TOXICOLOGICAL CHEMISTRY AND BIOCHEMISTRY

THIRD EDITION

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Stanley E. Manahan

LEWIS PUBLISHERS

A CRC Press Company

Boca Raton London New York Washington, D.C.

Library of Congress Cataloging-in-Publication Data

Manahan, Stanley E.
Toxicological chemistry and biochemistry / by Stanley E. Manahan.-- 3rd ed.
p. cm.
Includes bibliographical references and index.
ISBN 1-56670-618-1
1. Toxicological chemistry. 2. Environmental chemistry. 3. Biochemical toxicology. I. Title.

RA1219.3 .M36 2002
815.9′001′54--dc21 2002072486

International Standard Book Number 1-56670-618-1
Library of Congress Card Number 2002072486
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

Preface

The first edition of *Toxicological Chemistry* (1989) was written to bridge the gap between toxicology and chemistry. It defined toxicological chemistry as the science that deals with the chemical nature and reactions of toxic substances, their origins and uses, and the chemical aspects of their exposure, transformation, and elimination by biological systems. It emphasized the chemical formulas, structures, and reactions of toxic substances. The second edition of *Toxicological Chemistry* (1992) was significantly enlarged and increased in scope compared to the first edition. In addition to toxicological chemistry, it addressed the topic of environmental biochemistry, which pertains to the effects of environmental chemical substances on living systems and the influence of life-forms on such chemicals. It did so within a framework of environmental chemistry, defined as that branch of chemistry that deals with the origins, transport, reactions, effects, and fates of chemical species in the water, the air, and terrestrial and living environments.

The third edition has been thoroughly updated and expanded into areas important to toxicological chemistry based upon recent advances in several significant fields. In recognition of the increased emphasis on the genetic aspects of toxicology, the toxic effects to various body systems, and xenobiotics analysis, the title has been changed to *Toxicological Chemistry and Biochemistry*. The new edition has been designed to be useful to a wide spectrum of readers with various interests and a broad range of backgrounds in chemistry, biochemistry, and toxicology. For readers who have had very little exposure to chemistry, Chapter 1, "Chemistry and Organic Chemistry," outlines the basic concepts of general chemistry and organic chemistry needed to understand the rest of the material in the book. The er chapter, "Environmental Chemistry," is an overview of that topic, presented so that the reader may understand the remainder of the book within a framework of environmental chemistry. Chapter 3, "Biochemistry," gives the fundamentals of the chemistry of life processes essential to understanding toxicological chemistry and biochemistry. Chapter 4, "Metabolic Processes," covers the basic principles of metabolism needed to understand how toxicants interact with organisms. Chapter 5, "Environmental Biological Processes and Ecotoxicology," is a condensed and updated version of three chapters from the second edition dealing with microbial processes, biodegradation and bioaccumulation, and biochemical processes that occur in aquatic and soil environments; the major aspects of ecotoxicology are also included. Chapter 6, "Toxicology," defines and explains toxicology as the science of poisons. Chapter 7, "Toxicological Chemistry," bridges the gap between toxicology and chemistry, emphasizing chemical aspects of toxicological phenomena, including fates and effects of xenobiotic chemicals in living systems. Chapter 8, "Genetic Aspects of Toxicology," is new; it recognizes the importance of considering the crucial role of nucleic acids, the basic genetic material of life, in toxicological chemistry. It provides the foundation for understanding the important ways in which chemical damage to DNA can cause mutations, cancer, and other toxic effects. It also considers the role of genetics in determining genetic susceptibilities to various toxicants. Also new is Chapter 9, "Toxic Responses," which considers toxicities to various systems in the body, such as the endocrine and reproductive systems. It is important for understanding the specific toxic effects of various toxicants on certain body organs, as discussed in later chapters. Chapters 10 to 18 discuss toxicological chemistry within an organizational structure based on classes of chemical substances, and Chapter 19 deals with toxicants from natural sources. Another new addition is Chapter 20, "Analysis of Xenobiotics," which deals with the determination of toxicants and their metabolites in blood and other biological materials.

Every effort has been made to retain the basic information and structure that have made the first two editions of this book popular among and useful to students, faculty, regulatory agency personnel, people working with industrial hygiene aspects, and any others who need to understand toxic effects of chemicals from a chemical perspective. The chapters that have been added are designed to enhance the usefulness of the book and to modernize it in important areas such as genetics and xenobiotics analysis.

This book is designed to be both a textbook and a general reference book. Questions at the end of each chapter are written to summarize and review the material in the chapter. References are given for specific points covered in the book, and supplementary references are cited at the end of each chapter for additional reading about the topics covered.

The assistance of David Packer, Publisher, CRC Press, in developing the third edition of *Toxicological Chemistry and Biochemistry* is gratefully acknowledged. The author would also like to acknowledge the excellent work of Judith Simon, Project Editor, and the staff of CRC Press in the production of this book.

The Author

Stanley E. Manahan is a professor of chemistry at the University of Missouri–Columbia, where he has been on the faculty since 1965, and is president of ChemChar Research, Inc., a firm developing nonincinerative thermochemical waste treatment processes. He received his A.B. in chemistry from Emporia State University in 1960 and his Ph.D. in analytical chemistry from the University of Kansas in 1965. Since 1968, his primary research and professional activities have been in environmental chemistry, toxicological chemistry, and waste treatment. He teaches courses on environmental chemistry, hazardous wastes, toxicological chemistry, and analytical chemistry. He has lectured on these topics throughout the United States as an American Chemical Society local section tour speaker, in Puerto Rico, at Hokkaido University in Japan, at the National Autonomous University in Mexico City, and at the University of the Andes in Merida, Venezuela. He was the recipient of the Year 2000 Award of the environmental chemistry division of the Italian Chemical Society.

Professor Manahan is the author or coauthor of approximately 100 journal articles in environmental chemistry and related areas. In addition to *Fundamentals of Environmental Chemistry,* 2nd ed., he is the author of *Environmental Chemistry,* 7th ed. (Lewis Publishers, 2000), which has been published continuously in various editions since 1972. Other books that he has written include *Industrial Ecology: Environmental Chemistry and Hazardous Waste* (Lewis Publishers, 1999), *Environmental Science and Technology* (Lewis Publishers, 1997), *Toxicological Chemistry,* 2nd ed. (Lewis Publishers, 1992), *Hazardous Waste Chemistry, Toxicology, and Treatment* (Lewis Publishers, 1992), *Quantitative Chemical Analysis* (Brooks/Cole, 1986), and *General Applied Chemistry*, 2nd ed. (Willard Grant Press, 1982).

Contents

CHAPTER 1

Chemistry and Organic Chemistry

1.1 INTRODUCTION

This book is about toxicological chemistry, the branch of chemical science dealing with the toxic effects of substances. In order to understand this topic, it is essential to have an understanding of **chemistry**, the science of matter. The nature of toxic substances depends upon their chemical characteristics, how they are bonded together, and how they react. Mechanisms of toxicity are basically chemical in nature. Chemical processes carried out by organisms play a strong role in determining the fates of toxic substances. In some cases, chemical modification of toxicants by organisms reduces the toxicity of chemical substances or makes them entirely nontoxic. In other cases, chemical activation of foreign compounds makes them more toxic. For example, benzo(a)pyrene, a substance produced by the partial combustion of organic matter, such as that which occurs when smoking cigarettes, is not itself toxic, but it reacts with oxygen through the action of enzymes in the body to produce a species that can bind with DNA and cause cancer.

The chemical processes that occur in organisms are addressed by biochemistry, which is discussed in Chapter 3. In order to understand biochemistry, however, it is essential to have a basic understanding of chemistry. Since most substances in living organisms, as well as most toxic substances, are organic materials containing carbon, it is also essential to have an understanding of organic chemistry in order to consider toxicological chemistry. Therefore, this chapter starts with a brief overview of chemistry and includes the basic principles of organic chemistry as well.

It is important to consider the effects of toxic substances within the context of the environment through which exposure of various organisms occurs. Furthermore, toxic substances are created, altered, or detoxified by environmental chemical processes in water, in soil, and when substances are exposed to the atmosphere. Therefore, Chapter 2 deals with environmental chemistry and environmental chemical processes. The relationship of toxic substances and the organisms that they affect in the environment is addressed specifically by ecotoxicology in Chapter 5.

1.2 ELEMENTS

All substances are composed of only about a hundred fundamental kinds of matter called **elements**. Elements themselves may be of environmental and toxicological concern. The heavy metals, including lead, cadmium, and mercury, are well recognized as toxic substances in the environment. Elemental forms of otherwise essential elements may be very toxic or cause environmental damage. Oxygen in the form of ozone, O_3, is the agent most commonly associated with atmospheric smog pollution and is very toxic to plants and animals. Elemental white phosphorus is highly flammable and toxic.

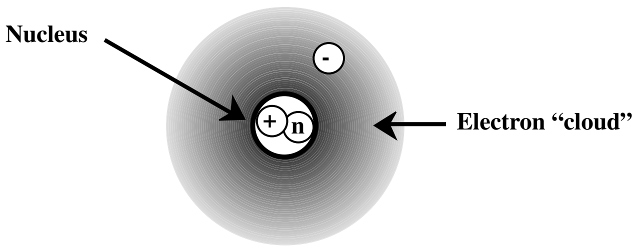


Figure 1.1 Representation of a deuterium atom. The nucleus contains one proton (+) and one neutron (n). The electron (–) is in constant, rapid motion around the nucleus, forming a cloud of negative electrical charge, the density of which drops off with increasing distance from the nucleus.

Table 1.1 Properties of Protons, Neutrons, and Electrons

Subatomic Particle	Symbol[a]	Unit Charge	Mass Number	Mass in μ	Mass in Grams
Proton	*p*	+1	1	1.007277	1.6726×10^{-24}
Neutron	*n*	0	1	1.008665	1.6749×10^{-24}
Electron	*e*	–1	0	0.000549	9.1096×10^{-28}

[a] The mass number and charge of each of these kinds of particles can be indicated by a superscript and subscript, respectively, in the symbols ${}^{1}_{1}p$, ${}^{1}_{0}n$, ${}^{0}_{-1}e$.

Each element is made up of very small entities called **atoms**; all atoms of the same element behave identically chemically. The study of chemistry, therefore, can logically begin with elements and the atoms of which they are composed. Each element is designated by an atomic number, a name, and a **chemical symbol**, such as carbon, C; potassium, K (for its Latin name kalium); or cadmium, Cd. Each element has a characteristic **atomic mass** (atomic weight), which is the average mass of all atoms of the element.

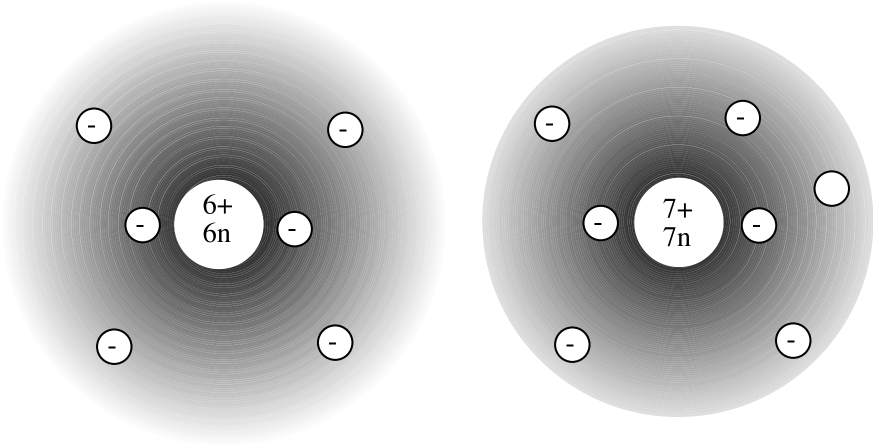
1.2.1 Subatomic Particles and Atoms

Figure 1.1 represents an atom of deuterium, a form of the element hydrogen. As shown, such an atom is made up of even smaller **subatomic particles**: positively charged **protons**, negatively charged **electrons**, and uncharged (neutral) **neutrons**.

1.2.2 Subatomic Particles

The subatomic particles differ in mass and charge. Their masses are expressed by the **atomic mass unit**, u (also called the **dalton**), which is also used to express the masses of individual atoms, and molecules (aggregates of atoms). The atomic mass unit is defined as a mass equal to exactly 1/12 that of an atom of carbon-12, the isotope of carbon that contains six protons and six neutrons in its nucleus.

The proton, *p*, has a mass of 1.007277 u and a unit charge of +1. This charge is equal to 1.6022×10^{-19} coulombs; a coulomb is the amount of electrical charge involved in a flow of electrical current of 1 ampere for 1 sec. The neutron, *n*, has no electrical charge and a mass of 1.008665 u. The proton and neutron each have a mass of essentially 1 u and are said to have a *mass number* of 1. (Mass number is a useful concept expressing the total number of protons and neutrons, as well as the approximate mass, of a nucleus or subatomic particle.) The electron, *e*, has an electrical charge of –1. It is very light, however, with a mass of only 0.000549 u, about 1/1840 that of the proton or neutron. Its mass number is 0. The properties of protons, neutrons, and electrons are summarized in Table 1.1.



An atom of carbon, symbol C. Each C atom has 6 protons (+) in its nucleus, so the atomic number of C is 6. The atomic mass of C is 12.

An atom of nitrogen, symbol N. Each N atom has 7 protons (+) in its nucleus, so the atomic number of N is 7. The atomic mass of N is 14.

Figure 1.2 Atoms of carbon and nitrogen.

Although it is convenient to think of the proton and neutron as having the same mass, and each is assigned a mass number of 1, Table 1.1 shows that their exact masses differ slightly from each other. Furthermore, the mass of an atom is not exactly equal to the sum of the masses of subatomic particles composing the atom. This is because of the energy relationships involved in holding the subatomic particles together in an atom so that the masses of the atom's constituent subatomic particles do not add up to exactly the mass of the atom.

1.2.3 Atom Nucleus and Electron Cloud

Protons and neutrons are contained in the positively charged **nucleus** of the atom. Protons and neutrons have relatively high masses compared to electrons. Therefore, the nucleus has essentially all of the mass, but occupies virtually none of the volume, of the atom. An uncharged atom has the same number of electrons as protons. The electrons in an atom are contained in a cloud of negative charge around the nucleus that occupies most of the volume of the atom. These concepts are illustrated in Figure 1.2.

1.2.4 Isotopes

Atoms with the *same* number of protons, but *different* numbers of neutrons in their nuclei are chemically identical atoms of the same element, but have different masses and may differ in their nuclear properties. Such atoms are **isotopes** of the same element. Some isotopes are **radioactive isotopes**, or **radionuclides**, which have unstable nuclei that give off charged particles and gamma rays in the form of **radioactivity**. Radioactivity may have detrimental, or even fatal, health effects; a number of hazardous substances are radioactive, and they can cause major environmental problems. The most striking example of such contamination resulted from a massive explosion and fire at a power reactor in the Ukrainian city of Chernobyl in 1986.

1.2.5 Important Elements

An abbreviated list of a few of the most important elements, which the reader may find useful, is given in Table 1.2. A complete list of the well over 100 known elements which may be found in any

Table 1.2 The More Important Common Elements

Element	Symbol	Atomic Number	Atomic Mass	Significance
Aluminum	Al	13	26.9815	Abundant in Earth's crust
Argon	Ar	18	39.948	Noble gas
Arsenic	As	33	74.9216	Toxic metalloid
Bromine	Br	35	79.904	Toxic halogen
Cadmium	Cd	48	112.40	Toxic heavy metal
Calcium	Ca	20	40.08	Abundant essential element
Carbon	C	6	12.011	Life element
Chlorine	Cl	17	35.453	Halogen
Copper	Cu	29	63.54	Useful metal
Fluorine	F	9	18.998	Halogen
Helium	He	2	4.0026	Lightest noble gas
Hydrogen	H	1	1.008	Lightest element
Iodine	I	53	126.904	Halogen
Iron	Fe	26	55.847	Important metal
Lead	Pb	82	207.19	Toxic heavy metal
Magnesium	Mg	12	24.305	Light metal
Mercury	Hg	80	200.59	Toxic heavy metal
Neon	Ne	10	20.179	Noble gas
Nitrogen	N	7	14.0067	Important nonmetal
Oxygen	O	8	15.9994	Abundant, essential nonmetal
Phosphorus	P	15	30.9738	Essential nonmetal
Potassium	K	19	39.0983	Alkali metal
Silicon	Si	14	28.0855	Abundant metalloid
Silver	Ag	47	107.87	Valuable, reaction-resistant metal
Sodium	Na	11	22.9898	Essential, abundant alkali metal
Sulfur	S	16	32.064	Essential element, occurs in air pollutant sulfur dioxide, SO_2
Tin	Sn	50	118.69	Useful metal
Uranium	U	92	238.03	Fissionable metal used for nuclear fuel
Zinc	Zn	30	65.37	Useful metal

standard chemistry book is given on the inside front cover of this book. Fortunately, most of the chemistry covered in this book requires familiarity only with the shorter list of elements in Table 1.2.

1.2.6 The Periodic Table

The properties of elements listed in order of increasing atomic number repeat in a periodic manner. For example, elements with atomic numbers 2, 10, and 18 are gases that do not undergo chemical reactions and consist of individual atoms, whereas those with atomic numbers larger by 1 — elements with atomic numbers 3, 11, and 19 — are unstable, highly reactive metals. An arrangement of the elements reflecting this recurring behavior is the **periodic table** (Figure 1.3). This table is extremely useful in understanding chemistry and predicting chemical behavior because it organizes the elements in a systematic manner related to their chemical behavior as a consequence of the structures of the atoms that compose the elements. As shown in Figure 1.3, the entry for each element in the periodic table gives the element's atomic number, symbol, and atomic mass. More detailed versions of the table include other information as well.

1.2.6.1 Features of the Periodic Table

Groups of elements having similar chemical behavior are contained in vertical columns in the periodic table. **Main group** elements may be designated as A groups (IA and IIA on the left, IIIA through VIIIA on the right). **Transition elements** are those between main groups IIA and IIIA. **Noble gases** (group VIIIA), a group of gaseous elements that are virtually chemically unreactive,