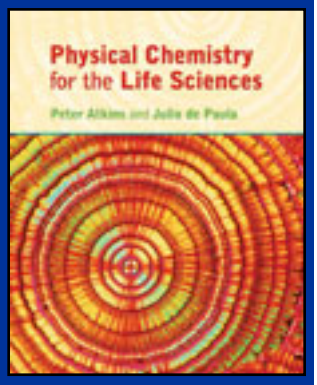

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Preface

The principal aim of this text is to ensure that it presents all the material required for a course in physical chemistry for students of the life sciences, including biology and biochemistry. To that end we have provided the foundations and biological applications of thermodynamics, kinetics, quantum theory, and molecular spectroscopy.

The text is characterized by a variety of pedagogical devices, most of them directed towards helping with the mathematics that must remain an intrinsic part of physical chemistry. One such device is what we have come to think of as a "bubble". A bubble is a little flag on an equals sign to show how to go from the left of the sign to the right—as we explain in more detail in "About the book" that follows. Where a bubble has insufficient capacity to provide the appropriate level of help, we include a Comment on the margin of the page to explain the mathematical procedure we have adopted.

Another device that we have invoked is the Note on good practice. We consider that physical chemistry is kept as simple as possible when people use terms accurately and consistently. Our Notes emphasize how a particular term should and should not be used (by and large, according to IUPAC conventions). Finally, background information from mathematics, physics, and introductory chemistry is reviewed in the Appendices at the end of the book.

Elements of biology and biochemistry are incorporated into the text's narrative in a number of ways. First, each numbered section begins with a statement that places the concepts of physical chemistry about to be explored in the context of their importance to biology. Second, the narrative itself shows students how physical chemistry gives quantitative insight into biology and biochemistry. To achieve this goal, we make generous use of illustrations (by which we mean quick numerical exercises) and worked examples, which feature more complex calculations than do the illustrations. Third, a unique feature of the text is the use of Case studies to develop more fully the application of physical chemistry to a specific biological or biomedical problem, such as the action of ATP, pharmacokinetics, the unique role of carbon in biochemistry, and the biochemistry of nitric oxide. Finally, in The biochemist's toolbox sections, we highlight selected experimental techniques in modern biochemistry and biomedicine, such as differential scanning calorimetry, gel electrophoresis, fluorescence resonance energy transfer, and magnetic resonance imaging.

A text cannot be written by authors in a vacuum. To merge the languages of phys ical chemistry and biochemistry we relied on a great deal of extraordinarily useful and insightful advice from a wide range of people. We would particularly like to acknowledge the following people who reviewed draft chapters of the text:
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Walkthrough Preface

There are numerous features in this text that are designed to help you learn physical chemistry and its applications to biology, biochemistry, and medicine. One of the problems that makes the subject so daunting is the sheer amount of information. To help with that problem, we have introduced several devices for organizing the material: see Organizing the information. We appreciate that mathematics is often troublesome, and therefore have included several devices for helping you with this enormously important aspect of physical chemistry: see Mathematics support. Problem solvingCespecially, "where do I start?"Cis often a problem, and we have done our best to help you find your way over the first hurdle: see Problem solving. Finally, the web is an extraordinary resource, but you need to know where to go for a particular piece of information; we have tried to point you in the right direction: see Using the Web. The following paragraphs explain the features in more detail.

Organizing the information

Checklist of key ideas. Here we collect together the major concepts that we have introduced in the chapter. You might like to check off the box that precedes each entry when you feel that you are confident about the topic.

Case studies. We incorporate general concepts of biology and biochemistry throughout the text, but in some cases it is useful to focus on a specific problem in some detail. Each Case study contains some background information about a biological process, such as the action of adenosine triphosphate or the metabolism of drugs, followed by a series of calculations that give quantitative insight into the phenomena.

The biochemist's toolbox. A Toolbox contains descriptions of some of the modern techniques of biology, biochemistry, and medicine. In many cases, you will use these techniques in laboratory courses, so we focus not on the operation of instruments but on the physical principles that make the instruments performed a specific task.

Notes on good practice. Science is a precise activity, and using its language accurately can help you to understand the concepts. We have used this feature to help you to use the language and procedures of science in conformity to international practice and to avoid common mistakes.

Derivations. On first reading you might need the "bottom line" rather than a detailed derivation. However, once you have collected your thoughts, you might want to go back to see how a particular expression was obtained. The Derivations let you adjust the level of detail that you require to your current needs. However, don=t forget that **the derivation of results is an essential part of physical chemistry, and should not be ignored.

Further information. In some cases, we have judged that a derivation is too long, too detailed, or too different in level for it to be included in the text. In these cases, you will find the derivation at the end of the chapter.

Appendices. Physical chemistry draws on a lot of background material, especially in mathematics and physics. We have included a set Appendices to provide a quick survey of some of the information that we draw on in the text.

Mathematics support

Bubbles. You often need to know how to develop a mathematical expression, but how do you go from one line to the next? A "bubble" is a little reminder about the approximation that has been used, the terms that have been taken to be constant, the substitution of an expression, and so on.

Comments. We often need to draw on a mathematical procedure or concept of physics; a Comment is a quick reminder of the procedure or concept. Don=t forget Appendices 2 and 3 (referred to above) where some of these Comments are discussed at greater length.

Problem solving

Illustrations. An Illustration (don=t confuse this with a diagram!) is a short example of how to use an equation that has just been introduced in the text. In particular, we show how to use data and how to manipulate units correctly.

Worked examples. A Worked Example is a much more structured form of Illustration, often involving a more elaborate procedure. Every Worked Example has a Strategy section to suggest how you might set up the problem (you might prefer another way: setting up problems is a highly personal business). Then there is the worked-out Answer.

Self-tests. Every Worked Example and Illustration has a Self-test, with the answer provided, so that you can check whether you have understood the procedure. There are also free-standing Self-tests where we thought it a good idea to provide a question for you to check your understanding. Think of Self-tests as in-chapter Exercises designed to help you to monitor your progress.

Discussion questions. The end-of-chapter material starts with a short set of questions that are intended to encourage you to think about the material you have encountered and to view it in a broader context than is obtained by solving numerical problems.

Exercises. The real core of testing your progress is the collection of end-of-chapter Exercises. We have provided a wide variety at a range of levels.

Projects. Longer and more involved exercises are presented as Projects at the end of each chapter. In many cases, the projects encourage you to make connections between concepts discussed in more than one chapter, either by performing calculations or by pointing you to the original literature.

Web support

You will find a lot of additional material at **www.whfreeman.compchemls**

Living graphs. A Living Graph is indicated in the text by the icon [] attached to a graph. If you go to the web site, you will be able to explore how a property changes as you change a variety of parameters.

Weblinks. There is a huge network of information available about physical chemistry, and it can be bewildering to find your way to it. Also, you often need a piece of information that we have not included in the text. You should go to our web site to find the data you require, or at least to receive information about where additional data can be found.

Artwork. Your instructor may wish to use the illustrations from this text in a lecture. Almost all the illustrations are available in full color and can be used for lectures without charge (but not for commercial purposes without specific permission).

Prologue

Chemistry is the science of matter and the changes it can undergo. **Physical chemistry** is the branch of chemistry that establishes and develops the principles of the subject in terms of the underlying concepts of physics and the language of mathematics. Its concepts are used to explain and interpret observations on the physical and chemical properties of matter.

This text develops the principles of physical chemistry and their applications to the study of the life sciences, particularly biochemistry and medicine. The resulting combination of the concepts of physics, chemistry, and biology into an intricate mosaic leads to a unique and exciting understanding of the processes responsible for life.

The structure of physical chemistry

Applications of physical chemistry to biology and medicine

(a) Techniques for the study of biological systems

(b) Protein folding

(c) Rational drug design

(d) Biological energy conversion

The structure of physical chemistry

Like all scientists, physical chemists build descriptions of nature on a foundation of careful and systematic inquiry. The observations that physical chemistry organizes and explains are summarized by scientific laws. A **law** is a summary of experience. Thus, we encounter the *laws of thermodynamics*, which are summaries of observations on the transformations of energy. Laws are often expressed mathematically, as in the *perfect gas law* (or *ideal gas law;* see Section F.7):

Perfect gas law: $pV = nRT$

This law is an approximate description of the physical properties of gases (with p the pressure, V the volume, n the amount, R a universal constant, and T the temperature). We also encounter the *laws of quantum mechanics*, which summarize observations on the behavior of individual particles, such as molecules, atoms, and subatomic particles.

The first step in accounting for a law is to propose a **hypothesis**, which is essentially a guess at an explanation of the law in terms of more fundamental concepts. Dalton's *atomic hypothesis*, which was proposed to account for the laws of chemical composition and changes accompanying reactions, is an example. When a hypothesis has become established, perhaps as a result of the success of further experiments it has inspired or by a more elaborate formulation (often in terms of mathematics) that puts it into the context of broader aspects of science, it is promoted to the status of a **theory**. Among the theories we encounter are the theories of *chemical equilibrium*, *atomic structure*, and the *rates of reactions*.

A characteristic of physical chemistry, like other branches of science, is that to develop theories, it adopts models of the system it is seeking to describe. A **model** is a simplified version of the system that focuses on the essentials of the problem. Once a successful model has been constructed and tested against known observations and any experiments the model inspires, it can be made more sophisticated

and incorporate some of the complications that the original model ignored. Thus, models provide the initial framework for discussions, and reality is progressively captured rather like a building is completed, decorated, and furnished. One example is the *nuclear model* of an atom, and in particular a hydrogen atom, which is used as a basis for the discussion of the structures of all atoms. In the initial model, the interactions between electrons are ignored; to elaborate the model, repulsions between the electrons are taken into account progressively more accurately.

The text begins with an investigation of **thermodynamics**, the study of the transformations of energy and the relations between the bulk properties of matter. Thermodynamics is summarized by a number of laws that allow us to account for the natural direction of physical and chemical change. Its principal relevance to biology is its application to the study of the deployment of energy by organisms.

We then turn to **chemical kinetics**, the study of the rates of chemical reactions. To understand the molecular mechanism of change, we need to understand how molecules move, either in free flight in gases or by diffusion through liquids. Then we shall establish how the rates of reactions can be determined and how experimental data give insight into the molecular processes by which chemical reactions occur. Chemical kinetics is a crucial aspect of the study of organisms because the array of reactions that contribute to life form an intricate network of processes occurring at different rates under the control of enzymes.

Next, we develop the principles of **quantum theory** and use them to describe the structures of atoms and molecules, including the macromolecules found in biological cells. Quantum theory is important to the life sciences because the structures of its complex molecules and the migration of electrons cannot be understood except in its terms. Once the properties of molecules are known, a bridge can be built to the properties of bulk systems treated by thermodynamics: the bridge is provided by **statistical thermodynamics**. This important topic provides techniques for calculating bulk properties, and in particular equilibrium constants, from molecular data.

Finally, we explore the information about biological structure and function that can be obtained from **spectroscopy**, the study of interactions between molecules and electromagnetic radiation.

Applications of physical chemistry to biology and medicine

Here we discuss some of the important problems in biology and medicine being tackled with the tools of physical chemistry. We shall see that physical chemists contribute importantly not only to fundamental questions, such as the unraveling of intricate relationships between the structure of a biological molecule and its function, but also to the application of biochemistry to new technologies.

(a) Techniques for the study of biological systems

Many of the techniques now employed by biochemists were first conceived by physicists and then developed by physical chemists for studies of small molecules and chemical reactions before they were applied to the investigation of complex biological systems. Here we mention a few examples of physical techniques that are used routinely for the analysis of the structure and function of biological molecules.

X-ray diffraction and **nuclear magnetic resonance (NMR) spectroscopy** are two very important tools commonly used for the determination of the three-

dimensional arrangement of atoms in biological assemblies. An example of the power of the X-ray diffraction technique is the recent determination of the three-dimensional structure of the ribosome, a complex of protein and ribonucleic acid with a molar mass exceeding 2×10^6 g mol^{-1} that is responsible for the synthesis of proteins from individual amino acids in the cell. Nuclear magnetic resonance spectroscopy has also advanced steadily through the years and now entire organisms may be studied through **magnetic resonance imaging** (MRI), a technique used widely in the diagnosis of disease. Throughout the text we shall describe many tools for the structural characterization of biological molecules.

Advances in biotechnology are also linked strongly to the development of physical techniques. The ongoing effort to characterize the entire genetic material, or **genome**, of organisms as simple as bacteria and as complex as *Homo sapiens* will lead to important new insights into the molecular mechanisms of disease, primarily through the discovery of previously unknown proteins encoded by the deoxyribonucleic acid (DNA) in genes. However, decoding genomic DNA will not always lead to accurate predictions of the amino acids present in biologically active proteins. Many proteins undergo chemical modification, such as cleavage into smaller proteins, after being synthesized in the ribosome. Moreover, it is known that one piece of DNA may encode more than one active protein. It follows that it is also important to describe the **proteome**, the full complement of functional proteins of an organism, by characterizing directly the proteins after they have been synthesized and processed in the cell.

The procedures of **genomics** and **proteomics**, the analysis of the genome and proteome, of complex organisms are time-consuming because of the very large number of molecules that must be characterized. For example, the human genome contains about 30 000 genes and the number of active proteins is likely to be much larger. Success in the characterization of the genome and proteome of any organism will depend on the deployment of very rapid techniques for the determination of the order in which molecular building blocks are linked covalently in DNA and proteins. An important tool is **gel electrophoresis**, in which molecules are separated on a gel slab in the presence of an applied electrical field. It is believed that **mass spectrometry**, a technique for the accurate determination of molecular masses, will be of great significance in proteomic analysis. We discuss the principles and applications of gel electrophoresis and mass spectrometry in Chapters 8 and 11, respectively.

(b) Protein folding

Proteins consist of flexible chains of amino acids. However, for a protein to function correctly, it must have a well-defined conformation. Though the amino acid sequence of a protein contains the necessary information to create the active conformation of the protein from a newly synthesized chain, the prediction of the conformation from the sequence, the so-called **protein folding problem**, is extraordinarily difficult and is still the focus of much research. Solving the problem of how a protein finds its functional conformation will also help us understand why some proteins fold improperly under certain circumstances. Misfolded proteins are thought to be involved in a number of diseases, such as cystic fibrosis, Alzheimer's disease, and "mad cow" disease (variant Creutzfeldt-Jakob disease, v-CJD).

To appreciate the complexity of the mechanism of protein folding, consider a small protein consisting of a single chain of 100 amino acids in a well-defined sequence. Statistical arguments lead to the conclusion that the polymer can exist in

about 10^{49} distinct conformations, with the correct conformation corresponding to a minimum in the energy of interaction between different parts of the chain and the energy of interaction between the chain and surrounding solvent molecules. In the absence of a mechanism that streamlines the search for the interactions in a properly folded chain, the correct conformation can be attained only by sampling every one of the possibilities. If we allow each conformation to be sampled for 10^{-20} s, a duration far shorter than that observed for the completion of even the fastest of chemical reactions, it could take more than 10^{21} years, which is much longer than the age of the Universe, for the proper fold to be found. However, it is known that proteins can fold into functional conformations in less than 1 s.

The preceding arguments form the basis for *Levinthal's paradox* and lead to a view of protein folding as a complex problem in thermodynamics and chemical kinetics: how does a protein minimize the energies of all possible molecular interactions with itself and its environment in such a relatively short period of time? It is no surprise that physical chemists are important contributors to the solution of the protein folding problem.

We discuss the details of protein folding in Chapters 8 and 12. For now, it is sufficient to outline the ways in which the tools of physical chemistry can be applied to the problem. Computational techniques that employ both classical and quantum theories of matter provide important insights into molecular interactions and can lead to reasonable predictions of the functional conformation of a protein. For example, in a **molecular mechanics** simulation, mathematical expressions from classical physics are used to determine the structure corresponding to the minimum in the energy of molecular interactions within the chain at the absolute zero of temperature. Such calculations are usually followed by **molecular dynamics** simulations, in which the molecule is set in motion by heating it to a specified temperature. The possible trajectories of all atoms under the influence of intermolecular interactions are then calculated by consideration of Newton's equations of motion. These trajectories correspond to the conformations that the molecule can sample at the temperature of the simulation. Calculations based on quantum theory are more difficult and time-consuming, but theoretical chemists are making progress toward merging classical and quantum views of protein folding.

As is usually the case in physical chemistry, theoretical studies inform experimental studies and vice versa. Many of the sophisticated experimental techniques in chemical kinetics to be discussed in Chapter 6 continue to yield details of the mechanism of protein folding. For example, the available data indicate that, in a number of proteins, a significant portion of the folding process occurs in less than 1 ms (10^{-3} s). Among the fastest events is the formation of helical and sheet-like structures from a fully unfolded chain. Slower events include the formation of contacts between helical segments in a large protein.

(c) Rational drug design

The search for molecules with unique biological activity represents a significant portion of the overall effort expended by pharmaceutical and academic laboratories to synthesize new drugs for the treatment of disease. One approach consists of extracting naturally occurring compounds from a large number of organisms and testing their medicinal properties. For example, the drug paclitaxel (sold under the tradename Taxol), a compound found in the bark of the Pacific yew tree, has been found to be effective in the treatment of ovarian cancer. An alternative approach to the discovery of drugs is **rational drug design**, which begins with the identifica-

tion of molecular characteristics of a disease causing agent—a microbe, a virus, or a tumor—and proceeds with the synthesis and testing of new compounds to react specifically with it. Scores of scientists are involved in rational drug design, as the successful identification of a powerful drug requires the combined efforts of microbiologists, biochemists, computational chemists, synthetic chemists, pharmacologists, and physicians.

Many of the targets of rational drug design are **enzymes**, proteins or nucleic acids that act as biological catalysts. The ideal target is either an enzyme of the host organism that is working abnormally as a result of the disease or an enzyme unique to the disease-causing agent and foreign to the host organism. Because enzyme-catalyzed reactions are prone to inhibition by molecules that interfere with the formation of product, the usual strategy is to design drugs that are specific inhibitors of specific target enzymes. For example, an important part of the treatment of acquired immune deficiency syndrome (AIDS) involves the steady administration of a specially designed protease inhibitor. The drug inhibits an enzyme that is key to the formation of the protein envelope surrounding the genetic material of the human immunodeficiency virus (HIV). Without a properly formed envelope, HIV cannot replicate in the host organism.

The concepts of physical chemistry play important roles in rational drug design. First, the techniques for structure determination described throughout the text are essential for the identification of structural features of drug candidates that will interact specifically with a chosen molecular target. Second, the principles of chemical kinetics discussed in Chapters 6 and 7 govern several key phenomena that must be optimized, such as the efficiency of enzyme inhibition and the rates of drug uptake by, distribution in, and release from the host organism. Finally, and perhaps most importantly, the computational techniques discussed in Chapter 10 are used extensively in the prediction of the structure and reactivity of drug molecules. In rational drug design, computational chemists are often asked to predict the structural features that lead to an efficient drug by considering the nature of a receptor site in the target. Then, synthetic chemists make the proposed molecules, which are in turn tested by biochemists and pharmacologists for efficiency. The process is often iterative, with experimental results feeding back into additional calculations, which in turn generate new proposals for efficient drugs, and so on. Computational chemists continue to work very closely with experimental chemists to develop better theoretical tools with improved predictive power.

(d) Biological energy conversion

The unraveling of the mechanisms by which energy flows through biological cells has occupied the minds of biologists, chemists, and physicists for many decades. As a result, we now have a very good molecular picture of the physical and chemical events of such complex processes as oxygenic photosynthesis and carbohydrate metabolism:

$$6\,CO_2(g) + 6\,H_2O(l) \underset{\text{Carbohydrate metabolism}}{\overset{\text{Oxygenic photosynthesis}}{\rightleftharpoons}} C_6H_{12}O_6(s) + 6\,O_2(g)$$

where $C_6H_{12}O_6$ denotes the carbohydrate glucose. In general terms, oxygenic photosynthesis uses solar energy to transfer electrons from water to carbon dioxide.

In the process, high-energy molecules (carbohydrates, such as glucose) are synthesized in the cell. Animals feed on the carbohydrates derived from photosynthesis. During carbohydrate metabolism, the O_2 released by photosynthesis as a waste product is used to oxidize carbohydrates to CO_2. This oxidation drives biological processes, such as biosynthesis, muscle contraction, cell division, and nerve conduction. Hence, the sustenance of much of life on Earth depends on a tightly regulated carbon-oxygen cycle that is driven by solar energy.

We delve into the details of photosynthesis and carbohydrate metabolism throughout the text. Before we do so, we consider the contributions that physical chemists have made to research in biological energy conversion.

The harvesting of solar energy during photosynthesis occurs very rapidly and efficiently. Within about 100–200 ps (1 ps = 10^{-12} s) of the initial light absorption event, more than 90% of the energy is trapped within the cell and is available to drive the electron transfer reactions that lead to the formation of carbohydrates and O_2. Sophisticated spectroscopic techniques pioneered by physical chemists for the study of chemical reactions are being used to track the fast events that follow the absorption of solar energy. The strategy, discussed in more detail in Chapter 13, involves the application of very short laser pulses to initiate the light-induced reactions and monitor the rise and decay of intermediates.

The electron transfer processes of photosynthesis and carbohydrate metabolism drive the flow of protons across the membranes of specialized cellular compartments. The *chemiosmotic theory*, discussed in Chapter 5, describes how the energy stored in a proton gradient across a membrane can be used to synthesize adenosine triphosphate (ATP), a mobile energy carrier. Intimate knowledge of thermodynamics and chemical kinetics is required to understand the details of the theory and the experiments that eventually verified it.

The structures of nearly all the proteins associated with photosynthesis and carbohydrate metabolism have been characterized by X-ray diffraction or NMR techniques. Together, the structural data and the mechanistic models afford a nearly complete description of the relationships between structure and function in biological energy conversion systems. The knowledge is now being used to design and synthesize molecular assemblies that can mimic oxygenic photosynthesis. The goal is to construct devices that trap solar energy in products of light-induced electron transfer reactions. One example is light-induced water splitting:

$$H_2O(l) \xrightarrow{\text{Light}} \tfrac{1}{2}\, O_2(g) + H_2(g)$$

The hydrogen gas produced in this manner can be used as a fuel in a variety of other devices. The preceding is an example of how a careful study of the physical chemistry of biological systems can yield surprising insights into new technologies.

Fundamentals

We begin by reviewing material fundamental to the whole of physical chemistry, but which should be familiar from introductory courses. Matter and energy will be the principal focus of our discussion.

F.1 The states of matter

The broadest classification of matter is into one of three **states of matter**, or forms of bulk matter, namely gas, liquid, and solid. Later we shall see how this classification can be refined, but these three broad classes are a good starting point.

We distinguish the three states of matter by noting the behavior of a substance enclosed in a rigid container:

A **gas** is a fluid form of matter that fills the container it occupies.

A **liquid** is a fluid form of matter that possesses a well-defined surface and (in a gravitational field) fills the lower part of the container it occupies.

A **solid** retains its shape regardless of the shape of the container it occupies.

One of the roles of physical chemistry is to establish the link between the properties of bulk matter and the behavior of the particles—atoms, ions, or molecules—of which it is composed. As we work through this text, we shall gradually establish and elaborate the following models for the states of matter:

A gas is composed of widely separated particles in continuous rapid, disordered motion. A particle travels several (often many) diameters before colliding with another particle. For most of the time the particles are so far apart that they interact with each other only very weakly.

A liquid consists of particles that are in contact but are able to move past one another in a restricted manner. The particles are in a continuous state of motion but travel only a fraction of a diameter before bumping into a neighbor. The overriding image is one of movement but with molecules jostling one another.

A solid consists of particles that are in contact and unable to move past one another. Although the particles oscillate around an average location, they are essentially trapped in their initial positions and typically lie in ordered arrays.

The main difference between the three states of matter is the freedom of the particles to move past one another. If the average separation of the particles is large, there is hardly any restriction on their motion, and the substance is a gas. If the particles interact so strongly with one another that they are locked together rigidly, then the substance is a solid. If the particles have an intermediate mobility between

these extremes, then the substance is a liquid. We can understand the melting of a solid and the vaporization of a liquid in terms of the progressive increase in the liberty of the particles as a sample is heated and the particles become able to move more freely.

F.2 Physical state

The term "state" has many different meanings in chemistry, and it is important to keep them all in mind. We have already met one meaning in the expression "the states of matter" and specifically "the gaseous state." Now we meet a second: by **physical state** (or just "state") we shall mean a specific condition of a sample of matter that is described in terms of its physical form (gas, liquid, or solid) and the volume, pressure, temperature, and amount of substance present. (The precise meanings of these terms are described below.) So, 1 kg of hydrogen gas in a container of volume 10 L (where 1 L = 1 dm^3) at a specified pressure and temperature is in a particular state. The same mass of gas in a container of volume 5 L is in a different state. Two samples of a given substance are in the same state if they are the same state of matter (that is, are both present as gas, liquid, or solid) *and* if they have the same mass, volume, pressure, and temperature.

To see more precisely what is involved in specifying the state of a substance, we need to define the terms we have used. The **mass**, m, of a sample is a measure of the quantity of matter it contains. Thus, 2 kg of lead contains twice as much matter as 1 kg of lead and indeed twice as much matter as 1 kg of anything. The *Système International* (SI) unit of mass is the kilogram (kg), with 1 kg currently defined as the mass of a certain block of platinum-iridium alloy preserved at Sèvres, outside Paris. For typical laboratory-sized samples it is usually more convenient to use a smaller unit and to express mass in grams (g), where 1 kg = 10^3 g.

COMMENT F.1 *Appendix 1* and the text's web site contain additional information about the international system of units. ■

The **volume**, V, of a sample is the amount of space it occupies. Thus, we write V = 100 cm^3 if the sample occupies 100 cm^3 of space. The units used to express volume (which include cubic meters, m^3; cubic decimeters, dm^3, or liters, L; milliliters, mL), and units and symbols in general, are reviewed in *Appendix 1*.

Pressure and temperature need more introduction, for even though they may be familiar from everyday life, they need to be defined carefully for use in science.

F.3 Force

One of the most basic concepts of physical science is that of *force*. In classical mechanics, the mechanics originally formulated by Isaac Newton at the end of the seventeenth century, a body of mass m travels in a straight line at constant speed until a force acts on it. Then it undergoes an acceleration, a rate of change of velocity, given by Newton's second law of motion:

$$\textit{Force} = \textit{mass} \times \textit{acceleration} \qquad F = ma$$

The acceleration of a freely falling body at the surface of the Earth is 9.81 m s^{-2}, so the gravitational force acting on a mass of 1.0 kg is

$$F = (1.0\ \text{kg}) \times (9.81\ \text{m s}^{-2}) = 9.8\ \text{kg m s}^{-2} = 9.8\ \text{N}$$

The derived unit of force is the newton, N:

$$1\ \text{N} = 1\ \text{kg m s}^{-2}$$

Therefore, we can report the force we have just calculated as 9.8 N. It might be helpful to note that a force of 1 N is approximately the gravitational force exerted on a small apple (of mass 100 g).

Force is a directed quantity, in the sense that it has direction as well as magnitude. For a body on the surface of the Earth, the force of gravitational attraction is directed toward the center of the Earth.

When an object is moved through a distance s against an opposing force, we say that **work** is done. The magnitude of the work (we worry about signs later) is the product of the distance moved and the opposing force:

$$\textit{Work} = \textit{force} \times \textit{distance}$$

Therefore, to raise a body of mass 1.0 kg on the surface of the Earth through a vertical distance of 1.0 m requires us to expend the following amount of work:

$$\textit{Work} = (9.8\ \text{N}) \times (1.0\ \text{m}) = 9.8\ \text{N m}$$

As we shall see more formally in a moment, the unit 1 N m (or, in terms of base units, 1 kg $\text{m}^2\ \text{s}^{-2}$) is called 1 joule (1 J). So, 9.8 J is needed to raise a mass of 1.0 kg through 1.0 m on the surface of the Earth.

F.4 Energy

A property that will occur in just about every chapter of the following text is the *energy*, E. Everyone uses the term "energy" in everyday language, but in science it has a precise meaning, a meaning that we shall draw on throughout the text. **Energy** is the capacity to do work. A fully wound spring can do more work than a half-wound spring (that is, it can raise a weight through a greater height or move a greater weight through a given height). A hot object has the potential for doing more work than the same object when it is cool and therefore has a higher energy.

The SI unit of energy is the joule (J), named after the nineteenth-century scientist James Joule, who helped to establish the concept of energy (see Chapter 1). It is defined as

$$1\ \text{J} = 1\ \text{kg m}^2\ \text{s}^{-2}$$

A joule is quite a small unit, and in chemistry we often deal with energies of the order of kilojoules ($1\ \text{kJ} = 10^3\ \text{J}$).

There are two contributions to the total energy of a collection of particles. The **kinetic energy,** E_K, is the energy of a body due to its motion. For a body of mass m moving at a speed v,

$$E_\text{K} = \tfrac{1}{2}mv^2 \qquad \textbf{(F.1)}$$

That is, a heavy object moving at the same speed as a light object has a higher kinetic energy, and doubling the speed of any object increases its kinetic energy by a factor of 4. A ball of mass 1 kg traveling at 1 m s^{-1} has a kinetic energy of 0.5 J.

The **potential energy**, E_P, of a body is the energy it possesses due to its position. The precise dependence on position depends on the type of force acting on the body. For a body of mass m on the surface of the Earth, the potential energy depends on its height, h, above the surface as

$$E_\text{P} = mgh \qquad \textbf{(F.2)}$$

where g is a constant known as the **acceleration of free fall**, which is close to 9.81 m s^{-2} at sea level. Thus, doubling the height of an object above the ground doubles its potential energy. Equation F.2 is based on the convention of taking the potential energy to be zero at sea level. A ball of mass 1.0 kg at 1.0 m above the surface of the Earth has a potential energy of 9.8 J. Another type of potential energy is that of one electric charge in the vicinity of another electric charge: we specify and use this hugely important "Coulombic" potential energy in Chapter 5. As we shall see as the text develops, most contributions to the potential energy that we need to consider in chemistry are due to this Coulombic interaction.

The **total energy**, E, of a body is the sum of its kinetic and potential energies:

$$E = E_K + E_P \qquad \textbf{(F.3)}$$

Provided no external forces are acting on the body, its total energy is constant. This remark is elevated to a central statement of classical physics known as the **law of the conservation of energy**. Potential and kinetic energy may be freely interchanged: for instance, a falling ball loses potential energy but gains kinetic energy as it accelerates, but its total energy remains constant provided the body is isolated from external influences.

F.5 Pressure

Pressure, p, is force, F, divided by the area, A, on which the force is exerted:

$$\textit{Pressure} = \frac{\textit{force}}{\textit{area}} \qquad p = \frac{F}{A} \qquad \textbf{(F.4)}$$

When you stand on ice, you generate a pressure on the ice as a result of the gravitational force acting on your mass and pulling you toward the center of the Earth. However, the pressure is low because the downward force of your body is spread over the area equal to that of the soles of your shoes. When you stand on skates, the area of the blades in contact with the ice is much smaller, so although your downward *force* is the same, the *pressure* you exert is much greater (Fig. F.1).

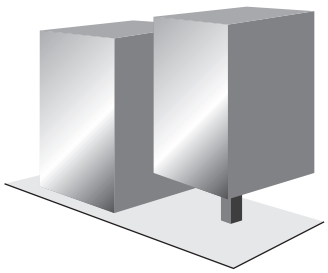


Fig. F.1 These two blocks of matter have the same mass. They exert the same force on the surface on which they are standing, but the block on the right exerts a stronger pressure because it exerts the same force over a smaller area than the block on the left.

Pressure can arise in ways other than from the gravitational pull of the Earth on an object. For example, the impact of gas molecules on a surface gives rise to a force and hence to a pressure. If an object is immersed in the gas, it experiences a pressure over its entire surface because molecules collide with it from all directions. In this way, the atmosphere exerts a pressure on all the objects in it. We are incessantly battered by molecules of gas in the atmosphere and experience this battering as the "atmospheric pressure." The pressure is greatest at sea level because the density of air, and hence the number of colliding molecules, is greatest there. The atmospheric pressure is very considerable: it is the same as would be exerted by loading 1 kg of lead (or any other material) onto a surface of area 1 cm^2. We go through our lives under this heavy burden pressing on every square centimeter of our bodies. Some deep-sea creatures are built to withstand even greater pressures: at 1000 m below sea level the pressure is 100 times greater than at the surface. Creatures and submarines that operate at these depths must withstand the equivalent of 100 kg of lead loaded onto each square centimeter of their surfaces. The pressure of the air in our lungs helps us withstand the relatively low but still substantial pressures that we experience close to sea level.

When a gas is confined to a cylinder fitted with a movable piston, the position of the piston adjusts until the pressure of the gas inside the cylinder is equal

to that exerted by the atmosphere. When the pressures on either side of the piston are the same, we say that the two regions on either side are in **mechanical equilibrium**. The pressure of the confined gas arises from the impact of the particles: they batter the inside surface of the piston and counter the battering of the molecules in the atmosphere that is pressing on the outside surface of the piston (Fig. F.2). Provided the piston is weightless (that is, provided we can neglect any gravitational pull on it), the gas is in mechanical equilibrium with the atmosphere whatever the orientation of the piston and cylinder, because the external battering is the same in all directions.

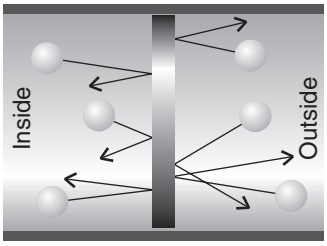


Fig. F.2 A system is in mechanical equilibrium with its surroundings if it is separated from them by a movable wall and the external pressure is equal to the pressure of the gas in the system.

The SI unit of pressure is the pascal, Pa:

$$1\ \text{Pa} = 1\ \text{kg m}^{-1}\ \text{s}^{-2}$$

The pressure of the atmosphere at sea level is about 10^5 Pa (100 kPa). This fact lets us imagine the magnitude of 1 Pa, for we have just seen that 1 kg of lead resting on 1 cm^2 on the surface of the Earth exerts about the same pressure as the atmosphere; so $1/10^5$ of that mass, or 0.01 g, will exert about 1 Pa, we see that the pascal is rather a small unit of pressure. Table F.1 lists the other units commonly used to report pressure.[1] One of the most important in modern physical chemistry is the bar, where 1 bar = 10^5 Pa exactly. Normal atmospheric pressure is close to 1 bar.

EXAMPLE F.1 Converting between units

A scientist was exploring the effect of atmospheric pressure on the rate of growth of a lichen and measured a pressure of 1.115 bar. What is the pressure in atmospheres?

Strategy Write the relation between the "old units" (the units to be replaced) and the "new units" (the units required) in the form

1 old unit = x new units

then replace the "old unit" everywhere it occurs by "x new units" and multiply out the numerical expression.

Solution From Table F.1 we have

1.013 25 bar = 1 atm

[1]See *Appendix 1* for a fuller description of the units.

Table F.1 Pressure units and conversion factors*

pascal, Pa	1 Pa = 1 N m^{-2}
bar	1 bar = 10^5 Pa
atmosphere, atm	1 atm = **101.325** kPa = **1.013 25** bar
torr, Torr†	**760** Torr = 1 atm
	1 Torr = 133.32 Pa

*Values in bold are exact.

†The name of the unit is torr; its symbol is Torr.

with atm the "new unit" and bar the "old unit." As a first step we write

$$1 \text{ bar} = \frac{1}{1.013\ 25} \text{ atm}$$

Then we replace bar wherever it appears by (1/1.013 25) atm:

$$p = 1.115 \text{ bar} = 1.115 \left(\frac{1}{1.013\ 25} \text{ atm} \right) = 1.100 \text{ atm}$$

A note on good practice: The number of significant figures in the answer (4) is the same as the number of significant figures in the data; the relation between old and new units in this case is exact.

SELF-TEST F.1 The pressure in the eye of a hurricane was recorded as 723 Torr. What is the pressure in kilopascals?

Answer: 96.4 kPa ■

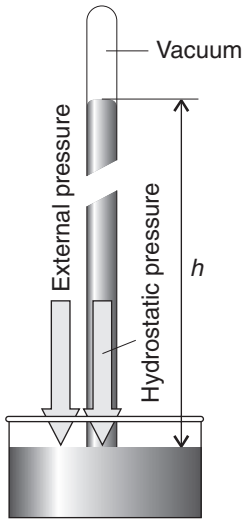


Fig. F.3 The operation of a mercury barometer. The space above the mercury in the vertical tube is a vacuum, so no pressure is exerted on the top of the mercury column; however, the atmosphere exerts a pressure on the mercury in the reservoir and pushes the column up the tube until the pressure exerted by the mercury column is equal to that exerted by the atmosphere. The height, h, reached by the column is proportional to the external pressure, so the height can be used as a measure of this pressure.

Atmospheric pressure (a property that varies with altitude and the weather) is measured with a **barometer**, which was invented by Torricelli, a student of Galileo's. A mercury barometer consists of an inverted tube of mercury that is sealed at its upper end and stands with its lower end in a bath of mercury. The mercury falls until the pressure it exerts at its base is equal to the atmospheric pressure (Fig. F.3). We can calculate the atmospheric pressure p by measuring the height h of the mercury column and using the relation (see *Derivation* F.1)

$$p = \rho g h \qquad \textbf{(F.5)}$$

where ρ (rho) is the mass density (commonly just "density"), the mass of a sample divided by the volume it occupies:

$$\rho = \frac{m}{V} \qquad \textbf{(F.6)}$$

With the mass measured in kilograms and the volume in meters cubed, density is reported in kilograms per cubic meter (kg m^{-3}); however, it is equally acceptable and often more convenient to report mass density in grams per cubic centimeter (g cm^{-3}) or grams per milliliter (g mL^{-1}). The relation between these units is

$$1 \text{ g cm}^{-3} = 1 \text{ g mL}^{-1} = 10^3 \text{ kg m}^{-3}$$

Thus, the density of mercury may be reported as either 13.6 g cm^{-3} (which is equivalent to 13.6 g mL^{-1}) or as 1.36×10^4 kg m^{-3}.

DERIVATION F.1 Hydrostatic pressure

The strategy of the calculation is to relate the mass of the column to its height, to calculate the downward force exerted by that mass, and then to divide the force by the area over which it is exerted. Consider Fig. F.4. The volume of a cylinder of liquid of height h and cross-sectional area A is hA. The mass, m, of this cylinder of liquid is the volume multiplied by the density, ρ, of the liquid, or $m = \rho \times hA$. The downward force exerted by this mass is mg, where g is the acceleration of free fall, a measure of the Earth's gravitational pull on an object.

Therefore, the force exerted by the column is $\rho \times hA \times g$. This force acts over the area A at the foot of the column, so according to eqn F.4, the pressure at the base is ρhAg divided by A, which is eqn F.5.

ILLUSTRATION F.1 Calculating a hydrostatic pressure

The pressure at the foot of a column of mercury of height 760 mm (0.760 m) and density 13.6 g cm^{-3} (1.36×10^4 kg m^{-3}) is

$$p = (9.81 \text{ m s}^{-2}) \times (1.36 \times 10^4 \text{ kg m}^{-3}) \times (0.760 \text{ m})$$
$$= 1.01 \times 10^5 \text{ kg m}^{-1} \text{ s}^{-2} = 1.01 \times 10^5 \text{ Pa}$$

This pressure corresponds to 101 kPa (1.00 atm).

A note on good practice: Write units at *every* stage of a calculation and do not simply attach them to a final numerical value. Also, it is often sensible to express all numerical quantities in terms of base units when carrying out a calculation. ■

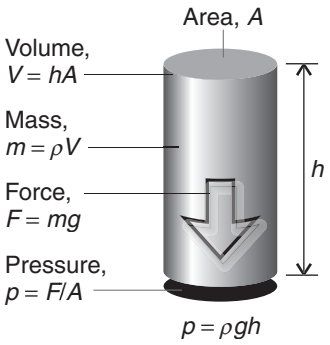


Fig. F.4 The calculation of the hydrostatic pressure exerted by a column of height h and cross-sectional area A.

F.6 Temperature

In everyday terms, the temperature is an indication of how "hot" or "cold" a body is. In science, **temperature**, T, is the property of an object that determines in which direction energy will flow when it is in contact with another object: energy flows from higher temperature to lower temperature. When the two bodies have the same temperature, there is no net flow of energy between them. In that case we say that the bodies are in **thermal equilibrium** (Fig. F.5).

Temperature in science is measured on either the Celsius scale or the Kelvin scale. On the **Celsius scale**, in which the temperature is expressed in degrees Celsius (°C), the freezing point of water at 1 atm corresponds to 0°C and the boiling point at 1 atm corresponds to 100°C. This scale is in widespread everyday use. Temperatures on the Celsius scale are denoted by the Greek letter θ (theta) throughout this text. However, it turns out to be much more convenient in many scientific applications to adopt the **Kelvin scale** and to express the temperature in kelvin (K; note that the degree sign is not used for this unit). *Whenever we use T to denote a temperature, we mean a temperature on the Kelvin scale*. The Celsius and Kelvin scales are related by

$$T \text{ (in kelvins)} = \theta \text{ (in degrees Celsius)} + 273.15$$

That is, to obtain the temperature in kelvins, add 273.15 to the temperature in degrees Celsius. Thus, water at 1 atm freezes at 273 K and boils at 373 K; a warm day (25°C) corresponds to 298 K.

A more sophisticated way of expressing the relation between T and θ, and one that we shall use in other contexts, is to regard the value of T as the product of a number (such as 298) and a unit (K), so that T/K (that is, the temperature divided by K) is a pure number. For example, if $T = 298$ K, then $T/\text{K} = 298$. Likewise, $\theta/°\text{C}$ is a pure number. For example, if $\theta = 25°\text{C}$, then $\theta/°\text{C} = 25$. With this convention, we can write the relation between the two scales as

$$T/\text{K} = \theta/°\text{C} + 273.15 \qquad \textbf{(F.7)}$$

This expression is a relation between pure numbers.

COMMENT F.2 Equation F.7, in the form $\theta/°\text{C} = T/\text{K} - 273.15$, also *defines* the Celsius scale in terms of the more fundamental Kelvin scale. ■

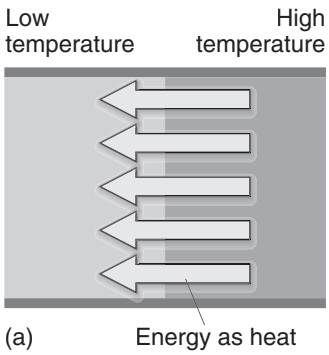


Fig. F.5 The temperatures of two objects act as a signpost showing the direction in which energy will flow as heat through a thermally conducting wall: (a) heat always flows from high temperature to low temperature. (b) When the two objects have the same temperature, although there is still energy transfer in both directions, there is no net flow of energy.

COMMENT F.3 As reviewed in *Appendix 4*, chemical amounts, n, are expressed in moles of specified entities. *Avogadro's constant*, $N_A = 6.022\ 141\ 99 \times 10^{23}\ \text{mol}^{-1}$, is the number of particles (of any kind) per mole of substance. ■

SELF-TEST F.2 Use eqn F.7 to express body temperature, 37°C, in kelvins.

Answer: 310 K

The **absolute zero** of temperature is the temperature below which it is impossible to cool an object. The Kelvin scale ascribes the value $T = 0$ to this absolute zero of temperature. Note that we refer to absolute zero as $T = 0$, not $T = 0$ K. There are other "absolute" scales of temperature, all of which set their lowest value at zero. Insofar as it is possible, all expressions in science should be independent of the units being employed, and in this case the lowest attainable temperature is $T = 0$ regardless of the absolute scale we are using.

F.7 Equations of state

We have already remarked that the state of any sample of substance can be specified by giving the values of the following properties:

V, the volume the sample occupies
p, the pressure of the sample
T, the temperature of the sample
n, the amount of substance in the sample

However, an astonishing experimental fact is that *these four quantities are not independent of one another*. For instance, we cannot arbitrarily choose to have a sample of 0.555 mol H_2O in a volume of 100 cm^3 at 100 kPa and 500 K: it is found *experimentally* that that state simply does not exist. If we select the amount, the volume, and the temperature, then we find that we have to accept a particular pressure (in this case, close to 230 kPa). The same is true of all substances, but the pressure in general will be different for each one. This experimental generalization is summarized by saying the substance obeys an **equation of state**, an equation of the form

$$p = f(n,V,T) \qquad \textbf{(F.8)}$$

This expression tells us that the pressure is some function of amount, volume, and temperature and that if we know those three variables, then the pressure can have only one value.

The equations of state of most substances are not known, so in general we cannot write down an explicit expression for the pressure in terms of the other variables. However, certain equations of state are known. In particular, the equation of state of a low-pressure gas is known and proves to be very simple and very useful. This equation is used to describe the behavior of gases taking part in reactions, the behavior of the atmosphere, as a starting point for problems in chemical engineering, and even in the description of the structures of stars.

We now pay some attention to gases because they are the simplest form of matter and give insight, in a reasonably uncomplicated way, into the time scale of events on a molecular scale. They are also the foundation of the equations of thermodynamics that we start to describe in Chapter 1, and much of the discussion of energy conversion in biological systems calls on the properties of gases.

The equation of state of a low-pressure gas was among the first results to be established in physical chemistry. The original experiments were carried out by

Table F.2 The gas constant in various units

$R =$	8.314 47	J K^{-1} mol^{-1}
	8.314 47	L kPa K^{-1} mol^{-1}
	$8.205\ 74 \times 10^{-2}$	L atm K^{-1} mol^{-1}
	62.364	L Torr K^{-1} mol^{-1}
	1.987 21	cal K^{-1} mol^{-1}

Robert Boyle in the seventeenth century, and there was a resurgence in interest later in the century when people began to fly in balloons. This technological progress demanded more knowledge about the response of gases to changes of pressure and temperature and, like technological advances in other fields today, that interest stimulated a lot of experiments.

The experiments of Boyle and his successors led to the formulation of the following **perfect gas equation of state**:

$$pV = nRT \qquad \textbf{(F.9)}$$

In this equation (which has the form of eqn F.8 when we rearrange it into $p = nRT/V$), the **gas constant**, R, is an experimentally determined quantity that turns out to have the same value for all gases. It may be determined by evaluating $R = pV/nRT$ as the pressure is allowed to approach zero or by measuring the speed of sound (which depends on R). Values of R in different units are given in Table F.2. In SI units the gas constant has the value

$$R = 8.314\ 47\ \text{J K}^{-1}\ \text{mol}^{-1}$$

The perfect gas equation of state—more briefly, the "perfect gas law"—is so called because it is an idealization of the equations of state that gases actually obey. Specifically, it is found that all gases obey the equation ever more closely as the pressure is reduced toward zero. That is, eqn F.9 is an example of a **limiting law**, a law that becomes increasingly valid as the pressure is reduced and is obeyed exactly at the limit of zero pressure.

A hypothetical substance that obeys eqn F.9 at *all* pressures is called a **perfect gas**.[2] From what has just been said, an actual gas, which is termed a **real gas**, behaves more and more like a perfect gas as its pressure is reduced toward zero. In practice, normal atmospheric pressure at sea level ($p \approx 100$ kPa) is already low enough for most real gases to behave almost perfectly, and unless stated otherwise, we shall always assume in this text that the gases we encounter behave like a perfect gas. The reason why a real gas behaves differently from a perfect gas can be traced to the attractions and repulsions that exist between actual molecules and that are absent in a perfect gas (Chapter 11).

EXAMPLE F.2 Using the perfect gas law

A biochemist is investigating the conversion of atmospheric nitrogen to usable form by the bacteria that inhabit the root systems of certain legumes and needs

[2]The term "ideal gas" is also widely used.

to know the pressure in kilopascals exerted by 1.25 g of nitrogen gas in a flask of volume 250 mL at 20°C.

Strategy For this calculation we need to arrange eqn F.9 ($pV = nRT$) into a form that gives the unknown (the pressure, p) in terms of the information supplied:

$$p = \frac{nRT}{V}$$

To use this expression, we need to know the amount of molecules (in moles) in the sample, which we can obtain from the mass, m, and the molar mass, M, the mass per mole of substance, by using $n = m/M$. Then, we need to convert the temperature to the Kelvin scale (by adding 273.15 to the Celsius temperature). Select the value of R from Table F.2 using the units that match the data and the information required (pressure in kilopascals and volume in liters).

Solution The amount of N_2 molecules (of molar mass 28.02 g mol^{-1}) present is

$$n_{N_2} = \frac{m}{M_{N_2}} = \frac{1.25\ \text{g}}{28.02\ \text{g mol}^{-1}} = \frac{1.25}{28.02}\ \text{mol}$$

The temperature of the sample is

$$T/\text{K} = 20 + 273.15$$

Therefore, from $p = nRT/V$,

$$p = \frac{\overbrace{(1.25/28.02)\ \text{mol}}^{n} \times \overbrace{(8.314\ 47\ \text{kPa L K}^{-1}\ \text{mol}^{-1})}^{R} \times \overbrace{(20 + 273.15\ \text{K})}^{T = 293\ \text{K}}}{\underbrace{0.250\ \text{L}}_{V = 250\ \text{mL}}}$$

$$= 435\ \text{kPa}$$

Note how all units (except kPa in this instance) cancel like ordinary numbers.

A note on good practice: It is best to postpone the actual numerical calculation to the last possible stage and carry it out in a single step. This procedure avoids rounding errors.

SELF-TEST F.3 Calculate the pressure exerted by 1.22 g of carbon dioxide confined to a flask of volume 500 mL at 37°C.

Answer: 143 kPa ■

It will be useful time and again to express properties as molar quantities, calculated by dividing the value of an extensive property by the amount of molecules. An example is the **molar volume**, V_m, the volume a substance occupies per mole

of molecules. It is calculated by dividing the volume of the sample by the amount of molecules it contains:

$$V_m = \frac{V}{n} \quad \text{(F.10)}$$

(Volume of sample; Amount of molecules (mol))

We can use the perfect gas law to calculate the molar volume of a perfect gas at any temperature and pressure. When we combine eqns F.9 and F.10, we get

$$V_m = \frac{V}{n} = \frac{nRT}{np} = \frac{RT}{p} \quad \text{(F.11)}$$

($V = nRT/p$)

This expression lets us calculate the molar volume of any gas (provided it is behaving perfectly) from its pressure and its temperature. It also shows that, for a given temperature and pressure, provided they are behaving perfectly, all gases have the same molar volume.

Chemists have found it convenient to report much of their data at a particular set of *standard* conditions. By **standard ambient temperature and pressure** (SATP) they mean a temperature of 25°C (more precisely, 298.15 K) and a pressure of exactly 1 bar (100 kPa). The **standard pressure** is denoted $p^\ominus$, so $p^\ominus = 1$ bar exactly. The molar volume of a perfect gas at SATP is 24.79 L mol^{-1}, as can be verified by substituting the values of the temperature and pressure into eqn F.11. This value implies that at SATP, 1 mol of perfect gas molecules occupies about 25 L (a cube of about 30 cm on a side). An earlier set of standard conditions, which is still encountered, is **standard temperature and pressure** (STP), namely 0°C and 1 atm. The molar volume of a perfect gas at STP is 22.41 L mol^{-1}.

We can obtain insight into the molecular origins of pressure and temperature, and indeed of the perfect gas law, by using the simple but powerful **kinetic model of gases** (also called the "kinetic molecular theory," KMT, of gases), which is based on three assumptions:

1. A gas consists of molecules in ceaseless random motion (Fig. F.6).
2. The size of the molecules is negligible in the sense that their diameters are much smaller than the average distance traveled between collisions.
3. The molecules do not interact, except during collisions.

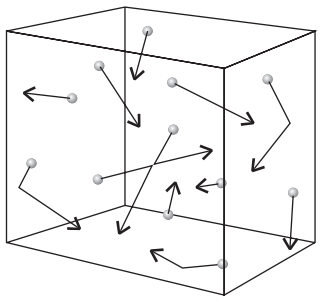


Fig. F.6 The model used for discussing the molecular basis of the physical properties of a perfect gas. The pointlike molecules move randomly with a wide range of speeds and in random directions, both of which change when they collide with the walls or with other molecules.

The assumption that the molecules do not interact unless they are in contact implies that the potential energy of the molecules (their energy due to their position) is independent of their separation and may be set equal to zero. The total energy of a sample of gas is therefore the sum of the kinetic energies (the energy due to motion) of all the molecules present in it. It follows that the faster the molecules travel (and hence the greater their kinetic energy), the greater the total energy of the gas.

The kinetic model accounts for the steady pressure exerted by a gas in terms of the collisions the molecules make with the walls of the container. Each collision gives rise to a brief force on the wall, but as billions of collisions take place

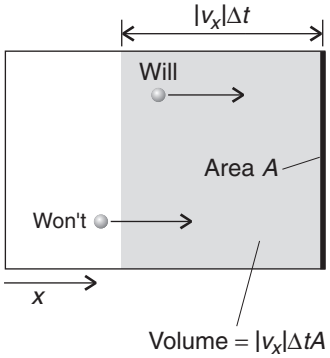


Fig. F.7 The model used for calculating the pressure of a perfect gas according to the kinetic molecular theory. Here, for clarity, we show only the x-component of the velocity (the other two components are not changed when the molecule collides with the wall). All molecules within the shaded area will reach the wall in an interval Δt provided they are moving toward it.

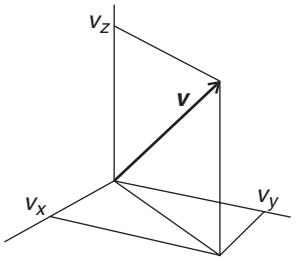
every second, the walls experience a virtually constant force, and hence the gas exerts a steady pressure. On the basis of this model, the pressure exerted by a gas of molar mass M in a volume V is

$$p = \frac{nMc^2}{3V} \qquad \textbf{(F.12)}$$

where c is the **root-mean-square speed** (r.m.s. speed) of the molecules and is defined as the square root of the mean value of the squares of the speeds, v, of the molecules. That is, for a sample consisting of N molecules with speeds v_1, v_2,..., v_N, we square each speed, add the squares together, divide by the total number of molecules (to get the mean, denoted by $\langle ... \rangle$), and finally take the square root of the result:

$$c = \langle v^2 \rangle^{1/2} = \left(\frac{{v_1}^2 + {v_2}^2 + \cdots + {v_N}^2}{N} \right)^{1/2} \qquad \textbf{(F.13)}$$

COMMENT F.4 The velocity, $\boldsymbol{v}$, is a vector, a quantity with both magnitude and direction. The magnitude of the velocity vector is the speed, v, given by $v = ({v_x}^2 + {v_y}^2 + {v_z}^2)^{1/2}$, where v_x, v_y, and v_z, are the components of the vector along the x-, y-, and z-axes, respectively (see the illustration). The magnitude of each component, its value without a sign, is denoted $|...|$. For example, $|v_x|$ means the magnitude of v_x. The linear momentum, $\boldsymbol{p}$, of a particle of mass m is the vector $\boldsymbol{p} = m\boldsymbol{v}$ with magnitude $p = mv$. ■



DERIVATION F.2 The pressure according to the kinetic molecular theory

Consider the arrangement in Fig. F.7. When a particle of mass m that is traveling with a component of velocity v_x parallel to the x-axis ($v_x > 0$ corresponding to motion to the right and $v_x < 0$ to motion to the left) collides with the wall on the right and is reflected, its linear momentum changes from $+m|v_x|$ before the collision to $-m|v_x|$ after the collision (when it is traveling in the opposite direction at the same speed). The x-component of the momentum therefore changes by $2m|v_x|$ on each collision (the y- and z-components are unchanged). Many molecules collide with the wall in an interval Δt, and the total change of momentum is the product of the change in momentum of each molecule multiplied by the number of molecules that reach the wall during the interval.

Next, we need to calculate that number. Because a molecule with velocity component v_x can travel a distance $|v_x|\Delta t$ along the x-axis in an interval Δt, all the molecules within a distance $|v_x|\Delta t$ of the wall will strike it if they are traveling toward it. It follows that if the wall has area A, then all the particles in a volume $A \times |v_x|\Delta t$ will reach the wall (if they are traveling toward it). The number density, the number of particles divided by the total volume, is nN_A/V (where n is the total amount of molecules in the container of volume V and N_A is Avogadro's constant), so the number of molecules in the volume $A|v_x|\Delta t$ is $(nN_A/V) \times A|v_x|\Delta t$. At any instant, half the particles are moving to the right and half are moving to the left. Therefore, the average number of collisions with the wall during the interval Δt is $\frac{1}{2}nN_A A|v_x|\Delta t/V$.

Newton's second law of motion states that the force acting on a particle is equal to the rate of change of the momentum, the change of momentum divided by the interval during which it occurs. In this case, the total momentum change in the interval Δt is the product of the number we have just calculated and the change $2m|v_x|$:

$$\textit{Momentum change} = \frac{nN_A A|v_x|\Delta t}{2V} \times 2m|v_x| = \frac{nmAN_A {v_x}^2 \Delta t}{V} = \frac{nMA{v_x}^2 \Delta t}{V}$$

where $M = mN_A$. Next, to find the force, we calculate the rate of change of momentum:

$$Force = \frac{Change\ of\ momentum}{Time\ interval} = \frac{nMAv_x^2}{V}$$

It follows that the pressure, the force divided by the area, is

$$Pressure = \frac{nMv_x^2}{V}$$

Not all the molecules travel with the same velocity, so the detected pressure, p, is the average (denoted $\langle ... \rangle$) of the quantity just calculated:

$$p = \frac{nM\langle v_x^2 \rangle}{V}$$

To write an expression of the pressure in terms of the root-mean-square speed, c, we begin by writing the speed of a single molecule, v, as $v^2 = v_x^2 + v_y^2 + v_z^2$. Because the root-mean-square speed, c, is defined as $c = \langle v^2 \rangle^{1/2}$ (eqn F.13), it follows that

$$c^2 = \langle v^2 \rangle = \langle v_x^2 \rangle + \langle v_y^2 \rangle + \langle v_z^2 \rangle$$

However, because the molecules are moving randomly and there is no net flow in a particular direction, the average speed along x is the same as that in the y and z directions. It follows that $c^2 = 3\langle v_x^2 \rangle$. Equation F.12 follows when $\langle v_x^2 \rangle = \frac{1}{3}c^2$ is substituted into $p = nM\langle v_x^2 \rangle / V$.

The r.m.s. speed might at first encounter seem to be a rather peculiar measure of the mean speeds of the molecules, but its significance becomes clear when we make use of the fact that the kinetic energy of a molecule of mass m traveling at a speed v is $E_K = \frac{1}{2}mv^2$, which implies that the mean kinetic energy, $\langle E_K \rangle$, is the average of this quantity, or $\frac{1}{2}mc^2$. It follows that

$$c = \left(\frac{2\langle E_K \rangle}{m} \right)^{1/2} \qquad \textbf{(F.14)}$$

Therefore, wherever c appears, we can think of it as a measure of the mean kinetic energy of the molecules of the gas. The r.m.s. speed is quite close in value to another and more readily visualized measure of molecular speed, the **mean speed**, $\bar{c}$, of the molecules:

$$\bar{c} = \frac{v_1 + v_2 + \cdots + v_N}{N} \qquad \textbf{(F.15)}$$

For samples consisting of large numbers of molecules, the mean speed is slightly smaller than the r.m.s. speed. The precise relation is

$$\bar{c} = \left(\frac{8}{3\pi} \right)^{1/2} c \approx 0.921c \qquad \textbf{(F.16)}$$

For elementary purposes and for qualitative arguments, we do not need to distinguish between the two measures of average speed, but for precise work the distinction is important.

SELF-TEST F.4 Cars pass a point traveling at 45.00 (5), 47.00 (7), 50.00 (9), 53.00 (4), 57.00 (1) km h^{-1}, where the number of cars is given in parentheses. Calculate (a) the r.m.s speed and (b) the mean speed of the cars. (*Hint:* Use the definitions directly; the relation in eqn F.16 is unreliable for such small samples.)

Answer: (a) 49.06 km h^{-1}, (b) 48.96 km h^{-1}

Equation F.12 already resembles the perfect gas equation of state, for we can rearrange it into

$$pV = \tfrac{1}{3}nMc^2 \qquad \textbf{(F.17)}$$

and compare it to $pV = nRT$. Equating the expression on the right of eqn F.17 to nRT gives

$$\tfrac{1}{3}nMc^2 = nRT$$

The n's now cancel. The great usefulness of this expression is that we can rearrange it into a formula for the r.m.s. speed of the gas molecules at any temperature:

$$c = \left(\frac{3RT}{M}\right)^{1/2} \qquad \textbf{(F.18)}$$

Substitution of the molar mass of O_2 (32.0 g mol^{-1}) and a temperature corresponding to 25°C (that is, 298 K) gives an r.m.s. speed for these molecules of 482 m s^{-1}. The same calculation for nitrogen molecules gives 515 m s^{-1}.

The important conclusion to draw from eqn F.18 is that *the r.m.s. speed of molecules in a gas is proportional to the square root of the temperature*. Because the mean speed is proportional to the r.m.s. speed, the same is true of the mean speed. Therefore, doubling the temperature (on the Kelvin scale) increases the mean and the r.m.s. speed of molecules by a factor of $2^{1/2} = 1.414\ldots$.

ILLUSTRATION F.2 The effect of temperature on mean speeds

Cooling a sample of air from 25°C (298 K) to 0°C (273 K) reduces the original r.m.s. speed of the molecules by a factor of

$$\left(\frac{273\ \text{K}}{298\ \text{K}}\right)^{1/2} = \left(\frac{273}{298}\right)^{1/2} = 0.957$$

So, on a cold day, the average speed of air molecules (which is changed by the same factor) is about 4% less than on a warm day. ■

So far, we have dealt only with the *average* speed of molecules in a gas. Not all molecules, however, travel at the same speed: some move more slowly than the

average (until they collide and get accelerated to a high speed, like the impact of a bat on a ball), and others may briefly move at much higher speeds than the average but be brought to a sudden stop when they collide. There is a ceaseless redistribution of speeds among molecules as they undergo collisions. Each molecule collides once every nanosecond (1 ns = 10^{-9} s) or so in a gas under normal conditions.

The mathematical expression that tells us the fraction of molecules that have a particular speed at any instant is called the **distribution of molecular speeds**. Thus, the distribution might tell us that at 20°C, 19 out of 1000 O_2 molecules have a speed in the range between 300 and 310 m s^{-1}, that 21 out of 1000 have a speed in the range 400 to 410 m s^{-1}, and so on. The precise form of the distribution was worked out by James Clerk Maxwell toward the end of the nineteenth century, and his expression is known as the **Maxwell distribution of speeds**. According to Maxwell, the fraction f of molecules that have a speed in a narrow range between s and $s + \Delta s$ (for example, between 300 m s^{-1} and 310 m s^{-1}, corresponding to s = 300 m s^{-1} and Δs = 10 m s^{-1}) is

$$f = F(s)\Delta s \qquad \text{with} \qquad F(s) = 4\pi\left(\frac{M}{2\pi RT}\right)^{3/2} s^2 e^{-Ms^2/2RT} \tag{F.19}$$

This formula was used to calculate the numbers quoted above.

Although eqn F.19 looks complicated, its features can be picked out quite readily. One of the skills to develop in physical chemistry is the ability to interpret the message carried by equations. Equations convey information, and it is far more important to be able to read that information than simply to remember the equation. Let's read the information in eqn F.19 piece by piece.

Before we begin, and in preparation for the large number of occurrences of exponential functions throughout the text, it will be useful to know the shape of exponential functions. Here we deal with two types, e^{-ax} and e^{-ax^2}. An exponential function of the form e^{-ax} starts off at 1 when $x = 0$ and decays toward zero, which it reaches as x approaches infinity (Fig. F.8). This function approaches zero more rapidly as a increases. The function e^{-ax^2} is called a **Gaussian function**. It also starts off at 1 when $x = 0$ and decays to zero as x increases, however, its decay is initially slower but then plunges down more rapidly than e^{-ax}. The illustration also shows the behavior of the two functions for negative values of x. The exponential function e^{-ax} rises rapidly to infinity, but the Gaussian function falls back to zero and traces out a bell-shaped curve.

Now let's consider the content of eqn F.19.

1. Because f is proportional to the range of speeds Δs, we see that the fraction in the range Δs increases in proportion to the width of the range. If at a given speed we double the range of interest (but still ensure that it is narrow), then the fraction of molecules in that range doubles too.
2. Equation F.19 includes a decaying exponential function, the term $e^{-Ms^2/2RT}$. Its presence implies that the fraction of molecules with very high speeds will be very small because e^{-x^2} becomes very small when x^2 is large.
3. The factor $M/2RT$ multiplying s^2 in the exponent is large when the molar mass, M, is large, so the exponential factor goes most rapidly toward zero when M is large. That tells us that heavy molecules are unlikely to be found with very high speeds.

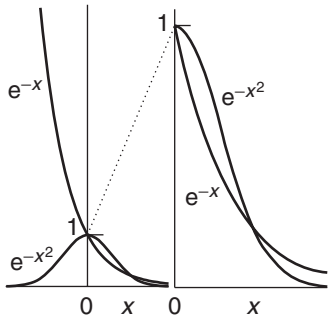


Fig. F.8 The exponential function, e^{-x}, and the bell-shaped Gaussian function, e^{-x^2}. Note that both are equal to 1 at $x = 0$, but the exponential function rises to infinity as $x \longrightarrow -\infty$. The enlargement shows the behavior for $x > 0$ in more detail.

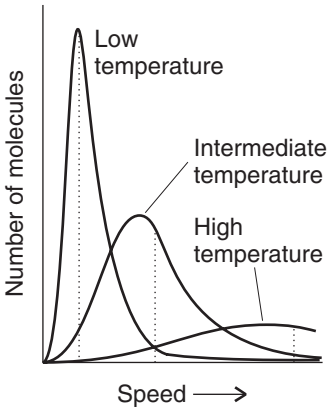


Fig. F.9 The Maxwell distribution of speeds and its variation with the temperature. Note the broadening of the distribution and the shift of the r.m.s. speed (denoted by the locations of the vertical lines) to higher values as the temperature is increased.

4. The opposite is true when the temperature, T, is high: then the factor $M/2RT$ in the exponent is small, so the exponential factor falls toward zero relatively slowly as s increases. This tells us that at high temperatures, a greater fraction of the molecules can be expected to have high speeds than at low temperatures.
5. A factor s^2 (the term before the e) multiplies the exponential. This factor goes to zero as s goes to zero, so the fraction of molecules with very low speeds will also be very small.

The remaining factors (the term in parentheses in eqn F.19 and the 4π) simply ensure that when we add together the fractions over the entire range of speeds from zero to infinity, then we get 1.

Figure F.9 is a graph of the Maxwell distribution and shows these features pictorially for the same gas (the same value of M) but different temperatures. As we deduced from the equation, we see that only small fractions of molecules in the sample have very low or very high speeds. However, the fraction with very high speeds increases sharply as the temperature is raised, as the tail of the distribution reaches up to higher speeds. This feature plays an important role in the rates of gas-phase chemical reactions, for (as we shall see in Chapter 6) the rate of a reaction in the gas phase depends on the energy with which two molecules crash together, which in turn depends on their speeds.

Figure F.10 is a plot of the Maxwell distribution for molecules with different molar masses at the same temperature. As can be seen, not only do heavy molecules have lower average speeds than light molecules at a given temperature, but they also have a significantly narrower spread of speeds. That narrow spread means that most molecules will be found with speeds close to the average. In contrast, light molecules (such as H_2) have high average speeds and a wide spread of speeds: many molecules will be found traveling either much more slowly or much more quickly than the average. This feature plays an important role in determining the composition of planetary atmospheres, because it means that a significant fraction of light molecules travel at sufficiently high speeds to escape from the planet's gravitational attraction. The ability of light molecules to escape is one reason why hydrogen (molar mass 2.02 g mol^{-1}) and helium (4.00 g mol^{-1}) are very rare in the Earth's atmosphere.

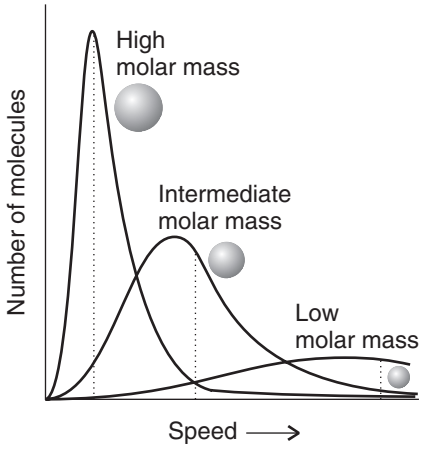


Fig. F.10 The Maxwell distribution of speeds also depends on the molar mass of the molecules. Molecules of low molar mass have a broad spread of speeds, and a significant fraction may be found traveling much faster than the r.m.s. speed. The distribution is much narrower for heavy molecules, and most of them travel with speeds close to the r.m.s. value (denoted by the locations of the vertical lines).

Checklist of Key Ideas

You should now be familiar with the following concepts:

□ **1.** The states of matter are gas, liquid, and solid.

□ **2.** Work is done when a body is moved against an opposing force.

□ **3.** Energy is the capacity to do work.

□ **4.** The contributions to the energy of matter are the kinetic energy (the energy due to motion) and the potential energy (the energy due to position).

□ **5.** The total energy of an isolated system is conserved, but kinetic and potential energy may be interchanged.

□ **6.** Pressure, p, is force divided by the area on which the force is exerted.

□ **7.** Two systems in contact through movable walls are in mechanical equilibrium when their pressures are equal.

□ **8.** Two systems in contact through thermally conducting walls are in thermal equilibrium when their temperatures are equal.

□ **9.** Temperatures on the Kelvin and Celsius scales are related by $T/\mathrm{K} = \theta/°\mathrm{C} + 273.15$.

□ **10.** An equation of state is an equation relating pressure, volume, temperature, and amount of a substance.

□ **11.** The perfect gas equation of state ($pV = nRT$) is a limiting law applicable as $p \longrightarrow 0$.

□ **12.** The kinetic model of gases expresses the properties of a perfect gas in terms of a collection of mass points in ceaseless random motion.

□ **13.** The mean speed and root-mean-square speed of molecules are proportional to the square root of the (absolute) temperature and inversely proportional to the square root of the molar mass.

□ **14.** The properties of the Maxwell distribution of speeds are summarized in Figs. F.9 and F.10.

Discussion questions

F.1 Explain the differences between gases, liquids, and solids.

F.2 Define the terms force, work, energy, kinetic energy, and potential energy.

F.3 Distinguish between mechanical and thermal equilibrium.

F.4 Provide a molecular interpretation of the pressure exerted by a perfect gas.

Exercises

Treat all gases as perfect unless instructed otherwise.

F.5 Calculate the work that a person of mass 65 kg must do to climb between two floors of a building separated by 3.5 m.

F.6 What is the kinetic energy of a tennis ball of mass 58 g served at 30 m s^{-1}?

F.7 A car of mass 1.5 t (1 t = 10^3 kg) traveling at 50 km h^{-1} must be brought to a stop. How much kinetic energy must be dissipated?

F.8 Consider a region of the atmosphere of volume 25 L, which at 20°C contains about 1.0 mol of molecules. Take the average molar mass of the molecules as 29 g mol^{-1} and their average speed as about 400 m s^{-1}. Estimate the energy stored as molecular kinetic energy in this volume of air.

F.9 What is the difference in potential energy of a mercury atom between the top and bottom of a column of mercury in a barometer when the pressure is 1.0 atm?

F.10 Calculate the minimum energy that a bird of mass 25 g must expend in order to reach a height of 50 m.

F.11 Express **(a)** 110 kPa in torr, **(b)** 0.997 bar in atmospheres, **(c)** 2.15×10^4 Pa in atmospheres, **(d)** 723 Torr in pascals.

F.12 Calculate the pressure in the Mindañao trench, near the Philippines, the deepest region of the oceans. Take the depth there as 11.5 km and for the average mass density of seawater use 1.10 g cm^{-3}.

F.13 The atmospheric pressure on the surface of Mars, where $g = 3.7\ \text{m s}^{-2}$, is only 0.0060 atm. To what extent is that low pressure due to the low gravitational attraction and not to the thinness of the atmosphere? What pressure would the same atmosphere exert on Earth, where $g = 9.81\ \text{m s}^{-2}$?

F.14 What pressure difference must be generated across the length of a 15 cm vertical drinking straw in order to drink a water-like liquid of mass density $1.0\ \text{g cm}^{-3}$ **(a)** on Earth, **(b)** on Mars? For data, see Exercise F.13.

F.15 The unit millimeters of mercury (mmHg) has been replaced by the unit torr (Torr): 1 mmHg is defined as the pressure at the base of a column of mercury exactly 1 mm high when its density is $13.5951\ \text{g cm}^{-3}$ and the acceleration of free fall is $9.806\ 65\ \text{m s}^{-2}$. What is the relation between the two units?

F.16 Given that the Celsius and Fahrenheit temperature scales are related by $\theta_{\text{Celsius}}/°\text{C} = \frac{5}{9}(\theta_{\text{Fahrenheit}}/°\text{F} - 32)$, what is the temperature of absolute zero ($T = 0$) on the Fahrenheit scale?

F.17 Imagine that Pluto is inhabited and that its scientists use a temperature scale in which the freezing point of liquid nitrogen is 0°P (degrees Plutonium) and its boiling point is 100°P. The inhabitants of Earth report these temperatures as −209.9°C and −195.8°C, respectively. What is the relation between temperatures on **(a)** the Plutonium and Kelvin scales, **(b)** the Plutonium and Fahrenheit scales?

F.18 Much to everyone's surprise, nitrogen monoxide (nitric oxide, NO) has been found to act as a neurotransmitter. To prepare to study its effect, a sample was collected in a container of volume 250.0 cm^3. At 19.5°C its pressure is found to be 24.5 kPa. What amount (in moles) of NO has been collected?

F.19 A domestic water-carbonating kit uses steel cylinders of carbon dioxide of volume 250 cm^3. They weigh 1.04 kg when full and 0.74 kg when empty. What is the pressure of gas in the cylinder at 20°C?

F.20 The effect of high pressure on organisms, including humans, is studied to gain information about deep-sea diving and anesthesia. A sample of air occupies 1.00 L at 25°C and 1.00 atm. What pressure is needed to compress it to 100 cm^3 at this temperature?

F.21 You are warned not to dispose of pressurized cans by throwing them onto a fire. The gas in an aerosol container exerts a pressure of 125 kPa at 18°C. The container is thrown on a fire, and its temperature rises to 700°C. What is the pressure at this temperature?

F.22 Until we find an economical way of extracting oxygen from seawater or lunar rocks, we have to carry it with us to inhospitable places and do so in compressed form in tanks. A sample of oxygen at 101 kPa is compressed at constant temperature from 7.20 L to 4.21 L. Calculate the final pressure of the gas.

F.23 Hot-air balloons gain their lift from the lowering of density of air that occurs when the air in the envelope is heated. To what temperature should you heat a sample of air, initially at 340 K, to increase its volume by 14%?

F.24 At sea level, where the pressure was 104 kPa and the temperature 21.1°C, a certain mass of air occupied 2.0 m^3. To what volume will the region expand when it has risen to an altitude where the pressure and temperature are **(a)** 52 kPa, −5.0°C, **(b)** 880 Pa, −52.0°C?

F.25 A diving bell has an air space of 3.0 m^3 when on the deck of a boat. What is the volume of the air space when the bell has been lowered to a depth of 50 m? Take the mean density of seawater to be $1.025\ \text{g cm}^{-3}$ and assume that the temperature is the same as on the surface.

F.26 A meteorological balloon had a radius of 1.0 m when released at sea level at 20°C and expanded to a radius of 3.0 m when it had risen to its maximum altitude, where the temperature was −20°C. What is the pressure inside the balloon at that altitude?

F.27 A determination of the density of a gas or vapor can provide a quick estimate of its molar mass even though for practical work, mass spectrometry is far more precise. The density of a gaseous compound was found to be $1.23\ \text{g L}^{-1}$ at 330 K and 25.5 kPa. What is the molar mass of the compound?

F.28 The composition of planetary atmospheres is determined in part by the speeds of the molecules of the constituent gases, because the faster-moving molecules can reach escape

velocity and leave the planet. Calculate the mean speed of **(a)** He atoms, **(b)** CH_4 molecules at **(i)** 77 K, **(ii)** 298 K, **(iii)** 1000 K.

F.29 Use the Maxwell distribution of speeds to confirm that the mean speed of molecules of molar mass M at a temperature T is equal to $(8RT/\pi M)^{1/2}$. *Hint:* You will need an integral of the form $\int_0^\infty x^3 e^{-ax^2}\,dx = \frac{1}{2}a^2$.

F.30 Use the Maxwell distribution of speeds to confirm that the root-mean-square speed of molecules of molar mass M at a temperature T is equal to $(3RT/M)^{1/2}$ and hence confirm eqn F.18. *Hint*: You will need an integral of the form $\int_0^\infty x^4 e^{-ax^2}\,dx = (\frac{3}{8}a^2)(\pi/a)^{1/2}$.

F.31 Use the Maxwell distribution of speeds to find an expression for the most probable speed of molecules of molar mass M at a temperature T. *Hint:* Look for a maximum in the Maxwell distribution (the maximum occurs as $dF/ds = 0$).

F.32 Use the Maxwell distribution of speeds to estimate the fraction of N_2 molecules at 500 K that have speeds in the range 290 to 300 m s^{-1}.

Project

F.33 You will now explore the gravitational potential energy in some detail, with an eye toward discovering the origin of the value of the constant g, the acceleration of free fall, and the magnitude of the gravitational force experienced by all organisms on the Earth.

(a) The gravitational potential energy of a body of mass m at a distance r from the center of the Earth is $-Gmm_E/r$, where m_E is the mass of the Earth and G is the gravitational constant (see inside front cover). Consider the difference in potential energy of the body when it is moved from the surface of the Earth (radius r_E) to a height h above the surface, with $h << r_E$, and find an expression for the acceleration of free fall, g, in terms of the mass and radius of the Earth. *Hint:* Use the approximation $(1 + h/r_E)^{-1} = 1 - h/r_E + \cdots$. See *Appendix 2* for more information on series expansions.

(b) You need to assess the fuel needed to send the robot explorer *Spirit*, which has a mass of 185 kg, to Mars. What was the energy needed to raise the vehicle itself from the surface of the Earth to a distant point where the Earth's gravitational field was effectively zero? The mean radius of the Earth is 6371 km and its average mass density is 5.5170 g cm^{-3}. *Hint:* Use the full expression for gravitational potential energy in part (a).

(c) Given the expression for gravitational potential energy in part (a), (i) what is the gravitational force on an object of mass m at a distance r from the center of the Earth? (ii) What is the gravitational force that you are currently experiencing? For data on the Earth, see part (b).

I

Biochemical Thermodynamics

The branch of physical chemistry known as **thermodynamics** is concerned with the study of the transformations of energy. That concern might seem remote from chemistry, let alone biology; indeed, thermodynamics was originally formulated by physicists and engineers interested in the efficiency of steam engines. However, thermodynamics has proved to be of immense importance in both chemistry and biology. Not only does it deal with the energy output of chemical reactions but it also helps to answer questions that lie right at the heart of biochemistry, such as how energy flows in biological cells and how large molecules assemble into complex structures like the cell.

CHAPTER

1

The First Law

Classical thermodynamics, the thermodynamics developed during the nineteenth century, stands aloof from any models of the internal constitution of matter: we could develop and use thermodynamics without ever mentioning atoms and molecules. However, the subject is greatly enriched by acknowledging that atoms and molecules do exist and interpreting thermodynamic properties and relations in terms of them. Wherever it is appropriate, we shall cross back and forth between thermodynamics, which provides useful relations between observable properties of bulk matter, and the properties of atoms and molecules, which are ultimately responsible for these bulk properties. The theory of the connection between atomic and bulk thermodynamic properties is called **statistical thermodynamics** and is treated in Chapter 12.

Throughout the text, we shall pay special attention to **bioenergetics**, the deployment of energy in living organisms. As we master the concepts of thermodynamics in this and subsequent chapters, we shall gradually unravel the intricate patterns of energy trapping and utilization in biological cells.

The conservation of energy

Almost every argument and explanation in chemistry boils down to a consideration of some aspect of a single property: the *energy*. Energy determines what molecules can form, what reactions can occur, how fast they can occur, and (with a refinement in our conception of energy) in which direction a reaction has a tendency to occur.

As we saw in the *Fundamentals*:

Energy is the capacity to do work.

Work is motion against an opposing force.

These definitions imply that a raised weight of a given mass has more energy than one of the same mass resting on the ground because the former has a greater capacity to do work: it can do work as it falls to the level of the lower weight. The definition also implies that a gas at a high temperature has more energy than the same gas at a low temperature: the hot gas has a higher pressure and can do more work in driving out a piston. In biology, we encounter many examples of the relationship between energy and work. As a muscle contracts and relaxes, energy stored in its protein fibers is released as the work of walking, lifting a weight, and so on. In biological cells, nutrients, ions, and electrons are constantly moving across membranes and from one cellular compartment to another. The synthesis of biological molecules and cell division are also manifestations of work at the molecular level. The energy that produces all this work in our bodies comes from food.

People struggled for centuries to create energy from nothing, for they believed that if they could create energy, then they could produce work (and wealth) endlessly. However, without exception, despite strenuous efforts, many of which degenerated into deceit, they failed. As a result of their failed efforts, we have come to recognize that energy can be neither created nor destroyed but merely converted from one form into another or moved from place to place. This "law of the conservation of energy" is of great importance in chemistry. Most chemical reactions—including the majority of those taking place in biological cells—release energy or absorb it as they occur; so according to the law of the conservation of energy, we can be confident that all such changes—including the vast collection of physical and chemical changes we call life—must result only in the *conversion* of energy from one form to another or its transfer from place to place, not its creation or annihilation.

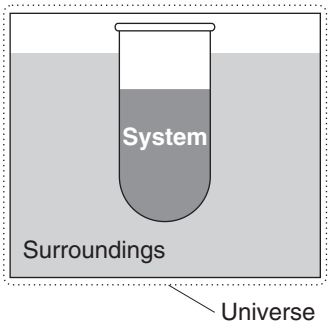


Fig. 1.1 The sample is the system of interest; the rest of the world is its surroundings. The surroundings are where observations are made on the system. They can often be modeled, as here, by a large water bath. The universe consists of the system and surroundings.

1.1 Systems and surroundings

We need to understand the unique and precise vocabulary of thermodynamics before applying it to the study of bioenergetics.

In thermodynamics, a **system** is the part of the world in which we have a special interest. The **surroundings** are where we make our observations (Fig. 1.1). The surroundings, which can be modeled as a large water bath, remain at constant temperature regardless of how much energy flows into or out of them. They are so huge that they also have either constant volume or constant pressure regardless of any changes that take place to the system. Thus, even though the system might expand, the surroundings remain effectively the same size.

We need to distinguish three types of system (Fig. 1.2):

An **open system** can exchange both energy and matter with its surroundings and hence can undergo changes of composition.

A **closed system** is a system that can exchange energy but not matter with its surroundings.

An **isolated system** is a system that can exchange neither matter nor energy with its surroundings.

An example of an open system is a flask that is not stoppered and to which various substances can be added. A biological cell is an open system because nutrients and waste can pass through the cell wall. You and I are open systems: we ingest, respire, perspire, and excrete. An example of a closed system is a stoppered flask: energy can be exchanged with the contents of the flask because the walls may be able to conduct heat. An example of an isolated system is a sealed flask that is thermally, mechanically, and electrically insulated from its surroundings.

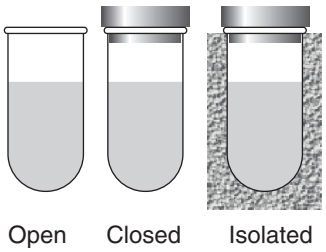
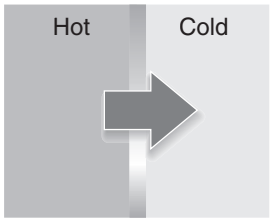


Fig. 1.2 A system is *open* if it can exchange energy and matter with its surroundings, *closed* if it can exchange energy but not matter, and *isolated* if it can exchange neither energy nor matter.

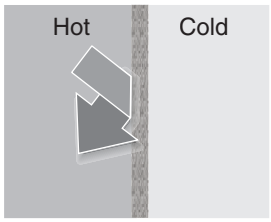
1.2 Work and heat

Organisms can be regarded as vessels that exchange energy with their surroundings, and we need to understand the modes of such transfer.

Energy can be exchanged between a closed system and its surroundings by doing work or by the process called "heating." A system does work when it causes



(a) Diathermic



(b) Adiabatic

Fig. 1.3 (a) A diathermic wall permits the passage of energy as heat; (b) an adiabatic wall does not, even if there is a temperature difference across the wall.

motion against an opposing force. We can identify when a system does work by noting whether the process can be used to change the height of a weight somewhere in the surroundings. **Heating** is the process of transferring energy as a result of a temperature difference between the systems and its surroundings. To avoid a lot of awkward circumlocution, it is common to say that "energy is transferred as work" when the system does work and "energy is transferred as heat" when the system heats its surroundings (or vice versa). However, we should always remember that "work" and "heat" are *modes of transfer* of energy, not *forms* of energy.

Walls that permit heating as a mode of transfer of energy are called **diathermic** (Fig. 1.3). A metal container is diathermic and so is our skin or any biological membrane. Walls that do not permit heating even though there is a difference in temperature are called **adiabatic**.[1] The double walls of a vacuum flask are adiabatic to a good approximation.

As an example of these different ways of transferring energy, consider a chemical reaction that is a net producer of gas, such as the reaction between urea, $(NH_2)_2CO$, and oxygen to yield carbon dioxide, water, and nitrogen:

$$(NH_2)_2CO(s) + \tfrac{3}{2}\,O_2(g) \longrightarrow CO_2(g) + 2\,H_2O(l) + N_2(g)$$

Suppose first that the reaction takes place inside a cylinder fitted with a piston, then the gas produced drives out the piston and raises a weight in the surroundings (Fig. 1.4). In this case, energy has migrated to the surroundings as a result of the system doing work, because a weight has been raised in the surroundings: that weight can now do more work, so it possesses more energy. Some energy also migrates into the surroundings as heat. We can detect that transfer of energy by immersing the reaction vessel in an ice bath and noting how much ice melts. Alternatively, we could let the same reaction take place in a vessel with a piston locked in position. No work is done, because no weight is raised. However, because it is found that more ice melts than in the first experiment, we can conclude that more energy has migrated to the surroundings as heat.

A process in a system that heats the surroundings (we commonly say "releases heat into the surroundings") is called **exothermic**. A process in a system that is

[1]The word is derived from the Greek words for "not passing through."

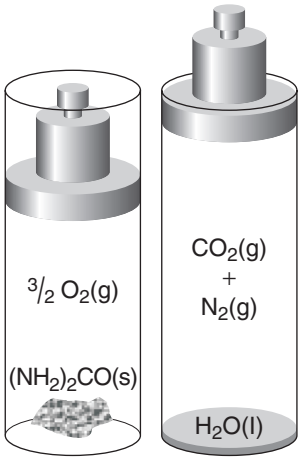


Fig. 1.4 When urea reacts with oxygen, the gases produced (carbon dioxide and nitrogen) must push back the surrounding atmosphere (represented by the weight resting on the piston) and hence must do work on its surroundings. This is an example of energy leaving a system as work.

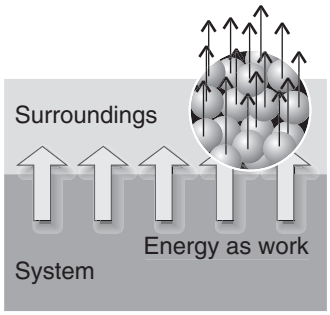
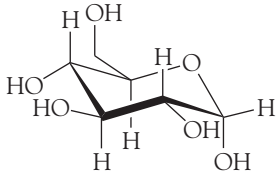
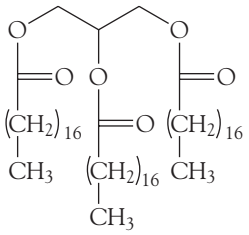


Fig. 1.5 Work is transfer of energy that causes or utilizes uniform motion of atoms in the surroundings. For example, when a weight is raised, all the atoms of the weight (shown magnified) move in unison in the same direction.

heated by the surroundings (we commonly say "absorbs heat from the surroundings") is called **endothermic**. Examples of exothermic reactions are all **combustions**, in which organic compounds are completely oxidized by O_2 gas to CO_2 gas and liquid H_2O if the compounds contain C, H, and O, and also to N_2 gas if N is present. The oxidative breakdown of nutrients in organisms are combustions. So we expect the reactions of the carbohydrate glucose ($C_6H_{12}O_6$, **1**) and of the fat tristearin ($C_{57}H_{110}O_6$, **2**) with O_2 gas to be exothermic, with much of the released heat being converted to work in the organism (Section 1.3):



1 α-D-glucose



2 Tristearin

$$C_6H_{12}O_6(s) + 6\ O_2(g) \longrightarrow 6\ CO_2(g) + 6\ H_2O(l)$$

$$2\ C_{57}H_{110}O_6(s) + 163\ O_2(g) \longrightarrow 114\ CO_2(g) + 110\ H_2O(l)$$

Endothermic reactions are much less common. The endothermic dissolution of ammonium nitrate in water is the basis of the instant cold packs that are included in some first-aid kits. They consist of a plastic envelope containing water dyed blue (for psychological reasons) and a small tube of ammonium nitrate, which is broken when the pack is to be used.

The clue to the molecular nature of work comes from thinking about the motion of a weight in terms of its component atoms. When a weight is raised, all its atoms move in the same direction. This observation suggests that *work is the transfer of energy that achieves or utilizes uniform motion in the surroundings* (Fig. 1.5). Whenever we think of work, we can always think of it in terms of uniform motion of some kind. Electrical work, for instance, corresponds to electrons being pushed in the same direction through a circuit. Mechanical work corresponds to atoms being pushed in the same direction against an opposing force.

Now consider the molecular nature of heating. When energy is transferred as heat to the surroundings, the atoms and molecules oscillate more rapidly around their positions or move from place to place more vigorously. The key point is that the motion stimulated by the arrival of energy from the system as heat is random, not uniform as in the case of doing work. This observation suggests that *heat is the mode of transfer of energy that achieves or utilizes random motion in the surroundings* (Fig. 1.6). A fuel burning, for example, generates random molecular motion in its vicinity.

An interesting historical point is that the molecular difference between work and heat correlates with the chronological order of their application. The release of energy when a fire burns is a relatively unsophisticated procedure because the energy emerges in a disordered fashion from the burning fuel. It was developed—stumbled upon—early in the history of civilization. The generation of work by a burning fuel, in contrast, relies on a carefully controlled transfer of energy so that

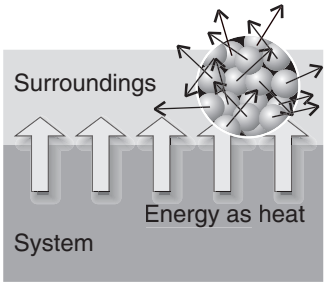


Fig. 1.6 Heat is the transfer of energy that causes or utilizes random motion in the surroundings. When energy leaves the system (the shaded region), it generates random motion in the surroundings (shown magnified).

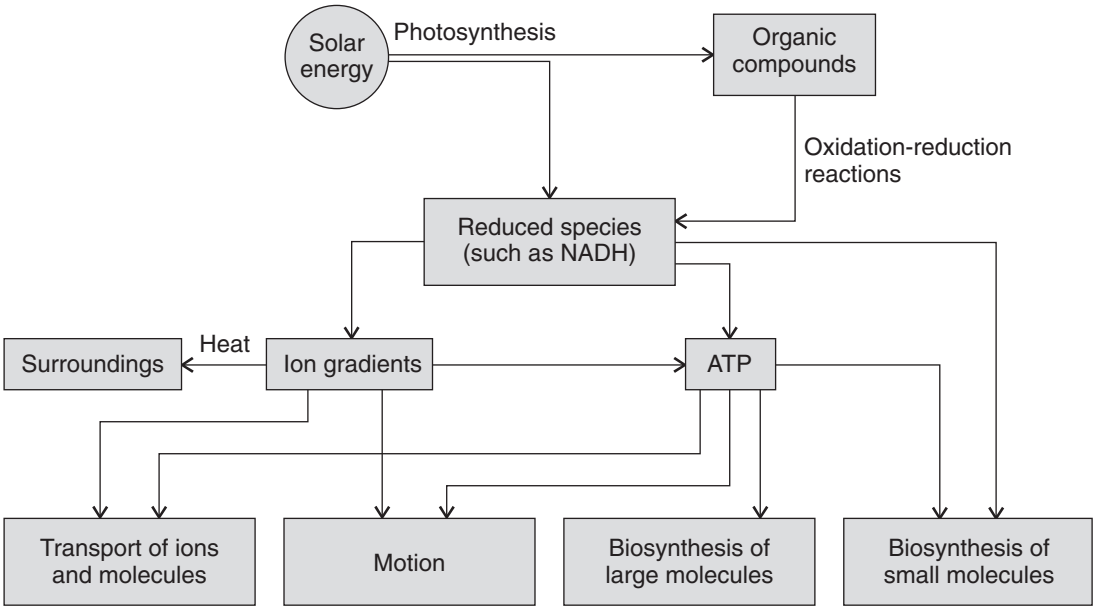


Fig. 1.7 Diagram demonstrating the flow of energy in living organisms. Arrows point in the direction in which energy flows. We focus only on the most common processes and do not include less ubiquitous ones, such as bioluminescence. (Adapted from D.A. Harris, *Bioenergetics at a glance,* Blackwell Science, Oxford [1995].)

vast numbers of molecules move in unison. Apart from Nature's achievement of work through the evolution of muscles, the large-scale transfer of energy by doing work was achieved thousands of years later than the liberation of energy by heating, for it had to await the development of the steam engine.

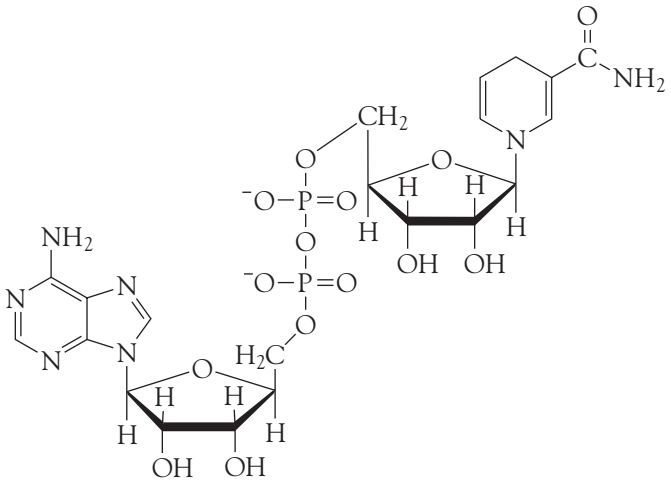
1.3 Energy conversion in living organisms

To begin our study of bioenergetics, we need to trace the general patterns of energy flow in living organisms.

Figure 1.7 outlines the main processes of **metabolism**, the collection of chemical reactions that trap, store, and utilize energy in biological cells. Most chemical reactions taking place in biological cells are either endothermic or exothermic, and cellular processes can continue only as long as there is a steady supply of energy to the cell. Furthermore, as we shall see in Section 1.6, only the *conversion* of the supplied energy from one form to another or its transfer from place to place is possible.

The primary source of energy that sustains the bulk of plant and animal life on Earth is the Sun.[2] We saw in the *Prologue* that energy from solar radiation is ultimately stored during photosynthesis in the form of organic molecules, such as carbohydrates, fats, and proteins, that are subsequently oxidized to meet the energy demands of organisms. **Catabolism** is the collection of reactions associated with the oxidation of nutrients in the cell and may be regarded as highly controlled combustions, with the energy liberated as work rather than heat. Thus, even though the oxidative breakdown of a carbohydrate or fat to carbon dioxide and water is

[2]Some ecosystems near volcanic vents in the dark depths of the oceans do not use sunlight as their primary source of energy.



3 NADH

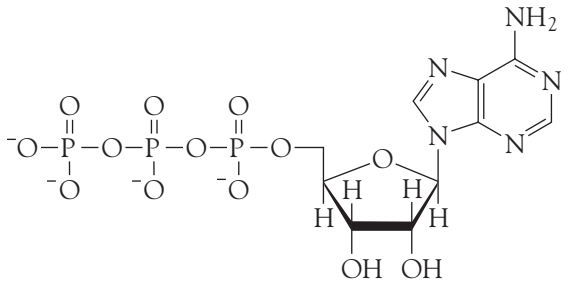
highly exothermic, we expect much of the energy to be expended by doing useful work, with only slight temperature increases resulting from the loss of energy as heat from the organism.

Because energy is extracted from organic compounds as a result of oxidation reactions, the initial energy carriers are reduced species, species that have gained electrons, such as reduced nicotinamide adenine dinucleotide, NADH (**3**). Light-induced electron transfer in photosynthesis also leads to the formation of reduced species, such as NADPH, the phosphorylated derivative of NADH. The details of the reactions leading to the production of NADH and NADPH are discussed in Chapter 5.

COMMENT 1.1 See *Appendix 4* for a review of oxidation-reduction reactions. ■

Oxidation-reduction reactions transfer energy out of NADH and other reduced species, storing it in the mobile carrier adenosine triphosphate, ATP (**4**), and in ion gradients across membranes. As we shall see in Chapter 4, the essence of ATP's action is the loss of its terminal phosphate group in an energy-releasing reaction. Ion gradients arise from the movement of charged species across a membrane and we shall see in Chapter 5 how they store energy that can be used to drive biochemical processes and the synthesis of ATP.

Figure 1.7 shows how organisms distribute the energy stored by ion gradients and ATP. The net outcome is incomplete conversion of energy from controlled combustion of nutrients to energy for doing work in the cell: transport of ions and



4 ATP

neutral molecules (such as nutrients) across cell membranes, motion of the organism (for example, through the contraction of muscles), and **anabolism**, the biosynthesis of small and large molecules. The biosynthesis of DNA may be regarded as an anabolic process in which energy is converted ultimately to useful information, the genome of the organism.

Living organisms are not perfectly efficient machines, for not all the energy available from the Sun and oxidation of organic compounds is used to perform work as some is lost as heat. The dissipation of energy as heat is advantageous because it can be used to control the organism's temperature. However, energy is eventually transferred as heat to the surroundings. In Chapter 2 we shall explore the origin of the incomplete conversion of energy supplied by heating into energy that can be used to do work, a feature that turns out to be common to all energy conversion processes.

Now we need to say a few words about how we shall develop the concepts of thermodynamics necessary for a full understanding of bioenergetics. Throughout the text we shall initiate discussions of thermodynamics with the perfect gas as a model system. Although a perfect gas may seem far removed from biology, its properties are crucial to the formulation of thermodynamics of systems in aqueous environments, such as biological cells. First, it is quite simple to formulate the thermodynamic properties of a perfect gas. Then—and this is the crucially important point—because a perfect gas is a good approximation to a vapor and a vapor may be in equilibrium with a liquid, the thermodynamic properties of a perfect gas are mirrored (in a manner we shall describe) in the thermodynamic properties of the liquid. In other words, we shall see that a description of the gases (or "vapors") that hover above a solution opens a window onto the description of physical and chemical transformations occurring in the solution itself. Once we become equipped with the formalism to describe chemical reactions in solution, it will be easy to apply the concepts of thermodynamics to the complex environment of a biological cell. That is, we need to make a modest investment in the study of systems that may seem removed from our concerns so that, in the end, we can collect sizable dividends that will enrich our understanding of biological processses.

1.4 The measurement of work

In bioenergetics, the most useful outcome of the breakdown of nutrients during metabolism is work, so we need to know how work is measured.

We saw in Section F.3 that if the force is the gravitational attraction of the Earth on a mass m, the force opposing raising the mass vertically is mg, where g is the acceleration of free fall (9.81 m s^{-2}), and therefore that the work needed to raise the mass through a height h on the surface of the Earth is

$$Work = mgh \qquad \textbf{(1.1)}$$

It follows that we have a simple way of measuring the work done by or on a system: we measure the height through which a weight is raised or lowered in the surroundings and then use eqn 1.1.

ILLUSTRATION 1.1 The work of moving nutrients through the trunk of a tree

Nutrients in the soil are absorbed by the root system of a tree and then rise to reach the leaves through a complex vascular system in its trunk and branches.

From eqn 1.1, the work required to raise 10 g of liquid water (corresponding to a volume of about 10 mL) through the trunk of a 20 m tree from its roots to its topmost leaves is

$$Work = (1.0 \times 10^{-2}\ \text{kg}) \times (9.81\ \text{m s}^{-2}) \times (20\ \text{m}) = 2.0\ \text{kg m}^2\ \text{s}^{-2} = 2.0\ \text{J}$$

This quantity of work is equivalent to the work of raising a book like this one (of mass about 1.0 kg) by a vertical distance of 20 cm (0.20 m):

$$Work = (1.0\ \text{kg}) \times (9.81\ \text{m s}^{-2}) \times (0.20\ \text{m}) = 2.0\ \text{kg m}^2\ \text{s}^{-2} = 2.0\ \text{J}$$

A note on good practice: Whenever possible, find a relevant derived unit that corresponds to the collection of base units in a result. We used 1 kg m^2 s^{-2} = 1 J, hence verifying that the answer has units of energy. ■

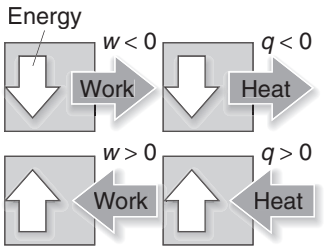


Fig. 1.8 The sign convention in thermodynamics: w and q are positive if energy enters the system (as work and heat, respectively) but negative if energy leaves the system.

When a system does work, such as by raising a weight in the surroundings or forcing the movement of an ion across a biological membrane, the energy transferred, w, is reported as a negative quantity. For instance, if a system raises a weight in the surroundings and in the process does 100 J of work (that is, 100 J of energy leaves the system by doing work), then we write $w = -100$ J. When work is done on the system—for example, when we stretch a muscle from its relaxed position—w is reported as a positive quantity. We write $w = +100$ J to signify that 100 J of work has been done on the system (that is, 100 J of energy has been transferred to the system by doing work). The sign convention is easy to follow if we think of changes to the energy of the system: its energy decreases (w is negative) if energy leaves it and its energy increases (w is positive) if energy enters it (Fig. 1.8).

We use the same convention for energy transferred by heating, q. We write $q = -100$ J if 100 J of energy leaves the system by heating its surroundings, so reducing the energy of the system, and $q = +100$ J if 100 J of energy enters the system when it is heated by the surroundings.

To see how energy flow as work can be determined experimentally, we deal first with **expansion work**, the work done when a system expands against an opposing pressure. In bioenergetics we are not generally concerned with expansion work, which can flow as a result of gas-producing or gas-consuming chemical reactions, but rather with work of making and moving molecules in the cell, muscle contraction, or cell division. However, it is far easier to begin our discussion with expansion work because we have at our disposal a simple equation of the state—the perfect gas equation of state (Section F.7)—that allows us to write simple expressions that provide important insights into the nature of work.

Consider the combustion of urea illustrated in Fig. 1.4 as an example of a reaction in which expansion work is done in the process of making room for the gaseous products, carbon dioxide and nitrogen in this case. We show in the following *Derivation* that when a system expands through a volume ΔV against a constant external pressure p_{ex}, the work done is

$$w = -p_{ex}\Delta V \qquad (1.2)$$

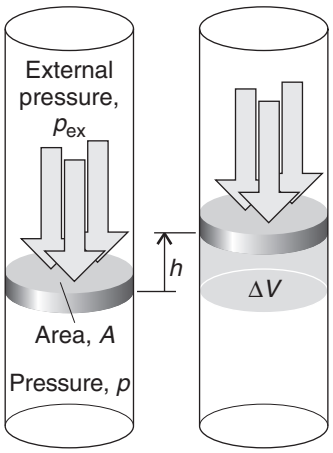


Fig. 1.9 When a piston of area A moves out through a distance h, it sweeps out a volume $\Delta V = Ah$. The external pressure p_{ex} opposes the expansion with a force $p_{ex}A$.

DERIVATION 1.1 Expansion work

To calculate the work done when a system expands from an initial volume V_i to a final volume V_f, a change $\Delta V = V_f - V_i$, we consider a piston of area A moving out through a distance h (Fig. 1.9). There need not be an actual piston:

we can think of the piston as representing the boundary between the expanding gas and the surrounding atmosphere. However, there may be an actual piston, such as when the expansion takes place inside an internal combustion engine.

The force opposing the expansion is the constant external pressure p_{ex} multiplied by the area of the piston (because force is pressure times area; Section F.5). The work done is therefore

$$\textit{Work done by the system} = \textit{distance} \times \textit{opposing force}$$
$$= h \times (p_{ex}A) = p_{ex} \times (hA) = p_{ex} \times \Delta V$$

The last equality follows from the fact that hA is the volume of the cylinder swept out by the piston as the gas expands, so we can write $hA = \Delta V$. That is, for expansion work,

$$\textit{Work done by system} = p_{ex}\Delta V$$

Now consider the sign. A system does work and thereby loses energy (that is, w is negative) when it expands (when ΔV is positive). Therefore, we need a negative sign in the equation to ensure that w is negative (when ΔV is positive), so we obtain eqn 1.2.

According to eqn 1.2, the *external* pressure determines how much work a system does when it expands through a given volume: the greater the external pressure, the greater the opposing force and the greater the work that a system does. When the external pressure is zero, $w = 0$. In this case, the system does no work as it expands because it has nothing to push against. Expansion against zero external pressure is called **free expansion**.

ILLUSTRATION 1.2 The work of exhaling air

Exhalation of air during breathing requires work because air must be pushed out from the lungs against atmospheric pressure. Consider the work of exhaling 0.50 L (5.0×10^{-4} m^3) of air, a typical value for a healthy adult, through a tube into the bottom of the apparatus shown in Fig. 1.9 and against an atmospheric pressure of 1.00 atm (101 kPa). The exhaled air lifts the piston so the change in volume is $\Delta V = 5.0 \times 10^{-4}$ m^3 and the external pressure is $p_{ex} = 101$ kPa. From eqn 1.2 the work of exhaling is

$$w = -p_{ex}\Delta V = -(1.01 \times 10^5 \text{ Pa}) \times (5.0 \times 10^{-4} \text{ m}^3) = -51 \text{ Pa m}^3 = -51 \text{ J}$$

where we have used the relation 1 Pa m^3 = 1 J. We now follow the approach in *Illustration* 1.1 and compare this quantity of work with that required to raise an object against the force of gravity. We use eqn 1.1 to show that −51 J is approximately the same as the work of lifting seven books like this one (a total of 7.0 kg) from the ground to the top of a standard desk (a vertical distance of 0.75 m):

$$w = -(7.0 \text{ kg}) \times (9.81 \text{ m s}^{-2}) \times (0.75 \text{ m}) = -52 \text{ kg m}^2 \text{ s}^{-2} = -52 \text{ J}$$

A note on good practice: Always keep track of signs by considering whether stored energy has left the system as work (w is then negative) or has entered it (w is then positive). ■

SELF-TEST 1.1 Calculate the work done by a system in which a reaction results in the formation of 1.0 mol CO_2(g) at 25°C and 100 kPa. (*Hint:* The increase in volume will be 25 L under these conditions if the gas is treated as perfect; use the relation 1 Pa m^3 = 1 J.)

Answer: 2.5 kJ

Equation 1.2 shows us how to get the *least* expansion work from a system: we just reduce the external pressure—which provides the opposing force—to zero. But how can we achieve the *greatest* work for a given change in volume? According to eqn 1.2, the system does maximum work when the external pressure has its maximum value. The force opposing the expansion is then the greatest and the system must exert most effort to push the piston out. However, that external pressure cannot be greater than the pressure, p, of the gas inside the system, for otherwise the external pressure would compress the gas instead of allowing it to expand. Therefore, *maximum work is obtained when the external pressure is only infinitesimally less than the pressure of the gas in the system.* In effect, the two pressures must be adjusted to be the same at all stages of the expansion. In Section F.5 we called this balance of pressures a state of mechanical equilibrium. Therefore, we can conclude that *a system that remains in mechanical equilibrium with its surroundings at all stages of the expansion does maximum expansion work.*

There is another way of expressing this condition. Because the external pressure is infinitesimally less than the pressure of the gas at some stage of the expansion, the piston moves out. However, suppose we increase the external pressure so that it became infinitesimally greater than the pressure of the gas; now the piston moves in. That is, *when a system is in a state of mechanical equilibrium, an infinitesimal change in the pressure results in opposite directions of change.* A change that can be reversed by an *infinitesimal* change in a variable—in this case, the pressure—is said to be **reversible**. In everyday life "reversible" means a process that can be reversed; in thermodynamics it has a stronger meaning—it means that a process can be reversed by an *infinitesimal* modification in some variable (such as the pressure).

We can summarize this discussion by the following remarks:

1. A system does maximum expansion work when the external pressure is equal to that of the system at every stage of the expansion ($p_{ex} = p$).
2. A system does maximum expansion work when it is in mechanical equilibrium with its surroundings at every stage of the expansion.
3. Maximum expansion work is achieved in a reversible change.

All three statements are equivalent, but they reflect different degrees of sophistication in the way the point is expressed. The last statement is particularly important in our discussion of bioenergetics, especially when we consider how the reactions of catabolism drive anabolic processes. The arguments we have developed lead to the conclusion that maximum work (whether it is expansion work or some other type of work) will be done if cellular processes are reversible. However, no process can be performed in a perfectly reversible manner, so the ultimate energetic limits of life can be estimated but never achieved.

We cannot write down the expression for maximum expansion work simply by replacing p_{ex} in eqn 1.2 by p (the pressure of the gas in the cylinder) because, as the piston moves out, the pressure inside the system falls. To make sure the entire process occurs reversibly, we have to adjust the external pressure to match the internal pressure at each stage, and to calculate the work, we must take into account the fact that the external pressure must change as the system expands. Suppose that we conduct the expansion isothermally (that is, at constant temperature) by immersing the system in a water bath held at a specified temperature. As we show in the following *Derivation*, the work of isothermal, reversible expansion of a perfect gas from an initial volume V_i to a final volume V_f at a temperature T is

$$w = -nRT \ln \frac{V_f}{V_i} \qquad \textbf{(1.3)}$$

where n is the amount of gas in the system.

DERIVATION 1.2 Reversible, isothermal expansion work

Because (to ensure reversibility) the external pressure changes in the course of the expansion, we have to think of the process as taking place in series of small steps during each one of which the external pressure is constant. We calculate the work done in each step for the prevailing external pressure and then add all these values together. To ensure that the overall result is accurate, we have to make the steps as small as possible—infinitesimal, in fact—so that the pressure is truly constant during each one. In other words, we have to use the calculus, in which case the sum over an infinite number of infinitesimal steps becomes an integral.

When the system expands through an infinitesimal volume dV, the infinitesimal work, dw, done is

$$dw = -p_{ex}dV$$

This is eqn 1.2, rewritten for an infinitesimal expansion. However, at each stage, we ensure that the external pressure is the same as the current pressure, p, of the gas (Fig. 1.10), in which case

$$dw = -pdV$$

We can use the system's pressure to calculate the expansion work only for a reversible change, because then the external pressure is matched to the internal pressure for each infinitesimal change in volume.

The total work when the system expands from V_i to V_f is the sum (integral) of all the infinitesimal changes between the limits V_i and V_f, which we write

$$w = -\int_{V_i}^{V_f} pdV$$

To evaluate the integral, we need to know how p, the pressure of the gas in the system, changes as it expands. For this step, we suppose that the gas is perfect, in which case we can use the perfect gas law to write

$$p = \frac{nRT}{V}$$

COMMENT 1.2 For a review of calculus, see *Appendix 2*. As indicated there, the replacement of Δ by d always indicates an infinitesimal change: dV is positive for an infinitesimal increase in volume and negative for an infinitesimal decrease. ■

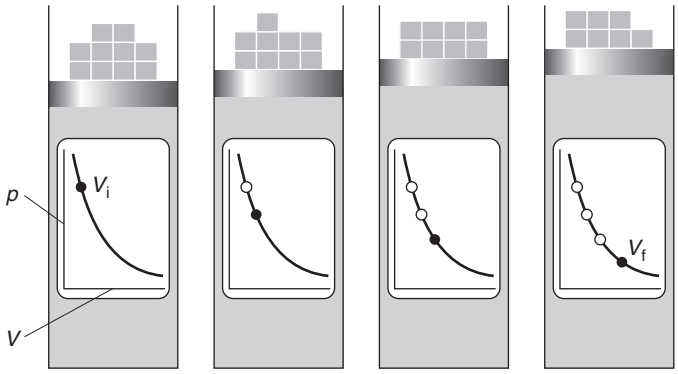


Fig. 1.10 For a gas to expand reversibly, the external pressure must be adjusted to match the internal pressure at each stage of the expansion. This matching is represented in this illustration by gradually unloading weights from the piston as the piston is raised and the internal pressure falls. The procedure results in the extraction of the maximum possible work of expansion.

At this stage we have

$$\textit{For the reversible expansion of a perfect gas:}\quad w = -\int_{V_i}^{V_f} \frac{nRT}{V}\,\mathrm{d}V$$

In general, the temperature might change as the gas expands, so in general T depends on V. For isothermal expansion, however, the temperature is held constant and we can take n, R, and T outside the integral and write

$$\textit{For the isothermal, reversible expansion of a perfect gas:}\quad w = -nRT\int_{V_i}^{V_f} \frac{\mathrm{d}V}{V}$$

The integral is the area under the isotherm $p = nRT/V$ between V_i and V_f (Fig. 1.11) and evaluates to

$$\int_{V_i}^{V_f} \frac{\mathrm{d}V}{V} = \ln \frac{V_f}{V_i}$$

When we insert this result into the preceding one, we obtain eqn 1.3.

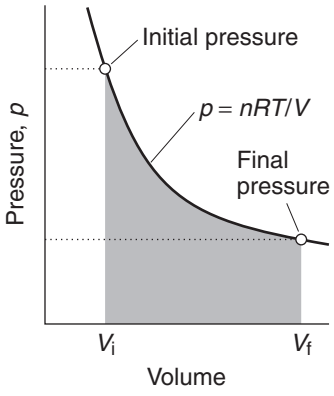


Fig. 1.11 The work of reversible isothermal expansion of a gas is equal to the area beneath the corresponding isotherm evaluated between the initial and final volumes (the tinted area). The isotherm shown here is that of a perfect gas, but the same relation holds for any gas.

COMMENT 1.3 A very useful integral in physical chemistry is

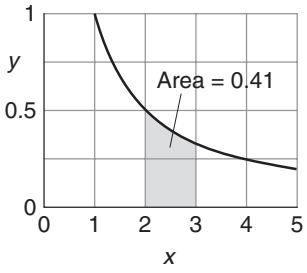
$$\int \frac{\mathrm{d}x}{x} = \ln x + \text{constant}$$

where $\ln x$ is the natural logarithm of x. To evaluate the integral between the limits $x = a$ and $x = b$, we write

$$\begin{aligned}\int_a^b \frac{\mathrm{d}x}{x} &= (\ln x + \text{constant})\Big|_a^b \\ &= (\ln b + \text{constant}) - (\ln a + \text{constant}) \\ &= \ln b - \ln a = \ln \frac{b}{a}\end{aligned}$$

We encounter integrals of this form throughout this text.

It will be helpful to bear in mind that we can always interpret a "definite" integral (an integral with the two limits specified, in this case a and b) as the area under a graph of the function being integrated (in this case the function $1/x$) between the two limits. For instance, the area under the graph of $1/x$ lying between $a = 2$ and $b = 3$ is $\ln(3/2) = 0.41$. ■



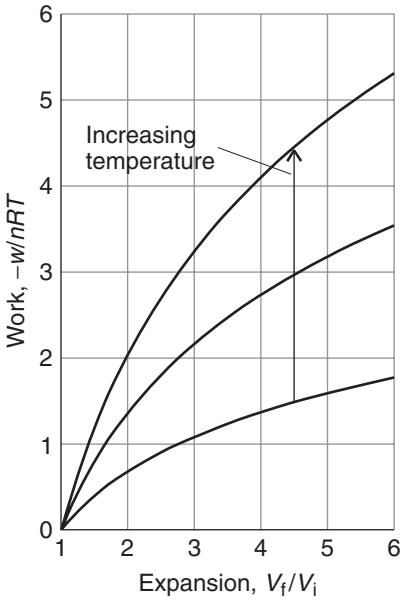


Fig. 1.12 The work of reversible, isothermal expansion of a perfect gas. Note that for a given change of volume and fixed amount of gas, the work is greater the higher the temperature.

A note on good practice: Introduce (and keep note of) the restrictions only as they prove necessary, as you might be able to use a formula without needing to restrict it in some way.

Equation 1.3 will turn up in various disguises throughout this text. Once again, it is important to be able to interpret it rather than just remember it. First, we note that in an expansion $V_f > V_i$, so $V_f/V_i > 1$ and the logarithm is positive ($\ln x$ is positive if $x > 1$). Therefore, in an expansion, w is negative. That is what we should expect: energy *leaves* the system as the system does expansion work. Second, for a given change in volume, we get more work the higher the temperature of the confined gas (Fig. 1.12). That is also what we should expect: at high temperatures, the pressure of the gas is high, so we have to use a high external pressure, and therefore a stronger opposing force, to match the internal pressure at each stage.

SELF-TEST 1.2 Calculate the work done when 1.0 mol Ar(g) confined in a cylinder of volume 1.0 L at 25°C expands isothermally and reversibly to 2.0 L.

Answer: $w = -1.7$ kJ

1.5 The measurement of heat

A thermodynamic assessment of energy output during metabolic processes requires knowledge of ways to measure the energy transferred as heat.

When a substance is heated, its temperature typically rises.[3] However, for a specified energy, q, transferred by heating, the size of the resulting temperature change,

[3]We say "typically" because the temperature does not always rise. The temperature of boiling water, for instance, remains unchanged as it is heated (see Chapter 3).

ΔT, depends on the "heat capacity" of the substance. The **heat capacity**, C, is defined as

$$C = \frac{q}{\Delta T} \qquad \textbf{(1.4a)}$$

(Energy supplied as heat; Change in temperature)

where the temperature change may be expressed in kelvins (ΔT) or degrees Celsius ($\Delta\theta$); the same numerical value is obtained but with the units joules per kelvin (J K^{-1}) and joules per degree Celsius (J $°C^{-1}$), respectively. It follows that we have a simple way of measuring the energy absorbed or released by a system as heat: we measure a temperature change and then use the appropriate value of the heat capacity and eqn 1.4a rearranged into

$$q = C\Delta T \qquad \textbf{(1.4b)}$$

For instance, if the heat capacity of a beaker of water is 0.50 kJ K^{-1} and we observe a temperature rise of 4.0 K, then we can infer that the heat transferred to the water is

$$q = (0.50 \text{ kJ K}^{-1}) \times (4.0 \text{ K}) = 2.0 \text{ kJ}$$

Heat capacities will occur extensively in the following sections and chapters, and we need to be aware of their properties and how their values are reported. First, we note that the heat capacity is an extensive property, a property that depends on the amount of substance in the sample: 2 kg of iron has twice the heat capacity of 1 kg of iron, so twice as much heat is required to change its temperature to the same extent. It is more convenient to report the heat capacity of a substance as an intensive property, a property that is independent of the amount of substance in the sample. We therefore use either the **specific heat capacity**, C_s, the heat capacity divided by the mass of the sample ($C_s = C/m$, in joules per kelvin per gram, J K^{-1} g^{-1}), or the **molar heat capacity**, C_m, the heat capacity divided by the amount of substance ($C_m = C/n$, in joules per kelvin per mole, J K^{-1} mol^{-1}). In common usage, the specific heat capacity is often called the *specific heat*.

For reasons that will be explained shortly, the heat capacity of a substance depends on whether the sample is maintained at constant volume (like a gas in a sealed vessel) as it is heated or whether the sample is maintained at constant pressure (like water in an open container) and free to change its volume. The latter is a more common arrangement, and the values given in Table 1.1 are for the **heat capacity at constant pressure**, C_p. The **heat capacity at constant volume** is denoted C_V.

COMMENT 1.4 Recall from introductory chemistry that an *extensive property* is a property that depends on the amount of substance in the sample. Mass, pressure, and volume are examples of extensive properties. An *intensive property* is a property that is independent of the amount of substance in the sample. The molar volume and temperature are examples of intensive properties. ■

ILLUSTRATION 1.3 Using the heat capacity

The high heat capacity of water is ecologically advantageous because it stabilizes the temperatures of lakes and oceans: a large quantity of energy must be lost or gained before there is a significant change in temperature. The molar heat capacity of water at constant pressure, $C_{p,m}$, is 75 J K^{-1} mol^{-1}. It follows that the

Table 1.1 Heat capacities of selected substances*

Substance	Molar heat capacity, $C_{p,m}$/(J K^{-1} mol^{-1})*
Air	29
Benzene, $C_6H_6(l)$	136.1
Ethanol, $C_2H_5OH(l)$	111.46
Glycine, $CH_2(NH_2)COOH(s)$	99.2
Oxalic acid, $(COOH)_2$	117
Urea, $CO(NH_2)_2(s)$	93.14
Water, $H_2O(s)$	37
$H_2O(l)$	75.29
$H_2O(g)$	33.58

*For additional values, see the *Data section.*

increase in temperature of 100 g of water (5.55 mol H_2O) when 1.0 kJ of energy is supplied by heating a sample free to expand is approximately

$$\Delta T = \frac{q}{C_p} = \frac{q}{nC_{p,m}} = \frac{1.0 \times 10^3 \text{ J}}{(5.55 \text{ mol}) \times (75 \text{ J K}^{-1} \text{ mol}^{-1})} = +2.4 \text{ K} \quad \blacksquare$$

In certain cases, we can relate the value of q to the change in volume of a system and so can calculate, for instance, the flow of energy as heat into the system when a gas expands. The simplest case is that of a perfect gas undergoing isothermal expansion. Because the expansion is isothermal, the temperature of the gas is the same at the end of the expansion as it was initially. Therefore, the mean speed of the molecules of the gas is the same before and after the expansion. That implies in turn that the total kinetic energy of the molecules is the same. But for a perfect gas, the *only* contribution to the energy is the kinetic energy of the molecules (recall Section F.7), so we have to conclude that the *total* energy of the gas is the same before and after the expansion. Energy has left the system as work; therefore, a compensating amount of energy must have entered the system as heat. We can therefore write

For the isothermal expansion of a perfect gas: $q = -w$ **(1.5)**

For instance, if we find that $w = -100$ J for a particular expansion (meaning that 100 J has left the system as a result of the system doing work), then we can conclude that $q = +100$ J (that is, 100 J must enter as heat). For free expansion, $w = 0$, so we conclude that $q = 0$ too: there is no influx of energy as heat when a perfect gas expands against zero pressure.

If the isothermal expansion is also reversible, we can use eqn 1.3 for the work in eqn 1.5 and write

For the isothermal, reversible expansion of a perfect gas: $q = nRT \ln \dfrac{V_f}{V_i}$ **(1.6)**

When $V_f > V_i$, as in an expansion, the logarithm is positive and we conclude that $q > 0$, as expected: energy flows as heat into the system to make up for the energy lost as work. We also see that the greater the ratio of the final and initial volumes, the greater the influx of energy as heat.

Internal energy and enthalpy

Heat and work are *equivalent* ways of transferring energy into or out of a system in the sense that once the energy is inside, it is stored simply as "energy": regardless of how the energy was supplied, as work or as heat, it can be released in either form. The experimental evidence for this **equivalence of heat and work** goes all the way back to the experiments done by James Joule, who showed that the same rise in temperature of a sample of water is brought about by transferring a given quantity of energy either as heat or as work.

1.6 The internal energy

To understand how biological processes can store and release energy, we need to describe a very important law that relates work and heat to changes in the energy of all the constituents of a system.

We need some way of keeping track of the energy changes in a system. This is the job of the property called the **internal energy**, U, of the system, the sum of all the kinetic and potential contributions to the energy of all the atoms, ions, and molecules in the system. The internal energy is the grand total energy of the system with a value that depends on the temperature and, in general, the pressure. It is an extensive property because 2 kg of iron at a given temperature and pressure, for instance, has twice the internal energy of 1 kg of iron under the same conditions. The **molar internal energy**, $U_m = U/n$, the internal energy per mole of material, is an intensive property.

In practice, we do not know and cannot measure the total energy of a sample, because it includes the kinetic and potential energies of all the electrons and all the components of the atomic nuclei. Nevertheless, there is no problem with dealing with the *changes* in internal energy, ΔU, because we can determine those changes by monitoring the energy supplied or lost as heat or as work. All practical applications of thermodynamics deal with ΔU, not with U itself. A change in internal energy is written

$$\Delta U = w + q \qquad \textbf{(1.7)}$$

where w is the energy transferred to the system by doing work and q the energy transferred to it by heating. The internal energy is an accounting device, like a country's gold reserves for monitoring transactions with the outside world (the surroundings) using either currency (heat or work).

We have seen that a feature of a perfect gas is that for any *isothermal* expansion, the total energy of the sample remains the same and that $q = -w$. That is, any energy lost as work is restored by an influx of energy as heat. We can express this property in terms of the internal energy, for it implies that the internal energy remains constant when a perfect gas expands isothermally: from eqn 1.7 we can write

$$\textit{Isothermal expansion of a perfect gas: } \Delta U = 0 \qquad \textbf{(1.8)}$$

In other words, *the internal energy of a sample of perfect gas at a given temperature is independent of the volume it occupies*. We can understand this independence by realizing that when a perfect gas expands isothermally, the only feature that changes is the average distance between the molecules; their average speed and therefore

total kinetic energy remains the same. However, as there are no intermolecular interactions, the total energy is independent of the average separation, so the internal energy is unchanged by expansion.

EXAMPLE 1.1 Calculating the change in internal energy

Nutritionists are interested in the use of energy by the human body, and we can consider our own body as a thermodynamic "system." Suppose in the course of an experiment you do 622 kJ of work on an exercise bicycle and lose 82 kJ of energy as heat. What is the change in your internal energy? Disregard any matter loss by perspiration.

Strategy This example is an exercise in keeping track of signs correctly. When energy is lost from the system, w or q is negative. When energy is gained by the system, w or q is positive.

Solution To take note of the signs, we write $w = -622$ kJ (622 kJ is lost by doing work) and $q = -82$ kJ (82 kJ is lost by heating the surroundings). Then eqn 1.7 gives us

$$\Delta U = w + q = (-622 \text{ kJ}) + (-82 \text{ kJ}) = -704 \text{ kJ}$$

We see that your internal energy falls by 704 kJ. Later, that energy will be restored by eating.

A note on good practice: Always attach the correct signs: use a positive sign when there is a flow of energy into the system and a negative sign when there is a flow of energy out of the system. Also, the quantity ΔU always carries a sign explicitly, even if it is positive: we never write $\Delta U = 20$ kJ, for instance, but always $+20$ kJ.

SELF-TEST 1.3 An electric battery is charged by supplying 250 kJ of energy to it as electrical work (by driving an electric current through it), but in the process it loses 25 kJ of energy as heat to the surroundings. What is the change in internal energy of the battery?

Answer: $+225$ kJ ■

An important characteristic of the internal energy is that it is a **state function**, a physical property that depends only on the present state of the system and is independent of the path by which that state was reached. If we were to change the temperature of the system, then change the pressure, then adjust the temperature and pressure back to their original values, the internal energy would return to its original value too. A state function is very much like altitude: each point on the surface of the Earth can be specified by quoting its latitude and longitude, and (on land areas, at least) there is a unique property, the altitude, that has a fixed value at that point. In thermodynamics, the role of latitude and longitude is played by the pressure and temperature (and any other variables needed to specify the state of the system), and the internal energy plays the role of the altitude, with a single, fixed value for each state of the system.

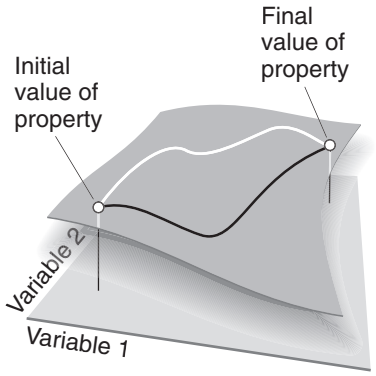


Fig. 1.13 The curved sheet shows how a property (for example, the altitude) changes as two variables (for example, latitude and longitude) are changed. The altitude is a state property, because it depends only on the current state of the system. The change in the value of a state property is independent of the path between the two states. For example, the difference in altitude between the initial and final states shown in the diagram is the same whatever path (as depicted by the dark and light lines) is used to travel between them.

The fact that U is a state function implies that *a change, ΔU, in the internal energy between two states of a system is independent of the path between them* (Fig. 1.13). Once again, the altitude is a helpful analogy. If we climb a mountain between two fixed points, we make the same change in altitude regardless of the path we take between the two points. Likewise, if we compress a sample of gas until it reaches a certain pressure and then cool it to a certain temperature, the change in internal energy has a particular value. If, on the other hand, we changed the temperature and then the pressure but ensured that the two final values were the same as in the first experiment, then the overall change in internal energy would be exactly the same as before. This path independence of the value of ΔU is of the greatest importance in chemistry, as we shall soon see.

Suppose we now consider an isolated system. Because an isolated system can neither do work nor heat the surroundings, it follows that its internal energy cannot change. That is,

The internal energy of an isolated system is constant.

This statement is the **First Law of thermodynamics**. It is closely related to the law of conservation of energy but allows for transaction of energy by heating as well as by doing work. Unlike thermodynamics, mechanics does not deal with the concept of heat.

The experimental evidence for the First Law is the impossibility of making a "perpetual motion machine," a device for producing work without consuming fuel. As we have already remarked, try as people might, they have never succeeded. No device has ever been made that creates internal energy to replace the energy drawn off as work. We cannot extract energy as work, leave the system isolated for some time, and hope that when we return, the internal energy will have become restored to its original value. The same is true of organisms: energy required for the sustenance of life must be supplied continually in the form of food as work is done by the organism.

The definition of ΔU in terms of w and q points to a very simple method for measuring the change in internal energy of a system when a reaction takes place. We have seen already that the work done by a system when it pushes against a fixed external pressure is proportional to the change in volume. Therefore, if we carry out a reaction in a container of constant volume, the system can do no expansion work, and provided it can do no other kind of work (so-called non-

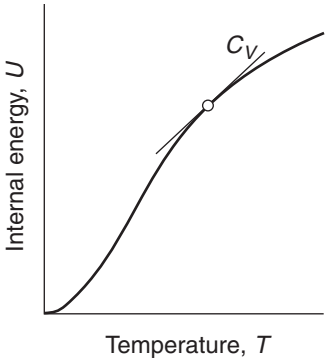


Fig. 1.14 The constant-volume heat capacity is the slope of a curve showing how the internal energy varies with temperature. The slope, and therefore the heat capacity, may be different at different temperatures.

expansion work, such as electrical work), we can set $w = 0$. Then eqn 1.7 simplifies to

$$\textit{At constant volume, no non-expansion work: } \Delta U = q \qquad \textbf{(1.9a)}$$

This relation is commonly written

$$\Delta U = q_V \qquad \textbf{(1.9b)}$$

The subscript V signifies that the volume of the system is constant. An example of a chemical system that can be approximated as a constant-volume container is an individual biological cell.

We can use eqn 1.9 to obtain more insight into the heat capacity of a substance. The definition of heat capacity is given in eqn 1.4 ($C = q/\Delta T$). At constant volume, q may be replaced by the change in internal energy of the substance, so

$$C_V = \frac{\Delta U}{\Delta T} \text{ at constant volume} \qquad \textbf{(1.10a)}$$

The expression on the right is the slope of the graph of internal energy plotted against temperature, with the volume of the system held constant, so C_V tells us how the internal energy of a constant-volume system varies with temperature. If, as is generally the case, the graph of internal energy against temperature is not a straight line, we interpret C_V as the slope of the tangent to the curve at the temperature of interest (Fig. 1.14). That is, the constant-volume heat capacity is the derivative of the function U with respect to the variable T at a specified volume, or

$$C_V = \frac{dU}{dT} \text{ at constant volume} \qquad \textbf{(1.10b)}$$

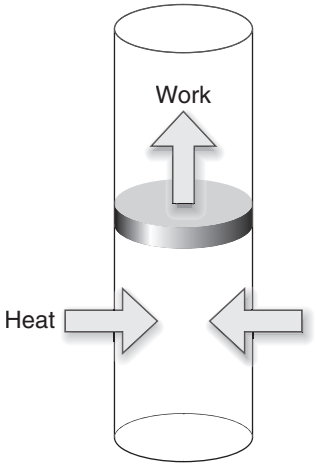


Fig. 1.15 The change in internal energy of a system that is free to expand or contract is not equal to the energy supplied by heating because some energy may escape back into the surroundings as work. However, the change in enthalpy of the system under these conditions *is* equal to the energy supplied by heating.

1.7 The enthalpy

Most biological processes take place in vessels that are open to the atmosphere and subjected to constant pressure and not maintained at constant volume, so we need to learn how to treat quantitatively the energy exchanges that take place by heating at constant pressure.

In general, when a change takes place in a system open to the atmosphere, the volume of the system changes. For example, the thermal decomposition of 1.0 mol $CaCO_3(s)$ at 1 bar results in an increase in volume of 89 L at 800°C on account of the carbon dioxide gas produced. To create this large volume for the carbon dioxide to occupy, the surrounding atmosphere must be pushed back. That is, the system must perform expansion work. Therefore, although a certain quantity of heat may be supplied to bring about the endothermic decomposition, the increase in internal energy of the system is not equal to the energy supplied as heat because some energy has been used to do work of expansion (Fig. 1.15). In other words, because the volume has increased, some of the heat supplied to the system has leaked back into the surroundings as work.

Another example is the oxidation of a fat, such as tristearin, to carbon dioxide in the body. The overall reaction is

$$2\ C_{57}H_{110}O_6(s) + 163\ O_2(g) \longrightarrow 114\ CO_2(g) + 110\ H_2O(l)$$

In this exothermic reaction there is a net *decrease* in volume equivalent to the elimination of (163 − 114) mol = 49 mol of gas molecules for every 2 mol of tristearin molecules that reacts. The decrease in volume at 25°C is about 600 mL for the consumption of 1 g of fat. Because the volume of the system decreases, the atmosphere does work *on* the system as the reaction proceeds. That is, energy is transferred to the system as it contracts.[4] For this reaction, the decrease in the internal energy of the system is less than the energy released as heat because some energy has been restored by doing work.

We can avoid the complication of having to take into account the work of expansion by introducing a new property that will be at the center of our attention throughout the rest of the chapter and will recur throughout the book. The **enthalpy**, H, of a system is defined as

$$H = U + pV \qquad \textbf{(1.11)}$$

That is, the enthalpy differs from the internal energy by the addition of the product of the pressure, p, and the volume, V, of the system. This expression applies to *any* system or individual substance: don't be mislead by the pV term into thinking that eqn 1.11 applies only to a perfect gas. A change in enthalpy (the only quantity we can measure in practice) arises from a change in the internal energy and a change in the product pV:

$$\Delta H = \Delta U + \Delta(pV) \qquad \textbf{(1.12a)}$$

where $\Delta(pV) = p_fV_f - p_iV_i$. If the change takes place at constant pressure p, the second term on the right simplifies to

$$\Delta(pV) = pV_f - pV_i = p(V_f - V_i) = p\Delta V$$

and we can write

$$\textit{At constant pressure: } \Delta H = \Delta U + p\Delta V \qquad \textbf{(1.12b)}$$

We shall often make use of this important relation for processes occurring at constant pressure, such as chemical reactions taking place in containers open to the atmosphere.

Enthalpy is an extensive property. The **molar enthalpy**, $H_m = H/n$, of a substance, an intensive property, differs from the molar internal energy by an amount proportional to the molar volume, V_m, of the substance:

$$H_m = U_m + pV_m \qquad \textbf{(1.13a)}$$

[4]In effect, a weight has been lowered in the surroundings, so the surroundings can do less work after the reaction has occurred. Some of their energy has been transferred into the system.

This relation is valid for all substances. For a perfect gas we can go on to write $pV_m = RT$ and obtain

For a perfect gas: $H_m = U_m + RT$ **(1.13b)**

At 25°C, $RT = 2.5$ kJ mol^{-1}, so the molar enthalpy of a perfect gas differs from its molar internal energy by 2.5 kJ mol^{-1}. Because the molar volume of a solid or liquid is typically about 1000 times less than that of a gas, we can also conclude that the molar enthalpy of a solid or liquid is only about 2.5 J mol^{-1} (note: joules, not kilojoules) more than its molar internal energy, so the numerical difference is negligible.

Although the enthalpy and internal energy of a sample may have similar values, the introduction of the enthalpy has very important consequences in thermodynamics. First, notice that because H is defined in terms of state functions (U, p, and V), *the enthalpy is a state function*. The implication is that the change in enthalpy, ΔH, when a system changes from one state to another is independent of the path between the two states. Second, we show in the following *Derivation* that the change in enthalpy of a system can be identified with the heat transferred to it at constant pressure:

At constant pressure, no non-expansion work: $\Delta H = q$ **(1.14a)**

This relation is commonly written

$\Delta H = q_p$ **(1.14b)**

the subscript p signifying that the pressure is held constant. Therefore, by imposing the constraint of constant pressure, we have identified an observable quantity (the energy transferred as heat) with a change in a state function, the enthalpy. Dealing with state functions greatly extends the power of thermodynamic arguments, because we don't have to worry about how we get from one state to another: all that matters is the initial and final states. For the particular case of the combustion of tristearin mentioned at the beginning of the section, in which 90 kJ of energy is released as heat at constant pressure, we would write $\Delta H = -90$ kJ regardless of how much expansion work is done.

DERIVATION 1.3 Heat transfers at constant pressure

Consider a system open to the atmosphere, so that its pressure p is constant and equal to the external pressure p_{ex}. From eqn 1.13a we can write

$$\Delta H = \Delta U + p\Delta V = \Delta U + p_{ex}\Delta V$$

However, we know that the change in internal energy is given by eqn 1.7 ($\Delta U = w + q$) with $w = -p_{ex}\Delta V$ (provided the system does no other kind of work). When we substitute that expression into this one we obtain

$$\Delta H = (-p_{ex}\Delta V + q) + p_{ex}\Delta V = q$$

which is eqn 1.14.

An endothermic reaction ($q > 0$) taking place at constant pressure results in an increase in enthalpy ($\Delta H > 0$) because energy enters the system as heat. On the other hand, an exothermic process ($q < 0$) taking place at constant pressure corresponds to a decrease in enthalpy ($\Delta H < 0$) because energy leaves the system as heat. All combustion reactions, including the controlled combustions that contribute to respiration, are exothermic and are accompanied by a decrease in enthalpy. These relations are consistent with the name *enthalpy*, which is derived from the Greek words meaning "heat inside": the "heat inside" the system is increased if the process is endothermic and absorbs energy as heat from the surroundings; it is decreased if the process is exothermic and releases energy as heat into the surroundings.[5]

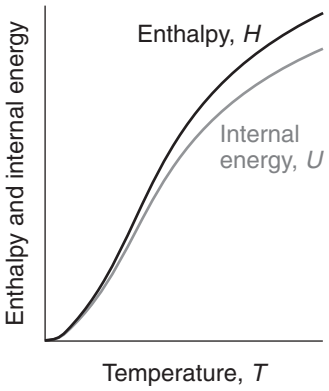


Fig. 1.16 The enthalpy of a system increases as its temperature is raised. Note that the enthalpy is always greater than the internal energy of the system and that the difference increases with temperature.

1.8 The temperature variation of the enthalpy

To make full use of the enthalpy in biochemical calculations, we need to describe its properties, such as its dependence on temperature.

We have seen that the internal energy of a system rises as the temperature is increased. The same is true of the enthalpy, which also rises when the temperature is increased (Fig. 1.16). For example, the enthalpy of 100 g of water is greater at 80°C than at 20°C. We can measure the change by monitoring the energy that we must supply as heat to raise the temperature through 60°C when the sample is open to the atmosphere (or subjected to some other constant pressure); it is found that $\Delta H \approx +25$ kJ in this instance.

Just as we saw that the constant-volume heat capacity tells us about the temperature-dependence of the internal energy at constant volume, so the constant-pressure heat capacity tells us how the enthalpy of a system changes as its temperature is raised at constant pressure. To derive the relation, we combine the definition of heat capacity in eqn 1.4 ($C = q/\Delta T$) with eqn 1.14 and obtain

$$C_p = \frac{\Delta H}{\Delta T} \qquad \text{at constant pressure} \qquad \textbf{(1.15a)}$$

That is, the constant-pressure heat capacity is the slope of a plot of enthalpy against temperature of a system kept at constant pressure. Because the plot might not be a straight line, in general we interpret C_p as the slope of the tangent to the curve at the temperature of interest (Fig. 1.17), Table 1.1). That is, the constant-pressure heat capacity is the derivative of the function H with respect to the variable T at a specified pressure or

$$C_p = \frac{dH}{dT} \qquad \text{at constant pressure} \qquad \textbf{(1.15b)}$$

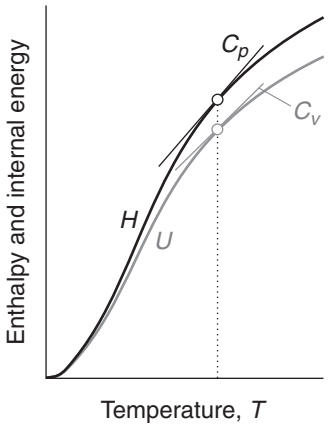


Fig. 1.17 The heat capacity at constant pressure is the slope of the curve showing how the enthalpy varies with temperature; the heat capacity at constant volume is the corresponding slope of the internal energy curve. Note that the heat capacity varies with temperature (in general) and that C_p is greater than C_V.

ILLUSTRATION 1.4 Using the constant-pressure heat capacity

Provided the heat capacity is constant over the range of temperatures of interest, we can write eqn 1.15a as $\Delta H = C_p \Delta T$. This relation means that when the

[5]But heat does not actually "exist" inside: only energy exists in a system; heat is a means of recovering that energy or increasing it. Heat is energy in transit, not a form in which energy is stored.

temperature of 100 g of water (5.55 mol H_2O) is raised from 20°C to 80°C (so $\Delta T = +60$ K) at constant pressure, the enthalpy of the sample changes by

$$\Delta H = C_p \Delta T = nC_{p,m}\Delta T = (5.55 \text{ mol}) \times (75.29 \text{ J K}^{-1} \text{ mol}^{-1}) \times (60 \text{ K}) = +25 \text{ kJ}$$

The greater the temperature rise, the greater the change in enthalpy and therefore the more heating required to bring it about. Note that this calculation is only approximate, because the heat capacity depends on the temperature, and we have used an average value for the temperature range of interest. ■

The difference between $C_{p,m}$ and $C_{V,m}$ is significant for gases (for oxygen, $C_{V,m} = 20.8$ J K^{-1} mol^{-1} and $C_{p,m} = 29.1$ J K^{-1} mol^{-1}), which undergo large changes of volume when heated, but is negligible for most solids and liquids. For a perfect gas, you will show in Exercise 1.19 that

$$C_{p,m} - C_{V,m} = R \qquad \textbf{(1.16)}$$

Physical change

We shall focus on the use of the enthalpy as a useful bookkeeping property for tracing the flow of energy as heat during physical processes and chemical reactions at constant pressure. The discussion will lead naturally to a quantitative treatment of the factors that optimize the suitability of fuels, including "biological fuels," the foods we ingest to meet the energy requirements of daily life.

First, we consider physical change, such as when one form of a substance changes into another form of the same substance, as when ice melts to water. We shall also include the breaking and formation of a bond in a molecule.

1.9 The enthalpy of phase transition

To begin to understand the complex structural changes that biological macromolecules undergo when heated or cooled, we need to understand how simpler physical changes occur.

To describe physical change quantitatively, we need to keep track of the numerical value of a thermodynamic property with varying conditions, such as the states of the substances involved, the pressure, and the temperature. To simplify the calculations, chemists have found it convenient to report their data for a set of standard conditions at the temperature of their choice:

The **standard state** of a substance is the pure substance at exactly 1 bar.[6]

We denote the standard state value by the superscript $^{\ominus}$ on the symbol for the property, as in $H_m^{\ominus}$ for the standard molar enthalpy of a substance and $p^{\ominus}$ for the standard pressure of 1 bar. For example, the standard state of hydrogen gas is the pure gas at 1 bar and the standard state of solid calcium carbonate is the pure solid at 1 bar, with either the calcite or aragonite form specified. The physical state needs

[6]Remember that 1 bar = 10^5 Pa exactly. Solutions are a special case and are dealt with in Chapter 3.

to be specified because we can speak of the standard states of the solid, liquid, and vapor forms of water, for instance, which are the pure solid, the pure liquid, and the pure vapor, respectively, at 1 bar in each case.

In older texts you might come across a standard state defined for 1 atm (101.325 kPa) in place of 1 bar. That is the old convention. In most cases, data for 1 atm differ only a little from data for 1 bar. You might also come across standard states defined as referring to 298.15 K. That is incorrect: temperature is not a part of the definition of standard state, and standard states may refer to any temperature (but it should be specified). Thus, it is possible to speak of the standard state of water vapor at 100 K, 273.15 K, or any other temperature. It is conventional, though, for data to be reported at the so-called **conventional temperature** of 298.15 K (25.00°C), and from now on, unless specified otherwise, all data will be for that temperature. For simplicity, we shall often refer to 298.15 K as "25°C." Finally, a standard state need not be a stable state and need not be realizable in practice. Thus, the standard state of water vapor at 25°C is the vapor at 1 bar, but water vapor at that temperature and pressure would immediately condense to liquid water.

Before going on, we need to add a few more terms to our vocabulary. A **phase** is a specific state of matter that is uniform throughout in composition and physical state. The liquid and vapor states of water are two of its phases. The term "phase" is more specific than "state of matter" because a substance may exist in more than one solid form, each one of which is a solid phase. There are at least twelve forms of ice. No substance has more than one gaseous phase, so "gas phase" and "gaseous state" are effectively synonyms. The only substance that exists in more than one liquid phase is helium, although evidence is accumulating that water may also have two liquid phases.

The conversion of one phase of a substance to another phase is called a **phase transition**. Thus, vaporization (liquid ⟶ gas) is a phase transition, as is a transition between solid phases (such as aragonite ⟶ calcite in geological processes). With a few exceptions, most phase transitions are accompanied by a change of enthalpy, for the rearrangement of atoms or molecules usually requires or releases energy.

The vaporization of a liquid, such as the conversion of liquid water to water vapor when a pool of water evaporates at 20°C or a kettle boils at 100°C, is an endothermic process ($\Delta H > 0$), because heating is required to bring about the change. At a molecular level, molecules are being driven apart from the grip they exert on one another, and this process requires energy. One of the body's strategies for maintaining its temperature at about 37°C is to use the endothermic character of the vaporization of water, because the evaporation[7] of perspiration requires energy and withdraws it from the skin.

The energy that must be supplied as heat at constant pressure per mole of molecules that are vaporized under standard conditions (that is, pure liquid at 1 bar changing to pure vapor at 1 bar) is called the **standard enthalpy of vaporization** of the liquid and is denoted $\Delta_{vap}H^{\ominus}$ (Table 1.2).[8] For example, 44 kJ of heat is required to vaporize 1 mol H_2O(l) at 1 bar and 25°C, so $\Delta_{vap}H^{\ominus} = 44\ \text{kJ mol}^{-1}$.

[7]Evaporation is virtually synonymous with vaporization but commonly denotes vaporization to dryness.

[8]The attachment of the subscript vap to the Δ is the modern convention; however, the older convention in which the subscript is attached to the H, as in ΔH_{vap}, is still widely used.

Table 1.2 Standard enthalpies of transition at the transition temperature*

Substance	Freezing point, T_f/K	$\Delta_{fus}H^{\ominus}$/(kJ mol^{-1})	Boiling point, T_b/K	$\Delta_{vap}H^{\ominus}$/(kJ mol^{-1})
Ammonia, NH_3	195.3	5.65	239.7	23.4
Argon, Ar	83.8	1.2	87.3	6.5
Benzene, C_6H_6	278.7	9.87	353.3	30.8
Ethanol, C_2H_5OH	158.7	4.60	351.5	43.5
Helium, He	3.5	0.02	4.22	0.08
Hydrogen peroxide, H_2O_2	272.7	12.50	423.4	51.6
Mercury, Hg	234.3	2.292	629.7	59.30
Methane, CH_4	90.7	0.94	111.7	8.2
Methanol, CH_3OH	175.5	3.16	337.2	35.3
Propanone, CH_3COCH_3	177.8	5.72	329.4	29.1
Water, H_2O	273.15	6.01	373.2	40.7

*For values at 298.15 K, use the information in the *Data section*.

All enthalpies of vaporization are positive, so the sign is not normally given. Alternatively, we can report the same information by writing the **thermochemical equation**[9]

$$H_2O(l) \longrightarrow H_2O(g) \qquad \Delta H^{\ominus} = +44 \text{ kJ}$$

A thermochemical equation shows the standard enthalpy change (including the sign) that accompanies the conversion of an amount of reactant equal to its stoichiometric coefficient in the accompanying chemical equation (in this case, 1 mol H_2O). If the stoichiometric coefficients in the chemical equation are multiplied through by 2, then the thermochemical equation would be written

$$2\ H_2O(l) \longrightarrow 2\ H_2O(g) \qquad \Delta H^{\ominus} = +88 \text{ kJ}$$

This equation signifies that 88 kJ of heat is required to vaporize 2 mol H_2O(l) at 1 bar and (recalling our convention) at 298.15 K.

There are some striking differences in standard enthalpies of vaporization: although the value for water is 44 kJ mol^{-1}, that for methane, CH_4, at its boiling point is only 8 kJ mol^{-1}. Even allowing for the fact that vaporization is taking place at different temperatures, the difference between the enthalpies of vaporization signifies that water molecules are held together in the bulk liquid much more tightly than methane molecules are in liquid methane. We shall see in Chapter 11 that the interaction responsible for the low volatility of water is the hydrogen bond, an attractive interaction between two species that arises from a link of the form A–H···B, where A and B are highly electronegative elements (such as oxygen) and B possesses one or more lone pairs of electrons (such as oxygen in H_2O).

The high enthalpy of vaporization of water has profound ecological consequences, for it is partly responsible for the survival of the oceans and the generally

COMMENT 1.5 The electronegativity of an element is the power of its atoms to draw electrons to itself when it is part of a compound. The concept should be familiar from introductory chemistry but is also discussed in Chapter 10. ■

[9]Unless otherwise stated, all data in this text are for 298.15 K.

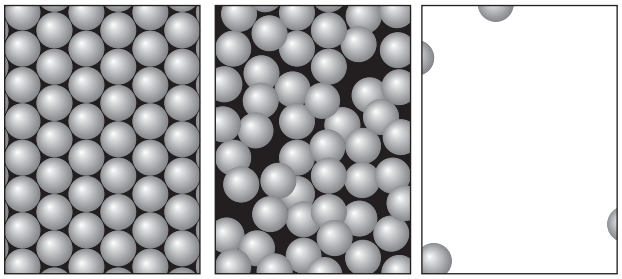


Fig. 1.18 When a solid (a) melts to a liquid (b), the molecules separate from one another only slightly, the intermolecular interactions are reduced only slightly, and there is only a small change in enthalpy. When a liquid vaporizes (c), the molecules are separated by a considerable distance, the intermolecular forces are reduced almost to zero, and the change in enthalpy is much greater.

low humidity of the atmosphere. If only a small amount of heat had to be supplied to vaporize the oceans, the atmosphere would be much more heavily saturated with water vapor than is in fact the case.

Another common phase transition is **fusion**, or melting, as when ice melts to water. The change in molar enthalpy that accompanies fusion under standard conditions (pure solid at 1 bar changing to pure liquid at 1 bar) is called the **standard enthalpy of fusion**, $\Delta_{fus}H^{\ominus}$. Its value for water at 0°C is 6.01 kJ mol^{-1} (all enthalpies of fusion are positive, and the sign need not be given), which signifies that 6.01 kJ of energy is needed to melt 1 mol H_2O(s) at 0°C and 1 bar. Notice that the enthalpy of fusion of water is much less than its enthalpy of vaporization. In vaporization the molecules become completely separated from each other, whereas in melting the molecules are merely loosened without separating completely (Fig. 1.18).

COMMENT 1.6 Links to computer animations illustrating changes in molecular motion during phase transitions will be found on the web site for this book. ■

The reverse of vaporization is **condensation** and the reverse of fusion (melting) is **freezing**. The molar enthalpy changes are, respectively, the negative of the enthalpies of vaporization and fusion, because the energy that is supplied (during heating) to vaporize or melt the substance is released when it condenses or freezes.[10] It is always the case that *the enthalpy change of a reverse transition is the negative of the enthalpy change of the forward transition* (under the same conditions of temperature and pressure):

$$H_2O(s) \longrightarrow H_2O(l) \qquad \Delta H^{\ominus} = +6.01 \text{ kJ}$$
$$H_2O(l) \longrightarrow H_2O(s) \qquad \Delta H^{\ominus} = -6.01 \text{ kJ}$$

and in general

$$\Delta_{forward}H^{\ominus} = -\Delta_{reverse}H^{\ominus} \qquad (1.17)$$

This relation follows from the fact that H is a state property, so it must return to the same value if a forward change is followed by the reverse of that change (Fig. 1.19). The high standard enthalpy of vaporization of water (+44 kJ mol^{-1}),

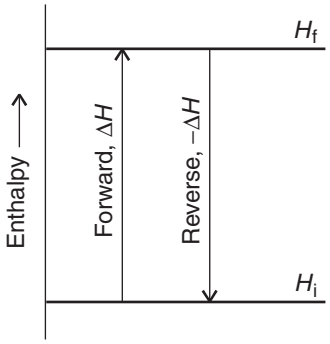


Fig. 1.19 An implication of the First Law is that the enthalpy change accompanying a reverse process is the negative of the enthalpy change for the forward process.

[10]This relation is the origin of the obsolescent terms "latent heat" of vaporization and fusion for what are now termed the enthalpy of vaporization and fusion.

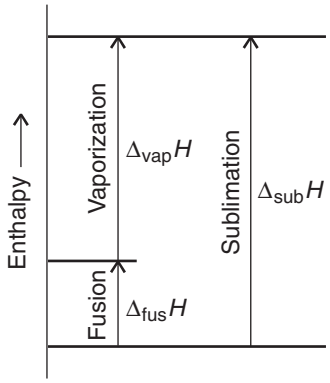


Fig. 1.20 The enthalpy of sublimation at a given temperature is the sum of the enthalpies of fusion and vaporization at that temperature. Another implication of the First Law is that the enthalpy change of an overall process is the sum of the enthalpy changes for the possibly hypothetical steps into which it may be divided.

signifying a strongly endothermic process, implies that the condensation of water (-44 kJ mol^{-1}) is a strongly exothermic process. That exothermicity is the origin of the ability of steam to scald severely, because the energy is passed on to the skin.

The direct conversion of a solid to a vapor is called **sublimation**. The reverse process is called **vapor deposition**. Sublimation can be observed on a cold, frosty morning, when frost vanishes as vapor without first melting. The frost itself forms by vapor deposition from cold, damp air. The vaporization of solid carbon dioxide ("dry ice") is another example of sublimation. The standard molar enthalpy change accompanying sublimation is called the **standard enthalpy of sublimation**, $\Delta_{sub}H^{\ominus}$. Because enthalpy is a state property, the same change in enthalpy must be obtained both in the *direct* conversion of solid to vapor and in the *indirect* conversion, in which the solid first melts to the liquid and then that liquid vaporizes (Fig. 1.20):

$$\Delta_{sub}H^{\ominus} = \Delta_{fus}H^{\ominus} + \Delta_{vap}H^{\ominus} \qquad \textbf{(1.18)}$$

This result is an example of a more general statement that will prove useful time and again during our study of thermochemistry:

> *The enthalpy change of an overall process is the sum of the enthalpy changes for the steps (observed or hypothetical) into which it may be divided.*

ILLUSTRATION 1.5 The enthalpy of sublimation of water

To use eqn 1.18 correctly, the two enthalpies that are added together must be for the same temperature, so to get the enthalpy of sublimation of water at 0°C, we must add together the enthalpies of fusion (6.01 kJ mol^{-1}) and vaporization (45.07 kJ mol^{-1}) for this temperature. Adding together enthalpies of transition for different temperatures gives a meaningless result. It follows that

$$\begin{aligned}\Delta_{sub}H^{\ominus} &= \Delta_{fus}H^{\ominus} + \Delta_{vap}H^{\ominus} = 6.01 \text{ kJ mol}^{-1} + 45.07 \text{ kJ mol}^{-1} \\ &= 51.08 \text{ kJ mol}^{-1}\end{aligned}$$

A note on good practice: Molar quantities are expressed as a quantity per mole (as in kilojoules per mole, kJ mol^{-1}). Distinguish them from the magnitude of a property *for* 1 mol of substance, which is expressed as the quantity itself (as in kilojoules, kJ). All enthalpies of transition, denoted $\Delta_{trs}H$, are molar quantities. ■

1.10 Toolbox: Differential scanning calorimetry

> *We need to describe experimental techniques that can be used to observe phase transitions in biological macromolecules.*

A **differential scanning calorimeter**[11] (DSC) is used to measure the energy transferred as heat to or from a sample at constant pressure during a physical or chemical change. The term "differential" refers to the fact that the behavior of the sample is compared to that of a reference material that does not undergo a physical or chemical change during the analysis. The term "scanning" refers to the fact that the temperatures of the sample and reference material are increased, or scanned, systematically during the analysis.

[11]The word *calorimeter* comes from "calor," the Latin word for *heat*.

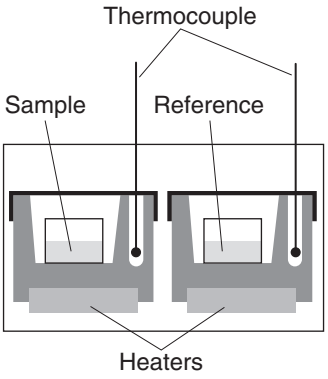


Fig. 1.21 A differential scanning calorimeter. The sample and a reference material are heated in separate but identical compartments. The output is the difference in power needed to maintain the compartments at equal temperatures as the temperature rises.

A DSC consists of two small compartments that are heated electrically at a constant rate (Fig. 1.21). The temperature, T, at time t during a linear scan is

$$T = T_0 + \alpha t$$

where T_0 is the initial temperature and α is the temperature scan rate (in kelvin per second, K s^{-1}). A computer controls the electrical power output in order to maintain the same temperature in the sample and reference compartments throughout the analysis.

The temperature of the sample changes significantly relative to that of the reference material if a chemical or physical process that involves heating occurs in the sample during the scan. To maintain the same temperature in both compartments, excess energy is transferred as heat to the sample during the process. For example, an endothermic process lowers the temperature of the sample relative to that of the reference and, as a result, the sample must be supplied with more energy (as heat) than the reference in order to maintain equal temperatures.

If no physical or chemical change occurs in the sample at temperature T, we can use eqn 1.4 to write $q_p = C_p\Delta T$, where $\Delta T = T - T_0 = \alpha t$ and we have assumed that C_p is independent of temperature. If an endothermic process occurs in the sample, we have to supply additional "excess" energy by heating, $q_{p,\text{ex}}$, to achieve the same change in temperature of the sample and can express this excess energy in terms of an additional contribution to the heat capacity, $C_{p,\text{ex}}$, by writing $q_{p,\text{ex}} = C_{p,\text{ex}}\Delta T$. It follows that

$$C_{p,\text{ex}} = \frac{q_{p,\text{ex}}}{\Delta T} = \frac{q_{p,\text{ex}}}{\alpha t} = \frac{P_{\text{ex}}}{\alpha}$$

where $P_{\text{ex}} = q_{p,\text{ex}}/t$ is the excess electrical power necessary to equalize the temperature of the sample and reference compartments.

A DSC trace, also called a *thermogram*, consists of a plot of P_{ex} or $C_{p,\text{ex}}$ against T (Fig. 1.22). Broad peaks in the thermogram indicate processes requiring the transfer of energy by heating. We show in the following *Derivation* that the enthalpy change of the process is

$$\Delta H = \int_{T_1}^{T_2} C_{p,\text{ex}}\mathrm{d}T \qquad \textbf{(1.19)}$$

That is, the enthalpy change is the area under the curve of $C_{p,\text{ex}}$ against T between the temperatures at which the process begins and ends.

COMMENT 1.7 Electrical charge is measured in *coulombs*, C. The motion of charge gives rise to an electric current, I, measured in coulombs per second, or *amperes*, A, where

$1\ \text{A} = 1\ \text{C}\ \text{s}^{-1}$

If current flows through a potential difference $\mathscr{V}$ (measured in volts, V), the total energy supplied in an interval t is

Energy supplied $= I\mathscr{V}t$

Because

$1\ \text{A V s} = 1\ (\text{C}\ \text{s}^{-1})\ \text{V s}$
$= 1\ \text{C V} = 1\ \text{J}$

the energy is obtained in joules with the current in amperes, the potential difference in volts, and the time in seconds. For instance, if a current of 0.50 A from a 12 V source is passed for 360 s,

Energy supplied $= (0.50\ \text{A}) \times (12\ \text{V}) \times (360\ \text{s}) = 2.2 \times 10^3\ \text{J}$, or 2.2 kJ

The *rate of change of energy* is the power, expressed as joules per second, or *watts*, W:

$1\ \text{W} = 1\ \text{J}\ \text{s}^{-1}$

Because 1 J = 1 A V s, in terms of electrical units 1 W = 1 A V. We write the electrical power, P, as

$P = (\textit{energy supplied})/t$
$= I\mathscr{V}t/t = I\mathscr{V}$ ■

COMMENT 1.8
Infinitesimally small quantities may be treated like any other quantity in algebraic manipulations. So, the expression $dy/dx = a$ may be rewritten as $dy = a dx$, $dx/dy = a^{-1}$, and so on. ■

DERIVATION 1.4 The enthalpy change of a process from DSC data

To calculate an enthalpy change from a thermogram, we begin by rewriting eqn 1.15b as

$$dH = C_p dT$$

We proceed by integrating both sides of this expression from an initial temperature T_1 and initial enthalpy H_1 to a final temperature T_2 and enthalpy H_2.

$$\int_{H_1}^{H_2} dH = \int_{T_1}^{T_2} C_{p,ex} dT$$

Now we use the integral $\int dx = x + \text{constant}$ to write

$$\int_{H_1}^{H_2} dH = H_2 - H_1 = \Delta H$$

It follows that

$$\Delta H = \int_{T_1}^{T_2} C_{p,ex} dT$$

which is eqn 1.19.

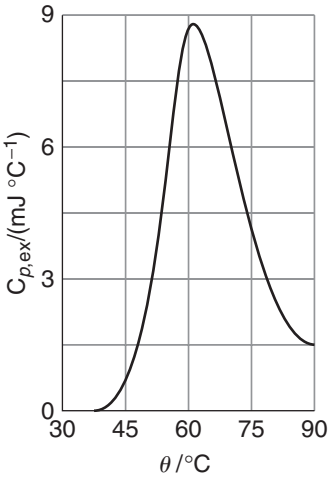


Fig. 1.22 A thermogram for the protein ubiquitin. The protein retains its native structure up to about 45°C and then undergoes an endothermic conformational change. (Adapted from B. Chowdhry and S. LeHarne, *J. Chem. Educ.* **74**, 236 [1997].)

CASE STUDY 1.1 Thermal Denaturation of a Protein

An important type of phase transition occurs in biological macromolecules, such as proteins and nucleic acids, and aggregates, such as biological membranes. Such large systems attain complex three-dimensional structures due to intra- and intermolecular interactions (Chapter 11). The disruption of these interactions is called **denaturation**. It can be achieved by adding chemical agents (such as urea, acids, or bases) or by changing the temperature, in which case the process is called **thermal denaturation**. Cooking is an example of thermal denaturation. For example, when eggs are cooked, the protein albumin is denatured irreversibly.

Differential scanning calorimetry is a useful technique for the study of denaturation of biological macromolecules. Every biopolymer has a characteristic temperature, the melting temperature T_m, at which the three-dimensional structure unravels with attendant loss of biological function. For example, the thermogram shown in Fig. 1.22 indicates that the widely distributed protein ubiquitin retains its native structure up to about 45°C and "melts" into a disordered state at higher temperatures. Differential scanning calorimetry is a convenient method for such studies because it requires small samples, with masses as low as 0.5 mg. ■

Chemical change

In the remainder of this chapter we concentrate on enthalpy changes accompanying chemical reactions, such as the fermentation of glucose into ethanol and CO_2, a reaction used by anaerobic organisms to harness energy stored in carbohydrates:

$$C_6H_{12}O_6(s) \longrightarrow 2\ C_2H_5OH(l) + 2\ CO_2(g) \qquad \Delta H^{\ominus} = -72\ kJ$$

The value of $\Delta H^{\ominus}$ given here signifies that the enthalpy of the system decreases by 72 kJ (and, if the reaction takes place at constant pressure, that 72 kJ of energy is released by heating the surroundings) when 1 mol $C_6H_{12}O_6(s)$ decomposes into 2 mol $C_2H_5OH(l)$ to give 2 mol $CO_2(g)$ at 1 bar, all at 25°C.

1.11 The bond enthalpy

To understand bioenergetics, we need to account for the flow of energy during chemical reactions as individual chemical bonds are broken and made.

The thermochemical equation for the dissociation, or breaking, of a chemical bond can be written with the hydroxyl radical OH(g) as an example:

$$HO(g) \longrightarrow H(g) + O(g) \qquad \Delta H^{\ominus} = +428 \text{ kJ}$$

The corresponding standard molar enthalpy change is called the **bond enthalpy**, so we would report the H–O bond enthalpy as 428 kJ mol^{-1}. All bond enthalpies are positive, so bond dissociation is an endothermic process.

Some bond enthalpies are given in Table 1.3. Note that the nitrogen-nitrogen bond in molecular nitrogen, N_2, is very strong, at 945 kJ mol^{-1}, which helps to account for the chemical inertness of nitrogen and its ability to dilute the oxygen in the atmosphere without reacting with it. In contrast, the fluorine-fluorine bond in molecular fluorine, F_2, is relatively weak, at 155 kJ mol^{-1}; the weakness of this bond contributes to the high reactivity of elemental fluorine. However, bond enthalpies alone do not account for reactivity because, although the bond in molecular iodine is even weaker, I_2 is less reactive than F_2, and the bond in CO is stronger than the bond in N_2, but CO forms many carbonyl compounds, such as $Ni(CO)_4$. The types and strengths of the bonds that the elements can make to other elements are additional factors.

A complication when dealing with bond enthalpies is that their values depend on the molecule in which the two linked atoms occur. For instance, the total

COMMENT 1.9 Recall that a radical is a very reactive species containing one or more unpaired electrons. To emphasize the presence of an unpaired electron in a radical, it is common to use a dot (·) when writing the chemical formula. For example, the chemical formula of the hydroxyl radical may be written as ·OH. Hydroxyl radicals and other reactive species containing oxygen can be produced in organisms as undesirable by-products of electron transfer reactions and have been implicated in the development of cardiovascular disease, cancer, stroke, inflammatory disease, and other conditions. ■

Table 1.3 Selected bond enthalpies, $\Delta H(A—B)/(kJ\ mol^{-1})$

Diatomic molecules

H—H	436	O=O	497	F—F	155	H—F	565
		N≡N	945	Cl—Cl	242	H—Cl	431
		O—H	428	Br—Br	193	H—Br	366
		C≡O	1074	I—I	151	H—I	299

Polyatomic molecules

$H—CH_3$	435	$H—NH_2$	431	H—OH	492
$H—C_6H_5$	469	$O_2N—NO_2$	57	HO—OH	213
$H_3C—CH_3$	368	O=CO	531	$HO—CH_3$	377
$H_2C=CH_2$	699			$Cl—CH_3$	452
HC≡CH	962			$Br—CH_3$	293
				$I—CH_3$	234

standard enthalpy change for the atomization (the complete dissociation into atoms) of water:

$$H_2O(g) \longrightarrow 2\ H(g) + O(g) \qquad \Delta H^{\ominus} = +927\ kJ$$

is not twice the O–H bond enthalpy in H_2O even though two O–H bonds are dissociated. There are in fact two different dissociation steps. In the first step, an O–H bond is broken in an H_2O molecule:

$$H_2O(g) \longrightarrow HO(g) + H(g) \qquad \Delta H^{\ominus} = +499\ kJ$$

In the second step, the O–H bond is broken in an OH radical:

$$HO(g) \longrightarrow H(g) + O(g) \qquad \Delta H^{\ominus} = +428\ kJ$$

The sum of the two steps is the atomization of the molecule. As can be seen from this example, the O–H bonds in H_2O and HO have similar but not identical bond enthalpies.

Although accurate calculations must use bond enthalpies for the molecule in question and its successive fragments, when such data are not available, there is no choice but to make estimates by using **mean bond enthalpies**, ΔH_B, which are the averages of bond enthalpies over a related series of compounds (Table 1.4). For ex-

Table 1.4 Mean bond enthalpies, $\Delta H_B/(kJ\ mol^{-1})$*

	H	C	N	O	F	Cl	Br	I	S	P	Si
H	436										
C	412	348 (1) 612 (2) 838 (3) 518 (a)†									
N	388	305 (1) 613 (2) 890 (3)	163 (1) 409 (2) 945 (3)								
O	463	360 (1) 743 (2)	157	146 (1) 97 (2)							
F	565	484	270	185	155						
Cl	431	338	200	203	254	242					
Br	366	276				219	193				
I	299	238				210	178	151			
S	338	259			496	250	212		264		
P	322									200	
Si	318		374	466							226

*Values are for single bonds except where otherwise stated (in parentheses).

†(a) Denotes aromatic.

ample, the mean HO bond enthalpy, $\Delta H_B(H–O) = 463$ kJ mol^{-1}, is the mean of the O–H bond enthalpies in H_2O and several other similar compounds, including methanol, CH_3OH.

EXAMPLE 1.2 Using mean bond enthalpies

Use information from the *Data section* and bond enthalpy data from Tables 1.3 and 1.4 to estimate the standard enthalpy change for the reaction

$$2\ H_2O_2(l) \longrightarrow 2\ H_2O(l) + O_2(g)$$

in which liquid hydrogen peroxide decomposes into O_2 and water at 25°C. In the aqueous environment of biological cells, hydrogen peroxide—a very reactive species—is formed as a result of some processes involving O_2. The enzyme catalase helps rid organisms of toxic hydrogen peroxide by accelerating its decomposition.

Strategy In calculations of this kind, the procedure is to break the overall process down into a sequence of steps such that their sum is the chemical equation required. Always ensure, when using bond enthalpies, that all the species are in the gas phase. That may mean including the appropriate enthalpies of vaporization or sublimation. One approach is to atomize all the reactants and then to build the products from the atoms so produced. When explicit bond enthalpies are available (that is, data are given in the tables available), use them; otherwise, use mean bond enthalpies to obtain estimates.

Solution The following steps are required:

	$\Delta H^\ominus$/kJ
Vaporization of 2 mol H_2O_2(l), $2\ H_2O_2(l) \longrightarrow 2\ H_2O_2(g)$	$2 \times (+51.6)$
Dissociation of 4 mol O–H bonds:	$4 \times (+463)$
Dissociation of 2 mol O–O bonds in HO–OH:	$2 \times (+213)$
Overall, so far: $2\ H_2O_2(l) \longrightarrow 4\ H(g) + 4\ O(g)$	+2381

We have used the mean bond enthalpy value from Table 1.4 for the O–H bond and the exact bond enthalpy value for the O–O bond in HO–OH from Table 1.3. In the second step, four O–H bonds and one O=O bond are formed. The standard enthalpy change for bond formation (the reverse of dissociation) is the negative of the bond enthalpy. We can use exact values for the enthalpy of the O–H bond in $H_2O(g)$ and for the O=O bond in $O_2(g)$:

	$\Delta H^\ominus$/kJ
Formation of 4 mol O–H bonds:	$4 \times (-492)$
Formation of 1 mol O_2:	−497
Overall, in this step: $4\ O(g) + 4\ H(g) \longrightarrow 2\ H_2O(g) + O_2(g)$	−2465

The final stage of the reaction is the condensation of 2 mol $H_2O(g)$:

$$2\ H_2O(g) \longrightarrow 2\ H_2O(l) \qquad \Delta H^\ominus = 2 \times (-44\ \text{kJ}) = -88\ \text{kJ}$$

The sum of the enthalpy changes is

$$\Delta H^{\ominus} = (+2381\ \text{kJ}) + (-2465\ \text{kJ}) + (-88\ \text{kJ}) = -172\ \text{kJ}$$

The experimental value is −196 kJ.

SELF-TEST 1.4 Estimate the enthalpy change for the reaction between liquid ethanol, a fuel made by fermenting corn, and $O_2(g)$ to yield $CO_2(g)$ and $H_2O(l)$ under standard conditions by using the bond enthalpies, mean bond enthalpies, and the appropriate standard enthalpies of vaporization.

Answer: −1348 kJ; the experimental value is −1368 kJ ■

1.12 Thermochemical properties of fuels

We need to understand the molecular origins of the energy content of biological fuels, the carbohydrates, fats, and proteins.

We saw in Section 1.3 that photosynthesis and the oxidation of organic molecules are the most important processes that supply energy to organisms. Here, we begin a quantitative study of biological energy conversion by assessing the thermochemical properties of fuels.

(a) Enthalpies of combustion

The consumption of a fuel in a furnace or an engine is the result of a combustion. An example is the combustion of methane in a natural gas flame:

$$CH_4(g) + 2\ O_2(g) \longrightarrow CO_2(g) + 2\ H_2O(l) \qquad \Delta H^{\ominus} = -890\ \text{kJ}$$

The **standard enthalpy of combustion**, $\Delta_c H^{\ominus}$, is the standard change in enthalpy per mole of combustible substance. In this example, we would write $\Delta_c H^{\ominus}(CH_4, g) = -890\ \text{kJ mol}^{-1}$. Some typical values are given in Table 1.5. Note that $\Delta_c H^{\ominus}$ is a molar quantity and is obtained from the value of $\Delta H^{\ominus}$ by dividing by the amount of organic reactant consumed (in this case, by 1 mol CH_4).

According to the discussion in Section 1.6 and the relation $\Delta U = q_V$, the energy transferred as heat at constant volume is equal to the change in internal energy, ΔU, not ΔH. To convert from ΔU to ΔH, we need to note that the molar enthalpy of a substance is related to its molar internal energy by $H_m = U_m + pV_m$ (eqn 1.13a). For condensed phases, pV_m is so small, it may be ignored. For example, the molar volume of liquid water is 18 $\text{cm}^3\ \text{mol}^{-1}$, and at 1.0 bar

$$\begin{aligned} pV_m &= (1.0 \times 10^5\ \text{Pa}) \times (18 \times 10^{-6}\ \text{m}^3\ \text{mol}^{-1}) = 1.8\ \text{Pa m}^3\ \text{mol}^{-1} \\ &= 1.8\ \text{J mol}^{-1} \end{aligned}$$

However, the molar volume of a gas, and therefore the value of pV_m, is about 1000 times greater and cannot be ignored. For gases treated as perfect, pV_m may be replaced by RT. Therefore, if in the chemical equation the difference (products − reactants) in the stoichiometric coefficients of *gas phase* species is $\Delta\nu_{\text{gas}}$, we can write

$$\Delta_c H = \Delta_c U + \Delta\nu_{\text{gas}} RT \qquad \textbf{(1.20)}$$

Note that $\Delta\nu_{\text{gas}}$ (where ν is nu) is a dimensionless number.

Table 1.5 Standard enthalpies of combustion

Substance	$\Delta_c H^\circ/(\text{kJ mol}^{-1})$
Carbon, C(s, graphite)	−394
Carbon monoxide, CO(g)	−394
Citric acid, $C_6H_8O_7$(s)	−1985
Ethanol, C_2H_5OH(l)	−1368
Glucose, $C_6H_{12}O_6$(s)	−2808
Glycine, $CH_2(NH_2)COOH$(s)	−969
Hydrogen, H_2(g)	−286
iso-Octane,* C_8H_{18}(l)	−5461
Methane, CH_4(g)	−890
Methanol, CH_3OH(l)	−726
Methylbenzene, $C_6H_5CH_3$(l)	−3910
Octane, C_8H_{18}(l)	−5471
Propane, C_3H_8(g)	−2220
Pyruvic acid, $CH_3(CO)COOH$(l)	−950
Sucrose, $C_{12}H_{22}O_{11}$(s)	−5645
Urea, $CO(NH_2)_2$(s)	−632

*2,2,4-Trimethylpentane.

ILLUSTRATION 1.6 Converting between $\Delta_c H$ and $\Delta_c U$

The energy released as heat by the combustion of the amino acid glycine is 969.6 kJ mol^{-1} at 298.15 K, so $\Delta_c U = -969.6$ kJ mol^{-1}. From the chemical equation

$$NH_2CH_2COOH(s) + \tfrac{9}{4}\,O_2(g) \longrightarrow 2\,CO_2(g) + \tfrac{5}{2}\,H_2O(l) + \tfrac{1}{2}\,N_2(g)$$

we find that $\Delta\nu_{gas} = (2 + \frac{1}{2}) - \frac{9}{4} = \frac{1}{4}$. Therefore,

$$\begin{aligned}\Delta_c H &= \Delta_c U + \tfrac{1}{4}RT = -969.6\ \text{kJ mol}^{-1} \\ &\quad + \tfrac{1}{4} \times (8.3145 \times 10^{-3}\ \text{J K}^{-1}\ \text{mol}^{-1}) \times (298.15\ \text{K}) \\ &= -969.6\ \text{kJ mol}^{-1} + 0.62\ \text{kJ mol}^{-1} = -969.0\ \text{kJ mol}^{-1}\end{aligned}$$ ■

We shall see in Chapter 2 that the best assessment of the ability of a compound to act as a fuel to drive many of the processes occurring in the body makes use of the "Gibbs energy." However, a useful guide to the resources provided by a fuel, and the only one that matters when energy transferred as heat is being considered, is the enthalpy, particularly the enthalpy of combustion. The thermochemical properties of fuels and foods are commonly discussed in terms of their *specific enthalpy*, the enthalpy of combustion per gram of material, or the *enthalpy density*, the magnitude of the enthalpy of combustion per liter of material. Thus, if the standard enthalpy of combustion is $\Delta_c H^\ominus$ and the molar mass of the compound is M, then the specific enthalpy is $\Delta_c H^\ominus/M$. Similarly, the enthalpy density is $\Delta_c H^\ominus/V_m$, where V_m is the molar volume of the material.

Table 1.6 lists the specific enthalpies and enthalpy densities of several fuels. The most suitable fuels are those with high specific enthalpies, as the advantage of a high molar enthalpy of combustion may be eliminated if a large mass of fuel is to be transported. We see that H_2 gas compares very well with more traditional fuels such as methane (natural gas), octane (gasoline), and methanol. Furthermore, the

Table 1.6 Thermochemical properties of some fuels

Fuel	Combustion equation	$\Delta_c H°/(\text{kJ mol}^{-1})$	Specific enthalpy/ (kJ g^{-1})	Enthalpy density*/ (kJ L^{-1})
Hydrogen	$2\ H_2(g) + O_2(g) \rightarrow 2\ H_2O(l)$	−286	142	13
Methane	$CH_4(g) + 2\ O_2(g) \rightarrow CO_2(g) + 2\ H_2O(l)$	−890	55	40
iso-Octane†	$2\ C_8H_{18}(l) + 25\ O_2(g) \rightarrow 16\ CO_2(g) + 18\ H_2O(l)$	−5461	48	3.3×10^4
Methanol	$2\ CH_3OH(l) + 3\ O_2(g) \rightarrow 2\ CO_2(g) + 4\ H_2O(l)$	−726	23	1.8×10^4

*At atmospheric pressures and room temperature.

†2,2,4-Trimethylpentane.

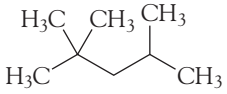
combustion of H_2 gas does not generate CO_2 gas, a pollutant implicated in the mechanism of global warming. As a result, H_2 gas has been proposed as an efficient, clean alternative to fossil fuels, such as natural gas and petroleum. However, we also see that H_2 gas has a very low enthalpy density, which arises from the fact that hydrogen is a very light gas. So, the advantage of a high specific enthalpy is undermined by the large volume of fuel to be transported and stored. Strategies are being developed to solve the storage problem. For example, the small H_2 molecules can travel through holes in the crystalline lattice of a sample of metal, such as titanium, where they bind as metal hydrides. In this way it is possible to increase the effective density of hydrogen atoms to a value that is higher than that of liquid H_2. Then the fuel can be released on demand by heating the metal.

We now assess the factors that optimize the enthalpy of combustion of carbon-based fuels, with an eye toward understanding such biological fuels as carbohydrates, fats, and proteins. Let's consider the combustion of 1 mol $CH_4(g)$. The reaction involves changes in the oxidation numbers of carbon from −4 to +4, an oxidation, and of oxygen from 0 to −2, a reduction. From the thermochemical equation, we see that 890 kJ of energy is released as heat per mole of carbon atoms that are oxidized. Now consider the oxidation of 1 mol $CH_3OH(g)$:

COMMENT 1.10 See *Appendix 4* for a review of oxidation numbers. ■

$$CH_3OH(g) + \tfrac{3}{2}\ O_2(g) \longrightarrow CO_2(g) + 2\ H_2O(l) \qquad \Delta H^{\ominus} = -401\ \text{kJ}$$

This reaction is also exothermic, but now only 401 kJ of energy is released as heat per mole of carbon atoms that undergo oxidation. Much of the observed change in energy output between the reactions can be explained by noting that the carbon atom in CH_3OH has an oxidation number of −2, and not −4 as in CH_4. That is, the replacement of a C–H bond by a C–O bond renders the carbon in methanol more oxidized than the carbon in methane, so it is reasonable to expect that less energy is released to complete the oxidation of carbon in methanol to CO_2. In general, we find that the presence of partially oxidized carbon atoms (that is, carbon atoms bonded to oxygen atoms) in a material makes it a less suitable fuel than a similar material containing more highly reduced carbon atoms.



5 2,2,4-Trimethylpentane

Another factor that determines the enthalpy of combustion reactions is the number of carbon atoms in hydrocarbon compounds. For example, from the value of the standard enthalpy of combustion for methane we know that for each mole of CH_4 supplied to a furnace, 890 kJ of heat can be released, whereas for each mole of iso-octane (C_8H_{18}, 2,2,4-trimethylpentane, **5**, a typical component of gasoline)

supplied to an internal combustion engine, 5471 kJ of energy is released as heat (Table 1.6). The much larger value for iso-octane is a consequence of each molecule having eight C atoms to contribute to the formation of carbon dioxide, whereas methane has only one.

(b) Biological fuels

A typical 18- to 20-year-old man requires a daily energy input of about 12 MJ (1 MJ = 10^6 J); a woman of the same age needs about 9 MJ. If the entire consumption were in the form of glucose, which has a specific enthalpy of 16 kJ g^{-1}, meeting energy needs would require the consumption of 750 g of glucose by a man and 560 g by a woman. In fact, the complex carbohydrates (polymers of carbohydrate units, such as starch, as discussed in Chapter 11) more commonly found in our diets have slightly higher specific enthalpies (17 kJ g^{-1}) than glucose itself, so a carbohydrate diet is slightly less daunting than a pure glucose diet, as well as being more appropriate in the form of fiber, the indigestible cellulose that helps move digestion products through the intestine.

The specific enthalpy of fats, which are long-chain esters such as tristearin, is much greater than that of carbohydrates, at around 38 kJ g^{-1}, slightly less than the value for the hydrocarbon oils used as fuel (48 kJ g^{-1}). The reason for this difference lies in the fact that many of the carbon atoms in carbohydrates are bonded to oxygen atoms and are already partially oxidized, whereas most of the carbon atoms in fats are bonded to hydrogen and other carbon atoms and hence have lower oxidation numbers. As we saw above, the presence of partially oxidized carbons lowers the energy output of a fuel.

Fats are commonly used as an energy store, to be used only when the more readily accessible carbohydrates have fallen into short supply. In Arctic species, the stored fat also acts as a layer of insulation; in desert species (such as the camel), the fat is also a source of water, one of its oxidation products.

Proteins are also used as a source of energy, but their components, the amino acids, are also used to construct other proteins. When proteins are oxidized (to urea, $CO(NH_2)_2$), the equivalent enthalpy density is comparable to that of carbohydrates.

We have already remarked that not all the energy released by the oxidation of foods is used to perform work. The energy that is also released as heat needs to be discarded in order to maintain body temperature within its typical range of 35.6 to 37.8°C. A variety of mechanisms contribute to this aspect of **homeostasis**, the ability of an organism to counteract environmental changes with physiological responses. The general uniformity of temperature throughout the body is maintained largely by the flow of blood. When energy needs to be dissipated rapidly by heating, warm blood is allowed to flow through the capillaries of the skin, so producing flushing. Radiation is one means of heating the surroundings; another is evaporation and the energy demands of the enthalpy of vaporization of water.

ILLUSTRATION 1.7 Dissipation of energy through perspiration

From the enthalpy of vaporization ($\Delta_{vap}H^{\ominus}$ = 44 kJ mol^{-1}), molar mass (M = 18 g mol^{-1}), and mass density ($\rho = 1.0 \times 10^3$ g L^{-1}) of water, the energy removed as heat through evaporation per liter of water perspired is

$$q = \frac{\rho\Delta_{vap}H^{\ominus}}{M} = \frac{(1.0 \times 10^3\ \text{g L}^{-1}) \times (44\ \text{kJ mol}^{-1})}{18\ \text{g mol}^{-1}} = 2.4\ \text{MJ L}^{-1}$$

where we have used 1 MJ = 10^6 J. When vigorous exercise promotes sweating (through the influence of heat selectors on the hypothalamus), 1 to 2 L of perspired water can be produced per hour, corresponding to a loss of energy of approximately 2.4 to 5.0 MJ h^{-1}. ■

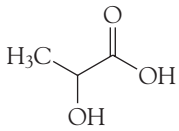
1.13 The combination of reaction enthalpies

To make progress in our study of bioenergetics, we need to develop methods for predicting the reaction enthalpies of complex biochemical reactions.

It is often the case that a reaction enthalpy is needed but is not available in tables of data. Now the fact that enthalpy is a state function comes in handy, because it implies that we can construct the required reaction enthalpy from the reaction enthalpies of known reactions. We have already seen a primitive example when we calculated the enthalpy of sublimation from the sum of the enthalpies of fusion and vaporization. The only difference is that we now apply the technique to a sequence of chemical reactions. The procedure is summarized by **Hess's law**:

> The standard enthalpy of a reaction is the sum of the standard enthalpies of the reactions into which the overall reaction may be divided.

Although the procedure is given the status of a law, it hardly deserves the title because it is nothing more than a consequence of enthalpy being a state function, which implies that an overall enthalpy change can be expressed as a sum of enthalpy changes for each step in an indirect path. The individual steps need not be actual reactions that can be carried out in the laboratory—they may be entirely hypothetical reactions, the only requirement being that their equations should balance. Each step must correspond to the same temperature.



6 Lactic acid

EXAMPLE 1.3 Using Hess's law

In biological cells that have a plentiful supply of O_2, glucose is oxidized completely to CO_2 and H_2O (Section 1.12). Muscle cells may be deprived of O_2 during vigorous exercise and, in that case, one molecule of glucose is converted to two molecules of lactic acid (**6**) by the process of glycolysis (Section 4.9). Given the thermochemical equations for the combustions of glucose and lactic acid:

$$C_6H_{12}O_6(s) + 6\ O_2(g) \longrightarrow 6\ CO_2(g) + 6\ H_2O(l) \qquad \Delta H^\ominus = -2808\ \text{kJ}$$

$$CH_3CH(OH)COOH(s) + 3\ O_2(g) \longrightarrow 3\ CO_2(g) + 3\ H_2O(l) \qquad \Delta H^\ominus = -1344\ \text{kJ}$$

calculate the standard enthalpy for glycolysis:

$$C_6H_{12}O_6(s) \longrightarrow 2\ CH_3CH(OH)COOH(s)$$

Is there a biological advantage of complete oxidation of glucose compared with glycolysis? Explain your answer.

Strategy We need to add or subtract the thermochemical equations so as to reproduce the thermochemical equation for the reaction required.

Solution We obtain the thermochemical equation for glycolysis from the following sum:

	$\Delta H^{\ominus}$/kJ
$C_6H_{12}O_6(s) + 6\ O_2(g) \longrightarrow 6\ CO_2(g) + 6\ H_2O(l)$	−2808
$6\ CO_2(g) + 6\ H_2O(l) \longrightarrow 2\ CH_3CH(OH)COOH(s) + 6\ O_2(g)$	$2 \times (+1344$ kJ)
Overall: $C_6H_{12}O_6(s) \longrightarrow 2\ CH_3CH(OH)COOH(s)$	−120

It follows that the standard enthalpy for the conversion of glucose to lactic acid during glycolysis is -120 kJ mol^{-1}, a mere 4% of the enthalpy of combustion of glucose. Therefore, full oxidation of glucose is metabolically more useful than glycolysis, because in the former process more energy becomes available for performing work.

SELF-TEST 1.5 Calculate the standard enthalpy of the fermentation $C_6H_{12}O_6(s) \longrightarrow 2\ C_2H_5OH(l) + 2\ CO_2(g)$ from the standard enthalpies of combustion of glucose and ethanol (Table 1.5).

Answer: −72 kJ ■

1.14 Standard enthalpies of formation

We need to simplify even further the process of predicting reaction enthalpies of biochemical reactions.

The **standard reaction enthalpy**, $\Delta_r H^{\ominus}$, is the difference between the standard molar enthalpies of the reactants and the products, with each term weighted by the stoichiometric coefficient, ν (nu), in the chemical equation

$$\Delta_r H^{\ominus} = \sum \nu H_m^{\ominus}(\text{products}) - \sum \nu H_m^{\ominus}(\text{reactants}) \qquad \textbf{(1.21)}$$

where Σ (uppercase sigma) denotes a sum. Because the $H_m^{\ominus}$ are molar quantities and the stoichiometric coefficients are pure numbers, the units of $\Delta_r H^{\ominus}$ are kilojoules per mole. The standard reaction enthalpy is the change in enthalpy of the system when the reactants in their standard states (pure, 1 bar) are completely converted into products in their standard states (pure, 1 bar), with the change expressed in kilojoules per mole of reaction as written.

The problem with eqn 1.21 is that we have no way of knowing the absolute enthalpies of the substances. To avoid this problem, we can imagine the reaction as taking place by an indirect route, in which the reactants are first broken down into the elements and then the products are formed from the elements (Fig. 1.23). Specifically, the **standard enthalpy of formation**, $\Delta_f H^{\ominus}$, of a substance is the standard enthalpy (per mole of the substance) for its formation from its elements in their reference states. The **reference state** of an element is its most stable form under the prevailing conditions (Table 1.7). Don't confuse "reference state" with "standard state": the reference state of carbon at 25°C is graphite (not diamond); the standard state of carbon is any specified phase of the element at 1 bar. For

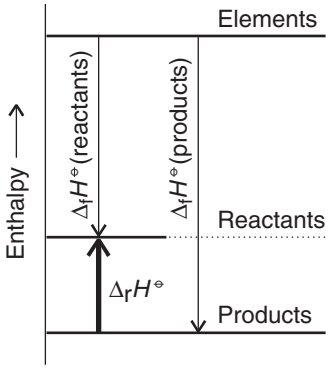


Fig. 1.23 An enthalpy of reaction may be expressed as the difference between the enthalpies of formation of the products and the reactants.

Table 1.7 Reference states of some elements at 298.15 K

Element	Reference state
Arsenic	gray arsenic
Bromine	liquid
Carbon	graphite
Hydrogen	gas
Iodine	solid
Mercury	liquid
Nitrogen	gas
Oxygen	gas
Phosphorus	white phosphorus
Sulfur	rhombic sulfur
Tin	white tin, α-tin

example, the standard enthalpy of formation of liquid water (at 25°C, as always in this text) is obtained from the thermochemical equation

$$H_2(g) + \tfrac{1}{2}\,O_2(g) \longrightarrow H_2O(l) \qquad \Delta H^\ominus = -286\ \text{kJ}$$

and is $\Delta_f H^\ominus(H_2O, l) = -286\ \text{kJ mol}^{-1}$. Note that enthalpies of formation are molar quantities, so to go from $\Delta H^\ominus$ in a thermochemical equation to $\Delta_f H^\ominus$ for that substance, divide by the amount of substance formed (in this instance, by 1 mol H_2O).

With the introduction of standard enthalpies of formation, we can write

$$\Delta_r H^\ominus = \sum \nu \Delta_f H^\ominus(\text{products}) - \sum \nu \Delta_f H^\ominus(\text{reactants}) \qquad \textbf{(1.22)}$$

COMMENT 1.11 The text's web site contains links to online databases of thermochemical data, including enthalpies of combustion and standard enthalpies of formation. ■

The first term on the right is the enthalpy of formation of all the products from their elements; the second term on the right is the enthalpy of formation of all the reactants from their elements. The fact that the enthalpy is a state function means that a reaction enthalpy calculated in this way is identical to the value that would be calculated from eqn 1.21 if absolute enthalpies were available.

The values of some standard enthalpies of formation at 25°C are given in Table 1.8, and a longer list is given in the *Data section*. The standard enthalpies of formation of elements in their reference states are zero by definition (because their formation is the null reaction: element ⟶ element). Note, however, that the standard enthalpy of formation of an element in a state other than its reference state is not zero:

$$C(s, \text{graphite}) \longrightarrow C(s, \text{diamond}) \qquad \Delta H^\ominus = +1.895\ \text{kJ}$$

Therefore, although $\Delta_f H^\ominus(C, \text{graphite}) = 0$, $\Delta_f H^\ominus(C, \text{diamond}) = +1.895\ \text{kJ mol}^{-1}$.

EXAMPLE 1.4 Using standard enthalpies of formation

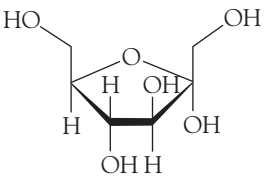
Glucose and fructose (**7**) are simple carbohydrates with the molecular formula $C_6H_{12}O_6$. Sucrose (**8**), or table sugar, is a complex carbohydrate with molecular

Table 1.8 Standard enthalpies of formation at 298.15 K*

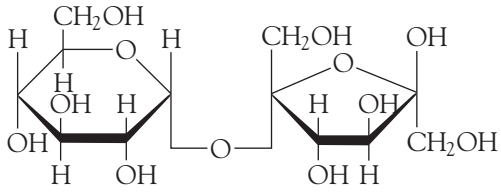
Substance	$\Delta_f H^\ominus$/(kJ mol^{-1})	Substance	$\Delta_f H^\ominus$/(kJ mol^{-1})
Inorganic compounds		*Organic compounds*	
Ammonia, $NH_3(g)$	−46.11	Adenine, $C_5H_5N_5(s)$	+96.9
Carbon monoxide, $CO(g)$	−110.53	Alanine, $CH_3CH(NH_2)COOH(s)$	−604.0
Carbon dioxide, $CO_2(g)$	−393.51	Benzene, $C_6H_6(l)$	+49.0
Hydrogen sulfide, $H_2S(g)$	−20.63	Butanoic acid, $CH_3(CH_2)_2COOH(l)$	−533.8
Nitrogen dioxide, $NO_2(g)$	+33.18	Ethane, $C_2H_6(g)$	−84.68
Nitrogen monoxide, $NO(g)$	+90.25	Ethanoic acid, $CH_3COOH(l)$	−484.3
Sodium chloride, $NaCl(s)$	−411.15	Ethanol, $C_2H_5OH(l)$	−277.69
Water, $H_2O(l)$	−285.83	α-D-Glucose, $C_6H_{12}O_6(s)$	−1268
$H_2O(g)$	−241.82	Guanine, $C_5H_5N_5O(s)$	−183.9
		Glycine, $CH_2(NH_2)COOH(s)$	−528.5
		N-Glycylglycine, $C_4H_8N_2O_3(s)$	−747.7
		Hexadecanoic acid, $CH_3(CH_2)_{14}COOH(s)$	−891.5
		Leucine, $(CH_3)_2CHCH_2CH(NH_2)COOH(s)$	−637.4
		Methane, $CH_4(g)$	−74.81
		Methanol, $CH_3OH(l)$	−238.86
		Sucrose, $C_{12}H_{22}O_{11}(s)$	−2222
		Thymine, $C_5H_6N_2O_2(s)$	−462.8
		Urea, $(NH_2)_2CO(s)$	−333.1

*A longer list is given in the *Data section* at the end of the book.

formula $C_{12}H_{22}O_{11}$ that consists of a glucose unit covalently linked to a fructose unit (a water molecule is released as a result of the reaction between glucose and fructose to form sucrose). Estimate the standard enthalpy of combustion of sucrose from the standard enthalpies of formation of the reactants and products.



7 α-D-Fructose



8 Sucrose

Strategy We write the chemical equation, identify the stoichiometric numbers of the reactants and products, and then use eqn 1.22. Note that the expression has the form "products − reactants." Numerical values of standard enthalpies of formation are given in the *Data section*. The standard enthalpy of combustion is the enthalpy change per mole of substance, so we need to interpret the enthalpy change accordingly.

Solution The chemical equation is

$$C_{12}H_{22}O_{11}(s) + 12\ O_2(g) \longrightarrow 12\ CO_2(g) + 11\ H_2O(l)$$

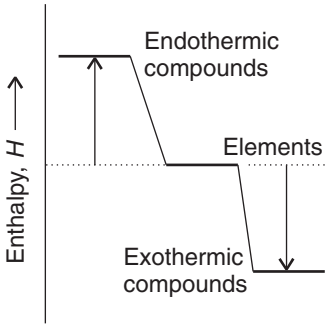


Fig. 1.24 The enthalpy of formation acts as a kind of thermochemical "altitude" of a compound with respect to the "sea level" defined by the elements from which it is made. Endothermic compounds have positive enthalpies of formation; exothermic compounds have negative energies of formation.

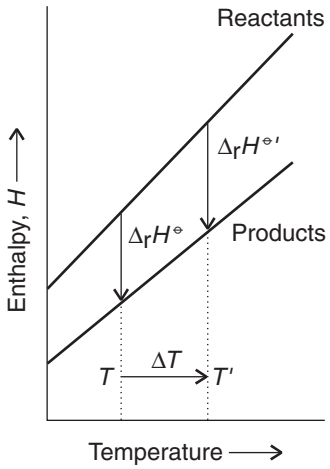


Fig. 1.25 The enthalpy of a substance increases with temperature. Therefore, if the total enthalpy of the reactants increases by a different amount from that of the products, the reaction enthalpy will change with temperature. The change in reaction enthalpy depends on the relative slopes of the two lines and hence on the heat capacities of the substances.

It follows that

$$\begin{aligned}\Delta_r H^{\ominus} &= \{12\Delta_f H^{\ominus}(CO_2, g) + 11\Delta_f H^{\ominus}(H_2O, l)\} \\ &\quad - \{\Delta_f H^{\ominus}(C_{12}H_{22}O_{11}, g) + 12\Delta_f H^{\ominus}(O_2, g)\} \\ &= \{12 \times (-393.51 \text{ kJ mol}^{-1}) + 11 \times (-285.83 \text{ kJ mol}^{-1})\} \\ &\quad - \{(-2222 \text{ kJ mol}^{-1}) + 0\} \\ &= -5644 \text{ kJ mol}^{-1}\end{aligned}$$

Inspection of the chemical equation shows that, in this instance, the "per mole" is per mole of sucrose, which is exactly what we need for an enthalpy of combustion. It follows that the estimate for the standard enthalpy of combustion of sucrose is -5644 kJ mol^{-1}. The experimental value is -5645 kJ mol^{-1}.

A note on good practice: The standard enthalpy of formation of an element in its reference state (oxygen gas in this example) is written 0, not 0 kJ mol^{-1}, because it is zero whatever units we happen to be using.

SELF-TEST 1.6 Use standard enthalpies of formation to calculate the enthalpy of combustion of solid glycine to CO_2(g), H_2O(l), and N_2(g).

Answer: -969.7 kJ mol^{-1}, in agreement with the experimental value (see the *Data section*) ■

The reference states of the elements define a thermochemical "sea level," and enthalpies of formation can be regarded as thermochemical "altitudes" above or below sea level (Fig. 1.24). Compounds that have negative standard enthalpies of formation (such as water) are classified as **exothermic compounds**, for they lie at a lower enthalpy than their component elements (they lie below thermochemical sea level). Compounds that have positive standard enthalpies of formation (such as carbon disulfide) are classified as **endothermic compounds** and possess a higher enthalpy than their component elements (they lie above sea level).

1.15 The variation of reaction enthalpy with temperature

We need to know how to predict reaction enthalpies of biochemical reactions at different temperatures, even though we may have data at only one temperature.

Suppose we want to know the enthalpy of a particular reaction at body temperature, 37°C, but have data available for 25°C, or suppose we to know whether the oxidation of glucose is more exothermic when it takes place inside an Arctic fish that inhabits water at 0°C than when it takes place at mammalian body temperatures. In precise work, every attempt would be made to measure the reaction enthalpy at the temperature of interest, but it is useful to have a rapid way of estimating the sign and even a moderately reliable numerical value.

Figure 1.25 illustrates the technique we use. As we have seen, the enthalpy of a substance increases with temperature; therefore the total enthalpy of the reactants and the total enthalpy of the products increases as shown in the illustration. Provided the two total enthalpy increases are different, the standard reaction enthalpy (their difference) will change as the temperature is changed. The change in the enthalpy of a substance depends on the slope of the graph and therefore on the constant-pressure heat capacities of the substances (recall Fig. 1.17). We can there-

fore expect the temperature dependence of the reaction enthalpy to be related to the difference in heat capacities of the products and the reactants. We show in the following *Derivation* that this is indeed the case and that, when the heat capacities do not vary with temperature, the standard reaction enthalpy at a temperature T' is related to the value at a different temperature T by a special formulation of **Kirchhoff's law**:

$$\Delta_r H^\ominus(T') = \Delta_r H^\ominus(T) + \Delta_r C_p^\ominus \times (T' - T) \qquad \textbf{(1.23)}$$

where $\Delta_r C_p^\ominus$ is the difference between the weighted sums of the standard molar heat capacities of the products and the reactants:

$$\Delta_r C_p^\ominus = \sum \nu C_{p,m}^\ominus(\text{products}) - \sum \nu C_{p,m}^\ominus(\text{reactants}) \qquad \textbf{(1.24)}$$

Values of standard molar constant-pressure heat capacities for a number of substances are given in the *Data section*. Because eqn 1.23 applies only when the heat capacities are constant over the range of temperature of interest, its use is restricted to small temperature differences (of no more than 100 K or so).

DERIVATION 1.5 Kirchhoff's law

To derive Kirchhoff's law, we consider the variation of the enthalpy with temperature. We begin by rewriting eqn 1.15b to calculate the change in the standard molar enthalpy $H_m^\ominus$ of each reactant and product as the temperature of the reaction mixture is increased:

$$dH_m^\ominus = C_{p,m}^\ominus dT$$

where $C_{p,m}^\ominus$ is the standard molar constant-pressure heat capacity, the molar heat capacity at 1 bar. We proceed by integrating both sides of the expression for $dH_m^\ominus$ from an initial temperature T and initial enthalpy $H_m^\ominus(T)$ to a final temperature T' and enthalpy $H_m^\ominus(T')$:

$$\int_{H_m^\ominus(T)}^{H_m^\ominus(T')} dH = \int_T^{T'} C_{p,m}^\ominus dT$$

It follows that for each reactant and product (assuming that no phase transition takes place in the temperature range of interest):

$$H_m^\ominus(T') = H_m^\ominus(T) + \int_T^{T'} C_{p,m}^\ominus dT$$

Because this equation applies to each substance in the reaction, we use it and eqn 1.22 to write the following expression for $\Delta_r H^\ominus(T')$:

$$\Delta_r H^\ominus(T') = \Delta_r H^\ominus(T) + \int_T^{T'} \Delta_r C_p^\ominus dT$$

where $\Delta_r C_p^\ominus$ is given by eqn 1.24. This equation is the exact form of Kirchhoff's law. The special case given by eqn 1.23 can be derived readily from it by

making the approximation that $\Delta_r C_p^\ominus$ is independent of temperature. Then the integral on the right evaluates to

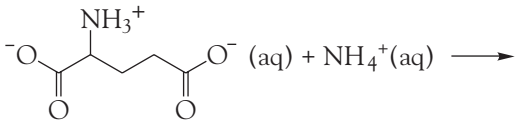
$$\int_T^{T'} \Delta_r C_p^\ominus dT = \Delta_r C_p^\ominus \int_T^{T'} dT = \Delta_r C_p^\ominus \times (T' - T)$$

and we obtain eqn 1.23.

A note on good practice: Because heat capacities can be measured more accurately than some reaction enthalpies, the exact form of Kirchhoff's law, with numerical integration of $\Delta_r C_p^\ominus$ over the temperature range of interest, sometimes gives results more accurate than a direct measurement of the reaction enthalpy at the second temperature.

EXAMPLE 1.5 Using Kirchhoff's law

The enzyme glutamine synthetase mediates the synthesis of the amino acid glutamine (Gln, **10**) from the amino acid glutamate (Glu, **9**) and ammonium ion:



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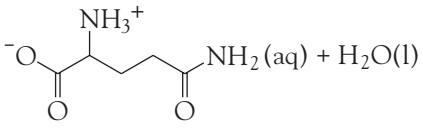


10

$\Delta_r H^\ominus = +21.8$ kJ mol^{-1} at 25°C

The process is endothermic and requires energy extracted from the oxidation of biological fuels and stored in ATP (Section 1.3). Estimate the value of the reaction enthalpy at 60°C by using data found in this text (see the *Data section*) and the following additional information: $C_{p,m}^\ominus$(Gln, aq) = 187.0 J K^{-1} mol^{-1} and $C_{p,m}^\ominus$(Glu, aq) = 177.0 J K^{-1} mol^{-1}.

Strategy Calculate the value of $\Delta_r C_p^\ominus$ from the available data and eqn 1.24 and use the result in eqn 1.23.

Solution From the *Data section*, the standard molar constant-pressure heat capacities of $H_2O(l)$ and $NH_4^+(aq)$ are 75.3 J K^{-1} mol^{-1} and 79.9 J K^{-1} mol^{-1}, respectively. It follows that

$$\begin{aligned}\Delta_r C_p^\ominus &= \{C_{p,m}^\ominus(\text{Gln, aq}) + C_{p,m}^\ominus(H_2O, l)\} \\ &\quad - \{C_{p,m}^\ominus(\text{Glu, aq}) + C_{p,m}^\ominus(NH_4^+, \text{aq})\} \\ &= \{(187.0 \text{ J K}^{-1} \text{ mol}^{-1}) + (75.3 \text{ J K}^{-1} \text{ mol}^{-1})\} \\ &\quad - \{(177.0 \text{ J K}^{-1} \text{ mol}^{-1}) + (79.9 \text{ J K}^{-1} \text{ mol}^{-1})\} \\ &= +5.4 \text{ J K}^{-1} \text{ mol}^{-1} = +5.4 \times 10^{-3} \text{ kJ K}^{-1} \text{ mol}^{-1}\end{aligned}$$

Then, because $T' - T = +35$ K, from eqn 1.23 we find

$$\begin{aligned}\Delta_r H^\ominus(333\text{ K}) &= (+21.8\text{ kJ mol}^{-1}) + (5.4 \times 10^{-3}\text{ kJ K}^{-1}\text{ mol}^{-1}) \times (35\text{ K}) \\ &= (+21.8\text{ kJ mol}^{-1}) + (0.19\text{ kJ mol}^{-1}) \\ &= +22.0\text{ kJ mol}^{-1}\end{aligned}$$

SELF-TEST 1.7 Estimate the standard enthalpy of combustion of solid glycine at 340 K from the data in Self-test 1.6 and the *Data section*.

Answer: -973 kJ mol^{-1} ■

The calculation in Example 1.5 shows that the standard reaction enthalpy at 60°C is only slightly different from that at 25°C. The reason is that the change in reaction enthalpy is proportional to the *difference* between the molar heat capacities of the products and the reactants, which is usually not very large. It is generally the case that provided the temperature range is not too wide, enthalpies of reactions vary only slightly with temperature. A reasonable first approximation is that standard reaction enthalpies are independent of temperature. However, notable exceptions are processes involving the unfolding of macromolecules, such as proteins (*Case study* 1.1). The difference in molar heat capacities between the folded and unfolded states of proteins is usually rather large, on the other of a few kilojoules per mole, so the enthalpy of protein unfolding varies significantly with temperature.

Checklist of Key Ideas

You should now be familiar with the following concepts:

- ☐ **1.** A system is classified as open, closed, or isolated.
- ☐ **2.** The surroundings remain at constant temperature and either constant volume or constant pressure when processes occur in the system.
- ☐ **3.** An exothermic process releases energy as heat, q, to the surroundings; an endothermic process absorbs energy as heat.
- ☐ **4.** The work of expansion against constant external pressure is $w = -p_{ex}\Delta V$.
- ☐ **5.** Maximum expansion work is achieved in a reversible change.
- ☐ **6.** The change in internal energy can be calculated from $\Delta U = w + q$.
- ☐ **7.** The First Law of thermodynamics states that the internal energy of an isolated system is constant.
- ☐ **8.** The enthalpy is defined as $H = U + pV$.
- ☐ **9.** A change in internal energy is equal to the energy transferred as heat at constant volume ($\Delta U = q_V$); a change in enthalpy is equal to the energy transferred as heat at constant pressure ($\Delta H = q_p$).
- ☐ **10.** The constant-volume heat capacity is the slope of the tangent to the graph of the internal energy of a constant-volume system plotted against temperature ($C_V = \mathrm{d}U/\mathrm{d}T$) and the constant-pressure heat capacity is the slope of the tangent to the graph of the enthalpy of a constant-pressure system plotted against temperature ($C_p = \mathrm{d}H/\mathrm{d}T$).
- ☐ **11.** The standard state of a substance is the pure substance at 1 bar.
- ☐ **12.** The standard enthalpy of transition, $\Delta_{trs}H^\ominus$, is the change in molar enthalpy when a substance in one phase changes into another phase, both phases being in their standard states.
- ☐ **13.** The standard enthalpy of the reverse of a process is the negative of the standard enthalpy of the forward process, $\Delta_{reverse}H^\ominus = -\Delta_{forward}H^\ominus$.
- ☐ **14.** The standard enthalpy of a process is the sum of the standard enthalpies of the individual processes into which it may be regarded as divided, as in $\Delta_{sub}H^\ominus = \Delta_{fus}H^\ominus + \Delta_{vap}H^\ominus$.
- ☐ **15.** Differential scanning calorimetry (DSC) is a useful technique for the investigation of phase transitions, especially those observed in biological macromolecules.

□ **16.** Hess's law states that the standard enthalpy of a reaction is the sum of the standard enthalpies of the reactions into which the overall reaction can be divided.

□ **17.** The standard enthalpy of formation of a compound, $\Delta_f H^\ominus$, is the standard reaction enthalpy for the formation of the compound from its elements in their reference states.

□ **18.** The standard reaction enthalpy, $\Delta_r H^\ominus$, is the difference between the standard enthalpies of formation of the products and reactants, weighted by their stoichiometric coefficients ν: $\Delta_r H^\ominus = \sum \nu \Delta_f H^\ominus(\text{products}) - \sum \nu \Delta_f H^\ominus(\text{reactants})$.

□ **19.** At constant pressure, exothermic compounds are those for which $\Delta_f H^\ominus < 0$; endothermic compounds are those for which $\Delta_f H^\ominus > 0$.

□ **20.** Kirchhoff's law states that the standard reaction enthalpies at different temperatures are related by $\Delta_r H^\ominus(T') = \Delta_r H^\ominus(T) + \Delta_r C_p^\ominus \times (T' - T)$, where $\Delta_r C_p^\ominus = \sum \nu C_{p,m}^\ominus(\text{products}) - \sum \nu C_{p,m}^\ominus(\text{reactants})$.

Discussion questions

1.1 Provide molecular interpretations of work and heat.

1.2 Explain the difference between the change in internal energy and the change in enthalpy of a chemical or physical process.

1.3 Explain the limitations of the following expressions: **(a)** $w = -nRT \ln(V_f/V_i)$; **(b)** $\Delta H = \Delta U + p\Delta V$; **(c)** $\Delta_r H^\ominus(T') = \Delta_r H^\ominus(T) + \Delta_r C_p^\ominus \times (T' - T)$.

1.4 A primitive air-conditioning unit for use in places where electrical power is not available can be made by hanging up strips of linen soaked in water. Explain why this strategy is effective.

1.5 In many experimental thermograms, such as that shown in Fig. 1.22, the baseline below T_1 is at a different level from that above T_2. Explain this observation.

1.6 Describe at least two calculational methods by which standard reaction enthalpies can be predicted. Discuss the advantages and disadvantages of each method.

1.7 Distinguish between **(a)** standard state and reference state of an element; **(b)** endothermic and exothermic compounds.

Exercises

Assume all gases are perfect unless stated otherwise. All thermochemical data are for 298.15 K.

1.8 How much metabolic energy must a bird of mass 200 g expend to fly to a height of 20 m? Neglect all losses due to friction, physiological imperfection, and the acquisition of kinetic energy.

1.9 Calculate the work of expansion accompanying the complete combustion of 1.0 g of glucose to carbon dioxide and **(a)** liquid water, **(b)** water vapor at 20°C when the external pressure is 1.0 atm.

1.10 We are all familiar with the general principles of operation of an internal combustion reaction: the combustion of fuel drives out the piston. It is possible to imagine engines that use reactions other than combustions, and we need to assess the work they can do. A chemical reaction takes place in a container of cross-sectional area 100 cm^2; the container has a piston at one end. As a result of the reaction, the piston is pushed out through 10.0 cm against a constant external pressure of 100 kPa. Calculate the work done by the system.

1.11 A sample of methane of mass 4.50 g occupies 12.7 L at 310 K. **(a)** Calculate the work done when the gas expands isothermally against a constant external pressure of 30.0 kPa until its volume has increased by 3.3 L. **(b)** Calculate the work that would be done if the same expansion occurred isothermally and reversibly.

1.12 Derivation 1.2 showed how to calculate the work of reversible, isothermal expansion of a perfect gas. Suppose that the expansion is reversible but not isothermal and that the temperature decreases as the expansion proceeds. **(a)** Find an expression

for the work when $T = T_i - c(V - V_i)$, with c a positive constant. **(b)** Is the work greater or smaller than for isothermal expansion?

1.13 Graphical displays often enhance understanding. Take your result from Exercise 1.12 and use an electronic spreadsheet to plot the work done by the system against the final volume for a selection of values of c. Include negative values of c (corresponding to the temperature rising as the expansion occurs).

1.14 The heat capacity of air is much smaller than that of water, and relatively modest amounts of heat are needed to change its temperature. This is one of the reasons why desert regions, though very hot during the day, are bitterly cold at night. The heat capacity of air at room temperature and pressure is approximately 21 J K^{-1} mol^{-1}. How much energy is required to raise the temperature of a room of dimensions 5.5 m × 6.5 m × 3.0 m by 10°C? If losses are neglected, how long will it take a heater rated at 1.5 kW to achieve that increase given that 1 W = 1 J s^{-1}?

1.15 The transfer of energy from one region of the atmosphere to another is of great importance in meteorology for it affects the weather. Calculate the heat needed to be supplied to a parcel of air containing 1.00 mol air molecules to maintain its temperature at 300 K when it expands reversibly and isothermally from 22 L to 30.0 L as it ascends.

1.16 A laboratory animal exercised on a treadmill, which, through pulleys, raised a mass of 200 g through 1.55 m. At the same time, the animal lost 5.0 J of energy as heat. Disregarding all other losses and regarding the animal as a closed system, what is its change in internal energy?

1.17 The internal energy of a perfect gas does not change when the gas undergoes isothermal expansion. What is the change in enthalpy?

1.18 A sample of a serum of mass 25 g is cooled from 290 K to 275 K at constant pressure by the extraction of 1.2 kJ of energy as heat. Calculate q and ΔH and estimate the heat capacity of the sample.

1.19 (a) Show that for a perfect gas, $C_{p,m} - C_{V,m} = R$. (b) When 229 J of energy is supplied as heat at constant pressure to 3.00 mol CO_2(g), the temperature of the sample increases by 2.06 K. Calculate the molar heat capacities at constant volume and constant pressure of the gas.

1.20 Use the information in Exercise 1.19 to calculate the change in **(a)** molar enthalpy, **(b)** molar internal energy when carbon dioxide is heated from 15°C (the temperature when air is inhaled) to 37°C (blood temperature, the temperature in our lungs).

1.21 Suppose that the molar internal energy of a substance over a limited temperature range could be expressed as a polynomial in T as $U_m(T) = a + bT + cT^2$. Find an expression for the constant-volume molar heat capacity at a temperature T.

1.22 The heat capacity of a substance is often reported in the form $C_{p,m} = a + bT + c/T^2$. Use this expression to make a more accurate estimate of the change in molar enthalpy of carbon dioxide when it is heated from 15°C to 37°C (as in Exercise 1.20), given $a = 44.22$ J K^{-1} mol^{-1}, $b = 8.79 \times 10^{-3}$ J K^{-2} mol^{-1}, and $c = -8.62 \times 10^5$ J K mol^{-1}. *Hint:* You will need to integrate $dH = C_p dT$.

1.23 Exercise 1.22 gives an expression for the temperature dependence of the constant-pressure molar heat capacity over a limited temperature range. **(a)** How does the molar enthalpy of the substance change over that range? **(b)** Plot the molar enthalpy as a function of temperature using the data in Exercise 1.22.

1.24 Classify as endothermic or exothermic **(a)** a combustion reaction for which $\Delta_r H^\ominus = -2020$ kJ mol^{-1}, **(b)** a dissolution for which $\Delta H^\ominus = +4.0$ kJ mol^{-1}, **(c)** vaporization, **(d)** fusion, **(e)** sublimation.

1.25 The pressures deep within the Earth are much greater than those on the surface, and to make use of thermochemical data in geochemical assessments, we need to take the differences into account. **(a)** Given that the enthalpy of combustion of graphite is -393.5 kJ mol^{-1} and that of diamond is -395.41 kJ mol^{-1}, calculate the standard enthalpy of the C(s, graphite) ⟶ C(s, diamond) transition. **(b)** Use the information in part (a) together with the densities of graphite (2.250 g cm^{-3}) and diamond (3.510 g cm^{-3}) to calculate the internal energy of the transition when the sample is under a pressure of 150 kbar.

1.26 A typical human produces about 10 MJ of energy transferred as heat each day through metabolic activity. If a human body were an isolated system of mass 65 kg with the heat capacity of water, what temperature rise would the body experience? Human bodies are actually open systems, and the main mechanism of heat loss is through the evaporation of water. What mass of water should be evaporated each day to maintain constant temperature?

1.27 Use the information in Tables 1.1 and 1.2 to calculate the total heat required to melt 100 g of ice at 0°C, heat it to 100°C, and then vaporize it at that temperature. Sketch a graph of temperature against time on the assumption that the sample is heated at a constant rate.

1.28 The mean bond enthalpies of C–C, C–H, C=O, and O–H bonds are 348, 412, 743, and 463 kJ mol^{-1}, respectively. The combustion of a fuel such as octane is exothermic because relatively weak bonds break to form relatively strong bonds. Use this information to justify why glucose has a lower specific enthalpy than the lipid decanoic acid ($C_{10}H_{20}O_2$) even though these compounds have similar molar masses.

1.29 Use bond enthalpies and mean bond enthalpies to estimate **(a)** the enthalpy of the anaerobic breakdown of glucose to lactic acid in cells that are starved of O_2, $C_6H_{12}O_6(aq) \longrightarrow 2\ CH_3CH(OH)COOH(aq)$, **(b)** the enthalpy of combustion of glucose. Ignore the contributions of enthalpies of fusion and vaporization.

1.30 Glucose and fructose are simple sugars with the molecular formula $C_6H_{12}O_6$. Sucrose (table sugar) is a complex sugar with molecular formula $C_{12}H_{22}O_{11}$ that consists of a glucose unit covalently bound to a fructose unit (a water molecule is eliminated as a result of the reaction between glucose and fructose to form sucrose). **(a)** Calculate the energy released as heat when a typical table sugar cube of mass 1.5 g is burned in air. **(b)** To what height could you climb on the energy a table sugar cube provides assuming 25% of the energy is available for work? **(c)** The mass of a typical glucose tablet is 2.5 g. Calculate the energy released as heat when a glucose tablet is burned in air. **(d)** To what height could you climb on the energy a tablet provides assuming 25% of the energy is available for work?

1.31 Camping gas is typically propane. The standard enthalpy of combustion of propane gas is -2220 kJ mol^{-1} and the standard enthalpy of vaporization of the liquid is $+15$ kJ mol^{-1}. Calculate **(a)** the standard enthalpy and **(b)** the standard internal energy of combustion of the liquid.

1.32 Ethane is flamed off in abundance from oil wells, because it is unreactive and difficult to use commercially. But would it make a good fuel? The standard enthalpy of reaction for $2\ C_2H_6(g) + 7\ O_2(g) \longrightarrow 4\ CO_2(g) + 6\ H_2O(l)$ is -3120 kJ mol^{-1}. **(a)** What is the standard enthalpy of combustion of ethane? **(b)** What is the specific enthalpy of combustion of ethane? **(c)** Is ethane a more or less efficient fuel than methane?

1.33 Estimate the difference between the standard enthalpy of formation of $H_2O(l)$ as currently defined (at 1 bar) and its value using the former definition (at 1 atm).

1.34 Use information in the *Data section* to calculate the standard enthalpies of the following reactions:

(a) the hydrolysis of a glycine-glycine dipeptide:

$$^{+}NH_3CH_2CONHCH_2CO_2^{-}(aq) + H_2O(l) \longrightarrow 2\ ^{+}NH_3CH_2CO_2^{-}(aq)$$

(b) the combustion of solid β-D-fructose

(c) the dissociation of nitrogen dioxide, which occurs in the atmosphere:

$$NO_2(g) \longrightarrow NO(g) + O(g)$$

1.35 During glycolysis, glucose is partially oxidized to pyruvic acid, $CH_3COCOOH$, by NAD^+ (see Chapter 4) without the involvement of O_2. However, it is also possible to carry out the oxidation in the presence of O_2:

$$C_6H_{12}O_6(s) + O_2(g) \longrightarrow 2\ CH_3COCOOH(s) + 2\ H_2O(l) \qquad \Delta_r H^{\ominus} = -480.7\ \text{kJ mol}^{-1}$$

From these data and additional information in the *Data section*, calculate the standard enthalpy of combustion and standard enthalpy of formation of pyruvic acid.

1.36 At 298 K, the enthalpy of denaturation of hen egg white lysozyme is $+217.6$ kJ mol^{-1} and the change in the constant-pressure molar heat capacity resulting from denaturation of the protein is $+6.3$ kJ K^{-1} mol^{-1}. **(a)** Estimate the enthalpy of denaturation of the protein at **(i)** 351 K, the "melting" temperature of the

macromolecule, and **(ii)** 263 K. State any assumptions in your calculations. **(b)** Based on your answers to part (a), is denaturation of hen egg white lysozyme always endothermic?

1.37 Estimate the enthalpy of vaporization of water at 100°C from its value at 25°C (+44.01 kJ mol^{-1}) given the constant-pressure heat capacities of 75.29 J K^{-1} mol^{-1} and 33.58 J K^{-1} mol^{-1} for liquid and gas, respectively.

1.38 Is the standard enthalpy of combustion of glucose likely to be higher or lower at blood temperature than at 25°C?

1.39 Derive a version of Kirchhoff's law (eqn 1.23) for the temperature dependence of the internal energy of reaction.

1.40 The formulation of Kirchhoff's law given in eqn 1.23 is valid when the difference in heat capacities is independent of temperature over the temperature range of interest. Suppose instead that $\Delta_r C_p^{\ominus} = a + bT + c/T^2$. Derive a more accurate form of Kirchhoff's law in terms of the parameters *a*, *b*, and *c*. *Hint:* The change in the reaction enthalpy for an infinitesimal change in temperature is $\Delta_r C_p^{\ominus} dT$. Integrate this expression between the two temperatures of interest.

Project

1.41 It is possible to see with the aid of a powerful microscope that a long piece of double-stranded DNA is flexible, with the distance between the ends of the chain adopting a wide range of values. This flexibility is important because it allows DNA to adopt very compact conformations as it is packaged in a chromosome (see Chapter 11). It is convenient to visualize a long piece of DNA as a *freely jointed chain*, a chain of *N* small, rigid units of length *l* that are free to make any angle with respect to each other. The length *l*, the *persistence length*, is approximately 45 nm, corresponding to approximately 130 base pairs. You will now explore the work associated with extending a DNA molecule.

(a) Suppose that a DNA molecule resists being extended from an equilibrium, more compact conformation with a *restoring force* $F = -k_F x$, where *x* is the difference in the end-to-end distance of the chain from an equilibrium value and k_F is the *force constant*. Systems showing this behavior are said to obey *Hooke's law*. **(i)** What are the limitations of this model of the DNA molecule? **(ii)** Using this model, write an expression for the work that must be done to extend a DNA molecule by *x*. Draw a graph of your conclusion.

(b) A better model of a DNA molecule is the *one-dimensional freely jointed chain*, in which a rigid unit of length *l* can only make an angle of 0° or 180° with an adjacent unit. In this case, the restoring force of a chain extended by $x = nl$ is given by

$$F = \frac{kT}{2l} \ln\left(\frac{1+\nu}{1-\nu}\right) \qquad \nu = n/N$$

where $k = 1.381 \times 10^{-23}$ J K^{-1} is *Boltzmann's constant* (not a force constant). **(i)** What are the limitations of this model? **(ii)** What is the magnitude of the force that must be applied to extend a DNA molecule with $N = 200$ by 90 nm? **(iii)** Plot the restoring force against ν, noting that ν can be either positive or negative. How is the variation of the restoring force with end-to-end distance different from that predicted by Hooke's law? **(iv)** Keeping in mind that the difference in end-to-end distance from an equilibrium value is $x = nl$ and, consequently, $dx = l dn = N l d\nu$, write an expression for the work of extending a DNA molecule. **(v)** Calculate the work of extending a DNA molecule from $\nu = 0$ to $\nu = 1.0$. *Hint:* You must integrate the expression for *w*. The task can be accomplished easily with mathematical software.

(c) Show that for small extensions of the chain, when $\nu << 1$, the restoring force is given by

$$F \approx \frac{\nu kT}{l} = \frac{nkT}{Nl}$$

Hint: See *Appendix 2* for a review of series expansions of functions.

(d) Is the variation of the restoring force with extension of the chain given in part (c) different from that predicted by Hooke's law? Explain your answer.

CHAPTER

2

The Second Law

Some things happen; some things don't. A gas expands to fill the vessel it occupies; a gas that already fills a vessel does not suddenly contract into a smaller volume. A hot object cools to the temperature of its surroundings; a cool object does not suddenly become hotter than its surroundings. Hydrogen and oxygen combine explosively (once their ability to do so has been liberated by a spark) and form water; water left standing in oceans and lakes does not gradually decompose into hydrogen and oxygen. These everyday observations suggest that changes can be divided into two classes. A **spontaneous change** is a change that has a tendency to occur without work having to be done to bring it about. A spontaneous change has a natural tendency to occur. A **non-spontaneous change** is a change that can be brought about only by doing work. A non-spontaneous change has no natural tendency to occur. Non-spontaneous changes can be *made* to occur by doing work: a gas can be compressed into a smaller volume by pushing in a piston, the temperature of a cool object can be raised by forcing an electric current through a heater attached to it, and water can be decomposed by the passage of an electric current. However, in each case we need to act in some way on the system to bring about the non-spontaneous change. There must be some feature of the world that accounts for the distinction between the two types of change.

Throughout the chapter we shall use the terms "spontaneous" and "non-spontaneous" in their thermodynamic sense. That is, we use them to signify that a change does or does not have a natural *tendency* to occur. In thermodynamics the term spontaneous has nothing to do with speed. Some spontaneous changes are very fast, such as the precipitation reaction that occurs when solutions of sodium chloride and silver nitrate are mixed. However, some spontaneous changes are so slow that there may be no observable change even after millions of years. For example, although the decomposition of benzene into carbon and hydrogen is spontaneous, it does not occur at a measurable rate under normal conditions, and benzene is a common laboratory commodity with a shelf life of (in principle) millions of years. Thermodynamics deals with the tendency to change; it is silent on the rate at which that tendency is realized.

We shall use the concepts introduced in this chapter to guide our study of bioenergetics and structure in biological systems. Our discussion of energy conversion in biological cells has focused on the chemical sources of energy that sustain life. We now begin an investigation—to be continued throughout the text—of the mechanisms by which energy in the form of radiation from the Sun or ingested as oxidizable molecules is converted to work of muscle contraction, neuronal activity, biosynthesis of essential molecules, and transport of material into and out of the cell. We shall also explain a remark made in Chapter 1, that only part of the energy of biological fuels leads to work, with the rest being dissipated in the surroundings as heat. Finally, we begin to describe some of the important thermodynamic and chemical factors that contribute to the formation and stability of proteins and biological membranes.

Entropy

A few moments' thought is all that is needed to identify the reason why some changes are spontaneous and others are not. That reason is *not* the tendency of the system to move toward lower energy. This point is easily established by identifying an example of a spontaneous change in which there is no change in energy. The isothermal expansion of a perfect gas into a vacuum is spontaneous, but the total energy of the gas does not change because the molecules continue to travel at the same average speed and so keep their same total kinetic energy. Even in a process in which the energy of a system does decrease (as in the spontaneous cooling of a block of hot metal), the First Law requires the total energy to be constant. Therefore, in this case the energy of another part of the world must increase if the energy decreases in the part that interests us. For instance, a hot block of metal in contact with a cool block cools and loses energy; however, the second block becomes warmer and increases in energy. It is equally valid to say that the second block has a tendency to go to higher energy as it is to say that the first block has a tendency to go to lower energy!

In the next few sections we shall develop the thermodynamic criteria for spontaneity by using an approach similar to that adopted in Chapter 1. At first sight the ideas, models, and mathematical expressions in our discussion may appear to be of no immediate concern to a biochemist. But in due course we shall see how they are of the greatest importance for an understanding of the flow of energy in biological systems and the reactions that sustain them.

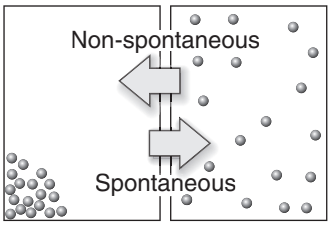


Fig. 2.1 One fundamental type of spontaneous process is the dispersal of matter. This tendency accounts for the spontaneous tendency of a gas to spread into and fill the container it occupies. It is extremely unlikely that all the particles will collect into one small region of the container. (In practice, the number of particles is of the order of 10^{23}.)

2.1 The direction of spontaneous change

To understand the spontaneous processes occurring in organisms, we need to identify the factors that drive any physical or chemical change.

We shall now show that *the apparent driving force of spontaneous change is the tendency of energy and matter to disperse*. For example, the molecules of a gas may all be in one region of a container initially, but their ceaseless disorderly motion ensures that they spread rapidly throughout the entire volume of the container (Fig. 2.1). Because their motion is so random, there is a negligibly small probability that all the molecules will find their way back simultaneously into the region of the container they occupied initially. In this instance, the natural direction of change corresponds to the dispersal of matter.

A similar explanation accounts for spontaneous cooling, but now we need to consider the dispersal of energy rather than that of matter. In a block of hot metal, the atoms are oscillating vigorously, and the hotter the block, the more vigorous their motion. The cooler surroundings also consist of oscillating atoms, but their motion is less vigorous. The vigorously oscillating atoms of the hot block jostle their neighbors in the surroundings, and the energy of the atoms in the block is handed on to the atoms in the surroundings (Fig. 2.2). The process continues until the vigor with which the atoms in the system are oscillating has fallen to that of the surroundings. The opposite flow of energy is very unlikely. It is highly improbable that there will be a net flow of energy into the system as a result of jostling from less vigorously oscillating molecules in the surroundings. In this case, the natural direction of change corresponds to the dispersal of energy.

The tendency toward dispersal of energy also explains the fact that, despite numerous attempts, it has proved impossible to construct an engine like that shown

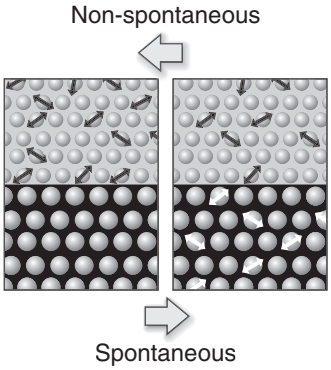


Fig. 2.2 Another fundamental type of spontaneous process is the dispersal of energy (represented by the small arrows). In these diagrams, the small spheres represent the system and the large spheres represent the surroundings. The double-headed arrows represent the thermal motion of the atoms.

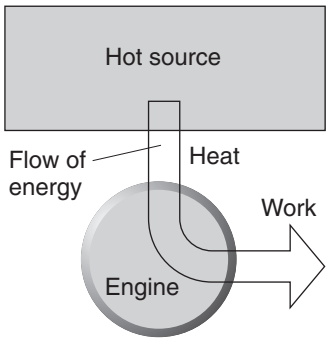


Fig. 2.3 The Second Law denies the possibility of the process illustrated here, in which heat is changed completely into work, there being no other change. The process is not in conflict with the First Law, because the energy is conserved.

in Fig 2.3, in which heat, perhaps from the combustion of a fuel, is drawn from a hot reservoir and completely converted into work, such as the work of moving an automobile. All actual heat engines have both a hot region, the "source," and a cold region, the "sink," and it has been found that some energy must be discarded into the cold sink as heat and not used to do work. In molecular terms, only some of the energy stored in the atoms and molecules of the hot source can be used to do work and transferred to the surroundings in an orderly way. For the engine to do work, some energy must be transferred to the cold sink as heat, to stimulate random motion of its atoms and molecules.

In summary, we have identified two basic types of spontaneous physical process:

1. Matter tends to become dispersed.
2. Energy tends to become dispersed.

Though it is convenient to regard the dispersal of matter and energy as two distinct processes, it is important to appreciate that they are sometimes related. To see why, consider the contraction and expansion of a gas. When a gas contracts isothermally, the kinetic energy of the atoms becomes localized. When it expands, the locations of the particles become more widely dispersed and so too does their kinetic energy.

Although it is easy to relate the spontaneous expansion of a perfect gas to the dispersal of matter and energy, we need to take the next step and see how these two fundamental processes result in some chemical reactions being spontaneous and others not. It may seem very puzzling that dispersal of matter can account for the formation of such organized systems as proteins and biological cells. Nevertheless, in due course we shall see that change in all its forms, including the formation of organized structures, can indeed emerge as energy and matter disperse.

2.2 Entropy and the Second Law

To make progress with our quantitative discussion of biological structure and reactivity, we need to associate the dispersal of energy and matter with the change in a state function.

The measure of the dispersal of energy or matter used in thermodynamics is called the **entropy**, S. We shall soon define entropy precisely and quantitatively, but for now all we need to know is that when matter and energy disperse, the entropy increases. That being so, we can combine the two remarks above into a single statement known as the **Second Law of thermodynamics**:

The entropy of an isolated system tends to increase.

The "isolated system" may consist of a system in which we have a special interest (a beaker containing reagents) and that system's surroundings: the two components jointly form a little "universe" in the thermodynamic sense.

To make progress and turn the Second Law into a quantitatively useful statement, we need to define entropy precisely. We shall use the following definition of a *change* in entropy:

$$\Delta S = \frac{q_{\text{rev}}}{T} \qquad \textbf{(2.1)}$$

That is, the change in entropy of a substance is equal to the energy transferred as heat to it *reversibly* divided by the temperature at which the transfer takes place. This definition can be justified thermodynamically, but we shall confine ourselves to showing that it is plausible and then show how to use it to obtain numerical values for a range of processes.

There are three points we need to understand about the definition in eqn 2.1: the significance of the term "reversible," why heat (not work) appears in the numerator, and why temperature appears in the denominator.

We met the concept of reversibility in Section 1.4, where we saw that it refers to the ability of an infinitesimal change in a variable to change the direction of a process. Mechanical reversibility refers to the equality of pressure acting on either side of a movable wall. Thermal reversibility, the type involved in eqn 2.1, refers to the equality of temperature on either side of a thermally conducting wall. Reversible transfer of heat is smooth, careful, restrained transfer between two bodies at the same temperature. By making the transfer reversible, we ensure that there are no hot spots generated in the object that later disperse spontaneously and hence add to the entropy.

Now consider why heat and not work appears in eqn 2.1. Recall from Section 1.2 that to transfer energy as heat, we make use of the random motion of molecules, whereas to transfer energy as work, we make use of orderly motion. It should be plausible that the change in entropy—the change in the degree of dispersal of energy and matter—is proportional to the energy transfer that takes place by making use of random motion rather than orderly motion.

Finally, the presence of the temperature in the denominator in eqn 2.1 takes into account the randomness of motion that is already present. If a given quantity of energy is transferred as heat to a hot object (one in which the atoms already undergo a significant amount of thermal motion), then the additional randomness of motion generated is less significant than if the same quantity of energy is transferred as heat to a cold object in which the atoms have less thermal motion. The difference is like sneezing in a busy street (an environment analogous to a high temperature), which adds little to the disorder already present, and sneezing in a quiet library (an environment analogous to a low temperature), which can be very disruptive.

ILLUSTRATION 2.1 Calculating a change in entropy

The transfer of 100 kJ of heat to a large mass of water at 0°C (273 K) results in a change in entropy of

$$\Delta S = \frac{q_{\text{rev}}}{T} = \frac{100 \times 10^3 \text{ J}}{273 \text{ K}} = +366 \text{ J K}^{-1}$$

We use a large mass of water to ensure that the temperature of the sample does not change as heat is transferred. The same transfer at 100°C (373 K) results in

$$\Delta S = \frac{100 \times 10^3 \text{ J}}{373 \text{ K}} = +268 \text{ J K}^{-1}$$

The increase in entropy is greater at the lower temperature. Notice that the units of entropy are joules per kelvin (J K^{-1}). Entropy is an extensive property. When we deal with molar entropy, an intensive property, the units will be joules per kelvin per mole (J K^{-1} mol^{-1}). ■

The entropy (it can be proved) is a state function, a property with a value that depends only on the present state of the system. The entropy is a measure of the current state of dispersal of energy and matter in the system, and how that change was achieved is not relevant to its current value. The implication of entropy being a state function is that a change in its value when a system undergoes a change of state is independent of how the change of state is brought about.

2.3 The entropy change accompanying heating

To calculate entropy changes associated with complex biological processes, we must first learn how to cope with simple physical changes, such as heating.

We can often rely on intuition to judge whether the entropy increases or decreases when a substance undergoes a physical change. For instance, the entropy of a sample of gas increases as it expands because the molecules are able to move in a greater volume and so are more widely dispersed. We should also expect the entropy of a sample to increase as the temperature is raised from T_i to T_f, because the thermal motion is greater at the higher temperature. To calculate the change in entropy, we go back to the definition in eqn 2.1 and find that, provided the heat capacity is constant over the range of temperatures of interest,

$$\Delta S = C \ln \frac{T_f}{T_i} \qquad \textbf{(2.2)}$$

where C is the heat capacity of the system; if the pressure is held constant during the heating, we use the constant-pressure heat capacity, C_p, and if the volume is held constant, we use the constant-volume heat capacity, C_V.

DERIVATION 2.1 The variation of entropy with temperature

Equation 2.1 refers to the transfer of heat to a system at a temperature T. In general, the temperature changes as we heat a system, so we cannot use eqn 2.1 directly. Suppose, however, that we transfer only an infinitesimal energy, dq, to the system; then there is only an infinitesimal change in temperature and we introduce negligible error if we keep the temperature in the denominator of eqn 2.1 equal to T during that transfer. As a result, the entropy increases by an infinitesimal amount dS given by

$$dS = \frac{dq_{rev}}{T}$$

To calculate dq, we recall from Section 1.5 that the heat capacity C is

$$C = \frac{q}{\Delta T}$$

where ΔT is macroscopic change in temperature. For the case of an infinitesimal change dT, we write

$$C = \frac{dq}{dT}$$

This relation also applies when the transfer of energy is carried out reversibly. Because infinitesimally small quantities may be treated like any other quantity in algebraic manipulations (*Comment* 1.8), it follows that

$$dq_{rev} = C dT$$

and therefore that

$$dS = \frac{C dT}{T}$$

The total change in entropy, ΔS, when the temperature changes from T_i to T_f is the sum (integral) of all such infinitesimal terms:

$$\Delta S = \int_{T_i}^{T_f} \frac{C dT}{T}$$

For many substances and for small temperature ranges we may take C to be constant. (This is strictly true only for a monatomic perfect gas.) Then C may be taken outside the integral and the latter evaluated as follows:

$$\Delta S = \int_{T_i}^{T_f} \frac{C dT}{T} = C \int_{T_i}^{T_f} \frac{dT}{T} = C \ln \frac{T_f}{T_i}$$

(Constant heat capacity)

We have used the same standard integral from *Comment* 1.3 and evaluated the limits similarly.

Equation 2.3 is in line with what we expect. When $T_f > T_i$, $T_f/T_i > 1$, which implies that the logarithm is positive, that $\Delta S > 0$, and therefore that the entropy increases (Fig. 2.4). Note that the relation also shows a less obvious point, that the higher the heat capacity of the substance, the greater the change in entropy for a given rise in temperature. A moment's thought shows this conclusion to be reasonable too: a high heat capacity implies that a lot of heat is required to produce a given change in temperature, so the "sneeze" must be more powerful than for when the heat capacity is low, and the entropy increase is correspondingly high.

SELF-TEST 2.1 Calculate the change in molar entropy when water vapor is heated from 160°C to 170°C at constant volume. ($C_{V,m} = 26.92$ J K^{-1} mol^{-1}.)

Answer: +0.615 J K^{-1} mol^{-1}

When we cannot assume that the heat capacity is constant over the temperature range of interest, which is the case for all solids at low temperatures, we have to allow for the variation of C with temperature. In *Derivation* 2.1 we found, before making the assumption that the heat capacity is constant, that

$$\Delta S = \int_{T_i}^{T_f} \frac{C dT}{T}$$

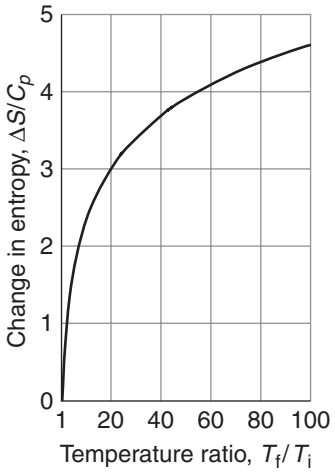


Fig. 2.4 The entropy of a sample with a heat capacity that is independent of temperature, such as a monatomic perfect gas, increases logarithmically (as ln T) as the temperature is increased. The increase is proportional to the heat capacity of the sample.

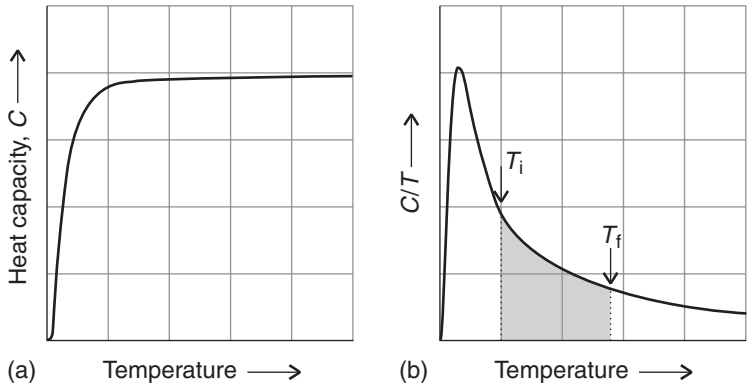


Fig. 2.5 The experimental determination of the change in entropy of a sample that has a heat capacity that varies with temperature, as shown in (a), involves measuring the heat capacity over the range of temperatures of interest, then plotting C_V/T against T and determining the area under the curve (the tinted area shown), as shown in (b). The heat capacity of all solids decreases toward zero as the temperature is reduced.

All we need to recognize is the standard result from calculus, illustrated in *Derivation* 1.2, that the integral of a function between two limits is the area under the graph of the function between the two limits. In this case, the function is C/T, the heat capacity at each temperature divided by that temperature, and it follows that

$$\Delta S = \text{area under the graph of } C/T \text{ plotted against } T, \text{ between } T_i \text{ and } T_f \quad \textbf{(2.3)}$$

This rule is illustrated in Fig. 2.5.

To use eqn 2.3, we measure the heat capacity throughout the range of temperatures of interest and make a list of values. Then we divide each one by the corresponding temperature to get C/T at each temperature, plot these C/T against T, and evaluate the area under the graph between the temperatures T_i and T_f.

2.4 The entropy change accompanying a phase transition

To prepare for being able to calculate the change in entropy associated with the unfolding of a biological macromolecule, we need to learn how to treat physical changes in general.

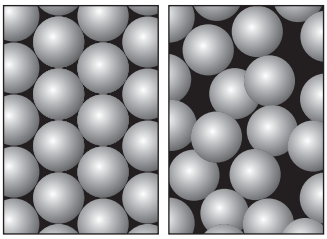
We can suspect that the entropy of a substance increases when it melts and when it vaporizes because its molecules become more dispersed as it changes from solid to liquid and from liquid to vapor. Likewise, we expect the unfolding of a protein from a compact, active three-dimensional conformation to a more flexible conformation, a process discussed in *Case study* 1.1, to be accompanied by an increase of entropy because the polypeptide chain becomes less organized.

The transfer of energy as heat occurs reversibly when a solid is at its melting temperature. If the temperature of the surroundings is infinitesimally lower than that of the system, then energy flows out of the system as heat and the substance freezes. If the temperature is infinitesimally higher, then energy flows into the system as heat and the substance melts. Moreover, because the transition occurs at constant pressure, we can identify the energy transferred by heating per mole of

substance with the enthalpy of fusion (melting). Therefore, the **entropy of fusion**, $\Delta_{fus}S$, the change of entropy per mole of substance, at the melting temperature, T_{fus}, is

$$\textit{At the melting temperature: } \Delta_{fus}S = \frac{\Delta_{fus}H(T_{fus})}{T_{fus}} \qquad \textbf{(2.4)}$$

Notice how we must use the enthalpy of fusion at the melting temperature. We get the standard entropy of fusion, $\Delta_{fus}S^{\ominus}$, if the solid and liquid are both at 1 bar; we use the melting temperature at 1 bar and the corresponding standard enthalpy of fusion at that temperature. All enthalpies of fusion are positive (melting is endothermic: it requires heat), so all entropies of fusion are positive too: disorder increases on melting. The entropy of water, for example, increases when it melts because the orderly structure of ice collapses as the liquid forms (Fig. 2.6).



(a) (b)

Fig. 2.6 When a solid, depicted by the orderly array of spheres (a), melts, the molecules form a liquid, the random array of spheres (b). As a result, the entropy of the sample increases.

ILLUSTRATION 2.2 The entropy change associated with unfolding of a protein

The protein lysozyme, an enzyme that breaks down bacterial cell walls, unfolds at a transition temperature of 75.5°C, and the standard enthalpy of transition is 509 kJ mol^{-1}. It follows that

$$\Delta_{trs}S^{\ominus} = \frac{\Delta_{trs}H^{\ominus}(T_{trs})}{T_{trs}} = \frac{+509\ \text{kJ mol}^{-1}}{(273.15 + 75.5)\ \text{K}} = +1.46\ \text{kJ K}^{-1}\ \text{mol}^{-1}$$

At the molecular level, the positive entropy change can be explained by the dispersal of matter and energy that accompanies the unraveling of the compact three-dimensional structure of lysozyme into a long, flexible chain that can adopt many different conformations as it writhes about in solution. ■

SELF-TEST 2.2 Calculate the standard entropy of fusion of ice at 0°C from the information in Table 1.2.

Answer: $+22\ \text{J K}^{-1}\ \text{mol}^{-1}$

The entropy of other types of transition may be discussed similarly. Thus, the entropy of vaporization, $\Delta_{vap}S$, at the boiling temperature, T_b, of a liquid is related to its enthalpy of vaporization at that temperature by

$$\textit{At the boiling temperature: } \Delta_{vap}S = \frac{\Delta_{vap}H(T_b)}{T_b} \qquad \textbf{(2.5)}$$

Note that to use this formula, we use the enthalpy of vaporization at the boiling temperature. Table 2.1 lists the entropy of vaporization of several substances at 1 atm. For the standard value, $\Delta_{vap}S^{\ominus}$, we use data corresponding to 1 bar. Because vaporization is endothermic for all substances, all entropies of vaporization are positive. The increase in entropy accompanying vaporization is in line with what we should expect when a compact liquid turns into a gas. To calculate the entropy of phase transition at a temperature other than the transition temperature, we have to do additional calculations, as shown in the following *Illustration*.

Table 2.1 Entropies of vaporization at 1 atm and the normal boiling point

	$\Delta_{vap}S/(J\ K^{-1}\ mol^{-1})$
Ammonia, NH_3	97.4
Benzene, C_6H_6	87.2
Bromine, Br_2	88.6
Carbon tetrachloride, CCl_4	85.9
Cyclohexane, C_6H_{12}	85.1
Ethanol, CH_3CH_2OH	104.1
Hydrogen sulfide, H_2S	87.9
Water, H_2O	109.1

ILLUSTRATION 2.3 The entropy of vaporization of water at 25°C

Suppose we want to calculate the entropy of vaporization of water at 25°C. The most convenient way to proceed is to perform three calculations. First, we calculate the entropy change for heating liquid water from 25°C to 100°C (using eqn 2.2 with data for the liquid from Table 1.1):

$$\Delta S_1 = C_{p,m}(H_2O, \text{liquid}) \ln \frac{T_f}{T_i} = (75.29\ J\ K^{-1}\ mol^{-1}) \times \ln \frac{373\ K}{298\ K}$$
$$= +16.9\ J\ K^{-1} mol^{-1}$$

Then, we use eqn 2.5 and data from Table 1.2 to calculate the entropy of transition at 100°C:

$$\Delta S_2 = \frac{\Delta_{vap}H(T_b)}{T_b} = \frac{4.07 \times 10^4\ J\ mol^{-1}}{373\ K} = +1.09 \times 10^2\ J\ K^{-1}\ mol^{-1}$$

Finally, we calculate the change in entropy for cooling the vapor from 100°C to 25°C (using eqn 2.2 again, but now with data for the vapor from Table 1.1):

$$\Delta S_3 = C_{p,m}(H_2O, \text{vapor}) \ln \frac{T_f}{T_i} = (33.58\ J\ K^{-1}\ mol^{-1}) \times \ln \frac{298\ K}{373\ K}$$
$$= -7.54\ J\ K^{-1}\ mol^{-1}$$

The sum of the three entropy changes is the entropy of transition at 25°C:

$$\Delta_{vap}S\ (298\ K) = \Delta S_1 + \Delta S_2 + \Delta S_3 = +118\ J\ K^{-1}\ mol^{-1}$$ ■

2.5 Entropy changes in the surroundings

To develop a complete picture of entropy changes, we need to consider how a process occurring in an organism can affect the entropy of its surroundings.

We can use the definition of entropy in eqn 2.1 to calculate the entropy change of the surroundings in contact with the system at the temperature T:

$$\Delta S_{sur} = \frac{q_{sur,rev}}{T}$$

The surroundings are so extensive that they remain at constant pressure regardless of any events taking place in the system, so $q_{sur,rev} = \Delta H_{sur}$. The enthalpy is a state function, so a change in its value is independent of the path and we get the same value of ΔH_{sur} regardless of how the heat is transferred. Therefore, we can drop the label "rev" from q and write

$$\Delta S_{sur} = \frac{q_{sur}}{T} \tag{2.6}$$

We can use this formula to calculate the entropy change of the surroundings regardless of whether the change in the system is reversible or not.

EXAMPLE 2.1 Estimating the entropy change of the surroundings due to metabolism

The metabolic rate is the rate at which an organism expends energy from the oxidation of food. At rest, organisms still consume energy at the so-called *basal metabolic rate*. It follows from Section 1.3 that even a resting human being heats the surroundings, typically at a rate of 100 J s^{-1}. Estimate the entropy a resting person generates in the surroundings in the course of a day at 20°C.

Strategy We can estimate the approximate change in entropy from eqn 2.6 once we have calculated the energy transferred as heat. To find this quantity, we use the fact that there are 86 400 s in a day. Convert the temperature to kelvins.

Solution The energy transferred by heating the surroundings in the course of a day is

$$q_{sur} = (86\ 400\ \text{s}) \times (100\ \text{J s}^{-1}) = 86\ 400 \times 100\ \text{J}$$

The increase in entropy of the surroundings is therefore

$$\Delta S_{sur} = \frac{q_{sur}}{T} = \frac{86\ 400 \times 100\ \text{J}}{293\ \text{K}} = +2.95 \times 10^4\ \text{J K}^{-1}$$

That is, the entropy production is about 30 kJ K^{-1}. Just to stay alive, each person on the planet contributes about 30 kJ K^{-1} each day to the entropy of their surroundings. The use of transport, machinery, and communications generates far more in addition.

SELF-TEST 2.3 Suppose a small reptile operates at 0.50 J s^{-1}. What entropy does it generate in the course of a day in the water in the lake that it inhabits, where the temperature is 15°C?

Answer: +150 J K^{-1} ■

Equation 2.6 is expressed in terms of the energy supplied to the *surroundings* as heat, q_{sur}. Normally, we have information about the heat supplied to or escaping from the system, q. The two quantities are related by $q_{sur} = -q$. For instance, if $q = +100$ J, an influx of 100 J, then $q_{sur} = -100$ J, indicating that the surroundings

have lost that 100 J. Therefore, at this stage we can replace q_{sur} in eqn 2.6 by $-q$ and write

$$\Delta S_{sur} = -\frac{q}{T} \tag{2.7}$$

This expression is in terms of the properties of the system. Moreover, it applies whether or not the process taking place in the system is reversible.

If a chemical reaction or a phase transition takes place at constant pressure, we can identify q in eqn 2.7 with the change in enthalpy of the system and obtain

$$\textit{For a process at constant pressure: } \Delta S_{sur} = -\frac{\Delta H}{T} \tag{2.8}$$

This enormously important expression will lie at the heart of our discussion of chemical equilibria. We see that it is consistent with common sense: if the process is exothermic, ΔH is negative and therefore ΔS_{sur} is positive. The entropy of the surroundings increases if heat is released into them. If the process is endothermic ($\Delta H > 0$), then the entropy of the surroundings decreases.

2.6 Absolute entropies and the Third Law of thermodynamics

To calculate entropy changes associated with biological processes, we need to see how to compile tables that list values of the entropies of substances.

The graphical procedure summarized by Fig. 2.5 and eqn 2.3 for the determination of the difference in entropy of a substance at two temperatures has a very important application. If $T_i = 0$, then the area under the graph between $T = 0$ and some temperature T gives us the value of $\Delta S = S(T) - S(0)$. However, at $T = 0$, all the motion of the atoms has been eliminated, and there is no thermal disorder. Moreover, if the substance is perfectly crystalline, with every atom in a well-defined location, then there is no spatial disorder either. We can therefore suspect that at $T = 0$, the entropy is zero.

The thermodynamic evidence for this conclusion is as follows. Sulfur undergoes a phase transition from its rhombic form to its monoclinic polymorph at 96°C (369 K) and the enthalpy of transition is +402 J mol^{-1}. The entropy of transition is therefore +1.09 J K^{-1} mol^{-1} at this temperature. We can also measure the molar entropy of each phase relative to its value at $T = 0$ by determining the heat capacity from $T = 0$ up to the transition temperature (Fig. 2.7). At this stage, we do not know the values of the entropies at $T = 0$. However, as we see from the illustration, to match the observed entropy of transition at 369 K, *the molar entropies of the two crystalline forms must be the same at* $T = 0$. We cannot say that the entropies are zero at $T = 0$, but from the experimental data we do know that they are the same. This observation is generalized into the **Third Law of thermodynamics**:

The entropies of all perfectly crystalline substances are the same at $T = 0$.

For convenience (and in accord with our understanding of entropy as a measure of dispersal of energy), we take this common value to be zero. Then, with this convention, according to the Third Law,

$S(0) = 0$ *for all perfectly ordered crystalline materials.*

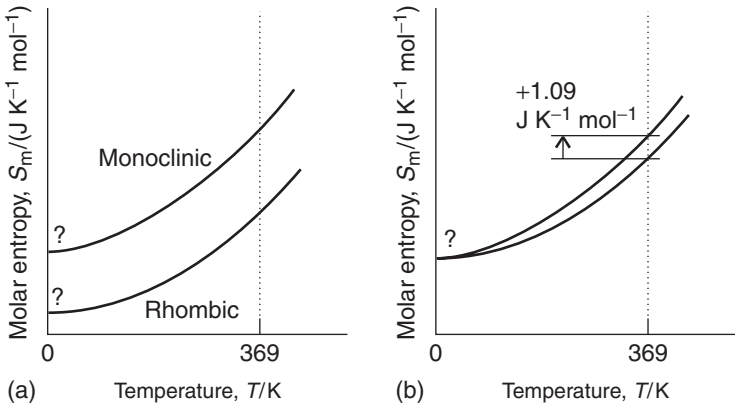


Fig. 2.7 (a) The molar entropies of monoclinic and rhombic sulfur vary with temperature as shown here. At this stage we do not know their values at $T = 0$. (b) When we slide the two curves together by matching their separation to the measured entropy of transition at the transition temperature, we find that the entropies of the two forms are the same at $T = 0$.

The **Third-Law entropy** at any temperature, $S(T)$, is equal to the area under the graph of C/T between $T = 0$ and the temperature T (Fig. 2.8). If there are any phase transitions (for example, melting) in the temperature range of interest, then the entropy of each transition at the transition temperature is calculated like that in eqn 2.4 and its contribution added to the contributions from each of the phases, as shown in Fig. 2.9. The Third-Law entropy, which is commonly called simply "the entropy," of a substance depends on the pressure; we therefore select a standard pressure (1 bar) and report the **standard molar entropy**, $S_m^{\ominus}$, the molar entropy of a substance in its standard state at the temperature of interest. Some values at 298.15 K (the conventional temperature for reporting data) are given in Table 2.2.

It is worth spending a moment to look at the values in Table 2.2 to see that they are consistent with our understanding of entropy. All standard molar entropies

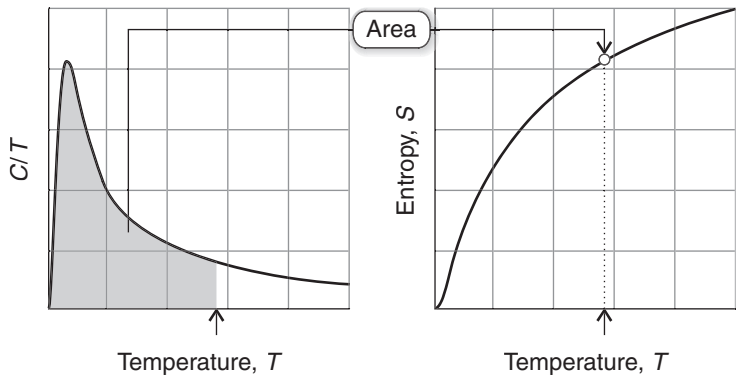


Fig. 2.8 The absolute entropy (or Third-Law entropy) of a substance is calculated by extending the measurement of heat capacities down to $T = 0$ (or as close to that value as possible) and then determining the area of the graph of C/T against T up to the temperature of interest. The area is equal to the absolute entropy at the temperature T.

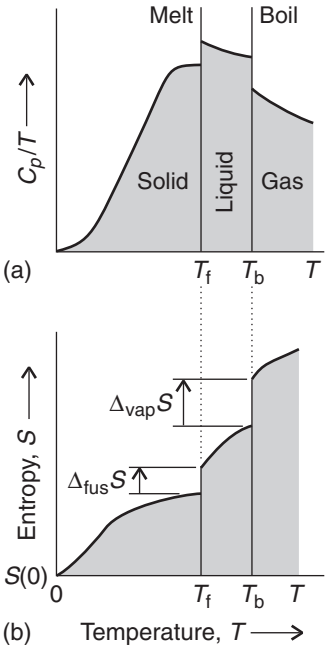


Fig. 2.9 The determination of entropy from heat capacity data. (a) Variation of C_p/T with the temperature of the sample. (b) The entropy, which is equal to the area beneath the upper curve up to the temperature of interest plus the entropy of each phase transition between $T = 0$ and the temperature of interest.

COMMENT 2.1 The text's web site contains links to online databases of thermochemical data, including tabulations of standard molar entropies. ■

Table 2.2 Standard molar entropies of some substances at 298.15 K*

Substance	$S_m^{\ominus}/(J\ K^{-1}\ mol^{-1})$
Gases	
Ammonia, NH_3	192.5
Carbon dioxide, CO_2	213.7
Hydrogen, H_2	130.7
Nitrogen, N_2	191.6
Oxygen, O_2	205.1
Water vapor, H_2O	188.8
Liquids	
Acetic acid, CH_3COOH	159.8
Ethanol, CH_3CH_2OH	160.7
Water, H_2O	69.9
Solids	
Calcium carbonate, $CaCO_3$	92.9
Diamond, C	2.4
Glycine, $CH_2(NH_2)COOH$	103.5
Graphite, C	5.7
Sodium chloride, NaCl	72.1
Sucrose, $C_{12}H_{22}O_{11}$	360.2
Urea, $CO(NH_2)_2$	104.60

*See the *Data section* for more values.

are positive, because raising the temperature of a sample above $T = 0$ invariably increases its entropy above the value $S(0) = 0$. Another feature is that the standard molar entropy of diamond (2.4 J K^{-1} mol^{-1}) is lower than that of graphite (5.7 J K^{-1} mol^{-1}). This difference is consistent with the atoms being linked less rigidly in graphite than in diamond and their thermal motion being correspondingly greater. The standard molar entropies of ice, water, and water vapor at 25°C are, respectively, 45, 70, and 189 J K^{-1} mol^{-1}, and the increase in values corresponds to the increasing dispersal of matter and energy on going from a solid to a liquid and then to a gas.

Heat capacities can be measured only with great difficulty at very low temperatures, particularly close to $T = 0$. However, it has been found that many nonmetallic substances have a heat capacity that obeys the **Debye T^3-law**:

$$\textit{At temperatures close to } T = 0,\ C_{V,m} = aT^3 \qquad \textbf{(2.9a)}$$

where a is a constant that depends on the substance and is found by fitting this equation to a series of measurements of the heat capacity close to $T = 0$. With a determined, it is easy to deduce the molar entropy at low temperatures, because

$$\textit{At temperatures close to } T = 0,\ S_m(T) = \tfrac{1}{3}C_{V,m}(T) \qquad \textbf{(2.9b)}$$

That is, the molar entropy at the low temperature T is equal to one-third of the constant-volume heat capacity at that temperature.

DERIVATION 2.2 Entropies close to $T = 0$

Once again, we use the general expression for the entropy change accompanying a change of temperature deduced in Section 2.3, with ΔS interpreted as $S(T_f) - S(T_i)$, taking molar values, and supposing that the heating takes place at constant volume:

$$S_m(T_f) - S_m(T_i) = \int_{T_i}^{T_f} \frac{C_{V,m}}{T}\, dT$$

If we set $T_i = 0$ and T_f some general temperature T, we can rearrange this expression into

$$S_m(T) - S_m(0) = \int_0^T \frac{C_{V,m}}{T}\, dT$$

According to the Third Law, $S(0) = 0$, and according to the Debye T^3-law, $C_{V,m} = aT^3$, so

$$S_m(T) = \int_0^T \frac{aT^3}{T}\, dT = a\int_0^T T^2 dT$$

At this point we can use the standard integral

$$\int x^2 dx = \tfrac{1}{3}x^3 + \text{constant}$$

to write

$$\begin{aligned}\int_0^T T^2 dT &= \left(\tfrac{1}{3}T^3 + \text{constant}\right)\Big|_0^T \\ &= \left(\tfrac{1}{3}T^3 + \text{constant}\right) - \text{constant} \\ &= \tfrac{1}{3}T^3\end{aligned}$$

We can conclude that

$$S_m(T) = \tfrac{1}{3}aT^3 = \tfrac{1}{3}C_{V,m}(T)$$

as in eqn 2.9b.

2.7 The standard reaction entropy

To move into the arena of biochemistry, where reactants are transformed into products, we need to establish procedures for using the tabulated values of absolute entropies to calculate entropy changes associated with chemical reactions.

Once again, we can use our intuition to predict the sign of the entropy change associated with a chemical reaction. When there is a net formation of a gas in a reaction, as in a combustion, we can usually anticipate that the entropy increases. When there is a net consumption of gas, as in the fixation of N_2 by certain

microorganisms, it is usually safe to predict that the entropy decreases. However, for a quantitative value of the change in entropy and to predict the sign of the change when no gases are involved, we need to do an explicit calculation.

The difference in molar entropy between the products and the reactants in their standard states is called the **standard reaction entropy**, $\Delta_r S^\ominus$. It can be expressed in terms of the molar entropies of the substances in much the same way as we have already used for the standard reaction enthalpy:

$$\Delta_r S^\ominus = \sum \nu S_m^\ominus(\text{products}) - \sum \nu S_m^\ominus(\text{reactants}) \qquad \textbf{(2.10)}$$

where the ν are the stoichiometric coefficients in the chemical equation.

ILLUSTRATION 2.4 Calculating a standard reaction entropy for an enzyme-catalyzed reaction

The enzyme carbonic anhydrase catalyzes the hydration of CO_2 gas in red blood cells:

$$CO_2(g) + H_2O(l) \longrightarrow H_2CO_3(aq)$$

We expect a negative entropy of reaction because a gas is consumed. To find the explicit value at 25°C, we use the information from the *Data section* to write

$$\begin{aligned}\Delta_r S^\ominus &= S_m^\ominus(H_2CO_3, aq) - \{S_m^\ominus(CO_2, g) + S_m^\ominus(H_2O, l)\} \\ &= (187.4 \text{ J K}^{-1} \text{ mol}^{-1}) \\ &\quad - \{(213.74 \text{ J K}^{-1} \text{ mol}^{-1}) + (69.91 \text{ J K}^{-1} \text{ mol}^{-1})\} \\ &= -96.3 \text{ J K}^{-1} \text{ mol}^{-1} \blacksquare\end{aligned}$$

SELF-TEST 2.4 (a) Predict the sign of the entropy change associated with the complete oxidation of solid sucrose, $C_{12}H_{22}O_{11}(s)$, by O_2 gas to CO_2 gas and liquid H_2O. (b) Calculate the standard reaction entropy at 25°C.

A note on good practice: Do not make the mistake of setting the standard molar entropies of elements equal to zero: they have nonzero values (provided $T > 0$), as we have already discussed.

Answer: (a) positive; (b) $+948.6 \text{ J K}^{-1} \text{ mol}^{-1}$

2.8 The spontaneity of chemical reactions

To assess the spontaneity of a biological process, we need to see how to take into account entropy changes in both the system and the surroundings.

A process may be spontaneous even though the entropy change that accompanies it is negative. Consider the binding of oxidized nicotinamide adenine dinucleotide (NAD^+), an important electron carrier in metabolism (Section 1.3), to the enzyme lactate dehydrogenase, which plays a role in catabolism and anabolism of carbohydrates. Experiments show that $\Delta_r S^\ominus = -16.8 \text{ J K}^{-1} \text{ mol}^{-1}$ for binding at 25°C and pH = 7.0. The negative sign of the entropy change is expected because the association of two reactants gives rise to a more compact structure. The reaction results in less dispersal of matter, yet it is spontaneous!

The resolution of this apparent paradox underscores a feature of entropy that recurs throughout chemistry and biology: *it is essential to consider the entropy of both the system and its surroundings when deciding whether a process is spontaneous or not*. The reduction in entropy by 16.8 J K^{-1} mol^{-1} relates only to the system, the reaction mixture. To apply the Second Law correctly, we need to calculate the *total* entropy, the sum of the changes in the system and the surroundings that jointly compose the "isolated system" referred to in the Second Law. It may well be the case that the entropy of the system decreases when a change takes place, but there may be a more than compensating increase in entropy of the surroundings, so that overall the entropy change is positive. The opposite may also be true: a large decrease in entropy of the surroundings may occur when the entropy of the system increases. In that case we would be wrong to conclude from the increase of the system alone that the change is spontaneous. *Whenever considering the implications of entropy, we must always consider the total change of the system and its surroundings*.

To calculate the entropy change in the surroundings when a reaction takes place at constant pressure, we use eqn 2.8, interpreting the ΔH in that expression as the reaction enthalpy. For example, for the formation of the NAD^+-enzyme complex discussed above, with $\Delta_r H^\ominus = -24.2$ kJ mol^{-1}, the change in entropy of the surroundings (which are maintained at 25°C, the same temperature as the reaction mixture) is

$$\Delta_r S_{sur} = -\frac{\Delta_r H}{T} = -\frac{(-24.2 \text{ kJ mol}^{-1})}{298 \text{ K}} = +81.2 \text{ J K}^{-1} \text{ mol}^{-1}$$

Now we can see that the total entropy change is positive:

$$\Delta_r S_{total} = (-16.8 \text{ J K}^{-1} \text{ mol}^{-1}) + (81.2 \text{ J K}^{-1} \text{ mol}^{-1}) = +4.8 \text{ J K}^{-1} \text{ mol}^{-1}$$

This calculation confirms that the reaction is spontaneous. In this case, the spontaneity is a result of the dispersal of energy that the reaction generates in the surroundings: the complex is dragged into existence, even though its has a lower entropy than the separated reactants, by the tendency of energy to disperse into the surroundings.

The Gibbs energy

One of the problems with entropy calculations is already apparent: we have to work out two entropy changes, the change in the system and the change in the surroundings, and then consider the sign of their sum. The great American theoretician J.W. Gibbs (1839–1903), who laid the foundations of chemical thermodynamics toward the end of the nineteenth century, discovered how to combine the two calculations into one. The combination of the two procedures in fact turns out to be of much greater relevance than just saving a little labor, and throughout this text we shall see consequences of the procedure he developed.

2.9 Focusing on the system

To simplify the discussion of the role of the total change in the entropy, we need to introduce a new state function, the Gibbs energy, which will be used extensively in our study of bioenergetics and biological structure.

The total entropy change that accompanies a process is

$$\Delta S_{\text{total}} = \Delta S + \Delta S_{\text{sur}}$$

where ΔS is the entropy change for the system; for a spontaneous change, $\Delta S_{\text{total}} > 0$. If the process occurs at constant pressure and temperature, we can use eqn 2.8 to express the change in entropy of the surroundings in terms of the enthalpy change of the system, ΔH. When the resulting expression is inserted into this one, we obtain

$$\textit{At constant temperature and pressure: } \Delta S_{\text{total}} = \Delta S - \frac{\Delta H}{T} \qquad \textbf{(2.11)}$$

The great advantage of this formula is that it expresses the total entropy change of the system and its surroundings in terms of properties of the system alone. The only restriction is to changes at constant pressure and temperature.

Now we take a very important step. First, we introduce the **Gibbs energy**, G, which is defined as[1]

$$G = H - TS \qquad \textbf{(2.12)}$$

Because H, T, and S are state functions, G is a state function too. A change in Gibbs energy, ΔG, at constant temperature arises from changes in enthalpy and entropy and is

$$\textit{At constant temperature: } \Delta G = \Delta H - T\Delta S \qquad \textbf{(2.13)}$$

By comparing eqns 2.11 and 2.13, we obtain

$$\textit{At constant temperature and pressure: } \Delta G = -T\Delta S_{\text{total}} \qquad \textbf{(2.14)}$$

We see that at constant temperature and pressure, the change in Gibbs energy of a system is proportional to the overall change in entropy of the system plus its surroundings.

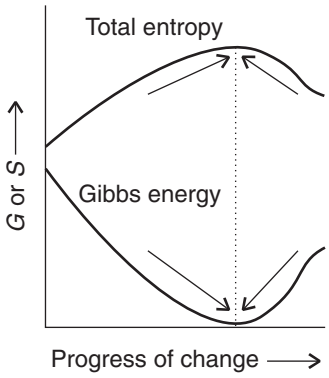


Fig. 2.10 The criterion of spontaneous change is the increase in total entropy of the system and its surroundings. Provided we accept the limitation of working at constant pressure and temperature, we can focus entirely on properties of the system and express the criterion as a tendency to move to lower Gibbs energy.

2.10 Spontaneity and the Gibbs energy

To see the basis of the central role of the Gibbs energy in the discussion of bioenergetics and biochemistry, we need to relate it to the spontaneity of processes.

The difference in sign between ΔG and ΔS_{total} implies that the condition for a process being spontaneous changes from $\Delta S_{\text{total}} > 0$ in terms of the total entropy (which is universally true) to $\Delta G < 0$ in terms of the Gibbs energy (for processes occurring at constant temperature and pressure). That is, *in a spontaneous change at constant temperature and pressure, the Gibbs energy decreases* (Fig. 2.10).

It may seem more natural to think of a system as falling to a lower value of some property. However, it must never be forgotten that to say that a system tends to fall toward lower Gibbs energy is only a modified way of saying that a system

[1]The Gibbs energy is still commonly referred to by its older name, the "free energy."

and its surroundings jointly tend toward a greater total entropy. The *only* criterion of spontaneous change is the total entropy of the system and its surroundings; the Gibbs energy merely contrives a way of expressing that total change in terms of the properties of the system alone and is valid only for processes that occur at constant temperature and pressure.

CASE STUDY 2.1 Life and the Second Law of thermodynamics

Every chemical reaction that is spontaneous under conditions of constant temperature and pressure, including those that drive the processes of growth, learning, and reproduction, is a reaction that changes in the direction of lower Gibbs energy, or—another way of expressing the same thing—results in the overall entropy of the system and its surroundings becoming greater. With these ideas in mind, it is easy to explain why life, which can be regarded as a collection of biological processes, proceeds in accord with the Second Law of thermodynamics.

It is not difficult to imagine conditions in the cell that may render spontaneous many of the reactions of catabolism described briefly in Section 1.3. After all, the breakdown of large molecules, such as sugars and lipids, into smaller molecules leads to the dispersal of matter in the cell. Energy is also dispersed, as it is released upon reorganization of bonds in foods. More difficult to rationalize is life's requirement of organization of a very large number of molecules into biological cells, which in turn assemble into organisms. To be sure, the entropy of the system—the organism—is very low because matter becomes less dispersed when molecules assemble to form cells, tissues, organs, and so on. However, the lowering of the system's entropy comes at the expense of an increase in the entropy of the surroundings. To understand this point, recall from Sections 1.3 and 2.1 that cells grow by converting energy from the Sun or oxidation of foods partially into work. The remaining energy is released as heat into the surroundings, so $q_{sur} > 0$ and $\Delta S_{sur} > 0$. As with any process, life is spontaneous and organisms thrive as long as the increase in the entropy of the organism's environment compensates for decreases in the entropy arising from the assembly of the organism. Alternatively, we may say that $\Delta G < 0$ for the overall sum of physical and chemical changes that we call life. ■

2.11 The Gibbs energy of assembly of proteins and biological membranes

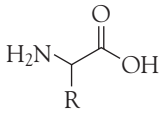
To gain insight into the thermodynamic factors that contribute to the spontaneous assembly of biological macromolecules, we need to examine in detail some of the interactions that bring molecular building blocks together.

Throughout the text we shall see how concepts of physical chemistry can be used to establish some of the known "rules" for the assembly of complex biological structures. Here, we describe how the Second Law can account for the formation of such organized assemblies as proteins and biological cell membranes.

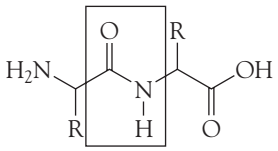
(a) The structures of proteins and biological membranes

Recall from your study of biochemistry that proteins are **polypeptides** formed from different α-amino acids of general form $NH_2CHRCOOH$ (**1**) strung together by the **peptide link**, –CONH– (**2**), formed in a condensation reaction. Each monomer unit in the chain is referred to as a peptide **residue**. About twenty amino acids

COMMENT 2.2 Recall that a hydrogen bond is an attractive interaction between two species that arises from a link of the form A–H···B, where A and B are highly electronegative elements and B possesses a lone pair of electrons. See Chapter 11 for a more detailed description of the molecular interactions that determine the three-dimensional structures of biological macromolecules. ■



1 General form of α-amino acids



2 The peptide link

Fig. 2.11 (a) A polypeptide adopts a highly organized helical conformation, an example of a secondary structure. (b) The formation of a helix may be visualized as the winding of the polypeptide chain around a cylinder. (c) A helical polypeptide is often represented as a cylinder.

occur naturally and differ in the nature of the group R, as summarized in the *Data section*.

The concept of the "structure" of a protein takes on different meanings for the different levels at which we think about the spatial arrangement of the polypeptide chain. The **primary structure** of a protein is the sequence in which the amino acids are linked in the polymer. The **secondary structure** of a protein is the (often local) spatial arrangement of the chain. Examples of secondary structure motifs are random coils, in which the amino acid residues do not interact with each other by hydrogen bonds or any other type of bond, and ordered structures, such as helices and sheets, held together primarily by hydrogen bonds (Fig 2.11). The **tertiary structure** is the overall three-dimensional structure of a macromolecule. For instance, the hypothetical protein shown in Fig 2.12 has helical regions connected by short random-coil sections. The helices interact to form a compact tertiary structure. The **quaternary structure** of a macromolecule is the manner in which large molecules are formed by the aggregation of others. Figure 2.13 shows how four molecular subunits, each with a specific tertiary structure, aggregate together.

As remarked in the *Prologue*, we do not know all the rules that govern the folding of proteins into well-defined three-dimensional structures. However, a number of general conclusions from experimental studies give some insight into the origin of tertiary and quaternary structure in proteins. Here we focus on the observation that, in an aqueous environment (including the interior of biological cells), the chains of a protein fold in such a way as to place hydrophobic groups (water-repelling, non-polar groups such as $-CHCH_2(CH_3)_2$) in the interior, which is often not very accessible to solvent, and hydrophilic groups (water-loving, polar or charged groups such as $-NH_3^+$) on the surface, which is in direct contact with the polar solvent.

The tendency of nonpolar groups to cluster together in aqueous environments is also responsible for the assembly of complex systems in solution and in biological cells. An **amphipathic** species[2] has both hydrophobic and hydrophilic regions. An example is a molecule consisting of a long hydrocarbon tail that dissolves in hydrocarbon and other nonpolar materials and a hydrophilic **head group**, such as a carboxylate group, $-CO_2^-$, that dissolves in a polar solvent (typically water). Soaps, for example, consist of the alkali metal salts of long-chain carboxylic acids, and the surfactant in detergents is typically a long-chain benzenesulfonic acid ($R-C_6H_4SO_3H$). The mode of action of soap is to dissolve in both the aqueous phase and the hydrocarbon phase where their surfaces are in contact and hence to solubilize the hydrocarbon phase so that it can be washed away (Fig. 2.14).

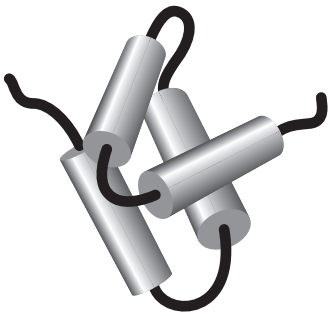


Fig. 2.12 Several helical segments connected by short random coils pack together, providing an example of tertiary structure.

Amphipathic molecules can group together as **micelles** even in the absence of grease droplets, for their hydrophobic tails tend to congregate, and their hydrophilic heads provide protection (Fig. 2.15). Micelles form only above the **critical micelle concentration** (CMC) and above the **Krafft temperature**. The shapes of the individual micelles vary with concentration. Although spherical micelles do occur, they are more commonly flattened spheres close to the CMC and are rodlike at higher concentrations. The interior of a micelle is like a droplet of oil, and experiments show that the hydrocarbon tails are mobile, but slightly more restricted than in the bulk.

Micelles are important in industry and biology on account of their solubilizing function: matter can be transported by water after it has been dissolved in their hy-

[2]The *amphi-* part of the name is from the Greek word for "both," and the *-pathic* part is from the same root (meaning "feeling") as *sympathetic*.

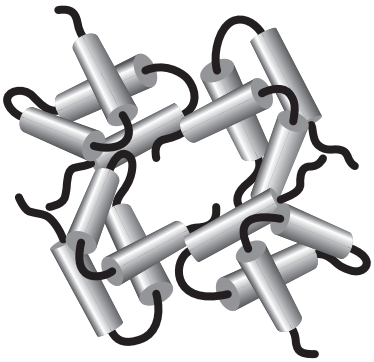
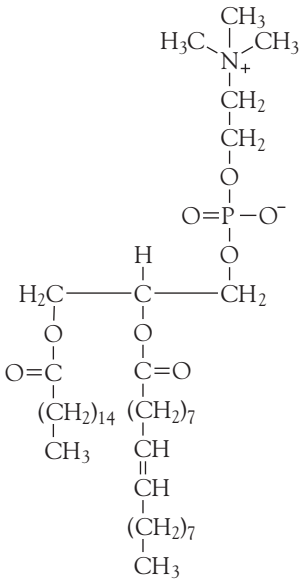


Fig. 2.13 Several subunits with specific structures pack together, providing an example of quaternary structure.



3 Phosphatidyl choline

drocarbon interiors. For this reason, micellar systems are used as detergents and drug carriers and for organic synthesis and petroleum recovery. They can be perceived as a part of a family of similar structures formed when amphipathic substances are present in water (Fig. 2.16). A **monolayer** forms at the air-water interface, with the hydrophilic head groups facing the water. Micelles are like monolayers that enclose a region. A **bilayer vesicle** is like a double micelle, with an inward-pointing inner surface of molecules surrounded by an outward-pointing outer layer. The "flat" version of a bilayer vesicle is the analog of a biological cell membrane. The basic structural element of a membrane is a phospholipid, such as phosphatidyl choline (**3**), which contains long hydrocarbon chains (typically in the range C_{14}–C_{24}) and a variety of polar groups, such as $-CH_2CH_2N(CH_3)_3^+$. The hydrophobic chains stack together to form an extensive bilayer about 5 nm across (Fig 2.17), leaving the polar groups exposed to the aqueous environment on either side of the membrane.

We see that important biological structures arise from the tendency of certain groups to avoid water in their immediate environment and to cluster together. Now we shall develop a molecular explanation for this effect in terms of the Second Law of thermodynamics.

(b) The hydrophobic interaction

Whenever we think about a tendency for an event to occur, we have to consider the total change in entropy of the system and its surroundings, not the system alone. The clustering together of hydrophobic groups results in a negative contribution to the change in entropy of the system because the clustering corresponds to a decrease in the disorder of the system. At first sight, therefore, we would not expect the hydrophobic groups to cluster together. However, we must not forget the role of the solvent.

Nonpolar molecules do dissolve slightly in polar solvents, but strong interactions between solute and solvent are not possible, and as a result it is found that each individual solute molecule is surrounded by a solvent cage (Fig 2.18). To understand the consequences of this effect, consider the thermodynamics of transfer of a nonpolar hydrocarbon solute from a nonpolar solvent to water, a polar solvent. Experiments indicate that the change in Gibbs energy for the transfer process is positive ($\Delta_{\text{transfer}}G > 0$), as expected on the basis of the increase in polarity of the solvent, but the enthalpy change is negative ($\Delta_{\text{transfer}}H < 0$). Therefore, it is a large decrease in the entropy of the system ($\Delta_{\text{transfer}}S < 0$) that accounts for the positive change in Gibbs energy. For example, the process

$$CH_4(\text{in } CCl_4) \longrightarrow CH_4(aq)$$

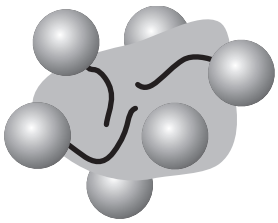


Fig. 2.14 An amphipathic molecule in a detergent or soap acts by sinking its hydrophobic hydrocarbon tail into the grease, so leaving its hydrophilic head groups on the surface of the grease where they can interact attractively with the surrounding water.

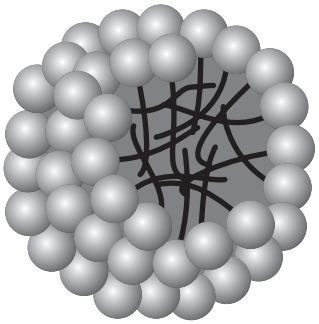


Fig. 2.15 A representation of a spherical micelle. The hydrophilic groups are represented by spheres and the hydrophobic hydrocarbon chains are represented by the stalks. The latter are mobile.

has $\Delta_{transfer}G = +12$ kJ mol^{-1}, $\Delta_{transfer}H = -10$ kJ mol^{-1}, and $\Delta_{transfer}S = -75$ J K^{-1} mol^{-1} at 298 K.

The hydrophobicity of a small molecular group R is reported by defining the **hydrophobicity constant**, π, as

$$\pi = \log \frac{S(RX)}{S(HX)} \qquad \textbf{(2.15)}$$

where S(RX) is the ratio of the molar solubility (the maximum chemical amount that can be dissolved to form 1 L of solution) of the compound R–X in octan-1-ol, a nonpolar solvent, to that in water, and S(HX) is the ratio of the molar solubility of the compound H–X in octan-1-ol to that in water. Therefore, positive values of π indicate hydrophobicity and negative values indicate hydrophilicity, the thermodynamic preference for water as a solvent. It is observed experimentally that the π values of most groups do not depend on the nature of X. However, measurements do suggest group additivity of π values:

–R	$-CH_3$	$-CH_2CH_3$	$-(CH_2)_2CH_3$	$-(CH_2)_3CH_3$	$-(CH_2)_4CH_3$
π	0.5	1	1.5	2	2.5

We see that acyclic saturated hydrocarbons become more hydrophobic as the carbon chain length increases. This trend can be rationalized by $\Delta_{transfer}H$ becoming more positive and $\Delta_{transfer}S$ more negative as the number of carbon atoms in the chain increases.

At the molecular level, formation of a cage of water around a hydrophobic molecule involves the formation of new hydrogen bonds among solvent molecules. This process is exothermic and accounts for the negative values of $\Delta_{transfer}H$. On the other hand, when a very large number of solvent cages must form, fewer molecules are free to disperse, and the result is a decrease in the entropy of the system that accounts for the negative values of $\Delta_{transfer}S$. However, when many solute molecules cluster together, fewer (albeit larger) cages are required, and more solvent molecules are free to move. The net effect of formation of large clusters of hydrophobic molecules is then a decrease in the organization of the solvent and therefore a net *increase* in entropy of the system. This increase in entropy of the solvent is large enough to result in the spontaneous association of hydrophobic molecules in a polar solvent.

The increase in entropy that results from putting fewer structural demands on the solvent by the clustering of non-polar molecules is the origin of the **hydrophobic interaction**, the favoring of the clustering of non-polar groups in an aqueous environment. The hydrophobic interaction is an example of a process that leads to the organization of solute molecules and is stabilized by a tendency toward greater dispersal of solvent molecules.

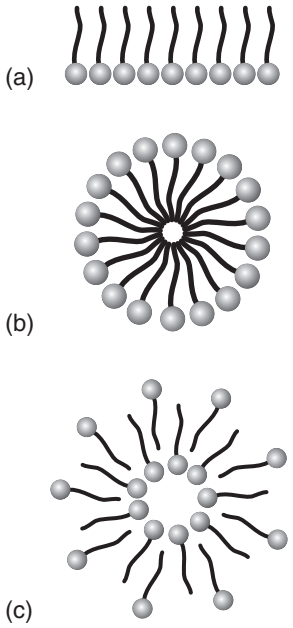


Fig. 2.16 Amphipathic molecules form a variety of related structures in water: (a) a monolayer, (b) a spherical micelle, (c) a bilayer vesicle.

SELF-TEST 2.5 Two long-chain hydrophobic polypeptides can associate end-to-end so that only the ends meet or side-by-side so that the entire chains are in contact. Which arrangement would produce a larger entropy change when they come together?

Answer: The side-by-side arrangement

One consequence of the hydrophobic interaction is that lower temperatures favor a more disorganized arrangement. To see why, we have to think about the entropy change in the surroundings. For a given transfer of heat into them, the change in their entropy increases as the temperature is decreased (eqn 2.1). Therefore, the entropy changes in the system become relatively less important, the system tends to change in its exothermic direction (the direction corresponding to an increase in entropy of the surroundings), and hydrophobic interactions become less important. This is the reason why some proteins dissociate into their individual subunits as the temperature is lowered to 0°C.

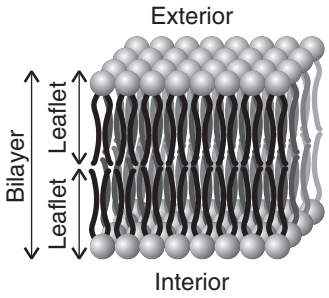


Fig. 2.17 The long hydrocarbon chains of a phospholipid can stack together to form a bilayer structure, with the polar groups (represented by the spheres) exposed to the aqueous environment.

2.13 Work and the Gibbs energy change

To understand how biochemical reactions can be used to release energy as work in the cell, we need to gain deeper insight into the Gibbs energy.

An important feature of the Gibbs energy is that *the value of* ΔG *for a process gives the maximum non-expansion work that can be extracted from the process at constant temperature and pressure*. By **non-expansion work**, w', we mean any work other than that arising from the expansion of the system. It may include electrical work, if the process takes place inside an electrochemical or biological cell, or other kinds of mechanical work, such as the winding of a spring or the contraction of a muscle (we saw an example in *Exercise* 1.41). To demonstrate this property, we need to combine the First and Second Laws, and then we find

$$\textit{At constant temperature and pressure: } \Delta G = w_{max}' \qquad \textbf{(2.16)}$$

DERIVATION 2.3 Maximum non-expansion work

We need to consider infinitesimal changes because dealing with reversible processes is then much easier. Our aim is to derive the relation between the infinitesimal change in Gibbs energy, dG, accompanying a process and the maximum amount of non-expansion work that the process can do, dw'. We start with the infinitesimal form of eqn 2.13,

$$\textit{At constant temperature: } dG = dH - TdS$$

where, as usual, d denotes an infinitesimal difference. A good rule in the manipulation of thermodynamic expressions is to feed in definitions of the terms that appear. We do this twice. First, we use the expression for the change in enthalpy at constant pressure (eqn 1.11, written as $dH = dU + pdV$) and obtain

$$\textit{At constant temperature and pressure: } dG = dU + pdV - TdS$$

Then we replace dU in terms of infinitesimal contributions from work and heat ($dU = dw + dq$):

$$dG = dw + dq + pdV - TdS$$

The work done on the system consists of expansion work, $-p_{ex}dV$, and non-expansion work, dw'. Therefore,

$$dG = -p_{ex}dV + dw' + dq + pdV - TdS$$

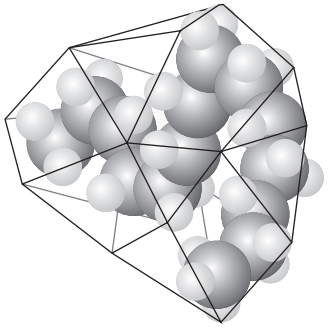


Fig. 2.18 When a hydrocarbon molecule is surrounded by water, the H_2O molecules form a cage. As a result of this acquisition of structure, the entropy of water decreases, so the dispersal of the hydrocarbon into the water is entropy opposed; its coalescence is entropy favored.

This derivation is valid for any process taking place at constant temperature and pressure.

Now we specialize to a reversible change. For expansion work to be reversible, we need to match p and p_{ex}, in which case the first and fourth terms on the right cancel. Moreover, because the transfer of energy as heat is also reversible, we can replace dq by TdS, in which case the third and fifth terms also cancel. We are left with

At constant temperature and pressure, for a reversible process: $dG = dw_{rev}'$

Maximum work is done during a reversible change (Section 1.4), so another way of writing this expression is

At constant temperature and pressure: $dG = dw_{max}'$

Because this relation holds for each infinitesimal step between the specified initial and final states, it applies to the overall change too. Therefore, we obtain eqn 2.16.

EXAMPLE 2.2 Estimating a change in Gibbs energy for a metabolic process

Suppose a certain small bird has a mass of 30 g. What is the minimum mass of glucose that it must consume to fly up to a branch 10 m above the ground? The change in Gibbs energy that accompanies the oxidation of 1.0 mol $C_6H_{12}O_6(s)$ to carbon dioxide gas and liquid water at 25°C is −2828 kJ.

Strategy First, we need to calculate the work needed to raise a mass m through a height h on the surface of the Earth. As we saw in eqn 1.1, this work is equal to mgh, where g is the acceleration of free fall. This work, which is non-expansion work, can be identified with ΔG. We need to determine the amount of substance that corresponds to the required change in Gibbs energy and then convert that amount to a mass by using the molar mass of glucose.

Solution The non-expansion work to be done is

$$w' = (30 \times 10^{-3}\ \text{kg}) \times (9.81\ \text{m s}^{-2}) \times (10\ \text{m}) = 3.0 \times 9.81 \times 1.0 \times 10^{-1}\ \text{J}$$

(because 1 kg m^2 s^{-2} = 1 J). The amount, n, of glucose molecules required for oxidation to give a change in Gibbs energy of this value given that 1 mol provides 2828 kJ is

$$n = \frac{3.0 \times 9.81 \times 1.0 \times 10^{-1}\ \text{J}}{2.828 \times 10^{6}\ \text{J mol}^{-1}} = \frac{3.0 \times 9.81 \times 1.0 \times 10^{-7}}{2.828}\ \text{mol}$$

Therefore, because the molar mass, M, of glucose is 180 g mol^{-1}, the mass, m, of glucose that must be oxidized is

$$\begin{aligned} m = nM &= \left(\frac{3.0 \times 9.81 \times 1.0 \times 10^{-7}}{2.828}\ \text{mol}\right) \times (180\ \text{g mol}^{-1}) \\ &= 1.9 \times 10^{-4}\ \text{g} \end{aligned}$$

That is, the bird must consume at least 0.19 mg of glucose for the mechanical effort (and more if it thinks about it).

SELF-TEST 2.6 A hardworking human brain, perhaps one that is grappling with physical chemistry, operates at about 25 J s^{-1}. What mass of glucose must be consumed to sustain that metabolic rate for an hour?

Answer: 5.7 g ■

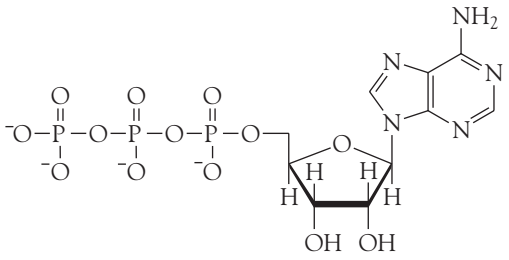
The great importance of the Gibbs energy in chemistry is becoming apparent. At this stage, we see that it is a measure of the non-expansion work resources of chemical reactions: if we know ΔG, then we know the maximum non-expansion work that we can obtain by harnessing the reaction in some way. In some cases, the non-expansion work is extracted as electrical energy. This is the case when electrons are transferred across cell membranes in some key reactions of photosynthesis and respiration (see Chapter 5).

CASE STUDY 2.2 The action of adenosine triphosphate

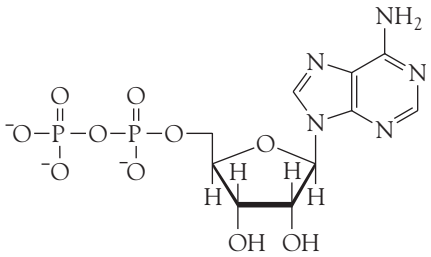
In biological cells, the energy released by the oxidation of foods (Section 1.3) is stored in adenosine triphosphate (ATP or ATP^{4-}, **4**). The essence of ATP's action is its ability to lose its terminal phosphate group by hydrolysis and to form adenosine diphosphate (ADP or ADP^{3-}, **5**):

$$ATP^{4-}(aq) + H_2O(l) \longrightarrow ADP^{3-}(aq) + HPO_4^{2-}(aq) + H_3O^+(aq)$$

At pH = 7.0 and 37°C (310 K, blood temperature) the enthalpy and Gibbs energy of hydrolysis are $\Delta_r H = -20$ kJ mol^{-1} and $\Delta_r G = -31$ kJ mol^{-1}, respectively. Under these conditions, the hydrolysis of 1 mol $ATP^{4-}(aq)$ results in the extraction of up to 31 kJ of energy that can be used to do non-expansion work,



4 ATP



5 ADP

such as the synthesis of proteins from amino acids, muscular contraction, and the activation of neuronal circuits in our brains, as we shall see in Chapter 5. If no attempt is made to extract any energy as work, then 20 kJ (in general, ΔH) of heat will be produced. ■

Some insight into the physical significance of G itself comes from its definition as $H - TS$. The enthalpy is a measure of the energy that can be obtained from the system as heat. The term TS is a measure of the quantity of energy stored in the *random* motion of the molecules making up the sample. Work, as we have seen, is energy transferred in an orderly way, so we cannot expect to obtain work from the energy stored randomly. The difference between the total stored energy and the energy stored randomly, $H - TS$, is available for doing work, and we recognize that difference as the Gibbs energy. In other words, the Gibbs energy is the energy stored in the uniform motion and arrangement of the molecules in the system.

Checklist of Key Ideas

You should now be familiar with the following concepts:

- ☐ **1.** A spontaneous change is a change that has a tendency to occur without work having to be done to bring it about.
- ☐ **2.** Matter and energy tend to disperse.
- ☐ **3.** The Second Law states that the entropy of an isolated system tends to increase.
- ☐ **4.** A change in entropy is defined as $\Delta S = q_{rev}/T$.
- ☐ **5.** The entropy change accompanying heating a system of constant heat capacity is $\Delta S = C \ln(T_f/T_i)$.
- ☐ **6.** In general, the entropy change accompanying the heating of a system is equal to the area under the graph of C/T against T between the two temperatures of interest.
- ☐ **7.** The entropy of transition at the transition temperature is given by $\Delta_{trs}S = \Delta_{trs}H(T_{trs})/T_{trs}$.
- ☐ **8.** The change in entropy of the surroundings is given by $\Delta S_{sur} = -q/T$.
- ☐ **9.** The Third Law of thermodynamics states that the entropies of all perfectly crystalline substances are the same at $T = 0$ (and may be taken to be zero).
- ☐ **10.** The standard reaction entropy is the difference in standard molar entropies of the products and reactants weighted by their stoichiometric coefficients, $\Delta_r S^\ominus = \sum \nu S_m^\ominus(\text{products}) - \sum \nu S_m^\ominus(\text{reactants})$.
- ☐ **11.** The Gibbs energy is defined as $G = H - TS$ and is a state function.
- ☐ **12.** At constant temperature, the change in Gibbs energy is $\Delta G = \Delta H - T\Delta S$.
- ☐ **13.** At constant temperature and pressure, a system tends to change in the direction of decreasing Gibbs energy.
- ☐ **14.** The hydrophobic interaction is a process that leads to the organization of solute molecules and is driven by a tendency toward greater dispersal of solvent molecules.
- ☐ **15.** At constant temperature and pressure, the change in Gibbs energy accompanying a process is equal to the maximum non-expansion work the process can do, $\Delta G = w_{max}'$.

Discussion questions

2.1 The following expressions have been used to establish criteria for spontaneous change: $\Delta S_{\text{isolated system}} > 0$ and $\Delta G < 0$. Discuss the origin, significance, and applicability of each criterion.

2.2 Explain the limitations of the following expressions: **(a)** $\Delta S = C \ln(T_f/T_i)$, **(b)** $\Delta G = \Delta H - T\Delta S$, **(c)** $\Delta G = w_{max}'$.

2.3 Suggest a procedure for the measurement of the entropy of unfolding of a protein with differential scanning calorimetry, a technique discussed in Section 1.10.

2.4 Without performing a calculation, predict whether the standard entropies of the following reactions are positive or negative:

(a) Ala–Ser–Thr–Lys–Gly–Arg–Ser $\xrightarrow{\text{Trypsin}}$ Ala–Ser–Thr–Lys + Gly–Arg

(b) $N_2(g) + 3\ H_2(g) \longrightarrow 2\ NH_3(g)$

(c) $ATP^{4-}(aq) + H_2O(l) \longrightarrow ADP^{3-}(aq) + HPO_4^{2-}(aq) + H_3O^+(aq)$

2.5 Provide a molecular interpretation of the hydrophobic interaction.

Exercises

2.6 A goldfish swims in a bowl of water at 20°C. Over a period of time, the fish transfers 120 J to the water as a result of its metabolism. What is the change in entropy of the water?

2.7 Suppose that when you exercise, you consume 100 g of glucose and that all the energy released as heat remains in your body at 37°C. What is the change in entropy of your body?

2.8 Whenever a gas expands—when we exhale, when a flask is opened, and so on—the gas undergoes an increase in entropy. Conversely, when a gas contracts, its entropy decreases. **(a)** Show that the entropy change due to reversible isothermal expansion or contraction of a perfect gas is $\Delta S = nR\ \ln(V_f/V_i)$, where V_i and V_f are the initial and final volumes, respectively. **(b)** Calculate the change in molar entropy when carbon dioxide expands isothermally from 1.5 L to 4.5 L. **(c)** A sample of carbon dioxide that initially occupies 15.0 L at 250 K and 1.00 atm is compressed isothermally. Into what volume must the gas be compressed to reduce its entropy by 10.0 J K^{-1}?

2.9 Suppose you put a cube of ice of mass 100 g into a glass of water at just above 0°C. When the ice melts, about 33 kJ of energy is absorbed from the surroundings as heat. What is the change in entropy of **(a)** the sample (the ice), **(b)** the surroundings (the glass of water)?

2.10 Calculate the change in entropy of 100 g of ice at 0°C as it is melted, heated to 100°C, and then vaporized at that temperature. Suppose that the changes are brought about by a heater that supplies energy at a constant rate, and sketch a graph showing **(a)** the change in temperature of the system, **(b)** the enthalpy of the system, **(c)** the entropy of the system as a function of time.

2.11 What is the change in entropy of 100 g of water when it is heated from room temperature (20°C) to body temperature (37°C)? Use $C_{p,m}$ = 75.5 J K^{-1} mol^{-1}.

2.12 Estimate the molar entropy of potassium chloride at 5.0 K given that its molar heat capacity at that temperature is 1.2 mJ K^{-1} mol^{-1}.

2.13 Equation 2.2 is based on the assumption that the heat capacity is independent of temperature. Suppose, instead, that the heat capacity depends on temperature as $C = a + bT + a/T^2$. Find an expression for the change of entropy accompanying heating from T_i to T_f. *Hint:* See *Derivation* 2.1.

2.14 Calculate the change in entropy when 100 g of water at 80°C is poured into 100 g of water at 10°C in an insulated vessel given that $C_{p,m}$ = 75.5 J K^{-1} mol^{-1}.

2.15 The protein lysozyme unfolds at a transition temperature of 75.5°C, and the standard enthalpy of transition is 509 kJ mol^{-1}. Calculate the entropy of unfolding of lysozyme at 25.0°C, given that the difference in the constant-pressure heat capacities upon unfolding is 6.28 kJ K^{-1} mol^{-1} and can be assumed to be independent of temperature. *Hint:* Imagine that the transition at 25.0°C occurs in three steps: **(i)** heating of the folded protein from 25.0°C to the transition temperature, **(ii)** unfolding at the transition temperature, and **(iii)** cooling of the unfolded protein to 25.0°C. Because the entropy is a state function, the entropy change at 25.0°C is equal to the sum of the entropy changes of the steps.

2.16 The enthalpy of the graphite ⟶ diamond phase transition, which under 100 kbar occurs at 2000 K, is +1.9 kJ mol^{-1}. Calculate the entropy of transition at that temperature.

2.17 The enthalpy of vaporization of methanol is 35.27 kJ mol^{-1} at its normal boiling point of 64.1°C. Calculate **(a)** the entropy of vaporization of methanol at this temperature and **(b)** the entropy change of the surroundings.

2.18 Trouton's rule summarizes the results of experiments showing that the entropy of vaporization measured at the boiling point, $\Delta_{vap}S = \Delta_{vap}H(T_b)/T_b$, is approximately the same and equal to about 85 J K^{-1} mol^{-1} for all liquids except when hydrogen bonding or some other kind of specific molecular interaction is present. **(a)** Provide a molecular interpretation for Trouton's rule. **(b)** Estimate the entropy of vaporization and the enthalpy of vaporization of octane, which boils at 126°C. **(c)** Trouton's rule does not apply to water because in the liquid, water molecules are held together by an extensive network of hydrogen bonds. Provide a molecular interpretation for the observation that Trouton's rule underestimates the value of the entropy of vaporization of water.

2.19 Calculate the entropy of fusion of a compound at 25°C given that its enthalpy of fusion is 32 kJ mol^{-1} at its melting point of 146°C and the molar heat capacities (at constant pressure) of the liquid and solid forms are 28 J K^{-1} mol^{-1} and 19 J K^{-1} mol^{-1}, respectively.

2.20 Calculate the standard reaction entropy at 298 K of the fermentation of glucose to ethanol: $C_6H_{12}O_6(s) \longrightarrow 2\ C_2H_5OH(l) + 2\ CO_2(g)$

2.21 In a particular biological reaction taking place in the body at 37°C, the change in enthalpy was −125 kJ mol^{-1} and the change in entropy was −126 J K^{-1} mol^{-1}. **(a)** Calculate the change in Gibbs energy. **(b)** Is the reaction spontaneous? **(c)** Calculate the total change in entropy of the system and the surroundings.

2.22 The change in Gibbs energy that accompanies the oxidation of $C_6H_{12}O_6(s)$ to carbon dioxide and water vapor at 25°C is −2828 kJ mol^{-1}. How much glucose does a person of mass 65 kg need to consume to climb through 10 m?

2.23 A non-spontaneous reaction may be driven by coupling it to a reaction that is spontaneous. The formation of glutamine from glutamate and ammonium ions requires 14.2 kJ mol^{-1} of energy input. It is driven by the hydrolysis of ATP to ADP mediated by the enzyme glutamine synthetase. **(a)** Given that the change in Gibbs energy for the hydrolysis of ATP corresponds to $\Delta G = -31$ kJ mol^{-1} under the conditions prevailing in a typical cell, can the hydrolysis drive the formation of glutamine? **(b)** How many moles of ATP must be hydrolyzed to form 1 mol glutamine?

2.24 The hydrolysis of acetyl phosphate has $\Delta G = -42$ kJ mol^{-1} under typical biological conditions. If acetyl phosphate were to be synthesized by coupling to the hydrolysis of ATP, what is the minimum number of ATP molecules that would need to be involved?

2.25 Suppose that the radius of a typical cell is 10 μm and that inside it 10^6 ATP molecules are hydrolyzed each second. What is the power density of the cell in watts per cubic meter (1 W = 1 J s^{-1})? A computer battery delivers about 15 W and has a volume of 100 cm^3. Which has the greater power density, the cell or the battery? (For data, see *Exercise* 2.23.)

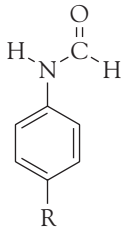
Projects

2.26 The following is an example of a structure-activity relation (SAR), in which it is possible to correlate the effect of a structural change in a compound with its biological function. The use of SARs can improve the design of drugs for the treatment of disease because it facilitates the prediction of the biological activity of a compound before it is synthesized. The binding of non-polar groups of amino acid to hydrophobic sites in the interior of proteins is governed largely by hydrophobic interactions.

(a) Consider a family of hydrocarbons R–H. The hydrophobicity constants, π, for R = CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $(CH_2)_3CH_3$, and $(CH_2)_4CH_3$ are, respectively, 0.5, 1.0, 1.5, 2.0, and 2.5. Use these data to predict the π value for $(CH_2)_6CH_3$.

(b) The equilibrium constants K_I for the dissociation of inhibitors (**6**) from the enzyme chymotrypsin were measured for different substituents R:

R	CH_3CO	CN	NO_2	CH_3	Cl
π	−0.20	−0.025	0.33	0.50	0.90
log K_I	−1.73	−1.90	−2.43	−2.55	−3.40



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Plot log K_I against π. Does the plot suggest a linear relationship? If so, what are the slope and intercept to the log K_I axis of the line that best fits the data?

(c) Predict the value of K_I for the case R = H.

2.27 An *exergonic reaction* is a reaction for which $\Delta G < 0$, and an *endergonic reaction* is a reaction for which $\Delta G > 0$. Here we investigate the molecular basis for the observation first discussed in *Case study* 2.2 that the hydrolysis of ATP is exergonic at pH = 7.0 and 310 K:

$$ATP^{4-}(aq) + H_2O(l) \longrightarrow ADP^{3-}(aq) + HPO_4{}^{2-}(aq) + H_3O^+(aq)$$
$$\Delta_r G = -31 \text{ kJ mol}^{-1}$$

(a) It is thought that the exergonicity of ATP hydrolysis is due in part to the fact that the standard entropies of hydrolysis of polyphosphates are positive. Why would an increase in entropy accompany the hydrolysis of a triphosphate group into a diphosphate and a phosphate group?

(b) Under identical conditions, the Gibbs energies of hydrolysis of H_4ATP and $MgATP^{2-}$, a complex between the Mg^{2+} ion and ATP^{4-}, are less negative than the Gibbs energy of hydrolysis of ATP^{4-}. This observation has been used to support the hypothesis that electrostatic repulsion between adjacent phosphate groups is a factor that controls the exergonicity of ATP hydrolysis. Provide a rationale for the hypothesis and discuss how the experimental evidence supports it. Do these electrostatic effects contribute to the $\Delta_r H$ or $\Delta_r S$ terms that determine the exergonicity of the reaction? *Hint:* In the $MgATP^{2-}$complex, the Mg^{2+} ion and ATP^{4-} anion form two bonds: one that involves a negatively charged oxygen belonging to the terminal phosphate group of ATP^{4-} and another that involves a negatively charged oxygen belonging to the phosphate group adjacent to the terminal phosphate group of ATP^{4-}.

(c) Stabilization due to resonance in ATP^{4-} and the $HPO_4{}^{2-}$ ion is thought to be one of the factors that controls the exergonicity of ATP hydrolysis. Provide a rationale for the hypothesis. Does stabilization through resonance contribute to the $\Delta_r H$ or $\Delta_r S$ terms that determine the exergonicity of the reaction?

CHAPTER

3

Phase Equilibria

Boiling, freezing, the conversion of graphite to diamond, the unfolding of proteins, and the unzipping of a DNA double helix are all examples of **phase transitions**, or changes of phase without change of chemical composition. Many phase changes are common everyday phenomena, and their description is an important part of physical chemistry. They occur whenever a solid changes into a liquid, as in the melting of ice, or a liquid changes into a vapor, as in the vaporization of water in our lungs. They also occur when one solid phase changes into another, as in the conversion of graphite into diamond under high pressure or the conversion of one phase of a biological membrane into another as it is heated.

The thermodynamics of phase changes prepares us for the study of mixtures. In turn, knowledge of the behavior of mixtures prepares us for the study of chemical equilibria (Chapter 4). Some of the thermodynamic concepts developed in this chapter also form the basis of important experimental techniques in biochemistry. More specifically, we consider methods for the measurement of molar masses of proteins and nucleic acids and the investigation of the binding of small molecules to proteins.

The thermodynamics of transition

The Gibbs energy, $G = H - TS$, of a substance will be at the center of all that follows. We need to know how its value depends on the pressure and temperature. As we work out these dependencies, we shall acquire deep insight into the thermodynamic properties of biologically important substances and the transitions they can undergo.

3.1 The condition of stability

To understand processes ranging from the melting of ice to the denaturation of biopolymers, we need to explore the thermodynamic origins of the stabilities of the phases of a substance.

First, we need to establish the importance of the *molar* Gibbs energy, $G_m = G/n$, in the discussion of phase transitions of a pure substance. The molar Gibbs energy, an intensive property, depends on the phase of the substance. For instance, the molar Gibbs energy of liquid water is in general different from that of water vapor at the same temperature and pressure. When an amount n of the substance changes from phase 1 (for instance, liquid) with molar Gibbs energy $G_m(1)$ to phase 2 (for instance, vapor) with molar Gibbs energy $G_m(2)$, the change in Gibbs energy is

$$\Delta G = nG_m(2) - nG_m(1) = n\{G_m(2) - G_m(1)\}$$

We know that a spontaneous change at constant temperature and pressure is accompanied by a negative value of ΔG. This expression shows, therefore, that a

change from phase 1 to phase 2 is spontaneous if the molar Gibbs energy of phase 2 is lower than that of phase 1. In other words, *a substance has a spontaneous tendency to change into the phase with the lowest molar Gibbs energy*.

If at a certain temperature and pressure the solid phase of a substance has a lower molar Gibbs energy than its liquid phase, then the solid phase is thermodynamically more stable and the liquid will (or at least has a tendency to) freeze. If the opposite is true, the liquid phase is thermodynamically more stable and the solid will melt. For example, at 1 atm, ice has a lower molar Gibbs energy than liquid water when the temperature is below 0°C, and under these conditions water converts spontaneously to ice.

3.2 The variation of Gibbs energy with pressure

To discuss how phase transitions depend on the pressure and to lay the foundation for understanding the behavior of solutions of biological macromolecules, we need to know how the molar Gibbs energy varies with pressure.

Why should biologists be interested in the variation of the Gibbs energy with the pressure of a gas, since in most cases their systems are at pressures close to 1 atm? You should recall the discussion in Section 1.3, where we pointed out that to study the thermodynamic properties of a liquid (in which biochemists do have an interest), we can explore the properties of a gas, which is easy to formulate, and then bring the gas into equilibrium with its condensed phase. Then the properties of the liquid mirror those of the vapor, and we can expect to find a similar dependence on the pressure. That is the strategy we adopt throughout this chapter. First we establish equations that apply to gases. Then we consider equilibria between gases and liquids and adapt the gas-phase expressions to describe what really interests us, the properties of liquids.

We show in the following *Derivation* that when the temperature is held constant and the pressure is changed by a small amount Δp, the molar Gibbs energy of a substance changes by

$$\Delta G_m = V_m \Delta p \qquad \textbf{(3.1)}$$

where V_m is the molar volume of the substance. This expression is valid when the molar volume is constant in the pressure range of interest.

DERIVATION 3.1 The variation of G with pressure

We start with the definition of Gibbs energy, $G = H - TS$, and change the temperature, volume, and pressure by an infinitesimal amount. As a result, H changes to $H + dH$, T changes to $T + dT$, S changes to $S + dS$, and G changes to $G + dG$. After the change

$$\begin{aligned} G + dG &= H + dH - (T + dT)(S + dS) \\ &= H + dH - TS - TdS - SdT - dTdS \end{aligned}$$

The G on the left cancels the $H - TS$ on the right, the doubly infinitesimal $dTdS$ can be neglected, and we are left with

$$dG = dH - TdS - SdT$$

To make progress, we need to know how the enthalpy changes. From its definition $H = U + pV$, in a similar way (letting U change to $U + \mathrm{d}U$, and so on, and neglecting the doubly infinitesimal term $\mathrm{d}p\mathrm{d}V$) we can write

$$\mathrm{d}H = \mathrm{d}U + p\mathrm{d}V + V\mathrm{d}p$$

At this point we need to know how the internal energy changes and write

$$\mathrm{d}U = \mathrm{d}q + \mathrm{d}w$$

If initially we consider only reversible changes, we can replace $\mathrm{d}q$ by $T\mathrm{d}S$ (because $\mathrm{d}S = \mathrm{d}q_{\mathrm{rev}}/T$) and $\mathrm{d}w$ by $-p\mathrm{d}V$ (because $\mathrm{d}w = -p_{\mathrm{ex}}\mathrm{d}V$ and $p_{\mathrm{ex}} = p$ for a reversible change) and obtain

$$\mathrm{d}U = T\mathrm{d}S - p\mathrm{d}V$$

Now we substitute this expression into the expression for $\mathrm{d}H$ and that expression into the expression for dG and obtain

$$\begin{aligned}\mathrm{d}G &= T\mathrm{d}S - p\mathrm{d}V + p\mathrm{d}V + V\mathrm{d}p - T\mathrm{d}S - S\mathrm{d}T \\ &= V\mathrm{d}p - S\mathrm{d}T\end{aligned}$$

Now here is a subtle but important point. To derive this result we have supposed that the changes in conditions have been made reversibly. However, G is a state function, and so the change in its value is independent of path. Therefore, the expression is valid for any change, not just a reversible change.

At this point we decide to keep the temperature constant and set $\mathrm{d}T = 0$; this leaves

$$\mathrm{d}G = V\mathrm{d}p$$

and, for molar quantities, $\mathrm{d}G_{\mathrm{m}} = V_{\mathrm{m}}\mathrm{d}p$. This expression is exact but applies only to an infinitesimal change in the pressure. For an observable change, we replace $\mathrm{d}G_{\mathrm{m}}$ and $\mathrm{d}p$ by ΔG_{m} and Δp, respectively, and obtain eqn 3.1, provided the molar volume is constant over the range of interest.

A note on good practice: When confronted with a proof in thermodynamics, go back to fundamental definitions (as we did three times in succession in this derivation: first of G, then of H, and finally of U).

Equation 3.1 tells us that, because all molar volumes are positive, *the molar Gibbs energy increases* ($\Delta G_{\mathrm{m}} > 0$) *when the pressure increases* ($\Delta p > 0$). We also see that, for a given change in pressure, the resulting change in molar Gibbs energy is greatest for substances with large molar volumes. Therefore, because the molar volume of a gas is much larger than that of a condensed phase (a liquid or a solid), the dependence of G_{m} on p is much greater for a gas than for a condensed phase. For most substances (water is an important exception), the molar volume of the liquid phase is greater than that of the solid phase. Therefore, for most substances, the slope of a graph of G_{m} against p is greater for a liquid than for a solid. These characteristics are illustrated in Fig. 3.1.

As we see from Fig. 3.1, when we increase the pressure on a substance, the molar Gibbs energy of the gas phase rises above that of the liquid, then the molar Gibbs energy of the liquid rises above that of the solid. Because the system has a tendency to convert into the state of lowest molar Gibbs energy, the graphs show that at low pressures the gas phase is the most stable, then at higher pressures the liquid phase becomes the most stable, followed by solid phase. In other words, under pressure the substance condenses to a liquid, and then further pressure can result in the formation of a solid.

We can use eqn 3.1 to predict the actual shape of graphs like those in Fig. 3.1. For a solid or liquid, the molar volume is almost independent of pressure, so eqn 3.1 is an excellent approximation to the change in molar Gibbs energy, and with $\Delta G_m = G_m(p_f) - G_m(p_i)$ and $\Delta p = p_f - p_i$ we can write

$$G_m(p_f) = G_m(p_i) + V_m(p_f - p_i) \qquad \textbf{(3.2a)}$$

This equation shows that the molar Gibbs energy of a solid or liquid increases linearly with pressure. However, because the molar volume of a condensed phase is so small, the dependence is very weak, and for typical ranges of pressure of interest to us, we can ignore the pressure dependence of G. The molar Gibbs energy of a gas, however, does depend on the pressure, and because the molar volume of a gas is large, the dependence is significant. We show in the following derivation that

$$G_m(p_f) = G_m(p_i) + RT \ln \frac{p_f}{p_i} \qquad \textbf{(3.2b)}$$

This equation shows that the molar Gibbs energy increases logarithmically (as ln p) with the pressure (Fig. 3.2). The flattening of the curve at high pressures reflects the fact that as V_m gets smaller, G_m becomes less responsive to pressure.

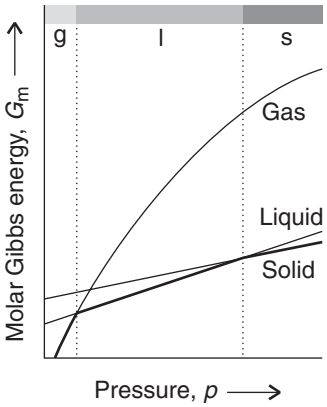


Fig. 3.1 The variation of molar Gibbs energy with pressure. The region where the molar Gibbs energy of a particular phase is least is shown by a dark line and the corresponding region of stability of each phase is indicated in the band at the top of the illustration.

DERIVATION 3.2 The pressure variation of Gibbs energy of a perfect gas

We start with the exact expression for the effect of an infinitesimal change in pressure obtained in *Derivation* 3.1, that $dG_m = V_m dp$. For a change in pressure

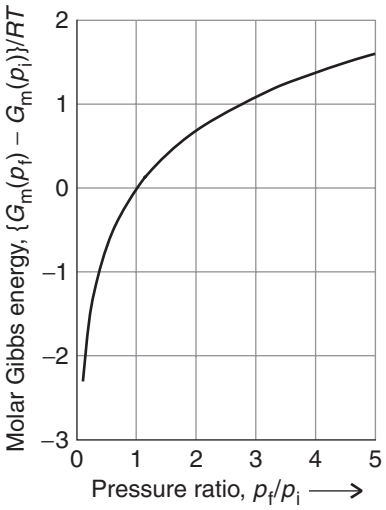


Fig. 3.2 The variation of the molar Gibbs energy of a perfect gas with pressure.

from p_i to p_f, we need to add together (integrate) all these infinitesimal changes and write

$$\Delta G_m = \int_{p_i}^{p_f} V_m dp$$

To evaluate the integral, we must know how the molar volume depends on the pressure. The easiest case to consider is a perfect gas, for which $V_m = RT/p$. Then

$$\Delta G_m = \int_{p_i}^{p_f} V_m \, dp = \int_{p_i}^{p_f} \frac{RT}{p} \, dp = RT \int_{p_i}^{p_f} \frac{dp}{p}$$

(Perfect gas, $V_m = RT/p$; Isothermal, T constant)

$$= RT \ln \frac{p_f}{p_i}$$

We have used the standard integral described in *Comment* 1.3. Finally, with $\Delta G_m = G_m(p_f) - G_m(p_i)$, we get eqn 3.2b.

3.3 The variation of Gibbs energy with temperature

To understand why the denaturation of a biopolymer occurs at a specific temperature, we need to know how molar Gibbs energy varies with temperature.

For small changes in temperature, the change in molar Gibbs energy at constant pressure is

$$\Delta G_m = -S_m \Delta T \tag{3.3}$$

where $\Delta G_m = G_m(T_f) - G_m(T_i)$ and $\Delta T = T_f - T_i$. This expression is valid provided the entropy of the substance is unchanged over the range of temperatures of interest.

DERIVATION 3.3 The variation of the Gibbs energy with temperature

The starting point for this short derivation is the expression obtained in *Derivation* 3.1 for the change in molar Gibbs energy when both the pressure and the temperature are changed by infinitesimal amounts:

$$dG_m = V_m dp - S_m dT$$

If we hold the pressure constant, $dp = 0$, and

$$dG_m = -S_m dT$$

This expression is exact. If we suppose that the molar entropy is unchanged in the range of temperatures of interest, we can replace the infinitesimal changes by observable changes and so obtain eqn 3.3.

Equation 3.3 tells us that, because molar entropy is positive, *an increase in temperature* ($\Delta T > 0$) *results in a decrease in* G_m ($\Delta G_m < 0$). We see that for a given change of temperature, the change in molar Gibbs energy is proportional to the molar entropy. For a given substance, matter and energy are more dispersed in the gas phase than in a condensed phase, so the molar entropy of the gas phase is greater than that for a condensed phase. It follows that the molar Gibbs energy falls more steeply with temperature for a gas than for a condensed phase. The molar entropy of the liquid phase of a substance is greater than that of its solid phase, so the slope is least steep for a solid. Figure 3.3 summarizes these characteristics.

Figure 3.3 also reveals the thermodynamic reason why substances melt and vaporize as the temperature is raised. At low temperatures, the solid phase has the lowest molar Gibbs energy and is therefore the most stable. However, as the temperature is raised, the molar Gibbs energy of the liquid phase falls below that of the solid phase, and the substance melts. At even higher temperatures, the molar Gibbs energy of the gas phase plunges down below that of the liquid phase, and the gas becomes the most stable phase. In other words, above a certain temperature, the liquid vaporizes to a gas.

We can also start to understand why some substances, such as carbon dioxide, sublime to a vapor without first forming a liquid. There is no fundamental requirement for the three lines to lie exactly in the positions we have drawn them in Fig. 3.3: the liquid line, for instance, could lie where we have drawn it in Fig. 3.4. Now we see that at no temperature (at the given pressure) does the liquid phase have the lowest molar Gibbs energy. Such a substance converts spontaneously directly from the solid to the vapor. That is, the substance sublimes.

The **transition temperature** between two phases, such as between liquid and solid or between conformations of a protein, is the temperature, at a given pressure, at which the molar Gibbs energies of the two phases are equal. Above the solid-liquid transition temperature the liquid phase is thermodynamically more stable; below it, the solid phase is more stable. For example, at 1 atm, the transition temperature for ice and liquid water is 0°C. At the transition temperature itself, the molar Gibbs energies of the two phases are identical and there is no tendency for either phase to change into the other. At this temperature, therefore, the two phases are in equilibrium. At 1 atm, ice and liquid water are in equilibrium at 0°C.

As always when using thermodynamic arguments, it is important to keep in mind the distinction between the spontaneity of a phase transition and its rate. *Spontaneity is a tendency, not necessarily an actuality.* A phase transition predicted to be spontaneous may occur so slowly as to be unimportant in practice. For instance, at normal temperatures and pressures the molar Gibbs energy of graphite is 3 kJ mol^{-1} lower than that of diamond, so there is a thermodynamic tendency for diamond to convert into graphite. However, for this transition to take place, the carbon atoms of diamond must change their locations, and because the bonds between the atoms are so strong and large numbers of bonds must change simultaneously, this process is unmeasurably slow except at high temperatures. In gases and liquids the mobilities of the molecules normally allow phase transitions to occur rapidly, but in solids thermodynamic instability may be frozen in and a thermodynamically unstable phase may persist for thousands of years.

3.4 Phase diagrams

To prepare for being able to describe phase transitions in biological macromolecules, first we need to explore the conditions for equilibrium between phases of simpler substances.

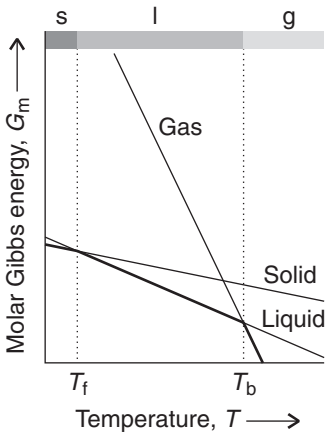


Fig. 3.3 The variation of molar Gibbs energy with temperature. All molar Gibbs energies decrease with increasing temperature. The regions of temperature over which the solid, liquid, and gaseous forms of a substance have the lowest molar Gibbs energy are indicated in the band at the top of the illustration.

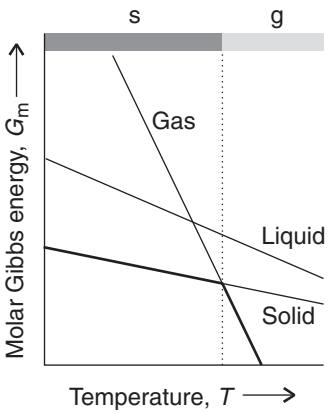


Fig. 3.4 If the line for the Gibbs energy of the liquid phase does not cut through the line for the solid phase (at a given pressure) before the line for the gas phase cuts through the line for the solid, the liquid is not stable at any temperature at that pressure. Such a substance sublimes.

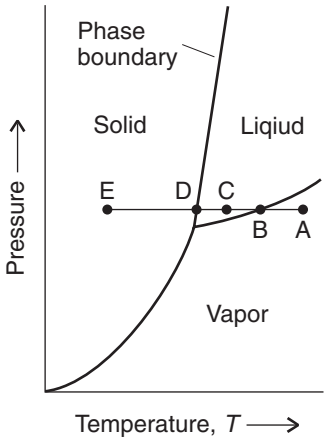


Fig. 3.5 A typical phase diagram, showing the regions of pressure and temperature at which each phase is the most stable. The phase boundaries (three are shown here) show the values of pressure and temperature at which the two phases separated by the line are in equilibrium. The significance of the letters A, B, C, D, and E (also referred to in Fig. 3.8) is explained in the text.

The **phase diagram** of a substance is a map showing the conditions of temperature and pressure at which its various phases are thermodynamically most stable (Fig. 3.5). For example, at point A in the illustration, the vapor phase of the substance is thermodynamically the most stable, but at C the liquid phase is the most stable.

The boundaries between regions in a phase diagram, which are called **phase boundaries**, show the values of p and T at which the two neighboring phases are in equilibrium. For example, if the system is arranged to have a pressure and temperature represented by point B, then the liquid and its vapor are in equilibrium (like liquid water and water vapor at 1 atm and 100°C). If the temperature is reduced at constant pressure, the system moves to point C, where the liquid is stable (like water at 1 atm and at temperatures between 0°C and 100°C). If the temperature is reduced still further to D, then the solid and the liquid phases are in equilibrium (like ice and water at 1 atm and 0°C). A further reduction in temperature takes the system into the region where the solid is the stable phase.

COMMENT 3.1 The text's web site contains links to online databases of data on phase transitions. ■

(a) Phase boundaries

The pressure of the vapor in equilibrium with its condensed phase is called the **vapor pressure** of the substance. Vapor pressure increases with temperature because, as the temperature is raised, more molecules have sufficient energy to leave their neighbors in the liquid.

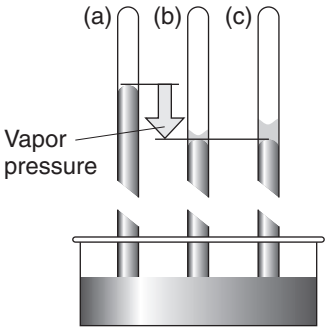


Fig. 3.6 When a small volume of water is introduced into the vacuum above the mercury in a barometer (a), the mercury is depressed (b) by an amount that is proportional to the vapor pressure of the liquid. (c) The same pressure is observed however much liquid is present (provided some is present).

The liquid-vapor boundary in a phase diagram is a plot of the vapor pressure against temperature. To determine the boundary, we can introduce a liquid into the near-vacuum at the top of a mercury barometer and measure by how much the column is depressed (Fig. 3.6). To ensure that the pressure exerted by the vapor is truly the vapor pressure, we have to add enough liquid for some to remain after the vapor forms, for only then are the liquid and vapor phases in equilibrium. We can change the temperature and determine another point on the curve and so on (Fig. 3.7).

Now suppose we have a liquid in a cylinder fitted with a piston. If we apply a pressure greater than the vapor pressure of the liquid, the vapor is eliminated, the piston rests on the surface of the liquid, and the system moves to one of the points in the "liquid" region of the phase diagram. Only a single phase is present. If instead we reduce the pressure on the system to a value below the vapor pressure, the system moves to one of the points in the "vapor" region of the diagram. Reducing the pressure will involve pulling out the piston a long way so that all the liquid evaporates; while any liquid is present, the pressure in the system remains constant at the vapor pressure of the liquid.

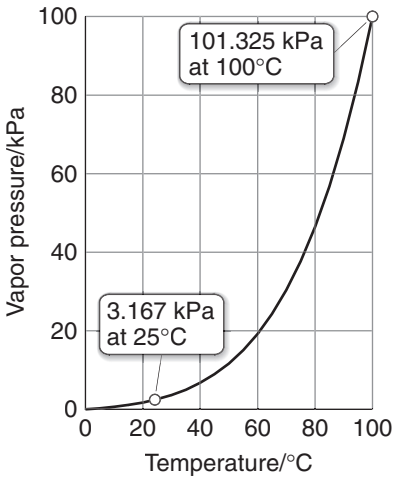


Fig. 3.7 The experimental variation of the vapor pressure of water with temperature.

SELF-TEST 3.1 What would be observed when a pressure of 50 Torr is applied to a sample of water in equilibrium with its vapor at 25°C, when its vapor pressure is 23.8 Torr?

Answer: The sample condenses entirely to liquid.

The same approach can be used to plot the solid-vapor boundary, which is a graph of the vapor pressure of the solid against temperature. The **sublimation vapor pressure** of a solid, the pressure of the vapor in equilibrium with a solid at a particular temperature, is usually much lower than that of a liquid because the molecules are more strongly bound together in the solid than in the liquid.

A more sophisticated procedure is needed to determine the locations of solid-solid phase boundaries like that between the different forms of ice, for instance, because the transition between two solid phases is more difficult to detect. One approach is to use **thermal analysis**, which takes advantage of the heat released during a transition. In a typical thermal analysis experiment, a sample is allowed to cool and its temperature is monitored. When the transition occurs, energy is released as heat and the cooling stops until the transition is complete (Fig. 3.8). The transition temperature is obvious from the shape of the graph and is used to mark a point on the phase diagram. The pressure can then be changed and the corresponding transition temperature determined.

Any point lying on a phase boundary represents a pressure and temperature at which there is a "dynamic equilibrium" between the two adjacent phases. A state of **dynamic equilibrium** is one in which a reverse process is taking place at the same rate as the forward process. Although there may be a great deal of activity at a molecular level, there is no net change in the bulk properties or appearance of the sample. For example, any point on the liquid-vapor boundary represents a state of dynamic equilibrium in which vaporization and condensation continue at matching rates. Molecules are leaving the surface of the liquid at a certain rate, and molecules already in the gas phase are returning to the liquid at the same rate; as a result, there in no net change in the number of molecules in the vapor and hence no net change in its pressure. Similarly, a point on the solid-liquid curve represents conditions of pressure and temperature at which molecules are ceaselessly breaking away from the surface of the solid and contributing to the liquid. However, they are doing so at a rate that exactly matches that at which molecules already in the liquid are settling onto the surface of the solid and contributing to the solid phase.

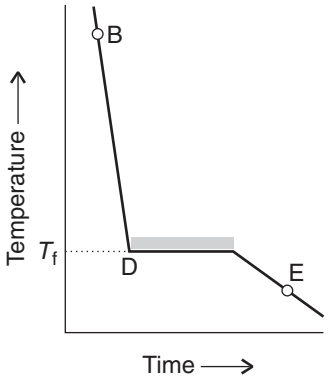


Fig. 3.8 The cooling curve for the B–E section of the horizontal line in Fig. 3.5. The halt at D corresponds to the pause in cooling while the liquid freezes and releases its enthalpy of transition. The halt lets us locate T_f even if the transition cannot be observed visually.

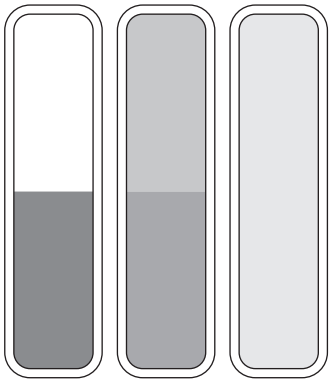


Fig. 3.9 When a liquid is heated in a sealed container, the density of the vapor phase increases and that of the liquid phase decreases, as depicted here by the changing density of shading. There comes a stage at which the two densities are equal and the interface between the two fluids disappears. This disappearance occurs at the critical temperature. The container needs to be strong: the critical temperature of water is at 373°C and the vapor pressure is then 218 atm.

(b) Characteristic points

We have seen that as the temperature of a liquid is raised, its vapor pressure increases. First, consider what we would observe when we heat a liquid in an open vessel. At a certain temperature, the vapor pressure becomes equal to the external pressure. At this temperature, the vapor can drive back the surrounding atmosphere and expand indefinitely. Moreover, because there is no constraint on expansion, bubbles of vapor can form throughout the body of the liquid, a condition known as **boiling**. The temperature at which the vapor pressure of a liquid is equal to the external pressure is called the **boiling temperature**. When the external pressure is 1 atm, the boiling temperature is called the **normal boiling point**, T_b. It follows that we can predict the normal boiling point of a liquid by noting the temperature on the phase diagram at which its vapor pressure is 1 atm.

Now consider what happens when we heat the liquid in a closed vessel. Because the vapor cannot escape, its density increases as the vapor pressure rises and in due course the density of the vapor becomes equal to that of the remaining liquid. At this stage the surface between the two phases disappears (Fig. 3.9). The temperature at which the surface disappears is the **critical temperature**, T_c. The vapor pressure at the critical temperature is called the **critical pressure**, p_c, and the critical temperature and critical pressure together identify the **critical point** of the substance (see Table 3.1). If we exert pressure on a sample that is above its critical temperature, we produce a denser fluid. However, no surface appears to separate the two parts of the sample and a single uniform phase, a **supercritical fluid**, continues to fill the container. That is, we have to conclude that *a liquid cannot be produced by the application of pressure to a substance if it is at or above its critical temperature*. That is why the liquid-vapor boundary in a phase diagram terminates at the critical point (Fig. 3.10).

A supercritical fluid is not a true liquid, but it behaves like a liquid in many respects—it has a density similar to that of a liquid and can act as a solvent. For example, supercritical carbon dioxide is used to extract caffeine in the manufacture of decaffeinated coffee, where, unlike organic solvents, it does not result in the formation of an unpleasant and possibly toxic residue.

The temperature at which the liquid and solid phases of a substance coexist in equilibrium at a specified pressure is called the **melting temperature** of the substance. Because a substance melts at the same temperature as it freezes, the melting temperature is the same as the **freezing temperature**. The solid-liquid boundary therefore shows how the melting temperature of a solid varies with pressure.

Table 3.1 Critical constants*

	p_c/atm	V_c/(cm^3 mol^{-1})	T_c/K
Ammonia, NH_3	111	73	406
Argon, Ar	48	75	151
Benzene, C_6H_6	49	260	563
Carbon dioxide, CO_2	73	94	304
Hydrogen, H_2	13	65	33
Methane, CH_4	46	99	191
Oxygen, O_2	50	78	155
Water, H_2O	218	55	647

*The critical volume, V_c, is the molar volume at the critical pressure and critical volume.

The melting temperature when the pressure on the sample is 1 atm is called the **normal melting point** or the **normal freezing point**, T_f. A liquid freezes when the energy of the molecules in the liquid is so low that they cannot escape from the attractive forces of their neighbors and lose their mobility.

There is a set of conditions under which three different phases (typically solid, liquid, and vapor) all simultaneously coexist in equilibrium. It is represented by the **triple point**, where the three phase boundaries meet. The triple point of a pure substance is a characteristic, unchangeable physical property of the substance. For water the triple point lies at 273.16 K and 611 Pa, and ice, liquid water, and water vapor coexist in equilibrium at no other combination of pressure and temperature.[1] At the triple point, the rates of each forward and reverse process are equal (but the three individual rates are not necessarily the same).

The triple point and the critical point are important features of a substance because they act as frontier posts for the existence of the liquid phase. As we see from Fig. 3.11a, if the slope of the solid-liquid phase boundary is as shown in the diagram:

> The triple point marks the lowest temperature at which the liquid can exist.
>
> The critical point marks the highest temperature at which the liquid can exist.

We shall see in the following section that for water, the solid-liquid phase boundary slopes in the opposite direction, and then only the second of these conclusions is relevant (see Fig. 3.11b).

[1]The triple point of water is used to define the Kelvin scale of temperatures: the triple point is defined as lying at 273.16 K exactly. The normal freezing point of water is found experimentally to lie approximately 0.01 K below the triple point, at very close to 273.15 K.

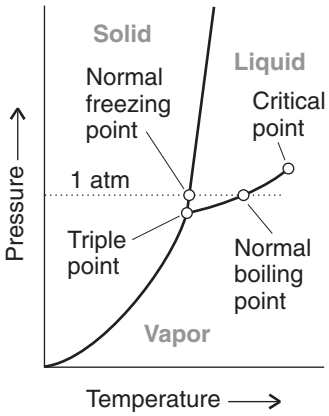


Fig. 3.10 The significant points of a phase diagram. The liquid-vapor phase boundary terminates at the *critical point*. At the *triple point*, solid, liquid, and vapor are in dynamic equilibrium. The *normal freezing point* is the temperature at which the liquid freezes when the pressure is 1 atm; the *normal boiling point* is the temperature at which the vapor pressure of the liquid is 1 atm.

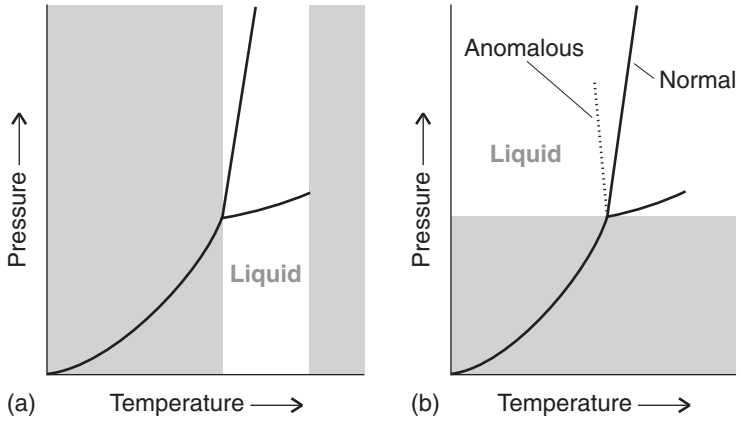


Fig. 3.11 (a) For substances that have phase diagrams resembling the one shown here (which is common for most substances, with the important exception of water), the triple point and the critical point mark the range of temperatures over which the substance can exist as a liquid. The shaded areas show the regions of temperature in which a liquid cannot exist as a stable phase. (b) A liquid cannot exist as a stable phase if the pressure is below that of the triple point for normal or anomalous liquids.

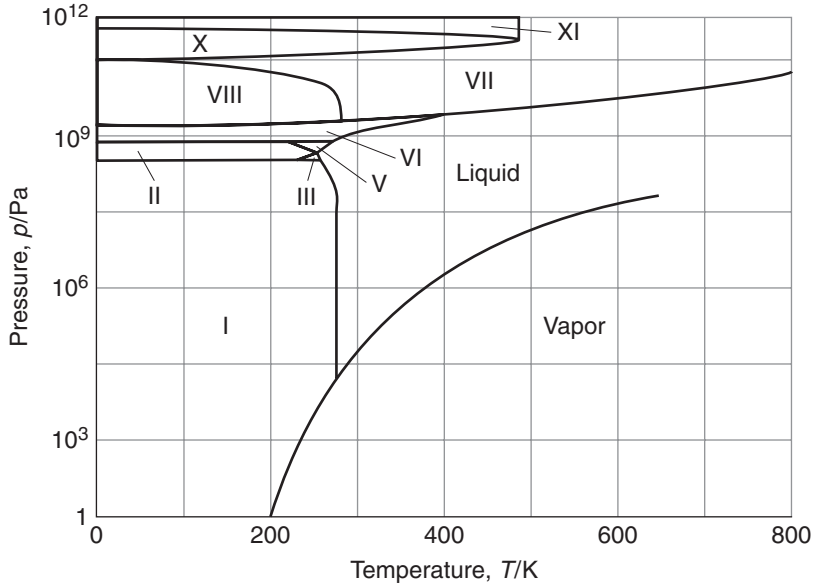


Fig. 3.12 The phase diagram for water showing the different solid phases.

(c) The phase diagram of water

Figure 3.12 is the phase diagram for water. The liquid-vapor phase boundary shows how the vapor pressure of liquid water varies with temperature. We can use this curve, which is shown in more detail in Fig. 3.13, to decide how the boiling temperature varies with changing external pressure. For example, when the external pressure is 149 Torr (at an altitude of 12 km), water boils at 60°C because that is the temperature at which the vapor pressure is 149 Torr (19.9 kPa).

SELF-TEST 3.2 What is the minimum pressure at which liquid is the thermodynamically stable phase of water at 25°C?

Answer: 23.8 Torr, 3.17 kPa (see Fig. 3.13)

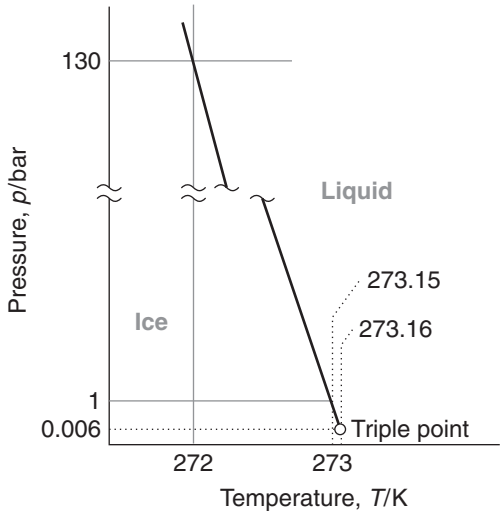


Fig. 3.13 The solid-liquid boundary of water in more detail. The graph is schematic and not to scale.

The solid-liquid boundary line in Fig. 3.12, which is shown in more detail in Fig. 3.13, shows how the melting temperature of water depends on the pressure. For example, although ice melts at 0°C at 1 atm, it melts at −1°C when the pressure is 130 atm. The very steep slope of the boundary indicates that enormous pressures are needed to bring about significant changes. Notice that the line slopes down from left to right, which—as we anticipated—means that the melting temperature of ice falls as the pressure is raised. We can trace the reason for this unusual behavior to the decrease in volume that occurs when ice melts: it is favorable for the solid to transform into the denser liquid as the pressure is raised. The decrease in volume is a result of the very open structure of the crystal structure of ice: as shown in Fig 3.14, the water molecules are held apart, as well as together, by the hydrogen bonds between them, but the structure partially collapses on melting and the liquid is denser than the solid.

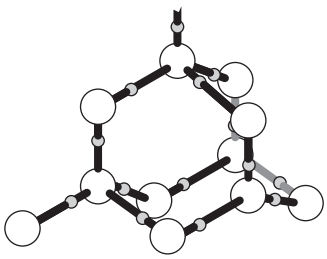


Fig. 3.14 The structure of ice I. Each O atom is at the center of a tetrahedron of four O atoms at a distance of 276 pm. The central O atom is attached by two short O–H bonds to two H atoms and by two long hydrogen bonds to the H atoms of two of the neighboring molecules. Overall, the structure consists of planes of puckered hexagonal rings of H_2O molecules (like the chair form of cyclohexane). This structure collapses partially on melting, leading to a liquid that is denser than the solid.

Figure 3.12 shows that water has one liquid phase[2] but many different solid phases other than ordinary ice ("ice I," shown in Fig 3.14). These solid phases differ in the arrangement of the water molecules: under the influence of very high pressures, hydrogen bonds buckle and the H_2O molecules adopt different arrangements. These **polymorphs**, or different solid phases, of ice may be responsible for the advance of glaciers, for ice at the bottom of glaciers experiences very high pressures where it rests on jagged rocks. The sudden apparent explosion of Halley's comet in 1991 may have been due to the conversion of one form of ice into another in its interior. Figure 3.12 also shows that four or more phases of water (such as two solid forms, liquid, and vapor) are never in equilibrium. This observation is justified and generalized to all substances by the *phase rule*, which is derived in *Further information* 3.1.

Phase transitions in biopolymers and aggregates

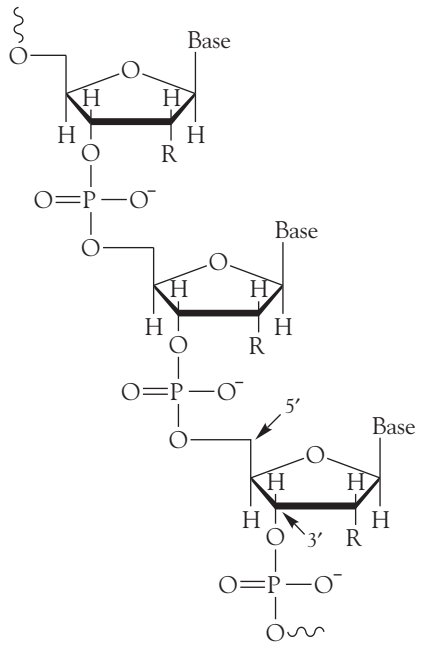
In Chapter 2 we saw that proteins and biological membranes can exist in ordered structures stabilized by a variety of molecular interactions, such as hydrogen bonds and hydrophobic interactions. However, when certain conditions are changed, the helical and sheet structures of a polypeptide chain may collapse into a random coil and the hydrocarbon chains in the interior of bilayer membranes may become more or less flexible. These structural changes may be regarded as phase transitions in which molecular interactions in compact phases are disrupted at characteristic transition temperatures to yield phases in which the atoms can move more randomly.

In the following sections we explore the molecular origins of phase transitions in proteins, nucleic acids, and biological membranes. We have already discussed the structures of proteins and biological membranes (Section 2.11), so before we begin our thermodynamic discussion, we explore the structures of another important biological polymer, deoxyribonucleic acid (DNA).[3] This material should be familiar from introductory courses in molecular biology, but we review the important points here for completeness.

Nucleic acids are key components of the mechanism of storage and transfer of genetic information in biological cells. Deoxyribonucleic acid, which contains the

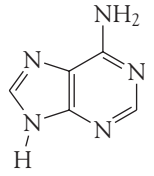
[2]Recent work has suggested that water may also have a superfluid liquid phase, so called because it flows without viscosity.

[3]See Chapter 11 for a more complete discussion of the structure of nucleic acids, including RNA.

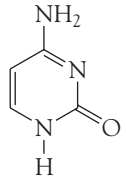


1 The general form of a polynucleotide
R = OH (β-D-ribose)
H (β-D-2-deoxyribose)

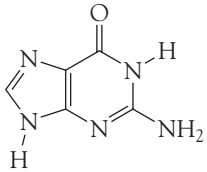
instructions for protein synthesis carried out by different forms of ribonucleic acid (RNA), is a *polynucleotide* (**1**) in which base-sugar-phosphate units are connected by phosphodiester bonds. As we see in **1**, the phosphodiester bonds connect the 3′ and 5′ carbons of the sugar parts of two adjacent units. In DNA the sugar is β-D-2-deoxyribose (as shown in **1**) and the bases are adenine (A, **2**), cytosine (C, **3**), guanine (G, **4**), and thymine (T, **5**). Under physiological conditions, each phosphate group of the chain carries a negative charge and the bases are deprotonated and neutral. This charge distribution leads to two important properties. One is that the polynucleotide chain is a **polyelectrolyte**, a macromolecule with many different charged sites, with a large and negative overall surface charge. The second is that the bases can interact by hydrogen bonding, as shown for A–T (**6**) and C–G base pairs (**7**).



2 Adenine (A)



3 Cytosine (C)



4 Guanine (G)

The secondary structure of DNA arises primarily from the winding of two polynucleotide chains wind around each other to form a double helix (Fig 3.15). The chains are held together by links involving A–T and C–G base pairs that lie parallel to each other and perpendicular to the major axis of the helix. The structure is stabilized further by π stacking interactions, attractive interactions between the planar π systems of the bases. In B-DNA, the most common form of DNA found in biological cells, the helix is right-handed with a diameter of 2.0 nm and a pitch (the distance between points separated by one full turn of the helix) of 3.4 nm.

3.5 The stability of nucleic acids and proteins

To understand melting of proteins and nucleic acids at specific transition temperatures, we need to explore quantitatively the effect of intermolecular interactions on the stability of compact conformations of biopolymers.

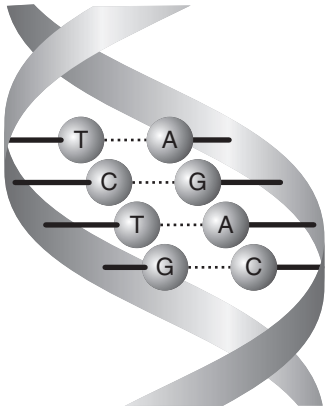
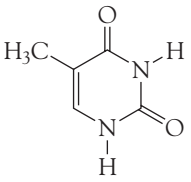
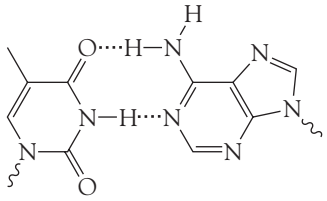


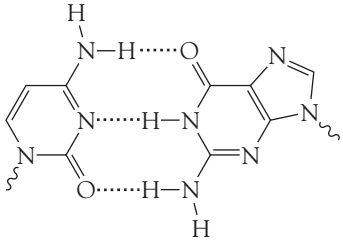
Fig. 3.15 The DNA double helix, in which two polynucleotide chains are linked together by hydrogen bonds between adenine (A) and thymine (T) and between cytosine (C) and guanine (G).



5 Thymine (T)



6 The T-A base pair



7 The C-G base pair

In *Case study* 1.1 we saw that thermal denaturation of a biopolymer may be thought of as a kind of intramolecular melting from an organized structure to a flexible coil. This melting occurs at a specific **melting temperature**, T_m, which increases with the strength and number of intermolecular interactions in the material. Denaturation is a **cooperative process** in the sense that the biopolymer becomes increasingly more susceptible to denaturation once the process begins. This cooperativity is observed as a sharp step in a plot of fraction of unfolded polymer against temperature (Fig 3.16). The melting temperature, T_m, is the temperature at which the fraction of unfolded polymer is 0.5.

Closer examination of thermal denaturation reveals some of the chemical factors that determine protein and nucleic acid stability. For example, the thermal stability of DNA increases with the number of G–C base pairs in the sequence because each G–C base pair has three hydrogen bonds, whereas each A–T base pair has only two. More energy is required to unravel a double helix that, on average, has more hydrogen bonding interactions per base pair.

EXAMPLE 3.1 Predicting the melting temperature of DNA

The melting temperature of a DNA molecule can be determined by differential scanning calorimetry (Section 1.10). The following data were obtained in aqueous

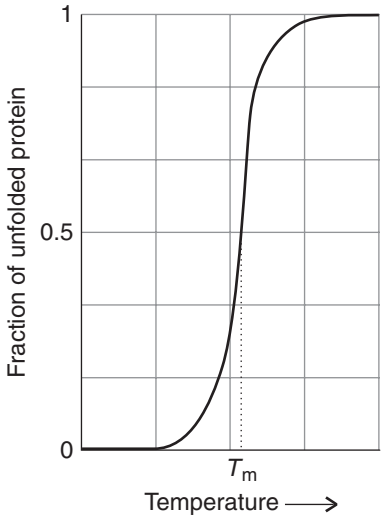


Fig. 3.16 A protein unfolds as the temperature of the sample increases. The sharp step in the plot of fraction of unfolded protein against temperature indicated that the transition is cooperative. The melting temperature, T_m, is the temperature at which the fraction of unfolded polymer is 0.5.

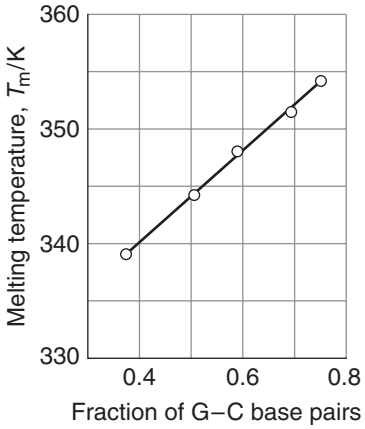


Fig. 3.17 Data for Example 3.1 showing the variation of the melting temperature of DNA molecules with the fraction of G–C base pairs. All the samples also contain 1.0×10^{-2} mol L^{-1} Na_3PO_4.

solutions containing 1.0×10^{-2} mol L^{-1} Na_3PO_4 for a series of DNA molecules with varying base pair composition, with f the fraction of G–C base pairs:

f	0.375	0.509	0.589	0.688	0.750
T_m/K	339	344	348	351	354

Estimate the melting temperature of a DNA molecule containing 40.0% G–C base pairs.

Strategy To make progress, we need to look for a quantitative relationship between the melting temperature and the composition of DNA. We can begin by plotting T_m against fraction of G–C base pairs and examining the shape of the curve. If visual inspection of the plot suggests a linear relationship, then the melting point at any composition can be predicted from the equation of the line that fits the data.

Solution Figure 3.17 shows that T_m varies linearly with the fraction of G–C base pairs, at least in this range of composition. The equation of the line that fits the data is

$$T_m/K = 325 + 39.7f$$

It follows that $T_m = 341$ K for 40.0% G–C base pairs (at $f = 0.400$).

A note on good practice: In this example we do not have a good theory to guide us in the choice of mathematical model to describe the behavior of the system over a wide range of parameters. We are limited to finding a purely empirical relation—in this case a simple first-order polynomial equation—that fits the available data. It follows that we should not attempt to predict the property of a system that falls outside the narrow range of the data used to generate the fit because the mathematical model may have to be enhanced (for example, by using higher-order polynomial equations) to describe the system over a wider range of conditions. In the present case, we should not attempt to predict the T_m of DNA molecules outside the range $0.375 < f < 0.750$.

SELF-TEST 3.3 The following calorimetric data were obtained in solutions containing 0.15 mol L^{-1} NaCl for the same series of DNA molecules studied in *Example* 3.1. Estimate the melting temperature of a DNA molecule containing 40.0% G–C base pairs under these conditions.

f	0.375	0.509	0.589	0.688	0.750
T_m/K	359	364	368	371	374

Answer: 360 K ■

Example 3.1 and *Self-test* 3.3 reveal that DNA is rather stable toward thermal denaturation, with T_m values ranging from about 340 K to 375 K, all significantly higher than body temperature (310 K). The data also show that increasing the concentration of ions in solution increases the melting temperature of DNA. The stabilizing effect of ions can be traced to the fact that DNA has negatively charged

phosphate groups decorating its surface. When the concentration of ions in solution is low, repulsive Coulomb interactions between neighboring phosphate groups destabilize the double helix and lower the melting temperature. On the other hand, positive ions, such as Na^+ in Self-test 3.3, bind electrostatically to the surface of DNA and mitigate repulsive interactions between phosphate groups. The result is stabilization of the double helical conformation and an increase in T_m.

In contrast to DNA, proteins are relatively unstable toward thermal and chemical denaturation. For example, $T_m = 320$ K for ribonuclease T_1 (an enzyme that cleaves RNA in the cell), which is low compared to the temperature at which the enzyme must operate (close to body temperature, 310 K). More surprisingly, the Gibbs energy for the unfolding of ribonuclease T_1 at pH = 7.0 and 298 K is only 22.5 kJ mol^{-1}, which is comparable to the energy required to break a single hydrogen bond (about 20 kJ mol^{-1}). Yet the formation of helices and sheets in proteins requires many hydrogen bonds involving the peptide link, –CONH–, which can act both as a donor of the H atom (the NH part of the link) and as an acceptor (the CO part). Therefore, unlike DNA, the stability of a protein does not increase in a simple way with the number of hydrogen bonding interactions. Although the reasons for the low stability of proteins are not known, the answer probably lies in a delicate balance of all intra- and inter-molecular interactions that allow a protein to fold into its active conformation, as discussed in Chapter 11.

3.6 Phase transitions of biological membranes

To understand why cell membranes are sufficiently rigid to encase life's molecular machines while being flexible enough to allow for cell division, we need to explore the factors that determine the melting temperatures of lipid bilayers.

All lipid bilayers undergo a transition from a state of high to low chain mobility at a temperature that depends on the structure of the lipid. To visualize the transition, we consider what happens to a membrane as we lower its temperature (Fig. 3.18). There is sufficient energy available at normal temperatures for limited bond rotation to occur and the flexible chains to writhe. However, the membrane is still highly organized in the sense that the bilayer structure does not come apart and the system is best described as a *liquid crystal*, a substance having liquid-like, imperfect long-range order in at least one direction in space but positional or orientational order in at least one other direction (Fig. 3.18a). At lower temperatures, the amplitudes of the writhing motion decrease until a specific temperature is reached at which motion is largely frozen. The membrane is said to exist as a *gel* (Fig. 3.18b). Biological membranes exist as liquid crystals at physiological temperatures.

Phase transitions in membranes are often observed as "melting" from gel to liquid crystal by differential scanning calorimetry (Section 1.10). The data show relations between the structure of the lipid and the melting temperature. For example, the melting temperature increases with the length of the hydrophobic chain of the lipid. This correlation is reasonable, as we expect longer chains to be held together more strongly by hydrophobic interactions than shorter chains (Section 2.11). It follows that stabilization of the gel phase in membranes of lipids with long chains results in relatively high melting temperatures. On the other hand, any structural elements that prevent alignment of the hydrophobic chains in the gel phase lead to low melting temperatures. Indeed, lipids containing unsaturated chains, those containing some C=C bonds, form membranes with lower melting temperatures than those formed from lipids with fully saturated chains, those consisting of C–C bonds only.

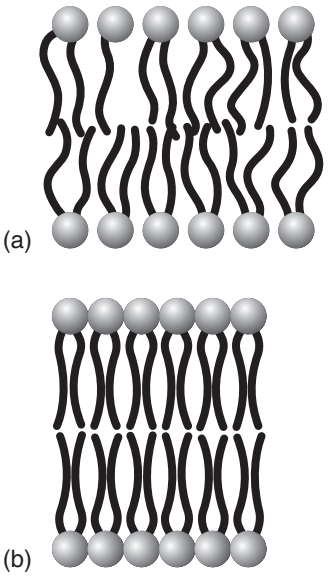
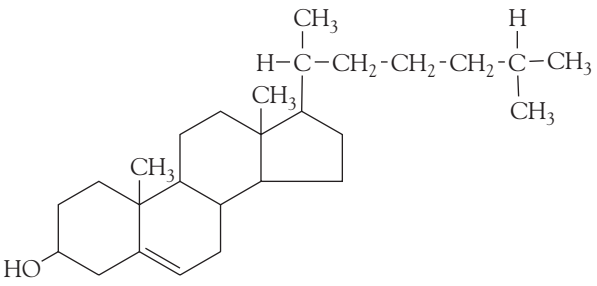


Fig. 3.18 A depiction of the variation with temperature of the flexibility of hydrocarbon chains in a lipid bilayer. (a) At physiological temperature, the bilayer exists as a liquid crystal, in which some order exists but the chains writhe. (b) At a specific temperature, the chains are largely frozen and the bilayer is said to exist as a gel.



8 Cholesterol

COMMENT 3.2 The web site contains links to databases of thermodynamic properties of lipids and to computer-generated models of the different phases of lipid bilayers. ■

Interspersed among the phospholipids of biological membranes are sterols, such as cholesterol (**8**), which is largely hydrophobic but does contain a hydrophilic –OH group. Sterols, which are present in different proportions in different types of cells, prevent the hydrophobic chains of lipids from "freezing" into a gel and, by disrupting the packing of the chains, spread the melting point of the membrane over a range of temperatures.

SELF-TEST 3.4 Organisms are capable of biosynthesizing lipids of different composition so that cell membranes have melting temperatures close to the ambient temperature. Why do bacterial and plant cells grown at low temperatures synthesize more phospholipids with unsaturated chains than do cells grown at higher temperatures?

Answer: Insertion of lipids with unsaturated chains lowers the plasma membrane's melting temperature to a value that is close to the lower ambient temperature.

The thermodynamic description of mixtures

We now leave pure materials and the limited but important changes they can undergo and examine mixtures. We shall consider only **homogeneous mixtures**, or solutions, in which the composition is uniform however small the sample. The component in smaller abundance is called the **solute** and that in larger abundance is the **solvent**. These terms, however, are normally but not invariably reserved for solids dissolved in liquids; one liquid mixed with another is normally called simply a "mixture" of the two liquids. In this chapter we consider mainly **nonelectrolyte solutions**, where the solute is not present as ions. Examples are sucrose dissolved in water, sulfur dissolved in carbon disulfide, and a mixture of ethanol and water. Though we also consider some of the special problems of **electrolyte solutions**, in which the solute consists of ions that interact strongly with one another, we defer a full study until Chapter 5.

3.7 Measures of concentration

To make progress with a discussion of the thermodynamics of complex mixtures, such as those found in the interior of cells, we need to know how to use different measures of concentration to account for the contribution of each component to a property of the system.

We are often concerned with mixtures of gases, such as when we are considering the properties of the atmosphere in meteorology or the composition of exhaled air

in medicine. A useful measure of concentration of a gas J in a mixture is its **mole fraction**, the amount of J molecules expressed as a fraction of the total amount of molecules in the mixture. In a mixture that consists of n_A A molecules, n_B B molecules, and so on (where the n_J are amounts in moles), the mole fraction of J (where J = A, B, . . .) is

$$x_J = \frac{n_J}{n} \qquad \text{(3.4a)}$$

(n_J: Amount of J (mol); n: Total amount of molecules (mol))

where $n = n_A + n_B + \cdots$. For a **binary mixture**, one that consists of two species, this general expression becomes

$$x_A = \frac{n_A}{n_A + n_B} \qquad x_B = \frac{n_B}{n_A + n_B} \qquad x_A + x_B = 1 \qquad \text{(3.4b)}$$

When only A is present, $x_A = 1$ and $x_B = 0$. When only B is present, $x_B = 1$ and $x_A = 0$. When both are present in the same amounts, $x_A = ½$ and $x_B = ½$. (Fig. 3.19).

SELF-TEST 3.5 Calculate the mole fractions of N_2, O_2, and Ar in dry air at sea level, given that 100.0 g of air consists of 75.5 g of N_2, 23.2 g of O_2, and 1.3 g of Ar. (*Hint:* Begin by converting each mass to an amount in moles.)

Answer: 0.780, 0.210, 0.009

We need to be able to assess the contribution that each component of a gaseous mixture makes to the total pressure. In the early nineteenth century, John Dalton carried out a series of experiments that led him to formulate what has become known as **Dalton's law**:

> The pressure exerted by a mixture of perfect gases is the sum of the pressures that each gas would exert if it were alone in the container at the same temperature:

$$p = p_A + p_B + \cdots \qquad \text{(3.5)}$$

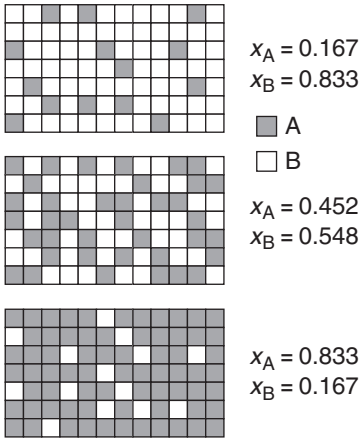


Fig. 3.19 A representation of the meaning of mole fraction. In each case, a small square represents one molecule of A (gray squares) or B (white squares). There are 84 squares in each sample.

In this expression, p_J is the pressure that the gas J would exert if it were alone in the container at the same temperature. Dalton's law is strictly valid only for mixtures of perfect gases, but it can be treated as valid under most conditions we encounter.

For any type of gas (perfect or not) in a mixture, the **partial pressure**, p_J, of the gas J is defined as

$$p_J = x_J p \tag{3.6}$$

where x_J is the mole fraction of the gas J in the mixture. For perfect gases, the partial pressure of a gas defined in this way is also the pressure that the gas would exert if it were alone in the container at the same temperature. Moreover, defined in this way, eqn 3.5 is true for mixtures of real gases as well as perfect gases, but the partial pressure so defined is no longer the pressure that a gas would exert if it were alone in the container.

ILLUSTRATION 3.1 Calculating partial pressures of the gases in air

From *Self-test* 3.5, we have $x_{N_2} = 0.780$, $x_{O_2} = 0.210$, and $x_{Ar} = 0.009$ for dry air at sea level. It then follows from eqn 3.6 that when the total atmospheric pressure is 100 kPa, the partial pressure of nitrogen is

$$p_{N_2} = x_{N_2} p = 0.780 \times (100 \text{ kPa}) = 78.0 \text{ kPa}$$

Similarly, for the other two components we find $p_{O_2} = 21.0$ kPa and $p_{Ar} = 0.9$ kPa. ■

Three measures of concentration are commonly used to describe the composition of mixtures of liquids or of solids dissolved in liquids. One, the *molar concentration*, is used when we need to know the amount of solute in a sample of known volume of solution. The other two, the *mole fraction*, which we already encountered (eqn 3.4), and the *molality*, are used when we need to know the relative numbers of solute and solvent molecules in a sample.

The **molar concentration**, [J] or c_J, of a solute J in a solution (more formally, the "amount of substance concentration") is the chemical amount of J divided by the volume of the solution:[4]

$$[J] = \frac{n_J}{V} \tag{3.7}$$

Amount of J (mol) — n_J

Volume of solution (L) — V

Molar concentration is typically reported in moles per liter (mol L^{-1}; more formally, as mol dm^{-3}). The unit 1 mol L^{-1} is commonly denoted 1 M (and read "molar"). Once we know the molar concentration of a solute, we can calculate the amount of that substance in a given volume, V, of solution by writing

$$n_J = [J]V \tag{3.8}$$

[4]Molar concentration is still widely called "molarity."

The **molality**, b_J, of a solute J in a solution is the amount of substance divided by the mass of solvent used to prepare the solution:

$$b_J = \frac{n_J}{m_{solvent}} \qquad \textbf{(3.9)}$$

(n_J: Amount of J (mol); $m_{solvent}$: Mass of solvent (kg))

Molality is typically reported in moles of solute per kilogram of solvent (mol kg^{-1}). This unit is sometimes (but unofficially) denoted *m*, with 1 *m* = 1 mol kg^{-1}. An important distinction between molar concentration and molality is that whereas the former is defined in terms of the volume of the solution, the molality is defined in terms of the mass of solvent used to prepare the solution. A distinction to remember is that molar concentration varies with temperature as the solution expands and contracts, but the molality does not. For dilute solutions in water, the numerical values of the molarity and molar concentration differ very little because 1 liter of solution is mostly water and has a mass close to 1 kg; for concentrated aqueous solutions and for all nonaqueous solutions with densities different from 1 g mL^{-1}, the two values are very different.

As we have indicated, we use molality when we need to emphasize the relative amounts of solute and solvent molecules. To see why this is so, we note that the mass of solvent is proportional to the amount of solvent molecules present, so from eqn 3.9 we see that the molality is proportional to the ratio of the amounts of solute and solvent molecules. For example, any 1.0 *m* aqueous nonelectrolyte solution contains 1.0 mol solute particles per 55.5 mol H_2O molecules, so in each case there is 1 solute molecule per 55.5 solvent molecules.

EXAMPLE 3.2 Relating mole fraction and molality

What is the mole fraction of glycine molecules in 0.140 *m* $NH_2CH_2COOH(aq)$? Disregard the effects of protonation and deprotonation.

Strategy We consider a sample that contains (exactly) 1 kg of solvent and hence an amount $n_J = b_J \times (1\text{ kg})$ of solute molecules. The amount of solvent molecules in exactly 1 kg of solvent is

$$n_{solvent} = \frac{1\text{ kg}}{M}$$

where M is the molar mass of the solvent. Once these two amounts are available, we can calculate the mole fraction by using eqn 3.4 with $n = n_J + n_{solvent}$.

Solution It follows from the discussion in the Strategy that the amount of glycine (gly) molecules in exactly 1 kg of solvent is

$$n_{gly} = (0.140\text{ mol kg}^{-1}) \times (1\text{ kg}) = 0.140\text{ mol}$$

The amount of water molecules in exactly 1 kg (10^3 g) of water is

$$n_{water} = \frac{10^3\text{ g}}{18.02\text{ g mol}^{-1}} = \frac{10^3}{18.02}\text{ mol}$$

The total amount of molecules present is

$$n = 0.140 \text{ mol} + \frac{10^3}{18.02} \text{ mol}$$

The mole fraction of glycine molecules is therefore

$$x_{\text{gly}} = \frac{0.140 \text{ mol}}{0.140 + (10^3/18.02) \text{ mol}} = 2.52 \times 10^{-3}$$

A note on good practice: We refer to *exactly* 1 kg of solvent to avoid problems with significant figures.

SELF-TEST 3.6 Calculate the mole fraction of sucrose molecules in 1.22 *m* $C_{12}H_{22}O_{11}$(aq).

Answer: 2.15×10^{-2} ■

3.8 The chemical potential

To assess the spontaneity of a biological process, we need to know how to compute the Gibbs energy of every component in a mixture.

A **partial molar property** is the contribution (per mole) that a substance makes to an overall property of a mixture. The most important partial molar property for our purposes is the **partial molar Gibbs energy**, G_J, of a substance J, which is the contribution of J (per mole of J) to the total Gibbs energy of a mixture. It follows that if we know the partial molar Gibbs energies of two substances A and B in a mixture of a given composition, then we can calculate the total Gibbs energy of the mixture by using

$$G = n_A G_A + n_B G_B \tag{3.10}$$

To gain insight into the significance of the partial molar Gibbs energy, consider a mixture of ethanol and water. Ethanol has a particular partial molar Gibbs energy when it is pure (and every molecule is surrounded by other ethanol molecules), and it has a different partial molar Gibbs energy when it is in an aqueous solution of a certain composition (because then each ethanol molecule is surrounded by a mixture of ethanol and water molecules).

The partial molar Gibbs energy is so important in chemistry that it is given a special name and symbol. From now on, we shall call it the **chemical potential** and denote it μ (mu). Then eqn 3.10 becomes

$$G = n_A \mu_A + n_B \mu_B \tag{3.11}$$

where μ_A is the chemical potential of A in the mixture and μ_B is the chemical potential of B. In the course of this chapter and the next we shall see that the name "chemical potential" is very appropriate, for it will become clear that μ_J is a measure of the ability of J to bring about physical and chemical change. A substance with a high chemical potential has a high ability, in a sense we shall explore, to drive a reaction or some other physical process forward.

To make progress, we need an explicit formula for the variation of the chemical potential of a substance with the composition of the mixture. Our starting point is eqn 3.2b, which shows how the molar Gibbs energy of a perfect gas depends on pressure. First, we set $p_f = p$, the pressure of interest, and $p_i = p^\ominus$, the standard pressure (1 bar). At the latter pressure, the molar Gibbs energy has its standard value, $G_m^\ominus$, so we can write

$$G_m(p) = G_m^\ominus + RT \ln \frac{p}{p^\ominus} \tag{3.12}$$

Next, for a *mixture* of perfect gases, we interpret p as the *partial* pressure of the gas, and the G_m is the *partial* molar Gibbs energy, the chemical potential. Therefore, for a mixture of perfect gases, for each component J present at a partial pressure p_J,

$$\mu_J = \mu_J^\ominus + RT \ln \frac{p_J}{p^\ominus} \tag{3.13a}$$

In this expression, $\mu_J^\ominus$ is the **standard chemical potential** of the gas J, which is identical to its standard molar Gibbs energy, the value of G_m for the pure gas at 1 bar. If we adopt the convention that, whenever p_J appears in a formula, it is to be interpreted as $p_J/p^\ominus$ (so, if the pressure is 2.0 bar, $p_J = 2.0$), we can write eqn 3.13a more simply as

$$\mu_J = \mu_J^\ominus + RT \ln p_J \tag{3.13b}$$

Figure 3.20 illustrates the pressure dependence of the chemical potential of a perfect gas predicted by this equation. Note that the chemical potential becomes negatively infinite as the pressure tends to zero, rises to its standard value at 1 bar (because $\ln 1 = 0$), and then increases slowly (logarithmically, as $\ln p$) as the pressure is increased further.

We can become familiar with an equation by listening to what it tells us. In this case, we note that as p_J increases, so does $\ln p_J$. Therefore, eqn 3.13 tells us that *the higher the partial pressure of a gas, the higher its chemical potential.* This conclusion is consistent with the interpretation of the chemical potential as an indication of the potential of a substance to be active chemically: the higher the partial pressure, the more active chemically the species. In this instance the chemical potential represents the tendency of the substance to react when it is in its standard state (the significance of the term $\mu^\ominus$) plus an additional tendency that reflects whether it is at a different pressure. A higher partial pressure gives a substance more chemical "punch," just like winding a spring gives a spring more physical punch (that is, enables it to do more work).

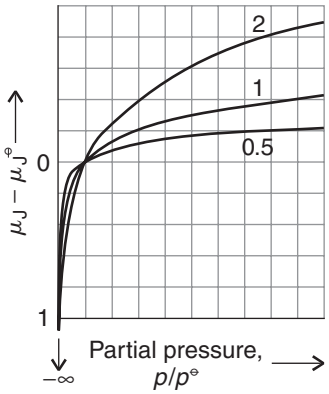


Fig. 3.20 The variation with partial pressure of the chemical potential of a perfect gas at three different temperatures (in the ratios 0.5:1:2). Note that the chemical potential increases with pressure and, at a given pressure, with temperature.

SELF-TEST 3.7 Suppose that the partial pressure of a perfect gas falls from 1.00 bar to 0.50 bar as it is consumed in a reaction at 25°C. What is the change in chemical potential of the substance?

Answer: -1.7 kJ mol^{-1}

We saw in Section 3.1 that the molar Gibbs energy of a pure substance is the same in all the phases at equilibrium. We can use the same argument to show that *a system is at equilibrium when the chemical potential of each substance has the same*

value in every phase in which it occurs. We can think of the chemical potential as the pushing power of each substance, and equilibrium is reached only when each substance pushes with the same strength in any phase it occupies.

DERIVATION 3.4 The uniformity of chemical potential

Suppose a substance J occurs in different phases in different regions of a system. For instance, we might have a liquid mixture of ethanol and water and a mixture of their vapors. Let the substance J have chemical potential $\mu_J(l)$ in the liquid mixture and $\mu_J(g)$ in the vapor. We could imagine an infinitesimal amount, dn_J, of J migrating from the liquid to the vapor. As a result, the Gibbs energy of the liquid phase falls by $\mu_J(l)dn_J$ and that of the vapor rises by $\mu_J(g)dn_J$. The net change in Gibbs energy is

$$dG = \mu_J(g)dn_J - \mu_J(l)dn_J = \{\mu_J(g) - \mu_J(l)\}dn_J$$

There is no tendency for this migration (and the reverse process, migration from the vapor to the liquid) to occur, and the system is at equilibrium if $dG = 0$, which requires that $\mu_J(g) = \mu_J(l)$. The argument applies to each component of the system. Therefore, *for a substance to be at equilibrium throughout the system, its chemical potential must be the same everywhere*.

3.9 Ideal solutions

Because in biochemistry we are concerned primarily with liquids, we need expressions for the chemical potentials of the substances in a liquid solution.

We can anticipate that the chemical potential of a species ought to increase with concentration, because the higher its concentration, the greater its chemical "punch." In the following, we use J to denote a substance in general, A to denote a solvent, and B a solute. This is where we implement the strategy described at the beginning of Section 3.2, to transform equations that work for gases into equations that work for liquids.

The key to setting up an expression for the chemical potential of a solute is the work done by the French chemist François Raoult (1830–1901), who spent most of his life measuring the vapor pressures of solutions. He measured the **partial vapor pressure,** p_J, of each component in the mixture, the partial pressure of the vapor of each component in dynamic equilibrium with the liquid mixture, and established what is now called **Raoult's law**:

> The partial vapor pressure of a substance in a liquid mixture is proportional to its mole fraction in the mixture and its vapor pressure when pure:

$$p_J = x_J p_J^* \qquad \textbf{(3.14)}$$

In this expression, p_J^* is the vapor pressure of the pure substance. For example, when the mole fraction of water in an aqueous solution is 0.90, then, provided Raoult's law is obeyed, the partial vapor pressure of the water in the solution is 90% that of pure water. This conclusion is approximately true whatever the identity of the solute and the solvent (Fig. 3.21).

The molecular origin of Raoult's law is the effect of the solute on the entropy of the solution. In the pure solvent, the molecules have some entropy due to their

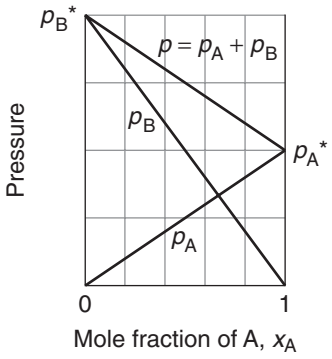


Fig. 3.21 The partial vapor pressures of the two components of an ideal binary mixture are proportional to the mole fractions of the components in the liquid. The total pressure of the vapor is the sum of the two partial vapor pressures.

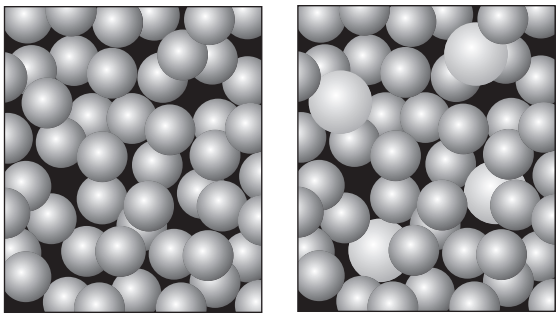


Fig. 3.22 (a) In a pure liquid, we can be confident that any molecule selected from the sample is a solvent molecule. (b) When a solute is present, we cannot be sure that blind selection will give a solvent molecule, so the entropy of the system is greater than in the absence of the solute.

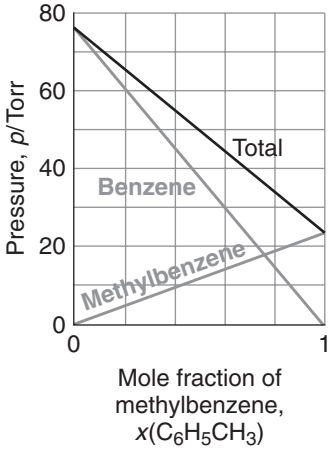


Fig. 3.23 Two similar substances, in this case benzene and methylbenzene (toluene), behave almost ideally and have vapor pressures that closely resemble those for the ideal case depicted in Fig. 3.21.

random motion; the vapor pressure then represents the tendency of the system and its surroundings to reach a higher entropy. When a solute is present, the molecules in the solution are more dispersed than in the pure solvent, so we cannot be sure that a molecule chosen at random will be a solvent molecule (Fig. 3.22). Because the entropy of the solution is higher than that of the pure solvent, the solution has a lower tendency to acquire an even higher entropy by the solvent vaporizing. In other words, the vapor pressure of the solvent in the solution is lower than that of the pure solvent.

A hypothetical solution of a solute B in a solvent A that obeys Raoult's law throughout the composition range from pure A to pure B is called an **ideal solution**. The law is most reliable when the components of a mixture have similar molecular shapes and are held together in the liquid by similar types and strengths of intermolecular forces. An example is a mixture of two structurally similar hydrocarbons. A mixture of benzene and methylbenzene (toluene) is a good approximation to an ideal solution, for the partial vapor pressure of each component satisfies Raoult's law reasonably well throughout the composition range from pure benzene to pure methylbenzene (Fig. 3.23).

No mixture is perfectly ideal, and all real mixtures show deviations from Raoult's law. However, the deviations are small for the component of the mixture that is in large excess (the solvent) and become smaller as the concentration of solute decreases (Fig. 3.24). We can usually be confident that Raoult's law is reliable for the solvent when the solution is very dilute. More formally, Raoult's law is a *limiting law* (like the perfect gas law) and is strictly valid only at the limit of zero concentration of solute.

The theoretical importance of Raoult's law is that, because it relates vapor pressure to composition and we know how to relate pressure to chemical potential, we can use the law to relate chemical potential to the composition of a solution. As we show in the following *Derivation*, the chemical potential of a solvent A present in solution at a mole fraction x_A is

$$\mu_A = \mu_A^* + RT \ln x_A \qquad (3.15)$$

where μ_A^* is the chemical potential of pure A.[5] This expression is valid throughout the concentration range for either component of a binary ideal solution. It is valid for the solvent of a real solution the closer the composition approaches pure solvent (pure A).

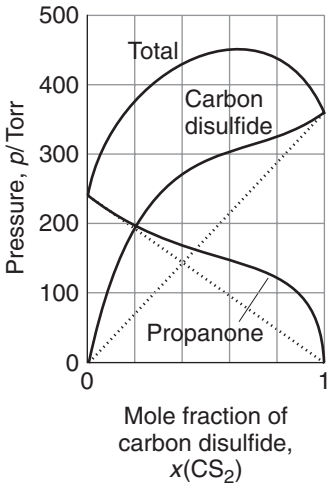


Fig. 3.24 Strong deviations from ideality are shown by dissimilar substances, in this case carbon disulfide and acetone (propanone). Note, however, that Raoult's law is obeyed by propanone when only a small amount of carbon disulfide is present (on the left) and by carbon disulfide when only a small amount of propanone is present (on the right).

[5]If the pressure is 1 bar, μ_A^* can be identified with the standard chemical potential of A, $\mu_A^\ominus$.

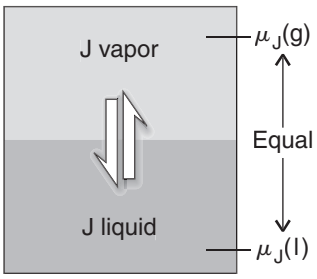


Fig. 3.25 At equilibrium, the chemical potential of a substance in its liquid phase is equal to the chemical potential of the substance in its vapor phase.

DERIVATION 3.5 The chemical potential of a solvent

We have seen that when a liquid A in a mixture is in equilibrium with its vapor at a partial pressure p_A, the chemical potentials of the two phases are equal (Fig. 3.25), and we can write $\mu_A(l) = \mu_A(g)$. However, we already have an expression for the chemical potential of a vapor, eqn 3.13, so at equilibrium

$$\mu_A(l) = \mu_A^{\ominus}(g) + RT \ln p_A$$

According to Raoult's law, $p_A = x_A p_A^*$, so we can use the relation $\ln x - \ln y = \ln(x/y)$ to write

$$\mu_A(l) = \mu_A^{\ominus}(g) + RT \ln x_A p_A^* = \mu_A^{\ominus}(g) + RT \ln p_A^* + RT \ln x_A$$

The first two terms on the right, $\mu_A^{\ominus}(g)$ and $RT \ln p_A^*$, are independent of the composition of the mixture. We can write them as the constant μ_A^*, the standard chemical potential of pure liquid A. Then eqn 3.15 follows.

Figure 3.26 shows the variation of chemical potential of the solvent predicted by this expression. Note that the chemical potential has its pure value at $x_A = 1$ (when only A is present). The essential feature of eqn 3.15 is that because $x_A < 1$ implies that $\ln x_A < 0$, *the chemical potential of a solvent is lower in a solution than when it is pure*. Provided the solution is almost ideal, a solvent in which a solute is present has less chemical "punch" (including a lower ability to generate a vapor pressure) than when it is pure.

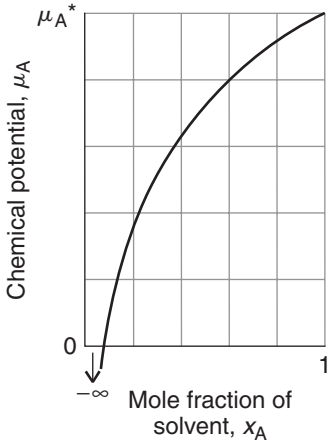


Fig. 3.26 The variation of the chemical potential of the solvent with the composition of the solution. Note that the chemical potential of the solvent is lower in the mixture than for the pure liquid (for an ideal system). This behavior is likely to be shown by a dilute solution in which the solvent is almost pure (and obeys Raoult's law).

SELF-TEST 3.8 By how much is the chemical potential of benzene reduced at 25°C by a solute that is present at a mole fraction of 0.10?

Answer: 0.26 kJ mol^{-1}

Is mixing to form an ideal solution spontaneous? To answer this question, we need to discover whether ΔG is negative for mixing. The first step is therefore to find an expression for ΔG when two components mix and then to decide whether it is negative. As we see in the following *Derivation*, when an amount n_A of A and n_B of B of two gases mingle at a temperature T,

$$\Delta G = nRT\{x_A \ln x_A + x_B \ln x_B\} \qquad \textbf{(3.16)}$$

with $n = n_A + n_B$ and the x_J the mole fractions in the mixture.

DERIVATION 3.6 The Gibbs energy of mixing

Suppose we have an amount n_A of a component A at a certain temperature T and an amount n_B of a component B at the same temperature. The two components are in separate compartments initially. The Gibbs energy of the system (the two unmixed components) is the sum of their individual Gibbs energies:

$$G_i = n_A \mu_A^* + n_B \mu_B^*$$

where the chemical potentials are those for the two pure components, obtained by the setting the mole fraction to 1 in eqn 3.15. When A and B are mixed, the

chemical potentials of A and B fall. Using eqn 3.15, the final Gibbs energy of the system is

$$\begin{aligned} G_f &= n_A\mu_A + n_B\mu_B \\ &= n_A\{\mu_A^* + RT \ln x_A\} + n_B\{\mu_B^* + RT \ln x_B\} \\ &= n_A\mu_A^* + n_ART \ln x_A + n_B\mu_B^* + n_BRT \ln x_B \end{aligned}$$

where the x_J are the mole fractions of the two components in the mixture. The difference $G_f - G_i$ is the change in Gibbs energy that accompanies mixing. The standard chemical potentials cancel, so

$$\Delta G = RT\{n_A \ln x_A + n_B \ln x_B\}$$

Because $x_J = n_J/n$, we can substitute $n_A = x_An$ and $n_B = x_Bn$ into the expression above and obtain

$$\Delta G = nRT\{x_A \ln x_A + x_B \ln x_B\}$$

which is eqn 3.16.

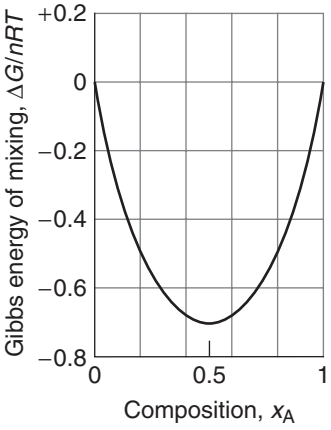


Fig. 3.27 The variation of the Gibbs energy of mixing with composition for two components at constant temperature and pressure. Note that $\Delta G < 0$ for all compositions, which indicates that two components mix spontaneously in all proportions.

Equation 3.16 tells us the change in Gibbs energy when two components mix at constant temperature and pressure (Fig. 3.27). The crucial feature is that because x_A and x_B are both less than 1, the two logarithms are negative ($\ln x < 0$ if $x < 1$), so $\Delta G < 0$ at all compositions. Therefore, *mixing is spontaneous in all proportions*. Furthermore, if we compare eqn 3.16 with $\Delta G = \Delta H - T\Delta S$, we can conclude that:

1. Because eqn 3.16 does not have a term that is independent of temperature,

$$\Delta H = 0 \qquad \textbf{(3.17a)}$$

2. Because $\Delta G = 0 - T\Delta S = nRT\{x_A \ln x_A + x_B \ln x_B\}$,

$$\Delta S = -nR\{x_A \ln x_A + x_B \ln x_B\} \qquad \textbf{(3.17b)}$$

The value of ΔH indicates that although there are interactions between the molecules, the solute-solute, solvent-solvent, and solute-solvent interactions are all the same, so the solute slips into solution without a change in enthalpy. There is an increase in entropy, because the molecules are more dispersed in the mixture than in the unmixed component. The entropy of the surroundings is unchanged because the enthalpy of the system is constant, so no energy escapes as heat into the surroundings. It follows that the increase in entropy of the system is the "driving force" of the mixing.

3.10 Ideal-dilute solutions

To calculate the chemical potential of a volatile solute, such as CO_2 in blood plasma, we need to develop an empirical relation between its vapor pressure and mole fraction.

Raoult's law provides a good description of the vapor pressure of the *solvent* in a very dilute solution, when the solvent A is almost pure. However, we cannot in general expect it to be a good description of the vapor pressure of the solute B because a solute in dilute solution is very far from being pure. In a dilute solution, each solute molecule is surrounded by nearly pure solvent, so its environment is quite unlike that in the pure solute, and except when solute and solvent are very similar (such as benzene and methylbenzene), it is very unlikely that the vapor pressure of the solute will be related in a simple manner to the vapor pressure of the pure solute. However, it is found experimentally that in dilute solutions, the vapor pressure of the solute is in fact proportional to its mole fraction, just as for the solvent. Unlike the solvent, though, the constant of proportionality is not in general the vapor pressure of the pure solute. This linear but different dependence was discovered by the English chemist William Henry (1774–1836) and is summarized as **Henry's law**:

COMMENT 3.3 The Web site contains links to online databases of Henry's law constants. ■

> The vapor pressure of a volatile solute B is proportional to its mole fraction in a solution:

$$p_B = x_B K_B \tag{3.18}$$

Here K_B, which is called **Henry's law constant**, is characteristic of the solute and chosen so that the straight line predicted by eqn 3.18 is tangent to the experimental curve at $x_B = 0$ (Fig. 3.28).

Henry's law is usually obeyed only at low concentrations of the solute (close to $x_B = 0$). Solutions that are dilute enough for the solute to obey Henry's law are called **ideal-dilute solutions**.

The Henry's law constants of some gases are listed in Table 3.2. The values given there are for the law rewritten to show how the molar concentration depends on the partial pressure, rather than vice versa:

$$[J] = K_H p_J \tag{3.19}$$

Henry's constant, K_H, is commonly reported in moles per cubic meter per kilopascal (mol m^{-3} kPa^{-1}). This form of the law and these units make it very easy to calculate the molar concentration of the dissolved gas, simply by multiplying the partial pressure of the gas (in kilopascals) by the appropriate constant. Equation 3.19 is used, for instance, to estimate the concentration of O_2 in natural waters or the concentration of carbon dioxide in blood plasma.

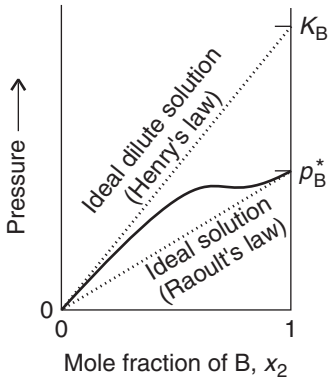


Fig. 3.28 When a component (the solvent) is almost pure, it behaves in accord with Raoult's law and has a vapor pressure that is proportional to the mole fraction in the liquid mixture and a slope p^*, the vapor pressure of the pure substance. When the same substance is the minor component (the solute), its vapor pressure is still proportional to its mole fraction, but the constant of proportionality is now K_B.

Table 3.2 Henry's law constants for gases dissolved in water at 25°C

	K_H/(mol m^{-3} kPa^{-1})
Carbon dioxide, CO_2	3.39×10^{-1}
Hydrogen, H_2	7.78×10^{-3}
Methane, CH_4	1.48×10^{-2}
Nitrogen, N_2	6.48×10^{-3}
Oxygen, O_2	1.30×10^{-2}

EXAMPLE 3.3 Determining whether a natural water can support aquatic life

The concentration of O_2 in water required to support aerobic aquatic life is about 4.0 mg L^{-1}. What is the minimum partial pressure of oxygen in the atmosphere that can achieve this concentration?

Strategy The strategy of the calculation is to determine the partial pressure of oxygen that, according to Henry's law (written as eqn 3.19), corresponds to the concentration specified.

Solution Equation 3.19 becomes

$$p_{O_2} = \frac{[O_2]}{K_H}$$

We note that the molar concentration of O_2 is

$$[O_2] = \frac{4.0 \times 10^{-3}\ \text{g L}^{-1}}{32\ \text{g mol}^{-1}} = \frac{4.0 \times 10^{-3}}{32}\ \frac{\text{mol}}{\text{L}} = \frac{4.0 \times 10^{-3}}{32 \times 10^{-3}}\ \frac{\text{mol}}{\text{m}^3}$$
$$= \frac{4.0}{32}\ \text{mol m}^{-3}$$

where we have used 1 L = 10^{-3} m^3. From Table 3.2, K_H for oxygen in water is 1.30×10^{-2} mol m^{-3} kPa^{-1}; therefore the partial pressure needed to achieve the stated concentration is

$$p_{O_2} = \frac{(4.0/32)\ \text{mol m}^{-3}}{1.30 \times 10^{-2}\ \text{mol m}^{-3}\ \text{kPa}^{-1}} = 9.6\ \text{kPa}$$

The partial pressure of oxygen in air at sea level is 21 kPa (158 Torr), which is greater than 9.6 kPa (72 Torr), so the required concentration can be maintained under normal conditions.

A note on good practice: The number of significant figures in the result of a calculation should not exceed the number in the data.

SELF-TEST 3.9 What partial pressure of methane is needed to dissolve 21 mg of methane in 100 g of benzene at 25°C ($K_B = 5.69 \times 10^4$ kPa, for Henry's law in the form given in eqn 3.18)?

Answer: 57 kPa (4.3×10^2 Torr) ■

CASE STUDY 3.1 Gas solubility and breathing

We inhale about 500 cm^3 of air with each breath we take. The influx of air is a result of changes in volume of the lungs as the diaphragm is depressed and the chest expands, which results in a decrease in pressure of about 100 Pa relative to atmospheric pressure. Expiration occurs as the diaphragm rises and the chest contracts and gives rise to a differential pressure of about 100 Pa above atmospheric pressure. The total volume of air in the lungs is about 6 L, and the ad-

ditional volume of air that can be exhaled forcefully after normal expiration is about 1.5 L. Some air remains in the lungs at all times to prevent the collapse of the alveoli.

A knowledge of Henry's law constants for gases in fats and lipids is important for the discussion of respiration. The effect of gas exchange between blood and air inside the alveoli of the lungs means that the composition of the air in the lungs changes throughout the breathing cycle. Alveolar gas is in fact a mixture of newly inhaled air and air about to be exhaled. The concentration of oxygen present in arterial blood is equivalent to a partial pressure of about 40 Torr (5.3 kPa), whereas the partial pressure of freshly inhaled air is about 104 Torr (13.9 kPa). Arterial blood remains in the capillary passing through the wall of an alveolus for about 0.75 s, but such is the steepness of the pressure gradient that it becomes fully saturated with oxygen in about 0.25 s. If the lungs collect fluids (as in pneumonia), then the respiratory membrane thickens, diffusion is greatly slowed, and body tissues begin to suffer from oxygen starvation. Carbon dioxide moves in the opposite direction across the respiratory tissue, but the partial pressure gradient is much less, corresponding to about 5 Torr (0.7 kPa) in blood and 40 Torr (5.3 kPa) in air at equilibrium. However, because carbon dioxide is much more soluble in the alveolar fluid than oxygen is, equal amounts of oxygen and carbon dioxide are exchanged in each breath.

A hyperbaric oxygen chamber, in which oxygen is at an elevated partial pressure, is used to treat certain types of disease. Carbon monoxide poisoning can be treated in this way, as can the consequences of shock. Diseases that are caused by anaerobic bacteria, such as gas gangrene and tetanus, can also be treated because the bacteria cannot thrive in high oxygen concentrations. ■

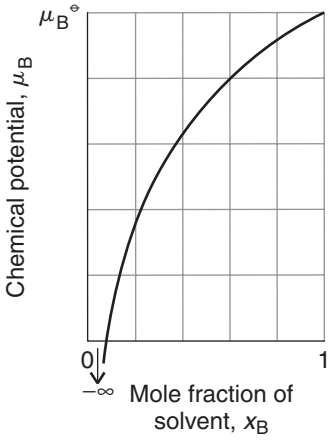


Fig. 3.29 The variation of the chemical potential of the solute with the composition of the solution expressed in terms of the mole fraction of solute. Note that the chemical potential of the solute is lower in the mixture than for the pure solute (for an ideal system). This behavior is likely to be shown by a dilute solution in which the solvent is almost pure and the solute obeys Henry's law.

Henry's law lets us write an expression for the chemical potential of a solute in a solution. By exactly the same reasoning as in *Derivation* 3.5, but with the empirical constant K_B used in place of the vapor pressure of the pure solute, p_B^*, the chemical potential of the solute when it is present at a mole fraction x_B is

$$\mu_B = \mu_B^* + RT \ln x_B \qquad \textbf{(3.20)}$$

This expression, which is illustrated in Fig. 3.29, applies when Henry's law is valid, in very dilute solutions. The chemical potential of the solute has its pure value when it is present alone ($x_B = 1$, $\ln 1 = 0$) and a smaller value when dissolved (when $x_B < 1$, $\ln x_B < 0$).

We often express the composition of a solution in terms of the molar concentration of the solute, [B], rather than as a mole fraction. The mole fraction and the molar concentration are proportional to each other in dilute solutions, so we write $x_B = \textit{constant} \times [B]$. To avoid complications with units, we shall interpret [B] wherever it appears as the numerical value of the molar concentration in moles per liter. Thus, if the molar concentration of B is 1.0 mol L^{-1}, then in this chapter we would write [B] = 1.0. Then eqn 3.20 becomes

$$\mu_B = \mu_B^* + RT \ln(\textit{constant}) + RT \ln [B]$$

We can combine the first two terms into a single constant, which we denote $\mu_B^{\ominus}$, and write this relation as

$$\mu_B = \mu_B^{\ominus} + RT \ln [B] \qquad \textbf{(3.21)}$$

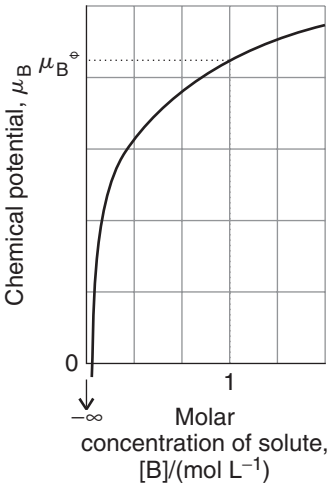


Fig. 3.30 The variation of the chemical potential of the solute with the composition of the solution that obeys Henry's law expressed in terms of the molar concentration of solute. The chemical potential has its standard value at [B] = 1 mol L^{-1}.

Figure 3.30 illustrates the variation of chemical potential with concentration predicted by this equation. The chemical potential of the solute has its standard value when the molar concentration of the solute is 1 mol L^{-1}.

3.11 Real solutions: activities

Because the liquid environment inside a cell cannot be described adequately as an ideal-dilute solution, we need to develop expressions that take into account significant deviations from the behavior treated so far.

No actual solutions are ideal, and many solutions deviate from ideal-dilute behavior as soon as the concentration of solute rises above a small value. In thermodynamics we try to preserve the form of equations developed for ideal systems so that it becomes easy to step between the two types of system.[6] This is the thought behind the introduction of the **activity**, a_J, of a substance, which is a kind of effective concentration. The activity is defined so that the expression

$$\mu_J = \mu_J^\ominus + RT \ln a_J \qquad \textbf{(3.22)}$$

is true at *all* concentrations and for both the solvent and the solute.

For ideal solutions, $a_J = x_J$, and the activity of each component is equal to its mole fraction. For ideal-dilute solutions using the definition in eqn 3.21, $a_B = [B]$, and the activity of the solute is equal to the numerical value of its molar concentration. For *non*-ideal solutions we write

$$\textit{For the solvent:}\ \ a_A = \gamma_A x_A$$
$$\textit{For the solute:}\ \ a_B = \gamma_B [B] \qquad \textbf{(3.23)}$$

where the γ (gamma) in each case is the **activity coefficient**. Activity coefficients depend on the composition of the solution, and we should note the following:

Because the solvent behaves more in accord with Raoult's law as it becomes pure, $\gamma_A \longrightarrow 1$ as $x_A \longrightarrow 1$.

[6] An added advantage is that there are fewer equations to remember!

Table 3.3 Activities and standard states*

Substance	Standard state	Activity, a
Solid	Pure solid, 1 bar	1
Liquid	Pure liquid, 1 bar	1
Gas	Pure gas, 1 bar	$p/p^{\ominus}$
Solute	Molar concentration of 1 mol L^{-1}	$[J]/c^{\ominus}$

$p^{\ominus} = 1$ bar ($= 10^5$ Pa), $c^{\ominus} = 1$ mol L^{-1} ($= 1$ mol dm^{-3}).

*Activities are for perfect gases and ideal-dilute solutions; all activities are dimensionless.

Because the solute behaves more in accord with Henry's law as the solution becomes very dilute, $\gamma_B \longrightarrow 1$ as $[B] \longrightarrow 0$.

These conventions and relations are summarized in Table 3.3.

Activities and activity coefficients are often branded as "fudge factors." To some extent that is true. However, their introduction does allow us to derive thermodynamically exact expressions for the properties of non-ideal solutions. Moreover, in a number of cases it is possible to calculate or measure the activity coefficient of a species in solution. In this text we shall normally derive thermodynamic relations in terms of activities, but when we want to make contact with actual measurements, we shall set the activities equal to the "ideal" values in Table 3.3.

Colligative properties

An ideal solute has no effect on the enthalpy of a solution in the sense that the enthalpy of mixing is zero. However, it does affect the entropy, and we found in eqn 3.17 that $\Delta S > 0$ when two components mix to give an ideal solution. We can therefore expect a solute to modify the physical properties of the solution. Apart from lowering the vapor pressure of the solvent, which we have already considered, a nonvolatile solute has three main effects: it raises the boiling point of a solution, it lowers the freezing point, and it gives rise to an osmotic pressure. (The meaning of the last will be explained shortly.) These properties, which are called **colligative properties**, stem from a change in the dispersal of solvent molecules that depends on the number of solute particles present but is independent of the identity of the species we use to bring it about.[7] Thus, a 0.01 mol kg^{-1} aqueous solution of any nonelectrolyte should have the same boiling point, freezing point, and osmotic pressure.

3.12 The modification of boiling and freezing points

To understand the origins of the colligative properties and their effect on biological processes, it is useful to explore the modification of the boiling and freezing points of a solvent in a solution.

As indicated above, the effect of a solute is to raise the boiling point of a solvent and to lower its freezing point. It is found empirically, and can be justified thermodynamically, that the **elevation of boiling point**, ΔT_b, and the **depression of freezing point**, ΔT_f, are both proportional to the molality, b_B, of the solute:

$$\Delta T_b = K_b b_B \qquad \Delta T_f = K_f b_B \tag{3.24}$$

[7]Hence, the name *colligative*, meaning "depending on the collection."

Table 3.4 Cryoscopic and ebullioscopic constants

Solvent	K_f/(K kg mol^{-1})	K_b/(K kg mol^{-1})
Acetic acid	3.90	3.07
Benzene	5.12	2.53
Camphor	40	
Carbon disulfide	3.8	2.37
Naphthalene	6.94	5.8
Phenol	7.27	3.04
Tetrachloromethane	30	4.95
Water	1.86	0.51

K_b is the **ebullioscopic constant** and K_f is the **cryoscopic constant** of the solvent.[8] The two constants can be estimated from other properties of the solvent, but both are best treated as empirical constants (Table 3.4).

SELF-TEST 3.10 Estimate the lowering of the freezing point of the solution made by dissolving 3.0 g (about one cube) of sucrose in 100 g of water.

Answer: −0.16 K

To understand the origin of these effects, we shall make two simplifying assumptions:

1. The solute is not volatile and therefore does not appear in the vapor phase.
2. The solute is insoluble in the solid solvent and therefore does not appear in the solid phase.

For example, a solution of sucrose in water consists of a solute (sucrose, $C_{12}H_{22}O_{11}$) that is not volatile and therefore never appears in the vapor, which is therefore pure water vapor. The sucrose is also left behind in the liquid solvent when ice begins to form, so the ice remains pure.

The origin of colligative properties is the lowering of chemical potential of the solvent by the presence of a solute, as expressed by eqn 3.15. We saw in Section 3.3 that the freezing and boiling points correspond to the temperatures at which the graph of the molar Gibbs energy of the liquid intersects the graphs of the molar Gibbs energy of the solid and vapor phases, respectively. Because we are now dealing with mixtures, we have to think about the *partial* molar Gibbs energy (the chemical potential) of the solvent. The presence of a solute lowers the chemical potential of the liquid, but because the vapor and solid remain pure, their chemical potentials remain unchanged. As a result, we see from Fig. 3.31 that the freezing point moves to lower values; likewise, from Fig. 3.32 we see that the boiling point moves to higher values. In other words, the freezing point is depressed, the boiling point is elevated, and the liquid phase exists over a wider range of temperatures.

The elevation of boiling point is too small to have any practical significance. A practical consequence of the lowering of freezing point, and hence the lowering of the melting point of the pure solid, is its employment in organic chemistry to judge the purity of a sample, for any impurity lowers the melting point of a sub-

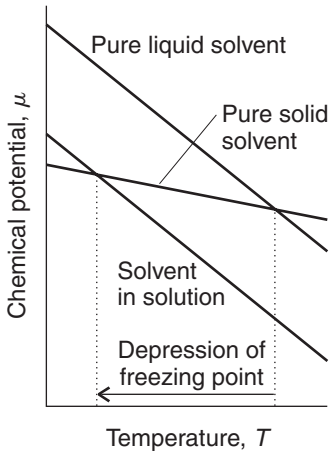


Fig. 3.31 The chemical potentials of pure solid solvent and pure liquid solvent also decrease with temperature, and the point of intersection, where the chemical potential of the liquid rises above that of the solid, marks the freezing point of the pure solvent. A solute lowers the chemical potential of the solvent but leaves that of the solid unchanged. As a result, the intersection point lies farther to the left and the freezing point is therefore lowered.

[8]They are also called the "boiling-point constant" and the "freezing-point constant."

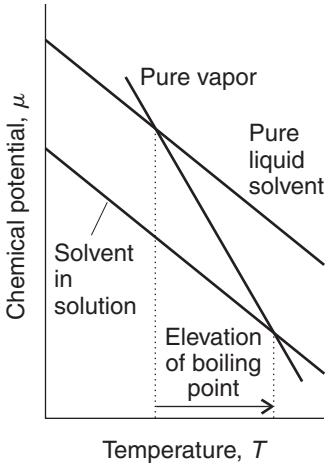


Fig. 3.32 The chemical potentials of pure solvent vapor and pure liquid solvent decrease with temperature, and the point of intersection, where the chemical potential of the vapor falls below that of the liquid, marks the boiling point of the pure solvent. A solute lowers the chemical potential of the solvent but leaves that of the vapor unchanged. As a result, the intersection point lies farther to the right, and the boiling point is therefore raised.

stance from its accepted value. The salt water of the oceans freezes at temperatures lower than that of fresh water, and salt is spread on highways to delay the onset of freezing. The addition of "antifreeze" to car engines and, by natural processes, to arctic fish, is commonly held up as an example of the lowering of freezing point, but the concentrations are far too high for the arguments we have used here to be applicable. The 1,2-ethanediol ("glycol") used as antifreeze and the proteins present in fish body fluids probably simply interfere with bonding between water molecules.

3.13 Osmosis

To understand why cells neither collapse nor burst easily, we need to explore the thermodynamics of transfer of water through cell membranes.

The phenomenon of **osmosis** is the passage of a pure solvent into a solution separated from it by a semipermeable membrane.[9] A **semipermeable membrane** is a membrane that is permeable to the solvent but not to the solute (Fig. 3.33). The membrane might have microscopic holes that are large enough to allow water molecules to pass through, but not ions or carbohydrate molecules with their bulky coating of hydrating water molecules. The **osmotic pressure**, Π (uppercase pi), is the pressure that must be applied to the solution to stop the inward flow of solvent.

In the simple arrangement shown in Fig. 3.33, the pressure opposing the passage of solvent into the solution arises from the hydrostatic pressure of the column of solution that the osmosis itself produces. This column is formed when the pure solvent flows through the membrane into the solution and pushes the column of solution higher up the tube. Equilibrium is reached when the downward pressure exerted by the column of solution is equal to the upward osmotic pressure. A complication of this arrangement is that the entry of solvent into the solution results in dilution of the latter, so it is more difficult to treat mathematically than an arrangement in which an externally applied pressure opposes any flow of solvent into the solution.

The osmotic pressure of a solution is proportional to the concentration of solute. In fact, we show in the following *Derivation* that the expression for the osmotic

[9]The name *osmosis* is derived from the Greek word for "push."

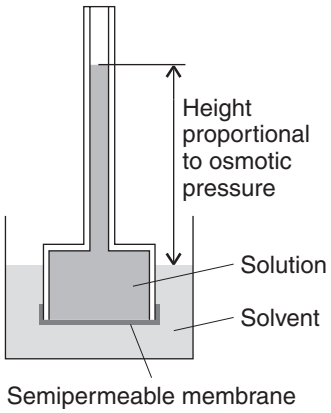


Fig. 3.33 In a simple osmosis experiment, a solution is separated from the pure solvent by a semipermeable membrane. Pure solvent passes through the membrane and the solution rises in the inner tube. The net flow ceases when the pressure exerted by the column of liquid is equal to the osmotic pressure of the solution.

pressure of an ideal solution, which is called the **van 't Hoff equation**, bears an uncanny resemblance to the expression for the pressure of a perfect gas:

$$\Pi V \approx n_B RT \qquad \textbf{(3.25a)}$$

Because $n_B/V = [B]$, the molar concentration of the solute, a simpler form of this equation is

$$\Pi \approx [B]RT \qquad \textbf{(3.25b)}$$

This equation applies only to solutions that are sufficiently dilute to behave as ideal-dilute solutions.

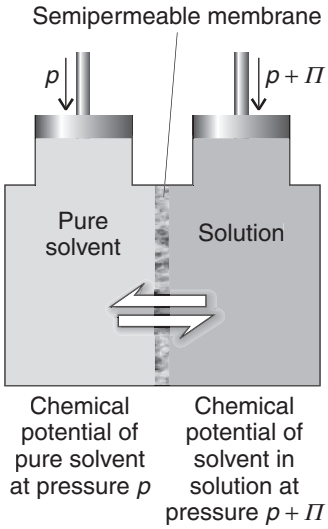


Fig. 3.34 The basis of the calculation of osmotic pressure. The presence of a solute lowers the chemical potential of the solvent in the right-hand compartment, but the application of pressure raises it. The osmotic pressure is the pressure needed to equalize the chemical potential of the solvent in the two compartments.

DERIVATION 3.7 The van 't Hoff equation

The thermodynamic treatment of osmosis makes use of the fact that, at equilibrium, the chemical potential of the solvent A is the same on each side of the membrane (Fig. 3.34). The starting relation is therefore

$$\mu_A(\text{pure solvent at pressure } p) = \mu_A(\text{solvent in the solution at pressure } p + \Pi)$$

The pure solvent is at atmospheric pressure, p, and the solution is at a pressure $p + \Pi$ on account of the additional pressure, Π, that has to be exerted on the solution to establish equilibrium. We shall write the chemical potential of the pure solvent at the pressure p as $\mu_A^*(p)$. The chemical potential of the solvent in the solution is lowered by the solute, but it is raised on account of the greater pressure, $p + \Pi$, acting on the solution. We denote this chemical potential by $\mu_A(x_A, p + \Pi)$. Our task is to find the extra pressure Π needed to balance the lowering of chemical potential caused by the solute.

The condition for equilibrium written above is

$$\mu_A^*(p) = \mu_A(x_A, p + \Pi)$$

We take the effect of the solute into account by using eqn 3.15:

$$\mu_A(x_A, p + \Pi) = \mu_A^*(p + \Pi) + RT \ln x_A$$

The effect of pressure on an (assumed incompressible) liquid is given by eqn 3.1 ($\Delta G_m = V_m \Delta p$) but now expressed in terms of the chemical potential and the partial molar volume of the solvent:

$$\mu_A^*(p + \Pi) = \mu_A^*(p) + V_A \Delta p$$

At this point we identify the difference in pressure Δp as Π. When the last three equations are combined, we get

$$\mu_A^*(p) = \mu_A^*(p) + V_A \Pi + RT \ln x_A$$

and therefore

$$-RT \ln x_A = \Pi V_A$$

The mole fraction of the solvent is equal to $1 - x_B$, where x_B is the mole fraction of solute molecules. In dilute solution, $\ln(1 - x_B)$ is approximately equal to $-x_B$ (for example, $\ln(1 - 0.01) = \ln 0.99 = -0.010\,050$), so this equation becomes

$$RTx_B \approx \Pi V_A$$

When the solution is dilute, $x_B = n_B/n \approx n_B/n_A$. Moreover, because $n_A V_A \approx V$, the total volume of the solution, this equation becomes eqn 3.25.

COMMENT 3.4 The series expansion of a natural logarithm (see *Appendix 2*) is

$$\ln(1 - x) = -x - \tfrac{1}{2}x^2 - \tfrac{1}{3}x^3 \cdots$$

If $x << 1$, then the terms involving x raised to a power greater than 1 are much smaller than x, so $\ln(1 - x) \approx -x$. ■

Osmosis helps biological cells maintain their structure. Cell membranes are semipermeable and allow water, small molecules, and hydrated ions to pass, while blocking the passage of biopolymers synthesized inside the cell. The difference in concentrations of solutes inside and outside the cell gives rise to an osmotic pressure, and water passes into the more concentrated solution in the interior of the cell, carrying small nutrient molecules. The influx of water also keeps the cell swollen, whereas dehydration causes the cell to shrink. These effects are important in everyday medical practice. To maintain the integrity of blood cells, solutions that are injected into the bloodstream for blood transfusions and intravenous feeding must be *isotonic* with the blood, meaning that they must have the same osmotic pressure as blood. If the injected solution is too dilute, or *hypotonic*, the flow of solvent into the cells, required to equalize the osmotic pressure, causes the cells to burst and die by a process called *hemolysis*. If the solution is too concentrated, or *hypertonic*, equalization of the osmotic pressure requires flow of solvent out of the cells, which shrink and die.

Osmosis also forms the basis of **dialysis**, a common technique for the removal of impurities from solutions of biological macromolecules. In a dialysis experiment, a solution of macromolecules containing impurities, such as ions or small molecules (including small proteins or nucleic acids), is placed in a bag made of a material that acts as a semipermeable membrane and the filled bag is immersed in a solvent. The membrane permits the passage of the small ions and molecules but not the larger macromolecules, so the former migrate through the membrane, leaving the macromolecules behind. In practice, purification of the sample requires several changes of solvent to coax most of the impurities out of the dialysis bag.

3.14 The osmotic pressure of solutions of biopolymers

To see how measurements of the osmotic pressure can be used in biochemistry, we need to account for the large deviations from ideality of solutions of large, and sometimes charged, biological macromolecules.

Biological macromolecules dissolve to produce solutions that are far from ideal, but we can still calculate the osmotic pressure by assuming that the van 't Hoff equation is only the first term of a lengthier expression:

$$\Pi = [B]RT\{1 + B[B] + \cdots\} \qquad \textbf{(3.26a)}$$

The empirical parameter B in this expression is called the **osmotic virial coeffi-**

cient. To use eqn 3.26a, we rearrange it into a form that gives a straight line by dividing both sides by [B]:

$$\frac{\Pi}{[B]} = RT + BRT[B] + \cdots \qquad \textbf{(3.26b)}$$

(Intercept: RT; Slope: BRT)

As we illustrate in the following example, we can find the molar mass of the solute B by measuring the osmotic pressure at a series of mass concentrations and making a plot of Π/[B] against [B] (Fig. 3.35).

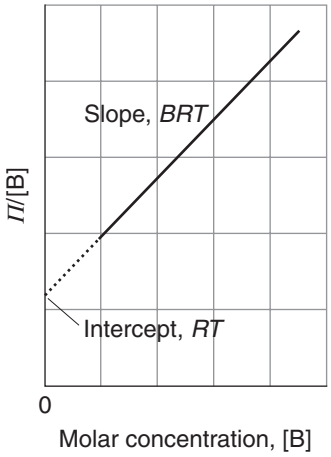


Fig. 3.35 The plot and extrapolation made to analyze the results of an osmometry experiment.

EXAMPLE 3.4 Determining the molar mass of an enzyme from measurements of the osmotic pressure

The osmotic pressures of solutions of an enzyme in water at 298 K are given below. Find the molar mass of the enzyme.

c/(g L^{-1})	1.00	2.00	4.00	7.00	9.00
Π/(10^{-2} kPa)	2.75	6.96	19.7	50.0	78.5

Strategy First, we need to express eqn 3.26b in terms of the mass concentration, c, so that we can use the data. The molar concentration [B] of the solute is related to the mass concentration $c_B = m_B/V$ by

$$c_B = \frac{m_B}{V} = \frac{m_B}{n_B} \times \frac{n_B}{V} = M \times [B]$$

where M is the molar mass of the solute (its mass, m_B, divided by its amount in moles, n_B), so $[B] = c_B/M$. With this substitution, eqn 3.26b becomes

$$\frac{\Pi}{c_B/M} = RT + \frac{BRTc_B}{M} + \cdots$$

Division through by M gives

$$\frac{\Pi}{c_B} = \frac{RT}{M} + \left(\frac{BRT}{M^2}\right) c_B + \cdots$$

It follows that, by plotting Π/c_B against c_B, the results should fall on a straight line with intercept RT/M on the vertical axis at $c_B = 0$. Therefore, by locating the intercept by extrapolation of the data to $c_B = 0$, we can find the molar mass of the solute.

Solution The following values of Π/c_B can be calculated from the data:

c_B/(g L^{-1})	1.00	2.00	4.00	7.00	9.00
(Π/10^{-2} kPa)/(c_B/g L^{-1})	2.75	3.48	4.93	7.15	8.72

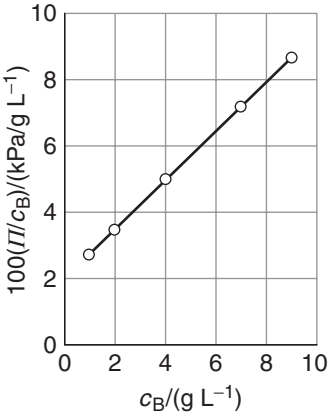


Fig. 3.36 The plot of the data in Example 3.4. The molar mass is determined from the intercept at $c_B = 0$.

The points are plotted in Fig. 3.36. The intercept with the vertical axis at $c_B = 0$ is at

$$\frac{\Pi/(10^{-2}\ \text{kPa})}{c_B/(\text{g L}^{-1})} = 1.98$$

which we can rearrange into

$$\Pi/c_B = 1.98 \times 10^{-2}\ \text{kPa g}^{-1}\ \text{L}$$

Therefore, because this intercept is equal to RT/M, we can write

$$M = \frac{RT}{1.98 \times 10^{-2}\ \text{kPa g}^{-1}\ \text{L}}$$

It follows that

$$M = \frac{(8.314\ 47\ \text{kPa L K}^{-1}\ \text{mol}^{-1}) \times (298\ \text{K})}{1.98 \times 10^{-2}\ \text{kPa g}^{-1}\ \text{L}} = 1.25 \times 10^{5}\ \text{g mol}^{-1}$$

The molar mass of the enzyme is therefore close to 125 kDa.

A note on good practice: Graphs should be plotted on axes labeled with pure numbers. Note how the plotted quantities are divided by their units, so that $c_B/(\text{g L}^{-1})$, for instance, is a dimensionless number. By carrying the units through every stage of the calculation, we end up with the correct units for M. It is far better to proceed systematically in this way than to try to guess the units at the end of the calculation.

SELF-TEST 3.11 The osmotic pressures of solutions of a protein at 25°C were as follows:

$c/(\text{g L}^{-1})$	0.50	1.00	1.50	2.00	2.50
$\Pi/(10^{-2}\ \text{kPa})$	4.00	11.0	20.0	33.0	49.0

What is the molar mass of the protein?

Answer: 49 kDa ■

We now discuss the osmotic pressure of solutions of polyelectrolytes, molecules bearing many charged groups, such as DNA. The term **Donnan equilibrium** refers to the distribution of ions between two solutions in contact through a semipermeable membrane, in one of which there is a polyelectrolyte and where the membrane is not permeable to the large charged macromolecule. This arrangement is one that actually occurs in living systems, where we have seen that osmosis is an important feature of cell operation. The thermodynamic consequences of the distribution and transfer of charged species across cell membranes is explored further in Chapter 5.

Consider the measurement of the osmotic pressure of a solution of a polyelectrolyte $Na_\nu P$, where $P^{\nu-}$ is a polyanion. In such experiments, it is customary to add

a high concentration of a salt such as NaCl to the solution on both sides of the membrane so that the number of cations that $P^{\nu-}$ provides is insignificant in comparison with the number supplied by the additional salt. Apart from small imbalances of charge close to the membrane (which have important consequences, as we shall see in Chapter 5), electrical neutrality must be preserved in the bulk on both sides of the membrane: if an anion migrates, a cation must accompany it. We use this condition to show in the following *Derivation* that, at equilibrium,

$$[Na^+]_L - [Na^+]_R = \frac{\nu[P^{\nu-}][Na^+]_L}{2[Cl^-] + \nu[P^{\nu-}]} \quad \textbf{(3.27a)}$$

$$[Cl^-]_L - [Cl^-]_R = -\frac{\nu[P^{\nu-}][Cl^-]_L}{2[Cl^-]} \quad \textbf{(3.27b)}$$

where $[Cl^-] = \frac{1}{2}([Cl^-]_L + [Cl^-]_R)$, and the subscripts L and R refer to the left-hand and right-hand compartments, respectively, separated by the semipermeable membrane. Note that cations will dominate over the anions in the compartment that contains the polyanion because the concentration difference is positive for Na^+ and negative for Cl^-. It also follows that from a measurement of the ion concentrations, it is possible to determine the net charge of the polyanion, which may be unknown.

DERIVATION 3.8 The Donnan equilibrium

Suppose that $Na_\nu P$ is at a molar concentration $[P^{\nu-}]$ on the left-hand compartment of the experimental arrangement and that NaCl is added to each compartment. In the left-hand compartment there are $P^{\nu-}$, Na^+, and Cl^- ions. In the right-hand compartment there are Na^+ and Cl^- ions. The condition for equilibrium is that the chemical potential of NaCl in solution is the same in both compartments, so a net flow of Na^+ and Cl^- ions occurs until $\mu_L(NaCl) = \mu_R(NaCl)$. This equality occurs when

$$\mu^\ominus(NaCl) + RT \ln a_L(Na^+) + RT \ln a_L(Cl^-) = \mu^\ominus(NaCl) + RT \ln a_R(Na^+) + RT \ln a_R(Cl^-)$$

or

$$RT \ln a_L(Na^+)a_L(Cl^-) = RT \ln a_R(Na^+)a_R(Cl^-)$$

If we ignore activity coefficients, the two expressions are equal when

$$[Na^+]_L[Cl^-]_L = [Na^+]_R[Cl^-]_R$$

As the Na^+ ions are supplied by the polyelectrolyte as well as the added salt, the conditions for bulk electrical neutrality lead to the following charge-balance equations:

$$[Na^+]_L = [Cl^-]_L + \nu[P^{\nu-}]$$
$$[Na^+]_R = [Cl^-]_R$$

We can now combine these three conditions to obtain expressions for the differences in ion concentrations across the membrane. For example, we write

$$[Na^+]_L = \frac{[Na^+]_R[Cl^-]_R}{[Cl^-]_L} = \frac{[Na^+]_R{}^2}{[Na^+]_L + \nu[P^{\nu-}]}$$

which rearranges to

$$[Na^+]_L{}^2 - [Na^+]_R{}^2 = \nu[P^{\nu-}][Na^+]_L$$

After applying the relation $a^2 - b^2 = (a + b)(a - b)$ and rearranging, we obtain

$$[Na^+]_L - [Na^+]_R = \frac{\nu[P^{\nu-}][Na^+]_L}{[Na^+]_L + [Na^+]_R}$$

It follows from the definition $[Cl^-] = \frac{1}{2}([Cl^-]_L + [Cl^-]_R)$ and the charge-balance equations that

$$[Na^+]_L + [Na^+]_R = [Cl^-]_L + [Cl^-]_R + \nu[P^{\nu-}] = 2[Cl^-] + \nu[P^{\nu-}]$$

Substitution of this result into the equation for $[Na^+]_L - [Na^+]_R$ leads to eqn 3.27a. Similar manipulations lead to an equation for the difference in chloride concentration:

$$[Cl^-]_L - [Cl^-]_R = -\frac{\nu[P^{\nu-}][Cl^-]_L}{[Cl^-]_L + [Cl^-]_R}$$

which becomes eqn 3.27b after substituting $2[Cl^-]$ for the expression in the denominator.

EXAMPLE 3.5 Analyzing a Donnan equilibrium

Suppose that two equal volumes of 0.200 M NaCl(aq) solution are separated by a membrane and that the left-hand compartment of the experimental arrangement contains a polyelectrolyte Na_6P at a concentration of 50 g L^{-1}. Assuming that the membrane is not permeable to the polyanion, which has a molar mass of 55 kg mol^{-1}, calculate the molar concentrations of Na^+ and Cl^- in each compartment.

Strategy We saw in *Derivation* 3.8 that the sum of the equilibrium concentrations of Na^+ in both compartments is

$$[Na^+]_L + [Na^+]_R = 2[Cl^-] + \nu[P^{\nu-}]$$

with $[Cl^-] = 0.200$ mol L^{-1}, and $[P^{\nu-}]$ being calculated from the mass concentration and the molar mass of the polyanion. At this point, we have one equation and two unknowns, $[Na^+]_L$ and $[Na^+]_R$, so we use a second equation, eqn 3.27a, to solve for both Na^+ ion concentrations. To calculate chloride ion concentrations, we use $[Cl^-]_R = [Na^+]_R$ and $[Cl^-]_L = [Na^+]_L - \nu[P^{\nu-}]$, with $\nu = 6$.

Solution The molar concentration of the polyanion is $[P^{\nu-}] = 9.1 \times 10^{-4}$ mol L^{-1}. It follows from eqn 3.27a that

$$[Na^+]_L - [Na^+]_R = \frac{6 \times (9.1 \times 10^{-4} \text{ mol L}^{-1}) \times [Na^+]_L}{2 \times (0.200 \text{ mol L}^{-1}) + 6 \times (9.1 \times 10^{-4} \text{ mol L}^{-1})}$$

The sum of Na^+ concentrations is

$$[Na^+]_L + [Na^+]_R = 2 \times (0.200 \text{ mol L}^{-1}) + 6 \times (9.1 \times 10^{-4} \text{ mol L}^{-1}) = 0.405 \text{ mol L}^{-1}$$

The solutions of these two equations are

$$[Na^+]_L = 0.204 \text{ mol L}^{-1} \qquad [Na^+]_R = 0.201 \text{ mol L}^{-1}$$

Then

$$[Cl^-]_R = [Na^+]_R = 0.201 \text{ mol L}^{-1}$$
$$[Cl^-]_L = [Na^+]_L - 6[P^{\nu-}] = 0.199 \text{ mol L}^{-1}$$

SELF-TEST 3.12 Repeat the calculation for 0.300 M NaCl(aq), a polyelectrolyte $Na_{10}P$ of molar mass 33 kg mol^{-1} at a mass concentration of 50.0 g L^{-1}.

Answer: $[Na^+]_L = 0.31$ mol L^{-1}, $[Na^+]_R = 0.30$ mol L^{-1} ■

One consequence of dealing with polyelectrolytes is that it is necessary to know the extent of ionization before osmotic data can be interpreted to yield a molar mass. For example, suppose the sodium salt of a polyelectrolyte is present in solution as νNa^+ ions and a single polyanion $P^{\nu-}$; then if it is fully dissociated in solution, it gives rise to $\nu + 1$ particles for each formula unit of salt that dissolves. If we guess that $\nu = 1$ when in fact $\nu = 10$, then the estimate of the molar mass will be wrong by an order of magnitude. We can find a way out of this difficulty by making osmotic pressure measurements under the conditions described in *Derivation* 3.8; that is, by adding a salt such as NaCl to the solutions on both sides of the semipermeable membrane. Then, as shown in the following *Derivation*, the osmotic pressure is

$$\Pi = RT[P^{\nu-}](1 + B[P^{\nu-}]) \qquad B = \frac{\nu^2[Cl^-]_{out}}{4[Cl^-]^2 + 2\nu[Cl^-][P^{\nu-}]} \tag{3.28}$$

where B is an osmotic virial coefficient. If the concentration of added salt is so great that $[Cl^-]_L$ and $[Cl^-]_R$ are both much larger than $[P^{\nu-}]$, then $B\,[P^{\nu-}] << 1$ and eqn 3.28 reduces to $\Pi = RT[P^{\nu-}]$, a result independent of the value of ν. Therefore, if we measure the osmotic pressure in the presence of high concentrations of salt, the molar mass may be obtained unambiguously.

DERIVATION 3.9 The osmotic pressure of polyelectrolyte solutions

The osmotic pressure of a solution depends on the difference in the numbers of solute particles on each side of the membrane. That being so, the van 't Hoff equation, $\Pi = RT$[solute], for the solution described in *Derivation* 3.8 becomes

$$\Pi = RT\{([P^{\nu-}] + [Na^+]_L + [Cl^-]_L) - ([Na^+]_R + [Cl^-]_R)\}$$
$$= RT\{[P^{\nu-}] + ([Na^+]_L - ([Na^+]_R) + ([Cl^-]_L - [Cl^-]_R)\}$$

It follows from eqn 3.27 that

$$\Pi = RT\left\{[P^{\nu-}] + \frac{\nu[P^{\nu-}][Na^+]_L}{2[Cl^-] + \nu[P^{\nu-}]} - \frac{\nu[P^{\nu-}][Cl^-]_L}{2[Cl^-]}\right\}$$

$$= RT[P^{\nu-}]\left\{1 + \frac{\nu[Na^+]_L}{2[Cl^-] + \nu[P^{\nu-}]} - \frac{\nu[Cl^-]_L}{2[Cl^-]}\right\}$$

We now use the definition of $[Cl^-]$ and the charge-balance equations of *Derivation* 3.8 to write

$$\Pi = RT[P^{\nu-}]\left\{1 + \frac{\nu[Cl^-]_R([Na^+]_L - [Cl^-]_L)}{4[Cl^-]^2 + 2\nu[Cl^-][P^{\nu-}]}\right\}$$

From the charge-balance equations we may also write $\nu[P^{\nu-}] = [Na^+]_L - [Cl^-]_L$. Then eqn 3.28 follows from substitution of this result into the equation above.

SELF-TEST 3.13 Supply the intermediate steps in the derivation of eqn 3.28. Use the guidelines provided in *Derivation* 3.9.

Checklist of Key Ideas

You should now be familiar with the following concepts:

- ☐ **1.** The molar Gibbs energy of a liquid or a solid is almost independent of pressure ($\Delta G_m = V_m \Delta p$).
- ☐ **2.** The molar Gibbs energy of a perfect gas increases logarithmically with pressure ($\Delta G_m = RT \ln(p_f/p_i)$).
- ☐ **3.** The molar Gibbs energy of a substance decreases as the temperature is increased ($\Delta G_m = -S_m \Delta T$).
- ☐ **4.** A phase diagram of a substance shows the conditions of pressure and temperature at which its various phases are most stable.
- ☐ **5.** A phase boundary depicts the pressures and temperatures at which two phases are in equilibrium.
- ☐ **6.** The boiling temperature is the temperature at which the vapor pressure is equal to the external pressure; the normal boiling point is the temperature at which the vapor pressure is 1 atm. The critical temperature is the temperature above which a substance does not form a liquid. The triple point is the condition of pressure and temperature at which three phases are in mutual equilibrium.
- ☐ **7.** Composition is commonly reported as molar concentration (molarity), molality, or mole fraction.
- ☐ **8.** The partial pressure of any gas is defined as $p_J = x_J p$, where x_J is its mole fraction in a mixture and p is the total pressure. Dalton's law states that the total pressure of a mixture of perfect gases is the sum of the pressures that each gas would exert if it were alone in the container at the same temperature.
- ☐ **9.** A partial molar quantity is the contribution of a component (per mole) to the overall property of a mixture.
- ☐ **10.** The chemical potential of a component is the partial molar Gibbs energy of that component in a mixture, and $G = n_A\mu_A + n_B\mu_B$.

□ **11.** For a perfect gas, $\mu_J = \mu_J^{\ominus} + RT \ln p_J$; for a solute in an ideal solution, $\mu_J = \mu_J^* + RT \ln x_J$.

□ **12.** An ideal solution is one in which both components obey Raoult's law, $p_J = x_J p_J^*$, over the entire composition range.

□ **13.** An ideal-dilute solution is one in which the solute obeys Henry's law, $p_J = x_J K_J$.

□ **14.** The activity of a substance is an effective concentration; see Table 3.3.

□ **15.** A colligative property is a property that depends on the number of solute particles, not their chemical identity; they arise from the effect of a solute on the entropy of the solution.

□ **16.** Colligative properties include lowering of vapor pressure, depression of freezing point, elevation of boiling point, and osmotic pressure.

□ **17.** The elevation of boiling point, ΔT_b, and the depression of freezing point, ΔT_f, are calculated from $\Delta T_b = K_b b_B$ and $\Delta T_f = K_f b_B$, respectively, where K_b is the ebullioscopic constant and K_f is the cryoscopic constant of the solvent.

□ **18.** The osmotic pressure, Π, of an ideal solution is given by the van 't Hoff equation, $\Pi V = n_B RT$.

□ **19.** The molar masses of biological polymers can be determined by measurements of the osmotic pressure of their solutions.

□ **20.** The Donnan equilibrium determines the distribution of ions between two solutions in contact through a semipermeable membrane, in one of which there is a polyelectrolyte and where the membrane is not permeable to the large charged macromolecule.

Further information 3.1 The phase rule

To explore whether *four* phases of a single substance could ever be in equilibrium (such as four of the many phases of ice), we think about the thermodynamic criterion for four phases to be in equilibrium. For equilibrium, the four molar Gibbs energies would all have to be equal, and we could write

$$G_m(1) = G_m(2) \quad G_m(2) = G_m(3) \quad G_m(3) = G_m(4)$$

(The other equalities, $G_m(1) = G_m(4)$, and so on, are implied by these three equations.) Each Gibbs energy is a function of the pressure and temperature, so we should think of these three relations as three equations for the two unknowns p and T. In general, three equations for two unknowns have no solution. For instance, the three equations $5x + 3y = 4$, $2x + 6y = 5$, and $x + y = 1$ have no solutions (try it). Therefore, we have to conclude that the four molar Gibbs energies cannot all be equal. In other words, *four phases of a single substance cannot coexist in mutual equilibrium*.

The conclusion we have reached is a special case of one of the most elegant results of chemical thermodynamics. The **phase rule** was derived by Gibbs and states that, for a system at equilibrium,

$$F = C - P + 2$$

Here F is the number of degrees of freedom, C is the number of components, and P is the number of phases. The **number of components**, C, in a system is the minimum number of independent species necessary to define the composition of all the phases present in the system. The definition is easy to apply when the species present in a system do not react, for then we simply count their number. For instance, pure water is a one-component system ($C = 1$), and a mixture of ethanol and water is a two-component system ($C = 2$). The **number of degrees of freedom**, F, of a system is the number of intensive variables (such as the pressure, temperature, or mole fractions) that can be changed independently without disturbing the number of phases in equilibrium.

For a one-component system, such as pure water, we set $C = 1$ and the phase rule simplifies to $F = 3 - P$. When only one phase is present, $F = 2$, which implies that p and T can be varied independently. In other words, a single phase is represented by an *area* on a phase diagram. When two phases are in equilibrium, $F = 1$, which implies that pressure is not freely variable if we have set the temperature. That is, the equilibrium of two phases is represented by a *line* in a phase diagram: a line in a graph shows how one variable must change if another variable is varied (Fig. 3.37). Instead of selecting the temperature, we can select the pressure, but having done so, the two phases come into equilibrium at a single definite temperature. Therefore, freezing (or any other phase transition of a single substance) occurs at a definite temperature at a given pressure. When three phases are in

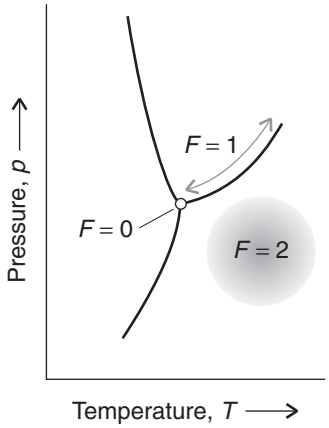


Fig. 3.37 The features of a phase diagram represent different degrees of freedom. When only one phase is present, $F = 2$ and the pressure and temperature can be varied at will. When two phases are present in equilibrium, $F = 1$: now if the temperature is changed, the pressure must be changed by a specific amount. When three phases are present in equilibrium, $F = 0$ and there is no freedom to change either variable.

equilibrium, $F = 0$. This special "invariant condition" can therefore be established only at a definite temperature and pressure. The equilibrium of three phases is therefore represented by a *point*, the triple point, on the phase diagram. If we set $P = 4$, we get the absurd result that F is negative; that result is in accord with the conclusion at the start of this section that four phases cannot be in equilibrium in a one-component system.

Discussion questions

3.1 Discuss the implications for phase stability of the variation of chemical potential with temperature and pressure.

3.2 State and justify the thermodynamic criterion for solution-vapor equilibrium.

3.3 How would you expect the shape of the curve shown in Fig. 3.16 to change if the degree of cooperativity of denaturation of a protein were to increase or decrease for a constant value of the melting temperature?

3.4 What is meant by the activity of a solute?

3.5 Explain the origin of colligative properties. Why do they not depend on the chemical identity of the solute?

3.6 Explain how osmometry can be used to determine the molar mass of a biological macromolecule.

Exercises

3.7 What is the difference in molar Gibbs energy due to pressure alone of **(a)** water (density 1.03 g cm^{-3}) at the ocean surface and in the Mindañao trench (depth 11.5 km), **(b)** mercury (density 13.6 g cm^{-3}) at the top and bottom of the column in a barometer? (*Hint:* At the very top, the pressure on the mercury is equal to the vapor pressure of mercury, which at 20°C is 160 mPa.)

3.8 The density of the fat tristearin is 0.95 g cm^{-3}. Calculate the change in molar Gibbs energy of tristearin when a deep-sea creature is brought to the surface ($p = 1.0$ atm) from a depth of 2.0 km. To calculate the hydrostatic pressure, take the mean density of water to be 1.03 g cm^{-3}.

3.9 Calculate the change in molar Gibbs energy of carbon dioxide (treated as a perfect gas) at 20°C when its pressure is changed isothermally from 1.0 bar to **(a)** 2.0 bar, **(b)** 0.000 27 atm, its partial pressure in air.

3.10 The standard molar entropies of water ice, liquid, and vapor are 37.99, 69.91, and 188.83 J K^{-1} mol^{-1}, respectively. On a single graph, show how the Gibbs energies of each of these phases varies with temperature.

3.11 An open vessel containing **(a)** water, **(b)** benzene, **(c)** mercury stands in a laboratory measuring 6.0 m × 5.3 m × 3.2 m at 25°C. What mass of each substance will be found in the air if there is no ventilation? (The vapor pressures are **(a)** 3.2 kPa, **(b)** 14 kPa, **(c)** 0.23 Pa.)

3.12 On a cold, dry morning after a frost, the temperature was −5°C and the partial pressure of water in the atmosphere fell to 2 Torr. Will the frost sublime? What partial pressure of water would ensure that the frost remained?

3.13 **(a)** Refer to Fig. 3.12 and describe the changes that would be observed when water vapor at 1.0 bar and 400 K is cooled at constant pressure to 260 K. **(b)** Suggest the appearance of a plot of temperature against time if energy is removed at a constant rate. To judge the relative slopes of the cooling curves, you need to know that the constant-pressure molar heat capacities of water vapor, liquid, and solid are approximately $4R$, $9R$, and $4.5R$; the enthalpies of transition are given in Table 1.2.

3.14 Refer to Fig. 3.12 and describe the changes that would be observed when cooling takes place at the pressure of the triple point.

3.15 A thermodynamic treatment allows predictions to be made of the temperature T_m for the unfolding of a helical polypeptide into a random coil. If a polypeptide has n amino acids, $n - 4$ hydrogen bonds are formed to form an α-helix, the most common type of helix in naturally occurring proteins (see Chapter 11). Because the first and last residues in the chain are free to move, $n - 2$ residues form the compact helix and have restricted motion. Based on these ideas, the molar Gibbs energy of unfolding of a polypeptide with $n \geq 5$ may be written as

$$\Delta G_m = (n-4)\Delta_{hb}H_m - (n-2)T\Delta_{hb}S_m$$

where $\Delta_{hb}H_m$ and $\Delta_{hb}S_m$ are, respectively, the molar enthalpy and entropy of dissociation of hydrogen bonds in the polypeptide. **(a)** Justify the form of the equation for the Gibbs energy of unfolding. That is, why are the enthalpy and entropy terms written as $(n-4)\Delta_{hb}H_m$ and $(n-2)\Delta_{hb}S_m$, respectively? **(b)** Show that T_m may be written as

$$T_m = \frac{(n-4)\Delta_{hb}H_m}{(n-2)\Delta_{hb}S_m}$$

(c) Plot $T_m/(\Delta_{hb}H_m/\Delta_{hb}S_m)$ for $5 \leq n \leq 20$. At what value of n does T_m change by less than 1% when n increases by one?

3.16 A thermodynamic treatment allows predictions of the stability of DNA. The table below lists the standard Gibbs energies, enthalpies, and entropies of formation at 298 K of short sequences of base pairs as two polynucleotide chains come together:

Sequence	5′–A–G ⋮ ⋮ 3′–T–C	5′–G–C ⋮ ⋮ 3′–C–G	5′–T–G ⋮ ⋮ 3′–A–C
$\Delta_{seq}G^\ominus$/(kJ mol^{-1})	−5.4	−10.5	−6.7
$\Delta_{seq}H^\ominus$/(kJ mol^{-1})	−25.5	−46.4	−31.0
$\Delta_{seq}S^\ominus$/(J K^{-1} mol^{-1})	−67.4	−118.8	−80.8

To estimate the standard Gibbs energy of formation of a double-stranded piece of DNA, $\Delta_{DNA}G^\ominus$, we sum the contributions from the formation of the sequences and add to that quantity the standard Gibbs energy of initiation of the process, which in the case treated in this exercise may be set equal to $\Delta_{init}G^\ominus = +7.5$ kJ mol^{-1}:

$$\Delta_{DNA}G^\ominus = \Delta_{init}G^\ominus + \sum \Delta_{seq}G^\ominus(\text{sequences})$$

Similar procedures lead to $\Delta_{DNA}H^\ominus$ and $\Delta_{DNA}S^\ominus$. **(a)** Provide a molecular explanation for the fact that $\Delta_{init}G^\ominus$ is positive and $\Delta_{seq}G^\ominus$ negative. **(b)** Estimate the standard Gibbs energy, enthalpy, and entropy changes for the following reaction:

5′–A–C–C–T–G–3′ + 5′–C–A–G–C–T– 3′ ⟶

5′–A–C–C–T–G–3′
⋮ ⋮ ⋮ ⋮ ⋮
3′–T–C–G–A–C–5′

(c) Estimate the "melting" temperature of the piece of DNA shown in part (b).

3.17 The vapor pressure of water at blood temperature is 47 Torr. What is the partial pressure of dry air in our lungs when the total pressure is 760 Torr?

3.18 A gas mixture being used to simulate the atmosphere of another planet consists of 320 mg of methane, 175 mg of argon, and 225 mg of nitrogen. The partial pressure of nitrogen at 300 K is 15.2 kPa. Calculate **(a)** the volume and **(b)** the total pressure of the mixture.

3.19 Calculate the mass of glucose you should use to prepare **(a)** 250.0 cm^3 of 0.112 M $C_6H_{12}O_6(aq)$, **(b)** 0.112 *m* $C_6H_{12}O_6(aq)$ using 250.0 g of water.

3.20 What is the mole fraction of alanine in 0.134 *m* $CH_3CH(NH_2)COOH(aq)$?

3.21 What mass of sucrose, $C_{12}H_{22}O_{11}$, should you dissolve in 100.0 g of water to obtain a solution in which the mole fraction of $C_{12}H_{22}O_{11}$ is 0.124?

3.22 Calculate **(a)** the (molar) Gibbs energy of mixing, **(b)** the (molar) entropy of mixing when the two major components of air (nitrogen and oxygen) are mixed to form air. The mole fractions of N_2 and O_2 are 0.78 and 0.22, respectively. Is the mixing spontaneous?

3.23 Suppose now that argon is added to the mixture in Exercise 3.22 to bring the composition closer to real air, with mole fractions 0.780, 0.210, and 0.0096, respectively. What is the additional change in molar Gibbs energy and entropy? Is the mixing spontaneous?

3.24 Estimate the vapor pressure of seawater at 20°C given that the vapor pressure of pure water is 2.338 kPa at that temperature and the solute is largely Na^+ and Cl^- ions, each present at about 0.50 mol dm^{-3}.

3.25 Hemoglobin, the red blood protein responsible for oxygen transport, binds about 1.34 cm^3 of oxygen per gram. Normal blood has a hemoglobin concentration of 150 g L^{-1}. Hemoglobin in the lungs is about 97% saturated with oxygen but in the capillary is only about 75% saturated. What volume of oxygen is given up by 100 cm^3 of blood flowing from the lungs in the capillary?

3.26 In scuba diving (where *scuba* is an acronym formed from "self-contained underwater breathing apparatus"), air is supplied at a higher pressure so that the pressure within the diver's chest matches the pressure exerted by the surrounding water. The latter increases by about 1 atm for each 10 m of descent. One unfortunate consequence of breathing air at high pressures is that nitrogen is much more soluble in fatty tissues than in water, so it tends to dissolve in the central nervous system, bone marrow, and fat reserves. The result is *nitrogen narcosis*, with symptoms like intoxication. If the diver rises too rapidly to the surface, the nitrogen comes out of its lipid solution as bubbles, which causes the painful and sometimes fatal condition known as *the bends*. Many cases of scuba drowning appear to be consequences of arterial embolisms (obstructions in arteries caused by gas bubbles) and loss of consciousness as the air bubbles rise into the head. The Henry's law constant in the form $c = Kp$ for the solubility of nitrogen is 0.18 μg/(g H_2O atm). **(a)** What mass of nitrogen is dissolved in 100 g of water saturated with air at 4.0 atm and 20°C? Compare your answer to that for 100 g of water saturated with air at 1.0 atm. (Air is 78.08 mole percent N_2.) **(b)** If nitrogen is four times as soluble in fatty tissues as in water, what is the increase in nitrogen concentration in fatty tissue in going from 1 atm to 4 atm?

3.27 Calculate the concentration of carbon dioxide in fat given that the Henry's law constant is 8.6×10^4 Torr and the partial pressure of carbon dioxide is 55 kPa.

3.28 The rise in atmospheric carbon dioxide results in higher concentrations of dissolved carbon dioxide in natural waters. Use Henry's law and the data in Table 3.2 to calculate the solubility of CO_2 in water at 25°C when its partial pressure is **(a)** 4.0 kPa, **(b)** 100 kPa.

3.29 The mole fractions of N_2 and O_2 in air at sea level are approximately 0.78 and 0.21. Calculate the molalities of the solution formed in an open flask of water at 25°C.

3.30 Estimate the freezing point of 150 cm^3 of water sweetened with 7.5 g of sucrose.

3.31 A compound A existed in equilibrium with its dimer, A_2, in an aqueous solution. Derive an expression for the equilibrium constant $K = [A_2]/[A]^2$ in terms of the depression in vapor pressure caused by a given concentration of compound. (*Hint:* Suppose that a fraction *f* of the A molecules are present as the dimer. The depression of vapor pressure is proportional to the total concentration of A and A_2 molecules regardless of their chemical identities.)

3.32 The osmotic pressure of an aqueous solution of urea at 300 K is 120 kPa. Calculate the freezing point of the same solution.

3.33 The molar mass of an enzyme was determined by dissolving it in water, measuring the osmotic pressure at 20°C and extrapolating the data to

zero concentration. The following data were used:

c/(mg cm^{-3})	3.221	4.618	5.112	6.722
h/cm	5.746	8.238	9.119	11.990

Calculate the molar mass of the enzyme. *Hint:* Begin by expressing eqn 3.26 in terms of the height of the solution by using $\Pi = \rho g h$; take $\rho = 1.000$ g cm^{-3}.

3.34 An investigation similar to that described in *Example* 3.5 of the composition of the solutions used to study the osmotic pressure due to a polyelectrolyte with $\nu = 20$ showed that at equilibrium, the concentrations corresponded to $[Cl^-] = 0.020$ mol L^{-1}. Calculate the osmotic virial coefficient B for $\nu = 20$.

Projects

3.35 As in the discussion of pure substances, the phase diagram of a mixture shows which phase is most stable for the given conditions. However, composition is now a variable in addition to the pressure and temperature. Phase equilibria in binary mixtures may be explored by collecting data at constant pressure and displaying the results as a *temperature-composition diagram*, in which one axis is the temperature and the other axis is the mole fraction.

(a) Use the phase rule described in *Further information* 3.1 to justify the statement that in a temperature-composition diagram for a binary mixture, two-phase equilibria define a line and a three-phase equilibrium is represented by a point.

(b) Denaturation may be brought about by treatment with substances, called *denaturants*, that disrupt the intermolecular interactions responsible for the native three-dimensional conformation of a biological macromolecule. For example, urea, $CO(NH_2)_2$, competes for NH and CO groups and interferes with hydrogen bonding in a polypeptide. In a theoretical study of a protein, the temperature-composition diagram shown in Fig. 3.38 was obtained. It shows three structural regions: the native form, the unfolded form, and a "molten globule" form, a partially unfolded but still compact form of the protein. **(i)** Is the molten globule form ever stable when the denaturant concentration is below 0.1? **(ii)** Describe what happens to the polymer as the native form is heated in the presence of denaturant at concentration 0.15.

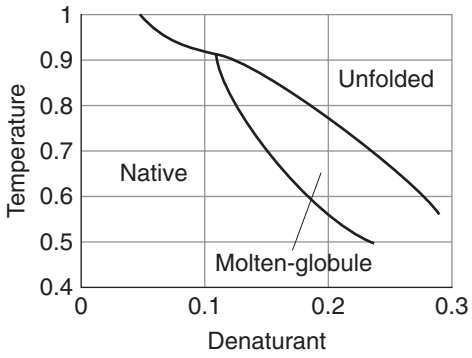


Fig. 3.38

(c) In an experimental study of membrane-like assemblies, a phase diagram like that shown in Fig. 3.39 was obtained. The two components are dielaidoylphosphatidylcholine (DEL) and dipalmitoylphosphatidylcholine (DPL). Explain what happens as a liquid mixture of composition $x_{DEL} = 0.5$ is cooled from 45°C.

3.36 Dialysis may also be used to study the binding of small molecules to macromolecules, such as an inhibitor to an enzyme, an antibiotic to DNA, and any other instance of cooperation or inhibition by small molecules attaching to large

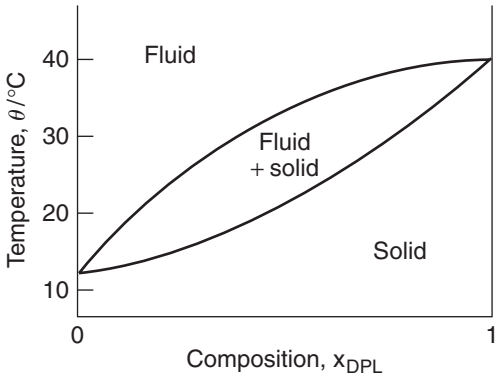


Fig. 3.39

ones. To see how this is possible, suppose inside the dialysis bag the molar concentration of the macromolecule M is [M] and the total concentration of small molecule A is $[A]_{in}$. This total concentration is the sum of the concentrations of free A and bound A, which we write $[A]_{free}$ and $[A]_{bound}$, respectively. At equilibrium, $\mu_{A,free} = \mu_{A,out}$, which implies that $[A]_{free} = [A]_{out}$, provided the activity coefficient of A is the same in both solutions. Therefore, by measuring the concentration of A in the solution outside the bag, we can find the concentration of unbound A in the macromolecule solution and, from the difference $[A]_{in} - [A]_{free} = [A]_{in} - [A]_{out}$, the concentration of bound A. Now we explore the quantitative consequences of the experimental arrangement just described.

(a) The average number of A molecules bound to M molecules, ν, is

$$\nu = \frac{[A]_{bound}}{[M]} = \frac{[A]_{in} - [A]_{out}}{[M]}$$

The bound and unbound A molecules are in equilibrium, $M + A \rightleftharpoons MA$. Recall from introductory chemistry that we may write the equilibrium constant for binding, K, as

$$K = \frac{[MA]}{[M]_{free}[A]_{free}}$$

Now show that

$$K = \frac{\nu}{(1 - \nu)[A]_{out}}$$

(b) If there are N *identical* and *independent* binding sites on each macromolecule, each macromolecule behaves like N separate smaller macromolecules, with the same value of K for each site. It follows that the average number of A molecules per site is ν/N. Show that, in this case, we may write the *Scatchard equation*:

$$\frac{\nu}{[A]_{out}} = KN - K\nu$$

(c) The Scatchard equation implies that a plot of $\nu/[A]_{out}$ against ν should be a straight line of slope $-K$ and intercept KN at $\nu = 0$. To apply the Scatchard equation, consider the binding of ethidium bromide (EB) to a short piece of DNA by a process called *intercalation*, in which the aromatic ethidium cation fits between two adjacent DNA base pairs. A 1.00×10^{-6} mol L^{-1} aqueous solution of the DNA sample was dialyzed against an excess of EB. The following data were obtained for the total concentration of EB:

[EB]/(μmol L^{-1})					
Side without DNA	0.042	0.092	0.204	0.526	1.150
Side with DNA	0.292	0.590	1.204	2.531	4.150

From these data, make a Scatchard plot and evaluate the equilibrium constant, K, and total number of sites per DNA molecule. Is the identical and independent sites model for binding applicable?

(d) For nonidentical independent binding sites, the Scatchard equation is

$$\frac{\nu}{[A]_{out}} = \sum_i \frac{N_i K_i}{1 + K_i[A]_{out}}$$

Plot $\nu/[A]$ for the following cases. **(a)** There are four independent sites on an enzyme molecule and the equilibrium constant is $K = 1.0 \times 10^7$. **(b)** There are a total of six sites per enzyme molecule. Four of the sites are identical and have an equilibrium constant of 1×10^5. The binding constants for the other two sites are 2×10^6.

CHAPTER

4

Chemical Equilibrium

Now we arrive at the point where real chemistry begins. Chemical thermodynamics is used to predict whether a mixture of reactants has a spontaneous tendency to change into products, to predict the composition of the reaction mixture at equilibrium, and to predict how that composition will be modified by changing the conditions. In biology, life is the avoidance of equilibrium, and the attainment of equilibrium is death, but knowing whether equilibrium lies in favor of reactants or products under certain conditions is a good indication of the feasibility of a biochemical reaction. Indeed, the material we cover in this chapter is of crucial importance for understanding the mechanisms of oxygen transport in blood, metabolism, and all the processes going on inside organisms.

There is one word of warning that is essential to remember: *thermodynamics is silent about the rates of reaction*. All it can do is to identify whether a particular reaction mixture has a tendency to form products; it cannot say whether that tendency will ever be realized. We explore what determines the rates of chemical reactions in Chapters 6 through 8.

Thermodynamic background

The thermodynamic criterion for spontaneous change at constant temperature and pressure is $\Delta G < 0$. The principal idea behind this chapter, therefore, is that, *at constant temperature and pressure, a reaction mixture tends to adjust its composition until its Gibbs energy is a minimum*. If the Gibbs energy of a mixture varies as shown in Fig. 4.1a, very little of the reactants convert into products before G has reached its minimum value, and the reaction "does not go." If G varies as shown in Fig. 4.1c, then a high proportion of products must form before G reaches its minimum and the reaction "goes." In many cases, the equilibrium mixture contains almost no reactants or almost no products. Many reactions have a Gibbs energy that varies as shown in Fig. 4.1b, and at equilibrium the reaction mixture contains substantial amounts of both reactants and products.

4.1 The reaction Gibbs energy

To explore metabolic processes, we need a measure of the driving power of a chemical reaction, and to understand the chemical composition of cells, we need to know what those compositions would be if the reactions taking place in them had reached equilibrium.

To keep our ideas in focus, we consider two important processes. One is the isomerism of glucose-6-phosphate (**1**, G6P) to fructose-6-phosphate (**2**, F6P), which is an early step in the anaerobic breakdown of glucose (Section 4.8):

$$\mathrm{G6P(aq)} \rightleftharpoons \mathrm{F6P(aq)} \qquad \textbf{(A)}$$

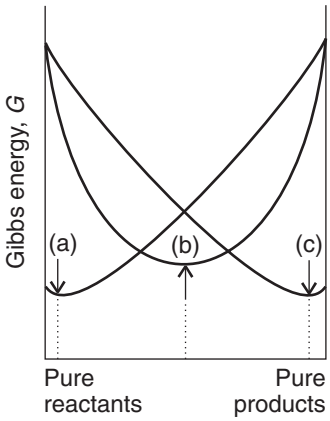
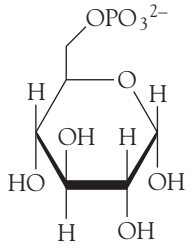
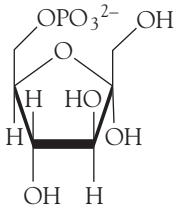


Fig. 4.1 The variation of Gibbs energy of a reaction mixture with progress of the reaction, pure reactants on the left and pure products on the right. (a) This reaction "does not go": the minimum in the Gibbs energy occurs very close to the reactants. (b) This reaction reaches equilibrium with approximately equal amounts of reactants and products present in the mixture. (c) This reaction goes almost to completion, as the minimum in Gibbs energy lies very close to pure products.



1 Glucose-6-phosphate



2 Fructose-6-phosphate

The second is the binding of $O_2(g)$ to the protein hemoglobin, Hb, in blood (*Case study* 4.1):

$$\mathrm{Hb(aq) + 4\,O_2(g) \rightleftharpoons Hb(O_2)_4(aq)} \qquad \textbf{(B)}$$

These two reactions are specific examples of a general reaction of the form

$$a\,\mathrm{A} + b\,\mathrm{B} \rightleftharpoons c\,\mathrm{C} + d\,\mathrm{D} \qquad \textbf{(C)}$$

with arbitrary physical states.

First, consider reaction A. Suppose that in a short interval while the reaction is in progress, the amount of G6P changes infinitesimally by $-\mathrm{d}n$. As a result of this change in amount, the contribution of G6P to the total Gibbs energy of the system changes by $-\mu_{\mathrm{G6P}}\mathrm{d}n$, where μ_{G6P} is the chemical potential (the partial molar Gibbs energy) of G6P in the reaction mixture. In the same interval, the amount of F6P changes by $+\mathrm{d}n$, so its contribution to the total Gibbs energy changes by $+\mu_{\mathrm{F6P}}\mathrm{d}n$, where μ_{F6P} is the chemical potential of F6P. The change in Gibbs energy of the system is

$$\mathrm{d}G = \mu_{\mathrm{F6P}}\mathrm{d}n - \mu_{\mathrm{G6P}}\mathrm{d}n$$

On dividing through by $\mathrm{d}n$, we obtain the **reaction Gibbs energy**, $\Delta_{\mathrm{r}}G$:

$$\frac{\mathrm{d}G}{\mathrm{d}n} = \mu_{\mathrm{F6P}} - \mu_{\mathrm{G6P}} = \Delta_{\mathrm{r}}G \qquad \textbf{(4.1a)}$$

There are two ways to interpret $\Delta_{\mathrm{r}}G$. First, it is the difference of the chemical potentials of the products and reactants *at the composition of the reaction mixture*. Second, we can think of $\Delta_{\mathrm{r}}G$ as the derivative of G with respect to n, or the slope of the graph of G plotted against the changing composition of the system (Fig. 4.2).

The binding of oxygen to hemoglobin provides a slightly more complicated example. If the amount of Hb changes by $-\mathrm{d}n$, then from the reaction stoichiometry we know that the change in the amount of O_2 will be $-4\mathrm{d}n$ and the change in the amount of $Hb(O_2)_4$ will be $+\mathrm{d}n$. Each change contributes to the change in the total Gibbs energy of the mixture, and the overall change is

$$\begin{aligned}\Delta G &= \mu_{\mathrm{Hb(O_2)_4}} \times \mathrm{d}n - \mu_{\mathrm{Hb}} \times \mathrm{d}n - \mu_{\mathrm{O_2}} \times 4\mathrm{d}n \\ &= (\mu_{\mathrm{Hb(O_2)_4}} - \mu_{\mathrm{Hb}} - 4\mu_{\mathrm{O_2}})\mathrm{d}n\end{aligned}$$

where the μ_J are the chemical potentials of the species in the reaction mixture. In this case, therefore, the reaction Gibbs energy is

$$\Delta_r G = \frac{dG}{dn} = \mu_{Hb(O_2)_4} - (\mu_{Hb} + 4\mu_{O_2}) \quad \textbf{(4.1b)}$$

Note that each chemical potential is multiplied by the corresponding stoichiometric coefficient and that reactants are subtracted from products. For the general reaction C,

$$\Delta_r G = (c\mu_C + d\mu_D) - (a\mu_A + b\mu_B) \quad \textbf{(4.1c)}$$

The chemical potential of a substance depends on the composition of the mixture in which it is present and is high when its concentration or partial pressure is high. Therefore, $\Delta_r G$ changes as the composition changes (Fig. 4.3). Remember that $\Delta_r G$ is the *slope* of G plotted against composition. We see that $\Delta_r G < 0$ and the slope of G is negative (down from left to right) when the mixture is rich in the reactants A and B because μ_A and μ_B are then high. Conversely, $\Delta_r G > 0$ and the slope of G is positive (up from left to right) when the mixture is rich in the products C and D because μ_C and μ_D are then high. At compositions corresponding to $\Delta_r G < 0$ the reaction tends to form more products; where $\Delta_r G > 0$, the *reverse* reaction is spontaneous, and the products tend to decompose into reactants. Where $\Delta_r G = 0$ (at the minimum of the graph where the derivative is zero), the reaction has no tendency to form either products or reactants. In other words, the reaction is at equilibrium. That is, *the criterion for chemical equilibrium at constant temperature and pressure* is

$$\Delta_r G = 0 \quad \textbf{(4.2)}$$

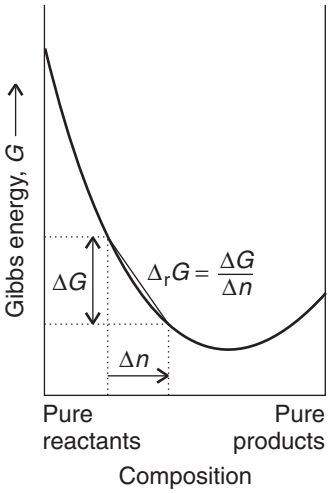


Fig. 4.2 The variation of Gibbs energy with progress of reaction showing how the reaction Gibbs energy, $\Delta_r G$, is related to the slope of the curve at a given composition. When ΔG and Δn are both infinitesimal, the slope is written dG/dn.

4.2 The variation of $\Delta_r G$ with composition

The reactants and products in a biological cell are rarely at equilibrium, so we need to know how the reaction Gibbs energy depends on their concentrations.

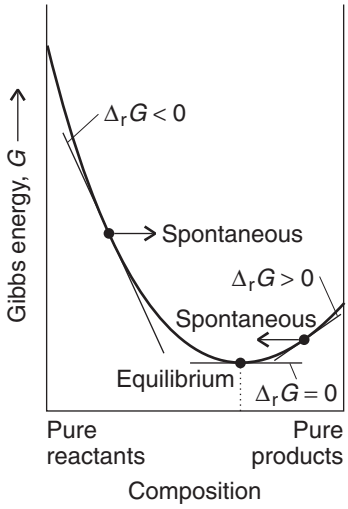


Fig. 4.3 At the minimum of the curve, corresponding to equilibrium, $\Delta_r G = 0$. To the left of the minimum, $\Delta_r G < 0$, and the forward reaction is spontaneous. To the right of the minimum, $\Delta_r G > 0$, and the reverse reaction is spontaneous.

Our starting point is the general expression for the composition dependence of the chemical potential derived in Section 3.11:

$$\mu_J = \mu_J^\ominus + RT \ln a_J \qquad \textbf{(4.3)}$$

where a_J is the activity of the species J. When we are dealing with systems that may be treated as ideal, which will be the case in this chapter, we use the identifications given in Table 3.3:

For solutes in an ideal solution, $a_J = [J]/c^\ominus$, the molar concentration of J relative to the standard value $c^\ominus = 1$ mol L^{-1}.

For perfect gases, $a_J = p_J/p^\ominus$, the partial pressure of J relative to the standard pressure $p^\ominus = 1$ bar.

For pure solids and liquids, $a_J = 1$.

As in Chapter 3, to simplify the appearance of expressions in what follows, we shall not write $c^\ominus$ and $p^\ominus$ explicitly.

Substitution of eqn 4.3 into eqn 4.1c gives

$$\begin{aligned}\Delta_r G &= \{c(\mu_C^\ominus + RT \ln a_C) + d(\mu_D^\ominus + RT \ln a_D)\} \\ &\quad - \{a(\mu_A^\ominus + RT \ln a_A) + b(\mu_B^\ominus + RT \ln a_B)\} \\ &= \{(c\mu_C^\ominus + d\mu_D^\ominus) - (a\mu_A^\ominus + b\mu_B^\ominus)\} \\ &\quad + RT\{c \ln a_C + d \ln a_D - a \ln a_A - b \ln a_B\}\end{aligned}$$

The first term on the right in the second equality is the **standard reaction Gibbs energy**, $\Delta_r G^\ominus$:

$$\Delta_r G^\ominus = \{c\mu_C^\ominus + d\mu_D^\ominus\} - \{a\mu_A^\ominus + b\mu_B^\ominus\} \qquad \textbf{(4.4a)}$$

Because the standard states refer to the pure materials, the standard chemical potentials in this expression are the standard molar Gibbs energies of the (pure) species. Therefore, eqn 4.4a is the same as

$$\Delta_r G^\ominus = \{cG_m^\ominus(C) + dG_m^\ominus(D)\} - \{aG_m^\ominus(A) + bG_m^\ominus(B)\} \qquad \textbf{(4.4b)}$$

We consider this important quantity in more detail shortly. At this stage, therefore, we know that

$$\Delta_r G = \Delta_r G^\ominus + RT\{c \ln a_C + d \ln a_D - a \ln a_A - b \ln a_B\}$$

and the expression for $\Delta_r G$ is beginning to look much simpler.

To make further progress, we rearrange the remaining terms on the right as follows:

$$\begin{aligned}c \ln a_C + d \ln a_D - a \ln a_A - b \ln a_B &\overset{a \ln x = \ln x^a}{=} \ln a_C^c + \ln a_D^d - \ln a_A^a - \ln a_B^b \\ &\overset{\ln x + \ln y = \ln xy}{=} \ln a_C^c a_D^d - \ln a_A^a a_B^b \\ &\overset{\ln x - \ln y = \ln x/y}{=} \ln \frac{a_C^c a_D^d}{a_A^a a_B^b}\end{aligned}$$

At this point, we have deduced that

$$\Delta_r G = \Delta_r G^{\ominus} + RT \ln \frac{a_C^c a_D^d}{a_A^a a_B^b}$$

To simplify the appearance of this expression still further, we introduce the (dimensionless) **reaction quotient**, Q, for reaction C:

$$Q = \frac{a_C^c a_D^d}{a_A^a a_B^b} \qquad \textbf{(4.5)}$$

Note that Q has the form of products divided by reactants, with the activity of each species raised to a power equal to its stoichiometric coefficient in the reaction. We can now write the overall expression for the reaction Gibbs energy at any composition of the reaction mixture as

$$\Delta_r G = \Delta_r G^{\ominus} + RT \ln Q \qquad \textbf{(4.6)}$$

This simple but hugely important equation will occur several times in different disguises.

EXAMPLE 4.1 Formulating a reaction quotient

Formulate the reaction quotients for reactions A (the isomerism of glucose-6-phosphate) and B (the binding of oxygen to hemoglobin).

Strategy Use Table 3.3 to express activities in terms of molar concentrations or pressures. Then use eqn 4.5 to write an expression for the reaction quotient Q. In reactions involving gases and solutes, the expression for Q will contain pressures and molar concentrations.

Solution The reaction quotient for reaction A is

$$Q = \frac{a_{F6P}}{a_{G6P}} = \frac{[F6P]/c^{\ominus}}{[G6P]/c^{\ominus}}$$

However, we are not writing the standard concentration explicitly, so this expression simplifies to

$$Q = \frac{[F6P]}{[G6P]}$$

with [J] the numerical value of the molar concentration of J in moles per liter (so if [F6P] = 2.0 mmol L^{-1}, corresponding to 2.0×10^{-3} mol L^{-1}, we just write [F6P] = 2.0×10^{-3} when using this expression). For reaction B, the binding of oxygen to hemoglobin, the reaction quotient is

$$Q = \frac{[Hb(O_2)_4]/c^{\ominus}}{([Hb]/c^{\ominus})(p_{O_2}/p^{\ominus})^4}$$

Similarly, because we are not writing the standard concentration and pressure explicitly, this expression simplifies to

$$Q = \frac{[Hb(O_2)_4]}{[Hb]p_{O_2}^4}$$

with p_J the numerical value of the partial pressure of J in bar (so if $p_{O_2} = 2.0$ bar, we just write $p_{O_2} = 2.0$ when using this expression).

SELF-TEST 4.1 Write the reaction quotient for the esterification reaction $CH_3COOH + C_2H_5OH \rightleftharpoons CH_3COOC_2H_5 + H_2O$. (All four components are present in the reaction mixture as liquids: the mixture is not an aqueous solution.)

Answer: $Q \approx [CH_3COOC_2H_5][H_2O]/[CH_3COOH][C_2H_5OH]$ ■

4.3 Reactions at equilibrium

We need to be able to identify the equilibrium composition of a reaction so that we can discuss deviations from equilibrium systematically.

At equilibrium, the reaction quotient has a certain value called the **equilibrium constant**, K, of the reaction:

$$K = \left(\frac{a_C^c a_D^d}{a_A^a a_B^b} \right)_{\text{equilibrium}} \quad \textbf{(4.7)}$$

We shall not normally write *equilibrium*; the context will always make it clear that Q refers to an *arbitrary* stage of the reaction, whereas K, the value of Q at equilibrium, is calculated from the equilibrium composition. It now follows from eqn 4.6 that at equilibrium

$$0 = \Delta_r G^\ominus + RT \ln K$$

and therefore that

$$\Delta_r G^\ominus = -RT \ln K \quad \textbf{(4.8)}$$

This is one of the most important equations in the whole of chemical thermodynamics. Its principal use is to predict the value of the equilibrium constant of any reaction from tables of thermodynamic data, like those in the *Data section*. Alternatively, we can use it to determine $\Delta_r G^\ominus$ by measuring the equilibrium constant of a reaction.

ILLUSTRATION 4.1 Calculating the equilibrium constant of a biochemical reaction

The first step in the metabolic breakdown of glucose is its phosphorylation to G6P:

$$\text{glucose(aq)} + P_i\text{(aq)} \longrightarrow \text{G6P(aq)}$$

where P_i denotes an inorganic phosphate group, such as $H_2PO_4^-$. The standard reaction Gibbs energy for the reaction is +14.0 kJ mol^{-1} at 37°C, so it follows from eqn 4.8 that

$$\ln K = -\frac{\Delta_r G^\ominus}{RT} = -\frac{1.40 \times 10^4 \text{ J mol}^{-1}}{(8.314\,47 \text{ J K}^{-1} \text{ mol}^{-1}) \times (310 \text{ K})}$$
$$= -\frac{1.40 \times 10^4}{8.314\,47 \times 310}$$

To calculate the equilibrium constant of the reaction, which (like the reaction quotient) is a dimensionless number, we use the relation $e^{\ln x} = x$ with $x = K$:

$$K = e^{-\frac{1.40 \times 10^4}{8.314\,47 \times 310}} = 4.4 \times 10^{-3}$$

A note on good practice: The exponential function (e^x) is very sensitive to the value of x, so evaluate it only at the end of a numerical calculation. ■

SELF-TEST 4.2 Calculate the equilibrium constant of the reaction $N_2(g) + 3\,H_2(g) \rightleftharpoons 2\,NH_3(g)$ at 25°C, given that $\Delta_r G^\ominus = -32.90$ kJ mol^{-1}.

Answer: 5.8×10^5

An important feature of eqn 4.8 is that it tells us that $K > 1$ if $\Delta_r G^\ominus < 0$. Broadly speaking, $K > 1$ implies that products are dominant at equilibrium, so we can conclude that *a reaction is thermodynamically feasible if* $\Delta_r G^\ominus < 0$ (Fig. 4.4). Conversely, because eqn 4.8 tells us that $K < 1$ if $\Delta_r G^\ominus > 0$, then we know that the reactants will be dominant in a reaction mixture at equilibrium if $\Delta_r G^\ominus > 0$. In other words, *a reaction with* $\Delta_r G^\ominus > 0$ *is not thermodynamically feasible*. Some care must be exercised with these rules, however, because the products will be significantly more abundant than reactants only if $K >> 1$ (more than about 10^3), and even a reaction with $K < 1$ may have a reasonable abundance of products at equilibrium.

Table 4.1 summarizes the conditions under which $\Delta_r G^\ominus < 0$ and $K > 1$. Because $\Delta_r G^\ominus = \Delta_r H^\ominus - T\Delta_r S^\ominus$, the standard reaction Gibbs energy is certainly negative if both $\Delta_r H^\ominus < 0$ (an exothermic reaction) and $\Delta_r S^\ominus > 0$ (a reaction system that becomes more disorderly, such as by forming a gas). The standard reaction Gibbs energy is also negative if the reaction is endothermic ($\Delta_r H^\ominus > 0$) and $T\Delta_r S^\ominus$ is sufficiently large and positive. Note that for an endothermic reaction to have $\Delta_r G^\ominus < 0$, its standard reaction entropy *must* be positive. Moreover, the temperature must be high enough for $T\Delta_r S^\ominus$ to be greater than $\Delta_r H^\ominus$ (Fig. 4.5). The switch of $\Delta_r G^\ominus$ from positive to negative, corresponding to the switch from $K < 1$ (the reaction "does not go") to $K > 1$ (the reaction "goes"), occurs at a temperature given by equating $\Delta_r H^\ominus - T\Delta_r S^\ominus$ to 0, which gives

$$T = \frac{\Delta_r H^\ominus}{\Delta_r S^\ominus} \qquad (4.9)$$

Table 4.1 Thermodynamic criteria of spontaneity

1. If the reaction is exothermic ($\Delta_r H^\ominus < 0$) and $\Delta_r S^\ominus > 0$	$\Delta_r G^\ominus < 0$ and $K > 1$ at all temperatures
2. If the reaction is exothermic ($\Delta_r H^\ominus < 0$) and $\Delta_r S^\ominus < 0$	$\Delta_r G^\ominus < 0$ and $K > 1$ provided that $T < \Delta_r H^\ominus/\Delta_r S^\ominus$
3. If the reaction is endothermic ($\Delta_r H^\ominus > 0$) and $\Delta_r S^\ominus > 0$	$\Delta_r G^\ominus < 0$ and $K > 1$ provided that $T > \Delta_r H^\ominus/\Delta_r S^\ominus$
4. If the reaction is endothermic ($\Delta_r H^\ominus > 0$) and $\Delta_r S^\ominus < 0$	$\Delta_r G^\ominus < 0$ and $K > 1$ at no temperature

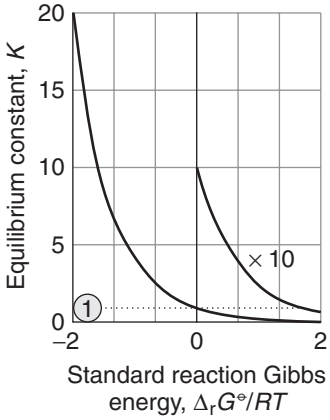


Fig. 4.4 The relation between standard reaction Gibbs energy and the equilibrium constant of the reaction. The curve labeled with "× 10" is magnified by a factor of 10.

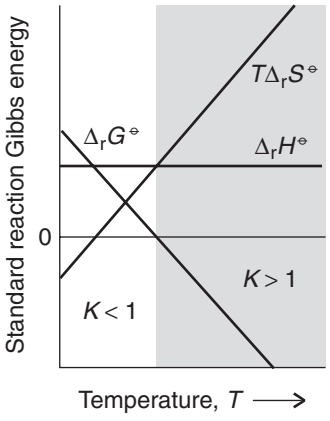


Fig. 4.5 An endothermic reaction may have $K > 1$ provided the temperature is high enough for $T\Delta_r S^\ominus$ to be large enough that, when subtracted from $\Delta_r H^\ominus$, the result is negative.

SELF-TEST 4.3 Calculate the decomposition temperature, the temperature at which the decomposition becomes spontaneous, of calcium carbonate given that $\Delta_r H^\ominus = +178$ kJ mol^{-1} and $\Delta_r S^\ominus = +161$ J K^{-1} mol^{-1} for the reaction $CaCO_3(s) \longrightarrow CaO(s) + CO_2(g)$.

Answer: 1.11×10^3 K

An equilibrium constant expresses the composition of an equilibrium mixture as a ratio of products of activities. Even if we confine our attention to ideal systems, it is still necessary to do some work to extract the actual equilibrium concentrations or partial pressures of the reactants and products given their initial values (see, for example, *Example* 4.5).

EXAMPLE 4.2 Calculating an equilibrium composition

Consider reaction A, for which $\Delta_r G^\ominus = +1.7$ kJ mol^{-1} at 25°C. Estimate the fraction f of F6P in equilibrium with G6P at 25°C, where f is defined as

$$f = \frac{[\text{F6P}]}{[\text{F6P}] + [\text{G6P}]}$$

Strategy Express f in terms of K. To do so, recognize that if the numerator and denominator in the expression for f are both divided by [G6P]; then the ratios [F6P]/[G6P] can be replaced by K. Calculate the value of K by using eqn 4.8.

Solution Division of the numerator and denominator by [G6P] gives

$$f = \frac{[\text{F6P}]/[\text{G6P}]}{([\text{F6P}]/[\text{G6P}]) + 1} = \frac{K}{K + 1}$$

We find the equilibrium constant by using $K = e^{\ln K}$ and rearranging eqn 4.8 into

$$K = e^{-\Delta_r G^\ominus/RT}$$

First, note that because $+1.7$ kJ mol^{-1} is the same as $+1.7 \times 10^3$ J mol^{-1},

$$\frac{\Delta_r G^\ominus}{RT} = \frac{1.7 \times 10^3 \text{ J mol}^{-1}}{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K})} = \frac{1.7 \times 10^3}{8.3145 \times 298}$$

Therefore,

$$K = e^{-\frac{1.7 \times 10^3}{8.3145 \times 298}} = 0.50$$

and

$$f = \frac{0.50}{1 + 0.50} = 0.33$$

That is, at equilibrium, 33% of the solute is F6P and 67% is G6P.

SELF-TEST 4.4 Estimate the composition of a solution in which two isomers A and B are in equilibrium (A $\rightleftharpoons$ B) at 37°C and $\Delta_r G^\ominus = -2.2$ kJ mol^{-1}.

Answer: The fraction of B at equilibrium is $f_{eq} = 0.30$. ■

CASE STUDY 4.1 Binding of oxygen to myoglobin and hemoglobin

Biochemical equilibria can be far more complex than those we have considered so far, but exactly the same principles apply. An example of a complex process is the binding of O_2 by hemoglobin in blood, which is described only approximately by reaction B. The protein myoglobin (Mb) stores O_2 in muscle, and the protein hemoglobin (Hb) transports O_2 in blood. These two proteins are related, for hemoglobin can be regarded, as a first approximation, as a tetramer of myoglobin (Fig. 4.6). There are, in fact, slight differences in the peptide sequence of the myoglobin-like components of hemoglobin, but we can ignore them at this stage. In each protein, the O_2 molecule attaches to an iron ion in a heme group (**3**). For our purposes here, we are concerned with the different equilibrium characteristics for the uptake of O_2 by myoglobin and hemoglobin.

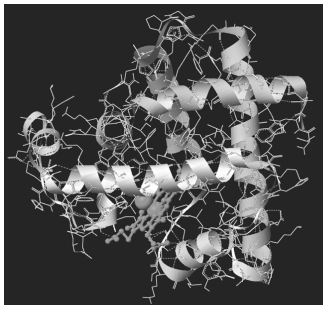


Fig. 4.6 One of the four polypeptide chains that make up the human hemoglobin molecule. The chains, which are similar to the oxygen storage protein myoglobin, consist of helical and sheet-like regions. The heme group is at the lower left.

First, consider the equilibrium between Mb and O_2:

$$\mathrm{Mb(aq) + O_2(g) \rightleftharpoons MbO_2(aq)} \qquad K = \frac{[\mathrm{MbO_2}]}{p[\mathrm{Mb}]}$$

where p is the numerical value of the partial pressure of O_2 gas in bar. It follows that the *fractional saturation*, s, the fraction of Mb molecules that are oxygenated, is

$$s = \frac{[\mathrm{MbO_2}]}{[\mathrm{Mb}]_{\mathrm{total}}} = \frac{[\mathrm{MbO_2}]}{[\mathrm{Mb}] + [\mathrm{MbO_2}]} = \frac{Kp}{1 + Kp}$$

The dependence of s on p is shown in Fig. 4.7.

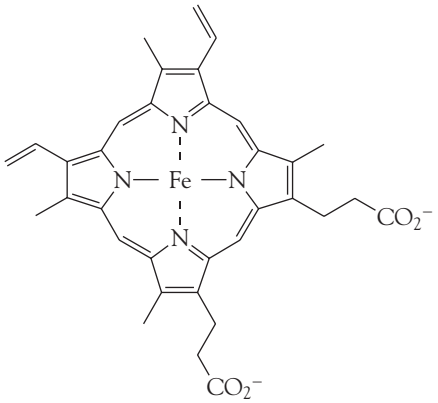
Now consider the equilibrium between Hb and O_2:

$$\mathrm{Hb(aq) + O_2(g) \rightleftharpoons HbO_2(aq)} \qquad K_1 = \frac{[\mathrm{HbO_2}]}{p[\mathrm{Hb}]}$$

$$\mathrm{HbO_2(aq) + O_2(g) \rightleftharpoons Hb(O_2)_2(aq)} \qquad K_2 = \frac{[\mathrm{Hb(O_2)_2}]}{p[\mathrm{HbO_2}]}$$

$$\mathrm{Hb(O_2)_2(aq) + O_2(g) \rightleftharpoons Hb(O_2)_3(aq)} \qquad K_3 = \frac{[\mathrm{Hb(O_2)_3}]}{p[\mathrm{Hb(O_2)_2}]}$$

$$\mathrm{Hb(O_2)_3(aq) + O_2(g) \rightleftharpoons Hb(O_2)_4(aq)} \qquad K_4 = \frac{[\mathrm{Hb(O_2)_4}]}{p[\mathrm{Hb(O_2)_3}]}$$



3 The heme group

To develop an expression for s, we express $[Hb(O_2)_2]$ in terms of $[HbO_2]$ by using K_2, then express $[HbO_2]$ in terms of [Hb] by using K_1, and likewise for all the other concentrations of $Hb(O_2)_3$ and $Hb(O_2)_4$. It follows that

$$[HbO_2] = K_1p[Hb] \qquad [Hb(O_2)_2] = K_1K_2p^2[Hb]$$
$$[Hb(O_2)_3] = K_1K_2K_3p^3[Hb] \qquad [Hb(O_2)_4] = K_1K_2K_3\,K_4p^4[Hb]$$

The total concentration of bound O_2 is

$$\begin{aligned}[O_2]_{bound} &= [HbO_2] + 2[Hb(O_2)_2] + 3[Hb(O_2)_3] + 4[Hb(O_2)_4] \\ &= (1 + 2K_2p + 3K_2K_3p^2 + 4K_2K_3K_4p^3)K_1p[Hb]\end{aligned}$$

where we have used the fact that n O_2 molecules are bound in $Hb(O_2)_n$, so the concentration of bound O_2 in $Hb(O_2)_2$ is $2[Hb(O_2)_2]$, and so on. The total concentration of hemoglobin is

$$[Hb]_{total} = (1 + K_1p + K_1K_2p^2 + K_1K_2K_3p^3 + K_1K_2K_3K_4p^4)[Hb]$$

Because each Hb molecule has four sites at which O_2 can attach, the fractional saturation is

$$s = \frac{[O_2]_{bound}}{4[Hb]_{total}} = \frac{(1 + 2K_2p + 3K_2K_3p^2 + 4K_2K_3K_4p^3)K_1p}{4(1 + K_1p + K_1K_2p^2 + K_1K_2K_3p^3 + K_1K_2K_3K_4p^4)}$$

A reasonable fit of the experimental data can be obtained with $K_1 = 0.01$, $K_2 = 0.02$, $K_3 = 0.04$, and $K_4 = 0.08$ when p is expressed in torr.

The binding of O_2 to hemoglobin is an example of **cooperative binding**, in which the binding of a ligand (in this case O_2) to a biopolymer (in this case Hb) becomes more favorable thermodynamically (that is, the equilibrium constant increases) as the number of bound ligands increases up to the maximum number of binding sites. We see the effect of cooperativity in Fig. 4.7. Unlike the myoglobin saturation curve, the hemoglobin saturation curve is *sigmoidal* (S shaped): the fractional saturation is small at low ligand concentrations, increases sharply at intermediate ligand concentrations, and then levels off at high ligand concentrations. Cooperative binding of O_2 by hemoglobin is explained by an **allosteric effect**, in

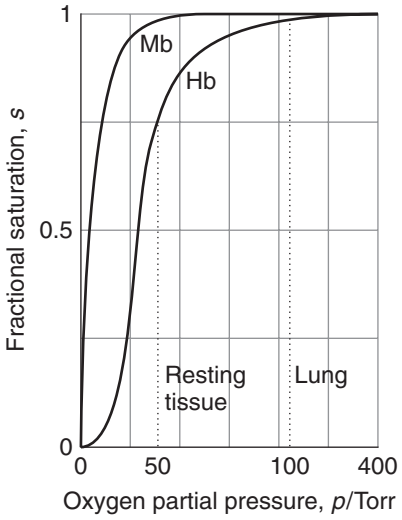


Fig. 4.7 The variation of the fractional saturation of myoglobin and hemoglobin molecules with the partial pressure of oxygen. The different shapes of the curves account for the different biological functions of the two proteins.

which an adjustment of the conformation of a molecule when one substrate binds affects the ease with which a subsequent substrate molecule binds. The details of the allosteric effect in hemoglobin will be explored in *Case study* 10.4.

The differing shapes of the saturation curves for myoglobin and hemoglobin have important consequences for the way O_2 is made available in the body: in particular, the greater sharpness of the Hb saturation curve means that Hb can load O_2 more fully in the lungs and unload it more fully in different regions of the organism. In the lungs, where $p \approx 105$ Torr (14 kPa), $s \approx 0.98$, representing almost complete saturation. In resting muscular tissue, p is equivalent to about 38 Torr (5 kPa), corresponding to $s \approx 0.75$, implying that sufficient O_2 is still available should a sudden surge of activity take place. If the local partial pressure falls to 22 Torr (3 kPa), s falls to about 0.1. Note that the steepest part of the curve falls in the range of typical tissue oxygen partial pressure. Myoglobin, on the other hand, begins to release O_2 only when p has fallen below about 22 Torr, so it acts as a reserve to be drawn on only when the Hb oxygen has been used up. ■

4.4 The standard reaction Gibbs energy

The standard reaction Gibbs energy is central to the discussion of chemical equilibria and the calculation of equilibrium constants. It is also a useful indicator of the energy available from catabolism to drive anabolic processes, such as the synthesis of proteins.

We have seen that standard reaction Gibbs energy, $\Delta_r G^\ominus$, is defined as the difference in standard molar Gibbs energies of the products and the reactants weighted by the stoichiometric coefficients, ν, in the chemical equation

$$\Delta_r G^\ominus = \sum \nu G_m^\ominus(\text{products}) - \sum \nu G_m^\ominus(\text{reactants}) \qquad \textbf{(4.10)}$$

For example, the standard reaction Gibbs energy for reaction A is the difference between the molar Gibbs energies of fructose-6-phosphate and glucose-6-phosphate in solution at 1 mol L^{-1} and 1 bar.

We cannot calculate $\Delta_r G^\ominus$ from the standard molar Gibbs energies themselves, because these quantities are not known. One practical approach is to calculate the standard reaction enthalpy from standard enthalpies of formation (Section 1.14), the standard reaction entropy from Third-Law entropies (Section 2.8), and then to combine the two quantities by using

$$\Delta_r G^\ominus = \Delta_r H^\ominus - T\Delta_r S^\ominus \qquad \textbf{(4.11)}$$

EXAMPLE 4.3 Calculating the standard reaction Gibbs energy of an enzyme-catalyzed reaction

Evaluate the standard reaction Gibbs energy at 25°C for the reaction $CO_2(g) + H_2O(l) \longrightarrow H_2CO_3(aq)$ catalyzed by the enzyme carbonic anhydrase in red blood cells.

Strategy Obtain the relevant standard enthalpies and entropies of formation from the *Data section*. Then calculate the standard reaction enthalpy and the standard reaction entropy from

$$\Delta_r H^\ominus = \sum \nu \Delta_f H^\ominus(\text{products}) - \sum \nu \Delta_f H^\ominus(\text{reactants})$$
$$\Delta_r S^\ominus = \sum \nu S_m^\ominus(\text{products}) - \sum \nu S_m^\ominus(\text{reactants})$$

and the standard reaction Gibbs energy from eqn 4.11.

Solution The standard reaction enthalpy is

$$\begin{aligned}\Delta_r H^\ominus &= \Delta_f H^\ominus(H_2CO_3, aq) - \{\Delta_f H^\ominus(CO_2, g) + \Delta_f H^\ominus(H_2O, l)\} \\ &= -699.65 \text{ kJ mol}^{-1} - \{(-110.53 \text{ kJ mol}^{-1}) + (-285.83 \text{ kJ mol}^{-1})\} \\ &= -303.29 \text{ kJ mol}^{-1}\end{aligned}$$

The standard reaction entropy was calculated in *Illustration* 2.4:

$$\Delta_r S^\ominus = -96.3 \text{ J K}^{-1} \text{ mol}^{-1}$$

which, because 96.3 J is the same as 9.63×10^{-2} kJ, corresponds to -9.63×10^{-2} kJ K^{-1} mol^{-1}. Therefore, from eqn 4.11,

$$\begin{aligned}\Delta_r G^\ominus &= (-303.29 \text{ kJ mol}^{-1}) - (298.15 \text{ K}) \times (-9.63 \times 10^{-2} \text{ kJ K}^{-1} \text{ mol}^{-1}) \\ &= -274.6 \text{ kJ mol}^{-1}\end{aligned}$$

SELF-TEST 4.5 Use the information in the *Data section* to determine the standard reaction Gibbs energy for $3\ O_2(g) \longrightarrow 2\ O_3(g)$ from standard enthalpies of formation and standard entropies.

Answer: $+326.4 \text{ kJ mol}^{-1}$ ■

We saw in Section 1.14 how to use standard enthalpies of formation of substances to calculate standard reaction enthalpies. We can use the same technique for standard reaction Gibbs energies. To do so, we list the **standard Gibbs energy of formation**, $\Delta_f G^\ominus$, of a substance, which is the standard reaction Gibbs energy (per mole of the species) for its formation from the elements in their reference states. The concept of reference state was introduced in Section 1.14; the temperature is arbitrary, but we shall almost always take it to be 25°C (298 K). For example, the standard Gibbs energy of formation of liquid water, $\Delta_f G^\ominus(H_2O, l)$, is the standard reaction Gibbs energy for

$$H_2(g) + \tfrac{1}{2}O_2(g) \longrightarrow H_2O(l)$$

and is -237 kJ mol^{-1} at 298 K. Some standard Gibbs energies of formation are listed in Table 4.2 and more can be found in the *Data section*. It follows from the definition that the standard Gibbs energy of formation of an element in its reference state is zero because reactions such as

$$C(s, \text{graphite}) \longrightarrow C(s, \text{graphite})$$

are null (that is, nothing happens). The standard Gibbs energy of formation of an element in a phase different from its reference state is nonzero:

$$C(s, \text{graphite}) \longrightarrow C(s, \text{diamond}) \qquad \Delta_f G^\ominus(C, \text{diamond}) = +2.90 \text{ kJ mol}^{-1}$$

Many of the values in the tables have been compiled by combining the standard enthalpy of formation of the species with the standard entropies of the compound and the elements, as illustrated above, but there are other sources of data and we encounter some of them later.

Table 4.2 Standard Gibbs energies of formation at 298.15 K*

Substance	$\Delta_f G^\ominus$/(kJ mol^{-1})
Gases	
Carbon dioxide, CO_2	−394.36
Methane, CH_4	−50.72
Nitrogen oxide, NO	+86.55
Water, H_2O	−228.57
Liquids	
Ethanol, CH_3CH_2OH	−174.78
Hydrogen peroxide, H_2O_2	−120.35
Water, H_2O	−237.13
Solids	
α-D-Glucose $C_6H_{12}O_6$	−917.2
Glycine, $CH_2(NH_2)COOH$	−532.9
Sucrose, $C_{12}H_{22}O_{11}$	−1543
Urea, $CO(NH_2)_2$	−197.33
Solutes in aqueous solution	
Carbon dioxide, CO_2	−385.98
Carbonic acid, H_2CO_3	−623.08
Phosphoric acid, H_3PO_4	−1018.7

*Additional values are given in the *Data section*.

Standard Gibbs energies of formation can be combined to obtain the standard Gibbs energy of almost any reaction. We use the now familiar expression

$$\Delta_r G^\ominus = \sum \nu \Delta_f G^\ominus(\text{products}) - \sum \nu \Delta_f G^\ominus(\text{reactants}) \qquad \textbf{(4.12)}$$

ILLUSTRATION 4.2 Calculating a standard reaction Gibbs energy from standard Gibbs energies of formation

To determine the standard reaction Gibbs energy for the complete oxidation of solid sucrose, $C_{12}H_{22}O_{11}(s)$, by oxygen gas to carbon dioxide gas and liquid water,

$$C_{12}H_{22}O_{11}(s) + 12\ O_2(g) \longrightarrow 12\ CO_2(g) + 11\ H_2O(l)$$

we carry out the following calculation:

$$\begin{aligned}\Delta_r G^\ominus &= \{12\Delta_f G^\ominus(CO_2, g) + 11\Delta_f G^\ominus(H_2O, l)\} \\ &\quad - \{\Delta_f G^\ominus(C_{12}H_{22}O_{11}, s) + 12\Delta_f G^\ominus(O_2, g)\} \\ &= \{12 \times (-394\ \text{kJ mol}^{-1}) + 11 \times (-237\ \text{kJ mol}^{-1})\} \\ &\quad - \{-1543\ \text{kJ mol}^{-1} + 0\} \\ &= -5.79 \times 10^3\ \text{kJ mol}^{-1}\ \blacksquare\end{aligned}$$

SELF-TEST 4.6 Calculate the standard reaction Gibbs energy of the oxidation of ammonia to nitric oxide according to the equation $4\ NH_3(g) + 5\ O_2(g) \longrightarrow 4\ NO(g) + 6\ H_2O(g)$.

Answer: $-959.42\ \text{kJ mol}^{-1}$

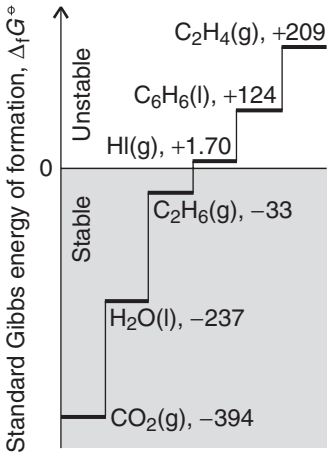


Fig. 4.8 The standard Gibbs energy of formation of a compound is like a measure of the compound's altitude above or below sea level: compounds that lie above sea level have a spontaneous tendency to decompose into the elements (and to revert to sea level). Compounds that lie below sea level are stable with respect to decomposition into the elements.

Standard Gibbs energies of formation of compounds have their own significance as well as being useful in calculations of K. They are a measure of the "thermodynamic altitude" of a compound above or below a "sea level" of stability represented by the elements in their reference states (Fig. 4.8). If the standard Gibbs energy of formation is positive and the compound lies above "sea level," then the compound has a spontaneous tendency to sink toward thermodynamic sea level and decompose into the elements. That is, $K < 1$ for their formation reaction. We say that a compound with $\Delta_f G^\ominus > 0$ is **thermodynamically unstable** with respect to its elements or that it is **endergonic**. Thus, the endergonic substance ozone, for which $\Delta_f G^\ominus = +163\ \text{kJ mol}^{-1}$, has a spontaneous tendency to decompose into oxygen under standard conditions at 25°C. More precisely, the equilibrium constant for the reaction $\frac{3}{2}\,O_2(g) \rightleftharpoons O_3(g)$ is less than 1 (much less, in fact: $K = 2.7 \times 10^{-29}$). However, although ozone is thermodynamically unstable, it can survive if the reactions that convert it into oxygen are slow. That is the case in the upper atmosphere, and the O_3 molecules in the ozone layer survive for long periods. Benzene ($\Delta_f G^\ominus = +124\ \text{kJ mol}^{-1}$) is also thermodynamically unstable with respect to its elements ($K = 1.8 \times 10^{-22}$). However, the fact that bottles of benzene are everyday laboratory commodities also reminds us of the point made at the start of the chapter, that *spontaneity is a thermodynamic tendency that might not be realized at a significant rate in practice*.

Another useful point that can be made about standard Gibbs energies of formation is that there is no point in searching for *direct* syntheses of a thermodynamically unstable compound from its elements (under standard conditions, at the temperature to which the data apply), because the reaction does not occur in the required direction: the *reverse* reaction, decomposition, is spontaneous. Endergonic compounds must be synthesized by alternative routes or under conditions for which their Gibbs energy of formation is negative and they lie beneath thermodynamic sea level.

Compounds with $\Delta_f G^\ominus < 0$ (corresponding to $K > 1$ for their formation reactions) are said to be **thermodynamically stable** with respect to their elements or **exergonic**. Exergonic compounds lie below the thermodynamic sea level of the elements (under standard conditions). An example is the exergonic compound ethane, with $\Delta_f G^\ominus = -33\ \text{kJ mol}^{-1}$: the negative sign shows that the formation of ethane gas is spontaneous in the sense that $K > 1$ (in fact, $K = 7.1 \times 10^5$ at 25°C).

The response of equilibria to the conditions

In introductory chemistry, we meet the empirical rule of thumb known as **Le Chatelier's principle**:

> When a system at equilibrium is subjected to a disturbance, the composition of the system adjusts so as to tend to minimize the effect of the disturbance.

Le Chatelier's principle is only a rule of thumb, and to understand why reactions respond as they do and to calculate the new equilibrium composition, we need to use thermodynamics. We need to keep in mind that some changes in conditions affect the value of $\Delta_r G^\ominus$ and therefore of K (temperature is the only instance), whereas others change the consequences of K having a particular fixed value without changing the value of K (the pressure, for instance).

4.5 The presence of a catalyst

Enzymes are biological versions of catalysts and are so ubiquitous that we need to know how their action affects chemical equilibria.

We study the action of catalysts (a substance that accelerates a reaction without itself appearing in the overall chemical equation) in Chapter 8 and at this stage do not need to know in detail how they work other than that they provide an alternative, faster route from reactants to products. Although the new route from reactants to products is faster, the initial reactants and the final products are the same. The quantity $\Delta_r G^\ominus$ is defined as the difference of the standard molar Gibbs energies of the reactants and products, so it is independent of the path linking the two. It follows that an alternative pathway between reactants and products leaves $\Delta_r G^\ominus$ and therefore K unchanged. That is, *the presence of a catalyst does not change the equilibrium constant of a reaction*.

4.6 The effect of temperature

In organisms, biochemical reactions occur over a very narrow range of temperatures, and changes by only a few degrees can have serious consequences, including death. Therefore, it is important to know how changes in temperature, such as those brought about by infections, affect biological processes.

According to Le Chatelier's principle, we can expect a reaction to respond to a lowering of temperature by releasing heat and to respond to an increase of temperature by absorbing heat. That is:

> When the temperature is raised, the equilibrium composition of an exothermic reaction will tend to shift toward reactants; the equilibrium composition of an endothermic reaction will tend to shift toward products.

In each case, the response tends to minimize the effect of raising the temperature. But *why* do reactions at equilibrium respond in this way? Le Chatelier's principle is only a rule of thumb and gives no clue to the reason for this behavior. As we shall now see, the origin of the effect is the dependence of $\Delta_r G^\ominus$, and therefore of K, on the temperature.

First, we consider the effect of temperature on $\Delta_r G^\ominus$. We use the relation $\Delta_r G^\ominus = \Delta_r H^\ominus - T\Delta_r S^\ominus$ and make the assumption that neither the reaction enthalpy nor the reaction entropy varies much with temperature (over small ranges, at least). It follows that

$$\text{Change in } \Delta_r G^\ominus = -(\text{change in } T) \times \Delta_r S^\ominus \qquad \textbf{(4.13)}$$

This expression is easy to apply when there is a consumption or formation of gas because, as we have seen (Section 2.8), gas formation dominates the sign of the reaction entropy.

Now consider the effect of temperature on K itself. At first, this problem looks troublesome, because both T and $\Delta_r G^\ominus$ appear in the expression for K. However, in fact the effect of temperature can be expressed very simply as the **van 't Hoff equation**.[1]

$$\ln K' - \ln K = \frac{\Delta_r H^\ominus}{R}\left(\frac{1}{T} - \frac{1}{T'}\right) \qquad \textbf{(4.14)}$$

[1]There are several "van 't Hoff equations." To distinguish them, this one is sometimes called the *van 't Hoff isochore*.

where K is the equilibrium constant at the temperature T and K' is its value when the temperature is T'. All we need to know to calculate the temperature dependence of an equilibrium constant, therefore, is the standard reaction enthalpy.

DERIVATION 4.1 The van 't Hoff equation

As before, we use the approximation that the standard reaction enthalpy and entropy are independent of temperature over the range of interest, so the entire temperature dependence of $\Delta_r G^\ominus$ stems from the T in $\Delta_r G^\ominus = \Delta_r H^\ominus - T\Delta_r S^\ominus$. At a temperature T,

$$\ln K = -\frac{\Delta_r G^\ominus}{RT} \overset{\text{Substitute } \Delta_r G^\ominus = \Delta_r H^\ominus - T\Delta_r S^\ominus}{=} -\frac{\Delta_r H^\ominus}{RT} + \frac{\Delta_r S^\ominus}{R}$$

At another temperature T', when $\Delta_r G^{\ominus\prime} = \Delta_r H^\ominus - T'\Delta_r S^\ominus$ and the equilibrium constant is K', a similar expression holds:

$$\ln K' = -\frac{\Delta_r H^\ominus}{RT'} + \frac{\Delta_r S^\ominus}{R}$$

The difference between the two is

$$\ln K' - \ln K = \frac{\Delta_r H^\ominus}{R}\left(\frac{1}{T} - \frac{1}{T'}\right)$$

which is the van 't Hoff equation.

Let's explore the information in the van 't Hoff equation. Consider the case when $T' > T$. Then the term in parentheses in eqn 4.14 is positive. If $\Delta_r H^\ominus > 0$, corresponding to an endothermic reaction, the entire term on the right is positive. In this case, therefore, $\ln K' > \ln K$. That being so, we conclude that $K' > K$ for an endothermic reaction. In general, *the equilibrium constant of an endothermic reaction increases with temperature*. The opposite is true when $\Delta_r H^\ominus < 0$, so we can conclude that *the equilibrium constant of an exothermic reaction decreases with an increase in temperature*.

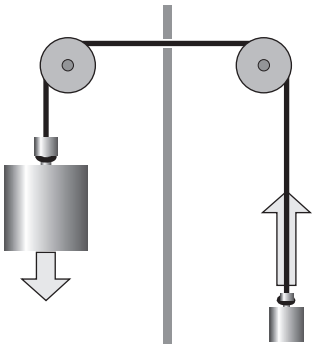
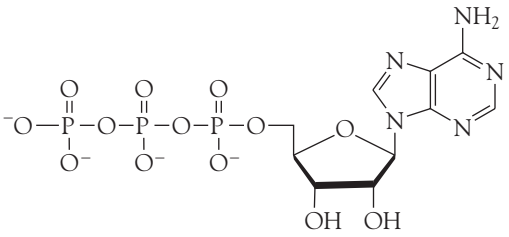


Fig. 4.9 If two weights are coupled as shown here, then the heavier weight will move the lighter weight in its non-spontaneous direction: overall, the process is still spontaneous. The weights are the analogues of two chemical reactions: a reaction with a large negative ΔG can force another reaction with a smaller ΔG to run in its non-spontaneous direction.

Coupled reactions in bioenergetics

A non-spontaneous reaction may be driven by coupling it to a reaction that is spontaneous. A simple mechanical analogy is a pair of weights joined by a string (Fig. 4.9): the lighter of the pair of weights will be pulled up as the heavier weight falls down. Although the lighter weight has a natural tendency to move downward, its coupling to the heavier weight results in it being raised. The thermodynamic analogue is an **endergonic reaction**, a reaction with a positive Gibbs energy, $\Delta_r G$ (the analogue of the lighter weight moving up), being forced to occur by coupling it to an **exergonic reaction**, a reaction with a negative Gibbs energy, $\Delta_r G'$ (the analogue of the heavier weight falling down). The overall reaction is spontaneous because the sum $\Delta_r G + \Delta_r G'$ is negative. The whole of life's activities depend on



4 ATP

couplings of this kind, for the oxidation reactions of food act as the heavy weights that drive other reactions forward and result in the formation of proteins from amino acids, the actions of muscles for propulsion, and even the activities of the brain for reflection, learning, and imagination.

4.7 The function of adenosine triphosphate

The compound adenosine triphosphate is of central importance in bioenergetics, and it is essential to understand its thermodynamic role.

The function of adenosine triphosphate, ATP^{4-}(**4**) or (more succinctly) ATP, is to store the energy made available when food is oxidized and then to supply it on demand to a wide variety of processes, including muscular contraction, reproduction, and vision. We saw in *Case study* 2.2 that the essence of ATP's action is its ability to lose its terminal phosphate group by hydrolysis and to form adenosine diphosphate, ADP^{3-} (**5**):

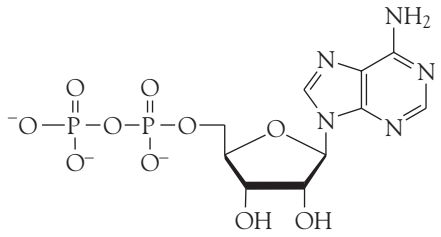
$$ATP^{4-}(aq) + H_2O(l) \longrightarrow ADP^{3-}(aq) + HPO_4^{2-}(aq) + H_3O^+(aq)$$

This reaction is exergonic under the conditions prevailing in cells and can drive an endergonic reaction forward if suitable enzymes are available to couple the reactions.

Before discussing the hydrolysis of ATP quantitatively, we need to note that the conventional standard state of hydrogen ions ($a_{H_3O^+} = 1$, corresponding to pH = 0, a strongly acidic solution) is not appropriate to normal biological conditions inside cells, where the pH is close to 7. Therefore, in biochemistry it is common to adopt the **biological standard state**, in which pH = 7, a neutral solution. We shall adopt this convention in this section and label the corresponding standard quantities as $G^{\oplus}$, $H^{\oplus}$, and $S^{\oplus}$.[2]

COMMENT 4.1 Recall that the hydronium ion concentration is commonly expressed in terms of the pH, which is defined as pH = $-\log a_{H_3O^+}$. In elementary work, we replace the hydronium ion activity by the numerical value of its molar concentration, $[H_3O^+]$. For more details, see Section 4.9. ■

[2]Another convention to denote the biological standard state is to write $X°'$ or $X^{\ominus\prime}$.



5 ADP

EXAMPLE 4.4 Converting between thermodynamic and biological standard states

The standard reaction Gibbs energy for the hydrolysis of ATP is +10 kJ mol^{-1} at 298 K. What is the biological standard state value?

Strategy Because protons occur as products, lowering their concentration (from 1 mol L^{-1} to 10^{-7} mol L^{-1}) suggests that the reaction will have a higher tendency to form products. Therefore, we expect a more negative value of the reaction Gibbs energy for the biological standard than for the thermodynamic standard. The two types of standard are related by eqn 4.6, with the activity of hydrogen ions 10^{-7} in place of 1.

Solution The reaction quotient for the hydrolysis reaction when all the species are in their standard states except the hydrogen ions, which are present at 10^{-7} mol L^{-1}, is

$$Q = \frac{a_{ADP^{3-}} a_{HPO_4^{2-}} a_{H_3O^+}}{a_{ATP^{4-}} a_{H_2O}} = \frac{1 \times 1 \times 10^{-7}}{1 \times 1} = 1 \times 10^{-7}$$

The thermodynamic and biological standard values are therefore related by eqn 4.6 in the form

$$\begin{aligned}\Delta_r G^{\oplus} &= \Delta_r G^{\ominus} + (8.314\ 47 \times 10^{-3}\ \text{J K}^{-1}\ \text{mol}^{-1}) \times (298\ \text{K}) \times \ln(1 \times 10^{-7}) \\ &= 10\ \text{kJ mol}^{-1} - 40\ \text{kJ mol}^{-1} = -30\ \text{kJ mol}^{-1}\end{aligned}$$

Note how the large change in pH changes the sign of the standard reaction Gibbs energy.

SELF-TEST 4.7 The overall reaction for the glycolysis reaction (Section 4.8) is $C_6H_{12}O_6(aq) + 2\ NAD^+(aq) + 2\ ADP^{3-}(aq) + 2\ HPO_4^{2-}(aq) + 2\ H_2O(l) \longrightarrow 2\ CH_3COCO_2^-(aq) + 2\ NADH(aq) + 2\ ATP^{4-}(aq) + 2\ H_3O^+(aq)$. For this reaction, $\Delta_r G^{\oplus} = -80.6$ kJ mol^{-1} at 298 K. What is the value of $\Delta_r G^{\ominus}$?

Answer: -0.7 kJ mol^{-1} ■

For a reaction of the form

$$\text{Reactants} + \nu\ H_3O^+(aq) \longrightarrow \text{products}$$

the biological and thermodynamic standard states are related by

$$\Delta_r G^{\oplus} = \Delta_r G^{\ominus} - \nu RT \times \ln 10^{-7} = \Delta_r G^{\ominus} + 7\nu RT \ln 10 \qquad \textbf{(4.15)}$$

where we have used the relation $\ln x^a = a \ln x$. It follows that at 298.15 K

$$\Delta_r G^{\oplus} = \Delta_r G^{\ominus} + (39.96\ \text{kJ mol}^{-1})\nu$$

and at 37°C (310 K, body temperature)

$$\Delta_r G^{\oplus} = \Delta_r G^{\ominus} + (41.5\ \text{kJ mol}^{-1})\nu$$

There is no difference between thermodynamic and biological standard values if hydrogen ions are not involved in the reaction ($\nu = 0$).

Now we are ready to explore the action of ATP quantitatively. The biological standard values for the hydrolysis of ATP at 37°C are

$$\Delta_r G^{\oplus} = -31 \text{ kJ mol}^{-1} \quad \Delta_r H^{\oplus} = -20 \text{ kJ mol}^{-1} \quad \Delta_r S^{\oplus} = +34 \text{ J K}^{-1} \text{ mol}^{-1}$$

The hydrolysis is therefore exergonic ($\Delta_r G < 0$) under these conditions, and 31 kJ mol^{-1} is available for driving other reactions. On account of its exergonic character, the ADP-phosphate bond has been called a "high-energy phosphate bond." The name is intended to signify a high tendency to undergo reaction and should not be confused with "strong" bond in its normal chemical sense (that of a high bond enthalpy). In fact, even in the biological sense it is not of very "high energy." The action of ATP depends on the bond being intermediate in strength. Thus ATP acts as a phosphate donor to a number of acceptors (such as glucose) but is recharged with a new phosphate group by more powerful phosphate donors in the phosphorylation steps in the respiration cycle.

CASE STUDY 4.2 The biosynthesis of proteins

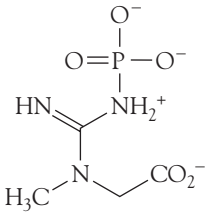
In the cell, each ATP molecule can be used to drive an endergonic reaction for which $\Delta_r G^{\oplus}$ does not exceed +31 kJ mol^{-1}. For example, the biosynthesis of sucrose from glucose and fructose can be driven by plant enzymes because the reaction is endergonic to the extent $\Delta_r G^{\oplus} = +23$ kJ mol^{-1}. The biosynthesis of proteins is strongly endergonic, not only on account of the enthalpy change but also on account of the large decrease in entropy that occurs when many amino acids are assembled into a precisely determined sequence. For instance, the formation of a peptide link is endergonic, with $\Delta_r G^{\oplus} = +17$ kJ mol^{-1}, but the biosynthesis occurs indirectly and is equivalent to the consumption of three ATP molecules for each link. In a moderately small protein such as myoglobin, with about 150 peptide links, the construction alone requires 450 ATP molecules and therefore about 12 mol of glucose molecules for 1 mol of protein molecules. ■

COMMENT 4.2 From now on, we shall represent biochemical reactions with chemical equations written with a shorthand method, in which some substances are given "nicknames" and charges are not always given explicitly. For example, $H_2PO_4^{2-}$ is written as P_i, ATP^{4-} as ATP, and so on. ■

SELF-TEST 4.8 Fats yield almost twice as much energy per gram as carbohydrates. What mass of fat would need to be metabolized to synthesize 1.0 mol of myoglobin molecules?

Answer: 7.6 kg

Adenosine triphosphate is not the only phosphate species capable of driving other less exergonic reactions. For instance, creatine phosphate (**6**) can release its phosphate group in a hydrolysis reaction, and $\Delta_r G^{\oplus} = -43$ kJ mol^{-1}. These different exergonicities give rise to the concept of **transfer potential**, which is the negative of the value of $\Delta_r G^{\oplus}$ for the hydrolysis reaction. Thus, the transfer potential of creatine phosphate is 43 kJ mol^{-1}. Just as one exergonic reaction can drive a less exergonic reaction, so the hydrolysis of a species with a high transfer potential can drive the phosphorylation of a species with a lower transfer potential (Table 4.3).



6 Creatine phosphate

4.8 The oxidation of glucose

The oxidation of glucose to CO_2 and H_2O by O_2 represents the process by which the breakdown of foods leads to the formation of ATP.

The breakdown of glucose in the cell begins with **glycolysis**, a partial oxidation of glucose by nicotinamide adenine dinucleotide (NAD^+, **7**) to pyruvate ion,

Table 4.3 Transfer potentials at 298.15 K

Substance	Transfer potential, $-\Delta_r G^{\oplus}$/(kJ mol^{-1})
AMP	14
ATP, ADP	31
1,3-Bis(phospho)glycerate	49
Creatine phosphate	43
Glucose-6-phosphate	14
Glycerol-1-phosphate	10
Phosphoenolpyruvate	62
Pyrophosphate, $HP_2O_7^{3-}$	33

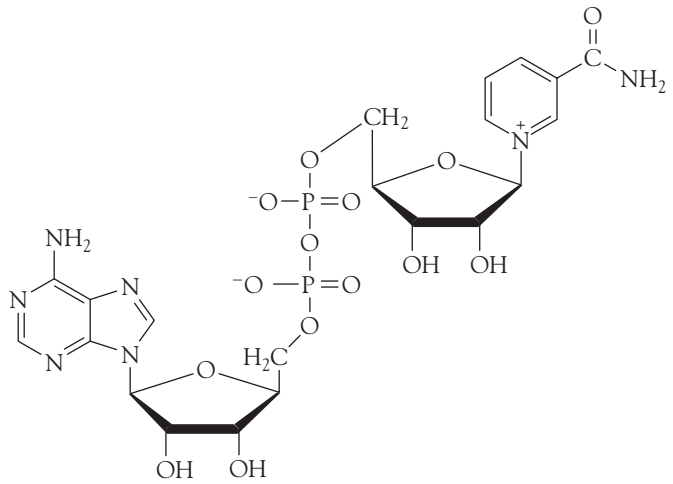
$CH_3COCO_2^-$. Metabolism continues in the form of the **citric acid cycle**, in which pyruvate ions are oxidized to CO_2, and ends with **oxidative phosphorylation**, in which O_2 is reduced to H_2O. Glycolysis is the main source of energy during **anaerobic metabolism**, a form of metabolism in which inhaled O_2 does not play a role. The citric acid cycle and oxidative phosphorylation are the main mechanisms for the extraction of energy from carbohydrates during **aerobic metabolism**, a form of metabolism in which inhaled O_2 does play a role.

Glycolysis occurs in the *cytosol*, the aqueous material encapsulated by the cell membrane, and consists of 10 enzyme-catalyzed reactions (Fig 4.10). The process needs to be initiated by consumption of two molecules of ATP per molecule of glucose. The first ATP molecule is used to drive the phosphorylation of glucose to glucose-6-phosphate (G6P):

$$\text{glucose(aq)} + \text{ATP (aq)} \longrightarrow \text{G6P(aq)} + \text{ADP(aq)} \qquad \Delta_r G^{\oplus} = -17 \text{ kJ mol}^{-1}$$

As we saw in Section 4.1, the next step is the isomerization of G6P to fructose-6-phosphate (F6P). The second ATP molecule consumed during glycolysis drives the phosphorylation of F6P to fructose-1,6-diphosphate (FDP):

$$\text{F6P(aq)} + \text{ATP(aq)} \longrightarrow \text{FDP(aq)} + \text{ADP(aq)} \qquad \Delta_r G^{\oplus} = -14 \text{ kJ mol}^{-1}$$



7 NAD^+

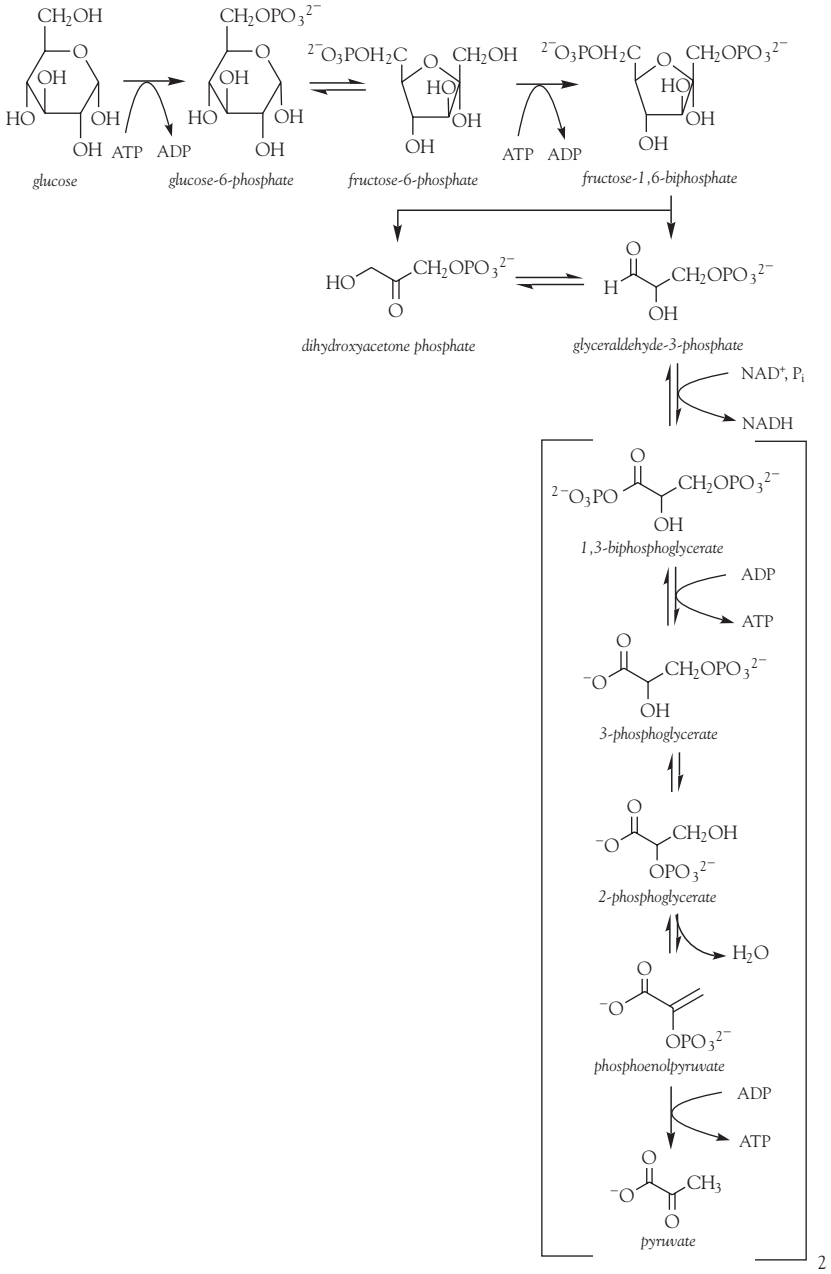
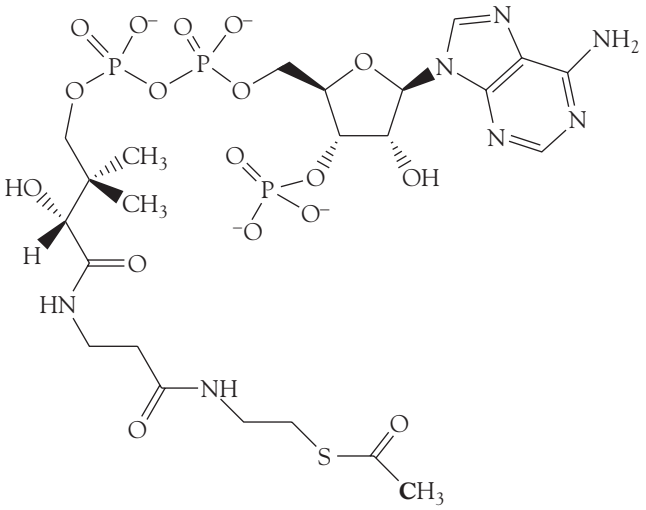


Fig. 4.10 The reactions of glycolysis, in which glucose is partially oxidized by nicotinamide adenine dinucleotide (NAD^+) to pyruvate ion.

In the next step, FDP is broken into two three-carbon units, dihydroxyacetone phosphate (1,3-dihydroxypropanone phosphate, $CH_2OHCOCH_2OPO_3^{2-}$) and glyceraldehyde-3-phosphate, which exist in mutual equilibrium. Only the glyceraldehyde-3-phosphate is oxidized by NAD^+ to pyruvate ion, with formation of two ATP molecules. As glycolysis proceeds, all the dihydroxyacetone phosphate is converted to glyceraldehyde-3-phosphate, so the result is the consumption of two NAD^+ molecules and the formation of four ATP molecules per molecule of glucose.

COMMENT 4.3 The text's web site contains links to databases of structures of many of the enzymes involved in glycolysis, the citric acid cycle, and oxidative phosphorylation. ■

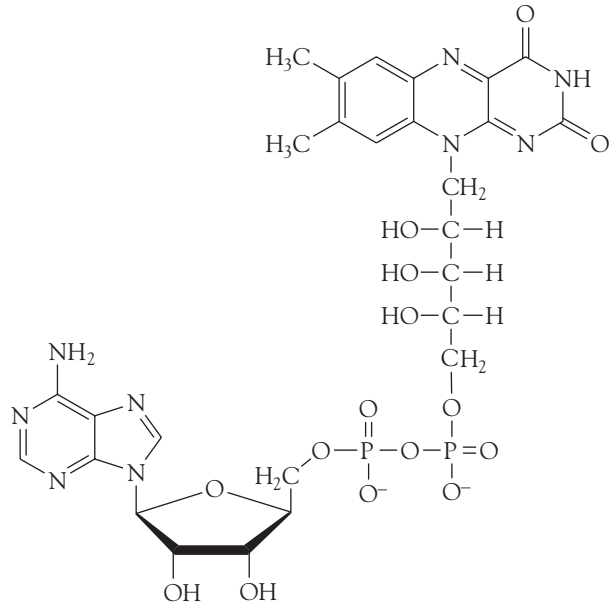


8 Acetyl coenzyme A (acetyl CoA), with the carbon derived from pyruvate in boldface

The oxidation of glucose by NAD^+ to pyruvate ions has $\Delta_r G^{\oplus} = -147$ kJ mol^{-1} at blood temperature. In glycolysis, the oxidation of one glucose molecule is coupled to the *net* conversion of two ADP molecules to two ATP molecules (two ATP molecules are consumed and four are formed), so the net reaction of glycolysis is

$$\text{glucose(aq)} + 2\ \text{NAD}^+\text{(aq)} + 2\ \text{ADP(aq)} + 2\ \text{P}_i\text{(aq)} + 2\ \text{H}_2\text{O(l)} \longrightarrow$$
$$2\ \text{CH}_3\text{COCO}_2^-\text{(aq)} + 2\ \text{NADH(aq)} + 2\ \text{ATP(aq)} + 2\ \text{H}_3\text{O}^+\text{(aq)}$$

The biological standard reaction Gibbs energy is $(-147) - 2(-31)$ kJ mol^{-1} = -85 kJ mol^{-1}. The reaction is exergonic and therefore spontaneous under



9 FAD

biological standard conditions: the oxidation of glucose is used to "recharge" the ATP.

In cells that are deprived of O_2, pyruvate ion is reduced to lactate ion, $CH_3C(OH)CO_2^-$, by NADH.[3] Very strenuous exercise, such as bicycle racing, can decrease sharply the concentration of O_2 in muscle cells, and the condition known as muscle fatigue results from increased concentrations of lactate ion.

The standard Gibbs energy of combustion of glucose is -2880 kJ mol^{-1}, so terminating its oxidation at pyruvate is a poor use of resources, akin to the partial combustion of hydrocarbon fuels in a badly tuned engine. In the presence of O_2, pyruvate is oxidized further during the citric acid cycle and oxidative phosphorylation, which occur in the mitochondria of cells.

The further oxidation of carbon derived from glucose begins with a reaction between pyruvate ion, NAD^+, and coenzyme A (CoA) to give acetyl CoA (**8**), NADH, and CO_2. Acetyl CoA is then oxidized by NAD^+ and flavin adenine dinucleotide (FAD, **9**) in the citric acid cycle (Fig. 4.11), which requires eight enzymes and results in the synthesis of GTP (**10**) from GDP or ATP from ADP:

$$\begin{aligned}\text{Acetyl CoA(aq)} + 3\,\text{NAD}^+\text{(aq)} + \text{FAD(aq)} + \text{GDP(aq)} \\ + \text{P}_\text{i}\text{(aq)} + 2\,\text{H}_2\text{O(l)} \longrightarrow 2\,\text{CO}_2\text{(g)} + 3\,\text{NADH(aq)} + 2\,\text{H}_3\text{O}^+\text{(aq)} \\ + \text{FADH}_2\text{(aq)} + \text{GTP(aq)} + \text{CoA(aq)} \\ \Delta_\text{r}G^\oplus = -57\ \text{kJ mol}^{-1}\end{aligned}$$

In cells that produce GTP, the enzyme nucleoside diphosphate kinase catalyzes the transfer of a phosphate group to ADP to form ATP:

$$\text{GTP(aq)} + \text{ADP(aq)} \longrightarrow \text{GDP(aq)} + \text{ATP(aq)}$$

[3]In yeast, the terminal products are ethanol and CO_2.

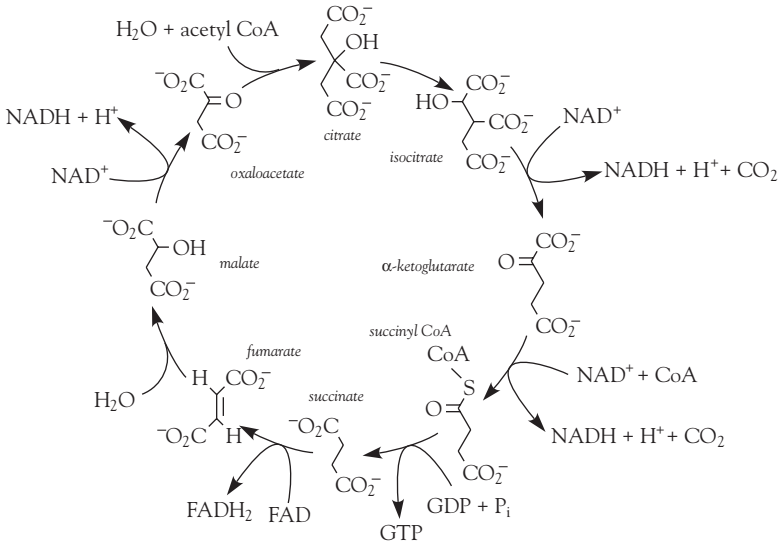
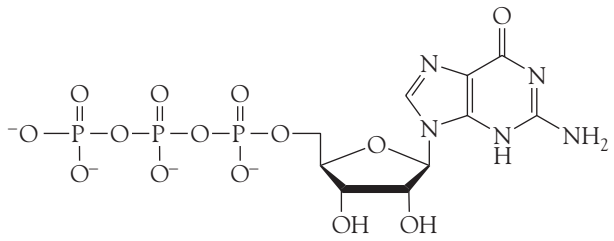


Fig. 4.11 The reactions of the citric acid cycle, in which acetyl CoA is oxidized by NAD^+ and FAD, resulting in the synthesis of GTP (shown) or ATP, depending on the type of cell. The GTP molecules are eventually converted to ATP.



10 GTP

For this reaction, $\Delta_r G^{\oplus} = 0$ because the phosphate group transfer potentials for GTP and ATP are essentially identical. Overall, we write the oxidation of glucose as a result of glycolysis and the citric acid cycle as

$$\begin{aligned}\text{glucose(aq)} + 10\ \text{NAD}^+\text{(aq)} + 2\ \text{FAD(aq)} + 4\ \text{ADP(aq)} \\ + 4\ \text{P}_i\text{(aq)} + 2\ \text{H}_2\text{O(l)} \longrightarrow 6\ \text{CO}_2\text{(g)} + 10\ \text{NADH(aq)} \\ + 6\ \text{H}_3\text{O}^+\text{(aq)} + 2\ \text{FADH}_2\text{(aq)} + 4\ \text{ATP(aq)}\end{aligned}$$

The NADH and $FADH_2$ go on to reduce O_2 during oxidative phosphorylation (Section 5.11), which also produces ATP. The citric acid cycle and oxidative phosphorylation generate as many as 38 ATP molecules for each glucose molecule consumed. Each mole of ATP molecules extracts 31 kJ from the 2880 kJ supplied by 1 mol $C_6H_{12}O_6$ (180 g of glucose), so 1178 kJ is stored for later use. Therefore, aerobic oxidation of glucose is much more efficient than glycolysis.

Proton transfer equilibria

An enormously important biological aspect of chemical equilibrium is that involving the transfer of protons (hydrogen ions, H^+) between species in aqueous environments, such as living cells. Even small drifts in the equilibrium concentration of hydrogen ions can result in disease, cell damage, and death. In this section we see how the general principles outlined earlier in the chapter are applied to proton transfer equilibria. Throughout our discussion, keep in mind that a free hydrogen ion does not exist in water: it is always attached to a water molecule and exists as H_3O^+, a *hydronium ion*.

4.9 Brønsted-Lowry theory

Cells have elaborate procedures for using proton transfer equilibria, and this function cannot be understood without knowing which species provide protons and which accept them and how to express the concentration of hydrogen ions in solution.

According to the **Brønsted-Lowry theory** of acids and bases, an **acid** is a proton donor and a **base** is a proton acceptor. The proton, which in this context means a hydrogen ion, H^+, is highly mobile and acids and bases in water are always in equilibrium with their deprotonated and protonated counterparts and hydronium ions (H_3O^+). Thus, an acid HA, such as HCN, immediately establishes the equilibrium

$$\text{HA(aq)} + \text{H}_2\text{O(l)} \rightleftharpoons \text{H}_3\text{O}^+\text{(aq)} + \text{A}^-\text{(aq)} \qquad K = \frac{a_{\text{H}_3\text{O}^+} a_{\text{A}^-}}{a_{\text{HA}} a_{\text{H}_2\text{O}}}$$

A base B, such as NH_3, immediately establishes the equilibrium

$$B(aq) + H_2O(l) \rightleftharpoons BH^+(aq) + OH^-(aq) \qquad K = \frac{a_{BH^+}a_{OH^-}}{a_B a_{H_2O}}$$

In these equilibria, A^- is the **conjugate base** of the acid HA, and BH^+ is the **conjugate acid** of the base B. Even in the absence of added acids and bases, proton transfer occurs between water molecules, and the **autoprotolysis equilibrium**[4]

$$2\ H_2O(l) \rightleftharpoons H_3O^+(aq) + OH^-(aq) \qquad K = \frac{a_{H_3O^+}a_{OH^-}}{a_{H_2O}^2}$$

is always present.

As will be familiar from introductory chemistry, the hydronium ion concentration is commonly expressed in terms of the pH, which is defined formally as

$$pH = -\log a_{H_3O^+} \tag{4.16}$$

where the logarithm is to base 10. In elementary work, the hydronium ion activity is replaced by the numerical value of its molar concentration, $[H_3O^+]$, which is equivalent to setting the activity coefficient γ equal to 1. For example, if the molar concentration of H_3O^+ is 2.0 mmol L^{-1} (where 1 mmol = 10^{-3} mol), then

$$pH \approx -\log(2.0 \times 10^{-3}) = 2.70$$

If the molar concentration were 10 times less, at 0.20 mmol L^{-1}, then the pH would be 3.70. Notice that *the higher the pH, the lower the concentration of hydronium ions in the solution* and that a change in pH by 1 unit corresponds to a 10-fold change in their molar concentration. However, it should never be forgotten that the replacement of activities by molar concentration is invariably hazardous. Because ions interact over long distances, the replacement is unreliable for all but the most dilute solutions.

SELF-TEST 4.9 Death is likely if the pH of human blood plasma changes by more than ±0.4 from its normal value of 7.4. What is the approximate range of molar concentrations of hydrogen ions for which life can be sustained?

Answer: 16 nmol L^{-1} to 100 nmol L^{-1} (1 nmol = 10^{-9} mol)

4.10 Protonation and deprotonation

The protonation and deprotonation of molecules are key steps in many biochemical reactions, and we need to be able to describe procedures for treating protonation and deprotonation processes quantitatively.

All the solutions we consider are so dilute that we can regard the water present as being a nearly pure liquid and therefore as having unit activity (see Table 3.3).

[4]Autoprotolysis is also called *autoionization*.

When we set $a_{H_2O} = 1$ for all the solutions we consider, the resulting equilibrium constant is called the **acidity constant**, K_a, of the acid HA:[5]

$$K_a = \frac{a_{H_3O^+} a_{A^-}}{a_{HA}} \approx \frac{[H_3O^+][A^-]}{[HA]} \qquad \textbf{(4.17)}$$

Data are widely reported in terms of the negative common (base 10) logarithm of this quantity:

$$pK_a = -\log K_a \qquad \textbf{(4.18)}$$

It follows from eqn 4.8 ($\Delta_r G^\ominus = -RT \ln K$) that pK_a is proportional to $\Delta_r G^\ominus$ for the proton transfer reaction. More explicitly, $pK_a = \Delta_r G^\ominus/(RT \ln 10)$, with $\ln 10 = 2.303\ldots$. Therefore, manipulations of pK_a and related quantities are actually manipulations of standard reaction Gibbs energies in disguise.

SELF-TEST 4.10 Show that $pK_a = \Delta_r G^\ominus/(RT \ln 10)$. *Hint:* $\ln x = \ln 10 \times \log x$.

The value of the acidity constant indicates the extent to which proton transfer occurs at equilibrium in aqueous solution. The smaller the value of K_a, and therefore the larger the value of pK_a, the lower is the concentration of deprotonated molecules. Most acids have $K_a < 1$ (and usually much less than 1), with $pK_a > 0$, indicating only a small extent of deprotonation in water. These acids are classified as **weak acids**. A few acids, most notably, in aqueous solution, HCl, HBr, HI, HNO_3, H_2SO_4 and $HClO_4$, are classified as **strong acids** and are commonly regarded as being completely deprotonated in aqueous solution.[6]

The corresponding expression for a base is called the **basicity constant**, K_b:

$$K_b = \frac{a_{BH^+} a_{OH^-}}{a_B} \approx \frac{[BH^+][OH^-]}{[B]} \qquad pK_b = -\log K_b \qquad \textbf{(4.19)}$$

A **strong base** is fully protonated in solution in the sense that $K_b > 1$. One example is the oxide ion, O^{2-}, which cannot survive in water but is immediately and fully converted into its conjugate acid OH^-. A **weak base** is not fully protonated in water in the sense that $K_b < 1$ (and usually much less than 1). Ammonia, NH_3, and its organic derivatives the amines are all weak bases in water, and only a small proportion of their molecules exist as the conjugate acid (NH_4^+ or RNH_3^+).

The **autoprotolysis constant** for water, K_w, is

$$K_w = a_{H_3O^+} a_{OH^-} \qquad \textbf{(4.20)}$$

At 25°C, the only temperature we consider in this chapter, $K_w = 1.0 \times 10^{-14}$ and $pK_w = -\log K_w = 14.00$. As may be confirmed by multiplying the two constants together, the acidity constant of the conjugate acid, BH^+, and the basicity constant of a base B (the equilibrium constant for the reaction $B + H_2O \rightleftharpoons BH^+ + OH^-$) are related by

$$K_a K_b = \frac{a_{H_3O^+} a_B}{a_{BH^+}} \times \frac{a_{BH^+} a_{OH^-}}{a_B} = a_{H_3O^+} a_{OH^-} = K_w \qquad \textbf{(4.21a)}$$

[5] Acidity constants are also called *acid ionization constants* and, less appropriately, *dissociation constants*.

[6] Sulfuric acid, H_2SO_4, is strong with respect only to its first deprotonation; HSO_4^- is weak.

The implication of this relation is that K_a increases as K_b decreases to maintain a product equal to the constant K_w. That is, *as the strength of a base decreases, the strength of its conjugate acid increases* and vice versa. On taking the negative common logarithm of both sides of eqn 4.21a, we obtain

$$pK_a + pK_b = pK_w \qquad \textbf{(4.21b)}$$

The great advantage of this relation is that the pK_b values of bases may be expressed as the pK_a of their conjugate acids, so the strengths of all weak acids and bases may be listed in a single table (Table 4.4). For example, if the acidity constant of the conjugate acid ($CH_3NH_3^+$) of the base methylamine (CH_3NH_2) is reported as $pK_a = 10.56$, we can infer that the basicity constant of methylamine itself is

$$pK_b = pK_w - pK_a = 14.00 - 10.56 = 3.44$$

Another useful relation is obtained by taking the negative common logarithm of both sides of the definition of K_w in eqn 4.20, which gives

$$pH + pOH = pK_w \qquad \textbf{(4.22)}$$

where $pOH = -\log a_{OH^-}$. This enormously important relation means that the activities (in elementary work, the molar concentrations) of hydronium and hydroxide ions are related by a seesaw relation: as one goes up, the other goes down to preserve the value of pK_w.

SELF-TEST 4.11 The molar concentration of OH^- ions in a certain solution is 0.010 mmol L^{-1}. What is the pH of the solution?

Answer: 9.00

The extent of deprotonation of a weak acid in solution depends on the acidity constant and the initial concentration of the acid, its concentration as prepared. The **fraction deprotonated**, the fraction of acid molecules HA that have donated a proton, is

$$\text{Fraction deprotonated} = \frac{\text{equilibrium molar concentration of conjugate base}}{\text{molar concentration of acid as prepared}}$$

$$f = \frac{[A^-]_{\text{equilibrium}}}{[HA]_{\text{as prepared}}} \qquad \textbf{(4.23)}$$

The extent to which a weak base B is protonated is reported in terms of the **fraction protonated**:

$$\text{Fraction protonated} = \frac{\text{equilibrium molar concentration of conjugate acid}}{\text{molar concentration of base as prepared}}$$

$$f = \frac{[BH^+]_{\text{equilibrium}}}{[B]_{\text{as prepared}}} \qquad \textbf{(4.24)}$$

The most precise way to estimate the pH of a solution of a weak acid is to consider the contributions from deprotonation of the acid and autoprotolysis of water

Table 4.4 Acidity and basicity constants* at 298.15 K

Acid/Base	K_b	pK_b	K_a	pK_a
Strongest weak acids				
Trichloroacetic acid, CCl_3COOH	3.3×10^{-14}	13.48	3.0×10^{-1}	0.52
Benzenesulfonic acid, $C_6H_5SO_3H$	5.0×10^{-14}	13.30	2×10^{-1}	0.70
Iodic acid, HIO_3	5.9×10^{-14}	13.23	1.7×10^{-1}	0.77
Sulfurous acid, H_2SO_3	6.3×10^{-13}	12.19	1.6×10^{-2}	1.81
Chlorous acid, $HClO_2$	1.0×10^{-12}	12.00	1.0×10^{-2}	2.00
Phosphoric acid, H_3PO_4	1.3×10^{-12}	11.88	7.6×10^{-3}	2.12
Chloroacetic acid, $CH_2ClCOOH$	7.1×10^{-12}	11.15	1.4×10^{-3}	2.85
Lactic acid, $CH_3CH(OH)COOH$	1.2×10^{-11}	10.92	8.4×10^{-4}	3.08
Nitrous acid, HNO_2	2.3×10^{-11}	10.63	4.3×10^{-4}	3.37
Hydrofluoric acid, HF	2.9×10^{-11}	10.55	3.5×10^{-4}	3.45
Formic acid, HCOOH	5.6×10^{-11}	10.25	1.8×10^{-4}	3.75
Benzoic acid, C_6H_5COOH	1.5×10^{-10}	9.81	6.5×10^{-5}	4.19
Acetic acid, CH_3COOH	5.6×10^{-10}	9.25	5.6×10^{-5}	4.75
Carbonic acid, H_2CO_3	2.3×10^{-8}	7.63	4.3×10^{-7}	6.37
Hypochlorous acid, HClO	3.3×10^{-7}	6.47	3.0×10^{-8}	7.53
Hypobromous acid, HBrO	5.0×10^{-6}	5.31	2.0×10^{-9}	8.69
Boric acid, $B(OH)_3H^{\dagger}$	1.4×10^{-5}	4.86	7.2×10^{-10}	9.14
Hydrocyanic acid, HCN	2.0×10^{-5}	4.69	4.9×10^{-10}	9.31
Phenol, C_6H_5OH	7.7×10^{-5}	4.11	1.3×10^{-10}	9.89
Hypoiodous acid, HIO	4.3×10^{-4}	3.36	2.3×10^{-11}	10.64
Weakest weak acids				
Weakest weak bases				
Urea, $CO(NH_2)_2$	1.3×10^{-14}	13.90	7.7×10^{-1}	0.10
Aniline, $C_6H_5NH_2$	4.3×10^{-10}	9.37	2.3×10^{-5}	4.63
Pyridine, C_5H_5N	1.8×10^{-9}	8.75	5.6×10^{-6}	5.35
Hydroxylamine, NH_2OH	1.1×10^{-8}	7.97	9.1×10^{-7}	6.03
Nicotine, $C_{10}H_{11}N_2$	1.0×10^{-6}	5.98	1.0×10^{-8}	8.02
Morphine, $C_{17}H_{19}O_3N$	1.6×10^{-6}	5.79	6.3×10^{-9}	8.21
Hydrazine, NH_2NH_2	1.7×10^{-6}	5.77	5.9×10^{-9}	8.23
Ammonia, NH_3	1.8×10^{-5}	4.75	5.6×10^{-10}	9.25
Trimethylamine, $(CH_3)_3N$	6.5×10^{-5}	4.19	1.5×10^{-10}	9.81
Methylamine, CH_3NH_2	3.6×10^{-4}	3.44	2.8×10^{-11}	10.56
Dimethylamine, $(CH_3)_2NH$	5.4×10^{-4}	3.27	1.9×10^{-11}	10.73
Ethylamine, $C_2H_5NH_2$	6.5×10^{-4}	3.19	1.5×10^{-11}	10.81
Triethylamine, $(C_2H_5)_3N$	1.0×10^{-3}	2.99	1.0×10^{-11}	11.01
Strongest weak bases				

*Values for polyprotic acids—those capable of donating more than one proton—refer to the first deprotonation.

†The proton transfer equilibrium is $B(OH)_3(aq) + 2\ H_2O(l) \rightleftharpoons H_3O^+(aq) + B(OH)_4^-(aq)$.

to the total concentration of hydronium ion in solution (see *Further information* 4.1). Autoprotolysis may be ignored if the weak acid is the main contributor of hydronium ions, a condition that is satisfied if the acid is not very weak and is present at not too low a concentration. Then we can estimate the pH of a solution of a weak acid and calculate either of these fractions by using the following strategy.

We organize the necessary work into a table with columns headed by the species and, in successive rows:

1. The initial molar concentrations of the species, ignoring any contributions to the concentration of H_3O^+ or OH^- from autoprotolysis of water
2. The changes in these quantities that must take place for the system to reach equilibrium
3. The resulting equilibrium values

Similar arguments apply to the estimation of the pH of a solution of a weak base. In most cases, we do not know the change that must occur for the system to reach equilibrium, so the change in the concentration is written as x and the reaction stoichiometry is used to write the corresponding changes in the other species. When the values at equilibrium (the last row of the table) are substituted into the expression for the equilibrium constant, we obtain an equation for x in terms of K. This equation can be solved for x, and hence the concentrations of all the species at equilibrium can be found. In general, solution of the equation for x results in several mathematically possible values of x. We select the chemically acceptable solution by considering the signs of the predicted concentrations: they must be positive.

EXAMPLE 4.5 Assessing the extent of deprotonation of a weak acid

Acetic acid lends a sour taste to vinegar and is produced by aerobic oxidation of ethanol by bacteria in fermented beverages, such as wine and cider:

$$CH_3CH_2OH(aq) + O_2(g) \longrightarrow CH_3COOH(aq) + H_2O(l)$$

Estimate the pH and the fraction of CH_3COOH molecules deprotonated in 0.15 M $CH_3COOH(aq)$.

Strategy The aim is to calculate the equilibrium composition of the solution. To do so, set up an equilibrium table with x as the change in molar concentration of H_3O^+ ions required to reach equilibrium. We ignore the tiny concentration of hydronium ions present in pure water. In this example, the equation for x is quadratic:

$$ax^2 + bx + c = 0 \quad \text{with the roots } x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

However, because we can anticipate that the extent of deprotonation is small (the acid is weak, $K_a << 1$), use the approximation that x is very small to simplify the equations. Once x has been found, calculate pH $= -\log x$. Confirm the accuracy of the calculation by substituting the calculated equilibrium concentrations into the expression for K_a to verify that the value so calculated is equal to the experimental value used in the calculation.

Solution We draw up the following equilibrium table:

Species	CH_3COOH	H_3O^+	$CH_3CO_2^-$
Initial concentration/(mol L^{-1})	0.15	0	0
Change to reach equilibrium/(mol L^{-1})	$-x$	$+x$	$+x$
Equilibrium concentration/(mol L^{-1})	$0.15 - x$	x	x

The value of x is found by inserting the equilibrium concentrations into the expression for the acidity constant:

$$K_a = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3COOH]} = \frac{x \times x}{0.15 - x}$$

We could arrange the expression into a quadratic equation. However, it is more instructive to make use of the smallness of x to replace $0.15 - x$ by 0.15 (this approximation is valid if $x << 0.15$). Then the simplified equation rearranges first to $0.15 \times K_a = x^2$ and then to

$$x = (0.15 \times K_a)^{1/2} = (0.15 \times 1.8 \times 10^{-5})^{1/2} = 1.6 \times 10^{-3}$$

where we have used $K_a = 1.8 \times 10^{-5}$ (Table 4.4). Therefore, pH = 2.80. Calculations of this kind are rarely accurate to more than one decimal place in the pH (and even that may be too optimistic) because the effects of ion-ion interactions have been ignored, so this answer would be reported as pH = 2.8. The fraction deprotonated, f, is

$$f = \frac{[CH_3CO_2^-]_{equilibrium}}{[CH_3COOH]_{added}} = \frac{x}{0.15} = \frac{1.6 \times 10^{-3}}{0.15} = 0.011$$

That is, only 1.1% of the acetic acid molecules have donated a proton.

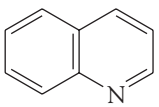
A note on good practice: When an approximation has been made, verify at the end of the calculation that the approximation is consistent with the result obtained. In this case, we assumed that $x << 0.15$ and have found that $x = 1.6 \times 10^{-3}$, which is consistent.

Another note on good practice: Acetic acid (ethanoic acid) is written CH_3COOH because the two O atoms are inequivalent; its conjugate base, the acetate ion (ethanoate ion), is written $CH_3CO_2^-$ because the two O atoms are now equivalent (by resonance).

SELF-TEST 4.12 Estimate the pH of 0.010 M $CH_3CH(OH)COOH(aq)$ (lactic acid) from the data in Table 4.4. Before carrying out the numerical calculation, decide whether you expect the pH to be higher or lower than that calculated for the same concentration of acetic acid.

Answer: 2.5 ■

The calculation of the pH of a solution of a base involves an additional step. The first step is to calculate the concentration of OH^- ions in the solution from the value of K_b by using the equilibrium-table technique and to express it as the pOH of the solution. The additional step is to convert that pOH into a pH by using the water autoprotolysis equilibrium, eqn 4.22, in the form $pH = pK_w - pOH$, with $pK_w = 14.00$ at 25°C.



11 Quinoline

SELF-TEST 4.13 The base quinoline (**11**) has $pK_b = 9.12$. Estimate the pH and the fraction of molecules protonated in an 0.010 M aqueous solution of quinoline.

Answer: 8.4; 1/3571

The ions present when a salt is added to water may themselves be either acids or bases and consequently affect the pH of the solution. For example, when ammonium chloride is added to water, it provides both an acid (NH_4^+) and a base (Cl^-). The solution consists of a weak acid (NH_4^+) and a very weak base (Cl^-). The net effect is that the solution is acidic. Similarly, a solution of sodium acetate consists of a neutral ion (the Na^+ ion) and a base ($CH_3CO_2^-$). The net effect is that the solution is basic, and its pH is greater than 7.

To estimate the pH of the solution, we proceed in exactly the same way as for the addition of a "conventional" acid or base, for in the Brønsted-Lowry theory, there is no distinction between "conventional" acids such as acetic acid and the conjugate acids of bases (such as NH_4^+). For example, to calculate the pH of 0.010 M NH_4Cl(aq) at 25°C, we proceed exactly as in *Example* 4.5, taking the initial concentration of the acid (NH_4^+) to be 0.010 mol L^{-1}. The K_a to use is the acidity constant of the acid NH_4^+, which is listed in Table 4.4. Alternatively, we use K_b for the conjugate base (NH_3) of the acid and convert that quantity to K_a by using eqn 4.21 ($K_aK_b = K_w$). We find pH = 5.63, which is on the acid side of neutral. Exactly the same procedure is used to find the pH of a solution of a salt of a weak acid, such as sodium acetate. The equilibrium table is set up by treating the anion $CH_3CO_2^-$ as a base (which it is) and using for K_b the value obtained from the value of K_a for its conjugate acid (CH_3COOH).

SELF-TEST 4.14 Estimate the pH of 0.0025 M $NH(CH_3)_3Cl$(aq) at 25°C.

Answer: 6.2

4.11 Polyprotic acids

Many biological macromolecules, such as the nucleic acids, contain multiple proton donor sites, and we need to see how to handle this complication quantitatively.

A **polyprotic acid** is a molecular compound that can donate more than one proton. Two examples are sulfuric acid, H_2SO_4, which can donate up to two protons, and phosphoric acid, H_3PO_4, which can donate up to three. A polyprotic acid is best considered to be a molecular species that can give rise to a series of Brønsted acids as it donates its succession of protons. Thus, sulfuric acid is the parent of two Brønsted acids, H_2SO_4 itself and HSO_4^-, and phosphoric acid is the parent of three Brønsted acids, namely H_3PO_4, $H_2PO_4^-$, and HPO_4^{2-}.

For a species H_2A with two acidic protons (such as H_2SO_4), the successive equilibria we need to consider are

$$H_2A(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + HA^-(aq) \qquad K_{a1} = \frac{a_{H_3O^+}a_{HA^-}}{a_{H_2A}}$$

$$HA^-(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + A^{2-}(aq) \qquad K_{a2} = \frac{a_{H_3O^+}a_{A^{2-}}}{a_{HA^-}}$$

In the first of these equilibria, HA^- is the conjugate base of H_2A. In the second, HA^- acts as the acid and A^{2-} is its conjugate base. Values are given in Table 4.5. In all cases, K_{a2} is smaller than K_{a1}, typically by three orders of magnitude for small molecular species, because the second proton is more difficult to remove, partly on account

Table 4.5 Successive acidity constants of polyprotic acids at 298.15 K

Acid	K_{a1}	pK_{a1}	K_{a2}	pK_{a2}	K_{a3}	pK_{a3}
Carbonic acid, H_2CO_3	4.3×10^{-7}	6.37	5.6×10^{-11}	10.25		
Hydrosulfuric acid, H_2S	1.3×10^{-7}	6.88	7.1×10^{-15}	14.15		
Oxalic acid, $(COOH)_2$	5.9×10^{-2}	1.23	6.5×10^{-5}	4.19		
Phosphoric acid, H_3PO_4	7.6×10^{-3}	2.12	6.2×10^{-8}	7.21	2.1×10^{-13}	12.67
Phosphorous acid, H_2PO_3	1.0×10^{-2}	2.00	2.6×10^{-7}	6.59		
Sulfuric acid, H_2SO_4	Strong		1.2×10^{-2}	1.92		
Sulfurous acid, H_2SO_3	1.5×10^{-2}	1.81	1.2×10^{-7}	6.91		
Tartaric acid, $C_2H_4O_2(COOH)_2$	6.0×10^{-4}	3.22	1.5×10^{-5}	4.82		

of the negative charge on HA^-. Enzymes are polyprotic acids, for they possess many protons that can be donated to a substrate molecule or to the surrounding aqueous medium of the cell. For them, successive acidity constants vary much less because the molecules are so large that the loss of a proton from one part of the molecule has little effect on the ease with which another some distance away may be lost.

EXAMPLE 4.6 Calculating the concentration of carbonate ion in carbonic acid

Groundwater contains dissolved carbon dioxide, carbonic acid, hydrogencarbonate ions, and a very low concentration of carbonate ions. Estimate the molar concentration of CO_3^{2-} ions in a solution in which water and $CO_2(g)$ are in equilibrium. We must be very cautious in the interpretation of calculations involving carbonic acid because equilibrium between dissolved CO_2 and H_2CO_3 is achieved only very slowly. In organisms, attainment of equilibrium is facilitated by the enzyme carbonic anhydrase.

Strategy We start with the equilibrium that produces the ion of interest (such as A^{2-}) and write its activity in terms of the acidity constant for its formation (K_{a2}). That expression will contain the activity of the conjugate acid (HA^-), which we can express in terms of the activity of *its* conjugate acid (H_2A) by using the appropriate acidity constant (K_{a1}). This equilibrium dominates all the rest provided the molecule is small and there are marked differences between its acidity constants, so it may be possible to make an approximation at this stage.

Solution The CO_3^{2-} ion, the conjugate base of the acid HCO_3^- is produced in the equilibrium

$$HCO_3^-(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + CO_3^{2-}(aq) \qquad K_{a2} = \frac{a_{H_3O^+}a_{CO_3^{2-}}}{a_{HCO_3^-}}$$

Hence,

$$a_{CO_3^{2-}} = \frac{a_{HCO_3^-}K_{a2}}{a_{H_3O^+}}$$

The HCO_3^- ions are produced in the equilibrium

$$H_2CO_3(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + HCO_3^-(aq)$$

One H_3O^+ ion is produced for each HCO_3^- ion produced. These two concentrations are not exactly the same, because a little HCO_3^- is lost in the second deprotonation and the amount of H_3O^+ has been increased by it. Also, HCO_3^- is a weak base and abstracts a proton from water to generate H_2CO_3 (see Section 4.12). However, those secondary changes can safely be ignored in an approximate calculation. Because the molar concentrations of HCO_3^- and H_3O^+ are approximately the same, we can suppose that their activities are also approximately the same and set $a_{HCO_3^-} \approx a_{H_3O^+}$. When this equality is substituted into the expression for $a_{CO_3^{2-}}$, we obtain

$$[CO_3^{2-}] \approx K_{a2}$$

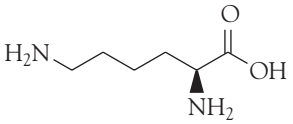
Because we know from Table 4.5 that $pK_{a2} = 10.25$, it follows that $[CO_3^{2-}] = 5.6 \times 10^{-11}$ and therefore that the molar concentration of CO_3^{2-} ions is 5.6×10^{-11} mol L^{-1}.

SELF-TEST 4.15 Calculate the molar concentration of S^{2-} ions in H_2S(aq).

Answer: 7.1×10^{-15} mol L^{-1} ■

CASE STUDY 4.3 The fractional composition of a solution of lysine

The amino acid lysine (Lys, **12**) can accept two protons on its nitrogen atoms and donate one from its carboxyl group. Let's see how the composition of an aqueous solution that contains 0.010 mol L^{-1} of lysine varies with pH. The pK_a values of amino acids are given in Table 4.6.



12 Lysine (Lys)

We expect the fully protonated species (H_3Lys^{2+}) at low pH, the partially protonated species (H_2Lys^+ and HLys) at intermediate pH, and the fully deprotonated species (Lys^-) at high pH. The three acidity constants (using the notation in Table 4.6) are

$$H_3Lys^{2+}(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + H_2Lys^+(aq)$$
$$K_{a1} = \frac{[H_3O^+][H_2Lys^+]}{[H_3Lys^{2+}]} = \frac{H[H_2Lys^+]}{[H_3Lys^{2+}]}$$

$$H_2Lys^+(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + HLys(aq)$$
$$K_{a2} = \frac{[H_3O^+][HLys]}{[H_2Lys^+]} = \frac{H[HLys]}{[H_2Lys^+]}$$

$$HLys(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + Lys^-(aq)$$
$$K_{a3} = \frac{[H_3O^+][Lys^-]}{[HLys]} = \frac{H[Lys^-]}{[HLys]}$$

where, for the sake of simplifying the forms of the expressions, we have set $[H_3O]^+$ equal to H. We also know that the total concentration of lysine in all its forms is

$$[H_3Lys^{2+}] + [H_2Lys^+] + [HLys] + [Lys^-] = L$$

Table 4.6 Acidity constants of amino acids at 298.15 K*

Acid	pK_{a1}	pK_{a2}	pK_{a3}
Ala	2.33	9.71	
Arg	2.03	9.00	12.10
Asn	2.16	8.73	
Asp	1.95	3.71	9.66
Cys	1.91	8.14	10.28
Gln	2.18	9.00	
Glu	2.16	4.15	9.58
Gly	2.34	9.58	
His	1.70	6.04	9.09
Ile	2.26	9.60	
Leu	2.32	9.58	
Lys	2.15	9.16	10.67
Met	2.16	9.08	
Phe	2.18	9.09	
Pro	1.95	10.47	
Ser	2.13	9.05	
Thr	2.20	9.96	
Trp	2.38	9.34	
Tyr	2.24	9.04	10.10
Val	2.27	9.52	

*For the identities of the acids, see the *Data section*. The acidity constants refer, respectively, to the most highly protonated form, the next most, and so on. So the values for Lys, for instance, refer to H_3Lys^{2+}, H_2Lys^{+}, and HLys (the electrically neutral molecule).

We now have four equations for four unknown concentrations. To solve the equations, we proceed systematically, using K_{a3} to express $[Lys^-]$ in terms of [HLys], then K_{a2} to express [HLys] in terms of $[H_2Lys^+]$, and so on:

$$[Lys^-] = \frac{K_{a3}[HLys]}{H} = \frac{K_{a3}K_{a2}[H_2Lys^+]}{H^2} = \frac{K_{a3}K_{a2}K_{a1}[H_3Lys^{2+}]}{H^3}$$

$$[HLys] = \frac{K_{a2}[H_2Lys^+]}{H} = \frac{K_{a2}K_{a1}[H_3Lys^{2+}]}{H^2}$$

$$[H_2Lys^+] = \frac{K_{a1}[H_3Lys^{2+}]}{H}$$

Then the expression for the total concentration can be written in terms of $[H_3Lys^{2+}]$, H, and L. If we write

$$K = H^3 + H^2K_{a1} + HK_{a1}K_{a2} + K_{a1}K_{a2}K_{a3}$$

then it follows that

$$L = \frac{K}{H^3}\,[H_3Lys^{2+}]$$

and the fractions of each species present in the solution are

$$f(H_3Lys^{2+}) = \frac{[H_3Lys^{2+}]}{L} = \frac{H^3}{K}$$

$$f(H_2Lys^{+}) = \frac{[H_2Lys^{+}]}{L} = \frac{H^2K_{a1}}{K}$$

$$f(HLys) = \frac{[HLys]}{L} = \frac{HK_{a2}K_{a1}}{K}$$

$$f(Lys^{-}) = \frac{[HLys^{-}]}{L} = \frac{K_{a3}K_{a2}K_{a1}}{K}$$

These fractions are plotted against pH $= -\log H$ in Fig. 4.12. Note how H_3Lys^{2+} is dominant for pH $<$ pK_{a1}, that H_3Lys^{2+} and H_2Lys^{+} have the same concentration at pH = pK_{a1}, and that H_2Lys^{+} is dominant for pH $>$ pK_{a1}, until HLys becomes dominant, and so on. In a neutral solution at pH = 7, the dominant species is H_2Lys^{+}, for pH = 7 lies between pK_{a1} and pK_{a2}: below pK_{a1}, H_3Lys^{2+} is dominant and above pK_{a2}, HLys is dominant.

A note on good practice: Take note of the symmetry of the expressions derived here. By doing so, it is easy to write down the corresponding expressions for species with different numbers of acidic protons without repeating the lengthy calculation. ■

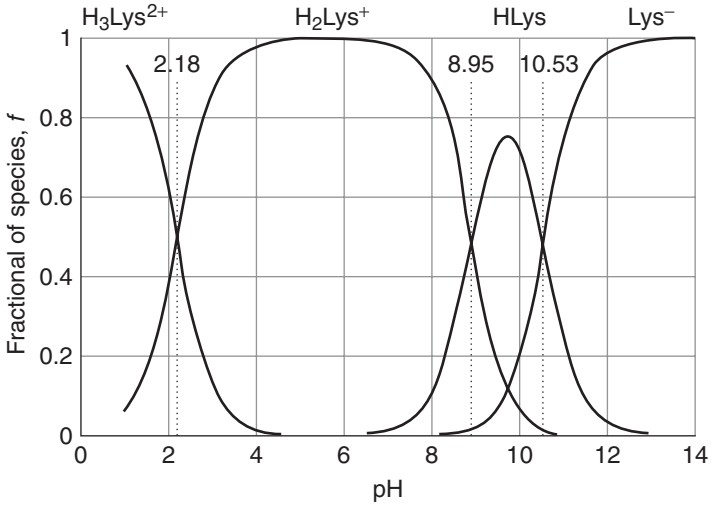
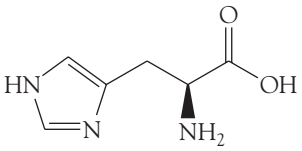


Fig. 4.12 The fractional composition of the protonated and deprotonated forms of lysine (Lys) in aqueous solution as a function of pH. Note that conjugate pairs are present at equal concentrations when the pH is equal to the pK_a of the acid member of the pair.



13 Histidine (His)

SELF-TEST 4.16 Construct the diagram for the fraction of protonated species in an aqueous solution of histidine (**13**).

Answer: Fig. 4.13

We can summarize the behavior discussed in *Case study* 4.3 and illustrated in Figs. 4.12 and 4.13 as follows. Consider each conjugate acid-base pair, with acidity constant K_a; then:

The acid form is dominant for $pH < pK_a$

The conjugate pair have equal concentrations at $pH = pK_a$

The base form is dominant for $pH > pK_a$

In each case, the other possible forms of a polyprotic system can be ignored, provided the pK_a values are not too close together.

4.12 Amphiprotic systems

Many molecules of biochemical significance (including the amino acids) can act as both proton donors and proton acceptors, and we need to be able to treat this dual function quantitatively.

An **amphiprotic** species is a molecule or ion that can both accept and donate protons. For instance, HCO_3^- can act as an acid (to form CO_3^{2-}) and as a base (to form H_2CO_3). Among the most important amphiprotic compounds are the amino acids, which can act as proton donors by virtue of their carboxyl groups and as bases by virtue of their amino groups. Indeed, in solution, amino acids are present largely in their **zwitterionic** ("double ion") form, in which the amino group is protonated and the carboxyl group is deprotonated: the acidic proton of the carboxyl group has been donated to the basic amino group (but not necessarily of the same molecule). The zwitterionic form of glycine, NH_2CH_2COOH, for instance, is $^+H_3NCH_2CO_2^-$.

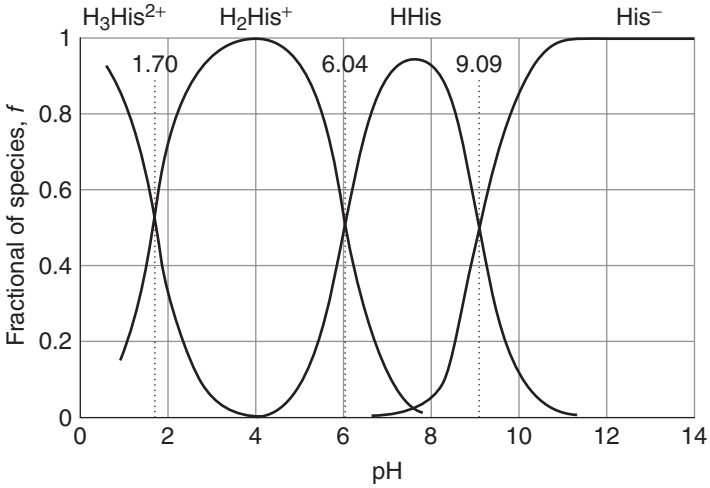


Fig. 4.13 The fractional composition of the protonated and deprotonated forms of histidine (His) in aqueous solution as a function of pH.

We can suppose that in an aqueous solution of glycine, the species present are NH_2CH_2COOH (and in general BAH, where B represents the basic amino group and AH the carboxylic acid group), $NH_2CH_2CO_2^-$ (BA^-), $^+NH_3CH_2COOH$ (^+HBAH), and the zwitterion $^+NH_3CH_2CO_2^-$ ($^+HBA^-$). The proton transfer equilibria in water are

$$\begin{aligned}
BAH(aq) + H_2O(l) &\rightleftharpoons H_3O^+(aq) + BA^-(aq) && K_1\\
{}^+HBAH(aq) + H_2O(l) &\rightleftharpoons H_3O^+(aq) + BAH(aq) && K_2\\
{}^+HBA^-(aq) + H_2O(l) &\rightleftharpoons H_3O^+(aq) + BA^-(aq) && K_3
\end{aligned}$$

By following the same procedure as in *Case study* 4.3, we find the following expressions for the composition of the solution, with $H = [H_3O^+]$:

$$f(BA^-) = \frac{K_1K_2K_3}{K} \qquad f(BAH) = \frac{HK_2K_3}{K}$$
$$f(^+HBA^-) = \frac{HK_1K_2}{K} \qquad f(^+HBAH) = \frac{H^2K_3}{K} \tag{4.25}$$

with $K = H^2K_3 + H(K_1 + K_3)K_2 + K_1K_2K_3$. The variation of composition with pH is shown in Fig. 4.14. Because we can expect the zwitterion to be a much weaker acid than the neutral molecule (because the negative charge on the carboxylate group hinders the escape of the proton from the conjugate acid of the amino group), we can anticipate that $K_3 << K_1$ and therefore that $f(BAH) << f(^+HBA^-)$ at all values of pH.

The further question we need to tackle is the pH of a solution of a salt with an amphiprotic anion, such as a solution of $NaHCO_3$. Is the solution acidic on

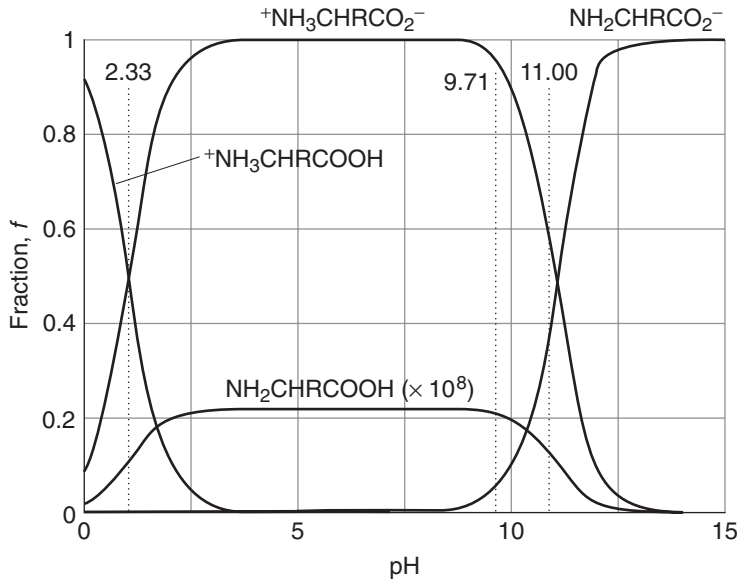


Fig. 4.14 The fractional composition of the protonated and deprotonated forms of an amino acid $NH_2CHRCOOH$, in which the group R does not participate in proton transfer reactions.

account of the acid character of HCO_3^-, or is it basic on account of the anion's basic character? As we show in the following *Derivation*, the pH of such a solution is given by

$$pH = \tfrac{1}{2}(pK_{a1} + pK_{a2}) \qquad \textbf{(4.26)}$$

DERIVATION 4.2 The pH of an amphiprotic salt solution

Let's suppose that we make up a solution of the salt MHA, where HA^- is the amphiprotic anion (such as HCO_3^-) and M^+ is a cation (such as Na^+). To reach equilibrium, in which HA^-, A^{2-}, and H_2A are all present, some HA^- (we write it x) is protonated to form H_2A and some HA^- (this we write y) deprotonates to form A^{2-}. The equilibrium table is as follows:

Species	H_2A	HA^-	A^{2-}	H_3O^+
Initial molar concentration/(mol L^{-1})	0	A	0	0
Change to reach equilibrium/(mol L^{-1})	$+x$	$-(x + y)$	$+y$	$+(y - x)$
Equilibrium concentration/(mol L^{-1})	x	$A - x - y$	y	$y - x$

The two acidity constants are

$$K_{a1} = \frac{[H_3O^+][HA^-]}{[H_2A]} = \frac{(y - x)(A - x - y)}{x}$$

$$K_{a2} = \frac{[H_3O^+][A^{2-}]}{[HA^-]} = \frac{(y - x)y}{A - x - y}$$

Multiplication of these two expressions, noting from the equilibrium table that at equilibrium $y - x$ is just $[H_3O^+]$, gives

$$K_{a1}K_{a2} = \frac{(y - x)^2 y}{x} = [H_3O^+]^2 \times \frac{y}{x}$$

Next, we show that, to a good approximation, $y/x \approx 1$ and therefore that $[H_3O^+] = (K_{a1}K_{a2})^{1/2}$. For this step we expand K_{a1} as follows:

$$xK_{a1} = Ay - y^2 - Ax + x^2$$

Because xK_{a1}, x^2, and y^2 are all very small compared with terms that have A in them, this expression reduces to

$$0 \approx Ay - Ax$$

We conclude that $x \approx y$ and therefore that $y/x \approx 1$, as required. Equation 4.26 now follows by taking the negative common logarithm of both sides of $[H_3O^+] = (K_{a1}K_{a2})^{1/2}$.

As an application of eqn 4.26, consider the pH of an aqueous solution of sodium hydrogencarbonate. Using values from Table 4.5, we can immediately conclude that the pH of the solution *of any concentration* is

$$pH = \tfrac{1}{2}(6.37 + 10.25) = 8.31$$

The solution is basic. We can treat a solution of potassium dihydrogenphosphate in the same way, taking into account only the second and third acidity constants of H_3PO_4 because protonation as far as H_3PO_4 is negligible (see Table 4.5):

$$pH = \tfrac{1}{2}(7.21 + 12.67) = 9.94$$

4.13 Buffer solutions

Cells cease to function and may be damaged irreparably if the pH changes significantly, so we need to understand how the pH is stabilized by a buffer.

Suppose that we make an aqueous solution by dissolving known amounts of a weak acid and its conjugate base. To calculate the pH of this solution, we make use of the expression for K_a of the weak acid and write

$$K_a = \frac{a_{H_3O^+}a_{base}}{a_{acid}} \approx \frac{a_{H_3O^+}[base]}{[acid]}$$

which rearranges first to

$$a_{H_3O^+} \approx \frac{K_a[acid]}{[base]}$$

and then, by taking negative common logarithms, to the **Henderson-Hasselbalch equation**:

$$pH \approx pK_a - \log\frac{[acid]}{[base]} \qquad \textbf{(4.27)}$$

When the concentrations of the conjugate acid and base are equal, the second term on the right of eqn 4.27 is $\log 1 = 0$, so under these conditions $pH = pK_a$.

ILLUSTRATION 4.3 Using the Henderson-Hasselbalch equation

To calculate the pH of a solution formed from equal amounts of $CH_3COOH(aq)$ and $NaCH_3CO_2(aq)$, we note that the latter dissociates (in the sense of separating into ions) fully in water, yielding the ions $Na^+(aq)$ and $CH_3CO_2^-(aq)$, the conjugate base of $CH_3COOH(aq)$. The equilibrium of interest is

$$CH_3COOH(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + CH_3CO_2^-(aq)$$

$$K_a = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3COOH]}$$

Because the pK_a of $CH_3COOH(aq)$ is 4.75 (Table 4.4), it follows from eqn 4.27 that pH = 4.8 (more realistically, pH = 5). ■

SELF-TEST 4.17 Calculate the pH of an aqueous buffer solution that contains equal amounts of NH_3 and NH_4Cl.

Answer: 9.25; more realistically: 9

It is observed that solutions containing known amounts of an acid and that acid's conjugate base show **buffer action**, the ability of a solution to oppose changes in pH when small amounts of strong acids and bases are added. An **acid buffer** solution, one that stabilizes the solution at a pH below 7, is typically prepared by making a solution of a weak acid (such as acetic acid) and a salt that supplies its conjugate base (such as sodium acetate). A **base buffer**, one that stabilizes a solution at a pH above 7, is prepared by making a solution of a weak base (such as ammonia) and a salt that supplies its conjugate acid (such as ammonium chloride). Physiological buffers are responsible for maintaining the pH of blood within a narrow range of 7.37 to 7.43, thereby stabilizing the active conformations of biological macromolecules and optimizing the rates of biochemical reactions.

An acid buffer stabilizes the pH of a solution because the abundant supply of A^- ions (from the salt) can remove any H_3O^+ ions brought by additional acid; furthermore, the abundant supply of HA molecules (from the acid component of the buffer) can provide H_3O^+ ions to react with any base that is added. Similarly, in a base buffer the weak base B can accept protons when an acid is added and its conjugate acid BH^+ can supply protons if a base is added. The following example explores the quantitative basis of buffer action.

EXAMPLE 4.7 Assessing buffer action

Estimate the effect of addition of 0.020 mol of hydronium ions (from a solution of a strong acid, such as hydrochloric acid) on the pH of 1.0 L of (a) 0.15 M $CH_3COOH(aq)$ and (b) a buffer solution containing 0.15 M $CH_3COOH(aq)$ and 0.15 M $NaCH_3CO_2(aq)$.

Strategy Before addition of hydronium ions, the pHs of solutions (a) and (b) are 2.8 (*Example* 4.5) and 4.8 (*Illustration* 4.3). After addition to solution (a) the initial molar concentration of $CH_3COOH(aq)$ is 0.15 M and that of $H_3O^+(aq)$ is (0.020 mol)/(1.0 L) = 0.020 M. After addition to solution (b), the initial molar concentrations of $CH_3COOH(aq)$, $CH_3CO_2^-(aq)$, and $H_3O^+(aq)$ are 0.15 M, 0.15 M, and 0.020 M, respectively. The weak base already present in solution, $CH_3CO_2^-(aq)$, reacts immediately with the added hydronium ion:

$$CH_3CO_2^-(aq) + H_3O^+(aq) \longrightarrow CH_3COOH(aq) + H_2O(l)$$

We use the adjusted concentrations of $CH_3COOH(aq)$ and $CH_3CO_2^-(aq)$ and eqn 4.27 to calculate a new value of the pH of the buffer solution.

Solution For addition of a strong acid to solution (a), we draw up the following equilibrium table to show the effect of the addition of hydronium ions:

Species	CH_3COOH	H_3O^+	$CH_3CO_2^-$
Initial concentration/(mol L^{-1})	0.15	0.02	0
Change to reach equilibrium/(mol L^{-1})	$-x$	$+x$	$+x$
Equilibrium concentration/(mol L^{-1})	$0.15 - x$	$0.020 + x$	x

The value of x is found by inserting the equilibrium concentrations into the expression for the acidity constant:

$$K_a = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3COOH]} = \frac{(0.020 + x) \times x}{0.15 - x}$$

As in *Example* 4.5, we assume that x is very small; in this case $x << 0.020$, and write

$$K_a \approx \frac{0.020 \times x}{0.15}$$

Then

$$x = (0.15/0.020) \times K_a = 7.5 \times 1.8 \times 10^{-5} = 1.4 \times 10^{-4}$$

We see that our approximation is valid and, therefore, $[H_3O^+] = 0.020 + x \approx 0.020$ and pH = 1.7. It follows that the pH of the unbuffered solution (a) changes dramatically from 4.8 to 1.7 upon addition of 0.020 M $H_3O^+(aq)$.

Now we consider the addition of 0.020 M $H_3O^+(aq)$ to solution (b). Reaction between the strong acid and weak base consumes the added hydronium ions and changes the concentration of $CH_3CO_2^-(aq)$ to 0.13 M and the concentration of $CH_3COOH(aq)$ to 0.17 M. It follows from eqn 4.27 that

$$pH = pK_a - \log \frac{[CH_3COOH]}{[CH_3CO_2^-]} = 4.75 - \log \frac{0.17}{0.13} = 4.6$$

The pH of the buffer solution (b) changes only slightly from 4.8 to 4.6 upon addition of 0.020 M $H_3O^+(aq)$.

SELF-TEST 4.18 Estimate the change in pH of solution (b) from *Example* 4.7 after addition of 0.020 mol of $OH^-(aq)$.

Answer: 4.9 ■

CASE STUDY 4.4 Buffer action in blood

The pH of blood in a healthy human being varies from 7.37 to 7.43. There are two buffer systems that help maintain the pH of blood relatively constant: one arising from a carbonic acid/bicarbonate (hydrogencarbonate) ion equilibrium and another involving protonated and deprotonated forms of hemoglobin, the protein responsible for the transport of O_2 in blood (*Case study* 4.1).

Carbonic acid forms in blood from the reaction between water and CO_2 gas, which comes from inhaled air and is also a by-product of metabolism (Section 4.8):

$$CO_2(g) + H_2O(l) \rightleftharpoons H_2CO_3(aq)$$

In red blood cells, this reaction is catalyzed by the enzyme carbonic anhydrase. Aqueous carbonic acid then deprotonates to form bicarbonate (hydrogencarbonate) ion:

$$H_2CO_3(aq) \rightleftharpoons H^+(aq) + HCO_3^-(aq)$$

The fact that the pH of normal blood is approximately 7.4 implies that $[HCO_3^-]/[H_2CO_3] \approx 20$. The body's control of the pH of blood is an example of **homeostasis**, the ability of an organism to counteract environmental changes with

physiological responses. For instance, the concentration of carbonic acid can be controlled by respiration: exhaling air depletes the system of $CO_2(g)$ and $H_2CO_3(aq)$ so the pH of blood rises when air is exhaled. Conversely, inhalation increases the concentration of carbonic acid in blood and lowers its pH. The kidneys also play a role in the control of the concentration of hydronium ions. There, ammonia formed by the release of nitrogen from some amino acids (such as glutamine) combines with excess hydronium ions and the ammonium ion is excreted through urine.

The condition known as *alkalosis* occurs when the pH of blood rises above about 7.45. *Respiratory alkalosis* is caused by hyperventilation, or excessive respiration. The simplest remedy consists of breathing into a paper bag in order to increase the levels of inhaled CO_2. *Metabolic alkalosis* may result from illness, poisoning, repeated vomiting, and overuse of diuretics. The body may compensate for the increase in the pH of blood by decreasing the rate of respiration.

Acidosis occurs when the pH of blood falls below about 7.35. In *respiratory acidosis*, impaired respiration increases the concentration of dissolved CO_2 and lowers the blood's pH. The condition is common in victims of smoke inhalation and patients with asthma, pneumonia, and emphysema. The most efficient treatment consists of placing the patient in a ventilator. *Metabolic acidosis* is caused by the release of large amounts of lactic acid or other acidic by-products of metabolism (Section 4.8), which react with bicarbonate ion to form carbonic acid, thus lowering the blood's pH. The condition is common in patients with diabetes and severe burns.

The concentration of hydronium ion in blood is also controlled by hemoglobin, which can exist in deprotonated (basic) or protonated (acidic) forms, depending on the state of protonation of several histidines (**13**) on the protein's surface (see Fig. 4.13 for a diagram of the fraction of protonated species in an aqueous solution of histidine). The carbonic acid/bicarbonate ion equilibrium and proton equilibria in hemoglobin also regulate the oxygenation of blood. The key to this regulatory mechanism is the **Bohr effect**, the observation that hemoglobin binds O_2 strongly when it is deprotonated and releases O_2 when it is protonated. It follows that when dissolved CO_2 levels are high and the pH of blood falls slightly, hemoglobin becomes protonated and releases bound O_2 to tissue. Conversely, when CO_2 is exhaled and the pH rises slightly, hemoglobin becomes deprotonated and binds O_2. ■

Checklist of Key Ideas

You should now be familiar with the following concepts:

- ☐ **1.** The reaction Gibbs energy, $\Delta_r G$, is the slope of a plot of Gibbs energy against composition.
- ☐ **2.** The condition of chemical equilibrium at constant temperature and pressure is $\Delta_r G = 0$.
- ☐ **3.** The reaction Gibbs energy is related to the composition by $\Delta_r G = \Delta_r G^\ominus + RT \ln Q$, where Q is the reaction quotient.
- ☐ **4.** The standard reaction Gibbs energy is the difference of the standard Gibbs energies of formation of the products and reactants weighted by the stoichiometric coefficients in the chemical equation $\Delta_r G^\ominus = \sum \nu \Delta_f G^\ominus(\text{products}) - \sum \nu \Delta_f G^\ominus(\text{reactants})$.
- ☐ **5.** The equilibrium constant is the value of the reaction quotient at equilibrium; it is related to the standard Gibbs energy of reaction by $\Delta_r G^\ominus = -RT \ln K$.
- ☐ **6.** A compound is thermodynamically stable with respect to its elements if $\Delta_f G^\ominus < 0$.
- ☐ **7.** The equilibrium constant of a reaction is independent of the presence of a catalyst.

- □ **8.** The variation of an equilibrium constant with temperature is expressed by the van 't Hoff equation, $\ln K' - \ln K = (\Delta_r H^\ominus/R)\{(1/T) - (1/T')\}$.
- □ **9.** The equilibrium constant K increases with temperature if $\Delta_r H^\ominus > 0$ (an endothermic reaction) and decreases if $\Delta_r H^\ominus < 0$ (an exothermic reaction).
- □ **10.** An endergonic reaction has a positive Gibbs energy; an exergonic reaction has a negative Gibbs energy.
- □ **11.** The biological standard state corresponds to pH = 7; the biological and thermodynamic standard reaction Gibbs energies of the reaction Reactants + ν $H_3O^+(aq) \longrightarrow$ products are related by $\Delta_r G^\oplus = \Delta_r G^\ominus + 7\nu RT \ln 10$.
- □ **12.** An endergonic reaction may be driven forward by coupling it to an exergonic reaction.
- □ **13.** The strength of an acid HA is reported in terms of its acidity constant, $K_a = a_{H_3O^+}a_{A^-}/a_{HA}$, and that of a base B in terms of its basicity constant, $K_b = a_{BH^+}a_{OH^-}/a_B$.
- □ **14.** The autoprotolysis constant of water is $K_w = a_{H_3O^+}a_{OH^-}$; this relation implies that pH + pOH = pK_w.
- □ **15.** The basicity constant of a base is related to the acidity constant of its conjugate acid by $K_aK_b = K_w$ (or pK_a + pK_b = pK_w).
- □ **16.** The acid form of a species is dominant if pH < pK_a, and the base form is dominant if pH > pK_a.
- □ **17.** The pH of the solution of an amphiprotic salt is pH = ½(pK_{a1} + pK_{a2}).
- □ **18.** The pH of a mixed solution of a weak acid and its conjugate base is given by the Henderson-Hasselbalch equation, pH = pK_a − log([acid]/[base]).
- □ **19.** The pH of a buffer solution containing equal concentrations of a weak acid and its conjugate base is pH = pK_a.

Further information 4.1 The complete expression for the pH of a solution of a weak acid

Some acids are so weak and undergo so little deprotonation that the autoprotolysis of water can contribute significantly to the pH. We must also take autoprotolysis into account when we find by using the procedures in *Example* 4.5 that the pH of a solution of a weak acid is greater than 6.

We begin the calculation by noting that, apart from water, there are four species in solution, HA, A^-, H_3O^+, and OH^-. Because there are four unknown quantities, we need four equations to solve the problem. Two of the equations are the expressions for K_a and K_w (eqns 4.17 and 4.20), written here in terms of molar concentrations:

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \quad \textbf{(4.28)}$$

$$K_w = [H_3O^+][OH^-] \quad \textbf{(4.29)}$$

A third equation takes **charge balance**, the requirement that the solution be electrically neutral, into account. That is, the sum of the concentrations of the cations must be equal to the sum of the concentrations of the anions. In our case, the charge balance equation is

$$[H_3O^+] = [OH^-] + [A^-] \quad \textbf{(4.30)}$$

We also know that the total concentration of A groups in all forms in which they occur, which we denote as A, must be equal to the initial concentration of the weak acid. This condition, known as **material balance**, gives our final equation:

$$A = [HA] + [A^-] \quad \textbf{(4.31)}$$

Now we are ready to proceed with a calculation of the hydronium ion concentration in the solution. First, we combine eqns 4.29 and 4.31 and write

$$[A^-] = [H_3O^+] - \frac{K_w}{[H_3O^+]} \quad \textbf{(4.32)}$$

We continue by substituting this expression into eqn 4.31 and solving for [HA]:

$$[HA] = A - [H_3O^+] + \frac{K_w}{[H_3O^+]} \quad \textbf{(4.33)}$$

Upon substituting the expressions for $[A^-]$ (eqn 4.32) and HA (eqn 4.33) into eqn 4.28, we obtain

$$K_a = \frac{[H_3O^+]\left([H_3O^+] - \dfrac{K_w}{[H_3O^+]}\right)}{A - [H_3O^+] + \dfrac{K_w}{[H_3O^+]}} \quad \textbf{(4.34)}$$

Rearrangement of this expression gives

$$[H_3O^+]^3 + K_a[H_3O^+]^2 - (K_w + K_aA)[H_3O^+] - K_aK_w = 0 \quad \textbf{(4.35)}$$

and we see that $[H_3O^+]$ is determined by solving this cubic equation, a task that is best accomplished with a calculator or mathematical software.

There are several experimental conditions that allow us to simplify eqn 4.34. For example, when $[H_3O^+] > 10^{-6}$ M (or pH < 6), $K_w/[H_3O^+] < 10^{-8}$ M and we can ignore this term in eqn 4.34. The resulting expression is

$$K_a = \frac{[H_3O^+]^2}{A - [H_3O^+]} \quad \textbf{(4.36)}$$

Rearrangement of eqn 4.36 gives a quadratic equation:

$$[H_3O^+]^2 + K_a[H_3O^+] - K_aA = 0 \quad \textbf{(4.37)}$$

which can be solved for $[H_3O^+]$. If the extent of deprotonation is very small, we let $[H_3O^+] \ll A$ and write

$$K_a = \frac{[H_3O^+]^2}{A} \quad \textbf{(4.38a)}$$

$$[H_3O^+] = (K_aA)^{1/2} \quad \textbf{(4.38b)}$$

Equations 4.36 and 4.38 are similar to the expressions used in *Example* 4.5, where we set $[H_3O^+]$ equal to x.

Discussion questions

4.1 Explain how the mixing of reactants and products affects the position of chemical equilibrium.

4.2 Explain how a reaction that is not spontaneous may be driven forward by coupling to a spontaneous reaction.

4.3 At blood temperature, $\Delta_rG^\oplus = -218$ kJ mol^{-1} and $\Delta_rH^\oplus = -120$ kJ mol^{-1} for the production of lactate ion during glycolysis. Provide a molecular interpretation for the observation that the reaction is more exergonic than it is exothermic.

4.4 Explain Le Chatelier's principle in terms of thermodynamic quantities.

4.5 Describe the basis of buffer action.

4.6 State the limits to the generality of the following expressions: **(a)** $pH = \frac{1}{2}(pK_{a1} + pK_{a2})$, **(b)** $pH = pK_a - \log([acid]/[base])$, and **(c)** the van 't Hoff equation, written as

$$\ln K' - \ln K = \frac{\Delta_rH^\ominus}{R}\left(\frac{1}{T} - \frac{1}{T'}\right)$$

Exercises

4.7 Write the expressions for the equilibrium constants for the following reactions, making the approximation of replacing activities by molar concentrations or partial pressures:

(a) G6P(aq) + H_2O(l) ⇌ G(aq) + P_i(aq), where G6P is glucose-6-phosphate, G is glucose, and P_i is inorganic phosphate.

(b) Gly(aq) + Ala(aq) ⇌ Gly–Ala(aq) + H_2O(l)

(c) Mg^{2+}(aq) + ATP^{4-}(aq) ⇌ $MgATP^{2-}$(aq)

(d) 2 $CH_3COCOOH$(aq) + 5 O_2(g) ⇌ 6 CO_2(g) + 4 H_2O(l)

4.8 The equilibrium constant for the reaction A + B ⇌ 2 C is reported as 3.4×10^4. What would it be for the reaction written as **(a)** 2 C ⇌ A + B, **(b)** 2 A + 2 B ⇌ 4 C, **(c)** ½ A + ½ B ⇌ C?

4.9 The equilibrium constant for the hydrolysis of the dipeptide alanylglycine by a peptidase enzyme is $K = 8.1 \times 10^2$ at 310 K. Calculate the standard reaction Gibbs energy for the hydrolysis.

4.10 One enzyme-catalyzed reaction in a biochemical cycle has an equilibrium constant that is 10 times the equilibrium constant of a second reaction. If the standard Gibbs energy of the former reaction is −300 kJ mol^{-1}, what is the standard reaction Gibbs energy of the second reaction?

4.11 What is the value of the equilibrium constant of a reaction for which $\Delta_rG^\ominus = 0$?

4.12 The standard reaction Gibbs energies (at pH = 7) for the hydrolysis of glucose-1-phosphate, glucose-6-phosphate, and glucose-3-phosphate are −21, −14, and −9.2 kJ mol^{-1}, respectively. Calculate the equilibrium constants for the hydrolyses at 37°C.

4.13 The standard Gibbs energy for the hydrolysis of ATP to ADP is −31 kJ mol^{-1}; what is the Gibbs energy of reaction in an environment at 37°C in which the ATP, ADP, and P_i concentrations are all **(a)** 1.0 mmol L^{-1}, **(b)** 1.0 μmol L^{-1}?

4.14 The distribution of Na^+ ions across a typical biological membrane is 10 mmol L^{-1} inside the cell and 140 mmol L^{-1} outside the cell. At equilibrium the concentrations are equal. What is the Gibbs energy difference across the membrane at 37°C? The difference in concentration must be sustained by coupling to reactions that have at least that difference of Gibbs energy.

4.15 For the hydrolysis of ATP at 37°C, $\Delta_r H^\oplus$ = −20 kJ mol^{-1} and $\Delta_r S^\oplus$ = +34 J K^{-1} mol^{-1}. Assuming that these quantities remain constant, estimate the temperature at which the equilibrium constant for the hydrolysis of ATP becomes greater than 1.

4.16 Two polynucleotides with sequences A_nU_n (where A and U denote adenine and uracil, respectively) interact through A–U base pairs, forming a double helix. When $n = 5$ and $n = 6$, the equilibrium constants for formation of the double helix are 5.0×10^3 and 2.0×10^5, respectively. **(a)** Suggest an explanation for the increase in the value of the equilibrium constant with n. **(b)** Calculate the contribution of a single A–U base pair to the Gibbs energy of formation of a double helix between A_nU_n polypeptides.

4.17 Under biochemical standard conditions, aerobic respiration produces approximately 38 molecules of ATP per molecule of glucose that is completely oxidized. **(a)** What is the percentage efficiency of aerobic respiration under biochemical standard conditions? **(b)** The following conditions are more likely to be observed in a living cell: $p_{CO_2} = 5.3 \times 10^{-2}$ atm, $p_{O_2} = 0.132$ atm, [glucose] = 5.6×10^{-2} mol L^{-1}, [ATP] = [ADP] = [P_i] = 1.0×10^{-4} mol L^{-1}, pH = 7.4, T = 310 K. Assuming that activities can be replaced by the numerical values of molar concentrations, calculate the efficiency of aerobic respiration under these physiological conditions.

4.18 The second step in glycolysis is the isomerization of glucose-6-phosphate (G6P) to fructose-6-phosphate (F6P). *Example* 4.2 considered the equilibrium between F6P and G6P. Draw a graph to show how the reaction Gibbs energy varies with the fraction f of F6P in solution. Label the regions of the graph that correspond to the formation of F6P and G6P being spontaneous, respectively.

4.19 The saturation curves shown Fig. 4.7 may also be modeled mathematically by the equation

$$\log \frac{s}{1-s} = \nu \log p - \nu \log K$$

where s is the saturation, p is the partial pressure of O_2, K is a constant (not the equilibrium constant for binding of one ligand), and ν is the *Hill coefficient*, which varies from 1, for no cooperativity, to N for all-or-none binding of N ligands ($N = 4$ in Hb). The Hill coefficient for Mb is 1, and for Hb it is 2.8. **(a)** Determine the constant K for both Mb and Hb from the graph of fractional saturation (at $s = 0.5$) and then calculate the fractional saturation of Mb and Hb for the following values of p/kPa: 1.0, 1.5, 2.5, 4.0, 8.0. **(b)** Calculate the value of s at the same p values assuming ν has the theoretical maximum value of 4.

4.20 Classify the following compounds as endergonic or exergonic: **(a)** glucose, **(b)** urea, **(c)** octane, **(d)** ethanol.

4.21 Consider the combustion of sucrose:

$$C_{12}H_{22}O_{11}(s) + 12\ O_2(g) \rightleftharpoons 12\ CO_2(g) + 11\ H_2O(l)$$

(a) Combine the standard reaction entropy with the standard reaction enthalpy and calculate the standard reaction Gibbs energy at 298 K. **(b)** In assessing metabolic processes, we are usually more interested in the work that may be performed for the consumption of a given mass of compound than the heat it can produce (which merely keeps the body warm). Recall

from Chapter 2 that the change in Gibbs energy can be identified with the maximum non-expansion work that can be extracted from a process. What is the maximum energy that can be extracted as **(i)** heat, **(ii)** non-expansion work when 1.0 kg of sucrose is burned under standard conditions at 298 K?

4.22 Is it more energy effective to ingest sucrose or glucose? Calculate the non-expansion work, the expansion work, and the total work that can be obtained from the combustion of 1.0 kg of glucose under standard conditions at 298 K when the product includes liquid water. Compare your answer with your results from *Exercise* 4.21b.

4.23 The oxidation of glucose in the mitochondria of energy-hungry brain cells leads to the formation of pyruvate ions, which are then decarboxylated to ethanal (acetaldehyde, CH_3CHO) in the course of the ultimate formation of carbon dioxide. **(a)** The standard Gibbs energies of formation of pyruvate ions in aqueous solution and gaseous ethanal are −474 and −133 kJ mol^{-1}, respectively. Calculate the Gibbs energy of the reaction in which pyruvate ions are converted to ethanal by the action of pyruvate decarboxylase with the release of carbon dioxide. **(b)** Ethanal is soluble in water. Would you expect the standard Gibbs energy of the enzyme-catalyzed decarboxylation of pyruvate ions to ethanal in solution to be larger or smaller than the value for the production of gaseous ethanal?

4.24 Calculate the standard biological Gibbs energy for the reaction

$$\text{Pyruvate}^- + \text{NADH} + \text{H}^+ \longrightarrow \text{lactate}^- + \text{NAD}^+$$

at 310 K given that $\Delta_r G^\ominus = -66.6$ kJ mol^{-1}. (NAD^+ is the oxidized form of nicotinamide dinucleotide.) This reaction occurs in muscle cells deprived of oxygen during strenuous exercise and can lead to cramping.

4.25 The standard biological reaction Gibbs energy for the removal of the phosphate group from adenosine monophosphate is −14 kJ mol^{-1} at 298 K. What is the value of the thermodynamic standard reaction Gibbs energy?

4.26 Estimate the values of the biological standard Gibbs energies of the following phosphate transfer reactions:

(a) GTP(aq) + ADP(aq) ⟶ GDP(aq) + ATP(aq)

(b) Glycerol(aq) + ATP(aq) ⟶ glycerol-1-phosphate + ADP(aq)

(c) 3-Phosphoglycerate(aq) + ATP(aq) ⟶ 1,3-bis(phospho)glycerate(aq) + ADP(aq)

4.27 Show that if the logarithm of an equilibrium constant is plotted against the reciprocal of the temperature, then the standard reaction enthalpy may be determined.

4.28 The conversion of fumarate ion to malate ion is catalyzed by the enzyme fumarase:

$$\text{Fumarate}^{2-}(\text{aq}) + \text{H}_2\text{O}(\text{l}) \longrightarrow \text{malate}^-(\text{aq})$$

Use the following data to determine the standard reaction enthalpy:

θ/°C	15	20	25	30	35	40	45	50
K	4.786	4.467	4.074	3.631	3.311	3.090	2.754	2.399

4.29 What is the standard enthalpy of a reaction for which the equilibrium constant is **(a)** doubled, **(b)** halved when the temperature is increased by 10 K at 298 K?

4.30 Numerous acidic species are found in living systems. Write the proton transfer equilibria for the following biochemically important acids in aqueous solution: **(a)** $H_2PO_4^-$ (dihydrogenphosphate ion), **(b)** lactic acid ($CH_3CHOHCOOH$), **(c)** glutamic acid ($HOOCCH_2CH_2CH(NH_2)COOH$), **(d)** glycine (NH_2CH_2COOH), **(e)** oxalic acid ($HOOCCOOH$).

4.31 For biological and medical applications we often need to consider proton transfer equilibria at body temperature (37°C). The value of K_w for water at body temperature is 2.5×10^{-14}. **(a)** What is the value of $[H_3O^+]$ and the pH of neutral water at 37°C? **(b)** What is the molar concentration of OH^- ions and the pOH of neutral water at 37°C?

4.32 Suppose that something had gone wrong in the Big Bang, and instead of ordinary hydrogen there was an abundance of deuterium in the universe. There would be many subtle changes in equilibria, particularly the deuteron transfer equilibria of heavy atoms and bases. The K_w for D_2O, heavy water, at 25°C is 1.35×10^{-15}.

(a) Write the chemical equation for the autoprotolysis (more precisely, autodeuterolysis) of D_2O. **(b)** Evaluate pK_w for D_2O at 25°C. **(c)** Calculate the molar concentrations of D_3O^+ and OD^- in neutral heavy water at 25°C. **(d)** Evaluate the pD and pOD of neutral heavy water at 25°C. **(e)** Formulate the relation between pD, pOD, and $pK_w(D_2O)$.

4.33 The molar concentration of H_3O^+ ions in the following solutions was measured at 25°C. Calculate the pH and pOH of the solution: **(a)** 1.5×10^{-5} mol L^{-1} (a sample of rainwater), **(b)** 1.5 mmol L^{-1}, **(c)** 5.1×10^{-14} mol L^{-1}, **(d)** 5.01×10^{-5} mol L^{-1}.

4.34 Calculate the molar concentration of H_3O^+ ions and the pH of the following solutions: **(a)** 25.0 cm^3 of 0.144 M HCl(aq) was added to 25.0 cm^3 of 0.125 M NaOH(aq), **(b)** 25.0 cm^3 of 0.15 M HCl(aq) was added to 35.0 cm^3 of 0.15 M KOH(aq), **(c)** 21.2 cm^3 of 0.22 M HNO_3(aq) was added to 10.0 cm^3 of 0.30 M NaOH(aq).

4.35 Determine whether aqueous solutions of the following salts have a pH equal to, greater than, or less than 7; if pH > 7 or pH < 7, write a chemical equation to justify your answer. **(a)** NH_4Br, **(b)** Na_2CO_3, **(c)** KF, **(d)** KBr.

4.36 **(a)** A sample of potassium acetate, KCH_3CO_2, of mass 8.4 g is used to prepare 250 cm^3 of solution. What is the pH of the solution? **(b)** What is the pH of a solution when 3.75 g of ammonium bromide, NH_4Br, is used to make 100 cm^3 of solution? **(c)** An aqueous solution of volume 1.0 L contains 10.0 g of potassium bromide. What is the percentage of Br^- ions that are protonated?

4.37 There are many organic acids and bases in our cells, and their presence modifies the pH of the fluids inside them. It is useful to be able to assess the pH of solutions of acids and bases and to make inferences from measured values of the pH. A solution of equal concentrations of lactic acid and sodium lactate was found to have pH = 3.08. **(a)** What are the values of pK_a and K_a of lactic acid? **(b)** What would the pH be if the acid had twice the concentration of the salt?

4.38 Calculate the pH, pOH, and fraction of solute protonated or deprotonated in the following aqueous solutions: **(a)** 0.120 M $CH_3CH(OH)COOH$(aq) (lactic acid), **(b)** 1.4×10^{-4} M $CH_3CH(OH)COOH$(aq), **(c)** 0.15 M NH_4Cl(aq), **(d)** 0.15 M $NaCH_3CO_2$(aq), **(e)** 0.112 M $(CH_3)_3N$(aq) (trimethylamine).

4.39 Show how the composition of an aqueous solution that contains 0.010 mol L^{-1} glycine varies with pH.

4.40 Show how the composition of an aqueous solution that contains 0.010 mol L^{-1} tyrosine varies with pH.

4.41 Calculate the pH of the following acid solutions at 25°C; ignore second deprotonations only when that approximation is justified. **(a)** 1.0×10^{-4} M H_3BO_3(aq) (boric acid acts as a monoprotic acid), **(b)** 0.015 M H_3PO_4(aq), **(c)** 0.10 M H_2SO_3(aq).

4.42 The amino acid tyrosine has $pK_a = 2.20$ for deprotonation of its carboxylic acid group. What are the relative concentrations of tyrosine and its conjugate base at a pH of **(a)** 7, **(b)** 2.2, **(c)** 1.5?

4.43 Appreciable concentrations of the potassium and calcium salts of oxalic acid, $(COOH)_2$, are found in many leafy green plants, such as rhubarb and spinach. **(a)** Calculate the molar concentrations of $HOOCCO_2^-$, $(CO_2)_2^{2-}$, H_3O^+, and OH^- in 0.15 M $(COOH)_2$(aq). **(b)** Calculate the pH of a solution of potassium hydrogenoxalate.

4.44 In green sulfur bacteria, hydrogen sulfide, H_2S, is the agent that brings about the reduction of CO_2 to carbohydrates during photosynthesis. Calculate the molar concentrations of H_2S, HS^-, S^{2-}, H_3O^+, and OH^- in 0.065 M H_2S(aq).

4.45 The *isoelectric point*, pI, of an amino acid is the pH at which the predominant species in solution is the zwitterionic form of the amino acid and only small but equal concentrations of positively and negatively charged forms of the amino acid are present. It follows that at the isoelectric point, the average charge on the amino acid is zero. Show that **(a)** $pI = \frac{1}{2}(pK_{a1} + pK_{a2})$ for amino acids with side chains that are neither acidic nor basic (such as glycine and alanine), **(b)** $pI = \frac{1}{2}(pK_{a1} + pK_{a2})$ for amino acids with acidic side chains (such as aspartic acid and glutamic acid), and **(c)** $pI = \frac{1}{2}(pK_{a2} + pK_{a3})$ for amino acids with basic side chains (such as lysine and histidine), where pK_{a1}, pK_{a2}, and pK_{a3} are given in Table 4.6. *Hint:* See *Case study* 4.3 and *Derivation* 4.2.

4.46 Predict the pH region in which each of the following buffers will be effective, assuming equal

molar concentrations of the acid and its conjugate base: **(a)** sodium lactate and lactic acid, **(b)** sodium benzoate and benzoic acid, **(c)** potassium hydrogenphosphate and potassium phosphate, **(d)** potassium hydrogenphosphate and potassium dihydrogenphosphate, **(e)** hydroxylamine and hydroxylammonium chloride.

4.47 From the information in Tables 4.4 and 4.5, select suitable buffers for **(a)** pH = 2.2 and **(b)** pH = 7.0.

4.48 The weak base colloquially known as Tris, and more precisely as tris(hydroxymethyl)aminomethane, has $pK_a = 8.3$ at 20°C and is commonly used to produce a buffer for biochemical applications. **(a)** At what pH would you expect Tris to act as a buffer in a solution that has equal molar concentrations of Tris and its conjugate acid? **(b)** What is the pH after the addition of 3.3 mmol NaOH to 100 cm^3 of a buffer solution with equal molar concentrations of Tris and its conjugate acid form? **(c)** What is the pH after the addition of 6.0 mmol HNO_3 to 100 cm^3 of a buffer solution with equal molar concentrations of Tris and its conjugate acid?

Projects

4.49 Here we continue our exploration of the thermodynamics of unfolding of biological macromolecules. Our focus is the thermal and chemical denaturation of chymotrypsin, one of many enzymes that catalyze the cleavage of polypeptides (see *Case study* 8.1).

(a) The denaturation of a biological macromolecule can be described by the equilibrium

$$\text{macromolecule in native form} \rightleftharpoons \text{macromolecule in denatured form}$$

Show that the fraction θ of denatured macromolecules is related to the equilibrium constant K_d for the denaturation process by

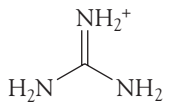
$$\theta = \frac{1}{1 + K_d}$$

(b) Now explore the thermal denaturation of a biological macromolecule. **(i)** Write an expression for the temperature dependence of K_d in terms of the standard enthalpy and standard entropy of denaturation. **(ii)** At pH = 2, the standard enthalpy and entropy of denaturation of chymotrypsin are +418 kJ mol^{-1} and +1.32 kJ K^{-1} mol^{-1}, respectively. Using these data and your results from parts (a) and (b.i), plot θ against T. Compare the shape of your plot with that of the plot shown in Fig. 3.16. **(iii)** The "melting temperature" of a biological macromolecule is the temperature at which $\theta = \frac{1}{2}$. Use your results from part (ii) to calculate the melting temperature of chymotrypsin at pH = 2. **(iv)** Calculate the standard Gibbs energy and the equilibrium constant for the denaturation of chymotrypsin at pH = 2.0 and T = 310 K (body temperature). Is the protein stable under these conditions?

(c) We saw in *Exercise* 3.35 that the unfolding of a protein may also be brought about by treatment with *denaturants*, substances such as guanidinium hydrochloride (GuHCl; the guanidinium ion is shown in **14**) that disrupt the intermolecular interactions responsible for the native three-dimensional conformation of a biological macromolecule. Data for a number of proteins denatured by urea or guanidinium hydrochloride suggest a linear relationship between the Gibbs energy of denaturation of a protein, ΔG_d, and the molar concentration of a denaturant [D]:

$$\Delta G_d^{\ominus} = \Delta G^{\ominus}_{d,water} - m[D]$$

where m is an empirical parameter that measures the sensitivity of unfolding to denaturant concentration and $\Delta G^{\ominus}_{d,water}$ is the Gibbs energy of denaturation of the protein in the absence of denaturant and is a measure of the thermal stability of the macromolecule. **(i)** At 27°C and



14 The guanidinium ion

pH 6.5, the fraction θ of denatured chymotrypsin molecules varies with the concentration of GuHCl as follows:

θ	1.00	0.99	0.78	0.44	0.23	0.08	0.06	0.01
[GuHCl]/(mol L^{-1})	0.00	0.75	1.35	1.70	2.00	2.35	2.70	3.00

Calculate m and $\Delta G^{\ominus}_{d,water}$ for chymotrypsin under these experimental conditions. **(ii)** Using the same data, plot θ against [GnHCl]. Comment on the shape of the curve. **(iii)** To gain insight into your results from part (c.ii), you will now derive an equation that relates θ to [D]. Begin by showing that $\Delta G^{\ominus}_{d,water} = m[D]_{1/2}$, where $[D]_{1/2}$ is the concentration of denaturant corresponding to $\theta = \frac{1}{2}$. Then write an expression for θ as a function of [D], $[D]_{1/2}$, m, and T. Finally, plot the expression using the values of $[D]_{1/2}$, m, and T from part (c.i). Is the shape of your plot consistent with your results from part (c.ii)?

4.50 In *Case study* 4.4, we discussed the role of hemoglobin in regulating the pH of blood. Now we explore the mechanism of regulation in detail.

(a) If we denote the protonated and deprotonated forms of hemoglobin as HbH and Hb^-, respectively, then the proton transfer equilibria for deoxygenated and fully oxygenated hemoglobin can be written as:

$$HbH \rightleftharpoons Hb^- + H^+ \qquad pK_a = 6.62$$
$$HbHO_2 \rightleftharpoons HbO_2^- + H^+ \qquad pK_a = 8.18$$

where we take the view (for the sake of simplicity) that the protein contains only one acidic proton. **(i)** What fraction of deoxygenated hemoglobin is deprotonated at pH = 7.4, the value for normal blood? **(ii)** What fraction of oxygenated hemoglobin is deprotonated at pH = 7.4? **(iii)** Use your results from parts (a.i) and (a.ii) to show that deoxygenation of hemoglobin is accompanied by the uptake of protons by the protein.

(b) It follows from the discussion in *Case study* 4.4 and part (a) that the exchange of CO_2 for O_2 in tissue is accompanied by complex proton transfer equilibria: the release of CO_2 into blood produces hydronium ions that can be bound tightly to hemoglobin once it releases O_2. These processes prevent changes in the pH of blood. To treat the problem more quantitatively, let us calculate the amount of CO_2 that can be transported by blood without a change in pH from its normal value of 7.4. **(i)** Begin by calculating the amount of hydronium ion bound per mole of oxygenated hemoglobin molecules at pH = 7.4. **(ii)** Now calculate the amount of hydronium ion bound per mole of deoxygenated hemoglobin molecules at pH = 7.4. **(iii)** From your results for parts (b.i) and (b.ii), calculate the amount of hydronium ion that can be bound per mole of hemoglobin molecules as a result of the release of O_2 by the fully oxygenated protein at pH = 7.4. **(iv)** Finally, use the result from part (b.iii) to calculate the amount of CO_2 that can be released into the blood per mole of hemoglobin molecules at pH = 7.4.

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Physical Chemistry for the Life Sciences
Preview Book Errata

Note: This chapter sampler is not a final product, but intended to provide a clear sense of the book before it publishes. Preview chapters are from early, uncorrected page proof and will be reviewed by the authors and error checkers before publication. An interim review has revealed the following:

Chapter 2, *Page 81*
D3 The denominator is *T* so the equation should look like:

$$\Delta S = \int_{T_i}^{T_f} \frac{C\mathrm{d}T}{T}$$

D4 Again, there are *T*'s missing from denominators, so the equation should look like (minus the bubble, which should remain as set on the preview page)

$$\Delta S = \int_{T_i}^{T_f} \frac{C\mathrm{d}T}{T} = C\int_{T_i}^{T_f} \frac{\mathrm{d}T}{T} = C\ln\frac{T_f}{T_i}$$

D5 Another missing denominator. The equation should look like

$$\Delta S = \int_{T_i}^{T_f} \frac{C\mathrm{d}T}{T}$$

Page 89
D1 More missing *T*'s in denominators. This equation should look like

$$S_m(T_f) - S_m(T_i) = \int_{T_i}^{T_f} \frac{C_{V,m}}{T}\mathrm{d}T$$

D2 The equation should look like

$$S_m(T) - S_m(0) = \int_0^T \frac{C_{V,m}}{T}\mathrm{d}T$$

D3 The equation should look like

$$S_m(T) = \int_0^T \frac{aT^3}{T}\mathrm{d}T = a\int_0^T T^2\mathrm{d}T$$

Chapter 3, *Page 147*, Column 2 Exercise 3.16
L3 after the data table: The *G* in $\Delta_{DNA}G^{\square}$ appears to be the wrong font
L7 after the data table: The *G* in $\Delta_{init}G^{\square}$ appears to be the wrong font

Page 149, Column 2 L1 the *g* and *h* in $\Pi = \rho g h$ should be italic

Chapter 5, *Page 229*

D-2 There are two problems with the typesetting of the ratio $\frac{[H^+]_{in}}{[H^+]_{out}}$ in this equation:

- The characters are in the wrong font
- The line separating denominator from numerator should not be broken up as in the page; it should appear as above