
Prolog

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

Like all scientists, physical chemists build descriptions of nature on a foundation of careful and systematic inquiry.

(a) The organization of science

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.2), $pV = nRT$. 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.

(b) The organization of our presentation

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. 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. To understand the molecular mechanism of change, we also explore how molecules move, either in free flight in gases or by diffusion through liquids. 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. We extend these theories of structure to solids, principally because that most revealing of all structural techniques, X-ray diffraction, depends on the availability and features of crystalline samples.

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. The spectroscopic techniques available for the investigation of structure, which includes shape, size, and the distribution of electrons in ground and excited states, make use of most of the electromagnetic spectrum. We conclude with an account of perhaps the most important of all spectroscopies, nuclear magnetic resonance (NMR).

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 unravelling 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 $2 \times 10^6 \text{ g mol}^{-1}$ that is responsible for the synthesis of proteins from individual amino acids in the cell. This work led to the 2009 Nobel Prize in Chemistry, awarded to Venkatraman Ramakrishnan, Thomas Steitz, and Ada Yonath. 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 the proteins directly 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 20 000 to 25 000 protein-encoding 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. Although 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 to 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 11. 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 identification 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.

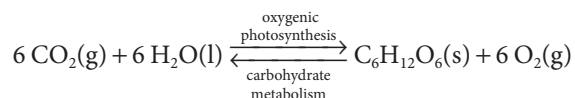
Many of the targets of rational drug design are **enzymes**, proteins, or nucleic acids that act as biological catalysts. The ideal target is either an enzyme of the host organism that is working abnormally as a result of the disease or an enzyme unique to the disease-causing agent and foreign to the 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 Chapters 10 and 11 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:

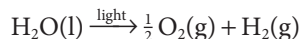


where $\text{C}_6\text{H}_{12}\text{O}_6$ denotes the carbohydrate glucose. In general terms, oxygenic photosynthesis uses solar energy to transfer electrons from water to carbon dioxide. In the process, high-energy molecules (carbohydrates, such as glucose) are synthesized in the cell. Animals feed 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 shall encounter photosynthesis and carbohydrate metabolism throughout the text. As we shall see in Chapter 12, 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 per cent 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 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 relations between structure and function in biological energy conversion systems. This 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:



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 not only surprising insights but also new technologies.

Fundamentals



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

F.1 Atoms, ions, and molecules

Atoms, ions, and molecules are the currency of discourse in the whole of chemistry and of biochemistry in particular. These concepts will be familiar from introductory chemistry and need little review here. However, it is important to keep in mind the following points.

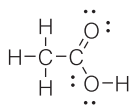
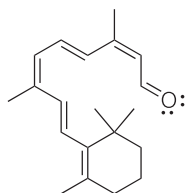
Atoms are characterized by their **atomic number**, Z , the number of protons in the nucleus. According to the nuclear model of an atom, a nucleus of charge Ze and containing most of the mass of the atom is surrounded by Z electrons, each of charge $-e$. **Isotopes** are atoms of the same atomic number but different **mass number** (or **nucleon number**), A , the total number of protons and neutrons in the nucleus. The loss of electrons results in **cations** (such as Na^+ and Ca^{2+}) and the gain of electrons results in **anions** (such as Cl^- and O^{2-}). When atoms are arranged in the order of increasing atomic number their properties show periodicities that are summarized by the periodic table with its familiar groups and periods (see inside the back cover).

(a) Bonding and nonbonding interactions

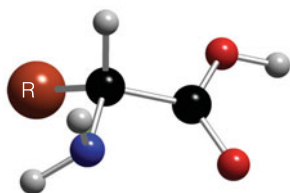
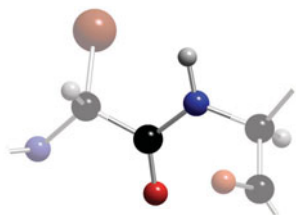
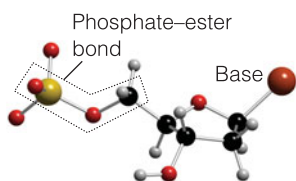
There are three types of interaction that result in atoms bonding together into more elaborate structures. **Ionic bonds** arise from the electrostatic attraction between cations and anions and give rise to typically hard, brittle arrays known as ‘ionic solids’. **Covalent bonds** are due to the sharing of electrons and are responsible for the existence of discrete molecules, such as H_2O and elaborate proteins. **Metallic bonds** arise when atoms are able to pool one or more of their electrons into a common sea and give rise to metals with their characteristic lustre and electrical conductivity.

Covalent bonding is of the greatest importance in biology as it is responsible for the stabilities of the frameworks of organic molecules, such as DNA and proteins. However, there are interactions between regions of molecules that although much weaker than covalent bonding play a very important role in determining their shapes, and in biology molecular shape is closely allied with function. One such interaction is the **hydrogen bond**, $\text{A-H}\cdots\text{B}$, where A and B are one of the atoms N, O, or F. Although only about 10 per cent as strong as a covalent bond, hydrogen bonding plays a major role in determining the shape of a biological macromolecule. Moreover, because it is quite weak, it permits the changes of

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1 Water, H_2O 2 Acetic acid, CH_3COOH 3 Ethene, C_2H_4 

4 Retinal (one form)

5 Amino acid, $\text{NH}_2\text{CHR}\text{COOH}$ 6 The peptide link, $-\text{CONH}-$ 7 β -D-2-Deoxyribose phosphate

shape that allow an enzyme or nucleic acid to function. Weaker still are non-bonding interactions, commonly called **van der Waals interactions**, which are attractions between groups of atoms in different regions of a macromolecule or between different molecules. These forces also contribute to the shapes of molecules and the interactions between them, as we shall see.

The **connectivity** of a molecule, the pattern of covalent bonds it forms, is commonly represented by a Lewis structure, in which bonds are shown by lines, with two lines for double bonds (two shared electron pairs) and three lines for triple bonds (three shared pairs). **Lone pairs**, electron pairs not involved directly in bonding are also shown in Lewis structures, such as that for water (1) and acetic acid (2). Structural formulas of organic molecules are essentially Lewis structures without the explicit display of lone pairs. The rules for writing Lewis structures (such as the 'octet rule' relating to the number of electrons around each atom) should be familiar from introductory chemistry courses. A crucially important aspect of a double bond between two atoms, such as that in ethene (3) and on a more extensive scale in the visual pigment retinal (4), is that it confers torsional rigidity (resistance to twisting) in the region of the bond.

Lewis structures of all but the simplest molecules do not show the shape of the molecule. A collection of rules known as **valence-shell electron repulsion theory** (VSEPR theory), in which regions of electron density (attached atoms and lone pairs) are supposed to adopt positions that minimize their repulsions, is often a helpful guide to the local shape at an atom, such as the tetrahedral arrangement of single bonds around a carbon atom. This theory should also be familiar from introductory chemistry courses.

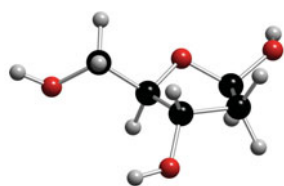
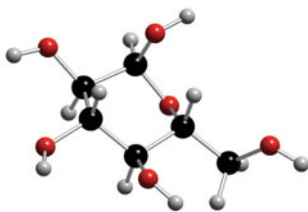
(b) Structural and functional units

Biochemistry effectively elaborates the concept of atoms by recognizing that characteristic groups of molecules can be regarded as building blocks from which the elaborate structures characteristic of organisms are constructed. These building blocks include the amino acids from which proteins are built as polypeptides, the bases that decorate the DNA double helix and constitute the genetic code, and carbohydrate molecules, such as glucose, that link together to form polysaccharides.

It will already be familiar from introductory courses that proteins, which are either structural or biochemically active molecules, are **polypeptides** formed from different α -amino acids of general form $\text{NH}_2\text{CHR}\text{COOH}$ (5) strung together by the **peptide link**, $-\text{CONH}-$ (6). Each monomer unit in the chain is referred to as a peptide **residue**. About 20 amino acids occur naturally and differ in the nature of the group R. These fundamental building blocks are illustrated in the *Atlas of structures*, Section A, in the *Resource section* at the end of the text.

Nucleic acids, which primarily store and transmit genetic information, are **polynucleotides** in which base-sugar-phosphate units are connected by **phosphodiester bonds** built from phosphate-ester links like that shown in (7). In DNA the sugar is β -D-2-deoxyribose (as shown in 8) and the bases are adenine (A), cytosine (C), guanine (G), and thymine (T); see the *Atlas of structures*, Section B. In RNA the sugar is β -D-ribose and uracil (U) replaces thymine.

Polysaccharides are polymers of simple carbohydrates, such as glucose (9), linked together by C-O-C groups. They perform a variety of structural and functional roles in the cell, including energy storage and the mediation of interactions between cells (including those involved in immunological response). See the *Atlas of structures*, Section S.

8 β -D-2-Deoxyribose9 Glucose (glucopyranose), $C_6H_{12}O_6$

Third among the major structural units are the **lipids**, which are long-chain hydrocarbons, typically in the range C_{14} – C_{24} , with a variety of polar head groups at one end of the chain, such as $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+$ and $-\text{COOH}$. The basic structural element of a cell membrane is a **phospholipid**, in which one or more hydrocarbon chains are attached to a phosphate group (see the *Atlas of structures*, Section L). Phospholipids form a membrane by stacking together to form a **lipid bilayer**, about 5 nm across (Fig. F.1), leaving the polar groups exposed to the aqueous environment on either side of the membrane.

(c) Levels of structure

The concept of the ‘structure’ of a biological macromolecule 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 macromolecule is the sequence in which the units are linked in the polymer (Fig. F.2a).
- The **secondary structure** of a macromolecule is the (often local) spatial arrangement of the chain.

Examples of secondary structure motifs are random coils and ordered structures, such as helices and sheets, held together primarily by hydrogen bonds (Fig. F.2b). The secondary structure of DNA arises primarily from the winding of two polynucleotide chains around each other to form a double helix (Fig. F.3) held

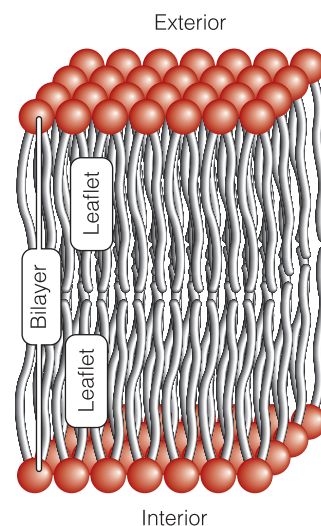


Fig. F.1 The long hydrocarbon chains of a phospholipid can stack together to form a bilayer structure with the polar groups (represented by the spheres) exposed to the aqueous environment.

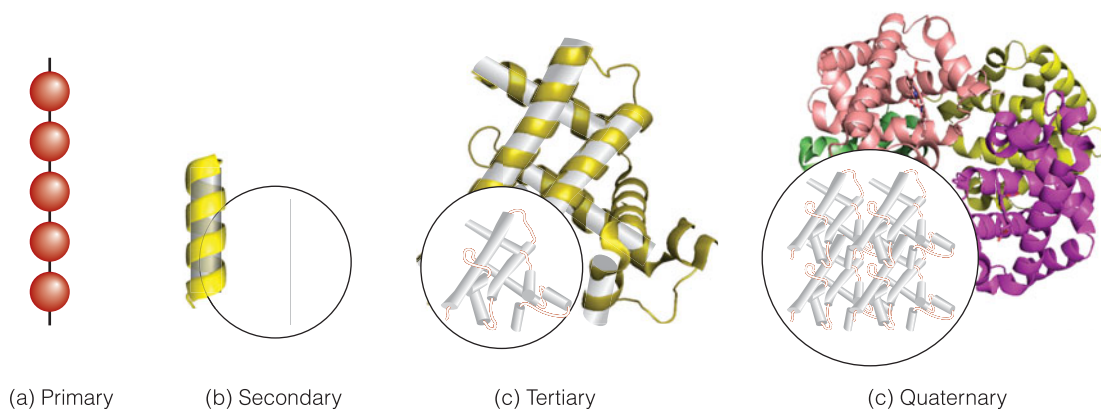


Fig. F.2 The structural hierarchy of a biological macromolecule, in this case a protein, and a simplified representation in terms of cylinders. (a) The primary structure, the sequence of amino acid residues; (b) the local secondary structure (in this case a helix); (c) the tertiary structure: several helical segments connected by short random coils pack together; (d) the quaternary structure: several subunits with specific structures pack together.

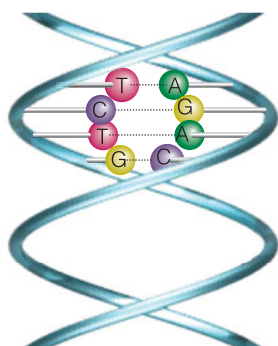


Fig. F.3 The DNA double helix, in which two polynucleotide chains are linked together by hydrogen bonds between adenine (A) and thymine (T), and between cytosine (C) and guanine (G).

together by hydrogen bonds involving A–T and C–G base pairs that lie parallel to each other and perpendicular to the major axis of the helix.

- The **tertiary structure** is the overall three-dimensional structure of a macromolecule.

The hypothetical protein shown in Fig. F.2c 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 F.2d shows how several molecular subunits, each with a specific tertiary structure, aggregate together.

F.2 Bulk matter

Atoms, ions, and molecules cohere to form bulk matter. The broadest classification of the resulting materials is as gas, liquid, or solid. The term ‘state’ has many different meanings in chemistry, and it is important to keep them all in mind. Here we review the terms ‘state of matter’ and ‘physical state’.

(a) States of matter

At a ‘macroscopic’ (observational) level, 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 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 at a ‘microscopic’ (atomic) level:

Mathematical toolkit F.1 *Quantities and units*

The result of a measurement is a **physical quantity** that is reported as a numerical multiple of a unit:

$$\text{physical quantity} = \text{numerical value} \times \text{unit}$$

It follows that units are treated like algebraic quantities and may be multiplied, divided, and canceled. Thus, the expression (physical quantity)/unit is the numerical value (a dimensionless quantity) of the measurement in the specified units. For instance, the mass m of an object could be reported as $m = 2.5 \text{ kg}$ or $m/\text{kg} = 2.5$. See *Resource section 2* for a list of units.

Units may be modified by a prefix that denotes a factor of a power of 10. Among the most common prefixes

are those listed in Table 3 of *Resource section 2*. Examples of the use of these prefixes are:

$$1 \text{ nm} = 10^{-9} \text{ m}$$

$$1 \text{ ps} = 10^{-12} \text{ s}$$

$$1 \text{ } \mu\text{mol} = 10^{-6} \text{ mol}$$

Powers of units apply to the prefix as well as the unit they modify. For example, $1 \text{ cm}^3 = 1 (\text{cm})^3$ and $(10^{-2} \text{ m})^3 = 10^{-6} \text{ m}^3$. But note that 1 cm^3 does not mean $1 \text{ c}(\text{m}^3)$. When carrying out numerical calculations, it is usually safest to write out the numerical value of an observable as powers of 10.

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.

(b) Physical state

By **physical state** (or just 'state') is meant 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 dm³ at a specified pressure and temperature is in a particular state. The same mass of gas in a container of volume 5 dm³ 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 report the physical state of a sample we need to specify a number of properties in terms of their appropriate units. The manipulation of units, which almost always will be from the **International System** of units (SI, from the French *Système International d'Unités*) described in the *Resource section*, is explained in *Mathematical toolkit* F.1. These properties and their units include the following:

- **Mass**, m , is a measure of the quantity of matter a sample contains. Unit: 1 kg.

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. 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 = 10³ g.

- **Volume**, V , is a measure of the space a sample occupies. Unit: 1 m³.

For volume we write $V = 100 \text{ cm}^3$ if the sample occupies 100 cm³ of space. Units used to express volume include cubic meters (m³), cubic decimeters (dm³), liters (L), and milliliters (mL). The liter is not an SI unit, but is exactly equal to 1 dm³.

- **Amount of substance**, n , is a measure of the number of specified entities a sample contains. Unit: 1 mol.

A note on good practice

Physical quantities are denoted by italic, and sometimes Greek, letters (as in m for mass or ρ for mass density). Units are denoted by Roman letters (as in m for meter).

A note on good practice

The unit mole should never be used without specifying the entities. Thus we speak of 1 mol H if we mean 1 mol of hydrogen atoms, and 1 mol H₂ if we mean 1 mol of H₂ molecules (the latter corresponds to 2 mol H).

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.

A note on good practice

The names of units derived from names of people are lowercase (as in newton and pascal), but their symbols are uppercase (as in N and Pa).

A brief comment

We shall see later (in Section F.3b) that temperature determines how molecules populate the energy levels available to them. Related to this interpretation is the fact that for molecules in a gas, the temperature determines their mean or average speed ($c_{\text{average}} \propto (T/M)^{1/2}$).

The amount is expressed in moles (mol), where 1 mole is defined as the same number of specified entities as there are atoms in exactly 12 g of carbon-12. In practice, the amount of substance is related to the number of entities, N , by $n = N/N_A$, where N_A is **Avogadro's constant** ($N_A = 6.022 \times 10^{23} \text{ mol}^{-1}$). Note that N_A is a constant with units, not a pure number.

To convert from an amount to an actual number, N , of entities we write

$$N = nN_A \quad \text{Relation between amount and number} \quad (\text{F.1})$$

To express a known mass of matter as an amount we use the molar mass, M , of the entities:

$$n = \frac{m}{M} \quad \text{Relation between mass and amount} \quad (\text{F.2})$$

The molar mass, M , is the mass of a sample of an element or compound divided by the amount of atoms, molecules, or formula units it contains:

$$M = \frac{m}{n} \quad \text{Definition of molar mass} \quad (\text{F.3})$$

The *atomic weight* of an element is the numerical value of the molar mass of the atoms it contains, the *molecular weight* of a molecular compound is the numerical value of the molar mass of its molecules, and the *formula weight* of an ionic compound is the molar mass of a specified formula unit of the compound. In each case 'numerical value' means $M/(\text{g mol}^{-1})$.

- **Pressure**, p , is the force a sample is subjected to divided by the area to which that force is applied. Unit: 1 Pa.

Because force (see later) is measured in newtons ($1 \text{ N} = 1 \text{ kg m s}^{-2}$), pressure is reported in newtons per square meter, or pascals ($1 \text{ Pa} = 1 \text{ N m}^{-2}$). The atmosphere (atm) is commonly used as a unit of pressure, but is not an SI unit. To convert between atmospheres and pascals use $1 \text{ atm} = 101.325 \text{ kPa}$ exactly. See Table F.1.

If an object is immersed in a gas, it experiences a pressure over its entire surface because molecules collide with it from all directions and exert a force during every collision. We are incessantly battered by molecules of gas in the atmosphere and experience this battering as '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 pressure of the atmosphere at sea level is about 100 kPa. 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** (Fig. F.4).

- **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. Unit: 1 K.

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). The symbol T is used to denote the **thermodynamic temperature**, which is an absolute scale with $T = 0$ as the lowest point. Temperatures above

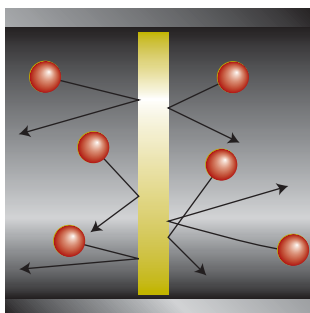


Fig. F.4 A system is in mechanical equilibrium with its surroundings if it is separated from them by a movable wall and the external pressure is equal to the pressure of the gas in the system.

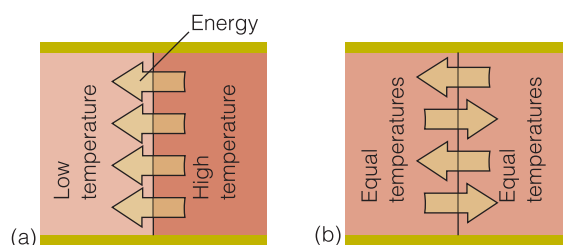


Fig. F.5 The temperatures of two objects act as a signpost showing the direction in which energy will flow as heat through a thermally conducting wall: (a) heat always flows from high temperature to low temperature. (b) When the two objects have the same temperature, although there is still energy transfer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

$T = 0$ are then most commonly expressed by using the **Kelvin scale**, in which the gradations of temperature are called kelvin (K). The Kelvin scale is defined by setting the triple point of water (the temperature at which ice, liquid water, and water vapour are in mutual equilibrium) at exactly 273.16 K. The freezing point of water (the melting point of ice) at 1 atm is then found experimentally to lie 0.01 K below the triple point, so the freezing point of water is approximately 273.15 K. The Kelvin scale is unsuitable for everyday measurements of temperature, and it is common to use the **Celsius scale**, which is defined in terms of the Kelvin scale as

$$\theta/^{\circ}\text{C} = T/\text{K} - 273.15$$

Relation between Kelvin and Celsius scales (F.4)

(The 273.15 is exact in this definition.) Thus, the freezing point of water is 0°C and its boiling point (at 1 atm) is found to be 100°C . Note that in this text T invariably denotes the thermodynamic (absolute) temperature and that temperatures on the Celsius scale are denoted θ (theta).

Self-test F.1 Use eqn F.4 to express body temperature, 37°C , in kelvins.

Answer: 310 K

A note on good practice

We refer to absolute zero as $T = 0$, not $T = 0\text{ K}$. 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 which absolute scale we are using. On the other hand, we write $\theta = 0^{\circ}\text{C}$ not $\theta = 0$ because the Celsius scale has an arbitrarily defined zero point.

Temperature is an example of an **intensive property**, a property that is independent of the size of the sample. A property that does depend on the size (‘extent’) of the sample is called an **extensive property**. More formally, if we think of a sample as being divided into portions (‘subsystems’), then the value of an extensive property is the sum of the contribution from each of the subsystems. For instance, the mass of a 10 mg sample of a protein is the sum of the masses of the 10 portions, each of 1 mg, into which it can be imagined as being divided. The value of an intensive property is the same for each of the subsystems and of the overall system itself. For instance, the temperature of a uniform 100 cm^3 flask of water is the same as that of each of the 10 regions, each of volume 10 cm^3 , into which it can be regarded as being divided. Mass, volume, and amount of substance are all

extensive properties. Temperature and pressure are intensive properties. Molar mass is intensive because the size-dependence of m and n cancel in the ratio m/n . All molar properties, $X_m = X/n$, where X is an extensive property, are intensive for the same reason. Mass density, $\rho = m/V$, is also intensive.

(c) Equations of state

Although the state of any sample of substance can be specified by giving the values of its volume, the pressure, the temperature, and the amount of substance, a remarkable experimental fact is that *these four quantities are not independent of one another*. For instance, we cannot arbitrarily choose to have a sample of 5.5 mmol 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

$$p = f(n, V, T) \quad \text{A general equation of state} \quad (\text{F.5})$$

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:

$$p = \frac{nRT}{V} \quad \text{Perfect gas equation of state} \quad (\text{F.6})$$

where R is the gas constant $R = 8.314\text{ J K}^{-1}\text{ mol}^{-1}$ (for values of R in other and sometimes more convenient units see Table F.2). Although the properties of gases might seem to be of little direct relevance to biochemistry, this equation is used to describe the behavior of gases taking part in a variety of biologically important processes (such as respiration), the properties of the gaseous environment we inhabit (the atmosphere), and as a starting point for the discussion of the properties of species in aqueous environments (such as the cell).

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.6 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.6 at *all* pressures is called a **perfect gas**.¹ 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 ($p \approx 100\text{ kPa}$) is already low enough for most real gases to behave almost perfectly and, unless stated

Table F.2 The gas constant in various units

$R = 8.314\ 47$	$\text{J K}^{-1}\text{ mol}^{-1}$
8.314 47	$\text{kPa dm}^3\text{ K}^{-1}\text{ mol}^{-1}$
$8.205\ 74 \times 10^{-2}$	$\text{atm dm}^3\text{ K}^{-1}\text{ mol}^{-1}$
62.364	$\text{Torr dm}^3\text{ K}^{-1}\text{ mol}^{-1}$
1.987 21	$\text{cal K}^{-1}\text{ mol}^{-1}$

¹ The term ‘ideal gas’ is also widely used.

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).

A brief illustration

Consider the calculation of the pressure in kilopascals exerted by 1.25 g of nitrogen gas in a flask of volume 250 mL (0.250 dm^3) at 20°C . The amount of N_2 molecules (of molar mass $M = 28.02 \text{ g mol}^{-1}$) present is

$$n = \frac{m}{M} = \frac{1.25 \text{ g}}{28.02 \text{ g mol}^{-1}} = \frac{1.25}{28.02} \text{ mol}$$

The temperature of the sample is $T/\text{K} = 20 + 273.15$. Therefore, from $p = nRT/V$,

$$p = \frac{\overbrace{(1.25/28.02) \text{ mol}}^n \times \overbrace{(8.3145 \text{ kPa dm}^3 \text{ K}^{-1} \text{ mol}^{-1})}^R \times \overbrace{(20 + 273.15 \text{ K})}^{T=293 \text{ K}}}{\underbrace{0.250 \text{ dm}^3}_{V=250 \text{ mL}}} = 435 \text{ kPa}$$

where we have used more convenient units for the constant R . Note how all units (except kPa in this instance) cancel like ordinary numbers (see *Mathematical toolkit F.1*).

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.2 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

The **molar volume**, V_m , is the volume a substance (not just a gas) occupies per mole of molecules. It is calculated by dividing the volume of the sample by the amount of molecules it contains:

$$V_m = \frac{V}{n} \quad \text{Definition of molar volume} \quad (\text{E.7})$$

The perfect gas law can be used to calculate the molar volume of a perfect gas at any temperature and pressure. When we combine eqns F.6 and E.7, we get

$$V_m = \frac{V}{n} = \frac{nRT}{np} = \frac{RT}{p} \quad \text{Molar volume of a perfect gas} \quad (\text{E.8})$$

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, as summarized in Table F.3. The ‘standard state’ of a substance (at a specified temperature, not necessarily 298 K) is discussed further in Section 1.7. The condition SATP for the discussion of gases is now favored over

Table F.3 A summary of standard conditions

Name	Conditions	Comment
Standard pressure, p°	$p^\circ = 1 \text{ bar}$	1 bar is exact
Standard ambient temperature and pressure (SATP)	25°C (more precisely, 298.15 K) and 1 bar	At SATP, $V_m = 24.79 \text{ dm}^3 \text{ mol}^{-1}$ for a perfect gas
Standard temperature and pressure (STP)	0°C and 1 atm	At STP, $V_m = 22.41 \text{ dm}^3 \text{ mol}^{-1}$ for a perfect gas
Standard state	Pure substance at 1 bar	Temperature to be specified. See Section 1.7.

the earlier STP on account on the shift of emphasis from 1 atm to 1 bar in the specification of standard states.

A mixture of perfect gases, such as to a good approximation the atmosphere, behaves like a single perfect gas. According to **Dalton's law**, the total pressure of such a mixture is the sum of the **partial pressures** of the constituents, the pressure to which each gas would give rise if it occupied the container alone:

$$p = p_A + p_B + \dots \quad \text{Dalton's law} \quad (\text{F.9})$$

Each partial pressure, p_j , can be calculated from the perfect gas law in the form $p_j = n_j RT/V$.

F.3 Energy

A property that will continue to occur in just about every chapter of the following text is 'energy'. Indeed, we begin the text with a discussion of the deployment of energy in living organisms. **Energy**, E , is the capacity to do work. **Work** is the process of moving against an opposing force. 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.

In his formulation of classical mechanics Isaac Newton focused on the role of **force**, F , an agent that changes the state of motion of a body. His mechanics was built on three laws, the second of which relates the **acceleration**, a , the rate of change of velocity, of a body of mass m to the strength of the force it experiences:

$$F = ma \quad \text{Newton's second law} \quad (\text{F.10})$$

A brief illustration

A stationary ball of mass 150 g is hit by a bat, and in 0.20 s reaches a speed of 80 km h^{-1} ($8.0 \times 10^4 \text{ m}/3600 \text{ s} = 22 \text{ m s}^{-1}$) before being slowed down by air resistance. The initial acceleration of the ball is $(22 \text{ m s}^{-1})/(0.20 \text{ s}) = 110 \text{ m s}^{-2}$. The force exerted by the bat on the ball is therefore

$$F = (0.150 \text{ kg}) \times (110 \text{ m s}^{-2}) = 16.5 \text{ kg m s}^{-2} = 16.5 \text{ N}$$

We have expressed the result in newtons, with $1 \text{ N} = 1 \text{ kg m s}^{-2}$.

Force, like acceleration, is actually a ‘vector’ quantity, a quantity with direction as well as magnitude, but in most instances in this text we need consider only its magnitude.

The magnitude of the work done in moving against a constant opposing force, w , is the product of the distance moved, d , and the strength of the force:

$$w = Fd \quad \text{Definition of work} \quad (\text{F.11})$$

A brief illustration

A bird of mass 50 g flies from the ground to a branch 10 m above. The force of gravity on an object of mass m close to the surface of the Earth is mg , where g is the ‘acceleration of free fall’: $g = 9.81 \text{ m s}^{-2}$. Therefore, the work it has to do against gravity is

$$w = mgd = (0.050 \text{ kg}) \times (9.81 \text{ m s}^{-2}) \times (10 \text{ m}) = 4.9 \text{ kg m}^2 \text{ s}^{-2}$$

We would report this value as 4.9 J, where $\text{J} = 1 \text{ kg m}^2 \text{ s}^{-2}$.

As implied in the *brief illustration*, 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 $1 \text{ J} = 1 \text{ N m} = 1 \text{ kg m}^2 \text{ s}^{-2}$. A joule is quite a small unit, and in chemistry we often deal with energies of the order of kilojoules ($1 \text{ kJ} = 10^3 \text{ J}$).

(a) Varieties of energy

We need to distinguish the energies possessed by matter and due to radiation. 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 ,

$$E_k = \frac{1}{2}mv^2 \quad \text{Definition of kinetic energy} \quad (\text{F.12})$$

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 (and commonly V), 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. An important type of potential energy is the Coulombic potential energy of interaction between two electric charges Q_1 and Q_2 separated by a distance r :

$$E_p = \frac{Q_1 Q_2}{4\pi\epsilon_0 r} \quad \text{Coulombic potential energy} \quad (\text{F.13})$$

The fundamental constant ϵ_0 is called the **vacuum permittivity**; its value (and those of other fundamental constants) is given inside the front cover. With the charges in coulombs (C) and the distance in meters, the energy is obtained in joules. Equation F.13 is based on the convention of taking the potential energy to be zero when the charges are infinitely apart. The Coulombic potential energy will inform our discussion of a range of topics, from atomic structure to the nature of interactions that give rise to levels of structure in biological assemblies.

A mass m close to the surface of the Earth has a potential energy that is proportional to its height above the ground, h :

$$E_p = mgh \quad \text{Gravitational potential energy} \quad (\text{F.14})$$

The constant $g = 9.81 \text{ m s}^{-2}$ is called the **acceleration of free fall**. It depends on the location on the Earth's surface, but the variation is quite small. In this case, the arbitrary zero of potential energy is taken as being at the surface of the Earth (at $h = 0$).

A brief illustration

The potential energy of the 50-g bird mentioned in the preceding *brief illustration* is higher by 4.9 J when it is on the branch than when it is on the ground. The potential energy of this book (of mass about 1 kg) is higher by about 10 J when it is on a table 1 m above the floor than when it is on the floor.

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

$$E = E_k + E_p \quad \text{Total energy} \quad (\text{F.15})$$

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, such as air resistance.

Energy may also be present even in the absence of matter in the form of **electromagnetic radiation**, a wave of electric and magnetic fields traveling through a vacuum at the 'speed of light', $c = 2.998 \times 10^8 \text{ m s}^{-1}$. The wave is characterized by its amplitude, frequency, and wavelength. The **amplitude** of the wave is the maximum displacement, and the perceived intensity of the wave is proportional to the square of the amplitude. The **frequency**, ν (nu), is a measure of the rate at which the field goes through a complete cycle of orientations. The SI unit of frequency is 1 hertz (1 Hz), which corresponds to one cycle per second: $1 \text{ Hz} = 1 \text{ s}^{-1}$. The **wavelength**, λ (lambda), is the distance between neighboring peaks of the wave (Fig. F.6). The frequency and wavelength are related by

$$\lambda \nu = c \quad \text{Relation between frequency and wavelength} \quad (\text{F.16})$$

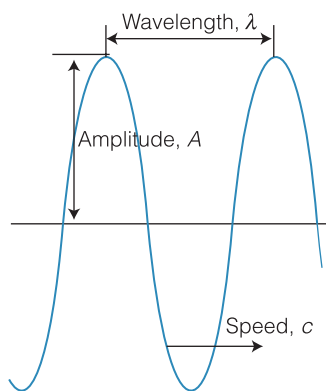
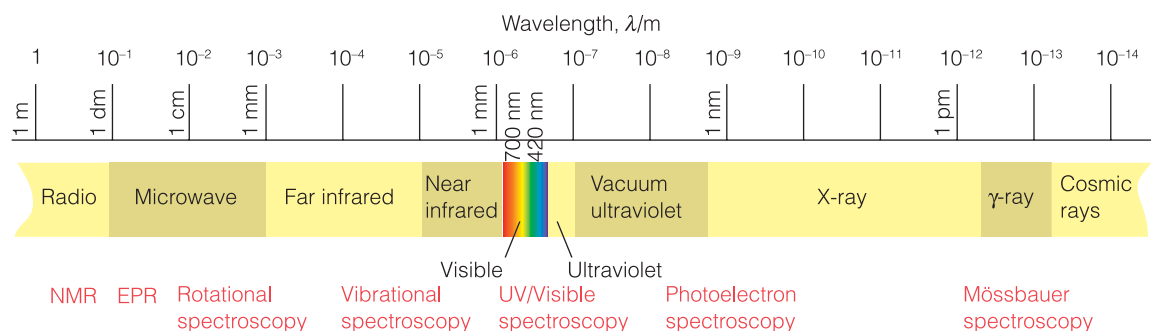


Fig. F.6 An electromagnetic wave is characterized by its amplitude, A , wavelength, λ , and frequency, ν ; the frequency is related to the wavelength by $\nu = c/\lambda$.

That is, high frequencies correspond to short wavelengths, and vice versa. This expression also applies to sound waves, with c interpreted as the speed of sound.

The **electromagnetic spectrum** runs—as far as we know—over all frequencies. Each range of frequencies is classified as shown in Fig. F.7. The boundaries between each region are only approximate. The **visible region** of the spectrum, the region to which our eyes are sensitive, occupies a very narrow band between 400 and 700 nm. As we shall see in later chapters, each region of the spectrum excites, or is excited by, different types of nuclear, atomic, or molecular transition. For instance, electronic excitations, where electrons are redistributed into



different regions of the molecule, are stimulated by or give rise to visible and ultraviolet radiation. Because the separation between energy levels is dictated by the arrangement of atoms in a molecule, measuring the frequencies of transitions facilitates the study of molecular structure and reactivity. Ultraviolet radiation can also cause such extreme electron redistributions that bonds are broken.

We need to be aware that electromagnetic energy is delivered in packets known as **photons**. The energy of a photon of electromagnetic radiation is related to the frequency of the radiation by

$$E = h\nu \quad \text{Energy of a photon} \quad (\text{F.17})$$

where h is a fundamental constant known as **Planck's constant** ($h = 6.626 \times 10^{-34} \text{ J s}$). In terms of photons, an intense ray of light consists of numerous photons, each of the same energy and each moving at the speed c . The higher the frequency of the radiation, the greater is the energy carried by each photon. Photons of visible light are sufficiently energetic to stimulate the processes of vision; photons of ultraviolet radiation are so energetic that they can destroy tissue.

A brief illustration

The energy of a photon of 350 nm ultraviolet radiation is

$$E = \frac{hc}{\lambda} = \frac{(6.626 \times 10^{-34} \text{ J s}) \times (2.998 \times 10^8 \text{ m s}^{-1})}{3.50 \times 10^{-7} \text{ m}} = 5.68 \times 10^{-19} \text{ J}$$

corresponding to 0.568 aJ. To know the energy per mole of photons, which helps us to assess the chemical potency of the radiation, we multiply by Avogadro's constant:

$$E = \frac{hcN_A}{\lambda} = \frac{(6.626 \times 10^{-34} \text{ J s}) \times (2.998 \times 10^8 \text{ m s}^{-1}) \times (6.022 \times 10^{23} \text{ mol}^{-1})}{3.50 \times 10^{-7} \text{ m}} = 342 \text{ kJ mol}^{-1}$$

Fig. F.7 The regions of the electromagnetic spectrum and some of the spectroscopic techniques that make use of them.

A note on good practice It is best to carry out a numerical calculation in one step or at least to avoid rounding at an intermediate stage.

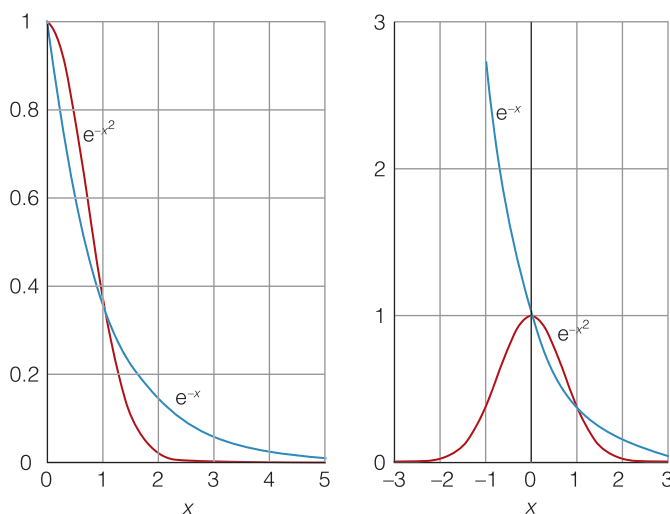
(b) The Boltzmann distribution

One of the most important expressions in science, the 'Boltzmann distribution', helps to elucidate the concept of temperature as well as underlying virtually all the bulk properties and reactions of matter and their variation with temperature.

Mathematical toolkit F.2 Exponential functions

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 (see the illustration). This function approaches zero more rapidly as a increases. The Boltzmann distribution is an example of an exponential function. 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} . Gaussian functions will appear several times through the text. 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.



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 $x \rightarrow -\infty$.

It should be familiar from introductory courses, and will be explained in detail later in the text, that atoms and molecules can possess only discrete amounts of energy. For instance, an electron in a hydrogen atom can possess only the energies 2.17 aJ, 0.54 aJ, 0.24 aJ, ... (where 1 aJ, 1 attojoule = 10^{-18} J) below that of a widely separated proton and electron, and a C-H bond in a molecule can vibrate only with the energies 0.029 aJ, 0.086 aJ, 0.144 aJ, ... Intermediate values of the energy are simply not allowed. The precise values of the allowed energies depend on the details of molecular structure, but it is generally the case that electronic energy levels are most widely spaced, then the energies of molecular vibration, and then the energies with which molecules rotate (Fig. F.8). The energies of translational motion are so close together even on an atomic scale (for instance, of the order of 10^{-44} J for a CO_2 molecule in a region 10 cm wide) that they may be treated as continuous.

The apparently random motion that molecules undergo at $T > 0$ is called **thermal motion**. The energy associated with this motion is the energy of thermal motion, but is commonly called simply **thermal energy**. A useful rule of thumb is

that the order of magnitude of the energy that a molecule possesses as a result of its thermal motion is kT , where $k = 1.381 \times 10^{-23} \text{ J K}^{-1}$ is a fundamental constant called **Boltzmann's constant**. The gas constant R is simply the 'molar' form of Boltzmann's constant:

$$R = N_A k \quad \text{Relation between the gas constant and Boltzmann's constant} \quad (\text{F.18})$$

Thermal motion ensures that molecules will be found spread over the energy levels available to them such that their mean energy is of order kT . The population of each energy level depends on the temperature, and a very important result is that in a system at a temperature T , the ratio of populations N_2 and N_1 in states with energies E_1 and E_2 is given by the **Boltzmann distribution**, one form of which is

$$\frac{N_2}{N_1} = e^{-(E_2 - E_1)/kT} \quad \text{The Boltzmann distribution} \quad (\text{F.19a})$$

This form of the distribution applies when the E_i are actual energies (in joules, for instance); when the E_i are molar quantities (in joules or kilojoules per mole, for instance), we use

$$\frac{N_2}{N_1} = e^{-(E_2 - E_1)/RT} \quad (\text{F.19b})$$

with R in place of k . We see that the greater the energy separation $E_2 - E_1$, the smaller the ratio of populations. Alternatively, for a given separation, the ratio becomes smaller as the temperature is lowered. In other words, as the temperature is lowered, more and more molecules are found in their lowest energy levels and fewer are found in high energy levels. The temperature, we see, is the single parameter we need in order to state the relative populations of energy levels.

A brief illustration

Suppose that two conformations of neighboring peptide groups in a polypeptide differ in energy by 7.5 kJ mol^{-1} , with conformation A higher in energy than conformation B. At body temperature (37°C , corresponding to 310 K) the ratio of populations of the two conformations is

$$\frac{N_A}{N_B} = e^{-(7500 \text{ J mol}^{-1})/(8.3145 \text{ J K}^{-1} \text{ mol}^{-1} \times 310 \text{ K})} = 0.054$$

That is, conformation B is about 18 times more abundant than conformation A.

The importance of the Boltzmann distribution will become apparent as the following chapters unfold. We shall see that it accounts for the stability of matter, for very few molecules are found in highly excited states at ordinary temperatures, but it allows for the possibility of reaction, as *some* molecules will be found with sufficient energy to react, and the proportion that can react increases as the temperature is raised. Already we are beginning to see why chemical reactions proceed more quickly as the temperature is raised.

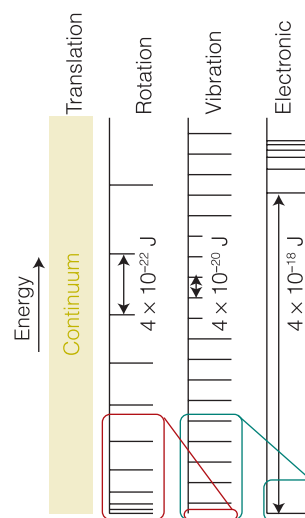


Fig. F.8 The energy level separations (in joules) typical of four types of motion.

We can obtain insight into the molecular origins of temperature by using the simple but powerful **kinetic model of gases** (also called the ‘kinetic molecular theory,’ KMT, of gases), which is based on a model of a gas that we mentioned earlier, in which the molecules are in ceaseless random motion, do not interact with one another except during collisions, and are much smaller than the average distance traveled between collisions (Fig. F.9). Different speeds correspond to different energies, so the Boltzmann formula can be used to predict the proportions of molecules having a specific speed at a particular temperature. The expression giving the fraction of molecules that have a particular speed is called the **Maxwell distribution** (sometimes the *Maxwell–Boltzmann distribution*) and has the features summarized in Figs F.10 and F.11. The Maxwell distribution, which is discussed more fully in *Further information 7.1*, can be used to show that the mean speed, $\bar{c}$, of the molecules depends on the temperature T and their molar mass M as

$$\bar{c} = \left(\frac{8RT}{\pi M} \right)^{1/2} \quad \text{Mean speed according to the Maxwell distribution} \quad (\text{F.20})$$

Thus, the mean or average speed is high for light molecules at high temperatures. The distribution itself gives more information. For instance, the tail towards high speeds is longer at high temperatures than at low, which indicates that at high temperatures more molecules in a sample have speeds much higher than average.

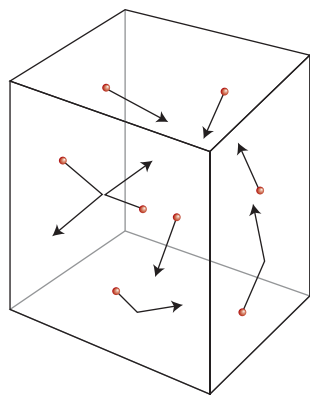


Fig. F.9 The model used for discussing the molecular basis of the physical properties of a perfect gas. The pointlike molecules move randomly with a wide range of speeds and in random directions, both of which change when they collide with the walls or with other molecules.

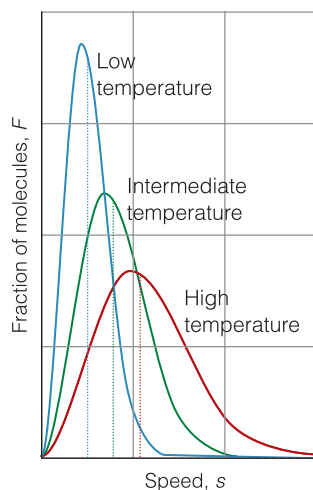


Fig. F.10 The Maxwell distribution of speeds and its variation with the temperature. Note the broadening of the distribution and the shift of the mean speed (denoted by the locations of the vertical dotted lines) to higher values as the temperature is increased.

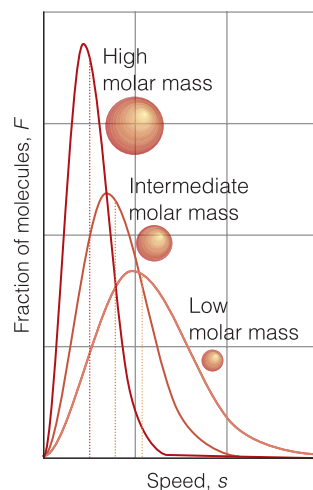


Fig. F.11 The Maxwell distribution of speeds also depends on the molar mass of the molecules. Molecules of low molar mass have a broad spread of speeds, and a significant fraction may be found traveling much faster than the mean speed. The distribution is much narrower for heavy molecules, and most of them travel with speeds close to the mean value (denoted by the locations of the vertical dotted lines).

Checklist of key concepts

- | | |
|--|--|
| ☐ 1. In the nuclear model, an atom of atomic number Z consists of a nucleus of charge $+Ze$ surrounded by Z electrons each of charge $-e$. | ☐ 10. The total energy of an isolated system is conserved, but kinetic and potential energy may be interchanged. |
| ☐ 2. Proteins, nucleic acids, and polysaccharides are long molecular chains with different levels of three-dimensional structure. | ☐ 11. Electromagnetic radiation is characterized by its amplitude, frequency, and wavelength. |
| ☐ 3. Cell membranes are formed by the stacking of lipid molecules into a bilayer structure. | ☐ 12. Electromagnetic radiation consists of photons, packets of energy of magnitude $h\nu$ and traveling at the speed of light. |
| ☐ 4. The states of matter are gas, liquid, and solid. | ☐ 13. The Boltzmann distribution gives the relative numbers of molecules in the energy levels available to them. |
| ☐ 5. An equation of state is an equation relating pressure, volume, temperature, and amount of a substance. | ☐ 14. The mean speed of molecules is proportional to the square root of the (absolute) temperature and inversely proportional to the square root of the molar mass. |
| ☐ 6. The perfect gas equation of state is a limiting law applicable as $p \rightarrow 0$. | ☐ 15. The properties of the Maxwell distribution of speeds are summarized in Figs F.10 and F.11. |
| ☐ 7. Energy is the capacity to do work. | |
| ☐ 8. Work is done when a body is moved against an opposing force. | |
| ☐ 9. 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). | |

Checklist of key equations

Property or process	Equation	Comment
Relation between number and amount	$N = nN_A$	N_A is Avogadro's constant
Molar quantity	$X_m = X/n$	Molar mass is denoted M
Temperature conversion	$\theta/^{\circ}\text{C} = T/\text{K} - 273.15$	273.15 is exact
Equation of state	$p = nRT/V$	Perfect (ideal) gas
Molar volume	$V_m = RT/p$	Perfect (ideal) gas
Dalton's law	$p = p_A + p_B + \dots$	Perfect (ideal) gas
Newton's second law	$F = ma$	
Work	$w = Fd$	F is the opposing force
Kinetic energy	$E_k = \frac{1}{2}mv^2$	
Coulomb potential energy	$E_p = Q_1Q_2/4\pi\epsilon_0r$	Charges in a vacuum
Gravitational potential energy	$E_p = mgh$	Close to surface of the Earth
Relation between wavelength and frequency	$\lambda\nu = c$	c is speed of propagation (e.g. speed of light)
Energy of a photon	$E = h\nu$	h is Planck's constant
Boltzmann distribution	$N_2/N_1 = e^{-(E_2-E_1)/kT}$	k is Boltzmann's constant, $R = N_A k$
Mean speed of molecules	$\bar{c} = (8RT/\pi M)^{1/2}$	Perfect (ideal) gas

Discussion questions

- F.1** Distinguish between ionic bonds, covalent bonds, hydrogen bonds, and van der Waals interactions.
- F.2** Distinguish between polypeptides, polynucleotides, and polysaccharides.
- F.3** Describe the main structural features of a lipid bilayer.
- F.4** Distinguish between primary, secondary, tertiary, and quaternary levels of structure in biological macromolecules.
- F.5** Explain the differences between gases, liquids, and solids at macroscopic and microscopic levels.
- F.6** Define the terms force, work, energy, kinetic energy, potential energy, and the energy of thermal motion.
- F.7** Distinguish between mechanical and thermal equilibrium.
- F.8** Describe the main features of electromagnetic radiation and the electromagnetic spectrum.
- F.9** Use the Boltzmann distribution to provide a molecular interpretation of temperature.

Exercises

Treat all gases as perfect unless instructed otherwise.

- F.10** You will see Lewis structures throughout the text. Using your knowledge of introductory chemistry, draw the Lewis structures of (a) SO_3^{2-} , (b) XeF_4 , (c) P_4 , (d) O_3 , (e) ClF_3^+ , and (f) N_3^- .
- F.11** Using your knowledge of VSEPR theory from introductory chemistry, predict the shapes of (a) PCl_3 , (b) PCl_5 , (c) XeF_2 , (d) XeF_4 , (e) H_2O_2 , (f) FSO_3^- , (g) KrF_2 , and (h) PCl_4^+ .
- F.12** Express (a) 110 kPa in torr, (b) 0.997 bar in atmospheres, (c) 2.15×10^4 Pa in atmospheres, and (d) 723 Torr in pascals.
- F.13** Given that the Celsius and Fahrenheit temperature scales are related by $\theta_{\text{Celsius}}/^{\circ}\text{C} = \frac{5}{9}(\theta_{\text{Fahrenheit}}/^{\circ}\text{F} - 32)$, what is the temperature of absolute zero ($T = 0$) on the Fahrenheit scale?
- F.14** 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, and (b) the Plutonium and Fahrenheit scales?
- F.15** 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.16** 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 dm^3 at 25°C and 1.00 atm. What pressure is needed to compress it to 100 cm^3 at this temperature?
- F.17** 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.18** 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 dm^3 to 4.21 dm^3 . Calculate the final pressure of the gas.
- F.19** 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 per cent?
- F.20** 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 and (b) 880 Pa, -52.0°C ?
- F.21** 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 g cm^{-3} and assume that the temperature is the same as on the surface.
- F.22** 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.23** What is the kinetic energy of a tennis ball of mass 58 g served at 30 m s^{-1} ?
- F.24** A car of mass 1.5 t ($1\text{ t} = 10^3\text{ kg}$) traveling at 50 km h^{-1} must be brought to a stop. How much kinetic energy must be dissipated?
- F.25** Consider a region of the atmosphere of volume 25 dm^3 , 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.26** Calculate the minimum energy that a bird of mass 25 g must expend in order to reach a height of 50 m.
- F.27** The potential energy of a charge Q_1 in the presence of another charge Q_2 can be expressed in terms of the *Coulomb potential*, ϕ (phi):
- $$V = Q_1\phi \quad \phi = \frac{Q_2}{4\pi\epsilon_0 r}$$
- The units of potential are joules per coulomb, J C^{-1} , so when ϕ is multiplied by a charge in coulombs, the result is in joules. The

combination joules per coulomb occurs widely and is called a volt (V), with $1 \text{ V} = 1 \text{ J C}^{-1}$. Calculate the Coulomb potential due to the nuclei at a point in a LiH molecule located 200 pm from the Li nucleus and 150 pm from the H nucleus. *Hint:* Use $Q = +Ze$, where Z is the atomic number and e is the elementary charge.

F.28 Plot the Coulomb potential (see *Exercise F.27*) due to the nuclei at a point in a Na^+Cl^- ion pair located on a line half-way between the nuclei (the internuclear separation is 283 pm) as the point approaches from infinity and ends at the mid point between the nuclei.

F.29 What is the wavelength of the radiation used by an FM radio transmitter broadcasting at 92.0 MHz?

F.30 What is the energy of (a) a single photon and (b) 1.00 mol of photons of wavelength 670 nm?

F.31 Suppose that a macromolecule can exist either as a random coil or fully stretched out, with the latter conformation 2.4 kJ mol^{-1} higher in energy. What is the ratio of the two conformations at 20°C ?

F.32 An electron spin can adopt either of two orientations in a magnetic field, and its energies are $\pm\mu_B\mathcal{B}$, where $\mu_B = 9.274 \times 10^{-24} \text{ J T}^{-1}$ is the Bohr magneton and $\mathcal{B}$ is the intensity of the magnetic field, often reported in teslas ($1 \text{ T} = 1 \text{ kg s}^{-2} \text{ A}^{-1}$). Calculate the relative populations of the spin states at (a) 4.0 K and (b) 298 K, when $\mathcal{B} = 1.0 \text{ T}$.

F.33 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 and (b) CH_4 molecules at (i) 77 K, (ii) 298 K, and (iii) 1000 K.

Project

F.34 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.

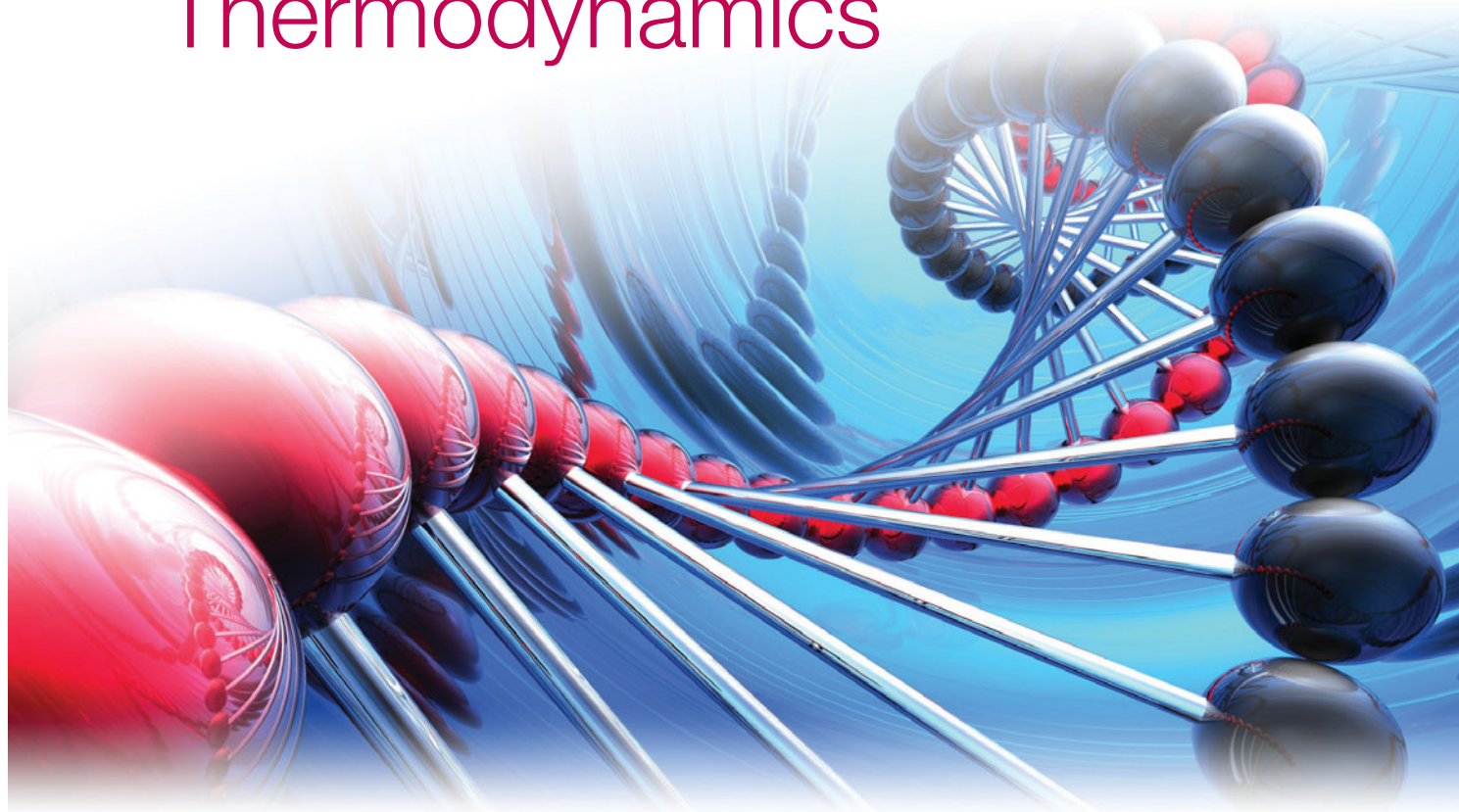
(a) The gravitational potential energy of a body of mass m at a distance r from the center of the Earth is $-Gmm_E/r$, where m_E is the mass of the Earth and G is the gravitational constant (see inside front cover). Consider the difference in potential energy of the body when it is moved from the surface of the Earth (radius r_E) to a height h above the surface, with $h \ll r_E$, 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 $(1 + h/r_E)^{-1} \approx 1 - h/r_E$. (See *Mathematical toolkit 3.2* for more information on series expansions and the approximations that can be made by using 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 the gravitational potential energy in part (a).

(c) Given the expression for the 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).

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PART 1 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.

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The First Law

1



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.

Throughout the text we shall pay special attention to **bioenergetics**, the deployment of energy in living organisms. 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 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 *Fundamentals*:

energy is the capacity to do work

work is the process of moving against an opposing force

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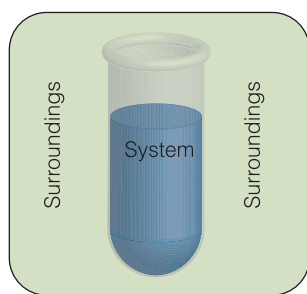


Fig. 1.1 The sample is the system of interest; the rest of the world is its surroundings. The surroundings are where observations are made on the system. They can often be modeled by a large water bath. The universe consists of the system and its surroundings.

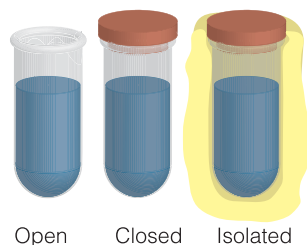


Fig. 1.2 A system is *open* if it can exchange energy and matter with its surroundings, *closed* if it can exchange energy but not matter, and *isolated* if it can exchange neither energy nor matter.

These definitions imply that a raised weight 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 relation 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.

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.

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.

1.2 Work and heat

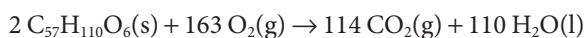
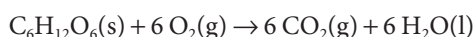
Organisms can be regarded as systems that exchange energy with their surroundings, and we need to understand how those transfers take place.

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 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 language, 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.

(a) Exothermic and endothermic processes

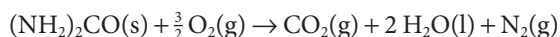
Walls that permit heating as a mode of transfer of energy are called **diathermic** (Fig. 1.3). A metal container is diathermic and so is our skin or any biological membrane. Walls that do not permit heating even though there is a difference in temperature are called **adiabatic**.¹ The double walls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

A process in a system that transfers energy as heat to the surroundings (we commonly say ‘releases heat into the surroundings’) is called **exothermic**. A process in a system that absorbs energy as heat from the surroundings (we commonly say ‘absorbs heat from the surroundings’) is called **endothermic**. All combustions are exothermic. The reactions leading to the oxidative breakdown of nutrients in organisms are also exothermic. These reactions include oxidation of the carbohydrate glucose ($\text{C}_6\text{H}_{12}\text{O}_6$, Atlas S4) and of the fat tristearin ($\text{C}_{57}\text{H}_{110}\text{O}_6$):



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.

As an example of these terms, consider a chemical reaction that is a net producer of gas, such as the combustion of urea, $(\text{NH}_2)_2\text{CO}$, to yield carbon dioxide, water, and nitrogen:



Suppose first that the reaction takes place inside a cylinder with diathermic walls and fitted with a movable 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. Because the reaction is exothermic and walls are diathermic, 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

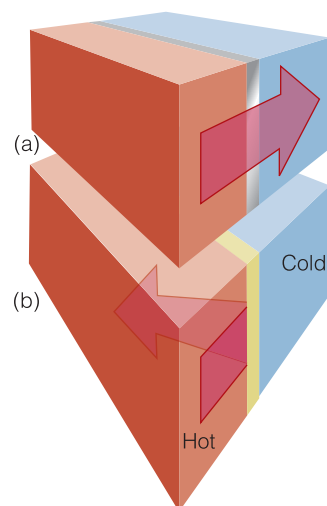


Fig. 1.3 (a) A diathermic wall permits the passage of energy as heat; (b) an adiabatic wall does not, even if there is a temperature difference across the wall.

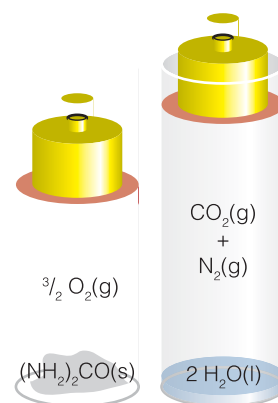


Fig. 1.4 When urea reacts with oxygen, the gases produced (carbon dioxide and nitrogen) must push back the surrounding atmosphere (represented by the weight resting on the piston) and hence must do work on its surroundings. This is an example of energy leaving a system as work.

¹ The word is derived from the Greek words for ‘not passing through’.

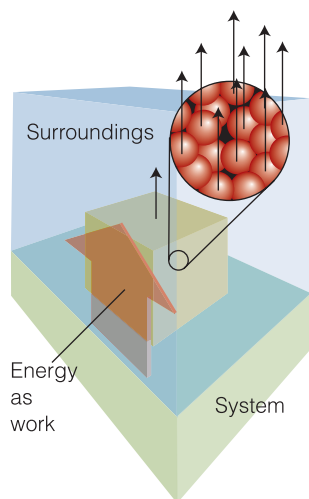


Fig. 1.5 Work is the transfer of energy that causes or utilizes uniform motion of atoms in the surroundings. For example, when a weight is raised, all the atoms of the weight (shown magnified) move in unison in the same direction.

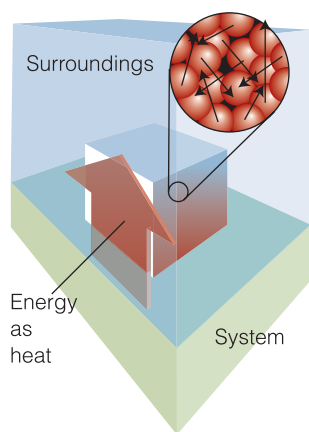


Fig. 1.6 Heat is the transfer of energy that causes or utilizes random motion in the surroundings. When energy leaves the system (the green region), it generates random motion in the surroundings (shown magnified).

much ice melts. Alternatively, we could let the same reaction take place in a diathermic 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.

(b) The molecular interpretation of work and heat

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 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.

(c) The molecular interpretation of temperature

We are now also in a position to understand the molecular basis of temperature (a concept first introduced in *Fundamentals* F.3). To do so, we consider an isolated system composed of N molecules. Although the total energy is constant at E , it is not possible to be definite about how that energy is shared between the molecules. Collisions result in the ceaseless redistribution of energy not only between the molecules but also among their different modes of motion (translation, rotation, and vibration). The closest we can come to a description of the distribution of energy is to report the **population** of a state, the average number of molecules that occupy it, and to say that on average there are N_i molecules in a state of energy ϵ_i . The populations of the states remain almost constant, but the precise identities of the molecules in each state may change at every collision.

Any individual molecule may exist in states with energies $\epsilon_0, \epsilon_1, \dots$. At any instant there are N_0 molecules in the state with energy ϵ_0 (the 'ground state'), N_1 with ϵ_1 (the 'first excited state'), and so on. The specification of the set of populations $N_0, N_1, \dots$ in the form $\{N_0, N_1, \dots\}$ is a statement of the 'instantaneous configuration' of the system. The instantaneous configuration fluctuates with

time because the populations change. We can picture a large number of different instantaneous configurations of 100 molecules. One configuration, for example, might be {98,0,2,...}, corresponding to every molecule except two being in the ground state. Another of the same total energy might be {96,1,1,1,...}, in which four molecules occupy the first four excited states. The latter configuration is intrinsically more likely to be found than the former because it can be achieved in more ways: {98,0,2,...} can be achieved in 4950 different ways but {96,1,1,1,...} can be achieved in 94 109 400 different ways, which is over 19 000 times more ways. (These numbers are obtained by counting how many ways there are of selecting molecules at random from 100.) If, as a result of molecular jostling, the system were to fluctuate between the configurations {98,0,2,...} and {96,1,1,1,...}, it would almost always be found in the second, more likely, configuration. In other words, a system free to switch between the two configurations would show properties characteristic almost exclusively of the second configuration. It should be easy to believe that there may be other configurations that have a much greater likelihood of occurring than both.

When the statistics of the distributions are analyzed, with energy distributed purely at random subject to its total being fixed at a certain value E , one configuration can be obtained in so many ways that it overwhelms all the rest in importance to such an extent that the system will almost always be found in it. The properties of the system will therefore be characteristic of that particular dominating configuration. The ratio of populations that correspond to this dominating configuration turns out to be given by the Boltzmann distribution, which we introduced and illustrated in *Fundamentals* F.3:

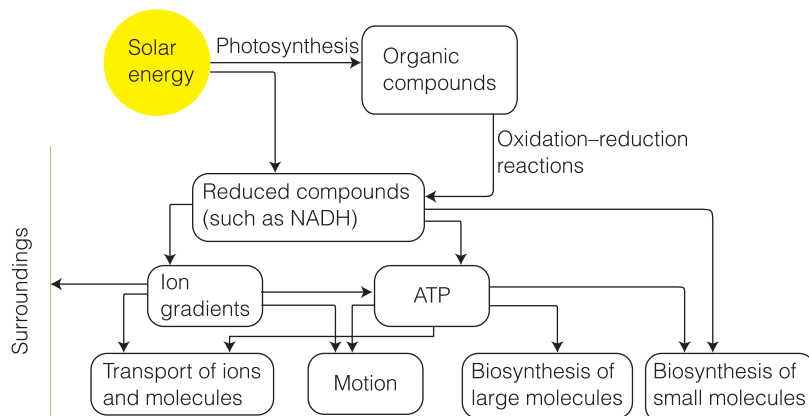
$$\frac{N_2}{N_1} = e^{-(E_2-E_1)/kT} = e^{-\Delta E/kT} \quad \text{The Boltzmann distribution} \quad (1.1)$$

where k is Boltzmann's constant ($k = 1.381 \times 10^{-23} \text{ J K}^{-1}$). We now see that the Boltzmann distribution, which is one of the most important concepts in the whole of physical chemistry, specifies the most probable distribution of molecules over their available energy levels subject only to the requirement that the total energy has a certain value. We also see that *the temperature is a parameter that characterizes that distribution*. A low temperature implies that only low-energy states are occupied; a high temperature indicates that high-energy states are also occupied. Zero temperature ($T = 0$) indicates that only the ground state is occupied. Infinite temperature ($T = \infty$) indicates that all available states are equally occupied. We can now begin to see that molecules are stable at low temperature because they occupy only low energy states; as the temperature is increased, they occupy more states of high energy and as a result can undergo reaction or, in the case of macromolecules, lose their secondary and higher levels of structure.

Case study 1.1 Energy conversion in 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.

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).)



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 reactions, with the energy liberated as work rather than as heat. Thus, even though the free combustion of a carbohydrate or fat to carbon dioxide and water is highly exothermic, in cells the equivalent oxidation is highly controlled and much of the energy is expended as useful work. The net outcome is the conversion of energy from controlled oxidation of nutrients to energy for doing work in the cell, including the transport of ions and neutral molecules (such as nutrients) across cell membranes, the physical 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.

Figure 1.7 also shows how organisms distribute the energy stored in a variety of ways. Because energy is extracted from organic compounds by oxidation, the initial energy carriers are reduced species, species that have gained electrons, such as NADH, the reduced form of nicotinamide adenine dinucleotide (NAD^+ , Atlas N4). Light-induced electron transfer in photosynthesis also leads to the formation of reduced species, such as NADPH from NADP^+ (Atlas N5), the phosphorylated derivative of NAD^+ . The details of the reactions leading to the production of NADH and NADPH are discussed in Chapter 5. Oxidation–reduction reactions (‘redox reactions’) transfer energy out of NADH and other reduced species, storing it in the mobile carrier adenosine triphosphate, ATP (Atlas N3), 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.

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

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.

1.3 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 , then the force opposing raising the mass vertically is mg , where g is the acceleration of free fall (9.81 m s^{-2}). Therefore, the work needed to raise the mass through a height h on the surface of the Earth is

$$\text{work} = mgh \quad \text{Work of raising a weight} \quad (1.2)$$

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 1.2.

A brief illustration

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 1.2, 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

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

It should be easy for you to show that this quantity of work is equivalent to the work of raising a book like this one (of mass about 1.0 kg) through a vertical distance of 20 cm (0.20 m).

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 $1 \text{ kg m}^2 \text{ s}^{-2} = 1 \text{ J}$, hence verifying that the answer has units of energy.

(a) Sign conventions

So far, we have referred only to the magnitude of the work done; now we need to consider its sign. 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 as work, 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 $w = -100 \text{ J}$. 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 $w = +100 \text{ J}$ 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

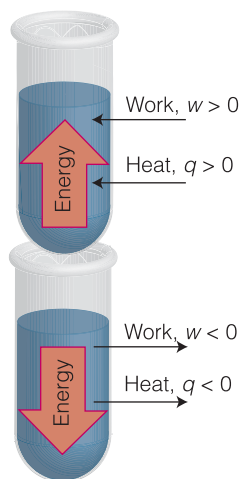


Fig. 1.8 The sign convention in thermodynamics: w and q are positive if energy enters the system (as work and heat, respectively) but negative if energy leaves the system.

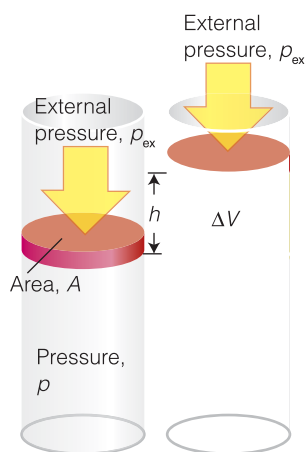


Fig. 1.9 When a piston of area A moves out through a distance h , it sweeps out a volume $\Delta V = Ah$. The external pressure p_{ex} opposes the expansion with a force $p_{\text{ex}}A$.

decreases (w is negative) if energy leaves it as work and its energy increases (w is positive) if energy enters it as work (Fig. 1.8).

(b) Expansion work

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 occur as a result of gas-producing or gas-consuming chemical reactions, but rather with the work of making and moving molecules in the cell, muscle contraction, or cell division. However, even though we might not be explicitly interested in it, expansion work is done in any chemical reaction that involves gases, such as the oxidation of fuels and photosynthesis, and for a proper analysis of energy resources it must be taken into account. We shall see that that can be done automatically in the following section, which will build on the material developed here.

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 *Justification* that when a system expands through a volume ΔV against a constant external pressure p_{ex} , the work done is

$$w = -p_{\text{ex}}\Delta V \quad \text{Work of expansion against a constant pressure} \quad (1.3)$$

Justification 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; *Fundamentals* F.2). The work done is therefore

$$\begin{aligned} \text{work done by the system} &= \text{distance } (h) \times \text{opposing force } (p_{\text{ex}}A) \\ &= h \times p_{\text{ex}}A = p_{\text{ex}} \times (hA) = p_{\text{ex}} \times \Delta V \end{aligned}$$

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,

$$\text{work done by the system} = p_{\text{ex}}\Delta V$$

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 1.3.

According to eqn 1.3, 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**.

A brief illustration

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 dm^3 ($5.0 \times 10^{-4} \text{ m}^3$) 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 $\Delta V = 5.0 \times 10^{-4} \text{ m}^3$ and the external pressure is $p_{\text{ex}} = 101 \text{ kPa}$. From eqn 1.3 the work of exhaling is

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

where we have used the relation $1 \text{ Pa m}^3 = 1 \text{ J}$. That value (51 J) might not seem much, but you should use eqn 1.2 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).

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 $1.0 \text{ mol CO}_2(\text{g})$ at 25°C and 100 kPa . (*Hint:* The increase in volume will be 25 dm^3 under these conditions if the gas is treated as perfect; use the relation $1 \text{ Pa m}^3 = 1 \text{ J}$.)

Answer: $w = -2.5 \text{ kJ}$

(c) Maximum work

Equation 1.3 can be used to show 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 1.3, 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: the external pressure must be progressively reduced so that it remains only infinitesimally lower than the pressure of the gas at each stage. As we remarked in *Fundamentals* F.2, this balance of pressures corresponds to 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 increased the external pressure so that at that stage of the expansion 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 in 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 ($p_{\text{ex}} = p$).
- 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) is done if the cellular process is reversible.

1.4 The measurement of heat

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

We use the same sign convention for energy transferred by heating, q , as we do for work. Thus, we write $q = -100 \text{ J}$ if 100 J of energy leaves the system by heating its surroundings, so reducing the energy of the system, and $q = +100 \text{ J}$ if 100 J of energy enters the system when it is heated by the surroundings.

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, 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

$$q = -w \quad \text{Isothermal expansion of a perfect gas} \quad (1.4)$$

A brief illustration

If we find that $w = -100 \text{ J}$ 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 $q = +100 \text{ J}$ (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.

(a) Heat capacity

When a substance is heated, its temperature typically rises.³ However, the change in temperature, ΔT , depends on the ‘heat capacity’ of the substance. The **heat capacity**, C , is defined as

$$C = \frac{q}{\Delta T} \quad \text{Definition of the heat capacity} \quad (1.5a)$$

where the temperature change may be expressed in kelvins (ΔT) or degrees Celsius ($\Delta\theta$); because the size of a kelvin is the same as that of a degree Celsius, the same numerical value is obtained but with the units joules per kelvin (J K^{-1}) and joules per degree Celsius ($\text{J } ^\circ\text{C}^{-1}$), 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 1.5a rearranged into

$$q = C\Delta T \quad (1.5b)$$

A brief illustration

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 occur in many places 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: 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. 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, $\text{J K}^{-1} \text{ g}^{-1}$), 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, $\text{J K}^{-1} \text{ mol}^{-1}$). In common usage, the specific heat capacity is often called simply 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 .

A brief illustration

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

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).

Table 1.1 Heat capacities of selected substances*

Substance	Molar heat capacity, $C_{p,m}$ / ($\text{J K}^{-1} \text{ mol}^{-1}$)
Air	29
Benzene, $\text{C}_6\text{H}_6(\text{l})$	136.1
Ethanol, $\text{C}_2\text{H}_5\text{OH}(\text{l})$	111.46
Glycine, $\text{CH}_2(\text{NH}_2)\text{COOH}(\text{s})$	99.2
Oxalic acid, $(\text{COOH})_2(\text{s})$	117
Urea, $\text{CO}(\text{NH}_2)_2(\text{s})$	93.14
Water, $\text{H}_2\text{O}(\text{s})$	37
$\text{H}_2\text{O}(\text{l})$	75.29
$\text{H}_2\text{O}(\text{g})$	33.58

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

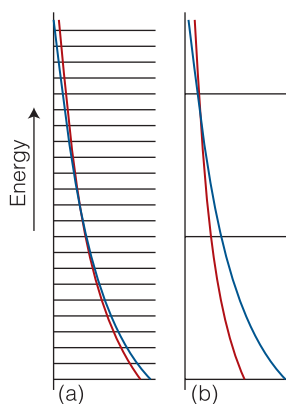


Fig. 1.10 The heat capacity depends on the availability of levels as explained in the text. In each case the blue line is the distribution at low temperature and the red line that at higher temperature.

lost or gained before there is a significant change in temperature. The molar heat capacity of liquid water at constant pressure, $C_{p,m}$, is $75 \text{ J K}^{-1} \text{ mol}^{-1}$. It follows that the increase in temperature of 100 g of water ($5.55 \text{ mol H}_2\text{O}$) when 1.0 kJ of energy is supplied by heating a sample free to expand is approximately

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

(b) The molecular interpretation of heat capacity

The molecular reason why different substances have different molar heat capacities can be traced to differences in the separations of their energy levels. As remarked in *Fundamentals* F.3, molecules can exist with only certain energies. When the available energy levels are close together, a given quantity of energy arriving as heat can be accommodated with little adjustment of the populations and hence with little modification of the temperature that occurs in the Boltzmann distribution and specifies the distribution of populations. The relative insensitivity of temperature to the arrival of energy corresponds to a high heat capacity (Fig. 1.10). When the energy levels are widely separated, the arriving energy must be accommodated by making use of the high energy levels with a consequent greater ‘reach’ of the Boltzmann distribution and hence a greater modification of the temperature. That is, widely spaced energy levels correlate with a low heat capacity. The translational energy levels of molecules in a gas are very close together, and all monatomic gases have similar molar heat capacities. The separation of the vibrational energies of atoms bound together in solids depends on the stiffness of the bonds between them and on the masses of the atoms. As we shall see in Sections 9.6 and 12.3, the stronger the bond and the lighter the atoms in a bond, the larger is the separation between vibrational energy levels. As a result, solids show a wide range of molar heat capacities. Biological macromolecules have large numbers of atoms and can vibrate in many different ways. Many of these ways correspond to the collective motion of many atoms, so the vibrational energies are spaced closely. Hence, heat capacities of biological macromolecules may be large.

Water, as so often, is anomalous. It is a small, rigid molecule but has a high heat capacity. Once again, the anomaly can be traced to hydrogen bonds in the liquid. These bonds link many molecules together into clusters that vibrate in numerous ways. Consequently, the vibrational energies are close together, and the heat capacity of water is larger than expected for a substance consisting of small molecules interacting weakly.

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 in the nineteenth century, who in effect 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.

1.5 The internal energy

To understand how biological processes can store and release energy, we need to be familiar with 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 atoms or molecules, is an intensive property.

(a) Changes in internal energy

In practice, we do not know and cannot measure the absolute value of 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

$$\Delta U = w + q \quad \text{Change in internal energy in terms of heat and work} \quad (1.6)$$

where w is the energy transferred to the system by doing work and q is the energy transferred to it by heating. The internal energy is an accounting device, like a country's gold reserves, which are used for monitoring transactions with the outside world (the surroundings) involving 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 1.6 we can write

$$\Delta U = 0 \quad \text{Change of internal energy during isothermal expansion of a perfect gas} \quad (1.7)$$

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.

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-expansion work, such as electrical work), we can set $w=0$. Then eqn 1.6 simplifies to

$$\Delta U = q_V \quad \text{Constant volume, no non-expansion work} \quad (1.8)$$

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

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 $\Delta U = 20 \text{ kJ}$, for instance, but always $+20 \text{ kJ}$.

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 $w = -622 \text{ kJ}$ (622 kJ is lost by doing work) and $q = -82 \text{ kJ}$ (82 kJ is lost by heating the surroundings). Then eqn 1.6 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.

Self-test 1.2 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: $+225 \text{ kJ}$

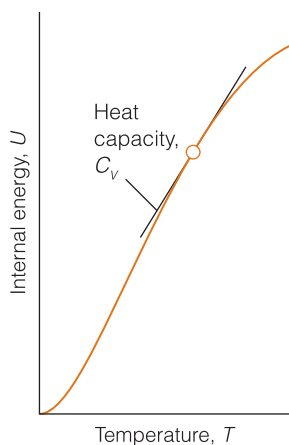


Fig. 1.11 The constant-volume heat capacity is the slope of a curve showing how the internal energy varies with temperature. The slope, and therefore the heat capacity, may be different at different temperatures.

We can use eqn 1.8 to obtain more insight into the heat capacity of a substance. The definition of heat capacity is given in eqn 1.5 ($C = q/\Delta T$). At constant volume, q may be replaced by the change in internal energy of the substance, so

$$C_V = \frac{\Delta U}{\Delta T} \quad \text{Definition of the constant-volume heat capacity} \quad (1.9a)$$

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. 1.11). That is, the constant-volume heat capacity is the derivative of the function U with respect to the variable T at a specified volume (see *Mathematical toolkit 1.1*):

Mathematical toolkit 1.1 *Differentiation*

Consider a function f with values $f(x)$ and $f(x + \delta x)$ at x and $x + \delta x$, respectively. The slope of this function at x is obtained by letting δx become zero, which we write as $\lim_{\delta x \rightarrow 0}$. In this limit, the δ is replaced by a d , and we write

$$\text{Slope at } x = \frac{df}{dx} = \lim_{\delta x \rightarrow 0} \frac{f(x + \delta x) - f(x)}{\delta x}$$

To work out the slope of any function, we develop the expression on the right: this process is called **differentiation**. The slope is called the **derivative** of the function. Examples of derivatives include:

$$\frac{dx^n}{dx} = nx^{n-1} \quad \frac{de^{ax}}{dx} = ae^{ax} \quad \frac{d \ln ax}{dx} = \frac{a}{x}$$

Most of the functions encountered in chemistry can be differentiated by using the following rules:

Rule 1. For two functions f and g :

$$\frac{d}{dx}(f + g) = \frac{df}{dx} + \frac{dg}{dx}$$

Rule 2 (the product rule). For two functions f and g :

$$\frac{d}{dx}fg = f \frac{dg}{dx} + g \frac{df}{dx}$$

Rule 3 (the quotient rule). For two functions f and g :

$$\frac{d}{dx} \frac{f}{g} = \frac{1}{g} \frac{df}{dx} - \frac{f}{g^2} \frac{dg}{dx}$$

Rule 4 (the chain rule). For a function $f = f(g)$, where $g = g(x)$,

$$\frac{df}{dx} = \frac{df}{dg} \frac{dg}{dx}$$

In the last rule, $f(g)$ is a ‘function of a function’, as in $\ln(1 + x^2)$.

$$C_V = \frac{dU}{dT}$$

Definition of the constant-volume heat capacity (1.9b)

(b) The internal energy as a state function

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.

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 and for the study of bioenergetics, as we shall soon see.

A brief comment

More precisely, the constant-volume heat capacity is the *partial derivative* of the function U with respect to the variable T , denoted as

$$C_V = \left(\frac{\partial U}{\partial T} \right)_V$$

with the symbol ∂ replacing the symbol d , and the subscript V denoting that the variable V is held constant. Generally, a partial derivative of a function of more than one variable is the slope of the function with respect to one of the variables, all the other variables being held constant (Fig. 1.12). For more detail about partial derivatives, see *Mathematical toolkit 8.1*.

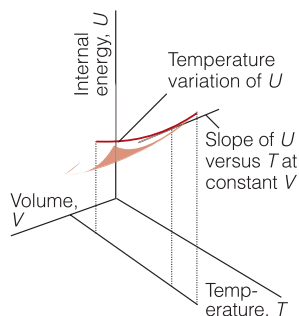


Fig. 1.12 The internal energy of a system varies with volume and temperature, perhaps as shown here by the surface. The variation of the internal energy with temperature at one particular constant volume is illustrated by the curve drawn parallel to T . The slope of this curve at any point is the partial derivative $(\partial U/\partial T)_V$.

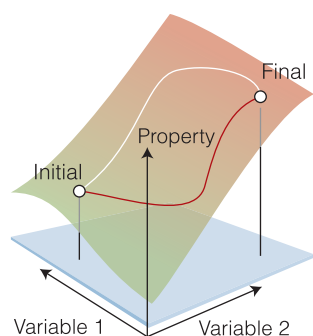


Fig. 1.13 The curved sheet shows how a property (for example, the altitude) changes as two variables (for example, latitude and longitude) are changed. The altitude is a state property because it depends only on the current state of the system. The change in the value of a state property is independent 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 red and white lines) is used to travel between them.

(c) The First Law of thermodynamics

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.

The First Law

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.

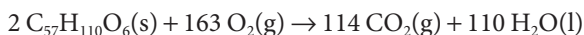
The experimental evidence for the First Law is the impossibility of making a ‘perpetual motion machine’, a device for producing work without consuming fuel. As we have already remarked, try as people might, they have never succeeded. No device has ever been made that creates internal energy to replace 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 of motion, metabolism, and catabolism is done by the organism.

1.6 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 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 $\text{CaCO}_3(\text{s})$ at 1 bar results in an increase in volume of 89 dm^3 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. 1.14). 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



In this exothermic reaction there is a net *decrease* in volume equivalent to the elimination of $(163 - 114) \text{ mol} = 49 \text{ mol}$ of gas molecules for every 2 mol of tristearin molecules that reacts. The decrease in volume at 25°C is about 600 cm^3 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.

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.

(a) The definition of enthalpy

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 centre of our attention throughout the rest of the chapter and will recur throughout the book. The **enthalpy**, H , of a system is defined as

$$H = U + pV \quad \text{Definition of the enthalpy} \quad (1.10)$$

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 misled by the pV term into thinking that eqn 1.10 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 :

$$\Delta H = \Delta U + \Delta(pV) \quad (1.11a)$$

where $\Delta(pV) = p_f V_f - p_i V_i$. 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

$$\Delta H = \Delta U + p\Delta V \quad \text{Enthalpy change at constant pressure} \quad (1.11b)$$

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:

$$H_m = U_m + pV_m \quad \text{Definition of the molar enthalpy} \quad (1.12a)$$

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

$$H_m = U_m + RT \quad \text{Molar enthalpy of a perfect gas} \quad (1.12b)$$

At 25°C, $RT = 2.5 \text{ kJ mol}^{-1}$, 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. However, the conceptual importance is considerable, as we shall see.

(b) Changes in enthalpy

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, H , when a system changes from one state to another is independent of

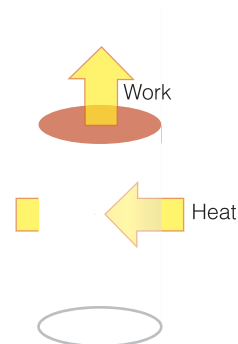


Fig. 1.14 The change in internal energy of a system that is free to expand or contract is not equal to the energy supplied by heating because some energy may escape back into the surroundings as work. However, the change in enthalpy of the system under these conditions is equal to the energy supplied by heating.

the path between the two states. Second, we show in the following *Justification* that the change in enthalpy of a system can be identified with the heat transferred to it at constant pressure:

$$\Delta H = q_p \quad \text{Enthalpy change at constant pressure, no non-expansion work} \quad (1.13)$$

with 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.

Justification 1.2 *Heat transfers at constant pressure*

This *Justification* fulfils our promise that the calculation of expansion work can be done silently and automatically in the background and need not be done explicitly.

Consider a system open to the atmosphere, so that its pressure p is constant and equal to the external pressure p_{ex} . From eqn 1.11 we can write

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

However, we know that the change in internal energy is given by eqn 1.6 ($\Delta U = w + q$) with $w = -p_{\text{ex}}\Delta V$ (provided the system does no other kind of work). When we substitute that expression into this one we obtain

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

which is eqn 1.13.

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. In summary:

exothermic process	endothermic process
$\Delta H < 0$	$\Delta H > 0$

Because all combustion reactions, including the controlled 'combustions' that contribute to respiration, are exothermic, they 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

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.

(c) The temperature dependence of the enthalpy

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. 1.15). 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 $\Delta H \approx +25 \text{ kJ}$ 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 1.5 ($C = q/\Delta T$) with eqn 1.13 and obtain

$$C_p = \frac{\Delta H}{\Delta T} \quad \text{Definition of constant-pressure heat capacity} \quad (1.14a)$$

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. 1.16, 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

$$C_p = \frac{dH}{dT} \quad (1.14b)$$

A brief illustration

Provided the heat capacity is constant over the range of temperatures of interest, we can write eqn 1.14a as $\Delta H = C_p \Delta T$. This relation means that when the temperature of 100 g of water (5.55 mol H_2O) is raised from 20°C to 80°C (so $\Delta T = +60 \text{ K}$) at constant pressure, the enthalpy of the sample changes by

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

The greater the temperature rise, the greater the change in enthalpy and therefore the greater the heating that is 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, $C_{v,m} = 20.8 \text{ J K}^{-1} \text{ mol}^{-1}$ and $C_{p,m} = 29.1 \text{ J K}^{-1} \text{ mol}^{-1}$), which undergo large changes of volume when heated, but is negligible for most solids and liquids. For a perfect gas, you are invited to show in Exercise 1.19 that

$$C_{p,m} - C_{v,m} = R \quad \text{Difference between the molar heat capacities of a perfect gas} \quad (1.15)$$

The molar heat capacity of a substance at constant pressure is always greater than the molar heat capacity at constant volume. The reason is that when a system is

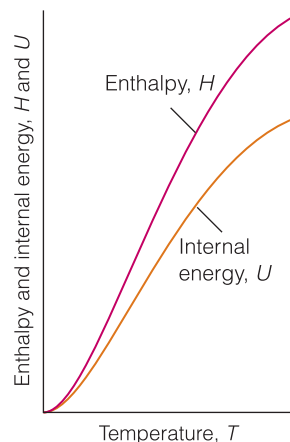


Fig. 1.15 The enthalpy of a system increases as its temperature is raised. Note that the enthalpy is always greater than the internal energy of the system and that the difference increases with temperature.

A brief comment

Again more precisely the constant-pressure heat capacity is the *partial derivative* of the function H with respect to the variable T , denoted as

$$C_p = \left(\frac{\partial H}{\partial T} \right)_p$$

and calculated by holding the variable p constant.

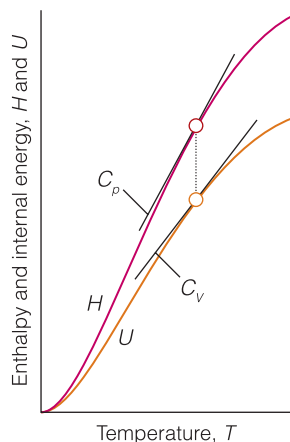


Fig. 1.16 The heat capacity at constant pressure is the slope of the curve showing how the enthalpy varies with temperature; the heat capacity at constant volume is the corresponding slope of the internal energy curve. Note that the heat capacity varies with temperature (in general) and that C_p is greater than C_v .

A brief comment

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 $1 \text{ A} = 1 \text{ C s}^{-1}$. If a constant current I flows through a potential difference $\mathcal{V}$ (measured in volts, V), the total energy supplied in an interval t is $I\mathcal{V}t$. Because $1 \text{ A V s} = 1 (\text{C s}^{-1}) \text{ V s} = 1 \text{ C V} = 1 \text{ J}$, the energy is obtained in joules with the current in amperes, the potential difference in volts, and the time in seconds.

free to expand, some of the energy supplied as heat is free to escape back into the surroundings as work. Therefore, the rise in temperature at constant pressure is not as great as at constant volume (when no expansion work can be done), and the heat capacity is correspondingly greater.

In the laboratory 1.1 Calorimetry

Calorimetry is the study of heat transfer during physical and chemical processes. A **calorimeter**⁶ is a device for measuring energy transferred as heat. Here we explore three common types of calorimeters used in investigations of nutrients, fuels, and biological processes.

(a) Bomb calorimeters

The most common device for measuring ΔU is an **adiabatic bomb calorimeter** (Fig. 1.17). The process under study is initiated inside a constant-volume container, the ‘bomb’. The bomb is immersed in a stirred water bath, and the whole device is the calorimeter. The calorimeter is also immersed in an outer water bath. The water in the calorimeter and of the outer bath are both monitored and adjusted to the same temperature. This arrangement ensures that there is no net loss of heat from the calorimeter to the surroundings (the bath) and hence that the calorimeter is adiabatic.

The change in temperature, ΔT , of the calorimeter is proportional to the energy that the process releases or absorbs as heat. Therefore, by measuring ΔT we can determine q_v and hence find ΔU . The conversion of ΔT to q_v is best achieved by calibrating the calorimeter using a process of known energy output and determining the **calorimeter constant**, the constant C in the relation

$$q = C\Delta T \quad \text{Calorimeter constant} \quad (1.16)$$

The calorimeter constant may be measured electrically by passing a constant current, I , from a source of known potential difference, $\mathcal{V}$, through a heater for a known period of time, t , for then

$$q = I\mathcal{V}t \quad (1.17)$$

A brief illustration

If we pass a current of 10.0 A from a 12 V supply for 300 s, then from eqn 1.17 the energy supplied as heat is

$$q = (10.0 \text{ A}) \times (12 \text{ V}) \times (300 \text{ s}) = 3.6 \times 10^4 \text{ A V s} = 36 \text{ kJ}$$

because $1 \text{ A V s} = 1 \text{ J}$. If the observed rise in temperature is 5.5 K, then the calorimeter constant is $C = (36 \text{ kJ})/(5.5 \text{ K}) = 6.5 \text{ kJ K}^{-1}$.

Alternatively, C may be determined by using a reaction of known heat output, such as the combustion of benzoic acid ($\text{C}_6\text{H}_5\text{COOH}$), for which the heat output is 3227 kJ per mole of $\text{C}_6\text{H}_5\text{COOH}$ consumed. With C known, it is simple to interpret an observed temperature rise as a release of energy as heat.

⁶ The word *calorimeter* comes from ‘calor’, the Latin word for *heat*.

Bomb calorimetry is used in nutritional studies to determine the total energy content of a nutrient, also called its *gross energy (G.E.) content*. The results may be expressed in a number of units, but common in nutritional studies is the *large calorie* or *nutritional calorie* (abbreviation: Cal), which is defined as 1 Cal = 4.184 kJ exactly. The large calorie is the unit of energy used colloquially and on labels on packages of food products. This unit is distinct from the *calorie* (abbreviation: cal), or ‘small calorie’, still encountered in the scientific literature, 1 cal = 4.184 J exactly. It follows that 1 Cal = 1 kcal.

Example 1.2 *Calibrating a calorimeter and measuring the energy content of a nutrient*

In an experiment to measure the heat released by the combustion of a sample of nutrient, the compound was burned in a calorimeter and the temperature rose by 3.22°C. When a current of 1.23 A from a 12.0 V source flowed through a heater in the same calorimeter for 156 s, the temperature rose by 4.47°C. What is the energy content of the nutrient, taken as the heat released by the combustion reaction?

Strategy We calculate the heat supplied electrically by using eqn 1.17 and 1 A V s = 1 J. Then we use the observed rise in temperature to find the heat capacity of the calorimeter. Finally, we use this heat capacity to convert the temperature rise observed for the combustion into a heat output by writing $q = C\Delta T$ (or $q = C\Delta\theta$ if the temperature is given on the Celsius scale).

Solution The heat supplied during the calibration step is

$$\begin{aligned} q &= I\mathcal{V}t = (1.23 \text{ A}) \times (12.0 \text{ V}) \times (156 \text{ s}) \\ &= 1.23 \times 12.0 \times 156 \text{ A V s} \\ &= 1.23 \times 12.0 \times 156 \text{ J} \end{aligned}$$

This product works out as 2.30 kJ, but to avoid rounding errors we save the numerical work to the final stage. The heat capacity of the calorimeter is

$$C = \frac{q}{\Delta\theta} = \frac{1.23 \times 12.0 \times 156 \text{ J}}{4.47^\circ\text{C}} = \frac{1.23 \times 12.0 \times 156}{4.47} \text{ J } ^\circ\text{C}^{-1}$$

The numerical value of C is 515 J °C⁻¹, but we don’t evaluate it yet in the actual calculation. The heat output of the combustion is therefore

$$\begin{aligned} q &= C\Delta\theta = \left(\frac{1.23 \times 12.0 \times 156}{4.47} \text{ J } ^\circ\text{C}^{-1} \right) \times 3.22^\circ\text{C} = 1.66 \text{ kJ} \\ &= 0.397 \text{ Cal} \end{aligned}$$

Self-test 1.3 In an experiment to measure the heat released by the combustion of a sample of fuel, the compound was burned in an oxygen atmosphere inside a calorimeter and the temperature rose by 2.78°C. When a current of 1.12 A from an 11.5 V source flowed through a heater in the same calorimeter for 162 s, the temperature rose by 5.11°C. What is the heat released by the combustion reaction?

Answer: 1.1 kJ

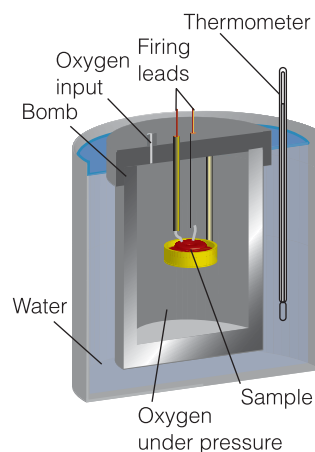


Fig. 1.17 A constant-volume adiabatic bomb calorimeter. The ‘bomb’ is the central vessel, which is strong enough to withstand high pressures. The calorimeter (for which the heat capacity must be known) is the entire assembly shown here. To ensure adiabaticity, the calorimeter is immersed in a water bath with a temperature continuously adjusted to that of the calorimeter at each stage of the combustion.

A note on good practice

As well as keeping the numerical evaluation to the final stage (or at least not rounding intermediate values obtained with a calculator), show the units at each stage of the calculation.

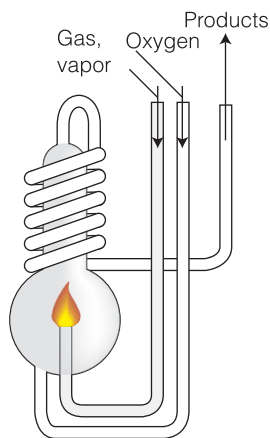


Fig. 1.18 An adiabatic flame calorimeter, an example of an isobaric calorimeter, consists of this component immersed in a stirred water bath. Combustion occurs as a known amount of reactant is passed through to fuel the flame and the rise of temperature is monitored.

A brief comment

The *rate of change of energy* is the power, expressed as joules per second, or *watts*, W : $1\text{ W} = 1\text{ J s}^{-1}$. Because $1\text{ J} = 1\text{ A V s}$, in terms of electrical units $1\text{ W} = 1\text{ A V}$. We write the electrical power, P , as $P = (\text{energy supplied})/t = I\mathcal{V}/t = I\mathcal{V}$.

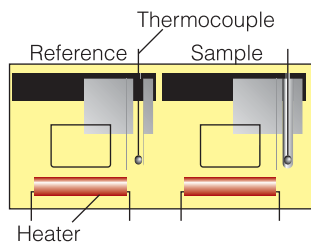


Fig. 1.19 A differential scanning calorimeter. The sample and a reference material are heated in separate but identical compartments. The output is the difference in power needed to maintain the compartments at equal temperatures as the temperature rises.

(b) Isobaric calorimeters

An enthalpy change can be measured calorimetrically by monitoring the temperature change that accompanies a physical or chemical change occurring at constant pressure. A calorimeter for studying processes at constant pressure is called an **isobaric calorimeter**. A simple example is a thermally insulated vessel open to the atmosphere: the heat released in the reaction is monitored by measuring the change in temperature of the contents. For a combustion reaction an **adiabatic flame calorimeter** may be used to measure ΔT when a given amount of substance burns in a supply of oxygen (Fig. 1.18). The relative efficiencies of fuels may be evaluated by this method (see Section 1.9).

(c) Differential scanning calorimeters

A **differential scanning calorimeter** (DSC) is more sophisticated than the calorimeters discussed so far. 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.

A DSC consists of two small compartments that are heated electrically at a constant rate (Fig. 1.19). 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 kelvins 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 1.5 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, which is called a **thermogram**, consists of a plot of P_{ex} or $C_{p,\text{ex}}$ against T (Fig. 1.20). Broad peaks in the thermogram indicate processes requiring the transfer of energy by heating. We show in the following *Justification* that the enthalpy change of the process is

$$\Delta H = \int_{T_1}^{T_2} C_{p,\text{ex}} dT \quad (1.18)$$

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.

Justification 1.3 *The enthalpy change of a process from DSC data*

To calculate an enthalpy change from a thermogram, we begin by rewriting eqn 1.14b as

$$dH = C_{p,\text{ex}}dT$$

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 .

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

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

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

which is eqn 1.18.

A brief comment

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

To appreciate the utility of a DSC in biochemical investigations, we consider an important type of transformation that occurs in biological macromolecules, such as proteins and nucleic acids, and aggregates, such as biological membranes. Such large systems adopt complex three-dimensional structures as a result of intra- and inter-molecular interactions (*Fundamentals* F.1 and Chapter 11). **Denaturation**, the disruption of these interactions, 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 powerful 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 and biological function is lost. For example, the thermogram shown in Fig. 1.20 indicates that the widely distributed protein ubiquitin retains its native structure up to about 45°C and ‘melts’ into a denatured state at higher temperatures. The area under the curve represents the heat absorbed in this process and can be identified with the enthalpy change. The thermogram also reveals the formation of new intermolecular interactions in the denatured form. The increase in heat capacity accompanying the native $\rightarrow$ denatured transition reflects the change from a more compact native conformation to one in which the more exposed amino acid side chains in the denatured form have more extensive interactions with the surrounding water molecules. Differential scanning calorimetry is a convenient method for such studies because it requires small samples, with masses as low as 0.5 mg.

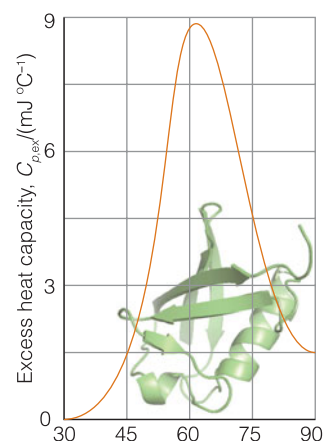


Fig. 1.20 A thermogram for the protein ubiquitin. The protein retains its native structure (shown as a green ribbon diagram) up to about 45°C and then undergoes an endothermic conformational change. (Adapted from B. Chowdhry and S. LeHarne, *J. Chem. Educ.* 74, 236 (1997).)

Physical and chemical change

We shall focus on the use of the enthalpy as a useful book-keeping 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.

1.7 Enthalpy changes accompanying physical processes

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 changes 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.⁷

Definition of
standard state

We denote the standard state value of a property by the superscript $^\circ$ on the symbol for the property, as in H_m° for the standard molar enthalpy of a substance and p° 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 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. The standard states of solutions, which are never ‘pure’, need to be treated differently (Section 3.8).

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, however, 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.

(a) Phase transitions

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

⁷ Remember that 1 bar = 10⁵ Pa exactly.

12 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 some evidence suggests that water might also have two liquid phases.

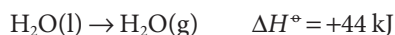
The conversion of one phase of a substance to another phase is called a **phase transition**. Thus, vaporization (liquid $\rightarrow$ gas) is a phase transition, as is a transition between solid phases (such as aragonite $\rightarrow$ calcite in geological processes). With a few exceptions, phase transitions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

(b) Enthalpies of vaporization, fusion, and sublimation

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 evaporation⁸ 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 $\Delta_{\text{vap}}H^\circ$ (Table 1.2). For example, 44 kJ of heat is required to vaporize 1 mol $\text{H}_2\text{O}(\text{l})$ at 1 bar and 25°C, so $\Delta_{\text{vap}}H^\circ = +44 \text{ kJ mol}^{-1}$.

Alternatively, we can report the same information by writing the **thermochemical equation**⁹



A note on good practice

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. All enthalpies of vaporization are positive, so the sign is not normally written explicitly in tables of data.

Table 1.2 Standard enthalpies of transition at the transition temperature*

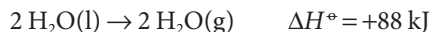
Substance	Freezing point, T_{fus}/K	$\Delta_{\text{fus}}H^\circ/(\text{kJ mol}^{-1})$	Boiling point, T_{b}/K	$\Delta_{\text{vap}}H^\circ/(\text{kJ mol}^{-1})$
Ammonia, NH_3	195.3	5.65	239.7	23.4
Argon, Ar	83.8	1.2	87.3	6.5
Benzene, C_6H_6	278.7	9.87	353.3	30.8
Ethanol, $\text{C}_2\text{H}_5\text{OH}$	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
				44.02 at 25°C
				45.07 at 0°C

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

⁸ Evaporation is virtually synonymous with vaporization but commonly denotes vaporization to dryness.

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

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



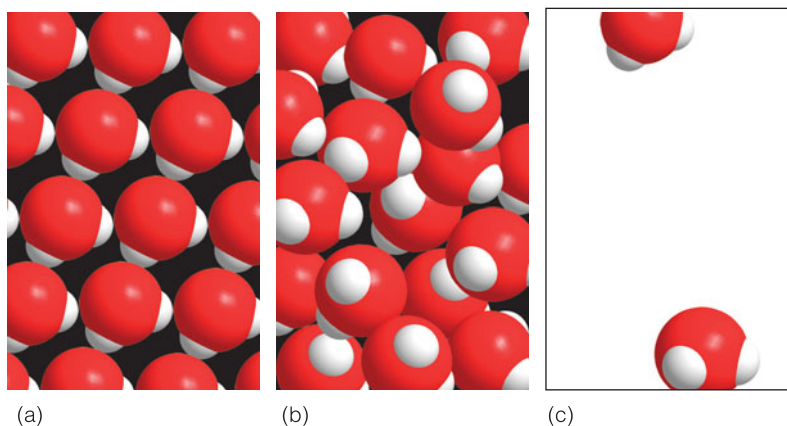
This equation signifies that 88 kJ of heat is required to vaporize 2 mol $\text{H}_2\text{O}(\text{l})$ at 1 bar and (recalling our convention) at 298.15 K.

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. As should be recalled from introductory courses, the interaction responsible for the low volatility of water is the hydrogen bonding between neighboring H_2O molecules. 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 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.

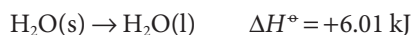
Another common phase transition is **fusion**, or melting, as when ice melts to water. The change in molar enthalpy that accompanies fusion under standard conditions (pure solid at 1 bar changing to pure liquid at 1 bar) is called the **standard enthalpy of fusion**, $\Delta_{\text{fus}} H^\circ$. Its value for water at 0°C is $+6.01 \text{ kJ mol}^{-1}$. As for enthalpies of vaporization, all enthalpies of fusion are positive, and the sign is not written explicitly in tables. 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. 1.21).

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

Fig. 1.21 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.



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):



and in general

$$\Delta_{\text{forward}} H^\circ = -\Delta_{\text{reverse}} H^\circ \quad (1.19)$$

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. 1.22). The high standard enthalpy of vaporization of water (+44 kJ mol⁻¹), 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**, $\Delta_{\text{sub}} H^\circ$. 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. 1.23):

$$\Delta_{\text{sub}} H^\circ = \Delta_{\text{fus}} H^\circ + \Delta_{\text{vap}} H^\circ \quad (1.20)$$

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.

A brief illustration

To use eqn 1.20 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

$$\Delta_{\text{sub}} H^\circ = \Delta_{\text{fus}} H^\circ + \Delta_{\text{vap}} H^\circ = 6.01 \text{ kJ mol}^{-1} + 45.07 \text{ kJ mol}^{-1} = 51.08 \text{ kJ mol}^{-1}$$

1.8 Bond enthalpy

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

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.

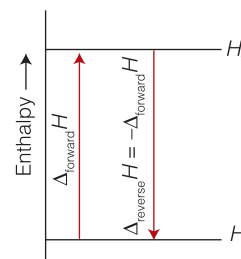


Fig. 1.22 An implication of the First Law is that the enthalpy change accompanying a reverse process is the negative of the enthalpy change for the forward process.

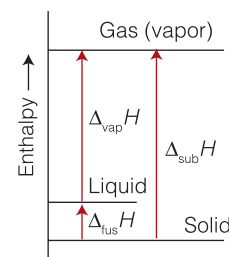


Fig. 1.23 The enthalpy of sublimation at a given temperature is the sum of the enthalpies of fusion and vaporization at that temperature. Another implication of the First Law is that the enthalpy change of an overall process is the sum of the enthalpy changes for the possibly hypothetical steps into which it may be divided.

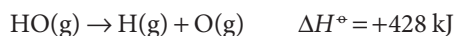
A note on good practice

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 $\Delta_{\text{trs}} H$, are molar quantities.

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

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 ₆ H ₅	469	O ₂ N-NO ₂	57	HO-OH	213		
H ₃ C-CH ₃	368	O=CO	531	HO-CH ₃	377		
H ₂ C=CH ₂	699			Cl-CH ₃	352		
HC≡CH	962			Br-CH ₃	293		
				I-CH ₃	234		

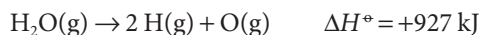
The thermochemical equation for the dissociation, or breaking, of a chemical bond can be written with the hydroxyl radical OH(g) as an example:



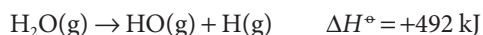
The corresponding standard molar enthalpy change is called the **bond enthalpy**, so we would report the H–O bond enthalpy as 428 kJ mol^{−1}. All bond enthalpies are positive, so bond dissociation is an endothermic process.

Some bond enthalpies are given in Table 1.3. Note that the bond in molecular nitrogen, N₂, 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 bond in molecular fluorine, F₂, 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, I₂ is less reactive than F₂, and the bond in CO is stronger than the bond in N₂, 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 when a new substance is formed from reactants are additional factors.

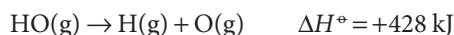
A complication when dealing with bond enthalpies is that their values depend on the molecule in which the two linked atoms occur. For instance, the total standard enthalpy change for the atomization (the complete dissociation into atoms) of water:



is not twice the O–H bond enthalpy in H₂O 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 H₂O molecule:



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



A brief comment

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 1.4 Mean bond enthalpies, $\Delta H_{\text{B}}/(\text{kJ mol}^{-1})^*$

	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) 497 (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).

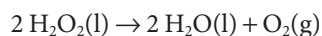
[†](a) Denotes aromatic.

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

Example 1.3 Using mean bond enthalpies

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



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. The enthalpy of vaporization of $\text{H}_2\text{O}_2(\text{l})$ at 298 K is 51.5 kJ mol^{-1} .

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:

	$\Delta H^\circ/\text{kJ}$
Vaporization of 2 mol $\text{H}_2\text{O}_2(\text{l})$, $2 \text{H}_2\text{O}_2(\text{l}) \rightarrow 2 \text{H}_2\text{O}_2(\text{g})$	$2 \times (+51.5)$
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: $2 \text{H}_2\text{O}_2(\text{l}) \rightarrow 4 \text{H}(\text{g}) + 4 \text{O}(\text{g})$	+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 $\text{H}_2\text{O}(\text{g})$ and for the O=O bond in $\text{O}_2(\text{g})$:

	$\Delta H^\circ/\text{kJ}$
Formation of 4 mol O–H bonds	$4 \times (-492)$
Formation of 1 mol O_2	–497
Overall, in this step: $4 \text{O}(\text{g}) + 4 \text{H}(\text{g}) \rightarrow 2 \text{H}_2\text{O}(\text{g}) + \text{O}_2(\text{g})$	–2465

The final stage of the reaction is the condensation of 2 mol $\text{H}_2\text{O}(\text{g})$



The sum of the enthalpy changes is

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

The experimental value is –196 kJ.

Self-test 1.4 Estimate the enthalpy change for the reaction between 1 mol $\text{C}_2\text{H}_5\text{OH}$ as liquid ethanol, a fuel made by fermenting corn, and $\text{O}_2(\text{g})$ to yield $\text{CO}_2(\text{g})$ and $\text{H}_2\text{O}(\text{l})$ under standard conditions by using the bond enthalpies, mean bond enthalpies, and the appropriate standard enthalpies of vaporization.

Answer: –1305 kJ; the experimental value is –1368 kJ

1.9 Thermochemical properties of fuels

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

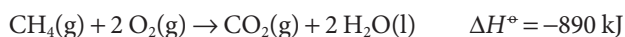
We saw in *Case study* 1.1 that photosynthesis and the oxidation of organic molecules are the most important processes that supply energy to organisms. In this section we begin our quantitative study of biological energy conversion by assessing the thermochemical properties of fuels.

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)	−283
Citric acid, C ₆ H ₈ O ₇ (s)	−1985
Ethanol, C ₂ H ₅ OH(l)	−1368
Glucose, C ₆ H ₁₂ O ₆ (s)	−2808
Glycine, CH ₂ (NH ₂)COOH(s)	−969
Hydrogen, H ₂ (g)	−286
<i>iso</i> -Octane, * C ₈ H ₁₈ (l)	−5461
Methane, CH ₄ (g)	−890
Methanol, CH ₃ OH(l)	−726
Methylbenzene, C ₆ H ₅ CH ₃ (l)	−3910
Octane, C ₈ H ₁₈ (l)	−5471
Propane, C ₃ H 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.

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:



The **standard enthalpy of combustion**, $\Delta_c H^\circ$, is the standard change in enthalpy per mole of combustible molecules. In this example, we would write $\Delta_c H^\circ(\text{CH}_4, \text{g}) = -890 \text{ kJ mol}^{-1}$. Some typical values are given in Table 1.5. Note that $\Delta_c H^\circ$ is a molar quantity and is obtained from the value of ΔH° by dividing by the amount of organic reactant consumed (in this case, by 1 mol CH₄).

According to the discussion in Sections 1.5 and 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 1.12a). For condensed phases, pV_m is so small that 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

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

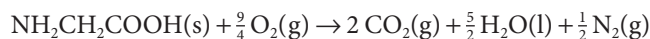
However, the molar volume of a gas, and therefore the value of pV_m , is about 1000 times greater and cannot be ignored. For gases treated as perfect, pV_m may be replaced by RT . Therefore, if in the chemical equation the difference (products – reactants) in the stoichiometric coefficients of *gas phase*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

$$\Delta_c H = \Delta_c U + \Delta \nu_{\text{gas}} RT \quad (1.21)$$

Note that ν_{gas} (where ν is nu) is a dimensionless number.

A brief illustration

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



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

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

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 magnitude of the enthalpy of combustion divided by the mass of the sample (typically in kilojoules per gram) or the **enthalpy density**, the magnitude of the enthalpy of combustion divided by the volume of the sample (typically in kilojoules per cubic decimeter). If the standard enthalpy of combustion is $\Delta_c H^\circ$ and the molar mass of the compound is M , then the specific enthalpy is $\Delta_c H^\circ/M$. Similarly, the enthalpy density is $\Delta_c H^\circ/V_m$, 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 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

Table 1.6 Thermochemical properties of some fuels

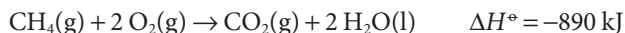
Fuel	Combustion equation	$\Delta_c H^\circ/(\text{kJ mol}^{-1})$	Specific enthalpy/ (kJ g^{-1})	Enthalpy density*/ (kJ dm^{-3})
Hydrogen	$2\text{H}_2(\text{g}) + \text{O}_2(\text{g}) \rightarrow 2\text{H}_2\text{O(l)}$	-286	142	13
Methane	$\text{CH}_4(\text{g}) + 2\text{O}_2(\text{g}) \rightarrow \text{CO}_2(\text{g}) + 2\text{H}_2\text{O(l)}$	-890	55	40
<i>iso</i> -Octane†	$2\text{C}_8\text{H}_{18}(\text{l}) + 25\text{O}_2(\text{g}) \rightarrow 16\text{CO}_2(\text{g}) + 18\text{H}_2\text{O(l)}$	-5461	48	3.3×10^4
Methanol	$2\text{CH}_3\text{OH(l)} + 3\text{O}_2(\text{g}) \rightarrow 2\text{CO}_2(\text{g}) + 4\text{H}_2\text{O(l)}$	-726	23	1.8×10^4

*At atmospheric pressures and room temperature.

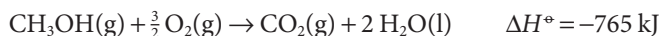
†2,2,4-Trimethylpentane.

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. The combustion of 1 mol $\text{CH}_4(\text{g})$ releases 890 kJ of energy as heat per mole of C atoms:



Now consider the combustion of 1 mol $\text{CH}_3\text{OH}(\text{g})$:



This reaction is also exothermic, but now only 765 kJ of energy is released as heat per mole of C atoms. Much of the observed change in energy output between the reactions can be explained by noting that 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, the presence of partially oxidized C atoms (that is, carbon atoms bonded to oxygen atoms) in a material makes it a less suitable fuel than a similar material containing less oxidized C atoms.

Another factor that determines the enthalpy of combustion is the number of carbon atoms in hydrocarbon compounds. For example, whereas the enthalpy of combustion of methane is -890 kJ mol^{-1} , that of iso-octane (C_8H_{18} , 2,2,4-trimethylpentane (1), a typical component of gasoline) is $-5461 \text{ kJ mol}^{-1}$ (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.

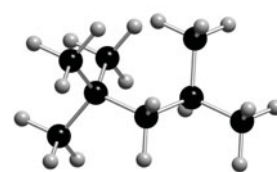
Case study 1.2 Biological fuels

A typical 18- to 20-year-old man requires a daily energy input of about 12 MJ ($1 \text{ MJ} = 10^6 \text{ J}$) or about 2870 Cal; a woman of the same age needs about 9 MJ or about 2150 Cal. 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 more commonly found in our diets have slightly higher specific enthalpies ($17 \text{ kJ g}^{-1} = 4 \text{ Cal g}^{-1}$) 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 fibre, the indigestible cellulose that helps move digestion products through the intestine.

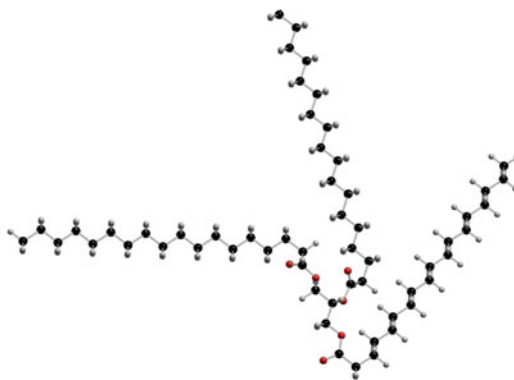
The specific enthalpy of fats, which are long-chain esters such as tristearin (2), is much greater than that of carbohydrates, at around 38 kJ g^{-1} (9 Cal g^{-1}), slightly less than the value for the hydrocarbon oils used as fuel ($48 \text{ kJ g}^{-1} = 11 \text{ Cal g}^{-1}$). The reason for this 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.

A brief comment

The concept of oxidation numbers, familiar from introductory chemistry, clarifies the point made in this paragraph. The formation of CO_2 from CH_4 involves an increase in the oxidation number—that is, an oxidation—of carbon from -4 in CH_4 to $+4$ in CO_2 . By contrast, the carbon atom in CH_3OH has an oxidation number of -2 and is in a higher oxidation state than the carbon in methane.



1 iso-Octane
(2,2,4-trimethylpentane),
 $(\text{CH}_3)_3\text{CCH}_2\text{CH}(\text{CH}_3)_2$

2 Tristearin $C_{57}H_{110}O_6$

As we have seen, 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 specific enthalpy is comparable to that of carbohydrates (about $17 \text{ kJ g}^{-1} = 4 \text{ Cal g}^{-1}$).

A brief illustration

A lunch consisting of a hamburger (about 350 Cal), potato chips (1 serving = 108 Cal), and a milk shake (about 502 Cal) would sum to about 960 Cal.^{11,12} By contrast, a lighter lunch of halibut (about 205 Cal for a $\frac{1}{4}$ -lb serving), a raw carrot (about 42 Cal), a large apple (101 Cal), and a glass of orange juice (about 120 Cal) would net only 468 Cal. The intake from these meals can be compared to the rates at which a 70-kg person can expend energy, depending on the nature of the activity:

Level of activity	Rate of energy expenditure/(Cal min ⁻¹)
Light (walking slowly)	2.5–5.0
Moderate (walking fast)	5.0–7.5
Heavy (running)	7.5–12.0

It follows that it would be necessary to walk slowly for about 3 to 6 hours (or run for 1 to 2 hours) to expend the energy taken in by eating the 960-Cal hamburger meal. Even though reading this textbook also requires energy, it would take about 16 hours for the hamburger meal to be ‘burned off’ by so sedentary an activity.

¹¹ Alarmingly, this single meal corresponds to about 33 per cent or 44 per cent of the daily energy requirements of a young man or woman, respectively.

¹² The data for this *brief illustration* are from C.H. Snyder, *The extraordinary chemistry of ordinary things*, Wiley (2002).

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.

A brief illustration

From the enthalpy of vaporization ($\Delta_{\text{vap}}H^\circ = 44 \text{ kJ mol}^{-1}$ at 298 K), molar mass ($M = 18 \text{ g mol}^{-1}$), and mass density ($\rho = 1.0 \text{ g cm}^{-3}$, corresponding to $1.0 \times 10^3 \text{ g dm}^{-3}$) of water, the energy removed as heat through evaporation per liter (cubic decimeter) of water perspired is

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

When vigorous exercise promotes sweating (through the influence of heat selectors on the hypothalamus), 1 to 2 dm³ of perspired water can be produced per hour, corresponding to a loss of energy of approximately 2.4 to 4.8 MJ h⁻¹.

1.10 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.

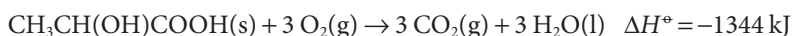
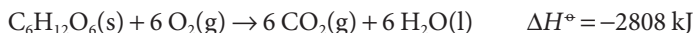
It is often the case that a reaction enthalpy is needed but is not available in tables of data. Now the fact that enthalpy is a state function comes in handy, because it implies that we can construct the required reaction enthalpy from the reaction enthalpies of known reactions. We have already seen 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**, which in its modern form is:

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.

Example 1.4 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 1.9 and *Case study* 1.2). 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 (Atlas C2) by the process of glycolysis (*Case study* 4.3). Given the thermochemical equations for the combustions of glucose and lactic acid:



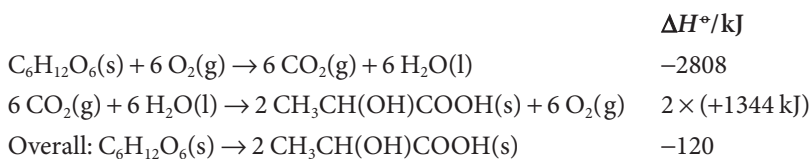
calculate the standard enthalpy for glycolysis:



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:



It follows that the standard enthalpy for the conversion of glucose to lactic acid during glycolysis is -120 kJ mol^{-1} , a mere 4 per cent 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 $C_6H_{12}O_6(s) \rightarrow 2 C_2H_5OH(l) + 2 CO_2(g)$ from the standard enthalpies of combustion of glucose and ethanol (Table 1.5).

Answer: -72 kJ

1.11 Standard enthalpies of formation

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

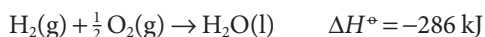
The **standard reaction enthalpy**, $\Delta_r H^\circ$, is the difference between the standard molar enthalpies of the reactants and the products, with each term weighted by the stoichiometric coefficient, ν (nu), in the chemical equation

$$\Delta_r H^\circ = \sum \nu H_m^\circ(\text{products}) - \sum \nu H_m^\circ(\text{reactants}) \quad \text{Definition of the standard reaction enthalpy} \quad (1.22)$$

where $\sum$ (uppercase sigma) denotes a sum. Because the H_m° are molar quantities and the stoichiometric coefficients are pure numbers, the units of $\Delta_r H^\circ$ 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 1.22 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. 1.24). Specifically, the **standard enthalpy of formation**, $\Delta_f H^\circ$, 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 example, the standard enthalpy of formation of liquid water (at 25°C, as always in this text) is obtained from the thermochemical equation



and is $\Delta_f H^\circ(\text{H}_2\text{O}, \text{l}) = -286 \text{ kJ mol}^{-1}$. Note that enthalpies of formation are molar quantities, so to go from ΔH° in a thermochemical equation to $\Delta_f H^\circ$ 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

$$\Delta_r H^\circ = \sum \nu \Delta_f H^\circ(\text{products}) - \sum \nu \Delta_f H^\circ(\text{reactants}) \quad \text{Calculation of standard reaction enthalpies} \quad (1.23)$$

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 1.22 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 *Resource section*. The standard enthalpies of formation of elements in their reference states are zero by definition (because their formation is the null reaction: element $\rightarrow$ element). Note, however, that the standard enthalpy of formation of an element in a state other than its reference state is not zero:



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

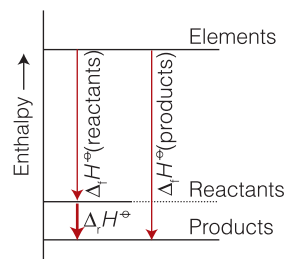


Fig. 1.24 An enthalpy of reaction may be expressed as the difference between the enthalpies of formation of the products and the reactants.

Table 1.7 Reference states of some elements at 298.15 K

Element	Reference state
Arsenic	Gray arsenic
Bromine	Liquid, $\text{Br}_2(\text{l})$
Carbon	Graphite
Hydrogen	Gas, $\text{H}_2(\text{g})$
Iodine	Solid, $\text{I}_2(\text{s})$
Mercury	Liquid
Nitrogen	Gas, $\text{N}_2(\text{g})$
Oxygen	Gas, $\text{O}_2(\text{g})$
Phosphorus	White phosphorus, $\text{P}_4(\text{s})$
Sulfur	Rhombic sulfur, $\text{S}_8(\text{s})$

Example 1.5 Using standard enthalpies of formation

Glucose and fructose (Atlas S3) are simple carbohydrates with the molecular formula $\text{C}_6\text{H}_{12}\text{O}_6$. Sucrose (Atlas S5), or table sugar, is a complex carbohydrate with molecular formula $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ 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.

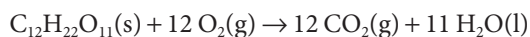
Table 1.8 Standard enthalpies of formation at 298.15 K*

Substance	$\Delta_f H^\circ / (\text{kJ mol}^{-1})$	Substance	$\Delta_f H^\circ / (\text{kJ mol}^{-1})$
<i>Inorganic compounds</i>		<i>Organic compounds</i>	
Ammonia, $\text{NH}_3(\text{g})$	-46.11	Adenine, $\text{C}_5\text{H}_5\text{N}_5(\text{s})$	+96.9
Carbon monoxide, $\text{CO}(\text{g})$	-110.53	Alanine, $\text{CH}_3\text{CH}(\text{NH}_2)\text{COOH}(\text{s})$	-604.0
Carbon dioxide, $\text{CO}_2(\text{g})$	-393.51	Benzene, $\text{C}_6\text{H}_6(\text{l})$	+49.0
Hydrogen sulfide, $\text{H}_2\text{S}(\text{g})$	-20.63	Butanoic acid, $\text{CH}_3(\text{CH}_2)_2\text{COOH}(\text{l})$	-533.8
Nitrogen dioxide, $\text{NO}_2(\text{g})$	+33.18	Ethane, $\text{C}_2\text{H}_6(\text{g})$	-84.68
Nitrogen monoxide, $\text{NO}(\text{g})$	+90.25	Ethanoic acid, $\text{CH}_3\text{COOH}(\text{l})$	-484.3
Sodium chloride, $\text{NaCl}(\text{s})$	-411.15	Ethanol, $\text{C}_2\text{H}_5\text{OH}(\text{l})$	-277.69
Water, $\text{H}_2\text{O}(\text{l})$	-285.83	α -D-Glucose, $\text{C}_6\text{H}_{12}\text{O}_6(\text{s})$	-1268
$\text{H}_2\text{O}(\text{g})$	-241.82	Guanine, $\text{C}_5\text{H}_5\text{N}_5\text{O}(\text{s})$	-183.9
		Glycine, $\text{CH}_2(\text{NH}_2)\text{COOH}(\text{s})$	-528.5
		N-Glycylglycine, $\text{C}_4\text{H}_8\text{N}_2\text{O}_3(\text{s})$	-747.7
		Hexadecanoic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{COOH}(\text{s})$	-891.5
		Leucine, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_2)\text{COOH}(\text{s})$	-637.4
		Methane, $\text{CH}_4(\text{g})$	-74.81
		Methanol, $\text{CH}_3\text{OH}(\text{l})$	-238.86
		Sucrose, $\text{C}_{12}\text{H}_{22}\text{O}_{11}(\text{s})$	-2222
		Thymine, $\text{C}_5\text{H}_6\text{N}_2\text{O}_2(\text{s})$	-462.8
		Urea, $(\text{NH}_2)_2\text{CO}(\text{s})$	-333.1

*A longer list is given in the *Resource section*.

Strategy We write the chemical equation, identify the stoichiometric numbers of the reactants and products, and then use eqn 1.23. Note that the expression has the form ‘products – reactants’. Numerical values of standard enthalpies of formation are given in the *Resource 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



It follows that

$$\begin{aligned} \Delta_r H^\circ &= \{12\Delta_f H^\circ(\text{CO}_2, \text{g}) + 11\Delta_f H^\circ(\text{H}_2\text{O}, \text{l})\} \\ &\quad - \{\Delta_f H^\circ(\text{C}_{12}\text{H}_{22}\text{O}_{11}, \text{s}) + 12\Delta_f H^\circ(\text{O}_2, \text{g})\} \\ &= \{12 \times (-393.51 \text{ kJ mol}^{-1}) + 11 \times (-285.83 \text{ kJ mol}^{-1})\} \\ &\quad - \{(-2222 \text{ kJ mol}^{-1}) + 0\} \\ &= -5644 \text{ kJ mol}^{-1} \end{aligned}$$

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 $-5644 \text{ kJ mol}^{-1}$. The experimental value is $-5645 \text{ kJ mol}^{-1}$.

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 $\text{CO}_2(\text{g})$, $\text{H}_2\text{O}(\text{l})$, and $\text{N}_2(\text{g})$.

Answer: -973 kJ mol^{-1} , in agreement with the experimental value (see the *Resource 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. 1.25). 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).

1.12 Enthalpies of formation and computational chemistry

Table 1.4 is useful for many calculations, but its data cannot be used to estimate the differences between the standard enthalpies of formation of conformational isomers. For example, we would obtain the same enthalpy of formation for the equatorial and axial conformers of methylcyclohexane (3 and 4, respectively) if we were to use mean bond enthalpies. However, it has been observed experimentally that these conformers have different standard enthalpies of formation due to the steric repulsions in the axial conformer, which raise its energy relative to that of the equatorial conformer.

Computational chemistry is becoming the technique of choice for estimating standard enthalpies of formation of molecules with complex three-dimensional structures. Commercial software packages use the principles developed in Chapter 10 to calculate the standard enthalpy of formation of a conformer drawn on a computer screen. The difference between calculated standard enthalpies of formation of two conformers is then an estimate of the conformational energy difference. In the case of methylcyclohexane, the calculated conformational energy difference ranges from 5.9 to 7.9 kJ mol^{-1} , with the equatorial conformer having a lower standard enthalpy of formation than the axial conformer. These estimates compare favorably with the experimental value of 7.5 kJ mol^{-1} . However, good agreement between calculated and experimental values is relatively rare. Computational methods almost always predict correctly which conformer is more stable but do not always predict the correct magnitude of the conformational energy difference.

The computational approach also makes it possible to gain insight into the effect of solvation on the enthalpy of formation without conducting experiments. A calculation performed in the absence of solvent molecules estimates the properties of the molecule of interest in the gas phase. Computational methods are available that allow for the inclusion of several solvent molecules around a solute molecule, thereby taking into account the effect of molecular interactions with the solvent on the enthalpy of formation of the solute. Again, the numerical results are only estimates, and the primary purpose of the calculation is to predict whether interactions with the solvent increase or decrease the enthalpy of formation. As an example, consider the amino acid glycine, which can exist in a neutral (5) or zwitterionic (6) form, in which the amino group is protonated and the

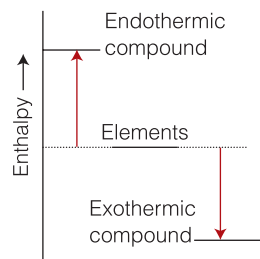
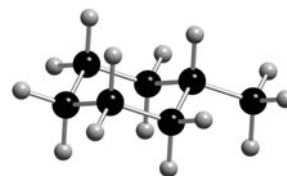
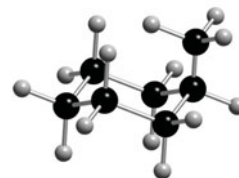


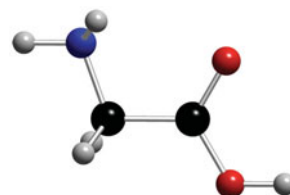
Fig. 1.25 The enthalpy of formation acts as a kind of thermochemical ‘altitude’ of a compound with respect to the ‘sea level’ defined by the elements from which it is made. Endothermic compounds have positive enthalpies of formation; exothermic compounds have negative energies of formation.



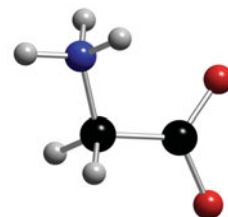
3 *eq*-Methylcyclohexane



4 *ax*-Methylcyclohexane



5 Glycine, $\text{NH}_2\text{CH}_2\text{COOH}$



6 Glycine, $^+\text{NH}_3\text{CH}_2\text{CO}_2^-$

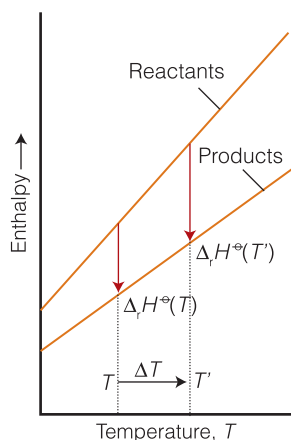


Fig. 1.26 The enthalpy of a substance increases with temperature, therefore if the total enthalpy of the reactants increases by a different amount from that of the products, the reaction enthalpy will change with temperature. The change in reaction enthalpy depends on the relative slopes of the two lines and hence on the heat capacities of the substances.

carboxyl group is deprotonated. It is possible to show computationally that in the gas phase the neutral form has a lower enthalpy of formation than the zwitterionic form. However, in water the opposite is true because of strong interactions between the polar solvent and the charges in the zwitterion.

1.13 The variation of reaction enthalpy with temperature

We need to know how to predict the reaction enthalpy of a biochemical reaction at one temperature from its value at other temperatures.

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 want 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 1.26 illustrates the technique. 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 increase, 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. 1.16). We can therefore 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 *Justification* 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**:

$$\Delta_r H^{\circ}(T') = \Delta_r H^{\circ}(T) + (T' - T)\Delta_r C_p^{\circ} \quad \text{Kirchhoff's law} \quad (1.24)$$

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

$$\Delta_r C_p^{\circ} = \sum \nu C_{p,m}^{\circ}(\text{products}) - \sum \nu C_{p,m}^{\circ}(\text{reactants}) \quad (1.25)$$

Values of standard molar constant-pressure heat capacities for a number of substances are given in the *Resource section*. Because eqn 1.24 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).

Justification 1.4 Kirchhoff's law

To derive Kirchhoff's law, we consider the variation of the enthalpy with temperature. We begin by rewriting eqn 1.14b to calculate the change in the standard molar enthalpy H_m° of each reactant and product as the temperature of the reaction mixture is increased:

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

where $C_{p,m}^{\circ}$ 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° from an initial temperature T and initial enthalpy $H_m^\circ(T)$ to a final temperature T' and enthalpy $H_m^\circ(T')$:

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

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

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

Because this equation applies to each substance in the reaction, we use it and eqn 1.23 to write the following expression for $\Delta_r H^\circ(T')$:

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

where $\Delta_r C_p^\circ$ is given by eqn 1.25. This equation is the exact form of Kirchhoff's law. The special case given by eqn 1.24 can be derived readily from it by making the approximation that $\Delta_r C_p^\circ$ is independent of temperature. Then the integral on the right evaluates to

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

and we obtain eqn 1.24.

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 $\Delta_r C_p^\circ$ over the temperature range of interest, sometimes gives results more accurate than a direct measurement of the reaction enthalpy at the second temperature.

Example 1.6 Using Kirchhoff's law

The enzyme glutamine synthetase mediates the synthesis of the amino acid glutamine (Gln, 8) from the amino acid glutamate (Glu, 7) and ammonium ion:

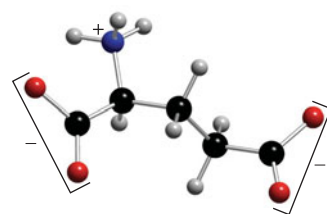
$$\Delta_r H^\circ = +21.8 \text{ kJ mol}^{-1} \text{ at } 25^\circ\text{C}$$

The process is endothermic and requires energy extracted from the oxidation of biological fuels and stored in ATP (*Case study* 1.1). Estimate the value of the reaction enthalpy at 60°C by using data found in this text (see the *Resource section*) and the following additional information: $C_{p,m}^\circ(\text{Gln, aq}) = 187.0 \text{ J K}^{-1} \text{ mol}^{-1}$ and $C_{p,m}^\circ(\text{Glu, aq}) = 177.0 \text{ J K}^{-1} \text{ mol}^{-1}$.

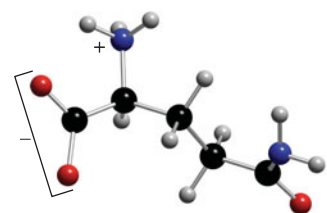
Strategy Calculate the value of $\Delta_r C_p^\circ$ from the available data and eqn 1.25 and use the result in eqn 1.24.

Solution From the *Resource section*, the standard molar constant-pressure heat capacities of $\text{H}_2\text{O}(\text{l})$ and $\text{NH}_4^+(\text{aq})$ are $75.3 \text{ J K}^{-1} \text{ mol}^{-1}$ and $79.9 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively. It follows that

$$\begin{aligned} \Delta_r C_p^\circ &= \{C_{p,m}^\circ(\text{Gln, aq}) + C_{p,m}^\circ(\text{H}_2\text{O, l})\} - \{C_{p,m}^\circ(\text{Glu, aq}) + C_{p,m}^\circ(\text{NH}_4^+, \text{aq})\} \\ &= \{(187.0 \text{ J K}^{-1} \text{ mol}^{-1}) + (75.3 \text{ J K}^{-1} \text{ mol}^{-1})\} - \{(177.0 \text{ J K}^{-1} \text{ mol}^{-1}) \\ &\quad + (79.9 \text{ J K}^{-1} \text{ mol}^{-1})\} \\ &= +5.4 \text{ J K}^{-1} \text{ mol}^{-1} = +5.4 \times 10^{-3} \text{ kJ K}^{-1} \text{ mol}^{-1} \end{aligned}$$



7 Glutamate ion



8 Glutamine

Then, because $T' - T = +35 \text{ K}$, from eqn 1.24 we find

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

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 *Resource section*.

Answer: $-9683 \text{ kJ mol}^{-1}$

The calculation in Example 1.6 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 (*In the laboratory* 1.1). The difference in molar heat capacities between the folded and unfolded states of proteins is usually rather large, in the order of a few kilojoules per mole, so the enthalpy of protein unfolding varies significantly with temperature.

Checklist of key concepts

- | | |
|--|---|
| ☐ 1. A system is classified as open, closed, or isolated. | ☐ 9. The standard state of a substance is the pure substance at 1 bar. |
| ☐ 2. The surroundings remain at constant temperature and either constant volume or constant pressure when processes occur in the system. | ☐ 10. Bomb calorimetry is a useful technique for the study of nutrients. |
| ☐ 3. An exothermic process releases energy as heat, q , to the surroundings; an endothermic process absorbs energy as heat. | ☐ 11. Isobaric calorimetry is a useful technique for the study of fuels. |
| ☐ 4. Metabolism is the collection of chemical reactions that trap, store, and utilize energy in biological cells. | ☐ 12. Differential scanning calorimetry (DSC) is a useful technique for the investigation of phase transitions, especially those observed in biological macromolecules. |
| ☐ 5. Catabolism is the collection of reactions associated with the oxidation of nutrients in the cell. Anabolism is the biosynthesis of small and large molecules. | ☐ 13. The standard enthalpy of transition, $\Delta_{\text{trs}} H^\circ$, is the change in molar enthalpy when a substance in one phase changes into another phase, both phases being in their standard states. |
| ☐ 6. Maximum expansion work is achieved in a reversible change. | ☐ 14. The standard enthalpy of the reverse of a process is the negative of the standard enthalpy of the forward process, $\Delta_{\text{reverse}} H^\circ = -\Delta_{\text{forward}} H^\circ$. |
| ☐ 7. The First Law of thermodynamics states that the internal energy of an isolated system is constant. | ☐ 15. 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 $\Delta_{\text{sub}} H^\circ = \Delta_{\text{fus}} H^\circ + \Delta_{\text{vap}} H^\circ$. |
| ☐ 8. 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 ($\Delta H = q_P$). | |

- 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, $\Delta_f H^\circ$, is the standard reaction enthalpy for the formation of the compound from its elements in their reference states.
- 18. At constant pressure, exothermic compounds are those for which $\Delta_f H^\circ < 0$; endothermic compounds are those for which $\Delta_f H^\circ > 0$.

Checklist of key equations

Property or process	Equation	Comment
Work of expansion	$w = -p_{\text{ex}}\Delta V$	Constant pressure
Heat capacity	$C = q/\Delta T$	General definition
Change in internal energy	$\Delta U = w + q$	
Constant-volume heat capacity	$C_V = dU/dT$	Definition
Enthalpy	$H = U + pV$	Definition
Enthalpy change	$\Delta H = \Delta U + p\Delta V$	Constant pressure
Constant-pressure heat capacity	$C_p = dH/dT$	Definition
Difference between the molar heat capacities	$C_{p,m} - C_{V,m} = R$	Perfect gas
Standard reaction enthalpy	$\Delta_r H^\circ = \sum \nu H_m^\circ(\text{products}) - \sum \nu H_m^\circ(\text{reactants})$ $\Delta_r H^\circ = \sum \nu \Delta_f H^\circ(\text{products}) - \sum \nu \Delta_f H^\circ(\text{reactants})$	Definition Practical implementation
Kirchhoff's law	$\Delta_r H^\circ(T') = \Delta_r H^\circ(T) + \Delta_r C_p^\circ(T' - T)$	Constant-pressure heat capacities are independent of temperature

Discussion questions

- 1.1** Provide molecular interpretations of work, heat, temperature, and heat capacity.
- 1.2** Suggest a reason why most molecules survive for long periods at room temperature.
- 1.3** Describe the general patterns of energy conversion in living organisms.
- 1.4** Explain the difference between the change in internal energy and the change in enthalpy of a chemical or physical process.
- 1.5** Explain the limitations of the following expressions:
(a) $\Delta H = \Delta U + p\Delta V$;
(b) $\Delta_r H^\circ(T') = \Delta_r H^\circ(T) + \Delta_r C_p^\circ \times (T' - T)$.
- 1.6** 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.
- 1.7** In many experimental thermograms, such as that shown in Fig. 1.20, the baseline below T_1 is at a different level from that above T_2 . Explain this observation.
- 1.8** Describe at least two calculational methods by which standard reaction enthalpies can be predicted. Discuss the advantages and disadvantages of each method.
- 1.9** Distinguish between (a) the standard state and the 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.

- 1.10** The unit 1 electronvolt (1 eV) is defined as the energy acquired by an electron as it moves through a potential difference of 1 V. Suppose two states differ in energy by 1.0 eV. What is the ratio of their populations at (a) 300 K and (b) 3000 K?
- 1.11** 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.
- 1.12** Calculate the work of expansion accompanying the complete combustion of 1.0 g of glucose to carbon dioxide and (a) liquid

water, and (b) water vapor at 20°C when the external pressure is 1.0 atm.

1.13 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 cm²; 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.

1.14 A sample of methane of mass 4.50 g occupies 12.7 dm³ at 310 K. Calculate the work done when the gas expands (a) isobarically against a constant external pressure of 30.0 kPa until its volume has increased by 3.3 dm³, and (b) isothermally by 3.3 dm³.

1.15 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, although 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?

1.16 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 dm³ to 30.0 dm³ as it ascends.

1.17 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?

1.18 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 CO₂(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 and (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 $a = 44.22 \text{ J K}^{-1} \text{ mol}^{-1}$, $b = 8.79 \times 10^{-3} \text{ J K}^{-2} \text{ mol}^{-1}$, and $c = -8.62 \times 10^5 \text{ J K mol}^{-1}$. *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 $\Delta_c H^\circ = -2020 \text{ kJ mol}^{-1}$, (b) a dissolution for which $\Delta H^\circ = +4.0 \text{ kJ mol}^{-1}$, (c) vaporization, (d) fusion, and (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 $-393.5 \text{ kJ mol}^{-1}$ and that of diamond is $-395.41 \text{ kJ mol}^{-1}$, calculate the standard enthalpy of the C(s, graphite) $\rightarrow$ 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. (a) 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? (b) 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 In preparation for a study of the metabolism of an organism, a small, sealed calorimeter was assembled. In the initial phase of the experiment, a current of 22.22 mA from an 11.8 V source was passed for 162 s through a heater inside the calorimeter. What is the change in internal energy of the calorimeter?

1.29 Water is heated to boiling under a pressure of 1.0 atm. When an electric current of 0.50 A from a 12 V supply is passed for 300 s through a resistance in thermal contact with it, it is found that 0.798 g of water is vaporized. Calculate the molar internal energy and enthalpy changes at the boiling point (373.15 K).

1.30 In an experiment to determine the energy content of a food, a sample of the food was burned in an oxygen atmosphere and the temperature rose by 2.89°C. When a current of 1.27 A from a 12.5 V source flowed through the same calorimeter for 157 s, the temperature rose by 3.88°C. What energy was released as heat by the combustion?

1.31 A sample of the sugar D-ribose (C₅H₁₀O₅) of mass 0.727 g was placed in a calorimeter and then ignited in the presence of excess oxygen. The temperature rose by 0.910 K. In a separate experiment in the same calorimeter, the combustion of 0.917 g of benzoic acid, for which the internal energy of combustion is $-3226 \text{ kJ mol}^{-1}$, gave a temperature rise of 1.940 K. Calculate the enthalpy of formation of D-ribose.

1.32 Figure 1.27 shows the experimental DSC scan of hen white lysozyme (G. Privalov et al., *Anal. Biochem.* 79, 232 (1995)) converted to kilojoules (from calories). Determine the enthalpy of unfolding of this protein by integration of the curve and the change in heat capacity accompanying the transition.

1.33 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

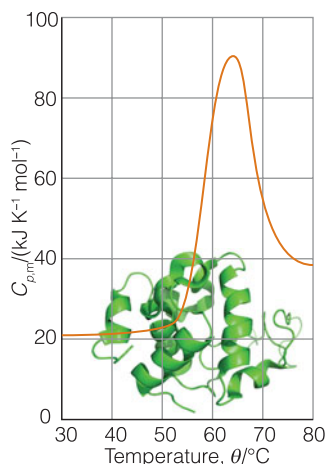


Fig. 1.27 Experimental DSC scan of hen white lysozyme.

break to form relatively strong bonds. Use this information to justify why glucose has a lower specific enthalpy than the lipid decanoic acid ($\text{C}_{10}\text{H}_{20}\text{O}_2$) even though these compounds have similar molar masses.

1.34 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 , $\text{C}_6\text{H}_{12}\text{O}_6(\text{aq}) \rightarrow 2 \text{CH}_3\text{CH}(\text{OH})\text{COOH}(\text{aq})$, and (b) the enthalpy of combustion of glucose. Ignore the contributions of enthalpies of fusion and vaporization.

1.35 Glucose and fructose are simple sugars with the molecular formula $\text{C}_6\text{H}_{12}\text{O}_6$. Sucrose (table sugar) is a complex sugar with molecular formula $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ 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 per cent 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 per cent of the energy released by the metabolism of glucose is available for work?

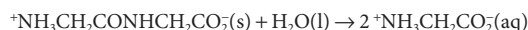
1.36 Camping gas is typically propane. The standard enthalpy of combustion of propane gas is $-2220 \text{ kJ mol}^{-1}$ and the standard enthalpy of vaporization of the liquid is $+15 \text{ kJ mol}^{-1}$. Calculate (a) the standard enthalpy and (b) the standard internal energy of combustion of the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

1.37 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 $2 \text{C}_2\text{H}_6(\text{g}) + 7 \text{O}_2(\text{g}) \rightarrow 4 \text{CO}_2(\text{g}) + 6 \text{H}_2\text{O}(\text{l})$ is -3120 kJ . (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?

1.38 Estimate the difference between the standard enthalpy of formation of $\text{H}_2\text{O}(\text{l})$ as currently defined (at 1 bar) and its value using the former definition (at 1 atm).

1.39 Use information in the *Resource section* to calculate the standard enthalpies of the following reactions:

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

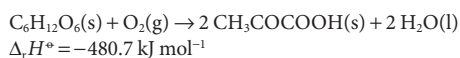


(b) the combustion of solid β -D-fructose

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



1.40 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 :



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

1.41 At 298 K, the enthalpy of denaturation of hen egg white lysozyme is $+217.6 \text{ kJ mol}^{-1}$ and the change in the constant-pressure molar heat capacity resulting from denaturation of the protein is $+6.3 \text{ kJ K}^{-1} \text{ mol}^{-1}$. (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?

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

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

1.44 Using the fact that the enthalpy is a state function, derive a version of Kirchhoff’s law (eqn 1.24) by adding contributions from the following processes: (a) the enthalpy change when the reactants are cooled from a temperature T to 298 K, (b) the reaction enthalpy at 298 K, and (c) the enthalpy change when the temperature of the products is increased from 298 K to T .

1.45 Derive a version of Kirchhoff’s law (eqn 1.24) for the temperature dependence of the internal energy of reaction.

1.46 The formulation of Kirchhoff’s law given in eqn 1.24 is valid when the difference in heat capacities is independent of temperature over the temperature range of interest. Suppose instead that $\Delta_r C_p^\circ = a + bT + c/T^2$. 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 $\Delta_r C_p^\circ dT$. Integrate this expression between the two temperatures of interest.

Projects

1.47 The Boltzmann distribution can be used to calculate the average energy associated with each mode of motion of a molecule. However, for certain modes of motion, such as translation, there is a short cut, called the *equipartition theorem*:

In a sample at a temperature T , all quadratic contributions to the total energy have the same mean value, namely $\frac{1}{2}kT$.

A 'quadratic contribution' means a contribution that depends on the square of the position or the velocity (or momentum).

(a) The kinetic energy of a particle of mass m free to undergo translation in three dimensions is $E_k = \frac{1}{2}mv_x^2 + \frac{1}{2}mv_y^2 + \frac{1}{2}mv_z^2$. What is the average kinetic energy of a particle free to move in three dimensions?

(b) Use the equipartition theorem to show that for a monatomic perfect gas:

$$U_m(T) = U_m(0) + \frac{3}{2}RT \quad C_{V,m} = \frac{3}{2}R$$

where $U_m(0)$ is the molar internal energy at $T = 0$, when all translational motion has ceased.

(c) When the gas consists of molecules, we need to take into account the effect of rotation and vibration. A linear molecule, such as N_2 and CO_2 , can rotate around two axes perpendicular to the line of the atoms, so it has two rotational modes of motion, each contributing a term $\frac{1}{2}kT$ to the internal energy. Show that

$$U_m(T) = U_m(0) + \frac{5}{2}RT \quad C_{V,m} = \frac{5}{2}R$$

(linear molecule, translation and rotation only)

(d) A non-linear molecule, such as CH_4 or H_2O , can rotate around three axes and, again, each mode of motion contributes a term $\frac{1}{2}kT$ to the internal energy. Show that

$$U_m(T) = U_m(0) + 3RT \quad C_{V,m} = 3R$$

(non-linear molecule, translation and rotation only)

(e) Molecules do not vibrate significantly at room temperature and, as a first approximation, the contribution of molecular vibrations to the internal energy is negligible except for very large molecules such as polymers and biological macromolecules. Use the information in this problem to justify the following statement: *the internal energy of a perfect gas does not change when the gas undergoes isothermal expansion*.

(f) Use the equipartition theorem to calculate the contribution of molecular motion to the total energy of a sample of 10.0 g of (i) argon, (ii) carbon dioxide, and (iii) methane at 20°C. *Hint*: For (ii) and (iii), take into account translation and rotation but not vibration.

(g) We saw in part (e) that the internal energy of a perfect gas does not change when the gas undergoes isothermal expansion. What is the change in enthalpy?

1.48 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 make an angle of only 0° or 180° with an adjacent unit. In this case, the restoring force of a chain extended by $x = nl$ is given by

$$F = \frac{kT}{2l} \ln \left(\frac{1+v}{1-v} \right) \quad v = x/Nl$$

where $k = 1.381 \times 10^{-23} \text{ J K}^{-1}$ 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 v , noting that v 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, $dx = ldn = Nldv$, write an expression for the work of extending a DNA molecule. (v) Calculate the work of extending a DNA molecule from $v = 0$ to $v = 1.0$. *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 $v \ll 1$, the restoring force is given by

$$F \approx \frac{vkT}{l} = \frac{nkT}{Nl}$$

Hint: See *Mathematical toolkit 3.2* 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.

The Second Law

2

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 this chapter and the rest of the text 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 as a basis for 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 into 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. We shall also

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see that the material discussed in this chapter is relevant not only to the transformations of energy but also to the structures of proteins.

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 universe 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, the reactions that sustain them, and the structures of biological macromolecules.

2.1 The direction of spontaneous change

To understand the 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 disorderly dispersal of matter.

A similar explanation accounts for spontaneous cooling, but now we need to consider the dispersal of energy rather than of matter. In a block of hot metal in which there is a temperature gradient, the atoms in the hot region are oscillating vigorously, and the hotter the region, the more vigorous their motion. The cooler region also consists of oscillating atoms, but their motion is less vigorous. The vigorously oscillating atoms jostle their neighbors in the cooler region, and the energy of the atoms in the block is handed on to the atoms in the cooler region (Fig. 2.2). The process continues until the vigor with which the atoms in the system are oscillating is uniform. The opposite flow of energy is very unlikely. It is highly improbable that there will be a net accumulation of energy in one

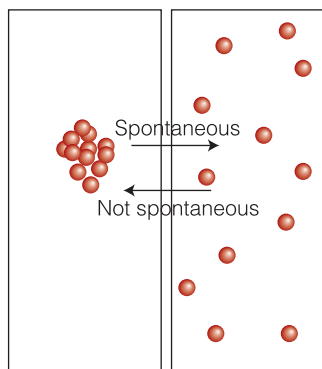


Fig. 2.1 One fundamental type of spontaneous process is the disorderly dispersal of matter. This tendency accounts for the spontaneous tendency of a gas to spread into and fill the container it occupies. It is extremely unlikely that all the particles will collect into one small region of the container. (In practice, the number of particles is of the order of 10^{23} .)

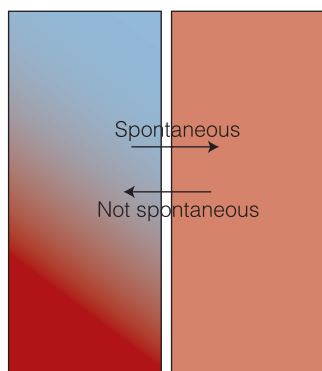


Fig. 2.2 Another fundamental type of spontaneous process is the disorderly dispersal of energy (represented by the color: red is high temperature, blue is low temperature).

region as a result of the jostling of molecules within the block. In this case, the natural direction of change corresponds to the disorderly dispersal of energy. Similar remarks apply to the cooling of a hot block to the temperature of its surroundings.

The tendency of energy to disperse also explains the fact that, despite countless attempts, it has proved impossible to construct an engine like that shown 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 for such engines to operate, 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. Before long, we shall see that the heat engine, although it looks like an engineering concept, when appropriately interpreted is directly applicable to biochemical processes even though there is no actual 'engine' present.

In summary, we have identified two basic types of spontaneous physical process:

- 1) Matter tends to disperse in disorder.
- 2) Energy tends to disperse in disorder.

We now 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 chaotic dispersal 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, is driven by the tendency of energy and matter to disperse in disorder.

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 disorderly 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 in disorder, 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 Second Law

The 'isolated system' may consist of a system in which we have a special interest (a beaker containing reagents, a biological cell, or even an organelle within a cell) and that system's surroundings: the two components jointly form a little 'universe' in the thermodynamic sense.

(a) The definition of entropy

To make progress and turn the Second Law into a quantitatively useful statement, we shall use the following definition of a *change* in entropy:

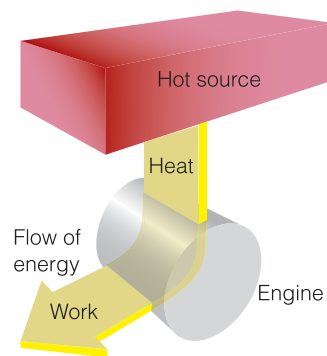


Fig. 2.3 The Second Law denies the possibility of the process illustrated here, in which heat is changed completely into work, there being no other change. The process is not in conflict with the First Law because the energy is conserved.

$$\Delta S = \frac{q_{\text{rev}}}{T} \quad \text{Definition of entropy change} \quad (2.1)$$

That is, the change in entropy of a system 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,¹ 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’

We met the concept of reversibility in Section 1.3, where we saw that it refers to the ability of an infinitesimal change in a control 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.

Why heat (not work) appears in the numerator

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 disorder of energy and matter—is proportional to the energy transfer that takes place by making use of random motion rather than orderly motion.

Why temperature appears in the denominator

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.

A brief illustration

An organism inhabits a pond. In the course of its life, the organism transfers 100 kJ of heat to the pond water at 0°C (273 K). The resulting change in entropy of the water due to this transfer is

$$\Delta S = \frac{q_{\text{rev}}}{T} = \frac{100 \times 10^3 \text{ J}}{273 \text{ K}} = +366 \text{ J K}^{-1}$$

The pond is large enough to ensure that the temperature of the water does not change as heat is transferred. The same transfer at 100°C (373 K) results in

¹ For a thermodynamic justification, see our *Physical chemistry* (2010).

$$\Delta S = \frac{100 \times 10^3 \text{ J}}{373 \text{ K}} = +268 \text{ J K}^{-1}$$

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 ($\text{J K}^{-1} \text{ mol}^{-1}$).

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.² 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.

(b) The entropy change accompanying 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. Similarly, we should expect the entropy of a sample to increase as the temperature is raised because the thermal motion is greater at the higher temperature. As we show in the following *Justification*, provided the heat capacity is constant over the range of temperatures of interest,

$$\Delta S = C \ln \frac{T_f}{T_i} \quad \text{Change in entropy on heating} \quad (2.2)$$

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 .

Justification 2.1 The change in 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 as heat, 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

$$dS = \frac{dq_{\text{rev}}}{T}$$

To calculate dq , we recall from Section 1.4 that the heat capacity $C = q/\Delta T$, where ΔT is macroscopic change in temperature. For an infinitesimal change dT brought about by an infinitesimal transfer of heat dq we write $C = dq/dT$ and therefore $dq = CdT$, so we can write $dq_{\text{rev}} = CdT$ and therefore

² Again see our *Physical chemistry* (2010) for a proof.

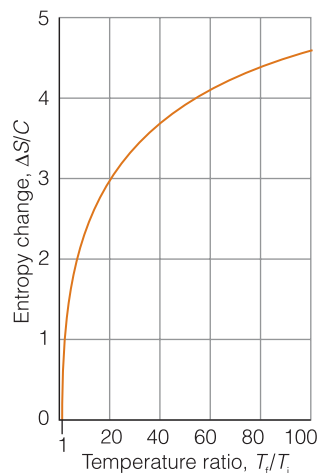


Fig. 2.4 The entropy of a sample with a heat capacity that can be regarded as independent of temperature in the range of interest increases as $\ln T$ as the temperature is increased. The increase is proportional to the heat capacity of the sample.

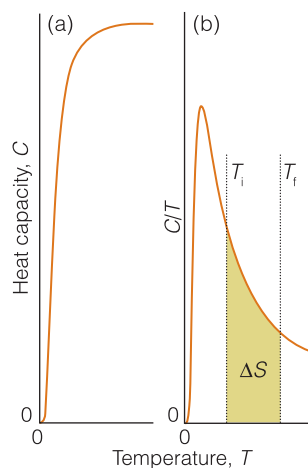


Fig. 2.5 The experimental determination of the change in entropy of a sample that has a heat capacity that varies with temperature, as shown in (a), involves measuring the heat capacity over the range of temperatures of interest, then plotting C/T against T and determining the area under the curve (the tinted area shown), as shown in (b). The heat capacity of all solids decreases toward zero as the temperature is reduced.

$$\Delta S = \frac{CdT}{T}$$

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:

$$\Delta S = \int_{T_i}^{T_f} \frac{CdT}{T}$$

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:

$$\Delta S = \int_{T_i}^{T_f} \frac{CdT}{T} = C \int_{T_i}^{T_f} \frac{dT}{T} = C \ln \frac{T_f}{T_i}$$

Equation 2.2 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' (in terms of the analogy mentioned earlier) must be more powerful than 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. ($C_{V,m} = 26.92 \text{ J K}^{-1} \text{ mol}^{-1}$.)

Answer: $+0.615 \text{ J K}^{-1} \text{ mol}^{-1}$

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 *Justification 2.1* we found, before making the assumption that the heat capacity is constant, that

$$\Delta S = \int_{T_i}^{T_f} \frac{CdT}{T} \quad (2.3)$$

All we need to recognize is the standard result from calculus, 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

$\Delta S = \text{area under the graph of } C/T \text{ plotted against } T, \text{ between } T_i \text{ and } T_f$

Experimental basis of determining an entropy change

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. Then we divide each measurement 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 . In practice, mathematical software is used to fit a curve to the variation of C with T and the integration carried out automatically.

A brief illustration

The molar heat capacity of chloroform between 20°C and 37°C was found to fit the following expression:

$$C_{p,m}(T) = 91.74 \text{ J K}^{-1} \text{ mol}^{-1} + 0.075 T \text{ J K}^{-2} \text{ mol}^{-1}$$

The change in entropy over this range is therefore

$$\begin{aligned} \Delta S_m &= S_m(310 \text{ K}) - S_m(293 \text{ K}) \\ &= \int_{293 \text{ K}}^{310 \text{ K}} \left(\frac{91.74 \text{ J K}^{-1} \text{ mol}^{-1}}{T} + 0.075 \text{ J K}^{-2} \text{ mol}^{-1} \right) dT \\ &= (91.74 \text{ J K}^{-1} \text{ mol}^{-1}) \ln \frac{310 \text{ K}}{293 \text{ K}} + (0.075 \text{ J K}^{-2} \text{ mol}^{-1})(310 \text{ K} - 293 \text{ K}) \\ &= +6.45 \text{ J K}^{-1} \text{ mol}^{-1} \end{aligned}$$

(c) The entropy change accompanying a phase transition

We can suspect that the entropy of a substance increases when it melts and when it vaporizes because its molecules become distributed in a more disorderly way 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 *In the laboratory* 1.1, to be accompanied by an increase of entropy because the secondary structure of the polypeptide chain is lost.

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**, $\Delta_{\text{fus}}S$, the change of entropy per mole of substance, at the melting temperature, T_{fus} , is

$$\text{At the melting temperature: } \Delta_{\text{fus}}S = \frac{\Delta_{\text{fus}}H(T_{\text{fus}})}{T_{\text{fus}}} \quad \text{Entropy of fusion} \quad (2.4)$$

Notice how we must use the enthalpy of fusion at the melting temperature and that this expression applies only at the melting temperature. We get the standard entropy of fusion, $\Delta_{\text{fus}}S^\circ$, 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).

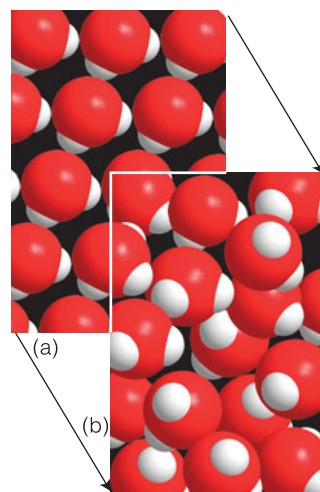


Fig. 2.6 (a) When a solid, here a highly stylized version of ice, melts, the molecules form a liquid. (b) As a result, the entropy of the sample increases.

A brief illustration

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 as determined using differential scanning calorimetry is +509 kJ mol⁻¹. It follows that

$$\Delta_{\text{trs}}S^\circ = \frac{\Delta_{\text{trs}}H^\circ(T_{\text{trs}})}{T_{\text{trs}}} = \frac{+509 \text{ kJ mol}^{-1}}{(273.15 + 75.5) \text{ K}} = +1.46 \text{ kJ K}^{-1} \text{ mol}^{-1}$$

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 J K⁻¹ mol⁻¹

Table 2.1 Entropies of vaporization at 1 atm and the normal boiling point

Substance	$\Delta_{\text{vap}}S/$ (J K ⁻¹ mol ⁻¹)
Ammonia, NH ₃	97.4
Benzene, C ₆ H ₆	87.2
Bromine, Br ₂	88.6
Carbon tetrachloride, CCl ₄	85.9
Cyclohexane, C ₆ H ₁₂	85.1
Ethanol, CH ₃ CH ₂ OH	109.7
Hydrogen sulfide, H ₂ S	87.9
Water, H ₂ O	109.1

The entropy of other types of transition may be discussed similarly. Thus, the entropy of vaporization, $\Delta_{\text{vap}}S$, at the boiling temperature, T_b , of a liquid is related to its enthalpy of vaporization at that temperature by

$$\text{At the boiling temperature: } \Delta_{\text{vap}}S = \frac{\Delta_{\text{vap}}H(T_b)}{T_b} \quad \text{Enthalpy of vaporization} \quad (2.5)$$

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, $\Delta_{\text{vap}}S$, we use data corresponding to 1 bar. Because vaporization is endothermic for all substances (with one exception of little relevance to biology: helium), 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 *brief illustration*.

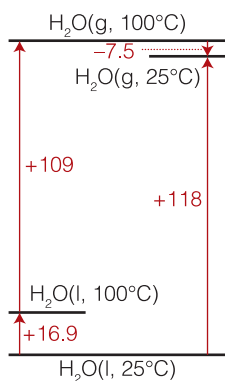


Fig. 2.7 The cycle of steps used to calculate the entropy of transition at a temperature other than the transition temperature.

A brief illustration

Suppose we want to calculate the entropy of vaporization of water at 25°C. We need to perform three calculations (Fig. 2.7). 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):

$$\begin{aligned} \Delta S_1 &= C_{p,m}(\text{H}_2\text{O, liquid}) \ln \frac{T_f}{T_i} = (75.29 \text{ J K}^{-1} \text{ mol}^{-1}) \times \ln \frac{373 \text{ K}}{298 \text{ K}} \\ &= +16.9 \text{ J K}^{-1} \text{ mol}^{-1} \end{aligned}$$

Then, we use eqn 2.5 and data from Table 1.2 to calculate the entropy of transition at 100°C:

$$\Delta S_2 = \frac{\Delta_{\text{vap}}H(T_b)}{T_b} = \frac{4.07 \times 10^4 \text{ J mol}^{-1}}{373 \text{ K}} = +109 \text{ J K}^{-1} \text{ mol}^{-1}$$

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):

$$\begin{aligned}\Delta S_3 &= C_{p,m}(\text{H}_2\text{O, vapor}) \ln \frac{T_f}{T_i} = (33.58 \text{ J K}^{-1} \text{ mol}^{-1}) \times \ln \frac{298 \text{ K}}{373 \text{ K}} \\ &= -7.5 \text{ J K}^{-1} \text{ mol}^{-1}\end{aligned}$$

The sum of the three entropy changes is the entropy of transition at 25°C:

$$\Delta_{\text{vap}}S(298 \text{ K}) = \Delta S_1 + \Delta S_2 + \Delta S_3 = +118 \text{ J K}^{-1} \text{ mol}^{-1}$$

(d) Entropy changes in the 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 : $\Delta S_{\text{sur}} = q_{\text{sur,rev}}/T$. However, surroundings are so extensive that the spread of heat through them is effectively reversible, so the ‘rev’ subscript can be dropped and we can write $\Delta S_{\text{sur}} = q_{\text{sur}}/T$. Moreover, the heat entering the surroundings is lost from the system, so $q_{\text{sur}} = -q$. (For instance, if $q = +100 \text{ J}$, an influx of 100 J into the system, then $q_{\text{sur}} = -100 \text{ J}$, indicating that the surroundings have lost that 100 J.) Therefore, at this stage we can write $\Delta S_{\text{sur}} = -q/T$. Finally, if the change in the system is taking place at constant pressure, we can identify q with the change of enthalpy ΔH , and so obtain

$$\text{for a process at constant pressure: } \Delta S_{\text{sur}} = -\frac{\Delta H}{T} \quad \text{Entropy change of the surroundings} \quad (2.6)$$

This enormously important expression will lie at the heart of our discussion of bioenergetics and the structural consequences of the Second Law. 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.

A brief illustration

The enthalpy of vaporization of water at 20°C is 44 kJ mol^{-1} . When 10 cm^3 of water (corresponding to 10 g or 0.55 mol H_2O) in an open vessel evaporates at that temperature, the change in entropy of the surroundings is

$$\Delta S_{\text{sur}} = -\frac{(0.55 \text{ mol}) \times (44 \text{ kJ mol}^{-1})}{293 \text{ K}} = -83 \text{ J K}^{-1}$$

The entropy of the surroundings decreases because heat flows out of them into the water.

2.3 Absolute entropies and the Third Law of thermodynamics

To calculate the entropy changes associated with biological processes, we need to see how to compile tables that list the 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

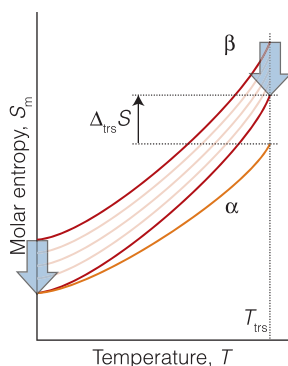


Fig. 2.8 The molar entropies of monoclinic and rhombic sulfur vary with temperature as shown here. Initially we do not know their values at $T = 0$. When we slide the two curves together by matching their separation to the measured entropy of transition at the transition temperature, we find that the entropies of the two forms are the same at $T = 0$.

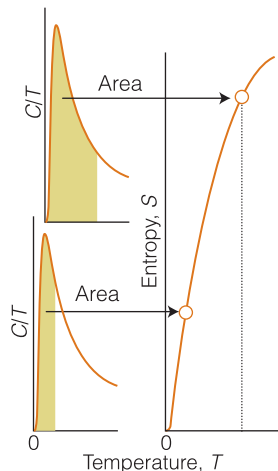


Fig. 2.9 The absolute entropy (or Third-Law entropy) of a substance is calculated by extending the measurement of heat capacities down to $T = 0$ (or as close to that value as possible) and then determining the area of the graph of C/T against T up to the temperature of interest. The area is equal to the absolute entropy at the temperature T .

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 based on observations like the following. Sulfur undergoes a phase transition from its rhombic form to its monoclinic polymorph at 96°C (369 K) and the enthalpy of transition is $+402 \text{ J mol}^{-1}$. The entropy of transition is therefore $+1.09 \text{ J K}^{-1} \text{ mol}^{-1}$ 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. 2.8). 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 $T = 0$.

The Third Law

For convenience (and in accordance with our understanding of entropy as a measure of disorder), 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.

The **Third-Law entropy**, which is commonly called simply ‘the entropy’, at any temperature, $S(T)$, is based on setting $S(0) = 0$. 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° , 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 taking a moment to look at the values in Table 2.2 to see that they are consistent with our understanding. All standard molar entropies are positive because raising the temperature of a sample above $T = 0$ invariably increases its entropy above the value $S(0) = 0$ because there is more thermal disorder. Another feature that we can understand in terms of disorder is illustrated by the standard molar entropy of diamond ($2.4 \text{ J K}^{-1} \text{ mol}^{-1}$), which is lower than that of graphite ($5.7 \text{ J K}^{-1} \text{ mol}^{-1}$). 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 $189 \text{ J K}^{-1} \text{ mol}^{-1}$, and the increase in values corresponds to the increasing molecular disorder on going from a solid to a liquid and then to a gas.

In the laboratory 2.1

The measurement of entropies

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. 2.9). If there are any phase transitions (for example, melting) in that range, then the entropy of each transition at the transition temperature is calculated like that in eqn 2.4 and

Table 2.2 Standard molar entropies of some substances at 298.15 K*

Substance	$S_m^\circ / (\text{J K}^{-1} \text{mol}^{-1})$
<i>Gases</i>	
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
<i>Liquids</i>	
Acetic acid, CH_3COOH	159.8
Ethanol, $\text{CH}_3\text{CH}_2\text{OH}$	160.7
Water, H_2O	69.9
<i>Solids</i>	
Calcium carbonate, CaCO_3	92.9
Diamond, C	2.4
Glycine, $\text{CH}_2(\text{NH}_2)\text{COOH}$	103.5
Graphite, C	5.7
Sodium chloride, NaCl	72.1
Sucrose, $\text{C}_{12}\text{H}_{22}\text{O}_{11}$	360.2
Urea, $\text{CO}(\text{NH}_2)_2$	104.60

*See the Resource section for more values.

its contribution added to the contributions from each of the phases, as shown in Fig. 2.10. The entropies of gas-phase species may also be calculated from spectroscopic data about bond lengths and angles using the techniques of statistical thermodynamics, but few biologically interesting substances can be treated in this way.

To implement the calorimetric procedure the heat capacity of the substance is measured (for instance, by using a differential scanning calorimeter (DSC)) down to as low a temperature as feasible and then using eqn 2.3. In practice, a polynomial in T is fitted to the experimental data and then C_p/T is integrated from the lowest temperature attainable up to the temperature of interest. Thus, if the function $C_p(T) = a + bT + cT^2 + \dots$ is fitted (for instance, by using a least-squares procedure in a software package) to the data between T_{lowest} and T_{trs} , where T_{trs} is the temperature of a phase transition, the entropy just before the phase transition is

$$S(T_{\text{trs}}) = S(T_{\text{lowest}}) + \int_{T_{\text{lowest}}}^{T_{\text{trs}}} \frac{C_p(T)}{T} dT$$

Then another polynomial is fitted to the heat capacities for the new phase up to the temperature of interest (or the next phase transition and a similar integral is evaluated). At each phase transition the enthalpy of transition is measured (once again, typically with a DSC), the entropy of transition is calculated as $\Delta_{\text{trs}}H(T_{\text{trs}})/T_{\text{trs}}$ by analogy with eqn 2.4, and this value is added to the value calculated by integrating the heat capacity.

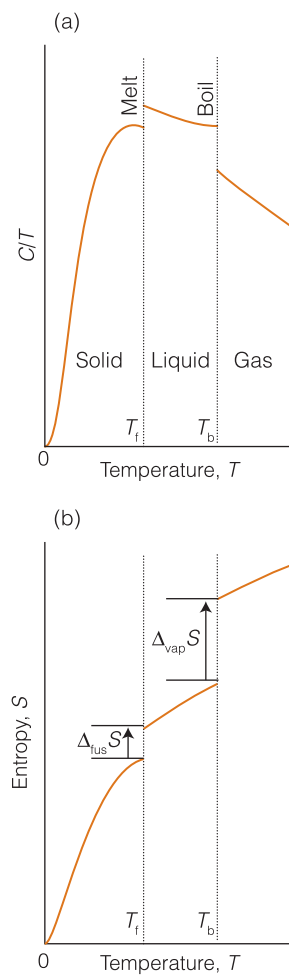


Fig. 2.10 The determination of entropy from heat capacity data. (a) Variation of C/T with the temperature of the sample. (b) The entropy, which is equal to the area beneath the upper curve up to the temperature of interest plus the entropy of each phase transition between $T = 0$ and the temperature of interest.

There remains the experimental problem of determining $S(T_{\text{lowest}})$, the entropy at the lowest attainable temperature. If very low temperatures (within a few kelvins of $T = 0$) can be reached and reliable measurements of C_p made, it is possible to use an extrapolation based on the observation that many non-metallic substances have a heat capacity that obeys the **Debye T^3 -law**:

$$\text{At temperatures close to } T = 0, C_p = aT^3 \quad \text{Debye } T^3\text{-law} \quad (2.7a)$$

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, the entropy at low temperatures is simply

$$\text{At temperatures close to } T = 0, S(T) = \frac{1}{3}C_p(T) \quad \text{Entropy at low temperatures} \quad (2.7b)$$

(See Exercise 2.21.) That is, the molar entropy at the low temperature T (which can be identified as T_{lowest}) is equal to one-third of the constant-pressure molar heat capacity at that temperature. Other extrapolation techniques have been developed that do not require reaching such low temperatures as those required for the Debye approximation to be reliable and are described in textbooks of laboratory procedures.

2.4 The molecular interpretation of the Second and Third Laws

To gain insight into the thermodynamic properties of biological assemblies and a deeper understanding of what drives a spontaneous change, we need to develop a molecular view of entropy.

The entry point into the molecular interpretation of the Second Law of thermodynamics is Boltzmann's insight into the manner in which molecules are distributed over their available energy levels, which we explored in *Fundamentals* F.3 and Section 1.2.

(a) The Boltzmann formula

Boltzmann made the link between the distribution of molecules over energy levels and the entropy. He proposed that the entropy of a system is given by

$$S = k \ln W \quad \text{Boltzmann formula for the entropy} \quad (2.8)$$

where k is Boltzmann's constant and W is the number of **microstates**, the ways in which the molecules of a system can be arranged for the same total energy. At $T = 0$, all the molecules must be in the lowest energy state, and there is only one way of achieving that arrangement, so $W = 1$ and $S(0) = 0$ (because $\ln 1 = 0$), in accord with the Third Law. As the temperature is raised, more arrangements correspond to the same energy, so W increases and S rises.

Suppose we raise the temperature just enough for two molecules of a 100-molecule system to be able to leave their lowest energy state and occupy the first excited state. Two possible microstates are

$$([3, 4, \dots, 100]_{\text{in state 0}} [1, 2]_{\text{in state 1}}) \quad \text{and} \\ ([1, 3, 4 \dots 42, 44, \dots 100]_{\text{in state 0}} [2, 43]_{\text{in state 1}})$$

where molecules 1 and 2 are excited in the first microstate and molecules 2 and 43 are excited in the second. Each microstate lasts only for an instant and corresponds to a particular distribution of molecules over the available energy levels. These two microstates and a large number of others all correspond to the same **configuration**, in this case the configuration {98,2,0,...} we introduced in Section 1.2(c). In this case, there are $W = 4950$ possible microstates (that corresponds to the number of ways of choosing two molecules from 100).

As we saw in Section 1.2(c), there is a dominating configuration of the system—the one corresponding to the greatest number of microstates for a given total energy—and the properties of the system are those of this most probable configuration. That configuration is the one with populations given by the Boltzmann distribution. To use Boltzmann's formula for the entropy, we set the W that occurs in it equal to the W of this dominating configuration.

A brief illustration

Suppose that a protein molecule of 100 amino acid residues denatured into a random coil can adopt 1.0×10^{31} different conformations of the same energy. We set $W = 1.0 \times 10^{31}$ and calculate the entropy as

$$S = (1.38 \times 10^{-23} \text{ J K}^{-1}) \times \ln(1.0 \times 10^{31}) = 9.9 \times 10^{-22} \text{ J K}^{-1}$$

The corresponding molar entropy of the protein is $600 \text{ J K}^{-1} \text{ mol}^{-1}$ (to 2 significant figures; that is, $6.0 \times 10^2 \text{ J K}^{-1} \text{ mol}^{-1}$).

(b) The relation between thermodynamic and statistical entropy

The concept of the number of microstates makes quantitative the ill-defined qualitative concepts of 'disorder' and 'the dispersal of matter and energy' that we have used to introduce the concept of entropy: a more 'disorderly' distribution of energy and matter corresponds to a greater number of microstates associated with the same total energy. For instance, when a perfect gas expands, the available translational energy levels get closer together (Fig. 2.11), so it is possible to distribute the molecules over them in more ways than when the volume of the container is small and the energy levels are further apart. Therefore, as the container expands, W and therefore S increase, just as for thermodynamic entropy.

The Boltzmann approach also illuminates the thermodynamic definition itself (eqn 2.1) and in particular the role of the temperature. Molecules in a system at high temperature can occupy a large number of the available energy levels, so a small additional transfer of energy as heat will lead to a relatively small change in the number of accessible energy levels. Consequently, the number of microstates does not increase appreciably and neither does the entropy of the system. In contrast, the molecules in a system at low temperature have access to far fewer energy levels (at $T = 0$, only the lowest level is accessible), and the transfer of the same quantity of energy by heating will increase the number of accessible energy levels and the number of microstates significantly. Hence, the change in entropy on heating will be greater when the energy is transferred to a cold body than when it is transferred to a hot body. This argument suggests that the change in entropy should be inversely proportional to the temperature at which the transfer takes place, as in eqn 2.1.

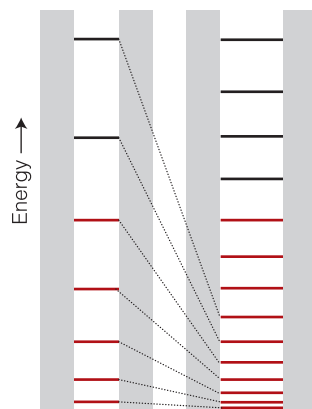


Fig. 2.11 When the size of a container is increased (shown here in two dimensions), the energy levels available to the molecules inside it move closer together so more are accessible at a given temperature (as indicated by the levels colored red).

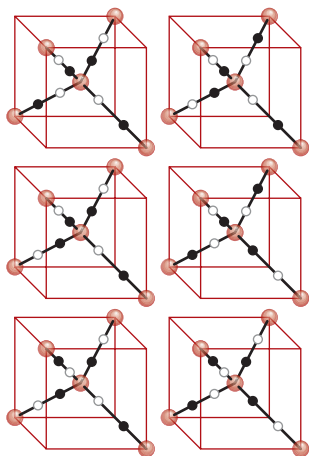


Fig. 2.12 The six possible arrangements of H atoms around a central O atom in ice. Occupied locations are indicated by black dots and unoccupied locations by a grey outline.

(c) The residual entropy

In most cases, $W = 1$ at $T = 0$ because there is only one way of putting all the molecules into the same, lowest state. Therefore, as we have seen, $S = 0$ at $T = 0$, in accord with the Third Law of thermodynamics. In certain cases, however, W may differ from 1 at $T = 0$. This is the case if disorder survives down to absolute zero because there is no energy advantage in adopting a particular orientation. For instance, there may be no energy difference between the arrangements $\dots AB AB AB \dots$ and $\dots BA AB BA \dots$, so $W > 1$ even at $T = 0$. If $S > 0$ at $T = 0$ we say that the substance has a **residual entropy**. Ice has a residual entropy of $3.4 \text{ J K}^{-1} \text{ mol}^{-1}$. It stems from the disorder in the hydrogen bonds between neighboring water molecules: a given O atom has two short O–H bonds and two long O $\cdots$ H bonds to its neighbors, but there is a degree of randomness in which two bonds are short and which two are long.

A brief illustration

Consider a sample of ice of N H_2O molecules. Each of the $2N$ H atoms can be either close to or relatively far from an O atom, resulting in 2^{2N} possible arrangements. However, of the $2^4 = 16$ possible arrangements around a single O atom, only 6 have two short and two long bonds (Fig. 2.12) and hence are acceptable. Therefore $W = 2^{2N}(\frac{6}{16})^N = (\frac{3}{2})^N$ and the residual entropy is

$$S(0) = k \ln W = k \ln \left(\frac{3}{2}\right)^N = Nk \ln \frac{3}{2}$$

The molar residual entropy (replace N by N_A and use $N_A k = R$) is therefore

$$S_m(0) = R \ln \frac{3}{2} = 3.4 \text{ J K}^{-1} \text{ mol}^{-1}$$

2.5 Entropy changes accompanying chemical reactions

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; 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.

Once again, we can sometimes 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 or the equivalent but controlled oxidations characteristic of organisms, 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 micro-organisms, 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.

(a) Standard reaction entropies

The difference in molar entropy between the products and the reactants in their standard states is called the **standard reaction entropy**, $\Delta_r S^\circ$. 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:

$$\Delta_r S^\circ = \sum \nu S_m^\circ(\text{products}) - \sum \nu S_m^\circ(\text{reactants}) \quad \text{The standard entropy of reaction} \quad (2.9)$$

where the ν are the stoichiometric coefficients in the chemical equation.

A brief illustration

The enzyme carbonic anhydrase catalyses the hydration of CO_2 gas in red blood cells: $\text{CO}_2(\text{g}) + \text{H}_2\text{O}(\text{l}) \rightarrow \text{H}_2\text{CO}_3(\text{aq})$. 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 *Resource section* to write

$$\begin{aligned}\Delta_r S^\circ &= S_m^\circ(\text{H}_2\text{CO}_3, \text{aq}) - \{S_m^\circ(\text{CO}_2, \text{g}) + S_m^\circ(\text{H}_2\text{O}, \text{l})\} \\ &= (187.4 \text{ J K}^{-1} \text{ mol}^{-1}) - \{(213.74 \text{ J K}^{-1} \text{ mol}^{-1}) + (69.91 \text{ J K}^{-1} \text{ mol}^{-1})\} \\ &= -96.3 \text{ J K}^{-1} \text{ mol}^{-1}\end{aligned}$$

A note on good practice

Do not make the mistake of setting the standard molar entropies of elements equal to zero: they have non-zero values (provided $T > 0$), as we have already discussed.

Self-test 2.3

(a) Predict the sign of the entropy change associated with the complete oxidation of solid sucrose, $\text{C}_{12}\text{H}_{22}\text{O}_{11}(\text{s})$, by O_2 gas to CO_2 gas and liquid H_2O . (b) Calculate the standard reaction entropy at 25°C .

Answer: (a) Positive; (b) $+512 \text{ J K}^{-1} \text{ mol}^{-1}$

(b) The spontaneity of chemical reactions

A process may be spontaneous even though the entropy change of the system itself is negative. Consider the binding of oxidized nicotinamide adenine dinucleotide (NAD^+ ; Atlas N4), an important electron carrier in metabolism (*Case studies* 1.1 and 1.2), to the enzyme lactate dehydrogenase, which plays a role in the catabolism and anabolism of carbohydrates. Experiments show that $\Delta_r S^\circ = -16.8 \text{ J K}^{-1} \text{ mol}^{-1}$ for binding at 25°C and $\text{pH} = 7.0$. 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 a more organized structure, 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 or not a process is spontaneous. The reduction in entropy by $16.8 \text{ J K}^{-1} \text{ mol}^{-1}$ 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 entire ‘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 the 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 in 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.

A brief illustration

To calculate the entropy change in the surroundings when a reaction takes place at constant pressure, we use eqn 2.6, interpreting the ΔH in that expression as the reaction enthalpy. For example, for the formation of the NAD^+ -enzyme complex discussed above, with $\Delta_r H^\circ = -24.2 \text{ kJ mol}^{-1}$, the change in entropy of the surroundings (which are maintained at 25°C , the same temperature as the reaction mixture) is

$$\Delta_r S_{\text{sur}} = -\frac{\Delta_r H}{T} = -\frac{(-24.2 \text{ kJ mol}^{-1})}{298 \text{ K}} = +81.2 \text{ J K}^{-1} \text{ mol}^{-1}$$

Now we can see that the total entropy change is positive:

$$\Delta_r S_{\text{total}} = (-16.8 \text{ J K}^{-1} \text{ mol}^{-1}) + (81.2 \text{ J K}^{-1} \text{ mol}^{-1}) = +64.4 \text{ J K}^{-1} \text{ mol}^{-1}$$

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 it 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, 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.

2.6 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

$$\Delta S_{\text{total}} = \Delta S + \Delta S_{\text{sur}} \quad \text{Total entropy change} \quad (2.10)$$

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 2.6 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

$$\text{At constant temperature and pressure: } \Delta S_{\text{total}} = \Delta S - \frac{\Delta H}{T} \quad (2.11)$$

The great advantage of this formula is that it expresses the total entropy change of the system and its surroundings in terms of the properties of the system alone. The only restriction is that the expression is confined to changes at constant pressure and temperature.

(a) The definition of the Gibbs energy

Now we take a very important step. First, we introduce the **Gibbs energy**, G , which is defined as³

³ The Gibbs energy is still commonly referred to by its older name, the ‘free energy’.

$$G = H - TS \quad \text{Definition of Gibbs energy} \quad (2.12)$$

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

$$\text{At constant temperature: } \Delta G = \Delta H - T\Delta S \quad \text{Change in } G \text{ at constant } T \quad (2.13)$$

By comparing eqns 2.11 and 2.13, we obtain

$$\text{At constant temperature and pressure: } \Delta G = -T\Delta S_{\text{total}} \quad (2.14)$$

We see that at constant temperature and pressure, the change in the Gibbs energy of a system is proportional to the overall change in the entropy of the system plus its surroundings.

(b) Spontaneity and the Gibbs energy

The difference in sign between ΔG and ΔS_{total} in eqn 2.14 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. 2.13).

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 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

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 proceeds 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 *Case study 1.1*. 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 on reorganization of bonds in foods when they are oxidized. More difficult to rationalize is life's requirement of the 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.

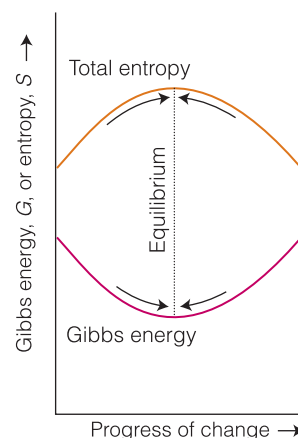


Fig. 2.13 The criterion of spontaneous change is the increase in total entropy of the system and its surroundings. Provided we accept the limitation of working at constant pressure and temperature, we can focus entirely on the properties of the system and express the criterion as a tendency to move to lower Gibbs energy.

To understand this point, recall from *Case study 1.1* and *Case study 1.2* 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 $q_{\text{sur}} > 0$ and $\Delta S_{\text{sur}} > 0$. 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.

2.7 The hydrophobic interaction

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.

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 $-\text{CH}_2\text{CH}(\text{CH}_3)_2$) in the interior, which is often not very accessible to solvent, and hydrophilic groups (water-loving, polar or charged groups such as $-\text{NH}_3^+$) on the surface, which is in direct contact with the polar solvent. A species with both hydrophobic and hydrophilic regions is called **amphipathic**.⁴ Phospholipids also are amphipathic molecules that can group together to form bilayer structures and cell membranes (recall Fig. F.1).

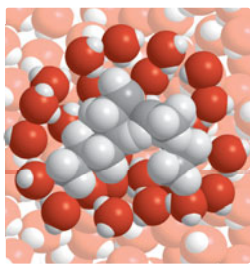


Fig. 2.14 When a hydrophobic molecule (in shades of gray) is surrounded by water, the H_2O molecules (with their oxygen atoms shown in red) form a cage, of which a cross-section is shown here. As a result of this acquisition of structure, the entropy of water decreases, so the dispersal of the hydrophobic molecule into the water is entropy opposed; its coalescence is entropy favored.

To understand the process in more detail, imagine a hypothetical initial state in which a polypeptide chain is immersed in water and has not acquired its final structure. Each hydrophobic group is surrounded by a cage of water molecules (Fig. 2.14). Now consider the actual final state in which hydrophobic groups are clustered together. Although the clustering together results in a negative contribution to the change in entropy of the system (the solution), fewer (albeit larger) cages are required and more solvent molecules are free to move. The net effect of the formation of clusters of hydrophobic groups is then a decrease in the organization of the solvent and a net *increase* in entropy of the system. This increase in entropy of the solvent is large enough to result in the association of hydrophobic groups in an aqueous environment being spontaneous. The process that drives the spontaneous clustering of hydrophobic groups in the presence of water is called the **hydrophobic interaction**.

⁴ 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*.

Self-test 2.4 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

To understand the hydrophobic interaction more completely we need to know more about the energetics of the interaction of hydrophobic groups and water. Experiments indicate that the dissolution of a largely hydrophobic molecule in water is commonly endothermic ($\Delta_{\text{diss}}H > 0$) but that the entropy change is positive ($\Delta_{\text{diss}}S > 0$):

	$\Delta_{\text{diss}}G^*/\text{kJ mol}^{-1}$	$\Delta_{\text{diss}}H^*/\text{kJ mol}^{-1}$	$\Delta_{\text{diss}}S^*/\text{J K}^{-1} \text{mol}^{-1}$
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	-10	+9	+65
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	-13	+8	+72

The positive entropy of dissolving is consistent with the solvent water becoming more disorganized in the presence of the hydrophobic tails of the alkanol molecules, as the hydrophobic interaction requires. These experimental values are consistent with a general rule that each additional $-\text{CH}_2-$ group contributes a further -3 kJ mol^{-1} to the Gibbs energy of dissolving.

An important consequence of this analysis is that low temperatures *disfavor* the hydrophobic interaction. Thus, from $\Delta G = \Delta H - T\Delta S$, lowering the temperature reduces the effect of ΔS and the ΔG can change from negative to positive. This is the reason why some proteins and viruses dissociate into their individual subunits as the temperature is lowered to 0°C .

A further aspect of this discussion is that we can set up a scale of hydrophobicities. The hydrophobicity of a small molecular group R is reported by defining the **hydrophobicity constant**, π , as

$$\pi = \log \frac{s(\text{RX})}{s(\text{HX})} \quad \text{Definition of hydrophobicity constant} \quad (2.15)$$

where $s(\text{RX})$ is the ratio of the molar solubility (the maximum chemical amount that can be dissolved to form 1 dm^3 of solution) of the compound RX in octan-1-ol, a non-polar solvent, to that in water, and $s(\text{HX})$ is the ratio of the molar solubility of the compound HX 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:

$-\text{R}$	$-\text{CH}_3$	$-\text{CH}_2\text{CH}_3$	$-(\text{CH}_2)_2\text{CH}_3$	$-(\text{CH}_2)_3\text{CH}_3$	$-(\text{CH}_2)_4\text{CH}_3$
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 $\Delta_{\text{diss}}H$ becoming more positive and $\Delta_{\text{diss}}S$ more negative as the number of carbon atoms in the chain increases.

2.8 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**, $w_{\text{non-exp}}$, 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. As we show in the following *Justification*,

At constant temperature and pressure: $\Delta G = w_{\text{max,non-exp}}$

$$\boxed{\text{Gibbs energy and non-expansion work}} \quad (2.16)$$

Justification 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, $dw_{\text{non-exp}}$. We start with the infinitesimal form of eqn 2.13,

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 1.11b, written as $dH = dU + pdV$) and obtain

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, $-p_{\text{ex}}dV$, and non-expansion work, $dw_{\text{non-exp}}$. Therefore,

$$dG = -p_{\text{ex}}dV + dw_{\text{non-exp}} + dq + pdV - TdS$$

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: $dG = dw_{\text{non-exp,rev}}$

Maximum work is done during a reversible change (Section 1.3(c)), so another way of writing this expression is

at constant temperature and pressure: $dG = dw_{\text{max, non-exp}}$

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 2.1 *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 $\text{C}_6\text{H}_{12}\text{O}_6(\text{s})$ to carbon dioxide gas and liquid water at 25°C is -2808 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 1.2, 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

$$w_{\text{non-exp}} = (30 \times 10^{-3} \text{ kg}) \times (9.81 \text{ m s}^{-2}) \times (10 \text{ m}) = 3.0 \times 9.81 \times 1.0 \times 10^{-1} \text{ J}$$

(because $1 \text{ kg m}^2 \text{ s}^{-2} = 1 \text{ J}$). The amount, n , of glucose molecules required for oxidation to give a change in Gibbs energy of this value given that 1 mol provides 2808 kJ is

$$n = \frac{3.0 \times 9.81 \times 1.0 \times 10^{-1} \text{ J}}{2.808 \times 10^6 \text{ J mol}^{-1}} = \frac{3.0 \times 9.81 \times 1.0 \times 10^{-7}}{2.808} \text{ mol}$$

Therefore, because the molar mass, M , of glucose is 180 g mol^{-1} , the mass, m , of glucose that must be oxidized is

$$m = nM = \left(\frac{3.0 \times 9.81 \times 1.0 \times 10^{-7}}{2.808} \text{ mol} \right) \times (180 \text{ g mol}^{-1}) = 1.9 \times 10^{-4} \text{ g}$$

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 2.5 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?

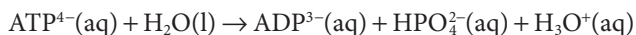
Answer: 5.8 g

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 Sections 5.10 and 5.11).

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.

Case study 2.2 The action of adenosine triphosphate

In biological cells, the energy released by the oxidation of foods (*Case study 1.1*) is stored in adenosine triphosphate (ATP or ATP^{4-} , Atlas N3). 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-} , Atlas N2):



At pH = 7.0 and 37°C (310 K, blood temperature) the enthalpy and Gibbs energy of hydrolysis are $\Delta_r H = -20 \text{ kJ mol}^{-1}$ and $\Delta_r G = -31 \text{ kJ mol}^{-1}$, respectively. Under these conditions, the hydrolysis of 1 mol $\text{ATP}^{4-}(\text{aq})$ results in the extraction of up to 31 kJ of energy that can be used to do non-expansion work, 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.

Checklist of key concepts

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|--|--|
| <p>☐ 1. A spontaneous change is a change that has a tendency to occur without work having to be done to bring it about.</p> <p>☐ 2. Matter and energy tend to disperse.</p> <p>☐ 3. The Second Law states that the entropy of an isolated system tends to increase.</p> <p>☐ 4. 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.</p> <p>☐ 5. 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).</p> | <p>☐ 6. The Boltzmann formula expresses the statistical entropy in terms of the number of microstates of a system.</p> <p>☐ 7. The Gibbs energy is defined as $G = H - TS$ and is a state function.</p> <p>☐ 8. At constant temperature and pressure, a system tends to change in the direction of decreasing Gibbs energy.</p> <p>☐ 9. 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.</p> <p>☐ 10. 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.</p> |
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Checklist of key equations

Property or process	Equation	Comment
Entropy change	$\Delta S = q_{\text{rev}}/T$	Definition
Entropy change of surroundings	$\Delta S_{\text{sur}} = -q/T$ $\Delta S_{\text{sur}} = -\Delta H/T$	q is heat supplied to the system ΔH is the enthalpy change of the system; constant pressure process
Boltzmann formula for the entropy	$S = k \ln W$	W is the number of microstates
Entropy of transition	$\Delta_{\text{trs}} S(T_{\text{trs}}) = \Delta_{\text{trs}} H(T_{\text{trs}})/T_{\text{trs}}$	At the transition temperature
Entropy change due to a change in temperature	$\Delta S = C \ln(T_2/T_1)$	Heat capacity constant in the range of interest
Standard reaction entropy	$\Delta_r S^\circ = \sum \nu S_m^\circ(\text{products}) - \sum \nu S_m^\circ(\text{reactants})$	Definition
Gibbs energy	$G = H - TS$	Definition
Change in Gibbs energy	$\Delta G = \Delta H - T\Delta S$	At constant temperature
Relation to maximum non-expansion work	$\Delta G = w_{\text{max,non-exp}}$	At constant temperature and pressure

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) $\Delta G = \Delta H - T\Delta S$, and (c) $\Delta G = w_{\text{max,non-exp}}$.

2.3 Suggest a procedure for the measurement of the entropy of unfolding of a protein with differential scanning calorimetry (see *In the laboratory* 1.1).

2.4 Justify the identification of the statistical entropy with the thermodynamic entropy.

2.5 Explain the origin of the residual entropy.

2.6 Without performing a calculation, predict whether the standard entropies of the following reactions are positive or negative:

- (a) $\text{Ala-Ser-Thr-Lys-Gly-Arg-Ser} \xrightarrow{\text{trypsin}} \text{Ala-Ser-Thr-Lys-Gly-Arg}$
 (b) $\text{N}_2(\text{g}) + 3 \text{H}_2(\text{g}) \xrightarrow{\text{trypsin}} 2 \text{NH}_3(\text{g})$
 (c) $\text{ATP}^{4-}(\text{aq}) + \text{H}_2\text{O}(\text{l}) \xrightarrow{\text{trypsin}} \text{ADP}^{3-}(\text{aq}) + \text{HPO}_4^{2-}(\text{aq}) + \text{H}_3\text{O}^+(\text{aq})$

2.7 Provide a molecular interpretation of the hydrophobic interaction.

Exercises

2.8 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?

2.9 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?

2.10 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) and (b) the surroundings (the glass of water)?

2.11 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, and (c) the entropy of the system as a function of time.

2.12 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 $C_{p,m} = 75.5 \text{ J K}^{-1} \text{ mol}^{-1}$.

2.13 Estimate the molar entropy of potassium chloride at 5.0 K given that its molar heat capacity at that temperature is $1.2 \text{ mJ K}^{-1} \text{ mol}^{-1}$.

2.14 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 *Justification* 2.1.

2.15 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 $C_{p,m} = 75.5 \text{ J K}^{-1} \text{ mol}^{-1}$.

2.16 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 on unfolding is $6.28 \text{ kJ K}^{-1} \text{ mol}^{-1}$ 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.

2.17 The enthalpy of the graphite $\rightarrow$ diamond phase transition, which under 100 kbar occurs at 2000 K, is $+1.9 \text{ kJ mol}^{-1}$. Calculate the entropy of transition at that temperature.

2.18 The enthalpy of vaporization of methanol is $35.27 \text{ kJ mol}^{-1}$ 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.

2.19 Trouton's rule summarizes the results of experiments showing that the entropy of vaporization measured at the boiling point, $\Delta_{\text{vap}}S = \Delta_{\text{vap}}H(T_b)/T_b$, is approximately the same and equal to about $85 \text{ J K}^{-1} \text{ mol}^{-1}$ 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.

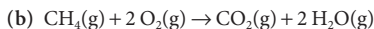
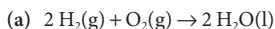
2.20 Calculate the entropy of fusion of a compound at 25°C given that its enthalpy of fusion is 32 kJ mol^{-1} at its melting point of 146°C and the molar heat capacities (at constant pressure) of the liquid and solid forms are $28 \text{ J K}^{-1} \text{ mol}^{-1}$ and $19 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively.

2.21 Show that at temperatures close to $T = 0$, $S(T) = \frac{1}{3}C_p(T)$.

2.22 Calculate the residual molar entropy of a solid in which the molecules can adopt (a) three, (b) five, and (c) six orientations of equal energy at $T = 0$.

2.23 Calculate the standard reaction entropy at 298 K of the fermentation of glucose to ethanol:
 $\text{C}_6\text{H}_{12}\text{O}_6(\text{s}) \rightarrow 2 \text{ C}_2\text{H}_5\text{OH}(\text{l}) + 2 \text{ CO}_2(\text{g})$.

2.24 The constant-pressure molar heat capacities of linear gaseous molecules are approximately $\frac{7}{2}R$ and those of non-linear gaseous molecules are approximately $4R$. Estimate the change in standard reaction entropy of the following two reactions when the temperature is increased by 10 K at constant pressure:



2.25 Use the information in Exercise 2.24 to calculate the standard Gibbs energy of reaction of $\text{N}_2 + 3 \text{ H}_2(\text{g}) \rightarrow 2 \text{ NH}_3(\text{g})$.

2.26 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 $-126 \text{ J K}^{-1} \text{ mol}^{-1}$. (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.

2.27 The change in Gibbs energy that accompanies the oxidation of $\text{C}_6\text{H}_{12}\text{O}_6(\text{s})$ to carbon dioxide and water vapor at 25°C is $-2808 \text{ kJ mol}^{-1}$. How much glucose does a person of mass 65 kg need to consume to climb through 10 m?

2.28 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 $\Delta G = -31 \text{ kJ mol}^{-1}$ 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?

2.29 The hydrolysis of acetyl phosphate has $\Delta G = -42 \text{ kJ mol}^{-1}$ under typical biological conditions. If the phosphorylation of acetic acid were to be coupled to the hydrolysis of ATP, what is the minimum number of ATP molecules that would need to be involved?

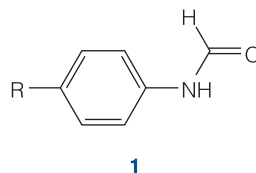
2.30 Suppose that the radius of a typical cell is $10 \mu\text{m}$ and that inside it 10^6 ATP molecules are hydrolyzed each second. What is the power density of the cell in watts per cubic meter ($1 \text{ W} = 1 \text{ J s}^{-1}$)? A computer battery delivers about 15 W and has a volume of 100 cm^3 . Which has the greater power density, the cell or the battery? (For data, see Exercise 2.28.)

Projects

2.31 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 $\text{R} = \text{CH}_3$, CH_2CH_3 , $(\text{CH}_2)_2\text{CH}_3$, $(\text{CH}_2)_3\text{CH}_3$, and $(\text{CH}_2)_4\text{CH}_3$ are, respectively, 0.5, 1.0, 1.5, 2.0, and 2.5. Use these data to predict the π value for $(\text{CH}_2)_6\text{CH}_3$.

(b) The equilibrium constants K_i for the dissociation of inhibitors (1) from the enzyme chymotrypsin (Atlas P3) were measured for different substituents R:

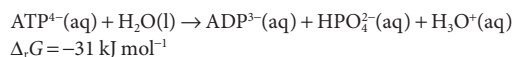


R	CH ₃ CO	CN	NO ₂	CH ₃	Cl
π	-0.20	-0.025	0.33	0.50	0.90
$\log K_1$	-1.73	-1.90	-2.43	-2.55	-3.40

Plot $\log K_1$ against π . Does the plot suggest a linear relationship? If so, what are the slope and intercept to the $\log K_1$ axis of the line that best fits the data?

(c) Predict the value of K_1 for the case R = H.

2.32 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:



(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 H₄ATP and MgATP²⁻, a complex between the Mg²⁺ ion and ATP⁴⁻, are less negative than the Gibbs energy of hydrolysis of ATP⁴⁻. 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 MgATP²⁻ complex, the Mg²⁺ ion and ATP⁴⁻ anion form two bonds: one that involves a negatively charged oxygen belonging to the terminal phosphate group of ATP⁴⁻ and another that involves a negatively charged oxygen belonging to the phosphate group adjacent to the terminal phosphate group of ATP⁴⁻.

(c) Stabilization due to resonance in ATP⁴⁻ and the HPO₄²⁻ 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?

3

Phase equilibria

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Boiling, freezing, 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 one phase of a biological membrane into another as it is heated.

The thermodynamics of phase changes of pure materials is also important because it prepares us first for the study of mixtures and then 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, such as 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

Because the Gibbs energy, $G = H - TS$, provides a signpost of spontaneous change when the pressure and temperature are constant, and we need to know the conditions under which a transition from one state to another becomes spontaneous, it is at the centre of all that follows. In particular, we need to know how G 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 understand the relative thermodynamic 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, is characteristic of 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 negative value of ΔG indicates that the change from phase 1 to phase 2 is spontaneous at constant temperature and pressure. It follows that the 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 lower 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 since in most cases their systems are at pressures close to 1 atm? You should recall the discussion in Chapter 1, 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 vapor which, as a gas, are easy to formulate, and then imagine bringing the vapor into equilibrium with the liquid. Then the properties of the liquid mirror those of the vapor. 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 *Justification* that when the temperature is held constant and the pressure is changed from p_i to p_f , the molar Gibbs energy of an incompressible liquid becomes

$$G_m(p_f) = G_m(p_i) + (p_f - p_i)V_m \quad \text{Variation of the Gibbs energy with pressure (for an incompressible liquid)} \quad (3.1)$$

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, which is true of most liquids (and solids) under normal circumstances. Even though gases are far from incompressible, we can also use eqn 3.1 for the *qualitative* discussion of the pressure dependence of G_m of a gas provided the change in pressure is small.

Justification 3.1 The variation of G of an incompressible liquid with pressure

When the temperature, volume, and pressure of a substance are changed by infinitesimal amounts, H changes to $H + dH$, T changes to $T + dT$, and S changes to $S + dS$. As a result, G changes to $G + dG$, where

$$G + dG = (H + dH) - (T + dT)(S + dS) = H + dH - TS - TdS - SdT - dTdS$$

The G on the left cancels the $H - TS$ on the right, the doubly infinitesimal $dTdS$ can be neglected, and we are left with

$$dG = dH - TdS - SdT$$

In a similar way, from the definition $H = U + pV$, letting U change to $U + dU$, and so on, and neglecting the doubly infinitesimal term $dpdV$, we can write

$$dH = dU + pdV + Vdp$$

At this point we need to know how the internal energy changes, and write

$$dU = dq + dw$$

If initially we consider only reversible changes, we can replace dq by TdS (because $dS = dq_{\text{rev}}/T$) and dw by $-pdV$ (because $dw = -p_{\text{ex}}dV$ and $p_{\text{ex}} = p$ for a reversible change) and obtain

$$dU = TdS - pdV$$

Now we substitute this expression into the expression for dH and that expression into the expression for dG and obtain

$$dG = TdS - pdV + pdV + Vdp - TdS - SdT$$

It follows that

$$dG = Vdp - SdT \quad \text{Variation of the Gibbs energy with pressure and temperature} \quad (3.2)$$

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 within a system of known composition, not just a reversible change.

At this point we decide to keep the temperature constant and set $dT = 0$; this leaves

$$dG = Vdp$$

and, for molar quantities, $dG_m = V_m dp$. This expression is exact but applies only to an infinitesimal change in the pressure. For an observable change, we replace dG_m by $G_m(p_f) - G_m(p_i)$ and dp by $p_f - p_i$, respectively, and obtain eqn 3.1, provided the molar volume is constant over the range of interest.

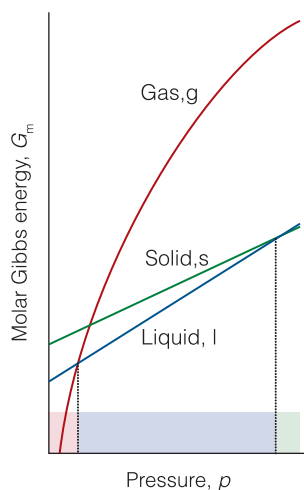


Fig. 3.1 The variation of molar Gibbs energy with pressure. The region of stability of each phase is indicated in the band at the bottom of the illustration.

Equation 3.1 tells us that, because all molar volumes are positive, *the molar Gibbs energy increases* ($G_m(p_f) > G_m(p_i)$) *when the pressure increases* ($p_f > p_i$). 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. Again bearing in mind that we can apply eqn 3.1 *qualitatively* to gases over small changes in pressure, we see that 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

Mathematical toolkit 3.1 *Integration*

The area under a graph of any function f is found by the techniques of integration. For instance, the area under the graph of the function $f(x)$ between $x = a$ and $x = b$ is denoted by

$$\text{area between } a \text{ and } b = \int_a^b f(x) dx$$

The elongated S symbol on the right is called the **integral** of the function f . When written as $\int$ alone, it is the **indefinite integral** of the function. When written with limits (as in the expression above), it becomes the **definite integral** of the function. The definite integral is the indefinite integral evaluated at the upper limit (b) minus the indefinite integral evaluated at the lower limit (a).

A very useful integral in physical chemistry is

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

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

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

We see that the constant cancels. For instance, the area under the graph of $1/x$ lying between $a = 2$ and $b = 3$ is $\ln(\frac{3}{2}) = 0.41$.

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 the 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. It 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. To find a quantitative expression for the pressure dependence that is valid over a substantial pressure range, we have to take into account the fact that a gas is compressible and that the molar volume decreases as pressure is applied. We therefore expect the Gibbs energy to increase with pressure, but for it to become less sensitive to pressure as the pressure rises (because the molar volume is decreasing). We show in the following *Justification* that

$$G_m(p_f) = G_m(p_i) + RT \ln \frac{p_f}{p_i} \quad (3.3)$$

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 we anticipated, as V_m gets smaller, G_m becomes less responsive to pressure.

Justification 3.2 *The pressure variation of the Gibbs energy of a perfect gas*

We start with the exact expression for the effect of an infinitesimal change in pressure obtained in *Justification 3.1*, that $dG_m = V_m dp$. For a change in pressure

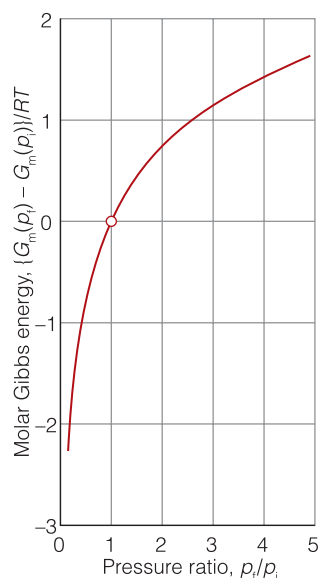


Fig. 3.2 The variation of the molar Gibbs energy of a perfect gas with pressure.

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

$$\Delta G_m = \int_{p_i}^{p_f} \frac{RT}{p} dp = RT \int_{p_i}^{p_f} \frac{dp}{p} = RT \ln \frac{p_f}{p_i}$$

We have used the standard integral described in *Mathematical toolkit* 3.1. Finally, with $\Delta G_m = G_m(p_f) - G_m(p_i)$, we get eqn 3.3.

3.3 The variation of Gibbs energy with temperature

To understand why phase transitions, including the denaturation of a biopolymer, occur at a specific temperature, we need to know how molar Gibbs energy varies with temperature.

For small changes in temperature, we show in the following *Justification* that the change in molar Gibbs energy at constant pressure may be written as

$$G_m(T_f) = G_m(T_i) - (T_f - T_i)S_m \quad \text{Variation of the Gibbs energy with temperature} \quad (3.4)$$

This expression is valid provided the entropy of the substance is unchanged over the range of temperatures of interest.

Justification 3.3 The variation of the Gibbs energy with temperature

The starting point for this short derivation is eqn 3.2 in *Justification* 3.1, which we rewrite as 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 3.4.

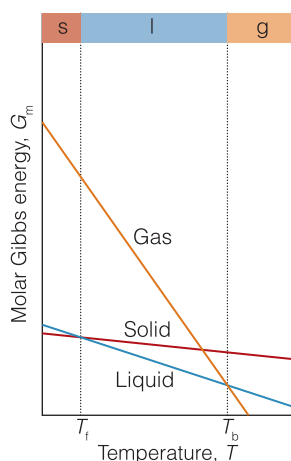


Fig. 3.3 The variation of molar Gibbs energy with temperature. All molar Gibbs energies decrease with increasing temperature. The regions of temperature over which the solid, liquid, and gaseous forms of a substance have the lowest molar Gibbs energy are indicated in the band at the top of the illustration.

Equation 3.4 tells us that, because molar entropy is positive, *an increase in temperature* ($T_f > T_i$) *results in a decrease in* G_m ($G_m(T_f) < G_m(T_i)$). Moreover, for a given change of temperature, the change in molar Gibbs energy is proportional to the molar entropy. For a given substance, because the molar entropy of the gas phase is greater than that for a condensed phase, 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 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 vapor plunges down below that of the liquid phase, and the vapor becomes the most stable phase. In other words, above a certain temperature, the liquid vaporizes.

We can also start to understand why some substances, such as solid 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 sublimates.

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 two phases are in equilibrium and therefore their molar Gibbs energies are equal. At 1 atm, for instance, ice and liquid water are in equilibrium at 0°C and $G_m(\text{H}_2\text{O}, \text{l}) = G_m(\text{H}_2\text{O}, \text{s})$.

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 immeasurably 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. The molecules of liquids are mobile, so this ‘metastability’ is much less likely to occur. Nevertheless, even a liquid may persist above its boiling point as a **superheated liquid** if it is heated carefully and there are no so-called **nucleation centers**, such as scratches on the interior of the containing vessel, at which the vapor can form.

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.

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

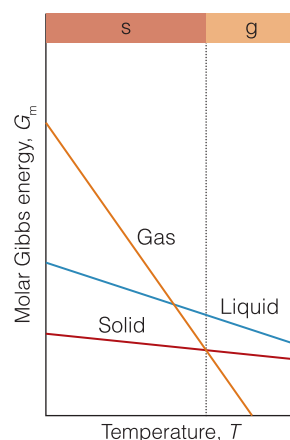


Fig. 3.4 If the line for the Gibbs energy of the liquid phase does not cut through the line for the solid phase (at a given pressure) before the line for the gas phase cuts through the line for the solid, the liquid is not stable at any temperature at that pressure. Such a substance sublimates.

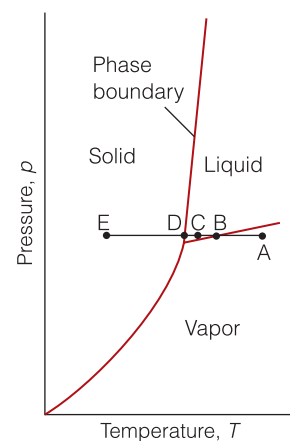


Fig. 3.5 A typical phase diagram, showing the regions of pressure and temperature at which each phase is the most stable. The phase boundaries (three are shown here) show the values of pressure and temperature at which the two phases separated by the line are in equilibrium. The significance of the letters A, B, C, D, and E (also referred to in Fig. 3.8) is explained in the text.

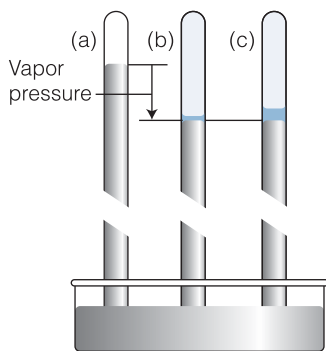


Fig. 3.6 When a small volume of water is introduced into the vacuum above the mercury in a barometer (a), the mercury is depressed (b) by an amount that is proportional to the vapor pressure of the liquid. (c) The same pressure is observed however much liquid is present (provided some is present).

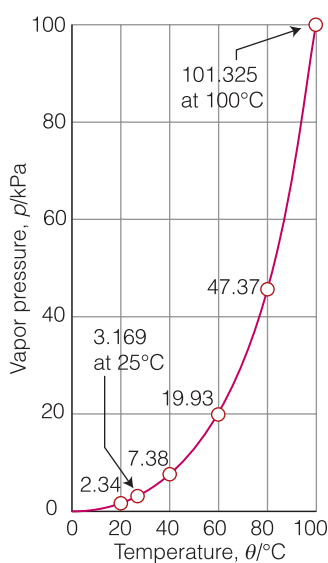


Fig. 3.7 The experimental variation of the vapor pressure of water with temperature.

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 liquid phases are in equilibrium (like ice and water at 1 atm and 0°C). A further reduction in temperature to E takes the system into the region where the solid is the stable phase.

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 is 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.

(a) Phase boundaries

The pressure of a vapor that is 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. To determine the vapor pressure, a small amount of liquid can be introduced into the near-vacuum at the top of a mercury barometer and the depression of the column measured (Fig. 3.6). To ensure that the pressure exerted by the vapor is truly the vapor pressure, enough liquid must be added for some to remain after the vapor forms, for only then are the liquid and vapor phases in equilibrium. The temperature can be changed to determine another point on the curve, and so on (Fig. 3.7).

The plot of the vapor pressure against temperature is also the liquid–vapor boundary in a phase diagram. To appreciate that interpretation, suppose we have a liquid in a cylinder fitted with a piston. If at some temperature 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. If instead we reduce the pressure on the system to a value below the vapor pressure at that temperature, the system moves to one of the points in the ‘vapor’ region of the diagram. At the vapor pressure itself, vapor and liquid are in equilibrium, and the state of the system is represented by a point on the phase boundary.

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.

(b) The location of phase boundaries

Thermodynamics provides us with a way of predicting the location of the phase boundaries and relating their location and shape to the thermodynamic properties of the system. For instance, the shape of the vapor pressure curve (the liquid–vapor boundary) is related to the enthalpy of vaporization of the liquid.

Suppose two phases, such as liquid and vapor, are in equilibrium at a given pressure and temperature. As we have seen, at a given temperature, the pressure corresponding to equilibrium is the vapor pressure of the liquid. If we change the temperature, the vapor pressure changes to a different value. That is, there is a relation between the change in temperature, dT , and the accompanying change in vapor pressure, dp . If we were considering the equilibrium between a solid and a liquid, the focus would be different: in this case we would typically be interested in the change in melting point as the pressure is increased. We show in the following *Justification* that the relation between dT and dp that ensures that in either case the two phases remain in equilibrium is given by the **Clapeyron equation** for the slope of the phase boundary at any temperature

$$\frac{dp}{dT} = \frac{\Delta_{\text{trs}}H}{T\Delta_{\text{trs}}V} \quad \text{Clapeyron equation} \quad (3.5)$$

where $\Delta_{\text{trs}}H$ is the enthalpy of transition and $\Delta_{\text{trs}}V$ is the volume of transition (the change in molar volume that accompanies the transition) at the temperature of interest. For the liquid–vapor equilibrium, the equation in the form $dp = (\Delta_{\text{vap}}H/T\Delta_{\text{vap}}V)dT$ gives the change in vapor pressure when the temperature is changed; for the solid–liquid equilibrium, the equation in the form $dT = (T\Delta_{\text{fus}}V/\Delta_{\text{fus}}H)dp$ gives the change in melting point caused by a change in pressure.

For the solid–liquid phase boundary, the enthalpy of fusion is positive because melting is endothermic for all substances of interest in biology. For most substances, the molar volume increases slightly on melting, so $\Delta_{\text{fus}}V$ is positive but small. It follows that the melting temperature changes very little when the pressure is changed. In other words, the slope of the phase boundary is large and positive (up from left to right). Water, however, is quite different, for although its melting is endothermic, its molar volume decreases on melting (liquid water is denser than ice at 0°C, which is why ice floats on water), so $\Delta_{\text{fus}}V$ is small but negative. Consequently, an increase in pressure brings about a decrease in the melting point of ice.

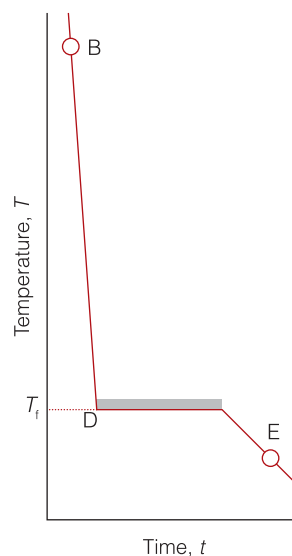


Fig. 3.8 The cooling curve for the B–E section of the horizontal line in Fig. 3.5. The halt at D corresponds to the pause in cooling while the liquid freezes and releases its enthalpy of transition. The halt lets us locate T_f even if the transition cannot be observed visually.

A brief illustration

For water at 1 bar, $\Delta_{\text{fus}}H^\circ = 6.008 \times 10^3 \text{ J mol}^{-1}$ and $\Delta_{\text{fus}}V^\circ = -1.634 \times 10^{-6} \text{ m}^3 \text{ mol}^{-1}$. It follows from eqn 3.5 that at $T = 273.15 \text{ K}$, the melting point of ice,

$$\frac{dp}{dT} = \frac{6.008 \times 10^3 \text{ J mol}^{-1}}{(273.15 \text{ K}) \times (-1.634 \times 10^{-6} \text{ m}^3 \text{ mol}^{-1})} = -1.346 \times 10^7 \text{ Pa K}^{-1}$$

where we have used $1 \text{ Pa} = 1 \text{ N m}^{-2}$ and $1 \text{ J} = 1 \text{ N m}$ to write $1 \text{ Pa} = 1 \text{ J m}^{-3}$. In other words, the slope of the ice–water phase boundary is steep but negative (down from left to right).

For the liquid–vapor boundary (the vapor pressure curve), both the enthalpy and volume of vaporization are invariably positive, so the vapor pressure invariably increases with temperature (dp is positive if dT is positive). However, we have to be cautious because although the enthalpy of vaporization is not very sensitive to temperature, the volume of vaporization depends strongly on the temperature (through the effect of temperature on the volume of a gas). If we suppose that the vapor behaves as a perfect gas, then we show in the following *Justification* that the relation between a change in temperature and a change in vapor pressure is given by the **Clausius–Clapeyron equation**:

$$\frac{d \ln p}{dT} = \frac{\Delta_{\text{vap}}H}{RT^2} \quad \text{Clausius–Clapeyron equation} \quad (3.6)$$

A brief illustration

For water at 1 bar and 373.2 K (the boiling point of water), $\Delta_{\text{vap}}H^\circ = 4.07 \times 10^4 \text{ J mol}^{-1}$, and it follows that

$$\frac{d \ln p}{dT} = \frac{4.07 \times 10^4 \text{ J mol}^{-1}}{(8.314 \text{ J K}^{-1} \text{ mol}^{-1}) \times (373.2 \text{ K})^2} = 3.51 \times 10^{-2} \text{ K}^{-1}$$

The liquid–vapor boundary of the phase diagram for water has a positive slope, and we shall see in Section 3.4(d) that the slope of the liquid–vapor phase boundary is much less steep than the slope of the ice–water phase boundary.

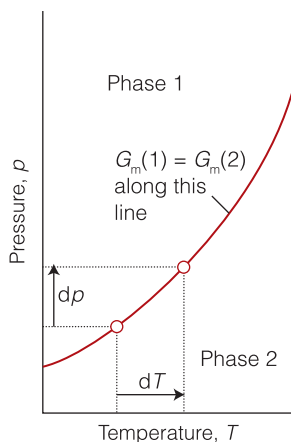


Fig. 3.9 At equilibrium, two phases have the same molar Gibbs energy. When the temperature is changed by dT , for the two phases to remain in equilibrium, the pressure must be changed by dp so that the Gibbs energies of the two phases remain equal.

Justification 3.4 *The Clapeyron and Clausius–Clapeyron equations*

The derivation of the Clapeyron equations is based on eqn 3.2, written as $dG_m = V_m dp - S_m dT$. At a certain pressure and temperature two phases, which we call 1 and 2 but can imagine to be a liquid and a vapor, respectively, are in equilibrium and $G_m(1) = G_m(2)$ (Fig. 3.9). When the temperature is changed by dT and the pressure changes by dp , the molar Gibbs energies change as follows:

$$dG_m(1) = V_m(1)dp - S_m(1)dT \quad dG_m(2) = V_m(2)dp - S_m(2)dT$$

The two phases are in equilibrium before the change and remain in equilibrium after the change, so the two changes in molar Gibbs energy must be equal, $dG_m(1) = dG_m(2)$. It follows that

$$V_m(1)dp - S_m(1)dT = V_m(2)dp - S_m(2)dT$$

and therefore

$$\{V_m(2) - V_m(1)\}dp = \{S_m(2) - S_m(1)\}dT$$

With $\Delta_{\text{trs}}V = V_m(2) - V_m(1)$ and $\Delta_{\text{trs}}S = S_m(2) - S_m(1)$, this equation becomes

$$\Delta_{\text{trs}}V dp = \Delta_{\text{trs}}S dT$$

or

$$\frac{dp}{dT} = \frac{\Delta_{\text{trs}}S}{\Delta_{\text{trs}}V}$$

We saw in Section 2.2 that the transition entropy is related to the enthalpy of transition by $\Delta_{\text{trs}}S = \Delta_{\text{trs}}H/T_{\text{trs}}$, so eqn 3.5 follows immediately. We have dropped the 'trs' subscript from the temperature in eqn 3.5 because all the points on the phase boundary—the only points we are considering in eqn 3.5—are transition temperatures.

To move on to the Clausius–Clapeyron equation, we consider the case of vaporization. Because the molar volume of a gas is much larger than the molar volume of a liquid, we can replace $\Delta_{\text{vap}}V = V_m(\text{g}) - V_m(\text{l})$ by $V_m(\text{g})$ alone and write

$$\frac{dp}{dT} \approx \frac{\Delta_{\text{vap}}H}{TV_m(\text{g})}$$

Next, we suppose that the vapor behaves as a perfect gas and write its molar volume as $V_m(\text{g}) = RT/p$. Then

$$\frac{dp}{dT} = \frac{\Delta_{\text{vap}}H}{T(RT/p)} = \frac{p\Delta_{\text{vap}}H}{RT^2}$$

and therefore

$$\frac{1}{p} \frac{dp}{dT} = \frac{\Delta_{\text{vap}}H}{RT^2}$$

A standard result of calculus is $d \ln x/dx = 1/x$, and therefore (by multiplying both sides by dx), $dx/x = d \ln x$. In this case, $dp/p = d \ln p$, and eqn 3.6 follows.

(c) Characteristic points

We have seen that as the temperature of a liquid is raised, its vapor pressure increases. What we observe, however, depends on whether the heating takes place in a closed or an open container.

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, the 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. 3.10).

A note on good practice

Keep a note of any approximations made in a derivation, for they limit the range of applicability of an expression. We have made two approximations in the derivation of the Clausius–Clapeyron equation: (1) the molar volume of a gas is much greater than that of a liquid and (2) the vapor behaves as a perfect gas.

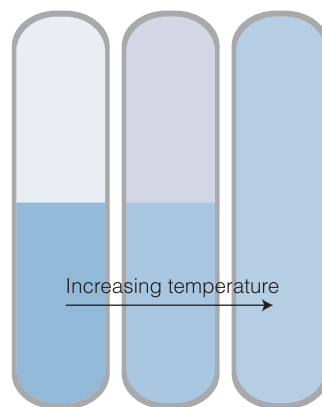


Fig. 3.10 When a liquid is heated in a sealed container, the density of the vapor phase increases and that of the liquid phase decreases, as depicted here by the changing density of shading. There comes a stage at which the two densities are equal and the interface between the two fluids disappears. 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.

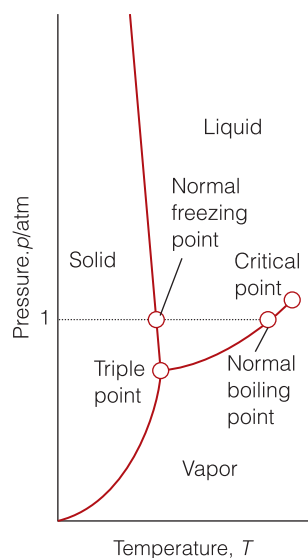


Fig. 3.11 The significant points of a phase diagram. The liquid–vapor phase boundary terminates at the *critical point*. At the *triple point*, solid, liquid, and vapor are in dynamic equilibrium. The *normal freezing point* is the temperature at which the liquid freezes when the pressure is 1 atm; the *normal boiling point* is the temperature at which the vapor pressure of the liquid is 1 atm.

Table 3.1 Critical constants*

	p_c/atm	$V_c/(\text{cm}^3 \text{mol}^{-1})$	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 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. 3.11). A supercritical fluid is not a true liquid, but it behaves like a liquid in many respects—for example, it has a density similar to that of a liquid.

A brief illustration

Supercritical carbon dioxide, scCO_2 , is the center of attention for an increasing number of solvent-based processes. The critical temperature of CO_2 , 304.2 K (31.0°C) and its critical pressure, 72.9 atm, are readily accessible, it is cheap, and it can readily be recycled. A great advantage of scCO_2 is that there are no noxious residues once the solvent has been allowed to evaporate, so, coupled with its low critical temperature, scCO_2 is ideally suited to food processing and the production of pharmaceuticals. It is used, for instance, to remove caffeine from coffee or fats from milk. The supercritical fluid is also increasingly being used for dry cleaning, which avoids the use of carcinogenic and environmentally damaging chlorinated hydrocarbons.

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.

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. 3.12a, 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. 3.12b).

(d) The phase diagram of water

Figure 3.13 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 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).

The solid–liquid boundary line in Fig. 3.14 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. 3.15, 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.

Figure 3.13 shows that water has one liquid phase but many different solid phases other than ordinary ice (‘ice I’, shown in Fig. 3.15). These solid phases differ in the arrangement of the water molecules: under the influence of very high pressures, hydrogen bonds buckle and the H₂O molecules adopt different

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.

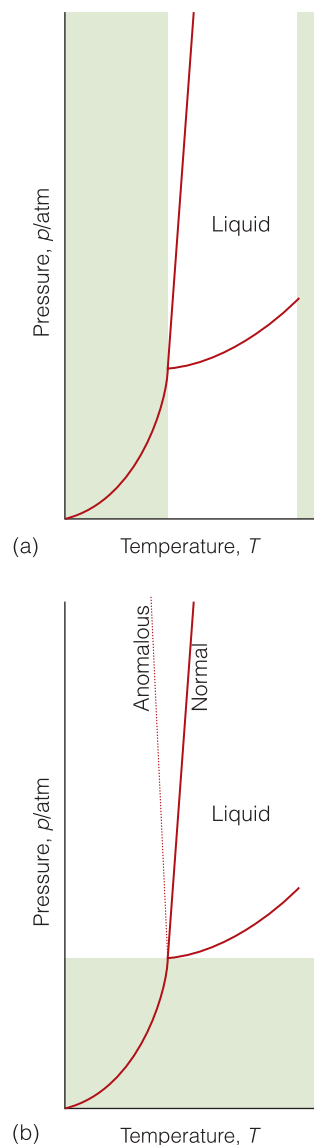


Fig. 3.12 (a) For substances that have phase diagrams resembling the one shown here (which is common for most substances, with the important exception of water), the triple point and the critical point mark the range of temperatures over which the substance can exist as a liquid. The shaded areas show 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.

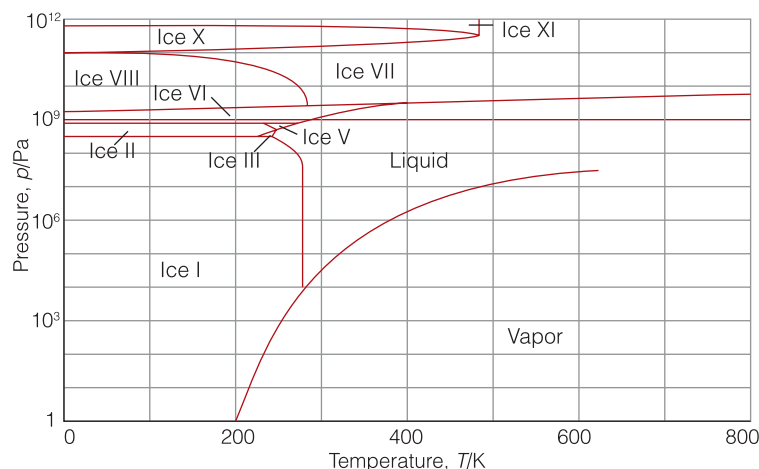


Fig. 3.13 The phase diagram for water showing the different solid phases.

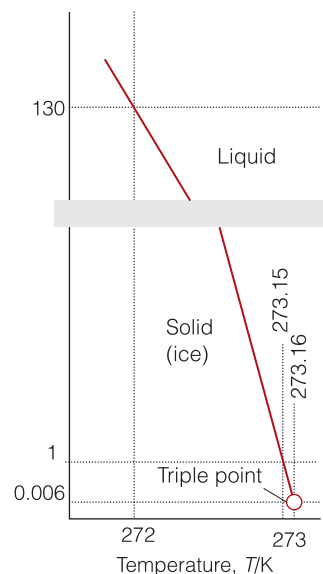


Fig. 3.14 The solid–liquid boundary of water in more detail. The graph is schematic and not to scale.

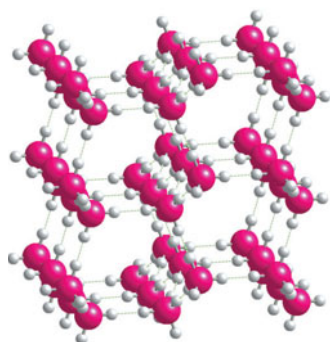


Fig. 3.15 The structure of ice I. Each O atom is at the center of a tetrahedron of four O atoms at a distance of 276 pm. The central O atom is attached by two short O–H bonds to two H atoms and by two long hydrogen bonds to the H atoms of two of the neighboring molecules. Overall, the structure consists of planes of puckered hexagonal rings of H₂O molecules (like the chair form of cyclohexane). This structure collapses partially on melting, leading to a liquid that is denser than the solid.

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 3.13 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

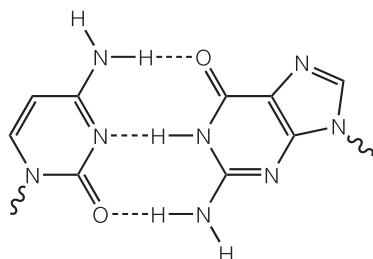
In *Fundamentals* F.1 and Chapter 2 we saw that proteins and biological membranes can exist in ordered structures stabilized by a variety of molecular interactions, such as hydrogen bonds and hydrophobic interactions. However, when certain conditions are changed, the helical and sheet structures of a 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.

3.5 The stability of nucleic acids and proteins

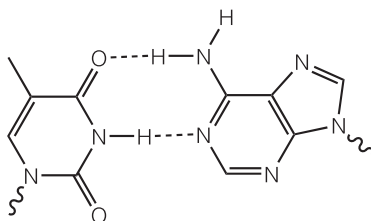
To understand melting of proteins and nucleic acids at specific transition temperatures, we need to explore quantitatively the effect of intermolecular interactions on the stability of compact conformations of biopolymers.

From *In the laboratory* 1.1 we learned that the 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 intramolecular and 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 C–G base pairs in the sequence because each C–G base pair has three hydrogen bonds (1), whereas each T–A base pair has only two (2). More energy is required to unravel a double helix that has a higher proportion of hydrogen bonding interactions per base pair.



1 C–G base pair



2 T–A 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 (*In the laboratory* 1.1). The following data were obtained in 0.010 M $\text{Na}_3\text{PO}_4(\text{aq})$ for a series of DNA molecules with varying base pair composition, with f the fraction of C–G 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 per cent C–G base pairs.

Strategy We need to look for a quantitative relation between the melting temperature and the composition of DNA. We can begin by plotting T_m against fraction of C–G base pairs and examining the shape of the curve. If visual inspection of the plot suggests a linear relation, 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 C–G base pairs, at least in this range of composition. The equation of the line that fits the data is

$$T_m/\text{K} = 325 + 39.7f$$

It follows that $T_m = 341 \text{ K}$ for 40.0 per cent C–G base pairs (at $f = 0.400$).

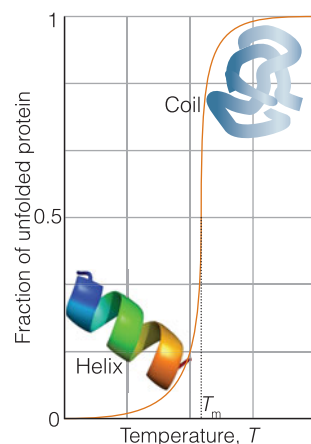


Fig. 3.16 A protein unfolds as the temperature of the sample increases. The sharp step in the plot of fraction of unfolded protein against temperature indicates that the transition is cooperative. The melting temperature, T_m , is the temperature at which the fraction of unfolded polymer is 0.5.

A note on good practice

In this example we do not have a good theory to guide us in the choice of a 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 $0.375 < f < 0.750$.

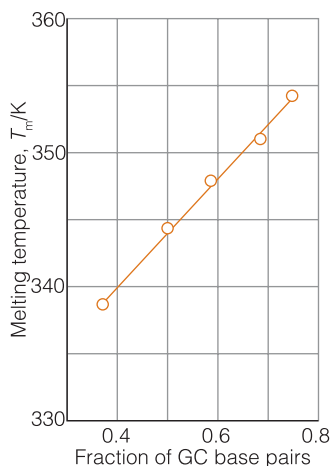


Fig. 3.17 Data for Example 3.1 showing the variation of the melting temperature of DNA molecules with the fraction of C–G base pairs. All the samples also contain $1.0 \times 10^{-2} \text{ mol dm}^{-3} \text{ Na}_3\text{PO}_4$.

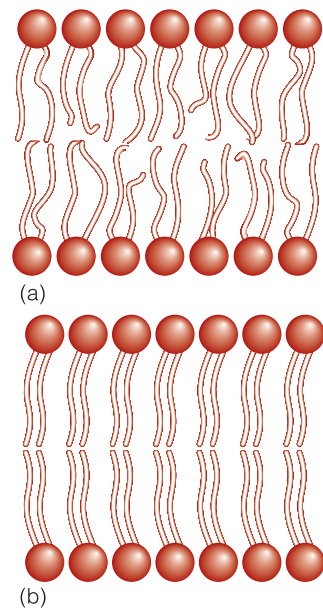


Fig. 3.18 A depiction of the variation with temperature of the flexibility of hydrocarbon chains in a lipid bilayer. (a) At physiological temperature, the bilayer exists as a liquid crystal, in which some order exists but the chains writhe. (b) At a specific temperature, the chains are largely frozen and the bilayer is said to exist as a gel.

Self-test 3.2 The following calorimetric data were obtained in solutions containing 0.15 M NaCl(aq) for the same series of DNA molecules studied in Example 3.1. Estimate the melting temperature of a DNA molecule containing 40.0 per cent C–G 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 3.2 reveal that DNA is rather stable toward thermal denaturation, with T_m values ranging from about 340 K to 375 K, which is 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 the Na^+ ions in Self-test 3.2, 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 denaturation. For example, $T_m = 320 \text{ K}$ for ribonuclease T_1 (an enzyme that cleaves RNA in the cell), which is close to body temperature. More surprisingly, the Gibbs energy for the unfolding of ribonuclease T_1 at $\text{pH} = 7.0$ and 298 K is only $+22.5 \text{ kJ mol}^{-1}$, which is comparable to the energy required to break a single hydrogen bond (about 20 kJ mol^{-1}) despite the fact that the formation of helices and sheets in proteins requires many hydrogen bonds. 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 intermolecular interactions that allow a protein to fold into its active conformation (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 around. 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 then

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 (*In the laboratory* 1.1). 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 2.7). It follows that stabilization of the gel phase in the 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.

Interspersed among the phospholipids of biological membranes are sterols, such as cholesterol (Atlas L1), 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 3.3 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.

Case study 3.1 The use of phase diagrams in the study of proteins

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 or concentration.

Temperature–composition diagrams may be used to characterize intermediates in the unfolding of a protein caused by denaturation with a chemical agent. For example, urea, $\text{CO}(\text{NH}_2)_2$, competes for NH and CO groups, interferes with hydrogen bonding in a polypeptide, and disrupts the intramolecular interactions responsible for its native three-dimensional conformation. A temperature–composition diagram, such as the idealized form shown in Fig. 3.19, can reveal conditions under which different forms of the polypeptide can exist. The idealized diagram shows three structural regions, or phases: the native form, the unfolded form, and a ‘molten globule’ form, a partially unfolded but still compact form of the protein. As usual, two phases in equilibrium

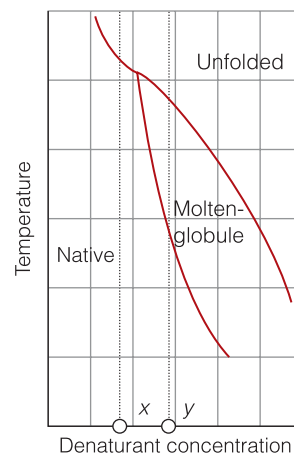


Fig. 3.19 An example of a temperature–composition diagram showing denaturation of a protein in a native phase into molten globule and fully unfolded phases. The concentrations marked *x* and *y* will be used in Exercise 3.39.

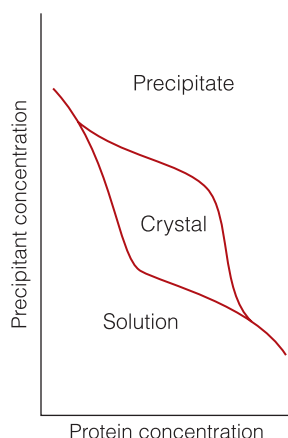


Fig. 3.20 An example of a phase diagram in which the mole fraction of a precipitant, a substance that causes precipitation, is plotted against the mole fraction of a protein. The data help biochemists find conditions under which a protein crystallizes.

define a line in the diagram, and a point represents a unique set of conditions under which the three phases are in equilibrium.

In another type of phase diagram, the mole fraction or concentration of one component of a mixture is plotted against the mole fraction or concentration of another component, and experiments are conducted at constant temperature and pressure. Phase diagrams so constructed help biochemists find conditions under which a protein may form an ordered crystal amenable to study by X-ray diffraction techniques, which can reveal the three-dimensional arrangement of atoms in biological assemblies (see the *Prologue* and Chapter 11). A common crystallization technique for charged proteins consists of adding large amounts of a salt, such as $(\text{NH}_4)_2\text{SO}_4$, to a buffer solution containing the biopolymer. The increase in the ionic strength of the solution decreases the solubility of the protein to such an extent that the protein precipitates. The idealized phase diagram in Fig. 3.20 shows that ordered crystals precipitate over a relatively narrow range of protein and salt concentrations. Precise knowledge of crystallization conditions is a key to the reproducibility of X-ray diffraction experiments.

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. Although 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. The measures of concentration commonly encountered in physical chemistry are reviewed in *Further information 3.2*.

3.7 The chemical potential

To assess the spontaneity of a biological process involving a mixture, we need to know how to compute the contribution of each substance to the total Gibbs energy of the 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**, $G_{J,m}$, 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

$$G = n_A G_{A,m} + n_B G_{B,m} \quad (3.7)$$

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 3.7 becomes

$$G = n_A \mu_A + n_B \mu_B \quad (3.8)$$

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.

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 in the following *Justification* 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.

Justification 3.5 *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, as asserted in the text.

3.8 Ideal and ideal-dilute solutions

Because in biochemistry we are concerned primarily with liquid solutions, we need expressions for the chemical potentials of solutes and solvents.

We need an explicit formula for the variation of the chemical potential of a substance with the composition of the mixture. Here we use the strategy mentioned at the start of the chapter: we begin by considering the chemical potential of a gas, not because gases are particularly interesting in biology but because we can use the resulting expression to derive results for solutions.

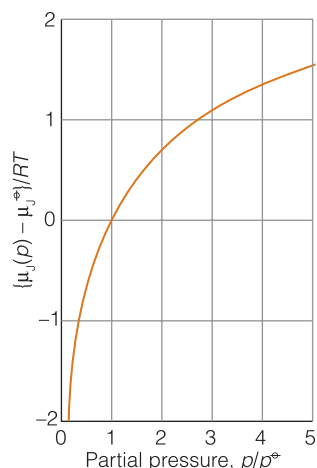


Fig. 3.21 The variation with partial pressure of the chemical potential of a perfect gas. Note that the chemical potential increases with pressure.

(a) The chemical potential of a gas

Our starting point is eqn 3.3, $G_m(p_f) = G_m(p_i) + RT \ln(p_f/p_i)$, 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

$$G_m(p) = G_m^\ominus + RT \ln(p/p^\ominus) \quad (3.9)$$

Next, for a *mixture* of perfect gases, we interpret p as the *partial* pressure of the gas, and 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 ,

$$\mu_J = \mu_J^\ominus + RT \ln(p_J/p^\ominus) \quad (3.10a)$$

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 3.10a more simply as

$$\mu_J = \mu_J^\ominus + RT \ln p_J \quad (3.10b)$$

Figure 3.21 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.

Equation 3.10 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).

Self-test 3.4 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}

(b) The chemical potential of a solvent

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 to denote a solute.

The key to linking the properties of a solution to those of a gas and 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: $p_i = x_i p_i^*$ Raoult's law (3.11)

In this expression, p_i^* is the vapor pressure of the pure substance.

A brief illustration

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 per cent that of pure water. This conclusion is approximately true whatever the identity of the solute and the solvent (Fig. 3.22).

The molecular origin of Raoult's law is the effect of the solute on the entropy of the solution. The entropy of the solvent arises from the random locations and the thermal motion of its molecules. 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. 3.23). 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. 3.24).

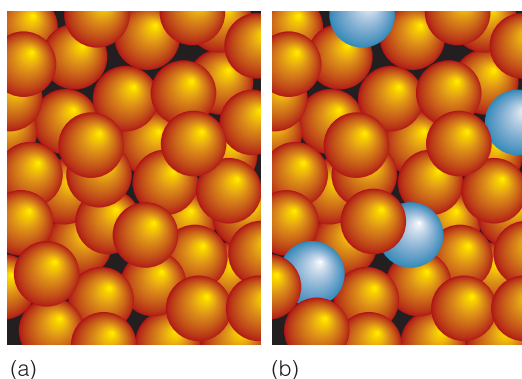


Fig. 3.23 (a) In a pure liquid, we can be confident that any molecule selected from the sample is a solvent molecule. (b) When a solute is present, we cannot be sure that blind selection will give a solvent molecule, so the entropy of the system is greater than in the absence of the solute.

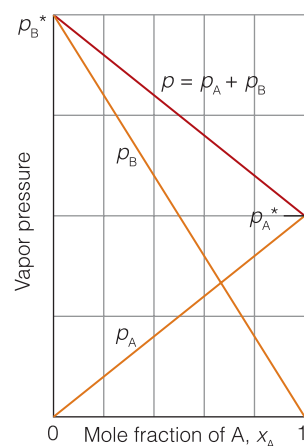


Fig. 3.22 The partial vapor pressures of the two components of an ideal binary mixture are proportional to the mole fractions of the components in the liquid. The total pressure of the vapor is the sum of the two partial vapor pressures.

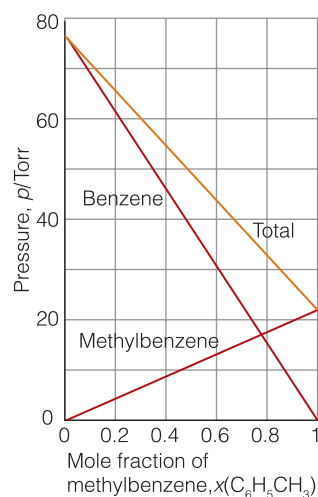


Fig. 3.24 Two similar substances, in this case benzene and methylbenzene (toluene), behave almost ideally and have vapor pressures that closely resemble those for the ideal case depicted in Fig. 3.22.

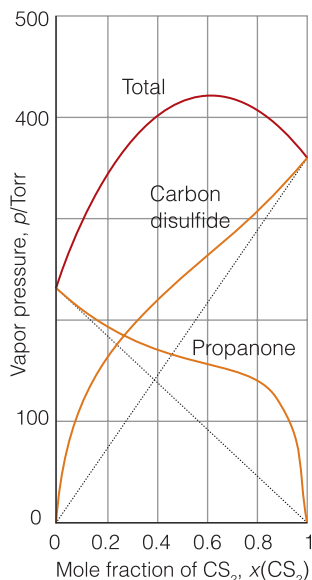


Fig. 3.25 Strong deviations from ideality are shown by dissimilar substances, in this case carbon disulfide and acetone (propanone). Note, however, that Raoult's law is obeyed by propanone when only a small amount of carbon disulfide is present (on the left) and by carbon disulfide when only a small amount of propanone is present (on the right).

A note on good practice

An asterisk (*) denotes a pure substance, but not one that is necessarily in its standard state. Only if the pressure is 1 bar would μ_A^* be the standard chemical potential of A, and it would then be written as μ_A° .

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. 3.25). 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 *Justification*, the chemical potential of a solvent A present in solution at a mole fraction x_A is

$$\mu_A = \mu_A^* + RT \ln x_A \quad \text{Chemical potential of the solvent in an ideal solution} \quad (3.12)$$

where μ_A^* is the chemical potential of pure A. 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).

Justification 3.6 The chemical potential of a solvent

When a solvent A in a solution is in equilibrium with its vapor at a partial pressure p_A , the chemical potentials of the two phases are equal and we can write $\mu_A(l) = \mu_A(g)$ (Fig. 3.26). However, we have just derived an expression for the chemical potential of a vapor, eqn 3.10, so at equilibrium

$$\mu_A(l) = \mu_A^\circ(g) + RT \ln p_A$$

According to Raoult's law, $p_A = x_A p_A^*$, so we can use the relation $\ln(xy) = \ln x + \ln y$ to write

$$\mu_A(l) = \mu_A^\circ(g) + RT \ln(x_A p_A^*) = \mu_A^\circ(g) + RT \ln p_A^* + RT \ln x_A$$

The first two terms on the right, $\mu_A^\circ(g)$ and $RT \ln p_A^*$, are independent of the composition of the mixture and can be combined into the constant μ_A^* , the chemical potential of pure liquid A. Equation 3.12 then follows.

Figure 3.27 shows the variation of the 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 3.12 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.

Self-test 3.5 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

(c) The chemical potential of a solute

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

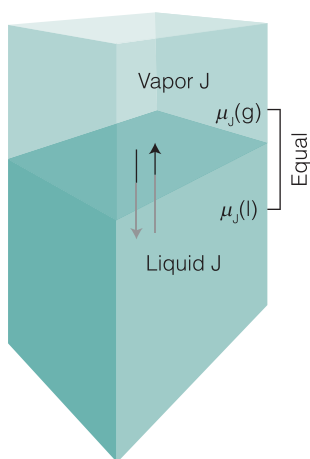


Fig. 3.26 At equilibrium, the chemical potential of a substance in its liquid phase is equal to the chemical potential of the substance in its vapor phase.

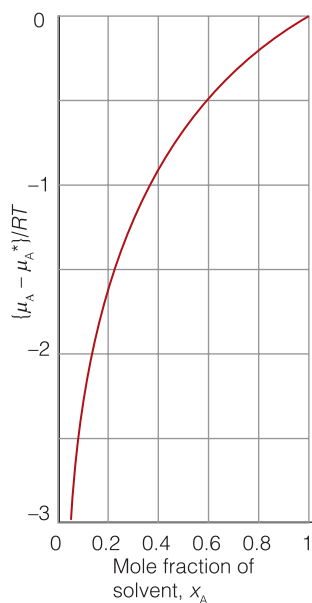


Fig. 3.27 The variation of the chemical potential of the solvent with the composition of the solution. Note that the chemical potential of the solvent is lower in the mixture than for the pure liquid (for an ideal system). This behavior is likely to be shown by a dilute solution in which the solvent is almost pure (and obeys Raoult's law).

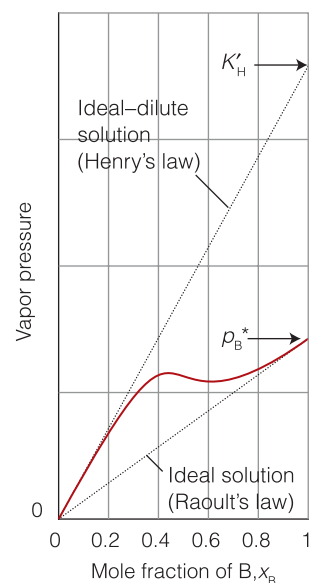


Fig. 3.28 When a component (the solvent) is almost pure, it behaves in accord with Raoult's law and has a vapor pressure that is proportional to the mole fraction in the liquid mixture and a slope p^* , the vapor pressure of the pure substance. When the same substance is the minor component (the solute), its vapor pressure is still proportional to its mole fraction, but the constant of proportionality is now K'_H .

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, however, 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**:

The vapor pressure of a volatile solute B is proportional to its mole fraction in a solution: $p_B = K'_H x_B$ (Henry's law) (3.13)

Here K'_H , which is called **Henry's law constant**, is characteristic of the solute and chosen so that the straight line predicted by eqn 3.13 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:

$$[J] = K_H p_J \quad \text{Another version of Henry's law} \quad (3.14)$$

Table 3.2 Henry's law constants for gases dissolved in water at 25°C

	$K_H / (\text{mol m}^{-3} \text{ kPa}^{-1})$
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}

The Henry's law constant, K_{H} , is commonly reported in moles per cubic metre per kilopascal ($\text{mol m}^{-3} \text{kPa}^{-1}$). 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 3.14 is used, for instance, to estimate the concentration of O_2 in natural waters or the concentration of carbon dioxide in blood plasma.

Example 3.2 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 dm^{-3} . 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 3.14), corresponds to the concentration specified.

Solution Equation 3.14 becomes

$$p_{\text{O}_2} = \frac{[\text{O}_2]}{K_{\text{H}}}$$

We note that the molar concentration of O_2 is

$$[\text{O}_2] = \frac{4.0 \times 10^{-3} \text{ g dm}^{-3}}{32 \text{ g mol}^{-1}} = \frac{4.0 \times 10^{-3} \text{ mol}}{32 \text{ dm}^3} = \frac{4.0 \times 10^{-3} \text{ mol}}{32 \times 10^{-3} \text{ m}^3} = \frac{4.0}{32} \text{ mol m}^{-3}$$

From Table 3.2, K_{H} for oxygen in water is $1.30 \times 10^{-2} \text{ mol m}^{-3} \text{kPa}^{-1}$, therefore the partial pressure needed to achieve the stated concentration is

$$p_{\text{O}_2} = \frac{(4.0/32) \text{ mol m}^{-3}}{1.30 \times 10^{-2} \text{ mol m}^{-3} \text{kPa}^{-1}} = 9.6 \text{ kPa}$$

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.

Self-test 3.6 What partial pressure of methane is needed to dissolve 21 mg of methane in 100 g of benzene at 25°C ($K'_{\text{H}} = 5.69 \times 10^4 \text{ kPa}$, for Henry's law in the form given in eqn 3.13)?

Answer: 57 kPa (4.3×10^2 Torr)

A note on good practice

The number of significant figures in the result of a calculation should not exceed the number in the data.

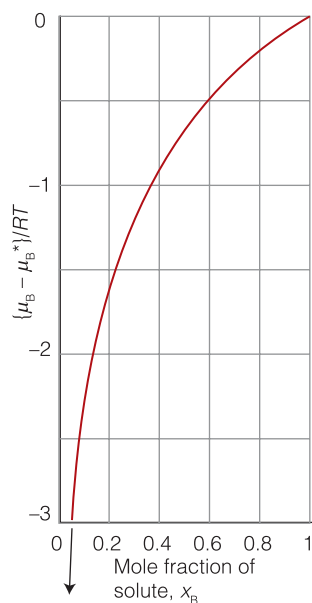


Fig. 3.29 The variation of the chemical potential of the solute with the composition of the solution expressed in terms of the mole fraction of solute. Note that the chemical potential of the solute is lower in the mixture than for the pure solute (for an ideal system). This behavior is likely to be 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. We show in the following *Justification* that the chemical potential of the solute when it is present at a mole fraction x_{B} is

$$\mu_{\text{B}} = \mu_{\text{B}}^* + RT \ln x_{\text{B}} \quad \text{Chemical potential of the solute in terms of the mole fraction} \quad (3.15)$$

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 ($x_{\text{B}} = 1$, $\ln 1 = 0$) and a smaller value when dissolved (when $x_{\text{B}} < 1$, $\ln x_{\text{B}} < 0$).

Justification 3.7 *The chemical potential of the solute*

We apply the same reasoning as in *Justification 3.6*. When a solute B in a solution is in equilibrium with its vapor at a partial pressure p_B , we can write $\mu_B(l) = \mu_B(g)$ and (from eqn 3.10)

$$\mu_B(l) = \mu_B^*(g) + RT \ln p_B$$

According to Henry's law, $p_B = K'_H x_B$, so it follows that

$$\mu_B(l) = \mu_B^*(g) + RT \ln K'_H x_B = \mu_B^*(g) + RT \ln K'_H + RT \ln x_B$$

The terms $\mu_B^*(g)$ and $RT \ln K_H$ are independent of the composition of the mixture and can be combined into the constant μ_B^* , the chemical potential of pure liquid B. Equation 3.15 then follows.

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 $x_B = \text{constant} \times [B]/c^\ominus$, where $c^\ominus = 1 \text{ mol dm}^{-3}$ is introduced to ensure that the constant is dimensionless. We shall call $c^\ominus$ the **standard molar concentration**. Then eqn 3.15 becomes

$$\mu_B = \mu_B^* + RT \ln(\text{constant}) + RT \ln([B]/c^\ominus)$$

We can combine the first two terms into a single constant, which we denote $\mu_B^\oplus$, and write this relation as

$$\mu_B = \mu_B^\oplus + RT \ln([B]/c^\ominus) \quad \text{Chemical potential of the solute in terms of the molar concentration} \quad (3.16a)$$

This equation is the best way to write the relation, but it is cumbersome, and for the rest of the chapter we shall write $[B]/c^\ominus$ simply as $[B]$ and—to conform to the requirement stated in the *note on good practice*—interpret $[B]$ as the molar concentration with the units deleted (we treated pressure similarly earlier in the chapter). Thus, if in fact $[B] = 0.1 \text{ mol dm}^{-3}$, so $[B]/c^\ominus = 0.1$, from now on we shall write $[B] = 0.1$ and use eqn 3.16a in the form

$$\mu_B = \mu_B^\oplus + RT \ln[B] \quad \text{Simplified form of eqn 3.16a} \quad (3.16b)$$

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 $c^\ominus = 1 \text{ mol dm}^{-3}$.

At this stage a summary of the results so far might be helpful:

Species	Chemical potential	Comment
Gas, J	$\mu_J = \mu_J^\ominus + RT \ln p_J$	Perfect gas
Solvent, A	$\mu_A = \mu_A^* + RT \ln x_A$	Dilute solution
Solute, B	$\mu_B = \mu_B^* + RT \ln x_B$ $\mu_B = \mu_B^\oplus + RT \ln[B]$	Dilute solution

Case study 3.2 *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

A note on good practice

It is meaningless to take logarithms of quantities with units, so always ensure that the x of $\ln x$ is a pure number.

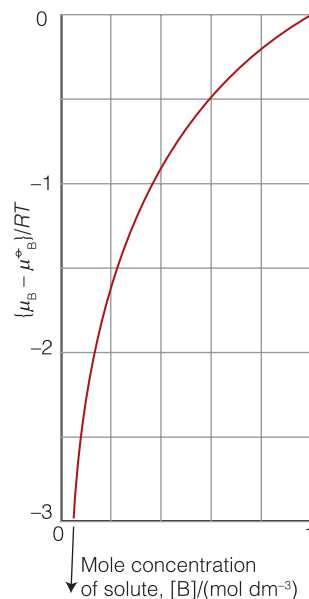


Fig. 3.30 The variation of the chemical potential of the solute with the composition of the solution that obeys Henry's law expressed in terms of the molar concentration of solute. The chemical potential has its standard value at $[B] = 1 \text{ mol dm}^{-3}$.

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 dm³, and the additional volume of air that can be exhaled forcefully after normal expiration is about 1.5 dm³. Some air remains in the lungs at all times to prevent the collapse of the alveoli.

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 is different from that in the atmosphere, and 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 in the alveoli of the lungs is about 100 Torr (13.3 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 in the alveoli of the lungs. 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.

(d) Real solutions: activities

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.² 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

$$\mu_j = \mu_j^\ominus + RT \ln a_j \quad \text{The chemical potential in terms of the activity} \quad (3.17)$$

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 3.17, $a_B = [B]/c^\ominus$, and the activity of the solute is equal to the numerical value of its molar concentration. For *non*-ideal solutions we write

$$\begin{aligned} \text{For the solvent: } a_A &= \gamma_A x_A \\ \text{For the solute: } a_B &= \gamma_B [B]/c^\ominus \end{aligned} \quad \text{The activity in terms of the activity coefficient} \quad (3.18)$$

² 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°
Solute	Molar concentration of 1 mol dm ⁻³	$[J]/c^\circ$

$p^\circ = 1 \text{ bar} (= 10^5 \text{ Pa})$, $c^\circ = 1 \text{ mol dm}^{-3}$.

*Activities are for perfect gases and ideal-dilute solutions; all activities are dimensionless.

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, $\gamma_A \rightarrow 1$ as $x_A \rightarrow 1$.

Because the solute behaves more in accord with Henry's law as the solution becomes very dilute, $\gamma_B \rightarrow 1$ as $[B] \rightarrow 0$.

Conventions concerning standard states and activities of ideal systems 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 nonideal 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.

Case study 3.3 The Donnan equilibrium

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, such as Na_vP (with P^{v-} a polyanion), 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 a situation in which a high concentration of a salt such as NaCl is added to the solution on both sides of the membrane so that the number of cations that P^{v-} 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. For simplicity, we take the volumes of the solutions on each side of the membrane to be equal.

On one side of the membrane—call it the 'left-hand' side—there are P^{v-} , Na^+ , and Cl^- ions. In the 'right-hand' side there are Na^+ and Cl^- ions. The condition

for equilibrium is that the chemical potentials of the Na^+ and Cl^- ions in solution are the same in both sides, so a net flow of Na^+ and Cl^- ions occurs until the chemical potentials are equalized. This equality occurs when

$$\begin{aligned}\mu^\circ(\text{Na}^+) + \mu^\circ(\text{Cl}^-) + RT \ln a_L(\text{Na}^+) + RT \ln a_L(\text{Cl}^-) \\ = \mu^\circ(\text{Na}^+) + \mu^\circ(\text{Cl}^-) + RT \ln a_R(\text{Na}^+) + RT \ln a_R(\text{Cl}^-)\end{aligned}$$

where the subscripts L and R refer to the left-hand and right-hand sides, respectively, separated by the membrane. It follows that

$$RT \ln a_L(\text{Na}^+)a_L(\text{Cl}^-) = RT \ln a_R(\text{Na}^+)a_R(\text{Cl}^-)$$

If we ignore activity coefficients and interpret $[\text{Na}^+]/c^\circ$ and $[\text{Cl}^-]/c^\circ$ as $[\text{Na}^+]$ and $[\text{Cl}^-]$, respectively, the two expressions are equal when $[\text{Na}^+]_L[\text{Cl}^-]_L = [\text{Na}^+]_R[\text{Cl}^-]_R$. As the Na^+ ions are supplied by the polyelectrolyte as well as the added salt, the conditions for bulk electrical neutrality lead to the charge-balance equations $[\text{Na}^+]_L = [\text{Cl}^-]_L + v[\text{P}^{v-}]$ and $[\text{Na}^+]_R = [\text{Cl}^-]_R$. We can now combine these three conditions to obtain expressions for the differences in ion concentrations across the membrane. For example, we write

$$[\text{Na}^+]_L = \frac{[\text{Na}^+]_R[\text{Cl}^-]_R}{[\text{Cl}^-]_L} = \frac{[\text{Na}^+]_R^2}{[\text{Na}^+]_L - v[\text{P}^{v-}]}$$

which rearranges to

$$[\text{Na}^+]_L^2 - [\text{Na}^+]_R^2 = v[\text{P}^{v-}][\text{Na}^+]_L$$

After applying the relation $a^2 - b^2 = (a + b)(a - b)$ and rearranging, we obtain

$$[\text{Na}^+]_L - [\text{Na}^+]_R = \frac{v[\text{P}^{v-}][\text{Na}^+]_L}{[\text{Na}^+]_L + [\text{Na}^+]_R}$$

It follows from the definition $[\text{Cl}^-] = \frac{1}{2}([\text{Cl}^-]_L + [\text{Cl}^-]_R)$ and the charge-balance equations that

$$[\text{Na}^+]_L + [\text{Na}^+]_R = [\text{Cl}^-]_L + [\text{Cl}^-]_R + v[\text{P}^{v-}] = 2[\text{Cl}^-] + v[\text{P}^{v-}]$$

Substitution of this result into the equation for $[\text{Na}^+]_L - [\text{Na}^+]_R$ leads to

$$[\text{Na}^+]_L - [\text{Na}^+]_R = \frac{v[\text{P}^{v-}][\text{Na}^+]_L}{2[\text{Cl}^-] + v[\text{P}^{v-}]} \quad (3.19a)$$

Similar manipulations lead to an equation for the difference in chloride ion concentration:

$$[\text{Cl}^-]_L - [\text{Cl}^-]_R = -\frac{v[\text{P}^{v-}][\text{Cl}^-]_L}{[\text{Cl}^-]_L + [\text{Cl}^-]_R}$$

which becomes

$$[\text{Cl}^-]_L - [\text{Cl}^-]_R = -\frac{v[\text{P}^{v-}][\text{Cl}^-]_L}{2[\text{Cl}^-]} \quad (3.19b)$$

Note that cations will dominate 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.

Example 3.3 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 side of the experimental arrangement contains a polyelectrolyte Na₆P at a concentration of 50 g dm⁻³. 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 above that the sum of the equilibrium concentrations of Na⁺ in both compartments is

$$[\text{Na}^+]_{\text{L}} + [\text{Na}^+]_{\text{R}} = 2[\text{Cl}^-] + \nu[\text{P}^{\nu-}]$$

with $[\text{Cl}^-] = 0.200 \text{ mol dm}^{-3}$, and $[\text{P}^{\nu-}]$ being calculated from the mass concentration and the molar mass of the polyanion. At this point, we have one equation and two unknowns, $[\text{Na}^+]_{\text{L}}$ and $[\text{Na}^+]_{\text{R}}$, so we use a second equation, eqn 3.19a, to solve for both Na⁺ ion concentrations. To calculate the Cl⁻ ion concentrations, we use $[\text{Cl}^-]_{\text{R}} = [\text{Na}^+]_{\text{R}}$ and $[\text{Cl}^-]_{\text{L}} = [\text{Na}^+]_{\text{L}} - \nu[\text{P}^{\nu-}]$, with $\nu = 6$.

Solution The molar concentration of the polyanion is $[\text{P}^{\nu-}] = 9.1 \times 10^{-4} \text{ mol dm}^{-3}$. It follows from eqn 3.19a that

$$[\text{Na}^+]_{\text{L}} - [\text{Na}^+]_{\text{R}} = \frac{6 \times (9.1 \times 10^{-4} \text{ mol dm}^{-3}) \times [\text{Na}^+]_{\text{L}}}{2 \times (0.200 \text{ mol dm}^{-3}) + 6 \times (9.1 \times 10^{-4} \text{ mol dm}^{-3})}$$

The sum of Na⁺ concentrations is

$$\begin{aligned} [\text{Na}^+]_{\text{L}} + [\text{Na}^+]_{\text{R}} &= 2 \times (0.200 \text{ mol dm}^{-3}) + 6 \times (9.1 \times 10^{-4} \text{ mol dm}^{-3}) \\ &= 0.405 \text{ mol dm}^{-3} \end{aligned}$$

The solutions of these two equations are

$$[\text{Na}^+]_{\text{L}} = 0.204 \text{ mol dm}^{-3} \quad [\text{Na}^+]_{\text{R}} = 0.201 \text{ mol dm}^{-3}$$

Then

$$\begin{aligned} [\text{Cl}^-]_{\text{R}} &= [\text{Na}^+]_{\text{R}} = 0.201 \text{ mol dm}^{-3} \\ [\text{Cl}^-]_{\text{L}} &= [\text{Na}^+]_{\text{L}} - 6[\text{P}^{\nu-}] = 0.199 \text{ mol dm}^{-3} \end{aligned}$$

Self-test 3.7 Repeat the calculation for 0.300 M NaCl(aq), a polyelectrolyte Na₁₀P of molar mass 33 kg mol⁻¹ at a mass concentration of 50.0 g dm⁻³.

Answer: $[\text{Na}^+]_{\text{L}} = 0.31 \text{ mol dm}^{-3}$, $[\text{Na}^+]_{\text{R}} = 0.30 \text{ mol dm}^{-3}$

(e) The thermodynamics of dissolving

We now have enough information to formulate a thermodynamic description of dissolving to form an ideal solution. As we see in the following *Justification*, when an amount n_{B} of a solute B dissolves in an amount n_{A} of a solvent A at a temperature T ,

$$\Delta G = nRT\{x_{\text{A}} \ln x_{\text{A}} + x_{\text{B}} \ln x_{\text{B}}\} \quad \text{Gibbs energy of dissolving} \quad (3.20)$$

with $n = n_{\text{A}} + n_{\text{B}}$ and the x_i the mole fractions in the mixture.

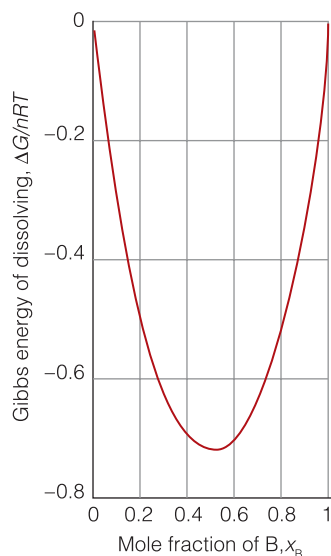


Fig. 3.31 The variation of the Gibbs energy of dissolving with composition for two components at constant temperature and pressure. Note that $\Delta G < 0$ for all compositions, which indicates that two components mix spontaneously in all proportions.

Justification 3.8 The Gibbs energy of dissolving

The Gibbs energy of the two unmixed components is the sum of their individual Gibbs energies:

$$G_i = n_A \mu_A^* + n_B \mu_B^*$$

When B is dissolved in A to form an ideal solution, the Gibbs energy becomes

$$\begin{aligned} G_f &= n_A \mu_A + n_B \mu_B = n_A \{\mu_A^* + RT \ln x_A\} + n_B \{\mu_B^* + RT \ln x_B\} \\ &= n_A \mu_A^* + n_A RT \ln x_A + n_B \mu_B^* + n_B RT \ln x_B \end{aligned}$$

where the x_i are the mole fractions of the two components in the solution. The difference $G_f - G_i$ is the change in Gibbs energy that accompanies dissolving. The pure chemical potentials cancel, so

$$\Delta G = RT \{n_A \ln x_A + n_B \ln x_B\}$$

Because $x_i = n_i/n$, we can substitute $n_A = x_A n$ and $n_B = x_B n$ into the expression above and obtain

$$\Delta G = nRT \{x_A \ln x_A + x_B \ln x_B\}$$

which is eqn 3.20.

Equation 3.20 tells us the change in Gibbs energy when a solute dissolves to give an ideal solution (Fig. 3.31). 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, *dissolving to form an ideal solution is spontaneous in all proportions*. Furthermore, if we compare eqn 3.20 with $\Delta G = \Delta H - T\Delta S$, we can conclude that:

$$\Delta H = 0 \quad \text{Enthalpy of dissolving} \quad (3.21a)$$

$$\Delta S = -nR \{x_A \ln x_A + x_B \ln x_B\} \quad \text{Entropy of dissolving} \quad (3.21b)$$

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 solution than in the unmixed components. 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 dissolving.

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 3.21 that $\Delta S > 0$ when a solute dissolves in a solvent 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.

Table 3.4 Cryoscopic and ebullioscopic constants

Solvent	$K_f/(\text{K kg mol}^{-1})$	$K_b/(\text{K kg mol}^{-1})$
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

(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.³ Thus, a 0.01 mol kg^{-1} aqueous solution of any nonelectrolyte should have the same boiling point, freezing point, and osmotic pressure.

3.9 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.

It is found empirically, and can be justified thermodynamically, that the **elevation of boiling point**, T_b , and the **depression of freezing point**, T_f , are both proportional to the molality, b_B , of the solute:

$$\Delta T_b = K_b b_B$$

Elevation of the boiling point

$$\Delta T_f = K_f b_B$$

Depression of the freezing point (3.22)

where K_b is the **ebullioscopic constant** and K_f is the **cryoscopic constant** of the solvent.⁴ 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 3.8 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.

³ Hence, the name *colligative*, meaning 'depending on the collection'.

⁴ They are also called the 'boiling-point constant' and the 'freezing-point constant'.

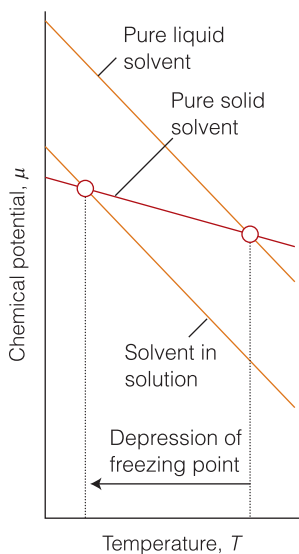


Fig. 3.32 The chemical potentials of pure solid solvent and pure liquid solvent also decrease with temperature, and the point of intersection, where the chemical potential of the liquid rises above that of the solid, marks the freezing point of the pure solvent. A solute lowers the chemical potential 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.

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 3.12. 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. 3.32 that the freezing point moves to lower values; likewise, from Fig. 3.33 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 substance 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 probably just interferes with bonding between water molecules. Likewise, the antifreeze proteins of arctic fish act by binding to small ice crystals and preventing larger crystals from forming.

Mathematical toolkit 3.2 Power series and expansions

A **power series** has the form

$$c_0 + c_1(x-a) + c_2(x-a)^2 + \dots + c_n(x-a)^n + \dots$$

$$= \sum_{n=0}^{\infty} c_n(x-a)^n$$

where c_n and a are constants. It is often useful to express a function $f(x)$ in the vicinity of $x=a$ as a special power series called the **Taylor series**, or **Taylor expansion**, which has the form

$$f(x) = f(a) + \left(\frac{df}{dx}\right)_a (x-a) + \frac{1}{2!} \left(\frac{d^2f}{dx^2}\right)_a (x-a)^2 + \dots + \frac{1}{n!} \left(\frac{d^n f}{dx^n}\right)_a (x-a)^n + \dots$$

$$= \sum_{n=0}^{\infty} \frac{1}{n!} \left(\frac{d^n f}{dx^n}\right)_a (x-a)^n$$

where $n!$ denotes a **factorial** given by $n! = n(n-1)(n-2) \dots 1$.

The following Taylor expansions are often useful:

$$(1+x)^{-1} = 1 - x + x^2 - \dots$$

$$e^x = 1 + x + \frac{1}{2}x^2 + \dots$$

$$\ln x = (x-1) - \frac{1}{2}(x-1)^2 + \frac{1}{3}(x-1)^3 - \frac{1}{4}(x-1)^4 + \dots$$

$$\ln(1+x) = x - \frac{1}{2}x^2 + \frac{1}{3}x^3 - \dots$$

If $x \ll 1$, then

$$(1+x)^{-1} \approx 1 - x$$

$$e^x \approx 1 + x$$

$$\ln(1+x) \approx x.$$

3.10 Osmosis

To understand why cells neither collapse nor burst easily, we need to explore the thermodynamics of the 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**,⁵ a membrane that is permeable to the solvent but not to the solute (Fig. 3.34). 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. 3.34, 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 *Justification* that the expression for the osmotic 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:

$$\Pi V \approx n_B RT \quad \text{van 't Hoff equation} \quad (3.23a)$$

Because $n_B/V = [B]$, the molar concentration of the solute, a simpler form of this equation is

$$\Pi \approx [B]RT \quad \text{Another version of the van 't Hoff equation} \quad (3.23b)$$

This equation applies only to solutions that are sufficiently dilute to behave as ideal–dilute solutions.

Justification 3.9 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. 3.35). 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.

⁵ The name *osmosis* is derived from the Greek word for ‘push’.

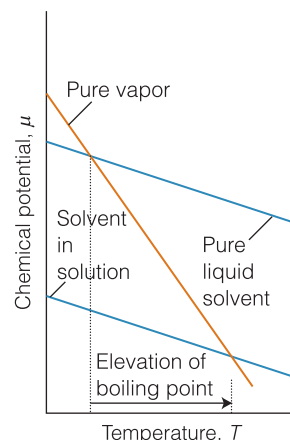


Fig. 3.33 The chemical potentials of pure solvent vapor and pure liquid solvent decrease with temperature, and the point of intersection, where the chemical potential of the vapor falls below that of the liquid, marks the boiling point of the pure solvent. A solute lowers the chemical potential of the 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.

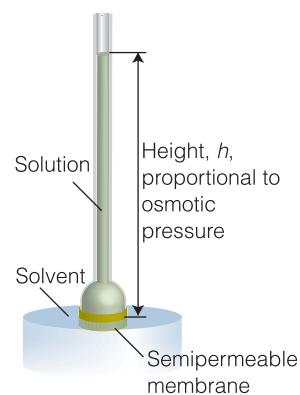


Fig. 3.34 In a simple osmosis experiment, a solution is separated from the pure solvent by a semipermeable membrane. Pure solvent passes through the membrane and the solution rises in the inner tube. The net flow ceases when the pressure exerted by the column of liquid is equal to the osmotic pressure of the solution.

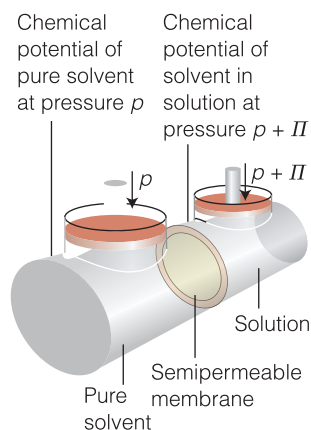


Fig. 3.35 The basis of the calculation of osmotic pressure. The presence of a solute lowers the chemical potential of the solvent in the right-hand compartment, but the application of pressure raises it. The osmotic pressure is the pressure needed to equalize the chemical potential of the solvent in the two compartments.

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 using eqn 3.12:

$$\mu_A(x_A, p + \Pi) = \mu_A^*(p + \Pi) + RT \ln x_A$$

The effect of pressure on an (assumed incompressible) liquid is given by eqn 3.1 ($G_m(p_f) = G_m(p_i) + (p_f - p_i)V_m$) but now expressed in terms of the chemical potential and the partial molar volume of the solvent:

$$\mu_A^*(p + \Pi) = \mu_A^*(p) + (p + \Pi - p)V_A = \mu_A^*(p) + \Pi V_A$$

When the last three equations are combined, we get

$$\mu_A^*(p) = \mu_A^*(p) + \Pi V_A + RT \ln x_A$$

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 $-x_B$ (see *Mathematical toolkit* 3.2), 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 3.23.

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.

In the laboratory 3.1 Osmometry

Osmometry is the determination of molar mass by the measurement of osmotic pressure. 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:

$$\Pi = [B]RT\{1 + B[B] + \dots\} \quad \text{Expanded van 't Hoff equation} \quad (3.24a)$$

The empirical parameter B in this expression is called the **osmotic virial coefficient**. To use eqn 3.24a, we rearrange it into a form that gives a straight line by dividing both sides by $[B]$:

$$\Pi/[B] = RT + BRT[B] + \dots \quad (3.24b)$$

As we illustrate in the following example, the molar mass of the solute B can be found by measuring the osmotic pressure at a series of mass concentrations and making a plot of $\Pi/[B]$ against $[B]$ (Fig. 3.36).

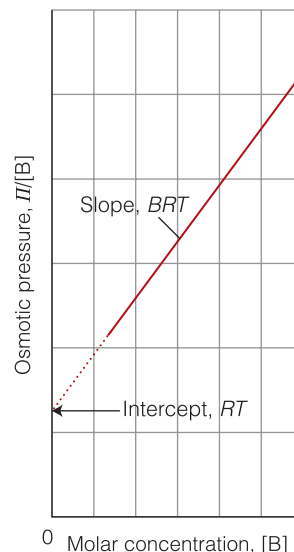


Fig. 3.36 The plot and extrapolation made to analyze the results of an osmometry experiment.

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.

$c/(\text{g dm}^{-3})$	1.00	2.00	4.00	7.00	9.00
Π/Pa	27.5	69.6	197	500	785

Strategy First, we need to express eqn 3.24b 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 ($M = m_B/n_B$), so $[B] = c_B/M$. With this substitution, eqn 3.24b becomes

$$\frac{\Pi}{c_B/M} = RT + \frac{BRTc_B}{M} + \dots$$

Division through by M gives

$$\frac{\Pi}{c_B} = \frac{RT}{M} + \left(\frac{BRT}{M^2}\right)c_B + \dots$$

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:

$c_B/(\text{g dm}^{-3})$	1.00	2.00	4.00	7.00	9.00
$(\Pi/\text{Pa})/(c_B/\text{g dm}^{-3})$	27.5	34.8	49.3	71.5	87.2

The points are plotted in Fig. 3.37. The intercept with the vertical axis at $c_B = 0$ is at

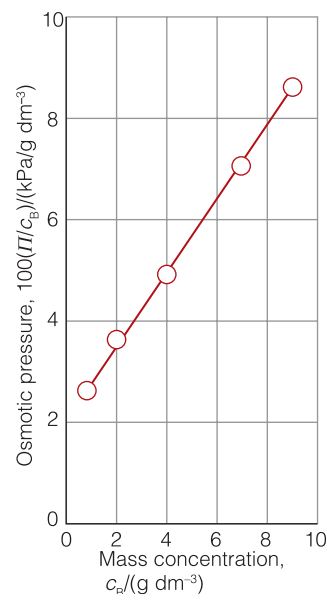


Fig. 3.37 The plot of the data in Example 3.4.

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 $c_B/(\text{g dm}^{-3})$, 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.

$$\frac{\Pi/\text{Pa}}{c_B/(\text{g dm}^{-3})} = 19.8$$

which we can rearrange into

$$\Pi/c_B = 19.8 \text{ Pa g}^{-1} \text{ dm}^3$$

Therefore, because this intercept is equal to RT/M , we can write

$$M = \frac{RT}{19.8 \text{ Pa g}^{-1} \text{ dm}^3}$$

It follows that

$$M = \frac{(8.314 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K})}{19.8 \text{ Pa g}^{-1} \text{ dm}^3} = 1.25 \times 10^5 \text{ g mol}^{-1}$$

The molar mass of the enzyme is therefore close to 125 kg mol^{-1} (corresponding to a molecular mass of 125 kDa).

Self-test 3.9

The osmotic pressures of solutions of a protein at 25°C were as follows:

$c/(\text{g dm}^{-3})$	0.50	1.00	1.50	2.00	2.50
Π/Pa	40.0	110	200	330	490

What is the molar mass of the protein?

Answer: 49 kg mol^{-1}

Checklist of key concepts

- ☐ 1. A phase diagram of a substance shows the conditions of pressure and temperature at which its various phases are most stable.
- ☐ 2. A phase boundary depicts the pressures and temperatures at which two phases are in equilibrium.
- ☐ 3. 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 triple point is the condition of pressure and temperature at which three phases are in mutual equilibrium.
- ☐ 4. A partial molar quantity is the contribution of a component (per mole) to the overall property of a mixture.
- ☐ 5. The chemical potential of a component is the partial molar Gibbs energy of that component in a mixture.
- ☐ 6. An ideal solution is one in which both components obey Raoult's law over the entire composition range.
- ☐ 7. An ideal-dilute solution is one in which the solute obeys Henry's law.
- ☐ 8. The activity of a substance is an effective concentration; see Table 3.3.
- ☐ 9. The Donnan equilibrium determines the distribution of ions between two solutions in contact through a membrane, in one of which there is a polyelectrolyte and where the membrane is not permeable to the large charged macromolecule.
- ☐ 10. A colligative property is a property that depends on the number of solute particles, not their chemical identity; it arises from the effect of a solute on the entropy of the solution.
- ☐ 11. Colligative properties include lowering of vapor pressure, depression of freezing point, elevation of boiling point, and osmotic pressure.
- ☐ 12. The molar masses of biological polymers can be determined by measurements of the osmotic pressure of their solutions.

Checklist of key equations

Property or process	Equation	Comment
Dependence of the Gibbs energy on pressure	$\Delta G_m = V_m \Delta p$ $\Delta G_m = RT \ln(p_i/p_i)$	Liquids and solids Perfect gases
Dependence of the Gibbs energy on temperature	$\Delta G_m = -S_m \Delta T$	
Clapeyron equation	$dp/dT = \Delta_{\text{trs}} H / T \Delta_{\text{trs}} V$	
Clausius–Clapeyron equation	$d \ln p / dT = \Delta_{\text{vap}} H / RT^2$	Vapor behaves as a perfect gas
Gibbs energy of a binary mixture	$G = n_A \mu_A + n_B \mu_B$	
Chemical potential	$\mu_i = \mu_i^\circ + RT \ln p_i$ $\mu_i = \mu_i^\circ + RT \ln x_i$	Perfect gas Solvent and solute in a dilute solution
Raoult's law	$p_i = x_i p_i^\circ$	For an ideal solution
Henry's law	$p_B = x_B K'_H, [B] = K_H p_B$	For an ideal–dilute solution
Elevation of the boiling point	$\Delta T_b = K_b b_B$	
Depression of the freezing point	$\Delta T_f = K_f b_B$	
van 't Hoff equation	$\Pi V \approx n_B RT$	Ideal solution

Further information

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. 3.38). 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 equilibrium, $F = 0$. This special ‘invariant condition’ can

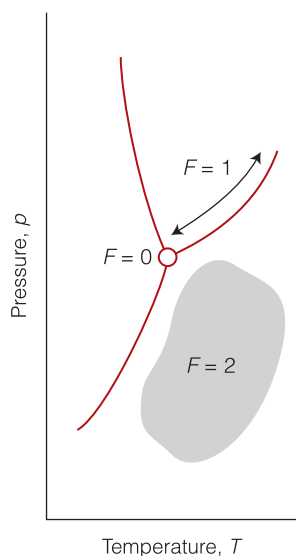


Fig. 3.38 The features of a phase diagram represent different degrees of freedom. When only one phase is present, $F=2$ and the pressure and temperature can be varied at will. When two phases are present in equilibrium, $F=1$: now if the temperature is changed, the pressure must be changed by a specific amount. When three phases are present in equilibrium, $F=0$ and there is no freedom to change either variable.

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.

Further information 3.2 Measures of concentration

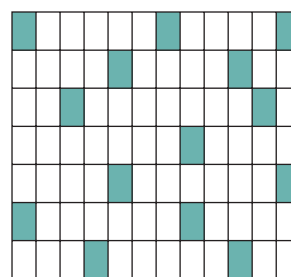
A useful measure of concentration of component J of a mixture is its **mole fraction**, the amount of J molecules expressed as a fraction of the total amount of molecules in the mixture. In a mixture that consists of n_A A molecules, n_B B molecules, and so on (where the n_j are amounts in moles), the mole fraction of J (where J = A, B, ...) is

$$x_j = \frac{n_j}{n} \quad \text{Definition of the mole fraction} \quad (3.25a)$$

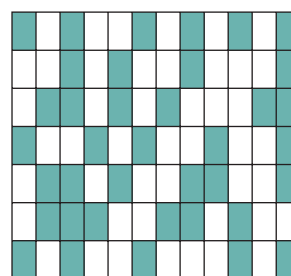
where $n = n_A + n_B + \dots$. For a **binary mixture**, one that consists of two species, this general expression becomes

$$x_A = \frac{n_A}{n_A + n_B} \quad x_B = \frac{n_B}{n_A + n_B} \quad x_A + x_B = 1 \quad (3.25b)$$

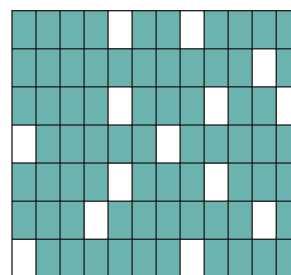
When only A is present, $x_A = 1$ and $x_B = 0$. When only B is present, $x_B = 1$ and $x_A = 0$. When both are present in the same amounts, $x_A = \frac{1}{2}$ and $x_B = \frac{1}{2}$ (Fig. 3.39).



(a) $x_A = 0.167$, $x_B = 0.833$



(b) $x_A = 0.452$, $x_B = 0.548$



(c) $x_A = 0.833$, $x_B = 0.167$

■ A □ B

Fig. 3.39 The mole fraction is an indication of the fraction of molecules in a sample that are of the specified identity. In this figure, the mole fraction x_A of component A (in blue) of a binary mixture increases from (a) 0.167, to (b) 0.452, to (c) 0.833.

Self-test 3.10 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

For any type of gas (perfect or not) in a gaseous mixture, the **partial pressure**, p_j , of the gas J is defined as

$$p_j = x_j p \quad \text{Definition of the partial pressure} \quad (3.26)$$

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.

A brief illustration

From *Self-test* 3.10, we have $x_{\text{N}_2} = 0.780$, $x_{\text{O}_2} = 0.210$, and $x_{\text{Ar}} = 0.009$ for dry air at sea level. It then follows from eqn 3.26 that when the total atmospheric pressure is 100 kPa, the partial pressure of nitrogen is $p_{\text{N}_2} = x_{\text{N}_2}p = 0.780 \times (100 \text{ kPa}) = 78.0 \text{ kPa}$. Similarly, for the other two components we find $p_{\text{O}_2} = 21.0 \text{ kPa}$ and $p_{\text{Ar}} = 0.9 \text{ kPa}$.

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:⁶

$$[J] = \frac{n_J}{V} \quad \text{Definition of the molar concentration} \quad (3.27)$$

Molar concentration is typically reported in moles per cubic decimeter (and commonly as moles per liter, mol L^{-1}). The unit 1 mol dm^{-3} 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

$$n_J = [J]V \quad (3.28)$$

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:

$$b_J = \frac{n_J}{m_{\text{solvent}}} \quad \text{Definition of molality} \quad (3.29)$$

Molality is typically reported in moles of solute per kilogram of solvent (mol kg^{-1}). This unit is sometimes (but unofficially) denoted m, with $1 \text{ m} = 1 \text{ mol kg}^{-1}$. 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 molality and molar concentration differ very little because 1 dm^3 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 cm^{-3} , 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 3.29 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 3.5 Relating mole fraction and molality

What is the mole fraction of glycine molecules in 0.140 m $\text{NH}_2\text{CH}_2\text{COOH}(\text{aq})$? 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

$$n_{\text{solvent}} = \frac{1 \text{ kg}}{M}$$

where M is the molar mass of the solvent. Once these two amounts are available, we can calculate the mole fraction by using eqn 3.25 with $n = n_J + n_{\text{solvent}}$.

Solution It follows from the discussion in the Strategy that the amount of glycine (gly) molecules in exactly 1 kg of solvent is

$$n_{\text{gly}} = (0.140 \text{ mol kg}^{-1}) \times (1 \text{ kg}) = 0.140 \text{ mol}$$

The amount of water molecules in exactly 1 kg (10^3 g) of water is

$$n_{\text{water}} = \frac{10^3 \text{ g}}{18.02 \text{ g mol}^{-1}} = \frac{10^3}{18.02} \text{ mol}$$

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 3.11 Calculate the mole fraction of sucrose molecules in 1.22 m $\text{C}_{12}\text{H}_{22}\text{O}_{11}(\text{aq})$.

Answer: 2.15×10^{-2}

⁶ Molar concentration is still widely called ‘molarity’.

Discussion questions

- 3.1** Why does the chemical potential vary with (a) temperature and (b) pressure?
- 3.2** Discuss the implications for phase stability of the variation of chemical potential with temperature and pressure.
- 3.3** State and justify the thermodynamic criterion for solution–vapor equilibrium.
- 3.4** Explain the significance of the Clapeyron equation and the Clausius–Clapeyron equation.
- 3.5** 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?
- 3.6** What is meant by the activity of a solute?
- 3.7** Explain the origin of colligative properties. Why do they not depend on the chemical identity of the solute?
- 3.8** Explain how osmometry can be used to determine the molar mass of a biological macromolecule.

Exercises

- 3.9** 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 Mindaño trench (depth 11.5 km) and (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.
- 3.10** 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 ($p = 1.0 \text{ atm}$) 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} .
- 3.11** 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 and (b) 0.000 27 atm, its partial pressure in air.
- 3.12** The standard molar entropies of water ice, liquid, and vapor are 37.99, 69.91, and $188.83 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively. On a single graph, show how the Gibbs energies of each of these phases vary with temperature.
- 3.13** An open vessel containing (a) water, (b) benzene, and (c) mercury stands in a laboratory measuring $6.0 \text{ m} \times 5.3 \text{ m} \times 3.2 \text{ m}$ at 25°C . What mass of each substance will be found in the air if there is no ventilation? (The vapor pressures are (a) 2.3 kPa, (b) 10 kPa, and (c) 0.30 Pa.)
- 3.14** (a) Use the Clapeyron equation to estimate the slope of the solid–liquid phase boundary of water given that the enthalpy of fusion is $6.008 \text{ kJ mol}^{-1}$ and the densities of ice and water at 0°C are 0.916 g cm^{-3} and 0.999 g cm^{-3} , respectively. *Hint:* Express the entropy of fusion in terms of the enthalpy of fusion and the melting point of ice. (b) Estimate the pressure required to lower the melting point of ice by 1°C .
- 3.15** (a) Use the Clausius–Clapeyron equation to show that the vapor pressure p' at a temperature T' is related to the vapor pressure p at a temperature T by
- $$\ln p' = \ln p + \frac{\Delta_{\text{vap}}H}{R} \left(\frac{1}{T} - \frac{1}{T'} \right)$$
- (b) The vapor pressure of mercury at 20°C is 160 mPa. What is its vapor pressure at 40°C given that its enthalpy of vaporization is $59.30 \text{ kJ mol}^{-1}$?
- 3.16** (a) The vapor pressures of substances are commonly reported as $\log(p/\text{kPa}) = A - B/T$, where A and B are constants. Show that the expression you derived in Exercise 3.15 reduces to this form, and write expressions for the constants A and B . (b) For benzene in the range 0 – 42°C , $A = 7.0871$ and $B = 1785 \text{ K}$. What is the enthalpy of vaporization of benzene?
- 3.17** 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?
- 3.18** (a) Refer to Fig. 3.13 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.
- 3.19** Refer to Fig. 3.13 and describe the changes that would be observed when cooling takes place at the pressure of the triple point.
- 3.20** 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, it follows that $n - 2$ 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
- $$\Delta G_m = (n - 4)\Delta_{\text{hb}}H_m - (n - 2)T\Delta_{\text{hb}}S_m$$
- where $\Delta_{\text{hb}}H_m$ and $\Delta_{\text{hb}}S_m$ 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 $(n - 4)\Delta_{\text{hb}}H_m$ and $(n - 2)\Delta_{\text{hb}}S_m$, respectively?
- (b) Show that T_m may be written as
- $$T_m = (n - 4)\Delta_{\text{hb}}H_m / (n - 2)\Delta_{\text{hb}}S_m$$

(c) Plot $T_m/(\Delta_{\text{hb}}H_m/\Delta_{\text{hb}}S_m)$ for $5 \leq n \leq 20$. At what value of n does T_m change by less than 1 per cent when n increases by one?

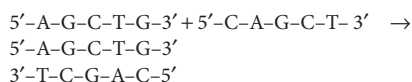
3.21 A thermodynamic treatment allows predictions of the stability of DNA. The table below lists the standard Gibbs energies, enthalpies, and entropies of formation at 298 K of short sequences of base pairs as two polynucleotide chains come together:

Sequence	5'-A-G 3'-T-C	5'-G-C 3'-C-G	5'-T-G 3'-A-C
$\Delta_{\text{seq}}G^\circ/(\text{kJ mol}^{-1})$	-5.4	-10.5	-6.7
$\Delta_{\text{seq}}H^\circ/(\text{kJ mol}^{-1})$	-25.5	-46.4	-31.0
$\Delta_{\text{seq}}S^\circ/(\text{kJ mol}^{-1})$	-67.4	-118.8	-80.8

To estimate the standard Gibbs energy of formation of a double-stranded piece of DNA, $\Delta_{\text{DNA}}G^\circ$, 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 $\Delta_{\text{init}}G^\circ = +14.2 \text{ kJ mol}^{-1}$:

$$\Delta_{\text{DNA}}G^\circ = \Delta_{\text{init}}G^\circ + \Delta_{\text{seq}}G^\circ(\text{sequences})$$

Similar procedures lead to $\Delta_{\text{DNA}}H^\circ$ and $\Delta_{\text{DNA}}S^\circ$. (a) Provide a molecular explanation for the fact that $\Delta_{\text{init}}G^\circ$ is positive and $\Delta_{\text{seq}}G^\circ$ negative. (b) Estimate the standard Gibbs energy, enthalpy, and entropy changes for the following reaction:



Use $\Delta_{\text{init}}H^\circ = +2.5 \text{ kJ mol}^{-1}$ and $\Delta_{\text{init}}S^\circ = -37.7 \text{ J K}^{-1} \text{ mol}^{-1}$. (c) Estimate the 'melting' temperature of the piece of DNA shown in part (b).

3.22 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?

3.23 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.

3.24 Calculate the mass of glucose you should use to prepare (a) 250.0 cm³ of 0.112 M C₆H₁₂O₆(aq) and (b) 0.112 M C₆H₁₂O₆(aq) using 250.0 g of water.

3.25 What is the mole fraction of alanine in 0.134 M CH₃CH(NH₂)COOH(aq)?

3.26 What mass of sucrose, C₁₂H₂₂O₁₁, should you dissolve in 100.0 g of water to obtain a solution in which the mole fraction of C₁₂H₂₂O₁₁ is 0.124?

3.27 Calculate (a) the (molar) Gibbs energy of mixing and (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 N₂ and O₂ are 0.78 and 0.22, respectively. Is the mixing spontaneous?

3.28 Suppose now that argon is added to the mixture in Exercise 3.27 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?

3.29 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.

3.30 Hemoglobin, the red blood protein responsible for oxygen transport, binds about 1.34 cm³ of oxygen per gram. Normal blood has a hemoglobin concentration of 150 g dm⁻³. Hemoglobin in the lungs is about 97 per cent saturated with oxygen but in the capillary is only about 75 per cent saturated. What volume of oxygen is given up by 100 cm³ of blood flowing from the lungs in the capillary?

3.31 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 H₂O 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 per cent N₂.) (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?

3.32 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.

3.33 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 CO₂ in water at 25°C when its partial pressure is (a) 4.0 kPa and (b) 100 kPa.

3.34 The mole fractions of N₂ and O₂ 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.

3.35 Estimate the freezing point of 150 cm³ of water sweetened with 7.5 g of sucrose.

3.36 A compound A existed in equilibrium with its dimer, A₂, 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 A₂ molecules regardless of their chemical identities.

3.37 The osmotic pressure of an aqueous solution of urea at 300 K is 120 kPa. Calculate the freezing point of the same solution.

3.38 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:

$c/(\text{mg cm}^{-3})$	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 3.24 in terms of the height of the solution by using $\Pi = \rho gh$; take $\rho = 1.000 \text{ g cm}^{-3}$.

Projects

3.39 We now explore further the use of temperature–composition diagrams in the study of biological systems.

(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) Consider Fig. 3.19. (i) Is the molten globule form ever stable when the denaturant concentration is below the level marked x ? (ii) Describe what happens to the polymer as the native form is heated in the presence of denaturant at concentration y .

(c) In an experimental study of membrane-like assemblies, a phase diagram like that shown in Fig. 3.40 was obtained. The two components are dielaidoylphosphatidylcholine (DEL) and dipalmitoylphosphatidylcholine (DPL). Explain what happens as a liquid mixture of composition $x_{\text{DPL}} = 0.5$ is cooled from 45°C.

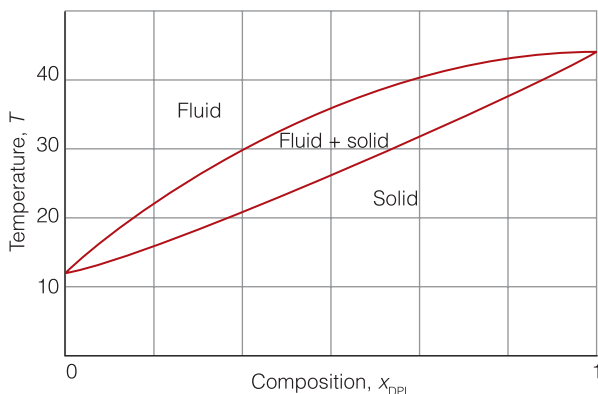


Fig. 3.40

3.40 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 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 $[A]_{\text{in}}$. This total concentration is the sum of the concentrations of free A and bound A , which we write $[A]_{\text{free}}$ and $[A]_{\text{bound}}$, respectively. At equilibrium, $\mu_{A,\text{free}} = \mu_{A,\text{out}}$, which implies that $[A]_{\text{free}} = [A]_{\text{out}}$, 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 $[A]_{\text{in}} - [A]_{\text{free}} = [A]_{\text{in}} - [A]_{\text{out}}$, 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

$$\nu = \frac{[A]_{\text{bound}}}{[M]} = \frac{[A]_{\text{in}} - [A]_{\text{out}}}{[M]}$$

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

$$K = \frac{[MA]}{[M]_{\text{free}}[A]_{\text{free}}}$$

Now show that

$$K = \frac{\nu}{(1 - \nu)[A]_{\text{out}}}$$

(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*:

$$\frac{\nu}{[A]_{\text{out}}} = KN - K\nu$$

(c) The Scatchard equation implies that a plot of $\nu/[A]_{\text{out}}$ 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 $1.00 \times 10^{-6} \text{ mol dm}^{-3}$ 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]/($\mu\text{mol dm}^{-3}$)					
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

$$\frac{\nu}{[A]_{\text{out}}} = \sum_i \frac{N_i K_i}{1 + K_i [A]_{\text{out}}}$$

Plot $\nu/[A]$ for the following cases. (i) There are four independent sites on an enzyme molecule and the equilibrium constant is $K = 1.0 \times 10^7$. (ii) 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 .

Chemical equilibrium

4



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; the attainment of equilibrium is death. 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. One very important feature of life is that one reaction can drive another in a vast web of processes. Broadly speaking, that is why we have to eat. We shall see later in the chapter how thermodynamics can be used to assess the ability of one reaction to drive another.

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.

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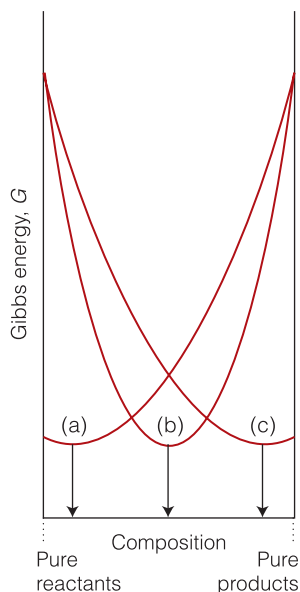
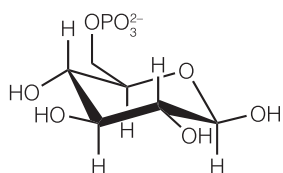
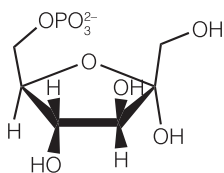


Fig. 4.1 The variation of Gibbs energy of a reaction mixture with progress of the reaction, pure reactants on the left and pure products on the right. (a) This reaction ‘does not go’: the minimum in the Gibbs energy occurs very close to the reactants. (b) This reaction reaches equilibrium with approximately 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

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 (*Case study 4.3*):



The second is the binding of $\text{O}_2(\text{g})$ to the protein hemoglobin, Hb, in blood:



These two reactions are specific examples of a general reaction of the form



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 $-dn$. As a result of this change in amount, the contribution of G6P to the total Gibbs energy of the system changes by $-\mu_{\text{G6P}}dn$, 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 $+dn$, so its contribution to the total Gibbs energy changes by $+\mu_{\text{F6P}}dn$, where μ_{F6P} is the chemical potential of F6P. The change in Gibbs energy of the system is

$$dG = \mu_{\text{F6P}}dn - \mu_{\text{G6P}}dn$$

On dividing through by dn , we obtain the **reaction Gibbs energy**, $\Delta_r G$:

$$\frac{dG}{dn} = \mu_{\text{F6P}} - \mu_{\text{G6P}} = \Delta_r G \quad (4.1a)$$

There are two ways to interpret $\Delta_r G$. First, it is the difference of the chemical potentials of the products and reactants *at the current composition of the reaction mixture*. Second, we can think of $\Delta_r G$ as the derivative of G with respect to n , which is the slope of the graph of G plotted against the changing composition of the system (Fig. 4.2). As we see from the illustration, that slope changes as the reaction proceeds because the two chemical potentials change as the composition of the reaction mixture changes.

The binding of oxygen to hemoglobin provides a slightly more complicated example. When the amount of Hb changes by $-dn$, from the reaction stoichiometry the change in the amount of O_2 is $-4dn$ and the change in the amount of $\text{Hb(O}_2)_4$ is $+dn$. The overall change in the Gibbs energy of the mixture is therefore

$$\begin{aligned} dG &= \mu_{\text{Hb(O}_2)_4} \times dn - \mu_{\text{Hb}} \times dn - \mu_{\text{O}_2} \times 4dn \\ &= (\mu_{\text{Hb(O}_2)_4} - \mu_{\text{Hb}} - 4\mu_{\text{O}_2})dn \end{aligned}$$

where the μ_i are the chemical potentials of the species in the reaction mixture. In this case, therefore, the reaction Gibbs energy is

$$\Delta_r G = \frac{dG}{dn} = \mu_{\text{Hb(O}_2)_4} - \mu_{\text{Hb}} - 4\mu_{\text{O}_2} \quad (4.1b)$$

Note that each chemical potential is multiplied by the corresponding stoichiometric coefficient and that reactants are subtracted from products. For the general reaction C,

$$\Delta_r G = (c\mu_C + d\mu_D) - (a\mu_A + b\mu_B) \quad \text{Gibbs energy of reaction} \quad (4.1c)$$

where the chemical potentials are those for each substance at the current composition of the mixture.

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 slope 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*

$$\Delta_r G = 0 \quad \text{Criterion of chemical equilibrium} \quad (4.2)$$

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.

Our starting point is the general expression for the composition dependence of the chemical potential derived in Section 3.8:

$$\mu_J = \mu_J^\circ + RT \ln a_J \quad \text{Chemical potential of a species J} \quad (4.3)$$

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, $a_J = [J]/c^\circ$, the molar concentration of J relative to the standard value $c^\circ = 1 \text{ mol dm}^{-3}$.

For perfect gases, $a_J = p_J/p^\circ$, the partial pressure of J relative to the standard pressure $p^\circ = 1 \text{ bar}$.

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° and p° explicitly.

(a) The reaction quotient

Substitution of eqn 4.3 into eqn 4.1c gives

$$\begin{aligned} \Delta_r G &= \{c(\mu_C^\circ + RT \ln a_C) + d(\mu_D^\circ + RT \ln a_D)\} \\ &\quad - \{a(\mu_A^\circ + RT \ln a_A) + b(\mu_B^\circ + RT \ln a_B)\} \\ &= \{c\mu_C^\circ + d\mu_D^\circ - (a\mu_A^\circ + b\mu_B^\circ)\} \\ &\quad + RT\{c \ln a_C + d \ln a_D - a \ln a_A - b \ln a_B\} \end{aligned}$$

The first term on the right in the second equality is the **standard reaction Gibbs energy**, $\Delta_r G^\circ$:

$$\Delta_r G^\circ = \{c\mu_C^\circ + d\mu_D^\circ\} - \{a\mu_A^\circ + b\mu_B^\circ\} \quad (4.4a)$$

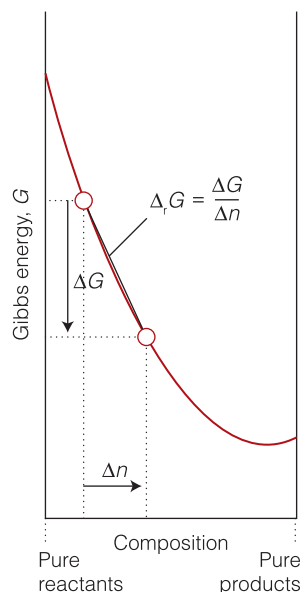


Fig. 4.2 The variation of Gibbs energy with progress of reaction showing how the reaction Gibbs energy, $\Delta_r G$, is related to the slope of the curve at a given composition. When ΔG and Δn are both infinitesimal, the slope is written dG/dn .

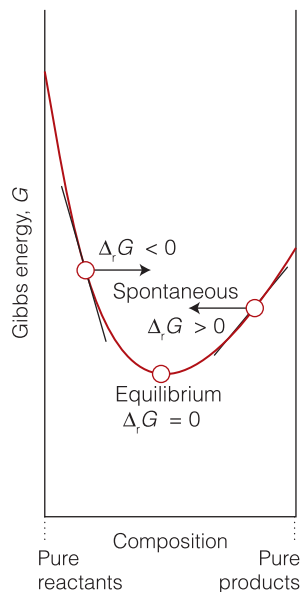


Fig. 4.3 At the minimum of the curve, corresponding to equilibrium, $\Delta_r G = 0$. To the left of the minimum, $\Delta_r G < 0$, and the forward reaction is spontaneous. To the right of the minimum, $\Delta_r G > 0$, and the reverse reaction is spontaneous.

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

$$\Delta_r G^\circ = \{cG_m^\circ(C) + dG_m^\circ(D)\} - \{aG_m^\circ(A) + bG_m^\circ(B)\} \quad \text{Standard Gibbs energy of reaction} \quad (4.4b)$$

We consider this important quantity in more detail shortly. At this stage, therefore, we know that

$$\Delta_r G = \Delta_r G^\circ + RT\{c \ln a_C + d \ln a_D - a \ln a_A - b \ln a_B\}$$

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:

$$\begin{aligned} c \ln a_C + d \ln a_D - a \ln a_A - b \ln a_B &= \ln a_C^c + \ln a_D^d - \ln a_A^a - \ln a_B^b \\ &= \ln a_C^c a_D^d - \ln a_A^a a_B^b = \ln \frac{a_C^c a_D^d}{a_A^a a_B^b} \end{aligned}$$

At this point, we have deduced that

$$\Delta_r G = \Delta_r G^\circ + RT \ln \frac{a_C^c a_D^d}{a_A^a a_B^b} \quad (4.5)$$

To simplify the appearance of this expression still further, we introduce the (dimensionless) **reaction quotient**, Q , for reaction C:

$$Q = \frac{a_C^c a_D^d}{a_A^a a_B^b} \quad \text{Definition of reaction quotient} \quad (4.6)$$

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; because activities are dimensionless quantities, Q is a dimensionless quantity. We can now write the overall expression for the reaction Gibbs energy at any composition of the reaction mixture as

$$\Delta_r G = \Delta_r G^\circ + RT \ln Q \quad \text{Reaction Gibbs energy} \quad (4.7)$$

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 4.6 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

$$Q = \frac{a_{\text{F6P}}}{a_{\text{G6P}}} = \frac{[\text{F6P}]/c^\ominus}{[\text{G6P}]/c^\ominus} = \frac{[\text{F6P}]}{[\text{G6P}]}$$

For reaction B, the binding of oxygen to hemoglobin, the reaction quotient is

$$Q = \frac{a_{\text{Hb}(\text{O}_2)_4}}{a_{\text{Hb}} a_{\text{O}_2}^4} = \frac{[\text{Hb}(\text{O}_2)_4]/c^\ominus}{([\text{Hb}]/c^\ominus)(p_{\text{O}_2}/p^\ominus)^4}$$

Because we are not writing the standard concentration and pressure explicitly, this expression simplifies to

$$Q = \frac{[\text{Hb}(\text{O}_2)_4]}{[\text{Hb}] p_{\text{O}_2}^4}$$

with p_j the numerical value of the partial pressure of J in bar (so if $p_{\text{O}_2} = 2.0$ bar, we just write $p_{\text{O}_2} = 2.0$ when using this expression).

Self-test 4.1 Write the reaction quotient for the esterification reaction $\text{CH}_3\text{COOH} + \text{C}_2\text{H}_5\text{OH} \rightarrow \text{CH}_3\text{COOC}_2\text{H}_5 + \text{H}_2\text{O}$. (All four components are present in the reaction mixture as liquids: the mixture is not an aqueous solution.)

Answer: $Q \approx [\text{CH}_3\text{COOC}_2\text{H}_5][\text{H}_2\text{O}]/[\text{CH}_3\text{COOH}][\text{C}_2\text{H}_5\text{OH}]$

(b) Biological standard states

The thermodynamic definition of standard states of solutes takes them as being at unit activity (in elementary work, at $c^\ominus = 1 \text{ mol dm}^{-3}$). The conventional standard state of hydrogen ions ($a_{\text{H}^+} = 1$, corresponding to $\text{pH} = 0$, 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 $\text{pH} = 7$, a neutral solution. When we adopt this convention we label the corresponding standard quantities as $G^\oplus$, $H^\oplus$, and $S^\oplus$.¹ Equation 4.8 allows us to relate the two standard Gibbs energies of formation.

For a reaction of the form



the biological and thermodynamic standard states are related by

$$\Delta_r G^\oplus = \Delta_r G^\ominus - RT \ln(10^{-7})^\nu = \Delta_r G^\ominus + 7\nu RT \ln 10 \quad (4.8)$$

Relation between standard values

where we have used the relations $(x^a)^b = x^{ab}$ and $\ln x^{ab} = ab \ln x$. It follows that

$$\text{at } 298.15 \text{ K:} \quad \Delta_r G^\oplus = \Delta_r G^\ominus + \nu(39.96 \text{ kJ mol}^{-1})$$

$$\text{at } 37^\circ\text{C} (310 \text{ K, body temperature):} \quad \Delta_r G^\oplus = \Delta_r G^\ominus + \nu(41.5 \text{ kJ mol}^{-1})$$

There is no difference between thermodynamic and biological standard values if hydrogen ions are not involved in the reaction ($\nu = 0$).

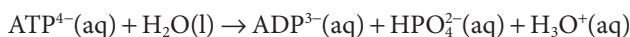
¹ Another convention to denote the biological standard state is to write $X^{\circ'}$ or $X^{\circ\prime}$.

Example 4.2*Converting between thermodynamic and biological standard states*

The standard reaction Gibbs energy for the hydrolysis of ATP is $+10 \text{ kJ mol}^{-1}$ at 298 K. What is the biological standard state value?

Strategy Because protons occur as products, lowering their concentration (from 1 mol dm^{-3} to $10^{-7} \text{ mol dm}^{-3}$) 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 4.8, 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 $10^{-7} \text{ mol dm}^{-3}$, is

$$Q = \frac{a_{\text{ADP}^{3-}} a_{\text{HPO}_4^{2-}} a_{\text{H}_3\text{O}^+}}{a_{\text{ATP}^{4-}} a_{\text{H}_2\text{O}}} = \frac{1 \times 1 \times 10^{-7}}{1 \times 1} = 10^{-7}$$

The thermodynamic and biological standard values are therefore related by eqn 4.8 in the form

$$\Delta_r G^\oplus = \Delta_r G^\ominus + RT \ln(10^{-7})$$

At 298 K

$$\begin{aligned} \Delta_r G^\oplus &= 10 \text{ kJ mol}^{-1} + (8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K}) \times \ln(10^{-7}) \\ &= 10 \text{ kJ mol}^{-1} - 40 \text{ kJ mol}^{-1} \\ &= -30 \text{ kJ mol}^{-1} \end{aligned}$$

Note how the large change in pH changes the sign of the standard reaction Gibbs energy.

Self-test 4.2

The overall reaction for the glycolysis reaction (*Case study 4.3*) is $\text{C}_6\text{H}_{12}\text{O}_6(\text{aq}) + 2 \text{ NAD}^+(\text{aq}) + 2 \text{ ADP}^{3-}(\text{aq}) + 2 \text{ HPO}_4^{2-}(\text{aq}) + 2 \text{ H}_2\text{O}(\text{l}) \rightarrow 2 \text{ CH}_3\text{COCO}_2^-(\text{aq}) + 2 \text{ NADH}(\text{aq}) + 2 \text{ ATP}^{4-}(\text{aq}) + 2 \text{ H}_3\text{O}^+(\text{aq})$. For this reaction, $\Delta_r G^\ominus = -80.6 \text{ kJ mol}^{-1}$ at 298 K. What is the value of $\Delta_r G^\oplus$?

Answer: -0.7 kJ mol^{-1}

4.3 Reactions at equilibrium

We need to be able to identify the equilibrium composition of a reaction so that we can discuss the approach to equilibrium systematically.

At equilibrium, the reaction quotient has a certain (dimensionless) value called the **equilibrium constant**, K , of the reaction:

$$K = \left(\frac{a_{\text{C}}^c a_{\text{D}}^d}{a_{\text{A}}^a a_{\text{B}}^b} \right)_{\text{equilibrium}} \quad \text{Definition of equilibrium constant} \quad (4.9)$$

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 4.7 that at equilibrium

$$0 = \Delta_r G^\ominus + RT \ln K$$

and therefore that

$$\Delta_r G^\ominus = -RT \ln K \quad \text{Expression for calculating an equilibrium constant} \quad (4.10a)$$

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 *Resource section*. Alternatively, we can use it to determine $\Delta_r G^\ominus$ by measuring the equilibrium constant of a reaction.

A brief illustration

The first step in the metabolic breakdown of glucose is its phosphorylation to G6P:



The standard reaction Gibbs energy for the reaction is -34 kJ mol^{-1} at 37°C , so it follows from eqn 4.10a that

$$\ln K = -\frac{\Delta_r G^\ominus}{RT} = -\frac{(-3.4 \times 10^4 \text{ J mol}^{-1})}{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (310 \text{ K})} = \frac{3.4 \times 10^4}{8.3145 \times 310}$$

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 $x = K$:

$$K = e^{3.4 \times 10^4 / 8.3145 \times 310} = 5.4 \times 10^5$$

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 4.3 Calculate the equilibrium constant of the reaction $\text{N}_2(\text{g}) + 3 \text{H}_2(\text{g}) \rightleftharpoons 2 \text{NH}_3(\text{g})$ at 25°C , given that $\Delta_r G^\ominus = -32.90 \text{ kJ mol}^{-1}$.

Answer: 5.8×10^5

If the biological standard state is used in place of the thermodynamic standard state, we write eqn 4.10a in the same way,

$$\Delta_r G^\oplus = -RT \ln K \quad \text{Expression for calculating an equilibrium constant} \quad (4.10b)$$

but interpret the concentration of any hydronium ions that occurs in K as relative to $c^\oplus = 10^{-7} \text{ mol dm}^{-3}$ rather than relative to $c^\ominus = 1 \text{ mol dm}^{-3}$. That is, we interpret the activity of hydronium ions in the expression for K as $a_{\text{H}_3\text{O}^+} = [\text{H}_3\text{O}^+]/c^\oplus$.

A brief illustration

The biological standard reaction Gibbs energy for the reaction in the preceding brief illustration is $-75.5 \text{ kJ mol}^{-1}$. The same calculation illustrated there but with this value gives $K' = 5.3 \times 10^{12}$. This value is for

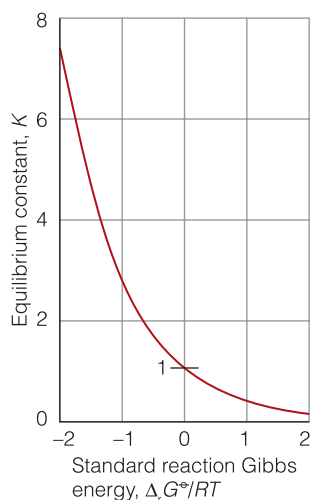


Fig. 4.4 The relation between standard reaction Gibbs energy and the equilibrium constant of the reaction.

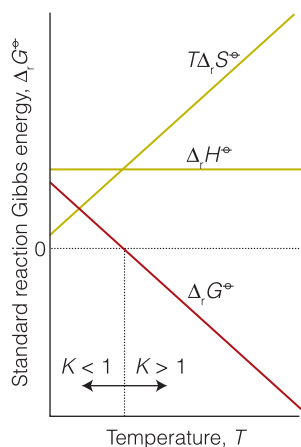


Fig. 4.5 An endothermic reaction may have $K > 1$ provided the temperature is high enough for $T\Delta_r S^\circ$ to be large enough that, when subtracted from $\Delta_r H^\circ$, the result is negative.

$$K' = \frac{[\text{G6P}][\text{ADP}]([\text{H}_3\text{O}^+]/10^{-7})}{[\text{glucose}][\text{ATP}]} = 5.3 \times 10^{12}$$

whereas the former value was for

$$K = \frac{[\text{glucose}][\text{ADP}][\text{H}_3\text{O}^+]}{[\text{F6P}][\text{ATP}]} = 5.4 \times 10^5$$

Multiplication of both sides of the first equation of this pair by 10^{-7} gives a result in accord with the second equation.

(a) The significance of the equilibrium constant

An important feature of eqn 4.10a is that it tells us that $K > 1$ if $\Delta_r G^\circ < 0$ (and correspondingly that $K' > 1$ if $\Delta_r G^\oplus < 0$). Broadly speaking, $K > 1$ implies that products are dominant at equilibrium, so we can conclude that *a reaction is thermodynamically feasible if $\Delta_r G^\circ < 0$* (Fig. 4.4). Conversely, because eqn 4.10a tells us that $K < 1$ if $\Delta_r G^\circ > 0$, then we know that the reactants will be dominant in a reaction mixture at equilibrium if $\Delta_r G^\circ > 0$. In other words, *a reaction with $\Delta_r G^\circ > 0$ 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 $K \gg 1$ (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 $\Delta_r G^\circ < 0$ and $K > 1$. Because $\Delta_r G^\circ = \Delta_r H^\circ - T\Delta_r S^\circ$, the standard reaction Gibbs energy is certainly negative if both $\Delta_r H^\circ < 0$ (an exothermic reaction) and $\Delta_r S^\circ > 0$ (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 ($\Delta_r H^\circ > 0$) and $T\Delta_r S^\circ$ is sufficiently large and positive. Note that for an endothermic reaction to have $\Delta_r G^\circ < 0$, its standard reaction entropy *must* be positive. Moreover, the temperature must be high enough for $T\Delta_r S^\circ$ to be greater than $\Delta_r H^\circ$ (Fig. 4.5). The switch of $\Delta_r G^\circ$ 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 $\Delta_r H^\circ - T\Delta_r S^\circ$ to 0, which gives

$$T = \frac{\Delta_r H^\circ}{\Delta_r S^\circ} \quad \text{Temperature at which an endothermic reaction becomes spontaneous} \quad (4.11)$$

Table 4.1 Thermodynamic criteria of spontaneity

1. If the reaction is exothermic ($\Delta_r H^\circ < 0$) and $\Delta_r S^\circ > 0$
 $\Delta_r G^\circ < 0$ and $K > 1$ at all temperatures
2. If the reaction is exothermic ($\Delta_r H^\circ < 0$) and $\Delta_r S^\circ < 0$
 $\Delta_r G^\circ < 0$ and $K > 1$ provided that $T < \Delta_r H^\circ / \Delta_r S^\circ$
3. If the reaction is endothermic ($\Delta_r H^\circ > 0$) and $\Delta_r S^\circ > 0$
 $\Delta_r G^\circ < 0$ and $K > 1$ provided that $T > \Delta_r H^\circ / \Delta_r S^\circ$
4. If the reaction is endothermic ($\Delta_r H^\circ > 0$) and $\Delta_r S^\circ < 0$
 $\Delta_r G^\circ < 0$ and $K > 1$ at no temperature

Self-test 4.4 Suppose that the enthalpy change accompanying the dissociation of base pairs is of the order of +15 kJ per mole of base pairs and the corresponding entropy change is 45 J K⁻¹ mol⁻¹. At what temperature can you expect a DNA chain to denature spontaneously?

Answer: 60°C

(b) The composition at equilibrium

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 4.3 Calculating an equilibrium composition

Consider reaction A, for which $\Delta_r G^\circ = +1.7 \text{ kJ mol}^{-1}$ 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 $[\text{G6P}]$; then the ratios $[\text{F6P}]/[\text{G6P}]$ can be replaced by K . Calculate the value of K by using eqn 4.10a.

Solution Division of the numerator and denominator by $[\text{G6P}]$ gives

$$f = \frac{[\text{F6P}]/[\text{G6P}]}{[\text{F6P}]/[\text{G6P}] + 1} = \frac{K}{K + 1}$$

We find the equilibrium constant by rearranging eqn 4.10a into

$$K = e^{-\Delta_r G^\circ / RT}$$

with

$$\frac{\Delta_r G^\circ}{RT} = \frac{1.7 \times 10^3 \text{ J mol}^{-1}}{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K})} = \frac{1.7 \times 10^3}{8.3145 \times 298}$$

Therefore,

$$K = e^{-1.7 \times 10^3 / 8.3145 \times 298} = 0.50$$

and

$$f = \frac{0.50}{0.50 + 1} = 0.33$$

That is, at equilibrium, 33 per cent of the solute is F6P and 67 per cent is G6P.

Self-test 4.5 Estimate the composition of a solution in which two isomers A and B are in equilibrium ($A \rightleftharpoons B$) at 37°C and $\Delta_r G^\circ = -2.2 \text{ kJ mol}^{-1}$.

Answer: The fraction of B at equilibrium is $f_{\text{eq}} = 0.70$.

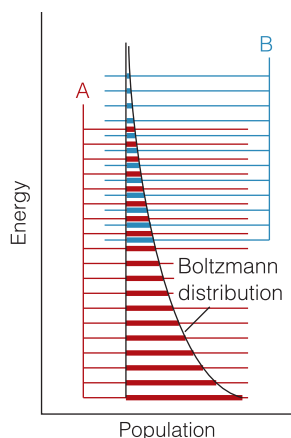


Fig. 4.6 The Boltzmann distribution of populations over the energy levels of two species A and B with similar densities of energy levels; the reaction $A \rightarrow B$ is endothermic in this example. The bulk of the population is associated with the species A, so that species is dominant at equilibrium.

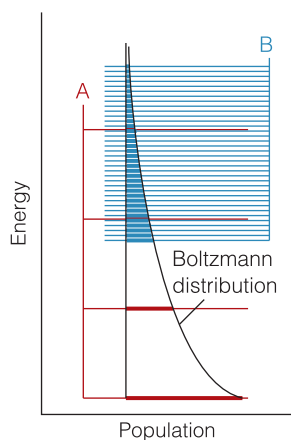


Fig. 4.7 Even though the reaction $A \rightarrow B$ is endothermic, the density of energy levels in B is so much greater than that in A, the population associated with B is greater than that associated with A; hence B is dominant at equilibrium.

(c) The molecular origin of chemical equilibrium

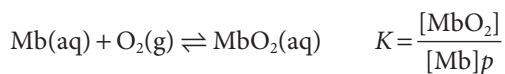
We can obtain a deeper insight into the origin and significance of the equilibrium constant by considering the Boltzmann distribution of molecules over the available states of a system composed of reactants and products. When atoms can exchange partners, as in a chemical reaction, the available states of the system include arrangements in which the atoms are present in the form of reactants and other atoms are present in the form of products. These arrangements have their characteristic sets of energy levels, but the Boltzmann distribution does not distinguish between their identities, only their energies. The atoms distribute themselves over both sets of energy levels in accord with the Boltzmann distribution (Fig. 4.6). At a given temperature, there is a specific distribution of populations and hence a specific composition of the reaction mixture.

It can be appreciated from Fig. 4.6 that if the reactants and products both have similar arrays of molecular energy levels, then the dominant species in a reaction mixture at equilibrium will be the species with the lower set of energy levels. However, the fact that the equilibrium constant is related to the *Gibbs* energy (through $\ln K = -\Delta_r G^\circ/RT$) is a signal that entropy plays a role as well as energy. Its role can be appreciated by referring to Fig. 4.7. We see that although the B energy levels lie higher than the A energy levels, in this instance they are much more closely spaced. As a result, their total population may be considerable and B could even dominate in the reaction mixture at equilibrium. Closely spaced energy levels correlate with a high entropy, so in this case we see that entropy effects dominate adverse energy effects. That is, a positive reaction enthalpy results in a lowering of the equilibrium constant (that is, an endothermic reaction can be expected to have an equilibrium composition that favors the reactants). However, if there is positive reaction entropy, then the equilibrium composition may favor products, despite the endothermic character of the reaction.

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, Atlas P10) stores O_2 in muscle, and the protein hemoglobin (Hb, Atlas P7) transports O_2 in blood. These two proteins are related, for hemoglobin is a tetramer of four myoglobin-like molecules. In each protein, the O_2 molecule attaches to an iron ion in a heme group (Atlas R2) (Fig. 4.8).

First, consider the equilibrium between Mb and O_2 :

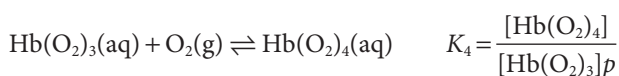
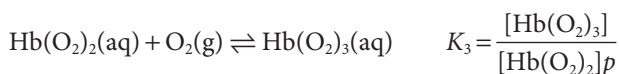
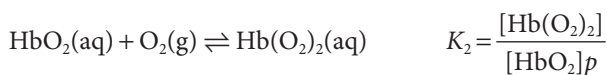
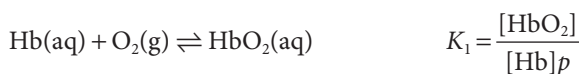


where p is the numerical value of the partial pressure of O_2 gas in bar. It follows that the *fractional saturation*, s , the fraction of Mb molecules that are oxygenated, is

$$s = \frac{[\text{MbO}_2]}{[\text{Mb}]_{\text{total}}} = \frac{[\text{MbO}_2]}{[\text{Mb}] + [\text{MbO}_2]} = \frac{Kp}{1 + Kp} \quad \text{Fractional saturation of myoglobin} \quad (4.12)$$

The dependence of s on p is shown in Fig. 4.9.

Now consider the equilibrium between Hb and O₂:



To develop an expression for s , we express $[\text{Hb(O}_2)_2]$ in terms of $[\text{HbO}_2]$ by using K_2 , then express $[\text{HbO}_2]$ in terms of $[\text{Hb}]$ by using K_1 , and likewise for all the other concentrations of $\text{Hb(O}_2)_3$ and $\text{Hb(O}_2)_4$. It follows that

$$\begin{aligned} [\text{HbO}_2] &= K_1[\text{Hb}]p & [\text{Hb(O}_2)_2] &= K_1K_2[\text{Hb}]p^2 \\ [\text{Hb(O}_2)_3] &= K_1K_2K_3[\text{Hb}]p^3 & [\text{Hb(O}_2)_4] &= K_1K_2K_3K_4[\text{Hb}]p^4 \end{aligned}$$

The total concentration of bound O₂ is

$$\begin{aligned} [\text{O}_2]_{\text{bound}} &= [\text{HbO}_2] + 2[\text{Hb(O}_2)_2] + 3[\text{Hb(O}_2)_3] + 4[\text{Hb(O}_2)_4] \\ &= (1 + 2K_2p + 3K_2K_3p^2 + 4K_2K_3K_4p^3)K_1[\text{Hb}]p \end{aligned}$$

where we have used the fact that n O₂ molecules are bound in $\text{Hb(O}_2)_n$, so the concentration of bound O₂ in $\text{Hb(O}_2)_2$ is $2[\text{Hb(O}_2)_2]$, and so on. The total concentration of hemoglobin is

$$[\text{Hb}]_{\text{total}} = (1 + K_1p + K_1K_2p^2 + K_1K_2K_3p^3 + K_1K_2K_3K_4p^4)[\text{Hb}]$$

Because each Hb molecule has four sites at which O₂ can attach, the fractional saturation is

$$\begin{aligned} s &= \frac{[\text{O}_2]_{\text{bound}}}{4[\text{Hb}]_{\text{total}}} \\ &= \frac{(1 + 2K_2p + 3K_2K_3p^2 + 4K_2K_3K_4p^3)K_1p}{4(1 + K_1p + K_1K_2p^2 + K_1K_2K_3p^3 + K_1K_2K_3K_4p^4)} \end{aligned} \quad \text{Fractional saturation of hemoglobin} \quad (4.13)$$

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 O₂ to hemoglobin is an example of **cooperative binding**, in which the binding of a ligand (in this case O₂) 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. 4.9. 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 O₂ by hemoglobin is explained by an **allosteric effect**, in 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*.

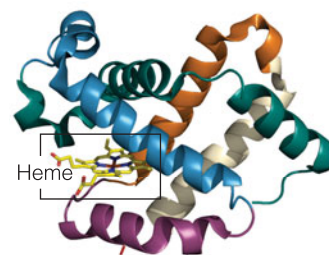


Fig. 4.8 One of the four polypeptide chains that make up the human hemoglobin molecule. The chains, which are similar to the oxygen storage protein myoglobin, consist of helical and sheet-like regions. The heme group is at the lower left.

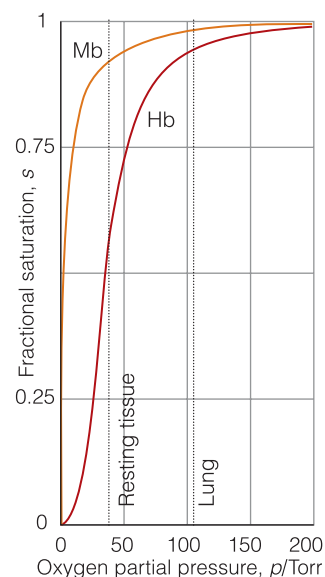


Fig. 4.9 The variation of the fractional saturation of myoglobin and hemoglobin molecules with the partial pressure of oxygen. The different shapes of the curves account for the different biological functions of the two proteins.

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, $\Delta_r G^\circ$, 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

$$\Delta_r G^\circ = \sum_{\text{Products}} \nu G_m^\circ - \sum_{\text{Reactants}} \nu G_m^\circ \quad \text{Definition of standard Gibbs energy of reaction} \quad (4.14)$$

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 dm^{-3} and 1 bar.

We cannot calculate $\Delta_r G^\circ$ 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 1.11), the standard reaction entropy from Third-Law entropies (Section 2.5), and then to combine the two quantities by using

$$\Delta_r G^\circ = \Delta_r H^\circ - T \Delta_r S^\circ \quad \text{Construction of } \Delta_r G^\circ \quad (4.15)$$

Example 4.4 Calculating the standard reaction Gibbs energy of an enzyme-catalyzed reaction

Evaluate the standard reaction Gibbs energy at 25°C for the reaction $\text{CO}_2(\text{g}) + \text{H}_2\text{O}(\text{l}) \rightarrow \text{H}_2\text{CO}_3(\text{aq})$ catalyzed by the enzyme carbonic anhydrase in red blood cells.

Strategy Obtain the relevant standard enthalpies of formation and standard entropies from the *Resource section*. Then calculate the standard reaction enthalpy and the standard reaction entropy from

$$\begin{aligned} \Delta_r H^\circ &= \sum_{\text{Products}} \nu \Delta_f H^\circ - \sum_{\text{Reactants}} \nu \Delta_f H^\circ \\ \Delta_r S^\circ &= \sum_{\text{Products}} \nu S_m^\circ - \sum_{\text{Reactants}} \nu S_m^\circ \end{aligned}$$

and the standard reaction Gibbs energy from eqn 4.14.

Solution The standard reaction enthalpy is

$$\begin{aligned}\Delta_r H^\circ &= \Delta_f H^\circ(\text{H}_2\text{CO}_3, \text{aq}) - \{\Delta_f H^\circ(\text{CO}_2, \text{g}) + \Delta_f H^\circ(\text{H}_2\text{O}, \text{l})\} \\ &= -699.65 \text{ kJ mol}^{-1} - \{(-393.51 \text{ kJ mol}^{-1}) + (-285.83 \text{ kJ mol}^{-1})\} \\ &= -20.31 \text{ kJ mol}^{-1}\end{aligned}$$

The standard reaction entropy was calculated in the *brief illustration* in Section 2.5:

$$\Delta_r S^\circ = -96.3 \text{ J K}^{-1} \text{ mol}^{-1}$$

which, because 96.3 J is the same as 9.63×10^{-2} kJ, corresponds to $-9.63 \times 10^{-2} \text{ kJ K}^{-1} \text{ mol}^{-1}$. Therefore, from eqn 4.15,

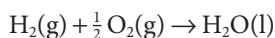
$$\begin{aligned}\Delta_r G^\circ &= (-20.31 \text{ kJ mol}^{-1}) - (298.15 \text{ K}) \times (-9.63 \times 10^{-2} \text{ kJ K}^{-1} \text{ mol}^{-1}) \\ &= +8.40 \text{ kJ mol}^{-1}\end{aligned}$$

Self-test 4.6 Use the information in the *Resource section* to determine the standard reaction Gibbs energy for $3 \text{ O}_2(\text{g}) \rightarrow 2 \text{ O}_3(\text{g})$ from standard enthalpies of formation and standard entropies.

Answer: $+326.4 \text{ kJ mol}^{-1}$

(a) Standard Gibbs energies of formation

We saw in Section 1.11 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**, $\Delta_f G^\circ$, 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 1.11 (a reminder: it is the most stable form of the element under the prevailing conditions; do not confuse ‘reference state’ with ‘standard state’, but be aware that a reference state of an element will also be in its standard state if the pressure is 1 bar); 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, $\Delta_f G^\circ(\text{H}_2\text{O}, \text{l})$, is the standard reaction Gibbs energy for



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 *Resource 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 $\text{C}(\text{s, graphite}) \rightarrow \text{C}(\text{s, graphite})$ 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:



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 in *Example 4.4*, but there are other sources of data and we encounter some of them later.

Standard Gibbs energies of formation can be combined to obtain the standard Gibbs energy of almost any reaction. We use the now familiar expression

Table 4.2 Standard Gibbs energies of formation at 298.15 K*

Substance	$\Delta_f G^\circ / (\text{kJ mol}^{-1})$
<i>Gases</i>	
Carbon dioxide, CO_2	-394.36
Methane, CH_4	-50.72
Nitrogen oxide, NO	+86.55
Water, H_2O	-228.57
<i>Liquids</i>	
Ethanol, $\text{CH}_3\text{CH}_2\text{OH}$	-174.78
Hydrogen peroxide, H_2O_2	-120.35
Water, H_2O	-237.13
<i>Solids</i>	
α -D-Glucose $\text{C}_6\text{H}_{12}\text{O}_6$	-917.2
Glycine, $\text{CH}_2(\text{NH}_2)\text{COOH}$	-532.9
Sucrose, $\text{C}_{12}\text{H}_{22}\text{O}_{11}$	-1543
Urea, $\text{CO}(\text{NH}_2)_2$	-197.33
<i>Solutes in aqueous solution</i>	
Carbon dioxide, CO_2	-385.98
Carbonic acid, H_2CO_3	-623.08
Phosphoric acid, H_3PO_4	-1018.7

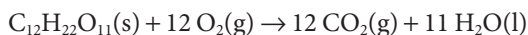
*Additional values are given in the Data section.

$$\Delta_r G^\circ = \sum_{\text{Products}} \nu \Delta_f G^\circ - \sum_{\text{Reactants}} \nu \Delta_f G^\circ \quad \text{Calculation of standard Gibbs energy of reaction} \quad (4.16)$$

If we need the biological standard reaction Gibbs energy, we convert $\Delta_r G^\circ$ to $\Delta_r G^\oplus$ by using eqn 4.8.

A brief illustration

To determine the standard reaction Gibbs energy for the complete oxidation of solid sucrose, $\text{C}_{12}\text{H}_{22}\text{O}_{11}(\text{s})$, by oxygen gas to carbon dioxide gas and liquid water,



we carry out the following calculation:

$$\begin{aligned} \Delta_r G^\circ &= \{12\Delta_f G^\circ(\text{CO}_2, \text{g}) + 11\Delta_f G^\circ(\text{H}_2\text{O}, \text{l})\} - \{\Delta_f G^\circ(\text{C}_{12}\text{H}_{22}\text{O}_{11}, \text{s}) + 12\Delta_f G^\circ(\text{O}_2, \text{g})\} \\ &= \{12(-394 \text{ kJ mol}^{-1}) + 11(-237 \text{ kJ mol}^{-1})\} - \{-1543 \text{ kJ mol}^{-1} + 0\} \\ &= -5.79 \times 10^3 \text{ kJ mol}^{-1} \end{aligned}$$

Self-test 4.7 Calculate the standard reaction Gibbs energy of the oxidation of ammonia to nitric oxide according to the equation $4 \text{NH}_3(\text{g}) + 5 \text{O}_2(\text{g}) \rightarrow 4 \text{NO}(\text{g}) + 6 \text{H}_2\text{O}(\text{g})$.

Answer: $-959.42 \text{ kJ mol}^{-1}$

(b) Stability and instability

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. 4.10). 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 $\Delta_f G^\circ > 0$ is **thermodynamically unstable** with respect to its elements or that it is **endergonic**. Thus, the endergonic substance ozone, for which $\Delta_f G^\circ = +163 \text{ kJ mol}^{-1}$, has a spontaneous tendency to decompose into oxygen under standard conditions at 25°C. More precisely, the equilibrium constant for the reaction $\frac{3}{2} \text{O}_2(\text{g}) \rightleftharpoons \text{O}_3(\text{g})$ 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 ($\Delta_f G^\circ = +124 \text{ kJ mol}^{-1}$) 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 $\Delta_f G^\circ < 0$ (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 $\Delta_f G^\circ = -33 \text{ kJ mol}^{-1}$: the negative sign shows that the formation of ethane gas from its elements is spontaneous in the sense that $K > 1$ (in fact, $K = 7.1 \times 10^5$ at 25°C).

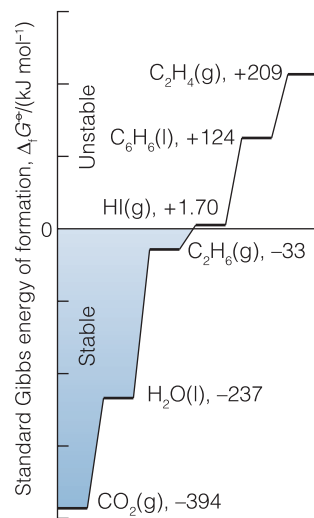


Fig. 4.10 The standard Gibbs energy of formation of a compound is like a measure of the compound's altitude above or below sea level: compounds that lie above sea level have a spontaneous tendency to decompose into the elements (and to revert to sea level). Compounds that lie below sea level are stable with respect to decomposition into the elements.

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 $\Delta_r G^\circ$ 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), especially enzymes, 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 $\Delta_r G^\circ$ 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 $\Delta_r G^\circ$ 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 $\Delta_r G^\circ$, and therefore of K , on the temperature.

First, we consider the effect of temperature on $\Delta_r G^\circ$. We use the relation $\Delta_r G^\circ = \Delta_r H^\circ - T\Delta_r S^\circ$ 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

$$\text{change in } \Delta_r G^\circ = -(\text{change in } T) \times \Delta_r S^\circ \quad (4.17)$$

This expression is easy to apply when there is a consumption or formation of gas because, as we have seen (Section 2.5), 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 $\Delta_r G^\circ$ appear in the expression for K . However, as we show in the following *Justification*, the effect of temperature can be expressed very simply as the **van 't Hoff equation**.²

$$\ln K_2 = \ln K_1 + \frac{\Delta_r H^\circ}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right) \quad \text{van 't Hoff equation} \quad (4.18)$$

² There are several 'van 't Hoff equations'. To distinguish them, this one is sometimes called the *van 't Hoff isochore*.

where K_1 is the equilibrium constant at the temperature T_1 and K_2 is its value when the temperature is T_2 . All we need to know to calculate the temperature dependence of an equilibrium constant, therefore, is the standard reaction enthalpy.

Justification 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 $\Delta_r G^\circ$ stems from the T in $\Delta_r G^\circ = \Delta_r H^\circ - T\Delta_r S^\circ$. At a temperature T_1 ,

$$\ln K_1 = -\frac{\Delta_r G^\circ}{RT_1} = -\frac{\Delta_r H^\circ}{RT_1} + \frac{\Delta_r S^\circ}{R}$$

At another temperature T_2 , when $\Delta_r G^\circ = \Delta_r H^\circ - T_2\Delta_r S^\circ$ and the equilibrium constant is K_2 , a similar expression holds:

$$\ln K_2 = -\frac{\Delta_r H^\circ}{RT_2} + \frac{\Delta_r S^\circ}{R}$$

The difference between the two is eqn 4.18.

Let's explore the information in the van 't Hoff equation. Consider the case when $T_2 > T_1$. Then the term in parentheses in eqn 4.18 is positive. If $\Delta_r H^\circ > 0$, corresponding to an endothermic reaction, the entire term on the right is positive. In this case, therefore, $\ln K_2 > \ln K_1$. That being so, we conclude that $K_2 > K_1$ for an endothermic reaction. In general, *the equilibrium constant of an endothermic reaction increases with temperature*. The opposite is true when $\Delta_r H^\circ < 0$, so we can conclude that *the equilibrium constant of an exothermic reaction decreases with an increase in temperature*.

Statistical principles also give us insight into the temperature dependence of the equilibrium constant. The typical arrangement of energy levels for an endothermic reaction is shown in Fig. 4.11a. When the temperature is increased, the Boltzmann distribution adjusts and the populations change as shown. The change corresponds to an increased population of the higher energy states at the expense of the population of the lower-energy states. We see that the states that arise from the B molecules become more populated at the expense of the A molecules. Therefore, the total population of B states increases, and B becomes more abundant in the equilibrium mixture. Conversely, if the reaction is exothermic (Fig. 4.11b), then an increase in temperature increases the population of the A states (which start at higher energy) at the expense of the B states, so the reactants become more abundant.

Coupled reactions in bioenergetics

We remarked in the introduction to this chapter that thermodynamics enables us to determine whether one reaction can drive another forward. We now have enough information to take this step. A simple mechanical analogy is a pair of weights joined by a string (Fig. 4.12): the lighter of the pair of weights will be pulled up as the heavier weight falls down. Although the lighter weight has a

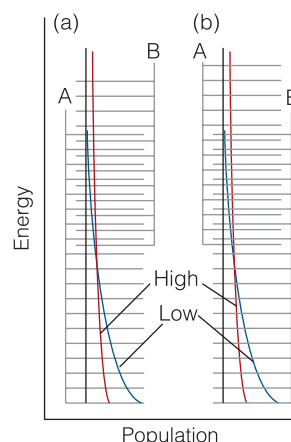


Fig. 4.11 The effect of temperature on a chemical equilibrium can be interpreted in terms of the change in the Boltzmann distribution with temperature and the effect of that change in the population of the species. (a) In an endothermic reaction, the population of B increases at the expense of A as the temperature is raised. (b) In an exothermic reaction, the opposite happens.

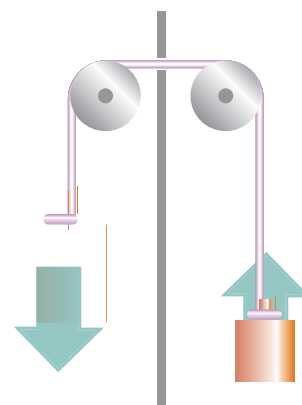


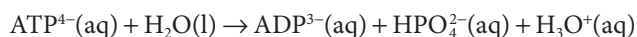
Fig. 4.12 If two weights are coupled as shown here, then the heavier weight will move the lighter weight in its nonspontaneous direction: overall, the process is still spontaneous. The weights are the analogs of two chemical reactions: a reaction with a large negative $\Delta_r G$ can force another reaction with a smaller $\Delta_r G$ to run in its nonspontaneous direction.

natural tendency to move downward, its coupling to the heavier weight results in it being raised. The thermodynamic analog is an **endergonic reaction**, a reaction with a positive Gibbs energy, $\Delta_r G$ (the analog 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 analog 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 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.

Case study 4.2

ATP and the biosynthesis of proteins

The function of adenosine triphosphate, ATP^{4-} (Atlas N3) 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-} (Atlas N2):



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. One reason why ATP is so potent is that its concentration in cells is high, so its chemical potential is also high.

The biological standard values for the hydrolysis of ATP at 37°C are

$$\Delta_r G^\ominus = -31 \text{ kJ mol}^{-1} \quad \Delta_r H^\ominus = -20 \text{ kJ mol}^{-1} \quad \Delta_r S^\ominus = +34 \text{ J K}^{-1} \text{ mol}^{-1}$$

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.

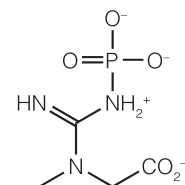
In the cell, each ATP molecule can be used to drive an endergonic reaction for which $\Delta_r G^\ominus$ does not exceed 31 kJ mol⁻¹. For example, the biosynthesis of sucrose from glucose and fructose can be driven by enzyme-catalyzed processes in plants because the reaction is endergonic to the extent $\Delta_r G^\ominus = +23 \text{ kJ mol}^{-1}$. 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 acid residues are assembled into a precisely determined sequence. For instance, the formation of a peptide link is endergonic, with $\Delta_r G^\ominus = +17 \text{ kJ mol}^{-1}$, 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.

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: 1.1 kg

Adenosine triphosphate is not the only phosphate species capable of driving other less exergonic reactions. For instance, creatine phosphate (3) can release its phosphate group in a hydrolysis reaction, and $\Delta_r G^\ominus = -43 \text{ kJ mol}^{-1}$. These different exergonicities give rise to the concept of **transfer potential**, which is the negative of the value of $\Delta_r G^\ominus$ for the hydrolysis reaction. Thus, the transfer potential of creatine phosphate is $+43 \text{ kJ mol}^{-1}$. 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).



3 Creatine phosphate

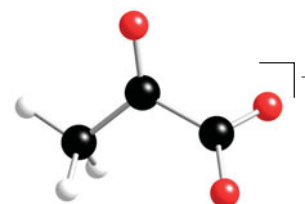
Table 4.3 Transfer potentials at 298.15 K

Substance	Transfer potential, $-\Delta_r G^\ominus / (\text{kJ mol}^{-1})$
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, $\text{HP}_2\text{O}_7^{3-}$	33

Case study 4.3 The oxidation of glucose

The breakdown of glucose in the cell begins with *glycolysis*, a partial oxidation of glucose by nicotinamide adenine dinucleotide (NAD^+ , Atlas N4) to pyruvate ion, $\text{CH}_3\text{COCO}_2^-$ (4). 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. 4.13).



4 Pyruvate ion

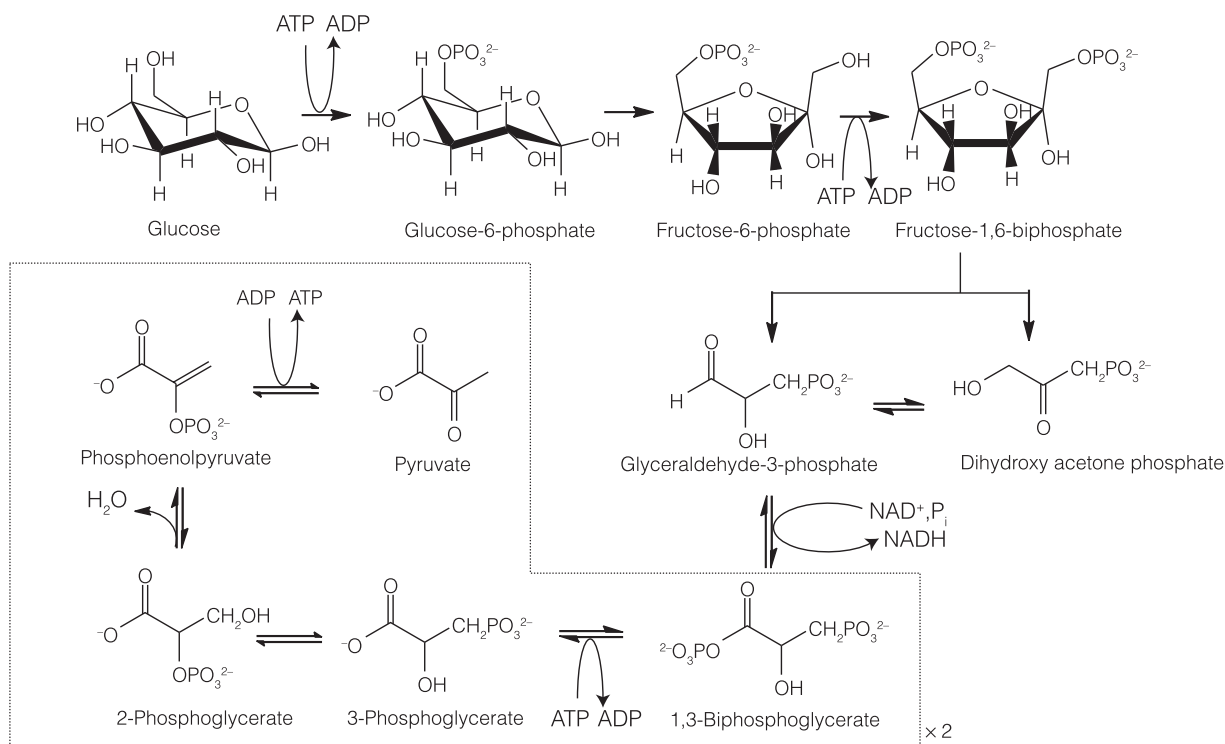


Fig. 4.13 The reactions of glycolysis, in which glucose is partially oxidized by nicotinamide adenine dinucleotide (NAD⁺, Atlas N4) to pyruvate ion.

A brief comment

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, H₂PO₄²⁻ is written as P_i, ATP⁴⁻ as ATP, and so on. We need to show hydrogen ions explicitly (because they account for differences between thermodynamic and biological standard states and for the role of pH); in such cases charges will not seem to be balanced.

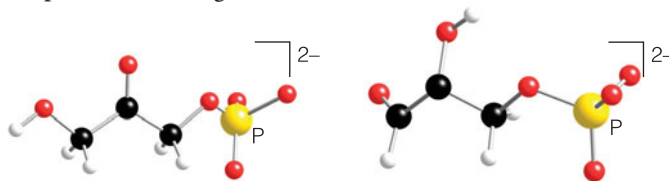
The process needs to be initiated by consumption of two molecules of ATP per molecule of glucose. The first ATP molecule is used to drive the phosphorylation of glucose to glucose-6-phosphate (G6P):



(Note that ATP, ADP, and G6P denote charged species, so charges are in fact balanced in this and similar equations, but charge balance is not displayed explicitly.) 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):

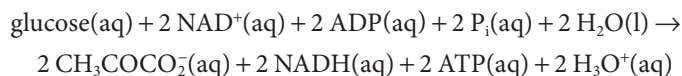


In the next step, FDP is broken into two three-carbon units, dihydroxyacetone phosphate (1,3-dihydroxypropanone phosphate, CH₂OHCOCH₂OPO₃²⁻, 5) and glyceraldehyde-3-phosphate (6), which exist in mutual equilibrium. Only the glyceraldehyde-3-phosphate is oxidized by NAD⁺ to pyruvate ion, with formation 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.



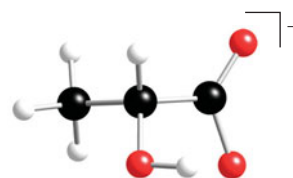
5 Dihydroxypropanone phosphate 6 Glyceraldehyde-3-phosphate

The oxidation of glucose by NAD^+ to pyruvate ions has $\Delta_r G^\ominus = -147 \text{ kJ mol}^{-1}$ 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 ('net' because two ATP molecules are consumed and four are formed), so the net reaction of glycolysis is



The biological standard reaction Gibbs energy is $(-147) - 2(-31) \text{ kJ mol}^{-1} = -85 \text{ kJ mol}^{-1}$. The reaction is exergonic and therefore spontaneous under 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, $\text{CH}_3\text{CH}(\text{OH})\text{CO}_2^-$ (7) 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.



7 Lactate ion

The standard Gibbs energy of combustion of glucose is $-2880 \text{ kJ mol}^{-1}$, 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, Atlas N6) to give acetyl CoA, NADH , and CO_2 . Acetyl CoA is then oxidized by NAD^+ and flavin adenine dinucleotide (FAD, Atlas N7) in the citric acid cycle (Fig. 4.14), which

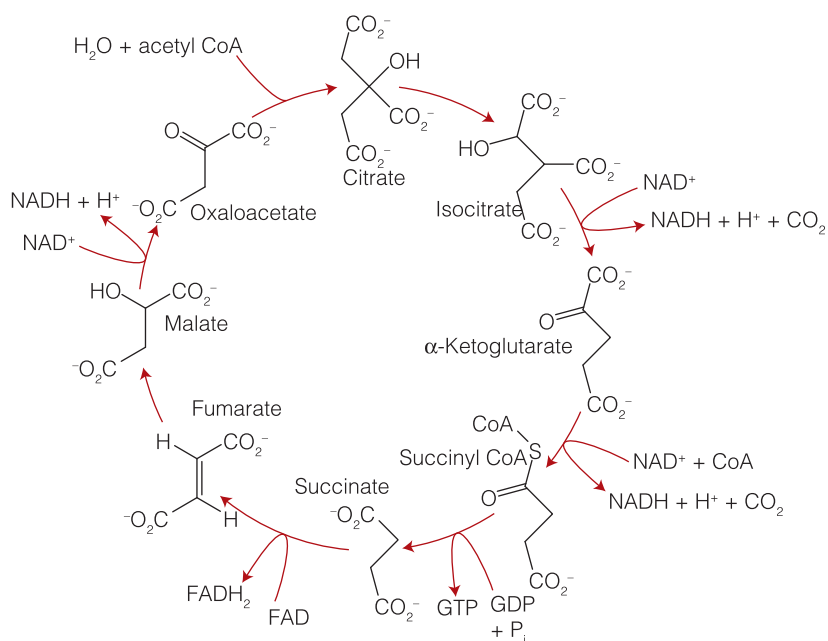
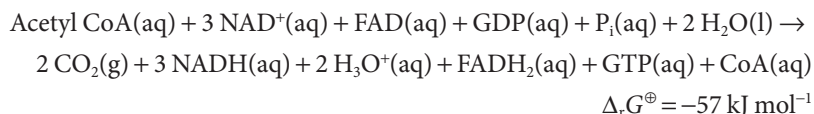


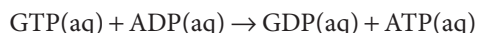
Fig. 4.14 The reactions of the citric acid cycle, in which acetyl CoA is oxidized by NAD^+ and FAD, resulting in the synthesis of GTP (shown) or ATP, depending on the type of cell. The GTP molecules are eventually converted to ATP.

³ In yeast, the terminal products are ethanol and CO_2 .

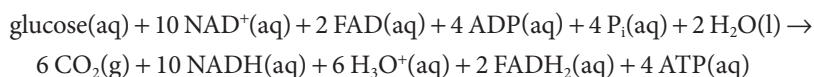
requires eight enzymes and results in the synthesis of guanosine triphosphate (GTP, Atlas N8) from guanosine diphosphate, GDP, or of ATP from ADP:



In cells that produce GTP, the enzyme nucleoside diphosphate kinase catalyzes the transfer of a phosphate group to ADP to form ATP:



For this reaction, $\Delta_r G^\ominus = 0$ 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



The NADH and FADH₂ go on to reduce O₂ during oxidative phosphorylation (Section 5.10b), 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 C₆H₁₂O₆ (180 g of glucose), so 1178 kJ is stored for later use. Therefore, aerobic oxidation of glucose is much more efficient than glycolysis.

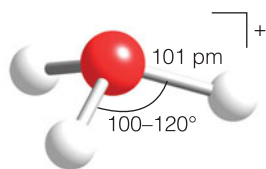
Proton transfer equilibria

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.

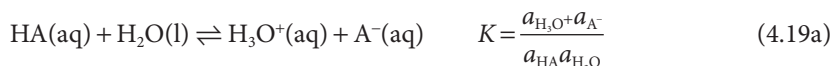
4.7 Brønsted–Lowry theory

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.

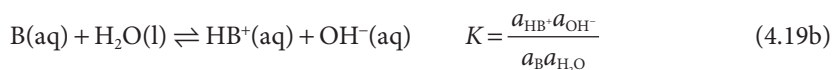
According to the **Brønsted–Lowry theory** of acids and bases, an **acid** is a proton donor and a **base** is a proton acceptor. The proton, which in this context means a hydrogen ion, H⁺, is highly mobile and acids and bases in water are always in equilibrium with their deprotonated and protonated counterparts and hydronium ions (H₃O⁺, 8). Thus, an acid HA, such as HCN, immediately establishes the equilibrium



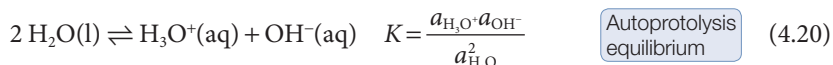
8 Hydronium ion, H₃O⁺



A base B, such as NH_3 , immediately establishes the equilibrium



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



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

$$\text{pH} = -\log a_{\text{H}_3\text{O}^+} \quad \text{Definition of pH} \quad (4.21)$$

where the logarithm is to base 10. In elementary work, the hydronium ion activity is replaced by the numerical value of its molar concentration, $[\text{H}_3\text{O}^+]$, which is equivalent to setting the activity coefficient γ equal to 1.

A brief illustration

If the molar concentration of H_3O^+ is 2.0 mmol dm^{-3} (where $1 \text{ mmol} = 10^{-3} \text{ mol}$), then

$$\text{pH} \approx -\log(2.0 \times 10^{-3}) = 2.70$$

If the molar concentration were 10 times less, at $0.20 \text{ mmol dm}^{-3}$, 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 dm^{-3} to 100 nmol dm^{-3} ($1 \text{ nmol} = 10^{-9} \text{ mol}$)

4.8 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.

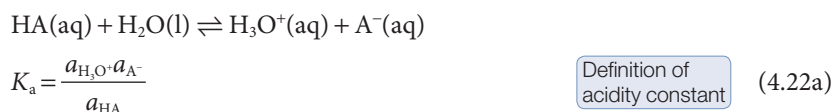
All the solutions we consider are so dilute that we can regard the water present as being a nearly pure liquid and therefore as having unit activity (see Table 3.3).

⁴ Autoprotolysis is also called *autoionization*.

This feature leads to convenient expressions for quantities that measure the strengths of acids and bases and the extent of protonation of bases and deprotonation of acids.

(a) The strengths of acids and bases

When we set $a_{\text{H}_2\text{O}} = 1$ for all the solutions we consider, the resulting equilibrium constant is called the **acidity constant**, K_a , of the acid HA:⁵



In elementary applications, the activities are replaced by the numerical values of the molar concentrations, and we write

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \quad (4.22b)$$

Data are widely reported in terms of the negative common (base 10) logarithm of this quantity:

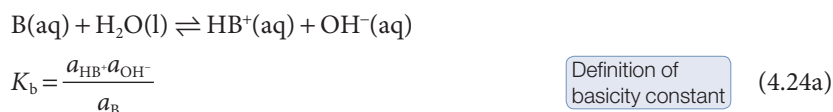
$$\text{p}K_a = -\log K_a \quad \text{Definition of } \text{p}K_a \quad (4.23)$$

It follows from eqn 4.10a ($\Delta_r G^\circ = -RT \ln K$) that $\text{p}K_a$ is proportional to $\Delta_r G^\circ$ for the proton transfer reaction. More explicitly, $\text{p}K_a = \Delta_r G^\circ / (RT \ln 10)$, with $\ln 10 = 2.303 \dots$. Therefore, manipulations of $\text{p}K_a$ and related quantities are actually manipulations of standard reaction Gibbs energies in disguise.

Self-test 4.10 Show that $\text{p}K_a = \Delta_r G^\circ / (RT \ln 10)$. *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 (for instance 10^{-8} compared with 10^{-6}) and therefore the larger the value of $\text{p}K_a$ (for instance, 8 compared with 6), the lower is the concentration of deprotonated molecules. Most acids have $K_a < 1$ (and usually much less than 1), with $\text{p}K_a > 0$, 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, HNO₃, H₂SO₄, and HClO₄, 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 :



and the corresponding value of $\text{p}K_b = -\log K_b$. As for acids, in elementary applications the activities are replaced by the numerical values of the molar concentrations and we use

⁵ Acidity constants are also called *acid ionization constants* and, less appropriately, *dissociation constants*.

⁶ Sulfuric acid, H₂SO₄, is strong with respect only to its first deprotonation; HSO₄⁻ is weak.

$$K_b = \frac{[\text{HB}^+][\text{OH}^-]}{[\text{B}]} \quad (4.24b)$$

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 obtained in a similar way by setting the activity of water in eqn 4.19 to its 'pure' value:

$$K_w = a_{\text{H}_3\text{O}^+} a_{\text{OH}^-} \approx [\text{H}_3\text{O}^+][\text{OH}^-] \quad (4.25)$$

Definition of the autoprotolysis constant of water

At 25°C, $K_w = 1.0 \times 10^{-14}$ and $\text{p}K_w = -\log K_w = 14.00$.

As may be confirmed by multiplying the two constants together, the basicity constant of a base B and the acidity constant of its conjugate acid, HB^+ ,

$$\text{B(aq)} + \text{H}_2\text{O(l)} \rightleftharpoons \text{HB}^+(\text{aq}) + \text{OH}^-(\text{aq}) \quad K_b = \frac{a_{\text{HB}^+} a_{\text{OH}^-}}{a_{\text{B}}}$$

$$\text{HB}^+(\text{aq}) + \text{H}_2\text{O(l)} \rightleftharpoons \text{H}_3\text{O}^+(\text{aq}) + \text{B(aq)} \quad K_a = \frac{a_{\text{H}_3\text{O}^+} a_{\text{B}}}{a_{\text{HB}^+}}$$

are related by

$$K_a K_b = \frac{a_{\text{H}_3\text{O}^+} a_{\text{B}}}{a_{\text{HB}^+}} \times \frac{a_{\text{HB}^+} a_{\text{OH}^-}}{a_{\text{B}}} = a_{\text{H}_3\text{O}^+} a_{\text{OH}^-} = K_w \quad (4.26a)$$

Relation between K_a and K_b

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 4.26a, we obtain

$$\text{p}K_a + \text{p}K_b = \text{p}K_w \quad (4.26b)$$

Relation between $\text{p}K_a$ and $\text{p}K_b$

The great advantage of this relation is that the $\text{p}K_b$ values of bases may be expressed as the $\text{p}K_a$ of their conjugate acids, so the strengths of all weak acids and bases may be listed in a single table (Table 4.4).

A brief illustration

If the acidity constant of the conjugate acid (CH_3NH_3^+) of the base methylamine (CH_3NH_2) is reported as $\text{p}K_a = 10.56$, we can infer that the basicity constant of methylamine itself is

$$\text{p}K_b = \text{p}K_w - \text{p}K_a = 14.00 - 10.56 = 3.44$$

Another useful relation is obtained by taking the negative common logarithm of both sides of the definition of K_w in eqn 4.24, which gives

$$\text{pH} + \text{pOH} = \text{p}K_w \quad (4.27)$$

Relation between pH and pOH

Table 4.4 Acidity and basicity constants* at 298.15 K

Acid/base	K_b	pK_b	K_a	pK_a
<i>Strongest weak acids</i>				
Trichloroacetic acid, CCl_3COOH	3.3×10^{-14}	13.48	3.0×10^{-1}	0.52
Benzenesulfonic acid, $\text{C}_6\text{H}_5\text{SO}_3\text{H}$	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, $\text{CH}_3\text{CH}(\text{OH})\text{COOH}$	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, $\text{C}_6\text{H}_5\text{COOH}$	1.5×10^{-10}	9.81	6.5×10^{-4}	4.19
Acetic acid, CH_3COOH	5.6×10^{-10}	9.25	1.8×10^{-4}	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, $\text{B}(\text{OH})_3\text{H}^+$	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, $\text{C}_6\text{H}_5\text{OH}$	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
<i>Weakest weak bases</i>				
Urea, $\text{CO}(\text{NH}_2)_2$	1.3×10^{-14}	13.90	7.7×10^{-1}	0.10
Aniline, $\text{C}_6\text{H}_5\text{NH}_2$	4.3×10^{-10}	9.37	2.3×10^{-5}	4.63
Pyridine, $\text{C}_5\text{H}_5\text{N}$	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, $\text{C}_{10}\text{H}_{11}\text{N}_2$	1.0×10^{-6}	5.98	1.0×10^{-8}	8.02
Morphine, $\text{C}_{17}\text{H}_{19}\text{O}_3\text{N}$	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, $(\text{CH}_3)_3\text{N}$	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, $(\text{CH}_3)_2\text{NH}$	5.4×10^{-4}	3.27	1.9×10^{-11}	10.73
Ethylamine, $\text{C}_2\text{H}_5\text{NH}_2$	6.5×10^{-4}	3.19	1.5×10^{-11}	10.81
Triethylamine, $(\text{C}_2\text{H}_5)_3\text{N}$	1.0×10^{-3}	2.99	1.0×10^{-11}	11.01
<i>Strongest weak bases</i>				

*Values for polyprotic acids—those capable of donating more than one proton—refer to the first deprotonation.

†The proton transfer equilibrium is $\text{B}(\text{OH})_3(\text{aq}) + 2 \text{H}_2\text{O}(\text{l}) \rightleftharpoons \text{H}_3\text{O}^+(\text{aq}) + \text{B}(\text{OH})_4^-(\text{aq})$.

where $\text{pOH} = -\log a_{\text{OH}^-}$. This enormously important relation means that the activities (in elementary work, the molar concentrations) of hydronium and hydroxide ions of a given solution are related by a seesaw relation: as one goes up, the other goes down to preserve the value of $\text{p}K_{\text{w}}$.

Self-test 4.11 The molar concentration of OH^- ions in a certain solution is $0.010 \text{ mmol dm}^{-3}$. What is the pH of the solution?

Answer: 9.00

(b) The pH of a solution of a weak acid

The most reliable 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 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:

Organize the necessary work into a table with columns headed by the species present in the mixture (ignoring H_2O) and, in successive rows write:

1. The initial molar concentrations of the species, ignoring any contributions to the concentration of H_3O^+ or OH^- from the autoprotolysis of water.
2. The changes in these quantities that must take place for the system to reach equilibrium.
3. The resulting equilibrium values.

In most cases, we do not know the change that must occur for the system to reach equilibrium, so the change in the concentration of H_3O^+ 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 acidity constant, we obtain an equation for x in terms of K_{a} . This equation can be solved for x . 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 Estimating the pH of a solution 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: $\text{CH}_3\text{CH}_2\text{OH}(\text{aq}) + \text{O}_2(\text{g}) \rightarrow \text{CH}_3\text{COOH}(\text{aq}) + \text{H}_2\text{O}(\text{l})$. Estimate the pH of (a) $0.15 \text{ M CH}_3\text{COOH}(\text{aq})$ and (b) $1.5 \times 10^{-4} \text{ M CH}_3\text{COOH}(\text{aq})$.

Strategy Proceed as outlined above.

Solution We draw up the following equilibrium table based on the proton transfer equilibrium $\text{CH}_3\text{COOH}(\text{aq}) + \text{H}_2\text{O}(\text{l}) \rightleftharpoons \text{H}_3\text{O}^+(\text{aq}) + \text{CH}_3\text{CO}_2^-(\text{aq})$.

Species	CH_3COOH	H_3O^+	CH_3CO_2^-
Initial concentration/ (mol dm^{-3})	0.15	0	0
Change to reach equilibrium/ (mol dm^{-3})	$-x$	$+x$	$+x$
Equilibrium concentration/ (mol dm^{-3})	$0.15 - x$	x	x

(a) The value of x is found by inserting the equilibrium concentrations into the expression for the acidity constant:

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{CH}_3\text{CO}_2^-]}{[\text{CH}_3\text{COOH}]} = \frac{x \times x}{0.15 - x}$$

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 $x \ll 0.15$ 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).

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 $x \ll 0.15$). 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, $\text{pH} = 2.80$. 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 $\text{pH} = 2.8$.

(b) Had we proceeded in the same way with the new concentration, we would calculate $x = 5.2 \times 10^{-5}$, which although less than the initial concentration is not much less. Therefore, we must solve the quadratic equation

$$x^2 + K_a x - (1.5 \times 10^{-4})K_a = 0$$

by setting $a = 1$, $b = 1.8 \times 10^{-5}$, and $c = -1.5 \times 1.8 \times 10^{-9}$:

$$x = \frac{-1.8 \times 10^{-5} \pm ((-1.8 \times 10^{-5})^2 - 4(-1.5 \times 1.8 \times 10^{-9}))^{1/2}}{2}$$

$$= 4.4 \times 10^{-5} \text{ or } -6.2 \times 10^{-5}$$

Because x is equal to the concentration of H_3O^+ , it cannot be negative, so we select $x = 4.4 \times 10^{-5}$. It follows that $\text{pH} = 4.4$. (The illegal calculation would have given 4.3.)

Self-test 4.12 Estimate the pH of 0.010 M $\text{CH}_3\text{CH}(\text{OH})\text{COOH}(\text{aq})$ (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: 2.6

Mathematical toolbox 4.1 Quadratic equations

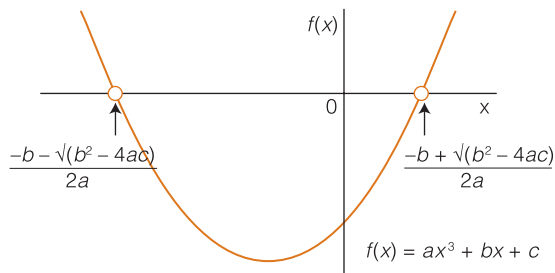
A quadratic equation is an equation of the form

$$ax^2 + bx + c = 0$$

where a , b , and c are constants. The two roots (solutions) of the equation are given by the expression

$$x = \frac{-b \pm (b^2 - 4ac)^{1/2}}{2a}$$

The graph of the function $ax^2 + bx + c$ is a parabola, which cuts the x -axis at the two roots of the corresponding quadratic equation:



(c) The pH of a solution of a weak base

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 4.27, in the form $\text{pH} = \text{p}K_w - \text{pOH}$, with $\text{p}K_w = 14.00$ at 25°C .

Example 4.6 *Estimating the pH of a solution of a weak base*

Calculate the pH of an 0.20 M aqueous solution of methylamine, CH_3NH_2 , for which $\text{p}K_b = 3.44$.

Strategy Proceed as outlined above.

Solution We draw up the following equilibrium table based on the proton transfer equilibrium $\text{CH}_3\text{NH}_2(\text{aq}) + \text{H}_2\text{O}(\text{l}) \rightleftharpoons \text{CH}_3\text{NH}_3^+(\text{aq}) + \text{OH}^-(\text{aq})$.

Species	CH_3NH_2	CH_3NH_3^+	OH^-
Initial concentration/(mol dm ⁻³)	0.20	0	0
Change to reach equilibrium/(mol dm ⁻³)	$-x$	$+x$	$+x$
Equilibrium concentration/(mol dm ⁻³)	$0.20 - x$	x	x

Then, because $K_b = 10^{-3.44} = 3.6 \times 10^{-4}$, and anticipating that $x \ll 0.2$,

$$\frac{[\text{CH}_3\text{NH}_3^+][\text{OH}^-]}{[\text{CH}_3\text{NH}_2]} = \frac{x \times x}{0.20 - x} \approx \frac{x^2}{0.2} = 3.6 \times 10^{-4}$$

It follows that $[\text{OH}^-] = x = 0.0085$, so $\text{pOH} = -\log(0.0085) = 2.07$. Therefore, $\text{pH} = 14.00 - 2.07 = 11.93$ (more realistically, 11.9).

Self-test 4.13 The base quinoline has $\text{p}K_b = 9.12$. Estimate the pH of an 0.010 M aqueous solution of quinoline.

Answer: 8.4

(d) The extent of protonation and deprotonation

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

$$f_{\text{deprotonated}} = \frac{[\text{A}^-]_{\text{at equilibrium}}}{[\text{HA}]_{\text{as prepared}}} \quad \text{Fraction of HA deprotonated} \quad (4.28a)$$

The extent to which a weak base B is protonated is reported in terms of the **fraction protonated**:

$$f_{\text{protonated}} = \frac{[\text{HB}^+]_{\text{at equilibrium}}}{[\text{B}]_{\text{as prepared}}} \quad \text{Fraction of B protonated} \quad (4.28b)$$

The calculation of either f proceeds in the same way as for the calculation of the pH of a solution, the only difference being how the calculated value of x in the equilibrium table is used.

A brief illustration

The fraction of acetic acid molecules deprotonated in the solution referred to in Example 4.5a is

$$f_{\text{deprotonated}} = \frac{[\text{CH}_3\text{CO}_2^-]_{\text{at equilibrium}}}{[\text{CH}_3\text{COOH}]_{\text{as prepared}}} = \frac{x}{0.15} = \frac{1.6 \times 10^{-3}}{0.15} = 0.011$$

That is, 1.1 per cent of CH_3COOH molecules have lost their acidic proton.

Self-test 4.14 Estimate the fraction of quinoline molecules protonated in a 0.010 M aqueous solution of quinoline.

Answer: 1/3600

(e) The pH of solutions of salts

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 an ion that is neither acidic nor basic (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^+).

A brief illustration

To calculate the pH of 0.010 M $\text{NH}_4\text{Cl}(\text{aq})$ 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 dm⁻³. 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 4.26a ($K_a K_b = K_w$). 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 4.15 Estimate the pH of 0.0025 M $\text{NH}(\text{CH}_3)_3\text{Cl}(\text{aq})$ at 25°C.

Answer: 6.2

4.9 Polyprotic acids

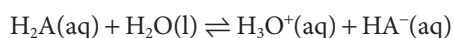
Many biological macromolecules, such as the nucleic acids, contain multiple proton donor sites, and we need to see how to handle this complication quantitatively.

Table 4.5 Successive acidity constants of polyprotic acids at 298.15 K

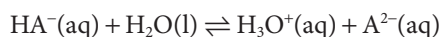
Acid	K_{a1}	pK_{a1}	K_{a2}	pK_{a2}	K_{a3}	pK_{a3}
Carbonic acid, H_2CO_3	4.3×10^{-7}	6.37	5.6×10^{-11}	10.25		
Hydrosulfuric acid, H_2S	1.3×10^{-7}	6.89	7.1×10^{-15}	14.15		
Oxalic acid, $(COOH)_2$	5.9×10^{-2}	1.23	6.5×10^{-5}	4.19		
Phosphoric acid, H_3PO_4	7.6×10^{-3}	2.12	6.2×10^{-8}	7.21	2.1×10^{-13}	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		

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



$$K_{a1} = \frac{a_{H_3O^+} a_{HA^-}}{a_{H_2A}} \quad \text{First deprotonation} \quad (4.29a)$$



$$K_{a2} = \frac{a_{H_3O^+} a_{A^{2-}}}{a_{HA^-}} \quad \text{Second deprotonation} \quad (4.29b)$$

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 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.

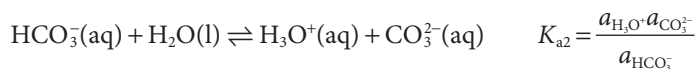
Example 4.7 *Calculating the concentration of carbonate ion in carbonic acid*

Groundwater contains dissolved carbon dioxide, carbonic acid, hydrogen-carbonate 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.

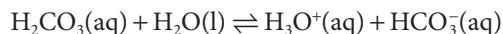
Solution The CO_3^{2-} ion, the conjugate base of the acid HCO_3^- is produced in the equilibrium



Hence,

$$a_{\text{CO}_3^{2-}} = \frac{a_{\text{HCO}_3^-} K_{a2}}{a_{\text{H}_3\text{O}^+}}$$

The HCO_3^- ions are produced in the equilibrium



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 4.10). 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 $a_{\text{HCO}_3^-} \approx a_{\text{H}_3\text{O}^+}$. When this equality is substituted into the expression for $a_{\text{CO}_3^{2-}}$, we obtain

$$[\text{CO}_3^{2-}] \approx K_{a2}$$

Because we know from Table 4.5 that $\text{p}K_{a2} = 10.25$, it follows that $[\text{CO}_3^{2-}] = 5.6 \times 10^{-11}$ and therefore that the molar concentration of CO_3^{2-} ions is 56 pmol dm^{-3} .

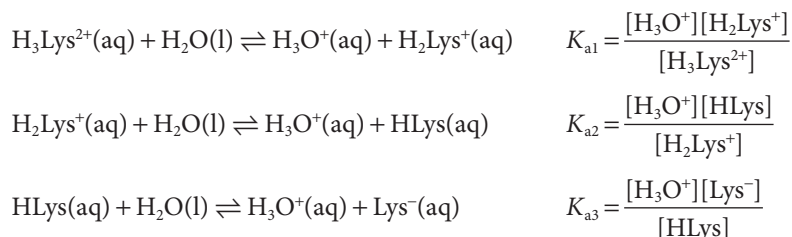
Self-test 4.16 Calculate the molar concentration of S^{2-} ions in $\text{H}_2\text{S}(\text{aq})$.

Answer: 7.1 fmol dm^{-3}

Case study 4.4 The fractional composition of a solution of lysine

The amino acid lysine (HLys, Atlas A12) can accept two protons on its nitrogen atoms and donate one from its carboxyl group. The neutral acid is HLys and the fully protonated form is $\text{H}_3\text{Lys}^{2+}$. Let's see how the composition of an aqueous solution that contains $0.010 \text{ mol dm}^{-3}$ of lysine varies with pH. The $\text{p}K_a$ values of amino acids are given in Table 4.6.

We expect the fully protonated species ($\text{H}_3\text{Lys}^{2+}$) at low pH (high H_3O^+ concentration), 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 and replacing activities by molar concentrations) are



We also know that the total concentration of lysine in all its forms is

$$L = [\text{H}_3\text{Lys}^{2+}] + [\text{H}_2\text{Lys}^+] + [\text{HLys}] + [\text{Lys}^-] \quad \text{Total concentration of lysine} \quad (4.30)$$

We now have four equations for four unknown concentrations. To solve the equations, we proceed systematically, using K_{a3} to express $[\text{Lys}^-]$ in terms of $[\text{HLys}]$, then K_{a2} to express $[\text{HLys}]$ in terms of $[\text{H}_2\text{Lys}^+]$, and so on:

$$\begin{aligned}[\text{Lys}^-] &= \frac{K_{a3}[\text{HLys}]}{[\text{H}_3\text{O}^+]} = \frac{K_{a2}K_{a3}[\text{H}_2\text{Lys}^+]}{[\text{H}_3\text{O}^+]^2} = \frac{K_{a1}K_{a2}K_{a3}[\text{H}_3\text{Lys}^{2+}]}{[\text{H}_3\text{O}^+]^3} \\ [\text{HLys}] &= \frac{K_{a2}[\text{H}_2\text{Lys}^+]}{[\text{H}_3\text{O}^+]} = \frac{K_{a1}K_{a2}[\text{H}_3\text{Lys}^{2+}]}{[\text{H}_3\text{O}^+]^2} \\ [\text{H}_2\text{Lys}^+] &= \frac{K_{a1}[\text{H}_3\text{Lys}^{2+}]}{[\text{H}_3\text{O}^+]}\end{aligned}$$

Then the expression for the total concentration L can be written in terms of $[\text{H}_3\text{Lys}^{2+}]$:

$$L = \frac{H[\text{H}_3\text{Lys}^{2+}]}{[\text{H}_3\text{O}^+]^3}$$

where

$$H = [\text{H}_3\text{O}^+]^3 + K_{a1}[\text{H}_3\text{O}^+]^2 + K_{a1}K_{a2}[\text{H}_3\text{O}^+] + K_{a1}K_{a2}K_{a3} \quad (4.31)$$

It then it follows that the fractions of each species present in the solution are

$$\begin{aligned}f(\text{H}_3\text{Lys}^{2+}) &= \frac{[\text{H}_3\text{Lys}^{2+}]}{L} = \frac{[\text{H}_3\text{O}^+]^3}{H} \\ f(\text{H}_2\text{Lys}^+) &= \frac{[\text{H}_2\text{Lys}^+]}{L} = \frac{K_{a1}[\text{H}_3\text{O}^+]^2}{H} \\ f(\text{HLys}) &= \frac{[\text{HLys}]}{L} = \frac{K_{a1}K_{a2}[\text{H}_3\text{O}^+]}{H} \\ f(\text{Lys}^-) &= \frac{[\text{Lys}^-]}{L} = \frac{K_{a1}K_{a2}K_{a3}}{H}\end{aligned} \quad \text{Fractional composition} \quad (4.32)$$

These fractions are plotted against pH (by using $[\text{H}_3\text{O}^+] = 10^{-\text{pH}}$) in Fig. 4.15. Note that:

Table 4.6 Acidity constants of amino acids at 298.15 K*

Acid	$\text{p}K_{a1}$	$\text{p}K_{a2}$	$\text{p}K_{a3}$
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 *Atlas* of structures. 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 $\text{H}_3\text{Lys}^{2+}$, H_2Lys^+ , and HLys (the electrically neutral molecule).

Fig. 4.15 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.

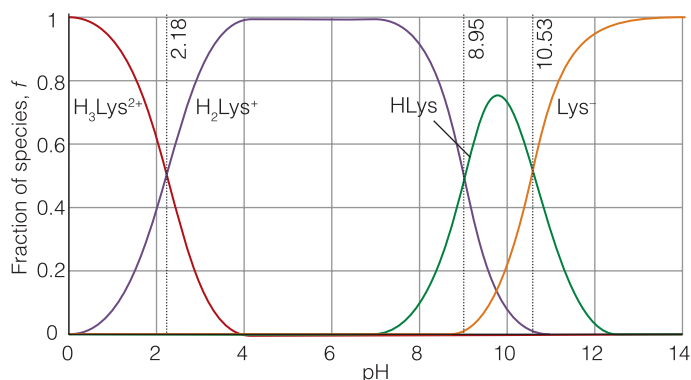
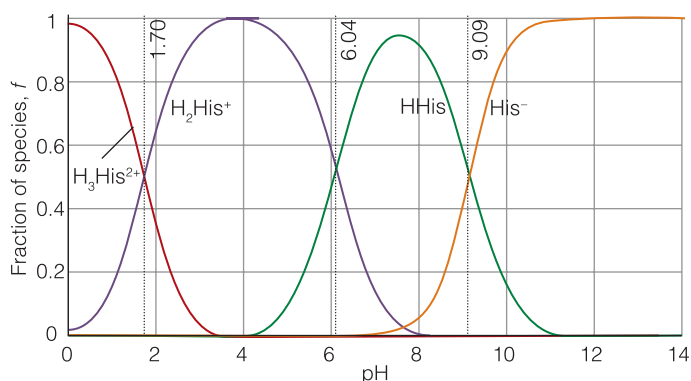


Fig. 4.16 The fractional composition of the protonated and deprotonated forms of histidine (His) in aqueous solution as a function of pH.



- H_3Lys^{2+} is dominant for $pH < pK_{a1}$
- H_3Lys^{2+} and H_2Lys^+ have the same concentration at $pH = pK_{a1}$
- H_2Lys^+ is dominant for $pH > pK_{a1}$ until HLys becomes dominant, and so on.

A note on good practice

Take note of the symmetry of the expressions in eqn 4.31. 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.

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.

Self-test 4.17 Construct the diagram for the fraction of protonated species in an aqueous solution of histidine (Atlas A9).

Answer: Fig. 4.16

We can summarize the behavior discussed in *Case study 4.4* and illustrated in Figs 4.15 and 4.16 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.

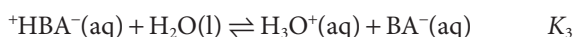
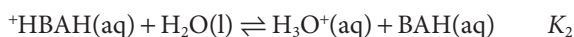
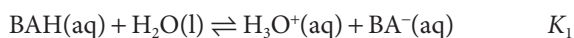
4.10 Amphiprotic systems

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.

(a) The fractional composition of amino acid solutions

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, $\text{NH}_2\text{CH}_2\text{COOH}$, for instance, is $^+\text{H}_3\text{NCH}_2\text{CO}_2^-$. We can suppose that in an aqueous solution of glycine, the species present are $\text{NH}_2\text{CH}_2\text{COOH}$ (and in general BAH , where B represents the basic amino group and AH the carboxylic acid group), $\text{NH}_2\text{CH}_2\text{CO}_2^-$ (BA^-), $^+\text{NH}_3\text{CH}_2\text{COOH}$ ($^+\text{HBAH}$), and the zwitterion $^+\text{NH}_3\text{CH}_2\text{CO}_2^-$ ($^+\text{HBA}^-$). The proton transfer equilibria in water are



By following the same procedure as in *Case study 4.4*, we find the following expressions for the composition of the solution:

$$\begin{aligned} f(\text{BA}^-) &= \frac{K_1 K_2 K_3}{H} \\ f(\text{BAH}) &= \frac{K_2 K_3 [\text{H}_3\text{O}^+]}{H} \\ f(^+\text{HBA}^-) &= \frac{K_1 K_2 [\text{H}_3\text{O}^+]}{H} \\ f(^+\text{HBAH}) &= \frac{K_3 [\text{H}_3\text{O}^+]^2}{H} \end{aligned} \quad \text{Fractional composition} \quad (4.33)$$

with $H = [\text{H}_3\text{O}^+]^2 K_3 + [\text{H}_3\text{O}^+](K_1 + K_3)K_2 + K_1 K_2 K_3$. The variation of composition with pH is shown in Fig. 4.17. 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 $K_3 \ll K_1$ and therefore that $f(\text{BAH}) \ll f(^+\text{HBA}^-)$ at all values of pH.

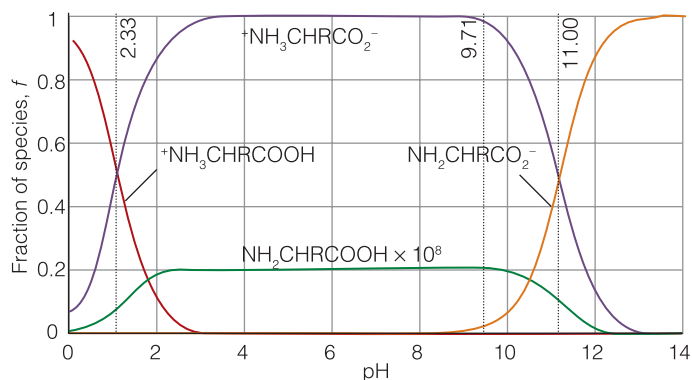
(b) The pH of solutions of amphiprotic anions

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 account of the acid character of HCO_3^- or is it basic on account of the anion's basic character? As we show in *Further information 4.2*, under the circumstances specified there ($K_{a2} \ll K_{a1}$, $S \gg K_w/K_{a2}$, and $S \gg K_{a1}$), where S is the numerical

A note on good practice

Distinguish between *amphiprotic*, which means that a species can both accept and donate protons, and *amphoteric*, which means that a substance can react with both an acid and a base. Aluminum is amphoteric but not amphiprotic.

Fig. 4.17 The fractional composition of the protonated and deprotonated forms of an amino acid $\text{NH}_2\text{CHRCOOH}$ (with arbitrarily chosen values of pK), in which the group R does not participate in proton transfer reactions.



value of the molar concentration of the salt providing the anion), the pH of such a solution is given by

$$\text{pH} = \frac{1}{2}(\text{p}K_{\text{a}1} + \text{p}K_{\text{a}2}) \quad \text{The pH of the solution of an amphiprotic anion} \quad (4.34)$$

A brief illustration

Using values from Table 4.5, we can immediately conclude that the pH of the solution of sodium hydrogencarbonate of *any concentration* (subject to the conditions just quoted) is

$$\text{pH} = \frac{1}{2}(6.37 + 10.25) = 8.31$$

The solution is basic. We can treat a solution of potassium hydrogenphosphate 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):

$$\text{pH} = \frac{1}{2}(7.21 + 12.67) = 9.94$$

4.11 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 (which provides the species HA) and its conjugate base (which provides the species A^-). To calculate the pH of this solution, we make use of the expression for K_{a} of the weak acid, eqn 4.22, with $[\text{HA}] = [\text{acid}]$ and $[\text{A}^-] = [\text{base}]$, and write

$$K_{\text{a}} = \frac{a_{\text{H}_3\text{O}^+} a_{\text{base}}}{a_{\text{acid}}} \approx \frac{a_{\text{H}_3\text{O}^+} [\text{base}]}{[\text{acid}]}$$

which rearranges first to

$$a_{\text{H}_3\text{O}^+} \approx \frac{K_{\text{a}} [\text{acid}]}{[\text{base}]}$$

and then, by taking negative common logarithms, to the **Henderson–Hasselbalch equation**:

$$\text{pH} = \text{p}K_{\text{a}} - \log \frac{[\text{acid}]}{[\text{base}]}$$

Henderson–Hasselbalch equation:

(4.35)

When the concentrations of the conjugate acid and base are equal, the second term on the right of eqn 4.35 is $\log 1 = 0$, so under these conditions $\text{pH} = \text{p}K_{\text{a}}$. Although the equation has been derived without making any assumptions about $[\text{acid}]$ and $[\text{base}]$, it is common to suppose that, because the acid is weak, $[\text{acid}]$ and $[\text{base}]$ are unchanged from the values used to make up the solution; that is, we disregard the small amount of deprotonation of the added acid and the small amount of protonation of the added base.

A brief illustration

To calculate the pH of a solution formed from equal amounts of $\text{CH}_3\text{COOH}(\text{aq})$ and $\text{NaCH}_3\text{CO}_2(\text{aq})$, we note that the latter dissociates (in the sense that the ions separate) fully in water, yielding $\text{Na}^+(\text{aq})$ and $\text{CH}_3\text{CO}_2^-(\text{aq})$, the conjugate base of $\text{CH}_3\text{COOH}(\text{aq})$. Because $[\text{CH}_3\text{COOH}] = [\text{CH}_3\text{CO}_2^-]$ (that is, $[\text{acid}] = [\text{base}]$), for this solution provided we disregard protonation and deprotonation, $\text{pH} \approx \text{p}K_{\text{a}}$. Because the $\text{p}K_{\text{a}}$ of $\text{CH}_3\text{COOH}(\text{aq})$ is 4.75 (Table 4.4), it follows that $\text{pH} = 4.8$ (more realistically, $\text{pH} = 5$).

Self-test 4.18 Calculate the pH of an aqueous solution that contains equal amounts of NH_3 and NH_4Cl .

Answer: 9.25; more realistically: 9

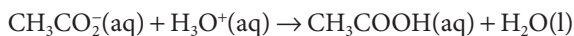
It is observed that solutions containing known amounts of an acid and that acid's conjugate base show **buffer action**, the ability of a solution to oppose changes in pH when small amounts of strong acids and bases are added. An **acid buffer** solution, one that stabilizes the solution at a pH below 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 strong acid; furthermore, the abundant supply of HA molecules (from the acid component of the buffer) can provide H_3O^+ ions to react with any strong base that is added. Similarly, in a base buffer the weak base B can accept protons when a strong acid is added and its conjugate acid BH^+ can supply protons if a strong base is added. The following example explores the quantitative basis of buffer action.

Example 4.8 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 dm³ of (a) 0.15 M CH₃COOH(aq) and (b) a buffer solution containing 0.15 M CH₃COOH(aq) and 0.15 M NaCH₃CO₂(aq).

Strategy Before addition of hydronium ions, the pH of solutions (a) and (b) is 2.8 (Example 4.5) and 4.8 (see the preceding *brief illustration*). After addition to solution (a) the initial molar concentration of CH₃COOH(aq) is 0.15 M and that of H₃O⁺(aq) is (0.020 mol)/(1.0 dm³) = 0.020 M. After addition to solution (b), the initial molar concentrations of CH₃COOH(aq), CH₃CO₂⁻(aq), and H₃O⁺(aq) are 0.15 M, 0.15 M, and 0.020 M, respectively. The weak base already present in solution, CH₃CO₂⁻(aq), reacts immediately with the added hydronium ions:



We use the adjusted concentrations of CH₃COOH(aq) and CH₃CO₂⁻(aq) and eqn 4.45 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 ₃ COOH	H ₃ O ⁺	CH ₃ CO ₂ ⁻
Initial concentration/(mol dm ⁻³)	0.15	0.020	0
Change to reach equilibrium/(mol dm ⁻³)	-x	+x	+x
Equilibrium concentration/(mol dm ⁻³)	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:

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{CH}_3\text{CO}_2^-]}{[\text{CH}_3\text{COOH}]} = \frac{(0.020 + x)x}{0.15 - x}$$

As in Example 4.5, we assume that x is very small; in this case $x \ll 0.020$, and write

$$K_a \approx \frac{0.020x}{0.15}$$

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, $[\text{H}_3\text{O}^+] = 0.020 + x \approx 0.020$ and pH = 1.7. It follows that the pH of the unbuffered solution (a) changes from 2.8 to 1.7 on addition of 0.020 M H₃O⁺(aq).

Now we consider the addition of 0.020 M H₃O⁺(aq) to solution (b). Reaction between the strong acid and weak base consumes the added hydronium ions and changes the concentration of CH₃CO₂⁻(aq) to 0.13 M and the concentration of CH₃COOH(aq) to 0.17 M. It follows from eqn 4.35 that

$$\text{pH} = \text{p}K_a - \log \frac{[\text{CH}_3\text{COOH}]}{[\text{CH}_3\text{CO}_2^-]} = 4.75 - \log \frac{0.17}{0.13} = 4.6$$

The pH of the buffer solution (b) changes only slightly from 4.8 to 4.6 on addition of 0.020 M H₃O⁺(aq).

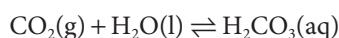
Self-test 4.19 Estimate the change in pH of solution (b) from *Example 4.8* after addition of 0.020 mol of $\text{OH}^-(\text{aq})$.

Answer: 4.9

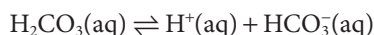
Case study 4.5 Buffer action in blood

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.

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 (*Case study 4.3*):



In red blood cells, this reaction is catalyzed by the enzyme carbonic anhydrase. Aqueous carbonic acid then deprotonates to form bicarbonate (hydrogencarbonate) ion:



The fact that the pH of normal blood is approximately 7.4 implies that $[\text{HCO}_3^-]/[\text{H}_2\text{CO}_3] \approx 20$. 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 $\text{CO}_2(\text{g})$ and $\text{H}_2\text{CO}_3(\text{aq})$ so the pH of blood rises when air is exhaled. 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 (*Case study 4.3*), 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 on the protein's surface (see Fig. 4.16 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 concepts

- | | |
|--|--|
| ☐ 1. The reaction Gibbs energy, $\Delta_r G$, is the slope of a plot of Gibbs energy against composition. | ☐ 8. An endergonic reaction has a positive Gibbs energy; an exergonic reaction has a negative Gibbs energy. |
| ☐ 2. The condition of chemical equilibrium at constant temperature and pressure is $\Delta_r G = 0$. | ☐ 9. The biological standard state corresponds to pH = 7. |
| ☐ 3. 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. | ☐ 10. An endergonic reaction may be driven forward by coupling it to an exergonic reaction. |
| ☐ 4. The equilibrium constant is the value of the reaction quotient at equilibrium. | ☐ 11. The strength of an acid HA is reported in terms of its acidity constant and that of a base B in terms of its basicity constant. |
| ☐ 5. A compound is thermodynamically stable with respect to its elements if $\Delta_f G^\circ < 0$. | ☐ 12. The acid form of a species is dominant if $pH < pK_a$, and the base form is dominant if $pH > pK_a$. |
| ☐ 6. The equilibrium constant of a reaction is independent of the presence of a catalyst. | ☐ 13. The pH of a buffer solution containing equal concentrations of a weak acid and its conjugate base is $pH = pK_a$. |
| ☐ 7. The equilibrium constant K increases with temperature if $\Delta_r H^\circ > 0$ (an endothermic reaction) and decreases if $\Delta_r H^\circ < 0$ (an exothermic reaction). | |

Checklist of key equations

Property	Equation	Comment
Reaction quotient	$Q = a_{\text{C}}^c a_{\text{D}}^d / a_{\text{A}}^a a_{\text{B}}^b$	Dimensionless
Equilibrium constant	$K = (a_{\text{C}}^c a_{\text{D}}^d / a_{\text{A}}^a a_{\text{B}}^b)_{\text{equilibrium}}$	Dimensionless
Reaction Gibbs energy	$\Delta_r G = \Delta_r G^\circ + RT \ln Q$	
Standard reaction Gibbs energy	$\Delta_r G^\circ = \sum_{\text{Products}} \nu \Delta_f G^\circ - \sum_{\text{Reactants}} \nu \Delta_f G^\circ$	Procedure for calculation
Relation to K	$\Delta_r G^\circ = -RT \ln K$	
van 't Hoff equation	$\ln K_2 = \ln K_1 + (\Delta_r H^\circ / R)(1/T_1 - 1/T_2)$	Assumes $\Delta_r H^\circ$ constant over range
Relation between standard states	$\Delta_r G^\ominus = \Delta_r G^\circ + 7\nu RT \ln 10$	
pH	$\text{pH} = -\log a_{\text{H}_3\text{O}^+}$	Definition
Relation between pH and pOH	$\text{pH} + \text{pOH} = \text{p}K_w$	
Acidity constant	$K_a = a_{\text{H}_3\text{O}^+} a_{\text{A}} / a_{\text{HA}}$	Dilute solutions ($a_{\text{H}_2\text{O}} = 1$)
Basicity constant	$K_b = a_{\text{HB}^+} a_{\text{OH}^-} / a_{\text{B}}$	Dilute solutions ($a_{\text{H}_2\text{O}} = 1$)
Autoprotolysis constant	$K_w = a_{\text{H}_3\text{O}^+} a_{\text{OH}^-}$	
Relation between $\text{p}K_a$ and $\text{p}K_b$	$\text{p}K_a + \text{p}K_b = \text{p}K_w$	
pH of amphiprotic anion solution	$\text{pH} = \frac{1}{2}(\text{p}K_{a1} + \text{p}K_{a2})$	$K_{a2} \ll K_{a1}$, $S \gg K_w/K_{a2}$, and $S \gg K_{a1}$
Henderson–Hasselbalch equation	$\text{pH} = \text{p}K_a - \log[\text{acid}]/[\text{base}]$	

Further information

Further information 4.1 The contribution of autoprotolysis to pH

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[−], H₃O⁺, 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 4.20 and 4.24), written here in terms of molar concentrations:

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \quad K_w = [\text{H}_3\text{O}^+][\text{OH}^-] \quad (4.36)$$

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

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{A}^-] \quad (4.37)$$

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:

$$A = [\text{HA}] + [\text{A}^-] \quad (4.38)$$

Now we are ready to proceed with a calculation of the hydronium ion concentration in the solution. First, we combine eqns 4.36 and 4.37 and write

$$[\text{A}^-] = [\text{H}_3\text{O}^+] - \frac{K_w}{[\text{H}_3\text{O}^+]} \quad (4.39)$$

We continue by substituting this expression into eqn 4.39 and solving for [HA]:

$$[\text{HA}] = A - [\text{H}_3\text{O}^+] + \frac{K_w}{[\text{H}_3\text{O}^+]} \quad (4.40)$$

On substituting the expressions for [A[−]] (eqn 4.39) and [HA] (eqn 4.40) into the first of eqn 4.36, we obtain

$$K_a = \frac{[\text{H}_3\text{O}^+] \left([\text{H}_3\text{O}^+] - \frac{K_w}{[\text{H}_3\text{O}^+]} \right)}{A - [\text{H}_3\text{O}^+] + \frac{K_w}{[\text{H}_3\text{O}^+]}} \quad (4.41)$$

Rearrangement of this expression gives

$$[\text{H}_3\text{O}^+]^3 + K_a[\text{H}_3\text{O}^+]^2 - (K_w + K_a A)[\text{H}_3\text{O}^+] - K_a K_w = 0 \quad (4.42)$$

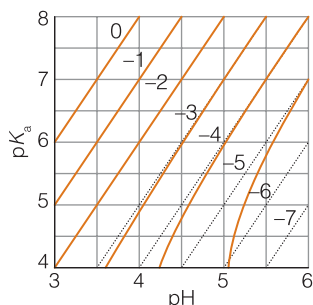


Fig. 4.18 The orange lines are the exact solutions of eqn 4.41 for a series of values of A (expressed as 10^{-x} , with $-x$ displayed). The dotted lines are the corresponding approximate solutions obtained from eqn 4.42b.

and we see that $[\text{H}_3\text{O}^+]$ is determined by solving this cubic equation, a task that is best accomplished with a calculator or mathematical software. Figure 4.18 summarizes the outcome.

There are several experimental conditions that allow us to simplify eqn 4.42. For example, when $K_{\text{a1}} \gg K_{\text{w}}$ and $A[\text{H}_3\text{O}^+] \gg K_{\text{w}}$ it becomes

$$[\text{H}_3\text{O}^+]^2 + K_{\text{a1}}[\text{H}_3\text{O}^+] - K_{\text{a1}}A = 0 \quad (4.43a)$$

which can be solved for $[\text{H}_3\text{O}^+]$. If the extent of deprotonation is very small, we let $[\text{H}_3\text{O}^+] \ll A$ and write

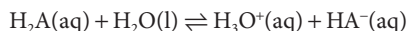
$$K_{\text{a1}} = \frac{[\text{H}_3\text{O}^+]^2}{A}, \text{ so } [\text{H}_3\text{O}^+] = (AK_{\text{a1}})^{1/2} \quad (4.43b)$$

Equations 4.43 are similar to the expressions used in Example 4.5, where we set $[\text{H}_3\text{O}^+]$ equal to x .

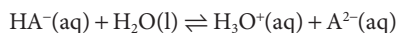
Further information 4.2 The pH of an amphiprotic salt solution

The aim is to calculate the pH of a solution of a salt MHA, where HA^- is an amphiprotic anion (HCO_3^- is an example).

We consider the following two equilibria:



$$K_{\text{a1}} = \frac{[\text{H}_3\text{O}^+][\text{HA}^-]}{[\text{H}_2\text{A}]}$$



$$K_{\text{a2}} = \frac{[\text{H}_3\text{O}^+][\text{A}^{2-}]}{[\text{HA}^-]}$$

together with the autoprotolysis equilibrium, K_{w} . The total concentration of the group A is the sum of the concentrations of the species in which it occurs, which is equal to the concentration of the salt that was added. If we denote the concentration of added salt as S ,

$$\text{Mass conservation: } [\text{H}_2\text{A}] + [\text{HA}^-] + [\text{A}^{2-}] = S \quad (4.44)$$

The solution is electrically neutral overall, so

$$\text{Charge balance: } [\text{M}^+] + [\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{HA}^-] + 2[\text{A}^{2-}] \quad (4.45)$$

with $[\text{M}^+] = S$. The difference of these two equations can be expressed as

$$\begin{aligned} [\text{H}_3\text{O}^+] &= [\text{OH}^-] + [\text{A}^{2-}] - [\text{H}_2\text{A}] \\ &= \frac{K_{\text{w}}}{[\text{H}_3\text{O}^+]} + \frac{[\text{HA}^-]K_{\text{a2}}}{[\text{H}_3\text{O}^+]} - \frac{[\text{HA}^-][\text{H}_3\text{O}^+]}{K_{\text{a1}}} \end{aligned} \quad (4.46)$$

Multiplication through by $[\text{H}_3\text{O}^+]K_{\text{a1}}$ turns this expression into

$$K_{\text{a1}}[\text{H}_3\text{O}^+]^2 = K_{\text{w}}K_{\text{a1}} + [\text{HA}^-]K_{\text{a1}}K_{\text{a2}} - [\text{H}_3\text{O}^+]^2[\text{HA}^-] \quad (4.47)$$

The mass conservation expression can also be written in terms of $[\text{H}_3\text{O}^+]$:

$$\begin{aligned} S &= \frac{[\text{H}_3\text{O}^+][\text{HA}^-]}{K_{\text{a1}}} + [\text{HA}^-] + \frac{[\text{HA}^-]K_{\text{a2}}}{[\text{H}_3\text{O}^+]} \\ &= \left\{ 1 + \frac{[\text{H}_3\text{O}^+]}{K_{\text{a1}}} + \frac{K_{\text{a2}}}{[\text{H}_3\text{O}^+]} \right\} [\text{HA}^-] = H[\text{HA}^-] \end{aligned}$$

When this expression is rearranged for $[\text{HA}^-]$ in terms of S and substituted into eqn 4.46 we find

$$[\text{H}_3\text{O}^+] = \frac{K_{\text{w}}}{[\text{H}_3\text{O}^+]} + \left(\frac{K_{\text{a2}}}{[\text{H}_3\text{O}^+]} - \frac{[\text{H}_3\text{O}^+]}{K_{\text{a1}}} \right) \frac{S}{H} \quad (4.48)$$

To simplify this expression we multiply through by $[\text{H}_3\text{O}^+]H$:

$$H[\text{H}_3\text{O}^+]^2 = HK_{\text{w}} + K_{\text{a2}}S - \frac{[\text{H}_3\text{O}^+]^2S}{K_{\text{a1}}}$$

and then collect terms in $[\text{H}_3\text{O}^+]^2$:

$$\left(H + \frac{S}{K_{\text{a1}}} \right) [\text{H}_3\text{O}^+]^2 = HK_{\text{w}} + K_{\text{a2}}S \quad (4.49)$$

Of course, H depends on $[\text{H}_3\text{O}^+]$, but we take care of that feature later (it will turn out that under the conditions to be specified, $H \approx 1$). The solution is

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \left(\frac{HK_{\text{w}} + K_{\text{a2}}S}{H + S/K_{\text{a1}}} \right)^{1/2} = \left(\frac{HK_{\text{w}}K_{\text{a1}} + K_{\text{a1}}K_{\text{a2}}S}{HK_{\text{a1}} + S} \right)^{1/2} \\ &= \left(\frac{HK_{\text{w}}K_{\text{a1}}/S + K_{\text{a1}}K_{\text{a2}}}{HK_{\text{a1}}/S + 1} \right)^{1/2} \\ &= (K_{\text{a1}}K_{\text{a2}})^{1/2} \left\{ \frac{1 + HK_{\text{w}}/SK_{\text{a2}}}{1 + HK_{\text{a1}}/S} \right\}^{1/2} \end{aligned} \quad (4.50)$$

On taking the negative logarithm, we obtain

$$\text{pH} = \frac{1}{2}(\text{p}K_{\text{a1}} + \text{p}K_{\text{a2}}) - \frac{1}{2} \log f(H) \quad (4.51a)$$

where

$$f(H) = \frac{1 + HK_{\text{w}}/SK_{\text{a2}}}{1 + HK_{\text{a1}}/S} \quad (4.51b)$$

Provided $HK_{\text{w}}/SK_{\text{a2}} \ll 1$ and $HK_{\text{a1}}/S \ll 1$, $f(H) \approx 1$, eqn 4.8a simplifies to

$$\text{pH} = \frac{1}{2}(\text{p}K_{\text{a1}} + \text{p}K_{\text{a2}}) \quad (4.52)$$

which is the form quoted in the text.

The conditions for the validity of eqn 4.52 may be expressed more simply because if eqn 4.52 is a good approximation, we

may use it in the form $[H_3O^+] = (K_{a1}K_{a2})^{1/2}$ to estimate the value of f by noting that

$$H = 1 + \frac{[H_3O^+]}{K_{a1}} + \frac{K_{a2}}{[H_3O^+]} \approx 1 + 2(K_{a2}/K_{a1})^{1/2} \quad (4.53)$$

For small polyprotic species, $K_{a2} \ll K_{a1}$ (this is not always the case for polyprotic enzymes), so $H \approx 1$ and so

$$f(H) \approx \frac{1 + K_w/SK_{a2}}{1 + K_{a1}/S} \quad (4.54)$$

Therefore, eqn 4.52 is valid provided $K_{a2} \ll K_{a1}$, $S \gg K_w/K_{a2}$, and $S \gg K_{a1}$. If these conditions are not fulfilled, then eqn 4.51 must be solved iteratively.

A brief illustration

Suppose we want to know the pH of 0.010 M KHS(aq). Because $K_{a1} = 1.3 \times 10^{-7}$ and $K_{a2} = 7.1 \times 10^{-15}$ ($pK_{a1} = 6.89$,

$pK_{a2} = 14.15$), we test whether we can use eqn 4.52 by forming $K_w/K_{a2} = 1.4$. This ratio is not small compared to $S = 0.010$, so eqn 4.52 cannot be used to obtain the final pH. However, it can be used as a first approximation, and we find $pH = 10.52$, which corresponds to $[H_3O^+] = 3.0 \times 10^{-11}$. This value corresponds to $f(H) = 142.318$, which gives the following improved estimate of the pH:

$$pH = \frac{1}{2}(6.89 + 14.15) - \frac{1}{2} \log 142.318 = 9.44$$

Next, we use this value to calculate an improved value of f , namely $f(H) = 142.650$, so

$$pH = \frac{1}{2}(6.89 + 14.15) - \frac{1}{2} \log 142.650 = 9.44$$

This value is unchanged from the previous estimate, so we accept it as the final value. Note that the estimate from eqn 4.51 is significantly different but that only one round of improvement is necessary in this case.

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, $\Delta_r G^\ominus = -218 \text{ kJ mol}^{-1}$ and $\Delta_r H^\ominus = -120 \text{ kJ mol}^{-1}$ 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 Use the Boltzmann distribution to describe the molecular features that determine the magnitudes of equilibrium constants and their variation with temperature.

4.6 Describe the basis of buffer action.

4.7 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 $\ln K_2 = \ln K_1 + (\Delta_r H^\ominus/R)(1/T_1 - 1/T_2)$.

Exercises

4.8 Write the expressions for the equilibrium constants for the following reactions, making the approximation of replacing activities by molar concentrations or partial pressures:

- $G6P(aq) + H_2O(l) \rightleftharpoons G(aq) + P_i(aq)$, where G6P is glucose-6-phosphate, G is glucose, and P_i is inorganic phosphate.
- $Gly(aq) + Ala(aq) \rightleftharpoons Gly-Ala(aq) + H_2O(l)$
- $Mg^{2+}(aq) + ATP^{4-}(aq) \rightleftharpoons MgATP^{2-}(aq)$
- $2 CH_3COCOOH(aq) + 5 O_2(g) \rightleftharpoons 6 CO_2(g) + 4 H_2O(l)$

4.9 The equilibrium constant for the reaction $A + B \rightleftharpoons 2 C$ is reported as 3.4×10^4 . What would it be for the reaction written as (a) $2 C \rightleftharpoons A + B$, (b) $2 A + 2 B \rightleftharpoons 4 C$, and (c) $\frac{1}{2} A + \frac{1}{2} B \rightleftharpoons C$?

4.10 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.

4.11 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?

4.12 What is the value of the equilibrium constant of a reaction for which $\Delta_r G^\ominus = 0$?

4.13 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 .

4.14 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 dm^{-3} and (b) $1.0 \text{ } \mu\text{mol dm}^{-3}$?

4.15 The distribution of Na^+ ions across a typical biological membrane is 10 mmol dm^{-3} inside the cell and 140 mmol dm^{-3} 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.

4.16 For the hydrolysis of ATP at 37°C , $\Delta_r H^\ominus = -20 \text{ kJ mol}^{-1}$ and $\Delta_r S^\ominus = +34 \text{ J K}^{-1} \text{ mol}^{-1}$. Assuming that these quantities remain constant, estimate the temperature at which the equilibrium constant for the hydrolysis of ATP becomes greater than 1.

4.17 Calculate the standard biological Gibbs energy for the reaction

$$\text{pyruvate}^-(\text{aq}) + \text{NADH}(\text{aq}) + \text{H}^+(\text{aq}) \rightarrow \text{lactate}^-(\text{aq}) + \text{NAD}^+(\text{aq})$$

at 310 K given that $\Delta_r G^\ominus = -66.6 \text{ kJ mol}^{-1}$. (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.

4.18 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?

4.19 Estimate the values of the biological standard Gibbs energies of the following phosphate transfer reactions:

- $\text{GTP}(\text{aq}) + \text{ADP}(\text{aq}) \rightarrow \text{GDP}(\text{aq}) + \text{ATP}(\text{aq})$
- $\text{Glycerol}(\text{aq}) + \text{ATP}(\text{aq}) \rightarrow \text{glycerol-1-phosphate} + \text{ADP}(\text{aq}) + \text{H}^+(\text{aq})$
- $3\text{-Phosphoglycerate}(\text{aq}) + \text{ATP}(\text{aq}) \rightarrow 1,3\text{-bis(phospho)glycerate}(\text{aq}) + \text{ADP}(\text{aq})$

4.20 Two polynucleotides with sequences $A_n U_n$ (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 $A_n U_n$ polypeptides.

4.21 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: $p_{\text{CO}_2} = 53 \text{ mbar}$, $p_{\text{O}_2} = 132 \text{ mbar}$, $[\text{glucose}] = 5.6 \times 10^{-2} \text{ mol dm}^{-3}$, $[\text{ATP}] = [\text{ADP}] = [\text{P}_i] = 1.0 \times 10^{-4} \text{ mol dm}^{-3}$, $\text{pH} = 7.4$, $T = 310 \text{ K}$. Assuming that activities can be replaced by the numerical values of molar concentrations, calculate the efficiency of aerobic respiration under these physiological conditions.

4.22 The second step in glycolysis is the isomerization of glucose-6-phosphate (G6P) to fructose-6-phosphate (F6P). Example 4.3 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.

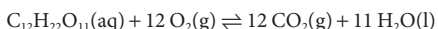
4.23 The saturation curves shown in Fig. 4.9 may also be modeled mathematically by the equation

$$\log \frac{s}{1-s} = v \log p - v \log K$$

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 v 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 v has the theoretical maximum value of 4.

4.24 Classify the following compounds as endergonic or exergonic: (a) glucose, (b) urea, (c) octane, and (d) ethanol.

4.25 Consider the combustion of sucrose:



(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 nonexpansion work that can be extracted from a process. What is the maximum energy that can be extracted as (i) heat and (ii) nonexpansion work when 1.0 kg of sucrose is burned under standard conditions at 298 K ?

4.26 Is it more energy effective to ingest sucrose or glucose? Calculate the nonexpansion 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 4.25b.

4.27 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?

4.28 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.

4.29 The conversion of fumarate ion to malate ion is catalyzed by the enzyme fumarase:



Use the following data to determine the standard reaction enthalpy:

$\theta/^\circ\text{C}$	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

4.30 What is the standard enthalpy of a reaction for which the equilibrium constant is (a) doubled and (b) halved when the temperature is increased by 10 K at 298 K ?

4.31 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 ($\text{CH}_3\text{CHOHCOOH}$), (c) glutamic acid

($\text{HOOCCH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$), (d) glycine ($\text{NH}_2\text{CH}_2\text{COOH}$), and (e) oxalic acid (HOOCCOOH).

4.32 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 $[\text{H}_3\text{O}^+]$ 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 ?

4.33 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 $pK_w(\text{D}_2\text{O})$.

4.34 The molar concentration of H_3O^+ ions in the following solutions was measured at 25°C . Calculate the pH and pOH of the solutions: (a) $15 \mu\text{mol dm}^{-3}$ (a sample of rainwater), (b) 1.5 mmol dm^{-3} , (c) $5.1 \times 10^{-14} \text{ mol dm}^{-3}$, and (d) $5.01 \times 10^{-5} \text{ mol dm}^{-3}$.

4.35 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) , and (c) 21.2 cm^3 of $0.22 \text{ M HNO}_3\text{(aq)}$ was added to 10.0 cm^3 of 0.30 M NaOH(aq) .

4.36 Determine whether aqueous solutions of the following salts have a pH equal to, greater than, or less than 7; if $\text{pH} > 7$ or $\text{pH} < 7$, write a chemical equation to justify your answer: (a) NH_4Br , (b) Na_2CO_3 , (c) KF , (d) KBr .

4.37 (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 dm^3 contains 10.0 g of potassium bromide. What is the percentage of Br^- ions that are protonated?

4.38 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 $\text{pH} = 3.08$. (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?

4.39 Calculate the pH, pOH, and fraction of solute protonated or deprotonated in the following aqueous solutions: (a) $0.120 \text{ M CH}_3\text{CH}(\text{OH})\text{COOH(aq)}$ (lactic acid), (b) $1.4 \times 10^{-4} \text{ M CH}_3\text{CH}(\text{OH})\text{COOH(aq)}$, (c) $0.15 \text{ M NH}_4\text{Cl(aq)}$, (d) $0.15 \text{ M NaCH}_3\text{CO}_2\text{(aq)}$, and (e) $0.112 \text{ M (CH}_3)_3\text{N(aq)}$ (trimethylamine).

4.40 Show graphically the variation with pH of the composition of the following aqueous solutions: (a) $0.010 \text{ M glycine(aq)}$ and (b) $0.010 \text{ M tyrosine(aq)}$.

4.41 Calculate the pH of the following acid solutions at 25°C ; ignore second deprotonations only when that approximation is justified: (a) $1.0 \times 10^{-4} \text{ M H}_3\text{BO}_3\text{(aq)}$ (boric acid acts as a monoprotic acid), (b) $0.015 \text{ M H}_3\text{PO}_4\text{(aq)}$, and (c) $0.10 \text{ M H}_2\text{SO}_4\text{(aq)}$.

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, and (c) 1.5?

4.43 Appreciable concentrations of the potassium and calcium salts of oxalic acid, $(\text{COOH})_2$, are found in many leafy green plants, such as rhubarb and spinach. (a) Calculate the molar concentrations of HOOCO_2^- , $(\text{CO}_2)_2^{2-}$, H_3O^+ , and OH^- in $0.15 \text{ M (COOH)}_2\text{(aq)}$. (b) Calculate the pH of a solution of 0.15 M 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 $0.065 \text{ M H}_2\text{S(aq)}$.

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 4.4 and Section 4.10.

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, and (e) hydroxylamine and hydroxylammonium chloride.

4.47 From the information in Tables 4.4 and 4.5, select suitable buffers for (a) $\text{pH} = 2.2$ and (b) $\text{pH} = 7.0$.

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 The denaturation of a biological macromolecule can be described by the equilibrium

macromolecule in native form $\rightleftharpoons$ macromolecule in denatured form

(a) Show that the fraction θ of denatured macromolecules is related to the equilibrium constant K_d for the denaturation process by

$$\theta = \frac{K_d}{1 + K_d}$$

(b) Write an expression for the temperature dependence of K_d in terms of the standard enthalpy and standard entropy of denaturation.

(c) At pH = 2, the standard enthalpy and entropy of denaturation of the enzyme 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), plot θ against T . Compare the shape of your plot with that of the plot shown in Fig. 3.16.

(d) The ‘melting temperature’ of a biological macromolecule is the temperature at which $\theta = \frac{1}{2}$. Use your results from part (c) to calculate the melting temperature of chymotrypsin at pH = 2.

(e) 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?

4.50 The unfolding of a protein may be brought about by treatment with *denaturants*, substances such as guanidinium hydrochloride (GuHCl; the guanidinium ion is (NH₂)₂C=NH₂⁺) 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 $[D]$:

$$\Delta G_d^\circ = \Delta G_{d,\text{water}}^\circ - m[D]$$

where m is an empirical parameter that measures the sensitivity of unfolding to denaturant concentration and $\Delta G_{d,\text{water}}^\circ$ 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.

(a) At 27°C and pH 6.5, the fraction θ of native 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 dm ⁻³)	0.00	0.75	1.35	1.70	2.00	2.35	2.70	3.00

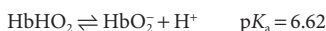
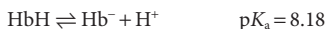
Calculate m and $\Delta G_{d,\text{water}}^\circ$ for chymotrypsin under these experimental conditions.

(b) Using the same data and the expression for θ from Exercise 4.49, plot θ against $[\text{GuHCl}]$. Comment on the shape of the curve.

(c) To gain insight into your results from part (b), you will now derive an equation that relates θ to $[D]$. Begin by showing that $\Delta G_{d,\text{water}}^\circ = m[D]_{1/2}$, 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 (a). Is the shape of your plot consistent with your results from part (b)?

4.51 In *Case study* 4.5 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:



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 CO₂ for O₂ in tissue is accompanied by complex proton transfer equilibria: the release of CO₂ into blood produces hydronium ions that can be bound tightly to hemoglobin once it releases O₂. These processes prevent changes in the pH of blood. To treat the problem more quantitatively, let us calculate the amount of CO₂ 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 O₂ by the fully oxygenated protein at pH = 7.4. (iv) Finally, use the result from part (b.iii) to calculate the amount of CO₂ that can be released into the blood per mole of hemoglobin molecules at pH = 7.4.

Thermodynamics of ion and electron transport

5



Measurements such as the ones we describe in this chapter lead to collections of data that are very useful for discussing the characteristics of electrolyte solutions and the migration of ions across biological membranes. They are used to discuss the details of the propagation of signals in neurons and of the synthesis of ATP.

We shall also see that such apparently unrelated processes as oxidation of fuels, respiration, and photosynthesis are actually all closely related, for in each of them an electron, sometimes accompanied by a group of atoms, is transferred from one species to another. Indeed, together with the proton transfer typical of acid–base reactions, processes in which electrons are transferred, the so-called **redox reactions**, account for many of the reactions encountered in chemistry and biology.

Transport of ions across biological membranes

The cell membrane may be regarded as a barrier that slows down the transfer of material into or out of the cell. Here we focus on the transport of ions across biological membranes. We begin by developing some general ideas about solutions of electrolytes. Then we describe the thermodynamics of ion transport mediated by special membrane-spanning proteins. In Section 5.10 we shall see how electron transfer reactions during the later stages of aerobic metabolism of glucose couple to the movement of protons across biological membranes and contribute to the synthesis of ATP.

5.1 Ions in solution

To prepare for the discussion of biological redox reactions and the role of ions in physiological processes, we need to describe the factors that influence the activities of ions in aqueous solutions.

The most significant difference between the solution of an electrolyte and a non-electrolyte is that there are long-range Coulombic interactions between the ions in the former. As a result, electrolyte solutions exhibit nonideal behavior even at very low concentrations because the solute particles, the ions, do not move independently of one another. Some idea of the importance of ion–ion interactions is obtained by noting their average separations in solutions of different molar concentration c and, to appreciate the scale, the typical number of H_2O molecules that can fit between them:

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$c/\text{mol dm}^{-3}$	0.001	0.01	0.1	1	10
Separation/nm	90	40	20	9	4
Number of H_2O molecules	30	14	6	3	1

(a) Activity coefficients

To take the interactions into account—which become very serious for concentrations of 0.01 mol dm^{-3} and more—we work with the activities of the charged solutes. We saw in Section 3.8 that the activity, a_j , is a kind of effective concentration and is related to concentrations by multiplication by an activity coefficient, γ_j . There are various ways of expressing concentration; in the first part of this chapter we use the molality, b_j , and write

$$a_j = \gamma_j b_j / b^\ominus \quad (5.1a)$$

with $b^\ominus = 1 \text{ mol kg}^{-1}$. For notational simplicity, we often replace $b_j/b^\ominus$ by b_j , interpret b_j as the numerical value of the molality, and write

$$a_j = \gamma_j b_j \quad (5.1b)$$

Because the solution becomes more ideal as the molality approaches zero, we know that $\gamma_j \rightarrow 1$ as $b_j \rightarrow 0$. Once we know the activity of the species J, we can write its chemical potential by using

$$\mu_j = \mu_j^\ominus + RT \ln a_j \quad (5.2)$$

Mathematical toolkit 5.1 Exponentials and logarithms

The **exponential function**, e^x (where $e = 2.718 \dots$) has the following important properties:

$$e^x \times e^y = e^{x+y}$$

$$\frac{e^x}{e^y} = e^{x-y}$$

$$(e^x)^a = e^{ax}$$

The **natural logarithm** of a number x is denoted as $\ln x$ and is defined as the power to which e must be raised for the result to be equal to x . It follows from the definition of logarithms that

$$\ln x + \ln y = \ln xy$$

$$\ln x - \ln y = \ln \frac{x}{y}$$

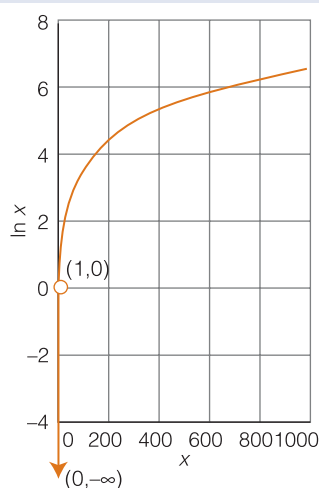
$$a \ln x = \ln x^a$$

Useful points about logarithms are summarized in the graph below:

- Logarithms increase only very slowly as x increases.
- The logarithm of 1 is 0: $\ln 1 = 0$.
- The logarithms of numbers less than 1 are negative.
- In elementary mathematics the logarithms of negative numbers are not defined.

The **common logarithm** of a number is the logarithm compiled with 10 in place of e ; common logarithms are denoted $\log x$. Common logarithms follow the same rules of addition and subtraction as natural logarithms. Common and natural logarithms ($\log$ and $\ln$, respectively) are related by

$$\ln x = \ln 10 \times \log x \approx 2.303 \log x$$



The thermodynamic properties of the solution—such as the equilibrium constants of reactions involving ions—can then be derived in the same way as for ideal solutions but with activities in place of concentrations. However, when we want to relate the results we derive, we need to know how to relate activities to concentrations. We ignored that problem when discussing acids and bases and simply assumed that all activity coefficients were 1. The cytoplasm and other fluids in organisms have ion concentrations that are far too high to behave ideally, so $\gamma = 1$ is a poor approximation; in this chapter, we see how to improve that approximation.

One problem that confronts us from the outset is that cations and anions always occur together in solution. As a result, there is no experimental procedure for distinguishing the deviations from ideal behavior due to the cations from those of the anions: we cannot measure the activity coefficients of cations and anions separately. The best we can do experimentally is to ascribe deviations from ideal behavior equally to each kind of ion and to talk in terms of a **mean activity coefficient**, $\gamma_{\pm}$. For a salt MX, such as NaCl, we show in the following *Justification* that the mean activity coefficient is related to the activity coefficients of the individual ions as follows:

$$\gamma_{\pm} = (\gamma_+ \gamma_-)^{1/2} \quad \text{Mean activity coefficient for a salt MX} \quad (5.3a)$$

For a salt M_pX_q , the mean activity coefficient is related to the activity coefficients of the individual ions as follows:

$$\gamma_{\pm} = (\gamma_+^p \gamma_-^q)^{1/s} \quad s = p + q \quad \text{Mean activity coefficient for a salt } M_pX_q \quad (5.3b)$$

Justification 5.1 Mean activity coefficients

In this *Justification*, we use the relation $\ln xy = \ln x + \ln y$ several times (sometimes as $\ln x + \ln y = \ln xy$) and its implication (by setting $y = x$) that $\ln x^2 = 2 \ln x$ (see *Mathematical toolkit* 5.1). For a salt MX that dissociates completely in solution, the molar Gibbs energy of the ions is

$$G_m = \mu_+ + \mu_-$$

where μ_+ and μ_- are the chemical potentials of the cations and anions, respectively. Each chemical potential can be expressed in terms of a molality b and an activity coefficient γ by using eqn 5.2 ($\mu = \mu^\circ + RT \ln a$) and then eqn 5.1 ($a = \gamma b$) together with $\ln \gamma b = \ln \gamma + \ln b$, which gives

$$\begin{aligned} G_m &= (\mu_+^\circ + RT \ln \gamma_+ b_+) + (\mu_-^\circ + RT \ln \gamma_- b_-) \\ &= (\mu_+^\circ + RT \ln \gamma_+ + RT \ln b_+) + (\mu_-^\circ + RT \ln \gamma_- + RT \ln b_-) \end{aligned}$$

We now use $\ln x + \ln y = \ln xy$ again to combine the two terms involving the activity coefficients as

$$RT \ln \gamma_+ + RT \ln \gamma_- = RT(\ln \gamma_+ + \ln \gamma_-) = RT \ln \gamma_+ \gamma_-$$

and write

$$G_m = (\mu_+^\circ + RT \ln b_+) + (\mu_-^\circ + RT \ln b_-) + RT \ln \gamma_+ \gamma_-$$

We now write the term inside the logarithm as $\gamma_{\pm}^2$ and use $\ln x^2 = 2 \ln x$ to obtain

$$\begin{aligned} G_m &= (\mu_+^{\circ} + RT \ln b_+) + (\mu_-^{\circ} + RT \ln b_-) + 2RT \ln \gamma_{\pm} \\ &= (\mu_+^{\circ} + RT \ln b_+ + RT \ln \gamma_{\pm}) + (\mu_-^{\circ} + RT \ln b_- + RT \ln \gamma_{\pm}) \\ &= (\mu_+^{\circ} + RT \ln \gamma_{\pm} b_+) + (\mu_-^{\circ} + RT \ln \gamma_{\pm} b_-) \end{aligned}$$

We see that, with the mean activity coefficient defined as in eqn 5.3a, the deviation from ideal behavior (as expressed by the activity coefficient) is now shared equally between the two types of ion. In exactly the same way, the Gibbs energy of a salt M_pX_q can be written

$$G_m = p(\mu_+^{\circ} + RT \ln \gamma_{\pm} b_+) + q(\mu_-^{\circ} + RT \ln \gamma_{\pm} b_-)$$

with the mean activity coefficient defined as in eqn 5.3b.¹

A brief illustration

Suppose that we have devised a method for determining the activity coefficients of Na^+ and SO_4^{2-} ions in 0.010 m $\text{Na}_2\text{SO}_4(\text{aq})$ and found them to be 0.98 and 0.84, respectively. It follows from eqn 5.3b that the mean activity coefficient is

$$\gamma_{\pm} = \{(0.98)^2 \times (0.84)\}^{1/3} = 0.93$$

because $p = 2$, $q = 1$, and $s = 3$. From eqn 5.1b, the activities of the two ions are

$$a_+ = \gamma_{\pm} b_+ = 0.93 \times (2 \times 0.010) = 0.019$$

$$a_- = \gamma_{\pm} b_- = 0.93 \times (0.010) = 0.0093$$

Self-test 5.1 Write an expression for the mean activity coefficient of Mg^{2+} and PO_4^{3-} in an aqueous solution of $\text{Mg}_3(\text{PO}_4)_2$.

Answer: $\gamma_{\pm} = (\gamma_+^3 \gamma_-^2)^{1/5}$

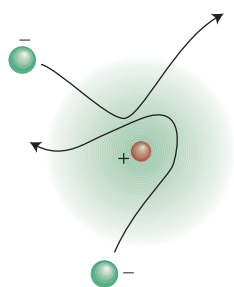


Fig. 5.1 The ionic atmosphere surrounding an ion consists of a slight excess of opposite charge as ions move through the vicinity of the central ion, with counter-ions lingering longer than ions of the same charge. The ionic atmosphere lowers the energy of the central ion.

(b) Debye–Hückel theory

The question still remains about how the mean activity coefficients can be estimated. A theory that accounts for their values in very dilute solutions was developed by Peter Debye and Erich Hückel in 1923. They supposed that each ion in solution is surrounded by an **ionic atmosphere** of counter-charge. This ‘atmosphere’ is actually the slight imbalance of charge arising from the competition between the stirring effect of thermal motion, which tends to keep all the ions distributed uniformly throughout the solution, and the Coulombic interaction between ions, which tends to attract counter-ions (ions of opposite charge) into each other’s vicinity and repel ions of like charge (Fig. 5.1). As a result of this competition, there is a slight preponderance of cations near any anion, giving a positively charged ionic atmosphere around the anion, and a slight preponderance of anions near any cation, giving a negatively charged ionic atmosphere around the cation. Because each ion is in an atmosphere of opposite charge, its

¹ For the details of this general case, see our *Physical chemistry* (2010).

energy is lower than in a uniform, ideal solution, and therefore its chemical potential is lower than in an ideal solution. A lowering of the chemical potential of an ion below its ideal solution value is equivalent to the activity coefficient of the ion being less than 1 (because $\ln \gamma$ is negative when $\gamma < 1$). Debye and Hückel were able to derive an expression that is a limiting law in the sense that it becomes increasingly valid as the concentration of ions approaches zero. The **Debye–Hückel limiting law**² is

$$\log \gamma_{\pm} = -A |z_+ z_-| I^{1/2} \quad \text{Debye–Hückel limiting law} \quad (5.4)$$

(Note the common logarithm.) In this expression, A is a constant that for water at 25°C works out as 0.509. The z_i are the charge numbers of the ions (so $z_+ = +1$ for Na^+ and $z_- = -2$ for SO_4^{2-}); the vertical bars mean that we ignore the sign of the product. The quantity I is the dimensionless **ionic strength** of the solution, which is defined in terms of the molalities of the ions as

$$I = \frac{1}{2} (z_+^2 b_+ + z_-^2 b_-) / b^\circ \quad (5.5a)$$

When using this expression, we must include all the ions present in the solution, not just those of interest. For instance, if you are calculating the ionic strength of a solution of silver chloride and potassium nitrate, there are contributions to the ionic strength from all four types of ion. When more than two ions contribute to the ionic strength, we write

$$I = \frac{1}{2} \sum_i z_i^2 b_i / b^\circ \quad \text{General expression for the ionic strength} \quad (5.5b)$$

where the symbol $\sum$ denotes a sum (in this case of all terms of the form $z_i^2 b_i$), z_i is the charge number of an ion i (positive for cations and negative for anions), and b_i is its molality.

A brief illustration

The sulfate ion, SO_4^{2-} , is an important source of sulfur used in the synthesis of the amino acids cysteine and methionine in plants and bacteria. To estimate the mean activity coefficient for the ions in 0.0010 m $\text{Na}_2\text{SO}_4(\text{aq})$ at 25°C, we begin by evaluating the ionic strength of the solution from eqn 5.5:

$$I = \frac{1}{2} \{ (+1)^2 \times (2 \times 0.0010) + (-2)^2 \times (0.0010) \} = 0.0030$$

Then we use the Debye–Hückel limiting law (eqn 5.4), with $A = 0.509$, to calculate $\log \gamma_{\pm}$:

$$\log \gamma_{\pm} = -0.509 \times |(+1)(-2)| \times (0.0030)^{1/2} = -2 \times 0.509 \times (0.0030)^{1/2}$$

(This expression evaluates to -0.056 .) On taking the antilogarithm of $\log \gamma_{\pm}$ (by using $x = 10^{\log x}$), we conclude that $\gamma_{\pm} = 0.88$.

Self-test 5.2 Estimate the mean activity coefficient of NaCl in a solution that is 0.020 m $\text{NaCl}(\text{aq})$ and 0.035 m $\text{Ca}(\text{NO}_3)_2(\text{aq})$.

Answer: 0.661

² For a derivation of the Debye–Hückel limiting law, see our *Physical chemistry* (2010).

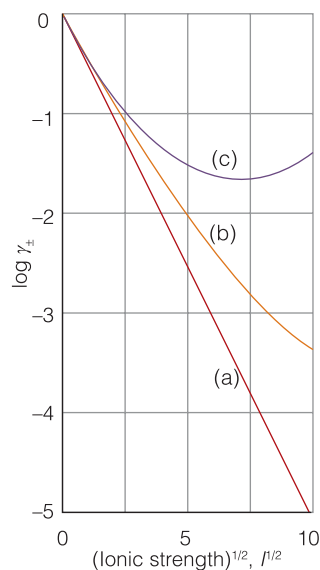


Fig. 5.2 The variation of the mean activity coefficient with ionic strength according to the extended Debye–Hückel theory. (a) The limiting law for a 1,1-electrolyte. (b) The extended law with $B = 0.5$. (c) The extended law, extended further by the addition of a term CI ; in this case with $C = 0.02$. The last form of the law reproduces the observed behavior reasonably well.

As we have stressed, eqn 5.4 is a *limiting* law and is reliable only in very dilute solutions. For solutions more concentrated than about 10^{-3} M, it is better to use an empirical modification known as the **extended Debye–Hückel law**:

$$\log \gamma_{\pm} = \frac{A |z_+ z_-| I^{1/2}}{1 + BI^2} + CI \quad \text{Extended Debye–Hückel law} \quad (5.6)$$

with B and C empirically determined constants (Fig. 5.2).

5.2 Passive and active transport of ions across biological membranes

Nature has devised complex strategies for controlling the flow of ions across cell membranes, some of which are thermodynamic and others kinetic. Here we consider thermodynamic aspects of ion transport.

With a better understanding of how ions behave in solution, we are now prepared to discuss their behavior in cells. The concepts developed in the previous sections can be applied to the aqueous environment inside and outside cells. But we also need to know how ions traverse cell membranes and how such transport controls important biological processes, such as the synthesis of ATP and neuronal activity.

The thermodynamic tendency to transport a species A through a biological cell membrane is partially determined by an activity gradient across the membrane, which results in a difference in molar Gibbs energy between the inside and the outside of the cell

$$\Delta G_m = G_{m,\text{in}} - G_{m,\text{out}} = RT \ln a_{\text{in}}/a_{\text{out}} \quad (5.7)$$

The equation implies that transport into the cell of either neutral or charged species is thermodynamically favorable if $a_{\text{in}} < a_{\text{out}}$ or, if we set the activity coefficients to 1, if $[A]_{\text{in}} < [A]_{\text{out}}$. An ion also needs to cross a membrane potential difference $\Delta\phi = \phi_{\text{in}} - \phi_{\text{out}}$ that arises from differences in Coulomb repulsions on each side of the bilayer. This potential difference is measured in volts (V, where $1 \text{ V} = 1 \text{ J C}^{-1}$). We show in the following *Justification* that the Gibbs energy of transfer of an ion of charge number z across a potential difference $\Delta\phi$ adds a term $zF\Delta\phi$ to eqn 5.7, where F is **Faraday's constant**, the magnitude of electric charge per mole of electrons:

$$F = eN_A = 96.485 \text{ kC mol}^{-1}$$

The final expression for G_m is then

$$\Delta G_m = RT \ln \frac{[A]_{\text{in}}}{[A]_{\text{out}}} + zF\Delta\phi \quad \text{Gibbs energy of transfer of an ion across a membrane potential gradient} \quad (5.8)$$

Justification 5.2 *The Gibbs energy of transfer of an ion across a membrane potential gradient*

The charge transferred per mole of ions of charge number z that cross a lipid bilayer is $N_A \times (ze)$, or zF , where $F = eN_A$. The work w' of transporting this charge is equal to the product of the charge and the potential difference $\Delta\phi$:

$$w' = zF \times \Delta\phi$$

Provided the work is done reversibly at constant temperature and pressure, we can equate this work to the molar Gibbs energy of transfer and write

$$\Delta G_m = zF\Delta\phi$$

Adding this term to eqn 5.7 gives eqn 5.8, the total Gibbs energy of transfer of an ion across both an activity and a membrane potential gradient.

Example 5.1 Estimating a membrane potential

Estimate the equilibrium membrane potential of a cell at 298 K by using the fact that the concentration of K^+ inside the cell is about 20 times that on the outside. Repeat the calculation, this time using the fact that the concentration of Na^+ outside the cell is about 10 times that on the inside.

Strategy Because the cell is at equilibrium, set $\Delta G_m = 0$ in eqn 5.8 and, after rearrangement, write

$$\Delta\phi = -\frac{RT}{zF} \ln \frac{[A]_{in}}{[A]_{out}}$$

where $z = +1$ for both K^+ and Na^+ . Then calculate the equilibrium membrane potential from the given temperature and concentration ratios.

Solution When $[K^+]_{in}/[K^+]_{out} = 20$, we obtain

$$\Delta\phi = -\frac{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K})}{9.648 \times 10^4 \text{ C mol}^{-1}} \ln 20 = -7.69 \times 10^{-2} \text{ V} = -76.9 \text{ mV}$$

where we have used $1 \text{ V} = 1 \text{ J C}^{-1}$. The negative sign denotes that the inside has the lower potential. When $[Na^+]_{in}/[Na^+]_{out} = 0.10$, we obtain

$$\Delta\phi = -\frac{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K})}{9.648 \times 10^4 \text{ C mol}^{-1}} \ln 0.10 = +5.91 \times 10^{-2} \text{ V} = +59.1 \text{ mV}$$

and the positive sign denotes that the outside has the lower potential.

Self-test 5.3 Is the transport of Na^+ ions across a cell membrane spontaneous when $[Na^+]_{in}/[Na^+]_{out} = 0.10$ and $\Delta\phi = +50 \text{ mV}$?

Answer: Yes, because $\Delta G_m < 0$

Equation 5.8 implies that there is a tendency, called **passive transport**, for a species to move down concentration and membrane potential gradients. In **active transport**, a species moves against these gradients and the process is driven by its coupling to the exergonic hydrolysis of ATP. That is, when the sum of $RT \ln([A]_{in}/[A]_{out})$ and $zF\Delta\phi$ is positive, the overall Gibbs energy of transport can be made negative (and the process becomes spontaneous) by a large and negative Gibbs energy of ATP hydrolysis. It follows that the overall Gibbs energy of transport into a cell may be written as

$$\Delta G_m = RT \ln \frac{[A]_{in}}{[A]_{out}} + zF\Delta\phi + \Delta_r G^{\text{ATP}} \quad (5.9)$$

Overall Gibbs energy of transfer of an ion across a biological membrane

where $\Delta_r G^{\text{ATP}}$ is the Gibbs energy of hydrolysis of ATP at specific concentrations of ATP, ADP, P_i , and hydronium ion.

5.3 Ion channels and ion pumps

The mechanism of signal propagation along neurons in organisms is due to the migration of ions through membranes.

The transport of ions into or out of a cell needs to be mediated (that is, involve other species) because charged species do not partition well into the hydrophobic environment of the membrane. There are two mechanisms for ion transport: mediation by a carrier molecule or transport through a **channel former**, a protein that creates a hydrophilic pore through which the ion can pass. An example of a channel former is the polypeptide gramicidin A, which increases the membrane permeability to cations such as H^+ , K^+ , and Na^+ .

Ion channels are proteins that permit the movement of specific ions down a membrane potential gradient. They are highly selective, so there is a channel protein for Ca^{2+} , another for Cl^- , and so on. In a *voltage-gated channel*, the opening of the gate is triggered by a membrane potential. In a *ligand-gated channel* ion transport is initiated by the binding of a molecule (called an 'effector molecule') to a specific receptor site on the channel.

Ions such as H^+ , Na^+ , K^+ , and Ca^{2+} are often transported actively across membranes by membrane-spanning proteins called **ion pumps**. Ion pumps are molecular machines that work by adopting conformations that are permeable to one type of ion but not others, depending on the state of phosphorylation of the protein. Because protein phosphorylation requires dephosphorylation of ATP, the conformational change that opens or closes the pump is endergonic and requires the use of energy stored during metabolism. In Sections 5.10 and 8.8 we discuss the ion pump H^+ -ATPase, which plays an important role in oxidative phosphorylation.

Case study 5.1 Action potentials

A striking example of the importance of ion channels is their role in the propagation of impulses by neurons, the fundamental units of the nervous system. Here we give a thermodynamic description of the process.

The cell membrane of a neuron is more permeable to K^+ ions than to either Na^+ or Cl^- ions. The key to the mechanism of action of a nerve cell is its use of Na^+ and K^+ channels to move ions across the membrane, modulating its potential. For example, the concentration of K^+ inside an inactive nerve cell is about 20 times that on the outside, whereas the concentration of Na^+ outside the cell is about 10 times that on the inside. The difference in concentrations of ions results in a transmembrane potential difference of about -62 mV. This potential difference is also called the **resting potential** of the cell membrane.

To estimate the resting potential, we need to understand that the cell is never at equilibrium, so the approach taken in *Example 5.1* is not appropriate. Ions continually cross the membrane, which is more permeable to some ions than others. To take into account membrane permeability, we use the **Goldman equation** to calculate the resting potential:

$$\Delta\phi = \frac{RT}{F} \ln \frac{y}{y'} \quad \text{Goldman equation} \quad (5.10)$$

with

$$y = \sum_i P_i [M_i^+]_{\text{out}} + \sum_j P_j [X_j^-]_{\text{in}}, \quad y' = \sum_i P_i [M_i^+]_{\text{in}} + \sum_j P_j [X_j^-]_{\text{out}}$$

where P_i and P_j are the relative permeabilities, respectively, for the cation M_i^+ and the anion X_j^- and the sum is over all ions.

A brief illustration

For example, taking the permeabilities of the K^+ , Na^+ , and Cl^- ions as $P_{K^+} = 1.0$, $P_{Na^+} = 0.04$, and $P_{Cl^-} = 0.45$, respectively, the temperature as 298 K, and the concentrations as $[K^+]_{\text{in}} = 400 \text{ mmol dm}^{-3}$, $[Na^+]_{\text{in}} = 50 \text{ mmol dm}^{-3}$, $[Cl^-]_{\text{in}} = 50 \text{ mmol dm}^{-3}$, $[K^+]_{\text{out}} = 20 \text{ mmol dm}^{-3}$, $[Na^+]_{\text{out}} = 500 \text{ mmol dm}^{-3}$, and $[Cl^-]_{\text{out}} = 560 \text{ mmol dm}^{-3}$, we obtain

$$\begin{aligned} y &= (1.0 \times 20) + (0.04 \times 500) + (0.45 \times 50) \text{ mmol dm}^{-3} = 62.5 \text{ mmol dm}^{-3} \\ y' &= (1.0 \times 400) + (0.04 \times 50) + (0.45 \times 560) \text{ mmol dm}^{-3} = 654 \text{ mmol dm}^{-3} \\ \Delta\phi &= \frac{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298 \text{ K})}{9.648 \times 10^4 \text{ J mol}^{-1}} \times \ln \left(\frac{62.5}{654} \right) \\ &= -6.0 \times 10^{-2} \text{ V} = -60 \text{ mV} \end{aligned}$$

(The concentration units in the logarithm all cancel.) We see that the Goldman equation leads to an estimate that agrees well with the experimental value of -62 mV .

The transmembrane potential difference plays a particularly interesting role in the transmission of nerve impulses. On receiving an impulse, which is called an **action potential**, a site in the nerve cell membrane becomes transiently permeable to Na^+ and the transmembrane potential changes. To propagate along a nerve cell, the action potential must change the transmembrane potential by at least 20 mV to values that are less negative than -40 mV . Propagation occurs when an action potential at one site of the membrane triggers an action potential at an adjacent site, with sites behind the moving action potential relaxing back to the resting potential.

Redox reactions

We now embark on an investigation of the thermodynamics of redox reactions. Our ultimate goal is a description of electron transfer in plant photosynthesis and in the last stages of the oxidative breakdown of glucose. However, before we can understand these complex processes, we must examine a very much simpler system with a more controllable environment where precise measurements can be made. That is, we must consider electron transfer in an **electrochemical cell**, a device that consists of two electronic conductors (metal or graphite, for instance) dipping into an electrolyte (an ionic conductor), which may be a solution, a liquid, or a solid.

A brief comment

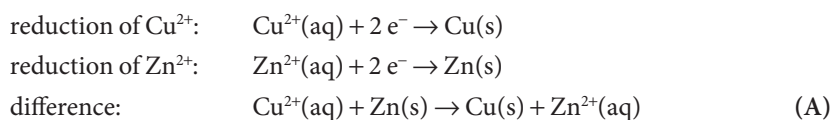
The oxidation number of a monatomic ion is equal to its charge number. An oxidation number is assigned to an element in a compound by supposing that it is present as an ion with a characteristic charge; for instance, oxygen is supposed—for this purpose—to be present as O^{2-} in most of its compounds, and hydrogen is supposed to be present as H^+ .

5.4 Half-reactions

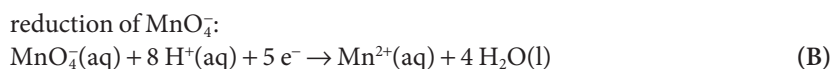
A redox reaction, such as the breakdown of glucose by O_2 in biological cells, is the outcome of the loss of electrons, and perhaps atoms, from one species and their gain by another species; we need to be able to write chemical equations for redox reactions and the corresponding reaction quotients.

It will be familiar from introductory chemistry that we identify the loss of electrons (oxidation) by noting whether or not an element has undergone an increase in oxidation number. We identify the gain of electrons (reduction) by noting whether or not an element has undergone a decrease in oxidation number. The requirement to break and form covalent bonds in some redox reactions, as in the conversion of H_2O to O_2 (during plant photosynthesis) or of N_2 to NH_3 (during nitrogen fixation by certain microorganisms) is one of the reasons why redox reactions often achieve equilibrium quite slowly, often much more slowly than acid–base proton transfer reactions.

Any redox reaction may be expressed as the difference of two reduction half-reactions. Two examples are



A half-reaction in which atom transfer accompanies electron transfer is



where oxygen atoms are transferred from $MnO_4^-(aq)$ to $H_2O(l)$. In the discussion of redox reactions, the hydrogen ion is commonly denoted simply $H^+(aq)$ rather than treated as a hydronium ion, $H_3O^+(aq)$, as proton transfer is less of an issue and the chemical equations are simplified.

Half-reactions are *conceptual*. Redox reactions normally proceed by a much more complex mechanism in which the electron is never free. The electrons in these conceptual reactions are regarded as being ‘in transit’ and are not ascribed a state. The oxidized and reduced species in a half-reaction form a **redox couple**, denoted Ox/Red. Thus, the redox couples mentioned so far are Cu^{2+}/Cu , Zn^{2+}/Zn , and $MnO_4^-/H^+/Mn^{2+}$, H_2O . In general, we adopt the notation

couple: Ox/Red

half-reaction: $Ox + \nu e^- \rightarrow Red$

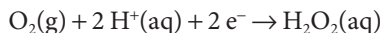
Example 5.2 Expressing a reaction in terms of half-reactions

Express the oxidation of nicotinamide adenine dinucleotide, which participates in aerobic metabolism, to NAD^+ (Atlas N4) by oxygen, when the latter is reduced to H_2O_2 , in aqueous solution as the difference of two reduction half-reactions. The overall reaction is $NADH(aq) + O_2(g) + H^+(aq) \rightarrow NAD^+(aq) + H_2O_2(aq)$.

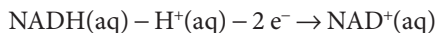
Strategy To express a reaction as the difference of two reduction half-reactions, identify one reactant species that undergoes reduction and its corresponding reduction product, then write the half-reaction for this process. To find the second half-reaction, subtract the first half-reaction from

the overall reaction and rearrange the species so that all the stoichiometric coefficients are positive and the equation is written as a reduction.

Solution Oxygen is reduced to H_2O_2 , so one half-reaction is



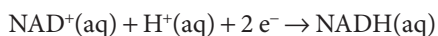
Subtraction of this half-reaction from the overall equation gives



Addition of $\text{H}^+(\text{aq}) + 2 \text{e}^-$ to both sides gives



This is an oxidation half-reaction. We reverse it to find the corresponding reduction half-reaction:



Self-test 5.4 Express the formation of H_2O from H_2 and O_2 in acidic solution as the difference of two reduction half-reactions.

Answer: $4 \text{H}^+(\text{aq}) + 4 \text{e}^- \rightarrow 2 \text{H}_2(\text{g})$, $\text{O}_2(\text{g}) + 4 \text{H}^+(\text{aq}) + 4 \text{e}^- \rightarrow 2 \text{H}_2\text{O}(\text{l})$

We saw in Chapter 4 that a natural way to express the composition of a system is in terms of the reaction quotient Q . The quotient for a half-reaction is defined like the quotient for the overall reaction, but with the electrons ignored. Thus, for the half-reaction of the NAD^+/NADH couple in Example 5.2 we would write

$$\text{NAD}^+(\text{aq}) + \text{H}^+(\text{aq}) + 2 \text{e}^- \rightarrow \text{NADH}(\text{aq}) \quad Q = \frac{a_{\text{NADH}}}{a_{\text{NAD}^+} a_{\text{H}^+}} \approx \frac{[\text{NADH}]}{[\text{NAD}^+][\text{H}^+]}$$

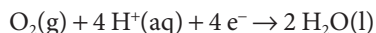
In elementary work, and provided the solution is very dilute, the activities are interpreted as the numerical values of the molar concentrations (see Table 3.3). The replacement of activities by molar concentrations is very hazardous for ionic solutions and intracellular fluids, as we have seen, so wherever possible we delay taking that final step.

Example 5.3 *Writing the reaction quotient for a half-reaction*

During the last stage of oxidative phosphorylation in mitochondria (Section 5.10), oxygen is reduced to water with the accompanying uptake of protons. Write the half-reaction and the reaction quotient for the reduction of oxygen to water in acidic solution.

Strategy Write the chemical equation for the half-reaction. Then express the reaction quotient in terms of the activities and the corresponding stoichiometric coefficients, with products in the numerator and reactants in the denominator. Pure (and nearly pure) solids and liquids do not appear in Q (because their activities are 1), nor does the electron. The activity of a gas is set equal to the numerical value of its partial pressure in bar (more formally: $a_i = p_i/p^\circ$).

Solution The equation for the reduction of O_2 in acidic solution is



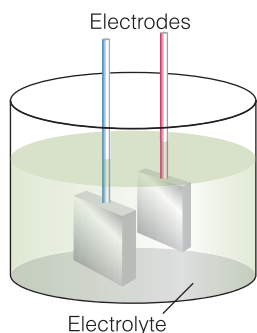


Fig. 5.3 The arrangement for an electrochemical cell in which the two electrodes share a common electrolyte.

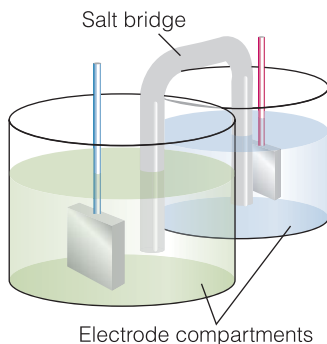


Fig. 5.4 When the electrolytes in the electrode compartments of a cell are different, they need to be joined so that ions can travel from one compartment to another. One device for joining the two compartments is a salt bridge.

The reaction quotient for the half-reaction is therefore

$$Q = \frac{1}{p_{\text{O}_2} a_{\text{H}^+}^4}$$

Note the very strong dependence of Q on the hydrogen ion activity.

Self-test 5.5 Write the half-reaction and the reaction quotient for the reduction of chlorine gas to chloride ion.

Answer: $\text{Cl}_2(\text{g}) + 2 \text{e}^- \rightarrow 2 \text{Cl}^-(\text{aq})$, $Q = a_{\text{Cl}^-}^2 / p_{\text{Cl}_2}$

5.5 Reactions in electrochemical cells

The electron transfer processes that occur in respiration and photosynthesis can be modeled by electrochemical cells in which electrons are transferred between proteins.

In an electrochemical cell, the electronic conductor and its surrounding electrolyte is an **electrode**. The physical structure containing them is called an **electrode compartment**. The two electrodes may share the same compartment (Fig. 5.3). If the electrolytes are different, then the two compartments may be joined by a **salt bridge**, which is an electrolyte solution that completes the electrical circuit by permitting ions to move between the compartments (Fig. 5.4). Alternatively, the two solutions may be in direct physical contact (for example, through a porous membrane) and form a **liquid junction**. However, a liquid junction introduces complications to the interpretation of measurements, and we shall not consider it further.

(a) Galvanic and electrolytic cells

A **galvanic cell** is an electrochemical cell that produces electricity as a result of the spontaneous reaction occurring inside it.³ An **electrolytic cell** is an electrochemical cell in which a nonspontaneous reaction is driven by an external source of direct current. The commercially available dry cells, mercury cells, nickel–cadmium ('nicad'), and lithium ion cells used to power electrical equipment are all galvanic cells and produce electricity as a result of the spontaneous chemical reaction between the substances built into them at manufacture. A **fuel cell** is a galvanic cell in which the reagents, such as hydrogen and oxygen or methane and oxygen, are supplied continuously from outside. Fuel cells are used on manned spacecraft, are beginning to be considered for use in automobiles, and gas supply companies hope that one day they may be used as a convenient, compact source of electricity in homes. Electric eels and electric catfish are biological versions of fuel cells in which the fuel is food and the cells are adaptations of muscle cells. It is hoped that biological versions of fuel cells will be developed to power the nanostructure-based entities that are being devised for inclusion in organisms.

In an electrochemical cell, the **anode** is where oxidation takes place; the **cathode** is where reduction takes place. As the reaction proceeds in a galvanic cell, the electrons released at the anode travel through the external circuit (Fig. 5.5). They re-enter the cell at the cathode, where they bring about reduction. This flow of current in the external circuit, from anode to cathode, corresponds to the cathode having a higher potential than the anode and arises from the tendency of

³ The term *voltic cell* is also used.

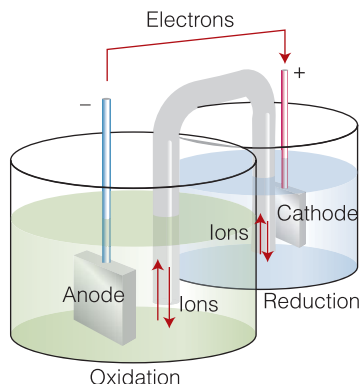


Fig. 5.5 The flow of electrons in the external circuit is from the anode of a galvanic cell, where they have been lost in the oxidation reaction, to the cathode, where they are used in the reduction reaction. Electrical neutrality is preserved in the electrolytes by the flow of cations and anions in opposite directions through the salt bridge.

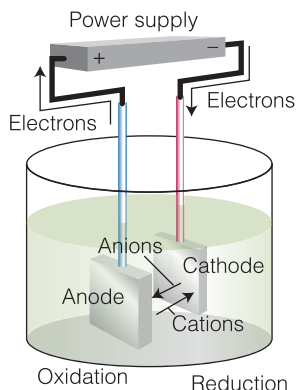


Fig. 5.6 The flow of electrons and ions in an electrolytic cell. An external supply forces electrons into the cathode, where they are used to bring about a reduction, and withdraws them from the anode, which results in an oxidation reaction at that electrode. Cations migrate toward the negatively charged cathode and anions migrate toward the positively charged anode. An electrolytic cell usually consists of a single compartment, but a number of industrial versions have two compartments.

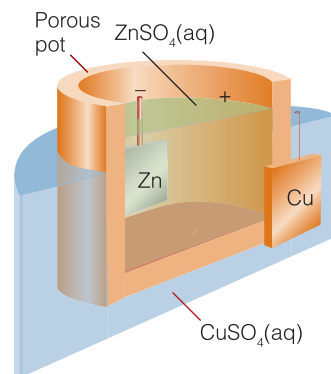


Fig. 5.7 A Daniell cell consists of copper in contact with copper(II) sulfate solution and zinc in contact with zinc sulfate solution; the two compartments are in contact through the porous pot that contains the zinc sulfate solution. The copper electrode is the cathode and the zinc electrode is the anode.

negatively charged electrons to travel to regions of higher potential. In an electrolytic cell, the anode is also the location of oxidation (by definition). Now, however, electrons must be withdrawn from the species in the anode compartment, so the anode must be connected to the positive terminal of an external supply. Similarly, electrons must pass from the cathode to the species undergoing reduction, so the cathode must be connected to the negative terminal of a supply (Fig. 5.6).

The simplest type of galvanic cell has a single electrolyte common to both electrodes (as in Fig. 5.3). In some cases it is necessary to immerse the electrodes in different electrolytes, as in the *Daniell cell* (Fig. 5.7), in which the redox couple at one electrode is Cu^{2+}/Cu and at the other is Zn^{2+}/Zn . In an **electrolyte concentration cell**, which would be constructed like the cell in Fig. 5.4, the electrode compartments are of identical composition except for the concentrations of the electrolytes. In an **electrode concentration cell** the electrodes themselves have different concentrations, either because they are gas electrodes operating at different pressures or because they are amalgams (solutions in mercury) with different concentrations.

In an electrochemical cell with two different electrolyte solutions in contact, as in the Daniell cell or an electrolyte concentration cell, the **liquid junction potential**, E_j , the potential difference across the interface of the two electrolytes, contributes to the overall potential difference generated by the cell. The contribution of the liquid junction to the potential can be decreased (to about 1 to 2 mV) by joining the electrolyte compartments through a salt bridge consisting of a saturated electrolyte solution (usually KCl) in agar jelly (as in Fig. 5.4). The reason for the success of the salt bridge is that the liquid junction potentials at either end are largely independent of the concentrations of the two more dilute solutions in the electrode compartments and so nearly cancel each other out.

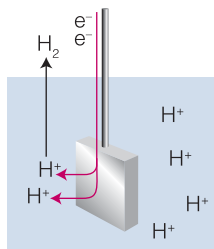


Fig. 5.8 The schematic structure of a hydrogen electrode, which is like other gas electrodes. Hydrogen is bubbled over a black (that is, finely divided) platinum surface that is in contact with a solution containing hydrogen ions. The platinum, as well as acting as a source or sink for electrons, speeds the electrode reaction because hydrogen attaches to (adsorbs on) the surface as atoms.

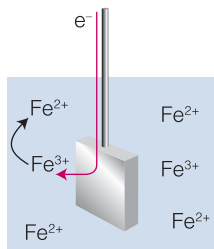


Fig. 5.9 The schematic structure of a redox electrode. The platinum metal acts as a source or sink for electrons required for the interconversion of (in this case) Fe^{2+} and Fe^{3+} ions in the surrounding solution.

(b) Varieties of electrodes

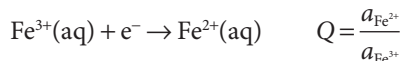
In a **gas electrode** (Fig. 5.8), a gas is in equilibrium with a solution of its ions in the presence of an inert metal. The inert metal, which is often platinum, acts as a source or sink of electrons but takes no other part in the reaction except perhaps to act as a catalyst. One important example is the *hydrogen electrode*, in which hydrogen is bubbled through an aqueous solution of hydrogen ions and the redox couple is H^+/H_2 .

The term **redox electrode** is normally reserved for an electrode in which the couple consists of the same element in two nonzero oxidation states (Fig. 5.9). An example is an electrode in which the couple is $\text{Fe}^{3+}/\text{Fe}^{2+}$. In general, the reaction is



A brief illustration

For the electrode corresponding to the $\text{Fe}^{3+}/\text{Fe}^{2+}$ couple the reduction half-reaction and reaction quotient are



(c) Electrochemical cell notation

It is useful to develop a short-hand to denote the processes taking place in an electrochemical cell. The notation scheme has a few rules:

- An interface between phases is denoted by a vertical bar, |.
- A double vertical line || denotes an interface for which the junction potential has been eliminated.
- A redox electrode is denoted $\text{M} | \text{Red}, \text{Ox}$, where M is an inert metal (typically platinum) making electrical contact with the solution.

It follows that the electrode corresponding to the $\text{Fe}^{3+}/\text{Fe}^{2+}$ couple discussed in the previous *brief illustration* is denoted $\text{Pt}(\text{s}) | \text{Fe}^{2+}(\text{aq}), \text{Fe}^{3+}(\text{aq})$. An electrochemical cell in which the left-hand electrode, in an arrangement like that in Fig. 5.4, is zinc in contact with aqueous zinc sulfate and the right-hand electrode is copper in contact with aqueous copper(II) sulfate is denoted



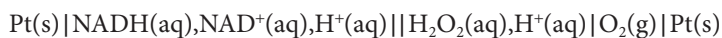
A brief illustration

The hydrogen electrode is denoted $\text{Pt}(\text{s}) | \text{H}_2(\text{g}) | \text{H}^+(\text{aq})$. In this electrode, the junctions are between the platinum and the gas and between the gas and the liquid containing its ions.

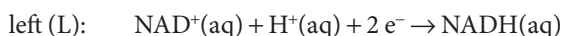
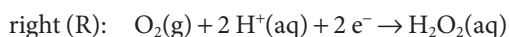
The current produced by a galvanic cell arises from the spontaneous reaction taking place inside it. The **cell reaction** is the reaction in the electrochemical cell written on the assumption that the right-hand electrode is the cathode and hence

that reduction is taking place in the right-hand compartment. Later we see how to predict if the right-hand electrode is in fact the cathode; if it is, then the cell reaction is spontaneous as written. If the left-hand electrode turns out to be the cathode, then the reverse of the cell reaction is spontaneous.

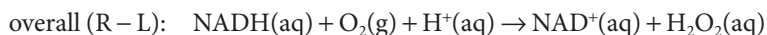
To write the cell reaction corresponding to the electrochemical cell diagram, we first write the half-reactions at both electrodes as reductions and then subtract the equation for the left-hand electrode from the equation for the right-hand electrode. Thus, we saw in *Example 5.2* that for the electrochemical cell used to study the reaction between NADH and O_2 ,



the two reduction half-reactions are



The equation for the cell reaction is the difference:



In other cases, it may be necessary to match the numbers of electrons in the two half-reactions by multiplying one of the equations through by a numerical factor: there should be no spare electrons showing in the overall equation.

5.6 The Nernst equation

The concentrations of electroactive species in biological systems do not normally have their standard values, so we need to be able to relate the potential difference of a cell to the actual concentrations.

A galvanic cell does electrical work as the reaction drives electrons through an external circuit. The work done by a given transfer of electrons depends on the potential difference between the two electrodes. When the potential difference is large (for instance, 2 V), a given number of electrons traveling between the electrodes can do a lot of electrical work. When the potential difference is small (such as 2 mV), the same number of electrons can do only a little work. An electrochemical cell in which the reaction is at equilibrium can do no work and the potential difference between its electrodes is zero.

According to the discussion in Section 2.8, we know that the maximum non-expansion work that a system (in this context, the electrochemical cell performing electrical work, w') can do is given by the value of ΔG and in particular that

$$w'_{\max} = \Delta G \quad \text{Maximum non-expansion work at constant temperature and pressure} \quad (5.11)$$

Therefore, by measuring the potential difference and converting it to the electrical work done by the reaction, we have a means of determining a thermodynamic quantity, the reaction Gibbs energy. Conversely, if we know ΔG for a reaction, then we have a route to the prediction of the potential difference between the electrodes of an electrochemical cell. However, to use eqn 5.11, we need to recall that maximum work is achieved only when a process occurs reversibly. In the present context, reversibility means that the electrochemical cell should be connected to an external source of potential difference that opposes and exactly matches the potential difference generated by the cell. Then an infinitesimal change of the external potential difference will allow the reaction to proceed in its spontaneous direction and an opposite infinitesimal change will drive the

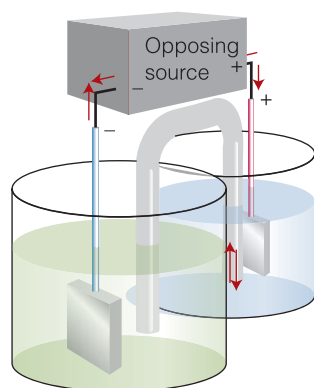


Fig. 5.10 The zero-current cell potential is measured by balancing the cell against an external potential that opposes the reaction in the cell. When there is no current flow, the external potential difference is equal to the zero-current cell potential.

reaction in its reverse direction.⁴ The potential difference measured when an electrochemical cell is balanced against an external source of potential is called the **zero-current cell potential** (or simply the *cell potential*) and denoted E_{cell} (Fig. 5.10).⁵ In practice, to determine the cell potential all we need do is to measure the potential difference with a voltmeter that draws negligible current.

As we show in the following *Justification*, the relation between the cell potential and the Gibbs energy of the electrochemical cell reaction is

$$-vFE_{\text{cell}} = \Delta_r G \quad \text{Relation between the cell potential and } \Delta_r G \quad (5.12)$$

where F is Faraday's constant and v is the stoichiometric coefficient of the electrons in the matching half-reactions used to construct the overall reaction.

Justification 5.3 The electrochemical cell potential

Suppose the cell reaction can be broken down into half-reactions of the form $A + ve^- \rightarrow B$. Then, when the reaction takes place, vN_A electrons are transferred from the reducing agent to the oxidizing agent per mole of reaction events, so the charge transferred between the electrodes is $vN_A \times (-e)$, or $-vF$. Now we proceed as in *Justification 5.2* and write the electrical work w' done when this charge travels from the anode to the cathode as the product of the charge and the potential difference E_{cell} :

$$w' = -vF \times E_{\text{cell}}$$

Provided the work is done reversibly at constant temperature and pressure, we can equate this electrical work to the reaction Gibbs energy and obtain eqn 5.12.

Equation 5.12 shows that the sign of E_{cell} is opposite to that of the reaction Gibbs energy, which we should recall is the slope of a graph of G plotted against the composition of the reaction mixture (Section 4.1). When the reaction is spontaneous in the forward direction, $\Delta_r G < 0$ and $E_{\text{cell}} > 0$. When $\Delta_r G > 0$, the reverse reaction is spontaneous and $E_{\text{cell}} < 0$. At equilibrium $\Delta_r G = 0$ and therefore $E_{\text{cell}} = 0$ too.

Equation 5.12 provides an electrical method for measuring a reaction Gibbs energy at any composition of the reaction mixture: we simply measure the zero-current cell potential and convert it to $\Delta_r G$. Conversely, if we know the value of $\Delta_r G$ at a particular composition, then we can predict the cell potential.

A brief illustration

Suppose $\Delta_r G \approx -1 \times 10^2 \text{ kJ mol}^{-1}$ and $v = 1$; then

$$E_{\text{cell}} = \frac{-\Delta_r G}{vF} = \frac{-(-1 \times 10^5 \text{ J mol}^{-1})}{1 \times (9.6485 \times 10^5 \text{ C mol}^{-1})} = 1 \text{ V}$$

Most electrochemical cells bought commercially are indeed rated at between 1 and 2 V.

⁴ We saw in Chapter 1 that the criterion of thermodynamic reversibility is the reversal of a process by an infinitesimal change in the external conditions.

⁵ This quantity was called the *electromotive force*, *emf*, of the electrochemical cell, but that name is deprecated by IUPAC because a potential difference is not a force.

Our next step is to see how E_{cell} varies with composition by combining eqn 5.12 and eqn 4.6, showing how the reaction Gibbs energy varies with composition:

$$\Delta_r G = \Delta_r G^\circ + RT \ln Q$$

In this expression, $\Delta_r G^\circ$ is the standard reaction Gibbs energy and Q is the reaction quotient for the cell reaction. When we substitute this relation into eqn 5.12 written as $E_{\text{cell}} = -\Delta_r G / \nu F$, we obtain the **Nernst equation**:

$$E_{\text{cell}} = E_{\text{cell}}^\circ - \frac{RT}{\nu F} \ln Q \quad \text{Nernst equation} \quad (5.13)$$

E_{cell}° is the standard cell potential:

$$E_{\text{cell}}^\circ = -\frac{\Delta_r G^\circ}{\nu F} \quad \text{The standard cell potential} \quad (5.14)$$

The standard cell potential is often interpreted as the cell potential when all the reactants and products are in their standard states (unit activity for all solutes, pure gases, and solids, a pressure of 1 bar). However, because such an electrochemical cell is not in general attainable, it is better to regard E_{cell}° simply as the standard Gibbs energy of the reaction expressed as a potential. Note that if all the stoichiometric coefficients in the equation for a cell reaction are multiplied by a factor, then $\Delta_r G^\circ$ is increased by the same factor, but so too is ν , so the standard cell potential is unchanged. Likewise, Q is raised to a power equal to the factor (so if the factor is 2, Q is replaced by Q^2), and because $\ln Q^2 = 2 \ln Q$, and likewise for other factors, the second term on the right-hand side of the Nernst equation is also unchanged. That is, E_{cell} is independent of how we write the balanced equation for the cell reaction.

A brief illustration

At 25.00°C,

$$\frac{RT}{F} = \frac{(8.31447 \text{ J K}^{-1}) \times (298.15 \text{ K})}{9.6485 \times 10^4 \text{ C mol}^{-1}} = 2.5693 \times 10^{-2} \text{ J C}^{-1}$$

Because 1 J = 1 V C, 1 J C⁻¹ = 1 V, and 10⁻³ V = 1 mV, we can write this result as

$$\frac{RT}{F} = 25.693 \text{ mV}$$

or approximately 25.7 mV. It follows from the Nernst equation that for a reaction in which $\nu = 1$, if Q is decreased by a factor of 10, then the potential of the electrochemical cell becomes more positive by $(25.7 \text{ mV}) \times \ln 10 = 59.2 \text{ mV}$. The reaction has a greater tendency to form products. If Q is increased by a factor of 10, then the cell potential falls by 59.2 mV and the reaction has a lower tendency to form products.

5.7 Standard potentials

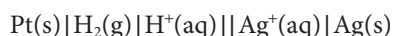
To discuss the thermodynamics of biological processes, we need to be able to predict the standard reaction Gibbs energies of biological electron transfer reactions and their variation with pH.

Each electrode in a galvanic cell makes a characteristic contribution to the overall cell potential. Although it is not possible to measure the contribution of a single electrode, one electrode can be assigned a value zero and the others assigned relative values on that basis. The specially selected electrode is the **standard hydrogen electrode** (SHE):



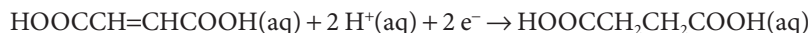
(a) Thermodynamic standard potentials

The (thermodynamic) **standard potential**, $E^\circ(\text{Ox/Red})$, of a couple Ox/Red is measured by constructing an electrochemical cell in which the couple of interest forms the right-hand electrode and the standard hydrogen electrode is on the left. For example, the standard potential of the Ag^+/Ag couple is the standard potential of the cell



and is +0.80 V. Table 5.1 lists a selection of standard potentials; a longer list will be found in the *Resource section*.

We saw in Section 4.2 that in biochemical work it is common to adopt the biological standard state (pH = 7, corresponding to neutral solution), rather than the thermodynamic standard state (pH = 0). To convert standard potentials to **biological standard potentials**, $E^\oplus$, we must first consider the variation of potential with pH. The two potentials differ when hydrogen ions are involved in the half-reaction, as in the fumaric acid/succinic acid couple fum/suc with fum = $\text{HOOCCH}=\text{CHCOOH}$ and suc = $\text{HOOCCH}_2\text{CH}_2\text{COOH}$, which plays a role in the citric acid cycle (*Case study* 4.3):



When hydrogen ions occur as reactants, as in this example, an increase in pH, corresponding to a decrease in hydrogen ion activity, favors the formation of reactants, so the fumaric acid has a lower thermodynamic tendency to become reduced. We expect, therefore, the potential of the fumaric/succinic acid couple to decrease as the pH is increased.

(b) Variation of potential with pH

To establish the quantitative variation of reduction potential with pH for a reaction as a first step in determining the effect of changing from pH = 0 to pH = 7 we use the Nernst equation. Thus, for fixed fumaric acid and succinic acid concentrations, the potential of the fumaric/succinic redox couple is

$$E = E^\circ - \frac{RT}{2F} \ln \frac{a_{\text{suc}}}{a_{\text{fum}} a_{\text{H}^+}^2} = \overbrace{E^\circ - \frac{RT}{2F} \ln \frac{a_{\text{suc}}}{a_{\text{fum}}}}^{E'} + \frac{RT}{T} \ln a_{\text{H}^+}$$

We then use a result from *Mathematical toolkit* 5.1 to write

$$\ln a_{\text{H}^+} = \ln 10 \times \log a_{\text{H}^+} = -\ln 10 \times \text{pH}$$

and obtain

$$E = E' - \frac{RT \ln 10}{F} \times \text{pH} \quad (5.15a)$$

A brief comment

Standard potentials are also called *standard electrode potentials* and *standard reduction potentials*. If in an older source of data you come across a 'standard oxidation potential', reverse its sign and use it as a standard reduction potential.

Table 5.1 Standard potentials at 25°C

Reduction half-reaction			E°/V
Oxidizing agent		Reducing agent	
<i>Strongly oxidizing</i>			
F_2	$+ 2 e^-$	$\rightarrow 2 \text{F}^-$	+2.87
$\text{S}_2\text{O}_8^{2-}$	$+ 2 e^-$	$\rightarrow 2 \text{SO}_4^{2-}$	+2.05
Au^+	$+ e^-$	$\rightarrow \text{Au}$	+1.69
Pb^{4+}	$+ 2 e^-$	$\rightarrow \text{Pb}^{2+}$	+1.67
Ce^{4+}	$+ e^-$	$\rightarrow \text{Ce}^{3+}$	+1.61
$\text{MnO}_4^- + 8 \text{H}^+$	$+ 5 e^-$	$\rightarrow \text{Mn}^{2+} + 4 \text{H}_2\text{O}$	+1.51
Cl_2	$+ 2 e^-$	$\rightarrow 2 \text{Cl}^-$	+1.36
$\text{Cr}_2\text{O}_7^{2-} + 14 \text{H}^+$	$+ 6 e^-$	$\rightarrow 2 \text{Cr}^{3+} + 7 \text{H}_2\text{O}$	+1.33
$\text{O}_2 + 4 \text{H}^+$	$+ 4 e^-$	$\rightarrow 2 \text{H}_2\text{O}$	+1.23, +0.81 at pH = 7
Br_2	$+ 2 e^-$	$\rightarrow 2 \text{Br}^-$	+1.09
Ag^+	$+ e^-$	$\rightarrow \text{Ag}$	+0.80
Hg_2^{2+}	$+ 2 e^-$	$\rightarrow 2 \text{Hg}$	+0.79
Fe^{3+}	$+ e^-$	$\rightarrow \text{Fe}^{2+}$	+0.77
I_2	$+ e^-$	$\rightarrow 2 \text{I}^-$	+0.54
$\text{O}_2 + 2 \text{H}_2\text{O}$	$+ 4 e^-$	$\rightarrow 4 \text{OH}^-$	+0.40, 0.81 at pH = 7
Cu^{2+}	$+ 2 e^-$	$\rightarrow \text{Cu}$	+0.34
AgCl	$+ e^-$	$\rightarrow \text{Ag} + \text{Cl}^-$	+0.22
2H^+	$+ 2 e^-$	$\rightarrow \text{H}_2$	0, by definition
Fe^{3+}	$+ 3 e^-$	$\rightarrow \text{Fe}$	-0.04
$\text{O}_2 + \text{H}_2\text{O}$	$+ 2 e^-$	$\rightarrow \text{HO}_2^- + \text{OH}^-$	-0.08
Pb^{2+}	$+ 2 e^-$	$\rightarrow \text{Pb}$	-0.13
Sn^{2+}	$+ 2 e^-$	$\rightarrow \text{Sn}$	-0.14
Fe^{2+}	$+ 2 e^-$	$\rightarrow \text{Fe}$	-0.44
Zn^{2+}	$+ 2 e^-$	$\rightarrow \text{Zn}$	-0.76
$2 \text{H}_2\text{O}$	$+ 2 e^-$	$\rightarrow \text{H}_2 + 2 \text{OH}^-$	-0.83, -0.42 at pH = 7
Al^{3+}	$+ 3 e^-$	$\rightarrow \text{Al}$	-1.66
Mg^{2+}	$+ 2 e^-$	$\rightarrow \text{Mg}$	-2.36
Na^+	$+ e^-$	$\rightarrow \text{Na}$	-2.71
Ca^{2+}	$+ 2 e^-$	$\rightarrow \text{Ca}$	-2.87
K^+	$+ e^-$	$\rightarrow \text{K}$	-2.93
Li^+	$+ e^-$	$\rightarrow \text{Li}$	-3.05
<i>Strongly reducing</i>			

For a more extensive table, see the *Resource section*.

Note that this result is valid only for a half-reaction in which $\nu_e = 2$ and the stoichiometric coefficient of $\text{H}^+(\text{aq})$ is 2 and appears as a reactant. In general:

$$E = E' - \frac{\nu_{\text{H}^+} RT \ln 10}{\nu_e F} \times \text{pH} \quad \text{Variation of potential with pH} \quad (5.15\text{b})$$

A brief illustration

At 25°C and when $\nu_{\text{H}^+} = \nu_e$,

$$E = E' - (59.2 \text{ mV}) \times \text{pH}$$

We see that an increase of 1 unit in pH decreases the potential by 59.2 mV, which is in agreement with the remark above, that the reduction of fumaric acid is discouraged by an increase in pH.

For a hydrogen electrode half-reaction, $\frac{1}{2} \text{H}_2(\text{g}) + \text{e}^- \rightarrow \text{H}^+(\text{aq})$, with $E^\circ = 0$, the same calculation gives

$$E = -\frac{RT \ln 10}{F} \times \text{pH}$$

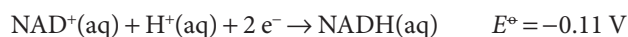
This expression is the basis of a method for measuring the pK_a of an acid electrically. As we saw in Section 4.11, the pH of a solution containing equal amounts of the acid and its conjugate base is $\text{pH} = \text{pK}_a$. Therefore, by measuring the potential of the cell $\text{SHE} || \text{solution} | \text{HE}$, where SHE is a standard hydrogen electrode and HE is a hydrogen electrode dipping into the solution, we can determine the latter's pH and therefore the pK_a of the acid. It is in fact unwieldy to use an actual hydrogen electrode, and a far more convenient approach is developed later (*In the laboratory* 5.1).

(c) The biological standard potential

We can now use eqn 5.15 to convert standard potentials to biological standard potentials. If the hydrogen ions appear as reactants in the reduction half-reaction, then the potential is decreased below its standard value (for the fumaric/succinic couple, by $7 \times 59.2 \text{ mV} = 414 \text{ mV}$, or about 0.4 V). If the hydrogen ions appear as products, then the biological standard potential is higher than the thermodynamic standard potential. The precise change depends on the number of electrons and protons participating in the half-reaction, as expressed by eqn 5.15b and illustrated in *Example 5.4*. Biological standard potentials are important in the discussion of the electron transfer reactions of oxidative phosphorylation (Section 5.10). Table 5.2 is a partial list of biological standard potentials for redox couples that participate in important biochemical electron transfer reactions.

Example 5.4 *Converting a standard potential to a biological standard value*

Calculate the biological standard potential of the NAD/NADH couple at 25°C (*Example 5.2*) from its thermodynamic value. The reduction half-reaction is



Strategy Write the Nernst equation for the potential, and express the reaction quotient in terms of the activities of the species. All species except H^+ are in their standard states, so their activities are all equal to 1. The remaining task is to express the hydrogen ion activity in terms of the pH, exactly as was done in the text, and set $\text{pH} = 7$.

Solution The Nernst equation for the half-reaction, with $\nu_e = 2$, is

Table 5.2 Biological standard potentials at 25°C

Reduction half-reaction			$E^\ominus/\text{V}$
Oxidizing agent		Reducing agent	
<i>Strongly oxidizing</i>			
$\text{O}_2 + 4 \text{H}^+$	$+ 4 \text{e}^-$	$\rightarrow 2 \text{H}_2\text{O}$	+0.81
$\text{Fe}^{3+} (\text{Cyt } f)$	$+ \text{e}^-$	$\rightarrow \text{Fe}^{2+} (\text{Cyt } f)$	+0.36
$\text{O}_2 + 2 \text{H}_2\text{O}$	$+ 4 \text{e}^-$	$\rightarrow 2 \text{H}_2\text{O}_2$	+0.30
$\text{Fe}^{3+} (\text{Cyt } c)$	$+ \text{e}^-$	$\rightarrow \text{Fe}^{2+} (\text{Cyt } c)$	+0.25
$\text{Fe}^{3+} (\text{Cyt } b)$	$+ \text{e}^-$	$\rightarrow \text{Fe}^{2+} (\text{Cyt } b)$	+0.08
Dehydroascorbic acid $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ Ascorbic acid	+0.08
Coenzyme Q $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ Coenzyme QH ₂	+0.04
Oxaloacetate ²⁻ $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ Malate ²⁻	-0.17
Pyruvate ⁻ $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ Lactate ⁻	-0.18
FAD $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ FADH ₂	-0.22
Glutathione (ox) $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ Glutathione (red)	-0.23
Lipoic acid (ox) $+ 2 \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ Lipoic acid (red)	-0.29
NAD ⁺ $+ \text{H}^+$	$+ 2 \text{e}^-$	$\rightarrow$ NADH	-0.32
$2 \text{H}_2\text{O}$	$+ 2 \text{e}^-$	$\rightarrow \text{H}_2 + 2 \text{OH}^-$	-0.42
Ferredoxin (ox)	$+ \text{e}^-$	$\rightarrow$ Ferredoxin (red)	-0.43
O_2	$+ \text{e}^-$	$\rightarrow \text{O}_2^-$	-0.45
<i>Strongly reducing</i>			

For a more extensive table, see the *Resource section*.

$$E = E^\ominus - \frac{RT}{2F} \ln \frac{\overbrace{a_{\text{NADH}}^1}}{a_{\text{H}^+} \underbrace{a_{\text{NAD}^+}}_1} = E^\ominus + \frac{RT}{2F} \ln a_{\text{H}^+}$$

We rearrange this expression to

$$E = E^\ominus + \frac{RT}{2F} \ln a_{\text{H}^+} = E^\ominus - \frac{RT \ln 10}{2F} \times \text{pH} = E^\ominus - (29.58 \text{ mV}) \times \text{pH}$$

The biological standard potential (at pH = 7) is therefore

$$E^\ominus = (-0.11 \text{ V}) - (29.58 \times 10^{-3} \text{ V}) \times 7 = -0.32 \text{ V}$$

Self-test 5.6 Calculate the biological standard potential of the half-reaction $\text{O}_2(\text{g}) + 4 \text{H}^+(\text{aq}) + 4 \text{e}^- \rightarrow 2 \text{H}_2\text{O}(\text{l})$ at 25°C given its value +1.23 V under thermodynamic standard conditions.

Answer: +0.82 V

A note on good practice

Whenever possible, avoid replacing activities by concentrations, especially when aiming to relate the electrode potential to pH, for the latter is defined in terms of the activity of hydrogen ions.

In the laboratory 5.1 Ion-selective electrodes

Special electrodes can be constructed to measure concentrations of ionic species, such as Na⁺, K⁺, Ca²⁺, and hydronium ions, which are important in biochemical reactions. The potential of a hydrogen electrode is directly

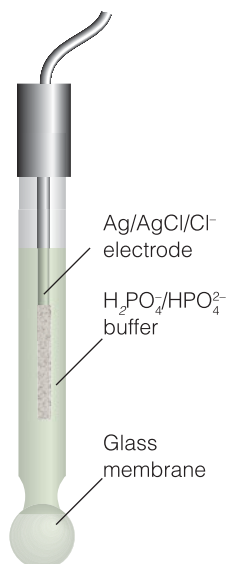


Fig. 5.11 A glass electrode has a potential that varies with the hydrogen ion concentration in the medium in which it is immersed. It consists of a thin glass membrane containing an electrolyte and a silver chloride electrode, $\text{Ag(s)}|\text{AgCl(s)}|\text{Cl}^-(\text{aq})$. The electrode is used in conjunction with a reference electrode, such as a calomel electrode, $\text{Hg(l)}|\text{Hg}_2\text{Cl}_2(\text{s})|\text{Cl}^-(\text{aq})$, that makes contact with the test solution through a salt bridge.

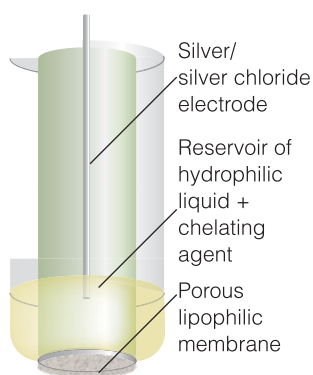


Fig. 5.12 The structure of an ion-selective electrode. Ions bound to a compound, the chelating agent, in the hydrophilic liquid are able to migrate through the lipophilic membrane.

proportional to the pH of the solution. However, in practice, indirect methods are much more convenient to use than one based on the standard hydrogen electrode, and the hydrogen electrode is replaced by a *glass electrode* (Fig. 5.11). A glass electrode is an example of an **ion-selective electrode**, an electrode that generates a potential in response to the presence of a solution of specific ions.

The glass of a glass electrode is based on lithium silicate doped with heavy-metal oxides; it is filled with a phosphate buffer solution containing Cl^- ions. Conveniently, the electrode has $E_{\text{cell}} \approx 0$ when the external medium is at $\text{pH} = 7$. The electrode is calibrated using solutions of known pH (for example, one of the buffer solutions described in Section 4.11).

Self-test 5.7 What range should a voltmeter have (in volts) to display changes of pH from 1 to 14 at 25°C if it is arranged to give a reading of zero when $\text{pH} = 7$?

Answer: From -0.42 V to $+0.35\text{ V}$, a range of 0.77 V

Glass electrodes can be made responsive to Na^+ , K^+ , and NH_4^+ ions by using glasses doped with Al_2O_3 and B_2O_3 . More sophisticated devices can extend the range of ions that can be detected in a test solution. For example, a porous hydrocarbon-attracting membrane can be attached to a small reservoir of a hydrophobic liquid, such as dioctylphenylphosphonate, that saturates it (Fig. 5.12). The liquid contains a compound, such as $(\text{RO})_2\text{PO}_2^-$ with R a C_8 to C_{18} chain, which binds to the ion. The bound ions traverse the membrane and give rise to a transmembrane potential, which is detected by an electrode in the assembly. Electrodes of this construction can be designed to be sensitive to a variety of ionic species, including Ca^{2+} ions.

Applications of standard potentials

The measurement of the potential of an electrochemical cell is a convenient source of thermodynamic information on reactions. In practice the standard values (and the biological standard values) of these quantities are the ones normally determined.

5.8 The determination of thermodynamic functions

Calorimetry is not always practicable, especially for biochemically important reactions, but in some cases their thermodynamic properties can be measured electrochemically.

We have seen that the standard potential of an electrochemical cell is related to the standard reaction Gibbs energy by eqn 5.14 ($\Delta_r G^\circ = -vFE_{\text{cell}}^\circ$), therefore, by measuring the standard potential of a cell driven by the reaction of interest, we can obtain the standard reaction Gibbs energy. If we were interested in the biological standard state, then we would use the same expression but with the standard potential at $\text{pH} = 7$ ($\Delta_r G^\oplus = -vFE_{\text{cell}}^\oplus$). From the standard reaction Gibbs

energy, the equilibrium constant, standard entropy, and standard enthalpy can be calculated.

(a) Calculation of the equilibrium constant

A special case of the Nernst equation has great importance in chemistry. Suppose the reaction has reached equilibrium; then $Q = K$, where K is the equilibrium constant of the cell reaction. However, because a chemical reaction at equilibrium cannot do work, it generates zero potential difference between the electrodes. Setting $Q = K$ and $E_{\text{cell}} = 0$ in the Nernst equation gives

$$\ln K = \frac{\nu F E_{\text{cell}}^{\circ}}{RT} \quad \text{The equilibrium constant in terms of the standard cell potential} \quad (5.16)$$

This very important equation—which is simply eqn 4.10 expressed electrochemically—lets us predict equilibrium constants from the standard potential of an electrochemical cell. Note that

- If $E_{\text{cell}}^{\circ} > 0$, then $K > 1$ and at equilibrium the cell reaction lies in favor of products.
- If $E_{\text{cell}}^{\circ} < 0$, then $K < 1$ and at equilibrium the cell reaction lies in favor of reactants.

A brief illustration

Because the standard potential of the Daniell cell is +1.10 V, the equilibrium constant for the cell reaction (reaction A) is

$$\begin{aligned} \ln K &= \frac{2 \times (9.6485 \times 10^4 \text{ C mol}^{-1}) \times (1.10 \text{ V})}{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298.15 \text{ K})} \\ &= \frac{2 \times 9.6485 \times 1.10 \times 10^4}{8.3145 \times 298.15} \end{aligned}$$

(where we have used $1 \text{ C V} = 1 \text{ J}$ to cancel units) and therefore $K = 1.5 \times 10^{37}$. Hence, the displacement of copper by zinc goes virtually to completion in the sense that the ratio of concentrations of Zn^{2+} ions to Cu^{2+} ions at equilibrium is about 10^{37} . This value is far too large to be measured by classical analytical techniques, but its electrochemical measurement is straightforward. Note that a standard cell potential of +1 V corresponds to a very large equilibrium constant (and −1 V would correspond to a very small one).

It is also possible to use the data in Tables 5.1 and 5.2 to calculate the standard potential of an electrochemical cell formed from any pair of electrodes and, from the standard cell potential, the equilibrium constant of the cell reaction. To calculate the standard potential of an electrochemical cell, we take the difference of the standard potentials of the appropriate electrodes:

$$E_{\text{cell}}^{\circ} = E_{\text{R}}^{\circ} - E_{\text{L}}^{\circ} \quad \text{The standard cell potential from standard potentials} \quad (5.17a)$$

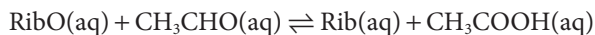
where E_{R}° is the standard potential of the right-hand electrode and E_{L}° is that of the left. The analogous expression for the biological standard state is

$$E_{\text{cell}}^{\oplus} = E_{\text{R}}^{\oplus} - E_{\text{L}}^{\oplus} \quad \text{The biological standard cell potential from biological standard potentials} \quad (5.17b)$$

When dealing with biological systems, the focus is not necessarily on reactions occurring at electrodes but on electron transfer processes in the cytosol or membranes of biological cells. We can still estimate the standard reaction Gibbs energy (and hence the equilibrium constant) of biological electron transfer reactions by using eqn 5.14 (written as $\Delta_r G^{\circ} = -vFE_{\text{cell}}^{\circ}$) if we express the chemical equation for the redox reaction as the difference of two reduction half-reactions with known standard potentials. We then find $E_{\text{cell}}^{\oplus}$ or $E_{\text{cell}}^{\oplus}$ from eqn 5.17 and use eqn 5.14 for the calculation of the standard reaction Gibbs energy or eqn 5.16 for the calculation of the equilibrium constant. The approach is illustrated in the following example.

Example 5.5 Calculating the equilibrium constant of a biological electron transfer reaction

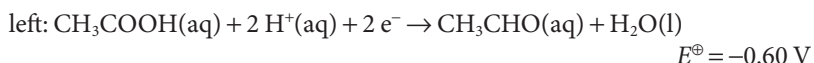
The reduced and oxidized forms of riboflavin form a couple with $E^{\oplus} = -0.21 \text{ V}$ and the acetate/acetaldehyde couple has $E^{\oplus} = -0.60 \text{ V}$ under the same conditions. What is the equilibrium constant for the reduction of riboflavin (Rib) by acetaldehyde (ethanal) in neutral solution at 25°C ? The reaction is



where RibO is the oxidized form of riboflavin and Rib is the reduced form.

Strategy The aim is to find the values of $E_{\text{cell}}^{\oplus}$ and v corresponding to the reaction, for then we can use a modified form of eqn 5.16 to calculate the value of K in neutral solution from $E_{\text{cell}}^{\oplus}$. To do so, we express the equation as the difference of two reduction half-reactions. The stoichiometric number of the electron in these matching half-reactions is the value of v we require. We then look up the biological standard potentials for the couples corresponding to the half-reactions and calculate their difference to find $E_{\text{cell}}^{\oplus}$.

Solution The two reduction half-reactions are



and their difference is the redox reaction required. Note that $v = 2$. The corresponding standard cell potential is

$$E_{\text{cell}}^{\oplus} = (-0.21 \text{ V}) - (-0.60 \text{ V}) = +0.39 \text{ V}$$

It follows that

$$\begin{aligned} \ln K &= \frac{2FE_{\text{cell}}^{\oplus}}{RT} = \frac{2 \times (9.6485 \times 10^4 \text{ C mol}^{-1}) \times (0.39 \text{ V})}{(8.3145 \text{ J K}^{-1} \text{ mol}^{-1}) \times (298.15 \text{ K})} \\ &= \frac{2 \times 9.6485 \times 0.39 \times 10^4}{8.3145 \times 298.15} \end{aligned}$$

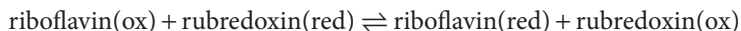
Therefore, because $K = e^{\ln K}$,

$$K = e^{(2 \times 9.6485 \times 0.39 \times 10^4) / (8.3145 \times 298.15)} = 1.5 \times 10^{13}$$

We conclude that riboflavin can be reduced by acetaldehyde in neutral solution. However, there may be mechanistic reasons—the energy required to

break covalent bonds, for instance—that make the reduction too slow to be feasible in practice. Note that, because hydrogen ions do not appear in the chemical equation, the equilibrium constant is independent of pH.

Self-test 5.8 What is the equilibrium constant for the reduction of riboflavin with rubredoxin, a bacterial iron–sulfur protein, in the reaction



given that the biological standard potential of the rubredoxin couple is -0.06 V ?

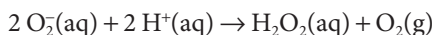
Answer: 8.5×10^{-6} ; the reactants are favored

(b) Calculation of standard potentials

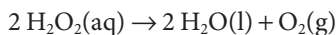
The relation between the standard cell potential and the standard reaction Gibbs energy is a convenient route for the calculation of the standard potential of a couple from two other standard potentials. We make use of the fact that G is a state function and that the Gibbs energy of an overall reaction is the sum of the Gibbs energies of the reactions into which it can be divided. In general, we cannot combine the E values directly because they depend on the value of ν , which may be different for the two couples.

Example 5.6 Calculating a standard potential from two other standard potentials

The superoxide ion (O_2^-) is an undesirable by-product of some enzyme-catalyzed reactions. It is metabolized by the enzyme superoxide dismutase (SOD) in a *disproportionation* (or *dismutation*), a reaction that both oxidizes and reduces a species. The reaction catalyzed by SOD is



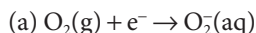
where O_2^- is oxidized to O_2 and reduced to O_2^- (in H_2O_2). Hydrogen peroxide, H_2O_2 , is also produced by other biochemical reactions. It is a toxic substance that is metabolized by catalases and peroxidases. The disproportionation catalyzed by catalase is



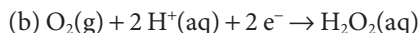
Given the standard potentials $E^\ominus(\text{O}_2, \text{O}_2^-) = -0.45 \text{ V}$ and $E^\ominus(\text{O}_2, \text{H}_2\text{O}_2) = +0.30 \text{ V}$, calculate $E^\ominus(\text{O}_2^-, \text{H}_2\text{O}_2)$, the biological standard potential for the SOD-catalyzed reduction of O_2^- to H_2O_2 .

Strategy We need to convert the two $E^\ominus$ to $\Delta_r G^\ominus$ by using eqn 5.14 modified for the biological standard state, add them appropriately, and then convert the overall $\Delta_r G^\ominus$ so obtained to the required $E^\ominus$ by using eqn 5.14 again. Because the F s cancel at the end of the calculation, carry them through.

Solution The electrode reactions are as follows:



$$E^\ominus = -0.45 \text{ V} \quad \Delta_r G^\ominus(a) = -F \times (-0.45 \text{ V}) = (+0.45 \text{ V}) \times F$$

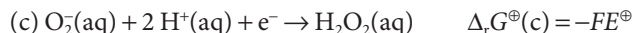


$$E^\ominus = +0.30 \text{ V} \quad \Delta_r G^\ominus(b) = -2F \times (0.30 \text{ V}) = (-0.60 \text{ V}) \times F$$

A note on good practice

Whenever combining standard potentials to obtain the standard potential of a third couple, always work via the Gibbs energies because they are additive, whereas in general standard potentials are not.

The required reaction is



Because (c) = (b) – (a), it follows that

$$\Delta_r G^\oplus(c) = \Delta_r G^\oplus(b) - \Delta_r G^\oplus(a)$$

Therefore, from eqn 5.14,

$$FE^\oplus(c) = -\{(-0.60 \text{ V})F - (+0.45 \text{ V})F\}$$

The F s cancel, and we are left with $E^\oplus(c) = +1.05 \text{ V}$.

Self-test 5.9

Given the standard potentials $E^\oplus(\text{Fe}^{3+}, \text{Fe}) = -0.04 \text{ V}$ and $E^\oplus(\text{Fe}^{2+}, \text{Fe}) = -0.44 \text{ V}$, calculate $E^\oplus(\text{Fe}^{3+}, \text{Fe}^{2+})$.

Answer: +0.76 V

(c) Calculation of the standard reaction entropy and enthalpy

Once $\Delta_r G^\oplus$ has been measured, we can use thermodynamic relations to determine other properties. For instance, the entropy of the cell reaction can be obtained from the change in the potential with temperature:

$$\Delta_r S^\oplus = \nu F \frac{dE_{\text{cell}}^\oplus}{dT} \quad \text{The standard reaction entropy from the standard cell potential} \quad (5.18)$$

A brief comment

Infinitesimally small quantities may be treated like any other quantity in algebraic manipulations. Thus, the expression $dy = adx$ may be rewritten as $dy/dx = a$, $dx/dy = 1/a$, and so on.

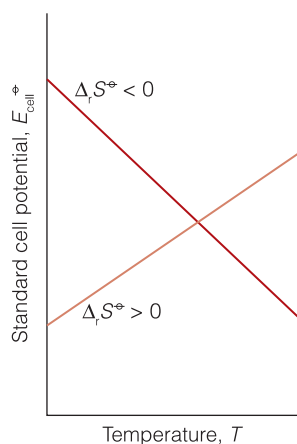


Fig. 5.13 The variation of the standard potential of a cell with temperature depends on the standard entropy of the cell reaction.

Justification 5.4 *The reaction entropy from the electrochemical cell potential*

In Section 3.3 we used the fact that, at constant pressure, when the temperature changes by dT , the Gibbs energy changes by $dG = -SdT$. Because this equation applies to the reactants and the products, it follows that

$$d(\Delta_r G^\oplus) = -\Delta_r S^\oplus \times dT$$

Substitution of $\Delta_r G^\oplus = -\nu FE_{\text{cell}}^\oplus$ then gives

$$\nu F \times dE_{\text{cell}}^\oplus = \Delta_r S^\oplus \times dT$$

which rearranges into eqn 5.18.

We see from eqn 5.18 that the standard cell potential increases with temperature if the standard reaction entropy is positive and that the slope of a plot of potential against temperature is proportional to the reaction entropy (Fig. 5.13). An implication is that if the cell reaction produces a lot of gas (corresponding to a positive reaction entropy), then its potential will increase with temperature. The opposite is true for a reaction that consumes gas.

Finally, we can combine the results obtained so far by using $G = H - TS$ in the form $H = G + TS$ to obtain the standard reaction enthalpy:

$$\Delta_r H^\oplus = \Delta_r G^\oplus + T\Delta_r S^\oplus \quad \text{The standard reaction enthalpy from the standard reaction Gibbs energy and entropy} \quad (5.19)$$

with $\Delta_r G^\oplus$ determined from the cell potential and $\Delta_r S^\oplus$ from its temperature variation. Thus, we now have a noncalorimetric method of measuring a reaction enthalpy.

5.9 The electrochemical series

Some organic co-factors and metal centers in proteins act as electron transfer agents in a number of biological processes; we need to be able to predict which species is reduced or oxidized in a redox reaction.

We have seen that a cell reaction has $K > 1$ if $E_{\text{cell}}^{\circ} > 0$ and that $E_{\text{cell}}^{\circ} > 0$ corresponds to reduction at the right-hand electrode. We have also seen that E_{cell}° may be written as the difference of the standard potentials of the redox couples in the right and left electrodes (eqn 5.17, $E_{\text{cell}}^{\circ} = E_{\text{R}}^{\circ} - E_{\text{L}}^{\circ}$). A reaction corresponding to reduction at the right-hand electrode therefore has $K > 1$ if $E_{\text{L}}^{\circ} < E_{\text{R}}^{\circ}$, and we can conclude that

A couple with a low standard potential has a thermodynamic tendency to reduce a couple with a high standard potential.

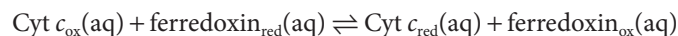
More briefly: *low reduces high* and, equivalently, *high oxidizes low*. The same arguments apply to the biological standard values of the potentials.

A brief illustration

Consider the iron-containing protein ferredoxin, which participates in plant photosynthesis (Section 5.11), and cytochrome *c*, which participates in the last steps of respiration (Section 5.10). It follows from Table 5.2 that

$$E^{\oplus}(\text{ferredoxin}_{\text{ox}}, \text{ferredoxin}_{\text{red}}) = -0.43 \text{ V} < E^{\oplus}(\text{cyt } c_{\text{ox}}, \text{Cyt } c_{\text{red}}) = +0.25 \text{ V}$$

and ferredoxin has a thermodynamic tendency to reduce cytochrome *c* at pH = 7. Hence, $K > 1$ for the reaction

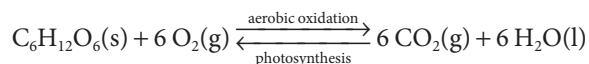


Self-test 5.10 Does NAD^{+} have a thermodynamic tendency to oxidize the pyruvate ion at pH = 7?

Answer: No

Electron transfer in bioenergetics

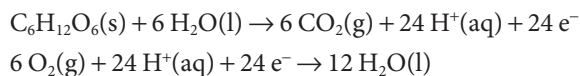
Electron transfer between protein-bound cofactors or between proteins plays a role in a number of biological processes, such as the oxidative breakdown of foods, photosynthesis, nitrogen fixation, the reduction of atmospheric N_2 to NH_3 by certain microorganisms, and the mechanisms of action of oxidoreductases, which are enzymes that catalyze redox reactions. Here, we examine the redox reactions associated with photosynthesis and the aerobic oxidation of glucose. These processes are related by the reactions



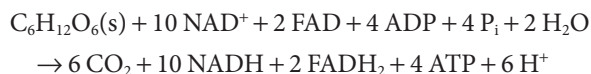
5.10 The respiratory chain

The centrally important processes of biochemistry include the electrochemical reactions between proteins in the mitochondrion of the cell, for they are responsible for delivering the electrons extracted from glucose to water.

The half-reactions for the oxidation of glucose and the reduction of O₂ are



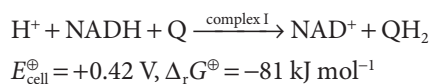
We see that the exergonic oxidation of one C₆H₁₂O₆ molecule requires the transfer of 24 electrons to six O₂ molecules. However, the electrons do not flow directly from glucose to O₂. In biological cells, glucose is oxidized to CO₂ by NAD⁺ and FAD during glycolysis and the citric acid cycle (*Case study 4.3*):



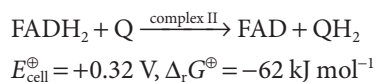
In the **respiratory chain**, electrons from the powerful reducing agents NADH and FADH₂ pass through four membrane-bound protein complexes and two mobile electron carriers before reducing O₂ to H₂O. We shall see that the electron transfer reactions drive the synthesis of ATP at three of the membrane protein complexes.

(a) Electron transfer reactions

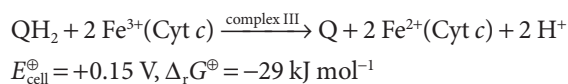
The respiratory chain begins in complex I (NADH-Q oxidoreductase), where NADH is oxidized by coenzyme Q (Q, Atlas M5) in a two-electron reaction:



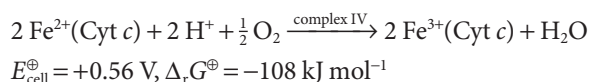
where the reduction of Q to Q²⁻ is accompanied by uptake of two H⁺ ions to yield QH₂. Additional Q molecules are reduced by FADH₂ in complex II (succinate-Q reductase):



Reduced Q migrates to complex III (Q-cytochrome *c* oxidoreductase), which catalyzes the reduction of the protein cytochrome *c* (Cyt *c*). Cytochrome *c* contains the heme *c* group, the central iron ion of which can exist in oxidation states +3 and +2. The net reaction catalyzed by complex III is



Reduced cytochrome *c* carries electrons from complex III to complex IV (cytochrome *c* oxidase), where O₂ is reduced to H₂O:



(b) Oxidative phosphorylation

The reactions that occur in complexes I, II, III, and IV are exergonic and together could drive the synthesis of ATP:



We saw in *Case study 4.2* that the phosphorylation of ADP to ATP can be coupled to the exergonic dephosphorylation of other molecules. Indeed, this is

the mechanism by which ATP is synthesized during glycolysis and the citric acid cycle (*Case study 4.3*). However, the process of **oxidative phosphorylation** taking place in mitochondria operates by a different mechanism.

The structure of a mitochondrion is shown in Fig 5.14. The protein complexes associated with the electron transport chain span the inner membrane, and phosphorylation takes place in the intermembrane space. The Gibbs energy of the reactions in complexes I, III, and IV is first used to do the work of moving protons across the mitochondrial membrane. The complexes are oriented asymmetrically in the inner membrane so that the protons abstracted from one side of the membrane can be deposited on the other side. For example, the oxidation of NADH by Q in complex I is coupled to the transfer of four protons across the membrane. The coupling of electron transfer and proton pumping in complexes III and IV contribute further to a gradient of proton concentration across the membrane. Then the enzyme H^+ -ATPase uses the energy stored in the proton gradient to phosphorylate ADP to ATP. Experiments show that 11 molecules of ATP are made for every three molecules of NADH and one molecule of $FADH_2$ that are oxidized by the respiratory chain. The ATP is then hydrolyzed on demand to perform useful biochemical work throughout the cell. Complex II does not contribute to oxidative phosphorylation because it does not have a proton pump.

The **chemiosmotic theory** proposed by Peter Mitchell explains how H^+ -ATPases use the energy stored in a transmembrane proton gradient to synthesize ATP from ADP. It follows from eqn 5.8 that we can estimate the Gibbs energy available for phosphorylation by writing

$$\Delta G_m = RT \ln \frac{[H^+]_{in}}{[H^+]_{out}} + F\Delta\phi \quad (5.20)$$

The Gibbs energy available for phosphorylation according to the chemiosmotic theory

where $\Delta\phi = \phi_{in} - \phi_{out}$ is the membrane potential difference and we have used $z = +1$. After using $\ln [H^+] = (\ln 10) \log [H^+]$ and substituting $\Delta pH = pH_{in} - pH_{out} = -\log [H^+]_{in} + \log [H^+]_{out}$, it follows that

$$\Delta G_m = F\Delta\phi - (RT \ln 10)\Delta pH \quad (5.21)$$

A brief illustration

In the mitochondrion, $\Delta pH \approx -1.4$ and $\Delta\phi \approx 0.14$ V, so it follows from eqn 5.20 that $\Delta G_m \approx +21.5$ kJ mol⁻¹. Because 31 kJ mol⁻¹ is needed for phosphorylation (*Case study 4.2*), we conclude that at least 2 mol H^+ (and probably more) must flow through the membrane for the phosphorylation of 1 mol ADP.

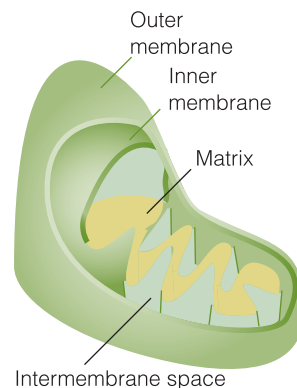


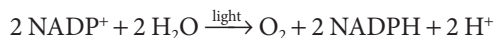
Fig. 5.14 The general structure of a mitochondrion.

5.11 Plant photosynthesis

We need to appreciate that the mechanism of formation of glucose from carbon dioxide and water in photosynthetic organisms is distinctly different from the mechanism of glucose breakdown.

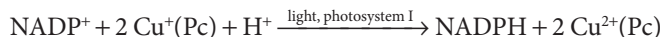
In plant photosynthesis, solar energy drives the endergonic reduction of CO_2 to glucose, with concomitant oxidation of water to O_2 ($\Delta_r G^\ominus = +2880$ kJ mol⁻¹). The process takes place in the *chloroplast*, a special organelle of the plant cell. Electrons flow from reductant to oxidant via a series of electrochemical reactions that are coupled to the synthesis of ATP. First, the leaf absorbs solar energy and transfers

it to membrane protein complexes known as photosystem I and photosystem II.⁶ The absorption of energy from light decreases the reduction potential of special dimers of chlorophyll *a* molecules (Atlas R3) known as P700 (in photosystem I) and P680 (in photosystem II). In their high-energy or excited states, P680 and P700 initiate electron transfer reactions that culminate in the oxidation of water to O₂ and the reduction of NADP⁺ (Atlas N5) to NADPH:



It is clear that energy from light is required to drive this reaction because, in the dark, $E_{\text{cell}}^{\oplus} = -1.135 \text{ V}$ and $\Delta_r G^{\oplus} = +438.0 \text{ kJ mol}^{-1}$.

Working together, photosystem I and the enzyme ferredoxin:NADP⁺ oxidoreductase catalyze the light-induced reduction of NADP⁺ to NADPH. The electrons required for this process come initially from P700 in its excited state. The resulting P700 is then reduced by the mobile carrier plastocyanin (Pc), a protein in which the bound copper ion can exist in oxidation states +2 and +1. The net reaction is

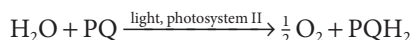


Oxidized plastocyanin accepts electrons from reduced plastoquinone (PQ). The process is catalyzed by the cytochrome *b₆f* complex, a membrane protein complex that resembles complex III of mitochondria:



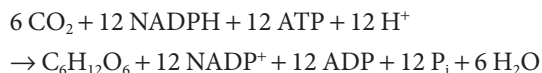
$$E_{\text{cell}}^{\oplus} = +0.370 \text{ V}, \Delta_r G^{\oplus} = -71.4 \text{ kJ mol}^{-1}$$

Plastoquinone is reduced by water in a process catalyzed by light and photosystem II. The electrons required for the reduction of plastoquinone come initially from P680 in its excited state. The resulting P680 is then reduced ultimately by water. The net reaction is



Electron transfer reactions are coupled to the movement of protons across membranes. **Photophosphorylation** uses the energy stored in the transmembrane proton gradient to phosphorylate ADP to ATP in H⁺-ATPases (Fig. 5.15). We see that plant photosynthesis uses an abundant source of electrons (water) and of energy (the Sun) to drive the endergonic reduction of NADP⁺, with concomitant synthesis of ATP. Experiments show that for each molecule of NADPH formed in the chloroplast of green plants, one molecule of ATP is synthesized.

The ATP and NADPH molecules formed by the light-induced electron transfer reactions of plant photosynthesis participate directly in the reduction of CO₂ to glucose in the chloroplast:



In summary, electrochemical reactions mediated by membrane protein complexes harness energy in the form of ATP. Plant photosynthesis uses solar energy to transfer electrons from a poor reductant (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.

⁶ See Chapter 13 for details of the energy transfer process.

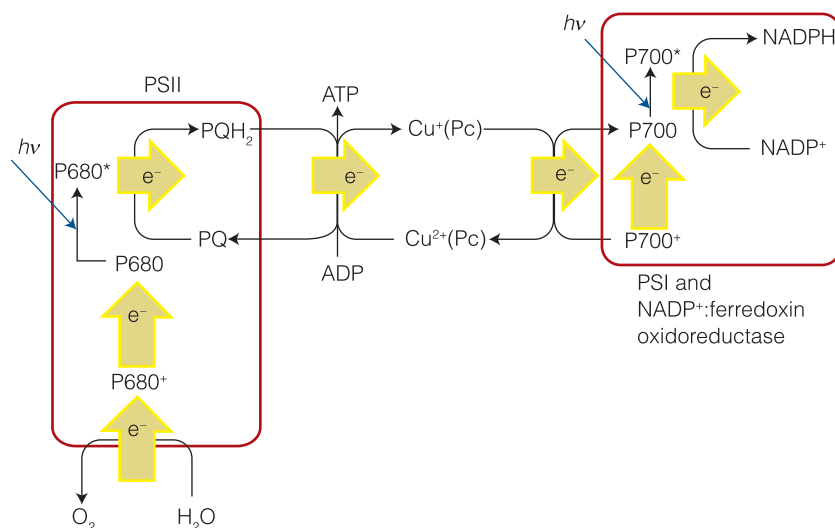


Fig. 5.15 In plant photosynthesis, light-induced electron transfer processes lead to the oxidation of water to O₂ and the reduction of NADP⁺ to NADPH, with concomitant production of ATP. The energy stored in ATP and NADPH is used to reduce CO₂ to carbohydrate in a separate set of reactions. The scheme summarizes the general patterns of electron flow and does not show all the intermediate electron carriers in photosystems I and II, the cytochrome *b₆f* complex, and ferredoxin:NADP⁺ oxidoreductase.

During aerobic metabolism, the O₂ released by photosynthesis as a waste product is used to oxidize carbohydrates to CO₂, driving biological processes such as biosynthesis, muscle contraction, cell division, and nerve conduction. Hence, the sustenance of life on Earth depends on a tightly regulated carbon–oxygen cycle that is driven by solar energy.

Checklist of key concepts

- ☐ 1. Deviations from ideal behavior in ionic solutions are ascribed to the interaction of an ion with its ionic atmosphere.
- ☐ 2. According to the Debye–Hückel limiting law, the mean activity coefficient of ions in a solution is related to the ionic strength of the solution.
- ☐ 3. The Gibbs energy of transfer of an ion across a cell membrane is determined by an activity gradient and a membrane potential difference that arises from differences in Coulomb repulsions on each side of the bilayer.
- ☐ 4. A galvanic cell is an electrochemical cell in which a spontaneous chemical reaction produces a potential difference.
- ☐ 5. An electrolytic cell is an electrochemical cell in which an external source of current is used to drive a non-spontaneous chemical reaction.
- ☐ 6. A redox reaction is expressed as the difference of two reduction half-reactions.
- ☐ 7. In an electrochemical cell, a cathode is the site of reduction; an anode is the site of oxidation.
- ☐ 8. The cell potential is the potential difference that the cell produces when operating reversibly.
- ☐ 9. The standard potential of a couple is the standard potential of a cell in which it forms the right-hand electrode and a hydrogen electrode is on the left.
- ☐ 10. Biological standard potentials are measured in neutral solution (pH = 7).
- ☐ 11. A couple with a low standard potential has a thermodynamic tendency (in the sense $K > 1$) to reduce a couple with a high standard potential.
- ☐ 12. In the respiratory chain, electrons from NADH and FADH₂ pass through four membrane-bound protein complexes and two mobile electron carriers before reducing O₂ to H₂O.
- ☐ 13. The chemiosmotic theory explains how H⁺-ATPases use the energy stored in a transmembrane proton gradient to synthesize ATP from ADP.
- ☐ 14. Plant photosynthesis uses solar energy to transfer electrons from a poor reductant (water) to carbon dioxide.

Checklist of key equations

Property	Equation	Comment
Mean activity coefficient	$\gamma_{\pm} = (\gamma_+ \gamma_-)^{1/2}$	MX salt
	$\gamma_{\pm} = (\gamma_+^p \gamma_-^q)^{1/s} \quad s = p + q$	$M_p X_q$ salt
Debye–Hückel limiting law	$\log \gamma_{\pm} = -A z_+ z_- I^{1/2}$	Valid as $I \rightarrow 0$
Ionic strength	$I = \frac{1}{2} \sum_i z_i^2 b_i / b^\circ$	Definition
Extended Debye–Hückel law	$\log \gamma_{\pm} = -\{A z_+ z_- I^{1/2} / (1 + BI^2)\} + CI$	
Gibbs energy of transfer of an ion across a biological membrane	$\Delta G_m = RT \ln([A]_{\text{in}}/[A]_{\text{out}}) + zF \Delta \phi + \Delta_r G^{\text{ATP}}$	
Maximum non-expansion work	$w'_{\text{max}} = \Delta G$	Constant pressure and temperature
Relation between the cell potential and the reaction Gibbs energy	$-\nu F E_{\text{cell}} = \Delta_r G$	
Nernst equation	$E_{\text{cell}} = E_{\text{cell}}^\circ - (RT/\nu F) \ln Q$	
Standard cell potential	$E_{\text{cell}}^\circ = -\Delta_r G^\circ / \nu F$	
Equilibrium constant in terms of the standard cell potential	$\ln K = \nu F E_{\text{cell}}^\circ / RT$	
Standard reaction entropy from the standard cell potential	$\Delta_r S^\circ = \nu F (dE_{\text{cell}}^\circ / dT)$	
Standard reaction enthalpy	$\Delta_r H^\circ = \Delta_r G^\circ + T \Delta_r S^\circ$	
Gibbs energy available for phosphorylation	$\Delta G_m = RT \ln ([H^+]_{\text{in}}/[H^+]_{\text{out}}) + F \Delta \phi$	Chemiosmotic theory

Discussion questions

5.1 Describe the general features of the Debye–Hückel theory of electrolyte solutions.

5.2 Describe the mechanism of proton conduction in water.

5.3 Distinguish between galvanic, electrolytic, and fuel cells.

5.4 Explain why some reactions that are not redox reactions may be used to generate an electric current.

5.5 Describe a method for the determination of the standard potential of an electrochemical cell.

5.6 Review the concepts in Chapters 1 through 5 and prepare a summary of the experimental and calculational methods that can be used to measure or estimate the Gibbs energies of phase transitions and chemical reactions.

5.7 Review the concepts in Chapters 1 through 5 and discuss how ATP is formed during the metabolism of glucose.

Exercises

5.8 Relate the ionic strengths of (a) KCl, (b) FeCl₃, and (c) CuSO₄ solutions to their molalities, b .

5.9 Calculate the ionic strength of a solution that is 0.10 mol kg⁻¹ in KCl(aq) and 0.20 mol kg⁻¹ in CuSO₄(aq).

5.10 Calculate the masses of (a) Ca(NO₃)₂ and, separately, (b) NaCl to add to a 0.150 mol kg⁻¹ solution of KNO₃(aq) containing 500 g of solvent to raise its ionic strength to 0.250.

5.11 Express the mean activity coefficient of the ions in a solution of CaCl₂ in terms of the activity coefficients of the individual ions.

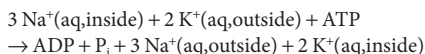
5.12 Estimate the mean ionic activity coefficient and activity of a solution that is 0.010 mol kg⁻¹ CaCl₂(aq) and 0.030 mol kg⁻¹ NaF(aq).

5.13 The mean activity coefficients of HBr in three dilute aqueous solutions at 25°C are 0.930 (at 5.0 mmol kg⁻¹), 0.907 (at 10.0 mmol kg⁻¹), and 0.879 (at 20.0 mmol kg⁻¹). Estimate the value of B in the extended Debye–Hückel law, with $C = 0$.

5.14 The addition of a small amount of a salt, such as (NH₄)₂SO₄, to a solution containing a charged protein increases the solubility of the protein in water. This observation is called the *salting-in effect*. However, the addition of large amounts of salt can decrease the

solubility of the protein to such an extent that the protein precipitates from solution. This observation is called the *salting-out effect* and is used widely by biochemists to isolate and purify proteins. Consider the equilibrium $PX_v(s) \rightleftharpoons P^{v+}(aq) + vX^-(aq)$, where P^{v+} is a polycationic protein of charge $+v$ and X^- is its counter-ion. Use Le Chatelier's principle and the physical principles behind the Debye–Hückel theory to provide a molecular interpretation for the salting-in and salting-out effects.

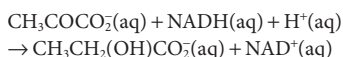
5.15 The overall reaction for the active transport of Na^+ and K^+ ions by the Na^+/K^+ pump is



At 310 K, $\Delta_r G^\ominus$ for the hydrolysis of ATP is $-31.3 \text{ kJ mol}^{-1}$. Given that the $[ATP]/[ADP]$ ratio is of the order of 100, is the hydrolysis of 1 mol ATP sufficient to provide the energy for the transport of Na^+ and K^+ according to the equation above? Take $[P_i] = 1.0 \text{ mol dm}^{-3}$.

5.16 Vision begins with the absorption of light by special cells in the retina. Ultimately, the energy is used to close ligand-gated ion channels, causing sizable changes in the transmembrane potential. The pulse of electric potential travels through the optical nerve and into the optical cortex, where it is interpreted as a signal and incorporated into the web of events we call visual perception (see Chapter 13). Taking the resting potential as -30 mV , the temperature as 310 K, permeabilities of the K^+ and Cl^- ions as $P_{K^+} = 1.0$ and $P_{Cl^-} = 0.45$, respectively, and the concentrations as $[K^+]_{in} = 100 \text{ mmol dm}^{-3}$, $[Na^+]_{in} = 10 \text{ mmol dm}^{-3}$, $[Cl^-]_{in} = 10 \text{ mmol dm}^{-3}$, $[K^+]_{out} = 5 \text{ mmol dm}^{-3}$, $[Na^+]_{out} = 140 \text{ mmol dm}^{-3}$, and $[Cl^-]_{out} = 100 \text{ mmol dm}^{-3}$, calculate the relative permeability (*Case study* 5.1) of the Na^+ ion.

5.17 Is the conversion of pyruvate ion to lactate ion



a redox reaction?

5.18 Express the reaction in Exercise 5.17 as the difference of two half-reactions.

5.19 Express the reaction in which ethanol is converted to acetaldehyde (propanal) by NAD^+ in the presence of alcohol dehydrogenase as the difference of two half-reactions and write the corresponding reaction quotients for each half-reaction and the overall reaction.

5.20 Express the oxidation of cysteine, $HSCH_2CH(NH_2)COOH$, to cystine, $HOOCCH(NH_2)CH_2SSCH_2CH(NH_2)COOH$, as the difference of two half-reactions, one of which is $O_2(g) + 4 H^+(aq) + 4 e^- \rightarrow 2 H_2O(l)$.

5.21 One of the steps in photosynthesis is the reduction of $NADP^+$ by ferredoxin (fd) in the presence of ferredoxin:NADP oxidoreductase: $2 fd_{red}(aq) + NADP^+(aq) + 2 H^+(aq) \rightarrow 2 fd_{ox}(aq) + NADPH(aq)$. Express this reaction as the difference of two half-reactions. How many electrons are transferred in the reaction event?

5.22 From the biological standard half-cell potentials $E_{cell}^\ominus(O_2, H^+, H_2O) = +0.82 \text{ V}$ and $E_{cell}^\ominus(NAD, H^+, NADH) = -0.32 \text{ V}$, calculate the standard potential arising from the reaction in which NADH is oxidized to NAD^+ and the corresponding biological standard reaction Gibbs energy.

5.23 Cytochrome *c* oxidase receives electrons from reduced cytochrome *c* (cyt-*c*_{red}) and transmits them to molecular oxygen, with the formation of water. (a) Write a chemical equation for this

process, which occurs in an acidic environment. (b) Estimate the values of $E_{cell}^\ominus$, $\Delta_r G^\ominus$, and K for the reaction at 25°C .

5.24 A fuel cell develops an electric potential from the chemical reaction between reagents supplied from an outside source. What is the cell potential of a cell fuelled by (a) hydrogen and oxygen, each at 1 bar and 298 K, and (b) the combustion of butane at 1.0 bar and 298 K?

5.25 Consider a hydrogen electrode in $HBr(aq)$ at 25°C operating at 1.45 bar. Estimate the change in the electrode potential when the solution is changed from 5.0 mmol dm^{-3} to $25.0 \text{ mmol dm}^{-3}$.

5.26 A hydrogen electrode can, in principle, be used to monitor changes in the molar concentrations of weak acids in biologically active solutions. Consider a hydrogen electrode in a solution of lactic acid as part of an overall galvanic cell at 25°C and 1 bar. Estimate the change in the electrode potential when the concentration of lactic acid in the solution is changed from 5.0 mmol dm^{-3} to $25.0 \text{ mmol dm}^{-3}$.

5.27 Write the cell reactions and electrode half-reactions for the following cells:

- $Pt(s) | H_2(g, p_L) | HCl(aq) | H_2(g, p_R) | Pt(s)$
- $Pt(s) | Cl_2(g) | HCl(aq) || HBr(aq) | Br_2(l) | Pt(s)$
- $Pt(s) | NAD^+(aq), H^+(aq), NADH(aq) || \text{oxaloacetate}^{2-}(aq), H^+(aq), \text{malate}^{2-}(aq) | Pt(s)$
- $Fe(s) | Fe^{2+}(aq) || Mn^{2+}(aq), H^+(aq) | MnO_2(s) | Pt(s)$

5.28 Write the Nernst equations for the cells in the preceding exercise.

5.29 Devise cells to study the following biochemically important reactions. In each case state the value for ν to use in the Nernst equation.

- $CH_3CH_2OH(aq) + NAD^+(aq) \rightarrow CH_3CHO(aq) + NADH(aq) + H^+(aq)$
- $ATP^{4-}(aq) + Mg^{2+}(aq) \rightarrow MgATP^{2-}(aq)$
- $2 \text{ cyt-}c(\text{red}, aq) + CH_3COCO_2^-(aq) + 2 H^+(aq) \rightarrow 2 \text{ cyt-}c(\text{ox}, aq) + CH_3CH(OH)CO_2^-(aq)$

5.30 Use the standard potentials of the electrodes to calculate the standard potentials of the cells devised in Exercise 5.29.

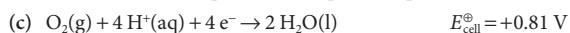
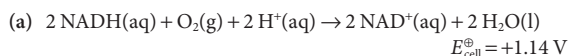
5.31 The permanganate ion is a common oxidizing agent. What is the standard potential of the $MnO_4^-, H^+/Mn^{2+}$ couple at (a) $pH = 6.00$ and (b) general pH ?

5.32 State what you would expect to happen to the cell potential when the following changes are made to the corresponding cells in Exercise 5.27. Confirm your prediction by using the Nernst equation in each case. (a) The pressure of hydrogen in the left-hand compartment is increased. (b) The concentration of HCl is increased. (c) Acid is added to both compartments. (d) Acid is added to the right-hand compartment.

5.33 State what you would expect to happen to the cell potential when the following changes are made to the corresponding cells devised in Exercise 5.29. Confirm your prediction by using the Nernst equation in each case. (a) The pH of the solution is raised. (b) A solution of Epsom salts (magnesium sulfate) is added. (c) Sodium lactate is added to the solution.

5.34 (a) Calculate the standard potential of the cell $Hg(l) | HgCl_2(aq) | TiNO_3(aq) | Ti(s)$ at 25°C . (b) Calculate the cell potential when the molar concentration of the Hg^{2+} ion is $0.150 \text{ mol dm}^{-3}$ and that of the Ti^+ ion is 0.93 mol dm^{-3} .

5.35 Calculate the biological standard Gibbs energies of reactions of the following reactions and half-reactions:



5.36 The silver–silver chloride electrode, $\text{Ag}(\text{s}) | \text{AgCl}(\text{s}) | \text{Cl}^-(\text{aq})$, consists of metallic silver coated with a layer of silver chloride (which does not dissolve in water) in contact with a solution containing chloride ions. (a) Write the half-reaction for the silver–silver chloride half-electrode. (b) Estimate the potential of the cell $\text{Ag}(\text{s}) | \text{AgCl}(\text{s}) | \text{KCl}(\text{aq}, 0.025 \text{ mol kg}^{-1}) || \text{AgNO}_3(\text{aq}, 0.010 \text{ mol kg}^{-1}) | \text{Ag}(\text{s})$ at 25°C.

5.37 (a) Calculate the standard potential of the cell $\text{Pt}(\text{s}) | \text{cysteine}(\text{aq}), \text{cystine}(\text{aq}) || \text{H}^+(\text{aq}) | \text{O}_2(\text{g}) | \text{Pt}(\text{s})$ and the standard Gibbs energy and enthalpy of the cell reaction at 25°C. (b) Estimate the value of $\Delta_r G^\circ$ at 35°C. Use $E^\circ = -0.34 \text{ V}$ for the cystine/cysteine couple.

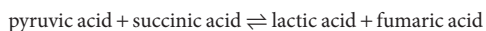
5.38 The biological standard potential of the couple pyruvic acid/lactic acid is -0.19 V . What is the thermodynamic standard potential of the couple? Pyruvic acid is CH_3COCOOH and lactic acid is $\text{CH}_3\text{CH}(\text{OH})\text{COOH}$.

5.39 Calculate the biological standard values of the potentials (the two potentials and the cell potential) for the system in Exercise 5.37 at 310 K.

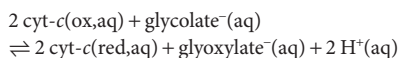
5.40 (a) Does FADH_2 have a thermodynamic tendency to reduce coenzyme Q at pH = 7? (b) Does oxidized cytochrome *b* have a thermodynamic tendency to oxidize reduced cytochrome *f* at pH = 7?

5.41 Radicals, very reactive species containing one or more unpaired electrons, are among the by-products of metabolism. Evidence is accumulating that radicals are involved in the mechanism of aging and in the development of a number of conditions, ranging from cardiovascular disease to cancer. *Antioxidants* are substances that reduce radicals readily. Which of the following known antioxidants is the most efficient (from a thermodynamic point of view): ascorbic acid (vitamin C), reduced glutathione, reduced lipoic acid, or reduced coenzyme Q?

5.42 The biological standard potential of the redox couple pyruvic acid/lactic acid is -0.19 V and that of the fumaric acid/succinic acid couple is $+0.03 \text{ V}$ at 298 K. What is the equilibrium constant at pH = 7 for the reaction



5.43 Tabulated thermodynamic data can be used to predict the standard potential of a cell even if it cannot be measured directly. The presence of glyoxylate ion produced by the action of the enzyme glycolate oxidase on glycolate ion can be monitored by the following redox reaction:



The equilibrium constant for the reaction above is 2.14×10^{11} at pH = 7.0 and 298 K. (a) Calculate the biological standard potential of the corresponding galvanic cell and (b) the biological standard potential of the glyoxylate[−]/glycolate[−] couple.

5.44 One ecologically important equilibrium is that between carbonate and hydrogencarbonate (bicarbonate) ions in natural water. (a) The standard Gibbs energies of formation of $\text{CO}_3^{2-}(\text{aq})$ and $\text{HCO}_3^-(\text{aq})$ are $-527.81 \text{ kJ mol}^{-1}$ and $-586.77 \text{ kJ mol}^{-1}$, respectively. What is the standard potential of the $\text{HCO}_3^-/\text{CO}_3^{2-}, \text{H}_2$ couple? (b) Calculate the standard potential of a cell in which the cell reaction is $\text{Na}_2\text{CO}_3(\text{aq}) + \text{H}_2\text{O}(\text{l}) \rightarrow \text{NaHCO}_3(\text{aq}) + \text{NaOH}(\text{aq})$. (c) Write the Nernst equation for the cell, (d) Predict and calculate the change in potential when the pH is changed to 7.0. (e) Calculate the value of $\text{p}K_a$ for $\text{HCO}_3^-(\text{aq})$.

5.45 The dichromate ion in acidic solution is a common oxidizing agent for organic compounds. Derive an expression for the potential of an electrode for which the half-reaction is the reduction of $\text{Cr}_2\text{O}_7^{2-}$ ions to Cr^{3+} ions in acidic solution.

5.46 The potential of the cell $\text{Pt}(\text{s}) | \text{H}_2(\text{g}) | \text{HCl}(\text{aq}) | \text{AgCl}(\text{s}) | \text{Ag}(\text{s})$ is $+0.312 \text{ V}$ at 25°C. What is the pH of the electrolyte solution?

5.47 The standard potential of the $\text{AgCl}/\text{Ag}, \text{Cl}^-$ couple fits the expression

$$E^\circ/\text{V} = 0.23659 - 4.8564 \times 10^{-4}(\theta/^\circ\text{C}) - 3.4205 \times 10^{-6}(\theta/^\circ\text{C})^2 + 5.869 \times 10^{-9}(\theta/^\circ\text{C})^3$$

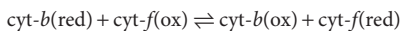
Calculate the standard Gibbs energy and enthalpy of formation of $\text{Cl}^-(\text{aq})$ and its entropy (relative to H^+) at 298 K.

5.48 If the mitochondrial electric potential between the matrix and the intermembrane space were 70 mV, as is common for other membranes, how much ATP could be synthesized from the transport of 4 mol H^+ , assuming the pH difference remains the same?

5.49 Under certain stress conditions, such as viral infection or hypoxia, plants have been shown to have an intercellular pH increase of about 0.1 pH. Suppose this pH change also occurs in the mitochondrial intermembrane space. How much ATP can now be synthesized for the transport of 2 mol H^+ , assuming no other changes occur?

5.50 In anaerobic bacteria, the source of carbon may be a molecule other than glucose and the final electron acceptor some molecule other than O_2 . Could a bacterium evolve to use the ethanol/nitrate pair instead of the glucose/ O_2 pair as a source of metabolic energy?

5.51 The following reaction occurs in the cytochrome *b₆f* complex, a component of the electron transport chain of plant photosynthesis:

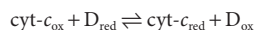


(a) Calculate the biological standard Gibbs energy of this reaction. (b) The Gibbs energy for hydrolysis of ATP under conditions found in the chloroplast is -50 kJ mol^{-1} and the synthesis of ATP by ATPase requires the transfer of four protons across the membrane. How many electrons must pass through the cytochrome *b₆f* complex to lead to the generation of a transmembrane proton gradient that is large enough to drive ATP synthesis in the chloroplast?

Project

5.52 The standard potentials of proteins are not commonly measured by the methods described in this chapter because proteins often lose their native structure and their function when they react on the surfaces of electrodes. In an alternative method, the oxidized protein is allowed to react with an appropriate electron donor in solution. The standard potential of the protein is then determined from the Nernst equation, the equilibrium concentrations of all species in solution, and the known standard potential of the electron donor. We shall illustrate this method with the protein cytochrome *c*.

(a) The one-electron reaction between cytochrome *c*, cyt-*c*, and 2,6-dichloroindophenol, D, can be written as



Consider E_{cyt}° and E_D° to be the standard potentials of cytochrome *c* and D, respectively. Show that, at equilibrium (eq), a plot of $\ln([D_{\text{ox}}]_{\text{eq}}/[D_{\text{red}}]_{\text{eq}})$ against $\ln([\text{cyt-}c_{\text{ox}}]_{\text{eq}}/[\text{cyt-}c_{\text{red}}]_{\text{eq}})$ is linear with a slope of 1 and

y -intercept $F(E_{\text{cyt}}^\circ - E_D^\circ)/RT$, where equilibrium activities are replaced by the numerical values of equilibrium molar concentrations.

(b) The following data were obtained for the reaction between oxidized cytochrome *c* and reduced D at pH 6.5 buffer and 298 K. The ratios $[D_{\text{ox}}]_{\text{eq}}/[D_{\text{red}}]_{\text{eq}}$ and $[\text{cyt-}c_{\text{ox}}]_{\text{eq}}/[\text{cyt-}c_{\text{red}}]_{\text{eq}}$ were adjusted by adding known volumes of a solution of sodium ascorbate, a reducing agent, to a solution containing oxidized cytochrome *c* and reduced D. From the data and the standard potential of D of +0.237 V, determine the standard potential of cytochrome *c* at pH = 6.5 and 298 K.

$[D_{\text{ox}}]_{\text{eq}}/$	0.002 79	0.008 43	0.0257	0.0497	0.0748	0.238	0.534
$[D_{\text{red}}]_{\text{eq}}$							
$[\text{cyt-}c_{\text{ox}}]_{\text{eq}}/$	0.0106	0.0230	0.0894	0.197	0.335	0.809	1.39
$[\text{cyt-}c_{\text{red}}]_{\text{eq}}$							

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