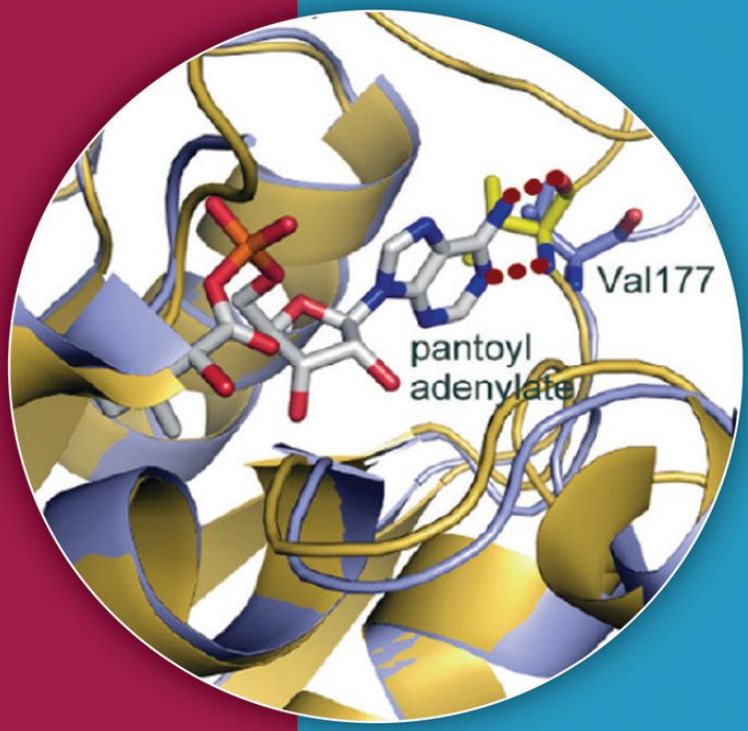
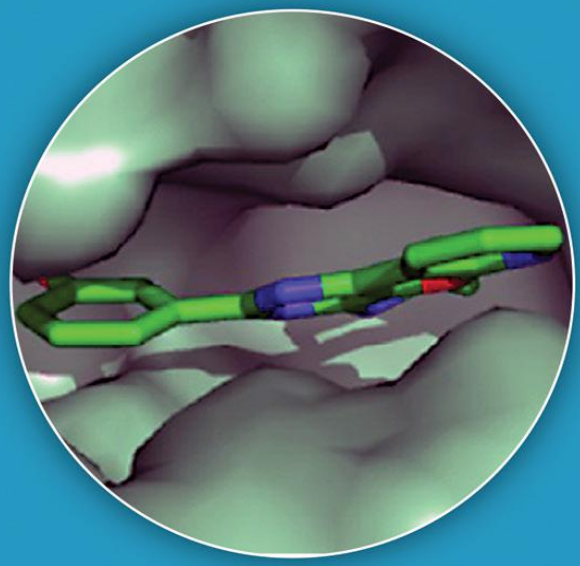
MICHAEL B. SMITH





THIRD EDITION

ORGANIC CHEMISTRY

AN ACID–BASE APPROACH

CRC Press
Taylor & Francis Group

Organic Chemistry

Organic Chemistry

An Acid–Base Approach

Third Edition

Michael B. Smith

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This book is dedicated to Professor Madeleine M. Joullié

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Preface to the Third Edition

In my first edition of *Organic Chemistry. An Acid-Base Approach*, I introduced the idea of using an acid–base approach to teach organic chemistry. This concept continued in the second edition, and I used these books to teach several classes of the typical sophomore organic chemistry class. My class sizes each semester ranged from 250 to 400 students. These students were primarily STEM majors, including pre-pharmacy, pre-med, several of the biological sciences, and some chemistry majors.

The rationale for an acid–base approach rests on the fact that most reactions in organic chemistry involve an acid or a base. Laying a good foundation in acid–base chemistry greatly improves a student's understanding of nucleophiles and nucleophilic reactions. Amines, for example, are important bases and generate weakly acidic ammonium salts by reaction with an acid. Both ethers and alcohols react with a suitable acid to generate an oxonium ion as a reactive intermediate. Aldehydes and ketones react with an acid to give a resonance-stabilized oxocarbenium ion, which enhances the reactivity of acyl addition reactions with water, alcohols, or amines. Acid derivatives react with an acid catalyst to generate an oxocarbenium ion intermediate that facilitates formation of a tetrahedral intermediate for acyl substitution reactions. Alkenes react as Brønsted-Lowry bases with Brønsted-Lowry acids to give a carbocation intermediate for addition reactions. Similarly, alkynes react as bases to give a vinyl carbocation for addition reactions. When an alkene or an alkyne reacts with mercury derivatives, the product is a mercury-stabilized carbocation, facilitating oxymercuration-demercuration reactions. When an alkyne or an alkyne reacts with borane in hydroboration reactions, the product is an alkylborane via a four-center transition state. Both reactions are Lewis-base-like. Neither reaction forms an "ate"-complex, but the alkene or alkyne donates two electrons to mercury or boron to form a C—Hg or C—B bond. When a benzene ring reacts with an electrophilic species such as Br^+, Cl^+, or NO_2^+, the benzene ring donates two electrons in a Lewis-base-like reaction to give an arenium ion, which leads to S_EAr reactions. Alcohols react with a base to generate an alkoxide, which is both a base and a nucleophile. Alkyl halides or a pertinent substrate have a weakly acidic β-hydrogen that reacts with a suitable base to give an alkene in E2 and E1 reactions. The proton of a terminal alkyne reacts with a suitable base to generate the nucleophilic alkyne anion. Enolate anions are generated by reaction of the α-hydrogen of an aldehyde, ketone, or an acid derivative with a strong base. Enolate anion chemistry, which includes the aldol condensation and the Claisen condensation, is rooted in acid–base chemistry. Most of the steps in the chemistry of carboxylic acid derivatives involve acid–base chemistry. The hydrolytic workup for many reactions is an acid–base reaction.

Nucleophiles and their reactions are the basis of most organic chemistry books. Nucleophiles are electron donors to carbon, which is nothing more than a variation of the Lewis-base definition. A nucleophile donates electrons to an electrophilic carbon in a S_N2 or S_N1 reaction or to an acyl carbon of an aldehyde, ketone, or acid derivative. Understanding the two-electron donor properties of Lewis bases is an obvious and important lead-in to understanding how and why nucleophiles react in substitution reactions, in acyl addition, or in acyl substitution reactions.

Over the years, students who shared their views commented that this approach made the concepts of organic reactions easier to understand. This approach provides a "safety-net" of fundamental principles that allowed them to understand principles rather than simply memorizing information. This third edition was rewritten largely with the comments of those students in mind. It is also based on my classroom experiences of using the first and second editions and my observations of how organic chemistry has changed over the years. Therefore, several important changes are incorporated in the third edition.

Many classical chemical reactions are presented in this revision, but there are also reactions used in modern organic chemistry. These new reactions are presented to show how organic chemistry has matured and changed as a science over the last 50 years or so. Apart from Grignard reagents, organolithium reagent, and organocuprates, many organometallic reactions using Pd, Rh, Fe, and Cr

catalysts are included in this edition. These reactions include metathesis reactions, ylid reactions other than the Wittig reaction, the Mizoroki-Heck reaction, the Suzuki-Miyaura reaction and other aryl coupling reactions, C—H coupling reactions, the Nazarov cyclization, the Grob fragmentation, Negishi coupling, Fukuyama coupling, the Nozaki-Hiyama-Kishi reaction, the Tsuji-Trost reaction, the Mukaiyama aldol reaction, the Mitsunobu reaction, and Sonogashira coupling. Models for predicting stereoselectivity are discussed, including the Cram model and the Zimmerman-Traxler model. The Sharpless asymmetric epoxidation, the Jacobson-Katsuki reaction, the Shi epoxidation, and Noyori annulation are discussed. Many reactions that are important in biochemistry but have their roots in organic chemistry are presented at the end of many chapters and in Chapters 24 and 25. Research done by 35 current organic chemists is also included in this revision. Their cutting edge work illustrates the breadth and variety of modern organic chemistry.

Before retirement I put together online courses for both semesters of organic chemistry. I recorded more than 200 short videos for use as the lecture part of those courses. I made these videos available to my regular lectures and found they were extremely valuable as a course auxiliary. For this new edition I recorded 329 new video clips in a .mov format. These clips are distributed throughout the book and each is available in the e-book as a hyperlink. These videos are a "built-in" teaching ancillary, and they are accessible via any browser by clicking on the URL hyperlink from the e-book. I do not appear on these videos but give a voice presentation of pertinent concepts. There are a total of just over 36 hours of video, and the average video is 6.4 minutes in length. The longest video is 17.2 minutes and the shortest is 0.32 minutes. For those who have purchased this book but do not have the e-book, the URL for the video clips of each chapter can be found at the top of the respective chapter opener. The URL can be entered into any browser to access the video clips.

The first and second editions of this book, as well as most other organic chemistry textbooks, lack the diversity that is so important to organic chemistry. I attempt to correct this oversight in the third edition by introducing the work of 69 scientists who have not appeared in organic textbooks. Of these scientists, the contributions of 35 chemists who worked in the latter part of the 19th century or during the 20th century but have not been recognized in textbooks are distributed throughout the book. The work of 34 current organic chemists is also included throughout the chapters to show the research done in modern organic chemistry. The photos of all 69 of these scientists are also shown to highlight the diversity in organic chemistry.

Every chapter in this third edition has been extensively revised. Chapter 1 presents a brief history of organic chemistry. Chapter 1 also introduces 19 scientists who made significant contributions to organic chemistry but whose work has not been reported in a textbook prior to this work. Chapters 2 and 6 introduce acid–base reactions based on general chemistry principles and the organic chemistry of organic chemicals. Chapter 6 elaborates the acid–base properties of organic functional groups. The structure of alkanes and the fundamentals of nomenclature are presented in Chapter 4. Chapter 5 introduces important functional groups, along with their nomenclature. The energy considerations that are important to reactions in organic chemistry are discussed in Chapter 7. Bond rotation and conformations are discussed in Chapter 8, as well as a discussion of large ring compounds. The concepts and applications of chirality and stereochemistry are discussed in Chapter 9.

The reactions in Chapter 10 introduce reactions of carbocations, including the acid–base reactions of π-bonds reacting as bases with Brønsted-Lowry acids or with Lewis acids. Such reactions are traditionally labeled as addition reactions. Metathesis reactions are discussed as well as radical reactions and polymerization. Chapter 11 discusses S_N2, S_N1, and S_Ni reactions of alkyl halides. Substitution reactions of alcohols and ethers are also discussed. Chapter 12 discusses E2, E1, and Ei reactions. The Grob fragmentation is also introduced. Chapter 12 also summarizes the competition between substitution and elimination reactions of alkyl halides, showing how simple assumptions allow one to predict the product of these reactions. Chapter 13 discusses various spectroscopic methods and more or less stands apart from the remainder of the book. This chapter discusses mass spectrometry, infrared spectroscopy, ^{1}H NMR, and ^{13}C NMR and 2D NMR. Beginning with Chapter 8, clearly marked spectroscopic homework problems are presented at the end of each chapter. Therefore, spectroscopy can be introduced any time the instructor chooses to discuss it.

The preparation and reactions of Grignard reagents, organolithium reagents, and organocuprates are discussed in Chapter 14. Other organometallic compounds are also introduced. Chapter 15 discusses the oxidation reaction of alcohols and alkenes and also oxidative cleavage reactions. Chapter 16 introduces acyl addition reactions of aldehydes and ketones with strong and weak nucleophiles. The reaction of aldehydes and ketones to give an oxocarbenium intermediate to facilitate reactions with weak nucleophiles is also discussed. Chapter 17 introduces reduction reactions of carbonyl compounds, alkenes, and alkynes. Hydride reductions, catalytic hydrogenation, and dissolving metal reductions are discussed.

Chapter 18 discusses the acid–base reactions and the acyl substitution reactions of carboxylic acid and sulfonic acid derivatives. Dicarboxylic acid derivatives are discussed as well as derivatives of nitric acid, sulfuric acid, and phosphoric acid. Fatty acids and lipids are introduced. Chapter 19 discusses aromatic derivatives, their nomenclature, and aromatic substitution reactions. Both S_EAr and S_NAr reactions are discussed, as well as benzyne reactions and reactions of diazonium salts. A

variety of aromatic compounds are introduced including polynuclear aromatic systems. Chapter 20 discusses enolate anion reactions including the aldol condensation and the Claisen condensation. The Cram model and the Zimmerman-Traxler model are introduced to predict the diastereoselectivity of these reactions. Decarboxylation is introduced and ylid reactions are discussed. Chapter 21 introduces the properties and reactions of conjugated systems including the Michael reaction, Robinson annulation, and the Nazarov cyclization. The fundamentals of photochemistry are presented, and there is a brief introduction to ultraviolet spectroscopy. Chapter 22 discusses pericyclic reactions, including the Diels-Alder reaction [4+2]-cycloaddition, [2+2]-cycloaddition, and [3+2]-cycloaddition reactions. Sigmatropic rearrangements are discussed, including the Cope rearrangement and the Claisen rearrangement. Chapter 23 discusses heteroaromatic compounds and also reduced forms of heteroaromatic compounds. This chapter focuses on heterocycles that contain nitrogen, oxygen, and sulfur. Monocyclic, bicyclic, and polycyclic heterocyclic compounds are presented. Simple chemical transformations of monocyclic and bicyclic heterocycles are included. Chapters 24 and 25 offer brief discussions of biochemistry, with a focus on amino acids and proteins, carbohydrates, and nucleic acids. Chapter 24 focuses on amino acids, peptides, proteins enzymes, and hormones. There is a section of combinatorial chemistry. Chapter 25 focuses on carbohydrates, primarily monosaccharides, although disaccharides and polysaccharides are discussed. Reactions of carbohydrates are included. There is a discussion of glycosides, nucleosides, nucleotides, and polynucleotides such as DNA and RNA.

The homework in the third edition is largely the same as that in the second edition, but there are changes. This decision was taken with the recognition that substantive changes have been made in the discussions of every chapter, as well as the examples that are used. The solutions manual is a free download, as a pdf file, that is available from the CRC website to those who purchase the book.

I thank the many students I taught in my undergraduate organic chemistry classes over many years. Their interest, enthusiasm, and input not only inspired this book but have made it significantly better and hopefully more useable. If not for them, this book and this organization would not exist. I thank Courtney Stanford (Rochester), Dee Casteel (Bucknell), Fred Luzzio (Louisville), Amber Onorato (Northern Kentucky), John D'Angelo (Alfred University), and Spencer Knapp (Rutgers). They reviewed portions of the manuscript, provided many suggestions and comments that improved the textbook, and I thank them very much. I thank the many other friends and acquaintances who made suggestions that influenced this book.

I give my sincere thanks to the organic chemists who agreed to participate in this book, for their help and for their many contributions to organic chemistry. They not only provided photos and descriptions of their research but provided inspiration for the chemistry and examples used. This endeavor has cemented my belief that diversity of the people and of ideas in organic chemistry lies at the heart of our science and keeps it growing. Incorporation in an undergraduate textbook is long overdue.

I thank Hilary Rowe, the editor for the third edition, and Dr. Fiona MacDonald, the publisher. Their help, dedication to the project, and their willingness and ability to solve problems were essential to completion of this revision. I thank Ms. Danielle Zarfati and Cynthia Klivecka for their expertise in bringing the manuscript to fruition as a typeset book. I thank Ms. Christine Elder for her graphic arts expertise to render several images in a form that is clearer and more attractive. Ms. Elder's graphics appear in several places throughout the book: Figures 3.9, 3.11, 3.12, 5.1, 5.2, 5.3, 5.4, 5.12, 5.15, 8.2, 8.11, 9.1, and 9.4I. I thank Dr. Warren Hehre and Dr. Sean Ohlinger of Wavefunction Inc. for their gift of Spartan 18 v. 1.4.8 (200921), which was used to generate the molecular models used throughout the book. I thank PerkinElmer Inc. for their gift of ChemDraw Professional v. 18.0.0.231 (4318), which was used to draw all reaction figures and schemes in this book and also used to render ^{1}H and ^{13}C NMR spectra throughout the book.

Finally, I thank my wife Sarah for her love and continued support throughout the months required to revise this book.

Michael B. Smith
Professor Emeritus
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Willington, Connecticut

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Common Abbreviations

Other, less common, abbreviations are given in the text when the term is used.

Ac	Acetyl	
AIBN	Azobisisobutyronitrile	
aq	Aqueous	
AIBN	Azobisisobutyronitrile	
Ax	Axial	
	9-Borabicyclo[3.3.1] nonylboryl	
9-BBN	9-Borabicyclo[3.3.1] nonane	
Bn	Benzyl	$-CH_2Ph$
Boc	***tert*-Butoxycarbonyl**	
Bu	***n*-Butyl**	$-CH_2CH_2CH_2CH_3$
BUN	Blood urea nitrogen	
Bz	Benzoyl	
°C	Temperature in Degrees Celcius	
^{13}C NMR	Carbon Nuclear Magnetic Resonance	
cat	Catalytic	
Cbz	Carbobenzyloxy	
CIP	Cahn-Ingold-Prelog	
CoA	Coenzyme A	
mCPBA	3-Chloroperoxybenzoic acid	
DCC	1,3-Dicyclohexylcarbodiimide	***c*-C_6H_{11}-N=C=N-*c*-C_6H_{11}**
DDT	Dichlorodiphenyltrichloroethane	
DEA	Diethylamine	$HN(CH_2CH_3)_2$
DMAP	4-Dimethylaminopyridine	
DME	Dimethoxyethane	$MeOCH_2CH_2OMe$
DMF	***N,N'*-Dimethylformamide**	
DMSO	Dimethyl sulfoxide	
DNA	Deoxyribonuleic acid	
EA	Electron affinity	
EDTA	Ethylenediaminetetraacetic acid	
ee or % ee	% Enantiomeric excess	
Equiv	Equivalent(s)	
Er	Enantiomeric ratio	
Et	Ethyl	$-CH_2CH_3$
Ether	Diethyl ether	$CH_3CH_2OCH_2C_3$
Eq	Equatorial	
FC	Formal charge	
FDNB	Sanger's reagent, 1-fluoro-2,4-dinitrobenzene	
FMO	Frontier molecular orbitals	
FVP	Flash Vacuum Pyrolysis	
GC	Gas chromatography	
h	Hour (hours)	
^1H NMR	Proton Nuclear Magnetic Resonance	
HDL	High-density lipoprotein	
HDPE	High-density poly(ethylene)	
HIV	Human immunodeficiency virus	
HMPA	Hexamethylphosphoramide	
HOMO	Highest occupied molecular orbital	
HPLC	High performance liquid chromatography	
hv	Irradiation with light	
IP	Ionization potential	
*i*Pr	Isopropyl	$-CH(Me)_2$
IR	Infrared	
IUPAC	International Union of Pure and Applied Chemistry	
K	Temperature in Kelvin	
LCAO	Linear combination of atomic orbitals	
LDA	Lithium diisopropylamide	$LiN(i\text{-}Pr)_2$
LDL	Low-density lipoprotein	
LTA	Lead tetraacetate	
LUMO	Lowest unoccupied molecular orbital	
mcpba	*meta*-Chloroperoxybenzoic acid	

MDPE	Medium-density poly(ethylene)	
Me	Methyl	$-CH_3$ or Me
min	Minutes	
MO	Molecular orbital	
MRI	Magnetic resonance imaging	
mRNA	Messenger ribonucleic acid	
MS	Mass spectrometry	
NMR	Nuclear magnetic resonance	
N.R.	No reaction	
NAD^+	Nicotinamide adenine dinucleotide	
NADH	Reduced nicotinamide adenine dinucleotide	
$NADP^+$	Nicotinamide adenine dinucleotide phosphate	
NADPH	Reduced nicotinamide adenine dinucleotide phosphate	
NBS	***N*-Bromosuccinimide**	
NCS	***N*-Chlorosuccinimide**	
Ni(R)	Raney nickel	
NMO	***N*-Methylmorpholine *N*-oxide**	
Nu (Nuc)	Nucleophile	
Oxone®	$2\ KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$	
PCB	Polychlorobiphenyl	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Poly(ethylene glycol)	
PES	Photoelectron spectroscopy	
Ph	Phenyl	
PhMe	Toluene	
PPA	Polyphosphoric acid	
Ppm	Parts per million	
Pr	***n*-Propyl**	$-CH_2CH_2CH_3$
PTFE	Poly(tetrafluoroethylene)	
PVC	Poly(vinyl chloride)	
Py	Pyridine	
rf	Radio frequency	
RNA	Ribonucleic acid	
ROS	Reactive oxygen species	
rt	Room temperature	
s	Seconds	
SCF	self-consistent field	
$(Sia)_2BH$	Disiamylborane (Siamyl is ***sec*-Isoamyl)**	
sBuLi	***sec*-Butyllithium**	$CH_3CH_2CH(Li)CH_3$
S_EAr	Electrophilic aromatic substitution	
SET	Single electron transfer	
S_NAr	Nucleophilic aromatic substitution	
SOMO	singly occupied molecular orbital	
T	Temperature	
***t*-Bu**	***tert*-Butyl**	$-CMe_3$
TBHP (***t*-BuOOH)**	***tert*-Butylhydroperoxide**	Me_3COOH
TFA	Trifluoroacetic acid	CF_3COOH
$ThexBH_2$	Thexylborane (***tert*-hexylborane)**	
THF	Tetrahydrofuran	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$Me_2NCH_2CH_2NMe_2$
Tol	Tolyl	$4\text{-}(Me)C_6H_4$
TS	Transition state	
Ts(Tos)	Tosyl = ***p*-Toluenesulfonyl**	$4\text{-}(Me)C_6H_4SO_2$
TTP	Thiamine pyrophosphate	
TTP	Thiamine pyrophosphate	
UTP	Uridine 5′-triphosphate	
UV	Ultraviolet spectroscopy	
VIS	Visible	
VDW	van der Walls	

Videos to Accompany the Third Edition

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(*Continued*)

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			http://icons.niherst.gov.tt/icon/bertram-fraser-reid-ci2/
p659.	David Mootoo	0076-c25-d-mootoo.jpg	Photo reproduced by the courtesy of and with the permission of Professor Mootoo.
p660.	Laura Lee Kiessling	0073-c25-l-kiessling.jpg	This photo is reproduced by the courtesy of and with the permission of Professor Kiessling.
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p673.	Har Gobind Khorana	0070-c25-h-g-khorana .jpgx	WikiCommons photo. https://en.wikipedia.org/wiki/Har_Gobind_Khorana

Infrared Spectra Reprinted from SBDS

Obtained from Appendix A, from Integrated Spectral Data Base System for Organic Compounds (SDBS) by the National Metrology Institute of Japan (NMIJ), National Institute of Advanced Industrial Science and Technology. Umezono 1-1-1, Tsukuba, Ibaraki, 305-8563, Japan

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490	isobutyronitrile	IR-NIDA-04675
507	2-butanol	IR-NIDA-06521
542	3-methoxy-1-butanol	IR-NIDA-05740
568	1-hexyne	IR-NIDA-05748
580	4-methyl-2-pentanone	IR-NIDA-05410
654	2,3-dimethylbutane	IR-NIDA-02888
798	1,1,3,3-tetramethybutylamine	IR-NIDA-00510
898	benzene	IR-NIDA-63541
899	p-xylene	IR-NIDA-63598
1275	diethyl allylmalonate	IR-NIDA-17726
1305	2,5-dimethyl-2,4-hexadiene	IR-NIDA-07292
1672	dibutylamine	IR-NIDA-04481
1891	isobutyl formate	IR-NIDA-06512
2208	diisopropylamine	IR-NIDA-55790
2396	heptane	IR-NIDA-05790
2673	2-pentanone	IR-NIDA-06910
3047	dipropyl ether	IR-NIDA-07299
3978	2,4-dimethyl-3-pentanone	IR-NIDA-01636
4000	N,N-dimethylethylamine	IR-NIDA-01670
4613	2-methylbutyronitrile	IR-NIDA-02476
4717	2-hexene	IR-NIDA-05742
5399	4-pentenoic acid	IR-NIDA-14245
5487	4-pyridinemethanol	IR-NIDA-09156
5745	1-ethyl-1-cyclopentene	IR-NIDA-13591
5894	priopionaldehyde diethyl acetal	IR-NIDA-18293
6064	2,2-diethoxypropane	IR-NIDA-58274
10224	2-methylpentanal	IR-NIDA-02541
10223	3-methylvaleric acid	IR-NIDA-67865
10231	2-hexyne	IR-NIDA-02550
10415	DL-alanyl-DL-serine	IR-NIDA-13812
17066	p-isopropylphentole	IR-NIDA-61290
19312	p-isobutylbenzaldehyde	IR-NIDA-62348
21918	allyl ethyl ether	IR-NIDA-29522
22747	trans-2-pentenal	IR-NIDA-26937
24541	N-benzylacetoacetamide	IR-NIDA-31737
26023	2,6-dimethylbenzonitrile	IR-NIDA-35184
26368	N,2,2-trimethylpropionamide	IR-NIDA-35950
27416	hexaethylbenzene	IR-NIDA-38383
34191	N-formyl-2-phenyl alanine methyl ester	IR-NIDA-52915
51928	1-phenyl-1-butanol	IR2007-86343TK
52449	3-bromo-2-(bromomethyl) propionate	IR2009-87596TK
52793	2-methylbutyl isobutyrate	IR2010-88216TK
53258	ethyldipropylamine	IR2013-89281TK

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1

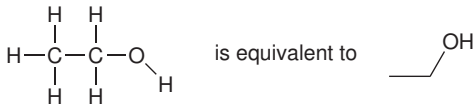
Introduction

Since you are taking organic chemistry, it is likely that you are a STEM major, in a class of students with a wide range of interests and career choices. Why is organic chemistry important? The answer lies in the fact that virtually every aspect of life, mammalian and non-mammalian as well as plant and microscopic life, involves organic chemistry. In addition, many of the products used every day (pharmaceuticals, plastics, clothing, etc.) involve organic molecules. Organic chemistry holds a central place in chemical studies because its applications touch virtually all other disciplines.

Most organic chemistry textbooks have a brief section to introduce organic chemistry. I was a graduate student when I first read an organic chemistry textbook that presented some historical facts as part of the normal presentation. The book was *Advanced Organic Chemistry*[1] by Louis F. Fieser (USA; 1899–1977). This book gave a perspective to my studies that helped me to better understand many of the concepts. I believe that putting a subject into its proper context makes it easier to understand. I am therefore introducing an abbreviated history of organic chemistry as an introduction to this book. I will include material from Fieser's book, and also from a book on the history of chemistry by Henry M. Leicester.[2] The early work described in these books laid the foundations of modern organic chemistry and many classical chemical reactions that are important in modern organic chemistry. This book will also introduce the work of many chemists whose contributions have not been heretofore recognized in a textbook. The contributions of women scientists and scientists of diverse ethnicity will be discussed. Further, the research of current chemists will be introduced to show the scope of modern organic chemistry and the diversity of the scientists.

1.1 A BRIEF HISTORY OF ORGANIC CHEMISTRY

In the 19th century, organic chemistry was defined as the chemistry of *carbon* compounds. For most of human history, however, both simple chemicals and complex mixtures of chemicals have been used without an understanding of the science behind them. Indeed, plants have been "milked," cut, boiled, and eaten for thousands of years as folk medicine remedies. Modern science has determined that many of these plants contain organic chemicals with effective medical uses, and many modern medicines are derived from them.

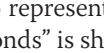


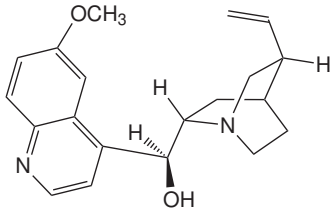
Ethyl alcohol (ethanol)

A simple but common organic chemical is ethyl alcohol (ethanol), produced by fermentation of grains and fruits. Ethanol has been known and consumed for thousands of years in various forms, including in a beer consumed by ancient Egyptians beginning around 5000 BCE. The structure shown requires some explanation. Each hydrogen atom bonded to a

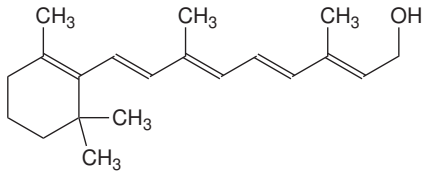
[1] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry*, Reinhold, NY, 1961, pp. 1–31.
[2] Leicester, H.M. *The Historical Background of Chemistry*, Wiley, NY, 1956, pp. 172–188.

DOI: 10.1201/9781003174929-1

carbon atom is represented as H—C, where the "line" (—) represents a chemical bond and C—C is a carbon–carbon bond. Likewise there is a C—O bond and an O—H bond. In the second structure, the carbon atoms (C) are omitted, but a line — is used as a shorthand notation to represent a bond between two atoms. In this simplified drawing, the "intersection of two bonds" is shown by a "bend" or an "angle" (), and each point of the bend or angle represents a carbon atom in what is called *line notation*. Although the hydrogen atoms connected to each point (each carbon) are not shown in line notation, they are understood to be there. The C—O bond (carbon–oxygen) is shown by —O. The O—H unit is shown as just OH. Line notation uses one line for each bond, so C=C can be shown as = to indicate two bonds between the carbon atoms (a carbon-carbon double bond). A C=O bond (=O) has two bonds between carbon and oxygen (a carbon-oxygen double bond). Similarly, C≡C is shown as ≡ to represent three bonds between the two carbon atoms, a carbon–carbon triple bond.



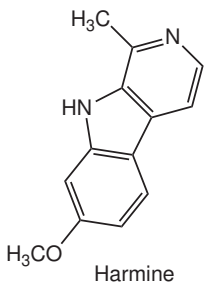
Quinine



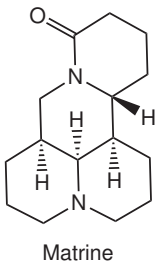
Vitamin A

Many naturally occurring materials contain important organic compounds that are well known in human history. The bark of the *Cinchona* tree, for example, has been used by the indigenous peoples of modern-day Peru, Bolivia, and Ecuador to treat symptoms of malaria. In the 19th century, it was discovered that this bark contains *quinine*, which is an antipyretic (fever reducing), an analgesic (pain reducing), an anti-inflammatory, and an anti-malarial. Ancient Egyptians ate roasted ox liver in the belief that it improved night vision. Ox liver is rich in *Vitamin A*. The structure of Vitamin A was determined in the 20th century, and it is a chemical important for maintaining healthy eyesight.

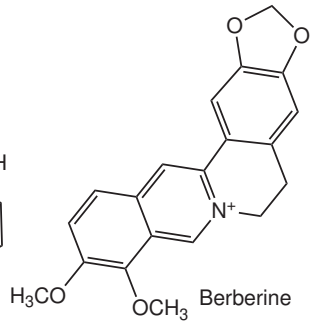
Quinine is an example of an *alkaloid*. Alkaloids (Section 23.6) are structurally diverse nitrogenous compounds, usually of plant origin, that are physiologically active and exhibit reactivity as a chemical base. There are thousands of known alkaloids but three illustrative examples of alkaloids with physiological properties are *harmine*, *matrine*, and *berberine*. Harmine, a beta-carboline alkaloid, is isolated from natural sources so it is a *natural product*. It has therapeutic potential as an antitumor compound, and it shows anti-HIV activity. Matrine is the most abundant alkaloid found in many *Sophora* plants, small trees, and shrubs in the pea family *Fabaceae*. It exhibits antibacterial, antiviral, anti-inflammatory, anti-asthmatic, anti-arrhythmic, anti-obesity, anti-cancer, diuretic, choleretic, hepatoprotective, nephroprotective, and cardioprotective effects. *Berberine* is isolated from Chinese herbs such as *Coptidis Rhizome*. It has been used for the treatment of diarrhea as an antibacterial drug, and it has beneficial effects on the metabolism disorders associated with diabetes.



Harmine



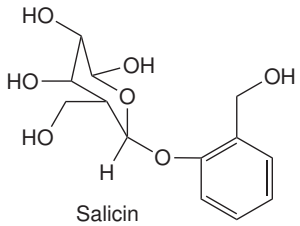
Matrine



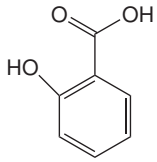
Berberine

People in ancient Assyria, Sumer, and Egypt chewed willow bark as an antipyretic treatment. In the 19th century it was discovered that willow bark contained *salicin*, a derivative

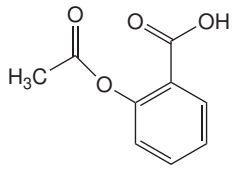
of *salicylic acid*. Nowadays it is recognized that salicin is a glycoside, which is a compound formed from a simple sugar and another compound (Section 25.4). *Synthesis* is the conversion of one compound into another, often in several chemical steps, and an important application is the preparation of organic molecules with a more complex structure from compounds that are structurally simple.



Salicin



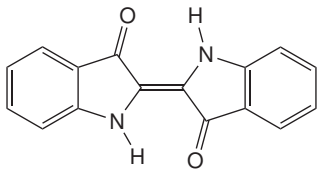
Salicylic acid



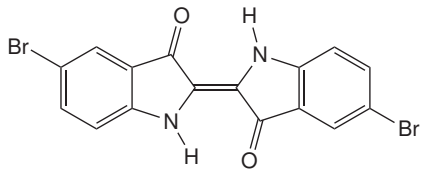
Acetylsalicylic acid (Aspirin)

In the mid-19th century a new compound was synthesized (chemically prepared from other chemicals) called *acetylsalicylic acid*, better known as aspirin. Aspirin is an effective analgesic, and it is an example of a so-called non-steroidal anti-inflammatory drug (an NSAID).

In ancient India, Java, and Guatemala certain plants provided a deep blue substance used to color clothing. In recent times, the main constituent was identified as *indigo*. The ancient Phoenicians discovered an extract from a sea snail (*Bolinus brandaris*, originally called *Murex brandaris*) found in the Mediterranean, traditionally off the coast of Tyre (now called Lebanon). This snail was the source of a beautiful and very expensive dye called *Tyrian purple*. This dye was so prized that Roman emperors used it to color their clothing, and for many years no one else was permitted to wear this color, which gave rise to the term "born to the purple." When the actual structure of the organic chemical Tyrian purple is compared with indigo, the only difference is the presence of two bromine atoms in the latter.



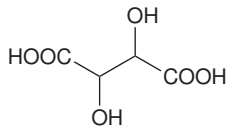
Indigo



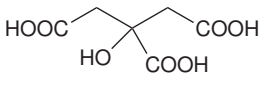
Tyrian purple

For most of history the actual chemical structure of the material isolated and used from natural sources was unknown. However, the importance of these materials led people to isolate pure compounds and then attempt to identify them. Isolation and purification was followed by characterization of the physical properties (melting point, boiling point, solubility in water, etc.) of these compounds. It was not until the mid- to late-19th century and even into the early-20th century that the structures of most of these compounds were known absolutely. Many of the pertinent identification procedures for the analysis of organic compounds were instituted and perfected by Justus von Liebig (Germany; 1803–1873), who built on the early work of Antoine Lavoisier (France; 1743–1794).

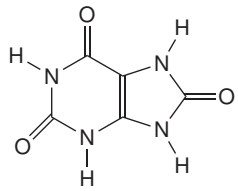
In the 18th century, Lavoisier made an important contribution to understanding the structure of organic molecules by burning natural materials in air. Lavoisier knew that air was composed mainly of oxygen (O_2) and nitrogen (N_2). He discovered that carbon in the burned material was converted to carbon dioxide (CO_2) and that hydrogen in the material was converted to water (H_2O). By trapping and weighing the carbon dioxide and the water, he was able to calculate the percentage of carbon and hydrogen in molecules. This knowledge allowed a determination of the *empirical formula* (Section 4.6). Organic molecules are composed of substantial amounts of carbon and hydrogen, and this *elemental analysis* procedure known as *combustion analysis* was, and is, an invaluable tool for determining structure (Section 4.6).



Tartaric acid



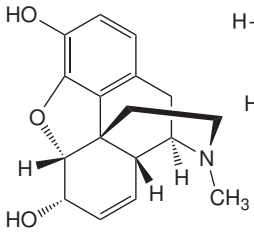
Citric acid



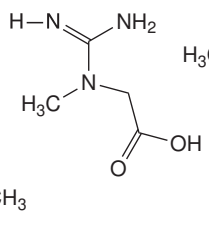
Uric acid

One of the first people to identify specific chemicals from natural sources was Carl Wilhelm Scheele (Sweden; 1742–1786). He isolated acidic components from grapes and lemons by forming precipitates with calcium or lead salts, and then added mineral acids to obtain the actual compounds. The acidic compound isolated from grapes is now known to be *tartaric acid*, and the one from lemon is now known to be *citric acid*. Scheele also isolated *uric acid* (Section 23.3) from urine. Friedrich W. Serturner (Germany; 1783–1841) isolated a compound from opium extracts in 1805 that is now known to be the alkaloid *morphine*. In 1815, Michel E. Chevreul (France; 1786–1889) isolated a material from skeletal muscle now known to be *creatine*, which has been used as a dietary supplement despite the observation that it can cause kidney damage and muscle cramping. He isolated *butyric acid* from rancid butter. He also elucidated the structure of simple soaps, which are salts of *fatty acids*. A fatty acid has the structure RCOOH, where "R" is a long chain of carbon atoms with hydrogen atoms on each carbon (Section 18.12). Between 1818 and 1820, Pierre J. Pelletier (France; 1788–1842) and Joseph Caventou (France; 1795–1877) isolated a poisonous alkaloid from Saint-Ignatius'-beans (*S. ignatii)* now known to be *strychnine* [found in the seeds of the nux vomica tree (*S. nux-vomica*) and also from related plants of the genus *Strychnos*]. The practice of isolating specific compounds (now known to be organic compounds) from natural sources continues today.

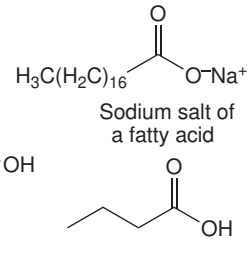
In the structures of matrine, morphine, and strychnine, some of the lines used for chemical bonds have been replaced with *solid wedges* or *dashed lines*. These are used to indicate the three-dimensional spatial relationship of atoms and groups within a molecule. The solid wedge indicates that the group is projected *in front of the plane* of the page, and the dashed line indicates that the group is projected *behind the plane* of the page. This three-dimensional representation correlates with the spatial relationship of the atoms or groups and will be used throughout this book. This structural feature is known as the *stereochemistry* of an atom or group (Chapter 9).



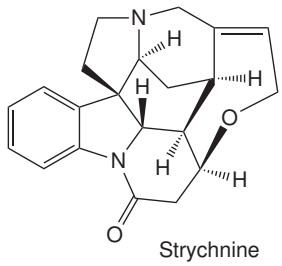
Morphine



Creatine

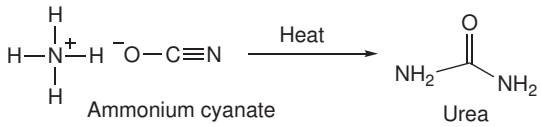


Butyric acid



Strychnine

In 1807, a Swedish chemist named Jöns J. von Berzelius (Sweden; 1779–1848) described the substances obtained from living organisms as *organic compounds*. He proposed that they were composed of only a few selected elements, including carbon and hydrogen. All organic compounds known at that time had been isolated from living organisms, and Berzelius and Charles F. Gerhardt (France; 1816–1856) described what was known as the *vital force theory*. This theory subscribed to the notion that "all organic compounds arise with the operation of a vital force inherent to living cells." The vital force theory was widely believed at the time. In 1828 Friedrich Wöhler (Germany; 1800–1882) synthesized the organic molecule urea from chemicals that had not been obtained from living organisms. Wöhler heated ammonium cyanate, and urea was isolated as the product. Urea is an organic compound that is a component of urine and also a component of bird droppings (commonly used for centuries as fertilizer). This work, along with that of others, demonstrated the fallacy of the vital force theory because it showed that an organic compound could be obtained from a source that was not associated with a living organism. However, it was not until Pierre Eugene-Marcellin Berthelot (France; 1827–1907) showed that all classes of organic compounds could be synthesized that the vital force theory finally disappeared.



By the middle of the 19th century, chemists were beginning to understand that organic molecules were discreet entities that could be prepared in the laboratory. The structures of these compounds (how the atoms are connected together) had to be determined before they could prepared, however, and structure determination posed many problems. Aleksandr M. Butlerov (Russia; 1828–1886) introduced the term *chemical structure* in 1861. In 1859, August Kekulé (Germany; 1829–1896) suggested the idea of discrete *valence bonds*. Until that time, there was no accepted method to determine how atoms in a molecule were arranged in a molecular structure. The idea of *valence*, which is how many bonds a given atom can form to remain neutral, was introduced by C.W. Wichelhaus (1842–1927) in 1868. It was actually Jacobus H. van't Hoff (Netherlands; 1852–1911) and Joseph A. Le Bel (France; 1847–1930) who deduced that when carbon appeared in organic compounds, it was connected to four other atoms, and the atoms around carbon assumed a *tetrahedral shape.* In other words, carbon is joined to other elements by *four chemical bonds*.

In the 19th century, the concept of a bond was vague and largely undefined. It was not until 1916 that Gilbert N. Lewis (USA; 1875–1946) introduced the modern concept of a bond, *formed by sharing two electrons.* He called a bond connecting two atoms by two shared electrons a *covalent bond* (Section 3.3). Understanding covalent bonds is essential for an understanding of the structure of an organic molecule. An example is *methane*, with four covalent bonds to carbon represented as a line (C—H).

Each line in the structure connecting the atoms represents a chemical bond as mentioned above for ethanol. If the structure is drawn again using ":" to represent the two shared electrons, this structure is commonly known as a *Lewis electron dot structure*, after G.N. Lewis. In 1923, Lewis suggested that a molecule that accepts an electron pair should be called an acid and a molecule that donates an electron pair should be called a base. Such compounds are called *Lewis acids* and *Lewis bases* to this day (Sections 2.7 and 6.8). Understanding the position of electrons in an organic molecule and how they are transferred is important for an understanding of both the structure and chemical reactions of molecules.

Maria Goeppert-Mayer

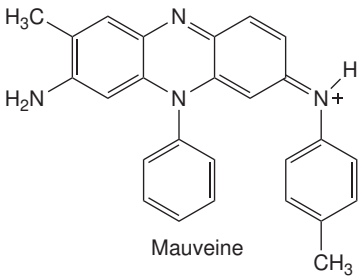
Nobel laureate Maria Goeppert-Mayer (Germany; 1906–1972) formulated the nuclear shell model that protons and neutrons within the nucleus are distributed in shells, according to their energy level (Section 3.1.2). Quantum mechanics was developed by several physicists, including Niels Bohr, Louis de Broglie, Max Born, Werner Heisenberg, Pascual Jordan, Wolfgang Pauli, Erwin Schrödinger, and Paul Adrien Maurice Dirac. Erwin Rudolf Josef Alexander Schrödinger (Austria-Ireland; 1887–1961) was a Nobel Prize-winning physicist who developed the Schrödinger equation, which describes the wave function of a system (Section 3.1.1). *Quantum chemistry* is considered to be the application of quantum mechanics to chemical systems. An early application of quantum mechanics examined the structure of diatomic hydrogen molecules and contributed to a understanding of the chemical bond. In 1925 two physicists, W. Karl Heisenberg (Germany; 1901–1976) and Erwin Schrödinger, described the orbital concept of molecular structure. In other words, they introduced the idea of *orbitals in chemistry and bonding* (Section 3.1). Erich Hückel (Germany; 1896–1980) developed theories of bonding and orbitals. Today, these ideas are combined by saying that electrons reside in orbitals, and orbital interactions control chemical reactions and explain chemical bonding. Joyce Jacobson Kaufman (USA; 1929–2016) advanced quantum chemistry and introduced the concept of conformational topology (see Chapter 8) and applied it to biomedical molecules. She also described a new theoretical method for coding and retrieving certain carcinogenic hydrocarbons.

Joyce Jacobson Kaufman

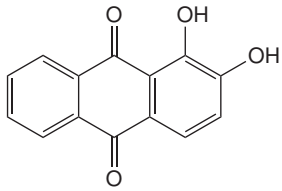
As part of his work on bonding, Hückel speculated on the nature of the C=C unit, although it was Alexander Crum Brown (England; 1838–1922) who first used C=C to represent a "double bond" for ethylene ($H_2C{=}CH_2$) in 1864. The research of Julia Lermontova (Russia; 1846–1919) focused on oil research, and she contributed to the development of a new method for the preparation of hydrocarbons that we now know as alkenes (Section 5.1). In 1862, Emil Erlenmeyer (Germany; 1825–1909) first represented the structure of acetylene with a triple bond, HC≡CH.

Julia Lermontova

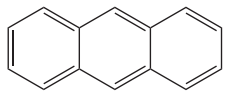
The synthesis of organic molecules began in the mid-19th century, beginning with molecules that have a relatively simple structure. Hermann Kolbe (Germany; 1818–1884) prepared ethane (CH_3CH_3) by electrolysis of potassium acetate ($CH_3CO_2^-K^+$), and Sir Edward Frankland (England; 1825–1899) prepared butane ($CH_3CH_2CH_2CH_3$) from iodoethane (CH_3CH_2I) and zinc (Zn). Charles A. Wurtz (France; 1817–1884) discovered *amines* in 1849, and August W. von Hofmann (Germany-England; 1818–1892) prepared many amines and also their ammonium salts by an acid-base reaction (Chapters 2 and 6) of the amine with a mineral acid. Amines are organic compounds that contain nitrogen and will be described in Section 5.5.3. Alexander W. Williamson (England; 1824–1904) showed that *ethers* contain the C—O—C linkage (Section 5.5.2). He showed that ethers can be prepared from the potassium salt of an alcohol. An *alcohol* contains a C—O—H unit, and the potassium salt is ROK (Section 5.7.1). An *alkyl halide* is represented as RX, where "R" is an *alkyl* or carbon group and X is a halogen, Cl, Br, I (Section 4.3.3). The nomenclature for all of these compounds will be described in Chapters 4 and 5.



Mauveine



Alizarin



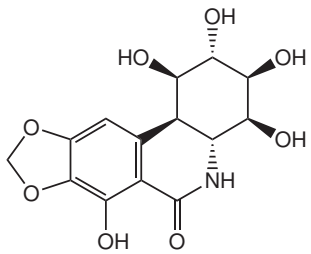
Anthracene

As the structure of more complex molecules and their chemistry is better understood, the synthesis of such molecules has become an important part of organic chemistry. In addition to molecules derived from nature, molecules that were unknown in nature could be envisioned and prepared. In 1863, William H. Perkin (England; 1838–1907) prepared the first commercially useful dye, *mauveine*, which was made from simpler molecules and possessed a purple color that had *not* been previously known. In 1869, the synthesis of a dye was reported by Carle Graebe (Germany; 1841–1927) and Carl Liebermann (Germany; 1882–1914). They prepared the natural dye *alizarin* from *anthracene* (Section 19.9.1), which was

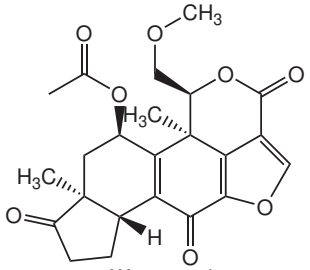
obtained from petroleum distillates. Adolf von Baeyer (Germany; 1835–1917) was the first to synthesize the previously mentioned dye *indigo*. *Aspirin*, also mentioned previously, was first prepared by Felix Hoffmann (Germany; 1868–1946) and later commercialized. The synthesis of the various dyes and of aspirin were important to the economies of both England and Germany in the late-19th and early-20th centuries.

In several structures cited in this chapter, including matrine, quinine, morphine, and strychnine, some of the lines used for chemical bonds were replaced with solid wedges or dashed lines. As previously noted, this three-dimensional drawing represents the *stereochemistry* of atoms or groups (Chapter 9). It was not until the mid- and late-20th century that the stereochemistry of organic compounds could be accurately determined, although its discovery dates to the mid-19th century. In 1848, Louis Pasteur (France; 1822–1895) found that there were two different crystalline forms of the sodium ammonium salt of tartaric acid. These crystals had a different *morphology*, defined here as their external structure. He was able to differentiate these two crystalline forms through a microscope and used a pair of tweezers to physically separate them (Section 9.10). They are examples of *stereoisomers* (Sections 9.1–9.3). This experiment showed that tartaric acid exists as two different compounds, now called *enantiomers* (Section 9.1). Enantiomers are stereoisomers that differ only in their ability to rotate plane-polarized light in different directions. Note that most enantiomers cannot be separated in this manner (Section 9.10). Van't Hoff, mentioned above, found that alkenes existed as a different type of stereoisomer now identified as an *(E)*- or a *(Z)-isomer*, a concept that is discussed in Section 9.8. Many scientists have helped develop the concept of stereochemistry, including John Cornforth (Australia-England 1917–2013), Vladimir Prelog (Yugoslavia-Switzerland; 1906–1998), and Donald J. Cram (USA; 1919–2001).

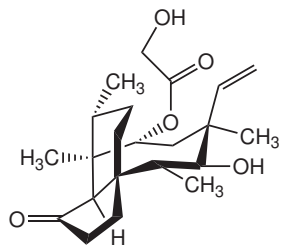
The isolation of organic compounds from natural resources continues to be important. New organic molecules are isolated from terrestrial and marine plants, fungi, bacteria, as well as some animals. G. Robert Pettit (USA, 1929–2021) and S. Morris Kupchan (USA, 1922–1976) are two of many organic chemists who discovered new and interesting organic compounds with potent biological activity against cancer and other human diseases. Inspired in large part by the isolation of new compounds with interesting structures, the synthesis of organic compounds has continued unabated since the 19th century. Over the years, increasingly more complex molecules have been synthesized, as illustrated by *pancratistatin*, *wortmannin*, and *pleuromutilin*. A discussion of the theory and practice of modern organic synthesis and many examples can be found in the book[3] by Nobel laureate Elias J. Corey (USA; 1928–). Many syntheses reported in the last 50 years have contributed enormously to organic chemistry, and ever more complex organic molecules continue to be synthesized. In addition, new chemical reactions as well as new chemical reagents (molecules that induce a chemical transformation in another molecule) have been developed.



Pancratistatin



Wortmannin



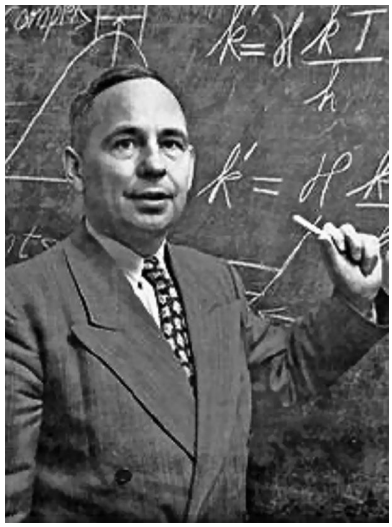
Plueromutilin

Prior to the late 1940s and 1950s, chemists did not really understand *how* chemical reactions occurred. In other words, what happened during the bond-making and bond-breaking processes remained a mystery. Understanding these processes, now called *reaction mechanisms*, required an enormous amount of work in the period of the late 1940s throughout the 1960s, and it continues today. Pioneers in this area include Franz Sondheimer (Germany-England; 1926–1981), Saul Winstein (Canada-USA; 1912–1969), Sir Christopher. K. Ingold

[3] Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, NY, 1989.

(England; 1893–1970), John D. Roberts (USA; 1918–2016), and three Nobel laureates Donald J. Cram (USA; 1919–2001), Herbert C. Brown (England-USA; 1912–2004), and George A. Olah (Hungary-USA; 1927–2017), as well as many others. Nobel laureates Roald Hoffman (Poland-USA; 1937–) and Robert Woodward (USA; 1919–1979), and Kenichi Fukui (Japan; 1918–1998) pioneered the use of orbital symmetry considerations and then frontier molecular orbital theory (Section 22.1) to explain many concerted or synchronous reactions. The concept of *reaction mechanism* allows a fundamental understanding of how organic reactions work. It is perhaps the most important aspect, however, because understanding the mechanism of chemical reactions allows chemists to predict products and reaction conditions without having to memorize everything.

An important part of a mechanism is the identification of transient products in many reactions called *intermediates*. Indeed, an intermediate is a transient and high-energy product that is formed initially but not isolated. An intermediate reacts further to give either other intermediates or a more stable and isolable product (Section 7.2). Reactions have been studied that have reactive ionic intermediates such as a *carbocation*, which is a carbon having three covalent bonds and a positive charge on carbon. Another ionic intermediate is a *carbanion*, which is a carbon having three covalent bonds and a negatively charged carbon atom. A non-ionic intermediate is a carbon *radical*, which is a carbon having three covalent bonds and one extra electron. Methods were developed to ascertain the presence of these intermediates.



Henry Eyring

The concept of reaction *kinetics* was developed for organic chemistry. Reaction kinetics examines how fast products are formed (the *reaction rate*) and how fast reactants disappear. Henry Eyring (Mexico/USA; 1901–1981) was a theoretical chemist who studied chemical reaction rates and intermediates. He developed the absolute rate theory or transition state theory for chemical reactions. This information gives clues as to how the reaction proceeds and what, if any, intermediates may be involved.

How are organic compounds isolated and identified? In early work, inorganic materials (e.g., metal salts and acids or bases) were added to force precipitation of organic compounds. In other cases, liquids were distilled from a mixture or solids were crystallized. In the 1950s, Nobel laureates Archer J.P. Martin (USA; 1910–2002) and Richard Synge (England; 1914–1994) developed the concept of *chromatography*. This technique allowed chemists to conveniently separate mixtures of organic compounds into individual components.

The origins for determining the mass of compounds dates to the 1890s. Instruments were developed that could exploit this concept. Bombarding an organic molecule with a high energy electron beam induces fragmentation of that molecule. Identifying these fragments gives important structural formation. This technique is known as *mass spectrometry* (MS),

built on the accomplishments of Arthur J. Dempster (Canada-USA, 1886–1990). This methodology has been greatly expanded and modified in recent years to become a very powerful tool for structural identification of organic molecules, including the field of *proteomics*, which is used for structural evaluation of proteins.

Mary Elliott Hill

Light has always been an important tool in chemistry, as will be described in Chapter 13. Both *ultraviolet spectroscopy* and *infrared spectroscopy* are major tools for the identification of organic compounds. In the early mid-20th century, ultraviolet (UV) light was shown to interact with organic molecules at certain wavelengths. Mary Elliott Hill (USA; 1907–1969) worked on the properties of ultraviolet light and developed analytic methodology to track the progress of chemical reactions that utilized ultraviolet spectrophotometry. In the 1940s and 1950s, molecules were exposed to infrared (IR) light, and individual molecules were found to absorb only certain wavelengths. Alma Levant Hayden (USA; 1927–1967) was an American chemist who used infrared and other techniques for analyzing chemicals. Identification of the wavelengths of light absorbed can be correlated with structure, a major step in the structure elucidation of organic molecules.

Alma Levant Hayden

It was discovered in the late 1940s that some atoms in organic molecules interact with electromagnetic radiation at wavelengths in the radio signal range if the molecules are suspended in a strong magnetic field. Initially, it was shown that hydrogen atoms in an organic molecule interacted with the radio signal and the magnetic field. The connectivity of different hydrogen atoms in an organic molecule can be identified, allowing the chemical structure to be puzzled together. This technique is now known as *nuclear magnetic resonance* (*NMR*) *spectroscopy* and it is one of the most essential tools for an organic chemist. With the power of modern computers, NMR analysis is used to determine the number and type of carbon, nitrogen, fluorine, and lithium atoms, as well as any other atoms in an organic molecule. Stable but not always the most abundant natural isotopes of atoms are used in NMR: ^{13}C, ^{15}N, ^{19}F, and ^{6}Li for example. Structural information on large enzyme/inhibitor complexes

can be obtained using NMR techniques. Mildred Cohn (USA; 1913–2009) studied chemical reactions within animal cells, pioneering the use of nuclear magnetic resonance spectroscopy (NMR) to study enzyme reactions and enzymatic catalysis. It is noteworthy that the important medical tool MRI (magnetic resonance imaging) is in reality an NMR technique that was developed in the 1970s. Note that MRI was developed at the height of the Cold War. It was decided that the word "nuclear" would be kept out of the technique name. The focus was kept on magnets to keep from alarming the public.

Mildred Cohn

Other tools include *X-ray crystallography*, known for many years and used to determine the crystal structure of molecules. When X-rays interact with a molecule with a distinct crystal structure, the resulting X-ray scattering patterns provide clues to its chemical structure. With modern computer technology, a picture of the structural features of a molecule can be produced, and the methodology has been expanded to include structures of proteins, biologically active small molecules docked to a protein and other biological molecules (see Section 25.6). Dorothy June Sutor (New Zealand; 1929–1990) studied attractive hydrogen bonding interactions involving hydrogen atoms attached to carbon atoms. She used crystallography to study the crystal structure of 1,3,7,9-tetramethyluric acid (theacrine); and she measured the distance between the methyl hydrogen and the oxygen. With modern electron tunneling microscopes, pictures of atoms have been made. Scanning Transmission Electron Microscopes can image objects a million times smaller than a human hair; and they have been used to visualize atoms in molecules.

Dorothy June Sutor

1.2 THE VARIETY AND BEAUTY OF ORGANIC MOLECULES

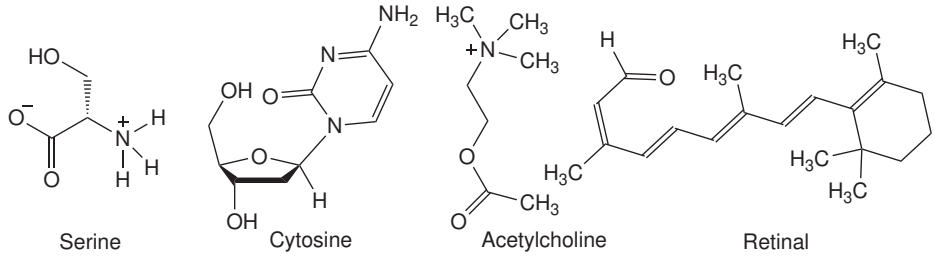
Weisun Tao

Marie Maynard Daly

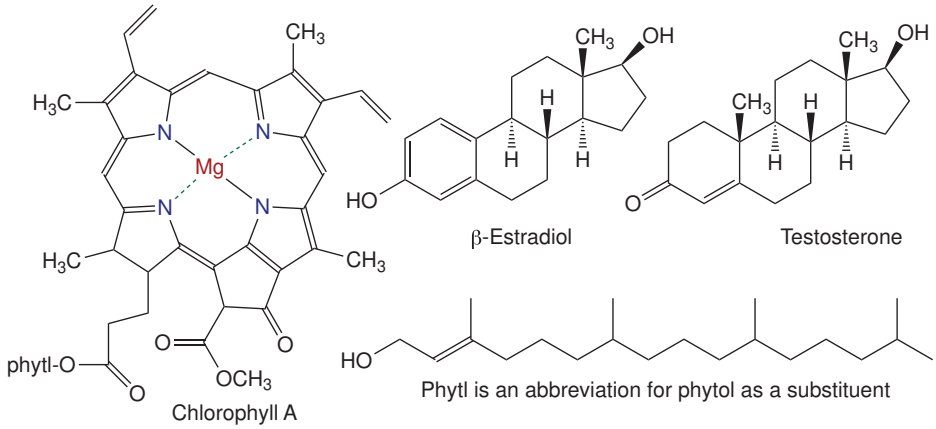
Section 1.1 described the development of organic chemistry as a unique science. Chemical reactions involving organic molecules are a part of the life process. In one sense, much of molecular biology and biochemistry can be categorized as organic chemistry at the cellular level. Proteins (Section 24.5) are large structures composed of many small organic chemical units known as amino acids (e.g., *serine*; Section 24.3). Weisun Tao (China; 1895–1982) was one of the founders of protein chemistry research in China. Enzymes (Section 24.6) are proteins that function as biological catalysts so almost all cellular metabolic processes occur at rates fast enough to sustain life. Marie Maynard Daly (USA; 1921–2003) made important contributions in four areas of research: the chemistry of histones, protein synthesis, the relationship between cholesterol and hypertension, and the update of creatine by muscle cells. The genetic instructions for the development, functioning, growth, and reproduction of all known organisms and many viruses are carried by DNA (deoxyribonucleic acid; Sections 25.5,6) and the RNA (ribonucleic acid; Sections 25.5,6), which is essential for many biological roles in coding, decoding, regulation, and expression of genes. DNA is made up of many nucleobase units such as *cytosine*.

If you are blinking an eye while reading, or moving your arm to turn the page, that nerve impulse from your brain was induced, in part, by one of several important organic molecules

called neurotransmitters. An important neurotransmitter is *acetylcholine*. If you see this page, the light is interacting with a photopigment in your eye called rhodopsin, which releases *retinal* upon exposure to the light. Retinal reacts with a lysine fragment (another amino acid; Section 24.3) of a protein as part of the process known as vision.



Note the similarity of retinal to Vitamin A (Section 1.1), which is simply the reduced form of retinal. Oxidation and reduction are discussed in Chapters 15 and 17. What you see, at least the color associated with what you see, is due to one or more organic molecules in each object. If the leaves on trees and the grass in your yard appear green, one of the chemicals responsible is called *chlorophyll A*. The ------ in the structure of chlorophyll A means there is an interaction between N and Mg (a coordinate bond) rather than a formal covalent N—Mg bond (see Chapter 14).

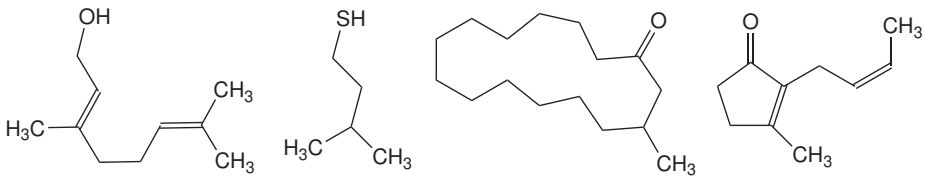


Percy Lavon Julian

There are many other things about human physiology that involve organic chemistry, including the physiological influences of organic chemicals. One of the principal female sex hormones is the steroid β-*estradiol*, and the principle male sex hormone is the steroid *testosterone*. Note that each gender has both hormones (and others), but in quite different proportions. Note also how the chemical structures of estradiol and testosterone have some structural similarities. A steroid (Section 5.4) is a biologically active organic compound composed of four fused rings in a 6:6:6:5 membered ring arrangement. Steroids are important components of cell membranes and are found in plants, animals, and fungi (Section 5.4). Some steroids are hormones, produced by your body to help your organs, tissues, and cells do their jobs. Steroids produced in animals and synthetic steroid drugs include sex hormones, corticosteroids, and anabolic steroids. Many steroids have been produced chemically by synthesis. Percy Lavon Julian (USA; 1899–1975) played a major role in the chemical synthesis of medicinal drugs from plants. He was the first to synthesize physostigmine, and he was a leader in developing industrial syntheses of the steroids progesterone, testosterone, cortisone, and other corticosteroids as well as birth control pills. Luis Ernesto Miramontes Cárdenas (Mexico; 1925–2004) was an organic chemist known as the co-inventor of the progestin norethisterone used in one of the first three oral female contraceptives. He was the first to synthesize norethisterone.

Luis Ernesto Miramontes Cárdenas

Smells are a very important part of life. What are smells anyway? They are the interaction of organic chemicals with olfactory receptors in your nose. If you walk into a garden and smell a rose, one of the chemicals in that aroma is *geraniol*, which interacts with those olfactory receptors. If a skunk has ever sprayed your dog or cat, many organic chemicals are part of the spray, including the mercaptan (also called a thiol; Section 5.5.1) *3-methylbutane-1-thiol*. Clearly, this odor is an unpleasant smelling organic chemical.

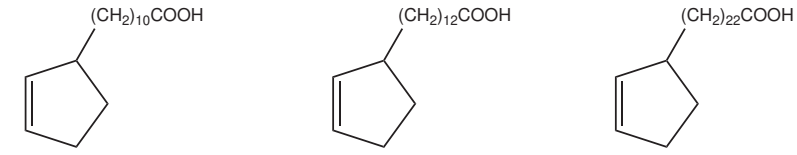


Geraniol 3-Methylbutane-1-thiol Muscone Jasmone

If you are wearing musk cologne, it probably contains *muscone* if it is natural musk (scraped from the hind-quarters of a male musk deer). If you are wearing a jasmine perfume it probably contains *jasmone*, which is part of the essential oil of jasmine flowers. If your feet have not been washed recently, you probably detect a pungent odor which is due to a chemical called *butyric acid*, among other things. Butyric acid ($CH_3CH_2CH_2COOH$) is a simple member of a carboxylic acid (Sections 5.6.3 and 18.1), an organic acid that contains a

carboxyl group (COOH) attached to an alkyl, alkenyl, aryl, or other group, generically represented as an R group. The general formula of a carboxylic acid is therefore R–COOH. In early work that focused on carboxylic acid derivatives, Alice Augusta Ball (USA; 1892–1916) developed the most effective treatment for leprosy known at that time.

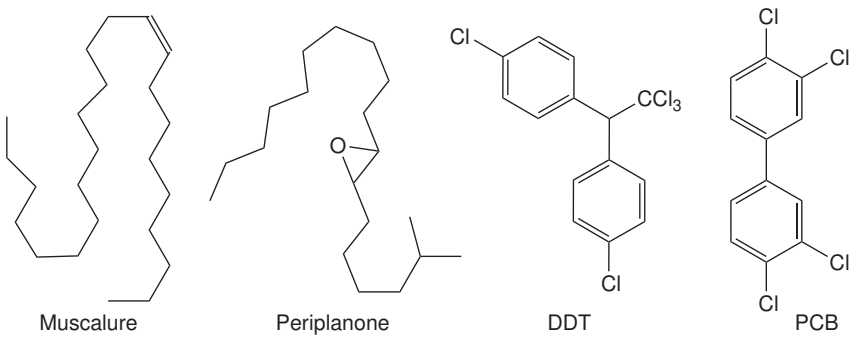
Alice Augusta Ball



Hydnocarpic acid Chaulmoogric acid Gorlic acid

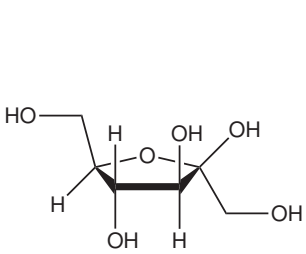
The best available treatment was chaulmoogra oil from the seeds of the *Hydnocarpus wightianus* from India. Ball isolated the ester components from the oil (esters have the formula RCOOR', where R' is derived from an alcohol; Sections 18.2,8). She chemically modified them and developed a technique to make the oil injectable and absorbable by the body. Derivatives of three carboxylic acids are found in chaulmoogra oil: hydnocarpic acid, chaulmoogric acid, and gorlic acid.

If you see a housefly, know that they use a chemical called a pheromone (in this case *muscalure*) in order to attract a mate and reproduce. The American cockroach (hopefully there are none in your dorm) similarly attracts a mate by exuding *periplanone*.

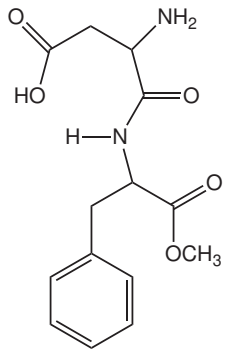


Muscalure Periplanone DDT PCB

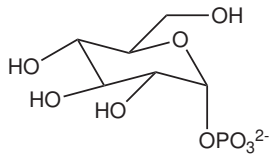
To control insect pests, we sometimes use the pheromone of that pest to attract it to a trap. A pheromone is a secreted or excreted chemical factor that triggers a social response in members of the same species. Alternatively, insecticides such as *DDT* can be used, sometimes with devastating environmental consequences. The chemical name is 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane, but DDT comes from the trade name, *p,p'*-**D**ichloro**D**iphenyl**T**richloroethane.



Fructose



Aspartame



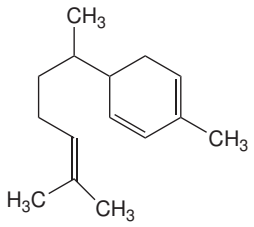
Glucose 1-phosphate
(Cori ester)

Poly**C**hlorinated **B**iphenyls (PCBs) are in the news as environmental pollutants. These *PCB*s are also used in transformers and as stabilizers in poly(vinyl chloride) coatings (PVC coatings). PCBs can leach into soil and water, with serious environmental consequences. Understanding of organic chemistry is important for the development of new and environmentally safer compounds.

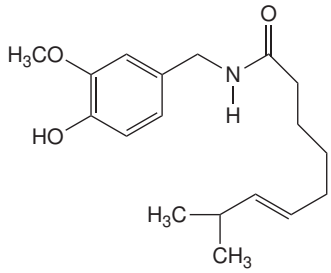

Gerty Theresa Cori

Eating is obviously an important part of life, and the taste of the food is important. What are tastes? They are the interaction of organic chemicals (and other chemicals as well) with receptors on your tongue, although smell is also associated with taste. Are you drinking a soda? Does it taste sweet? If it is not a diet soda, it probably contains a sugar called *fructose*, but if it is a diet drink it may contain one of the "sugar substitutes" (e.g., *aspartame*). Fructose is an example of a carbohydrate (Sections 25.1,2,3). Carbohydrates literally mean hydrates of carbon, and they contain carbon, hydrogen, and oxygen in a 1:2:1 ratio. A carbohydrate is an organic compound found in foods and living tissues that includes sugars, starch, and cellulose. Many carbohydrates are broken down to release energy in the animal body. Gerty Theresa Cori (Austro-Hungary/USA; 1896–1957) was

a biochemist who won the Nobel Prize in medicine for her work leading to the discovery of the course of the catalytic conversion of glycogen. She helped discover the so-called *Cori ester*, *glucose-1-phosphate*, an intermediate compound in frog muscles that enabled the breakdown of glycogen. She helped establish the compound's structure, identified the enzyme *phosphorylase* that catalyzed its chemical formation, and showed that the Cori ester is the beginning step in the conversion of the carbohydrate glycogen into glucose.

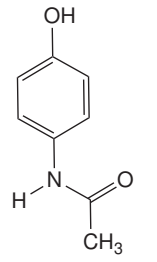


Zingiberene

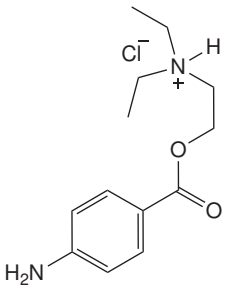


Capsaisin

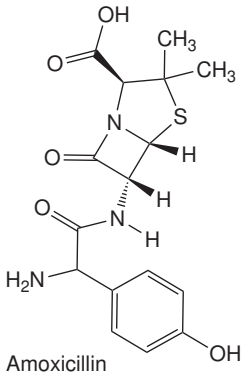
Different chemicals in different foods have their own unique tastes. Do you like the taste of ginger? The active ingredient that gives ginger (from ginger root, *Zingiber officinale* Roscoe) its "spicy" taste is an organic compound called *zingiberene*. Do you like the taste of red chili peppers? If so, the "hot" taste is due to an organic chemical called *capsaicin*. These chemicals interact with your taste buds to produce each characteristic taste. Capsaicin is also found in some topical ointments and creams used to alleviate symptoms of arthritis and muscular aches.



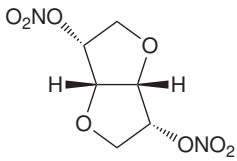
Acetaminophen



Novocain



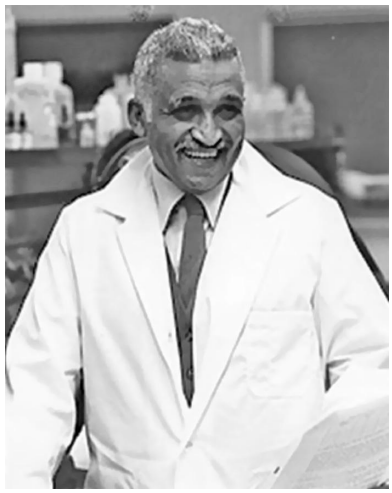
Amoxicillin



Isosorbide dinitrate

Sir Prafulla Chandra Ray

Most medicines used today are organic chemicals. Do you have a headache after reading all of this stuff? If so, you are probably looking for a bottle of aspirin. An alternative is *acetaminophen*, better known as Tylenol. Have you been to the dentist recently? If so, you might have had a shot of *Novocaine* (procaine hydrochloride) so you would not feel the pain (it is a local anesthetic). If you have recently been ill, you may have been given a prescription for an antibiotic from your physician. Commonly prescribed antibiotics include the penicillin *amoxicillin* or a tetracycline antibiotic (e.g., *aureomycin*). Nitrate compounds are used for treating or preventing heart pain (angina, chest pain) caused by heart disease, usually of the arteries in the heart. Common nitrate medicines include *isosorbide dinitrate* and isosorbide mononitrate. Sir Prafulla Chandra Ray (India; 1861–1944) contributed to understanding nitrite chemistry. His work focused on nitrites and hyponitrites of different metals, and on nitrites of ammonia and organic amines.



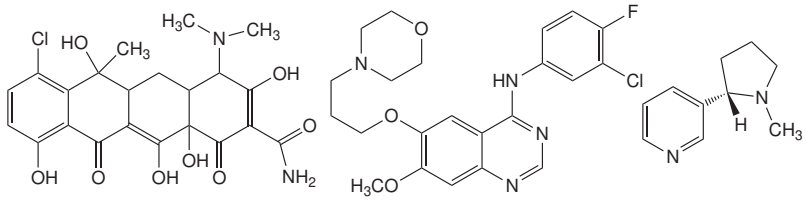
Samuel Proctor Massie, Jr.

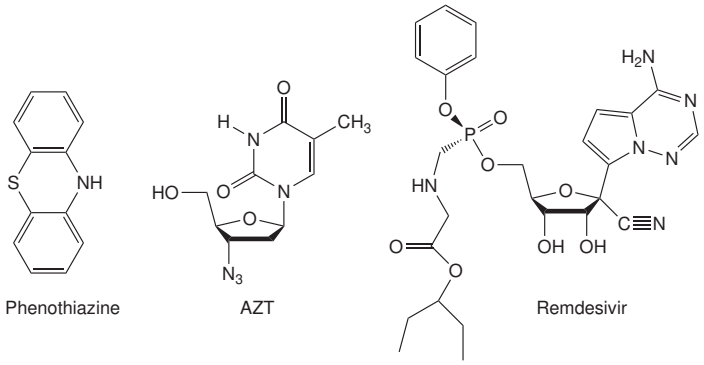
There are many devastating diseases that afflict humans and myriad drugs have been developed to treat many of them. Has a friend or relative been treated for cancer? *Gefitinib* was approved by the FDA in 2003 for the treatment of locally advanced or metastatic non-small-cell lung cancer in patients, but who did not respond to platinum-based and/or docetaxel chemotherapy. Do you smoke? If so, you are breathing in *nicotine* as well as many other organic compounds into your lungs, which then make their way into your bloodstream. *Azidothymidine (AZT)* is used to treat HIV, the virus that causes AIDS (acquired immunodeficiency syndrome). Samuel Proctor Massie, Jr. (USA; 1919–2005) was a chemist who made major contributions to the development of therapeutic drugs, including *phenothiazine*. Phenothiazine is one member of a class of agents exhibiting antiemetic, antipsychotic, antihistaminic, and anticholinergic activities. During the recent pandemic one of the anti-viral medications used to treat some patients affected by COVID-19 is *remdesivir*, whose structure is shown.

Asima Chatterjee

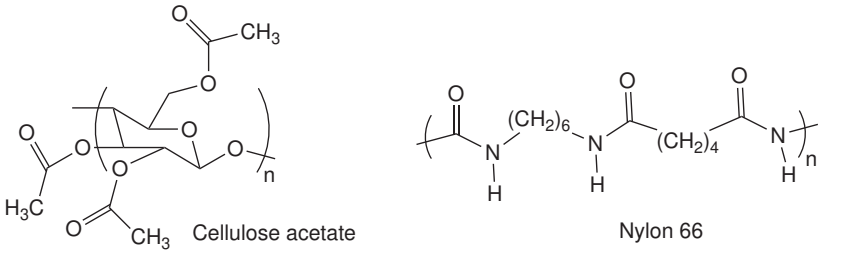
Many drugs have been developed based on the structures of natural alkaloids. Asima Chatterjee (India; 1917–2006) was noted for her work in the fields of organic chemistry and phytomedicine and she worked with vinca alkaloids, developed anti-epileptic, and anti-malarial drugs. Her work focused primarily on alkaloids.

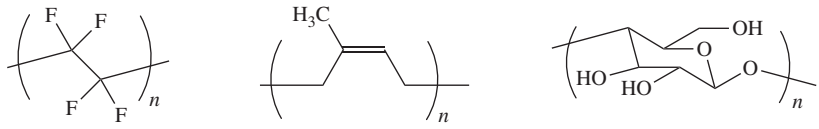
Finally, there are organic molecules that touch vast areas of your life, often in subtle ways. When I say they touch you, I mean that quite literally. Are you wearing clothes? If so, you might be wearing a synthetic blend of cloth made from a polymer, rayon (*cellulose acetate*). A polymer is a large molecule made by bonding many individual units together.

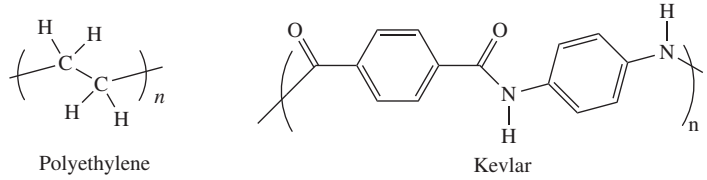




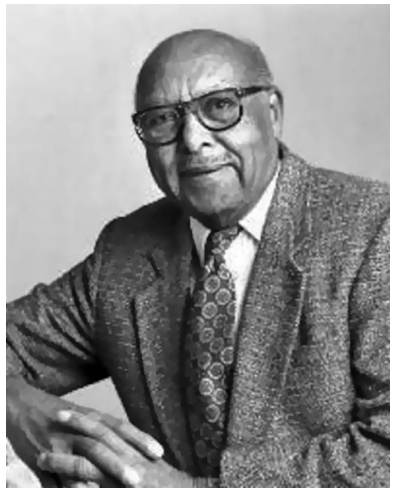
The *"n"* beside the bracket represents the number of repeating units, which is common nomenclature for all polymers. You might be wearing Nylon, specifically something made from *Nylon 6-6*. There are several types of Nylon, a family of synthetic polymers composed of polyamides. Many things are made of Nylon, including gears for fine machines and guitar strings for classical guitars.







Stephanie Louise Kwolek



Walter Lincoln Hawkins

Have you ever heard of *Teflon*? This polymer finds uses in many machines and devices that you use every day. Natural rubber is a polymer obtained from the sap of certain trees, and it is used for automobile tires and other things. Nowadays, tires have a more complex composition, but natural rubber is *poly(isoprene)*, obtained from latex by tapping certain trees. You might be using a piece of paper to describe your thoughts about organic chemistry at this moment. If so, you are probably writing on something with *cellulose* in it. Cellulose is the main constituent of wood fiber, and it is found in many plants, including trees. When you crumple up the paper and throw it into a "plastic" waste container (Section 10.11), that container might be made of *poly(ethylene).* Many pipes and "plastic" wrap are made from poly(ethylene). Stephanie Louise Kwolek (USA; 1923–2014) discovered the first of a family of synthetic fibers of exceptional strength, *Kevlar*, which is *poly(paraphenylene terephthalamide)*. Walter Lincoln Hawkins (USA; 1911–1992) made significant contributions to polymer chemistry. He worked at Bell Laboratories and was a key player in the design of a long-lasting plastic and a polymer-based cable sheath for telephone cables. Later in his career he shifted his research focus towards minimizing plastic waste.

A lot of structures have been thrown at you. Why? Organic chemistry is all around you and it is an integral part of your life. Understanding these things will help as you move into the program of your dreams. Such an understanding can also help you make informed choices in problems and issues that will confront you throughout your life. The journey begins here. Good luck!

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-2.php

2

Why Is an Acid–Base Theme Important?

A study of acid and base chemistry is fundamental to organic chemistry. The understanding of many reactions can be predicted by the application of acid-base principles. To begin, this chapter will review the principles of acid-base reactions found in general chemistry.

You should know the following points from standard general chemistry courses:

- Define and recognize the structures of simple Brønsted–Lowry acids and bases.
- Define and recognize the structures of simple Lewis acids and bases.
- Understand the definitions of a conjugate acid and a conjugate base.
- Understand the fundamentals of acid-base strength in aqueous media.
- Understand K_a and pK_a.
- Recognize classical mineral acids and mineral bases.

2.1 TRADITIONAL ACID AND BASE THEORY

Traditional Acid and Base Theory

In 1884, Svante Arrhenius (Sweden; 1859–1927) defined an acid as a material that can release a *proton*, which is a hydrogen ion (H^+) via ionization. A "free" proton does not exist. In water H^+ is actually a hydronium ion, H_3O^+. Using Arrhenius' original definition, a base (then called an alkali) is a material that can release a hydroxide ion (^-OH) in water. Sodium hydroxide in water solution ionizes to hydrated sodium ions and hydrated hydroxide ions. A related definition of acids and bases was reported by Thomas M. Lowry (England; 1874–1936) and Johannes Nicolas Brønsted (Denmark; 1879–1947), independently in 1923. According to this *Brønsted-Lowry definition*, an acid is a material that donates a hydrogen ion, and a base is a material that can accept a hydrogen ion.[1] An acid has an ionizable hydrogen atom, a *proton*. In water, an aqueous solution of hydronium ions is produced. An acid-base reaction is an equilibrium reaction that generates a conjugate acid and a conjugate base. The reaction of hydrated HCl with water, for example, leads to a proton transfer from HCl to water to generate the conjugate acid, the hydronium ion H_3O^+, as well as the conjugate base, the chloride ion. The term hydrated means that each ion is surrounded by water molecules, which is indicated by the subscript (aq).

Water at pH 7 is neutral and the hydrogen ion concentration is 1.0×10^{-7} M. An acid is ionized in water and the concentration of H_3O^+ ions is $> 1.0 \times 10^{-7}$ M. The mineral acids HCl, HBr, HI, H_2SO_4, HNO_3, H_3PO_4, and $HClO_4$ are all strong acids that give a high concentration of H_3O^+ ions. Bases are ionized in water, and there is a decrease in the concentration of

[1] Lowry, T.M. *Chemistry and Industry* 1923, 42, 43–47; Brønsted, J.N. *Recueil des Travaux Chimiques* 1923, 42, 718–728.

DOI: 10.1201/9781003174929-2

hydrogen ions, $< 1.0 \times 10^{-7}$ M. Common strong bases include NaOH (soda lye), KOH (potash lye), LiOH, CsOH, $Mg(OH)_2$, $Ca(OH)_2$, and $Ba(OH)_2$. Weak acids and weak bases will only partially ionize in water relative to the strong acids or bases.

2.1 Write out the structures of hydrochloric acid, hydrobromic acid, sulfuric acid, and nitric acid. Show the lone electron pairs.
2.2 What is the conjugate base formed when HNO_3 reacts with NaOH?

Weak acids are defined as solutes that partially ionize in a reaction with water molecules. Simple examples of weak acids include hydrofluoric acid (HF), nitrous acid (HNO_2), sulfurous acid (H_2SO_3), and phosphoric acid (H_3PO_4). Many common organic acids are weak acids. Examples include acetic acid (CH_3COOH), butanoic acid ($CH_3CH_2CH_2COOH$), and formic acid (HCOOH). The structure and properties of these carboxylic acids will be discussed in Sections 5.6.3 and 18.1,2. Weak bases are defined as solutes that partially ionize in a reaction with water molecules. An example is ammonia, which reacts with an acid to give the ammonium cation. The most common type of organic base is probably an amine, discussed in Section 5.5.3. An amine has the structural fragments CNH_2, C_2NH, or C_3N, where each "C" represents a carbon group. Amines are weak bases when compared to mineral bases. Amines such as methanamine (CH_3NH_2) and trimethylamine [*N*,*N*-dimethylmethanamine, $(CH_3)_3N$]) react with an acid, HX, to form ammonium salt conjugate acids: $[CH_3NH_3]^+X^-$ and $[(CH_3)_3NH]^+X^-$, respectively, where X is usually a halide counterion.

2.3 In the reaction of nitric acid and KOH, which atom in nitric acid (HNO_3) accepts the electron pair from the base, and which atom in KOH donates the electrons to that proton?
2.4 If carbonic acid (H_2CO_3) reacts with a suitable base, what is the conjugate base of this reaction?

How are the Two Acid-Base Definitions Related?

2.2 THERE ARE TWO ACID-BASE DEFINITIONS: HOW ARE THEY RELATED?

As noted in Section 2.1, a *Brønsted-Lowry acid* is defined as a proton donor, and a *Brønsted-Lowry base* is a proton acceptor. In 1923, Gilbert N. Lewis (USA; 1875–1946) proposed an alternative definition of acids and bases, with a focus on transfer of electrons from one species to another. A *Lewis acid* is defined as a species that accepts an electron pair from a *Lewis base*, which is defined as an electron-pair donor. There may be confusion about how these two different definitions are related, not just how they differ. When HCl reacts with water, for example, the Brønsted-Lowry definition states that the proton (H^+) is "donated" to water, forming the hydronium ion. In this reaction, the oxygen atom of the water "accepts" the proton. How does an oxygen accept a proton?

2.5 If HCl were to react with ammonia rather than water, which atom accepts the proton?

In the acid-base reaction of water with a proton (H^+), the oxygen atom in water "accepts" the proton to form the hydronium ion. To form the H—O bond in a hydronium ion the oxygen atom *donates* two electrons to H^+. The H—O bond is known as a σ-covalent bond, which *requires two shared electrons* (Section 3.3). In the reaction of water with H^+, the oxygen atom reacts as a *base and* "accepts" a proton by donating two electrons to H^+ to form the new bond. Therefore, a Brønsted-Lowry base accepts a proton, by donating two electrons to that proton. A Lewis base is defined by donating two electrons to an atom other than a proton. *In an acid-base reaction, both a Brønsted-Lowry and a Lewis base donate electrons from an*