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***TOXICOLOGICAL***  
***CHEMISTRY*** AND  
***BIOCHEMISTRY***  
**THIRD EDITION**

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# ***TOXICOLOGICAL CHEMISTRY* AND *BIOCHEMISTRY***

**THIRD EDITION**

**Stanley E. Manahan**



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## 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 next 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.

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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.

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## 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
- 1.2 Elements
  - 1.2.1 Subatomic Particles and Atoms
  - 1.2.2 Subatomic Particles
  - 1.2.3 Atom Nucleus and Electron Cloud
  - 1.2.4 Isotopes
  - 1.2.5 Important Elements
  - 1.2.6 The Periodic Table
    - 1.2.6.1 Features of the Periodic Table
  - 1.2.7 Electrons in Atoms
    - 1.2.7.1 Lewis Symbols of Atoms
  - 1.2.8 Metals, Nonmetals, and Metalloids
- 1.3 Chemical Bonding
  - 1.3.1 Chemical Compounds
  - 1.3.2 Molecular Structure
  - 1.3.3 Ionic Bonds
  - 1.3.4 Summary of Chemical Compounds and the Ionic Bond
  - 1.3.5 Molecular Mass
  - 1.3.6 Oxidation State
- 1.4 Chemical Reactions and Equations
  - 1.4.1 Reaction Rates
- 1.5 Solutions
  - 1.5.1 Solution Concentration
  - 1.5.2 Water as a Solvent
  - 1.5.3 Solutions of Acids and Bases
    - 1.5.3.1 Acids, Bases, and Neutralization Reactions
    - 1.5.3.2 Concentration of H<sup>+</sup> Ion and pH
    - 1.5.3.3 Metal Ions Dissolved in Water
    - 1.5.3.4 Complex Ions Dissolved in Water
  - 1.5.4 Colloidal Suspensions
- 1.6 Organic Chemistry
  - 1.6.1 Molecular Geometry in Organic Chemistry .
- 1.7 Hydrocarbons
  - 1.7.1 Alkanes
    - 1.7.1.1 Formulas of Alkanes
    - 1.7.1.2 Alkanes and Alkyl Groups
    - 1.7.1.3 Names of Alkanes and Organic Nomenclature
    - 1.7.1.4 Summary of Organic Nomenclature as Applied to Alkanes
    - 1.7.1.5 Reactions of Alkanes
  - 1.7.2 Alkenes and Alkynes
    - 1.7.2.1 Addition Reactions
  - 1.7.3 Alkenes and *Cis-trans* Isomerism
  - 1.7.4 Condensed Structural Formulas
  - 1.7.5 Aromatic Hydrocarbons
    - 1.7.5.1 Benzene and Naphthalene
    - 1.7.5.2 Polycyclic Aromatic Hydrocarbons

- 
- 1.8 Organic Functional Groups and Classes of Organic Compounds
    - 1.8.1 Organooxygen Compounds
    - 1.8.2 Organonitrogen Compounds
    - 1.8.3 Organohalide Compounds
      - 1.8.3.1 Alkyl Halides
      - 1.8.3.2 Alkenyl Halides
      - 1.8.3.3 Aryl Halides
      - 1.8.3.4 Halogenated Naphthalene and Biphenyl
      - 1.8.3.5 Chlorofluorocarbons, Halons, and Hydrogen-Containing Chlorofluorocarbons
      - 1.8.3.6 Chlorinated Phenols
    - 1.8.4 Organosulfur Compounds
      - 1.8.4.1 Thiols and Thioethers
      - 1.8.4.2 Nitrogen-Containing Organosulfur Compounds
      - 1.8.4.3 Sulfoxides and Sulfones
      - 1.8.4.4 Sulfonic Acids, Salts, and Esters
      - 1.8.4.5 Organic Esters of Sulfuric Acid
    - 1.8.5 Organophosphorus Compounds
      - 1.8.5.1 Alkyl and Aromatic Phosphines
      - 1.8.5.2 Organophosphate Esters
      - 1.8.5.3 Phosphorothionate Esters
  - 1.9 Optical Isomerism
  - 1.10 Synthetic Polymers
  - Supplementary References
  - Questions and Problems

## **Chapter 2** Environmental Chemistry

- 2.1 Environmental Science and Environmental Chemistry
  - 2.1.1 The Environment
  - 2.1.2 Environmental Chemistry
- 2.2 Water
- 2.3 Aquatic Chemistry
  - 2.3.1 Oxidation–Reduction
  - 2.3.2 Complexation and Chelation
  - 2.3.3 Water Interactions with Other Phases
  - 2.3.4 Water Pollutants
  - 2.3.5 Water Treatment
- 2.4 The Geosphere
  - 2.4.1 Solids in the Geosphere
- 2.5 Soil
- 2.6 Geochemistry and Soil Chemistry
  - 2.6.1 Physical and Chemical Aspects of Weathering
  - 2.6.2 Soil Chemistry
- 2.7 The Atmosphere
- 2.8 Atmospheric Chemistry
  - 2.8.1 Gaseous Oxides in the Atmosphere
  - 2.8.2 Hydrocarbons and Photochemical Smog
  - 2.8.3 Particulate Matter
- 2.9 The Biosphere



---

## 2.10 The Anthrosphere and Green Chemistry

### 2.10.1 Green Chemistry

References

Supplementary References

Questions and Problems

## **Chapter 3** Biochemistry

### 3.1 Biochemistry

#### 3.1.1 Biomolecules

### 3.2 Biochemistry and the Cell

#### 3.2.1 Major Cell Features

### 3.3 Proteins

#### 3.3.1 Protein Structure

#### 3.3.2 Denaturation of Proteins

### 3.4 Carbohydrates

### 3.5 Lipids

### 3.6 Enzymes

### 3.7 Nucleic Acids

#### 3.7.1 Nucleic Acids in Protein Synthesis

#### 3.7.2 Modified DNA

### 3.8 Recombinant DNA and Genetic Engineering

### 3.9 Metabolic Processes

#### 3.9.1 Energy-Yielding Processes

Supplementary References

Questions and Problems

## **Chapter 4** Metabolic Processes

### 4.1 Metabolism in Environmental Biochemistry

#### 4.1.1 Metabolism Occurs in Cells

#### 4.1.2 Pathways of Substances and Their Metabolites in the Body

### 4.2 Digestion

#### 4.2.1 Carbohydrate Digestion

#### 4.2.2 Digestion of Fats

#### 4.2.3 Digestion of Proteins

### 4.3 Metabolism of Carbohydrates, Fats, and Proteins

#### 4.3.1 An Overview of Catabolism

#### 4.3.2 Carbohydrate Metabolism

#### 4.3.3 Metabolism of Fats

#### 4.3.4 Metabolism of Proteins

### 4.4 Energy Utilization by Metabolic Processes

#### 4.4.1 High-Energy Chemical Species

#### 4.4.2 Glycolysis

#### 4.4.3 Citric Acid Cycle

#### 4.4.4 Electron Transfer in the Electron Transfer Chain

#### 4.4.5 Electron Carriers

#### 4.4.6 Overall Reaction for Aerobic Respiration

#### 4.4.7 Fermentation

### 4.5 Using Energy to Put Molecules Together: Anabolic Reactions

- 
- 4.6 Metabolism and Toxicity
    - 4.6.1 Stereochemistry and Xenobiotics Metabolism
  - Supplementary References
  - Questions and Problems

## **Chapter 5** Environmental Biological Processes and Ecotoxicology

- 5.1 Introduction
- 5.2 Toxicants
- 5.3 Pathways of Toxicants into Ecosystems
  - 5.3.1 Transfers of Toxicants between Environmental Spheres
  - 5.3.2 Transfers of Toxicants to Organisms
- 5.4 Bioconcentration
  - 5.4.1 Variables in Bioconcentration
  - 5.4.2 Biotransfer from Sediments
- 5.5 Bioconcentration and Biotransfer Factors
  - 5.5.1 Bioconcentration Factor
  - 5.5.2 Biotransfer Factor
  - 5.5.3 Bioconcentration by Vegetation
- 5.6 Biodegradation
  - 5.6.1 Biochemical Aspects of Biodegradation
  - 5.6.2 Cometabolism
  - 5.6.3 General Factors in Biodegradation
  - 5.6.4 Biodegradability
- 5.7 Biomarkers
- 5.8 Endocrine Disrupters and Developmental Toxicants
- 5.9 Effects of Toxicants on Populations
- 5.10 Effects of Toxicants on Ecosystems
- Supplementary References
- Questions and Problems

## **Chapter 6** Toxicology

- 6.1 Introduction
  - 6.1.1 Poisons and Toxicology
  - 6.1.2 History of Toxicology
  - 6.1.3 Future of Toxicology
  - 6.1.4 Specialized Areas of Toxicology.
  - 6.1.5 Toxicological Chemistry
- 6.2 Kinds of Toxic Substances
- 6.3 Toxicity-Influencing Factors
  - 6.3.1 Classification of Factors
  - 6.3.2 Form of the Toxic Substance and Its Matrix
  - 6.3.3 Circumstances of Exposure
  - 6.3.4 The Subject
- 6.4 Exposure to Toxic Substances
  - 6.4.1 Percutaneous Exposure
    - 6.4.1.1 Skin Permeability
  - 6.4.2 Barriers to Skin Absorption
    - 6.4.2.1 Measurement of Dermal Toxicant Uptake
    - 6.4.2.2 Pulmonary Exposure

- 
- 6.4.3 Gastrointestinal Tract
  - 6.4.4 Mouth, Esophagus, and Stomach
  - 6.4.5 Intestines
  - 6.4.6 The Intestinal Tract and the Liver
  - 6.5 Dose–Response Relationships
    - 6.5.1 Thresholds
  - 6.6 Relative Toxicities
    - 6.6.1 Nonlethal Effects
  - 6.7 Reversibility and Sensitivity
    - 6.7.1 Hypersensitivity and Hyposensitivity
  - 6.8 Xenobiotic and Endogenous Substances
    - 6.8.1 Examples of Endogenous Substances
  - 6.9 Kinetic and Nonkinetic Toxicology
    - 6.9.1 Kinetic Toxicology
  - 6.10 Receptors and Toxic Substances
    - 6.10.1 Receptors
  - 6.11 Phases of Toxicity
  - 6.12 Toxicification and Detoxification
    - 6.12.1 Synergism, Potentiation, and Antagonism
  - 6.13 Behavioral and Physiological Responses
    - 6.13.1 Vital Signs
    - 6.13.2 Skin Symptoms
    - 6.13.3 Odors
    - 6.13.4 Eyes
    - 6.13.5 Mouth
    - 6.13.6 Gastrointestinal Tract
    - 6.13.7 Central Nervous System
  - 6.14 Reproductive and Developmental Effects
- References
- Supplementary References
- Questions and Problems

## **Chapter 7** Toxicological Chemistry

- 7.1 Introduction
  - 7.1.1 Chemical Nature of Toxicants
  - 7.1.2 Biochemical Transformations
- 7.2 Metabolic Reactions of Xenobiotic Compounds
  - 7.2.1 Phase I and Phase II Reactions
- 7.3 Phase I Reactions
  - 7.3.1 Oxidation Reactions
  - 7.3.2 Hydroxylation
  - 7.3.3 Epoxide Hydration
  - 7.3.4 Oxidation of Noncarbon Elements
  - 7.3.5 Alcohol Dehydrogenation
  - 7.3.6 Metabolic Reductions
  - 7.3.7 Metabolic Hydrolysis Reactions
  - 7.3.8 Metabolic Dealkylation
  - 7.3.9 Removal of Halogen
- 7.4 Phase II Reactions of Toxicants
  - 7.4.1 Conjugation by Glucuronides
  - 7.4.2 Conjugation by Glutathione

- 
- 7.4.3 Conjugation by Sulfate
  - 7.4.4 Acetylation
  - 7.4.5 Conjugation by Amino Acids
  - 7.4.6 Methylation
  - 7.5 Biochemical Mechanisms of Toxicity
  - 7.6 Interference with Enzyme Action
    - 7.6.1 Inhibition of Metalloenzymes
    - 7.6.2 Inhibition by Organic Compounds
  - 7.7 Biochemistry of Mutagenesis
  - 7.8 Biochemistry of Carcinogenesis
    - 7.8.1 Alkylating Agents in Carcinogenesis
    - 7.8.2 Testing for Carcinogens
  - 7.9 Ionizing Radiation
  - References
  - Questions and Problems

## **Chapter 8** Genetic Aspects of Toxicology

- 8.1 Introduction
  - 8.1.1 Chromosomes
  - 8.1.2 Genes and Protein Synthesis
  - 8.1.3 Toxicological Importance of Nucleic Acids
- 8.2 Destructive Genetic Alterations
  - 8.2.1 Gene Mutations
  - 8.2.2 Chromosome Structural Alterations, Aneuploidy, and Polyploidy
  - 8.2.3 Genetic Alteration of Germ Cells and Somatic Cells
- 8.3 Toxicant Damage to DNA
- 8.4 Predicting and Testing for Genotoxic Substances
  - 8.4.1 Tests for Mutagenic Effects
  - 8.4.2 The Bruce Ames Test and Related Tests
  - 8.4.3 Cytogenetic Assays
  - 8.4.4 Transgenic Test Organisms
- 8.5 Genetic Susceptibilities and Resistance to Toxicants
- 8.6 Toxicogenomics
  - 8.6.1 Genetic Susceptibility to Toxic Effects of Pharmaceuticals
- References
- Supplementary Reference
- Questions and Problems

## **Chapter 9** Toxic Responses

- 9.1 Introduction
- 9.2 Respiratory System
- 9.3 Skin
  - 9.3.1 Toxic Responses of Skin
  - 9.3.2 Phototoxic Responses of Skin
  - 9.3.3 Damage to Skin Structure and Pigmentation
  - 9.3.4 Skin Cancer
- 9.4 The Liver .
- 9.5 Blood and the Cardiovascular System
  - 9.5.1 Blood
  - 9.5.2 Hypoxia
  - 9.5.3 Leukocytes and Leukemia

- 
- 9.5.4 Cardiotoxicants
  - 9.5.5 Vascular Toxicants
  - 9.6 Immune System
  - 9.7 Endocrine System
  - 9.8 Nervous System
  - 9.9 Reproductive System
  - 9.10 Developmental Toxicology and Teratology
    - 9.10.1 Thalidomide
    - 9.10.2 Accutane
    - 9.10.3 Fetal Alcohol Syndrome
  - 9.11 Kidney and Bladder
  - References
  - Supplementary References
  - Questions and Problems

## **Chapter 10** Toxic Elements

- 10.1 Introduction
- 10.2 Toxic Elements and the Periodic Table
- 10.3 Essential Elements
- 10.4 Metals in an Organism
  - 10.4.1 Complex Ions and Chelates
  - 10.4.2 Metal Toxicity
  - 10.4.3 Lithium
  - 10.4.4 Beryllium
  - 10.4.5 Vanadium
  - 10.4.6 Chromium
  - 10.4.7 Cobalt
  - 10.4.8 Nickel
  - 10.4.9 Cadmium
  - 10.4.10 Mercury
    - 10.4.10.1 Absorption and Transport of Elemental and Inorganic Mercury
    - 10.4.10.2 Metabolism, Biologic Effects, and Excretion
    - 10.4.10.3 Minimata Bay
  - 10.4.11 Lead
    - 10.4.11.1 Exposure and Absorption of Inorganic Lead Compounds
    - 10.4.11.2 Transport and Metabolism of Lead
    - 10.4.11.3 Manifestations of Lead Poisoning
    - 10.4.11.4 Reversal of Lead Poisoning and Therapy
  - 10.4.12 Defenses Against Heavy Metal Poisoning
- 10.5 Metalloids: Arsenic
  - 10.5.1 Sources and Uses
  - 10.5.2 Exposure and Absorption of Arsenic .
  - 10.5.3 Metabolism, Transport, and Toxic Effects of Arsenic
- 10.6 Nonmetals
  - 10.6.1 Oxygen and Ozone
  - 10.6.2 Phosphorus
  - 10.6.3 The Halogens
    - 10.6.3.1 Fluorine
    - 10.6.3.2 Chlorine
    - 10.6.3.3 Bromine
    - 10.6.3.4 Iodine

- 10.6.4 Radionuclides
  - 10.6.4.1 Radon
  - 10.6.4.2 Radium
  - 10.6.4.3 Fission Products

References

Supplementary Reference

Questions and Problems

**Chapter 11** Toxic Inorganic Compounds

- 11.1 Introduction
  - 11.1.1 Chapter Organization
- 11.2 Toxic Inorganic Carbon Compounds
  - 11.2.1 Cyanide
    - 11.2.1.1 Biochemical Action of Cyanide
  - 11.2.2 Carbon Monoxide
  - 11.2.3 Biochemical Action of Carbon Monoxide
  - 11.2.4 Cyanogen, Cyanamide, and Cyanates
- 11.3 Toxic Inorganic Nitrogen Compounds
  - 11.3.1 Ammonia
  - 11.3.2 Hydrazine
  - 11.3.3 Nitrogen Oxides
  - 11.3.4 Effects of NO<sub>2</sub> Poisoning
  - 11.3.5 Nitrous Oxide
- 11.4 Hydrogen Halides
  - 11.4.1 Hydrogen Fluoride
  - 11.4.2 Hydrogen Chloride
  - 11.4.3 Hydrogen Bromide and Hydrogen Iodide
- 11.5 Interhalogen Compounds and Halogen Oxides
  - 11.5.1 Interhalogen Compounds
  - 11.5.2 Halogen Oxides
  - 11.5.3 Hypochlorous Acid and Hypochlorites
  - 11.5.4 Perchlorates
- 11.6 Nitrogen Compounds of the Halogens
  - 11.6.1 Nitrogen Halides
  - 11.6.2 Azides
  - 11.6.3 Monochloramine and Dichloramine
- 11.7 Inorganic Compounds of Silicon
  - 11.7.1 Silica
  - 11.7.2 Asbestos
  - 11.7.3 Silanes
  - 11.7.4 Silicon Halides and Halohydrides
- 11.8 Inorganic Phosphorus Compounds
  - 11.8.1 Phosphine
  - 11.8.2 Phosphorus Pentoxide
  - 11.8.3 Phosphorus Halides
  - 11.8.4 Phosphorus Oxyhalides
- 11.9 Inorganic Compounds of Sulfur
  - 11.9.1 Hydrogen Sulfide
  - 11.9.2 Sulfur Dioxide and Sulfites
  - 11.9.3 Sulfuric Acid

- 11.9.4 Carbon Disulfide
- 11.9.5 Miscellaneous Inorganic Sulfur Compounds

References

Questions and Problems

## **Chapter 12** Organometallics and Organometalloids

- 12.1 The Nature of Organometallic and Organometalloid Compounds
- 12.2 Classification of Organometallic Compounds
  - 12.2.1 Ionically Bonded Organic Groups
  - 12.2.2 Organic Groups Bonded with Classical Covalent Bonds
  - 12.2.3 Organometallic Compounds with Dative Covalent Bonds
  - 12.2.4 Organometallic Compounds Involving  $\pi$ -Electron Donors
- 12.3 Mixed Organometallic Compounds
- 12.4 Organometallic Compound Toxicity
- 12.5 Compounds of Group 1A Metals
  - 12.5.1 Lithium Compounds
  - 12.5.2 Compounds of Group 1A Metals Other Than Lithium
- 12.6 Compounds of Group 2A Metals
  - 12.6.1 Magnesium
  - 12.6.2 Calcium, Strontium, and Barium
- 12.7 Compounds of Group 2B Metals
  - 12.7.1 Zinc
  - 12.7.2 Cadmium
  - 12.7.3 Mercury
- 12.8 Organotin and Organogermanium Compounds
  - 12.8.1 Toxicology of Organotin Compounds
  - 12.8.2 Organogermanium Compounds
- 12.9 Organolead Compounds
  - 12.9.1 Toxicology of Organolead Compounds
- 12.10 Organoarsenic Compounds
  - 12.10.1 Organoarsenic Compounds from Biological Processes
  - 12.10.2 Synthetic Organoarsenic Compounds
  - 12.10.3 Toxicities of Organoarsenic Compounds
- 12.11 Organoselenium and Organotellurium Compounds
  - 12.11.1 Organoselenium Compounds
  - 12.11.2 Organotellurium Compounds

References

Supplementary References

Questions and Problems

## **Chapter 13** Toxic Organic Compounds and Hydrocarbons

- 13.1 Introduction
- 13.2 Classification of Hydrocarbons
  - 13.2.1 Alkanes
  - 13.2.2 Unsaturated Nonaromatic Hydrocarbons
  - 13.2.3 Aromatic Hydrocarbons
- 13.3 Toxicology of Alkanes
  - 13.3.1 Methane and Ethane
  - 13.3.2 Propane and Butane
  - 13.3.3 Pentane through Octane

- 
- 13.3.4 Alkanes above Octane
  - 13.3.5 Solid and Semisolid Alkanes
  - 13.3.6 Cyclohexane
  - 13.4 Toxicology of Unsaturated Nonaromatic Hydrocarbons
    - 13.4.1 Propylene
    - 13.4.2 1,3-Butadiene
    - 13.4.3 Butylenes
    - 13.4.4 Alpha-Olefins
    - 13.4.5 Cyclopentadiene and Dicyclopentadiene
    - 13.4.6 Acetylene
  - 13.5 Benzene and Its Derivatives
    - 13.5.1 Benzene
      - 13.5.1.1 Acute Toxic Effects of Benzene
      - 13.5.1.2 Chronic Toxic Effects of Benzene
      - 13.5.1.3 Metabolism of Benzene
    - 13.5.2 Toluene, Xylenes, and Ethylbenzene
    - 13.5.3 Styrene
  - 13.6 Naphthalene
    - 13.6.1 Metabolism of Naphthalene
    - 13.6.2 Toxic Effects of Naphthalene
  - 13.7 Polycyclic Aromatic Hydrocarbons
    - 13.7.1 PAH Metabolism

References

Questions and Problems

## **Chapter 14** Organooxygen Compounds

- 14.1 Introduction
  - 14.1.1 Oxygen-Containing Functional Groups
- 14.2 Alcohols
  - 14.2.1 Methanol
  - 14.2.2 Ethanol
  - 14.2.3 Ethylene Glycol
  - 14.2.4 The Higher Alcohols
- 14.3 Phenols
  - 14.3.1 Properties and Uses of Phenols
  - 14.3.2 Toxicology of Phenols
- 14.4 Oxides
- 14.5 Formaldehyde
  - 14.5.1 Properties and Uses of Formaldehyde
  - 14.5.2 Toxicity of Formaldehyde and Formalin
- 14.6 Aldehydes and Ketones
  - 14.6.1 Toxicities of Aldehydes and Ketones
- 14.7 Carboxylic Acids
  - 14.7.1 Toxicology of Carboxylic Acids
- 14.8 Ethers
  - 14.8.1 Examples and Uses of Ethers
  - 14.8.2 Toxicities of Ethers
- 14.9 Acid Anhydrides
  - 14.9.1 Toxicological Considerations
- 14.10 Esters
  - 14.10.1 Toxicities of Esters



---

## References

### Questions and Problems

## **Chapter 15** Organonitrogen Compounds

- 15.1 Introduction
- 15.2 Nonaromatic Amines
  - 15.2.1 Lower Aliphatic Amines
  - 15.2.2 Fatty Amines
  - 15.2.3 Alkyl Polyamines
  - 15.2.4 Cyclic Amines
- 15.3 Carbocyclic Aromatic Amines
  - 15.3.1 Aniline
  - 15.3.2 Benzidine
  - 15.3.3 Naphthylamines
- 15.4 Pyridine and Its Derivatives
- 15.5 Nitriles
- 15.6 Nitro Compounds
  - 15.6.1 Nitro Alcohols and Nitro Phenols
  - 15.6.2 Dinoseb
- 15.7 Nitrosamines
- 15.8 Isocyanates and Methyl Isocyanate
- 15.9 Pesticidal Compounds
  - 15.9.1 Carbamates
  - 15.9.2 Bipyridilium Compounds
- 15.10 Alkaloids

## References

### Questions and Problems

## **Chapter 16** Organohalide Compounds

- 16.1 Introduction
  - 16.1.1 Biogenic Organohalides
- 16.2 Alkyl Halides
  - 16.2.1 Toxicities of Alkyl Halides
  - 16.2.2 Toxic Effects of Carbon Tetrachloride on the Liver
  - 16.2.3 Other Alkyl Halides
  - 16.2.4 Hydrochlorofluorocarbons
  - 16.2.5 Halothane
- 16.3 Alkenyl Halides
  - 16.3.1 Uses of Alkenyl Halides
  - 16.3.2 Toxic Effects of Alkenyl Halides
  - 16.3.3 Hexachlorocyclopentadiene
- 16.4 Aryl Halides
  - 16.4.1 Properties and Uses of Aryl Halides
  - 16.4.2 Toxic Effects of Aryl Halides
- 16.5 Organohalide Insecticides
  - 16.5.1 Toxicities of Organohalide Insecticides
  - 16.5.2 Hexachlorocyclohexane
  - 16.5.3 Toxaphene
- 16.6 Noninsecticidal Organohalide Pesticides
  - 16.6.1 Toxic Effects of Chlorophenoxy Herbicides
  - 16.6.2 Toxicity of TCDD

- 16.6.3 Alachlor
- 16.6.4 Chlorinated Phenols
- 16.6.5 Hexachlorophene

References

Questions and Problems

## **Chapter 17** Organosulfur Compounds

- 17.1 Introduction
    - 17.1.1 Classes of Organosulfur Compounds
    - 17.1.2 Reactions of Organic Sulfur
  - 17.2 Thiols, Sulfides, and Disulfides
    - 17.2.1 Thiols
    - 17.2.2 Thiols as Antidotes for Heavy Metal Poisoning
    - 17.2.3 Sulfides and Disulfides
    - 17.2.4 Organosulfur Compounds in Skunk Spray
    - 17.2.5 Carbon Disulfide and Carbon Oxysulfide
  - 17.3 Organosulfur Compounds Containing Nitrogen or Phosphorus
    - 17.3.1 Thiourea Compounds
    - 17.3.2 Thiocyanates
    - 17.3.3 Disulfiram
    - 17.3.4 Cyclic Sulfur and Nitrogen Organic Compounds
    - 17.3.5 Dithiocarbamates
    - 17.3.6 Phosphine Sulfides
    - 17.3.7 Phosphorothionate and Phosphorodithioate Esters
  - 17.4 Sulfoxides and Sulfones
  - 17.5 Sulfonic Acids, Salts, and Esters
  - 17.6 Organic Esters of Sulfuric Acid
  - 17.7 Miscellaneous Organosulfur Compounds
    - 17.7.1 Sulfur Mustards
    - 17.7.2 Sulfur in Pesticides
    - 17.7.3 Sulfa Drugs
  - 17.8 Organically Bound Selenium
- References
- Questions and Problems

## **Chapter 18** Organophosphorus Compounds

- 18.1 Introduction
  - 18.1.1 Phosphine
- 18.2 Alkyl and Aryl Phosphines
- 18.3 Phosphine Oxides and Sulfides
- 18.4 Phosphonic and Phosphorous Acid Esters
- 18.5 Organophosphate Esters
  - 18.5.1 Orthophosphates and Polyphosphates
  - 18.5.2 Orthophosphate Esters
  - 18.5.3 Aromatic Phosphate Esters
  - 18.5.4 Tetraethylpyrophosphate
- 18.6 Phosphorothionate and Phosphorodithioate Esters
- 18.7 Organophosphate Insecticides
  - 18.7.1 Chemical Formulas and Properties
  - 18.7.2 Phosphate Ester Insecticides
  - 18.7.3 Phosphorothionate Insecticides

- 
- 18.7.4 Phosphorodithioate Insecticides
  - 18.7.5 Toxic Actions of Organophosphate Insecticides
    - 18.7.5.1 Inhibition of Acetylcholinesterase
    - 18.7.5.2 Metabolic Activation
    - 18.7.5.3 Mammalian Toxicities
    - 18.7.5.4 Deactivation of Organophosphates
  - 18.8 Organophosphorus Military Poisons
- References  
Supplementary Reference  
Questions and Problems

## **Chapter 19** Toxic Natural Products

- 19.1 Introduction
  - 19.2 Toxic Substances from Bacteria
    - 19.2.1 *In Vivo* Bacterial Toxins
      - 19.2.1.1 Toxic Shock Syndrome
    - 19.2.2 Bacterial Toxins Produced Outside the Body
  - 19.3 Mycotoxins
    - 19.3.1 Aflatoxins
    - 19.3.2 Other Mycotoxins
    - 19.3.3 Mushroom Toxins
  - 19.4 Toxins from Protozoa
  - 19.5 Toxic Substances from Plants
    - 19.5.1 Nerve Toxins from Plants
      - 19.5.1.1 Pyrethrins and Pyrethroids
    - 19.5.2 Internal Organ Plant Toxins
    - 19.5.3 Eye and Skin Irritants
    - 19.5.4 Allergens
    - 19.5.5 Mineral Accumulators
    - 19.5.6 Toxic Algae
  - 19.6 Insect Toxins
    - 19.6.1 Bee Venom
    - 19.6.2 Wasp and Hornet Venoms
    - 19.6.3 Toxicities of Insect Venoms
  - 19.7 Spider Toxins
    - 19.7.1 Brown Recluse Spiders
    - 19.7.2 Widow Spiders
    - 19.7.3 Other Spiders
  - 19.8 Reptile Toxins
    - 19.8.1 Chemical Composition of Snake Venoms
    - 19.8.2 Toxic Effects of Snake Venom
  - 19.9 Nonreptile Animal Toxins
- References  
Supplementary References  
Questions and Problems

## **Chapter 20** Analysis of Xenobiotics

- 20.1 Introduction
- 20.2 Indicators of Exposure to Xenobiotics
- 20.3 Determination of Metals

---

- 20.3.1 Direct Analysis of Metals
- 20.3.2 Metals in Wet-Ashed Blood and Urine
- 20.3.3 Extraction of Metals for Atomic Absorption Analysis
- 20.4 Determination of Nonmetals and Inorganic Compounds
- 20.5 Determination of Parent Organic Compounds
- 20.6 Measurement of Phase I and Phase II Reaction Products
  - 20.6.1 Phase I Reaction Products
  - 20.6.2 Phase II Reaction Products
  - 20.6.3 Mercapturates
- 20.7 Determination of Adducts
- 20.8 The Promise of Immunological Methods
- References
- Supplementary References
- Questions and Problems

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## CHAPTER 1

# Chemistry and Organic Chemistry

### 1.1 INTRODUCTION

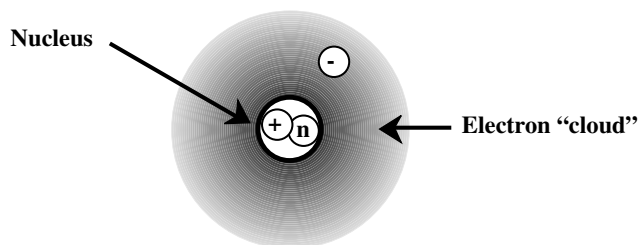
This book is about toxicological chemistry, the branch of chemical science dealing with the toxic effects of substances. In order to understand this topic, it is essential to have an understanding of **chemistry**, the science of matter. The nature of toxic substances depends upon their chemical characteristics, 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 <sup>a</sup>	Unit Charge	Mass Number	Mass in $\mu$	Mass in Grams
Proton	$p$	+1	1	1.007277	$1.6726 \times 10^{-24}$
Neutron	$n$	0	1	1.008665	$1.6749 \times 10^{-24}$
Electron	$e$	-1	0	0.000549	$9.1096 \times 10^{-28}$

<sup>a</sup> The mass number and charge of each of these kinds of particles can be indicated by a superscript and subscript, respectively, in the symbols  ${}^1_1p$ ,  ${}^1_0n$ ,  ${}^{-1}_1e$ .

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.

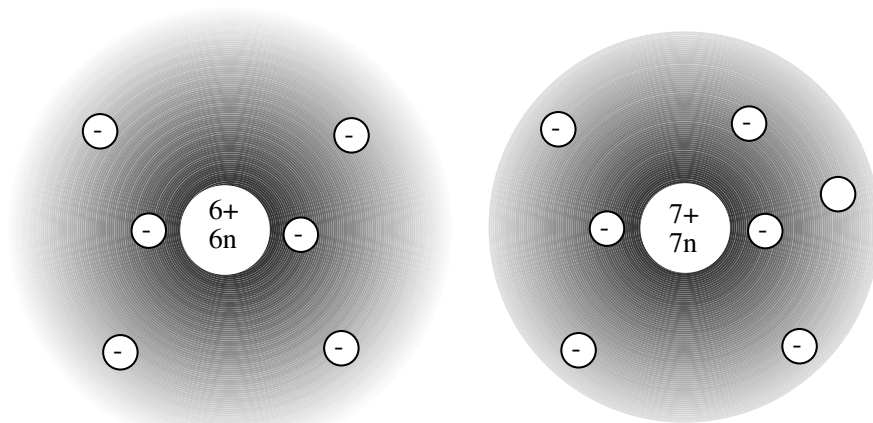
### 1.2.1 Subatomic Particles and Atoms

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  $1.6022 \times 10^{-19}$  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 <sub>2</sub>
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,



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