Chapter 3

Thermodynamic Principles: A Review

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You can't win.
First law of thermodynamics
You can't even break even.
Second law of thermodynamics
You can't stay out of the game.
Third law of thermodynamics

Thermodynamics (Greek: therme, heat + dynamis, power) is a marvelously elegant description of the relationships among the various forms of energy and how energy affects matter on the macroscopic as opposed to the molecular level; that is, it deals with amounts of matter large enough for their average properties, such as temperature and pressure, to be well defined. Indeed, the basic principles of thermodynamics were developed in the nineteenth century before the atomic theory of matter had been generally accepted.

With a knowledge of thermodynamics we can determine whether a physical process is possible. Thermodynamics is therefore essential for understanding why macromolecules fold to their native conformations, how metabolic pathways are designed, why molecules cross biological membranes, how muscles generate mechanical force, and so on. The list is endless. Yet the reader should be cautioned that thermodynamics does not indicate the rates at which possible processes actually occur. For instance, although thermodynamics tells us that glucose and oxygen react with the release of copious amounts of energy, it does not indicate that this mixture is indefinitely stable at room temperature in the absence of the appropriate enzymes. The prediction of reaction rates requires, as we shall see in Section 14-1C, a mechanistic description of molecular processes. Yet thermodynamics is also an indispensable guide in formulating such mechanistic models because such models must conform to thermodynamic principles.

Thermodynamics, as it applies to biochemistry, is most frequently concerned with describing the conditions under which processes occur spontaneously (by themselves). We shall consequently review the elements of thermodynamics that enable us to predict chemical and biochemical spontaneity: the first and second laws of thermodynamics, the concept of free energy, and the nature of processes at equilibrium. Familiarity with these principles is indispensable for understanding many of the succeeding discussions in this text. We shall, however, postpone consideration of the thermodynamic aspects of metabolism until Sections 16-4 through 16-6.
1 FIRST LAW OF THERMODYNAMICS: ENERGY IS CONSERVED

In thermodynamics, a system is defined as that part of the universe that is of interest, such as a reaction vessel or an organism; the rest of the universe is known as the surroundings. A system is said to be open, closed, or isolated according to whether or not it can exchange matter and energy with its surroundings, only energy, or neither matter nor energy. Living organisms, which take up nutrients, release waste products, and generate work and heat, are examples of open systems; if an organism were sealed inside an uninsulated box, it would, together with the box, constitute a closed system, whereas if the box were perfectly insulated, the system would be isolated.

A. Energy

The first law of thermodynamics is a mathematical statement of the law of conservation of energy: Energy can be neither created nor destroyed.

\[ \Delta U = U_{\text{final}} - U_{\text{initial}} = q - w \quad [3.1] \]

Here \( U \) is energy, \( q \) represents the heat absorbed by the system from the surroundings, and \( w \) is the work done by the system on the surroundings. Heat is a reflection of random molecular motion, whereas work, which is defined as force times the distance moved under its influence, is associated with organized motion. Force may assume many different forms, including the gravitational force exerted by one mass on another, the expansion force exerted by a gas, the tensional force exerted by a spring or muscle fiber, the electrical force of one charge on another, or the dissipative forces of friction and viscosity. Processes in which the system releases heat, which by convention are assigned a negative \( q \), are known as exothermic processes (Greek: exo, out of); those in which the system gains heat (positive \( q \)) are known as endothermic processes (Greek: endon, within). Under this convention, work done by the system against an external force is defined as a positive quantity.

The SI unit of energy, the joule (J), is steadily replacing the calorie (cal) in modern scientific usage. The large calorie (Cal, with a capital C) is a unit favored by nutritionists. The relationships among these quantities and other units, as well as the values of constants that will be useful throughout this chapter, are collected in Table 3-1.

<table>
<thead>
<tr>
<th>TABLE 3-1 Thermodynamic Units and Constants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joule (J)</strong></td>
</tr>
<tr>
<td>1 J = 1 kg \cdot m^2 \cdot s^{-2}</td>
</tr>
<tr>
<td>1 J = 1 C \cdot V (coulomb volt)</td>
</tr>
<tr>
<td>1 J = 1 N \cdot m (newton meter)</td>
</tr>
<tr>
<td><strong>Calorie (cal)</strong></td>
</tr>
<tr>
<td>1 cal heats 1 g of H_2O from 14.5 to 15.5°C</td>
</tr>
<tr>
<td>1 cal = 4.184 J</td>
</tr>
<tr>
<td><strong>Large calorie (Cal)</strong></td>
</tr>
<tr>
<td>1 Cal = 1 kcal</td>
</tr>
<tr>
<td>1 Cal = 4184 J</td>
</tr>
<tr>
<td><strong>Avogadro's number (N)</strong></td>
</tr>
<tr>
<td>( N = 6.0221 \times 10^{23} \text{molecules} \cdot \text{mol}^{-1} )</td>
</tr>
<tr>
<td><strong>Coulomb (C)</strong></td>
</tr>
<tr>
<td>1 C = 6.241 \times 10^{18} \text{electron charges}</td>
</tr>
<tr>
<td><strong>Faraday (F)</strong></td>
</tr>
<tr>
<td>1 ( F = N ) electron charges</td>
</tr>
<tr>
<td>1 ( F = 96,485 \text{C} \cdot \text{mol}^{-1} = 96,485 \text{J} \cdot \text{V}^{-1} \cdot \text{mol}^{-1} )</td>
</tr>
<tr>
<td><strong>Kelvin temperature scale (K)</strong></td>
</tr>
<tr>
<td>0 K = absolute zero</td>
</tr>
<tr>
<td>273.15 K = 0°C</td>
</tr>
<tr>
<td><strong>Boltzmann constant (k_B)</strong></td>
</tr>
<tr>
<td>( k_B = 1.3807 \times 10^{-23} \text{J} \cdot \text{K}^{-1} )</td>
</tr>
<tr>
<td><strong>Gas constant (R)</strong></td>
</tr>
<tr>
<td>( R = \frac{N k_B}{R} )</td>
</tr>
<tr>
<td>( R = 1.9872 \text{cal} \cdot \text{K}^{-1} \cdot \text{mol}^{-1} )</td>
</tr>
<tr>
<td>( R = 8.3145 \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1} )</td>
</tr>
<tr>
<td>( R = 0.08206 \text{L} \cdot \text{atm} \cdot \text{K}^{-1} \cdot \text{mol}^{-1} )</td>
</tr>
</tbody>
</table>

for any process in which the system returns to its initial state (a cyclic process).

Neither heat nor work is separately a state function because each is dependent on the path followed by a system in changing from one state to another. For example, in the process of changing from an initial to a final state, a gas may do work by expanding against an external force, or do no work by following a path in which it encounters no external resistance. If Eq. [3.1] is to be obeyed, heat must also be path dependent. It is therefore meaningless to refer to the heat or work content of a system (in the same way that it is meaningless to refer to the number of one dollar bills and ten dollar bills in a bank account containing $85.00). To indicate this property, the heat or work produced during a change of state is never referred to as \( \Delta q \) or \( \Delta w \) but rather as just \( q \) or \( w \).

B. Enthalpy

Any combination of only state functions must also be a state function. One such combination, which is known as enthalpy (Greek: enthalpein, to warm in), is defined

\[ H = U + PV \quad [3.2] \]

where \( V \) is the volume of the system and \( P \) is its pressure. Enthalpy is a particularly convenient quantity with which to describe biological systems because under constant pressure, a condition typical of most biochemical processes, the enthalpy change between the initial and final states of a process, \( \Delta H \), is the easily measured heat that it generates or absorbs. To show this, let us divide work into two categories: pressure-volume (P-V) work, which is work per-
formed by expansion against an external pressure ($P \Delta V$), and all other work ($w'$):

$$w = P \Delta V + w'$$  \[3.3\]

Then, by combining Eqs. [3.1], [3.2], and [3.3], we see that

$$\Delta H = \Delta U + P \Delta V = q_r - w + P \Delta V = q_r - w'$$  \[3.4\]

where $q_r$ is the heat transferred at constant pressure. Thus, if $w' = 0$, as is often true of chemical reactions, $\Delta H = q_r$. Moreover, the volume changes in most biochemical processes are negligible, so that the differences between their $\Delta U$ and $\Delta H$ values are usually insignificant.

We are now in a position to understand the utility of state functions. For instance, suppose we wished to determine the enthalpy change resulting from the complete oxidation of 1 g of glucose to CO$_2$ and H$_2$O by muscle tissue. To make such a measurement directly would present enormous experimental difficulties. For one thing, the enthalpy changes resulting from the numerous metabolic reactions not involving glucose oxidation that normally occur in living muscle tissue would greatly interfere with our enthalpy measurement. Since enthalpy is a state function, however, we can measure glucose's enthalpy of combustion in any apparatus of our choosing, say, a constant pressure calorimeter rather than a muscle, and still obtain the same value. This, of course, is true whether or not we know the mechanism through which muscle converts glucose to CO$_2$ and H$_2$O, as long as we can establish that these substances actually are the final metabolic products. In general, the change of enthalpy in any hypothetical reaction pathway can be determined from the enthalpy change in any other reaction pathway between the same reactants and products.

We stated earlier in the chapter that thermodynamics serves to indicate whether a particular process occurs spontaneously. Yet the first law of thermodynamics cannot, by itself, provide the basis for such an indication, as the following example demonstrates. If two objects at different temperatures are brought into contact, we know that heat spontaneously flows from the hotter object to the colder one, never vice versa. Yet either process is consistent with the first law of thermodynamics since the aggregate energy of the two objects is independent of their temperature distribution. Consequently, we must seek a criterion of spontaneity other than only conformity to the first law of thermodynamics.

2

SECOND LAW OF THERMODYNAMICS:
THE UNIVERSE TENDS TOWARD MAXIMUM DISORDER

When a swimmer falls into the water (a spontaneous process), the energy of the coherent motion of his body is converted to that of the chaotic thermal motion of the surrounding water molecules. The reverse process, the swimmer being ejected from still water by the sudden coherent motion of the surrounding water molecules, has never been witnessed even though such a phenomenon violates neither the first law of thermodynamics nor Newton's laws of motion. This is because spontaneous processes are characterized by the conversion of order (in this case the coherent motion of the swimmer's body) to chaos (the random thermal motion of the water molecules). The second law of thermodynamics, which expresses this phenomenon, therefore provides a criterion for determining whether a process is spontaneous. Note that thermodynamics says nothing about the rate of a process; that is the purview of chemical kinetics (Chapter 14). Thus a spontaneous process might proceed at only an infinitesimal rate.

A. Spontaneity and Disorder

The second law of thermodynamics states, in accordance with all experience, that spontaneous processes occur in directions that increase the overall disorder of the universe, that is, of the system and its surroundings. Disorder, in this context, is defined as the number of equivalent ways, $W$, of arranging the components of the universe. To illustrate this point, let us consider an isolated system consisting of two bulbs of equal volume containing a total of $N$ identical molecules of ideal gas (Fig. 3-1). When the stopcock connecting the bulbs is open, there is an equal probability that a given molecule will occupy either bulb, so there are a total of $2^N$ equally probable ways that the $N$ molecules may be distributed among the two bulbs. Since the gas molecules are indistinguishable from one another, there are only $(N + 1)$ different states of the system: those with 0, 1, 2, ... , $(N-1)$, or $N$ molecules in the left bulb. Probability theory indicates that the number of (indistinguishable) ways, $W_L$, of placing $L$ of the $N$ molecules in the left bulb is

$$W_L = \frac{N!}{L!(N - L)!}$$

The probability of such a state occurring is its fraction of the total number of possible states: $W_L/2^N$.

![FIGURE 3-1 Two bulbs of equal volumes connected by a stopcock. In (a), a gas occupies the left bulb, the right bulb is evacuated, and the stopcock is closed. When the stopcock is opened (b), the gas molecules diffuse back and forth between the bulbs and eventually become distributed, so that half of them occupy each bulb.](image-url)
For any value of \( N \), the state that is most probable, that is, the one with the highest value of \( W_L \), is the one with half of the molecules in one bulb (\( L = N/2 \) for \( N \) even). As \( N \) becomes large, the probability that \( L \) is nearly equal to \( N/2 \) approaches unity. For instance, when \( N = 10 \) the probability that \( L \) is within 20\% of \( N/2 \) (that is, 4, 5, or 6) is 0.66, whereas for \( N = 50 \) this probability (that \( L \) is in the range 20–30) is 0.88. For a chemically significant number of molecules, say \( N = 10^{23} \), the probability that the number of molecules in the left bulb differs from those in the right by as insignificant a ratio as 1 molecule in every 10 billion is \( 10^{-438} \), which, for all intents and purposes, is zero. Therefore, the reason the number of molecules in each bulb of the system in Fig. 3-1b is always observed to be equal is not because of any law of motion; the energy of the system is the same for any arrangement of the molecules. It is because the aggregate probability of all other states is so utterly insignificant (Fig. 3-2). By the same token, the reason that our swimmer is never thrown out of the water or even noticeably disturbed by the chance coherent motion of the surrounding water molecules is that the probability of such an event is nil.

**B. Entropy**

In chemical systems, \( W \), the number of equivalent ways of arranging a system in a particular state, is usually inconveniently immense. For example, when the above twin-bulb system contains \( N \) gas molecules, \( W_{NN} \approx 10^{N^2/2} \) so that for \( N = 10^{23} \), \( W_{10^{23}} \approx 10^{23 \times 10^{23}} \). In order to be able to deal with \( W \) more easily, we define, as did Ludwig Boltzmann in 1877, a quantity known as entropy (Greek: \( en \), in + trophe, turning):

\[
S = k_B \ln W \quad [3.5]
\]

that increases with \( W \) but in a more manageable way. Here \( k_B \) is the Boltzmann constant (Table 3-1). For our twin-bulb system, \( S = k_B N \ln 2 \), so the entropy of the system in its most probable state is proportional to the number of gas molecules it contains. Note that entropy is a state function because it depends only on the parameters that describe a state.

The laws of random chance cause any system of reasonable size to spontaneously adopt its most probable arrangement, the one in which entropy is a maximum, simply because this state is so overwhelmingly probable. For example, assume that all \( N \) molecules of our twin-bulb system are initially placed in the left bulb (Fig. 3-1a; \( W_N = 1 \) and \( S = 0 \) since there is only one way of doing this). After the stopcock is opened, the molecules will randomly diffuse in and out of the right bulb until eventually they

---

**FIGURE 3-2** The improbability of even a small amount of order. Consider a simple "universe" consisting of a square array of 9 positions that collectively contain 4 identical "molecules" (red dots). If the 4 molecules are arranged in a square, we shall call the arrangement a "crystal"; otherwise we shall call it a "gas." The total number of distinguishable arrangements of our 4 molecules in 9 positions is given by

\[
W = \frac{9 \times 8 \times 7 \times 6}{4 \times 3 \times 2 \times 1} = 126
\]

Here, the numerator indicates that the first molecule may occupy any of the universe's 9 positions, the second molecule may occupy any of the 8 remaining unoccupied positions, and so on, whereas the denominator corrects for the number of indistinguishable arrangements of the 4 identical molecules. Of the 126 arrangements this universe can have, only 4 are crystals (black squares). Thus, even in this simple universe, there is a more than 30-fold greater probability that it will contain a disordered gas, when arranged at random, than an ordered crystal. [Illustration, Irving Geis/Geis Archives Trust. Copyright Howard Hughes Medical Institute. Reproduced with permission.]
achieve their most probable (maximum entropy) state, that with half of the molecules in each bulb. The gas molecules will subsequently continue to diffuse back and forth between the bulbs, but there will be no further macroscopic (net) change in the system. The system is therefore said to have reached equilibrium.

According to Eq. [3.5], the foregoing spontaneous expansion process causes the system’s entropy to increase. In general, for any constant energy process (ΔU = 0), a spontaneous process is characterized by ΔS > 0. Since the energy of the universe is constant (energy can assume different forms but can be neither created nor destroyed), any spontaneous process must cause the entropy of the universe to increase:

\[ \Delta S_{\text{system}} + \Delta S_{\text{surroundings}} = \Delta S_{\text{universe}} > 0 \]  \[3.6\]

Equation [3.6] is the usual expression for the second law of thermodynamics. It is a statement of the general tendency of all spontaneous processes to disorder the universe; that is, the entropy of the universe tends toward a maximum.

The conclusions based on our twin-bulb apparatus may be applied to explain, for instance, why blood transports O2 and CO2 between the lungs and the tissues. Solute in solution behave analogously to gases in that they tend to maintain a uniform concentration throughout their occupied volume because this is their most probable arrangement. In the lungs, where the concentration of O2 is higher than that in the venous blood passing through them, more O2 enters the blood than leaves it. On the other hand, in the tissues, where the O2 concentration is lower than that in the arterial blood, there is net diffusion of O2 from the blood to the tissues. The reverse situation holds for CO2 transport since the CO2 concentration is low in the lungs but high in the tissues. Keep in mind, however, that thermodynamics says nothing about the rates at which O2 and CO2 are transported to and from the tissues. The rates of these processes depend on the physicochemical properties of the blood, the lungs, and the cardiovascular system.

Equation [3.6] does not imply that a particular system cannot increase its degree of order. As is explained in Section 3-3, however, a system can only be ordered at the expense of disordering its surroundings to an even greater extent by the application of energy to the system. For example, living organisms, which are organized at the molecular level upward and are therefore particularly well ordered, achieve this order at the expense of disordering the nutrients they consume. Thus, eating is as much a way of acquiring order as it is of gaining energy.

A state of a system may constitute a distribution of more complicated quantities than those of gas molecules in a bulb or simple solute molecules in a solvent. For example, our system consists of a protein molecule in aqueous solution, its various states differ, as we shall see, in the conformations of the protein’s amino acid residues and in the distributions and orientations of its associated water molecules. The second law of thermodynamics applies here because a protein molecule in aqueous solution assumes its native conformation largely in response to the tendency of its surrounding water structure to be maximally disordered (Section 8-4C).

C. Measurement of Entropy

In chemical and biological systems, it is impractical, if not impossible, to determine the entropy of a system by counting the number of ways, W, it can assume its most probable state. An equivalent and more practical definition of entropy was proposed in 1864 by Rudolf Clausius: For spontaneous processes

\[ \Delta S \approx \int_{\text{initial}}^{\text{final}} \frac{dq}{T} \]  \[3.7\]

where T is the absolute temperature at which the change in heat occurs. The proof of the equivalence of our two definitions of entropy, which requires an elementary knowledge of statistical mechanics, can be found in many physical chemistry textbooks. It is evident, however, that any system becomes progressively disordered (its entropy increases) as its temperature rises (e.g., Fig. 3-3). The equality in Eq. [3.7] holds only for processes in which the

![Figure 3-3](image-url)

**FIGURE 3-3** Relationship of entropy and temperature. The structure of water, or any other substance, becomes increasingly disordered, that is, its entropy increases, as its temperature rises.
system remains in equilibrium throughout the change; these are known as reversible processes.

For the constant temperature conditions typical of biological processes, Eq. [3.7] reduces to

\[ \Delta S = \frac{q}{T} \quad [3.8] \]

Thus the entropy change of a reversible process at constant temperature can be determined straightforwardly from measurements of the heat transferred and the temperature at which this occurs. However, since a process at equilibrium can only change at an infinitesimal rate (equilibrium processes are, by definition, unchanging), real processes can approach, but can never quite attain, reversibility. Consequently, the universe's entropy change in any real process is always greater than its ideal (reversible) value. This means that when a system departs from and then returns to its initial state via a real process, the entropy of the universe must increase even though the entropy of the system (a state function) does not change.

### 3 FREE ENERGY: THE INDICATOR OF SPONTANEITY

The disordering of the universe by spontaneous processes is an impractical criterion for spontaneity because it is rarely possible to monitor the entropy of the entire universe. Yet the spontaneity of a process cannot be predicted from a knowledge of the system's entropy change alone. This is because exothermic processes \( (\Delta H_{\text{system}} < 0) \) may be spontaneous even though they are characterized by \( \Delta S_{\text{system}} < 0 \). For example, 2 mol of \( H_2 \) and 1 mol of \( O_2 \), when sparked, react in a decidedly exothermic reaction to form 2 mol of \( H_2O \). Yet two water molecules, each of whose three atoms are constrained to stay together, are more ordered than are the three diatomic molecules from which they formed. Similarly, under appropriate conditions, many denatured (unfolded) proteins will spontaneously fold to assume their highly ordered native (naturally folded) conformations (Section 9-1A). What we really want, therefore, is a state function that predicts whether or not a given process is spontaneous. In this section, we consider such a function.

#### A. Gibbs Free Energy

The Gibbs free energy,

\[ G = H - TS \quad [3.9] \]

which was formulated by J. Willard Gibbs in 1878, is the required indicator of spontaneity for constant temperature and pressure processes. For systems that can only do pressure–volume work \( (w' = 0) \), combining Eqs. [3.4] and [3.9] while holding \( T \) and \( P \) constant yields

\[ \Delta G = \Delta H - T \Delta S = q_P - T \Delta S \quad [3.10] \]

But Eq. [3.8] indicates that \( T \Delta S \approx q \) for spontaneous processes at constant \( T \). Consequently, \( \Delta G \approx 0 \) is the criterion of spontaneity we seek for the constant \( T \) and \( P \) conditions that are typical of biochemical processes.

Spontaneous processes, that is, those with negative \( \Delta G \) values, are said to be exergonic (Greek: ergon, work); they can be utilized to do work. Processes that are not spontaneous, those with positive \( \Delta G \) values, are termed endergonic; they must be driven by the input of free energy (through mechanisms discussed in Section 3-4C). Processes at equilibrium, those in which the forward and backward reactions are exactly balanced, are characterized by \( \Delta G = 0 \). Note that the value of \( \Delta G \) varies directly with temperature. This is why, for instance, the native structure of a protein, whose formation from its denatured form has both \( \Delta H < 0 \) and \( \Delta S < 0 \), predominates below the temperature at which \( \Delta H = T \Delta S \) (the denaturation temperature), whereas the denatured protein predominates above this temperature. The variation of the spontaneity of a process with the signs of \( \Delta H \) and \( \Delta S \) is summarized in Table 3-2.

#### TABLE 3-2 Variation of Reaction Spontaneity (Sign of \( \Delta G \)) with the Signs of \( \Delta H \) and \( \Delta S \)

<table>
<thead>
<tr>
<th>( \Delta H )</th>
<th>( \Delta S )</th>
<th>( \Delta G = \Delta H - T \Delta S )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>The reaction is both enthalpically favored (exothermic) and entropically favored. It is spontaneous (exergonic) at all temperatures.</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>The reaction is enthalpically favored but entropically opposed. It is spontaneous only at temperatures below ( T &lt; \Delta H/\Delta S ).</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>The reaction is enthalpically opposed (endothermic) but entropically favored. It is spontaneous only at temperatures above ( T &gt; \Delta H/\Delta S ).</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>The reaction is both enthalpically and entropically opposed. It is unspontaneous (endergonic) at all temperatures.</td>
</tr>
</tbody>
</table>

#### B. Free Energy and Work

When a system at constant temperature and pressure does non-\( P-V \) work, Eq. [3.10] must be expanded to

\[ \Delta G = q_P - T \Delta S - w' \quad [3.11] \]

or, because \( T \Delta S \approx q_P \) (Eq. [3.8]),

\[ \Delta G \approx -w' \]

so that

\[ \Delta G \geq w' \quad [3.12] \]

Since \( P-V \) work is unimportant in biological systems, \( \Delta G \) for a biological process represents its maximum recoverable work. The \( \Delta G \) of a process is therefore indicative of the maximum charge separation it can establish, the maximum concentration gradient it can generate (Section 3-4A), the maximum muscular activity it can produce, and so on. In fact, for real processes, which can only approach re-
versatility, the inequality in Eq. [3.12] holds, so that the work put into any system can never be fully recovered. This is indicative of the inherent dissipative character of nature. Indeed, as we have seen, it is precisely this dissipative character that provides the overall driving force for any change.

It is important to reiterate that a large negative value of $\Delta G$ does not ensure a chemical reaction will proceed at a measurable rate. This depends on the detailed mechanism of the reaction, which is independent of $\Delta G$. For instance, most biological molecules, including proteins, nucleic acids, carbohydrates, and lipids, are thermodynamically unstable to hydrolysis but, nevertheless, spontaneously hydrolyze at biologically insignificant rates. Only with the introduction of the proper enzymes will the hydrolysis of these molecules proceed at a reasonable pace. Yet a catalyst, which by definition is unchanged by a reaction, cannot affect the $\Delta G$ of a reaction. Consequently, an enzyme can only accelerate the attainment of thermodynamic equilibrium; it cannot, for example, promote a reaction that has a positive $\Delta G$.

4 CHEMICAL EQUILIBRIA

The entropy (disorder) of a substance increases with its volume. For example, as we have seen for our twin-bulb apparatus (Fig. 3-1), a collection of gas molecules, in occupying all of the volume available to it, maximizes its entropy. Similarly, dissolved molecules become uniformly distributed throughout their solution volume. Entropy is therefore a function of concentration.

If entropy varies with concentration, so must free energy. Thus, as is shown in this section, the free energy change of a chemical reaction depends on the concentrations of both its reactants and its products. This phenomenon is of great biochemical significance because enzymatic reactions can proceed in either direction depending on the relative concentrations of their reactants and products. Indeed, the directions of many enzymatically catalyzed reactions depend on the availability of their substrates (reactants) and on the metabolic demand for their products (although most metabolic pathways operate unidirectionally; Section 16-6C).

A. Equilibrium Constants

The relationship between the concentration and the free energy of a substance $A$, which is derived in the appendix to this chapter, is approximately

$$\overline{G}_A - \overline{G}_A^0 = RT \ln[A]$$  \[3.13\]

where $\overline{G}_A$ is known equivalently as the partial molar free energy or the chemical potential of $A$ (the bar indicates the quantity per mole), $\overline{G}_A^0$ is the partial molar free energy of $A$ in its standard state (see Section 3-4B), $R$ is the gas constant (Table 3-1), and $[A]$ is the molar concentration of $A$. Thus for the general reaction,

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

since free energies are additive and the free energy change of a reaction is the sum of the free energies of the products less those of the reactants, the free energy change for this reaction is

$$\Delta G = e\overline{G}_C + d\overline{G}_D - a\overline{G}_A - b\overline{G}_B$$  \[3.14\]

Substituting this relationship into Eq. [3.13] yields

$$\Delta G = \Delta G^0 + RT \ln \left( \frac{[C]^c [D]^d}{[A]^a [B]^b} \right)$$  \[3.15\]

where $\Delta G^0$ is the free energy change of the reaction when all of its reactants and products are in their standard states. Thus the expression for the free energy change of a reaction consists of two parts: (1) a constant term whose value depends only on the reaction taking place, and (2) a variable term that depends on the concentrations of the reactants and the products, the stoichiometry of the reaction, and the temperature.

For a reaction at equilibrium, there is no net change because the free energy of the forward reaction exactly balances that of the backward reaction. Consequently, $\Delta G = 0$, so that Eq. [3.15] becomes

$$\Delta G^0 = -RT \ln K_{eq}$$  \[3.16\]

where $K_{eq}$ is the familiar equilibrium constant of the reaction:

$$K_{eq} = \frac{[C]^c [D]^d}{[A]^a [B]^b} = e^{-\Delta G^0/kT}$$  \[3.17\]

and the subscript "eq" in the concentration terms indicates their equilibrium values. (The equilibrium condition is usually clear from the context of the situation, so that equilibrium concentrations are often expressed without this subscript.) The equilibrium constant of a reaction may therefore be calculated from standard free energy data and vice versa. Table 3-3 indicates the numerical relationship between $\Delta G^0$ and $K_{eq}$: Note that a 10-fold variation of $K_{eq}$ at 25°C corresponds to a 5.7 kJ mol$^{-1}$ change in $\Delta G^0$, which is less than half of the free energy of even a weak hydrogen bond.

Equations [3.15] through [3.17] indicate that when the reactants in a process are in excess of their equilibrium

<table>
<thead>
<tr>
<th>Table 3-3 Variation of $K_{eq}$ with $\Delta G^0$ at 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{eq}$</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>$10^5$</td>
</tr>
<tr>
<td>$10^4$</td>
</tr>
<tr>
<td>$10^3$</td>
</tr>
<tr>
<td>$10^2$</td>
</tr>
<tr>
<td>$10^1$</td>
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<tr>
<td>$10^{-1}$</td>
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<tr>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>$10^{-3}$</td>
</tr>
<tr>
<td>$10^{-4}$</td>
</tr>
</tbody>
</table>
the forward direction. Thus, the free energy of ATP hydrolysis, a highly exergonic process, is harnessed to drive many otherwise endergonic biological processes to completion (Section 16-4C).

## APPENDIX: CONCENTRATION DEPENDENCE OF FREE ENERGY

To establish that the free energy of a substance is a function of its concentration, consider the free energy change of an ideal gas during a reversible pressure change at constant temperature (\( w = 0 \), since an ideal gas is incapable of doing non-\( P-V \) work). Substituting Eqs. [3.1] and [3.2] into Eq. [3.9] and differentiating the result yields

\[
dG = dq - dW + P \, dV + V \, dP - T \, dS \quad [3.81]
\]

On substitution of the differentiated forms of Eqs. [3.3] and [3.8] into this expression, it reduces to

\[
dG = V \, dP \quad [3.82]
\]

The ideal gas equation is \( PV = nRT \), where \( n \) is the number of moles of gas. Therefore

\[
dG = nRT \frac{dP}{P} = nRT \, d \ln P \quad [3.83]
\]

This gas phase result can be extended to the more biochemically relevant area of solution chemistry by application of Henry's law for a solution containing the solute \( A \) in equilibrium with the gas phase:

\[
P_A = K_A X_A \quad [3.84]
\]

Here \( P_A \) is the partial pressure of \( A \) when its mole fraction in the solution is \( X_A \), and \( K_A \) is the Henry's law constant of \( A \) in the solvent being used. It is generally more convenient, however, to express the concentrations of the relatively dilute solutions of chemical and biological systems in terms of molarity rather than mole fractions. For a dilute solution

\[
X_A \approx \frac{n_A}{n_{\text{solvent}}} = \frac{[A]}{[\text{solvent}]} \quad [3.85]
\]

where the solvent concentration, [solvent], is approximately constant. Thus

\[
P_A \approx K_A [A] \quad [3.86]
\]

where \( K'_A = K_A /[\text{solvent}] \). Substituting this expression into Eq. [3.83] yields

\[
dG_A = n_A RT \, d(\ln K'_A + \ln[A]) = n_A RT \, d \ln[A] \quad [3.87]
\]

Free energy, as energy and enthalpy, is a relative quantity that can only be defined with respect to some arbitrary standard state. The standard state is customarily taken to be 25°C, 1 atm pressure, and, for the sake of mathematical simplicity, \([A] = 1\). The integration of Eq. [3.87] from the standard state, \([A] = 1\), to the final state, \([A] = [A]\), results in

\[
G_A - G_A^0 = n_A RT \ln[A] \quad [3.88]
\]

where \( G_A^0 \) is the free energy of \( A \) in the standard state and \([A]\) really represents the concentration ratio \([A]/1\). Since Henry's law is valid for real solutions only in the limit of infinite dilution, however, the standard state is defined as the entirely hypothetical state of 1M solute with the properties that it has at infinite dilution.

The free energy terms in Eq. [3.88] may be converted from extensive quantities (those dependent on the amount of material) to intensive quantities (those independent of the amount of material) by dividing both sides of the equation by \( n_A \). This yields

\[
\bar{G}_A - \bar{G}_A^0 = RT \ln[A] \quad [3.89]
\]

Equation [3.89] has the limitation that it refers to solutions that exactly follow Henry's law, although real solutions only do so in the limit of infinite dilution if the solute is, in fact, volatile. These difficulties can all be eliminated by replacing \([A]\) in Eq. [3.89] by a quantity, \( a_A \), known as the activity of \( A \). This is defined

\[
a_A = \gamma_A [A] \quad [3.90]
\]

where \( \gamma_A \) is the activity coefficient of \( A \). Equation [3.89] thereby takes the form

\[
\bar{G}_A - \bar{G}_A^0 = RT \ln a_A \quad [3.91]
\]

in which all departures from ideal behavior, including the provision that the system may perform non-\( P-V \) work, are incorporated into the activity coefficient, which is an experimentally measurable quantity. Ideal behavior is only approached at infinite dilution; that is, \( \gamma_A \to 1 \) as \([A] \to 0\). The standard state in Eq. [3.91] is redefined as that of unit activity.

The concentrations of reactants and products in most laboratory biochemical reactions are usually so low (on the order of millimolar or less) that the activity coefficients of these various species are nearly unity. Consequently, the activities of most biochemical species under laboratory conditions can be satisfactorily approximated by their molar concentrations:

\[
\bar{G}_A - \bar{G}_A^0 = RT \ln [A] \quad [3.92]
\]

However, the activity coefficient of a particular species varies with the total concentration of all other species present as well as with its own concentration. Thus, despite the low concentrations of most biochemical species in the cell, their extraordinarily high combined concentrations (e.g., see Fig. 1-13) make the activity coefficients of the individual species deviate significantly from unity. Unfortunately, it is difficult to determine the values of these quantities in a cellular compartment (where it is likewise difficult to determine the concentration of any given species).
CHAPTER SUMMARY

1. First Law of Thermodynamics: Energy Is Conserved
   The first law of thermodynamics,
   \[ U = q - w \]  
   where \( q \) is heat and \( w \) is work, is a statement of the law of conservation of energy. Energy is a state function because the energy of a system depends only on the state of the system. Enthalpy,
   \[ H = U + PV \]
   where \( P \) is pressure and \( V \) is volume, is a closely related state function that represents the heat at constant pressure under conditions where only pressure-volume work is possible.

2. Second Law of Thermodynamics: The Universe Tends toward Maximum Disorder
   Entropy, which is also a state function, is defined
   \[ S = k_B \ln W \]
   where \( W \) is the number of equivalent ways the system can be arranged under the conditions governing it and \( k_B \) is the Boltzmann constant. The second law of thermodynamics states that the universe tends toward maximum disorder and hence \( \Delta S_{\text{universe}} > 0 \) for any real process.

3. Free Energy: The Indicator of Spontaneity
   The Gibbs free energy of a system
   \[ G = H - TS \]
   decreases in a spontaneous, constant pressure process. In a process at equilibrium, the system suffers no net change, so that \( \Delta G = 0 \). An ideal process, in which the system is always at equilibrium, is said to be reversible. All real processes are irreversible since processes at equilibrium can only occur at an infinitesimal rate.

4. Chemical Equilibria
   For a chemical reaction
   \[ aA + bB \rightleftharpoons cC + dD \]
   the change in the Gibbs free energy is expressed
   \[ \Delta G = \Delta G^\circ + RT \ln \left( \frac{[C]^c[D]^d}{[A]^a[B]^b} \right) \]
   where \( \Delta G^\circ \), the standard free energy change, is the free energy change at 25°C, 1 atm pressure, and unit activities of reactants and products. The biochemical standard state, \( \Delta G^\circ \), is similarly defined but in dilute aqueous solution at pH 7 in which the activities of water and H\(^+\) are both defined as unity. At equilibrium
   \[ \Delta G^\circ = -RT \ln K_{eq} = -RT \ln \left( \frac{[C]^c[D]^d}{[A]^a[B]^b} \right) \]
   where \( K_{eq} \) is the equilibrium constant under the biochemical convention. An endergonic reaction (\( \Delta G > 0 \)) may be driven by an exergonic reaction (\( \Delta G < 0 \)) if they are coupled and if the overall reaction is exergonic.

REFERENCES

[An insightful but nonmathematical exposition of the second law of thermodynamics.]

PROBLEMS

1. A common funeral litany is the Biblical verse: “Ashes to ashes, dust to dust.” Why might a bereaved family of thermodynamicists be equally comforted by a recitation of the second law of thermodynamics?

2. How many flights of 4-m high stairs must an overweight person weighing 75 kg climb to atone for the indirection of eating a 500-Cal hamburger? Assume that there is a 20% efficiency in converting nutritional energy to mechanical energy. The gravitational force of an object of mass \( m \) kg is \( F = mg \), where the gravitational constant \( g \) is 9.8 m \( \cdot \) s\(^{-2} \).

3. In terms of thermodynamic concepts, why is it more difficult to park a car in a small space than it is to drive it out from such a space?

4. It has been said that an army of dedicated monkeys, typing at random, would eventually produce all of Shakespeare’s works. How long, on average, would it take 1 million monkeys, each typing on a 46-key typewriter (space included but no shift key) at the rate of 1 keystroke per second, to type the phrase “to be or not to be”? How long, on average, would it take one monkey to do so at a computer if the computer would only accept the
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correct letter in the phrase and then would shift to its next letter (i.e., the computer knew what it wanted)? What do these results indicate about the probability of order randomly arising from disorder or order arising through a process of evolution?

5. Show that the transfer of heat from an object of higher temperature to one of lower temperature, but not the reverse process, obeys the second law of thermodynamics.

6. Carbon monoxide crystallizes with its CO molecules arranged in parallel rows. Since CO is a nearly ellipsoidal molecule, in the absence of polarity effects, adjacent CO molecules could equally well line up in a head-to-tail or a head-to-head fashion. In a crystal consisting of $10^{25}$ CO molecules, what is the entropy of all the CO molecules being aligned head to tail?

7. The U.S. Patent Office has received, and continues to receive, numerous applications for perpetual motion machines. Perpetual motion machines have been classified as those of the first kind, which violate the first law of thermodynamics, and those of the second kind, which violate the second law of thermodynamics. The fallacy in a perpetual motion machine of the first kind is generally easy to detect. An example would be a motor-driven electrical generator that produces energy in excess of that input by the motor. The fallacy in a perpetual motion machine of the second type, however, is usually more subtle. Take, for example, a ship that uses heat energy extracted from the sea by a heat pump to boil water so as to power a steam engine that drives the ship as well as the heat pump. Show, in general terms, that such a propulsion system would violate the second law of thermodynamics.

8. Using the data in Table 3-4, calculate the values of $\Delta G^\circ$ at 25°C for the following metabolic reactions:

(a) $\text{C}_6\text{H}_12\text{O}_6 + 6 \text{O}_2 \rightleftharpoons 6 \text{CO}_2(aq) + 6 \text{H}_2\text{O}(l)$

(b) $\text{C}_6\text{H}_12\text{O}_6 \rightleftharpoons 2(\text{CH}_3\text{CH}_2\text{OH}) + 2 \text{CO}_2(aq)$

(c) $\text{C}_6\text{H}_12\text{O}_6 \rightleftharpoons 2(\text{CH}_3\text{CHOHCOO}^-) + 2 \text{H}^+$

[These reactions, respectively, constitute oxidative metabolism, alcoholic fermentation in yeast deprived of oxygen, and homolactic fermentation in skeletal muscle requiring energy faster than oxidative metabolism can supply it (Section 17-3B).]

9. The native and denatured forms of a protein are generally in equilibrium as follows:

$\text{Protein (denatured)} \rightleftharpoons \text{protein (native)}$

For a certain solution of the protein ribonuclease A, in which the total protein concentration is $2.0 \times 10^{-3} \text{M}$, the concentrations of the denatured and native proteins at both 50 and 100°C are given in the following table:

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>[Ribonuclease A (denatured)] (M)</th>
<th>[Ribonuclease A (native)] (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>$5.1 \times 10^{-6}$</td>
<td>$2.0 \times 10^{-3}$</td>
</tr>
<tr>
<td>100</td>
<td>$2.8 \times 10^{-4}$</td>
<td>$1.7 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

(a) Determine $\Delta H^\circ$ and $\Delta S^\circ$ for the folding reaction assuming that these quantities are independent of temperature. (b) Calculate $\Delta G^\circ$ for ribonuclease A folding at 25°C. Is this process spontaneous under standard state conditions at this temperature? (c) What is the denaturation temperature of ribonuclease A under standard state conditions?

10. Using the data in Table 3-4, calculate $\Delta G^\circ'$ for the following compounds at 25°C: (a) $\text{H}_2\text{O}(l)$; (b) sucrose (sucrose $\rightleftharpoons$ glucose + fructose: $\Delta G^\circ' = -29.3 \text{ kJ} \cdot \text{mol}^{-1}$); and (c) ethyl acetate (ethyl acetate $\rightleftharpoons$ ethanol + acetate$^-$ + $\text{H}^+$: $\Delta G^\circ' = -19.7 \text{ kJ} \cdot \text{mol}^{-1}$; the pK of acetic acid is 4.76).

11. Calculate the equilibrium constants for the hydrolysis of the following compounds at pH 7 and 25°C: (a) phosphoenolpyruvate ($\Delta G^\circ'' = -61.9 \text{ kJ} \cdot \text{mol}^{-1}$); (b) pyrophosphate ($\Delta G^\circ'' = -33.5 \text{ kJ} \cdot \text{mol}^{-1}$); and (c) glucose-1-phosphate ($\Delta G^\circ'' = -20.9 \text{ kJ} \cdot \text{mol}^{-1}$).