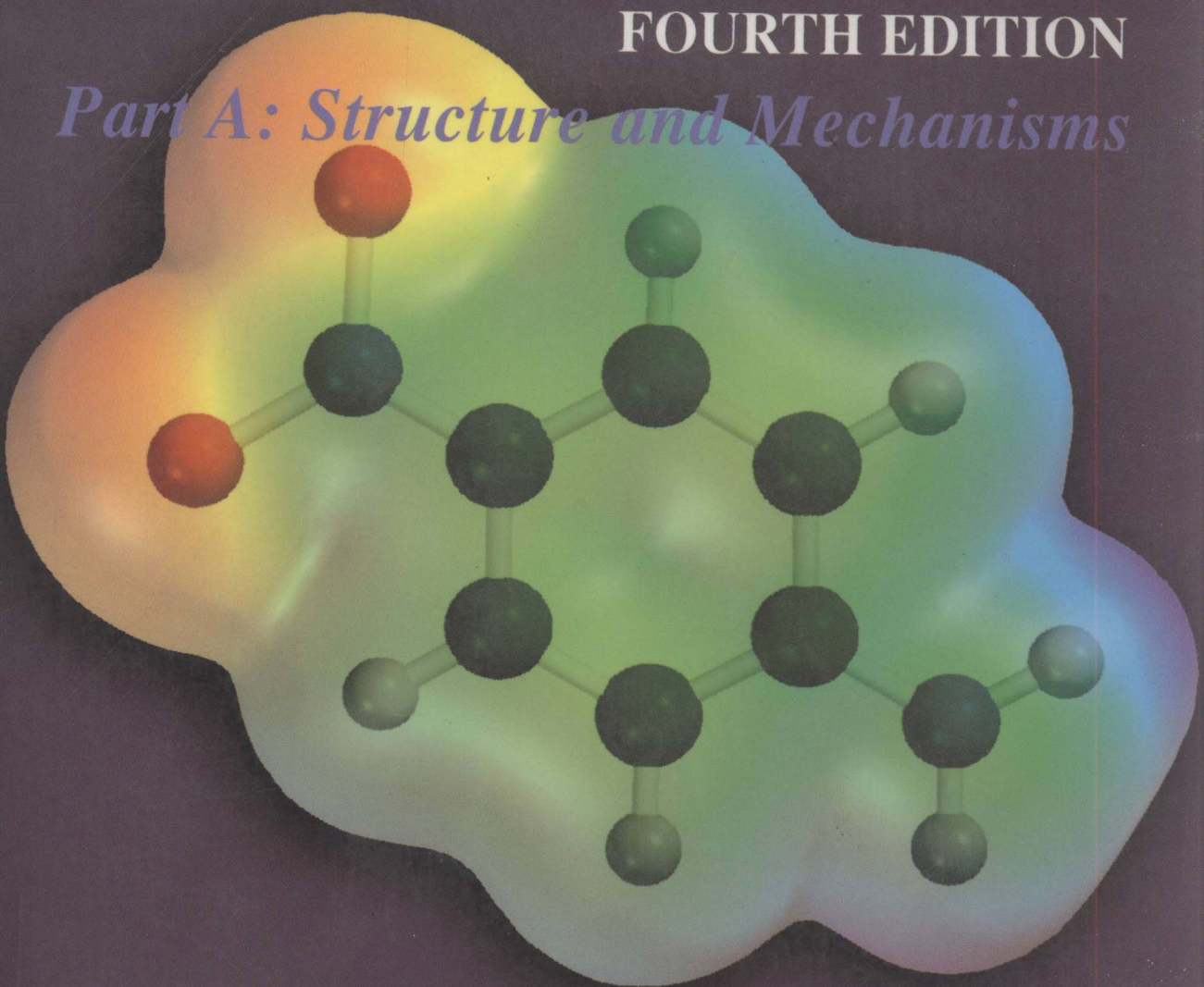


ADVANCED ORGANIC CHEMISTRY

FOURTH EDITION

Part A: Structure and Mechanisms



FRANCIS A. CAREY
and RICHARD J. SUNDBERG

062
C273
E.4
V.1

Advanced Organic Chemistry

FOURTH
EDITION

Part A: Structure and Mechanisms

FRANCIS A. CAREY
and RICHARD J. SUNDBERG

*University of Virginia
Charlottesville, Virginia*



E200201509

Kluwer Academic / Plenum Publishers
New York, Boston, Dordrecht, London, Moscow

Library of Congress Cataloging-in-Publication Data

Carey, Francis A., 1937–

Advanced organic chemistry/Frank A. Carey and Richard J. Sundberg.—4th ed.
p. cm.

Includes bibliographical references and index.

Contents: pt. A. Structure and mechanisms

ISBN 00-306-46242-7 (hard: pt. A)—ISBN 0-306-46243-5 (pbk.: pt. A)

I. Chemistry, Organic. I. Sundberg, Richard J., 1938– II. Title.

QD251.2 .C36 2000

547—dc21

00-027456

ISBN: 0-306-46242-7 (Hardbound)

ISBN: 0-306-46243-5 (Paperback)

©2000, 1990, 1984, 1977 Kluwer Academic/Plenum Publishers
233 Spring Street, New York, New York 10013

<http://www.wkap.nl>

10 9 8 7 6 5 4 3 2

A C.I.P. record for this book is available from the Library of Congress

All rights reserved

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise, without written permission from the Publisher.

Printed in the United States of America

Advanced Organic Chemistry

FOURTH
EDITION

Part A: Structure and Mechanisms

Advanced Organic Chemistry

PART A: Structure and Mechanisms

PART B: Reactions and Synthesis

Preface to the Fourth Edition

The goal of this text is to build on the foundation of introductory organic chemistry to provide students and other readers a deeper understanding of structure and mechanism and the relationships between them. We have provided specific data and examples with which to illustrate the general principles that are discussed. Our purpose is to solidify the student's understanding of the basic concepts, but also to illustrate the way specific structural changes influence mechanism and reactivity.

The first three chapters discuss fundamental bonding theory, stereochemistry, and conformation, respectively. Chapter 4 discusses the means of study and description of reaction mechanisms. Chapter 9 focuses on aromaticity and aromatic stabilization and can be used at an earlier stage of a course if an instructor desires to do so. The other chapters discuss specific mechanistic types, including nucleophilic substitution, polar additions and eliminations, carbon acids and enolates, carbonyl chemistry, aromatic substitution, concerted reactions, free-radical reactions, and photochemistry.

Both the language of valence bond theory and of molecular orbital theory are used in discussing structural effects on reactivity and mechanism. Our intent is to illustrate both approaches to interpretation. A decade has passed since the publication of the Third Edition. That decade has seen significant developments in areas covered by the text. Perhaps most noteworthy has been the application of computational methods to a much wider range of problems of structure and mechanism. We have updated the description of computational methods and have included examples throughout the text of application of computational methods to specific reactions.

References to the primary literature are provided for specific issues of structure, reactivity, and mechanism. These have been chosen to illustrate the topic of discussion and, of course, cannot be comprehensive. The examples and references chosen do not imply any priority of concept or publication. References to general reviews which can provide a broader coverage of the various topics are usually given.

The problems at the end of each chapter represent application of concepts to new structures and circumstances, rather than review of material explicitly presented in the text. The level of difficulty is similar to that of earlier editions, and we expect that many will present a considerable challenge to students. Some new problems have been added in this

edition. References to the literature material upon which the problems are based are given at the end of the book.

The companion volume, Part B, has also been revised to reflect the continuing development of synthetic methodology. Part B emphasizes synthetic application of organic reactions. We believe that the material in Part A and Part B will provide advanced undergraduate and beginning graduate students with a background which will permit them to understand, analyze, and apply the primary and review literature in organic chemistry. We hope that this new edition will continue to serve students and teachers in fostering both an understanding of the structural and mechanistic foundations of organic chemistry and a broad knowledge of the most fundamental reaction types in organic chemistry. We welcome comments and suggestions which can improve the text or correct errors.

F. A. Carey
R. J. Sundberg

Charlottesville, Virginia

Contents of Part B

- Chapter 1. Alkylation of Nucleophilic Carbon. Enolates and Enamines**
- Chapter 2. Reactions of Carbon Nucleophiles with Carbonyl Groups**
- Chapter 3. Functional Group Interconversion by Nucleophilic Substitution**
- Chapter 4. Electrophilic Additions to Carbon–Carbon Multiple Bonds**
- Chapter 5. Reduction of Carbonyl and Other Functional Groups**
- Chapter 6. Cycloaddition, Unimolecular Rearrangements, and Thermal Eliminations**
- Chapter 7. Organometallic Compounds of the Group I and II Metals**
- Chapter 8. Reactions Involving the Transition Metals**
- Chapter 9. Carbon–Carbon Bond-Forming Reactions of Compounds of Boron, Silicon, and Tin**
- Chapter 10. Reactions Involving Carbocations, Carbenes, and Radicals as Reactive Intermediates**
- Chapter 11. Aromatic Substitution Reactions**
- Chapter 12. Oxidations**
- Chapter 13. Planning and Execution of Multistep Syntheses**

Contents of Part A

Chapter 1. Chemical Bonding and Structure	1
1.1. Valence Bond Description of Chemical Bonding.	2
1.1.1. Orbital Hybridization.	4
1.1.2. Resonance	9
1.2. Bond Energy, Polarity, and Polarizability	13
1.2.1. Bond Energies	13
1.2.2. Electronegativity and Polarity	15
1.2.3. Polarizability—Hardness and Softness	20
1.3. Molecular Orbital Theory and Methods	23
1.4. Hückel Molecular Orbital Theory	31
1.5. Qualitative Application of Molecular Orbital Theory	36
1.6. Application of Molecular Orbital Theory to Reactivity	46
1.7. Interactions between σ and π Systems—Hyperconjugation	54
1.8. Other Quantitative Descriptions of Molecular Structure	57
1.8.1. Atoms in Molecules	57
1.8.2. Electron Density Functionals	59
1.8.3. Modern Valence Bond Approaches	64
General References	65
Problems	65
 Chapter 2. Principles of Stereochemistry	 75
2.1. Enantiomeric Relationships	76
2.2. Diastereomeric Relationships	84
2.3. Stereochemistry of Reactions	97
2.4. Prochiral Relationships	105

General References	114
Problems	114

Chapter 3. Conformational, Steric, and Stereoelectronic Effects 123

3.1. Strain and Molecular Mechanics	124
3.2. Conformations of Acyclic Molecules	129
3.3. Conformations of Cyclohexane Derivatives	135
3.4. Carbocyclic Rings Other Than Six-Membered	146
3.5. The Effect of Heteroatoms on Conformational Equilibria	149
3.6. The Anomeric Effect	151
3.7. Conformational Effects on Reactivity	157
3.8. Angle Strain and Its Effect on Reactivity	162
3.9. Relationships between Ring Size and Rate of Cyclization	166
3.10. Torsional and Stereoelectronic Effects on Reactivity	171
General References	177
Problems	177

Chapter 4. Study and Description of Organic Reaction Mechanisms 187

4.1. Thermodynamic Data.	187
4.2. Kinetic Data.	192
4.3. Substituent Effects and Linear Free-Energy Relationships	204
4.4. Basic Mechanistic Concepts: Kinetic versus Thermodynamic Control, Hammond's Postulate, the Curtin-Hammett Principle	215
4.4.1. Kinetic versus Thermodynamic Control	215
4.4.2. Hammond's Postulate	217
4.4.3. The Curtin-Hammett Principle	220
4.5. Isotope Effects	222
4.6. Isotopes in Labeling Experiments	225
4.7. Characterization of Reaction Intermediates	226
4.8. Catalysis by Brønsted Acids and Bases.	228
4.9. Lewis Acid Catalysis.	233
4.10. Solvent Effects	237
4.11. Substituent Effects in the Gas Phase.	243
4.12. Stereochemistry	247
4.13. Conclusion.	248
General References	248
Problems	250

Chapter 5. Nucleophilic Substitution 263

5.1. The Limiting Cases—Substitution by the Ionization (S_N1) Mechanism.	264
5.2. The Limiting Cases—Substitution by the Direct Displacement (S_N2) Mechanism	267
5.3. Detailed Mechanistic Description and Borderline Mechanisms	269

5.4. Carbocations	276
5.5. Nucleophilicity and Solvent Effects	290
5.6. Leaving-Group Effects	295
5.7. Steric and Strain Effects on Substitution and Ionization Rates	298
5.8. Effects of Conjugation on Reactivity	300
5.9. Stereochemistry of Nucleophilic Substitution	302
5.10. Neighboring-Group Participation	309
5.11. Mechanism of Rearrangements of Carbocations	316
5.12. The Norbornyl Cation and Other Nonclassical Carbocations	327
General References	334
Problems	335

Chapter 6. Polar Addition and Elimination Reactions 351

6.1. Addition of Hydrogen Halides to Alkenes	352
6.2. Acid-Catalyzed Hydration and Related Addition Reactions	358
6.3. Addition of Halogens	361
6.4. Electrophilic Additions Involving Metal Ions	369
6.5. Additions to Alkynes and Allenes.	371
6.6. The E2, E1, and E1cb Mechanisms	378
6.7. Regiochemistry of Elimination Reactions.	383
6.8. Stereochemistry of E2 Elimination Reactions	386
6.9. Dehydration of Alcohols	392
6.10. Eliminations Not Involving C—H Bonds	393
General References	398
Problems	398

Chapter 7. Carbanions and Other Nucleophilic Carbon Species 405

7.1. Acidity of Hydrocarbons.	405
7.2. Carbanions Stabilized by Functional Groups.	416
7.3. Enols and Enamines.	425
7.4. Carbanions as Nucleophiles in S_N2 Reactions.	432
General References	439
Problems	440

Chapter 8. Reactions of Carbonyl Compounds 449

8.1. Hydration and Addition of Alcohols to Aldehydes and Ketones.	449
8.2. Addition–Elimination Reactions of Ketones and Aldehydes	456
8.3. Addition of Carbon Nucleophiles to Carbonyl Groups	462
8.4. Reactivity of Carbonyl Compounds toward Addition	470
8.5. Ester Hydrolysis	474
8.6. Aminolysis of Esters	479
8.7. Amide Hydrolysis	481
8.8. Acylation of Nucleophilic Oxygen and Nitrogen Groups	484

8.9. Intramolecular Catalysis	488
General References	495
Problems	496
 Chapter 9. Aromaticity	 509
9.1. The Concept of Aromaticity	509
9.2. The Annulenes	514
9.3. Aromaticity in Charged Rings	524
9.4. Homoaromaticity	529
9.5. Fused-Ring Systems	530
9.6. Heterocyclic Rings	540
General References	543
Problems	543
 Chapter 10. Aromatic Substitution	 551
10.1. Electrophilic Aromatic Substitution Reactions	551
10.2. Structure-Reactivity Relationships	557
10.3. Reactivity of Polycyclic and Heteroaromatic Compounds	568
10.4. Specific Substitution Mechanisms	571
10.4.1. Nitration	571
10.4.2. Halogenation	575
10.4.3. Protonation and Hydrogen Exchange	579
10.4.4. Friedel-Crafts Alkylation and Related Reactions	580
10.4.5. Friedel-Crafts Acylation and Related Reactions	583
10.4.6. Coupling with Diazonium Compounds	587
10.4.7. Substitution of Groups Other Than Hydrogen	588
10.5. Nucleophilic Aromatic Substitution by the Addition-Elimination Mechanism	589
10.6. Nucleophilic Aromatic Substitution by the Elimination-Addition Mechanism	593
General References	597
Problems	597
 Chapter 11. Concerted Pericyclic Reactions	 605
11.1. Electrocyclic Reactions	606
11.2. Sigmatropic Rearrangements	619
11.3. Cycloaddition Reactions	636
General References	651
Problems	651
 Chapter 12. Free-Radical Reactions	 663
12.1. Generation and Characterization of Free Radicals	663

12.1.1.	Background	663
12.1.2.	Stable and Persistent Free Radicals.	664
12.1.3.	Direct Detection of Radical Intermediates	667
12.1.4.	Sources of Free Radicals	672
12.1.5.	Structural and Stereochemical Properties of Radical Intermediates	675
12.1.6.	Charged Radical Species	680
12.2.	Characteristics of Reaction Mechanisms Involving Radical Intermediates . .	683
12.2.1.	Kinetic Characteristics of Chain Reactions.	683
12.2.2.	Structure-Reactivity Relationships	685
12.3.	Free-Radical Substitution Reactions	703
12.3.1.	Halogenation	703
12.3.2.	Oxidation.	706
12.4.	Free-Radical Addition Reactions	708
12.4.1.	Addition of Hydrogen Halides.	708
12.4.2.	Addition of Halomethanes	712
12.4.3.	Addition of Other Carbon Radicals	713
12.4.4.	Addition of Thiols and Thiocarboxylic Acids.	714
12.5.	Halogen, Sulfur, and Selenium Group Transfer Reactions.	714
12.6.	Intramolecular Free-Radical Reactions.	718
12.7.	Rearrangement and Fragmentation Reactions of Free Radicals.	719
12.7.1.	Rearrangement Reactions	719
12.7.2.	Fragmentation.	722
12.8.	Electron-Transfer Reactions Involving Transition-Metal Ions.	724
12.9.	S _{RN} 1 Substitution Processes	727
	General References	733
	Problems	734
Chapter 13.	Photochemistry	743
13.1.	General Principles	743
13.2.	Orbital Symmetry Considerations Related to Photochemical Reactions . . .	747
13.3.	Photochemistry of Carbonyl Compounds	753
13.4.	Photochemistry of Alkenes and Dienes	766
13.5.	Photochemistry of Aromatic Compounds	779
	General References	781
	Problems	781
References to Problems		791
Index		807

Chemical Bonding and Structure

Introduction

Organic chemistry is a broad field which intersects with such diverse areas as biology, medicine and pharmacology, polymer technology, agriculture, and petroleum engineering. At the heart of organic chemistry are fundamental concepts of molecular structure and reactivity of carbon-containing compounds. The purpose of this text is to explore this central core, which is concerned with how the structures of organic compounds are related to reactivity. Reactivity, in turn, determines the methods that can be used for synthesis. Understanding of *structure*, *reactivity*, and *synthesis* can be used within organic chemistry or applied to other fields, such as those named above, which require contributions from organic chemistry. *Structure* includes the description of bonding in organic molecules and the methods for determining, analyzing, and predicting molecular structure. Dynamic aspects of structure, such as conformational equilibria, are also included. Stereochemistry is also a crucial aspect of structure in organic chemistry. *Reactivity* pertains to the aspects of a given structure that determine its chemical transformations. Is the molecule electron-rich or electron-poor? Is it easily reduced or oxidized? What is the distribution of the most reactive electrons? Which bonds are weakest and therefore most likely to engage in reactions? Unlike structure, which is an inherent property of the molecule, reactivity usually describes an interaction with other molecules. Understanding reactivity includes describing the mechanisms, that is, the stepwise process by which reactions occur. Reactivity also encompasses the *stereochemical aspects* of the transformation. *Synthesis* encompasses those activities which are directed toward finding methods that convert existing substances into different compounds. Synthesis involves the control of reactivity to achieve specified transformations. It involves the choice of reagents, catalysts, and reaction conditions that will accomplish a given transformation within the required parameters. In various circumstances, the limiting parameters might include yield, purity of product, stereochemical control, availability or cost of reagents, or safety and environmental consequences. Structure, reactivity, and synthesis are all interrelated.

Synthesis is built on knowledge of both structure and reactivity, and understanding reactivity ultimately rests on detailed knowledge about molecular structure. A firm grounding in the principles of structure and chemical bonding is therefore an essential starting point for fuller appreciation of reactivity and synthesis. In this first chapter, we will discuss the ideas that have proven most useful to organic chemists for describing and organizing facts, concepts, and theories about the structure of organic molecules.

Structural formulas serve as key devices for communication of chemical information, and it is important to recognize the symbolic relationship between structural formulas and molecular structure. The current system of structural formulas arose largely as a result of research done in the last half of the 19th century. Elemental analyses, interrelation of various compounds, and systematic investigation of the reactivity of various "functional groups" permitted chemists to correctly deduce much information about molecular structure. For most molecules, it became possible to draw conclusions as to which atoms were directly connected (*constitution*). Lines drawn between atoms were used to represent direct connections or bonds. It was recognized that the various elements formed a characteristic numbers of bonds. The capacity of an element to form bonds was called valence, and the number of bonds a given element could form was called its *valence number*. These structural deductions predated modern electronic concepts of atomic and molecular structure and the nature of the forces that bind atoms together in molecules. Nevertheless, structural formulas proved to be readily adaptable to description of chemical bonding in terms of electron-pair bonds since the bonds came to symbolize the shared pair of electrons.

The precise description of molecular structure specifies nuclear positions with respect to other nuclei in the molecule and the distribution of the electrons associated with the nuclei. Because chemical properties are primarily determined by the outer shell of valence electrons, chemists focus attention primarily on these electrons. Spectroscopic methods and diffraction methods, especially X-ray crystal structure determination, have provided a large amount of information about atomic positions and bond lengths. Dynamic aspects of molecular structure involving such issues as alternative molecular shapes arising by bond rotations (*conformations*) can also be characterized by spectroscopic methods, especially nuclear magnetic resonance (NMR) spectroscopy. These *experimental methods* for structure determination have been joined by *computational methods*. Computational approaches for calculating molecular structures are based on systematic searching for the most stable arrangement of the atoms having a particular bonding pattern (molecular connectivity). Computational methods can be based on observed relationships between energy and structure (*molecular mechanics*) or on theoretical descriptions of bonding based on quantum chemistry.

Theories of molecular structure attempt to describe the nature of chemical bonding both qualitatively and quantitatively. To be useful to chemists, the bonding theories must provide insight into the properties and reactivity of molecules. The structural theories and concepts that are most useful in organic chemistry are the subject of this chapter. Our goal is to be able to relate molecular structure, as depicted by structural formulas and other types of structural information, such as bond lengths and electronic distributions, to the chemical reactivity and physical properties of molecules.

1.1. Valence Bond Approach to Chemical Bonding

The idea put forth by G. N. Lewis in 1916 that chemical bonding results from a sharing of electron pairs between two atoms was a fundamental advance in bonding

theory.¹ The concept of valence is related to the number of electrons available to each atom and, for the second-row elements, to the “octet rule,” that is, to the stability associated with four pairs of electrons. Lewis’s proposal was put on the sound ground of quantum mechanics by Heitler and London’s treatment of the hydrogen molecule in 1927. This treatment marked the beginning of what we now know as *valence bond theory*.² A central feature of this theory was the conclusion that most of the binding energy between the two atoms at the most stable internuclear separation results from sharing of the electrons between the two nuclei. This conclusion arose in a direct way from the Heitler–London calculations. If electron 1 were constrained to be associated only with nucleus 1, and electron 2 with nucleus 2, then the calculated binding energy was only a small fraction of the experimentally determined bond energy. If this constraint was removed so that the electrons were indistinguishable and permitted to interact equally with both nuclei, the calculated potential energy curve exhibited a deep minimum at the equilibrium internuclear distance. The bonding energy associated with this minimum corresponded quite well with the experimental bond energy. The covalent bond represented by a line in the simple notation $\text{H}-\text{H}$ then takes on more precise meaning. It symbolizes the presence of *two bonding electrons* in the region between the two nuclei. The region of space occupied by an electron is called an *orbital*. In the H_2 molecule, the bonding arises from the two electrons in an orbital formed by overlap of the spherically symmetrical $1s$ atomic orbital of each hydrogen atom, as shown in Fig. 1.1. Similarly, the bonding orbitals of other molecules arise from the atomic orbitals of the constituent atoms.

Application of valence bond theory to more complex molecules involves writing as many plausible Lewis structures as possible that correspond to the correct molecular connectivity. Valence bond theory assumes that the actual molecule is a hybrid of these “canonical forms.” As a simple example, the hydrogen chloride molecule is considered to be a hybrid of the limiting canonical forms $\text{H}-\text{Cl}$, H^+Cl^- , and H^-Cl^+ . In mathematical terms, the molecule can be represented as the weighted combination of the contributing structures. Unfortunately, the extension of this approach to larger molecules results in a large number of canonical structures, which makes both conceptual and computational interpretation difficult. For example, more than 175 individual structures, most with charge separation, can be written for benzene.³ For this reason, qualitative concepts which arise from the valence bond treatment of simple molecules are applied to larger molecules. The key ideas that are used to adapt the concepts of valence bond theory to complex molecules are *hybridization* and *resonance*. In this qualitative form, valence bond theory describes molecules in terms of orbitals that are mainly localized between two atoms. The shapes of these orbitals are assumed to be similar to those of orbitals described by more quantitative

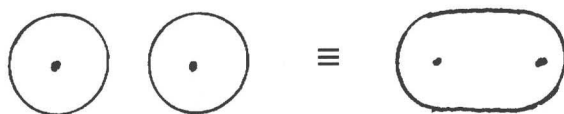


Fig. 1.1. Representation of σ bond of H_2 formed by overlap of $1s$ orbitals.

1. G. N. Lewis, *J. Am. Chem. Soc.* **38**:762 (1916).
2. W. Heitler and F. London, *Z. Phys.* **44**:455 (1927). For a historical review, see M. Simonetta, in *Structural Chemistry and Molecular Biology*, A. Rich and N. Davidson, eds., W. H. Freeman, San Francisco, 1968, pp. 769–782.
3. C. Amovilli, R. D. Harcourt, and R. McWeeny, *Chem. Phys. Lett.* **187**:494 (1991).

treatment of simpler molecules. The properties of complex molecules are regarded as derived from the combination of the properties of the constituent bonds. This conceptual approach is in accord with a large body of chemical knowledge which indicates that structure and reactivity of similar bonds and groups are relatively constant in different molecules.

1.1.1. Orbital Hybridization

The concepts of *directed valence* and *orbital hybridization* were developed by Linus Pauling soon after the description of the hydrogen molecule by the valence bond theory. These concepts were applied to an issue of specific concern to organic chemistry, the tetrahedral orientation of the bonds to tetracoordinate carbon.⁴ Pauling reasoned that because covalent bonds require mutual overlap of orbitals, stronger bonds would result from better overlap. Orbitals that possess directional properties, such as p orbitals, should therefore be more effective than spherically symmetric s orbitals.

The electronic configuration of a carbon atom in its ground state is $1s^2 2s^2 2p^2$, and is not consistent with a simple rationalization of the tetrahedral bonding at carbon. Pauling suggested that four atomic orbitals ($2s$, $2p_x$, $2p_y$, $2p_z$) are replaced by a set of four equivalent *hybrid orbitals*, designated sp^3 . The approximate shapes of these orbitals are shown in Fig. 1.2. Notice particularly that the probability distribution is highly directional for the sp^3 orbitals, with the region of greatest probability concentrated to one side of the nucleus.

Orbital hybridization has two important consequences. First, four bonds, rather than two, can be formed to carbon. Second, the highly directional sp^3 orbitals provide for more effective overlap and stronger bonds. Thus, although an isolated carbon atom with one electron in each of four equivalent sp^3 -hybridized orbitals would be of higher energy than the ground state, the energy required in a formal sense to promote two electrons from a $2s$ orbital to sp^3 orbitals is more than compensated for by the formation of four bonds rather than two. In addition, each of the bonds is stronger owing to the directional properties of the hybrid orbitals. Tetrahedral geometry is predicted by the mathematical description of hybridization. Methane is found experimentally to be a perfect tetrahedron, with each H—C—H bond angle equal to 109.5° . The valence bond representation of methane in Fig. 1.3 shows the orbital overlaps that give rise to four equivalent C—H bonds. These bonds, in which the electron density is cylindrically symmetric about the internuclear axis are called σ bonds.

The hybridization concept can also be applied to molecules containing double and triple bonds. The descriptive valence bond approach to the bonding in ethylene and

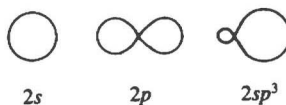


Fig. 1.2. Cross section of angular dependence of orbitals.

4. L. Pauling, *J. Am. Chem. Soc.* **53**:1367 (1931).