

Heat, Work, and Energy

1.1 INTRODUCTION

Thermodynamics is deceptively simple or exceedingly complex, depending on how you approach it. In this book, we will be concerned with the principles of thermodynamics that are especially useful in thinking about biological phenomena. The emphasis will be on concepts, with a minimum of mathematics. Perhaps an accurate description might be rigor without *rigor mortis*. This may cause some squirming in the graves of thermodynamic purists, but the objective is to provide a foundation for researchers in experimental biology to use thermodynamics. This includes cell biology, microbiology, molecular biology, and pharmacology, among others. A more advanced treatment of some aspects of thermodynamics is presented in Chapter 4. Excellent texts are available that present a more complete exposition of thermodynamics (cf. Refs. 1–3).

In point of fact, thermodynamics can provide a useful way of thinking about biological processes and is indispensable when considering molecular and cellular mechanisms. For example, what reactions and coupled physiological processes are possible? What are the allowed mechanisms involved in cell division or in protein synthesis? What are the thermodynamic considerations that cause proteins, nucleic acids, and membranes to assume their active structures? It is easy to postulate biological mechanisms that are inconsistent with thermodynamic principles—but just as easy to postulate those that are consistent. Consequently, no active researcher in biology should be without a rudimentary knowledge of the principles of thermodynamics. The ultimate goal of this exposition is to understand what determines equilibrium in biological systems and how these equilibrium processes can be coupled together to produce living systems, even though we recognize that living organisms are not at equilibrium. Thermodynamics provides a unifying framework for diverse systems in biology. Both a qualitative and a quantitative understanding are important and will be developed.

The beauty of thermodynamics is that a relatively small number of postulates can be used to develop the entire subject. Perhaps the most important part of this development is to be very precise with regard to concepts and definitions, without

getting bogged down with mathematics. Thermodynamics is a macroscopic theory, not molecular. As far as thermodynamics is concerned, molecules need not exist. However, we will not be purists in this regard: If molecular descriptions are useful for understanding or introducing concepts, they will be used. We will not hesitate to give molecular descriptions of thermodynamic results, but we should recognize that these interpretations are not inherent in thermodynamics itself. It is important to note, nevertheless, that large collections of molecules are assumed so that their behavior is governed by Boltzmann statistics; that is, the normal thermal energy distribution is assumed. This is almost always the case in practice. Furthermore, thermodynamics is concerned with time-independent systems, that is, systems at equilibrium. Thermodynamics has been extended to nonequilibrium systems, but we will not be concerned with the formal development of this subject here.

The first step is to define the *system*. A thermodynamic system is simply that part of the universe in which we are interested. The only caveat is that the system must be large relative to molecular dimensions. The system could be a room, it could be a beaker, it could be a cell, etc. An *open system* can exchange energy and matter across its boundaries, for example, a cell or a room with open doors and windows. A *closed system* can exchange energy but not matter, for example, a closed room or box. An *isolated system* can exchange neither energy nor matter, for example, the universe or, approximately, a closed Dewar flask. We are free to select the system as we choose, but it is very important that we specify what it is. This will be illustrated as we proceed. The *properties* of a system are any measurable quantities characterizing the system. Properties are either *extensive*, proportional to the amount of material in the system, or *intensive*, independent of the amount of material. Examples of extensive properties are mass and volume. Examples of intensive properties are temperature, pressure, and color.

1.2 TEMPERATURE

We are now ready to introduce three important concepts: temperature, heat, and work. None of these are unfamiliar, but we must define them carefully so that they can be used as we develop thermodynamics.

Temperature is an obvious concept, as it simply measures how hot or cold a system is. We will not belabor its definition and will simply assert that thermodynamics requires a unique temperature scale, namely, the Kelvin temperature scale. The Kelvin temperature scale is related to the more conventional Celsius temperature scale by the definition

$$T_{\text{Kelvin}} = T_{\text{Celsius}} + 273.16 \quad (1-1)$$

Although the temperature on the Celsius scale is referred to as “degrees Celsius,” by convention degrees are not stated on the Kelvin scale. For example, a temperature of 100 °C is 373 K. (Thermodynamics is entirely logical—some of the conventions used are not.) The definition of *thermal equilibrium* is very simple: When two systems are at the same temperature, they are at thermal equilibrium.

1.3 HEAT

Heat flows across the system boundary during a change in the state of the system because a temperature difference exists between the system and its surroundings. We know of many examples of heat: Some chemical reactions produce heat, such as the combustion of gas and coal. Reactions in cells can produce heat. By convention, heat flows from higher temperature to lower temperature. This fixes the sign of the heat change. It is important to note that this is a convention and is not required by any principle. For example, if the temperature of the surroundings decreases, heat flows to the system, and the sign of the heat change is positive (+). A simple example will illustrate this sign convention as well as the importance of defining the system under consideration.

Consider two beakers of the same size filled with the same amount of water. In one beaker, A, the temperature is 25 °C, and in the other beaker, B, the temperature is 75 °C. Let us now place the two beakers in thermal contact and allow them to reach thermal equilibrium (50 °C). This situation is illustrated in Figure 1-1. If the system is defined as A, the temperature of the system increases, so the heat change is positive. If the system is defined as B, the temperature of the system decreases, so the heat change is negative. If the system is defined as A and B, no heat flow occurs across the boundary of the system, so the heat change is zero! This illustrates how important it is to define the system before asking questions about what is occurring.

The heat change that occurs is proportional to the temperature difference between the initial and final states of the system. This can be expressed mathematically as

$$q = C(T_f - T_i) \quad (1-2)$$

where q is the heat change, the constant C is the *heat capacity*, T_f is the final temperature, and T_i is the initial temperature. This relationship assumes that the heat capacity is constant, independent of the temperature. In point of fact, the heat capacity often changes as the temperature changes, so that a more precise definition puts this relationship in differential form:

$$dq = C dT \quad (1-3)$$

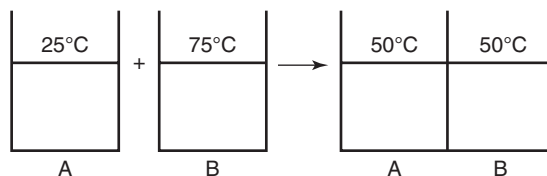


FIGURE 1-1. Illustration of the establishment of thermal equilibrium and importance of defining the *system* carefully. Two identical vessels filled with the same amount of liquid, but at different temperatures, are placed in contact and allowed to reach thermal equilibrium. A discussion of this figure is given in the text.

Note that the heat change and the heat capacity are extensive properties—the larger the system, the larger the heat capacity and the heat change. Temperature, of course, is an intensive property.

1.4 WORK

The definition of *work* is not as simple as that for heat. Many different forms of work exist, for example, mechanical work, such as muscle action, and electrical work, such as ions crossing charged membranes. We will use a rather artificial, but very general, definition of work that is easily understood. Work is a quantity that can be transferred across the system boundary and can always be converted to lifting and lowering a weight in the surroundings. By convention, work done on a system is positive: this corresponds to lowering the weight in the surroundings.

You may recall that mechanical work, w , is defined as the product of the force in the direction of movement, F_x , times the distance moved, x , or in differential form

$$dw = F_x dx \quad (1-4)$$

Therefore, the work to lower a weight is $-mgh$, where m is the mass, g is the gravitational constant, and h is the distance the weight is lowered. This formula is generally useful: for example, mgh is the work required for a person of mass m to walk up a hill of height h . The work required to stretch a muscle could be calculated with Eq. (1-4) if we knew the force required and the distance the muscle was stretched. Electrical work, for example, is equal to $-EIt$, where E is the electromotive force, I is the current, and t is the time. In living systems, membranes often have potentials (voltages) across them. In this case, the work required for an ion to cross the membrane is $-zF\Psi$, where z is the charge of the ion, F is the Faraday (96,489 coulombs/mole), and Ψ is the potential. A specific example is the cotransport of Na^+ and K^+ , Na^+ moving out of the cell and K^+ moving into the cell. A potential of -70 mV is established on the inside so that the electrical work required to move a mole of K^+ ions to the inside is $-(1)(96,489)(0.07) = -6750$ Joules. ($\Psi = \Psi_{\text{outside}} - \Psi_{\text{inside}} = +70$ mV.) The negative sign means that work is done by the system.

Although not very biologically relevant, we will now consider in some detail pressure–volume work, or $P - V$ work. This type of work is conceptually easy to understand, and calculations are relatively easy. The principles discussed are generally applicable to more complex systems, such as those encountered in biology. As a simple example of $P - V$ work, consider a piston filled with a gas, as pictured in Figure 1-2. In this case, the force is equal to the external pressure, P_{ex} , times the area, A , of the piston face, so the infinitesimal work can be written as

$$dw = -P_{\text{ex}}A dx = -P_{\text{ex}}dV \quad (1-5)$$

If the piston is lowered, work is done on the system and is positive, whereas if the piston is raised, work is done by the system and is negative. Note that the work done

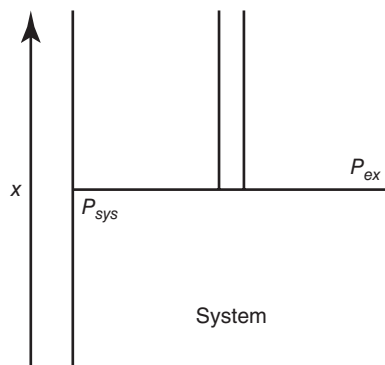


FIGURE 1-2. Schematic representation of a piston pushing on the system. P_{ex} is the external pressure and P_{sys} is the pressure of the system.

on or by the system by lowering or raising the piston depends on what the external pressure is. Therefore, the work can have any value from 0 to ∞ , depending on how the process is done. This is a very important point: the work associated with a given change in state depends on *how* the change in state is carried out.

The idea that work depends on how the process is carried out can be illustrated further by considering the expansion and compression of a gas. The $P - V$ isotherm for an ideal gas is shown in Figure 1-3. An ideal gas is a gas that obeys the ideal gas law, $PV = nRT$ (n is the number of moles of gas and R is the gas constant). The behavior of most gases at moderate pressures is well described by this relationship. Let us consider the expansion of the gas from P_1, V_1 to P_2, V_2 . If this expansion is done with the external pressure equal to zero, that is, into a vacuum, the work is zero. Clearly, this is the minimum amount of work that can be done for this change in state. Let us now carry out the same expansion with the external pressure equal to P_2 . In this case, the work is

$$w = - \int_{V_1}^{V_2} P_{\text{ex}} dV = -P_2(V_2 - V_1) \quad (1-6)$$

which is the striped area under the $P - V$ curve. The expansion can be broken into stages; for example, first expand the gas with $P_{\text{ex}} = P_3$ followed by $P_{\text{ex}} = P_2$, as shown in Figure 1-3. The work done by the system is then the sum of the two rectangular areas under the curve. It is clear that as the number of stages is increased, the magnitude of the work done increases. The maximum work that can be done by the system is when the external pressure is set equal to the pressure of the system minus a small differential pressure, dP , throughout the expansion. This can be expressed as

$$w_{\text{max}} = - \int_{V_1}^{V_2} PdV \quad (1-7)$$

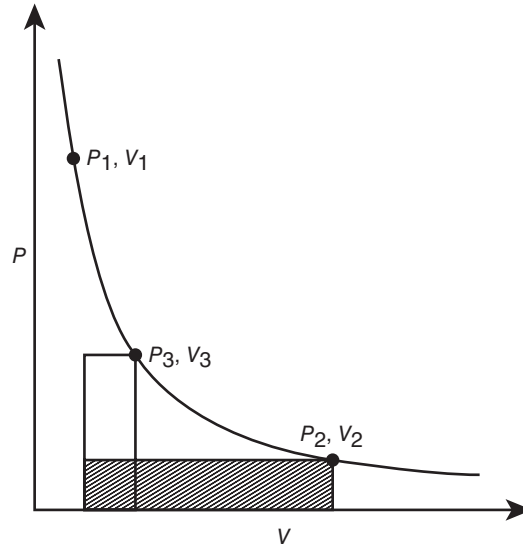


FIGURE 1-3. A P - V isotherm for an ideal gas. The narrow rectangle with both hatched and open areas is the work done in going from P_1, V_1 to P_3, V_3 with an external pressure of P_3 . The hatched area is the work done by the system in going from P_1, V_1 to P_2, V_2 with an external pressure of P_2 . The maximum amount of work done by the system for this change in state is the area under the curve between P_1, V_1 and P_2, V_2 .

By a similar reasoning process, it can be shown that for a compression the minimum work done on the system is

$$w_{\min} = - \int_{V_2}^{V_1} P dV \quad (1-8)$$

This exercise illustrates two important points. First, it clearly shows that the work associated with a change in state depends on how the change in state is carried out. Second, it demonstrates the concept of a *reversible path*. When a change in state is carried out such that the surroundings and the system are not at equilibrium only by an infinitesimal amount, in this case dP , during the change in state, the process is called reversible. The concept of reversibility is only an ideal—it cannot be achieved in practice. Obviously, we cannot really carry out a change in state with only an infinitesimal difference between the pressures of the system and surroundings. We will find this concept very useful, nevertheless.

Now let us think about a cycle whereby an expansion is carried out followed by a compression that returns the system back to its original state. If this is done as a one-stage process in each case, the total work can be written as

$$w_{\text{total}} = w_{\text{exp}} + w_{\text{comp}} \quad (1-9)$$

or

$$w_{\text{total}} = -P_2(V_2 - V_1) - P_1(V_1 - V_2) \quad (1-10)$$

or

$$w_{\text{total}} = (P_1 - P_2)(V_2 - V_1) > 0 \quad (1-11)$$

In this case, net work has been done on the system. For a reversible process, however, the work associated with compression and expansion is

$$w_{\text{exp}} = - \int_{V_1}^{V_2} P dV \quad (1-12)$$

and

$$w_{\text{comp}} = - \int_{V_2}^{V_1} P dV \quad (1-13)$$

so that the total work for the cycle is equal to zero. Indeed, for reversible cycles the net work is always zero.

To summarize this discussion of the concept of work, the work done on or by the system depends on how the change in state of the system occurs. In the real world, changes in state always occur irreversibly, but we will find the concept of a reversible change in state to be very useful.

Heat changes also depend on how the process is carried out. Generally, a subscript is appended to q , for example, q_P and q_V for heat changes at constant pressure and volume, respectively. As a case in point, the heat change at constant pressure is greater than that at constant volume if the temperature of a gas is raised. This is because not only must the temperature be raised, but the gas must also be expanded.

Although this discussion of gases seems far removed from biology, the concepts and conclusions reached are quite general and can be applied to biological systems. The only difference is that exact calculations are usually more difficult. It is useful to consider why this is true. In the case of ideal gases, a simple equation of state is known, $PV = nRT$, that is obeyed quite well by real gases under normal conditions. This equation is valid because gas molecules, on average, are quite far apart and their energetic interactions can be neglected. Collisions between gas molecules can be approximated as billiard balls colliding. This situation obviously does not prevail in liquids and solids where molecules are close together and the energetics of their interactions cannot be neglected. Consequently, simple equations of state do not exist for liquids and solids.

1.5 DEFINITION OF ENERGY

The first law of thermodynamics is basically a definition of the energy change associated with a change in state. It is based on the experimental observation that heat and work can be interconverted. Probably the most elegant demonstration of this is the experimental work of James Prescott Joule in the late 1800s. He carried out experiments in which he measured the work necessary to turn a paddle wheel in water and the concomitant rise in temperature of the water. With this rather primitive experiment, he was able to calculate the conversion factor between work and heat with

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amazing accuracy, namely, to within 0.2%. The first law states that the energy change, ΔE , associated with a change in state is

$$\Delta E = q + w \quad (1-14)$$

Furthermore, the energy change is the same regardless of how the change in state is carried out. In this regard, energy clearly has quite different properties than heat and work. This is true for both reversible and irreversible processes. Because of this property, the energy (usually designated the internal energy in physical chemistry textbooks) is called a *state function*. State functions are extremely important in thermodynamics, both conceptually and practically.

Obviously we cannot prove the first law, as it is a basic postulate of thermodynamics. However, we can show that without this law events could occur that are contrary to our experience. Assume, for example, that the energy change in going from state 1 to state 2 is greater than the negative of that for going from state 2 to 1 because the changes in state are carried out differently. We could then cycle between these two states and produce energy as each cycle is completed, essentially making a perpetual motion machine. We know that such machines do not exist, consistent with the first law. Another way of looking at this law is as a statement of the conservation of energy.

It is important that thermodynamic variables are not just hypothetical—we must be able to relate them to laboratory experience, that is, to measure them. Thermodynamics is developed here for practical usage. Therefore, we must be able to relate the concepts to what can be done in the laboratory. How can we measure energy changes? If we only consider $P - V$ work, the first law can be written as

$$\Delta E = q - \int_{V_1}^{V_2} P_{\text{ex}} dV \quad (1-15)$$

If the change in state is measured at constant volume, then

$$\Delta E = q_V \quad (1-16)$$

At first glance, it may seem paradoxical that a state function, the energy change, is equal to a quantity whose magnitude depends on how the change in state is carried out, namely, the heat change. However, in this instance we have specified how the change in state is to occur, namely, at constant volume. Therefore, if we measure the heat change at constant volume associated with a change in state, we have also measured the energy change.

Temperature is an especially important variable in biological systems. If the temperature is constant during a change in state, the process is *isothermal*. On the other hand, if the system is insulated so that no heat escapes or enters the system during the change in state ($q = 0$), the process is *adiabatic*.

1.6 ENTHALPY

Most experiments in the laboratory and in biological systems are done at constant pressure, rather than at constant volume. At constant pressure,

$$\Delta E = q_P - P(V_2 - V_1) \quad (1-17)$$

or

$$E_2 - E_1 = q_P - P(V_2 - V_1) \quad (1-18)$$

The heat change at constant pressure can be written as

$$q_P = (E_2 + PV_2) - (E_1 + PV_1) \quad (1-19)$$

This relationship can be simplified by defining a new state function, the *enthalpy*, H :

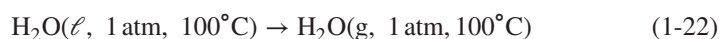
$$H = E + PV \quad (1-20)$$

The enthalpy is obviously a state function since E , P , and V are state functions. The heat change at constant pressure is then equal to the enthalpy change:

$$q_P = \Delta H = H_2 - H_1 \quad (1-21)$$

For biological reactions and processes, we will usually be interested in the enthalpy change rather than the energy change. It can be measured experimentally by determining the heat change at constant pressure.

As a simple example of how energy and enthalpy can be calculated, let us consider the conversion of liquid water to steam at 100°C and 1 atm, that is, boiling water:



The heat required for this process, $\Delta H (=q_P)$, is 9.71 kilocalories/mol. What is ΔE for this process? This can be calculated as follows:

$$\Delta E = \Delta H - \Delta(PV) = \Delta H - P\Delta V$$

$$\Delta V = V_g - V_\ell = 22.4 \text{ liters/mol} - 18.0 \times 10^{-3} \text{ liters/mol} \approx PV_g \approx RT$$

$$\Delta E = \Delta H - RT = 9710 - 2(373) = 8970 \text{ calories/mol}$$

Note that the Kelvin temperature must be used in thermodynamic calculations and that ΔH is significantly greater than ΔE .

Let us do a similar calculation for the melting of ice into liquid water



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In this case, the measured heat change, $\Delta H (=q_p)$, is 1.44 kcal/mol. The calculation of ΔE parallels the previous calculation.

$$\begin{aligned}\Delta E &= \Delta H - P\Delta V \\ \Delta V &= V_\ell - V_s \approx 18.0 \text{ ml/mol} - 19.6 \text{ ml/mol} \approx -1.6 \text{ ml/mol} \\ P\Delta V &\approx -1.6 \text{ ml atm} = -0.04 \text{ cal} \\ \Delta E &= 1440 + 0.04 = 1440 \text{ cal/mol}\end{aligned}$$

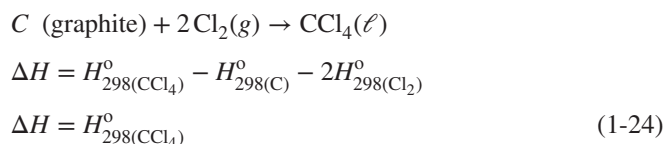
In this case, ΔE and ΔH are essentially the same. In general, they do not differ greatly in condensed media, but the differences can be substantial in the gas phase.

The two most common units for energy are the calorie and the joule (J). (One calorie equals 4.184 J.) The official MKS unit is the joule, but many research publications use the calorie. We will use both in this text, in order to familiarize the student with both units.

1.7 STANDARD STATES

Only changes in energy states can be measured. Therefore, it is arbitrary what we set as the zero for the energy scale. As a matter of convenience, a common zero has been set for both the energy and the enthalpy. Elements in their stablest forms at 25°C (298 K) and 1 atm are assigned an enthalpy of zero. This is called a *standard state* and is usually written as H_{298}^0 . The superscript means 1 atm and the subscript is the temperature in Kelvin.

As an example of how this concept is used, consider the formation of carbon tetrachloride from its elements:



The quantity $H_{298(\text{CCl}_4)}^0$ is called the heat of formation of carbon tetrachloride. Tables of heats of formation are available for hundreds of compounds and are useful in calculating the enthalpy changes associated with chemical reactions (cf. Refs. 4, 5).

In the case of substances of biological interest in solutions, the definitions of standard states and heats of formation are a bit more complex. In addition to pressure and temperature, other factors must be considered such as pH, salt concentration, metal ion concentration, etc. A universal definition has not been established. In practice, it is best to use heats of formation under a defined set of conditions and likewise to define the standard state as these conditions. Tables of heats of formation for some compounds of biological interest are given in Appendix 4 (6). A prime is often added to the symbol for these heats of formation ($H_f^{0'}$) to indicate the unusual nature of the

standard state. We will not make that distinction here, but it is essential that a consistent standard state is used when making thermodynamic calculations for biological systems.

A useful way of looking at chemical reactions is as algebraic equations. A characteristic enthalpy can be assigned to each product and reactant. Consider the “reaction”



For this reaction, $\Delta H = H_{\text{products}} - H_{\text{reactants}}$, or

$$\Delta H = dH_D + cH_C - aH_A - bH_B$$

where the H_i are molar enthalpies. At 298 K and 1 atm, the molar enthalpies of the elements are zero, whereas for compounds, the molar enthalpies are equal to the heats of formation, which are tabulated. Before we apply these considerations to biological reactions, a brief digression will be made to discuss how heats of reactions are determined experimentally.

1.8 CALORIMETRY

The area of science concerned with the measurement of heat changes associated with chemical reactions is designated as calorimetry. Only a brief introduction is given here, but it is important to relate the theoretical concepts to laboratory experiments. To begin this discussion, we will return to our earlier discussion of heat changes and the heat capacity, Eq. (1-3). Since the heat change depends on how the change in state is carried out, we must be more precise in defining the heat capacity. The two most common conditions are constant volume and constant pressure. The heat changes in these cases can be written as

$$dq_V = dE = C_V dT \quad (1-26)$$

$$dq_P = dH = C_P dT \quad (1-27)$$

A more exact mathematical treatment of these definitions would make use of partial derivatives, but we will avoid this complexity by using subscripts to indicate what is held constant. These equations can be integrated to give

$$\Delta E = \int_{T_1}^{T_2} C_V dT \quad (1-28)$$

$$\Delta H = \int_{T_1}^{T_2} C_P dT \quad (1-29)$$

Thus, heat changes can readily be measured if the heat capacity is known. The heat capacity of a substance can be determined by adding a known amount of heat to the

substance and determining the resulting increase in temperature. The known amount of heat is usually added electrically since this permits very precise measurement. (Recall that the electrical heat is I^2R , where I is the current and R is the resistance of the heating element.) If heat is added repeatedly in small increments over a large temperature range, the temperature dependence of the heat capacity can be determined. Tabulations of heat capacities are available and are usually presented with the temperature dependence described as a power series:

$$C_p = a + bT + cT^2 + \dots \quad (1-30)$$

where a , b , c , ... are constants determined by experiment.

For biological systems, two types of calorimetry are commonly carried out—batch calorimetry and scanning calorimetry. In batch calorimetry, the reactants are mixed together and the ensuing temperature rise (or decrease) is measured. A simple experimental setup is depicted in Figure 1-4, where the calorimeter is a Dewar flask and the temperature increase is measured by using a thermocouple or thermometer.

For example, if we wished to measure the heat change for the hydrolysis of adenosine 5'-triphosphate (ATP),



a solution of known ATP concentration would be put in the Dewar at a defined pH, metal ion concentration, buffer, etc. The reaction would be initiated by adding a small amount of adenosine triphosphatase (ATPase), an enzyme that efficiently catalyzes the hydrolysis, and the subsequent temperature rise is measured. The enthalpy of reaction can be calculated from the relationship

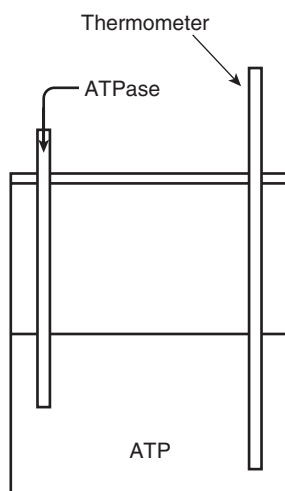


FIGURE 1-4. Schematic representation of a simple batch calorimeter. The insulated vessel is filled with a solution of ATP in a buffer containing salt and Mg^{2+} . The hydrolysis of ATP is initiated by the addition of the ATPase enzyme and the subsequent rise in temperature is measured.

$$\Delta H = C_p \Delta T \quad (1-32)$$

The heat capacity of the system is calculated by putting a known amount of heat into the system through an electrical heater and measuring the temperature rise of the system. The enthalpy change calculated is for the number of moles of ATP in the system. Usually, the experimental result is reported as a molar enthalpy, that is, the enthalpy change for a mole of ATP being hydrolyzed. This result can be obtained by dividing the observed enthalpy change by the moles of ATP hydrolyzed. Actual calorimeters are much more sophisticated than this primitive experimental setup. The calorimeter is well insulated, mixing is carried out very carefully, and very precise temperature measurements are made with a thermocouple. The enthalpy changes for many biological reactions have been measured, but unfortunately this information is not conveniently tabulated in a single source. However, many enthalpies of reaction can be derived from the heats of formation in the table in Appendix 4.

Scanning calorimetry is a quite different experiment and measures the heat capacity as a function of temperature. In these experiments, a known amount of heat is added to the system through electrical heating and the resulting temperature rise is measured. Very small amounts of heat are used, so the temperature changes are typically very small. This process is repeated automatically so that the temperature of the system slowly rises. The heat capacity of the system is calculated for each heat increment as $q_p/\Delta T$ and the data are presented as a plot of C_p versus T .

This method has been used, for example, to study protein unfolding and denaturation. Proteins unfold as the temperature is raised, and denaturation usually occurs over a very narrow temperature range. This is illustrated schematically in Figure 1-5, where the fraction of denatured protein, f_D , is plotted versus the temperature along with the corresponding plot of heat capacity, C_p , versus temperature.

As shown in Figure 1-5, the plot of heat capacity versus temperature is a smooth, slowly rising curve for the solvent. With the protein present, a peak in the curve occurs

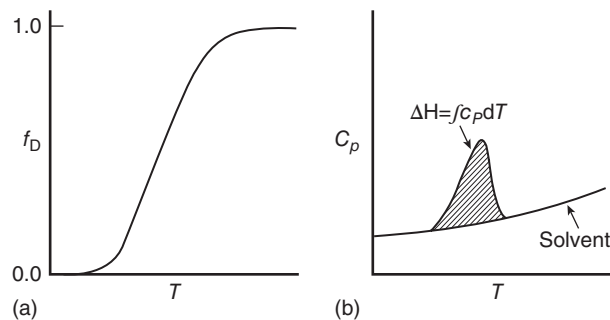


FIGURE 1-5. Schematic representation of the denaturation of a protein and the resulting change in heat capacity, C_p . In (a), the fraction of denatured protein, f_D , is shown as a function of temperature, T . In (b), the heat capacity, as measured by scanning calorimetry, is shown as a function of temperature. The lower curve is the heat capacity of the solvent. The hatched area is the excess heat capacity change due to the protein denaturing and is equal to ΔH for the unfolding.

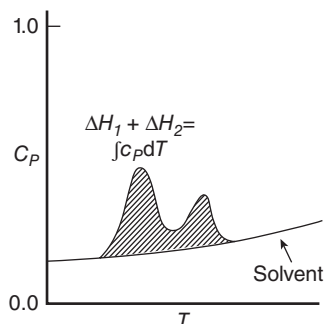


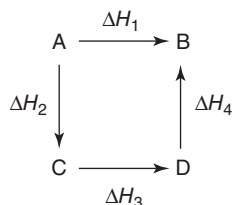
FIGURE 1-6. Schematic representation of a calorimeter scan in which the denaturation occurs in two steps. The hatched area permits the sum of the enthalpy changes to be determined, and the individual enthalpies of the unfolding reactions can be determined by a detailed analysis. As in Figure 1-5, C_p is the measured heat capacity and T is the temperature.

as the protein is denatured. The enthalpy change associated with denaturation is the area under the peak (striped area = $\int C_p dT$). In some cases, the protein denaturation may occur in multiple stages, in which case more than one peak can be seen in the heat capacity plot. This is shown schematically in Figure 1-6 for a two-stage unfolding process.

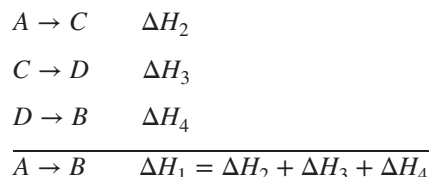
The enthalpies associated with protein unfolding are often interpreted in molecular terms such as hydrogen bonds, electrostatic interactions, and hydrophobic interactions. It should be borne in mind that these interpretations are not inherent in thermodynamic quantities, which do not explicitly give information at the molecular level. Consequently, such interpretations should be scrutinized very critically.

1.9 REACTION ENTHALPIES

We now return to a consideration of reaction enthalpies. Because the enthalpy is a state function, it can be added and subtracted for a sequence of reactions—it does not matter how the reaction occurs or in what order. In this regard, chemical reactions can be considered as algebraic equations. For example, consider the reaction cycle below:



If these reactions are written sequentially, it can readily be seen how the enthalpies are related.

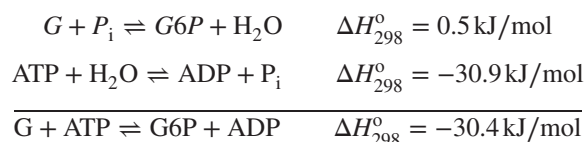


This ability to relate enthalpies of reaction in reaction cycles in an additive fashion is often called Hess's law, although it really is derived from thermodynamic principles as discussed. We will find that this "law" is extremely useful, as it allows determination of the enthalpy of reaction without studying a reaction directly if a sequence of reactions is known that can be added to give the desired reaction.

As an illustration, we will calculate the enthalpy of reaction for the transfer of a phosphoryl group from ATP to glucose, a very important physiological reaction catalyzed by the enzyme hexokinase.



The standard enthalpy changes for the hydrolysis of these four compounds are given in Table 1-1. These data are for very specific conditions: $T = 298 \text{ K}$, $P = 1 \text{ atm}$, $\text{pH} = 7.0$, $\text{pMg} = 3$, and an ionic strength of 0.25 M . The ionic strength is a measure of the salt concentration that takes into account the presence of both monovalent and divalent ions ($= \frac{1}{2} \sum c_i z_i^2$, where c_i is the concentration of each ion, z_i is its charge, and the sum is over all of the ions present). The enthalpy change for the hexokinase reaction can easily be calculated from these data:



The ability to calculate thermodynamic quantities for biochemical reactions that have not yet been studied is very useful. Even if data are not available to deal with the

TABLE 1-1. Standard Enthalpy Changes of Hydrolysis

Reaction	ΔH_{298}° (kJ/mol)
$\text{ATP} + \text{H}_2\text{O}(\ell) \rightleftharpoons \text{ADP} + P_i$	-30.9
$\text{ADP} + \text{H}_2\text{O}(\ell) \rightleftharpoons \text{AMP} + P_i$	-28.9
$\text{AMP} + \text{H}_2\text{O}(\ell) \rightleftharpoons \text{A} + P_i$	-1.2
$\text{G6P} + \text{H}_2\text{O}(\ell) \rightleftharpoons \text{G} + P_i$	-0.5

reaction of specific interest, very often data are available for closely related reactions. Appendix 5 contains a tabulation of ΔH_{298}° for some biochemical reactions.

The enthalpy change associated with the hexokinase reaction could also be derived from the heats of formation in the table in Appendix 4:

$$\begin{aligned}\Delta H &= H_{f,\text{ADP}}^{\circ} + H_{f,\text{G6P}}^{\circ} - H_{f,\text{ATP}}^{\circ} - H_{f,\text{G}}^{\circ} \\ \Delta H &= -2000.2 - 2279.1 + 2981.8 + 1267.1 = -30.4 \text{ kJ/mol}\end{aligned}$$

In point of fact, the heats of formation are usually derived from measured heats of reaction as these are the primary experimental data.

A source of potential confusion is the practice of reporting enthalpies of reaction as “per mole.” There is no ambiguity for the hexokinase reaction as written above. However, in many cases, the stoichiometric coefficients for reactants and products differ. For example, the reaction catalyzed by the enzyme myokinase is



Even though 2 moles of ADP are used, the reaction enthalpy is referred to as “per mole.” The reaction enthalpy is always given as “per mole of reaction as it is written.”

It is important, therefore, that the equation for the reaction under consideration be explicitly stated. The myokinase reaction could be written as



In this case, the reaction enthalpy per mole would be one-half of that reported for Eq. (1-34).

1.10 TEMPERATURE DEPENDENCE OF THE REACTION ENTHALPY

In principle, the enthalpy changes as the pressure and temperature change. We will not worry about the dependence of the enthalpy on pressure, as it is usually very small for reactions in condensed phases. The temperature dependence of the enthalpy is given by Eq. (1-27). This can be used directly to determine the temperature dependence of reaction enthalpies. If we assume the standard state enthalpy is known for each reactant, then the temperature dependence of the enthalpy for each reactant, i , is

$$H_{T,i} = H_{298,i}^{\circ} + \int_{298}^T C_{P,i} dT \quad (1-36)$$

If we apply this relationship to the reaction enthalpy for the generalized reaction of Eq. (1-25), we obtain the following:

$$\begin{aligned}\Delta H_T &= cH_{T,C} + dH_{T,D} - aH_{T,A} - bH_{T,B} \\ \Delta H_T &= \Delta H_{298}^{\circ} + \int_{298}^T \Delta C_P dT\end{aligned}$$

with

$$\Delta H_{298}^{\circ} = cH_{298,C}^{\circ} + dH_{298,D}^{\circ} - aH_{298,A}^{\circ} - bH_{298,B}^{\circ}$$

and

$$\Delta C_p = cC_{p,C} + dC_{p,D} - aC_{p,A} - bC_{p,B}$$

More generally,

$$\Delta H_T = \Delta H_{T_0} + \int_{T_0}^T \Delta C_p dT \quad (1-37)$$

Equation (1-37) is known as Kirchhoff's law. It can also be stated in differential form:

$$d\Delta H/dT = \Delta C_p \quad (1-38)$$

It is important to remember that this discussion of the temperature dependence of the reaction enthalpy assumes that the pressure is constant.

The conclusion of these considerations of reaction enthalpies is that available tabulations are often sufficient to calculate the reaction enthalpy of many biological reactions. Moreover, if this is carried out at a standard temperature, the reaction enthalpy at other temperatures can be calculated if appropriate information about the heat capacities is known or estimated. For most chemical reactions of biological interest, the temperature dependence of the reaction enthalpy is small. In contrast, for processes such as protein folding and unfolding, the temperature dependence is often significant and must be taken into account in data analysis and thermodynamic calculations. This will be discussed further in Chapter 3.

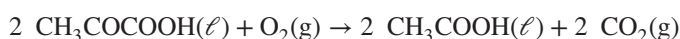
The first law of thermodynamics, namely, the definition of energy and its conservation, is obviously of great importance in understanding the nature of chemical reactions. As we shall see, however, the first law is not sufficient to understand what determines chemical equilibria.

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PROBLEMS

- 1-1.** When a gas expands rapidly through a valve, you often feel the valve get colder. This is an adiabatic expansion ($q = 0$). Calculate the decrease in temperature of 1.0 mol of ideal gas as it is expanded from 0.20 to 1.00 liters under the conditions given subsequently. Assume a constant volume molar heat capacity, C_V , of $\frac{3}{2}R$. Note that the energy, E , of an ideal gas depends only on the temperature: it is independent of the volume of the system.
- The expansion is irreversible with an external pressure of 1 atm and an initial temperature of 300 K.
 - The expansion is reversible with an initial temperature of 300 K.
 - Calculate ΔE for the changes in state described in parts A and B.
 - Assume that the expansion is carried out *isothermally* at 300 K, rather than adiabatically. Calculate the work done if the expansion is carried out irreversibly with an external pressure of 1.0 atm.
 - Calculate the work done if the isothermal expansion is carried out reversibly.
 - Calculate q and ΔE for the changes in state described in parts D and E.
- 1-2. a.** Calculate the enthalpy change for the conversion of glucose [$C_6H_{12}O_6(s)$] and oxygen [$O_2(g)$] to $CO_2(aq)$ and $H_2O(\ell)$ under standard conditions. The standard enthalpies of formation of glucose(s), $CO_2(aq)$, and $H_2O(\ell)$ are -304.3 , -98.7 , and -68.3 kcal/mol, respectively.
- b.** When organisms metabolize glucose, approximately 50% of the energy available is utilized for chemical and mechanical work. Assume that 25% of the total energy from eating 1 mole of glucose can be utilized to climb a mountain. How high a mountain can a 70 kg person climb?
- 1-3.** Calculate the enthalpy change for the oxidation of pyruvic acid to acetic acid under standard conditions.

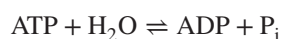


The heats of combustion of pyruvic acid and acetic acid under standard conditions are -279 kcal/mol and -207 kcal/mol, respectively. Heats of combustion are determined by reacting pyruvic or acetic acid with $O_2(g)$ to give $H_2O(\ell)$ and $CO_2(g)$. *Hint:* First write balanced chemical equations for the combustion processes.

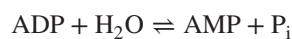
- 1-4.** Calculate the amount of water (in liters) that would have to be vaporized at 40°C (approximately body temperature) to expend the 2.5×10^6 calories of heat generated by a person in one day (commonly called sweating). The heat of vaporization of water at this temperature is 574 cal/g. We normally do not sweat that much. What is wrong with this calculation? If 1% of the energy produced as heat could be utilized as mechanical work, how large a weight could be lifted 1 meter?

1-5. a. One hundred milliliters of 0.200 M ATP is mixed with an ATPase in a Dewar at 298 K, 1 atm, pH 7.0, pMg 3.0, and 0.25 M ionic strength. The temperature of the solution increases 1.48 K. What is ΔH° for the hydrolysis of ATP to adenosine 5'-diphosphate (ADP) and phosphate? Assume that the heat capacity of the system is 418 J/K.

b. The hydrolysis reaction can be written as



Under the same conditions, the hydrolysis of ADP



has a heat of reaction, ΔH° , of -28.9 kJ/mol. Under the same conditions, calculate ΔH° for the adenylate kinase reaction:



1-6. The alcohol dehydrogenase reaction



removes ethanol from the blood. Use the enthalpies of formation in Appendix 4 to calculate ΔH° for this reaction. If 10.0 g of ethanol (a generous martini) is completely converted to acetaldehyde by this reaction, how much heat is produced or consumed?

