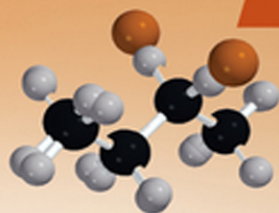
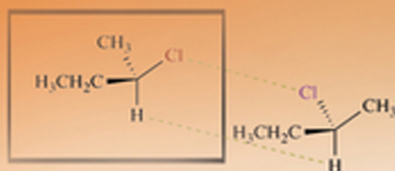


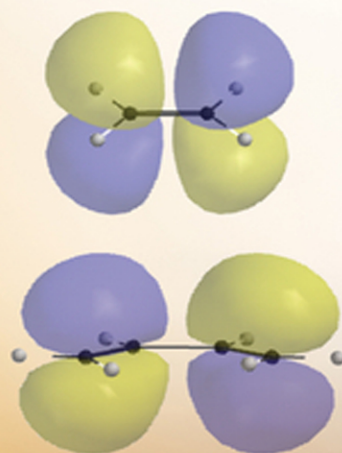
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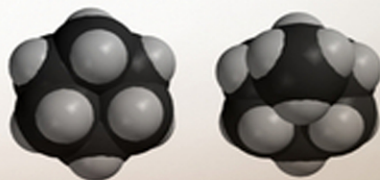
March's Advanced Organic Chemistry



Reactions, Mechanisms, and Structure



Michael B. Smith



WILEY

**MARCH'S ADVANCED
ORGANIC CHEMISTRY**

MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS,
AND STRUCTURE

SEVENTH EDITION

Michael B. Smith
Professor of Chemistry

WILEY

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PREFACE

This seventh edition of *March's Advanced Organic Chemistry* has been thoroughly updated to include new advances in areas of Organic chemistry published between 2005 and 2010. Every topic retained from the sixth edition has been brought up to date if there was activity in that area during that five year period. Changes also include a significant rewrite of most of the book. More than 5500 new references have been added for work published since 2005. As with the sixth edition, many older references were deleted to make room for new ones, and in cases where a series of papers by the same principal author were cited, all but the most recent were deleted. The older citations are usually found by referring to the more recent publication(s). Many of the figures relating to molecular orbitals dated to the 1960s. In all cases possible, they have been replaced by molecular orbitals drawings using Spartan software from Wavefunction, Inc. The fundamental structure of the seventh edition is essentially the same as that of all previous ones.

The goal, as in previous editions is to give equal weight to the three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. A student who has completed a course based on this book should be able to approach the literature directly, with a sound knowledge of modern organic chemistry. Major special areas of organic chemistry: terpenes, carbohydrates, proteins, many organometallic reagents, combinatorial chemistry, polymerization and electrochemical reactions, steroids, and so on, have been treated lightly or ignored completely. The use of this book in the first year of graduate study should help master the fundamentals. It is hoped that this book will lead a student to consult the many excellent books and review articles cited for various topics in order to understand the subject in more detail. Indeed, many of these topics are so vast, they cannot be explained completely in this book.

The organization is based on reaction types, and a relatively few principles suffice to explain nearly all of them despite the large number of organic reactions. Accordingly, the reactions-mechanisms section of this book (Part II) is divided into 10 chapters (10–19), each concerned with a different type of reaction. In the first part of each chapter, the appropriate basic mechanisms are discussed along with considerations of reactivity and orientation, while the second part consists of numbered sections devoted to individual reactions, where the scope and the mechanism of each reaction are discussed. Numbered sections are used for the reactions and are set in boldface. Since the methods for the preparation of individual classes of compounds (ketones, nitriles, etc.) are not treated all in one place, an updated and revised index has been provided (Appendix B) by use of which the synthesis of a given type of compound will be found. It is important to note that the numbers for each reaction in the 7th edition are *different* from editions 1–5 in many cases, but are the same as found in the 6th edition. For this reason, a correlation table is included at the end of this Preface that directly correlates the sections found in the 5th edition with the new ones in both the 6th and 7th editions.

The structure of organic compounds is discussed in Chapters 1–5 (Part I). This section provides a necessary background for understanding mechanisms and is also important in its own right. The discussion begins with chemical bonding (Chapt. 1) and ends with a chapter on stereochemistry (Chapt. 4). Two chapters follow (Chapt 6–7) on reaction mechanisms in general, one for ordinary reactions and the other for photochemical reactions. Part 1 concludes with two more chapters (Chapt 8 and 9) that give further background to the study of mechanisms.

The IUPAC names for many organic transformations are included, first introduced in the 3rd edition. Since then the rules have been broadened to cover additional cases; hence more such names are given in this edition. Furthermore, International Union of Pure and Applied Chemistry (IUPAC) has now published a system for designating reaction mechanisms, and some of the simpler designations are included.

Appendix A is devoted to the literature of organic chemistry.



In treating subjects as broad as structure, reactions, and mechanisms of organic chemistry, it is impossible to cover each topic in great depth, and this would not be desirable even if possible. This book is intended to point the reader to the primary literature of the areas it covers. To this end, there are >20,000 references to original papers. Secondary literature sources including reviews, books, and monographs have been included as well. Appendix A provides a brief introduction to using computer-based search engines (e.g., *Reaxys*[®] and *SciFinder*[®]).

Although basically designed as a reference text for a one-year course on the graduate level, this book can also be used in advanced undergraduate courses, but only after completion of a one-year course in organic chemistry. A one year course in both inorganic and physical chemistry would be most helpful. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material and greatly profit from a representation of the material if it is easily accessible. The material in the first nine chapters, particularly Chapters 1, 2, 4, 6, and 8 may be helpful for reviewing such material when this book is used in connection with a course.


This book is probably most valuable as a reasonably up-to-date reference work. Students preparing for qualifying examinations and practicing organic chemists will find that Part II contains a survey of what is known about the mechanism and scope of a large number of reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed.

For units of energy, IUPAC mandates joules, and many journals do use this unit exclusively. However, organic chemists who publish in United States journals commonly use calories. Virtually all energy values are presented in both calories and joules. Although IUPAC does not recommend angstrom units for bond distances, but rather picometers (pm), a vast number of bond distances published in the literature are in angstrom units, and this book therefore uses angstrom units.

I would like to acknowledge the contributions of those chemists cited and thanked by Professor March in the first-four editions, and those I thanked in the 5th and 6th editions. This book would not be possible without their contributions. For the 7th edition, I thank Lou Allinger for pointing out the deficiencies in the hyperconjugation section, and graciously helping me write the new section appearing in this new edition. I thank Warren Hehre for his invaluable help in calculating and presenting the molecular orbital drawings using Spartan. I also thank Adrian Shell (Elsevier) for facilitating the transfer of material relating to the program *Reaxys*, discussed in Appendix A. I thank the many people who have contributed comments or have pointed out errors in the 6th edition that were

HMO	Hückel molecular orbital	
HMPA	Hexamethylphosphoramide	$(\text{Me}_2\text{N})_3\text{P}=\text{O}$
HMPT	Hexamethylphosphorus triamide	$(\text{Me}_2\text{N})_3\text{P}$
^1H NMR	Proton nuclear magnetic resonance spectroscopy	
HOMO	Highest occupied molecular orbital	
HPLC	High-performance liquid chromatography	
HSAB	Hard-Soft Acid-Base	
IBX	<i>o</i> -Iodoxybenzoic acid	
<i>i</i> -Pr	Isopropyl	$-\text{CH}(\text{Me})_2$
IR	Infrared spectroscopy	
IUPAC	International Union of Pure and Applied Chemistry	
ISC	Intersystem crossing	
LCAO	Linear combination of atomic orbitals	
LICA	Lithium <i>N</i> -isopropyl- <i>N</i> -cyclohexylamide	
(LIPCA)		
LDA	Lithium diisopropylamide	$\text{LiN}(\textit{i}\text{-Pr})_2$
LHMDS	Lithium hexamethyl disilazide	$\text{LiN}(\text{SiMe}_3)_2$
LTMP	Lithium 2,2,6,6-tetramethylpiperidide	
LUMO	Lowest unoccupied molecular orbital	
Mcpba	<i>m</i> -Chloroperoxybenzoic acid	
Me	Methyl	$-\text{CH}_3$ or Me
MEM	β -Methoxyethoxymethyl	$\text{MeOCH}_2\text{CH}_2\text{OCH}_2-$
Mes	Mesityl	2,4,6-tri-Me- C_6H_2
min	minutes	
MMPP	Magnesium monoperoxyphthalate	
MO	Molecular Orbital	
MOM	Methoxymethyl	MeOCH_2-
Ms	Methanesulfonyl	MeSO_2-
MTO	Methyl trioxorhenium	
NBS	<i>N</i> -Bromosuccinimide	
NCS	<i>N</i> -Chlorosuccinimide	
NHS	<i>N</i> -Hydroxysuccinimide	
NIS	<i>N</i> -Iodosuccinimide	
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide	
NMP	<i>N</i> -Methylpyrrolidinone	
NMR	Nuclear magnetic resonance	
NOESY	Nuclear overhauser effect spectroscopy	
NOE	Nuclear overhauser effect	
Nu (Nuc)	Nucleophile	
OBs	<i>O</i> -(4-Bromophenyl)sulfinate	
Oxone [®]	2 $\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$	
	Polymeric backbone	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Polyethylene glycol	
PES	Photoelectron spectroscopy	
Ph	Phenyl	
PhH	Benzene	
PhMe	Toluene	

xxiv COMMON ABBREVIATIONS

PIFA	Phenyliodine (III)-bis-(trifluoroacetate)	
PPHF	Pyridinium poly(hydrogen fluoride)	
PMHS	Polymethylhydrosiloxane	
Pr	<i>n</i> -Propyl	$-\text{CH}_2\text{CH}_2\text{CH}_3$
Py	Pyridine	
Quant	Quantitative yield	
Red-Al	$[(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{AlH}_2]\text{Na}$	
ROESY	Rotating-frame NOE spectroscopy	
rt	Room temperature	
<i>s</i> BuLi	<i>sec</i> -Butyllithium	$\text{CH}_3\text{CH}_2\text{CH}(\text{Li})\text{CH}_3$
s	seconds	
salen	Bis (salicylidene) ethylenediamine	
sc CO ₂	supercritical CO ₂	
SCF	self-consistent field	
SDS	Sodium dodecyl sulfate	
Sec.	Section(s)	
SET	Single electron transfer	
Siamyl		
(Sia) ₂ BH	Disiamylborane <i>sec</i> -Isoamyl	
SOMO	Singly occupied molecular orbital	
Tr	Tritium	
TBAF	Tetrabutylammonium fluoride	$n\text{-Bu}_4\text{N}^+ \text{F}^-$
<i>t</i> -Bu	<i>tert</i> -Butyl	$-\text{CMe}_3$
TEAB	Tetraethylammonium bromide	
TEBA	Triethylbenzylammonium	$\text{Bn}(\text{Et}_3)_3\text{N}^+$
TED	Tetraethylenediamine	
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy free radical	
TFA	Trifluoroacetic acid (solvent)	CF_3COOH
tfa	Trifluoroacetic acid (ligand)	$(\text{CF}_3\text{CO})_2\text{O}$
Tf (OTf)	Triflate	$-\text{SO}_2\text{CF}_3$ ($-\text{OSO}_2\text{CF}_3$)
THF	Tetrahydrofuran (solvent)	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$
TMS	Trimethylsilyl or tetramethylsilane	$-\text{Si}(\text{CH}_3)_3$
Tol	Tolyl	$4\text{-(Me)C}_6\text{H}_4$
TOSMIC	Toluenesulfonylmethyl isocyanide	
TPAP	Tetrapropylammonium perruthenate	$\text{Pr}_4\text{N}^+ \text{RuO}_4^-$
TPP	Triphenylphosphine (solvent)	
tpp	Triphenylphosphine (ligand)	pPh_3
Ts(Tos)	Tosyl = <i>p</i> -Toluenesulfonyl	$4\text{-(Me)C}_6\text{H}_4\text{SO}_2$
UV	Ultraviolet spectroscopy	
VCD	Vibrational circular dichroism	
VDW	van der Waals	
vis	Visible	
XPS	X-ray photoelectron spectroscopy	

■■■■■ BIOGRAPHICAL STATEMENT

Professor Michael B. Smith was born in Detroit, Michigan in 1946. In 1957, he and his family moved to Madison Heights, Virginia. After graduation from Amherst County high school, he entered Ferrum Jr. College and graduated with an A.A. Professor Smith transferred to Virginia Polytechnic Institute (Virginia Tech), where he did undergraduate research with Professor Harold Bell, and graduated with a B.S in chemistry in 1969. After working as an analytical chemist at the Newport News Shipbuilding and Dry Dock Co. (Tenneco) in Newport News, Virginia for three years, he began graduate studies at Purdue University under the mentorship of Professor Joseph Wolinsky. Professor Smith graduated with a Ph.D. in Organic chemistry in 1977. He spent one year as a faculty research associate at the Arizona State University in the Cancer Research Institute, directed by Professor George R. Pettit, and a second year doing postdoctoral work at the Massachusetts Institute of Technology under the mentorship of Professor Sidney Hecht. In 1979 he began his independent academic career, where he now holds the rank of full professor.

Professor Smith is the author of approximately 90 independent research articles, and 20 published books. The books include the 5th and 6th edition of *March's Advanced Organic Chemistry* (Wiley), volumes 6–12 of the *Compendium of Organic Synthetic Methods* (Wiley), *Organic Chemistry a Two Semester Course* (HarperCollins) into its 2nd edition, and *Organic Synthesis* (Elsevier) in its 3rd edition. A new undergraduate organic chemistry book, *Organic Chemistry: An Acid-Base Approach*, was published in 2011 by the CRC Press.

Professor Smith's current research involves the synthesis and structural verification of lipids obtained from the dental pathogen *Porphyromonas gingivalis*, which show inflammatory activity, induce bone degeneration and are involved in triggering multiple sclerosis. A main area of research is the synthesis of fluorescent dye-heterocyclic conjugates that target hypoxic cancerous tumors, allowing non-invasive fluorescence imaging in the near IR. The synthesis of anti-cancer alkaloids is also ongoing.

INTRODUCTION

This book contains 19 chapters. Chapters 1–9 may be thought of as an introduction to Part II. The first-five chapters deal with the structure of organic compounds. These chapters discuss the kinds of bonding important in organic chemistry, the fundamental principles of conformation and stereochemistry of organic molecules, and reactive intermediates in organic chemistry. Chapters 6–9 are concerned with general principles of mechanism in organic chemistry, including acids and bases, photochemistry, sonochemistry and microwave irradiation, and finally the relationship between structure and reactivity.

Chapters 10–19, which make up Part II, are directly concerned with the nature and the scope of organic reactions and their mechanisms.

