THERMODYNAMICS OF PHARMACEUTICAL SYSTEMS

An Introduction for Students of Pharmacy

Kenneth A. Connors

School of Pharmacy
University of Wisconsin—Madison

WILEY-
INTERSCIENCE
A JOHN WILEY & SONS, INC., PUBLICATION

THERMODYNAMICS OF PHARMACEUTICAL SYSTEMS

THERMODYNAMICS OF PHARMACEUTICAL SYSTEMS

An Introduction for Students of Pharmacy

Kenneth A. Connors

School of Pharmacy
University of Wisconsin—Madison

WILEY-
INTERSCIENCE

A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2002 by John Wiley & Sons, Inc. All rights reserved.

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400, fax 978-750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, e-mail: permcoordinator@wiley.com.

For general information on our other products and services please contact our Customer Care Department within the U.S. at 877-762-2974, outside the U.S. at 317-572-3993 or fax 317-572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print, however, may not be available in electronic format.

Library of Congress Cataloging-in-Publication Data:

Connors, Kenneth A. (Kenneth Antonio), 1932-
Thermodynamics of pharmaceutical systems: an introduction for students of pharmacy / Kenneth A. Connors.
p. cm.
Includes bibliographical references and index.
ISBN 0-471-20241-X (paper : alk. paper)
1. Pharmaceutical chemistry. 2. Thermodynamics. I. Title.
[DNLM: 1. Thermodynamics. 2. Chemistry, Pharmaceutical.
QC 311 C752t 2003]
RS403.C665 2003
615′.19–dc21

2002011151

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

To my brothers and sisters
Joy Connors Mojon, Lawrence M. Connors,
Peter G. Connors, Francis P. Connors,
and Kathleen Connors Hitchcock

CONTENTS

PREFACE xi

I BASIC THERMODYNAMICS 1

1 Energy and the First Law of Thermodynamics / 3

1.1. Fundamental Concepts / 3
1.2. The First Law of Thermodynamics / 9
1.3. The Enthalpy / 12

2 The Entropy Concept / 17

2.1. The Entropy Defined / 17
2.2. The Second Law of Thermodynamics / 24
2.3. Applications of the Entropy Concept / 26

3 The Free Energy / 30

3.1. Properties of the Free Energy / 30
3.2. The Chemical Potential / 34

4 Equilibrium / 42

4.1. Conditions for Equilibrium / 42
4.2. Physical Processes / 44
4.3. Chemical Equilibrium / 49

II THERMODYNAMICS OF PHYSICAL PROCESSES 59

5 Introduction to Physical Processes / 61

5.1. Scope / 61
5.2. Concentration Scales / 62
5.3. Standard States / 63

6 Phase Transformations / 67

6.1. Pure Substances / 67
6.2. Multicomponent Systems / 72

7 Solutions of Nonelectrolytes / 77

7.1. Ideal Solutions / 77
7.2. Nonideal Solutions / 80
7.3. Partitioning between Liquid Phases / 83

8 Solutions of Electrolytes / 96

8.1. Coulombic Interaction and Ionic Dissociation / 96
8.2. Mean Ionic Activity and Activity Coefficient / 99
8.3. The Debye–Hückel Theory / 101

9 Colligative Properties / 106

9.1. Boiling Point Elevation / 106
9.2. Freezing Point Depression / 108
9.3. Osmotic Pressure / 109
9.4. Isotonicity Calculations / 111

10 Solubility / 116

10.1. Solubility as an Equilibrium Constant / 116
10.2. The Ideal Solubility / 117
10.3. Temperature Dependence of the Solubility / 120
10.4. Solubility of Slightly Soluble Salts / 123
10.5. Solubilities of Nonelectrolytes: Further Issues / 126

11 Surfaces and Interfaces / 135

11.1. Thermodynamic Properties / 136
11.2. Adsorption / 143

III THERMODYNAMICS OF CHEMICAL PROCESSES 155

12 Acid–Base Equilibria / 157

12.1. Acid–Base Theory / 157
12.2. pH Dependence of Acid–Base Equilibria / 163
12.3. Calculation of Solution pH / 172

12.4. Acid–Base Titrations / 177
12.5. Aqueous Solubility of Weak Acids and Bases / 185
12.6. Nonaqueous Acid–Base Behavior / 189
12.7. Acid–Base Structure and Strength / 193

13 Electrical Work / 206

13.1. Introduction / 206
13.2. Oxidation–Reduction Reactions / 207
13.3. Electrochemical Cells / 209
13.4. pH Measurement / 221
13.5. Ion-Selective Membrane Electrodes / 228

14 Noncovalent Binding Equilibria / 237

14.1. Introduction / 237
14.2. The Noncovalent Interactions / 238
14.3. Binding Models / 243
14.4. Measurement of Binding Constants / 248

APPENDIXES 259

A Physical Constants / 261

B Review of Mathematics / 262

B.1. Introduction / 262
B.2. Logarithms and Exponents / 263
B.3. Algebraic and Graphical Analysis / 266
B.4. Dealing with Change / 281
B.5. Statistical Treatment of Data / 295
B.6. Dimensions and Units / 309

ANSWERS TO PROBLEMS 324

BIBLIOGRAPHY 333

INDEX 337

PREFACE

Classical thermodynamics, which was largely a nineteenth-century development, is a powerful descriptive treatment of the equilibrium macroscopic properties of matter. It is powerful because it is general, and it is general because it makes no assumptions about the fundamental structure of matter. There are no atoms or molecules in classical thermodynamics, so if our ideas about the atomic structure of matter should prove to be wrong (a very possible outcome to many nineteenth-century scientists), thermodynamics will stand unaltered. What thermodynamics does is to start with a few very general experimental observations expressed in mathematical form, and then develop logical relationships among macroscopic observables such as temperature, pressure, and volume. These relationships turn out to have great practical value.

Of course, we now have firm experimental and theoretical reasons to accept the existence of atoms and molecules, so the behavior of these entities has been absorbed into the content of thermodynamics, which thereby becomes even more useful to us. In the following we will encounter the most fundamental ideas of this important subject, as well as some applications of particular value in pharmacy. In keeping with our needs, the treatment will in places be less rigorous than that in many textbooks, and we may omit descriptions of detailed experimental conditions, subtleties in the arguments, or limits on the conclusions when such omissions do not concern our practical applications. But despite such shortcuts, the thermodynamics is sound, so if you later study thermodynamics at a deeper level you will not have to “unlearn” anything. Thermodynamics is a subject that benefits from, or may require, repeated study, and the treatment here is intended to be the introductory exposition.

Here are a few more specific matters that may interest readers. Throughout the text there will be citations to the Bibliography at the end of the book and the Notes sections that appear at the end of most chapters. Students will probably not find it necessary to consult the cited entries in the Bibliography, but I encourage you to glance at the Notes, which you may find to be interesting and helpful. Two of my practices in the text may be regarded by modern readers as somewhat old-fashioned, and perhaps they are, but here are my reasons. I make considerable use of certain units, such as the kilocalorie and the dyne, that are formally obsolete; not only is the older literature expressed in terms of these units, but they remain in active use, so the student must learn to use them. Appendix B treats the conversion of units. My second peculiar practice, which may seem quaint to students who have never used a table of logarithms, is often to express logarithmic relationships in terms of Briggsian (base 10) logarithms rather than natural logarithms. There are two reasons for the continued use of base 10 logarithms; one is that certain functions, such as pH and pK, are defined by base 10 logs, and these definitions can be taken as invariant components of chemical description; and the second reason, related to the first, is that order-of-magnitude comparisons are simple with base 10 logarithms, since we commonly operate with a base 10 arithmetic.

Obviously there is no new thermodynamics here, and I have drawn freely from several of the standard references, which are cited. Perhaps the only unusual feature of the text is my treatment of entropy. The usual development of the entropy concept follows historical lines, invoking heat engines and Carnot cycles. I agree with Guggenheim (1957, p. 7), however, that the idea of a Carnot cycle is at least as difficult as is that of entropy. Guggenheim then adopts a postulational attitude toward entropy [a method of approach given very systematic form in a well-known book by Callen (1960)], whereas I have developed a treatment aimed at establishing a stronger intuitive sense in my student readers [Nash (1974, p. 35) uses a similar strategy]. My approach consists of these three stages: (1) the basic postulates of statistical mechanics are introduced, along with Boltzmann's definition of entropy, and the concept is developed that spontaneous processes take place in the direction of greater probability and therefore of increased entropy; (2) with the statistical definition in hand, the entropy change is calculated for the isothermal expansion of an ideal gas; and (3) finally, we apply classical thermodynamic arguments to analyze the isothermal expansion of an ideal gas. By comparing the results of the statistical and the classical treatments of the same process, we find the classical definition of entropy, $dS = dq/T$, that will provide consistency between the two treatments.

Lectures based on this text might reasonably omit certain passages, only incidentally to save time; more importantly, the flow of ideas may be better served by making use of analogy or chemical intuition, rather than rigorous mathematics, to establish a result. For a good example of this practice, see Eq. (4.1) and the subsequent discussion; it seems to me to be more fruitful educationally to pass from Eq. (4.1), which says that, for a pure substance, the molar free energies in two phases at equilibrium are equal, to the conclusion for mixtures, by analogy, that the chemical potentials are equal, without indulging in the proof, embodied in Eqs. (4.2)–(4.6). But different instructors will doubtless have different views on this matter.

I thank my colleague George Zografi for providing the initial stimulus that led to the writing of this book. The manuscript was accurately typed by Tina Rundle. Any errors (there are always errors) are my responsibility.

Kenneth A. Connors

Madison, Wisconsin

I

BASIC THERMODYNAMICS

1

ENERGY AND THE FIRST LAW OF THERMODYNAMICS

1.1. FUNDAMENTAL CONCEPTS

Temperature and the Zeroth Law. The concept of temperature is so familiar to us that we may not comprehend why scientists two centuries ago tended to confuse temperature with heat. We will start with the notion that temperature corresponds to "degree of hotness" experienced as a sensation. Next we assign a number to the temperature based on the observation that material objects (gases and liquids in particular) respond to "degree of hotness" through variations in their volumes. Thus we should be able to associate a number (its temperature) with the volume of a specified amount of material. We call the instrument designed for this purpose a thermometer.

The first requirement in setting up a scale of temperatures is to choose a zero point. In the common *Celsius* or *centigrade* scale we set the freezing point of water (which is also the melting point of ice) at 0°C [more precisely, 0°C corresponds to the freezing point of water (called the "ice point") in the presence of air at a pressure of 1 atmosphere (atm)]. The second requirement is that we must define the size of the degree, which is done for this scale by setting the boiling point of water (the "steam point") at 100°C. The intervening portion of the scale is then divided linearly into 100 segments. We will let t signify temperature on the Celsius scale.

Experience shows that different substances may give different temperature readings under identical conditions even though they agree perfectly at 0 and 100°C. For example, a mercury thermometer and an alcohol thermometer will not give precisely the same readings at (say) room temperature. In very careful work it would be advantageous to have available an "absolute" temperature scale that does not depend on the identity of the thermometer substance. Again we appeal to laboratory experience, which has shown that the dependence of the volume of a fixed amount of a gas on temperature, at very low pressures of the gas, is independent of the chemical nature of the gas. Later we will study the behavior of gases at low pressures in more detail; for the present we can call such gases "ideal gases" and use them to define an *absolute ideal-gas temperature scale*. We define the absolute temperature as directly proportional to the volume of a given mass of ideal gas at constant pressure (i.e., letting T be the absolute temperature and V the gas volume):

$$T \propto V$$

For convenience we define the size of the absolute temperature to be identical to the Celsius degree. If V_0 and V_{100} are the volumes of the ideal gas at the ice and steam points of water, respectively, the size of the degree is given by

$$\frac{V_{100} - V_0}{100}$$

Then our absolute temperature scale is defined by

$$T = \frac{V}{(V_{100} - V_0)/100} \tag{1.1}$$

Now suppose that we apply our ideal-gas thermometer to water at the ice point. In this special case Eq. (1.1) becomes

$$T_0 = \frac{V_0}{(V_{100} - V_0)/100}$$

Careful experimental work with numerous gases has revealed that $T_0 = 273.15\,\mathrm{K}$. Thus the Celsius and absolute scales are related by

$$T = t + 273.15 \tag{1.2}$$

The absolute temperature scale is also called the *thermodynamic scale* or the *Kelvin scale*, and temperatures on this scale are denoted K (pronounced Kelvin, with no degree symbol or word).

According to Eq. (1.1), when $T = 0\,\mathrm{K}$, $V = 0$; the volume of the ideal gas goes to zero at the *absolute zero*. Modern experimental techniques have achieved temperatures within microdegrees of the absolute zero, but $T = 0\,\mathrm{K}$ appears to be an unattainable condition.

The concept and practical use of temperature scales and thermometers is based on the experimental fact that if two bodies are each in thermal equilibrium with a third body, they are in thermal equilibrium with each other. This is the *zeroth law of thermodynamics*.

Work and Energy. Let us begin with the mechanical concept of *work* as the product of a force and a displacement:

$$\text{Work} = \text{force} \times \text{displacement} \tag{1.3}$$

The units of work are consequently those of force and length. Now from Newton's laws of motion,

$$\text{Force} = \text{mass} \times \text{acceleration} \tag{1.4}$$

In SI units, force therefore has the units $\mathrm{kg\,m\,s^{-2}}$, which is also called a newton, N. Hence the units of work are either $\mathrm{kg\,m^2\,s^{-2}}$ or N m.

Energy is defined as any property that can be produced from or converted into work (including work itself). Therefore work and energy have the same dimensions, although different units may be used to describe different manifestations of energy and work. For example, 1 Nm = 1 J (joule), and energy is often given in joules or kilojoules. Here are relationships to earlier energy units:

$$1\ \mathrm{J} = 10^7\ \mathrm{erg}$$
$$4.184\ \mathrm{J} = 1\ \mathrm{cal}(\text{calorie})$$

Note from the definition (1.3) that work is a product of an intensive property (force) and an extensive property (displacement). In general, work or energy can be expressed as this product:

$$\text{Work (energy)} = \text{intensity factor} \times \text{capacity factor} \tag{1.5}$$

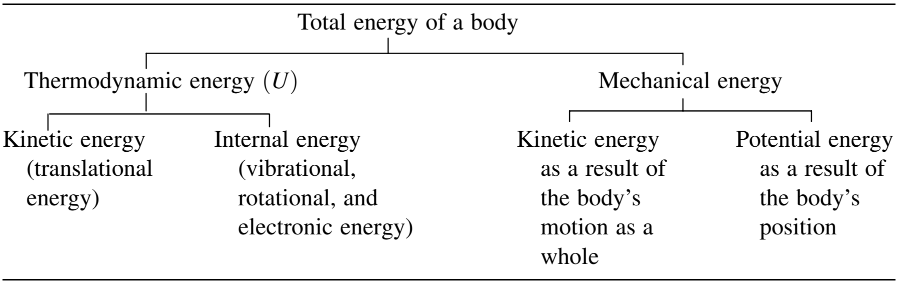
Here are several examples of Eq. (1.5):

Mechanical work = mechanical force × distance
Work of expansion = pressure × volume change
Electrical work = electric potential × charge
Surface work = surface tension × area change

All forms of work are, at least in principle, completely interconvertible. For example, one could use the electrical energy provided by a battery to drive a (frictionless) piston that converts the electrical work to an equivalent amount of work of expansion.

Heat and Energy. Heat has been described as *energy in transit* (Glasstone 1947, p. 7) or as a *mode of energy transfer* (Denbigh 1966, p. 18). Heat is that form of energy that is transferred from one place to another as a consequence of a difference in temperature between the two places. Numerically heat is expressed in joules (J) or calories (cal). Heat is not "degree of hotness," which, as we have seen, is measured by temperature.[1]

Table 1.1. The energy of a thermodynamic system


Total energy of a body
Thermodynamic energy (U)
Mechanical energy
Kinetic energy (translational energy)
Internal energy (vibrational, rotational, and electronic energy)
Kinetic energy as a result of the body's motion as a whole
Potential energy as a result of the body's position

Since both work and heat are forms of energy, they are closely connected. Work can be completely converted into an equivalent amount of heat (e.g., through friction). The converse is not possible, however; it is found experimentally that heat cannot be completely converted into an equivalent amount of work (without producing changes elsewhere in the surroundings). This point will be developed later; for the present we observe that this finding is the basis for the impossibility of a "perpetual-motion machine."

We find it convenient to divide energy into categories. This is arbitrary, but there is nothing wrong with it provided we are careful to leave nothing out. Now, we have seen that thermodynamics is not built on the atomic theory; nevertheless, we can very usefully invoke the atomic and molecular structure of matter in our interpretation of energy. In this manner we view heat as thermal energy, equivalent to, or manifesting itself as, motions of atoms and molecules. The scheme shown in Table 1.1 clarifies the several "kinds" of energy that a body (the "system") can possess.[2]

Chemical thermodynamics is concerned with the energy U. This energy is a consequence of the *electronic* distribution within the material, and of three types of atomic or molecular motion: (1) *translation*, the movement of individual molecules in space; (2) *vibration*, the movement of atoms or groups of atoms with respect to each other within a molecule; and (3) *rotation*, the revolution of molecules about an axis. If a material object is subjected to an external source of heat, so that the object absorbs heat and its temperature rises, the atoms and molecules increase their translational, vibrational, and rotational modes of motion. Energy is not a "thing"; it is rather one way of describing and measuring these molecular and atomic distributions and motions, as well as the electronic distribution within atoms and molecules.

Systems and States. In order to carry out experimental studies and to interpret the results, we must focus on some part of the universe that interests us. In thermodynamics this portion of the universe is called a *system*. The system typically consists of a specified amount of chemical substance or substances, such as a given mass of a gas, liquid, or solid. Whatever exists outside of the system is called the *surroundings*. Certain conditions give rise to several types of systems:

Isolated Systems. These systems are completely uninfluenced by their surroundings. This means that neither matter nor energy can flow into or out of the system.[3]

Closed Systems. Energy may be exchanged with the surroundings, but there can be no transfer of matter across the boundaries of the system.

Open Systems. Both energy and matter can enter or leave the system.

We can also speak of a *homogeneous* system, which is completely uniform in composition; or a *heterogeneous* system, which consists of two or more phases.

The *state* of a system, experiment has shown, can be completely defined by specifying four observable thermodynamic variables: the composition, temperature, pressure, and volume. If the system is homogeneous and consists of a single chemical substance, only three variables suffice. Moreover, it is known that these three variables are not all independent; if any two are known, the third is thereby fixed. Thus the thermodynamic state of a pure homogeneous system is completely defined by specifying any two of the variables pressure (P), volume (V), and temperature (T). The quantitative relationship, for a given system, among P, V, and T is called an *equation of state*. Generally the equation of state of a system must be established experimentally.

The fact that the state of a system can be completely defined by specifying so few (two or three) variables constitutes a vast simplification in the program of describing physicochemical systems, for this means that all the other macroscopic physical properties (density, viscosity, compressibility, etc.) are fixed. We don't know their values, but we know that they depend only on the thermodynamic variables, and therefore are not themselves independent. With this terminology we can now say that thermodynamics deals with changes in the energy U of a system as the system passes from one state to another state.

Thermodynamic Processes and Equilibrium. A system whose observable properties are not undergoing any changes with time is said to be in *thermodynamic equilibrium*. Thermodynamic equilibrium implies that three different kinds of equilibrium are established: (1) *thermal equilibrium* (all parts of the system are at the same temperature), (2) *chemical equilibrium* (the composition of the system is not changing), and (3) *mechanical equilibrium* (there are no macroscopic movements of material within the system).

Many kinds of processes can be carried out on thermodynamic systems, and some of these are of special theoretical or practical significance. *Isothermal processes* are those in which the system is maintained at a constant-temperature. (This is easy to do with a constant-temperature bath or oven.) Since it is conceivable that heat is given off or taken up by the system during the process, maintaining a constant temperature requires that the heat loss or gain be offset by heat absorbed from or given up to the surroundings. Thus an isothermal process requires either a closed or an open system, both of these allowing energy to be exchanged with the surroundings. An *adiabatic process* is one in which no heat enters or leaves the system. An adiabatic process requires an isolated system. Obviously if the process is adiabatic, the temperature of the system may change.

A *spontaneous process* is one that occurs "naturally"; it takes place without intervention. For example, if a filled balloon is punctured, much of the contained gas spontaneously expands into the surrounding atmosphere. In an equilibrium chemical reaction, which we may write as

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{M} + \mathrm{N}$$

it is conventional to consider the reaction as occurring from left to right as written. Thus if the position of equilibrium favors M + N (the products), the reaction is said to be spontaneous. If the reactants (A + B) are favored, the reaction is nonspontaneous as written. (Obviously we can change these designations simply by writing the reaction in the reverse direction.)

It is the business of thermodynamics to tell us whether a given process is spontaneous or nonspontaneous. However, thermodynamics, which deals solely with systems at equilibrium, cannot tell us how fast the process will be. For example, according to thermodynamic results, a mixture of hydrogen and oxygen gases will spontaneously react to yield water. This is undoubtedly correct—but it happens that (in the absence of a suitable catalyst) the process will take millions of years.

There is one more important type of thermodynamic process: the *reversible process*. Suppose we have a thermodynamic system at equilibrium. Now let an infinitesimal alteration be made in one of the thermodynamic variables (say, T or P). This will cause an infinitesimal change in the state of the system. If the alteration in the variable is reversed, the process will reverse itself exactly, and the original equilibrium will be restored. This situation is called *thermodynamic reversibility.* Reversibility in this sense requires that the system always be at, or infinitesimally close to, equilibrium, and that the infinitesimally small alterations in variables be carried out infinitesimally slowly. Because of this last factor, thermodynamically reversible processes constitute an idealization of real processes, but the concept is theoretically valuable. One feature of a reversible process is that it can yield the maximum amount of work; any other (irreversible) process would generate less work, because some energy would be irretrievably dissipated (e.g., by friction).

Now suppose that a system undergoes a process that takes it from state A to state B:

$$\mathrm{A} \rightarrow \mathrm{B}$$

We define a change in some property Q of the system by

$$\Delta Q = Q_{\mathrm{B}} - Q_{\mathrm{A}} \tag{1.6}$$

In other words, the incremental change in the property is equal to its value in the final state minus its value in the initial state.

Next consider this series of processes, which constitute a *thermodynamic cycle*:

$$\begin{tikzcd}
A \arrow[r, "1"] & B \arrow[d, "2"] \\
D \arrow[u, "4"] & C \arrow[l, "3"]
\end{tikzcd}$$

$$\begin{aligned}
\Delta Q_1 &= Q_B - Q_A \\
\Delta Q_2 &= Q_C - Q_B \\
\Delta Q_3 &= Q_D - Q_C \\
\Delta Q_4 &= Q_A - Q_D \\
\hline
\text{Sum: } \Delta Q &= 0
\end{aligned}$$

In any cycle in which the system is restored exactly to its original state, the total incremental change is zero.

1.2. THE FIRST LAW OF THERMODYNAMICS

Statement of the First Law. To this point we have been establishing a vocabulary and some basic concepts, and now we are ready for the first powerful thermodynamic result. This result is solidly based on extensive experimentation, which tells us that although energy can be converted from one form to another, it cannot be created or destroyed [this statement is completely general in the energy regime characteristic of chemical processes; relativistic effects (i.e., the famous equation $E = mc^2$) do not intrude here]. This is the great *conservation of energy* principle, which is expressed mathematically as Eq. (1.7), the *first law of thermodynamics.*

$$\Delta U = q - w \tag{1.7}$$

Here ΔU is the change in thermodynamic energy of the system, q is the amount of energy gained by the system as heat, and w is the amount of energy lost by the system by doing work on its surroundings. These are the sign conventions that we will use:

q is positive if the heat is taken up by the system (i.e., energy is gained by the system).

w is positive if work is done by the system (i.e., energy is lost by the system).[4]

Equation (1.7) is the incremental form of the first law. The differential form is

$$dU = dq - dw \tag{1.8}$$

But now we must make a very clear distinction between the quantity dU and the quantities dq and dw. U is a *state function* and dU is an *exact differential.* This terminology means that the value of ΔU, which is obtained by integrating dU over the limits from the initial state to the final state, is independent of the path (i.e., the process or mechanism) by which the system gets from the initial state to the final state. A state function depends only on the values of the quantity in the initial and final states.

It is otherwise with q and w, for these quantities may be path-dependent. For example, the amount of work done depends on the path taken (e.g., whether the process is reversible or irreversible). Therefore dq and dw are not exact differentials, and some authors use different symbols to indicate this. Nevertheless, although q and w individually may be path-dependent, the combination q–w is independent of path, for it is equal to ΔU.[5]

The Ideal Gas. Experimental measurements on gases have shown that, as the pressure is decreased, the volume of a definite amount of gas is proportional to the reciprocal of the pressure:

$$V \propto \frac{1}{P}$$

As P is decreased toward zero, all gases (at constant temperature) tend to behave in the same way, such that Eq. (1.9) is satisfied:

$$PV = \text{constant} \tag{1.9}$$

This result can be generalized as Eq. (1.10), which is called the *ideal-gas equation* (or the ideal-gas law):

$$PV = nRT \tag{1.10}$$

where P, V, and T have their usual meanings; n is the number of moles of gas; and R is a proportionality constant called the *gas constant*. Equation (1.10) is the equation of state for an ideal gas (sometimes called the "perfect gas"), and it constitutes a description of real-gas behavior in the limit of vanishingly low pressure.

Example 1.1. Experiment has shown that 1 mol of an ideal gas occupies a volume of 22.414 L at 1 atm pressure when $T = 273.15\,\mathrm{K}$. Calculate R:

$$\begin{aligned} R &= \frac{PV}{nT} = \frac{(1\,\mathrm{atm})(22.414\,\mathrm{L})}{(1\,\mathrm{mol})(273.15\,\mathrm{K})} \\ &= 0.082057\,\mathrm{L\,atm\,mol^{-1}\,K^{-1}} \end{aligned}$$

We can use a dimensional analysis treatment to convert to other energy units, as described in Appendix B:

$$\begin{aligned} R &= \left(\frac{0.082057\,\mathrm{L\,atm}}{\mathrm{mol\,K}}\right)\left(\frac{101325\,\mathrm{Pa}}{1\,\mathrm{atm}}\right)\left(\frac{1\,\mathrm{N\,m^{-2}}}{1\,\mathrm{Pa}}\right)\left(\frac{10^3\,\mathrm{cm^3}}{1\,\mathrm{L}}\right)\left(\frac{1\,\mathrm{J}}{1\,\mathrm{N\,m}}\right)\left(\frac{1\,\mathrm{m}}{10^2\,\mathrm{cm}}\right)^3 \\ &= 8.3144\,\mathrm{J\,mol^{-1}\,K^{-1}} \end{aligned}$$

and since 1 cal = 4.184 J, $R = 1.987\,\mathrm{cal\,mol^{-1}\,K^{-1}}$. Notice that, in this calculation of R, its units are energy per mol per K. That is, since $R = PV/nT$, the units of the product PV are energy, which we expressed in the particular units L atm, J, or cal. These several values of R are widely tabulated, and they can serve as readily accessible conversion factors among these energy units.

We earlier mentioned a type of work called *work of expansion*. This is the work done by a gas when it expands against a resisting pressure, as happens when a piston moves in a cylinder. We can obtain a simple expression for work of expansion. Suppose a piston of cross-sectional area A moves against a constant pressure P. We know that mechanical work is the product of force (F) and distance, or

$$w = F(L_2 - L_1)$$

where L_1 is the initial position of the piston and L_2 is its final position. Pressure is force per unit area (A), so $F = PA$, giving

$$w = PA(L_2 - L_1)$$

But $A(L_2 - L_1) = V_2 - V_1$, where V_1 and V_2 are volumes, so

$$w = P(V_2 - V_1) = P\,\Delta V \tag{1.11}$$

where ΔV is the volume displaced. Thus work of expansion is the product of the (constant) pressure and the volume change; in fact, we often refer to work of expansion as $P\,\Delta V$ work.

Now, if the process is carried out reversibly, so that the pressure differs only infinitesimally from the equilibrium pressure, the volume change will be infinitesimal, and Eq. (1.11) can be written

$$dw = P\,dV \tag{1.12}$$

We can integrate this between limits:

$$w = \int_{V_1}^{V_2} P\,dV \tag{1.13}$$

(In the case of an isothermal, reversible expansion, w does not depend upon the path, but this is a special case.) Now suppose that the gas is ideal and that the process is carried out isothermally. From the ideal gas law, $P = nRT/V$, so

$$w = nRT \int_{V_1}^{V_2} \frac{dV}{V} \tag{1.14}$$

$$w = nRT \ln \frac{V_2}{V_1} \tag{1.15}$$

If $V_2 > V_1$, the system does work on the surroundings, and w is positive. If $V_1 > V_2$, the surroundings do work on the system, and w is negative.

In developing Eq. (1.15) we saw an example of thermodynamic reasoning, and we obtained a usable equation from very sparse premises. Here is another example, again based on the ideal gas. Suppose that such a gas expands into a vacuum. Since the resisting pressure is zero, Eq. (1.11) shows that $w = 0$; that is, no work is done. Careful experimental measurements by Joule and Kelvin in the nineteenth century showed that there is no heat exchange in this process, so $q = 0$. The first law therefore tells us that $\Delta U = 0$. Since the energy depends on just two variables, say, volume and temperature, we can express the result as

$$\left(\frac{\partial U}{\partial V}\right)_T = 0 \tag{1.16}$$

which says that the energy of an ideal gas is independent of its volume at constant temperature. We can interpret this thermodynamic result in molecular terms as follows. A gas behaves ideally when the intermolecular forces of attraction and repulsion are negligible. (This is why real gases approach ideality at very low pressures, for then the molecules are so far apart that they do not experience each others' force fields.) If there are no forces between the molecules, no energy is required to change the intermolecular distances, and so expansion (or compression) results in no energy change.

1.3. THE ENTHALPY

Definition of Enthalpy. In most chemical studies we work at constant pressure. (The reaction vessel is open to the atmosphere, and $P = 1\,\text{atm}$, approximately.) Consequently the system is capable of doing work of expansion on the surroundings. From the first law we can write $q = \Delta U + w$, and since $w = P\,\Delta V$,

$$q = \Delta U + P\,\Delta V$$

at constant P. Writing out the increments, we obtain

$$q = (U_2 - U_1) + P(V_2 - V_1)$$

and rearranging, we have

$$q = (U_2 + PV_2) - (U_1 + PV_1) \tag{1.17}$$

where U, P, and V are all state functions. We define a new state function H, the *enthalpy*, by

$$H = U + PV \tag{1.18}$$

giving, from Eq. (1.17), the following:

$$q = \Delta H \tag{1.19}$$

Although Eq. (1.18) defines the enthalpy, it is usually interpreted according to Eq. (1.19), because we can only measure changes in enthalpy (as with all energy quantities). The enthalpy change is equal to the heat gained or lost in the process, at constant pressure (there is another restriction, viz., that work of expansion is the only work involved in the process). Since enthalpy is an energy, it is measured in the usual energy units.

From Eq. (1.18) we can write

$$\Delta H = \Delta U + P\,\Delta V \tag{1.20}$$

For chemical processes involving only solids and liquids, ΔV is usually quite small, so $\Delta H \approx \Delta U$, but for gases, where ΔV may be substantial, ΔH and ΔU are different. We can obtain an estimate of the difference by supposing that 1 mol of an ideal-gas is evolved in the process. From the ideal gas law we write

$$P\,\Delta V = (\Delta n)RT$$

For 1 mol, $\Delta n = 1$, so from Eq. (1.20), we have

$$\Delta H = \Delta U + RT$$

At 25°C, this gives

$$\begin{aligned}\Delta H &= \Delta U + (1.987\,\text{cal mol}^{-1}\,\text{K}^{-1})(298.15\,\text{K})\\ &= \Delta U + 592\,\text{cal mol}^{-1}\end{aligned}$$

which is a very appreciable difference.

When a chemical process is carried out at constant pressure, the heat evolved or absorbed, per mole, can be identified as ΔH. Specific symbols and names have been devised to identify ΔH with particular processes. For example, the heat absorbed by a solid on melting is called the *heat of fusion* and is labeled ΔH_m or ΔH_f. The *heat of solution* is the enthalpy change per mole when a solute dissolves in a solvent. For a chemical reaction ΔH is called a *heat of reaction*. The heat of reaction may be positive (heat is absorbed) or negative (heat is evolved). By writing a reaction on paper in reverse direction its ΔH changes sign. For example, this reaction absorbs heat:

$$6\text{C (s)} + 3\text{H}_2\text{ (g)} \rightarrow \text{C}_6\text{H}_6\text{ (l)} \qquad \Delta H = +11.7\,\text{kcal mol}^{-1}$$

This reaction, its reverse, therefore evolves heat:

$$\text{C}_6\text{H}_6\text{ (l)} \rightarrow 6\text{C (s)} + 3\text{H}_2\text{ (g)} \qquad \Delta H = -11.7\,\text{kcal mol}^{-1}$$

We will later see how enthalpy changes for chemical processes can be measured.

Heat Capacity. A quantity C, called the *heat capacity*, is defined as

$$C = \frac{dq}{dT} \tag{1.21}$$

where C is a measure of the temperature change in a body produced by an increment of heat. The concept of the heat capacity is essential in appreciating the distinction between heat and temperature.

Chemical processes can be carried out at either constant volume or constant pressure. First consider constant volume. If only work of expansion is possible, at constant volume $\Delta V = 0$, so $w = 0$, and from the first law $dq = dU$. We therefore define the heat capacity at constant volume by

$$C_V = \left(\frac{\partial U}{\partial T}\right)_V \tag{1.22}$$

At constant pressure, on the other hand, we have, from Eq. (1.19), $dq = dH$, and we define the heat capacity at constant pressure by

$$C_P = \left(\frac{\partial H}{\partial T}\right)_P \tag{1.23}$$

In the preceding section we had obtained, for one mole of an ideal gas, Eq. (1.24).

$$\Delta H = \Delta U + RT \tag{1.24}$$

Let us differentiate this with respect to temperature. Using Eqs. (1.22) and (1.23), we get

$$C_P = C_V + R \tag{1.25}$$

For argon, at room temperature, $C_P = 20.8\,\mathrm{J\,K^{-1}\,mol^{-1}}$ and $C_V = 12.5\,\mathrm{J\,K^{-1}\,mol^{-1}}$; hence $C_P - C_V = 8.3\,\mathrm{J\,K^{-1}\,mol^{-1}}$, which is R.

For most compounds only C_P has been measured. Values of C_P for typical organic compounds lie in the range 15–50 $\mathrm{cal\,K^{-1}\,mol^{-1}}$. As seen here, heat capacity is expressed on a per mole basis, and is sometimes called the *molar heat capacity.* When the heat capacity is expressed on a per gram basis it is called the *specific heat.*

Taking the constant-pressure condition of Eq. (1.23) as understood, we can write $C_P = dH/dT$, or $dH = C_P\,dT$. If we suppose that C_P is essentially constant over the temperature range T_1 to T_2, integration gives

$$\Delta H = C_P\,\Delta T \tag{1.26}$$

Example 1.2. The mean specific heat of water is $1.00\,\mathrm{cal\,g^{-1}\,K^{-1}}$. Calculate the heat required to increase the temperature of 1.5 L of water from 25°C to the boiling point.[6]

As a close approximation we may take the density of water as $1.00\,\mathrm{g\,mL^{-1}}$ and the boiling point as 100°C, so, from Eq. (1.26), we obtain

$$\Delta H = \left(\frac{1.00\,\mathrm{cal}}{\mathrm{g\,K}}\right)(1500\,\mathrm{g})(75\,\mathrm{K}) = 112{,}500\,\mathrm{cal}$$

or 112.5 kcal.

PROBLEMS

1.1. A piston 3.0 in. in diameter expands into a cylinder for a distance of 5.0 in. against a constant pressure of 1 atm. Calculate the work done in joules.

1.2. What is the work of expansion when the pressure on 0.5 mol of ideal gas is changed reversibly from 1 atm to 4 atm at 25°C? (*Hint*: For an ideal gas $P_1V_1 = P_2V_2$.)

1.3. Derive an equation giving the heat change in the isothermal reversible expansion of an ideal gas against an appreciable pressure. [*Hint*: Make use of Eq. (1.16) and the first law.]

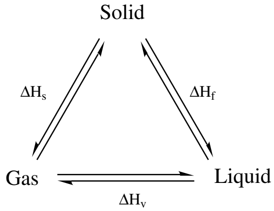
1.4. What is the molar heat capacity of water? (See Example 1.2 for the specific heat.)

1.5. The molar heat capacity of liquid benzene is $136.1\ \mathrm{J\,mol^{-1}\,K^{-1}}$. What is its specific heat?

1.6. The specific heat of solid aluminum is $0.215\ \mathrm{cal\,g^{-1}\,K^{-1}}$. If a 100-g block of aluminum, initially at 25°C, absorbs 1.72 kcal of heat, what will be its final temperature?

1.7. A 500-g piece of iron, initially at 25°C, is plunged into 0.5 L of water at 75°C in a Dewar flask. When thermal equilibrium has been reached, what will the temperature be? The specific heat of iron is $0.106\ \mathrm{cal\,g^{-1}\,K^{-1}}$.

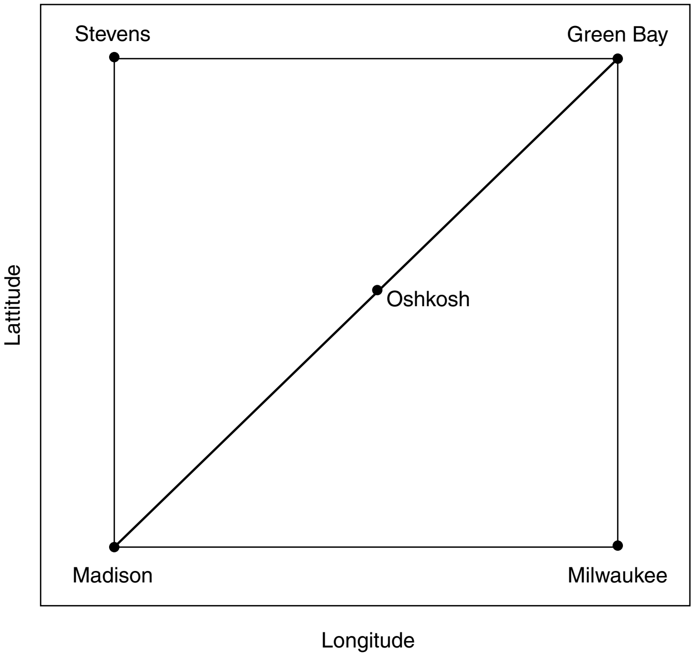
1.8. In the following thermodynamic cycle, ΔH_f, ΔH_v, and ΔH_s are, respectively, molar heats of fusion, vaporization, and sublimation for a pure substance. Obtain an equation connecting these three quantities. (*Hint*: Pay careful attention to the directions of the arrows.)



NOTES

1. Note that temperature is an intensive property, whereas heat is an extensive property. Two hot potatoes differing in size may have the same temperature,but the larger potato possesses more heat than the smaller one.
2. This scheme is consistent with the usage of most authors, but some variation is found in the literature. The thermodynamic energy *U* may also be symbolized *E*, and some authors label the thermodynamic energy the internal energy. The internal energy shown Table 1.1 may be identified with the potential energy of the molecules (to be distinguished from the potential energy of the body as a whole).

3. A truly isolated system is an idealization, but a very close approximation can be achieved inside a closed thermos (derived from the original trade name *Thermos* in 1907) bottle. (The laboratory version is called a *Dewar flask*.)
4. This is the sign convention used by most authors, but the International Union of Pure and Applied Chemistry (IUPAC) reverses the convention for w, giving as the first law $\Delta U = q + w$.
5. This analogy will clarify the difference between path-dependent and path-independent quantities. Suppose we wish to drive from Madison (WI) to Green Bay. Obviously there are numerous routes we might take. We could drive via Milwaukee, or via Oshkosh, or via Stevens Point, and so on. Graphically the possibilities can be represented on a map, as shown in the accompanying figure. Now, no matter which path we take, the changes in latitude, ΔLat, and in longitude, ΔLon, will be exactly the same for each route; for example, ΔLat = Lat(GB) − Lat(MAD), and this quantity is independent of the route. Thus latitude and longitude are state functions. But the amount of gasoline consumed, the time spent driving, and the number of miles driven all depend on the path taken; these are not state functions. This analogy is taken from Smith (1977).



6. It is not a coincidence that the specific heat of water is 1.00 cal g^{-1} K^{-1}, for this is how the calorie was originally defined: one calorie was the amount of heat required to raise the temperature of one gram of water by 1°C. Actually the specific heat of water varies slightly with the temperature.

2

THE ENTROPY CONCEPT

2.1. THE ENTROPY DEFINED

Why Energy Alone Is Not a Sufficient Criterion for Equilibrium. Let us try to develop an analogy, based on what we know from classical mechanics, between a mechanical system and a chemical (thermodynamic) system. The position of equilibrium in a mechanical system is controlled by potential energy. Consider a rock poised near the top of a hill. It possesses potential (gravitational) energy as a consequence of its position. If it is released, its potential energy will be converted to heat (through friction) and to kinetic energy as it rolls down the hill. It will come to rest, having zero potential energy, at the foot of the hill (since we can measure only *changes* in energy, we mean that the potential energy is zero relative to some arbitrary reference value, which we are free to take as the value at the foot of the hill). It is now at mechanical equilibrium. Thus the criterion for a spontaneous mechanical process is that the change in potential energy be negative (it gets smaller), and the criterion for mechanical equilibrium is that the change in potential energy be zero.

Why don't we simply apply an analogous criterion to chemical systems? We might argue that ΔU (for a system at constant volume) or ΔH (for a system at constant pressure) play the role of potential energy in the mechanical system. But we find experimentally that this suggestion is inadequate to account for the observations. Consider first the following experiment (Smith 1977, p. 6):

1. Dissolve some solid NaOH in water. The solution becomes warm; that is, heat is liberated in the process. This means that ΔH is negative in the spontaneous process of NaOH dissolving in water. (The reaction is said to be *exothermic*.) This is entirely in accord with the proposal we are examining.

2. Dissolve some solid $NaNO_3$ in water. The solution becomes cool; that is, heat is absorbed as the dissolution occurs, and this cools the solution. Therefore ΔH is positive in this spontaneous process. (It is an *endothermic* reaction.) This behavior is in conflict with the proposal.

Here is another pertinent experiment. Suppose that we have two identical chambers connected by a stopcock. With the stopcock closed, we let one chamber contain a gas and the other chamber be evacuated (i.e., it "contains" a vacuum). Now we open the stopcock. We know what will happen—the gas will spontaneously distribute itself uniformly throughout the two chambers. If the gas is ideal (and most gases behave nearly ideally at low pressures), we know [see Eq. (1.16)] that $\Delta U = 0$ for this spontaneous process. Thus, with *no energy change at all* the system spontaneously underwent a change to an equilibrium position.

This inability to predict the direction of chemical change based on energy considerations alone was one of the great nineteenth-century scientific problems. Since energy minimization alone is not an adequate criterion for chemical equilibrium, *something else* must be involved. This is our next concern, and we are going to use an approach somewhat different from that taken in many textbooks, which adopt an argument based on the historical development of the ideas. We are going to sidestep classical thermodynamic history by turning to a description based on the particulate (i.e., atomic) nature of matter.

The Statistical Mechanical Entropy. We have seen that classical thermodynamics is based on macroscopic observations and makes no assumptions about the ultimate structure of matter. An alternative viewpoint, called *statistical mechanics* (or *statistical thermodynamics* when applied to thermodynamic problems), adopts the assumption that matter is composed of vast numbers of very small particles (which we now identify as electrons, atoms, molecules, etc.). In many circumstances this point of view provides physical insight not available from classical thermodynamics, and we will turn to it to illuminate our present problem.

Let us reconsider the example of the apparatus with two chambers, in one of which a gas was initially confined. Suppose that only a single molecule of gas had been present. After the stopcock is opened (and presuming that both chambers have equal volumes), evidently the probability that the molecule will be in one specified chamber (say, the left chamber) is $\frac{1}{2}$. Next suppose we were to start with two molecules, say, a and b, and ask for the probability that both will be found, at equilibrium, in the left chamber. These are the only possible distributions:

Left	Right
a	b
b	a
a,b	—
—	a,b

Thus of four possible distributions only one places both a and b in the left chamber, so the probability[1] of this distribution is $\frac{1}{4} = (\frac{1}{2})^2$. Generalizing to N molecules we get $(\frac{1}{2})^N$ for the probability that at equilibrium all N molecules will be found in the left chamber. Since for chemical systems N, the number of atoms or molecules, can be very large indeed, we see that the probability is extremely small that all of the molecules will end up in one chamber. On the other hand, the probability is extremely high that the molecules will be distributed equally between the two chambers.

This simple example (Glasstone 1947, p. 184) suggests a general statement, which in fact constitutes a basic premise of statistical mechanics, namely, that *all spontaneous processes represent changes from a less probable to a more probable state*. This postulate leads us to the next stage of our inquiry, which consists essentially of counting all possible distributions that are accessible to a system, for this is how the probability of a state is to be established.

In this next example the system is more complicated, although still artificially simple. We imagine that two crystals of different elements, A and B, are placed in contact, so that atoms of A may diffuse into the B crystal and vice versa [this example is given by Denbigh (1966, p. 49)]. In this simple example we suppose that crystal A contains four A atoms (4A), and likewise crystal B contains four B atoms (4B). We can distinguish between A and B atoms, but all A atoms are indistinguishable among themselves, and similarly for B. The sites that the atoms occupy in the crystals are distinguishable. Initially let all A atoms be in the left-hand crystal and all B atoms in the right-hand crystal.

We are going to count all possible configurations (called *microstates*) of our system. There are 4A and 4B to be distributed among eight sites. (We assume that the energies of interaction are identical no matter which type of atom is on which site.) Clearly there is only one microstate having 4A in the left crystal and 4B in the right crystal:

A	A	B	B
A	A	B	B

Similarly, there is only one microstate with 4B in the left and 4A in the right crystal.

But now consider the number of ways we can have 3A + 1B on the left and 3B + 1A on the right. We could argue in this way—the A atom on the right has any one of 4 right-hand sites available to it, and likewise the B atom on the left has 4 sites available, making $4 \times 4 = 16$ configurations. These 16 microstates are explicitly shown in Fig. 2.1 Obviously the symmetrical arrangement of 1A + 3B on the left and 3A + 1B on the right will also have 16 microstates.

The remaining arrangement of 2A + 2B (left) and 2A + 2B (right) is slightly more difficult. First consider the left crystal. The first B atom has 4 sites available, whereas the second B atom has only 3 accessible sites. Hence there appear to be 4×3 possible configurations. However, the two B atoms are indistinguishable, so we have double-counted, and must compensate, giving $(4 \times 3)/2$ as the number of

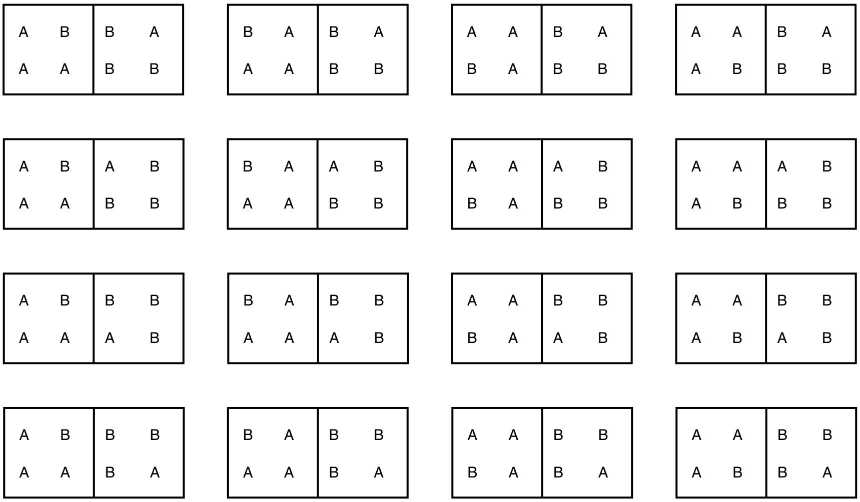

A B | B A
A A | B B
B A | B A
A A | B B
A A | B A
B A | B B
A A | B A
A B | B B
A B | A B
A A | B B
B A | A B
A A | B B
A A | A B
B A | B B
A A | A B
A B | B B
A B | B B
A A | A B
B A | B B
A A | A B
A A | B B
B A | A B
A A | B B
A B | A B
A B | B B
A A | B A
B A | B B
A A | B A
A A | B B
B A | B A
A A | B B
A B | B A

Figure 2.1. The 16 microstates possessing 3A + 1B on the left and 3B + 1A on the right.

microstates. But an equal number is contributed by the right-hand side, making in all $(4 \times 3)/2 \times (4 \times 3)/2 = 36$ microstates. Here are the results summarized.[2]

Atoms to Left	Atoms to Right	Number of Microstates
4A	4B	1
3A + 1B	1A + 3B	16
2A + 2B	2A + 2B	36
1A + 3B	3A + 1B	16
4B	4A	1
		70

In modern terminology, the microstates are called *quantum states*.

Now, another key premise of statistical mechanics is that the system is as likely to be in any one microstate as in another. That is, *all microstates are equally probable*. In our example above, there is a probability of $\frac{1}{35}$ that all of the A atoms will be found in a single crystal (either left or right); but there is a probability of $\frac{36}{70}$ that the atoms will be uniformly distributed. All the microstates are accessible, and the system is simply more likely to be found (at equilibrium) in the state possessing the largest number of microstates. (It can also be stated that the system spends an equal amount of time in each microstate, so it spends the most time in the system with the most microstates.)

For chemical systems the number of particles is extremely large (recall that Avogadro's number is about 6×10^{23}), so the number of microstates is vast, and the consequence is that the most probable state of the system is *so* probable that all other states (although possible in principle) may be disregarded in practice. The total number of microstates accessible to a system (which, we have just noted, is essentially equal to the number of microstates in the most probable state) we label W. (Some authors use Ω.) We now define a quantity S, called *entropy*, by Eq. (2.1), which is due to Boltzmann:

$$S = k \ln W \tag{2.1}$$

This is a definition. We will later establish the significance of the proportionality constant k. The equation says that the entropy S of a system increases logarithmically as W, the number of accessible microstates, increases.

We have noticed in our crystal diffusion example how W is composed of contributions from various configurations, and within each configuration the contributions are multiplicative; for example, for the 3A + 1B (left) and 1A + BB (right) state we had $4 \times 4 = 16$ microstates. Supposing, more generally, that we write $W = W_L \times W_R$, Eq. (2.1) gives us

$$S = k \ln W_L W_R = k \ln W_L + k \ln W_R = S_L + S_R$$

Thus, entropy is additive. (This is one reason why Boltzmann used a logarithmic function in his definition.)

Another point is to be made here. Our crystal diffusion example involved microstates all having the same energy, and we calculated all possible configurations. The resulting entropy is known as the *configurational entropy*. More generally, in chemical systems we must also consider a very large number of quantum states, most of which occupy different energy levels. The total entropy receives contributions from both sources: the microstates counting all configurations and those counting all energies.

Summarizing to this point, we conclude that spontaneous processes occur in a direction of increasing probability, and that entropy as calculated by the statistical mechanical definition is a quantitative measure of this probability. Therefore *spontaneous processes occur with an increase in entropy.*[3]

Before leaving the statistical mechanical treatment, let us apply our results to the calculation of the entropy change accompanying the isothermal expansion of an ideal gas from volume V_1 to volume V_2 (Glasstone 1947, p. 186; Denbigh 1966, p. 55; Rossini 1950, p. 73). (We will shortly see the point of this particular calculation.) Recall that $\Delta U = 0$ in this process, so the only driving force for the expansion is the increase in probability of the system.

If W_1 and W_2 are the numbers of microstates associated with volumes V_1 and V_2, then $S_1 = k \ln W_1$ and $S_2 = k \ln W_2$, so

$$\Delta S = S_2 - S_1 = k \ln \frac{W_2}{W_1} \tag{2.2}$$

The probability that a single molecule will be found in any volume V is proportional to that volume, and the number of microstates accessible to a molecule is