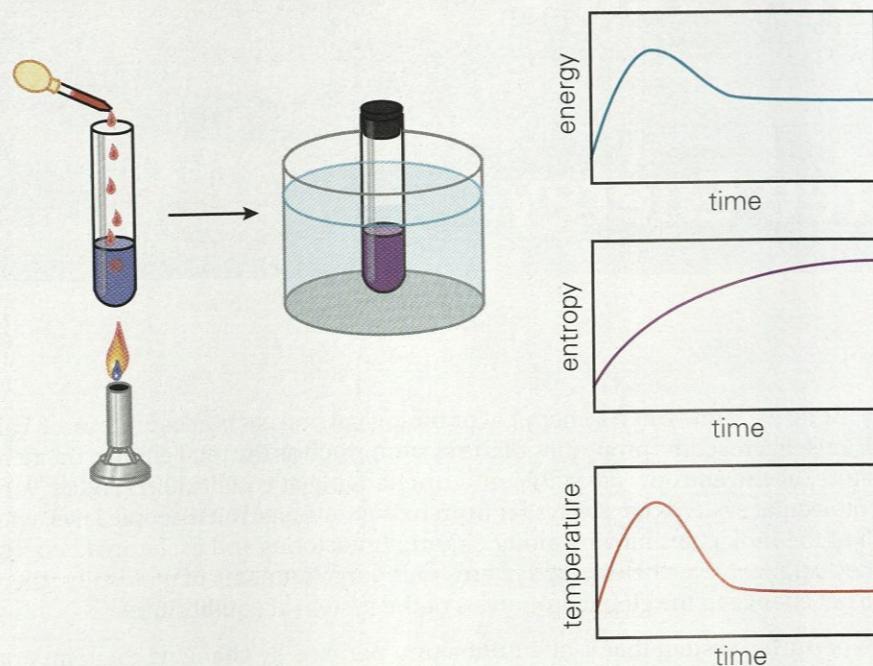


Figure 9.1 A system at equilibrium.
A system (the test tube and its contents) is shown immersed in a water bath (surroundings). The movements of the individual molecules within the system are chaotic and unpredictable, but the global properties of the entire system, such as the temperature and the total energy, are stable with time.

Figure 9.1 The quantum nature of the system. Although the motion of individual molecules is maximal at one point, the graph shows the overall behavior of the total entropy and energy of the system. At equilibrium, the entropy of the system is at its maximum, and there is essentially no change in either entropy or energy over time. An expanded view of the molecules in the system shows that the individual molecules move in a chaotic, unpredictable manner, but the overall properties of the system remain stable. The entropy of the system is represented by the area under the curve, and the total energy is represented by the area above the curve.

Figure 9.2 A perturbed system moves to a new equilibrium state after the perturbation. A system (test tube) is perturbed by adding more molecules to it (red) and by heating it. The system is then placed in a water bath and not perturbed further. The global properties of the system relax to new equilibrium values, which are stable as long as the system is not perturbed again.



by the second law). The free energy of a system always *decreases* when a process occurs spontaneously, and is at a minimum when the system is at equilibrium. As we shall see, the change in free energy that occurs during a process is equal to the maximum amount of work that can be extracted from the process.

A. FREE ENERGY

9.1 The combined entropy of the system and the surroundings increases for a spontaneous process

Recall from our study of entropy (Chapters 7 and 8) that spontaneous change in a system occurs in the direction that increases the combined entropy of the system *and* the surroundings (**Figure 9.3**). To develop the concept of free energy, we shall convert this condition on the combined entropy of the system and the surroundings into a new condition for equilibrium that depends *only* on the properties of the system.

Most biochemical processes occur under conditions of constant pressure and temperature, and so our analysis emphasizes a reaction or process that occurs under these conditions, as depicted in **Figure 9.4**. The reaction chamber is immersed in a bath that is so large that the system is essentially held at constant temperature. The reaction chamber and the heat bath are isolated from everything else, so there

Figure 9.3 The combined entropy of the system and the surroundings increases in a spontaneous process. (A) A system, denoted *syst*, is perturbed from equilibrium as new material is added to it. The system relaxes to equilibrium after the perturbation. (B) The graph shows the combined entropy of the system and the surroundings (denoted *surr*) as a function of time. The relaxation towards equilibrium is accompanied by an increase in the combined entropy of the system and the surroundings, in accordance with the second law of thermodynamics.

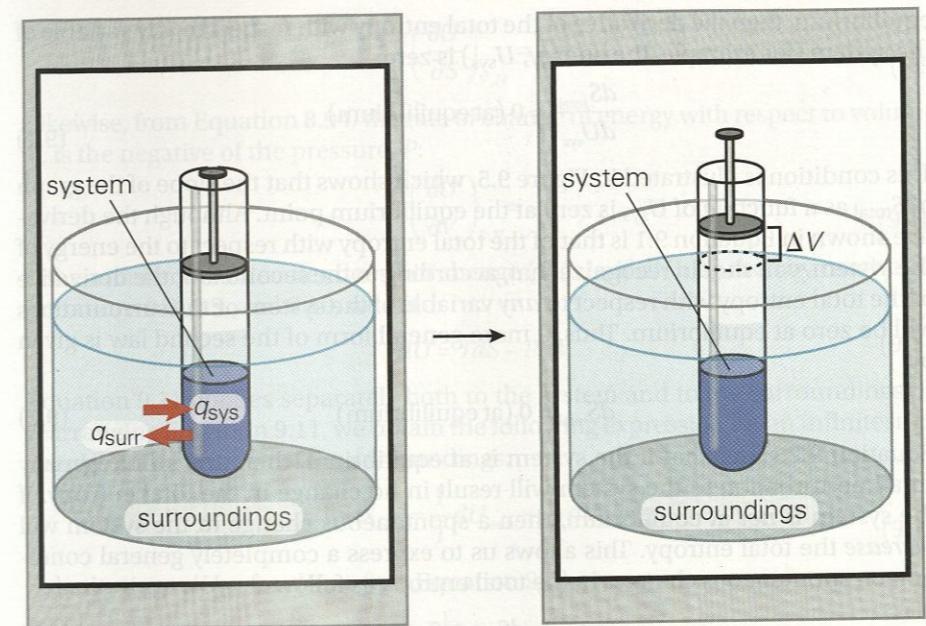
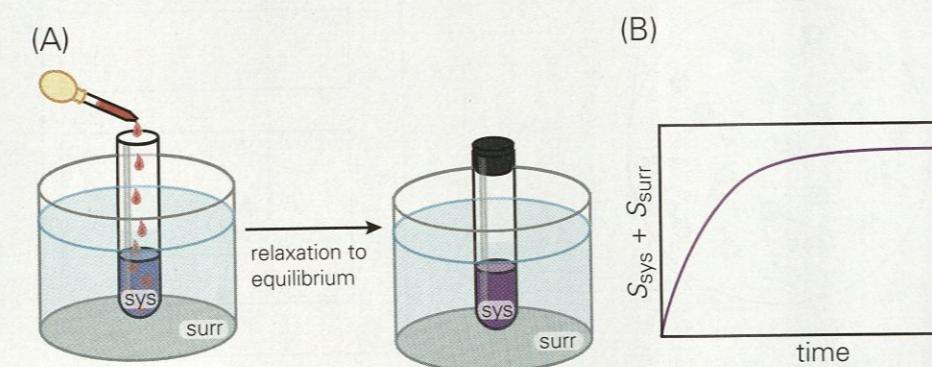


Figure 9.4 An idealization of a system at constant temperature and pressure. The system is shown schematically as a test tube that is capped by a frictionless piston. The diagram shows a process occurring, during which heat is exchanged between the system and the surroundings. The system expands, and the piston adjusts so as to maintain constant pressure.

is no heat transfer into or out of the combination of the chamber plus the bath. The chamber is capped by a frictionless piston, which adjusts itself so as to maintain the system at constant pressure.

The piston in the system shown in **Figure 9.4** is a conceptual device that lets us calculate the expansion work done by the system during a process. In a more realistic situation, there would be no piston, and the system would be open to the atmosphere. The expansion work done by the system would still be given by the change in volume of the system multiplied by the pressure, and would correspond to the work done to push against the atmosphere.

If we denote the experimental set-up (the reaction chamber and its contents) as the “system,” and everything else (the heat bath) as the “surroundings,” then the condition for equilibrium is given by the second law of thermodynamics, which states that the total entropy of the system and the surroundings, S_{total} , has a maximal value at equilibrium (**Figure 9.5**). This means is that if the system is at

$$S_{\text{total}} = S_{\text{sys}} + S_{\text{surr}} = \text{maximal} \quad \frac{dS_{\text{total}}}{dU_{\text{sys}}} = 0 \quad (\text{at equilibrium})$$

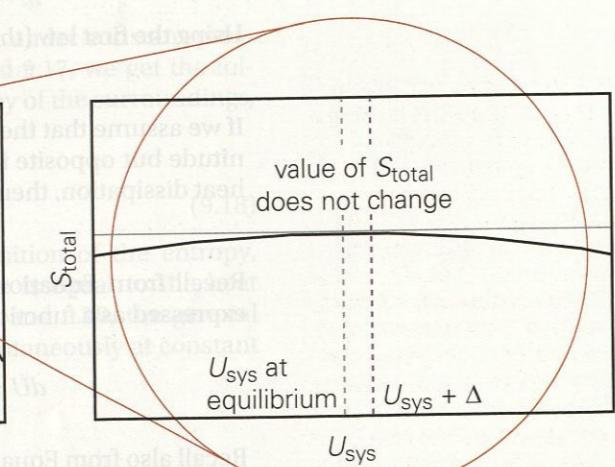
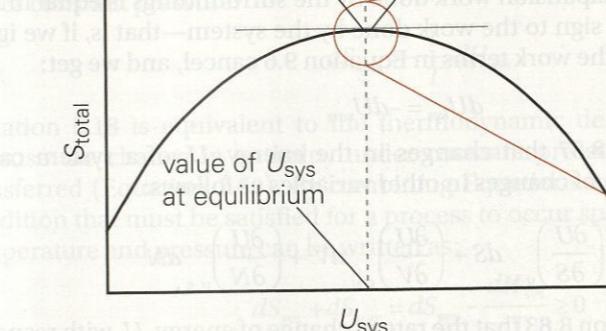


Figure 9.5 The combined entropy of the system and the surroundings is maximal at equilibrium. The graph shows the dependence of the total entropy, $S_{\text{total}} = S_{\text{sys}} + S_{\text{surr}}$, on the energy of the system (U_{sys}). At equilibrium, a small change in U_{sys} , denoted here by Δ , produces essentially no change in S_{total} . The expanded view shows the variation of S_{total} for values of U_{sys} that are very near the equilibrium value. The slope of the horizontal line, which is tangent to the curve describing the entropy, represents the derivative of the entropy with respect to the energy.

equilibrium, then the derivative of the total entropy with respect to any variable of the system (for example, the energy, U_{sys}) is zero:

$$\frac{dS_{\text{total}}}{dU_{\text{sys}}} = 0 \text{ (at equilibrium)} \quad (9.1)$$

This condition is illustrated in Figure 9.5, which shows that the slope of the graph of S_{total} as a function of U_{sys} is zero at the equilibrium point. Although the derivative shown in Equation 9.1 is that of the total entropy with respect to the energy of the system, you should recognize that, according to the second law, the derivative of the total entropy with respect to *any* variable of the system or the surroundings will be zero at equilibrium. Thus, a more general form of the second law is given by:

$$dS_{\text{total}} = 0 \text{ (at equilibrium)} \quad (9.2)$$

Equation 9.2 states that if the system is at equilibrium, then any infinitesimally small perturbation to the system will result in no change in the total entropy. If the system is *not* at equilibrium, then a spontaneous change in the system will *increase* the total entropy. This allows us to express a completely general condition on spontaneous changes in the total entropy as follows:

$$dS_{\text{total}} \geq 0 \quad (9.3)$$

If the system and the surroundings are at equilibrium, then the combined entropy is at a maximum and the right-hand side of Equation 9.3 is set to zero. If the system and its surroundings are *not* at equilibrium, then a spontaneous change will increase the combined entropies of the system and its surroundings—that is, $dS_{\text{total}} > 0$ for that change.

9.2 The change in entropy of the surroundings is related to the change in energy and volume of the system

Equation 9.3 defines the condition for spontaneous change in terms of the total entropy—that is, the entropy of the system *and* that of the surroundings. It would be more convenient, instead, if we could rewrite Equation 9.3 in a way that only involves system parameters. We begin by rewriting Equation 9.3 in terms of infinitesimal changes in the entropies of the system and the surroundings:

$$dS_{\text{total}} = dS_{\text{sys}} + dS_{\text{surr}} \geq 0 \quad (9.4)$$

We would like to rearrange Equation 9.4 in some way that focuses attention only on the properties of the system—that is, we want to get rid of the dS_{surr} term because it is only the system that we are directly interested in. We start by equating the heat transferred to the system with the heat lost by the surroundings:

$$dq_{\text{sys}} = -dq_{\text{surr}} \quad (9.5)$$

Using the first law (that is, $dU = dq + dw$; see Equation 6.5) gives:

$$dU_{\text{sys}} - dw_{\text{sys}} = -(dU_{\text{surr}} - dw_{\text{surr}}) \quad (9.6)$$

If we assume that the expansion work done by the surroundings is equal in magnitude but opposite in sign to the work done by the system—that is, if we ignore heat dissipation, then the work terms in Equation 9.6 cancel, and we get:

$$dU_{\text{sys}} = -dU_{\text{surr}} \quad (9.7)$$

Recall from Equation 8.87 that changes in the energy, U , of a system can be expressed as a function of changes in other variables as follows:

$$dU = \left(\frac{\partial U}{\partial S}\right)_{V,N} dS + \left(\frac{\partial U}{\partial V}\right)_{S,N} dV + \left(\frac{\partial U}{\partial N}\right)_{V,S} dN \quad (9.8)$$

Recall also from Equation 8.83 that the rate of change of energy, U , with respect to entropy, S , is the temperature, T :

$$\left(\frac{\partial U}{\partial S}\right)_{V,N} = T \quad (9.9)$$

Likewise, from Equation 8.94, the rate of change of energy with respect to volume, V , is the negative of the pressure, P :

$$\left(\frac{\partial U}{\partial V}\right)_{S,N} = -P \quad (9.10)$$

If the number of molecules does not change (that is, if $dN = 0$), then by combining Equations 9.8, 9.9, and 9.10, we get:

$$dU = TdS - PdV \quad (9.11)$$

Equation 9.11 applies separately both to the system and to the surroundings. By rearranging Equation 9.11, we obtain the following expression for an infinitesimal change in the entropy of the surroundings:

$$dS_{\text{surr}} = \frac{1}{T} dU_{\text{surr}} + \frac{P}{T} dV_{\text{surr}} \quad (9.12)$$

Substituting $-dU_{\text{sys}}$ for dU_{surr} (see Equation 9.7), we get:

$$dS_{\text{surr}} = -\frac{1}{T} dU_{\text{sys}} + \frac{P}{T} dV_{\text{surr}} \quad (9.13)$$

The change in the volume of the surroundings (dV_{surr}) has to be equal in magnitude but opposite in sign to the change in volume of the system (dV_{sys}):

$$dV_{\text{surr}} = -dV_{\text{sys}} \quad (9.14)$$

Substituting Equation 9.14 in Equation 9.13, we see that changes in the entropy of the surroundings can be expressed in terms of changes in the energy and the volume of the system:

$$dS_{\text{surr}} = -\frac{1}{T} dU_{\text{sys}} - \frac{P}{T} dV_{\text{sys}} \quad (9.15)$$

9.3 The Gibbs free energy (G) of the system always decreases in a spontaneous process occurring at constant pressure and temperature

Recall from Chapter 6 that the enthalpy of the system, H_{sys} , is given by:

$$H_{\text{sys}} = U_{\text{sys}} + PV_{\text{sys}} \quad (9.16)$$

According to Equation 9.16, an infinitesimal change in the enthalpy at constant pressure, dH_{sys} , is given by:

$$dH_{\text{sys}} = dU_{\text{sys}} + PdV_{\text{sys}} + V_{\text{sys}}dP = dU_{\text{sys}} + PdV_{\text{sys}} \quad (9.17)$$

The second equality in Equation 9.17 reflects the fact that under constant-pressure conditions, $dP = 0$. By combining Equations 9.15 and 9.17, we get the following expression for an infinitesimal change in the entropy of the surroundings, under constant pressure:

$$dS_{\text{surr}} = -\frac{1}{T} dH_{\text{sys}} \quad (9.18)$$

Equation 9.18 is equivalent to the thermodynamic definition of the entropy, because the change in enthalpy under constant pressure is equal to the heat transferred (Equation 7.60). By combining Equations 9.4 and 9.18, the general condition that must be satisfied for a process to occur spontaneously at constant temperature and pressure can be written as:

$$\begin{aligned} dS_{\text{sys}} + dS_{\text{surr}} &= dS_{\text{sys}} - \frac{dH_{\text{sys}}}{T} \geq 0 \\ \Rightarrow dH_{\text{sys}} - TdS_{\text{sys}} &\leq 0 \end{aligned} \quad (9.19)$$

We now define a new state function of the system, which we call the **Gibbs free energy** (G):

$$G = H - TS \quad (9.20)$$

Gibbs free energy

The Gibbs free energy, G , of a system is given by:

$$G = H - TS$$

For a system at constant pressure and temperature, the value of G always decreases in a spontaneous process.

All of the variables in Equation 9.20 refer to the system alone, and so we no longer use subscripts to distinguish them. The enthalpy (H), the temperature (T), and the entropy (S) in Equation 9.20 are all state variables, and so G is also a state function. The Gibbs free energy is named after Josiah Willard Gibbs, who first introduced the ideas that led to the definition given in Equation 9.20. As we discuss below, in part C of this chapter, the change in Gibbs free energy during a process is equal to the maximum amount of non-expansion work that can be extracted from the process. The change in Gibbs free energy is therefore the amount of energy (or heat) that is “free” to be converted to work (the rest is bound up in entropy).

An infinitesimally small change in G (that is, dG) is given by:

$$dG = dH - TdS - SdT$$

At constant temperature the value of dT is zero, and so this equation reduces to:

$$dG = dH - TdS \quad (9.21)$$

Substituting Equation 9.21 into Equation 9.19 yields:

$$dG \leq 0 \text{ (constant pressure and temperature)} \quad (9.22)$$

Thus, a spontaneous process at constant temperature and pressure always involves a *decrease* in the Gibbs free energy of the system (that is, $dG < 0$). It follows, then, that the value of the Gibbs free energy is at a minimum (that is, $dG = 0$) at equilibrium, as shown in Figure 9.6.

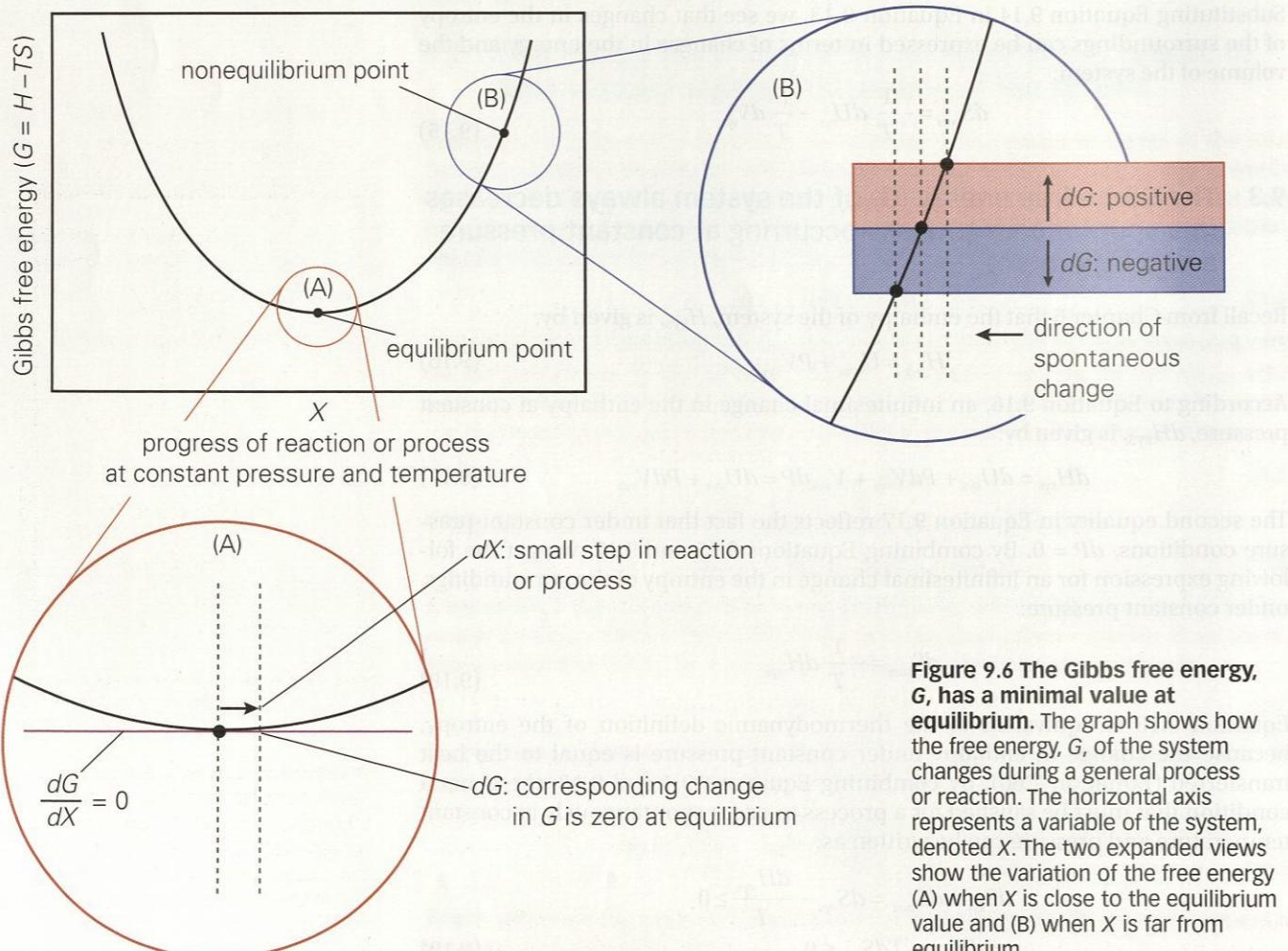


Figure 9.6 The Gibbs free energy, G , has a minimal value at equilibrium. The graph shows how the free energy, G , of the system changes during a general process or reaction. The horizontal axis represents a variable of the system, denoted X . The two expanded views show the variation of the free energy (A) when X is close to the equilibrium value and (B) when X is far from equilibrium.

The graph in Figure 9.6 shows how the free energy, G , of a system changes during a general process or reaction. The horizontal axis of the graph represents a change in the state of the system, such as during a chemical reaction or an energetic relaxation after a jump in the temperature. The equilibrium point is reached when small changes in any system variable, denoted X , lead to essentially no change in the free energy. That is, the derivative of the free energy, G , with respect to the variable X is zero at equilibrium:

$$\frac{dG}{dX} = 0 \quad (9.23)$$

The condition given by Equation 9.23 defines an extremum point of the function G —that is, the free energy is either at a maximum or a minimum when this condition holds true (Figure 9.7). Only the points of minimum free energy are stable. When the free energy is at a minimum, small fluctuations in the system parameters will increase the free energy and the system will relax back to the equilibrium point spontaneously.

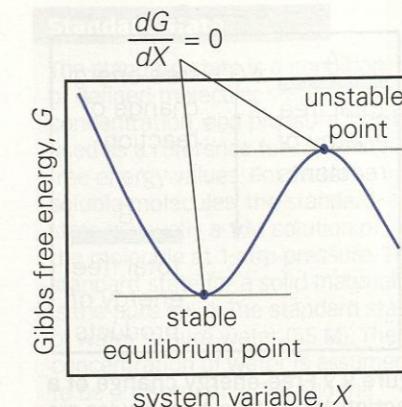


Figure 9.7 The Gibbs free energy (G) is at a minimum at equilibrium. The diagram shows the change in G as a function of a system variable, X . The derivative of G with respect to X is zero when G is either maximal or minimal. Values of X for which the value of G is maximal are unstable because small fluctuations in the system will cause the system to move away from that point.

9.4 The Helmholtz free energy (A) determines the direction of spontaneous change when the volume is constant

A slightly different expression for the free energy is obtained when a process occurs with no change in volume, as illustrated in Figure 9.8. Equation 9.15, which relates an infinitesimal change in the entropy of the surroundings to variables of the system, is modified as follows under constant-volume conditions:

$$dS_{\text{surr}} = -\frac{1}{T}dU_{\text{sys}} - \frac{P}{T}dV_{\text{sys}} = -\frac{1}{T}dU_{\text{sys}} \text{ (constant volume)} \quad (9.24)$$

The condition on changes in the total entropy (Equation 9.4) then becomes:

$$dS_{\text{sys}} + dS_{\text{surr}} = dS_{\text{sys}} - \frac{1}{T}dU_{\text{sys}} \geq 0 \quad (9.25)$$

Multiplying both sides of Equation 9.25 by the temperature (T) yields:

$$TdS_{\text{sys}} - dU_{\text{sys}} \geq 0 \quad (9.26)$$

$$\Rightarrow dU_{\text{sys}} - TdS_{\text{sys}} \leq 0 \quad (9.27)$$

We now define a new state function of the system called the **Helmholtz free energy**, named after Hermann von Helmholtz. The Helmholtz free energy is denoted A (after *arbeit*, the German word for work) and is defined as follows:

$$A = U - TS \quad (9.28)$$

At constant temperature (that is, $dT = 0$), an infinitesimal change in the Helmholtz free energy, dA , is given by:

$$dA = dU - TdS - SdT = dU - TdS \quad (9.29)$$

Comparing Equation 9.29 with Equation 9.27, we see that the change in A must satisfy the following condition for a process to occur spontaneously at constant volume:

$$dA < 0 \quad (9.30)$$

And, for a system at equilibrium, the value of the function A must be at a minimum:

$$dA = 0 \quad (9.31)$$

According to Equations 9.30 and 9.31, changes in system parameters that result in a reduction in the value of A will occur spontaneously under conditions of constant volume and temperature.

Biochemists usually use the Gibbs free energy rather than the Helmholtz free energy, because biochemical reactions almost always occur under conditions of

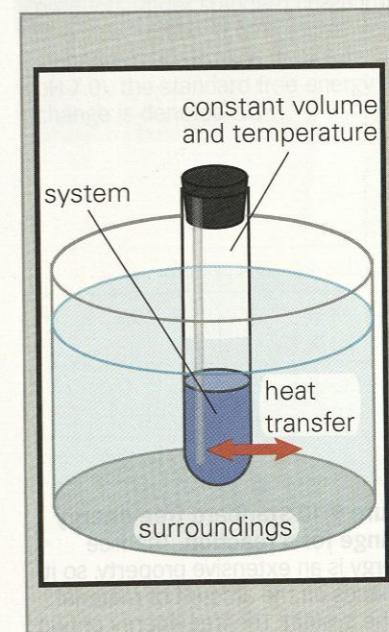


Figure 9.8 A process occurring under conditions of constant volume and temperature. The system is shown here schematically as a stoppered test tube. The system exchanges heat with the surroundings and is maintained at constant temperature.

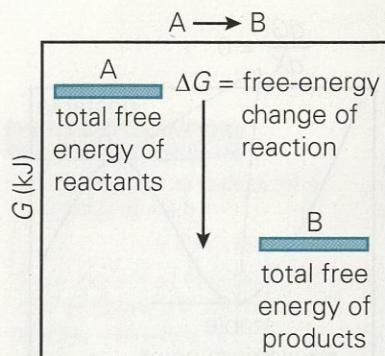


Figure 9.9 Free-energy change of a reaction. When type A molecules are converted to type B molecules, the free-energy change of the reaction, ΔG , is the difference between the free energies of the B and A molecules.

Helmholtz free energy

The Helmholtz free energy, A , of a system is given by:

$$A = U - TS$$

For a system at constant volume and temperature, the value of A always decreases in a spontaneous process.

constant pressure. For reactions that do not involve changes in the number of gas molecules, the change in volume is often negligible, and under such conditions the two forms of the free energy can be used interchangeably to determine the direction of spontaneous change.

B. STANDARD FREE-ENERGY CHANGES

9.5 Standard free-energy changes are defined with reference to defined standard states

Now that we have a prescription for identifying the direction of spontaneous change in terms of the free energy (that is, $dG < 0$), we are in a position to use it to determine the direction in which a chemical reaction will proceed under given conditions. We shall defer a discussion of how to determine the equilibrium points of chemical reactions until Chapter 10, when we discuss the concept of the equilibrium constant. Here we simply introduce some bookkeeping conventions so that we can calculate and compare free-energy values correctly.

Consider the hydrolysis of ATP:



where P_i represents the phosphate ion, $[\text{H}(\text{PO}_4)^2-/ \text{H}_2(\text{PO}_4)^{-}]$. In order to determine whether the reaction will proceed spontaneously from left to right, we need to know the value of the total change in free energy (ΔG) for the reaction (Figure 9.9):

$$\Delta G = \int_{\text{reactants}}^{\text{products}} dG = G(\text{products}) - G(\text{reactants}) \quad (9.33)$$

The integral in Equation 9.33 indicates that we are summing over all the infinitesimal changes in free energy as the reactants are converted to products, and the value of the integral is just the difference between the free energies of the products, G (products), and the reactants, G (reactants). Writing out the free energies of the individual molecules that constitute the reactants and the products explicitly, we get:

$$\Delta G = G(\text{ADP} + \text{P}_i) - G(\text{ATP} + \text{H}_2\text{O}) \quad (9.34)$$

The free energy is an extensive property of the system because it depends on enthalpy and entropy, which are both extensive properties. This means that the values of each of the individual terms in Equation 9.34 will depend on how much ATP and water enter into the reaction, as explained in Figure 9.10. In order to

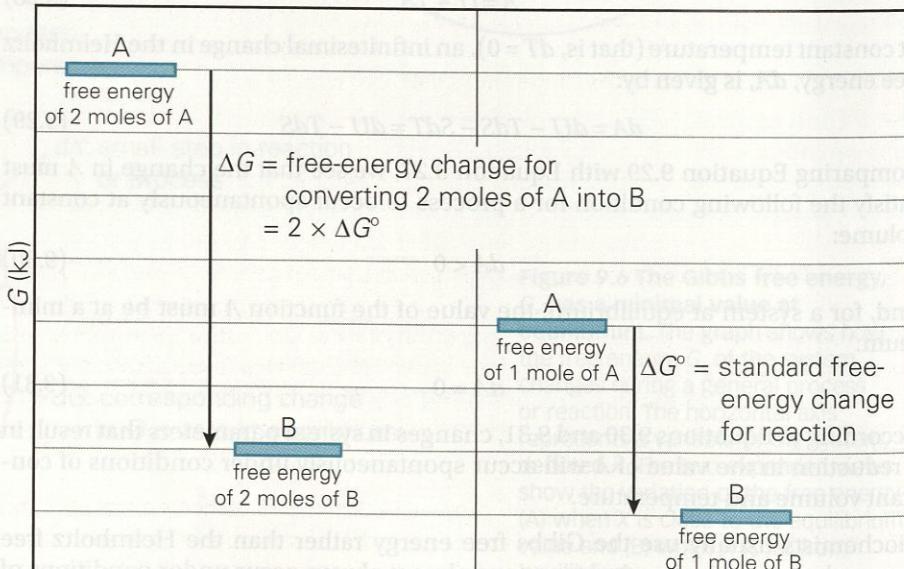


Figure 9.10 Standard free-energy change for a reaction. The free energy is an extensive property, so it depends on the amount of material in the system. The free energy of two moles of A-type molecules is twice that of one mole of A-type molecules. The standard free-energy change, ΔG° , for the reaction, $A \rightarrow B$, is the difference in free energy between one mole of B-type molecules and one mole of A-type molecules, under standard conditions of temperature, pressure, and concentration.

provide a standard reference value for the free-energy change, we define the **molar free energy** of a molecule as the free energy of one mole of that molecule. Since the free energy of a molecule changes with temperature, pressure, and whether it is pure or in a mixture, we need to know the conditions for which a free-energy change is being reported.

By convention, free-energy changes are quoted for the **standard state**, which refers to a condition of defined concentration and pressure. Most biochemical reactions occur in aqueous solution, and the standard state is set to be a one molar (M) solution of the molecules in water and 1 atm pressure. The free-energy change that occurs upon converting a stoichiometric equivalent of reactant molecules into the stoichiometric equivalent of product molecules, all under standard conditions, is known as the **standard free-energy change**, ΔG° , of the reaction (see Figure 9.10). Standard free-energy changes are usually reported at room temperature (298 K). The value of ΔG° is temperature dependent, and so if we are interested in the standard free-energy change at a different temperature, then we have to account for the change in ΔG° with temperature. This is discussed further in Chapter 10.

There are some important special cases in the definition of standard states. The standard state for water is pure water (55 M). For a solid material the standard state is the pure solid. The natural standard state for protons in water is that of an aqueous solution at pH 7 ($[\text{H}^+] = 10^{-7} \text{ M}$). This convention, common in biochemistry, defines the **biochemical standard state**, and is different from the convention in other branches of chemistry, where the standard states are set to be 1 M for *all* solutions, including H^+ in water. To remind us of this difference, standard free-energy changes in biochemistry are often denoted as $\Delta G'^\circ$ rather than ΔG° . We shall always use the biochemical definition of the standard state in this book, unless stated otherwise, and will therefore drop the “prime” notation.

The standard free-energy change (ΔG°) for the hydrolysis of ATP is $-28 \text{ kJ} \cdot \text{mol}^{-1}$. The value of ΔG° for the hydrolysis of ATP depends on the concentration of Mg^{2+} ions in the solution, as well as the pH. The value quoted here is for pH 7 and a magnesium ion concentration of 100 mM. The negative value of the free-energy change means that the reaction will proceed spontaneously to the right for a 1 M solution of pure ATP in water, because the free energy of ATP and water (the reactants) is higher than the free energy of ADP and P_i (the products).

The standard free-energy change is a hypothetical concept, corresponding to the complete conversion of one mole of ATP (as a 1 M solution) into one mole of ADP (as a 1 M solution). In reality, if we start the reaction with a 1 M solution of ATP, the reaction will *not* proceed to completion, but will instead come to an equilibrium point at which the concentration of ATP is not precisely zero (this effect arises from the concentration dependence of free energy, as we shall see in Section 10.8).

9.6 The zero point of the free-energy scale is set by the free energy of the elements in their most stable forms

If we know the molar free energies of the reactants and products, we can readily calculate the molar free-energy change of a reaction by using Equation 9.34, but how do we know these values in the first place? By convention, the molar free energy of a molecule is the standard free-energy change that results from converting stoichiometric amounts of the pure elements that are its constituents into one mole of the molecule of interest under standard conditions. This is referred to as the **standard free energy of formation** of the molecule ($\Delta_f G^\circ$).

We are usually interested only in differences in the values of free energies rather than the absolute values of the free energies. It therefore suffices to define a specific zero point for the free-energy scale, and to then measure all free-energy

Standard state

The standard state is a condition of defined molecular state, concentration, and pressure that is used as a reference for reporting free energy values. For water soluble molecules, the standard state is usually a 1 M solution of the molecule at 1 atm pressure. The standard state for a solid material is the pure solid. The standard state of water is pure water (55 M). The concentration of water is assumed to be constant at 55 M, and the concentration of H^+ is 10^{-7} M (that is, pH = 7.0). This definition of the standard state is the biochemical standard state. In other branches of chemistry, the standard state proton concentration is 1 M (that is, pH 0).

Standard free-energy change, ΔG°

ΔG° is the change in free energy when a molar equivalent of reactants are converted into products under standard conditions of concentration. If the biochemical standard state is used (that is, pH 7.0), the standard free-energy change is denoted $\Delta G'^\circ$.

Figure 9.11 Standard free energies of formation. By convention, the molar free energies of elemental molecules in their standard states are set to zero. The standard free-energy change for converting the pure elemental molecules into more complex molecules, in molar stoichiometry, is known as the standard free energy of formation, $\Delta_f G^\circ$, for the molecule.

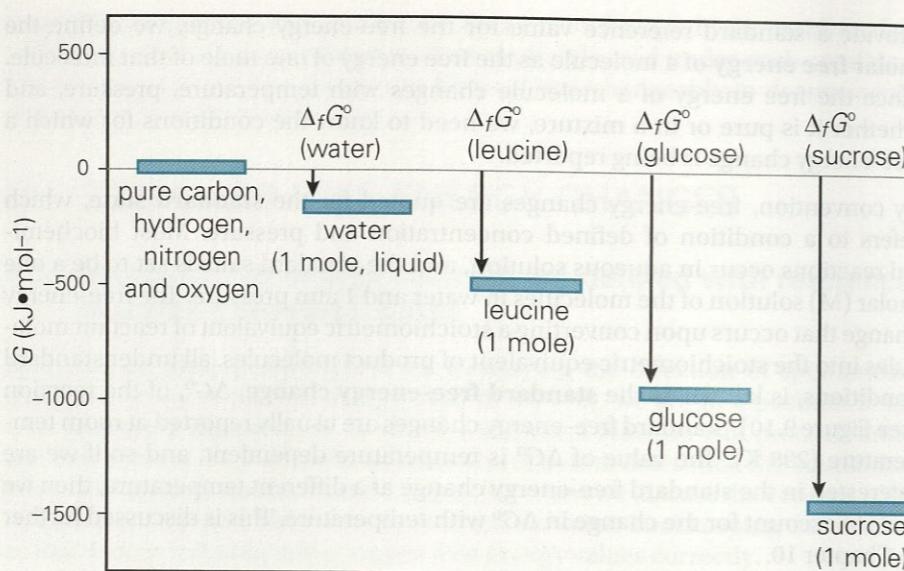


Table 9.1 Standard free energies of formation of some biochemical compounds (1 atm, 298 K).

Compound	ΔG° (kJ•mol ⁻¹)
acetate ⁻	-369.2
CO ₂ (gas)	-394.4
CO ₂ (aqueous solution)	-386.2
carbonate ion	-587.1
ethanol	-181.5
fructose	-915.4
fructose-6-phosphate ²⁻	-1758.3
α -D-glucose	-917.2
glucose-6-phosphate ²⁻	-1760.2
H ⁺ (aqueous solution)	0.0
H ₂ (gas)	0.0
H ₂ O (liquid)	-237.2
isocitrate ³⁻	-1160.0
lactate ⁻	-516.6
OH ⁻	-157.3
pyruvate ⁻	-474.5
succinate ²⁻	-690.2

changes relative to the zero values of this scale. By convention, the free energy of an element (for example, N₂, or O₂) in the most stable form of that element (for example, oxygen gas, O₂, and not ozone, O₃) has its free energy set to zero under standard conditions. The free energies of all other molecular forms or phases are measured relative to this set point for the zero on the free-energy scale (Figure 9.11). Using this convention, the free-energy change for any reaction under standard conditions is given by:

$$\Delta G^\circ = \sum_{\text{all products}} \Delta_f G^\circ(\text{product}) - \sum_{\text{all reactants}} \Delta_f G^\circ(\text{reactant}) \quad (9.35)$$

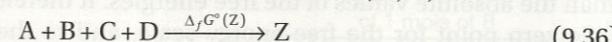
The free energies of formation of a few compounds that are important in biochemistry are given in Table 9.1. A more extensive list of such compounds may be found in biochemistry textbooks, or in compendia such as the *Handbook of Biochemistry and Molecular Biology* (see Further Reading at the end of this chapter).

9.7 Thermodynamic cycles allow the determination of the free energies of formation of complex molecules from simpler ones

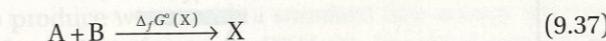
It is usually very difficult, if not impossible, to measure the free energy of formation of a complex molecule by converting elemental molecules directly into the complex molecule in one step. The free energy is a state function, however, and so the change in free energy for a process is independent of the path, and can be obtained by summing over the free-energy changes for any particular stepwise pathway that links reactants and products. We can break up the formation of a complex molecule into a series of intermediate reactions involving less complex molecules. If the values of $\Delta_f G^\circ$ for these less complex molecules can be determined experimentally, these values can then be combined to yield the value of $\Delta_f G^\circ$ for the more complex molecule.

We first illustrate this idea in an abstract way by considering the free energy of formation of a hypothetical molecule, denoted Z. Then, in the subsequent sections, we make these ideas concrete by discussing how the free energy of formation of a particular molecule, glucose, is determined experimentally.

Imagine that the molecule Z is formed from the elements A, B, C, and D:



The standard free-energy change for this reaction is the standard free energy of formation of Z, $\Delta_f G^\circ(Z)$. The reaction depicted in Equation 9.36 may be impossible to carry out in one step in a test tube, but imagine that we can carry out the following reactions without difficulty:



The standard free-energy changes for the reactions depicted in Equations 9.37–9.39 are noted above the arrows. Since A, B, C, and D are elements (for example, carbon or hydrogen), the standard free-energy changes for the first two reactions are the free energies of formation ($\Delta_f G^\circ$) of X and Y.

The free-energy changes along two different pathways in going from the elements A, B, C, and D to the complex molecule Z are illustrated using the **thermodynamic cycle** in Figure 9.12. A thermodynamic cycle is a set of reactions in which reactants and products are connected by two different pathways. The total free-energy change along either pathway is the same, but one pathway may be more accessible to experimental measurement than the other. Thermodynamic cycles allow free-energy changes to be determined for processes that are conceptually important but difficult to study directly. In Chapter 13, for example, we use thermodynamic cycles to determine the free-energy difference between correctly and incorrectly paired nucleotides in double-helical DNA.

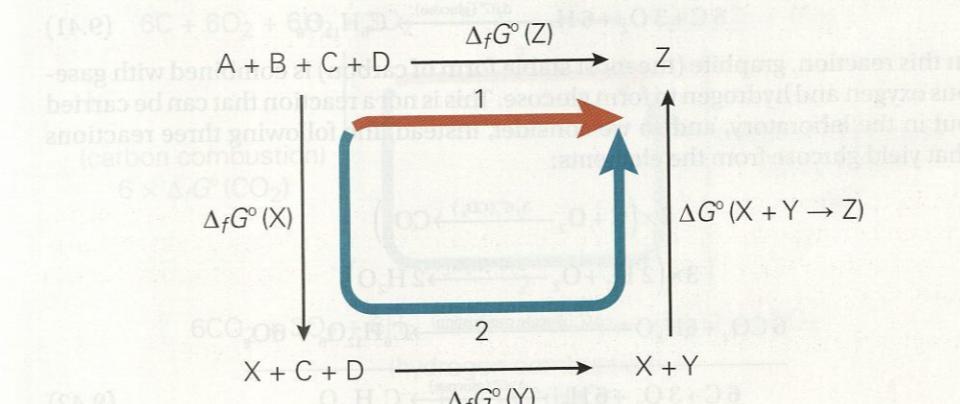
The free-energy change for the pathway denoted 1 in Figure 9.12 (red arrow) is the same as that for the set of transformations denoted 2 (green arrow). Hence:

$$\Delta_f G^\circ(Z) = \Delta_f G^\circ(X) + \Delta_f G^\circ(Y) + \Delta G^\circ(X+Y \rightarrow Z) \quad (9.40)$$

Thus, for this simple case, we can work out the free energy of formation of Z by adding up the standard free-energy changes for the three reactions shown in Equations 9.37–9.39 (Figure 9.13).

Over the years, scientists have painstakingly measured and tabulated the standard free energies of formation of most of the important biological molecules (a few of these are shown in Table 9.1). From these data, it is usually possible to work out the free-energy change for a particular reaction of interest under standard conditions.

We have said nothing so far about how we actually determine the values of the free-energy changes for reactions such as those that comprise pathway 2 in Figure 9.12. To provide some idea of how this is done, we discuss the experimental determination of the free energy of formation of glucose.



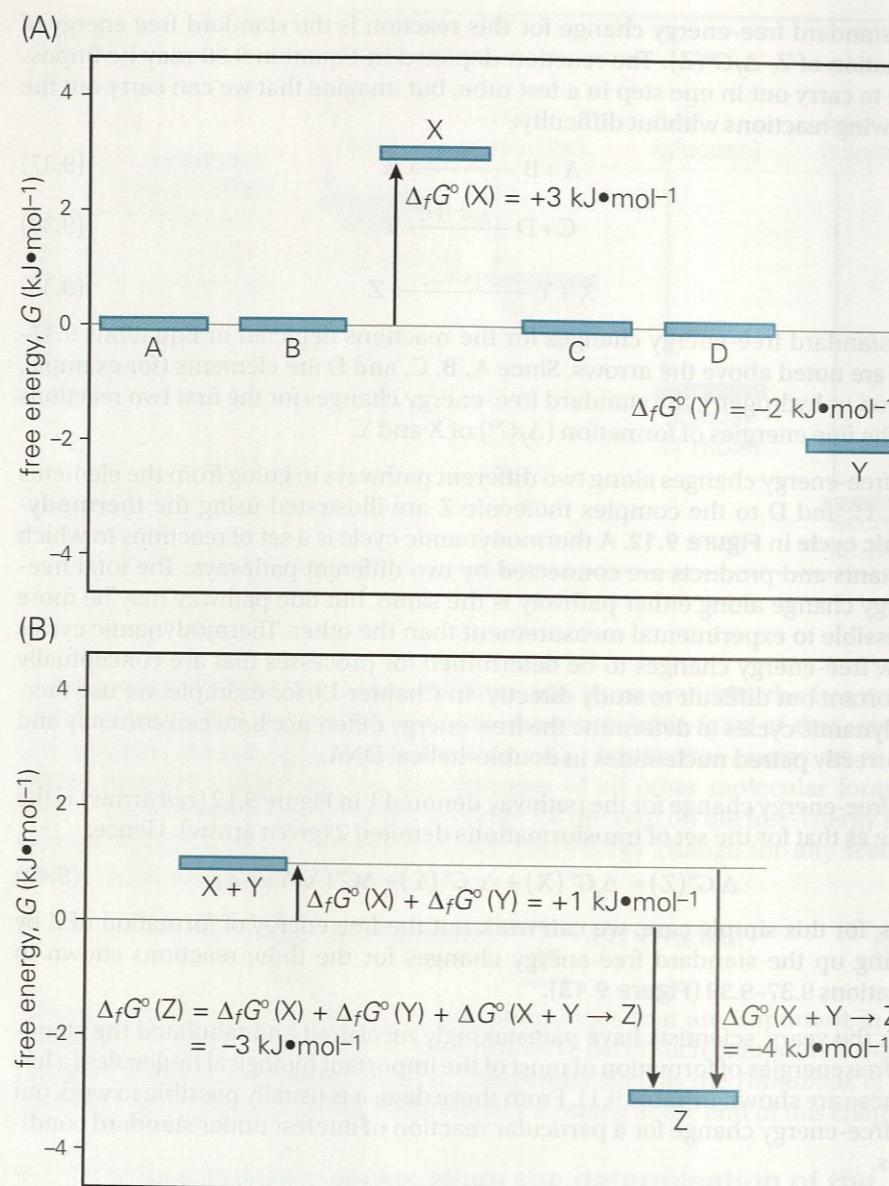
Two different pathways that connect the same set of reactants and products, with the same starting and ending conditions, define a thermodynamic cycle. The change in any state variable, such as the free energy, enthalpy, or entropy, must be the same following either pathway. Thermodynamic cycles are useful when one of the pathways is experimentally accessible, but the other one is not. Experimental measurements on one pathway provide information about the other pathway. See Figure 9.12 for an example of a thermodynamic cycle.

Thermodynamic cycle

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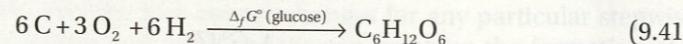
Figure 9.12 A thermodynamic cycle representing how free energies of formation are derived. The reaction depicted in Equations 9.36–9.39 are shown here. Compare this diagram with Figure 9.13, which shows the same free-energy changes in a different way.

Figure 9.13 The standard free energy of formation ($\Delta_f G^\circ$) of a complex molecule, Z. (A) Z is composed of the elementary molecules A, B, C, and D. A and B react to form X, and C and D react to form Y. (B) The standard free energy of formation of Z, $\Delta_f G^\circ(Z)$ is the sum of the free energies of formation of X and Y and the standard free-energy change of the reaction $X + Y \rightarrow Z$. The additivity of the free energies is illustrated in the form of a thermodynamic cycle in Figure 9.12.

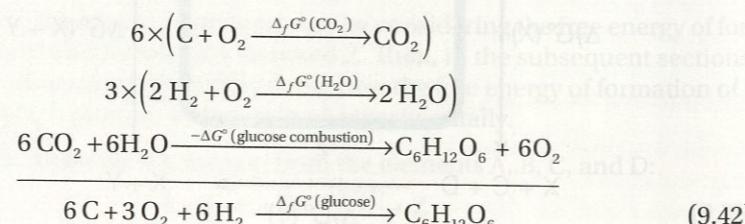


9.8 The free energy of formation of glucose is obtained by considering three combustion reactions

Recall from Section 3.1 that glucose has the chemical formula $C_6H_{12}O_6$. The free energy of formation of glucose is therefore given by the standard free-energy change of the following reaction:



In this reaction, graphite (the most stable form of carbon) is combined with gaseous oxygen and hydrogen to form glucose. This is not a reaction that can be carried out in the laboratory, and so we consider, instead, the following three reactions that yield glucose from the elements:



In the first reaction, elemental carbon (graphite) combines with oxygen to yield carbon dioxide, and the standard free-energy change for this reaction is the free energy of formation of carbon dioxide, $\Delta_f G^\circ(CO_2)$. This is a **combustion reaction**, involving the burning of a compound in oxygen. The second reaction is the combustion of hydrogen to produce water, with a standard free-energy change equal to the free energy of formation of water, $\Delta_f G^\circ(H_2O)$. The third reaction is the reverse of the combustion of glucose to produce carbon dioxide and water. The free-energy change of this reaction is the negative of the standard free-energy change for glucose combustion, ΔG° .

9.9 Enthalpies and entropies of formation can be combined to give the free energy of formation

Figure 9.14 shows the thermodynamic cycle formed by the chemical reactions depicted in Equation 9.42. Notice that all three reactions in pathway 2 are combustion reactions. Combustion reactions are difficult to initiate, but once initiated, they proceed essentially to completion. As we discuss in Chapter 10, one common way to determine the value of the standard free-energy change of a reaction is to determine the equilibrium constant by measuring the concentrations of the reactants and products at equilibrium. This is impractical for combustion reactions, because the concentrations of the reactants are negligible after the combustion takes place. Instead, the changes in enthalpy and entropy for the reactions are determined separately, and then combined to yield the change in free energy.

The **standard change in enthalpy** for a reaction is denoted ΔH° , and this is the change in enthalpy when one mole of reactants is converted to one mole of products under standard conditions. The **standard change in entropy** is defined similarly, and is denoted ΔS° . The **enthalpy of formation** of a compound, denoted $\Delta_f H^\circ$, is the difference in the enthalpy of one mole of the compound in the standard state and stoichiometric equivalents of the corresponding elements. The **entropy of formation** ($\Delta_f S^\circ$) is defined similarly.

From the definition of the free energy (Equation 9.20), the standard free-energy change for a reaction, ΔG° , can be written in terms of the standard changes in enthalpy and entropy as:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (9.43)$$

The enthalpy and the entropy are state functions, so changes in their values do *not* depend on the path followed between an initial state and a final state. Just as we did for the free energy, we can construct thermodynamic cycles for the changes in enthalpy and entropy. These cycles allow us to choose the most convenient experimental route to determine the values of the changes in enthalpy and entropy.

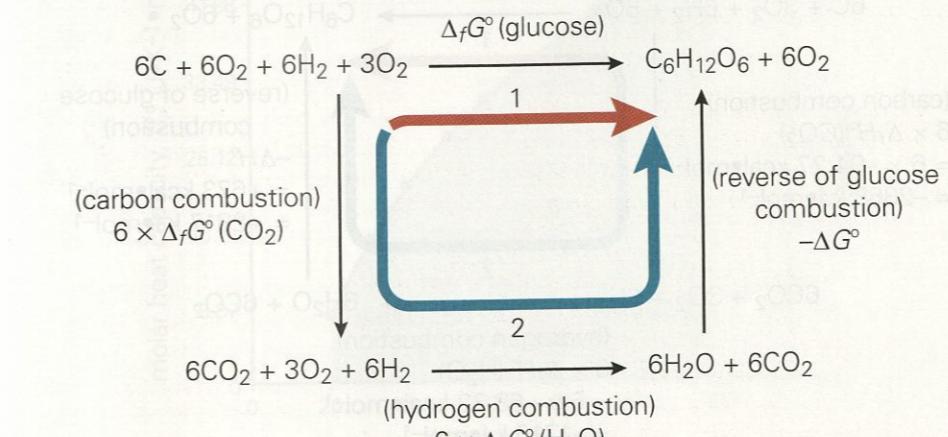


Figure 9.14 Thermodynamic cycle for the free energy of formation of glucose. Pathway 1 shows the formation of glucose from the elements. Pathway 2 involves three combustion reactions (one in reverse) that are combined to produce glucose from the elements.

9.10 Calorimetric measurements yield the standard enthalpy changes associated with combustion reactions

A thermodynamic cycle for enthalpy changes in the formation of glucose is shown in Figure 9.15. The figure also shows the experimentally determined values for the enthalpy changes for the three combustion steps. These enthalpy changes are combined as shown in Figure 9.15 to obtain the standard enthalpy of formation of glucose at 25°C, which turns out to be $-1266 \text{ kJ}\cdot\text{mol}^{-1}$.

The enthalpy changes shown in Figure 9.15 are obtained by using calorimeters to measure the heat released by the reaction. Recall that the change in enthalpy for a process occurring at constant pressure is equal to the heat transferred during the process (Section 6.4). An instrument known as a **bomb calorimeter** is used to determine the amount of heat released when a defined amount of a compound undergoes complete combustion. A bomb calorimeter is simply a chamber enclosed by a thick metal casing. The compound of interest is inserted into the chamber, which is then sealed and pressurized with oxygen. Combustion of the compound is initiated by an electric discharge, and the heat released is measured. Appropriate corrections for the changes in pressure that occur during the reaction are made, and the standard change in enthalpy for the reaction is obtained.

9.11 The entropy of formation of a compound is derived from heat capacity measurements

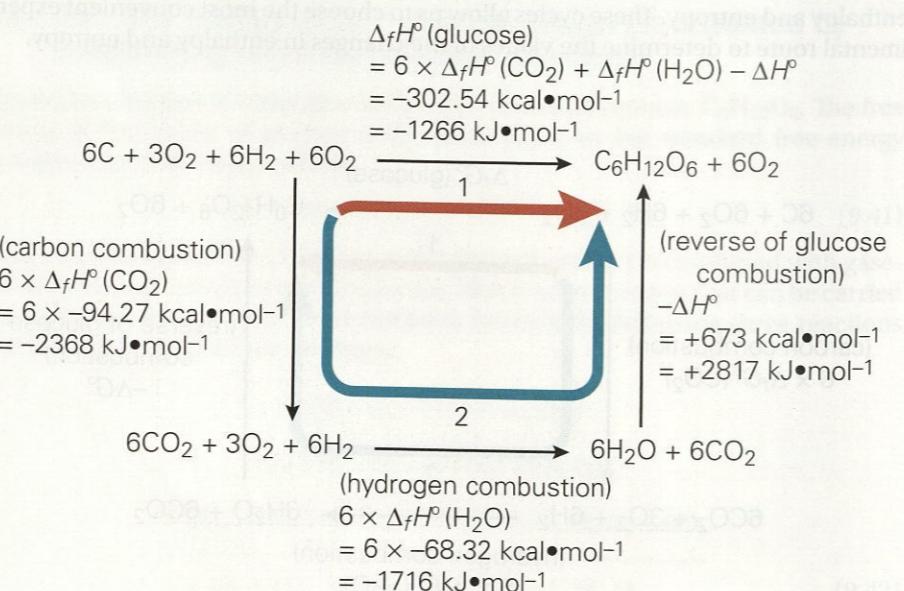
The standard entropy of formation of glucose, $\Delta_f S^\circ$, is given by:

$$\Delta_f S^\circ(\text{glucose}) = S^\circ(\text{glucose}) - (6 \times S^\circ(\text{carbon}) - 12 \times S^\circ(\text{hydrogen}) - 6 \times S^\circ(\text{carbon})) \quad (9.44)$$

where the S° values are the standard molar entropies of glucose and the elements. It turns out that these values have been determined experimentally, and so the entropy of formation of glucose can be calculated directly, without going around a thermodynamic cycle as we did for the enthalpy.

The thermodynamic definition of the entropy (Equation 7.60) tells us that the heat transferred during an infinitesimally small step in a reversible process, dq_{rev} , is related to the change in entropy, dS , in the following way:

$$dS = \frac{dq_{\text{rev}}}{T} \quad (9.45)$$



If the process is carried out at constant pressure, then the heat transferred is simply the change in enthalpy of the system, and is independent of the path connecting the initial and final states of the system:

$$dS = \frac{dH}{T} \quad (\text{for a process at constant pressure}) \quad (9.46)$$

We can integrate Equation 9.46 to obtain the change in entropy as the temperature is changed from an initial value, T_1 , to a final value, T_2 :

$$\Delta S^\circ = S^\circ(T_2) - S^\circ(T_1) = \int_{T_1}^{T_2} \frac{dH^\circ}{T} = \int_{T_1}^{T_2} \frac{C_p^\circ}{T} dT \quad (\text{at constant pressure}) \quad (9.47)$$

In Equation 9.47, the superscripts refer to the fact that we are considering one mole of the substance. We have used the fact that the change in enthalpy, dH° , is equal to $C_p^\circ dT$, where C_p° is the molar heat capacity of the system at constant pressure (see Equation 6.22). Thus, if we measure the heat capacity at constant pressure at a number of temperatures, we can use Equation 9.47 to calculate the change in entropy between the two temperatures.

It is assumed that the entropy of a pure substance is zero when the temperature is absolute zero on the Kelvin scale. This principle is sometimes referred to as the **third law of thermodynamics** and, as a consequence, the integral from 0 K to any temperature, T_2 , is equal to the entropy of the substance at the temperature T_2 :

$$\Delta S = S(T_2) - S(T=0 \text{ K}) = S(T_2) = \int_0^{T_2} \frac{C_p}{T} dT \quad (\text{at constant pressure}) \quad (9.48)$$

Figure 9.16 shows experimental measurements of the molar heat capacity of an aliphatic substance (C_p° ; that is, the heat capacity per mole) between 20 K and 120 K. The experimentally determined data points are fit by a polynomial function, which is used to extrapolate the values of the heat capacity down to 0 K. The integral of C_p°/T from 0 K to 298 K (25°C), using a combination of extrapolated values and actual data, yields the molar entropy of the substance at 298 K. Heat capacity measurements, such as the ones shown in Figure 9.16, have been used to determine that the standard entropy of formation of glucose is $-1.180 \text{ kJ}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$ at 298 K. If the substance undergoes a phase transition at temperature T_{pt} , then the associated entropy change calculated from the heat associated with the transition, q_{pt} , must also be added ($\Delta S_{\text{pt}} = q_{\text{pt}}/T_{\text{pt}}$).

Once the enthalpy and entropy of formation are both known, Equation 9.43 can be used to derive the free energy of formation of the substance. In the case of glucose at 298 K, $\Delta_f H^\circ = -1266 \text{ kJ}\cdot\text{mol}^{-1}$ (see Figure 9.15) and $\Delta_f S^\circ = -1.180 \text{ kJ}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$ (Figure 9.17), and so:

$$\Delta_f G^\circ = -1266 - 298 \times (-1.18) = -914.4 \text{ kJ}\cdot\text{mol}^{-1} \quad (9.49)$$

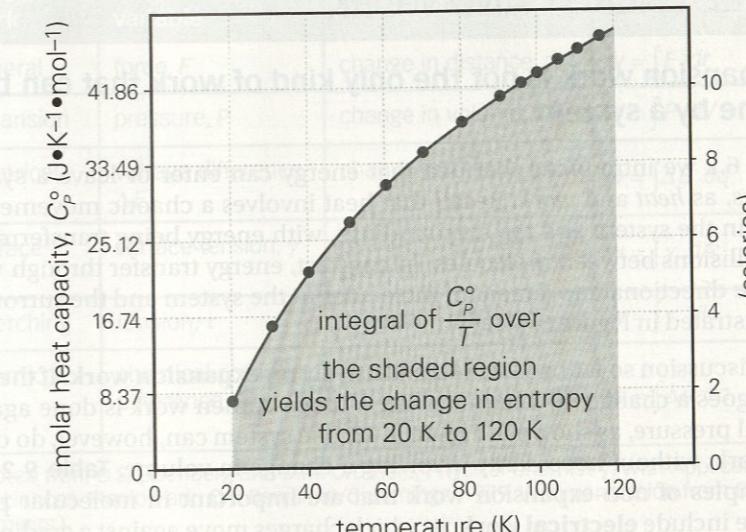


Figure 9.16 The heat capacity of an aliphatic compound. Shown here are experimental measurements (circles) of the molar heat capacity of a substance (C_p° ; that is, the heat capacity per mole) between 20 K and 120 K. The black line is a polynomial fit of the data, which is used to extrapolate the value of the heat capacity down to 0 K (the extrapolation is not shown here). The integral of $\frac{C_p}{T}$ over a temperature range (for example, the shaded region) gives the change in entropy over that temperature range. As in Figure 9.15, the calorie unit shown here is the so-called “15°C calorie,” which is equal to 4.186 J. (Adapted from G.S. Parks, K.K. Kelley, and H.M. Huffman, *J. Phys. Chem.* 33: 1802–1805, 1929.)

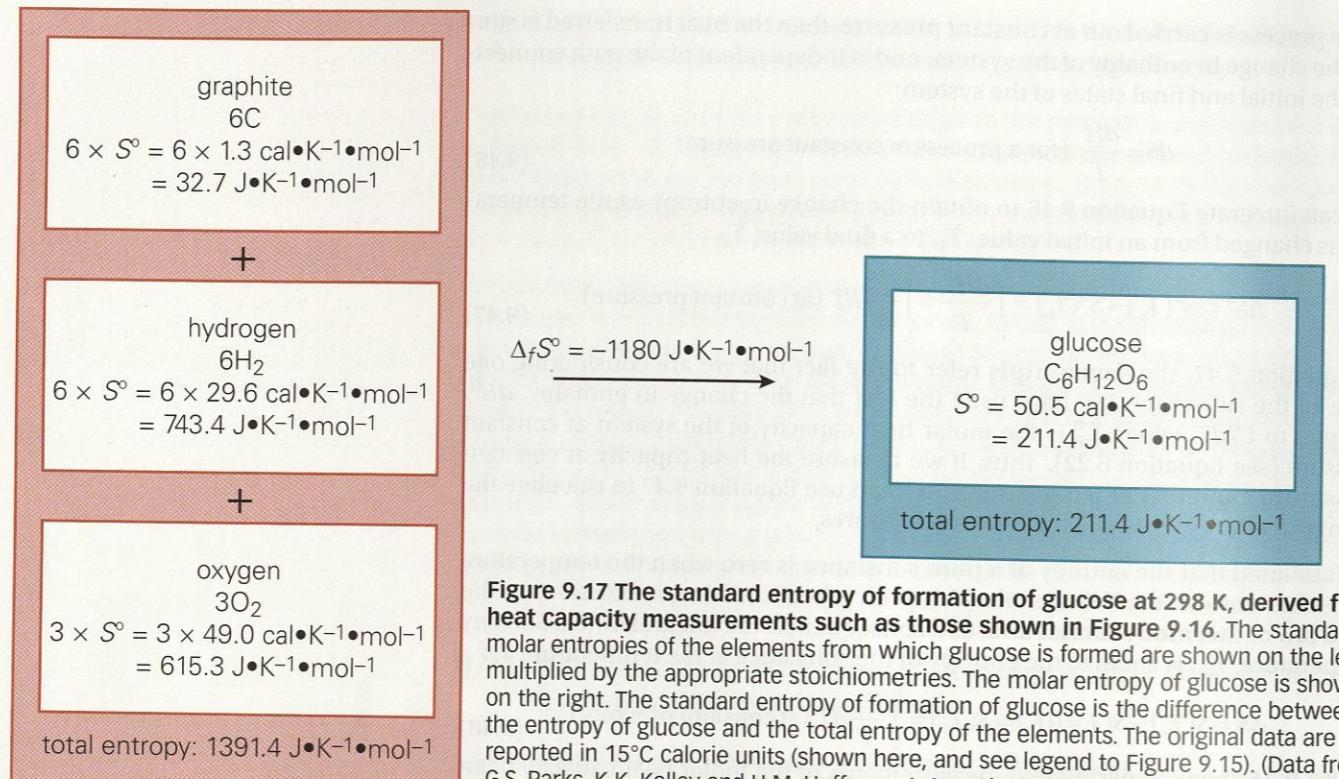


Figure 9.17 The standard entropy of formation of glucose at 298 K, derived from heat capacity measurements such as those shown in Figure 9.16. The standard molar entropies of the elements from which glucose is formed are shown on the left, multiplied by the appropriate stoichiometries. The molar entropy of glucose is shown on the right. The standard entropy of formation of glucose is the difference between the entropy of glucose and the total entropy of the elements. The original data are reported in 15°C calorie units (shown here, and see legend to Figure 9.15). (Data from G.S. Parks, K.K. Kelley and H.M. Huffman, *J. Am. Chem. Soc.* 51: 1969–1973, 1929.)

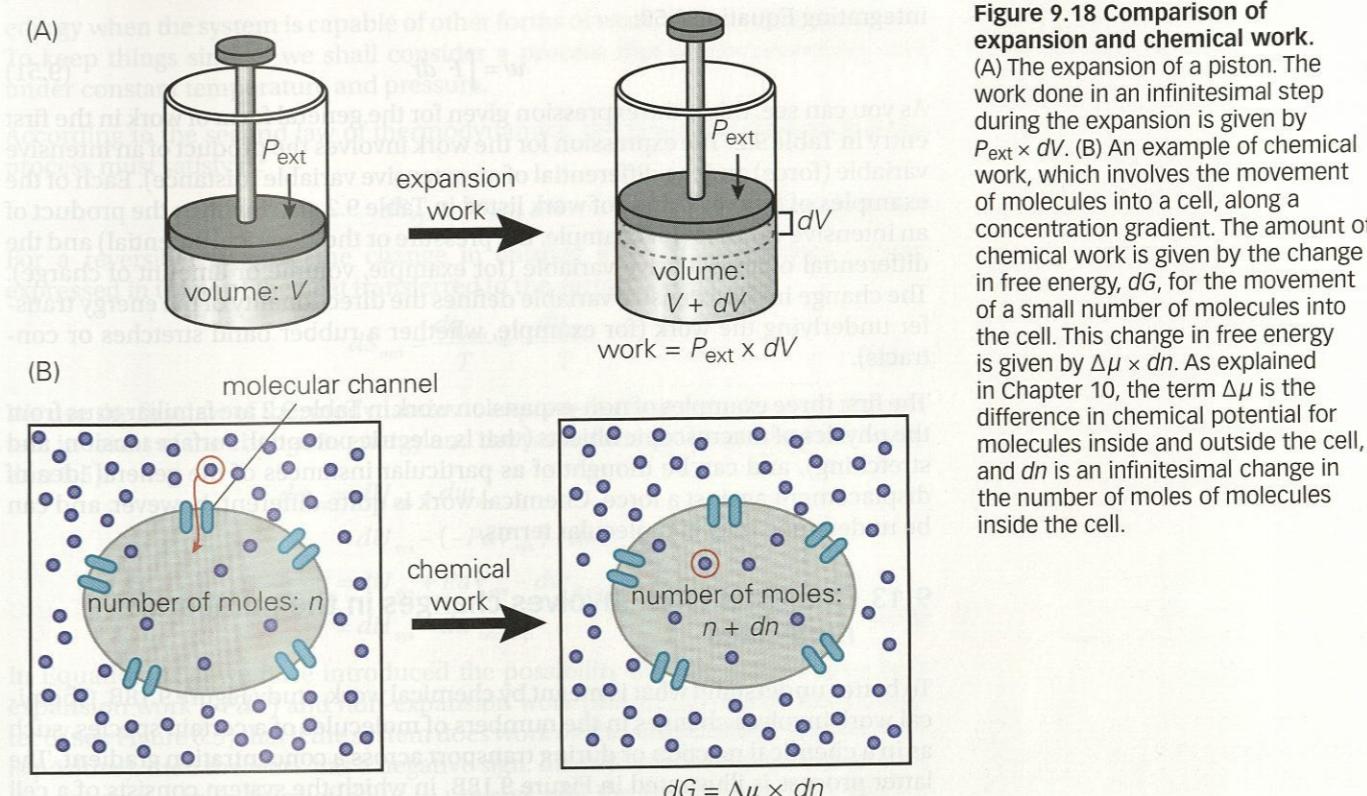
Note that this value for the standard free energy of formation of glucose ($-914.4 \text{ kJ}\cdot\text{mol}^{-1}$) is for pure, solid glucose. If one considers, instead, the free energy of formation of glucose in aqueous solution, one has to take into account the free-energy change that occurs upon dissolving glucose in water. The value of this free-energy change can be obtained by measuring the solubility of glucose in water, and turns out to be very small (about $-2 \text{ kJ}\cdot\text{mol}^{-1}$ for a 1 M solution of glucose). Thus, the standard free energy of formation of a standard state solution of glucose is $-917 \text{ kJ}\cdot\text{mol}^{-1}$, which is the value reported in Table 9.1. Most of the free energy of glucose is “stored” in the covalent bonds and, in comparison, the free energy of its interaction with water is very small.

C. FREE ENERGY AND WORK

9.12 Expansion work is not the only kind of work that can be done by a system

In Section 6.2 we introduced the idea that energy can enter or leave a system in two ways, as *heat* and *work*. Recall that heat involves a chaotic movement of molecules in the system and the surroundings, with energy being transferred by random collisions between molecules. In contrast, energy transfer through work involves the directional movement of molecules in the system and the surroundings, as illustrated in Figure 6.4.

All of our discussion so far has focused exclusively on **expansion work**. If the system undergoes a change in volume during a process, then work is done against the external pressure, as shown in Figure 9.18. The system can, however, do other kinds of work, without necessarily involving a change in volume. Table 9.2 lists some examples of non-expansion work that are important in molecular processes. These include **electrical work**, in which charges move against a gradient of



electrical potential (see Chapter 11), and **chemical work**, which involves changes in the free energy of the system that result from changes in the number of molecules.

The general definition of work involves the product of force and displacement. As explained in Section 6.9, the work, dw , done in an infinitesimal step of a process in which there is a displacement, dr , against a force, F , is given by:

$$dw = F dr \quad (9.50)$$

Note that the sign of the force will depend on whether the movement is against the force or aligned with it. The total work done during a process is obtained by

Table 9.2 Different kinds of work that can be done by a system.

Type of work	Intensive variable	Extensive differential	Expression for work
General	force, F	change in distance, dr	$w = \int F dr$
Expansion	pressure, P	change in volume, dV	$w = \int P dV$
Electrical	voltage difference, ΔE	change in charge, dq	$w = \int \Delta E dq$
Surface	surface tension, γ	change in surface area, dA	$w = \int \gamma dA$
Stretching	tension, τ	change in length, dl	$w = \int \tau dl$
Chemical	chemical potential difference, $\Delta\mu$	change in number of moles of the molecule, dn	$w = \int \Delta\mu dn$

(Adapted from D.S. Eisenberg and D.M. Crothers, *Physical Chemistry: With Applications to the Life Sciences*. Menlo Park, CA: Benjamin/Cummings, 1979. With permission from Benjamin/Cummings.)

Figure 9.18 Comparison of expansion and chemical work.
(A) The expansion of a piston. The work done in an infinitesimal step during the expansion is given by $P_{\text{ext}} \times dV$. (B) An example of chemical work, which involves the movement of molecules into a cell, along a concentration gradient. The amount of chemical work is given by the change in free energy, dG , for the movement of a small number of molecules into the cell. This change in free energy is given by $\Delta\mu \times dn$. As explained in Chapter 10, the term $\Delta\mu$ is the difference in chemical potential for molecules inside and outside the cell, and dn is an infinitesimal change in the number of moles of molecules inside the cell.

integrating Equation 9.50:

$$w = \int F \, dr \quad (9.51)$$

As you can see, this is the expression given for the general form of work in the first entry in Table 9.2. The expression for the work involves the product of an intensive variable (force) and the differential of an extensive variable (distance). Each of the examples of different kinds of work listed in Table 9.2 also involves the product of an intensive variable (for example, the pressure or the electrical potential) and the differential of an extensive variable (for example, volume or amount of charge). The change in the extensive variable defines the directionality of the energy transfer underlying the work (for example, whether a rubber band stretches or contracts).

The first three examples of non-expansion work in Table 9.2 are familiar to us from the physics of macroscopic objects (that is, electric potential, surface tension, and stretching), and can be thought of as particular instances of the general idea of displacement against a force. Chemical work is quite different, however, and can be understood only in molecular terms.

9.13 Chemical work involves changes in the numbers of molecules

To better understand what is meant by chemical work, study Figure 9.18B. Chemical work involves changes in the numbers of molecules of a certain species, such as in a chemical reaction or during transport across a concentration gradient. The latter process is illustrated in Figure 9.18B, in which the system consists of a cell with molecular channels in the membrane. In this example, chemical work refers to the movement of molecules into the cell through these channels, along a concentration gradient (there are more molecules outside the cell than inside).

Now consider what happens to the free energy when a small number of molecules move from outside the cell to the inside. The number of moles of molecules inside the cell changes from n initially to $n + dn$ after the movement. The variable corresponding to a force that enters into the expression for the chemical work associated with this movement is the difference in chemical potential, $\Delta\mu$, between molecules outside the cell and inside. We defer a detailed explanation of chemical potential to Chapter 10, and for the present it is sufficient to understand that the chemical potential of a type of molecule is simply the free energy of one mole of these molecules under the specified conditions. The change in free energy, dG , associated with the movement of dn moles of these molecules is therefore $\Delta\mu \times dn$. The net change in free energy as molecules move into the cell is given by:

$$\Delta G = \int \Delta\mu \, dn \quad (9.52)$$

As we shall see in the following sections, there is a close relationship between the work done during a process and the change in free energy associated with the process. Because of the similarity between Equation 9.52 and the general expression for work (Equation 9.51), the change in free energy associated with changes in the numbers of molecules is commonly referred to as **chemical work**. You should be aware, however, that chemical work is not the same as the other kinds of work described in Table 9.2, because it does not involve the movement of molecules against a physical force.

9.14 The decrease in the Gibbs free energy for a process is the maximum amount of non-expansion work that the system is capable of doing under constant pressure and temperature

In our earlier derivation of the condition that the free energy must decrease for a spontaneous process, we assumed that the system is only capable of expansion work (see Section 9.3). Now let us see what condition is imposed on the free

energy when the system is capable of other forms of work, such as chemical work. To keep things simple, we shall consider a process that occurs reversibly, and under constant temperature and pressure.

According to the second law of thermodynamics, the general condition that the process must satisfy is:

$$dS_{\text{sys}} + dS_{\text{surr}} \geq 0 \quad (\text{see Equation 9.4})$$

For a reversible process, the change in entropy of the surroundings can be expressed in terms of the heat transferred to the surroundings:

$$dS_{\text{surr}} = \frac{dq_{\text{surr}}}{T} = -\frac{dq_{\text{sys}}}{T} \quad (9.53)$$

We use the first law of thermodynamics to express the heat transferred to the system in terms of the change in energy and the work done by the system (see Equation 6.5):

$$\begin{aligned} dq_{\text{sys}} &= dU_{\text{sys}} - dw_{\text{sys}} \\ &= dU_{\text{sys}} - (-PdV_{\text{sys}}) - dw_{\text{non-exp}} \\ &= dU_{\text{sys}} + PdV_{\text{sys}} - dw_{\text{non-exp}} \\ &= dH_{\text{sys}} - dw_{\text{non-exp}} \end{aligned} \quad (9.54)$$

In Equation 9.54, we have introduced the possibility that the system does both expansion work ($-PdV$) and non-expansion work ($dw_{\text{non-exp}}$). Recall from Chapter 6 (see Figure 6.5) that if the system does work *on* the surroundings (that is, if ΔV is positive), then the work has a negative sign. Likewise, for non-expansion work, the negative sign in front of $dw_{\text{non-exp}}$ means that the second term in Equation 9.54 is positive if the system does work (some of the heat taken up by the system goes towards the work done). We have also equated $dU + PdV$ to an infinitesimal change in the enthalpy, dH (see Equation 9.17 and note that pressure is constant).

Combining Equations 9.53 and 9.54, we get:

$$dS_{\text{surr}} = -\left(\frac{1}{T}\right)(dH_{\text{sys}} - dw_{\text{non-exp}}) \quad (9.55)$$

Substituting this expression for dS_{surr} into the expression for the second law of thermodynamics (Equation 9.4) gives:

$$dS_{\text{sys}} + dS_{\text{surr}} = dS_{\text{sys}} - \left(\frac{1}{T}\right)(dH_{\text{sys}} - dw_{\text{non-exp}}) \geq 0 \quad (9.56)$$

Multiplying both sides of Equation 9.56 by the temperature, T , we get:

$$\begin{aligned} TdS - (dH - dw_{\text{non-exp}}) &\geq 0 \\ \Rightarrow TdS - dH + dw_{\text{non-exp}} &\geq 0 \\ \Rightarrow dH - TdS - dw_{\text{non-exp}} &\geq 0 \\ \Rightarrow dG - dw_{\text{non-exp}} &\leq 0 \end{aligned} \quad (9.57)$$

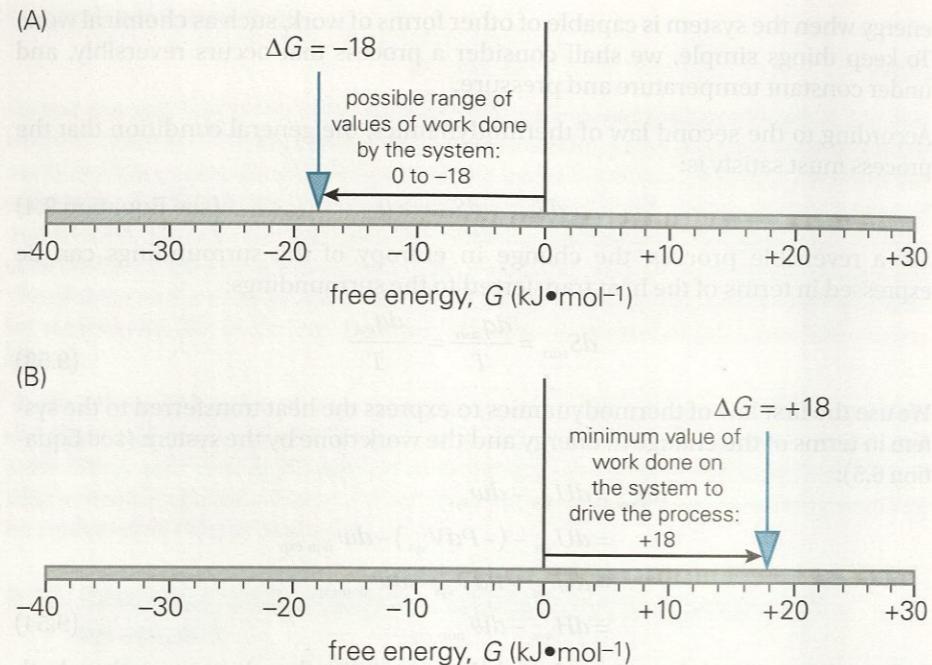
In the steps leading to Equation 9.57 all of the variables refer to the system. Adding $dw_{\text{non-exp}}$ to both sides of Equation 9.57, we obtain the following relationship between the change in free energy and the non-expansion work done:

$$dG \leq dw_{\text{non-exp}} \quad (9.58)$$

At first glance it looks as if Equation 9.58 is telling us that the work done by the system (dw) is greater than the change in the free energy (dG). But, as we discussed earlier, if the system does work *on* the surroundings (that is, if work is extracted from the system), then dw is a *negative* number (Figure 9.19A). This must mean that the absolute magnitude of dw is less than or equal to the magnitude of dG when work is extracted from the system. Integrating over the whole process, the total work done, w , and the net change in free energy, ΔG , must satisfy the following relationship for a spontaneous process:

$$|w_{\text{non-exp}}| \leq |\Delta G| \quad (9.59)$$

Figure 9.19 Comparing the values of the free-energy change, ΔG , and the non-expansion work done. (A) The work done is driven by a process with a negative change in free energy ($\Delta G = -18 \text{ kJ}\cdot\text{mol}^{-1}$). The possible values of the work done by the process range from 0 to $-18 \text{ kJ}\cdot\text{mol}^{-1}$. (B) A process occurs with an unfavorable change in free energy ($\Delta G = +18 \text{ kJ}\cdot\text{mol}^{-1}$). Although the process will not happen spontaneously, it can be made to happen if at least $18 \text{ kJ}\cdot\text{mol}^{-1}$ of work is done on the system by the surroundings.

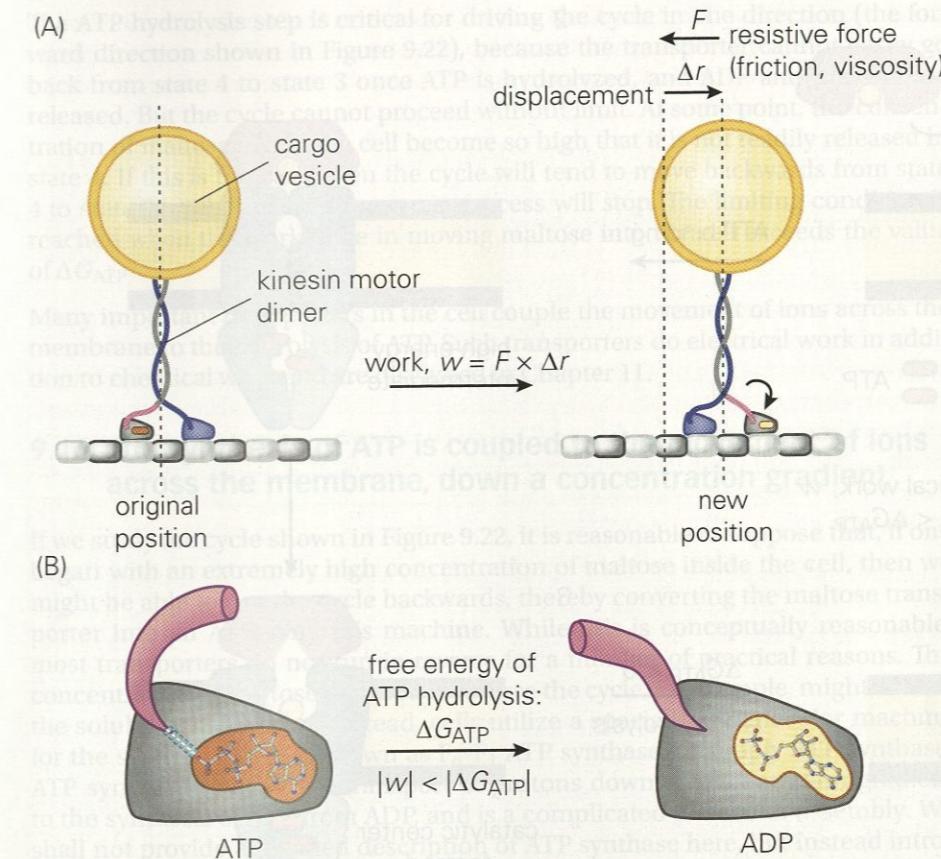


Thus, the maximum possible non-expansion work that can be extracted from the system (that is, when the system does work *on* the surroundings) is given by the magnitude of the change in free energy, ΔG , for the process driving the work. Work can be extracted from the system only if the free-energy change associated with the process is negative. If the free-energy change for a process is *greater* than zero, it will not happen spontaneously, and work cannot be extracted from it. The process can, however, be made to happen if work is done on the system by the surroundings, as illustrated schematically in Figure 9.19B. We provide specific examples of these two situations in the next two sections.

9.15 The coupling of ATP hydrolysis to work underlies many processes in biology

From the discussion in Section 9.14, you should now understand that the change in the free energy of a process is equal to the maximum amount of work that can be extracted from that process. Physical work, such as the compression of a piston, or the directed movement of an object, is visualized readily and the amount of work done can be calculated using the equations given in Table 9.2. One example of physical work at the cellular level is the action of molecular motors. Kinesin, which was introduced at the beginning of Chapter 6 and is discussed further in Section 17.26, is one such molecular motor, and it moves vesicles along microtubule tracks inside a cell (Figure 9.20). The work done by kinesin is given by the displacement (Δr) multiplied by the resistive force (F) due to friction and viscosity, as shown in Figure 9.20A. The movement of the vesicle is powered by the hydrolysis of ATP within the motor domain of the kinesin protein, with a change in free energy, ΔG_{ATP} , that depends on the conditions under which the motor is operating (see Figure 9.20B). The amount of work done is limited by the value of ΔG_{ATP} .

The generation of chemical work is particularly important for cellular function. In Section 4.39, we had discussed how proteins known as **active transporters** are able to move molecules across the cell membrane and against a concentration gradient. For example, nutrients are concentrated within cells by proteins, such as the maltose transporter, which hydrolyzes two molecules of ATP for every molecule of maltose moved across the membrane (see Section 4.43).



A schematic representation of ATP-coupled active transport is shown in Figure 9.21, in which a cell is indicated by a purple oval. A number of nutrient molecules are also shown, both inside and outside the cell. The active transport process moves nutrient molecules from outside the cell to the inside, generating a concentration gradient across the cell membrane. The net movement of molecules is in one direction, from inside to outside, which is sometimes referred to as **vectorial transport**. As we discuss in Section 10.4, the movement of molecules into the cell increases the chemical potential of these molecules inside the cell. Even

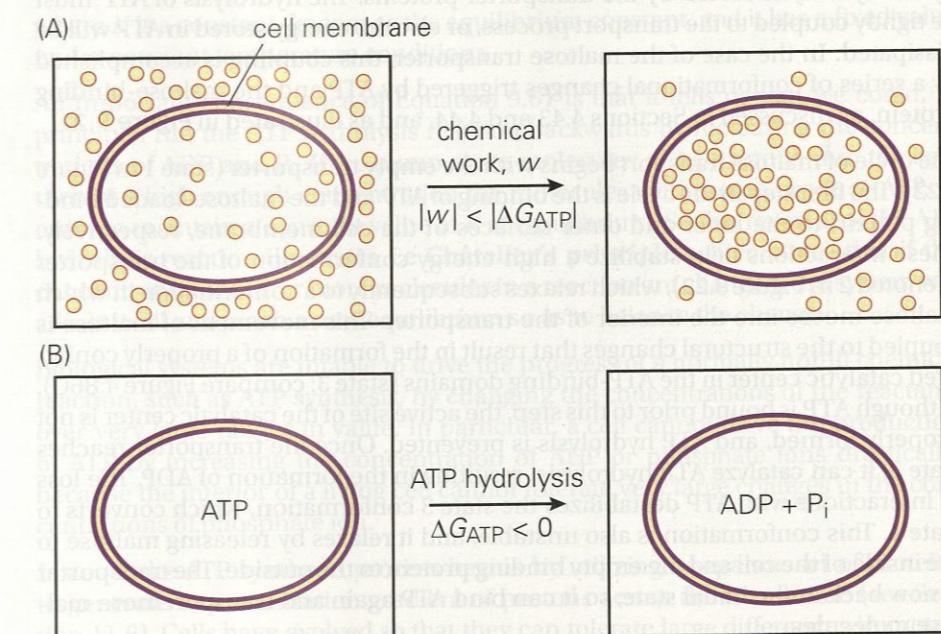


Figure 9.20 An example of physical work. (A) A kinesin motor protein moves a cargo vesicle along a microtubule track (refer to Figure 6.1 for more information). The work done is given by the displacement (Δr) multiplied by the resistive force due to friction and viscosity (F). (B) The work done is coupled to the hydrolysis of ATP by the motor domain. The value of the free-energy change for hydrolysis of ATP, ΔG_{ATP} , sets a limit on the amount of work that can be done.

Figure 9.21 The coupling of chemical work to ATP hydrolysis. (A) The process of concentrating molecules, such as nutrients, inside the cell is an example of chemical work. (B) The work done is coupled to the hydrolysis of ATP by transporter proteins, such as the one illustrated in Figure 9.22. The free-energy change upon ATP hydrolysis, ΔG_{ATP} , limits the extent to which molecules can be moved against a concentration gradient.