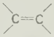
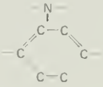
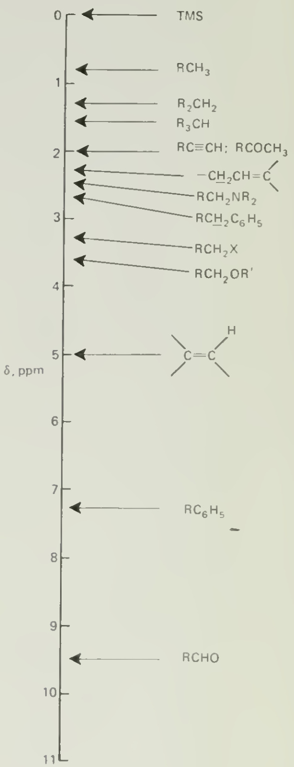
INTRODUCTION TO ORGANIC CHEMISTRY

Andrew Streitwieser, Jr. • Clayton H. Heathcock

COMMON ORGANIC FUNCTIONS

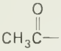
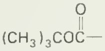
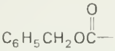
Class	Formula	Functional Group	IUPAC Prefix or suffix
acyl halide,	$R\overset{O}{\overset{\|}{C}}X$	$\overset{O}{\overset{\|}{C}}X$	-oyl halide
alcohol,	ROH	—OH	-ol
aldehyde,	$R\overset{O}{\overset{\|}{C}}H$	$-\overset{O}{\overset{\|}{C}}H$	-al
alkane,	RH	none	-ane
alkene,	$R_2C{=}CR_2$		-ene
alkyne,	$RC{\equiv}CR$	$-C{\equiv}C-$	-yne
amide,	$R\overset{O}{\overset{\|}{C}}NR_2$	$-\overset{O}{\overset{\|}{C}}N$	-amide
amine	R_3N	$-\underset{\|}{N}-$	amino-
arene,	ArH		
azide,	RN_3	$-N{=}\overset{+}{N}{=}\overset{-}{N}$	azido-
carboxylic acid	$R\overset{O}{\overset{\|}{C}}OH$	$-\overset{O}{\overset{\|}{C}}OH$	-oic acid
ester,	$R\overset{O}{\overset{\|}{C}}OR$	$-\overset{O}{\overset{\|}{C}}O-$	
ether,	R_2O	—O—	alkoxy-
halide,	RF, RCl, RBr, RI (RX)	—F, —Cl, —Br, —I (—X)	fluoro-, chloro-, bromo-, iodo- (halo-)
ketone	$R\overset{O}{\overset{\|}{C}}R$	$-\overset{O}{\overset{\|}{C}}-$	one
nitrile,	$RC{\equiv}N$	$-C{\equiv}N$	nitrile
nitro compound,	RNO_2	NO_2	nitro-
phenol,	ArOH	—OH	
sulfide,	R_2S	—S—	alkylthio-
sulfone,	$R\overset{O}{\underset{O}{S}}R$	$-\overset{O}{\underset{O}{S}}-$	
sulfonic acid,	RSO_3H	$\overset{O}{\underset{O}{S}}OH$	-sulfonic acid
sulfoxide	$R\overset{O}{\overset{\|}{S}}R$	$-\overset{O}{\overset{\|}{S}}-$	
thiol,	RSH	—SH	thiol

APPROXIMATE NMR CHEMICAL SHIFTS



—OH	2–5 ppm
—COOH	10–13 ppm
>NH	1–3 ppm

CHEMICAL ABBREVIATIONS

Ac	acetyl,  $CH_3\overset{\overset{O}{\|}}{C}—$
boc	*t*-butoxycarbonyl,  $(CH_3)_3CO\overset{\overset{O}{\|}}{C}—$
n-Bu	*n*-butyl, $CH_3CH_2CH_2CH_2—$
t-Bu	*t*-butyl, $(CH_3)_3C—$
cbz	benzyloxycarbonyl,  $C_6H_5CH_2O\overset{\overset{O}{\|}}{C}—$
DCC	dicyclohexylcarbodiimide, $C_6H_{11}N{=}C{=}NC_6H_{11}$
DIBAL	di-isobutylaluminum hydride, $[(CH_3)_2CHCH_2]_2AlH$
diglyme	bis-(2-methoxyethyl) ether, $(CH_3OCH_2CH_2)_2O$
DMF	dimethylformamide, $(CH_3)_2NCHO$
DMSO	dimethyl sulfoxide, $(CH_3)_2SO$
DNP	2,4-dinitrophenyl, 2,4-$(O_2N)_2C_6H_3—$
Et	ethyl, $CH_3CH_2—$
glyme	1,2-dimethoxyethane, $CH_3OCH_2CH_2OCH_3$
HMPT	hexamethylphosphoric triamide, $[(CH_3)_2N]_3PO$
LAH	lithium aluminum hydride, $LiAlH_4$
LDA	lithium diisopropylamide, $LiN[CH(CH_3)_2]_2$
Me	methyl, $CH_3—$
PPA	polyphosphoric acid
THF	tetrahydrofuran, $\overline{CH_2CH_2CH_2CH_2O}$
TMS	tetramethylsilane, $(CH_3)_4Si$
Ts	*p*-toluenesulfonyl, *p*-$CH_3C_6H_4SO_2—$

EQUILIBRIA AND FREE ENERGY

$$A \rightleftharpoons B \qquad K = \frac{[B]}{[A]}$$

$$\Delta G^\circ = -RT \ln K$$

K	%B	%A	ΔG° at 25°C kcal mole^{-1}
0.0001	0.01	99.99	+5.46
0.001	0.1	99.9	+4.09
0.01	0.99	99.0	+2.73
0.1	9.1	90.9	+1.36
0.33	25	75	+0.65
1	50	50	0
3	75	25	0.65
10	90.9	9.1	−1.36
100	99.0	0.99	−2.73
1000	99.9	0.1	−4.09
10000	99.99	0.01	−5.46

SYMBOLS FOR AMINO ACIDS

ala	alanine
arg	arginine
asp	aspartic acid
asn	asparagine
cys	cysteine
gln	glutamine
glu	glutamic acid
gly	glycine
his	histidine
ile	isoleucine
leu	leucine
lys	lysine
met	methionine
phe	phenylalanine
pro	proline
ser	serine
thr	threonine
trp	tryptophane
tyr	tyrosine
val	valine

Digitized by the Internet Archive
in 2010

http://www.archive.org/details/introductiontoor00stre

Introduction to Organic Chemistry

A Series of Books in Organic Chemistry
Andrew Streitwieser, Jr., Editor

INTRODUCTION TO

ORGANIC CHEMISTRY

Andrew Streitwieser, Jr.
Clayton H. Heathcock

University of California, Berkeley

Macmillan Publishing Co., Inc.
NEW YORK

Collier Macmillan Publishers
LONDON

Copyright © 1976, Macmillan Publishing Co., Inc.
PRINTED IN THE UNITED STATES OF AMERICA

All rights reserved. No part of this book may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the Publisher.

Selected illustrations have been reprinted from *Orbital and Electron Density Diagrams: An Application of Computer Graphics*, by Andrew Streitwieser, Jr., and Peter H. Owens, copyright © 1973 by Macmillan Publishing Co., Inc.

Macmillan Publishing Co., Inc.
866 Third Avenue, New York, New York 10022

Collier Macmillan Canada, Ltd.

Library of Congress Cataloging in Publication Data

Streitwieser, Andrew, (date)
Introduction to organic chemistry.

(A Series of books in organic chemistry)
Bibliography: p.
Includes index.
1. Chemistry, Organic. I. Heathcock, Clayton H., joint author. II. Title. [DNLM: 1. Chemistry, Organic. QD258 S915i]
QD251.2.S76 547 74-33102
ISBN 0-02-418010-6

Printing: 3 4 5 6 7 8 Year: 7 8 9 0 1 2

PREFACE

With the dozens of textbooks now available for use in teaching organic chemistry, one may wonder why we add still another. The answer is simply that all of the existing textbooks we have used or studied have important limitations for instructional use. The present book was developed from draft versions used for several years in teaching the one-year course in organic chemistry (Chemistry 12AB, 112) at the University of California, Berkeley. As such it reflects some of the current trends in teaching organic chemistry.

In recent years, even the major's course in organic chemistry has become increasingly a service course for premedical students and others interested in biological sciences. We have recognized this trend by including examples and discussion of biological relevance, but we have tried to do so without slighting the chemistry major. One of the important aspects of organic chemical knowledge required by the nonmajor in subsequent careers is that of nomenclature. Yet, with the amount of material now covered, even in introductory studies of organic chemistry, nomenclature often gets short shrift in lectures. We have tried in this textbook to give adequate coverage to the naming of compounds, both with the IUPAC system and with common or trivial names that are actually used in practice in the real world.

Organic chemistry traditionally follows a year of general chemistry or "freshman chemistry," a course that has tended, in recent years, to emphasize physical chemistry at the expense of descriptive inorganic chemistry. To compensate for this development, we have included descriptions of the reagents that find important use in organic reactions. In fact, we have tried to present a feeling for chemicals as real stuff with physical attributes. This aspect of dealing with chemicals as materials is important to major and nonmajor alike; one reason many students are required to take organic chemistry courses is that they expect in their chosen careers to deal with, handle, and use organic compounds. One way in which we have tried to keep in touch with the real world in this textbook is the frequent use of actual reactions with reported yields. In many cases we have included some experimental details on how the reactions are actually run. This technique also serves the pedagogical purpose of emphasizing the important reactions to the student.

Another innovation has been the inclusion of stereo drawings, which make use of the capabilities of modern computer graphics. These figures require a stereo viewer for optimum use, and we expect that such viewers will become increasingly available in bookstores and familiar to students as the computer graphics techniques become useful in other textbooks. For physiological or psychological reasons some students cannot achieve three-dimensional perception, even with viewers. For such students the traditional use of molecular models and perspective diagrams must suffice. For most students the stereo diagrams emphasize the three-dimensional nature of organic structures and provide a useful supplement to the use of molecular models.

Throughout the text, we have made an effort to *explain* things—so much of organic chemistry reduces to Coulomb's law! Naturally, there is much use of reaction mechanisms. We have emphasized the use of resonance structures rather than molecular orbital theory. The knowledgeable reader will appreciate that we believe molecular orbital theory has an important application in organic chemistry, but he may be surprised at our belief that its role in an introductory course is quite limited.

The organization of this textbook differs somewhat from tradition. The growing tendency in organic chemistry courses to teach all the theory first has the unfortunate result of unduly delaying organic reactions. This type of organization may provide a logical organization of the science, but we believe it represents poor pedagogy. Instead, we have diffused theory through the text as needed. We start with alkanes because they form the basis of nomenclature, and proceed to halides, displacement reactions, alcohols, alkenes, alkynes, and carbonyl groups. Only after these important functional groups have been discussed are conjugated systems treated. Ring compounds and their conformations provide opportunity for reinforcement of some important reactions and lead naturally to glycols and hydroxy-carbonyl compounds and to the cyclic chemistry of epoxides, hemiacetals, and lactones. This discussion also provides a smooth introduction to carbohydrates. Condensation reactions, amines, amino acids, proteins, aromatic chemistry, and heterocycles conclude the organization. Chapter 36 consists of brief surveys of several additional topics that some instructors may wish to add as enrichment material. The book ends with a discussion of the chemical literature, complete with an abbreviated introduction to the use of Beilstein's *Handbuch der Organischen Chemie.*

Spectroscopy has become an increasingly important part of organic chemistry. We have introduced the four important spectroscopic methods as they become useful for individual functional groups. Nuclear magnetic resonance comes first and early because of its importance and because students like what they can achieve with nmr. Infrared spectroscopy is introduced after alcohols and multiple bonds are discussed. Mass spectroscopy follows the carbonyl group, and ultraviolet spectroscopy comes immediately after the introduction of conjugated systems.

The year course of organic chemistry at Berkeley consists of three quarters. The first quarter covers about Chapters 1 to 13. The second quarter finishes with Chapter 25, "Carbohydrates." In a two-semester sequence, the first semester should finish about Chapter 18 or 19. An advantage of starting the second semester with Chapter 19, "Organic Synthesis," is the opportunity it affords for reviewing important reactions covered in the first semester.

We are indebted to many people for their essential help in creating this text. We learned much from and appreciate the feedback we got from students who used early editions of the manuscript in our courses. The cmr spectra in Chapter 10 were measured by James Shoolery of Varian Associates. Infrared spectra were obtained on a Perkin-Elmer 735 infrared spectrometer by Robert Hannah, Ron Anderson, Mary Zeller, and Mark Juszli of Perkin-Elmer. John T. Dickman of Chemical Abstracts Service critically evaluated Chapter 37 and granted permission to reproduce illustrative material from *Chemical Abstracts.* Several of our students have prepared special compounds for the determination of spectra—Edward Binkley, Phyllis Toczko, and Lee Kozar. We are also grateful to numerous individuals who have supplied information, read portions of the text, and offered their criticism and suggestions—Joseph Lavigne, Joseph Casanova, Heinz Koch, Gene Ziegler, Donald Noyce, Henry Rapoport, Douglas Browne, Steven Kent, and David Streitwieser. Many of the computer-drawn stereo plots were prepared with the assistance of Peter Owens and John McKelvey. Others were reproduced from the chemical literature, cited with the permission and cooperation of the authors. Several of the plots used coordinates supplied by Professor Norman Allinger.

David Streitwieser provided most of the index, with computer alphabetization assistance by Glenn Toczko, Mrs. Suzanne Streitwieser, and Charles Buse. Last, but not least, we give special thanks to the expert typists who reduced our sometimes crude handwritten versions to legible typescript—Carolyn Craven, Cheryl Heathcock, June Smith, Wendy Zukas, and Lynne Gloria.

Andrew Streitwieser, Jr.
Clayton H. Heathcock
Berkeley, Caifornia

CONTENTS

1. *Introduction* 1

2. *Electronic Structure and Bonding* 5
   2.1 Periodic Table 5
   2.2 Lewis Structures 5
   2.3 Geometric Structure 9
   2.4 Resonance Structures 10
   2.5 Atomic Orbitals 15
   2.6 Electronic Structure of Atoms 17
   2.7 Bonds and Overlap 20
   2.8 Hybrid Orbitals and Bonds 23
   2.9 Organic Structures 28
   2.10 Functional Groups 30
   2.11 The Determination of Organic Structures 35
   PROBLEMS 37

3. *Organic Reactions* 42
   3.1 Introduction 42
   3.2 An Example of an Organic Reaction: Equilibria 42
   3.3 Reaction Kinetics 44
   3.4 Reaction Profiles and Mechanism 46
   PROBLEMS 50

4. *Alkanes* 53
   4.1 *n*-Alkanes 53
   4.2 Physical Properties 54
   4.3 Barriers to Rotation 57
   4.4 Branched Chain Alkanes: IUPAC Nomenclature 62
   4.5 Branched Chain Alkanes: Conformations 66
   4.6 Cycloalkanes 68
   4.7 Occurrence of Alkanes 69
   PROBLEMS 71

5. *Reactions of Alkanes* 73
   5.1 Bond Dissociation Energies 73
   5.2 Pyrolysis of Alkanes: Cracking 76
   5.3 Halogenation of Alkanes 77
   5.4 Combustion of Alkanes 87
   5.5 Heats of Formation 89
   5.6 Average Bond Energies 92
   PROBLEMS 92

6. *Alkyl Halides* 95
   6.1 Nomenclature 95
   6.2 Structure 96
   6.3 Physical Properties 98
   6.4 Preparation 100

6.5 Conformations 100
6.6 Some Uses of Halogenated Hydrocarbons 102
PROBLEMS 104

7. *Stereoisomerism* **105**
7.1 Chirality and Enantiomers 105
7.2 Physical Properties of Enantiomers: Optical Activity 107
7.3 Nomenclature of Enantiomers: The (R-S) Convention 110
7.4 Racemic Mixtures 114
7.5 Compounds Containing More than One Asymmetric Atom: Diastereomers 116
7.6 Chemical Reactions and Stereoisomerism 119
PROBLEMS 124

8. *Reactions of Alkyl Halides* **127**
8.1 The Displacement Reaction 127
8.2 Stereochemistry of the Displacement Reaction 128
8.3 Generality of the Displacement Reaction 132
8.4 Nucleophilicity 135
8.5 Effect of Substrate Structure on Displacement Reactions 138
8.6 Some Typical S_N2 Reactions 141
8.7 E2 Elimination 145
8.8 S_N1 Reactions: Carbonium Ions 147
8.9 Summation: Elimination Versus Substitution: Unimolecular Versus Bimolecular 152
PROBLEMS 153

9. *Organometallic Compounds* **156**
9.1 Structure 156
9.2 Nomenclature 157
9.3 Physical Properties 157
9.4 Preparation of Organometallic Compounds 158
9.5 Reactions of Organometallic Compounds 163
9.6 Uses of Organometallic Compounds 165
PROBLEMS 167

10. *Nuclear Magnetic Resonance Spectroscopy* **169**
10.1 Structure Determination 169
10.2 Introduction to Spectroscopy 170
10.3 Nuclear Magnetic Resonance 171
10.4 Chemical Shift 174
10.5 Relative Peak Areas 178
10.6 Spin-spin Splitting 180
10.7 More Complex Splitting 187
10.8 Solving Spectral Problems 190
10.9 Nmr Spectroscopy of Other Nuclei 192
PROBLEMS 195

11. *Alcohols, Ethers, Thiols, and Sulfides* **206**
11.1 Introduction: Structure 206
11.2 Nomenclature of Alcohols 207

11.3 Physical Properties of Alcohols 211
11.4 Acidity of Alcohols: Inductive Effects 214
11.5 Nuclear Magnetic Resonance 218
11.6 Preparation of Alcohols 220
11.7 Reactions of Alcohols 224
11.8 Nomenclature of Ethers 234
11.9 Physical Properties of Ethers 235
11.10 Preparation of Ethers 236
11.11 Reactions of Ethers 239
11.12 Nomenclature of Thiols and Sulfides 241
11.13 Physical Properties of Thiols and Sulfides 242
11.14 Preparation of Thiols and Sulfides 242
11.15 Reactions of Thiols and Sulfides 243
PROBLEMS 245

12. ***Alkenes*** **251**
12.1 Electronic Structure 251
12.2 Nomenclature of Alkenes 256
12.3 Physical Properties of Alkenes 258
12.4 Relative Stabilities of Alkenes: Heats of Formation 264
12.5 Preparation of Alkenes 266
12.6 Reactions of Alkenes 275
PROBLEMS 296

13. ***Alkynes*** **301**
13.1 Electronic Structure 301
13.2 Nomenclature 302
13.3 Physical Properties 303
13.4 Acidity of Alkynes 306
13.5 Preparation of Alkynes 307
13.6 Reactions of Alkynes 311
13.7 Vinyl Halides 318
PROBLEMS 321

14. ***Infrared Spectroscopy*** **325**
14.1 The Electromagnetic Spectrum 325
14.2 Molecular Vibration 327
14.3 Characteristic Group Vibrations 332
14.4 Alkanes 333
14.5 Alkenes 334
14.6 Alkynes 336
14.7 Alkyl Halides 337
14.8 Alcohols and Ethers 338
14.9 Summary: Principal Functional Group Absorptions 340
14.10 Instrumentation 341
PROBLEMS 342

15. ***Aldehydes and Ketones*** **348**
15.1 Structure 348
15.2 Nomenclature 350
15.3 Physical Properties 352
15.4 Spectroscopy of Aldehydes and Ketones 354

15.5 Synthesis of Aldehydes and Ketones 357
15.6 Enolization 360
15.7 Carbonyl Addition Reactions 368
15.8 Oxidation and Reduction 391
PROBLEMS 399

16. *Mass Spectroscopy* **404**
16.1 Introduction 404
16.2 Instrumentation 405
16.3 The Molecular Ion: Molecular Formula 407
16.4 Fragmentation 410
PROBLEMS 417

17. *Carboxylic Acids* **423**
17.1 Structure 423
17.2 Nomenclature 423
17.3 Physical Properties 425
17.4 Acidity 426
17.5 Spectroscopy 432
17.6 Synthesis 433
17.7 Reactions 436
17.8 Occurrence of Carboxylic Acids 446
PROBLEMS 447

18. *Derivatives of Carboxylic Acids* **451**
18.1 Structure 451
18.2 Nomenclature 454
18.3 Physical Properties 456
18.4 Spectroscopy 458
18.5 Synthesis 460
18.6 Reactions of Carboxylic Acid Derivatives 463
18.7 Basicity of the Carbonyl Oxygen 463
18.8 Acidity of the α Protons 467
18.9 Nucleophilic Substitution Reactions 471
18.10 Reduction 489
18.11 Reactions of Amides Which Occur on Nitrogen 494
18.12 Pyrolytic Eliminations 495
18.13 Esters of Other Acids 498
18.14 Waxes and Fats 506
PROBLEMS 510

19. *Organic Synthesis* **516**
19.1 Introduction 516
19.2 Considerations in Synthesis Design 516
19.3 Planning a Synthesis 519
19.4 Protecting Groups 526
19.5 Industrial Synthesis 527
PROBLEMS 528

20. *Conjugation* **529**
20.1 Allylic Systems 529
20.2 Dienes 540

20.3 Unsaturated Carbonyl Compounds 550
20.4 Higher Conjugated Systems 564
PROBLEMS 565

21. ***Benzene and the Aromatic Ring*** **569**
21.1 Benzene 569
21.2 Aromatic Substitution 581
PROBLEMS 590

22. ***Ultraviolet Spectroscopy*** **593**
22.1 Electronic Transitions 593
22.2 $\pi \rightarrow \pi^*$ Transitions 594
22.3 $n \rightarrow \pi^*$ Transitions 596
22.4 Benzene Rings 599
22.5 Alkyl Substituents 600
22.6 Other Functional Groups 602
22.7 Photochemical Reactions 602
PROBLEMS 604

23. ***Cyclic Compounds*** **606**
23.1 Introduction 606
23.2 Structure and Energy of Cycloalkanes 607
23.3 Formation of Rings 616
23.4 Chemistry of Cyclohexane 618
23.5 Chemistry of Cyclopropanes 630
23.6 Chemistry of Cyclobutanes 635
23.7. Cyclopentane and Larger Ring Systems 638
23.8 Bicyclic Compounds 639
23.9 Terpenes and Steroids 643
23.10 Cyclic Ethers 648
23.11 Spectra of Cyclic Compounds 655
PROBLEMS 659

24. ***Difunctional Compounds I*** **664**
24.1 Introduction 664
24.2 Nomenclature of Difunctional Compounds 665
24.3 Diols 667
24.4 Hydroxy Aldehydes and Ketones 675
24.5 Hydroxy Acids 681
PROBLEMS 688

25. ***Carbohydrates*** **693**
25.1 Introduction 693
25.2 Stereochemistry and Configurational Notation of Sugars 695
25.3 Cyclic Hemiacetals: Anomerism; Glycosides 698
25.4 Conformations of the Pyranoses 702
25.5 Reactions of Monosaccharides 704
25.6 Relative Stereochemistry of the Monosaccharides: The Fischer Proof 718
25.7 Oligosaccharides 722
25.8 Polysaccharides 726

25.9 Sugar Phosphates 729
25.10 Natural Glycosides 731
PROBLEMS 732

26. ***Difunctional Compounds II*** **735**
26.1 Nomenclature 735
26.2 Dicarboxylic Acids 736
26.3 Synthesis of Dicarbonyl Compounds 741
26.4 Reactions 747
26.5 Summary 759
PROBLEMS 761

27. ***Amines*** **765**
27.1 Structure 765
27.2 Nomenclature of Amines 767
27.3 Physical Properties of Amines 768
27.4 Basicity 773
27.5 Nucleophilicity of Amines: Quaternary Ammonium Compounds 777
27.6 Synthesis of Amines 779
27.7 Reactions of Amines 787
27.8 Other Nitrogen Compounds 797
27.9 Alkaloids 805
PROBLEMS 807

28. ***Amino Acids, Peptides, and Proteins*** **814**
28.1 Introduction 814
28.2 Structure, Nomenclature, and Physical Properties of Amino Acids 815
28.3 Acid-base Properties of Amino Acids 818
28.4 Synthesis of Amino Acids 820
28.5 Reactions of Amino Acids 827
28.6 Peptides 830
28.7 Proteins 847
PROBLEMS 857

29. ***Substituted Benzenes and Electrophilic Aromatic Substitution*** **861**
29.1 Nomenclature 861
29.2 Determination of Structure 864
29.3 Orientation in Electrophilic Aromatic Substitution 869
29.4 Dipole Moments of Benzene Derivatives 870
29.5 Theory of Orientation in Electrophilic Aromatic Substitution 873
29.6 Quantitative Reactivities: Partial Rate Factors 879
29.7 Effects of Multiple Substituents 881
29.8 Synthetic Utility of Electrophilic Aromatic Substitution 883
PROBLEMS 886

30. ***Benzene Hydrocarbons and Halides*** **890**
30.1 Nomenclature 890

30.2 Preparation of Halobenzenes 892
30.3 Reactions of Halobenzenes 893
30.4 Preparation of Side Chain Halides 901
30.5 Reactions of Side Chain Halides 906
30.6 Preparation of Aromatic Hydrocarbons 909
30.7 Reactions of Alkylbenzenes 919
PROBLEMS 924

31. ***Aromatic Carbonyl Compounds and Sulfonic Acids*** **929**
31.1 Nomenclature 929
31.2 Preparation of Aromatic Ketones 931
31.3 Preparation of Aromatic Aldehydes 935
31.4 Reactions of Aromatic Aldehydes and Ketones 938
31.5 Aromatic Carboxylic Acids 941
31.6 Sulfonic Acids 950
PROBLEMS 955

32. ***Aromatic Nitrogen Compounds*** **960**
32.1 Nitroarenes 960
32.2 Aromatic Amines 965
32.3 Arenediazonium Salts 977
PROBLEMS 990

33. ***Phenols, Phenyl Ethers, and Quinones*** **998**
33.1 Nomenclature 998
33.2 Preparation and Properties of Phenols and Ethers 1000
33.3 Reactions of Phenols and Ethers 1005
33.4 Quinones 1021
PROBLEMS 1031

34. ***Polycyclic Aromatic Hydrocarbons*** **1037**
34.1 Nomenclature 1037
34.2 Biphenyl 1038
34.3 Naphthalene 1044
34.4 Anthracene and Phenanthrene 1053
34.5 Higher Polybenzenoid Hydrocarbons 1057
PROBLEMS 1061

35. ***Heterocyclic Compounds*** **1065**
35.1 Introduction 1065
35.2 Nonaromatic Heterocycles 1066
35.3 Furan, Pyrrole, and Thiophene 1072
35.4 Condensed Furans, Pyrroles, and Thiophenes 1083
35.5 Azoles 1088
35.6 Pyridine 1095
35.7 Quinoline and Isoquinoline 1104
35.8 Diazines 1109
PROBLEMS 1112

36. ***Special Topics*** **1119**
36.1 Aromaticity 1119
36.2 Pericyclic Transition States 1125

36.3 Nucleic Acids 1138
36.4 Organic Coloring Matters 1142
36.5 Photochemistry 1150
36.6 Biosynthesis 1156
36.7 Stereospecific Syntheses 1167

37. *The Chemical Literature* **1174**
37.1 Research Journals 1174
37.2 Books and Review Articles 1175
37.3 Abstract Journals 1177
37.4 Beilstein 1180

APPENDIX I *Heats of Formation* **1183**

APPENDIX II *Bond Dissociation Energies* **1186**

APPENDIX III *Average Bond Energies* **1187**

APPENDIX IV *Acidity and Basicity* **1188**
Inorganic Acids 1189
Organic Acids 1190

APPENDIX V *Proton Chemical Shifts* **1193**

APPENDIX VI *Infrared Bands* **1194**

APPENDIX VII *Symbols and Abbreviations* **1197**

APPENDIX VIII *Summary of Functional Group Preparations* **1199**

INDEX **1221**

Chapter 1
Introduction

Although chemistry did not emerge as a coherent science until the seventeenth century, its roots extend back into antiquity. Chemical changes were probably first brought about by paleolithic man when he discovered that he could make fire and use it to warm his body and roast his food. Being a curious and a resourceful creature, man observed and exploited other natural phenomena. By neolithic times he had discovered such arts as smelting, glass making, the dyeing of textiles, and the manufacture of beer, wine, butter, and cheese.

Matter and changes of matter were not systematically discussed in a theoretical sense until the period of the Greek philosophers, beginning in about 600 B.C. The popular theory that emerged during this period saw all matter as being made up of the four "elemental" substances: fire, earth, air, and water. For a time, the atomist school, of which Democritus was the chief spokesman, gained popularity. In this theory, all matter was considered to be made up of hypothetical particles called atoms, of which there were assumed to be but a finite number of different kinds. Although the atomists held sway for several centuries, the notion was highly speculative, being based on nothing directly observable. The demise of this theory was foreshadowed when it was rejected by the highly respected Aristotle; its burial was assured with the advent of stoicism and the subsequent rise of the popular religious movements in the Western world. The idea of fundamental particles was not resurrected for almost two millenia.

Some time around the time of Christ, the Greek philosophers hit upon the idea of changing (or "transmuting") base metals such as lead and iron into gold and silver. Although alchemy was first practiced in a serious sense by the Greeks, it quickly spread to other cultures and continued as a lively discipline throughout the world for over a thousand years. This alchemical period has often been put down as a "dark age" of science. However, one must recognize that there is nothing inherently wrong with the notion that one metal may be transformable into another. Chemistry is, in fact, based upon changes in the state of matter. The alchemists had no way of recognizing the elemental nature of the metals with which they dealt.

Although they were uniformly unsuccessful in their quest for the philosopher's stone, the alchemists contributed a great deal to the technology of handling matter. Not only did they develop numerous processes for the production of relatively pure compounds but they also invented tools and apparatus. Many of these inventions persist in general form to the present day—beakers, flasks, funnels, mortars, crucibles. Perhaps the most important invention of alchemy was the **still.**

The important technique of distillation was probably discovered by the early Greek alchemists when they noticed condensate on the lid of a vessel in which some liquid was being heated. It was only a short step from this observation to the realization that this technique could be used to separate volatile substances from nonvolatile animal and vegetable matter. Although the still was quite inefficient in its infancy, its design improved steadily. By 1300, actual fractionation was being practiced, and alcoholic distillates of fairly high alcohol concentration were available. The production of whiskey and brandy became an established industry in short order.

The invention and development of the still by the alchemists had an interesting consequence in another area—medicine. Through the middle ages, medicine was practiced as a mystical blend of magic and folklore. It had long been noticed that certain animal and plant substances seemed to possess curative powers. With the advent of the still, it became possible to concentrate the "essence" of various natural materials. The use of various distillates as medical remedies quickly became a widespread practice. For several hundred years, physicians and their associates distilled all manner of natural substances. In the process, a number of relatively pure organic compounds were discovered, such as acetic acid from vinegar and formic acid from ants.

During this pre-1600 period, as the tools for handling matter were being developed and as numerous relatively pure chemical substances were being discovered, there was relatively little serious experimentation and no advance at all in the theory of matter. However, during the seventeenth and eighteenth centuries, chemistry was born as a science in Europe. The first area of serious investigation was gases. Although Boyle, Cavendish, Priestly, and Scheele made important breakthroughs, it was Lavoisier who laid the real foundation for modern chemistry. During this period, there evolved the notion of elements and combining weights. By 1789, Lavoisier had assembled a Table of the Elements, containing 33 substances, most of which appear in the modern periodic table.

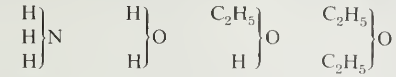
In this formative stage in the science of chemistry, the substances derived from the animal and vegetable worlds were largely ignored. These materials were recognized as being different—more complex—than the compounds of the atmosphere or those compounds derived from the mineral kingdom. Lavoisier himself noted that **organic compounds**, as they came to be known, differed from the inorganic compounds in that they all seemed to be composed of carbon and hydrogen and occasionally nitrogen or phosphorus. For a time it was believed that organic compounds did not obey the new law of definite proportions. Gradually throughout this period there arose the popular belief that a **vital force**, present only in living organisms, was responsible for the production of organic compounds.

The vitalism theory persisted until the middle of the nineteenth century. In 1828, Frederick Wöhler, working in Heidelberg, reported that, upon treating lead cyanate with ammonium hydroxide, he obtained urea. Since urea was a well known organic compound, having been isolated from human urine by Roulle in about 1780, Wöhler had succeeded in preparing an organic compound in the laboratory for the first time. Although the synthesis of urea was recognized by the leading chemists of the day, the concept of vitalism did not die quickly. It was not until the synthetic work of Kolbe in the 1840s and Berthelot in the 1850s that the demise of vitalism was complete.

At this time, chemists recognized that it was not the vital force which imparted uniqueness to organic chemistry but rather the simple fact that organic compounds are all compounds of carbon. This definition—organic chemistry is the chemistry of carbon compounds—has persisted.

As analytical methods were perfected, particularly the technique of combustion analysis for carbon and hydrogen, organic chemistry began to take on new dimensions. For the first time, accurate formulas were available for fairly complicated organic compounds. There ensued a confusing period, which lasted from about 1800 until about 1850, during which various theories were advanced in an attempt to explain such complexities as isomerism (the existence of two compounds with the same formula) and substitution (the substitution of one element for another in a complex organic formula).

Organic chemistry began to find its way out of this chaotic period in 1852 when Frankland advanced the concept of valence. In 1858, Kekulé and Couper, working independently, introduced a simple, but exceedingly important, concept. Making use of the new structural formulas shown, which had come into vogue since 1850,

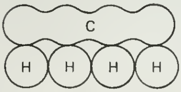


$$\left.\begin{matrix}H\\H\\H\end{matrix}\right\}N \qquad \left.\begin{matrix}H\\ \\H\end{matrix}\right\}O \qquad \left.\begin{matrix}C_2H_5\\ \\H\end{matrix}\right\}O \qquad \left.\begin{matrix}C_2H_5\\ \\C_2H_5\end{matrix}\right\}O$$

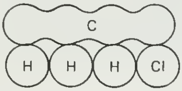
ammonia water alcohol ether

Kekulé and Couper proposed that the carbon atom is always tetravalent and that carbon atoms have the ability to link to each other.

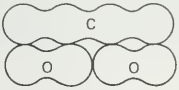
A third event, which ushered organic chemistry into its modern period, was the demonstration by Cannizzaro in 1858 that Avogadro's hypothesis, available since 1811, allowed the determination of accurate molecular weights for organic compounds. With this last piece of the structural puzzle available, it was possible to think in terms of molecular structure and the chemical bond. Kekulé introduced the idea of a bond between atoms and depicted it with his "sausage formulas" in the first edition of his textbook in 1861.



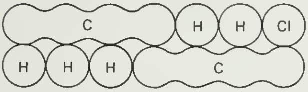
methane



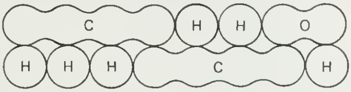
methyl chloride



carbon dioxide



ethyl chloride



ethyl alcohol

In the century since Kekulé, organic chemistry has matured as a scientific discipline in its own right. Well over 95% of all known chemical compounds are compounds of carbon. Over one half of present day chemists classify themselves as organic chemists. The organic chemical industry plays a major role in world economy. Finally, because organic chemicals are literally the "stuff of life," the significant advances in unravelling the nature of life are discoveries in organic chemistry.

Why study organic chemistry? There are different answers to this question depending upon who you are. It may be that you will devote your life to a career in organic chemistry *per se*, although if this is the case, you probably do not know it yet. Or you may plan to specialize in some other area of chemistry and want a knowledge of organic chemistry as an adjunct to your specialty area. You may be a future chemical engineer. If so, organic chemistry will be an important part of your life. Most of the industrial processes you will encounter will be organic reactions. Perhaps you are headed for medicine or nursing. Simply note that pharmaceutical products amounted to over $6 billion in 1972 and that chemotherapy is one of the major techniques in modern medicine. You may be going into biochemistry, molecular biology, or some other life science. If so, organic chemistry is a fundamental and essential platform upon which to build. Biochemistry is simply a study of organic chemistry as it goes on in living organisms and the molecules of molecular biology are organic molecules.

Even if you do not have any of the foregoing "reasons" to study organic chemistry, there are many other justifications. The previous arguments are vocational motivations. But organic chemistry can also provide a fascinating area of "natural philosophy" for the student who wants only to obtain a broad liberal arts education. If you approach the subject in the proper frame of mind, you will find it to be an extremely stimulating intellectual pursuit. Organic chemistry has a highly logical structure. As you will see, we make much use of symbolic logic, the logical principle of analogy, and deductive reasoning. In fact, it has been intimated that medical school admission boards value organic chemistry courses as much for the test in logical thinking that they provide as for their factual content.

Finally, organic chemistry has a unique content as an *art form*. The building up of complex molecular architecture by appropriate choice of a sequential combination of reactions provide syntheses that are described as "elegant" and "beautiful." The design of an experiment in reaction mechanism can be similarly imaginative. Such elegantly conceived experiments can evoke that delightful feeling of pleasure that man obtains from the appreciation of man's creativity —but only in the mind of the knowledgeable spectator. These unique works of art can only be appreciated by those who know some organic reactions and have tried to design some simple syntheses and experiments themselves, such as those suggested in problem sets throughout this textbook. Only one who has played chess can feel that special pleasure of following a game between Grand Masters.

CHAPTER 2

Electronic Structure and Bonding

2.1
Periodic Table

The periodic table of the elements was developed just over 100 years ago. At that time it was an empirical organization based on the chemical and physical properties of the known elements. The table now embraces over 100 elements. Compounds of carbon, organic compounds, are known that contain virtually all of the elements except the noble gases. However, only a small part of this organization is important in the introductory study of organic chemistry. In the condensed form of the periodic table shown in Table 2.1, the most important elements are emphasized with bold type: **C, H, N, O, S, Mg, Cl, Br,** and **I.** Secondary but still important elements are in italics: *Li, B, F,* and *P.*

TABLE 2.1
Abbreviated Periodic Table

H							He
Li	Be	*B*	**C**	**N**	**O**	*F*	Ne
Na	**Mg**	Al	Si	*P*	**S**	**Cl**	Ar
						Br	
						I	

2.2
Lewis Structures

The "noble" gases, He, Ne, Ar, Kr, Xe, and Ra, are almost inert chemically. Paradoxically, it is this very inert character that dominates much of the chemistry of all the rest of the elements. The noble gases have characteristic numbers of electrons, 2 for helium, 10 for neon (2 + 8), 18 for argon (2 + 8 + 8), and so on. They are described as having "filled shells," or, for neon and argon, as having filled outer octets. Other elements can achieve such stable electronic configurations by gaining or losing electrons.

The energy required to lose an electron is known as the ionization potential, IP.

$$\mathrm{M} \longrightarrow \mathrm{M}^+ + e \qquad \Delta H^\circ = \mathrm{IP}$$

For elements at the far left of the periodic table, loss of an electron produces the electronic configuration of the next lower noble gas. Examples are

$$\underset{\text{3 electrons}}{\mathrm{Li}} \xrightarrow{-e} \underset{\substack{\text{2 electrons,}\\ \text{same as helium}}}{\mathrm{Li}^+}$$

$$\underset{\text{11 electrons}}{\mathrm{Na}} \xrightarrow{-e} \underset{\substack{\text{10 electrons,}\\ \text{same as neon}}}{\mathrm{Na}^+}$$

Consequently, such elements have relatively low ionization potentials and are described as being **electropositive.**

The energy liberated when an electron is acquired is called the electron affinity, EA.

$$X + e \longrightarrow X^- \qquad -\Delta H^\circ = \text{EA}$$

The electron affinity of an atom is precisely the same as the ionization potential of the corresponding anion. Elements at the far right of the periodic table readily acquire electrons to produce the stable electronic configuration of the next higher noble gas. Examples are

$$\underset{\text{9 electrons}}{\text{F}} + e \longrightarrow \underset{\substack{\text{10 electrons,}\\ \text{same as neon}}}{\text{F}^-}$$

$$\underset{\text{17 electrons}}{\text{Cl}} + e \longrightarrow \underset{\substack{\text{18 electrons,}\\ \text{same as argon}}}{\text{Cl}^-}$$

Consequently, such elements have relatively high electron affinities and are described as being **electronegative.**

The electrons outside the shell of the next lower noble gas are the "valence electrons" and are the only ones normally included in symbols. The above ionization processes are then symbolized as

$$\text{Li}\cdot \longrightarrow \text{Li}^+ + e \qquad \text{IP} = 123.6 \text{ kcal mole}^{-1}$$

$$\text{Na}\cdot \longrightarrow \text{Na}^+ + e \qquad \text{IP} = 118.0 \text{ kcal mole}^{-1}$$

$$:\underset{..}{\overset{..}{\text{F}}}\cdot + e \longrightarrow :\underset{..}{\overset{..}{\text{F}}}:^- \qquad \text{EA} = 78.3 \text{ kcal mole}^{-1}$$

$$:\underset{..}{\overset{..}{\text{Cl}}}\cdot + e \longrightarrow :\underset{..}{\overset{..}{\text{Cl}}}:^- \qquad \text{EA} = 83.3 \text{ kcal mole}^{-1}$$

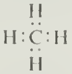
Electropositive elements such as the alkali metals tend to lose electrons to electronegative elements such as the halogens to form pairs of ions. Such compounds are described as having ionic bonding. Typical examples are lithium chloride ($\text{Li}^+ \; :\underset{..}{\overset{..}{\text{Cl}}}:^-$) and sodium fluoride ($\text{Na}^+ \; :\underset{..}{\overset{..}{\text{F}}}:^-$).

For elements in the middle of the periodic table, too much energy is required to gain or lose sufficient electrons to form similar octet ions. Compare the energy required to generate a triply positive boron or quadruply positive carbon with the energies required to form Li^+ or Na^+.

$$\cdot\overset{\cdot}{\text{B}}\cdot \longrightarrow 3\,\text{e} + \text{B}^{3+} \qquad \text{IP} = 870.4 \text{ kcal mole}^{-1}$$

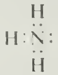
$$\cdot\underset{\cdot}{\overset{\cdot}{\text{C}}}\cdot \longrightarrow 4\,\text{e} + \text{C}^{4+} \qquad \text{IP} = 1480.7 \text{ kcal mole}^{-1}$$

Consequently, such elements tend to acquire their electron octets by *sharing* electrons, as in the following examples:



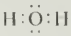
$$\begin{array}{c}\text{H}\\ \text{H}:\underset{..}{\overset{..}{\text{C}}}:\text{H}\\ \text{H}\end{array}$$

methane



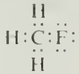
$$\begin{array}{c}\text{H}\\ \text{H}:\underset{..}{\overset{..}{\text{N}}}:\\ \text{H}\end{array}$$

ammonia



$$\text{H}:\underset{..}{\overset{..}{\text{O}}}:\text{H}$$

water



$$\begin{array}{c}\text{H}\\ \text{H}:\underset{..}{\overset{..}{\text{C}}}:\underset{..}{\overset{..}{\text{F}}}:\\ \text{H}\end{array}$$

methyl fluoride

Such bonds are described as covalent bonds.

The symbols used to describe the systems discussed are called **Lewis structures.** Such structures not only provide simple and convenient representations of ions and compounds but are also valuable in providing an accurate accounting for electrons. They form an important basis for predicting relative stabilities. Lewis structures are important in the study of organic chemistry and the student should be able to write them with facility. The following general rules are useful for deriving suitable structures.

1. *All valence electrons are shown.* The total number of such electrons is equal to the number contributed by each atom, with an additional number added or subtracted to account for any ionic charges. Some examples are worked out in Table 2.2.

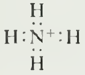
TABLE 2.2
Valence Electrons

Species	Atomic Contributions	−	Cation Charges	+	Anion Charges	=	Total Valence Electrons
CH_4	4(C) + 4 × 1 (H) = 8	−	0	+	0	=	8
NH_3	5(N) + 3 × 1 (H) = 8	−	0	+	0	=	8
H_2O	6(O) + 2 × 1 (H) = 8	−	0	+	0	=	8
H_3O^+	6(O) + 3 × 1 (H) = 9	−	1	+	0	=	8
HO^-	6(O) + 1 (H) = 7	−	0	+	1	=	8
BF_3	3(B) + 3 × 7 (F) = 24	−	0	+	0	=	24
NO_2^-	5(N) + 2 × 6 (O) = 17	−	0	+	1	=	18
CO_3^{2-}	4(C) + 3 × 6 (O) = 22	−	0	+	2	=	24

2. *Each element should, to the greatest extent possible, have a complete octet.* Exceptions are hydrogen, which has a duet shell, and elements beyond the first row, such as sulfur and phosphorus, which may accommodate more than eight valence electrons ("expand their octets") in certain circumstances.

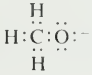
Correct Structure	*Incorrect Structures*
$:\ddot{O}::C::\ddot{O}:$	$:\underset{\cdot\cdot}{\ddot{O}}:C::\underset{\cdot\cdot}{\ddot{O}}:$ $:\underset{\cdot\cdot}{\ddot{O}}:C:\underset{\cdot\cdot}{\ddot{O}}:$ $:\underset{\cdot\cdot}{\ddot{O}}::C:\ddot{O}:$
$H:\underset{\cdot\cdot}{\ddot{Cl}}:$	$:H:\ddot{Cl}:$
$:N:::N:$	$:\ddot{N}::N:$ $:\ddot{N}:\ddot{N}:$

3. ***Formal charges** are assigned by dividing each bonding pair of electrons equally between the bonded atoms.* The number of electrons "belonging" in this way to each atom is compared with the neutral atom and appropriate positive or negative charges are assigned. Lone pairs "belong" to a single atom.



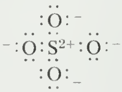
$$\begin{array}{c} H \\ H:\underset{\cdot\cdot}{\ddot{N}}{}^{+}:H \\ H \end{array}$$

ammonium ion



$$\begin{array}{c} H \\ H:\underset{\cdot\cdot}{\ddot{C}}:\underset{\cdot\cdot}{\ddot{O}}:^{-} \\ H \end{array}$$

methoxide ion



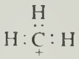
$$\begin{array}{c} :\ddot{O}:^{-} \\ {}^{-}:\underset{\cdot\cdot}{\ddot{O}}:\underset{\cdot\cdot}{\ddot{S}}{}^{2+}:\underset{\cdot\cdot}{\ddot{O}}:^{-} \\ :\underset{\cdot\cdot}{O}:_{-} \end{array}$$

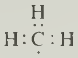
sulfate ion

In NH_4^+, each electron pair is divided between N and H. This gives one electron for each H, the same as a hydrogen atom. N has a total of 4, one less than atomic nitrogen; hence, the formal charge of +1 is associated with N. This procedure assigns the entire positive charge of $(NH_4)^+$ to the nitrogen; in practice, the electrons are spread over the entire molecule. However, this method of assigning formal charges does keep strict account of the total numbers of electrons and charges present and, when used with care, it helps to interpret chemistry. For example, the formal charge of −1 assigned to the oxygen of methoxide ion helps to explain why this ion is a strong base that readily adds a proton to the oxygen.

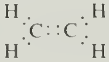
The example of sulfate ion is more complex. Some students tend to write this ion as $^{-}:\underset{..}{\ddot{O}}:\underset{..}{\ddot{O}}:\underset{..}{\ddot{S}}:\underset{..}{\ddot{O}}:\underset{..}{\ddot{O}}:^{-}$, an arrangement that has the proper number of valence electrons and a less complex formal structure assignment. However, sulfate ion is known experimentally to have each oxygen bound to sulfur in an equivalent manner.

When a species has an incomplete octet, it is usually unstable or highly reactive. Examples are methyl cation and methyl radical.


methyl cation


methyl radical

Multiple bonds are handled in a straightforward manner.


ethylene

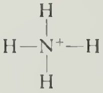
$H:C:::C:H$

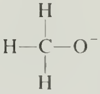
acetylene

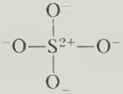
$^{-}:C:::N:$

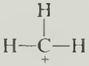
cyanide ion

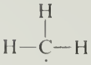
A further simplifying convention is to replace each electron pair bond by a line. For convenience, electron pairs are frequently omitted.

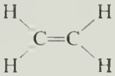










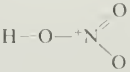


$H{-}C{\equiv}C{-}H$

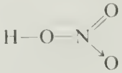
$^{-}C{\equiv}N$

In these symbolic representations, the lone pair electrons are understood to be present and their presence is signified by appropriate formal charges. This is another reason for assigning formal charges properly. *The use of such symbols is widespread in organic chemistry and practice in reading and writing these electronic representations cannot be overemphasized.* The simplified symbols correspond to an earlier notational system proposed by August Kekulé. Accordingly, such symbols, in which each electron pair bond is represented by a line and the lone pair electrons are omitted, are frequently called Kekulé structures.

The use of a "dative" or "coordinate covalence" bond is sometimes convenient. In this convention, an arrow represents a two-electron bond in which both electrons are considered to "belong" to the donor atom for the bookkeeping purpose of assigning formal charges.



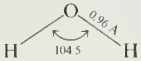
or



This type of symbolism finds most use in representing ligands in inorganic complexes and will rarely be used in this text.

2.3
Geometric Structure

One of the really important achievements of the physics of a half century ago was the determination of crystal structures by x-ray diffraction. Other methods that may be used for the precise determination of molecular structures include electron diffraction and microwave spectroscopy. These experimental approaches have yielded a wealth of detailed structures at the molecular level. For example, H_2O is known to have a structure with a bent H—O—H bond angle of 104.5° and an O—H bond distance of 0.96 Å ($1\ \text{Å} \equiv 1 \times 10^{-8}$ cm).



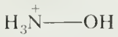
It should be emphasized that water is not a rigid molecule with the atoms fixed in this geometry. The atoms are constantly in motion, even at a temperature of absolute zero. This motion is conveniently described in terms of the bending and stretching of bonds. At any instant of time, the actual O—H distance may vary from 0.96 Å by several hundredths of an Ångstrom, but the average distance will be that given. Similarly, bond angles are constantly changing, and the value given is an average value.

An important result has emerged from these many structural studies. Specific bonds retain a remarkably constant geometry from one compound to another. For example, the O—H bond distance is almost always 0.96–0.97 Å.

Compound	*O—H Bond Distance,* Å
HO—H, water	0.96
HOO—H, hydrogen peroxide	0.97
H_2NO—H, hydroxylamine	0.97
CH_3O—H, methyl alcohol	0.96

In fact, it is this consistency that allows us to treat the O—H bond as an individual unit in different compounds.

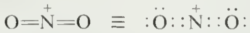
Lewis structures can be useful in the interpretation of bond distances. For example, the N—O bond distance is longer in hydroxylammonium ion than in nitronium ion:



$$H_3\overset{+}{N}\text{——}OH$$

1.45 Å

hydroxylammonium ion



$$O{=}\overset{+}{N}{=}O \equiv :\ddot{O}::\overset{+}{N}::\ddot{O}:$$

1.15 Å

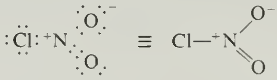
nitronium ion

> The hydroxylammonium ion should not be confused with ammonium hydroxide, $NH_4^+\ OH^-$. The hydroxylammonium ion is ammonium ion with one N—H bond replaced by an N—OH bond.

In $HONH_3^+$, one electron pair binds the nitrogen to the oxygen, and the compound is said to have a N—O **single bond.** In NO_2^+, the Lewis structure shows that each nitrogen-oxygen bond involves *two* pairs of electrons; the two bonds constitute a **double bond.** The equilibrium bond distance is that distance at which the net electrostatic attraction of the bonding electrons just balances the electrostatic repulsion between the two nuclei. For the N—O single bond, two bonding electrons are involved, and the balance of attraction and repulsion occurs at an internuclear distance of 1.45 Å. For the N=O double bond, more electrons are involved, with consequent greater net electrostatic attraction to the nuclei. The increased internuclear repulsion required to reach a balance occurs at the shorter distance of 1.15 Å.

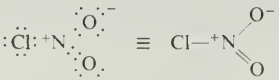
2.4
Resonance Structures

In some cases, it is not possible to describe the electronic structure of a species adequately with a single Lewis structure. An example is nitryl chloride, NO_2Cl.

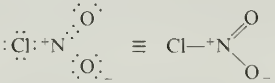


nitryl chloride

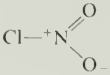
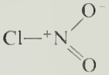
The Lewis structure shown has one N—O single bond and one N=O double bond. However, it has been determined experimentally that both N—O bonds are equivalent. Furthermore, the N—O bond distance of 1.21 Å is intermediate between the N—O single and double bond distances described in the previous section. Actually, two alternative structures may be written for nitryl chloride. The two structures differ only in the positions of electrons.



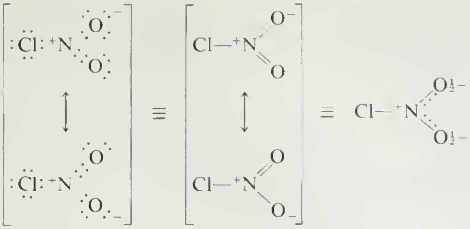
or



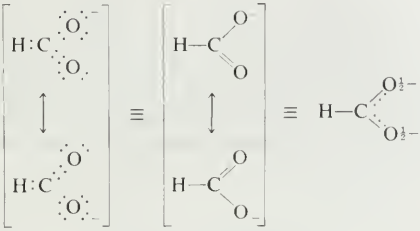
The actual electronic structure of NO_2Cl is a composite or weighted average of the two Lewis structures. The two alternative structures are called **resonance structures**, and the molecule is said to be a **resonance hybrid.**

It is important to recognize that nitryl chloride *has only one geometric structure,* that in which the two N—O bonds are equivalent. It is *not*  half of the time and  the other half. It is a hybrid in the same sense that a mule is a hybrid of a horse and a donkey. Resonance structures are necessary only because of inadequacies in our simplified system for describing the bonding and electron distribution in molecules. When one conventional Lewis structure does not adequately describe what we know to be the actual structure of a species, we use two or more structures (resonance structures) for the species and bear in mind that the species has some characteristics of each structure.

Resonance structures are written with a double headed arrow, and the resonance hybrid is frequently written with dotted lines to represent partial bonds. Even in such cases, the individual Lewis structures provide an accurate accounting of the electrons and are frequently to be preferred to dotted-line formulas. In the case of nitryl chloride, the Lewis structures indicate that the N—O bond is halfway between single and double, and we expect an intermediate bond distance. Because each N—O bond is single in one resonance structure and double in the other, the N—O bond in the resonance hybrid is said to have a bond order of $1\frac{1}{2}$.

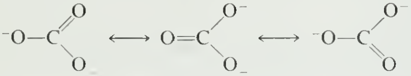


Another species that is not adequately described by a single structure is formate ion, HCO_2^-. As in the case of nitryl chloride, formate ion is a hybrid of two resonance structures.

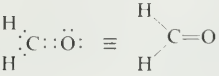


Both of the C—O bonds have a bond order of $1\frac{1}{2}$. Accordingly, the C—O bond distance of 1.26 Å is intermediate between the C—O double bond distance of 1.20 Å in $H_2C{=}O$ and the C—O single bond distance of 1.43 Å in $HO{-}CH_3$.

Carbonate ion, CO_3^{2-}, is somewhat more complicated in that three resonance structures are required. The resonance hybrid has three equivalent C—O bonds, each having a bond order of $1\frac{1}{3}$. Because the C—O bonds in carbonate ion (order $1\frac{1}{3}$) have more single bond character than those in formate ion (order $1\frac{1}{2}$), they are slightly longer (1.28 Å).

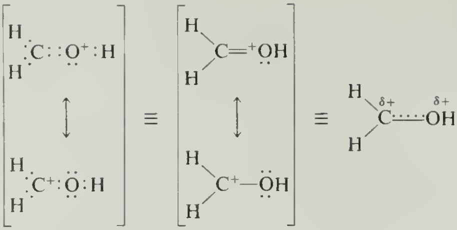


In each of the foregoing examples, the important resonance structures are equivalent. In some cases, a species is best described by two or more resonance structures that are not energetically equivalent. One such species is protonated formaldehyde, $(H_2COH)^+$. Formaldehyde itself may be represented by a Lewis structure in which there are two C—H single bonds and a C=O double bond.

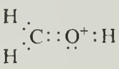


formaldehyde

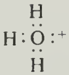
In protonated formaldehyde, an additional O—H single bond is present. Two Lewis structures may be written for $(H_2COH)^+$.



In one structure, there is a C=O double bond and the positive charge is assigned to oxygen. This **oxonium ion structure** is analogous to the hydronium ion, H_3O^+.

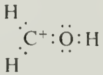


oxonium ion structure

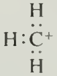


hydronium ion

In the alternative structure, there is a C—O single bond and the positive charge is assigned to carbon. This **carbonium ion structure** is analogous to the methyl cation, CH_3^+.



carbonium ion structure

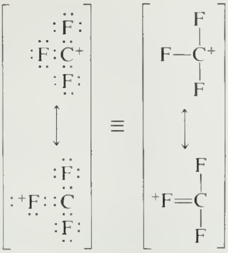


methyl cation

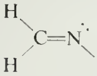
Which structure more adequately represents protonated formaldehyde? The C—O bond length in $(H_2COH)^+$ is 1.27 Å, which is much closer to the normal C=O double bond length of 1.20 Å than to the normal C—O single bond length of 1.43 Å. On this basis, we conclude that $(H_2COH)^+$ is more nearly described by the oxonium ion structure than by the carbonium ion structure. However, the C—O bond length *is* significantly longer than a normal double bond, and calculations show that there *is* a substantial partial positive charge on carbon. We shall see in Chapter 15 that much of the chemistry of $(H_2COH)^+$ is best explained by the contribution of the less important carbonium ion structure.

Again, let us reiterate that *neither oxonium nor carbonium ion structure provides a totally accurate description of* $(H_2COH)^+$. The actual ion is a resonance hybrid of the two structures. It "looks" more like the oxonium ion structure than like the carbonium ion structure, and it has some of the characteristics of each. The C—O bond order is something between 1 and 2, but closer to 2. The positive charge is spread over both atoms, but is mostly borne by oxygen. Because oxygen is more electronegative than carbon, the positive charge would rather be on carbon. However, in this structure, carbon does not have an electron octet. In order for carbon to fill its octet, the positive charge must be borne by the more electronegative oxygen. *In cases such as this, the more important resonance structure is generally that one with all octets filled, even if a positive charge is assigned to the more electronegative atom.*

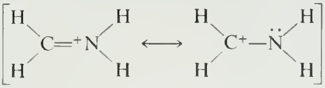
An extreme example of this principle is trifluoromethyl cation, CF_3^+. It has been calculated that the C—F bond length in this ion is 1.27 Å, much less than the normal C—F single bond length of 1.38 Å. Thus, the fluoronium ion structure is a major contributor to the resonance hybrid, even though the positive charge must be assigned to fluorine, the most electronegative of all the elements.



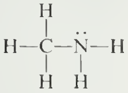
Another interesting example is provided by protonated methyleneimine, $(H_2CNH_2)^+$. The C—N bond length of 1.29 Å is almost exactly the same as the C—N double bond length in methyleneimine itself (1.27 Å), and is much less than the normal C—N single bond length of 1.47 Å.



methyleneimine
C—N length = 1.27 A



protonated methyleneimine
C—N length = 1.29 A

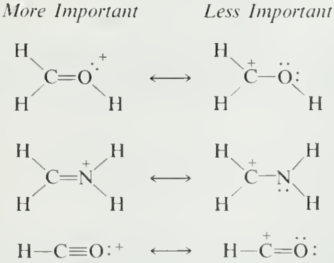


methylamine
C—N length = 1.47 A

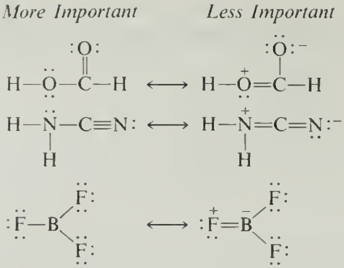
In this case, the ammonium ion structure dominates the hybrid even more than the oxonium ion structure does in the case of $(H_2COH)^+$ because the difference in electronegativity between carbon and nitrogen is less than that between carbon and oxygen.

In summary, let us set out some empirical rules for assessing the relative importance of the resonance structures of molecules and ions:

1. Resonance structures involve *no* change in the positions of nuclei; only the electron organization is involved.
2. Structures in which all first row atoms have filled octets are more important than structures with unfilled octets. The contribution of the nonoctet structure increases as the difference in electronegativity between the atoms increases.

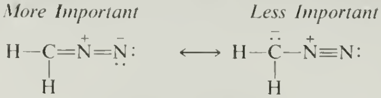


3. The more important structures are those involving a minimum of charge separation.

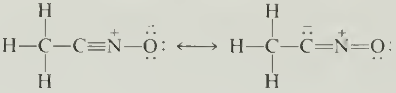


In cases such as these, however, the less important charge-separated structure still contributes significantly, and we shall find this contribution useful in interpreting some chemical reactions.

In some cases, Lewis structures with complete octets cannot be written without charge separation. In such alternative structures, the more important structure is again that in which the negative charge is borne by the more electronegative element and the positive charge by the more electropositive element.

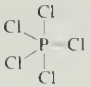


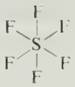
diazomethane



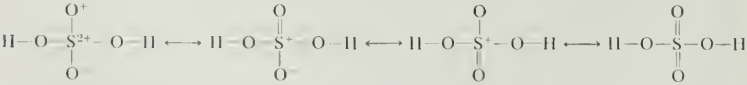
acetonitrile oxide

Elements beyond the first row can apparently "expand" their octets in appropriate cases. Examples are provided by phosphorus pentachloride, PCl_5, and sulfur hexafluoride, SF_6.





In the same manner, some compounds of these elements are often written as resonance hybrids with expanded octet resonance structures. An example is sulfuric acid.



The normal Lewis octet structure at the far left has a formal charge of +2 on sulfur. Sulfuric acid is known to be a strong acid and the high formal charge on sulfur helps to explain the ease of loss of a proton. However, the expanded octet structures have less separation of charge and may contribute significantly to the resonance hybrid.

2.5
Atomic Orbitals

Careful use of Lewis structures and the related straight-line structural shorthand is clearly important in understanding the physical and chemical properties of molecules. But these structures are themselves only symbolic representations of electronic structures. In the real world, electrons do not stand still in octets. A more complete understanding of the chemical bond and the structure of molecules requires a discussion of the modern theory of electronic structure in terms of wave functions or orbitals. Unfortunately, this theory involves new and unfamiliar concepts that do not relate to human experience. Atomic and molecular orbitals are usually covered in depth in courses on physical chemistry, but the qualitative aspects are so important to understanding modern organic chemistry that a brief survey of some results of quantum mechanics is highly desirable at this point. In the next few sections, we shall review those aspects of atomic and molecular orbital theory that are particularly important in the study of organic chemistry.

As mentioned in Section 2.1, the periodic table of the elements was first conceived in a purely empirical fashion. The various known elements were arranged into groups and rows on the basis of similarities in their chemical and physical properties. The "periodicity" of the table first became understandable with the early development of electronic theory. This early theory was based on the Bohr model, which is often taught by analogy of an atom to a miniature solar system in which electrons are pictured as revolving in stationary orbits around a nucleus, much in the same way that planets revolve about the sun.

With the advent of quantum mechanics about a half century ago, this analogy was shown to be seriously deficient in an extremely important respect. A basic tenet of quantum mechanics is the **Heisenberg uncertainty principle,** which states that it is not possible to determine simultaneously both the precise position and momentum of an electron. In other words, the laws of nature are such that we cannot determine an exact trajectory for an electron. The best we can do is to describe a probability distribution that gives the probability of finding an electron in any region around a nucleus. The mathematical description that leads to this probability distribution has the same form as that which describes a wave. Thus, we may use the mathematics and concepts of wave motion to describe electron distributions. Consequently, it is common to refer to the motion of an electron around a nucleus as a "wave motion" or in terms of a "wave function." This does not mean that the electron actually bobs up and down like a cork in a stormy sea. It is only a convenient language that helps to characterize the mathematical equations that describe the electron probability distribution.

In quantum mechanics, an **atomic orbital** is defined as a one-electron wave function, ψ. For each point in space there is associated a number whose square is proportional to the probability of finding an electron at that point. Such a probability distribution corresponds to the more useful concept of an **electron density** distribution. The mathematical function that describes this distribution has all the properties associated with waves. It has a numerical magnitude (its *amplitude*), which can be either positive or negative (corresponding to a wave crest or a wave trough, respectively), and *nodes*. A node is the region where a crest and a trough meet. For the three-dimensional waves characteristic of electronic motion, the nodes are two-dimensional surfaces at which $\psi = 0$. Consequently, atomic orbitals may be characterized by their corresponding nodes as given by *quantum numbers* (Table 2.3).

TABLE 2.3
Atomic Quantum Numbers

Quantum Number	Symbol	Possible Values	Relationship to Nodes
principal	n	1, 2, 3, . . .	one more than the total number of nodes*
azimuthal or angular momentum	l	$0, 1, \ldots, n-1$	number of nonspherical nodes
magnetic	m	$-l, \ldots, 0, \ldots +l$	character (planes or cones) and orientation of nonspherical nodes
spin	—	$-\frac{1}{2}, +\frac{1}{2}$	none

* Because atomic orbitals are exponential functions, they have very small values at distances far from the nucleus but never reach zero. The extra node could therefore be taken at infinity, but such a node could never be represented in conventional symbols. If the node "at infinity" is included, the principal quantum number is the same as the total number of nodes.

If one recognizes the relationship between quantum numbers and the number and character of the nodes in a wave, it is clear why quantum numbers are integers; that is, it is meaningless to talk of a fraction of a node. In labeling a particular atomic orbital, the principal, azimuthal, and magnetic quantum numbers are specified. The three quantum numbers are expressed in the order *nlm*, but in a particular manner. The principal quantum number n is given as the appropriate integer. The azimuthal number l is expressed in code, where $0 = s$, $1 = p$, $2 = d$, and $3 = f$. In spatial descriptions m is not given explicitly, but is implied in a subscript code that defines the orientation of the orbital.

Examples

$1s$ no nodes. This wave function is a spherically symmetric function whose numerical value decreases exponentially from the nucleus.
$2s$ one spherical node
$2p_x$ one node, the yz plane
$2p_y$ one node, the xz plane
$2p_z$ one node, the xy plane

These orbitals are the most important for the organic compounds we will study. They are usually represented symbolically as in Figure 2.1 (facing page). The plus and minus signs in Figure 2.1 have no relationship to electric charge. They are simply the arithmetic signs associated with the wave function, much as a positive sign for an ocean wave is a wave crest and a negative sign denotes a wave trough. We shall see in the next section that the positive and negative signs determine how two or more wave functions combine when they interact.

In the symbolic representations given in Figure 2.1, the solid line represents the angular part of the wave function and defines a three-dimensional closed surface. A useful approximation is to regard the surface as a locus of points of constant value of ψ such that some given, but arbitrary, proportion of the total electron density is contained within the surface. For example, the value of ψ may

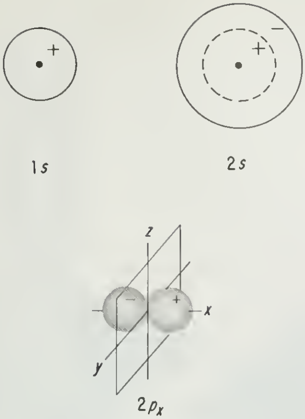


FIGURE 2.1 *Symbolic representation of some atomic orbitals.*

be selected so that the resulting surface will enclose 80%, 90%, 95%, and so on, of the electron density. The dotted lines in Figure 2.1 represent nodal surfaces. These nodes are a sphere for the 2*s* orbital and a plane for the 2*p* orbital. The strange shape of the *p* orbital is determined by the central attractive force of the nucleus and the constraint of a planar node.

The actual functions are depicted in Figure 2.2. In this figure, the value of ψ is plotted as the *z* component for each point in the *xy* plane of an atom. The parts of the wave function with positive sign appear above the grid plane, and the negative parts appear as depressions or holes below the grid plane.

The square of a wave function gives the electron density function. Electron density functions for 1*s*, 2*s*, and 2*p* orbitals are shown in Figure 2.3. Note how *s* orbitals have high electron density (electrons per unit volume) at the nucleus. The node shows up in the 2*s* and 2*p* orbitals as the valley floor where the electron density is zero.

The actual functions shown in Figures 2.2 and 2.3 point up the limitations of the symbolic representations of Figure 2.1. Despite these limitations, such symbols are simple and convenient and are widely used.

2.6
Electronic Structure of Atoms

The Pauli principle applied to atoms states that no two electrons can have identical quantum numbers. Three quantum numbers characterize an atomic orbital. Electrons have a fourth quantum number associated with the characteristics of spin. This quantum number may have a value of either $+\frac{1}{2}$ or $-\frac{1}{2}$. Consequently, each atomic orbital may have associated with it no more than two electrons, and these two electrons must have "opposite spin."

In general, the more nodes a wave function has, the higher is its energy. In

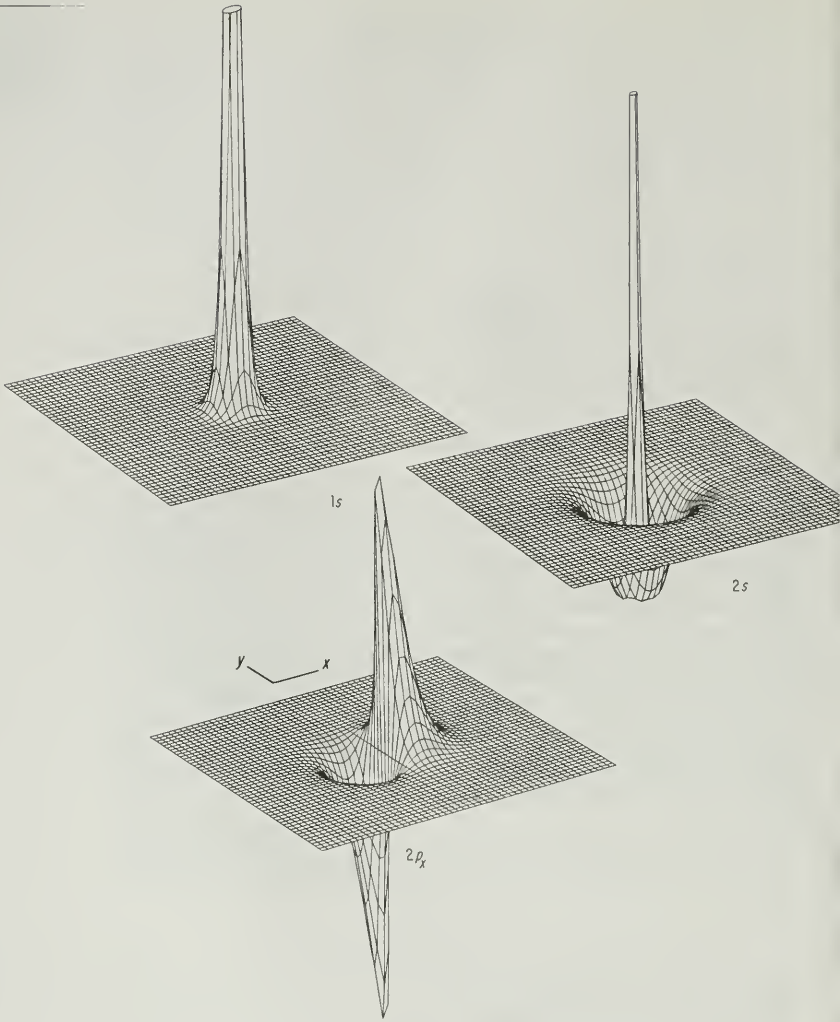


FIGURE 2.2 *Perspective plots of atomic orbitals.*

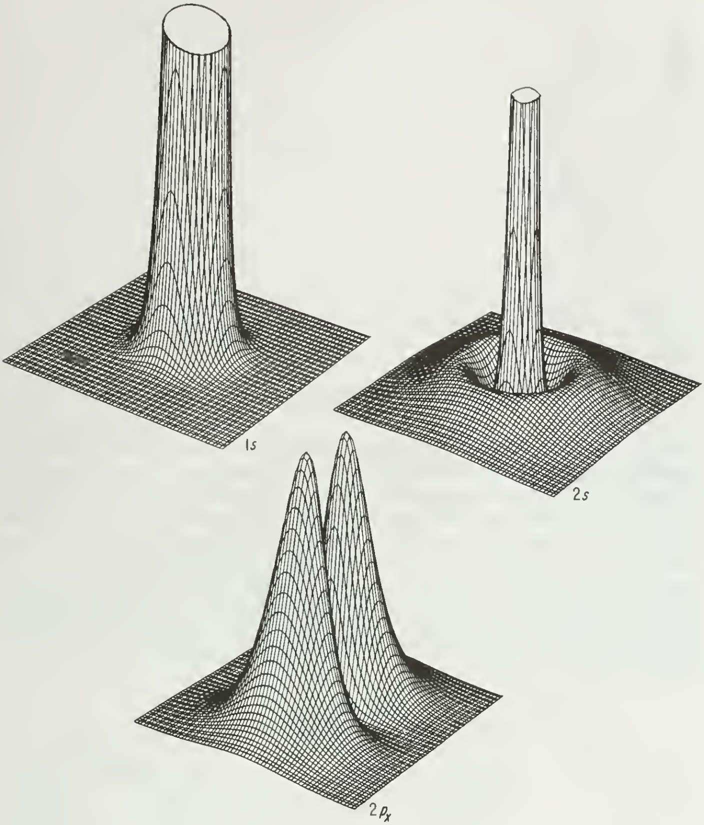


FIGURE 2.3 *Electron density plots of* 1s, 2s, *and* 2p *orbitals.*

atoms that have more than one electron, the energies of atomic orbitals increase in the order (see Figure 2.4):

$$1s < 2s < 2p < 3s < 3p, \text{ and so on}$$

The first electron is put into the lowest energy atomic orbital, 1*s*, to produce the hydrogen atom. The helium atom has two electrons, and the second electron can also be put into a 1*s* orbital if the second electron has a spin opposite that of the first electron. These two electrons "fill" the 1*s* shell, and helium has the stable electronic configuration characteristic of noble gases. The third electron of lithium must be put into a higher energy atomic orbital, 2*s*. The fourth electron of beryllium can also be put into the 2*s* orbital if its spin is opposite that of the third electron. The 2*s* orbital is now also filled, and the additional electrons of the first row elements must go into 2*p* atomic orbitals. The $2p_x$, $2p_y$, and $2p_z$

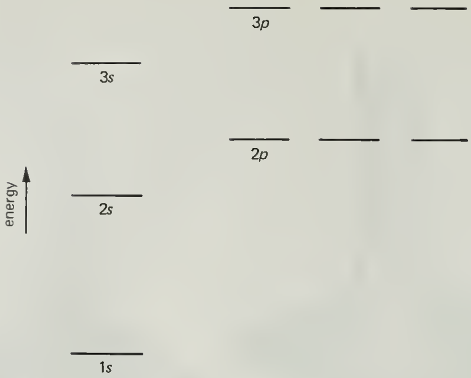


FIGURE 2.4 *Order of energy levels in an atom with more than one electron.*

orbitals may each accept two electrons, giving a total of six for the p set. Consequently, eight electrons fill the $n = 2$ shell and, again, give the stable filled-shell electronic configuration characteristic of the noble gases.

The process of filling successive atomic orbital levels with electron pairs is used to build up the entire periodic table. The atomic configurations of the first ten elements are summarized in Table 2.4. Each filled principal quantum shell corresponds to a stable noble gas. Other elements react in such a way as to achieve the stability associated with filled orbital shells. One way of achieving this higher stability is by combining atomic orbitals into molecular orbitals, as discussed in the next section.

TABLE 2.4
Electronic Configurations of Some Elements

H	$1s$	Li	$1s^22s$
He	$1s^2$	Be	$1s^22s^2$
		B	$1s^22s^22p$
		C	$1s^22s^22p^2$
		N	$1s^22s^22p^3$
		O	$1s^22s^22p^4$
		F	$1s^22s^22p^5$
		Ne	$1s^22s^22p^6$

2.7
Bonds and Overlap

One of the useful concepts derived from treating atomic orbitals as wave functions is that two such orbitals may overlap to form a **bond.** The combination of two waves having the same sign is reinforcing (Figure 2.5). This is true for

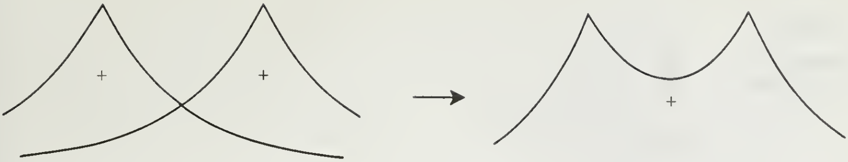


Figure 2.5 *Two interacting waves or wave functions of the same sign add or* **reinforce.**

light waves, sound waves, or the waves of an ocean. It is also true for the combination of two electron waves or wave functions having the same sign.

The increased magnitude of the wave function between the atoms corresponds to higher electron density in this region. Electrons are attracted electrostatically to both nuclei, and the increased electron density between the nuclei counterbalances the internuclear repulsion. The result is a **covalent bond.** An example is the combination of two 1*s* atomic orbitals to give a new wave function. This new function is a molecular orbital and encompasses both atoms, as shown in Figure 2.6. In Figure 2.6, the molecular orbital in (b) is a symbolic representation of the wave function, which is also plotted as the contour diagram (c) and as the three-dimensional perspective plot (d). In diagram (d), the vertical axis gives the value of ψ for each point in a plane through the molecule. This molecular

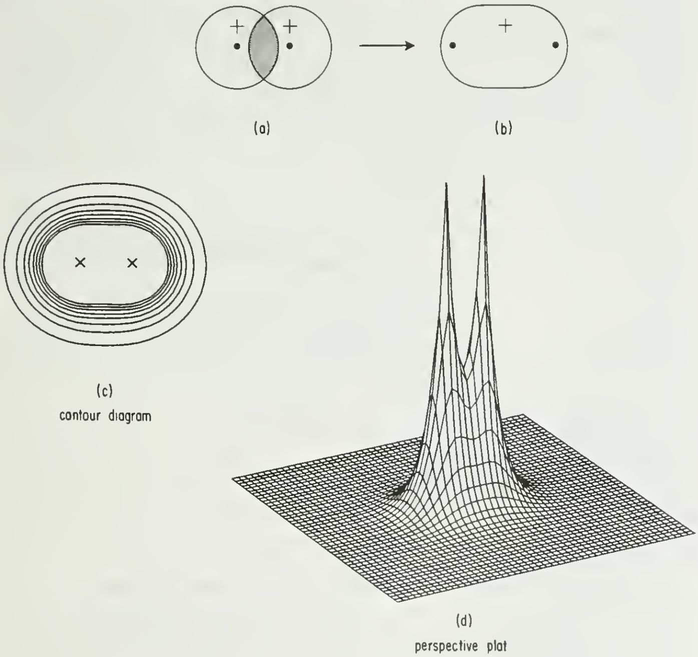


Figure 2.6 *The combination of two* H 1s *orbitals to form* H_2.

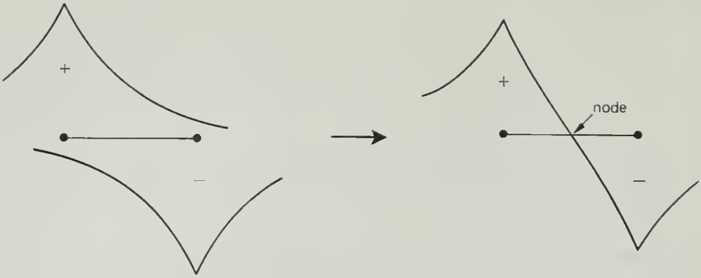


FIGURE 2.7 *Interaction of two waves of opposite sign gives subtraction of wave functions or* **interference.**

orbital is derived from the combination of two atomic orbitals overlapping as in (a). Each bond that we have heretofore symbolized by a shared electron pair or by a straight line may now be interpreted as a two-center molecular orbital (an orbital encompassing two nuclei). Each such two-center molecular orbital contains two electrons of opposite spin.

When two waves of opposite sign interact, they interfere, or cancel each other. It is this characteristic of waves that can produce regions of darkness in the interaction of two light beams or regions of silence from the combination of two sound waves. At the point of interference the wave function has the value of zero; that is, interference of waves creates a node. The same pattern holds for electron waves. The interaction of two orbitals of opposite sign produces a node between the nuclei, as illustrated in Figure 2.7. Because there is no electron density at a node, the reduced electron density between the nuclei in this case does not compensate for nuclear repulsion, and the net result is a higher energy or lower stability than that which corresponds to the noninteracting orbitals. Such a molecular orbital is called **antibonding.**

The interaction of two orbitals can be positive or reinforcing to give a bonding molecular orbital, or the combination can be negative or interfering to give an antibonding molecular orbital. The bonding combination corresponds to a de-

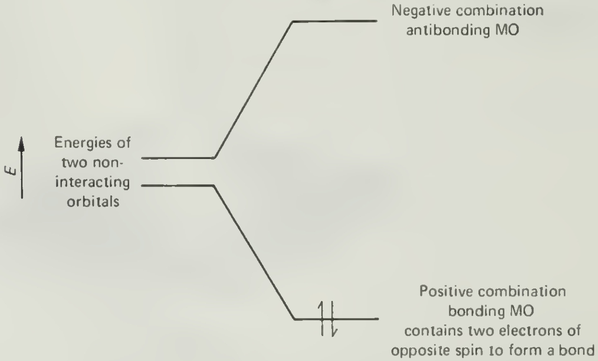


FIGURE 2.8 *Energy relationships of combining orbitals.*

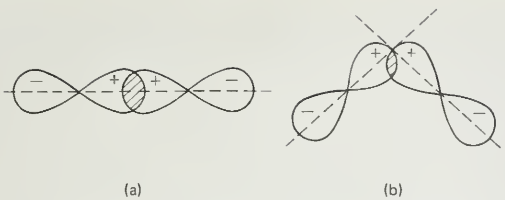


FIGURE 2.9 *Illustrating* (a) *the overlap of two* p *orbitals along the internuclear axis and* (b) *and* (c) *off the internuclear axis. The molecular orbital resulting from the overlap in* (a) *has lower energy than that for* (b) *or* (c).

crease in energy (greater stability); the antibonding combination corresponds to an increase in energy (lower stability). Two atomic orbitals give rise to two molecular orbitals. The two paired electrons of opposite spin available for the bond can be put into the bonding molecular orbital. We will not use the antibonding molecular orbital for most of the normal compounds important in organic chemistry, but we will make use of it in some reactions and in electronic spectroscopy (Chapter 22).

The energy relationships of two combining orbitals are summarized in Figure 2.8. Note how the energies of the two starting orbitals separate or spread apart when they interact to form the two molecular orbitals. The amount of the separation depends on the degree to which the orbitals overlap. A slight overlap gives two molecular orbitals that differ little in energy; a large overlap results in strong separation such as that shown in Figure 2.8. For axially symmetric orbitals, such as *p* orbitals, greatest overlap occurs when the orbitals are allowed to interact along the nuclear axis, that is, to form straight bonds. We shall see later that, if orbitals are so constrained that overlap is not along the internuclear axis, the resulting "bent bonds" (Figure 2.9b and c) are weaker than equivalent straight bonds (Figure 2.9a).

2.8
Hybrid Orbitals and Bonds

When more than two valence electrons on the same atom are involved in bonding, the individual bonds are not generally describable in terms of overlap of simple atomic orbitals as in the foregoing example. Consider the molecule BeH_2 as an example. Spectroscopic measurements show that the three atoms in BeH_2 lie in a straight line and that the two Be—H bonds are of equal length. These two bonds clearly cannot be described adequately by using the beryllium 2*s* orbital for one bond and a 2*p* orbital for the other. These two orbitals have different spatial extentions and different energies and would be expected to give different bonds. The bonding can be explained if we construct *two equivalent hybrid orbitals* by combining the 2*s* and a 2*p* orbital. This is done mathematically by taking the sum and the difference of the two orbitals, as in Figure 2.10. This example shows how the mathematical signs of wave functions enter into arithmetic operations.

The two orbitals that result from this operation are designated *sp* hybrid orbitals because they are each constructed from equal amounts of an *s* and a *p* orbital. The *sp* hybrid orbital is shown in contour form in Figure 2.11a, and as the three-dimensional perspective plot in Figure 2.11b. The two hybrid orbitals are each suited for bond formation by overlapping with an H 1*s* orbital. They are

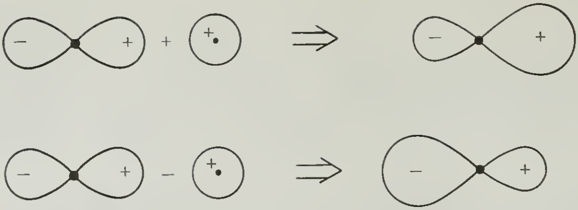


FIGURE 2.10 *Mathematical combination of* s *and* p *orbitals to yield two* sp *hybrid orbitals.*

equivalent and are directed opposite each other. Furthermore, the two lobes of a hybrid orbital are unequal in "size"—the larger lobe can overlap well with another orbital. That is, overlap at the large lobe can occur readily in a straight line to produce stronger bonding.

Why does beryllium form bonds in this manner rather than by overlap of the simple atomic orbitals? The answer is simply that stronger bonds and a more stable structure result when the system H-Be-H is linear and the two bonds are of equal length. In this manner *the two electron pairs involved in the bonds are directed as far apart from each other as possible.* This principle is a useful method for predicting the geometry of a molecule in which several groups are bonded to a central atom. In general, the bonding may be described by constructing as many hybrid orbitals from the simple *s* and *p* atomic orbitals as are needed to

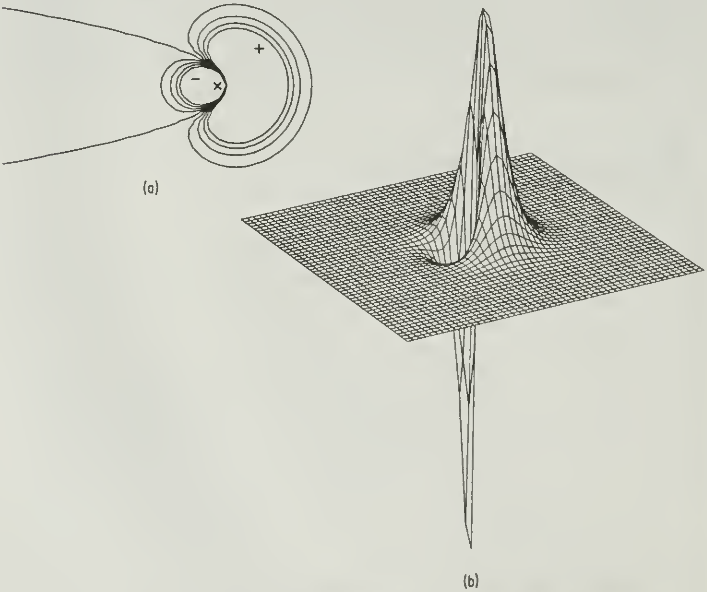


FIGURE 2.11 *Contour and perspective plots of an* sp *hybrid orbital.*

accommodate all of the valence electrons associated with the central atom. In the BeH_2 example, we used one *s* and one *p* orbital and constructed two equivalent hybrids. Each such hybrid is described as 50% *s* and 50% *p*. In constructing such combinations, we must again obey the "rule of conservation of orbitals." We must end up with as many orbitals as we started with. The beryllium atom has, of course, two remaining *p* orbitals that are not occupied by electrons in the molecule BeH_2.

As a further example, consider a species in which three groups are to be bonded to a central atom. From an *s* orbital and two *p* orbitals—for example, a p_x and p_y orbital—we may construct three equivalent sp^2 hybrids. Each such hybrid is $\frac{1}{3}$ *s* and $\frac{2}{3}$ *p*. The three equivalent hybrids lie in the *xy* plane (the same plane defined by the two *p* orbitals) and are directed 120° from each other (Figure 2.12).

Methyl cation, CH_3^+, is an example of such a species. It is planar and the three C—H bonds are equal in length. It may be regarded as being derived from overlap of three equivalent carbon sp^2 orbitals with hydrogen 1*s* orbitals. Each bond may be represented as C_{sp^2}-H_{1s}. The remaining carbon *p* orbital is perpendicular to the molecular plane and contains no electrons. In this process of conceptual development, we have used the sequence of combining three atomic orbitals to form three hybrid orbitals (Figure 2.12) that are allowed to overlap (Figure 2.13a) to form three two-center molecular orbitals (Figure 2.13b). Each of these molecular orbitals contains two electrons, and the carbon also has two electrons in its 1*s* orbital that are not normally represented in our simple valence symbols. The total electron density distribution for the molecular plane of CH_3^+ is shown in the perspective plot in Figure 2.13c.

Finally, from an *s* orbital and three *p* orbitals we may derive four sp^3 hybrids directed to the corners of a tetrahedron with an interorbital angle of 109.5°, the tetrahedral angle. Each such hybrid orbital is 25% *s* and 75% *p*. The tetrahedral structure of methane, CH_4, is illustrated in the stereo plot* in Figure 2.14a or by the perspective model in Figure 2.14b. Each bond between C and H may be described as a C_{sp^3}-H_{1s} bond. Each such bond is derived by the interaction of a C_{sp^3} hybrid orbital with a hydrogen 1*s*, as in 2.14c, to produce the resulting two-center molecular orbital shown in 2.14d. The actual wave function—the mathematical form of the molecular orbitals—for which 2.14d is only a symbolic representation, is shown in contour form in 2.14e and as a three-dimensional perspective diagram in 2.14f. The small "tail" of the carbon sp^3 hybrid is clearly

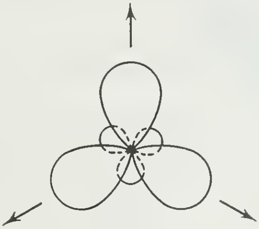


FIGURE 2.12 *Three* sp^2 *hybrids.*

---

* This textbook contains a number of stereo pictures to illustrate three-dimensional figures. Most bookstores carry inexpensive viewers for use with such figures. Some people cannot for various reasons "see" the three-dimensional effect, even with proper viewers. Even in such cases, however, the perspective in the stereo figures can be useful.

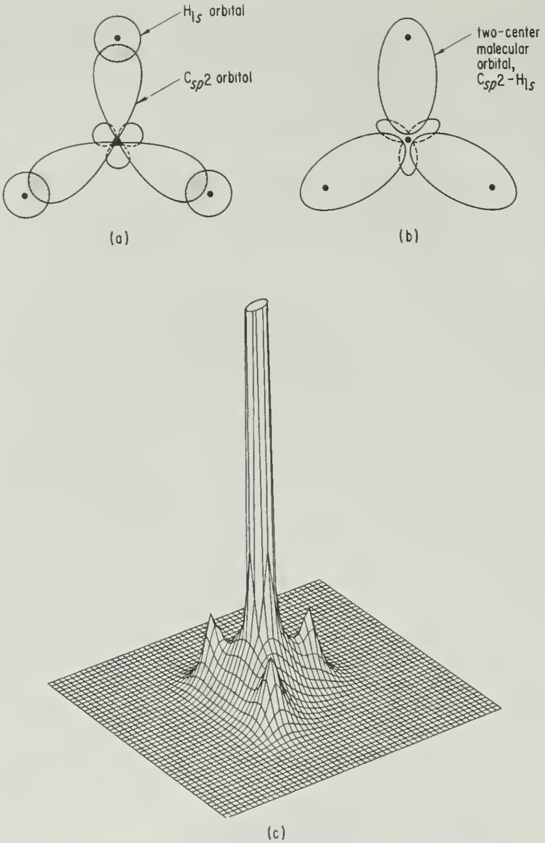


FIGURE 2.13 *Development of the electronic structure of* CH_3^+.

evident. So is the large magnitude of the wave function in the region between the C and H, characteristic of the high electron density between atoms that provides covalent bonding.

The hybrid orbitals considered thus far are equivalent, but it is not necessary that all orbitals on an atom be equivalent when the molecule lacks symmetry. It is possible to have a hybrid orbital that is, for example, 27% *s* and 73% *p*. In NH_3, for example, the H—N—H bond angle of 107.1° does not correspond to any simple hybrid. In addition to its three N—H bonds, ammonia also has a nonbonding pair of electrons on the nitrogen. These electrons are in an orbital which has slightly more *s* character than in a simple sp^3 orbital. Consequently, the three hybrid orbitals that overlap with the three hydrogen atoms contain slightly less *s* character than in a sp^3 orbital (actually, these orbitals are each approximately 23% *s* and 77% *p*). Electrons in *s* orbitals have lower energy than electrons in *p* orbitals. Therefore, bonds with more *s* character tend to be stronger.

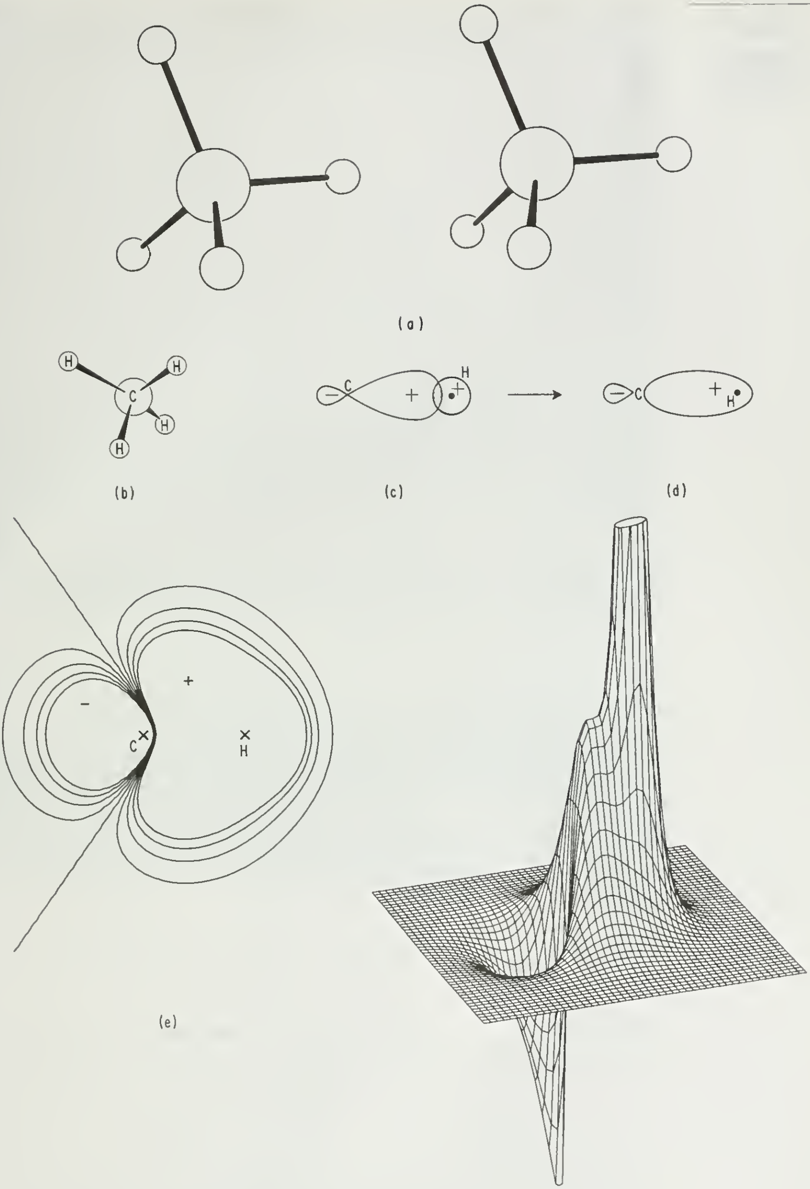

(a)
H
H
C
H
H
(b)
C
H
+
+
−
(c)
−
C
+
H
(d)
+
−
C
H
(e)
(f)

FIGURE 2.14 *Methane,* CH_4*, and its* C_{sp^3}—H_{1s} *bond.*

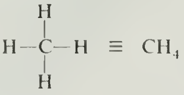
However, an electron pair in a bond is affected by two nuclei, whereas nonbonding electrons are attracted only by a single nucleus. Hence, *s* character is more important for lone pair electrons than for bonding electron pairs. In dividing the available *s* orbital among bonds and lone pairs, the lone pairs generally receive a higher proportion.

This type of result is general. In water, for example, the H—O—H bond angle is 104.5° and each O—H bond clearly involves an oxygen hybrid with more *p* character than in ammonia. The two oxygen lone pairs require a large fraction of the available oxygen 2*s* orbital. In HF, the H—F bond is an almost pure F_{2p}-H_{1s} bond, and the fluorine 2*s* orbital is used almost entirely for the three lone pairs. Nevertheless, despite these complexities, it is frequently convenient and sufficient to regard the two-center molecular orbitals that comprise electron-pair covalent bonds to be composed *approximately* of simple hybrids: sp, sp^2, sp^3, and so on.

The total electron density symbolized in the various perspective plots in this section is real in the sense that it can, in principle, be seen and measured. However, in order to understand such electron distributions, we generally dissect the total system into component parts that we can work with conceptually through the manipulation of symbols. Our concepts of orbitals, hybrids, and bonds should be regarded in this light. In principle, there are many possible ways of dissecting a total molecular electron density distribution into smaller and smaller parts. Our traditional way is merely one such method, but it is a method having historical roots and having evolved a grammar and language of its own. It is also a system that can be represented by simple symbols and serves as a powerful and widespread method for correlating and predicting a wide range of chemistry. As such, this symbolism and language have permeated many neighboring sciences such as biochemistry and molecular biology.

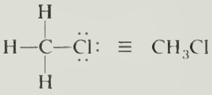
2.9
Organic Structures

Our structural representations with lines to indicate two-electron bonds between atoms were first interpreted in terms of Lewis structures. In modern orbital terms, each such line serves as a representation of a two-center molecular orbital, an orbital "localized" on a pair of atoms and derived from the overlap of two atomic or hybrid orbitals. These **structural formulas** are often further abbreviated for convenience by omitting the lines. The resulting expressions are called **condensed formulas.**



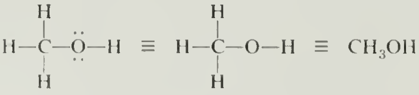
$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H \equiv CH_4}$$

methane



$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}\ddot{\underset{..}{Cl}}{:} \equiv CH_3Cl}$$

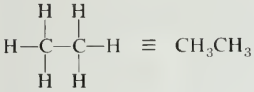
methyl chloride



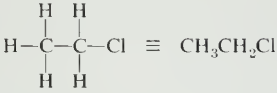
$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}\ddot{\underset{..}{O}}{-}H \equiv H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}O{-}H \equiv CH_3OH}$$

methyl alcohol

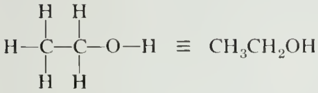
An important characteristic of organic compounds is the ubiquity of C—C bonds. Although some other atoms can bond to themselves to form short or long chains, carbon is unique in the extent and versatility of its **catenation** (chain formation; L., *catena,* a chain). Such C—C bonds are treated in the same way as others, as shown by the following examples.


$$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-H \equiv CH_3CH_3}$$

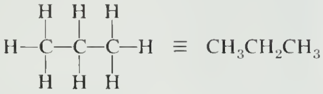
ethane


$$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-Cl \equiv CH_3CH_2Cl}$$

ethyl chloride


$$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-O-H \equiv CH_3CH_2OH}$$

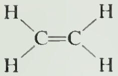
ethyl alcohol


$$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-H \equiv CH_3CH_2CH_3}$$

propane

The compounds involve C—H bonds that are all approximately C_{sp^3}-H_{1s}. Correspondingly, all of these C—H bonds have about the same length, 1.10 Å. Similarly, all of the C—C bonds in these compounds are approximately C_{sp^3}-C_{sp^3}, and these bond lengths are all about the same, 1.54 Å.

Compounds with multiple bonds can also be represented by condensed formulas.


$\equiv CH_2{=}CH_2$

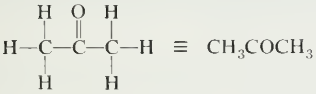
ethylene

$H{-}C{\equiv}C{-}H \equiv HC{\equiv}CH$

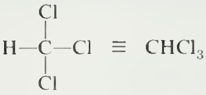
acetylene

The C—H bonds in ethylene are approximately C_{sp^2}-H_{1s} and are slightly shorter than C_{sp^3}-H_{1s} bonds. Similarly, the C—H bonds in acetylene are approximately C_{sp}-H_{1s} and are shorter still. The C—C double and triple bonds in ethylene and acetylene are also shorter and stronger than single bonds and are discussed in detail in subsequent chapters (Sections 12.1, 13.1).

Further examples in which several different types of bonds are involved are


$$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{H}{C}}-H \equiv CH_3COCH_3}$$

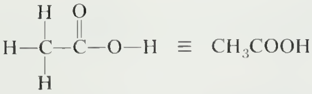
acetone


$$\mathrm{H-\overset{Cl}{\underset{Cl}{C}}-Cl \equiv CHCl_3}$$

chloroform

$O{=}C{=}O \equiv CO_2$

carbon dioxide


$$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-O-H \equiv CH_3COOH}$$

acetic acid

In our subsequent discussion of organic structures, we shall make common use of these simple bonding concepts and symbols. We shall find them to be common and powerful devices for understanding physical properties and reactions. Organic structures are generally so large and complex that it is essential to have such systematic methods for dissecting the whole molecule into component parts and individual bonds.

MOLECULAR MODELS. Organic compounds are three-dimensional, and the spatial interactions between parts of molecules can be complex and difficult to represent with two-dimensional diagrams. Two-dimensional structural symbols are still important for written discussions and we will discuss such representations in subsequent chapters, but they do have important limitations. Fortunately, however, bonds in organic compounds are formed from hybrid orbitals that approximate simple *sp*, sp^2 and sp^3 hybrids, and bond angles and distances are relatively constant from one molecule to another. This approximate constancy makes it feasible to examine organic structures and reactions with the aid of three-dimensional models. Various types of model sets are available for this purpose. Some are expensive precision constructions used primarily for research purposes, but several are relatively inexpensive and are designed for student use in the study of organic chemistry. Some of the sets available are summarized below.

Dreiding-Stereomodels are skeletal models constructed from welded stainless steel tubing. The bond lengths and angles are precisely proportional to the average molecular dimensions. They are relatively expensive and are widely used by professional chemists for research purposes.

Several types of skeletal model sets are marketed for student use. The Prentice-Hall Framework Molecular Models are constructed from flexible plastic tubing and small metal nuclei. The Science Related Materials, Inc., models are similar in design but use plastic nuclei and include separate pieces to designate hydrogens. The Benjamin-Maruzen models utilize plastic atoms with holes drilled to accommodate bonds. Models such as these are relatively inexpensive and are recommended as an aid in visualizing three-dimensional aspects of organic structures and reactions.

Corey-Pauling-Koltun (CPK^{TM}) Molecular Models are an example of space-filling models. The models are constructed from an acrylic polyester plastic and are proportional to the covalent and atomic radii of the atoms. They are held together by connectors made of a hard, rubber-like elastomer. They are fairly expensive and are mainly used by professional chemists for constructing models where a knowledge of molecular shape and intramolecular interactions is important. Figure 2.15 is a photograph of models of the ethyl alcohol molecule, constructed with each of the above types of models.

2.10
Functional Groups

The OH group in water reacts avidly with alkali metals such as potassium to form potassium hydroxide and molecular hydrogen.

$$H_2O + K \longrightarrow K^+\,OH^- + \tfrac{1}{2}\,H_2$$

A similar reaction occurs with the OH groups in nitric acid, sulfuric acid, and other acids containing hydroxy groups.

$$O_2NOH + K \longrightarrow K^+\,NO_3^- + \tfrac{1}{2}\,H_2$$

$$HOSO_2OH + 2\,K \longrightarrow 2\,K^+\,SO_4^{2-} + H_2$$

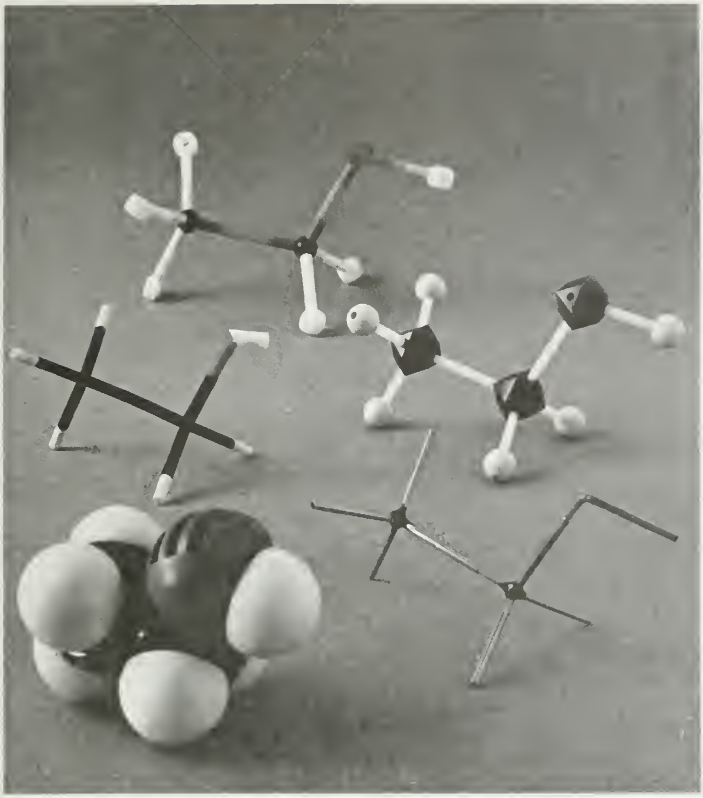


Figure 2.15 *Some molecular model representations of ethyl alcohol,* CH_3CH_2OH. *Models used are Science Related Materials (top), Framework (middle left), Benjamin (middle right), CPK (bottom left), and Dreiding (bottom right).*

It comes as no surprise, therefore, to find the same reaction occurring with methyl alcohol.

$$CH_3OH + K \longrightarrow CH_3O^- K^+ + \frac{1}{2} H_2$$

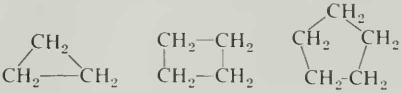
A large number of different alcohols are known. Each consists of an OH group attached to a carbon framework, and all show this same reaction. Because of this constancy in the chemical properties of the OH group, it is unnecessary to study in detail the reactions of each of these many alcohols. Instead, it suffices to study alcohols as a class of organic compounds that is characterized by the chemical properties of the hydroxy group. This is a fortunate situation, for it gives organic chemistry a logical and systematic structure. There are a number of atoms or groups of atoms that show a relative constancy of properties when attached to different carbon chains. Such groups are called **functional groups.** In our systematic study of organic chemistry we shall examine the chemistry of the important functional groups.

The simplest organic compounds are those that have no functional groups. These compounds consist only of carbon and hydrogen and are molecules in which carbons are joined to each other only by single bonds. These **saturated hydrocarbons** ("saturated" means having no double or triple bonds) may be noncyclic (the **alkanes**) or cyclic (the **cycloalkanes**). They form the framework to which functional groups may be attached. The symbol R is usually used to denote such an alkane or cycloalkane framework. With this symbolism the alkane class may be represented by RH. We will see in Chapter 5 that alkanes undergo only a limited number of reactions—precisely because they have no functional groups.

Some Alkanes

CH_4 $\quad$ CH_3CH_3 $\quad$ $CH_3CH_2CH_3$ $\quad$ $CH_3CH_2CH_2CH_3$

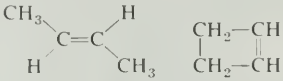
Some Cycloalkanes



In a similar manner, all hydrocarbons containing one or more C=C double bonds form a logical class, the **alkenes.** The hydrocarbons having a C≡C triple bond form a third structurally similar set, the **alkynes.**

Some Alkenes

$CH_2{=}CH_2$



Some Alkynes

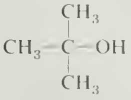
$CH_3{-}C{\equiv}C{-}H$ $\quad$ $CH_3CH_2CH_2{-}C{\equiv}C{-}CH_3$ $\quad$ $H{-}C{\equiv}C{-}H$

We will find a number of reactions characteristic of C—C multiple bonds that are not shared by single bonds.

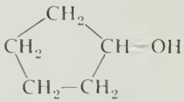
Organic compounds that contain C—O single bonds are classed as **alcohols** or **ethers**, depending on whether or not the oxygen is also bonded to a hydrogen.

Some Alcohols

$CH_3{-}OH$

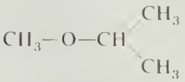


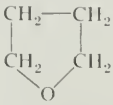
$CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}OH$



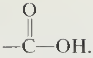
Some Ethers

$CH_3{-}O{-}CH_3$

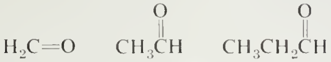




The C=O double bond, the carbonyl group, is found in **aldehydes** and **ketones.**

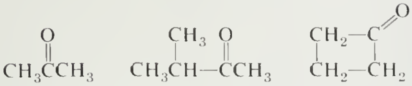
Combined with an OH group, it becomes a carboxy group,  $-\overset{\overset{\displaystyle O}{\|}}{C}-OH$. Compounds containing this functional group are **carboxylic acids.**

Some Aldehydes



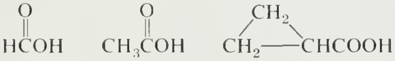
$H_2C{=}O \qquad CH_3\overset{\overset{\displaystyle O}{\|}}{C}H \qquad CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}H$

Some Ketones



$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \qquad CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}H-\overset{\overset{\displaystyle O}{\|}}{C}CH_3$

Some Carboxylic Acids



$H\overset{\overset{\displaystyle O}{\|}}{C}OH \qquad CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH$

Table 2.5 lists a number of the important functional groups. The structures and names of these groups should be committed to memory. They form an essential part of the language of organic chemistry. In our subsequent studies we will develop the chemistry of the individual functional groups in terms of structural and electronic theory, nomenclature (names), physical properties, the preparation from other functional groups, and the reactions that produce other groups.

Interconversions of functional groups constitute a large proportion of organic chemistry. After the individual groups have been studied, the effect of one group on another can be considered, for the organic chemistry of compounds with more than one functional group is not simply the sum of the parts. Groups affect each other, sometimes in complex ways. One of the reasons for studying the theory of organic chemistry is because of the understanding it can provide of the mutual interactions of functional groups.

TABLE 2.5

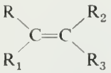
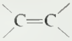
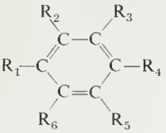
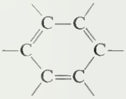
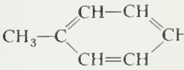
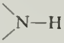
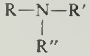
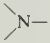
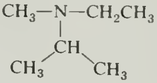
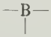
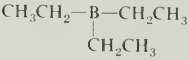
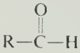
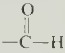
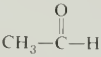
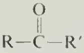
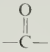
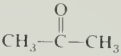
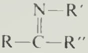
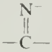
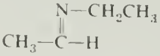
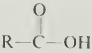
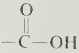
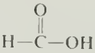
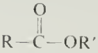
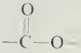
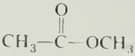
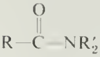
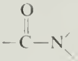
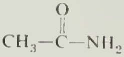
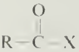
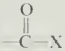
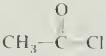
Class	General Structure	Characteristic Functional Group	Example
alkanes	R—H	none	CH_3CH_3
alkenes			$CH_3{-}CH{=}CH_2$
aromatic ring			
alkynes	$R{-}C{\equiv}C{-}R'$	$-C{\equiv}C-$	$CH_3{-}C{\equiv}C{-}CH_3$
alkyl halides	RF, RCl, RBr, RI	—F, —Cl, —Br, —I	CH_3Cl
alcohols	R—OH	—OH	CH_3CH_2OH

TABLE 2.5 (Continued)

Class	General Structure	Characteristic Functional Group	Example
ethers	$R-O-R'$	$-O-$	$CH_3-O-CH_2CH_3$
amines			
primary amines	$R-NH_2$	$-NH_2$	CH_3-NH_2
secondary amines	$R-NH-R'$		$CH_3-NH-CH_2CH_3$
tertiary amines	 $\underset{R''}{\underset{\vert}{R-N-R'}}$		
thiols	$R-SH$	$-SH$	CH_3SH
sulfides	$R-S-R'$	$-S-$	$CH_3-S-CH_2CH_3$
disulfides	$R-S-S-R'$	$-S-S-$	$CH_3-S-S-CH_3$
boranes	R_3B	 $\underset{\vert}{-B-}$	 $CH_3CH_2-\underset{CH_2CH_3}{\underset{\vert}{B}}-CH_2CH_3$
organometallic	RM, R_2M, R_3M	$-M$	CH_3Li, $(CH_3)_2Mg$, $(CH_3)_3Al$
aldehydes	 $R-\overset{O}{\overset{\Vert}{C}}-H$	 $-\overset{O}{\overset{\Vert}{C}}-H$	 $CH_3-\overset{O}{\overset{\Vert}{C}}-H$
ketones	 $R-\overset{O}{\overset{\Vert}{C}}-R'$	 $-\overset{O}{\overset{\Vert}{C}}-$	 $CH_3-\overset{O}{\overset{\Vert}{C}}-CH_3$
imines	 $R-\overset{N-R'}{\overset{\Vert}{C}}-R''$	 $-\overset{N-}{\overset{\Vert}{C}}-$	 $CH_3-\overset{N-CH_2CH_3}{\overset{\Vert}{C}}-H$
carboxylic acids	 $R-\overset{O}{\overset{\Vert}{C}}-OH$	 $-\overset{O}{\overset{\Vert}{C}}-OH$	 $H-\overset{O}{\overset{\Vert}{C}}-OH$
esters	 $R-\overset{O}{\overset{\Vert}{C}}-OR'$	 $-\overset{O}{\overset{\Vert}{C}}-O-$	 $CH_3-\overset{O}{\overset{\Vert}{C}}-OCH_3$
amides	 $R-\overset{O}{\overset{\Vert}{C}}-NR'_2$		 $CH_3-\overset{O}{\overset{\Vert}{C}}-NH_2$
acyl halides	 $R-\overset{O}{\overset{\Vert}{C}}-X$	 $-\overset{O}{\overset{\Vert}{C}}-X$	 $CH_3-\overset{O}{\overset{\Vert}{C}}-Cl$
nitriles	$R-C\equiv N$	$-C\equiv N$	$CH_3C\equiv N$
nitro compounds	$R-NO_2$	$-NO_2$	$CH_3CH_2-NO_2$
sulfones	$R-SO_2-R'$	$-SO_2-$	$CH_3-SO_2-CH_3$
sulfonic acids	$R-SO_2-OH$	$-SO_2-OH$	CH_3-SO_2-OH

The aromatic ring in Table 2.5 is written with three C=C double bonds. Nevertheless, we shall see later (Chapters 21, 29–35) that compounds containing this ring system differ substantially in their chemistry from the alkenes. Compounds containing this ring system are known collectively as **aromatic compounds.** Compounds with no aromatic ring are known as **aliphatic compounds.**

2.11
The Determination of Organic Structures

In the previous sections of this chapter, we have reviewed some basic concepts of electronic structure and bonding and have introduced the subject of organic structures and functional groups. In subsequent chapters, we shall take up the structures and chemical reactions of various classes of organic compounds and examine them in detail. Only one additional question remains to be answered before we embark upon our systematic study of organic chemistry. How does the chemist know the structure of a compound? The question is an important one and it is encountered over and over again by researchers in the field. In fact, the rate of development of organic chemistry as a science has been intimately related to our ability to *determine structure.*

Cast yourself, for a moment, in the role of a nineteenth-century scientist who has laboriously purified an organic substance from some source. How do you determine its structure? The substance has various physical properties that can be measured—boiling point, melting point, density, refractive index. It also undergoes various chemical reactions. It is relatively easy to assemble a catalog of physical and chemical properties for the compound and to decide that the compound is different from other previously isolated substances. But still, from all of this data, how do you write a molecular structure for the material? This problem challenged chemists for over a hundred years.

The first major breakthrough came with the development of methods of elemental analysis. The first attempts at elemental analysis were made by Lavoisier in the late eighteenth century, in connection with his pioneering work on the reactions of oxygen. Lavoisier examined the combustion products from various compounds and could deduce which elements were present in the substance burned. For example, combustion of methane gives carbon dioxide and water. Hence, methane must be built up from carbon and hydrogen in some way.

$$\text{methane} + O_2 \longrightarrow CO_2 + H_2O$$

Although Lavoisier's method of qualitative analysis sufficed to indicate which elements are present in various compounds, his results complicated rather than simplified organic chemistry. It showed that all known organic compounds were built up from a relatively small number of elements.

The next significant advance came in 1831, when Liebig developed the Lavoisier method into a precise quantitative technique for elemental analysis. For the first time, it was possible to determine accurate empirical formulas for organic compounds. In connection with methods for the determination of molecular weights, it was then possible to determine molecular formulas.

The method of combustion analysis, as developed by Lavoisier and Liebig, is conceptually very simple. A weighed quantity of the sample to be analyzed is burned in the presence of red-hot copper oxide, which is reduced to metallic copper. The sample is swept through the combustion tube with pure oxygen gas, which reoxidizes the copper to copper oxide.

$$\underset{\text{naphthalene}}{C_{10}H_{14}} + 27\ CuO \longrightarrow 10\ CO_2 + 7\ H_2O + 27\ Cu$$

$$2\ Cu + O_2 \longrightarrow 2\ CuO$$

The combustion products are swept through a calcium chloride tube, which absorbs the water formed, and then through a tube containing aqueous potassium hydroxide, which absorbs the carbon dioxide produced. The two tubes are weighed before and after combustion to determine the weights of water and carbon dioxide produced. From the weights of the two products, the weight of sample burned, and the atomic weights of carbon and hydrogen, it is possible to compute an empirical formula for the substance burned.

$$\text{weight of H in sample} = \text{weight of } H_2O \times \frac{2.016}{18.016}$$

$$\text{weight of C in sample} = \text{weight of } CO_2 \times \frac{12.01}{44.01}$$

$$\%\ \text{H in sample} = \frac{\text{weight of H}}{\text{weight of sample}} \times 100$$

$$\%\ \text{C in sample} = \frac{\text{weight of C}}{\text{weight of sample}} \times 100$$

If the percentages of carbon and hydrogen do not add up to 100 and no other element has been detected by qualitative tests, the deficiency is taken as the percentage of oxygen.

As an example, consider the analysis of propyl alcohol, C_3H_8O. An ideal analysis on a 0.5000 g sample would give 0.600 g of H_2O and 1.099 g of CO_2. The calculations proceed as follows:

$$\text{weight of H in sample} = 0.600\text{ g} \times \frac{2.016}{18.016} = 0.067\text{ g}$$

$$\text{weight of C in sample} = 1.099\text{ g} \times \frac{12.01}{44.01} = 0.300\text{ g}$$

$$\%\ \text{H in sample} = \frac{0.067}{0.500\text{ g}} \times 100 = 13.4$$

$$\%\ \text{C in sample} = \frac{0.300}{0.500} \times 100 = 60.0$$

The percentages of hydrogen and carbon add up to 73.4%, and the remaining 26.6% is taken as the percentage of oxygen in the sample. In actual practice, the analytical values are usually accurate to ±0.3%.

From the elemental analysis of a compound, one may easily calculate its **empirical formula,** which expresses the ratio of the elements present. In the present case, for example, the analysis tells us that 100 g of propyl alcohol contains 60.0 g of carbon, 13.4 g of hydrogen, and 26.6 g of oxygen. Dividing each of these weights by the appropriate atomic weights gives us the number of moles of each element in 100 g of sample.

$$\frac{60.0}{12.01} = 5.00\text{ moles of carbon}$$

$$\frac{13.4}{1.008} = 13.29\text{ moles of hydrogen}$$

$$\frac{26.6}{16} = 1.66\text{ moles of oxygen}$$

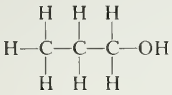
This gives us an empirical formula of $C_{5.00}H_{13.29}O_{1.66}$. However, because the atoms in a molecule must be present in whole numbers, the initially derived formula must be normalized. If we divide each of the factors derived above by the smallest, we have

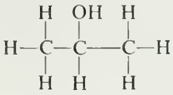
$$C_{\frac{5.00}{1.66}}H_{\frac{13.29}{1.66}}O_{\frac{1.66}{1.66}} = C_{3.01}H_{8.01}O_{1.00}$$

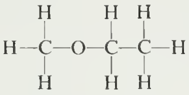
Thus, the empirical formula of propyl alcohol is calculated from its elemental analysis to be C_3H_8O. The **molecular formula** expresses the total number of each atom present and is the same as the empirical formula or some multiple of it. For example, if the molecular formula of propyl alcohol were $C_6H_{16}O_2$, the percentages of carbon, hydrogen and oxygen would be the same. (Actually, because of the rules of valence, $C_6H_{16}O_2$ is an impossible formula, as a little trial and error will readily reveal.)

The Lavoisier-Liebig method of analysis provided a tremendous boost to the development of organic chemistry, but required relatively large amounts of sample, on the order of 0.25–0.50 g. In 1911, Pregl introduced a technique of microanalysis that allows combustion analysis to be carried out on 3–4 mg of sample. Elements such as N, S, Cl, Br, I, P, and so on, are determined on a micro scale by other analytical methods that we shall not detail. Highly accurate molecular formulas may now be determined on a few micrograms of substance by the technique of high-resolution mass spectrometry (Chapter 16).

From the molecular formula, the next step is to derive a molecular structure. How are the atoms bonded to one another? For our present example of C_3H_8O, which of the following structures corresponds to propyl alcohol?







The answer to this question may be deduced by a careful consideration of the chemical and physical properties of the substance. The modern chemist makes much use of spectroscopic techniques, which we shall consider in subsequent chapters; nuclear magnetic resonance (Chapter 10), infrared spectroscopy (Chapter 14), mass spectrometry (Chapter 16), and ultraviolet spectrometry (Chapter 22).

PROBLEMS

1. Write a valid Lewis structure for each of the following inorganic compounds:
   - (a) bisulfate ion, HSO_4^-
   - (b) amide ion, NH_2^-
   - (c) nitrite ion, NO_2^- (arranged ONO)
   - (d) hypochlorite ion, ClO^-
   - (e) hydroxylamine, $HONH_2$
   - (f) hydroxylamine anion, $(ONH_2)^-$
   - (g) nitronium ion, NO_2^+ (arranged ONO)
   - (h) ozone, O_3 (arranged OOO)
   - (i) hydronium ion, H_3O^+
   - (j) nitrosonium ion, NO^+
   - (k) formyl cation, HCO^+ (arranged HCO)
   - (l) azide ion, N_3^- (arranged NNN)
   - (m) carbonate ion, CO_3^{2-}
   - (n) isocyanic acid, OCNH

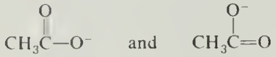
2. Write out the Lewis structures and corresponding Kekulé structures for each of the following organic compounds:
   - (a) methyl anion, CH_3^-
   - (b) ethyl cation, $CH_3CH_2^+$
   - (c) ethyl radical, $CH_3CH_2\cdot$
   - (d) methylacetylene, $CH_3C{\equiv}CH$
   - (e) methyl ethyl ketone, $CH_3COCH_2CH_3$
   - (f) dimethyl ether, CH_3OCH_3

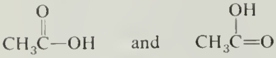
(g) Methylamine, CH_3NH_2
(h) methylammonium cation, $CH_3NH_3^+$
(i) methoxide ion, CH_3O^-
(j) methyloxonium ion, $CH_3OH_2^+$
(k) vinyl chloride, $CH_2{=}CHCl$

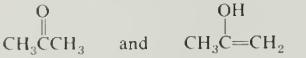
3. For each of the following compounds, describe each bond in terms of its component atomic orbitals.
   (a) ethane, CH_3CH_3
   (b) carbon tetrafluoride, CF_4
   (c) ethyl cation, $CH_3CH_2^+$
   (d) methylberyllium hydride, CH_3BeH
   (e) methanol, CH_3OH

4. Using Lewis structures, write a reaction that illustrates the action of methanol, CH_3OH, (a) as an acid; (b) as a base.

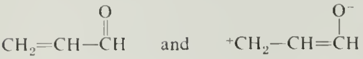
5. In each of the following pairs of Lewis structures, which pairs do *not* constitute resonance structures?

(a) 
$CH_3\overset{\overset{O}{\|}}{C}-O^-$ and $CH_3\overset{\overset{O^-}{|}}{C}=O$

(b) 
$CH_3\overset{\overset{O}{\|}}{C}-OH$ and $CH_3\overset{\overset{OH}{|}}{C}=O$

(c) 
$CH_3\overset{\overset{O}{\|}}{C}CH_3$ and $CH_3\overset{\overset{OH}{|}}{C}=CH_2$

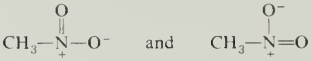
(d) ${}^+CH_2-CH=CH_2$ and $CH_2=CH-\overset{+}{C}H_2$

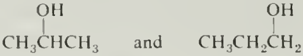
(e) 
$CH_2=CH-\overset{\overset{O}{\|}}{CH}$ and ${}^+CH_2-CH=\overset{\overset{O^-}{|}}{CH}$

(f) $CH_3CH=CHCH_3$ and $CH_3CH_2CH=CH_2$

(g) $CH_2=C=CH_2$ and $CH_3C\equiv CH$

(h) $H-C\equiv\overset{+}{N}H$ and $H-\overset{+}{C}=NH$

(i) 
$CH_3-\underset{+}{\overset{\overset{O}{\|}}{N}}-O^-$ and $CH_3-\underset{+}{\overset{\overset{O^-}{|}}{N}}=O$

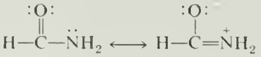
(j) 
$CH_3\overset{\overset{OH}{|}}{C}HCH_3$ and $CH_3CH_2\overset{\overset{OH}{|}}{C}H_2$

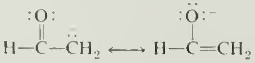
(k) $CH_3N=C=O$ and $CH_3O-C\equiv N$

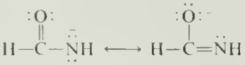
(l) $CH_3N=C=O$ and $CH_3\overset{+}{N}\equiv C-O^-$

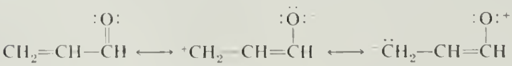
(m) ${}^-O-\overset{+}{O}=O$ and $O=\overset{+}{O}-O^-$

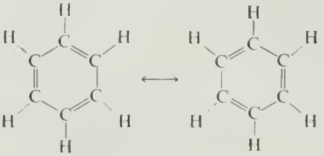
6. For each of the following resonance hybrids, rank the contributing structures in order of their relative importance.

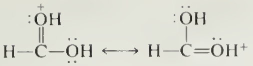
(a) 
$H-\overset{\overset{:O:}{\|}}{C}-\ddot{N}H_2 \longleftrightarrow H-\overset{\overset{:\ddot{O}:^-}{|}}{C}=\overset{+}{N}H_2$

(b) 
$H-\overset{\overset{:O:}{\|}}{C}-\ddot{C}H_2 \longleftrightarrow H-\overset{\overset{:\ddot{O}:^-}{|}}{C}=CH_2$

(c) 
$H-\overset{\overset{:O:}{\|}}{C}-\underset{\cdot\cdot}{\overset{-}{\ddot{N}}}H \longleftrightarrow H-\overset{\overset{:\ddot{O}:^-}{|}}{C}=\ddot{N}H$

(d) 
$CH_2=CH-\overset{\overset{:O:}{\|}}{CH} \longleftrightarrow {}^+CH_2-CH=\overset{\overset{:\ddot{O}:^-}{|}}{CH} \longleftrightarrow {}^-\ddot{C}H_2-CH=\overset{\overset{:O:^+}{|}}{CH}$

(e) 

(f) 
$H-\overset{\overset{+}{:OH}}{\overset{\|}{C}}-\ddot{O}H \longleftrightarrow H-\overset{:OH}{\overset{|}{C}}=\ddot{O}H^+$

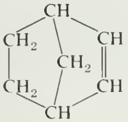
(g) $CH_3-\overset{+}{N}\equiv C-O^- \longleftrightarrow CH_3-{}^-N-C\equiv O^+$

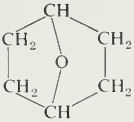
(h) $^-O-\overset{+}{O}=O \longleftrightarrow O=O=O$

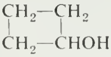
7. From the analytical values for each compound, derive its empirical formula.
   (a) hexanol: 70.4% C, 13.9% H
   (b) benzene: 92.1% C, 7.9% H
   (c) pyrrole: 71.6% C, 7.5% H, 20.9% N
   (d) morphine: 71.6% C, 6.7% H, 4.9% N
   (e) quinine: 74.1% C, 7.5% H, 8.6% N

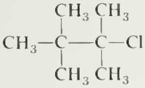
8. In each of the following examples, qualitative analysis shows the presence of no elements other than C, H, and O. Calculate the empirical formula for each case.
   (a) Combustion of 0.0132 g of camphor gave 0.0382 g of CO_2 and 0.0126 g of H_2O.
   (b) Combustion of 1.56 mg of the sex-attractant of the common honeybee (*Apis mellifera*) gave 3.73 mg of CO_2 and 1.22 mg of H_2O.
   (c) Benzo[a]pyrene is a potent carcinogenic compound that has been detected in tobacco smoke. Combustion of 2.16 mg gave 7.50 mg of CO_2 and 0.92 mg of H_2O.

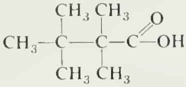
9. Each of the following molecules contains one principal functional group. Locate and name the group, and classify the molecule for each case.

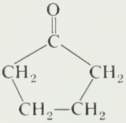
(a) 

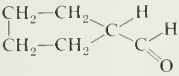
(b) 

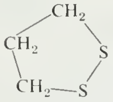
(c) 

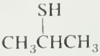
(d) 
$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{CH_3}{C}}-Cl$

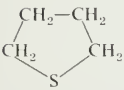
(e) 
$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-OH$

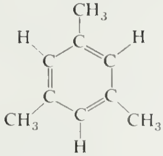
(f) 

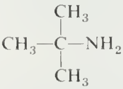
(g) 

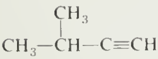
(h) 

(i) 
$CH_3\overset{SH}{\overset{|}{C}}HCH_3$

(j) 

(k) 

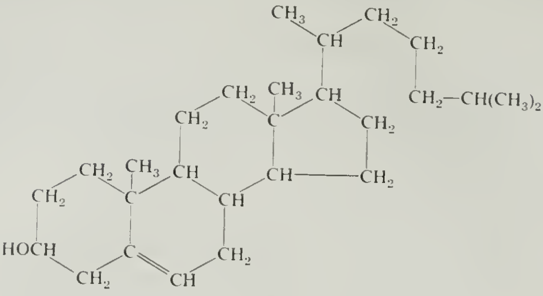
(l) 
$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-NH_2$

(m) 
$CH_3-\overset{CH_3}{\overset{|}{C}}H-C\equiv CH$

(n) $CH_3CH_2CH_2CH_2Li$

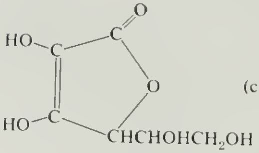
10. Each of the following structures is a significant organic molecule. For each structure identify and name every functional group in the structure.

(a)



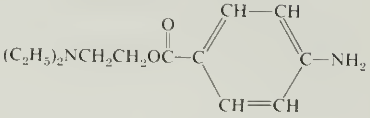
cholesterol

(b)



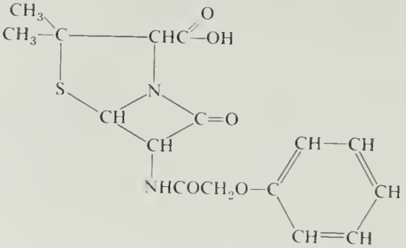
vitamin C

(c)



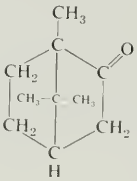
novocaine

(d)



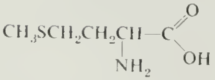
penicillin V

(e)



camphor

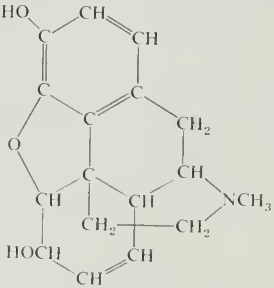
(f)



$CH_3SCH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{CH}}-\overset{\displaystyle O}{\overset{\|}{C}}-OH$

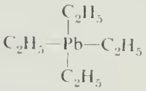
methionine
(essential amino acid)

(g)



morphine

(h)



$C_2H_5-\overset{\displaystyle C_2H_5}{\underset{\displaystyle C_2H_5}{Pb}}-C_2H_5$

tetraethyllead

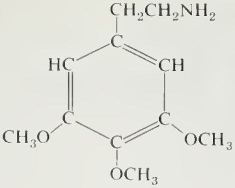
(i) $ClCH_2CH_2SCH_2CH_2Cl$

mustard gas

(j) $-(CH_2CH_2)_{1000}$

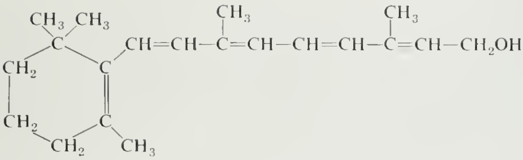
polyethylene

(k)



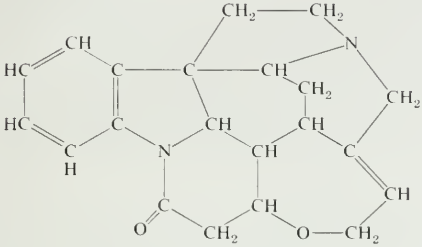
mescaline

(l)



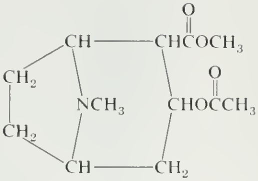
vitamin A

(m)



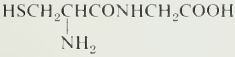
strychnine

(n)



cocaine

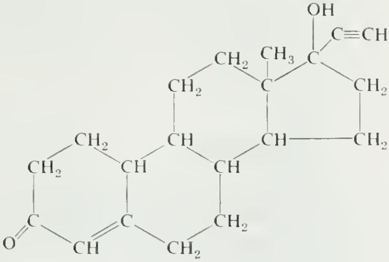
(o)



$HSCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCONHCH_2COOH$

a peptide

(p)



norethindrone
(oral contraceptive)

CHAPTER 3
Organic Reactions

3.1
Introduction

The two principal components of organic chemistry are **structure** and **reactions.** Each of these components has experimental and theoretical aspects, and they are interrelated. Structures in terms of bond angles and bond distances are available from the interpretation of experimentally obtained rotational spectra and x ray or electron diffraction patterns. In the last chapter we reviewed the symbolism used to represent such structures—structural formulas and Lewis structures—and their modern significance in terms of atomic, hybrid, and molecular orbitals.

In this chapter we introduce some concepts concerning reactions. Many reactions are known in organic chemistry that allow us to convert one structure to another. In this connection we must distinguish between **equilibrium** and **rate.** Equilibrium refers to the relative amounts of reactants and products expected by thermodynamics, *if a suitable pathway exists between them.* A simple example is glucose in the presence of oxygen. These two reagents can exist together for indefinite periods without change, but if the sugar is ignited it will burn to produce the equilibrium products, CO_2 and H_2O. Alternatively, the same result is accomplished in living organisms by a series of catalysts (enzymes) that accomplish this oxidation in a sequence of controlled steps.

Reactants can reach equilibrium at a variety of rates ranging from immeasurably slow to exceedingly fast. The rate at which equilibrium is reached depends on the reaction and on the structures of the reactants. Consequently, we will be much concerned with the effect of structural change on reactivity. We will also find that many reactions are characteristic of individual functional groups and form much of the chemistry of functional groups.

3.2
An Example of an Organic Reaction: Equilibria

Although methyl chloride is a gas at room temperature, it is sufficiently soluble in water to give a solution of about 0.1 *M* concentration. If the solution also contains hydroxide ion, reaction occurs to form methyl alcohol and chloride ion.

$$HO^- + \underset{\substack{\text{methyl}\\\text{chloride}}}{CH_3Cl} \rightleftharpoons \underset{\substack{\text{methyl}\\\text{alcohol}}}{CH_3OH} + Cl^- \tag{3-1}$$

At equilibrium all four compounds are present, but the equilibrium constant, *K*, is such an exceedingly large number that the amount of methyl chloride present in the equilibrium mixture is vanishingly small.

$$K = \frac{[CH_3OH][Cl^-]}{[CH_3Cl][OH^-]} = 10^{16}$$

If the reaction started with 0.1 M CH_3Cl and 0.2 M NaOH, at the end of the reaction we would have a solution of 0.1 M CH_3OH, 0.1 M NaCl, 0.1 M NaOH and 10^{-17} M CH_3Cl. That is, 1 ml of such a solution would contain only a few thousand molecules of CH_3Cl.

Such a reaction is said to **go to completion.** In practice a reaction may be considered to go to completion if the final equilibrium mixture contains less than about 0.1% of reactant.

The reaction of methyl chloride and hydroxide ion may also be characterized by the **Gibbs standard free energy, $\Delta G°$,** at equilibrium.

$$\Delta G° = -RT \ln K$$

$\Delta G°$ for reaction (3-1) is -22 kcal mole^{-1}, a rather large value. We may speak of this reaction as having a large **driving force.** That is, the driving force for a reaction is a qualitative description of an equilibrium property and is related to the overall free energy change. For comparison, $\Delta G°$ for a reaction that proceeds to 99.9% at equilibrium is 4.1 kcal mole^{-1} at 25°C.*

There is an important difference between ΔG and $\Delta G°$. ΔG is the free energy of a given system. $\Delta G°$ is the free energy of that system with the components in their standard states. For solutions, the standard state is normally chosen to be the ideal 1 M solution. The standard free energy of a system, $\Delta G°$, is defined as the free energy, ΔG, of an ideal solution in which each reactant and product is present in a concentration of 1 M. For such a system, $\Delta G = \Delta G°$. When reaction has reached equilibrium, the free energy of the system, $\Delta G = 0$. The concentrations of the components at this point are given as

$$\Delta G = \Delta G° + RT \ln K$$

where

$$K = \frac{[\text{products}]_{eq}}{[\text{reactants}]_{eq}}$$

Hence, the standard free energy is given by

$$\Delta G° = -RT \ln K$$

The Gibbs standard free energy may be dissected into **enthalpy, $\Delta H°$,** and **entropy, $\Delta S°$,** components.

$$\Delta G° = \Delta H° - T\Delta S°$$

Enthalpy is the heat of reaction and is generally associated with bonding. If stronger bonds are formed in a reaction, $\Delta H°$ is negative and the reaction is **exothermic.** A reaction with positive $\Delta H°$ is **endothermic.** Entropy is best thought of as freedom of motion. The more a molecule or portion of a molecule is restricted in motion, the more negative is the entropy. Both the formation of stronger bonds and greater freedom of motion can contribute to a favorable driving force for reaction (negative $\Delta G°$).

For reaction (3-1), $\Delta H° = -18$ kcal mole^{-1} and $\Delta S° = +13$ eu (ΔS is usually specified in entropy units, eu, which have the units cal deg^{-1}). The driving force in this case comes mostly from bond energy changes: a C—O bond is stronger than a C—Cl bond. The formation of stronger bonds is usually an important component of the driving force of a reaction.

---

* In general, temperatures will be given in degrees centigrade (Celsius) and the symbol C will be omitted, except where confusion might arise.

In the vapor phase, where intermolecular interactions are negligible, the strength of the internal bonds in a molecule is especially important in determining its stability. In solutions, however, one must also consider the intermolecular interactions with solvent molecules (**solvation**). Solvent interactions that involve varying degrees of ionic and covalent bonding are particularly important for ions. They provide the main driving force for breaking up the stable crystal lattices when ionic substances dissolve. Although solvation of an ion provides bonding stabilization which is reflected in $\Delta H°$, it is partially offset by a decrease in entropy, $\Delta S°$. The crowding of several solvent molecules around an ion restricts the freedom of motion of these molecules. In the present case the entropy of reaction, $\Delta S°$, is positive because chloride ion is less strongly solvated than hydroxide ion. That is, the solvent molecules are less restricted after reaction than before. Since $\Delta S°$ is positive, the quantity $(-T\Delta S°)$ contributes a negative value to $\Delta G°$ and provides an additional driving force for reaction to occur.

3.3
Reaction Kinetics

Because it has such a large driving force, it seems remarkable that the reaction of methyl chloride with hydroxide ion is relatively slow. For example, a 0.05 *M* solution of methyl chloride in 0.1 *M* aqueous sodium hydroxide will have reacted only to the extent of about 10% after 2 days at room temperature. It is an important principle in all reactions that favorable thermodynamics is not enough; a suitable reaction pathway is essential.

Reactions generally involve an **energy barrier** that must be surmounted in going from reactants to products. This barrier is called the **activation energy** or the **enthalpy of activation,** and is symbolized by $\Delta H^{\ddagger}$. In the reaction of methyl chloride with hydroxide ion, $\Delta H^{\ddagger}$ is about 25 kcal mole^{-1}. This appears to be a rather formidable hurdle when one realizes that the average kinetic energy of molecules at room temperature is only about 0.6 kcal mole^{-1}. However, this latter number is only an average. Molecules are continually colliding with each other at rapid rates and exchanging kinetic energy. At any given instant some molecules have less than this average energy, some have more, and a few even have very large energies—like 25 kcal mole^{-1}.

The relative number of molecules with any given energy is given by the Boltzmann distribution function, shown schematically in Figure 3.1. Most of the molecules have an energy close to the average energy represented by the large

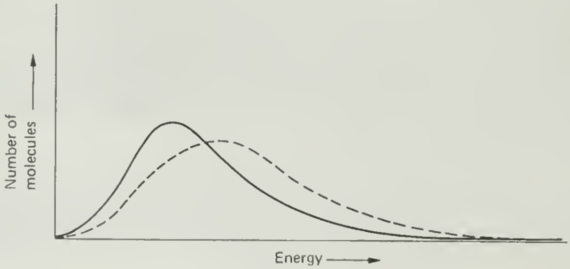


FIGURE 3.1 *A Boltzmann distribution function. Dotted line shows a higher temperature.*

hump. Only the minute fraction of molecules in the far end of the asymptotic tail have sufficient energy to overcome the barrier to reaction.

At a higher temperature, the average kinetic energy of the molecules is greater, and the entire distribution function is shifted to higher energies, as shown by the dotted curve in Figure 3.1. The fraction of molecules with kinetic energy sufficient for reaction is larger, and the rate of reaction is correspondingly larger. For example, the reaction of methyl chloride with hydroxide ion is 25 times faster at 50° than it is at 25°. A useful rule of thumb for many organic reactions is that a 10° change in temperature causes a two-to-three-fold change in rate of reaction.

The rate of a chemical reaction depends not only on the fraction of molecules that have sufficient energy for reaction but also on their concentration, because this determines the probability of an encounter that could lead to reaction. Reaction rates are directly proportional to the concentrations of the reactants, and the proportionality constant is called a **rate constant, *k*.** The reaction of methyl chloride with hydroxide ion is an example of a **second-order reaction,** since the rate depends on two concentrations:

$$\text{rate} = k[\mathrm{CH_3Cl}][\mathrm{OH^-}] \tag{3-2}$$

"Rate" involves a change in concentration of something per unit time, usually expressed as moles per liter per second, $M\,\mathrm{sec}^{-1}$. In equation (3-2), therefore, k must have units of $M^{-1}\,\mathrm{sec}^{-1}$:

$$(M^{-1}\,\mathrm{sec}^{-1})(M)(M) = M\,\mathrm{sec}^{-1}$$

The "something" whose concentration is changing is either a reactant or a product:

$$\text{rate} = -\frac{\Delta[\mathrm{CH_3Cl}]}{\Delta t} = -\frac{\Delta[\mathrm{OH^-}]}{\Delta t} = \frac{\Delta[\mathrm{CH_3OH}]}{\Delta t} = \frac{\Delta[\mathrm{Cl^-}]}{\Delta t} \tag{3-3}$$

The minus signs for the reactants indicate that their concentrations decrease with increasing time. All of the changes shown are equal by stoichiometry.

In the language of calculus, this rate equation becomes

$$-\frac{d[\mathrm{CH_3Cl}]}{dt} = -\frac{d[\mathrm{OH^-}]}{dt} = \frac{d[\mathrm{CH_3OH}]}{dt} = \frac{d[\mathrm{Cl^-}]}{dt} = k[\mathrm{CH_3Cl}][\mathrm{OH^-}]$$

The actual value of k at 25° is $6 \times 10^{-6}\,M^{-1}\,\mathrm{sec}^{-1}$.

The reaction of methyl chloride with hydroxide ion may be compared with its reaction with water. The reaction with water is an example of a **first-order reaction.** The reaction involves water molecules, but, because water is the solvent, it is present in large excess. Therefore the concentration of water remains effectively the same, even after all of the methyl chloride has reacted. Since the concentration of water appears not to change during the reaction, it does not appear in the kinetic expression; thus the rate of reaction depends only on the concentration of methyl chloride:

$$\text{rate} = k[\mathrm{CH_3Cl}] \tag{3-4}$$

Because only one concentration is involved, equation (3-4) is the equation of a first-order reaction. The rate is a change in concentration per unit time, for example, moles per liter per second, $M\,\mathrm{sec}^{-1}$. Therefore, k has the units of sec^{-1}. For methyl chloride at 25°, $k = 3 \times 10^{-10}\,\mathrm{sec}^{-1}$.

The reaction of methyl chloride with water is experimentally a first-order reaction because the concentration on one reactant (water) does not change significantly during the reaction. A second-order reaction becomes effectively a first-order reaction if the concentration of one component is much greater than the other. For example, in the reaction of a solution of 0.01 *M* CH_3Cl with 1 *M* NaOH, the concentration of hydroxide ion changes from 1 *M* to 0.99 *M* during the reaction. That is, its concentration remains essentially constant and the reaction of methyl chloride under these conditions appears to be a first-order reaction with a rate constant of 6×10^{-6} sec^{-1}. Such a reaction is also called a **pseudo first order reaction.**

3.4
Reaction Profiles and Mechanism

In the reaction of methyl chloride and hydroxide ion, atoms must move around and bonds must change in order to end up with the products methyl alcohol and chloride ion. One of the important concepts in organic chemistry involves the consideration of the structure of the system as reaction proceeds. Each configuration of the atoms during the process of changing from reactants to products has an associated energy. Since reaction generally involves bringing the reactants close together and breaking bonds, these structures generally have higher energy than the isolated reactants. That is, as the reactants approach each other and start to undergo the molecular changes that will eventually result in products, the potential energy of the reacting system increases. As the reaction encounter continues, the potential energy continues to increase until the system reaches a structure of **maximum energy.** Thereafter, the changes that result in the final products continue, but the structures represent lower and lower energy until the products are fully formed.

The difference in the energy of the isolated reactants and the maximum energy structure which the system passes through on the path to products is the **activation energy** of the reaction. This maximum energy corresponds to a definite structure, called the **transition state.** The measure of the progress of reaction from reactants to products is the **reaction coordinate.** This coordinate is usually not specified in detail because the qualitative concept is usually sufficient, but in our reaction, for example, it could be represented by the C—O bond length or C—Cl bond length as the reaction progresses, or by the net electronic charge on chlorine. Whatever measure is used, the general reaction profile is given by Figure 3.2.

In this figure, the energy shown is the potential energy. This quantity is related to but is not identical with $\Delta H°$. Similarly, the difference in potential energy between reactants and products contributes to $\Delta G°$ for the reaction. The magnitude of this difference determines the *position* of equilibrium. The magnitude of the activation energy determines the *rate* at which equilibrium is established.

The energy quantities involved in reactions are given more precise definitions in the **theory of absolute rates.** In this theory, the transition state is characterized by thermodynamic properties: free energy, enthalpy, and entropy. The rate constant for reaction is related to the Gibbs free energy difference between the transition state, sometimes called an **activated complex,** and the reactant state by the equation

$$k = \nu^{\ddagger} e^{-\Delta G^{\ddagger}/RT} = \nu^{\ddagger} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R}$$

The proportionality constant, $\nu^{\ddagger}$, is a kind of frequency. Its magnitude is 6.2×10^{12} sec^{-1} at 25°, a magnitude comparable to ordinary vibration frequencies. In fact, the reaction process can be described as one of the modes of vibration of the

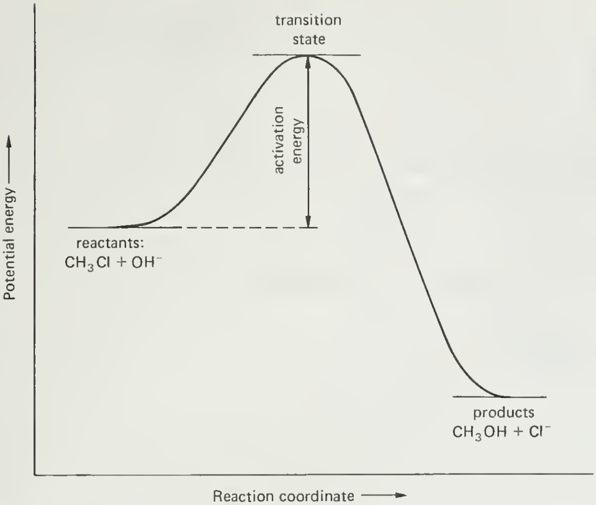


Figure 3.2 *A reaction profile for the reaction:* $CH_3Cl + OH^- \longrightarrow CH_3OH + Cl^-$.

activated complex. For this reason, the activated complex or transition state is not a normal molecule and is only a transient phase in the course of reaction.

The structure of the transition state is an important feature of a reaction. If we can estimate its energy, we can predict the reaction rate, at least roughly. For example, a transition state in which several bonds are broken is likely to correspond to high energy and a slow reaction. Furthermore, and most important, from the structure of the transition state we can often evaluate how a given change in structure will change the rate. Unfortunately, we cannot directly observe a transition state—we cannot take its spectrum or determine its structure by x-ray diffraction. Instead, we must infer its structure indirectly.

The reaction of hydroxide ion with methyl chloride is an example of an S_N2 reaction that we will study in Chapter 8. The structure of this transition state will be developed at that time. We will find, for example, that the S_N2 reaction probably involves a single step with one transition state, as suggested in Figure 3.2. Many other reactions, however, involve more than one step. A reaction profile such as that in Figure 3.3 is not uncommon. Such a reaction involves one or more intermediates, and each intermediate is flanked by transition states. Reaction intermediates correspond to energy minima on the reaction coordinate diagram. They may be sufficiently stable that they can be isolated and stored in bottles, or they may have such fleeting existence that their presence must be inferred from subtle observations of cleverly designed experiments.

The **reaction mechanism** is a sequential account of each transition state and intermediate in a total reaction. The overall rate of reaction is determined by the transition state of highest energy in the sequence, so that this structure has particular importance. The step involving this transition state is called the **rate-determining step.**

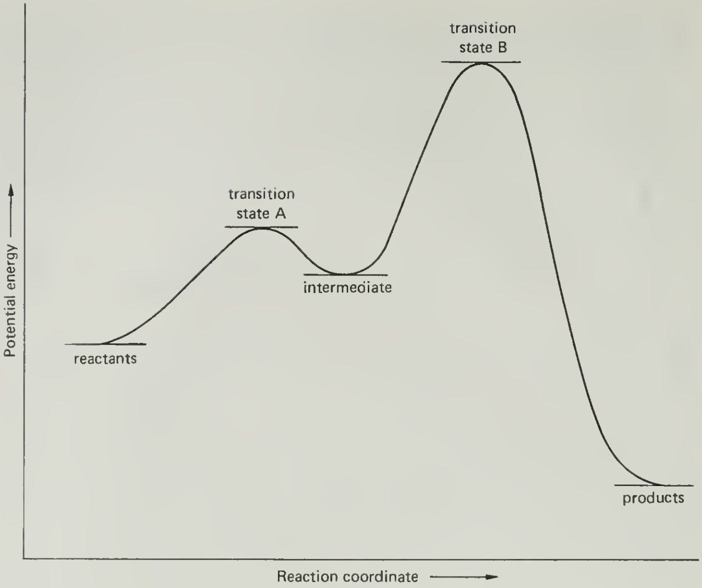


FIGURE 3.3 *Profile of a more complex reaction.*

The reaction profile shown in Figure 3.3 corresponds to the equations

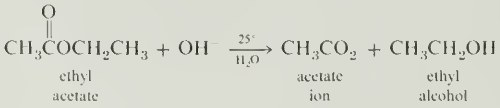
$$\text{reactants} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{products}$$

The relative energies in this figure correspond to relative rates having the relationship

$$k_2 > k_1 > k_3 > k_4$$

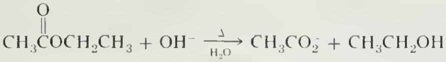
Remember that the lower the energy barrier the larger the rate constant and the faster the rate. Transition state B corresponds to the rate-determining step.

An example of a reaction with intermediates is the hydrolysis of ethyl acetate with aqueous sodium hydroxide.



$$\underset{\text{ethyl acetate}}{CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3} + OH^- \xrightarrow[H_2O]{25^\circ} \underset{\text{acetate ion}}{CH_3CO_2^-} + \underset{\text{ethyl alcohol}}{CH_3CH_2OH}$$

This example illustrates the way in which organic reactions are typically written. The arrow shows the direction of the reaction and implies that the equilibrium lies far to the right. Reaction conditions such as solvent, temperature, and any catalysts used are written with the arrow as shown. Abbreviations are often used in this formulation. An example is the use of the symbol Δ for heat. If our reaction mixture above was heated or refluxed in order to speed reaction, we could represent the reaction as

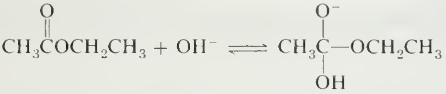


$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3 + OH^- \xrightarrow[H_2O]{\Delta} CH_3CO_2^- + CH_3CH_2OH$$

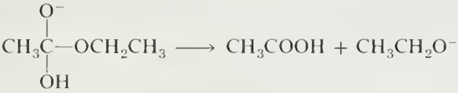
The rate expression for this reaction is

$$\text{rate} = 0.1\,[OH^-][CH_3COOCH_2CH_3]$$

The second-order rate constant, 0.1 M^{-1} sec^{-1}, is relatively large and corresponds to a rather fast reaction. As we shall learn in Chapter 18, the mechanism of this reaction appears to be



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3 + OH^- \rightleftharpoons CH_3\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}OCH_2CH_3$$



$$CH_3\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}OCH_2CH_3 \longrightarrow CH_3COOH + CH_3CH_2O^-$$

The reaction is effectively irreversible because the strong base, $CH_3CH_2O^-$, reacts immediately with acetic acid to produce ethyl alcohol and acetate ion.

$$\underset{\text{acetic acid}}{CH_3COOH} + CH_3CH_2O^- \xrightarrow{\text{fast}} CH_3CO_2^- + CH_3CH_2OH$$

The reaction profile for this reaction is shown in Figure 3.4.

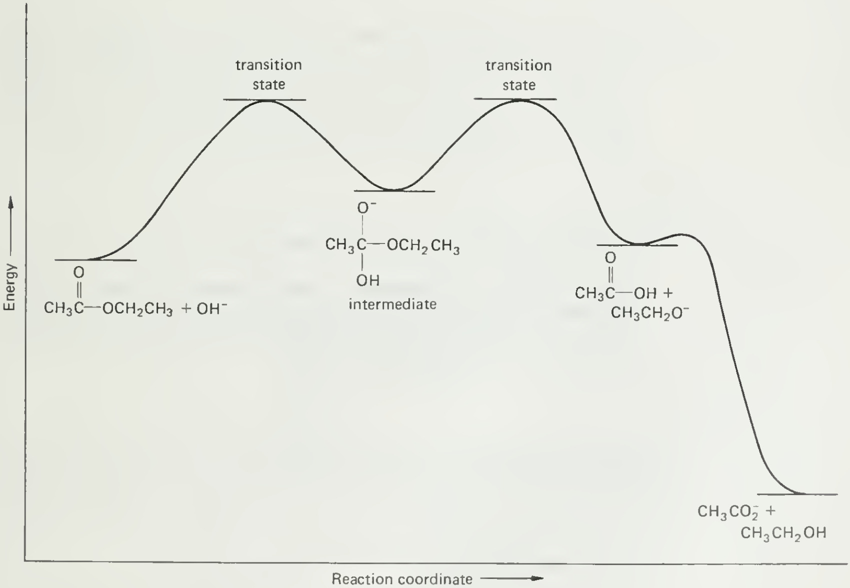


FIGURE 3.4 *Reaction profile for hydrolysis of an ester.*

The elucidation of reaction mechanisms is a fascinating branch of organic chemistry. In our study of organic chemistry, we will deal frequently with reaction mechanisms because they help enormously to classify and understand the vast array of organic reactions known. In some important cases, such as the hydrolysis of ethyl acetate, we will also study some of the experimental evidence from which the reaction mechanisms and transition state structures have been deduced.

PROBLEMS

1. In this chapter we discuss the hydrolysis of methyl chloride *in aqueous solution.* Consider the same reaction in the gas phase at 25°

$$CH_3Cl + H_2O \rightleftharpoons CH_3OH + HCl$$

(a) $\Delta H° = 7.3$ kcal mole^{-1}; $\Delta S° = 0.3$ eu. Calculate $\Delta G°$ at room temperature.
(b) Calculate the equilibrium constant.
(c) Can this reaction be said to "go to completion" in the direction shown?

2. Consider the equilibrium between butane and ethane plus ethylene.

$$C_4H_{10} \rightleftharpoons C_2H_6 + C_2H_4$$

(a) At 25°, $\Delta H° = 22.2$ kcal mole^{-1} and $\Delta S° = 33.5$ eu. What is $\Delta G°$? On which side does the equilibrium lie? (b) Calculate $\Delta G°$ at 800°K (527°C) and determine the position of equilibrium. (c) How does the relative effect of $\Delta H°$ and $\Delta S°$ change with temperature? (Actually, $\Delta H°$ and $\Delta S°$ change somewhat with temperature, but the effect is not large enough to change the qualitative result).

3. (a) At room temperature what change in free energy in units of kcal mole^{-1} will change an equilibrium constant by a factor of 10? By a factor of 100? This energy quantity is a handy number to remember. (b) These numbers can be converted to equivalent ΔH and ΔS values. Consider ΔG for the factor of 10 change in equilibrium constant. What is the equivalent value for ΔH in kcal mole^{-1} if $\Delta S = 0$; what is the equivalent value for ΔS in eu (cal deg^{-1}) if $\Delta H = 0$?

4. During the course of reaction, the concentration of reactants decreases; hence, the rate of reaction is reduced.
(a) In the example of 0.05 M methyl chloride and 0.10 M OH^- discussed on page 44, what is the rate of reaction at the start of the reaction, using the rate constant given on page 45? (b) Using this rate constant, determine the time required for 10% reaction. What are the concentrations of reactants after 10% reaction? What is the rate of reaction at this point? Using this rate, determine how long it takes for the second 10% of reaction to occur. (c) Repeat the calculation to estimate the time for 50% completion of the reaction.

5. The equilibrium reaction in the gas phase of ethylene and HCl to give ethyl chloride, $C_2H_4 + HCl = C_2H_5Cl$, has a favorable enthalpy, $\Delta H° = -15.5$ kcal mole^{-1}, but an unfavorable entropy, $\Delta S° = -31.3$ eu. (a) Why is the entropy negative? (b) What is $\Delta G°$ at room temperature (25°)? (c) If the reaction mixture started with 1 atm pressure each of HCl and C_2H_4, what pressure of each is left at equilibrium? (d) For the system to be at equilibrium with all three components present in equal amounts, what total pressure is required?

Incidentally, in this system a mixture of pure, dry HCl and C_2H_4 will not react at room temperature. Establishment of the equilibrium requires a suitable catalyst.

6. Consider the following reaction sequence in which B is an intermediate. Sketch energy profiles for each of the possible relationships among rate constants shown.

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$$

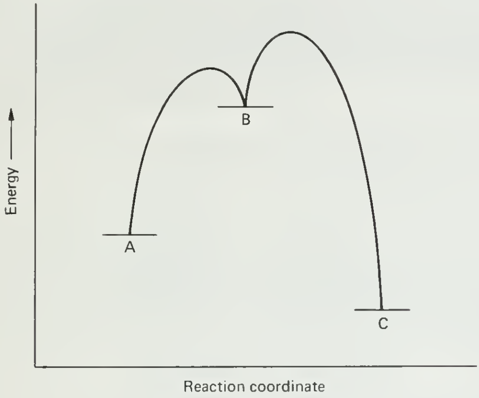
$$B \xrightarrow{k_3} C$$

The back-reaction from C is negligibly small.
(a) k_1 and k_2 fast; k_3 slow.
(b) k_1 slow; k_2 and k_3 fast but $k_2 > k_3$.
(c) k_1 and k_3 fast; k_2 slow.
(d) k_1 slow; k_2 and k_3 fast but $k_3 > k_2$.
The highest energy transition state is often referred to as the rate-determining transition state. Identify the rate-determining transition state for each of the above four cases.

7. Consider the hypothetical two-step reaction

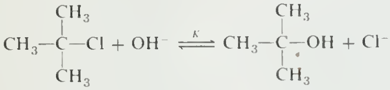
$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} C$$

which is described by the following energy profile.



(a) Is the overall reaction (A ⟶ C) exothermic or endothermic?
(b) Label the transition states. Which transition state is rate-determining?
(c) What is the correct order of magnitude of rate constants?
  (i) $k_1 > k_2 > k_3 > k_4$ (iii) $k_4 > k_1 > k_3 > k_2$
  (ii) $k_2 > k_3 > k_1 > k_4$ (iv) $k_3 > k_2 > k_4 > k_1$
(d) Which is the most stable compound?
(e) Which is the least stable compound?

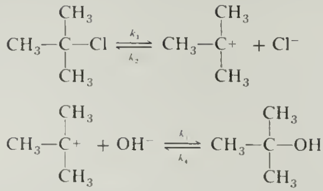
8. *t*-Butyl chloride reacts with hydroxide ion according to the following equation.



$$CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-Cl + OH^- \overset{K}{\rightleftharpoons} CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-OH + Cl^-$$

t-butyl chloride *t*-butyl alcohol

We will learn in Chapter 8 that the reaction is believed to proceed by the following mechanism:



$$\text{(1)}\quad \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}Cl} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{}^{+}} + \mathrm{Cl^-}$$

$$\text{(2)}\quad \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{}^{+}} + \mathrm{OH^-} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}OH}$$

The order of rate constants is $k_3 > k_2 > k_1 \gg k_4$.
(a) Construct a reaction coordinate diagram for the reaction.
(b) Is the first step exothermic or endothermic?
(c) Is the overall reaction exothermic or endothermic?
(d) Does the first or second step govern the rate of disappearance of *t*-butyl chloride?

9. Consider the reaction of A + B as a second-order reaction for which rate = $k[\mathrm{A}][\mathrm{B}]$. If A and B start off with equal concentrations, how has the rate changed at 50% reaction?

10. (a) The reaction of methyl chloride with water was described as a first-order reaction because the concentration of water does not change during the reaction. If the reaction with water is exactly analogous to the reaction with hydroxide ion, we should write the kinetic equation as

$$\text{rate} = k_2[\mathrm{CH_3Cl}][\mathrm{H_2O}]$$

What is the value of $[\mathrm{H_2O}]$ in this expression?

(b) Because $[\mathrm{H_2O}]$ remains constant, this case is an example of pseudo-first order kinetics. For the expression

$$\text{rate} = k_1[\mathrm{CH_3Cl}]$$

we found that $k_1 = 3 \times 10^{-10}\ \mathrm{sec^{-1}}$. Using the value of $[\mathrm{H_2O}]$ found above, derive k_2. How does the value of k_2 for the reaction of methyl chloride with water compare with that for reaction with hydroxide ion?

(c) For a first-order reaction, the time for half of the remaining reactant to react—the half-life—is given by

$$t_{1/2} = 0.693/k$$

From the value of k_1, calculate the half-life in years of an aqueous solution of methyl chloride.

★ **11.** Problem 4 was solved in an approximate manner. Using the methods of differential and integral calculus, derive the exact answers.

CHAPTER 4
Alkanes

4.1
n-Alkanes

The straight chain alkanes constitute a family of hydrocarbons in which a chain of —CH_2— groups is terminated at both ends by a hydrogen. They have the general formula H—$(CH_2)_n$—H or C_nH_{2n+2}. Such a family of compounds, which differ from each other by the number of CH_2 groups in the chain, is called an **homologous series.** The individual members of the family are known as **homologs** of one another. Straight chain alkanes are called **normal alkanes,** or simply ***n*-alkanes,** to distinguish them from the branched alkanes, which we shall study later.

Alkanes are sometimes called **saturated** hydrocarbons. This term means that the carbon skeleton is "saturated" with hydrogen. That is, in addition to its bonds to other carbons, each carbon bonds to enough hydrogens to give a maximum covalence of 4. In saturated hydrocarbons, there are only single bonds. Later, we shall study **unsaturated** hydrocarbons, compounds that contain double and triple C—C bonds. The normal alkanes are named according to the number of carbon atoms in the chain.

n	Name	Formula
1	methane	CH_4
2	ethane	CH_3CH_3
3	propane	$CH_3CH_2CH_3$
4	butane	$CH_3CH_2CH_2CH_3$
5	pentane	$CH_3(CH_2)_3CH_3$
6	hexane	$CH_3(CH_2)_4CH_3$
7	heptane	$CH_3(CH_2)_5CH_3$
8	octane	$CH_3(CH_2)_6CH_3$
9	nonane	$CH_3(CH_2)_7CH_3$
10	decane	$CH_3(CH_2)_8CH_3$
11	undecane	$CH_3(CH_2)_9CH_3$
12	dodecane	$CH_3(CH_2)_{10}CH_3$
13	tridecane	$CH_3(CH_2)_{11}CH_3$
14	tetradecane	$CH_3(CH_2)_{12}CH_3$
15	pentadecane	$CH_3(CH_2)_{13}CH_3$
20	eicosane	$CH_3(CH_2)_{18}CH_3$
21	heneicosane	$CH_3(CH_2)_{19}CH_3$
22	doeicosane	$CH_3(CH_2)_{20}CH_3$
30	triacontane	$CH_3(CH_2)_{28}CH_3$
40	tetracontane	$CH_3(CH_2)_{38}CH_3$

These names derive from the generic name alkane with the **alk**-stem replaced by a stem characteristic of the number of carbons in the chain. The first four members of this series, methane, ethane, propane, and butane, are names assigned to compounds before organic chemistry evolved as an organized science. The remaining names derive quite obviously from Greek numbers; compare **pent**agon, **oct**al, **dec**imal, and so on. The student should memorize the names of the *n*-alkanes up through dodecane and know the logical procedure for developing names for larger compounds.

A **radical** is a portion of a molecule in which a collection of atoms is considered together as a unit. For purposes of naming more complicated compounds, it is necessary to have names for such radicals. A radical name is derived by replacing the **-ane** of the corresponding alkane name by the suffix **-yl**.

Alkane	Radical	Sample Molecule
CH_4 methane	$CH_3—$ methyl radical	$CH_3—OH$ methyl alcohol
CH_3CH_3 ethane	$CH_3CH_2—$ ethyl radical	$CH_3CH_2—Cl$ ethyl chloride
$CH_3CH_2CH_3$ propane	$CH_3CH_2CH_2—$ propyl radical	$CH_3CH_2CH_2—Br$ propyl bromide

In Section 4.4, we shall consider alkanes in which the chain is branched and see how the radical names are used in naming these more complex structures.

4.2
Physical Properties

Table 4.1 lists the boiling points, melting points, and densities of some *n*-alkanes. These properties vary in a regular manner. The alkanes from methane through butane are gases at room temperature, pentane boils just above room temperature, and the remaining alkanes show regular increases in boiling point with each additional methylene unit. This regularity of physical properties stems from a regularity of structure. In all of the alkanes the bonds to carbon are nearly tetrahedral and the C—H bond lengths are all essentially constant at 1.095 ±0.01 Å. Similarly, the C—C bonds are uniformly 1.54 ±0.01 Å in length.

The boiling point of a substance is defined as the temperature at which its vapor pressure is equal to the external pressure, usually 760 torr.

Torr is a unit of pressure; 1 torr is equal to 1 mm of mercury at 25°. At 25°, standard atmospheric pressure is 760 torr.

The vapor pressure of a compound is inversely related to the energy that causes the molecules to attract one another. If the intermolecular attractive force is weak, little energy must be supplied in order for vaporization to occur and the compound has a high vapor pressure. If the intermolecular attractive force is large, more energy must be supplied to cause vaporization and the compound has a low vapor pressure. Interactions between neutral molecules generally result from **Van der Waals forces**, dipole-dipole electrostatic attraction, and hydrogen bonding. For hydrocarbons, only the Van der Waals interaction is important. This force of

TABLE 4.1
Physical Properties of n-Alkanes

Hydrocarbon	Boiling Point, °C	Melting Point, °C	Density* d^{20}
methane	−161.7	−182.5	
ethane	−88.6	−183.3	
propane	−42.1	−187.7	0.5005
butane	−0.5	−138.3	0.5787
pentane	36.1	−129.8	0.5572
hexane	68.7	−95.3	0.6603
heptane	98.4	−90.6	0.6837
octane	125.7	−56.8	0.7026
nonane	150.8	−53.5	0.7177
decane	174.0	−29.7	0.7299
undecane	195.8	−25.6	0.7402
dodecane	216.3	−9.6	0.7487
tridecane	235.4	−5.5	0.7564
tetradecane	253.7	5.9	0.7628
pentadecane	270.6	10	0.7685
eicosane	343	36.8	0.7886
triacontane	449.7	65.8	0.8097
polyethylene			0.965

* Note that densities vary with temperature; d^{20} refers to the density in grams per milliliter at 20°C.

attraction results from an electron correlation effect also called the **London force** or **dispersion force.**

Although we normally think of atoms and molecules in terms of smeared-out electron density distributions, it should be emphasized that this is a time-average picture. At any given instant electrons will be positioned as far from each other as possible although these positions are different from one instant to the next. Consider the simplified models shown in Figure 4.1. The system of charges on the left has a small net attraction that binds the two molecules together. In the system on the right, the electrons have all moved but there is still net attraction. The motion of the electrons is mutually *correlated* to produce net attraction at all times. This attractive force is sensitive to distance and varies as $1/r^6$. It is significant only for molecules close to each other—but not too close. As molecules get too close, the electron charge clouds overlap appreciably and electron repulsion dominates.

Van der Waals attraction depends on the approximate "area" of contact of two molecules—the greater this area, the greater is the attractive force. Because of the tetrahedral nature of carbon, alkane chains tend to have a zig-zag geometry.

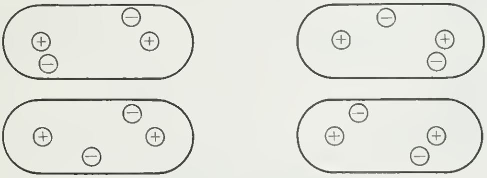


FIGURE 4.1 *Van der Waals attraction. Electronic motion is such as to produce net electrostatic attraction at every instant.*

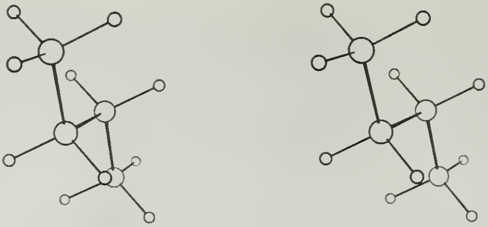


FIGURE 4.2 *One conformation of butane (stereo plot).*

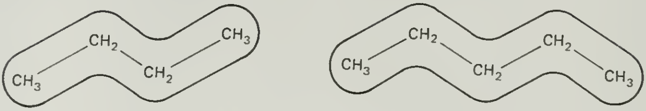

CH3
CH2
CH2
CH3
CH3
CH2
CH2
CH2
CH3

FIGURE 4.3 *Zig-zag geometry of alkanes.*

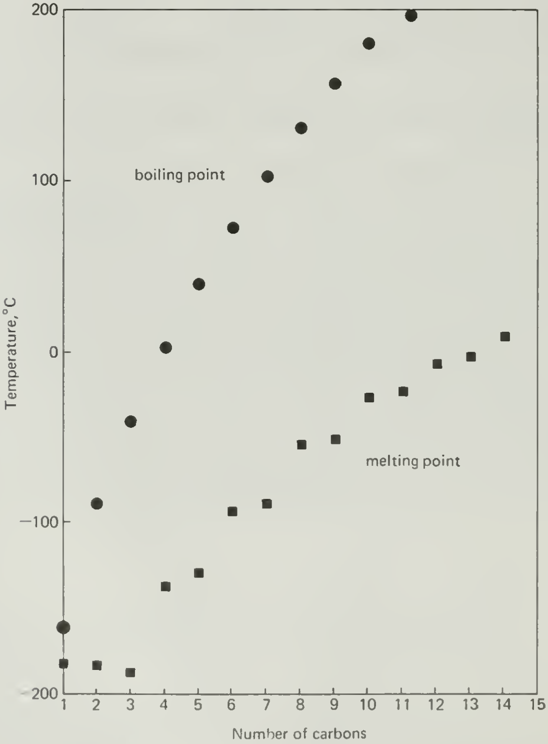


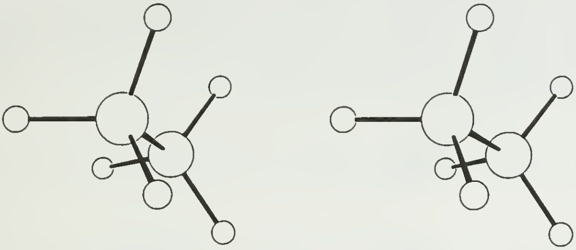
FIGURE 4.4 *Boiling points and melting points of* n*-alkanes.*

For example, one of the geometric arrangements adopted by butane is shown in stereo plot form in Figure 4.2. This type of zig-zag arrangement of butane and pentane is symbolized in Figure 4.3. Each additional methylene unit provides an additional area of contact that increases the total attractive force and gives rise to a greater boiling point. The energy of attraction per methylene group is approximately 1–1.5 kcal mole^{-1}.

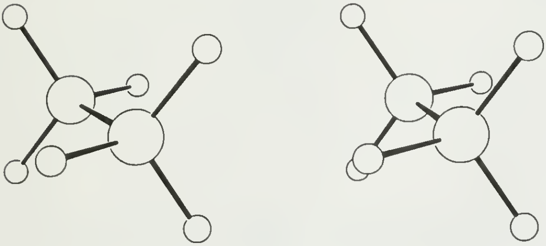
Van der Waals forces are even greater in solids and there is a progressive change in melting point with increasing chain length. Because of different packing requirements in the crystal for odd and even zig-zag chains, there is an alternation of melting points with increasing chain length (Figure 4.4).

4.3
Barriers to Rotation

In 1937 the entropy of ethane was found experimentally to be somewhat lower than that calculated for a molecule in which the methyl groups can rotate freely about the central C—C bond. This reduced entropy was interpreted to mean that the methyl groups have reduced freedom of motion. Subsequent experiments of several kinds have confirmed that the **eclipsed** structure for ethane is 3 kcal mole^{-1} higher in energy than the more stable **staggered** structure. These two different structures are shown in stereo plot form in Figure 4.5.

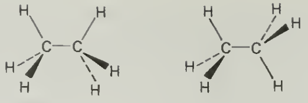


(a) eclipsed structure of ethane



(b) staggered structure of ethane

Figure 4.5 *Stereo plots illustrating the eclipsed and staggered structures of ethane.*

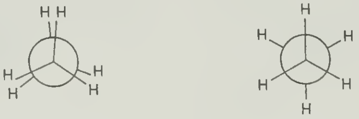


(a) eclipsed (b) staggered

Figure 4.6 *Sawhorse structures illustrating the eclipsed and staggered conformations of ethane.*

Structures that differ only by rotation about one or more single bonds are defined as **conformations** of a compound. In order to represent the three-dimensional character of such conformations, two useful systems are commonly employed. In Figure 4.6, the eclipsed and staggered conformations of ethane are depicted as "sawhorse" structures. In this representation, a dashed bond projects away from the viewer, a heavy wedge bond projects toward the viewer, and a normal bond lies in the plane of the page. Another useful representation is the Newman projection.

Newman projections for eclipsed and staggered ethane are shown in Figure 4.7. In a Newman projection, one is viewing the C—C bond end on. The nearer carbon is represented by a point. The three other groups attached to that carbon radiate as three lines from the point. The farther carbon is represented by a circle with its bonds radiating from the edge of the circle. These projections show that a rotation of 60° about the C—C axis converts the staggered form to the eclipsed structure. As the rotation is continued another 60°, a new staggered conformation is reached, which is identical with the first staggered conformation. A plot of potential energy versus degree of rotation for one complete 360° rotation about the C—C bond in ethane is shown in Figure 4.8.



(a) eclipsed (b) staggered

Figure 4.7 *Newman projections illustrating the eclipsed and staggered conformations of ethane.*

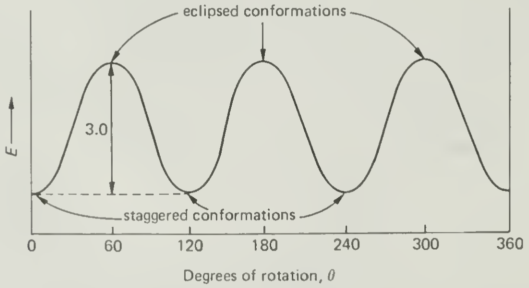


Figure 4.8 *Potential energy of ethane as a function of degree of rotation about the C—C bond.*

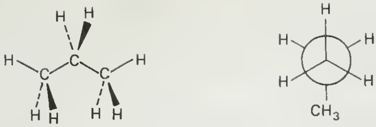


Figure 4.9 *Most stable conformation of propane.*

Thus, in rotating about the C—C bond, there is a 3.0 kcal mole^{-1} energy barrier in passing from one staggered conformation to another. The instability of the eclipsed form of ethane appears to result from repulsion of the nonbonded hydrogen orbitals. The hydrogen orbitals on one methyl group are rather far from those on the other. But they are closer in the eclipsed conformation than in the staggered one. The internuclear H-H distance in staggered ethane is 2.55 Å whereas it is only 2.29 Å in the eclipsed form. As the hydrogens approach each other more closely, the increased overlap between the nonbonded orbitals is antibonding or repulsive. The magnitude of this repulsion is small, only about 1 kcal mole^{-1} per pair of hydrogens, but this small energy effect has staggering structural consequences. As we shall see, staggered conformations are general in alkane chains and cycloalkane rings.

In propane the barrier to rotation now involves a C—CH_3 bond and is slightly higher in energy at 3.4 kcal mole^{-1}. The most stable conformation is illustrated in Figure 4.9. In this conformation the bonds are completely staggered.

A potential energy plot for rotation about the 2-3 bond in butane is shown in Figure 4.10. The conformations at the various unique maxima and minima are shown in Figure 4.11, both as Newman projections and as stereo plots. Note that there are two different staggered conformations, **anti,** in which the two methyl groups attached to carbons 2 and 3 are farthest apart, and **gauche,** in which these two methyl groups are adjacent. These two staggered conformations have different energies. The anti conformation is more stable than the gauche by 0.9 kcal mole^{-1}. At room temperature, butane is a mixture of 72% anti and 28% gauche conformations.

If these two structures could be isolated, they would have different physical properties such as density, spectra, melting points, and so on. However, the energy

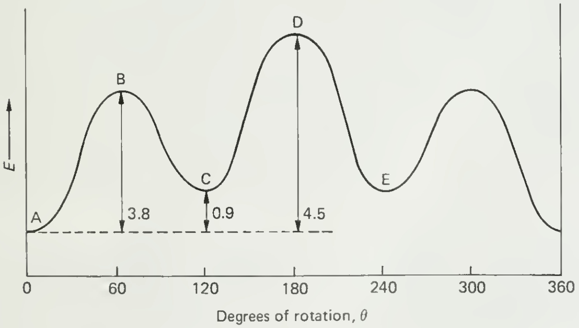
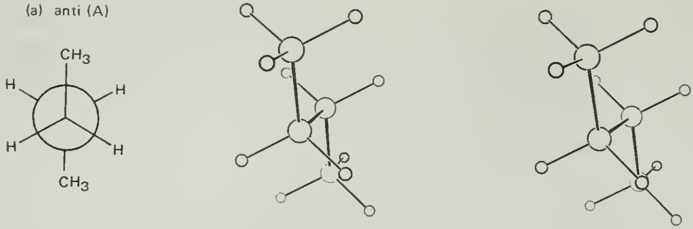
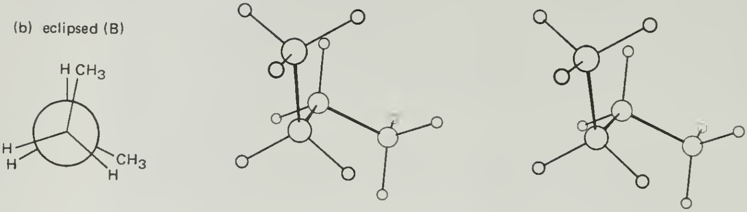


Figure 4.10 *Potential energy of butane as function of degree of rotation about the 2—3 bond.*

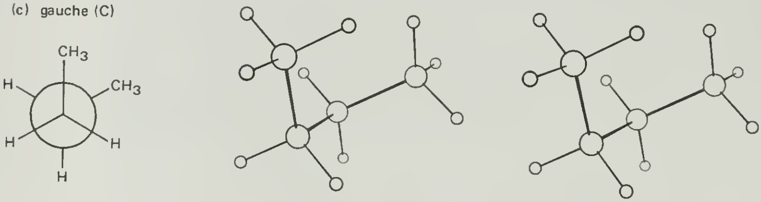
(a) anti (A)


CH$_3$
H
H
H
H
CH$_3$

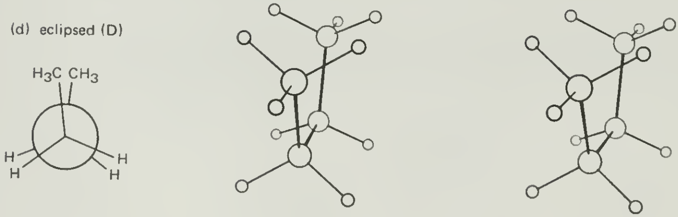
(b) eclipsed (B)


H CH$_3$
H
H
CH$_3$
H

(c) gauche (C)


CH$_3$
H
CH$_3$
H
H
H

(d) eclipsed (D)


H$_3$C CH$_3$
H
H
H
H

(e) gauche (E)

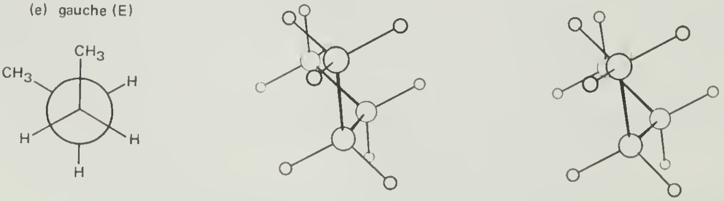

CH$_3$
CH$_3$
H
H
H
H

FIGURE 4.11 *Conformations of butane.*

barrier separating them is rather small, only 3.8 kcal mole^{-1}. A barrier of such magnitude is far too small to permit isolation of the separate anti and gauche conformations at normal temperatures. In order to separate these two species, one would have to slow the conversion by working at very low temperatures, below approximately −230°.

Also note that there are two distinct eclipsed conformations. One of these maxima is passed in rotation from the anti to a gauche conformation. In this conformation, there are two CH_3-H and one H-H eclipsed interactions. This conformation is 3.8 kcal mole^{-1} less stable than the anti conformation. The other eclipsed conformation, which is passed in rotation from one gauche conformation to the other, has one CH_3-CH_3 and two H-H eclipsed interactions. Its energy is about 4.5 kcal mole^{-1} above that of the anti conformation.

Finally, note that the gauche conformations labeled C and E, although energetically equivalent, are not really the same. They are actually mirror images of one another. They are the same only in the sense that your right and left hands are the same. We shall return to this phenomenon in Chapter 7.

Actually, the preceding description is somewhat oversimplified. The torsional motion around the C—C bond, like all motion, is quantized and given molecules will exist in one or more given torsional-rotational states. Such states are characterized by energy levels as shown in the more complete diagram in Figure 4.12.

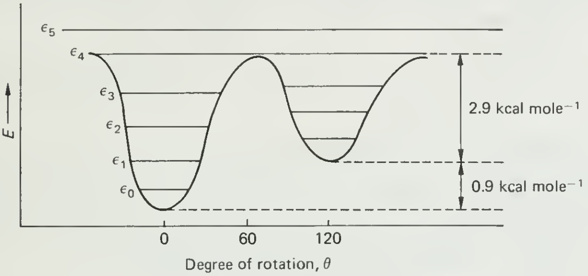
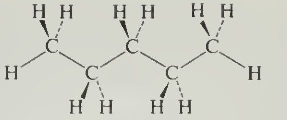


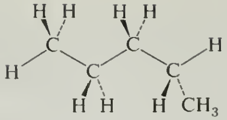
FIGURE 4.12 *Torsional quantum states for butane.*

The lowest level, the zero-point energy level, is about 0.5 kcal mole^{-1} above the potential minimum. No molecules can exist in a stationary position right at the potential minimum because then we would know precisely both the position and momentum in violation of Heisenberg's uncertainty principle. Instead, the lowest energy a molecule can have in this torsional motion is ε_0. In this lowest state the methyl groups oscillate back and forth through several degrees of rotation. As the molecule acquires additional energy quanta the system moves up to higher rotational levels. In these levels the oscillation has more energy and operates over a wider angle but only in about the fourth level does this oscillation continue over to the next staggered conformation. This and higher energy levels correspond to continuous rotation.

The same principles apply to larger alkanes. In general, the most stable structure is the completely staggered one, with all alkyl groups having an anti relationship to one another. However, keep in mind that gauche conformations are only slightly less stable, and there will always be a sizeable fraction of the molecules with these conformations. The two conformations of pentane given here are shown in stereo plot form in Figure 4.13.



pentane, anti-anti conformation, most stable



pentane, anti-gauche conformation, slightly less stable

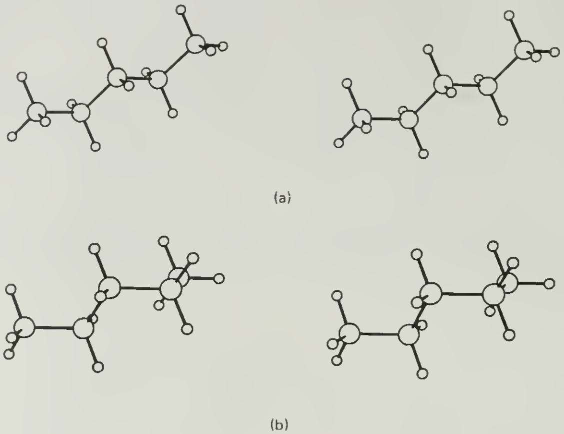
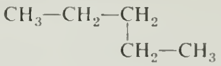


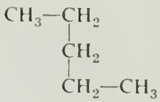
FIGURE 4.13 *Conformations of pentane:* (a) *anti-anti,* (b) *anti-gauche.*

When writing the structures of such compounds, it is usually inconvenient to depict the full geometry as is done in the preceeding structures. It is important to recognize that a given structure may be written in many ways. For example, the various structures that follow all represent pentane.

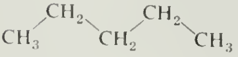
$CH_3-CH_2-CH_2-CH_2-CH_3$

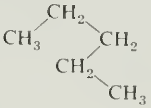


$$\begin{array}{l} CH_3-CH_2-CH_2 \\ \qquad\qquad\qquad\;| \\ \qquad\qquad\quad\; CH_2-CH_3 \end{array}$$



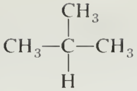
$$\begin{array}{l} CH_3-CH_2 \\ \qquad\quad\;\; | \\ \qquad\quad CH_2 \\ \qquad\quad\;\; | \\ \qquad\quad CH_2-CH_3 \end{array}$$





4.4
Branched Chain Alkanes: IUPAC Nomenclature

There is only one compound having each of the formulas CH_4, C_2H_6, and C_3H_8. There are two **isomeric** compounds having the formula C_4H_{10}. **Isomers** are defined as compounds that have identical formulas but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. One of the C_4H_{10} isomers is butane, discussed previously. The other is isobutane.



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C}}-CH_3$$

or $(CH_3)_3CH$

isobutane

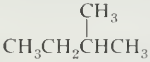
In general, isomers have different physical and chemical properties. Of the two C_4H_{10} compounds, isobutane has the lower melting point and boiling point. The lower boiling point reflects the branched chain structure of isobutane, which provides less effective contact area for Van der Waals attraction.

Interconversion of the two butane isomers requires breaking bonds rather than mere rotation about bonds. Since C—C bonds have bond strengths of about 80 kcal $mole^{-1}$, these isomers are completely stable under normal conditions. Interconversion requires very high temperatures or special catalysts.

There are three C_5H_{12} isomers.

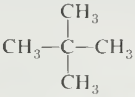
$CH_3CH_2CH_2CH_2CH_3$

pentane



$$CH_3CH_2\overset{\displaystyle CH_3}{C}HCH_3$$

isopentane



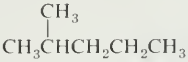
$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH_3$$

neopentane

The **iso-** prefix serves to name one of these isomers and the new prefix **neo-** provides an additional name. Three of the hexanes can be named using these special prefixes.

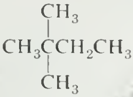
$CH_3CH_2CH_2CH_2CH_2CH_3$

n-hexane



$$CH_3\overset{\displaystyle CH_3}{C}HCH_2CH_2CH_3$$

isohexane



$$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CH_2CH_3$$

neohexane

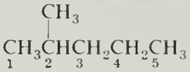
However, these are the only special prefixes in general use. With more carbons the number of possible isomers increases rapidly. As summarized in Table 4.2,

TABLE 4.2
Number of Isomers of C_nH_{2n+2}

n	Number of Isomers
4	2
5	3
6	5
7	9
8	18
9	35
10	75
11	159
12	355
13	802
14	1,858
15	4,347
16	10,359
17	24,894
18	60,523
19	148,284
20	366,319

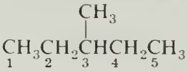
there are 5 possible hexanes, 9 heptanes, and 75 decanes. With larger alkanes the number of possible isomers becomes astronomic. Clearly, in this situation an essential requirement is a systematic nomenclature so that each different compound may be assigned an unambiguous name.

This problem was solved by an international group of chemists that met in Geneva as part of the first meeting of the International Union of Pure and Applied Chemistry. The Geneva rules of 1892 are being continuously updated and extended as new kinds of compounds are discovered. They now comprise a consistent and detailed nomenclature known as the IUPAC rules. The IUPAC system of alkane nomenclature is based on the simple fundamental principle of considering all compounds to be **derivatives of the longest single carbon chain** present in the compound. Appendages to this chain are designated by appropriate prefixes. The chain is then numbered from one end to the other. The end chosen as number 1 is that which gives the smaller number at the first point of difference.



$\underset{1}{CH_3}\overset{\displaystyle CH_3}{\underset{2}{C}}H\underset{3}{CH_2}\underset{4}{CH_2}\underset{5}{CH_3}$

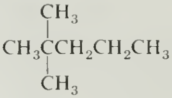
2-methylpentane



$\underset{1}{CH_3}\underset{2}{CH_2}\overset{\displaystyle CH_3}{\underset{3}{C}}H\underset{4}{CH_2}\underset{5}{CH_3}$

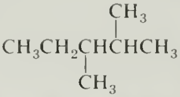
3-methylpentane

The modifying prefixes, di-, tri-, tetra-, penta-, hexa-, and so on, are used to indicate multiple identical appendages; but every appendage radical still gets its own number.



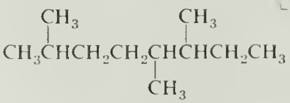
$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CH_2CH_2CH_3$

2,2-dimethylpentane
(not 2-dimethylpentane)



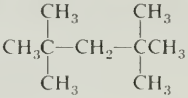
$CH_3CH_2\underset{\displaystyle CH_3}{C}H\overset{\displaystyle CH_3}{C}HCH_3$

2,3-dimethylpentane



$CH_3\overset{\displaystyle CH_3}{C}HCH_2CH_2\underset{\displaystyle CH_3}{C}H\overset{\displaystyle CH_3}{C}HCH_2CH_3$

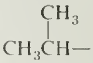
2,5,6-trimethyloctane
(not 3,4,7-trimethyloctane)



$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}—CH_2—\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CH_3$

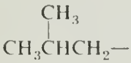
2,2,4,4-tetramethylpentane

Radicals derived from the terminal position of a *n*-alkane are named as shown in Section 4.1. Several other common radicals have special names that must be memorized by the student.



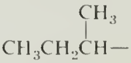
$CH_3\overset{\displaystyle CH_3}{C}H—$

isopropyl



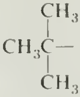
$CH_3\overset{\displaystyle CH_3}{C}HCH_2—$

isobutyl



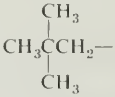
$CH_3CH_2\overset{\displaystyle CH_3}{C}H—$

sec-butyl



$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}—$

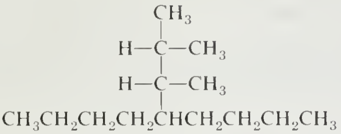
tert-butyl
or *t*-butyl



$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CH_2—$

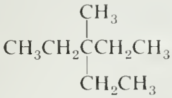
neopentyl

A more complex appendage radical is named as a derivative of the **longest carbon chain in the radical**, starting from the carbon that is attached to the principal chain. The description of the appendage is distinguished from that of the principal chain by enclosing it in parentheses.

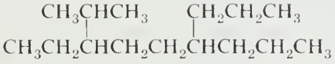

$$CH_3CH_2CH_2CH_2\overset{\begin{array}{c}CH_3\\ |\\ H-C-CH_3\\ |\\ H-C-CH_3\\ |\end{array}}{C}HCH_2CH_2CH_2CH_3$$

5-(1,2-dimethylpropyl)nonane

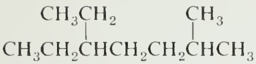
When two or more appendages of different nature are present, they are cited as prefixes in alphabetical order. Prefixes specifying the number of identical appendages (di, tri, tetra, and so on) and hyphenated prefixes (*tert-* or *t-*, *sec-*) are ignored in alphabetizing except when part of a complex substituent. The prefixes cyclo-, iso-, and neo-, count as a part of the radical name for purposes of alphabetizing.


$$CH_3CH_2\overset{CH_3}{\underset{CH_2CH_3}{C}}CH_2CH_3$$

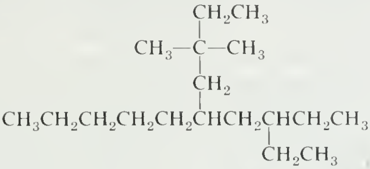
3-ethyl-3-methylpentane


$$CH_3CH_2\overset{CH_3CHCH_3}{C}HCH_2CH_2\overset{CH_2CH_2CH_3}{C}HCH_2CH_2CH_3$$

3-isopropyl-6-propylnonane

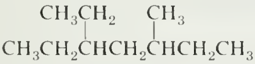

$$CH_3CH_2\overset{CH_3CH_2}{C}HCH_2CH_2\overset{CH_3}{C}HCH_3$$

5-ethyl-2-methylheptane
(not 3-ethyl-6-methylheptane)

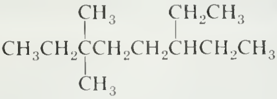

$$CH_3CH_2CH_2CH_2CH_2\overset{\begin{array}{c}CH_2CH_3\\ |\\ CH_3-C-CH_3\\ |\\ CH_2\\ |\end{array}}{C}HCH_2\underset{CH_2CH_3}{C}HCH_2CH_3$$

5-(2,2-dimethylbutyl)-3-ethyldecane

When two or more appendages are in equivalent positions, the lower number is assigned to the one that is cited first in the name (that is, the one that comes first in the alphabetic listing).


$$CH_3CH_2\overset{CH_3CH_2}{C}HCH_2\overset{CH_3}{C}HCH_2CH_3$$

3-ethyl-5-methylheptane
(not 5-ethyl-3-methylheptane)


$$CH_3CH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2CH_2\overset{CH_2CH_3}{C}HCH_2CH_3$$

3-ethyl-6,6-dimethyloctane
(not 6-ethyl-3,3-dimethyloctane)

The complete IUPAC rules actually allow a choice regarding the order in which the appendage groups may be cited. One may cite the appendages alphabetically, as above, or in order of increasing complexity. In this book, we shall adhere to the alphabetic order in citing appendage prefixes. The alphabetic order is also used by *Chemical Abstracts* for indexing purposes.

The IUPAC system of nomenclature is constructed so that each name corresponds to one and only one structure. The actual rules are quite extensive and allow for all sorts of special situations. More complete versions of the rules may be found in standard reference works, such as the *Chemical Rubber Handbook* *of Physics and Chemistry.* The simplified version of the system that we have outlined may be summarized as follows:

1. Find the longest carbon chain in the compound.
2. Name each appendage group that is attached to this principal chain.
3. Alphabetize the appendage groups.
4. Number the principal chain from one end in such a way that the smaller number is used as the first point of difference.
5. Assign to each appendage group a number signifying its point of attachment to the principal chain.

It is important that the student learn how to name alkanes correctly at this point because this basic system is fundamental to the correct naming of all other classes of compounds.

Nomenclature is an essential element of organic chemistry for several reasons. An important use of nomenclature is in **searching the chemical literature** for the physical and chemical properties of various compounds. We shall consider the chemical literature in Chapter 37; however, a brief mention at this point is appropriate to the subject of nomenclature.

New chemical information is made public for the first time as scientific **papers** which appear in various chemical magazines, called **journals.** Examples are the *Journal of the American Chemical Society,* the *Journal of Organic Chemistry,* and *Chemische Berichte.* Hundreds of such journals are published, mostly on a monthly or twice-monthly basis. The back issues of these basic journals contain all of the accumulated knowledge of the science. To facilitate the retrieval of information from this mass of data, the American Chemical Society publishes a reference journal known as *Chemical Abstracts.* This journal is published twice monthly and contains short abstracts of all of the chemical papers published in the basic journals. At the end of each year, an extensively cross-referenced index is published. At the end of each 5-year period (10-year period before 1957), a **cumulative index** covering that period is published. Thus, in order to search through the literature for information about a compound, one must know how to name the compound in order to locate it in these indices.

4.5
Branched Chain Alkanes: Conformations

We saw in Section 4.3 that alkanes occur as mixtures of rapidly interconverting staggered conformations. For example, there are two staggered conformations of isopentane (Figure 4.14). The rotational barrier separating these two conformations is about 5 kcal mole^{-1}. At room temperature, isopentane exists as a mixture of these two conformations, 90% of the one with only one gauche interaction and 10% of the one with two gauche interactions.

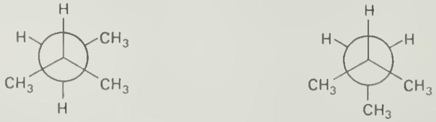


FIGURE 4.14 *Staggered conformations of isopentane.*

According to the definition of isomers given in Section 4.4, different conformations of a compound are isomers since they have the same formula but differ in the arrangement of the atoms in space. However, it is convenient to distinguish such isomers, which rapidly interconvert at ordinary temperatures, from other kinds of isomers that interconvert at high temperatures or not at all. Consequently, we refer to these easily interconvertible spatial isomers as **conformational isomers,** as **conformations,** or as **conformers,** to distinguish them from **structural isomers,** such as butane and isobutane.

Branched chain hydrocarbons are more compact than their straight chain isomers. For this reason, branched hydrocarbons tend to have lower boiling points and higher densities than their straight chain isomers. Physical properties for some branched hydrocarbons are summarized in Table 4.3.

Isolated branches interfere with the regular packing of linear alkanes in the crystal and cause a reduced melting point. That is, branched isomers have a smaller area of contact and Van der Waals attraction is reduced. Consequently, melting points and boiling points are lower. However, when a molecule has sufficient symmetry, it forms a crystal lattice *more* easily and therefore has a higher melting point but a relatively low boiling point. For an example of such a case, compare the melting points of pentane, isopentane, and neopentane. An extreme example is given by 2,2,3,3-tetramethylbutane, which boils only a few degrees above its melting point. Hydrocarbons having a high degree of symmetry or "ball-like" character tend to sublime rather than boil. On heating they pass directly from the solid to vapor state without passing through the intermediate liquid state.

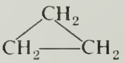
This result can be cast into entropy concepts in a straightforward way. In the crystal, molecules are locked in and have greatly restricted movement. In the liquid, molecules have enhanced freedom of movement. Consequently, the entropy of melting is a positive quantity whose magnitude is a measure of this increased freedom of movement. The entropy of melting of pentane is +14 eu, whereas that of neopentane is only +3 eu. Both molecules have increased freedom of translational motion in the liquid hydrocarbon. In addition, *n*-pentane has a floppy chain with many rotational degrees of freedom so that the liquid hydrocarbon is a mixture of many staggered conformational isomers having relatively high entropy. Rotation about the C—C bonds in neopentane, however, always gives back the same structure, and it has a lower entropy. Note that isopentane has an intermediate value of the entropy of melting of +11 eu.

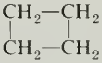
TABLE 4.3
Physical Properties of Some Branched Alkanes

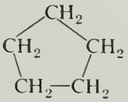
	Boiling Point, °C	Melting Point, °C	Density, d^{20}
isobutane	−11.7	−159.4	0.5572
isopentane	29.9	−159.9	.6196
neopentane	9.4	−16.8	.5904
2-methylpentane	60.3	−153.6	.6532
3-methylpentane	63.3		.6644
2,2-dimethylbutane	49.7	−100.0	.6492
2,3-dimethylbutane	58.0	−128.4	.6616
2,2,3,3-tetramethylbutane	106.3	100.6	.6568

4.6
Cycloalkanes

Carbon chains can also form rings. Because there are no ends to the carbon chain in a cyclic alkane, the general formula is $(CH_2)_n$ or C_nH_{2n}. Like straight chain alkanes, they are saturated hydrocarbons. They are named according to the number of carbons in the ring, with the prefix **cyclo-**.


cyclopropane
C_3H_6


cyclobutane
C_4H_8

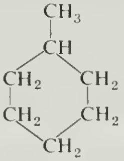

cyclopentane
C_5H_{10}

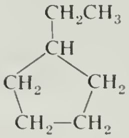
The physical properties of some cycloalkanes are summarized in Table 4.4. Note that their symmetry and more restricted rotations result in higher melting points and boiling points than the comparable *n*-alkanes.

Table 4.4
Physical Properties of Some Cycloalkanes

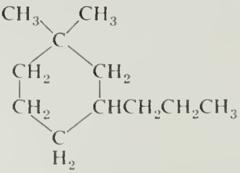
	Boiling Point, °C	Melting Point, °C	Density, d^{20}
cyclopropane	−32.7	−127.6	
cyclobutane	12.5	−50.0	
cyclopentane	49.3	−93.9	0.7457
cyclohexane	80.7	6.6	0.7786
cycloheptane	118.5	−12.0	0.8098
cyclooctane	150.0	14.3	0.8349

Because of symmetry, there is only one mono-substituted cycloalkane and a number to designate the position of the appendage is not necessary.

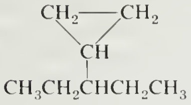

methylcyclohexane


ethylcyclopentane

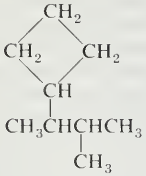
When there is more than one substituent, numbers are required. One substituent is always given the number 1 and the other is given the next lowest possible number.


1,1-dimethyl-3-propylcyclohexane

In naming more complex compounds, the cycloalkyl radical may be named as a prefix.

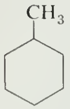


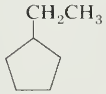
3-cyclopropylpentane

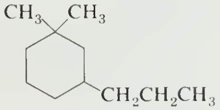


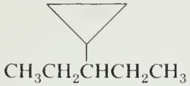
2-cyclobutyl-3-methylbutane

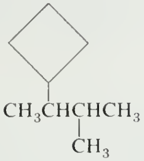
Cycloalkanes are often symbolized by simple geometric figures in which a carbon atom with its appropriate number of attached hydrogens is understood to be present at each apex. The foregoing compounds may be rewritten in this shorthand notation as











Much of the chemistry of cycloalkanes is similar to that of the alkanes. The cycloalkanes do present some special features of conformations, nomenclature, and chemistry that are discussed separately in Chapter 23. The alkanes and cycloalkanes are the parent structures in the general class of aliphatic compounds.

4.7
Occurrence of Alkanes

Alkanes are widespread natural products on earth. They are primarily the product of living processes. Methane is produced by the anaerobic bacterial decomposition of vegetable matter under water. Because it was first isolated in marshes, it was long called "marsh gas." It is also an important constituent of the gas produced in some sewage disposal processes. Methane also occurs in the atmosphere of coal mines, where it is called "fire damp" because of the explosive nature of methane-air mixtures.

Natural gas is a mixture of gaseous hydrocarbons, and consists primarily of methane and ethane, along with small amounts of propane. Natural gas production in the United States in 1971 was 22 trillion (22×10^{12}) cubic feet (ft^3), corresponding to about 10^{12} lb, or 400 million tons of methane! The smaller alkanes are also byproducts of petroleum refining operations. For example, propane is the major constituent of liquefied petroleum gas (LPG), a domestic fuel used in mobile homes.

Petroleum itself is a complex mixture of hydrocarbons, mostly alkanes and cycloalkanes. It is the end result of the decomposition of animal and vegetable matter which has been buried in the earth's crust for long periods of time. The hydrocarbon mixture collects as a viscous black liquid in underground pockets, whence it is obtained by drilling wells. The resulting **crude oil** is refined by distillation into useful fuels and lubricants. Crude oil has a very broad boiling range. The more volatile constituents are propane, which is used as LPG, and butane, which is used as a chemical raw material. **Light petroleum ether** consists of pentanes and hexanes and boils from 30 to 60°. **Ligroin** is a mixture of heptanes and boils from 60 to 90°. These relatively volatile mixtures are often used as solvents, both industrially and in chemical laboratories. The most important petroleum distillates are kerosene (jet fuel) and gasoline.

Fractional distillation of a typical crude oil yields the following fractions:

Fraction	Boiling Range, °C
natural gas (C_1 to C_4)	below 20
petroleum ether (C_5 to C_6)	30–60
ligroin or light naphtha (C_7)	60–90
straight-run gasoline (C_6 to C_{12})	85–200
kerosene (C_{12} to C_{15})	200–300
heating fuel oils (C_{15} to C_{18})	300–400
lubricating oil, greases, paraffin wax, asphalt (C_{16} to C_{24})	over 400

In 1971, the total production of crude oil in the United States was 4.2 billion barrels (bbl). Of this total, 2.2 billion bbl were converted into gasoline, 0.4 billion bbl into kerosene and jet fuel, and 1.2 billion bbl into fuel oils.

One of the major problems facing mankind is fuel. As the demand increases, and the resources diminish, the world faces a severe energy crunch. For example, United States usage of petroleum products increased from 2.9 billion bbl in 1960 to 4.2 billion bbl in 1971, an increase of 45% in only 11 years! There are many obvious solutions, such as nuclear energy, solar energy, and hydroelectric energy, and these are all being actively developed.

Although these types of energy will undoubtedly replace the fossil fuels as energy sources, there will still be a need for the fossil fuels as a source of **carbon.** At present, petroleum and coal hydrocarbons are the basic raw materials of much chemical industry. As the reserves become depleted, it is essential that we develop new sources of carbon raw materials to augment, and eventually replace petroleum and natural gas. One possible source is **shale oil,** petroleum that is not collected in pockets from which it is easily retrieved but is interspersed throughout a porous rock formation. There are enormous reserves of shale oil, particularly in the Western Rockies of the United States, and active research is directed toward improving the economics of its recovery.

An obvious source of additional petroleum is the vegetable matter from which it derives in the first place. However, the natural production of petroleum by the decomposition of vegetation requires eons of time. Some current research is directed toward developing ways to speed up this process, since vegetation may be grown relatively quickly and is therefore replaceable. An interesting recent development in this area uses animal wastes as a starting material for the production of petroleum. The total amount of animal waste that is produced in the

United States alone is astronomical. It is estimated that in 1971 alone, more than 2 billion tons of chicken, pig, and cattle manure was produced. A process has been developed in which this manure is heated with carbon monoxide at 1200 psi and 380°. The product is a crude oil, having properties similar to that obtained from natural sources, and it is produced in high yield (about 3 bbl of oil from a ton of manure). The process is not a solution to the energy crisis, because considerable energy is actually expended in manufacturing the product, but it may provide a future source for petroleum products when sufficient inexpensive nuclear or solar power is available. It also disposes of the animal wastes, which are becoming a major environmental pollutant.

Hydrocarbons also result from some inorganic reactions. Examples are the production of methane by the hydrolysis of beryllium carbide or aluminum carbide.

$$\mathrm{Be_2C + 4\,H_2O \longrightarrow CH_4 + 2\,Be(OH)_2}$$

$$\mathrm{Al_4C_3 + 12\,H_2O \longrightarrow 3\,CH_4 + 4\,Al(OH)_3}$$

Methane is also an important constituent of the atmospheres of the outer planets, Jupiter and Saturn. It has even been suggested that in some distant time, these planets may supply the earth with our hydrocarbon needs.

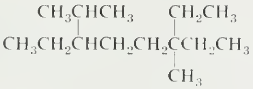
Methane and ethane are odorless, but many of the higher hydrocarbons have distinctive odors. Despite the absence of typical functional groups, hydrocarbons can effect the changes at olfactory centers that we sense as odor. At least one alkane functions as a **pheromone,** a chemical used for communication in nature. For example, 2-methylheptadecane is the sex-attractant for tiger moths.

PROBLEMS

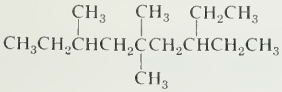
1. Write the structural formula of each of the following alkanes:
   - (a) neopentane
   - (b) isobutane
   - (c) isopentane
   - (d) *sec*-butylcyclohexane
   - (e) 2-cyclobutyl-3,3-dimethylheptane
   - (f) 3,4,5-trimethyl-4-propylheptane
   - (g) 5-(3-methylbutyl)undecane
   - (h) 4-*t*-butylheptane
   - (i) 1-methyl-4-neopentylcyclohexane
   - (j) isoheptane
   - (k) isobutylcycloheptane
   - (l) 2-methylheptadecane

2. Give the IUPAC name for each of the following hydrocarbons:

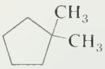
(a) $\mathrm{(CH_3)_2CHCH_2CH_2CH(CH_3)_2}$

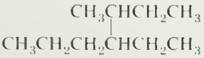
(d) 

$$\mathrm{CH_3CH_2\overset{CH_3CHCH_3}{\overset{|}{C}}HCH_2CH_2\underset{\underset{CH_3}{|}}{\overset{\overset{CH_2CH_3}{|}}{C}}CH_2CH_3}$$

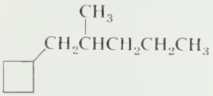
(b) 

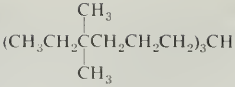
$$\mathrm{CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2\overset{\overset{CH_2CH_3}{|}}{C}HCH_2CH_3}$$

(e) 

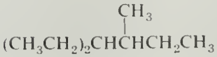
(c) 

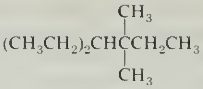
$$\mathrm{CH_3CH_2CH_2\overset{\overset{CH_3CHCH_2CH_3}{|}}{C}HCH_2CH_3}$$

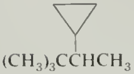
(f) 

(g) 
$(CH_3CH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2CH_2CH_2)_3CH$

(h) $(CH_3CH_2)_4C$

(i) 
$(CH_3CH_2)_2CH\overset{CH_3}{C}HCH_2CH_3$

(j) 
$(CH_3CH_2)_2CH\overset{CH_3}{\underset{CH_3}{C}}CH_2CH_3$

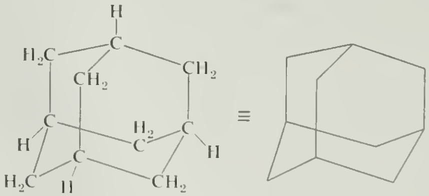
(k) 

3. Write out the structures of the nine possible heptanes and assign IUPAC names. Which structures correspond to the *common* names isoheptane and neoheptane? The b.p. of heptane is 101°. By referring to the b.p.s of the isomeric hexanes in Table 4.3, estimate the b.p.s of the heptane isomers. Check your answers by looking up these compounds in *The Handbook of Chemistry and Physics* or *Lange's Handbook of Chemistry*. Not all of these hydrocarbons are listed in these handbooks. Browse through your library and see if you can find their properties in other reference works.

4. With molecular models, compare the gauche and anti conformation of butane. In particular, estimate the distance between different pairs of hydrogens. Which pair of hydrogens is closest together? Compare their separation with that of eclipsed hydrogens in ethane. Does this comparison suggest a principal reason for the higher energy of the gauche conformation?

5. Write Newman projections and "sawhorse" structures for the three possible staggered conformations of 2,3-dimethylbutane. Note that two of these conformations are equivalent. The two different types of conformation differ in enthalpy by 0.9 kcal mole^{-1}. Which has the lower energy? Assume that $\Delta G° = \Delta H°$ and calculate the equilibrium composition at room temperature and compare your answer with that given for butane on page 59.

6. Examine a molecular model of adamantane. Give a rough estimate of its b.p. Would you expect the m.p. to be far below the b.p.? Look up its m.p. and b.p. in a handbook.



7. With a set of molecular models find each of the four staggered conformations of pentane. Sketch each of these structures using dotted bonds and wedges as appropriate. Try to rank these conformations in order of increased energy (remember that a gauche conformation is less stable than anti).

8. Construct potential energy diagrams for rotation about the C_2—C_3 bonds in isopentane, 2,3-dimethylbutane, and 2,2,3,3-tetramethylbutane. For each unique energy maximum or minimum, illustrate the structure with a Newman projection.

CHAPTER 5

Reactions of Alkanes

5.1
Bond Dissociation Energies

Heat is kinetic energy. When a substance is heated, this kinetic energy increases the motion of atoms and molecules. When methane is heated, much of the added energy goes into translational motion, and the molecules move about faster relative to one another. However, some of the energy absorbed appears as increased vibrational and rotational motion. Figure 5.1 is a schematic diagram of the potential energy of the C—H bond as a function of the C—H bond distance. It shows the vibrational quantum states for bond stretching. At room temperature, only the lowest quantum state is significantly populated.

> Remember that even at absolute zero the atoms are still vibrating. If the atoms were at rest, we would know both their position and momentum exactly, in violation of the Heisenberg uncertainty principle. This lowest vibrational quantum state has an energy ε_0 above the potential minimum. The quantity ε_0 is called the **zero point energy** of the vibration.

As heat is applied, higher vibrational states are increasingly populated. In the higher vibrational quantum states, the average C—H bond distance during a vibration is greater. When sufficient energy, D, is absorbed, the bond breaks. The distance $r_{\text{C-H}}$ increases to infinity and a hydrogen atom and a methyl radical result.

$$CH_4 \longrightarrow CH_3\cdot + H\cdot$$

The value of D is about 102 kcal mole^{-1}. It is generally more convenient to refer to the enthalpy of reaction at 25°C, $\Delta H°$. This quantity ($\Delta H°$ for dissociation

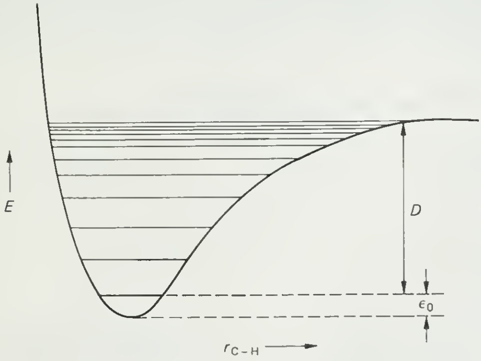


FIGURE 5.1 *Schematic diagram of potential function for a* C—H *bond in methane.*

of a bond at 25°) is given the special symbol $DH°$. For methane $DH°$ is 104 kcal mole^{-1}.

The value for $DH°$ usually differs from D by a small amount. D is an energy quantity at 0° K, where only the lowest energy state is populated. At higher temperatures, various rotational and vibrational states are populated and contribute to the experimental bond dissociation energy, $DH°$. The value of D is estimated by extrapolation to 0° K.

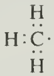
A $DH°$ of 104 kcal mole^{-1} represents a rather strong bond. Temperatures of the order of 1000° are required for dissociation of methane to occur at an appreciable rate. A C—H bond in ethane has a slightly lower $DH°$ (98 kcal mole^{-1}), but $DH°$ for the C—C bond is only 88 kcal mole^{-1}. Consequently, when ethane is heated C—C fission occurs more rapidly than does C—H bond fission.

$$CH_3CH_3 \longrightarrow 2\,CH_3\cdot$$

This reaction occurs at about 700°.

In general, pyrolysis of a compound results in fission of the weakest bond. The products are **free radicals.**

Free radicals contain an odd number of electrons. The Lewis structure for methyl radical is



$$\begin{array}{c} H \\ H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{C}}\cdot \\ H \end{array}$$

Alkyl radicals can exist only at low concentrations at ordinary temperatures. Nevertheless, many such radicals have been "seen" by various spectroscopic methods. For example, methyl radical has been shown by spectroscopic measurements to be essentially flat—all four atoms lie in the same plane. Free radicals are important intermediates in many organic reactions, and we shall encounter them in this context later in this chapter.

Bond dissociation energies, $DH°$, are listed for several hydrocarbons in Table 5.1. A more extensive table for a variety of compounds is given in Appendix II.

Note that $DH°$ depends on the character of the radical products. The $DH°$ for dissociation of a terminal C—H of an alkane is always about 98 kcal mole^{-1}.

TABLE 5.1

*Bond Dissociation Energies for Some Alkanes**

Compound	$DH°$, kcal mole^{-1}	Compound	$DH°$, kcal mole^{-1}
CH_3—H	104	CH_3—CH_3	88
C_2H_5—H	98		
$CH_3CH_2CH_2$—H	98	C_2H_5—CH_3	85
$(CH_3)_2CHCH_2$—H	98	C_3H_7—CH_3	85
$(CH_3)_2CH$—H	94.5	C_2H_5—C_2H_5	82
		$(CH_3)_2CH$—CH_3	84
$(CH_3)_3C$—H	91	$(CH_3)_3C$—CH_3	80

* The bond dissociated is shown as a bond.

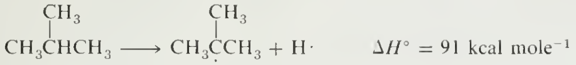
The product of this bond cleavage is called a **primary** alkyl radical. It has the structure $RCH_2\cdot$, where R is any alkyl group.

$$CH_3CH_3 \longrightarrow CH_3CH_2\cdot + H\cdot \qquad \Delta H^\circ = 98 \text{ kcal mole}^{-1}$$

When an interior C—H bond of a linear alkane is broken, the product, $R_2CH\cdot$, is a **secondary** alkyl radical. Such bonds have a lower DH° of 94–95 kcal mole^{-1}.

$$CH_3CH_2CH_3 \longrightarrow CH_3\dot{C}HCH_3 + H\cdot \qquad \Delta H^\circ = 94.5 \text{ kcal mole}^{-1}$$

A C—H bond at a branch point is the weakest type of C—H bond. Such bonds have DH° of about 91 kcal mole^{-1}. The product is a **tertiary** alkyl radical, $R_3C\cdot$.



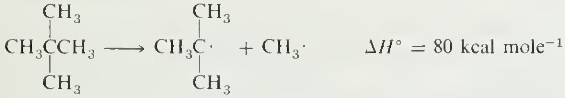
$$CH_3\overset{\overset{\large CH_3}{|}}{C}HCH_3 \longrightarrow CH_3\underset{\cdot}{\overset{\overset{\large CH_3}{|}}{C}}CH_3 + H\cdot \qquad \Delta H^\circ = 91 \text{ kcal mole}^{-1}$$

The relative stability of alkyl radicals depends on the number of alkyl groups attached to the radical carbon; alkyl radicals have the order of stability:

tertiary > secondary > primary > methyl ← ⊛ see M+B p.14

The same principle applies to C—C bonds. The strength of this bond also depends on the relative stabilities of the radical products.

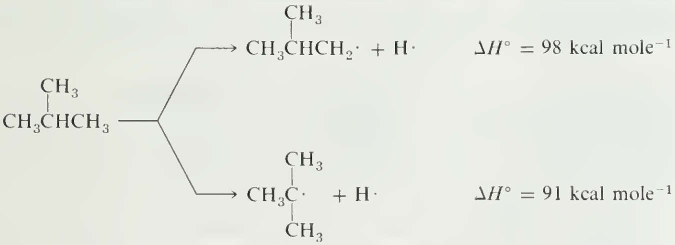
$$CH_3CH_3 \longrightarrow 2\,CH_3\cdot \qquad \Delta H^\circ = 88 \text{ kcal mole}^{-1}$$



$$CH_3\underset{\underset{\large CH_3}{|}}{\overset{\overset{\large CH_3}{|}}{C}}CH_3 \longrightarrow CH_3\underset{\underset{\large CH_3}{|}}{\overset{\overset{\large CH_3}{|}}{C}}\cdot + CH_3\cdot \qquad \Delta H^\circ = 80 \text{ kcal mole}^{-1}$$

Additional C—C bond dissociation energies are also tabulated in Table 5.1.

Consider fission of the two types of C—H bonds in isobutane (Table 5.1). In order to break one of the terminal C—H bonds, 98 kcal mole^{-1} of energy must be absorbed. In order to break the C—H bond at the branch point, only 91 kcal mole^{-1} is required.



$$CH_3\overset{\overset{\large CH_3}{|}}{C}HCH_3 \longrightarrow CH_3\overset{\overset{\large CH_3}{|}}{C}HCH_2\cdot + H\cdot \qquad \Delta H^\circ = 98 \text{ kcal mole}^{-1}$$

$$CH_3\overset{\overset{\large CH_3}{|}}{C}HCH_3 \longrightarrow CH_3\underset{\underset{\large CH_3}{|}}{\overset{\overset{\large CH_3}{|}}{C}}\cdot + H\cdot \qquad \Delta H^\circ = 91 \text{ kcal mole}^{-1}$$

We start at the same point for the two reactions and, because one of the products is the same in each case ($H\cdot$), the difference in ΔH°s for these reactions is a direct measure of the difference in stability of the two alkyl radicals. *The t-butyl radical is more stable than the isobutyl radical by 7 kcal mole*$^{-1}$ (Figure 5.2).

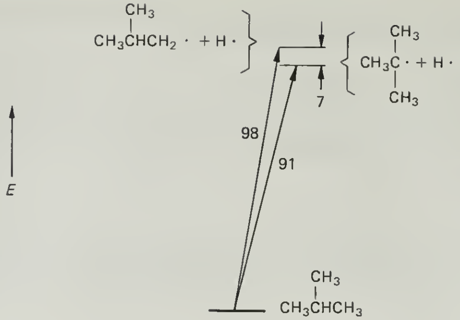
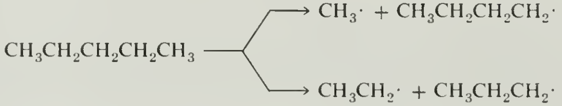


Figure 5.2 *The* DH° *s for the two* C—H *bonds in isobutane.*

5.2 Pyrolysis of Alkanes: Cracking

When a molecule is broken up by heat, the process is called **pyrolysis** (from Greek, *pyros,* fire; *lysis,* a loosening). When alkanes are pyrolyzed, the C—C bonds cleave to produce smaller alkyl radicals. With higher alkanes, the cleavage occurs randomly along the chain.



$$CH_3CH_2CH_2CH_2CH_3 \longrightarrow CH_3\cdot + CH_3CH_2CH_2CH_2\cdot$$
$$CH_3CH_2CH_2CH_2CH_3 \longrightarrow CH_3CH_2\cdot + CH_3CH_2CH_2\cdot$$

One possible reaction of these radicals is recombination to form an alkane. A mixture of different alkanes is produced.

$$CH_3\cdot + CH_3\cdot \longrightarrow CH_3CH_3$$
$$CH_3\cdot + CH_3CH_2\cdot \longrightarrow CH_3CH_2CH_3$$
$$CH_3CH_2\cdot + CH_3CH_2CH_2CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_3$$

Another reaction that occurs is **disproportionation.** In this process one radical transfers a hydrogen atom to another radical to produce an alkane plus an alkene.

$$CH_3CH_2\cdot + CH_3CH_2CH_2\cdot \longrightarrow CH_3CH_3 + CH_3CH{=}CH_2$$

The net result of pyrolysis is the conversion of a large alkane to a mixture of smaller alkanes and alkenes. This reaction is *not* a useful one in the organic laboratory where the aim is generally to produce a *single* pure compound in high yield. The reaction is, however, a tremendously important industrial process. It is the chief method for the production of hydrocarbon fuels. As outlined in Section 4.7, crude oil is a complex mixture of hydrocarbons, mostly alkanes and cycloalkanes. Direct distillation of crude oil yields a relatively small amount of the fraction that is useful for gasoline. In fact, if all gasoline were obtained simply by distillation of the appropriate mixture of hydrocarbons from crude oil, there would be no overpopulation of automobiles on the highways. In order to increase the percentage of usable fuel, refineries *crack* the crude oil by pyrolysis. The result is to increase the relative amount of lower hydrocarbons, particularly in the gasoline range. In practice, various catalysts are used to promote these reactions. In the petroleum industry, the process is known as "catalytic reforming." The reactor used for the process is called a "cat cracker." In a widely used catalytic process, platinum is used as the catalyst. This process is known as "platforming."

A typical example of the product distribution of catalytic cracking of a "gas oil" fraction boiling between 400–600° is given in the following table.

	Weight %
C_1 and C_2	3
propylene	6
propane	4
butenes	4
isobutane	9
n-butane	2
gasoline (b.p. 30–230°)	46
light gas oil (b.p. 230–400°)	15
heavy gas oil (b.p. 400–600°)	5
coke	6
	100

5.3
Halogenation of Alkanes

A. *Chlorination*

When a mixture of methane and chlorine is heated to about 120° or irradiated with light of a suitable wavelength, a highly exothermic reaction occurs.

$$CH_4 + Cl_2 \xrightarrow[\text{or light}]{\text{heat}} \underset{\substack{\text{methyl}\\ \text{chloride}}}{CH_3Cl} + HCl \qquad \Delta H^\circ = -24.7 \text{ kcal mole}^{-1}$$

The reaction is a significant industrial process for preparing methyl chloride. It has limited usefulness as a laboratory preparation because the reaction does not stop with the introduction of a single chlorine. As the concentration of methyl chloride builds up, this compound can be chlorinated in competition with methane:

$$CH_3Cl + Cl_2 \longrightarrow \underset{\substack{\text{methylene}\\ \text{chloride}}}{CH_2Cl_2} + HCl$$

$$CH_2Cl_2 + Cl_2 \longrightarrow \underset{\text{chloroform}}{CHCl_3} + HCl$$

$$CHCl_3 + Cl_2 \longrightarrow \underset{\text{carbon tetrachloride}}{CCl_4} + HCl$$

The actual product of the reaction of methane and chlorine is a mixture of methyl chloride (b.p. 23.8°), methylene chloride (CH_2Cl_2, b.p. 40.2°), chloroform ($CHCl_3$, b.p. 51.2°), and carbon tetrachloride (CCl_4, b.p. 76.8°). The composition of the mixture depends on the relative amounts of starting material used and on the reaction conditions. In this case the products can be readily separated by fractional distillation because of the difference in boiling points.

A good deal of experimental evidence is in accord with the following mechanism for the chlorination of methane. The reaction begins with the **homolysis** of a chlorine molecule to two chlorine atoms (equation 5-1).

When a covalent bond breaks in such a way that each fragment retains one electron of the bond, the process is called **homolytic cleavage** or **homolysis.**

$$A{:}B \longrightarrow A\cdot + B\cdot$$

When one fragment retains both electrons, the process is termed **heterolytic cleavage** or **heterolysis.**

$$A{:}B \longrightarrow A + B{:}$$

Since molecular chlorine has a rather low bond dissociation energy (DH° = 58 kcal mole^{-1}), chlorine atoms may be produced by light of relatively long wavelength or by heating to moderate temperatures.

$$Cl_2 \xrightarrow[\text{or } h\nu]{\Delta} 2\,Cl\cdot \qquad (5\text{-}1)$$

Once chlorine atoms are present in small amount, a **chain reaction** commences. A chlorine atom reacts with a methane molecule to give a methyl radical and HCl (equation 5-2). The methyl radical then reacts with a chlorine molecule to give methyl chloride and a chlorine atom (equation 5-3).

$$Cl\cdot + CH_4 \rightleftharpoons CH_3\cdot + HCl \qquad \Delta H^\circ = +1 \text{ kcal mole}^{-1} \qquad (5\text{-}2)$$
$$CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot \qquad \Delta H^\circ = -25.7 \text{ kcal mole}^{-1} \qquad (5\text{-}3)$$

The chlorine atom produced in equation (5-3) can react with another methane molecule to continue the chain. Reaction (5-1) is called the **initiation** step and reactions (5-2) and (5-3) are called the **propagation** steps.

In principle, only one chlorine molecule need homolyze in order to convert many moles of methane and chlorine to methyl chloride and HCl. In practice, the chain process only goes through, on the average, about 10,000 cycles before it is **terminated.** Termination occurs whenever two radicals happen to collide [for example, equations (5-4) and (5-5)].

$$CH_3\cdot + Cl\cdot \longrightarrow CH_3Cl \qquad (5\text{-}4)$$

$$CH_3\cdot + CH_3\cdot \longrightarrow CH_3CH_3 \qquad (5\text{-}5)$$

Another possible termination step involves the collision of two chlorine atoms (reverse of the initiation step, equation (5-1). However, when two chlorine atoms collide to form Cl_2, the resulting molecule has as vibrational energy all of the kinetic energy of translation of the two atoms. This energy is always in excess of the bond energy, and the two atoms simply separate again. Only if collision occurs in the presence of a third body or on the wall of the reaction vessel to remove some of this energy does the chlorine molecule formed stay intact.

$$Cl\cdot + Cl\cdot + M \longrightarrow Cl_2 + M$$

With polyatomic molecules the translational energy of the reactants of equations (5-4) and (5-5), can be transferred into other bond vibrations and reaction occurs directly. That is, the C—H bonds in these reactions serve as the third body.

Other reactions which may (and probably do) occur are unproductive and do not terminate the chain reaction.

$$CH_4 + CH_3\cdot \longrightarrow CH_3\cdot + CH_4$$

$$Cl_2 + Cl\cdot \longrightarrow Cl\cdot + Cl_2$$

Let us look at each of the foregoing propagation steps in some detail. Reaction (5-2) is slightly endothermic and reversible, but it has a low activation energy of only about 4 kcal $mole^{-1}$. The reaction may be considered in further detail in terms of attack by Cl· on hydrogen:

$$Cl\cdot + H{-}CH_3 \longrightarrow [Cl\cdots H\cdots CH_3]^{\ddagger} \longrightarrow Cl{-}H + \cdot CH_3$$

The H—Cl and H—CH_3 bonds have similar strength [the $DH°$s are 103 and 104 kcal $mole^{-1}$, respectively (Appendix II)]. As the Cl—H bond forms and becomes stronger, the H—C bond becomes weaker and breaks. The product methyl radical appears to be planar (Figure 5.3). Methyl radical can be described to a good approximation in terms of three C_{sp^2}-H_{1s} bonds with the odd electron contained in the remaining C_{2p} orbital. At the transition state the methyl group has started to flatten out from its original tetrahedral structure.

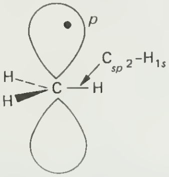
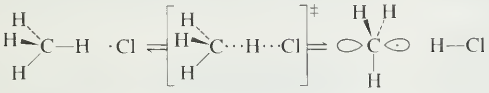


FIGURE 5.3 *Methyl radical.*

For the reverse process, HCl + $CH_3\cdot \longrightarrow CH_4 + Cl\cdot$, the same mechanism applies in reverse. The carbon radical attacks the hydrogen of HCl at the rear of the H—Cl bond and a C—H bond begins to form. As the forming C—H bond distance decreases and the bond strength increases, the remaining C—H bonds begin to bend back toward their tetrahedral geometry in CH_4. At the same time, the H—Cl bond distance increases.



A stereo representation of the transition state is shown in Figure 5.4.

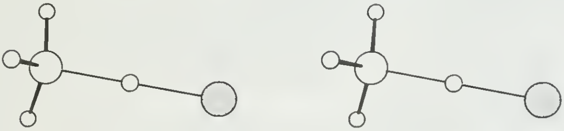


FIGURE 5.4 *Stereo representation of the transition state for the reaction:* $CH_4 + Cl\cdot \rightleftharpoons CH_3\cdot + HCl$.

The structure of the transition state is the same for both directions by the **principle of microscopic reversibility.** That is, the reverse reaction from products to reactants must have the same reaction mechanism as the forward reaction. If it did not, we could, in principle, set up a perpetual motion machine in violation of the second law of thermodynamics.

An equivalent description may be given in orbital terms. As the chlorine orbital containing one electron overlaps with the hydrogen 1*s* orbital, electron repulsion causes a decrease in the overlap of the H_{1s} orbital with the C_{sp^3} orbital, and the C—H bond begins to lengthen and become weaker. As this C—H bond gets weaker, it has less demand for *s* orbital character, and the carbon *s* orbital is used more for bonding to the other C—H bonds. Rehybridization occurs progressively from sp^3 toward sp^2. The carbon begins to flatten out, and the remaining C—H bonds become somewhat shorter and stronger. The structure of the transition state is depicted in terms of component atomic orbitals in Figure 5.5.

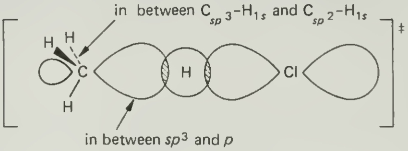

in between C_{sp^3}-H_{1s} and C_{sp^2}-H_{1s}
‡
H
H
C
H
H
Cl
in between sp^3 and *p*

FIGURE 5.5 *Orbital description of transition state for the reaction:* $CH_4 + Cl\cdot \rightleftharpoons CH_3\cdot + HCl$.

A reaction coordinate diagram for reaction (5-2) is shown in Figure 5.6.

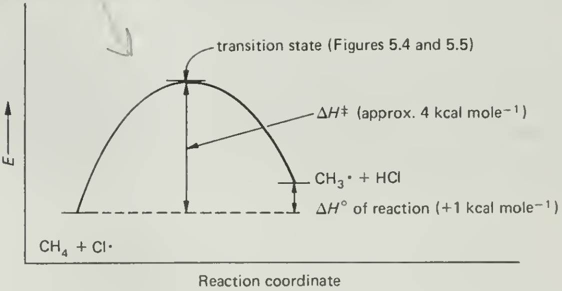


FIGURE 5.6

Reaction (5-3) has only a small activation energy of about 1 kcal mole^{-1}. This reaction is rapid and highly exothermic. The reverse reaction is highly endothermic and has a correspondingly high activation energy of 25.7 + 1 = 26.7 kcal mole^{-1}. Consequently, the overall forward reaction is effectively irreversible. A reaction coordinate diagram for this step is shown in Figure 5.7. The transition state for this reaction is one in which the C—Cl bond is partly formed and the Cl—Cl bond is partly broken.

$$[CH_3\cdot\cdots\cdots Cl\cdots Cl]^\ddagger$$

A stereo representation is given in Figure 5.8.

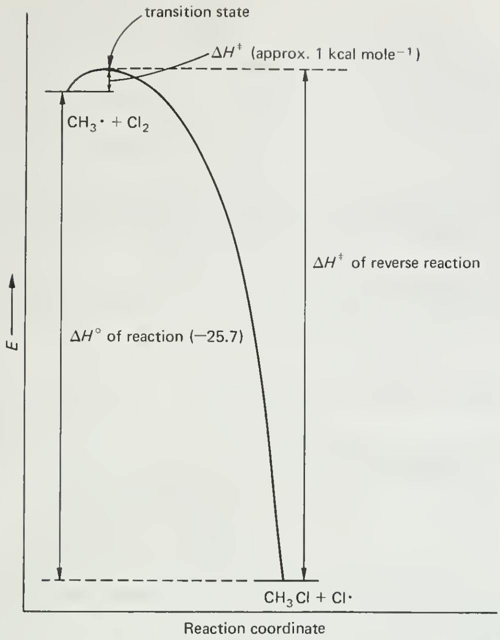


Figure 5.7 ← [RxN 5-3]

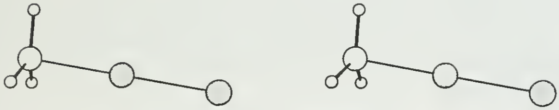


Figure 5.8 *Stereo representation of the transition state for the reaction:* $CH_3\cdot + Cl_2 \rightleftharpoons CH_3Cl + Cl\cdot$.

The overall ΔH° of the net chlorination reaction may be obtained by summing equations (5-2) and (5-3).

		ΔH°, kcal mole^{-1}
(5-2):	$CH_4 + \cancel{Cl}\cdot \longrightarrow \cancel{CH_3}\cdot + HCl$	+1
(5-3):	$\cancel{CH_3}\cdot + Cl_2 \longrightarrow CH_3Cl + \cancel{Cl}\cdot$	−25.7
	$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$	−24.7

Note that ΔH° for the initiation step is *not* added to the ΔH° values for the propagation steps in deriving ΔH° for the overall reaction. If one does this, one is actually calculating ΔH° for *another reaction:*

	$\Delta H°$, kcal $mole^{-1}$
$Cl_2 \longrightarrow 2\,Cl\cdot$	$+58$
$CH_4 + \cancel{Cl\cdot} \longrightarrow \cancel{CH_3}\cdot + HCl$	$+1$
$\cancel{CH_3}\cdot + Cl_2 \longrightarrow CH_3Cl + \cancel{Cl\cdot}$	-25.7
$Cl_2 + CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl + 2\,Cl\cdot$	$+32.3$

This equation is just the sum of the overall chlorination reaction and the chlorine homolysis.

This is often a point of confusion because the student reasons that heat had to be put in to initiate the reaction. However, the question is not how much heat is applied, but what is $\Delta H°$, the *heat of the reaction.*

Chlorination of higher alkanes is similar to chlorination of methane except that the product mixtures are more complex. Ethane gives not only ethyl chloride, but also 1,1-dichloroethane and 1,2-dichloroethane.

$$CH_3CH_3 + Cl_2 \longrightarrow CH_3CH_2Cl + HCl$$

$$CH_3CH_2Cl + Cl_2 \longrightarrow \underset{\text{1,1-dichloroethane}}{CH_3CHCl_2} + \underset{\text{1,2-dichloroethane}}{ClCH_2CH_2Cl} + HCl$$

With propane, two monochloro products may be formed. Both *n*-propyl chloride and isopropyl chloride are formed, but not in equal amounts.

$$CH_3CH_2CH_3 + Cl_2 \longrightarrow \underset{\substack{(43\%)\\ n\text{-propyl chloride}}}{CH_3CH_2CH_2Cl} + \underset{\substack{(57\%)\\ \text{isopropyl chloride}}}{CH_3CHClCH_3}$$

In carbon tetrachloride solution at 25°, the two isomers are produced in the relative amounts 43:57. Further reaction gives a mixture of the four possible dichloropropanes.

Let us examine the monochlorination of propane in greater detail. Recall that $DH°$ for the secondary hydrogen in propane is about 3.5 kcal $mole^{-1}$ lower than $DH°$ for the primary hydrogen (Table 5.1). We might anticipate, then, that the secondary hydrogen would be removed by a chlorine atom more easily than a primary hydrogen. However, there are six primary hydrogens that may be replaced, whereas there are only two secondary hydrogens. The **relative reactivity** per hydrogen is then

$$\frac{\text{secondary}}{\text{primary}} = \frac{57/2}{43/6} = \frac{4}{1}$$

A similar trend is noticed in the monochlorination of isobutane, which gives 36% *t*-butyl chloride and 64% isobutyl chloride.

$$(CH_3)_3CH + Cl_2 \longrightarrow \underset{\substack{(36\%)\\ t\text{-butyl chloride}}}{(CH_3)_3CCl} + \underset{\substack{(64\%)\\ \text{isobutyl chloride}}}{(CH_3)_2CHCH_2Cl}$$

The relative reactivity of tertiary and primary hydrogens, on a per hydrogen basis, is

$$\frac{\text{tertiary}}{\text{primary}} = \frac{36/1}{64/9} = \frac{5.1}{1}$$

Thus, the relative rates of reaction of different hydrogens with $Cl\cdot$ is just as we expect on the basis of $DH°$ for the various hydrogens:

$$\text{tertiary} > \text{secondary} > \text{primary}$$

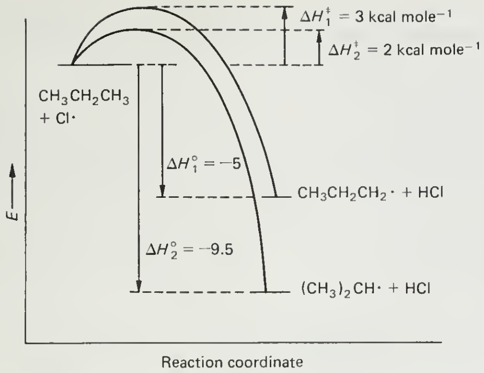
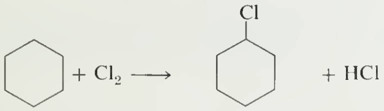


FIGURE 5.9 *Reaction profiles for the reaction of* Cl· *with* C_3H_8.

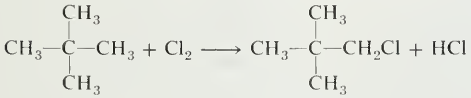
However, the degree of preference is relatively low. That is, there is less difference between the activation energies for the various reactions than there is between the heats of reaction (Figure 5.9).

In chlorination of propane, for example, the $\Delta\Delta H°$ is 4.5 kcal mole^{-1}, but $\Delta\Delta H^{\ddagger}$ is only about 1 kcal mole^{-1}. This result becomes reasonable when one realizes that in the transition state the free radical is not yet fully formed. Whatever it is that causes a secondary free radical to be more stable than a primary free radical will also affect the two transition states. However, that effect will be muted in the transition state to the extent that carbon has not achieved complete free radical character.

With even more complicated alkanes, chlorination mixtures are hopelessly complex. Hence, chlorination of alkanes is *not a good general reaction for preparing alkyl chlorides.* There is one type of compound for which chlorination has practical utility in laboratory preparations. When all hydrogens are equivalent there is only one possible monochloro product. In such cases, the desired product can generally be separated from hydrocarbon and di- and higher chlorinated species by fractional distillation. Two examples are the chlorination of cyclohexane and neopentane.



cyclohexyl chloride



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3 + Cl_2 \longrightarrow CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2Cl + HCl$$

neopentyl chloride

Since handling gaseous chlorine in the laboratory is inconvenient, such chlorinations are often done with sulfuryl chloride, SO_2Cl_2, instead.

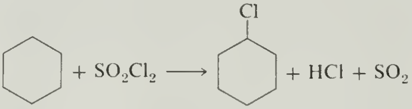
Sulfuryl chloride is a colorless liquid, b.p. 69°, produced by reaction of Cl_2 and SO_2. It fumes in moist air because it reacts rapidly with water according to the reaction

$$SO_2Cl_2 + 2\,H_2O \longrightarrow 2\,HCl + H_2SO_4$$

When sulfuryl chloride is used as a chlorinating agent, a special **initiator** must be used to provide the free radicals that start the chain reaction. **Peroxides** are often used for this purpose because the O—O bond is weak and readily broken at relatively low temperatures. (See Bond Dissociation Energies in Appendix II.)

$$ROOR \longrightarrow 2\,RO\cdot$$

The chlorination of cyclohexane by sulfuryl chloride provides a typical example.



A mixture of 1.8 mole of cyclohexane, 0.6 mole of sulfuryl chloride and 0.001 mole of benzoyl peroxide, $(C_6H_5COO)_2$, is refluxed for 1.5 hr. Fractional distillation gives 89% of chlorocyclohexane, b.p. 143°, and 11% of a mixture of dichlorocyclohexanes.

B. *Halogenation With Other Halogens*

The mechanism discussed in the preceding section for chlorination may also be applied to the other halogens, but the actual reactions show important differences. The overall enthalpies of halogenation of methane by various halogens are summarized in Table 5.2.

TABLE 5.2
$CH_4 + X_2 = CH_3X + HX$

X	$\Delta H°$, kcal mole^{-1}
F	−102.8
Cl	−24.7
Br	−7.3
I	+12.7

The reaction with fluorine is so highly exothermic that controlled fluorination is difficult to accomplish. The energy liberated is sufficient to break most bonds. The HF bond is so strong ($DH° = 136$ kcal mole^{-1}) that the following reaction is endothermic by only 6 kcal mole^{-1}.

$$CH_4 + F_2 \longrightarrow CH_3\cdot + F\cdot + HF \qquad \Delta H° = +6 \text{ kcal mole}^{-1}$$

Consequently, when methane and fluorine are mixed, a few radicals form spontaneously and initiate chain reactions. The heat of reaction that is liberated causes a rapid rise in temperature and more bonds break to form radicals that initiate more chain reactions. Radical chain reactions that are highly exothermic and produce radicals faster than they are destroyed result in explosions. Organofluorine compounds are important because they frequently have unique and desirable properties. However, they are generally *not* made by direct fluorination and this reaction is *not* a general laboratory preparation.

Iodination is at the opposite extreme. As shown in Table 5.2 the reaction of methane with iodine is endothermic. In fact, methyl iodide reacts with HI to generate CH_4 and I_2. Iodine atoms are relatively unreactive. For example, reaction with methane is so endothermic that no significant reaction occurs at ordinary temperatures.

$$CH_4 + I\cdot \longrightarrow HI + CH_3\cdot \qquad \Delta H^\circ = +33 \text{ kcal mole}^{-1}$$

Any iodine atoms produced ultimately dimerize to reform I_2.

The bromination of methane is less exothermic than is chlorination. Of the two chain propagation steps only one is relatively exothermic.

$$\begin{aligned} CH_4 + Br\cdot &\longrightarrow CH_3\cdot + HBr \qquad \Delta H^\circ = +16.5 \text{ kcal mole}^{-1} \\ CH_3\cdot + Br_2 &\longrightarrow CH_3Br + Br\cdot \qquad \Delta H^\circ = -23.8 \text{ kcal mole}^{-1} \end{aligned}$$

Consequently, bromination is much slower than chlorination. It is instructive to examine the bromination of methane from a mechanistic standpoint. The two propagation steps are plotted in reaction coordinate form in Figures 5.10 and 5.11.

In its reactions with other alkanes, bromine is a much *more selective* reagent than chlorine. For example, bromination of propane at 330° in the vapor phase gives 92% isopropyl bromide and only 8% *n*-propyl bromide.

$$CH_3CH_2CH_3 + Br_2 \longrightarrow \underset{\substack{(8\%) \\ n\text{-propyl bromide}}}{CH_3CH_2CH_2Br} + \underset{\substack{(92\%) \\ \text{isopropyl bromide}}}{(CH_3)_2CHBr}$$

The hydrogen abstraction steps for formation of the two isomers are

$$\begin{aligned} CH_3CH_2CH_3 + Br\cdot &\longrightarrow CH_3CH_2CH_2\cdot + HBr \qquad \Delta H^\circ = +10.5 \text{ kcal mole}^{-1} \\ CH_3CH_2CH_3 + Br\cdot &\longrightarrow (CH_3)_2CH\cdot + HBr \qquad \Delta H^\circ = +6.0 \text{ kcal mole}^{-1} \end{aligned}$$

The two reactions are plotted in reaction coordinate form in Figure 5.12.

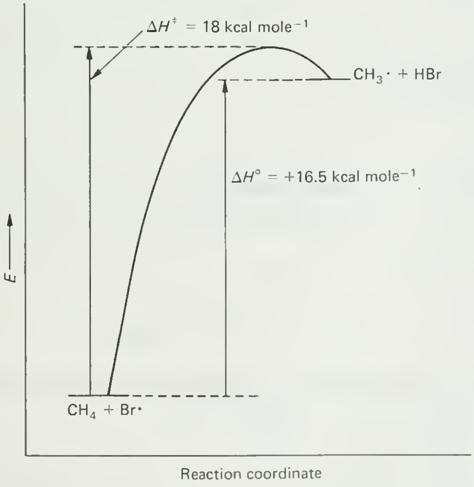


FIGURE 5.10 *Reaction profile for the reaction:* $CH_4 + Br\cdot \rightleftharpoons CH_3\cdot + HBr$.

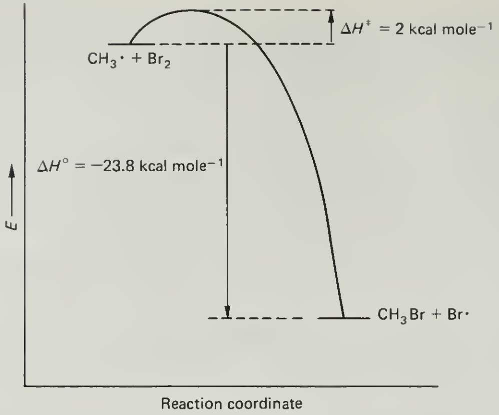

ΔH‡ = 2 kcal mole⁻¹
CH₃· + Br₂
ΔH° = −23.8 kcal mole⁻¹
E
CH₃Br + Br·
Reaction coordinate

FIGURE 5.11 *Reaction profile for the reaction:* $CH_3\cdot + Br_2 \rightleftharpoons CH_3Br + Br\cdot$.

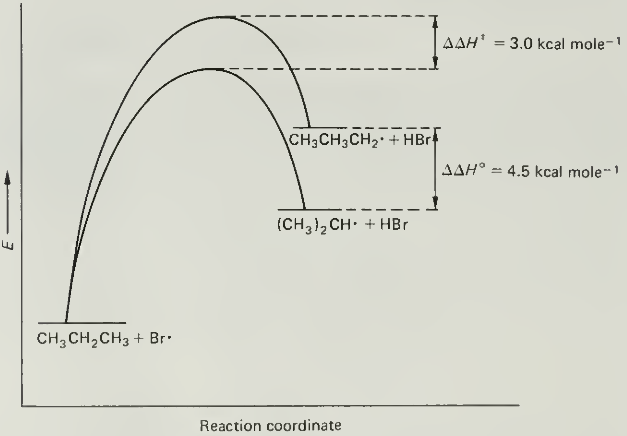

ΔΔH‡ = 3.0 kcal mole⁻¹
CH₃CH₃CH₂· + HBr
ΔΔH° = 4.5 kcal mole⁻¹
(CH₃)₂CH· + HBr
E
CH₃CH₂CH₃ + Br·
Reaction coordinate

FIGURE 5.12 *Reaction profiles for the reaction of* $Br\cdot$ *with* C_3H_8.

The rates of reaction of a bromine atom with the two types of hydrogen in propane are given by

$$\text{rate }(1^\circ) = k_{1^\circ}[CH_3CH_2CH_3][Br\cdot]$$
$$\text{rate }(2^\circ) = k_{2^\circ}[CH_3CH_2CH_3][Br\cdot]$$

The ratio of the products formed is simply the ratio of the two rate constants.

$$\frac{\text{rate }(2^\circ)}{\text{rate }(1^\circ)} = \frac{k_{2^\circ}}{k_{1^\circ}}$$

For two similar reactions such as these, the ratio of the rate constants is related in an exponential manner to the two activation energies. The reaction with the larger activation energy has the smaller rate constant. Recall that in the chlorination of propane, $\Delta\Delta H^\ddagger$ is only 1 kcal mole^{-1} and consequently chlorination is relatively nonselective. For bromination, $\Delta\Delta H^\ddagger$ is 3 kcal mole^{-1} and hence bromination gives a greater *ratio* of secondary to primary products.

The selectivity of bromine relative to chlorine is even more apparent when there are tertiary hydrogens in the alkane. For example, 2,2,3-trimethylbutane undergoes bromination to give more than 96% of the tertiary bromide, even though the alkane has only one tertiary hydrogen and 15 primary hydrogens.

$$(CH_3)_3CCH(CH_3)_2 + Br_2 \xrightarrow[CCl_4]{h\nu} \underset{(>96\%)}{(CH_3)_3CCBr(CH_3)_2}$$

Thus, bromination is a somewhat more useful process for preparative purposes than chlorination. However, when there is only one tertiary hydrogen and many secondary hydrogens in a molecule, complex mixtures will still be produced.

It is interesting to speculate as to why bromine atoms are so much more discriminating than chlorine atoms. A straightforward explanation is based on the concept of "early" and "late" transition states. Chlorination is believed to proceed through an "early" transition state. By an early transition state, we mean that C—H bond cleavage has not proceeded very far. Consequently, H—Cl bond making has not happened to a very great extent. Such an early transition state may be symbolized as

$$[R{-}{-}{-}H{-}{-}{-}{-}{-}{-}{-}{-}Cl]^\ddagger$$

In contrast to chlorination, bromination is believed to proceed through a "late" transition state, in which C—H bond breaking and H—Br bond making are well advanced. Such a late transition is symbolized as

$$[R{-}{-}{-}{-}{-}{-}{-}{-}H{-}{-}{-}Br]^\ddagger$$

If the transition state is early and the C—H bond has not been stretched very much, the carbon is still essentially tetrahedral. Its geometry resembles the starting alkane. Conversely, if the transition state is late and C—H bond breaking has proceeded to a greater extent, then the geometry of carbon is more nearly planar. It resembles the product free radical.

In a reaction proceeding through an early transition state, the stability of the product has little influence on rate because the structure and energy of the transition state are similar to the reactants. Thus, in chlorination of isobutane, the two possible transition states are of similar energy and the two competing reactions proceed at comparable rates.

However, if the transition state is late, the stability of the product is reflected in the transition state. In the bromination of isobutane, one transition state looks like a primary free radical and the other resembles a tertiary free radical. These two transition states differ in energy considerably. Consequently, the reaction leading to a tertiary free radical is much more rapid.

5.4
Combustion of Alkanes

In terms of the mass of material involved, combustion of alkanes is one of the most important organic reactions. All burning of natural gas, gasoline, and fuel oil involves mostly the combustion of alkanes. However, this combustion is an atypical organic reaction in two respects. First, mixtures of alkanes are normally the "reactants" in this reaction. Second, the desired product of the reaction is not the chemical products but the heat of reaction. Indeed, the chemical products are frequently undesirable and their sheer mass creates significant problems of disposal. The equation for complete combustion of an alkane is simple:

$$C_nH_{2n+2} + \left(\frac{3n+1}{2}\right)O_2 \longrightarrow n\,CO_2 + (n+1)\,H_2O$$

However, many combustion processes, such as the burning of gasoline in an internal combustion engine, do not result in complete combustion. In an automobile, 1 gal of gasoline produces more than 1 lb of carbon monoxide. There are many other products resulting from incomplete combustion. Among these other products are aldehydes (RCHO), compounds that contribute significantly to the smog problem.

The mechanism by which alkanes react with oxygen is an exceedingly complex one and has not been worked out in detail. There are many partially oxidized intermediates. Radical chain steps are certainly involved. An especially important reaction is the combination of alkyl radicals with oxygen to give **alkylperoxy** radicals, which abstract hydrogen from an alkane to give intermediate alkyl hydroperoxides:

$$\begin{gathered} R\cdot + O_2 \longrightarrow ROO\cdot \\ ROO\cdot + RH \longrightarrow ROOH + R\cdot \end{gathered}$$

Alkyl hydroperoxides contain a weak O—O bond ($DH° \approx 44$ kcal mole^{-1}) which breaks readily at elevated temperatures to produce more radicals.

$$ROOH \longrightarrow RO\cdot + HO\cdot$$

Thus, combustion is another example of a radical-multiplying reaction that leads to explosions under proper conditions.

> When such an explosion occurs in the reaction chamber of an internal combustion engine, the piston is driven forward with a violent, rather than a gentle, stroke. Such premature explosions cause the phenomenon known as "knocking." The tendency of a fuel to knock depends markedly on the nature of the hydrocarbons used. In general, branching of an alkane chain tends to inhibit knocking. The knocking characteristic of a fuel is expressed quantitatively by an "octane number." On this arbitrary scale, *n*-heptane is given a value of 0 and 2,2,4-trimethylpentane ("isooctane") is assigned the value of 100. An octane number of 90, typical of a medium grade "standard" or "regular" gasoline has a knocking characteristic that is equivalent to that of a mixture of 90% 2,2,4-trimethylpentane and 10% *n*-heptane. The octane rating may be upgraded by the addition of small amounts of tetraethyllead $(C_2H_5)_4Pb$, which is called an "antiknock" agent. Its function is to control the concentration of free radicals and prevent the premature explosions which are characteristic of knocking.

The **heat of combustion** is defined as the enthalpy of the complete oxidation. The heat of combustion of a pure alkane can be measured experimentally with high precision (±0.02%) and constitutes an important thermochemical quantity. For example, the heat of combustion of butane is $\Delta H° = -687.42 \pm 0.15$ kcal mole^{-1}, whereas that of isobutane is $\Delta H° = -685.37 \pm 0.11$ kcal mole^{-1}. The general equation for combustion of these two isomers is the same.

$$C_4H_{10} + 6\tfrac{1}{2}\,O_2 \longrightarrow 4\,CO_2 + 5\,H_2O$$

A direct comparison of these two heats of combustion shows that the branched hydrocarbon is 2.0 kcal mole^{-1} more stable than the straight chain hydrocarbon at room temperature (Figure 5.13). The products, carbon dioxide and water, are

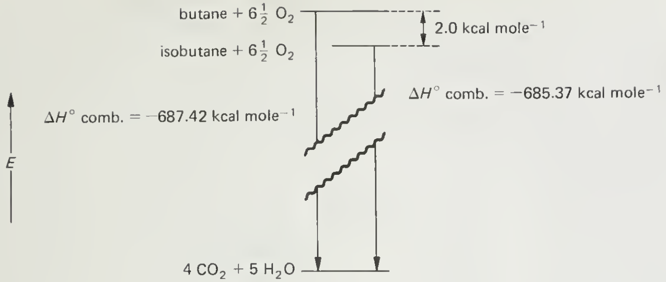

butane + $6\frac{1}{2}$ O_2
isobutane + $6\frac{1}{2}$ O_2
2.0 kcal mole^{-1}
$\Delta H°$ comb. = −685.37 kcal mole^{-1}
$\Delta H°$ comb. = −687.42 kcal mole^{-1}
E
4 CO_2 + 5 H_2O

FIGURE 5.13 *Illustrating the heats of combustion of butane and isobutane.*

more stable than the reactants. Because the products have a lower energy content, energy is released as heat—the heat of combustion. The *less* stable the reactants, the *more* heat is evolved. Since butane has a heat of combustion of higher magnitude than isobutane, butane must have a higher energy content and is less stable thermodynamically than isobutane.

5.5
Heats of Formation

Heats of combustion for many compounds have now been measured, but for convenience they have been converted into **heats of formation** from the elements in their standard states. The heat of formation of a compound is defined as the enthalpy of the reaction of elements in their standard states to form the compound. The standard states are generally the most stable states of each element at 25°. The standard state of carbon is taken as graphite whereas those of hydrogen and oxygen are H_2 and O_2 gases, respectively. The standard heat of formation, $\Delta H_f°$, of butane is -30.36 ± 0.16 kcal mole^{-1} and that for isobutane is -32.41 ± 0.13 kcal mole^{-1}.

$$4\,\text{C(graphite)} + 5\,\text{H}_2(g) = n\text{-C}_4\text{H}_{10}(g) \qquad \Delta H° \equiv \Delta H_f°(n\text{-C}_4\text{H}_{10}) = -30.36 \text{ kcal mole}^{-1}$$

$$4\,\text{C(graphite)} + 5\,\text{H}_2(g) = (\text{CH}_3)_3\text{CH}(g) \qquad \Delta H° \equiv \Delta H_f°(i\text{-C}_4\text{H}_{10}) = -32.41 \text{ kcal mole}^{-1}$$

The negative signs of these heats of formation mean that heat would be liberated if these hydrocarbons could be prepared from the reaction of graphite with hydrogen. That is, these hydrocarbons are more stable than the elements in their standard states. These relationships are depicted graphically in Figure 5.14. Note that the conversion of the heats of combustion of butane and isobutane to heats of formation requires only the heats of combustion of graphite and of hydrogen.

In using energy diagrams such as Figure 5.14 remember that *down* represents less energy and greater stability ("downhill in energy") whereas the *up* direction represents higher energy and lower stability.

Some values for heats of formation are listed in Table 5.3. A more complete list is given in Appendix 1. These $\Delta H_f°$ values are useful for estimating possible reactions, providing that a pathway or reaction mechanism is possible. For example, the hydrogenation of butane to ethane is exothermic by 10 kcal mole^{-1}.

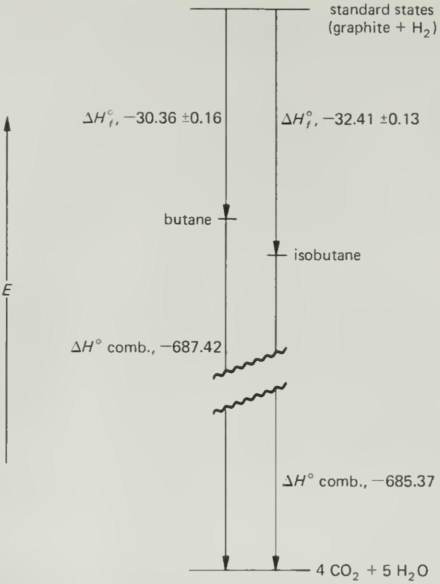


FIGURE 5.14 *The relationship between the heats of formation and combustion of butane and isobutane.*

$$\begin{array}{llll} & C_4H_{10} + H_2 = 2\,C_2H_6 & & \\ \Delta H_f^\circ: & -30.4 + \quad 0 \qquad 2 \times -20.2 & & \Delta H^\circ = -10.0 \text{ kcal mole}^{-1} \end{array}$$

If a suitable catalyst or reaction pathway could be found, this reaction would proceed toward the right. However, no such catalyst or pathway is known at ordinary temperatures. The reaction remains hypothetical even though, if realized, it would be exothermic. This example illustrates the difference between thermodynamics and kinetics. A given reaction may have favorable thermodynamics but will occur only if a pathway with a sufficiently low activation barrier can be found. Because of the importance of pathways our studies of organic reactions will also often include discussions of reaction mechanism. The importance of enzymes in biochemical reactions is that they provide such pathways for reaction.

The hydrogenation of ethylene to ethane is also highly exothermic.

$$\begin{array}{ll} C_2H_4 + H_2 = C_2H_6 & \\ 12.5 + \quad 0 \qquad -20.2 & \Delta H^\circ = -32.7 \text{ kcal mole}^{-1} \end{array}$$

In this case a number of catalysts are known that provide a reaction pathway, and this reaction is an important general reaction of alkenes (Section 12.6.A).

One important limitation on the use of heats of formation is that equilibria are determined by free energy rather than by enthalpy alone.

$$\Delta G^\circ = -RT \ln K = \Delta H^\circ - T\Delta S^\circ$$

That is, an entropy change plays a large role in determining an equilibrium constant. Since entropy is a measure of freedom of motion, the largest entropy changes result from a difference in numbers of molecules on the two sides of

TABLE 5.3
Some Heats of Formation

Compound	Heat of Formation at 25° ΔH_f°, kcal mole^{-1}
CH_4	−17.9
CH_3CH_3	−20.2
$CH_3CH_2CH_3$	−24.8
$CH_3CH_2CH_2CH_3$	−30.4
$(CH_3)_3CH$	−32.4
$CH_3CH_2CH_2CH_2CH_3$	−35.1
$(CH_3)_2CHCH_2CH_3$	−36.9
$(CH_3)_4C$	−40.3
$H\cdot$	52.1
$CH_3\cdot$	34
$C_2H_5\cdot$	26
$CH_3CH_2CH_2\cdot$	21
$(CH_3)_2CH\cdot$	17.5
$(CH_3)_3C\cdot$	6.7
C (atomic)	170.9
O	59.6
CO	−26.4
CO_2	−94.1
H_2O (g)	−57.8
H_2O (l)	−68.3
H_2	0
O_2	0
C (graphite)	0

an equilibrium. The magnitude of this effect depends on the physical state (gas, liquid, and so on), the molecular weight, and the temperature. For a gas at ordinary temperature and pressure, a difference of one molecule on the two sides of an equilibrium (for example, A = B + C) corresponds to about 30–40 eu, which is equivalent to 9–12 kcal mole^{-1} in enthalpy at room temperature. At higher temperatures any entropy change has a still greater effect. For example, the disproportionation of butane, the cracking reaction, is highly endothermic at room temperature.

$$C_4H_{10} = C_2H_6 + C_2H_4$$

$$\Delta H_f^\circ\text{:}\ -30.4 \qquad -20.2 + 12.5$$

$$\begin{aligned}\Delta H^\circ &= \Delta H_f^\circ\,(\text{products} = -20.2 + 12.5) - \Delta H_f^\circ\ (\text{reactants} = -30.4)\\ &= +22.6\ \text{kcal mole}^{-1}\end{aligned}$$

Even though this reaction involves one molecule going to two the resulting ΔS° of 33 eu still leaves a positive free energy change at room temperature; $\Delta G^\circ = +12.7$ kcal mole^{-1}. However, at 500° the equilibrium is still highly endothermic in enthalpy but the positive entropy change gives a ΔG° of -3.8 kcal mole^{-1}. The equilibrium now favors the products.

5.6
Average Bond Energies

Table 5.3 for heats of formation includes values for a number of free atoms. With these values we can calculate **heats of atomization**, the enthalpy required to dissociate a compound into all of its constituent atoms. For example, the heat of atomization of methane is 397 kcal mole^{-1}.

$$\begin{array}{llll} & CH_4 = & C & + 4\,H \\ \Delta H_f^\circ: & -17.9 & 170.9 + (4 \times 52.1) & \qquad \Delta H^\circ = 397.2 \text{ kcal mole}^{-1} \end{array}$$

(Note that ΔH_f° of atomic carbon is much higher than ΔH_f° of C(graphite), carbon bound as graphite and defined as the standard state.) This reaction requires breaking four C—H bonds. Hence, we can consider each bond to have an **average bond energy** of $397/4 = 99$ kcal mole^{-1}. Note that this number differs from the bond dissociation energy of methane ($DH^\circ = 104$ kcal mole^{-1}), which is the energy required to break only *one* C—H bond in methane.

A similar calculation for ethane gives 674.6 kcal mole^{-1} as the heat of atomization required to break six C—H bonds and one C—C bond. If we *assume* that the average C—H bond energy in ethane is the same as it is in methane, we obtain $675 - (6 \times 99) = 81$ kcal mole^{-1}, a number that we could call the average bond energy of the C—C bond in ethane. If the same technique is applied to propane we find a C—C bond energy similar to that in ethane.

In practice, data for a large number of compounds have been used to derive best overall values for such average bond energies. A table of such values is given in Appendix III. With this table one can calculate heats of atomization that are accurate to a few kilocalories per mole. The use of such a table is important for determining the approximate energy content of molecules whose heats of formation have not been determined experimentally or are too unstable to be isolated. Note that the results are only approximations. Butane and isobutane, for example, have the same numbers of C—C and C—H bonds. Such an approximate calculation using average bond energies results in identical heats of atomization; however, accurate heats of combustion show that butane and isobutane differ in energy content by 2.0 kcal mole^{-1}. Nevertheless, such approximate values will be found to have important uses in our study of organic chemistry.

PROBLEMS

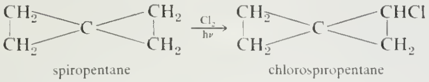
1. (a) What products are expected from cracking pentane? (b) Write reaction mechanisms leading to each product. (c) From heats of formation calculate the enthalpy of each of the net reactions involved.

2. Using the appropriate DH° values from Appendix II, calculate ΔH° for each of the reactions shown.
   (a) $Br_2 \longrightarrow 2\,Br\cdot$
   (b) $CH_3CH_3 + Br\cdot \longrightarrow CH_3CH_2\cdot + HBr$
   (c) $CH_3CH_2\cdot + Br_2 \longrightarrow CH_3CH_2Br + Br\cdot$
   What is the overall ΔH° for bromination of ethane given as the sum of reactions (b) and (c)?
   (d) $CH_3CH_3 + Br_2 \longrightarrow CH_3CH_2Br + HBr$
   How does this value compare with that obtained using heats of formation?

3. In the course of the bromination of ethane (problem 2), both bromine atoms and

ethyl radicals will be present but not in equal amounts. Which is present in larger quantity? Explain.

4. The reaction of the unusual hydrocarbon spiropentane with chlorine and light is one of the best ways of preparing chlorospiropentane.



(a) Explain why chlorination is such a useful preparative method in this case.
(b) Write the reaction mechanism.

5. For each of the following compounds, write the structures of all of the possible monochlorination products and predict the relative amounts in which they will be produced.
(a) butane
(b) 2-methylbutane
(c) 2,2,4-trimethylpentane
(d) 2,2,3-trimethylbutane
(e) pentane

6. Answer problem 5 for bromination, using the relative reactivities of C—H bonds towards bromine atoms at 40°C: prim., 1; sec., 220; tert., 19000.

7. In the chlorination of ethane, the observed reaction is

$$CH_3CH_3 + Cl_2 \longrightarrow CH_3CH_2Cl + HCl$$

An alternative reaction that might have occurred is

$$CH_3CH_3 + Cl_2 \longrightarrow 2\ CH_3Cl$$

(a) Calculate $\Delta H°$ for each reaction.
(b) Propose a radical chain mechanism by which the alternative reaction might occur. Calculate $\Delta H°$ for each of the propagation steps.
(c) Suggest a reason why the alternative reaction does not occur.

8. From Table 5.3 calculate the heat of atomization of *n*-butane. Compare this value with the approximate one obtained from the use of average bond energies, (Appendix III).

9. From the heats of formation given in Appendix I calculate the heat of combustion of cyclopropane and cyclohexane. For combustion of an equal *weight* under the same conditions, which is the better fuel?

★10. Nitromethane, CH_3NO_2, is prepared by reaction of methane with nitric acid in the gas phase at temperatures over 400°. The Table of Heats of Formation in Appendix I includes values for some nitrogen compounds. Calculate $\Delta H°$ (298°K) for the equilibrium

$$CH_4 + HNO_3 \rightleftharpoons CH_3NO_2 + H_2O$$

It may seem strange that such an exothermic reaction requires such a high temperature. The actual reaction steps are believed to be

$$CH_4 + \cdot NO_2 \rightleftharpoons CH_3\cdot + HNO_2$$

$$HNO_2 + HNO_3 \rightleftharpoons 2\ NO_2\cdot + H_2O$$

$$CH_3\cdot + NO_2\cdot \rightleftharpoons CH_3NO_2$$

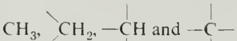
Calculate $\Delta H°$ for each step. Which step is expected to be the slow step that requires the high temperature? The reaction is initiated by traces of oxygen or radicals to produce some $NO_2\cdot$ radicals which start the reaction. Note that this reaction sequence involves a radical chain propagation. Nitrogen dioxide is a rather stable radical and its concentration in the reaction mixture is relatively high. It reacts rapidly with the methyl radicals and keeps these radicals at a very low concentration so that alternative free radical chain reactions are kept to minor importance; that is, nitrogen dioxide *scavanges* the methyl radicals. List several possible reactions of methyl radicals with nitric acid to produce methyl alcohol or nitromethane directly and show that these reactions are exothermic.

Nitrogen dioxide is a resonance-stabilized radical in which the odd electron can be placed on both oxygens and nitrogen. Write Lewis structures to demonstrate this point. In view of these structures it may seem surprising that methyl radical reacts with the nitrogen of NO_2. Actually, reaction at oxygen also occurs to give methyl nitrite, CH_3ONO. Compare $\Delta H°$ for this reaction with that for production of nitromethane:

$$CH_3NO_2 \longleftarrow CH_3\cdot + NO_2\cdot \longrightarrow CH_3ONO$$

Methyl nitrite is unstable under the reaction conditions and gives other products. The entire reaction is complex, and the discussion has treated only the most important of the many reactions that actually occur in this system.

★ 11. Careful inspection of the heats of formation in Table 5.3 will show regular increments per CH_2 group in a homologous series. In fact, $\Delta H_f°$ increments can be associated with the groups



$$CH_3,\ >CH_2,\ -\overset{|}{\underset{|}{C}}H \text{ and } -\overset{|}{\underset{|}{C}}-$$

Determine average values for these groups from Table 5.3, or, if you have access to a small computer, calculate the values that give the best least squares fit to the experimental data. Use your results to estimate $\Delta H_f°$ for hexane, 2-methylpentane, 3-methylpentane, 2,2-dimethylbutane, and 2,3-dimethylbutane. Compare with the experimental values in Appendix I.

You can see how far your "group equivalents" will go by comparing your calculated value with the experimental $\Delta H_f°$ for nonane of -54.7 kcal mole^{-1}. You should agree to several tenths of a kilocalorie per mole. However, compare your calculated value for 2,2,4,4-tetramethylpentane with the experimental $\Delta H_f°$ of -57.8 kcal mole^{-1}. Why is there a discrepancy? (*Hint:* Look at a molecular model. Will steric interferences or *strain* increase or decrease $\Delta H_f°$?)

★ 12. Isobutane is thermodynamically more stable than butane. Which has the lower boiling point? Is there any relationship between thermodynamic stability and boiling point? Would you expect such a relationship between thermodynamic stability and melting point?

CHAPTER 6

Alkyl Halides

6.1
Nomenclature

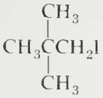
As with many other classes of organic compounds, alkyl halides may be named with both a common and a systematic nomenclature. Simple alkyl halides may be named as though they were salts of alkyl radicals. This nomenclature may be used whenever the alkyl group has a common name.

CH_3F

methyl fluoride

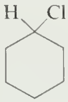
$(CH_3)_2CHBr$

isopropyl bromide

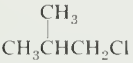


$$\begin{array}{c} CH_3 \\ | \\ CH_3CCH_2I \\ | \\ CH_3 \end{array}$$

neopentyl iodide



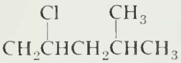
cyclohexyl chloride



$$\begin{array}{l} \quad CH_3 \\ \quad | \\ CH_3CHCH_2Cl \end{array}$$

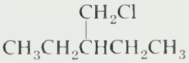
isobutyl chloride

The systematic nomenclature of alkyl halides is an extension of the IUPAC system for naming alkanes. In this system, the compounds are named as halogen derivatives of a parent hydrocarbon; that is, as **haloalkanes.** The alkane parent is named and numbered first, as outlined in Section 4.4. The name of the halogen is then grafted on as a prefix (fluoro, chloro, bromo, iodo), together with a number showing its point of attachment to the chain. In most cases, this number is fixed unambiguously in correctly numbering the alkane chain.



$$\begin{array}{l} \quad Cl \qquad CH_3 \\ \quad | \qquad\quad | \\ CH_3CHCH_2CHCH_3 \end{array}$$

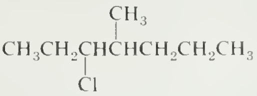
4-chloro-2-methylpentane



$$\begin{array}{l} \qquad\qquad CH_2Cl \\ \qquad\qquad | \\ CH_3CH_2CHCH_2CH_3 \end{array}$$

3-(chloromethyl)pentane

When the alkane parent may be correctly numbered from either end (when it is symmetrical), it is numbered in such a way as to give the halogen the lower of two alternative numbers.



$$\begin{array}{l} \qquad\qquad\quad CH_3 \\ \qquad\qquad\quad | \\ CH_3CH_2CHCHCH_2CH_2CH_3 \\ \qquad\quad | \\ \qquad\quad Cl \end{array}$$

3-chloro-4-methylheptane
(not 5-chloro-4-methylheptane)

When there are two or more halogens, the appropriate prefix is used: di-, tri-, tetra-, and so on. Each halogen is given a position number.

$CH_3CCl_2CH_3$
2,2-dichloropropane

$BrCH_2CH_2CHBrCH_2Br$
1,2,4-tribromobutane

If the halogens are different, they are named in alphabetical order.

$ClCH_2CH_2CH_2CH_2Br$
1-bromo-4-chlorobutane

$\mathrm{BrCH_2CHF\overset{\overset{CH_3}{|}}{C}HCH_2I}$
4-bromo-3-fluoro-1-iodo-
2-methylbutane

The symbol X is often used as a generic symbol for halogen. The general formula for an alkyl halide is therefore RX. The polyhalomethanes are common industrial compounds and are usually called by trivial names, as shown in the following table.

Formula	Type Name	Example
CH_2X_2	methylene halide	methylene bromide, CH_2Br_2
CHX_3	haloform	iodoform, CHI_3
CX_4	carbon tetrahalide	carbon tetrachloride, CCl_4

6.2
Structure

The carbon atoms in alkyl halides are essentially tetrahedral. The C—X bond may be regarded to a good approximation as resulting from overlap of a C_{sp^3} orbital with a hybrid orbital from the halogen. Molecular orbital calculations suggest that the hybrid halogen orbital is mostly *p* with only a small amount of *s* character. In methyl fluoride, for example, the hybrid orbital from fluoride in the C—F bond is calculated to be about 15% *s* and 85% *p*. The reason for the relatively small amount of *s* character is that the halogen has three lone pairs and most of the X_{2s} atomic orbital is used to bind these lone pair electrons. Only a small amount of *s* orbital is available for the orbital bonded to carbon.

Note that the hybridization of the halogen must be computed; it is not amenable to experimental test with currently available methods. With other atoms, bond angles may be experimentally determined by various techniques. If one assumes a relationship between hybridization of the orbitals forming two bonds and the angle between the bonds, then the orbital hybridization has been experimentally measured. For example, the angle between two sp^3 orbitals is 109.5°; that between two *p* orbitals is 90°. From the measured H—O—H bond angle in water, 104.4°, we may say that the oxygen orbitals that bind the two hydrogens are made up of 20% *s* and 80% *p*. In methylene bromide, where the Br—C—Br angle is 116°, the carbon orbitals that bind the bromines are made up approximately of 30% *s* and 70% *p*; those that bind the hydrogens are made up approximately of 20% *s* and 80% *p*.

The carbon-halogen bond lengths of the methyl halides are shown in Table 6.1. The size of the halogen atoms increases as we go down the periodic table. The fluorine atom is somewhat larger than hydrogen, but smaller than carbon: compare the C—F bond distance of 1.385 Å with C—C, 1.54 Å, and C—H, 1.10 Å. The higher halogens are all substantially larger than carbon.

The **Van der Waals radius** of a group is the effective size of the group. As two

Table 6.1
Bond Lengths of Methyl Halides

Compound	r_{C-X}, Å
CH_3F	1.385
CH_3Cl	1.784
CH_3Br	1.929
CH_3I	2.139

molecules approach each other, the Van der Waals attractive force (Section 4.2) increases to a maximum, then decreases and becomes repulsive (Figure 6.1). The Van der Waals radius is defined as one half the distance between two equivalent atoms at the point of the energy minimum. It is an equilibrium bond distance and is usually evaluated from the structures of molecular crystals. Van der Waals radii for several atoms and groups are summarized in Table 6.2. The Van der Waals radius of bromine (1.95 Å) is about the same as that for a methyl group (2.0 Å).

Although the C—X bonds in alkyl halides are covalent, they have a polar character because halogens are more electronegative than carbon. That is, the "center of gravity" of the electron density does not coincide with the center of nuclear positive charge. This imbalance results in a **dipole moment,** μ, which is expressed as the product of the charge, q, and the distance of separation, d: $\mu = qd$. The distance involved has direction; hence, dipole moments are vectors. In the case of methyl halides this vector is directed along the C—X bond and is usually

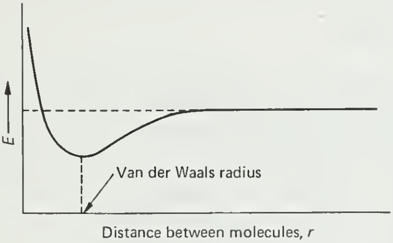


Figure 6.1 *Van der Waals forces.*

Table 6.2
Van der Waals Radii, (Å)

H	N	O	F
1.2	1.5	1.4	1.35
CH_2	P	S	Cl
2.0	1.9	1.85	1.8
CH_3			Br
2.0			1.95
			I
			2.15

symbolized as

$$\overset{+\!\!\longrightarrow}{CH_3{-}X}$$

The direction of the arrow goes from positive charge to negative charge. The magnitudes of the dipole moment vectors for methyl halides are summarized in Table 6.3.

TABLE 6.3
Dipole Moments of Methyl Halides (Vapor Phase)

Compound	μ, D
CH_3F	1.82
CH_3Cl	1.94
CH_3Br	1.79
CH_3I	1.64

Since the charge involved is on the order of 10^{-10} esu and the distance is on the order of 10^{-8} cm, dipole moments are on the order of 10^{-18} esu-cm. This unit is defined as the *Debye* abbreviated D, after the late Professor Peter Debye who discovered this molecular property. Thus, if a positive and a negative charge of 10^{-10} esu are separated by 10^{-8} cm, the system has a dipole moment of 1 Debye, or 1 D.

6.3
Physical Properties

The lower molecular weight *n*-alkyl halides are gases at room temperature. Starting with *n*-butyl fluoride, *n*-propyl chloride, ethyl bromide, and methyl iodide, the alkyl halides are liquids at room temperature. This result comes mostly from the increasing effective "size" of the halogens as we proceed down the periodic table. We saw in the previous section how this changing size is reflected in increasing C—X bond distances along the series from fluorine to iodine. Increasing size carries with it an increase in the effective "area of contact" at the Van der Waals radius that produces Van der Waals attraction.

However, size does more than increase this area of contact. We learned on page 55 that Van der Waals attraction results from the mutual correlation of electronic motions. The movement of one electron describes a changing electric field. The ability of a second electron to respond to such a changing field is measured by its **polarizability**. The smaller and "tighter" the atom, the lower the polarizability of its electrons and the lower the Van der Waals attraction for a given area of contact. Consequently, along the series F, Cl, Br, I, the polarizability increases. Furthermore, lone pair electrons are generally held more loosely than bonding electrons and can be more polarizable. Although bromine has a Van der Waals radius similar to that of a methyl group, it has much higher polarizability, and an alkyl bromide, RBr, has a much higher boiling point than that of the corresponding RCH_3. We have emphasized the role of Van der Waals attractions in boiling points but it should be mentioned that molecular weight also plays a role because of the effect of mass on kinetic energy. Along a given homologous series, however, the Van der Waals force depends on the overall size of the molecule which, in turn, parallels the molecular weight.

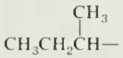
> The tightly held electrons and consequent low polarizability of fluorine results in the unique and distinctive properties of fluorocarbons, compounds composed entirely of carbon and fluorine. The boiling points of fluorocarbons are much closer to those of related hydrocarbons than might have been expected from the difference in molecular weights or size; for example, C_2H_6 has b.p. $-89°$; C_2F_6 has b.p. $-79°$.

Increasing the alkyl chain also causes a normal progressive increase in boiling point. As with the alkanes themselves, branched systems have lower boiling points than isomeric linear systems. Some boiling point data are summarized in Table 6.4 and in Figure 6.2.

Alkyl halides are insoluble in water, but are soluble in most organic solvents. They vary greatly in stability. Monofluoroalkanes are difficult to keep pure; on distillation they tend to lose HF to form alkenes. Chlorides are relatively stable and generally can be purified by distillation. However, higher molecular weight tertiary alkyl chlorides tend to lose HCl on heating and must be handled more carefully. Indeed, this property holds for most tertiary alkyl halides. Note in Table 6.4 that *t*-butyl iodide decomposes on attempted distillation at atmospheric pressure.

Chloroform slowly decomposes on exposure to light. This tendency is diminished by the presence of small amounts of alcohol. Commercially available chloroform has about 0.5% alcohol added as a stabilizer. Alkyl bromides and iodides are also light-sensitive. Upon exposure to light they slowly liberate the free halogen and turn brown or violet, respectively. Thus, these halides are generally stored in opaque vessels or brown bottles and should generally be redistilled before use.

Table 6.4
Boiling Points of Alkyl Halides (RX)

	Boiling Point, °C				
R	X = H	F	Cl	Br	I
CH_3—	−161.7	−78.4	−24.2	3.6	42.4
CH_3CH_2—	−88.6	−37.7	12.3	38.4	72.3
$CH_3(CH_2)_2$—	−42.1	−2.5	46.6	71.0	102.5
$CH_3(CH_2)_3$—	−0.5	32.5	78.4	101.6	130.5
$CH_3(CH_2)_4$—	36.1	62.8	107.8	129.6	157.
$CH_3(CH_2)_5$—	69.0	91.5	134.5	155.3	181.3
$CH_3(CH_2)_6$—	98.4	117.9	159.	178.9	204.
$CH_3(CH_2)_7$—	125.7	142.	182.	200.3	225.5
$(CH_3)_2CH$—	−42.1	−9.4	34.8	59.4	89.5
$(CH_3)_2CHCH_2$—	−11.7		68.8		
 $CH_3CH_2CH(CH_3)$—	−0.5		68.3	91.2	120.
$(CH_3)_3C$—	−11.8		50.7	73.1	dec.

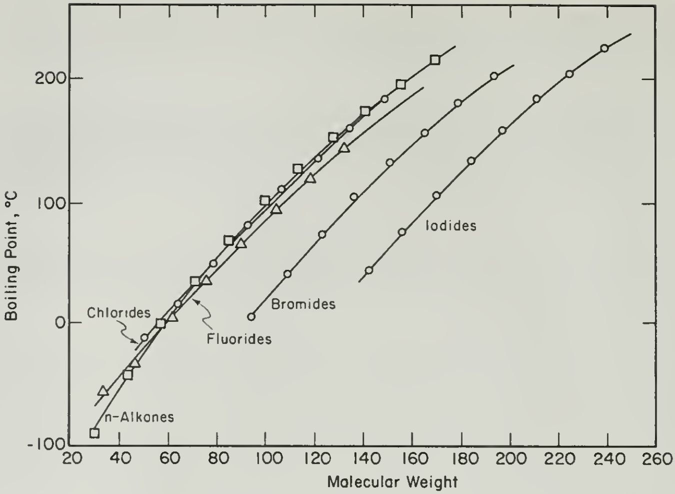


Figure 6.2 *Boiling points of* n-*alkanes and* n-*alkyl halides.*

6.4
Preparation

Alkyl halides are important as solvents and as starting materials for the synthesis of other compounds. Several reactions of alkyl halides will be discussed in Chapters 8 and 9. The simple alkyl halides (those containing five or fewer carbons) are almost all commercially available. The simple chlorides and bromides are often prepared industrially by direct halogenation of alkanes (Chapter 5). Other important methods of preparation utilize alcohols or alkenes as starting materials. These methods are discussed in Chapters 11 and 12, respectively.

For industrial uses, chlorides are used almost exclusively because of the high cost of bromine and iodine. For laboratory uses, where cost is not as great a consideration, bromides are used preferentially because alkyl bromides are generally more reactive than alkyl chlorides. Methyl iodide is a commonly used laboratory reagent because it is the only methyl halide which is liquid at room temperature.

6.5
Conformations

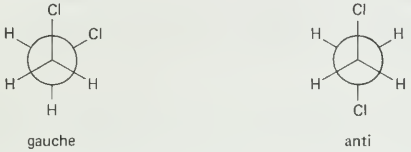
Barriers to rotation about C—C bonds bearing halogens are comparable to those in hydrocarbons, and these compounds also prefer staggered configurations. Some rotation barriers are summarized in Table 6.5. Note that there is no simple relationship between the barrier and the size of the halogen. In all of the compounds where rotation involves eclipsing C—H with C—H and C—H with C—X, the barriers are about 3.2–3.7 kcal mole^{-1}. Even for hexafluoroethane, where rotation involves eclipsing three pairs of C—F bonds, the barrier is only 3.9 kcal

TABLE 6.5
Barriers to Rotation in Alkyl Halides

Compound	Rotation Barrier kcal mole^{-1}
CH_3—CH_2F	3.3
CH_3—CHF_2	3.2
CH_3—CF_3	3.25
CF_3—CF_3	3.9
CH_3—CH_2Cl	3.7
CH_3—$CHCl_2$	3.5
CCl_3—CCl_3	10.8
CH_3—CH_2Br	3.7
CH_3—CH_2I	3.2

mole^{-1}. However, rotation of one C—Cl bond past another is more difficult; the barrier in hexachloroethane is 10.8 kcal mole^{-1}.

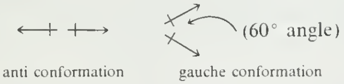
1,2-Dichloroethane, like butane, exists in two conformations, gauche and anti:



One conformation is converted to another by rotating a C—Cl bond past a C—H bond. It is not necessary to rotate C—Cl past C—Cl. Accordingly, the barrier between these conformations is only about 3.2 kcal mole^{-1}, not much different than for rotation in ethyl chloride.

We saw in Chapter 4 that the gauche and anti conformations of butane differ in energy by about 0.9 kcal mole^{-1}. We might expect, therefore, that the two analogous conformations of 1,2-dichloroethane will also have different energies. In fact, in the vapor phase, the anti conformation is more stable by 1.2 kcal mole^{-1}. Remarkably, however, the energy difference in the pure liquid is about zero!

How do we account for this interesting observation? One explanation involves two opposing factors, dipole repulsion and Van der Waals attraction. Each C—Cl bond has an associated dipole moment. The electrostatic repulsion for two dipoles oriented as in the anti conformation is lower than that for two dipoles oriented as in the gauche conformation.



The other factor involved is Van der Waals attraction. Two chlorines separated by little more than the sum of their Van der Waals radii attract each other in exactly the same manner as two neighboring alkanes (Section 4.2). Such Van der Waals attraction is especially important for the large halogen atoms because the lone pair electrons are spread through a relatively large volume and respond easily to changing neighboring charge fields. That is, such electrons have relatively high polarizability.

The net result for the gauche and anti conformations is a balance. Van der Waals attraction favors the gauche conformation, but dipole-dipole repulsion favors the anti conformation. In the vapor phase, the dipole effect dominates and the anti structure is more stable. In the liquid phase, there are many other molecules close by that reduce the importance of the intramolecular dipole factor. The two effects now just cancel.

This is not the whole story, however. Recent molecular orbital treatments have shown that for halogen atoms on adjacent carbons there is an additional attractive interaction that results from overlap of orbitals. In the specific case of such vicinal halogens, the bonding interaction given by such orbital overlap exceeds the repulsion interaction of the lone pair electrons by a small but significant amount.

6.6
Some Uses of Halogenated Hydrocarbons

The simple alkyl halides and polyhaloalkanes are readily available and are used extensively as solvents. Chlorides are most important because of the low cost of chlorine relative to bromine and iodine. In fact, chlorine is one of the basic raw materials of the chemical industry. The United States production of chlorine in 1973 was 10,300,000 tons, of which 59% was used to produce chlorinated hydrocarbons.

The polychloromethanes are produced industrially by the chlorination of methane. Carbon tetrachloride has been used extensively in dry cleaning establishments. However, it must be handled with care because it is an accumulative poison that causes severe liver damage. Consequently, its use in dry cleaning has declined. Chloroform was once used as an anesthetic, but its use for this purpose has now been abandoned due to its toxicity. More recently, the mixed halogenated compound, $CF_3CHClBr$, "Halothane" has found important use as an inhalative anesthetic because it is effective and relatively nontoxic.

Several theories have been proposed for the action of anesthetics but the detailed mode of action is not yet known. Anesthetics can be chemically inert; for example, xenon has anesthetic action. Different compounds vary in the concentration required; even nitrogen under pressure functions as an anesthetic. Nitrogen narcosis is a danger to deep divers. It is remarkable that the effective concentration of an anesthetic is species-independent. The same partial pressure of anesthetic functions as well in man as in a goldfish. The application of anesthetics needs to be carefully monitored. Lethal concentrations are typically only about double the useful anesthetic concentration.

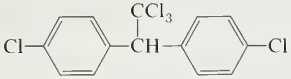
A number of partially fluorinated alkanes are widely marketed for use as cooling fluids in refrigeration systems and as aerosol propellants. These compounds are often known by their trade names.

Compound	Trade Name	Systematic Name
$CFCl_3$	Freon 11	trichlorofluoromethane
CF_2Cl_2	Freon 12	dichlorodifluoromethane
CF_3Cl	Freon 13	chlorotrifluoromethane
CF_4	Freon 14	tetrafluoromethane

Ethyl chloride is used as a local anesthetic. It is a gas at ambient temperature (b.p. 12°) and is kept in pressurized containers. In use, it is sprayed onto the skin and rapid vaporization occurs. The heat required to cause vaporization is drawn from the local surroundings, in this case the skin, and the resultant cooling deadens the nerve endings.

Another significant use of chlorinated hydrocarbons is as pesticides, a general term that includes fungicides, herbicides, insecticides, fumigants, and rodenticides. There are three main types of pesticides in use: carbamates, organophosphorous compounds, and chlorinated hydrocarbons. The use of such compounds for the control of disease-bearing pests has increased sharply during the past three decades.

The most well-known pesticide is DDT, which has been used extensively since 1939.



1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane
DDT

DDT is effective against many organisms, but its most spectacular success has been in control of the *Anopheles* mosquito, which transmits malaria. Malaria has been a scourge of mankind for centuries. According to the World Health Organization, malaria is still the chief cause of human death in the world, aside from natural causes. The disease acquired its name in ancient Rome (L. *mala*, bad; *aria*, air), where it was believed to be a result of the bad air in the city. It is actually caused by a parasite of the *Plasmodium* family which infects and ruptures erythrocytes in the blood stream. The organism has a complex life cycle requiring both vertebrate and invertebrate hosts. Humans are infected by sporozoites of the organism which are injected into the bloodstream by the bite of an infected mosquito.

Although malaria may be treated, the most effective method of controlling it is to eliminate the insect vector which is essential for its transmission. DDT is especially effective for this purpose, and malaria has been essentially eliminated from large areas of the world through its use. It has been estimated that, because of the efficacy of DDT in checking malaria and other mosquito-borne diseases (yellow fever, encephalitis), more than 75,000,000 human deaths have been averted. A striking example is the island of Ceylon. In 1934–35, there were 1.5 million cases of malaria resulting in 80,000 deaths. After an intensive mosquito-abatement program using DDT, malaria effectively disappeared and there were only 17 cases reported in 1963. When the use of DDT was discontinued in Ceylon, malaria rebounded and there were over 600,000 cases reported in 1968 and the first quarter of 1969.

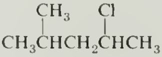
In spite of its obvious value in combatting diseases such as malaria, DDT has been abused. It is a "hard" insecticide, in that its residues accumulate in the environment. Although it is not especially toxic to mammals (the fatal human dose is 500 mg kg^{-1} of body weight, about 35 g for a 150-lb person), it is concentrated by lower organisms such as plankton and accumulates in the fatty tissues of fish and birds. The toxicity of DDT was first noted in 1949 by the Fish and Wildlife Service, but indiscriminate use as an agricultural pesticide for the control of crop-destroying pests continued to grow. In 1962, following the publication of *Silent Spring* by biologist Rachel Carson, an intensive campaign against the use of pesticides such as DDT commenced and in 1972 its use as an agricultural pesticide in the United States was banned by the Environmental Protection Agency. Active research is being directed toward developing new types of pesticides that are species-specific and biodegradable and will not accumulate in the environment.

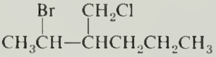
PROBLEMS

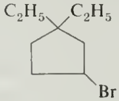
1. Write structures and both common and IUPAC names for all isomers corresponding to each of the following formulas.
   (a) C_3H_7Cl (b) C_4H_9Br (c) $C_5H_{11}I$

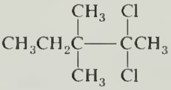
2. We will find it useful to refer to groups as being primary ($-CH_2X$), secondary ($>CHX$), or tertiary ($-\overset{|}{\underset{|}{C}}-X$). For each compound in problem 1 determine whether the halogen is primary, secondary, or tertiary.

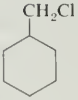
3. Give IUPAC names for the following compounds:

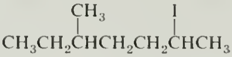
(a) 
$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{Cl}{\overset{|}{C}}HCH_3$

(d) 
$CH_3\overset{Br}{\overset{|}{C}}H-\overset{CH_2Cl}{\overset{|}{C}}HCH_2CH_2CH_3$

(b) 

(e) 
$CH_3CH_2\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}-\overset{Cl}{\underset{Cl}{\overset{|}{\underset{|}{C}}}}CH_3$

(c) 

(f) 
$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{I}{\overset{|}{C}}HCH_3$

4. Write Newman projections for the conformations of 1,1,2-trichloroethane. Two of these are the same and the third is different. The two types of conformation differ in energy by 2.6 kcal $mole^{-1}$ in the vapor phase. Which is the more stable? This energy difference reduces to 0.2 kcal $mole^{-1}$ in the liquid. Explain why. Interconversion of the two similar conformations requires about 2 kcal $mole^{-1}$, but conversion of either to the third structure requires about 5 kcal $mole^{-1}$. Explain why these two rotation barriers differ.

5. Which has the higher melting point, *n*-butyl bromide or *t*-butyl bromide? Explain. Compare your answer with the melting points found in a handbook.

6. From the generalizations and data provided in this chapter and in Chapter 4, estimate the boiling points of $CH_3CH_2CH_2CH(CH_3)CH_2CH_2Cl$ and $CH_3(CH_2)_3CH(C_2H_5)CH_2Cl$. Look up these boiling points in a handbook.

CHAPTER 7
Stereoisomerism

7.1
Chirality and Enantiomers

The two polyhedra depicted in Figure 7.1 appear to be congruent in all respects. For every edge, face, or angle on one there is a corresponding edge, face, or angle on the other. And yet the two objects are not superimposable upon each other and are therefore *different objects.* They are related to one another as an object is related to its mirror image.

Another pair of familiar objects related to each other in this way are your right and left hands. They are (to a first approximation) identical in all respects. Yet your right hand will fit into a right glove and not into a left glove. The general property of "handedness" is called **chirality.** An object that is not superimposable upon its mirror image is **chiral.** If an object and its mirror image can be made to coincide in space, then they are said to be **achiral.**

Careful inspection of 2-iodobutane reveals that it is a chiral compound. There are actually two isomeric 2-iodobutanes that are nonsuperimposable mirror images (Figure 7.2). Two compounds that differ in handedness in this way are called **enantiomers.** They are said to have an **enantiomeric** relationship to each other. In order to convert one of the enantiomers into the other, it is necessary to break and reform bonds. Such a process requires substantial energy and, consequently, there is a rather large energy barrier to interconversion of this type of enantiomers. One may have a flask which contains only one of the enantiomers and it will be stable indefinitely under normal conditions. This type of isomerism is called **stereoisomerism. Stereoisomers** are compounds that have the same sequence of covalent bonds and differ in the relative disposition of their atoms in space.

2-Iodobutane owes its chirality to carbon number 2, which has *four different groups* attached to it. Such a carbon is called an **asymmetric** carbon atom. Notice that 1,1-dichloroethane, which contains three different groups on carbon number 1, is achiral; it is superimposable upon its mirror image (Figure 7.3). When a compound has one asymmetric carbon atom, the molecule is always chiral. However, an asymmetric atom is not a necessary condition for chirality, as we

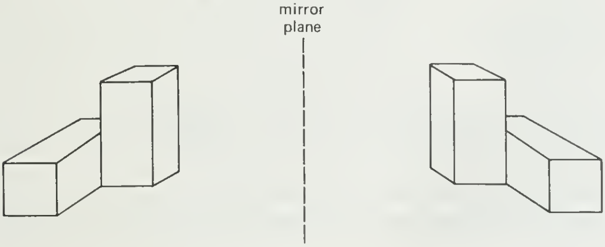


FIGURE 7.1 *Two nonsuperimposable mirror-image objects.*

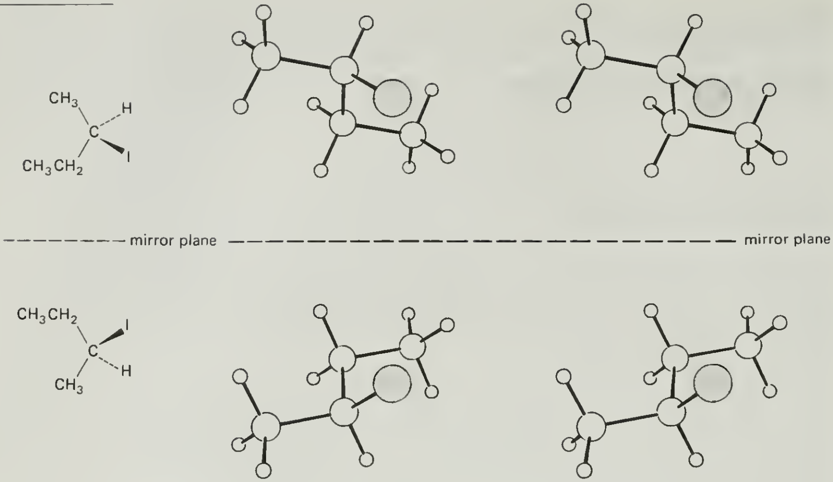

CH3
H
C
CH3CH2
I
mirror plane
mirror plane
CH3CH2
I
C
H
CH3

FIGURE 7.2 *The mirror-image relationship of the two 2-iodobutanes.*

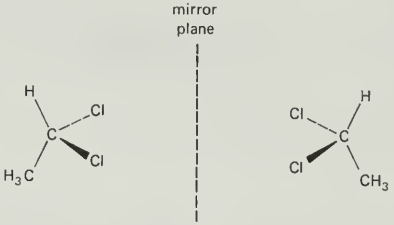

mirror plane
H
Cl
C
Cl
H3C
H
Cl
C
Cl
CH3

FIGURE 7.3 *The achirality of* 1,1*-dichloroethane.*

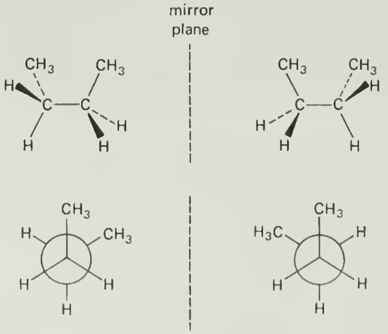
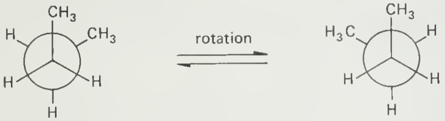

mirror plane
CH3
CH3
H
C
C
H
H
H
CH3
CH3
H
C
C
H
H
H
CH3
H
CH3
H
H
H
CH3
H3C
H
H
H
H

FIGURE 7.4 *The enantiomeric relationship between the two gauche conformations of butane.*

shall soon see. Also, as we shall see in Section 7.5, a molecule may still be achiral if it contains more than one asymmetric atom.

Two of the conformational isomers of butane (Section 4.3) also have an enantiomeric relationship to each other (Figure 7.4). In this case, however, the two enantiomers may interconvert simply by rotation about the central C—C bond.



Since rotational barriers are generally quite small, enantiomers such as these interconvert rapidly at room temperature. The individual enantiomers could be obtained in a pure state only by working at exceedingly low temperatures, on the order of −230° (page 61).

7.2
Physical Properties of Enantiomers: Optical Activity

Most of the physical properties of the two enantiomeric 2-iodobutanes are identical. They have identical melting points, boiling points, solubilities in common solvents, densities, refractive indices, and spectra. However, they differ in one important respect, the way in which they interact with **polarized light.**

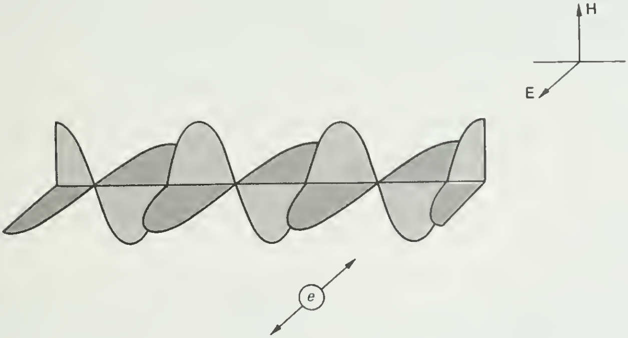
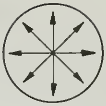
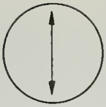


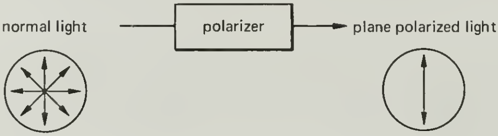
FIGURE 7.5 *The interaction of an electron with the electric field component of a light wave.*

Light may be treated as a wave motion of changing electric and magnetic fields which are at right angles to each other (Figure 7.5). When an electron interacts with light, it oscillates at the frequency of the light in the direction of the electric field and in phase with it. In normal light, the electric field vectors of the light waves are oriented in all possible planes. **Plane polarized light** is light in which the electric field vectors of all the light waves lie in the same plane, the **plane of polarization.**

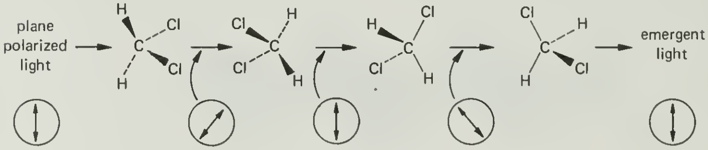

normal light


plane polarized light

Plane polarized light may be produced by passing normal light through a polaroid lens, or a device known as a **Nicol prism.**



In a molecule, an electron is not free to oscillate equally in all directions; that is, its polarizability is **anisotropic,** which means different in different directions. When electrons in molecules oscillate in response to plane polarized light, they generally tend, because of their anisotropic polarizability, to oscillate out of the plane of polarization. Because of its interaction with the oscillating electrons, the light has its electric and magnetic fields changed. Thus, when plane polarized light interacts with a molecule, the plane of polarization rotates slightly. In a large collection of achiral molecules, however, for any orientation of a molecule that changes the plane of polarization of the light, there is apt to be another molecule with a mirror image orientation which has the opposite effect. Consequently, when a beam of plane polarized light is passed through such a compound, it emerges with the plane of polarization unchanged.



For molecules such as one of the enantiomers of 2-iodobutane, however, no such mirror image orientations exist, and the plane of polarization of the light is usually measurably altered in its passage through the sample. Such compounds are said to be **optically active.** If a compound causes the plane of polarization to rotate in a clockwise (positive) direction on facing the beam, it is called **dextrorotatory.** If it causes the plane to rotate in a counterclockwise (negative) direction, it is called **levorotatory.** The amount by which the plane is rotated is expressed as the angle of rotation, α, and by the appropriate sign which shows whether rotation is in the dextro (+) or levo (−) sense.

Rotations are measured with a device called a polarimeter. Since the degree of rotation depends on wavelength, monochromatic light (light having a single wavelength) is necessary. Common polarimeters use the sodium D line (5890 Å). The monochromatic light is first passed through the polarizer (usually a Nicol prism), from which it emerges polarized in one plane. The plane-polarized light is then passed through a tube that contains the sample, either as a liquid or dissolved in some achiral solvent. It emerges from the sample with the plane of polarization rotated in either the plus or minus direction by some amount. The light beam then passes through a second Nicol prism, which is mounted on a circular marked dial (the analyzer). The analyzer is rotated by an amount sufficient to allow the light beam to pass through at maximum intensity. Readings are compared with and without the sample tube to obtain the rotation value. Precision polarimeters using the sodium yellow line (D line) or the mercury green line are generally precise to about ±0.01°. Modern spectropolarimeters use photocells in place of visual observation and can give even more precise data over a wide spectral region. A schematic representation of a polarimeter is shown in Figure 7.6.

> The student may easily experience the phenomenon of optical rotation by performing a simple experiment. Take two pairs of polaroid sunglasses and line them up, one in front of the other. Look through one lens of each pair of glasses at a bright light. Now rotate one of the lenses. When the glasses are parallel, the maximum amount of light is transmitted. When they are oriented at right angles to each other, no light is transmitted. What you have constructed is a simple polarimeter. The first pair of glasses corresponds to the polarizer and the second to the analyzer. Now dissolve several tablespoons of table sugar (sucrose, an optically active compound) in a small glass of water and place the glass between the two sunglasses. Again rotate one pair of glasses and note that the orientation for maximum and minimum transmission of light is now different. It is easier to observe the change at the point of minimum transmission.

The observed angle of rotation, α, is proportional to the number of optically active molecules in the path of the light beam. Therefore, α is proportional to the length of the sample tube and to the concentration of the solution being observed. The **specific rotation,** $[\alpha]$, is obtained by dividing α by the concentration (expressed in g ml^{-1} solution) and by the length of the cell (expressed in decimeters). The wavelength of light used is given as a subscript, and the temperature at which the measurement was made is given as a superscript.

$$[\alpha]_{\mathrm{D}}^{t} = \frac{\alpha}{l \cdot c} \qquad \text{for solutions}$$

Decimeters are used as the unit of length simply because a 1-dc (10-cm) tube

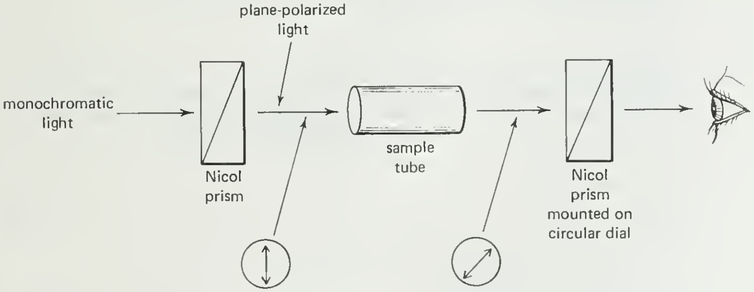


FIGURE 7.6 *Polarimeter schematic.*

is a common length for measurements of rotation. For a pure liquid, the definition of c (g ml^{-1}) is simply the density of the compound, d.

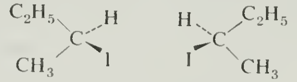
$$[\alpha]_D^t = \frac{\alpha}{l \cdot d} \qquad \text{for liquids}$$

When the temperature is not given, the rotation is assumed to be that at room temperature.

Actually, it is not possible to determine whether the rotation is (+) or (−) from a single measurement. Is a reading of 60° to be interpreted as +60° or −300°? The sign may be determined by measuring the rotation at different sample concentrations. For example, if a 1 M sample gives a reading of 60 on the polarimeter, this may be either +60° or −300°. For a 1.1 M sample, the values would be either +66° or −330°, which are easily distinguished.

As was mentioned earlier, enantiomers differ from one another in the manner in which they interact with plane-polarized light. In fact, two enantiomers cause the plane of polarization to rotate by exactly the same amount, but in *opposite directions.* For example, one of the two enantiomeric 2-iodobutanes has $[\alpha]_D^{24°} = +15.9°$, and the other has $[\alpha]_D^{25.9°} = -15.9°$. This knowledge still does not tell us which enantiomer is which. *There is no simple relationship between the sign of α and the absolute stereostructure of a molecule.*

Absolute stereostructure can be determined by X-ray diffraction using a technique known as **anomalous dispersion.** Although the technique is too sophisticated to discuss here, suffice it to say that absolute stereostructures for some optically active compounds have been established in this way. Once the absolute stereostructures for a few optically active compounds are known, other molecular configurations may be determined by correlating them chemically with the compounds of known structure. We shall show how this is done in later sections. By these methods, the structures of (+)- and (−)-2-iodobutane are known to be



(+)-2-iodobutane $[\alpha]_D^{24} = +15.9°$ (−)-2-iodobutane $[\alpha]_D^{24} = -15.9°$

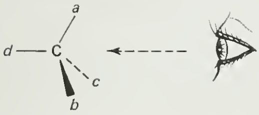
7.3
Nomenclature of Enantiomers: The R-S Convention

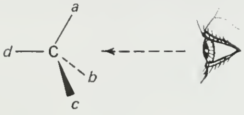
Suppose we have one bottle that contains only one of the two enantiomeric 2-iodobutanes and another bottle that contains only the other enantiomer. What labels do we attach to the two bottles? We cannot simply label each bottle "2-iodobutane," because they contain different compounds. We can label the bottles "(+)-2-iodobutane" and "(−)-2-iodobutane." By this we mean: "This bottle contains the 2-iodobutane that rotates the plane of polarized light in the dextro sense." And "This bottle contains the 2-iodobutane that rotates the plane of polarized light in the levo sense." Since it has also been determined which absolute stereostructure corresponds to (+)-2-iodobutane, these labels are sufficient to define unambiguously which compounds are in the bottles.

However, if a chemist were to encounter a bottle labeled (+)-2-iodobutane, chances are that he would not know which of the two absolute configurations correspond to dextrorotation. For this reason, it is highly desirable to have a system whereby the **absolute configuration** may be specified in the name of the compound. The system of nomenclature that has been adopted for this purpose by the IUPAC is called the R-S convention, or the "sequence rule."

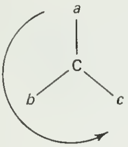
The application of the sequence rule to naming enantiomers which owe their chirality to one or more asymmetric atoms is quite straightforward and involves the following simple steps:

1. Identify the four different substituents attached to the asymmetric atom. Assign to each of the four substituents a priority *a, b, c,* or *d,* using the sequence rule, such that $a > b > c > d$.
2. Orient the molecule in space so that one may look down the bond from the asymmetric atom to the substituent with lowest priority, *d.*

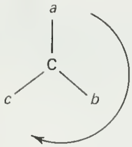




When one looks along that bond, one will see the asymmetric atom with the three attached substituents *a, b* and *c* radiating from it like the spokes of a wheel. Trace a path from *a* to *b* to *c.* If the path describes a *clockwise* motion, then the asymmetric atom is called (R) (*rectus,* L., right). If the path describes a *counterclockwise* motion, then the asymmetric atom is called (S) (*sinister,* L., left).



S

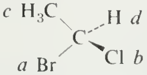


R

Stereo representations of R and S structures are shown in Figure 7.7.

The sequence rule is the method whereby the four substituents are assigned priorities *a, b, c,* and *d* so that the symbols (R) and (S) may be assigned. There are a number of parts to the sequence rule, but we need only consider four aspects of it.

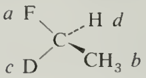
1. For the four atoms directly attached to the asymmetric atom, **higher atomic number precedes lower.** In some cases, this will be sufficient to rank the four substituent groups. For example, in 1-bromo-1-chloroethane, the four atoms involved are Br, Cl, C and H.



(S)-1-bromo-1-chloroethane

2. In cases where two of the attached atoms are isotopes of each other, **higher**

atomic mass precedes lower. In 1-deuterio-1-fluoroethane, the four groups are therefore ranked F > C > D > H.



(R)-1-deuterio-1-fluoroethane

3. For many chiral compounds, two of the atoms directly attached to the asymmetric carbon will be the same. In this case, work outward concurrently along the two chains atom by atom until a point of difference is reached. **The priorities are then assigned at that first point of difference,** using the considerations of atomic number and atomic mass. In 2-iodobutane, the iodine is assigned *a* and the hydrogen is assigned *d*. The two remaining groups are $—CH_2—CH_3$ and $—CH_2—H$. The first point of difference is at the two carbons attached to the asymmetric atom. The group $—CH_2—CH_3$ takes priority over $—CH_2—H$ because carbon has a higher atomic number

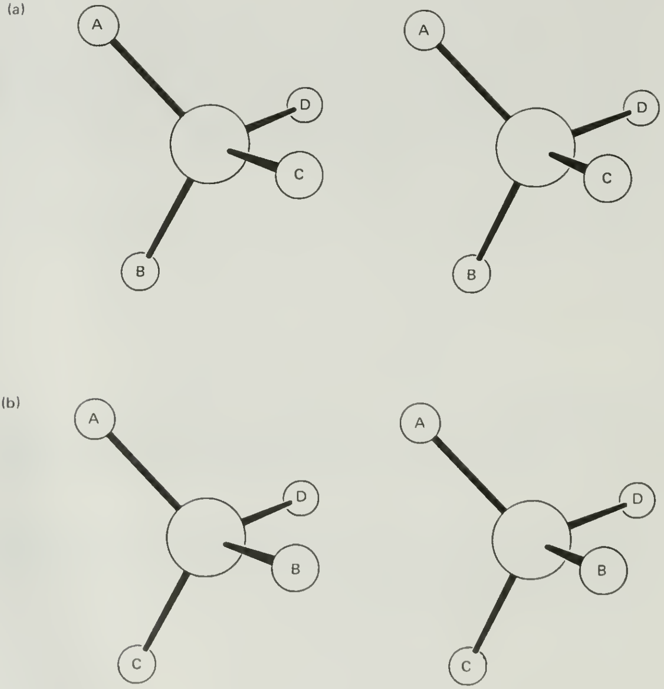
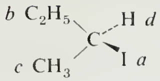
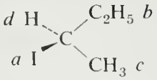


FIGURE 7.7 *Stereo diagrams of an asymmetric carbon, illustrating the arrangement of* a, b, c, *and* d *priority groups for assignment of configurations as* (a) S *and* (b) R.

than hydrogen. Thus, we may assign (R) and (S) configurations to the two enantiomers as

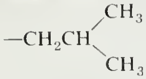


(S)-2-iodobutane



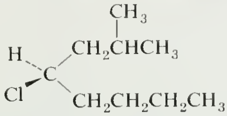
(R)-2-iodobutane

For 4-chloro-2-methyloctane, the four atoms attached to the asymmetric carbon are Cl(*a*), H(*d*), C, and C. In order to rank the isobutyl and butyl groups, we work along the chains until we reach the second carbon from the asymmetric carbon before we reach a point of difference. The group



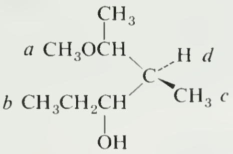
takes priority over $—CH_2CH_2—CH_2CH_3$ because, at the first point of difference, the carbon in isobutyl has *two other carbons* attached to it whereas the analogous carbon in *n*-butyl has only *one other attached carbon.*

Note

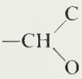


(R)-4-chloro-2-methyloctane

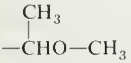
In some cases, one must make a choice at a branch point as to which branch to follow. The rule here is that one decides, if possible, by **proceeding along the branch of higher priority.** Consider the following example:



We must decide between two groups, both beginning with

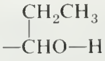


We proceed along the branch of higher priority in each chain, oxygen. Thus,



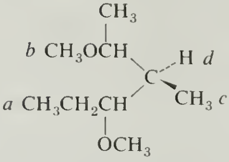
$$—\overset{\displaystyle CH_3}{\overset{|}{C}}HO—CH_3$$

precedes



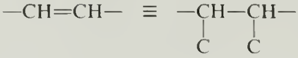
$$—\overset{\displaystyle CH_2CH_3}{\overset{|}{C}}HO—H$$

because C has a higher atomic number than H. The example shown is (S). In some cases, following the branch of higher priority does not lead to a distinction. In such a case, assignment must be made by following the secondary branches.

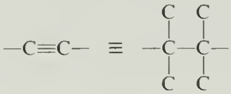

CH3
b CH3OCH
H d
C
a CH3CH2CH
CH3 c
OCH3

(R)

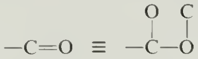
4. **Double and triple bonds are treated by assuming that each such bonded atom is duplicated or triplicated.**



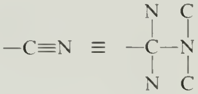
$$-CH{=}CH- \equiv -\underset{\underset{C}{|}}{C}H-\underset{\underset{C}{|}}{C}H-$$



$$-C{\equiv}C- \equiv -\underset{\underset{C}{|}}{\overset{\overset{C}{|}}{C}}-\underset{\underset{C}{|}}{\overset{\overset{C}{|}}{C}}-$$

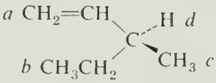


$$-C{=}O \equiv -\overset{\overset{O}{|}}{C}-\overset{\overset{C}{|}}{O}$$

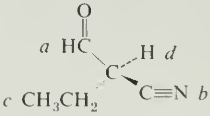


$$-C{\equiv}N \equiv -\underset{\underset{N}{|}}{\overset{\overset{N}{|}}{C}}-\underset{\underset{C}{|}}{\overset{\overset{C}{|}}{N}}$$

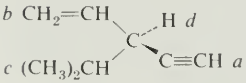
Several examples of compounds containing multiple bonds follow.


a CH2=CH
H d
C
b CH3CH2
CH3 c

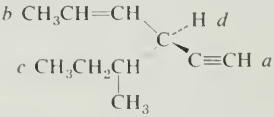
(S)


O
a HC
H d
C
c CH3CH2
C≡N b

(R)


b CH2=CH
H d
C
c (CH3)2CH
C≡CH a

(S)


b CH3CH=CH
H d
C
c CH3CH2CH
CH3
C≡CH a

(S)

7.4
Racemic Mixtures

An equimolar mixture of two enantiomers is called a **racemic mixture**, or a **racemate**. Since a racemic mixture contains equal numbers of dextrorotating and levorotating molecules, the net optical rotation is zero. A racemic mixture is often specified by prefixing the name of the compound with the symbol (±); for example, (±)-2-iodobutane.

The physical properties of a racemic mixture are not necessarily the same as those of the pure enantiomers. A sample composed solely of right-handed molecules will experience different intermolecular interactions than will a sample composed of equal numbers of right- and left-handed molecules. (In order to verify this in a simple way, use your right hand to shake hands with another person. The interaction is clearly different depending on whether the other person extends his right or his left hand.)

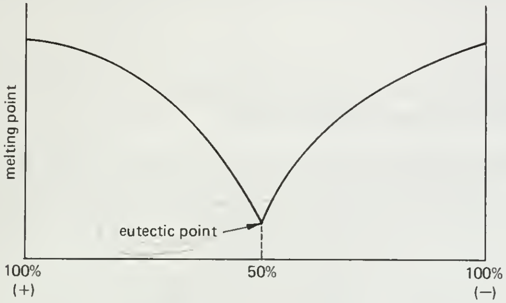


FIGURE 7.8 *Melting point diagram for a racemic mixture.*

A racemic mixture may crystallize in several ways. In some cases, separate crystals of the (+) and (−) forms result. In this case, the crystalline racemate ① is a mechanical mixture of two different crystalline compounds. The melting point diagram for such a mixture is like that for any other mixture of two compounds, Figure 7.8. The eutectic point in such a case is always at the 50:50 point. Addition of a little of either pure enantiomer will cause the melting point of the mixture to increase. The racemate may also crystallize as a **racemic compound.** In this ② case, only one type of crystal is formed, and it contains equal numbers of (+) and (−) molecules. The racemic compound acts as though it were a separate compound; its melting point is a peak on the phase diagram. However, the racemic compound may melt either higher or lower than the pure enantiomers. Addition of a small amount of either pure enantiomer causes a melting point depression (Figure 7.9).

Because of these differential intermolecular interactions, racemates frequently

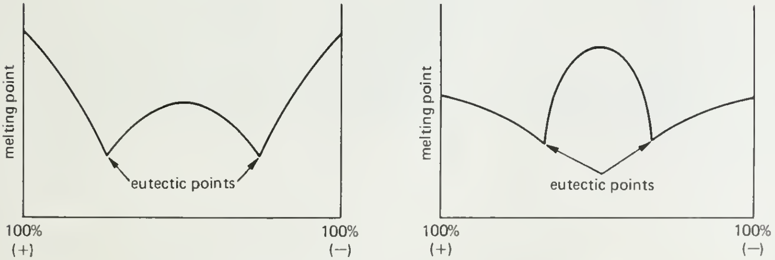


FIGURE 7.9 *Representative melting point diagrams for racemic compounds.*

differ from the pure enantiomers in other physical properties. Differences have been observed in density, refractive index, and in various spectra.

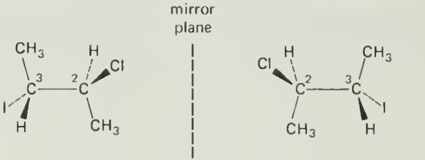
The process whereby a pure enantiomer is converted into a racemic mixture is called **racemization.** Racemization may be accomplished in a trivial sense by simply mixing equal amounts of two pure enantiomers. Racemization may also result from chemical interconversion; we shall see many examples of this in future chapters. We have already encountered one racemization process in Section 7.1, the interconversion of the two enantiomeric gauche forms of butane by rotation about the central C—C bond.

7.5
Compounds Containing More Than One Asymmetric Atom, Diastereomers

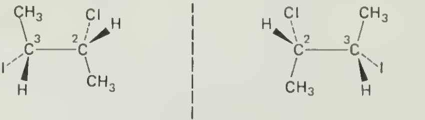
A molecule may have more than one asymmetric atom. In this case, the number of possible stereoisomers is correspondingly larger. Consider 2-chloro-3-iodobutane as an example. There are four isomers, which are depicted in Figure 7.10. Of the four stereoisomeric 2-chloro-3-iodobutanes, two pairs bear an enantiomeric relationship to one another. The (2R,3R) and (2S,3S) compounds are one enantiomeric pair, and the (2R,3S) and (2S,3R) compounds are another enantiomeric pair. As with the other enantiomeric pairs previously discussed, the (2R,3R) and (2S,3S) compounds have identical boiling points, melting points, densities, solubilities, and spectra. They cause the plane of polarized light to rotate to the same degree, but in opposite directions; one is dextrorotatory and the other is levorotatory. A similar correspondence in physical properties is observed for the (2R,3S) and (2S,3R) compounds.

Compounds that are stereoisomers of one another, but are not enantiomers, are called **diastereomers** and are said to have a **diastereomeric relationship.** The stereoisomeric relationships for a compound having two unlike asymmetric atoms are summarized in schematic form in Figure 7.11.

In general, the maximum number of stereoisomers that are possible for a compound having n asymmetric atoms is given by 2^n. Thus, for a compound with one asymmetric atom, there are $2^1 = 2$ stereoisomers. For a compound with two asymmetric atoms, there may be $2^2 = 4$ stereoisomers. In some cases, there are fewer than the maximum number of possible stereoisomers. As an example,



(2S,3R)-2-chloro-3-iodobutane (2R,3S)-2-chloro-3-iodobutane



(2R,3R)-2-chloro-3-iodobutane (2S,3S)-2-chloro-3-iodobutane

FIGURE 7.10 *Stereoisomers of 2-chloro-3-iodobutane.*

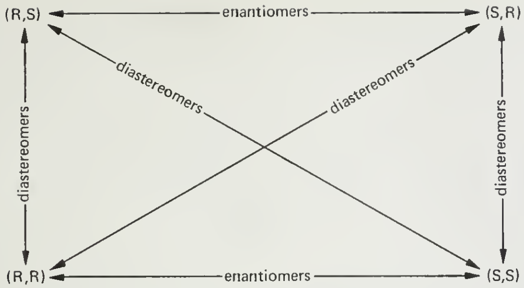
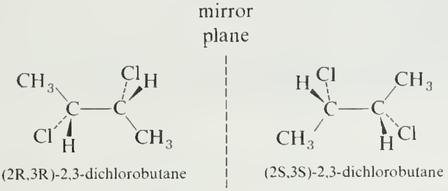

(R,S)
enantiomers
(S,R)
diastereomers
diastereomers
diastereomers
diastereomers
(R,R)
enantiomers
(S,S)

FIGURE 7.11 *Stereoisomeric relationships for a compound having two unlike asymmetric atoms.*

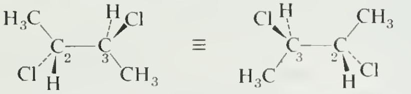
consider 2,3-dichlorobutane. The (2R,3R) and (2S,3S) compounds are enantiomers of one another.


mirror plane
CH3
Cl
H
Cl
H
CH3
H
Cl
CH3
CH3
H
Cl

(2R,3R)-2,3-dichlorobutane (2S,3S)-2,3-dichlorobutane

However, careful inspection reveals that the (2R,3S) and (2S,3R) compounds are actually the same compound (mentally perform a 180° rotation of the entire molecule about the axis of the central C—C bond).

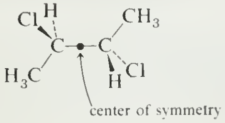
MESO


H3C
Cl
H
2
H
Cl
3
CH3
≡
Cl
H
3
H3C
CH3
2
H
Cl

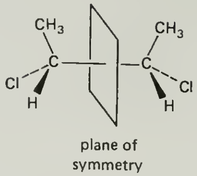
(2R,3S)-2,3-dichlorobutane (2S,3R)-2,3-dichlorobutane

Since this isomer of 2,3-dichlorobutane is achiral, it is not optically active. Such a compound, which has asymmetric atoms yet is achiral, is called a **meso compound**. It is important not to confuse meso compounds with racemic mixtures, which are actually equimolar mixtures of two enantiomers. Both show no optical activity, but a meso compound is a single achiral substance, whereas a racemic mixture is a 50 mole-% mixture of two chiral substances.

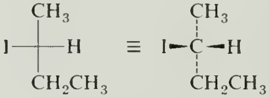
Meso compounds may be recognized by looking for a plane or a center of symmetry *within a molecule* which has asymmetric atoms. When such an element of symmetry exists, the maximum number of possible stereoisomers is less than 2^n. One staggered conformation of meso-2,3-dichlorobutane shown has a center of symmetry.


Cl
H
H3C
CH3
H
Cl
center of symmetry

In an alternative eclipsed conformation of the molecule a plane of symmetry is clearly obvious.



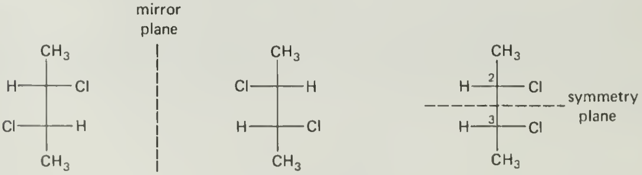
For acyclic compounds having one or two asymmetric atoms, the projection representations used so far in this chapter are useful and relatively unambiguous in meaning. However, for compounds with even more asymmetric atoms, such representations become very awkward. An alternative projection system that is widely used is called the Fischer system. In a **Fischer projection**, an asymmetric atom is represented by the intersection point of the two lines of a cross. The horizontal lines extending to the left and right of this point represent bonds extending forward from the plane of the paper. The two vertical lines extending to the top and bottom represent bonds extending back away from the plane of the paper. A Fischer projection for (R)-2-iodobutane is compared to a "wedge-and-dotted line" structure as follows:



$$\begin{array}{c} CH_3 \\ I-\!\!\!+\!\!\!-H \\ CH_2CH_3 \end{array} \equiv \begin{array}{c} CH_3 \\ I-C-H \\ CH_2CH_3 \end{array}$$

For compounds with two or more asymmetric atoms, the same convention is used. The molecule is first mentally arranged in a conformation such that the backbone bonds extend from top to bottom and the appendage bonds extend to the right and left. Fischer projections for the three stereoisomers of 2,3-dichlorobutane are shown in Figure 7.12. Note that the enantiomeric relationship of the (2S,3S) and (2R,3R) compounds is clearly apparent using these projections, as is the plane of symmetry in the meso isomer. It is important to remember that Fischer projections are two-dimensional representations of three-dimensional objects. For purposes of visualizing whether or not two structures are identical, these projections can be manipulated only in certain ways. The various Fischer projections for (R)-1-bromo-1-chloroethane are shown in Figure 7.13.

In order to change one Fischer projection to another correct projection for the



(2S,3S)-2,3-dichlorobutane (2R,3R)-2,3-dichlorobutane (2S,3R)-2,3-dichlorobutane (meso)

FIGURE 7.12 *Fischer projections of the 2,3-dichlorobutane isomers.*

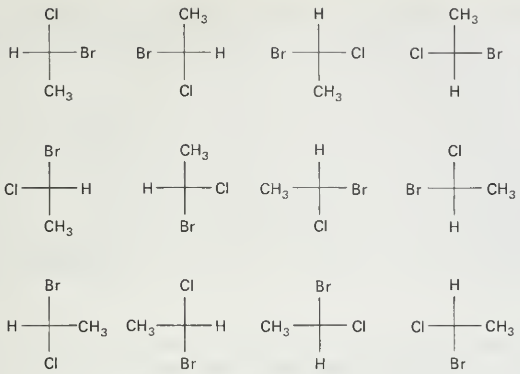
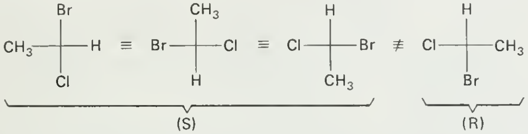
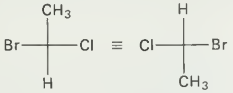

Cl
H
Br
CH3
CH3
Br
H
Cl
H
Br
Cl
CH3
CH3
Cl
Br
H
Br
Cl
H
CH3
CH3
H
Cl
Br
H
CH3
Br
Cl
Cl
Br
CH3
H
Br
H
CH3
Cl
Cl
CH3
H
Br
Br
CH3
Cl
H
H
Cl
CH3
Br

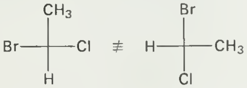
FIGURE 7.13 *Fischer projections for* (R)-1-bromo-1-chloroethane. *These structures are all equivalent.*

same enantiomer, one may interchange any *two* pairs of substituents. If only one pair of groups is interchanged, a projection for the enantiomer is generated.


Br
CH3
H
Cl
≡
CH3
Br
Cl
H
≡
H
Cl
Br
CH3
≢
H
Cl
CH3
Br
(S)
(R)

A Fischer projection may be rotated in the plane of the paper by 180°, but *not by 90°.*

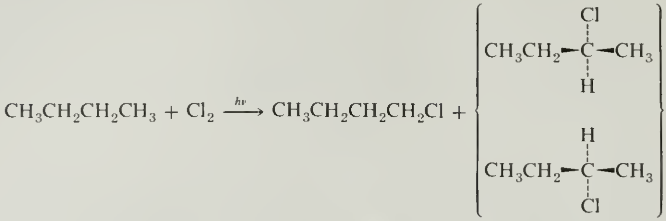

CH3
Br
Cl
H
≡
H
Cl
Br
CH3


CH3
Br
Cl
H
≢
Br
H
CH3
Cl

If in doubt about the identity of two Fischer projections, use "wedge-and-dotted line" projections or molecular models to settle the matter.

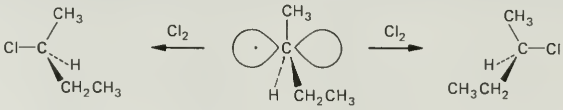
7.6
Chemical Reactions and Stereoisomerism

When a chemical reaction involves only achiral reactants, solvents, and reagents, the products of the reaction must be achiral or racemic mixtures. As an example, consider the monochlorination of butane. After the monochlorobutane fraction has been isolated, it is found to be a mixture of 1-chlorobutane and 2-chlorobutane. The 1-chlorobutane is, of course, achiral. The 2-chlorobutane formed in the reaction is a racemic mixture; it is an equimolar mixture of (R)-2-chlorobutane and (S)-2-chlorobutane.



$$CH_3CH_2CH_2CH_3 + Cl_2 \xrightarrow{h\nu} CH_3CH_2CH_2CH_2Cl + \left\{ \begin{array}{c} \begin{array}{c} Cl \\ CH_3CH_2\text{—}\overset{|}{\underset{|}{C}}\text{—}CH_3 \\ H \end{array} \\ \\ \begin{array}{c} H \\ CH_3CH_2\text{—}\overset{|}{\underset{|}{C}}\text{—}CH_3 \\ Cl \end{array} \end{array} \right\}$$

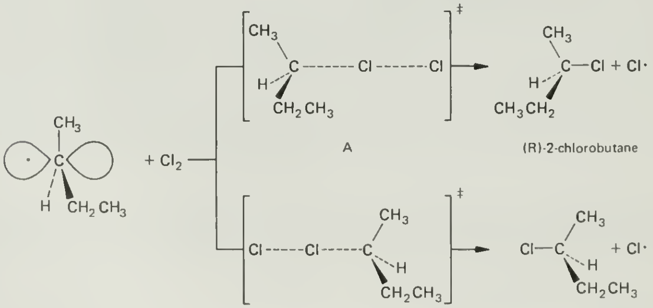
Moreover, recall that the reactive intermediate in the reaction leading to 2-chlorobutane is the *sec*-butyl free radical, which is approximately planar. Being planar, it is achiral and may react with Cl_2 on either side of the molecule. Reaction on one side yields (R)-2-chlorobutane, and reaction on the other side yields (S)-2-chlorobutane. Since reaction is equally probable on the two faces, a racemic mixture results. Consequently, any reaction that involves an achiral intermediate will give racemic products.



(S)-2-chlorobutane

(R)-2-chlorobutane

This result may also be discussed in terms of the relative rates of two competing reactions, *sec*-butyl free radical reacting with chlorine to give either (R)- or (S)-2-chlorobutane. The transition states for the two reactions are depicted as follows:



A

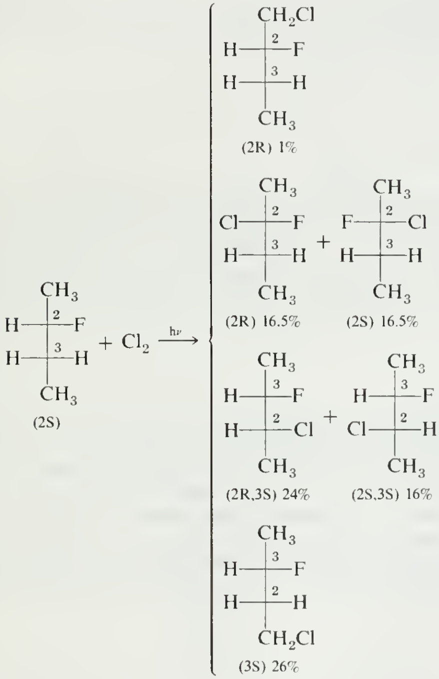
(R)-2-chlorobutane

B

(S)-2-chlorobutane

Notice that transition state A, leading to the (R) enantiomer, and transition state B, leading to the (S) enantiomer, are themselves enantiomeric. Because they are enantiomeric, they have identical physical properties, including bond angles, bond lengths, *and free energies of formation*. Since the two competing reactions begin at the same place and pass through transition states of equal energy, they have identical activation energies, and a 50 : 50 mixture of (R)- and (S)-2-chlorobutane results (Figure 7.14, page 122).

Let us now examine the vapor phase chlorination of a chiral compound, (S)-2-fluorobutane. The monochlorination fraction of the reaction product contains 1-chloro-2-fluorobutane, 2-chloro-2-fluorobutane, 2-chloro-3-fluorobutane, and 1-chloro-3-fluorobutane. Substitution of one of the C-1 hydrogens by chlorine yields the 1-chloro-2-fluoro isomer. Since no bond to the asymmetric atom is broken in the formation of this product, this 1-chloro-2-fluoro isomer is chiral. (Note that the 1-chloro-2-fluoro isomer has the (2R) configuration, even though the starting 2-fluorobutane is 2S.) Similarly, substitution of a C-4 hydrogen gives the 1-chloro-3-fluoro isomer, which is also chiral and has the configuration (3S). (Note that the chain is numbered from the other end in this isomer.)



Substitution at C-2 involves forming the intermediate free radical at this position. Since the free radical is achiral, reaction with chlorine proceeds through two enantiomeric transition states and gives equal amounts of the (2R) and (2S) products. The 2-chloro-2-fluoro product is therefore a racemic mixture.

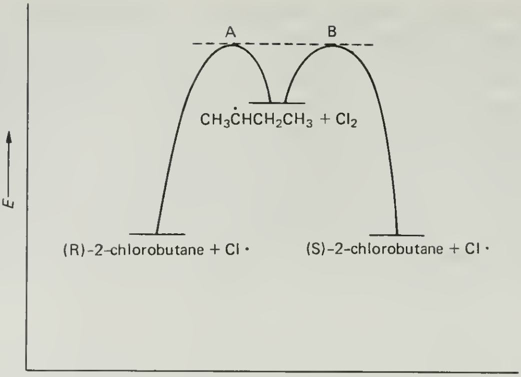
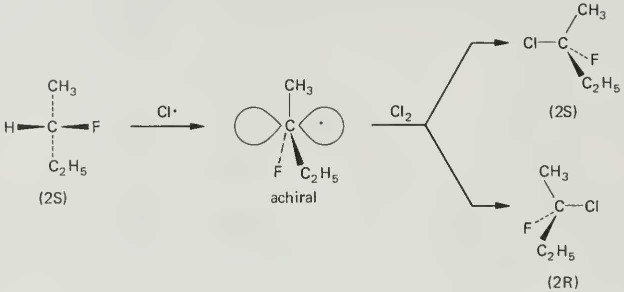
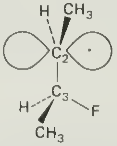


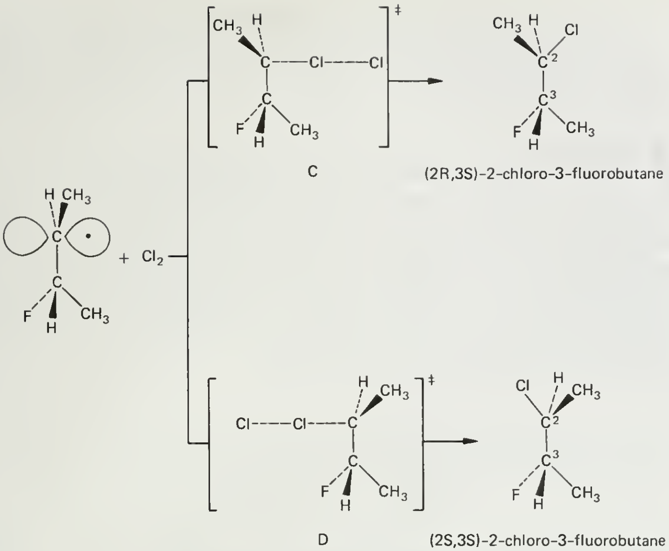
Figure 7.14 *An achiral intermediate gives enantiomeric transition states with equal activation energies.*



Substitution of a hydrogen at C-3 generates a new asymmetric atom, but no bond to the existing asymmetric atom is broken in the process. Therefore, the absolute configuration at C-3 in the 2-chloro-3-fluoro products must be the same as it is in the starting 2-fluorobutane. However, the diastereomeric 2-chloro-3-fluorobutanes *need not be formed in equal amounts.* In order to understand this, consider the reaction of the intermediate free radical with chlorine. Again, the free radical carbon is approximately planar and has the odd electron in a *p* orbital. However, in this case the species is chiral, due to the asymmetric carbon, at C-3.



This free radical may react with Cl_2 from either side, giving either transition state C or D. Transition state C yields the (2S,3R) diastereomer and transition state D yields the (2S,3S) diastereomer.


C
(2R,3S)-2-chloro-3-fluorobutane
D
(2S,3S)-2-chloro-3-fluorobutane

In this case, the two transition states C and D *are not enantiomeric,* but are diastereomeric. Since they are not enantiomeric, they will have different physical properties, including different free energies of formation. Since the two competing reactions start at the same place, and pass through transition states of different energies, the two activation energies are different. Therefore, one diastereomer will be formed in greater amount than the other (Figure 7.15).

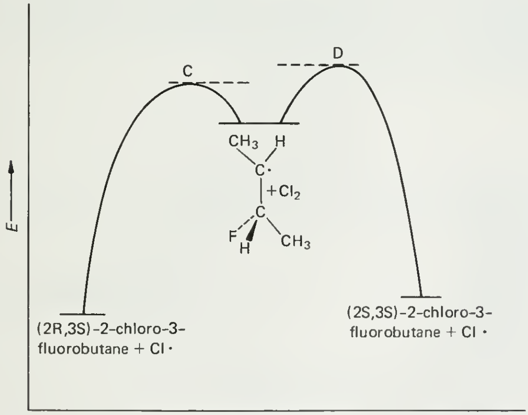
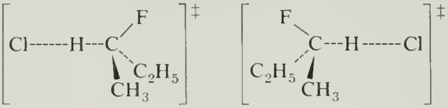

C
D
E
(2R,3S)-2-chloro-3-fluorobutane + Cl ·
(2S,3S)-2-chloro-3-fluorobutane + Cl ·

Figure 7.15 *A chiral intermediate yields diasteriomeric products, generally in unequal amounts.*

> The reaction is actually a good deal more complicated than it appears in the foregoing simplified discussion. There are several transition states that can lead to either diastereomer. Nevertheless, because of the asymmetric atom already present in the molecule, the free radical is chiral and it will usually give rise to unequal amounts of the two diastereomers.

In the reaction leading to the 2-chloro-3-fluoro products, asymmetry is generated at C-2 in a preferred sense, due to the asymmetric atom already present in the compound. This phenomenon is called **asymmetric induction.**

Now let us consider briefly one further aspect of chemical reactivity and stereoisomerism, the relative reactivity of enantiomers. *Enantiomers show equal reactivities toward achiral reagents.* Thus, (R)-2-fluorobutane and (S)-2-fluorobutane will undergo chlorination at exactly the same rate. In order to see this clearly, consider the transition states for abstraction of, for example, the C-2 hydrogen by a chlorine atom from the two enantiomers. The two transition states are enantiomeric and therefore have equal energies.



Since the reactants have equal energies and the transition states have equal energies, the two reactions must proceed at the same rate.

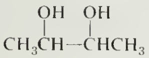
When two enantiomers of a chiral compound react with another chiral compound, the two enantiomers generally do not react at equal rates, because, in this case, the two transition states are diastereomeric rather than enantiomeric. Since diastereomers are not necessarily equal in energy, two diastereomeric transition states are generally unequal in energy and one of the enantiomers will react faster with the chiral reagent than the other. To visualize this relationship, consider the interaction of your right and left hands with an achiral object such as a baseball and a chiral object such as a right glove. You can grasp the achiral object equally well with either hand, but your right hand interacts much more easily than your left with the right glove.

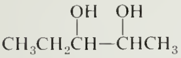
PROBLEMS

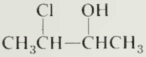
1. Which of the following familiar objects are chiral?
   - (a) a football
   - (b) an egg
   - (c) a corkscrew
   - (d) a golf club
   - (e) a crescent wrench
   - (f) a person
   - (g) a catcher's mitt
   - (h) a spiral staircase
   - (i) a pencil
   - (j) a slide rule
   - (k) a pair of scissors
   - (l) a screw-cap bottle top
   - (m) a Greek vase
   - (n) a portrait

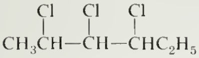
2. Calculate $[\alpha]_D$ for each of the following compounds:
   - (a) A 1 *M* solution of 2-chloropentane in chloroform in a 10-cm cell gives an observed α of $+3.64°$.
   - (b) A solution containing 0.96 g of 2-bromooctane in 10 ml of ether gives an observed α of $-1.80°$ in a 5-cm cell.

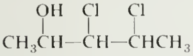
3. How many stereoisomers may exist for each of the following compounds?

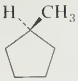
(a) 
$\mathrm{CH_3\overset{OH}{C}H{-}\overset{OH}{C}HCH_3}$

(b) 
$\mathrm{CH_3CH_2\overset{OH}{C}H{-}\overset{OH}{C}HCH_3}$

(c) 
$\mathrm{CH_3\overset{Cl}{C}H{-}\overset{OH}{C}HCH_3}$

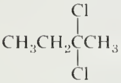
(d) 
$\mathrm{CH_3\overset{Cl}{C}H{-}\overset{Cl}{C}H{-}\overset{Cl}{C}HC_2H_5}$

(e) 
$\mathrm{CH_3\overset{OH}{C}H{-}\overset{Cl}{C}H{-}\overset{Cl}{C}HCH_3}$

(f) 

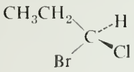
(g) 1,2-dimethylcyclopropane

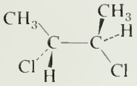
(h) 1,1-dimethylcyclopropane

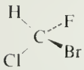
(i) 
$\mathrm{CH_3CH_2\overset{Cl}{\underset{Cl}{C}}CH_3}$

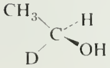
4. For parts (a)–(e) in problem 3, write Fischer projections for the different stereoisomers. Show which pairs of stereoisomers are enantiomeric and which pairs are diasteromeric. Assign (R) or (S) to each asymmetric atom.

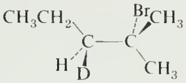
5. Write each of the following compounds in Fischer projection and assign (R) or (S) to each asymmetric atom.

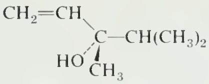
(a) 
CH3CH2
H
C
Cl
Br

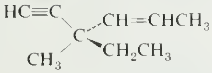
(b) 
CH3
CH3
H
C
C
Cl
H
Cl

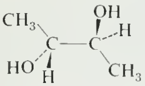
(c) 

(d) 

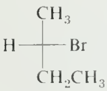
(e) 
CH3CH2
Br
CH3
C
C
H
D
CH3

(f) 
CH2=CH
C—CH(CH3)2
HO
CH3

(g) 
HC≡C
CH=CHCH3
C
CH2CH3
CH3

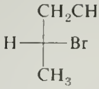
(h) 
CH3
OH
H
C
C
HO
H
CH3

6. Given the Fischer projection

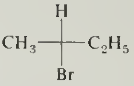

CH3
H
Br
CH2CH3

Is this structure (R) or (S)?

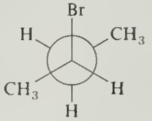
Determine whether each of the following structural symbols is equivalent to the above Fischer projection or to its enantiomer.

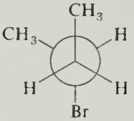
(a) 

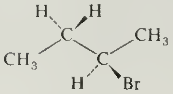
$$\begin{array}{c} CH_2CH_3 \\ H - \!\!+\!\! - Br \\ CH_3 \end{array}$$

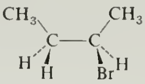
(b) 

$$\begin{array}{c} H \\ CH_3 - \!\!+\!\! - C_2H_5 \\ Br \end{array}$$

(c) 

(d) 

(e) 

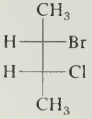
(f) 

7. Consider the chlorination of 3-methylpentane.
   (a) Write all of the different monochloro products that may be obtained.
   (b) Which pairs of isomers in part (a) are enantiomers?
   (c) Which pairs of isomers are diastereomers?
   (d) Which isomers are achiral?

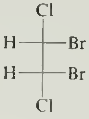
8. Answer problem 7 for methylcyclopentane.

9. Write the 2-iodobutane enantiomers of Figure 7.2 in Fischer projection and assign (R) and (S) appropriately.

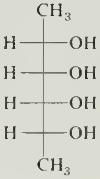
10. Assign (R) or (S) to each asymmetric atom in the following compounds:

(a) 

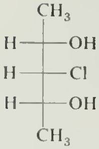
$$\begin{array}{c} CH_3 \\ H - \!\!+\!\! - Br \\ H - \!\!+\!\! - Cl \\ CH_3 \end{array}$$

(b) 

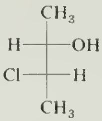
$$\begin{array}{c} Cl \\ H - \!\!+\!\! - Br \\ H - \!\!+\!\! - Br \\ Cl \end{array}$$

(c) 

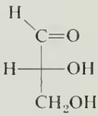
$$\begin{array}{c} CH_3 \\ H - \!\!+\!\! - OH \\ H - \!\!+\!\! - OH \\ H - \!\!+\!\! - OH \\ H - \!\!+\!\! - OH \\ CH_3 \end{array}$$

(d) 

$$\begin{array}{c} CH_3 \\ H - \!\!+\!\! - OH \\ H - \!\!+\!\! - Cl \\ H - \!\!+\!\! - OH \\ CH_3 \end{array}$$

(e) 

$$\begin{array}{c} CH_3 \\ H - \!\!+\!\! - OH \\ Cl - \!\!+\!\! - H \\ CH_3 \end{array}$$

(f) 

$$\begin{array}{c} H \diagdown C{=}O \\ H - \!\!+\!\! - OH \\ CH_2OH \end{array}$$

11. (S)-1-chloro-2-methylbutane has been shown to have (+) rotation. Among the products of light-initiated chlorination are (−)-1,4-dichloro-2-methylbutane and (±)-1,2-dichloro-2-methylbutane.
    (a) Write out the absolute configuration of the (−)-1,4-dichloro-2-methylbutane produced by the reaction and assign the proper (R) or (S) label. What relationship does this example show between sign of rotation and configuration?
    (b) What does the fact that the 1,2-dichloro-2-methylbutane produced is totally racemic indicate about the reaction mechanism and the nature of the intermediates?

Chapter 8
Reactions of Alkyl Halides

8.1
The Displacement Reaction

The replacement of the halogen in an alkyl halide by another group is one of the most important reactions in organic chemistry. In Section 3.1, we took a brief look at one such reaction, the reaction of methyl chloride with hydroxide ion.

$$HO^- + CH_3Cl \xrightarrow{H_2O} CH_3OH + Cl^-$$

Another example is the reaction of ethyl bromide with potassium iodide in acetone solution.

$$CH_3CH_2Br + K^+I^- \xrightarrow{\text{acetone}} CH_3CH_2I + KBr\downarrow$$

Although this is an equilibrium process, the reaction proceeds virtually to completion because potassium iodide is soluble in acetone and potassium bromide is not.

Like the reaction discussed in Section 3.1, the reaction of ethyl bromide with iodide ion is relatively slow. In order for complete reaction to occur, it is necessary to heat the mixture for several hours. The rate of the reaction may be determined by following the rate of disappearance of reactants or the rate of appearance of products. It is proportional to the *product* of the concentrations of the two reactants.

$$\text{rate} = -\frac{d[C_2H_5Br]}{dt} = -\frac{d[I^-]}{dt} = \frac{d[C_2H_5I]}{dt} = \frac{d[KBr]}{dt} = k[C_2H_5Br][I^-]$$

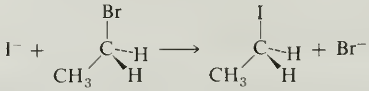
This equation is expressed in the symbolism of calculus. The expression

$$\frac{d[C_2H_5Br]}{dt}$$

means simply the rate with which the concentration of C_2H_5Br changes with time. The negative sign indicates that the concentration of C_2H_5Br decreases as time increases. Note that in this case [KBr] refers to amount rather than concentration because of its low solubility in acetone.

The concentrations of C_2H_5Br, I^-, C_2H_5I, and KBr may be determined at different times during the reaction by chemical or spectroscopic analysis. As the reaction proceeds, the concentrations of the reactants become reduced and the rate of reaction decreases. For example, at 50°, with the two reactants each present in an initial concentration of 0.1 *M*, the reaction is 50% complete in 7 min but only 95% complete after 2 hr. Furthermore, the reaction has an activation energy, $\Delta H^\ddagger$, of 19 kcal mole^{-1}; it is 10 times slower at 25° than it is at 50°. This activation energy is considerably higher than those of the free radical reactions we studied in Chapter 5.

When the rate of a chemical reaction depends on the concentration of two species, as in this case, it is said to display **second order kinetics.** This suggests a **bimolecular** mechanism, one in which one molecule of each reactant collide and react. The relatively high activation energy shows that only a minute fraction of such collisions actually result in reaction—those involving reactant molecules with sufficient kinetic energy. We might imagine that a straightforward mechanism would be one in which the attacking group, I^- in this case, simply displaces the *leaving group,* Br^-, from its bond to carbon.



However, a large mass of evidence has been accumulated which shows that this **front-side** attack is *not* the mechanism of this reaction.

> This does not mean that this is not a perfectly good mechanism, only that another mechanism is better for this particular reaction. The activation energy of the frontal-attack mechanism is so much higher than that of the actual mechanism that no significant number of product molecules are formed by such a path. Since rates are exponential functions of activation energy, a small energy change can have a dramatic effect on rate. For example, if two reactions differ in activation energy by 10 kcal mole^{-1}, the ratio of their reaction rates is 10,000,000:1. Thus, it is only necessary that we consider the most probable reaction mechanisms for a given reaction—those with the lowest activation energies.

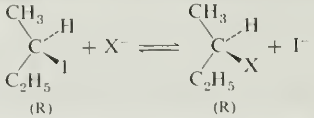
Instead of such a simple frontal attack, the reaction actually proceeds by a more complex mechanism that involves attack at the *rear of the C—Br bond.*

8.2
Stereochemistry of the Displacement Reaction

It has long been known that, when an optically active alkyl halide is exposed to halide ion in solution, the optical activity gradually diminishes to zero. This is an example of racemization; the optically active halide is converted to an equimolar mixture of (+) and (−) enantiomers. The rate of racemization is dependent on the concentration of both the alkyl halide and the added halide. The rate constant for the racemization process is called k_α. The conditions under which such racemization occurs are the same as those that lead to substitutions such as those discussed in Section 8.1.

The fact that optical activity is lost shows unequivocally that the frontal-attack mechanism cannot be the sole mechanism for such substitution reactions, because that mechanism leads to retention of absolute configuration at the asymmetric atom. For example, if the frontal-attack mechanism were the only mechanism for substitution in (R)-2-iodobutane, then a system containing this optically active halide would always contain only alkyl halides of the (R) configuration.

frontal attack mechanism:

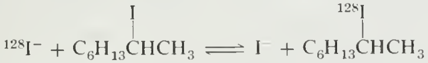


There must be a mechanism for substitution that allows racemization at C-2. To determine how often each replacement of one halide by another is accompanied by a change from the (+) enantiomer to the (−) enantiomer, it is necessary to know both the rate of racemization and the rate of the substitution reaction itself.

This experiment was first done in 1935 by the late Professor E. D. Hughes and his colleagues at the University of London. The experiment was an extremely elegant one, which used sodium iodide containing a radioactive isotope of iodine, ^{128}I, as the attacking group and optically active 2-iodooctane containing normal ^{127}I as the alkyl halide.

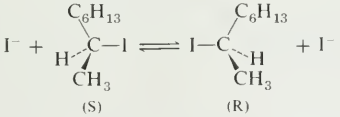
^{128}I is prepared by exposing normal ^{127}I to neutrons. The radioisotope decays with a half-life of 25 min.

At equilibrium, the radioactive iodine is distributed equally between 2-iodooctane and iodide ion.

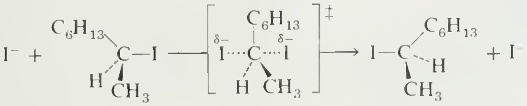


$$^{128}I^- + C_6H_{13}\overset{\overset{\large I}{|}}{C}HCH_3 \rightleftharpoons I^- + C_6H_{13}\overset{\overset{\large ^{128}I}{|}}{C}HCH_3$$

The reaction was found to have a rate constant at 30°, $k_{exch} = (1.36 \pm 0.11) \times 10^{-3}\ M^{-1}\,sec^{-1}$. Under identical conditions, the rate constant for racemization of optically active 2-iodooctane was found to be $k_\alpha = (2.62 \pm 0.03) \times 10^{-3}\ M^{-1}\,sec^{-1}$. Within experimental error, *the rate of racemization is exactly twice that of exchange*. Consequently, each act of replacement of one iodide by the other is accompanied by a change from one enantiomer to another. In this way, the rotation of one molecule of product cancels that of one reactant molecule, and is equivalent to two molecules of racemic material. Looking at it in a slightly different way, *all* of the beginning molecules must undergo reaction with $^{128}I^-$ before incorporation of the radioisotope is complete, whereas only one half of the beginning molecules must undergo inversion of stereochemistry before racemization is complete. Thus, if inversion of stereochemistry occurs every time substitution occurs, k_α must be exactly twice k_{exch}, as is found.



This observation has been combined with many other studies to infer that, in a bimolecular displacement reaction, the attacking group attacks at the carbon atom at the rear of the bond to the leaving group. During reaction, the carbon forms a progressively stronger bond to the attacking group, while the bond to the leaving group is being weakened. During this change, the other three bonds to the central carbon progressively flatten out and end up on the other side of the carbon in a manner similar to the spokes of an umbrella inverting in a windstorm.



The reaction is formulated as above, with the transition state geometry in brackets. The dotted lines indicate a partially formed or partially broken bond. The symbol

δ^- indicates that the negative charge is spread over both iodines in the transition state.

During the course of the reaction, the reacting system has greater potential energy than either the reactants or the products. The two weak bonds to the entering and leaving groups are weaker than the single bond in either the reactant or the product. Hence, energy is required in order for reaction to occur. The necessary potential energy is supplied by the conversion of kinetic energy. But only the minute fraction of reactants that have sufficient kinetic energy can react. Furthermore, even if the colliding reactants have sufficient kinetic energy, they must have the proper orientation or they will simply bounce apart. Recall that the point of highest energy is called the **transition state.** It is important to remember that the transition state is a point of *maximum* energy. It is not a discrete molecule that can be isolated and studied. In fact the whole act of displacement occurs in the space of about 10^{-12} sec, the period of a single vibration, so the system has the transition state geometry for only a fleeting moment.

The geometry of the transition state appears to be that in which the incoming and leaving groups are both weakly bonded to carbon in a linear fashion and in which the three remaining bonds to carbon lie in a plane perpendicular to the two weak bonds. The reaction mechanism for reaction of an entering group, Y^-, and a leaving group, X^-, is shown in Figure 8.1, where the structure of the reacting system at several points along the reaction coordinate is illustrated. At point (b) the C—X bond has started to lengthen and the central carbon has started to flatten out. At the transition state, point (c), the central carbon is approximately flat and both the bonds to the leaving and entering group are long. Point (d)

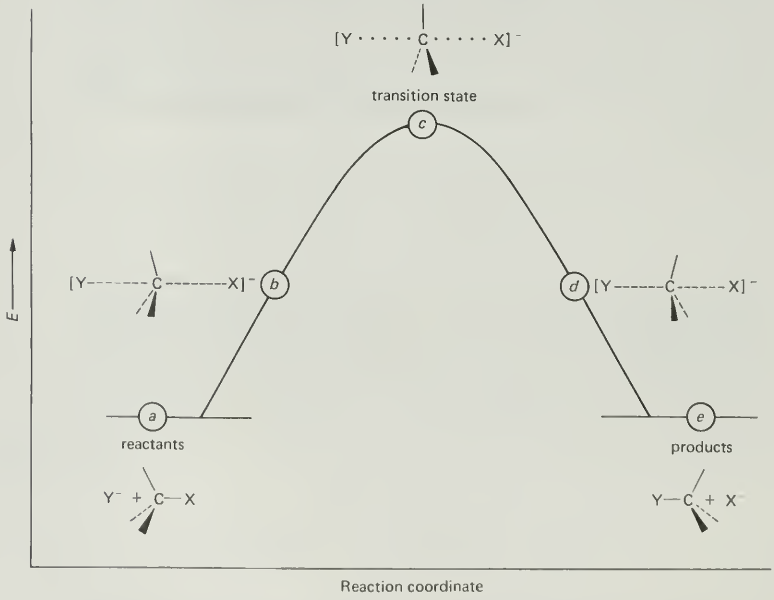


FIGURE 8.1 *Reaction mechanism profile for a displacement reaction by Y⁻ on RX.*

occurs on the final road to products (e); the central carbon has bent, the C—Y bond is approaching normal length, and the leaving group, X, is receding. The structures at points (a) through (e) are represented in stereo form in Figure 8.2.

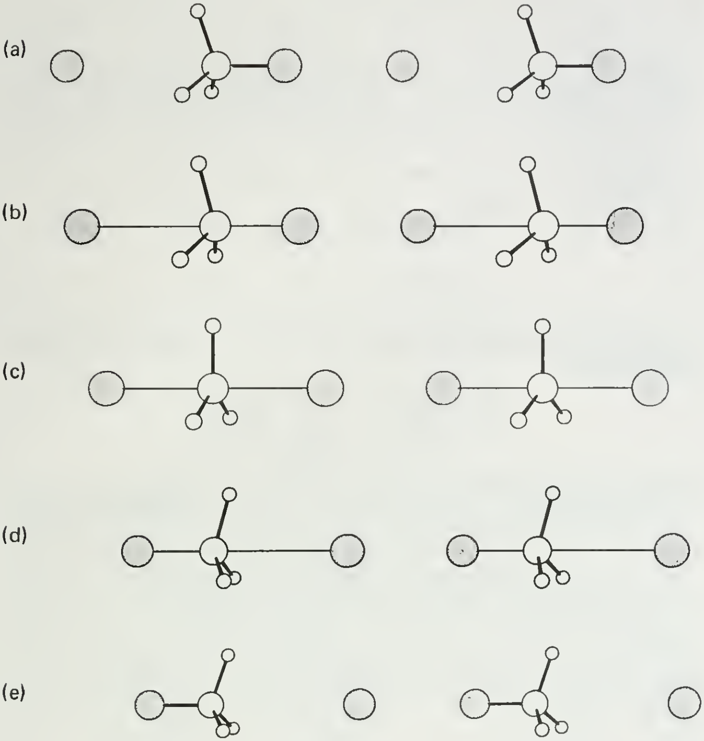


FIGURE 8.2 *The structure of the reaction system at points* (a) *through* (e) *in Figure* 8.1.

In orbital terms, both the reactant and the product are tetrahedral. The C—X bond in each case is C_{sp^3}-X. In the transition state, the weak bonds to X and Y may be considered to derive from overlap of a halogen orbital with the two lobes of a *p* orbital on the central carbon. The other three bonds to this carbon are formed from sp^2 hybrid orbitals, as shown in Figure 8.3.

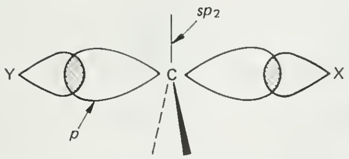


FIGURE 8.3 *Orbital formulation of the transition state of a displacement reaction.*

8.3
Generality of the Displacement Reaction

LEWIS
BASE

The importance of the displacement reaction lies in its generality. Although the reaction was introduced in the preceding sections with halide ions as entering groups, analogous reactions are known with a wide range of anions and neutral molecules. The only requirement is that the attacking group be a Lewis base, a species which contains an atom that has a pair of electrons available for bonding. The examples in Table 8.1 demonstrate the range of attacking groups that undergo the reaction.

A base may generally be regarded as the conjugate base of an acid, and it may be neutral or charged.

$$\text{BH} \overset{K_a}{\rightleftharpoons} \text{B:}^- + \text{H}^+$$

$$\underset{\text{conjugate acid}}{\text{BH}^+} \overset{K_a}{\rightleftharpoons} \underset{\text{conjugate base}}{\text{B:}} + \text{H}^+$$

A quantitative measure of the **basicity** of a base is the acidity, or pK_a,* of its conjugate acid.

$$K_a = \frac{[\text{B:}^-][\text{H}^+]}{[\text{BH}]} \quad \text{or} \quad \frac{[\text{B:}][\text{H}^+]}{[\text{BH}^+]}$$

$$pK_a = -\log K_a$$

))

A weak conjugate acid (more positive pK_a) corresponds to a strong base; a strong

TABLE 8.1

Some Displacement Reactions with Ethyl Bromide

Attacking Reagent		Product	
Formula	Name	Formula	Name
HO^-	hydroxide ion	C_2H_5OH	ethyl alcohol
$C_2H_5O^-$	ethoxide ion	$CH_3CH_2OCH_2CH_3$	diethyl ether
HS^-	hydrosulfide ion	CH_3CH_2SH	ethanethiol
SCN^-	thiocyanate ion	CH_3CH_2SCN	ethyl thiocyanate
CN^-	cyanide ion	CH_3CH_2CN	ethyl cyanide, propionitrile
N_3^-	azide ion	$CH_3CH_2N_3$	ethyl azide
NH_3	ammonia	$CH_3CH_2NH_3^+ Br^-$	ethylammonium bromide
H_2O	water	$CH_3CH_2OH_2^+ Br^-$	ethyloxonium bromide
$CH_3CO_2^-$	acetate ion	$CH_3CO_2C_2H_5$	ethyl acetate
NO_3^-	nitrate ion	$CH_3CH_2ONO_2$	ethyl nitrate
$P(CH_3)_3$	trimethylphosphine	$C_2H_5P(CH_3)_3^+ Br^-$	ethyltrimethylphosphonium bromide
$N(C_2H_5)_3$	triethylamine	$(C_2H_5)_4N^+Br^-$	tetraethylammonium bromide

---

*For a review of pK, see sections 11.4, 17.4, and Appendix IV.

conjugate acid (less positive pK_a) corresponds to a weak base. A few common bases, with the pK_as of the corresponding conjugate acids, are given in Table 8.2. Other values are given in Appendix IV.

The basicity of a base depends on the strength of its bond to a proton in solution. In the displacement reaction, the base forms a bond to carbon. Consequently, we might expect to find some correlation between the energy involved in the protonation of a base and the activation energy for its reaction in a displacement reaction. Instead of energies or enthalpies, many correlations of this type have been found using the Gibb's free energies, ΔG. The pK of an acid is proportional to the standard free energy of the acid-base equilibrium:

$$\Delta G^\circ = 2.303\, RT\, pK$$

This equation follows by combining the relation between an equilibrium constant and the standard free energy with the definition of pK:

$$\Delta G^\circ = -RT \ln K$$

Recall from Chapter 3 that rate constants are also related to free energies of activation, $\Delta G^\ddagger$

$$k = \text{constant} \times e^{-\Delta G^\ddagger/RT}$$

$$-\log k = \frac{\Delta G^\ddagger}{2.303\, RT} - \log(\text{constant})$$

To test the existence of a correlation between basicity and reactivity in displacement reactions, we first need to determine the second-order rate constants for reaction of a series of bases with some common substrate under the same experimental conditions; that is, for the same solvent and temperature. Next, we plot the logarithms of these rate constants against the corresponding pK_a values. For a perfect correlation every point will fall exactly on a straight line. Figure 8.4 shows a plot of this type for the reactions of a series of bases with methyl iodide in methyl alcohol solution. We see that there is a rough correlation in the anticipated direction. There is a tendency for bases with high pK_a (stronger bases) to react faster with methyl iodide. The points cluster in a linear fashion but there is a good deal of scatter.

TABLE 8.2
Some Common Bases

WEAK BASE

Base	Conjugate Acid	pK_a
I^-	HI	−9.5
Br^-	HBr	−9
Cl^-	HCl	−7
HSO_4^-	H_2SO_4	−5
H_2O	H_3O^+	−1.7
F^-	HF	3.2
CH_3COO^-	CH_3COOH	4.8
HS^-	H_2S	7.0
CN^-	HCN	9.2
HO	H_2O	15.7
H_2N^-	H_3N	35

STRONG BASE

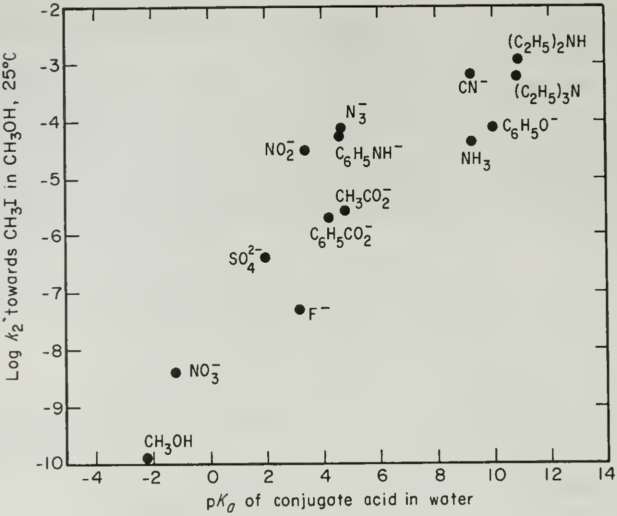


FIGURE 8.4 *Correlation of basicity with reactivity toward methyl iodide.*

There are a number of reasons why the correlation is not perfect. One reason is that we have compared reactions in two different solvents, a displacement reaction in methyl alcohol and an acid-base equilibrium in water. Water is not a useful solvent for displacement reactions because most organic compounds are not sufficiently soluble. However, only a limited number of pK_a values are available for nonaqueous solvents.

Another reason why the correlation is not perfect is to be found in comparing the types of bonding in the two systems. In an acid-base equilibrium, the bond involved is to a small and relatively "tight" 1*s* orbital of a hydrogen (Figure 8.5a). In the transition state of a displacement reaction, the orbital containing the lone pair of the base overlaps instead with the larger, more diffuse, 2*p* orbital of a carbon (Figure 8.5b).

These two kinds of reactivity of a base are given different names. **Basicity is the affinity of a base for a proton,** and is measured by the equilibrium pK_a of the conjugate acid in water. **Nucleophilicity** (from *nucleus,* L., kernel, and *philos,* Gr., loving; hence, "nucleus-loving") **is the affinity of a base for a carbon atom**

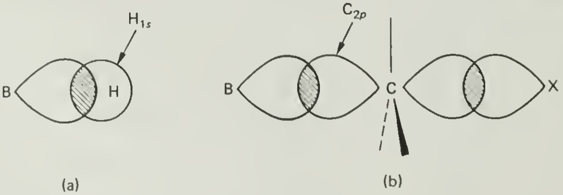


FIGURE 8.5 *Comparison of orbital overlaps of a base with a proton and with the central carbon of a displacement reaction.*

in a displacement reaction transition state. Nucleophilicity is measured by the rate of reaction of the base with a suitable compound, usually methyl bromide or iodide, in some standard solvent.

The displacement reaction is often referred to as an S_N2 reaction for **substitution, nucleophilic, bimolecular.**

> The **molecularity** of a reaction is defined as the number of molecules involved in the rate-determining transition state. It is sometimes, but not always, equal to the **kinetic order** of the reaction. For example, consider a reaction of the type
>
> $$A + B \underset{\underset{\text{fast}}{k_{-1}}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow[\text{slow}]{k_2} D$$
>
> The rate of appearance of the product D is given by the rate law
>
> $$\begin{matrix}\text{rate of}\\ \text{formation of D}\end{matrix} = \frac{d[\mathrm{D}]}{dt} = \frac{k_1k_2}{k_{-1}}[\mathrm{A}][\mathrm{B}] = k'[\mathrm{A}][\mathrm{B}]$$
>
> which shows second-order kinetics. However, in the slow step (k_2), the rate-determining step, only one molecule, species C, is involved. Hence, the reaction is unimolecular.

The mechanistic label S_N2 covers a wide variety of specific reactions (see, for example, Table 8.1 and Figure 8.4). All of the reactions in this category occur by the common mechanism discussed in this section. They all proceed with inversion of configuration at the reacting carbon, and they all show second-order kinetics. The rates of S_N2 reactions are markedly affected by a number of factors, including the nucleophilicity of the attacking group, the structural environment of the carbon where displacement occurs, the nature of the leaving group, and the nature of the solvent. The important principles that enter into evaluating the effect of these variables recur frequently in organic chemistry, and therefore warrant careful study at this time.

8.4
Nucleophilicity

In constructing Figure 8.4, only a fraction of the available data was used. In fact, the bases, or nucleophiles, used in that plot all involve reaction with atoms in the first row of the periodic table—C, N, O, F. The rough correlation evident in Figure 8.4 shows that *more basic electron pairs tend to be more nucleophilic.*

Now let us add more data and expand the plot to that shown in Figure 8.6. The points in Figure 8.4 have been retained as unlabeled open circles. The additional points for other nucleophilic reagents produce still more scatter. However, a second important generalization can be drawn from Figure 8.6. **Second- and third-row elements are invariably more nucleophilic than first-row elements of comparable basicity.** The reason for this generalization appears to be that the larger elements have relatively diffuse lone pairs that are more polarizable. These more diffuse lone pairs tend to bond more strongly to the more diffuse *p* orbital of the S_N2 transition state than to the small, tight 1*s* orbital of a hydrogen. Consequently, such lone pairs tend to be more nucleophilic than their basicity would indicate. The first-row elements have smaller orbitals and the lone pairs are held more tightly. These elements are relatively more basic and less nucleo-

[[illegible] proton [illegible]]

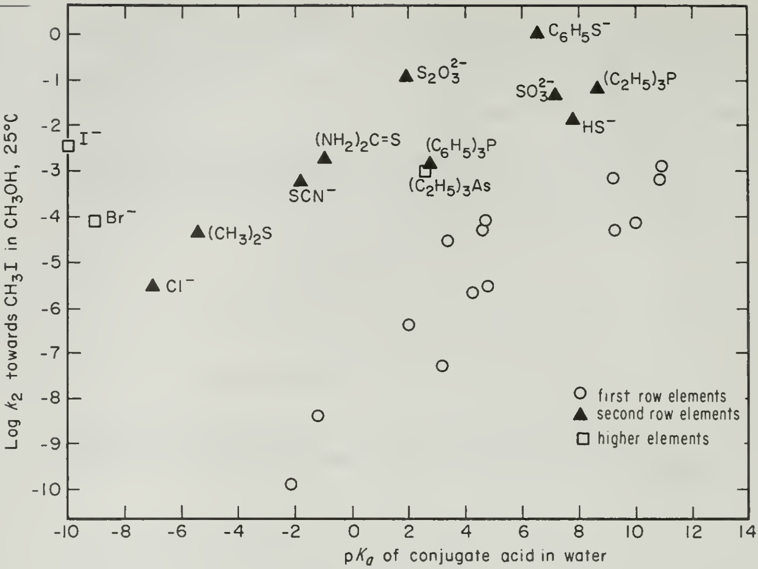


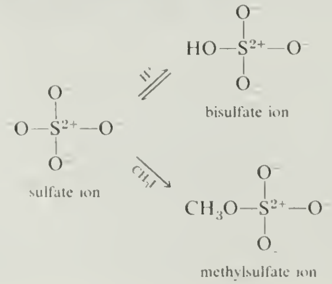
Figure 8.6 *Comparison of nucleophilicities and basicities of various reactants. Open circles refer to points in Figure* 8.4.

philic. Examples of reactivity towards methyl iodide are

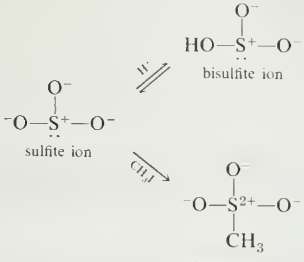
$$(CH_3)_2S > CH_3OH$$
$$HS^- > HO^-$$
$$Cl^- > F^-$$
$$C_6H_5S^- > C_6H_5O^-$$
$$(C_2H_5)_3P > (C_2H_5)_3N$$

In each case, the group with the first-row element is the more basic and also the less nucleophilic.

At this point we can now interpret an interesting experimental result. Sulfate ion is straightforward in its reaction with either H^+ or CH_3I in an S_N2 reaction. Both types of reaction occur at an oxygen

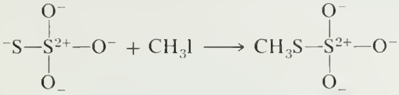


Sulfite ion, however, behaves quite differently. It reacts with a proton on oxygen to form bisulfite ion, and with methyl iodide on sulfur to form the methanesulfonate ion.



methanesulfonate ion

The oxygen in sulfite ion is the more basic atom and prefers to attack H^+, but the lone pair on sulfur is more nucleophilic, and it has preference in the S_N2 transition state. Sulfate ion has no lone pair on sulfur, and both reactions have no alternative but to occur at the oxygen. Thiosulfate ion is a simple sulfur analog of sulfate. This ion reacts with methyl iodide exclusively on sulfur, even though there are three oxygens and only one sulfur.



$$^-S-\overset{O^-}{\underset{O^-}{S^{2+}}}-O^- + CH_3I \longrightarrow CH_3S-\overset{O^-}{\underset{O^-}{S^{2+}}}-O^-$$

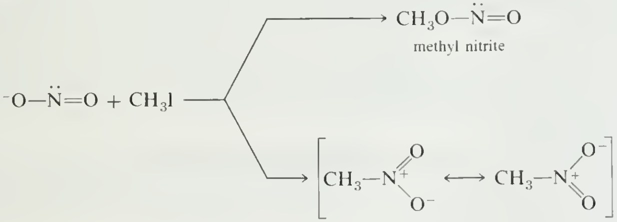
thiosulfate ion   methylthiosulfate ion

Finally, there are some nucleophiles that show measurable nucleophilic properties at two different atoms. Nitrite ion is an example. The ion undergoes protonation exclusively on oxygen to give nitrous acid.

$$\left[{}^-O-\ddot{N}=O \longleftrightarrow O=\ddot{N}-O^-\right] \xrightarrow{H^+} HO-\ddot{N}=O$$

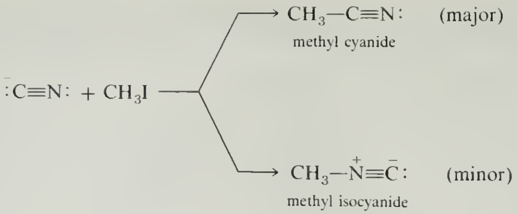
nitrite ion   nitrous acid

However, the reaction of nitrite ion with methyl iodide gives both methyl nitrite and nitromethane.



nitromethane

In this case, both nitrogen and oxygen are first-row elements and have comparable nucleophilicities. The ratio of the products actually depends on the reaction conditions. Another example is the reaction with cyanide ion. In addition to methyl cyanide, the major product, small amounts of methyl isocyanide are also produced.



Anions such as these, which can react at two different positions, are called **ambident** (*ambo,* L., both; *dentis,* L., tooth), "two-fanged" nucleophiles.

8.5
Effect of Substrate Structure on Displacement Reactions

"αC"

A large variety of alkyl halides undergo substitution by the S_N2 mechanism. The ease of reaction depends markedly upon the structure of the alkyl group to which the halogen is attached. Reactivities vary widely and in a consistent manner. Branching of the chain at the carbon where substitution occurs (the α-carbon) has a significant effect on the rate of reaction. Relative rates of S_N2 reactions for methyl, ethyl, isopropyl, and *t*-butyl halides are approximately as shown in Table 8.3.

TABLE 8.3
Effect of Branching at the α-Carbon on the Rate of S_N2 Reactions

Alkyl Halide	Relative Rate
$CH_3—$	30
$CH_3CH_2—$	1
$(CH_3)_2CH—$	0.03
$(CH_3)_3C—$	≈ 0

These effects on reaction rate are interpreted with the concept of **steric hindrance** to attack of the attacking nucleophile. The rear of a methyl group is relatively exposed to such attack. As the hydrogens of the methyl group are replaced by methyl groups, the area in the rear of the leaving group becomes more encumbered. It becomes more difficult for the attacking group to approach closely enough to the rear of the C—X bond for reaction to occur, and the rate of reaction diminishes (Figure 8.7).

A similar effect may be seen in branching at the β-carbon. Some typical relative rates are shown in Table 8.4. This reduction in rate is also attributable to steric hindrance. In one conformation, the rear of a *n*-propyl carbon is seriously blocked (Figure 8.8a) but in two other conformations, the situation is no worse than for ethyl (Figure 8.8b). Consequently, *n*-propyl halides undergo S_N2 displacement only slightly less readily than do ethyl halides.

For the isobutyl group, it is possible to rotate both of the β-methyl groups out of the way of the attacking group, but the resulting conformation is highly congested and has relatively high energy (Figure 8.9). Accordingly, isobutyl halides are much less reactive than either ethyl or *n*-propyl compounds.

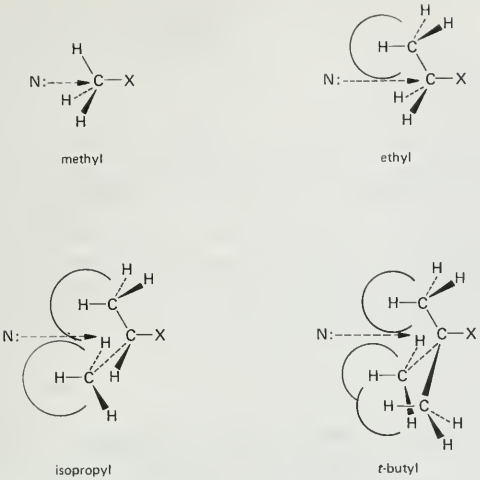

methyl
ethyl
isopropyl
t-butyl
N:
C—X

Figure 8.7 *Effect of α branching on* S_N2 *reactions.*

Table 8.4
Effect of Branching at the β-Carbon on the Rate of S_N2 *Reactions*

Alkyl Halide	Relative Rate
$CH_3CH_2—$	1
$CH_3CH_2CH_2—$	0.4
$(CH_3)_2CHCH_2—$	0.03
$(CH_3)_3CCH_2—$	0.00001

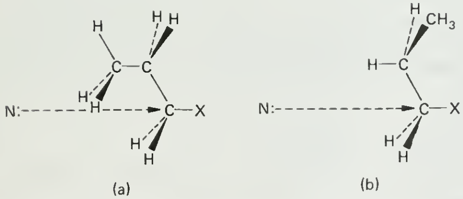


Figure 8.8 S_N2 *attack at two conformations of* n-*propyl compounds.*

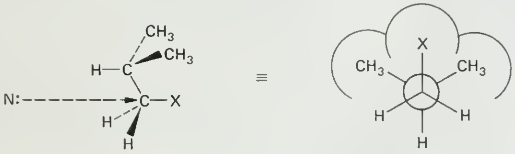

CH3
CH3
H—C
N:
C—X
≡
X
CH3
CH3
H
H
H

Figure 8.9 S_N2 *reaction at isobutyl systems.*

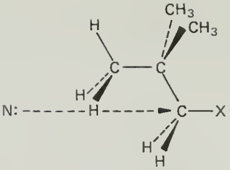


Figure 8.10 S_N2 *reaction at neopentyl compounds.*

Neopentyl halides are particularly interesting because there is no conformation in which a blocking methyl group can be avoided (Figure 8.10). Neopentyl halides are essentially unreactive in S_N2 reactions except under very drastic conditions.

Substitution of sites more remote than the β-carbon have little or no effect on the ease of S_N2 reactions. For example, *n*-butyl and *n*-pentyl halides react at essentially the same rate as *n*-propyl halides.

The type of steric interaction we have discussed here forces groups to bend away from each other. Such deformation often forces orbitals to overlap in a noncolinear fashion, which provides less effective bonding than colinear overlap (Figure 8.11). Overlap of orbitals that are not colinear gives bonds which may be described as "bent." Such bent bonds are generally of higher energy than the corresponding "straight bonds." These principles apply not only to the transition states for displacement reactions but to certain strained molecules as well (Chapter 23).

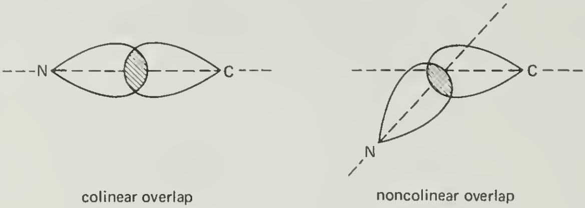


Figure 8.11 *Bent bonds have reduced orbital overlap.*

In summary, the effect of the structure of the alkyl group on the rate of S_N2 reaction is apparent in two ways.

1. **Branching at the α-carbon hinders reaction: rate order is methyl $>$ primary $>$ secondary $\gg$ tertiary.**
2. **Branching at the β-carbon hinders reaction: neopentyl compounds are particularly slow.**

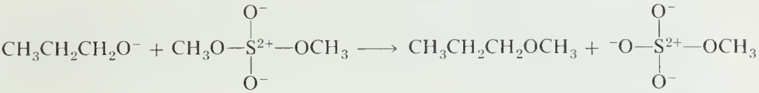
Displacements that proceed by the S_N2 mechanism are most successful with primary compounds having no branches at the β-carbon. Yields are poor to fair with secondary halides and with primary halides having branches at C-2. Neopentyl systems undergo the reaction only under very drastic conditions and tertiary halides do not react by this mechanism at all. When the rate of the S_N2 reaction is slowed down by these structural effects, alternative side reactions begin to compete. With tertiary halides, and to an important degree with secondary and highly branched primary halides, the side reactions tend to dominate. These side reactions are discussed in Sections 8.7 and 8.8.

8.6
Some Typical S_N2 Reactions

A. *Leaving Groups*

Alkyl chlorides, bromides, and iodides all react satisfactorily by the S_N2 mechanism. The ease of reaction is dependent on the nature of the **leaving group**, alkyl iodides reacting most rapidly and alkyl chlorides most slowly. Alkyl fluorides are essentially unreactive by the S_N2 mechanism. Since chlorine is much cheaper than bromine, alkyl chlorides are the least expensive alkyl halides. However, for laboratory uses where only small amounts of material are involved, alkyl bromides are commonly used because they are 50–100 times more reactive than the corresponding chlorides. Iodides are somewhat more reactive than bromides but are quite a bit more expensive, and this slightly increased reactivity does not justify their additional cost. In industrial processes, where massive amounts of materials are involved and cost is a prime consideration, alkyl chlorides are used almost exclusively.

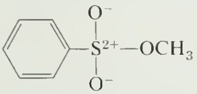
The S_N2 reaction is not restricted to alkyl halides. Any group that is the conjugate base of a strong acid can act as a leaving group. An example is bisulfate ion, HSO_4^-, which is the conjugate base of sulfuric acid, $pK_a - 5$. Dimethyl sulfate is an inexpensive commercial compound that reacts readily by the S_N2 mechanism. The leaving group is the methylsulfate ion, which is similar in its base strength to bisulfate ion.



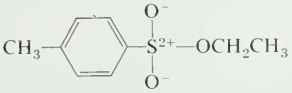
$$CH_3CH_2CH_2O^- + CH_3O-\overset{O^-}{\underset{O^-}{S^{2+}}}-OCH_3 \longrightarrow CH_3CH_2CH_2OCH_3 + {}^-O-\overset{O^-}{\underset{O^-}{S^{2+}}}-OCH_3$$

methylsulfate ion

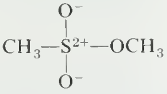
The chief disadvantage of dimethyl sulfate is its toxicity. It is water soluble and reacts readily with the nucleophilic groups in body tissues and fluids. Although dimethyl sulfate is the only sulfate in common use, alkyl sulfonates are often employed. Sulfonic acids, RSO_2OH, are similar to sulfuric acid in acidity and the sulfonate ion, RSO_3^-, is an excellent leaving group. Alkyl benzenesulfonates, alkyl *p*-toluenesulfonates, and alkyl methanesulfonates are extremely useful substrates for S_N2 reactions. These compounds are readily prepared from alcohols as described in Sections 11.7.D and 18.13.A.



methyl
benzenesulfonate



ethyl
p-toluenesulfonate

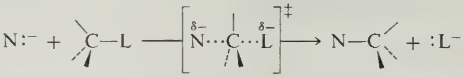


$$CH_3-\overset{O^-}{\underset{O^-}{S^{2+}}}-OCH_3$$

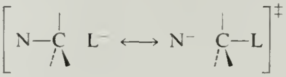
methyl
methanesulfonate

Alkyl nitrates undergo reaction by the S_N2 mechanism because nitric acid is a strong acid and nitrate ion is a weak base. However, alkyl nitrates are more prone to side reactions than the corresponding halides and, therefore, the yield of substitution product is lower. Consequently, nitrates are rarely used.

The facility with which a group can function as a leaving group in an S_N2 reaction is related to its **basicity.** If a group is a weak base (that is, the conjugate base of a strong acid), it will generally be a "good" leaving group. This is readily understood by considering the electronic structure of the transition state:



The negative charge which is introduced with the attacking nucleophile is distributed over several atoms in the transition state. The charge is borne mostly by the entering and leaving groups, as shown by the resonance structures for the transition state.



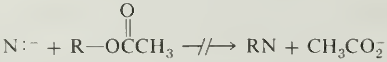
The leaving group has gained an appreciable amount of electron density in going from reactant to transition state. The more this electron density or negative charge is stabilized, the lower is the energy of the transition state and the faster is the rate of reaction. The degree to which a group can accommodate a negative charge is also related to its affinity for a proton, its basicity. The acids HCl, HBr, HI, and H_2SO_4 are all strong acids because the anions Cl^-, Br^-, I^-, and HSO_4^- are stable anions. These anions are also good leaving groups in S_N2 reactions.

HCN is a weak acid ($pK_a = 10$) and the displacement of cyanide is never observed.

$$N:^- + RCN \not\longrightarrow R{-}N + CN^-$$

Hydrazoic acid (HN_3) and acetic acid (CH_3CO_2H) are also weak acids (pK_as of 5.8 and 4.8, respectively). Correspondingly, azide ion and acetate ion are extremely poor leaving groups.

$$N:^- + R{-}N_3 \not\longrightarrow RN + N_3^-$$



$$N:^- + R{-}O\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \not\longrightarrow RN + CH_3CO_2^-$$

The reason that alkyl fluorides are ineffective substrates in the S_N2 reaction is related to the relatively low acidity of HF ($pK_a = 3$).

By comparing S_N2 reactivity with relative acidity, we can understand the operation of **acid catalysis** in certain displacement processes. Alcohols do not undergo S_N2 reactions because hydroxide ion is too basic (the pK_a of its conjugate acid, H_2O, is 15.7).

$$N:^- + R{-}OH \not\longrightarrow R{-}N + OH^-$$

However, in the presence of a strong mineral acid, such as HCl, HBr, or H_2SO_4, the alcohol oxygen is protonated. An S_N2 reaction can now occur because the leaving group is water, which is a much weaker base than OH^- (the conjugate acid of water, H_3O^+, has $pK_a = -1.7$).

$$R{-}OH + H^+ \rightleftharpoons R{-}\overset{+}{O}H_2 + N:^- \longrightarrow R{-}N + H_2O$$

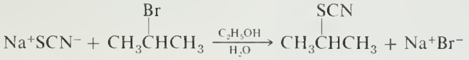
Note that the same principles of electron density and relative basicity are involved in this reaction, even though the leaving group is not an anion. This is a useful and important reaction of alcohols and it will be developed more fully in Section 11.7.

B. *Solvents*

A number of solvents may be used as reaction media for S_N2 reactions. Ethanol and methanol are particularly useful because they are inexpensive, relatively inert, and dissolve many organic substrates and inorganic salts. Sometimes some additional water is added to increase the solubility of the inorganic salt used as the displacing agent. Some typical examples follow:

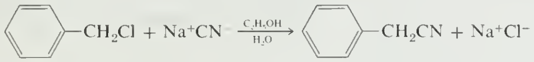
$$CH_3O^- + CH_3CH_2CH_2CH_2Br \xrightarrow{CH_3OH} CH_3CH_2CH_2CH_2OCH_3 + Br^-$$

n-Butyl bromide is refluxed with sodium methoxide in methanol for $\frac{1}{2}$ hr. Water is added and the organic layer is separated, dried, and distilled to give methyl *n*-butyl ether.



$$Na^+SCN^- + CH_3\overset{\displaystyle Br}{\overset{|}{C}}HCH_3 \xrightarrow[H_2O]{C_2H_5OH} CH_3\overset{\displaystyle SCN}{\overset{|}{C}}HCH_3 + Na^+Br^-$$

Isopropyl bromide and sodium thiocyanate (NaSCN) are refluxed in 90% aqueous alcohol for 6 hr. The precipitated sodium bromide is filtered. The filtrate is diluted with water and extracted with ether. Distillation gives isopropyl thiocyanate, $(CH_3)_2CHSCN$, in 76–79% yield.



Benzyl chloride, $C_6H_5CH_2Cl$, is refluxed with sodium cyanide for 4 hr in aqueous alcohol. The sodium chloride is filtered, the solvent is distilled and the product benzyl cyanide, $C_6H_5CH_2CN$, is distilled under vacuum to give a 80–90% yield. Sodium and potassium cyanides are highly toxic white solids that are very soluble in water and slightly soluble in ethanol. Organic cyanides may be hydrolyzed to carboxylic acids (Section 17.6).

The use of acetone as a solvent for halide exchange reactions was illustrated at the beginning of this chapter. Acetone is an example of a **polar aprotic** solvent, that is, a solvent without hydroxy groups but with a relatively high dipole moment and dielectric constant. Polar aprotic solvents are useful because of their ability to solvate ions and, thereby, to dissolve many salts. Other examples are acetonitrile, CH_3CN; dimethylformamide, $(CH_3)_2NCHO$; dimethyl sulfoxide, $(CH_3)_2SO$; and hexamethylphosphoric triamide, $[(CH_3)_2N]_3PO$.

Displacement reactions in polar aprotic solvents are frequently much faster than they are in hydroxylic solvents. For example, the reaction of methyl bromide with iodide ion is about 500 times faster in acetone than in methyl alcohol. An even more striking example is the reaction of chloride ion with methyl iodide, which is a *million times* faster in dimethylformamide than it is in methyl alcohol. The relative rate of reaction of azide ion with *n*-butyl bromide in various solvents is shown for comparison in Table 8.5. One important reason for this effect is hydrogen bonding. In a hydroxylic solvent, the OH groups can solvate anions by hydrogen bonding:

$$ROH{-}{-}{-}X^-{-}{-}{-}HOR$$

Hydrogen bonding will be discussed in detail in Section 11.3. For the present, suffice it to say that such bonding tends to tie up an anion and make it less reactive. Aprotic solvents have no hydrogens capable of hydrogen bonding. Hence, the anions are more free and have greater effective nucleophilicity.

Table 8.5
Relative Rates for the Reaction
$N_3^- + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_4H_9N_3 + Br^-$

Solvent	Relative Rate
CH_3OH	1
$(CH_3)_2SO$ (DMSO)	1,300
$(CH_3)_2NCHO$ (DMF)	2,800
CH_3CN	5,000
$[(CH_3)_2N]_3PO$ (HMPT)	200,000

Protic

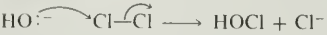
This type of solvation effect can even change the relative reactivities of different nucleophilic groups. For example, the order of reactivity of halide ions in S_N2 reaction in water or in alcohols is

$$I^- > Br^- > Cl^-$$

In acetone, the reactivities tend to be closer together and in dimethylformamide the order is even reversed! More basic anions tend to be hydrogen bonded more firmly and are less reactive in hydroxylic solvents. Consequently, nucleophilicity is not a simple and invariant property, but depends on the specific reagents, conditions, and solvents. We make frequent use of qualitative rather than quantitative generalizations, and it is still useful to know that iodide ion is *frequently* more reactive than chloride ion, and that second-row elements are *usually* more reactive in displacement reaction than first-row elements. Even though anions are generally more reactive in polar aprotic solvents than in aqueous alcohols, the aqueous solvents are still frequently used in practice because they are inexpensive, convenient, and, for many reactions, serve perfectly adequately.

C. *Displacement Reactions at Atoms Other than Carbon*

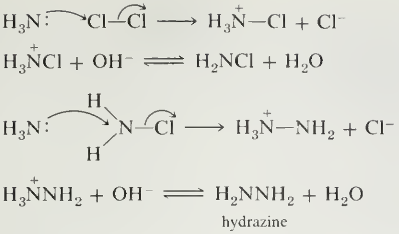
Displacement reactions are very common and may occur at atoms other than carbon. Many well-known inorganic reactions can be formulated as nucleophilic displacement reactions. One example is the formation of hypochlorite (household bleach) by the reaction of hydroxide ion with chlorine. The reaction may be considered as an S_N2 reaction in which hydroxide ion displaces chloride ion from a chlorine molecule.



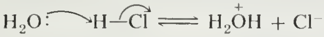
$$HO\!:^- \; Cl{-}Cl \longrightarrow HOCl + Cl^-$$

The preceding equation illustrates the use of arrows for "electron-pushing," a useful device for keeping track of electron pairs when describing the bond reorganizations that occur during a reaction. An arrow symbolizes the flow of an electron pair in a reaction. The arrow begins at the electron pair in a reactant and points to where the electron pair "goes" in the reaction. In the example given, an electron pair on hydroxide ion attacks a chlorine and forms a new covalent bond. At the same time, the electron pair that had bonded the two chlorines together is released and departs with the leaving chloride ion. It is conventional to use curved arrows, ↷.

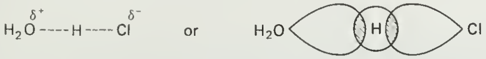
Another example is the Raschig process for the synthesis of hydrazine, which involves two such displacement steps.



Even ordinary acid-base reactions can be regarded as displacement reactions on hydrogen.



Such reactions are extremely rapid and we generally consider them only as facile equilibria. However, with special techniques, the rates of proton transfer reactions can be measured, even though the second-order rate constants are as high as $10^{10}\ M^{-1}\ \mathrm{sec}^{-1}$. This is many orders of magnitude faster than the analogous second-order rate constants for displacements on carbon. The transition state for such a proton-transfer reaction may be formulated as



In such a transition state the 1*s* orbital of the hydrogen is partially bound to both the incoming and the leaving base.

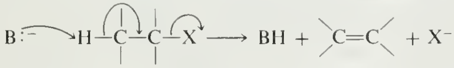
Many reactions of atoms and radicals with molecules can be regarded as radical displacement reactions. Mechanistically, such displacements are classified as **bimolecular homolytic substitution** reactions, $\boxed{S_H2.}$ We have already discussed such reactions in Chapter 5, but now they take their place in a family of related reactions.

$$Cl\cdot + H{-}CH_3 \longrightarrow ClH + \cdot CH_3$$

$$H_3C\cdot + Cl{-}Cl \longrightarrow CH_3Cl + \cdot Cl$$

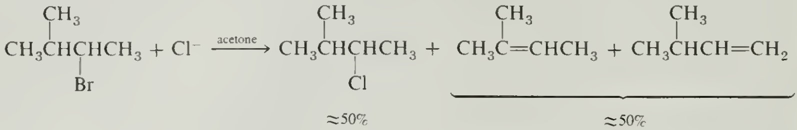
8.7
E2 Elimination

One of the side reactions that occurs in varying degree in displacement reactions is the elimination of the elements of HX to product an alkene.



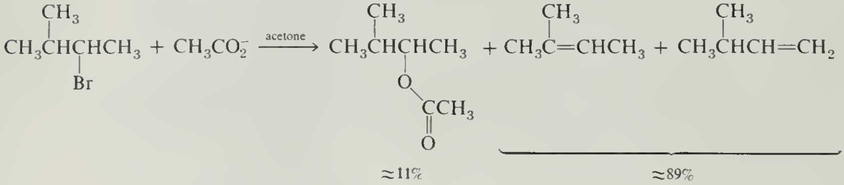
Under appropriate conditions, this reaction can be the principal reaction and becomes a method for preparing alkenes. Accordingly, it is discussed in more detail in Section 12.5.A. For the present, it suffices to know that this reaction occurs by attack of a base on a hydrogen with concommitant formation of a C=C double bond and breaking of the C—X bond to form halide ion.

Mechanistically, the reaction is classified as **bimolecular elimination,** or E2. Since attack on a proton is involved, it is the *basicity*, rather than the nucleophilicity, of the Lewis base that is important. Strongly basic species such as alkoxide or hydroxide ions favor elimination; highly nucleophilic species such as second- and third-row elements favor substitution. For example, the S_N2 and E2 reactions of 3-bromo-2-methylbutane with chloride ion in acetone occur at about equal rates.



$$CH_3\overset{CH_3}{C}H\underset{Br}{C}HCH_3 + Cl^- \xrightarrow{\text{acetone}} \underset{\approx 50\%}{CH_3\overset{CH_3}{C}H\underset{Cl}{C}HCH_3} + \underbrace{CH_3\overset{CH_3}{C}{=}CHCH_3 + CH_3\overset{CH_3}{C}HCH{=}CH_2}_{\approx 50\%}$$

With acetate ion, however, elimination is about 8 times faster than substitution.

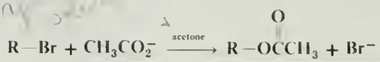


$$CH_3\overset{CH_3}{C}H\underset{Br}{C}HCH_3 + CH_3CO_2^- \xrightarrow{\text{acetone}} \underset{\approx 11\%}{CH_3\overset{CH_3}{C}H\underset{O\underset{\underset{O}{\|}}{C}CH_3}{C}HCH_3} + \underbrace{CH_3\overset{CH_3}{C}{=}CHCH_3 + CH_3\overset{CH_3}{C}HCH{=}CH_2}_{\approx 89\%}$$

The structure of the substrate compound is also important in determining the substitution/elimination ratio. Straight chain primary compounds show little tendency toward elimination, mainly since the S_N2 reaction is rapid. For example, ethyl bromide reacts with N_3^-, Cl^-, or $CH_3CO_2^-$ in acetone to give only substitution products. Even the strong base sodium ethoxide in ethanol gives virtually none of the elimination product. However, with more highly branched compounds, the S_N2 reaction is slower and attack at hydrogen can compete more favorably. Consequently, larger amounts of the elimination product are obtained. Some data are presented in Tables 8.6 and 8.7 for the reactions of various alkyl halides with acetate ion in acetone and ethoxide ion in ethanol.

Note the resulting generalizations that elimination byproducts are quite minor with simple primary halides, but with branching at either the α- or β-carbon, the alkene elimination products become increasingly important. The behavior of tertiary halides is more complex. Since they undergo S_N2 reactions so very slowly, one would expect that tertiary halides would give complete elimination, even with weak bases. However, tertiary halides can undergo substitution by another mechanism (next section). Consequently, the elimination/substitution ratio for tertiary

TABLE 8.6



$$R{-}Br + CH_3CO_2^- \xrightarrow{\text{acetone}} R{-}O\overset{O}{\overset{\|}{C}}CH_3 + Br^-$$

RBr	Per Cent Substitution	Per Cent Elimination
CH_3CH_2Br	100	0
$(CH_3)_2CHBr$	100	0
$(CH_3)_3CBr$	0	100
$(CH_3)_2CHCHBrCH_3$	11	89

TABLE 8.7

$$\text{R—Br} + CH_3CH_2O^- \xrightarrow{CH_3CH_2OH} ROCH_2CH_3 + Br^-$$

RBr	Per Cent Substitution	Per Cent Elimination
CH_3CH_2Br	99	1
$CH_3CH_2CH_2Br$	91	9
$CH_3CH_2CH_2CH_2Br$	90	10
$(CH_3)_2CHCH_2Br$	40	60
$(CH_3)_2CHBr$	20	80
$CH_3CH_2CHBrCH_2CH_3$	12	88

halides is highly dependent on reaction conditions. In general, they give mainly the elimination products, especially under conditions that favor the bimolecular mechanism (high concentrations of strong base).

8.8
S_N1 Reactions: Carbonium Ions

Ethyl bromide reacts very rapidly with ethoxide ion in refluxing ethanol (78°); reaction is complete after a few minutes. If ethyl bromide is refluxed in ethanol not containing any added sodium ethoxide, S_N2 displacement still occurs, but the reaction is exceedingly slow. After refluxing for 4 days, the reaction is only 50% complete. This reactivity difference is due to the fact that the negatively charged ethoxide ion is much more nucleophilic than the neutral ethanol molecule. On an equal concentration basis, ethoxide ion is more than 10,000 times more reactive than ethanol itself.

We saw earlier that tertiary alkyl halides do not react by the S_N2 mechanism. Yet *t*-butyl bromide reacts quite rapidly in pure ethanol. In refluxing ethanol, the half-life for reaction is only a few minutes! Various observations show that this reaction does not proceed by an S_N2 displacement even though the principal product is ethyl *t*-butyl ether, $(CH_3)_3COCH_2CH_3$. For one thing, the addition of ethoxide ion to an ethanol solution of ethyl bromide causes a large increase in the rate of reaction. The rate law for the reaction of ethyl bromide is

$$\text{rate} = k_1[C_2H_5Br] + k_2[C_2H_5Br][C_2H_5O^-]$$

The first term represents the reaction of ethyl bromide with neutral ethanol; because ethanol is the solvent and its concentration remains virtually unchanged, its concentration does not appear in the rate equation. The second term represents the reaction of ethyl bromide with ethoxide ion. For ethyl bromide, as we saw above, the reaction with ethoxide is much faster than the reaction with ethanol, that is, $k_2 \gg k_1$. Since k_1 is so small relative to k_2, the rate expression is approximately

$$\text{rate} = k_2[C_2H_5Br][C_2H_5O^-]$$

The rate of reaction of *t*-butyl bromide (*t*-BuBr) is given by a similar equation:

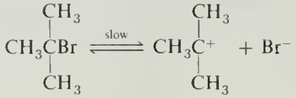
$$\text{rate} = k_1[t\text{-BuBr}] + k_2[t\text{-BuBr}][C_2H_5O^-]$$

Here, however, the second term is unimportant; $k_1 \gg k_2$. Addition of sodium ethoxide has no effect on the rate of reaction. Therefore, in this case the rate is effectively

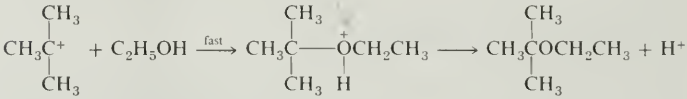
$$\text{rate} = k_1[t\text{-BuBr}]$$

This is true only for small concentrations of sodium ethoxide. As we saw earlier (sect. 8.7) high concentrations of strong base lead to bimolecular elimination. (E_2)

This change in kinetic behavior is consistent with a change in mechanism. With the tertiary alkyl halide, the rear of the molecule is effectively blocked and the S_N2 mechanism cannot operate. However, a competing mechanism is possible. A great deal of experimental work over the past several decades has established that this mechanism involves two steps. In the first step, ionization of the C—Br bond occurs and an intermediate **carbonium ion** is produced. The carbonium ion then reacts rapidly with solvent or whatever other nucleophiles are around.

(1) 

$$(CH_3)_3CBr \xrightleftharpoons{\text{slow}} (CH_3)_3C^+ + Br^-$$

(2) 

$$(CH_3)_3C^+ + C_2H_5OH \xrightarrow{\text{fast}} (CH_3)_3C\overset{+}{O}(H)CH_2CH_3 \longrightarrow (CH_3)_3COCH_2CH_3 + H^+$$

When a compound reacts with the solvent, as is the case here, the process is called a **solvolysis reaction.** This solvolysis reaction is classified mechanistically as **unimolecular nucleophilic substitution,** or **S_N1,** because only one species is involved in the rate-limiting step. A reaction coordinate diagram for the reaction is shown in Figure 8.12. In the intermediate carbonium ion, the central carbon has only a sextet of electrons (compare with the Lewis structure of methyl cation, Section 2.2). In orbital terms, the ion is best described in terms of a central sp^2 hybridized carbon with an empty p orbital (Figure 8.13).

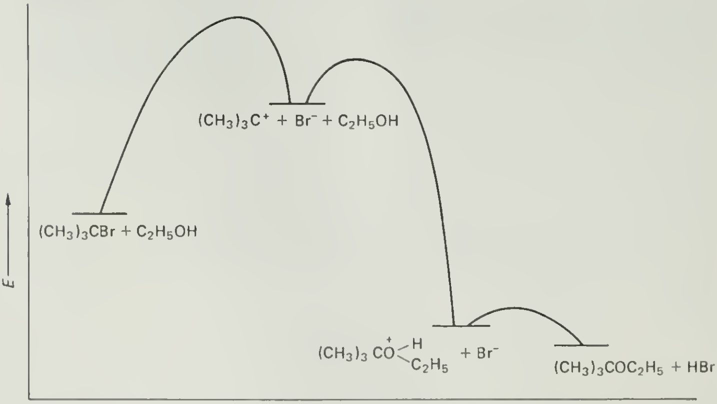


FIGURE 8.12 *Reaction coordinate diagram for the solvolysis of* t*-butyl bromide.*

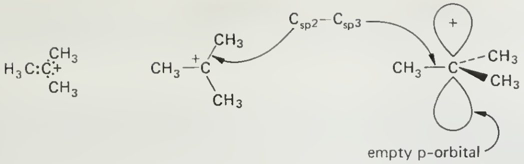


Figure 8.13 *The* t-*butyl cation.*

> The term **carbonium ion** has a long history of use in organic chemistry as a generic name for organic cations having an electron-deficient carbon with a sextet of electrons. This name has recently been challenged because comparable oxonium ions (for example, H_3O^+) and ammonium ions (NH_4^+) have electron octets, and the terms **carbocation** or **carbenium ion** have been suggested instead. In this text we will use the traditional term, carbonium ion, as a generic name for a class of organic cations, but specific ions will be referred to as alkyl cations (for example, methyl cation, *t*-butyl cation).

Note that the carbonium ion is planar; the central carbon and its three attached atoms all lie in one plane. This structure is favored because it places the three groups as far apart from one another as possible and allows the carbonium ion to achieve the strongest bonds and lowest energy. Alternatively, electrons in a 2*s* orbital are more stable than electrons in a 2*p* orbital. By using the *s* orbital to form three sp^2 hybrid orbitals, it is used most effectively in bonding; the remaining 2*p* orbital is left vacant.

It is important to point out that carbonium ions are highly reactive reaction intermediates. They have only a short, but finite, lifetime in solution. Under normal conditions, they cannot be observed directly in the reaction mixture because they react almost as soon as they are produced. However, carbonium ions vary widely in stability with structure. The enthalpies for ionization of various alkyl halides *in the gas phase* are summarized in Table 8.8. Note that ethyl cation is more stable than methyl cation but *n*-propyl and *n*-butyl cations are of similar stability. These systems may be described as **primary carbonium ions,** RCH_2^+. Isopropyl cation is an example of a **secondary carbonium ion,** R_2CH^+, and *t*-butyl cation is a **tertiary carbonium ion.**

CH_3^+	methyl cation
$CH_3CH_2^+$	ethyl cation, a **primary carbonium ion**
$(CH_3)_2CH^+$	isopropyl cation, a **secondary carbonium ion**
$(CH_3)_3C^+$	*t*-butyl cation, a **tertiary carbonium ion**

Table 8.8

Enthalpy for Ionization of Alkyl Chlorides in the Gas Phase

$RCl = R^+ + Cl^-$

R	$\Delta H°$, kcal mole^{-1}
CH_3	227
CH_3CH_2	195
$CH_3CH_2CH_2$	197
$CH_3CH_2CH_2CH_2$	197
$(CH_3)_2CH$	173
$(CH_3)_3C$	157

Table 8.8 shows that the relative stabilities of various carbonium ions is

$$\text{tertiary} > \text{secondary} > \text{primary} > \text{methyl}$$

Note that the difference in the ionization energy between methyl chloride and *t*-butyl chloride is 50 kcal mole^{-1} in the gas phase. In solution, the ions are solvated and ionization is facilitated. Consequently, the $\Delta H°$ for ionization is much lower than given in Table 8.8. Thus, the energy required to ionize *t*-butyl chloride in hydroxylic solvents is low enough that reaction proceeds at normal rates. Tertiary carbonium ions are rather common intermediates in organic reactions. Secondary carbonium ions are considerably less stable and much more difficult to produce, but they do occur as intermediates in some reactions. Primary carbonium ions are so much less stable that they virtually *never occur as reaction intermediates in solution.* These generalizations may be summarized as follows:

Alkyl Group	Occurrence of Carbonium Ion Intermediates	Occurrence of S_N2 Displacement Reactions
tertiary	common	never
secondary	sometimes	sometimes
primary	never	common
methyl	never	common

What factor is responsible for the difference in stability of various types of carbonium ions? Consider the methyl cation, CH_3^+. The C—H bonds in methyl cation *lie in the nodal plane of the vacant $2p_z$ orbital and hence cannot overlap with it.* In the ethyl cation, $CH_3CH_2^+$, there can be some overlap between this empty orbital and one of the bonds of the methyl group (Figure 8.14). This type of overlap is readily shown by quantum mechanical calculations. It has the effect of stabilizing the ion because electron density from an adjacent bond can "spill over" into the empty orbital. This results in spreading the positive charge over a larger volume. We shall see frequently that ions with concentrated charge are less stable and more reactive than ions in which the charge is spread over a greater volume. As more alkyl groups are attached to the carbonium ion carbon, it becomes even more stable.

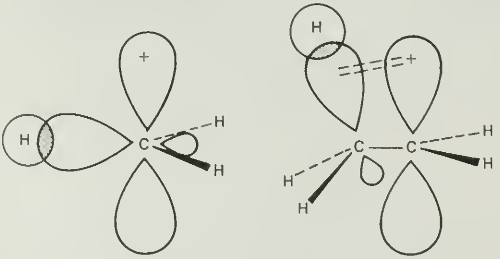


FIGURE 8.14 *Overlap of a* C—H *bond orbital with empty* p *orbital of a carbonium ion.*

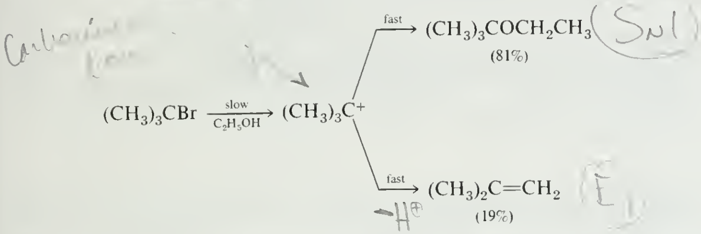
The interaction of a bond orbital with a p orbital as shown in Figure 8.14 is referred to as **hyperconjugation.** Its relationship to **conjugation** will become apparent when we get to Chapter 20.

The relative stabilities of carbonium ions can be understood on the basis of simple electrostatics. Electrons are attracted to nuclei and are repelled from other electrons. The electrons in a bond repel each other, but they are prevented from getting too far apart because of their attraction to the two nuclei in the bonded atoms. When there is an adjacent atom with a vacant orbital available for overlap and a positive charge, the original bonding pair of electrons can reduce their mutual repulsion by getting farther apart; they can do this and still maintain the stability of being associated with a positive nucleus. Electron repulsion is decreased in such a carbonium ion, and it is convenient to describe the result in terms of a spreading out of positive charge.

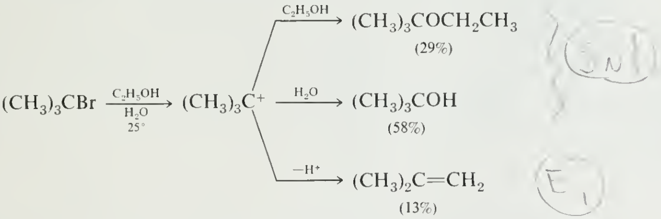
The solvolysis reaction of tertiary alkyl halides is only in part an S_N1 reaction. The intermediate carbonium ion can react rapidly in several alternative ways. Two of these reaction paths are

1. Reaction with any nucleophiles present (the S_N1 process)
2. Elimination of a proton (the E1 process).

These reactions are illustrated by the behavior of *t*-butyl bromide in ethanol at 25°. The solvolysis product, ethyl *t*-butyl ether, is produced along with a significant amount of the elimination product, an alkene.



In a mixed solvent, the carbonium ion can react with both components in addition to eliminating a proton. For example, in a mixture of 80% ethanol and 20% water, *t*-butyl bromide gives three products.



Because of the product mixtures that are so frequently obtained, solvolysis reactions are generally *not important* synthetic methods. Such reactions have been studied in great detail over the past several decades, but primarily for the purpose of studying the properties and relative stabilities of carbonium ions.

8.9
Summation: Elimination Versus Substitution; Unimolecular Versus Bimolecular

As we have seen in the preceding sections, alkyl halides may react with bases or nucleophiles in a variety of ways. We must recognize competitive elimination and substitution and must also consider whether the mechanism is unimolecular or bimolecular. How does one predict which of the four mechanisms, S_N1, S_N2, E1, or E2, will operate? Can the chemist control the reaction so as to produce a given product? There are no simple answers to these questions, but we may set out some broad generalizations.

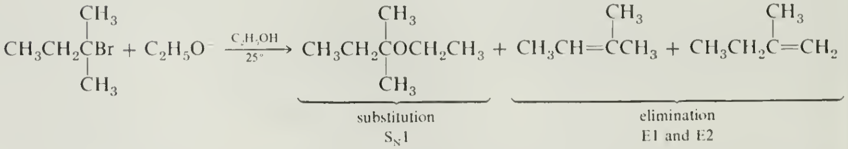
1. Primary alkyl halides that are not branched at C-2 always react by the bimolecular mechanisms, S_N2 or E2. With "good" nucleophiles, such as I^-, Br^-, Cl^-, HO^-, RO^-, R_3N, R_2S, and so on, the S_N2 mechanism dominates and high yields of the substitution products are obtained. Elimination may be achieved only by using bulky bases. We shall discuss the latter point in Section 12.5.A when we consider the preparation of alkenes.

Primary alkyl halides that are branched at C-2 give more elimination, because the S_N2 process is retarded. With good nucleophiles, substitution is still the principal product. With poor nucleophiles which are strong bases, elimination may dominate. Neopentyl halides undergo substitution only very slowly and cannot undergo elimination because there are no hydrogens on C-2.

2. In the absence of a strong base, tertiary halides react only by the unimolecular mechanisms, S_N1 and E1. Mixtures of substitution and elimination products result, and such reactions are usually not synthetically useful. However, the relative amounts of substitution and elimination products are strongly dependent on reaction conditions. In the presence of a strong base, elimination increases.

$$(CH_3)_3CBr + \underset{(2M)}{C_2H_5O^-Na^+} \xrightarrow[25^\circ]{C_2H_5OH} \underset{(7\%)}{(CH_3)_3COCH_2CH_3} + \underset{(93\%)}{(CH_3)_2C{=}CH_2}$$

In this reaction, the substitution product and part of the elimination product are produced by the unimolecular pathway, just as above. However, the main product is now the elimination product, most of which is produced by the E2 mechanism. Since the rate of the E2 process increases as we increase the base concentration whereas the rates of the S_N1 and E1 processes do not, tertiary halides give more elimination at high base concentrations. Such behavior is typical for tertiary alkyl halides. Another example is 2-bromo-2-methylbutane, which gives the corresponding ether by the S_N1 mechanism and a mixture of two elimination products.



$$CH_3CH_2C(CH_3)_2Br + C_2H_5O^- \xrightarrow[25^\circ]{C_2H_5OH} \underbrace{CH_3CH_2C(CH_3)_2OCH_2CH_3}_{\substack{\text{substitution}\\ S_N1}} + \underbrace{CH_3CH{=}C(CH_3)CH_3 + CH_3CH_2C(CH_3){=}CH_2}_{\substack{\text{elimination}\\ \text{E1 and E2}}}$$

Data for the product composition as a function of base concentration are given in Table 8.9. Thus, in many cases, *elimination* of a tertiary alkyl halide is a useful preparative process.

3. Secondary alkyl halides present the most complex behavior. With a good nucleophile, the S_N2 mechanism is favored and good yields of the substitution

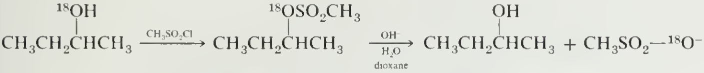
TABLE 8.9
Reaction of 2-Bromo-2-methylbutane with $NaOC_2H_5$ *in* C_2H_5OH

$[C_2H_5O^-]$, *M*	Per Cent Substitution	Per Cent Elimination
0	64	36
0.02	54	46
0.08	44	56
1.00	2	98

product may be obtained. With high concentrations of a strong base, the E2 mechanism is favored, and good yields of the elimination products may be obtained.

PROBLEMS

1. (R)-2-Butanol, labeled with ^{18}O, is subjected to the following sequence of reactions:



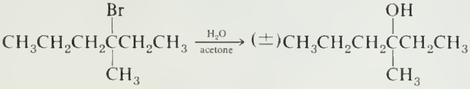
$$CH_3CH_2\overset{^{18}OH}{C}HCH_3 \xrightarrow{CH_3SO_2Cl} CH_3CH_2\overset{^{18}OSO_2CH_3}{C}HCH_3 \xrightarrow[H_2O \text{ dioxane}]{OH^-} CH_3CH_2\overset{OH}{C}HCH_3 + CH_3SO_2{-}^{18}O^-$$

What is the absolute configuration of the product?

refers to R-S co [illegible]

2. 2-Bromo-, 2-chloro- and 2-iodo-2-methylbutanes react at different rates with pure methyl alcohol but produce the same mixture of 2-methoxy-2-methylbutane, 2-methyl-1-butene, and 2-methyl-2-butene as products. Explain these results briefly in terms of the reaction mechanism.

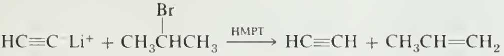
3. Explain each of the following observations:
   (a) (S)-3-Bromo-3-methylhexane reacts in aqueous acetone to give racemic 3-methyl-3-hexanol.



$$CH_3CH_2CH_2\underset{CH_3}{\overset{Br}{C}}CH_2CH_3 \xrightarrow[\text{acetone}]{H_2O} (\pm)CH_3CH_2CH_2\underset{CH_3}{\overset{OH}{C}}CH_2CH_3$$

   (b) When lithium acetylide is treated with *n*-propyl bromide in hexamethylphosphoric triamide, 1-pentyne is produced in 75% yield. However, if isopropyl bromide is used, the major products are acetylene and propene.

$$HC{\equiv}C^-Li^+ + CH_3CH_2CH_2Br \xrightarrow{HMPT} \underset{(75\%)}{CH_3CH_2CH_2C{\equiv}CH}$$



$$HC{\equiv}C^-Li^+ + CH_3\overset{Br}{C}HCH_3 \xrightarrow{HMPT} HC{\equiv}CH + CH_3CH{=}CH_2$$

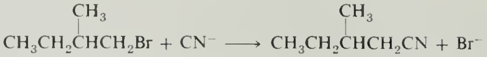
4. For each of the following pairs of reactions, predict which one is faster and explain why.

$$\text{(a)}\quad (CH_3)_2CHCH_2Cl + N_3^- \xrightarrow{C_2H_5OH} (CH_3)_2CHCH_2N_3 + Cl^-$$

$$(CH_3)_2CHCH_2I + N_3^- \xrightarrow{C_2H_5OH} (CH_3)_2CHCH_2N_3 + I^-$$

(b) $(CH_3)_3CBr \xrightarrow[\Delta]{H_2O} (CH_3)_3COH + HBr$

$(CH_3)_2CHBr \xrightarrow[\Delta]{H_2O} (CH_3)_2CHOH + HBr$

(c) 
$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2Br + CN^- \longrightarrow CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2CN + Br^-$

$CH_3CH_2CH_2CH_2Br + CN^- \longrightarrow CH_3CH_2CH_2CH_2CN + Br^-$

(d) $CH_3CH_2Br + SH^- \xrightarrow[\text{(solvent)}]{CH_3OH} CH_3CH_2SH + Br^-$

$CH_3CH_2Br + SH^- \xrightarrow[\text{(solvent)}]{(CH_3)_2NCHO} CH_3CH_2SH + Br^-$

(e) $(CH_3)_2CHBr + NH_3 \xrightarrow{CH_3OH} (CH_3)_2CH\overset{+}{N}H_3\ Br^-$

$CH_3CH_2CH_2Br + NH_3 \xrightarrow{CH_3OH} CH_3CH_2CH_2\overset{+}{N}H_3\ Br^-$

(f) $CH_3I + Na^+OH^- \xrightarrow{H_2O} CH_3OH + Na^+I^-$

$CH_3I + Na^+SH^- \xrightarrow{H_2O} CH_3SH + Na^+I^-$

(g) $CH_3Br + (CH_3)_3N \longrightarrow (CH_3)_4N^+Br^-$

$CH_3Br + (CH_3)_3P \longrightarrow (CH_3)_4P^+Br^-$

(h) $SCN^- + CH_3CH_2Br \xrightarrow{\text{aq. } C_2H_5OH} CH_3CH_2SCN + Br^-$

$SCN^- + CH_3CH_2Br \xrightarrow{\text{aq. } C_2H_5OH} CH_3CH_2NCS + Br^-$

(i) $N_3^- + (CH_3)_2CHCH_2Br \xrightarrow{C_2H_5OH} (CH_3)_2CHCH_2N_3 + Br^-$

$C_6H_5S^- + (CH_3)_2CHCH_2Br \xrightarrow{C_2H_5OH} (CH_3)_2CHCH_2SC_6H_5 + Br^-$

[Note $pK_a(HN_3) \simeq pK_a(C_6H_5SH)$.]

5. Of the following nucleophilic substitution reactions, which ones will probably occur and which will probably not occur or be very slow. Explain.
   (a) $CH_3CN + I^- \longrightarrow CH_3I + CN^-$
   (b) $CH_3F + Cl^- \longrightarrow CH_3Cl + F^-$
   (c) $(CH_3)_3COH + NH_2^- \longrightarrow (CH_3)_3CNH_2 + OH^-$
   (d) $CH_3OSO_2OCH_3 + Cl^- \longrightarrow CH_3Cl + CH_3OSO_3^-$
   (e) $CH_3NH_2 + I^- \longrightarrow CH_3I + NH_2^-$
   (f) $CH_3CH_2I + N_3^- \longrightarrow CH_3CH_2N_3 + I^-$
   (g) $CH_3CH_2OH + F^- \longrightarrow CH_3CH_2F + OH^-$

6. Give a specific example of two related reactions having different rates for which the principal reason for the relative reactivities is each of the following:
   (a) The less basic leaving group is more reactive.
   (b) Sulfur is more polarizable than nitrogen.
   (c) Tertiary carbonium ions are more stable than secondary carbonium ions.
   (d) Steric hindrance.
   (e) Protic solvents can form hydrogen bonds.
   (f) E2 elimination is favored by less polarizable bases.

7. Of the following statements, which are true for nucleophilic substitutions occurring by the S_N2 mechanism?
   (a) Tertiary alkyl halides react faster than secondary.
   (b) The absolute configuration of the product is opposite to that of the reactant when an optically active substrate is used.

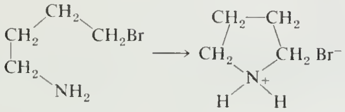
(c) The reaction shows first-order kinetics.
(d) The rate of reaction depends markedly on the nucleophilicity of the attacking nucleophile.
(e) The probable mechanism involves only one step.
(f) Carbonium ions are intermediates.
(g) The rate of reaction is proportional to the concentration of the attacking nucleophile.
(h) The rate of reaction depends on the nature of the leaving group.

8. Answer problem 7 for nucleophilic substitutions occurring by the S_N1 mechanism.

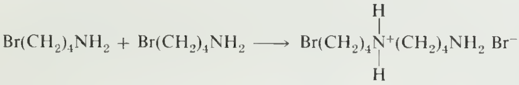
9. The reaction of methyl bromide with methylamine to give dimethylammonium bromide is a typical S_N2 reaction that shows second-order kinetics.

$$CH_3Br + CH_3NH_2 \longrightarrow (CH_3)_2NH_2{}^+Br^-$$

However, the analogous cyclization of 4-bromobutylamine shows first-order kinetics. Explain.



The foregoing **intramolecular** displacement reaction is a useful method for making **cyclic amines.** However, a competing side-reaction is the intermolecular displacement



$$Br(CH_2)_4NH_2 + Br(CH_2)_4NH_2 \longrightarrow Br(CH_2)_4\overset{\displaystyle H}{\underset{\displaystyle H}{N^+}}(CH_2)_4NH_2\ Br^-$$

Suggest a way in which this side reaction may be minimized.

10. Consider the reaction of isopropyl iodide with various nucleophiles. For each pair, predict which will give the larger substitution/elimination ratio.
(a) SCN^- or OCN^-
(b) I^- or Cl^-
(c) $N(CH_3)_3$ or $P(CH_3)_3$
(d) CH_3S^- or CH_3O^-

11. HCN has $pK_a = 9.21$; acetic acid has $pK_a = 4.76$.
(a) What is the difference in the standard free energies ($\Delta\Delta G°$) for these two acid-base equilibria?
(b) What is the equilibrium constant and $\Delta G°$ for the reaction

$$HCN + CH_3CO_2^- \longrightarrow CN^- + CH_3CO_2H$$

(c) The second-order rate constants, k_2, for reaction with methyl iodide in methyl alcohol at 25° for cyanide ion and acetate ion are, respectively, 6.5×10^{-4} and $2.7 \times 10^{-6}\ M^{-1}\ \text{sec}^{-1}$. What is the relative rate, $k_2(CN^-)/k_2(CH_3CO_2^-)$? To what value of $\Delta\Delta G^\ddagger$ does this relative rate correspond?

12. (a) In Figure 8.4 the nucleophiles with first-row elements form an approximately linear relation. What is the slope of this correlation line?* What does this slope suggest about the amount of charge remaining on the attacking group?
(b) Methyl iodide is 40 times more reactive than methyl chloride towards thiosulfate ion in water solution. HI is about 2.5 pK_a units more acidic than HCl. What do these data imply concerning the amount of negative charge on the leaving group in the transition state of this S_N2 reaction?

---

*If you have access to a small computer and suitable programs, calculate the least squares slope and the standard deviation and correlation coefficient of the slope.

CHAPTER 9
Organometallic Compounds

9.1
Structure

Organometallic compounds are substances in which an organic radical is bonded directly to a metal, R—M. Since metals are **electropositive** elements, C—M bonds can have a high degree of **ionic character.** That is, dipolar resonance structures are often important contributers to the structure of such compounds.

$$\left[\mathrm{R{-}M} \longleftrightarrow \mathrm{R^{-}\ M^{+}}\right] \equiv \overset{\delta-}{\mathrm{R}}{-}\overset{\delta+}{\mathrm{M}}$$

The degree of covalency of such C—M bonds depends markedly on the metal and is related to the **electronegativity** of the metal. Electronegativity is defined as the tendency of an element to attract electrons. A semiquantitative scale has been constructed in which each element is assigned an electronegativity value. On this scale, a larger number signifies a greater affinity for electrons. When two elements of differing electronegativity are bonded, the bond will be polar, with the "center of gravity" of electron density in the bond closer to the more electronegative element. The greater the difference in electronegativity, the more polar is the bond. Pauling electronegativities for carbon and several metals are listed in Table 9.1.

Factors other than electronegativity differences are also important in determining the degree of covalency of a C—M bond, but we shall not go into these other factors here. The net result is a gradation. In some cases, such as alkylmercury, alkyllead, and alkylsilicon compounds, the bonds are not polarized to any great degree. For other compounds, such as alkyllithium and alkylmagnesium compounds, the C—M bond is more highly polar, but the bonds are still covalent.

TABLE 9.1
Electronegativity Values for Some Elements

Group	IA	IIA	IB	IIB	IIIA	IVA
	H 2.1					
	Li 1.0	Be 1.5			B 2.0	C 2.5
	Na 0.9	Mg 1.2			Al 1.5	Si 1.8
	K 0.8	Ca 1.0	Cu 1.9	Zn 1.6		Ge 1.7
				Cd 1.7		Sn 1.7
				Hg 1.9		Pb 1.7

In other cases, such as alkylsodium and alkylpotassium compounds, the bonds are highly ionic and the compounds have salt-like properties.

9.2
Nomenclature

Organometallic compounds are named by prefixing the name of the metal with the appropriate organic radical name. The names are written as one word.

$(CH_3)_3CLi$ *t*-butyllithium	$(CH_3CH_2)_2Mg$ diethylmagnesium	$(CH_3)_3Al$ trimethylaluminum
$(CH_3CH_2CH_2)_2Cd$ dipropylcadmium	$(CH_3CH_2)_2Zn$ diethylzinc	$(CH_3)_2Hg$ dimethylmercury
CH_3Cu methylcopper	$(CH_3)_4Si$ tetramethylsilicon	$(CH_3CH_2)_4Pb$ tetraethyllead

Compounds of boron, tin, and silicon are also named as derivatives of the simple hydrides, borane, BH_3; stannane, SnH_4; and silane, SiH_4. These compounds are indexed by *Chemical Abstracts* in this manner.

$(CH_3CH_2)_3B$ triethylborane	$(CH_3CH_2)_4Sn$ tetraethylstannane	$(CH_3)_3SiCH_2CH_3$ ethyltrimethylsilane

In some organometallic compounds, the valences of the metal are not all utilized in bonding to carbon but include bonds to inorganic atoms as well. Such compounds are named as organic derivatives of the corresponding inorganic salt.

CH_3CH_2MgBr ethylmagnesium bromide	CH_3HgCl methylmercuric chloride	$CH_3CH_2AlCl_2$ ethylaluminum dichloride

Compounds of the type RMgX are known as **Grignard reagents.** As we shall see, they are exceedingly important intermediates in organic synthesis.

9.3
Physical Properties

The melting points and boiling points of some organometallic compounds are summarized in Table 9.2. If sufficient caution is exercised, many organometallics may be prepared and handled in the same manner as other organic compounds. However, as we shall see, many organometallics react vigorously with water or other protic compounds and with oxygen. Consequently, care must be taken in performing such operations as distillation and recrystallization.

Most of the organometallic compounds in Table 9.2 decompose in water, but they are soluble in various inert aprotic organic solvents. Typical solvents are ethers and alkanes. Because of their solubility in convenient organic solvents and their extreme reactivity, many organometallic compounds used in organic syntheses are normally not purified, but are prepared and used in such solutions without isolation.

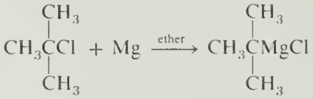
TABLE 9.2
Physical Properties of Organometallic Compounds

Compound	Melting Point, °C	Boiling Point, °C
CH_3CH_2Li	95	subl. 95 (aggregated)
$CH_3CH_2CH_2CH_2Li$	—	dec. 150 (aggregated)
$(CH_3)_2Mg$	>240	—(probably polymeric)
$(CH_3)_3Al$	0	130
$(CH_3CH_2)_3Al$	−51	194
CH_3AlCl_2	73	97–100 (100 torr)
$(CH_3)_4Si$	—	26.5
$(CH_3CH_2)_4Si$	—	153
$(CH_3)_2Zn$	−42	46
$(CH_3CH_2)_2Zn$	—	118
$(CH_3CH_2CH_2)_2Zn$	—	146
$(CH_3)_2Cd$	−4.5	106
$(CH_3CH_2)_2Cd$	−21	64 (19 torr)
$(CH_3)_2Hg$	—	96
$(CH_3CH_2)_2Hg$	—	159
CH_3CH_2HgI	186	—
CH_3CH_2HgCl	193	subl. 40

9.4
Preparation of Organometallic Compounds

A. *Reaction of an Alkyl Halide with a Metal*

This method is most generally used for the laboratory preparation of organolithium and organomagnesium compounds. The reaction is normally carried out by treating the metal with an ether or hydrocarbon solution of the alkyl halide.

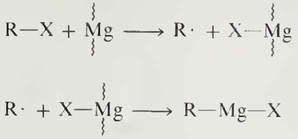


$$(CH_3)_3CCl + Mg \xrightarrow{\text{ether}} (CH_3)_3CMgCl$$

A solution of 227 g of *t*-butyl chloride in 1300 ml of dry ether is stirred in contact with 61 g of magnesium turnings for 6-8 hr. A cloudy gray solution approximately 2 *M* in *t*-butylmagnesium chloride is obtained. This solution is used directly for further reactions.

This type of reaction is our first example of a heterogeneous reaction—a reaction that occurs at the interface between two different phases. The alkyl halide in solution must react with magnesium on the surface of solid magnesium. In such reactions the surface area and its character are important. In the preparation of Grignard reagents the magnesium is usually used in the form of metal turnings.

The reaction mechanism consists of several steps:



$$R{-}X + \underset{\wr}{\overset{\wr}{Mg}} \longrightarrow R\cdot + X{-}\underset{\wr}{\overset{\wr}{Mg}}$$

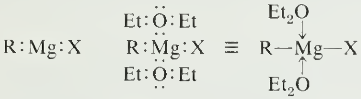
$$R\cdot + X{-}\underset{\wr}{\overset{\wr}{Mg}} \longrightarrow R{-}Mg{-}X$$

Reaction of RX at the magnesium surface produces an alkyl radical and a Mg—X bond probably still associated with the metal surface. The resulting free radical, R·, then reacts with the ·MgX to produce the Grignard reagent, RMgX. The principal side reactions involve alternative reactions of organic radicals, dimerization, and disproportionation.

$$CH_3CH_2CH_2CH_2\cdot + CH_3CH_2CH_2CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$$
$$CH_3CH_2CH_2CH_2\cdot + CH_3CH_2CH_2CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_3 + CH_3CH_2CH{=}CH_2$$

However, for simple alkyl halides the yields of alkylmagnesium halide are high—frequently above 90%. The reaction works well with chlorides, bromides, and iodides. Reaction of alkyl chlorides is frequently somewhat sluggish and iodides are generally expensive. Hence, alkyl bromides are common laboratory reagents in Grignard syntheses.

A suitable solvent is essential for formation of the Grignard reagent because of the necessity for solvating the magnesium. Magnesium metal has two valence electrons that can be donated to form the Mg^{2+} ion. However, in an alkylmagnesium halide, the bonds to the magnesium have some covalent character. The Lewis structure of a covalent alkylmagnesium compound has an incomplete octet which it fills by coordinating with any available Lewis base—such as an ether.



$$R{:}Mg{:}X \qquad \begin{matrix} Et{:}\ddot{\underset{\cdot\cdot}{O}}{:}Et \\ R{:}\ddot{\underset{\cdot\cdot}{Mg}}{:}X \\ Et{:}\ddot{\underset{\cdot\cdot}{O}}{:}Et \end{matrix} \equiv \begin{matrix} Et_2O \\ \downarrow \\ R{-}Mg{-}X \\ \uparrow \\ Et_2O \end{matrix}$$

The symbol "Et" stands for the ethyl group, CH_3CH_2—. Specific alkyl groups are frequently abbreviated in this way; that is, Me ≡ CH_3—, *n*-Pr ≡ $CH_3CH_2CH_2$—, and so on.

The reaction is commonly carried out by adding an ether solution of the alkyl halide to magnesium turnings stirred in ether in a three-necked flask. The reaction is exothermic, particularly with bromides and iodides and a reflux condenser is provided for returning the boiling ether. It is essential to maintain anhydrous conditions throughout the reaction because Grignard reagents react rapidly with traces of moisture.

Alkyllithium compounds are prepared in the same manner.

$$CH_3CH_2CH_2CH_2Br + 2Li \xrightarrow{\text{ether}} CH_3CH_2CH_2CH_2Li + LiBr$$

A solution of 68.5 g of *n*-butyl bromide in 300 ml of dry ether is added slowly to 8.6 g of lithium wire. The mixture is stirred at −10° for about 1 hr, during which time all of the lithium dissolves. The resulting ether solution of butyllithium is stored under nitrogen in a well-stoppered flask.

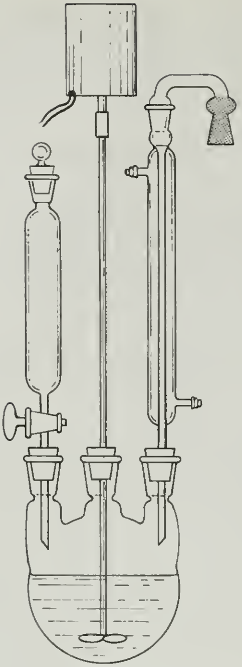


Figure 9.1 *Typical apparatus used for Grignard reactions. The three-necked flask carries a dropping funnel, stirring motor, and reflux condenser equipped with a drying tube.*

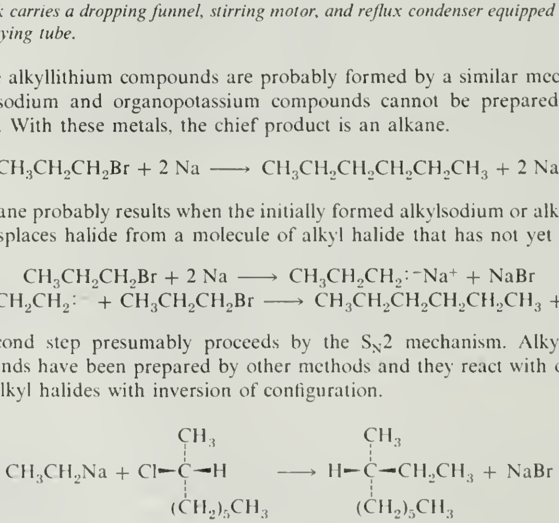
These alkyllithium compounds are probably formed by a similar mechanism. Organosodium and organopotassium compounds cannot be prepared in this manner. With these metals, the chief product is an alkane.

$$2\ CH_3CH_2CH_2Br + 2\ Na \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_3 + 2\ NaBr$$

The alkane probably results when the initially formed alkylsodium or alkylpotassium displaces halide from a molecule of alkyl halide that has not yet reacted.

$$CH_3CH_2CH_2Br + 2\ Na \longrightarrow CH_3CH_2CH_2{:}^-Na^+ + NaBr$$
$$CH_3CH_2CH_2{:}\ + CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_3 + Br^-$$

The second step presumably proceeds by the S_N2 mechanism. Alkylsodium compounds have been prepared by other methods and they react with optically active alkyl halides with inversion of configuration.



$$CH_3CH_2Na + \begin{array}{c} CH_3 \\ | \\ Cl-C-H \\ | \\ (CH_2)_5CH_3 \end{array} \longrightarrow \begin{array}{c} CH_3 \\ | \\ H-C-CH_2CH_3 \\ | \\ (CH_2)_5CH_3 \end{array} + NaBr$$

(R)-2-chlorooctane

(R)-3-methylnonane

Note that in this example, inversion has occurred at the reaction center. However, the reactant and product are both (R) because the leaving group has priority *a* and the incoming group has priority *b*.

The reactions of alkali metals with alkyl halides are heterogeneous surface reactions and may be more complex than the foregoing discussion would indicate. In some cases radical coupling reactions are required to explain the reaction products. For an example, see problem 7, part (e).

Tetraethyllead, which is important as an "antiknock" compound (Section 5.4), is prepared commercially by a version of this method. In this case, ethyl chloride is allowed to react with a lead-sodium alloy.

$$4\ C_2H_5Cl + 4\ Na{-}Pb \longrightarrow (C_2H_5)_4Pb + 3\ Pb + 4\ NaCl$$

The metallic lead produced in the reaction is recovered, reconverted to Na-Pb, and recycled. Over a million tons of tetraethyllead were produced in 1969 and used almost entirely in gasoline. However, the use of lead-free gasoline is currently being encouraged in order to reduce the dispersion of lead into the environment by automobiles.

Although many other organometallic compounds may be prepared by direct reaction of the metal with an alkyl halide (for example, C_2H_5ZnI, CH_3HgCl), a more convenient and general laboratory method is metal exchange with an organolithium or organomagnesium compound (next section).

B. *Reaction of Organometallic Compounds with Salts*

One of the most useful methods for preparing most organometallic compounds in the laboratory is the exchange reaction of one organometallic with a salt to give a new organometallic and a new salt.

$$RM + M'X \rightleftharpoons RM' + MX$$

Although this is an equilibrium process, the equilibrium constant is dominated by the reduction potentials of the two metal cations. An abbreviated list of **standard reduction potentials** is contained in Table 9.3.

TABLE 9.3
Standard Reduction Potentials

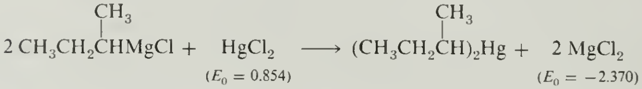
Reaction	E_0, volts
$Li^+ + e = Li$	−3.045
$Mg^{2+} + 2\,e = Mg$	−2.370
$Al^{3+} + 3\,e = Al$	−1.660
$Si^{4+} + 4\,e = Si$	−0.840
$Zn^{2+} + 2\,e = Zn$	−0.763
$Cd^{2+} + 2\,e = Cd$	−0.402
$H^+ + e = \frac{1}{2}H_2$	0
$Sn^{4+} + 4\,e = Sn$	0.014
$Cu^+ + e = Cu$	0.522
$Hg^{2+} + 2\,e = Hg$	0.854

In general, reaction will proceed so that the more electropositive metal (more negative E_0) will exist as the more ionic inorganic salt. For example, Grignard reagents react readily with cadmium chloride to give the organocadmium compound and magnesium chloride.

$$2\,CH_3CH_2MgCl + \underset{(E_0 = 0.402)}{CdCl_2} \xrightarrow{\text{ether}} (CH_3CH_2)_2Cd + \underset{(E_0 = -2.370)}{2\,MgCl_2}$$

In a similar way, Grignard reagents may be used to prepare tetraalkylsilanes and dialkylmercury compounds.

$$4\,CH_3MgCl + \underset{(E_0 = -0.840)}{SiCl_4} \longrightarrow (CH_3)_4Si + \underset{(E_0 = -2.370)}{4\,MgCl_2}$$



$$2\,CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HMgCl + \underset{(E_0 = 0.854)}{HgCl_2} \longrightarrow (CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}H)_2Hg + \underset{(E_0 = -2.370)}{2\,MgCl_2}$$

This observation may be understood by considering the nature of the C—M bond in organometallic compounds. The standard reduction potential of a metal is a measure of its tendency to give up electrons and become an ion in aqueous solution. Metals with very negative reduction potentials give up electrons readily (that is, are good reducing agents). Metals with positive reduction potentials prefer to "hold on" to their electrons (that is, are poor reducing agents). The C—M bond has some covalent character, as do the M—M bonds in the free metal itself; in both cases the metal is formally neutral. In equilibria such as those above, the metal with the more positive reduction potential tends more to acquire electrons and prefers to exist as the organometallic compound. The metal with the more negative reduction potential prefers to exist as the ionic salt. Because lithium and magnesium are such highly electropositive elements and because their alkyl derivatives are so readily available, alkyllithium compounds and Grignard reagents are usually used as starting materials in this synthetic route to other organometallics. Examples using alkyllithium compounds are

$$CH_3Li + \underset{(E_0 = +0.522)}{CuI} \longrightarrow CH_3Cu + \underset{(E_0 = -3.045)}{LiI}$$

$$4\,n\text{-}C_4H_9Li + \underset{(E_0 = +0.014)}{SnCl_4} \longrightarrow (n\text{-}C_4H_9)_4Sn + \underset{(E_0 = -3.045)}{4\,LiCl}$$

One final point should be specified. The standard reduction potentials as given in Table 9.3 refer to the electrical potentials associated with conversion of a dilute aqueous solution of the metal salt to the free metal. Such potentials will be different for different metal salts in organic solvents, but the relative ranking of electropositive character generally remains unchanged.

C. *Special Methods of Preparation*

We shall see in Chapter 12 that some organometallic compounds may be prepared by additions to alkenes. Hydroboration and oxymercuration, which we shall study in Section 12.6, are examples. Some organometallic compounds may be prepared by treating other organometallics with a free metal or by the disproportionation of two organometallics.

$$(CH_3CH_2)_2Hg + 2\,Na \longrightarrow 2\,CH_3CH_2Na + Hg$$
$$(CH_3)_2Hg + 2\,CH_3CH_2Li \longrightarrow (CH_3CH_2)_2Hg + 2\,CH_3Li$$

However, these reactions are complicated and difficult to generalize. We shall not consider them further.

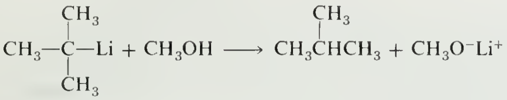
9.5
Reactions of Organometallic Compounds

A. *Hydrolysis*

Organometallic compounds in which the metal has an electronegativity value of about 1.7 or less (Table 9.1) react with water to give the hydrocarbon and a metal hydroxide. The more electropositive the metal is, the faster is the hydrolysis. Alkyllithium, alkylmagnesium, and alkylaluminum compounds react violently with water.

$$CH_3Li + H_2O \longrightarrow CH_4 + LiOH$$
$$CH_3CH_2MgBr + H_2O \longrightarrow CH_3CH_3 + HOMgBr$$
$$(CH_3)_3Al + 3\,H_2O \longrightarrow 3\,CH_4 + Al(OH)_3$$

Such compounds react similarly with other hydroxylic compounds, such as alcohols and carboxylic acids.

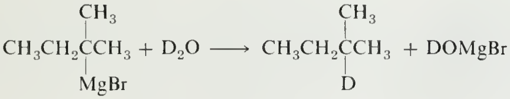


$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}Li + CH_3OH \longrightarrow CH_3\overset{CH_3}{C}HCH_3 + CH_3O^-Li^+$$

They also react with other compounds having relatively acidic hydrogens, such as thiols and amines.

Since the product of hydrolysis is an alkane, hydrolysis is not a very useful preparative reaction. However, it is important to recognize the limitation that this ready hydrolysis puts on the use of such organometallic compounds for other purposes. For example, it is not possible to prepare a Grignard reagent from an alkyl halide which also has an acidic hydrogen in the molecule, such as $ClCH_2CH_2CH_2OH$.

One important use for such hydrolysis reactions is **specific deuteration.** When one carries out the hydrolysis with heavy water, deuterium oxide, the product is an alkane containing a deuterium at the position formerly occupied by the metal.



$$CH_3CH_2\overset{CH_3}{\underset{MgBr}{C}}CH_3 + D_2O \longrightarrow CH_3CH_2\overset{CH_3}{\underset{D}{C}}CH_3 + DOMgBr$$

2-methylbutane-2-*d*

The nomenclature used for isotopically labeled compounds is implied in this example. The use of -*d* for deuterium and -*t* for tritium is common although generally the isotope is specified by the atomic symbol and a prefixed superscript giving the atomic mass of the isotope; for example, our labeled compound may also be named as 2-methylbutane-2-^{2}H. Finally, deuterium may be specified by a prefix as in 2-deuterio-2-methylbutane.

Heavy water is now readily available and this reaction is an excellent way of making hydrocarbons "labeled" with deuterium in a specific position. After reaction, the magnesium salts are removed and the ether solution of the labeled hydrocarbon is dried and distilled.

Alkylzinc and alkylcadmium compounds also react with protic materials, but their reactions are not so violent. Compounds of silicon, tin, mercury, and lead are unaffected by water, but in acidic solution they also undergo hydrolysis.

$$(C_2H_5)_4Si + 4\,HCl \xrightarrow{H_2O} 4\,CH_3CH_3 + SiCl_4$$

B. *Reaction with Halogens*

Most organometallic reagents react vigorously with chlorine and bromine (the reduction potential $Cl_2 + 2\,e = 2\,Cl^-$ is +1.358 volts).

$$RM + Cl_2 \longrightarrow RCl + M^+Cl^-$$

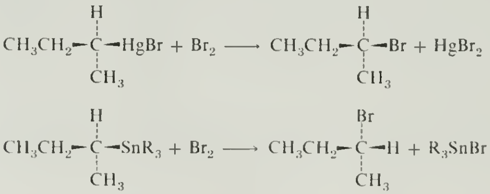
The reaction is not preparatively useful because the product is an alkyl halide and the organometallic is ultimately derived from the alkyl halide.

There has been considerable interest in this reaction because it may be considered as an **electrophilic substitution** reaction.

$$RM + Br^+ \longrightarrow RBr + M^+$$

The symbol Br^+ is a simplified representation that emphasizes the ability of Br_2 to react as an electrophile. Mechanistically, there seem to be two paths for such reactions, corresponding to the S_N1 and S_N2 mechanisms we studied in Chapter 8. In this case, the mechanisms are called S_E1, **unimolecular electrophilic substitution**, and S_E2, **bimolecular electrophilic substitution.**

The S_E1 mechanism is only important with organometallic compounds in which the C—M bond is highly ionic. Bimolecular electrophilic substitution is more common and may occur with either **retention** or **inversion** of stereochemistry at the alkyl group.

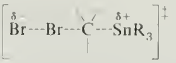


$$CH_3CH_2\text{—}\overset{H}{\underset{CH_3}{C}}\text{—}HgBr + Br_2 \longrightarrow CH_3CH_2\text{—}\overset{H}{\underset{CH_3}{C}}\text{—}Br + HgBr_2$$

$$CH_3CH_2\text{—}\overset{H}{\underset{CH_3}{C}}\text{—}SnR_3 + Br_2 \longrightarrow CH_3CH_2\text{—}\overset{Br}{\underset{CH_3}{C}}\text{—}H + R_3SnBr$$

Current research is directed toward the detailed study of these mechanisms.

The transition state for the S_E2 mechanism may be depicted as:



$$\left[\overset{\delta-}{Br}\text{---}Br\text{---}C\text{---}\overset{\delta+}{Sn}R_3\right]^{\ddagger}$$

Note the similarity between this transition state and that for the S_N2 mechanism (Section 8.2). Steric factors *at carbon* in the two transition states are almost identical. In fact, if one plots the logarithms of the rates of the S_N2 reaction of a series of alkyl halides versus the logarithms of the rates of the S_E2 reaction of a comparable alkyltin compound, a straight-line relationship is observed.

C. *Reaction with Oxygen*

Organic compounds of many metals react rapidly with oxygen. Some are so reactive that they spontaneously inflame in air, often with spectacular consequences.

> Alkylboranes burn with a brilliant green flame. In his graduate student days, one of the authors was briefly immersed in a sea of such green fire. Only the rapid reflexes of a lab partner with a fire extinguisher allowed the current textbook to come to fruition.

Because of this reactivity, it is common to carry out all organometallic reactions under an inert atmosphere such as nitrogen or argon.

D. *Reaction with Other Organometallic Compounds*

There are many reactions of one organometallic compound with another. Rather than going extensively into this fairly complex area, we shall simply mention one reaction, because the product is itself a reagent of considerable utility. Alkylcopper compounds react with alkyllithium compounds to give products known as **cuprates.** An example is the reaction of methyllithium with methylcopper to yield lithium dimethylcopper.

$$CH_3Li + CH_3Cu \longrightarrow (CH_3)_2CuLi$$

In practice, the cuprates can be prepared more conveniently by simply adding one equivalent of cuprous iodide to two equivalents of the alkyllithium compound. Since Cu^+ has a much more positive reduction potential than lithium, methylcopper is formed and then reacts with the second equivalent of methyllithium, giving the cuprate.

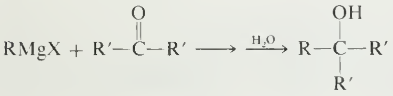
$$2\,CH_3CH_2CH_2Li + CuI \longrightarrow (CH_3CH_2CH_2)_2CuLi + LiI$$

The exact structures of these cuprates are not known, but in solution, they appear to exist in a dimeric or tetrameric form.

9.6
Uses of Organometallic Compounds

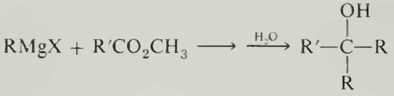
Organometallic compounds are important reagents for the synthesis of other organic compounds. The most important compounds in this respect are the Grignard reagents. In subsequent chapters, we shall encounter many reactions of these versatile compounds, a few of which are summarized briefly here.

$$RMgX + CO_2 \longrightarrow \xrightarrow{H_3O^+} RCOOH \qquad \text{(Section 17.6.B)}$$



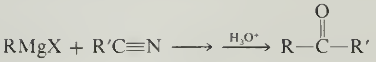
$$RMgX + R'-\overset{\overset{\large O}{\|}}{C}-R' \longrightarrow \xrightarrow{H_2O} R-\underset{\underset{\large R'}{|}}{\overset{\overset{\large OH}{|}}{C}}-R'$$

(Section 15.7.D)



$$\mathrm{RMgX + R'CO_2CH_3 \longrightarrow \xrightarrow{H_2O} R'{-}\underset{\displaystyle R}{\overset{\displaystyle OH}{C}}{-}R}$$

(Section 18.9.E)



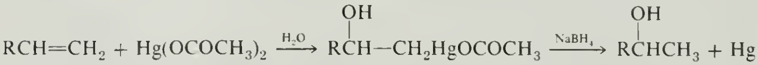
$$\mathrm{RMgX + R'C{\equiv}N \longrightarrow \xrightarrow{H_3O^+} R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R'}$$

(Section 18.9.E)

Alkyllithium compounds also undergo most of these reactions, and are used in some cases. Alkylboranes are also important and hydroboration will be discussed in Section 12.6.D as a method for preparing alcohols.

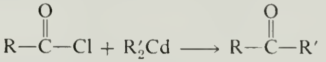
$$\mathrm{3\,RCH{=}CH_2 + (BH_3)_2 \longrightarrow 2\,(RCH_2CH_2)_3B \xrightarrow[OH^-]{H_2O_2} RCH_2CH_2OH}$$

Alkylmercury compounds are useful as intermediates in the formation of alcohols and ethers (Section 12.6.B).

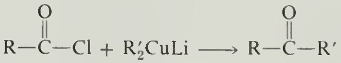


$$\mathrm{RCH{=}CH_2 + Hg(OCOCH_3)_2 \xrightarrow{H_2O} R\overset{\displaystyle OH}{C}H{-}CH_2HgOCOCH_3 \xrightarrow{NaBH_4} R\overset{\displaystyle OH}{C}HCH_3 + Hg}$$

Organic compounds of cadmium and the cuprates are often used for the preparation of ketones from acyl halides (Section 18.9.E).



$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}Cl + R'_2Cd \longrightarrow R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R'}$$

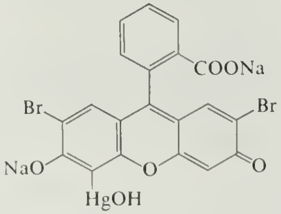


$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}Cl + R'_2CuLi \longrightarrow R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R'}$$

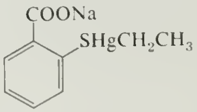
These reactions and many others have firmly established organometallic compounds as extremely important tools of the synthetic chemist.

Some organometallic compounds have found application in the everyday world. We have already mentioned the importance of tetraethyllead as an antiknock agent in gasoline. This material has not only had an economic impact on society, but it now appears that it may have an ecological impact as well.

Mercury compounds are extremely toxic, particularly toward plant life. They have been employed extensively as bactericides, algicides, fungicides, and herbicides. Two of the most familiar childhood remedies are, in fact, organomercury compounds.



mercurochrome



merthiolate

The toxicity of organomercury compounds has also had its impact on ecology. For example, during more than a decade following 1953, thousands of inhabitants around the fishing village of Minamata in the Japanese island of Kyushu became ill with

> a mysterious and debilitating disease which resulted in many deaths. The disease was subsequently shown to be methylmercury poisoning. Waste streams containing mercury compounds from a nearby industrial plant entered the food cycle of the Shiranni Sea. The mercury was converted by organisms to methylmercury, CH_3Hg^+, an insidious and cumulative poison which concentrated in fish caught for food.

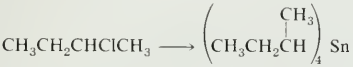
The chemistry of the organometallic compounds is an exceedingly large and complex field. Organic derivatives are known for almost every element in the periodic table, and each type has its own characteristic chemistry. In this brief chapter, we have barely scratched the surface. Indeed, it may be said that research itself in this area has only just begun.

PROBLEMS

1. Show how the following conversions may be accomplished.

(a) $(CH_3)_3CCH(CH_3)_2 \longrightarrow (CH_3)_3CCD(CH_3)_2$

(b)



$$CH_3CH_2CHClCH_3 \longrightarrow \left(CH_3CH_2\overset{CH_3}{\overset{|}{C}}H\right)_4 Sn$$

(c) $(CH_3)_4C \longrightarrow (CH_3)_3CCH_2MgCl$

(d) $CH_3CH_2Cl \longrightarrow (CH_3CH_2)_2Cd$

2. Predict the geometry of dimethylmercury. The measured dipole moments of $(CH_3)_2Hg$ and $(C_2H_5)_2Hg$ are $\mu = 0.0$ D. Explain.

3. Predict whether the equilibrium constant will be greater than or less than unity for each of the following reactions.

(a) $2\,(CH_3)_3Al + 3\,CdCl_2 \rightleftharpoons 3\,(CH_3)_2Cd + 2\,AlCl_3$

(b) $(CH_3)_2Hg + ZnCl_2 \rightleftharpoons (CH_3)_2Zn + HgCl_2$

(c) $2\,(CH_3)_2Mg + SiCl_4 \rightleftharpoons (CH_3)_4Si + 2\,MgCl_2$

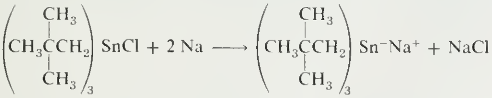
(d) $CH_3Li + HCl \rightleftharpoons CH_4 + LiCl$

(e) $(CH_3)_2Zn + 2\,LiCl \rightleftharpoons 2\,CH_3Li + ZnCl_2$

4. Trimethylborane reacts with methyllithium to give a product having the formula $C_4H_{12}BLi$. Propose a structure for this substance. What is the hybridization of boron? Describe the geometry of the species.

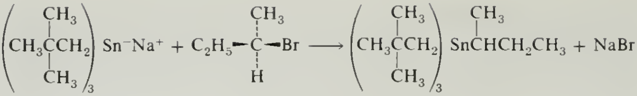
5. The reaction of alkyl halides with sodium metal was once used as a method for preparing certain alkanes (**Würtz** reaction). What do you think are the limitations of this reaction as a preparative method? Write out several alkanes that could be prepared this way in good yield.

★ **6.** When trineopentyltin chloride is treated with sodium metal a salt is formed.

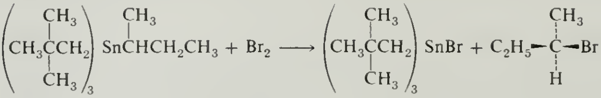


$$\left(CH_3\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_2\right)_3 SnCl + 2\,Na \longrightarrow \left(CH_3\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_2\right)_3 Sn^-Na^+ + NaCl$$

This salt is treated with (R)-2-bromobutane to give *sec*-butyltrineopentyltin (9-1). Treatment of the tetraalkyltin compound with bromine gives (R)-2-bromobutane and trineopentyltin bromide (9-2).



$$\left(CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\right)_3 Sn^-Na^+ + C_2H_5-\overset{CH_3}{\underset{H}{C}}-Br \longrightarrow \left(CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\right)_3 Sn\overset{CH_3}{C}HCH_2CH_3 + NaBr \qquad (9\text{-}1)$$



$$\left(CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\right)_3 Sn\overset{CH_3}{C}HCH_2CH_3 + Br_2 \longrightarrow \left(CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\right)_3 SnBr + C_2H_5-\overset{CH_3}{\underset{H}{C}}-Br \qquad (9\text{-}2)$$

(a) What is the probable mechanism of reaction (9-1)?
(b) Comment on the overall stereochemistry of the two steps.
(c) Why is it the *sec*-butyl group, rather than one of the neopentyl groups, that reacts in reactions (9-1) and (9-2)?

★ 7. An alternate mechanism for coupling two alkyl halides by sodium metal (page 160) is dimerization of the free radicals produced during formation of the organosodium compound.

$$2\,RCl + 2\,Na \longrightarrow 2\,R\cdot + 2\,NaCl$$

$$2\,R\cdot \longrightarrow R\text{-}R$$

This mechanism has been tested by treating (R)-2-chlorooctane with sodium. The product is a mixture of (S,S)- and (R,S)-7,8-dimethyltetradecane.
(a) What does this result show about the free radical coupling mechanism above? Remember that free radicals are effectively planar and thus achiral.
(b) One of the dimethyltetradecanes is meso and one is optically active. Which is which?
(c) Are the two products necessarily formed in equal amounts? Explain.
(d) Does this experiment rigorously exclude either mechanism? Explain.

In another experiment aimed at probing the mechanism of the Würtz reaction, a 50:50 mixture of n-pentyl iodide and neopentyl iodide was treated with metallic sodium. The coupling products, n-decane, 2,2-dimethyloctane, and 2,2,5,5-tetramethylhexane, were formed in a ratio of 1.2:1.7:1.1.
(e) With which mechanism is this result most compatible?

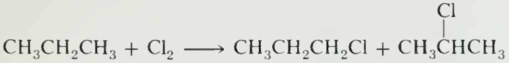
CHAPTER 10

Nuclear Magnetic Resonance Spectroscopy

10.1
Structure Determination

Structure determination is one of the fundamental operations in chemistry. How does the chemist determine the structure of a compound? Imagine that we carry out a reaction between propane (C_3H_8) and chlorine, both of which are gases at room temperature. After the reaction is completed, we obtain a liquid product. We distil this liquid and obtain two main fractions, one boiling at 36° and one boiling at 47°. These two liquids are obviously reaction products because they have different physical properties (b.p.) from the reactants. What are they?

As a first step, we might perform an elemental analysis (Section 2.11) and determine their empirical formulas. When we do this, we find that they both have the formula C_3H_7Cl. We conclude that a reaction has occurred in which a hydrogen has been replaced by a chlorine, and that two isomeric products have been produced in the reaction. Since there are only two types of hydrogen in propane, we can write structures for the two products. One is 1-chloropropane and the other is 2-chloropropane. The reaction is therefore

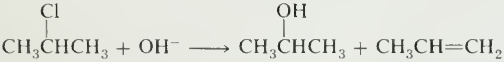


$$CH_3CH_2CH_3 + Cl_2 \longrightarrow CH_3CH_2CH_2Cl + CH_3\overset{\overset{\displaystyle Cl}{|}}{C}HCH_3$$

But which is which? Is the product which boils at 36° 1-chloropropane or 2-chloropropane?

One way to answer this question is to look up the boiling points of 1-chloropropane and 2-chloropropane in a handbook. But suppose for a moment that the two compounds have never been prepared before and their boiling points are not known. Another way to answer our question would be to convert the two isomers into compounds that *are* known. For example, suppose we have samples of 1-propanol and 2-propanol and that we know which is which. We take our two C_3H_7Cl isomers and treat each with aqueous KOH. The isomer that boils at 47° gives 1-propanol and the isomer that boils at 36° gives 2-propanol. (In addition, both isomers give some propene). If we assume that the nucleophilic substitution occurs without rearrangement, then we may assign structures to the two isomers on the basis of their conversion to products of known structure.

$$\underset{\substack{\text{1-chloropropane}\\ \text{b.p. } 47^\circ}}{CH_3CH_2CH_2Cl} + OH^- \longrightarrow \underset{\text{1-propanol}}{CH_3CH_2CH_2OH} + CH_3CH{=}CH_2$$



$$\underset{\substack{\text{2-chloropropane}\\ \text{b.p. } 36^\circ}}{CH_3\overset{\overset{\displaystyle Cl}{|}}{C}HCH_3} + OH^- \longrightarrow \underset{\text{2-propanol}}{CH_3\overset{\overset{\displaystyle OH}{|}}{C}HCH_3} + CH_3CH{=}CH_2$$

2-chloropropane
b.p. 36°

2-propanol

A more direct method of structure determination involves a consideration of the physical properties of the compound of unknown structure. The most useful properties for this purpose are spectra. Spectroscopy is a powerful tool for structure determination. There are many different types of spectroscopy. In the following section we shall have a brief introduction to spectroscopy generally, and then we shall take up one specific type of spectroscopy, nuclear magnetic resonance spectroscopy, in detail.

10.2
Introduction to Spectroscopy

Molecules are associated with several different types of **motion.** The entire molecule rotates, the bonds vibrate, and even the electrons move—albeit so rapidly that we generally deal only with electron density distributions. Each of these kinds of motion is **quantized.** That is, the molecule can exist only in distinct states that correspond to discrete energy contents. Each state is characterized by one or more quantum numbers. The energy difference between two such states, ΔE, is related to a light frequency, ν, by Planck's constant, h.

$$\Delta E = h\nu \tag{10-1}$$

Spectroscopy is an experimental process in which the energy differences between allowed states of a system are measured by determining the frequencies of the corresponding light absorbed.

The energy difference between the different quantum states depends on the type of motion involved. Thus, the wavelength of light required to bring about a transition is different for the different types of motion. That is, each type of motion corresponds to the absorption of light in a different region of the electromagnetic spectrum. Because the wavelengths required are so vastly different, different instrumentation is required for each spectral region. For example, the energy differences between molecular rotational states are rather small, on the order of 1 cal mole^{-1}. Light having this energy has a wavelength of about 3 cm and is called microwave radiation. The energy spacings of molecular rotational states depend on bond distances and angles and the atomic masses of the bonded atoms (moments of inertia). Hence, **microwave spectroscopy** is a powerful tool for precise structure determination. However, the technique must be applied in the vapor phase and it is restricted to rather simple molecules. Although it is an important technique in the hands of a specialist, it is not commonly used by organic chemists.

Energy differences between different states of bond vibration are of the order 1–10 kcal mole^{-1} and correspond to light having wavelengths of 30–3 μ ($1\ \mu \equiv 10^{-3}$ mm). This is the **infrared** region of the spectrum. Infrared spectrometers are relatively inexpensive and easy to use, and infrared spectroscopy is an important technique in organic chemistry. It is used mainly to determine which

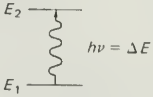


FIGURE 10.1 *Light of frequency* ν *corresponds to an energy difference* ΔE *between states corresponding to energies* E_1 *and* E_2.

functional groups are present in a compound. We will study its use in more detail in Chapter 14.

Different electronic states of organic compounds correspond to energies in the visible (4000–7500 Å; 1 Å ≡ 10^{-8} cm; 70–40 kcal mole^{-1}) and ultraviolet (1000–4000 Å; 300–70 kcal mole^{-1}) regions of the electromagnetic spectrum. Spectrometers for this region are also common and ultraviolet-visible spectroscopy is an important technique in organic chemistry, especially for conjugated systems. Such compounds will be discussed in detail later, and our study of this spectroscopy will be deferred to Chapter 22.

10.3 Nuclear Magnetic Resonance

Nuclear magnetic resonance (nmr) spectroscopy has only been important in organic chemistry since the mid-1950s, yet in this relatively brief time it has taken its place as one of our most important spectroscopic tools. In nmr spectroscopy, a solution of the sample is inserted in the instrument—actually the sample tube is fitted precisely between the poles of a powerful magnet—and the spectrum is recorded as a curve. A typical example is the nmr spectrum of 1-chloropropane shown in Figure 10.2. Some appreciation of the usefulness of this technique can be sensed by comparing the spectrum of the isomeric compound, 2-chloropropane, shown in Figure 10.3. In this chapter we will develop the rules for interpreting such spectra. We will find it rather simple, for example, to *deduce* the structures of 1-chloropropane and 2-chloropropane from their nmr spectra. It is possible to treat the nmr spectrometer as a "magic box" and simply memorize a few rules that suffice for deducing the structure of a compound from its spectrum. In this chapter we will also go into some of the theoretical background to nmr spectroscopy to show why the rules take the form they do.

Nuclear magnetic resonance spectroscopy differs from the spectroscopic techniques discussed in the previous section in that the differences in energy in the

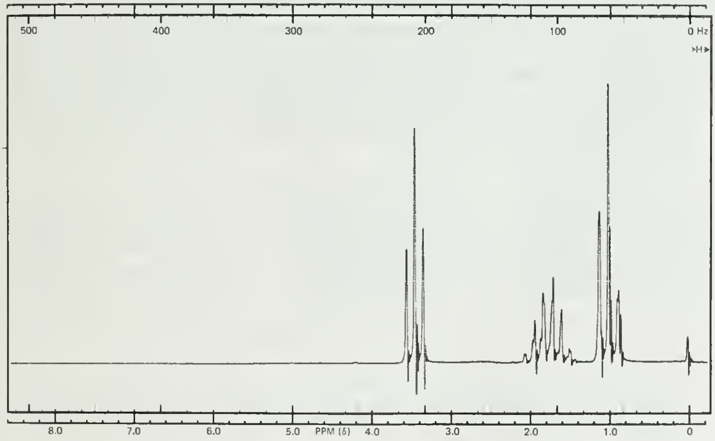


FIGURE 10.2 Nmr *spectrum of* 1-*chloropropane,* $CH_3CH_2CH_2Cl$.

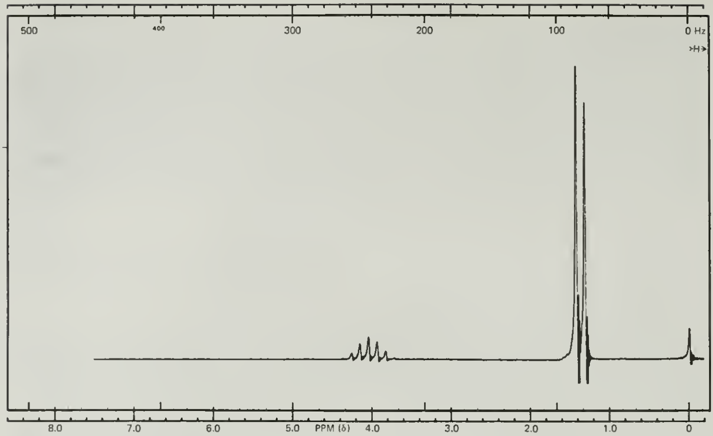


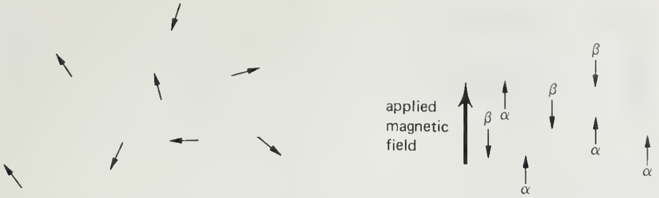
FIGURE 10.3 Nmr *spectrum of 2-chloropropane*, $CH_3CHClCH_3$.

states being examined are created by a magnetic field. That is, the molecules are placed in a powerful magnetic field to create different energy states which are then detected by absorption of light of the appropriate energy. In the absence of the magnetic field, these different states all have nearly the same energy.

The motion involved in nmr spectroscopy is that of **nuclear spin.** The nuclei of many atoms behave as though they were spinning on an axis. Since they are positively charged, such nuclei follow the physical laws of spinning charged particles. A moving charge, positive or negative, is associated with a magnetic field. Consequently, the spinning nuclei behave as though they were tiny bar magnets; that is, such nuclei have **magnetic moments.** These magnetic moments are oriented in random fashion in field-free space, but they have the important quantization property that in a magnetic field only certain discrete orientations are allowed. For some important nuclei, ^1H (but not ^2H), ^{13}C (but not ^{12}C), and ^{19}F (the only common fluorine isotope), the nuclear spin can have only two alternative values associated with the quantum numbers, $+\frac{1}{2}\,(=\alpha)$ and $-\frac{1}{2}\,(=\beta)$. When these nuclei are placed in a magnetic field their magnetic moments tend either to align with the field (corresponding to α spin) or against the field (corresponding to β spin) (Figure 10.4).

In an applied field, a magnetic moment tends to align with the field (for example, a compass needle in the earth's magnetic field). A magnet aligned against the magnetic field is in a higher energy state than one aligned with the field. For ^1H, ^{13}C, and ^{19}F the β spin state with the magnetic moment aligned against the field corresponds to a higher energy state than the α spin state. If the system is irradiated with light of the proper frequency or wavelength, a nucleus with α spin can absorb a light quantum and be converted to the higher energy β spin state, a process colloquially described as "flipping the spin" (Figure 10.5).

To recapitulate, the nuclei of ^1H, ^{13}C and ^{19}F have spinning nuclei with spins of $\pm\frac{1}{2}$. Because of the restrictions imposed by quantization, only two orientations are permitted for these nuclei in a magnetic field: α spin $(+\frac{1}{2})$, nuclear magnetic moment aligned with the applied magnetic field, lower energy; and β spin $(-\frac{1}{2})$,



Nuclear magnetic moments with no magnetic field

Nuclear magnetic moments in a magnetic field. Nuclei with α spin are aligned with the field; those with β spin are aligned against the field.

FIGURE 10.4 *Orientation of nuclear magnetic moments.*

nuclear magnetic moment aligned against the applied magnetic field, higher energy.

Many nuclei have no spin. All even-even nuclei (those having an even number of protons and an even number of neutrons) are in this class. In this important class, which includes ^{12}C and ^{16}O, individual pairs of protons and neutrons have opposed spins so that the net spin of the nucleus as a whole is zero. Other nuclei have three or more possible spin states in a magnetic field. ^{14}N is an important example that has three such states. We will not consider such cases, but will restrict our attention primarily to those nuclei that have spin of $\pm\frac{1}{2}$, ^{1}H, ^{13}C, ^{19}F, and so on. For such cases, the energy difference between the two states is given by

$$\nu = \frac{\gamma \mathbf{H}}{2\pi} \tag{10-2}$$

in which **H** is the magnetic field strength *at the nucleus* and γ is the magnetogyric ratio of the nucleus. This quantity is the ratio of the angular momentum (from the rotating nuclear mass) and the magnetic moment (from the rotating nuclear charge), and is characteristic and different for each nucleus. That is, the energy difference between the α and β spin states in a magnetic field is proportional to the strength of the magnetic field with a proportionality constant that is characteristic of the nucleus (Figure 10.6).

For the proton, γ has the value 2.6753×10^{4} radians sec^{-1} gauss^{-1}. When **H** is given in units of gauss, the frequency, ν, is given in units of cycles per second, or Hertz, Hz. This energy unit is used commonly in nmr, and it may be converted to the more familiar units of cal mole^{-1} by the conversion

$$E(\text{cal mole}^{-1}) = 9.54 \times 10^{-11}\, \nu\, (\text{Hz}) \tag{10-3}$$

According to equation (10-2), the energy differences involved are proportional to the magnetic field and are exceedingly small. For example, for an isolated hydrogen atom in a magnetic field of 14,092 gauss, the energy difference between

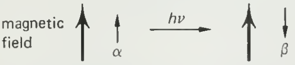


FIGURE 10.5 *Absorption of light of proper frequency changes the nuclear spin state.*

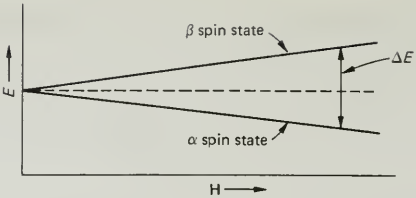


Figure 10.6 *The difference in energy, ΔE, between the α and β spin states is a function of the magnetic field at the nucleus.*

α and β spin states is given by $\Delta E = (26{,}753)(14{,}092)/2\pi = 60 \times 10^6$ Hz = 60 MHz (megaHertz). From equation (10-3), this energy value is equivalent to only 0.0057 cal mole^{-1} (not kcal!). The frequency of 60 MHz corresponds to a wavelength of 500 cm and is in the radio region of the electromagnetic spectrum. A field of 14,000 gauss is a rather strong magnetic field but one that is readily accessible with modern technology. The 60 MHz nmr spectrometer is now relatively common, and commercial instruments are also available with larger field strengths in which the proton "flip" corresponds to 100 MHz. With superconducting magnets, 220 MHz and 360 MHz instruments are now available.

10.4
Chemical Shift

If nmr spectroscopy related only to free protons floating in a magnetic field, we would hardly expect to find the thousands of nmr spectrometers now spread in laboratories throughout the world. It is when we look at magnetic phenomena in bonds to protons in molecules that we find why nmr is such an invaluable asset to the organic chemist. A proton in a molecule is surrounded by a cloud of electronic charge. In a magnetic field, electrons move in such a way that their motion induces a magnetic field characterized by a magnetic moment that is **opposed** to the applied field. Consequently, the net magnetic field at the hydrogen atom is slightly less than the applied field (Figure 10.7).

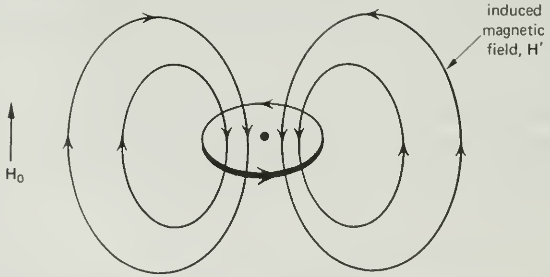


Figure 10.7 *An external magnetic field induces an electron flow in an electron cloud that, in turn, induces a magnetic field. At the nucleus, the induced field opposes the external field.*

A frequent source of confusion is the difference between electron flow and electrical current. By a convention established before the discovery of electrons, current flows from anode (+) to cathode (−), exactly the opposite of the actual movement of electrons. The figures in this book such as Figure 10.7 represent the actual flow of electrons and are the reverse of the direction of a positive electrical current.

The magnetic field experienced by the nucleus, **H**, is therefore

$$\mathbf{H} = \mathbf{H}_0 - \mathbf{H}' \qquad (10\text{-}4)$$

In equation 10-4, $\mathbf{H}_0$ is the applied field and $\mathbf{H}'$ is the induced field. Because the nucleus experiences a smaller magnetic field than that applied externally, it is said to be **shielded.** This particular type of shielding is called **diamagnetic shielding.** If we are irradiating the proton with radiowaves of exactly 60 MHz frequency, the change of $\alpha \longrightarrow \beta$ energy states of "spin-flipping" requires a field of 14,092 gauss *at the proton.* However, since the nucleus is shielded by electrons, *the applied field* has to be made somewhat higher than 14,092 gauss in order for the field at the nucleus to have the **resonance** value of 14,092 gauss, the field strength that corresponds to the radio frequency required to produce spin-flipping. Protons in different electronic environments experience different amounts of shielding, and the resonance absorption of light energy will occur at different values for the applied field or irradiating light frequency. These changes are referred to as **chemical shifts.**

A nuclear magnetic resonance spectrometer is arranged schematically as shown in Figure 10.8. A liquid sample or solution contained in a narrow glass tube is put between the poles of the powerful magnet. The magnetic field creates the two energy states for various hydrogen nuclei in the sample. The sample is irradiated with radio waves from a simple coil. In one mode of operation we fix the radio frequency at say, 60 MHz, as in the Varian A-60 nmr spectrometer. We then vary the magnetic field and, as the field at each kind of proton reaches the **resonance** value, energy is absorbed from the radiowaves as the nuclear spins "flip," and this absorption is measured and recorded on a graph.

For example, 1,2,2-trichloropropane, $CH_3CCl_2CH_2Cl$, gives the spectrum shown in Figure 10.9. This spectrum consists of two sharp peaks, corresponding to the methylene group and the methyl group. The CH_2 group is attached to chlorine, an electronegative element that withdraws electrons from carbon and hydrogen. Since there is less electron density around the methylene protons, the diamagnetic shielding of these protons is less than it is for the methyl protons. The induced

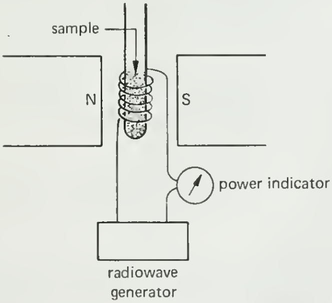


FIGURE 10.8 *Schematic of an* nmr *spectrometer.*

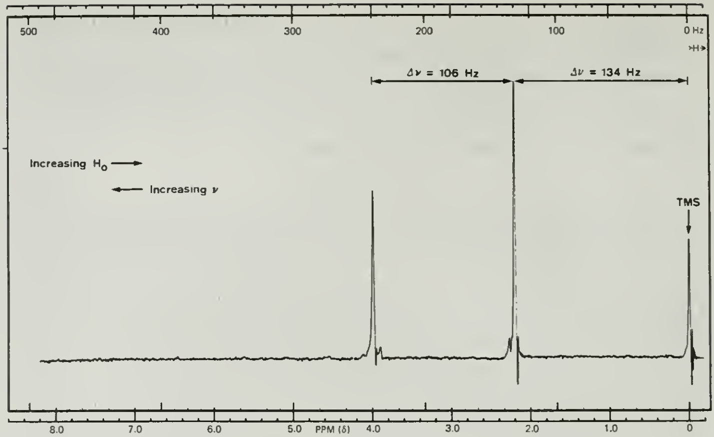


Figure 10.9 60 MHz nmr *spectrum of* $CH_3CCl_2CH_2Cl$.

magnetic field is therefore lower at CH_2 than at CH_3, and the applied field must be increased less in order to achieve resonance. Consequently, the methylene protons appear to the left or **downfield** compared to the methyl protons. Note that the difference is exceedingly minute—about 0.004 gauss compared to a total applied field of about 14,000 gauss.

Alternatively, we can keep the magnetic field constant and vary the frequency of the radio electromagnetic irradiation. The lower the electronic shielding of the nucleus, the higher the effective magnetic field at a proton, and the higher the frequency required to reach the resonance condition. If we plot the frequency increasing from right to left as in a Varian T-60 nmr spectrometer, the resulting spectrum looks exactly like Figure 10.9. The methylene hydrogens now appear at higher frequency than the methyl hydrogens, the frequency difference being 106 Hz. Frequency differences can be measured more precisely than differences in magnetic field strength. Consequently, the difference in peaks is always given in frequency units, regardless of the specific mode of operation of the nmr spectrometer. The kind of language in common use is illustrated by the statement that, in Figure 10.9, the methylene group appears downfield with a frequency difference of 106 Hz. Note again that this is a small difference between large numbers; if the methyl group resonates at 60,000,000 Hz, the methylene is at 60,000,106 Hz! Since these *absolute numbers* are difficult to reproduce, in practice we compare differences relative to a standard.

The standard compound used for most proton nmr spectra is tetramethylsilane, $(CH_3)_4Si$, commonly abbreviated **TMS**, a volatile liquid, b.p. 26.5°. It is inert to most reagents and soluble in most organic liquids. A small amount has been added to our sample of 1,2,2-trichloropropane and it gives rise to the peak at the far right in Figure 10.9. All of the hydrogens in TMS are equivalent and give rise to the single sharp line 134 Hz upfield from the methyl of the trichloropropane. Furthermore, silicon is electropositive relative to carbon and tends to donate electron density to the methyl groups, thereby increasing their shielding. The relatively high shielding of the protons in TMS causes it to resonate upfield from most other protons commonly encountered in organic compounds.

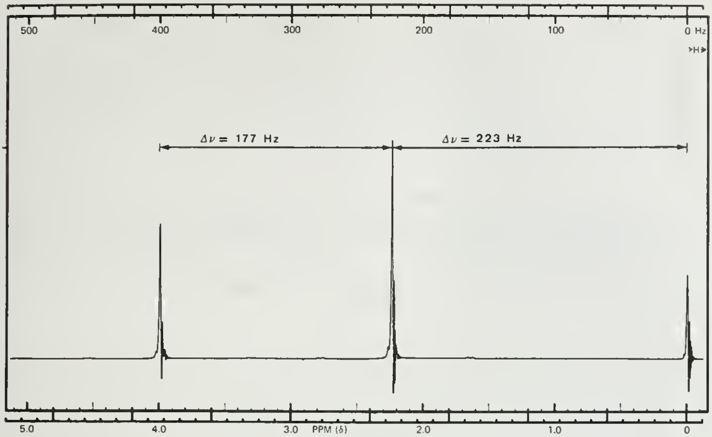


FIGURE 10.10 100 MHz nmr *spectrum of* $CH_3CCl_2CH_2Cl$.

When the spectrum is run on a spectrometer operating at 23,487 gauss, the resonance frequency of hydrogen is 100 MHz. The larger magnetic field induces a larger electron current, which causes a larger diamagnetic shielding at the nucleus. The difference in diamagnetic shielding is proportionally larger and the peaks spread apart as shown in Figure 10.10. The chemical shift of the methyl group is now 223 Hz downfield from TMS, instead of 134 Hz. Because different nmr instruments are in common use, it is convenient to define a unitless measure that is independent of field strength. The unit used is δ. It is simply the ratio of the chemical shift of the resonance in question, in Hertz, to the total light frequency used. Since the resulting number is small, it is multiplied by 10^6. Thus, δ has the units of parts per million (ppm) and represents a chemical shift downfield (higher frequency) from TMS.

$$\delta_i = \frac{\nu_i - \nu_{\mathrm{TMS}}}{\nu_0} \times 10^6 \text{ ppm} \tag{10-5}$$

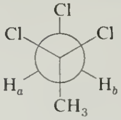
In eq. 10-5, δ_i is the chemical shift of proton i, ν_i is the resonance frequence of that proton, ν_{TMS} is the resonance frequency of TMS, and ν_0 is the operating frequency of the instrument. Thus, for $CH_3CCl_2CH_2Cl$, $\delta(CH_3) = 134/60 = 2.23$ ppm, and $\delta(CH_2) = 240/60 = 4.00$ ppm. If a resonance is upfield from TMS, its δ value has a negative sign.

Most protons have δ values of 1–10 ppm downfield from TMS, and a second unit of chemical shift has been used with the definition

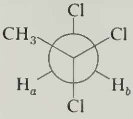
$$\tau = 10 - \delta \tag{10-6}$$

Both τ and δ scales will be found in the chemical literature, although the use of the τ scale appears to be decreasing.

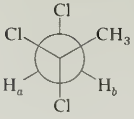
In the preceding discussion, it seemed quite natural to expect both hydrogens in the methylene group to absorb in the same place because they appear to be equivalent. However, if we examine the structure of 1,2,2-trichloropropane in more detail, this equivalence is not so apparent. The compound actually exists as an equilibrium mixture of three conformations, symbolized by the following Newman projections:



A



B



C

In structure A, both hydrogens H_a and H_b are clearly equivalent, but this is not the case in B and C. In B, for example, H_b is flanked by two chlorines and would be expected to be deshielded relative to H_a. Why then do we not see two or more peaks for these hydrogens?

The answer comes from the Heisenberg uncertainty principle of quantum mechanics. One expression of this principle is

$$\Delta E\,\Delta t \approx \frac{1}{2\pi}$$

where ΔE and Δt are the uncertainties in energy and time in units of Hertz and seconds, respectively. That is, we cannot know precisely both the energy and the lifetime of a given state. The longer lived the state, the more precisely can its energy content be evaluated. In our nmr case above, suppose that $\delta(H_a)$ and $\delta(H_b)$ differ by 1 ppm. This amount in a 60-MHz instrument corresponds to an energy difference of 60 Hz or 6×10^{-9} cal mole^{-1}, an exceedingly small energy quantity. In order to measure this small difference for H_a and H_b as separate states, they would have to have lifetimes in each conformation of at least

$$\Delta t \cong 1/(2\pi\,\Delta E) = 1/(2\pi \cdot 60) = 0.0027 \text{ sec}$$

But with an energy barrier of only 3–4 kcal mole^{-1} between one conformer and another, the average lifetime of a given conformation is only about 10^{-10} to 10^{-11} sec! (See Section 4.3.) In other words, the lifetime of a given methylene hydrogen in the magnetic environment of a given conformation is too short to permit us to distinguish it from the other methylene hydrogen. The "state" measured in a nmr spectrometer is a weighted average of all of the rotational conformations. The energy differences measured in nmr are so small that one frequently refers to the "nmr time scale," a time period ranging from milliseconds to seconds.

To summarize, a consequence of the Heisenberg uncertainty principle and the small energy changes characteristic of nmr spectroscopy is that two hydrogen states that are interconvertable but which have separate lifetimes of more than about 1 sec can be seen as two sharp peaks whose separation can be measured accurately. If the lifetimes are less than about 1 msec, they can be seen only as a combined single sharp peak; that is, on the "nmr time scale" the two hydrogens are **magnetically equivalent.** If the lifetimes are in an intermediate region, a broad peak results. An example is discussed later (Section 23.2.D) in connection with conformational interconversions of cyclohexane.

The foregoing discussion also shows why the nmr sample tube is spun rapidly between the magnet faces. It is difficult to prevent slight changes in a magnetic field at different places. In a tube placed between the pole faces of even high quality magnets, different protons would experience slightly different fields at different points. The result would be a rather broad nmr signal. By rapidly spinning the tube, all of the protons experience the same average field *on the nmr time scale.*

10.5
Relative Peak Areas

We saw in the previous section that we can obtain a valuable piece of information from an nmr spectrum—the number of magnetically different hydrogens in the compound. The amount of energy absorbed at each resonance frequency is proportional to the number of nuclei that are absorbing energy at that frequency. By measuring the **areas** of each of the resonance lines, we may determine the relative number of each different kind of hydrogen. In practice, this is accomplished with an electronic integrator. After the nmr spectrum has been recorded, the instrument is switched to an "integrator mode" of operation, and the spectrum is recorded again. The recorder output in this mode of operation is illustrated in Figure 10.11.

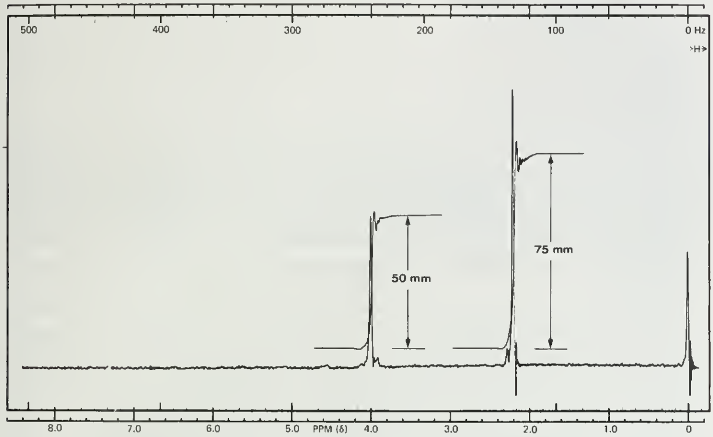


FIGURE 10.11 *Integrated intensities superimposed on the* nmr *spectrum are proportional to the relative numbers of hydrogens.*

The integral line for each of the two peaks in the spectrum of 1,2,2-trichloropropane is shown superimposed on the appropriate peak. The ratio of the heights of the two integral lines is equal to the ratio of the number of protons giving rise to the two peaks, in this case 3/2. In the remaining sample spectra in this book, we will usually not show the integral lines, but will simply indicate the relative areas of peaks where necessary.

We should note that the nmr experiment does not measure all of the protons but just those that have α spin and absorb energy in "flipping" to β spin. The difference in the population of α and β spins is rather small. We learned above that the energy difference between the proton α and β spin states in the magnetic field of a 60 MHz nmr instrument is only 0.006 cal mole^{-1}. At equilibrium, the population difference is given by the Boltzman distribution as

$$\frac{N_\alpha}{N_\beta} = e^{0.006/RT} = 1.000004$$

When we now turn on the applied radio frequency field we excite the slight excess of α nuclei to β. If there were no other mechanism for converting β back to α, we would quickly have exactly equal populations in both spin states and could no longer observe any absorption of energy; there would be no spectrum. With a sufficiently strong radio frequency field this can generally be done and the system is then said to be **saturated.** However, in normal operation, hydrogens in the β spin state continually **relax** back to the α state because of local fields, and equilibrium imbalance is maintained. These local fields are associated with other spinning nuclei. That is, even in the absence of the applied radio frequency field, individual protons convert from one state to another quite readily because, in moving about the liquid, they experience the magnetic fields of other nearby nuclear magnetic moments. Occasionally, such moving and changing fields happen to have the resonance value, and energy interchange can occur resulting in spin flipping. In the nmr experiment the net result of all this activity is the conversion of our measuring radio waves into heat within the sample. In normal operation the distribution of α and β spins remains close to the equilibrium value and the amount of energy absorbed is proportional to the number of protons.

10.6
Spin-spin Splitting

We have seen that the nmr spectrum of 1,2,2-trichloropropane shows two sharp peaks that are easy to interpret. From the fact that there are two peaks, we deduce that the compound has two types of hydrogen that are magnetically nonequivalent, and, from the relative areas of the two peaks, we conclude that they are present in a ratio of 3/2. Let us now consider the nmr spectrum of a related trihaloalkane, 3,4,4-tribromo-2,2-dimethylbutane, $(CH_3)_3CCHBrCHBr_2$, shown in Figure 10.12.

We recognize the small peak at $\delta = 0.0$ as that of TMS added as a standard to define the zero on our scale. The large peak at $\delta = 1.2$ ppm comes from the nine equivalent methyl protons. The other two protons are responsible for the downfield resonances; the downfield shifts are explained by their proximity to the electronegative bromines. But these resonances are now represented by a pair of peaks. Each resonance appears as a **doublet.** This "splitting" of peaks is common in nmr spectra—it is an additional complication that requires study, but it is also a powerful tool for the determination of molecular structure. The phenomenon has its origin in the magnetic field associated with each individual spinning proton.

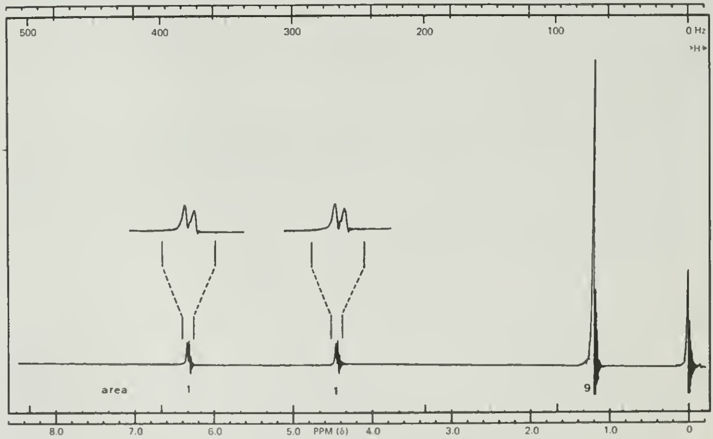
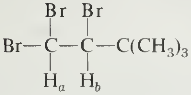


FIGURE 10.12 Nmr *spectrum of* $(CH_3)_3CCHBrCHBr_2$.

These small magnetic fields affect the total magnetic field experienced by another proton.

For convenience we will label these hydrogens as H_a and H_b.



$$\mathrm{Br{-}\overset{Br}{\underset{H_a}{C}}{-}\overset{Br}{\underset{H_b}{C}}{-}C(CH_3)_3}$$

In the applied magnetic field of the nmr spectrometer we would expect H_a normally to show up as a single peak. However, the magnetic field associated with the spin of the nearby proton, H_b, contributes to the net field experienced by H_a. If H_b has α spin, its magnetic moment is aligned with the applied field and the total magnetic field at H_a is slightly stronger than that provided by the nmr instrument's applied field alone. Consequently, *less* applied field is required to achieve resonance than in the absence of H_b and we find a slight downfield shift (Figure 10.13). But only half of the H_b nuclei have α spin. The rest have β spin in which the magnetic moments are aligned against the field. For these molecules, the net magnetic field at H_a is slightly *weaker* than that given by the applied field alone. The nmr spectrometer must then provide slightly *more* magnetic field in order to achieve the "spin-flipping" resonance condition with H_a. Now the result is an upfield shift (Figure 10.13).

Let us recapitulate the conditions of the experiment. We start with a low magnetic field in the nmr instrument and irradiate our sample with a radio signal of an accurately constant frequency (energy). As we slowly increase the magnetic field, we reach a point where the magnetic field at those half of the H_a protons that are in molecules where the H_b protons have α spin now matches the energy of the irradiating radio waves. H_a protons of α spin absorb radio photons and "flip" to β spins. Motion in the liquid sample provides a mechanism for the β spins to change to α with the excess energy given up as heat. The absorption of radio waves is recorded by the nmr instrument as a "peak." As the applied magnetic field is increased still more, the resonance condition is destroyed and

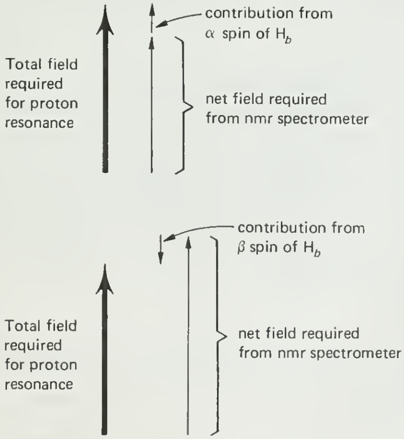

contribution from
α spin of H_b
Total field required for proton resonance
net field required from nmr spectrometer
contribution from
β spin of H_b
Total field required for proton resonance
net field required from nmr spectrometer

FIGURE 10.13 *Source of spin-spin splitting.*

the recorder pen returns to the base line (usually with the oscillations known as "ringing," a normal phenomenon that we will not detail). At a still higher applied field we reach a point where the other half of the H_a protons absorb radio energy. These H_a protons are in molecules where H_b has β spin, whose magnetic field subtracts from the applied field, and a stronger field must therefore be applied to achieve resonance.

Note that only one kind of hydrogen is in resonance at any given point in the spectrum. Both lines in the low field doublet in Figure 10.13 correspond to transitions of H_a. At these field strengths, H_b, with its different chemical shift, is not in resonance even though its presence is "felt" by H_a and produces two resonance positions instead of one. As the field strength is increased still further, the H_b nuclei eventually come into resonance. However, now we must reckon with the effect of α or β spin of H_a on the net magnetic field experienced by H_b.

The effect is an exact reciprocity—the effect of H_a on H_b is exactly the same as the effect of H_b on H_a. Consequently, the splitting of the H_a peaks has the same magnitude as that of the H_b peaks. The spacing between the peaks is conventionally labeled J and is given in units of cycles per second or Hertz. J is the **coupling constant** between two protons. For our case $J_{ab} = 1.6$ Hz. These relationships are illustrated in Figure 10.14. Since J arises from the magnetic field of the proton, its magnitude is not dependent on the applied magnetic field. That is, the same J value applies for spectra determined at 40 MHz, 60 MHz, 100 MHz, and so on.

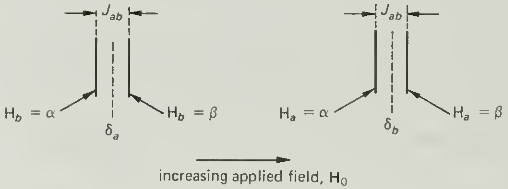
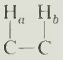


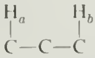
FIGURE 10.14 J_{ab} *causes equal spin-spin splitting on both* H_a *and* H_b.

In the foregoing example, we note that there is no coupling to the methyl protons. For simplicity we discussed the coupling phenomenon above in terms of a "through space" magnetic field effect. Actually, the effects of proton spin are relayed via bonding electrons. The effect is attenuated rapidly with the number of bonds and is usually quite small if more than two atoms intervene between the protons. Thus, the methyl protons do indeed couple to the other two protons in our example, but the magnitude of each such J is so small as to be unobservable in normal spectrometers. As a further example, in the spectrum of 1,2,2-trichloropropane, which was discussed in Section 10.4, the protons on C-1 and C-3 do not noticeably split each other.



$\overset{H_a}{\overset{|}{C}}-\overset{H_b}{\overset{|}{C}}$

spin-spin splitting normally observed



$\overset{H_a}{\overset{|}{C}}-C-\overset{H_b}{\overset{|}{C}}$

spin-spin splitting normally not observed

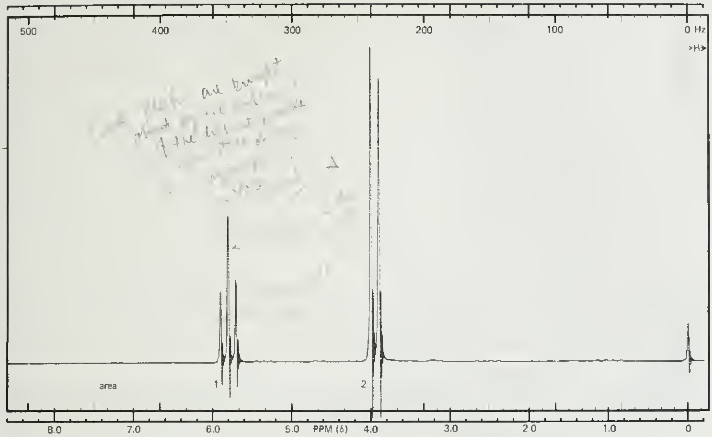
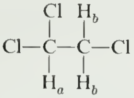


FIGURE 10.15 Nmr *spectrum of* $CHCl_2CH_2Cl$.

Now let us consider a slightly more complex spectrum, that of 1,1,2-trichloroethane (Figure 10.15). In this compound, there are two types of hydrogen.



$$\begin{array}{ccccccc} & & \mathrm{Cl} & & \mathrm{H}_b & & \\ & & | & & | & & \\ \mathrm{Cl} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{Cl} \\ & & | & & | & & \\ & & \mathrm{H}_a & & \mathrm{H}_b & & \end{array}$$

The spectrum shows two resonances, a triplet centered at $\delta = 5.8$ ppm and a doublet centered at $\delta = 3.9$ ppm. The triplet is associated with H_a, which is more deshielded because it is bonded to a carbon that also has two chlorines. The two equivalent H_b hydrogens are less deshielded because their carbon has only one attached chlorine. In any given molecule, the two H_b nuclei may have their spins as $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, or $\beta\beta$. When both H_b nuclei have α spin, aligned with the field, their magnetic field augments the applied field and less field is required for H_a to be in resonance. When the H_b spins are $\alpha\beta$ or $\beta\alpha$, there is no effect on the field experienced by H_a, because the opposed spins of the two H_b nuclei cancel. When both H_b nuclei have β spin, their combined magnetic field subtracts from $\mathbf{H}_0$ and a greater applied field is necessary to achieve resonance at H_a. Thus, the H_a resonance appears as three lines, with relative intensities of 1:2:1.

At the resonance frequency of the two H_b hydrogens we find two lines because H_a can have either α or β spin. In this case, the coupling constant, J, has the value 7 Hz (Figure 10.16). The chemical shift of the H_a triplet corresponds to the center line. The chemical shift of H_b is the midpoint of the doublet. The combined area of the triplet is one and the combined area of the doublet is two. *The chemical shift of a given proton depends on itself, but the nature of its splitting depends on its proton neighbors.* Consequently, the splitting phenomenon in nmr spectroscopy is an extremely valuable tool for determining structure.

Extension to different numbers of equivalent neighboring hydrogens is straightforward. Three hydrogens, as in a methyl group, can have the possible spin states: $\alpha\alpha\alpha$; $\alpha\alpha\beta$, $\alpha\beta\alpha$, $\beta\alpha\alpha$; $\alpha\beta\beta$, $\beta\alpha\beta$, $\beta\beta\alpha$; $\beta\beta\beta$, and would cause an

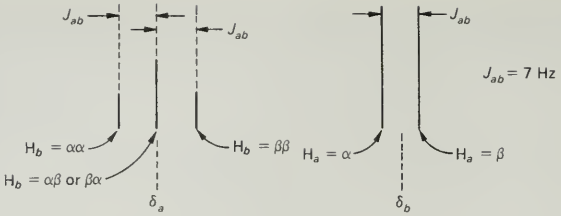


FIGURE 10.16 *Spin-spin splitting analysis of* 1,1,2-*trichloroethane.*

adjacent proton to give four peaks with area ratios of approximately 1:3:3:1. These numbers are simply the binomial coefficients and are summarized in Table 10.1. In general, *n* neighboring equivalent hydrogens cause splitting into $n + 1$ peaks.

These simple prescriptions apply for cases where splitting is small compared to the difference in chemical shift between the neighboring hydrogens; that is, $J \ll \Delta\nu$. As $\Delta\nu$ is reduced (that is, as the peaks for two nonequivalent hydrogens approach each other), the inner peaks increase in intensity and the outer ones diminish. In practice, such perturbations are almost always apparent. This effect may be seen in the spectrum in Figure 10.15.

Ethyl chloride and ethyl iodide present an interesting comparison (Figures 10.17 and 10.18). In each case, the three hydrogens of the methyl group give a quartet for the methylene hydrogens, and the two methylene hydrogens in turn produce a triplet with equal splitting for the methyl hydrogens. The area ratio of all four methylene peaks to the three methyl peaks is still 2:3, the ratio of the total number of hydrogens involved. For ethyl chloride, the highly electronegative chlorine produces a large downfield shift for the methylene hydrogens. That is, $\Delta\nu$ between CH_2 and CH_3 is rather large compared to *J*, and the peak intensities differ little from the simple ratios expected. For ethyl iodide, however, the less electronegative iodine has a smaller effect on δ and $\Delta\nu$ is smaller. Note that the asymmetry in both groups of peaks is now greater.

If $\Delta\nu$ is too small compared to *J*, the simple rules do not apply at all. Such spectra are quite complex and require a detailed analysis beyond the scope of this book. One especially simple case, however, is the extreme one for which $\Delta\nu = 0$. Such hydrogens are *magnetically equivalent and do not split each other.* In the cases discussed previously, for example, a methylene group was treated as a unit—because the two hydrogens are magnetically equivalent they have no effect on each other. This effect is a direct and exact outcome of the quantum

TABLE 10.1

Number of Equivalent Adjacent Hydrogens	Total Number of Peaks	Area Ratios
0	1	1
1	2	1:1
2	3	1:2:1
3	4	1:3:3:1
4	5	1:4:6:4:1
5	6	1:5:10:10:5:1
6	7	1:6:15:20:15:6:1

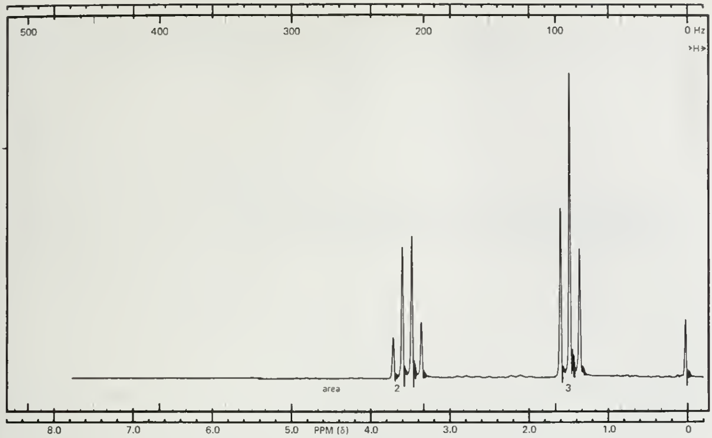


FIGURE 10.17 Nmr *spectrum of ethyl chloride,* CH_3CH_2Cl.

mechanics of magnetic resonance and the detailed reason is not important for our purposes.

The following simple explanation may be helpful. Because the nmr experiment does not distinguish magnetically equivalent hydrogens, different spin properties cannot be assigned to individual protons. For example, in a methylene group in which the protons have α and β spin, we cannot assign one spin to one proton and the other spin to the remaining proton. Instead, the $\alpha\beta$ spin property belongs to the methylene protons *as a unit.* Since we cannot assign individual spins to individual equivalent protons, it follows that we should not observe the splitting or J coupling normally associated with such assignments.

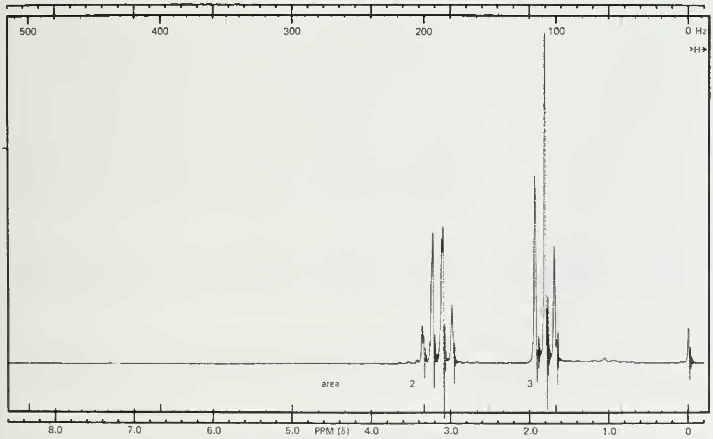


FIGURE 10.18 Nmr *spectrum of ethyl iodide,* CH_3CH_2I.

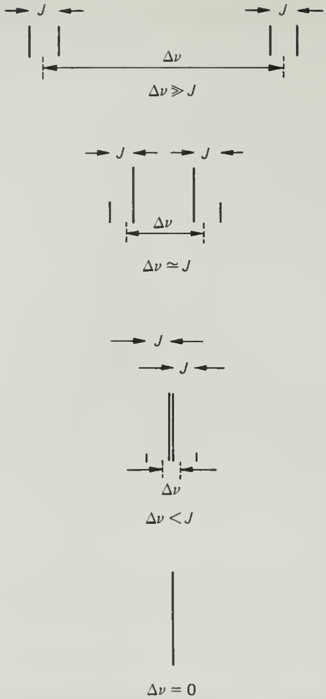
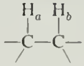


FIGURE 10.19 Nmr *spectra for*



$$-\overset{\displaystyle H_a}{\overset{|}{C}}-\overset{\displaystyle H_b}{\overset{|}{C}}-$$

The effect of the relative magnitudes of J and $\Delta\nu$ is illustrated in Figure 10.19. The first spectrum, for $\Delta\nu \gg J$, is that given by the "first-order" analysis that we outlined above. As $\Delta\nu$ and J become of comparable magnitude, the inner peaks increase in intensity and the outer ones fade until, in the limit where $\Delta\nu = 0$, the two inner peaks have merged and the outer peaks have vanished. Note that our example of ethyl iodide (Figure 10.18) shows the beginnings of breakdown of the simple rules in the slight additional splitting of the peaks. This splitting results entirely from $\Delta\nu$ being insufficiently large compared to J; first-order analysis is only a first approximation.

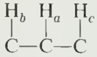
Some simple generalizations are important in our use of nmr. J values are generally significant for hydrogens on adjacent carbons and are usually of the order of magnitude of 4–10 Hz.

> The J value of 1.6 Hz observed in Figure 10.12 falls well outside of this range. Such abnormally low coupling constants are sometimes observed when several electronegative atoms are present.

Also, remember that J is independent of applied field, whereas the normal shielding by electrons, $\Delta\nu$, results from an induced field and is proportional to the applied field. One of the incentives for seeking larger magnetic fields for nmr instruments is the spreading of $\Delta\nu$ relative to J. At a sufficiently high field strength, all spectra reduce to the simple "first order" type ($\Delta\nu \gg J$) we have treated.

10.7
More Complex Splitting

Splitting becomes more complex if coupling occurs to more than one type of hydrogen. Consider the case of H_a coupled to two different hydrogens, H_b and H_c, with $J_{ab} > J_{ac}$.



$$\begin{array}{ccccc} H_b & & H_a & & H_c \\ | & & | & & | \\ C & - & C & - & C \end{array}$$

H_a is split into a doublet by H_b and each of the lines of the doublet is split into a further doublet to give a total of four lines as shown in Figure 10.20. The four lines will have approximately the same intensity. The four lines correspond to transitions of H_a when the H_b and H_c nuclei have the following spin states:

Line	Spin of H_b	Spin of H_c
1	α	α
2	α	β
3	β	α
4	β	β

In this example, $J_{ab} > J_{ac}$. This means that the effect of nucleus H_b on H_a is greater than the effect of nucleus H_c on H_a. Thus, line 2 appears at lower field than the resonance position of H_a in the absence of H_b and H_c, because the α and β spins of the two nuclei do not cancel. Similarly, line 3, which corresponds to a transition of H_a when H_b is β and H_c is α, is at slightly higher field than the resonance

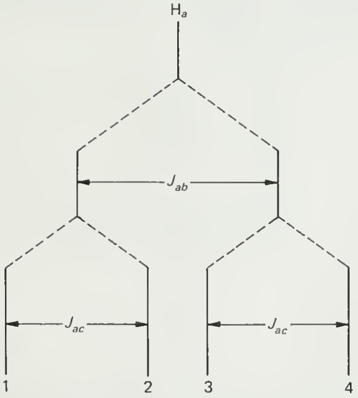


FIGURE 10.20 *Effect of two J couplings,* $J_{ab} > J_{ac}$.

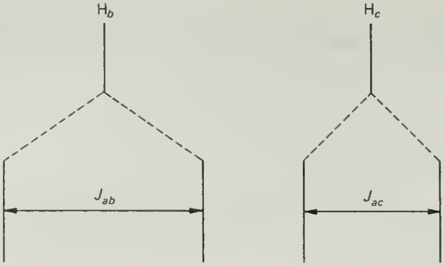


FIGURE 10.21 *The* H_b *and* H_c *resonances of the system* H_b-H_a-H_c *when* $J_{ab} > J_{ac}$.

position of H_a in the absence of the other nuclei. The remainder of the spectrum will show H_b and H_c each as doublets, due to their respective couplings to H_a (Figure 10.21).

Note what happens if $J_{ab} = J_{ac}$. This will occur if H_b and H_c are magnetically equivalent (that is, if they have the same chemical shift) or if the two *J*s accidentally have the same value. In such a case the two inner lines of the quartet occur at the same point and appear as a single line of double the intensity. The net result is a triplet with intensity ratios of 1:2:1 (Figure 10.22).

The spectra of 1,3-dichloropropane (Figure 10.23) and 1-bromo-3-chloropropane (Figure 10.24) are interesting examples. In 1,3-dichloropropane, the four CH_2Cl protons are magnetically equivalent. Each CH_2Cl group is adjacent to the middle CH_2 and therefore appears as a 1:2:1 triplet centered at $\delta = 3.66$ ppm. The center CH_2 appears at $\delta = 2.1$ ppm. This resonance is a quintet with an approximate intensity ratio of 1:4:6:4:1 due to splitting by the four magnetically equivalent CH_2Cl hydrogens (Table 10.1).

In 1-bromo-3-chloropropane the CH_2Cl hydrogens and the CH_2Br hydrogens are not magnetically equivalent and, therefore, they do not have the same chemical shift. Each is adjacent to two hydrogens (the center CH_2 group) and each appears as a 1:2:1 triplet. The chemical shifts for CH_2Cl ($\delta = 3.66$ ppm) and CH_2Br ($\delta = 3.54$ ppm) are almost the same, so the two triplets **overlap** one another. Even though CH_2Cl and CH_2Br are not magnetically equivalent, the two *J*s are accidentally equal. Therefore, the center CH_2 still appears as a 1:4:6:4:1 quintet with $\delta = 2.15$ ppm.

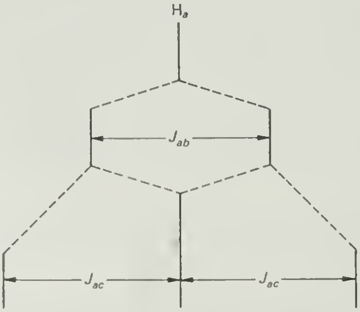


FIGURE 10.22 *Effect of equal* J *values,* $J_{ab} = J_{ac}$.

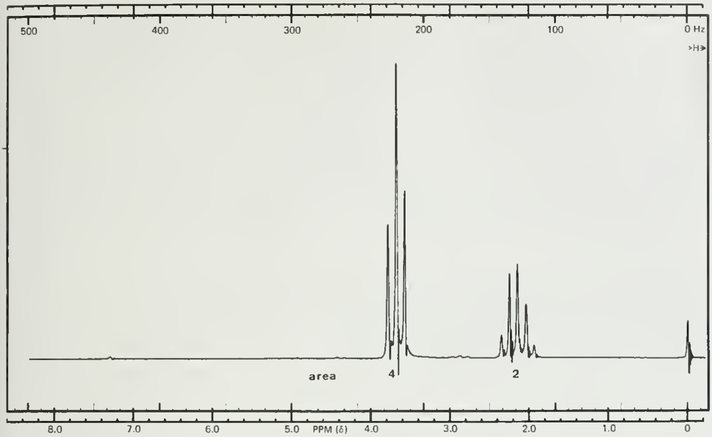


FIGURE 10.23 Nmr *spectrum of* 1,3-*dichloropropane,* $ClCH_2CH_2CH_2Cl$.

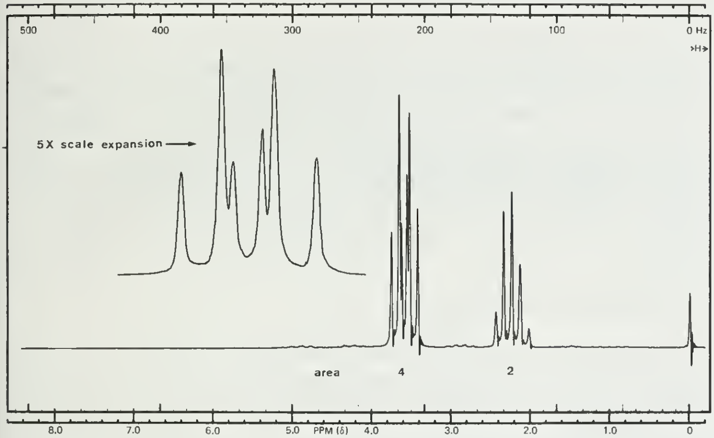
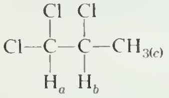


FIGURE 10.24 Nmr *spectrum of* 1-*bromo*-3-*chloropropane,* $BrCH_2CH_2CH_2Cl$.

Figure 10.25 shows the spectrum of 1,1,2-trichloropropane, a compound in which there are two different coupling constants. There are three different types of hydrogen, which we may label H_a, H_b, and H_c.



$$Cl{-}\underset{H_a}{\overset{Cl}{C}}{-}\underset{H_b}{\overset{Cl}{C}}{-}CH_{3(c)}$$

The H_a hydrogen is most deshielded and appears as a low field resonance with relative area of unity. It is a doublet due to coupling with H_b and the separation

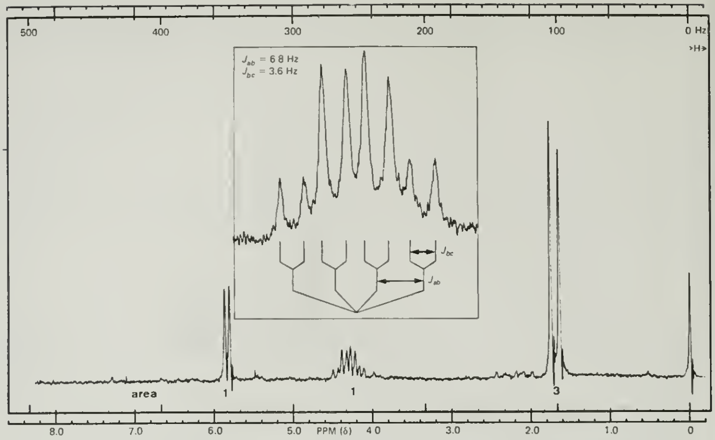


FIGURE 10.25 Nmr *spectrum of* 1,1,2-*trichloropropane*, $CH_3CHClCHCl_2$. *The center band is expanded in the insert.*

between the two lines, J_{ab}, is 3.6 Hz. The three equivalent CH_3 hydrogens, H_c, are least deshielded and appear as a high field resonance of area 3. They are also coupled to H_b and appear as a doublet. In this case, the separation between the lines, J_{bc}, is 6.8 Hz. The two coupling constants in this case are unequal. The resonance for H_b is in between those of H_a and H_c and it has a relative area of unity. Because of the two unequal *J*s, it appears as a "doubled quartet" and may be analyzed as shown on the insert in Figure 10.25. The chemical shift for H_b is $\delta = 4.3$ ppm, the midpoint of the multiplet.

10.8
Solving Spectral Problems

Going back to our spectra of the propyl chlorides in Section 10.2, we can now apply our knowledge to interpret those spectra. In the nmr spectrum of *n*-propyl chloride (Figure 10.2), for example, the methyl group is clearly distinguished as the group farthest upfield ($\delta = 1.2$), split into a triplet by its neighboring methylene group. The chlorine-bearing methylene group is farthest downfield ($\delta = 3.6$), also split into a triplet by its neighboring methylene group. The center methylene group is expected to be split into a quartet by the adjacent methyl and into a triplet by the adjacent methylene. If these two interactions had different *J* values, we would indeed see a total of twelve lines under sufficient resolution. However, because the two *J* values are approximately the same (note that the CH_3 quartet and the CH_2Cl triplet have approximately equal splittings), the splitting in the middle CH_2 group is that expected for five magnetically equivalent hydrogens, namely six peaks.

The spectrum of isopropyl chloride in Figure 10.3 is simpler. Both methyl groups are equivalent and appear as a doublet caused by the C-2 hydrogen and having a total area six times that of the downfield resonance of the single C-2 hydrogen. The downfield position of $\delta = 4.05$ ppm results from deshielding of the neighboring electronegative chlorine. This peak is split into seven peaks by the six adjacent methyl hydrogens and appears as a multiplet.

The chemical shift of a given proton depends on its immediate neighborhood. Hence, hydrogens in different functional groups tend to have characteristic δ values, and the appearance of peaks having such δ values can be diagnostic of the presence of such functional groups. The relative area indicates the number of hydrogens of a given type, and the splitting provides information as to neighboring hydrogens. Extensive tables of δ values associated with different kinds of hydrogens have been compiled; an example is given in Appendix V. As we discuss different functional groups, we will also discuss any characteristic features of their spectra.

At the present time, we have discussed alkanes and halogenated alkanes in some detail. The appropriate nmr characteristics of these compounds are summarized in Table 10.2. Several important generalizations should be learned; these suffice for solving many problems without resorting to detailed tables:

1. Alkyl hydrogens have $\delta \simeq 1$ ppm.
2. δ (tertiary) $>$ δ (secondary) $>$ δ (primary).
3. A halogen atom on the same carbon causes a downfield shift by 2–3 ppm.
4. A halogen removed by one carbon still has an effect of about 0.5 ppm.
5. J for neighboring hydrogens on an alkane chain is usually in the range of 4–10 Hz.

An example of the way in which data are frequently presented and a structural problem is solved is shown in the Example.

Example. A compound, $C_4H_7Cl_3$, has the following spectrum:

δ, ppm: 0.9 (t, 3H); 1.7 (m, 2H); 4.3 (m, 1H); 5.8 (d, 1H).

In this shorthand the δ value in ppm is given for the center of a group of peaks. The number of peaks in the group is indicated by the code: s = singlet, d = doublet, t = triplet. Quartet and quintet are obvious, but it may not always be possible to resolve all of these peaks, and such multiple peak groups are

Table 10.2
Some Nmr Characteristics

Type of Hydrogen	δ, ppm (Measured Downfield from TMS)
RCH_3	0.9
R_2CH_2	1.25
R_3CH	1.5
RCH_2I	3.15
R_2CHI	4.2
RCH_2Br	3.3
R_2CHBr	4.1
RCH_2Cl	3.4
R_2CHCl	4.0
$-CH_2-\overset{\vert}{\underset{\vert}{C}}-X$	about 1.7

frequently recorded as m = multiplet. Finally, the number of hydrogens as determined from the area of each group of peaks is indicated.

To solve the problem shown, we generate hypotheses of structural units from the information given about δ values and put the units together with the help of the splitting information. The peaks at $\delta = 0.9$ ppm clearly correspond to a methyl group; the number of hydrogens indicated fits this hypothesis. The group at $\delta = 4.3$ ppm corresponds roughly to H—C—Cl but is somewhat shifted downfield, and $\delta = 5.8$ ppm is so far downfield it must correspond to $—CHCl_2$. We are left with a $—CH_2—$ group to assign to $\delta = 1.7$ ppm. Our structural units are:

$$\begin{gathered} CH_3— \\ —CH_2— \\ —CHCl— \\ CHCl_2— \end{gathered}$$

Since the methyl group is a triplet, it must be attached to the $—CH_2—$ group. Since $—CHCl_2$ is a doublet, it must be attached to —CHCl—. The entire structure then becomes

$$CH_3—CH_2—CHCl—CHCl_2$$

The CH_2 and CHCl protons give rise to complex multiplets because of the unequal coupling constants to their adjacent neighbors (see Figure 10.25).

Nmr

10.9
Nmr Spectroscopy of Other Nuclei

Up until now, we have discussed solely proton nmr (pmr), because this is the technique most commonly used by organic chemists. However, nmr experiments may be done with any element whose nuclei have a net magnetic spin. A few examples are given in Table 10.3.

TABLE 10.3
The Magnetic Properties of Some Nuclei

Isotope	Natural Abundance, %	Spin States	Resonance Frequency at 14,092 Gauss, MHz
^{1}H	99.88	$\pm\frac{1}{2}$	60
^{13}C	1.1	$\pm\frac{1}{2}$	15.1
^{19}F	100	$\pm\frac{1}{2}$	56.4
^{31}P	100	$\pm\frac{1}{2}$	24.4

^{19}F nmr and ^{13}C nmr (cmr) are used extensively. Cmr, in particular, is of great use in organic chemistry. Relatively inexpensive (about $50,000) cmr spectrometers are now available and the method is being used more and more. Within the next few years, cmr spectroscopy will probably become as indispensable to the practicing organic chemist as proton nmr is today.

Cmr is a perfect complement to pmr. While pmr allows us to "see" the protons attached to the carbon framework of an organic compound, cmr allows us to see the carbons themselves. However, there is one important difference between the two techniques. In pmr, we are observing the most abundant isotope, ^{1}H. For carbon, the most abundant isotope, ^{12}C, has an even-even nucleus that has no net nuclear spin or magnetic moment. Therefore, we must observe the isotope

^{13}C, which has a natural abundance of only about 1%. This low abundance is both a blessing and a curse. A simplifying feature is that, since the natural abundance of ^{13}C is so low, the chance that we will find two ^{13}C nuclei adjacent to each other in the same molecule is very small ($10^{-2} \times 10^{-2} = 10^{-4}$). Therefore, one does not observe spin-spin splitting between the carbon nuclei. However, the low abundance means that the spectrometer must be much more sensitive than is sufficient for pmr.

The problem of sensitivity has been overcome in several ways. One obvious way is to use much larger samples. However, in most cases this method is impractical. Another method for enhancing the weak ^{13}C signals is to run the spectrum over and over again and store the individual spectra in a computer. The computer averages the spectra and plots out the accumulated spectrum in a conventional manner. In this way, the many small signals eventually add up to give signals of sufficient intensity so that they may be distinguished from the normal electronic "noise." Since the electronic noise is random, it eventually averages out to a relatively low value. In practice, many scans of the spectrum are required to achieve the required enhancement in the signal-to-noise ratio (100–10,000). In a normal mode of operation, a scan requires on the order of 5–10 minutes. Therefore, this technique would be very time-consuming (8 hr to 5 weeks for a single spectrum). By using a pulse technique in connection with Fourier transform (FT) mathematical analysis, this barrier is overcome. We shall not review the principles of the method here but simply mention that it enables a single scan to be accomplished in about 1 sec. Thus, it is possible to obtain cmr spectra with good signal-to-noise ratios in reasonable periods of time.

Figure 10.26 shows the cmr spectrum of 1,2,2-trichloropropane. The spectrum was determined on a Varian CFT-20 spectrometer, operating at a field strength

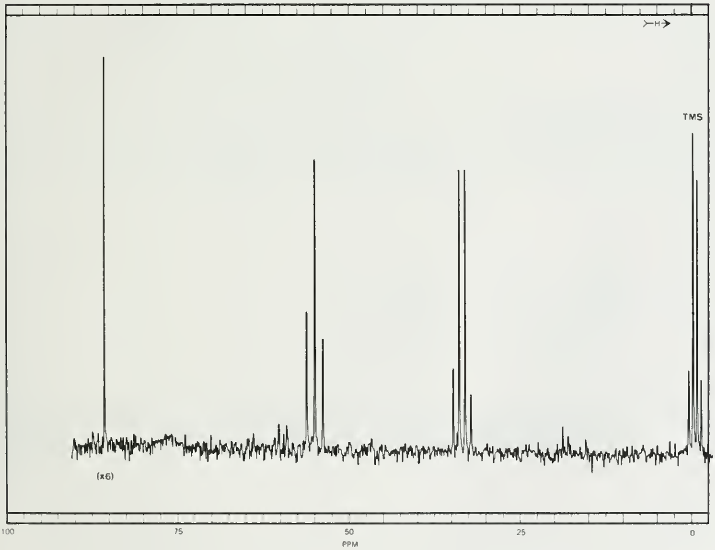


Figure 10.26 *Cmr spectrum of 1,2,2-trichloropropane.*

of 18,665 gauss, which corresponds to a frequency of 20 MHz for ^{13}C. The spectrum was determined by a method called "proton off-resonance decoupling." In this mode of operation, one observes only one-bond couplings, that is, $^{13}C—H$, and these are reduced in magnitude by a considerable factor. Two-bond couplings, $^{13}C—C—H$, are not observed.

In the spectrum in Figure 10.26 note that we see three signals corresponding to the three carbon atoms. The small multiplet at the right is our standard, TMS, which appears as a quartet, due to coupling to the three hydrogens joined to each methyl carbon. In cmr, as in pmr, the TMS resonances appear at high field, because of the electropositive silicon. The three carbon atoms in trichloropropane appear as a singlet, triplet, and quartet, due to spin-spin splitting by their attached hydrogens (zero, two, and three, respectively). As in pmr, the electronegative chlorines result in C-1 and C-2 resonating downfield from C-3. Note that the chemical shifts in cmr are much greater than in pmr.

The spectrum in Figure 10.27 is also of 1,2,2-trichloropropane, but in this case the spectrum was measured while simultaneously applying a strong radio frequency field of 80 MHz. At the field strength of 18,665 gauss, protons resonate at this frequency. Since the hydrogen nuclei are being constantly excited, they do not spend sufficient time in either the α or β spin state to couple with the ^{13}C nuclei. That is, on the nmr time scale each hydrogen is in an average or effectively constant state and the result is that no coupling is observed. This process is called **decoupling** and the spectrum in Figure 10.26 is said to be **proton decoupled.** Each carbon nucleus now appears as a sharp singlet and the entire spectrum is greatly simplified.

10.2

In Figures 10.26 and 10.27, the signal due to C-2, which appears 88.3 ppm downfield from TMS has been amplified by a factor of 6. In cmr, unlike pmr, the peak areas

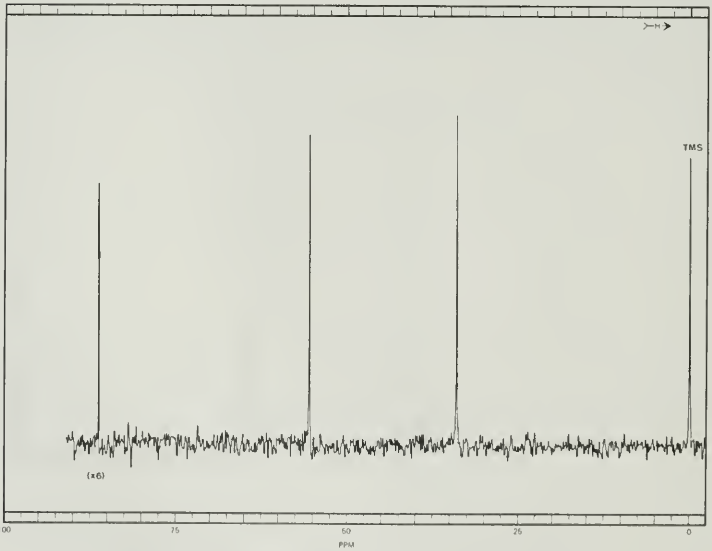


FIGURE 10.27 *Proton-decoupled* cmr *spectrum of* 1,2,2-*trichloropropane.*

are not always proportional to the number of atoms involved. Some carbon nuclei, particularly those with no attached hydrogens, relax from an excited spin state to the ground state rather slowly compared to the pulse time. Hence, such carbons tend to be magnetically partially saturated.

For structure work, it is convenient to obtain both types of spectra. For complex molecules, the proton decoupled spectrum often allows one to "see" each carbon resonance and to measure its chemical shift accurately. The proton coupled spectrum then allows the analyst to determine the number of hydrogens attached to each carbon. By using this data, together with the pmr spectrum, even complex structures may be solved.

PROBLEMS

Be able to do probs 1–6

1. Fill in the blank spaces in the following statement:
In the nmr spectrum of ethyl bromide, the methyl hydrogens have $\delta = 1.7$ ppm, the methylene hydrogens have $\delta = 3.3$ ppm, and $J = 7$ Hz. The number of peaks given by the methyl hydrogens is ________ with the approximate area ratio: ________. These peaks are separated by ________ Hz. The number of peaks given by the methylene hydrogens is ________ with the approximate area ratio: ________. These peaks are separated by ________ Hz. The total area of the methyl peaks compared to the methylene peaks is in the ratio: ________. Of these two groups of peaks, the ________ peaks are farther downfield. The chemical shift difference between these peaks of 1.6 ppm corresponds in a 60 MHz instrument to ______ Hz.

2. The nmr spectra for some isomers of $C_5H_{10}Br_2$ are summarized as follows. Deduce the structure corresponding to each spectrum.
(a) δ, 1.0 (s, 6H); 3.4 (s, 4H).
(b) δ, 1.0 (t, 6H); 2.4 (quart, 4H).
(c) δ, 0.9 (d, 6H); 1.5 (m, 1H); 1.85 (t, 2H); 5.3 (t, 1H).
(d) δ, 1.0 (s, 9H); 5.3 (s, 1H).
(e) δ, 1.0 (d. 6H); 1.75 (m, 1H); 3.95 (d, 2H); 4.7 (quart, 1H).
(f) δ, 1.3 (m, 2H); 1.85 (m, 4H); 3.35 (t, 4H).

3. Free radical chlorination of propane, using 1 mole of C_3H_8 and 2 moles of Cl_2 gives a complex mixture of chlorination products. By careful fractional distillation of the product mixture, one may isolate four dichloropropanes, A, B, C, and D. From the nmr spectra of the four isomers, deduce their structures.

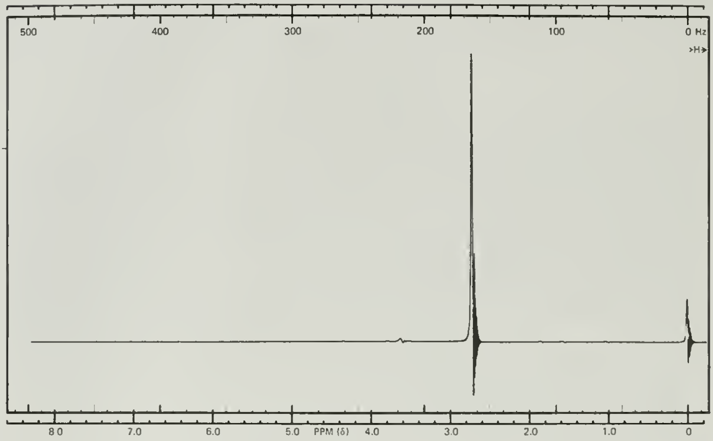
Compound	Boiling Point, °C	Nmr
A	69	δ2.4 (s, 6H)
B	88	δ1.2 (t, 3H); δ1.9 (quint, 2H); δ5.8 (t, 1H)
C	96	δ1.4 (d, 3H); δ3.8 (d, 2H); δ4.3 (sext, 1H)
D	120	δ2.2 (quint, 2H); δ3.7 (t, 4H)

4. There are 9 possible isomers (not counting stereoisomers) of $C_4H_8Br_2$. Two of them have the following nmr spectra. Deduce the structures of each and indicate the logic used in your assignment.
(a) δ, 1.7 (d, 6H)
δ, 4.4 (quart, 2H)
(b) δ, 1.7 (d, 3H)
δ, 2.3 (quart, 2H)
δ, 3.5 (t, 2H)
δ, 4.2 (m, 1H)

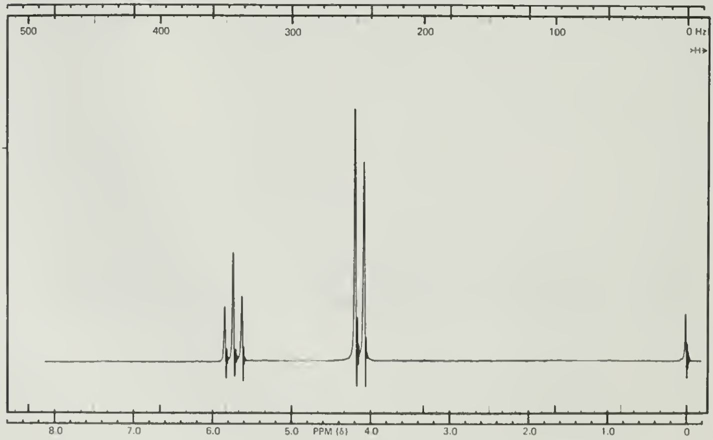
5. Sketch the expected nmr spectra of the following compounds. Be sure to represent the expected δ for each group of peaks, the relative areas and the splittings.
   - (a) $CH_3CBr_2CH_3$
   - (b) CH_3CH_2Br
   - (c) $CH_3CHBrCHBrCH_3$
   - (d) $CH_3CBr_2CH_2CH_3$
   - (e) $CH_3CHClCH_2CH_2Cl$

6. Deduce the structure corresponding to each of the following nmr spectra:

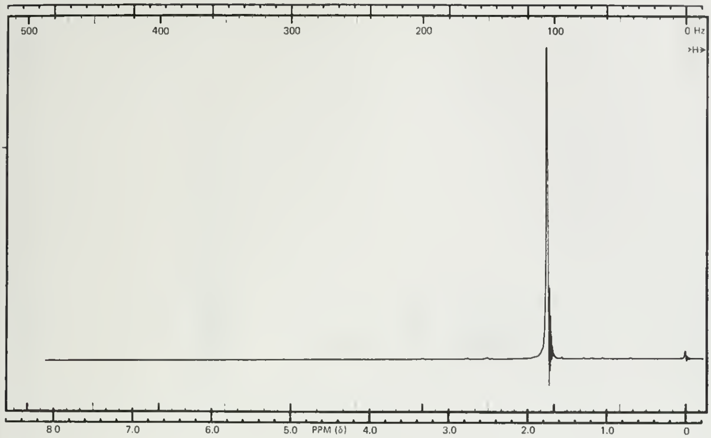
(a.) $C_2H_3Cl_3$



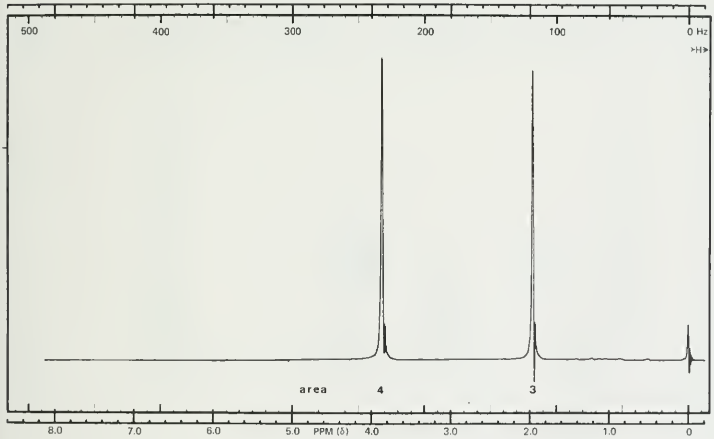
(b) $C_2H_3Br_2$



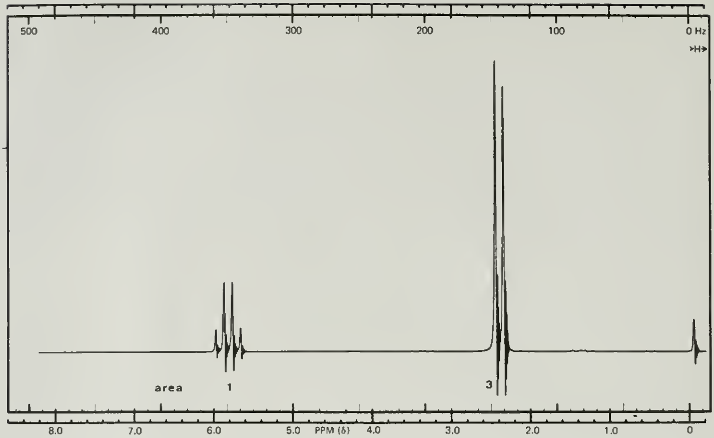
(c) C_4H_9Br



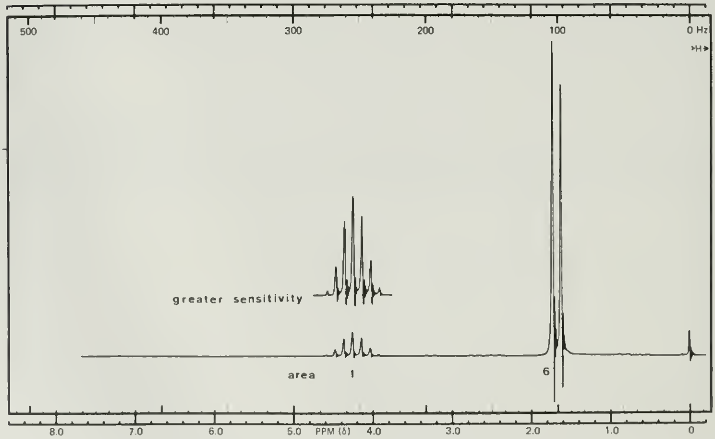
(d) $C_4H_7Br_3$



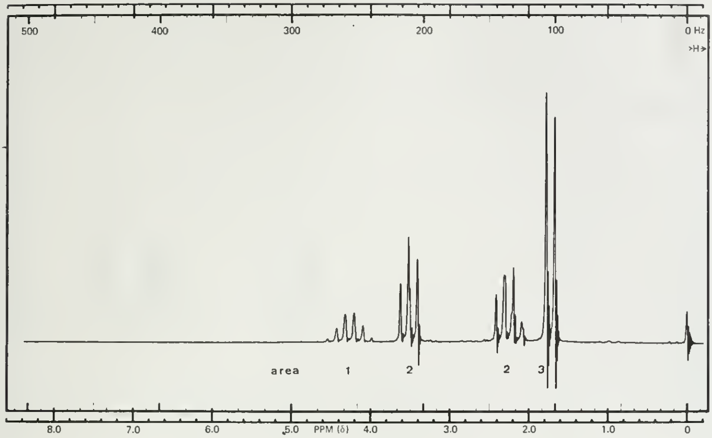
(e) $C_2H_4Br_2$



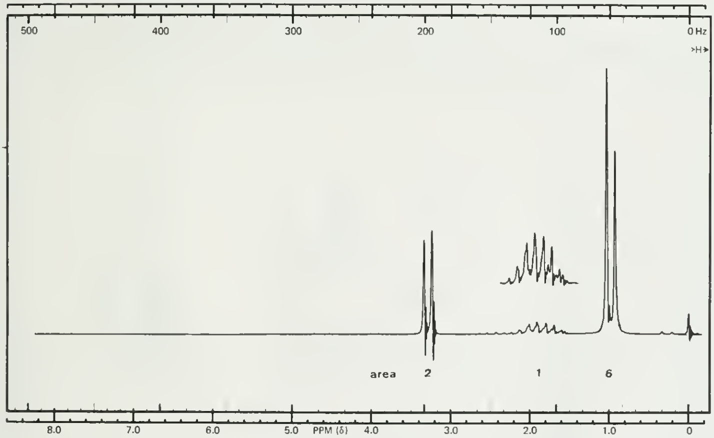
(f) C_3H_7Br



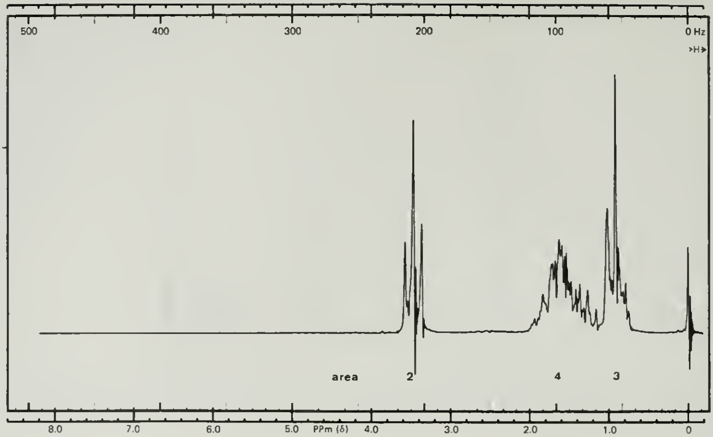
(g) $C_4H_8Br_2$



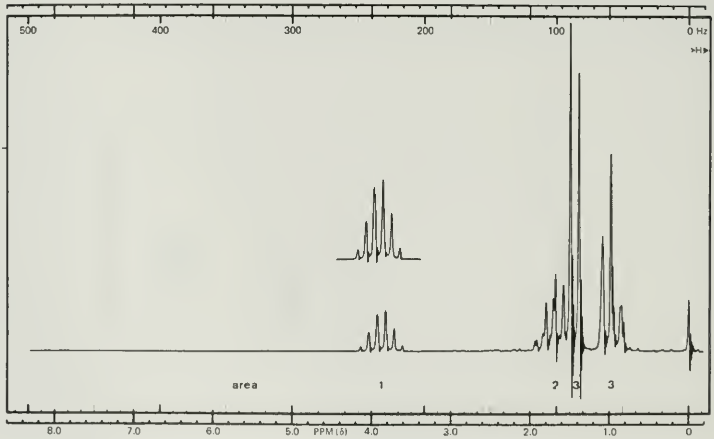
(h) C_4H_9Cl



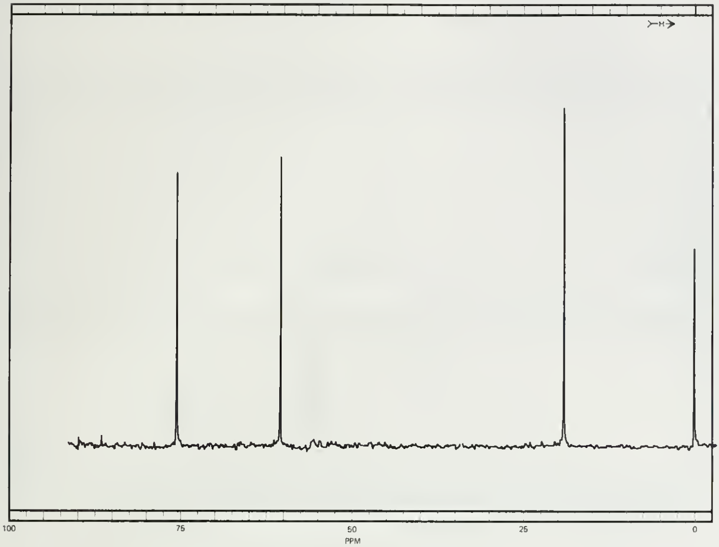
(i) C_4H_9Cl

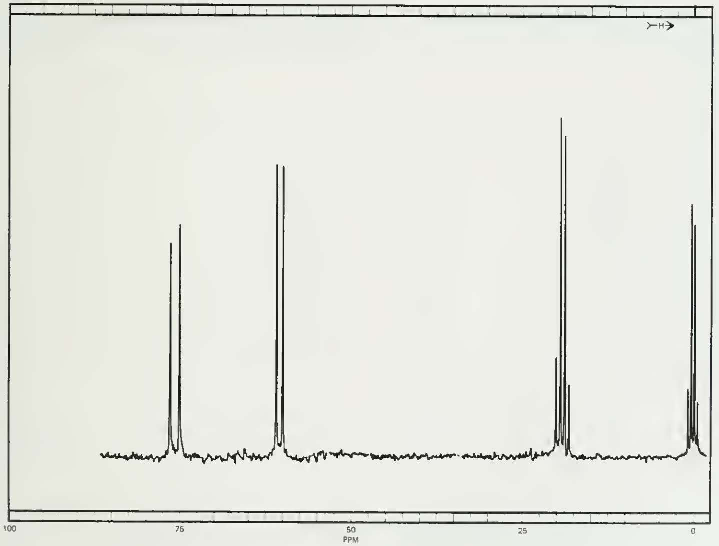


(j) C_4H_9Cl



7. While in the process of writing this chapter, the authors ordered a sample of 1,2,2-trichloropropane from a chemical supplier in order to obtain its nmr spectra. The proton coupled and decoupled cmr spectra of the commercial sample were determined first and are reproduced below. The bottle was obviously mislabeled. What is the actual structure of this compound?

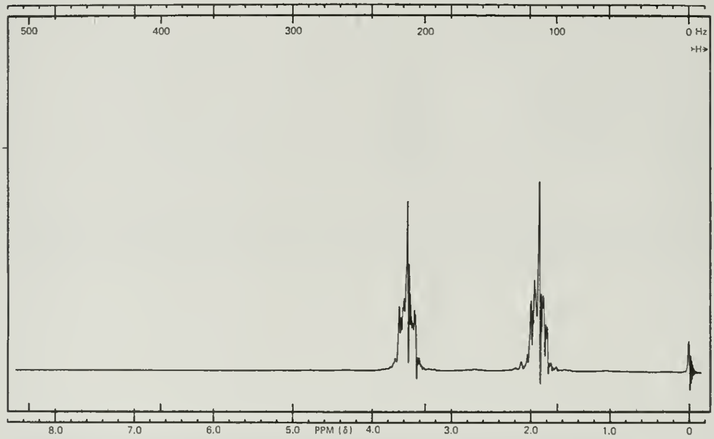


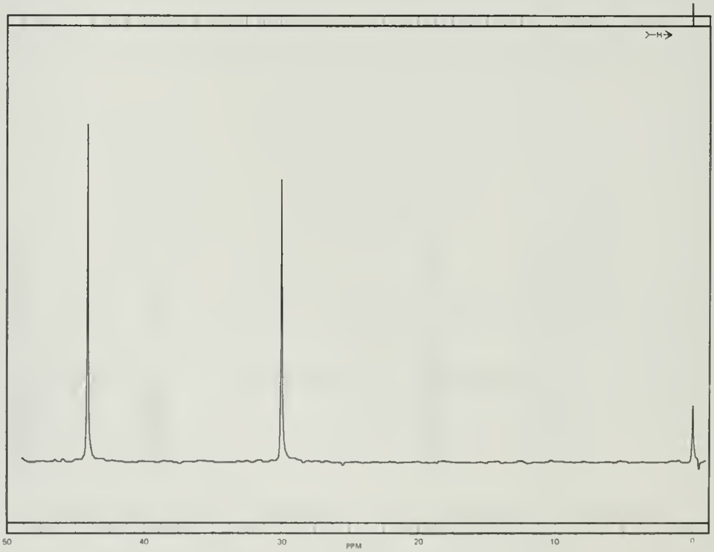


8. The pmr spectrum of chloroform shows a single intense peak at $\delta = 7.27$ ppm. Careful examination, however, shows a small peak 104.5 Hz above and below the main peak. These peaks are associated with $^{13}CHCl_3$. Explain. What sort of cmr spectrum would you expect for $^{13}CHCl_3$?

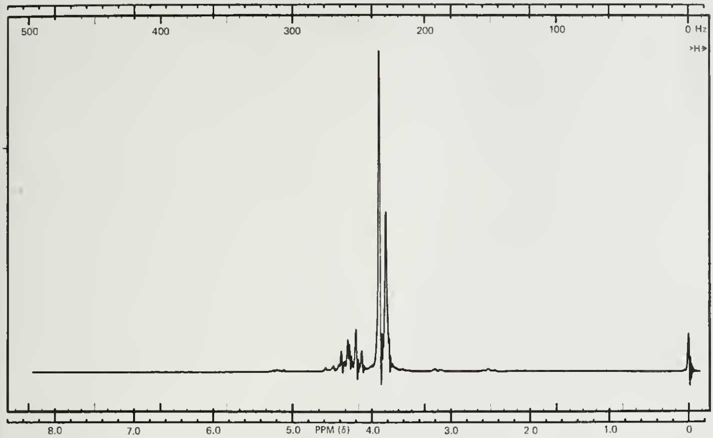
9. Deduce the structure of each of the following compounds from the pmr and proton decoupled cmr spectra.

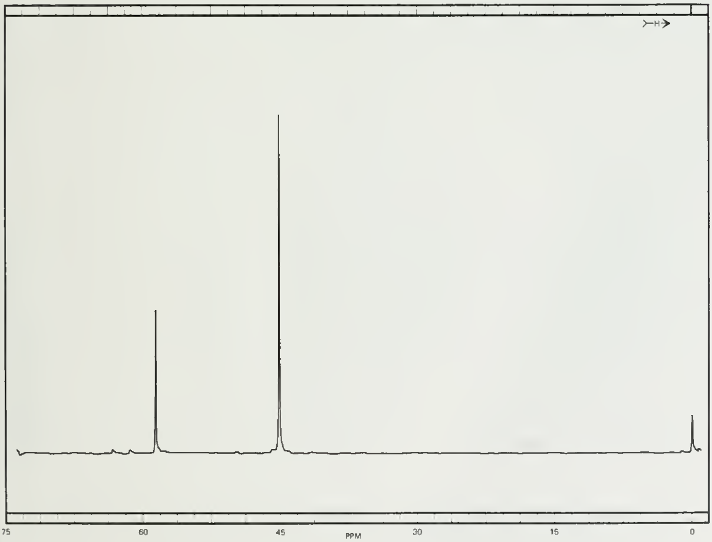
(a) $C_4H_8Cl_2$



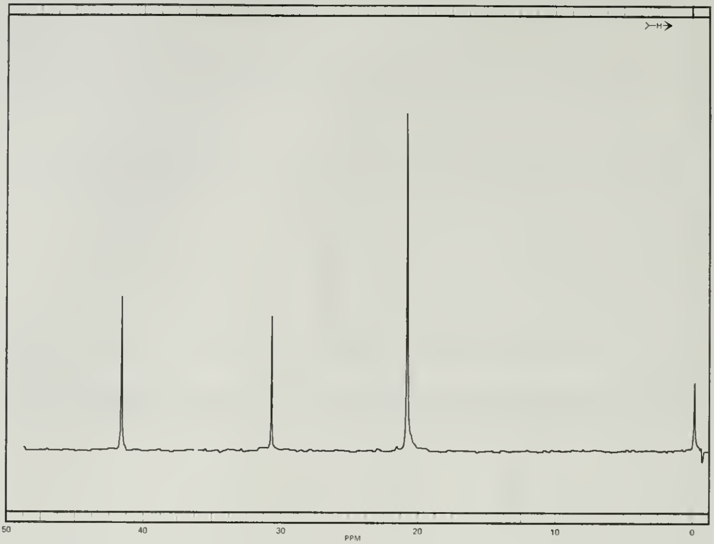


(b) $C_3H_5Cl_3$

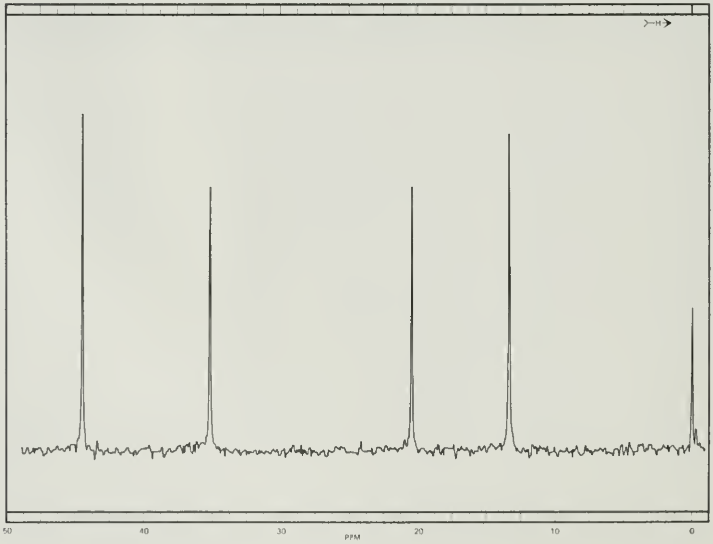

500
400
300
200
100
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


75
60
45
PPM
30
15
0

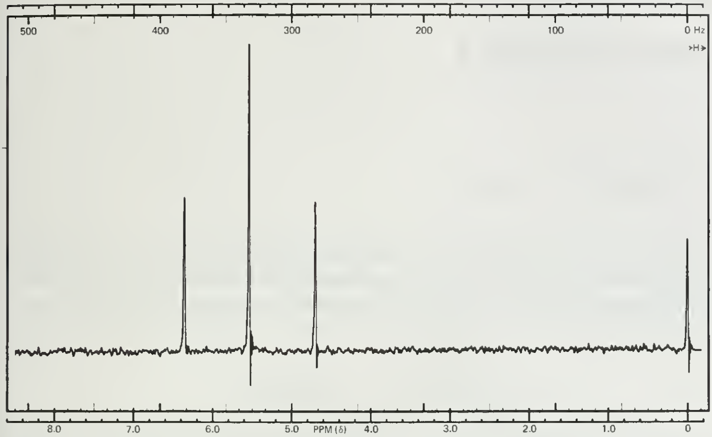
10. Deduce the structure of the following compound (C_4H_9Br) from its proton-decoupled cmr spectrum. What will its pmr spectrum look like?



11. There are four compounds with the formula C_4H_9Cl. The proton-decoupled cmr spectrum of one of the isomers is shown below. Which isomers are eliminated by the spectrum? Which isomers might give such a spectrum? Describe how the proton-coupled cmr spectrum can be used to decide which C_4H_9Cl isomer the compound is.



★ **12.** The pmr spectrum of difluoromethane, measured as a dilute solution in carbon tetrachloride, is shown below. Provide an interpretation of the spectrum. (*Hint*: recall that the fluorine nucleus, ^{19}F, also has spin of $\pm\frac{1}{2}$.)



★ **13.** The radio waves used to irradiate the nmr sample are absorbed in converting α spin states to β and are converted ultimately to heat. To see how much heat is involved calculate approximately the temperature increase produced in 1 ml of an nmr solution containing 0.01 moles of protons in a 60 MHz nmr instrument. For the purpose of this calculation consider that the entire excess population of α spins is converted to β and that the heat capacity of the solution is 1 cal deg^{-1} ml^{-1}.

CHAPTER 11

Alcohols, Ethers, Thiols, and Sulfides

11.1
Introduction: Structure

Alcohols are compounds in which an alkyl group replaces one of the hydrogens of water. They are organic compounds that contain the functional group —OH. As we shall see, this functional group dominates the chemistry of alcohols. **Ethers** are analogs of water in which both hydrogens are replaced by alkyl groups.

$$CH_3{-}OH \qquad CH_3{-}O{-}CH_3$$

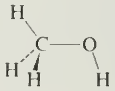
an alcohol (methyl alcohol) — an ether (dimethyl ether)

Thiols, or **mercaptans**, contain the functional group —SH. **Sulfides** have two alkyl groups attached to sulfur. Thiols and sulfides are related to hydrogen sulfide in the same way that alcohols and ethers are related to water.

$$CH_3{-}SH \qquad CH_3{-}S{-}CH_3$$

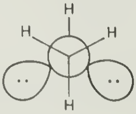
a thiol (methyl mercaptan) — a sulfide (dimethyl sulfide)

The geometry of methyl alcohol, as determined by microwave spectroscopy, is shown as follows·

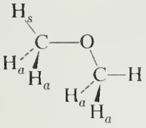


Bond Lengths, A		Bond Angles, deg	
C—H	1.10	H—C—H	109
O—H	0.96	H—C—O	110
C—O	1.43	C—O—H	108.9

The hybridization of carbon is approximately sp^3. The hybridization of oxygen may also be described as approximately sp^3. Oxygen makes one bond to carbon and one to hydrogen. The O—H bond distance is precisely the same as the O—H bond distance in water. Conformationally, the molecule exists in a structure that has the O—H bond staggered between two C—H bonds and the barrier to rotation about the C—O bond is 1.1 kcal mole^{-1}. It is frequently useful to consider the oxygen lone pair electrons to occupy orbitals that are each approximately sp^3; such lone pair orbitals are each staggered between two adjacent C—H bonds.

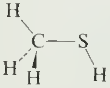


In dimethyl ether, the methyl groups are bent apart to minimize nonbonded interactions between the hydrogens marked *a* in the following structural formula. There are two O—C—H and two H—C—H angles, but all of the angles are close to the tetrahedral value of 109.5°.



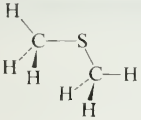
Bond Distances, A		Bond Angles, deg	
C—H	1.10	C—O—C	111.7
C—O	1.41	O—C—H_a	110.8
		O—C—H_s	107.2
		H_a—C—H_a	108.7
		H_a—C—H_s	109.5

Methyl mercaptan differs from methyl alcohol mainly in the length of the C—S bond, relative to C—O, and in the relatively sharp C—S—H angle. In thiols, as in H_2S itself, sulfur uses orbitals for bonding that are rich in *p* character. The barrier to rotation about the C—S bond is identical to that in methanol, 1.1 kcal mole^{-1}.



Bond Distances, A		Bond Angles, deg	
C—H	1.10	H—C—H	110.2
C—S	1.82	H—C—S	108
S—H	1.33	C—S—H	100.3

A similar structure is found for dimethyl sulfide. Again, the C—S—C angle is relatively small, corresponding to C—S bonds in which sulfur uses a high percentage of its 3*p* orbitals.



Bond Distances, A		Bond Angles, deg	
C—H	1.09	H—C—H	109.5
C—S	1.80	H—C—S	106.7
		C—S—C	98.9

The simple alcohols are important industrial materials. They are also used extensively as laboratory reagents and as solvents. The most important representative of the class is undoubtedly ethyl alcohol. Dilute solutions of this compound containing flavorsome impurities have been known since the dawn of civilization. Indeed, it has been suggested that the discovery of alcohol fermentation and the physiological effects of its product provided a major incentive for agriculture and the start of civilization! Alcohols can be prepared readily from many other classes of compounds and can, in turn, be transformed into many others. For this reason, alcohols play a key role as synthetic intermediates.

11.2
Nomenclature of Alcohols

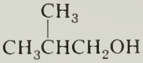
As with most other classes of organic compounds, alcohols can be named in several ways. Common names are useful only for the simpler members of a class.

However, common names are widely used in colloquial conversation and in the scientific literature. In order to communicate freely, the student must know common names. Since the systematic IUPAC names are often used for indexing the scientific literature, the student must be thoroughly familiar with systematic names in order to retrieve data from the literature.

1. THE ALKYL ALCOHOL SYSTEM. In this system of common nomenclature, the name of an alcohol is derived by combining the name of the alkyl group with the word alcohol. The names are written as two words.

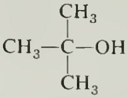
$CH_3CH_2CH_2CH_2OH$

n-butyl alcohol



$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2OH$

isobutyl alcohol



$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-OH$

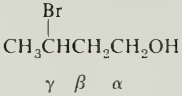
t-butyl alcohol

In this common system, the position of an additional substituent is indicated by use of the Greek alphabet rather than by numbers.

$ClCH_2CH_2OH$

$\beta \quad \alpha$

β-chloroethyl alcohol



$CH_3\overset{\overset{Br}{|}}{C}HCH_2CH_2OH$

$\gamma \quad \beta \quad \alpha$

γ-bromobutyl alcohol

This use of the Greek alphabet is widespread in organic chemistry and it is important to learn the first few letters, at least through delta. The entire Greek alphabet is given in Table 11.1. Many of the letters, small and capital, have evolved standard meanings in the mathematical and physical sciences (for example, the number π). In organic chemistry, the lower case letters are used more frequently than the capital letters.

The last letter of the Greek alphabet is omega, ω. Correspondingly, this letter is used to refer to difunctional compounds when the secondary substituent is on the end carbon of the chain.

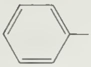
$Br(CH_2)_nOH$

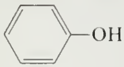
ω-bromo alcohols

TABLE 11.1
Greek Alphabet

Symbol			Symbol		
Lower case	Capital	Name	Lower case	Capital	Name
α	Α	alpha	ν	Ν	nu
β	Β	beta	ξ	Ξ	xi
γ	Γ	gamma	ο	Ο	omicron
δ	Δ	delta	π	Π	pi
ε	Ε	epsilon	ρ	Ρ	rho
ζ	Ζ	zeta	σ	Σ	sigma
η	Η	eta	τ	Τ	tau
θ	Θ	theta	υ	Υ	upsilon
ι	Ι	iota	φ	Φ	phi
κ	Κ	kappa	χ	Χ	chi
λ	Λ	lambda	ψ	Ψ	psi
μ	Μ	mu	ω	Ω	omega

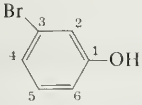
Any simple radical that has a common name may be used in the alkyl alcohol system, with one important exception. The grouping C_6H_5— has the special name **phenyl**, but the compound C_6H_5OH is **phenol**, not phenyl alcohol.


phenyl radical

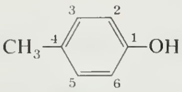


phenol
(not phenyl alcohol)

Substituted phenols are named as derivatives of the parent compound phenol.



3-bromophenol

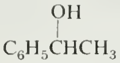


4-methylphenol

The reason for this difference is historical and arose from the fact that phenol and its derivatives have many chemical properties that are very different from those of alkyl alcohols. In this text, phenols are considered as a separate class of compounds (Chapter 33).

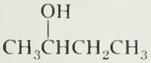
However, phenyl substituted alkyl alcohols are normal alcohols and often have common names. Examples are

$C_6H_5CH_2OH$
benzyl alcohol

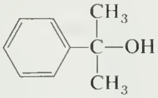

$C_6H_5\overset{OH}{\overset{|}{C}}HCH_3$
α-phenylethyl alcohol

$C_6H_5CH_2CH_2OH$
β-phenylethyl alcohol

2. **The Carbinol System.** In this system, the simplest alcohol, CH_3OH, is called **carbinol.** More complex alcohols are named as alkyl substituted carbinols. The names are written as one word.


$CH_3\overset{OH}{\overset{|}{C}}HCH_2CH_3$
ethylmethylcarbinol

$(CH_3CH_2)_3COH$
triethylcarbinol



dimethylphenylcarbinol

The number of carbons attached to the carbinol carbon distinguishes primary, secondary, and tertiary carbinols. As in the case of the alkyl halides, this classification is useful because the different types of alcohols show important differences in reactivity under given conditions. The carbinol system of nomenclature has been falling into disuse in recent years. However, it is found extensively in the older organic chemical literature.

3. **The IUPAC System.** In the IUPAC system of nomenclature, alcohols are named by replacing the **-e** of the corresponding alkane name by the suffix **-ol**, that is, as **alkanols**.

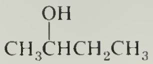
CH_3OH
methanol

CH_3CH_2OH
ethanol

The **alkan-** stem corresponds to the longest carbon chain in the molecule *which* *contains the —OH group.* The chain is numbered so that the OH group gets the smaller of two possible numbers.

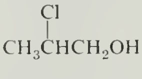
$CH_3CH_2CH_2CH_2OH$

1-butanol
or butan-1-ol

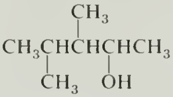

$CH_3\overset{OH}{\overset{|}{C}}HCH_2CH_3$

2-butanol
or butan-2-ol

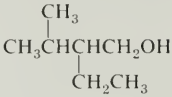
Substituents are appended as prefixes and are numbered according to the numbering system established by the position of the OH group. Names are written as one word, with no spaces.


$CH_3\overset{Cl}{\overset{|}{C}}HCH_2OH$

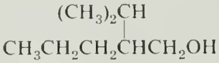
2-chloro-1-propanol


$CH_3\underset{CH_3}{\underset{|}{C}}H\overset{CH_3}{\overset{|}{C}}H\underset{OH}{\underset{|}{C}}HCH_3$

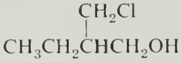
3,4-dimethyl-2-pentanol
(not 2,3-dimethyl-
4-pentanol)


$CH_3\overset{CH_3}{\overset{|}{C}}H\underset{CH_2CH_3}{\underset{|}{C}}HCH_2OH$

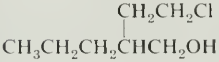
2-ethyl-3-methyl-
1-butanol
(not 2-isopropyl-
1-butanol; choose
chain with most
substituents)


$CH_3CH_2CH_2\overset{(CH_3)_2CH}{\overset{|}{C}}HCH_2OH$

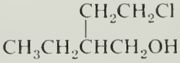
2-isopropyl-1-pentanol
(not 3-methyl-2-propyl-1-
butanol; pentanol has
longer chain)


$CH_3CH_2\overset{CH_2Cl}{\overset{|}{C}}HCH_2OH$

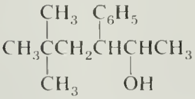
2-(chloromethyl)-1-butanol


$CH_3CH_2CH_2\overset{CH_2CH_2Cl}{\overset{|}{C}}HCH_2OH$

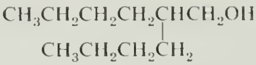
2-(2-chloroethyl)-1-pentanol
(not β-chloroethyl; do not
mix common and IUPAC systems)


$CH_3CH_2\overset{CH_2CH_2Cl}{\overset{|}{C}}HCH_2OH$

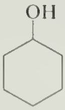
4-chloro-2-ethyl-1-butanol


$CH_3\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_2\overset{C_6H_5}{\overset{|}{C}}H\underset{OH}{\underset{|}{C}}HCH_3$

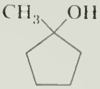
5,5-dimethyl-3-phenyl-2-hexanol


$CH_3CH_2CH_2CH_2\underset{CH_3CH_2CH_2CH_2}{\underset{|}{C}}HCH_2OH$

2-butyl-1-hexanol



cyclohexanol

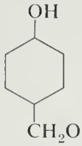


1-methylcyclopentanol

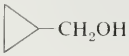
The general rule in the IUPAC system is that a functional group named as a suffix becomes a parent system that dominates the numbering scheme. Prefix groups are substituents or appendages to the parent.

Some kinds of alcohols are too difficult or cumbersome to name as alkanols.

For such compounds it is preferable to use the appropriate hydroxyalkyl name as a prefix.



4-(hydroxymethyl)cyclohexanol



(hydroxymethyl)cyclopropane

11.3
Physical Properties of Alcohols

The lower alcohols are liquids with characteristic odors and sharp tastes. One striking feature is their relatively high boiling points (Table 11.2). The OH group is roughly equivalent to a methyl group in approximate size and polarizability, but alcohols have much higher boiling points than the corresponding hydrocarbons; for example, compare ethanol (mol. wt. 46, b.p. 78.5°) and propane (mol. wt. 44, b.p. −42°). A plot of boiling point versus molecular weight for straight chain alcohols and alkanes is shown in Figure 11.1.

The abnormally high boiling points of alcohols are the result of a special type of dipolar association in the liquid phase. Both the C—O and the O—H bonds

TABLE 11.2
Physical Properties of Alcohols

Compound	Common Name	IUPAC Name	Melting Point, °C	Boiling Point, °C	Density, d^{20}	Sol. in Water, g/100 ml
CH_3OH	methyl alcohol	methanol	− 97.8	65.0	0.7914	∞
CH_3CH_2OH	ethyl alcohol	ethanol	−114.7	78.5	0.7893	∞
$CH_3CH_2CH_2OH$	*n*-propyl alcohol	1-propanol	−126.5	97.4	0.8035	∞
$CH_3CHOHCH_3$	isopropyl alcohol	2-propanol	− 89.5	82.4	0.7855	∞
$CH_3CH_2CH_2CH_2OH$	*n*-butyl alcohol	1-butanol	− 89.5	117.3	0.8098	8.0
$CH_3CH_2CHOHCH_3$	*sec*-butyl alcohol	2-butanol	−114.7	99.5	0.8063	12.5
$(CH_3)_2CHCH_2OH$	isobutyl alcohol	2-methyl-1-propanol		107.9	0.8021	11.1
$(CH_3)_3COH$	*tert*-butyl alcohol	2-methyl-2-propanol	25.5	82.2	0.7887	∞
$CH_3(CH_2)_4OH$	*n*-pentyl alcohol	1-pentanol	− 79	138	0.8144	2.2
$C_2H_5(CH_3)_2COH$	*tert*-pentyl alcohol	2-methyl-2-butanol	− 8.4	102	0.8059	∞
$CH_3CH_2CH_2CHOHCH_3$	—	2-pentanol		119.3	0.809	4.9
$CH_3CH_2CHOHCH_2CH_3$	—	3-pentanol		115.6	0.815	5.6
$(CH_3)_3CCH_2OH$	neopentyl alcohol	2,2-dimethyl-1-propanol	53	114	0.812	∞
$CH_3(CH_2)_5OH$	*n*-hexyl alcohol	1-hexanol	− 46.7	158	0.8136	0.7

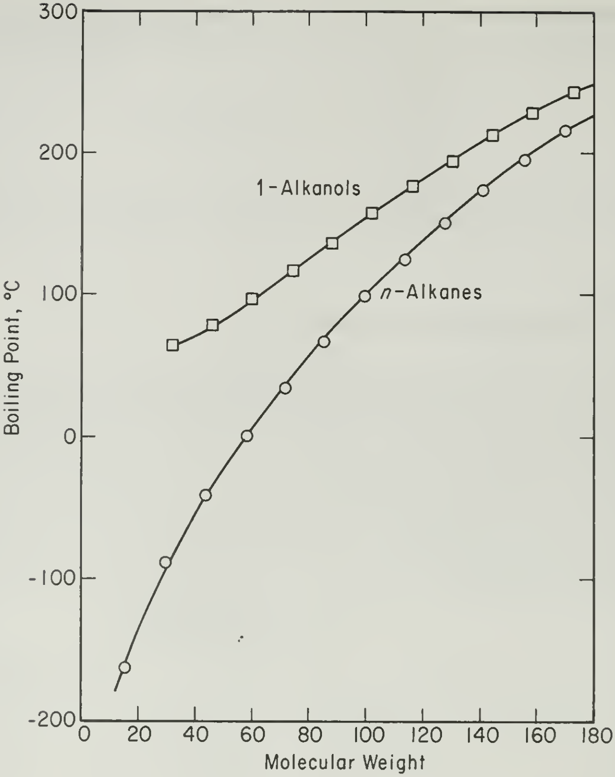


FIGURE 11.1 *Boiling points of 1-alkanols as a function of molecular weight.*

are polar because of the different electronegativities of carbon, oxygen, and hydrogen. These polar bonds contribute to the substantial dipole moments. However, the dipole moments of alcohols are no greater than those of corresponding chlorides.

$$CH_3OH,\ \mu = 1.71\ D \qquad CH_3Cl,\ \mu = 1.94\ D$$

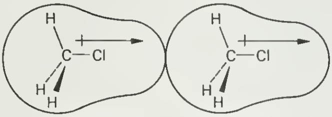
$$CH_3CH_2OH,\ \mu = 1.70\ D \qquad CH_3CH_2Cl,\ \mu = 2.04\ D$$

We expect electrostatic interaction between dipoles of the type, $+\!\!\longrightarrow\ +\!\!\longrightarrow$, but alcohols boil much higher than the corresponding chlorides. In fact, alkyl chlorides differ very little in boiling point from alkanes of corresponding molecular weight (Figure 6.2). It would seem, then, that dipolar attraction is not the cause of the elevated boiling points of alcohols. Or is it? The magnitudes of the individual dipole moments are not the only important factor. How closely the negative and positive ends of the dipoles can approach one another is also important.

By Coulomb's law two opposite charges attract each other with an energy proportional to $1/r$ where r is the distance between the charges. The electrostatic

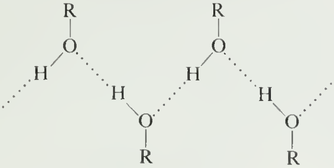
Va. der Waals radius [illegible] — the size of the atom [illegible] bonded [illegible]

energy of two dipoles depends on $1/r^2$, and therefore falls off sharply with distance. In alkyl halides the negative end of the dipoles is out at the lone pair electrons, but the positive end is in the C—X bond close to carbon. Because of the Van der Waals size of carbon the positive and negative ends of adjacent dipoles cannot get close together and the electrostatic energy of dipole-dipole attraction is relatively small.



Consequently, such dipole association does not have much of an effect on the energy required to separate alkyl halide molecules.

For alcohols the negative end of the dipole is out at the oxygen lone pairs, and the positive end is close to the small hydrogen. For hydrogen atoms bonded to electronegative elements dipole-dipole interaction is uniquely important and is called a **hydrogen bond.** This proximity of approach is shown by bond distance data. The O—H bond length in alcohols is 0.96 Å. The hydrogen bonded H···O distance is 2.07 Å, about twice as large. In fact, this distance is sufficiently small that some hydrogen bonds may have a significant amount of covalent or shared electron character. In condensed phases, alcohols are associated via a chain of hydrogen bonds:



The O—H bond in alcohols is stronger than most C—H bonds. It has a bond dissociation energy of 103 kcal mole^{-1}. The hydrogen bond is far weaker—only about 5 kcal mole^{-1}. Nevertheless, this additional energy must be supplied to produce monomeric molecules. This additional heat term in the heat of vaporization results in relatively high boiling points. A bond strength of 5 kcal mole^{-1} does not sound like much. However, when there are many such bonds, as in polyhydroxy compounds such as carbohydrates, the total strength is sufficient to hold up tall redwoods. We will also see that the combination of small individual strength and large combined group strength is exactly the kind of bonding required for the genetic code. Life as we know it is impossible without hydrogen bonds.

Since alcohols and water both contain the OH group, they have many properties in common. We should emphasize that water is a remarkable substance. Its boiling point of 100° is exceedingly high for a compound having a molecular weight of only 18. The extensive hydrogen bonding networks in liquid water make it a highly polar liquid having a dielectric constant of 78.5 at 25°.

The dielectric constant of a substance is the factor by which an electrostatic interaction in a vacuum is reduced by a medium of the substance. Coulomb's law

TABLE 11.3
Dielectric Constants of Alcohols

Compound	Dielectric Constant
H_2O	78.5
CH_3OH	32.6
CH_3CH_2OH	24.3
$CH_3(CH_2)_3OH$	17.1
$CH_3(CH_2)_4OH$	13.9
$CH_3(CH_2)_{11}OH$	6.5

for the electrostatic interaction of two charges, q_1 and q_2, separated by a distance, r, in a medium of dielectric constant, D, is given as:

$$E = \frac{q_1 q_2}{Dr}$$

In aqueous solution the interaction between ions is relatively small; hence, water is a good solvent for ionic compounds. The lower alcohols also have relatively high dielectric constants (Table 11.3). As the carbon chain gets longer, the importance of the OH group is reduced and the dielectric constant approaches the alkane value of about 2.

Methanol and ethanol are reasonably good solvents for salt-like compounds. Because they are also good solvents for organic compounds, they are used frequently for organic reactions such as S_N2 displacement reactions.

The OH group of alcohols can participate in the hydrogen bond network of water. The lower alcohols are completely soluble in water. As the hydrocarbon chain gets larger, the compound begins to look more like an alkane, and more of the hydrogen bonds in water must be broken to make room for the hydrocarbon chain. Since the hydrogen bonds that are lost are not completely compensated by bonding to the alcohol OH, solubility decreases as the hydrocarbon chain gets larger. A rough point of division is four carbons to one oxygen. Above this ratio, alcohols tend to have little solubility in water. This guideline is only approximate because the shape of the hydrocarbon portion is also important. *t*-Butyl alcohol is much more soluble than *n*-butyl alcohol because the *t*-butyl group is more compact and requires less room or broken water hydrogen bonds in an aqueous solution. A similar phenomenon is seen with the branched pentyl alcohols.

11.4
Acidity of Alcohols: Inductive Effects

One of the important properties of water is its self-ionization:

$$H_2O + H_2O \xrightleftharpoons{K_w} H_3O^+ + OH^-$$

In pure water, the concentrations of H_3O^+ and OH^- are very low, only 10^{-7} moles liter^{-1}. The ion product or self dissociation constant, K_w, is defined as

$$K_w = [H_3O^+][OH^-] = 1.0 \times 10^{-14} \text{ moles}^2 \text{ liter}^{-2} \text{ (or } M^2\text{)}$$

Remember that this is not a normal equilibrium constant, which includes the concentrations of reactants and products. For water, the concentration is 55.5 moles liter^{-1}.

The equilibrium constant for dissociation is therefore

$$K = \frac{(10^{-7})(10^{-7})}{(55.5)(55.5)} = 3.25 \times 10^{-18}$$

Note that K is unitless. The relationship between K and K_w is

$$K_w = K \times (55.5\ M)^2$$

Alcohols also undergo self-dissociation, but to a much smaller extent than water.

$$2CH_3OH \rightleftharpoons CH_3OH_2^+ + CH_3O^-$$

For methanol, the ion product $K_{CH_3OH} = 1.2 \times 10^{-17}\ M^2$, and for higher alcohols the value is even smaller.

$$K_{CH_3OH} = [CH_3OH_2^+][CH_3O^-] = 1.2 \times 10^{-17}\ M^2$$

The reduced value comes in large part from the lower dielectric constant of alcohols—it takes greater energy to separate charges. But the relative acidities and basicities of alcohols are also important.

Acidity usually refers to an ionization equilibrium in dilute aqueous solution. Thus, the acidity of a substance is a measure of its tendency to give up a proton to the standard base water.

$$ROH + H_2O \overset{K_a}{\rightleftharpoons} H_3O^+ + RO^-$$

The acid dissociation constant, K_a, is defined as

$$K_a = \frac{[H_3O^+][RO^-]}{[ROH]}$$

Since these equilibria refer to dilute water solutions, the concentration of water is generally omitted in the expression for an equilibrium constant and K_a has units of mole liter^{-1} or molarity, M. The acid dissociation constant is generally such a small number that it is usually more convenient to refer to the negative logarithm or pK_a:

$$pK_a = -\log K_a$$

Values of pK_a for some alcohols are listed in Table 11.4 and are compared with some common inorganic acids. Note that the pK_a for water is obtained by dividing

TABLE 11.4
pK_a Values for Alcohols and Some Inorganic Acids

Compound	pK_a	Compound	pK_a
H_2O	15.7	HI	−9.5
CH_3OH	15.5	HBr	−9
C_2H_5OH	15.9	HCl	−7
$(CH_3)_3COH$	≈18	H_2SO_4	−5
$ClCH_2CH_2OH$	14.3	H_3PO_4	2.15
CF_3CH_2OH	12.4	HF	3.18
C_6H_5OH	10.0	H_2S	6.97
CH_3COOH	4.8	HOCl	7.53
		H_2O_2	11.64

K_w by the concentration of water, 55.5 moles liter^{-1}. This change is necessary to put all of the ionizations on the same scale and in the same units. Recall that the ion product of water, K_w, has units of moles^2 liter^{-2} or M^2, whereas K_a values are given in units of moles liter^{-1} or M.

Methanol and ethanol are about as acidic as water itself. The higher alcohols are less acidic. Water and the alcohols are generally much less acidic than other compounds commonly regarded as acids. Strong acids, such as HI, HBr, HCl, H_2SO_4, have negative pK_a values. Such compounds are completely dissociated in water and are 10^{15} to 10^{25} more acidic than alcohols. Typical "weak acids" such as acetic acid (to be discussed in Chapter 17), HF, H_2S, and HOCl are still 10^7 to 10^{10} stronger than alcohols. A discussion of the acidity of some relatively weak inorganic acids is found in Appendix IV.

The character of alcohols as weak acids emerges primarily in reactions with strong base. Alcohols, like water, react with alkali metals to liberate hydrogen and form the corresponding metal alkoxide.

$$CH_3OH + Na \longrightarrow CH_3O^- + Na^+ + \tfrac{1}{2}H_2$$

The reaction tends to be less vigorous than that with water. In fact, isopropyl alcohol is often used to decompose scraps of sodium in the laboratory because its reaction is relatively slow and moderate. When sodium reacts with water the reaction is so rapid that the heat produced cannot be dissipated quickly enough. The evolved hydrogen catches fire and an explosion results. Tertiary alcohols react so sluggishly with sodium that potassium must often be used to convert such an alcohol to the alkoxide.

> Potassium has a relatively low m.p., 64°. In laboratory use, it is often converted to a finely divided state in order to render it more reactive. Solid pieces of potassium are added to benzene (b.p. 80°) and the mixture is heated to reflux. The potassium melts and the mixture is allowed to cool with vigorous stirring. The potassium solidifies as small particles of "potassium sand." The alcohol is added to this mixture with stirring and generally reacts readily because of the large surface area of the potassium sand. This procedure is especially useful with tertiary alcohols.

Another reagent commonly used instead of sodium itself is sodium hydride, NaH. This compound is a nonvolatile, insoluble salt, Na^+H^-, and reacts readily with acidic hydrogens

$$CH_3OH + Na^+H^- \longrightarrow CH_3O^- + Na^+ + H_2$$

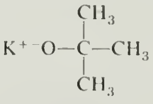
The reaction may be regarded as a combination of hydride ion with a proton.

$$H\!:^- + H^+ \longrightarrow H_2$$

The sodium salts of primary alcohols are common reagents in organic chemistry.

$Na^{+-}OCH_3$	$Na^{+-}OCH_2CH_3$
sodium methoxide	sodium ethoxide

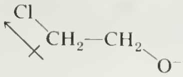
Because sodium and sodium hydride react so sluggishly with tertiary alcohols, the corresponding potassium salts are more commonly used as reagents.



$$K^{+\,-}O{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}CH_3$$

potassium *t*-butoxide

Note in Table 11.4 that 2-chloroethanol is significantly more acidic than is ethanol. This increase in acidity is best understood in terms of the electrostatic interaction of the C—Cl dipole with the negative charge of the alkoxide ion.



The positive end of the dipole is closer to the negative charge than is the negative end of the dipole. Electrostatic attraction exceeds repulsion, and the result is a net stabilization of the anion. Stabilization of the anion increases its ease of formation and the conjugate acid, 2-chloroethanol (or β-chloroethyl alcohol) is more acidic than the unsubstituted alcohol (Figure 11.2).

This effect is generally called an **inductive field effect,** or more simply, just an **inductive effect.** The magnitude of the effect falls off as the distance between the dipolar group and the charged group is increased. The effect increases with the number of dipolar groups. Note the relatively large effect of the three fluorines in β,β,β-trifluoroethyl alcohol. Halogen groups are said to be **electron attracting** and stabilize anions. The effect is present in inorganic systems as well: HOCl is a stronger acid than HOH. Conversely, alkyl groups are generally considered to be somewhat **electron donating** and, therefore, weaken acids. We will make use of inductive effects frequently in our subsequent discussions of the effects of structure on reactivity.

Alcohols, like water, are not only acids, but bases. Hydrogen chloride passed into an alcohol protonates the oxygen just as in water:

$$H_2O + HCl \longrightarrow H_3O^+ + Cl^-$$

$$ROH + HCl \rightleftharpoons \underset{\text{alkyloxonium chloride}}{ROH_2^+\,Cl^-} \rightleftharpoons ROH_2^+ + Cl^-$$

The initially formed species in such a protonation is an **ion pair** (two ions in close juxtaposition). In water and the lower alcohols, the dielectric constant is sufficiently high that the initially formed ion pairs can largely dissociate to free ions. As the dielectric constant becomes smaller, however, too much work is required to separate the ion pairs, and the oxonium chloride remains largely associated.

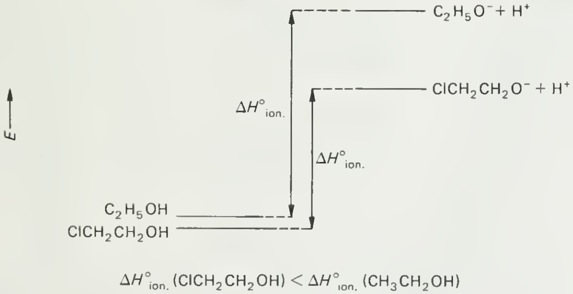


FIGURE 11.2 *The effect of a dipolar substituent on the ionization energy of an alcohol. The stabilizing effect of the substituent is greater in the anion (charge-dipole interaction) than in the alcohol (dipole-dipole interaction).*

11.5
Nuclear Magnetic Resonance

Primary and secondary alcohols have hydrogen at a carbon bearing an electronegative oxygen. We expect to find resonance of such protons downfield from normal alkane protons, as in the case of alkyl halides. The downfield shift is

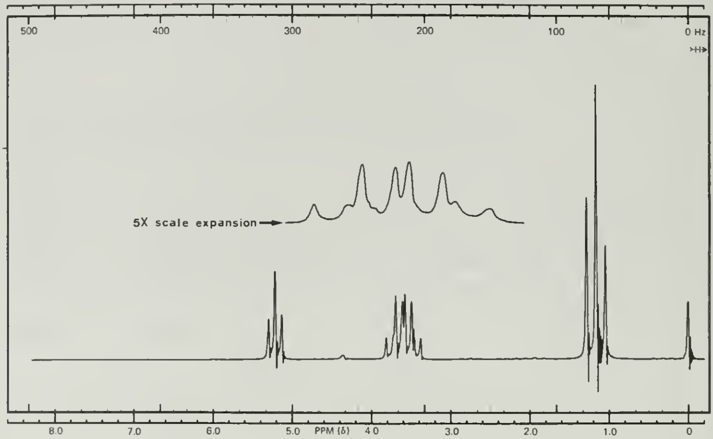


FIGURE 11.3 Nmr *spectrum of pure ethyl alcohol.*

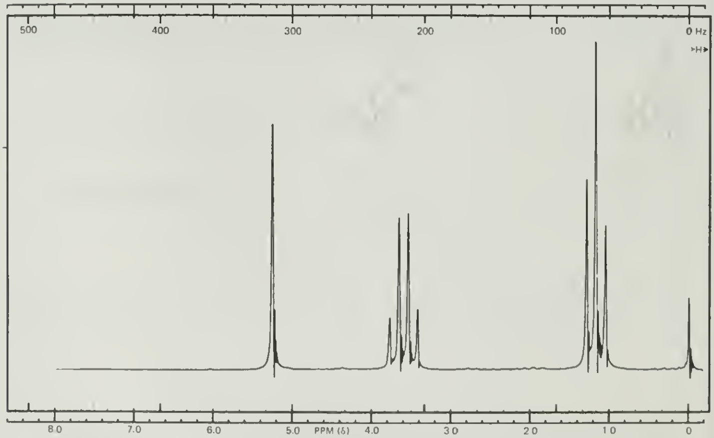


FIGURE 11.4 Nmr *spectrum of ethyl alcohol containing 1% formic acid.*

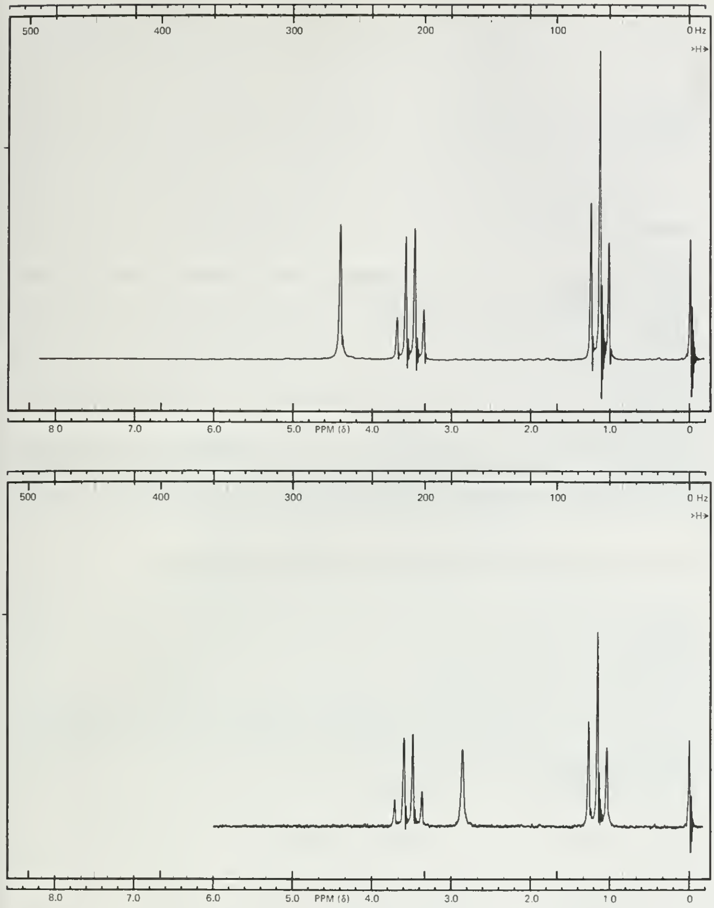


FIGURE 11.5 Nmr *spectra of slightly impure ethyl alcohol in carbon tetrachloride. The concentration in the top spectrum is* 1.0 M; *in the bottom* 0.25 M.

2.3–2.5 ppm from the corresponding alkane position. The actual positions depend on the number of protons on the carbinol carbon:

	CH_3—R	R′CH_2—R	R′R″CH—R
δ, ppm:	0.9	1.25	1.5
	CH_3—OH	R′CH_2—OH	R′R″CH—OH
δ, ppm:	3.4	3.6	3.85

Protons β to oxygen are shifted slightly downfield—about 0.1–0.3 ppm.

The hydroxy proton itself shows more complex behavior. In rigorously purified alcohols, the hydroxy proton shows normal splitting by adjacent carbinol protons.

In this case, the proton exchange caused by autoprotolysis is sufficiently slow that a given proton is associated with a given oxygen on the nmr time scale. However, the protons are still hydrogen bonded and this leads to deshielding. The spectrum of pure ethyl alcohol in Figure 11.3 is illustrative. Note that the H—C—C—H and the H—C—O—H couplings have different magnitudes. The CH_2 resonance appears as a complex multiplet, rather than a simple quartet.

Traces of acid or base cause the resonance of the hydroxy proton to collapse to a sharp singlet (see Figure 11.4). In such cases, proton exchange is rapid on the nmr time scale and the "state" observed is that of a proton in a weighted average of a number of environments. No spin-spin splitting is observed for such a proton.

When an alcohol is diluted by an inert solvent, its hydroxy proton resonance shifts to higher field because hydrogen bonding becomes less important (compare Figure 11.5 with Figure 11.3). In very dilute solutions the hydroxy proton may resonate as high as 0.5 ppm. Often these extreme cases are not observed in the nmr spectrum of an alcohol. Usually the hydroxy proton, due to a combination of hydrogen bonding and some exchange, is observed as a broad, featureless peak at a position varying from 2–4.5 ppm.

The exact appearance and position depend on the solvent, purity, temperature, and structure. One simple diagnosis for an OH group in the nmr is the addition of D_2O to the nmr solution. Rapid exchange replaces the OH groups by OD

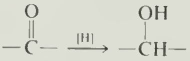
$$\mathrm{ROH} + \mathrm{D_2O} \rightleftharpoons \mathrm{ROD} + \mathrm{DOH}$$

and the nmr signal for OH vanishes or becomes less intense.

11.6
Preparation of Alcohols

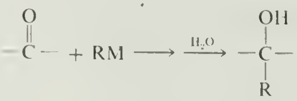
Alcohols can be obtained from many other classes of compounds. Preparations from alkyl halides and from hydrocarbons will be discussed in this section. The following important ways of preparing alcohols will be discussed later, as reactions of the appropriate functional groups.

1. Reduction of Aldehydes and Ketones (Section 15.8)



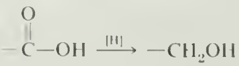
$$-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}- \xrightarrow{[\mathrm{H}]} -\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{H}-$$

2. Addition of Organometallics to Aldehydes and Ketones (Section 15.7D and E.)



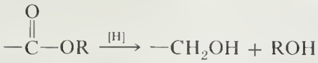
$$-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}- + \mathrm{RM} \longrightarrow \xrightarrow{\mathrm{H_2O}} -\underset{\underset{\mathrm{R}}{|}}{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}}-$$

3. Reduction of Carboxylic Acids (Section 17.7.C)



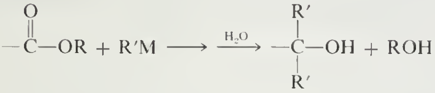
$$-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OH} \xrightarrow{[\mathrm{H}]} -\mathrm{CH_2OH}$$

4. Reduction of Esters (Section 18.10.B)



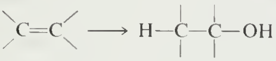
$$-\overset{\overset{\displaystyle O}{\|}}{C}-OR \xrightarrow{[H]} -CH_2OH + ROH$$

5. Addition of Organometallics to Esters (Section 18.9.E)



$$-\overset{\overset{\displaystyle O}{\|}}{C}-OR + R'M \longrightarrow \xrightarrow{H_2O} -\underset{\underset{\displaystyle R'}{|}}{\overset{\overset{\displaystyle R'}{|}}{C}}-OH + ROH$$

6. Additions to Alkenes (Section 12.6.B, D)



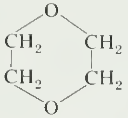
$$>C=C< \longrightarrow H-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-OH$$

A. *Preparation from Alkyl Halides*

Hydrolysis of alkyl halides in aqueous solvents may occur by either the S_N1 or S_N2 mechanism. With some halides, elimination is a major side reaction (Chapter 8). The hydrolysis of most primary halides occurs by the S_N2 path and is sufficiently clean that this reaction is a good preparative method.

$$CH_3CH_2CH_2CH_2Cl + OH^- \xrightarrow[100^\circ]{H_2O} CH_3CH_2CH_2CH_2OH + Cl^-$$

The reaction can be carried out in refluxing aqueous sodium hydroxide, especially with lower halides. Although the alkyl halides are not soluble in water, a two-phase reaction takes place. If the alcohol is water-soluble, the end of the hydrolysis is marked by a homogeneous solution. Alternatively, the reaction can be carried out in a mixture of water and some inert organic solvent such as dioxane, which is miscible with water and helps to dissolve the alkyl halide.



dioxane

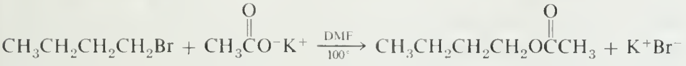
2° R

1° R w/ β branch

For secondary alkyl halides and for primary halides with a β branch, elimination is an important side reaction and may be the principal reaction:

$$(CH_3)_2CHCH_2Br \xrightarrow{OH^-} (CH_3)_2C=CH_2$$

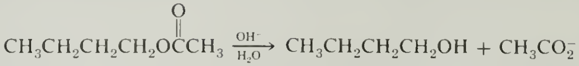
An alternative procedure that avoids the use of strong base makes use of acetate ion ($CH_3CO_2^-$) as the nucleophilic reagent. Since acetate is much less basic than hydroxide (the pK_a of acetic acid (CH_3CO_2H) is 4.8 whereas that of water is 15.7), the E2 mechanism is suppressed, and alkene formation is minimized.



$$CH_3CH_2CH_2CH_2Br + CH_3\overset{\overset{\displaystyle O}{\|}}{C}O^-K^+ \xrightarrow[100^\circ]{DMF} CH_3CH_2CH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + K^+Br^-$$

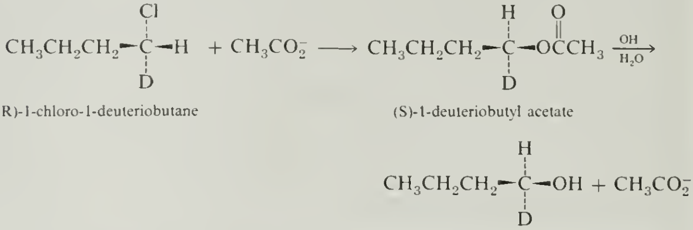
(95–98%)

The product, an ester, can be readily hydrolyzed to the desired alcohol (Section 18.9.A).



$$CH_3CH_2CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[H_2O]{OH^-} CH_3CH_2CH_2CH_2OH + CH_3CO_2^-$$

Since displacement by acetate ion proceeds by the S_N2 mechanism, the alcohol product has an absolute configuration opposite to that of the starting halide.



$$CH_3CH_2CH_2-\underset{D}{\overset{Cl}{C}}-H + CH_3CO_2^- \longrightarrow CH_3CH_2CH_2-\underset{D}{\overset{H}{C}}-O\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[H_2O]{OH} CH_3CH_2CH_2-\underset{D}{\overset{H}{C}}-OH + CH_3CO_2^-$$

(R)-1-chloro-1-deuteriobutane

(S)-1-deuteriobutyl acetate

(S)-1-deuteriobutanol

Tertiary halides also undergo hydrolysis. In this case, the reaction occurs by the S_N1 rather than the S_N2 mechanism. The reaction is best carried out by shaking the halide with aqueous sodium carbonate. The carbonate neutralizes the acid formed by hydrolysis

$$RX + H_2O \longrightarrow ROH + HX$$

but avoids the high concentration of hydroxide ion that encourages E2 elimination. Elimination by the E1 path is more difficult to avoid. However, this side reaction may be minimized by using highly aqueous solvents and by operating at low temperature. Nevertheless, hydrolysis of tertiary halides goes by way of carbonium ion intermediates, and such intermediates have several modes of reaction available besides reaction with water. Rearrangements can occur as discussed in Section 11.7.B.

Oxidation of a Grignard reagent is another general reaction leading to alcohols. The direct reaction with oxygen first yields the salt of a hydroperoxide

$$RMgX + O_2 \longrightarrow R-O-O-MgX$$

With excess Grignard reagent, the salt of the alcohol is formed,

$$ROOMgX + RMgX \longrightarrow 2\,ROMgX$$

On normal workup with dilute acid, the alcohol is produced:

$$ROMgX + HCl \longrightarrow ROH + MgXCl$$

An example is the conversion of 5-bromo-2,2-dimethylpentane into the corresponding alcohol.

$$(CH_3)_3CCH_2CH_2CH_2MgBr \xrightarrow{O_2} \xrightarrow[H_2O]{NH_4Cl} \underset{(90\%)}{(CH_3)_3CCH_2CH_2CH_2OH}$$

4,4-dimethyl-1-pentanol

Oxidation is a side reaction of all Grignard syntheses run in the presence of air. For this reason, Grignard reagents are normally handled under a nitrogen or argon atmosphere.

The hydroperoxide is formed in good yield at low temperatures (−70°) and can be isolated in the usual way by reaction with dilute acid, separating and drying the ether layer and evaporating the ether.

$$\mathrm{RMgX} + \mathrm{O_2} \xrightarrow{-78^\circ} \mathrm{ROOMgX} \xrightarrow{\mathrm{H_3O^+}} \mathrm{ROOH}$$

Alkyl hydroperoxides contain a weak O—O bond and decompose at temperatures over 100°, sometimes with explosive violence. They must be handled with extreme care. They may be reduced by catalytic hydrogenation to the corresponding alcohol.

$$\mathrm{ROOH} \xrightarrow{\mathrm{H_2,\ Pt\ or\ Pd}} \mathrm{ROH} + \mathrm{H_2O}$$

The conversions of alkyl halides to alcohols discussed in this section are, by and large, *not important synthetic laboratory processes.* This is not due solely to deficiencies in the methods (although there obviously are some) but also to the practical fact that the halides are commonly obtained from alcohols in the first place. Hydrolysis of sulfonate esters is also a perfectly good reaction, but they are invariably prepared from alcohols. Hydrolysis of halides is an important industrial reaction for those halides obtained commercially by direct halogenation of hydrocarbons. In such hydrolyses water is the preferred system, often with additional catalysts. More important laboratory syntheses of alcohols will be discussed in subsequent chapters as reactions of other functional groups.

B. *Preparation from Hydrocarbons*

Hydroperoxides are also obtained from hydrocarbons having tertiary hydrogens by reaction with oxygen and free radical initiators:

$$\mathrm{R\cdot} + \mathrm{O_2} \longrightarrow \mathrm{R{-}O{-}O\cdot}$$

$$\mathrm{R{-}O{-}O\cdot} + \mathrm{RH} \longrightarrow \mathrm{ROOH} + \mathrm{R\cdot}$$

The bond dissociation energy of the ROO—H bond is 90 kcal mole^{-1} and is comparable to that of a tertiary R—H bond but weaker than primary and secondary C—H bonds. Consequently, the reaction is highly selective and is important only for tertiary hydrogens in alkanes. Because of the ready decomposition of alkyl hydroperoxides, the oxidation is generally carried only to low conversion. The reaction is a significant industrial process but is not a common organic laboratory reaction.

C. *Special Preparations*

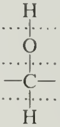
Methanol at one time was prepared commercially by the dry distillation of wood and once had the commercial name of **wood alcohol.** It is now prepared on a large scale by the economically superior method of catalytic hydrogenation of carbon monoxide. Methanol is toxic; small amounts cause nausea and blindness. Death can result from 100 ml or less. It is an important industrial solvent and reagent and is also used to denature ethanol.

Ethanol is prepared for consumption in beverages by fermentation of sugars, but industrial alcohol is prepared by other routes such as the hydration of ethylene (Section 12.6.B). Ethanol is toxic in large quantities but is a normal intermediate in metabolism and, unlike methanol, is metabolized by normal enzymatic body processes. It is an important solvent and reagent in industrial processes and in such use is often "denatured" by addition of toxic and unappetizing diluents. Alcohol for consumption is heavily taxed but denatured alcohol is not (for example, the 1974 price of 95% ethanol was \$0.92 per gal: the federal excise tax was \$19.95 per gal).

11.7
Reactions of Alcohols

start

The reactions of alcohols generally involve breaking one or more of three types of bonds in the carbinol structure and may be characterized as



acidity, formation of esters

displacement, carbonium ions, elimination

oxidation

alkoxides = strong bases

A. *Acidity: Alkoxide Ions*

The alkali alkoxides, produced by reaction of alcohols with alkali metals, are important reagents as bases in nonaqueous media and as nucleophilic reagents. An example of the latter use is

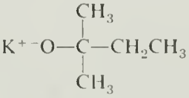
$$(C_2H_5)_3COH + K \longrightarrow \tfrac{1}{2}H_2 + (C_2H_5)_3CO^-K^+$$

$$(C_2H_5)_3CO^-K^+ + CH_3I \longrightarrow (C_2H_5)_3COCH_3 + KI$$

This is a typical S_N2 reaction and works best with primary halides having no β substituents. In such cases, the reaction is a good method for preparing ethers (Section 11.10.A). Other kinds of halides give more or less elimination.

$$(C_2H_5)_3CCl + CH_3O^-K^+ \longrightarrow \underset{\text{100\% elimination}}{(C_2H_5)_2C{=}CHCH_3 + KCl + CH_3OH}$$

In cases where the amount of elimination is high, the reaction is an important route to alkenes (Section 12.5). Potassium *t*-butoxide and potassium *t*-pentoxide are frequently used as reagents for dehydrohalogenation because of their high basicity and because they are moderately soluble in nonpolar organic solvents such as benzene (C_6H_6).



$$K^{+\,-}O-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH_2CH_3$$

potassium *t*-pentoxide

B. *Alkyloxonium Salts*

Sodium bromide is slightly soluble in ethanol. Such a solution can be refluxed indefinitely with no reaction; ethyl bromide and hydroxide ion are *not* formed.

Recall that the *reverse* reaction, hydrolysis of ethyl bromide, can be carried out readily.

$$C_2H_5OH + Br^- \overset{K}{\rightleftharpoons} C_2H_5Br + OH^-$$

For this system, the thermodynamics is such that equilibrium lies far to the left (Section 3.2).

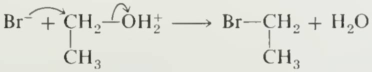
$$K = \frac{[C_2H_5Br][OH^-]}{[C_2H_5OH][Br^-]} = \text{about } 10^{-19}$$

Hence, the rate of reaction of ethanol with bromide ion is very slow. However, if some sulfuric acid is added or if a mixture of ethanol and hydrogen bromide is refluxed, a reaction does occur.

$$C_2H_5OH + HBr \longrightarrow C_2H_5Br + H_2O$$

Why this dramatic difference? The displacement reaction in this case actually occurs on the intermediate **alkyloxonium salt** which is formed when the strong acid protonates the ethanol.

$$C_2H_5OH + HBr \rightleftharpoons C_2H_5OH_2^+ + Br^-$$

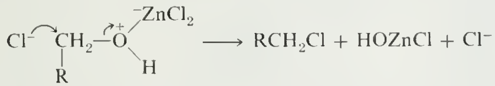


$$Br^- + \underset{\displaystyle CH_3}{\underset{|}{CH_2}}-OH_2^+ \longrightarrow Br-\underset{\displaystyle CH_3}{\underset{|}{CH_2}} + H_2O$$

Protonation converts the substrate from one with a very poor leaving group (hydroxide ion) to one with a better leaving group (water). The reaction is therefore only another example of an S_N2 reaction. For primary alcohols, the reaction is carried out by refluxing the alcohol with a mixture of concentrated sulfuric acid and either sodium bromide or hydrobromic acid.

> A mixture of 71 ml of 48% hydrobromic acid, 30.5 ml of concentrated sulfuric acid, and 37 g of *n*-butyl alcohol is refluxed for 2 hr. The product is separated, washed, and distilled to yield 50 g (95%) of *n*-butyl bromide.

For preparation of the corresponding chlorides, more vigorous conditions are required because chloride ion is a poorer nucleophile than bromide. A mixture of concentrated hydrochloric acid and zinc chloride, the so-called Lucas reagent, is frequently used. Zinc chloride is a powerful Lewis acid which serves the same purpose as does a proton in coordinating with the hydroxy oxygen.



$$Cl^- \; \underset{\displaystyle R}{\underset{|}{CH_2}}-\overset{+}{O}\begin{matrix}{}^-ZnCl_2\\ H\end{matrix} \longrightarrow RCH_2Cl + HOZnCl + Cl^-$$

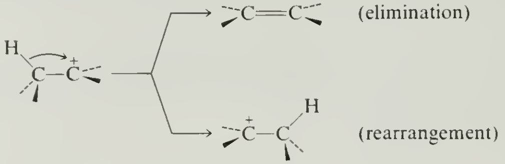
Secondary alcohols react more readily under these conditions than primary alcohols, and tertiary alcohols react the most rapidly of all. Tertiary alcohols are converted to alkyl chlorides by simply shaking with concentrated hydrochloric acid in the cold. The reaction clearly follows a rate trend that is characteristic of a carbonium ion process (tertiary > secondary > primary).

$$ROH_2^+ \rightleftharpoons R^+ + H_2O$$

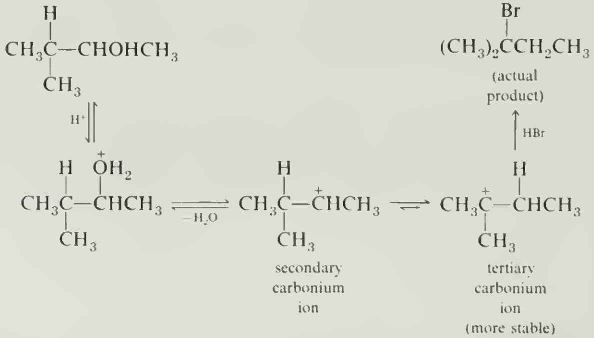
$$R^+ + Cl^- \longrightarrow RCl$$

Similarly, cold concentrated hydrobromic acid converts tertiary alcohols to the bromides. One convenient procedure is to pass the hydrogen halide gas into the alcohol at 0°; reaction is complete within minutes.

One important drawback in carbonium ion reactions is the alternative reaction pathways available. We have already discussed one such reaction, E1 elimination. The electron-deficient carbonium ion center tends to attract electron density from adjacent bonds, and these bonds become weaker. One result is the ready loss of a proton to a basic solvent molecule. In some systems, another important side reaction can occur—rearrangement. The hydrogen attached by the weakened bond *and its bonding electrons can move to the cationic center,* thus generating a new carbonium ion.



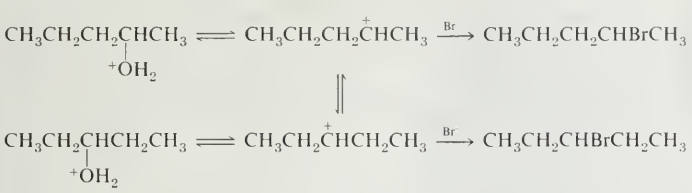
Note that in this process the positive charge moves to the carbon to which the hydrogen was originally attached. Such rearrangements are especially important when the new carbonium ion is more stable than the old, but the reaction can occur even when both carbonium ions have comparable stability. Such reactions are common for secondary and tertiary carbonium ions but almost never involve primary carbonium ions. For example, treatment of 3-methyl-2-butanol with HBr gives solely the rearranged product 2-bromo-2-methylbutane.



Upon heating with hydrobromic acid, both 2-pentanol and 3-pentanol give a mixture of 2- and 3-bromopentane.

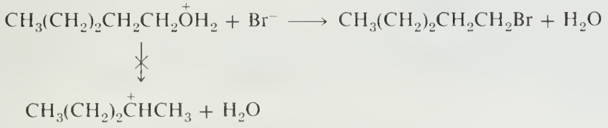
	$CH_3CH_2CH_2CHBrCH_3$	+ $CH_3CH_2CHBrCH_2CH_3$
$CH_3CH_2CH_2CHOHCH_3 \xrightarrow{HBr}$	86%	14%
$CH_3CH_2CHOHCH_2CH_3 \xrightarrow{HBr}$	20%	80%

The mechanism whereby these two products are formed is



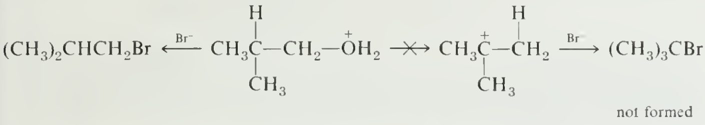
$$\begin{array}{ccccc}
\underset{^{+}OH_2}{CH_3CH_2CH_2\underset{|}{C}HCH_3} & \rightleftharpoons & CH_3CH_2CH_2\overset{+}{C}HCH_3 & \xrightarrow{Br^-} & CH_3CH_2CH_2CHBrCH_3 \\
 & & \Updownarrow & & \\
\underset{^{+}OH_2}{CH_3CH_2\underset{|}{C}HCH_2CH_3} & \rightleftharpoons & CH_3CH_2\overset{+}{C}HCH_2CH_3 & \xrightarrow{Br^-} & CH_3CH_2CHBrCH_2CH_3
\end{array}$$

Note that the equilibration of the carbonium ions is not complete. The rate of reaction of the carbonium ion with bromide ion is comparable to the rate of rearrangement. It is important to recognize when this reaction gives rearrangement products or mixtures. 1-Pentanol gives a good yield of 1-bromopentane with $HBr + H_2SO_4$; this reaction is an S_N2 reaction and carbonium ions are not involved.



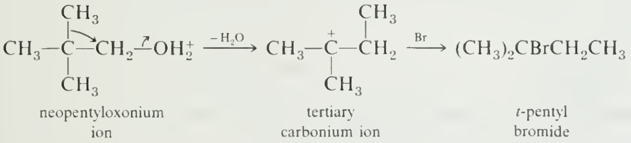
$$\begin{array}{l}
CH_3(CH_2)_2CH_2CH_2\overset{+}{O}H_2 + Br^- \longrightarrow CH_3(CH_2)_2CH_2CH_2Br + H_2O \\
\qquad\quad \not\updownarrow \\
CH_3(CH_2)_2\overset{+}{C}HCH_3 + H_2O
\end{array}$$

Even isobutyl alcohol on heating with HBr and H_2SO_4 gives isobutyl bromide. The formation of a relatively stable tertiary carbonium in this case does not compete with displacement.



$$(CH_3)_2CHCH_2Br \xleftarrow{Br^-} CH_3\overset{H}{\underset{CH_3}{C}}-CH_2-\overset{+}{O}H_2 \not\longrightarrow CH_3\overset{H}{\underset{CH_3}{\overset{+}{C}}}-CH_2 \xrightarrow{Br^-} (CH_3)_3CBr$$

Certain primary compounds do give rise to rearrangements. These compounds contain a quaternary carbon next to the carbinol carbon.



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-OH_2^+ \xrightarrow{-H_2O} CH_3-\overset{CH_3}{\underset{CH_3}{\overset{+}{C}}}-CH_2 \xrightarrow{Br^-} (CH_3)_2CBrCH_2CH_3$$

Recall that S_N2 reactions at neopentyl-type carbons are very slow (Section 8.5). Hence, the alternative reaction of rearrangement is able to compete and becomes the dominating reaction. Note also that alkyl groups can rearrange as well as hydrogen.

In the transition state for the rearrangement of neopentyloxonium ion, the C—O bond has lengthened and weakened and the methyl group has started to migrate in order to give the transition state some of the character of a tertiary carbonium ion. Many experiments have shown that the migrating alkyl group attacks the carbon at the rear of the leaving group, much as in S_N2 displacement. The structure of this transition state is given approximately in the stereo plot of Figure 11.6.

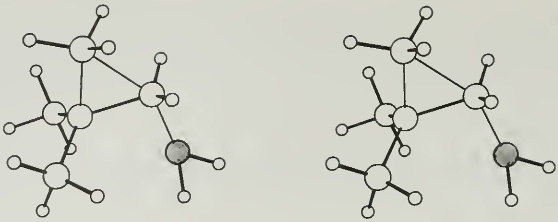
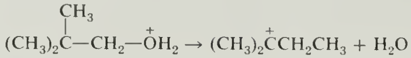


FIGURE 11.6 *Stereo representation of the transition state for rearrangement of neopentyloxonium cation*



$$(CH_3)_2\overset{CH_3}{\underset{|}{C}}—CH_2—\overset{+}{O}H_2 \rightarrow (CH_3)_2\overset{+}{C}CH_2CH_3 + H_2O$$

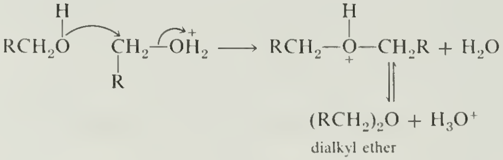
When a primary alcohol is treated with sulfuric acid alone, the product is the **alkylsulfuric acid.** The reaction is an equilibrium process—the product alkylsulfuric acid is readily hydrolyzed by excess water. If excess ("xs") sulfuric acid is used at 0°, the reaction proceeds to completion and the alkylsulfuric acid may be isolated.

$$C_2H_5OH + \text{xs } H_2SO_4 \xrightarrow{0°} C_2H_5OSO_2OH + H_2O$$

However, if ethanol is *heated* with concentrated sulfuric acid, ethyl ether is produced in high yield.

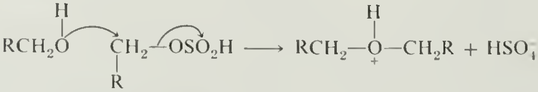
$$C_2H_5OH + H_2SO_4 \xrightarrow{140°} \underset{(95\%)}{C_2H_5OC_2H_5} + H_2O$$

The detailed mechanism of the reaction under these conditions is not known. Bisulfate ion is a poor nucleophile and one possibility is that the initial alkyloxonium ion is attacked by another alcohol molecule instead.



$$RCH_2\overset{H}{\overset{|}{O}}\quad \underset{\underset{R}{|}}{C}H_2—\overset{+}{O}H_2 \longrightarrow RCH_2—\underset{+}{\overset{H}{\overset{|}{O}}}—CH_2R + H_2O \rightleftharpoons \underset{\text{dialkyl ether}}{(RCH_2)_2O} + H_3O^+$$

Alternatively, the alkylsulfuric acid may be an intermediate.



$$RCH_2\overset{H}{\overset{|}{O}}\quad \underset{\underset{R}{|}}{C}H_2—OSO_2H \longrightarrow RCH_2—\underset{+}{\overset{H}{\overset{|}{O}}}—CH_2R + HSO_4^-$$

In the case of primary alcohols, the reaction is an acceptable way of preparing symmetrical ethers.

n-Butyl alcohol and concentrated sulfuric acid are refluxed with provision to remove water as it is formed, either with a suitable trap or by a fractionating column. The reaction mixture is maintained at 130–140°. The reaction mixture is allowed to cool, and, after washing and drying, is distilled to give *n*-butyl ether.

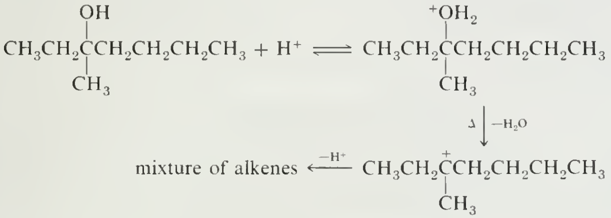
At still higher temperature, elimination occurs to give the alkene.

$$C_2H_5OH \xrightarrow[170^\circ]{H_2SO_4} CH_2{=}CH_2 + H_2O$$

Secondary and tertiary alcohols give only elimination without forming an ether.

> 2- (or 3-) pentanol is heated with 50% sulfuric acid with distillation of product until the reaction mixture reaches 120°. The distillate is washed, dried, and distilled to give 2-pentene.

Tertiary alcohols eliminate water readily on heating with even traces of acid. If elimination is to be avoided, the alcohols should be distilled at low temperature (vacuum distillation) or in apparatus that has been rinsed with ammonia.



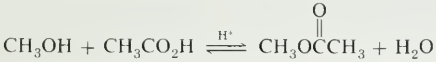
$$CH_3CH_2\underset{CH_3}{\overset{OH}{C}}CH_2CH_2CH_2CH_3 + H^+ \rightleftharpoons CH_3CH_2\underset{CH_3}{\overset{^+OH_2}{C}}CH_2CH_2CH_2CH_3$$

$$\Big\downarrow \Delta \; -H_2O$$

$$\text{mixture of alkenes} \xleftarrow{-H^+} CH_3CH_2\underset{CH_3}{\overset{+}{C}}CH_2CH_2CH_2CH_3$$

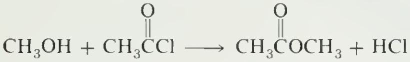
C. *Formation of Organic Esters*

Alcohols react with carboxylic acids to give esters:



$$CH_3OH + CH_3CO_2H \overset{H^+}{\rightleftharpoons} CH_3O\overset{O}{\overset{\|}{C}}CH_3 + H_2O$$

The reaction is catalyzed by strong acids and is discussed in detail in Section 17.7.C. Reaction with acyl halides is also an important way of preparing esters.



$$CH_3OH + CH_3\overset{O}{\overset{\|}{C}}Cl \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OCH_3 + HCl$$

This reaction is discussed in Section 18.9.B.1.

D. *Formation of Inorganic Esters and Conversion to Alkyl Halides*

Various inorganic halides may be regarded as mixed anhydrides of some inorganic acid and HCl or HBr. Important examples are

1. Thionyl chloride, $SOCl_2$, a colorless liquid with b.p. 79°, is the mixed anhydride of sulfurous acid and HCl. It is corrosive and attacks rubber. It reacts rapidly with water to give sulfur dioxide and HCl.

$$SOCl_2 + H_2O \longrightarrow 2\,HCl + SO_2$$

2. Phosphorus tribromide, PBr_3, is the mixed anhydride of phosphorous acid and HBr. It is a dense, colorless liquid with b.p. 173°, and is prepared by the direct reaction of phosphorus with bromine. It reacts with water to give phosphorous acid and HBr.

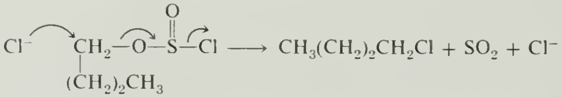
$$PBr_3 + 3\,H_2O \longrightarrow 3\,HBr + H_3PO_3$$

3. Phosphorus pentachloride, PCl_5, is the mixed anhydride of phosphoric acid and HCl. It is a yellowish-white solid with m.p. 162°. Upon hydrolysis, it yields phosphoric acid and HCl.

$$PCl_5 + 4\,H_2O \longrightarrow 5\,HCl + H_3PO_4$$

These compounds react readily with alcohols to form products that are esters of inorganic acids. Since the inorganic acids are strong acids, their anions are good leaving groups for subsequent S_N1 and S_N2 reactions. An example is the reaction of 1-butanol with thionyl chloride. The intermediate chlorosulfite ester may be isolated if desired. However, reaction with the chloride ion produced in the reaction occurs simply upon warming the alcohol with $SOCl_2$. The products are 1-chlorobutane, SO_2, and HCl.

$$CH_3(CH_2)_2CH_2OH + SOCl_2 \longrightarrow \underset{n\text{-butyl chlorosulfite}}{CH_3(CH_2)_2CH_2OSOCl} + HCl$$



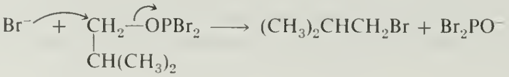
$$Cl^- \quad \underset{(CH_2)_2CH_3}{CH_2}\!-\!O\!-\!\overset{O}{\overset{\|}{S}}\!-\!Cl \longrightarrow CH_3(CH_2)_2CH_2Cl + SO_2 + Cl^-$$

A tertiary amine, R_3N, is often used to catalyze the reaction by forming chloride ion from the HCl produced.

$$R_3N + HCl \rightleftharpoons R_3NH^+ + Cl^-$$

Similarly, reaction of an alcohol with PBr_3 produces first a dibromophosphite ester which immediately reacts further.

$$(CH_3)_2CHCH_2OH + PBr_3 \longrightarrow \underset{\text{isobutyl dibromophosphite}}{(CH_3)_2CHCH_2OPBr_2} + HBr$$



$$Br^- + \underset{CH(CH_3)_2}{CH_2}\!-\!OPBr_2 \longrightarrow (CH_3)_2CHCH_2Br + Br_2PO^-$$

The dibromophosphite ion produced reacts with more alcohol so that the net reaction is

$$3\,(CH_3)_2CHCH_2OH + PBr_3 \longrightarrow 3\,(CH_3)_2CHCH_2Br + H_3PO_3$$

Isobutyl alcohol is maintained at 0° with PBr_3 for 4 hr. The product is washed, dried, and distilled to give 60% of isobutyl bromide.

This reaction also works well with many secondary alcohols.

Reaction of an alcohol with PCl_5 can be carried out at a 1:1 molar ratio to produce the alkyl chloride,

$$ROH + PCl_5 \longrightarrow RCl + HCl + POCl_3$$

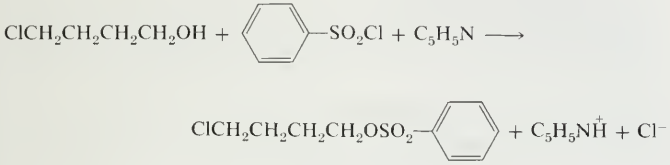
Phosphorus oxychloride is a liquid, b.p. 105°, and will also react further with alcohols to form alkyl chlorides and phosphoric acid.

The above reagents are commercially available and are common laboratory chemicals. Phosphorus triiodide is a red solid that decomposes on heating. It is usually prepared *in situ* by heating red phosphorus, iodine, and the appropriate alcohol.

$$3\,CH_3OH + \tfrac{3}{2}\,I_2 + P \longrightarrow 3\,CH_3I + H_3PO_3$$

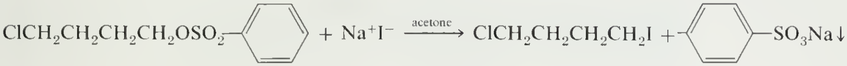
Iodine is added over a period of several hours to a refluxing mixture of red phosphorus and methanol. Methyl iodide is distilled, washed, dried, and redistilled: yield 94%.

Acid chlorides of sulfonic acids are also readily available. Common examples are benzenesulfonyl chloride, $C_6H_5SO_2Cl$, and *p*-toluenesulfonyl chloride, $CH_3C_6H_4SO_2Cl$ (Section 31.6). These compounds react with primary and secondary alcohols, generally in the presence of a tertiary amine such as pyridine, C_5H_5N, to produce sulfonate esters,

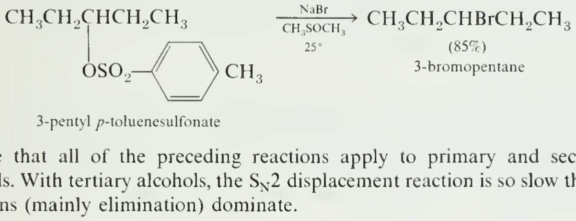

$ClCH_2CH_2CH_2CH_2OH$ +
$-SO_2Cl + C_5H_5N \longrightarrow$
$ClCH_2CH_2CH_2CH_2OSO_2-$
$+ C_5H_5N\overset{+}{H} + Cl^-$

4-chlorobutyl benzenesulfonate

Since the sulfonate anion is the conjugate base of a strong acid, it is a weak base and a good leaving group in displacement reactions (Section 8.6.A). Such esters react with halide ion in inert solvent to give alkyl halides and the sulfonate ion.


$ClCH_2CH_2CH_2CH_2OSO_2-$
$+ Na^+I^- \xrightarrow{\text{acetone}} ClCH_2CH_2CH_2CH_2I +$
$-SO_3Na\downarrow$

Sodium and potassium iodides are somewhat soluble in hot acetone but the benzenesulfonate salts are not and precipitate. Other common reagents of this type are lithium chloride in dimethylformamide or ethanol and sodium bromide in dimethylformamide or dimethyl sulfoxide.


$CH_3CH_2CHCH_2CH_3$
OSO_2-
CH_3
$\xrightarrow[\substack{CH_3SOCH_3 \\ 25°}]{NaBr}$
$CH_3CH_2CHBrCH_2CH_3$

(85%)
3-bromopentane

3-pentyl *p*-toluenesulfonate

Note that all of the preceding reactions apply to primary and secondary alcohols. With tertiary alcohols, the S_N2 displacement reaction is so slow that side reactions (mainly elimination) dominate.

We thus have a number of reactions available for accomplishing the important conversion, $ROH \longrightarrow RX$, and we have various complications to watch out for. The best overall methods may be summarized as follows:

Primary alcohols with no β branching
- chloride: $SOCl_2$ + pyridine, C_5H_5N (generally better than PCl_5 or $ZnCl_2$—HCl)
- bromide: PBr_3 or HBr—H_2SO_4
- iodide: $P + I_2$

Primary alcohols with β branching
- chloride: $SOCl_2$ + pyridine
- bromide: PBr_3

Secondary alcohols
- chloride: $SOCl_2$ + pyridine

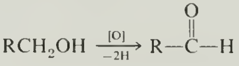
bromide: PBr_3 (low temperature, less than 0°C)
(If highly pure halide is required, use the two-step sequence: alcohol ⟶ sulfonate ester ⟶ halide)

Tertiary alcohols
chloride: HCl at 0°.
bromide: HBr at 0°.
(Rearrangement in particularly sensitive cases cannot generally be avoided.)

E. *Oxidation of Alcohols*

Primary and secondary alcohols can be oxidized to carbonyl compounds:

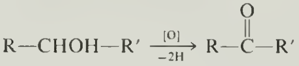
[illegible]



$$RCH_2OH \xrightarrow[-2H]{[O]} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H$$

an aldehyde

[illegible]



$$R{-}CHOH{-}R' \xrightarrow[-2H]{[O]} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R'$$

a ketone

Many procedures are available for accomplishing these transformations, but the most common general oxidizing agent is some form of Cr(VI), which becomes reduced to Cr(III).

Chromium trioxide, CrO_3, also known as chromic anhydride, forms red, deliquescent crystals. It is very soluble in water and in sulfuric acid.

Sodium or potassium dichromate forms orange aqueous solutions that convert to the yellow chromate salt under basic conditions.

$$\underset{\text{yellow}}{2\,CrO_4^{2-}} + 2\,H^+ \rightleftharpoons \underset{\text{orange}}{Cr_2O_7^{2-}} + H_2O$$

1°

Primary alcohols give aldehydes on warming with sodium dichromate and aqueous sulfuric acid. However, aldehydes are also readily oxidized under these conditions to give carboxylic acids (Section 15.8.A). This method is only successful for aldehydes of sufficiently low molecular weight that they may be distilled from solution as formed. In this way, *n*-butyl alcohol gives butyraldehyde in 50% yield.

$$CH_3CH_2CH_2CH_2OH + H_2Cr_2O_7 \longrightarrow \underset{\substack{(50\%)\\ \text{butyraldehyde}}}{CH_3CH_2CH_2CHO}$$

Only aldehydes that boil significantly below 100° can be conveniently prepared in this manner. Since this effectively limits the method to the production of a few simple aldehydes, it is not an important synthetic method. Other special oxidants have been developed that help to circumvent this problem. They will be discussed in Section 15.8.A.

BALANCING OXIDATION-REDUCTION REACTIONS. Organic redox reactions may be balanced by any method that works. The method of half-cells often taught in beginning chemistry courses for inorganic redox reactions applies just as well to organic reactions.

$$\begin{array}{rcl} 3 \times [\mathrm{RCH_2OH} & \rightleftharpoons & \mathrm{RCHO} + 2\,\mathrm{H^+} + 2\,e^-] \\ [6\,e^- + \mathrm{Cr_2O_7^{2-}} + 14\,\mathrm{H^+} & \rightleftharpoons & 2\,\mathrm{Cr^{3+}} + 7\,\mathrm{H_2O}] \\ \hline 3\,\mathrm{RCH_2OH} + \mathrm{Cr_2O_7^{2-}} + 8\,\mathrm{H^+} & \rightleftharpoons & 3\,\mathrm{RCHO} + 2\,\mathrm{Cr^{3+}} + 7\,\mathrm{H_2O} \end{array}$$

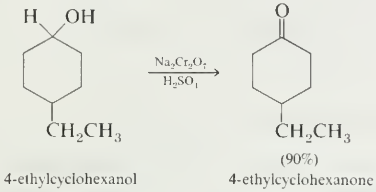
Alternatively, one may use a method based on hypothetical oxygen equivalents, [O].

$$\begin{array}{rcl} 3 \times [\mathrm{RCH_2OH} + [\mathrm{O}] & \rightleftharpoons & \mathrm{RCHO} + \mathrm{H_2O}] \\ [\mathrm{Cr_2O_7^{2-}} + 8\,\mathrm{H^+} & \rightleftharpoons & 2\,\mathrm{Cr^{3+}} + 3\,[\mathrm{O}] + 4\,\mathrm{H_2O}] \\ \hline 3\,\mathrm{RCH_2OH} + \mathrm{Cr_2O_7^{2-}} + 8\,\mathrm{H^+} & \rightleftharpoons & 3\,\mathrm{RCHO} + 2\,\mathrm{Cr^{3+}} + 7\,\mathrm{H_2O} \end{array}$$

In this method, each half-reaction is balanced for charges before the oxidation equivalents are added for chemical balance. One or both half-reactions must be multiplied by appropriate factors such that the [O]s cancel out. Both methods, of course, give the same total balanced equation.

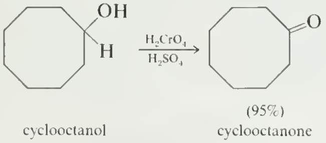
Since ketones are more stable to general oxidation conditions than aldehydes, chromic acid oxidations are more important for secondary alcohols. In one common procedure a 20% excess of sodium dichromate is added to an aqueous mixture of the alcohol and a stoichiometric amount of acid.

2° ROH

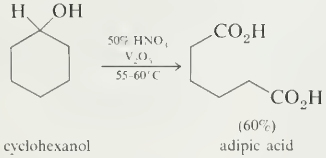


An especially convenient oxidizing agent is Jones reagent, a solution of chromic acid in dilute sulfuric acid. The secondary alcohol in acetone solution is "titrated" with the reagent with stirring at 15–20°. Oxidation is rapid and efficient. The green chromium salts separate from the reaction mixture as a heavy sludge; the supernatant liquid consists mainly of an acetone solution of the product ketone.

2° ROH



Under these conditions tertiary alcohols do not react. Vigorous oxidizing conditions result in cleavage of C—C bonds. Aqueous nitric acid is such a reagent. Oxidation all the way to carboxylic acids is the normal result.



Nitric acid may also be used as an oxidant for primary alcohols; again the product is a carboxylic acid.

$$ClCH_2CH_2CH_2OH \xrightarrow[25\text{-}30°C]{71\%\ HNO_3} ClCH_2CH_2COOH$$

(78%)

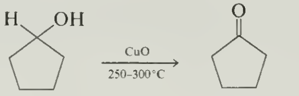
3-chloropropanol 3-chloropropanoic acid

Instead of oxidation, direct dehydrogenation can be accomplished with various catalysts and conditions. The reaction is of industrial interest but is not much used in the laboratory because of the specialized equipment and conditions required. Catalysts include copper metal, copper chromite, or copper-chromium oxides prepared in special ways. Examples of dehydrogenation are

$$CH_3CH_2CH_2CH_2OH \xrightarrow[300\text{-}345°C]{Cu\text{-}Cr\ oxides\ on\ Celite} CH_3CH_2CH_2CHO$$

(62%)

n-butyl alcohol butyraldehyde



(92%)

cyclopentanol cyclopentanone

11.8
Nomenclature of Ethers

The common names of ethers are derived by naming the two alkyl groups and adding the word ether.

$CH_3OCH_2CH_3$ methyl ethyl ether

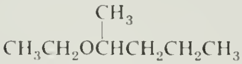
$CH_3OC(CH_3)_3$ methyl *t*-butyl ether

In symmetrical ethers, the prefix di- is used. Although the prefix is often omitted, it is better to include it to avoid confusion.

$CH_3CH_2OCH_2CH_3$ diethyl ether (or ethyl ether)

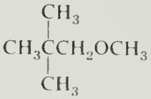
$(CH_3)_2CHOCH(CH_3)_2$ diisopropyl ether (or isopropyl ether)

In the IUPAC systematic rules, ethers are named as alkoxyalkanes. The larger alkyl group is chosen as the stem.



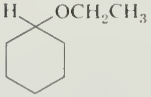
$CH_3CH_2OCH(CH_3)CH_2CH_2CH_3$

2-ethoxypentane



$CH_3C(CH_3)_2CH_2OCH_3$

1-methoxy-2,2-dimethylpropane



ethoxycyclohexane

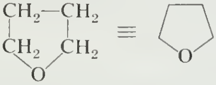
$CH_3OCH_2CH_2OCH_3$

1,2-dimethoxyethane

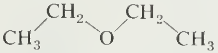
11.9
Physical Properties of Ethers

The physical properties of some ethers are listed in Table 11.5. Note that dimethyl ether is a gas at room temperature and that diethyl ether has a boiling point only about 10°C above normal room temperature. Diethyl ether is an important solvent and has a characteristic odor. It was once used as an anesthetic, but it has been largely replaced for this purpose by other compounds.

The rule of thumb that compounds having no more than four carbons per oxygen are water soluble holds for ethers as well as for alcohols. Dimethyl ether is completely miscible with water. The solubility of diethyl ether in water is about 10 g per 100 g of H_2O at 25°. Tetrahydrofuran (b.p. 67°) is another important solvent. This cyclic ether, commonly abbreviated THF, has essentially the same molecular weight as diethyl ether, but it is much more soluble in water.



tetrahydrofuran (THF)
(b.p. 67°; miscible with H_2O in all portions at 25°)



diethyl ether
(b.p. 34.5; 10 g dissolves in 100 g H_2O at 25°)

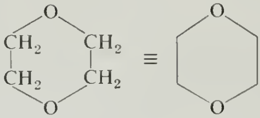
Because of its cyclic structure, the lone pair electrons in THF are more accessible for hydrogen bonding than they are in diethyl ether. In the acyclic compound, the "floppy" ethyl groups interfere with hydrogen bonding and cause the water solubility of diethyl ether to be lower. Also note that the cyclic compound has a significantly higher boiling point. Its more compact structure allows for more efficient Van der Waals attraction between molecules.

As we shall see, ethers are fairly inert to many reagents. Because of their unreactivity, they are not generally important as chemical reagents. However, their general lack of reactivity, combined with their favorable solvent properties, make ethers useful solvents for many other reactions. Several ethers that are important

TABLE 11.5
Physical Properties of Ethers

Compound	Name	Melting Point, °C	Boiling Point, °C
CH_3OCH_3	dimethyl ether	−138.5	−23
$CH_3OCH_2CH_3$	ethyl methyl ether		10.8
$(CH_3CH_2)_2O$	diethyl ether	−116.62	34.5
$CH_3CH_2OCH_2CH_2CH_3$	ethyl propyl ether	−79	63.6
$(CH_3CH_2CH_2)_2O$	dipropyl ether	−122	91
$(CH_3\overset{\overset{CH_3}{\mid}}{C}H)_2O$	diisopropyl ether	−86	68
$(CH_3CH_2CH_2CH_2)_2O$	dibutyl ether	−95	142

as solvents are 1,4-dioxane, 1,2-dimethoxyethane (glyme), and bis-β-methoxyethyl ether (diglyme).



1,4-dioxane
(dioxane)

$CH_3OCH_2CH_2OCH_3$
1,2-dimethoxyethane
(glyme)

$CH_3OCH_2CH_2OCH_2CH_2OCH_3$
bis-β-methoxyethyl ether
(diglyme)

Ethers have nmr spectra similar to those of alcohols, except for the absence of an OH signal. Hydrogens on the same carbon as the ether oxygen usually absorb in the range $\delta = 3.3\text{–}3.9$ ppm. Hydrogens at carbons β to the ether oxygen are only slightly affected (Figure 11.7).

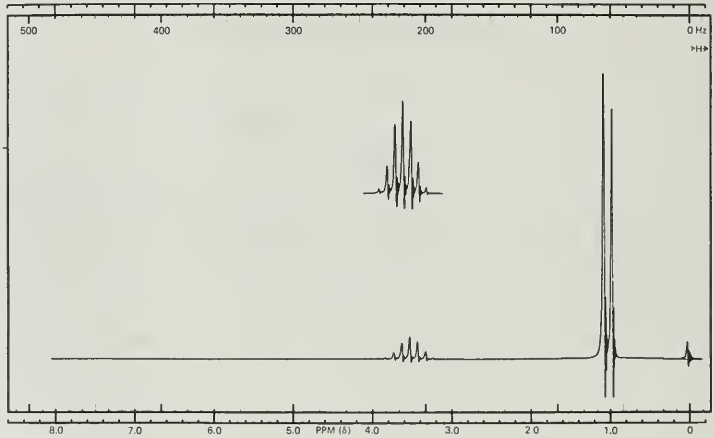


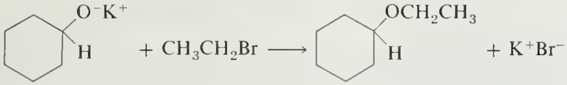
Figure 11.7 Nmr *spectrum of diisopropyl ether,* $(CH_3)_2CHOCH(CH_3)_2$.

11.10
Preparation of Ethers

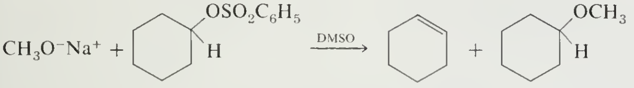
Ethers may be prepared by the Williamson ether synthesis, by the reaction of alcohols with sulfuric acid, or by the alkoxymercuration of alkanes.

A. *Williamson Ether Synthesis*

This method, first used by A. W. Williamson, one of the pioneers in organic chemistry, is simply an S_N2 displacement of a primary alkyl halide or sulfonate ester by an alkoxide ion. The alkoxide may be derived from a primary, secondary, or tertiary alcohol, but the substrate must be primary and have no β branches.



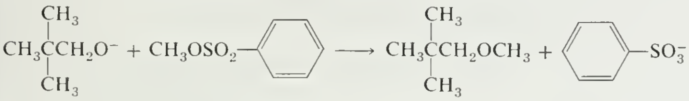
Other halides and sulfonates give too much elimination for the reaction to be of preparative value.



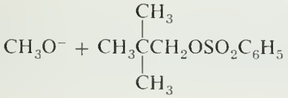
(85%) cyclohexene

(5%) methoxycyclohexane

Since the reaction is a classic example of an S_N2 reaction, one must keep in mind the principles of that mechanism (Sections 8.5, 8.6) when planning an ether synthesis by this route. For example, methyl neopentyl ether can be prepared readily from sodium neopentoxide and methyl benzenesulfonate.



However, the other possible combination will not work. Recall that the β branching in neopentyl systems causes them to react exceedingly slowly in S_N2 reactions.



$$CH_3O^- + CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2OSO_2C_6H_5$$

very slow, impractical

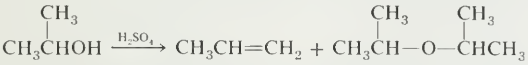
B. *Reaction of Alcohols with Sulfuric Acid*

This method, which was discussed in Section 11.7, is most often used for the conversion of simple primary alcohols into symmetrical ethers.

$$ClCH_2CH_2OH \xrightarrow{H_2SO_4} ClCH_2CH_2OCH_2CH_2Cl$$

(75%)
bis-β-chloroethyl ether

Secondary and tertiary alcohols undergo predominant dehydration when subjected to these conditions. Occasionally, some of the symmetrical ether is formed as a by-product in the case of secondary alcohols



$$CH_3\overset{CH_3}{C}HOH \xrightarrow{H_2SO_4} CH_3CH{=}CH_2 + CH_3\overset{CH_3}{C}H{-}O{-}\overset{CH_3}{C}HCH_3$$

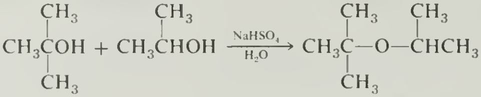
major product

by-product

The method is generally useless for the preparation of unsymmetrical ethers because complex mixtures are formed.

$$ROH + R'OH \xrightarrow{H^+} ROR + ROR' + R'OR'$$

An exception is the case where one alcohol is tertiary and the other alcohol is primary or secondary. Since tertiary carbonium ions form under very mild conditions, this method is generally a satisfactory synthetic method.

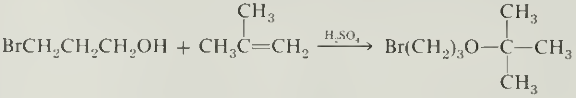


$$CH_3\overset{CH_3}{\underset{CH_3}{C}}OH + CH_3\overset{CH_3}{C}HOH \xrightarrow[H_2O]{NaHSO_4} CH_3\overset{CH_3}{\underset{CH_3}{C}}-O-\overset{CH_3}{C}HCH_3$$

(82%)

> *t*-Butyl alcohol is added to a mixture of 15% aqueous sodium bisulfate and isopropyl alcohol at room temperature. The mixture is neutralized with NaOH and distilled to yield *t*-butyl isopropyl ether (82%).

The tertiary cation may also be produced by protonation of an alkene in the presence of a primary or secondary alcohol (Section 12.6.B).

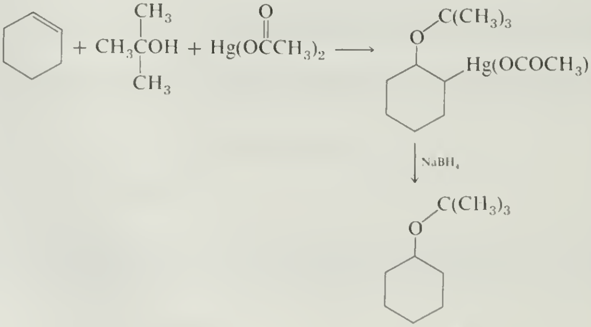


$$BrCH_2CH_2CH_2OH + CH_3\overset{CH_3}{C}{=}CH_2 \xrightarrow{H_2SO_4} Br(CH_2)_3O-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$$

(80%)
γ-bromopropyl *t*-butyl ether

C. *Alkoxymercuration of Alkenes*

This method is successful for the preparation of a wide variety of unsymmetrical ethers. The alkene is added to a mixture of THF and an alcohol containing a stoichiometric amount of mercuric acetate. An intermediate alkoxy organomercury compound is formed, which is then reduced by sodium borohydride.



(90%)
cyclohexyl *t*-butyl ether

We shall discuss the mechanism of these reactions in Section 12.6.B.

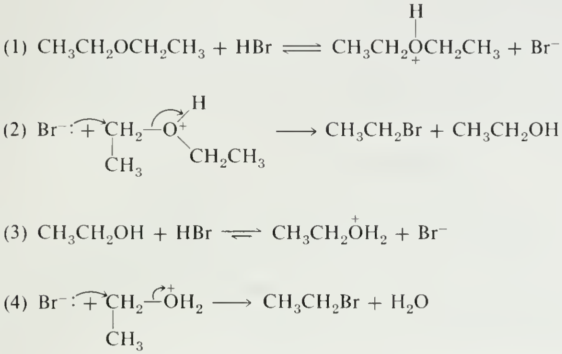
11.11
Reactions of Ethers

A. *Reaction with Acids*

Ethers are relatively inert to most reagents. They are stable to base, to catalytic hydrogenation, and to most other reducing agents. They are stable to dilute acid but do react with hot concentrated acids. Strong HBr or HI causes cleavage.

$$CH_3CH_2OCH_2CH_3 + 2\,HBr \xrightarrow{\Delta} 2\,CH_3CH_2Br + H_2O$$

The mechanism of the reaction involves an S_N2 displacement by bromide ion on the protonated ether. The alcohol produced reacts further with HBr to yield more alkyl bromide.



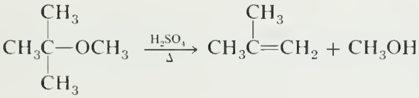
$$\text{(1)}\ CH_3CH_2OCH_2CH_3 + HBr \rightleftharpoons CH_3CH_2\overset{H}{\underset{+}{O}}CH_2CH_3 + Br^-$$

$$\text{(2)}\ Br^-: + \underset{CH_3}{CH_2}-\overset{+}{O}\overset{H}{\underset{CH_2CH_3}{}} \longrightarrow CH_3CH_2Br + CH_3CH_2OH$$

$$\text{(3)}\ CH_3CH_2OH + HBr \rightleftharpoons CH_3CH_2\overset{+}{O}H_2 + Br^-$$

$$\text{(4)}\ Br^-: + \underset{CH_3}{CH_2}-\overset{+}{O}H_2 \longrightarrow CH_3CH_2Br + H_2O$$

With secondary and tertiary ethers, carbonium ions are involved and the reactions tend to be much more complex. Heating such ethers with strong acid generally leads to elimination as the major reaction.

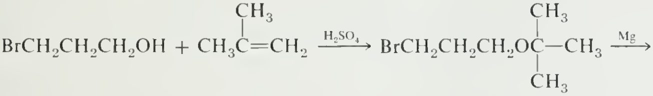


$$CH_3\overset{CH_3}{\underset{CH_3}{C}}-OCH_3 \xrightarrow[\Delta]{H_2SO_4} CH_3\overset{CH_3}{C}=CH_2 + CH_3OH$$

methyl *t*-butyl ether

isobutylene

The reaction is not generally useful for preparations unless one of the alkyl groups of the ether is a small tertiary group. In such a case the alkene formed upon elimination volatilizes as it is produced. The *t*-butyl group is often used as a **protecting group** in organic synthesis in order to render an alcohol temporarily unreactive.

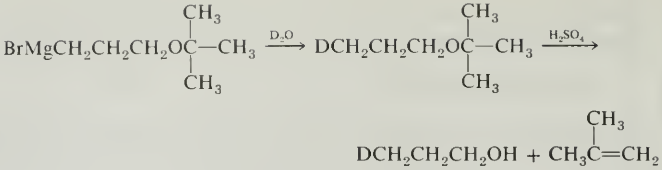


$$BrCH_2CH_2CH_2OH + CH_3\overset{CH_3}{C}=CH_2 \xrightarrow{H_2SO_4} BrCH_2CH_2CH_2O\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \xrightarrow{Mg}$$

3-bromopropanol

(excess under pressure)

3-*t*-butoxy-1-bromopropane



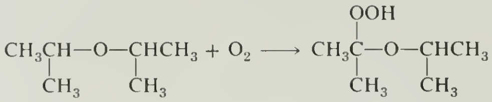
$$\mathrm{BrMgCH_2CH_2CH_2O}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{-CH_3} \xrightarrow{\mathrm{D_2O}} \mathrm{DCH_2CH_2CH_2O}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{-CH_3} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{DCH_2CH_2CH_2OH} + \mathrm{CH_3}\overset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{{=}CH_2}$$

3-deuterio-1-propanol
or 1-propanol-3-*d*

isobutylene
b.p. −7°C

B. *Oxidation*

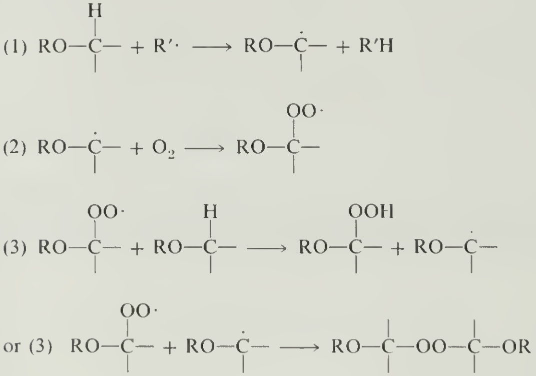
One of the most important reactions of ethers is an undesirable one—the reaction with atmospheric oxygen to form peroxides **(autoxidation).**



$$\mathrm{CH_3}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{-O-}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{CH_3} + \mathrm{O_2} \longrightarrow \mathrm{CH_3}\overset{\mathrm{OOH}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{-O-}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{CH_3}$$

a hydroperoxide

Autoxidation occurs by a free radical mechanism.



$$\text{(1)}\quad \mathrm{RO-}\overset{\mathrm{H}}{\underset{|}{\mathrm{C}}}\mathrm{-} + \mathrm{R'}\cdot \longrightarrow \mathrm{RO-}\underset{|}{\dot{\mathrm{C}}}\mathrm{-} + \mathrm{R'H}$$

$$\text{(2)}\quad \mathrm{RO-}\underset{|}{\dot{\mathrm{C}}}\mathrm{-} + \mathrm{O_2} \longrightarrow \mathrm{RO-}\overset{\mathrm{OO}\cdot}{\underset{|}{\mathrm{C}}}\mathrm{-}$$

$$\text{(3)}\quad \mathrm{RO-}\overset{\mathrm{OO}\cdot}{\underset{|}{\mathrm{C}}}\mathrm{-} + \mathrm{RO-}\overset{\mathrm{H}}{\underset{|}{\mathrm{C}}}\mathrm{-} \longrightarrow \mathrm{RO-}\overset{\mathrm{OOH}}{\underset{|}{\mathrm{C}}}\mathrm{-} + \mathrm{RO-}\underset{|}{\dot{\mathrm{C}}}\mathrm{-}$$

$$\text{or (3)}\quad \mathrm{RO-}\overset{\mathrm{OO}\cdot}{\underset{|}{\mathrm{C}}}\mathrm{-} + \mathrm{RO-}\underset{|}{\dot{\mathrm{C}}}\mathrm{-} \longrightarrow \mathrm{RO-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{-OO-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{-OR}$$

a peroxide

Ethers of almost any type that have been exposed to the atmosphere for any length of time invariably contain peroxides. Isopropyl ether is especially treacherous in this regard, but ethyl ether and tetrahydrofuran are also dangerous. Peroxides and hydroperoxides are hazardous because they decompose violently at elevated temperatures, and serious explosions may result. When an ether that contains peroxides is distilled, the less volatile peroxides concentrate in the residue. At the end of the distillation, the temperature increases, and the residual peroxides may explode. For this reason, ethers should never be evaporated to dryness, unless care has been taken to exclude peroxides rigorously.

A simple test for peroxides is to shake a small volume of the ether with aqueous KI solution. If peroxides are present, they oxidize I^- to I_2. The characteristic purple-to-brown color of I_2 is diagnostic of the presence of peroxides. Contaminated ether may be purified by shaking with aqueous ferrous sulfate to reduce the peroxides.

> Several years ago, one of the authors had an impressive demonstration of the violence of a peroxide explosion. In a laboratory adjacent to his office, a laboratory technician was engaged in purifying about 2 liters of old THF, later found to contain substantial amounts of peroxides. The material exploded, virtually demolishing the laboratory, and moving the wall several inches toward the author's desk. Several large bookshelves were knocked over and emptied their contents onto his desk and chair. Only by good fortune was no one injured.

11.12
Nomenclature of Thiols and Sulfides

Although sulfur is in the same column of the periodic table as oxygen, it has various oxidation states besides −2 in its compounds. Some of these classes of compounds will be discussed in subsequent chapters, but the compounds in which sulfur is divalent have direct analogies to corresponding oxygen functions.

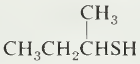
Thiols are commonly called **mercaptans.** Simple thiols are frequently called alkyl mercaptans, in analogy to the alkyl alcohol system for naming alcohols.

CH_3SH
methyl mercaptan

$CH_3CH_2CH_2CH_2SH$
butyl mercaptan

The mercaptan names are falling into disuse in favor of the IUPAC systematic names wherein thiols are named as alkanethiols. In the IUPAC system, the alkane name is combined with the suffix **-thiol** in the same way that alcohols are named as alkanols. Note, however, that the final **-e** of the alkane name is retained in naming thiols.

CH_3CH_2SH
ethanethiol

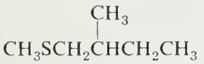

$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HSH$
2-butanethiol

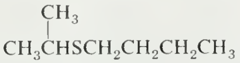
Sulfides are commonly named in a manner analogous to the common nomenclature of ethers. The two alkyl group names are followed by the word **sulfide.**

CH_3SCH_3
dimethyl sulfide

$CH_3CH_2SCH_2CH_2CH_3$
ethyl propyl sulfide

In the IUPAC system, sulfides are named as alkylthioalkanes. The prefix **alkylthio-** is analagous to **alkoxy-,** and refers to a group RS—. As with ethers, the larger of the two alkyl groups is taken as the stem.


$CH_3SCH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_3$
2-methyl-1-(methylthio)butane


$CH_3\overset{\overset{CH_3}{|}}{C}HSCH_2CH_2CH_2CH_3$
1-isopropylthiobutane

The IUPAC system for naming sulfides is only used in practice for complex structures which are not conveniently named as dialkyl sulfides.

11.13
Physical Properties of Thiols and Sulfides

Thiols have boiling points that are almost normal for their molecular weight; they generally boil somewhat higher than the corresponding chlorides. For example, ethanethiol has b.p. 37° compared to ethyl chloride, b.p. 13°. Thiols are stronger acids than alcohols just as H_2S is a stronger acid than water. The pK_a of ethanethiol, 10.50, indicates that the compound is completely converted to its anion by hydroxide ion.

$$\underset{pK_a\ 10.5}{C_2H_5SH} + OH^- \rightleftharpoons C_2H_5S^- + \underset{pK_a\ 15.7}{H_2O}$$

Although the thiols are more acidic than alcohols, sulfur is less electronegative than oxygen. Hence, thiols have lower dipole moments (CH_3SH, $\mu = 1.26$ D; CH_3OH, $\mu = 1.71$ D) and hydrogen bonding between thiol molecules is much weaker than for alcohols. However, hydrogen bonding from the acidic SH protons to water oxygen is significant, and the thiols have some water solubility.

The most impressive property of thiols is their odor. Their intensely disagreeable odors discourage use as laboratory reagents. Thiols contribute to the characteristic odors of skunk and onion. Two methanethiol esters are known to give urine a distinctive odor after eating asparagus. The nose is more sensitive than any laboratory instrument in detecting ethanethiol; one part in 50 billion parts of air can be detected. Small amounts are included in heating gas, which is otherwise almost odorless, as an effective warning device against leaks. The lower molecular weight sulfides have similarity repugnant odors.

11.14
Preparation of Thiols and Sulfides

Thiols can be prepared from alkyl halides by displacement with hydrosulfide ion, HS^-, in ethanol solution.

$$CH_3(CH_2)_{16}CH_2I + Na^+SH^- \xrightarrow{C_2H_5OH} \underset{\text{1-octadecanethiol}}{CH_3(CH_2)_{16}CH_2SH} + Na^+Br^-$$

In preparing thiols by this method it is necessary to employ a large excess of hydrosulfide because of the equilibrium

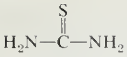
$$HS^- + RSH \rightleftharpoons H_2S + RS^-$$

The thiol anion produced by this equilibrium is itself a good nucleophile and can react with the alkyl halide to give the corresponding sulfide.

$$RS^- + RBr \longrightarrow RSR + Br^-$$

The use of a large excess of hydrosulfide makes its reaction with the alkyl halide more probable and maximizes the yield of thiol.

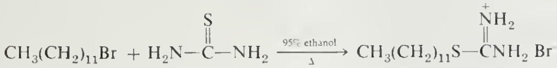
For this reason HS^- in such displacement reactions has been almost exclusively replaced by thiourea.



$$H_2N-\overset{\overset{S}{\|}}{C}-NH_2$$

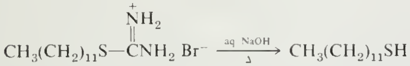
Thiourea

Thiourea is a commercially available solid, m.p. 178°, and is soluble in water and alcohols. The sulfur is nucleophilic in S_N2 displacement reactions on alkyl halides. The product salt is readily hydrolyzed to the alkanethiol.



$$CH_3(CH_2)_{11}Br + H_2N-\overset{\overset{S}{\|}}{C}-NH_2 \xrightarrow[\Delta]{95\%\ ethanol} CH_3(CH_2)_{11}S-\overset{\overset{\overset{+}{N}H_2}{\|}}{C}NH_2\ Br^-$$

n-dodecyl bromide



$$CH_3(CH_2)_{11}S-\overset{\overset{\overset{+}{N}H_2}{\|}}{C}NH_2\ Br^- \xrightarrow[\Delta]{aq\ NaOH} CH_3(CH_2)_{11}SH$$

(79–83%)
1-dodecanethiol

This route avoids formation of sulfides. The other product of the hydrolysis is urea, H_2NCONH_2 (Section 26.2.A).

Thiols can also be prepared by reaction of Grignard reagents with sulfur.

$$(CH_3)_3CMgBr + S_8 \longrightarrow (CH_3)_3CSMgBr \xrightarrow{HCl} (CH_3)_3CSH + MgBrCl$$

t-butyl mercaptan

Both symmetrical and unsymmetrical sulfides can be prepared by S_N2 displacement of alkylthio anions on alkyl halides or sulfonates.

$$CH_3CH_2SH + OH^- \xrightarrow{H_2O} CH_3CH_2S^-$$

$$CH_3CH_2S^- + (CH_3)_2CHCH_2Br \longrightarrow (CH_3)_2CHCH_2SCH_2CH_3$$

(95%)
ethyl isobutyl sulfide

This general method for preparing dialkyl sulfides is directly analogous to the Williamson ether synthesis (Section 11.10.A).

11.15
Reactions of Thiols and Sulfides

Thiols are readily oxidized to **disulfides.** The disulfide bond is weak and is easily reduced to give the thiol.

$$2\ RSH \underset{reduction}{\overset{oxidation}{\rightleftharpoons}} RS-SR$$

a disulfide

Mild oxidizing agents suffice for the oxidation. Iodine is often used for this purpose.

$$2\ CH_3CH_2SH + I_2 \longrightarrow CH_3CH_2SSCH_2CH_3 + 2\ HI$$

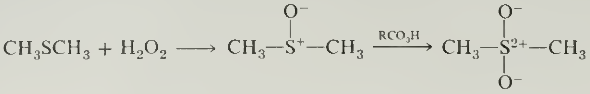
diethyl disulfide

A commonly used reducing agent for regeneration of the thiol is lithium in liquid ammonia.

$$CH_3CH_2SSCH_2CH_3 \xrightarrow[NH_3]{Li} 2\ CH_3CH_2SH$$

The facile thiol-disulfide redox system is especially important in biological systems. The disulfide link occurs in proteins and hormones and the redox reaction itself plays an important role in molecular biology. It has been suggested that this reaction may be involved in the mechanism of memory in the brain.

Sulfides are also easily oxidized. The initial oxidation product is a **sulfoxide.** Further oxidation of the sulfoxide yields a **sulfone.**



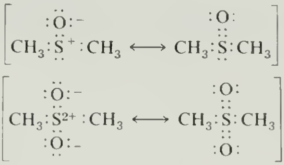
$$CH_3SCH_3 + H_2O_2 \longrightarrow CH_3-\overset{O^-}{\overset{|}{S^+}}-CH_3 \xrightarrow{RCO_3H} CH_3-\underset{O^-}{\underset{|}{\overset{O^-}{\overset{|}{S^{2+}}}}}-CH_3$$

dimethyl sulfoxide
(DMSO)

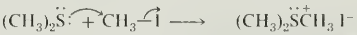
dimethyl sulfone

Dimethyl sulfoxide, commonly abbreviated DMSO, is an important organic solvent because of its ability to dissolve a variety of inorganic salts as well as most organic compounds. It is a relatively inexpensive colorless liquid, b.p. 189°. It is miscible with water and is hygroscopic. Dimethyl sulfoxide is prepared industrially by the NO_2-catalyzed air-oxidation of dimethyl sulfide, a by-product of the sulfite pulping process in paper manufacture.

> Note that sulfur can form stable tricovalent and tetracovalent compounds. The Lewis structures of dimethyl sulfoxide and dimethyl sulfone together with alternative structures with expanded sulfur octets are:



The sulfur in dialkyl sulfides is still nucleophilic. Consequently, sulfides react readily with alkyl halides by a normal S_N2 process to produce **trialkylsulfonium salts**, which are generally crystalline solids.



$$(CH_3)_2\ddot{S}: + CH_3-I \longrightarrow (CH_3)_2\overset{\cdot\cdot +}{S}CH_3\ I^-$$

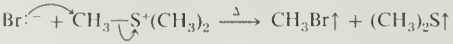
trimethylsulfonium iodide

As with other S_N2 displacements, the reaction works best with primary halides.

$$(CH_3)_2CHCH_2Br + (CH_3)_2S \longrightarrow (CH_3)_2CHCH_2\overset{+}{S}(CH_3)_2\ Br^-$$

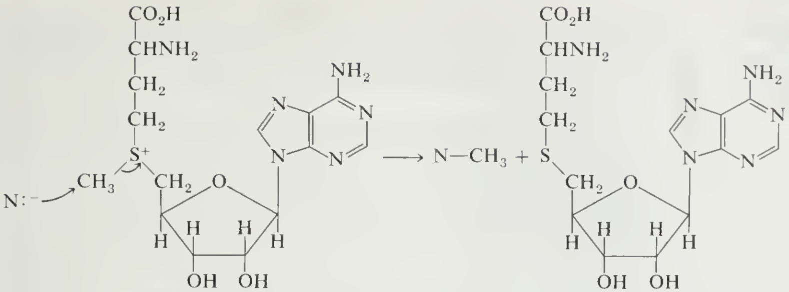
isobutyldimethylsulfonium bromide

When trialkylsulfonium salts are heated, the reaction reverses. Halide ion acts as the nucleophile and the dialkyl sulfide is the leaving group. The driving force for reaction is vaporization of the volatile products.



$$Br:^- + CH_3-S^+(CH_3)_2 \xrightarrow{\Delta} CH_3Br\uparrow + (CH_3)_2S\uparrow$$

Nature makes extensive use of this S_N2 reaction. The compound *S*-adenosylmethionine is a methylating agent in biochemical S_N2 reactions, which are catalyzed by appropriate enzymes. It can be regarded as the body's equivalent of methyl iodide.

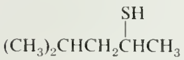


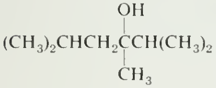
S-adenosylmethionine

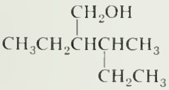
PROBLEMS

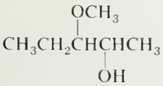
1. Give the structure corresponding to each of the following names:
   - (a) methyl isobutyl ether
   - (b) neopentyl alcohol
   - (c) 3-ethoxy-2-methylhexane
   - (d) 4-methyl-2-pentanol
   - (e) triphenylcarbinol
   - (f) ethyl isopropyl sulfide
   - (g) butyl mercaptan
   - (h) 4-*t*-butyl-3-methoxyheptane
   - (i) 2,3-dimethoxybutane
   - (j) α,β-diphenylethyl alcohol
   - (k) 3-methylthiooctane
   - (l) dibutyl disulfide
   - (m) 3-pentanethiol

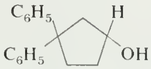
2. Give the IUPAC name corresponding to each of the following structures:

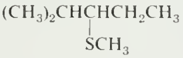
(a) 
$(CH_3)_2CHCH_2CH(SH)CH_3$

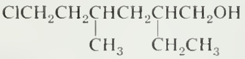
(b) 
$(CH_3)_2CHCH_2C(OH)(CH_3)CH(CH_3)_2$

(c) 
$CH_3CH_2CH(CH_2OH)CH(CH_2CH_3)CH_3$

(d) 
$CH_3CH_2CH(OCH_3)CH(OH)CH_3$

(e) 

(f) 
$(CH_3)_2CHCH(SCH_3)CH_2CH_3$

(g) 
$ClCH_2CH_2CH(CH_3)CH_2CH(CH_2CH_3)CH_2OH$

3. How many isomeric ethers correspond to the molecular formula $C_5H_{12}O$? Give common and IUPAC names for each structure and sketch the expected nmr spectrum of each. Which of these ethers is capable of optical activity? Write out the structures of the two mirror images and show that they are not superimposable.

4. There are 17 isomeric alcohols of the formula $C_6H_{13}OH$. Write out the structure and give the IUPAC name of each one. Identify the primary, secondary, and tertiary alcohols.

5. A naive graduate student attempted the preparation of $CH_3CH_2CDBrCH_3$ from

$CH_3CH_2CDOHCH_3$ by heating the deuterioalcohol with HBr and H_2SO_4. He obtained a product having the correct boiling point, but a careful examination of the spectral properties by his research director showed that the product was a mixture of $CH_3CHDCHBrCH_3$ and $CH_3CH_2CDBrCH_3$. What happened?

6. (a) In a popular handbook the compound $CH_3CH_2C(CH_3)_2OCH_3$ is listed as ether, *sec*-butyl methyl, 2-methyl-. Does this name accord with any approved nomenclature you have studied? Give correct common and IUPAC names.
   (b) Note the resemblance in appearance of this ether to 3,3-dimethylpentane. Compare the boiling points of both compounds as given in a handbook.
   (c) 2,2-Dimethyl-3-pentanol and *t*-butyl isopropyl ether are isomers that are not listed in common handbooks. How would you expect their boiling points to compare? See if you can find these compounds and their boiling points in the important compendium, *Beilstein*, found in almost all chemistry libraries. (*Beilstein*, a series of volumes written in German, is discussed in Chapter 37.)

7. (a) In a handbook look up the boiling points of 1-butanethiol, diethyl sulfide, and methyl *n*-propyl sulfide. What do these boiling points indicate about the magnitude of hydrogen bonding in thiols?
   (b) Compare these boiling points with those of *n*-butyl chloride and bromide and isobutyl chloride and bromide. Sulfur has a lower atomic weight than chlorine or bromine. How important is molecular weight in determining the boiling point? The Van der Waals radii of sulfur, chlorine, and bromine are 1.85, 1.80, and 1.95 Å, respectively. Is there a parallel between this radius and boiling point? Rationalize the result.

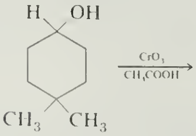
8. Give the principal product(s) from each of the following reactions:

(a) $CH_3CH_2CH_2OH \xrightarrow[130^\circ]{H_2SO_4}$

(b) $CH_3CH_2CH_2O^- + (CH_3)_3CCl$

(c) $(CH_3)_3CO^- + CH_3CH_2CH_2Br$

(d) $CH_3CH_2CH_2OH + K_2Cr_2O_7 + H_2SO_4 \xrightarrow{50^\circ}$

(e) 

(f) $CH_3CH_2CH_2S^- + CH_3CH_2CH_2Br$

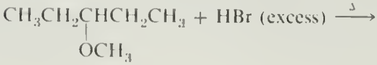
(g) $CH_3CH_2CH_2OH \xrightarrow[H_2SO_4,\ \Delta]{HBr}$

(h) $(CH_3CH_2)_3CCH_2OH \xrightarrow[H_2SO_4,\ \Delta]{HBr}$

(i) $(CH_3CH_2)_3CBr + CH_3S^- \xrightarrow[\Delta]{\text{acetone}}$

(j) $(CH_3CH_2)_2CHOH + CH_3MgBr \longrightarrow$

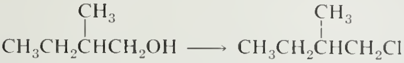
(k) $(CH_3CH_2CH_2)_2O + HI\ (\text{excess}) \xrightarrow{\Delta}$

(l) 

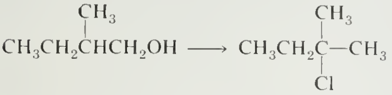
$CH_3CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2CH_3 + HBr\ (\text{excess}) \xrightarrow{\Delta}$

9. Give the reagents and conditions for the best conversions of alcohol to alkyl halide as shown:

(a) $CH_3CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH_2CH_2Cl$

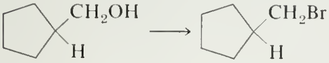
(b) 

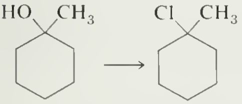
$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2OH \longrightarrow CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2Cl$

(c) 

$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2OH \longrightarrow CH_3CH_2\underset{Cl}{\overset{CH_3}{C}}-CH_3$

(d) $CH_3CH_2CH_2CHOHCH_3 \longrightarrow CH_3CH_2CH_2CHICH_3$

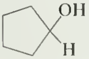
(e) 

(f) 

10. Show how to accomplish each of the following conversions in a practical manner:

(a) $(CH_3)_3CCH_2Br \longrightarrow (CH_3)_3CCH_2SH$
(b) $(CH_3)_2CHCHOHCH_3 \longrightarrow (CH_3)_2CHCHDCH_3$
(c) $(CH_3CH_2)_3COH \longrightarrow (CH_3CH_2)_2C{=}CHCH_3$
(d) $CH_3CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH_2CH_2CN$
(e) $(CH_3)_3CCl + CH_3I \longrightarrow (CH_3)_3COCH_3$
(f) $(CH_3)_2CHCH_2OH \longrightarrow (CH_3)_3CH$
(g) $CH_3CH_2CH_2CH_2OH \longrightarrow (CH_3CH_2CH_2CH_2)_2S$

11. Write balanced equations for the following reactions:

(a) 

$+ HNO_3 \longrightarrow HOOC(CH_2)_3COOH + H_2O + NO_2$

(b) $ClCH_2CH_2CH_2OH + HNO_3 \longrightarrow ClCH_2CH_2COOH + NO_2 + H_2O$

(c) $CH_3CHOHCH_3 + CrO_3 + H^+ \longrightarrow CH_3COCH_3 + H_2O + Cr^{3+}$

(d) $CH_3SCH_3 + HNO_3 \longrightarrow CH_3SO_2CH_3 + H_2O + NO_2$

12. To minimize the odor released by traces of mercaptans on reaction vessels it is recommended that they be rinsed with aqueous potassium permanganate as soon as possible. The thiols are oxidized to alkanesulfonic acids (Section 18.13.A), and the sulfides are oxidized to sulfones. Write balanced equations for

(a) $CH_3SH + KMnO_4 \xrightarrow{H_2O} CH_3SO_3K + MnO_2 + KOH$

(b) $(CH_3)_2S + KMnO_4 \xrightarrow{H_2O} CH_3SO_2CH_3 + MnO_2 + KOH$

13. (a) Although isobutyl alcohol reacts with HBr and H_2SO_4 to give isobutyl bromide without rearrangement, 3-methyl-2-butanol reacts on heating with conc. HBr to give 2-bromo-2-methylbutane. Explain this difference using the reaction mechanisms involved.

(b) Unsymmetrical ethers are generally not prepared by heating two alcohols with sulfuric acid. Why not? Yet, when *t*-butyl alcohol is heated in methanol containing sulfuric acid, a good yield of methyl *t*-butyl ether results. Explain this result by means of the reaction mechanism.

(c) Prolonged reaction of ethyl ether with HI gives ethyl iodide. Write out the reaction mechanism.

14. Fusel oil is a toxic by-product of carbohydrate fermentation that consists mostly of two five-carbon alcohols. It concentrates in the higher boiling residues of distillation of ethanol in fermentation and, if such distillation is not monitored, will distil to give the product that special toxic "kick" associated with bootleg liquor. The nmr spectra of the two principal constituents of fusel oil are given in Figures 11.8 and 11.9. Determine their structures. One of these compounds is obtained in optically active

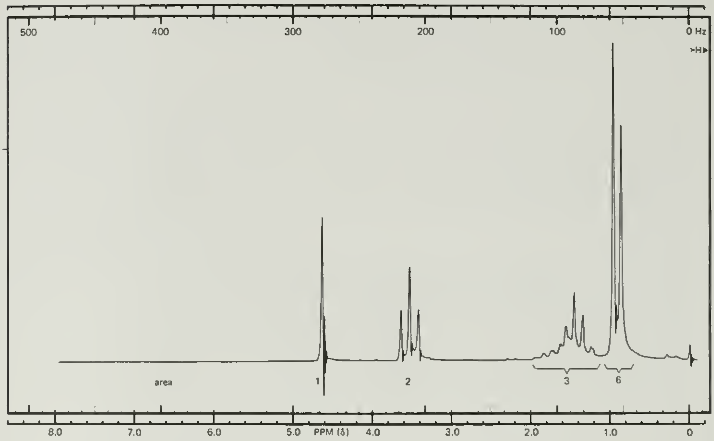


FIGURE 11.8 Nmr *spectrum of constituent of fusel oil.*

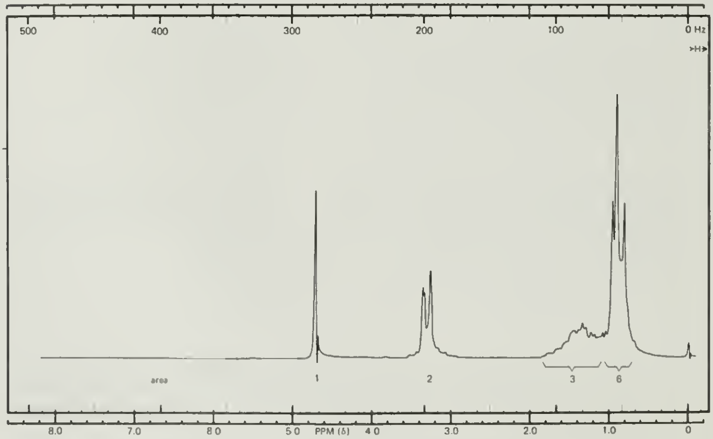


FIGURE 11.9 Nmr *spectrum of another constituent of fusel oil.*

form by fermentation and has the trivial name of "active amyl alcohol." Which structure belongs to it?

15. The thermodynamics of reactions in a solution are often quite different from those in the gas phase because of the importance of solvation energies. However, thermodynamic data for solvents other than water are sparse, whereas many heats of formation are now available for the gas phase. If one considers reactions in which the number of ions or ion pairs remains the same, the relative gas phase values can be instructive. Compare $\Delta H°$ for the following two reactions in the gas phase:

$$CH_3CH_2OH + Br^- \rightleftharpoons CH_3CH_2Br + OH^-$$
$$CH_3CH_2OH + HBr \rightleftharpoons CH_3CH_2Br + H_2O$$

In addition to the values in Appendix 1, the following $\Delta H_f°$ are required: Br^-, -50.8 kcal mole^{-1}; OH^-, -32.9 kcal mole^{-1}.

16. Thiols are used as inhibitors in free radical reactions. In such use they end up as disulfides. The bond dissociation energy of $CH_3S{-}H$ is about 75 kcal mole^{-1}. Calculate $\Delta H°$ for the reaction,

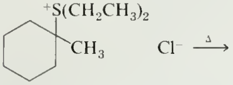
$$CH_4 + CH_3S\cdot \rightleftharpoons CH_3\cdot + CH_3SH$$

In which direction does the equilibrium lie? Explain how CH_3SH works as an inhibitor.

17. Predict the products when each of the following trialkylsulfonium salts is heated:

(a) $CH_3CH_2S^+(CH_3)_2\ I^- \xrightarrow{\Delta}$

(b) $(CH_3)_3CCH_2S^+(CH_2CH_3)_2\ Br^- \xrightarrow{\Delta}$

(c) 

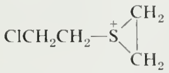
18. Ethyl *n*-butyl ether is cleaved by hot conc. HBr to give both ethyl bromide and *n*-butyl bromide. Ethyl *t*-butyl ether, however, is cleaved readily by cold conc. HBr to give primarily *t*-butyl bromide and ethyl alcohol. Write the reaction mechanisms of both reactions, showing all intermediates, and explain briefly how the reaction mechanisms relate to these experimental observations.

19. Triethyloxonium cation can be prepared as a crystalline fluoborate salt, $(C_2H_5)_3O^+BF_4^-$, that is appreciably soluble in methylene chloride. Write the Lewis structure of this salt. The compound is a reactive ethylating reagent and reacts with alcohols, for example, to yield ethers:

$$ROH + (CH_3CH_2)_3O^+ \longrightarrow ROC_2H_5 + (C_2H_5)_2O + H^+$$

Write out the mechanism of the reaction. Why is the reagent so reactive in this process?

20. Mustard gas or bis-(β-chloroethyl) sulfide, $(ClCH_2CH_2)_2S$, is an oily liquid that was used extensively as a poison gas in World War I. It is a deadly vesicant that causes blindness and numerous other effects. The active agent is actually the cyclic sulfonium salt



which reacts with nucleophilic materials in the body. The formation of the cyclic sulfonium salt can be regarded as an internal or intramolecular S_N2 displacement reaction. Write out this reaction mechanism. What mechanism does this process suggest for the subsequent reaction of the cyclic sulfonium salt with nucleophilic reagents?

21. 1-Butanol-1-*d*, $CH_3CH_2CH_2CHDOH$, has a relatively small but easily measured optical activity, $[\alpha]_D = 0.5°$, due solely to a difference between hydrogen isotopes. The (−) enantiomer has been shown to have the (R) configuration. On treatment with thionyl chloride, (−)-1-butanol-1-*d* gives (+)-1-chlorobutane-1-*d*. What is the configuration of the chloride? Draw perspective diagrams of both compounds. Show how (R)-$CH_3CH_2CH_2CHDOH$ may be converted to (S)-$CH_3CH_2CH_2CHDOCH_3$.

★22. (a) One useful measure of the energy of hydrogen bonding derives from heats of vaporization, ΔH_v. The following table gives the vapor pressure of ethanol at different temperatures:

Temperature, °C	Vapor Pressure, torr
−31.3	1
−2.3	10
+19.0	40
34.9	100
64.5	400
78.4	760

From

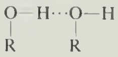
$$\frac{d\ln P}{dT} = -\frac{\Delta H_v}{RT^2} \quad \text{or} \quad \frac{d\ln P}{d(1/T)} = -\frac{\Delta H_v}{R}$$

plot ln P versus $1/T$ and calculate ΔH_v for ethanol. For comparison, ΔH_v of propane is 4.49 kcal mole^{-1}.

(b) This difference can be compared to an electrostatic model. The dipole moment of ethanol is 1.7 D. Consider the approximation that this dipole results from partial charges at oxygen and hydrogen. The O—H bond distance is 0.96 Å. What fraction of positive and negative electronic charges separated by 0.96×10^{-8} cm correspond to a dipole moment of 1.7×10^{-18} esu-cm? The charge on an electron is 4.8×10^{-10} esu. Calculate the electrostatic energy of attraction of a pattern of such charges arranged as

$$\underset{q^-}{\mathrm{O}} \xleftrightarrow{0.96\ \text{Å}} \underset{q^+}{\mathrm{O}} \xleftrightarrow{2.07\ \text{Å}} \underset{q^-}{\mathrm{O}} \xleftrightarrow{0.96\ \text{Å}} \underset{q^+}{\mathrm{O}}$$

An electron and a proton 1 Å apart have an electrostatic energy of attraction of 332 kcal mole^{-1}. This electrostatic energy calculation is only a crude model for a hydrogen bond



$$\underset{\mathrm{R}}{\mathrm{O}}\text{—H}\cdots\underset{\mathrm{R}}{\mathrm{O}}\text{—H}$$

but it does give a rough idea of the magnitude of the energy quantities involved.

★23. By using a collection of point charges, show that the electrostatic interaction between a charge and a dipole varies as $1/r^2$ and that between two dipoles varies as $1/r^3$, where r is the distance to the center of the dipole. The dipole can be treated as two point charges close together relative to r.

Chapter 12

Alkenes

Alkenes are hydrocarbons with a C=C double bond. The double bond is a stronger bond than a single bond, yet, paradoxically, the C=C double bond is much more reactive than a C—C single bond. Unlike the generally nonspecific reactions of alkanes, the double bond is the site of many specific reactions and is a functional group.

12.1
Electronic Structure

The geometric structure of ethylene, the simplest alkene, is well known from spectroscopic and diffraction experiments and is shown in Figure 12.1. The entire molecule is planar, as shown in the stereo plot in Figure 12.2.

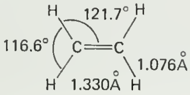


Figure 12.1 *Structure of ethylene.*

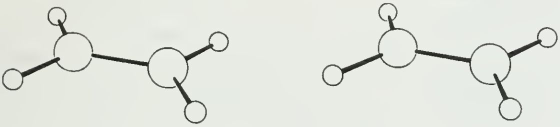
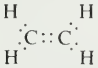


Figure 12.2 *Stereo plot structure of ethylene.*

In the Lewis structure of ethylene the double bond is characterized as a region with two pairs of electrons.



In orbital descriptions, we need one orbital for each pair of electrons. Hence, we need two orbitals between the carbons to accommodate the electrons. Many possible schemes can be devised to arrange such orbitals, but only two are important.

A. *Bent-bond Model*

In one scheme we take two equivalent hybrid orbitals on each carbon and allow them to overlap in a nonlinear fashion as in Figure 12.3. For this kind of "bent-

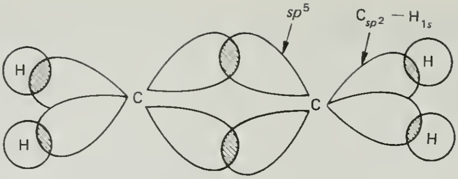


FIGURE 12.3 *Bent-bond orbital model of ethylene.*

bond" overlap, better overlap results from hybrids that have greater *p* character. To a useful approximation, each of the hybrid orbitals making up the two bent bonds has sp^5 hybridization. That is, each of the orbitals is made up from $\frac{1}{6}$ of an *s* orbital and $\frac{5}{6}$ of a *p* orbital. The two hybrid orbitals together use up $\frac{1}{3}$ of an *s* orbital and $1\frac{2}{3}$ *p* orbitals. This leaves just enough for each carbon to have two additional sp^2 hybrid orbitals for bonding to the hydrogens.

As shown in Figure 12.2, all six atoms lie in the same plane. Bonds with more *s* character tend to be shorter and stronger. The C—H bonds are 1.076 Å long and are slightly shorter than the bonds in methane, 1.085 Å. The H—C—H bond angle is much wider than the tetrahedral angle of 109.5° but is not quite as large as the angle expected for two sp^2 hybrids, 120°. The orbital picture given is an approximate one. The C=C double bond distance of 1.33 Å is much shorter than the normal C—C single bond of 1.54 Å. The extra electron density between the carbon nuclei provides additional attraction to the nuclei to help overcome the added nuclear repulsion of the shorter internuclear distance.

B. π *Bond Model*

A different orbital model of ethylene starts with the two sp^2 hybrids from each carbon to the hydrogens. A third sp^2 hybrid on each carbon is used to form a C_{sp^2}—C_{sp^2} single bond. This leaves a *p* orbital "left over" on each carbon. This *p* orbital lies perpendicular to the plane of the six atoms. The two *p* orbitals are parallel to each other and have regions of overlap above and below the molecular plane. This type of bond in which there are two bonding regions above and below a nodal plane is called a π bond. This notation is used in order to distinguish it from the type of bond formed by overlap of two carbon sp^2 orbitals. Such a bond has no node and is called a σ bond (Figure 12.4). This orbital picture of ethylene is shown in Figure 12.5.

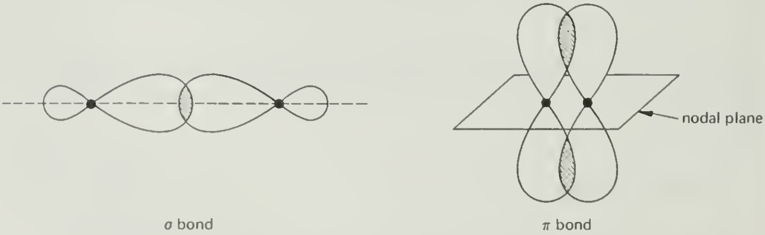


FIGURE 12.4 *σ and π bonds.*

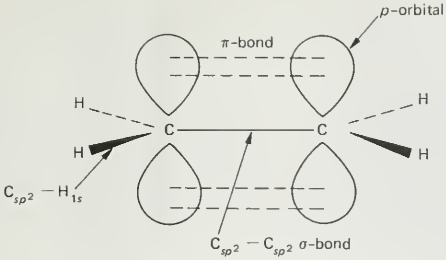
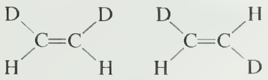


FIGURE 12.5 *σ-π bond model of ethylene.*

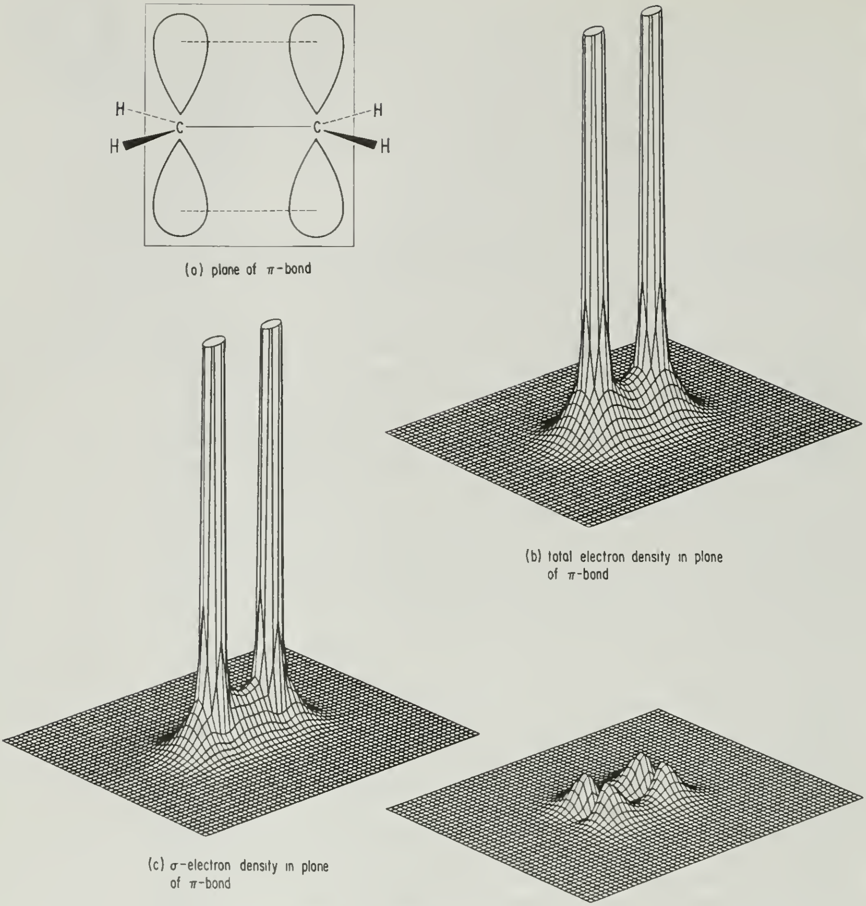
Superficially, this model appears to be completely different from the bent-bond model illustrated in Figure 12.3, but this difference is totally in the inadequacies of the kinds of symbolic representations shown in these figures. *The two orbital models are actually exactly equivalent!* They are simply two different visualizations of the same mathematical function. In effect, we have taken the same total electron density distribution between the carbons and have split it in two different ways. The total electron density is the same for both. The σ-π description is a common and useful one. The total electron density in the plane of the π bond is shown in Figure 12.6b as a perspective plot. The electron density is very high close to the carbon nuclei, but there is substantial electron density in the region between the carbons, indicative of substantial covalent or shared electron bonding. This total electron density is dissected into a σ portion in Figure 12.6c and the π bond in Figure 12.6d. Note that π bonding has little electron density in the region between the carbons, and the π bond is much weaker than the σ bond. This difference will be shown to be important in our study of the reactions of double bonds.

Another important view of the double bond electron density is that of a plane in the center of the C—C bond and perpendicular to the bond axis, as shown in Figure 12.7a. The σ electron density in Figure 12.7c is high at the center of the bond axis and falls off exponentially away from the axis. The contours are oval rather than circular because of electron repulsion by the π electrons. The π electron density in Figure 12.7d is much less than the σ density, and the total electron density in Figure 12.7b has a smooth oval character. This total electron distribution does not have the appearance one might expect from the simple kinds of representations in Figures 12.3 or 12.5. One important consequence of the noncylindrically symmetric electron density about the C—C bond axis is that there is a barrier to rotation about this axis. For example, two dideuterioethylenes are known and can be distinguished by their different spectroscopic properties.



two different dideuterioethylenes

Interconversion of these isomers takes place only at high temperatures (≈500°) and has an activation energy of 65 kcal $mole^{-1}$. The transition state for the reaction has a half-twisted structure in which the *p* orbitals have zero overlap. This structure is represented in Figure 12.8.



(a) plane of π-bond

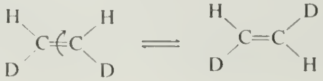
(b) total electron density in plane of π-bond

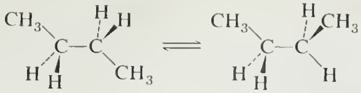
(c) σ-electron density in plane of π-bond

(d) π-electron density in plane of π-bond

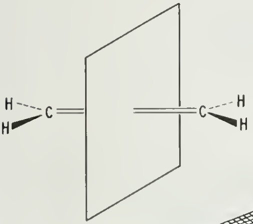
FIGURE 12.6 *Electron density of ethylene double bond.*

The two forms of dideuterioethylene represent another case of stereoisomerism (Chapter 7). Recall that stereoisomers are compounds that have the same sequence of covalently bonded atoms but differ in the orientation of the atoms in space. The two dideuterioethylene stereoisomers may be interconverted by rotation about a bond, just as the anti and gauche stereoisomers of butane.

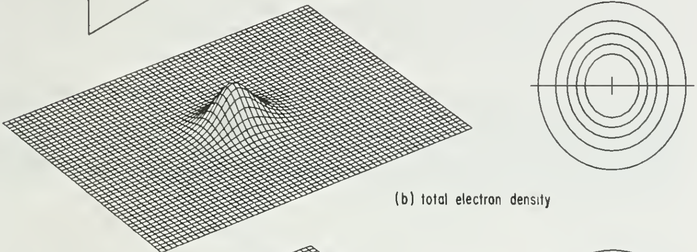




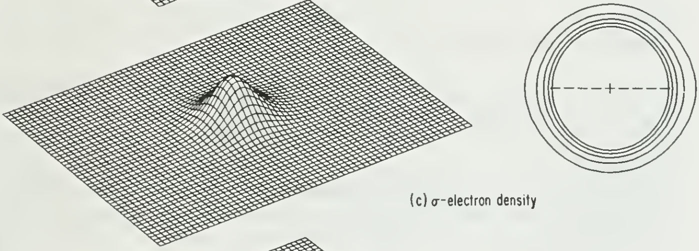
However, in one case the barrier to interconversion (the rotational barrier) is 65 kcal mole^{-1} and in the other it is only 3.3 kcal mole^{-1}. The dideuterioethylene stereoisomers may be obtained separately, and each isomer is perfectly stable at normal temperatures. On the other hand, the anti and gauche butane stereoisomers interconvert easily at temperatures above about −230°. This difference



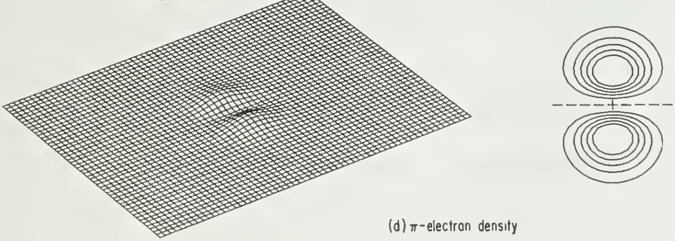
(a) perpendicular plane at center of double bond



(b) total electron density



(c) σ-electron density



(d) π-electron density

FIGURE 12.7 *Electron density distribution in center of ethylene double bond. Both perspective plots and contour diagrams are shown.*

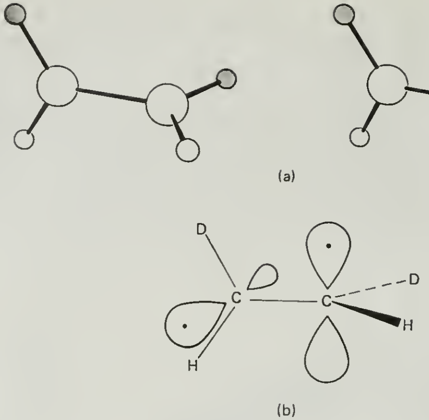


Figure 12.8 *The half-twisted transition state for interconversions of dideuterioethylenes. (a) The structure is shown in the stereo plot. (b) The orbital representation shows one electron in each of the noninteracting* p*-orbitals at right angles to each other.*

in the ease of interconversion has resulted in the two types of stereoisomers having different names. Stereoisomers that can be easily interconverted by rotation about a bond are called **conformational isomers.** Stereoisomers that are not easily interconverted are called **configurational isomers.** The dideuterioethylenes are two such configurational isomers.

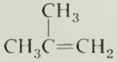
12.2
Nomenclature of Alkenes

Historically, hydrocarbons with a double bond were known as **olefins.** This rather strange class name comes from the Latin words *oleum,* an oil, and *ficare,* to make. It arose because derivatives of such compounds often had an oily appearance.

As with other classes of organic compounds, there are two systems of nomenclature that are used, common and systematic. In the common system, which is only used for fairly simple compounds, the final **-ane** of the alkane name is replaced by **-ylene.**

$CH_2{=}CH_2$
ethylene

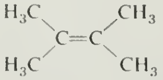
$CH_3CH{=}CH_2$
propylene



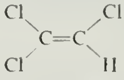
$CH_3\overset{\overset{CH_3}{|}}{C}{=}CH_2$

isobutylene

A few simple molecules are named as derivatives of ethylene.

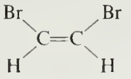


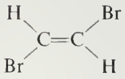
tetramethylethylene



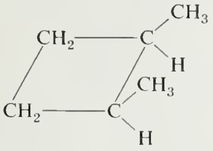
trichloroethylene

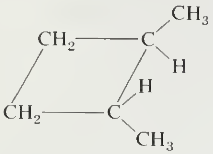
Configurational isomers are distinguished by the use of the prefixes *cis-* (L., on this side) and *trans-* (L., across).

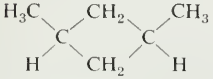

cis-dibromoethylene

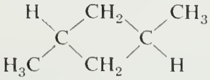

trans-dibromoethylene

Disubstituted cycloalkanes can also exist as distinct configurational isomers. These isomers are distinguished by the *cis-trans* nomenclature.


cis-1,2-dimethylcyclobutane


trans-1,2-dimethylcyclobutane


cis-1,3-dimethylcyclobutane


trans-1,3-dimethylcyclobutane

This topic is discussed in detail in Chapter 23.

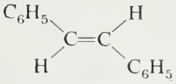
Some monosubstituted ethylenes are named as radical combinations in which the radical from ethylene is called **vinyl.**

$CH_2{=}CHCl$
vinyl chloride

$CH_2{=}CHOCH_3$
methyl vinyl ether

A few special trivial names are in common use.

$C_6H_5CH{=}CH_2$
styrene

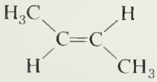

trans-stilbene

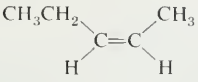
In the IUPAC system, alkenes are named as derivative of a parent alkane. The **alk** stem specifies the number of carbons in the chain and the **ene** suffix specifies a double bond. A number is used to indicate the position of the double bond along the chain. Since the double bond joins one carbon to a carbon with the next higher number, only one number need be given. Finally, a prefix *cis-* or *trans-* is included where necessary.

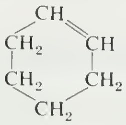
$CH_2{=}CH_2$
ethene

$CH_3CH{=}CH_2$
propene

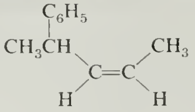
$CH_3CH_2CH{=}CH_2$
1-butene


trans-2-butene

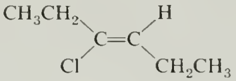

cis-2-pentene


cyclohexene
(no number necessary)

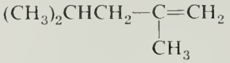
Substituent groups are included as prefixes with appropriate numbers to specify position. Since the **ene** stem is a suffix, it dominates the numbering. That is, the parent alkene chain is named first, including *cis-* or *trans-* where necessary, and then the substituents are appended as prefixes.



4-phenyl-*cis*-2-pentene
(not 2-phenyl-3-pentene)

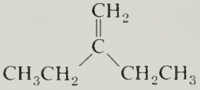


3-chloro-*trans*-3-hexene



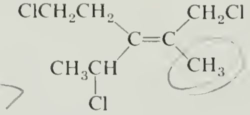
$(CH_3)_2CHCH_2-C(CH_3)=CH_2$

2,4-dimethyl-1-pentene



2-ethyl-1-butene
(parent is longest chain that includes the double bond)

The *cis-trans* system for naming configurational isomers frequently leads to confusion. The Chemical Abstracts Service has proposed an unambiguous system that has been adopted by the IUPAC. In this system, the two groups attached to each end of the double bond are assigned priority numbers as is done in naming enantiomers by the (R-S) system (Chapter 7). When the two groups of higher priority number are on the **same side** of the molecule, the compound is the **Z** isomer (from the German *zusammen*, together). When the two groups of highest priority are on **opposite sides** of the molecule, the compound is the E form (from the German *entgegen*, across).



(E)-1,4-dichloro-3-(2-chloroethyl)-2-pentene

Mistake!
1st printing

In normal use, several common compounds are almost invariably called by their common or trivial names as given above, but more complex compounds are named by the IUPAC system.

Finally, when two suffix groups are present, such as -ol and -ene, the priority is ol > ene. Such compounds are named as en-ol, and the final suffix group determines the numbering system.

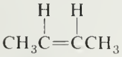
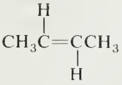
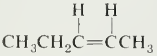
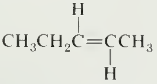
$$CH_2{=}CHCH_2CH_2OH$$

but-3-en-1-ol
(not but-1-en-4-ol)

12.3
Physical Properties of Alkenes

Physical properties of some alkenes are summarized in Table 12.1. These properties are similar to those of the corresponding alkanes as shown by the boiling point plot in Figure 12.9. The lower members are gases at room tempera-

TABLE 12.1
Physical Properties of Alkenes

Name	Structure	Boiling Point, °C	Density, d^{20}
ethylene	$CH_2{=}CH_2$	−103.7	
propylene	$CH_3CH{=}CH_2$	−47.4	0.5193
1-butene	$CH_3CH_2CH{=}CH_2$	−6.3	0.5951
cis-2-butene	 $CH_3\overset{H}{\overset{\vert}{C}}{=}\overset{H}{\overset{\vert}{C}}CH_3$	3.7	0.6213
trans-2-butene	 $CH_3\overset{H}{\overset{\vert}{C}}{=}\underset{H}{\underset{\vert}{C}}CH_3$	0.9	0.6042
2-methyl-1-propene	$(CH_3)_2C{=}CH_2$	−6.9	0.5942
1-pentene	$CH_3CH_2CH_2CH{=}CH_2$	30.0	0.6405
cis-2-pentene	 $CH_3CH_2\overset{H}{\overset{\vert}{C}}{=}\overset{H}{\overset{\vert}{C}}CH_3$	36.9	0.6556
trans-2-pentene	 $CH_3CH_2\overset{H}{\overset{\vert}{C}}{=}\underset{H}{\underset{\vert}{C}}CH_3$	36.4	0.6482
2-methyl-2-butene	$(CH_3)_2C{=}CHCH_3$	38.6	0.6623

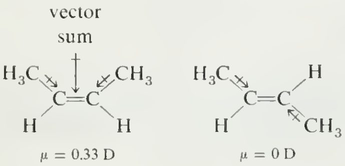
ture. Starting with the five-carbon compounds the alkenes are volatile liquids. Isomeric alkenes have similar boiling points and mixtures can be separated only by careful fractional distillation with efficient columns. 1-Alkenes tend to boil a few degrees lower than internal olefins and can be separated by such careful fractionation.

A. *Dipole Moments*

In an alkyl-substituted double bond, the carbon orbitals making up the =C—C bond have different amounts of *s* character. Such a bond may be approximated as C_{sp^2}—C_{sp^3}. The resulting change in electron density distribution gives such bonds an effective dipole moment in the direction

$$\mathrm{C}\overset{+}{\rightarrow}\mathrm{C{=}C}$$

These dipole moments are small for hydrocarbons, but still permit a distinction between *cis* and *trans* isomers. For example, *cis*-2-butene has a small dipole moment, whereas *trans*-2-butene has a resultant dipole moment of zero because of its symmetry.



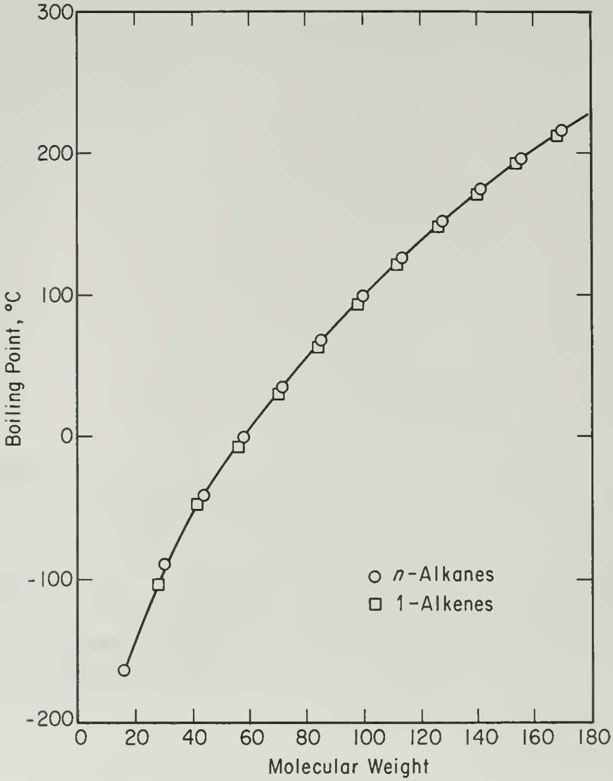
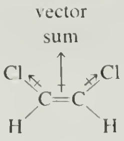
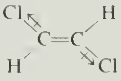


Figure 12.9 *Boiling point relationships of alkenes and alkanes.*

With substituents such as halogens the dipole moment differences are greater.



$\mu = 2.95$ D



$\mu = 0$ D

B. *Nmr Spectra*

Hydrogens attached to a double bond ("vinyl hydrogens") appear at about $\delta = 5$ ppm. The actual values vary from about $\delta = 4.7$ ppm when the vinyl hydrogens are at the end of a chain to about $\delta = 5.3$ ppm when the vinyl hydrogen is at some other position along the chain.

$CH_3CH_2CH{=}CH_2$ $\delta = 5.3$ ppm $\delta = 4.7$ ppm $CH_3CH{=}CHCH_3$ $\delta = 5.3$ ppm

These values may appear to be rather far downfield for a C—H function. It is true that the increased *s* character of the carbon orbital makes the carbon effectively more electronegative, but the observed change is too large to be a simple electronegativity effect.

The effect has its origin in the induced motion of bond electrons, just as discussed earlier in the diamagnetic shielding (Section 10.4) by electrons around the hydrogen nucleus. In a double bond, the π electrons are more polarizable than σ electrons and are freer to move in response to a magnetic field. As shown in Figure 12.10, the circular motion of the π electrons produces an induced magnetic field opposed to the applied field *at the middle of the double bond.* Out by the vinyl hydrogens, the magnetic lines of force are in the same direction as the applied field. Hence, a lower applied field is necessary for the total field at the hydrogen nucleus to have the resonance value. For double bonds with orientations other than that shown, the effect will be smaller and the actual effect will be the average for all orientations because the tumbling and rotation of molecules in the normal nmr technique is fast on the nmr time scale.

It should be emphasized that vinyl hydrogens are still subject to the normal diamagnetic shielding effects of nearby electron clouds. The net effect is still a chemical shift far upfield from a bare proton. However, the effect of the **π electron circulation** partially opposes the normal effect of local electrons in such a way that resonance occurs downfield from that observed for a saturated C—H by a significant amount. The resulting chemical shift of vinyl hydrogens provides an important analytical method for establishing both their presence and number.

The applied magnetic field also induces electron currents in C—C and C—H single bonds, and it is these induced currents rather than electronegativity effects that give rise to the characteristic pattern of chemical shifts for differently substituted alkyl hydrogens.

$$\delta(\geqq\mathrm{CH}) > \delta(-\mathrm{CH_2}-) > \delta(-\mathrm{CH_3})$$

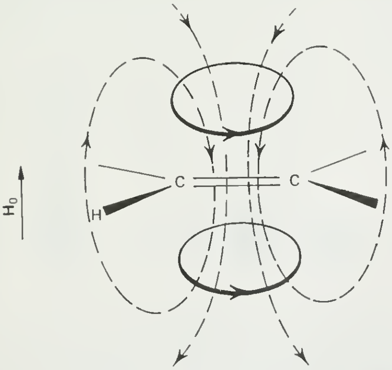
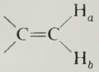
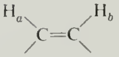
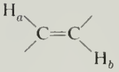


FIGURE 12.10 *Induced motion of π electrons of a double bond in a magnetic field, showing that the applied field and the induced field have the same direction at a vinyl proton.*

TABLE 12.2
Coupling Constants for Vinyl Protons

Structure		J_{ab}, Hz
	geminal	0–3 (≃ 2 in simple alkenes)
	*cis*	5–14
	*trans*	11–19

But nmr can tell even more about the structure of double bonds in alkenes. The magnitude of the coupling constant J between vinyl hydrogens varies with structure, as shown in Table 12.2. For two hydrogens that are attached to the same carbon (**geminal** hydrogens), the coupling constant is relatively small. In simple alkenes, J_{ab} is about 2 Hz and becomes smaller in alkenes with electron-withdrawing substituents.

The magnitude of J differs for *cis* and *trans* hydrogens. Although the ranges of both sets overlap, for a pair of isomeric *cis* and *trans* alkenes, J_{trans} is invariably greater than J_{cis}. It may seem strange that hydrogens separated by the greater distance should have the greater effect on each other, but magnetic effects are frequently rather subtle. The coupling effect of hydrogen nuclei is transmitted through bonding electrons—not through space. Orientation of the bonds is as important as distance. The difference between J_{cis} and J_{trans} is an important tool for distinguishing *cis* and *trans* alkenes. Of course, this technique is useful only when the two hydrogens are not equivalent, because equivalent hydrogens do not split each other.

In a monosubstituted ethylene, $CH_2{=}CHY$, all three hydrogens are non-

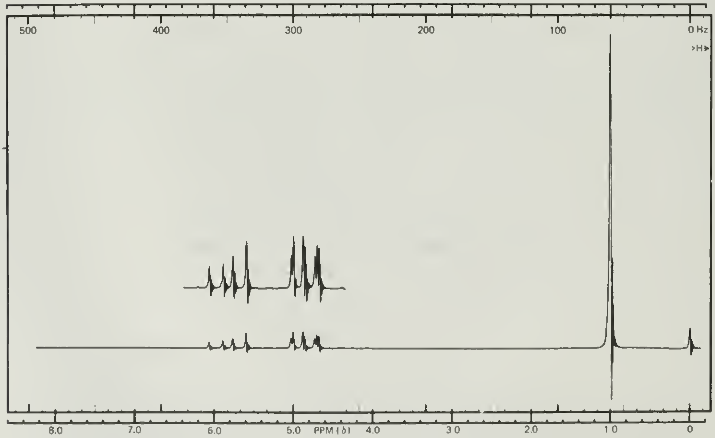


FIGURE 12.11 Nmr *spectrum of* 3,3-*dimethyl*-1-*butene*, $(CH_3)_3CCH{=}CH_2$.

equivalent. They all each split each other to produce a complex multiplet that cannot be easily analyzed by our first-order approximation.

Finally, a C—H group attached to a double bond is shifted downfield by about 0.8 ppm. The important generalizations to remember about nmr of alkenes are δ (=C—H) $\approx$ 5 ppm, $CH_2{=}CH{-}$ is generally a complex multiplet, and $J_{trans} > J_{cis}$. These generalizations are exemplified in the nmr examples shown in Figures 12.11, 12.12, and 12.13. Note in Figures 12.12 and 12.13 that the two

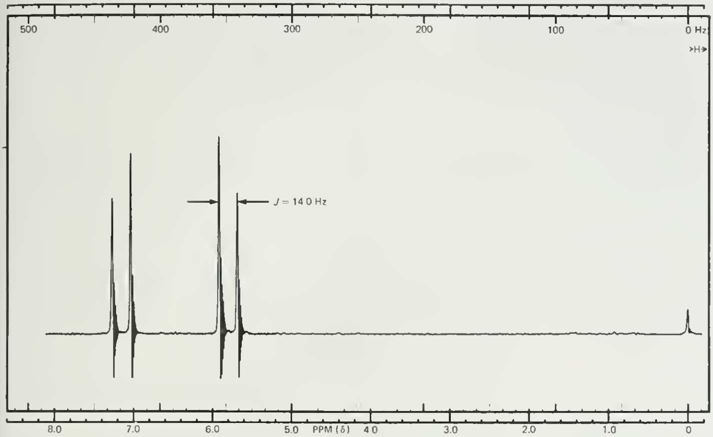
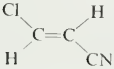


FIGURE 12.12 Nmr spectrum of



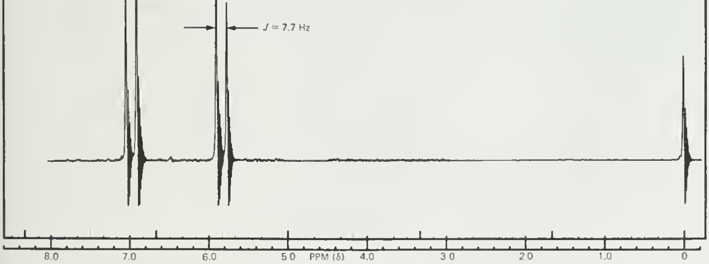
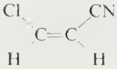


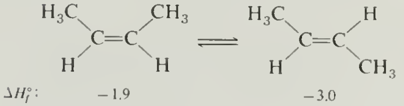
FIGURE 12.13 Nmr spectrum of



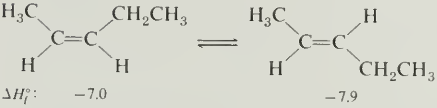
vinyl hydrogens have different chemical shifts because of the different inductive effects of Cl and CN.

12.4
Relative Stabilities of Alkenes: Heats of Formation

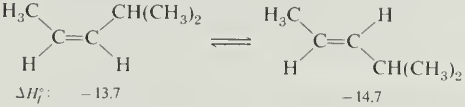
Heats of formation have been evaluated for a number of alkenes. Examination of these values shows that *trans*-alkenes are generally more stable than the isomeric *cis*-alkenes by about 1 kcal mole^{-1}. (Remember that a *more negative* heat of formation, ΔH_f°, corresponds to a *more stable* compound.)



$\Delta H^\circ = -1.1$ kcal mole^{-1}



$\Delta H^\circ = -0.9$ kcal mole^{-1}



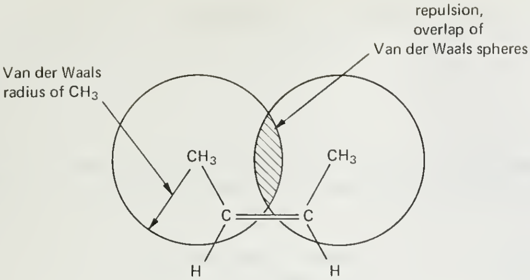
$\Delta H^\circ = -1.0$ kcal mole^{-1}

The distance between the adjacent methyl groups in *cis*-2-butene is about 3 Å. Since the sum of the Van der Waals radii for two methyl groups is 4 Å, the hydrogens in these two groups are sufficiently close that there is a net repulsion not present in the *trans* compound. This effect of repulsion for sterically congested systems is called **steric hindrance** (Figure 12.14).

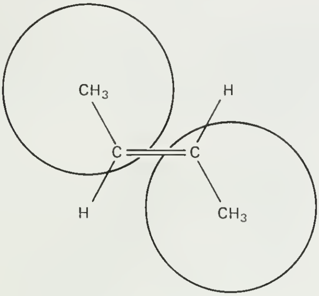
Monosubstituted ethylenes are 2–3 kcal mole^{-1} less stable than disubstituted ethylenes. The examples in the following table may be compared with the corresponding isomers listed above.

Compound	ΔH_f°
$CH_3CH_2CH{=}CH_2$	-0.2
$CH_3CH_2CH_2CH{=}CH_2$	-5.3
$(CH_3)_2CHCH_2CH{=}CH_2$	-12.3

The stabilizing effect of substituents on the double bond continues with additional substituents, although the incremental effect is reduced because of *cis* interactions. For example, trimethylethylene (2-methyl-2-butene), with $\Delta H_f^\circ = -10.1$ kcal



cis-2-butene



trans-2-butene

FIGURE 12.14 *Steric hindrance in* cis-2-*butene,* relative to trans-2-*butene.*

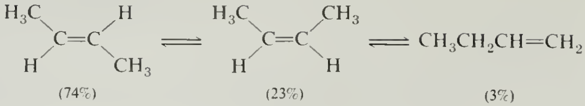
mole^{-1}, is the most stable five-carbon alkene. Similarly, tetramethylethylene (2,3-dimethyl-2-butene) is the most stable six-carbon alkene.

These results are most simply interpreted on the basis of relative bond strengths. A C_{sp^2}-H bond is a stronger bond than is a C_{sp^3}-H bond. If this were the only important factor, the least substituted alkenes would be the most stable. However, a C_{sp^2}-C_{sp^3} bond is also stronger than a C_{sp^3}-C_{sp^3} bond; and it seems that putting more *s* character in a C—C bond has a greater effect than in a C—H bond. This hybridization effect may also be observed in the bond lengths because bond lengths are inversely related to bond strengths. We noted earlier that the C—H bond in ethylene is about 0.01 Å shorter than the C—H bond in ethane. The C—C bond in propylene (1.505 Å) is 0.03 Å shorter than is the C—C bond in propane. The difference, $r(C_{sp^3}\text{-}C_{sp^3}) - r(C_{sp^2}\text{-}C_{sp^3})$ is greater than $r(C_{sp^3}\text{-H}) - r(C_{sp^2}\text{-H})$.

The difference in stability of various alkene isomers is only a few kilocalories per mole, but this makes an important difference in equilibria. From the thermodynamic equation

$$\Delta G^\circ = -RT \ln K$$

a free energy difference of 1.4 kcal mole^{-1} at room temperature corresponds to an equilibrium constant of 10 (Table 12.3). Consequently, in an equilibrium mixture of alkenes, the more highly substituted isomers predominate. For example, the equilibrium composition of the butenes is



We will find that such equilibria can be established and that the relative stabilities of alkene isomers are important in some synthetic methods.

TABLE 12.3
Equilibrium Concentrations as a Function of ΔG° at 25°C
$A \rightleftharpoons B$

$\Delta G°$, kcal mole^{-1}	Per Cent A	Per Cent B
−5	0.02	99.98
−2	3.3	96.7
−1	15.6	84.4
−0.5	30.1	69.9
0	50.0	50.0
+0.5	69.9	30.1
+1	84.4	15.6
+2	96.7	3.3
+5	99.98	0.02

12.5
Preparation of Alkenes

The important preparations of alkenes discussed thus far have all been elimination reactions: E1 and E2 eliminations of alkyl halides and dehydration of alcohols. Other important procedures for introducing double bonds will be discussed in subsequent chapters.

A. *E2 Bimolecular Elimination of Alkyl Halides*

This reaction was discussed previously (Section 8.7), but primarily as a side reaction in S_N2 displacement reactions. E2 elimination can often be made the principal reaction by using a strong base in a nonpolar solvent. One common reagent used for this purpose is potassium hydroxide in refluxing ethanol. This solution is really a solution primarily of potassium ethoxide in ethanol because of the equilibrium

$$OH^- + C_2H_5OH \rightleftharpoons C_2H_5O^- + H_2O$$

This method gives satisfactory results for secondary and tertiary halides, but not for most primary halides. For primary halides, especially with no β branches, the S_N2 reaction is so facile that it dominates, and ethers are the principal products.

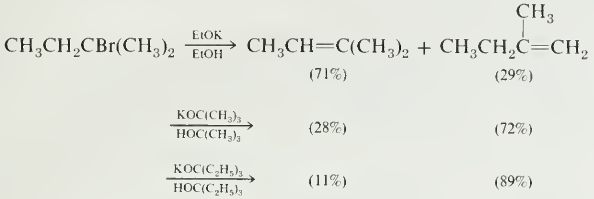
$$n\text{-}C_5H_{11}Br \xrightarrow[\text{EtOH, } 55^\circ C]{\text{EtONa}} \underset{(12\%)}{CH_3CH_2CHCH{=}CH_2} + \underset{(88\%)}{n\text{-}C_5H_{11}OC_2H_5}$$

$$C_2H_5Br \xrightarrow[\text{EtOH, } 55^\circ C]{\text{EtONa}} \underset{(1\%)}{CH_2{=}CH_2} + \underset{(99\%)}{(C_2H_5)_2O}$$

Bimolecular elimination almost invariably gives a mixture of the possible alkene products. The mixture usually reflects the thermodynamic stabilities of the isomeric alkenes; the most stable isomers tend to predominate.

$$CH_3CH_2CH_2CHBrCH_3 \xrightarrow[\text{EtOH, } \Delta]{\text{EtOK}} \underset{\substack{(51\%\ trans)\\(18\%\ cis)}}{CH_3CH_2CH{=}CHCH_3} + \underset{(31\%)}{CH_3CH_2CH_2CH{=}CH_2}$$

In this example note that the *trans* isomer is produced in greater amount than is the *cis* and that the combined 2-pentenes are produced to a greater extent than is 1-pentene. However, the more basic and bulkier reagent potassium *t*-butoxide in the less polar solvent *t*-butyl alcohol tends to give more of the terminal olefin.



$$CH_3CH_2CBr(CH_3)_2 \xrightarrow[\text{EtOH}]{\text{EtOK}} \underset{(71\%)}{CH_3CH{=}C(CH_3)_2} + \underset{(29\%)}{CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2}$$

$$\xrightarrow[\text{HOC(CH}_3)_3]{\text{KOC(CH}_3)_3} \quad (28\%) \qquad (72\%)$$

$$\xrightarrow[\text{HOC(C}_2\text{H}_5)_3]{\text{KOC(C}_2\text{H}_5)_3} \quad (11\%) \qquad (89\%)$$

Potassium *t*-butoxide gives good yields of E2 product even with straight chain primary halides.

$$n\text{-}C_{18}H_{37}Br \xrightarrow[\text{HOC(CH}_3)_3,\ 40^\circ]{\text{KOC(CH}_3)_3} \underset{(85\%)}{n\text{-}C_{16}H_{32}CH{=}CH_2} + \underset{(12\%)}{n\text{-}C_{18}H_{37}OC(CH_3)_3}$$

These various effects of structure are best rationalized in the context of reaction mechanism. A correct mechanism needs to explain these facts as well as several other generalizations that can be made about such eliminations:

1. The rate of E2 reactions depends on the concentration of both the alkyl halide *and* the base.
2. The rate of reaction depends on the nature of the leaving group. In general, bromides react faster than chlorides.
3. The reaction has a high primary hydrogen isotope effect; that is, C—D bonds are broken more slowly than C—H bonds.
4. The reaction is **stereospecific.** The leaving hydrogen must generally be conformationally **anti** to the leaving halide.

The first generalization has an obvious consequence on any proposed mechanism. Both the base and the alkyl halide must be involved in the rate-determining step. In fact, it is this observation that gives the mechanism its name—E2 or "elimination, bimolecular." [In another type of elimination reaction, the rate of reaction depends only on the concentration of the alkyl halide. This type of elimination is distinguished by the name E1 or "elimination, unimolecular." E1 elimination is one of the possible modes of reaction of carbonium ion intermediates (Section 8.8, 11.7.B)].

The second generalization also has an obvious consequence: The bond to the leaving halide must be partially broken in the transition state. Bonds that are broken more easily lead to a lower energy transition state and a faster reaction rate.

The third generalization establishes that the bond to the leaving hydrogen is also partially broken in the transition state. To a first approximation, it effectively takes more energy to break a C—D bond than it does to break a C—H bond.

To be more precise, isotope effects originate in the nature of vibrational energy levels for bonds. These quantum states were discussed previously in connection with hindrance to rotation (Section 4.3) and bond dissociation energies (Section 5.1) of alkanes, and we will encounter them again in studying infrared spectra (Section 14.2). For the present purpose, consider the two C—H bond motions in Figure 12.15. In the strong C—H bond, the potential energy is very sensitive to the value of the C—H bond distance. Thus, in order to accommodate the Heisenberg uncertainty principle, the lowest vibrational energy state is relatively high above the potential minimum. That is, the zero point energy, ε_0, is relatively large. For the C—H bond in alkanes, ε_0 is about 4 kcal mole^{-1}. For a weaker bond, as shown in Figure 12.15b, a given uncertainty in the position of the hydrogen corresponds to a smaller change in potential energy. Hence, ε_0 is smaller.

A deuterium atom is twice as heavy as hydrogen because its nucleus has a neutron as well as a proton. Because of its greater mass, the same momentum corresponds to a slower velocity. A given uncertainty in momentum corresponds to a smaller uncertainty in position compared to the hydrogen case. Accordingly, the zero point energy for a C—D bond is less than that for C—H, as shown in Figure 12.15.

In a reaction in which a C—H bond is broken, the bond is weaker in the transition state. In the change from reactant to transition state, the C—H bond has lost some zero point energy. In the corresponding case of a C—D bond, the loss in zero point energy is lower because the heavier isotope had less zero point energy to begin with. As a result, as shown in Figure 12.16, the activation energy for breaking a C—D bond is greater than that for a C—H bond. The difference in reaction rates can be substantial. For hydrogen isotopes, the effect on ε_0 is approximately the square root of the ratio of masses. If ε_0(H) is 4 kcal mole^{-1}, the corresponding ε_0(D) is 2.8 kcal mole^{-1}. If all of this zero point energy were lost in the transition state, the difference in activation energies would correspond to a reaction rate difference of a factor of

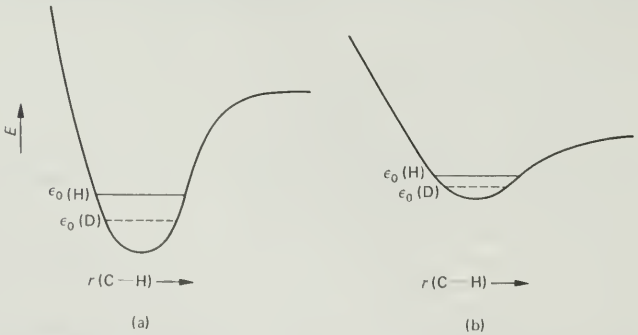


FIGURE 12.15 *Potential energies for stretching motion of an* (a) *strong and* (b) *weak* C—H *bond.*

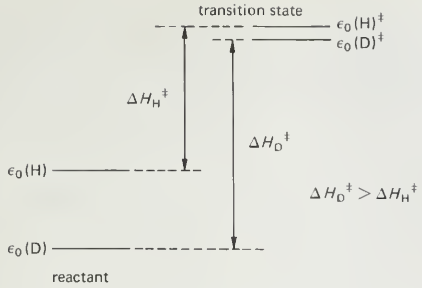

transition state
$\epsilon_0(\mathrm{H})^\ddagger$
$\epsilon_0(\mathrm{D})^\ddagger$
$\Delta H_\mathrm{H}^\ddagger$
$\Delta H_\mathrm{D}^\ddagger$
$\epsilon_0(\mathrm{H})$
$\Delta H_\mathrm{D}^\ddagger > \Delta H_\mathrm{H}^\ddagger$
$\epsilon_0(\mathrm{D})$
reactant

FIGURE 12.16 *The effect on the activation energy of loss of zero point energy in a reaction.*

about 9. In practice, primary isotope effects for E2 reactions have been observed commonly in the range of 4–8.

$$CD_3CHBrCD_3 \xrightarrow{EtO^-} CD_2{=}CHCD_3$$

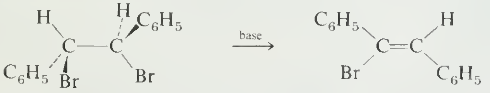
$$\frac{k(CH_3CHBrCH_3)}{k(CD_3CHBrCD_3)} = 6.7$$

$$C_6H_5CD_2CH_2Br \xrightarrow{(CH_3)_3CO^-} C_6H_5CD{=}CH_2$$

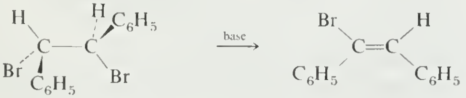
$$\frac{k(C_6H_5CH_2CH_2Br)}{k(C_6H_5CD_2CH_2Br)} = 7.9$$

If no bond to hydrogen is broken at the transition state, isotope effects are generally rather small. For example, in S_N2 reactions, deuterium compounds react at virtually the same rates as the corresponding hydrogen compounds.

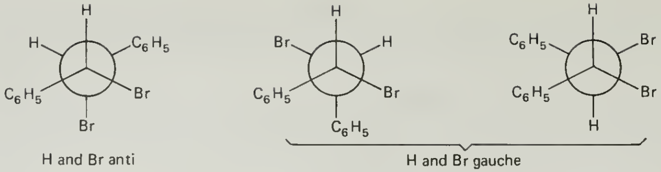
The fourth generalization has been established by many examples, frequently in complex or cyclic systems or by the use of isotopes. The application to cyclohexane derivatives will be discussed later (Section 23.4.C). For the present we will cite a single example:


H
H
C_6H_5
C
C
C_6H_5
Br
Br
base
C_6H_5
H
C=C
Br
C_6H_5

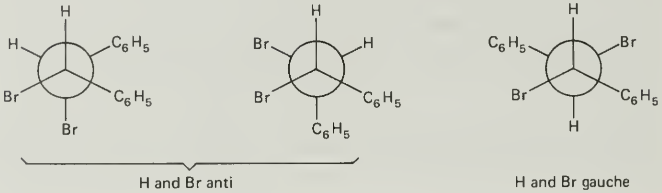
(R,R)-1,2-dibromo-1,2-diphenylethane 1-bromo-*trans*-1,2-diphenylethene


H
H
C_6H_5
C
C
Br
C_6H_5
Br
base
Br
H
C=C
C_6H_5
C_6H_5

meso-1,2-dibromo-1,2-diphenylethane 1-bromo-*cis*-1,2-diphenylethene


H
H
C6H5
C6H5
Br
Br
H and Br anti
H and Br gauche

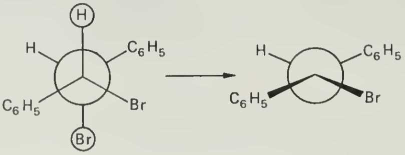
(a) staggered conformations of (R,R) - 1,2 - dibromo - 1,2 - diphenylethane


H
Br
C6H5
H and Br anti
H and Br gauche

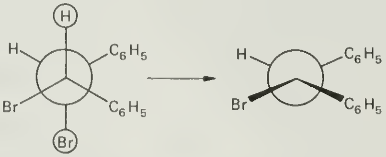
(b) staggered conformations of *meso* - 1,2 - dibromo - 1,2 - diphenylethane

FIGURE 12.17 *Newman projections illustrating the staggered conformations of the stereoisomeric* 1,2-*dibromo*-1,2-*diphenylethanes.*

The two diastereomeric 1,2-dibromo-1,2-diphenylethanes undergo E2 elimination to give two different products. Both stereoisomers react in a conformation that has H anti to Br. The staggered conformations of the two compounds are shown in Newman projection form in Figure 12.17. Note that removal of H and Br from opposite sides of the molecule results in conversion of the (R,R) stereoisomer into the alkene having the two phenyl groups *trans.*

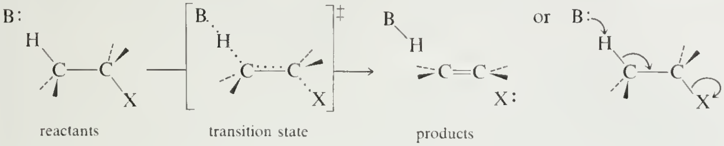

H
H
C6H5
C6H5
Br
Br

Similarly, anti elimination in the *meso* stereoisomer gives the alkene having the phenyl groups *cis.*


H
H
C6H5
Br
Br

This example demonstrates that anti elimination can give either a *cis-* or a *trans*-alkene, depending on the structure of the starting halide.

The mechanism that results from putting these facts together is one in which the attacking base removes a proton concurrently with loss of halide ion from the other side of the molecule. As the C—H bond lengthens and weakens, the C—X bond also lengthens and weakens. The remaining four groups on the two carbons start to move into coplanarity, and a C=C double bond starts to form. We may represent this reaction as



Recall that each curved arrow represents the movement of one pair of electrons. The proton has been displaced in a typical acid-base proton-transfer reaction, and the leaving halide has been displaced by a pair of electrons at the rear of the C—X bond. The transition state for the E2 reaction is represented in stereo form in Figure 12.18.

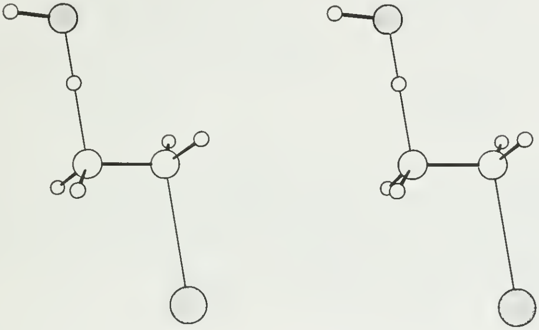


FIGURE 12.18 *Stereo representation of the transition state of an* E2 *reaction.*

In orbital terms the bonds on the alkyl halide all involve C_{sp^3} orbitals. In the product alkene, some orbitals are C_{sp^2} and others are C_p. At the transition state, the orbitals have an intermediate character, as illustrated in Figure 12.19. Because π bonding is significant in the transition state, those effects that stabilize double bonds, such as added substituents, also stabilize the transition state. However, inasmuch as π overlap is only partial, these stabilizing effects are not as important as they are in the product olefins.

It is clear that for π bonding to be significant in the transition state, the C—H and C—X bonds to be broken must lie in the same plane, but we may well ask why this requires anti elimination. The answer is simply that in the corresponding syn elimination, groups are eclipsed to each other and represent a structure of higher energy.

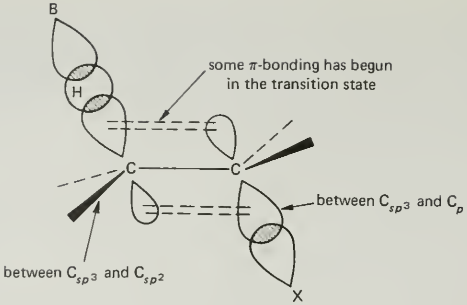
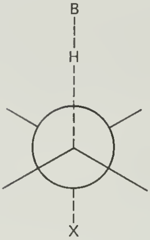
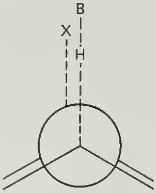

B
H
some π-bonding has begun in the transition state
C
C
between C_{sp^3} and C_p
between C_{sp^3} and C_{sp^2}
X

FIGURE 12.19 *Orbital representations of* E2 *transition state.*



anti-elimination:
bonds staggered



syn-elimination:
bonds eclipsed

Finally, primary hydrogens are less sterically hindered and more open to attack than secondary or tertiary hydrogens. Refer back to the reaction of 2-bromopentane with potassium ethoxide in ethanol (page 267). 1-Pentene is formed in 31% yield although at equilibrium it would constitute only about 3% of a mixture of pentene isomers. With the larger bases, this disparate amount of the 1-alkene is even greater (compare the examples on page 267).

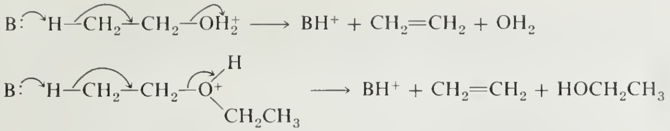
B. *Alcohol Eliminations*

As we mentioned in Section 11.7, alcohols undergo dehydration upon heating with strong acids. In the case of ethyl alcohol, the reaction requires concentrated sulfuric acid at 170°. At lower temperatures (140°), diethyl ether is the major reaction product.

$$2\ CH_3CH_2OH \xrightarrow[140^\circ]{H_2SO_4} CH_3CH_2OCH_2CH_3 + H_2O$$

$$CH_3CH_2OH \xrightarrow[170^\circ]{H_2SO_4} CH_2{=}CH_2 + H_2O$$

The mechanism of alkene formation under these conditions is undoubtedly complex. At high temperature and with strong acid catalysts, the alcohol and the corresponding ether are in equilibrium with one another. The elimination process itself is probably of the E2 type in which a base attacks a protonated alcohol or protonated ether.



$$B{:}\ H-CH_2-CH_2-\overset{+}{O}H_2 \longrightarrow BH^+ + CH_2{=}CH_2 + OH_2$$

$$B{:}\ H-CH_2-CH_2-\overset{+}{O}(H)CH_2CH_3 \longrightarrow BH^+ + CH_2{=}CH_2 + HOCH_2CH_3$$

The base involved may be bisulfate ion, HSO_4^-, or an alcohol or ether molecule. *n*-Propyl alcohol may be similarly dehydrated to propene.

$$CH_3CH_2CH_2OH \xrightarrow[170^\circ]{H_2SO_4} CH_3CH{=}CH_2 + H_2O$$

For primary alcohols larger than propyl, mixtures of alkenes result.

$$CH_3(CH_2)_6CH_2OH \xrightarrow[\Delta]{H_3PO_4} \underbrace{CH_3(CH_2)_4CH{=}CHCH_3 + CH_3(CH_2)_3CH{=}CHCH_2CH_3}_{\text{major products}}$$

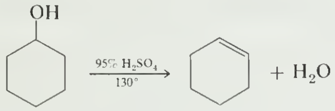
Essentially no 1-octene is produced in this reaction. The problem with the larger primary alcohols is isomerization of the product alkene which is the initial product.

$$CH_3(CH_2)_6CH_2OH \longrightarrow CH_3(CH_2)_4CH_2CH{=}CH_2 \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}}$$

$$CH_3(CH_2)_4CH_2\overset{+}{C}HCH_3 \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} CH_3(CH_2)_4CH{=}CHCH_3 \rightleftharpoons \text{etc.}$$

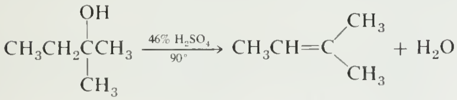
Consequently, acid-catalyzed dehydration is not a generally useful procedure for the conversion of primary alcohols to alkenes.

In contrast, secondary and tertiary alcohols are more easily dehydrated by acids.



(83%)

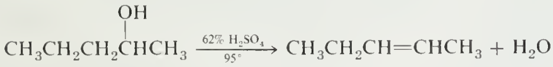
cyclohexanol cyclohexene



$$CH_3CH_2C(OH)(CH_3)CH_3 \xrightarrow[90^\circ]{46\%\ H_2SO_4} CH_3CH{=}C(CH_3)_2 + H_2O$$

(84%)

2-methyl-2-butanol 2-methyl-2-butene



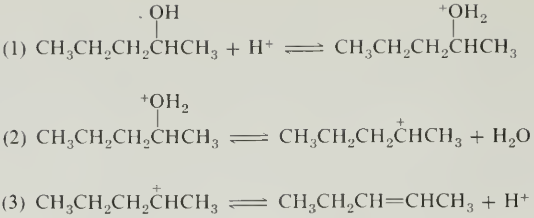
$$CH_3CH_2CH_2CH(OH)CH_3 \xrightarrow[95^\circ]{62\%\ H_2SO_4} CH_3CH_2CH{=}CHCH_3 + H_2O$$

(65–80%)

2-pentanol *cis*- and *trans*-2-pentene

> 2-Pentanol, 214 ml, is heated with a mixture of 200 ml of sulfuric acid and 200 ml of water and the alkene produced is distilled as formed. The distillate is washed, dried and redistilled; yield, 65–80%. This product is mostly 2-pentenes. The small amount of 1-pentene also present can be removed by careful fractional distillation.

In these cases, dehydration probably occurs by the E1 mechanism, by way of intermediate carbonium ions.

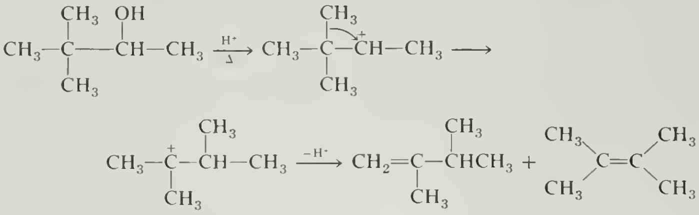


$$\text{(1)}\quad \mathrm{CH_3CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3 + H^+ \rightleftharpoons CH_3CH_2CH_2\overset{^+OH_2}{\overset{|}{C}}HCH_3}$$

$$\text{(2)}\quad \mathrm{CH_3CH_2CH_2\overset{^+OH_2}{\overset{|}{C}}HCH_3 \rightleftharpoons CH_3CH_2CH_2\overset{+}{C}HCH_3 + H_2O}$$

$$\text{(3)}\quad \mathrm{CH_3CH_2CH_2\overset{+}{C}HCH_3 \rightleftharpoons CH_3CH_2CH{=}CHCH_3 + H^+}$$

This method is especially suitable for relatively simple alcohols. In more complex cases, rearrangements may occur.



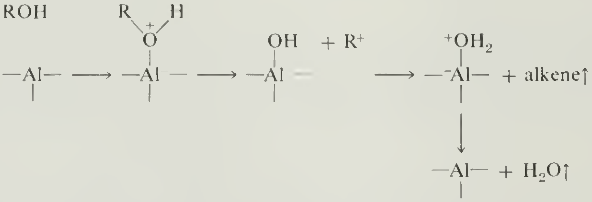
2,3-dimethyl-1-butene
minor product

2,3-dimethyl-2-butene
major product

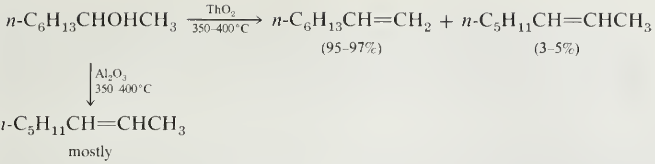
A simple and effective procedure for dehydration of many alcohols, including primary alcohols, involves passing the vapors over alumina at 350–400°.

> Alumina, aluminum oxide, Al_2O_3, occurs naturally in crystalline form as ruby, sapphire, and corundum. Commercial alumina for laboratory use is a white powder which is available in many grades. It is highly insoluble in water and in organic solvents and has an extremely high melting point (over 2000°). It is used as an adsorbant in liquid chromatography, as a catalyst for some reactions, and as a catalyst support in other cases.

Alumina, like many aluminum salts, is a Lewis acid. The dehydration reaction probably occurs by some version of the E1 mechanism on the alumina surface.



Accordingly, isomerization of olefins and rearrangements are common. These reactions can be suppressed by first treating the alumina with a base such as ammonia. Alternatively, thorium oxide, ThO_2, may be used. In this case the reaction mechanism on the oxide surface is apparently quite different, because 2-alkanols produce mostly 1-alkenes.



$$\begin{tikzcd} n\text{-}C_6H_{13}CHOHCH_3 \arrow[r, "ThO_2", "350\text{-}400^\circ C"'] \arrow[d, "Al_2O_3", "350\text{-}400^\circ C"'] & \underset{(95\text{-}97\%)}{n\text{-}C_6H_{13}CH{=}CH_2} + \underset{(3\text{-}5\%)}{n\text{-}C_5H_{11}CH{=}CHCH_3} \\ \underset{\text{mostly}}{n\text{-}C_5H_{11}CH{=}CHCH_3} & \end{tikzcd}$$

C. *Industrial Preparation of Alkenes*

Ethylene is an important item of commerce. It is used in large quantities for the manufacture of polyethylene and as an intermediate in the preparation of a host of other chemicals. It is obtained primarily as a cracking product in petroleum refining (Section 5.2). Although any hydrocarbon may be cracked to yield mainly ethylene, in the United States the primary material used for this purpose is ethane.

$$CH_3CH_3 \xrightarrow[\text{1 atm}]{700\text{-}900^\circ C} CH_2{=}CH_2 + H_2$$

When higher hydrocarbons are submitted to the cracking process, significant amounts of propylene are produced.

$$n\text{-}C_6H_{14} \xrightarrow{700\text{-}900^\circ C} \underset{(15\%)}{CH_4} + \underset{(40\%)}{CH_2{=}CH_2} + \underset{(20\%)}{CH_3CH{=}CH_2} + \underset{(25\%)}{\text{other}}$$

A large amount of the propylene produced in this country goes into the manufacture of polypropylene. Other important industrial alkenes are the butenes and 1,3-butadiene.

The 1973 industrial production of various alkenes is summarized in Table 12.4.

Table 12.4
1973 Production of Alkenes

Compound	Production, tons
$CH_2{=}CH_2$	11,210,000
$CH_3CH{=}CH_2$	4,380,000
$C_6H_5CH{=}CH_2$	3,000,000
$CH_2{=}CHCl$	2,680,000
$CH_2{=}CHCH{=}CH_2$	1,830,000

12.6
Reactions of Alkenes

In the table of Average Bond Energies in Appendix III, we find that the value for C=C is 146 kcal mole^{-1}. This is 63 kcal mole^{-1} higher than the normal C—C bond strength of 83 kcal mole^{-1}. The difference is reminiscent of the 65 kcal mole^{-1} required for rotation about the double bond in ethylene (Section 12.1) and may be considered roughly as the bond strength of the second or π bond in ethylene. That is, the "second" bond of a double bond is substantially weaker than the first.

As we saw in Section 12.1, this view of alkenes as having two different kinds of bonds is simply a convenient way of visualizing a molecule and is mathematically equivalent to the "bent bond" model. In the latter picture, as one of the two **equivalent** bonds breaks, the other actually becomes stronger. The total energy required to break one of the two bonds is thus 65 kcal mole^{-1}.

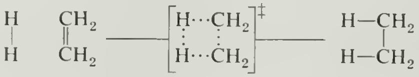
The reaction of this "weak" π bond with a normal single bond to produce a molecule containing two new single bonds is generally a thermodynamically favorable process. For example, in gas phase reactions at 25°C:

$$CH_2{=}CH_2 + H_2 \longrightarrow CH_3CH_3 \qquad \Delta H^\circ = -32.7 \text{ kcal mole}^{-1}$$
$$CH_2{=}CH_2 + Cl_2 \longrightarrow CH_2ClCH_2Cl \qquad \Delta H^\circ = -43.2 \text{ kcal mole}^{-1}$$
$$CH_2{=}CH_2 + HBr \longrightarrow CH_3CH_2Br \qquad \Delta H^\circ = -19.0 \text{ kcal mole}^{-1}$$
$$CH_2{=}CH_2 + H_2O \longrightarrow CH_3CH_2OH \qquad \Delta H^\circ = -10.9 \text{ kcal mole}^{-1}$$

Not only do such *additions across a double bond* have favorable thermodynamics, but many have accessible pathways or reaction mechanisms. Such additions form an important part of the chemistry of alkenes.

A. *Catalytic Hydrogenation*

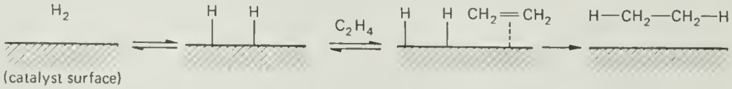
Even though the reaction is highly exothermic ($\Delta H^\circ = -32.7$ kcal mole^{-1}), ethylene does not react with hydrogen at an appreciable rate without an appropriate catalyst. The conceptually simple "four-center" mechanism



cyclic 4-membered transition state

is apparently not an accessible mechanism. Such four-center mechanisms are rare because cyclic four-membered transition states, such as that shown, have unusually high energy. The high activation energy corresponds to an impractically slow reaction rate. The relatively high energies of such four-center transition states can be explained by molecular orbital concepts and further discussion is deferred to Section 36.2.

The hydrogenation reaction does take place readily on the surface of some metals, particularly platinum, palladium, and nickel. These metals are known to coordinate with double bonds and form hydrides. The detailed reaction mechanism is complex and involves various types of metal-carbon bonds. A schematic representation that is suitable for our purposes is approximated as follows.



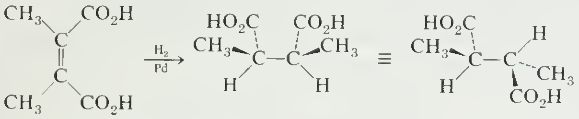
Platinum is usually used as the black oxide known as "Adams' catalyst." The oxide is prepared by fusion of chloroplatinic acid, $H_2PtCl_6 \cdot 6H_2O$, hygroscopic red-brown crystals, or ammonium chloroplatinate, $(NH_4)_2PtCl_6$, yellow crystals, with sodium nitrate. It reacts readily with hydrogen gas even at low pressures to form a finely divided platinum metal catalyst. This is usually accomplished by stirring with a suitable inert solvent such as ethanol or acetic acid. The alkene is then added, and when the solution is stirred with the suspension of platinum under an atmosphere of hydrogen, hydrogen gas is absorbed rapidly. The hydrogen is usually contained in a gas buret so that the amount absorbed can be measured. The resulting mixture is filtered and the product is isolated from the filtrate. Only small amounts of platinum catalyst are required, but the filter paper residues are normally saved for recovery of the platinum, a rare and expensive material.

Palladium is usually used as a commercial preparation in which the finely divided metal is supported on a suitable inert surface, frequently charcoal (Pd/C) or barium sulfate (Pd/BaSO$_4$). Alkenes are normally hydrogenated in ethanol solution by stirring with Pd/C at room temperature under an atmosphere of hydrogen.

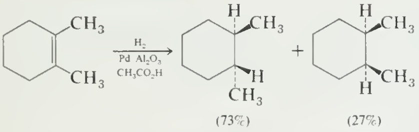
Nickel is usually used in a finely divided state called "Raney nickel." The catalyst is prepared by allowing nickel-aluminum alloy to react with aqueous sodium hydroxide. The aluminum dissolves and leaves the nickel as a finely divided suspension. Typical hydrogenations are conducted at moderately high pressures of hydrogen ($\approx$1000 psi).

Other hydrogenation catalysts used for specific purposes are rhodium, ruthenium, and copper-chromium oxide, but platinum, palladium, and nickel in their various forms are the most common. They are subject to "poisoning" by some compounds, notably sulfur containing compounds such as thiols and sulfides. These compounds bind firmly to the catalyst surface and destroy its catalytic activity.

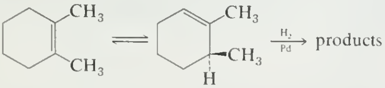
One important characteristic of hydrogenation catalysts is the tendency towards *cis* addition. Hydrogen tends to add to the side of the double bond coordinated to the catalyst surface.



Although *cis* addition is the general rule, *trans* addition is sometimes observed. For example



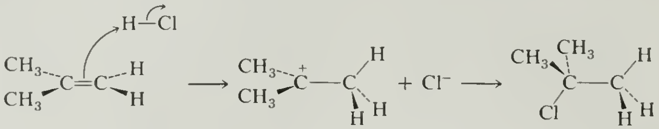
Trans addition probably results when double bond isomerization occurs more rapidly than hydrogenation. In the case shown, it has been established that isomerization preceeds reduction:



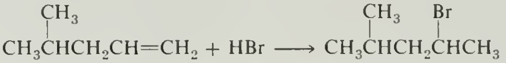
Palladium is particularly prone to catalyze double bond isomerization. Platinum, rhodium, or iridium should be used if isomerization is a problem.

B. *Electrophilic Additions*

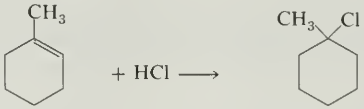
1. **Addition of HX.** The region above and below a double bond is electron-rich because of the π bond. Consequently, double bonds have a tendency to act as Lewis bases and react with electrophilic reagents. An example is the reaction of isobutylene with HCl. In the first step, the double bond reacts with a proton to give a carbonium ion, which combines with chloride ion to give *t*-butyl chloride.



Some further examples of this reaction are

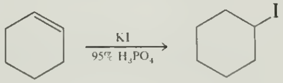

$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH{=}CH_2 + HBr \longrightarrow CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\overset{\displaystyle Br}{\overset{|}{C}}HCH_3$$

4-methyl-1-pentene 4-bromo-2-methylpentane



1-methylcyclohexene 1-chloro-1-methylcyclohexane

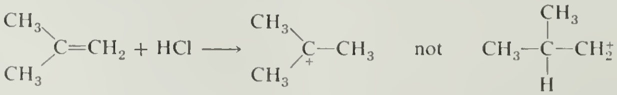
For the addition of HI, a mixture of potassium iodide and phosphoric acid is often used; the HI is generated *in situ*.



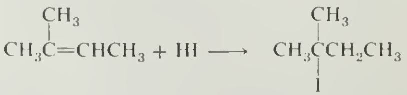
(88-90%)

cyclohexene cyclohexyl iodide

With unsymmetrical alkenes, the initial protonation occurs so as to afford the *more stable carbonium ion.* Since alkyl substituents stabilize carbonium ions, the proton adds to the less substituted carbon of the double bond.

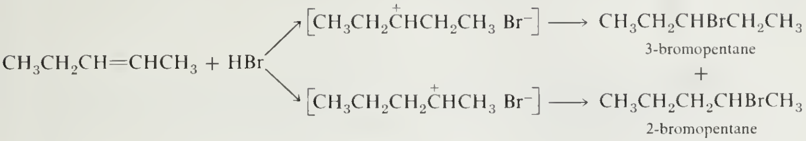


This generalization is commonly referred to as **Markovnikov's rule.** It was formulated by Markovnikov long before the foregoing mechanistic interpretation was developed to explain it.


$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CHCH_3 + HI \longrightarrow CH_3\underset{\displaystyle I}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CH_2CH_3$$

2-methyl-2-butene 2-iodo-2-methylbutane

If two intermediate carbonium ions of comparable stability can be formed, a mixture of products results.



$$CH_3CH_2CH{=}CHCH_3 + HBr \begin{cases} \nearrow \left[CH_3CH_2\overset{+}{C}HCH_2CH_3\ Br^-\right] \longrightarrow CH_3CH_2CHBrCH_2CH_3 \\ \searrow \left[CH_3CH_2CH_2\overset{+}{C}HCH_3\ Br^-\right] \longrightarrow CH_3CH_2CH_2CHBrCH_3 \end{cases}$$

3-bromopentane
+
2-bromopentane

The addition of HX to a double bond is a significant reaction because of what it reveals about the general chemistry of alkenes, but it is not an important method for preparing the simpler alkyl halides. Better methods are generally available from alcohols.

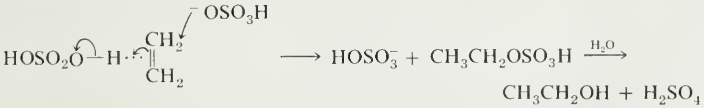
The hydration of alkenes is an important industrial method for the manufacture of alcohols. Industrially, the hydration is usually accomplished by passing the alkene into a mixture of sulfuric acid and water. Isobutylene is absorbed in 60–65% aqueous sulfuric acid. The intermediate formed is undoubtedly the *t*-butyl cation, which reacts with water to give *t*-butyl alcohol.

$$(CH_3)_2C{=}CH_2 + H^+ \rightleftharpoons (CH_3)_3C^+ \xrightarrow{H_2O}$$

$$(CH_3)_3C{-}\overset{+}{O}H_2 \rightleftharpoons (CH_3)_3COH + H^+$$

The reaction is the reverse of acid-catalyzed dehydration. Low temperatures and aqueous solution favor formation of the alcohol, whereas high temperatures and distillation of the alkene as it is formed shift the equilibrium towards the alkene. Under more vigorous conditions (Section 12.6.F), dimeric and polymeric products are produced.

Ethylene is also absorbed by sulfuric acid, but in this case, 98% H_2SO_4 is required. The product is ethylsulfuric acid, which is hydrolyzed to ethyl alcohol in a separate step. This reaction almost certainly does *not* involve the primary carbonium ion, ethyl cation. Instead, ethylene appears first to form a sort of hydrogen-bonded complex with sulfuric acid. The resulting complex is attacked by bisulfate ion to give ethylsulfuric acid.



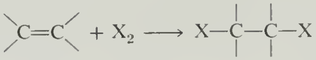
$$HOSO_2O{-}H\cdots\overset{CH_2}{\underset{CH_2}{\|}}\ \ {}^-OSO_3H \longrightarrow HOSO_3^- + CH_3CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH + H_2SO_4$$

Although direct hydration is an important industrial process, it is seldom used as a laboratory procedure. Yields of alcohol are highly sensitive to reaction conditions, and more convenient laboratory reactions will be developed later.

There is one further implication of the facile protonation and deprotonation of alkenes. Isomerization of double bonds frequently occurs readily in strongly acidic media. Of course, the ratio of isomers produced will be the thermodynamic mixture under the conditions used.

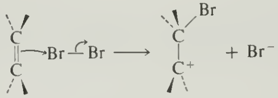
$$\underset{\text{1-butene}}{CH_3CH_2CH{=}CH_2} \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} CH_3CH_2\overset{+}{C}H{-}CH_3 \underset{H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{\textit{cis}\text{ and }\textit{trans}\text{-2-butene}}{CH_3CH{=}CHCH_3}$$

2. **Addition of Halogens.** An important general reaction of double bonds is the addition of halogens.

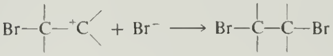


X = Cl, Br

This reaction is rapid and serves as a simple diagnostic method for unsaturation. The reaction can be regarded as a nucleophilic displacement reaction on a halogen. The alkene is the nucleophile and halide ion is the leaving group.



The resulting cation reacts with halide ion to give the observed product.



The intermediate cation contains an electron-deficient carbonium ion carbon and a halogen atom with nonbonding electron pairs. Consequently, there is a tendency for overlap to produce a **cyclic halonium ion** as in Figure 12.20.

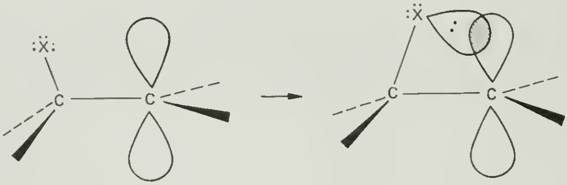
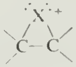


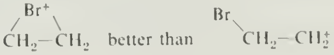
Figure 12.20 *Formation of cyclic halonium ion.*

The cyclic halonium ion may be written in Lewis form as

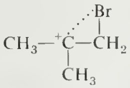


The advantage in terms of energy in forming such a structure is primarily the formation of an additional covalent bond. Furthermore, all of the atoms now have an octet electronic configuration. However, a price is paid for these gains. The bond angles in the three-membered ring structure are bent far from the desired tetrahedral geometry, and the positive charge is localized on the more electronegative halogen atom rather than on carbon.

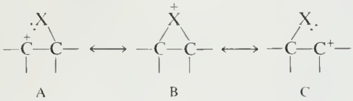
In practice, the tendency of such a cation to exist in the cyclic form depends on the stability of the "open" carbonium ion. The intermediate formed from the addition of bromine to ethylene is best described as a symmetrical bromonium ion with relatively strong C—Br bonds. The alternative open form would be a highly unstable primary carbonium ion.



The ion formed by addition of bromine to isobutylene is better described as a tertiary carbonium ion with a long and weak bond to bromine.

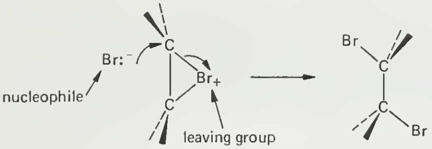


Cations such as these may be described in terms of three resonance structures: The actual ion is a composite or hybrid of the three structures A, B, and C. If both

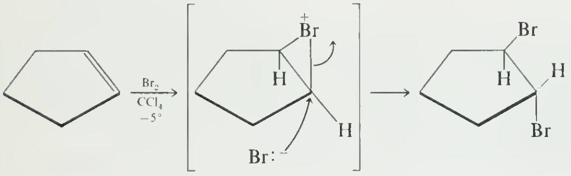


A and C correspond to unstable carbonium ions, then structure B is a more important contributor to the actual structure of the ion. If either A or C corresponds to a relatively stable carbonium ion, then that structure contributes more and the ion has substantial carbonium ion character without as much halonium ion character.

The cyclic halonium ion intermediate has an important effect on the **stereochemistry** of halogen additions. When halide ion reacts with the cyclic ion, the reaction is a nucleophilic displacement reaction.



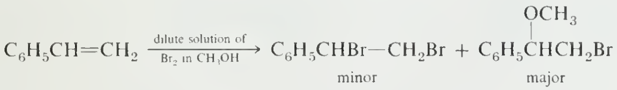
Since the nucleophile Br^- must approach carbon to the rear of the leaving group, the net result is ***trans* addition** of Br_2,



cyclopentene

trans-1,2-dibromocyclopentane

When a solution of bromine is used in an inert solvent such as carbon tetrachloride, the only nucleophilic reagent available for reaction with the intermediate cation is bromide ion. In hydroxylic solvents, the solvent itself is nucleophilic and can react in competition with the bromide ion.



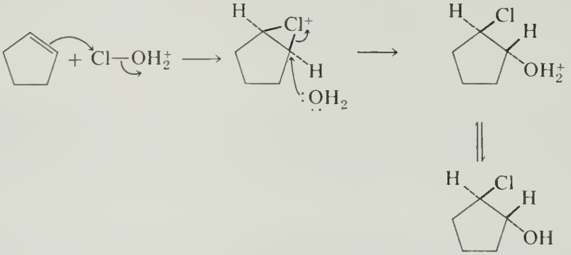
$$C_6H_5CH{=}CH_2 \xrightarrow[\text{Br}_2\text{ in CH}_3\text{OH}]{\text{dilute solution of}} \underset{\text{minor}}{C_6H_5CHBr{-}CH_2Br} + \underset{\text{major}}{C_6H_5\overset{\overset{\displaystyle OCH_3}{|}}{C}HCH_2Br}$$

The relative amounts of dibromide and bromoether produced depend on the concentration. Generally, for dilute solutions, the product is almost exclusively the bromoether.

Halogens in water are in equilibrium with the corresponding hypohalous acids.

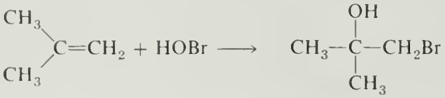
$$H_2O + Cl_2 \rightleftharpoons H_2\overset{+}{O}{-}Cl + Cl^- \rightleftharpoons HOCl + HCl$$

The reaction involves a displacement reaction by water on chlorine. Hypochlorous acid reacts with alkenes to form chloro alcohols that are called chlorohydrins. The addition is again *trans*.



trans-2-chlorocyclo-
pentanol
(cyclopentene chlorohydrin)

If the alkene is unsymmetrical, water attacks at the carbon that would correspond to the more stable carbonium ion. The halogen ends up on the carbon with the greater number of hydrogens.



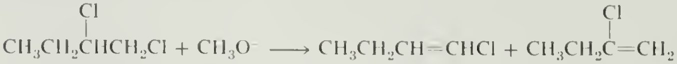
$$(CH_3)_2C{=}CH_2 + HOBr \longrightarrow CH_3{-}\underset{CH_3}{\overset{OH}{C}}{-}CH_2Br$$

1-bromo-2-methyl-2-propanol
(isobutylene bromohydrin)

The 1,2-dihalides produced by the addition of halogens to alkenes are called **vicinal** dihalides (L., *vicinus*, near). They have many chemical properties in common with simple alkyl halides. For example, 1,2-dibromoethane readily enters into nucleophilic displacement reactions.

$$BrCH_2CH_2Br + 2\ CN^- \longrightarrow NCCH_2CH_2CN + 2\ Br^-$$

As with the simple monohalides, nucleophilic displacement is usually accompanied by some elimination, particularly when one or both of the halogens is attached to a secondary carbon. With strong bases, elimination is the principal reaction.

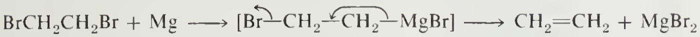


$$CH_3CH_2\overset{Cl}{C}HCH_2Cl + CH_3O^- \longrightarrow CH_3CH_2CH{=}CHCl + CH_3CH_2\overset{Cl}{C}{=}CH_2$$

1,2-dichlorobutane 1-chloro-1-butene 2-chloro-1-butene

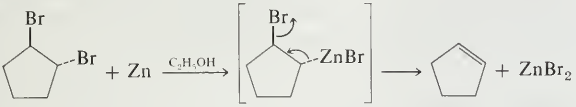
Such **dehydrohalogenations** are not generally useful ways to prepare haloalkenes because both isomers are usually produced. Dehydrohalogenation of both halogens is much more important as a method for preparing alkynes (Section 13.5).

Vicinal dihalides do *not* undergo normal Grignard reactions because of the ease of elimination of the adjacent halide ion.

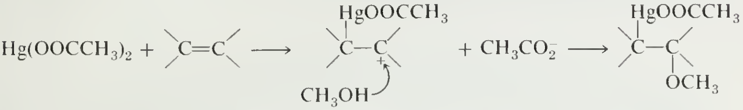


$$BrCH_2CH_2Br + Mg \longrightarrow [Br{-}CH_2{-}CH_2{-}MgBr] \longrightarrow CH_2{=}CH_2 + MgBr_2$$

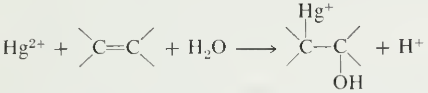
A similar reaction occurs when a vicinal dihalide is treated with zinc and alcohol. The intermediate organozinc compound ejects halide ion to form the alkene and zinc halide.



3. ADDITION OF MERCURIC ACETATE. Mercuric ion, Hg^{2+}, is an electrophilic reagent that adds to double bonds to form organomercury derivatives. Mercuric acetate in methanol or ethanol readily yields the corresponding alkoxyalkylmercuric acetate.



Trans addition is the usual stereochemical result, although a few cases of *cis* addition are known. Mercuric acetate or perchlorate in water gives the hydroxyalkylmercuric salt.



These compounds are readily reduced with sodium borohydride, which replaces the C—Hg bond by C—H with liberation of free mercury. The intermediate organomercury compounds need not be isolated. The net result of mercuration in alcohol or water, followed by sodium borohydride reduction, is addition of alcohol or water to the alkene. The reduction is an excellent method for the synthesis of alcohols and ethers. Addition follows the Markovnikov rule, Hg^{2+} going to the less substituted carbon.

$$\underset{\text{1-hexene}}{n\text{-}C_4H_9CH{=}CH_2} \xrightarrow[\text{aq. THF}]{Hg(OOCCH_3)_2} \xrightarrow[NaOH]{NaBH_4} \underset{\text{2-hexanol}}{\underset{(96\%)}{n\text{-}C_4H_9CHOHCH_3}} + Hg$$

1-Hexene is added with stirring to an equivalent amount of mercuric acetate in 1:1 water: THF. After stirring for 10 min at 25°, aqueous NaOH is added, followed by a 0.5 *M* solution of $NaBH_4$ in 3 *M* NaOH. The organic layer is separated, dried and distilled to yield 2-hexanol.

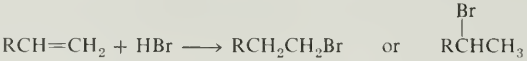
The sodium borohydride used in this reaction is an important reagent in organic chemistry.

Sodium borohydride, $NaBH_4$, is the sodium salt of the borohydride ion, BH_4^-, a tetrahedral ion that can be regarded as derived from BH_3 and hydride ion, H^-. It is a white powder and dissolves in water to form stable solutions at basic pH. In acid the compound reacts rapidly to form hydrogen and sodium borate. Sodium borohydride is soluble in methanol and ethanol, but decomposes slowly in these solvents. It is appreciably soluble in diglyme (5.5 g per 100 g of solvent) but is almost insoluble in glyme or tetrahydrofuran. Sodium borohydride is a useful reducing agent for aldehydes and ketones (Section 15.8).

The reaction combination of mercuration and reduction is a useful laboratory alternative to acid-catalyzed hydration of olefins. Of course, it cannot compete with sulfuric acid in large scale commercial productions.

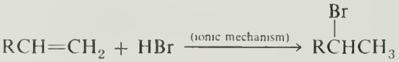
C. *Radical Additions*

The early literature of organic chemistry contained considerable disagreement on the mode of addition of HBr to terminal olefins. In some cases, Markovnikov's rule appeared to hold; in other cases it did not. Often two chemists would add HBr to the same alkene and obtain contradictory results.



$$RCH{=}CH_2 + HBr \longrightarrow RCH_2CH_2Br \quad \text{or} \quad R\overset{\displaystyle Br}{\overset{|}{C}}HCH_3$$

In the 1930s, this apparent dilemma was resolved when it was discovered that HBr (but *not* HCl or HI) can add to alkenes by two different mechanisms. Pure materials and pure solvents encourage addition by the electrophilic mechanism discussed in Section 12.6.B under Addition of HX. This mechanism leads to normal Markovnikov addition.



$$RCH{=}CH_2 + HBr \xrightarrow{\text{(ionic mechanism)}} R\overset{\displaystyle Br}{\overset{|}{C}}HCH_3$$

Impure materials, oxygen, and some other additives were found to promote "abnormal" addition by a mechanism involving **free radical** intermediates.

$$RCH{=}CH_2 + HBr \xrightarrow[\text{mechanism)}]{\text{(free radical}} RCH_2CH_2Br$$

The free radical mechanism starts with an initiation step that results in oxidation of HBr to bromine atoms.

$$HBr + O_2 \text{ (or other radical initiators)} \longrightarrow Br\cdot$$

The bromine atom then adds to the alkene to give a free radical that continues the chain by abstracting hydrogen from a molecule of HBr. Both of the propagation steps are exothermic and have low activation energies.

$$RCH{=}CH_2 + Br\cdot \longrightarrow R\dot{C}HCH_2Br \qquad \Delta H^\circ = -9 \text{ kcal mole}^{-1}$$

$$R\dot{C}HCH_2Br + HBr \longrightarrow RCH_2CH_2Br + Br\cdot \qquad \Delta H^\circ = -7 \text{ kcal mole}^{-1}$$

Note that the bromine atom adds to the alkene in such a way as to give the more highly substituted (more stable) free radical. The overall outcome is thus **anti-Markovnikov** orientation. This abnormal addition or "peroxide effect" is a useful reaction with HBr but is not significant with HCl or HI. The C—I bond is so weak that the addition of iodine atoms to double bonds is endothermic. It becomes exothermic only at elevated temperatures.

$$RCH{=}CH_2 + I\cdot \longrightarrow R\dot{C}HCH_2I \qquad \Delta H^\circ = +5 \text{ kcal mole}^{-1}$$
$$R\dot{C}HCH_2I + HI \longrightarrow RCH_2CH_2I + I\cdot \qquad \Delta H^\circ = -24 \text{ kcal mole}^{-1}$$

The H—Cl bond is so strong that the second step in the sequence is endothermic and slow.

$$RCH{=}CH_2 + Cl\cdot \longrightarrow R\dot{C}HCH_2Cl \qquad \Delta H^\circ = -22 \text{ kcal mole}^{-1}$$
$$R\dot{C}HCH_2Cl + HCl \longrightarrow RCH_2CH_2Cl + Cl\cdot \qquad \Delta H^\circ = +8 \text{ kcal mole}^{-1}$$

Free radical chain reactions work best when both propagation steps are exothermic. An endothermic step corresponds to a slow and reversible reaction that breaks the chain.

Other compounds that have appropriate bond strengths can add to double bonds under free radical conditions. Examples include chlorine, bromine, hydrogen sulfide, thiols, and polyhaloalkanes.

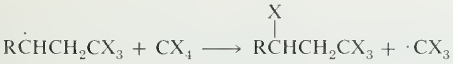
$$CH_3CH_2CH{=}CH_2 + H_2S \xrightarrow[0^\circ]{h\nu} \underset{(68\%)}{CH_3CH_2CH_2CH_2SH} + \underset{(12\%)}{(CH_3CH_2CH_2CH_2)_2S}$$

$$(CH_3)_2C{=}CH_2 + CH_3CH_2SH \xrightarrow[O_2]{100^\circ} \underset{(94\%)}{(CH_3)_2CHCH_2SCH_2CH_3}$$

ethyl isobutyl sulfide

Carbon tetrachloride and carbon tetrabromide react readily with olefins and free radical initiators to give 1:1 adducts. The propagation steps are

$$RCH{=}CH_2 + \cdot CX_3 \longrightarrow R\dot{C}HCH_2CX_3$$



$$R\dot{C}HCH_2CX_3 + CX_4 \longrightarrow R\overset{X}{\overset{|}{C}}HCH_2CX_3 + \cdot CX_3$$

$$CH_3(CH_2)_5CH{=}CH_2 + CCl_4 \xrightarrow[\Delta]{\text{peroxide}} \underset{(75\%)}{CH_3(CH_2)_5CHClCH_2CCl_3}$$

1,1,1,3-tetrachlorononane

$$CH_3(CH_2)_5CH{=}CH_2 + CBr_4 \xrightarrow[75^\circ]{h\nu} \underset{(88\%)}{CH_3(CH_2)_5CHBrCH_2CBr_3}$$

1,1,1,3-tetrabromononane

In some cases and especially with ethylene itself, such reactions yield a mixture of **telomer** products in which the intermediate radicals have reacted with alkenes in the following way:

$$Cl_3CCH_2CH_2\cdot + CH_2{=}CH_2 \longrightarrow Cl_3CCH_2CH_2CH_2CH_2\cdot \xrightarrow{CH_2=CH_2}$$

$$\mathrm{Cl_3CCH_2CH_2CH_2CH_2CH_2CH_2\cdot} \xrightarrow{\text{etc.}} \mathrm{Cl_3C(CH_2CH_2)_xCH_2CH_2\cdot} \xrightarrow{\mathrm{CCl_4}} \underset{\text{a telomer}}{\mathrm{Cl_3C(CH_2CH_2)_xCH_2CH_2Cl}} + \mathrm{\cdot CCl_3}$$

$$\underset{(100\ \text{atm})}{\mathrm{CH_2{=}CH_2}} + \mathrm{CCl_4} \underset{\text{peroxide}}{\xrightarrow[110^\circ]{\mathrm{H_2O}}} \mathrm{Cl(CH_2CH_2)_xCCl_3}$$

$$\begin{array}{ll} 9\% & x = 1 \\ 57\% & x = 2 \\ 24\% & x = 3 \end{array}$$

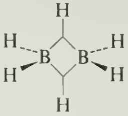
D. *Hydroboration*

Although the reaction of C═C double bonds with diborane was discovered less than two decades ago, it has become one of the most important reactions in the repertoire of the synthetic chemist.

Diborane, B_2H_6, is a colorless, toxic gas that is spontaneously flammable in air. It is usually prepared by the reaction of sodium borohydride with boron trifluoride.

$$3\ \mathrm{NaBH_4} + 4\ \mathrm{BF_3} \longrightarrow 2\ \mathrm{B_2H_6} + 3\ \mathrm{NaBF_4}$$

Borane itself, BH_3, is not known. In this compound boron has a sextet of electrons and is a Lewis acid. In ethers such as tetrahydrofuran or diglyme, common solvents for hydroboration reactions, diborane is readily soluble as an ether-monomer complex, $R_2O\text{-}BH_3$. Diborane has an unusual bridged structure because it is an electron-deficient compound. The 12 valence electrons are too few to provide enough normal two-electron bonds for an ethane-like structure with six B—H bonds. In the actual structure



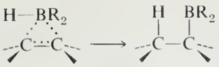
diborane

four hydrogens and the two borons define a plane with four two-electron B—H bonds. The other two hydrogens lie above and below this plane and involve the unusual three-center, two-electron bonds symbolized by . Higher boron hydrides such as pentaborane, B_5H_9, hexaborane, B_6H_{10}, and decaborane, $B_{10}H_{14}$ are known. All are electron-deficient compounds with unusual structures involving bridged hydrogens and three-center bonds. These compounds have a fascinating chemistry of their own but are not important in organic chemistry.

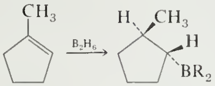
The B—H bond adds rapidly and quantitatively to many multiple bonds including C═C double bonds. With simple alkenes the product is a trialkylborane.

$$6\ \mathrm{RCH{=}CH_2} + \mathrm{B_2H_6} \longrightarrow 2\ \mathrm{(RCH_2CH_2)_3B}$$

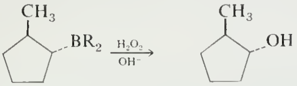
The addition appears to be dominated by steric considerations. The boron generally becomes attached to the less substituted and less sterically congested carbon. With highly substituted or hindered olefins, addition may stop at the mono- or dialkylborane stage. The reaction appears to involve initial coordination of BH_3 with the π electrons of the double bond followed by formation of the C—H bond.



In cases where stereochemistry may be defined, exclusive *cis* addition is observed.

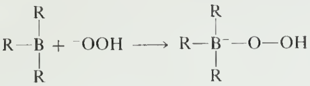


The alkylboranes are generally not isolated but are converted by subsequent reactions directly into desired products. The most important general reaction of alkylboranes is that with alkaline hydrogen peroxide.



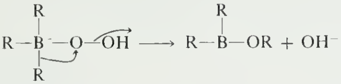
trans-2-methylcyclopentanol

Three separate processes are involved in the oxidation of alkylboranes to alcohols. In the first step, hydroperoxide anion adds to the electron-deficient boron atom.



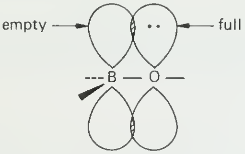
$$R_3B + {}^{-}OOH \longrightarrow R_3B^{-}\text{—}O\text{—}OH$$

The resulting intermediate rearranges with loss of hydroxide ion. The driving force for the rearrangement is liberation of the stable anion OH^- and formation of the strong B—O bond.

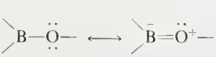


$$R_3B^{-}\text{—}O\text{—}OH \longrightarrow R_2B\text{—}OR + OH^-$$

The B—O bond is much stronger than a B—C bond because of overlap of an oxygen *p* orbital with its lone pair of electrons and the empty *p* orbital on boron:



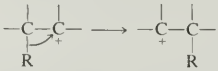
The resulting double bond character is evident in the corresponding resonance structures.



$$>B\text{—}\ddot{O}\text{—} \longleftrightarrow >\bar{B}{=}\dot{O}^{+}\text{—}$$

Hydrogen peroxide is available as the anhydrous liquid, b.p. 152°, or as aqueous solutions ranging from 3 to 90% in concentration. The compound is thermodynamically unstable with respect to water and oxygen, and high strength solutions are explosively hazardous. The 3% solution is used medicinally as a topical antiseptic, but the 30% solution is commonly used in the organic laboratory. Even with the 30% reagent, experiments should be carried out behind safety shields and the material should be kept out of contact with skin and eyes.

The migration of an alkyl group, and its bonding electron pair, is analogous to the rearrangement of carbonium ions (Section 11.7.B).



$$-\overset{|}{\underset{\substack{| \\ R}}{C}}-\overset{|}{\underset{+}{C}}- \longrightarrow -\overset{|}{\underset{+}{C}}-\overset{|}{\underset{\substack{| \\ R}}{C}}-$$

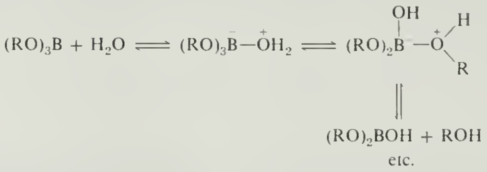
The reaction of boranes with alkaline hydrogen peroxide is rapid and exothermic. The product R_2BOR reacts further by the same process to give a trialkyl borate ester.

$$R_2BOR + 2\,OOH^- \longrightarrow B(OR)_3 + 2\,OH^-$$

The borate ester is then hydrolyzed under the reaction conditions to the alcohol and sodium borate.

$$B(OR)_3 + 3\,OH^- \longrightarrow 3\,ROH + BO_3^{3-}$$

Alkyl borates can be prepared by heating a mixture of the alcohol and boric acid or boric anhydride, B_2O_3. The esters distill readily (trimethyl borate, b.p. 68°; triethyl borate, b.p. 120°). The esters are mild Lewis acids and are rapidly hydrolyzed by water.



$$(RO)_3B + H_2O \rightleftharpoons (RO)_3\overset{-}{B}-\overset{+}{O}H_2 \rightleftharpoons (RO)_2\overset{\substack{OH \\ |}}{B}-\overset{+}{O}\genfrac{}{}{0pt}{}{H}{R}$$

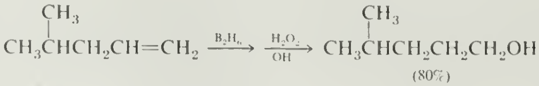
$$\Updownarrow$$

$$(RO)_2BOH + ROH$$

etc.

Borate esters are not generally important in organic chemistry.

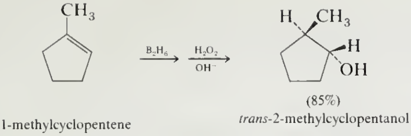
The net reaction of hydroboration and oxidation-hydrolysis is anti-Markovnikov hydration of a double bond. The reaction is a relatively simple and convenient laboratory procedure and has become an important synthetic reaction in organic chemistry.



$$CH_3\overset{\substack{CH_3 \\ |}}{C}HCH_2CH=CH_2 \xrightarrow{B_2H_6} \xrightarrow[OH^-]{H_2O_2} CH_3\overset{\substack{CH_3 \\ |}}{C}HCH_2CH_2CH_2OH \quad (80\%)$$

4-methyl-1-pentene 4-methyl-1-pentanol

A mixture of 4-methyl-1-pentene and sodium borohydride in THF is stirred for several hours with boron trifluoride etherate, $(C_2H_5)_2O{:}BF_3$; aqueous sodium hydroxide is added followed by hydrogen peroxide. The organic layer is separated and the aqueous layer is extracted with ether. The combined organic layers are dried and distilled giving 4-methyl-1-pentanol in 80% yield.



Diborane prepared by reaction of sodium borohydride and boron trifluoride etherate in diglyme is swept by a stream of nitrogen into a solution of 1-methylcyclopentene in THF at 0°. Excess diborane is hydrolyzed by addition of ice. The reaction is completed by addition of aqueous sodium hydroxide followed slowly by 30% hydrogen peroxide. After stirring for an additional period the layers are separated, the aqueous phase is extracted with ether and the combined organic layers are dried and distilled to give 85% of *trans*-2-methylcyclopentanol. Note that the net reaction corresponds to anti-Markovnikov addition of H—OH *cis* across the double bond.

E. *Oxidation*

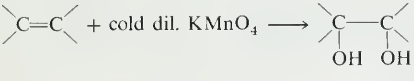
Alkenes are oxidized readily by potassium permanganate, $KMnO_4$, but the products depend on the reaction conditions.

Potassium permanganate forms dark purple crystals that dissolve in water to give intense red solutions. In permanganate anion, MnO_4^-, manganese has an oxidation state of +7. As an oxidizing agent in basic solution, manganese is reduced to manganese dioxide, MnO_2, an insoluble brown compound that is frequently difficult to filter because it tends to form colloidal suspensions. Treatment with SO_2 at this point forms the soluble $MnSO_4$. In acid solution reduction of permanganate to Mn^{2+} occurs. The two half-reactions are

$$3\,e + MnO_4^- + 2\,H_2O \longrightarrow MnO_2 + 4\,OH^-$$
$$5\,e + MnO_4^- + 8\,H^+ \longrightarrow Mn^{2+} + 4\,H_2O$$

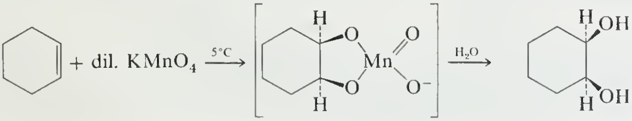
In acid solution potassium permanganate is a strong reagent that attacks organic compounds almost indiscriminantly. It will even oxidize HCl to Cl_2. Hence, in organic use potassium permanganate is almost always used in neutral or alkaline solutions in which MnO_2 is produced.

Cold dilute potassium permanganate reacts with double bonds to give vicinal diols, which are commonly called glycols.



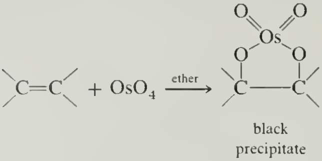
a glycol

Reaction conditions need to be carefully controlled. Yields are variable and usually low. The reaction occurs with *cis* addition and is thought to involve an intermediate cyclic manganate ester that is rapidly hydrolyzed.



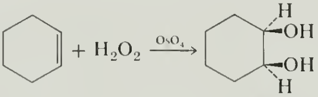
(30–33%)
cis-1,2-cyclohexanediol

The same overall reaction can be accomplished with osmium tetroxide, which forms isolable cyclic esters with alkenes.



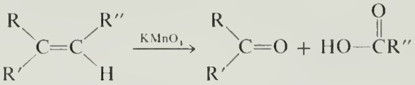
Osmium tetroxide, osmic acid, OsO_4, forms colorless or yellow crystals soluble in water and in organic solvents. The compound sublimes readily *and is highly toxic.* It is an expensive reagent (greater than \$19 per gram). It is supplied commercially in small sealed tubes.

The *cis*-diol can be isolated from the osmate ester with H_2S, but a more convenient (and less expensive) procedure involves the combination of hydrogen peroxide with a catalytic amount of osmium tetroxide. The osmate ester is formed but is converted by the peroxide to the *cis*-diol. Osmium tetroxide is constantly regenerated, so that only a small amount need be used.



(58%)

When more concentrated solutions of potassium permanganate are used in the oxidation of alkenes, the initially formed glycol is oxidized further. The product is a mixture of ketones or carboxylic acids, depending on the extent of substitution of the double bond.



$$RCH{=}CH_2 \xrightarrow{KMnO_4} RCOOH + CO_2$$

This is not a common reaction in organic synthesis because the yields are usually low. Oxidative cleavage of the double bond can generally be accomplished in better yield by reaction with ozone.

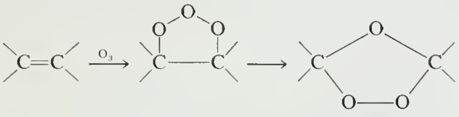
Ozone, O_3, is an important constituent of the upper atmosphere where it is produced by action of solar ultraviolet radiation on atmospheric oxygen. Ozone, in turn, absorbs in the ultraviolet region of the spectrum and provides an important screen to limit the amount of this radiation that reaches the earth's surface. Ozone is thermodynamically unstable with respect to oxygen:

$$O_3 \longrightarrow \tfrac{3}{2}\,O_2 \qquad \Delta H^\circ = -34\text{ kcal mole}^{-1}$$

One of the important concerns raised with respect to supersonic transport aircraft is that the nitrogen oxides produced as combustion products are catalysts for the conversion of ozone to oxygen. Extensive use of the SST may reduce the ozone screen, thus allowing more of the harmful ultraviolet radiation to reach the surface of the earth.

Ozone is produced in the laboratory with an "ozonator," a special apparatus in which an electrodeless discharge is induced in dry air passing through an alternating electric field. Ozone concentrations as high as 4% in air can be produced. The gas has a characteristic odor usually associated with electric arcs.

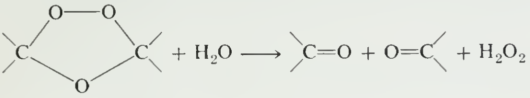
Reactions of alkenes with ozone are normally carried out by passing ozone-containing air through a solution of the alkene in an inert solvent at low temperatures (usually $-80°$). Reaction is rapid and completion of reaction is determined by testing the effluent gas with potassium iodide. Unreacted ozone reacts to give iodine. Suitable solvents for ozonizations include methylene chloride, alcohol, and ethyl acetate. The first formed addition product, the molozonide, rearranges rapidly, even at low temperatures, to the ozonide structure:



molozonide ozonide

In some cases polymeric structures are obtained. Some ozonides, especially the polymeric structures, decompose with explosive violence on heating; hence, the ozonides are generally not isolated but are decomposed directly to desired products.

Hydrolysis with water occurs readily to give carbonyl compounds and hydrogen peroxide.



Aldehydes are oxidized by hydrogen peroxide to carboxylic acids. Hence, *reduction* conditions are often used in decomposing the ozonides. Such conditions include zinc dust and acetic acid, catalytic hydrogenation, and dimethyl sulfide.

$$(CH_3)_2CHCH_2CH_2CH_2CH{=}CH_2 \xrightarrow{O_3} \xrightarrow[CH_3COOH]{Zn} \underset{(62\%)}{(CH_3)_2CHCH_2CH_2CH_2CHO}$$

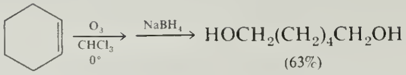
6-methyl-1-heptene 5-methylhexanal

6-Methyl-1-heptene in methylene chloride at $-78°$ is treated with ozone and is then added to a stirred mixture of zinc dust and 50% aqueous acetic acid. The mixture is refluxed for 1 hr and extracted with ether. Peroxides are removed from the ether with aqueous potassium iodide and the washed and dried solution is distilled to give 5-methylhexanal, b.p. 144°.

$$n\text{-}C_6H_{13}CH{=}CH_2 + O_3 \xrightarrow[-60^\circ]{CH_3OH} \xrightarrow{(CH_3)_2S} \underset{(73\%)}{n\text{-}C_6H_{13}CHO} + (CH_3)_2SO + CH_2O$$

1-octene heptanal dimethyl sulfoxide (DMSO)

Treatment of the ozonide with sodium borohydride gives the corresponding alcohols.



$$\xrightarrow[\substack{CHCl_3\\0^\circ}]{O_3} \xrightarrow{NaBH_4} HOCH_2(CH_2)_4CH_2OH$$

(63%)
1,6-hexanediol

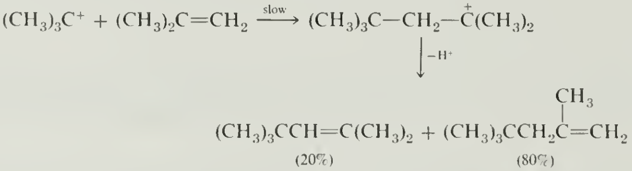
F. *Polymerization*

Polymerization is the process wherein a small organic compound (a **monomer**) reacts with itself in such a way as to form a high molecular weight compound (a **polymer**). For example, ethylene can undergo polymerization to give polyethylene.

$$\underset{\text{ethylene}}{CH_2{=}CH_2} \longrightarrow \underset{\text{polyethylene}}{XCH_2CH_2(CH_2CH_2)_nCH_2CH_2Y}$$

In the case of alkenes, polymerization amounts merely to the exchange of π bonds for σ bonds and is thermodynamically feasible. Polymerization may involve intermediate carbonium ions (**cationic polymerization**), free radicals (**radical polymerization**), or carbanions (**anionic polymerization**).

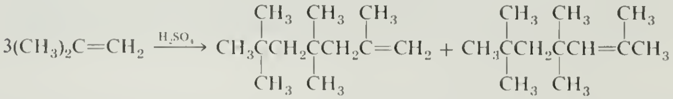
Cationic polymerization is not generally a practical method for preparing useful polymers. The process is used for the **dimerization** and **trimerization** of certain alkenes. As mentioned in Section 12.6.B under Addition of HX, isobutylene is absorbed and hydrated by 60–65% aqueous sulfuric acid. Under more vigorous conditions (50% H_2SO_4 at 100°), the intermediate carbonium ion can react with alkene to form a new tertiary carbonium ion. Deprotonation of this new carbonium ion gives a mixture of alkenes known as "diisobutylenes."



$$(CH_3)_3C^+ + (CH_3)_2C{=}CH_2 \xrightarrow{\text{slow}} (CH_3)_3C{-}CH_2{-}\overset{+}{C}(CH_3)_2$$
$$\downarrow -H^+$$
$$\underset{(20\%)}{(CH_3)_3CCH{=}C(CH_3)_2} + \underset{(80\%)}{(CH_3)_3CCH_2\overset{CH_3}{C}{=}CH_2}$$

Catalytic hydrogenation of this mixture gives 2,2,4-trimethylpentane, the so-called "isooctane" used as a standard for octane ratings of gasolines (Section 5.4).

Under still more vigorous conditions, isobutylene reacts with sulfuric acid to produce a mixture of trimeric alkenes, "triisobutylenes."

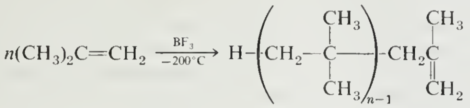


$$3(CH_3)_2C{=}CH_2 \xrightarrow{H_2SO_4} CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{CH_3}{C}{=}CH_2 + CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{CH_3}{\underset{CH_3}{C}}CH{=}\overset{CH_3}{C}CH_3$$

triisobutylenes

Higher polymers and undesirable tars generally result from the reaction of other alkenes with strong hot acid.

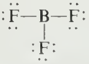
In the absence of suitable alternative nucleophilic compounds to react with the carbonium ion intermediates, reaction with alkene is the only reaction mode possible. Reaction of isobutylene with a small amount of boron trifluoride occurs at low temperature to produce a high molecular weight polymer.



$$n(CH_3)_2C{=}CH_2 \xrightarrow[-200°C]{BF_3} H\!\left(CH_2-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}-\right)_{\!n-1}\!-CH_2\overset{CH_3}{\underset{\underset{CH_2}{\|}}{\overset{|}{C}}}$$

(n = a large number)

Boron trifluoride is a colorless gas, b.p. −100°, and is available commercially in cylinders. The compound has a planar structure. The Lewis structure shows that there are only six electrons around boron.



$$:\underset{..}{\overset{..}{F}}-\underset{\underset{:\underset{..}{\overset{|}{F}}:}{}}{B}-\underset{..}{\overset{..}{F}}:$$

The tendency of boron to combine with an electron pair to form an octet is augmented by the electron-attracting character of the attached fluorines. Boron trifluoride is a strong Lewis acid. It reacts avidly with water to form a hydrate, $F_3\overset{-}{B}-\overset{+}{O}H_2$, which is itself a strong acid but slowly hydrolyzes in water to form boric acid and HF. In fact, BF_3 has a strong affinity generally for oxygen, nitrogen, and fluorine. With HF it forms fluoboric acid, HBF_4, a strong acid in aqueous solution. With ethyl ether it forms the complex, $(C_2H_5)_2O{:}BF_3$, boron trifluoride etherate, which can be formulated as $(C_2H_5)_2\overset{+}{O}-\overset{-}{B}F_3$. This compound is a distillable liquid, b.p. 126°, and is water-white when pure. We will encounter it as a useful acid catalyst.

Boron trifluoride does not react with alkenes in the rigorous absence of moisture. With traces of water, carbonium ions are produced. With isobutylene, for example, the intermediate salt, $(CH_3)_3C^+\ {}^-BF_3OH$, is produced in low concentration. The anion $F_3\overset{-}{B}OH$ has low nucleophilicity, and the *t*-butyl cation is free to react with isobutylene to start the cationic polymerization.

In some cases the carbonium ion will abstract a tertiary hydrogen from an alkane. A reaction of this type is used to produce "isooctane" directly from isobutylene and isobutane.

$$(CH_3)_3CH + (CH_3)_2C{=}CH_2 \xrightarrow[-25°C]{HF} \underset{\text{"isooctane"}}{\underset{\text{2,2,4-trimethylpentane}}{(CH_3)_3CCH_2CH(CH_3)_2}}$$

A reasonable mechanism for this alkylation reaction is

$$(CH_3)_2C{=}CH_2 \overset{HF}{\rightleftharpoons} (CH_3)_3C^+ \xrightarrow{(CH_3)_2C=CH_2} (CH_3)_3CCH_2C^+(CH_3)_2$$

$$(CH_3)_3CCH_2C^+(CH_3)_2 + (CH_3)_3CH \rightleftharpoons (CH_3)_3CCH_2CH(CH_3)_2 + (CH_3)_3C^+$$

Under these conditions the dimeric carbonium ion does not react with more isobutylene but instead abstracts hydrogen from isobutane to provide more *t*-butyl cation to continue the chain of reactions.

Anhydrous hydrofluoric acid is a low boiling (b.p. 19°), colorless liquid with a density similar to that of water. It reacts with glass and is kept and handled in polyethylene equipment. The pure liquid is a strong acid and is highly corrosive to living tissues.

Free radical polymerization may be initiated by the addition of many types of free radicals to an alkene double bond. The **telomerization** of ethylene in

Section 12.6.C is an example. In that case, the initiating group was $\cdot CX_3$. After the chain grows to four or five monomer units, the growing radical abstracts $X\cdot$ from CX_4 to give the telomer.

If no suitable radical addition reagent is available, the reaction of hydrocarbon radicals with alkenes can become the principal reaction to produce high molecular weight polymer chains. This reaction is an exceedingly important industrial process. Billions of pounds of polyethylene are made annually. The polymerization of ethylene requires high temperature and pressures.

$$n\mathrm{CH_2{=}CH_2} \xrightarrow[>100°;\ 15{,}000\ \text{psi}]{\text{trace } O_2 \text{ or peroxides}} \mathrm{Y{-}(CH_2CH_2)_n{-}Z}$$

Where n is a large number of the of 1000.

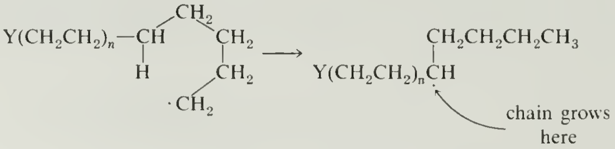
The end groups Y and Z depend on the initiators used and the termination reactions involved. The principal termination steps for ethylene polymerization are disproportionation and combination, as summarized in the following sequence of steps:

$$\mathrm{Y\cdot + CH_2{=}CH_2 \longrightarrow Y{-}CH_2{-}CH_2\cdot}$$

$$\mathrm{YCH_2CH_2\cdot + CH_2{=}CH_2 \longrightarrow YCH_2CH_2CH_2CH_2\cdot \xrightarrow{\text{etc.}} Y(CH_2CH_2)_{\mathit{n}}CH_2CH_2\cdot}$$

$$\left.\begin{array}{c}\mathrm{Y(CH_2CH_2)_{\mathit{n}}CH_2CH_2\cdot} \\ + \\ \mathrm{Y(CH_2CH_2)_{\mathit{m}}CH_2CH_2\cdot}\end{array}\right\} \begin{array}{l}\xrightarrow{\text{disproportionation}} \mathrm{Y(CH_2CH_2)_{\mathit{n}}CH_2CH_3 + Y(CH_2CH_2)_{\mathit{m}}CH{=}CH_2} \\ \\ \xrightarrow{\text{combination}} \mathrm{Y(CH_2CH_2)_{\mathit{n}}CH_2CH_2CH_2CH_2(CH_2CH_2)_{\mathit{m}}Y}\end{array}$$

The product of this so-called "high temperature polymerization" of ethylene does not have the simple linear structure shown. Ethyl and butyl groups are known to occur along the polymethylene chain, probably because of hydrogen abstraction reactions of the type



Linear polyethylene is made by an entirely different process described later.

Vinyl chloride, tetrafluoroethylene, and styrene are other important **monomers** used in free radical polymerizations. The Markovnikov addition of radicals to vinyl chloride applies with high specificity so that the product polymer has a complete head-to-tail structure.

$$\mathrm{Y\cdot + CH_2{=}CHCl \longrightarrow Y{-}CH_2\dot{C}HCl \longrightarrow \longrightarrow} \underset{\text{polyvinyl chloride}}{\mathrm{Y(CH_2CHCl)_nZ}}$$

Vinyl chloride is manufactured on an enormous scale, mostly by dehydrochlorination of 1,2-dichloroethane (ethylene dichloride). In 1973, ethylene dichloride ranked fourteenth in chemicals produced in the United States. The only organic compounds produced in greater amount were ethylene, benzene, and propylene. The 1973 United States production of ethylene dichloride and vinyl chloride was 7.9 billion and 5.3 billion lb, respectively. In 1974, the Occupational Safety and Health Administration concluded that vinyl chloride is a human carcinogen and set maximum limits to exposure.

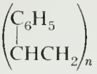
Polyvinyl chloride is an extremely hard resin. In order to alter the physical properties of the polymer, low molecular weight liquids called **plasticizers** are added in the polymer formulation. Bis-2-ethylhexyl phthalate is one of the compounds added to polyvinyl chloride as a plasticizer. The resulting polymer has a tough leathery or rubber-like texture. It is used in plastic squeeze bottles, imitation leather upholstery, pipes, and so on.

Polytetrafluoroethylene or "Teflon" is a perfluoro-polymer having great resistance to acids and organic solvents. It is used to coat "nonstick" frying pans and other cooking surfaces.

$$\underset{\text{Teflon}}{\mathrm{X{-}(CF_2CF_2)_{\mathit{n}}{-}Y}}$$

Two uses of the prefix **per-** are common in chemistry. One use designates a highly oxygenated compound that frequently, but not always, involves an O—O bond. Examples are hydrogen peroxide, permonosulfuric acid, H_2SO_5 ($HOSO_2OOH$, with O—O bond), and perchloric acid ($HOClO_3$, without an O—O bond). In its other use, per- refers to totally substituted, as in the examples perchloroethylene, $CCl_2{=}CCl_2$, and perfluoroalkane, C_nF_{2n+2}.

Polystyrene is an inexpensive plastic used to manufacture many familiar household items. It is a hard, colorless, somewhat brittle material.



$$\left(\begin{array}{l}\mathrm{C_6H_5}\\ \quad| \\ \mathrm{CHCH_2}\end{array}\right)_n$$

In the simple formulation of polystyrene, the end groups have been omitted. This simplification is common in the symbolism of polymer chemistry. The end groups constitute a minute portion of a high molecular weight polymer, although their character has a significant effect on the properties of the polymers.

In anionic polymerization, initiation is accomplished by addition of a nucleophile to a C=C double bond. Simple olefins are inert to most nucleophilic or basic reagents because most common anions are more stable than carbanions.

$$\mathrm{Y^- + CH_2{=}CH_2 \;\not\longrightarrow\; Y{-}CH_2CH_2^-}$$

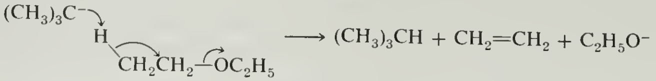
Only when the anion itself is an extremely powerful base will addition to the double bond occur. Amide ion (NH_2^-; pK of $NH_3 = 35$) is *not* generally a strong enough base for such a reaction. Neither are most Grignard reagents, RMgX. Although the R—Mg bond has polar character as indicated by the resonance structure, $R^{-+}MgX$, sufficiently significant to account for typical reactions of Grignard reagents as carbanions, the amount of such ionic character is too low to permit additions to simple double bonds:

$$\mathrm{RMgX + CH_2{=}CH_2 \;\not\longrightarrow\; RCH_2CH_2MgX}$$

t-Butyllithium (from *t*-butyl chloride and lithium in ether at −40°) does react with ethylene.

$$\mathrm{[(CH_3)_3C{-}Li \longleftrightarrow (CH_3)_3C^-Li^+] + CH_2{=}CH_2 \longrightarrow \begin{bmatrix}\mathrm{(CH_3)_3CCH_2CH_2{-}Li}\\ \updownarrow \\ \mathrm{(CH_3)_3CCH_2CH_2^-\ Li^+}\end{bmatrix}}$$

Since primary carbanions are more stable than tertiary carbanions, the reaction as shown has favorable thermodynamics. This particular reaction is of limited use because *t*-butyllithium is such a highly reactive compound. For example, in ether it must be kept at rather low temperatures. At room temperature it rapidly decomposes ether, in part by an E2 reaction:



$$(CH_3)_3C^- \quad H{-}CH_2CH_2{-}OC_2H_5 \longrightarrow (CH_3)_3CH + CH_2{=}CH_2 + C_2H_5O^-$$

Other kinds of organometallic intermediates provide rapid polymerization. A particularly important example is a catalyst prepared from aluminum alkyls (R_3Al) and titanium tetrachloride. This catalyst polymerizes simple olefins by a mechanism that involves the carbanion character of the C—Al bond and the ability of the transition metal, titanium, to coordinate with the π bonds of alkenes. The result is a rapid polymerization reaction that is used extensively with ethylene and propylene. Linear polyethylene, $(CH_2CH_2)_n$, prepared in this way, is more crystalline than high temperature polyethylene and has a higher density and melting point. The long chains of linear polyethylene can lie together in a regular manner in the solid without the defects in regularity imposed by the random branches of the high temperature polymer.

This example emphasizes how the properties of a polymer or macromolecular compound depend on molecular considerations of structure and interactions between chains. A polymer can have a regular structure characteristic of a crystal and at higher temperatures can melt to a viscous liquid. The liquid is viscous because the long chains form interpenetrating random coils and do not move freely past each other. An intermediate state is that of an amorphous glass, a solid in which the chains or coils are effectively frozen but not in the regular pattern typical of crystals. Polymers are characterized phenomenologically by two important types of temperatures that mark phase transitions, the crystalline melting point and the glass transition temperature (T_g).

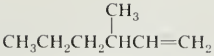
PROBLEMS

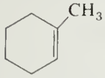
1. Give the structure and IUPAC name of each of the isomeric pentenes. Which ones are stereoisomers? Which ones are capable of optical activity?

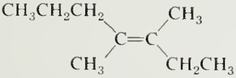
2. Write the correct structure for each of the following names:
   (a) isobutylene
   (b) 3,4-dimethyl-*trans*-2-pentene
   (c) 4-methyl-3-penten-1-ol
   (d) tetramethylethylene
   (e) styrene
   (f) vinyl fluoride
   (g) 1-bromocyclohexene
   (h) 3-methylcyclohexene
   (i) (Z)-2-bromo-2-pentene
   (j) (E)-3-methyl-2-hexene

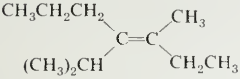
3. Each of the following names is incorrect. Give a correct name:
   (a) 2-methylcyclopentene
   (b) 2-methyl-*cis*-3-pentene
   (c) *trans*-1-butene
   (d) 1-bromoisobutylene
   (e) 4-chlorocyclopentene
   (f) (E)-3-ethyl-3-pentene

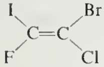
4. Name each of the following structures. For stereoisomers, use both the *cis-trans* and E-Z nomenclature.

(a) 
$CH_3CH_2CH_2\overset{CH_3}{C}HCH=CH_2$

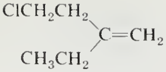
(b) 

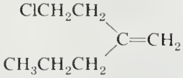
(c) 

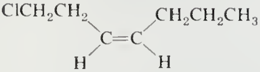
(d) 

(e) 

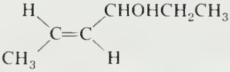
(f) $ClCH_2CH_2CH=CH_2$

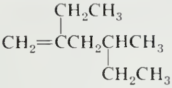
(g) 

(h) 

(i) 

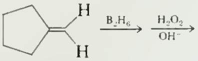
(j) $HOCH_2CH_2CH_2CH=CH_2$

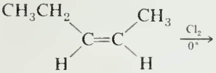
(k) 

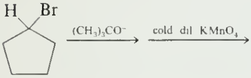
(l) 
$CH_2=\overset{CH_2CH_3}{C}CH_2\underset{CH_2CH_3}{C}HCH_3$

5. What is the principal organic product of each of the following reaction conditions? Specify stereochemistry where appropriate.

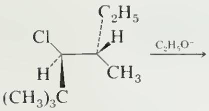
(a) $CH_3CH_2CH_2CHBrCH_3 \xrightarrow{(C_2H_5)_3CO^-}$

(b) 

(c) 

(d) 

(e) $CH_3CH_2CHClCD_2CH_3 \xrightarrow[\Delta]{\text{alc. KOH}}$

(f) 

6. Give the structure and name of the principal organic product(s) produced from 3-ethyl-2-pentene under each of the following reaction conditions:

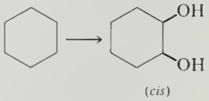
(a) H_2/Pd-C
(b) HOBr
(c) Cl_2/0°
(d) cold dilute $KMnO_4$
(e) (i) B_2H_6; (ii) NaOH-H_2O_2
(f) (i) aq. $Hg(ClO_4)_2$; (ii) $NaBH_4$
(g) (i) O_3; (ii) Zn dust, aq. CH_3COOH
(h) HBr, inhibitor
(i) HBr, peroxides
(j) Br_2, dilute solution in CH_3OH

7. Apply each of the reaction conditions in problem 6 to *cis*- and *trans*-3-hexene. For which reactions are the same products obtained from both stereoisomers? For which reactions do the products differ and how do they differ?

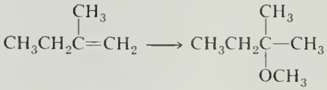
8. Show how one may accomplish each of the following transformations in a practical manner.

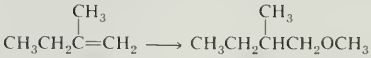
(a) $CH_3CHBrCH_3 \longrightarrow CH_3CH_2CH_2Br$

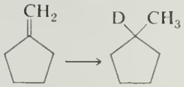
(b) $CH_3CHOHCH_3 \longrightarrow CH_3CH_2CH_2OH$

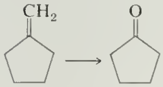
(c)


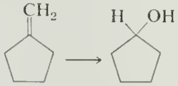
(d) $CH_3CH_2CHBrCH_2Br \longrightarrow CH_3CH_2CHBrCH_2CBr_3$

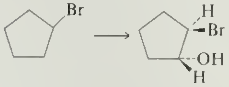
(e)

$CH_3CH_2C(CH_3){=}CH_2 \longrightarrow CH_3CH_2C(CH_3)(OCH_3){-}CH_3$

(f)

$CH_3CH_2C(CH_3){=}CH_2 \longrightarrow CH_3CH_2CH(CH_3)CH_2OCH_3$

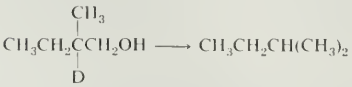
(g)


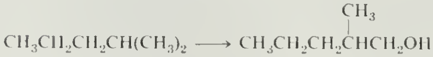
(h)


(i)


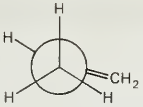
(j)


(k) $CH_3CH_2CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH_2CHBrCH_3$

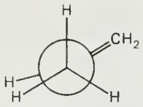
(l)

$CH_3CH_2C(CH_3)(D)CH_2OH \longrightarrow CH_3CH_2CH(CH_3)_2$

(m)

$CH_3CH_2CH_2CH(CH_3)_2 \longrightarrow CH_3CH_2CH_2CH(CH_3)CH_2OH$

9. The potential function for rotation of the methyl group in propylene is approximately that of a three-fold barrier with a barrier height of 2.0 kcal mole^{-1}. The most stable conformation is A in which a methyl hydrogen is eclipsed with the double bond. The least stable conformation is B in which H-2 is eclipsed to a methyl hydrogen.



A



B

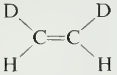
Plot the energy of the system as a function of a 360° rotation of the methyl group. Identify the points along this plot that correspond to conformations A and B.

10. Although the difference in energy between *cis* and *trans* olefins is generally about 1 kcal mole^{-1}, for 4,4-dimethyl-2-pentene the *cis* isomer is 3.8 kcal mole^{-1} less stable than the *trans* isomer. Explain.

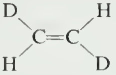
11. In the acid-catalyzed dehydration of 6-methyl-1,6-heptanediol, it is easy to find conditions that give smooth loss of one molecule of water to yield 6-methyl-5-penten-1-ol. Explain.

12. In the formation of diisobutylenes from isobutylene and sulfuric acid the disubstituted olefin isomer, 2,4,4-trimethyl-1-pentene was produced in greater amount than the trisubstituted olefin, 2,4,4-trimethyl-2-pentene. Explain.

13. Compare the product of addition of bromine to ethene-*cis*-1,2-d_2 and to ethene-*trans*-1,2-d_2.



ethene-*cis*-1,2-d_2



ethene-*trans*-1,2-d_2

On treatment with base each of the dibromides gives predominantly a single different dideuteriovinyl bromide. Show the structure in each case. (*Remember:* HBr is eliminated faster than DBr.)

14. The propagation steps for the radical addition of HY to propylene are

$$\begin{array}{ll}
\text{(a)} & CH_3CH{=}CH_2 + Y\cdot \longrightarrow CH_3\dot{C}HCH_2Y \\
\text{(b)} & CH_3\dot{C}HCH_2Y + HY \longrightarrow CH_3CH_2CH_2Y + Y\cdot \\
\hline
 & CH_3CH{=}CH_2 + HY \longrightarrow CH_3CH_2CH_2Y
\end{array}$$

$\Delta H°$ values are given in the table for steps (a) and (b) and for the net reaction with a number of reagents of the type HY in the gas phase. For which reagents is such a radical chain mechanism plausible?

Y:	F	Cl	Br	I	HS	HO	H_2N	CH_3	$(CH_3)_3C$
ΔH_a°	−48	−22	−9	+5	−13	−32	−19	−26	−18
ΔH_b°	+41	+8	−8	−24	−3	+24	+8	+9	−3
ΔH_{net}°	−7	−14	−17	−18	−16	−8	−11	−17	−22

15. When isopropyl bromide is treated with sodium ethoxide in ethanol, propylene and ethyl isopropyl ether are formed in a 3:1 ratio. If the hexadeuteroisopropyl bromide, $CD_3CHBrCD_3$ is used, $CD_3CH{=}CD_2$ and $(CD_3)_2CHOC_2H_5$ are formed in a ratio of 1:2. Explain.

16. The heat of hydrogenation, $\Delta H^\circ_{\text{hydrog}}$, is defined as the enthalpy of the reaction of an alkene with hydrogen to give the alkane.

$$CH_2{=}CH_2 + H_2 = CH_3CH_3 \qquad \Delta H^\circ_{\text{hydrog}} = -32.7 \text{ kcal mole}^{-1}$$

From the heats of formation given in Appendix 1 calculate heats of hydrogenation for a number of simple alkenes. Note that all monoalkyl ethylenes have about the same $\Delta H^\circ_{\text{hydrog}}$ which is less (more positive) than that for ethylene. Explain. How would you expect $\Delta H^\circ_{\text{hydrog}}$ to compare for isomeric *cis*- and *trans*-olefins?

17. Reaction of either 1-butene or 2-butene with HCl gives the same product, 2-chlorobutane, via the same carbonium ion, 2-butyl cation. Yet, the reaction of 1-butene is faster than that of 2-butene. Explain why, using simple energy diagrams. Using this explanation predict which is more reactive, *cis*-2-butene or *trans*-2-butene.

18. Consider a proposed free radical chain addition of HCN to $CH_3CH{=}CH_2$ to give *n*-propyl cyanide, $CH_3CH_2CH_2CN$. Use data in Appendix 1 and the following DH° values:

H—CN	130 kcal mole^{-1}
$CH_3\underset{\mid\atop H}{C}HCH_2CN$	95 kcal mole^{-1}

(a) Determine ΔH° for the net reaction, $CH_3CH{=}CH_2 + HCN = CH_3CH_2CH_2CN$
(b) Write the two chain-propagation steps for the proposed reaction and calculate ΔH° for each.
(c) Is the proposed reaction feasible? Explain.

19. The following free radical chain hydrogenation of ethylene is proposed:

$$CH_2{=}CH_2 + H\cdot = CH_3CH_2\cdot$$
$$CH_3CH_2\cdot + H_2 = CH_3CH_3 + H\cdot$$

Use data in Appendix 1 and determine whether this proposed reaction sequence is feasible.

20. Treatment of $C_7H_{15}Br$ with strong base gave an alkene mixture that was shown by careful gas chromatographic analysis and separation to consist of three alkenes, C_7H_{14}, A, B, and C. Catalytic hydrogenation of each alkene gave 2-methylhexane. Reaction of A with B_2H_6 followed by H_2O_2 and OH^- gave mostly an alcohol, D. Similar reaction of B or C gave approximately equal amounts of D and an isomeric alcohol E. What structural assignments can be made for A to E on the basis of these observations? What structural element is left undetermined by these data alone?

21. Reaction of 1-octene with light initiation occurs readily with $BrCCl_3$ to give an 88% yield of a single compound. Is this compound $CH_3(CH_2)_5CHClCH_2CBrCl_2$ or $CH_3(CH_2)_5CHBrCH_2CCl_3$? Explain.

CHAPTER 13
Alkynes

13.1
Electronic Structure

Acetylene is known experimentally to have a linear structure. Its C≡C bond distance of 1.20 Å is the shortest C—C bond distance known. The C—H bond distance of 1.06 Å is shorter than that in ethylene (1.08 Å) or in ethane (1.10 Å) (Figure 13.1). These structural details are readily interpreted by an extension of the σ-π electronic structure of double bonds. In acetylene the σ-framework consists of C_{sp} hybrid orbitals as indicated in Figure 13.2.

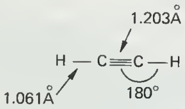


FIGURE 13.1 *Structure of acetylene.*

Recall (Section 12.1) that sp^2—s σ bonds are shorter than are sp^3—s σ bonds. The trend also holds for the sp—s bonds in acetylene. The effect of the amount of s character in the C—H bond distance is shown graphically in Figure 13.3. Superimposed on the σ electrons are two orthogonal π electron systems as shown in Figure 13.4.

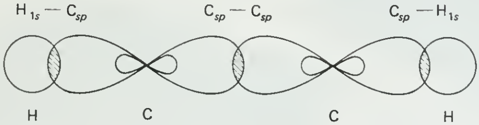


FIGURE 13.2 *σ electronic framework of acetylene.*

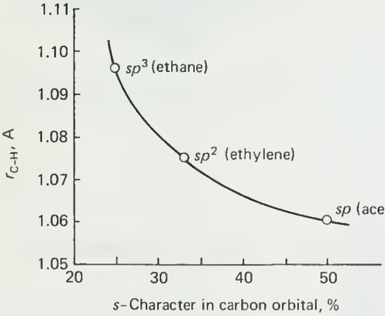


FIGURE 13.3 *Relationship between* C—H *bond distance and the approximate amount of* s *character in carbon orbital.*

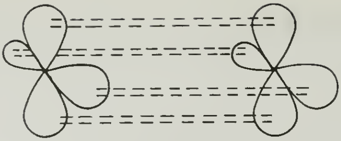
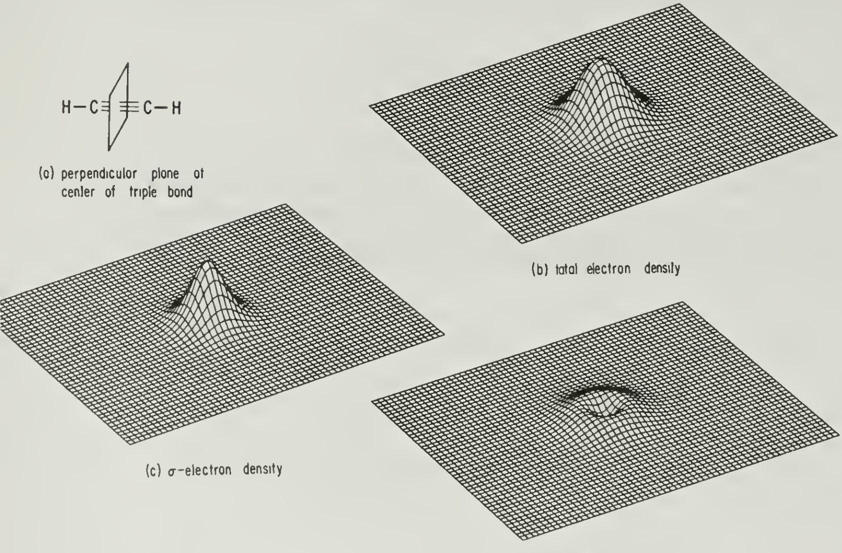


Figure 13.4 *π systems of acetylene.*

The symbolic representations in Figure 13.4 are actually misleading because the electrons in two orthogonal *p* orbitals form a cylindrically symmetrical torus or doughnut-like electron density distribution. The total (Figure 13.5b), σ (Figure 13.5c) and π (Figure 13.5d) electron density distributions are shown in Figure 13.5 for a perpendicular plane at the center of the triple bond (Figure 13.5a). The triple bond is a strong bond with a cylindrically symmetrical electron density distribution along the molecular axis.



(a) perpendicular plane of center of triple bond

(b) total electron density

(c) σ-electron density

(d) π-electron density

Figure 13.5 *Electron density distribution in center of acetylene triple bond.*

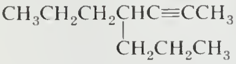
13.2
Nomenclature

The simple alkynes are readily named in the common system as derivatives of acetylene.

$CH_3C\equiv CH$	$C_6H_5C\equiv CC_6H_5$	$F_3CC\equiv CH$
methylacetylene	diphenylacetylene	trifluoromethylacetylene

In the IUPAC system the compounds are named as alkynes in which the final **-ane** of the parent alkane is replaced by the suffix **-yne**. The position of the triple bond is indicated by a number when necessary.

$CH_3C{\equiv}CH$ $(CH_3)_2CHC{\equiv}CH$



$$CH_3CH_2CH_2\underset{\displaystyle CH_2CH_2CH_3}{\underset{|}{C}}HC{\equiv}CCH_3$$

propyne 3-methyl-1-butyne 4-propyl-2-heptyne

In accordance with the general rule the -yne suffix controls the numbering system. If both -yne and -ol endings are used, the -ol is last and determines the numbering sequence.

$HC{\equiv}CCH_2CH_2OH$ $HOCH_2C{\equiv}CCH_2OH$

3-butyn-1-ol
(not but-4-ol-1-yne)

2-butyn-1,4-diol

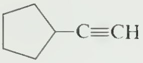
When both a double and triple bond are present, the hydrocarbon is named an **alkenyne** with numbers as low as possible given to the multiple bonds. In case of a choice, the double bond gets the lower number. This is an exception to the normal rule that the final suffix controls the numbering.

$CH_3CH{=}CHC{\equiv}CH$ $HC{\equiv}CCH_2CH{=}CH_2$

3-penten-1-yne
(not 2-penten-4-yne)

1-penten-4-yne
(not 4-penten-1-yne)

In complex structures the alkynyl group is used as a modifying prefix.



ethynylcyclopentane

13.3
Physical Properties

The physical properties of alkynes are similar to those of the corresponding alkenes. The lower members are gases with boiling points somewhat higher than the corresponding alkenes. Terminal alkynes have lower boiling points than isomeric internal alkynes and can be separated by careful fractional distillation.

TABLE 13.1
Physical Properties of Alkynes

Compound	Boiling Point, °C	Melting Point, °C	d^{20}
ethyne (acetylene)	−84.0[a]	−81.5[b]	
propyne	−23.2	−102.7	
1-butyne	8.1	−122.5	
2-butyne	27	−32.3	
1-pentyne	39.3	−90.0	
2-pentyne	55.5	−101	
1-hexyne	71	−132	0.7152
2-hexyne	84	−88	0.7317
3-hexyne	81	−105	0.7231
phenylacetylene	143	−43	
diphenylacetylene	300	63.5	

[a] Sublimation temperature. [b] Under pressure.

A. *Dipole Moments*

The $CH_3—C\equiv$ bond in propyne is formed by overlap of a C_{sp^3} hybrid orbital from the methyl carbon with a C_{sp} hybrid from the acetylenic carbon. The bond is C_{sp^3}-C_{sp}. Since one orbital has more *s* character than the other and is thereby more electronegative, the electron density in the resulting bond is not symmetrical. The unsymmetrical electron distribution results in a dipole moment, larger than that observed for an alkene, but still relatively small.

$$\underset{\mu = 0.80\text{ D}}{CH_3CH_2C{\equiv}CH} \qquad \underset{\mu = 0.30\text{ D}}{CH_3CH_2CH{=}CH_2} \qquad \underset{\mu = 0\text{ D}}{CH_3C{\equiv}CCH_3}$$

Symmetrically disubstituted acetylenes, of course, have no net dipole moment.

B. *Nuclear Magnetic Resonance*

Protons attached directly to a triply-bonded carbon resonate at $\delta = 2$–3 ppm. This is a much higher field resonance than that observed for vinyl protons. In fact, the resonance position for alkyne protons is only slightly downfield from the resonance position of alkane protons. The observed position is due to a deshielding effect of the "electronegative" triple bond superimposed on another effect due to magnetic anisotropy of the triple bond itself. Recall that a triple bond has a cylindrically symmetric sheath of π electrons. As shown in Figure 13.6, the electrons in this torus can circulate in a magnetic field. This electronic motion induces a small local field (dotted lines in Figure 13.6). At the acetylenic proton, the induced field opposes the applied field. Thus, a higher applied field is required to bring this proton into resonance. The result of the induced field in this case is an effective shielding of the alkyne proton.

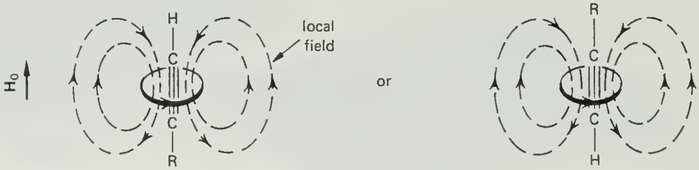


FIGURE 13.6 *Shielding of acetylenic protons by a triple bond in parallel orientation to the applied field.*

Actually, the diamagnetic shielding of acetylenic protons is a result of two factors. When the molecule is aligned perpendicular to $\mathbf{H}_0$, the acetylenic proton is deshielded, just as in the case of alkene hydrogens (Figure 13.7). This deshielding component

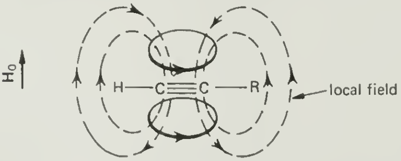


FIGURE 13.7 *Shielding of acetylenic protons for a triple bond perpendicular to the applied field.*

is smaller than the shielding component diagrammed in Figure 13.6. When averaged over all possible orientations, the effect is a net diamagnetic shielding.

This diamagnetic shielding diminishes the normal inductive effect. As a result of these two opposing effects, the resonance position of acetylenic protons is only slightly downfield from the resonance position of alkane protons. Similar effects operate on hydrogens bound to carbons adjacent to triple bonds, causing them to resonate about 1 ppm downfield from the corresponding alkane position.

The nmr spectra of 3,3-dimethyl-1-butyne and 1-hexyne are shown in Figures 13.8 and 13.9. Note that in the spectrum of 1-hexyne, the alkyne proton

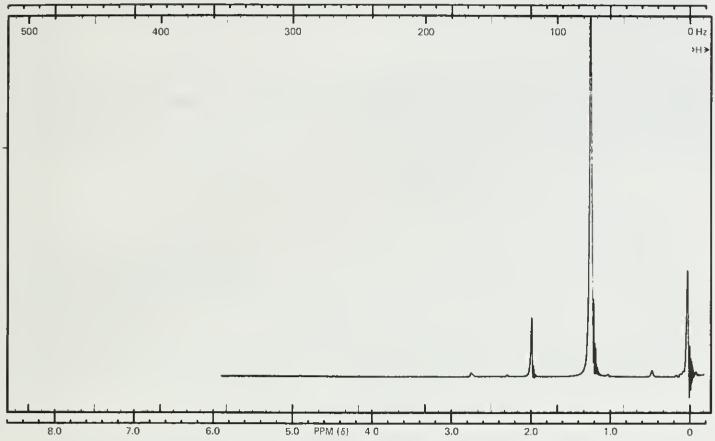


FIGURE 13.8 Nmr *spectrum of* 3,3-*dimethyl*-1-*butyne*.

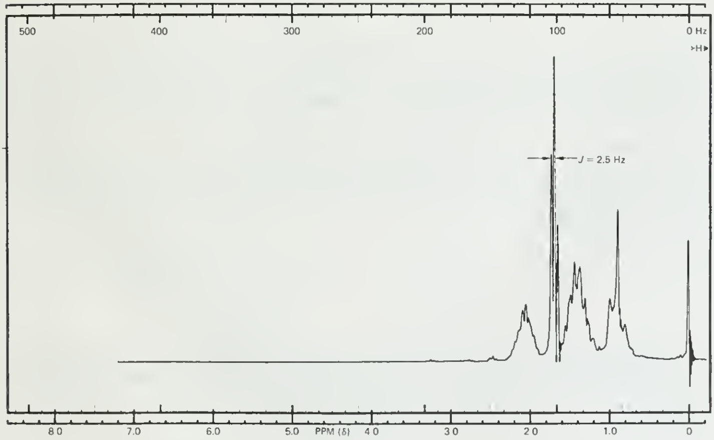


FIGURE 13.9 Nmr *spectrum of* 1-*hexyne*.

($\delta = 1.7$ ppm) appears as a triplet with $J = 2.5$ Hz. This small splitting is the result of **long range coupling** through the triple bond.

13.4
Acidity of Alkynes

The hydrogens in terminal alkynes are relatively acidic. Acetylene itself has a pK_a of about 25. It is a far weaker acid than water (pK_a 15.7) or the alcohols (pK_a 16–19), but it is much more acidic than ammonia (pK_a 35). Amide ion in liquid ammonia converts acetylene and other terminal alkynes into the corresponding carbanions.

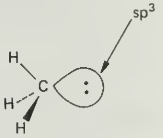
$$RC{\equiv}CH + NH_2^- \rightleftharpoons RC{\equiv}C^- + NH_3$$

This reaction does not occur with alkenes or alkanes. Ethylene has a pK_a of about 44 and methane has a pK_a of about 49.

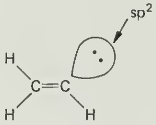
$$CH_2{=}CH_2 + NH_2^- \rightleftharpoons CH_2{=}CH^- + NH_3$$

$$CH_4 + NH_2^- \rightleftharpoons CH_3^- + NH_3$$

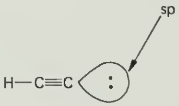
From the above pK_as, we see that there is a vast difference in the stability of the carbanions $RC{\equiv}C^-$, $CH_2{=}CH^-$, and CH_3^-. This difference is explainable in terms of the character of the orbital occupied by the lone pair electrons in the three anions. Methyl anion has a pyramidal structure with the lone pair electrons in an orbital that is approximately sp^3 ($\frac{1}{4}s$ and $\frac{3}{4}p$). In vinyl anion, the lone pair electrons are in an sp^2 orbital ($\frac{1}{3}s$ and $\frac{2}{3}p$). In acetylide ion, the lone pair is in an sp orbital ($\frac{1}{2}s$ and $\frac{1}{2}p$).



methyl anion



vinyl anion



acetylide ion

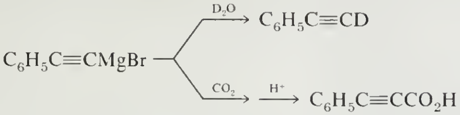
Electrons in s orbitals are held, on the average, closer to the nucleus than they are in p orbitals. This increased electrostatic attraction means that s electrons have lower energy and greater stability than p electrons. In general, the greater the amount of s orbital in a hybrid orbital containing a pair of electrons, the less basic is that pair of electrons. Lower basicity corresponds to higher acidity of the conjugate acid.

base strength ↑			acid strength ↓
	$CH_3{:}^-$	CH_4	
	$CH_2{=}CH{:}^-$	$CH_2{=}CH_2$	
	$HC{\equiv}C{:}^-$	$HC{\equiv}CH$	

One important way in which the acidity of an acetylenic hydrogen is manifest is in reaction with Grignard reagents. The hydrogens in a terminal alkyne are sufficiently acidic to protonate a Grignard reagent. The reaction is relatively slow and is usually accomplished by refluxing an ether solution for several hours.

$$C_6H_5C{\equiv}CH + C_2H_5MgBr \longrightarrow C_6H_5C{\equiv}CMgBr + C_2H_6$$

Once formed, the alkynyl Grignard reagent undergoes most of the usual reactions of Grignard reagents.



$$C_6H_5C{\equiv}CMgBr \xrightarrow{D_2O} C_6H_5C{\equiv}CD$$

$$C_6H_5C{\equiv}CMgBr \xrightarrow{CO_2} \xrightarrow{H^+} C_6H_5C{\equiv}CCO_2H$$

Terminal alkynes give insoluble salts with a number of heavy metal cations such as Ag^+ and Cu^+. The formation of the salts serves as a useful chemical diagnosis for the $RC{\equiv}CH$ function, but many of these salts are explosively sensitive when dry and should always be kept moist. The alkyne can be regenerated from the salt and the overall process serves as a method for purifying terminal alkynes.

Impure 1-hexyne is dissolved in 95% ethanol and aqueous silver nitrate is added. The white precipitate is filtered and washed with alcohol. On refluxing with sodium cyanide solution, the alkyne is regenerated and distilled. The cyanide converts silver cation to a stable complex.

$$RC{\equiv}CAg + H_2O + 2CN^- \longrightarrow RC{\equiv}CH + OH^- + Ag(CN)_2^-$$

13.5
Preparation of Alkynes

A. *Acetylene*

Acetylene itself is formed from the reaction of calcium carbide with water.

$$CaC_2 + H_2O \longrightarrow Ca(OH)_2 + HC{\equiv}CH$$

Calcium carbide is a high melting (m.p. 2300°) gray solid prepared by heating lime and coke in an electric furnace.

$$CaO + 3\,C \longrightarrow CaC_2 + CO$$

This method was once an important industrial process for the manufacture of acetylene. However, the method has now been replaced by a process in which methane is pyrolyzed in a flow system with short contact time.

$$2\,CH_4 \xrightarrow[0.01\text{–}0.1\text{ sec}]{1500^\circ C} HC{\equiv}CH + 3\,H_2$$

This reaction is endothermic at ordinary temperatures but is thermodynamically favored at high temperatures.

At room temperature, acetylene is thermodynamically unstable with respect to its elements as shown by its large *positive* heat of formation ($\Delta H_f^\circ = +54.3$ kcal mole^{-1} at 25°).

$$C_2H_2 = 2\,C(s) + H_2 \qquad \Delta H^\circ = -54.3 \text{ kcal mole}^{-1}$$

This instability causes certain problems in the handling and storage of the material. When under pressure or in the presence of copper, it can convert to carbon and hydrogen with explosive violence. Although acetylene gas can be condensed readily (b.p. −84°), the liquid is similarly unstable. Since the gas is extremely soluble in acetone, commercial cylinders of acetylene contain pieces of pumice which are saturated with acetone. When the cylinder is filled, the acetylene mostly dissolves, giving a relatively stable solution. Acetylene is also appreciably soluble in water. A saturated aqueous solution at 25° and 1 atm pressure has a concentration of 0.05 M (0.13 g C_2H_2 per 100 ml).

B. *Elimination reactions*

In principle, a triple bond can be introduced by elimination of two molecules of HX from either a **geminal** (L., *geminus,* twin) or a **vicinal** (L., *vicinus,* near) dihalide.

$$\underset{\text{a } gem\text{-dibromide}}{-CBr_2-CH_2-} \xrightarrow{-2HBr} -C\equiv C-$$

$$\underset{\text{a } vic\text{-dibromide}}{-CHBr-CHBr-} \xrightarrow{-2HBr} -C\equiv C-$$

Both types of dihalides are readily available. *gem*-Dihalides can be prepared from aldehydes or ketones (Section 15.7.I) and *vic*-dihalides are made by reaction of alkenes with halogen (Section 12.6.B).

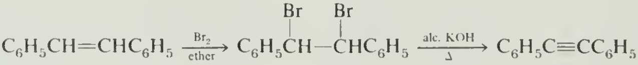
The dehydrohalogenation proceeds in stages, with the second molecule of HX being removed with greater difficulty than the first.

$$\left.\begin{array}{c} -CX_2CH_2- \\ \text{or} \\ -CHXCHX- \end{array}\right\} \xrightarrow{\text{faster}} -CX{=}CH- \xrightarrow{\text{slower}} -C\equiv C-$$

Typical reaction conditions for formation of alkynes involve the use of molten KOH, solid KOH moistened with alcohol, or concentrated alcoholic KOH solutions at temperatures of 100-200°. In practice, these conditions are so drastic that the method is only useful for the preparation of certain kinds of alkynes. Under these highly basic conditions, the triple bond can **migrate** along a chain.

$$CH_3CH_2C\equiv CH \xrightarrow[\Delta]{\text{alc. KOH}} CH_3C\equiv CCH_3$$

Disubstituted alkynes are thermodynamically more stable than terminal alkynes (because of the preference for s character in C—C bonds, Section 12.4). Consequently, these conditions may be used only where such rearrangement is not possible.



$$\underset{\text{stilbene}}{C_6H_5CH{=}CHC_6H_5} \xrightarrow[\text{ether}]{Br_2} \underset{(77\text{–}81\%)}{C_6H_5\overset{Br}{\overset{|}{C}}H-\overset{Br}{\overset{|}{C}}HC_6H_5} \xrightarrow[\Delta]{\text{alc. KOH}} \underset{(66\text{–}69\%)}{C_6H_5C\equiv CC_6H_5}$$

Sodium amide is an effective strong base that is particularly appropriate for the preparation of 1-alkynes.

Sodium amide, $NaNH_2$, is a white solid prepared by the reaction of sodium with liquid ammonia. Sodium dissolves in liquid ammonia to give a blue solution of "solvated electrons."

$$Na \xrightarrow{NH_3} Na^+ + e\ (NH_3)$$

Such solutions are useful reducing agents. (One example is the reduction of alkynes in Section 13.6.A). In the presence of small amounts of ferric ion, a reaction takes place with the liberation of hydrogen.

$$e + NH_3 \xrightarrow{Fe^{3+}} NH_2^- + \tfrac{1}{2}H_2$$

The net reaction is

$$2\,Na + 2\,NH_3 \xrightarrow{Fe^{3+}} 2\,NaNH_2 + H_2$$

In liquid ammonia, sodium amide is a strong base just as sodium hydroxide is in water.

Since NH_3 is much less acidic than water, sodium amide reacts quantitatively with water. Solutions of $NaNH_2$ in NH_3 readily absorb moisture from the atmosphere.

$$NH_2^- + H_2O \longrightarrow NH_3 + OH^-$$

In the organic laboratory, sodium amide is generally used as a solid suspension in some inert medium such as benzene or mineral oil or as a solution in liquid ammonia.

To dehydrohalogenate a dihalide, a suspension of sodium amide in mineral oil is heated to 150–165°. The dihalide is added slowly and a vigorous reaction ensues. Ammonia is evolved, and the sodium salt of the alkyne is formed. After cooling, the hydrocarbon is liberated by the addition of water.

$$\left.\begin{array}{r} RCX_2CH_3 \\ RCHXCH_2X \\ RCH_2CHX_2 \end{array}\right\} + 2\,NaNH_2 \longrightarrow RC{\equiv}CH \xrightarrow{NaNH_2} RC{\equiv}C^-Na^+ + NH_3$$

$$RC{\equiv}C^-Na^+ + H_2O \longrightarrow RC{\equiv}CH + Na^+OH^-$$

Since the reaction product is the salt of an alkyne, this method is useful for preparing terminal alkynes even when migration of the triple bond is possible.

$$n\text{-}C_{14}H_{29}CHBrCH_2Br \xrightarrow{NaNH_2} \underset{(65\%)}{n\text{-}C_{14}H_{29}C{\equiv}CH}$$

In fact, internal alkynes may be conveniently isomerized to terminal alkynes by the use of sodium amide at 150°.

$$\begin{tikzcd} n\text{-}C_5H_{11}C{\equiv}CCH_3 \arrow[r, "NaNH_2", "150^\circ C"'] & n\text{-}C_6H_{13}C{\equiv}C^-Na^+ + NH_3 \arrow[d, "H^+"] \\ & n\text{-}C_6H_{13}C{\equiv}CH \end{tikzcd}$$

C. *Displacement Reactions*

Acetylide anions are highly nucleophilic and participate readily in S_N2 displacement reactions.

$$RC{\equiv}C{:}^- + R'X \longrightarrow RC{\equiv}CR' + X^-$$

This method is a useful general method for the preparation of certain types of alkynes. It is actually one of the few good methods we have encountered thus far for **lengthening a carbon chain.** The reaction may be carried out in liquid ammonia solution or in a polar aprotic solvent such as HMPT (hexamethylphosphoric triamide) (Section 8.6.B). The acetylide anion is formed with sodium amide or with *n*-butyllithium.

> Liquid ammonia is available commercially in cylinders. Although the compound boils at −33°, it has a relatively high heat of vaporization, due to extensive hydrogen bonding in the liquid. Because of this high heat of vaporization, boiling is a relatively slow process at room temperature. When using liquid ammonia, the material is kept in a normal reaction flask which is equipped with a type of trap or condenser containing dry ice (−78°). The liquid ammonia in the flask refluxes gently and condenses on the dry ice condenser.
>
> The terminal alkyne is added to a solution of sodium amide in ammonia. After it has been converted into its salt, the alkyl halide is added. The mixture is stirred for a few hours and water is then added. The hydrocarbon is separated from the aqueous ammonia layer and purified.

There is a fair amount of variety possible using this method. Acetylene itself may be alkylated either once to make a terminal alkyne or twice to make an internal alkyne.

$$HC{\equiv}CH + NaNH_2 \xrightarrow[-33^\circ]{\text{liq. NH}_3} HC{\equiv}C^-Na^+ \xrightarrow{n\text{-}C_4H_9Br} \underset{\substack{(89\%)\\ \text{1-hexyne}}}{CH_3(CH_2)_3C{\equiv}CH}$$

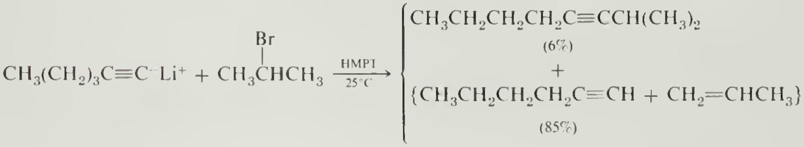
$$HC{\equiv}CH \xrightarrow[\substack{\text{liq. NH}_3\\ -33^\circ\text{C}}]{2\,NaNH_2} \xrightarrow{2\,n\text{-}C_3H_7Br} \underset{\substack{(60\text{–}66\%)\\ \text{4-octyne}}}{CH_3CH_2CH_2C{\equiv}CCH_2CH_2CH_3}$$

$$CH_3(CH_2)_3C{\equiv}CH + n\text{-}C_4H_9Li \xrightarrow[25^\circ\text{C}]{\text{HMPT}}$$

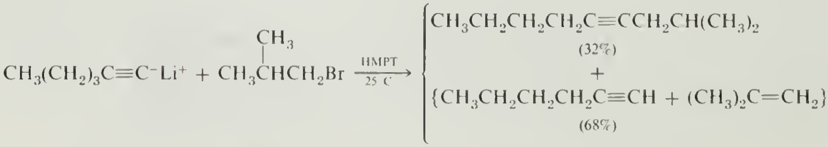
$$C_4H_{10}\uparrow + CH_3(CH_2)_3C{\equiv}C^-Li^+ \xrightarrow{CH_3(CH_2)_4Cl}$$

$$\underset{\substack{(90\%)\\ \text{5-undecyne}}}{CH_3CH_2CH_2CH_2C{\equiv}CCH_2CH_2CH_2CH_2CH_3}$$

Since acetylide ions are highly basic, they are also effective in E2 elimination reactions. For this reason, the displacement reaction is only a good method for the synthesis of acetylenes when applied to primary halides which do not have branches close to the reaction center.



$$CH_3(CH_2)_3C{\equiv}C^-Li^+ + CH_3\overset{\displaystyle Br}{\overset{|}{C}}HCH_3 \xrightarrow[25^\circ\text{C}]{\text{HMPT}} \left[\begin{array}{c} CH_3CH_2CH_2CH_2C{\equiv}CCH(CH_3)_2 \\ (6\%) \\ + \\ \{CH_3CH_2CH_2CH_2C{\equiv}CH + CH_2{=}CHCH_3\} \\ (85\%) \end{array}\right.$$



$$CH_3(CH_2)_3C{\equiv}C^-Li^+ + CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Br \xrightarrow[25^\circ\text{C}]{\text{HMPT}} \left[\begin{array}{c} CH_3CH_2CH_2CH_2C{\equiv}CCH_2CH(CH_3)_2 \\ (32\%) \\ + \\ \{CH_3CH_2CH_2CH_2C{\equiv}CH + (CH_3)_2C{=}CH_2\} \\ (68\%) \end{array}\right.$$

[illegible]

13.6
Reactions of Alkynes

Many of the reactions of alkynes involve the triple bond in a manner analogous to comparable reactions of alkenes. However, just as a double bond is weaker than two single bonds, a triple bond is weaker still than three single bonds. This comparison is apparent in the average bond energies tabulated in Table 13.2. As a result, the triple bond enters into some reactions not generally seen with alkenes.

TABLE 13.2
Average Bond Energies of C—C Bonds

Bond	Average Bond Energy kcal mole^{-1}
C—C	83
C=C	146
C≡C	200

A. *Reduction*

Hydrogenation of an alkyne to an alkane occurs readily with the same general catalysts used for the reduction of alkenes.

$$\text{R—C}\equiv\text{C—R}' + 2\,\text{H}_2 \xrightarrow{\text{Pt, Pd, Ni}} \text{R—CH}_2\text{CH}_2\text{—R}'$$

The first step in the reduction is a more exothermic reaction than is the second.

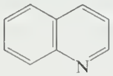
$$\text{HC}\equiv\text{CH} + \text{H}_2 \longrightarrow \text{CH}_2\text{=CH}_2 \qquad \Delta H^\circ = -41.9 \text{ kcal mole}^{-1}$$

$$\text{CH}_2\text{=CH}_2 + \text{H}_2 \longrightarrow \text{CH}_3\text{CH}_3 \qquad \Delta H^\circ = -32.7 \text{ kcal mole}^{-1}$$

The second reaction is so facile that, with most catalysts, it is not possible to stop the reduction at the alkene stage. However, with palladium or nickel, alkynes undergo hydrogenation extremely readily—faster than any other functional group. By taking advantage of this catalytic effect, one may accomplish the **selective hydrogenation** of an alkyne to an alkene. In practice, specially deactivated or **poisoned** catalysts are usually used. The most effective catalyst for this purpose is palladium metal which has been deposited in a finely divided state on solid $BaSO_4$ and then treated with quinoline (the actual poison). This catalyst is known as **Lindlar's catalyst.**

The function of the poison is to moderate the catalyst's activity to a point where triple bonds are still reduced at a reasonable rate but double bonds react only slowly. One can then readily stop the reduction after absorption of 1 mole of hydrogen and isolate the alkene in excellent yield.

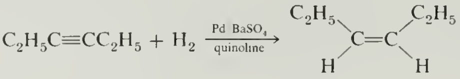
Quinoline is a heterocyclic amine and is discussed in Chapter 35.



quinoline

It is isolated commercially from coal tar, but the commercial material contains trace amounts of sulfur compounds that are difficult to remove. Divalent sulfur compounds are such exceedingly powerful catalyst poisons that they completely inhibit the catalytic activity. For this reason, only pure synthetic quinoline may be used for this purpose.

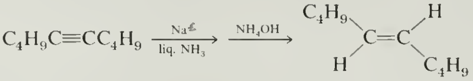
An important aspect of these hydrogenations is the fact that hydrogen is delivered from the catalyst to the triple bond in such a manner as to generate a *cis*-alkene.



$$C_2H_5C{\equiv}CC_2H_5 + H_2 \xrightarrow[\text{quinoline}]{\text{Pd BaSO}_4} (C_2H_5)(H)C{=}C(C_2H_5)(H)$$

An alternative synthetic method for the preparation of *cis*-alkenes involves hydroboration (Section 13.6.E).

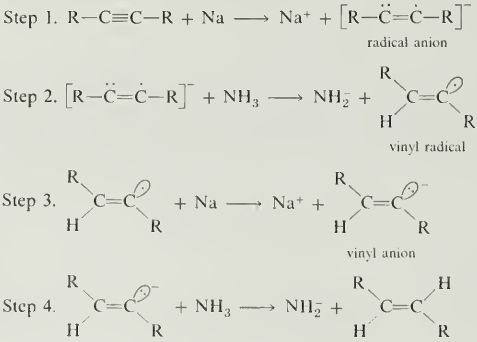
Reduction of triple bonds can also be accomplished by treating the alkyne with sodium in liquid ammonia at −33°. This reduction produces exclusively the *trans*-alkene.



$$C_4H_9C{\equiv}CC_4H_9 \xrightarrow[\text{liq. NH}_3]{\text{Na}} \xrightarrow{\text{NH}_4\text{OH}} (C_4H_9)(H)C{=}C(H)(C_4H_9)$$

(80–90%)
trans-5-decene

The mechanism of this reaction involves the reduction of the triple bond by two electrons from sodium atoms. The first electron goes into an antibonding π orbital to give a **radical anion.** This strongly basic species is protonated by ammonia to give a **vinyl radical,** which is reduced by another electron to give a **vinyl anion.** Final protonation of the vinyl anion by ammonia (acting as an acid) yields the *trans*-alkene and amide ion.



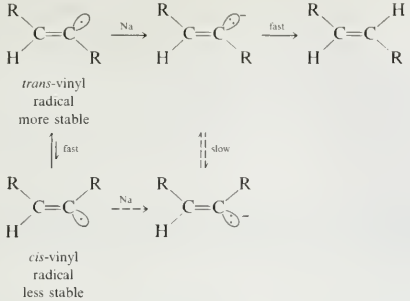
$$\text{Step 1. } R{-}C{\equiv}C{-}R + Na \longrightarrow Na^+ + [R{-}\ddot{C}{=}\dot{C}{-}R]^-$$

$$\text{Step 2. } [R{-}\ddot{C}{=}\dot{C}{-}R]^- + NH_3 \longrightarrow NH_2^- + (R)(H)C{=}\dot{C}(R)$$

$$\text{Step 3. } (R)(H)C{=}\dot{C}(R) + Na \longrightarrow Na^+ + (R)(H)C{=}\ddot{C}^-(R)$$

$$\text{Step 4. } (R)(H)C{=}\ddot{C}^-(R) + NH_3 \longrightarrow NH_2^- + (R)(H)C{=}C(H)(R)$$

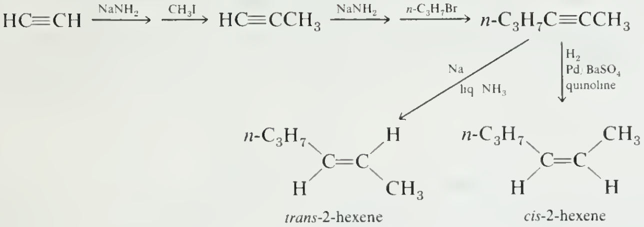
The stereochemistry of the final product is probably established in the reduction of the vinyl radical (step 3). The two vinyl radicals with the R groups *trans* or *cis* interconvert rapidly, but the *trans* form is preferred because of nonbonded interactions in the *cis* form. Since reduction of the two vinyl radicals probably proceeds at comparable rates and the *trans* form is present in much greater amount, the vinyl anion formed is mostly *trans*. The vinyl anion interconverts between *cis* and *trans* forms only relatively slowly and appears to protonate before it has a chance to isomerize.


Na
fast
trans-vinyl radical more stable
fast
slow
Na
cis-vinyl radical less stable

Note that we have used the term **vinyl** in two different senses. It refers to the common name for the specific organic function, $-CH{=}CH_2$ (for example, vinyl chloride, $CH_2{=}CHCl$) but it is also used generically to refer to substitution at a carbon that is part of an alkene double bond (for example, $CH_3CCl{=}CH_2$, a vinyl or vinylic chloride).

Simple alkenes are not reduced by sodium in liquid ammonia so it is easy to perform the selective reduction of an alkyne to an alkene by this method. It is important not to confuse a solution of Na in liquid NH_3 (which is actually a solution containing Na^+ ions and solvated electrons, *e*) with a solution of $NaNH_2$ in liquid NH_3 (which is a solution containing Na^+ ions and NH_2^- ions). The former solution *reduces* alkynes. The latter solution does not reduce alkynes but does deprotonate terminal alkynes.

By means of these several reactions, it is possible to construct larger chains from smaller ones and to prepare either *cis*- or *trans*-alkenes with little contamination from the other. For example


HC≡CH
NaNH₂
CH₃I
HC≡CCH₃
NaNH₂
n-C₃H₇Br
n-C₃H₇C≡CCH₃
Na
liq NH₃
H₂
Pd/BaSO₄
quinoline
trans-2-hexene
cis-2-hexene

We begin to see the sensitivity and power of organic syntheses and we have only barely scratched the surface of the many and varied reactions known and used in the organic laboratory.

B. *Electrophilic Additions*

The triple bond reacts with HX and X_2 in much the same manner as does the double bond. The reaction goes in stages and Markovnikov's rule is followed.

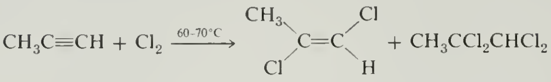
$$RC{\equiv}CH + HX \longrightarrow RCX{=}CH_2$$

$$RCX{=}CH_2 + HX \longrightarrow RCX_2CH_3$$

$$RC{\equiv}CR' + X_2 \longrightarrow RCX{=}CXR'$$
$$RCX{=}CXR' + X_2 \longrightarrow RCX_2CX_2R'$$

Some specific examples of such reactions are

$$CH_3(CH_2)_3C{\equiv}CH + HBr \xrightarrow[\text{FeBr}_3\ 15^\circ]{\text{inhibitor}} \underset{\substack{(40\%)\\ \text{2-bromo-1-hexene}}}{CH_3(CH_3)_3CBr{=}CH_2}$$



(20%)
(E)-1,2-dichloro-1-propene

(63%)
1,1,2,2-tetrachloropropane

Although addition across a triple bond is a more exothermic process than comparable addition across a double bond, alkynes are generally less reactive than alkenes towards electrophilic reagents. This apparent anomaly is rationalized by comparison of the intermediate carbonium ions produced from alkynes and alkenes.

$$RC{\equiv}CH + Y^+ \longrightarrow \underset{\text{a vinyl cation}}{R\overset{+}{C}{=}CHY}$$

$$RCH{=}CH_2 + Y^+ \longrightarrow \underset{\text{an alkyl cation}}{R\overset{+}{C}HCH_2Y}$$

The carbonium ion produced from the alkyne is a vinyl cation, $R\overset{+}{C}{=}CHY$, whose electronic structure is shown in Figure 13.10. This type of carbonium ion is substantially less stable than an ordinary alkyl cation such as $R\overset{+}{C}HCH_2Y$.

Vinyl cations can also be produced by S_N1 reactions of vinylic halides. We will return to this topic in Section 13.7.

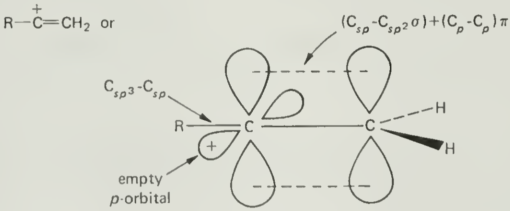
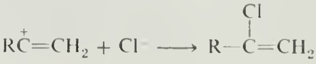

$R-\overset{+}{C}{=}CH_2$ or
$(C_{sp}\text{-}C_{sp^2}\sigma)+(C_p\text{-}C_p)\pi$
$C_{sp^3}\text{-}C_{sp}$
R
C
C
H
H
+
empty p-orbital

FIGURE 13.10 *Electronic structure of a vinyl cation,* $R\overset{+}{C}{=}CH_2$.

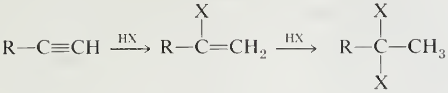
Once formed, the vinyl cation reacts with whatever nucleophiles are present. For example, the overall reaction with HCl involves initial formation of the vinyl cation, followed by its reaction with chloride ion.

$$RC{\equiv}CH + H^+ \longrightarrow R\overset{+}{C}{=}CH_2$$



$$R\overset{+}{C}{=}CH_2 + Cl^- \longrightarrow R-\overset{\overset{\displaystyle Cl}{|}}{C}{=}CH_2$$

The initially formed vinyl halide also undergoes electrophilic addition. In this case the product is a *gem*-dihaloalkane.

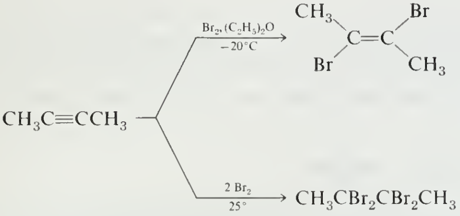


$$R{-}C{\equiv}CH \xrightarrow{HX} R{-}\overset{X}{\overset{|}{C}}{=}CH_2 \xrightarrow{HX} R{-}\underset{X}{\overset{X}{C}}{-}CH_3$$

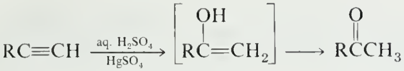
a *gem*-dihaloalkane

The addition can normally be stopped at the intermediate alkenyl halide stage.

The addition of halogen to a triple bond can also be stopped after the addition of 1 mole equivalent. The dihaloalkene produced generally has the *trans* structure.



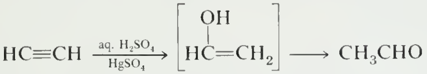
In reactions with aqueous sulfuric acid the intermediate carbonium ion reacts with water to produce an intermediate vinyl alcohol, $RC(OH){=}CH_2$. This reaction is poor with sulfuric acid alone but is catalyzed by mercuric salts. Vinyl alcohols are unstable and rearrange immediately under the reaction conditions to give either an aldehyde or a ketone (Section 15.6).



$$RC{\equiv}CH \xrightarrow[HgSO_4]{aq.\ H_2SO_4} \left[R\overset{OH}{\overset{|}{C}}{=}CH_2 \right] \longrightarrow R\overset{O}{\overset{\|}{C}}CH_3$$

a vinyl alcohol a ketone

Since the addition follows Markovnikov's rule, acetylene itself is the only alkyne that undergoes hydration to give an aldehyde.



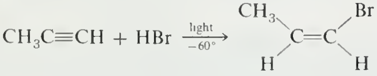
$$HC{\equiv}CH \xrightarrow[HgSO_4]{aq.\ H_2SO_4} \left[H\overset{OH}{\overset{|}{C}}{=}CH_2 \right] \longrightarrow CH_3CHO$$

acetaldehyde

The reaction is a useful method for synthesizing a few special kinds of ketones. We shall discuss it further in that context in Section 15.5.C.

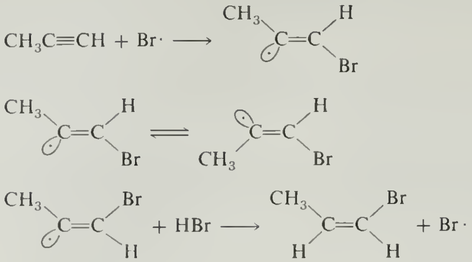
C. *Radical Additions*

Radicals and atoms add to triple bonds just as they do to double bonds. Again, anti-Markovnikov orientation is observed.



(88%)
(Z)-1-bromopropene

The reaction is a radical chain process involving the following propagation steps:



As shown in this example, such reactions frequently give net *trans* addition, but there are many exceptions. In cases where *trans* addition is observed, it appears that the intermediate vinyl radical reacts with HBr from its more accessible side.

D. *Nucleophilic Additions*

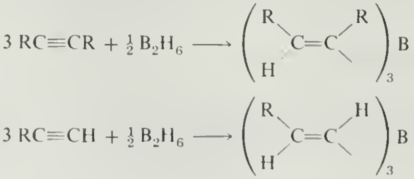
Unlike simple alkenes, alkynes undergo nucleophilic addition reactions. For example, acetylene reacts with alkoxides in alcoholic solution to yield vinyl ethers. The reaction usually requires conditions of high temperature and pressure.

$$HC\equiv CH + RO^- \xrightarrow[\substack{150^\circ C\\ \text{pressure}}]{ROH} ROCH{=}CH^- \xrightarrow{ROH} ROCH{=}CH_2 + RO^-$$

The reaction of a stable alkoxide ion to produce a less stable and more basic vinyl anion may seem surprising. However, the addition also involves the formation of a strong C—O bond at the expense of the relatively weak "third bond" of a triple bond. The net effect of stronger bonding is more than enough to compensate for the creation of a stronger base. The intermediate vinyl anion is immediately protonated by the alcohol solvent to regenerate the alkoxide ion.

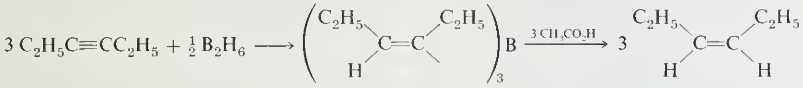
E. *Hydroboration*

Hydroboration of alkynes is a useful laboratory process for the synthesis of several types of compounds. Diborane reacts with alkynes at 0° to produce the intermediate trivinylborane.

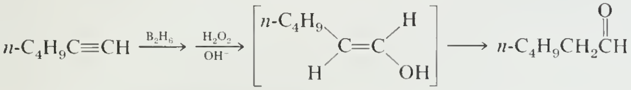


The reaction is generally useful for terminal alkynes. As with alkenes, the boron adds to the terminal carbon. The reaction is also useful with symmetrical disubstituted acetylenes. Unsymmetrical disubstituted acetylenes generally give a mixture of products. The net reaction is *cis* addition of H—BR$_2$ to the triple bond.

The resultant vinylboranes, like alkylboranes (Section 12.6.D), enter into several useful reactions. They undergo protonolysis to give the resulting alkene when treated with acetic acid. Protonolysis involves replacement of boron by the hydrogen of the carboxylic acid with *retention of configuration*. The overall process of hydroboration-protonolysis is a method for accomplishing *cis* hydrogenation of an alkyne to an alkene.



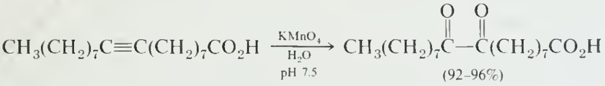
The C—B bond of a vinylborane can also be cleaved oxidatively with alkaline hydrogen peroxide. The initial product is a vinyl alcohol that rearranges quantitatively to the corresponding aldehyde or ketone (Section 15.6).



The overall effect of hydroboration-oxidation is that of hydration of the triple bond. Note that with terminal alkynes, the *aldehyde* is formed (anti-Markovnikov hydration) whereas with direct H_2SO_4-$HgSO_4$ hydration the *ketone* is produced.

F. *Oxidation*

Disubstituted acetylenes undergo oxidation by permanganate to yield 1,2-diketones and/or cleavage products. In a few cases, the reaction is a useful synthetic method for preparing 1,2-diketones.



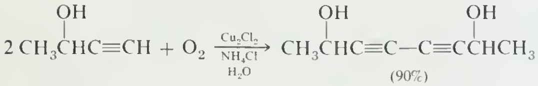
$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H \xrightarrow[\text{pH 7.5}]{\substack{KMnO_4\\H_2O}} CH_3(CH_2)_7\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}(CH_2)_7CO_2H \quad (92\text{–}96\%)$$

More vigorous conditions generally lead to cleavage in which mixtures of carboxylic acids result.

$$RC{\equiv}CR' \xrightarrow[100^\circ C]{\text{aq. }KMnO_4} RCO_2H + R'CO_2H$$

Although such cleavage reactions have been used to locate the position of a triple bond in a molecule, they are not generally useful synthetic procedures because yields are frequently poor.

Terminal alkynes undergo an **oxidative coupling** reaction, often referred to as the Glaser reaction. The reaction is carried out by treating the 1-alkyne with an aqueous cuprous chloride–ammonium chloride solution in an atmosphere of oxygen. The coupled diyne is formed in high yield.

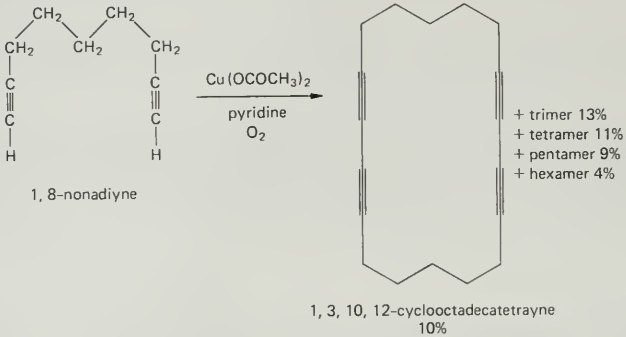


$$2\,CH_3\overset{OH}{\overset{|}{C}}HC{\equiv}CH + O_2 \xrightarrow[\substack{NH_4Cl\\H_2O}]{Cu_2Cl_2} CH_3\overset{OH}{\overset{|}{C}}HC{\equiv}C-C{\equiv}C\overset{OH}{\overset{|}{C}}HCH_3 \quad (90\%)$$

octa-3,5-diyne-2,7-diol

$$n\text{-}C_4H_9C{\equiv}CH \xrightarrow[\text{pyridine, }60^\circ C]{CuCl_2} \underset{\substack{(90\%)\\ \text{5,7-dodecadiyne}}}{n\text{-}C_4H_9C{\equiv}C{-}C{\equiv}CC_4H_9}$$

The oxidative coupling reaction has recently been used to prepare macrocyclic dimers, trimers, and so on, of diacetylenes.


CH2
CH2
CH2
CH2
CH2
C
C
H
C
C
H
1, 8-nonadiyne
Cu(OCOCH3)2
pyridine
O2
+ trimer 13%
+ tetramer 11%
+ pentamer 9%
+ hexamer 4%
1, 3, 10, 12-cyclooctadecatetrayne
10%

A related reaction is the Nieuwland enyne synthesis. This dimerization reaction is usually carried out by treating the alkyne with a mixture of cuprous chloride, ammonium chloride, and HCl. The reaction is an important industrial process for the synthesis of vinylacetylene.

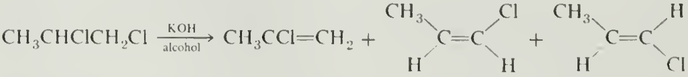
$$2\,HC{\equiv}CH \xrightarrow[HCl]{Cu_2Cl_2,\ NH_4Cl} \underset{\text{vinylacetylene}}{HC{\equiv}C{-}CH{=}CH_2}$$

13.7
Vinyl halides

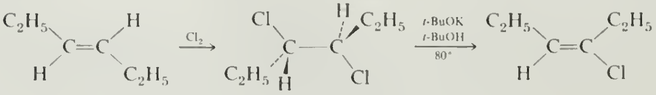
Alkenyl halides may be prepared by addition of 1 mole of hydrogen halide to an alkyne, often with the aid of a mild Lewis acid catalyst.

$$CH_3C{\equiv}CH + HCl \xrightarrow{CuCl} CH_3CCl{=}CH_2$$

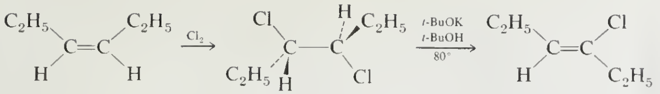
Alcoholic dehydrohalogenation of 1 mole of HX from a vicinal dihalide generally gives a mixture of possible haloalkenes.


CH3CHClCH2Cl
KOH
alcohol
CH3CCl=CH2 +
CH3
Cl
C=C
H
H
+
CH3
H
C=C
H
Cl

However, the *vic*-dichlorides obtained from symmetrical olefins give good yields of single products.

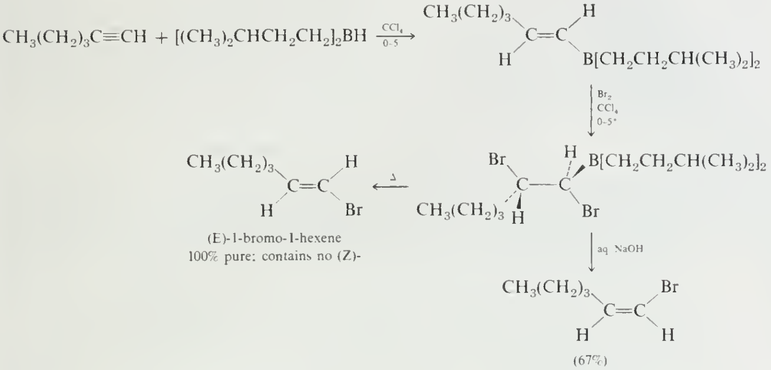

C2H5
H
C=C
H
C2H5
Cl2
Cl
H
C2H5
C—C
C2H5
H
Cl
t-BuOK
t-BuOH
80°
C2H5
C2H5
C=C
H
Cl

3-chloro-*cis*-3-hexene



3-chloro-*trans*-3-hexene

The hydroboration reaction of alkynes followed by bromination provides a convenient laboratory route to individual geometric isomers of vinyl bromides.



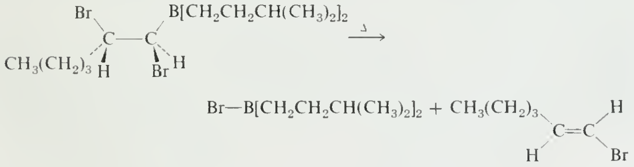
(E)-1-bromo-1-hexene
100% pure; contains no (Z)-

(67%)
(Z)-1-bromo-1-hexene
95% pure; contains 5% of (E)-

The intermediate dialkylborane is prepared by reaction of diborane with 3-methyl-1-butene. Because of steric effects, the addition occurs only twice.

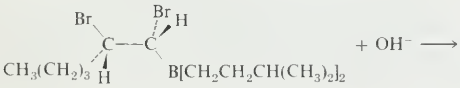
$$4(CH_3)_2CHCH{=}CH_2 + B_2H_6 \longrightarrow 2\,[(CH_3)_2CHCH_2CH_2]_2BH$$

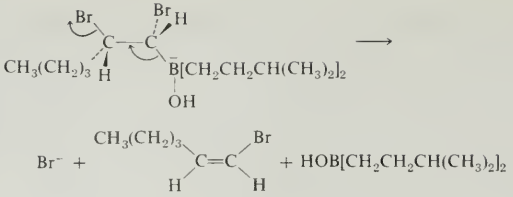
In the reaction sequence to the bromoalkene, the intermediates are not isolated. If the reaction mixture containing the dibromoborane is heated, a thermal *cis* elimination occurs.



Such pyrolytic *cis* eliminations will be discussed in greater detail in Section 18.12.

Treatment of the intermediate dibromoborane with base, however, gives a reaction related to an E_2 elimination to provide the other bromoalkene isomer in good yield and with high stereochemical purity.





Haloalkenes in which the halogen is attached directly on the double bond have exceptionally low reactivity in S_N1 and S_N2 reactions. For example, 1-chloropropene is inert to potassium iodide in acetone under conditions where *n*-propyl chloride undergoes rapid S_N2 substitution.

$$CH_3CH_2CH_2Cl + I^- \longrightarrow CH_3CH_2CH_2I + Cl^- \qquad \text{fairly fast}$$

$$CH_3CH{=}CHCl + I^- \longrightarrow \text{no reaction}$$

Similarly, simple alkenyl halides do not give carbonium ions—S_N1 reactions for such halides are so slow that other kinds of reactions occur instead, such as addition to the multiple bond. The relative difficulty of ionizing a vinylic C—Cl bond is shown by the gas phase enthalpies:

	$\Delta H°$, kcal mole^{-1}
$CH_3Cl \longrightarrow CH_3^+ + Cl^-$	227
$CH_3CH_2Cl \longrightarrow CH_3CH_2^+ + Cl^-$	191
$CH_2{=}CHCl \longrightarrow CH_2{=}CH^+ + Cl^-$	223
$(CH_3)_2CHCl \longrightarrow (CH_3)_2CH^+ + Cl^-$	170

The difference between the energy required to form a vinyl cation compared to a simple primary carbonium ion is comparable to the difference between primary and secondary carbonium ions. Recall that secondary carbonium ions are common intermediates in many reactions but that simple primary carbonium ions are virtually unknown in solution. Primary vinyl cations are similarly unknown in S_N1 reactions; however, secondary vinyl cations of the type $R\overset{+}{C}{=}CH_2$ have apparently been detected under special conditions. They are not important in most organic reactions of the simple vinyl halides.

This lack of reactivity is explained most simply as an increased difficulty in removing an atom with its pair of electrons from a bond to a vinyl orbital with its higher *s* character than from a simple primary sp^3 orbital. The increased strength of the vinyl-halogen bond compared to the ethyl-halogen bond is manifest also in the relative bond lengths as shown in the following examples:

	r(C—X), Å
$CH_3CH_2{-}Cl$	1.78
$CH_2{=}CH{-}Cl$	1.72
$CH_3CH_2{-}Br$	1.94
$CH_2{=}CH{-}Br$	1.89

The sp^2 carbon orbital involved in the vinyl halide bond is expected to produce a shorter and stronger bond than the ethyl sp^3 orbital. However, an additional component leading to a still shorter and stronger bond is π overlap between the

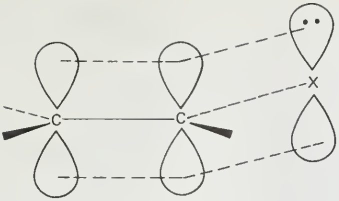


FIGURE 13.11 *π orbital overlap in a vinyl halide.*

π orbital of the double bond and a lone pair orbital of the halogen as depicted in Figure 13.11.

Such π overlap can also be represented by resonance involving Lewis structures:

$$\left[CH_2{=}CH{-}\ddot{\underset{..}{X}}: \longleftrightarrow \overset{-}{C}H_2{-}CH{=}\overset{+}{\underset{..}{X}}:\right]$$

As a result of such overlap the C—X bond in a vinyl halide has *partial double bond character*. The amount of double bond character (that is, the contribution of resonance structure $^-CH_2{-}CH{=}X^+$) is relatively small but has a significant effect on reactivity.

One useful and important reaction of vinyl halides involves their conversion to derivatives of carbanions such as Grignard reagents. The reaction of alkenyl bromides usually does not go well in ethyl ether, but the Grignard reagents are generally formed smoothly and in good yield if carried out in tetrahydrofuran.

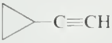
$$CH_3CH{=}CHBr \xrightarrow[\text{THF}]{\text{Mg}} \underset{(>80\%)}{CH_3CH{=}CHMgBr}$$

This reaction proceeds even at rather low temperature (−45°). Vinyl chloride itself also forms the Grignard reagent, but the reaction does not work satisfactorily with other alkenyl chlorides.

In this preparation of Grignard reagents, the configuration at the halo-carbon is lost; that is, a mixture of *cis* and *trans* alkene products is usually produced.

PROBLEMS

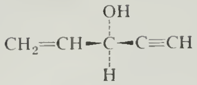
1. Write out the structure corresponding to each of the following names:
(a) methylisopropylacetylene
(b) (R)-3-methyl-1-pentyne
(c) vinylacetylene
(d) 1-ethynylcyclohexanol
(e) cyclodecyne
(f) isobutylacetylene
(g) methyl ethynyl ether
(h) 1-methylthio-1-butyne
(i) pent-2-yn-1-ol
(j) 3-methoxy-1-pentyne

2. Give an acceptable name for each of the following structures:
(a) $BrCH_2CH_2CH_2CH_2C{\equiv}CH$
(b) $(CH_3)_3CC{\equiv}CCH_2CH_3$
(c) $CH_2{=}CHI$
(d) 

(e) $C_6H_5C{\equiv}CCH_2C(CH_3)_3$

(f) $BrC{\equiv}CCH_3$

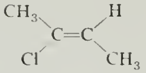
(g) $HC{\equiv}CCH_2Br$

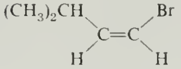
(h) 
$CH_2{=}CH{-}\overset{OH}{\underset{H}{C}}{-}C{\equiv}CH$

(i) $HOCH_2C{\equiv}CCH_2OH$

(j) $(CH_3)_2CHC{\equiv}CCH_2CH_3$

(k) $CH_2{=}CHCH_2CH_2C{\equiv}CH$

(l) 

(m) 

(n) $CH_3CHClC{\equiv}CCH_2CH_3$

3. Give the principal reaction product(s) for the reaction of 1-butyne with each of the following reagents. If no reaction is expected, so indicate with N.R.
(a) hot aq. $KMnO_4$
(b) H_2/Pt
(c) excess Br_2/CCl_4, 0°
(d) aq. NaCl
(e) aq. $AgNO_3$
(f) (i) B_2H_6; (ii) H_2O_2, NaOH
(g) aq. H_2SO_4; Hg^{2+}
(h) (i) B_2H_6; (ii) CH_3COOD
(i) H_2 (1 mole)/Pd ($BaSO_4$)-quinoline
(j) Cu_2Cl_2, NH_4Cl, O_2

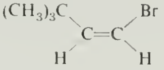
4. Answer problem 3 for 2-butyne.

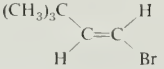
5. Sketch the nmr spectrum expected for each of the following compounds. Indicate the number of peaks expected, the approximate δ value for each group of peaks, and their area.

(a) $(CH_3)_3CC{\equiv}COCH_3$

(b) $CH_3C{\equiv}CH$

(c) $CH_3CHBrC{\equiv}CH$

(d) 

(e) 

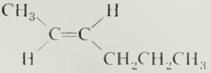
6. Using propyne as the only source of carbon, devise practical syntheses for the following compounds:

(a) $(CH_3)_2CHBr$

(b) CH_3COCH_3

(c) CH_3CH_2CHO

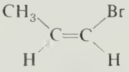
(d) $CH_3(CH_2)_4CH_3$

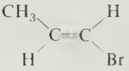
(e) 

(f) $CH_3CHCl{-}CH_2$

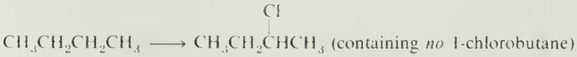
(g) $CH_3CBr_2CBr_2D$

(h) $CH_3C{\equiv}C{-}C{\equiv}CCH_3$

(i) 

(j) 

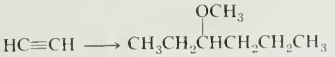
7. Show how each of the following conversions may be accomplished in good yield.

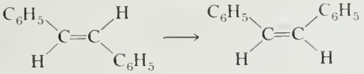
(a) 
$CH_3CH_2CH_2CH_3 \longrightarrow CH_3CH_2\overset{Cl}{C}HCH_3$ (containing *no* 1-chlorobutane)

(b) $CH_3CH_2CH_2CH{=}CH_2 \longrightarrow CH_3CH_2CH_2C{\equiv}CH$

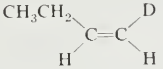
(c) $CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2C{\equiv}CCH_3$

(d) $HC{\equiv}CH \longrightarrow CH_3CH_2CH_2CH_2OH$

(e) 
$HC\equiv CH \longrightarrow CH_3CH_2CH(OCH_3)CH_2CH_2CH_3$

(f) 

(g) $CH_3CH_2CH_2OH \longrightarrow CH_3COCH_3$

(h) $CH_3CH_2C\equiv CH \longrightarrow$ 

(i) $CH_3CH_2C\equiv CH \longrightarrow CH_3CH_2CD{=}CH_2$

8. From isopentyl alcohol (3-methyl-1-butanol), acetylene, and any required straight chain primary alcohols, derive a practical synthesis for 2-methylheptadecane, the sex-attractant for the Tiger moth (Section 4.7).

9. Muscalure, *cis*-9-tricosene, is the sex-attractant insect pheromone of the common housefly. Give a practical synthesis of this compound from acetylene and straight chain alcohols.

10. By inspection of the conformations of propylene bromide, give a reasonable explanation for the fact that reaction with base gives mostly (E)-1-bromopropene and little (Z)-1-bromopropene.

11. The pK_as of ethane, ethylene, and acetylene are approximately 50, 44, and 25, respectively.

(a) The pK_a of NH_3 in liquid ammonia is approximately 35. What is the equilibrium constant for the following equilibrium in liquid ammonia for each of the above hydrocarbons:

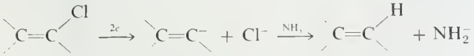
$$RH + NH_2^- \rightleftharpoons R^- + NH_3$$

Assume that the above pK_as apply unchanged to a liquid ammonia solution. Note that this is a gross approximation but the above values are themselves approximations.

(b) If each hydrocarbon is treated with sodium amide in liquid ammonia and the resulting solution then treated with methyl iodide, different results are obtained. There is no reaction with ethane or ethylene, but acetylene gives a good yield of propyne. Explain this observation using the results in (a).

(c) The bond dissociation energies, $DH°$, for the C—H bonds are ethane, 98; ethylene, 108; acetylene, 120 kcal mole^{-1}. The C—H bonds are progressively harder to break along this series, yet the compounds are increasingly acidic. Explain this apparent paradox.

12. Alkenyl chlorides react with a solution of sodium in liquid ammonia to replace the Cl by H with retention of configuration. This reaction may be regarded as a reduction with solvated electrons to produce a vinyl anion:



(a) What does the stereochemistry of the reaction reveal concerning the geometrical structure and configurational stability of the intermediate vinyl anion?

(b) This reaction is used in a sequence to invert the configuration of internal olefins. Show how *trans*-3-hexene may be converted to *cis*-3-hexene by use of this reaction as the final step.

13. The hydration of alkynes is catalyzed by Hg^{2+}. Write a mechanism for the hydration that accounts for this catalysis. (*Hint*: The mercuric ion adds to the triple bond to give a mercuri-carbonium ion).

14. Compound A has the formula C_8H_{12} and is optically active. It reacts with hydrogen in the presence of platinum metal to give B, which has the formula C_8H_{18} and is optically inactive. Careful hydrogenation of A using H_2 and Lindlar's catalyst gives C, which has the formula C_8H_{14} and is optically active. Compound A reacts with sodium in ammonia to give D, which also has the formula C_8H_{14} and is optically inactive. What are compounds A to D?

15. Compound E has the formula C_7H_{12}. It reacts with dry HCl at −20° to give F, $C_7H_{13}Cl$. Compound F reacts with potassium *t*-butoxide in *t*-butyl alcohol to give a small amount of E and mainly G, which has the formula C_7H_{12}. Ozonization of G gives cyclohexanone and formaldehyde. What are compounds E to G?

16. The reaction of (Z)-1,5-dibromo-1-pentene with ethanolic $NaOC_2H_5$ can give principally (Z)-1-bromo-5-ethoxy-1-pentene, 5-ethoxy-1-pentyne, or 2,5-diethoxy-1-pentene, depending on the reaction conditions. Explain. Why is 1,5-diethoxy-1-pentene not a principal product under any of these conditions?

17. The table of Bond Dissociation Energies in Appendix II gives values of $DH°$ for $CH_2{=}CH{-}Cl$ and $CH_2{=}CH{-}Br$. Compare with the corresponding values for ethyl halides and explain any difference. Estimate $DH°$ for vinyl fluoride and vinyl iodide.

CHAPTER 14
Infrared Spectroscopy

14.1
The Electromagnetic Spectrum

There are many different forms of radiant energy—cosmic rays, x-rays, radio waves, visible light—that display wave properties. These apparently different types of radiation are known collectively as **electromagnetic radiation.** They are all considered as waves that travel at a constant velocity (the "speed of light", $c = 3.0 \times 10^{10}$ cm sec^{-1}) and differ in wavelength or frequency. The **electromagnetic spectrum** is diagrammed in Figure 14.1, along with the wavelength in centimeters of its various regions. The divisions between regions are arbitrary and are established in practice by the different instrumentation required to produce and record electromagnetic radiation in the different regions. As pointed out in Section 10.2, compounds may absorb radiant energy in various regions of the electromagnetic spectrum and thereby become excited from their ground state to a more energetic state. **Spectroscopy** is a technique whereby we measure the amount of radiation a substance absorbs at various wavelengths. From the

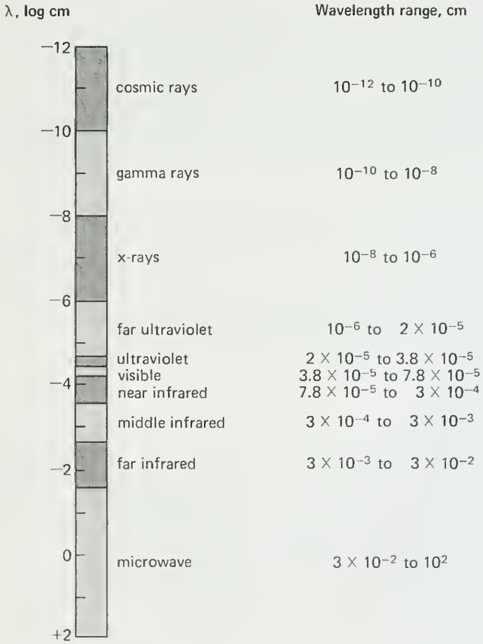

λ, log cm
Wavelength range, cm
−12
cosmic rays
10^{-12} to 10^{-10}
−10
gamma rays
10^{-10} to 10^{-8}
−8
x-rays
10^{-8} to 10^{-6}
−6
far ultraviolet
10^{-6} to 2×10^{-5}
ultraviolet
2×10^{-5} to 3.8×10^{-5}
visible
3.8×10^{-5} to 7.8×10^{-5}
−4
near infrared
7.8×10^{-5} to 3×10^{-4}
middle infrared
3×10^{-4} to 3×10^{-3}
−2
far infrared
3×10^{-3} to 3×10^{-2}
0
microwave
3×10^{-2} to 10^{2}
+2

FIGURE 14.1 *The electromagnetic spectrum.*

spectrum of a compound, we may often obtain useful information about the structure of the compound.

The relationship between the wavelength and frequency of radiation is given by

$$\nu = \frac{c}{\lambda}$$

where λ = wavelength in centimeters, ν = frequency in Hertz (Hz), and c = the velocity of light (2.998×10^{10} cm sec^{-1}). The relationship between energy and frequency is

$$\varepsilon = h\nu$$

where ε = the energy of a photon and h = Planck's constant (6.6242×10^{-27} erg sec), or

$$E = Nh\nu$$

where E = the energy of an Avogadro's number, N, of photons ($E = \varepsilon \times 6.023 \times 10^{23}$). Thus, when a compound absorbs radiation of a given wavelength, each molecule absorbs an amount of energy ε and each mole of the compound absorbs an amount of energy E. In organic chemistry, energy is traditionally expressed in units of kilocalories per mole:

$$E(\text{kcal mole}^{-1}) = \frac{2.857 \times 10^{-3}}{\lambda(\text{cm})}$$

Another system of units that is being adopted in many parts of the world is known as SI (Systéme International d'Unites). In this international system of units, the unit of energy is the joule, J; 1 cal $\equiv$ 4.184 J. The six fundamental units in SI are: length = meters (m), mass = kilograms (kg), time = seconds (s), electrical current = amperes (A), temperature = degrees Kelvin (°K), and luminosity = candelas (cd). These units are modified by 10^3 (kilo), 10^6 (mega), 10^{-3} (milli), 10^{-6} (micro), 10^{-9} (nano), 10^{-12} (pico). Many traditional units among chemists, such as calories (cal) or kilocalories (kcal) and centimeters (cm), are still in common use.

In this chapter, we are concerned with absorption of light in the **infrared** region of the electromagnetic spectrum. Wavelengths in this region are traditionally expressed in microns (μ), where $10^4\ \mu = 1$ cm. More commonly, another unit of measurement, the wave number, is used to describe infrared spectra. The wave number ($\tilde{\nu}$) is defined as the number of waves per centimeter and is expressed in units of cm^{-1} (reciprocal centimeters):

$$\tilde{\nu} = \frac{1}{\lambda}$$

By definition, the infrared region is split up into three parts (Figure 14.2): the **near infrared** ($\lambda = 0.78$–$3.0\ \mu$; $\tilde{\nu} = 12{,}820$–3333 cm^{-1}), the **middle infrared** ($\lambda = 3$–$30\ \mu$; $\tilde{\nu} = 3333$–333 cm^{-1}), and the **far infrared** ($\lambda = 30$–$300\ \mu$; $\tilde{\nu} = 333$–33 cm^{-1}). The near infrared region corresponds to energies in the range 37–10 kcal mole^{-1}. Since there are few absorptions of organic molecules in this range, it is seldom used for spectroscopic purposes. Radiation in the middle infrared region has $E = 10$–1 kcal mole^{-1}, which corresponds to the differences commonly encountered between vibrational states. Spectroscopy in this region is extremely

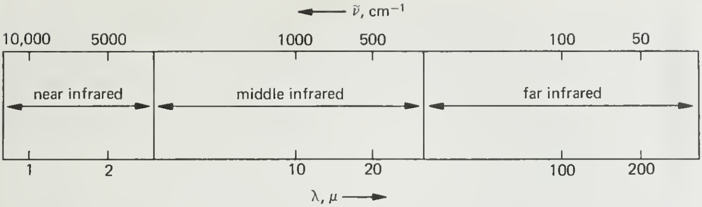

$\tilde{\nu}$, cm^{-1}
10,000
5000
1000
500
100
50
near infrared
middle infrared
far infrared
1
2
10
20
100
200
λ, μ

Figure 14.2 *Regions of the infrared spectrum. Notice that the scales are logarithmic.*

useful to the organic chemist. The far infrared region has $E = 1.0$–0.1 kcal mole^{-1}. This region has been little used for organic spectroscopy, again because few useful absorptions occur here.

14.2
Molecular Vibration

As discussed previously (Section 5.1), atoms in a molecule do not maintain fixed positions with respect to each other but actually vibrate back and forth about an average value of the interatomic distance. This vibrational motion is quantized, as shown in the accompanying familiar diagram for a diatomic molecule (Figure 14.3). At room temperature, most of the molecules in a given sample will be in the lowest vibrational state. However, absorption of light of the appropriate energy allows the molecule to become "excited" to the second vibrational level. In this level, the amplitude of the molecular vibration is greater. In general, such absorption of an infrared light quantum can occur only if the dipole moment of the molecule is different in the two vibrational levels. The variation of the dipole moment with the change in interatomic distance during the vibration corresponds

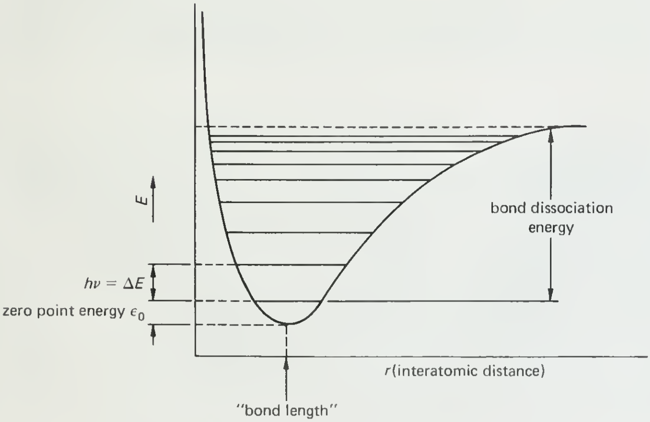

E
bond dissociation energy
$h\nu = \Delta E$
zero point energy ϵ_0
r(interatomic distance)
"bond length"

Figure 14.3 *Vibrational levels for vibrating bond.*

to an oscillating electric field that can interact with the oscillating electric field associated with electromagnetic radiation. The requirement that absorption of a vibrational quantum be accompanied by a change in dipole moment is known as a **selection rule.** Such a vibrational transition is said to be **infrared active.** Vibrational transitions that do not result in a change of dipole moment of the molecule are not observed directly and are referred to as **infrared inactive** transitions. Thus, carbon monoxide and iodine chloride absorb infrared light but hydrogen, nitrogen, chlorine, and other symmetrical diatomics do not.

$C{\equiv}O$, $I{-}Cl$	H_2, N_2, Cl_2
absorb in infrared	*do not absorb in infrared*

For more complex molecules, there are more possible vibrations. A nonlinear molecule containing n atoms has $3n$–6 possible **fundamental vibrational modes.** For polyatomic molecules, there are two distinct types of molecular vibration, **stretching** and **bending.** Vibrations of bonds involving hydrogens are especially significant because atoms of low mass tend to do a lot of moving compared to atoms of higher mass. The stretching and bending motions in a methylene group are diagrammed in Figure 14.4.

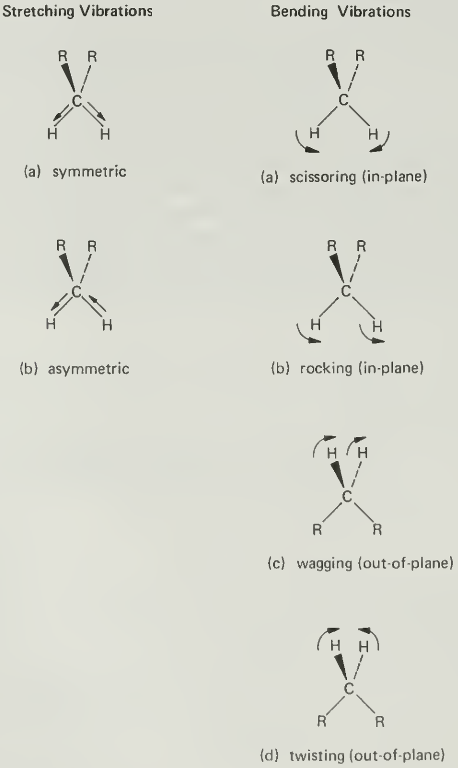

Stretching Vibrations
Bending Vibrations
R
R
C
H
H
(a) symmetric
(a) scissoring (in-plane)
(b) asymmetric
(b) rocking (in-plane)
(c) wagging (out-of-plane)
(d) twisting (out-of-plane)

FIGURE 14.4 *Some vibrational modes for the methylene group.*

Table 14.1

Compound	Possible Infrared Absorption Bands
pentane	45
decane	90
triacontane	270

For polyatomic molecules of the size of typical organic compounds, the possible number of infrared absorption bands becomes very large, as the examples in Table 14.1 demonstrate. Many of these vibrations occur at the same frequency (that is, some vibrations are **degenerate**), and not all of the possible bands are generally seen as independent absorptions. However, additional bands, usually of low intensity, may occur as **overtones** (at approximately $\frac{1}{2}$, $\frac{1}{3}$, $\frac{1}{4}$, . . . , and so on, the wavelength of the fundamental node).

Overtones may arise in two ways. If a molecule in the lowest or first vibrational state is excited to the third vibrational level, the energy required is almost twice that required for excitation to the second vibrational level. It is not exactly twice as much, because the higher levels tend to lie closer together than the lower levels (see Figure 14.3).

Another type of overtone, commonly referred to as a **combination band**, occurs when a single photon has precisely the correct energy to excite two vibrations at once. For this to happen, the energy of the combination band must be the exact sum of the two independent absorptions.

As a result, the infrared spectrum of an organic compound is usually rather complex.

The spectrum of *n*-octane, shown in Figure 14.5, illustrates several features of an infrared spectrum. Note that the wavelength is plotted against the per cent transmittance of the sample. An absorption band is therefore represented by a "trough" in the curve; zero transmittance corresponds to 100% absorption of light of that wavelength.

The curve in Figure 14.5 is a spectrum of pure *n*-octane. The spectrum was measured on a Perkin-Elmer model 735 spectrometer, using a cell 0.016 mm in length. Only four major absorption bands are apparent, at 2925, 1465, 1380, and

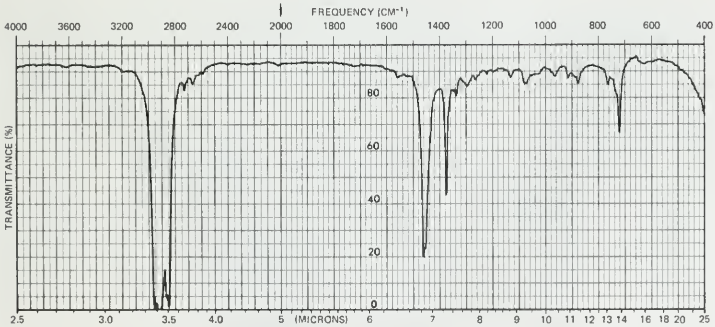


Figure 14.5 *Infrared spectrum of* n-*octane,* 0.016-mm *cell.*

720 cm^{-1}. These four bands correspond to the C—H stretching vibrations, the CH_2 and CH_3 scissoring mode, the CH_3 rocking mode, and the CH_2 rocking mode, respectively. Figure 14.6 is a spectrum of the same sample, but measured in a cell 0.20 mm long. Since the amount of light absorbed is proportional to the number of molecules encountered by the beam as it passes through the sample, the longer cell allows absorption bands of low intensity to be observed. Many more bands can now be seen, especially in the region from 700 to 1300 cm^{-1}.

Because of its complexity, the spectrum cannot be analyzed completely. However, a peak-by-peak correspondence in the infrared spectra of two different samples is an excellent criterion of identity, as a comparison of the *n*-octane spectrum in Figure 14.6 with the *n*-heptane spectrum in Figure 14.7 readily shows. That is, the ir spectrum of *n*-heptane is similar to but differs in significant respects from that of *n*-octane.

Molecular vibrations are actually rather complex. Generally, all of the atoms in a molecule contribute to a vibration. Fortunately, however, some molecular vibrations can be treated by considering the motion of a few atoms relative to one another and ignoring the rest of the atoms in the molecule. For example, it is convenient to refer to the vibration of individual bonds. To a useful approximation (the **harmonic oscillator approximation**), the vibration frequency of a bond

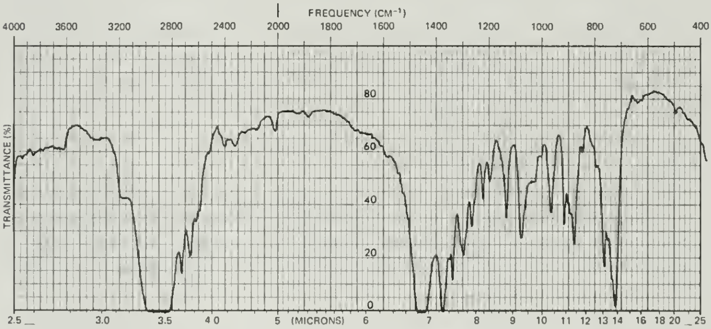


FIGURE 14.6 *Infrared spectrum of* n-*octane*, 0.2-mm *cell.*

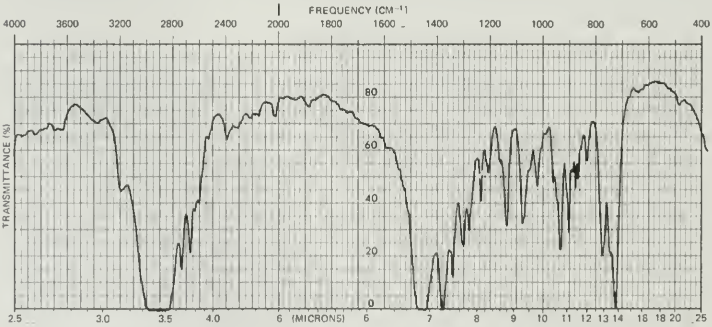


FIGURE 14.7 *Infrared spectrum of* n-*heptane*, 0.2-mm *cell.*

may be related to the masses of the vibrating atoms and the force constant, f, of the vibrating bond by equation (14-1). This equation corresponds to a simple Hooke's law model of two units coupled by a spring in which the force constant is the restoring force provided by the spring.

$$\tilde{\nu} = \frac{1}{2\pi c}\sqrt{\frac{f(m_1 + m_2)}{m_1 m_2}} \tag{14-1}$$

where $\tilde{\nu}$ = vibrational frequency in cm^{-1} (wave number)
c = velocity of light in cm sec^{-1}
m_1 = mass of atom 1 in g
m_2 = mass of atom 2 in g
f = force constant in dyne cm^{-1} (g sec^{-2})

The larger the force constant, the higher the vibration frequency and the greater the energy spacings between vibrational quantum levels. The force constants for single, double, and triple bonds are approximately 5×10^5, 10×10^5, and 15×10^5 dynes cm^{-1}, respectively.

> Recall that 1 dyne is the force required to accelerate a 1-g mass 1 cm sec^{-2}. Therefore, 1 dyne = 1 g cm sec^{-2}. The units of f, the force constant, are thus g sec^{-2}.

Force constants provide another measure of bond strength and generally are roughly proportional to bond dissociation energies. On the other hand, vibration frequencies relate inversely to the masses of the vibrating atoms. Bonds to hydrogen occur at relatively high frequencies compared to bonds between heavier atoms—a light weight on a spring oscillates faster than a heavy weight.

In spite of its gross assumptions, the Hooke's law approximation is useful, because it helps us to identify the *general region* in which a vibration will occur. For example, we may easily estimate the ^{12}C—^{1}H stretching frequency by

$$\tilde{\nu} = \frac{1}{2\pi\, 2.998 \times 10^{10}\ \text{cm sec}^{-1}} \sqrt{\frac{5 \times 10^5\ \text{g sec}^{-2}\left(\frac{12}{6.023} + \frac{1}{6.023}\right) \times 10^{-23}\ \text{g}}{\left(\frac{12}{6.023} \times 10^{-23}\ \text{g}\right)\left(\frac{1}{6.023} \times 10^{-23}\ \text{g}\right)}}$$

$$\tilde{\nu} = 3032\ \text{cm}^{-1}$$

The actual range for C—H absorptions is 2850–3000 cm^{-1}.

The approximate regions of the infrared spectrum where various bond vibrations are observed depend primarily on whether the bonds are single, double, triple or are bonds to hydrogen. These regions are summarized in Table 14.2.

TABLE 14.2
Approximate Values for Infrared Absorptions

Bond	General Absorption Region, cm^{-1}
C—C, C—N, C—O	800–1300
C=C, C=N, C=O	1500–1900
C≡C, C≡N	2000–2300
C—H, N—H, O—H	2850–3650

14.3
Characteristic Group Vibrations

As was pointed out in the previous section, the infrared spectrum of a polyatomic molecule is so complex that it is usually inconvenient to analyze it completely. However, extremely valuable information may be gleaned from the infrared spectrum of an organic compound using semiempirical methods. Consider the infrared spectra of 1-octene and 1-octadecene, shown in Figures 14.8 and 14.9. Aside from the C—H stretching and bending vibrations at 2925, 1450, and 1370 cm^{-1}, we see several distinctive bands that do not appear in the spectra of typical alkanes (see Figure 14.5). These new bands occur in the following general positions: 3080 cm^{-1}, 1640 cm^{-1}, 995 cm^{-1}, and 915 cm^{-1}. The Hooke's law approximation tells us that the band in the 3080 cm^{-1} region is the C—H stretch of the olefinic C—H bonds, and the 1640 cm^{-1} band is the C=C double bond stretching vibration. Other theoretical considerations suggest that the 995 cm^{-1} and 915 cm^{-1} bands are the olefinic C—H out-of-plane bending modes. The weak band near 1820 cm^{-1} is an overtone of the fundamental band at 915 cm^{-1}.

The absorption bands mentioned above are characteristic of compounds con-

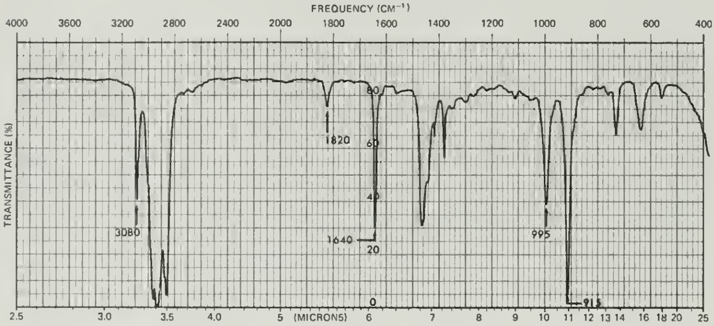


FIGURE 14.8 *Infrared spectrum of* 1*-octene.*

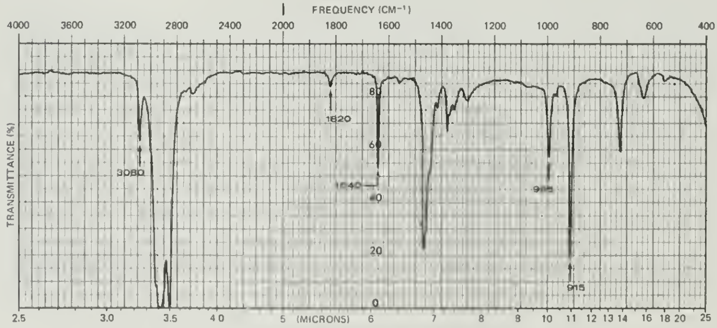


FIGURE 14.9 *Infrared spectrum of* 1*-octadecene.*

taining a C=C double bond and may be used to determine unsaturation in an organic compound. Organic chemists use infrared spectroscopy in this semi-empirical way. Most of the common functional groups give rise to characteristic absorption bands in defined regions of the infrared range. The chemist uses the presence or absence of a band in that region of the infrared spectrum as a diagnosis for the presence or absence of the corresponding functional group in this compound. One example will illustrate this point. The spectrum of 4-bromo-1-butene is shown in Figure 14.10. The spectrum is a fairly complex one, with a number of bands not characteristic of simple alkanes. The bands marked with arrows in Figure 14.10 are all due to vibrational transitions of the double bond. Note in particular the bands at 1842, 995, and 920 cm^{-1}. These bands are highly characteristic absorptions of a terminal vinyl group (R—CH=CH$_2$). The occurrence of these bands in the spectrum is taken as strong evidence for the presence of such a functional group in the molecule. (The bands at 3080 and 1640 cm^{-1}, although characteristic of alkenes, are not specific for compounds containing the group —CH=CH$_2$. As we shall see in a later section, other types of alkenes may also absorb in these regions.)

In the next few sections, we shall consider the characteristic group vibrations for various classes of compounds we have encountered.

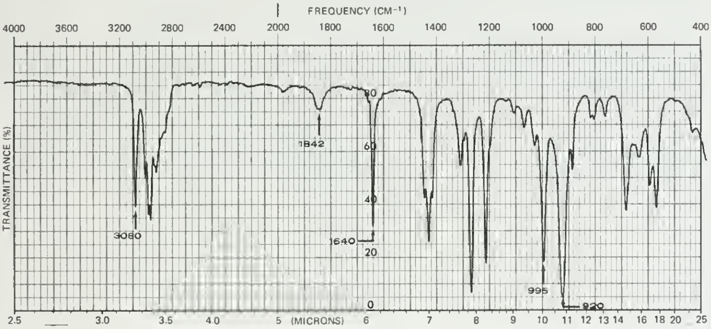


FIGURE 14.10 *Infrared spectrum of 4-bromo-1-butene,* CH$_2$=CHCH$_2$CH$_2$Br.

14.4 Alkanes

As we saw previously, the major bands that appear in the infrared spectra of alkanes are those due to C—H stretching in the 2850–3000 cm^{-1} region, those due to CH$_2$ and CH$_3$ scissoring in the 1450–1470 cm^{-1} region, the band due to CH$_3$ rocking at about 1370–1380 cm^{-1}, and the CH$_2$ rocking bands at 720–725 cm^{-1}. These bands are of only limited diagnostic value because most alkanes contain all of these groupings. Some information may be culled from hydrocarbon spectra, however, if one looks at the fine details of the spectrum. For example, when a molecule has two methyl groups attached to the same carbon, the band at 1370–1380 cm^{-1} always appears as a doublet, rather than as a single peak.

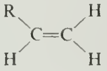
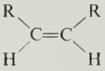
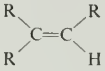
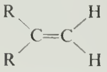
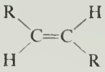
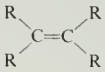
14.5
Alkenes

The alkene C—H stretching vibration occurs at higher wave number (shorter wavelength) than that due to an alkane C—H. Recall that alkene C—H bonds have greater *s* character and are stronger than alkane C—H bonds. Stronger bonds are more difficult to stretch (higher force constant) and require greater energy or higher light frequency. Thus, alkenes that have at least one hydrogen attached to the double bond normally absorb in the region 3050–3150 cm^{-1}. The relative intensity of this band, compared to the band for saturated C—H stretch, is roughly proportional to the relative numbers of the two types of hydrogens in the molecule.

The alkene C=C stretching mode occurs in the region 1645–1670 cm^{-1}. This band is most intense when there is only one alkyl group attached to the double bond. As more alkyl groups are added, the intensity of the absorption diminishes because the vibration now results in a smaller change of dipole moment. For tetrasubstituted alkenes, the band is of such low intensity that it is often not observable.

The C—H out-of-plane bending modes, which give rise to absorption bands in the region from 700 to 1000 cm^{-1}, are extremely useful for diagnosis. The characteristic positions of these bands for various types of alkenes are summarized in Table 14.3.

TABLE 14.3
C—H Out-of-Plane Bending Absorptions of Alkenes

		
910 cm^{-1} 990 cm^{-1}	675–725 cm^{-1}	790–840 cm^{-1}
		
890 cm^{-1}	970 cm^{-1}	none

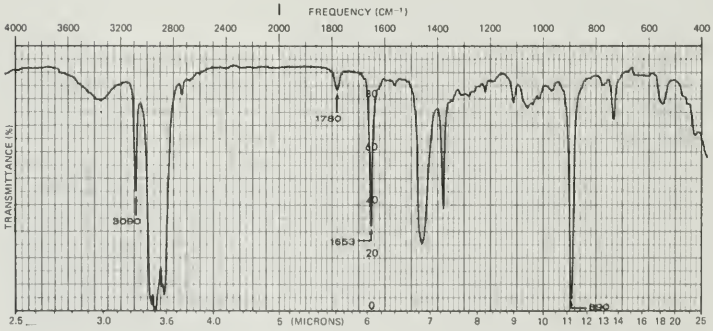


FIGURE 14.11 *Infrared spectrum of 2-methyl-1-heptene.*

The spectra that are reproduced in Figures 14.8–14.9 and 14.11–14.15 illustrate the characteristic vibrational bands of various types of alkenes. It is interesting to note that the C=C stretching band is absent in the spectrum of *trans*-4-octene, because that vibration in this molecule results in no change in dipole moment. The band is also absent in the spectrum of the tetrasubstituted alkene shown in Figure 14.15. Even though a change in dipole moment would result for this vibration, it is so minute that the band is extremely weak. Also note that the C—H out-of-plane bending band gives rise to a characteristic overtone at about 1820 cm^{-1} for alkenes of the type $R-CH=CH_2$ and at 1780 cm^{-1} for alkenes of the type $R_2C=CH_2$, but not for other alkenes.

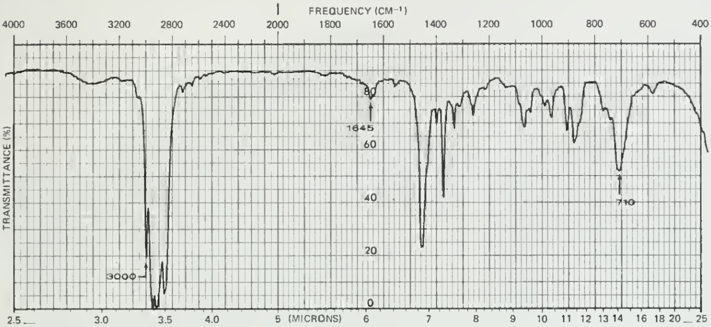


FIGURE 14.12 *Infrared spectrum of* cis-4-*octene.*

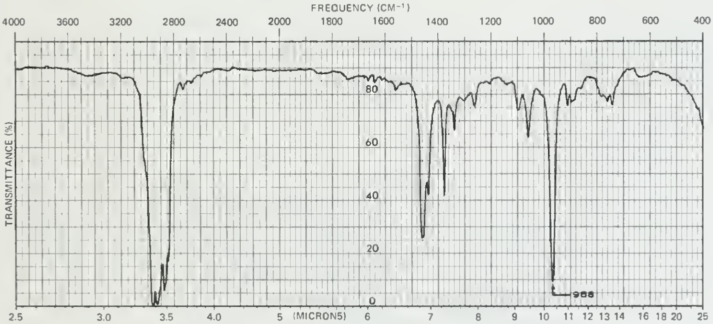


FIGURE 14.13 *Infrared spectrum of* trans-4-*octene.*

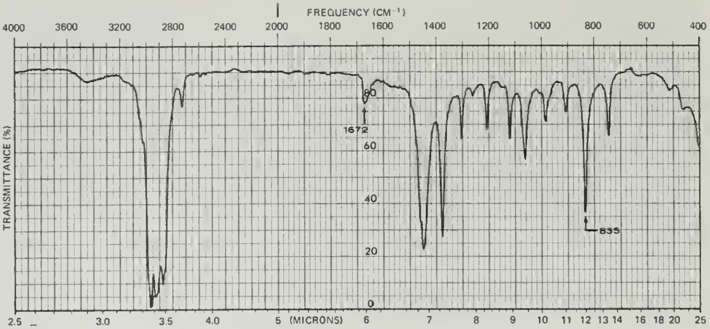


FIGURE 14.14 *Infrared spectrum of 2-methyl-2-pentene.*

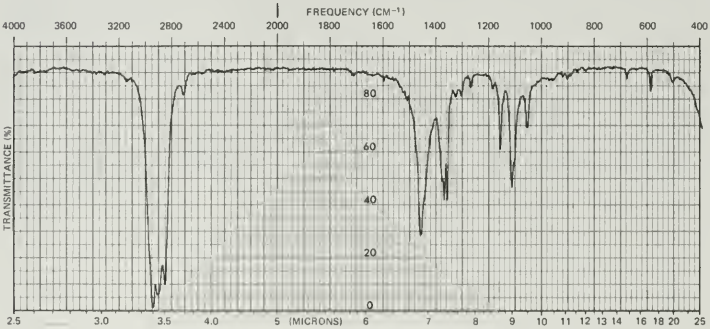


FIGURE 14.15 *Infrared spectrum of 2,3,4-trimethyl-2-pentene.*

14.6
Alkynes

Terminal alkynes show a sharp C—H stretching band at 3300–3320 cm^{-1} and an intense C—H bending mode at 600–700 cm^{-1}. The C$\equiv$C stretch for terminal alkynes appears as a sharp absorption of moderate intensity at 2100–2140 cm^{-1}. For internal alkynes, the C$\equiv$C stretch is a weak band occurring at 2200–2260 cm^{-1}; in hydrocarbons, this band is so weak that it is frequently not observed. Of course, if the molecule is symmetrical, the C$\equiv$C stretch is absent. These features are illustrated in the spectra shown in Figures 14.16 and 14.17.

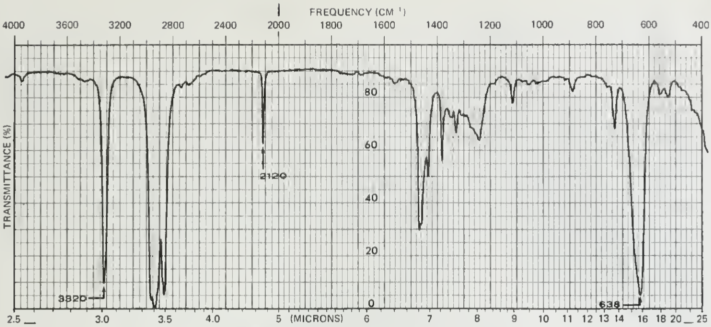


Figure 14.16 *Infrared spectrum of 1-octyne.*

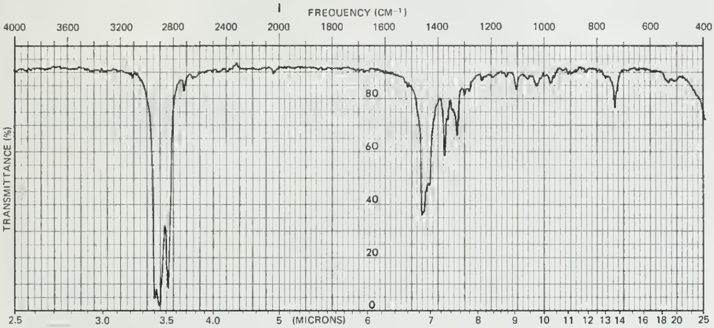


Figure 14.17 *Infrared spectrum of 2-octyne.*

14.7
Alkyl Halides

The characteristic absorption of alkyl halides is the band due to the C—X stretch. Typical positions for these bands are shown in Table 14.4. The C—Br and C—I stretching bands are used for diagnosis less than are the C—Cl and C—F bands, because many of the commonly used spectrometers do not operate at wavelengths longer than about 700 cm^{-1}.

Table 14.4
Carbon-Halogen Stretching Bands

Bond	Region, cm^{-1}	Intensity
C—F	1000–1350	very strong
C—Cl	750–850	strong
C—Br	500–680	strong
C—I	200–500	strong

14.8
Alcohols and Ethers

The characteristic infrared bands of alcohols and ethers are the C—O stretch (1050–1200 cm^{-1}) and (for alcohols) the O—H stretch, which occurs in the 3200–3600 cm^{-1} region. Although C—O stretching bands occur in a region of the spectrum where there are usually many other bands, they are relatively easy to identify, because they are so intense. They are often coupled to C—C absorptions and therefore exhibit fine structure. The exact location of the C—O bands depends on the degree of branching of the carbon atom that is attached to oxygen, as shown in Table 14.5.

TABLE 14.5
C—O Stretching Vibration of Alcohols

primary alcohols	about 1050 cm^{-1}
secondary alcohols	about 1125 cm^{-1}
tertiary alcohols	about 1200 cm^{-1}

The spectra in Figures 14.18–14.20 illustrate the C—O stretching bands of various alcohols, and also show the very intense O—H stretch that occurs in these spectra at 3250–3450 cm^{-1}.

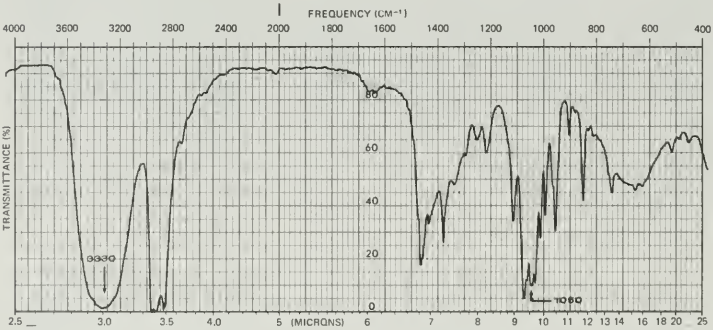


FIGURE 14.18 *Infrared spectrum of* 1-*butanol.*

The spectra shown in Figures 14.18–14.20, like all the other spectra depicted so far, were obtained on the pure liquid compounds. In Figure 14.21 are plotted the spectra of the O—H and C—H regions of *t*-butyl alcohol dissolved in carbon tetrachloride. (Carbon tetrachloride is a frequently used solvent for infrared studies, because it is relatively inert chemically and is "transparent" to infrared light in most of the useful spectra regions.) Notice that in the first spectrum the 3440 cm^{-1} O—H absorption is now accompanied by a sharp peak at 3620 cm^{-1}. As the solution is made more dilute, the 3620 cm^{-1} band becomes more intense relative to the 3440 cm^{-1} band. These two bands are both believed to be due to O—H stretch. The band at shorter wavelength (higher energy) is due to the

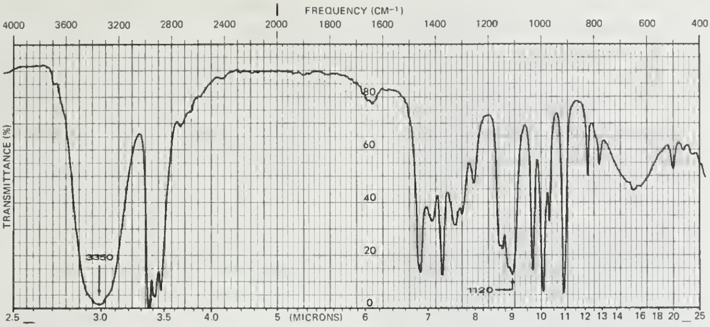


Figure 14.19 *Infrared spectrum of 2-butanol.*

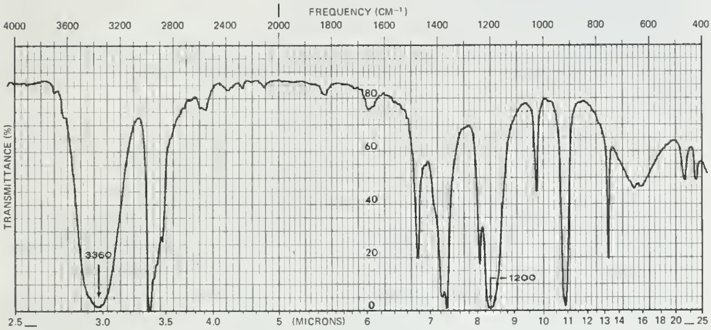


Figure 14.20 *Infrared spectrum of 2-methyl-2-propanol* (t-*butyl alcohol*).

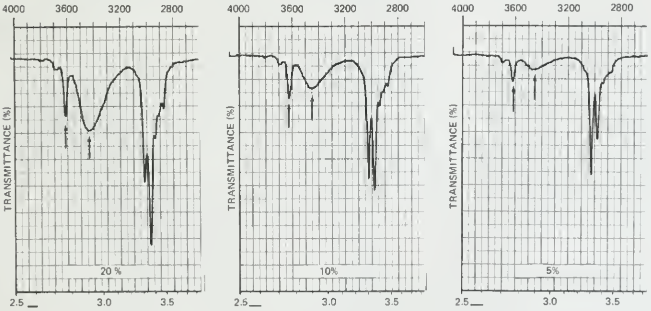


Figure 14.21 *Infrared spectra of various solutions of* t-*butyl alcohol in carbon tetrachloride.*

stretching mode of the "free" hydroxy. The stretching mode of hydrogen bonded, or "associated" O—H bonds occurs at lower energy:

free hydroxy	[O—H]	3620–3640 cm^{-1}
associated hydroxy	[O—H···O]	3250–3450 cm^{-1}

As the solution is made progressively more dilute, it is more likely that a molecule will exist in an unassociated state.

14.9
Summary: Principal Functional Group Absorptions

In this chapter, we have considered the infrared spectra of the classes of organic compounds taken up so far in this book. We have seen that the infrared spectra of organic compounds are so exceedingly complex that it is impractical to analyze a spectrum completely and assign each absorption to a given vibration. However, for each functional group there are characteristic absorptions that may be used empirically as a diagnosis for that particular functional group. Table 14.6 summarizes the infrared characteristics of alkanes, alkenes, alkynes, alkyl halides, alcohols, and ethers. As we consider other classes of compounds, we shall point out their characteristic infrared absorption bands. A further listing is given in Appendix VI.

TABLE 14.6
Principal Infrared Absorptions

Class	Absorption, cm^{-1}	Intensity*	Assignment
1. Alkanes	2850–3000	s	C—H stretch
	1450–1470	s	CH_2 and CH_3 bend
	1370–1380	s	
	720–725	m	
2. Alkenes			
(a) $RCH{=}CH_2$	3080–3140	m	=C—H stretch
	1800–1860	m	overtone
	1645	m	C=C stretch
	990	s	C—H out-of-plane bend
	910	s	
(b) $R_2C{=}CH_2$	3080–3140	m	=C—H stretch
	1750–1800	m	overtone
	1650	m	C=C stretch
	890	s	C—H out-of-plane bend
(c) *cis*-RCH=CHR	3020	w	=C—H stretch
	1660	w	C=C stretch
	675–725	m	C—H out-of-plane bend
(d) *trans*-RCH=CHR	3020	w	=C—H stretch
	1675	vw	C=C stretch
	970	s	C—H out-of-plane bend
(e) $R_2C{=}CHR$	3020	w	=C—H stretch
	1670	w	C=C stretch
	790–840	s	C—H out-of-plane bend
(f) $R_2C{=}CR_2$	1670	vw	C=C stretch

TABLE 14.6

Class	Absorption, cm^{-1}	Intensity*	Assignment
3. Alkynes			
(a) RC≡CH	3300	s	≡C—H stretch
	2100–2140	m	C≡C stretch
	600–700	s	≡C—H bend
(b) RC≡CR	2190–2260	vw	C≡C stretch
4. Alkyl Halides			
(a) R—F	1000–1350	vs	C—F stretch
(b) R—Cl	750–850	s	C—Cl stretch
(c) R—Br	500–680	s	C—Br stretch
(d) R—I	200–500	s	C—I stretch
5. Alcohols			
(a) RCH_2OH	3600	var	free O—H stretch
	3400	s	bonded O—H stretch
	1050	s	C—O stretch
(b) R_2CHOH	3600	var	free O—H stretch
	3400	s	bonded O—H stretch
	1100	s	C—O stretch
(c) R_3COH	3600	var	free O—H stretch
	3400	s	bonded O—H stretch
	1150	s	C—O stretch
6. Ethers	1070–1150	s	C—O stretch

* Where s = strong, m = medium, vs = very strong, w = weak, vw = very weak, var = variable.

14.10
Instrumentation

An infrared spectrometer may be designed either on the single beam or the double beam principle. In a **single beam** spectrophotometer, light from the radiation source (usually an oxide-coated ceramic rod that is heated electrically to about 1500°) is focused and passed through the sample, which is contained in a special cell. After passing through the sample, the emergent light beam is dispersed by a **monochromater** (either a prism or a diffraction grating) into its component wavelengths. The spectrum is scanned by slowly rotating the prism or grating. A **double beam** spectrophotometer operates on a similar principle, except that the original light is split into two beams, one of which passes through the sample while the other passes through a reference cell. The instrument records the difference in intensity of these two beams. This type of instrument is especially useful when spectra are to be measured in solution. In such a case, the reference cell contains pure solvent. Thus, if the solvent absorbs weakly in a given region of the spectrum, its absorption may be "cancelled out." Since glass absorbs strongly in the useful infrared region, it cannot be used for the optical parts of a spectrophotometer. The prism and sample cell walls are usually fabricated from large NaCl or KBr crystals.

Modern research spectrophotometers are highly precise instruments, which are both bulky and costly. Typical instruments cost from $4,000–20,000 and weigh from 200–500 lb. However, in 1969, two infrared spectrophotometers were packaged in space probes and sent to Mars! The purpose of this venture was to search for organic compounds such as methane in the atmosphere of the red planet.

The spectrophotometers, which operated on the single beam principle, were designed and built at the University of California in Berkeley. They weighed 25 lb each and occupied a volume only 1 ft^3 each. Using a sample length of about 6 miles (the effective depth of the Martian atmosphere), the spectrophotometers found water, carbon monoxide, and carbon dioxide—but no methane or other hydrocarbons. However, effective maximum levels, all in the parts per million range, were established for 39 other compounds. For example, NO_2, NH_3, SO_2, NO, O_3, CH_4, and CH_2O would have been detected had they been present in amounts as great as 4 ppm. An important spin-off of this space age research project has been the use of infrared as a method for analyzing for pollutants in the earth's atmosphere.

Infrared spectroscopy has recently found another interesting analytical use. A commercial instrument, called the Intoxalyzer, is used by police departments to analyze a person's breath for its alcohol content. The device is a single beam spectrophotometer that operates at a fixed wavelength (3.39 μ, 2950 cm^{-1}), corresponding to the C—H stretch of ethyl alcohol. Since exhaled breath rarely contains organic compounds other than alcohol, absorption at this wavelength is taken as a quantitative measure of drunkenness. A major disadvantage of this technique is that persons with certain illnesses exhale other organic compounds. For example, diabetics exhale acetone, which also absorbs at this wavelength. For this reason, crime labs that use the infrared method usually double-check their results with some other technique, such as gas chromatography.

PROBLEMS

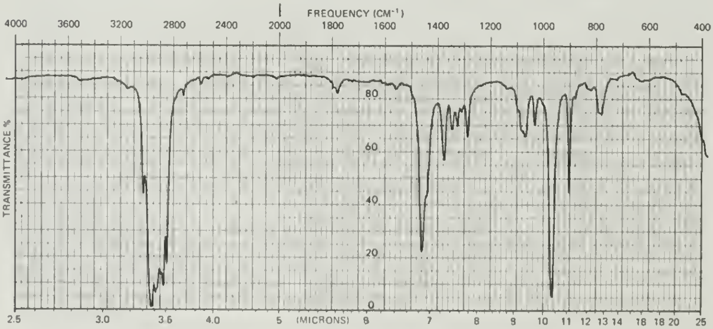
1. Using the Hooke's law approximation, estimate $\bar{\nu}$ for each of the following stretching vibrations. As force constants, use 5×10^5, 10×10^5, and 15×10^5 dynes cm^{-1} for single, double, and triple bonds, respectively.

(a) O—H	(d) C≡C	(g) C≡N
(b) O—D	(e) C—O	(h) C—F
(c) C=C	(f) C=O	

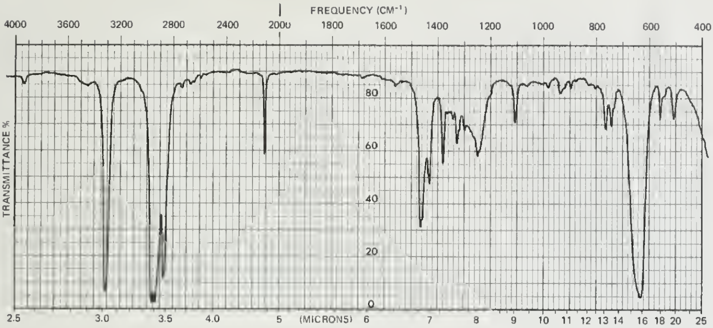
2. The acetylenic C—H stretch in 1-octyne occurs at 3350 cm^{-1}. Estimate the position of the C—D stretch in 1-deuterio-1-octyne and compare with the ^{13}C—H stretch in $CH_3(CH_2)_5C{\equiv}^{13}C{-}H$.

3. Identify the functional groups in each compound from the following infrared spectra.

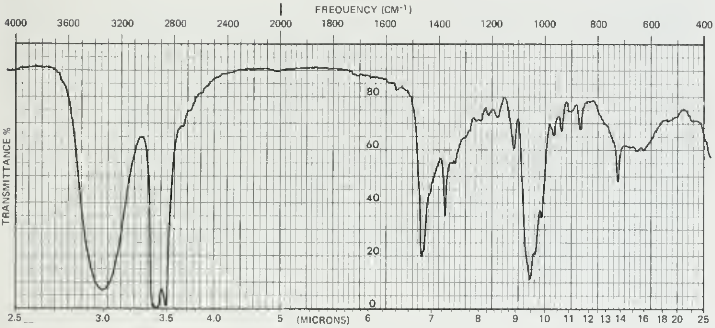
(a)



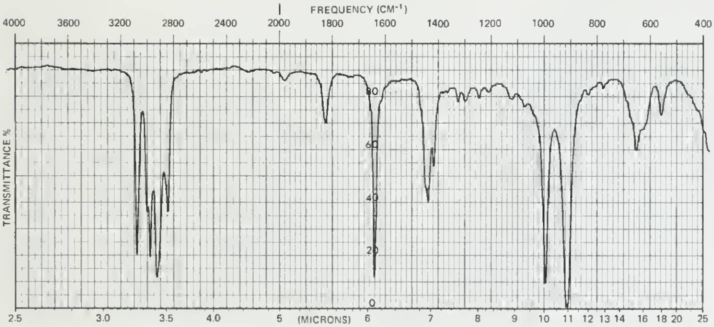
(b)


FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE %
80
60
40
20
0
2.5
3.0
3.5
4.0
5
(MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25

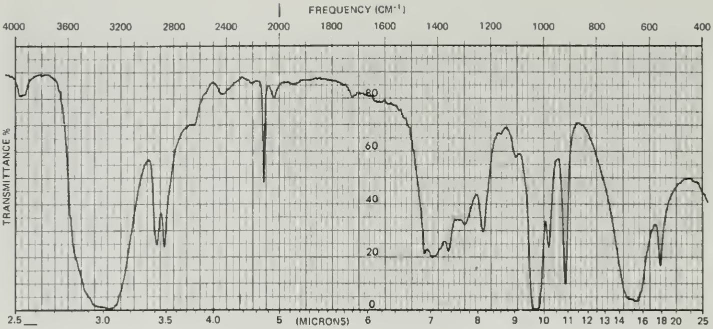
(c)


FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE %
80
60
40
20
0
2.5
3.0
3.5
4.0
5
(MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25

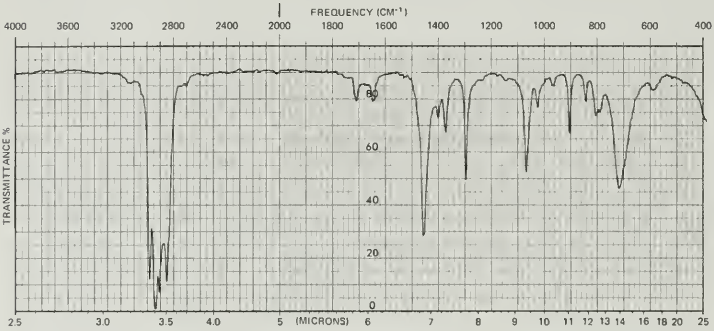
(d)


FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE %
80
60
40
20
0
2.5
3.0
3.5
4.0
5
(MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25

(e)

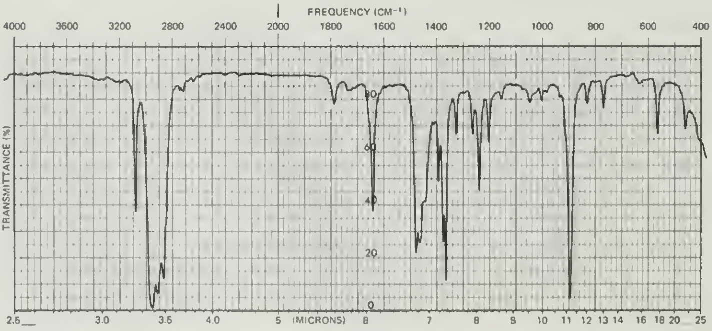


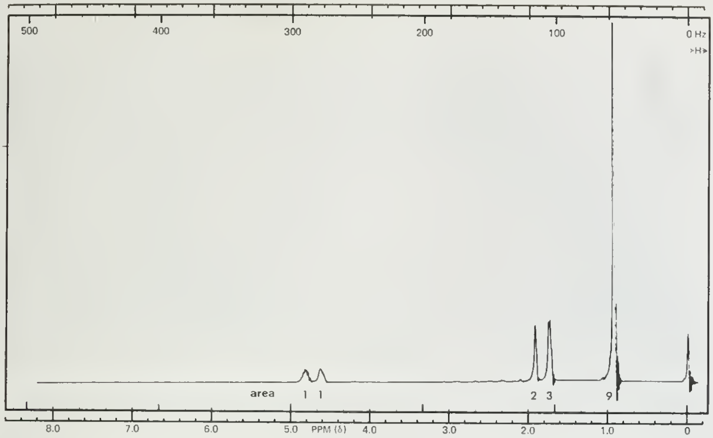
(f)



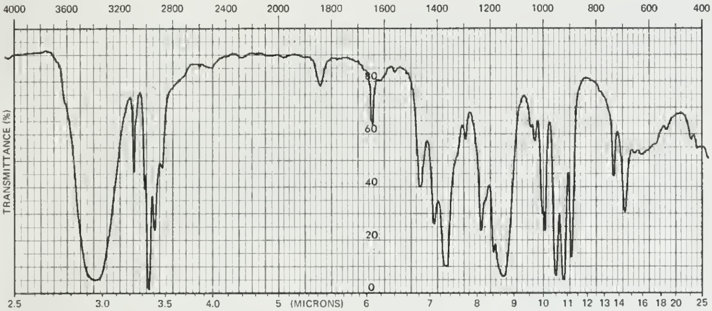
4. Identify each of the following compounds from its ir and nmr spectra.

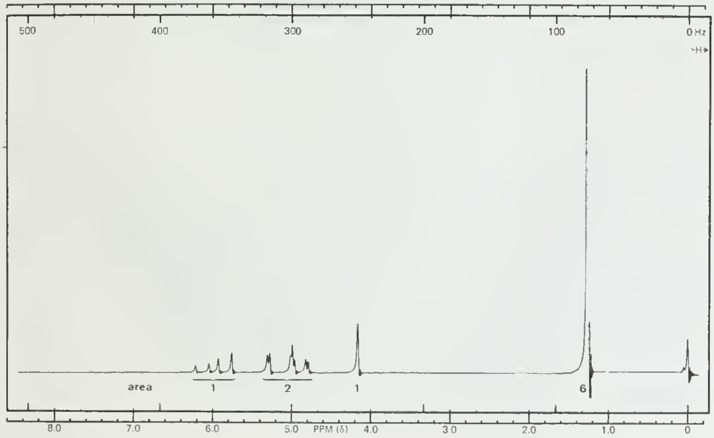
(a)



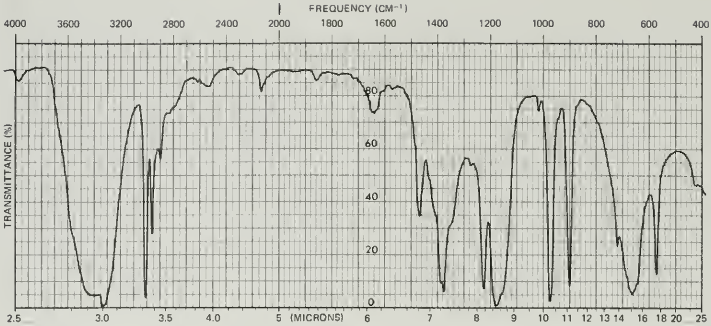

500
400
300
200
100
0 Hz
area
1 1
2 3
9
8.0
7.0
6.0
5.0 PPM (δ) 4.0
3.0
2.0
1.0
0

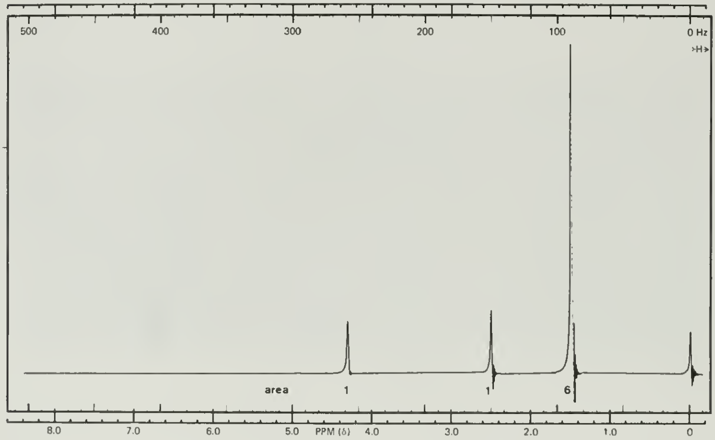
(b)


FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE (%)
80
60
40
20
0
2.5
3.0
3.5
4.0
5 (MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25

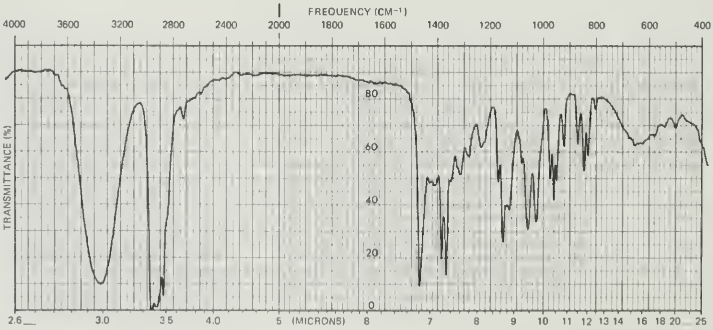

500
400
300
200
100
0 Hz
area
1
2
1
6
8.0
7.0
6.0
5.0 PPM (δ) 4.0
3.0
2.0
1.0
0

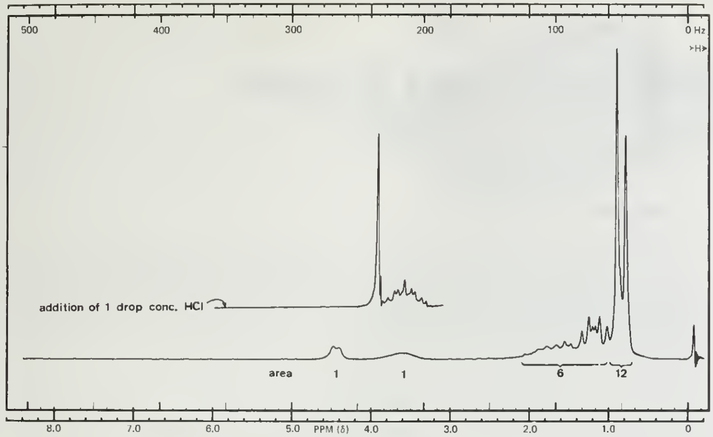
(c)


FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE (%)
80
60
40
20
0
2.5
3.0
3.5
4.0
5 (MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25


500
400
300
200
100
0 Hz
›H›
area
1
1
6
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

(d)


FREQUENCY (CM⁻¹)
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE (%)
80
60
40
20
0
2.6
3.0
3.5
4.0
5 (MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25



5. (a) For the heavier methyl halides, one infrared frequency can be treated to an excellent approximation as a C—X stretching vibration. The position of this band is CH_3Cl, 732 cm^{-1}; CH_3Br, 611 cm^{-1}; CH_3I, 533 cm^{-1}. Find the corresponding C—X force constants and determine whether they are proportional to the corresponding $DH°$ (CH_3—X) values (see Appendix II).
   (b) Astatine, element no. 85, is a halogen with no stable isotopes. The longest lived isotope is ^{210}At, with a half-life of 8.3 hr. At what value of $\tilde{\nu}$ would you expect to find the CH_3—At stretching band of methyl astatide?
   (c) Methanethiol has a corresponding vibration (C—S stretch) at 705 cm^{-1}. Use your results from (a) to calculate the corresponding $DH°$ value. The experimental value for $DH°$ (CH_3—SH) is about 76 kcal $mole^{-1}$.

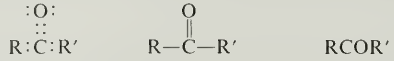
★6. Dialkyl peroxides, ROOR, have an absorption in the region 820–1000 cm^{-1}, but this band is extremely weak and difficult to detect. Explain. Using the Hooke's law approximation, find the force constant for an O—O stretch of 900 cm^{-1}. How does it compare with the normal single bond f of 5×10^5? Explain.

★7. For a harmonic oscillator, the potential energy $E = f(r - r_0)^2$. In calculus form, the radius of curvature is expressed as d^2E/dr^2. What is the relationship between the radius of curvature and the force constant, f, for a harmonic oscillator?

CHAPTER 15
Aldehydes and Ketones

15.1
Structure

Aldehydes and ketones are compounds containing the **carbonyl group,** C=O. When two alkyl groups are attached to the carbonyl, the compound is a **ketone.** When two hydrogens, or one hydrogen and one alkyl group are attached to the carbonyl, the compound is an **aldehyde.**

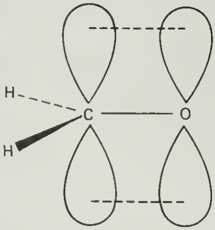


$$R-\overset{\overset{\displaystyle O}{\|}}{C}-R' \qquad RCOR'$$

Lewis structure Kekulé structure Condensed structure

R = H or alkyl

The structure of formaldehyde, the simplest member of the class, is depicted below, along with its experimental bond lengths and bond angles.



Bond lengths, Å		Bond Angles, deg	
C=O	1.203	H—C—O	121.8
C—H	1.101	H—C—H	116.5

The carbon atom is approximately sp^2 hybridized and forms σ bonds to two hydrogens and one oxygen. The molecule is planar and the H—C—O and H—C—H bond angles are close to 120°, the idealized sp^2 angles. The remaining carbon p orbital overlaps with the oxygen p_z orbital, giving rise to a π bond between these atoms. The oxygen atom also has two nonbonding electron pairs (the lone pairs) that occupy the remaining orbitals. A stereo representation of acetaldehyde is shown in Figure 15.1. Note the planarity of the carbonyl group. Also note that one C—H bond of the methyl group is eclipsed with the C—O bond and that the carbonyl C—H is staggered with respect to the other two C—H bonds.

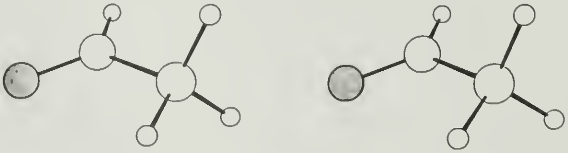


FIGURE 15.1 *Stereo representation of acetaldehyde.*

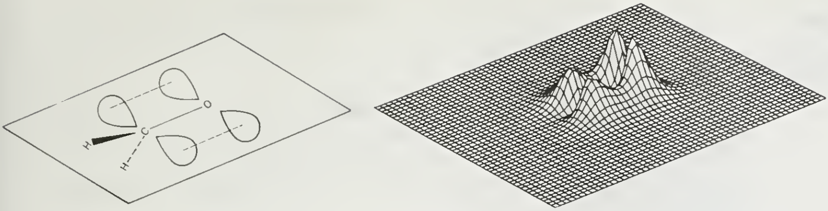
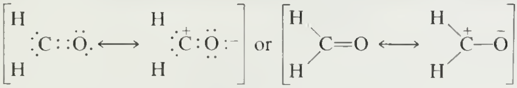


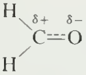
Figure 15.2 *Perspective plot of π electron density in formaldehyde,* $H_2C{=}O$.

Oxygen is more electronegative than carbon and attracts the bonding electrons more strongly; that is, the higher nuclear charge on oxygen provides a greater attractive force than carbon. Accordingly, the C—O bond is polarized in the direction $C^+{-}O^-$. This effect is especially pronounced for the π electrons. A perspective plot of the π electron density (Figure 15.2) shows the higher concentration of electron density around the oxygen atom.

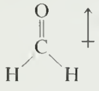
This effect can be represented by the resonance structures for formaldehyde



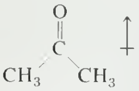
The actual structure is a composite of the normal octet structure, $CH_2{=}O$, and the polarized structure, ${}^+CH_2{-}O^-$, which corresponds to a carbonium oxide. The composite structure may be represented with dotted line symbolism which shows the partial charges in carbon and oxygen and the partial single bond character of the C—O bond.



One physical consequence of this bond polarity is that carbonyl compounds generally have rather high dipole moments. The experimental dipole moments of formaldehyde and acetone are 2.27 D and 2.85 D, respectively.



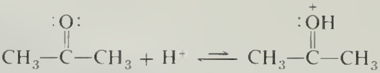
formaldehyde
dipole moment, 2.27 D



acetone
dipole moment, 2.85 D

The chemical consequences of this bond polarity will become apparent during our discussions of the reactions of carbonyl groups. We shall find that the positive carbon can react with bases and that much of the chemistry of the carbonyl function corresponds to that of a relatively stable carbonium ion.

The lone pair electrons in the carbonyl oxygen have weakly basic properties. In acidic solution, acetone acts as a Lewis base and is protonated to a small but significant extent.



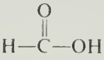
$$CH_3-\overset{\overset{:O:}{\|}}{C}-CH_3 + H^+ \rightleftharpoons CH_3-\overset{\overset{:\overset{+}{O}H}{\|}}{C}-CH_3$$

In fact, acetone is a much *weaker* Lewis base than is water. The material is one half protonated only in 82% sulfuric acid. This corresponds to an approximate pK_a for the conjugate acid of acetone of -7.2 (the approximate pK_a of H_3O^+ is -1.7). Even though the carbonyl group has only weakly basic properties, we shall find that this basicity plays an important role in the chemistry of aldehydes, ketones, and related compounds.

15.2
Nomenclature

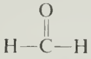
A. *Common Names*

Traditionally, aldehyde names were derived from the name of the corresponding acid (Section 17.2) by dropping the suffix **-ic** (or **-oic**) and adding in its place the suffix **-aldehyde.** These common names are still widely used for simpler aldehydes.



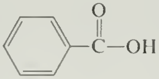
$$H-\overset{\overset{O}{\|}}{C}-OH$$

formic acid

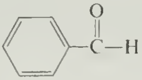


$$H-\overset{\overset{O}{\|}}{C}-H$$

formaldehyde

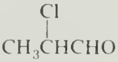


benzoic acid



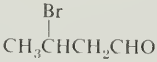
benzaldehyde

Appendage groups are designated by the appropriate prefixes. The chain is labelled by using the Greek letters α, β, γ, and so on (Table 11.1), beginning with the carbon next to the carbonyl group.



$$CH_3\overset{\overset{Cl}{|}}{C}HCHO$$

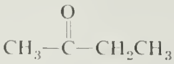
α-chloropropionaldehyde



$$CH_3\overset{\overset{Br}{|}}{C}HCH_2CHO$$

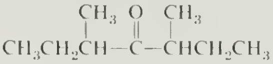
β-bromobutyraldehyde

The common names of ketones are derived by prefixing the word **ketone** by the names of the two alkyl radical groups; the separate parts are separate words.



$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2CH_3$$

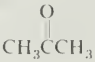
methyl ethyl ketone



$$CH_3CH_2\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_3}{|}}{C}HCH_2CH_3$$

di-*sec*-butyl ketone

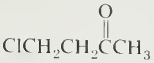
Dimethyl ketone has the additional trivial name **acetone,** which is universally used.



$$CH_3\overset{\overset{O}{\|}}{C}CH_3$$

acetone

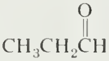
As with aldehydes, appendages may be designated by a prefix using the Greek letter notational system.


$\mathrm{ClCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3}$

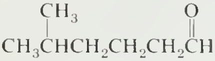
methyl β-chloroethyl ketone

B. *IUPAC Names*

In the IUPAC system, aldehyde names are derived from the name of the alkane of the same carbon number. The final **-e** of the alkane is replaced by the suffix **-al.** Since the carbonyl group is necessarily at the end of a chain, it is not necessary to designate its position by a number, but as a suffix group it controls the numbering as the number 1 carbon. Note that the carbonyl carbon is the number 1 carbon in the IUPAC system, although it is given no designation in the common system.

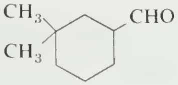

$\mathrm{CH_3CH_2\overset{O}{\overset{\|}{C}}H}$

propanal


$\mathrm{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H}$

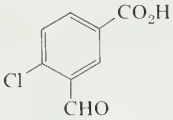
5-methylhexanal

More complicated aldehydes may be named using the suffix **-carbaldehyde.**



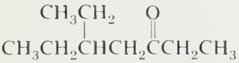
3,3-dimethylcyclohexane**carbaldehyde**

When it is necessary to name a compound as another functional group, the aldehyde grouping is designated **formyl.**

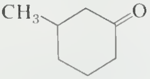


4-chloro-3-**formyl**benzoic acid

The IUPAC names of ketones are derived from the name of corresponding alkane by replacing the final **-e** by **-one.** In acyclic ketones, it is necessary to prefix the name by a number indicating which carbon along the longest chain is the carbonyl carbon. The longest chain containing the carbonyl group is numbered from the end that gives the carbonyl carbon the lower number. In cyclic ketones it is understood that the carbonyl carbon is number 1.

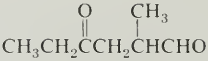

$\mathrm{CH_3CH_2\overset{CH_3CH_2}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}CH_2CH_3}$

5-ethyl-3-heptan**one**



3-methylcyclohexan**one**

Occasionally, it is necessary to name a molecule containing a carbonyl group as a derivative of a more important function. In such a case, the prefix **oxo-** is used, along with a number, to indicate the position and nature of the group. One such example is shown below.



$$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{CH_3}{|}}{C}HCHO$$

2-methyl-4-oxohexanal

It is generally desirable that the common and IUPAC nomenclature systems not be mixed. Ambiguity can result because counting by Greek letters in the common system starts from the carbon next to the carbonyl group, whereas the numbers in the IUPAC system always include the carbonyl group.

$ClCH_2CH_2CHO$

correct:	β-chloropropionaldehyde or 3-chloropropanal
incorrect:	β-chloropropanal
allowed but not recommended:	3-chloropropionaldehyde

15.3
Physical Properties

Physical data for a number of aldehydes and ketones are collected in Tables 15.1 and 15.2. The boiling points at 1 atm for straight chain aldehydes and methyl *n*-alkyl ketones are plotted in Figure 15.3, along with the corresponding data for straight chain alkanes. As in other homologous series, there is a smooth increase in boiling point with increasing molecular weight. Aldehydes and ketones boil

TABLE 15.1
Physical Properties of Some Aldehydes

Compound	Structure	Molecular Weight	Boiling Point, °C	Melting Point, °C
formaldehyde	$HCHO$	30	−21	−92
acetaldehyde	CH_3CHO	44	21	−121
propionaldehyde	CH_3CH_2CHO	58	49	−81
butyraldehyde	$CH_3(CH_2)_2CHO$	72	76	−99
valeraldehyde	$CH_3(CH_2)_3CHO$	86	103	−92
hexanal	$CH_3(CH_2)_4CHO$	100	128	−56
heptanal	$CH_3(CH_2)_5CHO$	114	153	−43
octanal	$CH_3(CH_2)_6CHO$	128	171	—
nonanal	$CH_3(CH_2)_7CHO$	142	192	—
decanal	$CH_3(CH_2)_8CHO$	156	209	−5
undecanal	$CH_3(CH_2)_9CHO$	170	—	−4
dodecanal	$CH_3(CH_2)_{10}CHO$	184	—	12

TABLE 15.2
Physical Properties of Some Ketones

Compound	Structure	Molecular Weight	Boiling Point, °C	Melting Point, °C	H_2O Solubility, wt. %, 25°
acetone	CH_3COCH_3	58	56	−95	∞
2-butanone	$CH_3CH_2COCH_3$	72	80	−86	25.6
2-pentanone	$CH_3(CH_2)_2COCH_3$	86	102	−78	5.5
3-pentanone	$CH_3CH_2COCH_2CH_3$	86	102	−40	4.8
2-hexanone	$CH_3(CH_2)_3COCH_3$	100	128	−57	1.6
3-hexanone	$CH_3(CH_2)_2COCH_2CH_3$	100	125	—	1.5
2-heptanone	$CH_3(CH_2)_4COCH_3$	114	151	−36	0.4
2-octanone	$CH_3(CH_2)_5COCH_3$	128	173	−16	—
2-nonanone	$CH_3(CH_2)_6COCH_3$	142	195	−7	—
2-decanone	$CH_3(CH_2)_7COCH_3$	156	210	14	—
2-undecanone	$CH_3(CH_2)_8COCH_3$	170	232	15	—
2-dodecanone	$CH_3(CH_2)_9COCH_3$	184	247	21	—

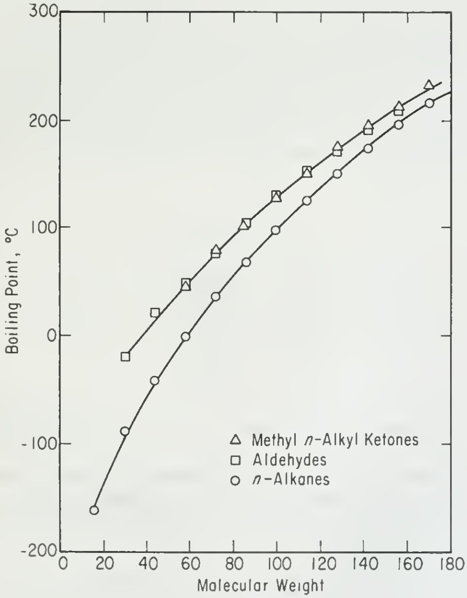
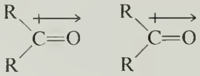


FIGURE 15.3 *Boiling points of aldehydes and ketones.*

higher than alkanes of comparable molecular weights. This boiling point elevation results from the interaction between dipoles.



The discrepancy is largest with the simplest aldehyde, formaldehyde (mol. wt. 30, b.p. −21°), which boils 68° higher than ethane (mol. wt. 30, b.p. −89°). With higher members of the series, as the polar functional group becomes a smaller and smaller part of the molecule, the boiling point tends to come closer and closer to that of a corresponding alkane (see 2-dodecanone, mol. wt. 184, b.p. 247°; *n*-tridecane, mol. wt. 184, b.p. 235°).

15.4
Spectroscopy of Aldehydes and Ketones

A. *Nuclear Magnetic Resonance Spectra*

Nmr is an important technique for identifying aldehydes. The hydrogen attached to the carbonyl carbon gives rise to a characteristic band at very low field, usually around $\delta = 9.5$ ppm. In a magnetic field the circulating π electrons produce an induced field that effectively deshields the aldehyde proton (Figure 15.4). That is, the induced field adds to the applied field in such a way that a smaller applied field is required to achieve resonance. The same phenomenon was discussed earlier with alkenes and accounts for the substantial downfield shift of vinyl protons (Section 12.3.B). In aldehydes the effect is greater and, in addition, the positive character of the carbonyl carbon provides a further downfield shift. The net result is a relatively large downfield resonance position for the aldehyde proton. Few other kinds of protons appear in this region; thus, a peak at $\delta = 9.5$ is strongly indicative of the presence of a CHO function.

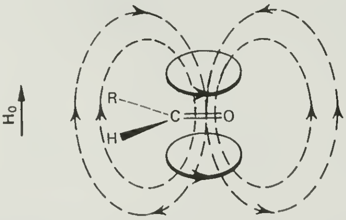
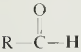
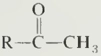
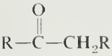
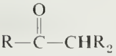


FIGURE 15.4 *The diamagnetic anisotropy of the carbonyl group.*

The same induced field that causes deshielding of a proton attached directly to a carbonyl group also produces significant deshielding of protons somewhat further away at the α-carbon atoms. Typical chemical shifts for these protons are summarized in Table 15.3.

The spectra of acetaldehyde and 3-methyl-2-butanone, shown in Figures 15.5 and 15.6 are characteristic. Note that the vicinal coupling constant in acetaldehyde is quite small, only 3 Hz.

TABLE 15.3
Chemical Shifts for Aldehyde and Ketone Hydrogens

Hydrogen	Approximate Chemical Shift, δ, ppm
 $R-\overset{O}{\overset{\|}{C}}-H$	9.5
 $R-\overset{O}{\overset{\|}{C}}-CH_3$	2.0
 $R-\overset{O}{\overset{\|}{C}}-CH_2R$	2.2
 $R-\overset{O}{\overset{\|}{C}}-CHR_2$	2.4

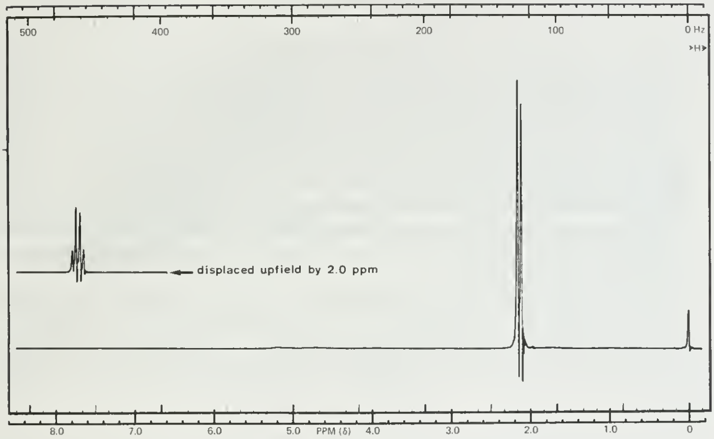


FIGURE 15.5 Nmr *spectrum of acetaldehyde*, CH_3CHO.

B. *Infrared Spectra*

The characteristic infrared absorption for aldehydes and ketones is the band due to the C=O stretching vibration. Since the carbonyl group is highly polar, stretching of this bond results in a relatively large change in dipole moment. Consequently, the carbonyl stretching band is an intense spectral feature. Because of its intensity, and also because it occurs in a region of the infrared spectrum commonly devoid of other absorptions, the carbonyl stretch is perhaps the most reliable method for deducing the presence of such a functional group in a com-

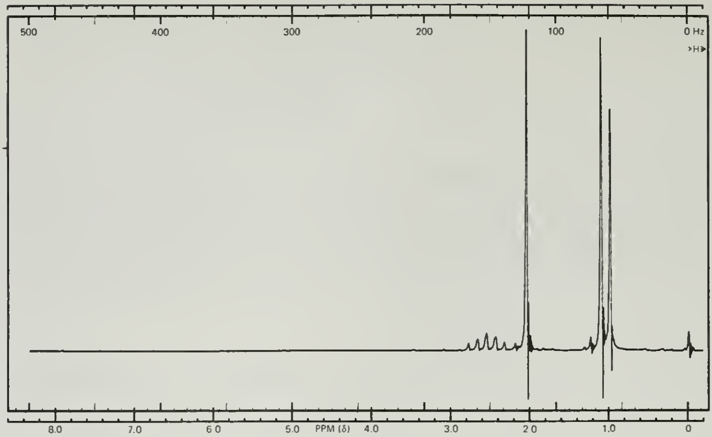


Figure 15.6 Nmr *spectrum of methyl isopropyl ketone,* $CH_3COCH(CH_3)_2$.

pound. For simple saturated aldehydes, the band occurs at about 1725 cm^{-1}. For saturated acyclic ketones, the band occurs at about 1715 cm^{-1}. The distinctive nature of the C=O stretch is apparent in the spectrum of 2-heptanone shown in Figure 15.7. Since the carbonyl stretch is such an intense absorption, it often gives rise to a noticeable overtone in the 3400–3500 cm^{-1} region. In 2-heptanone, the carbonyl overtone occurs at 3440 cm^{-1} and may be seen in Figure 15.7. One must be cautious not to mistake this overtone for an OH absorption.

Aldehydes also show a distinctive bond at 2720 cm^{-1}, due to the aldehyde C—H stretch. This band, which is of moderate intensity, is usually accompanied by another band at 2820 cm^{-1}.

In this section, we have discussed the infrared spectra of aldehydes and ketones and have emphasized the utility of the carbonyl stretching band as a diagnostic tool for the carbonyl group. In later sections, we will discuss the spectra of carboxylic acids, anhydrides, acyl halides, esters, and amides, all of which contain

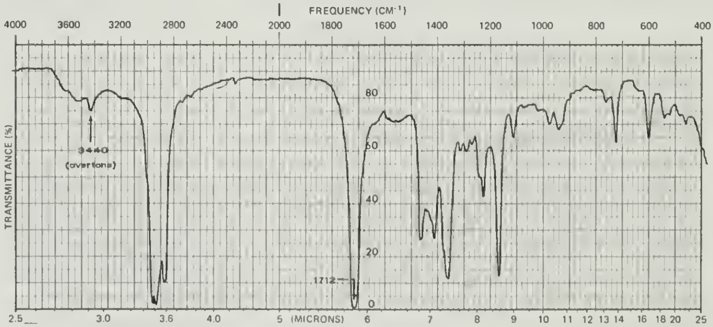


Figure 15.7 *Infrared spectrum of 2-heptanone.*

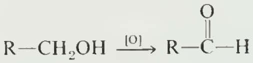
a carbonyl group. In general, one may determine the precise nature of a carbonyl compound from the exact location of the C═O stretch and from a consideration of other bands in the spectrum.

15.5
Synthesis of Aldehydes and Ketones

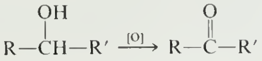
The carbonyl group in aldehydes and ketones is one of the most important functional groups. In this section, we shall review several reactions that are good methods for the synthesis of aldehydes and ketones.

A. *Oxidation of Alcohols*

As discussed in Section 11.7.E, aldehydes and ketones may be obtained by the oxidation of primary and secondary alcohols, respectively.

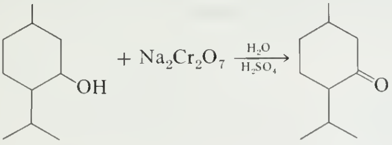


$$R-CH_2OH \xrightarrow{[O]} R-\overset{\overset{O}{\|}}{C}-H$$



$$R-\overset{\overset{OH}{|}}{C}H-R' \xrightarrow{[O]} R-\overset{\overset{O}{\|}}{C}-R'$$

In the latter case, the product is not easily oxidized further, so there is no special problem in controlling the reaction to obtain the ketone in good yield. Although many oxidants have been used, the most commonly employed ones are chromium(VI) compounds.

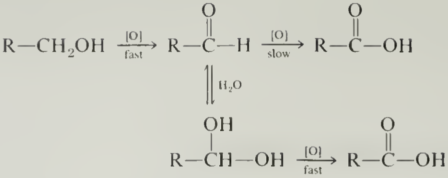


menthol

(84%)
menthone

> A mixture of 120 g of $Na_2Cr_2O_7$, 100 g of conc. H_2SO_4, and 600 ml of water is prepared. To this solution is added 90 g of menthol (2-isopropyl-5-methylcyclohexanol). Heat is evolved, the temperature of the mixture rising to 55°. As soon as the reaction is complete, the oily product layer is removed by ether extraction and distilled to obtain 75 g (84%) of menthone.

In the case of primary alcohols, this simple picture is clouded by the fact that the product aldehyde may be further oxidized to a carboxylic acid. In most cases, the primary alcohol undergoes oxidation *more rapidly* than the corresponding aldehyde. However, in aqueous solution, the product aldehyde forms a hydrate, which is oxidized even more rapidly than the primary alcohol. Aldehyde hydrates are discussed thoroughly in Section 15.7.A.



$$R{-}CH_2OH \xrightarrow[\text{fast}]{[O]} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H \xrightarrow[\text{slow}]{[O]} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH$$

$$\Big\Updownarrow H_2O$$

$$R{-}\overset{\overset{\displaystyle OH}{|}}{C}H{-}OH \xrightarrow[\text{fast}]{[O]} R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH$$

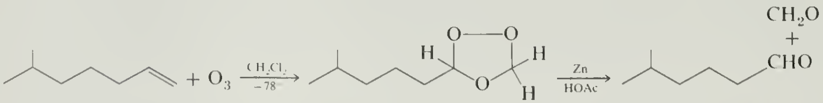
We mentioned previously (Section 11.7.E) that the preparation of aldehydes by oxidation of primary alcohols with aqueous chromic acid is limited to compounds of low molecular weight that can be distilled out as they are formed. In non-hydroxylic solvents, however, selective oxidation may be accomplished, and several oxidants that may be used in organic solvents have been developed for this purpose. One such oxidant is the complex formed between chromium trioxide and 2 moles of the heterocyclic base pyridine. This material, bispyridinechromium(VI) oxide, is soluble in chloroform and dichloromethane.

$$n\text{-}C_7H_{15}CH_2OH + CrO_3(C_5H_5N)_2 \xrightarrow[\substack{25^\circ \\ 1\text{ hr}}]{CH_2Cl_2} \underset{(95\%)}{n\text{-}C_7H_{15}CHO}$$

A mixture of 6.0 g of chromium trioxide and 9.5 g of pyridine is prepared in 150 ml of dichloromethane. Octanol (1.32 g) is added to the deep red solution and the resulting mixture is kept at 25° for 15 min. The reaction mixture is worked up to obtain 1.24 g (95%) of octanal.

B. *Oxidation of Alkenes*

Aldehydes and ketones may also be prepared by oxidative cleavage of C—C multiple bonds. A particularly useful reagent for this purpose is ozone (Section 12.6.E). Hydrolysis of the ozonide, usually under reductive conditions, results in the production of two carbonyl compounds.



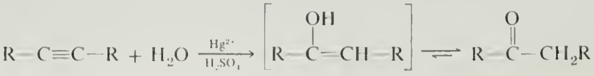
6-methyl-1-heptene

5-methylhexanal
(62%)

(Note the use in this example of a shorthand notation for carbon chains that follows simply from the line-drawing symbols used for rings.)

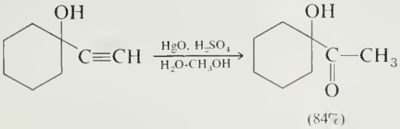
C. *Hydration of Alkynes*

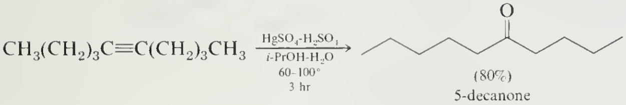
As was discussed in Section 13.6, alkynes undergo hydration to yield an unstable vinyl alcohol, which immediately rearranges to the corresponding ketone. The reaction is usually catalyzed by mercuric ion and sulfuric acid.



$$R{-}C{\equiv}C{-}R + H_2O \xrightarrow[H_2SO_4]{Hg^{2+}} \left[R{-}\overset{\overset{\displaystyle OH}{|}}{C}{=}CH{-}R\right] \rightleftharpoons R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_2R$$

The reaction is generally useful as a preparative method only when the alkyne is terminal, in which case a methyl alkyl ketone is always formed, or in cases where the molecule is symmetrical.



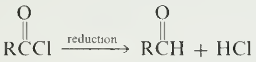


Since the direct addition of water to a terminal alkyne always occurs in such a way that the hydroxy group becomes attached to the carbon bearing the alkyl group, the only alkyne that will yield an aldehyde upon hydration is acetylene itself. Indirect hydration of the triple bond, by the hydroboration route, yields the opposite result—terminal alkynes yield aldehydes (Section 13.6.E).

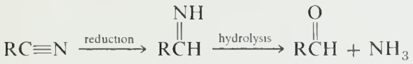
$$n\text{-}C_5H_{11}C\equiv CH \xrightarrow{B_2H_6} \xrightarrow[OH^-]{H_2O_2} n\text{-}C_6H_{13}CHO$$

D. *Preparation of Aldehydes and Ketones from Carboxylic Acid Derivatives*

Aldehydes may be prepared by the partial reduction of acyl halides or nitriles. These methods will be discussed in Section 18.10.

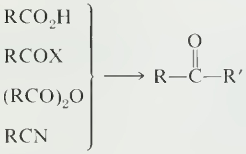


$$R\overset{O}{\overset{\|}{C}}Cl \xrightarrow{\text{reduction}} R\overset{O}{\overset{\|}{C}}H + HCl$$



$$RC\equiv N \xrightarrow{\text{reduction}} R\overset{NH}{\overset{\|}{C}}H \xrightarrow{\text{hydrolysis}} R\overset{O}{\overset{\|}{C}}H + NH_3$$

Several important methods for preparing ketones involve reactions of carboxylic acids, acyl halides, anhydrides, and nitriles with organometallic compounds.

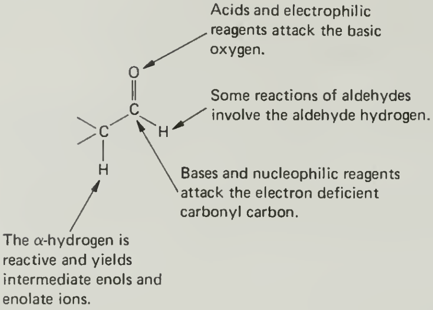


$$\left.\begin{array}{l} RCO_2H \\ RCOX \\ (RCO)_2O \\ RCN \end{array}\right\} \longrightarrow R\text{—}\overset{O}{\overset{\|}{C}}\text{—}R'$$

These reactions will be discussed in detail in sections 17.7 and 18.9.E.

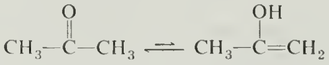
15.6
Enolization

The reactions of aldehydes and ketones can be divided into the following types:


Acids and electrophilic reagents attack the basic oxygen.
O
C
C
H
H
Some reactions of aldehydes involve the aldehyde hydrogen.
Bases and nucleophilic reagents attack the electron deficient carbonyl carbon.
The α-hydrogen is reactive and yields intermediate enols and enolate ions.

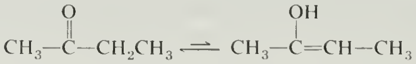
A. *Keto-Enol Equilibria*

Aldehydes and ketones exist in solution as an equilibrium mixture of two isomeric forms, the keto form and the **enol** (from **-ene** + **-ol,** unsaturated alcohol) form. For simple aliphatic ketones, there is very little of the enol form present at equilibrium, as shown by the following examples.



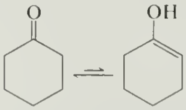
$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 \rightleftharpoons CH_3-\overset{\overset{\displaystyle OH}{|}}{C}=CH_2$$

$(1.5 \times 10^{-4}\%)$



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_3 \rightleftharpoons CH_3-\overset{\overset{\displaystyle OH}{|}}{C}=CH-CH_3$$

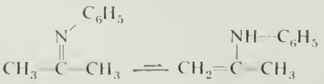
(0.12%)



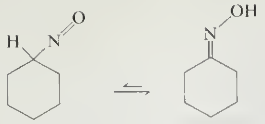
(1.2%)

This type of isomerism, where the isomers differ only by the placement of a proton and the corresponding location of a double bond, is commonly referred to as **tautomerism.** The isomers are known as **tautomers.**

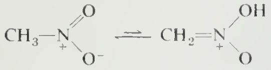
Strictly speaking, the tautomerism terminology is only used for this type of isomerism when there is a hetero atom such as nitrogen, oxygen, or sulfur present. In such cases, as exemplified in the following examples, the *rate of interconversion* of the isomers (tautomers) is relatively rapid.



$$CH_3-\overset{\overset{\displaystyle N-C_6H_5}{\|}}{C}-CH_3 \rightleftharpoons CH_2=\overset{\overset{\displaystyle NH-C_6H_5}{|}}{C}-CH_3$$



nitrosocyclohexane cyclohexanone oxime



$$\mathrm{CH_3{-}\overset{+}{N}(=O)O^-} \rightleftharpoons \mathrm{CH_2{=}\overset{+}{N}(OH)O}$$

nitromethane aci-nitromethane

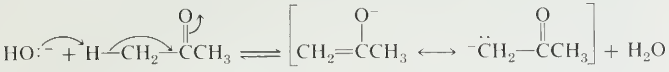
On the other hand, simple double bond isomerization is normally not considered as a case of tautomerism.

$$CH_3CH{=}CHCH_3 \rightleftharpoons CH_3CH_2CH{=}CH_2$$

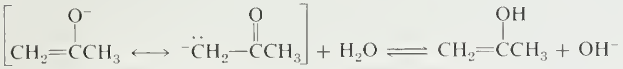
Although this is purely a matter of semantics, the *rate* of the latter isomerization is also relatively slow.

Even though the percentage of enol form at equilibrium is quite small, the enol is important in many reactions. As we shall soon see, many reactions of aldehydes and ketones occur by way of the unstable enol form.

Enolization is subject to both acid and base catalysis. In aqueous solutions the base is hydroxide ion. The base attacks a proton α to the carbonyl group to give an anion which is called an **enolate** ion. The enolate ion may be protonated on carbon, which regenerates the keto form, or on oxygen, which yields the enol form.

(1) 

$$\mathrm{HO{:}^- + H{-}CH_2{-}\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons \left[CH_2{=}\overset{O^-}{\overset{|}{C}}CH_3 \longleftrightarrow {}^-\ddot{C}H_2{-}\overset{O}{\overset{\|}{C}}CH_3\right] + H_2O}$$

(2) 

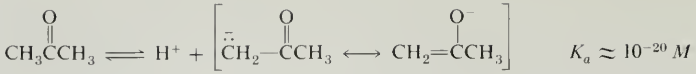
$$\mathrm{\left[CH_2{=}\overset{O^-}{\overset{|}{C}}CH_3 \longleftrightarrow {}^-\ddot{C}H_2{-}\overset{O}{\overset{\|}{C}}CH_3\right] + H_2O \rightleftharpoons CH_2{=}\overset{OH}{\overset{|}{C}}CH_3 + OH^-}$$

Note that the first step in base-catalyzed enolization is formally analogous to E2 elimination. The "leaving group" may be considered to be the π bond electron pair.

The first step of base-catalyzed enolization is an acid-base reaction, with acetone acting as a protic acid. The pK_a for acetone is approximately 20. Although acetone is an extremely weak acid when compared to such familiar acids as HCl (pK_a -7), HF (pK_a $+3$), acetic acid (pK_a $+5$) or water (pK_a $+15.7$), we must remember that acidity is relative. If we compare acetone to ethane (pK_a estimated to be approximately $+50$), we see that its acidic properties are considerably greater than that of a C—H bond in an alkane.

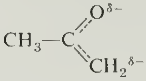
$$CH_3CH_3 \rightleftharpoons CH_3CH_2^- + H^+ \qquad K_a \approx 10^{-50}\,M$$

The reason for this enhanced acidity is apparent from a consideration of the conjugate bases produced by ionization of the two carbon acids. The anion produced from ethane has its negative charge localized on carbon. Since carbon is a fairly electropositive element, a carbanion is a high-energy species and the ionization that produces it is highly endothermic. On the other hand, the anion produced by ionization of acetone is not really a carbanion but a resonance hybrid of two structures.



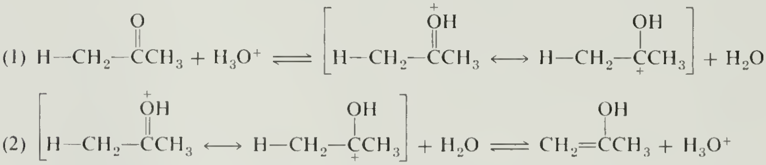
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_3 \rightleftharpoons H^+ + \left[\ddot{C}H_2{-}\overset{\overset{O}{\|}}{C}CH_3 \longleftrightarrow CH_2{=}\overset{\overset{O^-}{|}}{C}CH_3\right]} \qquad K_a \approx 10^{-20}\,M$$

In one of the resonance structures, the negative charge is borne by carbon, as in the ethyl anion. In the other, the negative charge is on the more electronegative oxygen. Although both structures contribute to the resonance hybrid, that in which the negative charge is on oxygen is clearly dominating. It is important to point out once again that the two structures connected above by the double headed arrow are *not isomers or tautomers*, but *resonance structures*. The anion derived from acetone is neither one nor the other of the two indicated structures; it has the character of both. An alternative symbol that gives a better picture of the electronic distribution is



wherein we see that the negative charge is divided between the carbon and the oxygen. When this anion reacts with water, it can undergo protonation either on carbon, in which case the keto form results, or on oxygen, in which case the enol form is produced. The rate-limiting step for base-catalyzed enolization is usually the deprotonation step.

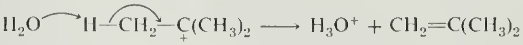
In neutral solution, the principal base present is H_2O. Since H_2O is a much weaker base than OH^-, proton transfer from an aldehyde or ketone is not as rapid and, consequently, enolization is slower. However, in acidic solution, some of the weakly basic carbonyl groups are protonated. The protonated aldehyde or ketone loses a proton from carbon with much greater ease, even to such a weak base as H_2O. A carbonyl group is not very basic and only a small amount of the protonated structure is present at equilibrium. The presence of the positive charge, however, greatly increases the rate of proton loss from carbon to solvent.



$$\text{(1)}\quad \mathrm{H{-}CH_2{-}\overset{\overset{O}{\|}}{C}CH_3 + H_3O^+ \rightleftharpoons \left[H{-}CH_2{-}\overset{\overset{\overset{+}{O}H}{\|}}{C}CH_3 \longleftrightarrow H{-}CH_2{-}\underset{+}{\overset{\overset{OH}{|}}{C}}CH_3\right] + H_2O}$$

$$\text{(2)}\quad \mathrm{\left[H{-}CH_2{-}\overset{\overset{\overset{+}{O}H}{\|}}{C}CH_3 \longleftrightarrow H{-}CH_2{-}\underset{+}{\overset{\overset{OH}{|}}{C}}CH_3\right] + H_2O \rightleftharpoons CH_2{=}\overset{\overset{OH}{|}}{C}CH_3 + H_3O^+}$$

In fact, the deprotonation of the protonated ketone (step 2) is analogous to the E1 elimination reaction, deprotonation of a carbonium ion.



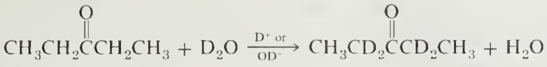
$$\mathrm{H_2O\;\; H{-}CH_2{-}\underset{+}{C}(CH_3)_2 \longrightarrow H_3O^+ + CH_2{=}C(CH_3)_2}$$

In acid-catalyzed enolization, the first step is a rapid equilibrium. Loss of a proton from carbon (step 2) is slower and is rate-determining.

Let us summarize. In aqueous solution aldehydes and ketones are in equilibrium with their corresponding enol forms. Interconversion of the enol and keto forms is catalyzed by either acid or base. At any given moment, the vast majority of molecules are present as the more stable keto form. However, as we shall see, the small amount of enol tautomer present is involved as an important **intermediate** in many of the reactions of aldehydes and ketones.

One way in which the intermediate enols and enolates can be detected is by

deuterium exchange. If one dissolves a ketone in D_2O containing DCl or Na^+OD^-, all of the α-hydrogens are exchanged for deuterium.



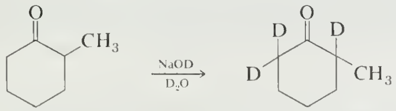
$$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3 + D_2O \xrightarrow[OD^-]{D^+\text{ or}} CH_3CD_2\overset{\overset{O}{\|}}{C}CD_2CH_3 + H_2O$$

3-pentanone 3-pentanone-2,2,4,4,-d_4

The amount of deuterium incorporation at equilibrium is related to the initial concentrations of the ketone and D_2O. In dilute solution, the D_2O is present in large excess and replacement of the α-hydrogens by deuterium is essentially complete. The *rate* of deuterium incorporation is proportional to the concentration of ketone and the catalyst, either D^+ or OD^-.

$$\text{rate}_{ex} = k[\text{ketone}][D^+] \qquad \text{or} \qquad k'[\text{ketone}][OD^-]$$

Such exchange reactions may be applied even when the aldehyde or ketone is not very soluble in water. Shaking such a compound with NaOD or DCl in D_2O for several hours results in virtually complete exchange.

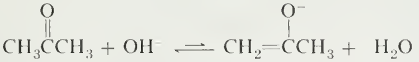


2-methylcyclohexanone 2-methylcyclohexanone-2,6,6-d_3

Since the number of deuteriums is easily determined by mass spectroscopy or by nmr, this reaction is a useful technique for counting the number of α-hydrogens.

B. *Enolate Ions*

From the pK_a of acetone, +20, it is clear that in aqueous solution where the strongest base is OH^-, the amount of enolate ion present is small.

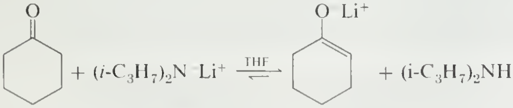


$$CH_3\overset{\overset{O}{\|}}{C}CH_3 + OH^- \rightleftharpoons CH_2{=}\overset{\overset{O^-}{|}}{C}CH_3 + H_2O$$

pK_a 20 pK_a 15.7

$$K = \frac{[\text{enolate}]\cancel{[H^+]}[H_2O]}{[\text{acetone}][OH^-]\cancel{[H^+]}} = \frac{10^{-20}}{10^{-15.7}} \approx 10^{-4}$$

However, if a ketone is treated with a much stronger base, it can be converted completely into the corresponding enolate ion.



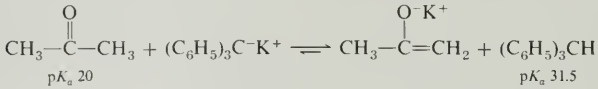
pK_a 16.7 $pK_a \approx 40$

$$K = \frac{[\text{enolate}]}{[\text{cyclohexanone}]} \times \frac{[\text{diisopropylamine}]}{[\text{lithium diisopropylamide}]} = \frac{10^{-16.7}}{10^{-40}} \approx 10^{23}$$

Lithium diisopropylamide, $(i\text{-}C_3H_7)_2N^-Li^+$, is prepared by treating a solution of diisopropylamine in ether, THF, or 1,2-dimethoxyethane, with *n*-butyllithium.

$$(i\text{-}C_3H_7)_2NH + n\text{-}BuLi \longrightarrow (i\text{-}C_3H_7)_2N^-Li^+ + C_4H_{10}$$

The base is widely used for converting ketones quantitatively into their corresponding lithium enolates.



$$\underset{pK_a\ 20}{CH_3-\overset{\overset{O}{\|}}{C}-CH_3} + (C_6H_5)_3C^-K^+ \rightleftharpoons CH_3-\overset{\overset{O^-K^+}{|}}{C}=CH_2 + \underset{pK_a\ 31.5}{(C_6H_5)_3CH}$$

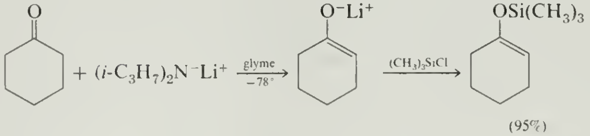
Potassium triphenylmethide, $(C_6H_5)_3C^-K^+$, is prepared by reaction of triphenylmethane or chlorotriphenylmethane with potassium metal in an ether solvent such as glyme or THF.

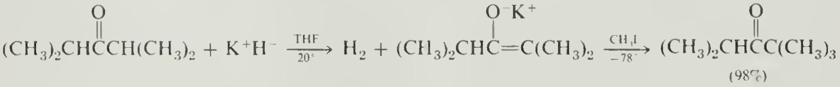
$$(C_6H_5)_3CH + K \longrightarrow (C_6H_5)_3C^-K^+ + \tfrac{1}{2}H_2$$
$$(C_6H_5)_3CCl + 2\,K \longrightarrow (C_6H_5)_3C^-K^+ + KCl$$

The base gives intense blood red solutions. Since enolate ions are colorless, a ketone may be converted into its enolate ion by titration with potassium triphenylmethide. So long as excess ketone remains, the solution is colorless. When sufficient base has been added to form the enolate ion completely, the red color of the triphenylmethide ion persists.

Solutions of enolate ions may be prepared and are quite stable if air and moisture are rigorously excluded. In many cases, such enolate ions are valuable synthetic intermediates.

Enolate ions are ambident anions (Section 8.4). Just as they may undergo protonation on either carbon or oxygen, they may also react with other electrophilic species at either of these two centers. Two examples that illustrate this ambident character are the reactions with chlorotrimethylsilane and methyl iodide.





$$(CH_3)_2CH\overset{\overset{O}{\|}}{C}CH(CH_3)_2 + K^+H^- \xrightarrow[20^\circ]{THF} H_2 + (CH_3)_2CH\overset{\overset{O^-K^+}{|}}{C}=C(CH_3)_2 \xrightarrow[-78^\circ]{CH_3I} \underset{(98\%)}{(CH_3)_2CH\overset{\overset{O}{\|}}{C}C(CH_3)_3}$$

Potassium hydride, KH, is commercially available as a grey microcrystalline material dispersed in white mineral oil. Potassium hydride is insoluble in hydrocarbons, ethers, ammonia, and amines. For use, the mineral oil is washed away with an appropriate solvent and the hydride is used as a slurry. It is much more reactive than sodium hydride. It converts ketones to the potassium enolates in minutes at room temperature.

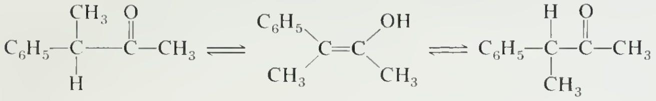
In one of the preceding reactions, reaction occurs exclusively on oxygen and in the other reaction occurs totally on carbon. Whether or not the oxygen or the carbon of an enolate ion is the site of reaction with an electrophile is determined by a number of factors. The most important factor, which is illustrated by the examples just given, is the *reactivity of the electrophile*. In general, the more reactive the electrophile, the greater is the percentage of reaction at the oxygen atom. Other important factors are the nature of the solvent and the nature of the associated cation.

The last two effects are both related to the **degree of association** of the enolate salt in solution. In an enolate ion, the negative charge is borne mostly by the more electronegative oxygen atom. In most organic solvents, the enolate salt exists in solution as an ion pair or as some higher aggregate of ions. In the ion pair, the metal cation is in close juxtaposition to the *oxygen* of the enolate ion (it is actually partly *solvated* by this oxygen). The cation thus "protects" or "shields" the oxygen and tends to direct reactions of the ambident anion to the carbon. Polar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide, solvate cations efficiently and tend to break up the ion pairs. The "bare" enolate ion has a greater tendency to undergo reaction on oxygen. With a given reagent, the major amount of reaction may still be on carbon, but the percentage of reaction on oxygen is invariably higher in such solvents. The chemistry of such systems is rather complex and the details have not yet been fully worked out.

Changing the metal cation from Li^+ to Na^+ to K^+ has a similar effect. Since the larger alkali metal ions require less solvation than does lithium, the corresponding enolate salts are more highly dissociated.

C. *Racemization*

When (R)-3-phenyl-2-butanone is dissolved in aqueous ethanol that contains NaOH or HCl, the optical rotation of the solution gradually drops to zero. Reisolation from the reaction mixture yields a racemic mixture of the (R) and (S) enantiomers. The rate of racemization is proportional to the concentration of ketone and the concentration of NaOH or HCl. Clearly, racemization occurs by way of the intermediate enol form in which the former asymmetric carbon is planar and hence achiral.



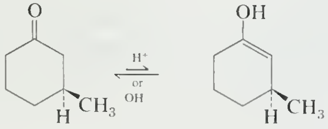
(R)-3-phenyl-2-butanone (achiral) (S)-3-phenyl-2-butanone

Since racemization involves the formation of the enol form, the rate of racemization is exactly equal to the rate of enolization:

$$\text{rate} = k[\text{ketone}][\text{H}^+] \qquad \text{or} \qquad k'[\text{ketone}][\text{OH}^-]$$

Furthermore, the rate of racemization is equal to the rate of deuterium incorporation because both reactions involve the same intermediate enol.

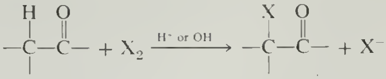
Note that racemization will occur *only* when the asymmetric carbon is α to the carbonyl group. If the aldehyde or ketone is chiral because of asymmetry at some other carbon, the enol form is also chiral and enolization does not result in racemization.



(S)-3-methylcyclohexanone (chiral)

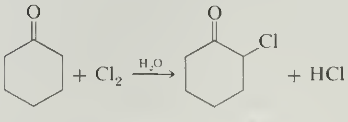
D. *Halogenation*

Aldehydes and ketones undergo acid- and base-catalyzed halogenation.

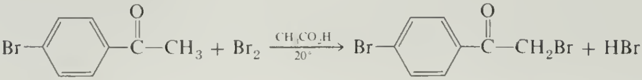


$$-\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}-\overset{\displaystyle O}{\overset{\|}{C}}- + X_2 \xrightarrow{H^+ \text{ or } OH^-} -\overset{\displaystyle X}{\overset{|}{\underset{|}{C}}}-\overset{\displaystyle O}{\overset{\|}{C}}- + X^-$$

The reaction occurs with chlorine, bromine, and iodine.

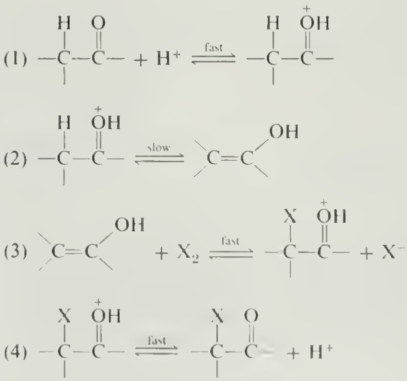


(61–66%)



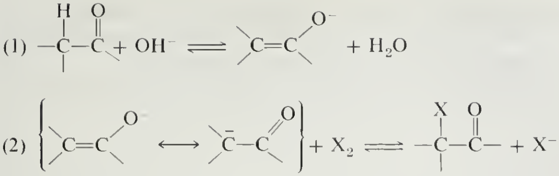
(69–77%)

Halogenation is often carried out without added catalyst. In this case, the reaction is autocatalytic because an equivalent of hydrohalic acid is formed in the reaction. In the base-catalyzed reaction, a full equivalent of base must obviously be used because an equivalent of HX is formed in the reaction. The actual species that reacts with the halogen is the enol form of the aldehyde or ketone; the purpose of the acid or base is simply to catalyze enolization. Acid-catalyzed halogenation is simply the normal electrophilic reaction of halogen with a double bond. The probable mechanism of the acid-catalyzed reaction is



There is considerable evidence for this mechanism. The rate of the reaction depends only upon the concentration of the ketone and the acid; it is independent of halogen concentration. Chlorination and bromination occur at the same rate. Halogenation occurs at the same rate as does acid-catalyzed exchange of an α-proton for deuterium.

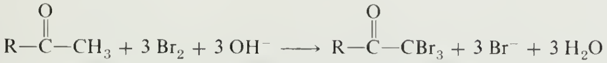
In the base-catalyzed reaction, the enolate ion is the probable intermediate.



The acid- and base-catalyzed halogenation reactions differ in several important aspects. In acid-catalyzed halogenation, each successive halogenation step is normally slower than the previous one. Therefore, it is usually possible to prepare a monohalo ketone in good yield by carrying out the halogenation under conditions of acid catalysis using one equivalent of halogen, as seen by the examples on page 366.

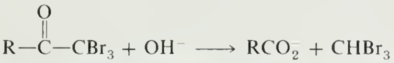
In the base-catalyzed reaction, each successive halogenation step is faster than the previous one, since the electron-attracting halogens increase the acidity of halogenated ketones; consequently, base-catalyzed halogenation is not a generally useful method for preparation of a monohalo ketone.

Methyl ketones undergo base-catalyzed halogenation to give the trihalo ketone, which is normally not isolated.



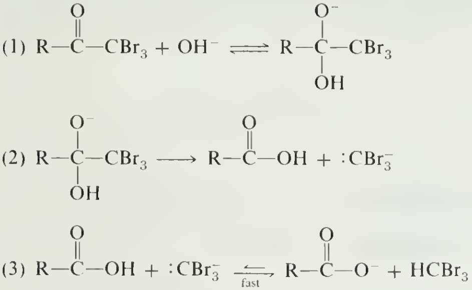
$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}CH_3 + 3\,Br_2 + 3\,OH^- \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}CBr_3 + 3\,Br^- + 3\,H_2O}$$

Instead, the α,α,α-trihaloketone reacts further with hydroxide ion to give a carboxylate salt and the corresponding trihalomethane:



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}CBr_3 + OH^- \longrightarrow RCO_2^- + CHBr_3} \qquad (15\text{-}1)$$

The overall reaction is known as the **haloform reaction.** The probable mechanism for the cleavage reaction is



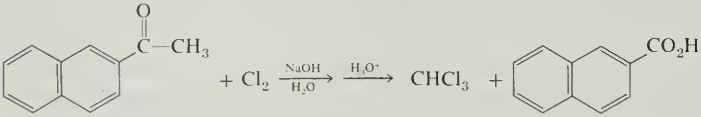
$$(1)\quad \mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}CBr_3 + OH^- \rightleftharpoons R{-}\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}{-}CBr_3}$$

$$(2)\quad \mathrm{R{-}\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}{-}CBr_3 \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}OH + {:}CBr_3^-}$$

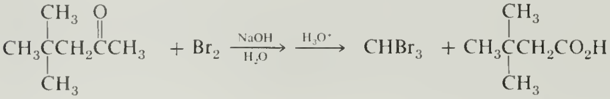
$$(3)\quad \mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}OH + {:}CBr_3^- \underset{\text{fast}}{\rightleftharpoons} R{-}\overset{\overset{O}{\|}}{C}{-}O^- + HCBr_3}$$

The proposed mechanism is an example of a nucleophilic addition-elimination process. The addition of bases to a carbonyl group is treated in the next section. Furthermore, as we shall see in Section 18.9, the addition-elimination mechanism is important in the chemistry of carboxylic acid derivatives. In the present case, the trihalomethyl anion is far more stable than methyl anion itself. (The pK_a of chloroform, $CHCl_3$, is about 25, and the other haloforms have comparable acidities.) Most of the time when hydroxide ion adds to the carbonyl group it comes right back off again, but sometimes the less stable CX_3^- ion comes off instead. This ion immediately becomes protonated so that the cleavage of the trihalomethyl ion, when it does occur, is irreversible. The net result is eventual cleavage of the halogenated ketone as shown in equation (15-1).

The haloform reaction is often a preparatively useful method for the indirect **oxidation** of a methyl ketone to the corresponding carboxylic acid.



2-acetylnaphthalene chloroform (87%) naphthalene-2-carboxylic acid



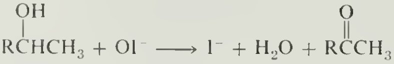
$$\mathrm{CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{\overset{O}{\|}}{C}CH_3 + Br_2 \xrightarrow[H_2O]{NaOH} \xrightarrow{H_3O^+} CHBr_3 + CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2CO_2H}$$

(89%)

4,4-dimethyl-2-pentanone bromoform 3,3-dimethylbutanoic acid

> To a solution of 525 g of NaOH in 2 liters of H_2O at 0° is added 240 ml of bromine. To this solution of sodium hypobromite is added 171 g of 4,4-dimethyl-2-pentanone. After 14 hr, the mixture is steam distilled to remove $CHBr_3$. The aqueous solution is then acidified with 600 ml of conc. H_2SO_4. Distillation of the resulting oil yields 155 g of 3,3-dimethylbutanoic acid (89%).

Because triiodomethane, iodoform, is crystalline and has a characteristic canary yellow color, this variant of the haloform reaction has been used in the past as a qualitative test for the presence of the methyl ketone or methylcarbinol grouping in a molecule of unknown structure. The methylcarbinol structure gives rise to iodoform because iodine in aqueous hydroxide is an oxidizing agent and produces the methyl ketone as an intermediate.



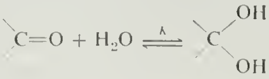
$$\mathrm{R\overset{OH}{\overset{|}{C}}HCH_3 + OI^- \longrightarrow I^- + H_2O + R\overset{\overset{O}{\|}}{C}CH_3}$$

15.7 Carbonyl Addition Reactions

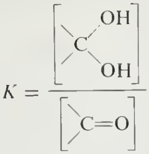
A. *Carbonyl Hydrates: Gem-diols*

The reaction of aldehydes and ketones with water to produce *gem*-diols is not a significant synthetic reaction but it points up many of the important principles of reactions of carbonyl groups. As with the enolization reaction, the addition reaction with water involves consideration of both equilibrium and rate.

The equilibrium involved may be written as



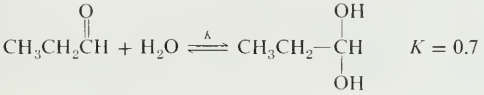
The magnitude of the equilibrium constant, K, is sensitive to the nature of the carbonyl group. In aqueous solution, the equilibrium constant is



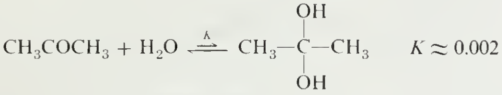
$$K = \frac{[\mathrm{C(OH)_2}]}{[\mathrm{C{=}O}]}$$

(Note that the concentration of water, which is present in large excess, remains essentially constant. In such cases, it is usually not included in the definition of the equilibrium constant.) The equilibrium constant has a value of about 10^3 for formaldehyde, roughly 1 for other aldehydes such as propionaldehyde and about 10^{-3} for ketones. Thus, a solution of formaldehyde in water is almost all $CH_2(OH)_2$. Aqueous solutions of other aldehydes contain comparable amounts of $RCHO$ and $RCH(OH)_2$ and ketones are present almost wholly as the keto form, $RCOR'$.

$$CH_2{=}O + H_2O \overset{K}{\rightleftharpoons} HOCH_2OH \qquad K \approx 2 \times 10^3$$

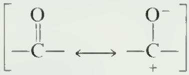


$$CH_3CH_2\overset{O}{\overset{\|}{C}}H + H_2O \overset{K}{\rightleftharpoons} CH_3CH_2{-}\underset{OH}{\overset{OH}{C}}H \qquad K = 0.7$$



$$CH_3COCH_3 + H_2O \overset{K}{\rightleftharpoons} CH_3{-}\underset{OH}{\overset{OH}{C}}{-}CH_3 \qquad K \approx 0.002$$

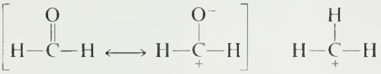
This phenomenon can be explained with concepts that come from carbonium ion chemistry. Two important resonance structures can be written for a carbonyl group:



$$\left[-\overset{O}{\overset{\|}{C}}- \longleftrightarrow -\underset{+}{\overset{O^-}{\overset{|}{C}}}- \right]$$

The structure with the double bond is the more important because in it all atoms have complete octets. However, the other structure contributes to a significant extent. This dipolar structure has the character of a carbonium ion. Recall that the order of carbonium ion stability is secondary > primary > methyl.

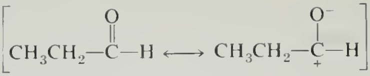
The dipolar resonance structure of formaldehyde, is analogous to a methyl cation:



$$\left[H{-}\overset{O}{\overset{\|}{C}}{-}H \longleftrightarrow H{-}\underset{+}{\overset{O^-}{\overset{|}{C}}}{-}H \right] \qquad H{-}\underset{+}{\overset{H}{\overset{|}{C}}}{-}H$$

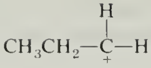
formaldehyde　　methyl cation

The dipolar resonance structure of a higher aldehyde is analogous to a primary carbonium ion, whereas that for a ketone is analogous to a secondary carbonium ion:



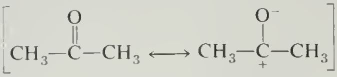
$$\left[CH_3CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-H \longleftrightarrow CH_3CH_2-\overset{\overset{\displaystyle O^-}{|}}{\underset{+}{C}}-H\right]$$

propionaldehyde



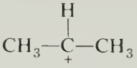
$$CH_3CH_2-\overset{\overset{\displaystyle H}{|}}{\underset{+}{C}}-H$$

n-propyl cation



$$\left[CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\overset{\overset{\displaystyle O^-}{|}}{\underset{+}{C}}-CH_3\right]$$

acetone



$$CH_3-\overset{\overset{\displaystyle H}{|}}{\underset{+}{C}}-CH_3$$

isopropyl cation

Just as isopropyl cation is more stable than *n*-propyl cation, acetone is more stable than propionaldehyde due to the extra stabilization imparted by the dipolar resonance structure.

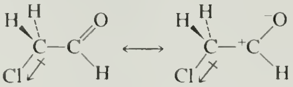
We can see this effect by an examination of heats of formation of isomeric aldehydes and ketones. Some of these comparisons are summarized in Table 15.4. Ketones are about 7 kcal mole^{-1} more stable than the isomeric aldehydes.

Consideration of the carbonium ion character of a carbonyl group has other corollaries as well. Consider the effect of a nearby polar substituent such as a chlorine, as in chloroacetaldehyde.

$$ClCH_2CHO$$

chloroacetaldehyde

The C—Cl dipole acts to destabilize the carbonium ion resonance structure. Hence, this structure contributes less to the overall resonance hybrid and the resonance hybrid is less stable as a result



contributes less

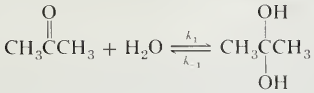
No comparable effect operates on the corresponding hydrate. Thus, such a substituent shifts the equilibrium and the aldehyde is more hydrated. The equilibrium constant for trichloroacetaldehyde, "chloral," is about 3 × 10^4. This compound exists almost wholly as the hydrate.

> Chloral hydrate, $CCl_3CH(OH)_2$, is a crystalline solid, m.p. 57°, having a distinctive odor. Its narcotic effect has lead to its illegal use as "knockout drops."

TABLE 15.4
Heats of Formation of Some Aldehydes and Ketones

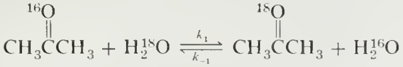
Aldehydes	ΔH_f°, kcal mole^{-1} 25°, gas	Ketones	ΔH_f°, kcal mole^{-1} 25°, gas
$HCHO$	−26.0		
CH_3CHO	−39.7		
CH_3CH_2CHO	−45.5	CH_3COCH_3	−51.9
$CH_3CH_2CH_2CHO$	−48.9	$CH_3CH_2COCH_3$	−57.0
$CH_3CH_2CH_2CH_2CHO$	−54.5	$CH_3CH_2CH_2COCH_3$	−61.8
		$CH_3CH_2COCH_2CH_3$	−61.8

The equilibrium between a carbonyl compound and its hydrate can also be described as the resultant of two rate constants:



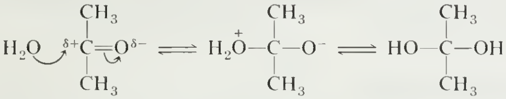
$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3\underset{OH}{\overset{OH}{C}}CH_3$$

The equilibrium constant is given by the ratio, $K = k_1/k_{-1}$. In the case of a ketone such as acetone, the amount of hydrate present is so small that its rate of formation cannot be determined directly. The rate constant, k_1, can be determined indirectly by an isotope exchange reaction. Water consists mostly of $H_2{}^{16}O$ but it also contains 0.20% of the heavy oxygen isotope as $H_2{}^{18}O$. Water enriched in the heavy isotope is available and the rate of hydration can be followed as a rate of incorporation of ^{18}O into acetone. The ^{18}O content of the ketone can be determined by mass spectroscopy (Chapter 16).



$$CH_3\overset{^{16}O}{\overset{\|}{C}}CH_3 + H_2^{18}O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3\overset{^{18}O}{\overset{\|}{C}}CH_3 + H_2^{16}O$$

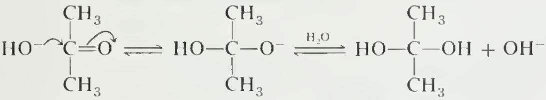
This exchange reaction is slow in pure water but is much faster in the presence of small amounts of acid or base. The exchange is both acid- and base-catalyzed. In the uncatalyzed reaction a molecule of water attacks the electron-deficient carbonyl carbon to produce an intermediate that undergoes rapid proton exchange to give the *gem*-diol.



$$H_2O \quad {}^{\delta+}\underset{CH_3}{\overset{CH_3}{C}}{=}O^{\delta-} \rightleftharpoons H_2\overset{+}{O}{-}\underset{CH_3}{\overset{CH_3}{C}}{-}O^- \rightleftharpoons HO{-}\underset{CH_3}{\overset{CH_3}{C}}{-}OH$$

The *gem*-diol decomposes to give back the ketone by an exact reversal of this sequence. If one of the oxygens in the diol is heavy oxygen, the dehydration process has an equal probability of losing the labeled oxygen in the leaving water or of retaining it in the ketone. However, water is a rather weakly basic reagent, and the carbonyl carbon is only slightly positive. Consequently, the direct attack by water on the carbonyl carbon is a slow process.

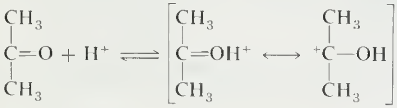
Hydroxide ion is a much more basic reagent and its reaction with a carbonyl group is much faster than that of water.



$$HO^- \quad \underset{CH_3}{\overset{CH_3}{C}}{=}O \rightleftharpoons HO{-}\underset{CH_3}{\overset{CH_3}{C}}{-}O^- \overset{H_2O}{\rightleftharpoons} HO{-}\underset{CH_3}{\overset{CH_3}{C}}{-}OH + OH^-$$

Note that the presence of hydroxide ion does not affect the *position* of equilibrium. It catalyzes the reverse reaction exactly as much as the forward reaction.

In the acid-catalyzed reaction, the ketone oxygen is first protonated in a rapid equilibrium process exactly as in enolization.

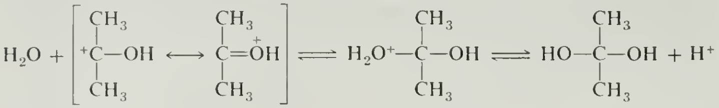


$$\underset{CH_3}{\overset{CH_3}{C}}{=}O + H^+ \rightleftharpoons \left[\underset{CH_3}{\overset{CH_3}{C}}{=}OH^+ \longleftrightarrow {}^+\underset{CH_3}{\overset{CH_3}{C}}{-}OH\right]$$

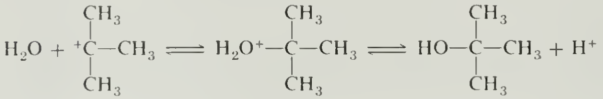
In the protonated compound the carbonyl carbon has more positive charge than in the neutral ketone. One resonance structure is that of a hydroxycarbonium ion.

A carbonyl group has dipolar character because oxygen is more electronegative than carbon and has greater attraction for electrons than carbon. The π bond of the carbonyl group is relatively polarizable, and the electron density in this bond is displaced toward oxygen. In a protonated carbonyl group the oxonium ion oxygen is even more electronegative, and the electron density is displaced even more towards oxygen leaving a more positive carbon.

The hydroxycarbonium ion reacts rapidly with water in a reaction that is analogous to the S_N1 solvolysis reaction involving carbonium ions (Section 8.8).



$$H_2O + \left[{}^{+}\overset{CH_3}{\underset{CH_3}{C}}-OH \longleftrightarrow \overset{CH_3}{\underset{CH_3}{C}}=\overset{+}{O}H \right] \rightleftharpoons H_2O^{+}-\overset{CH_3}{\underset{CH_3}{C}}-OH \rightleftharpoons HO-\overset{CH_3}{\underset{CH_3}{C}}-OH + H^{+}$$

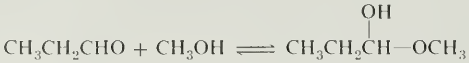


$$H_2O + {}^{+}\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \rightleftharpoons H_2O^{+}-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \rightleftharpoons HO-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 + H^{+}$$

The reverse reaction of dehydration of the ketone hydrate is analogous to an E1 elimination of an alcohol.

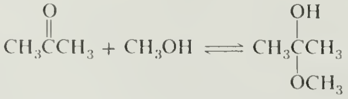
B. *Acetals and Ketals*

The equilibrium between carbonyl compounds and water is not a significant synthetic reaction because the *gem*-diols are generally unstable and readily dehydrate. However, the analogous reaction of alcohols has significant utility. The addition of 1 mole of an alcohol to the carbonyl group of an aldehyde or ketone yields a **hemiacetal** or a **hemiketal**, respectively.



$$CH_3CH_2CHO + CH_3OH \rightleftharpoons CH_3CH_2\overset{OH}{C}H-OCH_3$$

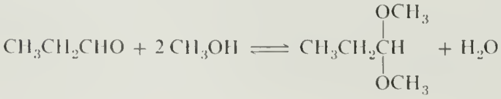
a hemiacetal



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + CH_3OH \rightleftharpoons CH_3\overset{OH}{\underset{OCH_3}{C}}CH_3$$

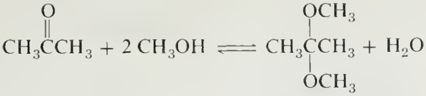
a hemiketal

Addition of 2 moles of an alcohol, with the consequent formation of 1 mole of water, yields an **acetal** or a **ketal**.



$$CH_3CH_2CHO + 2\,CH_3OH \rightleftharpoons CH_3CH_2\overset{OCH_3}{\underset{OCH_3}{C}}H + H_2O$$

an acetal

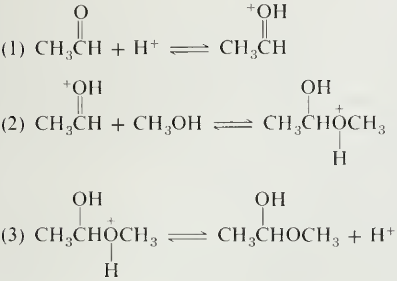


$$CH_3\overset{\overset{O}{\|}}{C}CH_3 + 2\,CH_3OH \rightleftharpoons CH_3\underset{\underset{OCH_3}{|}}{\overset{\overset{OCH_3}{|}}{C}}CH_3 + H_2O$$

a ketal

Formation of the hemiacetal or hemiketal is directly analogous to addition of water and is also subject to both acid and base catalysis. As with hydration, aldehydes give more of the addition product at equilibrium than do ketones.

Acid-catalyzed hemiacetal formation

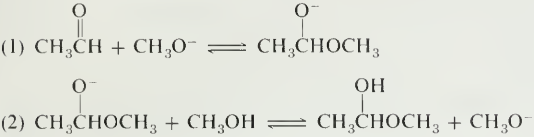


$$(1)\quad CH_3\overset{\overset{O}{\|}}{C}H + H^+ \rightleftharpoons CH_3\overset{\overset{^+OH}{\|}}{C}H$$

$$(2)\quad CH_3\overset{\overset{^+OH}{\|}}{C}H + CH_3OH \rightleftharpoons CH_3\overset{\overset{OH}{|}}{C}H\underset{\underset{H}{|}}{\overset{+}{O}}CH_3$$

$$(3)\quad CH_3\overset{\overset{OH}{|}}{C}H\underset{\underset{H}{|}}{\overset{+}{O}}CH_3 \rightleftharpoons CH_3\overset{\overset{OH}{|}}{C}HOCH_3 + H^+$$

Base-catalyzed hemiacetal formation



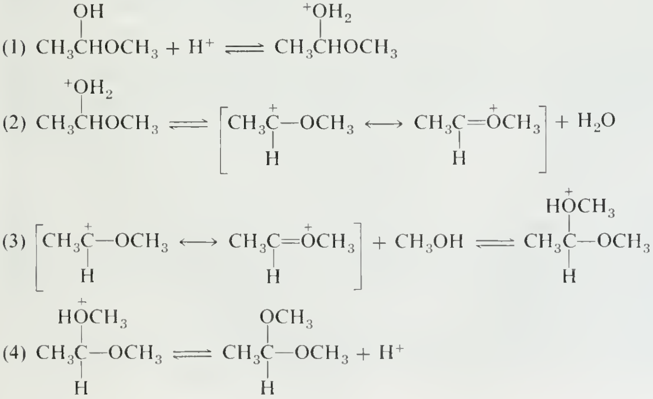
$$(1)\quad CH_3\overset{\overset{O}{\|}}{C}H + CH_3O^- \rightleftharpoons CH_3\overset{\overset{O^-}{|}}{C}HOCH_3$$

$$(2)\quad CH_3\overset{\overset{O^-}{|}}{C}HOCH_3 + CH_3OH \rightleftharpoons CH_3\overset{\overset{OH}{|}}{C}HOCH_3 + CH_3O^-$$

As with the hydrates, simple hemiacetals and hemiketals are generally not sufficiently stable for isolation.

Acetals and ketals are formed by way of the intermediate hemiacetal or hemiketal. Replacement of the —OH group by —OR is only acid-catalyzed.

Acid-catalyzed acetal formation



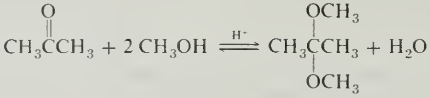
$$(1)\quad CH_3\overset{\overset{OH}{|}}{C}HOCH_3 + H^+ \rightleftharpoons CH_3\overset{\overset{^+OH_2}{|}}{C}HOCH_3$$

$$(2)\quad CH_3\overset{\overset{^+OH_2}{|}}{C}HOCH_3 \rightleftharpoons \left[CH_3\underset{\underset{H}{|}}{\overset{+}{C}}{-}OCH_3 \longleftrightarrow CH_3\underset{\underset{H}{|}}{C}{=}\overset{+}{O}CH_3\right] + H_2O$$

$$(3)\quad \left[CH_3\underset{\underset{H}{|}}{\overset{+}{C}}{-}OCH_3 \longleftrightarrow CH_3\underset{\underset{H}{|}}{C}{=}\overset{+}{O}CH_3\right] + CH_3OH \rightleftharpoons CH_3\underset{\underset{H}{|}}{\overset{\overset{H\overset{+}{O}CH_3}{|}}{C}}{-}OCH_3$$

$$(4)\quad CH_3\underset{\underset{H}{|}}{\overset{\overset{H\overset{+}{O}CH_3}{|}}{C}}{-}OCH_3 \rightleftharpoons CH_3\underset{\underset{H}{|}}{\overset{\overset{OCH_3}{|}}{C}}{-}OCH_3 + H^+$$

The net equilibrium that occurs when an aldehyde or ketone is treated with an alcohol and an acid catalyst is illustrated for acetone as follows:



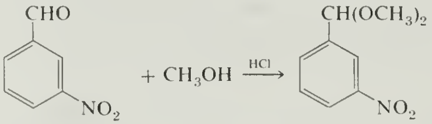
$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + 2\,CH_3OH \xrightleftharpoons{H^+} CH_3\underset{OCH_3}{\overset{OCH_3}{C}}CH_3 + H_2O$$

For simple aldehydes the overall equilibrium constant is favorable, and the acetal may be prepared simply by treating the aldehyde with two equivalents of alcohol and an acid catalyst.

$$CH_3CHO + 2\,CH_3CH_2OH \xrightleftharpoons{H^+} CH_3CH(OCH_2CH_3)_2 + H_2O$$

> A mixture of 1305 ml of ethanol (21.7 moles), 500 g of acetaldehyde (11.4 moles) and 200 g of anhydrous $CaCl_2$ is placed in a 4 liter bottle and kept at 25° for 1–2 days. At the end of this time the upper layer is washed with water and distilled to yield 790–815 g of 1,1-diethoxyethane, b.p. 101–103°. Note that $CaCl_2$ serves as a catalyst by hydrolyzing to give a small amount of HCl.

With larger aldehydes and with ketones, the equilibrium constant for acetalization or ketalization is generally unfavorable, more so for ketalization than for acetalization. For this reason, the reaction is usually carried out using the alcohol as solvent to drive the equilibrium to the right. For aldehydes, this usually allows the acetal to be produced in good yield.



(76–85%)

3-nitrobenzaldehyde

3-nitrobenzaldehyde dimethyl acetal

With ketones, the equilibrium lies even further to the left and special techniques are used to remove water and drive the equilibrium to the right. This is usually accomplished by using a technique known as **azeotropic distillation.** A mixture of the ketone and alcohol, along with the acid catalyst, is refluxed in benzene. The condensate from the reflux condenser is collected in a water separator known as a Dean-Stark trap (Figure 15.8). As the reaction occurs, water is formed and is distilled from the reaction flask as a binary azeotrope, which boils at 69°, and is 91% benzene and 9% water. The distillate condenses in the condenser and runs down into the water separator where it forms two layers. At 20°C, the composition of the upper layer is 99.94% benzene and 0.06% water. The composition of the lower layer is 0.07% benzene and 99.93% water. As the water separator fills, the essentially dry benzene, being less dense, overflows and runs back into the reaction vessel. After a steady state is achieved, a normal reflux situation holds, except that the water is trapped in the separator tube. This technique is a generally useful one for forcing equilibrium reactions to completion when one of the products is water. It may only be used when neither the ketone nor the alcohol is more volatile than benzene.

The acetal and ketal equilibria provide a fascinating example of the role of entropy in equilibria. As shown by the following examples, the formation of

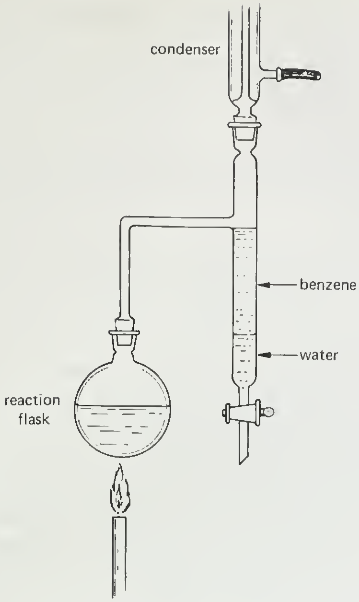


FIGURE 15.8 *The use of a water separator (Dean-Stark trap).*

acetals and ketals is exothermic. The additional C—O bond formed is stronger than the second or π bond of the carbonyl group.

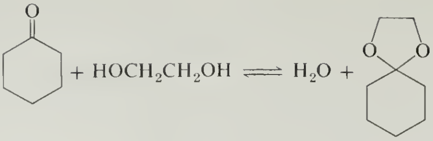
	ΔH°, gas, kcal mole^{-1}	
$CH_2O + 2\,CH_3OH \rightleftharpoons (CH_3O)_2CH_2 + H_2O$	-19.0	(15-2)
$CH_3CHO + 2\,CH_3OH \rightleftharpoons (CH_3O)_2CHCH_3 + H_2O$	-15.2	
$CH_3COCH_3 + 2\,CH_3OH \rightleftharpoons (CH_3O)_2C(CH_3)_2 + H_2O$	-11.7	

These ΔH° values reflect the greater stability of ketones compared to aldehydes and show how formaldehyde is the least stable of all. However, note that even the ketone equilibrium is quite exothermic, yet the equilibrium constant is unfavorable. We must recall that the equilibrium constant is governed by ΔG°, which depends on both enthalpy and entropy:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

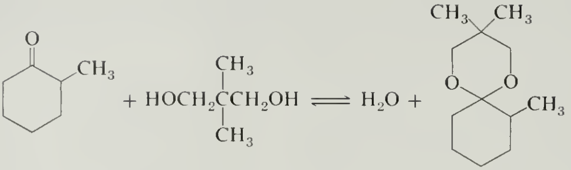
In these equilibria (15-2), three reactant molecules produce two product molecules. The resulting loss of the freedom of motion of one molecule corresponds to a negative entropy change. For aldehydes, the formation of acetals is so exothermic that the equilibrium lies far to the right despite the unfavorable entropy change. In the formation of ketals, however, the entropy term dominates.

This unfavorable entropy effect is avoided by the use of a 1,2- or 1,3-diol to form a cyclic ketal as in (15-3) and (15-4).


O
+ HOCH₂CH₂OH
H₂O +
O
O

(15-3)

(80%)

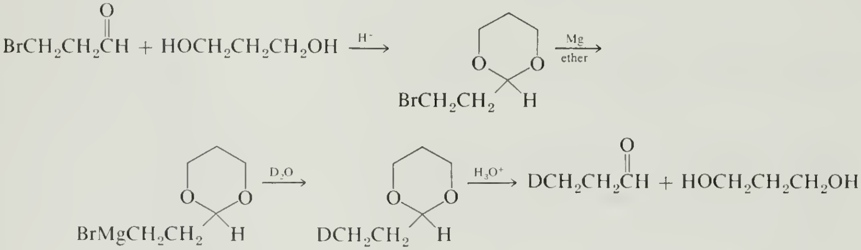

O
CH₃
CH₃
+ HOCH₂CCH₂OH
CH₃
H₂O +
CH₃
CH₃
O
O
CH₃

(15-4)

(83%)

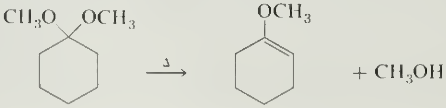
Note in these cases that two reactant molecules produce two product molecules. The overall entropy change is approximately zero and the exothermic enthalpy of the reaction results in favorable equilibria even for ketones.

Acetals and ketals are an important class of compounds in carbohydrate chemistry (Chapter 25). In other systems they are used principally to protect a carbonyl group during a synthetic scheme. Acetals and ketals are generally stable to basic conditions and are hydrolyzed back to carbonyl compounds in acidic solution. The following synthesis of 3-deuteriopropanal from 3-bromopropanal illustrates the use of an acetal as a **protecting group.**


O
BrCH₂CH₂CH + HOCH₂CH₂CH₂OH
H⁻
O
O
BrCH₂CH₂
H
Mg
ether
O
O
BrMgCH₂CH₂
H
D₂O
O
O
DCH₂CH₂
H
H₃O⁺
O
DCH₂CH₂CH + HOCH₂CH₂CH₂OH

In this case, it is desired to replace Br by D *via* the Grignard reagent. However, as we shall see in Section 15.7.D, Grignard reagents react with aldehydes and ketones, so that the direct conversion of 3-bromopropanal into a Grignard reagent is not possible. Therefore, the aldehyde is temporarily "protected" by conversion to the acetal, which is an ether and does not react with the Grignard reagent. At the end of the synthesis, the aldehyde is regenerated by hydrolysis of the acetal.

When acetals or ketals are pyrolyzed, one alcohol molecule is eliminated and the product is an alkyl vinyl ether. Such compounds are related structurally to the enol form of the aldehyde or ketone and they are commonly called **enol ethers.**

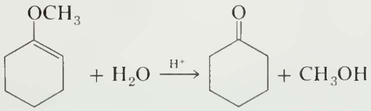

CH₃O
OCH₃
Δ
OCH₃
+ CH₃OH

1-methoxycyclohexene

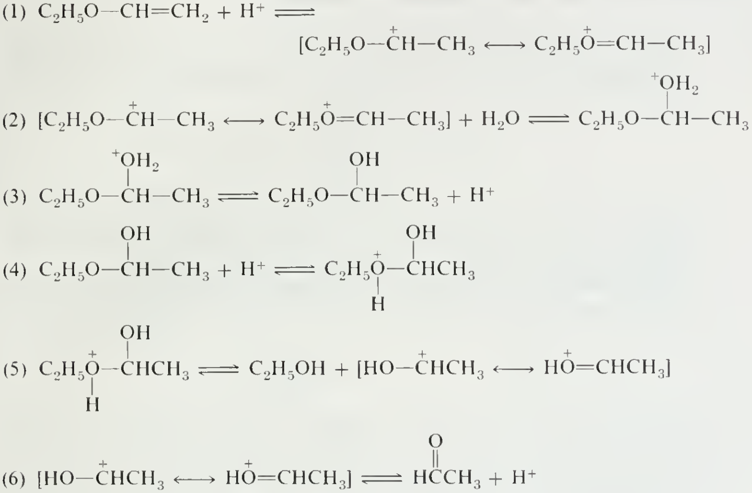
Enol ethers are also produced by the nucleophilic addition of alcohols to alkynes (Section 13.6.D).

$$HC{\equiv}CH + C_2H_5OH \xrightarrow{C_2H_5O^-} \underset{\text{ethyl vinyl ether}}{C_2H_5OCH{=}CH_2}$$

Like other ethers, enol ethers are stable to basic conditions and to basic reagents such as Grignard reagents. However, under acidic conditions, they undergo rapid hydrolysis to give the aldehyde or ketone and alcohol.



The mechanism of this ready hydrolysis involves the same type of intermediates as are involved in the formation and hydrolysis of acetals and ketals.



(1) $C_2H_5O{-}CH{=}CH_2 + H^+ \rightleftharpoons [C_2H_5O{-}\overset{+}{C}H{-}CH_3 \longleftrightarrow C_2H_5\overset{+}{O}{=}CH{-}CH_3]$

(2) $[C_2H_5O{-}\overset{+}{C}H{-}CH_3 \longleftrightarrow C_2H_5\overset{+}{O}{=}CH{-}CH_3] + H_2O \rightleftharpoons C_2H_5O{-}\overset{{}^{+}OH_2}{\overset{|}{C}}H{-}CH_3$

(3) $C_2H_5O{-}\overset{{}^{+}OH_2}{\overset{|}{C}}H{-}CH_3 \rightleftharpoons C_2H_5O{-}\overset{OH}{\overset{|}{C}}H{-}CH_3 + H^+$

(4) $C_2H_5O{-}\overset{OH}{\overset{|}{C}}H{-}CH_3 + H^+ \rightleftharpoons C_2H_5\underset{\underset{H}{|}}{\overset{+}{O}}{-}\overset{OH}{\overset{|}{C}}HCH_3$

(5) $C_2H_5\underset{\underset{H}{|}}{\overset{+}{O}}{-}\overset{OH}{\overset{|}{C}}HCH_3 \rightleftharpoons C_2H_5OH + [HO{-}\overset{+}{C}HCH_3 \longleftrightarrow H\overset{+}{O}{=}CHCH_3]$

(6) $[HO{-}\overset{+}{C}HCH_3 \longleftrightarrow H\overset{+}{O}{=}CHCH_3] \rightleftharpoons H\overset{O}{\overset{\|}{C}}CH_3 + H^+$

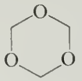
Enol ethers are important intermediates in several important organic reactions (for example, Section 33.3.D under Birch Reduction).

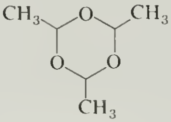
Acetals and ketals are ethers and will form dangerous peroxides on exposure to air. Appropriate precaution should be taken when heating acetals and ketals that have had long exposure to oxygen.

There is a final important consequence to be discussed relative to the tendency of aldehydes to form acetals. On standing, aldehydes tend to form cyclic or polymeric acetals that are isomeric with several molecules of aldehyde. Formaldehyde itself is a gas which is available commercially as a 37% aqueous solution called formalin or as a solid polymer, paraformaldehyde. Formaldehyde for use in syntheses is normally obtained by heating the dry polymer.

This linear polymer, $HO{-}(CH_2{-}O)_n{-}H$, forms the basis of some commercial plastics such as Delrin and Celcon. In these cases the terminal OH groups are "capped" with ester groups to prevent depolymerization or "unzipping" upon heating.

Formaldehyde forms a cyclic trimer, trioxane, a solid having m.p. 64°, which can be sublimed unchanged. Other aldehydes form similar trimers. Paraldehyde, from acetaldehyde, is a liquid, b.p. 128°, which regenerates acetaldehyde on heating with a trace of acid.

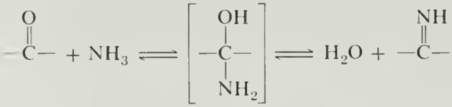

trioxane


paraldehyde

Acetaldehyde also forms a cyclic tetramer, metaldehyde, a solid that sublimes readily. Other low molecular weight aldehydes form cyclic trimers related to paraldehyde. This kind of behavior is not shown by ketones.

C. *Reaction with Derivatives of Ammonia*

Ammonia will react with aldehydes and ketones to form a compound containing the nitrogen analog of a carbonyl group. These compounds are called **imines.**



$$-\overset{\displaystyle O}{\overset{\|}{C}}- + NH_3 \rightleftharpoons \left[-\overset{\displaystyle OH}{\overset{|}{\underset{\underset{\displaystyle NH_2}{|}}{C}}}- \right] \rightleftharpoons H_2O + -\overset{\displaystyle NH}{\overset{\|}{C}}-$$

an imine

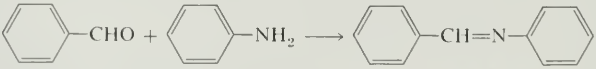
Imines derived from ammonia are an unimportant class of compounds. They hydrolyze rapidly even with water to generate carbonyl compounds.

The similar reaction with primary amines gives the more important substituted imine or **Schiff base.**

$$RCHO + R'NH_2 \rightleftharpoons RCH{=}NR' + H_2O$$

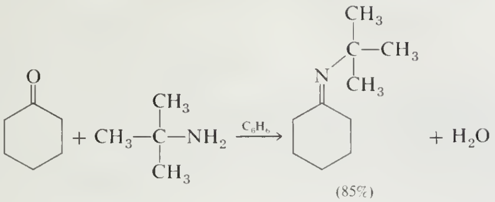
substituted imine
Schiff base

This type of reaction, in which two organic reagents are combined with the elimination of water, is generally referred to as a **condensation.** As in the case of the unsubstituted imines, most simple imines are fairly unstable compounds. They readily undergo hydrolysis back to the amine and carbonyl compound and are often prone to polymerization. However, when either the carbon or the nitrogen is substituted by a phenyl group, the resulting imine is generally rather stable.

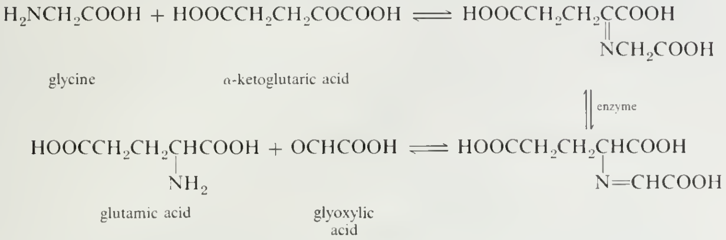


(84–87%)

Imines prepared from aliphatic aldehydes and ketones and aliphatic amines are less stable than aromatic analogs and somewhat more difficult to prepare. Since the equilibrium constant in this case is not as large as when there is a phenyl group attached to the C=N double bond, it is usually necessary to drive the reaction to completion by removal of water from the reaction mixture as it is formed, as in the formation of ketals. This is usually accomplished by azeotropic distillation, using benzene as solvent. An example of such a case is the condensation of cyclohexanone with *t*-butylamine.



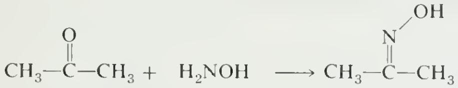
Although imines are not important organic reagents they are important intermediates in the biochemical process of **transamination.**



$$H_2NCH_2COOH + HOOCCH_2CH_2COCOOH \rightleftharpoons HOOCCH_2CH_2\underset{\underset{NCH_2COOH}{\|}}{C}COOH$$

$$HOOCCH_2CH_2\underset{\underset{NH_2}{|}}{C}HCOOH + OCHCOOH \rightleftharpoons HOOCCH_2CH_2\underset{\underset{N=CHCOOH}{|}}{C}HCOOH$$

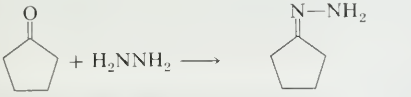
Aldehydes and ketones also react with other ammonia derivatives to give analogous adducts. Common reagents are hydroxylamine (H_2NOH), hydrazine (H_2NNH_2), phenylhydrazine ($H_2NNHC_6H_5$), and semicarbazide ($H_2NNH\overset{\overset{O}{\|}}{C}NH_2$). Examples of such reactions follow. Unlike imines, the products of these reactions are generally stable.



$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 + H_2NOH \longrightarrow CH_3-\overset{\overset{N-OH}{\|}}{C}-CH_3$$

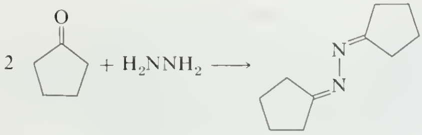
hydroxylamine

an **oxime**
acetone oxime

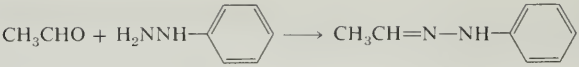


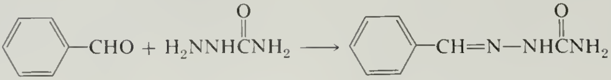
hydrazine

a **hydrazone**
cyclopentanone hydrazone

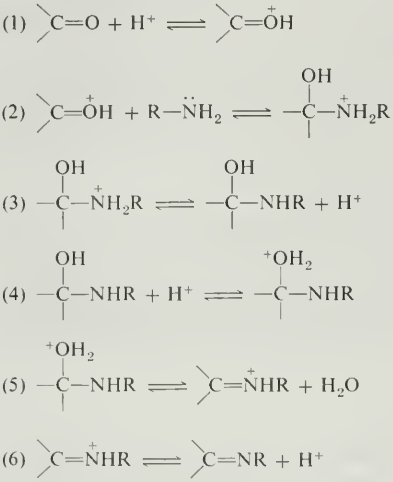


an **azine**
cyclopentanone azine





The reactions of carbonyl compounds with substituted ammonia compounds are generally catalyzed by mild acid. The mechanism is directly analogous to the reactions discussed previously with water and alcohols.



$$(1)\quad >\!\mathrm{C{=}O} + \mathrm{H^+} \rightleftharpoons\ >\!\mathrm{C{=}\overset{+}{O}H}$$

$$(2)\quad >\!\mathrm{C{=}\overset{+}{O}H} + \mathrm{R{-}\ddot{N}H_2} \rightleftharpoons -\underset{|}{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{\overset{+}{N}H_2R}$$

$$(3)\quad -\underset{|}{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{\overset{+}{N}H_2R} \rightleftharpoons -\underset{|}{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{NHR} + \mathrm{H^+}$$

$$(4)\quad -\underset{|}{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{NHR} + \mathrm{H^+} \rightleftharpoons -\underset{|}{\overset{\overset{^{+}\mathrm{OH_2}}{|}}{\mathrm{C}}}-\mathrm{NHR}$$

$$(5)\quad -\underset{|}{\overset{\overset{^{+}\mathrm{OH_2}}{|}}{\mathrm{C}}}-\mathrm{NHR} \rightleftharpoons\ >\!\mathrm{C{=}\overset{+}{N}HR} + \mathrm{H_2O}$$

$$(6)\quad >\!\mathrm{C{=}\overset{+}{N}HR} \rightleftharpoons\ >\!\mathrm{C{=}NR} + \mathrm{H^+}$$

Note that the overall result of the first three steps is a nucleophilic addition to the carbonyl group. The resulting product, which is a **hemiaminal**, is generally unstable and cannot normally be isolated. A second reaction occurs in which water is eliminated from the hemiaminal. The resulting product is the imine, oxime, or hydrazone, and so on.

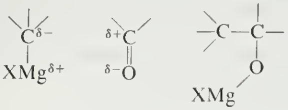
The rate-limiting step in the reaction is the second one, addition of the nucleophile to the protonated carbonyl group. The overall reaction obeys the following rate law:

$$\text{rate} = k[\text{ketone}][\mathrm{H^+}][\mathrm{RNH_2}]$$

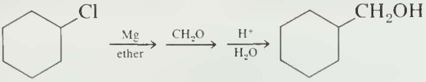
Although the reaction is acid-catalyzed at moderate pH, at higher acid concentration the rate actually diminishes with increasing acid concentration because the nitrogen base is itself protonated by acid. Therefore, the concentration of free nucleophile is inversely related to the acid concentration. At moderate acid concentrations both protonated carbonyl and some unprotonated nitrogen base are present and available for condensation. For this reason, the reaction is often run in the presence of a buffer such as sodium acetate. In some cases, particularly the formation of simple imines, the reaction proceeds satisfactorily without acid catalysis.

D. *Addition of Grignard Reagents*

Recall that the Grignard reagent contains a C—Mg bond which is polarized in the sense $C^- \, Mg^+$ (Section 9.1). Grignard reagents react readily and rapidly with carbonyl groups with the negative or carbanion carbon of the organometallic reacting with the positive or carbonium carbon of the carbonyl group.



Some examples show the scope of this important reaction:



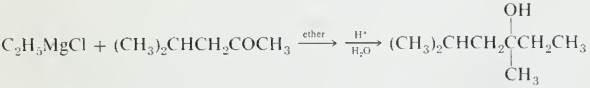
(64–69%)
cyclohexylmethanol

The Grignard reagent is prepared from 26.7 g of magnesium turnings and 118.5 g of cyclohexyl chloride in 450 ml of dry ether. In a separate flask 50 g of dry paraformaldehyde (page 377) is heated to 180–200° and the formaldehyde formed by depolymerization is carried by a stream of nitrogen gas into the Grignard solution. At the end of the reaction, ice and dilute sulfuric acid are added and the mixture is steam distilled. The distillate is extracted with ether and distilled at reduced pressure to yield 72.5–78.5 g of cyclohexylmethanol.

$$(CH_3)_2CHMgBr + CH_3CHO \xrightarrow{\text{ether}} \xrightarrow[H_2O]{H^+} (CH_3)_2CHCHOHCH_3$$

(53–54%)
3-methyl-2-butanol

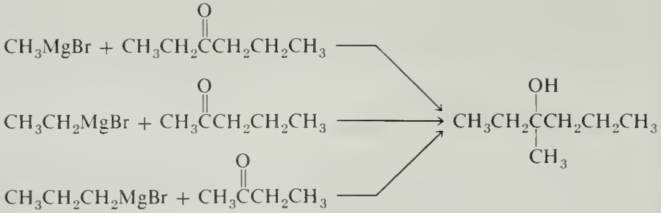
A solution of 600 g of isopropyl bromide in ether is slowly added to a mixture of 146 g of dry magnesium turnings in ether. The Grignard solution is then cooled to −5° and a solution of 200 g of acetaldehyde (prepared by heating paraldehyde (page 378) with a small amount of toluenesulfonic acid) in ether is added. Ice and dilute sulfuric acid are added and the mixture is extracted with ether. The dried extract is distilled to give 210–215 g of 3-methyl-2-butanol, b.p. 110–111.5°.



$$C_2H_5MgCl + (CH_3)_2CHCH_2COCH_3 \xrightarrow{\text{ether}} \xrightarrow[H_2O]{H^+} (CH_3)_2CHCH_2\overset{OH}{\underset{CH_3}{C}}CH_2CH_3$$

3,5-dimethyl-3-hexanol

As shown by these examples, the reaction is useful for preparation of primary, secondary, and tertiary alcohols. Reaction of a Grignard reagent with formaldehyde gives a primary alcohol, other aldehydes yield secondary alcohols, and ketones lead to tertiary alcohols. Note that secondary and tertiary alcohols may generally be prepared by more than one combination of Grignard reagent and carbonyl component.



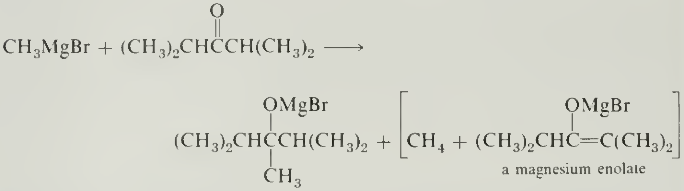
$$CH_3MgBr + CH_3CH_2\overset{\overset{\textstyle O}{\|}}{C}CH_2CH_2CH_3 \longrightarrow$$

$$CH_3CH_2MgBr + CH_3\overset{\overset{\textstyle O}{\|}}{C}CH_2CH_2CH_3 \longrightarrow CH_3CH_2\underset{\underset{\textstyle CH_3}{|}}{\overset{\overset{\textstyle OH}{|}}{C}}CH_2CH_2CH_3$$

$$CH_3CH_2CH_2MgBr + CH_3\overset{\overset{\textstyle O}{\|}}{C}CH_2CH_3 \longrightarrow$$

In such cases, the particular combination used is governed by practical matters, such as cost and availability of reagents, ease of handling reactants, and so on.

For the preparation of many alcohols the Grignard reaction is a simple and straightforward process. However, side reactions are important and can dominate in sterically congested cases where the normal carbonyl addition reaction is slowed. One such side reaction is enolization.



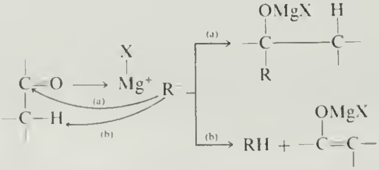
$$CH_3MgBr + (CH_3)_2CH\overset{\overset{\textstyle O}{\|}}{C}CH(CH_3)_2 \longrightarrow$$

$$(CH_3)_2CH\underset{\underset{\textstyle CH_3}{|}}{\overset{\overset{\textstyle OMgBr}{|}}{C}}CH(CH_3)_2 + \left[CH_4 + (CH_3)_2CH\overset{\overset{\textstyle OMgBr}{|}}{C}{=}C(CH_3)_2\right]$$

a magnesium enolate

When water is added during normal work-up the magnesium enolate is hydrolyzed to give back the starting ketone. In this side reaction the carbanionic carbon of the Grignard reagent is functioning as a base to produce the magnesium salt of the enolate ion.

The reaction is probably more complex than this. The magnesium can function as a Lewis acid and coordinates with the carbonyl oxygen. The carbanionic carbon can react with the carbonyl carbon or an α-hydrogen. The reactions may occur *via* aggregates and the magnesium and carbanion carbon may be different Grignard molecules. For simplicity, however, the reactions may be formulated as



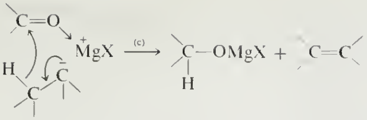
Another side reaction is important in hindered cases when the Grignard reagent has a β-hydrogen. In this reaction the carbonyl group is reduced and an alkene is formed.

$$(CH_3)_2CHCOCH(CH_3)_2 + (CH_3)_2CHMgBr \longrightarrow$$

diisopropyl ketone

$$(CH_3)_2CHCHOHCH(CH_3)_2 + CH_3CH{=}CH_2$$

This reaction can be formulated as an alternative mode of reaction of a Grignard reagent coordinated to a carbonyl group:



In these cases the use of alkyllithium reagents are especially useful because they are more reactive than Grignard reagents and can be used at low temperature where the alternative reduction and enolization reactions are less important. A spectacular example of a hindered system prepared by an organolithium reaction is

$$(CH_3)_3CCOC(CH_3)_3 + (CH_3)_3CLi \xrightarrow[-70°]{\text{ether}} [(CH_3)_3C]_3COH$$

(81%)

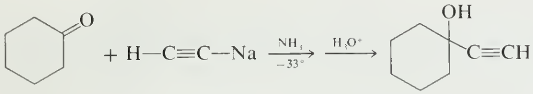
di-*t*-butyl ketone

t-butyllithium

3-*t*-butyl-2,2,4,4-tetramethyl-3-pentanol
(tri-*t*-butylcarbinol)

E. *Addition of Acetylide Anions*

Just as acetylide ions act as nucleophilic reagents in S_N2 reactions (Section 13.5.C) so also do they react with carbonyl groups in aldehydes and ketones to form the corresponding alkynylcarbinols. In practice, the sodium salts of terminal alkynes are prepared from sodium amide in liquid ammonia and are treated with the carbonyl compound.

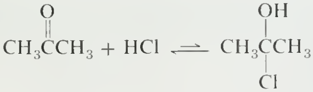


(65–75%)
1-ethynylcyclohexanol

> A stream of dry acetylene is passed into a solution of 23 g of sodium in 1 liter of liquid ammonia. After the sodium has been consumed, 98 g of cyclohexanone is added dropwise. The ammonia is allowed to evaporate and the residue is treated with 400 ml of ice water and acidified with 50% H_2SO_4. The product is extracted with ether and distilled. The yield of 1-ethynylcyclohexanol is 81–93 g (65–75%).

F. *Addition of HCN*

Most acids will add to the carbonyl group to some extent, but usually the adducts are not stable. With HCl, for example, the equilibrium lies far to the left and α-chloro alcohols cannot be isolated.

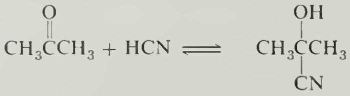


$$CH_3\overset{\overset{O}{\|}}{C}CH_3 + HCl \rightleftharpoons CH_3\underset{\underset{Cl}{|}}{\overset{\overset{OH}{|}}{C}}CH_3$$

If such an α-chloro alcohol is produced by some other process, it immediately decomposes to give HCl and the corresponding aldehyde or ketone.

Hydrocyanic acid does add to many carbonyl compounds to give stable adducts.

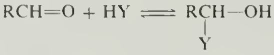
The product cyanoalcohols are commonly called **cyanohydrins.** Since a strong C—C bond is formed in the adduct, the equilibrium often favors the product cyanohydrin.



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + HCN \rightleftharpoons CH_3\underset{\underset{\displaystyle CN}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}CH_3$$

acetone cyanohydrin

The relative stabilities of 1-chloro alcohols and cyanohydrins can be appreciated by comparing bond energies:



$$RCH{=}O + HY \rightleftharpoons R\underset{\underset{\displaystyle Y}{|}}{C}H{-}OH$$

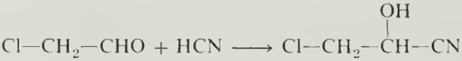
$$\Delta H^\circ = E(C{=}O) + E(H{-}Y) - E(O{-}H) - E(C{-}O) - E(C{-}Y)$$

The differences for ΔH° from one Y group to another are in the comparisons of $E(H{-}Y) - E(C{-}Y)$. To evaluate these bond strength differences compare the DH° values of H—Y and CH_3—Y for Y = Cl and CN:

$$Y = Cl\text{: } DH^\circ\ (H{-}Cl) - DH^\circ\ (CH_3{-}Cl) = 103 - 84 = 19 \text{ kcal mole}^{-1}$$
$$Y = CN\text{: } DH^\circ\ (H{-}CN) - DH^\circ\ (CH_3{-}CN) = 130 - 122 = 8 \text{ kcal mole}^{-1}$$

The difference in bond strengths between H—Cl and C—Cl is much greater than between H—CN and C—CN; hence, formation of the cyanohydrin has a more favorable energy change than formation of a 1-chloroalkanol.

For aldehydes and most aliphatic ketones, the equilibrium favors the adduct. For many aryl ketones and for some aliphatic ketones, the equilibrium constant is small and the reaction is not a useful one. The reaction is a typical nucleophilic addition, with the attacking nucleophile being CN^-. Addition is therefore catalyzed by base, which increases the cyanide concentration. The reaction can be carried out using liquid hydrogen cyanide (b.p. 26°) as the solvent.



$$Cl{-}CH_2{-}CHO + HCN \longrightarrow Cl{-}CH_2{-}\overset{\overset{\displaystyle OH}{|}}{C}H{-}CN$$

(95%)

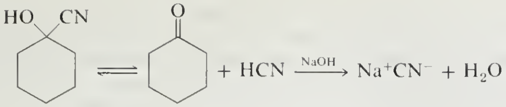
Because of the high toxicity of HCN, procedures such as the foregoing are seldom used. A more common procedure is to generate the HCN *in situ,* by the addition of HCl or H_2SO_4 to a mixture of the carbonyl compound and sodium or potassium cyanide.

$$CH_2O + KCN \xrightarrow[H_2O]{H_2SO_4} HO{-}CH_2{-}CN$$

(76–80%)

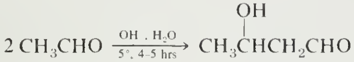
A mixture of 130 g of potassium cyanide in 250 ml of H_2O and 170 ml of 37% formaldehyde solution (formalin) is prepared. To this solution is added a mixture of 57 ml of conc. H_2SO_4 and 173 ml of H_2O. The product, obtained by exhaustive extraction with ether, weighs 87–91 g (76–80%).

Under strongly basic conditions cyanohydrin formation may be reversed. The equilibrium is shifted by transformation of the weakly acidic HCN ($pK_a = 11$) into its conjugate base.



G. *The Aldol Condensation*

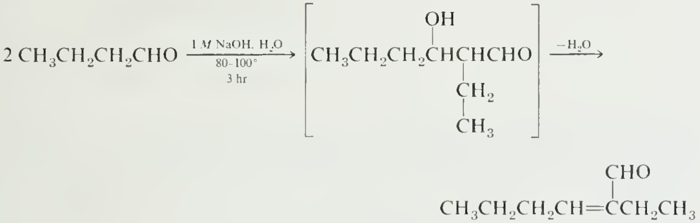
When acetaldehyde is treated with aqueous sodium hydroxide solution, 3-hydroxybutanal (trivial name, **aldol**) is formed in 50% yield.



$$2\,CH_3CHO \xrightarrow[5^\circ,\ 4\text{–}5\ hrs]{OH^-,\ H_2O} CH_3\overset{\begin{array}{c}OH\\|\end{array}}{C}HCH_2CHO$$

(50%)
aldol

The reaction is a general one for aldehydes that have a hydrogen α to the carbonyl group. The reaction is commonly known as the "aldol condensation," from the trivial name of the simplest β-hydroxyaldehyde obtainable by this reaction. The term "aldol" is used both as a trivial name for 3-hydroxybutanal and as a generic name for β-hydroxyaldehydes and ketones in general. Under more vigorous conditions (base concentration, temperature), elimination of the β-hydroxy group occurs and an **α,β-unsaturated aldehyde** is produced.

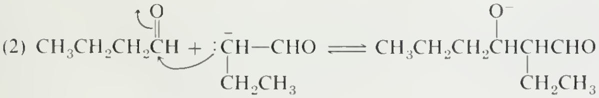


$$2\,CH_3CH_2CH_2CHO \xrightarrow[80\text{–}100^\circ,\ 3\ hr]{1\ M\ NaOH,\ H_2O} \left[CH_3CH_2CH_2\overset{\begin{array}{c}OH\\|\end{array}}{C}H\underset{\begin{array}{c}|\\CH_2\\|\\CH_3\end{array}}{C}HCHO\right] \xrightarrow{-H_2O} CH_3CH_2CH_2CH{=}\overset{\begin{array}{c}CHO\\|\end{array}}{C}CH_2CH_3$$

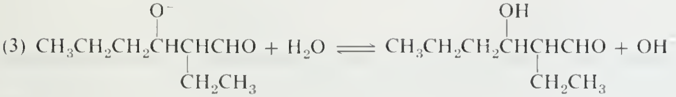
(86%)
2-ethylhex-2-enal

The probable mechanism for the aldol condensation is outlined below (illustrated for butyraldehyde).

$$(1)\quad CH_3CH_2CH_2CHO + OH^- \rightleftharpoons \{CH_3CH_2CH{=}CH{-}O^- \longleftrightarrow CH_3CH_2\bar{C}H{-}CH{=}O\} + H_2O$$

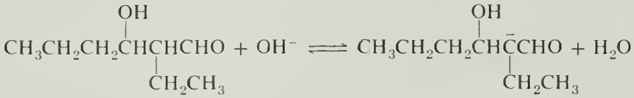


$$(2)\quad CH_3CH_2CH_2\overset{\begin{array}{c}O\\\|\end{array}}{C}H + :\underset{\begin{array}{c}|\\CH_2CH_3\end{array}}{\bar{C}H}{-}CHO \rightleftharpoons CH_3CH_2CH_2\overset{\begin{array}{c}O^-\\|\end{array}}{C}H\underset{\begin{array}{c}|\\CH_2CH_3\end{array}}{C}HCHO$$

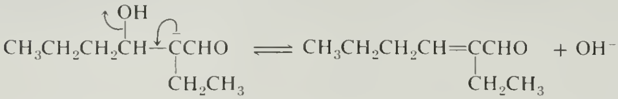


$$(3)\quad CH_3CH_2CH_2\overset{\begin{array}{c}O^-\\|\end{array}}{C}H\underset{\begin{array}{c}|\\CH_2CH_3\end{array}}{C}HCHO + H_2O \rightleftharpoons CH_3CH_2CH_2\overset{\begin{array}{c}OH\\|\end{array}}{C}H\underset{\begin{array}{c}|\\CH_2CH_3\end{array}}{C}HCHO + OH^-$$

The reaction is simply the nucleophilic addition of an enolate ion onto the carbonyl group of another, unionized, molecule. The slow, rate-limiting step, is usually this addition step. The dehydration of the β-hydroxyaldehyde or ketone formed by the above mechanism to produce an α,β-unsaturated carbonyl compound generally involves the enolate ion of the aldol product.

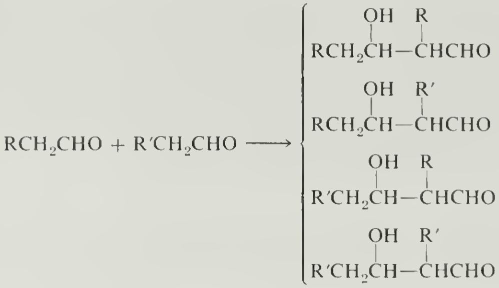
(4) 

$$CH_3CH_2CH_2\overset{OH}{C}H\underset{CH_2CH_3}{C}HCHO + OH^- \rightleftharpoons CH_3CH_2CH_2\overset{OH}{C}H\underset{CH_2CH_3}{\bar{C}}CHO + H_2O$$

(5) 

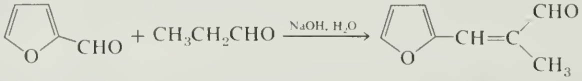
$$CH_3CH_2CH_2\overset{OH}{C}H-\underset{CH_2CH_3}{\bar{C}}CHO \rightleftharpoons CH_3CH_2CH_2CH{=}\underset{CH_2CH_3}{C}CHO + OH^-$$

When a mixture of two aldehydes is treated with base, four aldol products are possible.



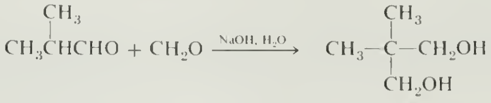
$$RCH_2CHO + R'CH_2CHO \longrightarrow \left\{\begin{array}{l} RCH_2\overset{OH}{C}H-\overset{R}{C}HCHO \\ RCH_2\overset{OH}{C}H-\overset{R'}{C}HCHO \\ R'CH_2\overset{OH}{C}H-\overset{R}{C}HCHO \\ R'CH_2\overset{OH}{C}H-\overset{R'}{C}HCHO \end{array}\right.$$

In practice, a complex mixture usually results in such a situation. However, when one of the aldehydes cannot form an enolate ion or when one has a fairly unreactive carbonyl group, such a "mixed aldol condensation" is often feasible.



furfural (72%)

A rather special case in which the mixed aldol condensation is useful employs formaldehyde as one component. The initial β-hydroxyaldehyde undergoes a further reaction with excess formaldehyde to give the diol and formate ion (a crossed Cannizzaro reaction, Section 15.8.D).

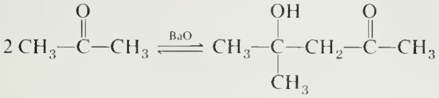


$$CH_3\overset{CH_3}{C}HCHO + CH_2O \xrightarrow{NaOH,\ H_2O} CH_3-\underset{CH_2OH}{\overset{CH_3}{C}}-CH_2OH$$

(90%)

isobutyraldehyde 2,2-dimethyl-1,3-propanediol

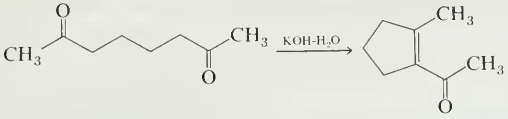
Although ketones also undergo the aldol condensation, the reaction in this case often requires rather special conditions. The overall reaction is an equilibrium process, and it appears that the equilibrium constant in most ketone aldol condensations is unfavorable. For example, acetone and its aldol product (4-hydroxy-4-methyl-2-pentanone, often known by the common name "diacetone alcohol") are in rapid equilibrium in the presence of base catalysts. The amount of the aldol product in the equilibrium is only a few per cent. However, if the product is removed from the basic catalyst as it is formed, the conversion can be accomplished in 80% yield.



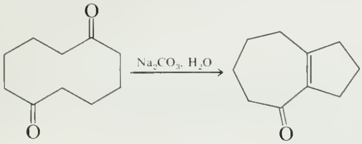
$$2\,\mathrm{CH_3}-\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3} \xrightleftharpoons{\mathrm{BaO}} \mathrm{CH_3}-\underset{\underset{\displaystyle \mathrm{CH_3}}{|}}{\overset{\overset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$$

"diacetone alcohol"

Intramolecular aldol condensation of diketones is an important method for the synthesis of cyclic compounds.

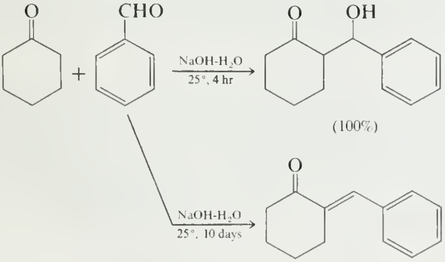


(83%)



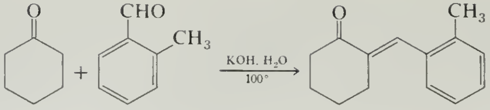
(96%)

Since ketones undergo self-condensation much more slowly than aldehydes, mixed aldol condensations between a ketone and a nonenolizable aldehyde are usually clean. In order to assure the formation of a 1 : 1 adduct, an excess of ketone is often used, and the reaction is carried out under fairly mild conditions.

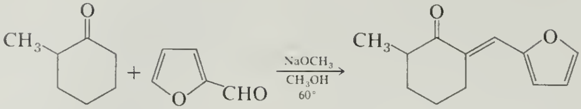


(76%)

In cases where the aldehyde carbonyl group is fairly hindered or when one side of the carbonyl group has only one hydrogen, 1:1 adducts form readily, with little complication from more extensive reaction.



(71%)

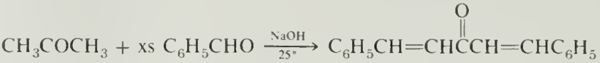


(84%)

However, with excess (xs) aldehyde, it is possible for reaction to occur at both sides of a ketone carbonyl group.

$$\text{xs } CH_3COCH_3 + C_6H_5CHO \xrightarrow[25^\circ]{NaOH} CH_3COCH{=}CHC_6H_5$$

(65–78%)
benzalacetone



$$CH_3COCH_3 + \text{xs } C_6H_5CHO \xrightarrow[25^\circ]{NaOH} C_6H_5CH{=}CH\overset{\overset{\displaystyle O}{\|}}{C}CH{=}CHC_6H_5$$

dibenzalacetone

H. *Wittig Reaction*

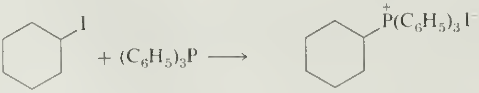
Alkyl halides react with triphenylphosphine, $(C_6H_5)_3P$, by the S_N2 mechanism to give crystalline **phosphonium salts.**

$$(C_6H_5)_3P + CH_3CH_2Br \longrightarrow (C_6H_5)_3\overset{+}{P}CH_2CH_3\,Br^-$$

ethyltriphenylphosphonium bromide

Phosphine, PH_3, is the phosphorus analog of ammonia. It is a poisonous gas and is usually spontaneously flammable because of the presence of impurities. Triphenylphosphine, $(C_6H_5)_3P$, is a commercially available crystalline solid, m.p. 80°. It is insoluble in water, but is soluble in most organic solvents. Although the pair of electrons on phosphorus is not appreciably basic, phosphines are generally reactive nucleophiles in S_N2 displacement reactions (Section 8.4).

Since phosphines are good nucleophiles and weak bases, competing elimination is not so important here as with other bimolecular substitutions. Consequently, most primary and secondary alkyl halides give good yields of phosphonium salts.



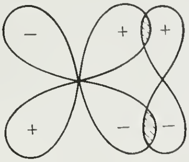
(72%)
cyclohexyltriphenylphosphonium iodide

The alkyl proton α to the positive phosphorus may be removed by a strong base such as butyllithium or sodium hydride to give a neutral phosphorus compound called an **ylid** or **phosphorane.**

$$(C_6H_5)_3\overset{+}{P}CH_2CH_3\,Br^- + n\text{-}C_4H_9Li \xrightarrow{\text{ether}}$$

$$[(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_3 \longleftrightarrow (C_6H_5)_3P{=}CHCH_3] + C_4H_{10} + LiBr$$

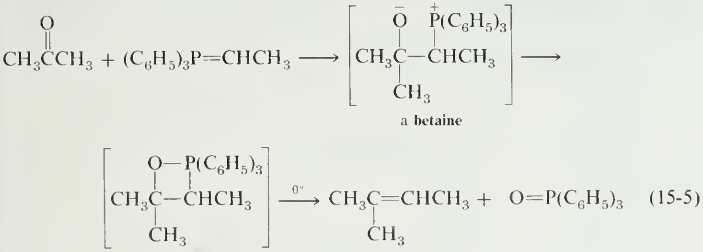
Other neutral pentacoordinate phosphorus compounds are known. Examples are PCl_5 and $P(C_6H_5)_5$. Such compounds apparently involve an expansion of the phosphorus octet and it has been frequently assumed that 3*d* orbitals are involved in such bonds. For phosphorus ylids the P=C double bond has been proposed to involve *p-d* π bonds of the type:



However, it has not yet been demonstrated that such *p-d* π bonds are actually involved to a significant degree in ylids.

Ylids react rapidly with aldehydes and ketones, even at −80°, to give neutral products called **oxaphosphetanes.**

The mechanism of this addition is still in dispute. It may involve an initial nucleophilic addition of the ylid carbon to the carbonyl group, giving a dipolar intermediate called a **betaine,** which then reacts further to give the oxaphosphetane. At −80° the oxaphosphetane is stable in solution. Upon warming the solution to 0°, it decomposes to give an alkene and triphenylphosphine oxide. The overall process, illustrated in equations (15-5) with acetone and the ylid derived from ethyl bromide is called the **Wittig reaction.**



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + (C_6H_5)_3P{=}CHCH_3 \longrightarrow \left[\begin{array}{c} \overset{-}{O}\quad \overset{+}{P}(C_6H_5)_3 \\ |\qquad | \\ CH_3C-CHCH_3 \\ | \\ CH_3 \end{array}\right] \longrightarrow$$

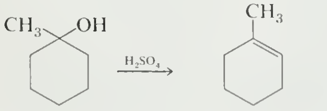
a betaine

$$\left[\begin{array}{c} O-P(C_6H_5)_3 \\ |\qquad | \\ CH_3C-CHCH_3 \\ | \\ CH_3 \end{array}\right] \xrightarrow{0^\circ} \underset{\displaystyle CH_3}{CH_3\overset{}{C}}{=}CHCH_3 + O{=}P(C_6H_5)_3 \qquad (15\text{-}5)$$

an oxaphosphetane

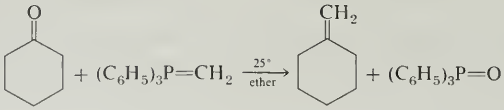
triphenylphosphine oxide

The Wittig reaction is an exceedingly useful method for the synthesis of alkenes. Although a mixture of *cis* and *trans* isomers often results, *only a single positional isomer is produced.* Consider, as an example, the synthesis of methylenecyclohexane. Dehydration of 1-methylcyclohexanol gives mainly 1-methylcyclohexene, since this isomer is more stable.



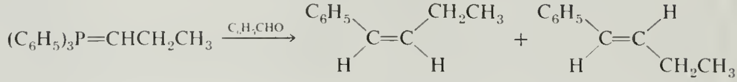
1-methylcyclohexene

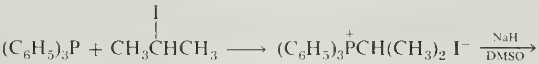
The less stable isomer may be readily prepared from cyclohexanone by the Wittig reaction.


O
$+ (C_6H_5)_3P{=}CH_2$
25°
ether
CH_2
$+ (C_6H_5)_3P{=}O$

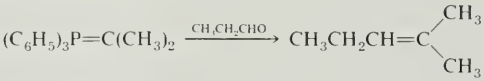
Several other examples which illustrate the utility of the method are

$$(C_6H_5)_3P + CH_3CH_2CH_2Br \longrightarrow (C_6H_5)_3\overset{+}{P}CH_2CH_2CH_3\ Br^- \xrightarrow[\text{ether}]{n\text{-BuLi}}$$


$(C_6H_5)_3P{=}CHCH_2CH_3$
C_6H_5CHO
C_6H_5
CH_2CH_3
C=C
H
H
+
C_6H_5
H
C=C
H
CH_2CH_3



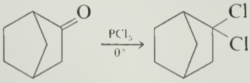
$$(C_6H_5)_3P + CH_3\overset{\overset{\large I}{|}}{C}HCH_3 \longrightarrow (C_6H_5)_3\overset{+}{P}CH(CH_3)_2\ I^- \xrightarrow[\text{DMSO}]{\text{NaH}}$$


$(C_6H_5)_3P{=}C(CH_3)_2$
CH_3CH_2CHO
$CH_3CH_2CH{=}C$
CH_3
CH_3

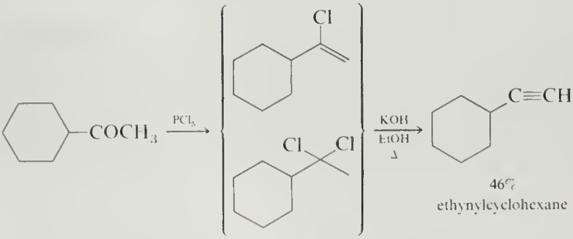
I. *Reaction with Phosphorus Pentachloride*

The reaction of ketones with phosphorus pentachloride at 0–5° generally gives *gem*-dichlorides or chloroalkenes or a mixture of the two. The mixture is usually suitable for direct conversion to the corresponding acetylene on treatment with strong base (Section 13.5.B).

$$\underset{}{(C_6H_5)_2CO} \xrightarrow{PCl_5} \underset{(90\%)}{(C_6H_5)_2CCl_2}$$

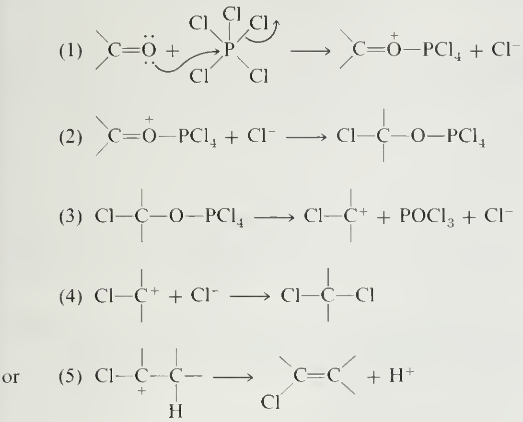

O
PCl_5
0°
Cl
Cl

(92%)


$COCH_3$
PCl_5
Cl
Cl
Cl
KOH
EtOH
Δ
C≡CH
46%
ethynylcyclohexane

(70–80%)

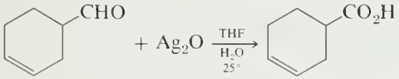
This procedure is most successful with aromatic ketones. Aliphatic ketones tend to give other side reactions as well. The reaction mechanism appears to involve the displacement of chloride ion from phosphorus, with the carbonyl oxygen acting as a nucleophile.



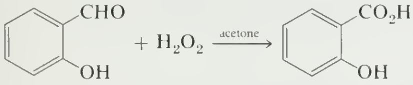
15.8
Oxidation and Reduction

A. *Oxidation of Aldehydes and Ketones*

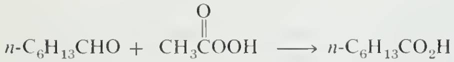
Aldehydes are oxidized to carboxylic acids with great ease. Oxidizing agents that have been used are Ag_2O, H_2O_2, $CH_3\overset{\overset{O}{\|}}{C}OOH$, $KMnO_4$, and CrO_3.



(97%)



(100%)

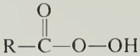


$$n\text{-}C_6H_{13}CHO + CH_3\overset{\overset{O}{\|}}{C}OOH \longrightarrow n\text{-}C_6H_{13}CO_2H$$

peroxyacetic acid (88%)

This oxidation is so facile that even atmospheric oxygen will bring it about. Most aldehyde samples that have been stored for some time before use are found to be contaminated with variable amounts of the corresponding carboxylic acid. In the case of oxidation by air **(autoxidation)**, the initial oxidation product is a **peroxycarboxylic acid.**

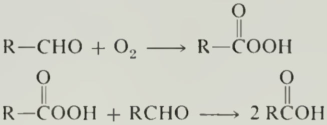
Peroxycarboxylic acids have the general formula:



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-OH$$

Like hydrogen peroxide, H_2O_2, peroxycarboxylic acids are oxidizing agents and are often used for that purpose.

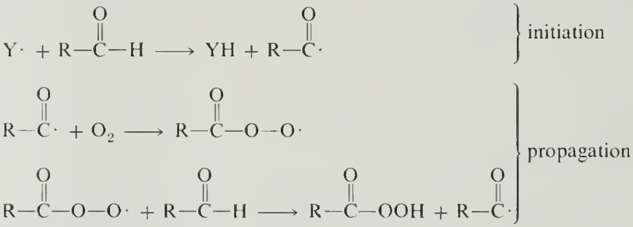
The peroxycarboxylic acid reacts with another molecule of aldehyde to give two carboxylic acid molecules.



$$R-CHO + O_2 \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}OOH$$

$$R-\overset{\overset{\displaystyle O}{\|}}{C}OOH + RCHO \longrightarrow 2\,R\overset{\overset{\displaystyle O}{\|}}{C}OH$$

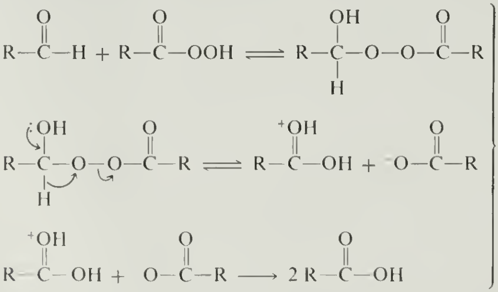
The initial oxidation (to the peroxycarboxylic acid stage) is a free radical chain process. A probable mechanism for this part of the reaction is as follows:



$$\left.Y\cdot + R-\overset{\overset{\displaystyle O}{\|}}{C}-H \longrightarrow YH + R-\overset{\overset{\displaystyle O}{\|}}{C}\cdot\right\}\text{initiation}$$

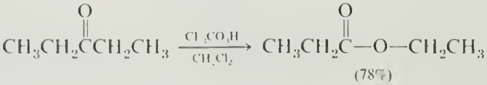
$$\left.\begin{array}{l} R-\overset{\overset{\displaystyle O}{\|}}{C}\cdot + O_2 \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-O-O\cdot \\ R-\overset{\overset{\displaystyle O}{\|}}{C}-O-O\cdot + R-\overset{\overset{\displaystyle O}{\|}}{C}-H \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-OOH + R-\overset{\overset{\displaystyle O}{\|}}{C}\cdot \end{array}\right\}\text{propagation}$$

The second stage, oxidation of the aldehyde by the initially formed peroxycarboxylic acid, is a special case of the **Baeyer-Villiger oxidation.** The probable course of this oxidation is shown in equations 15-6.



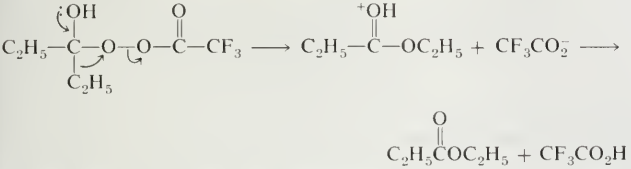
$$\left.\begin{array}{l} R-\overset{\overset{\displaystyle O}{\|}}{C}-H + R-\overset{\overset{\displaystyle O}{\|}}{C}-OOH \rightleftharpoons R-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-O-O-\overset{\overset{\displaystyle O}{\|}}{C}-R \\ R-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle \ddot{O}H}{|}}{C}}-O-O-\overset{\overset{\displaystyle O}{\|}}{C}-R \rightleftharpoons R-\overset{\overset{\displaystyle ^{+}OH}{\|}}{C}-OH + {}^{-}O-\overset{\overset{\displaystyle O}{\|}}{C}-R \\ R-\overset{\overset{\displaystyle ^{+}OH}{\|}}{C}-OH + {}^{-}O-\overset{\overset{\displaystyle O}{\|}}{C}-R \longrightarrow 2\,R-\overset{\overset{\displaystyle O}{\|}}{C}-OH \end{array}\right\} \qquad (15\text{-}6)$$

In contrast to aldehydes, ketones are oxidized only under rather special conditions. The Baeyer-Villiger oxidation, mentioned above, is one reaction in which a ketone undergoes oxidation. In this case, the product is an ester.



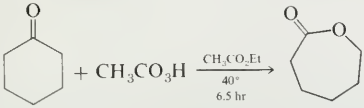
$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_3 \xrightarrow[CH_2Cl_2]{CF_3CO_3H} \underset{(78\%)}{CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2CH_3} \qquad (15\text{-}7)$$

The mechanism of the reaction is believed to be similar to that outlined in equations (15-6) for the oxidation of an aldehyde, except that the migrating group is an alkyl group rather than a hydrogen.



$$C_2H_5-\underset{C_2H_5}{\overset{OH}{C}}-O-O-\overset{O}{\overset{\|}{C}}-CF_3 \longrightarrow C_2H_5-\overset{^{+}OH}{\overset{\|}{C}}-OC_2H_5 + CF_3CO_2^- \longrightarrow C_2H_5\overset{O}{\overset{\|}{C}}OC_2H_5 + CF_3CO_2H \qquad (15\text{-}8)$$

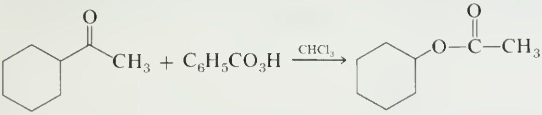
The reaction is a preparatively useful one for the oxidation of certain ketones to esters. Cyclic ketones give cyclic esters (lactones, Section 24.5.B).



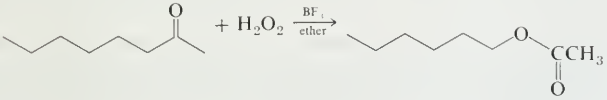
(90%)

(15-9)

Symmetrical ketones, such as those illustrated in (15-7), (15-8), and (15-9) can give only one product. Unsymmetrical ketones can give two oxidation products, and this is sometimes observed. When the two alkyl groups differ substantially, a clear selectivity can often be observed. The approximate order of *decreasing ease of migration* (the **migratory aptitude**) for various groups is hydrogen > phenyl > tertiary alkyl > secondary alkyl > primary alkyl > methyl. The following examples illustrate this selectivity.



(67%)

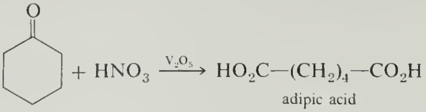


(62%)

Another rather special reaction that results in the oxidation of a ketone to a carboxylic acid is the haloform reaction discussed in Section 15.6.D.

Although ketones may be oxidized by other reagents in addition to the two discussed in the preceding paragraphs, oxidative cleavage is seldom a useful preparative method. The conditions required for the oxidation of most ketones are sufficiently vigorous that complex mixtures result. The chief exception to this generalization is in symmetrical cyclic ketones, where the reaction can be useful. The oxidation of cyclohexanone by nitric acid is catalyzed by vanadium pentoxide.

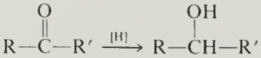
The product, adipic acid, is an important industrial chemical because it is one of the constituents of nylon 66 (Section 27.7.A).



B. *Metal Hydride Reduction*

Aldehydes and ketones are easily reduced to the corresponding primary and secondary alcohols, respectively.

$$\text{R—CHO} \xrightarrow{[\text{H}]} \text{R—CH}_2\text{OH}$$

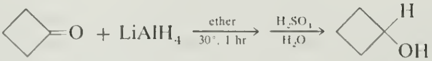


$$\text{R—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—R}' \xrightarrow{[\text{H}]} \text{R—}\overset{\overset{\text{OH}}{|}}{\text{C}}\text{H—R}'$$

Many different reducing agents may be used. For laboratory applications, the complex metal hydrides are particularly effective. Lithium aluminum hydride ($LiAlH_4$) is an extremely powerful reducing agent which has been used for this purpose.

> Lithium aluminum hydride, $LiAlH_4$, is a white salt-like compound prepared by reaction of lithium hydride with aluminum chloride:
>
> $$4\ \text{LiH} + \text{AlCl}_3 \longrightarrow \text{LiAlH}_4 + 3\ \text{LiCl}$$
>
> The compound is easily soluble in ethers such as ethyl ether, tetrahydrofuran and 1,2-dimethoxyethane (glyme). It has a clear relationship to sodium borohydride, $NaBH_4$, and is a salt of Li^+ and AlH_4^-. It reacts avidly with traces of moisture to liberate hydrogen.
>
> $$\text{LiAlH}_4 + 4\ \text{H}_2\text{O} \longrightarrow \text{LiOH} + \text{Al(OH)}_3 + 4\ \text{H}_2$$
>
> All hydroxylic compounds (such as alcohols, carboxylic acids, and so on) react similarly. The dry crystalline powder must be used with care. It produces dust particles that are highly irritating to mucous membranes. It may inflame spontaneously while being crushed with a mortar and pestle and explodes violently when heated to about 120°.

Reactions with $LiAlH_4$ are normally carried out by adding an ether solution of the aldehyde or ketone to an ether solution of $LiAlH_4$. Reduction is rapid even at −78° (dry ice temperature). At the end of the reaction, the alcohol is present as a mixture of lithium and aluminum salts and must be liberated by hydrolysis.



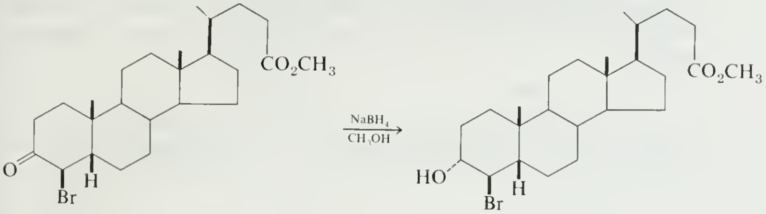
(90%)
cyclobutanol

The reagent also reduces many other oxygen and nitrogen-containing functional groups, as illustrated in Table 15.5. The chief drawbacks of the reagent are its cost, which renders it useful only for fairly small scale laboratory applications, and the hazards involved in handling it.

TABLE 15.5
Functional Groups Reduced by $LiAlH_4$

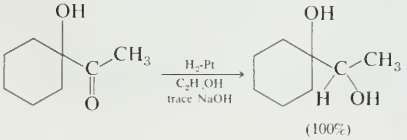
Functional Group	Product	Moles of $LiAlH_4$ Required
RCHO	RCH_2OH	0.25
$R_2C{=}O$	R_2CHOH	0.25
RCO_2R'	$RCH_2OH + R'OH$	0.5
RCO_2H	RCH_2OH	0.75
$R\overset{O}{\overset{\|}{C}}NH_2$	RCH_2NH_2	1
$RC{\equiv}N$	RCH_2NH_2	0.5
RNO_2	RNH_2	1.5
RCl(Br, I)	RH	0.25

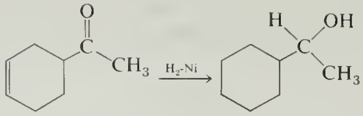
Sodium borohydride ($NaBH_4$) (page 284), offers certain advantages. This hydride is much less reactive than $LiAlH_4$, and is consequently more selective. Of the functional groups in Table 15.5 that are reduced by $LiAlH_4$, only aldehydes and ketones are reduced at a reasonable rate by $NaBH_4$. The reagent is moderately stable in aqueous and in alcoholic solution, especially at basic pH's. The example below illustrates the selectivity that may be achieved with the reagent.



C. *Catalytic Hydrogenation*

Aldehydes and ketones may also be reduced to alcohols by hydrogen gas in the presence of a metal catalyst (catalytic hydrogenation, see Section 12.6.A). The chief advantages of this method are that it is relatively simple to accomplish and usually affords a quantitative yield of product because no complicated work-up procedure is required. However, it suffers from the disadvantages that the many of the catalysts used (Pd, Pt, Ru, Rh) are relatively expensive and that other functional groups also react (C=C, —C≡C—, $-NO_2$, —C≡N).

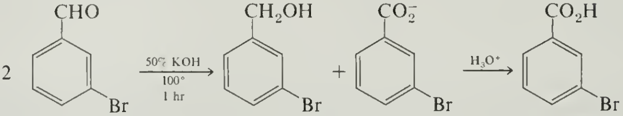




(96%)

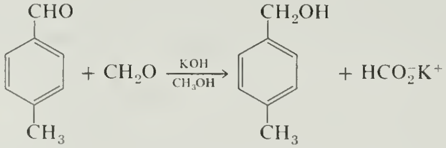
D. *Cannizzaro Reaction*

When an aldehyde that has no hydrogens α to the carbonyl group is treated with concentrated aqueous base, a disproportionation reaction occurs. One half of the aldehyde is reduced to a primary alcohol, and the other half is oxidized to the corresponding carboxylic acid.



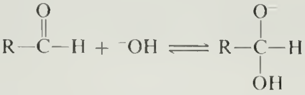
(45%) (48%)

The reaction is known as the **Cannizzaro reaction** and is general for such aldehydes. It is not normally useful for preparative purposes because the maximum yield of either alcohol or acid is 50%. However, when an aldehyde is treated with aqueous base and formaldehyde, it is the formaldehyde, rather than the other aldehyde, that is oxidized. Such a reaction is known as a "**crossed Cannizzaro reaction.**"

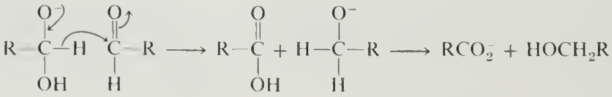


> To a solution of 500 g of KOH in 750 ml of methanol is added a mixture of 360 g of 4-methylbenzaldehyde, 300 ml of formalin (page 377) and 300 ml of methanol. The solution is kept at 60–70° for 3 hr, then worked up to obtain 331 g (90%) of 4-methylbenzyl alcohol.

The mechanism of the reaction starts with addition of hydroxide ion to the carbonyl group. Most of the time it comes right back off again. Occasionally, however, H^- is expelled by transfer to another carbonyl group.

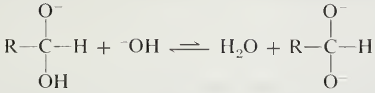


$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H + {}^{-}OH \rightleftharpoons R{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O^-}{|}}{C}}{-}H}$$



$$\mathrm{R{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O^-}{|}}{C}}{-}H \quad \underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle O}{\|}}{C}}{-}R \longrightarrow R{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle O}{\|}}{C}} + H{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle O^-}{|}}{C}}{-}R \longrightarrow RCO_2^- + HOCH_2R}$$

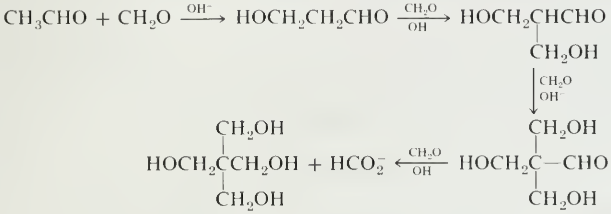
In some cases it appears that the active intermediate is a dianion. This strongly charged species encourages the distribution of negative charge by transfer of H^-.



$$R-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-H + {}^-OH \rightleftharpoons H_2O + R-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{C}}-H$$

The reaction is suitable only for aldehydes without an α-hydrogen because this H^- transfer process is slow and difficult. Any α-hydrogens present would react to give enolate ions and aldol condensation products far more rapidly than the Cannizzaro reaction.

An interesting combination of both the aldol condensation and crossed Cannizzaro reactions is the preparation of pentaerythritol from acetaldehyde and formaldehyde.

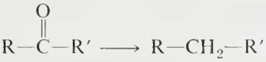


(55–57%)
pentaerythritol

This reaction involves three successive aldol condensations of acetaldehyde with formaldehyde. The product has no α-hydrogens left and is reduced by the alkaline formaldehyde to give 2,2-bis-hydroxymethyl-1,3-propanediol (pentaerythritol).

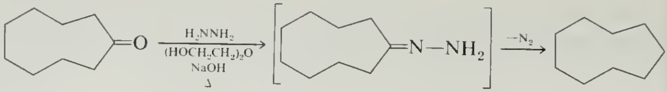
E. *Wolff-Kishner Reduction*

The Wolff-Kishner reduction is a useful method for direct conversion of a carbonyl group to a methylene group:



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-R' \longrightarrow R-CH_2-R'$$

The method involves first the formation of the hydrazone by reaction with hydrazine. At elevated temperatures with base the hydrazone loses nitrogen to give the hydrocarbon. The reaction is normally run by heating the ketone with hydrazine hydrate (Section 15.7.C) and sodium hydroxide in diethylene glycol, $HOCH_2CH_2OCH_2CH_2OH$, which has a b.p. of 245°. Alternatively, the reduction may be carried out in the polar aprotic solvent DMSO at 100°. The hydrazone forms and water distills out of the mixture. On refluxing, nitrogen is evolved and the product is isolated.



cyclononanone

(47%)
cyclononane

The decomposition of the hydrazone involves an anionic intermediate. In the presence of base the hydrazone is in equilibrium with a double bond isomer. This isomer forms an anion with base, which loses nitrogen to produce the alkyl anion. This carbanion is exceedingly unstable and rapidly abstracts a proton from the solvent. Alkyl anions are rarely encountered in reactions because of the low acidity of hydrocarbons. In the present case, they are formed only because the nitrogen also produced is an extremely stable molecule and its production provides the driving force for the reaction:

$$(1)\quad R_2C{=}N\ddot{N}H_2 + B^- \rightleftharpoons BH + [R_2C{=}N{-}\ddot{N}H^- \longleftrightarrow R_2\ddot{C}^-{-}N{=}NH]$$

$$(2)\quad [R_2C{=}N{-}\ddot{N}H^- \longleftrightarrow R_2\ddot{C}^-{-}N{=}NH] + BH \rightleftharpoons R_2\overset{\overset{\displaystyle H}{|}}{C}{-}N{=}NH + B^-$$

$$(3)\quad R_2CH{-}N{=}\ddot{N}H + B^- \rightleftharpoons R_2CH{-}N{=}\ddot{\underset{\cdot\cdot}{N}}^- + BH$$

$$(4)\quad R_2CH{-}N{=}\ddot{N}^- \xrightarrow{\text{slow}} R_2\ddot{C}H^- + N_2$$

$$(5)\quad R_2\ddot{C}H^- + BH \xrightarrow{\text{fast}} R_2CH_2 + B^-$$

F. *Clemmensen Reduction*

An alternative procedure for the direct reduction of a carbonyl group to a methylene group involves refluxing the aldehyde or ketone with amalgamated zinc and hydrochloric acid.

Amalgamated zinc is zinc with a surface layer of mercury. It is prepared by treating zinc with an aqueous solution of a mercuric salt. Since zinc is higher on the electromotive force scale than mercury, it displaces mercury from its salts:

$$Zn + Hg^{2+} \longrightarrow Zn^{2+} + Hg$$

The mercury formed alloys with the surface of zinc to produce an amalgam.

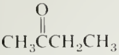
Reduction of the carbonyl compound occurs on the surface of the zinc and, like many heterogeneous reactions, this reaction does not have a simple mechanism.

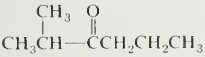
The Clemmensen reduction is suitable for compounds that can withstand treatment with hot acid. Many ketones are reduced in satisfactory yields.

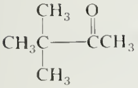
$$\underset{\text{acetophenone}}{C_6H_5COCH_3} \xrightarrow[\text{HCl}\ \Delta]{\text{Zn(Hg)}} \underset{\text{ethylbenzene}}{\underset{(80\%)}{C_6H_5CH_2CH_3}}$$

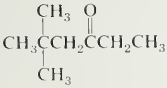
PROBLEMS

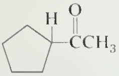
1. Provide common and IUPAC names for the following ketones and aldehydes.

(a) 
$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3$

(b) 
$CH_3\overset{CH_3}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$

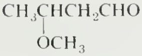
(c) 
$CH_3\overset{CH_3}{\underset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}CH_3$

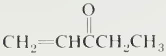
(d) 
$CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$

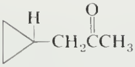
(e) 

(f) $(CH_3)_2CHCHO$

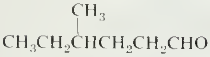
(g) $CH_3CHBrCHO$

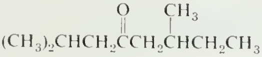
(h) 
$CH_3\underset{OCH_3}{C}HCH_2CHO$

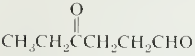
(i) 
$CH_2{=}CH\overset{O}{\overset{\|}{C}}CH_2CH_3$

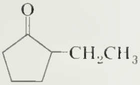
(j) 

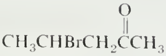
2. Write IUPAC names for the following compounds

(a) 
$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_2CHO$

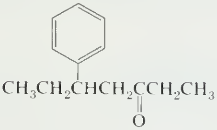
(b) 
$(CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$

(c) 
$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CHO$

(d) 

(e) 
$CH_3CHBrCH_2\overset{O}{\overset{\|}{C}}CH_3$

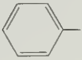
(f) $(CH_3)_2C{=}CHCH_2CHO$

(g) 

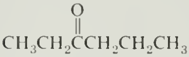
3. Write the structure of
- (a) methyl isobutyl ketone
- (b) propionaldehyde diethyl acetal
- (c) β-chlorobutyraldehyde
- (d) 2,2-dimethylcyclopentanone
- (e) cyclododecanone
- (f) formaldehyde phenylhydrazone
- (g) cyclohexanone oxime
- (h) acetone semicarbazone

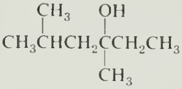
4. Show how 2-hexanone might be prepared by
- (a) oxidation of an alcohol.
- (b) oxidation of an alkene.
- (c) hydration of an alkyne.

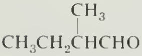
5. The pK_a of acetone is about 20, and acetone contains about 10^{-4}% of the enol form. Derive the pK_a of the enol form. How does this value compare with the pK_a values of alcohols?

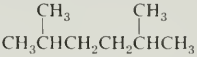
6. What is the product of the reaction of 4,4-dimethylcyclohexanone with each of the following reagents.
   - (a) Lithium diisopropylamide in THF, followed by CH_3CH_2Br.
   - (b) Br_2 in acetic acid.
   - (c) CH_3CO_3H.
   - (d) $LiAlH_4$ in ether, followed by H_2O.
   - (e) conc. HNO_3, V_2O_5.
   - (f) $NaBH_4$ in C_2H_5OH.
   - (g) $CH_3C{\equiv}C^-Na^+$ in liq. NH_3 at $-33°$, followed by H_2O.
   - (h) KCN + aqueous sulfuric acid.
   - (i) H_2NOH + sodium acetate and acetic acid.
   - (j) $\frac{1}{2}$ mole equivalent of H_2NNH_2 + sodium acetate and acetic acid.
   - (k)  —CHO + NaOH.
   - (l) $H_2NNH_2 + Na^{+-}OCH_2CH_2OCH_2CH_2OH$, 200°.
   - (m) $CH_3CH_2CH_2CH_2Li$ in ether, followed by H_2O.
   - (n) CH_3MgBr in ether, followed by H_2O.
   - (o) zinc amalgam + hot concentrated HCl.
   - (p) NaOD in D_2O at 25°.
   - (q) $(C_6H_5)_3P{=}CHCH_2CH_3$

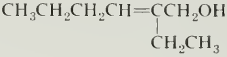
7. Show how each of the following compounds may be prepared from alkyl halides and alcohols containing four or fewer carbons.

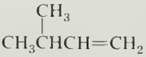
(a) 
$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$

(b) 
$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\underset{CH_3}{\underset{|}{\overset{OH}{\overset{|}{C}}}}CH_2CH_3$

(c) 
$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCHO$

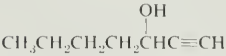
(d) 
$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3$

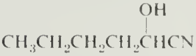
(e) 
$CH_3CH_2CH_2CH{=}\underset{CH_2CH_3}{\underset{|}{C}}CH_2OH$

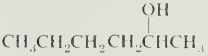
(f) 
$CH_3\overset{CH_3}{\overset{|}{C}}HCH{=}CH_2$

8. Show how each of the following compounds may be prepared from pentanal. Any other reagents, organic or inorganic, may be used.

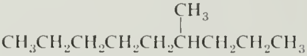
(a) $CH_3CH_2CH_2CH_2CH_3$

(b) 
$CH_3CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HC{\equiv}CH$

(c) 
$CH_3CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCN$

(d) 
$CH_3CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3$

(e) $CH_3CH_2CH_2CH_2CO_2H$

(f) 
$CH_3CH_2CH_2CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_2CH_3$

(g) $CH_3CH_2CH_2CH_2CH_2Br$

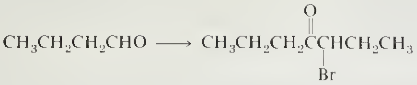
(h) $CH_3CH_2CH_2CH_2CH_2OCH_2CH_2CH_2CH_2CH_3$

(i) $CH_3CH_2CH_2CH_2CH{=}CH_2$

9. Show how one may accomplish each of the following conversions in a practical manner

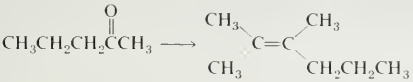
using any necessary organic or inorganic reagents:

(a)

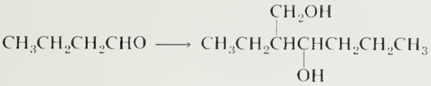


$$CH_3CH_2CH_2CHO \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}\underset{Br}{\underset{|}{C}}HCH_2CH_3$$

(b)

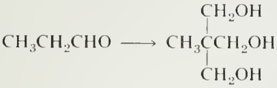


(c)



$$CH_3CH_2CH_2CHO \longrightarrow CH_3CH_2\overset{CH_2OH}{\overset{|}{C}}H\underset{OH}{\underset{|}{C}}HCH_2CH_2CH_3$$

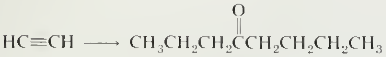
(d)



$$CH_3CH_2CHO \longrightarrow CH_3\overset{CH_2OH}{\overset{|}{\underset{CH_2OH}{\underset{|}{C}}}}CH_2OH$$

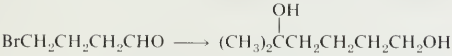
(e) $CH_3CH_2CH_2CH_2Br \longrightarrow CH_3CH_2CH_2CH_2CH_2CHO$

(f)



$$HC\equiv CH \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_3$$

(g)



$$BrCH_2CH_2CH_2CHO \longrightarrow (CH_3)_2\overset{OH}{\overset{|}{C}}CH_2CH_2CH_2CH_2OH$$

10. What three combinations of carbonyl compound and Grignard reagent can be used to prepare 3,5-dimethyl-3-hexanol?

11. In reactions of protonated acetone $CH_3\overset{^{+}OH}{\overset{\|}{C}}CH_3$, why does reaction with a base always occur at carbon rather than at the positive oxygen?

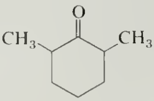
12. Compound A, $C_7H_{16}O$, reacts with sodium dichromate in aqueous H_2SO_4 to give B, $C_7H_{14}O$. When B is treated with Na^+OD^- at 25° for several hours and then analyzed by mass spectroscopy, it is found to have a molecular weight of 116. Compound B is not oxidized by Ag_2O. What are A and B?

13. Compound C has the formula $C_{12}H_{20}$ and is optically active. It reacts with H_2 and Pt to give two isomers, D_1 and D_2, $C_{12}H_{22}$. Ozonolysis of C gives only E, $C_6H_{10}O$, which is optically active. Compound E reacts with hydroxylamine to give F, $C_6H_{11}NO$. When E is treated with DCl in D_2O for several hours and then analyzed by mass spectroscopy, it is found to have a molecular weight of 101. The nmr spectrum of E shows that it has only one methyl group, which appears as a doublet with $J = 6.5$ Hz. What are compounds C through F?

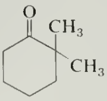
14. An unknown compound G has the formula C_6H_8O and shows a singlet methyl in the nmr. When treated with hydrogen gas and palladium it absorbs one equivalent of H_2 to give a product H with the formula $C_6H_{10}O$. Compound H has an infrared band at 1745 cm^{-1}. Compound H reacts with NaOD in D_2O to give a product shown by mass spectroscopy to have the formula $C_6H_7D_3O$. Compound H reacts with peroxyacetic acid, CH_3CO_3H, to give I, which has the formula $C_6H_{10}O_2$. The nmr spectrum of I contains one and only one absorption due to a CH_3 group, a doublet with $J = 8$ Hz at $\delta = 1.9$ ppm. Propose structures for compounds G, H, and I.

15. If the acid-catalyzed bromination of bromoacetone is analyzed *immediately after the* *bromine has all reacted,* the major product present is 1,1-dibromoacetone. If the reaction mixture is allowed to stir at room temperature for several hours and then analyzed, the sole product is found to be 1,3-dibromoacetone. Explain these observations with a reasonable mechanism for each step.

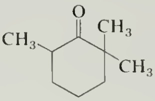
16. If 2-methylcyclohexanone is treated with 1 mole-equivalent of potassium *t*-butoxide and methyl iodide in *t*-butyl alcohol, the reaction product has the following composition:
Explain.



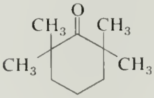
(9%)



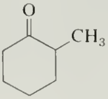
(41%)



(21%)

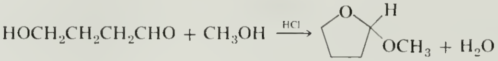


(6%)

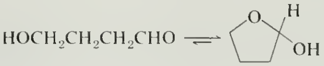


(23%)

17. When 4-hydroxybutanal is dissolved in methanol containing HCl, the following reaction occurs:



(a) What type of compound is the product?
(b) Propose a mechanism for this reaction
Actually, 4-hydroxybutanal exists in solution mostly in the cyclic form.



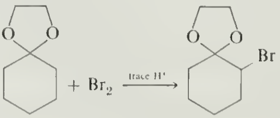
(c) What type of compound is this product?
(d) Propose a mechanism for the equilibrium.

18. 1,1-Diethoxyethane hydrolyzes readily to acetaldehyde and ethanol in water containing some sulfuric acid. Write a complete reaction mechanism for this transformation including each significant intermediate and reaction step.

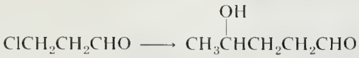
19. Is the equilibrium constant for the following equilibrium greater than, less than, or equal to unity? Explain briefly.

$$CF_3CHO + CH_3CH(OCH_3)_2 \rightleftharpoons CH_3CHO + CF_3CH(OCH_3)_2$$

20. Propose a mechanism for the following reaction:



21. Propose a method for accomplishing the following conversion:



$$\mathrm{ClCH_2CH_2CHO} \longrightarrow \mathrm{CH_3\overset{\overset{\displaystyle OH}{|}}{C}HCH_2CH_2CHO}$$

22. Write a plausible reaction mechanism for the trimerization of acetaldehyde to paraldehyde with a trace of acid. How does this mechanism compare to the acid-catalyzed depolymerization of paraldehyde?

23. Undecanal is a sex-attractant for the greater wax moth (*Galleria mellonella*). Show how to synthesize this compound efficiently from
(a) 1-nonanol (b) 1-decanol (c) 1-dodecanol

CHAPTER 16
Mass Spectroscopy

16.1
Introduction

When a beam of electrons of energy greater than the ionization potential [about 8–13 electron volts (ev) (185–300 kcal mole^{-1}) for most compounds] is passed through a sample of an organic compound in the vapor state, ionization of some molecules occurs. In one form of ionization, one of the valence electrons of the molecule is "knocked out," leaving behind a **radical cation.**

$$e + \mathrm{CH_4} \longrightarrow 2\,e + [\mathrm{CH_4}]^{\overset{+}{\cdot}}$$

In CH_4, eight valence electrons bond the four hydrogens to carbon. The symbol $[\mathrm{CH_4}]^{\overset{+}{\cdot}}$ represents a structure in which *seven* valence electrons bond the four hydrogens to carbon. The + sign shows that the species has a net positive charge. The · signifies that the species has an odd number of electrons. If a mixture of compounds is bombarded with electrons, a mixture of radical cations differing in mass will obviously be produced.

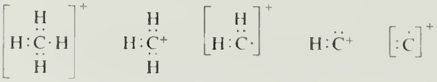
$$\begin{array}{lccc} \mathrm{CH_4,\ C_2H_6} & \longrightarrow & [\mathrm{CH_4}]^{\overset{+}{\cdot}}, & [\mathrm{C_2H_6}]^{\overset{+}{\cdot}} \\ m/e: & & 16 & 30 \end{array}$$

where $m/e \equiv$ mass to charge ratio.

In practice, even when a pure substance is bombarded with electrons, a mixture of cations is produced. This process, termed fragmentation, will be discussed later. For example, methane may give cations with masses of 16, 15, 14, 13, and 12.

$$\begin{array}{lcccccc} \mathrm{CH_4} & \longrightarrow & [\mathrm{CH_4}]^{\overset{+}{\cdot}}, & \mathrm{CH_3^+}, & [\mathrm{CH_2}]^{\overset{+}{\cdot}}, & \mathrm{CH^+}, & [\mathrm{C}]^{\overset{+}{\cdot}} \\ m/e: & & 16 & 15 & 14 & 13 & 12 \end{array}$$

Lewis structures for these cations are



$$\left[\begin{array}{c}\mathrm{H}\\ \mathrm{H}:\ddot{\underset{\cdot\cdot}{\mathrm{C}}}\cdot\mathrm{H}\\ \mathrm{H}\end{array}\right]^{+} \quad \begin{array}{c}\mathrm{H}\\ \mathrm{H}:\ddot{\underset{\cdot\cdot}{\mathrm{C}}}{}^{+}\\ \mathrm{H}\end{array} \quad \left[\begin{array}{c}\mathrm{H}\\ \mathrm{H}:\ddot{\mathrm{C}}\cdot\end{array}\right]^{+} \quad \mathrm{H}:\ddot{\mathrm{C}}{}^{+} \quad \left[:\dot{\mathrm{C}}\right]^{+}$$

Note that the cations having an even number of hydrogens are **radical cations**, whereas the cations having an odd number of hydrogens are normal **carbonium ions.**

A **mass spectrometer** is an instrument that is designed to ionize gaseous molecules, separate the ions produced on the basis of their mass-to-charge ratio, and record the relative number of different ions produced. A **mass spectrum** is a plot of the data obtained from the mass spectrometer. It is customary for the mass/charge ratio (m/e) to be plotted as the abscissa, and the relative number of ions of relative intensity (height of each peak) to appear as the ordinate. Mass spectroscopy differs from other forms of spectroscopy in that no absorption of light is involved. It is called a "spectroscopy" only because the mass "spectrum" resembles other kinds of spectra.

16.2 Instrumentation

The simplest and most common mass spectrometer currently in use is based on **single focusing magnetic deflection.** A schematic sketch of a semicircular instrument based on this principle is shown in Figure 16.1. The sample vapor is introduced at point *a*, usually at very low pressure (10^{-6} to 10^{-7} torr). A low pressure is necessary to minimize the number of collisions between ions and unionized molecules. Such collisions lead to reactions that produce new ions not related to the starting compound. Such ions can lead to errors in interpretation of the data. As the sample vapor enters the ionizing chamber (see enlarged insert), it passes through the electron beam *b* where ionization occurs. The resulting ions pass between two charged plates *c*, where there is a difference in potential of several thousand volts. In this region, the ions are accelerated and pass through a slit *d* into the magnetic field.

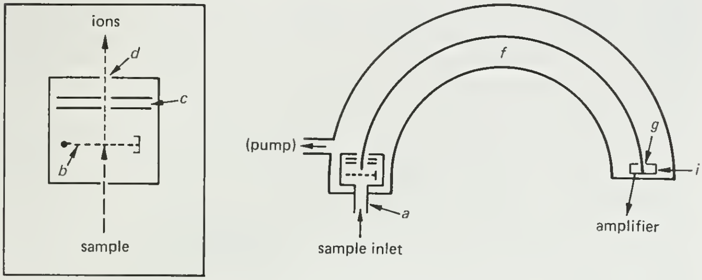


FIGURE 16.1 *Single focusing magnetic deflection mass spectrometer.*

The radius of the path followed by an ion of mass m in a magnetic field is proportional to its charge e and the accelerating potential (V). The potential energy of the accelerated ion (eV) equals its kinetic energy.

$$eV = \tfrac{1}{2}mv^2 \tag{16-1}$$

In a magnetic field of strength **H**, the ion will experience a centripedal force $\mathrm{H}ev$, which is balanced by a centrifugal force mv^2/r, where v is the velocity of the ion and r is the radius of the circular path followed by the ion.

$$\mathrm{H}ev = \frac{mv^2}{r} \tag{16-2}$$

$$r = \frac{mv}{e\mathrm{H}} \tag{16-3}$$

As a collection of ions of different mass enters the magnetic field region (f), each ion will follow a circular path described by equation (16-3). Ions of larger m/e will follow a path of greater radius, whereas ions of lesser m/e will follow a path of smaller radius. In the example diagrammed in Figure 16.2, the ions of $m/e = y$ are passing through the slit (g) and impinging upon the ion collector (i).

Elimination of the velocity term from equations (16-2) and (16-3) gives

$$\frac{m}{e} = \frac{\mathrm{H}^2r^2}{2V} \tag{16-4}$$

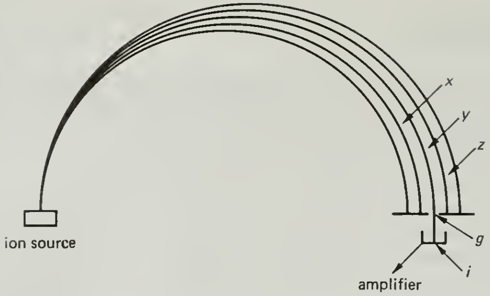


FIGURE 16.2 *Ions with* m/e = y *are focused on the collector* i *through slit* g.

This relationship shows that, for an ion of given mass to charge ratio (m/e), the radius of deflection r can be increased by either increasing V, the accelerating voltage, or by decreasing **H**, the magnetic field strength. For example, in the case diagrammed in Figure 16.2, a slight increase in V will cause the radius of deflection of all of the ions to increase somewhat. In Figure 16.3, ions of $m/e = y$ no longer pass through the slit and into the collector, but ions of $m/e = x$ do.

Note that the same effect might have been obtained by decreasing **H** slightly or by moving the collector slit slightly to the left. In actual practice, this last technique is not technically feasible. Scanning of the spectrum is achieved by either **magnetic** or **electrical scanning.** In the first technique, the accelerating voltage V is kept constant, while the magnetic field strength **H** is increased slowly. In the latter case, **H** is kept constant while V is decreased slowly. When either of these techniques is used, ions of progressively higher m/e attain the necessary radius of deflection to pass through the collector slit (g) and into the ion collector (i).

As the ions enter the collector, they impinge upon a photomultiplier tube where a minute current is produced. The magnitude of this current is proportional to the intensity of the ion beam. The current produced is amplified and fed to a recorder. Most present mass spectrometers use a recording oscillograph to record the spectrum. The current from the amplifier is fed to a mirror galvanometer. As the mirror is deflected, it reflects a narrow beam of light onto a sheet of

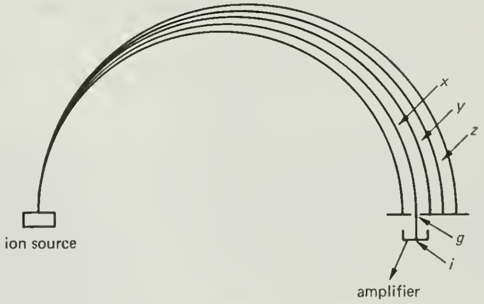


FIGURE 16.3 *At higher* V *or lower* **H**, *ions with* m/e = x *are now focused on the collector* i.

photographic paper which is moving through the recorder at a constant rate. If ultraviolet light is used, the photographic chart does not even have to be developed before examination.

In actual practice the mirror galvanometer usually has five mirrors arranged in such a manner that five scans of differing amplitude are obtained simultaneously. The relative sensitivities of the five simultaneous scans are usually 1:3:10:30:100. It is more convenient to plot the mass spectrum in the form of a bar graph. In this case, the most intense peak (the "base peak") is assigned the arbitrary value of 100, and all other peaks are given their proportionate value. Such a bar graph may be plotted manually, by measuring and normalizing all of the peaks in a spectrum, or it may be done automatically by computer. A mass spectrum recorded in this manner is shown in Figure 16.4.

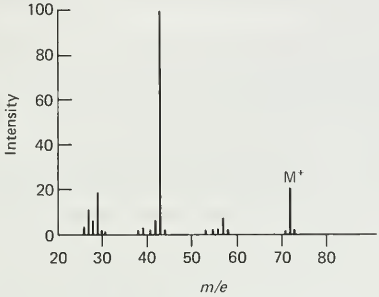


Figure 16.4 *Mass spectrum of* 2-*butanone.*

16.3
The Molecular Ion: Molecular Formula

The molecular weight of a compound is one datum that can usually be obtained by visual inspection of a mass spectrum. Although the radical cations produced by the initial electron impact usually undergo extensive fragmentation to give cations of smaller *m/e* (next section), the particle of highest *m/e* generally (but not always) corresponds to the ionized molecule and *m/e* for this particle (called the **molecular ion** and abbreviated **M**$^+$) gives the molecular weight of the compound.

If the spectrum is measured with a "high resolution" spectrometer, it is possible to determine a unique molecular formula for any peak in a mass spectrum, including the molecular ion. This is possible because atomic masses are not integers. For example, consider the molecules CO, N_2, and C_2H_4, all of which have a **nominal mass** of 28. The actual masses of the four atomic particles are: H = 1.007825, C = 12.000000 (by definition), N = 14.003050, O = 15.994914. Therefore, the actual masses of CO, N_2 and CH_4 are

^{12}C	12.0000	$^{14}N_2$	28.0061	$^{12}C_2$	24.0000
^{16}O	15.9949			$^{1}H_4$	4.0314
	27.9949				28.0314

Since a high resolution spectrometer can readily measure mass with an accuracy

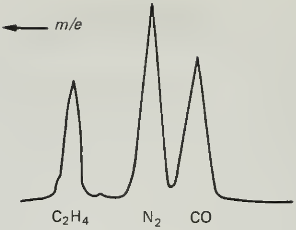


FIGURE 16.5 *High resolution mass spectrum of a mixture of ethylene, nitrogen, and carbon monoxide.*

of better than 1 part in 10,000, the above three masses are readily distinguishable, as shown in Figure 16.5.

Because the mass spectrometer measures the exact *m/e* for each ion and because most of the elements commonly found in organic compounds have more than one naturally occurring isotope, a given peak will usually be accompanied by several isotope peaks. Table 16.1 shows the common isotopes of some of the elements.

Consider the case of the molecular ion derived from methane. Most of the methane molecules are $^{12}C^1H_4$ and have the nominal mass 16. However, a few molecules are either $^{13}C^1H_4$ or $^{12}C^2H^1H_3$ and have the nominal mass 17. An even smaller number of molecules will have *both* a ^{13}C and an ^2H or will have two ^2H isotopes and will have the nominal mass 18. An exact expression for the ratio (M + 1)/(M) can be derived from probability mathematics but is rather complex. The theoretical intensities of the various isotope peaks may be looked up in special tables compiled for this purpose. However, the contributions of ^2H and ^{17}O to (M + 1)/(M) are relatively small and the ratio is given to a satisfactory approximation for most compounds having few N and S atoms by equation 16-5.

$$\frac{M+1}{M} = \frac{0.01107}{0.98893}c + 0.00015h + 0.00367n + 0.00037o + 0.0080s \qquad (16\text{-}5)$$

where

M = intensity of the molecular ion (ions containing no heavy isotopes)
M + 1 = intensity of the molecular ion + 1 peak (ions containing one ^{13}C, ^2H, ^{15}N, ^{17}O, or ^{33}S
c, h, n, o, s = number of carbons, hydrogens, nitrogens, oxygens, sulfurs.

Using this relationship, we may readily estimate the intensity of the M + 1 peak in mass spectrum of methane.

$$\frac{M+1}{M} = 0.01119(1) + 0.00015(4) = 0.01179$$

Thus, the peak of *m/e* 17 in the mass spectrum of methane should be approximately 1.18% as intense as the peak at *m/e* 16.

A similar relationship may be derived for calculation of the intensity of the M + 2 peak. However, in order to obtain an exact figure, a lengthy computation is required. For most compounds, the M + 2 peak is small and is not especially useful. However, for compounds containing chlorine or bromine, the M + 2 isotopic peak is substantial. The characteristic doublets observed in the mass spectra of compounds containing chlorine and bromine are an excellent way of diagnosing for the presence of these elements, as shown in Figures 16.6 and 16.7.

TABLE 16.1
Natural Abundance of Common Isotopes

Element	Abundance, %			
hydrogen	99.985 ^{1}H	0.015 ^{2}H		
carbon	98.893 ^{12}C	1.107 ^{13}C		
nitrogen	99.634 ^{14}N	0.366 ^{15}N		
oxygen	99.759 ^{16}O	0.037 ^{17}O	0.204 ^{18}O	
sulfur	95.0 ^{32}S	0.76 ^{33}S	4.22 ^{34}S	0.014 ^{36}S
fluorine	100 ^{19}F			
chlorine	75.53 ^{35}Cl	24.47 ^{37}Cl		
bromine	50.54 ^{79}Br	49.46 ^{81}Br		
iodine	100 ^{127}I			

One use to which isotope peaks may be put is in approximating the molecular formula of the parent ion in the mass spectrum of an unknown compound. However, one must exercise caution when applying the foregoing computations. Firstly, the M + 1 peak is generally much less intense than the parent ion. Unless the parent ion is a fairly strong one, its isotope peak may be too weak to measure accurately. Secondly, intermolecular proton transfer reaction can give M + 1

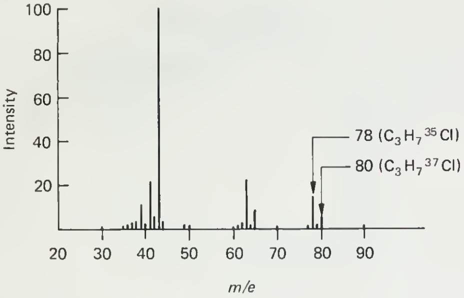


FIGURE 16.6 *Mass spectrum of 2-chloropropane.*

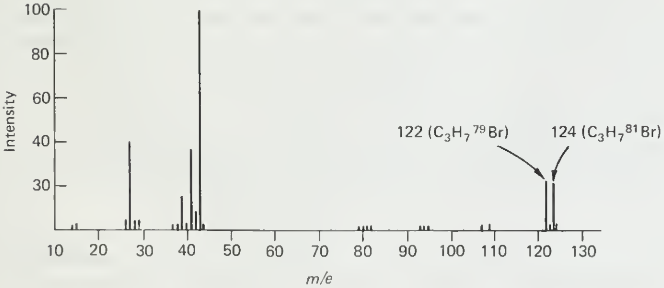


FIGURE 16.7 *Mass spectrum of 1-bromopropane.*

peaks that are *not due to isotopes*. Thirdly, the presence of a small amount of impurity with a strong peak at M + 1 of the sample will interfere with accurate measurement.

16.4
Fragmentation

A. *Simple Bond Cleavage*

When an electron collides with a molecule in the ionizing chamber of the mass spectrometer, ionization will occur if the impinging electron transfers to the molecule an amount of energy equal to or greater than its ionization potential. The ionization potentials for several organic molecules are given in Table 16.2. When the colliding electron has *excess energy*, a part of this excess energy will normally be carried away by the radical cation produced in the collision. If the molecular ion gains enough surplus energy, bond cleavage (fragmentation) may occur, with the resultant formation of a new cation and a free radical. Typically, the electron beams employed in the ionization process have an energy of 50–70 ev (1150–1610 kcal mole^{-1}). Since this is far in excess of the typical bond energies encountered in organic compounds (50–130 kcal mole^{-1}), fragmentation is normally extensive.

TABLE 16.2
Ionization Potentials

Compound	Ionization Potential, electron volts (ev)
benzene	9.25
aniline	7.70
acetylene	11.40
ethylene	10.52
methane	12.98
methanol	10.85
methyl chloride	11.35

Consider the case of the simplest hydrocarbon, methane. The mass spectrum of methane is shown in Figure 16.8 in bar graph form as well as tabular form. Note that the base peak (most intense peak) corresponds to the molecular ion (*m/e* 16). Note also the monoisotopic peak at *m/e* 17 (M + 1), which has an intensity 1.11% that of the molecular ion, within 0.07% of the intensity predicted by theory. Examination of the mass spectrum reveals that cations are also produced and measured that have *m/e* values of 15, 14, 13, 12, 2, and 1. The following modes of fragmentation may be postulated to explain these various cationic fragments. Initial ionization supplies the molecular ion, with *m/e* 16.

$$CH_4 + e \longrightarrow \underset{m/e\ 16}{[CH_4]^{\overset{+}{\cdot}}} + 2\,e$$

Some of these ions move into the accelerating region and are passed into the magnetic field. However, since they possess a large amount of excess energy, many

m/e	Intensity
1	3.4
2	0.2
12	2.8
13	8.0
14	16.0
15	86.0
16	100.0
17	1.11

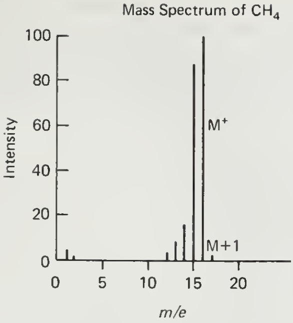


Figure 16.8 *Mass spectrum of methane.*

undergo fragmentation prior to entering the magnetic field, giving a methyl cation (m/e 15) and a hydrogen atom.

$$[CH_4]^{+\cdot} \longrightarrow \underset{m/e\ 15}{CH_3^+} + H\cdot$$

Occasionally this cleavage occurs in such a way as to produce a methyl radical and a bare proton (m/e 1).

$$[CH_4]^{+\cdot} \longrightarrow CH_3\cdot + \underset{m/e\ 1}{H^+}$$

The fragment CH_3^+ can be accelerated, deflected, and collected as a cation of m/e 15, or it too may undergo fragmentation, giving a hydrogen atom and a new radical cation of m/e 14.

$$CH_3^+ \longrightarrow \underset{m/e\ 14}{[CH_2]^{+\cdot}} + H\cdot$$

Similar events give rise to particles of m/e 13 and 12.

$$[CH_2]^{+\cdot} \longrightarrow \underset{m/e\ 13}{CH^+} + H\cdot$$

$$CH^+ \longrightarrow \underset{m/e\ 12}{[C]^{+\cdot}} + H\cdot$$

Occasionally, an ion may eject an ionized hydrogen molecule, giving rise to the weak peak at m/e 2.

$$[CH_4]^{+\cdot} \longrightarrow CH_2 + \underset{m/e\ 2}{[H_2]^{+\cdot}}$$

More complicated alkanes give very complicated spectra, with peaks at virtually every value of m/e. However, most of these fragment peaks are of extremely low intensity. The more intense fragment peaks have m/e values of M − 15, M − 29, M − 43, M − 57, and so on, corresponding to scission of the hydrocarbon chain at various places along its length. The spectrum of *n*-dodecane, plotted in Figure 16.9, is illustrative.

There is a reasonably intense molecular ion (4% of the base peak) at m/e 170.

The peak at m/e 155, corresponding to loss of CH_3 (M − 15) is so weak as not to be noticeable. However, the peaks at m/e 141 (M − 29), 127 (M − 43), and so on, are apparent. Note that intensity decreases regularly as mass increases, after the particle of m/e 43 (corresponding to $C_3H_7^+$). The modes of fragmentation responsible for the spectrum of *n*-dodecane are indicated in Figure 16.10.

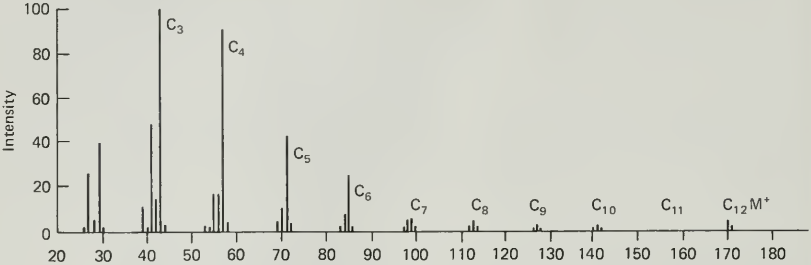
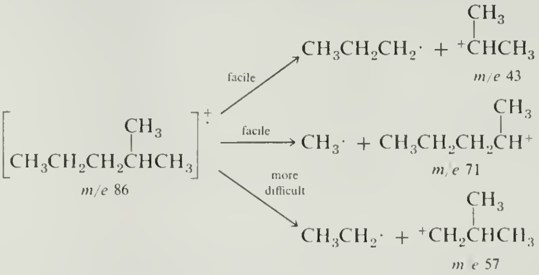


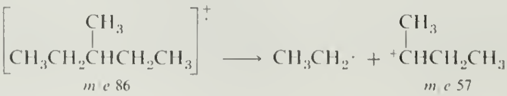
FIGURE 16.9 *Mass spectrum of* n-*dodecane.*

When there is a branch point in the chain, an unusually large amount of fragmentation will occur there because a more stable carbonium ion results. Thus, in 2-methylpentane, loss of C_3H_7 or CH_3 is much greater than loss of C_2H_5, since the former modes give secondary carbonium ions, whereas the latter gives a primary carbonium ion.


$\left[CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3\right]^{+\cdot}$
m/e 86
facile
$CH_3CH_2CH_2\cdot + {}^+\overset{CH_3}{\overset{|}{C}}HCH_3$
m/e 43
facile
$CH_3\cdot + CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}H^+$
m/e 71
more difficult
$CH_3CH_2\cdot + {}^+CH_2\overset{CH_3}{\overset{|}{C}}HCH_3$
m/e 57

The spectrum of 2-methylpentane, plotted in Figure 16.11, illustrates this behavior.

On the other hand, the isomeric hydrocarbon 3-methylpentane can cleave in three ways so as to give a secondary carbonium ion. Two of these cleavages amount to loss of C_2H_5. Correspondingly, the M − 29 peak in its spectrum, shown in Figure 16.12, is the most intense peak.



$$\underset{m/e\ 86}{\left[CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_3\right]^{+\cdot}} \longrightarrow CH_3CH_2\cdot + \underset{m/e\ 57}{{}^+\overset{CH_3}{\overset{|}{C}}HCH_2CH_3}$$

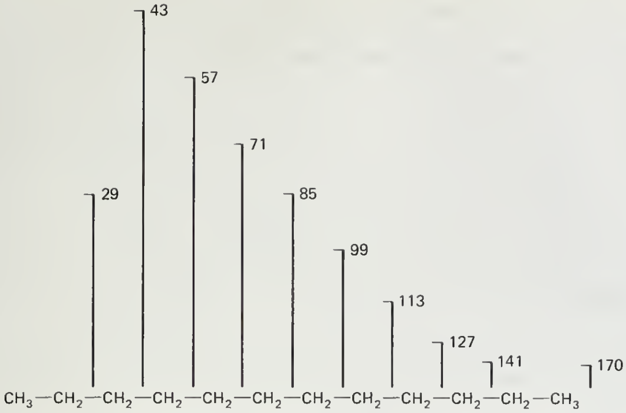

29
43
57
71
85
99
113
127
141
170
CH3—CH2—CH2—CH2—CH2—CH2—CH2—CH2—CH2—CH2—CH2—CH3

Figure 16.10 *Fragmentation of* n-*dodecane.*

Note that 3-methylpentane cannot undergo a simple cleavage to give a particle with *m/e* 43. The peak in its spectrum with this value must arise by a process involving some sort of skeletal rearrangement.

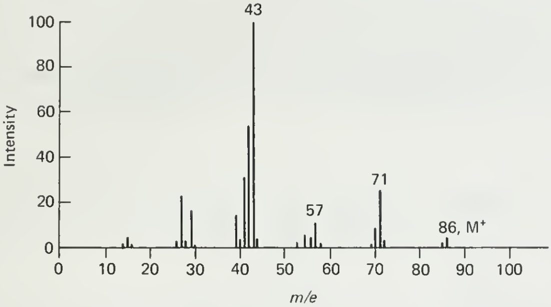


Figure 16.11 *Mass spectrum of 2-methylpentane.*

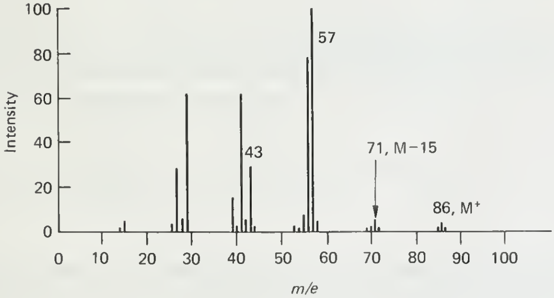


Figure 16.12 *Mass spectrum of 3-methylpentane.*

The mode of fragmentation in the preceding discussion is common in mass spectrometry. A radical cation undergoes bond cleavage in such a manner as to give the *most stable cationic fragment*. What we know about the relative stabilities of various cations from other areas of organic chemistry may often be used to predict how fragmentation will occur in a mass spectrometer. The case of the methylpentanes is a good example of this principle. In Chapter 8, we discussed the S_N1 reactions of alkyl halides to give carbonium ion intermediates and found a reactivity order tertiary > secondary > primary. From this order, and other data, we concluded that tertiary carbonium ions are more stable than secondary ones, which are, in turn, more stable than primary carbonium ions. Although these results are in solution and mass spectroscopy occurs in the vapor phase, we can use our qualitative knowledge of carbonium ion stabilities to "interpret" the fragmentation pattern of hydrocarbons.

Some of the enthalpy data for ionization of alkyl chlorides given in Table 8.8 on page 149 were actually obtained by mass spectrometric methods.

In alkanes with a quaternary carbon, fragmentation to give tertiary carbonium ions is so facile that such hydrocarbons frequently give no detectable parent peak.

B. *Two-bond Cleavage, Elimination of a Neutral Molecule*

Some compounds give extremely weak molecular ion peaks. This tends to happen when some form of fragmentation is particularly easy. Such behavior is typical of alcohols, which often give no detectable molecular ion whatsoever. The spectrum of 2-methyl-2-butanol in Figure 16.13 illustrates this phenomenon.

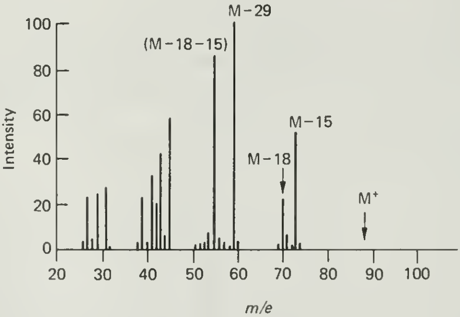
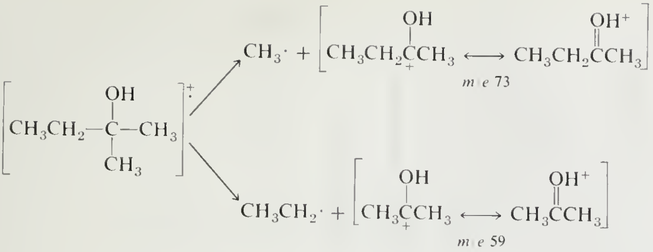
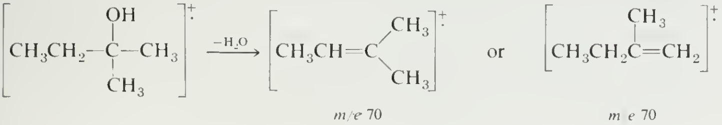


FIGURE 16.13 *Mass spectrum of 2-methyl-2-butanol.*

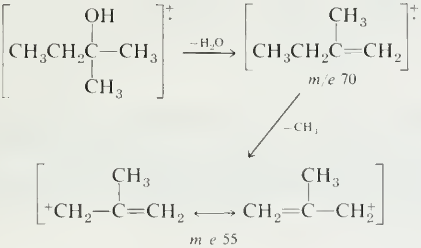
The molecular ion, which would appear at *m/e* 88, is not observed. Instead, sizeable peaks are observed at *m/e* values of 73 (M − 15) and 59 (M − 29), corresponding to cleavage of the radical ion so as to give stable oxonium ions.



In addition, there is a substantial peak at *m/e* 70, corresponding to *loss of water* from the molecular ion. This type of fragmentation, in which a radical cation expels a neutral molecule, giving a new radical cation, is common with alcohols and ethers.

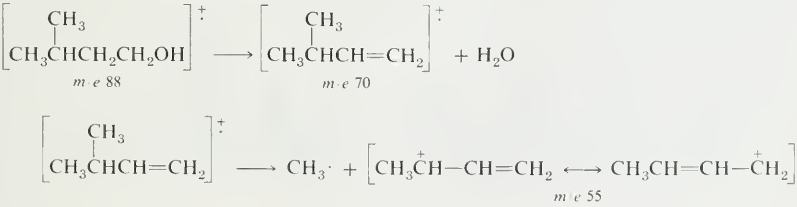


Of course, these new molecular ions can undergo fragmentation of the type first discussed. The peak at *m/e* 55 probably arises from such a stepwise path.



The *m/e* 55 fragment is a substituted allyl cation, a conjugated carbonium ion to be discussed in Chapter 20.

Another example of such behavior is 3-methyl-1-butanol, whose mass spectrum is plotted in Figure 16.14. This is a particularly dramatic example. Again the molecular ion is nonexistent. The spectrum of this alcohol is explainable in terms of the following fragmentation scheme.



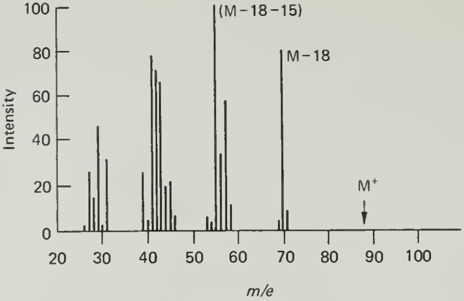
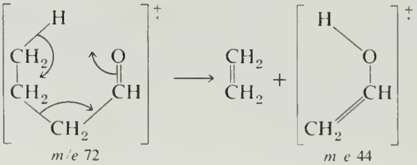
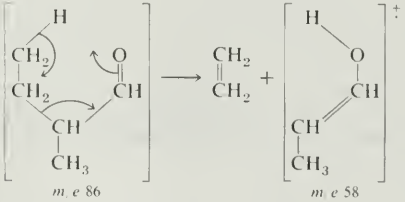


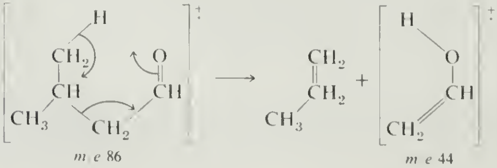
Figure 16.14 *Mass spectrum of* 3-*methyl*-1-*butanol.*

There is one other type of fragmentation, also involving expulsion of a neutral molecule, that we shall introduce at this point. The spectrum of butyraldehyde is plotted in Figure 16.15. The most striking thing about the spectrum is the fact that the base peak (*m/e* 44) is an even number. Thus, it must correspond to expulsion of a molecule, rather than a radical, from the molecular ion. Extensive studies suggest that this fragment arises in the following way.


H
CH₂
O
CH₂
CH
CH₂
m/e 72
CH₂
CH₂
+
H
O
CH
CH₂
m/e 44

This rearrangement reaction is called a **McLafferty rearrangement.** It can provide useful information concerning the structure of isomeric aldehydes and ketones. For example, 2-methylbutanal and 3-methylbutanal both undergo the rearrangement. In the former case, one observes an intense peak at *m/e* 58, but in the latter the rearrangement peak occurs at *m/e* 44.


H
CH₂
O
CH₂
CH
CH
CH₃
m/e 86
CH₂
CH₂
+
H
O
CH
CH
CH₃
m/e 58


H
CH₂
O
CH
CH
CH₃
CH₂
m/e 86
CH₂
CH
CH₃
+
H
O
CH
CH₂
m/e 44

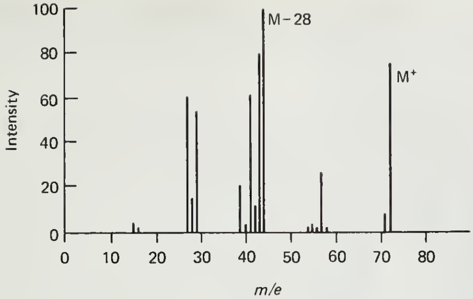
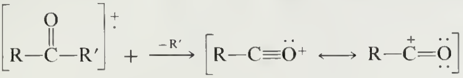


FIGURE 16.15 *Mass spectrum of butyraldehyde.*

An additional fragmentation common to ketones is cleavage of a bond to the carbonyl group to give a cation of the oxonium ion type.



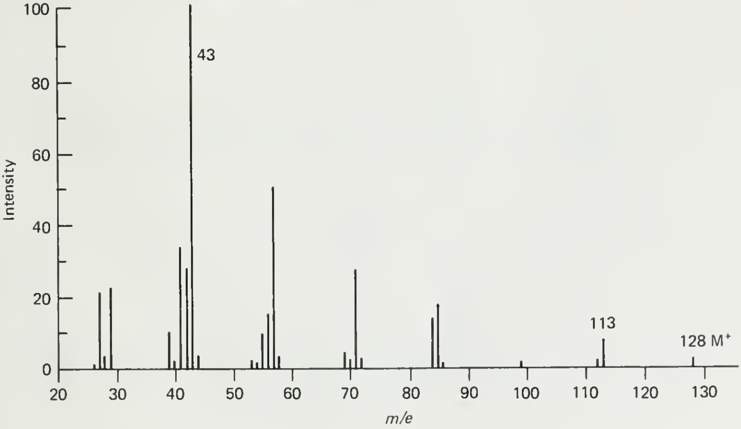
$$\left[R-\overset{\overset{\displaystyle O}{\|}}{C}-R'\right]^{\overset{+}{\cdot}} + \xrightarrow{-R'} \left[R-C\equiv\ddot{O}^{+} \longleftrightarrow R-\overset{+}{C}=\underset{\cdot\cdot}{\ddot{O}}\right]$$

PROBLEMS

1. Estimate the intensity of the M + 1 peak for each of the following compounds.
   (a) $C_8H_{16}O_4$
   (b) $C_{11}H_{16}N_2$
   (c) $C_{13}H_{20}$
   (d) $C_{60}H_{122}$
   (e) CH_3I
   (f) C_2F_6

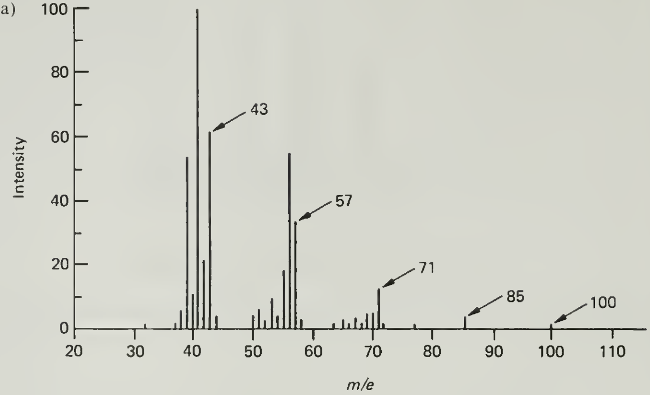
2. Estimate the relative intensity of the peaks at *m/e* 112, 114, and 116 in the mass spectrum of 1,2-dichloropropane.

3. An unknown compound contains only carbon and hydrogen. Its mass spectrum is shown. Propose a structure for the compound.

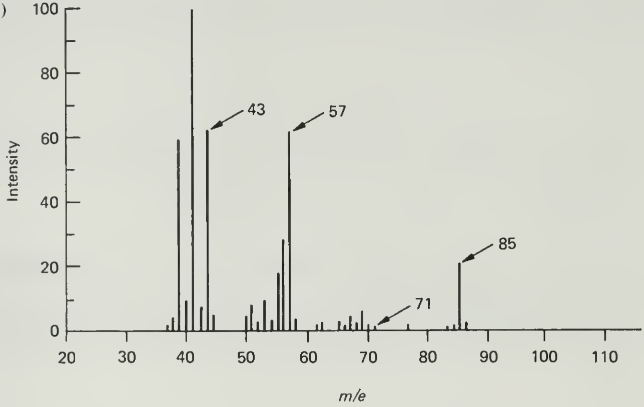


4. The following mass spectra are of 2,2-dimethylpentane, 2,3-dimethylpentane, and 2,4-dimethylpentane. Assign structures on the basis of the mass spectra.

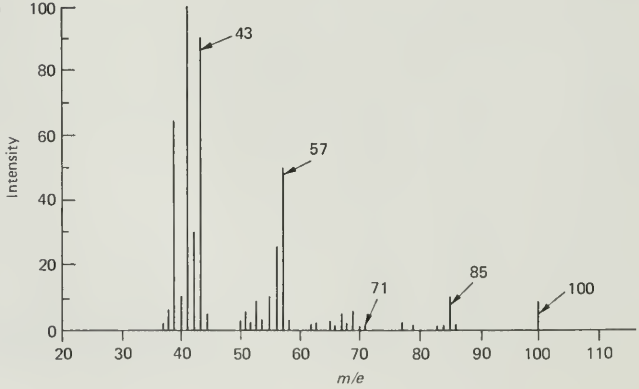
(a)



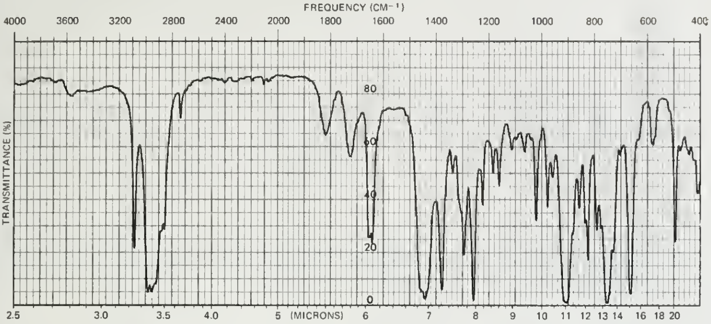
(b)

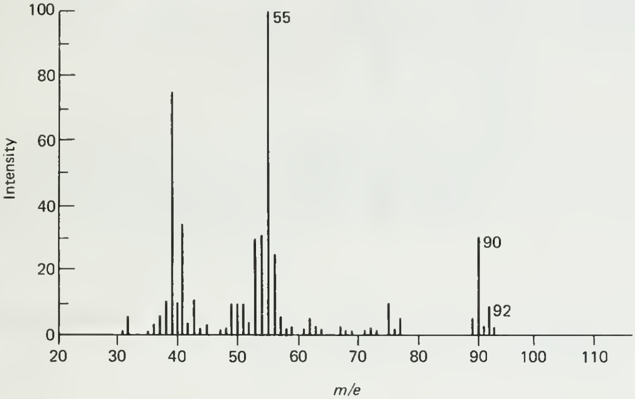


(c)

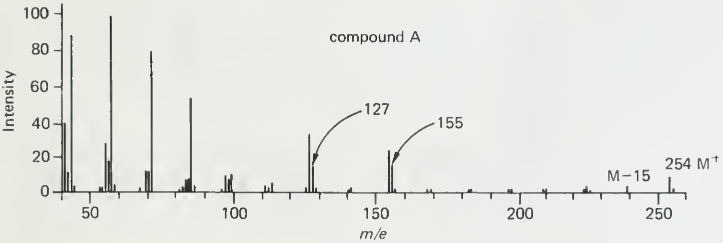


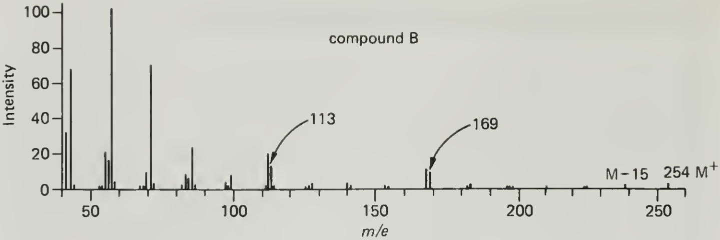
5. Identify the following compound from its ir and mass spectra.



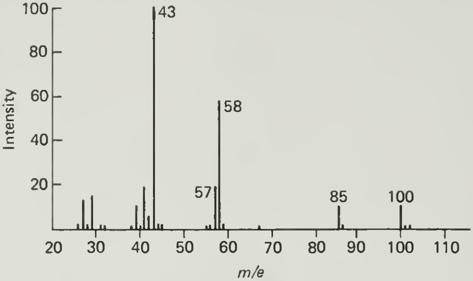


6. Two hydrocarbons were isolated from blue-green algae. The mass spectra of the two hydrocarbons, shown below, provided a clue to their structures. Suggest structures for the two hydrocarbons.

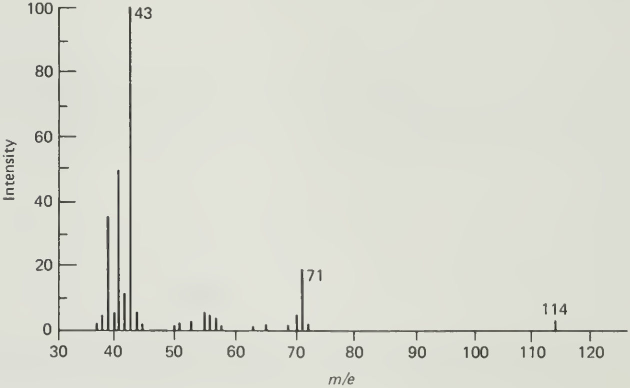




7. A compound has infrared absorption at 1710 cm^{-1}. Its mass spectrum is shown below. Suggest a structure of the compound.

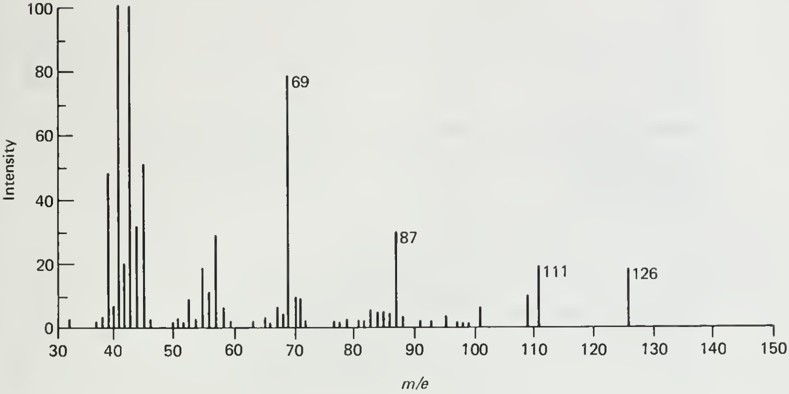


8. Propose a structure for the following compound from its mass spectrum. The ir spectrum shows a strong absorption at 1710 cm^{-1}.



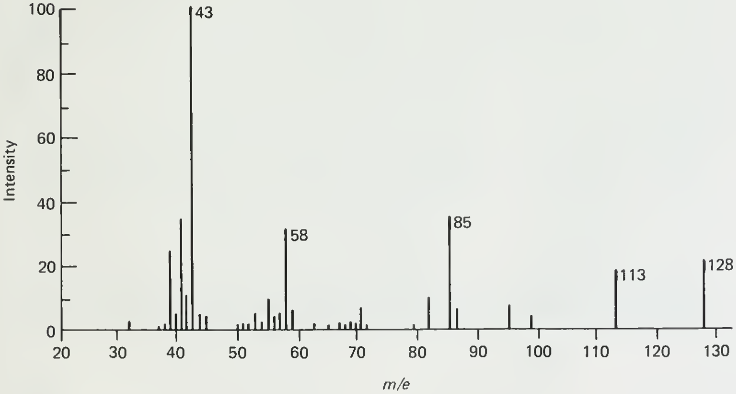
9. An unknown compound shows strong ir absorption at 3400 cm^{-1}. Its mass spectrum is shown below.

(a) Propose a possible structure for the compound.



(b) The ir and nmr spectra of the compound are shown in problem 4d, Chapter 14. Confirm your assignment by examination of these spectra.

10. The mass spectrum of 2-octanone is shown below. Write mechanisms showing the origin of the principal fragments.



11. The ionization potential of 2-methylbutane is 10.35 ev or 238.7 kcal mole^{-1} (1 ev ≡ 23.06 kcal mole^{-1}); hence, ΔH_f° for 2-methylbutane cation is obtained from ΔH_f° of

2-methylbutane as $-36.9 + 238.7 = 201.8$ kcal mole^{-1}. From the following ΔH_f° values given for possible fragmentation products of the radical cation, calculate ΔH° for each of the fragmentation reactions shown. On the basis of these results, what will be the relative intensity order of the fragment cations?

	ΔH_f°, kcal mole^{-1}		ΔH_f°, kcal mole^{-1}
CH_3^+	260	$CH_3\cdot$	34
$C_2H_5^+$	219	$C_2H_5\cdot$	26
$(CH_3)_2CHCH_2^+$	205	$(CH_3)_2CHCH_2\cdot$	13.5
$(CH_3)_2CH^+$	190	$(CH_3)_2CH\cdot$	17.5
$CH_3CH_2\overset{+}{C}HCH_3$	192	$CH_3CH_2\dot{C}HCH_3$	12

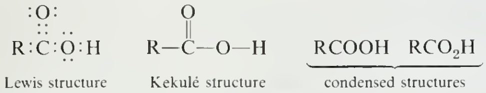
$$[(CH_3)_2CHCH_2CH_3]^{+\cdot}\ \begin{array}{l} \longrightarrow (CH_3)_2CHCH_2\cdot + CH_3^+ \\ \longrightarrow (CH_3)_2CHCH_2^+ + CH_3\cdot \\ \longrightarrow (CH_3)_2CH\cdot + C_2H_5^+ \\ \longrightarrow (CH_3)_2CH^+ + C_2H_5\cdot \\ \longrightarrow CH_3\cdot + CH_3\overset{+}{C}HCH_2CH_3 \\ \longrightarrow CH_3^+ + CH_3\dot{C}HCH_2CH_3 \end{array}$$

CHAPTER 17

Carboxylic Acids

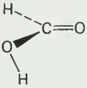
17.1 Structure

Carboxylic acids are distinguished by the functional grouping CO_2H. Four ways of writing this grouping, referred to as the **carboxy group**, are shown.



Either an organic group or a hydrogen may be attached to the carboxy group.

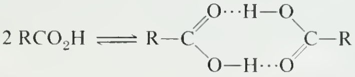
The carbon atom in a carboxy group uses three hybrid orbitals to bond to the oxygen of the OH group, the carboxy oxygen, and to hydrogen or an organic radical. These three orbitals are approximately sp^2 hybrids that lie in one plane. The remaining p orbital on the carbon forms a π bond to a p orbital on the carboxy oxygen. There are two distinct C—O bond distances, corresponding to C=O and C—O. The bond angles and bond lengths of formic acid, as determined by microwave spectroscopy, are shown in Figure 17.1. Note that the bond angles around the carboxy carbon are only approximately those expected for sp^2 hybridization. The array HCOO is planar and the hydroxy hydrogen lies outside of this plane.



Bond Lengths, Å		Bond Angles, deg	
C=O	1.202	H—C=O	124.1
C—O	1.343	O—C=O	124.9
C—H	1.097	H—C—O	111.0
O—H	0.972	H—O—C	106.3

FIGURE 17.1 *Structure of formic acid.*

In the solid and liquid phases, as well as in the vapor phase at moderately high pressure, carboxylic acids exist largely in the dimeric form depicted.



For formic acid in the vapor phase, $\Delta H°$ for the dimerization has been determined to be -14 kcal mole^{-1}. The factor that stabilizes the dimeric form is undoubtedly the reciprocal hydrogen bonding shown in the diagram.

17.2 Nomenclature

There are two systems of nomenclature currently in use for carboxylic acids, and the student should be acquainted with both. Since many of the simpler acids

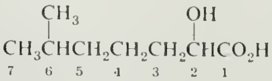
TABLE 17.1
Nomenclature of Carboxylic Acids

Compound	Common Name	IUPAC Name
HCO_2H	**formic acid**	methanoic acid
CH_3CO_2H	**acetic acid**	ethanoic acid
$CH_3CH_2CO_2H$	**propionic acid**	propanoic acid
$CH_3(CH_2)_2CO_2H$	**butyric acid**	butanoic acid
$CH_3(CH_2)_3CO_2H$	**valeric acid**	pentanoic acid
$CH_3(CH_2)_4CO_2H$	caproic acid	**hexanoic acid**
$CH_3(CH_2)_5CO_2H$	enanthic acid	**heptanoic acid**
$CH_3(CH_2)_6CO_2H$	caprylic acid	**octanoic acid**
$CH_3(CH_2)_7CO_2H$	pelargonic acid	**nonanoic acid**
$CH_3(CH_2)_8CO_2H$	capric acid	**decanoic acid**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	**dodecanoic acid**
$CH_3(CH_2)_{12}CO_2H$	myristic acid	**tetradecanoic acid**
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	**hexadecanoic acid**
$CH_3(CH_2)_{16}CO_2H$	stearic acid	**octadecanoic acid**

are naturally occurring and were discovered early in the history of organic chemistry, they have well-entrenched "common" names. At the 1892 IUPAC Congress, it was agreed to derive the name of a carboxylic acid systematically from that of the normal alkane having the same number of carbon atoms by dropping the ending **-e** and adding the suffix **-oic** acid. The common and IUPAC names for the first ten straight-chain acids, as well as other selected examples, are given in Table 17.1.

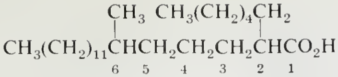
Past caproic acid, the even-numbered carboxylic acids are the most important because it is only the even-numbered acids that occur in nature. Carboxylic acids are **biosynthesized** (built up by living organisms) by the combination of acetic acid units. Since acetic acid is a two-carbon building block, most of the naturally occurring acids have an even number of carbon atoms in the chain. The name used by *Chemical Abstracts* in indexing is printed in Table 17.1 in bold type. For the last four entries in the table, *Chemical Abstracts* has retained the common name of the acid for references to the unsubstituted acid but uses the IUPAC name for all derivatives of the acid. Except for the exceptions noted in the table, and a few unsaturated acids, *Chemical Abstracts* utilizes solely the IUPAC name for a carboxylic acid.

For naming a substituted carboxylic acid in the IUPAC system, the longest carbon chain *containing the carboxy group* is numbered from **1** to ***n***, beginning with the carboxy carbon. The name of this parent straight-chain carboxylic acid is then prefixed by the names of the various substituents.



$$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2CH_2CH_2\overset{\overset{OH}{|}}{C}HCO_2H$$

2-hydroxy-6-methylheptanoic acid

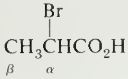


$$CH_3(CH_2)_{11}\overset{CH_3}{\overset{|}{C}}HCH_2CH_2CH_2\overset{CH_3(CH_2)_4CH_2}{\overset{|}{C}}HCO_2H$$

6-methyl-2-hexyloctadecanoic acid

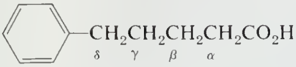
When using common names, the chain is labeled α, β, γ, δ, and so on, beginning with the carbon adjacent to the carboxy carbon (see Table 11.1, Greek Letters, page 208).

As in the case of aldehydes and ketones, it is desirable not to mix IUPAC and common nomenclature (page 352).



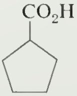
$$CH_3\overset{Br}{\overset{|}{C}}HCO_2H$$

α-bromopropionic acid
2-bromopropanoic acid
(not 2-bromopropionic acid)

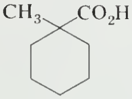


δ-phenylvaleric acid
5-phenylpentanoic acid
(not δ-phenylpentanoic acid)

In some cases, it is not possible or convenient to name a carboxylic acid in the foregoing way. This is the case with cyclic acids.

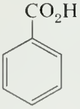


cyclopentanecarboxylic acid

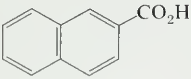


1-methylcyclohexanecarboxylic acid

Many of the common aromatic and heterocyclic carboxylic acids have common names which are used by *Chemical Abstracts* for referencing. The student should be aware of this and learn these names as he encounters them. Two examples are

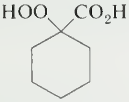


benzoic acid



2-naphthoic acid

In rare cases, it may be necessary to name a compound containing a carboxy group as a derivative of some other function. In this case, the CO_2H group is designated "carboxy." One such example is



1-carboxycyclohexyl hydroperoxide

17.3
Physical Properties

Table 17.2 lists the melting point, boiling point, and water solubility of the first 18 straight chain carboxylic acids. The boiling points of the straight chain acids

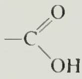
TABLE 17.2
Physical Properties of Carboxylic Acids

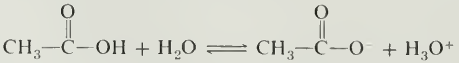
Acid	Melting Point, °C	Boiling Point, °C (760 mm)	Solubility in H_2O g/100 ml, 20°C
formic	8.4	101	∞
acetic	16.6	118	∞
propionic	−21	141	∞
butyric	−5	164	∞
valeric	−34	186	4.97
hexanoic	−3	205	0.968
heptanoic	−8	223	0.244
octanoic	17	239	0.068
nonanoic	15	255	0.026
decanoic	32	270	0.015
undecanoic	29	280	0.0093
dodecanoic	44	299	0.0055
tridecanoic	42	312	0.0033
tetradecanoic	54	251 (100 mm)	0.0020
pentadecanoic	53	257 (100 mm)	0.0015
hexadecanoic	63	267 (100 mm)	0.00072
heptadecanoic	63	—	0.00042
octadecanoic	72	—	0.00029

are plotted against molecular weight in Figure 18.5 on page 457. The boiling points of carboxylic acids are higher than expected for their molecular weights because of hydrogen bonding. The lower molecular weight acids are liquids at room temperature. The first four acids are fully miscible with water in all proportions. As the chain length is increased, the water solubility steadily decreases.

17.4
Acidity

A. *Ionization*

Compounds containing the functional group  are weakly acidic; in fact it is this property from which the class derives its name. When acetic acid is dissolved in water, the equilibrium shown in equation (17-1) exists.

 (17-1)

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-OH + H_2O \rightleftharpoons CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O^- + H_3O^+ \qquad (17\text{-}1)$$

The equilibrium constant for this reaction, denoted as K_a or the "acid dissociation constant" has the magnitude

$$K_a = \frac{[CH_3CO_2^-][H^+]}{[CH_3CO_2H]} = 1.8 \times 10^{-5}\,M \qquad (17\text{-}2)$$

Remember that the concentration of H_2O, which remains essentially invariant for dilute solutions (at 55.5 M) is not carried in the denominator of the expression for

K_a. More correctly, equation (17-2) is an expression for the equilibrium

$$CH_3CO_2H \rightleftharpoons CH_3CO_2^- + H^+$$

The exact equilibrium expression for equation (17-1) is

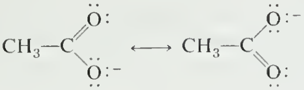
$$K = \frac{[CH_3CO_2^-][H_3O^+]}{[CH_3CO_2H][H_2O]} = 3.25 \times 10^{-7}$$

It follows that $K_a = [H_2O] \times K = 1.8 \times 10^{-5}\ M$

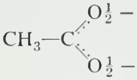
The corresponding $pK_a = -\log(1.8 \times 10^{-5}) = 5 - \log(1.8) = 4.74$.

Dissociation constants of this magnitude put the carboxylic acids in the class of relatively weak acids. For example, a 0.1 M aqueous solution of acetic acid is only 1.3% dissociated into ions. Strong acids, such as HCl and H_2SO_4, are completely dissociated in dilute aqueous solution. Nevertheless, the carboxylic acids are distinctly acidic—their aqueous solutions have the characteristic sour taste of hydronium ion. Although the carboxylic acids are weak acids compared to mineral acids, they are much stronger than alcohols. Recall that ethanol has a dissociation constant of about 10^{-16}; ethanol is only 10^{-11} as strong an acid as acetic acid.

The question immediately arises, "Why is acetic acid more acidic than ethanol?" The answer lies mostly in the relative stability of the negative charge of the anion. In ethoxide ion the negative charge is concentrated on a single oxygen atom; ethoxide ion is basic because this concentrated charge provides strong attraction for a proton. In acetate ion, however, the charge on the carboxy group is divided between two oxygens. Acetate ion is not well represented by a single Lewis structure. A second and equivalent structure may be written that differs only in the position of electrons:



Acetate ion is described as a resonance hybrid of these two principal structures (Section 2.4). The hybrid structure may also be written as



This symbol emphasizes that only half of a negative charge resides on each oxygen. The attraction for a proton is therefore reduced.

Another way of describing this phenomenon is wholly in terms of energy. The energies required to remove a proton from ethanol and acetic acid in the dilute gas phase are

$$CH_3CH_2OH = CH_3CH_2O^- + H^+ \qquad \Delta H^\circ = 379\ \text{kcal mole}^{-1}$$
$$CH_3COOH = CH_3CO_2^- + H^+ \qquad \Delta H^\circ = 346\ \text{kcal mole}^{-1}$$

It takes a large amount of energy to separate charges because of their Coulombic attraction. The energy required for dissociation of acetic acid is substantially less than that for ethanol because in acetate ion the negative charge is attracted by two oxygen nuclei and the reduced charge density has less internal Coulombic repulsion. This energy effect in acetate ion is sometimes referred to as "resonance" stabilization or as a resonance energy (Chapter 20).

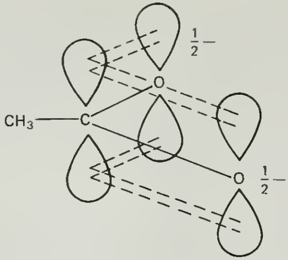


FIGURE 17.2 *π orbital interactions in acetate ion.*

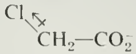
An alternative description can be given in terms of the overlap of atomic orbitals. Each oxygen contributes a *p* orbital that can overlap in π bonding to a *p* orbital of the carboxy carbon, as illustrated in Figure 17.2. The resulting three-center π molecular orbital system has four electrons with excess electron density put on the end oxygens. Such multi center π molecular orbital systems are characteristic of **conjugated systems** and are discussed in more detail in Chapter 20.

In either representation, the two C—O bonds in a carboxylate ion are equivalent. The C—O bond length of 1.26 Å is in between that of C=O and C—O in the carboxylic acid.

B. *Inductive Effects*

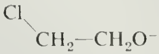
In Section 11.4 we found that electronegative groups whose bonds to carbon are highly polar have important effects on the acidity of alcohols. We saw that this effect could be interpreted in terms of the electrostatic interaction of a bond dipole with the anionic negative charge. The same behavior is manifest by substituent groups in carboxylic acids. Because of the higher acidity and ease of measurement of carboxylic acids, a wealth of quantitative acidity data is available. Some of these results are summarized in Table 17.3.

Atoms that have high electronegativity tend to withdraw electron density from carbon and have a marked acid-strengthening effect. Chloroacetic acid is 1.9 pK_a units more acidic than acetic acid. The C—Cl bond dipole is oriented in such a way that the positive end is closer to the negative charge on the carboxy group than is the negative end. Electrostatic attraction exceeds the repulsion and the negative charge of the anion is more stabilized.



$Cl—CH_2—CO_2^-$

We used the same explanation to interpret the effect of a chlorine substituent on the acidity of ethanol.



$Cl—CH_2—CH_2O^-$

The acid-strengthening effect, in this case of 1.6 pK_a units, is quite similar to that in chloroacetic acid. In both anions the negative charge is two atoms away from the C—Cl bond.

TABLE 17.3
Acidity of Some Substituted Acetic Acids

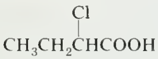
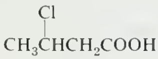
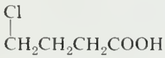
Acid	K_a, M	pK_a
CH_3COOH	1.8×10^{-5}	4.74
FCH_2COOH	2.6×10^{-3}	2.59
F_3CCOOH	0.59	0.23
$ClCH_2COOH$	1.4×10^{-3}	2.86
$Cl_2CHCOOH$	5.5×10^{-2}	1.26
Cl_3CCOOH	0.23	0.64
$BrCH_2COOH$	1.3×10^{-3}	2.90
ICH_2COOH	6.7×10^{-4}	3.18
$HOCH_2COOH$	1.5×10^{-4}	3.83
CH_3OCH_2COOH	2.9×10^{-4}	3.54
$CH_2{=}CHCH_2COOH$	4.5×10^{-5}	4.35
$HC{\equiv}CCH_2COOH$	4.8×10^{-4}	3.32
CH_3CH_2COOH	1.3×10^{-5}	4.87
$NCCH_2COOH$	3.4×10^{-3}	2.46
$C_6H_5CH_2COOH$	4.9×10^{-5}	4.31

Carbon-carbon double and triple bonds have a significant electron-attracting effect that is reflected in the enhanced acidity of vinylacetic and ethynylacetic acids. An sp^2 hybridized carbon orbital with its greater *s* character is effectively more electronegative than an sp^3 orbital. Recall that alkenes and alkynes do have small but significant dipole moments (Sections 12.3.A and 13.3.A.)

The higher alkanoic acids are somewhat less acidic than acetic acid. Alkyl groups manifest a small but significant electron-donating inductive effect in appropriate systems in solution.

The inductive effect of remote substituents falls off dramatically with increased distance from the charged center. This effect is expected because electrostatic interactions between charges are inversely proportional to the distance between them. This effect is exemplified by the chlorobutyric acids whose acidity constants are shown in Table 17.4. Beyond a few methylene groups, the effect becomes negligible.

TABLE 17.4
Acidity of Butyric Acids

Acid	K_a, M	pK_a
 $CH_3CH_2\overset{Cl}{\overset{\vert}{C}}HCOOH$	139×10^{-5}	2.86
 $CH_3\overset{Cl}{\overset{\vert}{C}}HCH_2COOH$	8.9×10^{-5}	4.05
 $\overset{Cl}{\overset{\vert}{C}}H_2CH_2CH_2COOH$	3.0×10^{-5}	4.52
$CH_3CH_2CH_2COOH$	1.5×10^{-5}	4.82

C. *Salt Formation*

There is one more aspect of acidity of carboxylic acids that we should consider. In Section 17.3, we saw that carboxylic acids of more than five carbons are essentially insoluble in water. Beyond this point, the polar portion of the molecule (COOH) becomes less important than the nonpolar hydrocarbon tail (—R). Now, consider the reaction of a carboxylic acid such as dodecanoic acid with a strong base like hydroxide ion.

$$CH_3(CH_2)_{10}CO_2H + OH^- \overset{K}{\rightleftharpoons} H_2O + CH_3(CH_2)_{10}CO_2^- \qquad (17\text{-}3)$$

The equilibrium constant for reaction (17-3) may be derived as follows:

$$K_a = \frac{[CH_3(CH_2)_{10}CO_2^-][H^+]}{[CH_3(CH_2)_{10}CO_2H]} = 1.3 \times 10^{-5}\,M \qquad (17\text{-}4)$$

$$K_w = [H^+][OH^-] = 10^{-14}\,M^2 \qquad (17\text{-}5)$$

Rearranging (17-5), we have

$$[H^+] = \frac{10^{-14}}{[OH^-]} \qquad (17\text{-}6)$$

Substituting (17-6) into (17-4) and expanding, we have

$$K = \frac{[CH_3(CH_2)_{10}CO_2^-]}{[CH_3(CH_2)_{10}CO_2H][OH^-]} = 1.3 \times 10^{9}\,M^{-1} \qquad (17\text{-}7)$$

Equation (17-7) is merely the equilibrium expression for reaction (17-3). The large value of K shows that the reaction proceeds to completion. Thus, dodecanoic acid is converted by aqueous sodium hydroxide completely into the salt, **sodium dodecanoate.** Note that the anions of carboxylic acids are named by dropping **-ic** from the name of the parent acid and adding the suffix **-ate.** Although dodecanoic acid is a neutral molecule, sodium dodecanoate is a salt. Dissolution of this salt gives an anion and a cation, which can be solvated by water. It is not surprising that the solubility of sodium dodecanoate (1.2 g per 100 ml) is much greater than that of dodecanoic acid itself (0.0055 g per 100 ml).

D. *Soaps*

The sodium and potassium salts of long chain carboxylic acids ("fatty acids") are obtained by the reaction of natural fats with sodium or potassium hydroxide. These salts, referred to as soaps, have the interesting and useful ability to solubilize nonpolar organic substances. This phenomenon can easily be understood if one considers the structure of such a salt.

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CO_2^-\ K^+$$

The molecule has a polar ionic region and a large nonpolar hydrocarbon region. In aqueous solution, a number of carboxylate ions tend to cluster together so that the hydrocarbon tails are close to each other, thus reducing their energy by the attractive Van der Waals forces enjoyed by normal hydrocarbons. The surface of the sphere-like cluster is then occupied by the highly polar $—CO_2^-$ groups. These polar groups face the medium, where they may be solvated by H_2O or paired with a cation. The resulting spherical structure, called a **micelle**, is depicted in cross section in Figure 17.3.

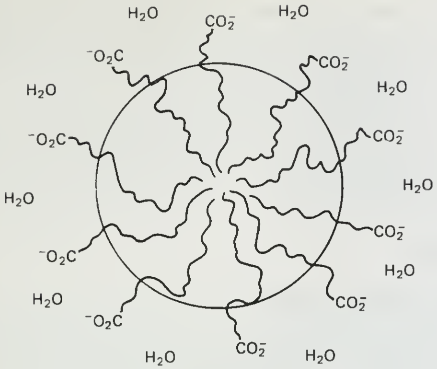
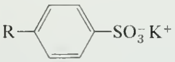


FIGURE 17.3 *Cross section of a micelle.*

Organic material not normally soluble in water (such as butter or motor oil) may "dissolve" in the hydrocarbon interior of a micelle. The overall process of soap solubilization is diagrammed schematically in Figure 17.4.

There are natural bacteria that can metabolize soaps. This degradation is most rapid when there are no branches in the hydrocarbon chain of the soap molecule. Since the naturally occurring fatty acids are all unbranched compounds, soaps derived from natural fats are said to be **biodegradable.** Before 1933, all cleaning materials were soaps. In that year, the first synthetic detergents were marketed. Detergents have the useful property of not forming the hard "scum" which often results from the use of a soap with hard water. This scum is actually the insoluble magnesium and calcium salts of the fatty acid. The first detergents were compounds called **alkylbenzenesulfonates.** Like soaps, they had a large, nonpolar hydrocarbon tail and a polar end.



R = branched alkyl chain

However, being branched compounds, these early detergents were not rapidly biodegradable. Since the bacteria that operate in sewage treatment plants could not

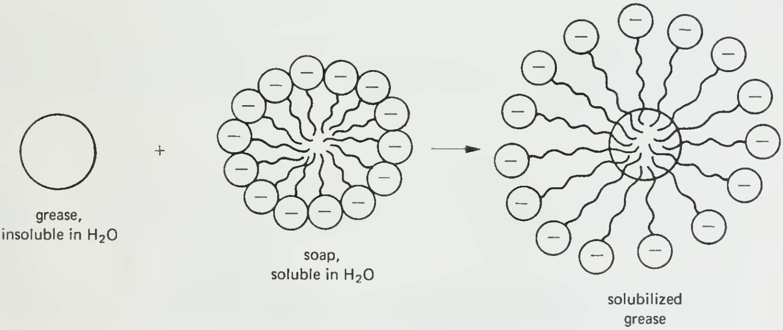


FIGURE 17.4 *Schematic diagram of soap solubilization.*

metabolize the materials completely, they were passed into natural waterways with the treated sewage. They often reappeared as foam or suds on the surface of lakes and rivers. After an intensive research project, the detergent industry in 1965 introduced **linear alkanesulfonate detergents.**

$$CH_3(CH_2)_nCH_2SO_3^- K^+$$

Since the new detergents are straight chain compounds, they can be metabolized rapidly by the natural bacteria.

17.5
Spectroscopy

A. *Nuclear Magnetic Resonance*

The resonance positions for various types of hydrogens in carboxylic acids are summarized in Table 17.5. Hydrogens attached to the number 2 carbon of a carboxylic acid resonate at roughly the same place as do the analogous hydrogens in aldehydes and ketones. The very low-field resonance of the carboxy proton is associated with the dimeric hydrogen-bonded structure discussed in Section 17.1.

TABLE 17.5
Chemical Shifts of Carboxylic Acid Hydrogens

Type of Hydrogen	Chemical Shift, δ, ppm
CH_3COOH	2.0
RCH_2COOH	2.36
$R_2CHCOOH$	2.52
RCOOH	about 10–13

The spectrum of isobutyric acid is shown in Figure 17.5.

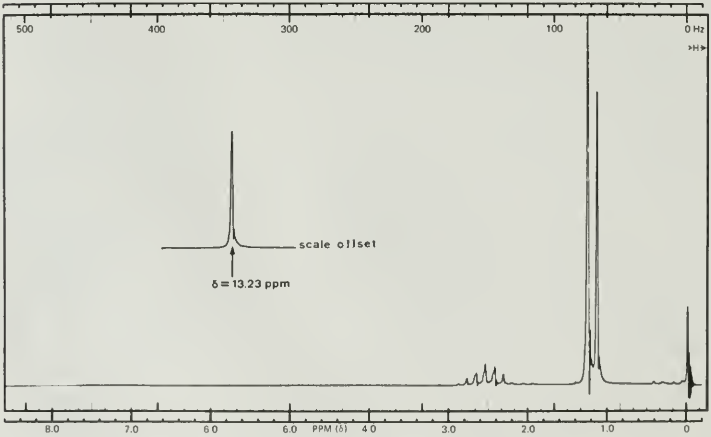


FIGURE 17.5 Nmr *spectrum of isobutyric acid,* $(CH_3)_2CHCOOH$.

B. *Infrared*

One of the characteristic absorptions of acids is the C=O stretch, which occurs in the region 1710–1760 cm^{-1}. The exact position and appearance of this absorption depends on the physical state in which the measurement is made. In pure liquids or in the solid state, the C=O stretch occurs as a broad band at about 1710 cm^{-1}. In dilute solution (CCl_4, $CHCl_3$), the absorption band is narrower and occurs at about 1760 cm^{-1}. The OH stretch occurs as a series of weak bands from 2500–3000 cm^{-1}. The spectrum of hexanoic acid in Figure 17.6 illustrates these bands.

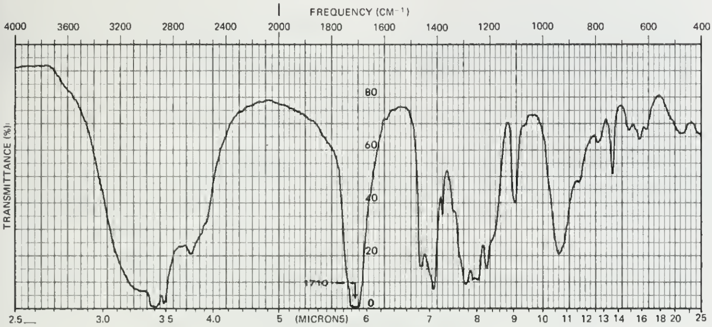


FIGURE 17.6 Ir *spectrum of hexanoic acid.*

17.6
Synthesis

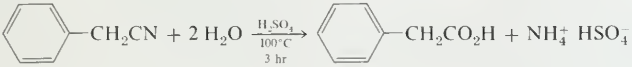
Carboxylic acids are most often prepared in the laboratory by: (a) hydrolysis of nitriles; (b) carbonation of organometallic compounds; (c) oxidation of primary alcohols or aldehydes; (d) decarboxylation of substituted malonic acids. In this section, we will discuss the first three of these methods: decarboxylation of malonic acids will be discussed in Chapter 26.

A. *Hydrolysis of Nitriles*

Nitriles are compounds containing the functional group —C≡N (Section 18.2.E). They undergo hydrolysis to give 1 mole of carboxylic acid and 1 mole of ammonia.

$$R{-}C{\equiv}N + 2\,H_2O \longrightarrow RCOOH + NH_3$$

In neutral solution, the reaction is immeasurably slow. However, the reaction is strongly catalyzed by either acid or base. Typical examples are the acidic hydrolysis of phenylacetonitrile and the basic hydrolysis of *n*-decyl cyanide.


$CH_2CN + 2\,H_2O \xrightarrow[100°C,\ 3\ hr]{H_2SO_4}$
$CH_2CO_2H + NH_4^+\ HSO_4^-$

phenylacetonitrile

phenylacetic acid

A mixture of 1150 ml water, 840 ml conc. H_2SO_4 and 700 g phenylacetonitrile is heated at reflux for 3 hr. Phenylacetic acid (630 g, 78% yield) is obtained when the reaction mixture is poured into cold water.

$$\underset{n\text{-decyl cyanide}}{CH_3(CH_2)_9CN} + 2\,H_2O \xrightarrow[\substack{C_2H_5OH\\ \text{reflux}\\ 77\text{ hr}}]{KOH} \xrightarrow{HCl} \underset{\text{undecanoic acid}}{CH_3(CH_2)_9CO_2H} + NH_3$$

A mixture of 27 g of *n*-decyl cyanide, 200 g of 20% ethanolic KOH, and 50 ml of water is refluxed for 77 hr, during which time ammonia is evolved. The solvent is evaporated and the residue is treated with conc. HCl. After washing with water, 24 g of undecanoic acid (80%), m.p. 29°, is obtained.

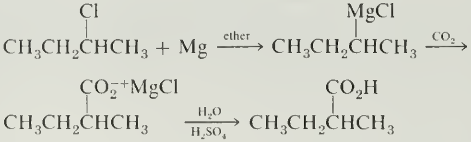
As we saw in Chapter 8, nitriles are conveniently prepared from primary alkyl halides by treatment with cyanide ion. Carboxylic acids may therefore be prepared from alkyl halides by conversion to the nitrile, which is then hydrolyzed.

$$\underset{n\text{-butyl bromide}}{CH_3CH_2CH_2CH_2Br} + NaCN \xrightarrow{CH_3SOCH_3} \underset{\substack{(92\%)\\ n\text{-butyl cyanide}}}{CH_3CH_2CH_2CH_2CN} \xrightarrow[\substack{H_2O\\ \text{ethylene}\\ \text{glycol}}]{KOH} \xrightarrow{H^+} \underset{\substack{(90\%)\\ \text{pentanoic acid}}}{CH_3CH_2CH_2CH_2COOH}$$

The mechanism of the hydrolysis reaction will be discussed in Section 18.9.A.

B. *Carbonation of Organometallic Reagents*

Carboxylic acids may also be prepared from alkyl halides by formation of an organometallic reagent, which is then allowed to react with carbon dioxide. The initial product, the salt of a carboxylic acid, is treated with dilute mineral acid to free the carboxylic acid.

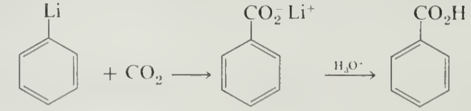


$$CH_3CH_2\overset{\overset{\large Cl}{|}}{C}HCH_3 + Mg \xrightarrow{\text{ether}} CH_3CH_2\overset{\overset{\large MgCl}{|}}{C}HCH_3 \xrightarrow{CO_2}$$

$$CH_3CH_2\overset{\overset{\large CO_2^-{}^+MgCl}{|}}{C}HCH_3 \xrightarrow[H_2SO_4]{H_2O} CH_3CH_2\overset{\overset{\large CO_2H}{|}}{C}HCH_3$$

Carbon dioxide gas is bubbled through a solution of *sec*-butylmagnesium chloride (prepared from 46 g of *sec*-butyl chloride and 13.4 g of magnesium in 400 ml of ether) at −10°. When CO_2 is no longer absorbed, the mixture is hydrolyzed with 25% aqueous H_2SO_4. Distillation of the crude product gives 40 g (80%) of 2-methylbutanoic acid.

A similar reaction occurs between carbon dioxide and an organolithium compound.

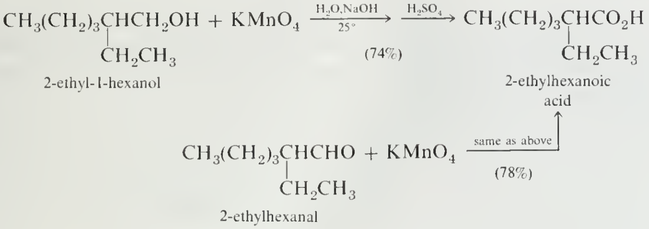


phenyllithium

benzoic acid

C. *Oxidation of Primary Alcohols or Aldehydes*

The third generally useful method for preparing carboxylic acids involves oxidation of aldehydes (obtained in the aldol condensation, Section 15.7.G) or primary alcohols (obtained, for example, by hydroboration of terminal alkenes, Section 12.6.D). A useful oxidizing agent for this purpose is potassium permanganate.



$$CH_3(CH_2)_3\underset{\displaystyle CH_2CH_3}{CH}CH_2OH + KMnO_4 \xrightarrow[25°]{H_2O, NaOH} \xrightarrow{H_2SO_4} CH_3(CH_2)_3\underset{\displaystyle CH_2CH_3}{CH}CO_2H \quad (74\%)$$

2-ethyl-1-hexanol

2-ethylhexanoic acid

$$CH_3(CH_2)_3\underset{\displaystyle CH_2CH_3}{CH}CHO + KMnO_4 \xrightarrow{\text{same as above}} \quad (78\%)$$

2-ethylhexanal

The initial product in oxidation of a primary alcohol is the corresponding aldehyde. However, with aqueous permanganate, the aldehyde undergoes subsequent oxidation *more rapidly* than the primary alcohol, so it is normally not observed in the reaction mixture.

Another reagent that may be used for the oxidation of either primary alcohols or aldehydes to carboxylic acids is nitric acid. Although this procedure works well on simple compounds, it is rather vigorous and cannot be used with compounds containing acid-sensitive functional groups elsewhere in the molecule.

$$HOCH_2CH_2CH_2CH_2CH_2CHO + HNO_3 \xrightarrow[0°C]{H_2O} HO_2CCH_2CH_2CH_2CH_2CO_2H \quad (75\%)$$

6-hydroxyhexanal

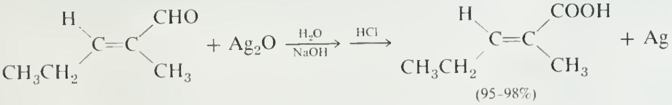
hexanedioic acid

$$ClCH_2CH_2CHO + \text{fuming } HNO_3 \xrightarrow{35°} ClCH_2CH_2CO_2H \quad (65\%)$$

3-chloropropanal

3-chloropropanoic acid

An extremely mild and selective reagent for the oxidation of aldehydes to carboxylic acids is silver oxide suspended in aqueous base. Although the method usually affords the desired acid in excellent yield, it is rather expensive to carry out on a large scale due to the cost of silver oxide unless one reclaims and recycles the silver metal.

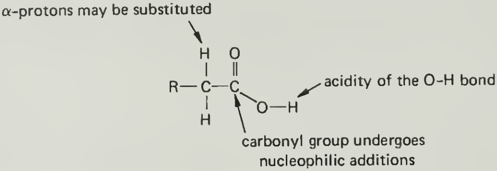


Note the advantageous use of Ag_2O in this case because the double bond is sensitive to stronger oxidizing agents.

Silver oxide is a brown solid that has only slight solubility in water. It is usually prepared as needed by mixing a solution of silver nitrate with sodium hydroxide. The precipitate may be filtered, washed with water, and used as an aqueous suspension. The use of silver oxide for such reactions as this diminished considerably in the Spring of 1974, when the price of silver nitrate rose sharply from $35 to $100 per lb.

17.7
Reactions

The chemistry of carboxylic acids may be divided mechanistically into four categories: (a) reactions involving the acidic O—H bond, (b) reactions occurring in the hydrocarbon side chain, (c) reactions occurring *at* the carboxy carbon atom, and (d) one-carbon degradations.


α-protons may be substituted
acidity of the O-H bond
carbonyl group undergoes nucleophilic additions

A. *Reactions Involving the OH Bond*

We have already seen one important reaction of carboxylic acids involving the OH bond—the reaction with bases to give salts.

$$CH_3CH_2CH_2CO_2H + Na^+OH^- \longrightarrow CH_3CH_2CH_2CO_2^- Na^+ + H_2O$$

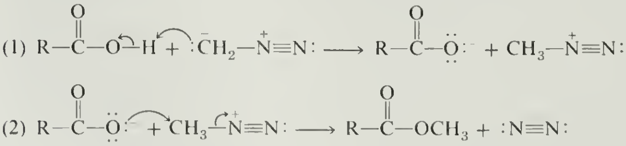
Another important reaction involving this bond is the reaction of carboxylic acids with diazomethane. The products of this reaction are the **methyl ester** and nitrogen.

$$RCOOH + CH_2N_2 \longrightarrow RCO_2CH_3 + N_2$$

Diazomethane is a yellow gas boiling at about 0°. It is highly toxic and, under certain conditions, explosive. Diazomethane is another example of a compound for which multiple Kekulé or Lewis structures can be written. The molecule is considered to be a resonance hybrid of the following forms:

$$:\overset{-}{C}H_2-\overset{+}{N}\equiv N: \longleftrightarrow CH_2=\overset{+}{N}=\overset{-}{\ddot{N}}:$$

The reaction of diazomethane with carboxylic acids probably involves the following steps:

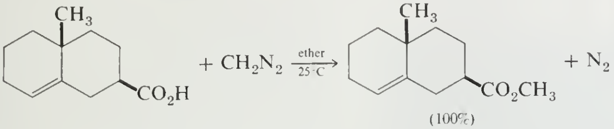


$$(1)\quad R-\overset{\overset{O}{\|}}{C}-O-H + :\overset{-}{C}H_2-\overset{+}{N}\equiv N: \longrightarrow R-\overset{\overset{O}{\|}}{C}-\underset{..}{\ddot{O}}:^- + CH_3-\overset{+}{N}\equiv N:$$

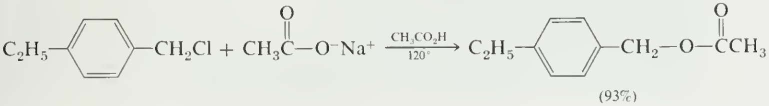
$$(2)\quad R-\overset{\overset{O}{\|}}{C}-\underset{..}{\ddot{O}}:^- + CH_3-\overset{+}{N}\equiv N: \longrightarrow R-\overset{\overset{O}{\|}}{C}-OCH_3 + :N\equiv N:$$

The first step is a simple acid-base reaction; the moderately acidic carboxylic acid transfers a proton to the basic carbon atom of diazomethane. The pair of ions thus formed immediately reacts, probably by the S_N2 mechanism; carboxylate ion is the entering nucleophile and nitrogen is the leaving group.

Because of the toxicity and danger of explosion, diazomethane reactions are almost never carried out on a large scale. However, because of the convenience of the procedure (yields are usually quantitative and the only by-product is a gas), it is frequently used for the small-scale conversion of an acid into its methyl ester, especially when the acid is a relatively precious one.



The sodium or silver salts of carboxylic acids also enter into the S_N2 reaction with alkyl halides, in a manner analogous to the second step of the preceding reaction with diazomethane. However, dehydrohalogenation is an important competing reaction, especially with secondary and tertiary halides (Chapters 8 and 12). In certain cases, where the side reaction is blocked, the reaction is sufficiently clean as to be of preparative value, as shown by the following example:



B. *Reactions Involving the Hydrocarbon Side Chain*

Carboxylic acids undergo the normal reactions of alkanes, as modified by the presence of the carboxy group, in the hydrocarbon chain of the molecule. For example, butyric acid undergoes combustion and free-radical chlorination.

$$CH_3CH_2CH_2CO_2H \xrightarrow{O_2} CO_2 + H_2O$$

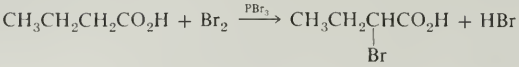
$$CH_3CH_2CH_2CO_2H \xrightarrow[\text{heat or light}]{Cl_2} \begin{array}{l}\text{mixture of mono- and}\\ \text{polychloro butyric}\\ \text{acids}\end{array}$$

Since these reactions are not selective for any particular position along the chain, they generally have no preparative utility.

The indiscriminate nature of such free-radical reactions is demonstrated by the light-initiated chlorination of butyric acid in CCl_4 at 25°.

$$CH_3CH_2CH_2CO_2H \xrightarrow[h\nu]{Cl_2} \left\{\begin{array}{ll} ClCH_2CH_2CH_2CO_2H & (31\%) \\ CH_3\overset{\overset{Cl}{|}}{C}HCH_2CO_2H & (64\%) \\ CH_3CH_2\overset{\overset{Cl}{|}}{C}HCO_2H & (5\%) \end{array}\right\}$$

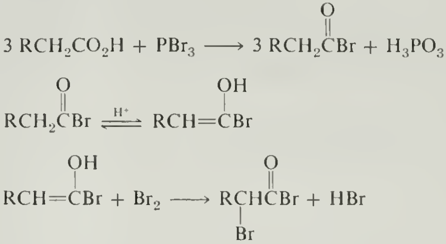
One reaction of the aliphatic chain that does have utility is the reaction of carboxylic acids with phosphorus tribromide and bromine. This reaction is sometimes known as the **Hell-Volhard-Zelinsky** reaction, after its discoverers.



$$CH_3CH_2CH_2CO_2H + Br_2 \xrightarrow{PBr_3} CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCO_2H + HBr$$

(82%)

Note that the reaction is *positionally selective*—only the hydrogen on C-2 is replaced. This is not a free-radical halogenation reaction. The overall result, α-bromination, is accomplished by a sequence of steps. The key step involves the reaction of bromine with the **enol form** of the corresponding **acyl bromide.** Phosphorus tribromide facilitates the reaction by reacting with the carboxylic acid to yield the acyl bromide (Section 17.7.C.2), which undergoes **enolization** much more readily than the acid itself.

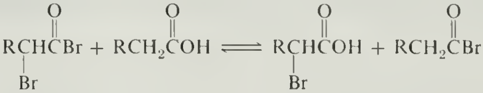


$$3\,RCH_2CO_2H + PBr_3 \longrightarrow 3\,RCH_2\overset{\displaystyle O}{\overset{\|}{C}}Br + H_3PO_3$$

$$RCH_2\overset{\displaystyle O}{\overset{\|}{C}}Br \overset{H^+}{\rightleftharpoons} RCH{=}\overset{\displaystyle OH}{\overset{|}{C}}Br$$

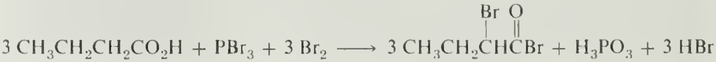
$$RCH{=}\overset{\displaystyle OH}{\overset{|}{C}}Br + Br_2 \longrightarrow R\underset{\displaystyle Br}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}Br + HBr$$

The reaction is completely analogous to the acid-catalyzed bromination of ketones (Section 15.6.D). It is only necessary to use a catalytic amount of PBr_3 because the product acyl bromide enters into the following equilibrium with the starting acid.



$$R\underset{\displaystyle Br}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}Br + RCH_2\overset{\displaystyle O}{\overset{\|}{C}}OH \rightleftharpoons R\underset{\displaystyle Br}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}OH + RCH_2\overset{\displaystyle O}{\overset{\|}{C}}Br$$

If a stoichiometric amount of PBr_3 is used, the product isolated is the α-bromoacyl bromide.

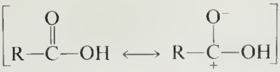


$$3\,CH_3CH_2CH_2CO_2H + PBr_3 + 3\,Br_2 \longrightarrow 3\,CH_3CH_2\overset{\displaystyle Br}{\overset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}Br + H_3PO_3 + 3\,HBr$$

Since phosphorus reacts rapidly with bromine to give PBr_3, the reaction is often carried out by simply heating the carboxylic acid with a mixture of phosphorus and bromine. In the Hell-Volhard-Zelinsky reaction, one normally begins with a carboxylic acid and ends up with the α-bromo carboxylic acid. However, note that the crucial reaction, introduction of the bromine, is actually a reaction of the acyl bromide.

C. *Reactions Occurring at the Carbonyl Carbon*

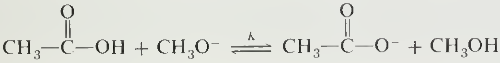
As in aldehydes and ketones, the carbonyl group in carboxylic acids is polarized. That is, the bonding electrons have higher density in the neighborhood of the oxygen than at the carbon.



$$\left[R-\overset{\overset{\displaystyle O}{\|}}{C}-OH \longleftrightarrow R-\overset{\overset{\displaystyle O^-}{|}}{\underset{+}{C}}-OH\right]$$

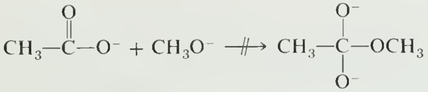
It is reasonable, then, to expect that *nucleophilic additions* to the carboxy group would occur. As with aldehydes and ketones, both *base-catalyzed* and *acid-catalyzed* nucleophilic additions are observed.

1. Base-catalyzed Nucleophilic Additions. With carboxylic acids, base-catalyzed nucleophilic additions are rare, and with good reason. Consider the reaction of acetic acid with sodium methoxide. Since methoxide ion is a strong base (the pK_a of methanol is about 16) and acetic acid is a moderately strong acid (pK_a about 5), the simple acid-base equilibrium below lies strongly to the right ($K \approx 10^{11}$) and is established very rapidly.



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-OH + CH_3O^- \overset{K}{\rightleftharpoons} CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O^- + CH_3OH$$

In other words, the acetic acid is converted immediately and quantitatively into acetate ion and the methoxide into methanol. Even in the presence of excess methoxide ion no further reaction occurs, since the acetate carbonyl is less electrophilic. That is, nucleophilic addition to the carbonyl would require that two anions combine to give a dianion. Since like charges repel one another, this reaction is unlikely.



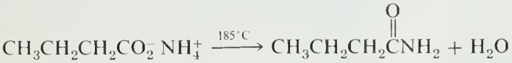
$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O^- + CH_3O^- \not\longrightarrow CH_3-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{C}}-OCH_3$$

Even so, several base-catalyzed nucleophilic additions of carboxylic acids are known. As we shall see, each involves rather special conditions.

The most common reaction of this type is the reaction of carboxylic acids with ammonia or amines to give **amides.** When ammonia is bubbled through butyric acid at 185°, butyramide is obtained in 85% yield. The reaction involves two stages. At room temperature, or even below, butyric acid reacts with the weak base ammonia to give the salt ammonium butyrate.

$$CH_3CH_2CH_2CO_2H + NH_3 \xrightarrow{25^\circ C} CH_3CH_2CH_2CO_2^-\ NH_4^+$$

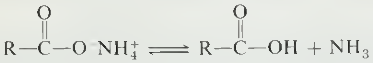
This salt is perfectly stable at normal temperatures. However, pyrolysis of the salt results in the elimination of water and formation of the amide.



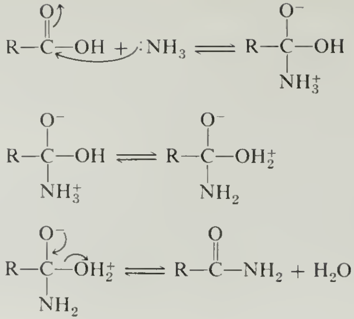
$$CH_3CH_2CH_2CO_2^-\ NH_4^+ \xrightarrow{185^\circ C} CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}NH_2 + H_2O$$

butyramide

The reaction occurs only because ammonium butyrate, being the salt of a weak acid and a weak base, is in equilibrium with a significant amount of ammonia and butyric acid. The actual dehydration step is probably the result of nucleophilic addition of ammonia to the carbonyl group of butyric acid itself.



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O\ NH_4^+ \rightleftharpoons R-\overset{\overset{\displaystyle O}{\|}}{C}-OH + NH_3$$

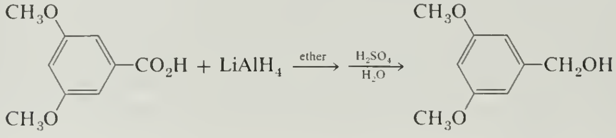


$$R-\overset{O}{\overset{\|}{C}}-OH + :NH_3 \rightleftharpoons R-\underset{NH_3^+}{\overset{O^-}{C}}-OH$$

$$R-\underset{NH_3^+}{\overset{O^-}{C}}-OH \rightleftharpoons R-\underset{NH_2}{\overset{O^-}{C}}-OH_2^+$$

$$R-\underset{NH_2}{\overset{O^-}{C}}-OH_2^+ \rightleftharpoons R-\overset{O}{\overset{\|}{C}}-NH_2 + H_2O$$

Another nucleophilic addition to the carboxylate group which is of some interest is in the reduction of carboxylic acids by lithium aluminum hydride.

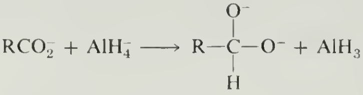


(93%)

The first step in this reaction is an acid-base reaction, giving the lithium salt of the acid, hydrogen gas, and aluminum hydride.

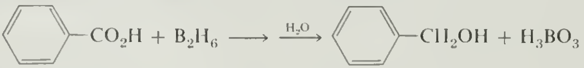
$$RCOOH + LiAlH_4 \longrightarrow RCOOLi + H_2 + AlH_3$$

The lithium carboxylate is then reduced further, eventually to the salt of the corresponding primary alcohol. Tetrahydroaluminate ion, AlH_4^-, is so reactive, it reduces even a carboxylate ion:



$$RCO_2^- + AlH_4^- \longrightarrow R-\underset{H}{\overset{O^-}{C}}-O^- + AlH_3$$

The reaction is undoubtedly assisted by the Lewis acid character of aluminum salts which reduce the effective negative charge on oxygen. The remaining steps in the reduction are still more complex but undoubtedly also involve lithium and aluminum salts. For example, further reaction of the bis-alkoxide dianion could involve expulsion of O^{2-} as an aluminum oxide with formation of an intermediate aldehyde. The aldehyde is then rapidly reduced to the alcohol with lithium aluminum hydride.

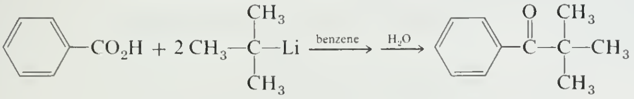


Diborane (Section 12.6.D) is a particularly useful reducing agent because of its unusual relative reactivity with various functional groups, as shown in Table 17.6.

TABLE 17.6
Relative Reactivity of Various Compounds with Diborane

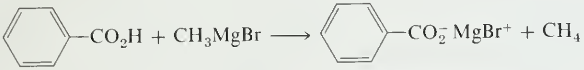
	Type of Compound	Product (after Hydrolysis)
↑ reactivity	$-COOH$	$R-CH_2OH$
	$-CH=CH-$	$-CH_2-\overset{\vert}{C}H-BH_2$ (before hydrolysis)
	$\rangle C=O$	$\rangle CHOH$
	$-C\equiv N$	$-CH_2-NH_2$
	$-CO_2R$	$-CH_2OH + ROH$
	$-COCl$	no reaction
	$-NO_2$	no reaction
	$-SO_2-$	no reaction

Carboxylic acids react with alkyllithium reagents to give ketones.



(70%)

The rationale for this reaction is similar to that given earlier for the reduction of acids by $LiAlH_4$. The first step is reaction with the proton of the carboxylic acid to produce 1 mole of alkane. Alkyllithiums have such high ionic character that they react even with carboxylate ions. In the case of Grignard reagents, the reaction does not occur, both because the initially formed magnesium salt is usually insoluble and because the C—Mg bond is not sufficiently ionic.



insoluble

2. ACID-CATALYZED NUCLEOPHILIC ADDITIONS. Although base-catalyzed nucleophilic additions to the carboxy group are relatively rare, acid-catalyzed additions are quite common. Carboxylic acids react readily with alcohols in the presence of catalytic amounts of mineral acids to yield compounds called **esters** (Chapter 18). The process is called **esterification.**

$$CH_3CO_2H + C_2H_5OH \xrightleftharpoons{H^+} CH_3CO_2C_2H_5 + H_2O \qquad (17\text{-}8)$$

Unlike most of the reactions we have encountered, this one has an equilibrium constant of relatively low magnitude. The experimental equilibrium constant for the reaction of acetic acid with ethanol is

$$K_{eq} = \frac{[CH_3CO_2C_2H_5][H_2O]}{[CH_3CO_2H][C_2H_5OH]} = 3.38$$

As in any equilibrium process, the reaction may be driven in one direction by controlling the concentration of either the reactants or products (LeChatelier's principle). For reaction (17-8), the equilibrium constant tells us that an equimolar

TABLE 17.7
Equilibrium Compositions for the Reaction
$CH_3CO_2H + C_2H_5OH \rightleftharpoons CH_3CO_2C_2H_5 + H_2O$

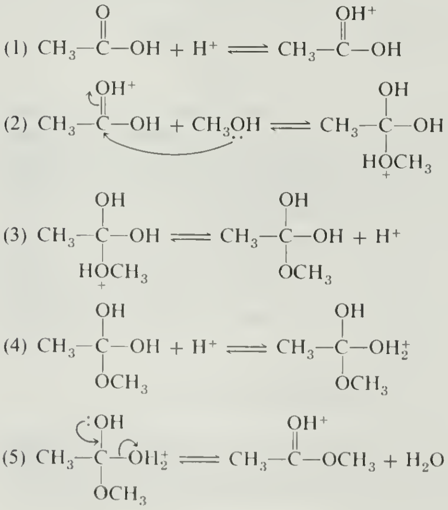
at start	1	1	0	0
at equilibrium	0.35	0.35	0.65	0.65
at start	1	10	0	0
at equilibrium	0.03	9.03	0.97	0.97
at start	1	100	0	0
at equilibrium	0.007	99.007	0.993	0.993

mixture of acetic acid and ethanol will eventually reach equilibrium to give a mixture containing 0.35 mole each of acetic acid and ethanol and 0.65 mole each of ethyl acetate and water. Of course, the same equilibrium mixture will be obtained if one starts with equimolar quantities of ethyl acetate and water.

If we increase the concentration of either reactant relative to the other, the reaction will be driven to the right and the equilibrium mixture will contain proportionately more ethyl acetate and water. Table 17.7 shows the equilibrium composition that will be achieved starting with various mixtures of acetic acid and ethanol.

Similar results will obviously be obtained by increasing the acetic acid concentration rather than the ethanol concentration. In a practical situation, when one wants to prepare an ester, it is desirable to obtain the maximum yield of pure product. It is often done as suggested in the preceding paragraph—by using a large excess of one of the reactants. For economic reasons, the reactant chosen is usually the less expensive of the two.

The mechanism of the acid-catalyzed esterification reaction has been studied thoroughly. All of the experimental facts are consistent with a mechanism involving the following steps (illustrated for acetic acid and methanol).



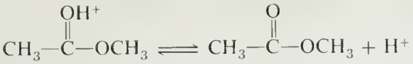
$$(1)\ CH_3-\overset{\overset{O}{\|}}{C}-OH + H^+ \rightleftharpoons CH_3-\overset{\overset{OH^+}{\|}}{C}-OH$$

$$(2)\ CH_3-\overset{\overset{OH^+}{\|}}{C}-OH + CH_3\ddot{O}H \rightleftharpoons CH_3-\underset{\underset{\overset{+}{H}OCH_3}{|}}{\overset{\overset{OH}{|}}{C}}-OH$$

$$(3)\ CH_3-\underset{\underset{\overset{+}{H}OCH_3}{|}}{\overset{\overset{OH}{|}}{C}}-OH \rightleftharpoons CH_3-\underset{\underset{OCH_3}{|}}{\overset{\overset{OH}{|}}{C}}-OH + H^+$$

$$(4)\ CH_3-\underset{\underset{OCH_3}{|}}{\overset{\overset{OH}{|}}{C}}-OH + H^+ \rightleftharpoons CH_3-\underset{\underset{OCH_3}{|}}{\overset{\overset{OH}{|}}{C}}-OH_2^+$$

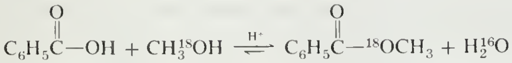
$$(5)\ CH_3-\underset{\underset{OCH_3}{|}}{\overset{\overset{:OH}{|}}{C}}-OH_2^+ \rightleftharpoons CH_3-\overset{\overset{OH^+}{\|}}{C}-OCH_3 + H_2O$$

(6) 

$$CH_3-\overset{\overset{OH^+}{\|}}{C}-OCH_3 \rightleftharpoons CH_3-\overset{\overset{O}{\|}}{C}-OCH_3 + H^+$$

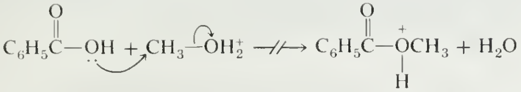
Steps (1), (3), (4), and (6) are rapid proton-transfer steps—simple acid-base reactions. Although we show "bare" protons in each case, they are actually solvated by some Lewis base, which may be methanol, water, or any of the other oxygenated species present. In steps (2) and (5), C—O bonds are formed or broken. These steps have higher activation energies than the proton-transfer steps.

The foregoing mechanism is an extremely important one in organic chemistry. As mentioned previously, it is based on a large amount of experimental data. Two of the more important experiments involved the use of ^{18}O labeled materials. The first of these interesting experiments demonstrated that the oxygen-carbonyl bond is broken during the esterification process. Benzoic acid was treated in the presence of HCl with methanol enriched in ^{18}O. The water produced in the reaction was isolated and shown to be normal $H_2{}^{16}O$.



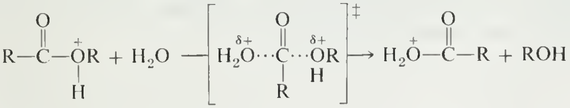
$$C_6H_5\overset{\overset{O}{\|}}{C}-OH + CH_3^{18}OH \xrightleftharpoons{H^+} C_6H_5\overset{\overset{O}{\|}}{C}-{}^{18}OCH_3 + H_2^{16}O$$

This experiment rules out mechanisms such as the following, in which the oxygen in the water produced comes from the alcohol.



$$C_6H_5\overset{\overset{O}{\|}}{C}-\ddot{O}H + CH_3-\overset{+}{O}H_2 \not\longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{\overset{+}{O}}CH_3 + H_2O$$

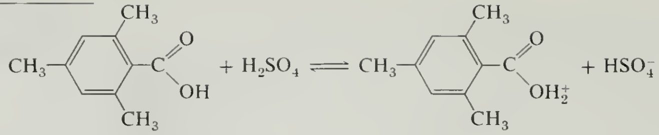
The second important labeling experiment showed that a symmetrical **intermediate** intervenes in the process. Ethyl benzoate enriched in ^{18}O in the carbonyl oxygen was hydrolyzed with HCl and normal water. The reaction was stopped short of completion and the recovered ethyl benzoate was analyzed. It was found that exchange of ^{18}O in the ester by ^{16}O had occurred. Although hydrolysis occurs approximately 5 times faster than exchange, this experiment demonstrates that an intermediate is formed that can go on to give acid or reverse to give exchanged ester. Mechanisms such as the following, which is analogous to the S_N2 displacement in saturated systems, are definitely ruled out.

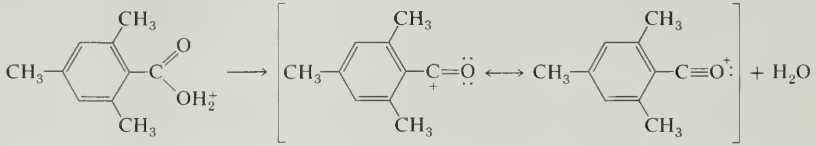


$$R-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{\overset{+}{O}}R + H_2O \longrightarrow \left[\overset{\delta+}{H_2O}\cdots\underset{\underset{R}{|}}{\overset{\overset{O}{\|}}{C}}\cdots\underset{H}{\overset{\delta+}{OR}}\right]^{\ddagger} \longrightarrow H_2\overset{+}{O}-\overset{\overset{O}{\|}}{C}-R + ROH$$

Note that the accepted mechanism involves simply an acid-catalyzed addition of an alcohol to the carbonyl group and is completely analogous to the similar reactions with aldehydes and ketones to form intermediate hemiacetals (Section 15.7.A and B).

Acid-catalyzed esterification is an important method for the preparation of carboxylic acid esters (Section 18.9). It is a general reaction for acids. Occasionally, however, the reaction is very slow or the equilibrium constant is very unfavorable. This situation often occurs when the acid is extensively branched near the carboxy group. In such cases, esters may be prepared in another way. When an acid is dissolved in concentrated sulfuric acid, the initially formed oxonium ion dissociates to form an **acylium ion.**



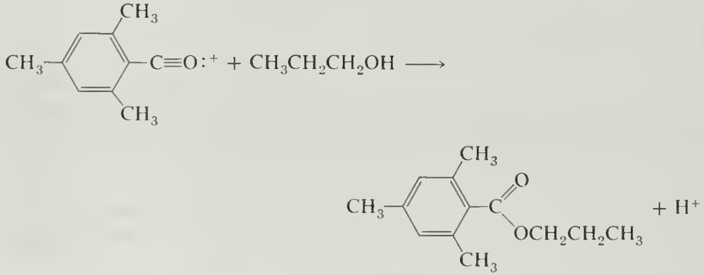


an acylium ion

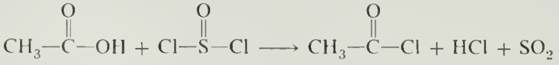
The water produced reacts with more sulfuric acid to give hydronium ion and bisulfate ion.

$$H_2O + H_2SO_4 \longrightarrow H_3O^+ + HSO_4^-$$

Since the solution contains only weakly nucleophilic species (H_2SO_4 and HSO_4^-), the acylium ion remains in solution. If this solution is rapidly diluted with an alcohol, immediate reaction occurs to give an ester.

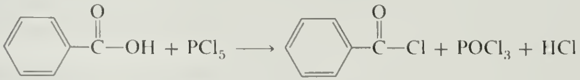


Carboxylic acids react with thionyl chloride, phosphorus pentachloride, and phosphorus tribromide in the same way that alcohols do (Section 11.7.D). The products are **acyl halides** (Chapter 18).

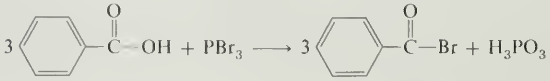


$$CH_3-\overset{O}{\overset{\|}{C}}-OH + Cl-\overset{O}{\overset{\|}{S}}-Cl \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-Cl + HCl + SO_2$$

acetyl chloride

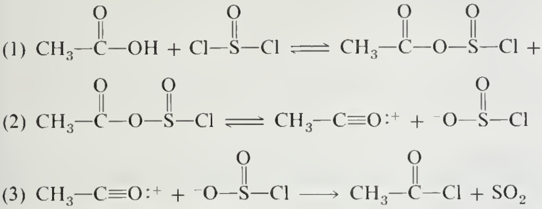


benzoyl chloride



benzoyl bromide

One reasonable mechanism for the reaction with thionyl chloride is



$$(1)\ CH_3{-}\overset{O}{\overset{\|}{C}}{-}OH + Cl{-}\overset{O}{\overset{\|}{S}}{-}Cl \rightleftharpoons CH_3{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{S}}{-}Cl + HCl$$

$$(2)\ CH_3{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{S}}{-}Cl \rightleftharpoons CH_3{-}C{\equiv}O{:}^+ + {}^-O{-}\overset{O}{\overset{\|}{S}}{-}Cl$$

$$(3)\ CH_3{-}C{\equiv}O{:}^+ + {}^-O{-}\overset{O}{\overset{\|}{S}}{-}Cl \longrightarrow CH_3{-}\overset{O}{\overset{\|}{C}}{-}Cl + SO_2$$

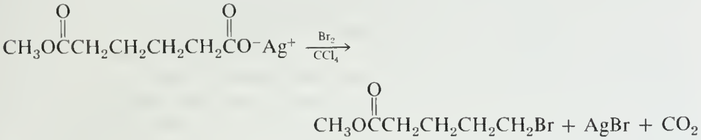
D. *One-carbon Degradation of Carboxylic Acids*

Carboxylic acids undergo several reactions in which the carboxy group is replaced by halogen.

$$RCO_2H \longrightarrow RX$$

Such reactions, in which carbons are lost from a molecule, are called "degradations".

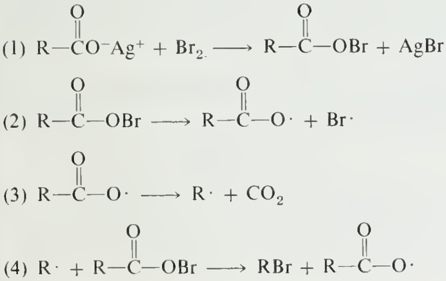
In the **Hunsdiecker reaction,** the silver salt of a carboxylic acid, prepared by treating the acid with silver oxide, is treated with a halogen. Bromine is the usual reagent, but iodine may also be used. Carbon dioxide is evolved and the corresponding alkyl halide is obtained, usually in fair to good yield.



$$CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}O^-Ag^+ \xrightarrow[CCl_4]{Br_2} CH_3O\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2Br + AgBr + CO_2$$

(65–68%)

The reaction appears to proceed by a free-radical path, and may be formulated as follows.



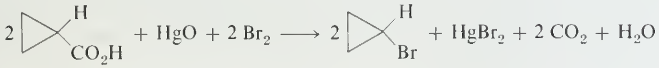
$$(1)\ R{-}\overset{O}{\overset{\|}{C}}O^-Ag^+ + Br_2 \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}OBr + AgBr$$

$$(2)\ R{-}\overset{O}{\overset{\|}{C}}{-}OBr \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot + Br\cdot$$

$$(3)\ R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot \longrightarrow R\cdot + CO_2$$

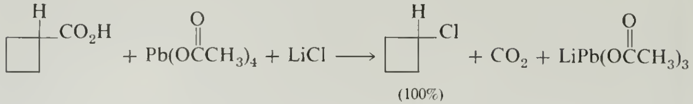
$$(4)\ R\cdot + R{-}\overset{O}{\overset{\|}{C}}{-}OBr \longrightarrow RBr + R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot$$

In a useful modification of the Hunsdiecker reaction, the carboxylic acid is treated with mercuric oxide and bromine.



(41–46%)

In the **Kochi reaction**, the carboxylic acid is treated with lead tetraacetate and lithium chloride; the product is an alkyl chloride.



The Hundsdiecker and Kochi reactions complement each other, the former giving best results with primary alkyl carboxylic acids, and the latter being preferred for secondary and tertiary alkyl carboxylic acids.

17.8
Occurrence of Carboxylic Acids

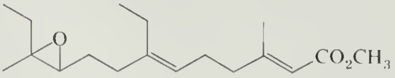
Carboxylic acids are widespread in nature, both as such and in the form of esters. Partly because they are easily isolated as salts, they were among the earliest known organic compounds.

Formic acid was first discovered in 1670 by the distillation of ants. Its name comes from the Latin word for ant, *formica*. Formic acid is partially responsible for the irritation resulting from the sting of the red ant and the stinging nettle.

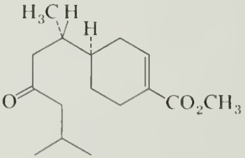
Acetic acid is a product of fermentation. The characteristic taste of sour wine is due to the oxidation of ethanol to acetic acid. Vinegar is a dilute solution of acetic acid. Although the acid has been known in the form of vinegar since antiquity, it was first isolated in pure form by Stahl in 1700. Pure acetic acid is known as **glacial** acetic acid. This term arises from the relatively high melting point of the compound (17°C, 63°F). In earlier times, when buildings were not heated as they are now, pure acetic acid was commonly observed to be a solid at “room temperature.” Acetic acid is also one of the products of pyrolysis of wood (destructive distillation).

Butyric acid is responsible for the sharp odor of rancid butter. It was first isolated from this source. Caproic acid also has a penetrating unpleasant odor described as “goat-like.” Indeed, its name as well as those of caprylic acid and capric acid are derived from the Latin word for goat, *caper*. These acids and their esters are widespread in nature.

Juvenile hormone and juvabione are examples of carboxylic acids that occur in nature in the form of their methyl esters.



juvenile hormone

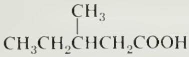


juvabione

These compounds are associated with the pupal development of various insects. Such compounds offer some promise as insect-control agents. Since they are highly species-specific and leave no residues, they have obvious advantages over other commonly used pesticides.

PROBLEMS

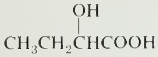
1. Give the IUPAC and common names for each of the following compounds:

(a)

$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2COOH$

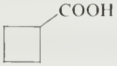
(b) $(CH_3)_3CCOOH$

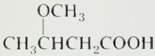
(c) $BrCH_2CH_2CH_2COOH$

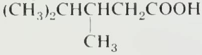
(d) ICH_2COOH

(e)

$CH_3CH_2\overset{\overset{OH}{|}}{C}HCOOH$

(f) $CH_3(CH_2)_8COOH$

(g)


(h)

$CH_3\overset{\overset{OCH_3}{|}}{C}HCH_2COOH$

(i)

$(CH_3)_2CH\underset{\underset{CH_3}{|}}{C}HCH_2COOH$

2. Write out the correct structure for each of the following names.

(a) β-chlorobutyric acid

(b) hexanoic acid

(c) γ-methoxyvaleric acid

(d) cyclopentanecarboxylic acid

(e) 3-phenylpropanoic acid

(f) *cis*-2-pentenoic acid

(g) 4-cyclohexanonecarboxylic acid

(h) α-chloro-β-bromopropionic acid

3. Give the products in each of the following reactions of cyclohexanecarboxylic acid.

(a) $LiAlH_4$ in ether, then dilute hydrochloric acid.

(b) B_2H_6 in ether, then dilute hydrochloric acid.

(c) $P + Br_2$, heat, then water.

(d) diazomethane in ether.

(e) isopropyl alcohol (excess), trace of H_2SO_4.

(f) isopropyllithium in benzene, then water.

(g) ammonia, 200°.

(h) $SOCl_2$, heat.

(i) PBr_3, heat.

(j) Pt/H_2, room temperature.

(k) dilute aqueous sodium hydroxide at room temperature.

(l) CH_3MgBr in ether, then dilute hydrochloric acid.

(m) $Pb(OAc)_4 + LiCl$.

4. Two general methods for converting alkyl halides to carboxylic acids are displacement by cyanide ion followed by hydrolysis and conversion to the Grignard reagent followed by carbonation with carbon dioxide. Which method is superior for each of the following transformations?

(a) $(CH_3)_3CCl \longrightarrow (CH_3)_3CCOOH$

(b) $BrCH_2CH_2Br \longrightarrow HOOCCH_2CH_2COOH$

(c) $CH_3COCH_2CH_2CH_2Br \longrightarrow CH_3COCH_2CH_2CH_2COOH$

(d) $(CH_3)_3CCH_2Br \longrightarrow (CH_3)_3CCH_2COOH$

(e) $CH_3CH_2CH_2CH_2Br \longrightarrow CH_3CH_2CH_2CH_2COOH$

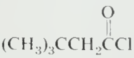
(f) $HOCH_2CH_2CH_2CH_2Br \longrightarrow HOCH_2CH_2CH_2CH_2COOH$

5. Show how neopentane may be converted into each of the following compounds.

(a) $(CH_3)_3CCH_2COOH$

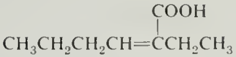
(b) $(CH_3)_3CCHBrCOOH$

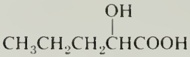
(c) $(CH_3)_3CCH_2CH_2OH$

(d)

$(CH_3)_3CCH_2\overset{\overset{O}{\|}}{C}Cl$

6. Show how butyraldehyde may be converted into each of the following compounds.

(a) $CH_3CH_2CH_2COOH$

(b) 
$CH_3CH_2CH_2CH{=}C(COOH)CH_2CH_3$

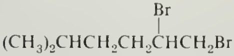
(c) 
$CH_3CH_2CH_2CH(OH)COOH$

(d) $CH_3CH_2CH_2CH_2COOH$

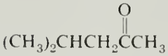
7. Show how 3-methylbutanoic acid may be converted into each of the following compounds.

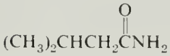
(a) $(CH_3)_2CHCH_2CH_2OH$

(b) $(CH_3)_2CHCH_2CH_2COOH$

(c) 
$(CH_3)_2CHCH_2CH_2CH(Br)CH_2Br$

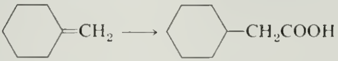
(d) $(CH_3)_2C{=}CHCO_2CH_3$

(e) 
$(CH_3)_2CHCH_2C(=O)CH_3$

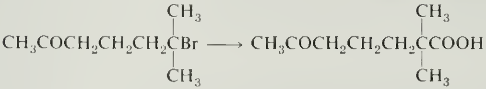
(f) 
$(CH_3)_2CHCH_2C(=O)NH_2$

(g) $(CH_3)_2CHCH_2Br$

8. Show how each of the following transformations may be accomplished in a practical manner.

(a) 

(b) $(CH_3)_3CCH{=}CH_2 \longrightarrow (CH_3)_3CCOOH$

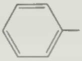
(c) 
$CH_3COCH_2CH_2CH_2C(CH_3)_2Br \longrightarrow CH_3COCH_2CH_2CH_2C(CH_3)_2COOH$

(d) $CH_3CH_2COOH \longrightarrow CH_3CH_2CH_2COOH$
(e) $CH_3CH_2CH_2COOH \longrightarrow CH_3CH_2COOH$
(f) $CH_3CH_2CH_2COOH \longrightarrow CH_3CH_2CH_2N_3$

9. The dissociation constant of acetic acid is $1.8 \times 10^{-5}\,M$. Calculate the percent dissociation when the following amounts of acetic acid are made up to 1 liter with water at 25°: (a) 0.1 moles; (b) 0.01 moles; (c) 0.001 moles.

10. The following dissociation constants are given. Calculate the corresponding pK_a values.

(a) $(CH_3)_2CHCH_2CH_2COOH$; $K_a = 1.4 \times 10^{-5}\,M$

(b) 
$-COOH$; $K_a = 6.3 \times 10^{-5}\,M$

(c) $Cl_2CHCOOH$; $K_a = 5.5 \times 10^{-2}\,M$

(d) Cl_3CCOOH; $K_a = 0.23\,M$

(e) $CH_3CONHCH_2COOH$; $K_a = 2.1 \times 10^{-4}\,M$

11. In each of the following pairs, which is the stronger *base?* Explain briefly.

(a) $CH_3CH_2O^-$; $CH_3CO_2^-$

(b) $ClCH_2CH_2CO_2^-$; $CH_3CH_2CH_2CO_2^-$

(c) $ClCH_2CH_2CO_2^-$; $CH_3CHClCO_2^-$

(d) $FCH_2CO_2^-$; $F_2CHCO_2^-$

(e) $HC{\equiv}CCH_2CO_2^-$; $CH_3CH_2CH_2CO_2^-$

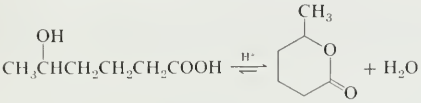
(f) Cl^-; $CH_3CO_2^-$

12. The two carboxy groups in 3-chlorohexanedioic acid are not equivalent and have different dissociation constants. Which carboxy group is the more acidic?

13. From the progression of acidity constants for chlorobutyric acids in Table 17.4 and the pK_a of γ-cyanobutyric acid, 4.44, estimate the pK_a of β-cyanobutyric acid.

14. When propionic acid is refluxed with some sulfuric acid in water enriched with $H_2{}^{18}O$, ^{18}O gradually appears in the carboxylic acid group. Write the mechanism for this reaction, showing each intermediate in the reaction pathway.

15. When 5-hydroxyhexanoic acid is treated with a trace of sulfuric acid in benzene solution, the following reaction occurs:



(a) Propose a mechanism for the reaction.

(b) The equilibrium constant for this process is much larger than that normally observed for an esterification reaction. Explain.

16. Propionic acid on refluxing with D_2O containing a strong acid is slowly converted to CH_3CD_2COOD. Write a plausible mechanism for this reaction.

17. Values of heats of formation, ΔH_f°, for the ideal gas state at 25° are given in the table that follows for several compounds. Calculate ΔH° for the following equilibrium in the gas phase:

$$CH_3COOH + C_2H_5OH \rightleftharpoons CH_3COOC_2H_5 + H_2O$$

In the liquid phase, ΔH° for this equilibrium is -0.9 kcal mole^{-1}. Why is there such a difference between the two values?

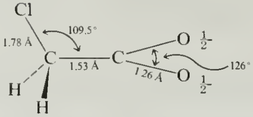
Compound	ΔH_f° at 25°, kcal mole ^{1}
CH_3COOH	-103.9
C_2H_5OH	-56.1
$CH_3COOC_2H_5$	-105.9
H_2O	-57.8

★**18.** The following reaction is exothermic in the gas phase:

$$CH_3CO_2^- + ClCH_2COOH \rightleftharpoons CH_3COOH + ClCH_2CO_2^- \qquad \Delta H^\circ = -13 \text{ kcal mole}^{-1}$$

(a) Explain briefly why this reaction is exothermic.

(b) Perform a simple calculation to determine whether the electrostatic interaction of a C—Cl dipole with a carboxylate anion has the proper magnitude to account for this energy difference. For this purpose treat $ClCH_2CO_2^-$ as having the following structure in which the CCCl plane is perpendicular to the OCO plane.



Consider the effect of the chlorine to be that of a point dipole of 1.9 D. The electrostatic energy for a point dipole and a charge is given by

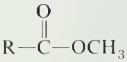
$$E = \frac{q\mu \cos\theta}{r^2}$$

in which θ is the angle between the dipole and the charge. For a charge, q, of one electron, $\mu = 1$ D and $r = 1$ Å, $\theta = 0°$, the energy, E, is 69 kcal $mole^{-1}$.

CHAPTER 18
Derivatives of Carboxylic Acids

18.1
Structure

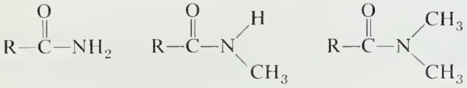
Functional group derivatives of carboxylic acids are those compounds that are transformed into carboxylic acids by simple hydrolysis. The most common such derivatives are **esters**, in which the hydroxy group is replaced by an alkoxy group.



$$R-\overset{\displaystyle O}{\overset{\|}{C}}-OCH_3$$

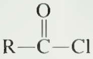
an ester

Amides are compounds in which the hydroxy group is replaced by an amino group. The nitrogen of the amino group may bear zero, one, or two alkyl groups.



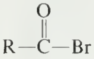
amides

Acyl halides are derivatives in which the carboxy OH is replaced by a halogen atom; **acyl chlorides** and **acyl bromides** are the most commonly encountered acyl halides.



$$R-\overset{\displaystyle O}{\overset{\|}{C}}-Cl$$

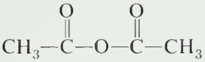
an acyl chloride



$$R-\overset{\displaystyle O}{\overset{\|}{C}}-Br$$

an acyl bromide

Acid anhydrides are molecules in which one molecule of water has been removed from two molecules of a carboxylic acid. The only acyclic anhydride of general importance is acetic anhydride.



$$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-O-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3$$

acetic anhydride

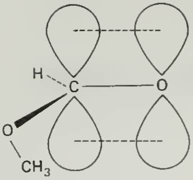
In a strict sense, **nitriles** are functional derivatives of carboxylic acids because they may be hydrolyzed to carboxylic acids (Section 17.6.A).

R—CN

a nitrile

The simplest ester, methyl formate, may be considered a simple derivative of formic acid in which the OH group is replaced by an OCH_3 group. Correspondingly, the molecular geometry of methyl formate is very similar to that of formic acid. Experimental bond lengths and bond angles, determined by microwave spectroscopy, are given in Figure 18.1.

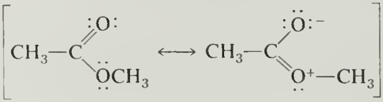
Note that the C_{sp^2}-O σ bond is considerably shorter than the C_{sp^3}-O σ bond.



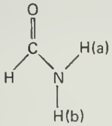
Bond Lengths, Å		Bond Angles, deg	
C=O	1.200	H—C=O	124.95
C(=O)—O	1.334	O—C=O	125.87
$C(H_3)$—O	1.437	H—C—O	109.18
C(=O)—H	1.101	CH_3—O—C	114.78

FIGURE 18.1 *Structure of methyl formate.*

Two factors are apparently important in accounting for this bond shortening. In Section 12.1 we saw that, because of the difference in "length" of various hybrid orbitals, C_{sp^3}-C_{sp^3} σ bonds are longer than C_{sp^2}-C_{sp^2} σ bonds. This factor is probably also important in methyl formate. Another factor involves the dipolar resonance form (18-1) as a contributor to the structure of methyl formate.


(18-1)

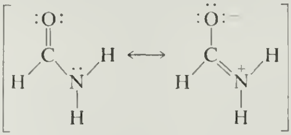
To the extent that this form contributes to the actual structure of the molecule, the C_{sp^2}-O σ bond will be shorter, because it has some **double bond character.** This latter factor is especially important in amides.



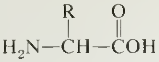
Bond Lengths, Å		Bond Angles, deg	
C=O	1.193	H—C=O	122.97
C—N	1.376	H—C—N	113.23
C—H	1.102	N—C=O	123.80
N—H(a)	1.014	C—N—H(a)	117.15
N—H(b)	1.002	C—N—H(b)	120.62
		H—N—H	118.88

FIGURE 18.2 *Structure of formamide.*

Microwave measurements on formamide indicate the structure shown in Figure 18.2. The entire molecule is planar. Note that the two hydrogens attached to nitrogen are distinguishable. The barrier to rotation about the C—N bond has been measured experimentally and is found to be 18 kcal mole^{-1}. A high degree of double bond character in this bond, as indicated in the dipolar resonance form (18-2) has been invoked to explain this relatively high rotational barrier.

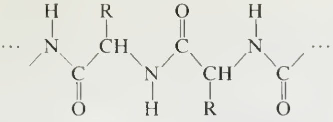

(18-2)

Because of the high barrier to rotation about the C—N bond amides have a relatively rigid structure. This rigidity has important consequences in nature. As we shall see in Chapter 28, proteins are high polymers of amino acids.



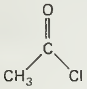
$H_2N-\overset{R}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}OH$

an amino acid



a protein

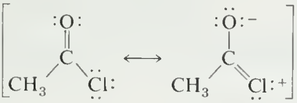
The rigidity of the succession of amide bonds in the protein chain confers special properties on these important biomolecules.



Bond Lengths, Å		Bond Angles, deg	
C=O	1.192	C—C=O	127.08
C—C	1.499	C—C—Cl	112.66
C—Cl	1.789	O=C—Cl	120.26
C—H	1.083		

Figure 18.3 *Structure of acetyl chloride.*

Since the simplest acyl chloride, formyl chloride, is not stable at temperatures above −60°, its structural parameters have not been measured. However, the bond lengths and bond angles have been determined for acetyl chloride (Figure 18.3). The C—Cl bond is not appreciably shorter than the analogous bond in methyl chloride (1.784 Å), suggesting that dipolar resonance structures are not particularly important in the case of acyl halides.



As judged by the $-\overset{O}{\overset{\|}{C}}-Y$ bond distances, the importance of such dipolar resonance structures decreases in the order NR_2, OR, Cl.

Acetonitrile (methyl cyanide) has a structure analogous to that of propyne. The nitrile carbon is *sp* hybridized. It forms a C_{sp^3}-C_{sp} σ bond to the methyl group and a C_{sp}-N_{sp} σ bond to nitrogen. The two remaining *p* orbitals on carbon overlap with two *p* orbitals on nitrogen, giving rise to a typical axially symmetric triple bond. The lone pair is in an *sp* orbital on nitrogen (Figure 18.4).

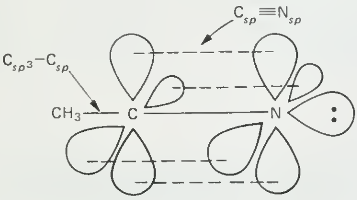
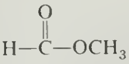


Figure 18.4 *Orbital structure of acetonitrile.*

18.2
Nomenclature

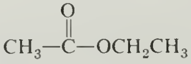
A. *Esters*

Esters are named in the following way. The first word of the name is the stem name of the alkyl group attached to oxygen. The second word of the name is the name of the parent acid with the suffix **-ic** replaced by **-ate.** This nomenclature applies for both common and IUPAC names of acids.



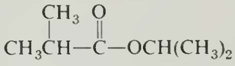
$H-\overset{\overset{O}{\|}}{C}-OCH_3$

methyl formate



$CH_3-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$

ethyl acetate



$CH_3\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-OCH(CH_3)_2$

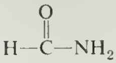
isopropyl isobutyrate

$(CH_3)_2CHCH_2CH_2CH_2CO_2CH_2CH_2CH(CH_3)_2$

3-methylbutyl 5-methylhexanoate

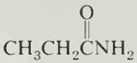
B. *Amides*

Amides are named in the common system by dropping the suffix **-ic** from the name of the parent acid and adding the suffix **-amide.**



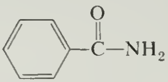
$H-\overset{\overset{O}{\|}}{C}-NH_2$

formamide



$CH_3CH_2\overset{\overset{O}{\|}}{C}NH_2$

propionamide

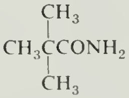


benzamide

In the IUPAC system, amides are named as alkanamides; for example

$CH_3CH_2CH_2CONH_2$

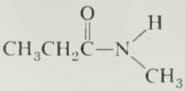
butanamide



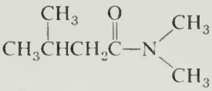
$CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}CONH_2$

2,2-dimethylpropanamide

When the nitrogen is substituted, this is indicated by prefixing the name of the simple amide by N-, followed by the name of the substituent group. This method is used for both systems of nomenclature.



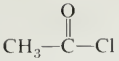
N-methylpropionamide
N-methylpropanamide



N,N,β-trimethylbutyramide
N,N,3-trimethylbutanamide

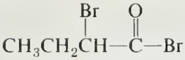
C. *Acyl halides*

Acyl halides are named in both the common and IUPAC systems by dropping the suffix **-ic** from the name of the parent acid and adding the suffix **-yl.** The halide name is then added as a second word.



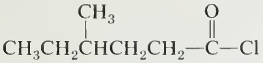
$$CH_3-\overset{O}{\overset{\|}{C}}-Cl$$

acetyl chloride
ethanoyl chloride



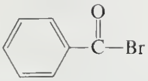
$$CH_3CH_2\overset{Br}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}-Br$$

α-bromobutyryl bromide
2-bromobutanoyl bromide



$$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_2-\overset{O}{\overset{\|}{C}}-Cl$$

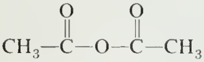
γ-methylcaproyl chloride
4-methylhexanoyl chloride



benzoyl bromide

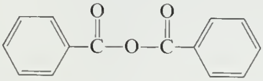
D. *Anhydrides*

Anhydrides are named by adding **anhydride** to the name of the corresponding carboxylic acid.

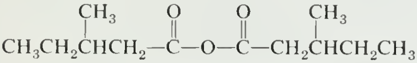


$$CH_3-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$$

acetic anhydride



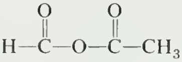
benzoic anhydride



$$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$$

β-methylvaleric anhydride
3-methylpentanoic anhydride

For mixed anhydrides, the parent name of each acid is given, followed by the word **anhydride.**



$$H-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-CH_3$$

acetic formic anhydride

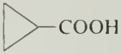
E. *Nitriles*

Nitriles are named in the common system according to the carboxylic acid to which they are hydrolyzable. The suffix **-ic** or **-oic** is replaced by **-onitrile.** In the IUPAC, these compounds are named as alkanenitriles.

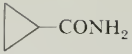
CH_3CN	$CH_3CH_2CH_2CN$	$BrCH_2CH_2CH_2CH_2CN$
acetonitrile	butyronitrile	δ-bromovaleronitrile
ethanenitrile	butanenitrile	5-bromopentanenitrile

F. *Group names*

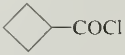
When the IUPAC name of a carboxylic acid ends in **-carboxylic acid,** the corresponding amide is named with the suffix **-carboxamide,** whereas the acyl halide and nitrile incorporate a **-carbon-** stem as in the following examples:



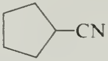
cyclopropanecarboxylic acid



cyclopropanecarboxamide



cyclobutanecarbonyl chloride



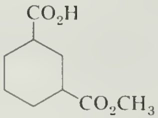
cyclopentanecarbonitrile

Occasionally, it is necessary to name an acid derivative function as a derivative of some other functional stem. The group names for the various radicals as prefixes are given in Table 18.1.

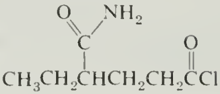
TABLE 18.1
Functional Group Names

Radical	Group Name as Prefix
$—CO_2CH_3$	methoxycarbonyl
$—CO_2CH_2CH_3$	ethoxycarbonyl
$—CONH_2$	carbamoyl
$—COCl$	chloroformyl
$—COBr$	bromoformyl
$—CN$	cyano

Examples of such names are

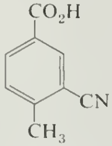


3-methoxycarbonylcyclohexanecarboxylic acid

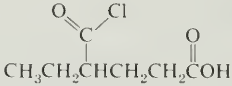


$CH_3CH_2CH(CONH_2)CH_2CH_2COCl$

4-carbamoylhexanoyl chloride



3-cyano-4-methylbenzoic acid



$CH_3CH_2CH(COCl)CH_2CH_2COOH$

4-chloroformylhexanoic acid

18.3
Physical Properties

In Figure 18.5 the boiling points of straight chain acids, nitriles, methyl esters, and acyl chlorides are plotted against molecular weight. For comparison, the boiling point curve for *n*-alkanes is also given. It can readily be seen that esters and acyl halides have approximately the boiling point expected for hydrocarbons of the same molecular weight. This correspondence indicates that the main attractive forces in the condensed phase for these compounds are the relatively weak van der Waals forces.

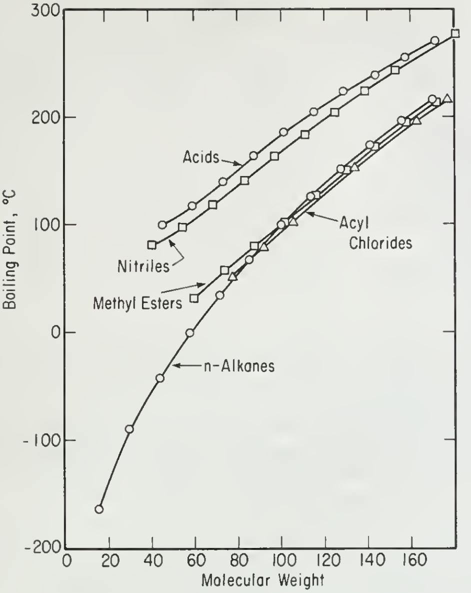
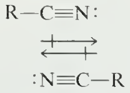


Figure 18.5 *Boiling points of various compounds.*

On the other hand, carboxylic acids and nitriles boil much higher than hydrocarbons of equivalent weight. In these compounds, polar intermolecular forces of the type depicted below must also be important in the liquid state. In the cases



$$\begin{array}{c} R{-}C{\equiv}N{:} \\ \overset{+}{\longrightarrow} \\ \overset{+}{\longleftarrow} \\ {:}N{\equiv}C{-}R \end{array}$$

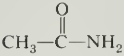
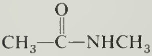
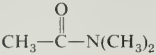
of carboxylic acids, hydrogen bonding in the condensed phase is an added factor. In addition to supplying enough energy to overcome the normal van der Waals attractive forces, additional energy must be supplied to overcome the "extra" polar attractive forces. The result is a higher boiling point.

All methyl and ethyl esters, acyl chlorides and nitriles for the straight chain acids lower than tetradecanoic are liquids at room temperature. Simple anhydrides above nonanoic anhydride are solid at room temperature.

Amides, in particular, show the strong effects of hydrogen bonding in the condensed phase. The melting points and boiling points of acetamide, N-methylacetamide, and N,N-dimethylacetamide are tabulated in Table 18.2. Note that acetamide boils 215° higher than a comparable alkane. Dimethylacetamide still boils 95° higher than a comparable alkane, but it has a boiling point almost exactly the same as that for an acid or nitrile of comparable weight. A similar downward trend is seen in the melting points of the three compounds.

The explanation of these interesting trends lies in the phenomenon of hydrogen bonding. Acetamide, with two hydrogens attached to nitrogen, is extensively hydrogen bonded in both the solid and liquid phases. In methylacetamide there

TABLE 18.2
Physical Properties for Acetamide Derivatives

	Molecular Weight	Melting Point, °C	Boiling Point, °C
 $CH_3-\overset{O}{\overset{\|}{C}}-NH_2$	59	82	221
 $CH_3-\overset{O}{\overset{\|}{C}}-NHCH_3$	73	28	204
 $CH_3-\overset{O}{\overset{\|}{C}}-N(CH_3)_2$	87	−20	165

is only one N—H and therefore the hydrogen bonding is less extensive. Finally, dimethylacetamide cannot engage in hydrogen bonding at all, since it has no hydrogens attached to nitrogen.

Esters, amides, nitriles, acyl halides, and anhydrides are generally soluble in common organic solvents (ether, chloroform, benzene, and so on). Acetonitrile, dimethylformamide, and dimethylacetamide are miscible with water in all proportions. Because of their polar, aprotic nature, these compounds are excellent solvents. Ethyl acetate, which is only sparingly soluble in water, is also a common solvent. Because of its excellent solvent properties, ethyl acetate is a common constitutent of many brands of paint remover and is also used as a fingernail polish remover. It may easily be recognized by its characteristic "fruity" odor.

18.4
Spectroscopy

A. *Nuclear Magnetic Resonance*

The chemical shifts of protons in the vicinity of the carbonyl group have similar resonance positions regardless of the exact nature of the compound. Typical values are summarized in Table 18.3. A typical example is the spectrum of methyl propionate, shown in Figure 18.6.

TABLE 18.3
Chemical Shifts in Compounds of the Type R—Y

	Chemical Shift in δ		
Y	CH_3Y	RCH_2Y	CH_3CH_2Y
—CHO	2.20	2.40	1.08
$—CO_2H$	2.10	2.36	1.16
$—CO_2CH_3$	2.03	2.13	1.12
—COCl	2.67		
$—CONH_2$	2.08	2.23	1.13
—CN	2.00	2.28	1.14

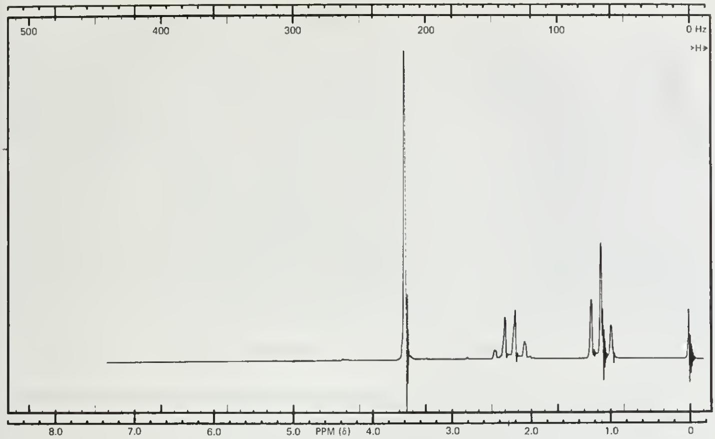
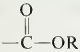
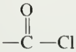
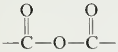
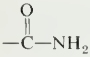
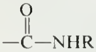
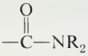


FIGURE 18.6 Nmr *spectrum of methyl propionate,* $CH_3CH_2CO_2CH_3$.

B. *Infrared*

In Chapter 15, we saw that the characteristic absorption of aldehydes and ketones is the C=O stretch which occurs in the 1710-1825 cm^{-1} region. Other compounds containing the carbonyl group also absorb in this general region. The exact position of the absorption depends on the nature of the functional group. Typical values are listed in Table 18.4.

TABLE 18.4
Carbonyl Stretching Bands of Carboxylic Acid Derivatives in Solution

Functional Group	C=O Stretch, cm^{-1}
 $-\overset{\overset{\large O}{\|}}{C}-OR$	1735
 $-\overset{\overset{\large O}{\|}}{C}-Cl$	1800
 $-\overset{\overset{\large O}{\|}}{C}-O-\overset{\overset{\large O}{\|}}{C}-$	1820 and 1760 (two peaks)
 $-\overset{\overset{\large O}{\|}}{C}-NH_2$	1690
 $-\overset{\overset{\large O}{\|}}{C}-NHR$	1680
 $-\overset{\overset{\large O}{\|}}{C}-NR_2$	1650

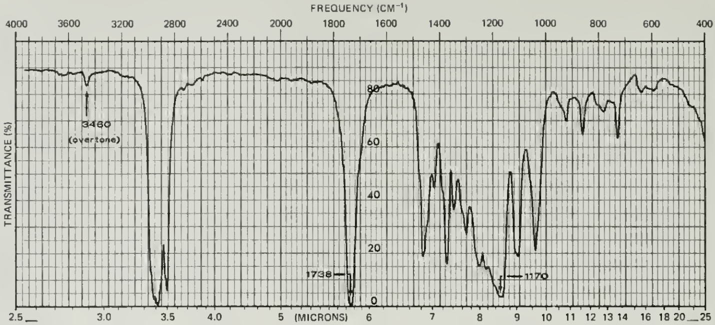


FIGURE 18.7 *Infrared spectrum of ethyl octanoate,* $CH_3(CH_2)_6CO_2CH_2CH_3$.

In addition to the carbonyl stretch, these derivatives have other useful infrared absorptions. Esters have a characteristic carbonyl C—O single bond stretch in the 1050–1250 cm^{-1} region. Both the C=O stretch at 1738 cm^{-1} and the C—O single bond stretch at 1170 cm^{-1} are clearly seen in the spectrum of ethyl octanoate in Figure 18.7.

Amides that have one or two hydrogens on nitrogen show a characteristic N-H stretch. For compounds of the type $RCONH_2$, the N-H absorption occurs as two peaks at 3400 and 3500 cm^{-1}. For RCONHR compounds, the N-H stretch comes at 3440 cm^{-1}.

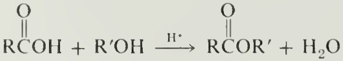
The typical absorption of nitriles is the C≡N stretch at 2110–2160 cm^{-1}. Note that this absorption occurs in the general region where the C≡C triple bond absorbs (Section 14.6).

18.5
Synthesis

Functional derivatives of carboxylic acids are prepared mostly from acids or other acid derivatives. Since all of this chemistry is discussed in detail in other sections, we simply summarize the most generally useful preparative methods here.

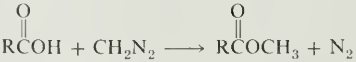
Esters

1. Acid-catalyzed esterification of carboxylic acids (Section 17.7.C).



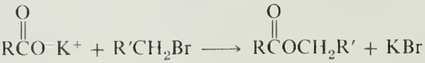
$$R\overset{O}{\overset{\|}{C}}OH + R'OH \xrightarrow{H^+} R\overset{O}{\overset{\|}{C}}OR' + H_2O$$

2. Diazomethane with a carboxylic acid (Section 17.7.A).



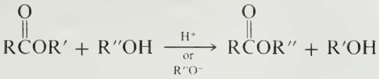
$$R\overset{O}{\overset{\|}{C}}OH + CH_2N_2 \longrightarrow R\overset{O}{\overset{\|}{C}}OCH_3 + N_2$$

3. Reaction of primary halides with carboxylate salts (Section 17.7.A).



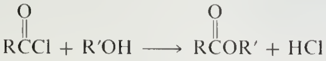
$$R\overset{O}{\overset{\|}{C}}O^-K^+ + R'CH_2Br \longrightarrow R\overset{O}{\overset{\|}{C}}OCH_2R' + KBr$$

4. Transesterification (Section 18.9.B).



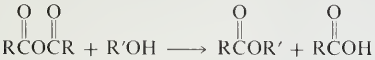
$$\mathrm{R\overset{O}{\overset{\|}{C}}OR' + R''OH \xrightarrow[\text{or}\ R''O^-]{H^+} R\overset{O}{\overset{\|}{C}}OR'' + R'OH}$$

5. Acyl halides and alcohols (Section 18.9.B).



$$\mathrm{R\overset{O}{\overset{\|}{C}}Cl + R'OH \longrightarrow R\overset{O}{\overset{\|}{C}}OR' + HCl}$$

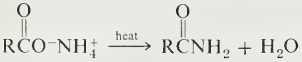
6. Acid anhydrides and alcohols (Section 18.9.B)



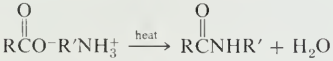
$$\mathrm{R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R + R'OH \longrightarrow R\overset{O}{\overset{\|}{C}}OR' + R\overset{O}{\overset{\|}{C}}OH}$$

Amides

1. Pyrolysis of ammonium carboxylates (Section 17.7.C).

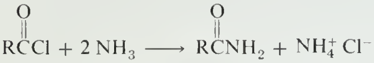


$$\mathrm{R\overset{O}{\overset{\|}{C}}O^-NH_4^+ \xrightarrow{heat} R\overset{O}{\overset{\|}{C}}NH_2 + H_2O}$$



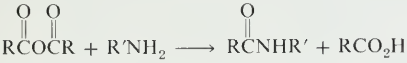
$$\mathrm{R\overset{O}{\overset{\|}{C}}O^-R'NH_3^+ \xrightarrow{heat} R\overset{O}{\overset{\|}{C}}NHR' + H_2O}$$

2. Acyl halides and ammonia or amines (Section 18.9.C)



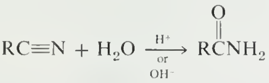
$$\mathrm{R\overset{O}{\overset{\|}{C}}Cl + 2\,NH_3 \longrightarrow R\overset{O}{\overset{\|}{C}}NH_2 + NH_4^+\,Cl^-}$$

3. Acid anhydrides and ammonia or amines (Section 18.9.C)



$$\mathrm{R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R + R'NH_2 \longrightarrow R\overset{O}{\overset{\|}{C}}NHR' + RCO_2H}$$

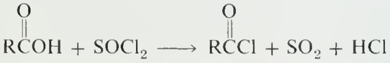
4. Partial hydrolysis of nitriles (Section 18.9.A)



$$\mathrm{RC{\equiv}N + H_2O \xrightarrow[\text{or}\ OH^-]{H^+} R\overset{O}{\overset{\|}{C}}NH_2}$$

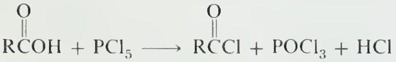
Acyl Halides

1. Carboxylic acids with $SOCl_2$ (Section 17.7.C).



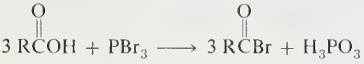
$$\mathrm{R\overset{O}{\overset{\|}{C}}OH + SOCl_2 \longrightarrow R\overset{O}{\overset{\|}{C}}Cl + SO_2 + HCl}$$

2. Carboxylic acids with PCl_5 (Section 17.7.C).



$$\mathrm{R\overset{O}{\overset{\|}{C}}OH + PCl_5 \longrightarrow R\overset{O}{\overset{\|}{C}}Cl + POCl_3 + HCl}$$

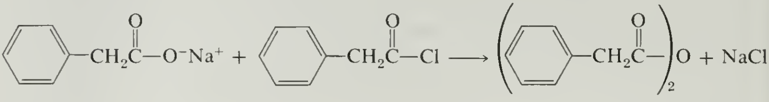
3. Carboxylic acids with PBr_3 (Section 17.7.C).



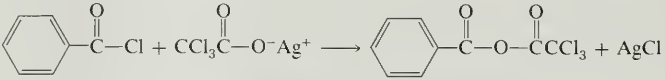
$$\mathrm{3\,R\overset{O}{\overset{\|}{C}}OH + PBr_3 \longrightarrow 3\,R\overset{O}{\overset{\|}{C}}Br + H_3PO_3}$$

Acid Anhydrides. The only simple anhydride commonly used is acetic anhydride, which is commercially available. Other simple anhydrides are most easily made from the corresponding acyl chloride (see below for examples). Since an anhydride is generally used as an "activated" carboxylic acid, it makes little sense to convert the acyl chloride into the acid anhydride. In special cases, however, this may be desirable. Cyclic anhydrides are often used as precursers to difunctional compounds.

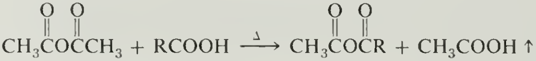
1. Acyl halides with carboxylate salts (Section 18.9.D).



(87%)

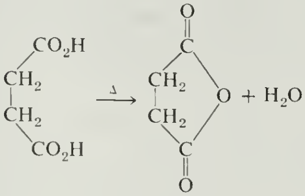


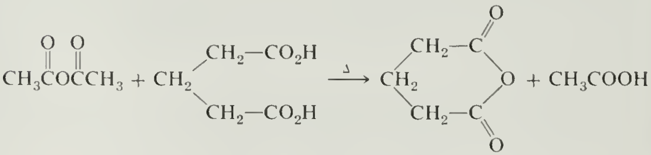
2. Acetic anhydride with carboxylic acids (Section 18.9.D).



$$CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 + RCOOH \xrightarrow{\Delta} CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R + CH_3COOH\uparrow$$

3. Cyclic anhydrides from diacids (Section 26.2.C).



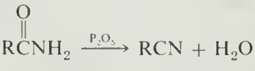


Nitriles

1. S_N2 displacement (Section 8.3).

$$RCH_2Br + CN^- \longrightarrow RCH_2CN + Br^-$$

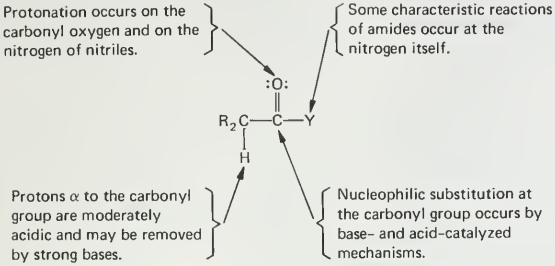
2. Dehydration of primary amides (Section 18.11).



$$R\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{P_2O_5} RCN + H_2O$$

18.6
Reactions of Carboxylic Acid Derivatives

Most of the important reactions of carboxylic acid derivatives fall into the following categories:



Protonation occurs on the carbonyl oxygen and on the nitrogen of nitriles.

Some characteristic reactions of amides occur at the nitrogen itself.

Protons α to the carbonyl group are moderately acidic and may be removed by strong bases.

Nucleophilic substitution at the carbonyl group occurs by base- and acid-catalyzed mechanisms.

In the remaining sections of this chapter, we shall discuss these reactions.

18.7
Basicity of the Carbonyl Oxygen

As in the case of aldehydes, ketones (Section 15.6), and carboxylic acids (Section 17.7), the carbonyl oxygen of carboxylic acid derivatives has basic properties. The conjugate acid, an oxonium salt, plays an important role as an intermediate in acid-catalyzed reactions of all of these types of compounds The actual basicity of the lone pair electrons of the carbonyl oxygen depends markedly on the nature of the radical attached to the carbonyl group. This basicity is generally expressed quantitatively in terms of the acidity or pK_a of the conjugate acid:

$$\mathrm{R\overset{\overset{+}{}OH}{\overset{\|}{C}}Y \rightleftharpoons R\overset{O}{\overset{\|}{C}}Y + H^+}$$

$$K_a = \frac{[\mathrm{RCOY}][\mathrm{H^+}]}{\left[\mathrm{R\overset{\overset{+}{}OH}{\overset{\|}{C}}Y}\right]}$$

$$\mathrm{p}K_a = -\log K_a$$

Some pK_a values are summarized in Table 18.5. Most protonated carbonyl compounds are strong acids, stronger than H_3O^+ and comparable in acidity to hydrochloric acid (pK_a = −7). That is, the carbonyl compounds themselves are weak bases in water, in a class with chloride ion. Some of the individual structural effects warrant comment.

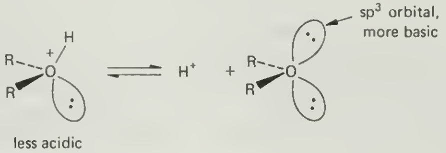
Alcohols are generally a little weaker as bases than water itself and ethers are weaker bases still. These variations are probably the result of solvation differences. The fewer the number of protons on an oxonium oxygen, the less the amount of solvation stabilization by hydrogen bonds to water. If the acid structure is less stable for whatever reason, the conjugate base has lower basicity.

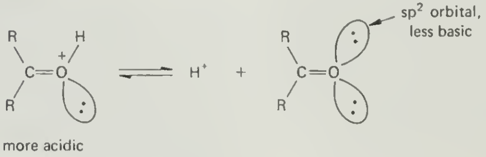
The carbonyl oxygen of aldehydes and ketones is less basic than an alcohol or ether oxygen by several powers of ten. The lone pair electrons of the carbonyl

TABLE 18.5
Acidities of Protonated Compounds

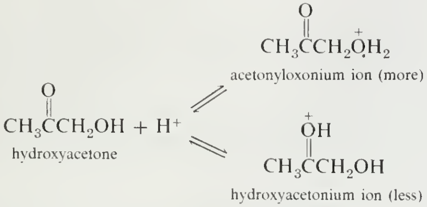
Compound	Conjugate Acid	pK_a of Conjugate Acid
CH_3CONH_2	$CH_3\overset{\overset{+}{O}H}{\overset{\|}{C}}NH_2$	0.0
H_2O	H_3O^+	−1.7
CH_3OH	$CH_3\overset{+}{O}H_2$	−2.2
$(CH_3CH_2)_2O$	$(CH_3CH_2)_2\overset{+}{O}H$	−3.6
CH_3COOH	$CH_3\overset{\overset{+}{O}H}{\overset{\|}{C}}OH$	−6
$CH_3COOC_2H_5$	$CH_3\overset{\overset{+}{O}H}{\overset{\|}{C}}OC_2H_5$	−6.5
CH_3COCH_3	$CH_3\overset{\overset{+}{O}H}{\overset{\|}{C}}CH_3$	−7.2
CH_3CHO	$CH_3\overset{\overset{+}{O}H}{\overset{\|}{C}}H$	≈ −8
CH_3COCl	$CH_3\overset{\overset{+}{O}H}{\overset{\|}{C}}Cl$	≈ −9
CH_3CN	$CH_3C{\equiv}\overset{+}{N}H$	−10.1

oxygen may be considered to be approximately sp^2 in character. These electrons have greater s character than the lone pairs of alcohol oxygens. Hence, the lone pair electrons of carbonyl oxygens are more tightly held. As a result, the carbonyl group as a conjugate base is more stable, and the corresponding protonated carbonyl is more acidic. This system is exactly analogous to the corresponding hydrocarbon cases. Recall that ethylene is more acidic than ethane (Section 11.4). In a protonated carbonyl group, the O—H bond is described approximately as O_{sp^2}-H. In a protonated alcohol or ether, the O—H bond involves an oxygen orbital that has greater p character.





The structure of protonated carboxylic acids and esters is shown in Table 18.5 with the proton on the carbonyl oxygen rather than on the OR oxygen, despite the argument just presented that carbonyl oxygens are generally less basic than singly bonded oxygens. This result is a manifestation of **conjugation.** If the carbonyl group and hydroxy or alkoxy group are separated by one or more carbons (for example, in hydroxyacetone), we would anticipate the carbonyl group to be the less basic. That is, in an acidic medium, the hydroxy or alkoxy group is protonated to a greater degree than is the carbonyl group.



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2OH + H^+ \rightleftharpoons CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2\overset{+}{O}H_2 \quad ; \quad CH_3\overset{\overset{\displaystyle \overset{+}{O}H}{\|}}{C}CH_2OH$$

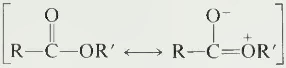
hydroxyacetone

acetonyloxonium ion (more)

hydroxyacetonium ion (less)

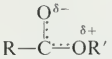
Note that both protonated isomers are more acidic than their monofunctional counterparts: acetonyloxonium ion is more acidic than propyloxonium ion, $CH_3CH_2CH_2OH_2^+$, and hydroxyacetonium ion is more acidic than acetonium ion. In both cases the substituent has an electron-attracting inductive effect that results in an increase in acidity, just as in the case of substituted acetic acids (Section 17.4.B).

When the OH or OR group is attached directly to the carbonyl group, electron density on the singly bonded oxygen can "leak over" to the electron-attracting carbonyl group as symbolized by the resonance structures



$$\left[R-\overset{\overset{\displaystyle O}{\|}}{C}-OR' \longleftrightarrow R-\overset{\overset{\displaystyle O^-}{|}}{C}=\overset{+}{O}R'\right]$$

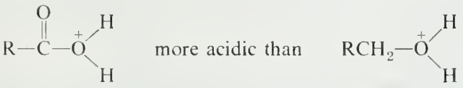
The actual electronic structure of the carboxylic acid or ester group may be represented as



$$R-\overset{\overset{\displaystyle O^{\delta-}}{\vdots}}{C}\text{=}\overset{\delta+}{O}R'$$

The partial positive charge or oxonium character of the OR group makes this oxygen less basic than an ether oxygen. The partial negative charge on the carbonyl oxygen makes it more basic than a ketone oxygen.

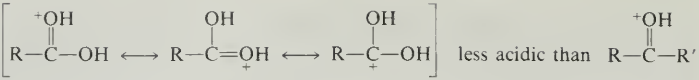
This argument does not mean that the alternative protonated compound cannot exist. It does say that this compound, an acyloxonium ion, is much more acidic than a simple oxonium ion.



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{+}{O}H_2 \quad \text{more acidic than} \quad RCH_2-\overset{+}{O}H_2$$

oxonium ion

On the other hand, the carbonyl-protonated carboxylic grouping is stabilized by conjugation; the positive charge is distributed between the two oxygens, much as the negative charge is distributed in acetate ion (Section 17.4.A).



$$\left[R-\overset{^{+}OH}{\overset{\|}{C}}-OH \longleftrightarrow R-\overset{OH}{\overset{|}{C}}=\underset{+}{O}H \longleftrightarrow R-\underset{+}{\overset{OH}{\overset{|}{C}}}-OH \right] \text{ less acidic than } R-\overset{^{+}OH}{\overset{\|}{C}}-R'$$

These same considerations apply to an even greater extent in the case of amides. Ammonia is much more basic than water: $pK_a(NH_4^+) = 9.5$; $pK_a(H_3O^+) = -1.7$. The nitrogen in an amide is far less basic than that in ammonia because of the important contribution of the dipolar resonance structure.

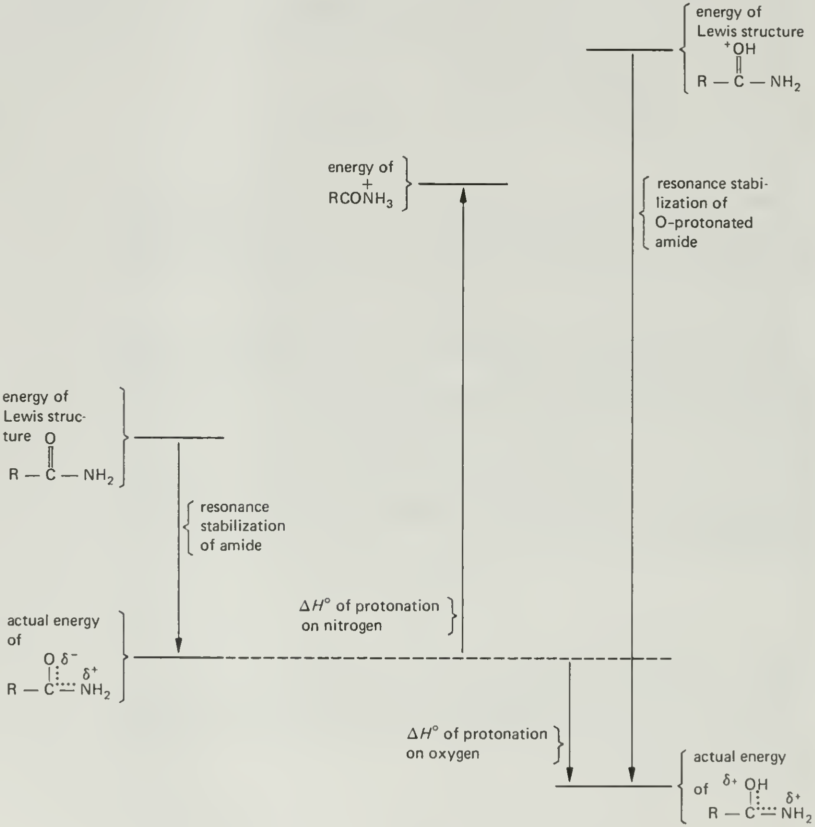
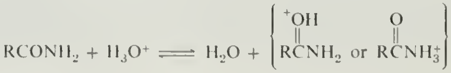
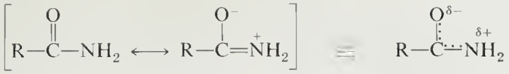

energy of Lewis structure ⁺OH ‖ R — C — NH₂
energy of RCONH₃⁺
resonance stabilization of O-protonated amide
energy of Lewis structure O ‖ R — C — NH₂
resonance stabilization of amide
ΔH° of protonation on nitrogen
actual energy of O δ⁻ R — C ⋯ NH₂ δ⁺
ΔH° of protonation on oxygen
actual energy of δ+ OH R — C ⋯ NH₂ δ+

FIGURE 18.8 *Illustrating why N-protonated amides are more acidic than O-protonated amides, even though* $H_3N{:}$ *is more basic than* $H_2O{:}$*. The schematic given is for the system*

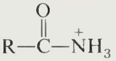


$$RCONH_2 + H_3O^+ \rightleftharpoons H_2O + \left\{ R\overset{^{+}OH}{\overset{\|}{C}}NH_2 \text{ or } R\overset{O}{\overset{\|}{C}}NH_3^+ \right\}$$



$$\left[R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \longleftrightarrow R-\overset{\overset{\displaystyle O^-}{|}}{C}=\overset{+}{N}H_2\right] \equiv R-\overset{\overset{\displaystyle O^{\delta-}}{\vdots}}{C}\overset{\delta+}{\cdots}NH_2$$

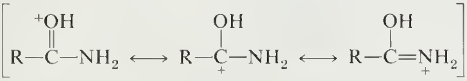
That is, the nitrogen in an amide already has some of the character of an ammonium ion. If this nitrogen becomes protonated, the resonance stabilization of the amide is lost.



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{+}{N}H_3$$

no lone pair for conjugation
with carbonyl group'

The situation is represented schematically in Figure 18.8. Note that the O-protonated amide is greatly stabilized by resonance.



$$\left[R-\overset{\overset{\displaystyle ^+OH}{\|}}{C}-NH_2 \longleftrightarrow R-\underset{+}{\overset{\overset{\displaystyle OH}{|}}{C}}-NH_2 \longleftrightarrow R-\overset{\overset{\displaystyle OH}{|}}{C}=\underset{+}{N}H_2\right]$$

In fact, as shown in Table 18.5, the O-protonated amide is almost 100 times less acidic than H_3O^+.

Finally, note that the triply bonded nitrogen in nitriles is far less basic than ammonia. That is, the protonated nitrile, $R\text{-}C\equiv\overset{+}{N}H$, is some 20 powers of ten more acidic than NH_4^+. Again, this difference points up the powerful effect that *s* character has on the relative stability of lone pair electrons. The lone pair electrons in a nitrile are approximately *sp* in character; those in ammonia are almost *sp*^{3} in character. Recall the effect of a corresponding change in hydrocarbons: acetylene is far more acidic than methane (Section 13.4).

$HC\equiv C-H$ $pK_a \approx 25$	CH_3-H $pK_a \approx 49$	$\Delta pK_a \approx 24$
$RC\equiv\overset{+}{N}-H$ $pK_a = -10$	$\overset{+}{N}H_3-H$ $pK_a = 9.5$	$\Delta pK_a \approx 20$

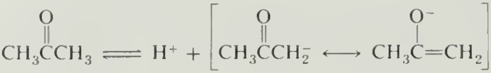
18.8
Acidity of the α Protons

Like the α protons of aldehydes and ketones (Section 15.6) protons adjacent to the carbonyl group in carboxylic acid derivatives are weakly acidic. Table 18.6 lists the pK_a values for some representative compounds. Recall that the main reason for the acidity of aldehydes and ketones relative to the alkanes is the fact that the resulting anion is resonance-stabilized. In fact, the resonance contributor with the negative charge on oxygen (the enolate ion) is the more important structure because of the greater electronegativity of oxygen. This stabilization of the anion greatly reduces the $\Delta H°$ for the ionization process and is responsible for the fact that acetone is approximately 30 powers of ten more acidic than ethane.

TABLE 18.6

Compound	pK_a of H
$CH_3\overset{O}{\overset{\|}{C}}Cl$	≈ 16
$CH_3\overset{O}{\overset{\|}{C}}H$	17
$CH_3\overset{O}{\overset{\|}{C}}CH_3$	20
$CH_3\overset{O}{\overset{\|}{C}}OCH_3$	25
CH_3CN	25
$CH_3\overset{O}{\overset{\|}{C}}N(CH_3)_2$	≈ 30
CH_3CH_3	≈ 50

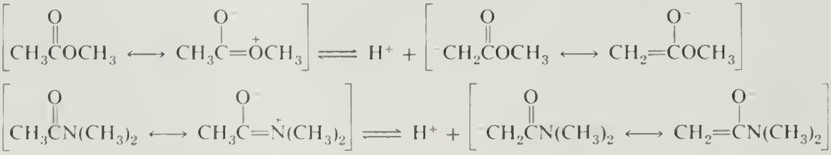
$$CH_3CH_3 \rightleftharpoons H^+ + \underset{\text{charge localized on carbon}}{CH_3CH_2^-}$$



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons H^+ + \left[CH_3\overset{O}{\overset{\|}{C}}CH_2^- \longleftrightarrow CH_3\overset{O^-}{\overset{|}{C}}{=}CH_2\right]$$

charge delocalized—
mainly on oxygen

In esters and amides, the conjugate base is also resonance-stabilized, with the negative charge delocalized over carbon and oxygen. However, in these cases, the neutral acids themselves are also resonance-stabilized to a significant extent, as shown by the shorter-than-usual C—O and C—N bond lengths (Section 18.1).



$$\left[CH_3\overset{O}{\overset{\|}{C}}OCH_3 \longleftrightarrow CH_3\overset{O^-}{\overset{|}{C}}{=}\overset{+}{O}CH_3\right] \rightleftharpoons H^+ + \left[{}^-CH_2\overset{O}{\overset{\|}{C}}OCH_3 \longleftrightarrow CH_2{=}\overset{O^-}{\overset{|}{C}}OCH_3\right]$$

$$\left[CH_3\overset{O}{\overset{\|}{C}}N(CH_3)_2 \longleftrightarrow CH_3\overset{O^-}{\overset{|}{C}}{=}\overset{+}{N}(CH_3)_2\right] \rightleftharpoons H^+ + \left[{}^-CH_2\overset{O}{\overset{\|}{C}}N(CH_3)_2 \longleftrightarrow CH_2{=}\overset{O^-}{\overset{|}{C}}N(CH_3)_2\right]$$

A ketone enolate and an ester enolate are probably of comparable stability, but the ester is resonance-stabilized to a greater extent than the ketone. Hence, $\Delta H°$ for dissociation of the ester is greater than $\Delta H°$ for dissociation of the ketone. These relationships are depicted graphically in Figure 18.9. Since the lone pair electrons on nitrogen are more basic than those on oxygen, dipolar resonance stabilization of amides is even more important than in the case of esters. Hence, amides are even less acidic than esters.

On the other hand, acyl halides are estimated to be more acidic than esters because resonance stabilization of the acyl halide itself is relatively unimportant. Since the halogen is an electron attracting group, and can stabilize the resulting

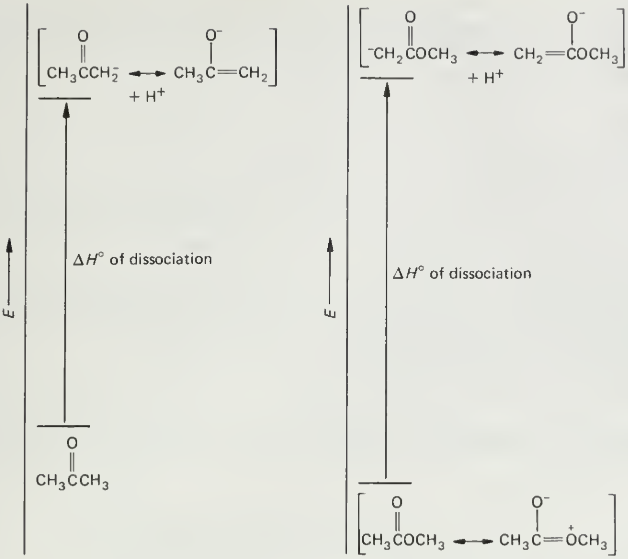
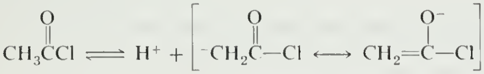

$CH_3\overset{O}{\overset{\|}{C}}CH_2^- \longleftrightarrow CH_3\overset{O^-}{\overset{|}{C}}=CH_2$
$+ H^+$
$\Delta H°$ of dissociation
E
$CH_3\overset{O}{\overset{\|}{C}}CH_3$
${}^-CH_2\overset{O}{\overset{\|}{C}}OCH_3 \longleftrightarrow CH_2=\overset{O^-}{\overset{|}{C}}OCH_3$
$+ H^+$
$\Delta H°$ of dissociation
E
$CH_3\overset{O}{\overset{\|}{C}}OCH_3 \longleftrightarrow CH_3\overset{O^-}{\overset{|}{C}}=\overset{+}{O}CH_3$

FIGURE 18.9 *The relative acidity of ketones and esters.*

enolate ion by its inductive effect (Section 17.4B), acyl halides are even more acidic than aldehydes and ketones.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}Cl \rightleftharpoons H^+ + \left[{}^-CH_2\overset{O}{\overset{\|}{C}}-Cl \longleftrightarrow CH_2=\overset{O^-}{\overset{|}{C}}-Cl\right]}$$

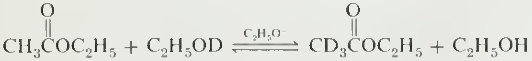
electronegative chlorine provides additional stabilization for anion

The anion derived by deprotonation of a nitrile is also resonance-stabilized.

$$\mathrm{CH_3C{\equiv}N \rightleftharpoons H^+ + [{}^-CH_2C{\equiv}N \longleftrightarrow CH_2{=}C{=}N^-]}$$

However, in this case, the negative charge on the anion is shared by carbon and nitrogen. Since nitrogen is not as electronegative as oxygen, nitriles are weaker acids than aldehydes and ketones.

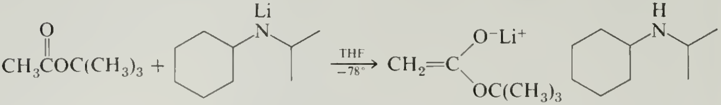
The α-proton acidity manifests itself in the chemistry of carboxylic acid derivatives in several ways. For example, if ethyl acetate is dissolved in deuterioethanol which contains a catalytic amount of sodium ethoxide, exchange of the α protons by deuterium occurs.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OD \xrightleftharpoons{C_2H_5O^-} CD_3\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OH}$$

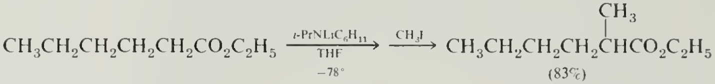
Ethyl acetate is a much weaker acid than ethanol (pK_a 15.9), so the above equilibrium is established relatively slowly. For example, a solution of ethyl acetate in deuterioethanol containing 0.1 *M* sodium ethoxide is only 50% exchanged after two weeks at 25°. For this reason, if one wishes to exchange the α protons of an ester, it is necessary to reflux the solution for several hours.

If an ester is treated with a sufficiently strong base, it can be completely converted to the corresponding anion. For example, *t*-butyl acetate reacts with lithium isopropylcyclohexylamide in THF at −78° to give *t*-butyl lithioacetate, which may be isolated as a white crystalline solid.



p$K_a \approx 25$ lithium isopropylcyclohexylamide *t*-butyl lithioacetate p$K_a \approx 40$

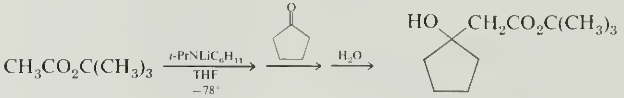
Such ester anions are strong bases and are also good nucleophiles. They undergo reactions similar to those of the corresponding enolate ions derived from ketones. Examples are S_N2 displacements with primary alkyl halides and additions to aldehyde and ketone carbonyl groups.



$$CH_3CH_2CH_2CH_2CH_2CO_2C_2H_5 \xrightarrow[\text{THF}, -78°]{i\text{-PrNLiC}_6\text{H}_{11}} \xrightarrow{CH_3I} CH_3CH_2CH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCO_2C_2H_5$$

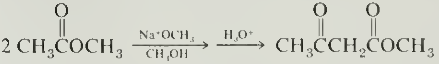
ethyl hexanoate

(83%)
ethyl 2-methylhexanoate



(93%)
t-butyl (1-hydroxycyclopentyl)acetate

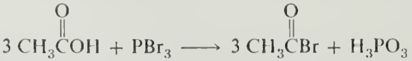
Ester and nitrile anions also undergo another reaction which is an important synthetic procedure, the Claisen condensation. In this reaction, the ester anion condenses with an unionized ester molecule to give a β-ketoester.



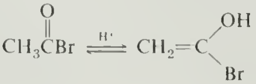
$$2\ CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 \xrightarrow[CH_3OH]{Na^+{}^-OCH_3} \xrightarrow{H_3O^+} CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2\overset{\overset{\displaystyle O}{\|}}{C}OCH_3$$

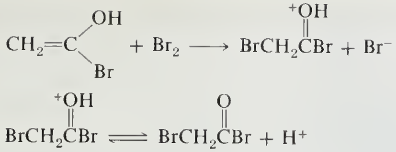
The overall process, which is analogous to the aldol condensation (Section 15.7.G), will be discussed in detail in Section 26.3.

The enol form of an acyl halide has previously been encountered as an intermediate in the Hell-Volhard-Zelinsky bromination of carboxylic acids (Section 17.7.B). In fact, the reason for using PBr_3 in this bromination is to convert the acid into the acyl bromide and thus render the α protons more acidic (see Table 18.6).



$$3\ CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH + PBr_3 \longrightarrow 3\ CH_3\overset{\overset{\displaystyle O}{\|}}{C}Br + H_3PO_3$$



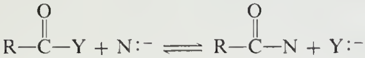


$$CH_2{=}C\begin{matrix}OH\\ Br\end{matrix} + Br_2 \longrightarrow BrCH_2\overset{{}^{+}OH}{\overset{\|}{C}}Br + Br^-$$

$$BrCH_2\overset{{}^{+}OH}{\overset{\|}{C}}Br \rightleftharpoons BrCH_2\overset{O}{\overset{\|}{C}}Br + H^+$$

18.9
Nucleophilic Substitution Reactions

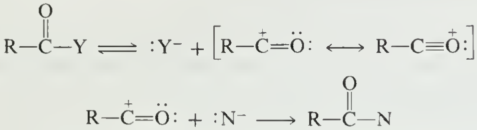
The general equation for the reaction of a carboxylic acid derivative with a nucleophile is



$$R{-}\overset{O}{\overset{\|}{C}}{-}Y + N{:}^- \rightleftharpoons R{-}\overset{O}{\overset{\|}{C}}{-}N + Y{:}^-$$

There are three distinct ways in which the bond-breaking and bond-making operations may be timed.

1. Bond-breaking may occur first, followed in a subsequent step by bond-making.

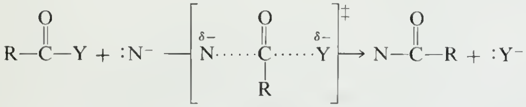


$$R{-}\overset{O}{\overset{\|}{C}}{-}Y \rightleftharpoons {:}Y^- + \left[R{-}\overset{+}{C}{=}\ddot{O}{:} \longleftrightarrow R{-}C{\equiv}\overset{+}{O}{:}\right]$$

$$R{-}\overset{+}{C}{=}\ddot{O}{:} + {:}N^- \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}N$$

This mechanism is analogous to the S_N1 process for nucleophilic substitution reactions in alkyl halides (Section 8.7). The intermediate carbonium ion in this case is called an **acylium ion.** Only relatively few reactions are known that occur by this mechanism. One example of a reaction proceeding by this path was seen on page 444.

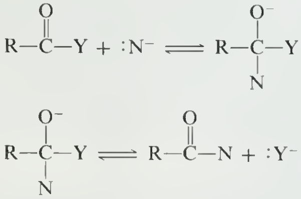
2. Bond-breaking and bond-making may occur more-or-less synchrononously.



$$R{-}\overset{O}{\overset{\|}{C}}{-}Y + {:}N^- \longrightarrow \left[\overset{\delta-}{N}\cdots\cdots\underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}}\cdots\cdots\overset{\delta-}{Y}\right]^{\ddagger} \longrightarrow N{-}\overset{O}{\overset{\|}{C}}{-}R + {:}Y^-$$

This mechanism is analogous to the S_N2 mechanism in that no intermediate is involved. It has been suggested by a few workers that some reactions of acyl halides may occur by this path, but actual evidence for the mechanism is sparse.

3. Bond-making may occur first, followed in a subsequent step by bond-breaking.

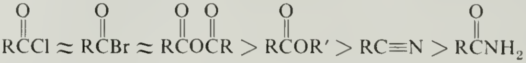


$$R{-}\overset{O}{\overset{\|}{C}}{-}Y + {:}N^- \rightleftharpoons R{-}\underset{\underset{N}{|}}{\overset{O^-}{\overset{|}{C}}}{-}Y$$

$$R{-}\underset{\underset{N}{|}}{\overset{O^-}{\overset{|}{C}}}{-}Y \rightleftharpoons R{-}\overset{O}{\overset{\|}{C}}{-}N + {:}Y^-$$

In this case, *addition* to the carbonyl group occurs first, giving an intermediate in which the former carbonyl carbon now has sp^3 hybridization. This intermediate then decomposes by ejection of a nucleophile, restoring the carbonyl group. This is an extremely important mechanism. Almost all nucleophilic substitution reactions of carboxylic acids and their derivatives occur by this pathway, the so-called **nucleophilic addition-elimination** mechanism.

Nucleophilic substitution reactions may be base catalyzed, or they may be acid catalyzed. In the base-catalyzed mechanism, an anion adds to the neutral carbonyl compound as shown above. In the acid-catalyzed mechanism, the nucleophile adds to the protonated carbonyl group (Section 18.7). In both mechanisms, the relative reactivity of various compounds is:

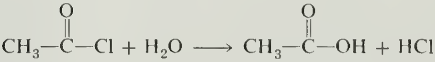


$$R\overset{\overset{O}{\|}}{C}Cl \approx R\overset{\overset{O}{\|}}{C}Br \approx R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R > R\overset{\overset{O}{\|}}{C}OR' > RC{\equiv}N > R\overset{\overset{O}{\|}}{C}NH_2$$

In this section, we shall discuss the important reactions of carboxylic acid derivatives with nucleophiles.

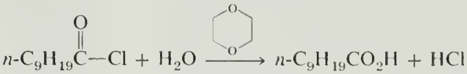
A. *Reaction with Water: Hydrolysis*

1. **Acyl Halides.** Carboxylic acid derivatives react with water to yield the parent carboxylic acid. As mentioned previously, acyl halides and acid anhydrides react most readily. Acetyl chloride reacts with water extremely vigorously, giving acetic acid and hydrogen chloride.



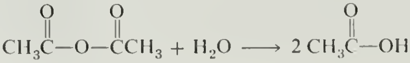
$$CH_3{-}\overset{\overset{O}{\|}}{C}{-}Cl + H_2O \longrightarrow CH_3{-}\overset{\overset{O}{\|}}{C}{-}OH + HCl$$

Higher acyl halides react much more slowly with water, but only because of their reduced solubility. In an inert solvent that dissolves both the acyl halide and water, hydrolysis occurs rapidly.



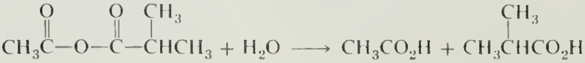
$$n\text{-}C_9H_{19}\overset{\overset{O}{\|}}{C}{-}Cl + H_2O \longrightarrow n\text{-}C_9H_{19}CO_2H + HCl$$

2. **Anhydrides.** Anhydrides react with water to yield two equivalents of the corresponding carboxylic acid.



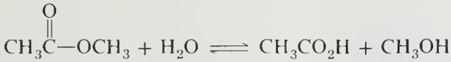
$$CH_3\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}CH_3 + H_2O \longrightarrow 2\,CH_3\overset{\overset{O}{\|}}{C}{-}OH$$

Although the hydrolysis is subject to acid or base catalysis, the uncatalyzed reaction is rapid, provided that the reaction mixture is homogeneous. Since most anhydrides are only sparingly soluble in water, the reaction between a pure anhydride and water appears to be slow. However, if the two reactants are brought together in a mutual solvent, such as dioxane or tetrahydrofuran, hydrolysis is rapid. In the case of an unsymmetrical anhydride, hydrolysis yields one molecule each of two carboxylic acids.



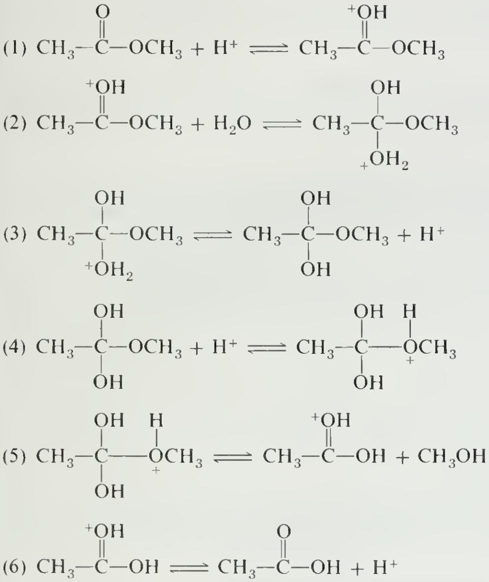
$$CH_3\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{CH_3}{|}}{C}HCH_3 + H_2O \longrightarrow CH_3CO_2H + CH_3\overset{\overset{CH_3}{|}}{C}HCO_2H$$

3. Esters. Esters react with water to yield the corresponding carboxylic acid and alcohol.



$$CH_3\overset{O}{\overset{\|}{C}}-OCH_3 + H_2O \rightleftharpoons CH_3CO_2H + CH_3OH$$

The reaction is generally slow, but is strongly catalyzed by either acid or base. The acid-catalyzed hydrolysis of esters of primary and secondary alcohols is simply the reverse of the acid-catalyzed esterification reaction (Section 17.7). The reaction is an equilibrium process, but can be driven practically to completion by using a large excess of water (page 442). The probable mechanism involves the following steps.



$$(1)\ CH_3-\overset{O}{\overset{\|}{C}}-OCH_3 + H^+ \rightleftharpoons CH_3-\overset{^+OH}{\overset{\|}{C}}-OCH_3$$

$$(2)\ CH_3-\overset{^+OH}{\overset{\|}{C}}-OCH_3 + H_2O \rightleftharpoons CH_3-\overset{OH}{\underset{_+OH_2}{\overset{|}{\underset{|}{C}}}}-OCH_3$$

$$(3)\ CH_3-\overset{OH}{\underset{^+OH_2}{\overset{|}{\underset{|}{C}}}}-OCH_3 \rightleftharpoons CH_3-\overset{OH}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-OCH_3 + H^+$$

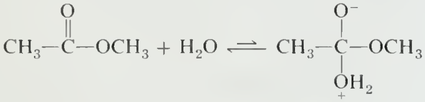
$$(4)\ CH_3-\overset{OH}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-OCH_3 + H^+ \rightleftharpoons CH_3-\overset{OH}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-\overset{H}{\underset{+}{\overset{|}{O}}}CH_3$$

$$(5)\ CH_3-\overset{OH}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-\overset{H}{\underset{+}{\overset{|}{O}}}CH_3 \rightleftharpoons CH_3-\overset{^+OH}{\overset{\|}{C}}-OH + CH_3OH$$

$$(6)\ CH_3-\overset{^+OH}{\overset{\|}{C}}-OH \rightleftharpoons CH_3-\overset{O}{\overset{\|}{C}}-OH + H^+$$

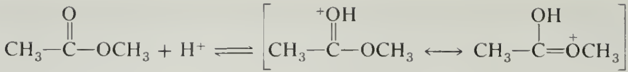
Notice that this mechanism is the exact reverse of that proposed in Section 17.6 for acid-catalyzed esterification.

Let us examine the role of the acid catalyst in the preceding reaction. In neutral water, the preponderant nucleophile present is water. Even though the carbonyl double bond is polarized, water is not a sufficiently strong nucleophile to add to it at a reasonable rate. Furthermore, addition of water to methyl acetate would produce an intermediate bearing both a positive and a negative charge. Since charge separation requires electrostatic energy, this type of addition is exceptionally slow.



$$CH_3-\overset{O}{\overset{\|}{C}}-OCH_3 + H_2O \rightleftharpoons CH_3-\overset{O^-}{\underset{\underset{+}{OH_2}}{\overset{|}{\underset{|}{C}}}}-OCH_3$$

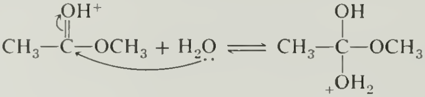
In the presence of mineral acids, the ester may be protonated (Section 18.7).



$$\mathrm{CH_3{-}\overset{O}{\overset{\|}{C}}{-}OCH_3 + H^+ \rightleftharpoons \left[CH_3{-}\overset{^+OH}{\overset{\|}{C}}{-}OCH_3 \longleftrightarrow CH_3{-}\overset{OH}{\overset{|}{C}}{=}\overset{+}{O}CH_3\right]}$$

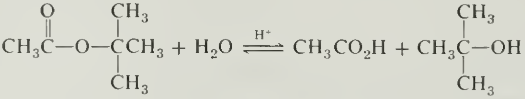
resonance stabilized cation

Since there is a very large excess of water molecules, and since the ester carbonyl is actually less basic than water (Table 18.5), only a small percentage of the ester is protonated at moderate acid concentration. However, the carbonyl carbon in the protonated species is much more electrophilic and reacts much faster with the weak nucleophile water than does the unprotonated ester. Furthermore, addition now involves no charge separation.



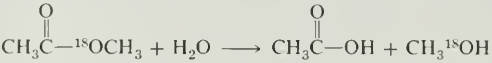
$$\mathrm{CH_3{-}\overset{OH^+}{\overset{\|}{C}}{-}OCH_3 + H_2\ddot{O} \rightleftharpoons CH_3{-}\underset{\underset{{}_+OH_2}{|}}{\overset{OH}{\overset{|}{C}}}{-}OCH_3}$$

In some cases, acid-catalyzed ester hydrolysis involves cleavage of the *alkyl-oxygen* bond, rather than the *acyl-oxygen* bond. Such is the case with *t*-butyl acetate (18-3).

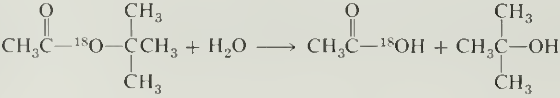


$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}{-}O{-}\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_3 + H_2O \xrightleftharpoons{H^+} CH_3CO_2H + CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{-}OH} \qquad (18\text{-}3)$$

Although the products are the same in both cases, the different mechanisms may be demonstrated by the labeling experiments (18-4) and (18-5).

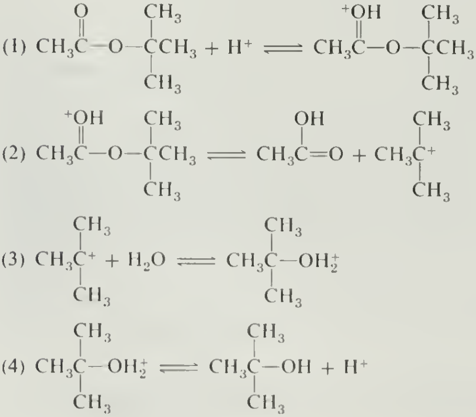


$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}{-}{}^{18}OCH_3 + H_2O \longrightarrow CH_3\overset{O}{\overset{\|}{C}}{-}OH + CH_3{}^{18}OH} \qquad (18\text{-}4)$$



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}{-}{}^{18}O{-}\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_3 + H_2O \longrightarrow CH_3\overset{O}{\overset{\|}{C}}{-}{}^{18}OH + CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{-}OH} \qquad (18\text{-}5)$$

The probable mechanism for this reaction involves the following steps.



$$(1)\ \mathrm{CH_3\overset{O}{\overset{\|}{C}}{-}O{-}\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_3 + H^+ \rightleftharpoons CH_3\overset{^+OH}{\overset{\|}{C}}{-}O{-}\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_3}$$

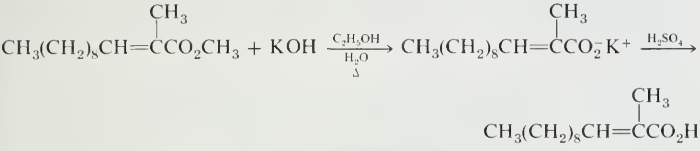
$$(2)\ \mathrm{CH_3\overset{^+OH}{\overset{\|}{C}}{-}O{-}\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_3 \rightleftharpoons CH_3\overset{OH}{\overset{|}{C}}{=}O + CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{}^+}$$

$$(3)\ \mathrm{CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{}^+ + H_2O \rightleftharpoons CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{-}OH_2^+}$$

$$(4)\ \mathrm{CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{-}OH_2^+ \rightleftharpoons CH_3\underset{\underset{CH_3}{|}}{\overset{CH_3}{\overset{|}{C}}}{-}OH + H^+}$$

It is reasonable that *t*-butyl acetate should react by this mechanism whereas methyl acetate does not. The reaction is simply an acid-catalyzed S_N1 process in which the nucleophile water replaces the nucleophile acetic acid. The reactive intermediate is the *t*-butyl cation. Esters of other alcohols that give rise to relatively stable carbonium ions also undergo hydrolysis by this mechanism.

As mentioned previously, ester hydrolysis is also strongly catalyzed by hydroxide ion. Since the carboxylic acid product neutralizes one equivalent of hydroxide, it is actually necessary to employ more than a stoichimetric amount of base. That is, hydroxide ion is actually a reagent instead of just a catalyst. The products are the salt of the carboxylic acid and the corresponding alcohol.

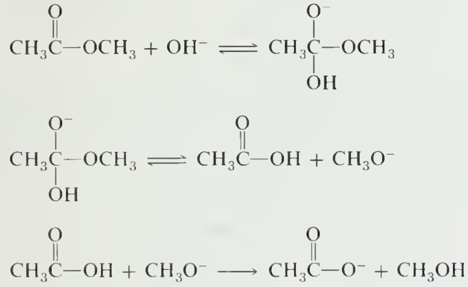


$$CH_3(CH_2)_8CH{=}\overset{CH_3}{\overset{|}{C}}CO_2CH_3 + KOH \xrightarrow[H_2O,\ \Delta]{C_2H_5OH} CH_3(CH_2)_8CH{=}\overset{CH_3}{\overset{|}{C}}CO_2^-K^+ \xrightarrow{H_2SO_4} CH_3(CH_2)_8CH{=}\overset{CH_3}{\overset{|}{C}}CO_2H$$

(68–83%)

To a solution of 20 g of methyl (E)-2-methyl-2-dodecenoate in 100 ml of 95% aqueous ethanol is added 8.8 g of potassium hydroxide. The solution is refluxed for 1.5 h, concentrated to 40 ml, and acidified by the addition of 5 *N* sulfuric acid. The product is isolated by extraction with petroleum ether. After removal of the petroleum ether, the crude product is distilled to yield 18 g of pure acid, m.p. 29.5–32.5°.

The probable mechanism for base-catalyzed hydrolysis is illustrated below with methyl acetate.



$$(1)\quad CH_3\overset{O}{\overset{\|}{C}}{-}OCH_3 + OH^- \rightleftharpoons CH_3\underset{OH}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}{-}OCH_3$$

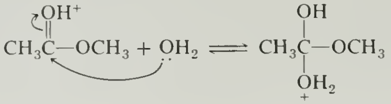
$$(2)\quad CH_3\underset{OH}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}{-}OCH_3 \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}{-}OH + CH_3O^-$$

$$(3)\quad CH_3\overset{O}{\overset{\|}{C}}{-}OH + CH_3O^- \longrightarrow CH_3\overset{O}{\overset{\|}{C}}{-}O^- + CH_3OH$$

In basic aqueous solution, two nucleophiles are present, H_2O and OH^-. As we saw above, H_2O is a poor nucleophile and therefore reacts slowly with the carbonyl carbon. On the other hand, OH^- is a much stronger nucleophile and adds more rapidly to the carbonyl carbon.

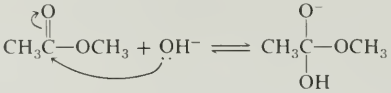
After addition has taken place, elimination of a nucleophile from the tetrahedral intermediate can occur. Elimination of hydroxide ion merely reverses the initial addition step. However, elimination of methoxide ion gives a new species—acetic acid. Since acetic acid is a weak acid and methoxide ion is a strong base, a rapid acid-base reaction then occurs, yielding acetate ion and methanol. Because of the great difference in acidity between acetic acid ($pK_a \approx 5$) and methanol ($pK_a \approx 16$), this last step is essentially irreversible (K for the last reaction $\approx 10^{11}$). Thus, basic hydrolysis of esters differs from acid-catalyzed hydrolysis in that the equilibrium constant for the overall reaction is very large, and it is sufficient to use only one equivalent of water in order for the reaction to proceed to completion.

It is interesting to compare the C—O bond-forming step in the acid-catalyzed and base-catalyzed mechanisms. In the former case, the "weak" nucleophile H_2O adds to the "strongly" electrophilic bond $\rangle C=OH^+$



$$CH_3\overset{\overset{OH^+}{\|}}{C}-OCH_3 + \ddot{O}H_2 \rightleftharpoons CH_3\underset{\underset{\overset{+}{O}H_2}{|}}{\overset{\overset{OH}{|}}{C}}-OCH_3$$

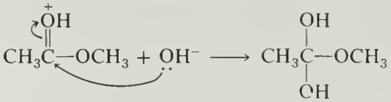
In the latter case, the "strong" nucleophile OH^- adds to the "weakly" electrophilic bond C=O



$$CH_3\overset{\overset{O}{\|}}{C}-OCH_3 + \ddot{O}H^- \rightleftharpoons CH_3\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}-OCH_3$$

Either case is better than the case where the "weak" nucleophile H_2O adds to the "weakly" electrophilic bond C=O.

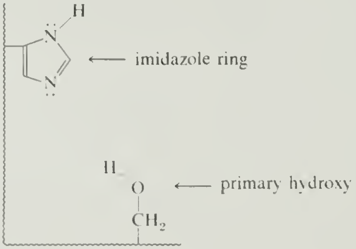
The most rapid hydrolysis would involve *both* acid and base catalysis.



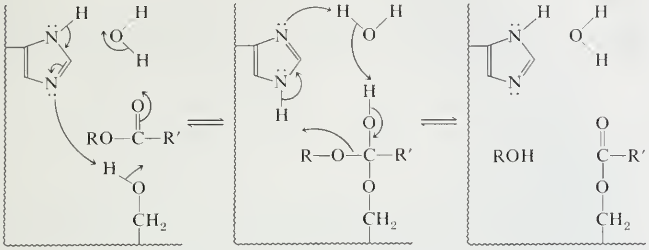
$$CH_3\overset{\overset{\overset{+}{O}H}{\|}}{C}-OCH_3 + \ddot{O}H^- \longrightarrow CH_3\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}-OCH_3$$

In aqueous solution, this mechanism is not observed for a simple reason. In acidic solution, where the concentration of $\rangle C=OH^+$ species is appreciable, the concentration of OH^- is very small. In basic solution, where the concentration of OH^- is appreciable, the concentration of $\rangle C=OH^+$ is low.

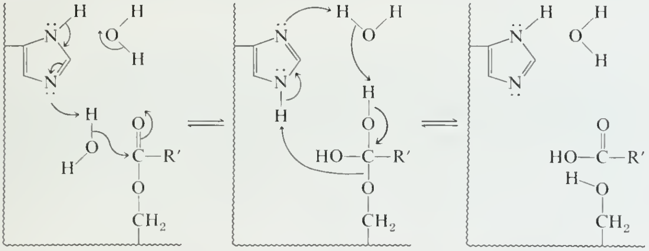
Certain **enzymes**, which catalyze the hydrolysis of esters and amides in living cells, appear to operate by precisely this type of mechanism. The enzyme **chymotrypsin** functions in the body as a catalyst for the hydrolysis of amide bonds. It also catalyzes the hydrolysis of esters. It is an extremely complicated molecule of high molecular weight. The structure of such enzymes will be considered in Chapter 28. For the present purpose, we need consider only two features of the chymotrypsin molecule. It is basically a polymer with many side chains extending from the main chain. Two of the side chains are a primary alcohol (belonging to the amino acid serine) and an imidazole ring (belonging to the amino acid histidine). We may abbreviate the structure of chymotrypsin as follows.



Because of the geometry of the chymotrypsin molecule, these two functional groups are held in close proximity. The way in which chymotrypsin is believed to catalyze ester hydrolysis is outlined schematically as follows.

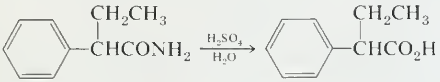


Note that the reaction is simultaneously acid- *and* base-catalyzed. As the nucleophile $—CH_2—O^-$ adds to the carbonyl carbon, it is being protonated by a water molecule. The water molecule does not become OH^- because it simultaneously is protonated by the imidazole ring proton. The ring also does not become negatively charged, as it accepts the proton from the primary hydroxy. The reaction is beautifully engineered so that no charged species are produced at all, yet a "good" nucleophile can add to a "strongly" electrophilic center. In the second step, the process reverses itself—almost. The only difference is that the imidazole proton is now transferred to the RO— oxygen, rather than to the serine oxygen. The result is a modified enzyme in which the serine hydroxy has been **acylated** and ROH is liberated. The hydrolysis is completed in an identical set of reactions, except that now a molecule of water slips in and occupies the space vacated when ROH diffuses out into the medium.



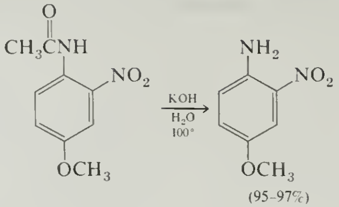
In the end, the enzyme is regenerated and can now move on and catalyze the hydrolysis of another ester molecule.

4. **AMIDES.** Amides react with water to give 1 mole of carboxylic acid and 1 mole of ammonia or amine. The reaction is catalyzed by acid or base. Amides undergo hydrolysis much more slowly than esters and therefore more vigorous conditions are normally required.



(88–90%)

A mixture of 600 g of α-phenylbutryamide, 1 liter of water, and 400 ml of conc. sulfuric acid is refluxed for 2 hr. After cooling the mixture and diluting with 1 liter of water, the oily organic layer is separated and distilled to yield 530–554 g of α-phenylbutyric acid, m.p. 42°.

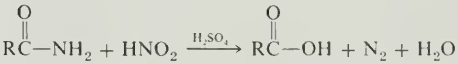


A mixture of 160 g of 2-nitro-4-methoxyacetanilide, 88 g of potassium hydroxide, and 170 ml of water is heated on a steam bath for 15 min. The mixture first becomes liquid and then sets to a thick, red paste. It is diluted with 250 ml of hot water, heated an additional 15 min, cooled to 5°C, and filtered to obtain 122–124 g of 2-nitro-4-methoxyaniline, m.p. 122.5–123°.

Both the acid- and base-catalyzed reactions are essentially irreversible. In the former case, ammonium ion is produced; in the latter case, a carboxylate anion is formed.

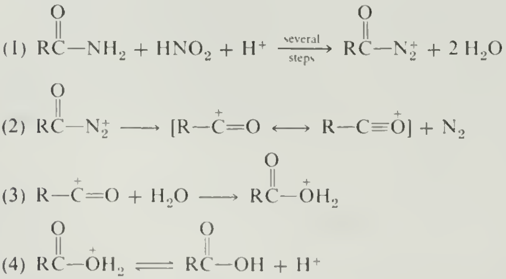
As we shall see later, proteins and peptides are important biological polymers containing many amide linkages. Hydrolysis of these amide linkages is one of the ways in which these biopolymers are degraded in living cells.

Because of the vigorous conditions required for the hydrolysis of amides, indirect methods for accomplishing the same result have been devised. One such method, applicable to primary amides, consists of treating the amide with nitrous acid.



$$R\overset{O}{\overset{\|}{C}}-NH_2 + HNO_2 \xrightarrow{H_2SO_4} R\overset{O}{\overset{\|}{C}}-OH + N_2 + H_2O$$

The mechanism of this reaction will be discussed in detail in Section 27.7.B, in connection with the chemistry of amines. In a series of steps, the nitrous acid converts the $—NH_2$ group of the amide into the grouping $—N_2^+$. The nucleophilic substitution reaction now occurs, with the leaving group being molecular nitrogen. Since N_2 is such a "good" leaving group, the substitution probably occurs by prior ionization to nitrogen and the acylium ion, which then reacts with water to give the carboxylic acid.



$$(1)\quad R\overset{O}{\overset{\|}{C}}-NH_2 + HNO_2 + H^+ \xrightarrow[\text{steps}]{\text{several}} R\overset{O}{\overset{\|}{C}}-N_2^+ + 2\,H_2O$$

$$(2)\quad R\overset{O}{\overset{\|}{C}}-N_2^+ \longrightarrow [R-\overset{+}{C}=O \longleftrightarrow R-C\equiv\overset{+}{O}] + N_2$$

$$(3)\quad R-\overset{+}{C}=O + H_2O \longrightarrow R\overset{O}{\overset{\|}{C}}-\overset{+}{O}H_2$$

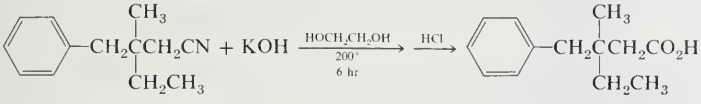
$$(4)\quad R\overset{O}{\overset{\|}{C}}-\overset{+}{O}H_2 \rightleftharpoons R\overset{O}{\overset{\|}{C}}-OH + H^+$$

5. **Nitriles.** Unlike the other types of compounds we have discussed in this chapter, nitriles do not contain the carbonyl group. They are considered to be

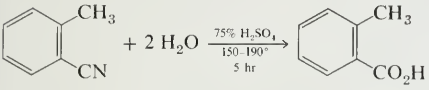
functional derivatives of carboxylic acids because exhaustive hydrolysis of the nitrile (cyano) group yields the carboxy group.

$$\mathrm{R{-}CN + H_2O \longrightarrow R{-}CO_2H + NH_3}$$

The actual conditions required for this hydrolysis, which proceeds by way of the intermediate amide, are quite severe.

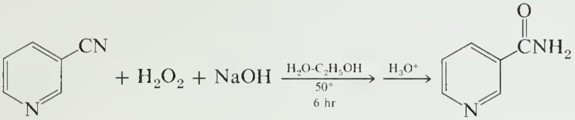


(91–93%)



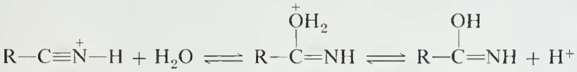
(80–89%)

Under appropriate conditions, the intermediate amide may be isolated. Reagents that have been used for this purpose include concentrated sulfuric acid at room temperature, aqueous sodium hydroxide, and aqueous sodium hydroxide containing 6–12% of hydrogen peroxide.



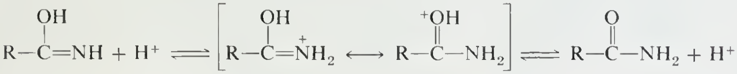
(88%)

The mechanism for hydrolysis of the nitrile grouping is probably similar to that observed in the hydrolysis of esters, amides, and acyl halides. The polarized C ≡ N triple bond is in many respects similar to a carbonyl group. Hydration of the neutral bond is extremely slow, but the poor nucleophile water adds easily to the conjugate acid.



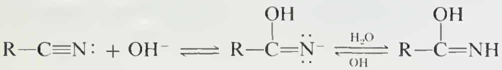
$$\mathrm{R{-}C{\equiv}\overset{+}{N}{-}H + H_2O \rightleftharpoons R{-}\overset{\overset{+}{O}H_2}{\overset{|}{C}}{=}NH \rightleftharpoons R{-}\overset{OH}{\overset{|}{C}}{=}NH + H^+}$$

The resulting neutral species is simply an unstable tautomer of a primary amide, which is then produced by a protonation-deprotonation sequence.



$$\mathrm{R{-}\overset{OH}{\overset{|}{C}}{=}NH + H^+ \rightleftharpoons \left[R{-}\overset{OH}{\overset{|}{C}}{=}\overset{+}{N}H_2 \longleftrightarrow R{-}\overset{{}^{+}OH}{\overset{\|}{C}}{-}NH_2\right] \rightleftharpoons R{-}\overset{O}{\overset{\|}{C}}{-}NH_2 + H^+}$$

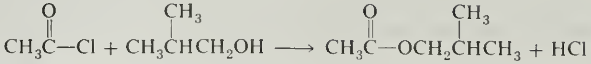
In a similar manner, nucleophilic hydroxide ion will add to the neutral nitrile grouping to yield, after protonation, the unstable amide tautomer.



$$\mathrm{R{-}C{\equiv}N\colon + OH^- \rightleftharpoons R{-}\overset{OH}{\overset{|}{C}}{=}\ddot{\underset{\cdot\cdot}{N}}^- \underset{OH^-}{\overset{H_2O}{\rightleftharpoons}} R{-}\overset{OH}{\overset{|}{C}}{=}NH}$$

B. *Reaction with Alcohols*

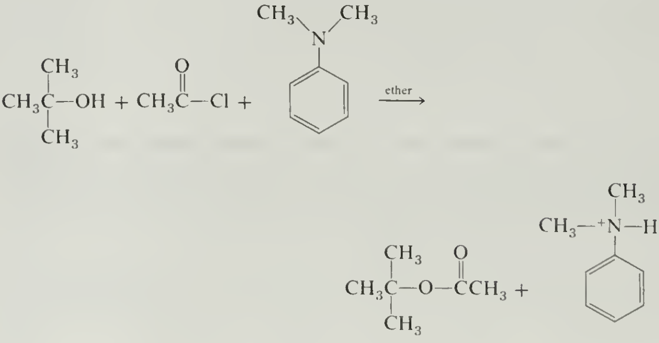
1. **ACYL HALIDES.** Acyl halides react with alcohols to yield esters and the corresponding hydrohalic acid.



$$CH_3\overset{\overset{O}{\|}}{C}-Cl + CH_3\overset{\overset{CH_3}{|}}{C}HCH_2OH \longrightarrow CH_3\overset{\overset{O}{\|}}{C}-OCH_2\overset{\overset{CH_3}{|}}{C}HCH_3 + HCl$$

acetyl chloride — isobutyl alcohol — isobutyl acetate

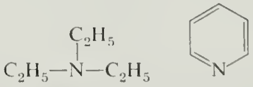
Such reactions are usually run in the presence of some base, which serves to neutralize the HX formed in the reaction.



(63–68%)

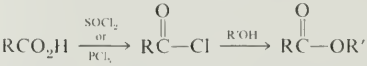
To a refluxing solution of 114 g of *t*-butyl alcohol and 202 g of N,N-dimethylaniline in 200 ml of dry ether is added dropwise 124 g of acetyl chloride. After addition of all the acyl chloride, the mixture is cooled in an ice bath, and the solid N,N-dimethylaniline hydrochloride is removed by filtration. The ether layer is extracted with aqueous sulfuric acid to remove excess amine, and worked up to yield 110–119 g of *t*-butyl acetate, b.p. 95–98°.

Other bases commonly used for this purpose are triethylamine and pyridine.



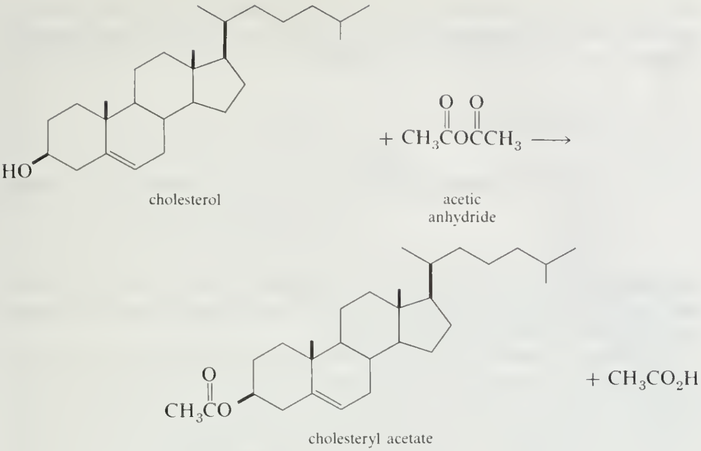
triethylamine — pyridine

Since acyl halides are readily available from the corresponding carboxylic acids (Section 17.7.C), the following sequence is often used for the preparation of esters.



$$RCO_2H \xrightarrow[PCl_5]{SOCl_2 \text{ or}} R\overset{\overset{O}{\|}}{C}-Cl \xrightarrow{R'OH} R\overset{\overset{O}{\|}}{C}-OR'$$

2. **ANHYDRIDES.** Anhydrides also react readily with alcohols. The product is 1 mole of ester and 1 mole of the carboxylic acid corresponding to the anhydride used.


cholesterol

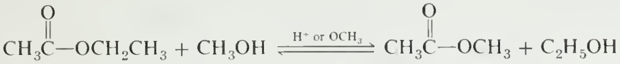
acetic anhydride

cholesteryl acetate

A mixture of 5 g of cholesterol and 7.5 ml of acetic anhydride is boiled for 1 hr. The mixture is cooled and filtered to yield 5 g of cholesteryl acetate, m.p. 114–115°.

The mechanism of the reaction is the same as that for the reaction of an alcohol with an acyl halide; the leaving group in this case is the carboxylate anion rather than a halide ion.

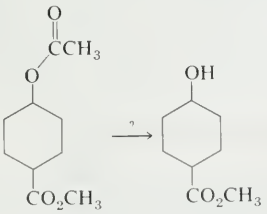
3. Esters. Esters undergo reaction with alcohols to give a new ester and a new alcohol. The reaction is catalyzed by either acid or base and is called **transesterification.**



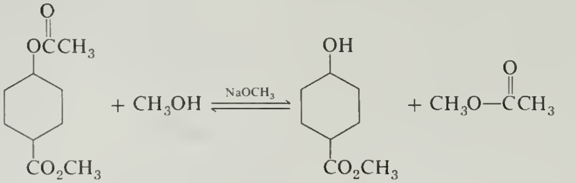
$$CH_3\overset{\overset{O}{\|}}{C}-OCH_2CH_3 + CH_3OH \xrightleftharpoons{H^+ \text{ or } OCH_3} CH_3\overset{\overset{O}{\|}}{C}-OCH_3 + C_2H_5OH$$

The mechanism for the transesterification process involves steps identical to those given for acid-catalyzed and base-catalyzed ester hydrolysis, with one significant exception. In base-catalyzed transesterification, step (3) of the mechanism on page 475 cannot occur, because the free carboxylic acid is never formed. Thus, base-catalyzed transesterification is subject to the same equilibrium conditions that apply to the acid-catalyzed reaction.

Transesterification can be a rather useful preparative method in certain cases. Suppose, for example, that it is desirable to accomplish the following transformation:

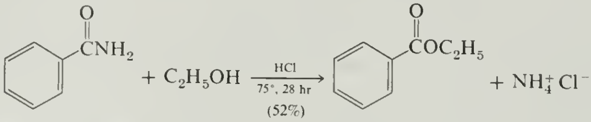


Selective hydrolysis of the acetate linkage would almost surely fail because both ester groups would hydrolyze at comparable rates. However, if the diester is dissolved in anhydrous methanol and a catalytic amount of sodium methoxide is added, equilibrium (18-6) will be established.


(18-6)

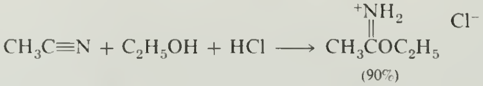
Since methanol is the solvent, and hence is present in large excess, the reaction will proceed to practical completion. Thus, the equivalent of selective hydrolysis can be achieved without using water at all.

4. **Amides.** Amides react with alcohols under acidic conditions to yield the corresponding ester and an ammonium salt.



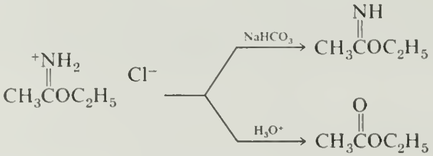
The base-catalyzed equivalent of this process requires such drastic conditions that it is rarely encountered.

5. **Nitriles.** If anhydrous HCl is added to a mixture of a nitrile and an alcohol, acid-catalyzed nucleophilic addition of the alcohol to the C≡N bond occurs. The product is the hydrochloride salt of an **imino ester**, the nitrogen analog of an ester.



$$CH_3C{\equiv}N + C_2H_5OH + HCl \longrightarrow \underset{(90\%)}{CH_3\overset{\overset{+}{N}H_2}{\overset{\|}{C}}OC_2H_5}\quad Cl^-$$

If the resulting salt is treated with a weak base such as sodium bicarbonate, the neutral imino ester may be isolated. Treatment of the imino ester with dilute aqueous acid causes rapid hydrolysis to the corresponding ester.

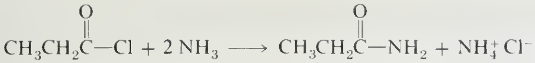


$$CH_3\overset{\overset{+}{N}H_2}{\overset{\|}{C}}OC_2H_5\ Cl^- \xrightarrow{NaHCO_3} CH_3\overset{NH}{\overset{\|}{C}}OC_2H_5$$

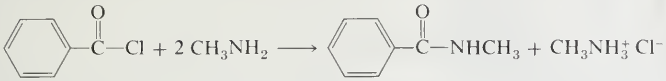
$$CH_3\overset{\overset{+}{N}H_2}{\overset{\|}{C}}OC_2H_5\ Cl^- \xrightarrow{H_3O^+} CH_3\overset{O}{\overset{\|}{C}}OC_2H_5$$

C. *Reaction with Amines and Ammonia*

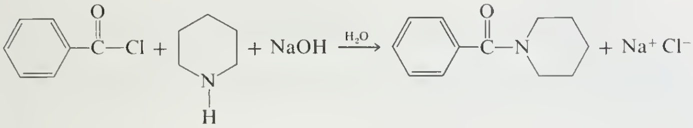
1. **Acyl Halides.** Acyl halides react with ammonia or amines that have at least one hydrogen bound to nitrogen to give amides. Since one equivalent of hydrogen chloride is formed in the reaction, two equivalents of ammonia or the amine must be used.



$$CH_3CH_2\overset{\overset{O}{\|}}{C}-Cl + 2\,NH_3 \longrightarrow CH_3CH_2\overset{\overset{O}{\|}}{C}-NH_2 + NH_4^+\,Cl^-$$

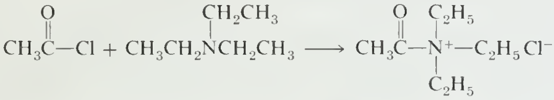


Alternatively, sodium hydroxide may be used to neutralize the HCl in a procedure known as the **Schotten-Baumann** method.



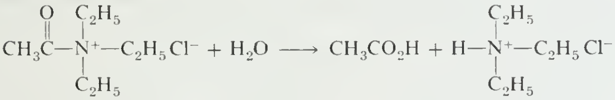
The acyl chloride used is generally insoluble in water and reacts slowly with the sodium hydroxide. The organic amine, however, dissolves in the acid chloride and reacts rapidly. The amine hydrochloride also produced dissolves in the aqueous phase and reacts rapidly with hydroxide ion to regenerate the amine.

Amines that contain three alkyl groups bound to nitrogen cannot react with acyl halides to give amides, since they have no replaceable hydrogen. However, such amines do react with acyl halides, giving highly reactive **acylammonium salts.**

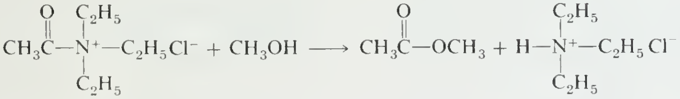


$$CH_3\overset{\overset{O}{\|}}{C}-Cl + CH_3CH_2\overset{\overset{CH_2CH_3}{|}}{N}CH_2CH_3 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_2H_5}{|}}{N^+}}-C_2H_5\,Cl^-$$

Acylammonium salts are difficult to isolate because they are so extremely reactive. They react instantaneously with water, alcohols, or other nucleophilic species.



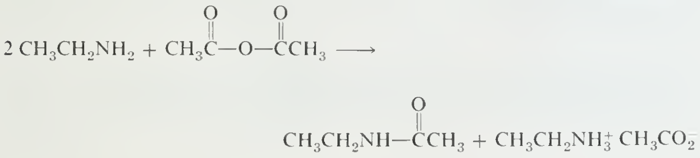
$$CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_2H_5}{|}}{N^+}}-C_2H_5\,Cl^- + H_2O \longrightarrow CH_3CO_2H + H-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_2H_5}{|}}{N^+}}-C_2H_5\,Cl^-$$



$$CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_2H_5}{|}}{N^+}}-C_2H_5\,Cl^- + CH_3OH \longrightarrow CH_3\overset{\overset{O}{\|}}{C}-OCH_3 + H-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_2H_5}{|}}{N^+}}-C_2H_5\,Cl^-$$

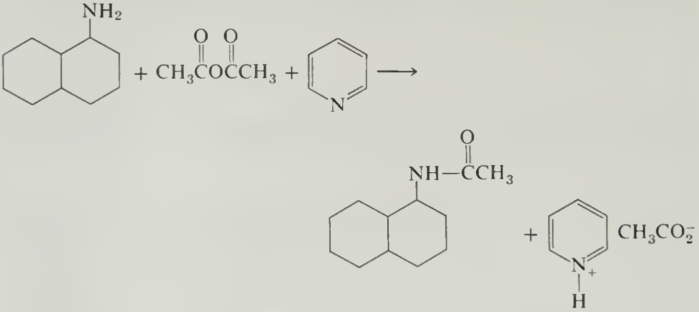
In fact, it seems likely that such species are intermediates in esterification reactions where triethylamine or pyridine is used to neutralize HCl (page 480).

2. ANHYDRIDES. The reaction of ammonia and amines with anhydrides follows a similar course; the products are 1 mole of amide and 1 mole of carboxylic acid. Since the liberated acid reacts to form a salt with the ammonia or the amine, it is necessary to employ an excess of that reactant.

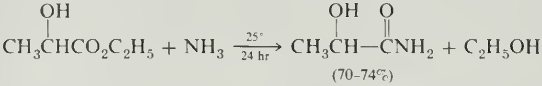


$$2\,CH_3CH_2NH_2 + CH_3\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}CH_3 \longrightarrow CH_3CH_2NH-\overset{\overset{O}{\|}}{C}CH_3 + CH_3CH_2NH_3^+\,CH_3CO_2^-$$

As in the analogous reaction of amines with acyl halides, one may carry out the reaction in the presence of one equivalent of tertiary amine.



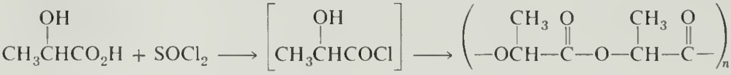
3. ESTERS. Esters also react with ammonia and amines to yield the corresponding amide and the alcohol of the ester. The reaction is synthetically useful in cases where the corresponding acyl halide or anhydride is unstable or not easily available. An interesting example of such a case is



$$CH_3\overset{OH}{\overset{|}{C}}HCO_2C_2H_5 + NH_3 \xrightarrow[24\text{ hr}]{25^\circ} CH_3\overset{OH}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}NH_2 + C_2H_5OH$$

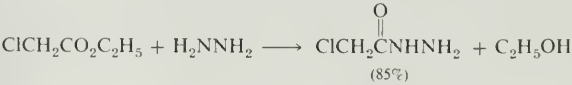
(70–74%)

In this case, the acyl halide method for preparing the amide may not be used. Since the molecule contains an OH group, which will react rapidly with an acyl halide, an attempt to prepare the acyl halide would lead to a polymer.



$$CH_3\overset{OH}{\overset{|}{C}}HCO_2H + SOCl_2 \longrightarrow \left[CH_3\overset{OH}{\overset{|}{C}}HCOCl\right] \longrightarrow \left(-O\overset{CH_3}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}-O-\overset{CH_3}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}-\right)_n$$

Similar reactions occur with other nitrogen nucleophiles.

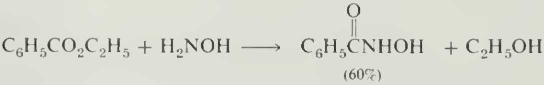


$$ClCH_2CO_2C_2H_5 + H_2NNH_2 \longrightarrow ClCH_2\overset{O}{\overset{\|}{C}}NHNH_2 + C_2H_5OH$$

(85%)

ethyl chloroacetate

chloroacetyl hydrazide



$$C_6H_5CO_2C_2H_5 + H_2NOH \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}NHOH + C_2H_5OH$$

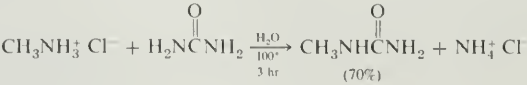
(60%)

ethyl benzoate

hydroxylamine

N-hydroxybenzamide

4. AMIDES. The exchange of one amino group for another in an amide **(transamination)** is known, but the reaction is rarely encountered. One example of a reaction of this type is



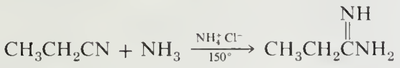
$$CH_3NH_3^+\,Cl^- + H_2N\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[100^\circ,\ 3\text{ hr}]{H_2O} CH_3NH\overset{O}{\overset{\|}{C}}NH_2 + NH_4^+\,Cl^-$$

(70%)

urea

methylurea

5. **Nitriles.** Nitriles undergo acid-catalyzed addition of ammonia. The product is an **amidine.**



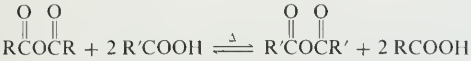
$$CH_3CH_2CN + NH_3 \underset{400\text{ psi}}{\xrightarrow[150°]{NH_4^+Cl^-}} CH_3CH_2\overset{NH}{\overset{\|}{C}}NH_2$$

(80%)

The reaction is not generally useful with amines. Only a few examples are known, and these require rather special conditions.

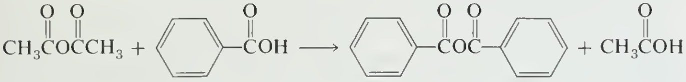
D. *Reaction with Carboxylic Acids and Carboxylate Salts*

A mixture of an acid anhydride and a carboxylic acid undergoes equilibration when heated.



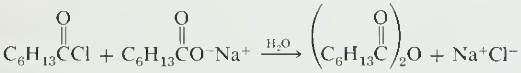
$$R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R + 2\,R'COOH \overset{\Delta}{\rightleftharpoons} R'\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R' + 2\,RCOOH$$

The reaction is preparatively useful when the anhydride is acetic anhydride. In this case, acetic acid can be distilled off as it is formed because it is the most volatile component in the equilibrium.



b.p. 142° — benzoic acid — (72–74%) benzoic anhydride — b.p. 117°

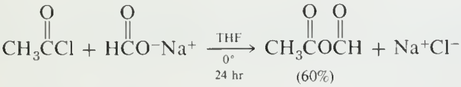
The only carboxylic acid derivatives that undergo a useful reaction with carboxylate salts are acyl halides. The product is an anhydride.



$$C_6H_{13}\overset{O}{\overset{\|}{C}}Cl + C_6H_{13}\overset{O}{\overset{\|}{C}}O^-Na^+ \xrightarrow{H_2O} \left(C_6H_{13}\overset{O}{\overset{\|}{C}}\right)_2O + Na^+Cl^-$$

heptanoyl chloride — sodium heptanoate — (60%) heptanoic anhydride

The procedure may also be used to prepare unsymmetrical anhydrides.

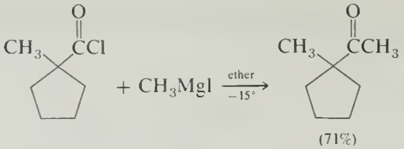


$$CH_3\overset{O}{\overset{\|}{C}}Cl + H\overset{O}{\overset{\|}{C}}O^-Na^+ \underset{24\text{ hr}}{\xrightarrow[0°]{THF}} CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}H + Na^+Cl^-$$

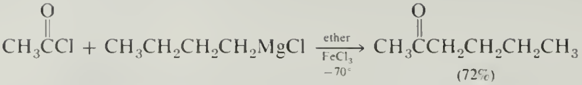
(60%) acetic formic anhydride

E. *Reaction with Organometallic Compounds*

1. **Acyl Halides.** Acyl halides react with various organometallic reagents to give ketones. When using a Grignard reagent, best results are obtained if the reaction is carried out at low temperature. Anhydrous ferric chloride is often added as a catalyst.



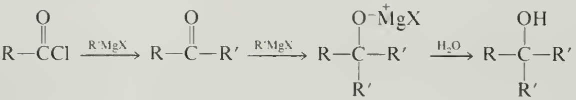
(71%)



$$CH_3\overset{O}{\overset{\|}{C}}Cl + CH_3CH_2CH_2CH_2MgCl \xrightarrow[\substack{FeCl_3 \\ -70^\circ}]{ether} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_3$$

(72%)

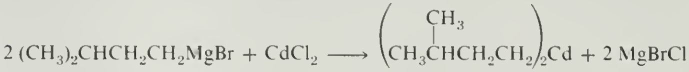
If excess Grignard reagent is used, the product ketone may react further, giving a tertiary alcohol after hydrolysis.



$$R{-}\overset{O}{\overset{\|}{C}}Cl \xrightarrow{R'MgX} R{-}\overset{O}{\overset{\|}{C}}{-}R' \xrightarrow{R'MgX} R{-}\underset{R'}{\underset{|}{\overset{O^-\overset{+}{M}gX}{\overset{|}{C}}}}{-}R' \xrightarrow{H_2O} R{-}\underset{R'}{\underset{|}{\overset{OH}{\overset{|}{C}}}}{-}R'$$

In fact, the reaction is a useful method for preparing ketones only because acyl halides are so very reactive.

Some of the less reactive organometallic compounds still react rapidly with acyl halides, but react with ketones only sluggishly or not at all. Such is the case with organocadmium compounds and with lithium dialkylcuprates. Organocadmium compounds have been particularly useful for converting acyl halides into ketones. The organocadmium compounds are prepared by adding anhydrous cadmium chloride to an ether solution of the corresponding Grignard reagent (Section 9.4.B).

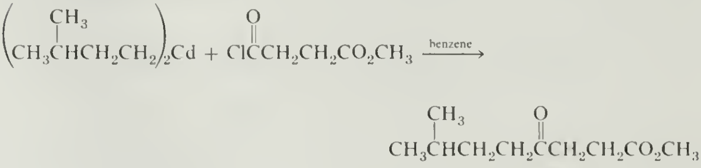


$$2\,(CH_3)_2CHCH_2CH_2MgBr + CdCl_2 \longrightarrow \left(CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\right)_2Cd + 2\,MgBrCl$$

3-methylbutylmagnesium bromide

di-(3-methylbutyl)cadmium

Both alkyl groups of the organocadmium compound are used in the reaction. Since the reagent does not react at all with the carbonyl group of esters or amides, such functional groups may be present in the substrate molecule.



$$\left(CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\right)_2Cd + Cl\overset{O}{\overset{\|}{C}}CH_2CH_2CO_2CH_3 \xrightarrow{benzene} CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CO_2CH_3$$

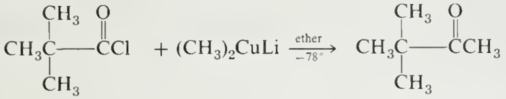
(75%)

The organocadmium procedure only works when the alkyl group of the organometallic is primary, vinyl, or phenyl. Secondary and tertiary alkylcadmium reagents fail, probably because of thermal instability of these organocadmium compounds.

An alternative procedure that has been introduced recently employs a lithium organocuprate, which is obtained by treating an organolithium compound with cuprous iodide in ether (Section 9.5.D).

$$2\ CH_3Li + CuI \xrightarrow{\text{ether}} LiCu(CH_3)_2 + LiI$$

The cuprate reacts rapidly with acyl halides and aldehydes, slowly with ketones, and not at all with esters, amides, and nitriles.

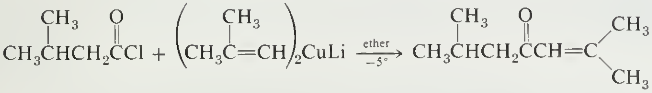


$$(CH_3)_3CCOCl + (CH_3)_2CuLi \xrightarrow[-78^\circ]{\text{ether}} (CH_3)_3CCOCH_3$$

(60%)

2,2-dimethylpropanoyl chloride (pivaloyl chloride)

3,3-dimethyl-2-butanone



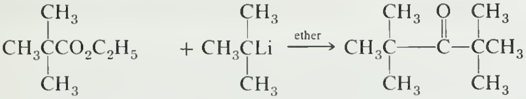
$$CH_3CH(CH_3)CH_2COCl + \left(CH_3C(CH_3){=}CH\right)_2CuLi \xrightarrow[-5^\circ]{\text{ether}} CH_3CH(CH_3)CH_2COCH{=}C(CH_3)_2$$

(70%)

3-methylbutanoyl chloride

2,6-dimethylhept-2-en-4-one

2. **Esters.** Since esters are generally less reactive than ketones, the preparation of ketones by nucleophilic substitution on an ester is generally unsatisfactory. The method is only useful when the product ketone is sterically hindered.



$$(CH_3)_3CCO_2C_2H_5 + (CH_3)_3CLi \xrightarrow{\text{ether}} (CH_3)_3CCOC(CH_3)_3$$

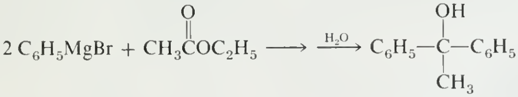
(80%)

ethyl α,α-dimethylpropionate

di-*t*-butyl ketone

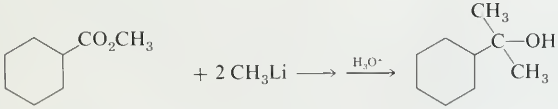
In less hindered cases, the only isolable product is the tertiary alcohol.

The reaction of esters with two equivalents of a Grignard reagent or an alkyllithium is a useful method for the synthesis of tertiary alcohols in which two of the alkyl groups are equivalent.



$$2\ C_6H_5MgBr + CH_3COOC_2H_5 \longrightarrow \xrightarrow{H_2O} C_6H_5{-}C(OH)(CH_3){-}C_6H_5$$

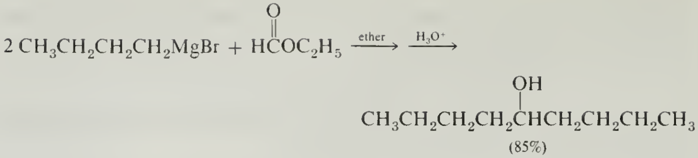
1,1-diphenylethanol



methyl cyclohexanecarboxylate

2-cyclohexyl-2-propanol

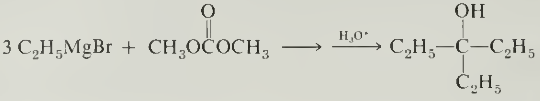
If an ester of formic acid is used, the product is a secondary alcohol.



$$2\,CH_3CH_2CH_2CH_2MgBr + H\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightarrow{\text{ether}} \xrightarrow{H_3O^+} CH_3CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_2CH_2CH_2CH_3$$

(85%)
5-nonanol

Carbonate esters yield tertiary alcohols in which all three of the carbinol alkyl groups come from the organometallic reagent.

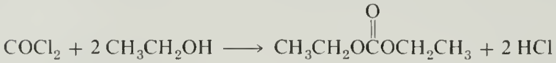


$$3\,C_2H_5MgBr + CH_3O\overset{O}{\overset{\|}{C}}OCH_3 \longrightarrow \xrightarrow{H_3O^+} C_2H_5-\overset{OH}{\overset{|}{\underset{C_2H_5}{\underset{|}{C}}}}-C_2H_5$$

(85%)

dimethyl carbonate triethylcarbinol

Dialkyl carbonates are generally prepared by reaction of alcohols with phosgene, $COCl_2$.



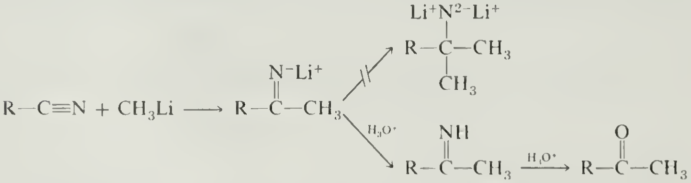
$$COCl_2 + 2\,CH_3CH_2OH \longrightarrow CH_3CH_2O\overset{O}{\overset{\|}{C}}OCH_2CH_3 + 2\,HCl$$

Phosgene is a highly toxic colorless gas, b.p. 7.6°, having a distinctive odor. It was used in World War I as a war gas. This compound is the diacid chloride of carbonic acid and reacts accordingly. It is hydrolyzed by water to give carbon dioxide and HCl:

$$COCl_2 + 2\,H_2O \longrightarrow 2\,HCl + [CO(OH)_2] \longrightarrow CO_2 + H_2O$$

Dimethyl carbonate is a colorless liquid, b.p. 90°, and is available commercially.

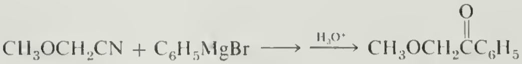
3. **Nitriles.** Nitriles undergo a synthetically useful reaction with Grignard reagents or alkyllithium reagents. The initial product of addition of the organometallic to the triple bond is the salt of an imine (Section 15.7.C). This imine salt, even though it still has a C=N double bond, does not easily react further with the organometallic reagent because the resulting product would be a species with *two* negative charges on the same atom. When dilute acid is added at the end of the reaction, the imine salt is protonated to yield the imine, which undergoes rapid hydrolysis to the corresponding ketone.



$$R-C\equiv N + CH_3Li \longrightarrow R-\overset{N^-Li^+}{\overset{\|}{C}}-CH_3 \;\not\longrightarrow\; R-\overset{Li^+N^{2-}Li^+}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_3$$

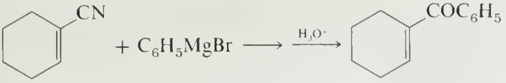
$$R-\overset{N^-Li^+}{\overset{\|}{C}}-CH_3 \xrightarrow{H_3O^+} R-\overset{NH}{\overset{\|}{C}}-CH_3 \xrightarrow{H_3O^+} R-\overset{O}{\overset{\|}{C}}-CH_3$$

The method serves as a convenient method for the preparation of ketones from nitriles. With acetonitrile itself higher yields result when ether is replaced by benzene as the solvent. Some specific examples are

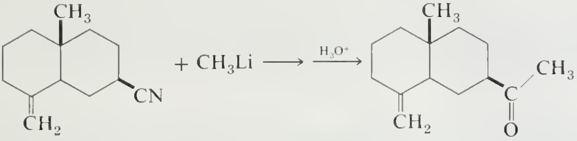


$$CH_3OCH_2CN + C_6H_5MgBr \longrightarrow \xrightarrow{H_3O^+} CH_3OCH_2\overset{O}{\overset{\|}{C}}C_6H_5$$

(78%)



(73%)



(91%)

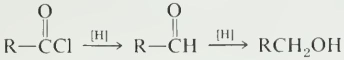
$$CH_3CN + CH_3(CH_2)_4MgBr \xrightarrow{\text{benzene}} \xrightarrow{H_3O^+} \underset{(44\%)}{CH_3CO(CH_2)_4CH_3}$$

18.10 Reduction

Carboxylic acids and their derivatives may be reduced in a variety of ways. We shall treat these reductions by compound class.

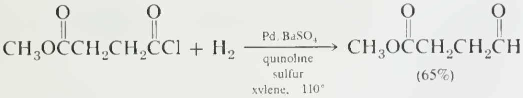
A. *Acyl Halides*

Acyl halides may be reduced to aldehydes or to primary alcohols.

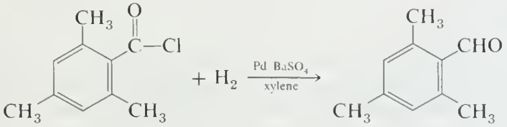


$$R-\overset{\overset{\displaystyle O}{\|}}{C}Cl \xrightarrow{[H]} R-\overset{\overset{\displaystyle O}{\|}}{C}H \xrightarrow{[H]} RCH_2OH$$

The selective reduction of an acyl halide is one of the most useful ways of preparing aldehydes. Such selective reduction is possible because acyl halides are generally more reactive than the product aldehydes. One procedure for accomplishing the selective reduction is catalytic hydrogenation; the method is called a **Rosenmund reduction.** The acyl halide is hydrogenated in the presence of a catalyst such as palladium deposited on barium sulfate. As in the reduction of alkynes to alkenes, a "regulator" or "catalyst poison" (page 311) is frequently added in order to moderate the effectiveness of the catalyst and thereby inhibit subsequent reduction of the product aldehyde.



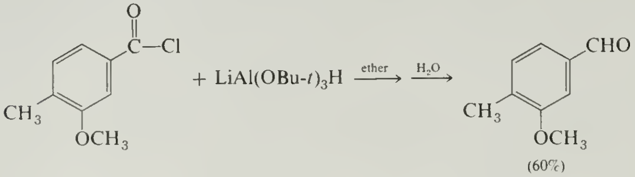
$$CH_3O\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}Cl + H_2 \xrightarrow[\substack{\text{quinoline}\\ \text{sulfur}\\ \text{xylene, } 110^\circ}]{\text{Pd, BaSO}_4} \underset{(65\%)}{CH_3O\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}H}$$



(80%)

To a solution of 90 g of 2,4,6-trimethylbenzoyl chloride in 270 g of xylene is added 20 g of 5% palladium on barium sulfate. The mixture is refluxed while a stream of hydrogen is passed through it. After no more hydrogen chloride is evolved, the catalyst is removed by filtration and the solvent is evaporated to obtain 60 g (80%) of 2,4,6-trimethylbenzaldehyde.

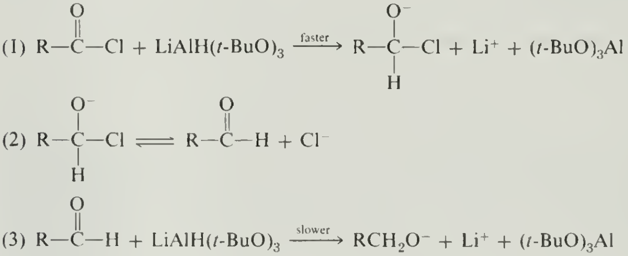
Another reagent that has found use for the selective reduction of an acyl halide to an aldehyde is lithium tri-*t*-butoxyaluminum hydride, $LiAl(OBu\text{-}t)_3H$.



In general, acyl halides are reduced more rapidly than aldehydes. However, lithium aluminum hydride is so extremely reactive that a selective reduction is difficult to accomplish. The tri-*t*-butoxy derivative, prepared by treating the hydride with three equivalents of *t*-butyl alcohol in ether, is less reactive, and therefore, more selective.

$$LiAlH_4 + 3t\text{-}C_4H_9OH \longrightarrow Li(t\text{-}C_4H_9O)_3AlH + 3H_2$$

If excess reducing agent is used, the product aldehyde is reduced further to a primary alcohol.

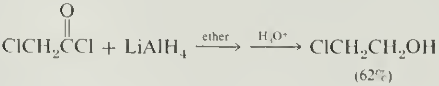


$$\text{(1)}\quad R-\overset{\overset{O}{\|}}{C}-Cl + LiAlH(t\text{-}BuO)_3 \xrightarrow{\text{faster}} R-\underset{H}{\overset{O^-}{C}}-Cl + Li^+ + (t\text{-}BuO)_3Al$$

$$\text{(2)}\quad R-\underset{H}{\overset{O^-}{C}}-Cl \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-H + Cl^-$$

$$\text{(3)}\quad R-\overset{\overset{O}{\|}}{C}-H + LiAlH(t\text{-}BuO)_3 \xrightarrow{\text{slower}} RCH_2O^- + Li^+ + (t\text{-}BuO)_3Al$$

With the more reactive lithium aluminum hydride, it is difficult to achieve selectivity, but the primary alcohol may easily be obtained.



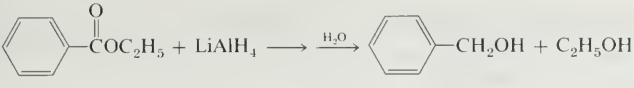
$$ClCH_2\overset{\overset{O}{\|}}{C}Cl + LiAlH_4 \xrightarrow{\text{ether}} \xrightarrow{H_3O^+} ClCH_2CH_2OH \quad (62\%)$$

chloroacetyl chloride

2-chloroethanol

B. *Esters*

Since esters are generally less reactive than aldehydes, they cannot be selectively reduced to the aldehyde stage. However, the reduction of an ester to a primary alcohol is an important preparative method. The most generally used reducing agents are lithium aluminum hydride and lithium borohydride.



(90%)

$$CH_3(CH_2)_{14}CO_2CH_2CH_2CH_2CH_3 + LiBH_4 \xrightarrow[\Delta]{THF} \xrightarrow{H_2O} CH_3(CH_2)_{15}OH + CH_3CH_2CH_2CH_2OH$$

(95%)

Lithium borohydride, $LiBH_4$, is a white solid, m.p. 284°, which is extremely hydroscopic. It is prepared by the reaction of sodium borohydride (page 284) with lithium chloride in ethanol.

$$NaBH_4 + LiCl \longrightarrow LiBH_4 + NaCl$$

It is a more reactive reducing agent than sodium borohydride but is less reactive than lithium aluminum hydride. It is much more soluble in ether (4 g per 100 ml) than is sodium borohydride.

Esters are also reduced by sodium in ethanol (the **Bouveault-Blanc reaction**). Before the discovery of lithium aluminum hydride, this was the most common laboratory method for reducing esters, and it is still an important method for large-scale preparations where reagent cost is a concern.

$$n\text{-}C_{11}H_{23}CO_2C_2H_5 + Na \xrightarrow[\Delta]{C_2H_5OH} n\text{-}C_{11}H_{23}CH_2OH + C_2H_5OH$$

ethyl dodecanoate

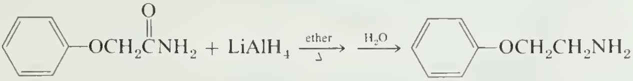
(65–75%)
1-dodecanol

The reaction mechanism is not known in detail, but undoubtedly involves electron transfer from sodium to the carbonyl group as a first step. The reaction is *not* a reduction by hydrogen liberated from the reaction of sodium with ethanol.

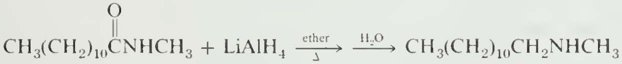
For large-scale or industrial reaction, catalytic hydrogenation at high temperature and pressure is often used.

C. *Amides*

The reduction of amides can give either amines or aldehydes. If an amide is refluxed with lithium aluminum hydride in ether or THF, the corresponding amine is produced.



(80%)

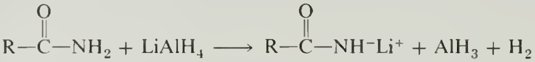


$$CH_3(CH_2)_{10}\overset{\overset{\large O}{\|}}{C}NHCH_3 + LiAlH_4 \xrightarrow[\Delta]{ether} \xrightarrow{H_2O} CH_3(CH_2)_{10}CH_2NHCH_3$$

(81–95%)

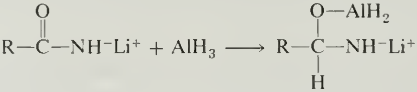
A solution of 38 g of lithium aluminum hydride in 1800 ml of dry ether is placed in a 5-liter three-necked flask equipped with a condenser and a mechanical stirrer. The solution is gently refluxed while 160 g of N-methyldodecanamide is slowly added over a period of 3 hr. The mixture is refluxed an additional 2 hr, then stirred overnight. The reaction mixture is worked up by the addition of 82 ml of water. After filtering away the solid aluminum and lithium salts, the ether is evaporated and the residue is distilled to yield 121-142 g of N-methyldodecylamine.

Although the exact mechanism of this reaction has not been elucidated, the first step is probably reaction of the strongly basic $LiAlH_4$ with the weakly acidic NH bond, giving the lithium salt of the amide.



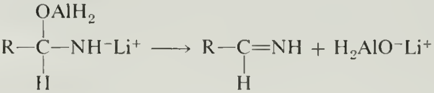
$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2 + LiAlH_4 \longrightarrow R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH^-Li^+ + AlH_3 + H_2$$

Aluminum hydride may then add to the carbonyl group.



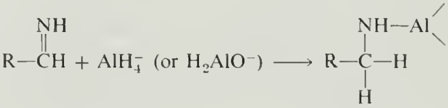
$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH^-Li^+ + AlH_3 \longrightarrow R{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle O{-}AlH_2}{|}}{C}}{-}NH^-Li^+$$

This tetrahedral intermediate may decompose by elimination of either $LiNH^-$ or H_2AlO^-. The latter species is actually not a bad leaving group (recall that aluminum is an amphoteric metal; H_3AlO_3 is a protonic acid).



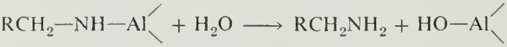
$$R{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle OAlH_2}{|}}{C}}{-}NH^-Li^+ \longrightarrow R{-}\underset{\underset{\displaystyle H}{|}}{C}{=}NH + H_2AlO^-Li^+$$

The resulting imine is now reduced by another hydride (from AlH_4^- or H_2AlO^-).



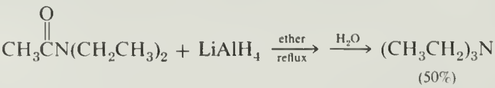
$$R{-}\overset{\overset{\displaystyle NH}{\|}}{C}H + AlH_4^- \text{ (or } H_2AlO^-) \longrightarrow R{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle NH{-}Al\langle}{|}}{C}}{-}H$$

Upon aqueous work-up, the N—Al bond is hydrolyzed to liberate the amine.



$$RCH_2{-}NH{-}Al\langle + H_2O \longrightarrow RCH_2NH_2 + HO{-}Al\langle$$

N,N-Dialkylamides may also be reduced to amines by lithium aluminum hydride.

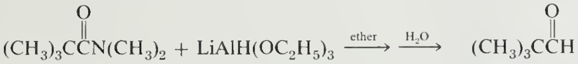


$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}N(CH_2CH_3)_2 + LiAlH_4 \xrightarrow[\text{reflux}]{\text{ether}} \xrightarrow{H_2O} \underset{(50\%)}{(CH_3CH_2)_3N}$$

N,N-diethylacetamide triethylamine

With disubstituted amides, the reduction may generally be controlled so that the aldehyde may be obtained. This occurs when the initial tetrahedral intermediate is sufficiently stable so that it survives until all of the hydride has been consumed. If one wishes to prepare an aldehyde in this manner, it is necessary to keep the amide in excess by slowly adding the reducing agent to it. Several modified hydrides have been used for this purpose. One reagent that is particularly useful with simple dimethylamides is lithium triethoxyaluminohydride, prepared *in situ* by the reaction of three equivalents of ethanol with one equivalent of lithium aluminum hydride.

$$LiAlH_4 + 3\,C_2H_5OH \xrightarrow{ether} LiAlH(OC_2H_5)_3 + 3\,H_2$$

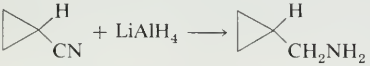


$$(CH_3)_3C\overset{O}{\overset{\|}{C}}N(CH_3)_2 + LiAlH(OC_2H_5)_3 \xrightarrow{ether} \xrightarrow{H_2O} (CH_3)_3C\overset{O}{\overset{\|}{C}}H$$

(88%)
2,2-dimethylpropanal
pivalaldehyde

D. *Nitriles*

The C≡N triple bond in nitriles is successfully reduced by a number of reagents. The most generally useful methods are lithium aluminum hydride reduction and catalytic hydrogenation.



(79%)

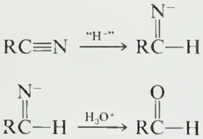
$$CH_3(CH_2)_{11}CN + LiAlH_4 \longrightarrow CH_3(CH_2)_{12}NH_2$$

(90%)

$$C_6H_5CH_2CN + 2\,H_2 \xrightarrow[\substack{120^\circ \\ 2000\text{ psi} \\ NH_3}]{Ni} C_6H_5CH_2CH_2NH_2$$

(83–87%)

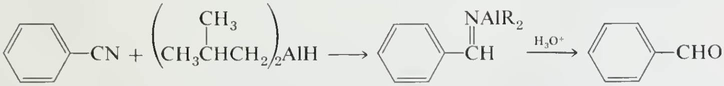
If the reduction is carried out under carefully controlled conditions, the initially formed imine salt may often be obtained. Hydrolysis of this salt gives the corresponding aldehyde.



$$RC{\equiv}N \xrightarrow{\text{“}H^-\text{”}} R\overset{N^-}{\overset{\|}{C}}{-}H$$

$$R\overset{N^-}{\overset{\|}{C}}{-}H \xrightarrow{H_3O^+} R\overset{O}{\overset{\|}{C}}{-}H$$

A particularly useful reagent for this purpose is diisobutylaluminum hydride (DIBAL).



(90%)

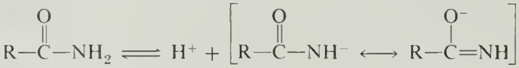
benzonitrile DIBAL benzaldehyde

Diisobutylaluminum hydride, DIBAL, is a clear, water-white liquid that boils at 140° at 4 torr. Like many other alkylaluminum and alkylboron compounds, it is flammable in air. It is supplied commercially in small tanks or lecture bottles. It is normally used as a benzene solution under an inert atmosphere such as nitrogen or argon.

18.11
Reactions of Amides which Occur on Nitrogen

A. *Acidity*

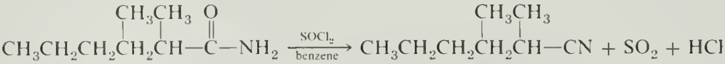
The NH group of amides is moderately acidic ($pK_a \approx 15$). The major reason for this acidity is the fact that the resulting anion is resonance-stabilized, with the negative charge shared between the nitrogen and the oxygen.



$$R-\overset{\overset{\large O}{\|}}{C}-NH_2 \rightleftharpoons H^+ + \left[R-\overset{\overset{\large O}{\|}}{C}-NH^- \longleftrightarrow R-\overset{\overset{\large O^-}{|}}{C}=NH\right]$$

B. *Dehydration*

The lability of the amide N—H bond is reflected in many of the reactions of amides. One of these is dehydration. A primary amide may be converted into the corresponding nitrile by treatment with an efficient dehydrating agent such as P_2O_5, $POCl_3$, $SOCl_2$, or acetic anhydride.



$$CH_3CH_2CH_2CH_2\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow[\text{benzene}]{SOCl_2} CH_3CH_2CH_2CH_2\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{CH_3}{|}}{C}H-CN + SO_2 + HCl$$

2,3-dimethylhexanamide

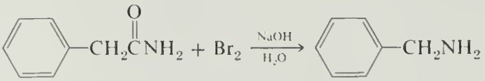
80°

(90%)

2,3-dimethylhexanenitrile

C. *Hofmann Degradation*

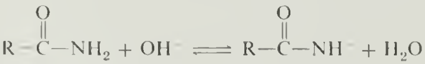
If a primary amide is treated with bromine in the presence of aqueous base, an interesting reaction occurs.



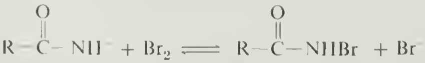
phenylacetamide

benzylamine

This reaction, known as the **Hofmann degradation of amides**, probably occurs by the following mechanism. The amide anion, formed in a small equilibrium concentration by reaction with hydroxide ion, reacts with bromine to give the N-bromo amide.



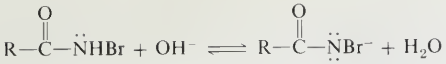
$$R-\overset{\overset{O}{\|}}{C}-NH_2 + OH^- \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-NH^- + H_2O$$



$$R-\overset{\overset{O}{\|}}{C}-NH^- + Br_2 \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-NHBr + Br^-$$

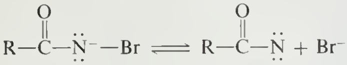
an N-bromo amide

The product still contains a proton bound to nitrogen and, because of the presence of the halogen, is more acidic than the original amide. A second deprotonation step now occurs.



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\ddot{N}HBr + OH^- \rightleftharpoons R{-}\overset{\overset{O}{\|}}{C}{-}\underset{\cdot\cdot}{\ddot{N}}Br^- + H_2O}$$

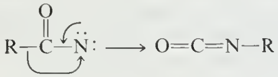
This intermediate now suffers **α elimination**, giving a species known as a **nitrene**, in which the nitrogen contains only six electrons in its valence shell.



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\underset{\cdot\cdot}{\ddot{N}}^-{-}Br \rightleftharpoons R{-}\overset{\overset{O}{\|}}{C}{-}\underset{\cdot\cdot}{\ddot{N}} + Br^-}$$

a nitrene

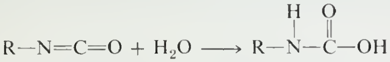
This highly unstable intermediate immediately rearranges to a stable molecule in which each atom again is surrounded by eight valence electrons.



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\ddot{N}\!: \longrightarrow O{=}C{=}N{-}R}$$

Note the similarity between this last reaction and the rearrangement of carbonium ions, discussed in Section 11.7.8. In both cases, an alkyl group *migrates*, together with a pair of electrons, to an electron-deficient atom.

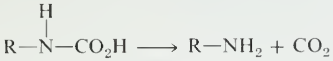
The product of the above rearrangement is an **alkyl isocyanate.** Although isocyanates are quite stable in the absence of water, they undergo immediate hydrolysis in its presence, to give a **carbamic acid**, a carboxylic acid in which the carbonyl group is bound directly to nitrogen.



$$\mathrm{R{-}N{=}C{=}O + H_2O \longrightarrow R{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}{-}OH}$$

an alkyl isocyanate — a carbamic acid

Carbamic acids **decarboxylate** (lose carbon dioxide) very easily, to give the corresponding amine.

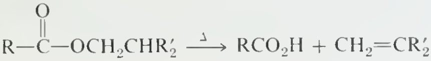


$$\mathrm{R{-}\overset{\overset{H}{|}}{N}{-}CO_2H \longrightarrow R{-}NH_2 + CO_2}$$

Note that the reaction results in the loss from the molecule of one carbon atom (as CO_2); the resulting amine contains *one carbon less* than the starting amide. The reaction is frequently used for the **degradation** of a carboxylic acid by one carbon.

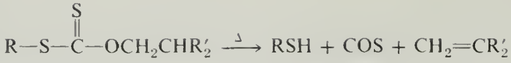
18.12
Pyrolytic Eliminations

Several types of organic compounds undergo elimination to give alkenes when heated to relatively high temperatures. Such **pyrolytic eliminations** are often preparatively useful. In this section, we shall discuss the pyrolytic elimination of esters and xanthates.



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}OCH_2CHR'_2 \xrightarrow{\Delta} RCO_2H + CH_2{=}CR'_2}$$

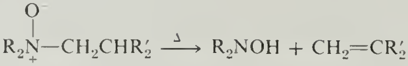
an ester



$$R{-}S{-}\overset{\overset{\large S}{\|}}{C}{-}OCH_2CHR'_2 \xrightarrow{\Delta} RSH + COS + CH_2{=}CR'_2$$

a xanthate

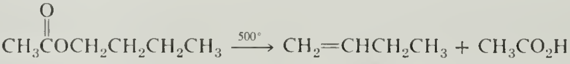
In Section 27.7.C, we shall discuss a similar pyrolytic elimination of **amine oxides.**



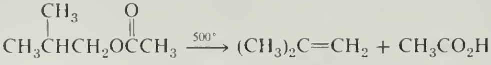
$$R_2\overset{\overset{\large O^-}{|}}{\underset{+}{N}}{-}CH_2CHR'_2 \xrightarrow{\Delta} R_2NOH + CH_2{=}CR'_2$$

an amine oxide

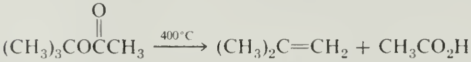
When a carboxylic ester is heated to 300–500°, elimination occurs to give the carboxylic acid and an alkene. The elimination may be accomplished by heating the ester in the liquid phase or by passing the gaseous ester through an electrically heated vapor-phase reactor. Several examples follow.



$$CH_3\overset{\overset{\large O}{\|}}{C}OCH_2CH_2CH_2CH_3 \xrightarrow{500^\circ} \underset{(100\%)}{CH_2{=}CHCH_2CH_3} + CH_3CO_2H$$

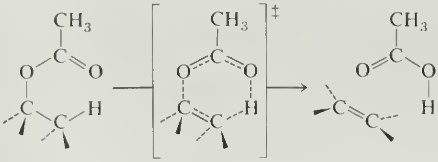


$$CH_3\overset{\overset{\large CH_3}{|}}{C}HCH_2O\overset{\overset{\large O}{\|}}{C}CH_3 \xrightarrow{500^\circ} \underset{(100\%)}{(CH_3)_2C{=}CH_2} + CH_3CO_2H$$

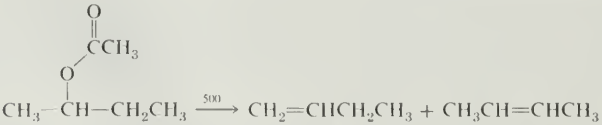


$$(CH_3)_3CO\overset{\overset{\large O}{\|}}{C}CH_3 \xrightarrow{400^\circ C} \underset{(100\%)}{(CH_3)_2C{=}CH_2} + CH_3CO_2H$$

The elimination is believed to occur by a concerted mechanism involving a six-center transition state (Section 36.2).

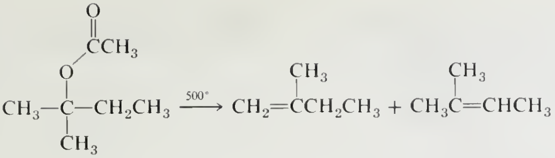


When the alkyl group of the ester has two or more β-hydrogens that may be lost, mixtures are obtained. For simple esters, the elimination is nearly statistical.



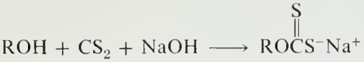
$$CH_3{-}\overset{\overset{\large O\overset{\overset{O}{\|}}{C}CH_3}{|}}{C}H{-}CH_2CH_3 \xrightarrow{500} CH_2{=}CHCH_2CH_3 + CH_3CH{=}CHCH_3$$

observed ratio: 57% 43%
(statistical: 60% 40%)



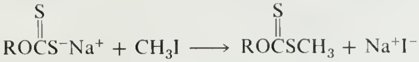
observed ratio: 76% 24%
(statistical: 75% 25%)

Xanthate salts are prepared by treating an alcohol with carbon disulfide and sodium hydroxide.



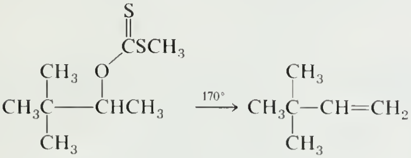
$$\mathrm{ROH + CS_2 + NaOH \longrightarrow RO\overset{S}{\overset{\|}{C}}S^-Na^+}$$

When the xanthate salt is treated with methyl iodide, S_N2 displacement occurs and a **xanthate ester** is formed.



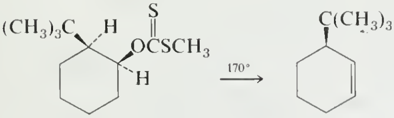
$$\mathrm{RO\overset{S}{\overset{\|}{C}}S^-Na^+ + CH_3I \longrightarrow RO\overset{S}{\overset{\|}{C}}SCH_3 + Na^+I^-}$$

Xanthates undergo pyrolytic elimination at somewhat lower temperatures than esters. The method, called the **Chugaev reaction,** has been widely used as a method of dehydrating alcohols.



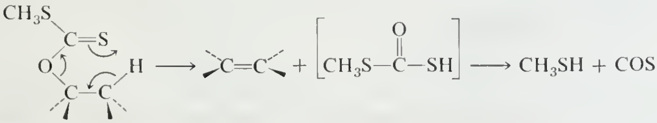
methyl 3,3-dimethyl-2-butylxanthate

(71%)
3,3-dimethyl-1-butene

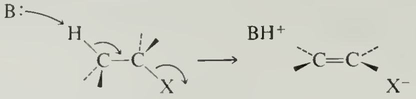


(61%)
3-*t*-butylcyclohexene

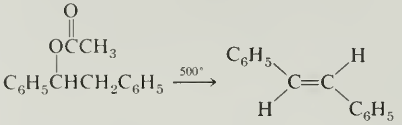
The mechanism of the elimination is similar to that discussed previously for ester pyrolysis.



Recall that the E2 elimination of alkyl halides to give alkenes is an anti elimination (Section 12.5.A). That is, the hydrogen and halogen depart from opposite sides of the molecule.


B:
H
C
C
X
BH⁺
C=C
X⁻

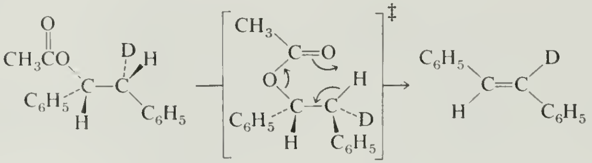
In contrast, ester and xanthate pyrolyses are syn eliminations; the leaving groups depart from the same side of the molecule. This stereochemistry was first demonstrated with an elegant labeling experiment by Curtin and Kellom in 1953. It was shown that 1,2-diphenylethyl acetate undergoes pyrolysis to give only *trans*-1,2-diphenylethylene (*trans*-stilbene).


O
OCCH₃
C₆H₅CHCH₂C₆H₅
500°
C₆H₅
H
C=C
H
C₆H₅

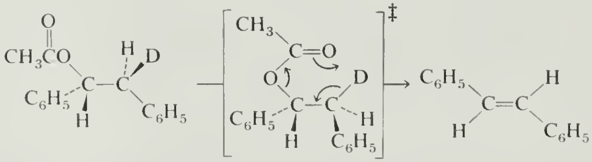
1,2-diphenylethyl acetate

trans-stilbene

The two deuterium-labeled analogs shown in (18-7) and (18-8) were then prepared and pyrolyzed. The (R,S) compound gave *trans*-stilbene, which contained one deuterium atom per molecule, and the (R,R) compound gave a product that had no deuterium.

 (18-7)
O
CH₃CO
D
H
C
C
C₆H₅
H
C₆H₅
CH₃
C=O
O
H
C
C
D
C₆H₅
H
C₆H₅
‡
C₆H₅
D
C=C
H
C₆H₅

(R,S)

 (18-8)
O
CH₃CO
H
D
C
C
C₆H₅
H
C₆H₅
CH₃
C=O
O
D
C
C
H
C₆H₅
H
C₆H₅
‡
C₆H₅
H
C=C
H
C₆H₅

(R,R)

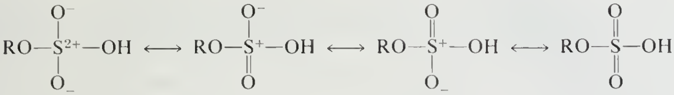
18.13
Esters of Other Acids

A. *Sulfates and Sulfonates*

Sulfuric acid, H_2SO_4, is a strong dibasic inorganic acid with $pK_1 \cong -5$ and $pK_2 = 1.99$.

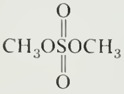
$$H_2SO_4 \rightleftharpoons H^+ + HSO_4^- \qquad K_a \cong 1 \times 10^5\ M$$
$$HSO_4^- \rightleftharpoons H^+ + SO_4^{2-} \qquad K_a = 1.0 \times 10^{-2}\ M$$

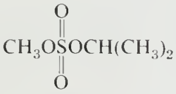
Both mono- and diesters of sulfuric acid are known. As with sulfuric acid itself, the sulfuric acid esters are often considered as resonance hybrids involving an expanded sulfur octet.


$$RO-\overset{\overset{O^-}{|}}{\underset{\underset{O^-}{|}}{S^{2+}}}-OH \longleftrightarrow RO-\overset{\overset{O^-}{|}}{\underset{\underset{O}{\|}}{S^{+}}}-OH \longleftrightarrow RO-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{S^{+}}}-OH \longleftrightarrow RO-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OH$$

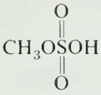
For convenience, we shall only use the Kekulé structure represented as having two S=O bonds.

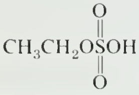
Diesters of sulfuric acid are named by combining the alkyl group name(s) with the word "sulfate," just as though they were salts of sulfuric acid.


$$CH_3O\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}OCH_3$$
dimethyl sulfate


$$CH_3O\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}OCH(CH_3)_2$$
methyl isopropyl sulfate

Monoesters are named as alkylsulfuric acids.


$$CH_3O\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}OH$$
methylsulfuric acid

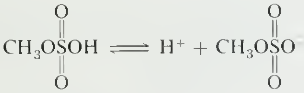

$$CH_3CH_2O\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}OH$$
ethylsulfuric acid

Dialkyl sulfates are highly polar compounds and generally have rather high boiling points. Their water solubility is surprisingly low. (Table 18.7).

TABLE 18.7
Physical Properties of Dialkyl Sulfates

	Melting Point, °C	Boiling Point, °C	Solubility in H_2O g/100 ml
$CH_3OSO_2OCH_3$	−27	188	2.8
$CH_3CH_2OSO_2OCH_2CH_3$	−25	210	very low

Alkylsulfuric acids are approximately as acidic as sulfuric acid itself.


$$CH_3O\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}OH \rightleftharpoons H^+ + CH_3O\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}O^-$$

They readily form inorganic salts, which are named as metal alkyl sulfates.

$CH_3OSO_3^-\,Na^+$ sodium methyl sulfate

$(CH_3CH_2OSO_3^-)_2Ba^{2+}$ barium ethyl sulfate

The monoesters are rarely encountered as reagents in organic chemistry. Ethylsulfuric acid is an intermediate in the industrial hydration of ethylene to give ethanol.

$$CH_2{=}CH_2 + H_2SO_4 \xrightarrow{0^\circ} CH_3CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH + H_2SO_4$$

Dimethyl sulfate and diethyl sulfate are encountered rather more frequently as organic reagents. Both diesters are readily available, inexpensive materials. They are prepared commercially from the corresponding alcohol and sulfuric acid.

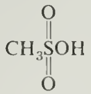
$$2\ ROH + H_2SO_4 \longrightarrow ROSO_2OR + H_2O$$

Since alkylsulfuric acids are such strong acids, the alkyl sulfate ion is a good leaving group, roughly comparable to iodide ion. Hence, dimethyl sulfate and diethyl sulfate readily enter into S_N2 displacement processes (Section 8.6.A).

$$(CH_3)_2CHCH_2O^- + CH_3OSO_2OCH_3 \longrightarrow (CH_3)_2CHCH_2OCH_3 + CH_3OSO_3^-$$

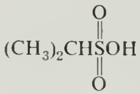
They are used in organic chemistry mainly for this purpose—as alkylating agents.

Sulfonic acids are organic compounds containing the functional group $—SO_3H$ joined to carbon. They are named as alkanesulfonic acids.



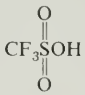
$$CH_3\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OH$$

methanesulfonic acid



$$(CH_3)_2CH\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OH$$

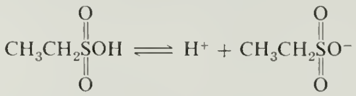
2-propanesulfonic acid



$$CF_3\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OH$$

trifluoromethanesulfonic acid

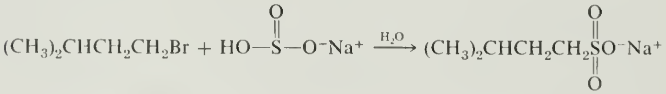
Alkanesulfonic acids are strong acids, as strong as typical mineral acids.



$$CH_3CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OH \rightleftharpoons H^+ + CH_3CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}O^-$$

Because of the inductive effect of the fluorines, trifluoromethanesulfonic acid is much more acidic and, indeed, is one of the strongest acids known.

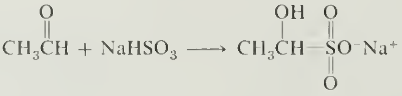
Sulfonic acids can be prepared by the nucleophilic displacement of alkyl halides with bisulfite ion, an ambident anion. Because of the greater nucleophilicity of sulfur, alkylation occurs primarily on sulfur, rather than on oxygen. The initial product is the salt of the sulfonic acid, which is converted into the sulfonic acid by treatment with strong acid.



$$(CH_3)_2CHCH_2CH_2Br + HO—\overset{\overset{O}{\|}}{S}—O^-Na^+ \xrightarrow{H_2O} (CH_3)_2CHCH_2CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}O^-Na^+$$

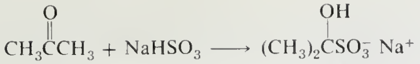
(96%)
sodium 3-methylbutanesulfonate

Sodium salts of α-hydroxysulfonic acids are obtained by the addition of sodium bisulfite to aldehydes and some ketones.



$$CH_3\overset{\overset{O}{\|}}{C}H + NaHSO_3 \longrightarrow CH_3\overset{\overset{OH}{|}}{C}H—\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}O^-Na^+$$

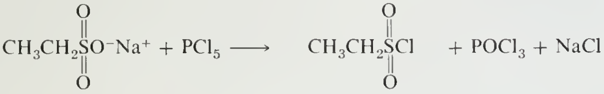
(89%)
sodium 1-hydroxyethanesulfonate



$$CH_3\overset{\overset{O}{\|}}{C}CH_3 + NaHSO_3 \longrightarrow (CH_3)_2\overset{\overset{OH}{|}}{C}SO_3^-\ Na^+$$

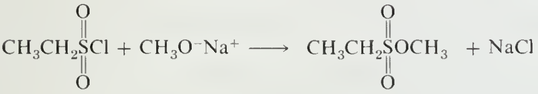
(59%)
sodium 2-hydroxy-2-propanesulfonate

Sulfonic acid esters are best prepared via the sulfonyl chlorides, which are obtained from the sodium sulfonate by treatment with phosphorus pentachloride (PCl_5) or thionyl chloride ($SOCl_2$).



$$CH_3CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}O^-Na^+ + PCl_5 \longrightarrow CH_3CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}Cl + POCl_3 + NaCl$$

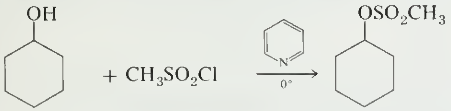
ethanesulfonyl chloride



$$CH_3CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}Cl + CH_3O^-Na^+ \longrightarrow CH_3CH_2\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}OCH_3 + NaCl$$

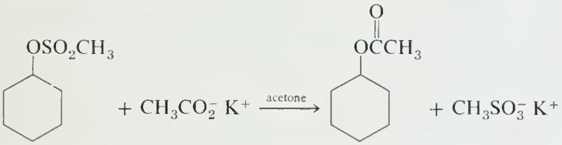
methyl ethanesulfonate

As with the alkyl sulfates, the alkanesulfonates are potent alkylating agents because the sulfonate ion is a reactive leaving group. The only class of alkanesulfonates in common use are the esters of methanesulfonic acid, which are prepared from methanesulfonyl chloride ("mesyl chloride"), an inexpensive commercial material. Methanesulfonates, frequently called "mesylates," are used in substitution and elimination processes, in the same way as alkyl halides.



methanesulfonyl chloride
"mesyl chloride"

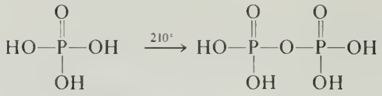
cyclohexyl methanesulfonate



Aromatic sulfonic acids and sulfonate esters are much more common and will be discussed in Section 31.6.

B. *Phosphates and Phosphonates*

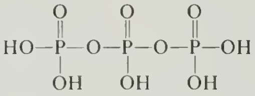
Phosphorus forms several oxyacids. The most common one is orthophosphoric acid, more commonly called simply phosphoric acid, H_3PO_4. When orthophosphoric acid is heated above 210°, it loses water with the formation of pyrophosphoric acid, which may be regarded as an anhydride of phosphoric acid.



$$\mathrm{HO{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}OH} \xrightarrow{210^\circ} \mathrm{HO{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}OH}$$

orthophosphoric acid pyrophosphoric acid

"Polyphosphoric acid" (PPA) is a mixture of phosphoric anhydrides which is prepared by heating H_3PO_4 with phosphorus pentoxide, P_2O_5. It consists of about 55% tripolyphosphoric acid, with the remainder being H_3PO_4 and higher polyphosphoric acids.



$$\mathrm{HO{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}OH}$$

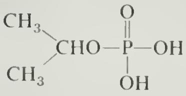
tripolyphosphoric acid

Polyphosphoric acid is commonly used as an acid catalyst in some organic reactions.

Orthophosphoric acid is a tribasic acid having $pK_1 = 2.15$, $pK_2 = 7.20$, and $pK_3 = 12.38$.

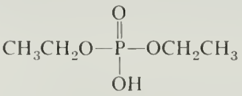
$$\begin{array}{lll} H_3PO_4 \rightleftharpoons H^+ + H_2PO_4^- & & K_a = 7.1 \times 10^{-3}M \\ H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-} & & K_a = 6.3 \times 10^{-8}M \\ HPO_4^{2-} \rightleftharpoons H^+ + PO_4^{3-} & & K_a = 4.2 \times 10^{-13}M \end{array}$$

It may form mono-, di-, and triesters.



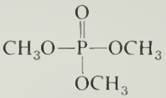
$$\mathrm{(CH_3)_2CHO{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}OH}$$

isopropyl phosphate



$$\mathrm{CH_3CH_2O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}{-}OCH_2CH_3}$$

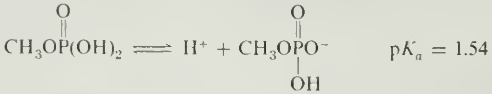
diethyl phosphate



$$\mathrm{CH_3O{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}{-}OCH_3}$$

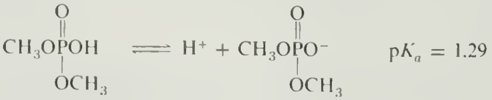
trimethyl phosphate

The mono- and diesters still contain OH groups and have acidic properties. They are actually stronger acids than phosphoric acid itself.



$$\mathrm{CH_3O\overset{\overset{\displaystyle O}{\|}}{P}(OH)_2} \rightleftharpoons \mathrm{H^+ + CH_3O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{P}}O^-} \qquad pK_a = 1.54$$

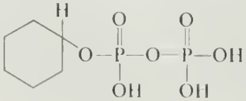
methyl phosphate



$$\mathrm{CH_3O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}OH} \rightleftharpoons \mathrm{H^+ + CH_3O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}O^-} \qquad pK_a = 1.29$$

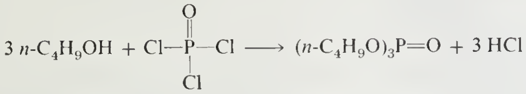
dimethyl phosphate

Analogous esters are possible for pyrophosphoric acid, but the most common are the monoesters.



cyclohexyl pyrophosphate

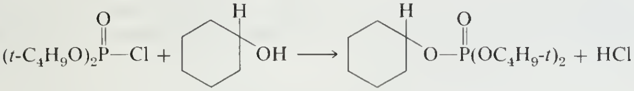
Phosphate triesters are commonly prepared from the alcohol and phosphorus oxychloride, which is the acyl halide corresponding to phosphoric acid.



$$3\ n\text{-}C_4H_9OH + Cl-\underset{\displaystyle Cl}{\overset{\overset{\displaystyle O}{\|}}{P}}-Cl \longrightarrow (n\text{-}C_4H_9O)_3P{=}O + 3\ HCl$$

tributyl phosphate

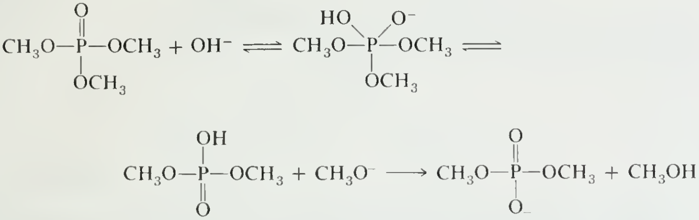
Compounds prepared by the replacement of two of the chlorines of $POCl_3$ (phosphorochloridates) may be used in a similar way to prepare mixed phosphates.



di-*t*-butyl phosphorochloridate

cyclohexyl di-*t*-butyl phosphate

The only reaction of phosphate esters that we shall consider here is hydrolysis. Hydrolysis may be either acid- or base-catalyzed and may involve either C—O or P—O bond rupture. Under basic conditions, hydrolysis occurs mainly by an addition-elimination mechanism, similar to that involved in the hydrolysis of carboxylic acid esters.

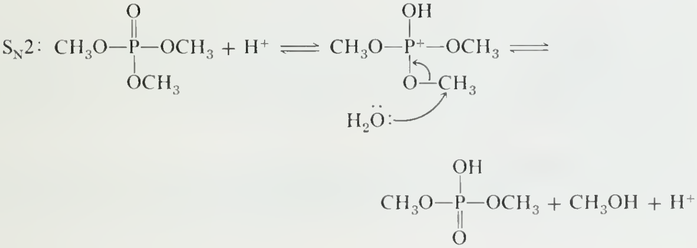


$$CH_3O-\underset{\displaystyle OCH_3}{\overset{\overset{\displaystyle O}{\|}}{P}}-OCH_3 + OH^- \rightleftharpoons CH_3O-\underset{\displaystyle OCH_3}{\overset{HO\ \ \ O^-}{P}}-OCH_3 \rightleftharpoons$$

$$CH_3O-\underset{\underset{\displaystyle O}{\|}}{\overset{\displaystyle OH}{P}}-OCH_3 + CH_3O^- \longrightarrow CH_3O-\underset{\displaystyle O^-}{\overset{\overset{\displaystyle O}{\|}}{P}}-OCH_3 + CH_3OH$$

The first alkyl group of a trialkyl phosphate is hydrolyzed most easily, with the second and third groups being hydrolyzed rather more sluggishly.

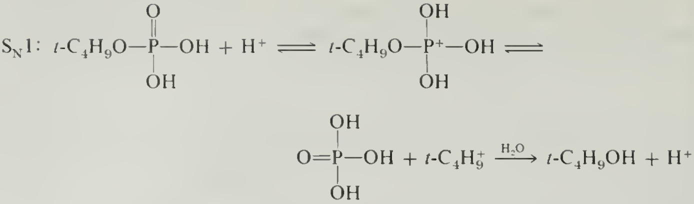
Under acidic conditions, C—O bond cleavage is the predominant mode of hydrolysis, although P—O rupture may also be observed. Cleavage of the C—O bonds may occur by either the S_N2 or the S_N1 mechanism, the former being preferred with primary alkyl phosphates and the latter with tertiary systems.



$$S_N2:\ CH_3O-\underset{\displaystyle OCH_3}{\overset{\overset{\displaystyle O}{\|}}{P}}-OCH_3 + H^+ \rightleftharpoons CH_3O-\underset{\displaystyle O-CH_3}{\overset{\displaystyle OH}{P^+}}-OCH_3 \rightleftharpoons$$

$$H_2\ddot{O}:$$

$$CH_3O-\underset{\underset{\displaystyle O}{\|}}{\overset{\displaystyle OH}{P}}-OCH_3 + CH_3OH + H^+$$



$$S_N1:\ t\text{-}C_4H_9O-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-OH + H^+ \rightleftharpoons t\text{-}C_4H_9O-\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{P^+}}-OH \rightleftharpoons$$

$$O{=}\overset{\overset{OH}{|}}{\underset{\underset{OH}{|}}{P}}-OH + t\text{-}C_4H_9^+ \xrightarrow{H_2O} t\text{-}C_4H_9OH + H^+$$

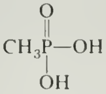
As a leaving group in such substitution reactions, phosphate is about as good as bromide ion. Alkyl pyrophosphates are somewhat better leaving groups, being about 10^2 more effective as leaving groups than iodide ion.

Phosphorous acid, H_3PO_3, is a less important oxyphosphorus acid. Trialkyl phosphites are generally prepared by treatment of phosphorus trichloride with the alcohol and pyridine.

$$PCl_3 + 3\ C_2H_5OH + 3\ C_5H_5N \longrightarrow (C_2H_5O)_3P + 3\ C_5H_5NH^+Cl^-$$

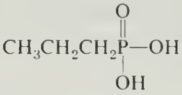
triethyl phosphite

Phosphonic acids contain the functional group $-PO_3H_2$ attached to carbon. They are named as alkylphosphonic acids.



$$CH_3\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-OH$$

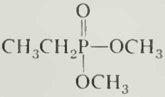
methylphosphonic acid



$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-OH$$

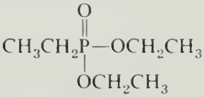
1-propylphosphonic acid

The most common derivatives are the diesters.



$$CH_3CH_2\overset{\overset{O}{\|}}{\underset{\underset{OCH_3}{|}}{P}}-OCH_3$$

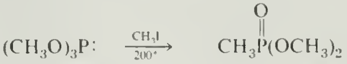
dimethyl ethylphosphonate



$$CH_3CH_2\overset{\overset{O}{\|}}{\underset{\underset{OCH_2CH_3}{|}}{P}}-OCH_2CH_3$$

diethyl ethylphosphonate

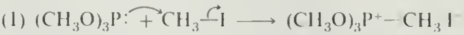
Dialkyl phosphonates are best prepared from trialkyl phosphites by a reaction known as the **Arbuzov-Michealis reaction.** For example, when trimethyl phosphite is heated at 200° with a catalytic amount of methyl iodide, dimethyl methylphosphonate is produced in virtually quantitative yield.



$$(CH_3O)_3P\colon \xrightarrow[200^\circ]{CH_3I} CH_3\overset{\overset{O}{\|}}{P}(OCH_3)_2$$

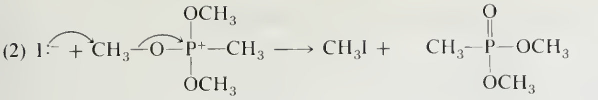
trimethyl phosphite — dimethyl methylphosphonate

The reaction mechanism involves two successive S_N2 processes. In the first step, the trialkyl phosphite displaces iodide from methyl iodide, giving an alkyltrialkoxyphosphonium salt. The liberated iodide ion then enters into a second displacement process on one of the methoxy groups, displacing the neutral dialkyl phosphonate.



$$(1)\ (CH_3O)_3P\colon + CH_3-I \longrightarrow (CH_3O)_3P^+-CH_3\ I^-$$

methyltrimethoxyphosphonium iodide

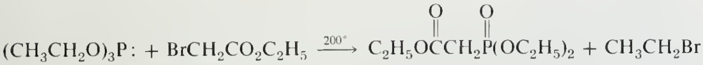


$$(2)\ I^- + CH_3{-}O{-}\overset{OCH_3}{\underset{OCH_3}{P^+}}{-}CH_3 \longrightarrow CH_3I + CH_3{-}\overset{O}{\underset{OCH_3}{\overset{\|}{P}}}{-}OCH_3$$

dimethyl methylphosphonate

Since the alkyl halide is regenerated in the second step, only a catalytic amount is required in order to initiate reaction.

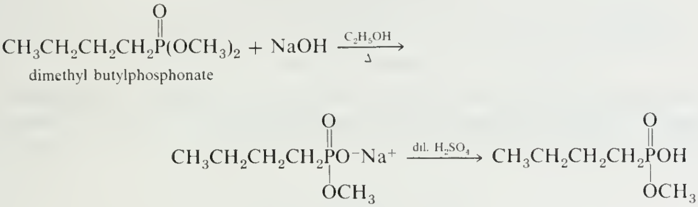
The Arbuzov reaction has been applied to the synthesis of numerous dialkyl phosphonates. If a full equivalent of alkyl halide is used, dialkyl phosphonates having different groups attached to oxygen and phosphorus may be prepared.



$$(CH_3CH_2O)_3P\colon + BrCH_2CO_2C_2H_5 \xrightarrow{200^\circ} C_2H_5O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{P}}(OC_2H_5)_2 + CH_3CH_2Br$$

triethyl phosphite | ethyl bromoacetate | triethylphosphonoacetate

Monoalkyl phosphonates are readily obtained from the diesters by alkaline hydrolysis. Hydrolysis of the second alkyl group is more difficult.



$$CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{P}}(OCH_3)_2 + NaOH \xrightarrow[\Delta]{C_2H_5OH}$$

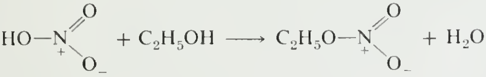
dimethyl butylphosphonate

$$CH_3CH_2CH_2CH_2\underset{OCH_3}{\overset{O}{\overset{\|}{P}}}O^-Na^+ \xrightarrow{\text{dil. }H_2SO_4} CH_3CH_2CH_2CH_2\underset{OCH_3}{\overset{O}{\overset{\|}{P}}}OH$$

sodium methyl butylphosphonate | methyl butylphosphonate

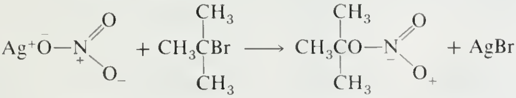
C. *Nitrates*

Nitrate esters are prepared from nitric acid and the appropriate alcohol or by the reaction of alkyl halides with silver nitrate.



$$HO{-}\overset{+}{N}(=O){-}O^- + C_2H_5OH \longrightarrow C_2H_5O{-}\overset{+}{N}(=O){-}O^- + H_2O$$

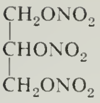
ethyl nitrate



$$Ag^+\bar{O}{-}\overset{+}{N}(=O){-}O^- + CH_3\underset{CH_3}{\overset{CH_3}{C}}Br \longrightarrow CH_3\underset{CH_3}{\overset{CH_3}{C}}O{-}\overset{-}{N}(=O){-}O_+ + AgBr$$

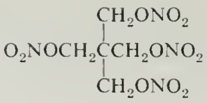
t-butyl nitrate

Nitrate esters which have a high nitrogen content have explosive properties and find wide use for this purpose. Examples are glycerol trinitrate ("nitroglycerin") and penterythritol tetranitrate (PETN).



$$\begin{array}{l} CH_2ONO_2 \\ | \\ CHONO_2 \\ | \\ CH_2ONO_2 \end{array}$$

nitroglycerin



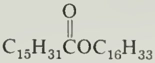
$$\begin{array}{c} CH_2ONO_2 \\ | \\ O_2NOCH_2CCH_2ONO_2 \\ | \\ CH_2ONO_2 \end{array}$$

PETN

18.14
Waxes and Fats

A. *Waxes*

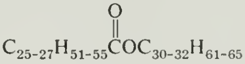
Waxes are naturally occurring esters of long chain carboxylic acids (C-16 or greater) with long chain alcohols (C-16 or greater). They are low-melting solids that have a characteristic "waxy" feel. Examples are **spermaceti,** a wax which separates from the oil of the sperm whale upon cooling. It is mainly cetyl palmitate (cetyl alcohol ≡ 1-hexadecanol) and melts at 42–47°.



$$C_{15}H_{31}\overset{\overset{\displaystyle O}{\|}}{C}OC_{16}H_{33}$$

spermaceti
cetyl palmitate
1-hexadecyl hexadecanoate

Beeswax is the material from which bees build honeycomb cells. It melts at 60–82° and is a mixture of esters. Hydrolysis yields mainly the C-26 and C-28 straight chain carboxylic acids and the C-30 and C-32 straight chain primary alcohols.



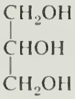
$$C_{25\text{-}27}H_{51\text{-}55}\overset{\overset{\displaystyle O}{\|}}{C}OC_{30\text{-}32}H_{61\text{-}65}$$

beeswax

Carnuba wax occurs as the coating on Brazilian palm leaves. It has a high melting point (80–87°) and is impervious to water. It is widely used as an ingredient in automobile and floor polish. It is a mixture of esters of the C-24 and C-28 carboxylic acids and the C-32 and C-34 1-alkanols. Other components are present in smaller amounts.

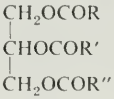
B. *Fats*

Fats are naturally occurring esters of long chain carboxylic acids and the triol glycerol (1,2,3-propanetriol). They are also called **glycerides.**



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

glycerol
1,2,3-propanetriol



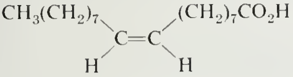
$$\begin{array}{l} CH_2OCOR \\ | \\ CHOCOR' \\ | \\ CH_2OCOR'' \end{array}$$

a fat or
glyceride

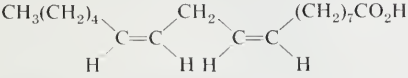
Hydrolysis of fats yields glycerol and the component carboxylic acids. The straight chain carboxylic acids which may be obtained from fats are frequently called **fat acids** or **fatty acids.** Fatty acids may be saturated or unsaturated. The most common saturated fatty acids are lauric acid, myristic acid, palmitic acid, and stearic acid.

$CH_3(CH_2)_{10}CO_2H$	$CH_3(CH_2)_{12}CO_2H$	$CH_3(CH_2)_{14}CO_2H$	$CH_3(CH_2)_{16}CO_2H$
lauric acid	myristic acid	palmitic acid	stearic acid
dodecanoic acid	tetradecanoic acid	hexadecanoic acid	octadecanoic acid

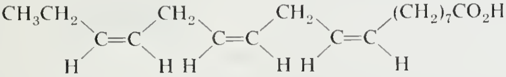
The most important unsaturated fatty acids have 18 carbon atoms, with one or more double bonds. Examples are oleic acid, linoleic acid, and linolenic acid.



oleic acid
(Z)-9-octadecenoic acid

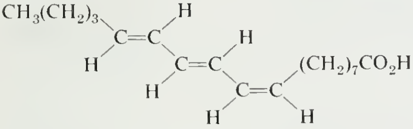


linoleic acid
(Z,Z)-9,12-octadecadienoic acid



linolenic acid
(Z,Z,Z)-9,12,15-octadecatrienoic acid

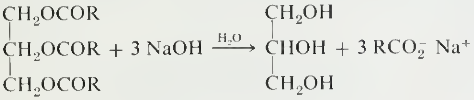
Almost invariably, the double bonds have the *cis* or (Z) configuration. A significant exception is eleostearic acid, which has one *cis* and two *trans* double bonds.



eleostearic acid
(Z,E,E)-9,11,13-octadecatrienoic acid

Natural fats are generally complex mixtures of triesters of glycerol **(triglycerides).** In general, the secondary hydroxy group is esterified with C-18 acids and the primary hydroxy groups are esterified either with C-18 or other fatty acids. For example, hydrolysis of palm oil yields 1–3% myristic acid, 34–43% palmitic acid, 3–6% stearic acid, 38–40% oleic acid, and 5–11% linoleic acid. Some natural fats yield large amounts of a single fatty acid on hydrolysis; tung oil yields 2–6% stearic acid, 4–16% oleic acid, 1–10% linoleic acid, and 74–91% eleostearic acid.

Fats undergo the typical reactions of esters. An important commercial reaction of fats is alkaline hydrolysis. The product fatty acid salts are used as soaps (Section 17.4.D).

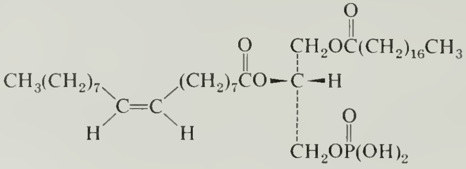


$$\begin{array}{l}CH_2OCOR\\ |\\ CH_2OCOR\\ |\\ CH_2OCOR\end{array} + 3\,NaOH \xrightarrow{H_2O} \begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ CH_2OH\end{array} + 3\,RCO_2^-\,Na^+$$

The alkaline hydrolysis of an ester is often referred to as **saponification,** from this process.

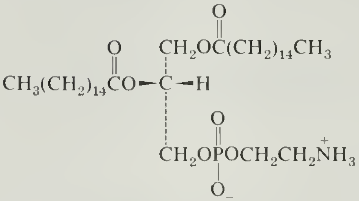
The melting point of a fat depends on the amount of unsaturation in the fatty acids. Fats with a preponderance of unsaturated fatty acids have melting points below room temperature and are called **oils.** Fats with little unsaturation are solid at normal temperatures. For the manufacture of soaps and for certain food uses, solid fats are preferable to oils. The melting point of a natural fat may be increased by hydrogenation. Industrially, the process is called **hardening.** Vegetable oils, such as cottonseed and peanut, are often hardened to the consistency of lard by partial hydrogenation.

Phosphoglycerides are fats in which glycerol is esterified to two fatty acids and to phosphoric acid. Such monophosphate esters are called **phosphatidic acids.** Most phosphatidic acids contain one saturated and one unsaturated fatty acid. Because different acids are esterified at the C-1 and C-3 hydroxy groups of glycerol, phosphatidic acids are chiral; the absolute configuration at the C-2 ester link is (R).

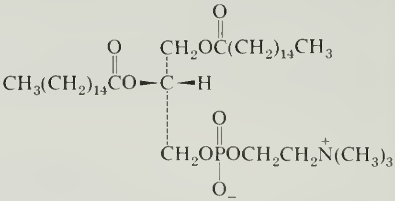


a phosphatidic acid

Free phosphatidic acids are rare in nature. Usually the phosphoric acid moiety is esterified to a second alcohol component. Important examples are **phosphatidyl ethanolamine** and **phosphatidyl choline.**



phosphatidyl ethanolamine



phosphatidyl choline

Phosphoglycerides are important biomolecules and occur widely in plants and animals. They are often referred to collectively as "phospholipids."

> **Lipid** is a term that has been used to describe the group of natural substances which are soluble in hydrocarbons and insoluble in water. It includes fats, waxes, phosphoglycerides, natural hydrocarbons, and so on. Most biochemists reserve the term lipid for natural compounds that yield fatty acids upon hydrolysis.

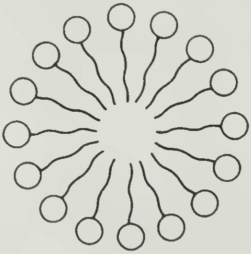
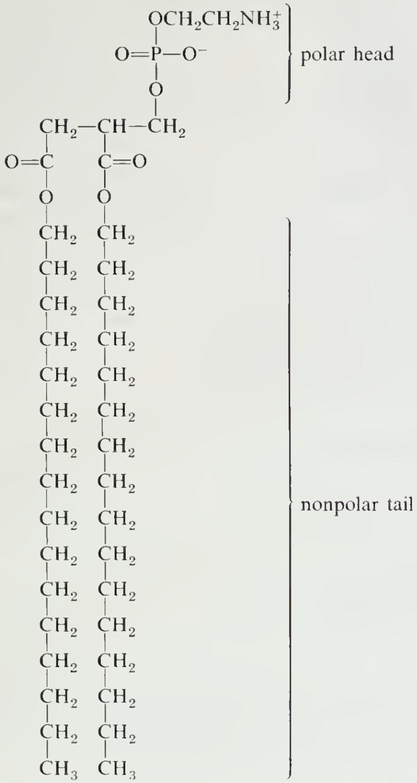


FIGURE 18.10 *Cross section of a phospholipid micelle.*

Phosphoglycerides have long nonpolar “tails” and a small, highly polar “head.”



In aqueous solution, they disperse to form micelles in the same way soaps do (Section 17.4.D). The nonpolar tails cluster together in the middle of the micelle, leaving the polar heads exposed to the aqueous environment (Figure 18.10). Phospholipids also form **bilayers**, particularly at the interface between two aqueous surfaces. In such bilayers, the hydrocarbon tails cluster toward one another, leaving a layer of polar heads on either side of the bilayer exposed to the aqueous phases (Figure 18.11). Such bilayers appear to form the fundamental framework of natural membranes.

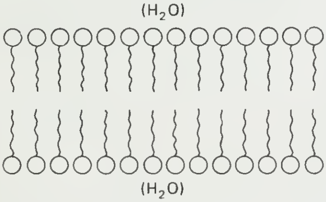


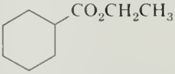
FIGURE 18.11 *Cross section of a phospholipid bilayer.*

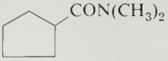
PROBLEMS

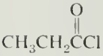
1. Write a structure that corresponds to each name.
   - (a) α-bromopropionitrile
   - (b) isopropyl isobutyrate
   - (c) N,3-diethylhexanamide
   - (d) N,N-dimethylformamide
   - (e) ethyl butyrate
   - (f) methyl β-chloropropionate
   - (g) acetic formic anhydride
   - (h) propionic anhydride
   - (i) acetonitrile
   - (j) butyryl bromide
   - (k) isopropylsulfuric acid
   - (l) diethyl sulfate
   - (m) tributyl phosphate
   - (n) propyl nitrate
   - (o) dibutyl methylphosphonate
   - (p) hexyl methanesulfonate
   - (q) cyclohexanecarbonitrile
   - (r) cyclohexanecarboxamide

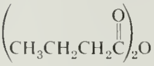
2. Write the correct IUPAC name for each compound.

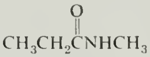
(a) $(CH_3CH_2)_2CHCH_2CO_2CH_2CH_2CH_3$

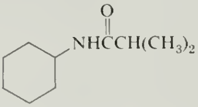
(b)


(c)


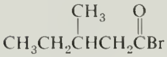
(d)

$CH_3CH_2\overset{O}{\overset{\|}{C}}Cl$

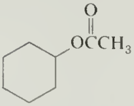
(e)

$\left(CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}\right)_2O$

(f)

$CH_3CH_2\overset{O}{\overset{\|}{C}}NHCH_3$

(g)


(h) $CH_3CH_2CH_2CH_2CN$

(i)

$CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}Br$

(j)


3. Many names are given in this chapter for reactions used as examples. For the types of compounds already studied, identify each name as trivial, common or IUPAC.

4. The C—O, C—N, C—F, and C—Cl bond lengths for a series of compounds are tabulated below.

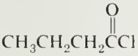
Compound	C—O	C—N	C—F	C—Cl
$CH_3—OCH_3$	1.42			
$CH_3\overset{O}{\overset{\|}{C}}—OCH_3$	1.36			
$CH_3—NH_2$		1.47		
$CH_3\overset{O}{\overset{\|}{C}}—NH_2$		1.36		
$CH_3—F$			1.38	
$CH_3\overset{O}{\overset{\|}{C}}—F$			1.37	
$CH_3—Cl$				1.78
$CH_3\overset{O}{\overset{\|}{C}}—Cl$				1.77

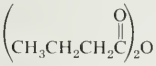
(a) Using these data, discuss the relative importance of dipolar resonance stabilization in esters, amides, and acyl halides.
(b) Explain how these data may be used to interpret the Lewis basicity of the carbonyl oxygen in amides, esters, and acyl halides.

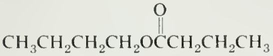
5. In a dilute solution of acetic acid in 0.1 *M* aqueous HCl, what percent of the acetic acid is present as $CH_3CO_2^-$ and as $CH_3C(OH)_2^+$?

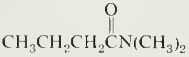
6. The pK_a of $CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH_2^+$ may be estimated to be approximately −12. Calculate the ratio of $CH_3\overset{\overset{\displaystyle OH^+}{\|}}{C}OH$ to $CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH_2^+$ in an acidic solution of acetic acid.

7. Show how butyric acid may be converted into each of the following compounds. More than one step may be required in some cases.

(a) 
$CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}Cl$

(b) 
$\left(CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}\right)_2O$

(c) 
$CH_3CH_2CH_2CH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2CH_3$

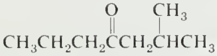
(d) 
$CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}N(CH_3)_2$

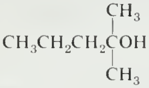
(e) $CH_3CH_2CH_2C{\equiv}N$

(f) $CH_3CH_2CH_2CH_2NH_2$

(g) $CH_3CH_2CH_2NH_2$

(h) $CH_3CH_2CH_2CH_2N(CH_2CH_3)_2$

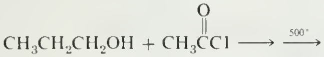
(i) 
$CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_3$

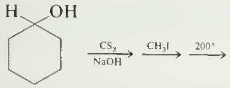
(j) 
$CH_3CH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}OH$

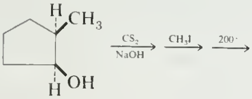
(k) $CH_3CH_2CH_2CHO$

(l) $CH_3CH_2CH_2CH_2OH$

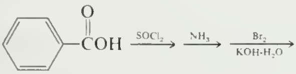
8. What are the organic products of each of the following reactions or sequences of reactions?

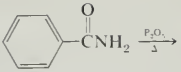
(a) 
$CH_3CH_2CH_2OH + CH_3\overset{\overset{\displaystyle O}{\|}}{C}Cl \longrightarrow \xrightarrow{500°}$

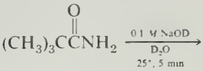
(b) 

(c) 

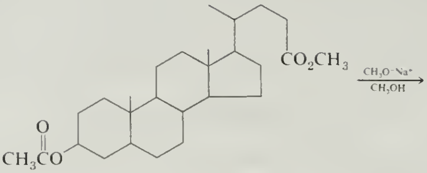
(d) $CH_3CH_2CH_2Cl \xrightarrow[\text{ethanol}\atop 75°]{NaCN} \xrightarrow[H_2O\atop 100°]{NaOH}$

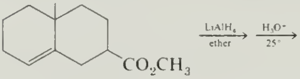
(e) 

(f) 

(g) 

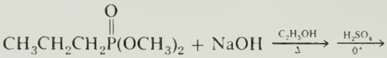
$(CH_3)_3C\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[D_2O,\ 25°,\ 5\ min]{0.1\ M\ NaOD}$

(h) 

(i) 

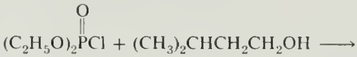
(j) $(CH_3CH_2CH_2CH_2O)_3P + \underset{(trace)}{CH_3CH_2CH_2CH_2Br} \xrightarrow{200°}$

(k) $t\text{-}BuO^-K^+ + CH_3OSO_2OCH_3 \xrightarrow[\Delta]{t\text{-}BuOH}$

(l) 

$CH_3CH_2CH_2\overset{O}{\overset{\|}{P}}(OCH_3)_2 + NaOH \xrightarrow[\Delta]{C_2H_5OH} \xrightarrow[0°]{H_2SO_4}$

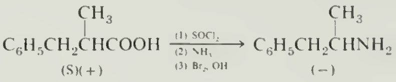
(m) $n\text{-}C_4H_9OH + HNO_3 \longrightarrow$

(n) 

$(C_2H_5O)_2\overset{O}{\overset{\|}{P}}Cl + (CH_3)_2CHCH_2CH_2OH \longrightarrow$

(o) $POCl_3 + CH_3OH$ (excess) $\longrightarrow$

9. The following reaction sequence is observed:

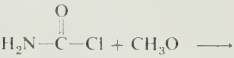


$$\underset{(S)(+)}{C_6H_5CH_2\overset{CH_3}{\overset{|}{C}}HCOOH} \xrightarrow[(2)\ NH_3,\ (3)\ Br_2,\ OH^-]{(1)\ SOCl_2} \underset{(-)}{C_6H_5CH_2\overset{CH_3}{\overset{|}{C}}HNH_2}$$

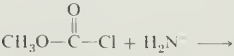
Using considerations of reaction mechanism, derive whether the configuration of the final product is (R) or (S).

10. A neutral compound $C_7H_{13}O_2Br$, does not give an oxime or phenylhydrazone derivative. The infrared spectrum shows bands at 2850–2950 cm^{-1}, but none above 3000 cm^{-1}. Another strong band is at 1740 cm^{-1}. The nmr shows the following pattern: $\delta = 1.0$ ppm (3H) triplet; $\delta = 1.3$ ppm (6H) doublet; $\delta = 2.1$ ppm (2H) mult; $\delta = 4.2$ ppm (1H) triplet; $\delta = 4.6$ ppm (1H) mult. Deduce the structure and assign their bands.

11. Predict the product of each of the following reactions. Rationalize your predictions.

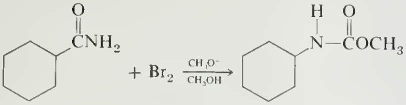
(a) 

$H_2N-\overset{O}{\overset{\|}{C}}-Cl + CH_3O^- \longrightarrow$

(b) 

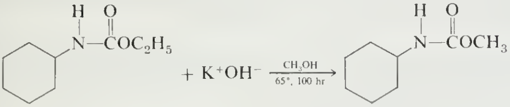
$CH_3O-\overset{O}{\overset{\|}{C}}-Cl + H_2N^- \longrightarrow$

12. When cyclohexanecarboxamide is treated with bromine and sodium methoxide in methanol, the product obtained is methyl N-cyclohexylcarbamate:



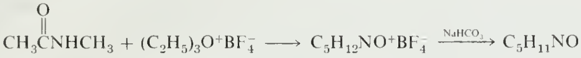
Rationalize with a plausible mechanism.

13. When ethyl N-cyclohexylcarbamate is refluxed with 1 *M* potassium hydroxide in methanol for 100 hr, the only product obtained is the methyl ester, in 95% yield.



Explain why no cyclohexylamine is produced.

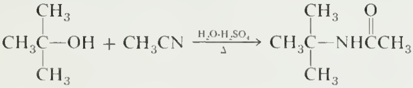
14. N-Methylacetamide reacts with triethyloxonium tetrafluoroborate to give a salt, $C_5H_{12}NO^+BF_4^-$. When this salt is treated with sodium bicarbonate, a compound $C_5H_{11}NO$ is produced.



$$CH_3\overset{O}{\overset{\|}{C}}NHCH_3 + (C_2H_5)_3O^+BF_4^- \longrightarrow C_5H_{12}NO^+BF_4^- \xrightarrow{NaHCO_3} C_5H_{11}NO$$

(a) What are the structures of the two compounds?
(b) Rationalize the formation of the salt in mechanistic terms.
(c) Predict the product that will be obtained if the salt is treated with aqueous acid.

15. Write a mechanism that explains the following reaction (the **Ritter** reaction):



$$CH_3\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}\!-OH + CH_3CN \xrightarrow[\Delta]{H_2O\text{-}H_2SO_4} CH_3\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}\!-NH\overset{O}{\overset{\|}{C}}CH_3$$

What product is expected when 2-methyl-2,4-pentanediol is treated with acetonitrile and aqueous sulfuric acid?

16. Explain why the pyrolysis of *cis*-2-methylcyclohexyl acetate gives only 3-methylcyclohexene, whereas *trans*-2-methylcyclohexyl acetate gives a mixture of 1-methylcyclohexene and 3-methylcyclohexene.

17. The elimination of a carboxylic acid from an ester is generally an endothermic process, for example

$$CH_3CH_2CH_2CH_2OCOCH_3 \longrightarrow$$
$$CH_3CH_2CH{=}CH_2 + CH_3COOH \qquad \Delta H^\circ = +12.6 \text{ kcal mole}^{-1}$$

Yet, the pyrolytic elimination is a useful preparative reaction. How do you account for this? Why is the pyrolytic elimination carried out at high temperature (300–500°)?

18. Orthoesters are compounds that have three alkoxy groups attached to the same carbon, for example, ethyl orthoacetate, $CH_3C(OC_2H_5)_3$. When ethyl orthoacetate is treated with dilute aqueous acid, ethyl acetate is obtained. Explain with a mechanism.

$$CH_3C(OC_2H_5)_3 + H_2O \xrightarrow{H^+} CH_3CO_2C_2H_5 + 2\ C_2H_5OH$$

19. The most intense peaks in the mass spectra of methyl valerate and methyl α-methylbutyrate are *m/e* 74 and *m/e* 88, respectively. Explain.

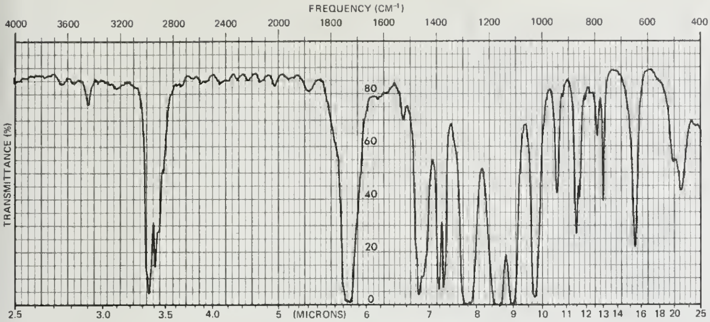
20. A solution of methyl cyclohexyl ketone in chloroform is treated with peroxybenzoic acid for 16 hr at 25°. The reaction mixture is worked up to obtain A, which has infrared absorption at 1740 cm^{-1} and 1250 cm^{-1}. The nmr spectrum of A shows a sharp three-proton singlet at $\delta = 2.0$ ppm and a one-proton multiplet at $\delta = 4.8$ ppm. The mass spectrum of A shows a molecular ion at *m/e* 142 and the most intense peak at *m/e* 43. What is A and how is it formed?

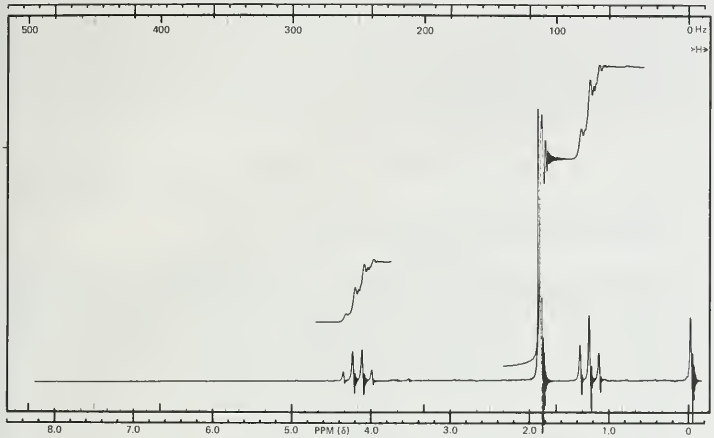
21. (R)-2-Butanol, $[\alpha]_D = -13.5°$, reacts with methanesulfonyl chloride to give a methanesulfonate. Treatment of the methanesulfonate with aqueous sodium hydroxide affords 2-butanol having $[\alpha]_D = +13.5°$.
    (a) From this result, what conclusions may you draw regarding the mechanism of the hydrolysis?
    (b) How may (S)-2-octanol be converted into (R)-2-methoxyoctane?

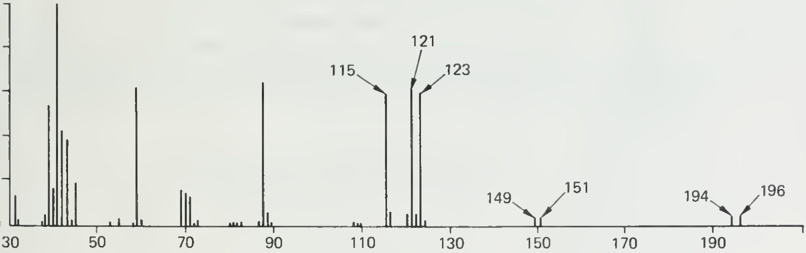
22. A useful preparation of deuterioethanol, C_2H_5OD, involves refluxing diethyl carbonate with D_2O and a small amount of strong acid. Why is this preparation so convenient?

23. Trimyristin is a white crystalline fat, m.p. 54–55°, obtainable from nutmeg, and is the principal constituent of nutmeg butter. Hydrolysis of trimyristin with hot aqueous sodium hydroxide gives an excellent yield of myristic acid, m.p. 52–53°, as the only fatty acid. What is the structure of trimyristin?

24. Identify the compound having the ir, nmr, and mass spectra on the following page.


FREQUENCY (CM^{-1})
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
TRANSMITTANCE (%)
80
60
40
20
0
2.5
3.0
3.5
4.0
5
(MICRONS)
6
7
8
9
10
11
12
13
14
16
18
20
25


500
400
300
200
100
0 Hz
>H>
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


115
121
123
149
151
194
196
30
50
70
90
110
130
150
170
190

Chapter 19
Organic Synthesis

19.1
Introduction

Organic synthesis is the preparation of a desired organic compound from a commercially available material, usually by some multistep procedure. It is an important element of organic chemistry and the cornerstone upon which the organic chemical industry is based. If a scientist wishes to study the physical, chemical, or physiological properties of a compound, he must obviously have a sample of it. Since relatively few organic compounds are commercially available from chemical suppliers, the scientist often must synthesize his desired material. In this chapter, we shall show how such a problem is approached using the chemistry we have learned so far.

19.2
Considerations in Synthesis Design

The goal in any synthesis is to obtain a pure sample of the desired product by the most efficient and convenient procedure possible. For this reason, one usually strives to use reactions that can reliably be expected to give only a single product and avoids reactions that will give a mixture of products. It is also important to plan a synthesis that entails the fewest possible steps. This is necessary both in terms of the amount of time consumed in an overly long route and in the ultimate yield that may be realized. A ten-step synthesis averaging 80% yield per step will give an overall yield of only 10.7%.

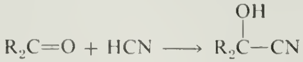
In planning a synthesis, three interrelated factors are involved:

1. Construction of the Proper Carbon Skeleton. In a sense, reactions that result in formation of a new C—C bond are the most important reactions in organic chemistry, because these reactions allow us to build up more complicated structures. Carbon-carbon bond forming reactions that we have encountered are summarized as follows.

(a) Reaction of primary alkyl halides with cyanide (Section 8.3).

$$RCH_2X + CN^- \longrightarrow RCH_2CN$$

(b) Addition of HCN to aldehydes and ketones (Section 15.7.F).

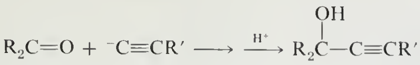


$$R_2C{=}O + HCN \longrightarrow R_2\overset{\displaystyle OH}{\overset{|}{C}}{-}CN$$

(c) Reaction of primary alkyl halides with acetylide ions (Sections 8.3 and 13.5.C).

$$RCH_2X + {}^-C{\equiv}CR' \longrightarrow RCH_2C{\equiv}CR'$$

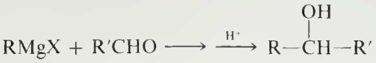
(d) Addition of acetylide ions to aldehydes and ketones (Section 15.7.E).



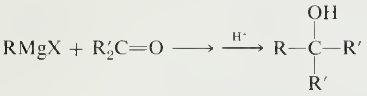
$$R_2C{=}O + {}^{-}C{\equiv}CR' \longrightarrow \xrightarrow{H^+} R_2\overset{\overset{OH}{|}}{C}{-}C{\equiv}CR'$$

(e) Reactions of Grignard reagents and alkyllithium compounds with carbon dioxide, aldehydes, ketones, and esters (Sections 17.6.B, 15.7.D, 18.9.E).

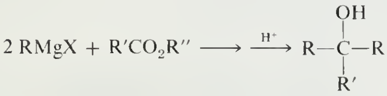
$$RMgX + CO_2 \longrightarrow \xrightarrow{H^+} RCO_2H$$



$$RMgX + R'CHO \longrightarrow \xrightarrow{H^+} R{-}\overset{\overset{OH}{|}}{C}H{-}R'$$

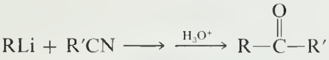


$$RMgX + R'_2C{=}O \longrightarrow \xrightarrow{H^+} R{-}\underset{\underset{R'}{|}}{\overset{\overset{OH}{|}}{C}}{-}R'$$



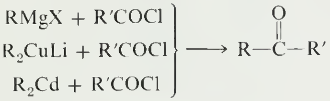
$$2\,RMgX + R'CO_2R'' \longrightarrow \xrightarrow{H^+} R{-}\underset{\underset{R'}{|}}{\overset{\overset{OH}{|}}{C}}{-}R$$

(f) Reaction of Grignard reagents and alkyllithium compounds with nitriles (Section 18.9.E).



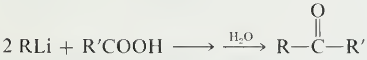
$$RLi + R'CN \longrightarrow \xrightarrow{H_3O^+} R{-}\overset{\overset{O}{\|}}{C}{-}R'$$

(g) Reaction of organometallic compounds with acyl halides (Section 18.9.E).



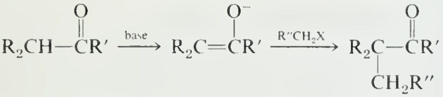
$$\left.\begin{array}{r} RMgX + R'COCl \\ R_2CuLi + R'COCl \\ R_2Cd + R'COCl \end{array}\right\} \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}R'$$

(h) Reaction of alkyllithium compounds with carboxylic acids (Section 17.7.C).

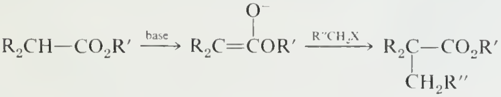


$$2\,RLi + R'COOH \longrightarrow \xrightarrow{H_2O} R{-}\overset{\overset{O}{\|}}{C}{-}R'$$

(i) Alkylation of enolate ions with primary alkyl halides (Sections 15.6.B and 18.8).



$$R_2CH{-}\overset{\overset{O}{\|}}{C}R' \xrightarrow{\text{base}} R_2C{=}\overset{\overset{O^-}{|}}{C}R' \xrightarrow{R''CH_2X} R_2\underset{\underset{CH_2R''}{|}}{C}{-}\overset{\overset{O}{\|}}{C}R'$$

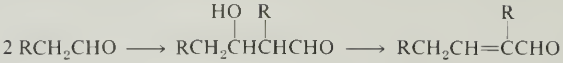


$$R_2CH{-}CO_2R' \xrightarrow{\text{base}} R_2C{=}\overset{\overset{O^-}{|}}{C}OR' \xrightarrow{R''CH_2X} R_2\underset{\underset{CH_2R''}{|}}{C}{-}CO_2R'$$

(j) The Wittig reaction (Section 15.7.H).

$$R_2C{=}O + R'CH{=}P(C_6H_5)_3 \longrightarrow R_2C{=}CHR'$$

(k) The aldol condensation (Section 15.7.G).

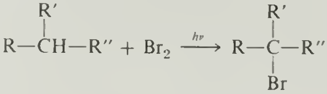


$$2\,RCH_2CHO \longrightarrow RCH_2\underset{}{\overset{HO}{\overset{|}{C}}}H\overset{R}{\overset{|}{C}}HCHO \longrightarrow RCH_2CH{=}\overset{R}{\overset{|}{C}}CHO$$

A more complete summary of C—C bond forming reactions is given in Appendix VIII.

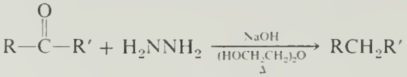
2. Placement of Desired Functional Groups in Their Proper Place. This aspect of a synthesis involves the introduction, removal, or interconversion of functional groups. We have encountered a great many such reactions. Rather than summarize them all, we shall only give a few illustrative examples.

(a) Introduction of a functional group.

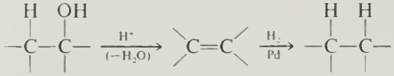


$$R{-}\overset{R'}{\overset{|}{C}}H{-}R'' + Br_2 \xrightarrow{h\nu} R{-}\underset{Br}{\underset{|}{\overset{R'}{\overset{|}{C}}}}{-}R''$$

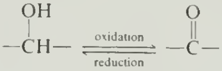
(b) Removal of a functional group.



$$R{-}\overset{O}{\overset{\|}{C}}{-}R' + H_2NNH_2 \xrightarrow[(HOCH_2CH_2)_2O,\ \Delta]{NaOH} RCH_2R'$$

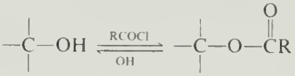


(c) Interconversion of functional groups.



$$-\overset{OH}{\overset{|}{C}}H- \underset{\text{reduction}}{\overset{\text{oxidation}}{\rightleftharpoons}} -\overset{O}{\overset{\|}{C}}-$$

$$-CH_2Br \underset{PBr_3}{\overset{OH^-}{\rightleftharpoons}} -CH_2OH$$

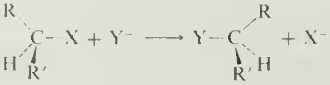


$$-\underset{|}{\overset{|}{C}}-OH \underset{OH^-}{\overset{RCOCl}{\rightleftharpoons}} -\underset{|}{\overset{|}{C}}-O-\overset{O}{\overset{\|}{C}}R$$

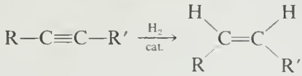
Insofar as is possible, one should choose reactions for building up the carbon skeleton so that the least amount of subsequent functional group manipulation is necessary. A complete summary of functional group interconversions is included in Appendix VIII.

3. Control of Stereochemistry Where Relevant. When more than one stereoisomer of the desired product is possible, it is necessary to design a synthesis which will yield only that isomer. In such cases, it is important to use reactions which are **stereospecific**; that is, reactions which yield largely one stereoisomer when two or more might result. The stereospecific reactions we have encountered are summarized as follows.

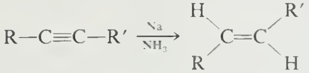
(a) S_N2 displacement reactions of secondary halides (Section 8.2).



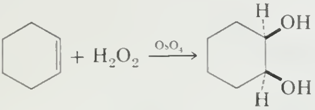
(b) Catalytic hydrogenation of alkynes (Section 13.6.A).



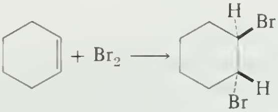
(c) Metal ammonia reduction of alkynes (Section 13.6.A).



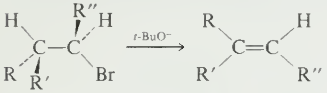
(d) Oxidation of alkenes with osmium tetroxide (Section 12.6.E).



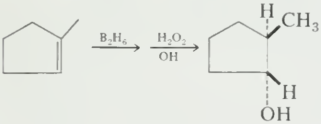
(e) Addition of halogens to alkenes (Section 12.6.B).



(f) E2 elimination of alkyl halides (Section 12.5.A).



(g) Hydroboration (Section 12.6D).

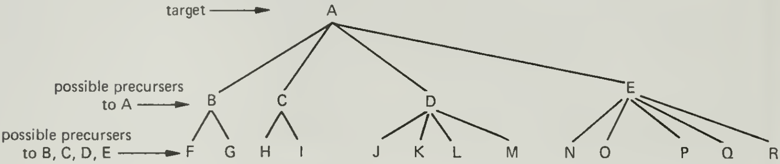


In some cases, it will not be possible to control a synthesis so that only the desired stereoisomer is produced because a method that will accomplish that goal is lacking. In such a case, the next best solution is to prepare the mixture of isomers and separate the desired isomer. At this point in our study of organic synthesis, we shall only touch on this subject of stereospecificity, but we will return to the topic in Section 36.7.

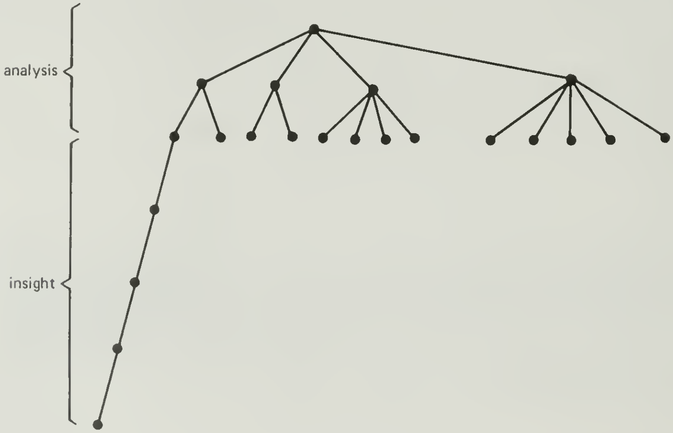
19.3
Planning a Synthesis

In planning a synthesis, one works from the product *backwards*. Remember that the goal is to connect the desired product with some commercially available starting material by a series of reactions each of which will, insofar as possible, give a single product in high yield. For this reason, the practicing chemist usually acquires a fairly good working knowledge of what types of starting materials are available from chemical suppliers. Of course, if he is not sure whether or not a possible starting material is available, he checks for its availability in the catalogs of various suppliers. A good rule of thumb is that most monofunctional compounds containing five or fewer carbons may be purchased. A great many others are also available, but this type of information is acquired only by experience. For the purpose of learning how to design a synthesis, we shall follow the "five or fewer carbons" rule.

For relatively simple synthetic problems, one may reason backwards in this way and soon arrive at possible starting materials that are known to be available. The result of such an analysis has been called a synthetic tree.



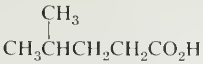
For more complex problems, the synthetic tree soon becomes unwieldy. In fact, current research is directed toward the application of computers to synthetic design. In most cases the practicing chemist solves such problems by a combination of such logical analysis and intuition. The synthetic tree is built until the chemist recognizes, by insight or intuition, a complete path from one of the possible intermediates to an available starting material.



The importance of insight and intuition, relative to analytical reasoning, should not be underestimated for science in general and synthetic design in particular. Nevertheless, insight and intuition cannot function in the absence of a body of facts, in the present case, a thorough knowledge of organic reactions.

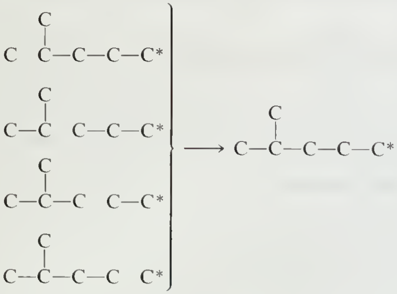
The best way to illustrate synthesis design is to demonstrate with a few specific simple examples.

Example 19-1. Plan a synthesis of 4-methylpentanoic acid

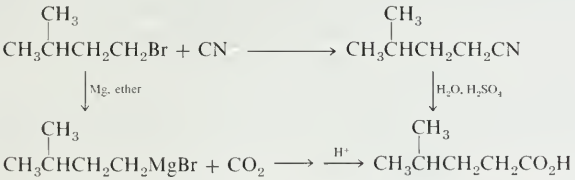


$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CO_2H$$

Since the product contains six carbons, we must build up the skeleton from a simpler starting material. In principle, there are a number of ways in which this may be done.



The carbon marked with an asterisk indicates the desired point of functionality, in this case a carboxy group. At this point, one immediately recognizes that the last combination might represent the reaction of isopentyl bromide with cyanide ion or the carbonation of isopentylmagnesium bromide.

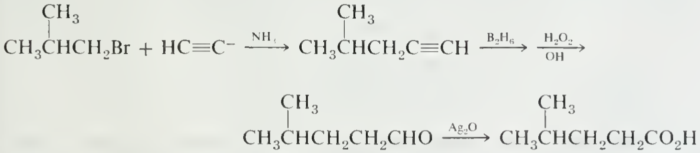


$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2Br + CN^- \longrightarrow CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CN \xrightarrow{H_2O,\ H_2SO_4} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CO_2H$$

$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2Br \xrightarrow{Mg,\ ether} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2MgBr + CO_2 \longrightarrow \xrightarrow{H^+} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CO_2H$$

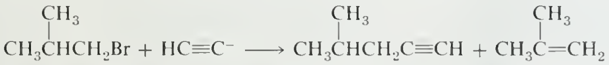
Both possible syntheses involve two steps and each step is reliable and expected to give a single product in high yield.

An alternative route one might have considered is outlined below.



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Br + HC{\equiv}C^- \xrightarrow{NH_3} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2C{\equiv}CH \xrightarrow{B_2H_6} \xrightarrow[OH^-]{H_2O_2} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CHO \xrightarrow{Ag_2O} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CO_2H$$

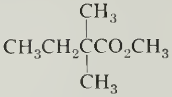
This route is inferior for two reasons. First, it is longer than either of the others. Second, the S_N2 displacement of bromide from isobutyl bromide will be accompanied by considerable E2 elimination due to the β-branch (Section 13.5.C).



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Br + HC{\equiv}C^- \longrightarrow CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2C{\equiv}CH + CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2$$

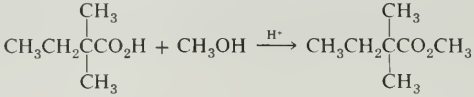
The overall yield will be greatly reduced because of this side reaction.

Example 19-2. Plan a synthesis of methyl 2,2-dimethylbutanoate



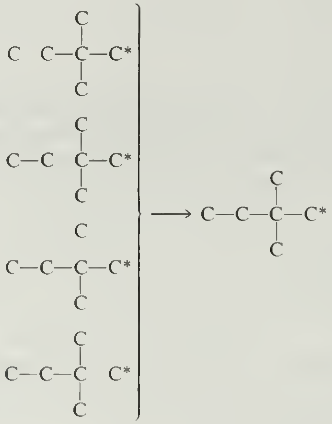
$$\mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{CO_2CH_3}$$

In this problem, we want to synthesize the methyl ester of a six-carbon carboxylic acid. The probable last step will be esterification of the acid.

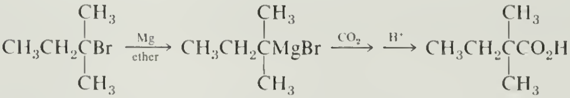


$$\mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{CO_2H} + \mathrm{CH_3OH} \xrightarrow{\mathrm{H^+}} \mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{CO_2CH_3}$$

We must now consider the synthesis of the acid itself. Analysis of the problem again reveals several combinations that can be used to construct the carbon skeleton from simpler precursors.

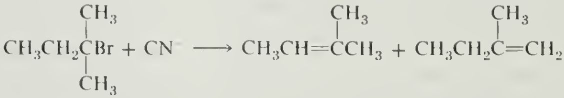


Again, the carbonation of the Grignard reagent derived from 2-bromo-2-methylbutane solves both the carbon skeleton and functional group problems.



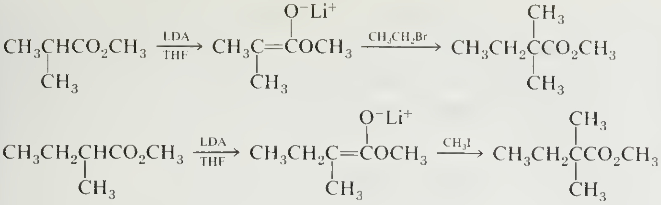
$$\mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{Br} \xrightarrow[\text{ether}]{\mathrm{Mg}} \mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{MgBr} \xrightarrow{\mathrm{CO_2}} \xrightarrow{\mathrm{H^+}} \mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{CO_2H}$$

In this case the cyanide displacement alternative is not viable. Since the required halide is tertiary, the S_N2 reaction will not proceed and only the elimination products will be formed.



$$\mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{Br} + \mathrm{CN^-} \longrightarrow \mathrm{CH_3CH{=}}\overset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{CH_3} + \mathrm{CH_3CH_2}\overset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{{=}CH_2}$$

An alternative process that must be considered is the alkylation of the ester anion (Section 18.8). Two combinations are possible.

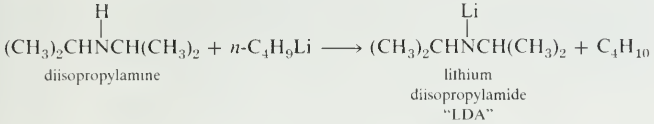


$$CH_3\underset{CH_3}{\underset{|}{C}}HCO_2CH_3 \xrightarrow[\text{THF}]{\text{LDA}} CH_3\underset{CH_3}{\underset{|}{C}}=\overset{O^-Li^+}{\overset{|}{C}}OCH_3 \xrightarrow{CH_3CH_2Br} CH_3CH_2\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}CO_2CH_3$$

$$CH_3CH_2\underset{CH_3}{\underset{|}{C}}HCO_2CH_3 \xrightarrow[\text{THF}]{\text{LDA}} CH_3CH_2\underset{CH_3}{\underset{|}{C}}=\overset{O^-Li^+}{\overset{|}{C}}OCH_3 \xrightarrow{CH_3I} CH_3CH_2\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}CO_2CH_3$$

Both of these reactions are "one-pot" processes; the anion is formed and alkylated in the same reaction vessel by the successive addition of the two reagents. These processes certainly appear to be equally as attractive as the Grignard carbonation route. In such a case as this, in which there are several good methods for the synthesis of a desired compound, the chemist chooses his method on secondary grounds.

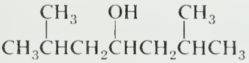
Although the starting materials for all of the routes may be commercially available, the chemist may have only one, and would have to order the others. In such a case, he would probably proceed using the starting material in hand. In some cases, the choice of routes may be made on economic grounds. In this case, for example, an examination of chemical catalogs shows that 2-bromo-2-methylbutane and methyl α-methylbutyrate are both much more expensive than methyl isobutyrate. Since ethyl bromide is also an inexpensive reagent, the most economic synthesis would appear to be the alkylation of methyl isobutyrate by ethyl bromide. However, if we consider costs, we must be careful to consider *all* of the costs, including the reagents. The base necessary to deprotonate an ester is lithium diisopropylamide (**LDA**), which is prepared by treating diisopropylamine with butyllithium, an expensive reagent.



$$\underset{\text{diisopropylamine}}{(CH_3)_2CH\overset{H}{\overset{|}{N}}CH(CH_3)_2} + n\text{-}C_4H_9Li \longrightarrow \underset{\substack{\text{lithium}\\ \text{diisopropylamide}\\ \text{"LDA"}}}{(CH_3)_2CH\overset{Li}{\overset{|}{N}}CH(CH_3)_2} + C_4H_{10}$$

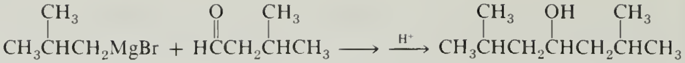
So, after a careful economic consideration, we are still left with the carbonation of the Grignard reagent derived from 2-bromo-2-methylbutane as the preferred synthetic route.

Example 19.3. Plan a synthesis of 2,6-dimethyl-4-heptanol.



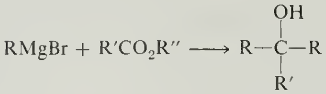
$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCH_3$$

In approaching the synthesis of this compound, one can follow the systematic type of approach outlined above and dissect the molecule into all the possible pairs of fragments that can lead to it. However, it is advantageous to cultivate the mental ability to relate certain types of compounds to a general method. In this case, one should realize that most acyclic alcohols can be prepared by some variation of the Grignard synthesis. In the present case, such a recognition immediately simplifies the problem to which combination of halide and aldehyde or ketone is most efficient. Since the desired alcohol is secondary, we note that it will result from treating an aldehyde with a Grignard reagent. It is symmetrical, so we need consider only one combination.



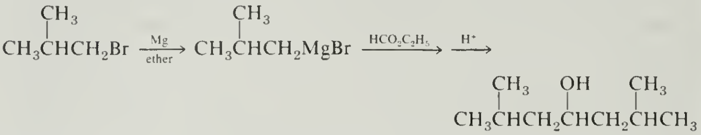
$$\mathrm{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2MgBr + H\overset{O}{\overset{\|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}HCH_3 \longrightarrow \xrightarrow{H^+} CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCH_3}$$

At this point, we should recall that symmetrical alcohols can also be produced by the reaction of a Grignard reagent with an ester.



$$\mathrm{RMgBr + R'CO_2R'' \longrightarrow R{-}\underset{R'}{\underset{|}{\overset{OH}{\overset{|}{C}}}}{-}R}$$

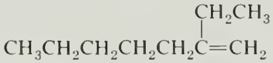
Since the desired alcohol is secondary, an ester of formic acid is required (R′ = H). The best synthesis is thus



$$\mathrm{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2Br \xrightarrow[ether]{Mg} CH_3\overset{CH_3}{\overset{|}{C}}HCH_2MgBr \xrightarrow{HCO_2C_2H_5} \xrightarrow{H^+} CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCH_3}$$

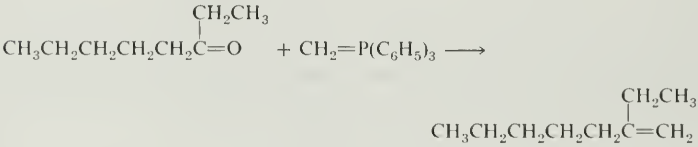
Although this method is no shorter than the route involving isobutylmagnesium bromide and 3-methylbutanal, it offers a practical advantage. Since low molecular weight aldehydes air-oxidize easily, one is more likely to have pure ethyl formate on hand than pure 3-methylbutanal.

Example 19-4. Plan a synthesis of 2-ethyl-1-heptene.



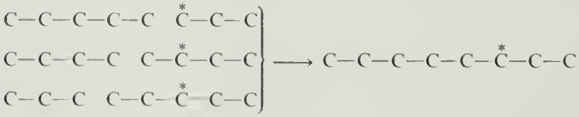
$$\mathrm{CH_3CH_2CH_2CH_2CH_2\overset{CH_2CH_3}{\overset{|}{C}}{=}CH_2}$$

Here is another case where it is advantageous to link a specific type of compound to a specific method that is particularly applicable to that type of compound. In looking at this structure, an immediate question is "how do I place the double bond specifically in that location?" The Wittig reaction is the best way to achieve that type of positional control.



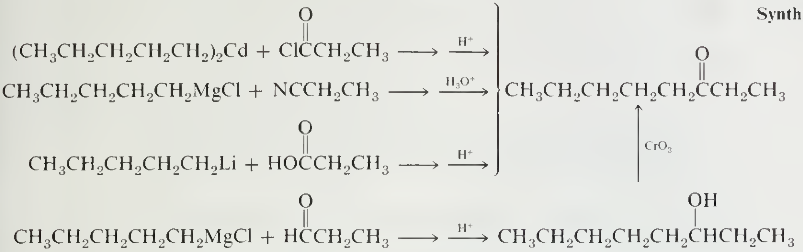
$$\mathrm{CH_3CH_2CH_2CH_2CH_2\overset{CH_2CH_3}{\overset{|}{C}}{=}O + CH_2{=}P(C_6H_5)_3 \longrightarrow CH_3CH_2CH_2CH_2CH_2\overset{CH_2CH_3}{\overset{|}{C}}{=}CH_2}$$

The synthesis is now directed toward 3-octanone. Again, there are several possible ways in which this eight-carbon compound could be built up. We should consider first those combinations that result in the greatest amount of simplification. We shall therefore ignore combinations that involve fragments containing more than five carbons. The remaining combinations are



$$\left.\begin{array}{ll} \mathrm{C{-}C{-}C{-}C{-}C} & \mathrm{\overset{*}{C}{-}C{-}C} \\ \mathrm{C{-}C{-}C{-}C} & \mathrm{C{-}\overset{*}{C}{-}C{-}C} \\ \mathrm{C{-}C{-}C} & \mathrm{C{-}C{-}\overset{*}{C}{-}C{-}C} \end{array}\right\} \longrightarrow \mathrm{C{-}C{-}C{-}C{-}C{-}\overset{*}{C}{-}C{-}C}$$

It is always productive to look first at the combinations in which the desired functional group is closest to the point where the attachment will be made, in this case C—C—C—C—C + C—C—C. Several possibilities come to mind.



$$(CH_3CH_2CH_2CH_2CH_2)_2Cd + Cl\overset{O}{\overset{\|}{C}}CH_2CH_3 \longrightarrow \xrightarrow{H^+} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$$

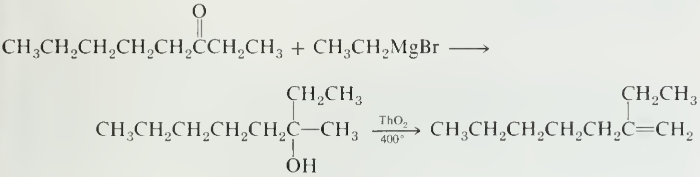
$$CH_3CH_2CH_2CH_2CH_2MgCl + NCCH_2CH_3 \longrightarrow \xrightarrow{H_3O^+} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$$

$$CH_3CH_2CH_2CH_2CH_2Li + HO\overset{O}{\overset{\|}{C}}CH_2CH_3 \longrightarrow \xrightarrow{H^+} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$$

$$CH_3CH_2CH_2CH_2CH_2MgCl + H\overset{O}{\overset{\|}{C}}CH_2CH_3 \longrightarrow \xrightarrow{H^+} CH_3CH_2CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_2CH_3 \xrightarrow{CrO_3} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$$

Because they are more direct, one of the first three methods is desirable. In actuality, a synthetic chemist would choose the one known by him to be most convenient (probably pentylmagnesium chloride and propionitrile).

An alternative route that might be considered is outlined as follows.

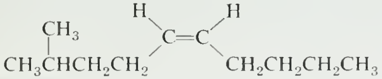


$$CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 + CH_3CH_2MgBr \longrightarrow$$

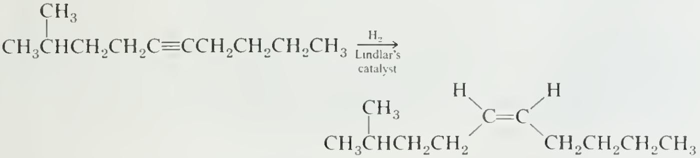
$$CH_3CH_2CH_2CH_2CH_2\underset{OH}{\underset{|}{\overset{CH_2CH_3}{\overset{|}{C}}}}-CH_3 \xrightarrow[400^\circ]{ThO_2} CH_3CH_2CH_2CH_2CH_2\overset{CH_2CH_3}{\overset{|}{C}}=CH_2$$

This route takes advantage of the fact that thorium dioxide dehydrations give mostly the terminal alkene (Section 12.5.B). From a practical standpoint, this route is inferior for two reasons. In the first place, the one-step Wittig reaction is replaced by a two-step procedure involving Grignard addition followed by dehydration. Also, vapor-phase reactions such as this are inconvenient to do on a laboratory scale unless one wishes to prepare a large amount of the desired product.

Example 19-5. Plan a synthesis of *cis*-2-methyl-5-decene.

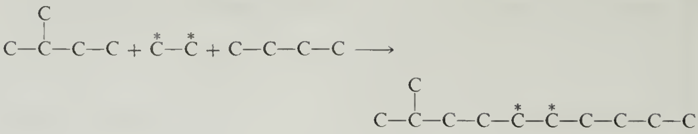


In this problem stereochemistry is important because only the *cis* isomer is desired. In this case, that consideration dominates the planning, since we have at this point only one method available for the stereospecific production of a *cis*-alkene.



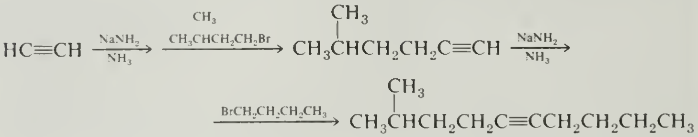
$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2C{\equiv}CCH_2CH_2CH_2CH_3 \xrightarrow[\text{Lindlar's catalyst}]{H_2}$$

Other methods for introducing the functional group would give a mixture of positional and/or stereoisomers. The required alkyne contains 11 carbons and must be built up from smaller fragments. If we consider making bonds closest to the functional group, we have



$$\mathrm{C{-}\overset{\overset{\displaystyle C}{|}}{C}{-}C{-}C} + \overset{*}{\mathrm{C}}{-}\overset{*}{\mathrm{C}} + \mathrm{C{-}C{-}C{-}C} \longrightarrow \mathrm{C{-}\overset{\overset{\displaystyle C}{|}}{C}{-}C{-}C{-}}\overset{*}{\mathrm{C}}{-}\overset{*}{\mathrm{C}}\mathrm{{-}C{-}C{-}C{-}C}$$

The reaction that allows us to accomplish this desired conversion is the S_N2 displacement of primary alkyl halides with the acetylene anion.

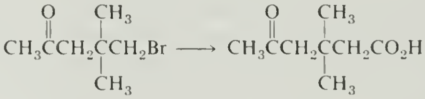


$$\mathrm{HC{\equiv}CH} \xrightarrow[NH_3]{NaNH_2} \xrightarrow{CH_3\overset{CH_3}{C}HCH_2CH_2Br} \mathrm{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_2C{\equiv}CH} \xrightarrow[NH_3]{NaNH_2}$$

$$\xrightarrow{BrCH_2CH_2CH_2CH_3} \mathrm{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_2C{\equiv}CCH_2CH_2CH_2CH_3}$$

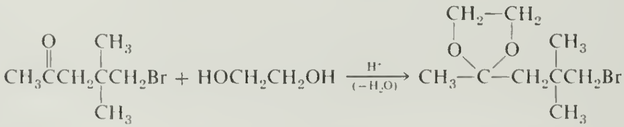
19.4
Protecting Groups

It often happens in the design of a synthesis that one wishes to carry out a transformation on one functional group with a reagent that would also react with some other functional group which is present. This may often be done by temporarily **protecting** one of the functional groups by changing it into another functional group that is unreactive to the reagent in question. For example, suppose it is desirable to carry out the following conversion:

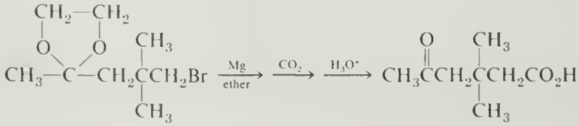


$$\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_2Br} \longrightarrow \mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_2CO_2H}$$

The cyanide displacement method of introducing the extra carbon will fail because the primary bromide has two β branches. The Grignard method cannot be used because the bromide has a carbonyl group in the molecule and Grignard reagents react with ketones. The problem can be circumvented by first transforming the ketone into a ketal.

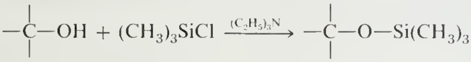


Since a ketal is an ether and ethers do not react with Grignard reagents, the Grignard synthesis may now be carried out. After the Grignard step, the ketal is hydrolyzed back to the ketone by treatment with acid and excess water.



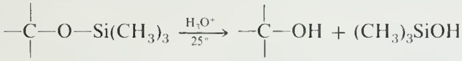
In this example, the ketal group is a protecting group. It is a good protecting group for aldehydes and ketones because it is easily introduced and removed and, since it is an ether, is stable to many reagents.

A method often used for the protection of primary alcohols is to convert them into *t*-butyl ethers. An example of this type of protection was discussed previously in Section 11.11.A. Another protecting group commonly used for alcohols is the trimethylsilyl ether, which is formed by treating the alcohol with trimethylchlorosilane and an organic base such as triethylamine.



$$-\overset{|}{\underset{|}{C}}-OH + (CH_3)_3SiCl \xrightarrow{(C_2H_5)_3N} -\overset{|}{\underset{|}{C}}-O-Si(CH_3)_3$$

The silyl ether grouping is stable to most neutral and basic conditions. When treated with mild aqueous acid, the alcohol is regenerated.



$$-\overset{|}{\underset{|}{C}}-O-Si(CH_3)_3 \xrightarrow[25^\circ]{H_3O^+} -\overset{|}{\underset{|}{C}}-OH + (CH_3)_3SiOH$$

19.5
Industrial Syntheses

Organic compounds are synthesized for two fundamentally different kinds of reasons. On the one hand, we may need a specific compound in order to study its properties or to use it for further research purposes. For such purposes, relatively small amounts generally suffice and cost is not an important criterion, within limits. On the other hand, a compound may have commercial significance, and for such purposes economic factors take on a vital importance. The cost of a medicinal used in small quantity where no other product will work is clearly of a different magnitude than that of a polymeric building material that must compete with wood and steel.

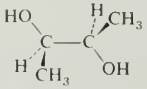
Most of the reactions and syntheses we have studied are useful for understanding the chemistry of different kinds of functional groups and for the laboratory preparation of various compounds. Few of these reactions, however, are suitable for the industrial preparation of compounds, some of which are produced in the amount of millions of pounds a year. An important distinction is the following: The reactions and laboratory preparations that we study have generality. These methods, with minor modifications, are suitable for the preparation of whole classes of compounds. On the other hand, many industrial preparations are specific. They apply for making one and only one specific compound. Many such reactions are gas phase catalytic processes with the precise catalysts and reaction conditions carefully worked out. An important advantage of such processes is that they are continuous rather than batch processes. Ideally, in a continuous process the reactants are fed into one end of a chemical plant and the product comes out at the other end without stopping, ready for marketing or for the next step. In practice, this ideal is rarely achieved. Catalysts lose their efficiency with time and need to be replaced. By-products build up and need to be cleaned out.

Much research in the chemical industry is devoted to discovering new products with useful properties. But much other research is devoted to existing products, improving processes to obtain these products cheaper and more efficiently, and, in many cases, purer. Research in *process development* is a fascinating area of its own that requires special talents of creativity, patience, and chemical knowledge. Increasing attention in process development is being given to the environment and to energy conservation. Today, a suitable industrial process must involve a minimum of waste products that require disposal.

PROBLEMS

1. Plan a synthesis for each of the following compounds from starting materials containing five or fewer carbons.
   - (a) 1-hexanol
   - (b) 3-hexanol
   - (c) 2-hexyl propionate
   - (d) 2-hydroxy-2,5-dimethylhexanoic acid
   - (e) 1-octyne
   - (f) 2,2,4-trimethyl-4-nonanol
   - (g) 5-deuterio-2-methylheptane
   - (h) 1-cyclopentyl-2-methyl-propene
   - (i) 2,2-dimethylnonane
   - (j) 3-methyl-1-hexen-3-ol

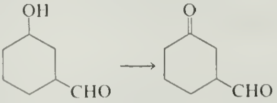
2. Plan a synthesis for each of the following compounds from monofunctional starting materials containing five or fewer carbons.
   - (a) *trans*-2-hexene
   - (b) *trans*-2-butylcyclopentanol
   - (c) (R)-2-methylpentanoic acid
   - (d) *cis*-4-octene
   - (e)



3. Plan a synthesis for each of the following compounds from starting materials containing five or fewer carbons. Difunctional starting materials may be used.
   - (a) 2-butyloctanoic acid
   - (b) 5-hydroxy-2-hexanone
   - (c) 1,4,7-heptanetriol
   - (d) 2,2-dimethylpentanoic acid
   - (e) *cis*-3,3-dimethyl-4-nonene

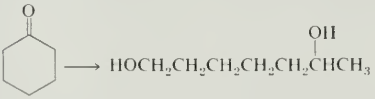
4. Show how one may carry out each of the following conversions in good yield.

(a)



(b) $BrCH_2CH_2CH_2CH_2CHO \longrightarrow CH_2{=}CHCH_2CH_2CHO$

(c)



$\longrightarrow HOCH_2CH_2CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}HCH_3$

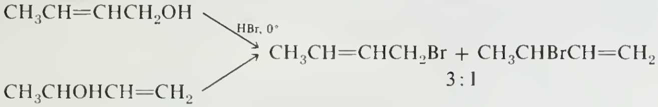
5. Consider the methods available for the general conversion of RY to RZ in which Y and Z are the eight groups given below. Set up a 8 × 8 matrix with Y down the side and Z across the top. Mark with a minus sign those conversions for which no *general* reaction sequence is presently known to you. Mark with a 1 those interconversions of functional groups that can be generally accomplished by a simple reaction process we have studied. Finally, mark with a + those interconversions that can be accomplished in a sequence of two or more reaction steps. Y and Z: H, Br, OH, CH_2OH, CHO, COOH, CN, $COCH_3$.

Chapter 20
Conjugation

20.1
Allylic Systems

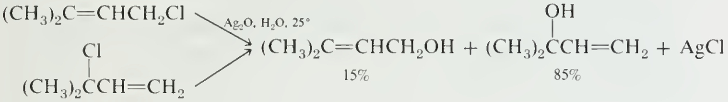
A. *Allylic Cations*

When 2-buten-1-ol is treated with hydrogen bromide at 0°, a mixture of about 3 parts of 1-bromo-2-butene to 1 part of 3-bromo-1-butene is produced. A comparable mixture is produced when 3-buten-2-ol is treated with HBr under the same conditions.



$$\left.\begin{array}{l} CH_3CH{=}CHCH_2OH \\ \\ CH_3CHOHCH{=}CH_2 \end{array}\right\} \xrightarrow{HBr,\ 0^\circ} \underset{3:1}{CH_3CH{=}CHCH_2Br + CH_3CHBrCH{=}CH_2}$$

Similarly, when 4-chloro-2-methyl-2-butene is hydrolyzed in water containing silver oxide at room temperature, a mixture of alcohols consisting of 15% of 3-methyl-2-buten-1-ol and 85% of 2-methyl-3-buten-2-ol is produced. Essentially the same mixture is obtained by the reaction of 3-chloro-3-methyl-1-butene with silver oxide in water.



$$\left.\begin{array}{l} (CH_3)_2C{=}CHCH_2Cl \\ (CH_3)_2\overset{Cl}{\overset{|}{C}}CH{=}CH_2 \end{array}\right\} \xrightarrow{Ag_2O,\ H_2O,\ 25^\circ} \underset{15\%}{(CH_3)_2C{=}CHCH_2OH} + \underset{85\%}{(CH_3)_2\overset{OH}{\overset{|}{C}}CH{=}CH_2} + AgCl$$

Silver cation catalyzes the formation of carbonium ions from alkyl halides. The Ag^+ tends to coordinate with the leaving halide group; that is, it provides a potent "pull" that contributes to the driving force of the reaction.

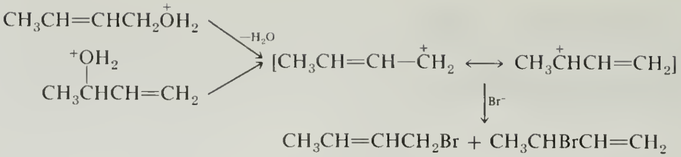
$$RX + Ag^+ \longrightarrow \underset{\text{(transition state)}}{[R\cdots X\cdots Ag]^+} \longrightarrow R^+ + AgX\downarrow$$

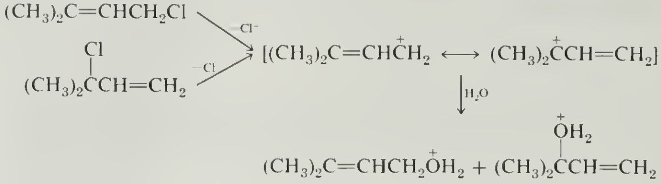
Furthermore, silver chloride, bromide and iodide are highly insoluble salts and remove the halide ion from further equilibration reactions. The net reaction of an alkyl halide with silver oxide is generally written as

$$2RX + Ag_2O + H_2O \longrightarrow 2\,ROH + 2\,AgX\downarrow$$

However, since these reactions often involve carbonium ion intermediates, other reactions such as rearrangements and eliminations frequently occur. Because of these reaction possibilities and the high cost of the reagent, the reaction of silver oxide with alkyl halides has little preparative significance and is used mainly to study the properties of carbonium ion intermediates.

These observations are explained by the formation of an intermediate cation in which the positive charge is delocalized over two carbons.





The intermediate carbonium ions in the foregoing reactions are described as resonance hybrids of two important structures. The simplest such cation is the 2-propen-1-yl or **allyl cation.**

$$[CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH_2] \equiv \overset{1/2+}{CH_2}\overset{\cdots}{=}CH\overset{\cdots}{=}\overset{1/2+}{CH_2}$$

allyl cation

Various symbols may be used to describe the hybrid electronic structure of the allyl cation. The two resonance structures in brackets show that the positive charge in the cation is divided equally between the two indicated positions. The alternative structure with dotted bonds shows that each C—C bond has an order of $1\frac{1}{2}$ and that each end carbon has $\frac{1}{2}$ of a positive charge.

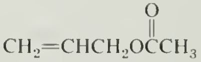
The grouping $CH_2{=}CHCH_2{-}$ is called the **allyl radical,** just as $CH_3CH_2{-}$ is called the ethyl radical. The radical name is used in naming many compounds containing the allyl group.

$CH_2{=}CHCH_2Cl$

allyl chloride

$CH_2{=}CHCH_2OH$

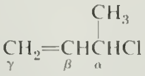
allyl alcohol



$CH_2{=}CHCH_2O\overset{\overset{\displaystyle O}{\|}}{C}CH_3$

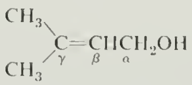
allyl acetate

Substituents may be indicated by the use of Greek letters.



$$\underset{\gamma}{CH_2}{=}\underset{\beta}{CH}\underset{\alpha}{\overset{\overset{\displaystyle CH_3}{|}}{C}HCl}$$

α-methylallyl chloride
3-chloro-1-propene



γ,γ-dimethylallyl alcohol
3-methyl-2-buten-1-ol

One important structural feature of allyl cation is that all of the atoms lie in one plane in such a way that the empty *p* orbital of the carbonium ion can overlap with the π orbital of the double bond. The electron density in the double bond is shared in the manner indicated by the symbols:

$$CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH_2$$

It is important to recall that resonance structures are used to symbolize alternative configurations of electron density. The geometry of the nuclei remains *precisely* the same in all resonance structures. The symbol, $CH_2{=}CH{-}\overset{+}{C}H_2$, would normally indicate a C=C having a short distance and a C—C having a longer distance. However, the alternative structure, $\overset{+}{C}H_2—CH=CH_2$, contributes equally to the actual structure symbolized by dotted lines as $(CH_2\overset{\cdots}{-}CH\overset{\cdots}{-}CH_2)^+$. Allyl cation has two equivalent C—C bonds of equal length. This length is shown by sophisticated quantum mechanical calculations to be in between that for single and double bonds. Similarly, the two terminal carbon atoms share an equal amount of positive charge.

A stereo representation of the planar structure of allyl cation and the corresponding orbital description are shown in Figure 20.1. The two electrons in the π orbital are in a molecular orbital extending over all three carbon atoms (Section 20.1.E).

Since the positive charge is spread over a larger volume, we expect allyl cation to be more stable than a simple primary alkyl carbonium ion. This expectation is confirmed by a comparison of gas phase enthalpies of ionization of alkyl chlorides:

$$RCl \longrightarrow R^+ + Cl^-$$

	$\Delta H°$, kcal mole^{-1}
CH_3CH_2Cl	192
$CH_2=CHCH_2Cl$	172
$(CH_3)_2CHCl$	170

In fact, *allyl cation is roughly comparable in relative stability to a secondary alkyl cation.* Similarly, methylallyl cation has the positive charge spread between a secondary and primary position, and the net stabilization is comparable to that of a tertiary alkyl cation.

$$[CH_3\overset{+}{C}HCH=CH_2 \longleftrightarrow CH_3CH=CH\overset{+}{C}H_2] \equiv CH_3\overset{\delta+}{C}H\overset{\cdots}{-}CH\overset{\cdots}{-}\overset{\delta+}{C}H_2$$

When an allylic cation reacts with a nucleophilic reagent, it can react at either positive center and generally produces a mixture of products. As a result, reactions that proceed by way of allyl cations often appear to give "rearranged" products. Such reactions are called **allylic rearrangement.** For example, in the first reaction we encountered in this chapter, 2-buten-1-ol reacts with HBr to give 1-bromo-

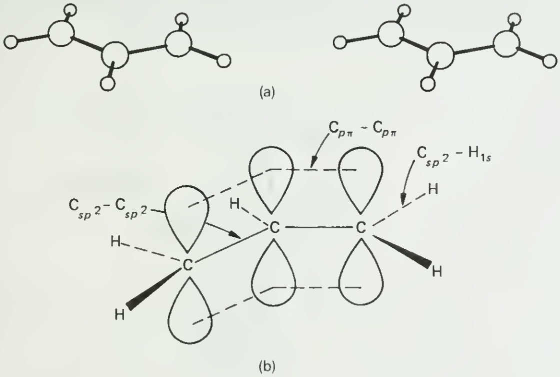


FIGURE 20.1 (a) *Stereo structure and* (b) *orbital description of allyl cation.*

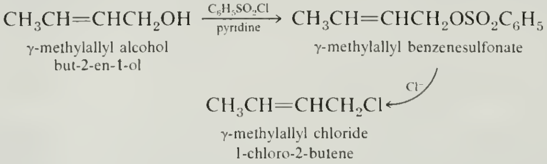
2-butene, a "normal" product. However, the reaction also gives 3-bromo-1-butene, a product of allylic rearrangement. Allylic rearrangement can be observed even with the parent system by labeling one carbon with radioactive ^{14}C:

$$CH_2{=}CH^{14}CH_2OH \xrightarrow{SOCl_2} CH_2{=}CH^{14}CH_2Cl + {}^{14}CH_2{=}CHCH_2Cl$$

(ratio depends on reaction conditions)

B. S_N2 Reactions

In addition to forming carbonium ions relatively readily, allylic systems are also rather reactive in S_N2 displacement reactions. In such reactions allyl bromide is about 40 times as reactive as ethyl bromide. The transition state is apparently stabilized by interaction with the double bond (Figure 20.2). By a careful choice of reaction conditions, it is possible to cause allylic compounds to react without allylic rearrangement, by way of the S_N2 mechanism.



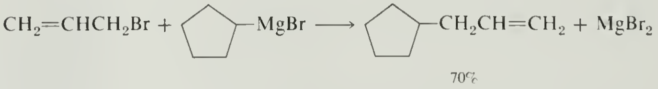
$$CH_3CH{=}CHCH_2OH \xrightarrow[\text{pyridine}]{C_6H_5SO_2Cl} CH_3CH{=}CHCH_2OSO_2C_6H_5 \xrightarrow{Cl^-} CH_3CH{=}CHCH_2Cl$$

γ-methylallyl alcohol
but-2-en-1-ol

γ-methylallyl benzenesulfonate

γ-methylallyl chloride
1-chloro-2-butene

The reactivity of allylic compounds in displacement reactions is sufficiently high that they even react with Grignard reagents.



Cyclopentylmagnesium bromide is prepared from 745 g of bromocyclopentane and 125 g of magnesium in 3 liters of anhydrous ether. The mixture is refluxed and 605 g of allyl bromide is added slowly. The mixture is stirred for 2 hr and cold 6*N* HCl is added. The ether layer is separated, washed, dried, and distilled to yield 70% of allylcyclopentane, 3-cyclopentyl-1-propene, b.p. 121–125°.

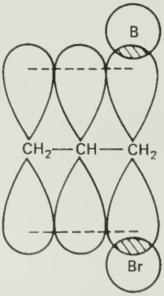


FIGURE 20.2 *Transition state of an S_N2 reaction with allyl bromide.*

This is a highly satisfactory method for preparing 1-alkenes. The corresponding reaction of Grignard reagents with normal alkyl halides does not occur.

C. *Allylic Anions*

The allyl Grignard reagent may be prepared by treating an allyl halide with magnesium.

$$\mathrm{CH_2{=}CHCH_2X + Mg \xrightarrow{ether} CH_2{=}CHCH_2MgX}$$

As we showed in the previous section, allyl halides react with Grignard reagents to give 1-alkenes. Consequently, care must be taken in preparing the allyl Grignard reagent. If the reaction is attempted at too high concentration, a large amount of the coupling product, 1,5-hexadiene or "biallyl," is formed.

$$\mathrm{CH_2{=}CHCH_2MgX + CH_2{=}CHCH_2X \longrightarrow \underset{\substack{\text{1,5-hexadiene}\\ \text{biallyl}}}{CH_2{=}CHCH_2CH_2CH{=}CH_2} + MgX_2}$$

The allyl Grignard reagent can be prepared in good yield by minimizing the further S_N2 reaction of the Grignard reagent with allyl halide. This result may be accomplished by adding a dilute solution of the allyl halide in ether slowly to a large excess of vigorously stirred magnesium. This technique is an example of the **dilution principle.** The rate of reaction of an alkyl halide with magnesium depends on the concentration of the alkyl halide and the surface area of the magnesium.

$$\text{rate}_1 = k_1[\mathrm{CH_2{=}CHCH_2X}][\text{Mg surface}]$$

The rate of the displacement step depends on the concentrations of allyl halide and Grignard reagent.

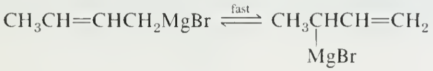
$$\text{rate}_2 = k_2[\mathrm{CH_2{=}CHCH_2X}][\mathrm{CH_2{=}CHCH_2MgX}]$$

When the solution is diluted, the concentrations of the allyl halide and the Grignard reagent decrease, but the surface area of the magnesium remains unchanged. Dilution retards both reactions, but it slows the second reaction more than the first.

Two isomeric allylic halides give Grignard reagents with indistinguishable properties.

$$\begin{tikzcd}
\mathrm{CH_3CH{=}CHCH_2Br} \arrow[dr, "\mathrm{Mg}"] & \\
& \mathrm{C_4H_7MgBr} \arrow[dd, "\mathrm{aq\ H^+}"] \\
\mathrm{CH_3CHBrCH{=}CH_2} \arrow[ur, "\mathrm{Mg}"] & \\
& \mathrm{\underset{(57\%)}{CH_3CH_2CH{=}CH_2} + \underset{\substack{27\%\ cis\\ 16\%\ trans}}{CH_3CH{=}CHCH_3}}
\end{tikzcd}$$

The allylic Grignard reagent undergoes a rapid isomerization.



$$\mathrm{CH_3CH{=}CHCH_2MgBr \overset{fast}{\rightleftharpoons} CH_3\underset{\underset{MgBr}{|}}{C}HCH{=}CH_2}$$

Although Grignard reagents have substantial C—Mg covalent bonding, we have seen that in many reactions the reagents behave as carbanion salts, $R{-}MgX \longleftrightarrow R^- \overset{+}{M}gX$. Similarly, allylic Grignard reagents have a high degree of ionic character involving the magnesium cation salt of an allylic anion:

$$CH_2{=}CH{-}CH_2{-}MgX \longleftrightarrow CH_2{=}CH{-}\overset{-}{C}H_2\ \overset{+}{M}gX \longleftrightarrow {}^-CH_2{-}CH{=}CH_2\ \overset{+}{M}gX$$

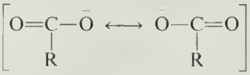
The negative charge is spread between two **conjugated** carbons. This spreading of ionic character facilitates rearrangement of the magnesium. In the reaction with an acid, protonation may occur at either of the carbons where there is negative charge. To summarize, the two isomeric allylic halides 1-bromo-2-butene and 3-bromo-1-butene can give *two* isomeric allylic Grignard reagents. The two isomers are in *rapid equilibrium* by allylic rearrangement of the magnesium. The net result on hydrolysis is protonation at either negative center of the corresponding allyl anion to give a mixture of product alkenes, 1-butene and 2-butene in the present example.

The spreading of charge in an allylic anion is a stabilizing mechanism; such anions are more stable than simple unconjugated anions. The allylic hydrogen of propylene, for example, is substantially more acidic than any hydrogen in ethane or propane.

$$\underset{\text{more acidic}}{CH_2{=}CHCH_3} + B{:}^- \longrightarrow BH + \underset{\text{delocalized allyl anion}}{[CH_2{=}CH{-}\ddot{C}H_2 \longleftrightarrow {}^-\ddot{C}H_2{-}CH{=}CH_2]}$$

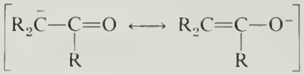
$$\underset{\substack{\text{less}\\ \text{acidic}}}{CH_3CH_3} + B{:}^- \longrightarrow BH + \underset{\substack{\text{localized}\\ \text{ethyl anion}}}{CH_3\ddot{C}H_2^-}$$

We have encountered similar kinds of conjugated or resonance-stabilized anions before: carboxylate ion (Section 17.4.A), enolate ion (Section 15.6.A), amidate ion (Section 18.10.C), even nitrite ion (Section 8.4).



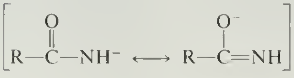
$$\left[O{=}\underset{\substack{|\\ R}}{C}{-}\overset{-}{O} \longleftrightarrow \overset{-}{O}{-}\underset{\substack{|\\ R}}{C}{=}O\right]$$

carboxylate ion



$$\left[R_2\overset{-}{C}{-}\underset{\substack{|\\ R}}{C}{=}O \longleftrightarrow R_2C{=}\underset{\substack{|\\ R}}{C}{-}O^-\right]$$

enolate ion



$$\left[R{-}\overset{\substack{O\\ \|}}{C}{-}NH^- \longleftrightarrow R{-}\overset{\substack{O^-\\ |}}{C}{=}NH\right]$$

amidate ion

$$[O{=}N{-}\overset{-}{O} \longleftrightarrow {}^-O{-}N{=}O]$$

nitrite ion

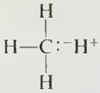
All such ions are described in the same way. The resonance structures provide a way of representing a rather complex electronic distribution by means of the formal symbolism of Lewis structures. The actual structure is a composite of the resonance structures.

The mathematics of linear combinations is especially useful for describing this situation. In this approach, the wave function of a molecule, Ψ, is represented as a linear combination of simpler wave functions, ψ.

$$\Psi = a\psi_a + b\psi_b + c\psi_c + \ldots$$

For many molecules a single structure provides a satisfactory representation. For example, methane is well represented by a single Lewis structure, ψ_a, and

$$\Psi = \psi_a$$

Other possible Lewis structures, such as $\psi_b =$  $H-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}:^- H^+$ are so unlikely that their contribution to the linear combination is negligible; that is, b for methane is a very small number.

In allyl cation and anion, carboxylate ion and nitrite ion, the two resonance structures are equivalent and in the linear combination must have equal coefficients.

$$\Psi(CH_2 \overset{\cdots}{-} CH \overset{\cdots}{-} CH_2)^+ = a\psi_a(CH_2{=}CH{-}\overset{+}{C}H_2) + b\psi_b(\overset{+}{C}H_2\ CH{=}CH_2)$$

where $a = b$.

In enolate ions the two structures are not equivalent. The structure with negative charge on the electronegative oxygen is more stable than that with the charge on carbon. Hence, these two structures enter into the linear combination with unequal coefficients:

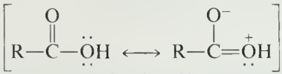
$$\Psi(CH_2 \overset{\cdots}{-} CH \overset{\cdots}{-} O)^- = a\psi_a(CH_2{=}CH{-}O^-) + b\psi_b(\overset{-}{C}H_2{-}CH{=}O)$$

where $a > b$.

We say that ψ_a contributes more than ψ_b; hence, the amount of negative charge on oxygen in Ψ, the resonance hybrid, is greater than that on carbon.

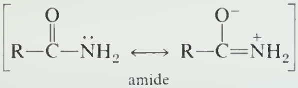
Resonance structures whose coefficients are very small contribute so little to the actual structure of the resonance hybrid that their contribution is generally neglected. It is this important property that allows us to represent even complex organic molecules by what is really a rather simple symbolism.

We have already encountered a number of neutral functions that have electronic structures closely related to that of allyl anion. In all such systems a lone pair of electrons is conjugated with a multiple bond.



$$\left[R-\overset{\overset{O}{\|}}{C}-\ddot{\underset{\cdot\cdot}{O}}H \longleftrightarrow R-\overset{\overset{O^-}{|}}{C}=\overset{+}{\underset{\cdot\cdot}{O}}H\right]$$

carboxylic acid



$$\left[R-\overset{\overset{O}{\|}}{C}-\ddot{N}H_2 \longleftrightarrow R-\overset{\overset{O^-}{|}}{C}=\overset{+}{N}H_2\right]$$

amide

These cases involve nonequivalent resonance structures. The dipolar structures involve charge separation and are generally less stable than the normal Lewis structures. Hence, the dipolar structures generally contribute less to the overall resonance hybrids. But they do contribute, and we have seen (Section 18.1) how consideration of such structures is essential to the understanding of the chemistry of such functional groups; the normal Lewis structures alone provide an inadequate description of the actual electronic structures of such groups.

D. *Allylic Radicals*

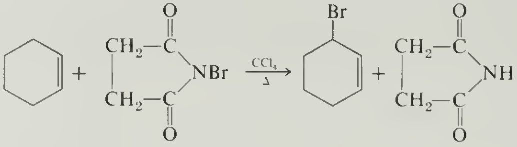
Allylic radicals are also stabilized by resonance.

$$[CH_2{=}CH{-}\dot{C}H_2 \longleftrightarrow \dot{C}H_2{-}CH{=}CH_2]$$

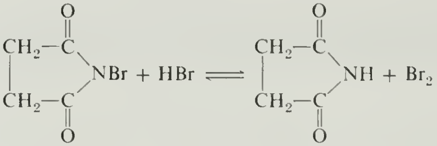
The odd-electron character is spread between two carbons and this radical is more stable than a simple alkyl radical. This increased stability is reflected in the relatively low bond dissociation energy of bonds conjugated to a double bond.

	$DH°$, kcal mole^{-1}
$CH_3CH_2—H$	98
$CH_2{=}CHCH_2—H$	85

Advantage can be taken of this low bond dissociation energy of allylic C—H bonds in free radical halogenation—but only under special circumstances because of the alternative reaction path of addition to the double bond. One method for accomplishing **allylic bromination** is with the reagent, N-bromosuccinimide. This material is available commercially and is prepared by bromination of the cyclic imide of succinic acid (Section 26.2.C).

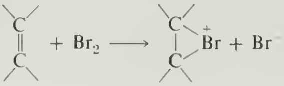


The reaction is not simple. It is important to use a medium in which N-bromosuccinimide is insoluble. Carbon tetrachloride is commonly used for this purpose. Reaction occurs in part on the surface of the N-bromosuccinimide, although the active reagent appears to be bromine formed in dilute solution from the reaction of traces of acid and moisture with the bromoimide:

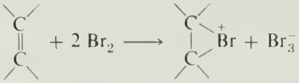


The bromine is then involved in free radical chain bromination of the allylic hydrogen. Under these conditions of high dilution no significant addition of bromine to the double bond occurs.

One of the reasons for using a nonpolar solvent such as CCl_4 in this reaction is that the normal addition of Br_2 to a double bond is an ionic reaction.



In the absence of a suitable solvent to solvate these ions, one or more excess bromine molecules are required for this role.



Thus, the reaction kinetics has a relatively high order in bromine and the ionic addition has a low reaction rate when bromine is kept in low concentration.

Free radical initiators or light are often used to promote the reaction. Because the reaction intermediate is a resonance-stabilized radical, two products can be obtained in unsymmetrical cases.

$$\mathrm{R{-}\dot{C}H{-}CH{=}CH{-}R'} \longleftrightarrow \mathrm{R{-}CH{=}CH{-}\dot{C}H{-}R'}$$
$$\Big\downarrow \mathrm{Br_2}$$
$$\mathrm{R{-}CHBrCH{=}CH{-}R' + R{-}CH{=}CHCHBr{-}R'}$$

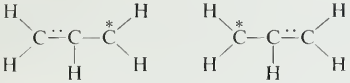
Allyl chloride is prepared commercially in large quantity by the direct free radical chlorination of propylene at high temperature. At higher temperatures the normal *addition* of chlorine atom to the double bond becomes *endothermic* and hydrogen abstraction is the principal reaction.

$$\mathrm{CH_3CH{=}CH_2 + Cl_2 \xrightarrow{500^\circ} ClCH_2CH{=}CH_2 + HCl}$$
$$\mathrm{Cl_2 \rightleftharpoons 2\,Cl\cdot}$$
$$\mathrm{CH_2{=}CHCH_3 + Cl\cdot \longrightarrow HCl + CH_2{=}CH\dot{C}H_2}$$
$$\mathrm{CH_2{=}CH\dot{C}H_2 + Cl_2 \longrightarrow Cl\cdot + CH_2{=}CHCH_2Cl}$$

Allyl alcohol is prepared from the chloride by hydrolysis.

E. *Molecular Orbital Description of Allylic Systems*

The resonance description of allylic conjugation involves alternative descriptions of bonding by pairs of electrons in normal Lewis structures.



The asterisk represents a positive or negative charge or an odd electron. Most of the electrons bond the skeleton of the compound and are not involved in the resonance-stabilization or conjugation. In the molecular orbital picture these electrons form the σ bonding framework of the molecule. Conjugation is a phenomenon associated more generally with the π electron system. The π system consists of *p* orbitals overlapping to form π bonds above and below the plane of the atoms that define the allylic system (Figure 20.3).

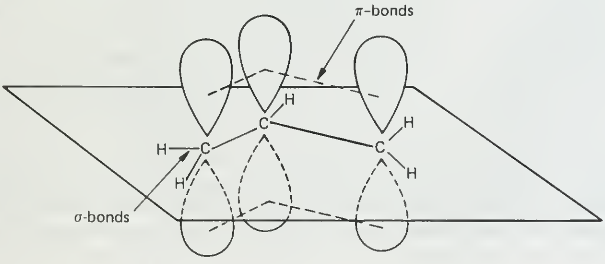


FIGURE 20.3 *σ and π bonds in allyl systems.*

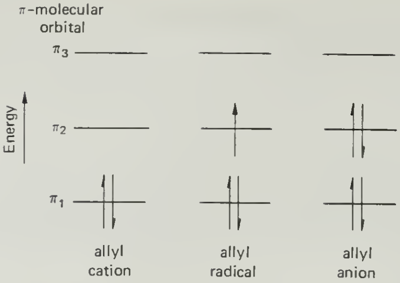


Figure 20.4 *π molecular orbital energies in allyl.*

The involvement of three *p* orbitals in this manner clearly gives greater bonding, and it is not difficult to understand the stabilization that such orbital overlap bestows on allyl cation. However, according to the Pauli principle, only two electrons of opposite spin can be associated with any single orbital. What are we to do with the third and fourth π electrons of allyl radical and anion?

Three p_z orbitals overlapping, as in allyl, generate *three* different molecular orbitals, each having its own energy. One is most bonding and is occupied by two electrons of opposite spin in allyl cation. The third electron of allyl radical must be put into the second molecular orbital. The fourth electron of allyl anion can also be put into this second molecular orbital. The third molecular orbital has high energy and is not involved in bonding in any of these compounds. These relationships are shown in Figure 20.4.

The π molecular orbitals can be regarded as having molecular orbital quantum numbers or their equivalent in nodes. When *p* orbitals overlap as in allyl, they do so in such a way as to generate one molecular orbital having no nodes, a second having one node, and a third having two nodes.

Since these molecular orbitals are made up of *p* orbitals overlapping in a π fashion, all of the molecular orbitals have one other node, the nodal plane of the component *p* orbitals. This plane is illustrated in Figure 20.3. The nodes referred to above are nodes in addition to this nodal plane.

These molecular orbitals for allyl are shown in Figure 20.5. Recall that when functions of the same sign overlap, electron density is put in the overlap region between the nuclei, and bonding results. Electron density does not exist at a node. The overlap of two wave functions of opposite sign creates a node in the overlap region and signifies a region devoid of electron density. The absence of such electron density to counter nuclear repulsion produces **antibonding.** Hence, the first allyl π molecular orbital, π_1, has no nodes and is completely bonding. In π_2 there is a node going through the middle carbon. The two remaining *p* orbital wave functions are so far apart that overlap is small and this molecular orbital is approximately **nonbonding.** The highest molecular orbital, π_3, has two nodes and is antibonding. In general, the greater the number of nodes, the higher the energy of an orbital and the lower the stability. The greatest stability (lowest energy) results when electrons are associated as far as possible with the most bonding molecular orbitals.

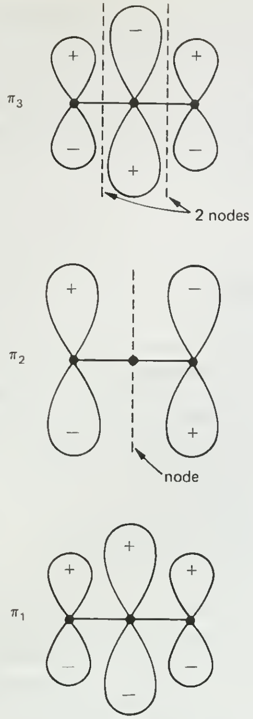


FIGURE 20.5 *π molecular orbitals of allyl.*

These molecular orbitals can be described analytically by the mathematical functions:

$$\pi_1 = \frac{1}{2}p_1 + \frac{\sqrt{2}}{2}p_2 + \frac{1}{2}p_3$$

$$\pi_2 = \frac{\sqrt{2}}{2}p_1 - \frac{\sqrt{2}}{2}p_3$$

$$\pi_3 = \frac{1}{2}p_1 - \frac{\sqrt{2}}{2}p_2 - \frac{1}{2}p_3$$

in which p_1, p_2, and p_3 are the mathematical functions for the three p atomic orbitals. Note that the node at the middle carbon of π_2 means simply that the coefficient of p_2 in this molecular orbital is zero.

This molecular orbital description has important uses in understanding why more than one electron pair can be associated with a single group of overlapping atomic orbitals. The approach is subject to more or less accurate numerical quantum mechanical calculation. But the molecular orbital description does not lend itself to the type of simple structural symbolism that is so facile with resonance structures. Accordingly, the use of resonance structures is important and widespread in the qualitative understanding and prediction of charge distributions and reactivities of conjugated systems. Resonance structures also provide an accurate accounting of all of the electrons. It is important to recognize that resonance structures and molecular orbitals are complementary views of the same reality. They offer different dissections of total electron density distributions that help us to understand the whole.

20.2
Dienes

A. *Structure and Stability*

Double bonds separated by one or more carbon atoms react more or less independently. The heats of hydrogenation of such double bonds are essentially those of independent units. For example, $\Delta H°$ for the reaction of 1,5-hexadiene with hydrogen is exothermic by 60 kcal mole^{-1}, exactly twice that for the reaction of 1-hexene with hydrogen. (Recall that the heat of hydrogenation of an alkene is $\Delta H°$ for the reaction: alkene + $H_2 \longrightarrow$ alkane.)

$$CH_2{=}CHCH_2CH_2CH{=}CH_2 + 2\,H_2 \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_3 \qquad \Delta H° = -60\ \text{kcal mole}^{-1}$$

$$CH_3CH_2CH_2CH_2CH{=}CH_2 + H_2 \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_3 \qquad \Delta H° = -30\ \text{kcal mole}^{-1}$$

Heats of hydrogenation for other alkenes and dienes are included in Table 20.1.

Note that 1,3-butadiene is a significant exception to the preceding generalization. Its hydrogenation is about 4 kcal mole^{-1} *less exothermic* than for the other two dienes. This compound is an example of a **conjugated diene,** a diene in which the two double bonds are on adjacent atoms. Dienes in which one or more atoms separate the double bonds are called **unconjugated dienes.** The double bonds in unconjugated dienes are called **isolated double bonds.**

Conjugated dienes are significantly more stable than would be expected for a compound with completely independent double bonds. This relatively small but significant difference is attributed to two effects that are shown in Figure 20.6. The two double bond distances are essentially normal but the C_2—C_3 single bond is shorter than the 1.54 Å distance normally associated with C—C single bonds. This decreased bond length results in part from the increased *s* character of the

TABLE 20.1
Heats of Hydrogenation

	$\Delta H°_{\text{hydrog}}$, kcal mole^{-1}
$CH_3CH_2CH{=}CH_2$	−30.2
$CH_3CH_2CH_2CH{=}CH_2$	−29.8
$CH_3CH_2CH_2CH_2CH{=}CH_2$	−30.0
$CH_2{=}CH{-}CH{=}CH_2$	−56.5
$CH_2{=}CHCH_2CH{=}CH_2$	−60.4
$CH_2{=}CHCH_2CH_2CH{=}CH_2$	−60.0

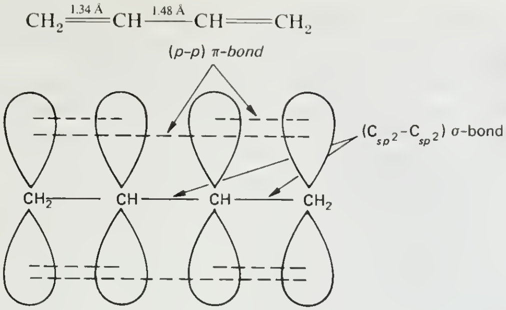

CH2 1.34 Å CH 1.48 Å CH CH2
(p-p) π-bond
(Csp2-Csp2) σ-bond
CH2
CH
CH
CH2

FIGURE 20.6 *Structure of* 1,3-*butadiene.*

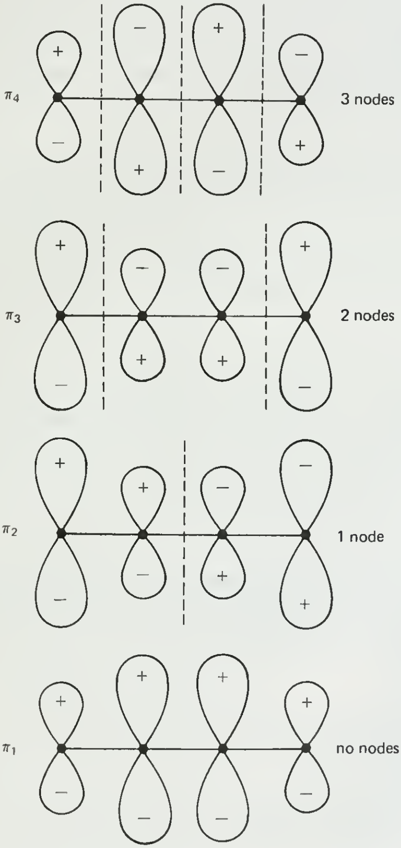

π4
3 nodes
π3
2 nodes
π2
1 node
π1
no nodes

FIGURE 20.7 *π molecular orbitals of* 1,3-*butadiene.*

carbon orbitals comprising this bond; the single bond between the double bonds may be described approximately as C_{sp^2}-C_{sp^2}. This shorter bond is somewhat stronger than C—C bonds having less *s* character.

As shown also in Figure 20.6 the p_z orbitals on carbons 2 and 3 can also overlap to give some double bond character to the 2-3 single bond. This factor also contributes some additional stability to the conjugated double bond system. However, overlap is much less than between the 1-2 and 3-4 carbons because of the greater distance between the 2 and 3 *p* orbitals.

The π overlap between the 2 and 3 carbons produces less bonding than that between the 1-2 and 3-4 carbons. The π system of 1,3-butadiene consists of four overlapping *p* orbitals which generate four molecular orbitals. These orbitals are shown schematically in Figure 20.7. π_1 has no nodes and is a completely bonding molecular orbital; in particular, this molecular orbital gives π bonding between the middle carbons. π_2 has one node between carbons 2 and 3; this molecular orbital contributes antibonding between the center carbons. The four electrons associated with the π system are in molecular orbitals π_1 and π_2 (Figure 20.8); thus, the π bonding between carbons 2 and 3 produced by π_1 is partially offset by the antibonding in π_2. As a result, there is little net π bonding across the center carbons and the net electronic structure is given to a reasonable approximation by the normal Lewis structure

$$H_2C::CH:CH::CH_2$$

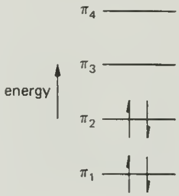
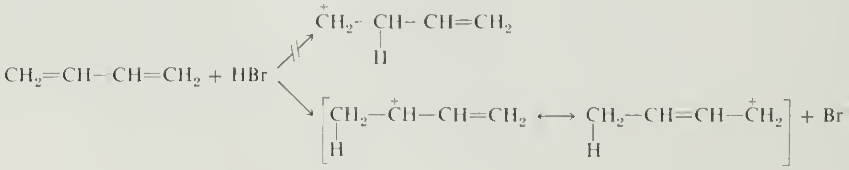


FIGURE 20.8 *Relative energies of π molecular orbitals of* 1,3-*butadiene.*

B. *Addition Reactions*

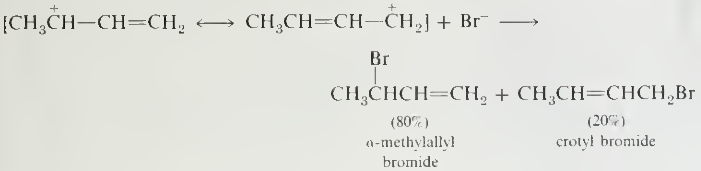
The conjugated character of 1,3-dienes is shown in two-step addition reactions. Such additions are almost invariably initiated at the end of a chain of conjugation to produce a resonance-stabilized allylic intermediate, rather than a nonconjugated intermediate.



$$CH_2{=}CH{-}CH{=}CH_2 + HBr \not\rightarrow \overset{+}{C}H_2{-}\underset{|\atop H}{C}H{-}CH{=}CH_2$$

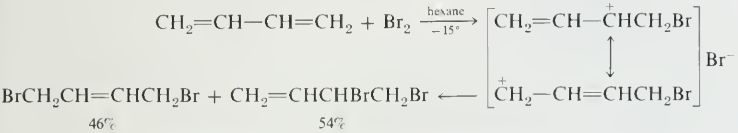
$$CH_2{=}CH{-}CH{=}CH_2 + HBr \rightarrow \left[\underset{|\atop H}{C}H_2{-}\overset{+}{C}H{-}CH{=}CH_2 \longleftrightarrow \underset{|\atop H}{C}H_2{-}CH{=}CH{-}\overset{+}{C}H_2\right] + Br^-$$

This intermediate reacts in a second step to give a mixture of products characteristic of the intermediate allylic system.



$$[CH_3\overset{+}{C}H{-}CH{=}CH_2 \longleftrightarrow CH_3CH{=}CH{-}\overset{+}{C}H_2] + Br^- \longrightarrow \underset{\substack{(80\%)\\ \alpha\text{-methylallyl}\\ \text{bromide}}}{CH_3\overset{\overset{\textstyle Br}{|}}{C}HCH{=}CH_2} + \underset{\substack{(20\%)\\ \text{crotyl bromide}}}{CH_3CH{=}CHCH_2Br}$$

A further example is seen in the addition of bromine to 1,3-butadiene.

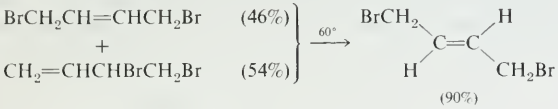


$$CH_2{=}CH{-}CH{=}CH_2 + Br_2 \xrightarrow[-15^\circ]{\text{hexane}} \left[\begin{array}{c} CH_2{=}CH{-}\overset{+}{C}HCH_2Br \\ \updownarrow \\ \overset{+}{C}H_2{-}CH{=}CHCH_2Br \end{array}\right] Br^-$$

$$\underset{46\%}{BrCH_2CH{=}CHCH_2Br} + \underset{54\%}{CH_2{=}CHCHBrCH_2Br} \longleftarrow$$

In this case, the allylic carbonium ion is sufficiently stabilized that the effect of a cyclic bromonium ion is minimized; see Section 12.6.B under Addition of Halogens.

When the mixture of dibromides in the last example is warmed to 60°, the composition of the mixture changes to one consisting of 90% of (E)-1,4-dibromo-2-butene. This compound is easy to isolate in a pure state because it is a solid, m.p. 54°, and crystallizes readily.



Thus, (E)-1,4-dibromo-2-butene is the most stable product, but it is formed at a rate that is comparable to the rate of formation of the other isomer.

This example illustrates an important concept in organic chemistry, **kinetic versus thermodynamic control.** In the addition reaction, the product composition is determined by the relative rates of reaction of the nucleophilic reagent at the two positions of positive charge. These relative reactivities need not, and generally do not, reflect the relative thermodynamic stabilities of the products. In the present case, the reaction of the intermediate carbonium ion with bromide ion occurs approximately equally at both cationic centers; the reaction shows little selectivity. However, 1,4-dibromo-2-butene has a disubstituted double bond and is somewhat more stable than 3,4-dibromo-1-butene, which has a monosubstituted double bond (Section 12.4). Under conditions where the dibromides can react further to reform the carbonium ion, the more stable isomer predominates. Such a process provides a mechanism for establishing equilibrium.

The situation is illustrated in Figure 20.9. The two alternative transition states derived from the intermediate carbonium ion have comparable energies and give the alternative products at approximately equal rates. Actually, the rate of formation of 3,4-dibromo-1-butene, which involves reaction at the more positive secondary carbonium ion, is a little faster than the formation of the 1,4-dibromo isomer. However, the 1,4 isomer is the more stable; it reforms the carbonium ion less readily than the 3,4 isomer. Hence, at equilibrium, some of the 3,4 isomer is converted to 1,4, and the latter predominates.

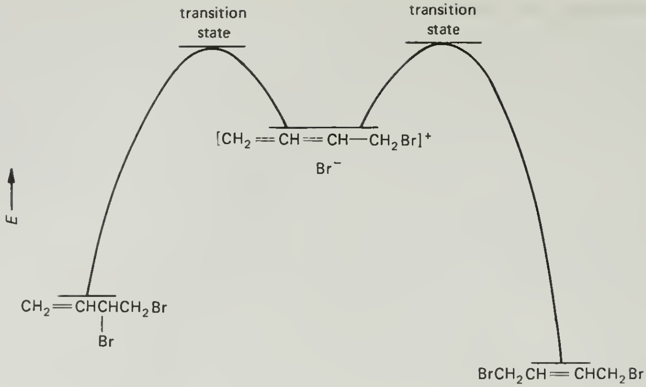

transition state
transition state
[CH₂═CH═CH—CH₂Br]⁺
Br⁻
E
CH₂═CHCHCH₂Br
Br
BrCH₂CH═CHCH₂Br

FIGURE 20.9 *Kinetic and thermodynamic effects in the formation of dibromobutenes.*

The contrast between kinetic and thermodynamic control is important and will be encountered from time to time in our further study of organic chemistry. Another example is found in the reaction products of butadiene with hydrogen bromide. As shown above, 3-bromo-1-butene (α-methylallyl bromide) is the dominant product of the addition reaction. However, the equilibrium mixture consists of only 15% of α-methylallyl bromide and 85% of 1-bromo-2-butene (crotyl bromide). Once again, equilibrium favors the more highly substituted double bond. On prolonged reaction or by treatment with strong Lewis acids such as ferric bromide, the equilibrium mixture is produced (Figure 20.10).

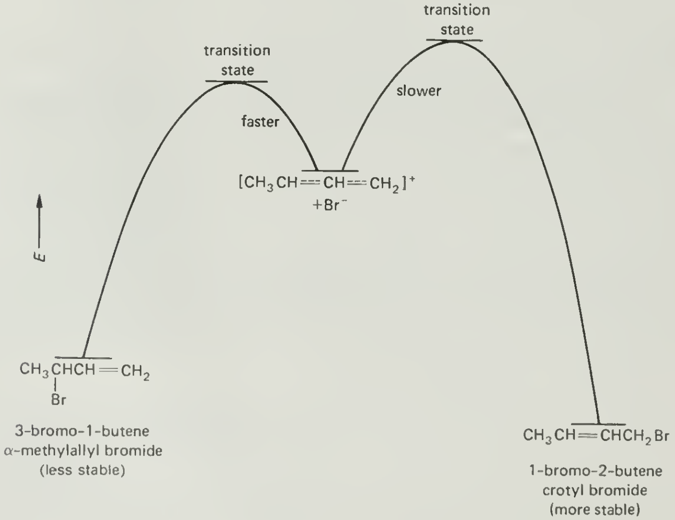

transition state
transition state
slower
faster
[CH₃CH═CH═CH₂]⁺
+Br⁻
E
CH₃CHCH═CH₂
Br
3-bromo-1-butene
α-methylallyl bromide
(less stable)
CH₃CH═CHCH₂Br
1-bromo-2-butene
crotyl bromide
(more stable)

FIGURE 20.10 *Kinetic and thermodynamic effects in the formation of bromobutenes.*

C. *1,2-Dienes: Allenes*

1,2-Propadiene, $CH_2{=}C{=}CH_2$, has the trivial name of allene. Both double bonds in this hydrocarbon are especially short; the bond distance of 1.31 Å is in between that for the double bond in ethylene, 1.34 Å, and the triple bond in acetylene, 1.20 Å. The electronic structure can be represented in terms of two double-bond systems *at right angles* as in Figure 20.11. Note that the central carbon is *sp* hybridized. The additional *s* character in these C=C double bonds accounts for the rather short length.

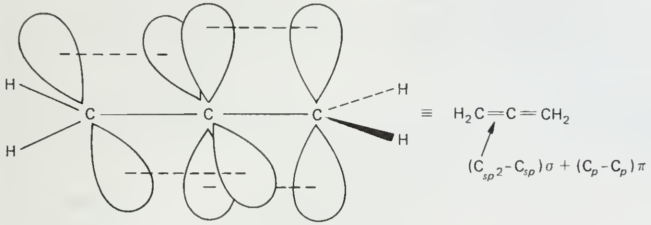
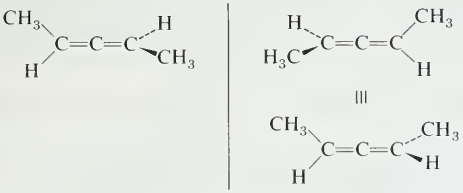


FIGURE 20.11 *Orbital structure of allene.*

One especially interesting feature of allenes that results from the nonplanar character of the molecule is that suitably substituted allenes are chiral and can be obtained as optically active enantiomers. For example, penta-2,3-diene has no plane of symmetry. Its mirror images are not superimposable, and this hydrocarbon is capable of existence in (+) and (−) enantiomers.



mirror images of penta-2,3-diene

A stereo representation of such an allene is given in Figure 20.12.

Molecules with **cumulated** double bonds, as in allene, do not constitute an important class of compounds. They are generally difficult to prepare and can frequently be isomerized to more stable dienes. Allene, for example, with $\Delta H_f^\circ = 45.9$ kcal mole^{-1} is 1.6 kcal mole^{-1} *less* stable than propyne with $\Delta H_f^\circ = 44.3$ kcal mole^{-1}. 1,2-Butadiene (methylallene, $CH_3CH{=}C{=}CH_2$, $\Delta H_f^\circ = 38.3$ kcal mole^{-1}) is slightly more stable than 1-butyne ($\Delta H_f^\circ = 39.5$ kcal

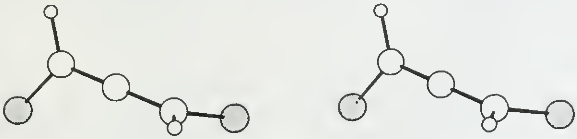
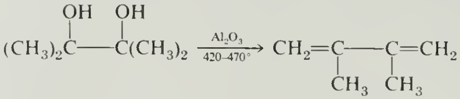


FIGURE 20.12 *Stereo representation of a 1,3 disubstituted allene.*

mole^{-1}) but is more than 4 kcal mole^{-1} less stable than 2-butyne ($\Delta H_f^\circ = 34.7$ kcal mole^{-1}) and almost 13 kcal mole^{-1} less stable than 1,3-butadiene ($\Delta H_f^\circ = 26.1$ kcal mole^{-1}).

D. *Preparation of Dienes*

Many dienes can be prepared in much the same way as monoenes except that two functional groups are involved. Some examples are



$$(CH_3)_2C(OH){-}C(OH)(CH_3)_2 \xrightarrow[420\text{-}470^\circ]{Al_2O_3} CH_2{=}C(CH_3){-}C(CH_3){=}CH_2$$

(79-85%)
2,3-dimethyl-1,3-butadiene

$$CH_3COOCH_2CH_2CH_2CH_2CH_2OOCCH_3 \xrightarrow{575^\circ}$$
$$2\,CH_3COOH + CH_2{=}CHCH_2CH{=}CH_2$$

(63-71%)
1,4-pentadiene

Many other synthetic methods are known, but most require difunctional compounds to be studied later.

Allylic halides are useful for preparing both conjugated and unconjugated dienes. Displacement by a vinylmagnesium halide on an allyl halide is another route to 1,4-dienes (see Section 20.1.B).

$$CH_2{=}CHCH_2Cl + CH_2{=}CHMgBr \xrightarrow{\text{ether}} CH_2{=}CHCH_2CH{=}CH_2$$

The Wittig reaction (Section 15.7.H) with allylphosphoranes gives 1,3-dienes.

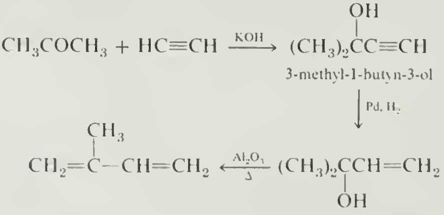
$$CH_2{=}CHCH_2Cl + P(C_6H_5)_3 \longrightarrow CH_2{=}CHCH_2\overset{+}{P}(C_6H_5)_3\ Cl^-$$

allyltriphenylphosphonium chloride

$$\begin{tikzcd} CH_2{=}CHCH_2\overset{+}{P}(C_6H_5)_3 \arrow[r, "LiOC_2H_5"] & {[CH_2{=}CH\overset{-}{C}H\overset{+}{P}(C_6H_5)_3]} \arrow[d, "C_6H_5CHO"] \\ & CH_2{=}CHCH{=}CHC_6H_5 + (C_6H_5)_3PO \end{tikzcd}$$

1-phenyl-1,3-butadiene

Another use of allylic intermediates is exemplified in one preparation of 2-methyl-1,3-butadiene (isoprene).



$$\begin{tikzcd} CH_3COCH_3 + HC{\equiv}CH \arrow[r, "KOH"] & (CH_3)_2C(OH)C{\equiv}CH \arrow[d, "Pd,\ H_2"] \\ CH_2{=}C(CH_3){-}CH{=}CH_2 & (CH_3)_2C(OH)CH{=}CH_2 \arrow[l, "Al_2O_3"', "\Delta"] \end{tikzcd}$$

3-methyl-1-butyn-3-ol

isoprene

3-methyl-1-buten-3-ol

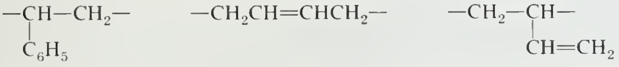
E. *Diene Polymers*

Butadiene is probably the most important of the dienes. It is prepared commercially in large quantity by the catalytic dehydrogenation of butane or of butane-butene mixtures.

$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{catalyst}]{600^\circ} CH_2{=}CH{-}CH{=}CH_2 + 2\ H_2$$

Butadiene is a gas at room temperature, b.p. -45°, m.p., -113°. Large amounts are used as an intermediate in organic syntheses. For example, its reaction with chlorine is used to prepare large quantities of 1,4-dichloro-2-butene, an important intermediate in one route to nylon (Section 27.7.A). However, most butadiene is used directly, often in conjunction with one or more other monomers, to produce polymers.

A copolymer of 4–5 moles of butadiene to 1 mole of styrene, $C_6H_5CH{=}CH_2$, is an **elastomer** known as the synthetic rubber Buna S or GRS. In this free radical polymerization, the butadiene adds by *cis*- and *trans*-1,4- and 1,2-addition. The repeating units in the polymer are

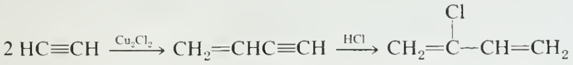


$$-\underset{\displaystyle C_6H_5}{\underset{|}{CH}}-CH_2- \qquad -CH_2CH{=}CHCH_2- \qquad -CH_2-\underset{\displaystyle CH{=}CH_2}{\underset{|}{CH}}-$$

cis and *trans*

Butadiene is also polymerized with Ziegler-Natta catalysts (alkylaluminum and titanium chloride) or by alkali metal catalysts based on alkylsodium formulations or lithium dispersions. Some of these methods are highly specific and give either *cis*- or *trans*-1,4- or 1,2-additions.

Neoprene is a synthetic elastomer obtained by the free radical polymerization of chloroprene, 2-chloro-1,3-butadiene, which in turn is prepared by a route starting with acetylene (page 318).

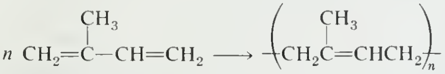


$$2\ HC{\equiv}CH \xrightarrow{Cu_2Cl_2} \underset{\text{vinylacetylene}}{CH_2{=}CHC{\equiv}CH} \xrightarrow{HCl} \underset{\text{chloroprene}}{CH_2{=}\overset{\displaystyle Cl}{\overset{|}{C}}{-}CH{=}CH_2}$$

vinylacetylene chloroprene

Neoprene has unique properties, such as resistance to oils, oxygen, and heat.

2-Methyl-1,3-butadiene, isoprene, also polymerizes under the influence of acids or Ziegler-Natta catalysts to a polyisoprene with rubber-like properties.



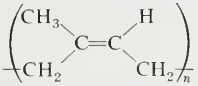
$$n\ CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH{=}CH_2 \longrightarrow \left(CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CHCH_2\right)_n$$

isoprene
2-methyl-1,3-butadiene

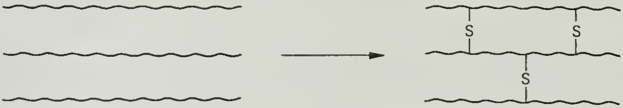
polyisoprene

The double bonds in this synthetic polyisoprene are both *cis* and *trans*.

Natural rubber consists mostly of polyisoprene with *cis*-1,4 head-to-tail units:

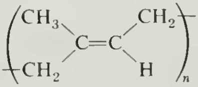


The natural latex is not a useful elastomer or rubber but requires a **vulcanization** process. One such process was discovered by Charles Goodyear in 1839 and involves heating the latex with sulfur. The process appears to involve the addition of sulfur units to the double bonds with the production of **crosslinks** between the polymer chains. Because of these crosslinks, the polymer resists distortion and tends to return to its original shape.



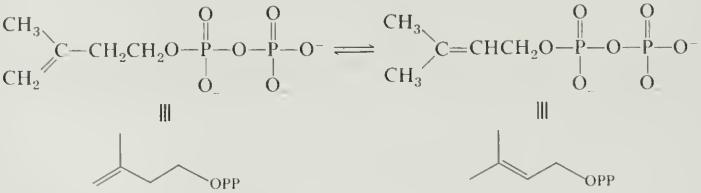
> Elasticity has important structural requirements. If a polymer has regular repeating units, regions of the polymer may pack together by van der Waals forces in a manner similar to crystals. Such polymers are more or less crystalline and tend to be hard solids. Polymers that have flexible and irregular chains tend to be less rigid, but such a polymer is not an elastomer unless it will restore when stress is removed. Hence, elastomers tend to have flexible chains with varying amounts of crosslinking.

Some plants produce a polyisoprene with *trans*-1,4 isoprene units.



This material is known as gutta-percha, a harder and less elastomeric natural polymer.

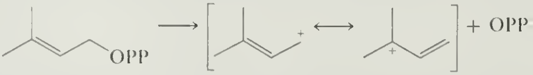
Natural rubber and gutta-percha are built up by plants **(biosynthesized)** from acetic acid units (Section 36.6). By a series of enzyme-catalyzed steps, acetic acid is transformed into the compound isopentenyl pyrophosphate, which is, in turn, isomerized to γ,γ-dimethylallyl pyrophosphate.



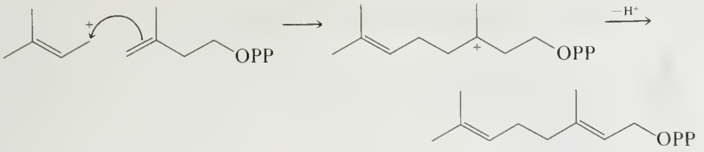
isopentenyl pyrophosphate

γ,γ-dimethylallyl pyrophosphate

The latter compound is the ester of pyrophosphoric acid (Section 18.13.B) and γ,γ-dimethylallyl alcohol. Since the pyrophosphate ion is a good leaving group, γ,γ-dimethylallyl pyrophosphate forms an allylic cation with ease (Section 20.1.A).

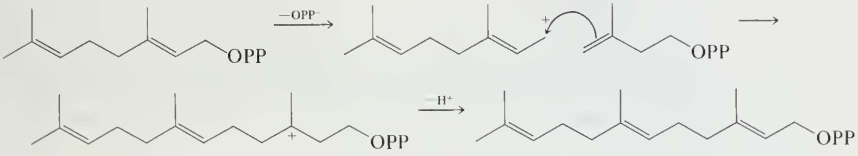


The dimethylallyl cation so produced reacts with isopentenyl pyrophosphate to give a new carbonium ion, which eliminates to give geranyl pyrophosphate.



geranyl pyrophosphate

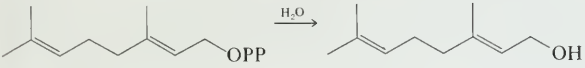
A repetition of the process yields farnesyl pyrophosphate.



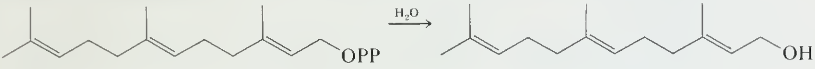
farnesyl pyrophosphate

If the process is continued through many more cycles, gutta-percha, with all *trans* double bonds, is produced. A similar set of enzyme-controlled coupling processes converts isopentenyl pyrophosphate into rubber.

Geranyl pyrophosphate and farnesyl pyrophosphate are the immediate precursers to the naturally occurring alcohols geraniol and farnesol, respectively.

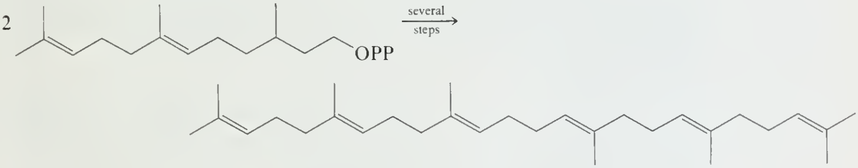


geraniol



farnesol

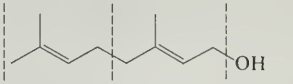
Another biological path exists whereby two farnesyl pyrophosphate molecules are coupled to yield the C_{30} hexaene **squalene.**



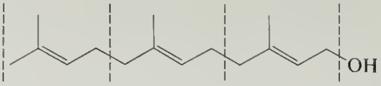
squalene

Squalene is a high-boiling, viscous oil which is found in large quantities in shark liver oil. It may be isolated in smaller amounts from olive oil, wheat germ oil, rice bran oil, and yeast, and is an intermediate in the biosynthesis of steroids (Section 36.6).

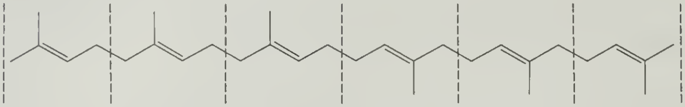
Geraniol, farnesol, and squalene are examples of **terpenes,** naturally occurring materials built up from isopentenyl or "isoprene" units. Geraniol is classed as a **monoterpene** (two isoprene units), farnesol as a **sesquiterpene** (three isoprene units), and squalene is a **triterpene** (six isoprene units)



geraniol



farnesol



squalene

Terpenes are widespread in nature, although most are cyclic compounds. We shall see examples of these more common members of the class in Section 23.9.

20.3
Unsaturated Carbonyl Compounds

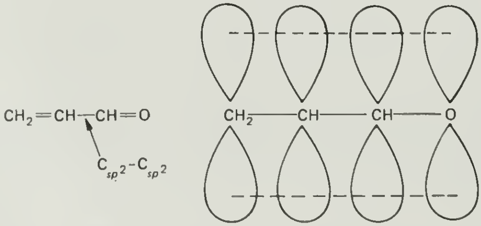
A. *Unsaturated Aldehydes and Ketones*

Compounds having both a carbonyl group and a double bond are known as unsaturated aldehydes or ketones. As with dienes, the two centers of unsaturation can be conjugated or unconjugated and the conjugated isomers are generally more stable. For example

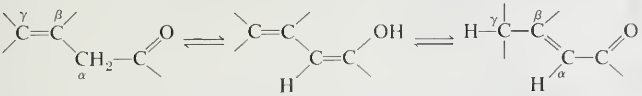
$$\underset{\text{unconjugated isomer}}{CH_2{=}CHCH_2CHO} \longrightarrow \underset{\text{conjugated isomer}}{CH_3CH{=}CHCHO} \qquad \Delta H^\circ = -6 \text{ kcal mole}^{-1}$$

$$\underset{\text{unconjugated isomer}}{CH_2{=}CHCH_2CH{=}CH_2} \longrightarrow \underset{\text{conjugated isomer}}{CH_3CH{=}CHCH{=}CH_2} \qquad \Delta H^\circ = -7 \text{ kcal mole}^{-1}$$

The stabilizing effect of conjugation in unsaturated carbonyl compounds is approximately of the same magnitude as for the corresponding dienes. It is explained in the same manner in terms of the stabilizing effect of the central C_{sp^2}-C_{sp^2} bond and by the overlap of p orbitals to give π bonding.



Because of the greater stability of the conjugated unsaturated aldehydes and ketones, an isolated double bond will tend to **move into conjugation** if a suitable pathway is available. This migration of double bonds is especially facile for double bonds that are β,γ to the carbonyl group by acid- and base-catalyzed reactions that involve the intermediate enol.



β,γ-unsaturated isomer (less stable) enol form α,β-unsaturated isomer (more stable)

For example, the methylene hydrogens in 3-butenal (vinylacetaldehyde), are appreciably acidic because they are α to the carbonyl group and give rise to a resonance-stabilized enolate ion. However, in this enolate ion a further resonance structure can be written that shows that negative charge is also spread to the γ-carbon.

$$\mathrm{CH_2{=}CHCH_2CHO} + \mathrm{OH^-} \rightleftharpoons \mathrm{H_2O} + \left[\begin{array}{c} \mathrm{CH_2{=}CH{-}\overset{\bar{..}}{C}H{-}CH{=}\underset{..}{\overset{..}{O}}} \\ \updownarrow \\ \mathrm{CH_2{=}CH{-}CH{=}CH{-}\underset{..}{\overset{\bar{..}}{O}}{:}} \\ \updownarrow \\ \mathrm{\overset{\bar{..}}{C}H_2{-}CH{=}CH{-}CH{=}\underset{..}{\overset{..}{O}}} \end{array}\right]$$

vinylacetaldehyde
3-butenal

The delocalized anion can be protonated by water on oxygen to give the enol form, on the α-carbon to regenerate vinylacetaldehyde, or at the γ-carbon to generate crotonaldehyde.

$$\left[\begin{array}{l} \mathrm{CH_2{=}CH{-}CH{=}CH{-}\underset{..}{\overset{..}{O}}{:}^-} \\ \qquad\quad\updownarrow \\ \mathrm{CH_2{=}CH{-}\overset{\bar{..}}{C}H{-}CH{=}O} \\ \qquad\quad\updownarrow \\ \mathrm{\overset{\bar{..}}{C}H_2{-}CH{=}CH{-}CH{=}O} \end{array}\right] + \mathrm{H_2O} \begin{array}{ll} \nearrow\!\!\!\swarrow & \mathrm{CH_2{=}CH{-}CH{=}CH{-}OH} \\ & \qquad\text{enol form} \\ \rightleftharpoons & \mathrm{CH_2{=}CH{-}CH_2{-}CH{=}O} \\ & \qquad\text{vinylacetaldehyde} \\ \searrow\!\!\!\nwarrow & \mathrm{CH_3{-}CH{=}CH{-}CH{=}O} \\ & \qquad\text{crotonaldehyde} \end{array}$$

All of these compounds are interconverted by base, but at equilibrium the most stable isomer, the conjugated crotonaldehyde, predominates to the extent of about 99.99% (Figure 20.13).

One way in which these interconversions can be established is by deuterium exchange. The enolate ion derived from crotonaldehyde or vinylacetaldehyde can react with D_2O at either of the carbons that bear the negative charge.

$$\left[\begin{array}{c} \mathrm{{}^-CH_2{-}CH{=}CHCHO} \\ \updownarrow \\ \mathrm{CH_2{=}CH{-}\bar{C}HCHO} \end{array}\right] \begin{array}{l} \xrightarrow{\mathrm{D_2O}} \mathrm{CH_2D{-}CH{=}CHCHO} \\ \\ \xrightarrow{\mathrm{D_2O}} \mathrm{CH_2{=}CH{-}CHDCHO} \end{array}$$

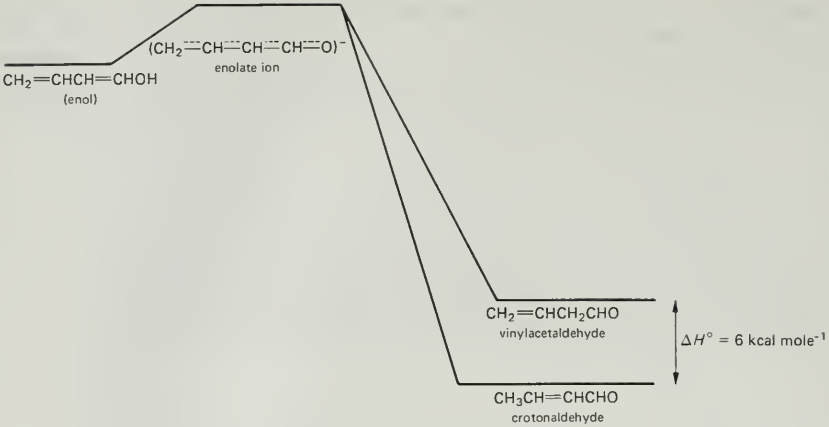
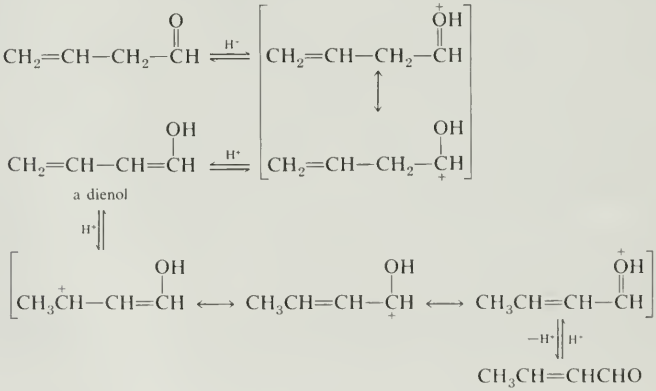


FIGURE 20.13 *Some energy relationships of an unsaturated aldehyde.*

Repeated reaction with base to reform the enolate ion and reaction with D_2O eventually produces the tetradeuterio compound, $CD_3CH{=}CDCHO$.

The acid-catalyzed interconversions involve the intermediate enol in exact analogy to simple aldehydes and ketones (Section 15.6). Rapid and reversible protonation occurs at the carbonyl oxygen to form a hydroxycarbonium ion which can lose a proton from carbon to form an enol. This enol is also a diene and can reprotonate at either the α- or γ-carbons to produce the β,γ- or α,β-unsaturated carbonyl, respectively.



$$\mathrm{CH_2{=}CH{-}CH_2{-}\overset{\overset{O}{\|}}{C}H} \xrightleftharpoons{H^+} \left[\mathrm{CH_2{=}CH{-}CH_2{-}\overset{\overset{\overset{+}{O}H}{\|}}{C}H} \longleftrightarrow \mathrm{CH_2{=}CH{-}CH_2{-}\underset{+}{\overset{\overset{OH}{|}}{C}H}}\right]$$

$$\underset{\text{a dienol}}{\mathrm{CH_2{=}CH{-}CH{=}\overset{\overset{OH}{|}}{C}H}} \xrightleftharpoons{H^+} \left[\mathrm{CH_2{=}CH{-}CH_2{-}\underset{+}{\overset{\overset{OH}{|}}{C}H}}\right]$$

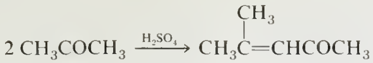
$$\Big\downarrow\!\!\Big\uparrow H^+$$

$$\left[\mathrm{CH_3\overset{+}{C}H{-}CH{=}\overset{\overset{OH}{|}}{C}H} \longleftrightarrow \mathrm{CH_3CH{=}CH{-}\underset{+}{\overset{\overset{OH}{|}}{C}H}} \longleftrightarrow \mathrm{CH_3CH{=}CH{-}\overset{\overset{\overset{+}{O}H}{\|}}{C}H}\right]$$

$$-H^+ \Big\downarrow\!\!\Big\uparrow H^+$$

$$\mathrm{CH_3CH{=}CHCHO}$$

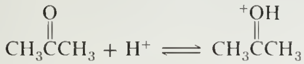
α,β-Unsaturated aldehydes and ketones are often obtained directly in the condensation of aldehydes and ketones under basic conditions (the aldol condensation, Section 15.7.G). They may also be obtained under acidic conditions. For example, the acid-catalyzed condensation of acetone produces 4-methylpent-3-en-2-one, commonly called "mesityl oxide."



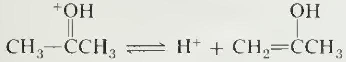
$$2\,CH_3COCH_3 \xrightarrow{H_2SO_4} CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CHCOCH_3$$

mesityl oxide
4-methylpent-3-en-2-one

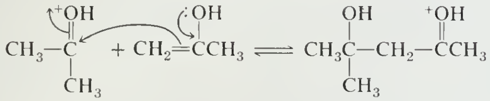
The mechanism of this condensation involves a number of straightforward steps. To start, the enol form of acetone adds to another protonated acetone molecule.

(1)


$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + H^+ \rightleftharpoons CH_3\overset{\overset{\displaystyle {}^+OH}{\|}}{C}CH_3$$

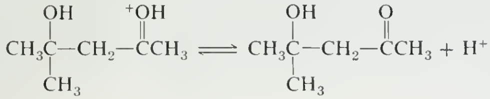
(2)


$$CH_3{-}\overset{\overset{\displaystyle {}^+OH}{\|}}{C}CH_3 \rightleftharpoons H^+ + CH_2{=}\overset{\overset{\displaystyle OH}{|}}{C}CH_3$$

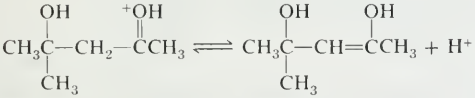
(3)


$$CH_3{-}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle {}^+OH}{\|}}{C}} + CH_2{=}\overset{\overset{\displaystyle \ddot{O}H}{|}}{C}CH_3 \rightleftharpoons CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}CH_2{-}\overset{\overset{\displaystyle {}^+OH}{\|}}{C}CH_3$$

The resulting oxonium ion can lose a proton from oxygen to give 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol, Section 15.7.G) or from carbon to give the enol form of diacetone alcohol.

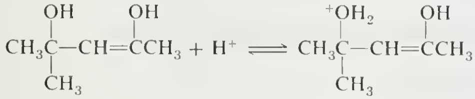
(4)


$$CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}CH_2{-}\overset{\overset{\displaystyle {}^+OH}{\|}}{C}CH_3 \rightleftharpoons CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}CH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + H^+$$

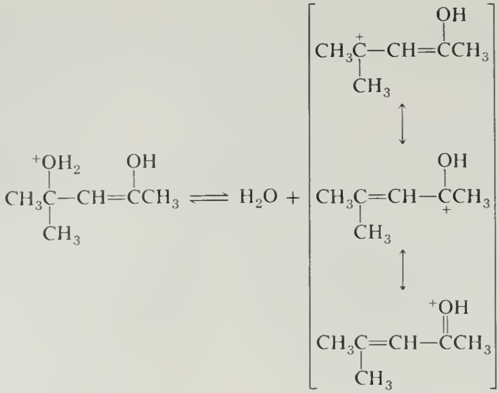
(4′)


$$CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}CH_2{-}\overset{\overset{\displaystyle {}^+OH}{\|}}{C}CH_3 \rightleftharpoons CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}CH{=}\overset{\overset{\displaystyle OH}{|}}{C}CH_3 + H^+$$

The latter species is an enol form of a ketone and is unstable relative to the ketone; it is present in only low concentration. Protonation on the tertiary hydroxy gives an oxonium ion which readily eliminates water to form a new cation. The cation is resonance-stabilized, with the positive charge spread over oxygen and two carbons. The oxonium ion structure is the more important structure because all atoms have octet configurations.

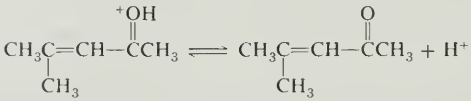
(5)


$$CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}{-}CH{=}\overset{\overset{\displaystyle OH}{|}}{C}CH_3 + H^+ \rightleftharpoons CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle {}^+OH_2}{|}}{C}}{-}CH{=}\overset{\overset{\displaystyle OH}{|}}{C}CH_3$$

(6) 

$$CH_3\underset{CH_3}{\overset{^{+}OH_2}{C}}-CH=\overset{OH}{C}CH_3 \rightleftharpoons H_2O + \left[CH_3\underset{CH_3}{\overset{+}{C}}-CH=\overset{OH}{C}CH_3 \updownarrow CH_3\underset{CH_3}{C}=CH-\underset{+}{\overset{OH}{C}}CH_3 \updownarrow CH_3\underset{CH_3}{C}=CH-\overset{^{+}OH}{\overset{\|}{C}}CH_3 \right]$$

Loss of the proton from oxygen gives the product, mesityl oxide.

(7) 

$$CH_3\underset{CH_3}{C}=CH-\overset{^{+}OH}{\overset{\|}{C}}CH_3 \rightleftharpoons CH_3\underset{CH_3}{C}=CH-\overset{O}{\overset{\|}{C}}CH_3 + H^+$$

It should be emphasized that in this reaction sequence, simple alkyl cations are not involved. *Every organic cationic intermediate is an oxonium ion.*

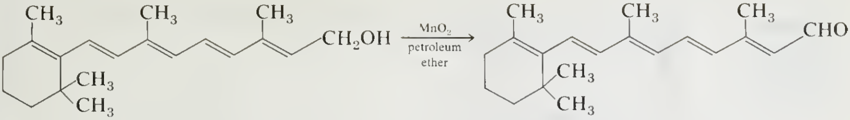
The simplest conjugated unsaturated carbonyl compound is propenal, $CH_2{=}CHCHO$, commonly known as acrolein. This compound is a liquid, b.p. 53°, having a powerful, pungent odor. It may be prepared by a special reaction in which the readily available triol, glycerol, is heated with sulfuric acid or potassium acid sulfate.

$$\underset{\substack{\text{glycerol}\\ \text{1,2,3-propanetriol}}}{HOCH_2CHOHCH_2OH} \xrightarrow[200\text{-}230°]{KHSO_4} \underset{\substack{\text{acrolein}\\ \text{propenal}}}{CH_2{=}CHCHO}$$

Most of us are familiar with the odor of acrolein because a similar dehydration occurs thermally when fats burn or decompose on a hot surface. Recall that fats are esters of glycerol (Section 18.14).

α,β-Unsaturated aldehydes and ketones are also available by oxidation of the corresponding unsaturated alcohols which, in turn, are frequently available by Grignard syntheses. The oxidation requires mild conditions in order not to oxidize the double bond. One reagent that is specific for allylic alcohols is manganese dioxide in a specially active form that is prepared by treatment of manganese sulfate with base and potassium permanganate.

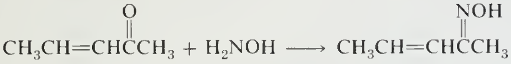
$$\underset{\text{allyl alcohol}}{CH_2{=}CHCH_2OH} \xrightarrow[\substack{\text{petroleum ether}\\ \text{reflux}}]{MnO_2} \underset{\substack{(99\%)\\ \text{acrolein}}}{CH_2{=}CHCHO}$$



vitamin A_1

(80%)
retinal
(vitamin A_1 aldehyde)

α,β-Unsaturated aldehydes and ketones undergo many of the reactions expected separately for the double bond and carbonyl functions. The C=O group forms normal derivatives such as oximes, phenylhydrazones, and so on (Section 15.7.C).



$$CH_3CH{=}CH\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + H_2NOH \longrightarrow CH_3CH{=}CH\overset{\overset{\displaystyle NOH}{\|}}{C}CH_3$$

an oxime

The aldehyde group is oxidized under mild conditions to a carboxylic acid (Section 15.8.A).

$$CH_2{=}CHCHO + Ag_2O \longrightarrow CH_2{=}CHCOOH + 2\ Ag$$

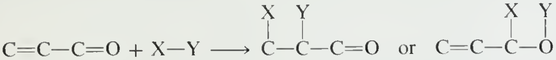
Bromine can be added to the double bond (Section 12.6.B under Addition of Halides).

$$C_6H_5CH{=}CHCOCH_3 + Br_2 \xrightarrow[10\text{–}20^\circ]{CCl_4} C_6H_5CHBrCHBrCOCH_3$$

(52–57%)

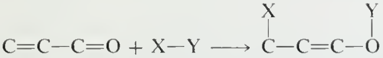
However, some reactions are unique to the conjugated system. Additions may occur across the ends of the conjugated system or to either one of the double bonds, just as in the case of conjugated dienes (Section 20.2.B). Additions which occur to a single double bond are called **1,2-additions,** or **normal additions.** Additions which occur across the ends of the conjugated system are called **1,4-additions** or **conjugate additions.**

1,2-additions



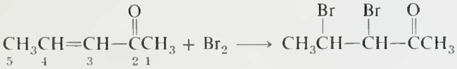
$$C{=}C{-}C{=}O + X{-}Y \longrightarrow \overset{\overset{\displaystyle X}{|}}{C}{-}\overset{\overset{\displaystyle Y}{|}}{C}{-}C{=}O \quad \text{or} \quad C{=}C{-}\overset{\overset{\displaystyle X}{|}}{C}{-}\overset{\overset{\displaystyle Y}{|}}{O}$$

1,4-additions



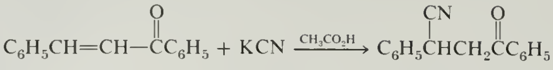
$$C{=}C{-}C{=}O + X{-}Y \longrightarrow \overset{\overset{\displaystyle X}{|}}{C}{-}C{=}C{-}\overset{\overset{\displaystyle Y}{|}}{O}$$

Do not be confused by the terms 1,2-addition and 1,4-addition. The numbers do not refer to the carbon numbers in any given compound. The terms mean that the addition is to the 1 and 2 positions or the 1 and 4 positions of a conjugated system. For example, the addition of Br_2 to the double bond in pent-3-en-2-one is an example of a 1,2-addition.



$$\underset{5}{C}H_3\underset{4}{C}H{=}\underset{3}{C}H{-}\overset{\overset{\displaystyle O}{\|}}{\underset{2}{C}}\underset{1}{C}H_3 + Br_2 \longrightarrow CH_3\overset{\overset{\displaystyle Br}{|}}{C}H{-}\overset{\overset{\displaystyle Br}{|}}{C}H{-}\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

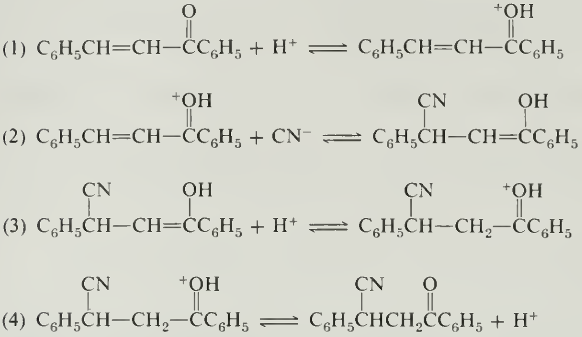
For example, cyanide ion, which normally adds to the C=O bond in aldehydes and ketones (Section 15.7.F), frequently adds to the C=C bond when it is conjugated with a carbonyl group.



$$C_6H_5CH{=}CH{-}\overset{\overset{\textstyle O}{\|}}{C}C_6H_5 + KCN \xrightarrow{CH_3CO_2H} C_6H_5\overset{\overset{\textstyle CN}{|}}{C}HCH_2\overset{\overset{\textstyle O}{\|}}{C}C_6H_5$$

(93–96%)

The reaction appears to be a 1,2-addition to the double bond. However, the mechanism actually involves a 1,4-addition of HCN to the conjugated system. The initial product of the 1,4-addition is an enol, which tautomerizes to the observed keto form.



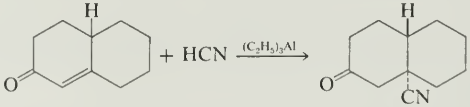
$$(1)\ C_6H_5CH{=}CH{-}\overset{\overset{\textstyle O}{\|}}{C}C_6H_5 + H^+ \rightleftharpoons C_6H_5CH{=}CH{-}\overset{\overset{\textstyle ^+OH}{\|}}{C}C_6H_5$$

$$(2)\ C_6H_5CH{=}CH{-}\overset{\overset{\textstyle ^+OH}{\|}}{C}C_6H_5 + CN^- \rightleftharpoons C_6H_5\overset{\overset{\textstyle CN}{|}}{C}H{-}CH{=}\overset{\overset{\textstyle OH}{|}}{C}C_6H_5$$

$$(3)\ C_6H_5\overset{\overset{\textstyle CN}{|}}{C}H{-}CH{=}\overset{\overset{\textstyle OH}{|}}{C}C_6H_5 + H^+ \rightleftharpoons C_6H_5\overset{\overset{\textstyle CN}{|}}{C}H{-}CH_2{-}\overset{\overset{\textstyle ^+OH}{\|}}{C}C_6H_5$$

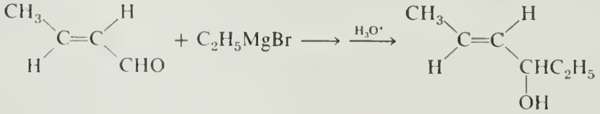
$$(4)\ C_6H_5\overset{\overset{\textstyle CN}{|}}{C}H{-}CH_2{-}\overset{\overset{\textstyle ^+OH}{\|}}{C}C_6H_5 \rightleftharpoons C_6H_5\overset{\overset{\textstyle CN}{|}}{C}HCH_2\overset{\overset{\textstyle O}{\|}}{C}C_6H_5 + H^+$$

A particularly effective method for accomplishing the 1,4-addition of HCN to α,β-unsaturated ketones employs triethylaluminum as a catalyst. The procedure gives high yields of the conjugate adduct even when the enone is highly substituted at the β position.

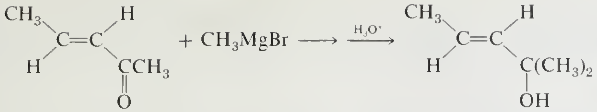


(85%)

Organometallic compounds may add either 1,2 or 1,4. Grignard reagents show variable behavior depending on the structure of the conjugated system. The most important factor in determining whether the addition is 1,2 or 1,4 seems to be steric hindrance. Most α,β-unsaturated aldehydes undergo normal 1,2-addition to the carbonyl group.

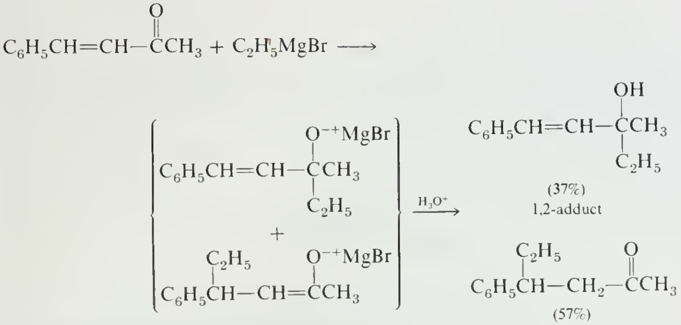


(70%)
trans-4-hexen-3-ol



(80%)
2-methyl-*trans*-3-penten-2-ol

However, many other α,β-unsaturated ketones give substantial amounts also of the 1,4-adduct.



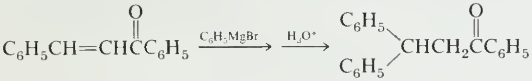
$$C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}CH_3 + C_2H_5MgBr \longrightarrow$$

$$\left[\begin{array}{c} C_6H_5CH{=}CH{-}\overset{O^{-+}MgBr}{\underset{C_2H_5}{C}}CH_3 \\ + \\ C_6H_5\overset{C_2H_5}{CH}{-}CH{=}\overset{O^{-+}MgBr}{C}CH_3 \end{array}\right] \xrightarrow{H_3O^+} \begin{array}{c} C_6H_5CH{=}CH{-}\overset{OH}{\underset{C_2H_5}{C}}CH_3 \\ \\ C_6H_5\overset{C_2H_5}{CH}{-}CH_2{-}\overset{O}{\overset{\|}{C}}CH_3 \end{array}$$

(37%)
1,2-adduct

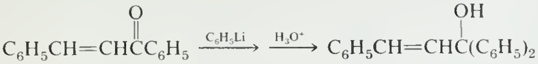
(57%)
1,4-adduct

In some cases, 1,4-addition is almost the sole product.



(96%)
1,3,3-triphenyl-1-propanone

Organolithium compounds show a much greater tendency to engage in 1,2-addition.



$$C_6H_5CH{=}CH\overset{O}{\overset{\|}{C}}C_6H_5 \xrightarrow{C_6H_5Li} \xrightarrow{H_3O^+} C_6H_5CH{=}CH\overset{OH}{\overset{|}{C}}(C_6H_5)_2$$

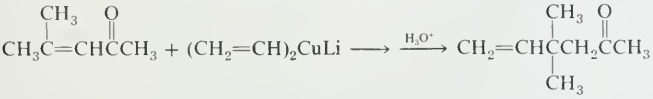
(75%)

When one wants to maximize 1,2-addition, it is customary to utilize the organolithium reagent.

On the other hand, 1,4-addition may be achieved by using lithium dialkylcuprates, which are readily prepared from the corresponding alkyllithium reagent and cuprous iodide (Section 9.5.D).

$$2\ CH_3Li + CuI \longrightarrow (CH_3)_2CuLi$$

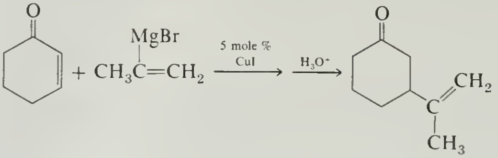
These reagents add exclusively in a 1,4 fashion.



$$CH_3\overset{CH_3}{\overset{|}{C}}{=}CH\overset{O}{\overset{\|}{C}}CH_3 + (CH_2{=}CH)_2CuLi \longrightarrow \xrightarrow{H_3O^+} CH_2{=}CH\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$$

(72%)

The same result may often be achieved by forming the dialkylcuprate *in situ* from the corresponding Grignard reagent. In practice, it is only necessary to use a catalytic amount of cuprous bromide or iodide.

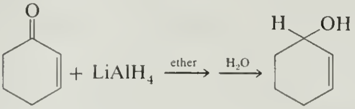

O
MgBr
+ CH$_3$C=CH$_2$
5 mole %
CuI
H$_3$O$^+$
O
CH$_2$
C
CH$_3$

(68%)

Reduction of α,β-unsaturated carbonyl compounds can also involve either the C=C or the C=O double bond. Lithium aluminum hydride reduction of most such compounds gives the highest amount of simple carbonyl reduction.

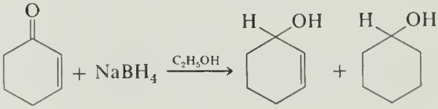
$$CH_3CH{=}CHCHO + LiAlH_4 \xrightarrow{\text{ether}} \xrightarrow{H_2O} CH_3CH{=}CHCH_2OH$$

(82%)


O
+ LiAlH$_4$
ether
H$_2$O
H
OH

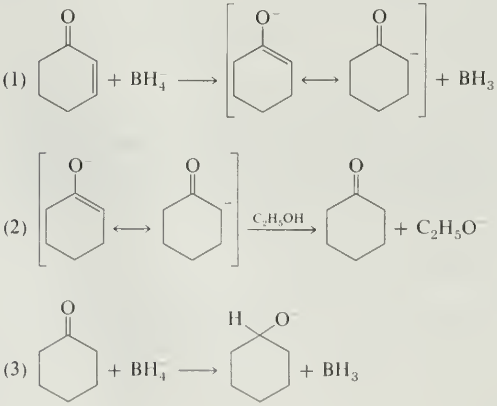
(97%)

In contrast, sodium borohydride in ethanol gives substantial amounts of 1,4-addition.

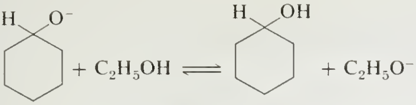

O
+ NaBH$_4$
C$_2$H$_5$OH
H
OH
+
H
OH

(59%) (41%)

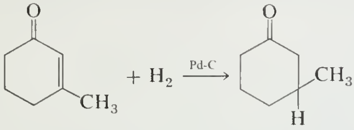
The fully reduced product in the preceeding example arises from the following pathway, which begins with the conjugate addition of hydride to the enone system.


(1)
O
+ BH$_4^-$
O$^-$
O
+ BH$_3$
(2)
O$^-$
O
C$_2$H$_5$OH
O
+ C$_2$H$_5$O$^-$
(3)
O
+ BH$_4^-$
H
O$^-$
+ BH$_3$

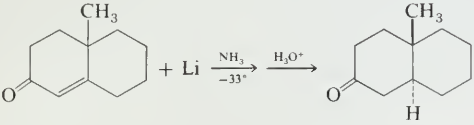
(4)



The double bond of such a conjugated system may generally be reduced cleanly by either of two procedures, catalytic hydrogenation or lithium-ammonia reduction.

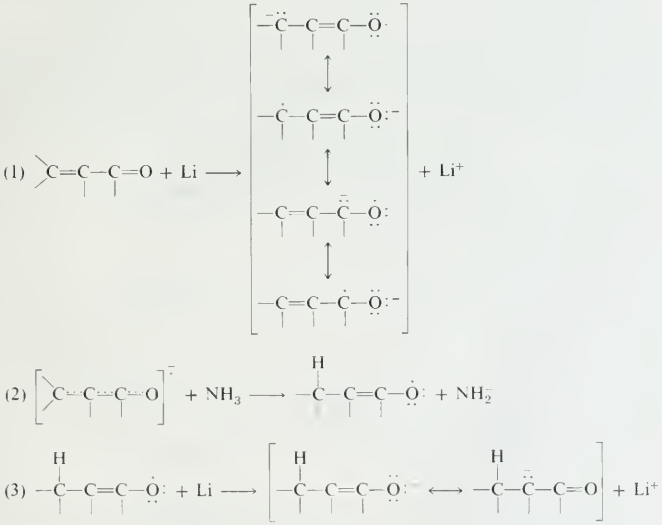


(100%)

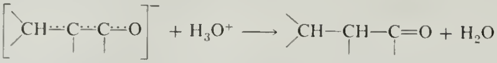


(95%)

The mechanism of the latter reduction is similar to that seen earlier in the reduction of alkynes to alkenes (Section 13.6.A). The first step involves addition of an electron to the conjugated system, giving a resonance-stabilized radical anion. This radical anion protonates on carbon giving a radical, which is reduced by another electron with the formation of an enolate ion.



Under the conditions of the reaction, the enolate ion is stable. Its reduction potential is too high for it to accept another electron and be reduced further, and it is not basic enough to be protonated by the weak acid ammonia. Upon aqueous workup, the enolate ion is protonated to give the ketone.



$$\left[\ \rangle CH \cdots C \cdots C \cdots O\ \right]^- + H_3O^+ \longrightarrow \rangle CH{-}CH{-}C{=}O + H_2O$$

The partial reduction of a conjugated enone in this reaction is a particularly impressive example of the special properties of conjugated systems, since isolated C=C double bonds are *not* reduced by lithium in ammonia and isolated C=O double bonds *are* reduced by the reagent.

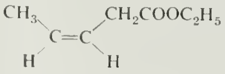
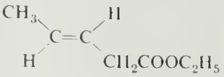
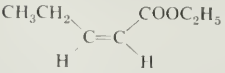
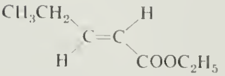
B. *Unsaturated Carboxylic Acids and Derivatives*

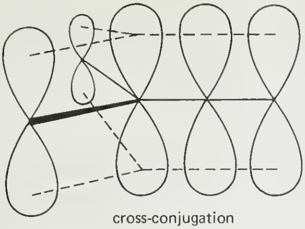
Both conjugated and unconjugated unsaturated carboxylic acids and acid derivatives are known. As with other multiply unsaturated systems, conjugation provides added stabilization, but the magnitude of this stabilization is rather small, substantially smaller than for dienes or unsaturated aldehydes and ketones. The heats of formation of isomeric ethyl pentenoates summarized in Table 20.2 demonstrate this point. In other words, the carboxylic function is less effective in conjugation than is a simple carbonyl group.

One way of rationalizing this behavior is to consider that the carbonyl group in a carboxylic function is already involved in conjugation to an atom with a pair of electrons to donate—such as the oxygen of OH or OR or the nitrogen of NH_2. Such a carbonyl group is less able to conjugate with another group. This situation is representative of a **cross-conjugated** system as illustrated by the π overlap of p orbitals in Figure 20.14. Much qualitative evidence as well as theoretical considerations show that cross-conjugation is less effective in stabilization of a molecule than is linear conjugation.

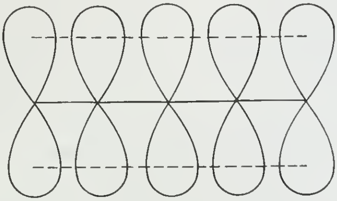
As a result of the reduced effectiveness of conjugation in unsaturated acid functions, in some compounds the unconjugated isomer may be the more stable.

TABLE 20.2
Heats of Formation of Ethyl Pentenoates

Isomer	ΔH_f°, kcal mole^{-1}
$CH_2{=}CHCH_2CH_2COOC_2H_5$	−92.1 ±0.6
	−92.6 ±0.9
	−93.2 ±0.7
	−94.3 ±0.7
	−94.2 ±0.9



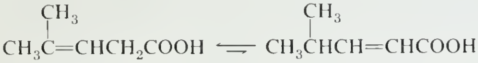
cross-conjugation



linear conjugation

FIGURE 20.14 *Comparison of linear conjugation and cross-conjugation.*

For example, 4-methylpent-3-enoic acid, with a trisubstituted double bond, is more stable than 4-methylpent-2-enoic acid. The latter compound has a conjugated π system but has only a disubstituted double bond.



$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CHCH_2COOH \rightleftharpoons CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH{=}CHCOOH$$

4-methylpent-3-enoic acid　　4-methylpent-2-enoic acid

Unsaturated carboxylic acids and their derivatives may be prepared by many of the same routes appropriate for the saturated analogs. An example is the sequence, RX → RCOOH, in which R contains a double bond:

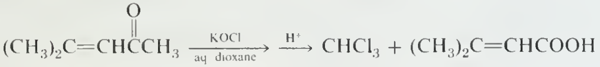
$$CH_2{=}CHCH_2Cl \xrightarrow{CuCN} CH_2{=}CHCH_2CN \xrightarrow[\Delta]{aq.\ HCl} CH_2{=}CHCH_2COOH$$

(52–62%)

allyl chloride

vinylacetic acid
but-3-enoic acid

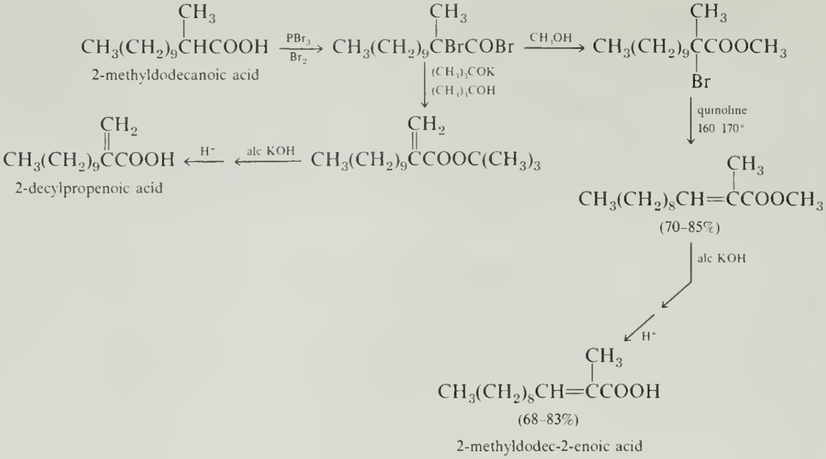
Another example involves the oxidation of a methyl ketone with hypohalite (Section 15.6.D):



$$(CH_3)_2C{=}CH\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \xrightarrow[aq\ dioxane]{KOCl} \xrightarrow{H^+} CHCl_3 + (CH_3)_2C{=}CHCOOH$$

(49–53%)
3-methylbut-2-enoic acid
β,β-dimethylacrylic acid

α,β-Unsaturated acids and derivatives are also available by E2 elimination from α-haloacids and esters. The direction of elimination can sometimes be controlled by the choice of basic reagent used.


CH3(CH2)9CH(CH3)COOH
2-methyldodecanoic acid
PBr3
Br2
CH3(CH2)9CBr(CH3)COBr
CH3OH
CH3(CH2)9CBr(CH3)COOCH3
(CH3)3COK
(CH3)3COH
CH3(CH2)9C(=CH2)COOC(CH3)3
alc KOH
H+
CH3(CH2)9C(=CH2)COOH
2-decylpropenoic acid
quinoline
160–170°
CH3(CH2)8CH=C(CH3)COOCH3
(70–85%)
alc KOH
H+
CH3(CH2)8CH=C(CH3)COOH
(68–83%)
2-methyldodec-2-enoic acid

Unsaturated acids and esters are also prepared by dehydration of hydroxyacids and esters and by condensation reactions to be discussed later (Section 26.4.E).

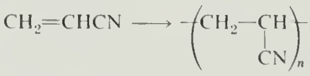
The simplest unsaturated carboxylic acid is propenoic acid, $CH_2{=}CHCOOH$, commonly known as acrylic acid, a liquid having b.p. 141.6°. The corresponding nitrile, $CH_2{=}CHCN$, acrylonitrile, is an important industrial material which is made in large quantity for use in synthetic fibers and polymers; its 1973 production in the United States was 700,000 tons. Acrylonitrile is also a liquid, b.p. 78.5°. It was once prepared industrially by addition of HCN to acetylene.

$$HC{\equiv}CH + HCN \xrightarrow[NH_4Cl]{CuCl} CH_2{=}CHCN$$

It is now prepared by a cheaper process that involves the catalytic oxidation of propylene in the presence of ammonia.

$$2\,CH_3CH{=}CH_2 + 3\,O_2 + 2\,NH_3 \xrightarrow[\text{catalyst}]{450^\circ} 2\,CH_2{=}CHCN + 6\,H_2O$$

Free radical polymerization of acrylonitrile in aqueous solution gives a polymer that can be spun to give the textile, Orlon or Acrilan.

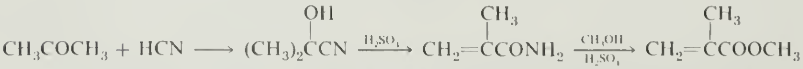


$$CH_2{=}CHCN \longrightarrow \left(CH_2{-}\underset{CN}{\underset{|}{C}H}\right)_n$$

Orlon, Acrilan

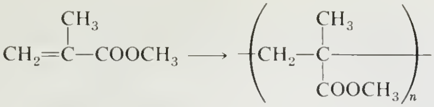
Copolymerization with butadiene and styrene gives an inexpensive plastic terpolymer known as ABS.

The methyl ester of α-methylacrylic acid is also an important monomer. It is prepared from acetone by the sequence



$$CH_3COCH_3 + HCN \longrightarrow (CH_3)_2\overset{OH}{\overset{|}{C}}CN \xrightarrow{H_2SO_4} CH_2{=}\overset{CH_3}{\overset{|}{C}}CONH_2 \xrightarrow[H_2SO_4]{CH_3OH} CH_2{=}\overset{CH_3}{\overset{|}{C}}COOCH_3$$

Poly(methyl methacrylate) prepared by free radical polymerization is a stiff transparent plastic known as Lucite or Plexiglas.



$$CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}COOCH_3 \longrightarrow \left(CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle COOCH_3}{\underset{|}{C}}}}{-} \right)_n$$

poly(methyl methacrylate)
Lucite, Plexiglas

Note that with both acrylonitrile and methyl methacrylate free radical polymerization involves almost exclusively head-to-tail combination of the monomers.

Unsaturated acids and esters are widespread in nature. Ricinoleic acid,

$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH,$$

is a derivative of stearic acid, $CH_3(CH_2)_{16}COOH$, and is obtained from castor oil. Other important unsaturated octadecanoic acids widespread as glyceryl esters in fats are oleic acid, $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$, linoleic acid, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$, and linolenic acid, $CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$ (Section 18.14). Linseed oil is an example of a **drying oil** and contains a high percentage of linolenic acid. On exposure to air, the highly unsaturated chain reacts with oxygen and crosslinks to give a tough transparent polymer. Oil-based paint is a combination of drying oil with suspended pigment. Varnish also contains such drying oils and also involves the formation of a tough waterproof film by oxygen-promoted free radical crosslinking.

C. *Ketenes*

The compound, $CH_2{=}C{=}O$, is known as ketene and is the carbonyl analog of allene. It is a toxic gas, b.p. $-48°$, and is prepared by the pyrolysis of acetone at high temperatures.

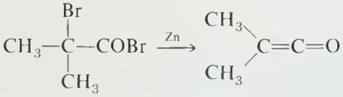
$$CH_3COCH_3 \xrightarrow{700°} CH_4 + CH_2{=}C{=}O$$

The reaction appears to be a free radical, chain decomposition.

$$\left.\begin{aligned} CH_3COCH_3 &\longrightarrow CH_3\cdot + CH_3CO\cdot \\ CH_3CO\cdot &\longrightarrow CH_3\cdot + CO \end{aligned}\right\}\ \text{initiation}$$

$$\left.\begin{aligned} CH_3COCH_3 + CH_3\cdot &\longrightarrow CH_3COCH_2\cdot + CH_4 \\ CH_3COCH_2\cdot &\longrightarrow CH_2{=}C{=}O + CH_3\cdot \end{aligned}\right\}\ \text{propagation}$$

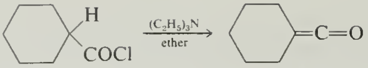
Preparation of substituted ketenes is accomplished by E2 elimination from acyl halides or by zinc dehalogenation of α-haloacyl halides.



$$CH_3{-}\overset{\displaystyle Br}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}{-}COBr \xrightarrow{Zn} (CH_3)_2C{=}C{=}O$$

α-bromoisobutyryl bromide

(46–54%)
dimethylketene



(32%)
pentamethyleneketene

Ketenes react as "super anhydrides." With water they give carboxylic acids and with alcohols they give esters. One commercial synthesis of acetic anhydride involves the combination of acetic acid with ketene. The United States production of acetic anhydride in 1973, mostly by this reaction, was 800,000 tons.

$$CH_3COOH + CH_2{=}C{=}O \longrightarrow (CH_3CO)_2O$$

The ketene group is extremely reactive and is a relatively unimportant functional group. Ketenes, like allenes, have two π systems at right angles. The two double bonds are *not* conjugated (Figure 20.15).

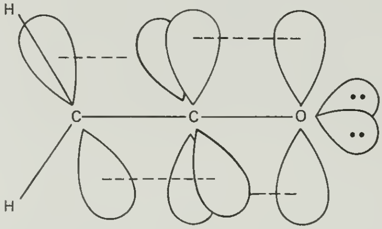
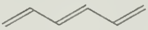


FIGURE 20.15 *Orbital structure of ketene.*

20.4
Higher Conjugated Systems

Many compounds are known with more than two conjugated double bonds. In such systems each double bond alternates with a single bond to allow extensive π overlap of p orbitals. One example is *trans*-1,3,5-hexatriene, a liquid, b.p. 79°.



trans-1,3,5-hexatriene

Another is vitamin A_1, an alcohol with five conjugated double bonds which we encountered in Section 20.3.A.

Despite the stabilization that such highly conjugated compounds derive from their extensive π electronic systems, they are generally *more* reactive, not less reactive, than their nonconjugated isomers. The reason for this apparent paradox is simply that the intermediate radicals or ions are even more stabilized by conjugation. For example, 1,3,5-hexatriene reacts rapidly with acids, bromine, free radicals, and other reagents. The addition of a proton to the terminal carbon atom gives a pentadienyl cation that is highly stabilized by resonance. That is, in this carbonium ion the positive charge is distributed among three carbons.

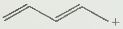
$$\mathrm{CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2 + H^+ \longrightarrow} \left[\begin{array}{c} \mathrm{CH_2{=}CH{-}CH{=}CH{-}\overset{+}{C}H{-}CH_3} \\ \updownarrow \\ \mathrm{CH_2{=}CH{-}\overset{+}{C}H{-}CH{=}CH{-}CH_3} \\ \updownarrow \\ \mathrm{\overset{+}{C}H_2{-}CH{=}CH{-}CH{=}CH{-}CH_3} \end{array}\right]$$

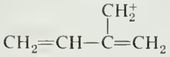
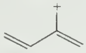
$$\mathrm{\overset{\delta+}{C}H_2{\cdots}CH{\cdots}\overset{\delta+}{C}H{\cdots}CH{\cdots}\overset{\delta+}{C}H{-}CH_3} \equiv$$

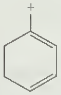
The resonance stabilization of such carbonium ion, carbanion, and free radical intermediates and the transition states leading to them is much greater than the stabilization afforded by π overlap in the starting polyenes. As a result, such polyenes are highly reactive. Exposure to air or light is often sufficient to initiate free radical chain polymerization.

PROBLEMS

1. Draw all of the important resonance structures for each of the following allylic type carbonium ions:

(a) $\mathrm{CH_2{=}CH{-}CH{=}CH{-}CH_2^+} \equiv$ 

(b) 
$\mathrm{CH_2{=}CH{-}\underset{}{\overset{\overset{\displaystyle CH_2^+}{|}}{C}}{=}CH_2} \equiv$ 

(c) 

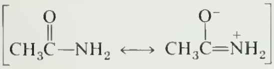
2. For each of the following pairs of allylic resonance structures, determine which is the more stable and contributes more to the resonance hybrid:

(a) $[\mathrm{^+CH_2{-}CH{=}CHCH_3 \longleftrightarrow CH_2{=}CH{-}\overset{+}{C}HCH_3}]$

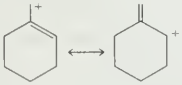
(b) $[\mathrm{CF_3\bar{C}H{-}CH{=}CHCH_3 \longleftrightarrow CF_3CH{=}CH{-}{}^-CHCH_3}]$

(c) $[\mathrm{CF_3\overset{+}{C}H{-}CH{=}CHCH_3 \longleftrightarrow CF_3CH{=}CH{-}{}^+CHCH_3}]$

(d) $[\mathrm{CH_2{=}CH{-}O^- \longleftrightarrow {}^-CH_2{-}CH{=}O}]$

(e) 
$\left[\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2 \longleftrightarrow CH_3\overset{\overset{\displaystyle O^-}{|}}{C}{=}\overset{+}{N}H_2}\right]$

(f) $[\mathrm{CH_2{=}CH{-}OCH_3 \longleftrightarrow {}^-CH_2{-}CH{=}\overset{+}{O}CH_3}]$

(g) 

3. (a) A common procedure for identifying $^{14}\mathrm{C}$ is to obtain it in the form of carbon dioxide which is passed into aqueous barium hydroxide and precipitated as barium carbonate. The white product is dried and pressed into a pellet, which is counted with a Geiger counter. Given $\mathrm{Ba^{14}CO_3}$ as starting material, present a practical

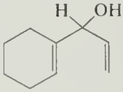
synthesis of $CH_2{=}CH^{14}CH_2OH$. How would you show that allylic rearrangement occurs when this labeled allyl alcohol reacts with thionyl chloride (page 532)?

(b) Allylic rearrangement can also be demonstrated with deuterium labeling. Present a practical synthesis of $CH_2{=}CHCD_2OH$. What would the nmr spectrum look like? What product would you expect on treatment with thionyl chloride? What is the expected nmr spectrum of this product?

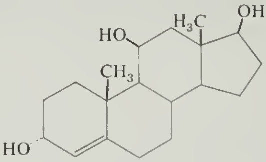
4. Illustrate the use of allylic halides and Grignard reagents by preparation of the following alkenes:
(a) $CH_3CH_2CH_2CH{=}CH_2$
(b) $C_6H_5CH_2CH{=}CH_2$
(c) $CH_2{=}CHCH_2CH{=}CH_2$
(d) $(CH_3)_3CCH_2CH{=}CH_2$

5. Write the principal organic reaction product from the treatment of each of the following alcohols with activated MnO_2:
(a) $CH_3CH{=}CHCH_2OH$
(b) $CH_3CH_2CH_2CH_2OH$
(c) $HOCH_2CH_2CH{=}CHCH_2OH$

(d)



(e)



(f) $CH_3C{\equiv}CCHOHCH_3$

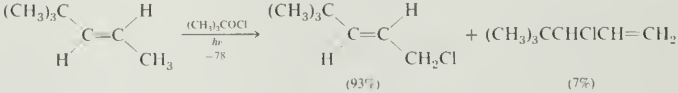
6. The nmr spectrum at −80° of the Grignard reagent prepared from γ,γ-dimethylallyl bromide (4-bromo-2-methyl-2-butene) shows the following signals: $\delta = 0.6$ ppm, doublet, 2H; $\delta = 1.6$ ppm, doublet, 6H; $\delta = 5.6$ ppm, triplet, 1H. Which structure for the Grignard reagent best fits this nmr spectrum?

$$(CH_3)_2C{=}CHCH_2MgBr \quad \text{or} \quad CH_2{=}CHC(CH_3)_2MgBr$$

On warming the solution to room temperature, the doublet at $\delta = 1.6$ ppm first broadens and then becomes a sharp singlet. How do you interpret this behavior?

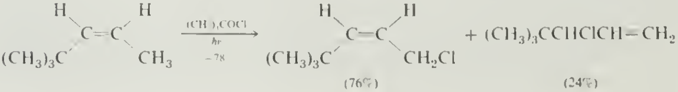
7. The reaction of 1-octene with N-bromosuccinimide in carbon tetrachloride with a small amount of benzoyl peroxide, $(C_6H_5COO)_2$, gives a mixture of 17% of 3-bromo-1-octene, 44% of *trans*-1-bromo-2-octene, and 39% of *cis*-1-bromo-2-octene. Account for these products with a reaction mechanism showing all significant intermediates.

8. Allylic chlorination can be accomplished by the use of *t*-butyl hypochlorite, a reagent prepared by passing chlorine into an alkaline solution of *t*-butyl alcohol.
(a) Write a plausible mechanism for this reaction.
(b) An example of the use of $(CH_3)_3COCl$ in allylic chlorination is



Write a reasonable reaction mechanism.

(c) In the example in (b), note that none of the *cis* isomer is obtained. If we start with the *cis*-olefin the reaction takes the following course:



What does this experiment reveal about the configurational stability about the C—C bond in an allyl radical, at least at −78°?

(d) Why was it necessary to do the experiment with both the *cis*- and *trans*-olefins? Could the conclusion in (c) have been derived from the results of part (b) alone?

(e) The rotation barrier in allyl radical is estimated to be about 10 kcal mole^{-1}. Explain why such a barrier exists.

9. When 1,3-butadiene is allowed to react with hydrogen chloride in acetic acid at room temperature, there is produced a mixture of 22% 1-chloro-2-butene and 78% 3-chloro-1-butene. On treatment with ferric chloride or on prolonged treatment with hydrogen chloride, this mixture is converted to 75% 1-chloro-2-butene and 25% 3-chloro-1-butene. Explain.

10. Reaction of butadiene with carbon tetrachloride at 110° in the presence of peroxides gives a 23% yield of 1,5,5,5-tetrachloro-2-pentene. Write a plausible mechanism for its formation.

11. Reaction of 2,3-dimethyl-1,3-butadiene with Cl_2 in carbon tetrachloride in the dark at −20° gives 45% of the expected product, 1,4-dichloro-2,3-dimethyl-2-butene, in addition to 54% of A and 1% of B.

Compound A shows mass spectral parent peaks at m/e 118 and 116, with an intense fragment peak at m/e 81. The nmr spectrum shows singlets at $\delta = 1.90$ ppm (3H) and $\delta = 4.20$ ppm (2H) and four peaks at $\delta = 6.06, 6.19, 6.22, 6.30$ ppm (4H).

Compound B shows mass spectral parent peaks at m/e 118 and 116. The nmr spectrum shows singlets at $\delta = 1.78$ ppm (3H), 1.85 ppm (3H), and 6.20 ppm (1H), and two peaks at $\delta = 5.08, 5.00$ ppm (2H).

Deduce the structures of A and B and write a plausible mechanism for their formation.

12. On heating 2-buten-1-ol with dilute sulfuric acid, a mixture of three structurally different isomeric ethers is produced of the type $(C_4H_7)_2O$. Give the structures of these ethers [do not count *cis-trans* or (R,S) isomers] and write a plausible reaction mechanism for their formation.

13. In the reaction of 1,3-cyclopentadiene with hydrogen chloride at 0°, no significant amount of 4-chlorocyclopentene is produced. By what mechanism would this compound be formed? Why is it not found?

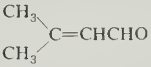
14. When 1-pentyne is treated with $4N$ alcoholic potassium hydroxide at 175°, it is converted slowly into an equilibrium mixture of 1.3% 1-pentyne, 95.2% 2-pentyne, and 3.5% 1,2-pentadiene. Calculate $\Delta G°$ differences between these isomers for the equilibrium composition. Write a reasonable reaction mechanism showing all intermediates in the equilibrium reaction.

Sodium amide in liquid ammonia is a stronger basic system than alcoholic KOH, yet even prolonged treatment of 1-pentyne by $NaNH_2$ in liquid ammonia leads to recovery of the 1-pentyne essentially unchanged. Explain.

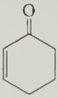
15. Reaction of 3-methyl-1,2-butadiene with Cl_2 under free radical conditions gives a good yield of 3-chloro-2-methyl-1,3-butadiene. Write a reasonable reaction mechanism.

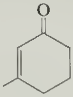
16. One convenient preparation of acrolein involves the treatment of glycerol, $CH_2OHCHOHCH_2OH$, with sulfuric acid. Write a plausible reaction mechanism.

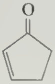
17. What deuterated compound is produced when each of the following carbonyl compounds is allowed to exchange in a large excess of basic D_2O?
(a) $(CH_3)_2CHCOCH_3$
(b) $CH_3CH{=}CHCOCH_3$

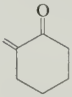
(c)


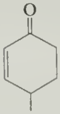
$$\begin{array}{l}CH_3\\ \qquad C{=}CHCHO\\ CH_3\end{array}$$

(e)


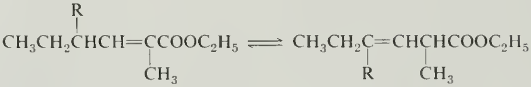
(g)


(d)


(f)


(h)


18. Consider the following equilibria between α,β and β,γ isomers. For R = CH_3, the equilibrium constant is about unity. For R = $(CH_3)_3C$, however, the equilibrium is displaced substantially in the α,β direction. Explain this result. The use of molecular models may be helpful.

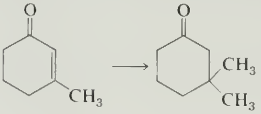


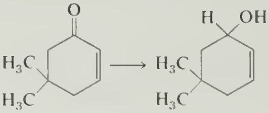
$$CH_3CH_2\overset{R}{\overset{|}{C}}HCH{=}\underset{\underset{CH_3}{|}}{C}COOC_2H_5 \rightleftharpoons CH_3CH_2\underset{\underset{R}{|}}{C}{=}CH\underset{\underset{CH_3}{|}}{C}HCOOC_2H_5$$

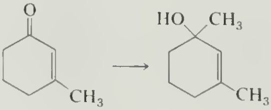
R = CH_3: 45% 55%
R = $C(CH_3)_3$: 86% 14%

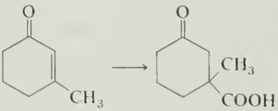
19. The gas phase enthalpy of ionization ($\Delta H°$ for $RCl \rightarrow R^+ + Cl^-$) for *trans*-1-chloro-2-butene is about 161 kcal $mole^{-1}$ and is significantly lower than that for 3-chloro-2-methyl-1-propene, 169 kcal $mole^{-1}$. Explain, using resonance structures where desirable.

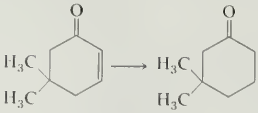
20. Show how each of the following conversions may be accomplished.

(a)


(d)


(b)


(e)


(c)


21. Propose a plausible mechanism for the reaction of ketene with water to give acetic acid.

Chapter 21

Benzene and the Aromatic Ring

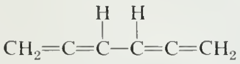
21.1
Benzene

A. *The Benzene Enigma*

The hydrocarbon now known as benzene was first isolated by Michael Faraday in 1825 from an oily condensate that deposited from illuminating gas. Faraday determined that is has equal numbers of carbons and hydrogens and named the new compound "carbureted hydrogen." In 1834, Mitscherlich found that the same hydrocarbon may be produced by pyrolysis with lime of benzoic acid, which had been isolated from gum benzoin. By vapor density measurements, Mitscherlich established the molecular formula to be C_6H_6. He named the compound benzin, but other influential chemists protested that this name implied a relationship to alkaloids such as quinine. Finally, the German name benzol, based on the German öl, oil, was adopted. In France and England, the name **benzene** was adopted, to avoid confusion with the typical alcohol ending.

> During the early history of benzene, Laurent proposed the name pheno, from the Greek, *phainein,* to shine, in keeping with the discovery of the material in illuminating gas. Although the name never gained acceptance, it still persists in **phenyl,** the name of the C_6H_5— radical.

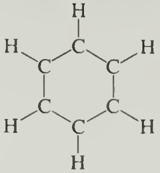
Other preparations of benzene followed these early discoveries and it was soon recognized that benzene is the parent hydrocarbon of a whole family of organic compounds. The physical properties of benzene (b.p. 80.1°, m.p. 5.5°) are consistent with its molecular formula of C_6H_6. For example, cyclohexane, C_6H_{12}, has b.p. 80.7° and m.p. 6.5°. A six-carbon saturated alkane would have the formula C_6H_{14}. Therefore, benzene must have four double bonds and/or rings. Yet, it does not exhibit the high reactivity of typical polyenes. In fact, it is remarkably inert to many reagents. For example, it does not react with aqueous potassium permanganate or with bromine water. It does not even react with concentrated sulfuric acid in the cold. It is stable to air and tolerates free radical initiators. It may be used as a solvent for Grignard reagents and alkyllithium compounds. All of these properties are totally inconsistent with such C_6H_6 structures as



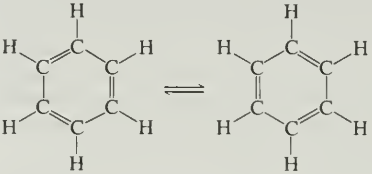
$$CH_2{=}C{=}\overset{H}{\overset{|}{C}}-\overset{H}{\overset{|}{C}}{=}C{=}CH_2 \qquad \text{or} \qquad CH_3C{\equiv}C-C{\equiv}CCH_3$$

The fact that benzene has a formula that suggests a polyene structure but does not behave at all like other polyenes was a dilemma for nineteenth century chemists. Furthermore, new compounds were continually being discovered that were structurally related to benzene. It was clear that there was something fundamentally different about benzene and its derivatives. As a group, the benzene-like compounds were called **aromatic** compounds because many of them have characteristic aromas. The Kekulé theory of valence, first proposed in 1859, allowed acceptable structures to be written for aliphatic compounds such as ethane and ethylene, but, at first, it did not appear to be applicable to aromatic compounds.

In 1865, Kekulé suggested a regular hexagon structure for benzene with a hydrogen attached at each corner of a hexagonal array of carbons.

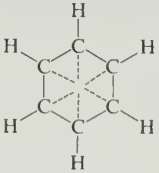


However, this structure violates the tetravalence of carbon inherent in his theory. He later modified his structure to treat benzene as an equilibrating mixture of cyclohexatrienes. However, this structure still did not account for the nonolefinic character of benzene.

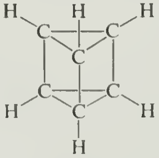


cyclohexatriene

Other attempts by nineteenth century chemists to explain the benzene problem only emphasize the frustrations inherent in the limited theory of the day. One such example was Armstrong's centroid formula, in which the fourth valence of each carbon is directed toward the center of the ring.



Ladenburg, in 1879, proposed an interesting structure that would solve the problem of why benzene displays no polyene properties. In the Ladenburg proposal, benzene was treated as a tetracyclic compound, with no double bonds.



Ladenburg's representation of benzene, while not the structure of benzene, is a perfectly valid structure for an organic compound. It has come to be known as

"Ladenburg benzene" or "prismane." After considerable effort, prismane was finally synthesized in 1973 by organic chemists at Columbia University. Upon heating to 90°, it isomerizes to benzene.

Only with the advent of modern wave mechanics did the structure of benzene take its place within a unified electronic theory. The x-ray crystal structure of benzene shows that the compound does indeed have a regular hexagonal structure as Kekulé had originally suggested. The C—C bond distance of 1.40° Å is intermediate between those for a single bond (1.54 Å) and a double bond (1.33 Å). In a regular hexagon, the bond angles are all 120°, and this suggests the involvement of sp^2 hybrid orbitals. The "fourth valence" that was so difficult for nineteenth century chemists to explain we can now recognize as being π bonds from p orbitals, *but extending equally around the ring*, as in Figure 21.1.

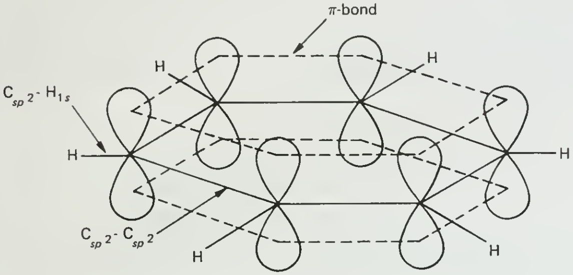
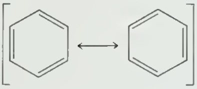
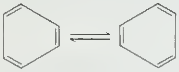


FIGURE 21.1 *Orbital structure of benzene.*

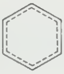
In resonance language, we may depict benzene by two equivalent resonance structures.



Note the important difference in meaning between this formulation and that of equilibrating cyclohexatrienes. Cyclohexatriene would have alternating single and double bonds, and the chemical equilibrium between the two alternative structures requires the movement of nuclei.

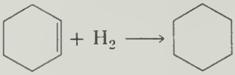


In the resonance structures, the C—C distances remain the same. The resulting resonance hybrid may be written with dotted lines to indicate the partial double bond character of the benzene bonds.

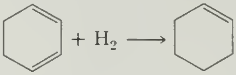


B. *Resonance Energy Of Benzene*

By examining the heat of hydrogenation of benzene, it is possible to estimate how much more stable benzene is compared to a hypothetical "cyclohexatriene." This imaginary quantity is called the **resonance energy** of benzene. The heat of hydrogenation of the double bond in cyclohexene is -28.4 kcal mole^{-1}. That for one double bond in 1,3-cyclohexadiene is -26.5 kcal mole^{-1}.

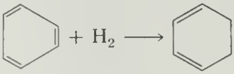


$\Delta H° = -28.4 \text{ kcal mole}^{-1}$



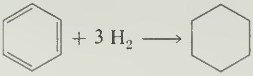
$\Delta H° = -26.5 \text{ kcal mole}^{-1}$

By a simple extrapolation, we might expect the heat of hydrogenation of a 1,3,5-cyclohexatriene with alternating single and double bonds to be about -24.5 kcal mole^{-1}.



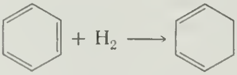
$\Delta H° \approx -24.5 \text{ kcal mole}^{-1}(?)$

Benzene can in fact be hydrogenated, but only with difficulty. It hydrogenates slowly under conditions where simple alkenes react rapidly. When hydrogenation does occur, it generally goes all the way and cyclohexane results. The heat of hydrogenation for the complete reduction of benzene to cyclohexane is -49.3 kcal mole^{-1}.



$\Delta H° = -49.3 \text{ kcal mole}^{-1}$

Since the heat of hydrogenation of 1,3-cyclohexadiene to cyclohexane is -54.9 kcal mole^{-1}, the heat of hydrogenation of benzene to 1,3-cyclohexadiene is $-49.3 - (-54.9)$, or $+5.6$ kcal mole^{-1}; the process is actually endothermic!



$\Delta H° = +5.6 \text{ kcal mole}^{-1}$

These energy relationships are shown graphically in Figure 21.2.

By comparison with the actual heat of hydrogenation of one bond in benzene, we find that benzene is about 30 kcal mole^{-1} more stable than it would be if it had the cyclohexatriene structure. This stabilization energy defines the resonance energy of benzene; that is, the resonance energy is the difference in energy between the real benzene and that of a single principal Lewis resonance structure. Other derivations of this quantity give somewhat different values; one commonly used number is 36 kcal mole^{-1}.

Actually, the true resonance energy of benzene should be referred not to a cyclohexatriene with alternating bonds of different lengths, but to a hypothetical model having the geometry of benzene but with π overlap only allowed between alternating

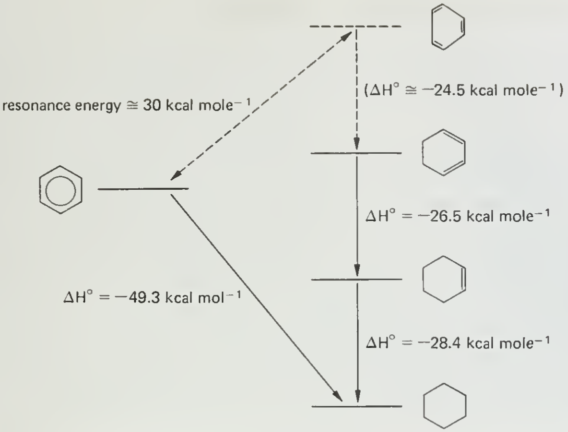
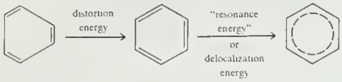


FIGURE 21.2 *Estimation of the resonance energy of benzene.*

bonds. Such a structure requires the deformation of cyclohexatriene—stretching the double bonds and compressing the single bonds

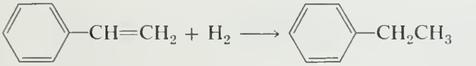


Various estimates have been made of this distortion energy, but one estimated value of about 30 kcal mole⁻¹ appears to be reasonable. This would make the actual resonance energy of benzene about 60 kcal mole⁻¹. To distinguish between these different energy quantities, this number of about 60 kcal mole⁻¹ is referred to as a **delocalization energy** because it is the energy liberated when electrons are allowed to *delocalize* or *relax* from a hypothetical compound with the benzene geometry having the electrons constrained to alternating single and double bonds to the electronic structure of benzene itself. The value of about 30 kcal mole⁻¹, derived from heats of hydrogenation, is referred to as the **empirical resonance energy.**

Furthermore, this use of the term *resonance* should not be confused with the resonance that occurs in, for example, nmr (nuclear magnetic resonance) in which resonance refers to a matching of the frequency of an irradiating electromagnetic beam with the energy difference between two nuclear spin states in a magnetic field. However, both kinds of resonance are in fact related to the resonance phenomena of vibrations that allowed Joshua's horn to bring down the walls of Jericho.

The benzene ring can also conjugate with other π electron groups and provide additional stabilization. Comparison of some heats of hydrogenation show that the benzene ring is less effective in this regard than a double bond.

$$CH_3CH_2CH{=}CH_2 + H_2 \longrightarrow CH_3CH_2CH_2CH_3 \qquad \Delta H^\circ = -30.2 \text{ kcal mole}^{-1}$$
$$CH_2{=}CH{-}CH{=}CH_2 + H_2 \longrightarrow CH_2{=}CHCH_2CH_3 \qquad \Delta H^\circ = -26.3 \text{ kcal mole}^{-1}$$



$\Delta H^\circ = -28.2$ kcal mole⁻¹

C. *Molecular Orbital Theory of Benzene*

The π system of benzene is made up of six overlapping p orbitals on carbon, which will therefore give rise to six π molecular orbitals. The lowest, most stable molecular orbital, ψ_1, has no nodes, and consists of all six p orbitals overlapping around the ring. The next two molecular orbitals, ψ_2 and ψ_3, are not as bonding as ψ_1 and have higher energy. Each has one node; the node in ψ_2 is at right angles to that in ψ_3. These two molecular orbitals have identical energies and are therefore said to be **degenerate.** The three molecular orbitals designated as ψ_1, ψ_2, and ψ_3 are the occupied molecular orbitals benzene; one pair of electrons can be put in each to accommodate all six π electrons of benzene. The three remaining π molecular orbitals have less bonding and higher energy; they are not occupied by electrons. The relative energies of all six π molecular orbitals and the molecular orbitals themselves are represented in Figure 21.3.

A characteristic feature of this molecular orbital pattern is that the lowest lying molecular orbital is a single molecular orbital; thereafter the molecular orbitals occur in pairs of equal energy until only one highest lying level is left. These

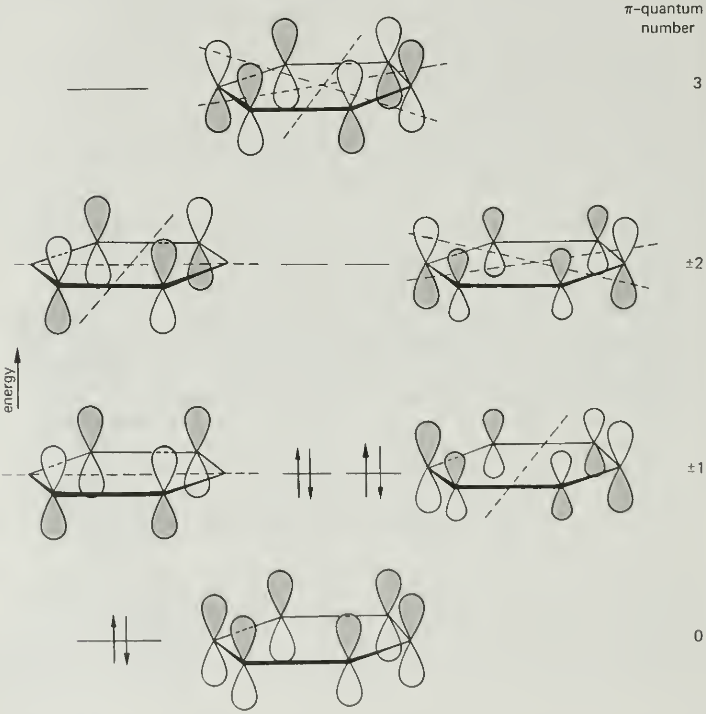


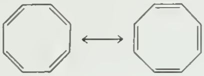
FIGURE 21.3 *The π molecular orbitals and energy levels for benzene. Positive lobes are shaded. Nodes are indicated by dashed lines. Recall that overlapping wave functions of the same sign are bonding; wave functions separated by a node have opposite signs and are antibonding.*

molecular orbital levels could be identified by quantum numbers, 0, ±1, ±2, and so on. Each quantum number represents a **shell** of orbitals, much as we have 2*s* and 2*p* shells in atomic structure. In benzene, the ±1 shell is filled and we can attribute the stability of benzene to this filled shell structure in much the same way as the noble gases (helium, neon, argon, and so on) have stability associated with filled atomic orbital shells.

It is important to distinguish between the π electronic system of benzene as symbolized commonly by a set of six *p* orbitals overlapping as in Figure 21.1 and the molecular orbitals as symbolized in Figure 21.3. The necessity for the distinction comes about because the π electronic system contains six electrons. According to the Pauli principle (Section 2.5) no two electrons can have the same quantum numbers. The six electrons can be divided into two groups of three based on electronic spin (a quantum number, $\pm\frac{1}{2}$) but each electron in the set of three must then belong to a different orbital. In the case of benzene, such orbitals are the π molecular orbitals characterized by quantum numbers of 0, +1, and −1.

This pattern of π molecular orbital energy levels is characteristic of all monocyclic π electronic systems. That is, in all such systems of simple conjugated polyenes, we have a lowest single molecular orbital level, and all higher levels occur as degenerate pairs as much as possible.

For example, if 1,3,5,7-cyclooctatetraene had the structure of a planar regular octagon analogous to the hexagon of benzene, we could write two resonance structures of the benzene type.



We would therefore anticipate a significant amount of resonance energy for such a structure. However, the π molecular orbital energy pattern is shown in Figure 21.4. Six of the eight π electrons are put into the three lowest molecular orbital levels, but the one pair left is not enough to fill the next shell. This structure of cyclooctatetraene has an incomplete orbital shell and would therefore not be expected to have the kind of stability characteristic of benzene.

Note that the last two electrons in Figure 21.4 are placed with the same spin, one in each of the degenerate orbitals. This arrangement is a consequence of Hund's rule,

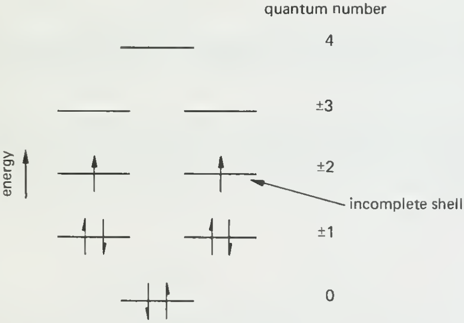


Figure 21.4 *The π molecular orbital energy level pattern for a planar octagonal cyclooctatetraene.*

just as in atomic structure. Two electrons of the same spin are prevented from close approach by the Pauli principle—two electrons with the same quantum numbers cannot occupy the same region of space. Two electrons of opposite spin stay apart only because of electrostatic repulsion; hence, such a system has higher net energy and is less stable than one in which the electrons have the same spin.

Cyclooctatetraene is a well-known hydrocarbon; it is a liquid, b.p. 142°, that shows all of the chemistry typical of conjugated polyenes. It polymerizes on exposure to light and air and reacts readily with acids, halogens, and other reagents. The structure of cyclooctatetraene has been determined, and the hydrocarbon does not have a planar octagonal structure. In fact, the molecule is tub-shaped and has bond lengths characteristic of alternating single and double bonds (Figure 21.5).

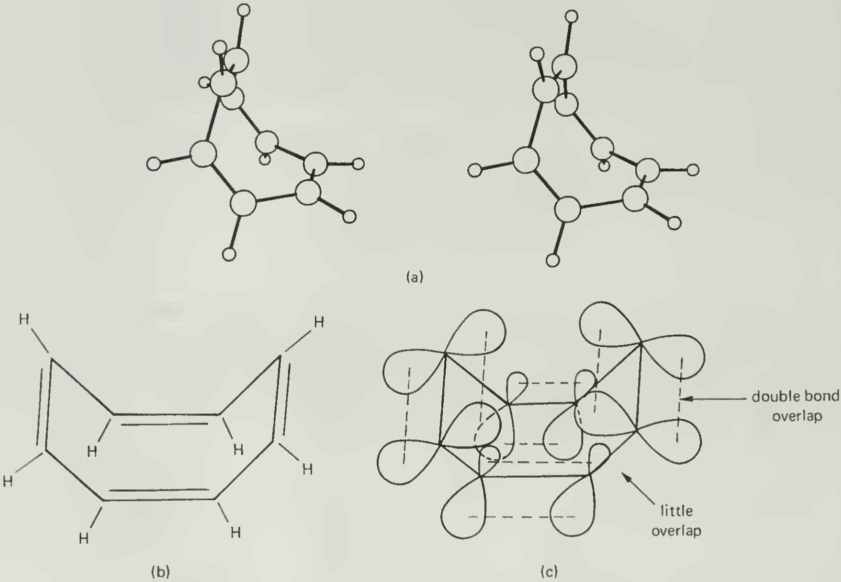
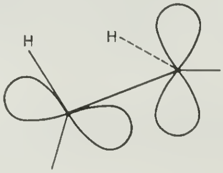


Figure 21.5 *Cyclooctatetraene:* (a) *stereo representation,* (b) *Kekulé structure,* (c) π *orbital structure.*

Because of its geometry, the π orbitals of adjacent double bonds are twisted with respect to each other and overlap is greatly reduced. That is, looking down any single bond, the π orbitals are almost at right angles to each other.



In short, because of the *instability* of the incomplete shell electronic structure of a planar geometry, cyclooctatetraene prefers a nonplanar configuration to give a structure in which the alternating double bonds are effectively not conjugated to each other!

Incomplete atomic orbital shells are associated with a relative ease of gaining or losing electrons to form an ion having a filled-shell electronic configuration, for example

$$\mathrm{Li}\cdot \longrightarrow \mathrm{Li}^+ + e$$

$$:\!\underset{..}{\overset{..}{\mathrm{F}}}\cdot + e \longrightarrow :\!\underset{..}{\overset{..}{\mathrm{F}}}\!:^-$$

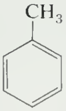
Cyclooctatetraene reacts readily with alkali metals in ethers to form the alkali metal salt of a dianion, cyclooctatetraene dianion.

$$\mathrm{C_8H_8} + 2\ \mathrm{K} \xrightarrow{\text{tetrahydrofuran}} \mathrm{C_8H_8^{2-}2K^+}$$

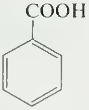
This dianion now has the planar structure of a regular octagon with C—C bond distances of 1.4 Å, quite similar to benzene! This dianion has 10 π electrons, enough to just fill the molecular orbital shell with π quantum numbers of ±2.

Monocyclic π systems of $4n + 2$ electrons (where n is an integer) have the special stability associated with filled orbital shells. For benzene, $n = 1$; whereas for cyclooctatetraene dianion, $n = 2$. Such systems are said to be **aromatic** and to have **aromatic stability.** Further aspects of the chemistry of nonbenzenoid aromatic systems are discussed in Section 36.1. Note that this modern use of *aromatic* has nothing whatsoever to do with smell. Although the term originated in the early days of organic chemistry when it was found that many compounds containing benzene rings had strong odors, it is now associated with compounds that have "aromatic" stability.

Many such compounds are known. They include derivatives of benzene that contain the benzene ring but with various groups attached to the ring. Examples are toluene and benzoic acid.

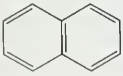


toluene

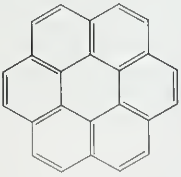


benzoic acid

There are polycyclic benzenoid compounds in which two or more benzene rings are fused together; examples are naphthalene and coronene.

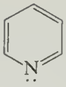


naphthalene

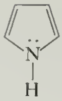


coronene

There are also aromatic heterocyclic compounds, compounds in which one or more atoms other than carbon participate in the cyclic conjugated ring. Examples are pyridine and pyrrole.



pyridine



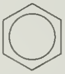
pyrrole

All of these cases involve cyclic systems of six π electrons. Their chemistry will be developed extensively later in this book.

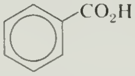
D. *Symbols for the Benzene Ring*

Finally, the symbolism used for the benzene ring deserves further comment. We have discussed the electronic structure of benzene in terms of resonance structures and molecular orbital theory and with reference to hypothetical formulations of cyclohexatriene. We have used symbolic representations of molecular orbitals and various symbols based on hexagons. These symbols are all in common use in various contexts and may be summarized as follows.

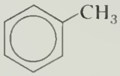
The molecular orbital representation is especially useful for understanding the high stability of the benzene ring, but it is too complex and cumbersome a symbolism for normal use. The hexagon with an inscribed circle is a simple and commonly used representation of the aromatic π system and is especially useful for the representation of aromatic structures.



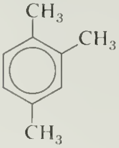
benzene



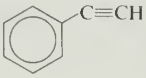
benzoic acid



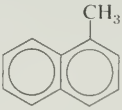
toluene



1,2,4-trimethylbenzene



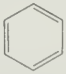
phenylacetylene



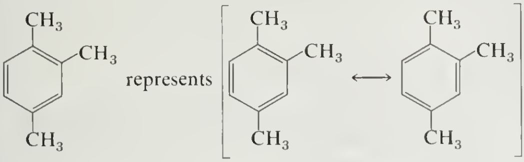
1-methylnaphthalene

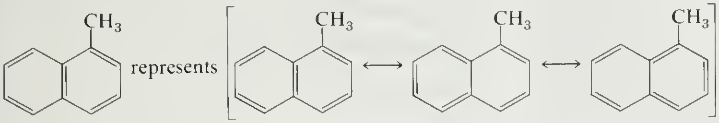
However, this symbol has an important disadvantage in not allowing an accurate accounting of electrons; that is, it does not correspond to a Lewis structure. In all of our other structural representations, a bond symbolized by a straight line corresponds to two electrons. No such simple correspondence applies to the inscribed circle; for example, the circle in benzene corresponds to six π electrons, whereas the two circles in naphthalene correspond to a total of ten π electrons.

The alternating double bonds symbol does allow a simple and accurate accounting of electrons and does correspond to a Lewis structure.



This symbol is used frequently to represent the benzene ring and the student must be wary not to read this symbol as that of cyclohexatriene; that is, as a cyclic polyene. Generally, this symbol is used as a shorthand for a resonance hybrid of Kekulé structures.





This is the symbol for benzene rings used generally throughout this textbook. We shall see later in this chapter how this symbol lends itself readily to following reaction mechanisms at the benzene ring.

E. *Nmr Spectrum of Benzene*

The nmr spectrum of benzene is shown in Figure 21.6. Since the six hydrogens are equivalent, the spectrum consists of a single line. The unusual feature of the spectrum is the position of the singlet, $\delta = 7.27$ ppm. Recall that δ for olefinic protons is generally about 5 ppm (Section 12.3.B).

The downfield shift of the benzene hydrogens results from the cyclic nature of the π electrons of the aromatic ring. This cyclic electronic system can be likened to a circular wire, which, in a magnetic field, produces a current around the ring. This current is exactly analogous to the current induced in the π electrons of a

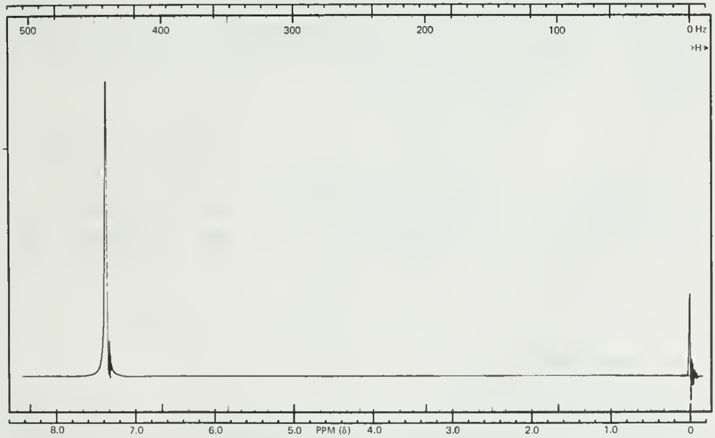


FIGURE 21.6 Nmr *spectrum of benzene.*

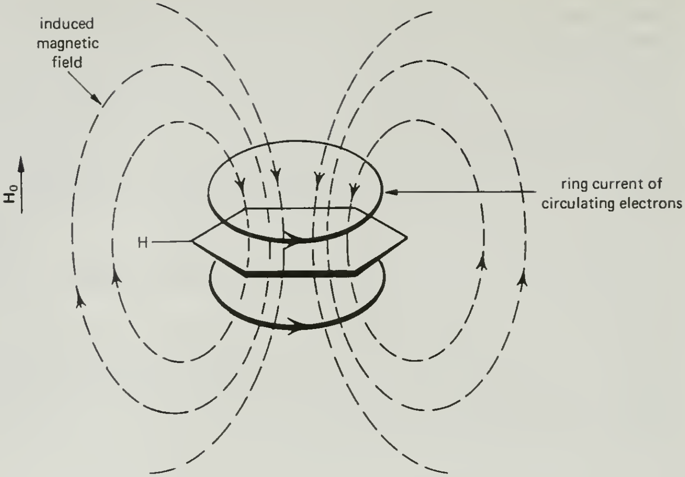
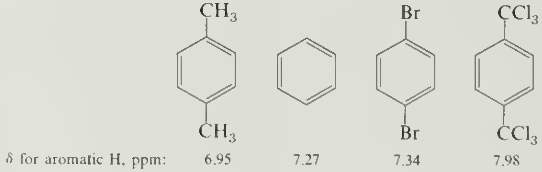


FIGURE 21.7 *Effect of ring current in benzene π system increases effective magnetic field at the proton.*

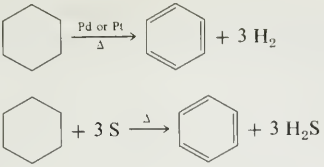
double bond (Figure 21.7), except that in benzene this electron current extends around the ring rather than being localized in one double bond. The resulting **ring current** has an induced magnetic field that *adds to* the externally applied field at the protons, just as in the related case of olefinic hydrogens (Figure 21.7). Since a smaller applied field is required to achieve resonance at the nucleus of the proton, the net result is a downfield shift.

The effect is greater for a benzene ring than for a simple alkene, in part because the benzene ring has six π electrons in the cycle. The proton resonance of substituted benzene rings occurs generally in the region of $\delta = 7\text{-}8$, a region in which few other kinds of proton resonances occur. Nmr peaks in this region are diagnostic for aromatic protons. Substituents have a normal type of effect: electronegative substituents generally cause a downfield shift, and electron-donating groups usually produce an upfield shift.

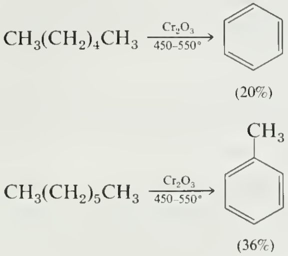


F. *Formation of Benzene*

The high stability of the benzene ring is further demonstrated by reactions that produce this ring system. Cyclohexane rings can be **dehydrogenated** with suitable reagents or catalysts.



Dehydrogenation with cyclization can be accomplished from aliphatic hydrocarbons.



Such reactions form the basis of the **hydroforming process** of petroleum refining. Gasoline fractions are heated with platinum catalysts (**platforming**) to produce mixtures of aromatic hydrocarbons by cyclization and dehydrogenation of aliphatic hydrocarbons. Most of the benzene used commercially comes from petroleum. United States production in 1973 was 10 billion lb. Benzene itself is an important starting material for the preparation of many other compounds. Many of these compounds result from electrophilic aromatic substitution, an important reaction that will be discussed in the next section.

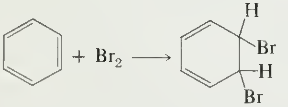
21.2
Aromatic Substitution

A. *Bromination*

Alkenes react rapidly with bromine even at low temperatures to give the product of *addition* of bromine.

$$CH_2{=}CH_2 + Br_2 \longrightarrow BrCH_2CH_2Br \qquad \Delta H^\circ = -29.2 \text{ kcal mole}^{-1}$$

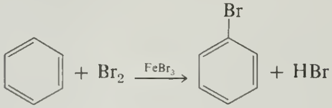
The reaction is highly *exothermic* because two C—Br bonds are substantially more stable than a Br—Br bond and the second bond of a double bond. The corresponding addition reaction of benzene is slightly *endothermic*.



$$\Delta H^\circ \approx 2 \text{ kcal mole}^{-1}$$

Such an addition reaction destroys the cyclic π electronic system of benzene. Note that the difference in ΔH° for the two cases is approximately the resonance energy of benzene.

Benzene does react with bromine, but the reaction requires the use of appropriate Lewis acids such as ferric bromide. The product of the reaction is the result of *substitution* rather than addition.



$\Delta H^\circ = -10.8 \text{ kcal mole}^{-1}$

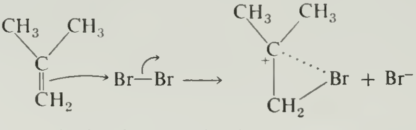
> Sixty grams of bromine is added slowly to a mixture of 33 g of benzene and 2 g of iron filings. The mixture is warmed for an additional half hour; the red vapors of bromine should no longer be visible. Water is added and the washed and dried organic layer is distilled to give 40 g of bromobenzene, b.p. 156°.

In this procedure, the iron reacts rapidly with bromine to give ferric bromide. Anhydrous ferric halides are Lewis acids and react avidly with bases such as water.

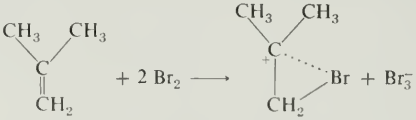
$$FeX_3 + H_2O \rightleftharpoons H_2O\cdot FeX_3 \longrightarrow \text{higher hydrates}$$

The anhydrous salts are difficult to keep pure and are frequently made from the elements as needed, as in the procedure given above for the bromination of benzene.

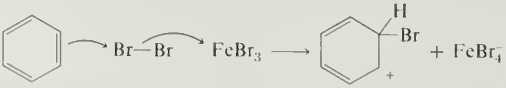
It is the Lewis acid character of ferric salts that allows them to function as catalysts in this reaction. Aluminum halides are used frequently for the same purpose. Recall that the first step in the bromination of an alkene is a displacement by the alkene as a nucleophile on bromine, with bromide ion as a leaving group (Section 12.6.B under Addition of Halogens).



In nonpolar solvents, the leaving bromide ion requires additional solvation by bromine (p. 536).

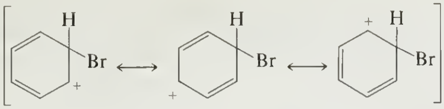


In this case, a bromine molecule serves as a mild Lewis acid to help pull bromide ion from bromine. This type of "pull" is provided more powerfully by a stronger Lewis acid such as ferric bromide.



Benzene is a much weaker nucleophilic reagent than a simple alkene and requires a more electrophilic reagent for reaction.

The intermediate in the bromination of benzene is a conjugated carbonium ion. Its structure may be expressed by three Lewis structures



The resulting structure is that of an approximately tetrahedral carbon attached to a planar pentadienyl cation, as shown by the stereo representation in Figure 21.8.

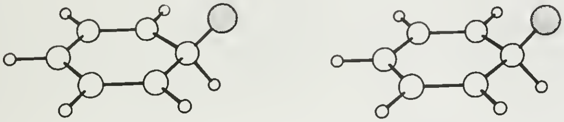
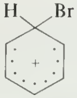


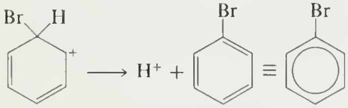
FIGURE 21.8 *Stereo representation of the intermediate in the bromination of benzene.*

This resonance-stabilized pentadienyl cation is often symbolized by using a dotted line to indicate that the positive charge is delocalized over the three positions indicated in the foregoing resonance structures.

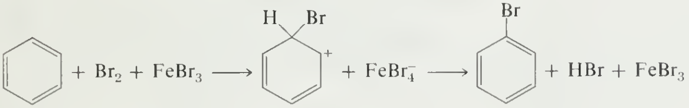


Again, however, this symbol conveys no accounting of electrons. The student is urged to use Lewis structures exclusively at this stage in order to understand more fully the electron displacements that occur in reactions.

Carbonium ions can generally react with a nucleophilic reagent, rearrange, or lose a proton. Reaction of the pentadienyl cation intermediate with a nucleophile would give a product without the benzene ring resonance. Consequently, this type of reaction is rarely observed in electrophilic aromatic reactions. Rearrangements are significant only in some special cases to be discussed in later chapters. The only important reaction of our bromination intermediate is loss of a proton to restore the cyclic π system and yield the substitution product.



The overall reaction sequence is



The first step is rate-determining, as indicated by the energy profile shown in Figure 21.9. The experimental evidence for this reaction mechanism comes from many studies of chemical kinetics, isotope effects, and structural effects. The way

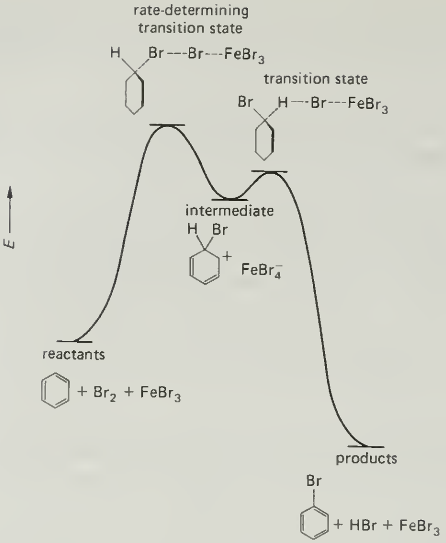
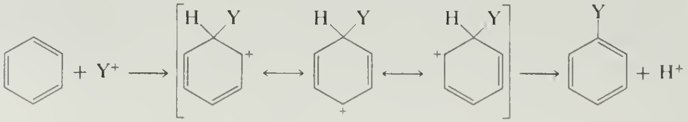


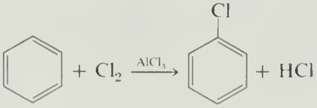
FIGURE 21.9 *Reaction profile for bromination of benzene.*

in which this mechanism allows an understanding of the reactions of substituted benzenes is detailed in Chapter 29.

This type of reaction mechanism is general for many substitution reactions of benzene. Reaction occurs within an electron-deficient or electrophilic species to give a pentadienyl cation intermediate, which, in turn, loses a proton to give the substituted benzene product.



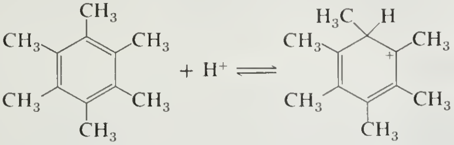
Chlorination is directly analogous to bromination.



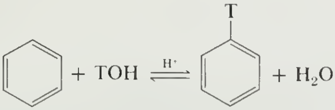
Other important aromatic substitution reactions are nitration, sulfonation, and Friedel-Crafts acylation. These reactions are discussed in the next sections.

B. *Protonation*

Benzene is an extremely weak base, much weaker than an alkene. Benzene is only slightly protonated in concentrated sulfuric acid, whereas isobutylene is significantly protonated, even in sulfuric acid containing water. Some protonation does occur, however, and the amount can be significant if substituents are present. For example, hexamethylbenzene is 50% protonated in 90% aqueous sulfuric acid.

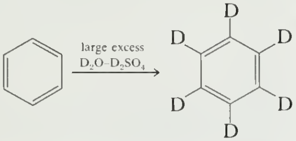


Protonation of benzene can be detected by hydrogen isotope exchange reactions in acid. If benzene is stirred for several days at room temperature with 80% aqueous sulfuric acid containing deuterium or tritium, the isotope distributes between the benzene and the aqueous acid.



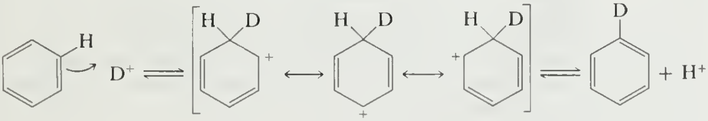
benzene-*t*

Tritium is normally used as a radioactive **tracer isotope.** It is typically used in a ratio of less than one part per million of ordinary hydrogen. Therefore, in an exchange process such as this, it is unlikely that a given molecule will have more than one tritium bound to it. The radioactivity of tritium can be measured by a sensitive instrument called a **liquid scintillation counter;** hence, tritium incorporation can be precisely measured by using only a small amount of the isotope. On the other hand, deuterium is used as a **macroscopic isotope.** Incorporation must be monitored by much less sensitive analytical techniques, such as nmr or mass spectroscopy. The exchange reaction will give mixtures of deuterated benzenes containing varying numbers of deuterium atoms attached to the ring. The amount of deuterium incorporation will depend on the relative amounts of ^1H and ^2H isotopes in the hydrogen "pool." If a large excess of D_2SO_4 and D_2O is used, benzene-d_6, C_6D_6, can be obtained.



benzene-d_6

The exchange reaction is a simple type of electrophilic aromatic substitution reaction in which the electrophilic reagent is D^+.

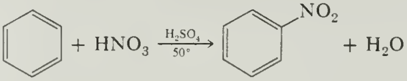


The intermediate pentadienyl cation undergoes only one significant reaction—loss of a proton (or a deuteron). This reaction, which regenerates the aromatic π

system, is much faster than its reaction with water. With ordinary carbonium ions, reaction with a nucleophilic species is an important reaction, but with such carbonium ions, elimination of a proton does not have the extraordinary driving force of the formation of an aromatic ring.

C. *Nitration*

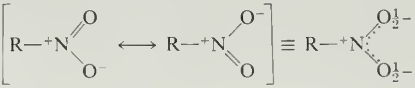
The reaction of alkenes with nitric acid is not a generally useful reaction. Addition of nitric acid to the double bond is accompanied by more or less oxidation. However, benzene is quite stable to most oxidizing agents, and its reaction with nitric acid is an important organic reaction. Actually, the nitrating reagent generally used is a mixture of concentrated nitric acid and sulfuric acid.



nitrobenzene

To a flask containing 65 g of benzene is added a mixture of 110 ml of conc. H_2SO_4 and 85 ml of conc. HNO_3. The acid mixture is added in portions so that the temperature does not exceed 50°. After all of the acid has been added, the reaction mixture is cooled and the oily nitrobenzene layer is separated, washed, and distilled. The yield of pure product is 85–88 g (83–86%).

The nitro group is an important functional group in aromatic chemistry because it may be converted into many other functional groups. The nitration reaction thus provides a route to many substituted aromatic compounds. The chemistry of the nitro group will be detailed in later chapters (Sections 27.8.C, 32.1). Many properties of the nitro group can be interpreted on the basis of a resonance hybrid of two Lewis structures:



In these structures, the O—N—O system is seen to have an allylic anion type of π system.

In a mixture of nitric and sulfuric acids, an equilibrium is established in which many species are present. One of these species is the nitronium ion, NO_2^+, which has been detected by spectroscopic methods. In the mixture of acids, it is produced by a process in which sulfuric acid functions as an acid and nitric acid functions as a base.

(1) $H_2SO_4 + HONO_2 \rightleftharpoons H_2\overset{+}{O}NO_2 + HSO_4^-$

(2) $H_2\overset{+}{O}NO_2 + H_2SO_4 \rightleftharpoons H_3O^+ + {}^+NO_2 + HSO_4^-$

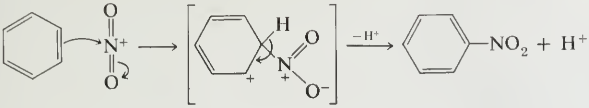
$2\,H_2SO_4 + HONO_2 \rightleftharpoons H_3O^+ + NO_2^+ + 2\,HSO_4^-$

The structure of nitronium ion is known from spectroscopic measurements. It is related to the isoelectronic compound, carbon dioxide. The molecule is linear, and is a powerful electrophilic reagent.

$$O{=}\overset{+}{N}{=}O$$

nitronium ion

It reacts directly with benzene to give a pentadienyl cation intermediate.

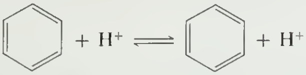


Note that reaction occurs on nitrogen rather than oxygen.

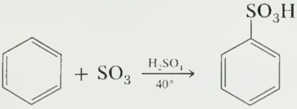
Reaction at oxygen gives a nitrite compound, R—O—NO. Nitrites are unstable under such strongly acidic conditions and decompose to products containing C—O bonds. These oxidation products react further to give highly colored polymeric compounds. The formation of more or less tarry byproducts is a usual side reaction in most aromatic nitration reactions.

D. *Sulfonation*

In the reactions of alkenes with sulfuric acid, the acid acts primarily as a protonating reagent to produce a carbonium ion, which reacts with nucleophiles present (Sections 12.6.B under Addition of HX and 12.6.F). We have seen that benzene itself undergoes protonation in strong sulfuric acid (Section 21.2.B). However, unless such a reaction is followed by use of a hydrogen isotope, it remains an *invisible* reaction.



With strong sulfuric acid, double bonds can react with the sulfur trioxide present. Such reactions of alkenes frequently result in oxidation of the organic material with concommitant reduction of sulfur trioxide to sulfur dioxide. Such reactions are not usually useful reactions of alkenes, although some exceptional cases do exist. The reaction of benzene with sulfur trioxide is a useful and important reaction. Sulfur trioxide is an electrophilic reagent and it reacts with benzene to give benzenesulfonic acid, the product of a sulfonation reaction. The reaction is usually carried out with a solution of sulfur trioxide in sulfuric acid, known as fuming sulfuric acid.

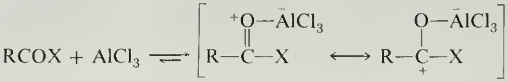


benzenesulfonic
acid

Sulfur trioxide, SO_3, exists in several allotropic forms. The so-called α and β forms are polymers that form long fibrous needles. The γ form is a liquid monomer available commercially with an inhibitor to prevent polymerization. Sulfur trioxide is prepared by the catalytic oxidation of sulfur dioxide with oxygen. Sulfur trioxide is the anhydride of sulfuric acid and reacts vigorously with water with evolution of much heat. The reaction with heavy water, D_2O, is used to prepare D_2SO_4. Sulfuric acid is prepared commercially by dissolving sulfur trioxide in sulfuric acid to produce "fuming sulfuric acid." Commercial fuming sulfuric acid contains 7–8% of SO_3. Dilution with water gives ordinary concentrated sulfuric acid.

E. *Friedel-Crafts Acylation*

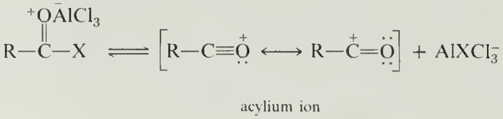
Friedel-Crafts reactions are substitution reactions in which the electrophile is a carbonium ion, which is usually produced with the use of strong Lewis acids. The **alkylation** reaction is a rather complex reaction of limited utility, which we will study later (Section 30.6.A). The **acylation** reaction involves the substitution by an acyl group, RCO—, which is derived from a carboxylic acid derivative, usually an acyl halide or anhydride. The carbonyl group in such acid derivatives is sufficiently basic that formation of a complex occurs with strong Lewis acids such as aluminum chloride.



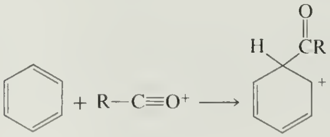
$$RCOX + AlCl_3 \rightleftharpoons \left[R-\overset{\overset{+}{O}-\bar{Al}Cl_3}{\overset{\|}{C}}-X \longleftrightarrow R-\underset{+}{\overset{O-\bar{Al}Cl_3}{\overset{|}{C}}}-X \right]$$

Aluminum chloride, $AlCl_3$, can be prepared by the direct reaction of aluminum with chlorine or hydrogen chloride. The anhydrous compound is available as a white powder that fumes in air and has the strong odor of HCl from reaction with atmospheric moisture. It can be sublimed and is soluble in many organic solvents such as benzene, nitrobenzene, and carbon tetrachloride. In benzene solution, aluminum chloride exists as a dimer, Al_2Cl_6. Anhydrous aluminum chloride reacts vigorously with water with evolution of HCl. It is a strong Lewis acid that forms complexes with most oxygen-containing compounds. In laboratory use it is kept in tightly sealed bottles, and the fine powder is handled in air as little as possible, preferably in a hood.

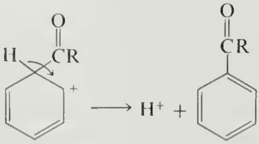
The carbonium ion character of a carbonyl carbon is tremendously enhanced by coordination to aluminum chloride and, in many cases, the complex itself is sufficiently electrophilic to react with aromatic rings. In other cases, the complex exists in equilibrium with a small amount of the corresponding **acylium ion,** which is itself a reactive electrophilic reagent.



$$R-\overset{\overset{+}{O}\bar{Al}Cl_3}{\overset{\|}{C}}-X \rightleftharpoons \underbrace{\left[R-C\equiv\overset{+}{\ddot{O}} \longleftrightarrow R-\overset{+}{C}=\ddot{O} \right]}_{\text{acylium ion}} + AlXCl_3^- \tag{21-1}$$

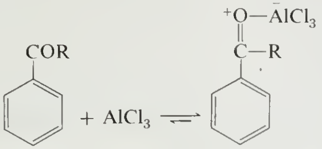


(21-2)

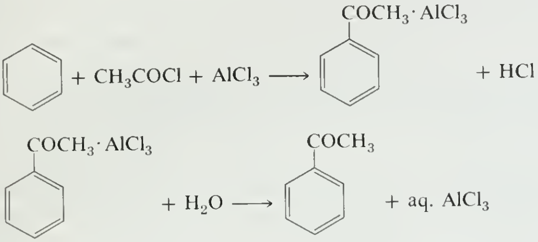


(21-3)

As shown in equations (21-1) to (21-3), the reaction mechanism for reaction of the acylium ion with benzene is completely analogous to that of other electrophilic reagents. The final product is an aromatic ketone whose carbonyl group is sufficiently basic to be complexed completely by aluminum chloride.



It is this complex that is the actual reaction product. The work-up procedure involves treatment with water or dilute hydrochloric acid to decompose the complex and dissolve the aluminum salts. The liberated ketone remains in the organic layer and is isolated by crystallization or distillation. Because it complexes with the product, aluminum chloride must be used in equimolar amounts. Furthermore, the complexed ketone is resistant to further reaction so that high yields of pure product are readily available by this reaction. Friedel-Crafts acylation is an important and useful reaction in aromatic chemistry. An example is the acylation of benzene with acetyl chloride.



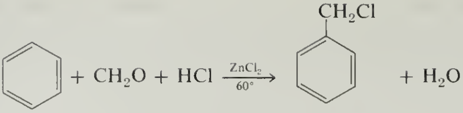
acetophenone

> To a cooled mixture of 40 g of anhydrous aluminum chloride in 88 g of dry benzene 29 g of acetyl chloride is added slowly with stirring or shaking. The HCl evolved is absorbed in a suitable trap. When the addition is complete, the mixture is warmed to 50° for 1 hr. After cooling, ice and water are added, and the benzene layer is washed, dried, and distilled. The product acetophenone is distilled, b.p. 201°, in a yield of 27 g.

The phenyl ketones resulting from such Friedel-Crafts acylation are important and useful intermediates for further transformations (Chapter 31).

F. *Other Electrophilic Substitution Reactions*

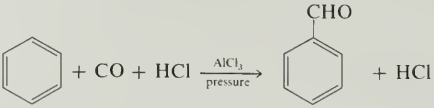
In this chapter we have reviewed only the most important and generally useful of the known electrophilic substitution reactions. Many variations of conditions and reagents exist, and many other reactions are related to those reviewed. For example, the chloromethylation reaction of aromatic compounds is related to the Friedel-Crafts reaction.



(79%)
benzyl chloride

The reaction undoubtedly involves carbonium ion intermediates generated with the help of a Lewis acid, zinc chloride.

The Gatterman-Koch aldehyde synthesis is a variation of Friedel-Crafts acylation:



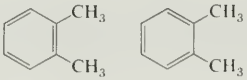
benzaldehyde

This reaction may conveniently be considered to occur by way of the electrophilic intermediate, $HCO^+AlCl_4^-$.

All of these electrophilic substitutions have in common an electron-deficient intermediate that is usually, but not always, positively charged or is the positive fragment in an ion pair. In this chapter we have only considered the reactions of benzene itself. Most of the reactions have wide generality and occur on substituted benzene rings as well. However, such reactions involve important changes in reactivity which seriously affect the reaction conditions and, with multiply substituted benzenes, we encounter isomers with the different ring positions. We shall see later how these variables are largely determined by substituents already present on the benzene ring and the degree to which the entire complex problem is understandable with modern electronic theory (Chapter 29).

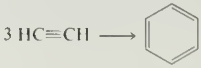
PROBLEMS

1. In Kekulé's day, one puzzling aspect of his dynamic theory for benzene was provided by 1,2-dimethylbenzene. According to his theory, there should be two distinct such compounds, one with a double bond between the two methyl-substituted carbons and one with a single bond in this position.



Only a single 1,2-dimethylbenzene is known, however.
(a) Does Ladenburg's formula solve this problem?
(b) Explain with modern resonance theory.

2. When passed through a hot tube, acetylene gives fair amounts of benzene. What is $\Delta H°$ for the reaction



The entropy change for this reaction is $\Delta S^\circ = -79.7$ eu. How do you explain the negative sign of this entropy change? Calculate ΔG° for the reaction at 25°. Where does the equilibrium lie at room temperature? This reaction does not occur spontaneously at room temperature. Can you give a reason?

3. Benzene can be iodinated with iodine and an oxidizing agent such as nitric acid or hydrogen peroxide. The actual electrophilic reagent in this reaction is probably IOH_2^+, which may be regarded as I^+ bound to a water molecule. Write a balanced equation for the generation of this intermediate from I_2 and H_2O_2. Include this as part of an overall mechanism for the reaction of I_2 and H_2O_2 with benzene to give iodobenzene, C_6H_5I.

4. Unlike most electrophilic substitution reactions at benzene, the sulfonation reaction is reversible. That is, we will learn later that benzenesulfonic acid reacts with water at 100° to give benzene and sulfuric acid.

$$C_6H_5SO_2OH \xrightarrow[100^\circ]{H_2O} C_6H_6 + H_2SO_4$$

Write a reaction mechanism taking account of the principle of microscopic reversibility and the mechanism of sulfonation of benzene.

5. The chloromethylation reaction of benzene with formaldehyde

$$C_6H_6 + CH_2O + HCl \xrightarrow{ZnCl_2} \underset{\text{benzyl chloride}}{C_6H_5CH_2Cl} + H_2O$$

could involve as the principal electrophilic reagent either $CH_2{=}\overset{+}{O}{-}\overset{-}{Z}nCl_2$ or $\overset{+}{C}H_2Cl$. Write complete reaction mechanisms using both intermediates. Note that under these reaction conditions, benzyl alcohol, $C_6H_5CH_2OH$, reacts rapidly with $ZnCl_2$ and HCl (Lucas reagent) to give benzyl chloride.

6. Benzene can be mercurated to give phenylmercuric acetate, $C_6H_5HgOOCCH_3$, with mercuric acetate in acetic acid containing some perchloric acid as an acid catalyst. The electrophilic reagent involved is probably $\overset{+}{H}gOOCCH_3$. Write a complete reaction mechanism.

7. (a) A common method for estimating the empirical resonance energy of benzene is to take the heat of hydrogenation of one Kekulé resonance structure as three times that of cyclohexene. What value of the empirical resonance energy does this procedure yield? Note how the exact value of the empirical resonance energy depends so markedly on the model used for a hypothetical system.

   (b) The heat of hydrogenation of cyclooctene to cyclooctane is -23.3 kcal mole^{-1}. That for 1,3,5,7-cyclooctatetraene is -100.9 kcal mole^{-1}. Use the procedure in (a) to calculate an empirical resonance energy for cyclooctatetraene. How do you interpret this result?

   (c) Another method for estimating empirical resonance energies makes use of the table of Average Bond Energies given in Appendix III. In this table, $E(C{-}H) = 99$, $E(C{-}C) = 83$, $E(C{=}C) = 146$ kcal mole^{-1}. Calculate the total bond energy of a hypothetical cyclohexatriene. This energy is the so-called heat of atomization, the heat required to dissociate a molecule into all of its constituent separated atoms. For benzene, this heat is actually $\Delta H^\circ_{\text{atom.}} = +1318$ kcal mole^{-1}. What value for the empirical resonance energy results?

   Apply this same method to cyclooctatetraene, for which the experimental $\Delta H^\circ_{\text{atom}} = +1713$ kcal mole^{-1}.

   (d) The heat of combustion of cyclooctatetraene (reactant and products in the gas phase) is $\Delta H_c^\circ = -1054.7$ kcal mole^{-1}. Derive the value of ΔH_c° per C—H group in C_8H_8. If we take this number to be a kind of group equivalent heat for a CH group in a conjugated system having little resonance energy, one can derive a corresponding ΔH_c° for a nonconjugated cyclohexatriene. The actual ΔH_c° for benzene is -757.5 kcal mole^{-1}. What is the derived empirical resonance energy of benzene?

(e) Benzene and cyclooctatetraene are two members of the class of monocyclic $(CH)_n$ compounds known as annulenes. Benzene is [6]annulene and cyclooctatetraene is [8]annulene in this nomenclature. [18]Annulene is a known compound that has been found, by x-ray structure analysis, to have a planar structure with equal C—C bond distances. Does [18]annulene fit the $4n + 2$ rule? From thermochemical methods, the derived experimental heat of atomization is $\Delta H^\circ_{\text{atom.}} = +3890$ kcal mole^{-1}. From the method of part (c), calculate the corresponding empirical resonance energy. How does this result compare with the $4n + 2$ evaluation? Compare the empirical resonance energy per C—H unit of [18]annulene and [6]annulene.

8. Identify all benzene derivatives illustrated so far in this textbook.

9. Consider the possible free radical chain chlorination of benzene:

$$C_6H_6 + Cl\cdot \longrightarrow C_6H_5\cdot + HCl$$

$$C_6H_5\cdot + Cl_2 \longrightarrow C_6H_5Cl + Cl\cdot$$

From the data in Appendix I calculate ΔH° for each reaction. Use these results to explain why this method is *not* a satisfactory way of preparing chlorobenzene.

CHAPTER 22

Ultraviolet Spectroscopy

22.1 Electronic Transitions

A molecule can absorb a quantum of microwave radiation (about 1 cal mole^{-1}) and change from one rotational state to another. Vibrational energy changes are associated with light quanta in the infrared region of the spectrum (about 3–10 kcal mole^{-1}). A change in the electronic energy of a molecule requires light in the ultraviolet (70–300 kcal mole^{-1}) or visible (40–70 kcal mole^{-1}) regions. The energies required for such **electronic transitions** are of the magnitude of bond strengths because the electrons involved are valence electrons. That is, the energy of light quanta in this region of the electromagnetic spectrum is sufficient to **excite** an electron from a bonding to an antibonding state.

The resulting **excited electronic states,** in contrast to the **ground electronic state,** are often difficult to describe by resonance symbolism. In simple diatomic molecules an excited state can sometimes be described rather simply. For example, one excited state of LiF can be described by the process

$$\underset{\text{ground state}}{\text{Li}^+\text{F}^-} \xrightarrow{h\nu} \underset{\text{excited state}}{\text{Li}\cdot\ \text{F}\cdot}$$

Absorption of a photon is accompanied by a shift in electron density from fluorine to lithium, and the resulting excited state resembles two atoms held in close proximity.

The excited states of polyatomic molecules are not usually described so simply. Fortunately, molecular orbital concepts can often be applied in a relatively simple and straightforward way. For example, the electronic transition of methane involves the excitation of an electron from a bonding molecular orbital, σ, to the corresponding antibonding molecular orbital, σ*, as illustrated in Figure 22.1.

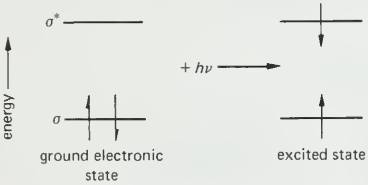


FIGURE 22.1 *Ground and excited states.*

Recall that the bonding molecular orbital between two atoms is formed by the positive overlap of two hybrid orbitals, and is symbolized as in Figure 22.2. The corresponding antibonding molecular orbital, σ*, is produced by the negative overlap of the hybrid orbitals. Note that this negative overlap produces an additional node between the nuclei and reduces the electron density that is so

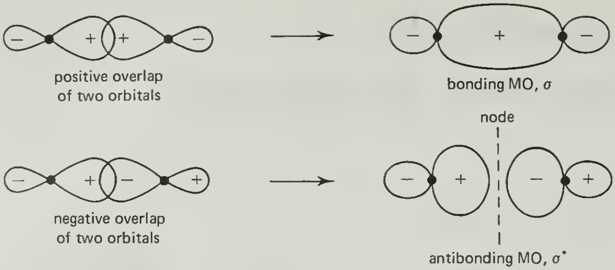

+
−
positive overlap of two orbitals
bonding MO, σ
node
negative overlap of two orbitals
antibonding MO, σ*

Figure 22.2 *Bonding and antibonding molecular orbitals.*

essential for covalent bonding. In the excited state, the electron in σ* partially cancels the bonding provided by the remaining electron in σ; hence, the energy required for excitation is of the order of magnitude of bond strengths.

The bonding molecular orbitals of methane, and of alkanes generally, are relatively stable and low in energy. Excitation of an electron requires light of high energy, having a wavelength about 150 nm (1500 Å) or less. Light in this region is strongly absorbed by the oxygen in air and spectroscopic measurements of such compounds require special instruments in which air is completely excluded. This region of the light spectrum is called the vacuum ultraviolet, and is unimportant in routine organic laboratory studies.

Wavelengths of light above about 200 nm are not absorbed by air, and it is this region that is most important for organic chemists. The range of about 200–400 nm is called the ultraviolet; the visible region of the spectrum ranges from wavelengths of about 400 nm (violet light) to about 750 nm (red light). The energy of such light is insufficient to affect most σ bonds, but it is in the range of π electron energies, especially for conjugated systems. That is, ultraviolet-visible spectroscopy is an important spectroscopic tool for the study of conjugated multiple bonds. The π molecular orbitals of such conjugated systems extend over several atoms. The highest occupied or least bonding of such molecular orbitals already have at least one node. Electronic excitation generally involves the transition of an electron to a molecular orbital having an additional node, and, as a general rule, the more nodes an electron has in a wave function, the less energy it takes to add another node.

22.2
$\pi \rightarrow \pi^*$ Transitions

Absorption of light that produces excitation of an electron from a bonding π to an antibonding π* molecular orbital is referred to as a $\pi \rightarrow \pi^*$ transition. For example, 1,3-butadiene has an intense absorption band at 217 nm (usually written as λ_{max} 217 nm; that is, lambda max = 217 nanometers) that results from the excitation of an electron from π_2 to π_3 (Figure 22.3). Recall that π_2 has one node and π_3 has two (Figure 20.7). 1,3,5-Hexatriene absorbs at longer wavelength, $\lambda_{max} = 258$ nm. It takes less energy to excite an electron from π_3, the highest occupied π molecular orbital of hexatriene which has two nodes, to π_4, which has three nodes. *The longer the chain of conjugation, the longer the wavelength*

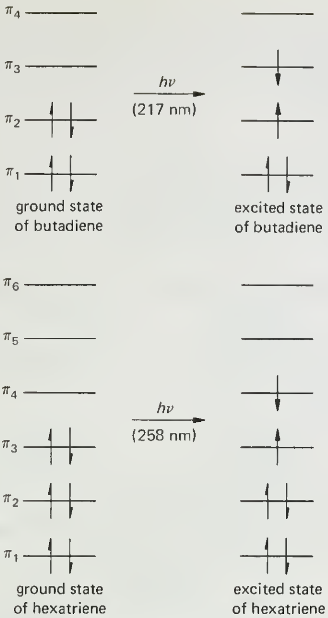
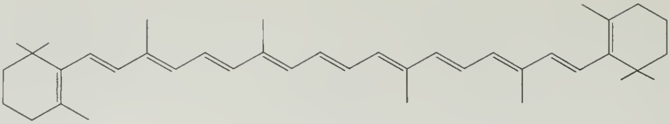

π_4
π_3
π_2
π_1
$h\nu$
(217 nm)
ground state of butadiene
excited state of butadiene
π_6
π_5
π_4
π_3
π_2
π_1
$h\nu$
(258 nm)
ground state of hexatriene
excited state of hexatriene

FIGURE 22.3 *Electronic states of butadiene,* $CH_2{=}CHCH{=}CH_2$, *and* 1,3,5-*hexatriene,* $CH_2{=}CHCH{=}CHCH{=}CH_2$.

of the absorption band. For example, the lowest energy $\pi \rightarrow \pi^*$ transition of 1,3,5,7-octatetraene occurs at the still longer wavelength of 304 nm, whereas ethylene itself absorbs in the vacuum ultraviolet at 175 nm.

Compounds generally have many excited electronic states, but organic chemists are mostly concerned with the lowest or more stable states, since these are the states that are accessible with the energies of ultraviolet and visible light. Many of these states can be described in terms of electron transitions that involve other than just the highest occupied and lowest vacant molecular orbitals. For example, other electronic states of butadiene arise from the electronic transition, $\pi_1 \rightarrow \pi_3$ or $\pi_1 \rightarrow \pi_4$, but such transitions occur in the vacuum ultraviolet. However, benzene has three absorption bands rather close together at 264 nm, 207 nm, and 179 nm that involve excited states that do not differ much in energy from each other—the corresponding energies are 108, 138, and 160 kcal $mole^{-1}$, respectively (see Section 22.4).

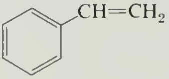
The highly conjugated hydrocarbon, *trans-β*-carotene, with 11 double bonds in conjugation, absorbs at 483 nm in hydrocarbon solution. This wavelength occurs in the visible region and corresponds to blue-green light. Since light of this color is absorbed by the compound, *β*-carotene appears orange. For further aspects of color, see Section 36.4.A.



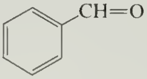
trans-β-carotene

α,β-Unsaturated aldehydes and ketones have absorptions that resemble the corresponding diene. Such spectra are interpreted in the same way as a transition of an electron from π_2 to π_3 and are referred to correspondingly as $\pi \rightarrow \pi^*$ transitions.

$CH_2{=}CHCH{=}CH_2$	$CH_2{=}CHCHO$
λ_{max} 217 nm	λ_{max} 218 nm



styrene
λ_{max} 244, 282 nm



benzaldehyde
λ_{max} 244, 280 nm

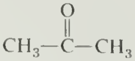
With these compounds also the wavelength of the light absorbed increases as the chain of conjugation is lengthened. This effect is illustrated in Table 22.1.

TABLE 22.1
Spectra of Some Polyene Aldehydes

Aldehyde	λ_{max}, nm
$CH_3CH{=}CHCHO$	220
$CH_3CH{=}CHCH{=}CHCHO$	270
$CH_3(CH{=}CH)_3CHO$	312
$CH_3(CH{=}CH)_4CHO$	343
$CH_3(CH{=}CH)_5CHO$	370
$CH_3(CH{=}CH)_6CHO$	393
$CH_3(CH{=}CH)_7CHO$	415

22.3
$n \rightarrow \pi^*$ Transitions

Carbonyl groups have another characteristic absorption associated with the lone pair electrons on oxygen. Since these electrons are bound to only a single atom, they are not held as tightly as σ electrons, and they can also be excited to π^* molecular orbitals. The process results in a so-called $n \rightarrow \pi^*$ transition and usually occurs at relatively long wavelength.



$$CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3$$

$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH{=}CH_2$$

$n \rightarrow \pi^*$	λ_{max} 270 nm	λ_{max} 324 nm
$\pi \rightarrow \pi^*$	187 nm	219 nm

The π system of methyl vinyl ketone is more extended than that of acetone, and less energy is required for the excitation in the former case. This difference is illustrated in Figure 22.4. Because of the more extensive π system of conjugated double bonds of methyl vinyl ketone compared to acetone, both the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of methyl vinyl ketone occur at longer wavelength (lower energy).

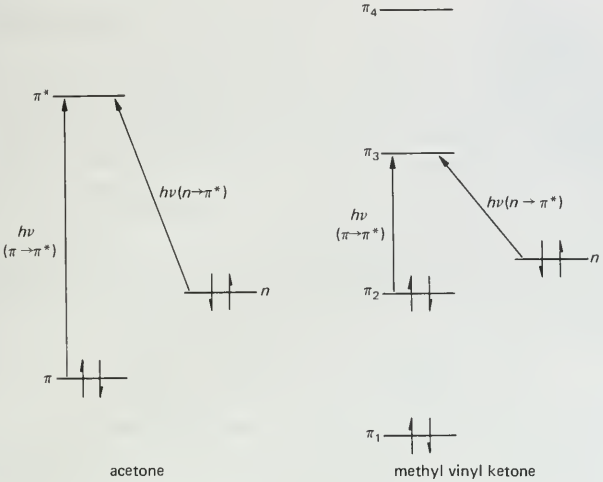

π^*
$h\nu(n \rightarrow \pi^*)$
$h\nu$
$(\pi \rightarrow \pi^*)$
n
π
acetone
π_4
π_3
$h\nu(n \rightarrow \pi^*)$
$h\nu$
$(\pi \rightarrow \pi^*)$
n
π_2
π_1
methyl vinyl ketone

FIGURE 22.4 *Illustrating $\pi \rightarrow \pi^*$ and n $\rightarrow \pi^*$ transitions in two ketones.*

One important distinguishing characteristic of $n \rightarrow \pi^*$ transitions results from the critical feature that the lone pair electrons tend to be concentrated in a different region of space from the π electrons (Figure 22.5). Although $n \rightarrow \pi^*$ transitions often occur at lower energy (longer wavelength) than $\pi \rightarrow \pi^*$ transitions, they are *less probable.* A given quantum of $n \rightarrow \pi^*$ light must encounter many more molecules before it is absorbed than is the case for $\pi \rightarrow \pi^*$ light quanta. This difference shows up experimentally in an absorption spectrum as an intensity difference; $\pi \rightarrow \pi^*$ absorptions are generally much more intense ("strong absorption") than $n \rightarrow \pi^*$ absorptions ("weak absorption"). The difference in intensity is two to three orders of magnitude.

The intensity is expressed as an **extinction coefficient, ε.** The amount of light

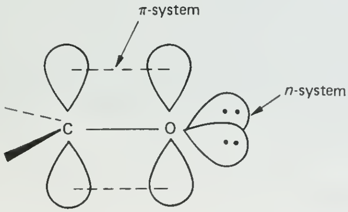


FIGURE 22.5 *Lone pair* (n) *and π systems of a carbonyl group.*

absorbed depends on the extinction coefficient and the number of molecules in the light path. The latter amount depends on the concentration of the solution and the path length of the absorption cell. The amount of light that passes through a solution (transmittance) is given by Beer's law,

$$\log \frac{I_0}{I} = \varepsilon c d$$

where I_0 is the intensity of the light before it encounters the cell, I is the intensity of the light emerging from the cell, c is the concentration in moles per liter, and d is the path length in centimeters.

As an example, the spectrum of two concentrations of mesityl oxide, $(CH_3)_2C{=}CHCOCH_3$, in the same 1-cm cell (a common path length) is shown in Figure 22.6. A highly dilute solution is used for the $\pi \rightarrow \pi^*$ absorption, at 235 nm. The extinction coefficient for this transition is calculated as

$$\varepsilon = \frac{\log I_0/I}{cd} = \frac{1.18}{(9.37 \times 10^{-5})(1)} = 12{,}600 \text{ l mole}^{-1} \text{ cm}^{-1}$$

In this dilute solution the absorption due to the $n \rightarrow \pi^*$ transition is so weak it is barely discernible. A more concentrated solution gives greater absorption and, from the second curve in Figure 22.6, we may calculate ε for this transition at 326 nm to be

$$\varepsilon = \frac{\log I_0/I}{cd} = \frac{0.47}{(9.37 \times 10^{-3})(1)} = 50$$

(Note that the units of ε are usually omitted)

This concentration is so high, however, that the $\pi \rightarrow \pi^*$ transition absorbs light essentially completely at its wavelength. The ratio of the two extinction coeffi-

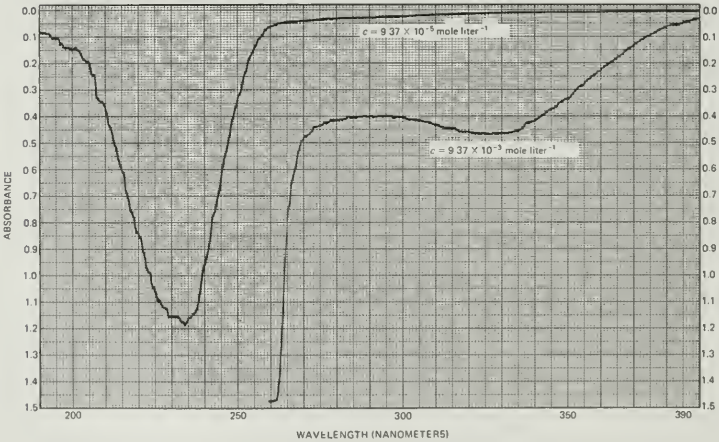


FIGURE 22.6 *Ultraviolet absorption spectra of mesityl oxide,* $(CH_3)_2C{=}CHCOCH_3$.

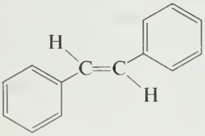
cients, 12,600/50 = 252 is typical for unsaturated carbonyl compounds. In general, the $\pi \rightarrow \pi^*$ transitions have ε of about 10^4 whereas ε for $n \rightarrow \pi^*$ transitions are about 10–100.

22.4
Benzene Rings

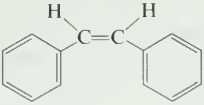
The π system of benzene has two highest occupied molecular orbitals, ψ_2 and ψ_3, and two lowest vacant molecular orbitals, ψ_4 and ψ_5 (Figure 21.3). We might expect to see four kinds of $\pi \rightarrow \pi^*$ transitions: $\psi_2 \rightarrow \psi_4$, $\psi_2 \rightarrow \psi_5$, $\psi_3 \rightarrow \psi_4$, and $\psi_3 \rightarrow \psi_5$. These four transitions all correspond to the same energy, and for this type of situation there is a breakdown in our simple picture of an electronic excitation as involving the transition from one molecular orbital to another. Several low-lying excited states of benzene exist that we would have to describe as various composites of the four simple transitions described above. An adequate treatment of the ultraviolet spectrum of benzene requires a rather complex quantum mechanical discussion, which we will not develop. The longest wavelength absorption of benzene gives a series of sharp bands centered at 255 nm with $\varepsilon = 230$, a relatively low intensity for a $\pi \rightarrow \pi^*$ transition. This low value results from the high symmetry of benzene which gives this absorption a relatively low probability. Such an absorption is called **symmetry-forbidden.**

A vinyl group attached to a benzene ring constitutes a conjugated system. Styrene has two principal absorption bands: λ_{max} 244 nm with $\varepsilon = 12{,}000$ and λ_{max} 282 nm with $\varepsilon = 450$. The more intense band is a polyene type of $\pi \rightarrow \pi^*$ transition, whereas the less intense band corresponds to a substituted benzene.

1,2-Diphenylethylene or stilbene allows a comparison of *cis* and *trans* isomers.



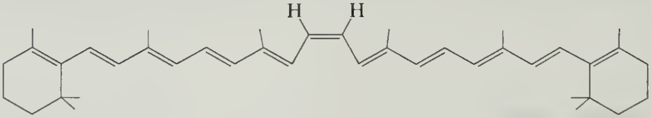
trans-stilbene
$\lambda_{max} = 295$ nm
$\varepsilon = 27000$



cis-stilbene
$\lambda_{max} = 280$ nm
$\varepsilon = 13500$

trans-Stilbene has no significant steric interactions. The compound has an extended coplanar π system. In *cis*-stilbene, however, the two phenyl groups are on the same side of the double bond and sterically interfere with each other. The rings cannot both be coplanar with the double bond and π conjugation is not as effective as in the *trans* isomer. The result is a small change in λ_{max} but a large decrease in the extinction coefficient.

This result is quite general: π systems that are prevented from achieving coplanarity show significant changes, particularly in absorption intensities. A further example is given by the β-carotenes. *trans*-β-Carotene (Section 22.2) has two long wavelength absorption maxima in alkane solution at 483 nm ($\varepsilon = 111{,}000$) and 453 nm ($\varepsilon = 130{,}000$). The *cis* isomer has two absorption peaks at essentially the same wavelengths but with lower extinction coefficients, $\varepsilon = 82{,}000$ and 100,000, respectively.



cis-β-carotene

22.5
Alkyl Substituents

We saw in Section 22.2 that 1,3-butadiene has a $\pi \rightarrow \pi^*$ transition at 217 nm. Alkyl-substituted butadienes have the same π system, but their absorption spectra vary significantly. Examples are

	λ_{max}, nm
$CH_2{=}CHCH{=}CH_2$	217
$CH_2{=}\overset{\overset{\large CH_3}{\vert}}{C}CH{=}CH_2$	220
$CH_3CH{=}CHCH{=}CH_2$	223.5
$CH_2{=}\overset{\overset{\large CH_3}{\vert}}{C}-\overset{\overset{\large CH_3}{\vert}}{C}{=}CH_2$	226
$CH_3CH{=}CHCH{=}CHCH_3$	227

Each methyl group increases the wavelength of the absorption peak by about 5 nm. A similar effect shows up with unsaturated carbonyl compounds:

	λ_{max}, nm ($\pi \rightarrow \pi^*$)
$CH_2{=}CHCOCH_3$	219
$CH_3CH{=}CHCOCH_3$	224
$(CH_3)_2C{=}CHCOCH_3$	235

This effect arises from the overlap of σ bonds in the alkyl substituent with the π system. The resulting **hyperconjugation** is symbolized in Figure 22.7.

Hyperconjugation is much less effective than conjugation. Adding a methyl group to butadiene has little more than 10% of the effect of adding another vinyl group. Nevertheless, even this small effect has been useful for structure proofs, and extensive empirical correlations have been compiled for determining the actual effect of an alkyl substituent in various positions of dienes, trienes, and

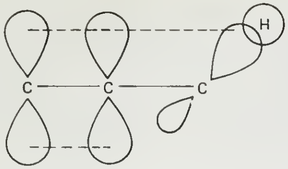
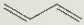
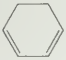
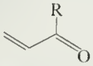


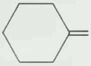
FIGURE 22.7 *Illustration of hyperconjugation between a* C—H *bond and a double bond.*

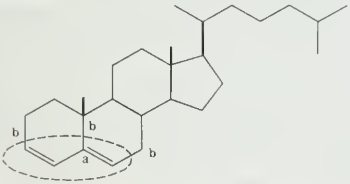
TABLE 22.2
Empirical Parameters for $\pi \rightarrow \pi^*$ Transitions of Conjugated Systems in Ethanol (Woodward's Rules)

Parent System	λ_{max}, nm	Substituent Corrections	
Polyenes			
		double bond[a]	+30
	214	alkyl group	+5
		exocyclic C=C double bond	+5
	253	OR groups	0
		Cl, Br	+5
α,β-Unsaturated ketones			
 R O	215	double bond[a]	+30
		alkyl group	+10
		exocyclic C=C double bond	+5

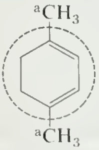
[a] The double bond must be attached at the end of the π system to produce a linear conjugated system.

unsaturated carbonyl compounds. Some correlations of this type (**Woodward's rules**) are summarized in Table 22.2 for use with conjugated dienes, trienes and α,β-unsaturated ketones. Some examples of the use of this table follow. *Note:* an exocyclic double bond is attached to a ring at one end, for example

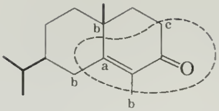




parent (circled)	214
1 exocyclic double bond (a)	5
3 alkyl substituents (b)	15
calcd λ_{max}	234 nm
expl λ_{max}	234 nm

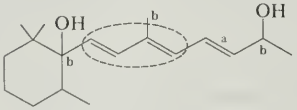


parent (circled)	253
2 alkyl substituents (a)	10
calcd λ_{max}	263 nm
expl λ_{max}	265 nm



parent (circled)	215
1 exocyclic double bond (a)	5
3 alkyl groups (b)	30
calcd λ_{max}	250 nm
expl λ_{max}	251 nm

Note that the parent is a ketone and therefore includes alkyl group (c). Note also that the correction for an exocyclic double bond does not apply to the carbonyl group.



parent (circled)	214
double bond (a)	30
3 alkyl groups (b)	15
calcd λ_{max}	259 nm
expl λ_{max}	263 nm

The rules reproduced here have been simplified to serve as an introduction to the general concept of the use of such empirical generalizations in ultraviolet spectroscopy. Note that the only substituents that are relevant are those attached directly to the conjugated π system. Alkyl groups and double bonds elsewhere in the molecule have little or no effect on the transitions of the π system. Extended correlations of this type are available for other parents and for other types of substituent and solvent corrections. The general approach constitutes one of the most useful applications of ultraviolet spectroscopy in structure proofs.

22.6
Other Functional Groups

Alcohols and ethers do not have conjugated π systems and are transparent in the normal ultraviolet and visible regions. Ethanol and ether are common solvents for recording ultraviolet spectra. Sulfides, however, have relatively intense absorption at about 210 nm with a weaker band at about 230 nm. These absorptions are probably associated with transition of a lone pair electron in sulfur to a sulfur 3*d* orbital.

The carbonyl group in carboxylic acid derivatives is significantly different from that in ketones. Alkanoic acids have a low intensity band about 200–210 nm, anhydrides absorb at somewhat longer wavelength and the acid chlorides are still longer at about 235 nm.

Simple acetylenes absorb in the vacuum ultraviolet. Conjugated triple bonds show the type of absorption in the accessible ultraviolet expected for extended π systems. The $C{\equiv}N$ group of nitriles also absorbs at short wavelength, below 160 nm.

The simple alkyl fluorides and chlorides have no absorption maxima in the normal ultraviolet region. Alkyl bromides and iodides, however, do have λ_{max} in the region about 250–260 nm. These absorptions are attributed to transition of a lone pair electron to an antibonding σ^* orbital. C—Br and C—I bonds are sufficiently weak that the corresponding σ^* orbitals have low enough energy to give transition energies in this ultraviolet region.

22.7
Photochemical Reactions

An excited state has more electronic energy than the ground state, and such states are generally rather short-lived. This excess energy is generally dissipated within less than 10^{-7} sec. One important way in which this energy is removed is by conversion of the electronic energy to vibrational and rotational energy. This energy may simply be distributed as translational energy to other colliding molecules, in which case the net result has been the conversion of light to heat.

Alternatively, the vibrational energy may suffice to cause rearrangements or to break bonds. We saw one example of bond breaking in the light-initiated chlorination of alkenes (Section 5.3.A).

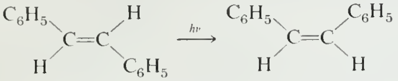
$$\mathrm{Cl_2} \xrightarrow{h\nu} 2\,\mathrm{Cl}\cdot$$

This reaction could have been expressed as

$$\mathrm{Cl_2} \xrightarrow{h\nu} \mathrm{Cl_2^*} \longrightarrow 2\,\mathrm{Cl}\cdot$$

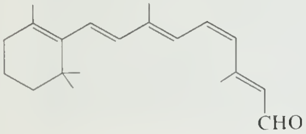
in which Cl_2^* refers to an electronically excited state of Cl_2. The light promotes an electron to a Cl—Cl σ^* orbital. An electron in an antibonding orbital produces a weaker bond than when such an orbital is vacant and generally gives rise to a lower bond dissociation energy.

Many examples of different types of photochemical reactions are known for organic compounds, but we will only discuss one at this point (for further examples see Section 36.5). In the electronically excited state of an alkene, the double bond is generally weaker than in the ground state and *cis-trans* isomerization is more facile.

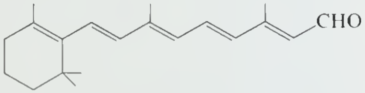


trans-stilbene   *cis*-stilbene

Use of this type of photochemical reaction is made in the chemistry of vision. Vitamin A is an alcohol that is oxidized enzymatically to vitamin A aldehyde (retinal), a *cis* form of which combines with a protein, opsin, to produce the light-sensitive compound rhodopsin or visual purple. This compound is contained in the rods of the retina and absorbs at 500 nm. Absorption of light quanta of this wavelength results in conversion to the *trans* isomer. This isomerization is accompanied by a conformational change that excites the nerve cell and produces a separation into opsin and *trans*-retinal. The *trans*-aldehyde is converted to the *cis* form by an enzyme, retinal isomerase, and the cycle starts anew. A wavelength of 500 nm corresponds to the blue-green region of the light spectrum and suggests why the rods are so sensitive to light of this color. Only a few light quanta are required to give a visual response to the dark-adapted eye. Bright light causes temporary impairment of vision because it depletes the rhodopsin and time is required for the protein to be reconstructed via the retinal isomerase cycle.



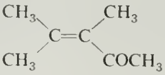
cis-retinal

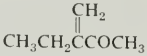


trans-retinal

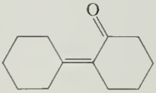
PROBLEMS

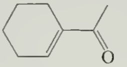
1. The labels fell off four bottles of ketones known to have the structures below. Measurement of the ultraviolet spectra of the contents of the four bottles gave λ_{max} at 221, 233, 249, and 258 nm. Assign structures to the appropriate λ_{max}.





$$CH_3CH_2\overset{\overset{\textstyle CH_2}{\|}}{C}COCH_3$$

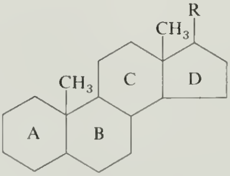




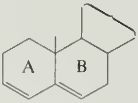
2. Alkyl bromides and iodides are normally stored in the dark or in dark bottles. On exposure to light they slowly turn brown or violet, respectively. Give an explanation for this phenomenon based on a reasonable photochemical mechanism.

3. Which of the following compounds would be suitable as solvents for recording normal ultraviolet spectra of substrates? Explain briefly.
methanol
ethyl ether
methyl butyl sulfide
acetonitrile
perfluoropropane
ethyl iodide
benzene
1-chlorobutane
methylene bromide
cyclohexane

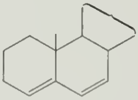
4. Steroids have the basic nucleus



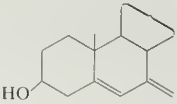
with the rings labeled as indicated. Many such steroid compounds are known. In the following examples only the A and B rings are indicated and significant. Using the empirical parameters in Table 22.2, calculate the expected λ_{max} and compare with the experimental values given.



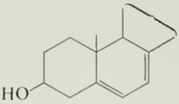
234 nm



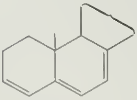
235 nm



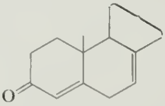
236 nm



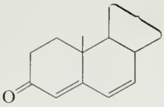
282 nm



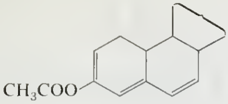
315 nm



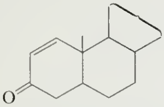
235 nm



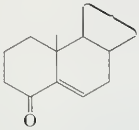
284 nm



306 nm



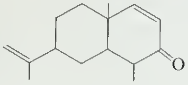
230 nm



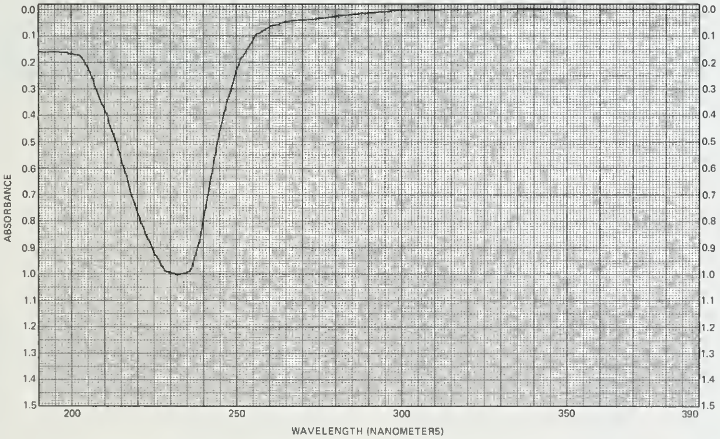
241 nm

5. A number of simple conjugated polyenes, $H(CH{=}CH)_nH$, are now known up to $n = 10$; λ_{max} in nanometers corresponding to values of n are as follows: 2, 217; 3, 268; 4, 304; 5, 334; 6, 364; 7, 390; 8, 410; 10, 447. A crude model of such a conjugated π system is that of an electron in a box having the dimensions of the π system. A quantum mechanical treatment of such a model suggests that $1/\lambda_{max}$ should be approximately a linear function of $1/n$. Test this prediction with the data given and try to interpolate to find λ_{max} for the missing polyene with $n = 9$.

6. The sesquiterpene, α-cyperone, was originally assigned the structure shown. Based on the ultraviolet absorption at λ_{max} 251 nm found for α-cyperone determine whether this structure is reasonable, and if not, propose an alternative with the same basic skeleton.



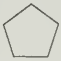
7. The ultraviolet spectrum of 3,6,6-trimethylcyclohex-2-en-1-one, is shown below. The concentration is 1.486×10^{-5} g ml^{-1} in ethanol. Calculate ϵ and compare λ_{max} with the value predicted by Woodward's rules.

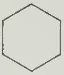


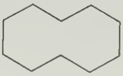
CHAPTER 23
Cyclic Compounds

23.1
Introduction

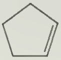
Ring compounds are important in organic chemistry. The simplest cyclic compounds are the cycloalkanes. Thus far, we have seen many examples of cycloalkanes that have chemistry comparable to that of the acyclic alkanes. Examples of such rings are

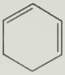

cyclopentane

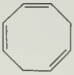

cyclohexane


cyclodecane

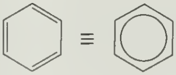
Hydrocarbon rings may also be unsaturated. Examples of a cycloalkene, a cycloalkadiene, and a cycloalkatriene are

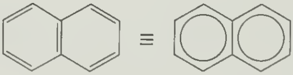

cyclopentene


1,3-cyclohexadiene


1,3,6-cyclooctatriene

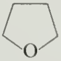
Aromatic compounds, such as benzene and naphthalene, form another class of cyclic compounds.


benzene

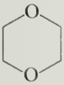

naphthalene

Rings may contain other atoms in addition to carbon. Such rings are known as **heterocycles,** to distinguish them from the **carbocycles.** Heterocyclic systems may also be saturated, unsaturated, or aromatic and may contain more than one **heteroatom.** Examples are

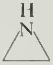
Saturated Heterocycles



tetrahydrofuran
a cyclic ether

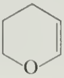


1,4-dioxane
a cyclic diether

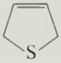


aziridine
a cyclic amine

Unsaturated Heterocycles

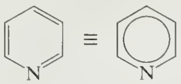


2,3-dihydropyran

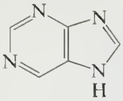


2,5-dihydrothiophene

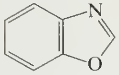
Aromatic Heterocycles



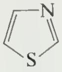
pyridine
an aromatic amine



purine



benzoxazole



thiazole

Some of these types of compounds will be considered in this chapter; others will be discussed as part of our further treatment of aromatic chemistry.

23.2
Structure and Energy of Cycloalkanes

A. *Ring Strain*

Although the cycloalkanes show many of the same properties and chemistry as the acyclic alkanes, there are some additional features that result from the constraint of binding the chains into a ring. Two of these additional features are **ring strain** and **conformational** effects. Ring strain is an energy effect that may be seen clearly in the heats of formation of the cycloalkanes. Recall that each CH_2 group in an alkane adds about -5 kcal mole^{-1} to ΔH_f°.

	ΔH_f°, kcal mole^{-1}
$4\,C + 5\,H_2 \longrightarrow n\text{-}C_4H_{10}$	-30.4
$5\,C + 6\,H_2 \longrightarrow n\text{-}C_5H_{12}$	-35.1
$6\,C + 7\,H_2 \longrightarrow n\text{-}C_6H_{14}$	-39.9

Since cycloalkanes have the empirical formula $(CH_2)_n$, one can obtain the ΔH_f° for each CH_2 group by simply dividing ΔH_f° for the molecule by n. The heats of formation for a number of cycloalkanes are tabulated in Table 23.1. Examination of the table shows that most of these cycloalkanes have values of $\Delta H_f^\circ/n$ that are less negative than the alkane value of about -5 kcal mole^{-1}. That is, many cycloalkanes have a higher energy content per CH_2 group than a typical acyclic alkane. This excess energy is called ring strain. Ethylene is included in the table for comparison; it may be considered a "two-membered ring." The total excess energy of a cycloalkane is simply the excess energy per CH_2 multiplied by the number of CH_2 groups in the particular cycloalkane.

Cyclohexane shows essentially no ring strain; its CH_2 groups have essentially the same ΔH_f° as do those of normal alkanes. For the purpose of computing the ring strain of a particular cycloalkane, cyclohexane is considered to be strain free; it is the standard for comparison. For cyclohexane, $\Delta H_f^\circ = -29.5$ kcal mole^{-1} and $\Delta H_f^\circ/n = -29.5/6 = -4.92$ kcal mole^{-1}. This value is taken as ΔH_f° for a "strainless" CH_2 group. For example, ΔH_f° for a hypothetical "strainless" cyclopentane would be -4.92 kcal mole$^{-1} \times 5 = -24.6$ kcal mole^{-1}. Hence, the strain

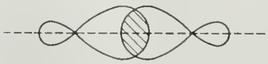
TABLE 23.1
ΔH_f° *of Cycloalkanes*, $(CH_2)_n$

n	Cycloalkane	ΔH_f°, kcal mole^{-1}	$\Delta H_f^\circ/n$, kcal mole^{-1} per CH_2 group	Total Strain Energy, kcal mole^{-1}
2	ethylene	+12.5	+6.2	22
3	cyclopropane	+12.7	+4.2	27
4	cyclobutane	+6.8	+1.7	26
5	cyclopentane	−18.4	−3.7	6
6	cyclohexane	−29.5	−4.9	(0)
7	cycloheptane	−28.2	−4.0	6
8	cyclooctane	−29.7	−3.7	10
9	cyclononane	−31.7	−3.5	13
10	cyclodecane	−36.9	−3.7	12
11	cycloundecane	−42.9	−3.9	11
12	cyclododecane	−55.0	−4.6	4
13	cyclotridecane	−58.9	−4.5	5
14	cyclotetradecane	−57.1	−4.1	12
15	cyclopentadecane	−72.0	−4.8	2
16	cyclohexadecane	−76.9	−4.8	2

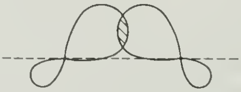
energy of cyclopentane = $(-18.4) - (-24.6) = +6.2$ kcal mole^{-1}. Cyclopentane is 6 kcal mole^{-1} less stable than it would be if each CH_2 group were in some hypothetical strain-free state. The source of these strain energies will be treated next.

B. *Cyclopropane and Cyclobutane*

The double bond in ethylene is less stable than two single bonds because orbital overlap is reduced when orbitals do not overlap along the internuclear bond axis.



stronger,
more efficient overlap



weaker,
less efficient overlap

The structure of cyclopropane is shown in Figure 23.1. For purely geometric reasons, the internuclear C—C—C angle in cyclopropane is 60°. The natural bond angle for C_{sp^3} orbitals overlapping linearly would be 109.5°. For hybrid orbitals having more p character, the natural angle is smaller, but even with pure p orbitals, the natural bond angle cannot be less than 90°. In practice, the C—C bond orbitals in small rings do have more p character than sp^3 (between sp^4 and sp^5) and the resulting orbitals form **bent bonds** (Figure 23.2). As a result, the C—C bonds in cyclopropane are weaker than those in normal alkanes. This reduced bond strength shows up in the chemistry to be discussed subsequently and also as a ring strain in the ΔH_f°. The ring strain in cyclopropane results primarily from bent bonds.

To compensate partially for ring strain, extra s character is used for the C—H

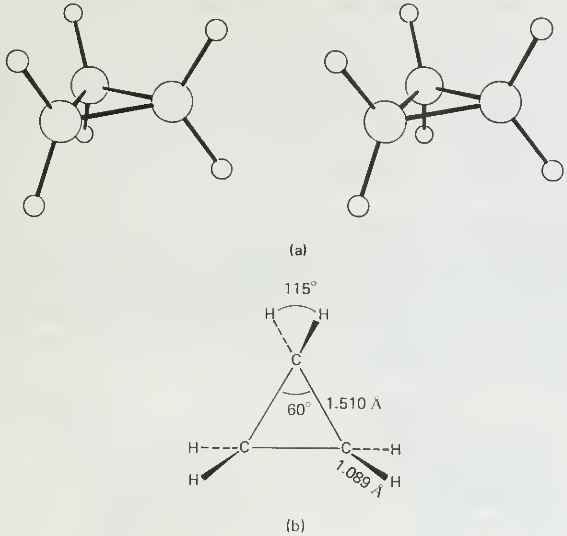


FIGURE 23.1 (a) *Stereo representation and* (b) *geometric structure of cyclopropane.*

bonds. These bonds are somewhat stronger than alkyl C—H bonds and the H—C—H bond angle is greater than tetrahedral. Another factor that contributes to the ring strain in cyclopropane is the eclipsing of the C—H bonds. Recall that the eclipsed conformation of ethane is 3.0 kcal mole^{-1} less stable than the staggered conformation; each pair of eclipsed hydrogens raises the energy by 1.0 kcal mole^{-1} (Section 4.3). In cyclopropane, there are six pairs of eclipsed hydrogens, which could contribute a maximum of 6 kcal mole^{-1} to the energy of the molecule. However, the eclipsed hydrogens are farther apart in cyclopropane than they are in ethane, due to the small C—C—C angle in the former. Therefore,

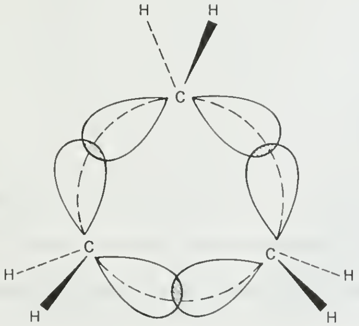
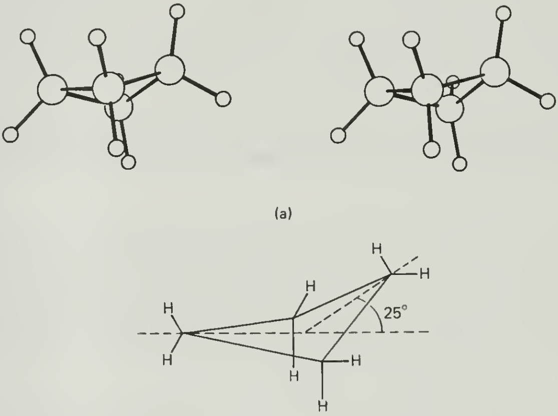


FIGURE 23.2 *Orbital structure of cyclopropane ring showing bent-bond strain.*

the actual magnitude of the eclipsing interaction is somewhat less than the maximum of 6 kcal $mole^{-1}$.

In cyclobutane, the internuclear angles of 90° are not so small as in cyclopropane. The C—C bonds are not so bent, and there is less strain per bond. However, there are four strained bonds rather than three, and there are eight pairs of eclipsed hydrogens rather than six. Also, the eclipsing in a planar cyclobutane would be more important than in cyclopropane because the hydrogens are closer. The result is that the total ring strain in the two compounds is about the same.

Since three points define a plane, the carbon framework of cyclopropane must have a planar structure. However, cyclobutane can exist in a nonplanar conformation. Spectroscopic studies show that cyclobutane and many of its derivatives do have nonplanar structures in which one methylene group is bent at an angle of about 25° from the plane of the other three ring carbons. In this structure, shown in Figure 23.3, some increase in bond angle strain is compensated by the reduction in the eclipsed hydrogen interactions.



(a)

(b)

Figure 23.3 *Bent cyclobutane:* (a) *stereo representation;* (b) *illustrating the angle of bend.*

C. *Cyclopentane*

A planar pentagonal ring structure for cyclopentane would have C—C—C bond angles of 108°, a value so close to the normal tetrahedral angle of 109.5° that no important strain effect would be expected. However, in such a structure, all of the hydrogens are completely eclipsed (Figure 23.4), and it would have about 10 kcal $mole^{-1}$ of strain energy.

The molecule finds it energetically worthwhile to twist somewhat from a planar conformation. The actual structure has the "envelope" shape shown in Figure

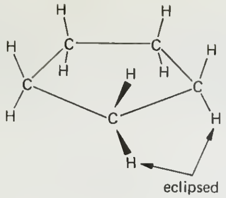


Figure 23.4 *Planar structure of cyclopentane showing eclipsed hydrogen pairs.*

23.5. The additional bond angle strain involved in this structure is more than compensated by the reduction in eclipsed hydrogens. The out-of-plane methylene group is approximately staggered with respect to its neighbors.

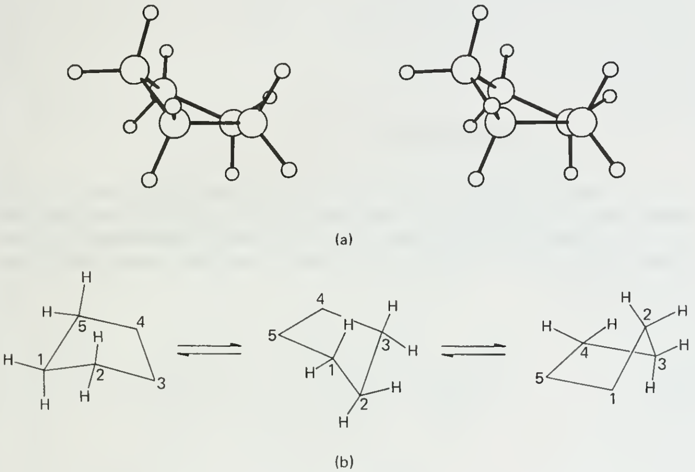


Figure 23.5 *Envelope structure of cyclopentane:* (a) *stereo representation;* (b) *pseudorotation.*

As also shown in Figure 23.5 the **envelope** structure of cyclopentane is dynamic. By twisting about the various C—C bonds, successive conformations are reached in which four carbons are in a plane and the fifth is out-of-plane. The concerted up-and-down movement of all of these carbons produces a series of structures that appear as if the molecule were rotated through 360° in 72° steps and constitutes a form of molecular motion known as **pseudorotation.**

D. *Cyclohexane*

Cyclohexane is the most important of the carbocycles; its structural unit is widespread in compounds of natural origin. Its importance no doubt stems from the fact that it can adopt a conformation that is essentially strain free. This structure, shown in Figure 23.6, is known as a **chair conformation.** In this structure

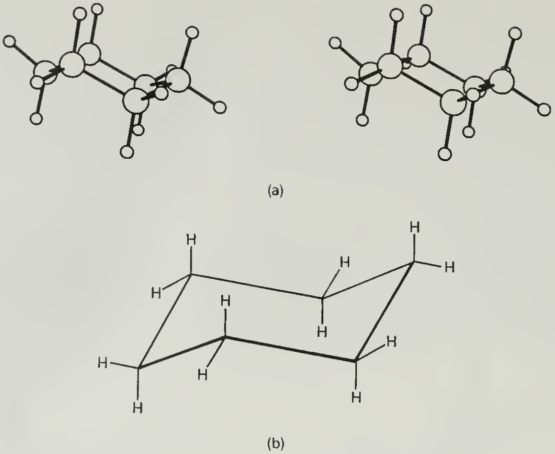


FIGURE 23.6 *Chair conformation of cyclohexane:* (a) *stereo representation;* (b) *conventional perspective drawing.*

the bond angles are all close to tetrahedral and all pairs of hydrogens are completely staggered with respect to each other. The latter point can easily be seen by looking down each C—C bond in turn to produce the Newman projection shown in Figure 23.7. Cyclohexane has neither bond angle strain nor eclipsed hydrogen strain.

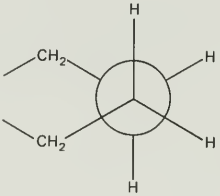


FIGURE 23.7 *Newman projection of one C—C bond in cyclohexane.*

The chair conformation has two distinct types of hydrogens. These different hydrogens correspond to two sets of exocyclic bonds, the **axial** and **equatorial** bonds shown in Figure 23.8.

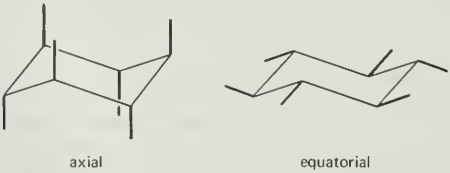


FIGURE 23.8 *Cyclohexane bonds.*

The chair conformation of cyclohexane is sufficiently important that the student should learn to draw it legibly. Notice should be taken of the sets of parallel lines in the structure as shown in Figure 23.9. The molecular axis shown in Figure 23.9 is a three-fold axis—rotation by 120° about this axis leaves the molecule unchanged.

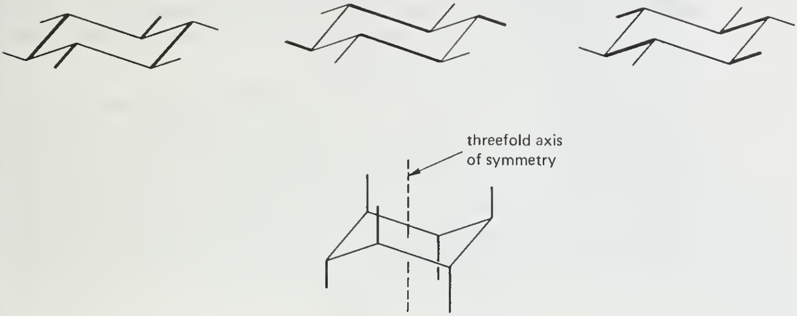
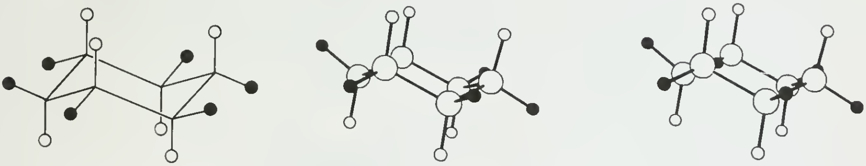


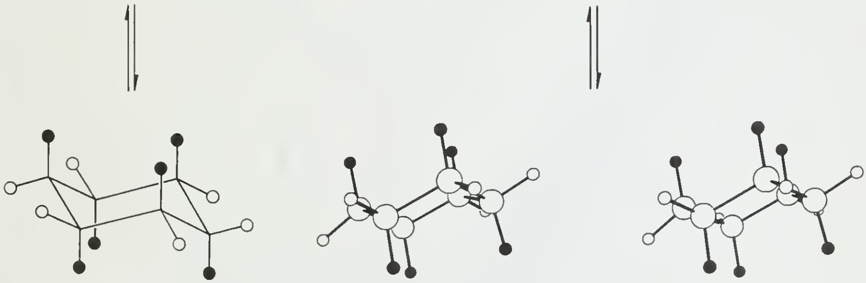
FIGURE 23.9 *Construction of chair conformations.*

Cyclohexane is also a dynamic structure. A concerted rotation about the C—C bonds changes one chair conformation to another in which the axial and equatorial bonds have changed places. This change is shown in Figure 23.10, in which one set of bonds is marked by circles.



black circles equatorial

(a)



black circles axial

(b)

FIGURE 23.10 *Two chair conformations of cyclohexane:* (a) *black balls equatorial;* (b) *black balls axial. Left: normal projection; right: stereo.*

The interconversion of the two conformations has an enthalpy of activation, $\Delta H^{\ddagger}$, of 10.8 kcal mole^{-1}. This value is relatively high compared to other conformational interchanges we have studied. The transition state involves a partially planar cyclohexane that now has both bond angle strain and eclipsed hydrogen strain. This transition state is clearly apparent with molecular models. However, because of this relatively high energy requirement, it is possible to "freeze out" the individual conformations in an nmr experiment. At sufficiently low temperature, $<-70°$, the rate of interconversion is so slow that the molecular state measured by nmr is a single conformation.

In one chair conformation, all equatorial hydrogens are equivalent, but are different from the axial hydrogens. The two sets of hydrogens have different chemical shifts and give rise to two broad bands separated by $\delta = 0.5$ ppm. The bands are broad because of J splittings between the two sets of protons. The nmr spectrum of cyclohexane-d_{11} is a simpler case to interpret because the J coupling between the proton nucleus and a deuteron is sufficiently small, and each cyclohexane now has only a single proton. The nmr spectrum is reproduced in Figure 23.11 as a function of temperature. At the lowest temperature ($-89°$), half of

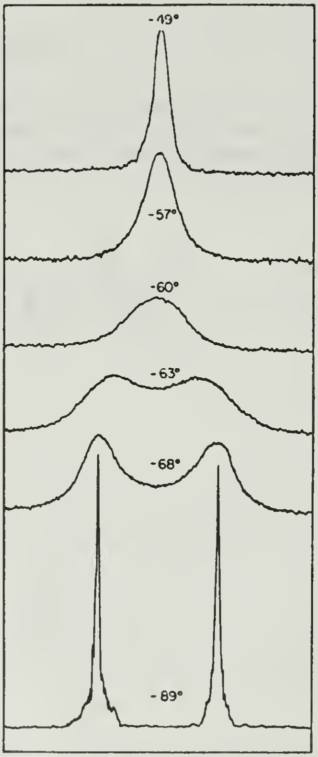


FIGURE 23.11 *Nmr of cyclohexane-*d_{11} *at different temperatures.* [*Reproduced with permission from F. A. Bovey:* Nuclear Magnetic Resonance Spectroscopy *Academic Press, New York, 1969.*]

the deuterated cyclohexane molecules have their lone proton in an axial position and the other half have the proton equatorial. Interconversion of the two isomers is slow and, since the chemical shifts differ, we see two sharp singlets. At the highest temperature (−49°), the ring interconversions are rapid and the nmr spectrometer "sees" only a time-average position, a singlet with δ midway between δ_{axial} and $\delta_{\text{equatorial}}$. At intermediate temperatures the rate of interconversion of the conformations is comparable to the frequency difference between the states, and a broad signal results.

E. *Larger Ring Cycloalkanes*

The larger cycloalkanes are less important and we will not dwell on them. In general, the medium ring cycloalkanes, C_7–C_{12}, have conformations in which some form of hydrogen repulsions is inescapable.

The most stable conformation of cycloheptane appears to be that represented in Figure 23.12. This conformation is a type of twisted chair structure. In this structure the hydrogens are all at least partially staggered with each other but not completely; partial eclipsing occurs which gives rise to a strain energy.

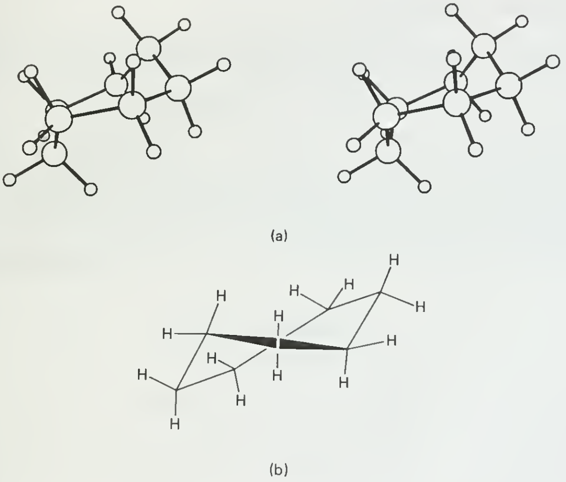


Figure 23.12 *Stable conformation of cycloheptane:* (a) *stereo representation;* (b) *conventional perspective drawing.*

Cyclooctane apparently is a mixture of several conformations that differ little from each other in energy. For all of the structures partial eclipsing of hydrogens is unavoidable and substantial strain energy results. The most stable conformation appears to be the boat-chair structure represented in Figure 23.13.

When the carbocyclic ring is sufficiently large, the constraint of ring formation is no longer significant. This point is reached by about C_{15}. Segments of such rings behave much as long linear alkanes; in such large rings there are generally a number of possible conformations in which the hydrogens are sufficiently separated and staggered from each other.

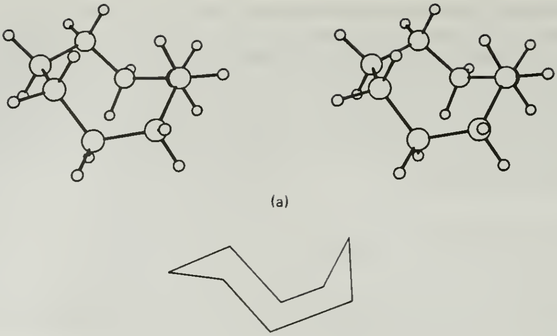

(a)
(b)

Figure 23.13 *Boat-chair conformation of cyclooctane;* (a) *stereo representation;* (b) *conventional line representation.*

23.3
Formation of Rings

The reaction of amines with alkyl halides is a typical S_N2 reaction (Section 27.5).

$$\mathrm{RCH_2NH_2 + R'CH_2Br \longrightarrow RCH_2\overset{+}{N}H_2CH_2R' + Br^-}$$

When both functional groups are present in the same molecule, the reaction is an **intramolecular** S_N2 reaction that creates a ring. Ring formation necessarily has been initiated at the transition state; hence, the relative energies of transition states depend on the ring size. Relative rates for reactions of ω-bromoalkylamines, $\mathrm{Br(CH_2)_{n-1}NH_2}$, are given in Table 23.2.

1-Amino-4-bromobutane, which gives a five-membered ring, is the most reactive

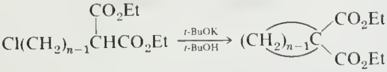
Table 23.2
Relative Rates of Cyclization of ω-Bromoalkylamines

$$\mathrm{Br(CH_2)_{n-1}NH_2 \longrightarrow (CH_2)_{n-1}NH_2^+\ Br^-}$$

n (Ring Size)	Relative Rate
3	0.1
4	0.002
5	100
6	1.7
7	0.03
10	10^{-8}
12	10^{-5}
14	3×10^{-4}
15	3×10^{-4}
17	6×10^{-4}

compound, followed by 1-amino-5-bromopentane, which gives a six-membered ring. We see that the stability of the ring is not the only factor—the probability that the ends can get together is also important. The three-membered ring, for example, has high energy, but the functional groups are so close together that ring formation is relatively probable. The pattern shown in Table 23.2 is common. The general order of ring formation is 5 > 6 > 3 with other rings being formed much more slowly.

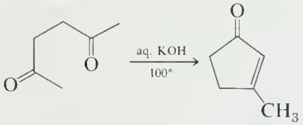
There are some exceptions to this generalization, particularly when cyclization involves the formation of a C—C bond. In such reactions, the order is 3 > 5 > 6. An example is the intramolecular alkylation of malonic esters (Section 26.4.D), leading to cycloalkane diesters.



n (ring size)	Relative Rate
3	1000
4	0.00015
5	100
6	0.0008

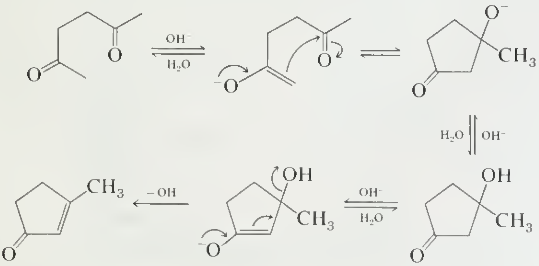
Large rings are relatively unstrained but the groups are so far apart that their probability of getting together for reaction is low. Indeed, it becomes more probable for reaction of one amino group to occur with another bromide. That is, **intermolecular** S_N2 reaction is an important side reaction for such cases unless conditions of high dilution are used. At ordinary concentrations the reaction product is a polymer chain.

These general properties of cyclization reactions will be evident in the preparations of individual ring systems. Many reactions are suitable only for formation of five-and six-membered rings. An example is the intramolecular aldol condensation (Section 15.7.G):

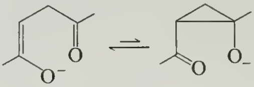


(75%)

The crucial step in this cyclization is the reaction of an enolate ion with a carbonyl group



An enolate ion is also formed at a methylene position but this does not lead to ring formation because the three-membered ring produced is too high in energy.



23.4
Chemistry of Cyclohexane

A. *Conformations of Substituted Cyclohexanes*

We start our discussion of the chemistry of individual cycloalkane structures with cyclohexane because of its unique importance and relative stability. Cyclohexane itself is a liquid, m.p. 6.5°, b.p. 81°, and is a useful solvent. Methylcyclohexane can exist in two different conformations in which the methyl group is either axial or equatorial (Figure 23.14).

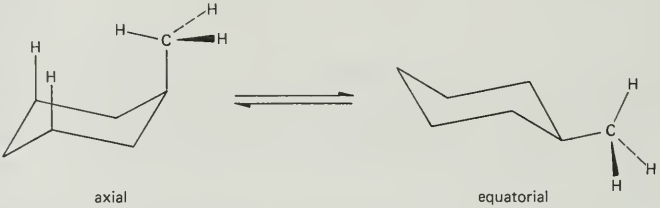


Figure 23.14 *Conformations of methylcyclohexane.*

It is instructive to look at Newman projections of the ring $C_1—C_2$ bond of methylcyclohexane as in Figure 23.15. In the equatorial conformation the methyl group is *anti* to the $C(3)H_2$ group of the ring, whereas in the axial conformation these groups have a *gauche* relationship. The interaction of a methyl hydrogen with the axial hydrogen of the $C(3)H_2$ group is much like the interaction of the corresponding hydrogens in a gauche conformation of butane (Section 4.3). Recall that this interaction in butane causes an enthalpy increase of 0.9 kcal mole^{-1}. There are two such interactions in axial methylcyclohexane—between the methyl group and $C(3)H_2$ and $C(5)H_2$ as shown in Figure 23.14. Correspondingly, the axial conformation of methylcyclohexane is expected to be about 1.8 kcal mole^{-1}

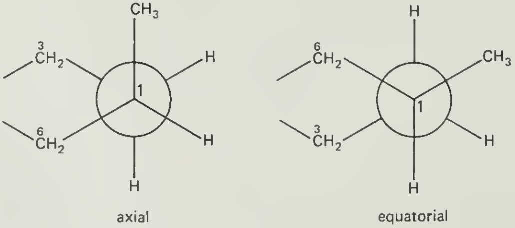
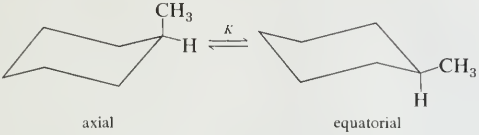


Figure 23.15 *Newman projections of methylcyclohexane.*

less stable than the equatorial conformation. This difference in energy for the two conformations may be approximated as $\Delta G°$ and transformed into an equilibrium constant for the equilibrium



$$K = \frac{[\text{equatorial}]}{[\text{axial}]}$$

$$\Delta G° = -RT \ln K$$

$$(-1.8 \text{ kcal mole}^{-1}) = -(1.987 \times 10^{-3} \text{ kcal mole}^{-1} \text{ deg}^{-1}) (298 \text{ deg}) \ln K$$

$$K = 21$$

Thus, at 25°, methylcyclohexane exists as an equilibrium mixture of the two conformations, with 95% of the molecules having the methyl-equatorial structure and 5% having the methyl-axial structure. Because of interaction of axial groups with the other axial hydrogens on the same side of the ring, axial conformations of substituted cyclohexanes are generally less stable than the corresponding equatorial conformations. Actual energy differences for various substituents, expressed as $\Delta G°$ values, are summarized in Table 23.3.

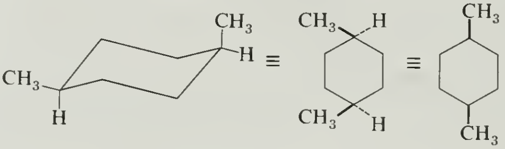
Bulky groups, such as isopropyl, *t*-butyl, and phenyl, have such strong interactions in the axial position that the proportion of axial conformation in the equi-

TABLE 23.3
Conformational Energies for Monosubstituted Cyclohexanes

Group	$-\Delta G°$ (axial $\rightleftharpoons$ equatorial), kcal mole^{-1}
F	0.25
Cl	0.5
Br	0.5
I	0.45
OH	1.0
OCH_3	0.55
$OCOCH_3$	0.71
CH_3	1.7
CH_2CH_3	1.8
$C{\equiv}CH$	0.41
$CH(CH_3)_2$	2.1
$C(CH_3)_3$	≈5–6
C_6H_5	3.1
COOR	1.3
COOH	1.4
CN	0.2
$OSO_2C_6H_4CH_3$	0.52

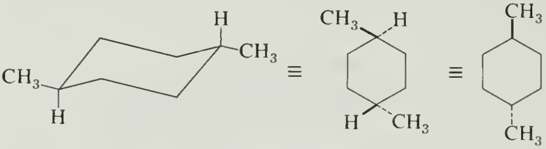
librium mixture is small. For example, the $\Delta G°$ of 3.1 for the phenyl group corresponds to an equilibrium constant at 25° of 189; 995 molecules out of every 1000 have the phenyl group equatorial.

For disubstituted cyclohexanes, stereoisomerism is possible. The *cis-trans* nomenclature is used to distinguish the isomers (Section 12.2). Thus, there are two 1,4-dimethylcyclohexanes. In one isomer, both methyls project up when the ring is viewed from the side. In this isomer, one substituent is equatorial and the other is axial, but *both* substituents project *above* the general plane of the ring. When writing a flat projection of such substituted ring compounds, substituents that project above the ring are indicated by heavy bonds, and groups that project below the ring are indicated by dashed bonds. Hydrogens are frequently omitted, for convenience.



cis-1,4-dimethylcyclohexane

In the other 1,4-dimethylcyclohexane stereoisomer, one methyl group projects above the ring and the other below. Since the substituents are on opposite sides of the ring, this isomer is called *trans*.

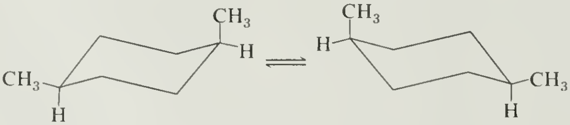


trans-1,4-dimethylcyclohexane

Note that both of the stereoisomeric 1,4-dimethylcyclohexanes are achiral.

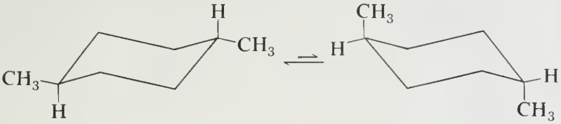
The lower energy of equatorial substituents compared to axial is also seen in the disubstituted compounds. For example, *trans*-1,4-dimethylcyclohexane ($\Delta H_f° = -44.1$ kcal mole^{-1}) is more stable than the *cis* isomer ($\Delta H_f° = -42.2$ kcal mole^{-1}) by 1.9 kcal mole^{-1}. In the *trans* isomer both methyl groups can be accommodated in equatorial positions whereas in the *cis* hydrocarbon, one methyl must be axial.

Both *cis*- and *trans*-1,4-dimethylcyclohexane can exist in two chair conformations. For the *cis* isomer; the two conformations are of equal energy, since each has one axial substituent and one equatorial substituent.



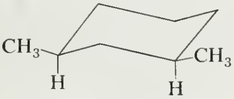
cis-1,4-dimethylcyclohexane, $\Delta G° = 0$

For the *trans* isomer, one conformation has both substituents axial and the other has both substituents equatorial. The diequatorial conformation predominates greatly at equilibrium ($\Delta G° \approx 3.4$ kcal mole^{-1}).

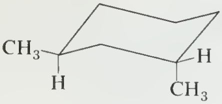


trans-1,4-dimethylcyclohexane, $\Delta G° \approx 3.4$ kcal mole^{-1}

For 1,3-dimethylcyclohexane the *cis* isomer is more stable than the *trans*. In *cis*-1,3-dimethylcyclohexane both methyls can be equatorial, whereas one methyl must be axial in the *trans* isomer.



cis-1,3-dimethylcyclohexane
both methyls equatorial



trans-1,3-dimethylcyclohexane
one methyl equatorial

The *t*-butyl group is so bulky that it effectively demands an equatorial position. Indeed, an axial *t*-butyl group represents so strained a structure that the $\Delta G°$ value in Table 23.3 for the difference between axial and equatorial *t*-butyl groups is only a rough estimate. In *cis*-4-methyl-1-*t*-butylcyclohexane, for example, the conformation with axial methyl and equatorial *t*-butyl groups dominates completely.

When excessive strain is involved, a distortion of the cyclohexane ring occurs. For example, phenyl and *t*-butyl are both rather bulky groups. A crystal structure analysis of a compound that has a *cis*-4-phenyl-1-*t*-butylcyclohexane structure shows that the ring has been stretched out somewhat but still has essentially a chair conformation with axial-phenyl and equatorial-*t*-butyl groups.

In *trans*-1,3-di-*t*-butylcyclohexane a chair-cyclohexane ring would require one *t*-butyl group to be axial as in Figure 23.16. Actually, in this compound the cyclohexane ring is twisted in order to avoid placing the *t*-butyl group in an axial position. This new conformation of cyclohexane is related to the hypothetical **boat** conformation shown in Figure 23.17. In this conformation, however, two of the hydrogens are so close together that a slight further twisting occurs to give the so-called "twist form" or "skew boat" structure as shown in Figure 23.18. This skew boat form occurs in several compounds containing bulky groups but is not an important conformation for cyclohexane itself. In the skew boat conformation several hydrogens are partially eclipsed. The structure has a strain energy of about 5 kcal mole^{-1} relative to chair cyclohexane.

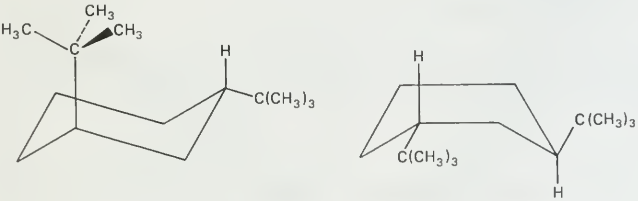


FIGURE 23.16 *Conformations of* trans-1,3-*di*-t-*butylcyclohexane.*

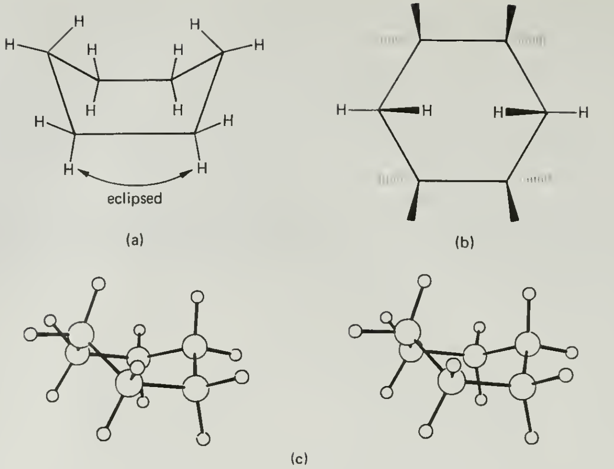

eclipsed
(a)
(b)
(c)

Figure 23.17 *Boat conformation of cyclohexane:* (a) *side view;* (b) *top view;* (c) *stereo view.*

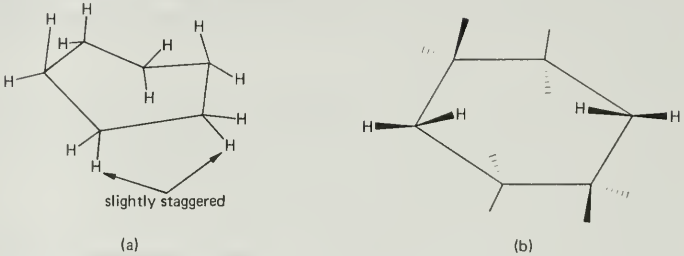

slightly staggered
(a)
(b)

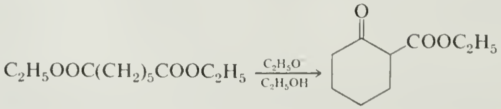
Figure 23.18 *Skew-boat conformation of cyclohexane:* (a) *side view;* (b) *top view.*

B. *Preparation of Cyclohexane Rings*

Cyclohexane derivatives are generally prepared by three types of methods:

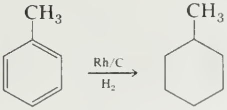
1. Cyclization
2. Reduction of aromatic rings
3. Diels-Alder cycloaddition

Cyclization reactions involve the interaction of two functional groups in the same molecule. One of the most important of these types of reaction is the Dieckmann condensation of esters of dicarboxylic acids.

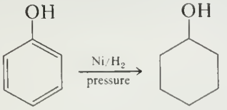

$C_2H_5OOC(CH_2)_5COOC_2H_5 \xrightarrow[C_2H_5OH]{C_2H_5O^-}$
O
$COOC_2H_5$

This type of intramolecular condensation reaction is an important reaction of diesters and will be discussed in Section 26.3.A.

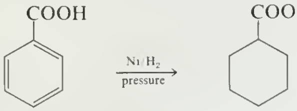
An important route to cyclohexane compounds is hydrogenation of benzene derivatives.



toluene methylcyclohexane



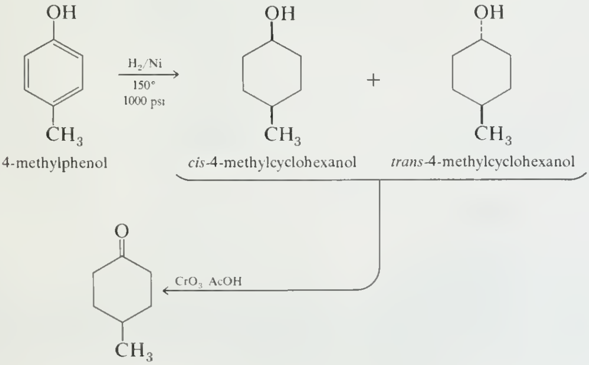
phenol cyclohexanol



benzoic acid cyclohexanecarboxylic acid

The ready availability of many aromatic compounds makes this a favorable route for simple cyclohexane derivatives and is an especially important industrial procedure. The benzene ring is resistant to hydrogenation and strenuous hydrogenation conditions are frequently required. The method is only useful when the ring bears functional groups that can survive such conditions, such as alkyl, OH, NH_2, and COOH. Groups that are not suitable in this approach are COR, X (halogen), NO_2, S (catalyst poison), alkenyl, or alkynyl.

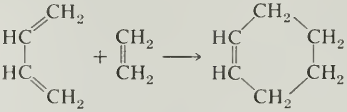
Hydrogenation of a disubstituted benzene generally gives a mixture of *cis* and *trans* disubstituted cyclohexanes. Such mixtures can often be separated in a practical manner or can be used without separation. For example



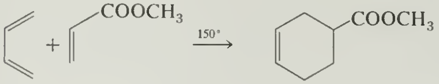
4-methylphenol *cis*-4-methylcyclohexanol *trans*-4-methylcyclohexanol

4-methylcyclohexanone

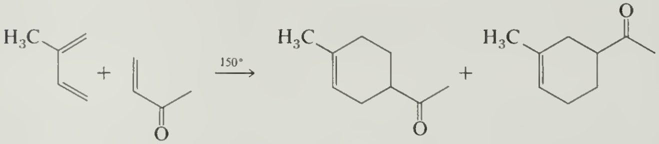
A particularly important and versatile method for constructing six-membered ring systems is the **Diels-Alder reaction,** a reaction between a multiple bond and a diene. The simplest Diels-Alder reaction is the reaction between ethylene and 1,3-butadiene to yield cyclohexene.



This example, however, is sluggish and requires heat and pressure. Reaction is facilitated by electron-donating groups on the diene and electron-attracting groups on the monoene (the "dienophile").



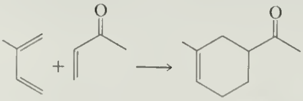
diene dienophile methyl 4-cyclohexenecarboxylate



isoprene | methyl vinyl ketone | (70%) methyl 4-methyl-3-cyclohexenyl ketone | (30%) methyl 3-methyl-3-cyclohexenyl ketone

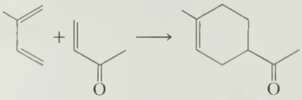
As shown by the foregoing example, many Diels-Alder reactions can give two isomers, depending on the orientation of the diene and the dienophile. The two different orientations are sometimes called head-to-head and head-to-tail.

Head-to-Head Orientation



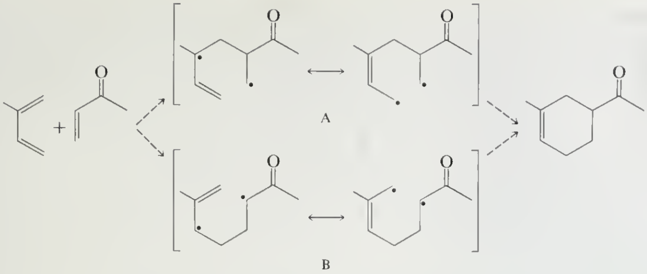
(30%)

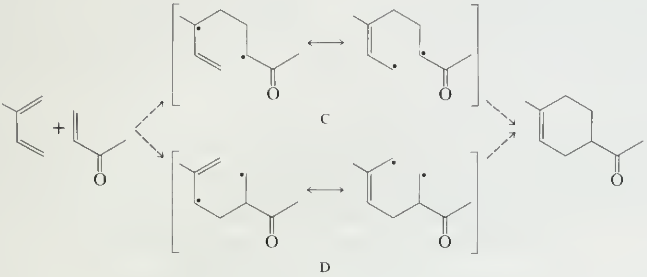
Head-to-Tail Orientation



(70%)

In general, the two isomeric products are formed in unequal amounts, as in the present example. A useful way to predict which isomer will predominate is to treat the reaction as though it proceeds in two steps, by way of free-radical intermediates. Then examine the four hypothetical diradical intermediates and decide which is the most stable. For example, in the present case

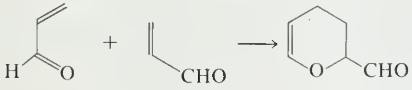




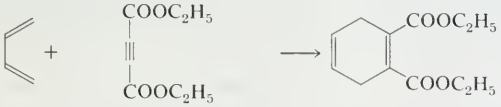
Of the four hypothetical intermediates, C is the most stable; one radical is primary-tertiary allylic and the other is stabilized by the adjacent carbonyl group. In A, there is also a primary-tertiary allylic radical, but the other odd electron is primary and is not stabilized by an adjacent carbonyl group.

It is important to remember that this method is simply a technique for predicting which product will predominate; it does not mean that the reaction actually proceeds by way of discrete diradical intermediates.

The reaction has wide scope because multiple bonds other than C=C may be used



acrolein



diethyl acetylenedicarboxylate

diethyl cyclohexa-1,4-diene-1,2-dicarboxylate

The Diels-Alder reaction is also known as a thermal cycloaddition reaction. The mechanism of the reaction involves σ overlap of the π orbitals of the two unsaturated systems as illustrated in Figure 23.19. The Diels-Alder reaction involves specifically four π electrons on one system and two on another and is

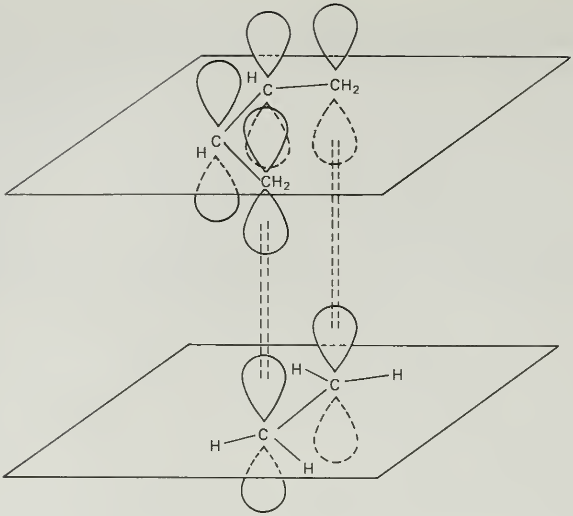
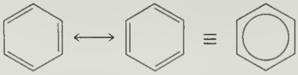
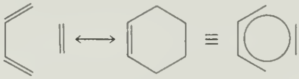


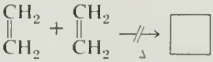
FIGURE 23.19 *Transition state of a Diels-Alder reaction.*

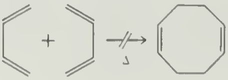
therefore referred to as a 4 + 2 cycloaddition. In the transition state for the cycloaddition shown in Figure 23.19, the six overlapping π orbitals give rise to a stable system of bonding molecular orbitals much as in benzene itself (Section 21.1.C). This resemblance holds despite the distinction that benzene involves all π overlap among the six p orbitals involved whereas the transition state for the Diels-Alder reaction involves two σ overlaps. The "aromatic" nature of the Diels-Alder transition state is also apparent by comparison of resonance structures.





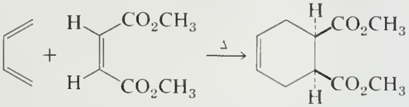
Just as six rather than four or eight p orbitals are required to give the closed-shell set of molecular orbitals characteristic of aromatic stability (Section 21.1.C), 2 + 2 or 4 + 4 thermal cycloaddition reactions do not normally occur.

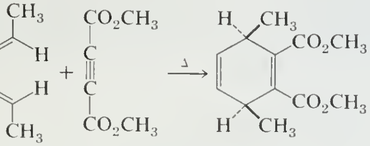




The net result of such a non-Diels-Alder cycloaddition can sometimes be accomplished, but only by other types of reaction conditions (see Section 36.2).

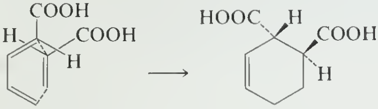
The transition state of the Diels-Alder reaction depicted in Figure 23.19 has stereochemical consequences. The following examples illustrate that the reaction is a *cis* addition, both with respect to the diene and the dienophile.



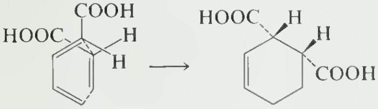


When both the diene and dienophile are suitably substituted, a further stereochemical feature arises because the reactants may approach each other in two distinct orientations. The substituent on the dienophile may be directed away from the diene ("exo" approach) or toward the diene ("endo" approach), resulting in two stereoisomers.

exo approach:



endo approach:



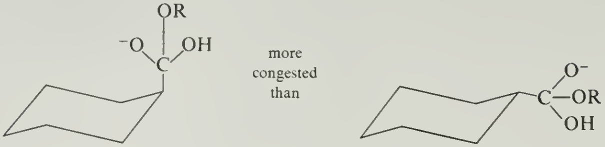
The Diels-Alder reaction shows a general preference for endo approach, but the endo/exo ratio depends on the reaction conditions, such as temperature and solvent polarity.

The direct product of a Diels-Alder reaction is a cyclohexene or 1,4-cyclohexadiene derivative, but these compounds can generally be converted to many other cyclohexane derivatives.

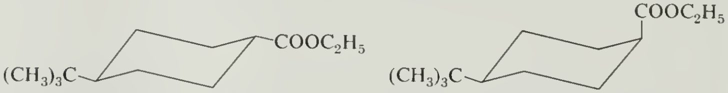
C. *Reactions of Cyclohexyl Functions*

Functional groups on cyclohexyl rings enter into most of the same reactions as they do in acyclic compounds. Indeed, many examples of reactions earlier in this book were chosen from cyclohexane chemistry. There are some significant differences to be found, but they are generally associated with the conformations of cyclohexane rings, particularly with the greater congestion of axial substituents.

For example, an equatorial ester group is hydrolyzed faster than an axial ester group. The tetrahedral intermediate in hydrolysis (Section 18.9.A) is bulkier than the ester group itself and is more difficult to form when axial.

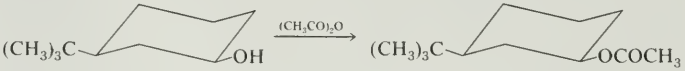

OR
⁻O
OH
C
more congested than
O⁻
C—OR
OH

An example of the magnitude of this effect is given by the hydrolysis of ethyl 4-*t*-butylcyclohexanecarboxylates with sodium hydroxide. The *trans* isomer, in which the carboethoxy group is equatorial, hydrolyzes with sodium hydroxide in 70% aqueous ethanol at 25° 20 times faster than the *cis* isomer in which the ester group is constrained to be axial.

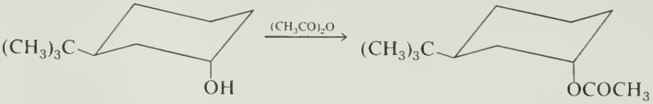

(CH3)3C
COOC2H5
(CH3)3C
COOC2H5

$k_{trans} = 8.5 \times 10^{-4}\ M^{-1}\ sec^{-1}$ $k_{cis} = 0.43 \times 10^{-4}\ M^{-1}\ sec^{-1}$

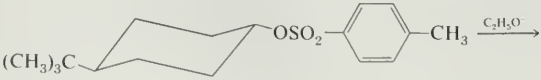
For similar reasons, equatorial hydroxy groups are esterified more rapidly and are effectively more nucleophilic in S_N2 reactions. For example, *trans*-3-*t*-butylcyclohexanol, having an axial hydroxy group, is acetylated about one half as fast as is the *cis* isomer in which the hydroxy group is equatorial.


(CH3)3C
OH
(CH3CO)2O
(CH3)3C
OCOCH3

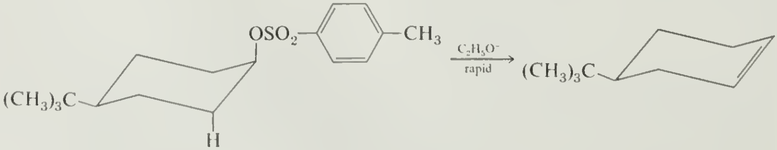
twice as fast as


(CH3)3C
OH
(CH3CO)2O
(CH3)3C
OCOCH3

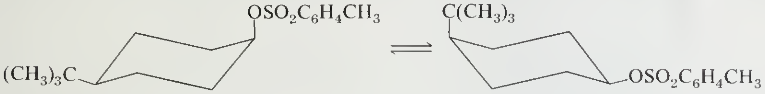
On the other hand, E2 elimination reactions require a *trans*-coplanar arrangement of hydrogen and leaving group (Section 12.5.A). Such an arrangement is impossible for equatorial leaving groups; hence, such E2 reactions can occur only when the leaving groups can assume the axial position. For example


(CH3)3C
OSO2
CH3
C2H5O⁻

elimination occurs very slowly


OSO2
CH3
(CH3)3C
H
C2H5O⁻
rapid
(CH3)3C

In this example, the *t*-butyl group is so sterically demanding that it effectively controls the conformation. *cis*-4-*t*-Butylcyclohexyl toluenesulfonate exists almost entirely in the conformation shown. To determine the relative energy of the axial-*t*-butyl, equatorial-toluenesulfonate conformation, the energies in Table 23.3 may be used.



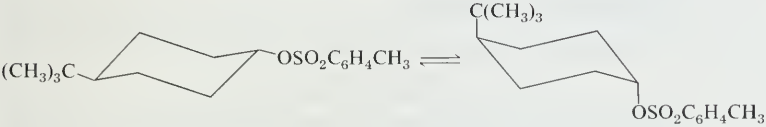
relative energy:
$0 + 0.5 = 0.5$ kcal mole^{-1}

relative energy:
$\approx 5 + 0 = \approx 5$ kcal mole^{-1}

$$\Delta G° \approx 4.5 \text{ kcal mole}^{-1}$$

The corresponding equilibrium constant, $K \approx 10^{-3}$; that is, *cis*-4-*t*-butylcyclohexyl toluenesulfonate exists at least 99.9% in the axial-toluenesulfonate conformation.

Applying the same approach to the *trans* isomer



relative energy:
$0 + 0 = 0$

relative energy:
$\approx 5 + 0.5 = \approx 5.5$ kcal mole^{-1}

$$\Delta G° \approx 5.5 \text{ kcal mole}^{-1}$$

the conformation with axial-toluenesulfonate is only about 0.01% of the total. If k_{E2} represents the rate constant for E2 elimination of an axial-toluenesulfonate, *cis*-4-*t*-butylcyclohexyltoluenesulfonate would react with a rate constant of $0.999\, k_{E2}$ whereas the *trans* isomer would have a rate constant of $10^{-4}\, k_{E2}$. *When a reaction mechanism demands a particular conformation, the relative reactivities depend on the population of that conformation in the equilibrium mixture.*

Conformational factors also govern the addition reactions of cyclohexene. The four groups attached to a double bond must lie in the same plane in order to provide the most effective overlap for the π bond. In cyclohexene this constraint gives a structure that is a half-chair (Figure 23.20). This structure provides effective

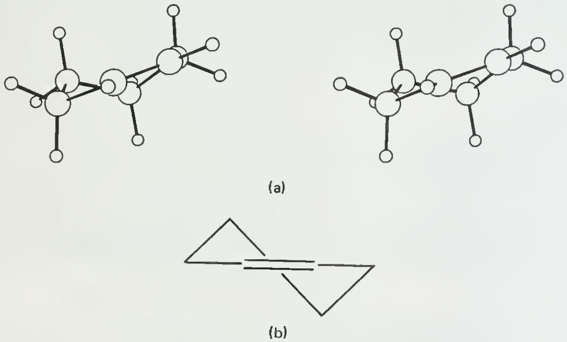
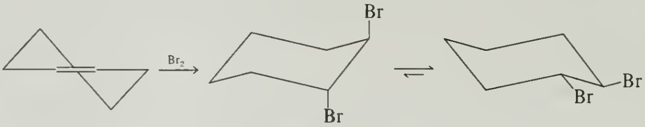


FIGURE 23.20 *Structure of cyclohexene:* (a) *stereo representation;* (b) *conventional symbolism.*

staggering of the four CH_2 groups and has little strain. The heat of hydrogenation of cyclohexene, $\Delta H^\circ_{\text{hydrog}} = -28.4$ kcal mole^{-1}, is the same as that of *cis*-2-butene. Cyclohexene behaves as a typical *cis*-alkene. Addition reactions that involve *trans* addition give first the diaxial cyclohexyl product which frequently goes rapidly over to the corresponding diequatorial conformer.



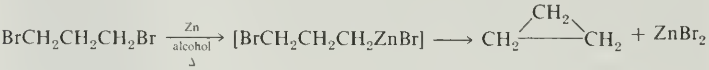
trans-1,2-dibromocyclohexane

23.5 Chemistry of Cyclopropanes

A. *Preparation of Cyclopropane Rings: Carbenes*

Despite the high ring strain, three-membered rings can be constructed with relative ease, primarily because the two functional groups involved in ring formation are close neighbors.

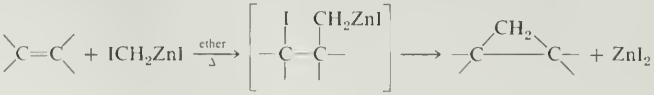
Cyclopropane itself can be prepared by treating 1,3-dibromopropane with zinc. The reaction probably involves the formation of an intermediate organozinc compound.



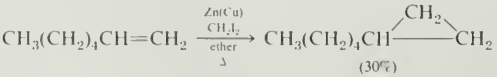
$$BrCH_2CH_2CH_2Br \xrightarrow[\Delta]{\text{Zn, alcohol}} [BrCH_2CH_2CH_2ZnBr] \longrightarrow CH_2\overset{CH_2}{\frown}CH_2 + ZnBr_2$$

A generally better method for accomplishing this ring closure starts with an alkene and the Simmons-Smith reagent, a material that appears to be an iodomethylzinc. The reagent was developed in 1959 by DuPont chemists, Howard E. Simmons and Ronald D. Smith, and is prepared as needed by treating zinc dust with cupric sulfate solution to give a zinc-copper **couple.** A suspension of the couple in ether is refluxed with the alkene and methylene iodide. Variations of this general procedure have since been developed.

$$CH_2I_2 + Zn(Cu) \longrightarrow ICH_2ZnI$$



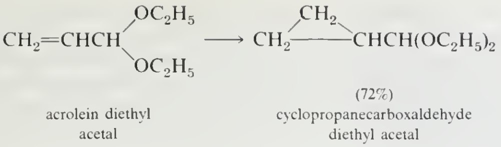
This reaction is applicable to many kinds of double bonds. The yields are generally only fair (30–70%), but the products are often difficult to prepare by alternative routes.



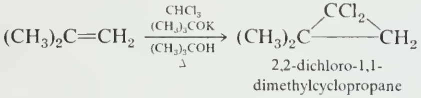
$$CH_3(CH_2)_4CH{=}CH_2 \xrightarrow[\text{ether, }\Delta]{\text{Zn(Cu), }CH_2I_2} CH_3(CH_2)_4CH\overset{CH_2}{\frown}CH_2$$

(30%)

1-heptene pentylcyclopropane


$CH_2=CHCH(OC_2H_5)_2$
acrolein diethyl acetal
(72%)
cyclopropanecarboxaldehyde diethyl acetal

Another method that is particularly useful for the preparation of halo- or dihalocyclopropanes involves the use of a transient halomethylene, XHC:, or dihalomethylene, X_2C:, intermediate known as a **carbene**. The net reaction is typified by the following example:


$(CH_3)_2C=CH_2$
$CHCl_3$
$(CH_3)_3COK$
$(CH_3)_3COH$
Δ
2,2-dichloro-1,1-dimethylcyclopropane

Recall the chloroform is rather acidic ($pK_a \approx 25$) because of the strong electron-attracting inductive effect of the three chlorines.

$$Cl_3CH \xrightarrow{\text{strong base}} Cl_3C:^-$$

When this ion is produced in aqueous solution as in the haloform reaction of methyl ketones (Section 15.6.D), the predominant reaction is protonation to give chloroform. An alternative reaction that dominates in a less protic solvent is elimination of chloride ion to give dichlorocarbene, a reactive species having a neutral divalent carbon.

$$Cl_3C:^- \longrightarrow Cl^- + \underset{\text{dichlorocarbene}}{Cl_2C:}$$

The electronic structure of dichlorocarbene has a pair of electrons in an approximately sp^2 hybrid orbital and a vacant p orbital (Figure 23.21). That is, the carbene combines a carbanion lone pair and a carbonium ion vacancy on a single carbon.

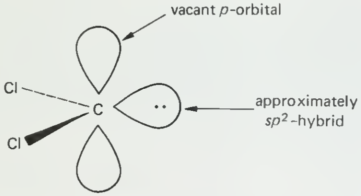
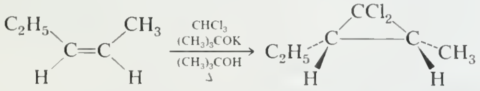

vacant p-orbital
Cl
C
Cl
approximately sp^2-hybrid

FIGURE 23.21 *Electronic structure of dichlorocarbene.*

Dichlorocarbene adds stereospecifically *cis* to many types of double bonds.

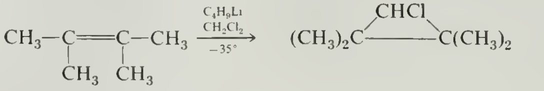

C_2H_5
CH_3
H
H
$CHCl_3$
$(CH_3)_3COK$
$(CH_3)_3COH$
Δ
CCl_2
C_2H_5
CH_3
H
H

no *trans* isomer is formed

This reaction can also be applied to bromoform, $CHBr_3$, to yield the corresponding dibromocyclopropanes.

The terms *cis* and *trans* are used both to describe the stereochemistry of reactions as well as geometric structure. For example, *cis* addition means that both new bonds form on the same side of the alkene, as in the foregoing example. In *trans* additions, the new bonds are formed on opposite sides of the alkene plane, as in bromination (sect. 12.6.B). Note that *cis* addition of a carbene to a *trans* alkene gives the corresponding *trans* disubstituted cyclopropane. To avoid possible confusion, it has been proposed that the terms *cis* and *trans* be replaced by *syn* and *anti*, respectively, when referring to the stereochemical course of reaction.

A related type of intermediate results when alkyllithium compounds are allowed to react with methylene chloride.

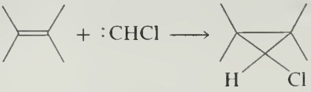


(67%)
3-chloro-1,1,2,2-tetramethylcyclopropane

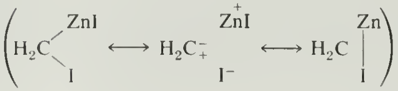
The reaction intermediate can be formulated as a chlorocarbene:

$$CH_2Cl_2 + C_4H_9Li \longrightarrow C_4H_{10} + LiCHCl_2$$

$$LiCHCl_2 \longrightarrow LiCl + \underset{\text{chlorocarbene}}{:CHCl}$$

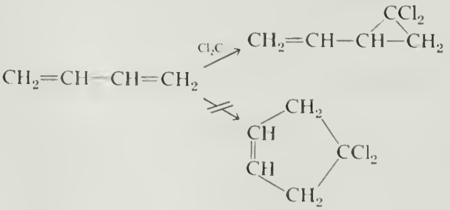


It is interesting to note that iodomethylzinc iodide behaves as a carbene-like reagent.



As a consequence, such organometallic reagents have been termed "carbenoid."

All three of these carbene or carbenoid reactions of alkenes involve addition of a single carbon to a single double bond. This reaction course is true even for conjugated dienes; none of the 1,4-addition product is obtained.



B. *Reactions of Cyclopropanes*

Chlorocyclopropanes are especially useful because they undergo normal Grignard reactions and may be converted to other functional groups. However, halocyclopropanes do not undergo S_N2 reactions. At the transition state the central carbon in such a reaction has sp^2 hybridization with a normal bond angle of 120°. The imposition of such an increased bond angle on a cyclopropyl ring would result in additional bond angle strain (Figure 23.22). As a result, cyclopropyl halides resemble vinyl halides in being inert to displacement reactions.

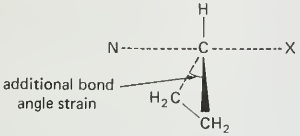
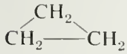


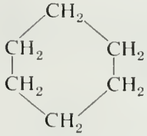
FIGURE 23.22 *Transition state for S_N2 reaction on a cyclopropyl halide.*

That the bent C—C bonds in a cyclopropyl ring are weaker than normal C—C bonds is demonstrated by the following thermodynamic data:

$$CH_2{=}CH_2 + H_2 \longrightarrow CH_3CH_3 \qquad \Delta H^\circ = -32.7 \text{ kcal mole}^{-1}$$



$$+ H_2 \longrightarrow CH_3CH_2CH_3 \qquad \Delta H^\circ = -37.6 \text{ kcal mole}^{-1}$$



$$+ H_2 \longrightarrow CH_3(CH_2)_4CH_3 \qquad \Delta H^\circ = -10.4 \text{ kcal mole}^{-1}$$

$$CH_3CH_2CH_2CH_3 + H_2 \longrightarrow 2\ CH_3CH_3 \qquad \Delta H^\circ = -10.1 \text{ kcal mole}^{-1}$$

A C—C bond in cyclohexane is about as strong as an interior bond in butane, but the ring strain in cyclopropane provides a C—C bond strength that is somewhat weaker than one of the bonds of a double bond. As a result, cleavage of one of the cyclopropane bonds is much more exothermic than cleavage of a normal single bond. However, not all of the relief of ring strain is obtained at the transition state, and cyclopropyl rings are generally substantially less reactive than alkene double bonds. Cyclopropane is unaffected by cold potassium permanganate or ozone, whereas alkenes react immediately with both reagents.

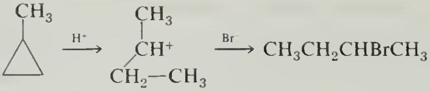
Cyclopropane and alkylcyclopropanes undergo ring opening with hydrogenation catalysts under conditions that are somewhat more vigorous than the conditions necessary to reduce alkenes.

$$\xrightarrow[\substack{H_2\ (1\ \text{atm}) \\ 50^\circ}]{Pt/C} CH_3CH_2CH_3$$

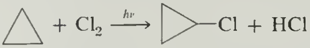
Reaction with aqueous acids, such as hydrobromic acid, is relatively fast to give *n*-propyl compounds.

$$\xrightarrow{\text{aq. HBr}} CH_3CH_2CH_2Br$$

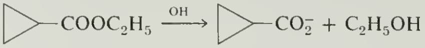
These reactions are probably of the carbonium ion type. In the case of substituted cyclopropanes, the mode of ring opening is that which gives the most stable carbonium ion, but the reaction has little practical use.

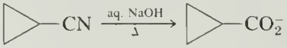


By contrast, cyclopropane undergoes normal photochemical chlorination to give cyclopropyl chloride.



Many functional groups on cyclopropane rings show their normal chemistry. For example, alcohols can be esterified and esters can be hydrolyzed, but in such reactions one must take cognizance of the possibility of ring opening. For example, basic hydrolysis of an ester of a cyclopropanecarboxylic acid is preferable to refluxing with aqueous acid; the latter conditions could give rise to ring-opened carbonium ions.





In other compounds, the almost-double-bond-like character of the cyclopropyl ring shows up. The cyclopropylmethyl cation is relatively stable, much as allyl cation, undoubtedly because of conjugation with the *p*-like orbitals of the ring (Figure 23.23). The cyclopropylmethyl cation rearranges readily.

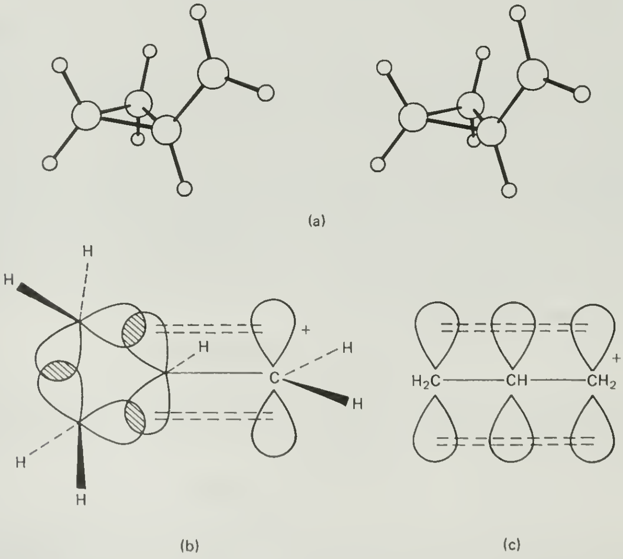
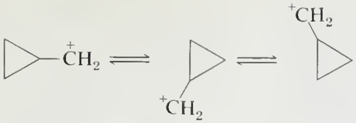
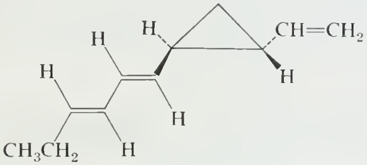


FIGURE 23.23 *Cyclopropylmethyl cation:* (a) *stereo representation;* (b) *orbital representation;* (c) *comparison to orbital structure of allyl cation.*



In this section we have only suggested the complex and fascinating chemistry of the three-membered carbocyclic ring. Further aspects of this chemistry are beyond the scope of this textbook although in a later section we will discuss the chemistry of three-membered ethers (epoxides, Section 23.10.A).

The cyclopropane ring plays a significant role in nature. It is implicated in some important biochemical reactions and is found in many naturally occurring compounds. For example, *trans*-1-(1E,3E-hexadienyl)-2-ethenylcyclopropane gives seaweed its characteristic odor. The pure hydrocarbon has such an intense odor that a minute amount will fill a room with the overpowering odor of seaweed.

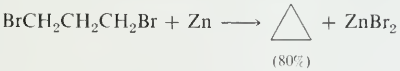


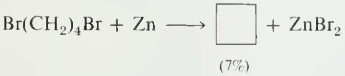
trans-1-(1E,3E-hexadienyl)-2-ethenylcyclopropane

23.6
Chemistry of Cyclobutanes

A. *Preparation of Cyclobutanes*

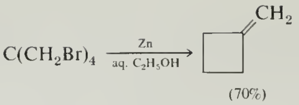
The cyclobutane ring is a relatively difficult one to obtain. The methods used to prepare three-membered rings generally do not work well for making four-membered rings. For example, the reaction of 1,4-dibromobutane with zinc gives a poor yield of cyclobutane; the corresponding reaction with 1,3-dibromopropane is far superior.



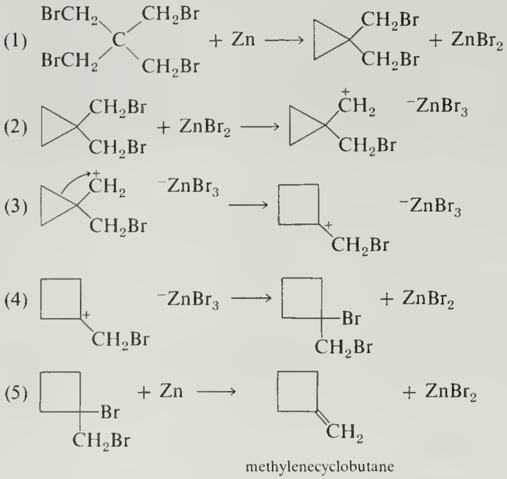


However, a variation of this method provides a useful entry into cyclobutane chemistry. Pentaerythritol,2,2-bis-hydroxymethyl-1,3-propanediol (Section 15.8.D), is readily converted into the corresponding tetrabromide. The tetrabromide reacts with zinc to give methylenecyclobutane, which can be converted to a number of cyclobutyl derivatives.

$$C(CH_2OH)_4 \xrightarrow{PBr_3} \underset{(69\text{–}76\%)}{C(CH_2Br)_4}$$

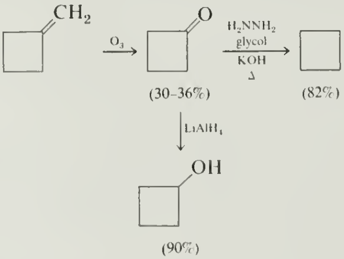

C(CH2Br)4
Zn
aq. C2H5OH
CH2
(70%)

The reaction involves a carbonium ion rearrangement of an intermediate cyclopropane compound and is catalyzed by the zinc bromide produced in the reaction.

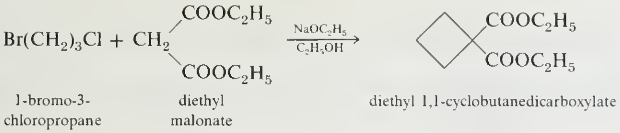

(1)
BrCH2
CH2Br
C
BrCH2
CH2Br
+ Zn
CH2Br
CH2Br
+ ZnBr2
(2)
CH2Br
CH2Br
+ ZnBr2
+
CH2
−ZnBr3
CH2Br
(3)
+
CH2
−ZnBr3
CH2Br
+
CH2Br
−ZnBr3
(4)
+
CH2Br
−ZnBr3
Br
CH2Br
+ ZnBr2
(5)
Br
CH2Br
+ Zn
CH2
+ ZnBr2
methylenecyclobutane

The cyclopropylmethyl cation formed is more stable than a simple primary carbonium ion (Section 23.5.B) but on rearrangement it produces a still more stable tertiary carbonium ion, which now has a four-membered ring. The final step is the normal debromination by zinc of a vicinal dibromide (Section 12.6.B under Addition of Halogens).

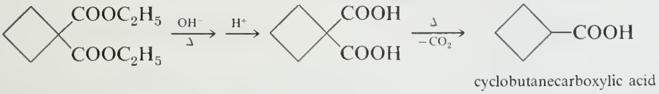
Methylenecyclobutane can be oxidized to cyclobutanone which undergoes normal ketone reactions, including Wolff-Kishner reduction (Section 15.8.E) to cyclobutane.


CH2
O3
O
H2NNH2
glycol
KOH
Δ
(30–36%)
(82%)
LiAlH4
OH
(90%)

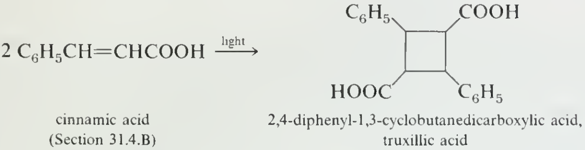
Another route to the cyclobutyl ring system involves a reaction of malonic esters of a type to be studied later (Section 26.4.D).


Br(CH₂)₃Cl + CH₂
COOC₂H₅
COOC₂H₅
NaOC₂H₅
C₂H₅OH
COOC₂H₅
COOC₂H₅
1-bromo-3-chloropropane
diethyl malonate
diethyl 1,1-cyclobutanedicarboxylate

The dicarboxylic ester can be converted readily to the monocarboxylic acid (Section 26.2.C).

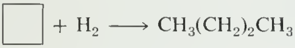

COOC₂H₅
COOC₂H₅
OH⁻
Δ
H⁺
COOH
COOH
Δ
−CO₂
COOH
cyclobutanecarboxylic acid

Cyclobutanecarboxylic acid can be converted to other cyclobutane derivatives and to cyclobutane itself. Alternative routes to cyclobutane derivatives involve specialized photochemical reactions which we will not detail here (see Section 36.5.B) except to give one example to show the general nature of the method.


2 C₆H₅CH=CHCOOH
light
C₆H₅
COOH
HOOC
C₆H₅
cinnamic acid
(Section 31.4.B)
2,4-diphenyl-1,3-cyclobutanedicarboxylic acid,
truxillic acid

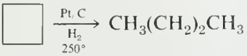
B. *Reactions of Cyclobutanes*

Although the cyclobutane ring has about as much ring strain as the cyclopropane ring, it is far more resistant to ring-opening reactions. The heat of hydrogenation of cyclobutane to butane is about the same as that of cyclopropane.


+ H₂
CH₃(CH₂)₂CH₃

$\Delta H^\circ = -37.2$ kcal mole^{-1}

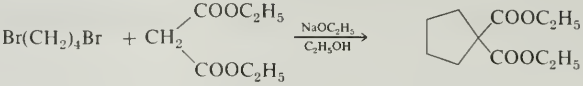
However, accomplishing this hydrogenation requires much higher temperatures than for cyclopropane.


Pt, C
H₂
250°
CH₃(CH₂)₂CH₃

At ordinary temperatures cyclobutane resists the actions of bromine and hydrobromic acids. In most reactions of cyclobutyl compounds the ring can be treated as just another alkyl group. Exceptions occur for some functional groups attached directly on the four-membered ring. For example, S_N2 displacement reactions on cyclobutyl halides are feasible but slow. The relatively low rate results from the constraint of the ring bond angle just as in the cyclopropyl case (Figure 23.22) except that the additional angle strain in the transition state is not as great for the 90° four-membered ring angle.

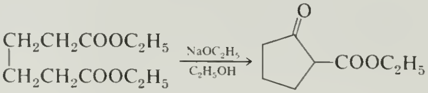
23.7
Cyclopentane and Larger Ring Systems

Cyclopentane derivatives can be prepared by variations of the same reaction used in the cyclobutane series and involving diethyl malonate.


Br(CH₂)₄Br
+ CH₂
COOC₂H₅
COOC₂H₅
NaOC₂H₅
C₂H₅OH
COOC₂H₅
COOC₂H₅

1,4-dibromobutane diethyl malonate diethyl 1,1-cyclopentanedicarboxylate

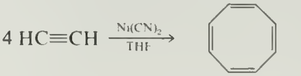
One of the best routes to the 5-membered ring involves cyclization reactions of adipic acid and its derivatives. We will take up this reaction in Section 26.3.A.


CH₂CH₂COOC₂H₅
CH₂CH₂COOC₂H₅
NaOC₂H₅
C₂H₅OH
O
COOC₂H₅

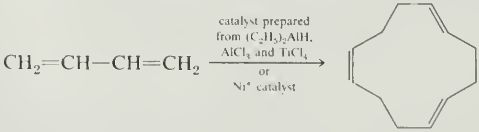
diethyl adipate

There are few general reactions for the formation of seven-membered and larger rings. Ring expansion methods are frequently useful for changing from one ring size to another. We saw one example of a ring expansion in the preparation of methylenecyclobutane. The best general ring expansion methods, however, involve the chemistry of nitrogen functions, which we will study later (Section 27.7.B).

Special reactions are known for preparing some individual ring compounds. Some of these methods involve organometallic intermediates, and the reactions appear almost fantastic. Reaction mechanisms at coordination sites of transition metals are usually involved in these unusual processes. This type of chemistry is a borderline region between organic and inorganic chemistry and is an area of active current research. Two examples of these types of syntheses are


4 HC≡CH
Ni(CN)₂
THF

cyclooctatetraene

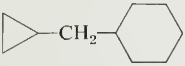

CH₂=CH—CH=CH₂
catalyst prepared from (C₂H₅)₂AlH, AlCl₃ and TiCl₄
or
Ni° catalyst

trans,trans,cis-1,5,9-cyclododecatriene

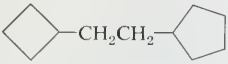
An unusual feature of the last example is that the 12-membered ring produced has two *trans* double bonds. The smallest stable *trans*-cycloalkene is *trans*-cyclooctene. In smaller rings the *trans* double bond is highly strained and reactive. Similarly, the smallest stable cycloalkyne is cyclooctyne. Smaller cycloalkynes are known but only as transient intermediates because of their high reactivities.

23.8
Bicyclic Compounds

In compounds containing two or more rings in which the rings are separated by one or more carbon atoms, the rings behave more or less independently and no special chemistry is involved.

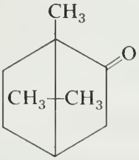


(cyclopropylmethyl)cyclohexane

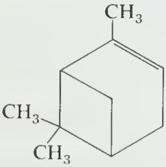


1-cyclobutyl-2-cyclopentylethane

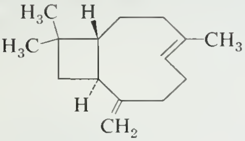
Compounds containing two rings in which the rings share one or more sides are called **bicyclic.** Examples of such compounds are



camphor



pinene
(principal constituent
of turpentine)

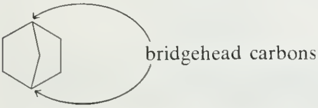


caryophyllene
(oil of cloves)

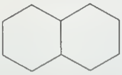
As indicated by these examples, bicyclic structures are widespread in nature and many such compounds have trivial names that derive from their natural origin. Caryophyllene, for example, occurs in oils derived from the stems and flowers of *Jambrosa caryophyllus.* The IUPAC nomenclature of such compounds derives from the fundamental topology of bicyclic structures. All such structures have in common:

1. Two bridgehead atoms
2. Three arms connecting the two bridgehead atoms.

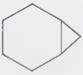
Bicyclic compounds are named as derivatives of the alkane corresponding to the total number of carbons in both ring skeletons. The term **bicyclo** is appended as a prefix together with the numbers of carbons in each of the three connecting arms inserted in brackets.



bicyclo[2.2.1]heptane

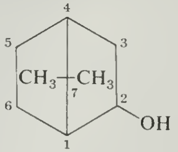


bicyclo[4.4.0]decane

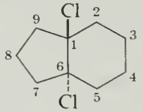


bicyclo[4.1.0]heptane

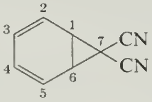
The numbering system used to assign substituents starts at a bridgehead position, proceeds along the *longest* arm to the other bridgehead position, and continues along the next longest arm. The bridgehead position chosen to start the numbering is that which gives the lower substituent number.



7,7-dimethylbicyclo[2.2.1]heptan-2-ol



trans-1,6-dichlorobicyclo[4.3.0]nonane



7,7-dicyanobicyclo[4.1.0]hepta-2,4-diene

In many bicyclic structures the stereochemistry at the bridgehead positions is established by steric constraints. There is only a single bicyclo[2.2.1]heptane, for example, that in which the methylene bridge is joined *cis* at the 1,4-positions of a boat cyclohexane. The corresponding compound with a *trans* attachment is too strained to exist (Figure 23.24). In other systems both *cis* and *trans* ring fusions can occur and are specified appropriately in the nomenclature.

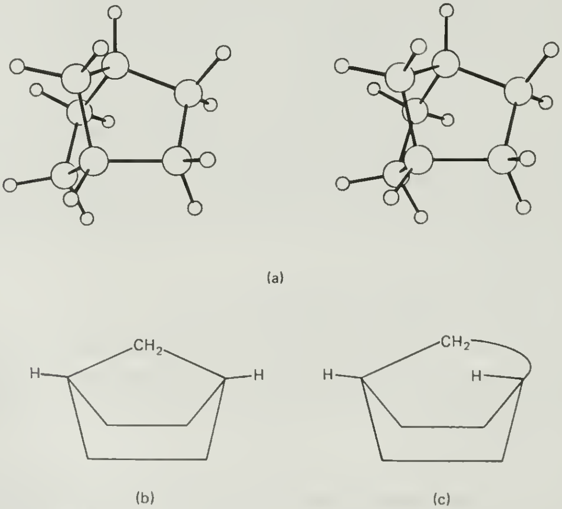
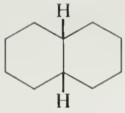
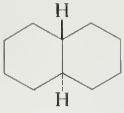


Figure 23.24 *Bicyclo*[2.2.1]*heptane* (*norbornane*): (a) *stereo view*, (b) *conventional perspective drawing;* (c) *hypothetical* trans *isomer,* too strained to exist.

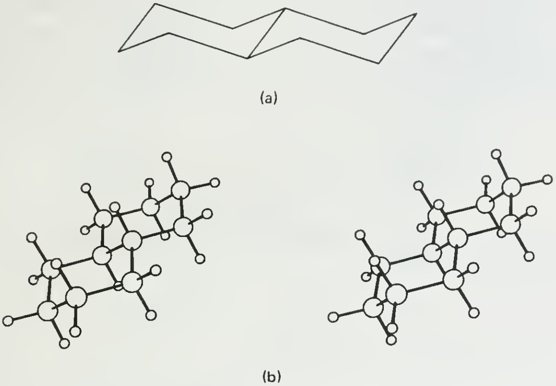


cis-bicyclo[4.4.0]decane
(*cis*-decalin)



trans-bicyclo[4.4.0]decane
(*trans*-decalin)

Bicyclo[4.4.0]decane has the trivial name of decalin. In both *cis*- and *trans*-decalin, both cyclohexane rings are present in the chair conformation. *trans*-Decalin has two chair cyclohexanes equatorial to each other (Figure 23.25). In *cis*-decalin, the cyclohexanes are joined to each other as equatorial and axial substituents (Figure 23.26).

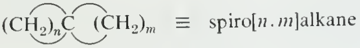


(a)

(b)

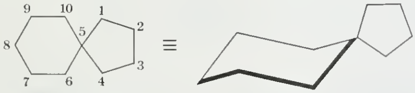
FIGURE 23.25 Trans-*bicyclo*[4.4.0]*decane,* trans-*decalin:* (a) *conventional representation;* (b) *stereo structure.*

Bicyclic compounds that have one carbon common to both rings are **spiro** compounds. The nomenclature is based on the following scheme:



$$(CH_2)_nC\ (CH_2)_m \equiv \text{spiro}[n.m]\text{alkane}$$

Numbering starts next to the common carbon and proceeds around the smaller ring first.



spiro[4.5]decane

Many bicyclic compounds can be prepared by reactions we have already studied. The carbene synthesis of cyclopropanes works well with cycloalkenes.

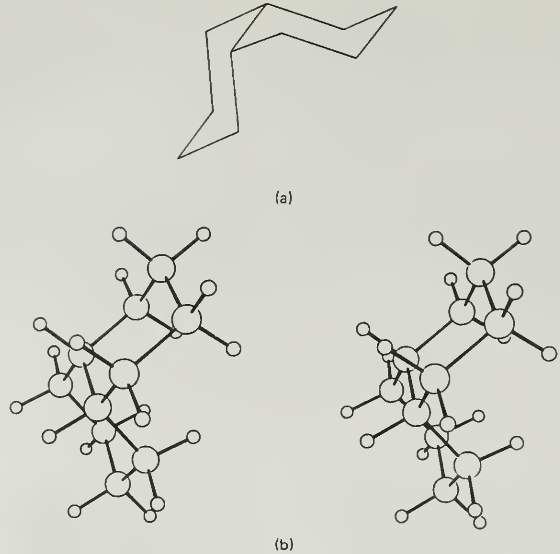
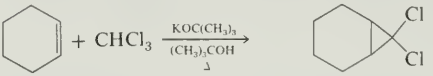
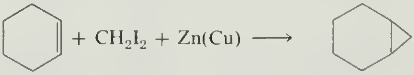


Figure 23.26 Cis-*bicyclo*[4.4.0]*decane,* cis-*decalin:* (a) *conventional representation;* (b) *stereo structure.*

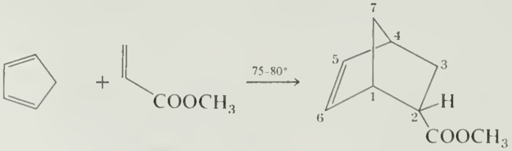

+ CHCl$_3$
KOC(CH$_3$)$_3$
(CH$_3$)$_3$COH
Δ
Cl
Cl

7,7-dichlorobicyclo[4.1.0]heptane



(56–58%)
bicyclo[4.1.0]heptane

The Diels-Alder reaction is an especially effective method for making bicyclic compounds that embody a six-membered ring.


+
COOCH$_3$
75–80°
7
4
5
3
1
H
6
2
COOCH$_3$

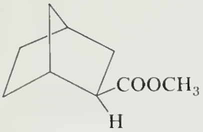
(79 91%)

cyclopentadiene

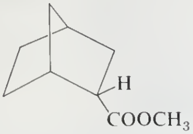
methyl
acrylate

methyl bicyclo[2.2.1]
hept-5-ene-*endo*-2-carboxylate

This example introduces a stereochemical aspect of bicyclic systems. Note that the carboxylate group could be either *cis* to the longer remaining arm (*endo*) or *cis* to the shorter arm (*exo*). The Diels-Alder reaction of cyclopentadiene generally produces the *endo* isomer.

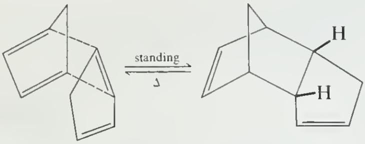


methyl bicyclo[2.2.1]-heptane-*exo*-2-carboxylate



methyl bicyclo[2.2.1]-heptane-*endo*-2-carboxylate

Cyclopentadiene is a useful compound for preparing many bicyclo[2.2.1]heptane derivatives. This low boiling hydrocarbon, b.p. 41°, is available commercially as a dimer that can be readily cracked thermally by heating; the dimer boils at 170°. Cyclopentadiene is used immediately on preparation because it dimerizes readily on standing. The dimerization reaction is a Diels-Alder reaction in which one molecule acts as the diene and another takes the role of the dienophile. The *endo* dimer is produced.

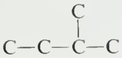


endo-addition

dicyclopentadiene

23.9
Terpenes and Steroids

The **terpenes** are a class of organic compounds that are the most abundant components of the **essential oils** of many plants and flowers. Essential oils are obtained by distilling the plants with water; the oil that separates from the distillate usually has highly characteristic odors identified with the plant origin. In the days of alchemists this procedure was common. The resulting mixture of organic compounds was thought to be the *essence* of the plant, hence the term essential oil. Terpenes are biosynthesized from acetic acid by way of isopentenyl pyrophosphate and may be dissected into "isoprene units" (Section 20.2.E).

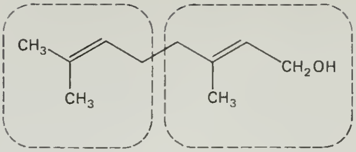


$$\mathrm{C{-}C{-}\overset{\overset{\displaystyle C}{|}}{C}{-}C}$$

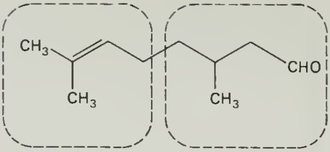
an isoprene unit

Compounds constructed from two isoprene units are **monoterpenes,** C_{10} compounds. Compounds built up from three isoprene units are **sesquiterpenes,** C_{15} compounds. **Diterpenes,** C_{20} compounds, consist of four isoprene units.

A number of terpenes are open chain systems (Section 20.2.E). Some examples (with the isoprene units indicated) are


CH_3
CH_3
CH_3
CH_2OH

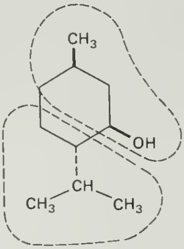
geraniol
(oil of rose)


CH_3
CH_3
CH_3
CHO

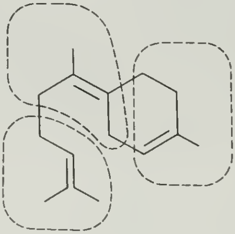
citronellal
(oil of lemon)

Natural rubber and gutta percha can be classified as polyterpenes (Section 20.2.E).

Many terpenes are monocyclic. Some examples are

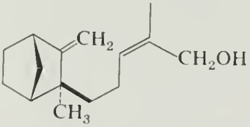

CH_3
OH
CH
CH_3
CH_3

menthol
(peppermint oil)

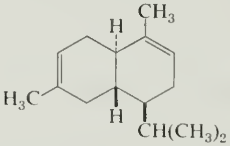


zingiberene
(ginger oil)

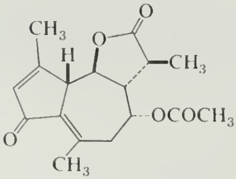
The majority of terpenes are bicyclic, tricyclic, or polycyclic.


CH_2
CH_2OH
CH_3

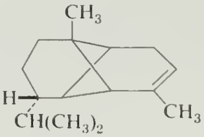
β-santalol
(sandalwood oil)


CH_3
H
H_3C
H
$CH(CH_3)_2$

β-cadinene
(cedar oil)

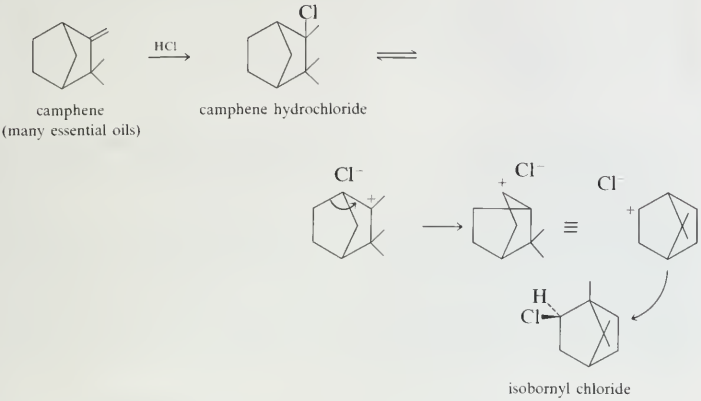

O
CH_3
O
H
CH_3
$OCOCH_3$
O
CH_3

matricarin
(oil of chamomile)

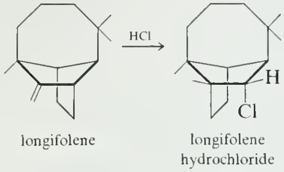

CH_3
H
$CH(CH_3)_2$
CH_3

copaene
(balsam oil)

The elucidation of the structures of the terpenes has provided a fascinating and important chapter in organic chemistry that really started only about a half century ago. Early terpene research led to the recognition of skeletal rearrangements that were among the first examples of carbonium ion rearrangements. A particularly important example is the camphene hydrochloride to isobornyl chloride rearrangement, which we can recognize as a simple 1,2-alkyl rearrangement.


HCl
Cl
camphene
(many essential oils)
camphene hydrochloride
Cl⁻
+
Cl⁻
+
Cl⁻
+
≡
H
Cl
isobornyl chloride

Similar rearrangements are widespread in terpene chemistry. A further example is the rearrangement of longifolene to longifolene hydrochloride.


HCl
H
Cl
longifolene
longifolene
hydrochloride

The stereo structure of longifolene hydrochloride is shown in Figure 23.27.

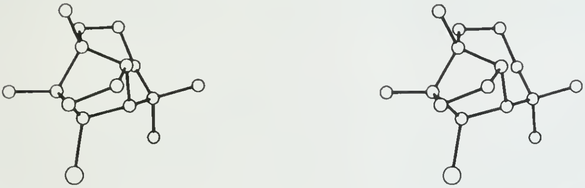
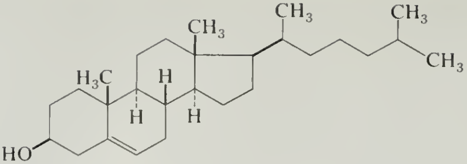


FIGURE 23.27 *Stereo structure of longifolene hydrochloride. Note that hydrogens are not shown. [Reproduced with permission from* Molecular Structures and Dimensions. *International Union of Crystallography, 1972.]*

Synthetic routes to the simpler terpenes are now available, but many of the more complex polycyclic terpenes provide synthetic challenges that intrigue present day synthetic research chemists.

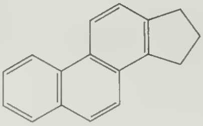
Steroids are tetracyclic natural products that are related to the terpenes in that they are biosynthesized by a similar route. An important example is cholesterol, which is the major component of human gall stones (Greek, *chole,* bile).



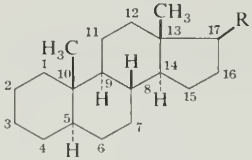
cholesterol

Actually, cholesterol is present in some amount in all normal animal tissues, but it is concentrated in the brain and in the spinal cord. The total amount present in a 180-lb person is 240 g, about $\frac{1}{2}$ lb! It is present partly as the free alcohol and partly esterified with fatty acids.

The structure of cholesterol illustrates the basic steroid skeleton, which is that of a hydrogenated 1,2-cyclopentenophenanthrene having two methyl substituents at C-10 and C-13 and an additional side chain at C-17. The stereochemistry at the various asymmetric carbons is almost invariably that shown, and in subsequent examples we shall not indicate stereochemistry unless it differs from that usually observed.

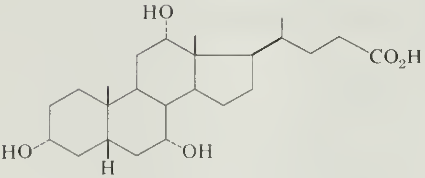


1,2-cyclopentenophenanthrene

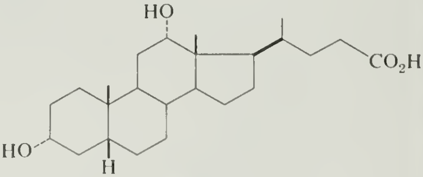


general steroid ring structure

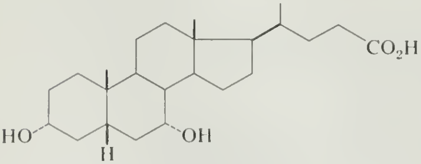
Other steroids are also common constituents of animal tissues and play important roles in normal biological process. Cholic acid, desoxycholic acid, and chenodesoxycholic acid occur in the bile duct.



cholic acid

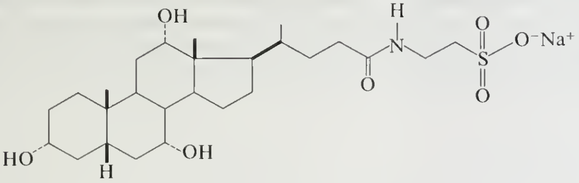


desoxycholic acid



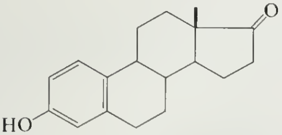
chenodesoxycholic acid

The bile acids exist as amides of the amino acid, glycine (H_2NCH_2COOH), or the amino sulfonic acid, taurine ($H_2NCH_2CH_2SO_3H$). The sodium salts have a large hydrocarbon region and a highly polar region and function in the intestinal tract as emulsifying agents to promote the absorption of fats. They are a type of biological "soap" (Section 17.4.D).

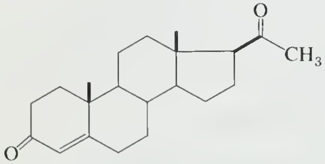


a bile salt

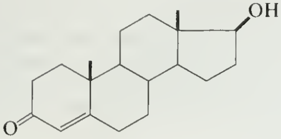
Estrone, progesterone, testosterone, and androsterone are steroid sex hormones.



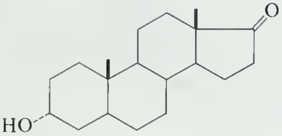
estrone



progesterone



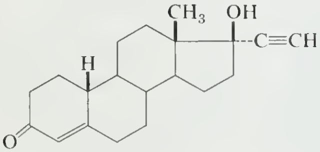
testosterone



androsterone

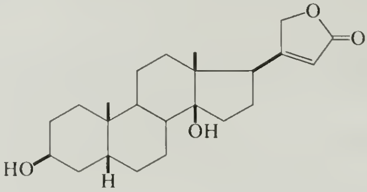
Estrone is an example of an **estrogen,** or female sex hormone. Estrogens are secreted by the ovary and are responsible for the typical female sexual characteristics. Progesterone is another type of female sex hormone. It is also produced in the ovary and is the progestational hormone of the placenta and corpus luteus. Testosterone and androsterone are **androgens,** or male sex hormones. They are produced in the testes and are responsible for the typical male sexual characteristics.

One of the most dramatic achievements of synthetic organic chemistry, and one which has already had profound impact on the history and mores of human societies, has been the development of "the pill." Actually, there are a number of different oral contraceptives in use. They are mainly synthetic steroids that interfere in some way with the normal estrus or progestational cycle in the female. One example is norethindrone, also known by the trade name Norlutin.



norethindrone
Norlutin

Steroids are widespread in the plant kingdom as well as in animals. One example is digitalis, a preparation made from the dried seeds and leaves of the purple foxglove. Historically, digitalis was used as a poison and as a medicine in heart therapy. The active agents in digitalis are **cardiac glycosides**, complex molecules built up from a steroid and several carbohydrates. Hydrolysis of digitoxin, one of the cardiac glycosides from digitalis, yields the steroid digitoxigenin.

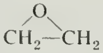


digitoxigenin

23.10 Cyclic Ethers

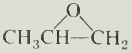
A. *Epoxides: Oxiranes*

The three-membered ring containing oxygen is the first class of heterocyclic compounds to be considered. Because they are readily prepared from alkenes they are commonly named as olefin oxides. Hence, the parent member is generally called ethylene oxide.

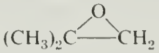


ethylene oxide

This type of compound is frequently called an epoxide although the formal IUPAC nomenclature is oxirane. Substituents on the oxirane ring require a numbering system. The general rule for heterocyclic rings is that the heteroatom (atom other than carbon) gets the number one.

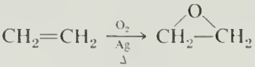


propylene oxide
2-methyloxirane

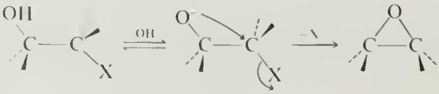


isobutylene oxide
2,2-dimethyloxirane

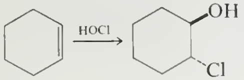
Ethylene oxide is a significant commercial item and is prepared industrially by the catalyzed air oxidation of ethylene.



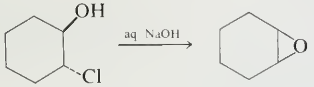
Several general laboratory preparations are available. One reaction is an internal S_N2 displacement reaction starting with an olefin halohydrin (Section 12.6.B).



Recall that the halohydrins are generally available from reaction of olefins with HOX. The internal S_N2 reaction is an intramolecular backside reaction and requires that the reacting groups have a *trans* or *anti* relationship, and this is just the form produced by reaction of olefin with HOX.

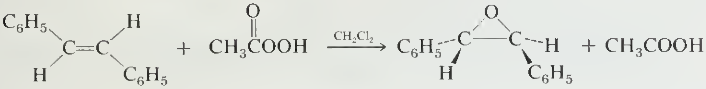


(70–73%)



(70–73%)
cyclohexene oxide

Another useful general preparation is the reaction of an alkene with a peroxycarboxylic acid.

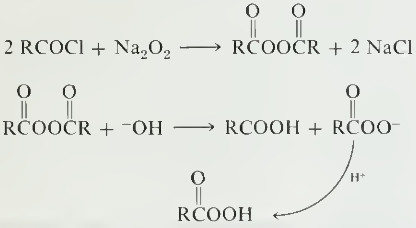


trans-stilbene

peroxyacetic acid

(78–83%)
trans-stilbene oxide
trans-2,3-diphenyloxirane

The peroxyacids are generally obtained by careful hydrolysis of diacyl peroxides which, in turn, are available from reaction of acyl chlorides with sodium peroxide.

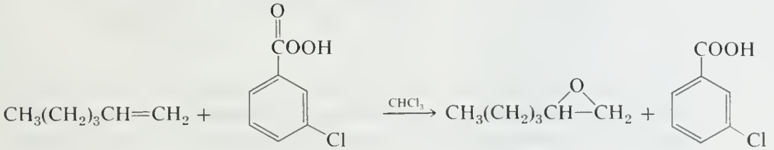


$$2\,RCOCl + Na_2O_2 \longrightarrow R\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R + 2\,NaCl$$

$$R\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R + {}^{-}OH \longrightarrow RCOOH + R\overset{O}{\overset{\|}{C}}OO^{-} \xrightarrow{H^+} R\overset{O}{\overset{\|}{C}}OOH$$

a peroxy acid

Peroxycarboxylic acids are generally unstable and must be stored in the cold or, preferably, be prepared as needed. An important exception is 3-chloroperoxybenzoic acid, an exceptionally stable crystalline solid now available commercially. This reagent provides a simple and convenient one-step route to epoxides.

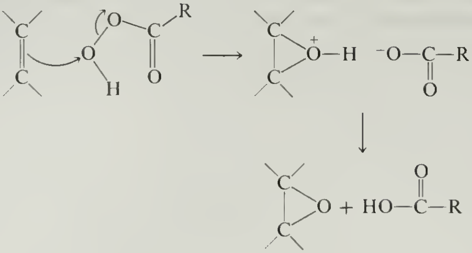


3-chloroperoxybenzoic acid

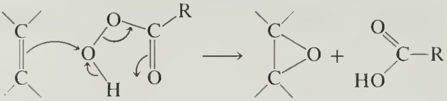
(60%)

3-chlorobenzoic acid

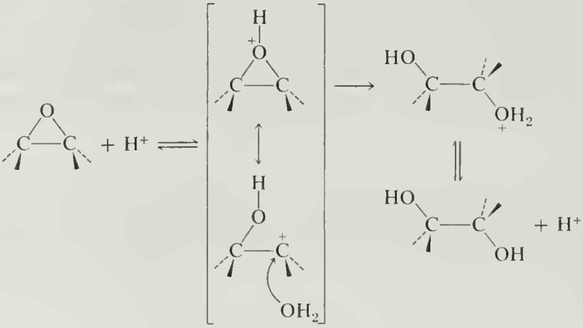
The mechanism of the reaction can be represented as a displacement reaction on an electrophilic oxygen by a nucleophilic alkene.



The reaction may actually take place in a single step.

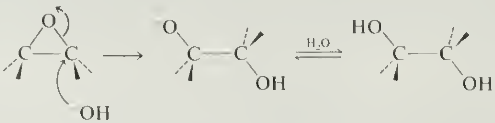


Like three-membered rings generally, the oxirane ring system is highly strained and opens readily. Ring opening is especially facile in the presence of acids.



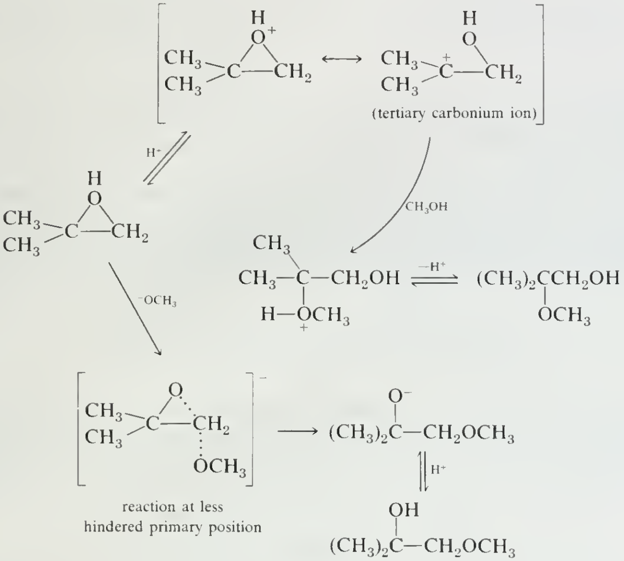
The product is a 1,2-diol or glycol (Section 24.3). The acid-catalyzed hydrolysis is related to the reaction of ethers with acids (Sect. 11.11), but it is far more facile due to the relief of ring strain which accompanies ring opening.

Ring opening can also be accomplished with base.

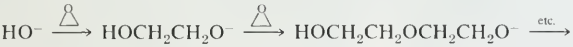


Base-catalyzed opening of an epoxide is an S_N2 displacement reaction with an alkoxide ion as the leaving group and has no counterpart with normal ethers. It occurs with epoxides only because the relief of ring strain provides a potent driving force for reaction.

The two ring opening reactions have different orientational preferences. The acid-catalyzed reaction is essentially a carbonium ion reaction, and reaction tends to occur at that ring carbon that corresponds to the more stable carbonium ion; that is, reaction with solvent occurs at the more highly substituted ring carbon. As in other S_N2 reactions, the base-catalyzed reaction is subject to steric influences. Reaction occurs at the less hindered carbon. The difference is exemplified by reaction of isobutylene oxide in methanol under acidic and basic conditions.


H⁺
(tertiary carbonium ion)
CH₃OH
−H⁺
(CH₃)₂CCH₂OH
OCH₃
⁻OCH₃
(CH₃)₂C—CH₂OCH₃
H⁺
reaction at less hindered primary position

Under the proper conditions, the first product from the reaction of ethylene oxide with hydroxide ion can react with more ethylene oxide.

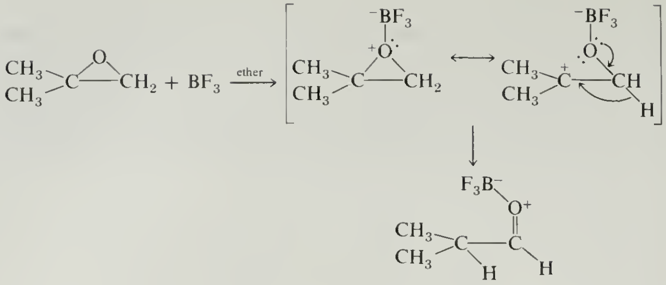

HO⁻
HOCH₂CH₂O⁻
HOCH₂CH₂OCH₂CH₂O⁻
etc.

The final products are polyether alcohols, which are called diethylene glycol, triethylene glycol, and so on. These polyether alcohols are methylated to produce the polyethers **glyme, diglyme, triglyme,** and so on, which are useful solvents.

$$HOCH_2CH_2OCH_2CH_2OH \longrightarrow CH_3OCH_2CH_2OCH_2CH_2OCH_3$$

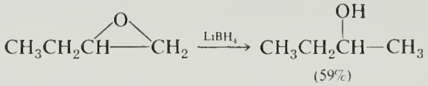
diethylene glycol — diethylene glycol dimethyl ether
"diglyme"

In the absence of a reactive nucleophilic reagent, a protonated epoxide rearranges to the more stable carbonyl compound. The rearrangement reaction is best carried out with a Lewis acid.



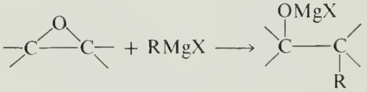
Note that rearrangement converts the more stable carbonium ion form of the epoxide–Lewis acid complex to the still more stable oxonium ion derived from a carbonyl group.

Lithium aluminum hydride and lithium borohydride react with epoxides to produce alcohols. A simple way to view the reaction is as an S_N2 reaction by H^- provided by the complex metal hydride. In accord with this view, reduction usually occurs at the less substituted epoxide carbon.

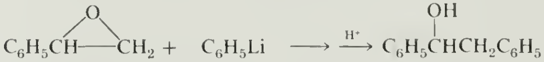


(59%)

The oxirane ring may also be opened by Grignard reagents or organolithium reagents. The reaction course is that of the organometallic compound acting as a carbanion.



For example,

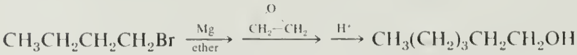


(70–72%)

styrene oxide
phenyloxirane

phenyllithium

1,2-diphenylethanol

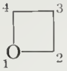


(60–62%)
1-hexanol

The reaction of Grignard reagents with ethylene oxide extends the chain by two carbon atoms. This reaction works best with ethylene oxide itself because the magnesium salts formed in the reaction are mild Lewis acids and cause ring opening and rearrangement side reactions with substituted oxiranes.

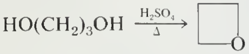
B. *Higher Cyclic Ethers*

Oxetanes are four-membered ring ethers.

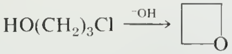


oxetane

This relatively unimportant class of compound can be prepared by normal cyclization reactions.



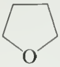
$$HO(CH_2)_3OH \xrightarrow[\Delta]{H_2SO_4}$$



$$HO(CH_2)_3Cl \xrightarrow{^-OH}$$

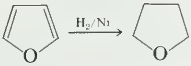
The oxetane ring is more stable than epoxides to ring opening reactions but the four-membered ring ethers are cleaved more readily than open chain ethers.

One of the most important of the cyclic ethers is tetrahydrofuran, THF, a material we have encountered frequently as a solvent.



tetrahydrofuran
THF

Tetrahydrofuran can be obtained by hydrogenation of furan, but a more important industrial process utilizes 1,4-butanediol.

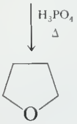


furan

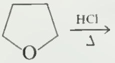
$$HC{\equiv}CH + CH_2O \longrightarrow HOCH_2C{\equiv}CCH_2OH \longrightarrow HO(CH_2)_4OH$$

2-butyn-1,4-diol

1,4-butanediol



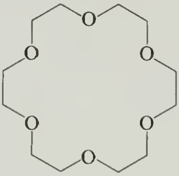
In common with many ethers, tetrahydrofuran reacts with oxygen to form dangerous peroxides. Its most important use is as a solvent. The five-membered ring is stable to ring opening, but ring opening can be accomplished under conditions that cause ether cleavage reactions of open chain ethers.



$$Cl(CH_2)_4OH$$

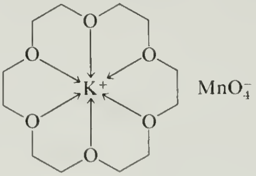
4-chloro-1-butanol

A group of large-ring polyethers that have attracted a good deal of recent attention are called **crown ethers.** The compounds are cyclic polymers of ethylene glycol, $(-OCH_2CH_2)_n$, and are named in the form: *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygens. An example is 18-crown-6, the cyclic hexamer of ethylene glycol.



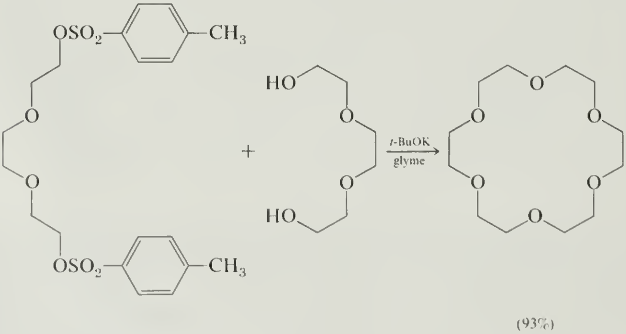
18-crown-6

The crown ethers are important for their ability to solvate cations strongly. The six oxygens in 18-crown-6 are ideally situated to solvate a potassium cation, just as water molecules would normally do. In the resulting complex, the cation is solvated by the polar oxygens, but the exterior has hydrocarbon properties. As a result, the complexed ion is soluble in nonpolar organic solvents. For example, the complex of 18-crown-6 and potassium permanganate is soluble in benzene.



18-crown-6-$KMnO_4$ complex
soluble in benzene

18-Crown-6 may be prepared in high yield by treating a mixture of triethylene glycol and triethylene glycol ditosylate with potassium *t*-butoxide.

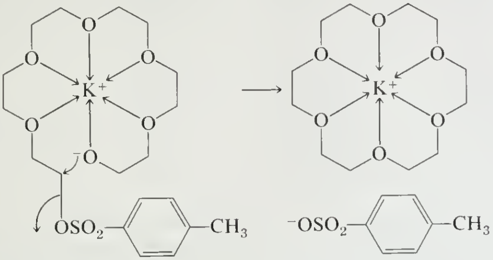


triethylene glycol ditosylate

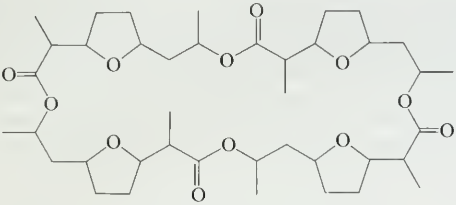
triethylene glycol

(93%)
18-crown-6

The reaction mechanism involves two successive S_N2 displacements with *p*-toluenesulfonate ion being the leaving group. Even though a large ring is being formed, the reaction need not be carried out at high dilution. After the initial alkylation, the potassium cation apparently acts as a "template" to bring the two reacting ends of the long chain close together for rapid reaction.



A number of naturally occurring cyclic compounds are now known with oxygens and nitrogens in the ring that coordinate with metal cations. Some of these compounds are involved in the transport of ions across biological membranes. An example is nonactin, an antibiotic that functions by transporting sodium ions into bacteria until the resulting osmotic pressure causes rupture of the cell wall.



nonactin

23.11
Spectra of Cyclic Compounds

Because of the hybridization changes in small rings and the rather rigid conformational requirements of small and medium sized rings, cyclic compounds frequently display distinctive and useful spectral characteristics.

A. *Infrared Spectra*

Although distinctive features appear in the infrared spectra of many cyclic compounds, the most important application has been to cyclic ketones. The carbonyl stretching band is a generally intense band that occurs for normal open chain ketones at 1715 cm^{-1}. For small ring ketones extra *p* character is required for the ring bonds so that the exocyclic bonds have extra *s*-character (Section 23.2.B). The resulting higher bond strength shows up generally in higher stretching frequencies.

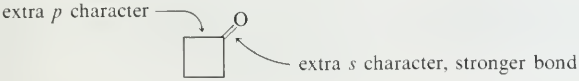
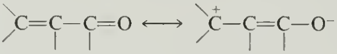


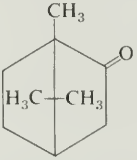
TABLE 23.4
Carbonyl Stretching Frequencies

Type of Ketone	Frequency, cm^{-1}
normal open chain	1715
cyclic	
three-membered	1820
four-membered	1780
five-membered	1745
six-membered	1715
α,β-unsaturated	1675

The magnitude of this effect in carbonyl stretching frequencies is summarized in Table 23.4. Note how the cyclohexyl system is again "normal." α,β-Unsaturated ketones are included as further reference systems. The lower stretching frequency is indicative of increased single bond character of conjugated carbonyl groups.

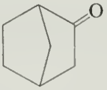


The characteristic stretching frequencies of cyclic carbonyl groups apply to polycyclic systems as well. For example, the carbonyl group of camphor is part of a five-membered ring and the stretching frequency of 1740 cm^{-1} is characteristic of a cyclopentanone. The fact that the CO group in the bicyclic camphor is also part of a six-membered ring is not relevant—it is the character of ring strain that shows up in the spectrum. However, since ring strain effects do depend somewhat on the detailed structure, variations of a few cm^{-1} from the values in Table 23.4 are to be expected.



ν(CO) = 1740 cm^{-1}

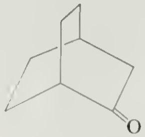
camphor



ν(CO) = 1751 cm^{-1}

2-bicyclo[2.2.1]heptanone
(norbornanone)

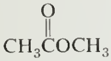
Bicyclo[2.2.2]octan-2-one is an apparent exception. Its CO stretching band at 1731 cm^{-1} is far higher than expected for a cyclohexanone ring. A second look at the structure of this bicyclic ketone reveals, however, that its six-membered ring is that of a boat conformation rather than a chair.



ν(CO) = 1731 cm^{-1}

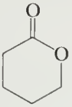
2-bicyclo[2.2.2]octanone

The increased carbonyl stretching frequency in small ring compounds is also seen in the infrared spectra of cyclic esters, lactones. The C=O stretch in an acyclic ester is about 1735 cm^{-1}, and a similar band occurs in the six-membered lactone. However, the four- and five-membered lactones absorb at 1800 cm^{-1} and 1770 cm^{-1}, respectively.

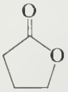


$CH_3\overset{\overset{O}{\|}}{C}OCH_3$

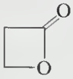
1736 cm^{-1}



1735 cm^{-1}



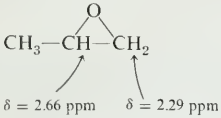
1770 cm^{-1}



1800 cm^{-1}

B. *Nuclear Magnetic Resonance*

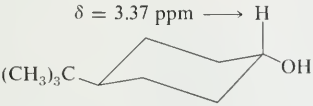
Cyclic compounds also show unique features in their nmr spectra, both in chemical shifts and in coupling constants. Chemical shift effects are most pronounced for cyclopropane rings. The parent hydrocarbon has $\delta = 0.22$ ppm, substantially upfield from the resonance position of normal methylene protons, although the enhanced *s*-character of the cyclopropyl C—H bond would have suggested a downfield shift. The effect has been attributed to a ring current associated with the bent bonds of the three-membered ring. The effect is also seen in epoxides. The ring hydrogens resonate upfield from normal hydrogens next to ether oxygens.

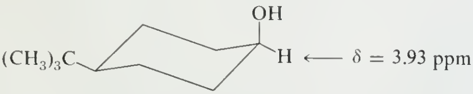


$CH_3CH_2OCH_2CH_3$

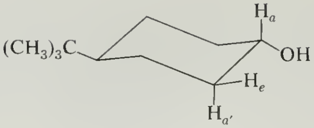
$\delta = 3.36$ ppm

In cyclohexyl compounds, the axial and equatorial protons have slightly different chemical shifts. For cyclohexane itself and for simple derivatives, the difference is not observed at normal temperatures because the alternative chair conformations are interconverting rapidly relative to the nmr time scale (Section 23.2.D). In compounds that are rigidly held in a single conformation, the effect can be seen. The difference in chemical shift is approximately 0.5–0.8 ppm, with the axial proton resonating at higher field.

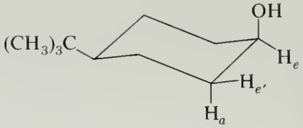




An important effect on vicinal (adjacent) coupling constants may also be seen in cyclohexyl compounds. The *J* value between vicinal axial hydrogens is 10–13 Hz, whereas *J* between axial and equatorial or between two equatorial hydrogens is 3–5 Hz.



$J_{aa'} = 11.1$ Hz
$J_{ae} = 4.3$ Hz



$J_{ee'} = 2.7$ Hz
$J_{ae} = 3.0$ Hz

This difference is reminiscent of the larger J for *trans* hydrogens in an alkene compared to *cis* hydrogens (Section 12.3.B). The dihedral angle between two axial hydrogens is 180°, whereas the axial-equatorial and equatorial-equatorial dihedral angle is 60° (Figure 23.28).

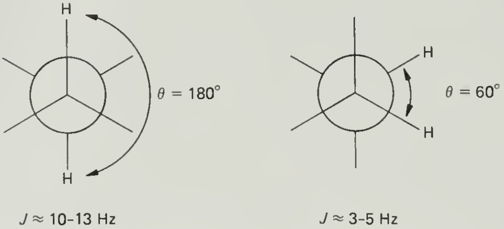


FIGURE 23.28 J_{HH} *and conformation. The angle θ is the dihedral angle between the hydrogens.*

In many cyclohexane derivatives the nmr spectra are sufficiently complex that this distinction between J values is not useful. The relation between J and the dihedral angle between hydrogens has been established theoretically and may be depicted in a familiar graphic form known as the Karplus curve (Figure 23.29). The coupling constant between two hydrogens reaches a minimum when the

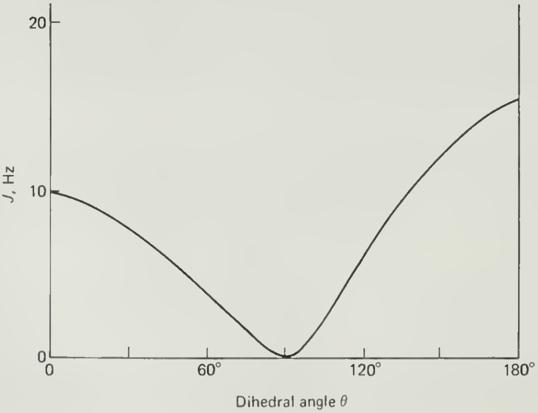


FIGURE 23.29 *Karplus curve.*

dihedral angle between them is 90°. The curve can be expressed analytically by two equations.

$$J_{HH'} = 10\cos^2\theta \qquad (0 \leq \theta \leq 90°)$$
$$J_{HH'} = 16\cos^2\theta \qquad (90 \leq \theta \leq 180°)$$

The Karplus curve and its analytical equivalent are especially useful in some bicyclic systems where steric constraints provide values for the dihedral angle other than 60° or 180°.

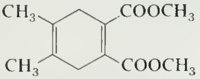
PROBLEMS

1. Provide a proper IUPAC name for each of the following terpenes:
   (a) geraniol
   (b) citronellal
   (c) camphor
   (d) menthol
   (e) cadinene
   (f) camphene hydrochloride
   (g) pinene
   (h) caryophyllene
   (i) squalene (Section 20.2.E)
   (j) farnesol (Section 20.2.E)

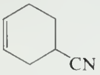
2. The hydrolysis of 5-chloro-2-methyl-2-pentene in water produces 2-cyclopropyl-2-propanol. Write a reasonable mechanism for the reaction.

3. What diene and dienophile produce the following Diels-Alder adducts:

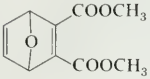
(a)



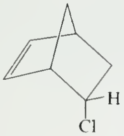
(b)



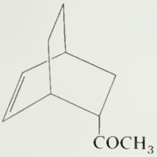
(c)



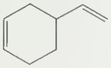
(d)



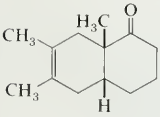
(e)



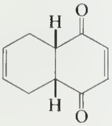
(f)



(g)

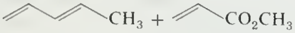


(h)

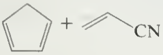


4. For each of the following Diels-Alder reactions, predict the orientation and stereochemistry.

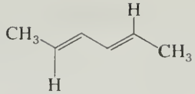
(a)



(b)

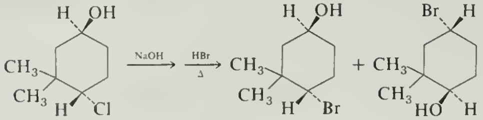


(c)



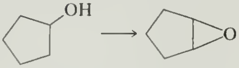
+ $HC\equiv CCO_2CH_3$

5. Provide a mechanistic rationalization for the following reaction course:



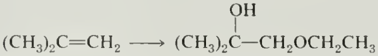
6. Show how to accomplish each of the following conversions in a practical manner:

(a)



(b) $(CH_3)_3COH \longrightarrow (CH_3)_3CCH_2CH_2OH$

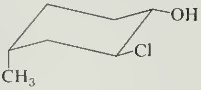
(c)



$(CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2\overset{\overset{\displaystyle OH}{|}}{C}{-}CH_2OCH_2CH_3$

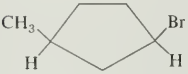
7. What is the principal organic reaction product of each of the following reactions:

(a)



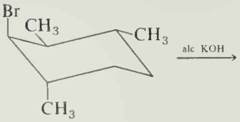
+ OH^- $\longrightarrow$

(b)

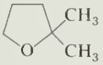


+ $C_6H_5S^-$ $\longrightarrow$

(c)



(d)



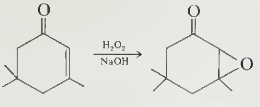
+ HCl $\longrightarrow$

8. From cyclooctatetraene or cyclododecatriene show how to prepare the following compounds.
(a) cyclooctane
(b) chlorocyclooctane
(c) *n*-propylcyclooctane
(d) cyclododecane
(e) cyclododecene
(f) dodecanedioic acid

9. Ethyl *cis*-4-methylcyclohexanecarboxylate exists with the ethoxycarbonyl group partially axial and partially equatorial. From the data in Table 23.3 calculate the relative amounts of the two conformations. Use the data on page 628 to calculate the rate of hydrolysis in 70% ethanolic sodium ethoxide at 25°.

10. A preparation of epoxides that is applicable to α,β-unsaturated ketones involves

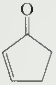
reaction with aqueous alkaline hydrogen peroxide. For example



(70 72%)

Formulate a reasonable mechanism for this reaction.

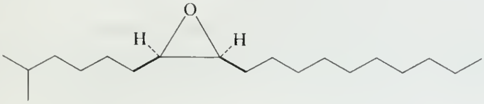
11. The Woodward rules (Section 22.5) apply to cyclopentenones if the parent α,β-unsaturated ketone is assigned a base value of 212 nm.



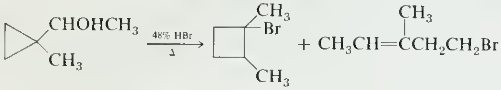
λ_{max} 212 nm

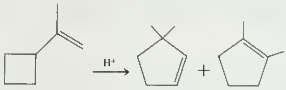
Calculate the λ_{max} expected for 3-methylcyclopent-2-enone which was synthesized on page 617.

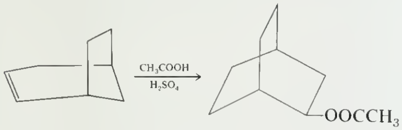
12. The following epoxide is a sex-attractant for the gypsy moth. What is its IUPAC name? (Note the *cis* configuration.) Propose a practical synthesis from available compounds.



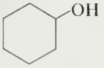
13. Write reasonable mechanisms for the following carbonium ion rearrangements:

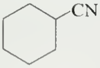
(a)

CHOHCH$_3$
CH$_3$
48% HBr
Δ
CH$_3$
Br
CH$_3$
CH$_3$
+ CH$_3$CH=CCH$_2$CH$_2$Br

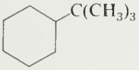
(b)


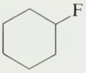
(c)

CH$_3$COOH
H$_2$SO$_4$
OOCCH$_3$

14. From the data in Table 23.3, calculate the percentage of molecules having the substituent in the equatorial position for each of the following compounds:

(a)


(b)


(c)


(d)


15. (a) Examine a molecular model of the chair conformation of cyclohexane. Identify the six axial and the six equatorial hydrogens. Mark the axial hydrogens in some way and flip the ring into the other chair conformation. Note that the marked hydrogens are now equatorial. In the chair conformation, note that all pairs of carbons are staggered. Now flip the ring into a boat conformation. Identify the pairs of eclipsed H,H and C,C interactions. How many of each are there?

(b) Make a model of cyclopentane in the envelope conformation. How many eclipsed interactions are there?

(c) Make a model of methylcyclohexane. Examine the model with the methyl group equatorial and compare it with a model of butane. How many "*gauche*" interactions are there in the equatorial-methylcyclohexane structure? Repeat the comparison for axial-methylcyclohexane.

(d) Learn to sketch accurately the chair form of cyclohexane, showing clearly the axial and equatorial groups of each carbon.

16. (a) Write flat projection structures for each of the seven dimethylcyclohexanes. Use heavy bonds to indicate substituents that project above the ring and dashed bonds for substituents that project below.

(b) Sketch the two chair forms for 1,1-dimethylcyclohexane. What is the free energy difference between the two conformations?

(c) Answer part (b) for *cis*-1,2-dimethylcyclohexane, *trans*-1,3-dimethylcyclohexane, and *cis*-1,4-dimethylcyclohexane.

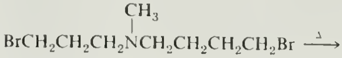
(d) Answer part (b) for *trans*-1,2-dimethylcyclohexane and *trans*-1,4-dimethylcyclohexane.

(e) Sketch the two chair forms for *cis*-1,3-dimethylcyclohexane. What interaction is present in one chair conformation of this isomer that does not occur in any of the other five isomers?

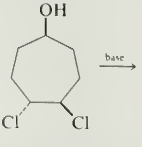
(f) For the seven dimethylcyclohexanes in parts (a)–(e), locate the gauche butane interactions in each of the chair conformations.

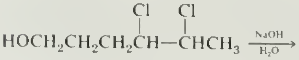
★(g) At room temperature, only two of the seven isomers may be obtained in optically active form. Which ones? In principle, one of other isomers may be obtained in optically active form at very low temperatures. Which one? Explain.

17. In each of the following reactions, there are two alternative modes of cyclization. Which product is expected in each case?

(a) 

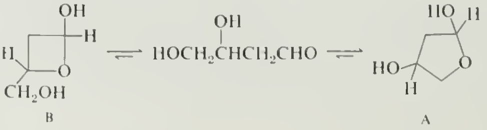
$$\mathrm{BrCH_2CH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{N}CH_2CH_2CH_2CH_2Br} \xrightarrow{\Delta}$$

(b) 

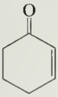
(c) 

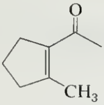
$$\mathrm{HOCH_2CH_2CH_2\overset{\overset{\displaystyle Cl}{|}}{C}H{-}\overset{\overset{\displaystyle Cl}{|}}{C}HCH_3} \xrightarrow[\mathrm{H_2O}]{\mathrm{NaOH}}$$

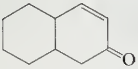
18. 3,4-Dihydroxybutanal exists in solution in a cyclic hemiacetal form. Explain why the only hemiacetal present is A and none of B is present.



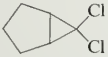
19. Each of the following compounds may be obtained by an intramolecular aldol condensation. Show the precursor in each case.

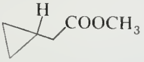
(a)


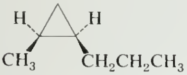
(b)


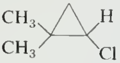
(c)


20. Show how to synthesize each of the following cyclopropane derivatives.

(a)


(b)


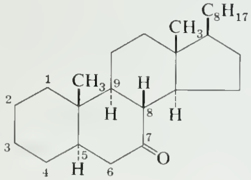
(c)


(d)


21. Show how an intramolecular Wittig reaction might be used to synthesize a ring compound.

22. See if you can think of any other reactions you have learned that might be used in an intramolecular sense to prepare ring compounds.

23. Bromination of 7-cholestanone gives 6-bromo-7-cholestanone with $J_{5H,6H} = 2.8$ Hz. This initial product slowly converts to the more stable 6-bromo stereoisomer that has $J_{5H,6H} = 11.8$ Hz. Assign stereostructures to the two isomers and explain their relative stabilities.



7-cholestanone

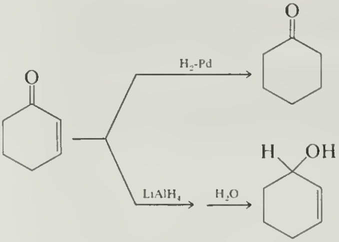
24. 4-Methyl-1,3-pentadiene is inert to dienophiles in Diels-Alder reactions. Propose an explanation (Hint: look at models).

CHAPTER 24

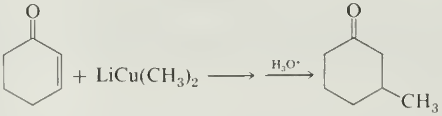
Difunctional Compounds I

24.1 Introduction

To a first approximation, the chemical properties of difunctional compounds are a summation of those of the individual functions. However, in many cases, the two groups interact in such a way as to give the compound chemical properties that are not observed with the simple monofunctional compounds. For example, cyclohex-2-en-1-one is a difunctional compound that undergoes typical alkene reactions (catalytic hydrogenation) and normal ketone reactions (reduction by lithium aluminum hydride).



However, since the two functional groups form a conjugated system (Chapter 20), it undergoes some special reactions, such as 1,4-addition of lithium dimethylcuprate (Section 20.3.A).



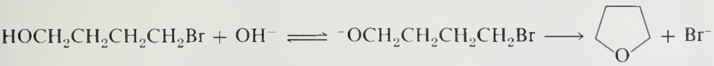
This is a special reaction of the difunctional compound, because neither simple alkenes nor simple ketones react with the reagent.

In other cases, the chemical properties of a difunctional compound are similar to those of a corresponding monofunctional compound in a qualitative sense but not in a quantitative sense. An example is the reaction of allyl bromide with azide ion. The reaction is a normal S_N2 replacement of a primary halide, but, since the organic group is allylic, the reaction is over 50 times faster than it is with propyl bromide (Section 20.1.A).

$$CH_2{=}CHCH_2Br + N_3^- \xrightarrow{\text{faster}} CH_2{=}CHCH_2N_3 + Br^-$$

$$CH_3CH_2CH_2Br + N_3^- \xrightarrow{\text{slower}} CH_3CH_2CH_2N_3 + Br^-$$

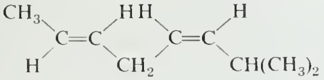
In still other cases, two functional groups in a molecule may enter into a chemical reaction *with each other.* An example is the intramolecular S_N2 reaction leading to cyclic ethers (Section 23.10).



As may be seen in the foregoing examples, we have already encountered the reactions of a number of difunctional compounds, mainly in the study of conjugated systems (Chapter 20) and in the formation of ring compounds (Chapter 23). In this chapter, we shall take up a few specific types of difunctional compounds, pointing out some of the unique chemistry that results from the cooperation or interaction of the two functional groups. The specific difunctional compounds that we shall consider at this time are diols, hydroxy aldehydes, hydroxy ketones, and hydroxy acids, because their chemistry is fundamental to a study of carbohydrates (Chapter 25). In Chapter 26 we shall return to difunctional compounds and take up dicarboxylic acids, diketones, and keto acids.

24.2
Nomenclature of Difunctional Compounds

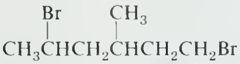
Recall that most simple monofunctional compounds are named in such a way that the ending of the name denotes the functional group; acetic **acid,** 3-pentan**ol,** cyclohexan**one,** 1-but**ene**. Alkyl halides are exceptions to this generalization, in that they are considered as derivatives of the parent alkane; for example, 2-chloroheptane. When a compound contains two like functional groups, it is generally named in the same way except that the typical group suffix is combined with **di** to indicate the presence of two groups. Numbers are used to locate the positions of the groups on the carbon skeleton.



7-methyl-(2E,5Z)-octa**diene**, or
trans,cis-7-methyl-2,5-octa**diene**

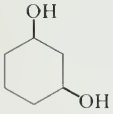
$CH_3C{\equiv}C{-}C{\equiv}CH$

1,3-pentadi**yne**

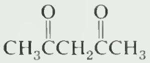


$$\overset{\displaystyle Br}{\overset{|}{CH_3CH}}CH_2\overset{\displaystyle CH_3}{\overset{|}{CH}}CH_2CH_2Br$$

1,5-dibromo-3-methylhexane



cis-1,3-cyclohexane**diol**



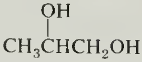
$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$$

2,4-pentane**dione**

Diols are sometimes called **glycols.** This is a trivial nomenclature widely used in the chemical industry, particularly for some of the simpler diols, which are important commercial items. For example, ethylene glycol (1,2-ethanediol) is the most widely used antifreeze additive for automobile radiators. Several examples of the glycol nomenclature are given below.

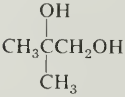
$HOCH_2CH_2OH$

ethylene glycol



$CH_3\overset{\overset{\displaystyle OH}{|}}{C}HCH_2OH$

propylene glycol



$CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}CH_2OH$

isobutylene glycol

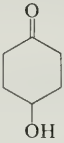
$HOCH_2CH_2CH_2OH$

trimethylene glycol

When a compound contains two different functional groups, one of the groups (the principal function) is usually expressed in the ending of the name and the other as a prefix.

$HOCH_2CH_2CO_2H$

3-hydroxypropanoic acid
β-hydroxypropionic acid

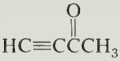


4-hydroxycyclohexanone

Alkenes and alkynes are exceptions in that the double or triple bond cannot be expressed as a prefix. For compounds containing a multiple bond and another functional group, two suffixes are used.

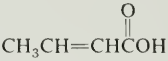
$CH_2{=}CHCH_2CH_2OH$

3-buten-1-ol



$HC{\equiv}C\overset{\overset{\displaystyle O}{\|}}{C}CH_3$

3-butyn-2-one

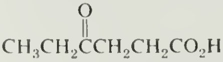


$CH_3CH{=}CH\overset{\overset{\displaystyle O}{\|}}{C}OH$

2-butenoic acid

When naming a difunctional compound, a choice must be made as to which group is the principal function. The generally accepted order is: sulfonic acid, carboxylic acid, acyl halide, amide, aldehyde, nitrile, ketone, alcohol, thiol, amine, alkyne, alkene. Since alkenes and alkynes cannot be designated by prefixes, they are always indicated by a second suffix, which is placed *before* the final suffix of any function higher in the order. Table 24.1 contains a listing of the common functions with the appropriate prefix and suffix used to designate each one.

Some examples of difunctional compound names follow. In some cases both IUPAC and common names are given.

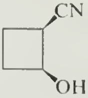


$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2CO_2H$

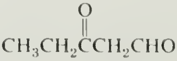
4-oxohexanoic acid
γ-ketocaproic acid

$HSCH_2CH_2CH_2OH$

3-mercaptopropanol



cis-2-hydroxycyclobutanecarbonitrile



$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2CHO$

3-oxopentanal
β-ketovaleraldehyde

$NCCH_2CO_2C_2H_5$
ethyl cyanoacetate

$H_2NCH_2CH_2CN$
3-aminopropanenitrile
β-aminopropionitrile

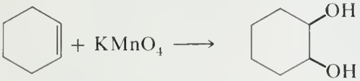
Table 24.1

Group	Prefix	Suffix
$-SO_3H$	sulfo-	-sulfonic acid
$-CO_2H$	carboxy-	-oic acid -carboxylic acid
$-COCl$	chloroformyl-	-oyl chloride -carbonyl chloride
$-CONH_2$	carbamoyl-	-amide -carboxamide
$-CHO$	formyl- oxo-	-al -carboxaldehyde
$-CN$	cyano-	-nitrile -carbonitrile
$-\overset{O}{\overset{\|}{C}}-$	oxo- (IUPAC) keto- (common)	-one
$-OH$	hydroxy-	-ol
$-SH$	mercapto-	-thiol
$-NH_2$	amino-	-amine
$-C\equiv C-$	—	-yne
$-C=C-$	—	-ene
$-Cl$	chloro-	—

24.3 Diols

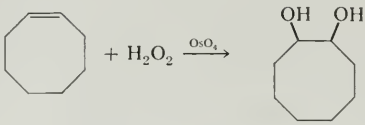
A. *Preparation of diols*

1. **Hydroxylation of Alkenes.** 1,2-Diols may be produced from the corresponding alkene by hydroxylation of the double bond with $KMnO_4$ or OsO_4 (Section 12.6.E). The reaction is **stereospecific** because the 1,2-diol results from the *cis* or *syn* (page 632) addition of the reagent to the double bond. For example, cyclohexene reacts with $KMnO_4$ to yield *cis*-1,2-cyclohexanediol.

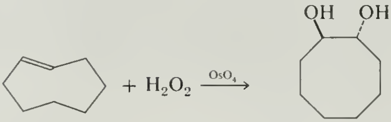


cis-1,2-cyclohexanediol

When the double bond in a cyclic alkene is *cis,* as in cyclohexene, the *syn*-hydroxylation process produces a *cis*-diol. For the cyclic alkenes up through cycloheptene, only the *cis* isomers of the double bond are stable enough to exist at room temperature. For the larger cycloalkenes, both *cis* and *trans* isomers may exist. For these compounds, *syn* addition to the *trans* isomer yields the *trans*-diol.

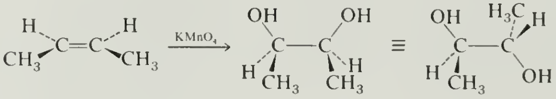


cis-cyclooctene   *cis*-1,2-cyclooctanediol



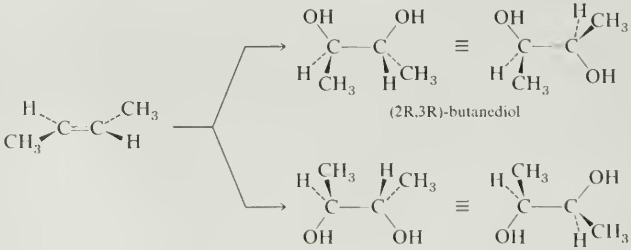
trans-cyclooctene   *trans*-1,2-cyclooctanediol

With acyclic alkenes, different diols result from addition to the *cis* or *trans* isomer of the alkene. For a symmetrical alkene, such as 2-butene, *syn*-hydroxylation of the *cis* isomer gives a *meso*-diol.



meso-2,3-butanediol

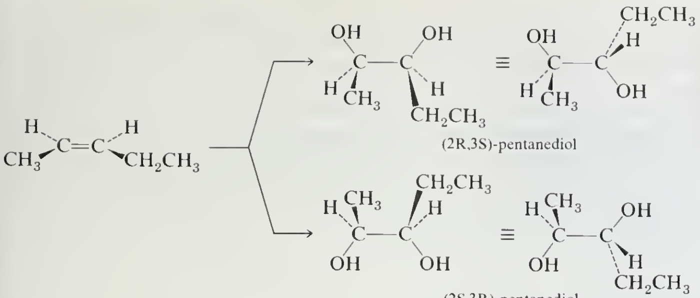
Syn-hydroxylation of the *trans* isomer gives a 50 : 50 mixture of two enantiomeric diols. These two products arise from addition of the reagent to the two faces of the planar alkene molecule. Since the reagent is achiral, the transition states leading to the two products are enantiomeric and equal in energy. The product is therefore a **racemic mixture** (Section 7.4). To distinguish this mixture of enantiomers from the *meso*-diol, it is frequently designated as (±) or *dl* (meaning an equimolar or racemic mixture of the dextrorotatory and levorotatory enantiomers).



(2R,3R)-butanediol

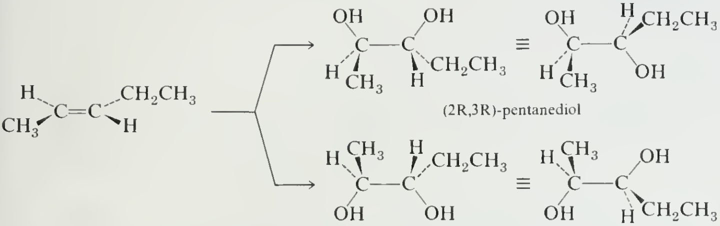
(2S,3S)-butanediol
[mixture = (±)-2,3-butanediol]

When the acyclic alkene is not symmetrical, such as 2-pentene, *syn* addition to each isomer yields a racemic mixture.



(2R,3S)-pentanediol

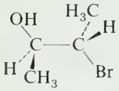
(2S,3R)-pentanediol



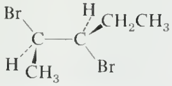
(2R,3R)-pentanediol

(2S,3S)-pentanediol

The (2R,3S) and (2S,3R) isomers of 2,3-pentanediol are called **erythro** isomers, and the (2R,3R) and (2S,3S) isomers are called **threo** isomers. These names derive from carbohydrate chemistry (Chapter 25) and are frequently used for other simple difunctional compounds. When a compound contains two asymmetric carbons that have two identical attached groups and a third that differs, *the isomer that would be meso if the third groups were identical is the erythro isomer*. The other isomer is the threo isomer.

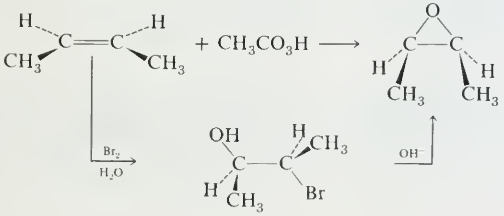


erythro-3-bromo-2-butanol



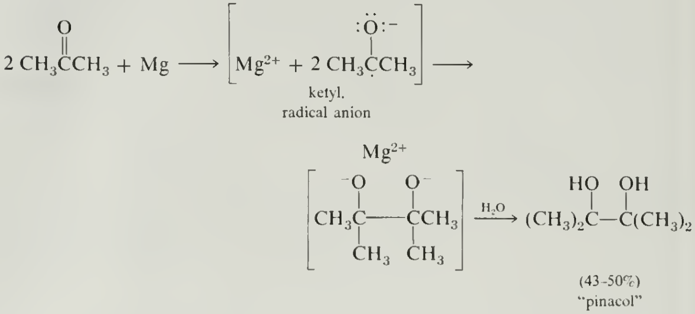
threo-2,3-dibromopentane

2. **RING-OPENING OF EPOXIDES.** Another method for the stereospecific synthesis of 1,2-diols involves the ring opening of epoxides, which may be prepared by the oxidation of alkenes with peroxyacids or by cyclization of 1,2-halohydrins (Section 23.10.A).



The ring opening of epoxides is subject to both acid- and base-catalysis. The reaction occurs by the S_N2 mechanism and involves inversion of configuration at the carbon undergoing reaction (Section 23.10A).

3. **The Pinacol Reaction.** Symmetrical 1,2-diols may be prepared by the **reductive dimerization** of ketones. The reducing agent is generally an electropositive metal, such as sodium or magnesium. The reaction occurs by electron transfer from the metal to the ketone to produce a **ketyl** or **radical anion.** Dimerization of two radical anions affords the dianion of a 1,2-diol, which is hydrolyzed in a separate step to the diol itself.



$$2\,CH_3\overset{\overset{O}{\|}}{C}CH_3 + Mg \longrightarrow \left[Mg^{2+} + 2\,CH_3\overset{\overset{:\ddot{O}:^-}{|}}{\dot{C}}CH_3\right] \longrightarrow$$

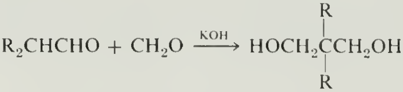
ketyl.
radical anion

$$\overset{Mg^{2+}}{\left[CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{^-O}{|}}{C}}\!-\!\!-\underset{\underset{CH_3}{|}}{\overset{\overset{O^-}{|}}{C}}CH_3\right]} \xrightarrow{H_2O} (CH_3)_2\overset{\overset{HO}{|}}{C}-\overset{\overset{OH}{|}}{C}(CH_3)_2$$

(43-50%)
"pinacol"

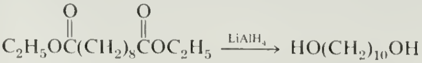
The diol produced from acetone has the trivial name **pinacol** and because of this the reaction is called the **pinacol reaction.**

4. **Miscellaneous Methods.** Certain 1,3-diols may be prepared by the mixed aldol condensation of α,α-dialkylacetaldehydes with formaldehyde. The product aldol is reduced to a 1,3-diol by the Cannizzaro reaction (Section 15.7.G; 15.8.D).



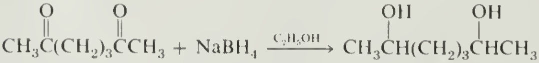
$$R_2CHCHO + CH_2O \xrightarrow{KOH} HOCH_2\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}CH_2OH$$

Other types of diols are generally prepared by reduction of the appropriate dicarbonyl compounds, as indicated by the following examples.



$$C_2H_5O\overset{\overset{O}{\|}}{C}(CH_2)_8\overset{\overset{O}{\|}}{C}OC_2H_5 \xrightarrow{LiAlH_4} HO(CH_2)_{10}OH$$

(75%)
1,10-decanediol

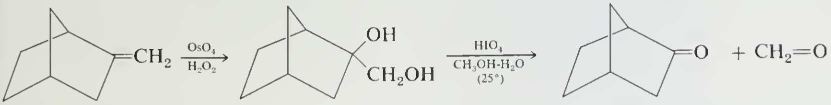


$$CH_3\overset{\overset{O}{\|}}{C}(CH_2)_3\overset{\overset{O}{\|}}{C}CH_3 + NaBH_4 \xrightarrow{C_2H_5OH} CH_3\overset{\overset{OH}{|}}{C}H(CH_2)_3\overset{\overset{OH}{|}}{C}HCH_3$$

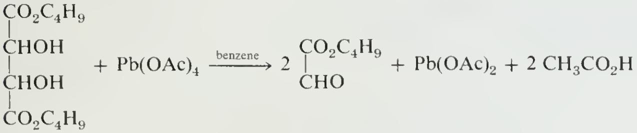
(80%)
2,6-heptanediol

B. *Reactions of diols*

1. **Oxidation.** In addition to the normal reactions of alcohols, certain diols undergo unique reactions. One example is oxidative cleavage of the C—C bond joining the two hydroxy carbons in vicinal diols. The oxidation is brought about by periodic acid or lead tetraacetate, and combined with the hydroxylation process, constitutes a method for the oxidative cleavage of alkenes.



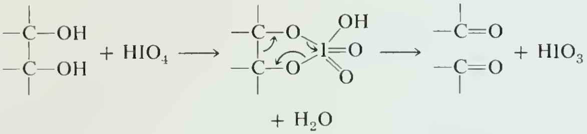
(85%)
bicyclo[2.2.1]heptan-2-one
norbornanone



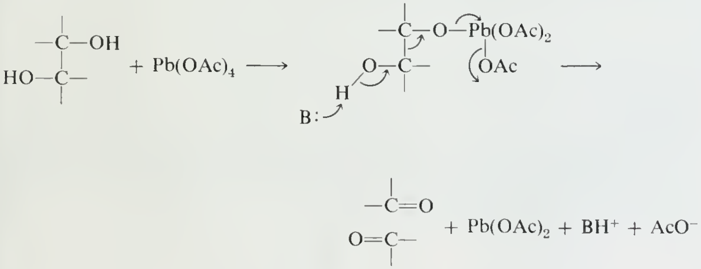
$$\mathrm{C_4H_9O_2C{-}CHOH{-}CHOH{-}CO_2C_4H_9} + \mathrm{Pb(OAc)_4} \xrightarrow{\text{benzene}} 2\,\mathrm{OHC{-}CO_2C_4H_9} + \mathrm{Pb(OAc)_2} + 2\,\mathrm{CH_3CO_2H}$$

(77–87%)

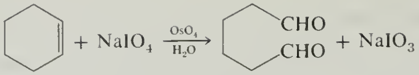
The mechanism of the periodic oxidation has been studied in detail and involves the formation of a cyclic diester of the periodic acid. Decomposition of this cyclic diester yields the two carbonyl fragments and iodic acid.



The lead tetraacetate oxidation is believed to occur by fragmentation of an alkoxy lead compound.



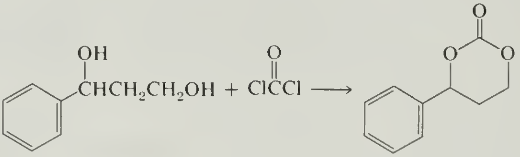
Various procedures have been developed in which alkene hydroxylation and the diol cleavage reactions are combined into one operation. One such reaction (the Lemieux-Johnson reaction) involves treating an alkene with sodium periodate and a catalytic amount of osmium tetroxide.

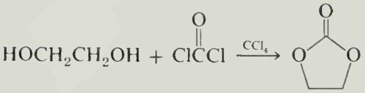


A mixture of 15 ml of ether, 15 ml of water, 0.41 g of cyclohexene, and 0.065 g of OsO_4 is stirred at 25° while 2.32 g of $NaIO_4$ is added over a period of 40 min. After an additional 80 min at 25°, the product adipaldehyde is isolated in 77% yield.

The net result of such reactions is the same as ozonization (Section 12.6.E).

2. FORMATION OF CYCLIC CARBONATE ESTERS. Certain 1,2- and 1,3-diols react with phosgene, $COCl_2$, to form cyclic carbonate esters.

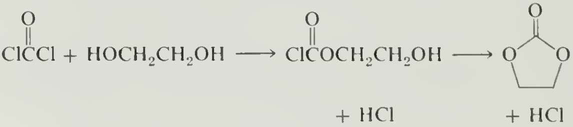




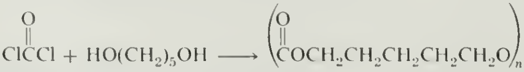
ethylene
carbonate

Gaseous phosgene (1200 g) is bubbled into a solution of 620 g of ethylene glycol in 2000 g of carbon tetrachloride at 30°. The reaction mixture is distilled to obtain 810 g of ethylene carbonate (92%).

The reaction occurs by way of an intermediate chlorocarbonate ester, which is itself a difunctional compound. When a five- or six-membered ring can result, a rapid intramolecular reaction occurs between the hydroxy group on one end of the chain and the acyl chloride on the other.

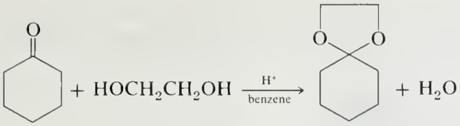


For diols in which the hydroxy groups are separated by more than three atoms, the rate of intramolecular cyclization is much slower. Treatment of such diols with phosgene generally leads to a polymer.



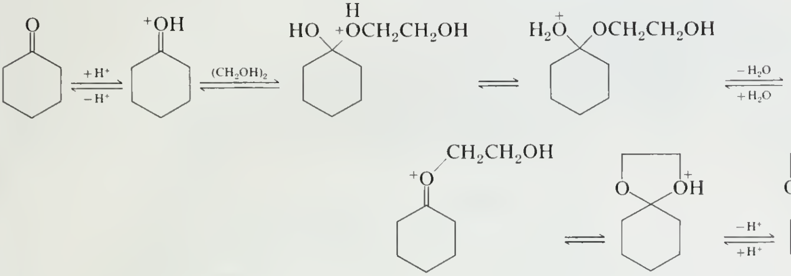
$$\mathrm{Cl}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\mathrm{Cl} + \mathrm{HO(CH_2)_5OH} \longrightarrow \left(\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\mathrm{OCH_2CH_2CH_2CH_2CH_2O}\right)_n$$

3. KETAL AND ACETAL FORMATION. Another reaction of 1,2- and 1,3-diols that results in ring formation is their reaction with aldehydes and ketones under conditions of acid catalysis to form cyclic acetals or ketals (Section 15.7.B).

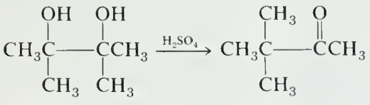


A mixture of 11.8 g of cyclohexanone, 8.2 g of ethylene glycol, 0.05 g of *p*-toluenesulfonic acid and 50 ml of benzene is refluxed under a Dean-Stark trap (page 375) until the theoretical amount of water (2.2 ml) has been collected. The benzene solution is washed with dil. NaOH solution, dried, and evaporated to obtain the ketal in 80% yield.

The probable mechanism for this reaction is identical to that given in Section 15.7.B for ketal formation, except that the addition of the second alcohol group is an *intramolecular* process.



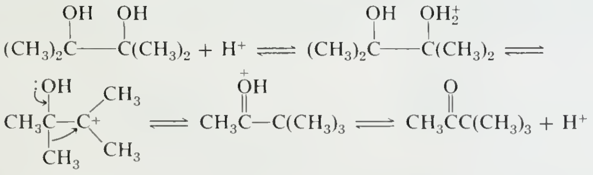
4. **Dehydration: The Pinacol Rearrangement.** Dehydration of 1,2-diols under acid catalysis is frequently accompanied by skeletal rearrangement. For example, pinacol (2,3-dimethylbutane-2,3-diol, page 670) reacts with sulfuric acid to give methyl *t*-butyl ketone, which has the trivial name "pinacolone."



$$CH_3C(OH)(CH_3)C(OH)(CH_3)CH_3 \xrightarrow{H_2SO_4} CH_3C(CH_3)_2COCH_3$$

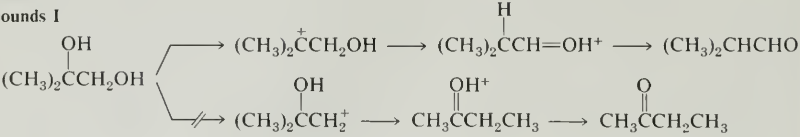
pinacol	pinacolone

The mechanism of this **pinacol rearrangement** involves 1,2 migration of a methyl group and its bonding electron pair from one carbinyl position to an adjacent electron deficient center (Section 11.7.B). The driving force for the rearrangement is formation of a stable oxonium ion, the conjugate acid of a ketone.

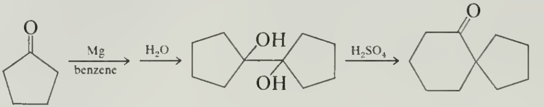


tertiary carbonium ion	oxonium ion

Rearrangement of isobutylene glycol gives only isobutyraldehyde, because the tertiary carbonium ion is formed much more easily than a primary one.

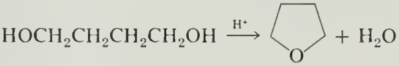

(CH3)2C(OH)CH2OH
(CH3)2C+CH2OH
(CH3)2C(H)CH=OH+
(CH3)2CHCHO
(CH3)2C(OH)CH2+
CH3C(=OH+)CH2CH3
CH3C(=O)CH2CH3

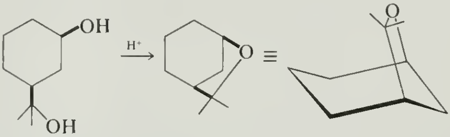
By combining the pinacol reaction with this acid-catalyzed rearrangement process, interesting and unusual compounds may be prepared.


Mg
benzene
H2O
OH
OH
H2SO4

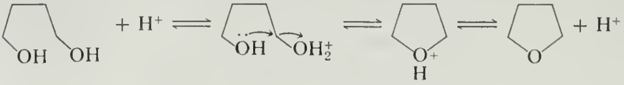
spiro[4.5]decan-6-one

Dehydration of 1,4- and 1,5-diols often leads to the formation of cyclic ethers, particularly when one of the hydroxy groups is tertiary.

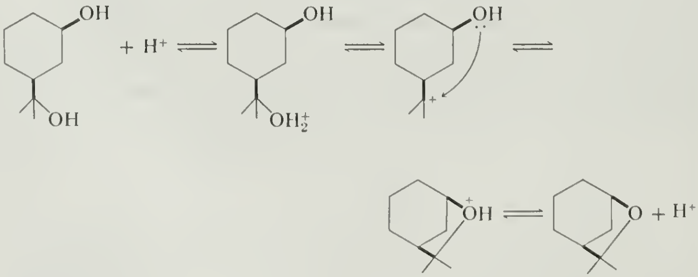

HOCH2CH2CH2CH2OH
H+
O
+ H2O



In the first case, the reaction undoubtedly occurs by intramolecular nucleophilic displacement on the initially formed oxonium ion.


OH
OH
+ H+
OH
OH2+
O+
H
O
+ H+

The second reaction probably involves the formation of a tertiary carbonium ion, which is trapped by the secondary hydroxy group.

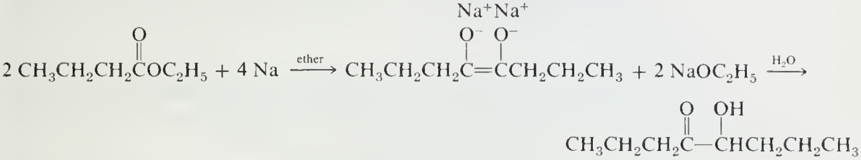

OH
OH
+ H+
OH
OH2+
OH
+
OH+
O
+ H+

In this case the cyclization is possible because the two groups are *cis*. The *trans* analog cannot give a cyclic product.

24.4
Hydroxy Aldehydes and Ketones

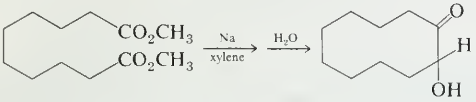
A. *Synthesis*

1. **The Acyloin Condensation.** α-Hydroxy ketones result from the treatment of esters with sodium in an inert solvent such as ether or benzene. Such compounds are called **acyloins** and the reaction is called the **acyloin condensation.** The initial product of the reaction is the disodium salt of an enediol, which is hydrolyzed to give the acyloin.



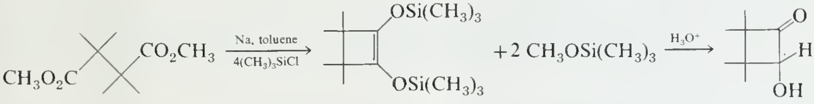
$$2\,CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 + 4\,Na \xrightarrow{\text{ether}} CH_3CH_2CH_2\overset{\overset{Na^+}{O^-}}{\overset{|}{C}}=\overset{\overset{Na^+}{O^-}}{\overset{|}{C}}CH_2CH_2CH_3 + 2\,NaOC_2H_5 \xrightarrow{H_2O} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}HCH_2CH_2CH_3$$

The acyloin condensation is a useful method for the synthesis of ring compounds, particularly for medium- sized rings (8–13 members). In such cases, the reaction must be carried out under conditions of high dilution, to suppress intermolecular reactions.



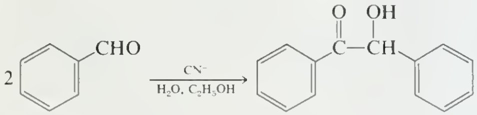
(66%)
2-oxocyclodecanol

The chief side reaction is the Claisen condensation (Section 26.3.A), which stems from the alkoxide ion produced as a by-product in the reaction. In a recent modification, which often leads to much higher yields, the reaction is carried out in the presence of chlorotrimethylsilane, which reacts with any alkoxide produced and also silylates the product. The product in this case is the bis-trimethylsilyl ether, which is cleaved by dilute acid to give the acyloin.



(60%)

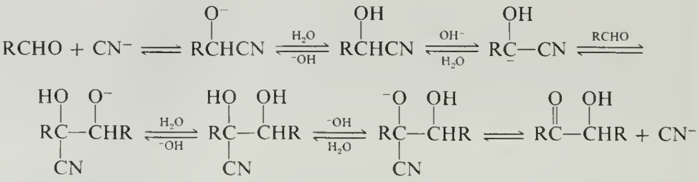
2. **The Benzoin Condensation.** Aromatic aldehydes are converted into acyloins by sodium cyanide in aqueous ethanol. The reaction is called the benzoin condensation, and cyanide ion is a specific catalyst.



(92%)
benzoin

benzaldehyde

The catalyst functions by first adding to the carbonyl group to form the cyanohydrin (see Section 15.7.F). The former aldehyde hydrogen is now α to a cyano group and is sufficiently acidic to be removed by a base. The resulting carbanion then adds to another molecule of aldehyde to give an intermediate cyano diol. Elimination of cyanide ion yields the acyloin and regenerates the catalyst.

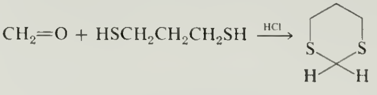


$$RCHO + CN^- \rightleftharpoons R\overset{O^-}{\overset{|}{C}}HCN \underset{^-OH}{\overset{H_2O}{\rightleftharpoons}} R\overset{OH}{\overset{|}{C}}HCN \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} R\overset{OH}{\overset{|}{\underset{-}{C}}}{-}CN \overset{RCHO}{\rightleftharpoons}$$

$$R\overset{HO}{\overset{|}{\underset{\underset{CN}{|}}{C}}}{-}\overset{O^-}{\overset{|}{C}}HR \underset{^-OH}{\overset{H_2O}{\rightleftharpoons}} R\overset{HO}{\overset{|}{\underset{\underset{CN}{|}}{C}}}{-}\overset{OH}{\overset{|}{C}}HR \underset{H_2O}{\overset{^-OH}{\rightleftharpoons}} R\overset{^-O}{\overset{|}{\underset{\underset{CN}{|}}{C}}}{-}\overset{OH}{\overset{|}{C}}HR \rightleftharpoons R\overset{O}{\overset{\|}{C}}{-}\overset{OH}{\overset{|}{C}}HR + CN^-$$

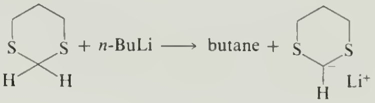
3. α-Hydroxy Aldehydes and Ketones from 1,3-dithianes. α-Hydroxy aldehydes and ketones are also available by way of a recently introduced method, which uses the anion of a 1,3-dithiane.

1,3-Dithiane itself is the thioacetal of formaldehyde, and it may be prepared by the treatment of formaldehyde with 1,3-propanedithiol.

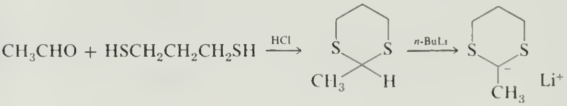


1,3-dithiane

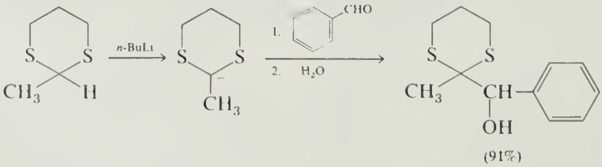
The hydrogens on the carbon between the two sulfur atoms are moderately acidic ($pK_a = 31.5$), and may be removed by such strong bases as n-butyllithium. The stability of the anion appears to be due to the polarizability of the adjacent sulfur atoms.



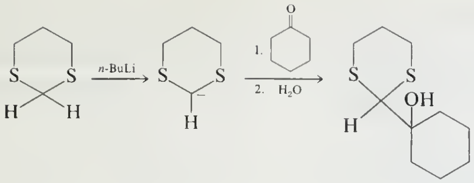
Analogous anions may be produced from other 1,3-dithianes.



The 1,3-dithianyl anions are nucleophilic and undergo addition to aldehyde and ketone carbonyl groups.

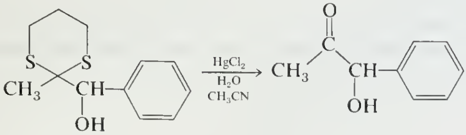


(91%)


n-BuLi
1.
2. H₂O
S
H
OH

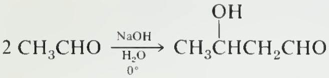
(85%)

The resulting thioacetals are stable to normal hydrolytic conditions, but hydrolyze easily when treated with mercuric chloride in aqueous acetonitrile.


CH₃
CH
OH
HgCl₂
H₂O
CH₃CN
O
C

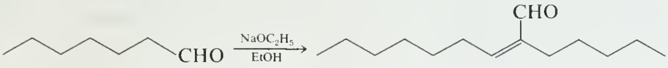
(90%)

4. THE ALDOL CONDENSATION. β-Hydroxy aldehydes and ketones are available by the aldol condensation, which has been discussed previously (Section 15.7.G).



$$2\ CH_3CHO \xrightarrow[H_2O,\ 0^\circ]{NaOH} CH_3\overset{\overset{\displaystyle OH}{|}}{C}HCH_2CHO$$

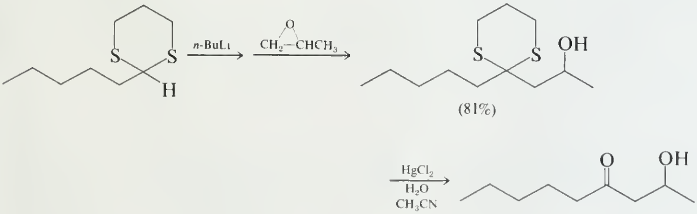
Under more forcing conditions, such as are necessary to accomplish the initial condensation with aldehydes of more than six carbons, the β-hydroxy aldehyde undergoes dehydration to give the α,β-unsaturated aldehyde.


CHO
NaOC₂H₅
EtOH
reflux
CHO

heptanal

(70%)
2-pentyl-2-nonenal

5. β-HYDROXY ALDEHYDES AND KETONES FROM 1,3-DITHIANES. β-Hydroxy ketones have also been prepared using 1,3-dithianyl anions (page 676). In this case, the anion is used in the ring opening of an epoxide. Hydrolysis of the thioketal grouping affords the β-hydroxy ketone.

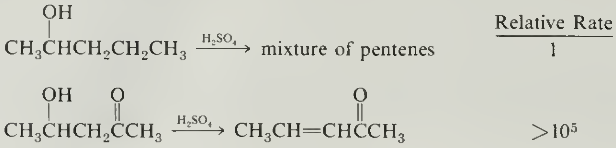

S
H
n-BuLi
O
CH₂—CHCH₃
OH
HgCl₂
H₂O
CH₃CN
O

(81%)

(83%)
4-oxo-2-nonanol

B. *Reactions*

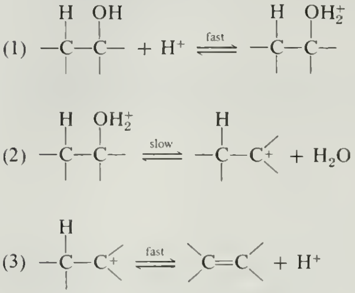
1. **DEHYDRATION.** β-Hydroxy aldehydes and ketones undergo acid-catalyzed dehydration more easily than normal alcohols. The following examples illustrate the magnitude of the differences.



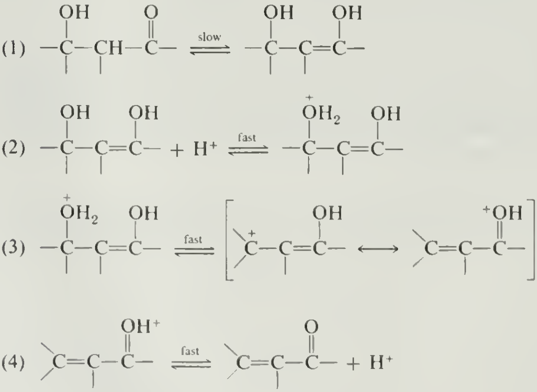
$$CH_3\overset{OH}{C}HCH_2CH_2CH_3 \xrightarrow{H_2SO_4} \text{mixture of pentenes}$$

$$CH_3\overset{OH}{C}HCH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{H_2SO_4} CH_3CH{=}CH\overset{O}{\overset{\|}{C}}CH_3$$

Recall that the dehydration of a secondary or tertiary alcohol involves the formation of an intermediate carbonium ion; the rate of formation of this intermediate determines the rate of dehydration (Section 11.7.B).

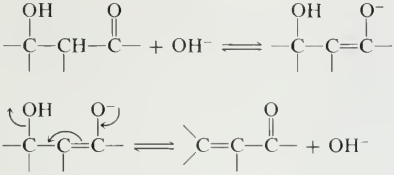


β-Hydroxy ketones undergo dehydration by a different mechanism, involving the *enol* form of the ketone. The rate-determining step is formation of the enol. Elimination of water from the protonated enol gives a stable oxonium ion, which is simply the protonated form of the α,β-unsaturated ketone.

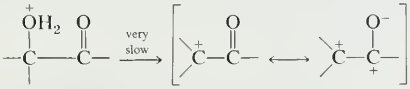


Normal alcohols do not undergo dehydration under basic conditions, as shown by the fact that *t*-butyl alcohol solutions of potassium *t*-butoxide are quite stable

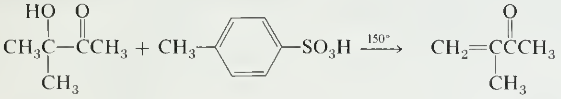
(Section 11.7.A). However, β-hydroxy aldehydes and ketones undergo dehydration fairly easily under basic conditions. In this case, the dehydration actually proceeds via the enolate ion (Section 15.6.B).



In contrast to the easy dehydration of β-hydroxy carbonyl compounds, α-hydroxy ketones undergo acid-catalyzed dehydration with even *more* difficulty than normal alcohols. In this case, the intermediate carbonium ion would be destabilized by the inductive effect of the adjacent carbonyl group.

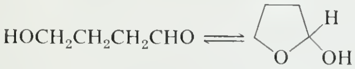


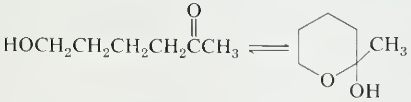
An example is the preparation of 3-methylbut-3-en-2-one by heating a mixture of the α-hydroxy ketone and p-toluenesulfonic acid in an oil bath at 150°. These conditions are far more vigorous than required for tertiary alcohols.



(74%)
3-methylbut-3-en-2-one

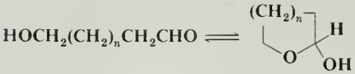
2. CYCLIC HEMIACETALS AND HEMIKETALS. Hydroxy aldehydes and ketones usually exist, to some extent, in a cyclic hemiacetal or hemiketal form (Section 15.7.B), particularly when the ring is five- or six-membered.





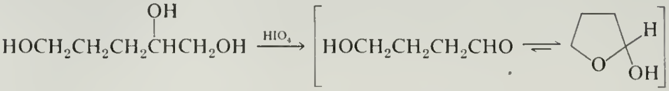
The data in Table 24.2 show that the cyclic form predominates with 4- and 5-hydroxy aldehydes. The formation of a cyclic hemiacetal from such a hydroxy carbonyl compound is subject to acid or base catalysis, as in the formation of acetals by intermolecular reaction (Section 15.7.B). However, when five- or six-membered rings are involved, the cyclization is so facile that it occurs even under neutral conditions. Thus, any reaction that would nominally give a 4- or 5-hydroxy

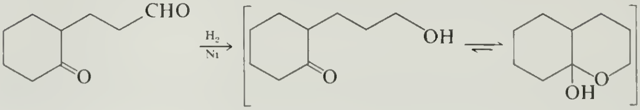
TABLE 24.2


HOCH$_2$(CH$_2$)$_n$CH$_2$CHO
(CH$_2$)$_n$
H
O
OH

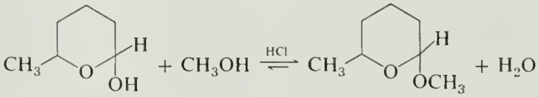
n	Ring Size	Per Cent Free Aldehyde
1	5	11
2	6	6
3	7	85

carbonyl compound will yield an equilibrium mixture of the open chain and ring closed isomers.

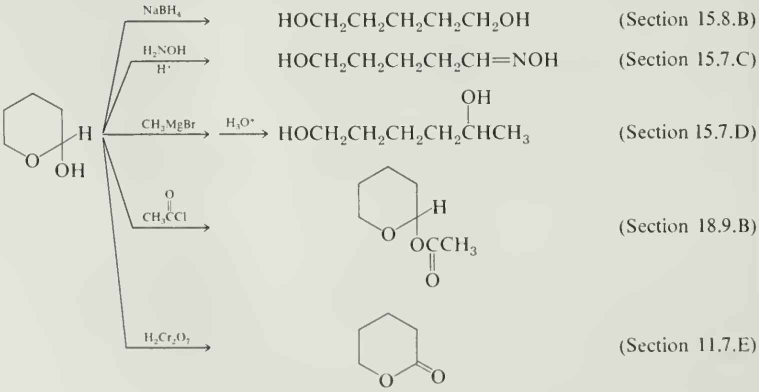

OH
HOCH$_2$CH$_2$CH$_2$CHCH$_2$OH
HIO$_4$
HOCH$_2$CH$_2$CH$_2$CHO
H
O
OH


CHO
O
H$_2$
Ni
OH
O
O
OH

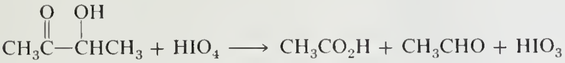
As with noncyclic hemiacetals, these compounds react with alcohols under acid catalysis to give acetals or ketals.


CH$_3$
O
H
OH
+ CH$_3$OH
HCl
CH$_3$
O
H
OCH$_3$
+ H$_2$O

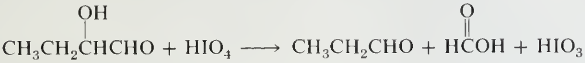
Since there is usually a small amount of the open chain hydroxy carbonyl compound in equilibrium with the cyclic hemiacetal form, solutions of such compounds can show reactions of either form, as the following examples show.


O
H
OH
NaBH$_4$
HOCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH
(Section 15.8.B)
H$_2$NOH
H$^+$
HOCH$_2$CH$_2$CH$_2$CH$_2$CH=NOH
(Section 15.7.C)
CH$_3$MgBr
H$_3$O$^+$
OH
HOCH$_2$CH$_2$CH$_2$CH$_2$CHCH$_3$
(Section 15.7.D)
O
CH$_3$CCl
O
H
OCCH$_3$
O
(Section 18.9.B)
H$_2$Cr$_2$O$_7$
O
O
(Section 11.7.E)

3. **Oxidation.** α-Hydroxy aldehydes and ketones, like 1,2-diols, are oxidized with C—C bond cleavage by periodic acid.



$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{C}HCH_3 + HIO_4 \longrightarrow CH_3CO_2H + CH_3CHO + HIO_3}$$



$$\mathrm{CH_3CH_2\overset{\overset{OH}{|}}{C}HCHO + HIO_4 \longrightarrow CH_3CH_2CHO + H\overset{\overset{O}{\|}}{C}OH + HIO_3}$$

The reaction constitutes a useful method for structure determination in the carbohydrate field (Chapter 25).

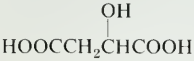
24.5
Hydroxy Acids

Many hydroxy acids are important in nature and, correspondingly, have trivial names that are in common use.

$\mathrm{HOCH_2COOH}$ glycolic acid

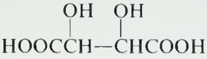
$\mathrm{CH_3CHOHCOOH}$ lactic acid

Glycolic acid is a constituent of cane sugar juice. Lactic acid is responsible for the characteristic odor and taste of sour milk. Other important hydroxy acids are dicarboxylic acids. Malic acid occurs in fruit juices. Tartaric acid has been known since antiquity as the mono potassium salt (cream of tartar) deposited in the lees of wine. The hydroxy acids with asymmetric carbons are optically active in nature.



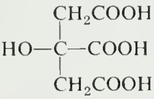
$$\mathrm{HOOCCH_2\overset{\overset{OH}{|}}{C}HCOOH}$$

malic acid



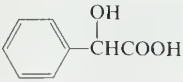
$$\mathrm{HOOC\overset{\overset{OH}{|}}{C}H-\overset{\overset{OH}{|}}{C}HCOOH}$$

tartaric acid



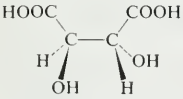
$$\mathrm{HO-\overset{\overset{CH_2COOH}{|}}{\underset{\underset{CH_2COOH}{|}}{C}}-COOH}$$

citric acid

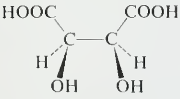


mandelic acid

Both the (+) and (−) forms of tartaric acid are found in nature, although the (+) acid is by far the more common: Two optically inactive forms are known. **Racemic acid,** m.p. 206°, is simply a mixture of (+)- and (−)-tartaric acid. *meso*-Tartaric acid, m.p. 140°, is the R,S diastereomer.



(+)-(R,R)-tartaric acid



meso-tartaric acid

Tartaric acid played an important role in the development of stereochemistry. In 1848, Louis Pasteur noticed that crystals of sodium ammonium tartrate are chiral and that all of the crystals show chirality in the same sense. He then proceeded to investigate 19 different tartrate salts and found that they all gave chiral crystals. He postulated that there was a relationship between the chirality of the crystals and the fact that, in solution, the salts rotate the plane of polarized light.

However, there was a problem. **Racemic acid**, obtained as a by-product in the crystallization of tartaric acid, was also known, and it was optically inactive. It was known that racemic acid and tartaric acid were isomers and Mitscherlich had reported that crystals of sodium ammonium tartrate and sodium ammonium racemate were identical in all respects except that the tartrate gave a dextrorotatory solution whereas the racemate gave an optically inactive solution.

Pasteur repeated Mitscherlich's work on sodium ammonium racemate and was disappointed to discover that Mitscherlich had been correct and that crystals of the racemate salt are indeed chiral. Upon closer examination, however, he noticed that the crystals are not all chiral in the same sense. In his words, "the hemihedral faces which in the tartrate are all turned one way are in the racemate inclined sometimes to the right and sometimes to the left." In short, the racemate salt gives a mixture of nonsuperimposable mirror image crystals. Using a pair of tweezers, Pasteur carefully separated the left-handed from the right-handed crystals, dissolved each in water, and measured their optical rotations. To his great excitement, he discovered that one solution was dextrorotatory and the other was levorotatory. When he converted the separated salts back to the free acids, he found that one was identical with natural (+)-tartaric acid and that the other was a new tartaric acid isomer, identical in all respects save the sign of its optical rotation. Pasteur had accomplished the first resolution—separation of a racemate into its component enantiomers.

Pasteur's work paved the way for an understanding of stereoisomerism. He made the important suggestion that, since the crystals of the enantiomeric salts show handedness, the molecules themselves might also show handedness—and this before the idea of chemical bonds had even been conceived.

Citric acid is a hydroxytricarboxylic acid that is widespread in nature and is especially prevalent, as its trivial name implies, in the juice of citrus fruits. These hydroxy acids are related to carbohydrates (Chapter 25) and to amino acids (Chapter 28).

A. *Synthesis*

1. **HYDROLYSIS OF HALOCARBOXYLIC ACIDS.** α-Hydroxy acids can be prepared from α-halo acids by hydrolysis.

$$CH_3CHBrCOOH \xrightarrow{OH^-} CH_3CHOHCO_2^-$$

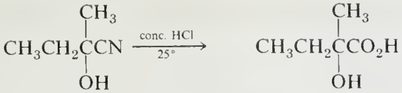
Recall that α-halo acids can be prepared from the carboxylic acids by the Hell-Vollhard-Zelinsky bromination (Section 17.7.B).

β-Halo acids eliminate readily in base to give unsaturated acids.

$$CH_3CHBrCH_2COOH \xrightarrow{OH} CH_3CH{=}CHCO_2^-$$

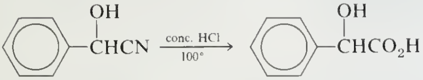
Hydrolysis is generally satisfactory for other halo acids.

2. **HYDROLYSIS OF CYANOHYDRINS.** The most general method for the formation of α-hydroxy acids is the hydrolysis of cyanohydrins, which are readily available from the reaction of HCN with aldehydes or ketones (Section 15.7.F). Since the addition of HCN to a carbonyl group is reversed by the strongly basic conditions necessary to hydrolyze a nitrile to an acid, the hydrolysis is done under acidic conditions.



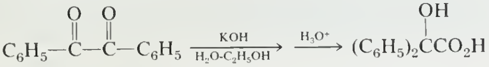
$$CH_3CH_2\overset{CH_3}{\underset{OH}{C}}CN \xrightarrow[25°]{\text{conc. HCl}} CH_3CH_2\overset{CH_3}{\underset{OH}{C}}CO_2H$$

(55%)
2-methyl-2-hydroxybutanoic acid



(70%)
α-hydroxyphenylacetic acid
mandelic acid

3. **THE BENZILIC ACID REARRANGEMENT.** α-Hydroxy acids also result when α-diketones are treated with strong base. The reaction is called the benzilic acid rearrangement after the trivial name of the parent system.



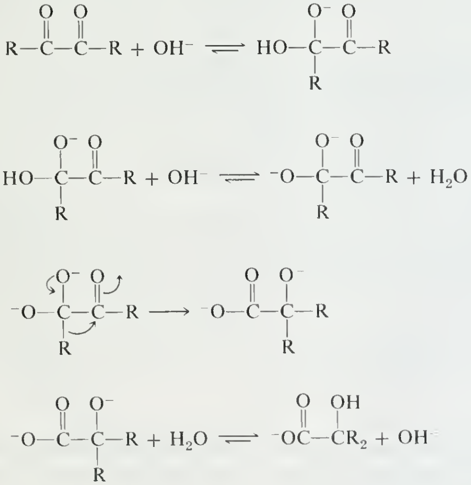
$$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5 \xrightarrow[\substack{H_2O\text{-}C_2H_5OH \\ 100°}]{KOH} \xrightarrow{H_3O^+} (C_6H_5)_2\overset{OH}{\overset{|}{C}}CO_2H$$

(95%)

benzil

benzilic acid

The mechanism of this rearrangement involves the addition of hydroxide ion to one of the carbonyl groups. This initially formed adduct is probably ionized further to a dianion (page 397), which undergoes a molecular rearrangement to give the dianion of the α-hydroxy acid. The involvement of a dianion explains the strongly basic conditions required.



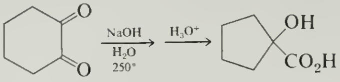
$$R-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R + OH^- \rightleftharpoons HO-\overset{O^-}{\underset{R}{C}}-\overset{O}{\overset{\|}{C}}-R$$

$$HO-\overset{O^-}{\underset{R}{C}}-\overset{O}{\overset{\|}{C}}-R + OH^- \rightleftharpoons {}^-O-\overset{O^-}{\underset{R}{C}}-\overset{O}{\overset{\|}{C}}-R + H_2O$$

$${}^-O-\overset{O^-}{\underset{R}{C}}-\overset{O}{\overset{\|}{C}}-R \longrightarrow {}^-O-\overset{O}{\overset{\|}{C}}-\overset{O^-}{\underset{R}{C}}-R$$

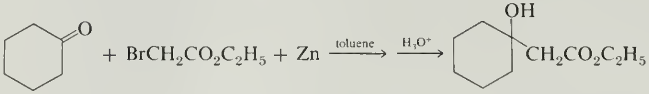
$${}^-O-\overset{O}{\overset{\|}{C}}-\overset{O^-}{\underset{R}{C}}-R + H_2O \rightleftharpoons {}^-O\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}R_2 + OH^-$$

When the α-diketone is cyclic, the rearrangement serves as a method of **ring contraction.**

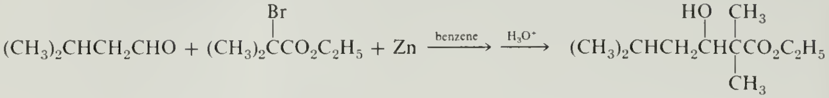


(80%)

4. **The Reformatsky Reaction.** β-Hydroxy esters result when an aldehyde or a ketone is treated with an α-halo ester and zinc in an inert solvent (the Reformatsky reaction).



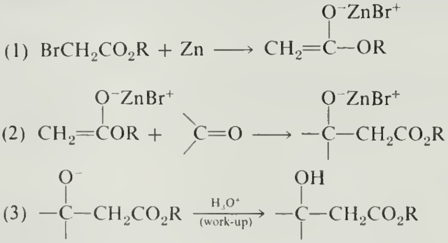
(70%)
ethyl (1-hydroxycyclohexyl)acetate



$$(CH_3)_2CHCH_2CHO + (CH_3)_2\overset{Br}{\overset{|}{C}}CO_2C_2H_5 + Zn \xrightarrow{\text{benzene}} \xrightarrow{H_3O^+} (CH_3)_2CHCH_2\overset{HO}{\overset{|}{C}}H\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}CO_2C_2H_5$$

(65%)
ethyl 2,2,5-trimethyl-3-hydroxyhexanoate

The reactive intermediate in the Reformatsky reaction is an organozinc reagent that may be regarded as the anion of an ester (Section 18.8), closely associated with a zinc cation. This carbanion has nucleophilic properties and undergoes addition to the carbonyl group of the aldehyde or ketone.

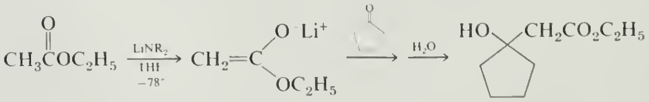


$$(1)\quad BrCH_2CO_2R + Zn \longrightarrow CH_2{=}\overset{O^-ZnBr^+}{\overset{|}{C}}{-}OR$$

$$(2)\quad CH_2{=}\overset{O^-ZnBr^+}{\overset{|}{C}}OR + \;\rangle C{=}O \longrightarrow -\overset{O^-ZnBr^+}{\overset{|}{\underset{|}{C}}}-CH_2CO_2R$$

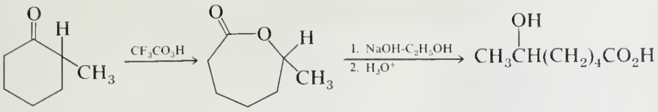
$$(3)\quad -\overset{O^-}{\overset{|}{\underset{|}{C}}}-CH_2CO_2R \xrightarrow[\text{(work-up)}]{H_3O^+} -\overset{OH}{\overset{|}{\underset{|}{C}}}-CH_2CO_2R$$

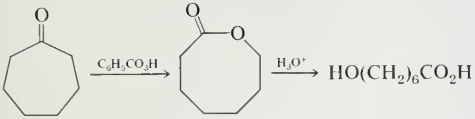
A more recent version of the same reaction utilizes the lithium enolate of an ester, which is prepared by treating the ester with a lithium dialkylamide (Section 18.8). Addition of an aldehyde or ketone gives the β-hydroxy ester in good yield.



(93%)

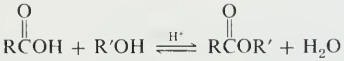
5. **Hydrolysis of Lactones.** Various hydroxy acids are available by the hydrolysis of lactones, which may be obtained by the Baeyer-Villiger oxidation of cyclic ketones (Section 15.8.A).





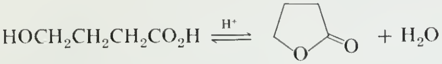
B. *Reactions*

1. **Formation of Lactones.** Recall that carboxylic acids react with alcohols under acid catalysis to yield esters (Section 17.7.C).



$$R\overset{O}{\overset{\|}{C}}OH + R'OH \overset{H^+}{\rightleftharpoons} R\overset{O}{\overset{\|}{C}}OR' + H_2O$$

A hydroxy acid contains both of these functional groups, and thus it can undergo intramolecular esterification to yield a cyclic ester, called a **lactone.**

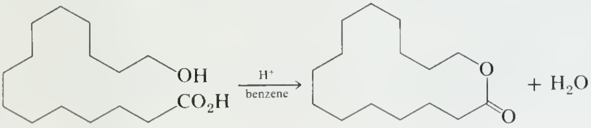


γ-hydroxybutyric acid

γ-butyrolactone

Lactonization, like normal esterification, is an equilibrium process. Only when the lactone has a five- or six-membered ring is there a substantial amount of lactone present under equilibrium conditions, as shown by the data in Table 24.3. The data in Table 24.3 also reveal that alkyl substitution on the ring increases the amount of lactone present at equilibrium.

Although the larger lactones do not exist to any appreciable extent in *equilibrium* with the free hydroxy acids, such lactones may be prepared under the proper conditions. In such cases, it is necessary to treat the hydroxy acid with acid under conditions where the water formed in the reaction is removed so as to shift the unfavorable equilibrium toward the lactone. It is also necessary to operate in very dilute solution so as to minimize the intermolecular esterification reaction, which leads to a polymer.

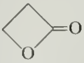
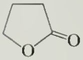
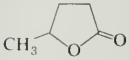
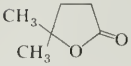
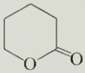
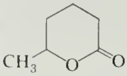
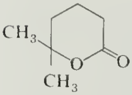
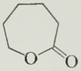


15-hydroxypentadecanoic acid
(0.007 *M*)

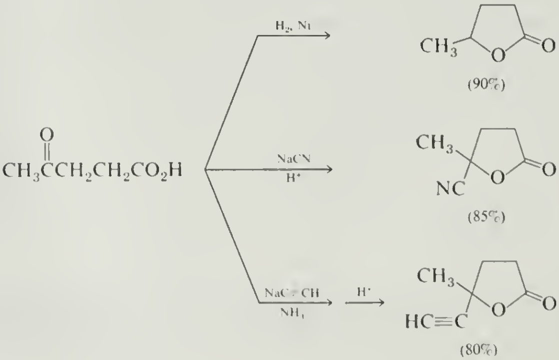
(100%)
15-hydroxypentadecanoic
acid lactone

γ-Lactones and δ-lactones form from the hydroxy acids so readily that it is often not necessary even to add acid to catalyze the intramolecular esterification; mere traces of acid in the solvent or on the glassware suffice to bring about

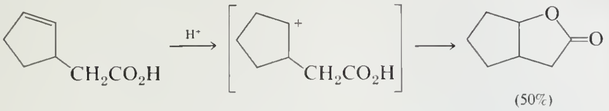
TABLE 24.3

	Equilibrium Composition	
Lactone Formula	Hydroxy Acid, %	Lactone, %
	100	0
	27	73
	5	95
	2	98
	91	9
	79	21
	75	25
	≈100	≈0

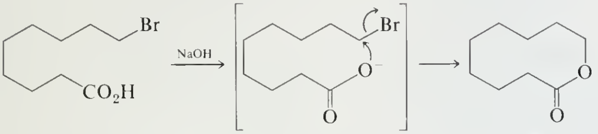
lactonization. Thus, in any reaction which would yield a 4- or 5-hydroxy acid, the corresponding lactone is often the isolated product.



Lactones may also result from reactions of other substituted carboxylic acids, as shown by the following examples.



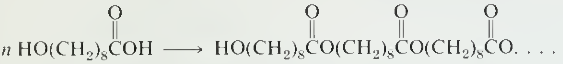
(50%)



(56%)

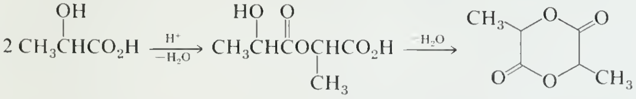
In the latter example, the reaction must be done under high dilution to suppress intermolecular displacement reactions.

2. **Polymerization, Lactides.** As discussed in the previous section, 4- and 5-hydroxy acids react rapidly in an intramolecular process to afford lactones. Other hydroxy acids, which cannot form 5- or 6-membered rings, undergo polymerization unless the reaction is carried out under high dilution conditions.



$$n\ \mathrm{HO(CH_2)_8\overset{\overset{O}{\|}}{C}OH} \longrightarrow \mathrm{HO(CH_2)_8\overset{\overset{O}{\|}}{C}O(CH_2)_8\overset{\overset{O}{\|}}{C}O(CH_2)_8\overset{\overset{O}{\|}}{C}O}\ldots$$

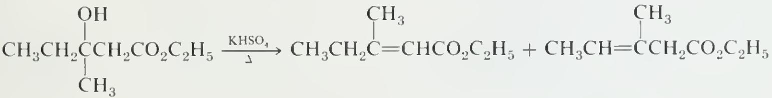
α-Hydroxy acids cannot form a stable lactone ring (three-membered), so they undergo intermolecular self-esterification under acid catalysis. However, the initial dimeric product is now a form of 5-hydroxy acid, so lactonization occurs. The product, which is a dilactone containing two molecules of the original α-hydroxy acid, is called a lactide.



lactic acid

lactide

3. **Dehydration.** Like β-hydroxy aldehydes and ketones, β-hydroxy acids and their derivatives undergo dehydration easily under acidic conditions. The mechanism is similar to that for dehydration of the other β-hydroxy carbonyl compounds discussed previously (Section 24.4.B under the Benzoin Condensation). Since conjugation of a double bond with an acid or ester carbonyl group is less stabilizing than with an aldehyde or ketone carbonyl (Section 20.3), mixtures of the α,β-unsaturated and β,γ-unsaturated acid often result from dehydration of a β-hydroxy acid.

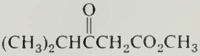


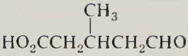
$$\mathrm{CH_3CH_2\overset{OH}{\underset{CH_3}{C}}CH_2CO_2C_2H_5} \xrightarrow[\Delta]{KHSO_4} \mathrm{CH_3CH_2\overset{CH_3}{C}{=}CHCO_2C_2H_5} + \mathrm{CH_3CH{=}\overset{CH_3}{C}CH_2CO_2C_2H_5}$$

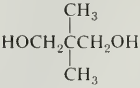
(57%) (43%)

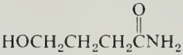
PROBLEMS

1. Name the following compounds:

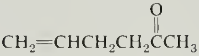
(a) 
$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_2CO_2CH_3$

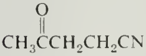
(e) 
$HO_2CCH_2\overset{CH_3}{\overset{|}{C}}HCH_2CHO$

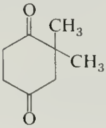
(b) 
$HOCH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2OH$

(f) 
$HOCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2$

(c) $HOCH_2CH_2CH_2CO_2H$

(g) 
$CH_2{=}CHCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

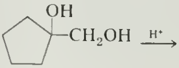
(d) 
$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CN$

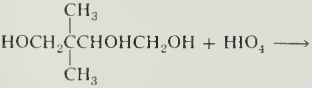
(h) 

2. The following names are a mixture of trivial, common, and IUPAC nomenclature. Which is which? Write a structure for each name.

(a) β-hydroxyvaleric acid
(b) methyl lactate
(c) tetramethylene glycol
(d) 3-hydroxypentanoic acid
(e) pinacol
(f) ethyl benzilate
(g) β-ketocaproic acid
(h) 3-oxohexanoic acid
(i) benzoin
(j) α-methoxyphenylacetic acid
(k) γ-valerolactone
(l) δ-valerolactone

3. Give the principal product(s) of each of the following reactions:

(a) 

(b) 
$HOCH_2\overset{CH_3}{\underset{CH_3}{C}}CHOHCH_2OH + HIO_4 \longrightarrow$

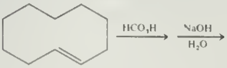
(c) $(CH_3)_2CHCHO + HOCH_2CH_2OH \xrightarrow{H^+}$

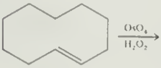
(d) $HO(CH_2)_6COOH \xrightarrow{\Delta}$

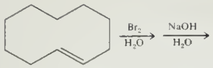
(e) $CH_3CH_2CHOHCOOH \xrightarrow{\Delta}$

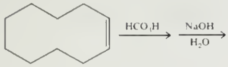
(f) $HOCH_2CH_2CH_2COOH \xrightarrow{\Delta}$

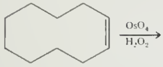
4. For each reaction, what is the stereochemistry of the 1,2-cyclodecanediol produced.

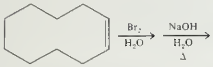
(a) 

(b) 

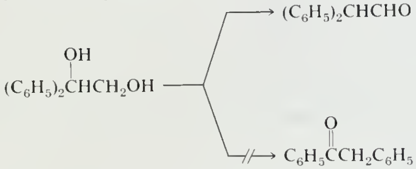
(c) 

(d) 

(e) 

(f) 

5. Pinacol rearrangement of 1,1-diphenyl-1,2-ethanediol gives diphenylacetaldehyde and not phenylacetophenone. Explain.



$$(C_6H_5)_2\overset{OH}{\overset{|}{C}}HCH_2OH \longrightarrow (C_6H_5)_2CHCHO$$

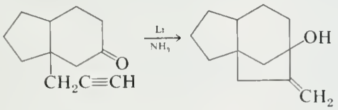
$$(C_6H_5)_2\overset{OH}{\overset{|}{C}}HCH_2OH \not\longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}CH_2C_6H_5$$

6. (a) Write alternative Lewis structures for periodic acid, $HOIO_3$, and iodic acid, $HOIO_2$, making use of $^-O—I^+$ or O=I bonds. Be careful to count electrons and assign formal charges properly; note that iodic acid has a lone pair of electrons on iodine. Follow the changes in electron pairs symbolized in the cyclic mechanism on page 671.
   (b) *cis*-1,2-Cyclopentanediol is oxidized to glutaraldehyde (1,5-pentanedial) by periodic acid much more rapidly than the *trans* isomer. Explain.
   (c) Suggest a method whereby periodic acid could be used to distinguish between 1,2,3-pentanetriol and 1,2,4-pentanetriol.

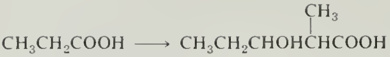
7. Suggest a method whereby one might distinguish *cis*-1,3-cyclohexanediol from *trans*-1,3-cyclohexanediol.

8. *cis*-1,2-Cyclopentanediol reacts with benzaldehyde (C_6H_5CHO) in the presence of HCl and anhydrous magnesium sulfate to give two compounds with the formula $C_{12}H_{14}O_2$. What are the structures of the two compounds? What is the function of the magnesium sulfate? Explain why *trans*-1,2-cyclopentanediol does not undergo a similar reaction.

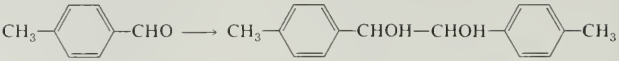
9. The following reaction is similar to the acyloin condensation. Propose a mechanism for the reaction.

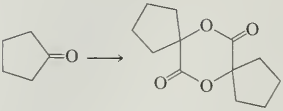


10. Show how one may accomplish each of the following conversions in a practical manner.
   (a) $CH_3COCH_3 \longrightarrow (CH_3)_3CCOOH$

(b) 

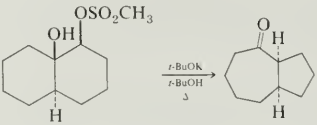
$$CH_3CH_2COOH \longrightarrow CH_3CH_2CHOH\overset{CH_3}{\overset{|}{C}}HCOOH$$

(c) 

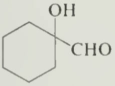
(d) 

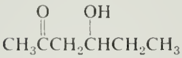
(e) $CH_3CH_2COOH \longrightarrow CH_3CH_2CHOHCHOHCH_2CH_3$

11. Propose a mechanism for the following reaction:

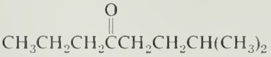


12. Making use of 1,3-dithiane, show how each of the following compounds may be synthesized.

(a) 

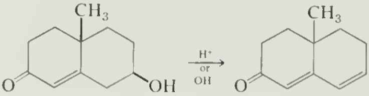
(b) 

$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{OH}{\overset{|}{C}}HCH_2CH_3$$

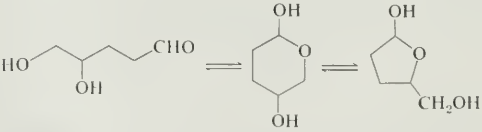
(c) 

$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH(CH_3)_2$$

13. The following dehydration is exceedingly facile. Explain.

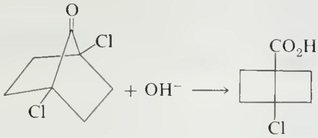


14. (a) 4,5-Dihydroxyhexanal exists in solution largely as a cyclic hemiacetal. From the data in Table 24.2, predict which form will predominate at equilibrium.



(b) When 4,5-dihydroxyhexanal is treated with silver oxide and the resulting dihydroxyhexanoic acid is treated with acid, a lactone results. What is the structure of the lactone (see Table 24.3)?

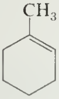
15. (a) Propose a mechanism for the following reaction:



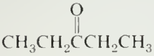
(b) Name the reactant and the product in the reaction.

16. Explain why *cis*-3-hydroxycyclohexanecarboxylic acid forms a lactone, whereas the *trans* isomer does not. Write a three-dimensional structure for the lactone. Molecular models will help greatly in answering this question.

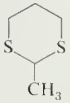
17. Give the expected product for each reaction sequence.

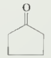
(a) 

$\xrightarrow[H_2O_2]{OsO_4} (C_7H_{14}O_2) \xrightarrow{HIO_4} (C_7H_{12}O_2)$

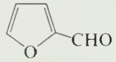
(b) 

$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 \xrightarrow[\text{benzene}]{Mg} \xrightarrow{H_2O} (C_{10}H_{22}O_2) \xrightarrow[\Delta]{H_3O^+} (C_{10}H_{20}O)$

(c) 

$\xrightarrow{BuLi}$ 

$\longrightarrow (C_{10}H_{18}OS_2) \xrightarrow[\text{aq } CH_3CN]{HgCl_2} C_7H_{12}O_2$

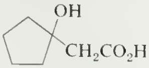
(d) 

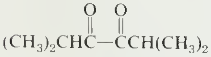
$\xrightarrow[C_2H_5OH]{KCN} (C_{10}H_8O_4) \xrightarrow{Cu(OAc)_2} (C_{10}H_6O_4) \xrightarrow[\Delta]{\text{conc KOH}} \xrightarrow{H_3O^+} (C_{10}H_8O_5)$

(e) *trans*-2-butene $\xrightarrow{HCO_3H} \xrightarrow[H_2O]{NaOH} (C_4H_{10}O_2)$

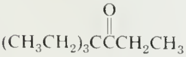
$\xrightarrow[H^+]{} (C_9H_{16}O_2)$

18. Show how each of the following compounds may be synthesized from starting materials containing five or fewer carbons.

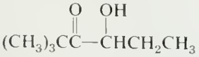
(a) 

(b) 

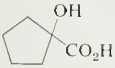
$(CH_3)_2CH\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}CH(CH_3)_2$

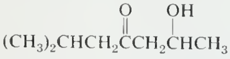
(c) 

$(CH_3CH_2)_3C\overset{O}{\overset{\|}{C}}CH_2CH_3$

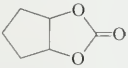
(d) 

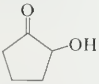
$(CH_3)_3C\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}HCH_2CH_3$

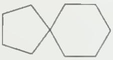
(e) 

(f) 

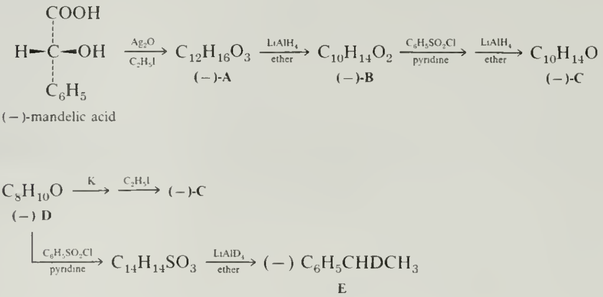
$(CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}CH_2\overset{OH}{\overset{|}{C}}HCH_3$

(g) 

(h) 

(i) 

19. 1-Phenylethane-1-*d*, $C_6H_5CHDCH_3$, **E**, has been prepared in optically active form. This compound is particularly interesting because its asymmetry is due entirely to the isotopic difference between H and D; nevertheless, the magnitude of its rotation has the relatively high value of $[\alpha]_D \pm 0.6°$. The absolute configuration of **E** is related to the known configuration of mandelic acid by the following sequence of reactions:



$$\mathrm{H{-}\overset{COOH}{\underset{C_6H_5}{C}}{-}OH} \xrightarrow[C_2H_5I]{Ag_2O} \underset{(-)\text{-}\mathbf{A}}{C_{12}H_{16}O_3} \xrightarrow[\text{ether}]{LiAlH_4} \underset{(-)\text{-}\mathbf{B}}{C_{10}H_{14}O_2} \xrightarrow[\text{pyridine}]{C_6H_5SO_2Cl} \xrightarrow[\text{ether}]{LiAlH_4} \underset{(-)\text{-}\mathbf{C}}{C_{10}H_{14}O}$$

(−)-mandelic acid

$$\underset{(-)\ \mathbf{D}}{C_8H_{10}O} \xrightarrow{K} \xrightarrow{C_2H_5I} (-)\text{-}\mathbf{C}$$

$$\xrightarrow[\text{pyridine}]{C_6H_5SO_2Cl} C_{14}H_{14}SO_3 \xrightarrow[\text{ether}]{LiAlD_4} \underset{\mathbf{E}}{(-)\ C_6H_5CHDCH_3}$$

Deduce the absolute configuration of (−)-**E** and the structure and configuration of each intermediate, **A** through **D**, in the sequence. Assign the proper R,S notation to each structure **A** through **E**.

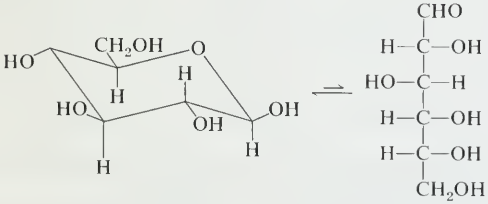
CHAPTER 25
Carbohydrates

25.1
Introduction

The carbohydrates are an important group of naturally occurring organic compounds. They are extremely widespread in plants, comprising up to 80% of the dry weight. Especially important in the vegetable kingdom are cellulose, the chief structural material of plants, starches, pectins, and the sugars sucrose and glucose. These sugars are obtained on an industrial scale from various plant sources. In higher animals, the simple sugar glucose is an essential constituent of blood and occurs in a polymeric form as glycogen in the liver and in muscle. Carbohydrates also occur in a bound form in adenosine triphosphate, a key material in biological energy storage and transport systems, and in the nucleic acids, which control the production of enzymes and the transfer of genetic information.

The term **carbohydrate** is used loosely to characterize the whole group of natural products that are related to the simple sugars. The name first arose because the simple sugars, such as glucose ($C_6H_{12}O_6$), have molecular formulas that appear to be "hydrates of carbon," that is $C_6H_{12}O_6 = (C \cdot H_2O)_6$. Although subsequent structural investigations revealed that this simple-minded view was erroneous, the term carbohydrate has persisted.

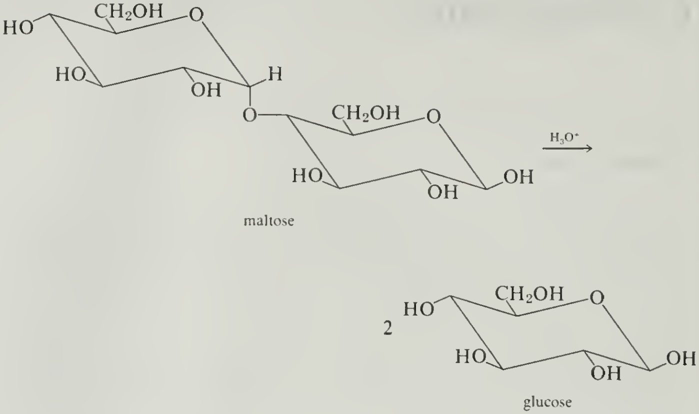
Sugars, also called **saccharides,** are the simplest type of carbohydrate. An example is glucose, which is the cyclic hemiacetal form of one of the diastereomers of 2,3,4,5,6-pentahydroxyhexanal. As we shall see in a later section, although glucose exists almost entirely in the cyclic form, in solution it appears to be in equilibrium with a minute amount of the noncyclic pentahydroxyaldehyde form. The structure of naturally occurring glucose is shown as an example of a simple sugar. The open chain form is drawn as a Fischer projection formula (page 118), which unambiguously specifies the stereochemistry at each of the four asymmetric carbons.



glucose

As is generally true for natural products, *the carbohydrates occur in optically active form,* and only one enantiomer is found in nature. Glucose is an example of a **monosaccharide,** a term that means glucose is not hydrolyzable into smaller units.

Maltose is an example of a **disaccharide**; upon hydrolysis under mildly acidic conditions, maltose yields two equivalents of the monosaccharide glucose.

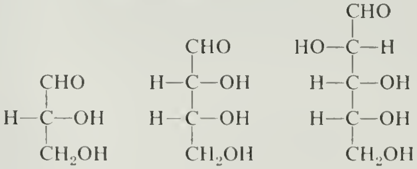


maltose

glucose

A **trisaccharide** yields three monosaccharides on hydrolysis, a **tetrasaccharide** four, and so forth. **Oligosaccharide** is a general term applied to sugar polymers containing up to eight units. **Polysaccharide** refers to polymers in which the number of subunits is greater than eight; the natural polysaccharides generally consist of 100–3000 subunits.

The monosaccharides are also characterized in terms of the number of carbons in the chain and the nature of the carbonyl group, aldehyde or ketone. Glucose, which is a six-carbon aldehyde, is a **hexose,** which specifies the number of carbons, and an **aldose,** which shows that it is an aldehyde. It is completely characterized by the general term **aldohexose.** Other aldoses are glyceraldehyde, an **aldotriose,** erythrose, an **aldotetrose,** and arabinose, an **aldopentose.** The structures of these examples are shown in Fischer projections as their open chain forms in (25-1).

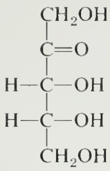


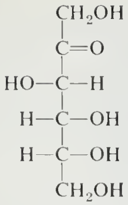
$$\begin{array}{ccc} & \mathrm{CHO} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array} \qquad \begin{array}{ccc} & \mathrm{CHO} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array} \qquad \begin{array}{ccc} & \mathrm{CHO} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array} \tag{25-1}$$

glyceraldehyde (an aldotriose)   erythrose (an aldotetrose)   arabinose (an aldopentose)

Most of the naturally occurring sugars are derived from the aldoses, and the most widespread are the aldohexoses and the aldopentoses.

A few important saccharides are **ketoses,** meaning that they contain a ketone, rather than an aldehyde, carbonyl group. Fructose is an example of a **ketohexose,** a six-carbon pentahydroxy ketone. An example of a **ketopentose** is ribulose. Both compounds are shown (25-2) in open chain form as Fischer projections.

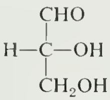

ribulose
(a ketopentose)

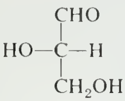

fructose
(a ketohexose)

(25-2)

25.2
Stereochemistry and Configurational Notation of Sugars

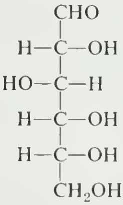
The simplest polyhydroxy aldehyde is the compound 2,3-dihydroxypropanal, or glyceraldehyde. The molecule has one asymmetric center, so there are two enantiomers (Chapter 7). The absolute configuration of the glyceraldehyde enantiomers are known, and the enantiomer with $[\alpha]_D = +8.7°$ has the structure shown in (25-3) on the left (Fischer projection).

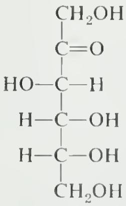

D-(+)-glyceraldehyde
R-(+)-glyceraldehyde


L-(−)-glyceraldehyde
S-(−)-glyceraldehyde

(25-3)

This enantiomer may be distinguished from the other by calling it (+)-glyceraldehyde, meaning "the dextrorotatory enantiomer of glyceraldehyde." A complete description, which specifies the absolute stereochemistry of the enantiomer is R-(+)-glyceraldehyde (Section 7.3). In the carbohydrate field, it is customary to use another and older system of configurational notation, wherein this enantiomer is called D-(+)-glyceraldehyde. Under this convention, all D-*sugars have the same stereochemistry as* D-(+)-*glyceraldehyde at the asymmetric carbon most distant from the carbonyl group*. Sugars with the opposite stereochemistry at this center are members of the L family. Thus, natural glucose is D-(+)-glucose and fructose is D-(−)-fructose.


D-(+)-glucose

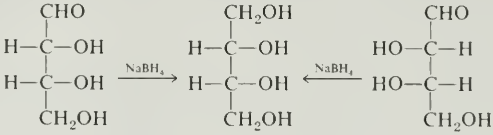

D-(−)-fructose

Recall that for a compound with n asymmetric centers, there are 2^n possible optical isomers. Thus, there are 2 aldotrioses, 4 aldotetroses, 8 aldopentoses, and

16 aldohexoses. Half of these compounds belong to the D family (are related to D-glyceraldehyde) and half belong to the L family. To avoid cumbersome names, each isomer has been given a trivial name; that is, D-(+)-glucose is 2R,3S,4R,5R,6-pentahydroxyhexanal. Fischer projections depicting the complete D family of the aldoses in their open chain forms are shown in Table 25.1. Note that abbreviated Fischer projections are used, in which the asymmetric carbons are omitted. The student should thoroughly review Section 7.5 on the use of these projection formulas.

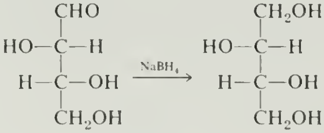
Although the naturally occurring sugars generally belong to the D family shown in Table 25.1, there are an equal number of compounds that have the L configuration. Each D sugar has an enantiomeric L counterpart.

Recall that a molecule with two or more asymmetric atoms may be achiral if it has a plane of symmetry. Such compounds are called *meso* compounds (page 117). It often happens in carbohydrate chemistry that a chiral compound undergoes a chemical reaction to yield a *meso* product. For example, consider the reduction of the aldotetrose D-(−)-erythrose by sodium borohydride. The product is *meso*-1,2,3,4-butanetetrol (erythritol). The same compound would be produced by the reduction of L-(+)-erythrose.

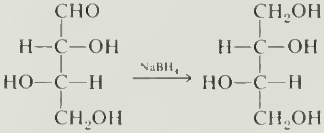


D-(−)-erythrose erythritol L-(+)-erythrose

On the other hand, the aldotetroses D-(−)-threose and L-(+)-threose each yield an optically active butanetetrol on reduction.



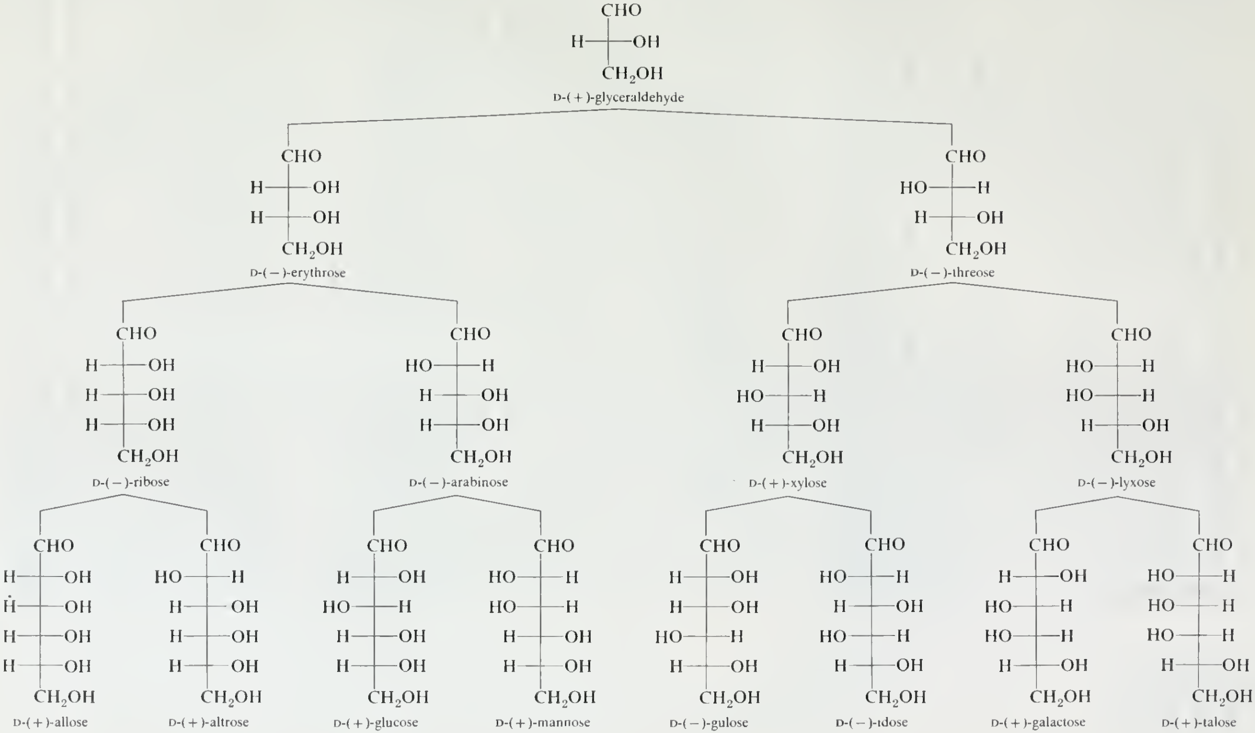
D-(−)-threose D-(+)-threitol



L-(+)-threose L-(−)-threitol

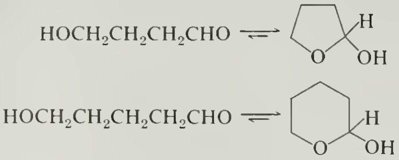
The formation of a *meso* compound can be a powerful piece of information for use in determining the relative stereochemistry of a compound. For example, the fact that erythrose undergoes reduction to give a *meso* tetrol proves that its two asymmetric centers are either (R,R) or (S,S). Conversely, since threose gives a tetrol that is optically active, it must have either the (R,S) or (S,R) configuration.

Table 25.1
The D*-Family Aldoses*

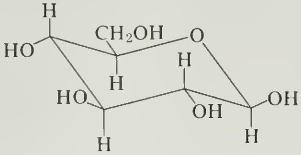

D-(+)-glyceraldehyde
D-(−)-erythrose
D-(−)-threose
D-(−)-ribose
D-(−)-arabinose
D-(+)-xylose
D-(−)-lyxose
D-(+)-allose
D-(+)-altrose
D-(+)-glucose
D-(+)-mannose
D-(−)-gulose
D-(−)-idose
D-(+)-galactose
D-(+)-talose

25.3
Cyclic Hemiacetals: Anomerism: Glycosides

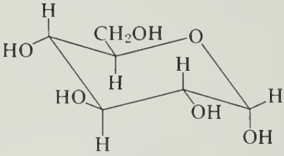
In the last chapter (Section 24.4.B), we learned that 4- and 5-hydroxy aldehydes and ketones exist mainly in the form of a cyclic hemiacetal or hemiketal.



It is not surprising, then, that the sugars also exist in such a cyclic form. Although either the five- or six-membered hemiacetal structure is possible, almost all of the simple sugars exist in the six membered ring form (see Table 24.2, page 680). Note that when the hemiacetal is formed, *the former aldehyde carbon becomes asymmetric*. Thus, there are two cyclic forms of glucose:



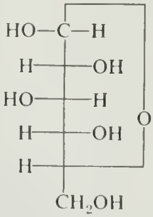
β-D-glucose



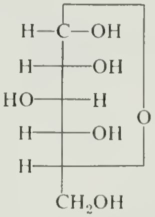
α-D-glucose

The two cyclic isomers of glucose differ only in the stereochemistry at C-1, the acetal carbon (former aldehyde carbon). Such isomers are called **anomers**, and the acetal carbon (or the ketal carbon in the case of a cyclic ketose) is called the **anomeric** carbon. The two anomers are commonly differentiated by the Greek letters α and β; for example, α-D-glucose, β-D-glucose. For the aldohexoses, the β anomer is the one that has the OH at C-1 and the CH_2OH at C-5, *cis* with respect to each other on the ring.

The Fischer projection formulas shown in Table 25.1 are a convenient way in which to represent the open chain form of sugars. Modified Fischer projections have frequently been used to depict the cyclic hemiacetal form. For example, the two D-glucose anomers may be represented as



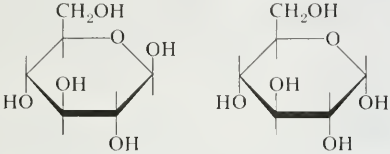
β-D-glucose



α-D-glucose

Note the convention used to represent stereochemistry at anomeric carbon. The OH at C-1 in the β anomer is written to the left and that in the α anomer is written to the right.

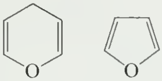
Because these modified projections lead to awkward drawings of bond lengths, which offend the sensibilities of many chemists, Haworth introduced an alternate projection formula, which is used extensively by sugar chemists. In a Haworth projection, the sugar ring is written as a planar hexagon with the oxygen in the upper right vertex. Substituents are indicated by straight lines through each vertex, either above or below the plane. The OH at the anomeric carbon is up in the β anomer and down in the α anomer. Hydrogens attached to the ring are omitted.



β-D-glucose α-D-glucose

There is a simple way to convert a Fischer projection to a Haworth projection, or vice versa. The OH groups that project to the *left* in a Fischer projection project *up* in a Haworth projection. In this book, we shall use Fischer projections to depict open chair sugars and the more accurate chair representations to depict cyclic forms.

The six-membered ring form of a sugar is called a **pyranose**, from the name of the simplest heterocyclic compound containing such a ring, pyran. Thus, β-D-glucose is a pyranose form, and it may be completely described by the name β-D-glucopyranose. Although the free sugars normally do not exist on the five-membered ring form, numerous derivatives are known that have such a structure. They are called **furanoses**, from the name of the parent heterocyclic compound, furan.



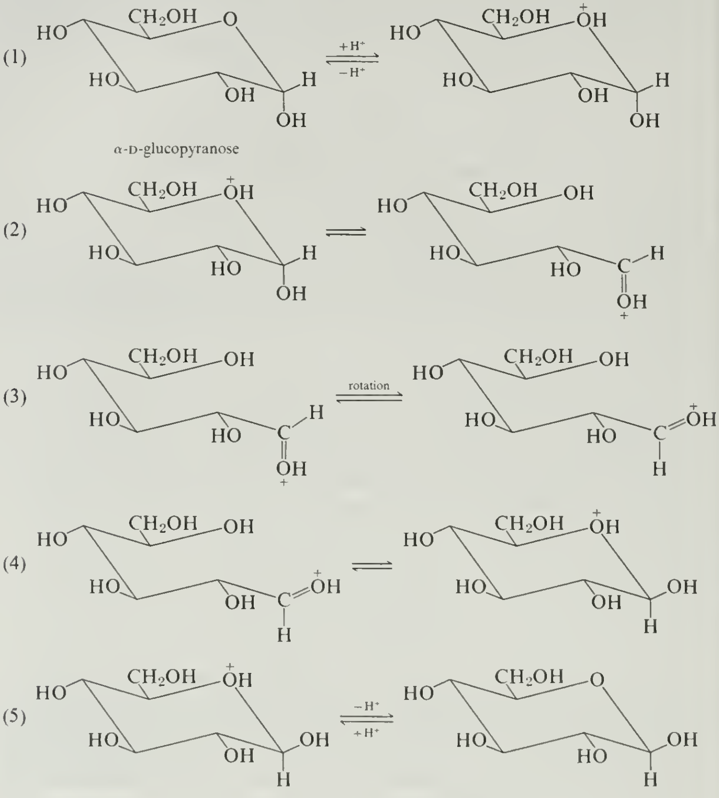
pyran furan

Pure β-D-glucose has an optical rotation $[\alpha]_D = +18.7°$; the α anomer has $[\alpha]_D = +112°$. Both anomers have been isolated in pure crystalline states. If either pure anomer is dissolved in water, the optical rotation of the solution gradually changes until it reaches an equilibrium value of $+52.7°$. This phenomenon, which was first observed in 1846, results from the interconversion of the two anomers in solution and is called **mutarotation.** At equilibrium, the solution contains 63.6% of the more stable β anomer and 36.4% of the α anomer.

> The phenomenon of anomerism caused considerable confusion for the early workers in carbohydrate chemistry, who believed the sugars to be acyclic compounds. After their cyclic structure was recognized, there arose the problem of how to name the two anomers for each sugar. In 1909, a system of nomenclature based purely on optical rotation was adopted. In the D series, the more dextrorotatory member of a pair of anomers is defined as the α-D anomer and the less dextrorotatory anomer as the β-D anomer. When reliable methods for determining the stereochemistry at C-1 became available, it turned out that all α anomers have the same absolute configuration at C-1.

Interconversion of the two anomers is subject to both acid and base catalysis, and occurs by the normal mechanism for acetal formation and hydrolysis (Sections

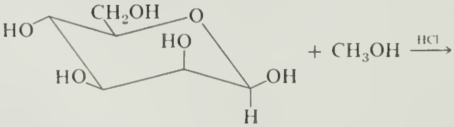
15.7.B and 24.4.B under Cyclic Hemiacetals and Hemiketals.) The open chain form is probably an intermediate in the process. The mechanism of acid-catalyzed interchange of the α and β anomers of glucose is outlined as follows (all ring hydrogens except the one on the anomeric carbon are omitted for clarity):



α-D-glucopyranose

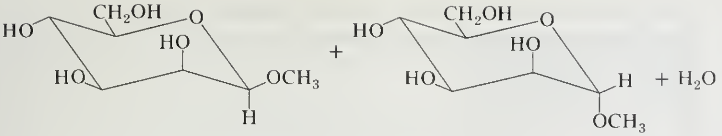
β-D-glucopyranose

When an aldose is dissolved in an alcohol and the solution is treated with a mineral acid catalyst, a cyclic acetal is produced (Section 24.4.B, p. 679). In carbohydrate chemistry, such cyclic acetals are called **glycosides.** A glycoside derived from glucose is a **glucoside;** one derived from mannose is a **mannoside,** and so on. Like the hemiacetal, these cyclic acetals may exist in both α and β anomeric forms, as shown in (25-4) for the methyl mannosides.



$+ CH_3OH \xrightarrow{HCl}$

β-D-mannose

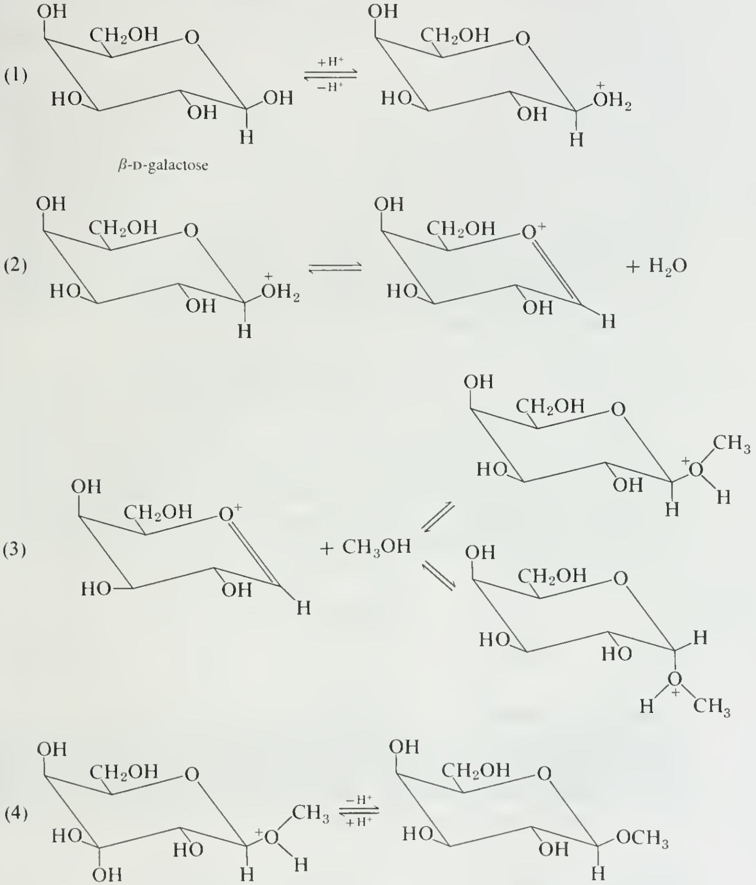


methyl β-D-mannoside, or,
methyl β-D-mannopyranoside

methyl α-D-mannoside, or,
methyl α-D-mannopyranoside

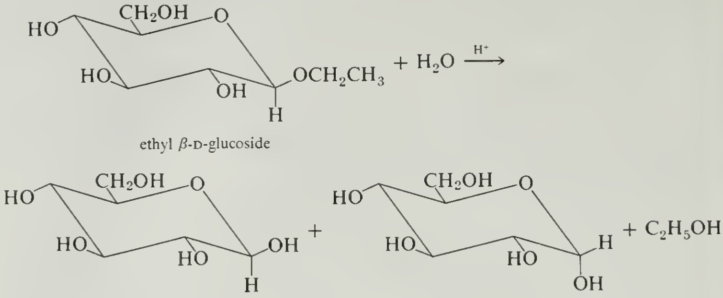
(25-4)

Glycosides form only under acid catalysis; the mechanism for the formation of the methyl galactosides is outlined as follows:



methyl β-D-galactoside, or,
methyl β-D-galactopyranoside

The formation of glycosides is a reversible process under acidic conditions. If a glycoside is treated with an acid catalyst in aqueous solution where water is present in excess, the equilibrium shifts and hydrolysis occurs. Of course, under acidic conditions a mixture of the anomeric sugars results.

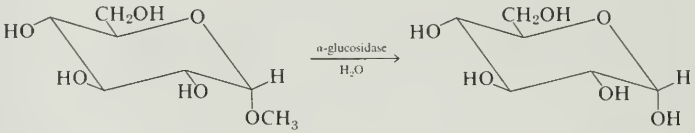


ethyl β-D-glucoside

β-D-glucose

α-D-glucose

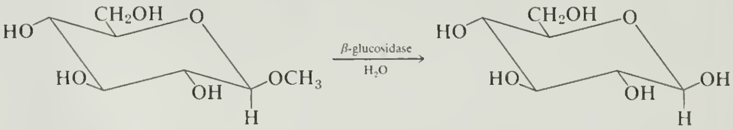
The hydrolysis of glycosides may also be brought about by certain **enzymes.** Enzymes are complex natural products, mainly protein in nature (Chapter 28), which function as catalysts in biological reactions. They are extremely potent catalysts, often speeding up reactions by factors as large as 10^{10}. They also show remarkable structural specificity, as shown by the present example. Methyl α-D-glucopyranoside is hydrolyzed in the presence of an enzyme isolated from yeast, called α-glucosidase. This particular enzyme only catalyzes the hydrolysis of α-glucoside linkages; methyl β-D-glucopyranoside is unaffected by it.



methyl α-D-glucopyranoside

α-D-glucopyranose

Another enzyme, β-glucosidase from almonds, has opposite properties; it only catalyzes the hydrolysis of β-glucosides.



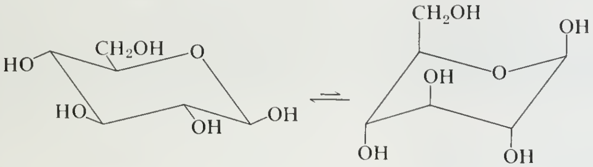
methyl β-D-glucopyranoside

β-D-glucopyranose

Similar enzymes are known that specifically catalyze the hydrolysis of α- and β-galactosides (α- and β-galactosidase) and other glycosidic bonds. These enzymes are very useful in determining the stereochemistry of the glycoside links in oligosaccharides and polysaccharides (Sections 25.7 and 25.8).

25.4
Conformations of the Pyranoses

As has been tacitly implied in the structures used thus far in this chapter, the pyranose forms of sugars exist in a chair conformation similar to the stable conformation of cyclohexane (Section 23.2.D). As in cyclohexane, two alternative chair forms are possible, and the one that predominates is the one with the fewest nonbonded interactions. For β-D-glucose, there is a large difference between the two forms. In one form, all five substituents are in equatorial positions, whereas they are all axial in the other conformation; the difference between these two conformations has been estimated to be 6 kcal mole^{-1}.



Of the eight D-aldohexoses, glucose is the only one that can have all five substituents equatorial. It is no accident that glucose is the most abundant natural monosaccharide. A stereo structure of β-D-glucose is given in Figure 25.1.

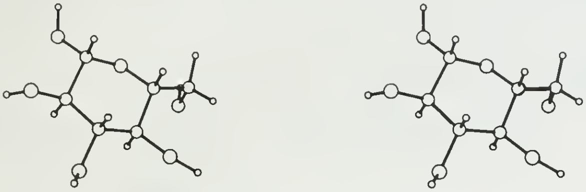
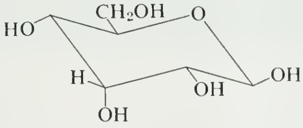


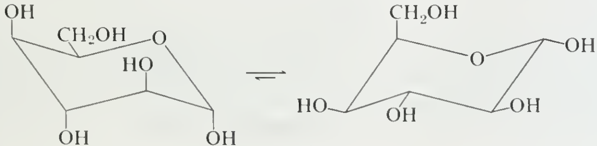
FIGURE 25.1 *Stereo structure of β-D-glucose. [Reproduced with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.*

If one remembers that β-D-glucose has all substituents equatorial, it is easy to write conformational structures for the other aldohexoses by simply referring to Table 25.1. For example, D-allose differs from D-glucose only in the configuration of C-3. Thus, β-D-allose is



β-D-allose

For most of the aldohexoses, the more stable conformation is that with the CH_2OH group in an equatorial position. However, in a few cases, the two conformations are nearly equal in energy and substantial amounts of both may be present at equilibrium. For α-D-idose, the stable conformation is that in which the CH_2OH group is axial.

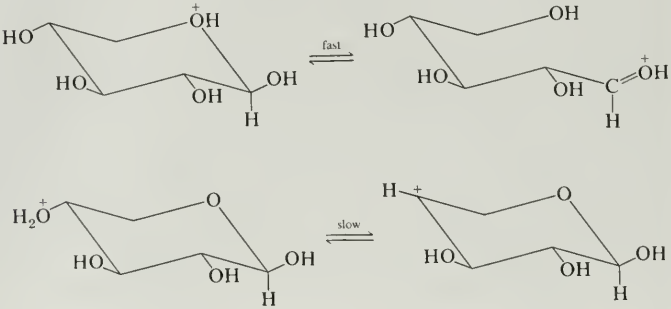


α-D-idose

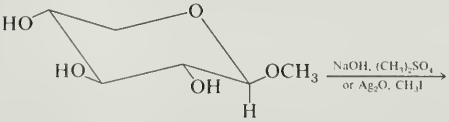
25.5
Reactions of Monosaccharides

A. *Ether Formation*

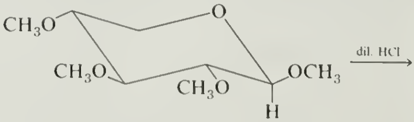
In Section 25.3, we discussed the formation of glycosides, in which the OH group at the anomeric carbon is replaced by an alkoxy group under mildly acidic conditions. The remaining hydroxy groups are unaffected by this process because such a process would involve a primary or secondary carbonium ion, rather than the far more stable oxonium ion which is involved in glycoside formation.


HO
HO
OH
OH
OH
H
fast
HO
HO
OH
OH
OH
H
H₂O
HO
O
OH
OH
H
slow
H
HO
O
OH
OH
H

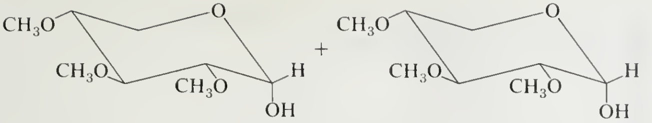
The other hydroxy groups can be converted into ethers by an application of the Williamson ether synthesis (Section 11.10.A). The most common ethers are the methyl ethers, which are prepared by treating the sugar with 30% aqueous sodium hydroxide and dimethyl sulfate, or with silver oxide and methyl iodide. Since the free aldehyde form of an aldose is not stable to strongly basic conditions, it is customary to **protect** the anomeric carbon by converting the sugar into the methyl glycoside. The glycoside linkage can then be cleaved by mild acid hydrolysis because the normal ether linkages are stable under these conditions.


HO
O
HO
OH
OCH₃
H
NaOH, (CH₃)₂SO₄
or Ag₂O, CH₃I

methyl β-D-xyloside


CH₃O
O
CH₃O
CH₃O
OCH₃
H
dil. HCl

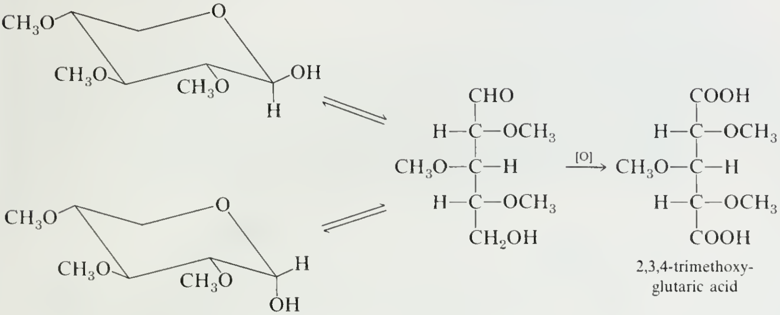
methyl 2,3,4-tri-O-methyl-β-D-xyloside


CH3O
O
CH3O
CH3O
H
OH
+
CH3O
O
CH3O
CH3O
H
OH

2,3,4-tri-O-methyl-β-D-xylose

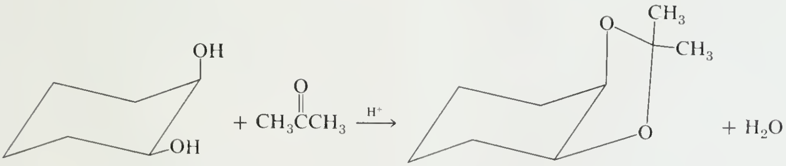
2,3,4-tri-O-methyl-α-D-xylose

Methylation can be a useful method for determining the size of the acetal ring in a glycoside. For example, oxidation of the above mixture of anomeric tri-O-methylxylose yields a 2,3,4-trimethoxyglutaric acid, thus establishing that the original methyl xyloside had the pyranose structure.

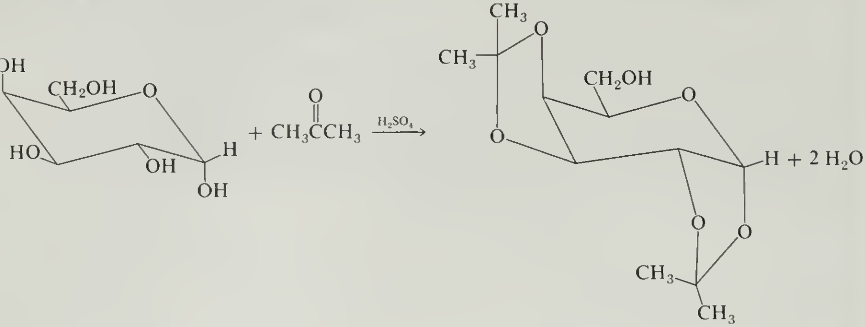

CH3O
O
CH3O
CH3O
OH
H
CHO
H—C—OCH3
CH3O—C—H
H—C—OCH3
CH2OH
[O]
COOH
H—C—OCH3
CH3O—C—H
H—C—OCH3
COOH
2,3,4-trimethoxy-glutaric acid
CH3O
O
CH3O
CH3O
H
OH

B. *Formation of Cyclic Acetals and Ketals*

Recall that 1,2- and 1,3-diols condense with aldehydes and ketones to form cyclic acetals or ketals (Section 24.3.C). If the diol is itself cyclic, the acetal or ketal forms only when the two OH groups are *cis*, for geometric reasons.


OH
OH
+ CH3CCH3
O
H+
O
CH3
CH3
O
+ H2O

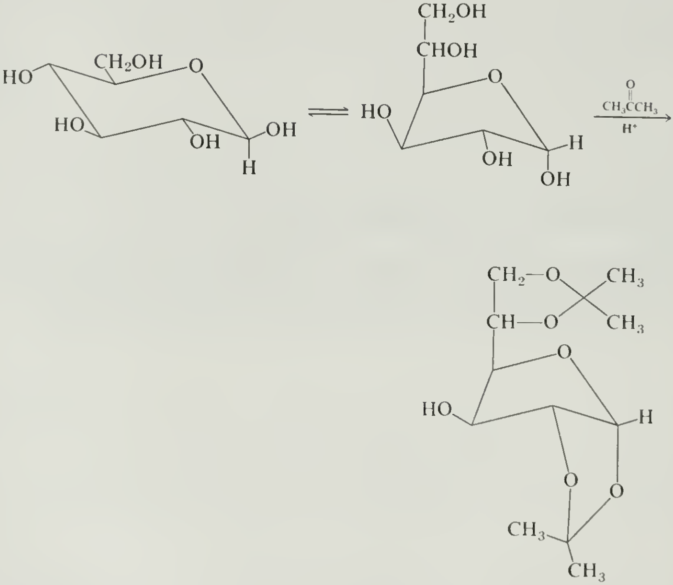
Since sugars are polyhydroxy compounds, they also undergo this reaction. The reaction is often complicated by the fact that the ring size in the product is not the same as it is in the free sugar. This usually occurs when the more stable pyranose form does not have *cis* vicinal hydroxy groups, but the furanose form does. Thus, galactose reacts with acetone to give the diketal shown because, in the α form, which is present under the acidic conditions of the reaction, there are two pairs of *cis* vicinal OH groups.


CH₂OH
O
HO
OH
H
OH
+ CH₃CCH₃
O
H₂SO₄
CH₃
CH₃
O
CH₂OH
H + 2 H₂O

α-D-galactose

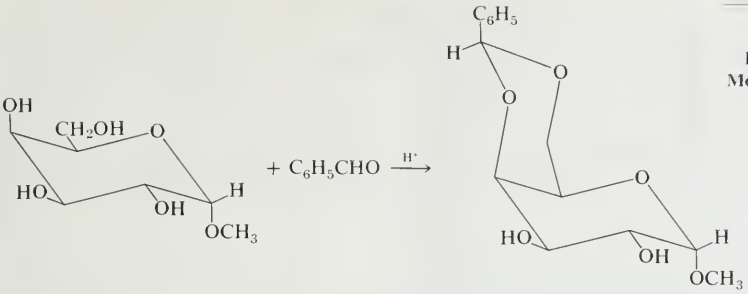
1,2:3,4-di-O-isopropylidine-α-D-galactopyranoside

Glucose, on the other hand, reacts by way of the furanose form.


CH₂OH
CHOH
HO
OH
H
CH₃CCH₃
H⁺
CH₂—O
CH—O
CH₃

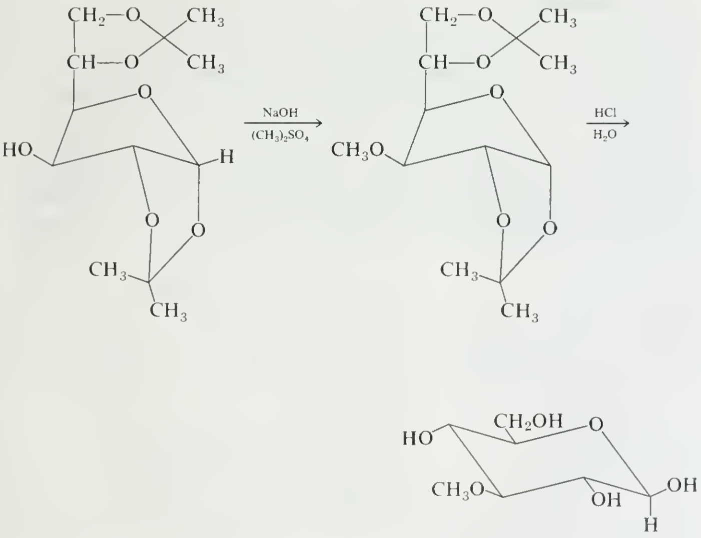
1,2:5,6-di-O-isopropylidine-α-D-glucofuranose

Similar condensations occur with aldehydes. Benzaldehyde shows a tendency to form six-membered ring acetals. Thus, benzaldehyde reacts with methyl α-D-galactoside to give the 4,6-benzylidine derivative.

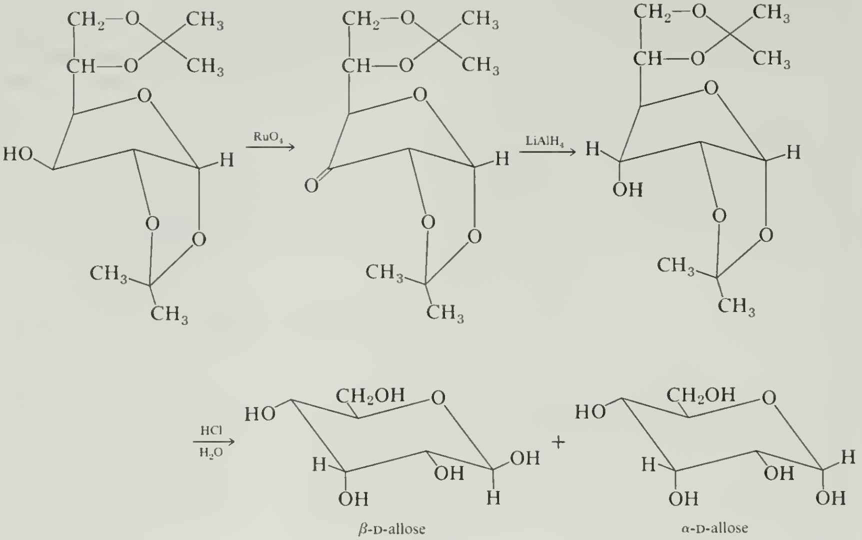

OH
CH₂OH
O
HO
OH
H
OCH₃
+ C₆H₅CHO
H⁺
C₆H₅
H
O
O
O
HO
OH
H
OCH₃

methyl 4,6-O-benzylidine-
α-D-galactopyranoside

These cyclic acetals and ketals serve the useful function of protecting either two or four of the OH groups normally present in the free sugar. The acetal groups are sensitive to acid but are relatively stable to neutral and basic conditions. Reactions may be carried out on the remaining OH groups, and the protecting groups may then be removed by mild acid hydrolysis. An example is the synthesis of 3-O-methylglucose, a feat that cannot be accomplished by selective methylation of glucose itself.

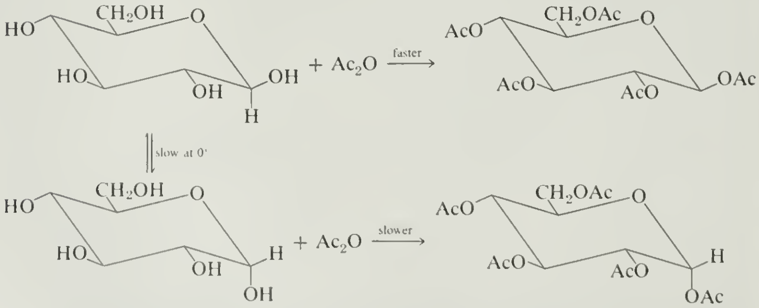

CH₂—O
CH₃
CH—O
CH₃
O
HO
H
O
O
CH₃
CH₃
NaOH
(CH₃)₂SO₄
CH₃O
HCl
H₂O
HO
CH₂OH
O
CH₃O
OH
OH
H

Another example is the following, which shows how D-glucose can be converted into D-allose by inversion of stereochemistry at C-3.

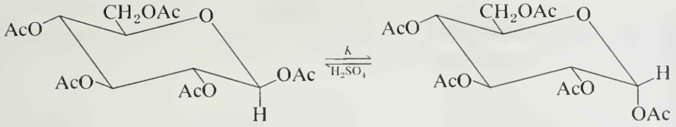


C. *Esterification*

The hydroxy groups in sugars may be esterified by normal methods (Section 18.9.B). The most common procedure to form acetates uses acetic anhydride and a mild basic catalyst such as sodium acetate or pyridine. At low temperature, acetylation in pyridine occurs more rapidly than interconversion of the anomers; at 0°, either α-D- or β-D-glucose gives the corresponding pentaacetate. At higher temperatures, the anomers interconvert rapidly and the β-pentaacetate is produced preferentially, since the equatorial OH of the β anomer reacts more rapidly than does the axial OH of the α anomer.



The more stable pentaacetate is actually the α form, but equilibrium is established only under still more drastic conditions.

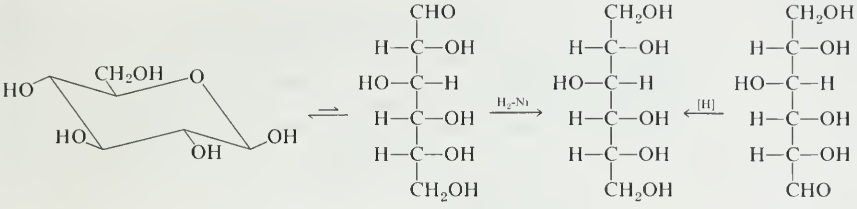

AcO
CH₂OAc
O
AcO
AcO
OAc
H
k
H₂SO₄
AcO
CH₂OAc
O
AcO
AcO
H
OAc

$K = 6.7$

This example provides a further illustration of the importance of kinetic and thermodynamic factors in organic reactions.

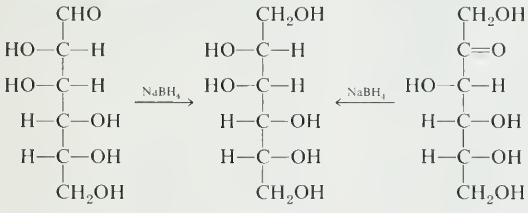
D. *Reduction: Alditols*

Monosaccharides may be reduced by various methods to the corresponding polyalcohols, which as a class are called **alditols.** Reduction of D-glucose gives D-glucitol (D-glucitol is referred to as D-sorbitol in the older literature), which also occurs in nature. The same compound is produced by the reduction of L-gulose. D-Glucitol is prepared on an industrial scale by catalytic hydrogenation of D-glucose over a nickel catalyst. The reduction probably occurs on the small amount of open chain form that is present in equilibrium with the cyclic form. As the open chain form is removed in this way, the equilibrium continually shifts until all of the sugar is reduced.


HO
CH₂OH
O
HO
OH
OH
CHO
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH
H₂-Ni
CH₂OH
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH
[H]
CH₂OH
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CHO

D-glucose D-glucitol L-gulose

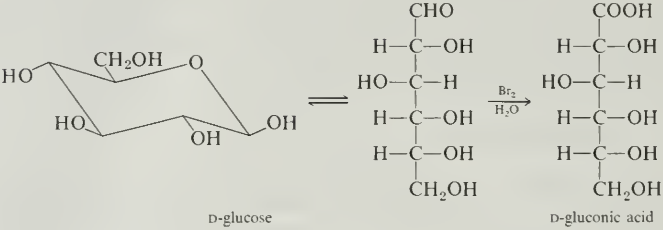
D-Mannitol, produced by the sodium borohydride reduction of D-mannose, is widespread in nature, occurring in such varied sources as olives, marine algae, onions, and mushrooms. It is also produced, along with a little D-glucitol, in the reduction of the ketohexose D-fructose.


CHO
HO—C—H
HO—C—H
H—C—OH
H—C—OH
CH₂OH
NaBH₄
CH₂OH
HO—C—H
HO—C—H
H—C—OH
H—C—OH
CH₂OH
NaBH₄
CH₂OH
C=O
HO—C—H
H—C—OH
H—C—OH
CH₂OH

D-mannose D-mannitol D-fructose

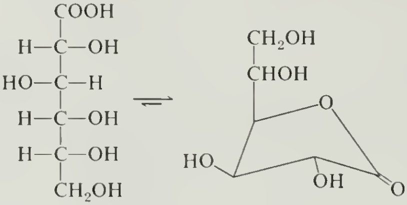
E. *Oxidation: Aldonic and Saccharic Acids*

Sugars are oxidizable in several ways. In the aldoses, the most susceptible group is the aldehyde group. For preparative purposes, the most convenient method employs bromine in a buffered solution at pH 5–6. Yields of the polyhydroxy carboxylic acids (**aldonic acids**) are usually in the range 50–70%. With glucose, yields as high as 95% have been achieved.


HO
CH₂OH
O
HO
OH
OH
CHO
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH
Br₂
H₂O
COOH
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH

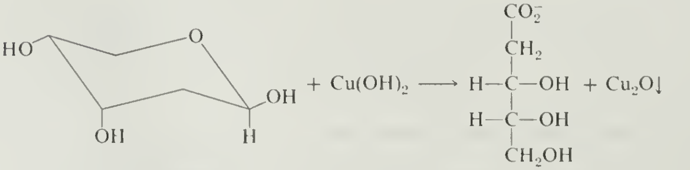
D-glucose D-gluconic acid

Since they are 4-hydroxyalkanoic acids, the aldonic acids lactonize readily (Section 24.5.B). Although either a five- or six-membered lactone might, in principle, be formed, the more stable lactones are those containing a five-membered ring (see Table 24.3).


COOH
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH
CH₂OH
CHOH
O
HO
OH
O

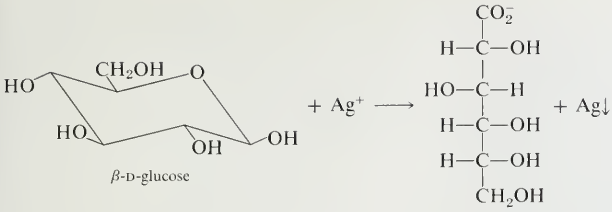
D-gluconic acid D-gluconic acid γ-lactone

The easy oxidation of aldoses provides a basis for an analytical method that has been widely used in sugar chemistry. Two examples are Fehling's test, employing cupric ion as the oxidant, and Tollens' test, in which silver ion is the oxidant. In the Fehling reaction (25-5), the presence of a potential aldehyde group is shown by the formation of cupric oxide as a brick-red precipitate. In Tollens' test (25-6), the silver ion is reduced to metallic silver, which deposits in the form of a mirror on the inside of the test tube.


HO
O
OH
OH
H
+ Cu(OH)₂
CO₂⁻
CH₂
H—C—OH
H—C—OH
CH₂OH
+ Cu₂O↓

(25-5)

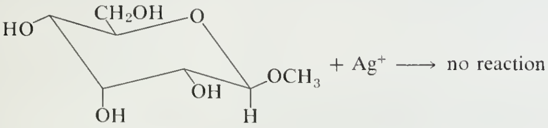
β-D-2-deoxyribose



β-D-glucose

(25-6)

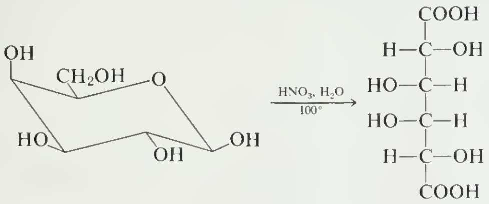
If the sugar is in the form of a glycoside, then the anomeric carbon is protected under basic conditions and the sugar is stable to these mild oxidizing conditions.



methyl β-D-allopyranoside

Such compounds are called **nonreducing sugars;** sugars that do reduce basic solutions of Cu^{2+} or Ag^+ are called **reducing sugars.**

Under more vigorous oxidizing conditions, one or more hydroxy groups may be oxidized. The primary OH groups are attacked most readily, and are generally oxidized all the way to the carboxylic acid stage. The product is a polyhydroxy dicarboxylic acid, called a **saccharic acid.** A convenient oxidizing agent for the preparation of saccharic acids is aqueous nitric acid.

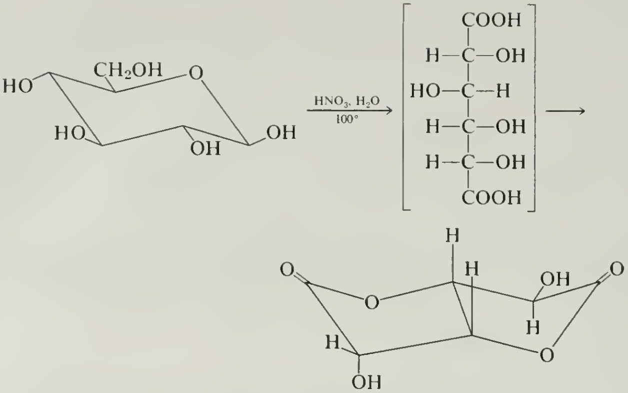


β-D-galactose

mucic acid
(galactaric acid)

The saccharic acids have proven to be useful in unraveling the puzzle of the relative configuration of the aldoses. Since the two ends of the chain in such a dicarboxylic acid are the same, *meso* compounds are possible, depending on the relative stereochemistry of the asymmetric carbons. Note, for example that mucic acid is a *meso* compound, and hence is optically inactive. The observation that galactose gives a *meso* saccharic acid automatically limits its structure to only 4 of the 16 possible aldohexoses.

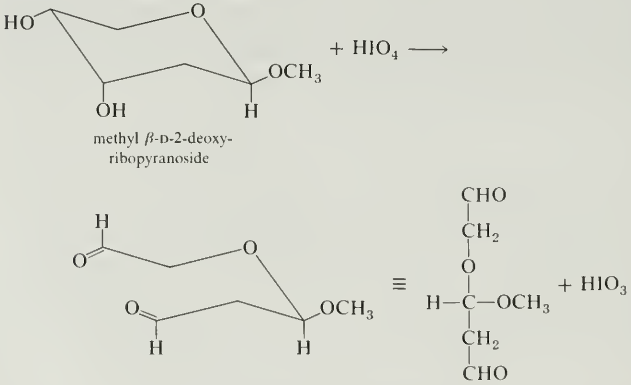
Like the aldonic acids, the saccharic acids lactonize readily and are generally found to be dilactones. The 1,4:3,6-dilactone of glucaric acid, derived from D-glucose, is shown in (25-7).


HNO_3, H_2O
100°

(25-7)

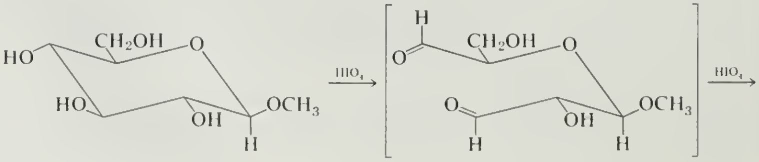
F. *Oxidation by Periodic Acid*

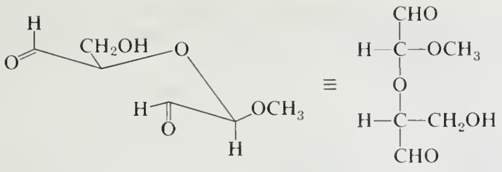
Like other vicinal diols, sugars are cleaved by periodic acid (Section 24.3.B). For example, methyl 2-deoxyribopyranoside reacts with one equivalent of periodic acid to give the dialdehyde shown in (25-8).


methyl β-D-2-deoxy-
ribopyranoside

(25-8)

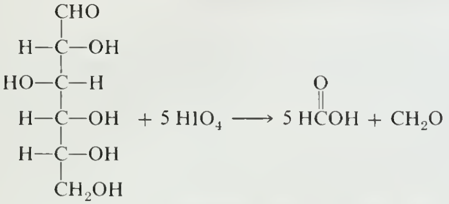
When there are more than two adjacent hydroxy groups, the initially formed α-hydroxy aldehyde undergoes further oxidation (Section 24.4.B).


HIO_4
HIO_4
methyl β-D-glucopyranoside



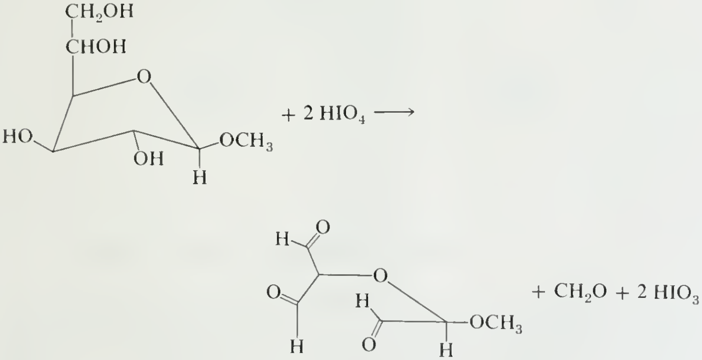
+ HCO_2H (25-9)

As shown in reaction (25-9) each time an α-hydroxy aldehyde is cleaved, one equivalent of formic acid is produced. With the free sugars, it is the open chain form that is oxidized, and complete oxidation occurs. Glucose yields five equivalents of formic acid and one equivalent of formaldehyde, which arises from C-6.

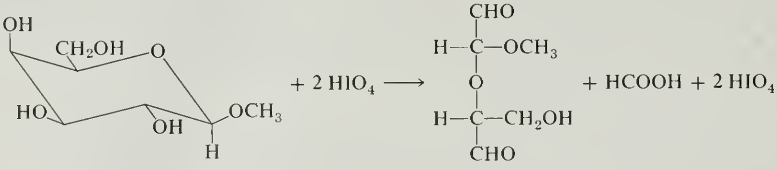


$$\begin{array}{c} CHO \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ CH_2OH \end{array} + 5\,HIO_4 \longrightarrow 5\,H\overset{\overset{O}{\|}}{C}OH + CH_2O \qquad (25\text{-}10)$$

Periodate oxidation has been applied as a method for determining whether glycosides have the furanose or the pyranose structure. For example, methyl D-glucopyranoside reacts with two equivalents of the reagent and gives one equivalent of formic acid along with the dialdehyde as shown in (25-9). The corresponding furanoside also reacts with two equivalents of reagent, but it yields only one equivalent of formaldehyde because the carbon lost corresponds to C-6.



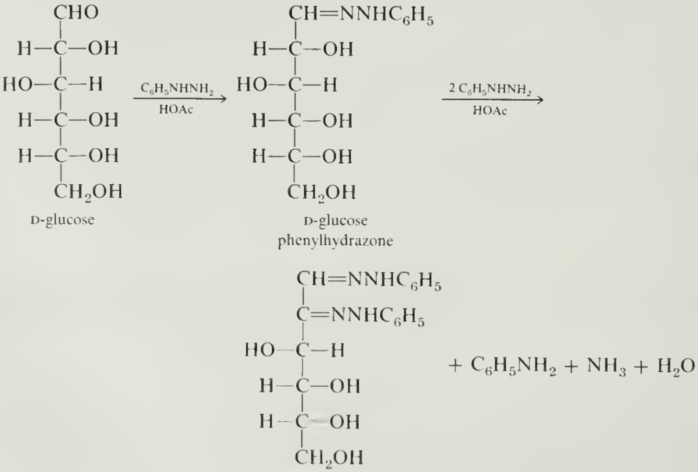
Periodic acid has also been used to determine the configuration at the anomeric carbon in the pyranosides. Note that oxidation of methyl β-D-glucopyranoside yields a dialdehyde that contains two asymmetric carbons, corresponding to C-1 and C-5 in the glucoside itself; C-3 is lost as formic acid, and C-2 and C-4 become achiral. The other D-aldohexoses differ from D-glucose only in the relative configuration at these three centers. Thus, the methyl β-D-glycosides of all of the aldohexoses give this same dialdehyde on oxidation. One asymmetric carbon in the product is determined by the D-configuration, whereas the other is determined by the β-glycoside linkage.


OH
CH₂OH
O
HO
OH
OCH₃
H
+ 2 HIO₄
CHO
H—C—OCH₃
O
H—C—CH₂OH
CHO
+ HCOOH + 2 HIO₄

methyl β-D-galactopyranoside

G. *Phenylhydrazones and Osazones*

Because of their polyhydroxy nature, sugars are rather difficult to isolate and purify. They are extremely water soluble, and they tend to form viscous syrups that crystallize poorly. Naturally occurring examples of such syrups are honey and molasses. These properties caused severe problems in working with sugars in the nineteenth century, before the advent of today's powerful spectroscopic methods of analysis. At that time, the only way to ascertain the identity or nonidentity of two compounds was to compare melting points. In 1884, Emil Fischer introduced the use of phenylhydrazine as a reagent in sugar chemistry and opened up a new vista in the subject. Fischer found that a monosaccharide, such as glucose, will react, by way of its open chain form, with phenylhydrazine in acetic acid to give a normal phenylhydrazone (Section 15.7.C). However, the initially formed phenylhydrazone reacts further with two more equivalents of phenylhydrazine to yield a derivative called an **osazone.**

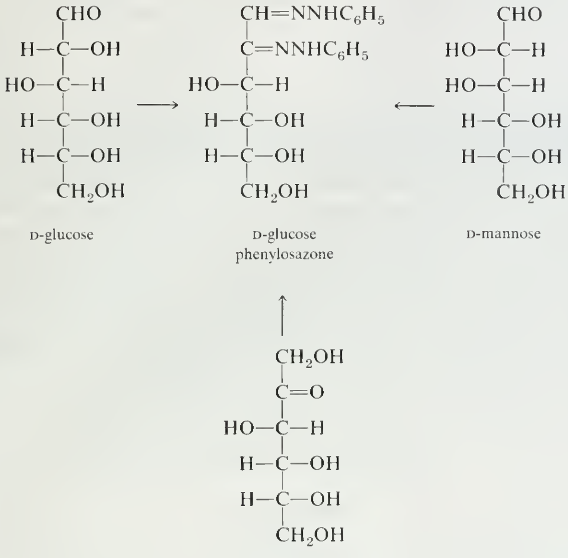

CHO
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH
C₆H₅NHNH₂
HOAc
CH=NNHC₆H₅
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH₂OH
2 C₆H₅NHNH₂
HOAc
CH=NNHC₆H₅
C=NNHC₆H₅
HO—C—H
H—C—OH
H—C—OH
CH₂OH
+ C₆H₅NH₂ + NH₃ + H₂O

D-glucose

D-glucose phenylhydrazone

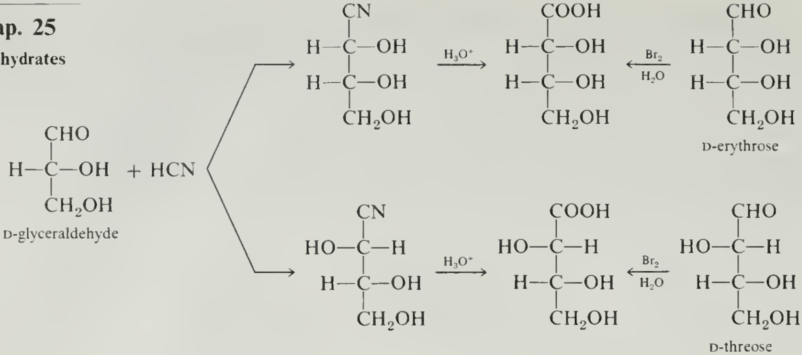
D-glucose phenylosazone

The osazones were found to be bright yellow crystalline materials with characteristic melting points. However, the osazones soon proved to be more valuable than it appeared at first sight. Notice that the chirality at C-2 in D-glucose is lost upon formation of glucose phenylosazone. Thus, *D-mannose gives the same phenylosazone as does D-glucose,* thus proving that the two aldohexoses have the same absolute stereochemistry at C-3, C-4, and C-5. Furthermore, the ketohexose, D-fructose, also gives glucose phenylosazone, thereby establishing that it also has this configuration at C-3, C-4, and C-5 (and, incidentally, that its carbonyl group is at C-2).

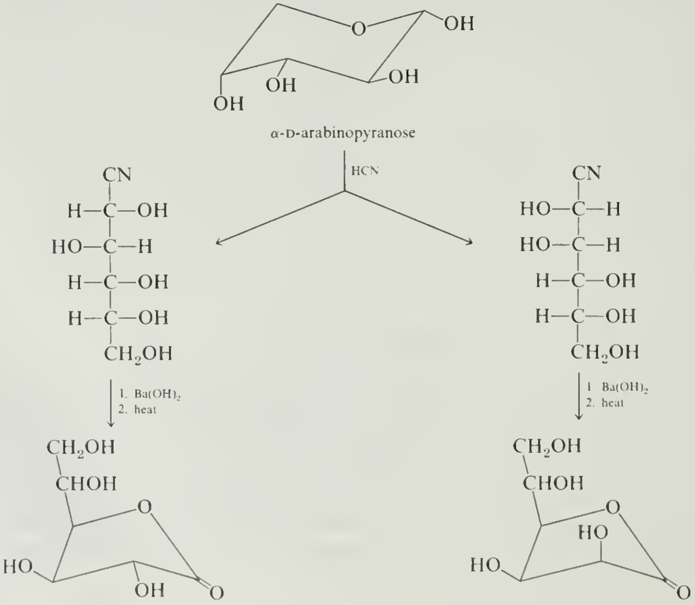

D-glucose
D-glucose phenylosazone
D-mannose
D-fructose

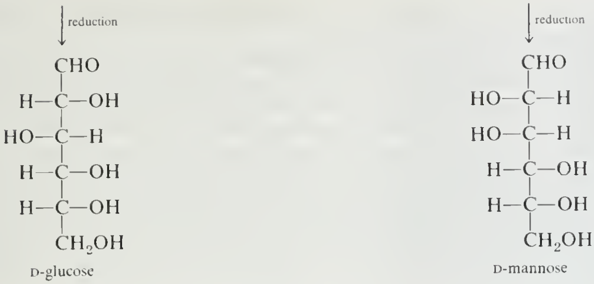
H. *Chain Extension: The Kiliani-Fischer Synthesis*

When D-glyceraldehyde is treated with HCN, a mixture of two cyanohydrins is produced. Both cyanohydrins have the R configuration at C-3, corresponding to the same configuration at C-2 in D-glyceraldehyde. They differ only in the configuration at C-2, the new asymmetric carbon. Hydrolysis of the two cyanohydrins yields the same aldonic acids as are produced by the mild oxidation of the aldotetroses D-erythrose and D-threose. Since glyceraldehyde is a chiral molecule, the transition states leading to the two cyanohydrins are diastereomeric, rather than enantiomeric, and two products are not produced in equal amounts (see Section 7.6).


CHO
H—C—OH
CH2OH
+ HCN
D-glyceraldehyde
CN
H—C—OH
H—C—OH
CH2OH
H3O+
COOH
H—C—OH
H—C—OH
CH2OH
Br2
H2O
CHO
H—C—OH
H—C—OH
CH2OH
D-erythrose
CN
HO—C—H
H—C—OH
CH2OH
H3O+
COOH
HO—C—H
H—C—OH
CH2OH
Br2
H2O
CHO
HO—C—H
H—C—OH
CH2OH
D-threose

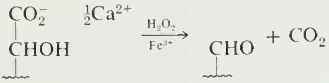
The cyanohydrin chain-lengthening procedure has been applied extensively in sugar chemistry and has come to be known as the **Kiliani-Fischer synthesis.** Fischer discovered that the aldonic acids produced by hydrolysis of the cyanohydrins lactonize on heating to aldonolactones. He also discovered that these lactones may be reduced with sodium amalgam at pH 3.0–3.5 to give a new aldose. A more modern method involves reduction of the lactone with aqueous sodium borohydride at pH 3–4. The complete Kiliani-Fischer synthesis provides a method for converting an aldopentose into an aldohexose or an aldohexose into an aldoheptose. The synthesis always provides two diastereomers, usually in unequal amounts, which differ only in their configuration at the new C-2 (old C-1). An example is D-arabinose, which yields a mixture of D-glucose and D-mannose.


O
OH
OH
OH
OH
α-D-arabinopyranose
HCN
CN
H—C—OH
HO—C—H
H—C—OH
H—C—OH
CH2OH
1. Ba(OH)2
2. heat
CH2OH
CHOH
O
HO
OH
O
CN
HO—C—H
HO—C—H
H—C—OH
H—C—OH
CH2OH
1. Ba(OH)2
2. heat
CH2OH
CHOH
O
HO
HO
O


reduction
reduction
D-glucose
D-mannose

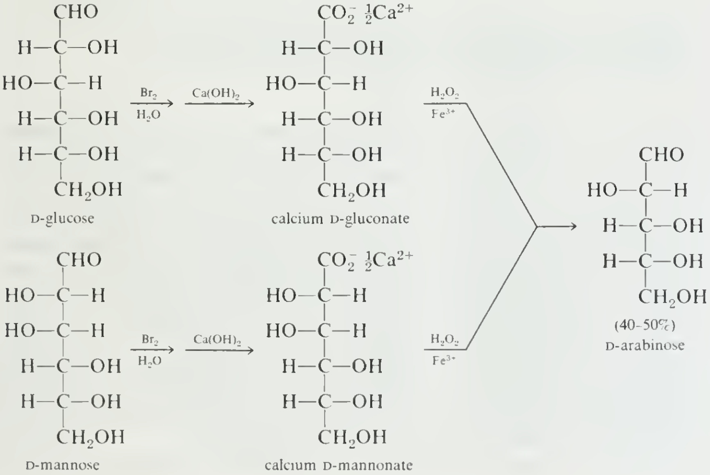
I. *Chain Shortening: The Ruff and Wohl Degradations*

In 1896, Ruff discovered that the calcium salts of aldonic acids are oxidized by hydrogen peroxide, the reaction being catalyzed by ferric salts. The oxidation occurs with cleavage of the C-1, C-2 bond and the product is the lower aldose.



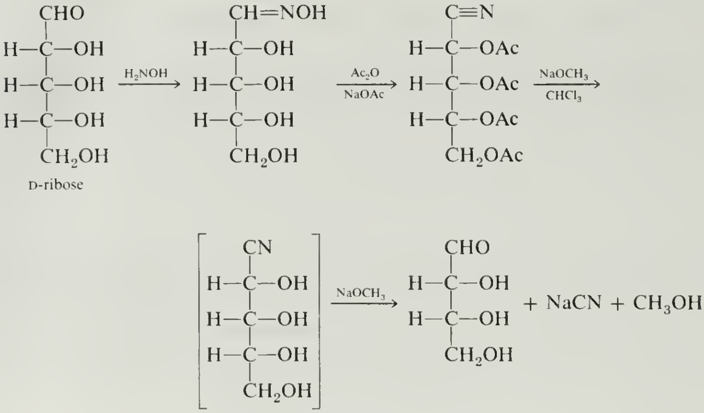
$$\overset{\mathrm{CO_2^-}\ \frac{1}{2}\mathrm{Ca^{2+}}}{\mathrm{CHOH}} \xrightarrow[\mathrm{Fe^{3+}}]{\mathrm{H_2O_2}} \mathrm{CHO} + \mathrm{CO_2}$$

Since aldohexoses may be readily oxidized to aldonic acids by bromine water (Section 25.5.E), the two-stage process provides a way of converting an aldohexose into an aldopentose; it is called the **Ruff degradation.** Although yields are not high, the Ruff degradation has been a useful technique for the synthesis of certain aldopentoses. Since asymmetry is lost at C-2, two aldohexoses that differ only in chirality at this center yield the same aldopentose.


D-glucose
Br₂
H₂O
Ca(OH)₂
calcium D-gluconate
H₂O₂
Fe³⁺
D-mannose
Br₂
H₂O
Ca(OH)₂
calcium D-mannonate
H₂O₂
Fe³⁺
(40-50%)
D-arabinose

Unfortunately, the process is not very useful for the conversion of aldopentoses into aldotetroses because of low yields.

Another process, called the **Wohl degradation,** accomplishes the same overall conversion, shortening the aldose chain by the removal of C-1. The Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis. The aldose is first converted into its oxime by treatment with hydroxylamine (Section 15.7.C). When the resulting polyhydroxy oxime is heated with acetic anhydride and sodium acetate, all of the hydroxy groups are acetylated and the oxime group is *dehydrated* to a cyano group. The product is the acetate ester of a cyanohydrin. The ester groups are removed by treatment with base. Under the basic conditions of hydrolysis, the cyanohydrin is decomposed to the corresponding aldehyde. Again, the process does not give especially high yields, but it is applicable to pentoses as well as to hexoses.



D-ribose

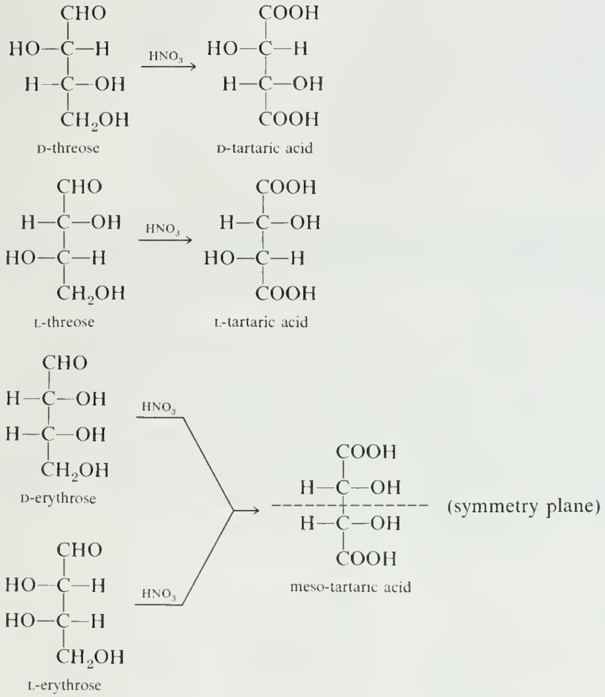
D-erythrose

25.6
Relative Stereochemistry of the Monosaccharides: The Fischer Proof

In the late nineteenth century, organic chemists were faced with a puzzling mystery regarding the structures of the monosaccharides. A number of compounds had been isolated which were known to have the same formula and which had the same connectivity. That is, the available evidence showed that glucose, galactose, and mannose were all 2,3,4,5,6-pentahydroxyhexanals. The Le Bel–Van't Hoff theory of stereoisomerism provided an explanation for this phenomenon. The challenging question was, which relative arrangement of the four asymmetric carbons corresponds to glucose, which to mannose, and so on?

The challenge was taken up by Emil Fischer, who succeeded in establishing the correct stereostructures for D-glucose, D-mannose, D-fructose, and D-arabinose in 1891. The structure proof consists of an elegant series of logical deductions and has come to be known as "the Fischer proof." We will present a modernized version of the proof here, because it typifies the method that has been used to establish the structures of all the sugars.

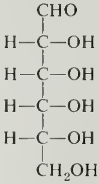
At the outset, Fischer realized that he could establish the *relative configuration* of the various asymmetric centers in a sugar, but that he had no way to determine the *absolute configuration* of any of the compounds. In order to understand this distinction, consider the four aldotetroses D- and L-threose and D- and L-erythrose. All four compounds are oxidized by nitric acid to saccharic acids. The enantiomeric D- and L-threoses give enantiomeric D- and L-2,3-dihydroxysuccinic acids, which are called D-tartaric acid and L-tartaric acid. However, both D- and L-erythrose are oxidized by nitric acid to a saccharic acid that is an optically inactive diacid, *meso*-tartaric acid. *Meso*-tartaric acid owes its optical inactivity to an internal symmetry plane, and hence the relative configuration of its two asymmetric carbons is fixed. It follows that one of the erythroses has the (R,R) configuration and the other has the (S,S) configuration. However, there was no way to tell which is which.



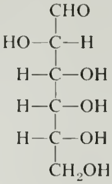
The question of the absolute configuration was not settled until 1954, when Bijvoet determined the absolute configuration of a salt of D-tartaric acid by an x-ray crystallographic technique known as anomalous dispersion.

1. Fischer started by arbitrarily choosing what is now called the (R) configuration for the stereochemistry at C-5 in D-glucose. He had a 50% chance of being correct in this assignment, but it has no bearing on the rest of the proof because the other centers were to be determined relative to C-5. In 1954, Bijvoet's work showed that Fischer had actually made the correct choice in an absolute sense. The structures of the eight aldohexoses having the (R) configuration at C-5 are shown in Table 25.2, and are designated **1** through **8**.

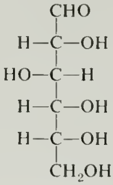
TABLE 25.2
The (5R)-Aldohexoses



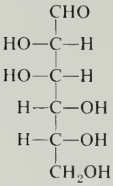
1



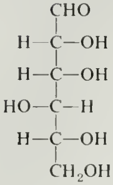
2



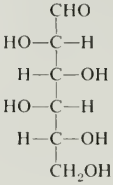
3



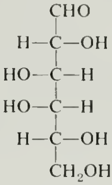
4



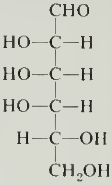
5



6



7

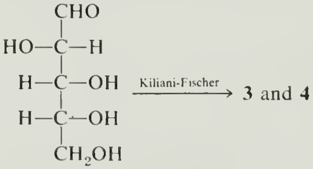


8

2. It was known that glucose and mannose give the same osazone (Section 25.5.G). Therefore, the two compounds have the same configuration at C-3, C-4, and C-5; they differ only at C-2. The two compounds must be **1** and **2**, **3** and **4**, **5** and **6**, or **7** and **8**.

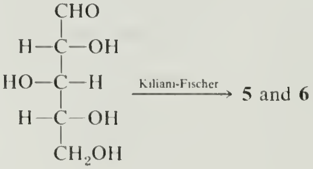
3. *Both* D-glucose and D-mannose are oxidized by nitric acid to *optically active* saccharic acids (Section 25.5.E). The aldohexoses with structures **1** and **7** would give *meso*-saccharic acids. Therefore, D-glucose and D-mannose must be either **3** and **4** or **5** and **6**. (Remember that the two compounds differ only at C-2, so eliminating **1** also eliminates **2**, and eliminating **7** also eliminates **8**.)

4. Kiliani-Fischer chain extension of the aldopentose D-arabinose yields both D-glucose and D-mannose (Section 25.5.H). Therefore, D-arabinose has the same configuration at its C-2, C-3, and C-4 as D-glucose and D-mannose at C-3, C-4, and C-5, respectively. D-Arabinose must be either



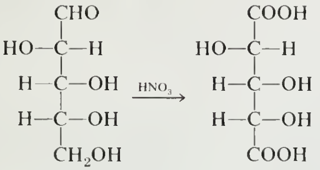
9

or



10

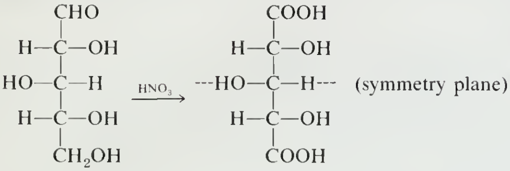
However, oxidation of D-arabinose gives an *optically active* diacid. The saccharic acid derived from aldopentose **10** would be *meso,* so D-arabinose must be **9**, and D-glucose and D-mannose must be **3** and **4**.



9, D-arabinose

optically active

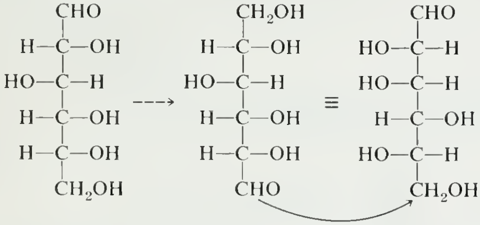
or



10

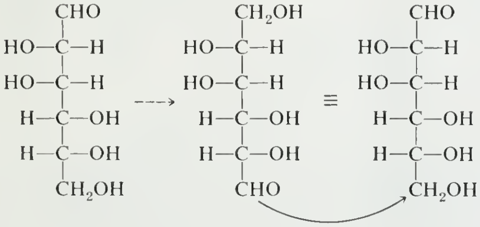
meso

5. Fischer developed a method that allowed him to *interchange* the two ends of an aldose chain. The method is fairly involved and we need not go into the chemical details here. However, consider the results when the method is applied to the aldohexoses that have structures **3** and **4**.



3

rotate structure 180°



4

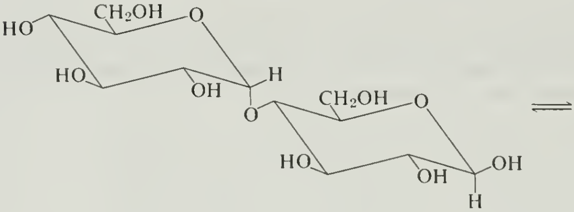
rotate structure 180°

When C-1 and C-6 are interchanged, compound **3** gives a *different aldohexose.* However, when the same operation is performed on compound **4**, the final product is the same as the starting material. Fischer applied his method to D-glucose, and discovered that a new aldohexose was produced, which he named L-gulose. The proof was complete; D-glucose must have structure **3** and D-mannose must have structure **4**!

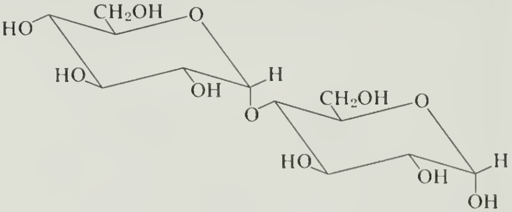
25.7
Oligosaccharides

Oligosaccharides (Greek, *oligos,* a few) are polysaccharides that yield from 2 to 8 monosaccharide units upon hydrolysis. The most common are the disaccharides, which are dimers composed of two monosaccharides. The two monosaccharides may be the same or different. Disaccharides are joined by a glycoside linkage from the OH group of one monosaccharide to the anomeric carbon of the other.

A simple example of a disaccharide is maltose, which is produced by the enzymatic hydrolysis of starch (Section 25.8). Maltose contains two D-glucose units, both in the pyranose form. The C-4 hydroxy group of one glucose is bound by an α-glycoside bond to the anomeric carbon of the other unit. The disaccharide is obtained in crystalline form in which the hydroxy group on the other anomeric carbon is β, but it mutarotates in solution to a mixture of the α and β forms.

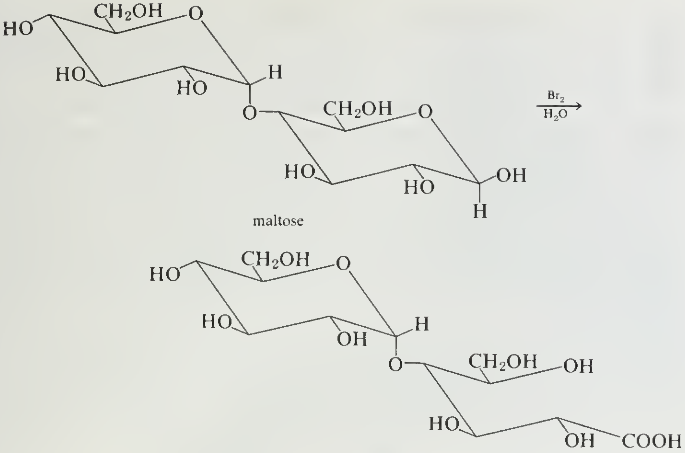


4-O-(α-D-glucopyranosyl)-β-D-glucopyranoside
β-maltose



4-O-(α-D-glucopyranosyl)-α-D-glucopyranoside
α-maltose

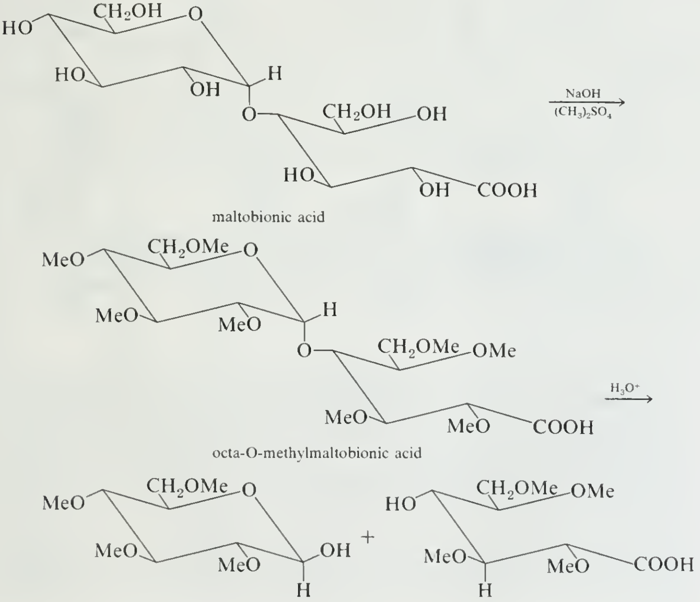
In maltose, one of the glucose units has its aldehyde carbon firmly bound in the glycosidic linkage to the other unit. However, the carbonyl group of the second ring is only in the hemiacetal form, and it may therefore undergo normal carbonyl reactions, just as the monosaccharides do. Thus, maltose is oxidized by Tollens reagent and by Fehling's solution and is a reducing sugar. Disaccharides undergo most of the same reactions as do the monosaccharides. For example, maltose is oxidized by bromine water to maltobionic acid.



maltose

maltobionic acid

The structure of maltose is shown by the following observations. Methylation of maltobionic acid gives octa-O-methylmaltobionic acid, which is hydrolyzed under acidic conditions. The products are 2,3,4,6-tetra-O-methyl-D-glucose and 2,3,5,6-tetra-O-methylgluconic acid. Thus, both rings in maltose exist in the pyranose form.



maltobionic acid

octa-O-methylmaltobionic acid

2,3,4,6-tetra-O-methyl-β-D-glucose

2,3,5,6-tetra-O-methyl-D-gluconic acid

The only remaining question is the stereochemistry of the glycoside link in maltose. This is established by the fact that the yeast enzyme α-glucosidase catalyzes the hydrolysis of maltose, whereas β-glucosidase does not affect the disaccharide (Section 25.3). Thus, the glycoside linkage in maltose is α.

Cellobiose is a disaccharide that is obtained by the partial hydrolysis of cellulose (Section 25.8). Its chemical properties are very similar to those of maltose. Like maltose, cellobiose is a reducing sugar; it is oxidized by bromine to cellobionic acid, which is methylated to octa-O-methylcellobionic acid. Hydrolysis of the latter gives the same two products as hydrolysis of octa-O-methylmaltobionic acid. The only difference is that the hydrolysis of cellobiose is catalyzed by β-glucosidase and not by α-glucosidase. Therefore, cellobiose is isomeric with maltose and contains a β-glycosidic linkage. The structure of β-cellobiose is shown in Figure 25.2.

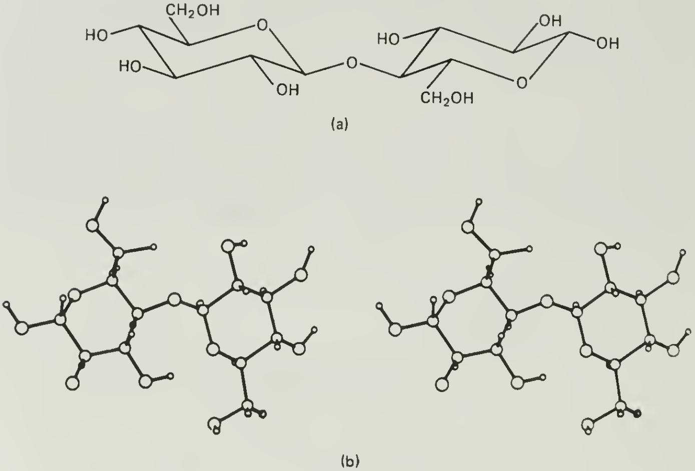
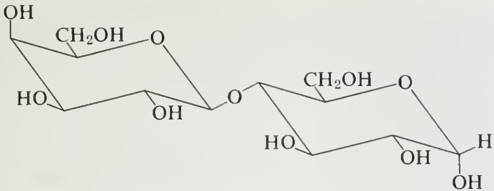


FIGURE 25.2 *β-Cellobiose,* 4-O-(β-D-*glucopyranosyl*)-β-D-*glucopyranoside:* (a) *conventional structure;* (b) *stereo structure.* [*Part* (b) *reproduced with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.*]

Lactose is an example of a disaccharide in which the two monosaccharide units are different. It constitutes about 5% by weight of mammalian milk. It is produced commercially from whey, which is obtained as a by-product in the manufacture of cheese. Evaporation of the whey at temperatures below 95° causes the less soluble α anomer to precipitate. Hydrolysis of lactose affords one equivalent of glucose and one equivalent of galactose. Application of the methylation technique to lactobionic acid shows that the galactose unit is bound in the glycoside form and that both rings are pyranoses. The hydrolysis of lactose is catalyzed by an enzyme called β-galactosidase, which is specific for the hydrolysis of β-galactoside links.



α-lactose
4-O-(β-D-galactopyranosyl)-α-D-glucopyranoside

Sucrose is one of the most widespread sugars in nature. It is produced commercially from sugar cane and sugar beets. It is a disaccharide composed of one D-glucose and D-fructose unit; these are joined by an acetal linkage *between the two anomeric carbons.* The glucose unit is in the pyranose form and the fructose is in the furanose form. The structure of sucrose is given in Figure 25.3. Since both anomeric carbons are bound in the acetal form, sucrose is a *nonreducing sugar.*

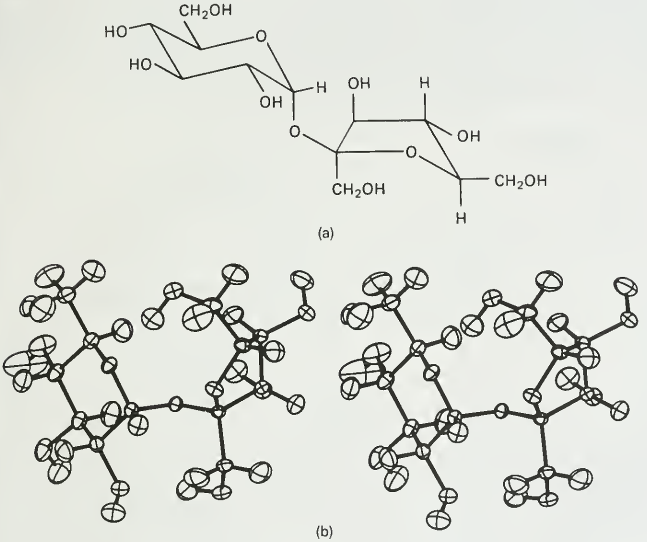


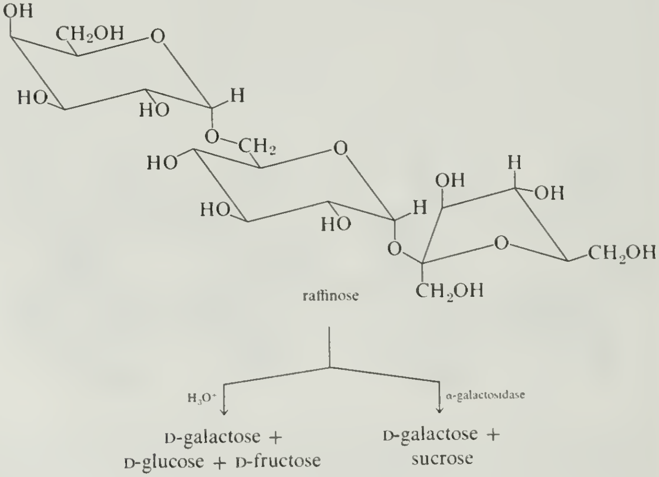
FIGURE 25.3 *Sucrose, α-D-glucopyranosyl-β-D-fructofuranoside or β-D-fructofuranosyl-α-D-glucopyranoside:* (a) *conventional structure;* (b) *stereo structure. The stereo structure also illustrates the way in which modern x-ray structure determinations are presented. The noncircular shapes of atoms are so-called "thermal ellipsoids" and represent thermal motions.* [*Part* (b) *reproduced with permission from G. M. Brown and H. A. Levy:* Acta Cryst., **B29:***790* (*1973*).]

Acidic hydrolysis of sucrose yields an equimolar mixture of D-glucose and D-fructose. Sucrose itself is dextrorotatory, having an optical rotation $[\alpha]_D = +66°$. D-Glucose is also dextrorotatory (the equilibrium mixture of α and β anomers has $[\alpha]_D = +52.5^\circ$), but D-fructose is strongly levorotatory (the equilibrium mixture of α and β anomers has $[\alpha]_D = -92.4^\circ$). In the early days of carbohydrate chemistry, D-glucose was known as "dextrose" and D-fructose was called "levulose," terms which were derived from the signs of rotation of the two monosaccharides.

In the process of hydrolysis, the dextrorotatory sucrose solution becomes levorotatory, because an equimolar mixture of D-glucose and D-fructose has $[\alpha]_D = -20^\circ$. This commonly encountered mixture is called "invert sugar," from the inversion in the sign of rotation that occurs during its formation. A number of organisms, including honey bees, have enzymes that catalyze the hydrolysis of sucrose. These enzymes are usually called **invertases**, and are specific for the β-D-fructofuranoside linkage. Honey is largely a mixture of D-glucose, D-fructose, and sucrose.

$$\underset{[\alpha]_D = +66^\circ}{\text{sucrose}} \xrightarrow[\text{or invertase}]{H_3O^+} \underbrace{\underset{[\alpha]_D = +52.5^\circ}{\alpha\text{- + }\beta\text{-D-glucose}} + \underset{[\alpha]_D = -92.4^\circ}{\alpha\text{- + }\beta\text{-D-fructose}}}_{[\alpha]_D = -20^\circ}$$

Raffinose is an example of a trisaccharide. It is a very minor constituent in sugar beets (0.01–0.02%), and is obtained as a by-product in the isolation of sucrose from this source. Raffinose is nonreducing, and on hydrolysis yields one equivalent each of D-galactose, D-glucose, and D-fructose. If the hydrolysis is catalyzed by the enzyme α-galactosidase, the products are galactose and sucrose.



25.8
Polysaccharides

Polysaccharides differ from the oligosaccharides only in the number of monosaccharide units that make up the molecule. The majority of the natural polysaccharides contain from 80 to 100 units, but some materials have much larger molecular weights; cellulose, for example, has an average of about 3000 glucose units per molecule. Polysaccharides may have a linear structure, in which the individual monosaccharides are joined one to the other by glycosidic bonds, or they may be branched. In a branched polysaccharide, there is a linear backbone, but, on some of the monosaccharide units, additional OH groups are involved in glycosidic bonding to another chain of sugars. A few cyclic polysaccharides are also known. The three types are illustrated schematically in Figure 25.4.

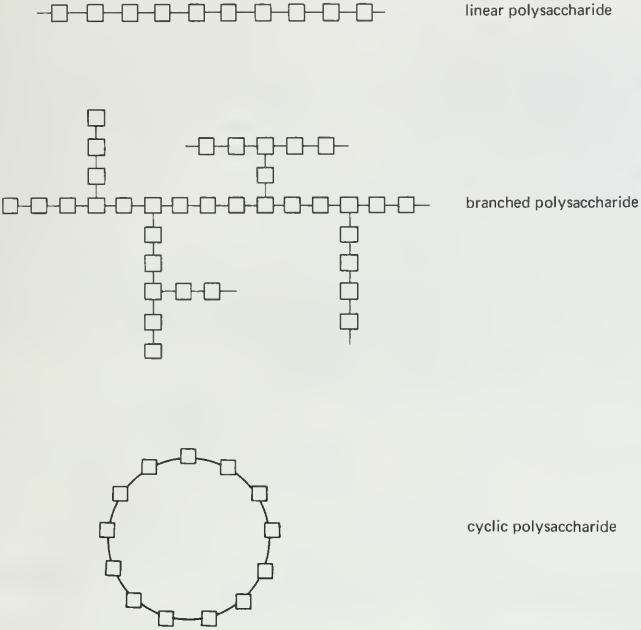
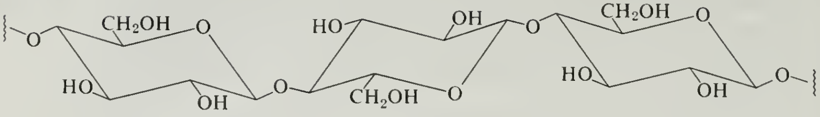


Figure 25.4 *Types of polysaccharides.*

Cellulose is probably the single most abundant organic compound that exists on the earth. It is the chief structural component of plant cells. For example, it comprises 10–20% of the dry weight of leaves, about 50% of the weight of tree wood and bark, and about 90% of the weight of cotton fibers, from which pure cellulose is most easily obtained. Filter paper is a source of almost pure cellulose in the laboratory.

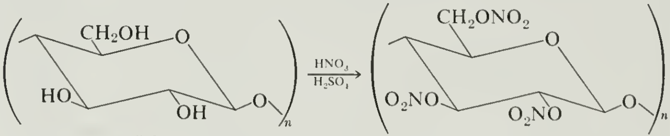
Structurally, cellulose is a polymer of D-glucose, in which the individual units are linked by β-glucoside links from the anomeric carbon of one unit to the C-4 hydroxy of the next unit. It may be hydrolyzed by 40% aqueous hydrochloric acid to give D-glucose in 95% yield. Partial hydrolysis, which may be brought about by enzymatic methods, yields the disaccharide cellobiose (Section 25.7). It is a linear polysaccharide, the isolated form containing an average of 3000 units per chain, corresponding to an average molecular weight of about 500,000. Some degradation occurs during the isolation; the actual "native cellulose," as it exists in plants, may contain as many as 10,000–15,000 glucose units per chain, corresponding to a molecular weight of 1.6–2.4 million. The strength of wood derives principally from hydrogen bonds of one chain with hydroxy groups of neighboring chains.



cellulose

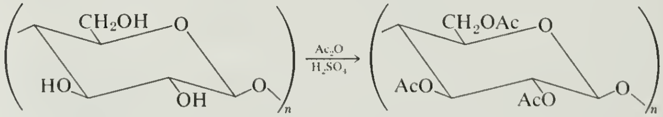
Although the higher animals do not have enzymes that can catalyze the degradation of cellulose to glucose, such enzymes (**cellulases**) are common in microorganisms. Cellulases produced by the microflora that reside in the digestive tracts of herbivorous animals permit these animals to utilize cellulose as a food source.

Various chemically modified forms of cellulose have long been used in commercial applications. Cellulose may be nitrated by a mixture of HNO_3 and H_2SO_4. The product is a partially degraded cellulose in which some of the free OH groups have been converted into nitrate esters (Section 18.13.C). The average number of nitrate ester groups per glucose unit is variable and depends on the composition of the nitrating mixture and the reaction time. Highly nitrated cellulose, in which 2.5–2.7 OH groups per glucose unit are nitrated, has explosive properties and has been used in the manufacture of blasting powder. Nitrated cellulose possessing a lower nitrogen content (2.1–2.5 ONO_2 groups per glucose unit) is used in the preparation of plastics (celluloid) and lacquers.



cellulose cellulose trinitrate

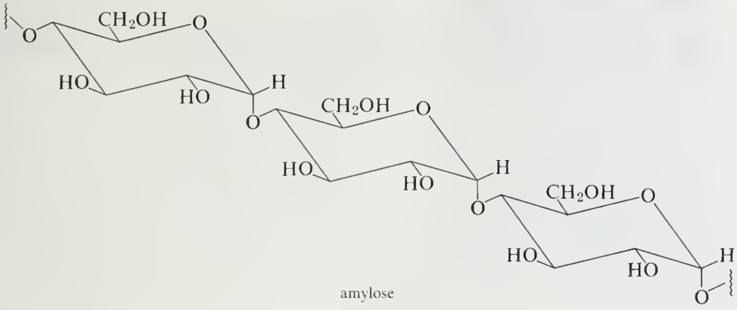
Cellulose acetate, prepared by acetylation of cellulose with acetic anhydride and sulfuric acid, is used in the manufacture of rayon.



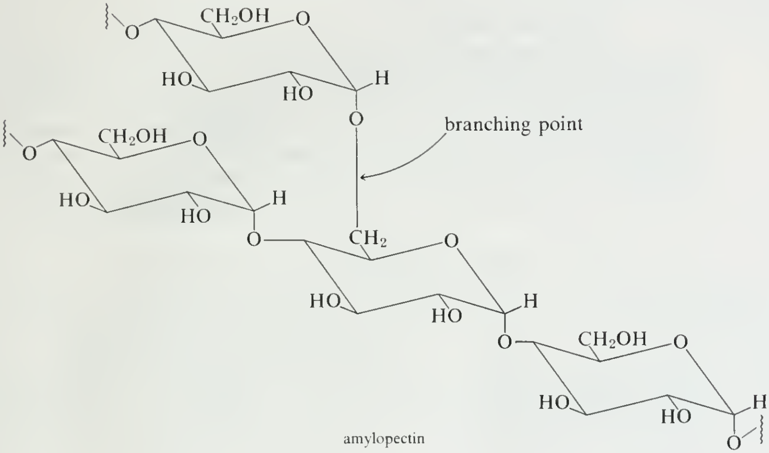
cellulose cellulose triacetate "rayon"

Starch is the second most abundant polysaccharide, and occurs in both the vegetable and animal kingdoms. It is the chief source of carbohydrate for humans and is therefore of considerable economic importance. The polysaccharide is deposited in the plant in the form of small insoluble particles, called starch granules. Like cellulose, the term starch is a general one; there is a considerable variety in the nature of the starch molecules produced by a given plant. Natural starch may be separated into two gross fractions, called **amylose** and **amylopectin.**

Like cellulose, starch yields only D-glucose on hydrolysis. Although amylose appears to be essentially unbranched, amylopectin has a highly branched structure. Both types of starch have very high molecular weights, corresponding to many thousands of glucose units per molecule. The main chain consists of D-glucose units bound through the C-4 OH group as in cellulose, but with the glucoside bond having the α configuration. In the branched form, the branches appear to be to the C-6 OH group.



amylose



amylopectin

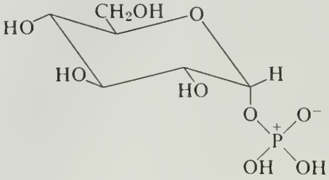
Partial hydrolysis of starch yields the disaccharide maltose (Section 25.7).

Glycogen is a polysaccharide that is structurally similar to starch. It is the form in which animals store glucose for further use. It is found in most tissues, but the best source is liver or muscle. Glycogen has a structure similar to that of amylopectin, but is more highly branched.

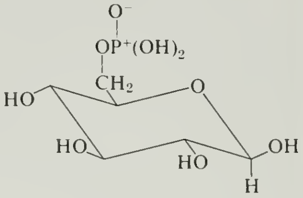
25.9
Sugar Phosphates

The sugar phosphates are a class of carbohydrates that is particularly important in living systems. The chemistry of phosphate esters was discussed in Section 18.13.B. Sugar phosphates are intermediates in many metabolic processes, such as the degradation of glycogen to lactic acid in muscle (glycolysis), the fermentation of sugars to alcohol, and the biosynthesis of carbohydrates in plants by the process of photosynthesis. They are also constituents of ribonucleic and deoxyribonucleic acids (RNA and DNA), which are of utmost importance in the transfer of genetic information.

Typical sugar phosphates, which are known to be involved in the biosynthesis and biodegradation of the polysaccharides glycogen and starch, are α-D-glucopyranosyl phosphate and D-glucose 6-phosphate.

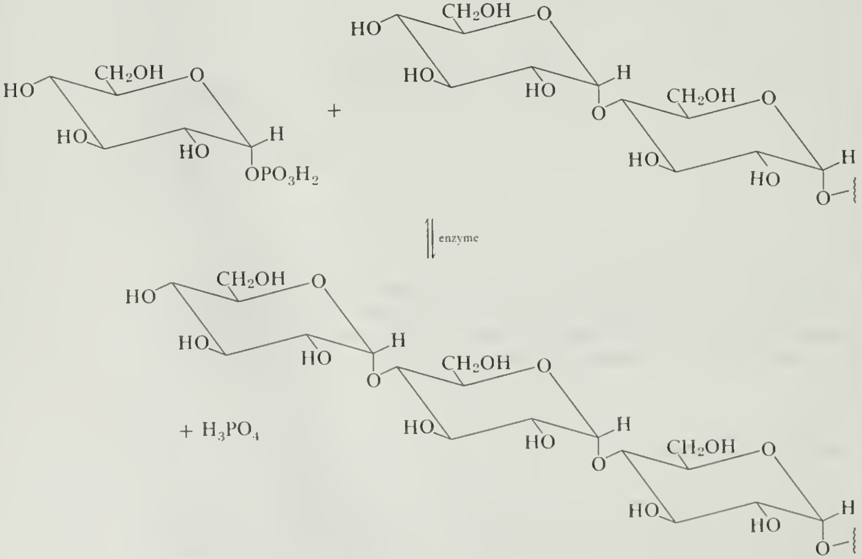


α-D-glucopyranosyl phosphate



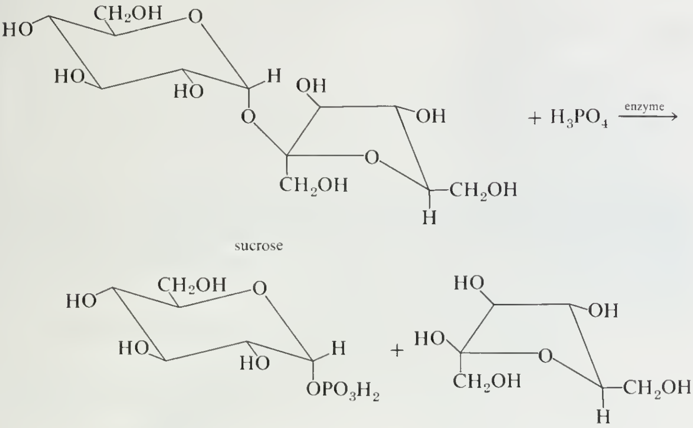
D-glucose 6-phosphate

These polysaccharides are synthesized in organisms by an enzyme-catalyzed process in which glucose units are added in a stepwise fashion onto the growing polysaccharide chain. The glucose units are in the form of α-D-glucopyranosyl phosphate, in which form the anomeric carbon is "activated" toward nucleophilic substitution processes (phosphate ion is a much better leaving group than hydroxide ion). The process is reversible, and the reverse process is the method whereby the organism degrades, or depolymerizes, the polysaccharide.



Similar enzymes catalyze the formation and cleavage of the 1 → 6 glycosidic bond by way of D-glucose 6-phosphate.

α-D-Glucopyranosyl phosphate is also involved in the formation and degradation of sucrose.



sucrose

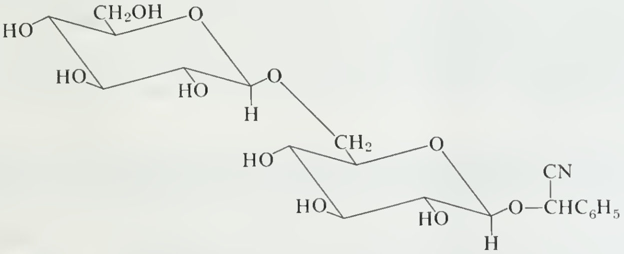
α-D-glucopyranosyl phosphate

D-fructose

25.10
Natural Glycosides

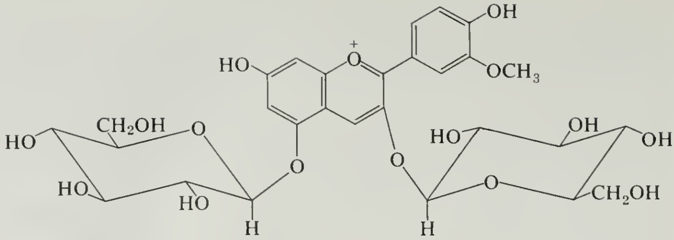
Sugars are often found to occur in organisms in the form of glycosides. Hydrolysis of a glycoside yields the sugar (the **glycosyl residue**) and the alkyl or aryl group to which it is bound (the **aglycon**). There are many types of glycosides and we shall only give a few examples here.

Amygdalin was one of the first glycosides to be discovered. It occurs in bitter almonds and is a glycoside formed from the disaccharide gentiobiose and the cyanohydrin of benzaldehyde. Almonds contain an enzyme that catalyzes the conversion of amygdalin to HCN, benzaldehyde, and two molecules of D-glucose.



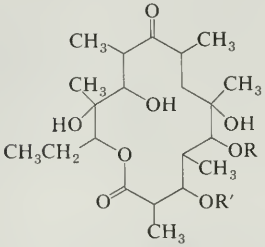
amygdalin

Another example is peonin, which is responsible for the color of the dark red peony.



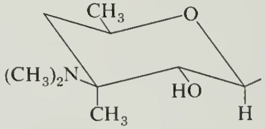
peonin

A number of naturally occurring antibiotics contain sugars bound as glycosides. The glycosyl groups often have unusual structures. An example is erythromycin, which is one of the most widely used antibiotics. The aglycon is a 14-membered lactone containing four hydroxy groups, two of which are bound to the rare monosaccharides cladinose and desoamine.



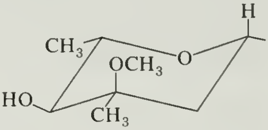
erythromycin

R =



desoamine

R′ =



cladinose

PROBLEMS

1. Assign (R) and (S) notations to all of the aldoses in Table 25.1.

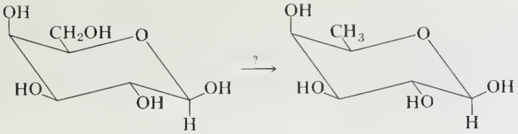
2. Construct a "family tree," similar to that in Table 25.1, that contains the structures for all of the D-ketoses having six or fewer carbons. Identify which aldoses and ketoses will give the same osazones.

3. Using Table 25.1, identify all of the aldoses that give *meso* saccharic acids on oxidation by nitric acid.

4. 5-Hydroxy-2-heptanal exists in two cyclic hemiacetal forms. Write three-dimensional structures for the two compounds. Which is the more stable? Write a mechanism for interconversion of the two forms under conditions of acid catalysis and base catalysis.

5. (a) Draw three-dimensional projection structures for the two conformations of β-D-xylopyranose. Predict which conformation predominates in solution.
   (b) Answer part (a) for α-D-arabinopyranose.

6. Suggest a method for the synthesis of 6-deoxygalactose from galactose. (*Hint:* see page 706.)



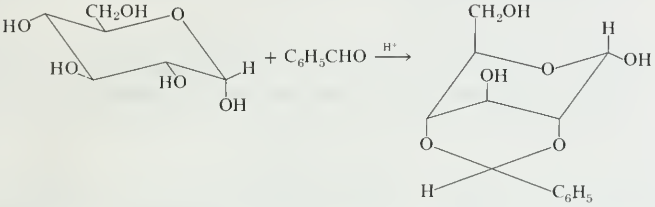
galactose 6-deoxygalactose

7. Consider the addition of HCN to 2-methylcyclopentanone. Write structures for the two diastereomeric cyanohydrins that can result. Construct molecular models for the two compounds. Assuming that addition of cyanide ion to the protonated ketone is the rate-limiting step, which diastereomeric cyanohydrin should form faster?

8. (a) Write equations that show the application of the Kiliani-Fischer synthesis to each of the D-aldotetroses. Which aldopentoses are obtained from D-threose and which from D-erythrose?
   (b) Answer part (a) for the aldopentoses.

9. Write equations that show the application of the Ruff degradation to each of the D-aldohexoses. Which aldopentoses are obtained from each aldohexose?

10. Under the proper conditions, D-glucose reacts with benzaldehyde to give 2,4-O-benzylidine-D-glucose.



2,4-O-benzylidine-D-glucose

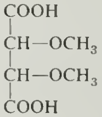
This compound is reduced to 2,4-O-benzylidine-D-glucitol, which reacts with periodic acid to give the benzylidine derivative of an aldopentose. Hydrolysis of the latter compound gives the aldopentose. What is the structure and name of the aldopentose?

11. Complete acid- or base-catalyzed hydrolysis of one class of nucleic acids yields a D-aldopentose, A, phosphoric acid, and several purine and pyrimidine bases. Nitric acid oxidation of A yields a *meso*-diacid, B. Treatment of A with hydroxylamine forms the oxime, C, which upon treatment with acetic anhydride is converted into an acetylated cyanohydrin, D. Hydrolysis of compound D gives an aldotetrose, E, which is oxidized by nitric acid to a *meso*-diacid, F. What are the structures of compounds A through F?

12. A disaccharide, G, $C_{11}H_{20}O_{10}$, is hydrolyzable by α-glucosidase, yielding D-glucose and a D-pentose. The disaccharide does not reduce Fehling's solution. Methylation of G with dimethyl sulfate in NaOH yields a heptamethyl ether, H, which upon acid hydrolysis yields 2,3,4,6-tetra-O-methyl-D-glucose and a pentose tri-O-methyl ether, (I). Oxidation of I by bromine water yields 2,3,4-tri-O-methyl-D-ribonic acid. Assign structures to compounds G through I compatible with these data.

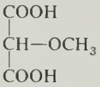
13. A naturally occurring compound (J) has the formula $C_7H_{14}O_6$. It is nonreducing and does not mutarotate. Compound J is hydrolyzed by aqueous HCl to compound K, $C_6H_{12}O_6$, a reducing sugar. Oxidation of K with dilute HNO_3 gives an optically

inactive diacid (L, $C_6H_{10}O_8$). Ruff degradation of K gives a new reducing sugar, M, $C_5H_{12}O_5$, which is oxidized by dilute HNO_3 to an optically active diacid (N, $C_5H_8O_7$). Compound J is treated successively with NaOH and dimethyl sulfate, aqueous HCl, and hot nitric acid. From the product mixture, one may isolate α,β-dimethoxysuccinic acid and α-methoxymalonic acid



$$\begin{array}{l} COOH \\ | \\ CH{-}OCH_3 \\ | \\ CH{-}OCH_3 \\ | \\ COOH \end{array}$$

α,β-dimethoxysuccinic acid



$$\begin{array}{l} COOH \\ | \\ CH{-}OCH_3 \\ | \\ COOH \end{array}$$

α-methoxymalonic acid

(a) Give structures for compounds J through N.
(b) What structural ambiguity exists, if any?

14. An aldopentose, O, is oxidized to a diacid, P, which is optically active. Compound O is also degraded to an aldotetrose, Q, which undergoes oxidation to an optically inactive diacid, R. Assuming that O has the D configuration (4R), what are the structures of O through R?

15. Aldohexose S is reduced by sodium borohydride ($NaBH_4$) to an optically inactive alditol, T. Ruff degradation of S gives an aldopentose, U, which is oxidized by nitric acid to an optically active saccharic acid, V. What are compounds S through V, assuming them to be D-sugars?

16. Oxidation of aldohexose W by nitric acid gives an optically active saccharic acid, X. Ruff degradation of W gives an aldopentose, Y, which yields an optically inactive diacid, Z, on nitric acid oxidation. When compound W is subjected to a series of reactions that exchange C-1 and C-6, the same aldohexose is obtained. Assuming them to be D-sugars, what are compounds W through Z?

17. The optical rotations for the α and β anomers of D-mannose are as follows: α, $[\alpha]_D = +29.3°$; β, $[\alpha]_D = -17.0°$. In water solution, each form mutarotates to an equilibrium value of $[\alpha]_D = +14.2°$. Calculate the percentage of each anomer present at equilibrium.

18. The disaccharide melibiose is hydrolyzed by dilute acid to a mixture of D-glucose and D-galactose. Melibiose is a reducing sugar and is oxidized by bromine water to melibionic acid, which is methylated by sodium hydroxide and dimethyl sulfate to octa-O-methylmelibionic acid. Hydrolysis of the latter gives a tetra-O-methylgluconic acid (AA) and a tetra-O-methylgalactose (BB). Compound AA is oxidized by nitric acid to tetra-O-methylglucaric acid. Compound BB is also obtained by the acidic hydrolysis of methyl 2,3,4,6-tetra-O-methylgalactopyranoside. Melibiose is hydrolysed by an α-galactosidase from almonds. What is the structure of melibiose?

19. The trisaccharide gentianose is hydrolyzed by acid to two equivalents of D-glucose and one of D-fructose. Partial acid hydrolysis yields D-fructuse and gentiobiose (page 731). The enzymes of almond emulsion cleave gentianose into D-glucose and sucrose. What is the structure of gentianose?

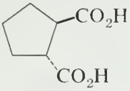
20. Write Haworth projections for the following saccharides:
(a) α-D-galactopyranose
(b) methyl β-D-mannoside
(c) α-maltose
(d) β-cellobiose

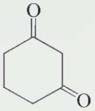
CHAPTER 26
Difunctional Compounds II

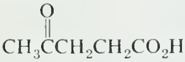
In Chapter 24, we considered the chemistry of diols and hydroxy carbonyl compounds. We saw how two functional groups in the same molecule may interact in such a way as to give the difunctional compound chemical properties that are not common to the simple monofunctional compounds. In this chapter, we shall extend that discussion and consider the chemistry of dicarbonyl compounds —dicarboxylic acids, diketones, keto acids, and their derivatives.

26.1
Nomenclature

The dicarbonyl compounds are named in the IUPAC system in the same way as the other difunctional compounds considered in Section 24.2.


trans-1,2-cyclopentane**dicarboxylic acid**

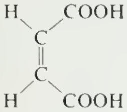

1,3-cyclohexane**dione**

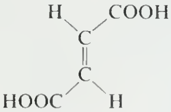

$CH_3\overset{\overset{\large O}{\|}}{C}CH_2CH_2CO_2H$

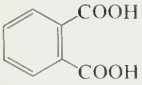
4-**oxo**pentan**oic acid**

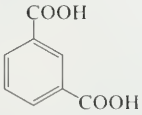
The acyclic dicarboxylic acids having up to ten carbon atoms in their chains have common names that are well entrenched in the chemical literature. The names of the diacids up to seven carbons, listed in Table 26-1, should be memorized by the student.

Some other dicarboxylic acids important in organic chemistry are unsaturated and aromatic acids.


maleic acid
cis-butenedioic acid


fumaric acid
trans-butenedioic acid


phthalic acid


isophthalic acid

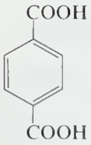
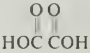
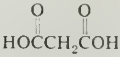
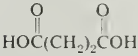
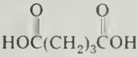
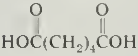
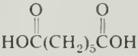
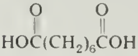
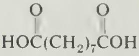
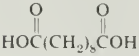
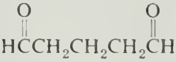

terephthalic acid

TABLE 26.1

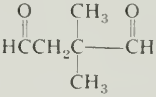
n	Formula	Common	IUPAC
C_2	 $HO\overset{\overset{O}{\|}}{C}\overset{\overset{O}{\|}}{C}OH$	oxalic acid	ethanedioic acid
C_3	 $HO\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OH$	malonic acid	propanedioic acid
C_4	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_2\overset{\overset{O}{\|}}{C}OH$	succinic acid	butanedioic acid
C_5	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_3\overset{\overset{O}{\|}}{C}OH$	glutaric acid	pentanedioic acid
C_6	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_4\overset{\overset{O}{\|}}{C}OH$	adipic acid	hexanedioic acid
C_7	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_5\overset{\overset{O}{\|}}{C}OH$	pimelic acid	heptanedioic acid
C_8	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_6\overset{\overset{O}{\|}}{C}OH$	suberic acid	octanedioic acid
C_9	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_7\overset{\overset{O}{\|}}{C}OH$	azelaic acid	nonanedioic acid
C_{10}	 $HO\overset{\overset{O}{\|}}{C}(CH_2)_8\overset{\overset{O}{\|}}{C}OH$	sebacic acid	decanedioic acid

The aromatic acids are discussed in detail in Section 31.5.

Aldehydes corresponding to these common diacids are frequently named as derivatives of the acids.

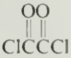

$H\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}H$

glutaraldehyde

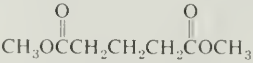

$H\overset{\overset{O}{\|}}{C}CH_2\overset{CH_3}{\underset{CH_3}{C}}-\overset{\overset{O}{\|}}{C}H$

α,α-dimethylsuccinaldehyde

Functional derivatives of the common diacids are named in an analogous manner.


$Cl\overset{\overset{O}{\|}}{C}\overset{\overset{O}{\|}}{C}Cl$

oxalyl chloride


$CH_3O\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OCH_3$

dimethyl glutarate

26.2
Dicarboxylic Acids

A. Preparation and Properties

The simple dicarboxylic acids are colorless crystalline compounds. Some have important commercial significance.

Oxalic acid occurs in many plants such as rhubarb, usually as the potassium salt. The insoluble calcium salt is found in plant cells and in some calculi, stony deposits found in the body. The acid is poisonous. It is prepared commercially by reaction of carbon monoxide with sodium hydroxide.

Several dicarboxylic acids may be prepared by methods involving the hydrolysis of nitriles. For example, malonic acid is prepared from chloroacetic acid via cyanoacetic acid. The displacement reaction and the alkaline hydrolysis are carried out in one operation and the product is isolated in about 80% yield.

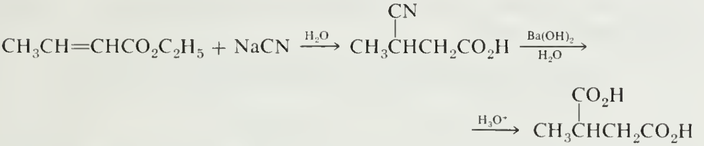
$$ClCH_2CO_2H + NaOH + NaCN \xrightarrow{H_2O} [NCCH_2CO_2^- \ Na^+] \xrightarrow[H_2O]{NaOH}$$

$$Na^{+-}O_2CCH_2CO_2^- \ Na^+ \xrightarrow{HCl} \underset{(77\text{–}82\%)}{HO_2CCH_2CO_2H}$$

A similar example is the synthesis of glutaric acid by the acid-catalyzed hydrolysis of 1,3-dicyanopropane.

$$BrCH_2CH_2CH_2Br \xrightarrow[H_2O]{NaCN} \underset{\substack{(82\%) \\ \text{glutaronitrile}}}{NCCH_2CH_2CH_2CN} \xrightarrow[H_2O]{HCl} \underset{\substack{(84\%) \\ \text{glutaric acid}}}{HO_2CCH_2CH_2CH_2CO_2H}$$

Succinic acid derivatives are often available by conjugate addition of cyanide to α,β-unsaturated esters (Section 20.3.A.). Hydrolysis of the β-cyano acid yields the corresponding succinic acid.

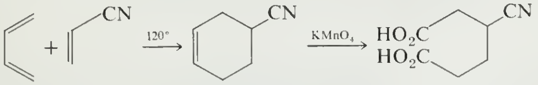


$$CH_3CH{=}CHCO_2C_2H_5 + NaCN \xrightarrow{H_2O} CH_3\overset{\overset{CN}{|}}{C}HCH_2CO_2H \xrightarrow[H_2O]{Ba(OH)_2}$$

$$\xrightarrow{H_3O^+} CH_3\overset{\overset{CO_2H}{|}}{C}HCH_2CO_2H$$

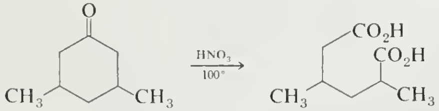
(66–70%)
α-methylsuccinic acid
2-methylbutanedioic acid

Certain diacids are conveniently prepared by the oxidation of cyclic alkenes or ketones. This is particularly true for adipic acid derivatives, because cyclohexane derivatives are generally readily available. Several examples are



cyclohex-3-ene-carbonitrile

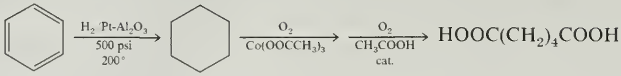
β-cyanoadipic acid
3-cyanohexanedioic acid



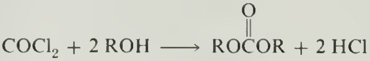
3,5-dimethylcyclohexanone

(60%)
α,β′-dimethyladipic acid
2,4-dimethylhexanedioic acid

Adipic acid is manufactured on a large scale by several methods, one of which is the oxidation of cyclohexane or cyclohexene. The United States production of adipic acid in 1971 was almost a billion pounds, and essentially all of it was used for making nylon and derived polymers (Section 27.7.A).



One acid that is usually considered to be an inorganic acid of carbon is carbonic acid. However, important organic derivatives are known. The diacyl chloride, phosgene, $COCl_2$, is prepared commercially by allowing CO and Cl_2 to react in the presence of a catalyst. Phosgene reacts with alcohols to give dialkyl carbonates.



$$COCl_2 + 2\,ROH \longrightarrow \underset{\substack{\text{dialkyl}\\ \text{carbonate}}}{RO\overset{\overset{\displaystyle O}{\|}}{C}OR} + 2\,HCl$$

The diamide of carbonic acid, urea, H_2NCONH_2, is a metabolic product that has important commercial and historical significance in organic chemistry (Chapter 1).

B. *Acidity of Dicarboxylic Acids*

The dicarboxylic acids are dihydric acids and are characterized by two dissociation constants, K_1 and K_2.

$$HOOC(CH_2)_nCOOH \overset{K_1}{\rightleftharpoons} HOOC(CH_2)_nCO_2^- + H^+$$

$$HOOC(CH_2)_nCO_2^- \overset{K_2}{\rightleftharpoons} {}^-O_2C(CH_2)_nCO_2^- + H^+$$

The dissociation constants for several diacids are summarized in Table 26.2. If we treat the COOH group as a substituent in acetic acid, YCH_2COOH, the higher acidity of malonic acid compared to acetic acid ($pK_\alpha = 4.76$) indicates that the COOH group acts as an electron-attracting inductive group.

Be careful of statistical effects in this comparison. Malonic acid has two COOH groups which can lose a proton and would be expected to have a dissociation constant twice that of acetic acid because of this statistical effect alone.

TABLE 26.2
Acidity of Alkanedioic Acids

Acid	$K_1 \times 10^{-5}$ M	$K_2 \times 10^{-5}$ M	pK_1	pK_2
oxalic	5400	5.4	1.27	4.27
malonic	140	0.20	2.85	5.70
succinic	6.2	0.23	4.21	5.64
glutaric	4.6	0.39	4.34	5.41
adipic	3.7	0.39	4.43	5.41

The acid-strengthening effect of a carboxylic acid substituent is not unexpected. All carbonyl groups have this effect because of the associated dipole which provides electrostatic stabilization of the negative charge of a carboxylate anion.

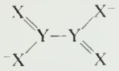
$$\overset{\text{electrostatic attraction}}{\overbrace{\overset{\longleftarrow\!+}{\text{HOOC}\sim\sim\text{CO}_2^-}}}$$

On the other hand, K_2 for a dicarboxylic acid is generally less than the dissociation constant of acetic acid. The presence of a carboxylate ion substituent reduces the acidity of an acid. This effect is clearly associated with the electrostatic repulsion of two negative charges in the dicarboxylate ion.

$$\overset{\text{electrostatic repulsion}}{\overbrace{{}^-\text{O}_2\text{C}\sim\sim\text{CO}_2^-}}$$

As expected for such a phenomenon, both the acid-strengthening effect of a carboxylic acid substituent and the acid-weakening effect of a carboxylate anion diminish with distance down a chain.

The second dissociation constant of oxalic acid seems anomolous by this comparison. Oxalate monoanion is *more* acidic than a neutral alkanoic acid despite the high electrostatic repulsion inherent in the oxalate dianion. X-ray crystal structure studies of alkali metal salts, such as dilithium and dipotassium oxalate, show an essentially planar oxalate dianion. There appears to be some special electronic stabilization in a planar eight-electron π system of the type



An isoelectronic inorganic compound that shows a related stabilization is N_2O_4. This apparent electronic phenomenon has not yet been extensively studied.

C. *Behavior on Heating*

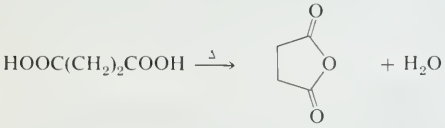
Anhydrous oxalic acid can be sublimed by careful heating, but at higher temperatures it decomposes to carbon dioxide and formic acid. Formic acid also decomposes under these conditions to carbon monoxide and water.

Malonic acid decarboxylates smoothly on heating to give acetic acid.

$$\text{HOOCCH}_2\text{COOH} \xrightarrow{150^\circ} \text{CO}_2 + \text{CH}_3\text{COOH}$$

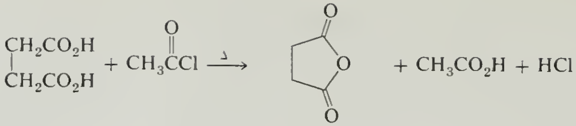
This reaction is general for all substituted malonic acids and for β-keto acids as well. The reaction will be discussed in greater detail in Section 26.4.A.

Succinic and glutaric acids lose water on heating to give cyclic anhydrides.



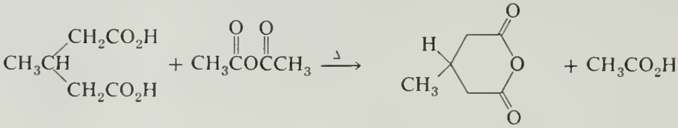
succinic anhydride

However, the preparation of these anhydrides is best accomplished by heating with acetyl chloride or acetic anhydride. These reagents react with the water produced by the dehydration.


CH2CO2H
CH2CO2H
+ CH3CCl
Δ
O
+ CH3CO2H + HCl

(95%)

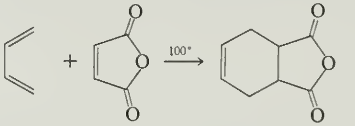
succinic acid succinic anhydride


CH3CH
CH2CO2H
CH2CO2H
+ CH3COCCH3
Δ
H
CH3
O
+ CH3CO2H

(76%)

β-methylglutaric acid β-methylglutaric anhydride

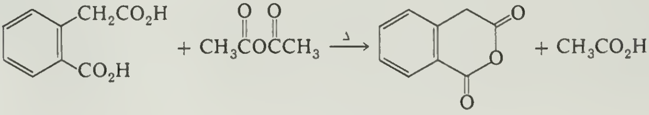
The formation of five- and six-membered ring anhydrides is a general reaction for related dicarboxylic acids. Maleic anhydride is an important organic reagent which is especially useful as a dienophile in Diels-Alder reactions (Section 23.4.B).



(90%)

butadiene maleic anhydride cyclohex-4-ene-1,2-dicarboxylic anhydride

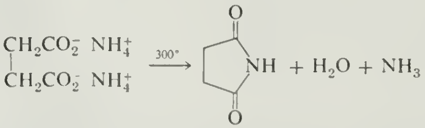
Phthalic anhydride is discussed in Section 31.5.A. Another example that shows the generality of formation of cyclic anhydrides is


CH2CO2H
CO2H
+ CH3COCCH3
Δ
O
+ CH3CO2H

(88%)

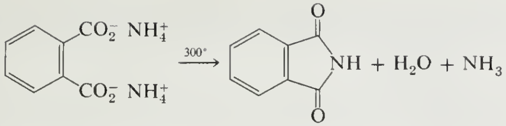
Other dehydrating agents which have been used for the formation of cyclic anhydrides are PCl_5, P_2O_5, $POCl_3$, and $SOCl_2$.

Succinic and glutaric acid and their derivatives also form cyclic **imides** with ammonia and primary amines. Five-membered ring imides form the most readily; pyrolysis of the diammonium salt often gives excellent yields.


CH2CO2- NH4+
CH2CO2- NH4+
300°
O
NH
+ H2O + NH3

(83%)

ammonium succinate succinimide

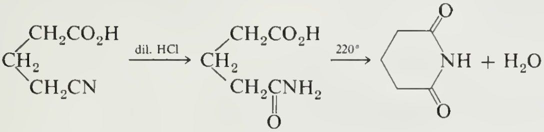


(97%)

ammonium phthalate

phthalimide

Six-membered ring imides form less readily; a convenient method of preparation involves pyrolysis of the monoamide of the corresponding dicarboxylic acid, as illustrated by the following example.



(65% overall)

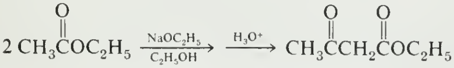
glutarimide

26.3
Synthesis of Dicarbonyl Compounds

Of the various possible types of keto acids, diketones and ketoaldehydes, the β-dicarbonyl or 1,3-dicarbonyl compounds are the most important, both because of their accessibility via the Claisen condensation and because of some important and distinctive chemical properties. We will first discuss the preparation of some types of dicarbonyl compounds and then develop their reactions. However, we shall see that the preparation of several types of dicarbonyl compounds depend on the chemical reactions of the β-dicarbonyl function.

A. *β-Dicarbonyl Compounds: The Claisen Condensation*

A number of different 1,3-dicarbonyl compounds are available by a reaction known as the **Claisen condensation.** A simple example is the self-condensation of ethyl acetate, which occurs when the ester is treated with sodium ethoxide in refluxing ethanol.



$$2\,CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 \xrightarrow[C_2H_5OH]{NaOC_2H_5} \xrightarrow{H_3O^+} CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5$$

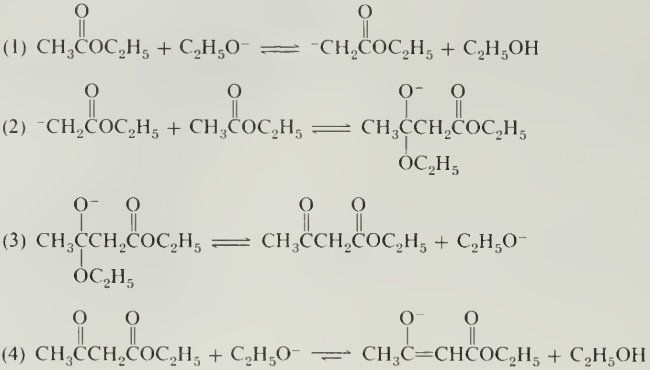
(75%)

A mixture of 1.2 moles of ethyl acetate and 0.2 moles of alcohol-free sodium ethoxide is heated at 78° for 8 hrs. The mixture is then cooled to 10° and 36 g of 33% aqueous acetic acid is slowly added. The aqueous layer is washed with ether and the combined organic layers are dried and distilled to give ethyl acetoacetate, b.p. 78–80° (16 Torr), in 75–76% yield.

The product in this example, ethyl 3-oxobutanoate, is known by the trivial names

ethyl acetoacetate, or simply **acetoacetic ester.** For this reason, the self-condensation of esters is sometimes called **the acetoacetic ester condensation,** even when other esters are involved.

The reaction is mechanistically similar to the aldol condensation (Section 15.7.G.) in that the conjugate base of the ester is a reactive intermediate.



$$(1)\ CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5O^- \rightleftharpoons {}^-CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OH$$

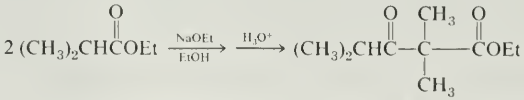
$$(2)\ {}^-CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 + CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 \rightleftharpoons CH_3\underset{OC_2H_5}{\overset{O^-}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5$$

$$(3)\ CH_3\underset{OC_2H_5}{\overset{O^-}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5O^-$$

$$(4)\ CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5O^- \rightleftharpoons CH_3\overset{O^-}{C}{=}CH\overset{O}{\overset{\|}{C}}OC_2H_5 + C_2H_5OH$$

In subsequent examples in this chapter, we shall use the abbreviations EtOH and MeOH for ethanol and methanol, and EtO^- and MeO^- for ethoxide and methoxide ions.

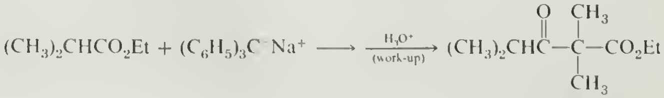
As we shall see in Section 26.4.C., 1,3-dicarbonyl compounds are fairly strong carbon acids; the pK_a of acetoacetic ester itself is about 11. Thus, the equilibrium for the last step in this mechanism lies far to the right. Since the pK_a of ethanol is about 16, K for step (4) is about 10^5. This final, essentially irreversible, step provides the driving force for the Claisen condensation. A dramatic illustration is provided by attempted Claisen condensation with ethyl isobutyrate.



$$2\,(CH_3)_2CH\overset{O}{\overset{\|}{C}}OEt \xrightarrow[EtOH]{NaOEt} \xrightarrow{H_3O^+} (CH_3)_2CH\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}OEt$$

(0%)

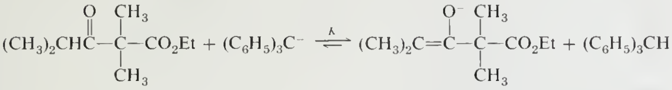
In this case, there are no protons in the normally acidic position between the two carbonyl groups; hence, the final step in the mechanism cannot occur. The overall equilibrium constant for steps (1) through (3) in the mechanism is apparently too small for condensation to be observed in the absence of step (4). The most acidic proton available in the hypothetical product is the proton at C-4, which is a normal proton α to a ketone carbonyl; its pK_a is therefore about 20. If a much stronger base is used to catalyze the reaction, this proton can be removed and reaction can now be observed.



$$(CH_3)_2CHCO_2Et + (C_6H_5)_3C^-\,Na^+ \longrightarrow \xrightarrow[(work\text{-}up)]{H_3O^+} (CH_3)_2CH\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et$$

(45–60%)

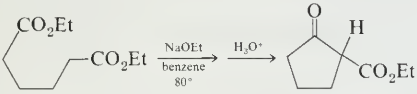
The base in the foregoing example, sodium triphenylmethide, is much more basic than ethoxide ion. It is the conjugate base of the weak carbon acid triphenylmethane, which has $pK_a = 31.5$, and it will be discussed in detail in Section 30.7.B. Since it is such a strong base, K for the last step in the Claisen condensation is very large ($\approx 10^{11}$), even though a normal ketone is being deprotonated.



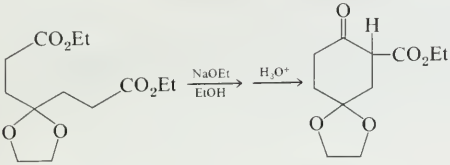
$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et + (C_6H_5)_3C^- \overset{K}{\rightleftharpoons} (CH_3)_2C=\overset{O^-}{C}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et + (C_6H_5)_3CH$$

$pK_a \approx 20$ pK_a 31.5

Adipic acid and pimelic acid esters undergo a cyclic Claisen condensation, known as a **Dieckmann condensation;** the products of such reactions are five- and six-membered cyclic β-keto esters.


CO₂Et
CO₂Et
NaOEt
benzene
80°
H₃O⁺
O
H
CO₂Et

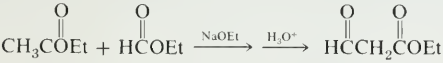
(80%)


CO₂Et
CO₂Et
O
O
NaOEt
EtOH
H₃O⁺
O
H
CO₂Et
O
O

(54%)

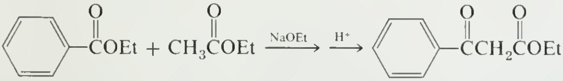
The Dieckmann condensation is not satisfactory for the preparation of other sized rings.

Mixed Claisen condensations between two esters are successful when one of the esters has no α-hydrogens, as shown by the following examples:

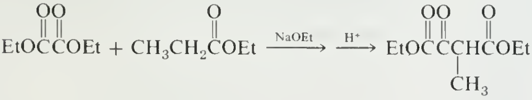


$$CH_3\overset{O}{\overset{\|}{C}}OEt + H\overset{O}{\overset{\|}{C}}OEt \xrightarrow{NaOEt} \xrightarrow{H_3O^+} H\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$$

(79%)
ethyl formylacetate

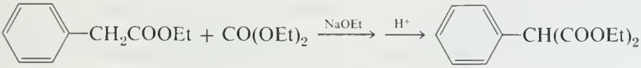

O
COEt
+
O
CH₃COEt
NaOEt
H⁺
O O
CCH₂COEt

(55–70%)
ethyl benzoylacetate



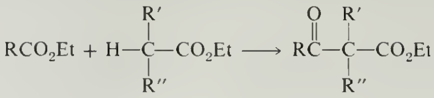
$$EtO\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}OEt + CH_3CH_2\overset{O}{\overset{\|}{C}}OEt \xrightarrow{NaOEt} \xrightarrow{H^+} EtO\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}\underset{CH_3}{CH}\overset{O}{\overset{\|}{C}}OEt$$

(60–70%)


CH₂COOEt + CO(OEt)₂
NaOEt
H⁺
CH(COOEt)₂

(86%)
diethyl phenylmalonate

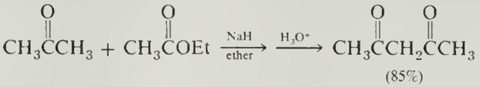
Thus, the overall result of a mixed Claisen condensation is given by the general equation



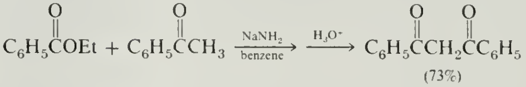
$$RCO_2Et + H-\underset{R''}{\overset{R'}{C}}-CO_2Et \longrightarrow R\overset{O}{\overset{\|}{C}}-\underset{R''}{\overset{R'}{C}}-CO_2Et$$

Best results are obtained when R has no α-hydrogens and either R′ or R″ is hydrogen.

Mixed Claisen condensations between ketones and various esters are particularly effective and constitute a general method for the synthesis of 1,3-diketones.

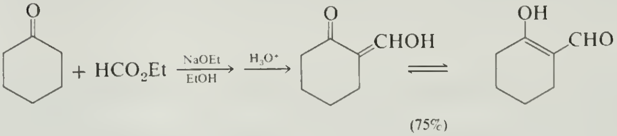


$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + CH_3\overset{O}{\overset{\|}{C}}OEt \xrightarrow[\text{ether}]{\text{NaH}} \xrightarrow{H_3O^+} \underset{(85\%)}{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3}$$

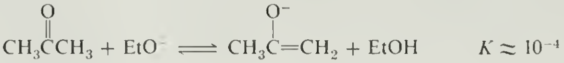


$$C_6H_5\overset{O}{\overset{\|}{C}}OEt + C_6H_5\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{benzene}]{\text{NaNH}_2} \xrightarrow{H_3O^+} \underset{(73\%)}{C_6H_5\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}C_6H_5}$$

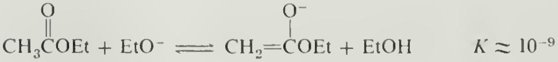
When ethyl formate is used in a mixed Claisen condensation, the product is a β-keto aldehyde, which exists almost entirely in the enolic form (Section 26.4.B).



The mixed Claisen condensation of ketones and esters works well because ketones are considerably more acidic than are esters (Section 18.8). Thus, in the basic medium, the ketone is deprotonated to a larger extent than the ester.

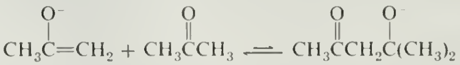


$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + EtO^- \rightleftharpoons CH_3\overset{O^-}{\overset{|}{C}}=CH_2 + EtOH \qquad K \simeq 10^{-4}$$



$$CH_3\overset{O}{\overset{\|}{C}}OEt + EtO^- \rightleftharpoons CH_2=\overset{O^-}{\overset{|}{C}}OEt + EtOH \qquad K \simeq 10^{-9}$$

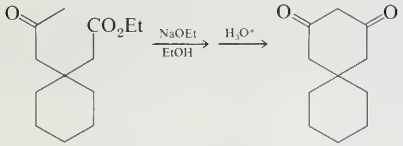
Of course, once the ketone enolate is formed, it may react with another unionized ketone molecule (aldol condensation) or with the ester. However, the aldol condensation of ketones is usually thermodynamically unfavorable (page 386), and this reaction is only a minor side reaction.



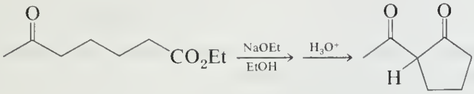
$$CH_3\overset{O^-}{\overset{|}{C}}=CH_2 + CH_3\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O^-}{\overset{|}{C}}(CH_3)_2$$

On the other hand, the Claisen condensation is driven by the all-important final deprotonation of the acidic product. Thus, the β-diketone is formed in high yield.

1,4- and 1,5-keto esters undergo intramolecular Claisen condensation to yield cyclic diketones. The reaction is a useful method for the formation of five- and six-membered rings. This reaction is clearly analogous to the Dieckmann condensation.

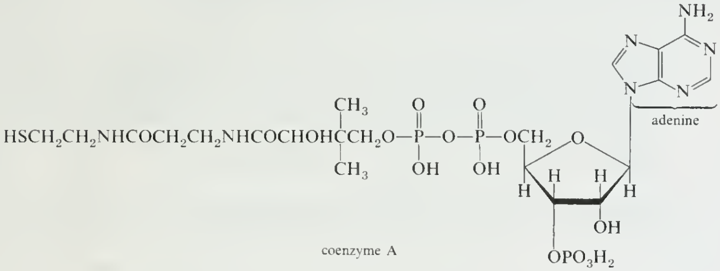

O
CO_2Et
NaOEt
EtOH
H_3O^+
O
O

(100%)


O
CO_2Et
NaOEt
EtOH
H_3O^+
O
O
H

(90%)

The Claisen condensation is used extensively in biological reactions to build up and degrade chains. Nature, however, does not use alcoholic sodium ethoxide as a reaction solvent (despite attempts of some persons to provide a suitable alcoholic medium). Instead of a normal ester, the biochemical processes make use of a thioester together with enzyme catalysts specific for each step. The key ingredient is coenzyme-A or CoA in the form of the thioacetate ester or acetyl-CoA.


NH_2
N
N
N
N
adenine
CH_3
O
O
$HSCH_2CH_2NHCOCH_2CH_2NHCOCHOHCCH_2O-P-O-P-OCH_2$
O
CH_3
OH
OH
H
H
H
H
OH
OPO_3H_2

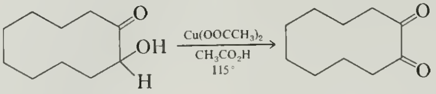
coenzyme A

$$\begin{array}{c} 2\,CH_3CO{-}CoA \rightleftharpoons CH_3COCH_2CO{-}CoA + CoA \\ \Big\updownarrow \\ CH_3CHOHCH_2CO{-}CoA \\ \Big\updownarrow \\ CH_3CH{=}CHCO{-}CoA \\ \Big\updownarrow \\ CH_3CH_2CH_2CO{-}CoA \rightleftharpoons \text{higher fatty acids} \end{array}$$

The initial condensation is of the Claisen type and is followed by reduction and dehydration reactions to give a butyrate ester than can react with acetyl-CoA to build up higher fatty acids. Note that these acids are built up and degraded two carbons at a time.

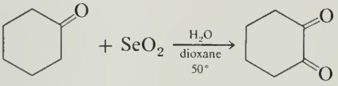
B. *Miscellaneous Methods*

α-Diketones may be obtained by the mild oxidation of α-hydroxy ketones, which are available by the acyloin condensation (Section 24.4.A under the Acyloin Condensation). Since the product α-diketones are also susceptible to oxidation (with cleavage of the carbonyl-carbonyl bond), especially mild oxidants must be used. Cupric acetate is especially effective.

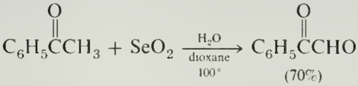


(88%)

α-Diketones and α-keto aldehydes are also available by the direct oxidation of simple ketones with selenium dioxide.



(60%)

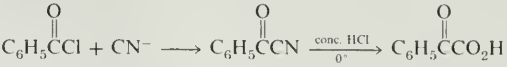


$$C_6H_5\overset{O}{\overset{\|}{C}}CH_3 + SeO_2 \xrightarrow[\text{dioxane}\ 100^\circ]{H_2O} C_6H_5\overset{O}{\overset{\|}{C}}CHO$$

(70%)

Selenium dioxide, SeO_2, is a white, crystalline material that melts at 340°. It is prepared by oxidizing selenium metal with nitric acid. Although it is rather high melting, it has a substantial vapor pressure at moderate temperatures (12.5 torr at 70°). The yellowish green vapor has a pungent odor. In the body, it is reduced to selenium metal, which may produce liver damage. Prolonged occupational exposure to selenium or SeO_2 leads to a garlic odor of breath and sweat.

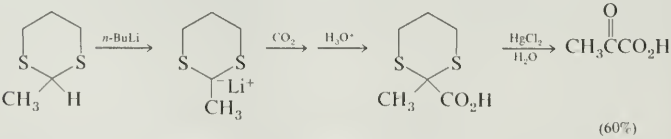
α-Keto acids are available by the acid-catalyzed hydrolysis of acyl cyanides, which may be prepared from acyl halides and cyanide ion.



$$C_6H_5\overset{O}{\overset{\|}{C}}Cl + CN^- \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}CN \xrightarrow[0^\circ]{\text{conc. HCl}} C_6H_5\overset{O}{\overset{\|}{C}}CO_2H$$

(97%)

They may also be prepared by the reaction of 1,3-dithiane anions with carbon dioxide, followed by hydrolysis of the dithioketal grouping.



2-methyl-
1,3-dithiane

(60%)
pyruvic acid

Pyruvic acid is a liquid, b.p. 165° with decomposition. Thermal decomposition gives CO and acetic acid. Pyruvic acid can be prepared by heating tartaric acid with

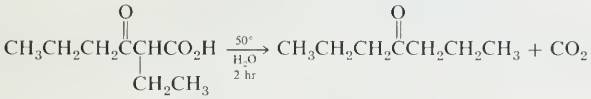
$KHSO_4$. It is an important biochemical intermediate and is involved in muscle action, sugar metabolism, and transamination processes.

A particularly effective method for the synthesis of 1,5-dicarbonyl compounds is the Michael addition reaction. Since this reaction involves some chemistry of dicarbonyl compounds that we have not yet covered, we shall defer discussion until Section 26.4.F.

26.4
Reactions

A. *Decarboxylation of 1,3-diacids and 1,3-keto Acids*

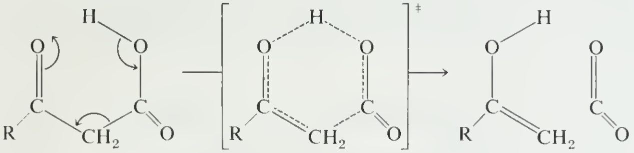
β-Diacids and β-keto acids **decarboxylate** (lose carbon dioxide) upon being heated to relatively modest temperatures. β-Keto acids are particularly heat sensitive; 2-ethyl-3-oxohexanoic acid has a half-life of only 15 min at 50°.



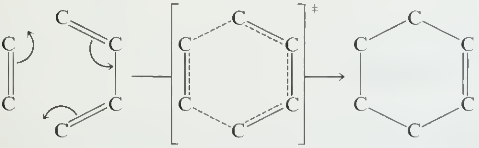
$$\mathrm{CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}\underset{\underset{CH_2CH_3}{|}}{C}HCO_2H \xrightarrow[\substack{H_2O\\ 2\ hr}]{50^\circ} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + CO_2}$$

The mechanism of this decarboxylation reaction may proceed through a cyclic six-center transition state similar to that discussed previously for the Diels-Alder reaction (Section 23.4.B). The initial product is an enol, which rapidly tautomerizes to the ketone.

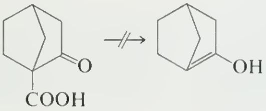
Decarboxylation



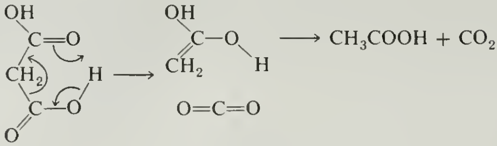
Diels Alder Reaction

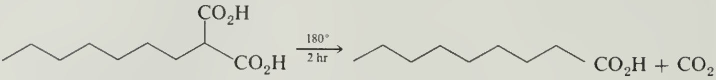


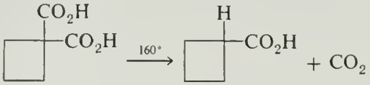
This mechanism is consistent with the resistance of bridgehead bicyclic β-keto acids to decarboxylation; the product would be a highly strained bridgehead olefin.

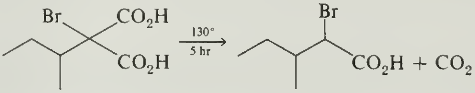


Malonic acid and its derivatives apparently decarboxylate by a similar mechanism, but they are considerably less reactive than β-keto acids. Typical decarboxylation conditions involve heating the diacid at 120–180° for several hours.

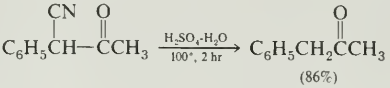




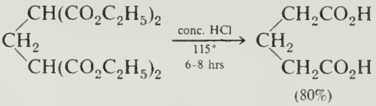




In many cases, 1,3-diacids and 1,3-keto acids are the initial products in hydrolysis reactions but undergo decarboxylation under the reaction conditions.

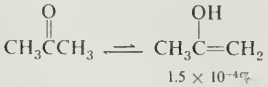


$$C_6H_5\overset{CN}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[100^\circ,\ 2\ hr]{H_2SO_4\text{-}H_2O} C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_3 \quad (86\%)$$



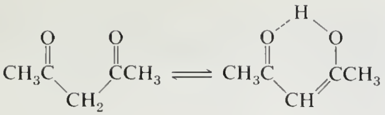
B. *Keto-enol Equilibria*

Recall that simple ketones exist very largely in the keto form, with but a trace of the enol (vinyl alcohol) form present at equilibrium (Section 15.6.A.).



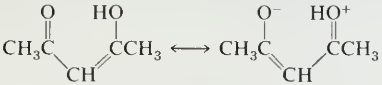
$$CH_3\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons CH_3\overset{OH}{\overset{|}{C}}=CH_2 \quad 1.5 \times 10^{-4}\%$$

In contrast, 1,2- and 1,3-dicarbonyl compounds often contain a large amount of enol form in equilibrium with the dicarbonyl form. For example, 2,4-pentanedione is a mixture of 84% dione and 16% enolic form in aqueous solution. In hexane solution, the compound exists almost entirely in the enolic form.

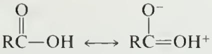

(26-1)

84% — 16% (water solution)
8% — 92% (hexane solution)

One important reason for this phenomenon is the ability of the enol to form an intramolecular hydrogen bond, as shown in (26-1). Such intramolecular hydrogen bonds are especially favorable when six-membered rings are formed. The enolic form also benefits from resonance stabilization in a way not available to the dicarbonyl compound itself.

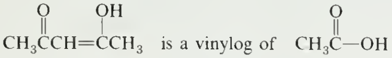

(26-2)

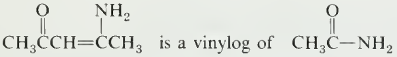
Note that the type of delocalization shown in (26-2) is precisely the kind that is involved in carboxylic acids.


$$\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}{-}OH \longleftrightarrow R\overset{\overset{\displaystyle O^-}{|}}{C}{=}OH^+}$$

In the enolic form of a 1,3-diketone, a hydroxy lone pair is delocalized, *through the double bond,* onto the carbonyl oxygen.

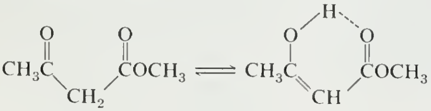
Whenever two functional groups are joined to a double bond in this way, the molecule has properties similar to the corresponding compound without the double bond. This empirical concept is called the *principle of vinylogy* and such compounds are called *vinylogs.*


$$\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH{=}\overset{\overset{\displaystyle OH}{|}}{C}CH_3}\quad \text{is a vinylog of}\quad \mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}OH}$$


$$\mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH{=}\overset{\overset{\displaystyle NH_2}{|}}{C}CH_3}\quad \text{is a vinylog of}\quad \mathrm{CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2}$$

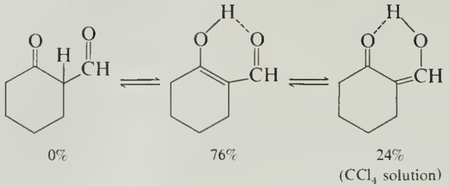
Note that the percentage of enol form at equilibrium is higher in nonpolar aprotic solvents because in such solvents the intramolecular hydrogen bond is most beneficial. In protic solvents, the dicarbonyl compound itself as well as the enol can hydrogen bond to solvent molecules and the ability of the enol to form an intramolecular hydrogen bond provides no extra stabilization.

Other 1,3-dicarbonyl compounds also contain substantial emounts of enolic forms in solution. β-Keto esters are in equilibrium with significant amounts of the form in which the ketone carbonyl is enolized.

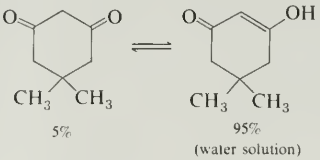


90% — 10% (water solution)
51% — 49% (hexane solution)

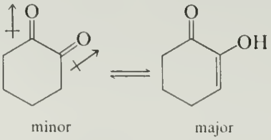
β-Keto aldehydes exist almost entirely in the enolic form; both carbonyl groups are enolized to an appreciable extent. The two enolic forms are easily interconvertible, since only small shifts in bond distances are required.



Cyclic 1,3-diketones also exist predominantly in the enolic form, even though they cannot participate in intramolecular hydrogen bonding for reasons of geometry.

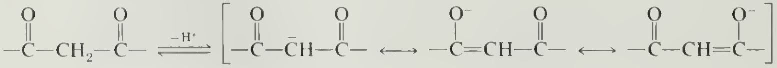


1,2-Diketones also show enhanced amounts of enol form. The main driving force for enolization in this case is relief of the electrostatic repulsion that occurs when the two electrophilic carbonyl groups are adjacent to each other.



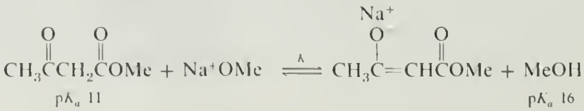
C. *Acidity of 1,3-dicarbonyl Compounds*

1,3-Dicarbonyl compounds, which have a hydrogen bound to the carbon between the two carbonyl groups, are much stronger acids than normal aldehydes, ketones, or esters because the charge in the resulting enolate ion can be delocalized into both carbonyl groups.

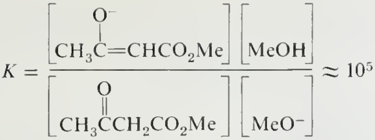


$$-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}- \xrightleftharpoons{-H^+} \left[-\overset{O}{\overset{\|}{C}}-\overset{-}{C}H-\overset{O}{\overset{\|}{C}}- \longleftrightarrow -\overset{O^-}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}- \longleftrightarrow -\overset{O}{\overset{\|}{C}}-CH=\overset{O^-}{\overset{|}{C}}-\right]$$

Some typical pK_as for such systems are contained in Table 26.3. The acidities of 1,3-dicarbonyl compounds are sufficiently high that they are converted to their conjugate bases essentially quantitatively by hydroxide ion in water or by alkoxide ion in alcoholic solvent.



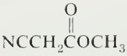
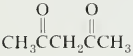
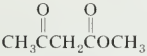
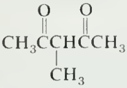
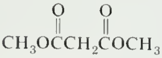
$$\underset{\text{p}K_a\ 11}{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OMe} + Na^+OMe \rightleftharpoons CH_3\overset{\overset{Na^+}{O^-}}{\overset{|}{C}}=CH\overset{O}{\overset{\|}{C}}OMe + \underset{\text{p}K_a\ 16}{MeOH}$$



$$K = \frac{\left[CH_3\overset{O^-}{\overset{|}{C}}{=}CHCO_2Me\right]\left[MeOH\right]}{\left[CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2Me\right]\left[MeO^-\right]} \approx 10^5$$

As we shall see in the next sections, these easily accessible carbanions are valuable synthetic intermediates.

TABLE 26.3
Acidity of β-Dicarbonyl Compounds

Compound	pK_a
 $NCCH_2\overset{O}{\overset{\|}{C}}CH_3$	9
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	9
 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_3$	11
 $CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}CH_3$	11
$NCCH_2CN$	11
 $CH_3O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_3$	13

D. *Alkylation of 1,3-dicarbonyl Compounds: The Malonic Ester and Acetoacetic Ester Syntheses*

The anions of 1,3-dicarbonyl compounds are nucleophiles and may take part in S_N2 displacement reactions with alkyl halides. Diethyl malonate and ethyl acetoacetate are inexpensive, commercial compounds that are often alkylated in this manner. Hydrolysis of the alkylated product, followed by decarboxylation of the resulting β-diacid or β-keto acid provides an important general synthesis of acids and methyl ketones. The overall processes are called the **malonic ester synthesis** or the **acetoacetic ester synthesis.** Some examples are given in (26-3) and (26-4).

$$CH_2(CO_2Et)_2 \xrightarrow[EtOH]{NaOEt} \xrightarrow{n\text{-}C_4H_9Br} n\text{-}C_4H_9CH(CO_2Et)_2 \xrightarrow[115^\circ]{conc.\ HCl} n\text{-}C_4H_9CH_2CO_2H$$

(80–90%)
diethyl *n*-butylmalonate

caproic acid
hexanoic acid

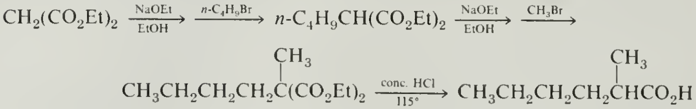
(26-3)

$$CH_2(CO_2Et)_2 \xrightarrow[EtOH]{NaOEt} \xrightarrow{(CH_3)_2CHI} (CH_3)_2CHCH(CO_2Et)_2 \xrightarrow[115^\circ]{conc.\ HCl} (CH_3)_2CHCH_2CO_2H \tag{26-4}$$

(70–75%)
diethyl isopropylmalonate

β-methylbutyric acid
3-methylbutanoic acid

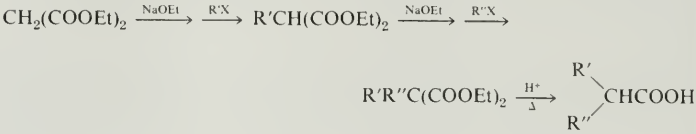
The initially formed alkylmalonic ester may be alkylated again, with the same alkyl halide or with a different one, to widen the scope of the procedure.



$$CH_2(CO_2Et)_2 \xrightarrow[EtOH]{NaOEt} \xrightarrow{n\text{-}C_4H_9Br} n\text{-}C_4H_9CH(CO_2Et)_2 \xrightarrow[EtOH]{NaOEt} \xrightarrow{CH_3Br} CH_3CH_2CH_2CH_2\overset{CH_3}{\overset{|}{C}}(CO_2Et)_2 \xrightarrow[115^\circ]{conc.\ HCl} CH_3CH_2CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCO_2H$$

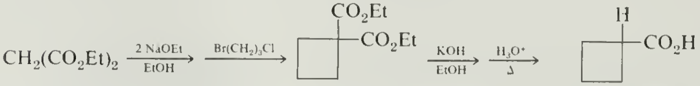
α-methylcaproic acid
2-methylhexanoic acid

The overall synthetic result of alkylation and decarboxylation of malonic ester is an alkyl or dialkylacetic acid.



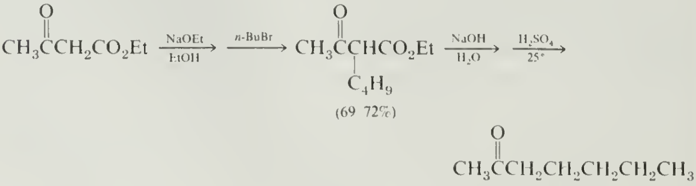
$$CH_2(COOEt)_2 \xrightarrow{NaOEt} \xrightarrow{R'X} R'CH(COOEt)_2 \xrightarrow{NaOEt} \xrightarrow{R''X} R'R''C(COOEt)_2 \xrightarrow[\Delta]{H^+} R'R''CHCOOH$$

A principal limitation in the synthetic sequence is that the alkylation process is an S_N2 reaction; E2 elimination is an expected side reaction whose importance depends on the structure of RX. If a suitable dihalide is used in the reaction, 2 moles of malonic ester can be added to both ends of a chain; alternatively, intramolecular alkylation in the second step leads to a cyclic diester.



(42–44%)
cyclobutanecarboxylic acid

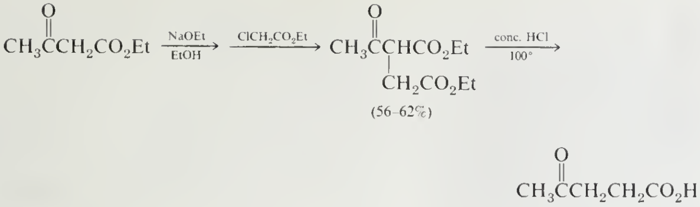
If ethyl acetoacetate is used as the starting material, the combination of alkylation, hydrolysis, and decarboxylation provides a synthesis of various methyl alkyl ketones.



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2Et \xrightarrow[EtOH]{NaOEt} \xrightarrow{n\text{-}BuBr} CH_3\overset{O}{\overset{\|}{C}}\underset{C_4H_9}{\underset{|}{C}}HCO_2Et \xrightarrow[H_2O]{NaOH} \xrightarrow[25^\circ]{H_2SO_4} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2CH_3$$

(69–72%)

(61% overall)
2-heptanone

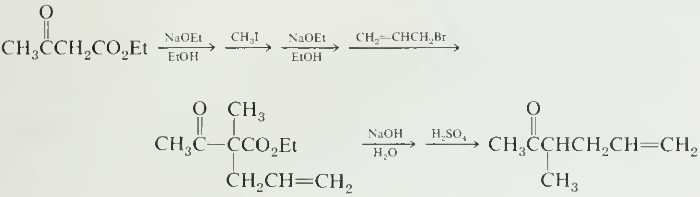


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2Et \xrightarrow[\text{EtOH}]{\text{NaOEt}} \xrightarrow{ClCH_2CO_2Et} CH_3\overset{O}{\overset{\|}{C}}\underset{CH_2CO_2Et}{\underset{|}{C}}HCO_2Et \xrightarrow[100^\circ]{\text{conc. HCl}} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CO_2H$$

(56-62%)

(50% overall)
γ-ketovaleric acid
4-oxopentanoic acid

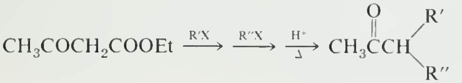
Again the starting β-keto ester may be alkylated successively with two different alkyl halides. After hydrolysis and decarboxylation, the product is a ketone that is branched at the α-carbon.



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2Et \xrightarrow[\text{EtOH}]{\text{NaOEt}} \xrightarrow{CH_3I} \xrightarrow[\text{EtOH}]{\text{NaOEt}} \xrightarrow{CH_2{=}CHCH_2Br} CH_3\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{\underset{CH_2CH=CH_2}{\underset{|}{C}}}}CO_2Et \xrightarrow[H_2O]{\text{NaOH}} \xrightarrow{H_2SO_4} CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}}HCH_2CH=CH_2$$

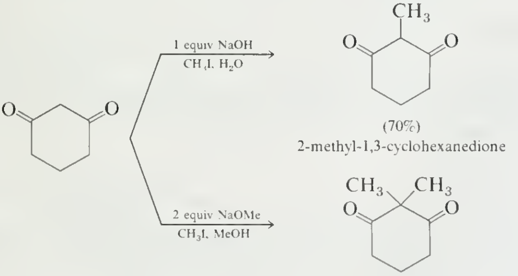
3-methylhex-5-en-2-one

The net result is summarized in (26-5) and is again subject to the usual limitations of S_N2 reactions.



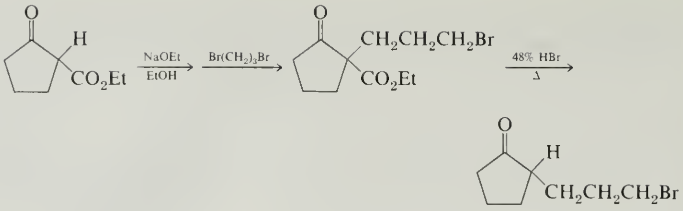
$$CH_3COCH_2COOEt \xrightarrow{R'X} \xrightarrow{R''X} \xrightarrow[\Delta]{H^+} CH_3\overset{O}{\overset{\|}{C}}CH\begin{matrix} R' \\ R'' \end{matrix} \tag{26-5}$$

Other β-diketones and β-keto esters may be alkylated in the same manner. The following examples show the tremendous utility of these reactions in building up complicated organic structures.

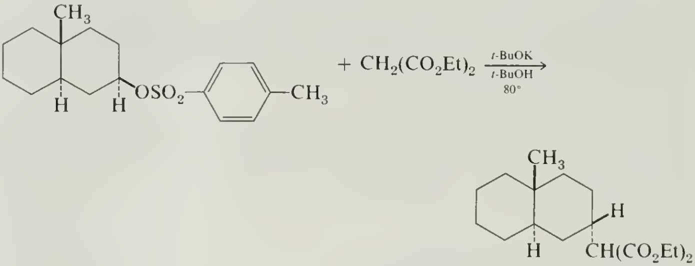


(70%)
2-methyl-1,3-cyclohexanedione

(80%)
2,2-dimethyl-1,3-cyclohexanedione



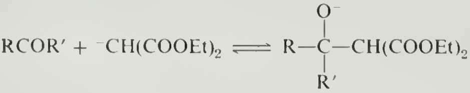
(60%)
2-(3-bromopropyl)cyclopentanone



(65%)

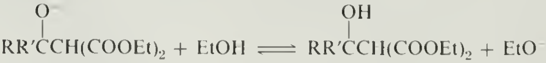
E. *The Knoevenagel Condensation*

We have seen that malonic ester is more acidic than normal ketones and aldehydes; that is, in equilibrium with base the carbanion from malonic ester is present in large excess over that from the ketone or aldehyde. The consequence is a condensation of malonic ester with the carbonyl group of the ketone or aldehyde. This result should be contrasted with the condensation of a ketone with a monoester (Section 26.3.A).

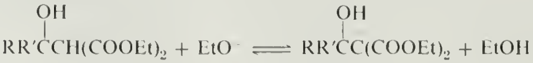


$$\mathrm{RCOR'} + {}^{-}\mathrm{CH(COOEt)_2} \rightleftharpoons \mathrm{R}-\overset{\displaystyle \mathrm{O}^-}{\underset{\displaystyle \mathrm{R'}}{\mathrm{C}}}-\mathrm{CH(COOEt)_2}$$

Several further equilibria occur:

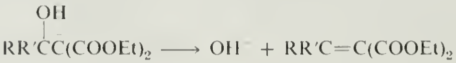


$$\mathrm{RR'}\overset{\displaystyle \mathrm{O}^-}{\mathrm{C}}\mathrm{H(COOEt)_2} + \mathrm{EtOH} \rightleftharpoons \mathrm{RR'}\overset{\displaystyle \mathrm{OH}}{\mathrm{C}}\mathrm{H(COOEt)_2} + \mathrm{EtO}^-$$



$$\mathrm{RR'}\overset{\displaystyle \mathrm{OH}}{\mathrm{C}}\mathrm{H(COOEt)_2} + \mathrm{EtO}^- \rightleftharpoons \mathrm{RR'}\overset{\displaystyle \mathrm{OH}}{\mathrm{C}}{}^{-}\mathrm{C(COOEt)_2} + \mathrm{EtOH}$$

The next step is an elimination reaction that pulls the whole equilibrium.



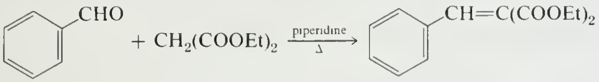
$$\mathrm{RR'}\overset{\displaystyle \mathrm{OH}}{\mathrm{C}}{}^{-}\mathrm{C(COOEt)_2} \longrightarrow \mathrm{OH}^- + \mathrm{RR'C{=}C(COOEt)_2}$$

The net result is a condensation *catalyzed* by base:

$$\mathrm{RR'CO + CH_2(COOEt)_2 \xrightarrow{base} H_2O + RR'C{=}C(COOEt)_2}$$

In the Claisen condensations discussed previously, the base was a reagent required in stoichiometric quantity. In the present case, catalytic amounts suffice and, in fact, the reaction works well with such weak base catalysts as amines. The overall reaction works best for aldehydes although ketones have been used. Some examples are

$$\mathrm{(CH_3)_2CHCH_2CHO + CH_2(COOEt)_2 \xrightarrow[\substack{\text{benzene}\\ \Delta}]{\text{piperidine}} \underset{(78\%)}{(CH_3)_2CHCH_2CH{=}C(COOEt)_2}}$$

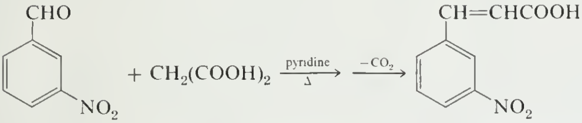


(80%)

A variation of this reaction makes use of malonic acid with an amine catalyst. In this case, some of the carboxylate anion is present but since amines are weak bases (Section 27.4) the fraction of carboxylate anion is small. The carbanion derived from the α-hydrogen is also present because the carbonyl groups of the carboxylic acid stabilize the carbanion just as they stabilize the ester carbonyls. The resulting condensation products decarboxylate on heating to give α,β-unsaturated acids. The basic catalyst frequently used in this reaction is the tertiary amine, pyridine.

$$\mathrm{\underset{\text{heptanal}}{CH_3(CH_2)_5CHO} + CH_2(COOH)_2 \xrightarrow[\Delta]{\text{pyridine}} [CH_3(CH_2)_5CH{=}C(COOH)_2] \xrightarrow{-CO_2}}$$

$$\mathrm{\underset{\substack{(75\text{–}85\%)\\ \text{non-2-enoic acid}}}{CH_3(CH_2)_5CH{=}CHCOOH}}$$



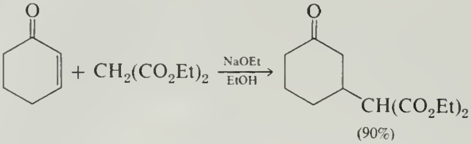
(75–80%)

The reaction is general for aldehydes, but can be applied to ketones although usually in lower yield.

$$\mathrm{(CH_3CH_2)_2CO + CH_2(COOH)_2 \xrightarrow[\substack{\text{piperidine}\\ \Delta}]{\text{pyridine}} \xrightarrow{-CO_2} \underset{(35\%)}{(CH_3CH_2)_2C{=}CHCOOH}}$$

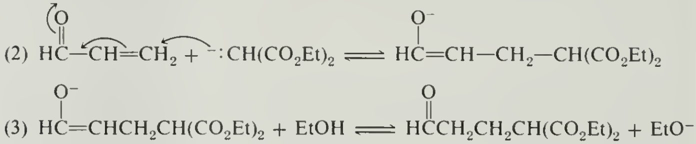
F. *The Michael Addition*

In Section 20.3.A., we saw that α,β-unsaturated carbonyl compounds may react with such nucleophiles as cyanide ion and Grignard reagents either by 1,2- or 1,4-addition. The 1,4-addition of a carbanion to an α,β-unsaturated carbonyl system is called a **Michael addition.** It is a common and useful reaction. For example, when a mixture of 2-cyclohexen-1-one and diethyl malonate is treated with a catalytic amount of sodium ethoxide in ethanol, the following addition reaction occurs.



The mechanism of the Michael addition is illustrated with diethyl malonate and acrolein; the product is obtained in 50% yield.

(1) $CH_2(CO_2Et)_2 + EtO^- \rightleftharpoons {}^{-}\!:CH(CO_2Et)_2 + EtOH$

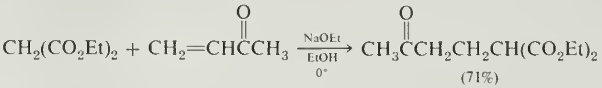


(2) $$H\overset{O}{\overset{\|}{C}}-CH=CH_2 + {}^{-}\!:CH(CO_2Et)_2 \rightleftharpoons H\overset{O^-}{\overset{|}{C}}=CH-CH_2-CH(CO_2Et)_2$$

(3) $$H\overset{O^-}{\overset{|}{C}}=CHCH_2CH(CO_2Et)_2 + EtOH \rightleftharpoons H\overset{O}{\overset{\|}{C}}CH_2CH_2CH(CO_2Et)_2 + EtO^-$$

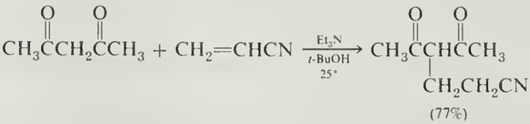
A Michael addition such as this is similar to the alkylation of a carbanion by an alkyl halide, with one important exception. In the alkylation with an alkyl halide, a stoichimetric amount of base is consumed; in the Michael addition, the base functions as a catalyst. Thus, only a small amount of base need be used in Michael additions, and the process is reversible. The driving force for the reaction is the formation of a new C—C single bond at the expense of the π bond of the unsaturated carbonyl compound; this driving force is essentially the same as that of all additions to a double bond.

Michael additions are observed between carbon acids containing an acidic proton and a variety of α,β-unsaturated carbonyl systems. A few representative examples are



$$CH_2(CO_2Et)_2 + CH_2=CH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{EtOH}\ 0^\circ]{\text{NaOEt}} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH(CO_2Et)_2$$

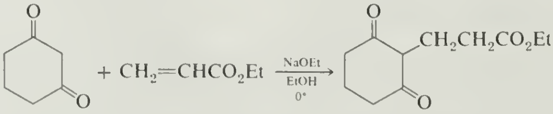
(71%)



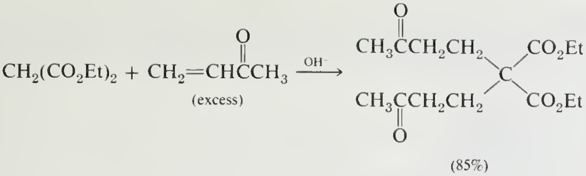
$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 + CH_2=CHCN \xrightarrow[t\text{-BuOH}\ 25^\circ]{Et_3N} CH_3\overset{O}{\overset{\|}{C}}\underset{CH_2CH_2CN}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}CH_3$$

(77%)

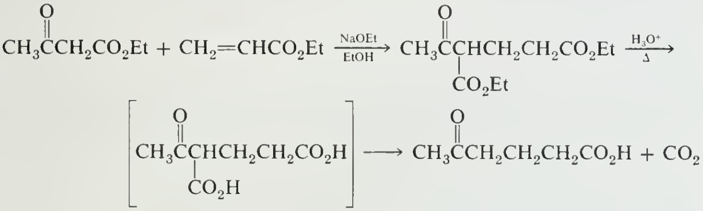
Triethylamine (Et_3N) is a weak organic base that is often used to catalyze such reactions where a stronger base is not necessary. The basic properties of amines will be discussed in Chapter 27.



If an excess of the α,β-unsaturated carbonyl component is used, it is possible to achieve **dialkylation.**



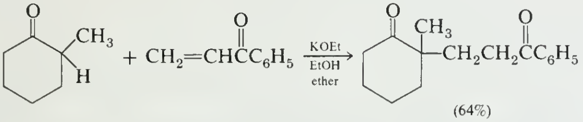
The Michael addition constitutes a useful method for the synthesis of 1,5-dicarbonyl systems. When diethyl malonate or acetoacetic ester are used as the adding group, the product may be hydrolyzed and decarboxylated to obtain the alkylated acid or ketone.

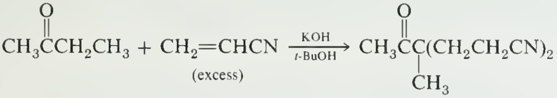


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2Et + CH_2{=}CHCO_2Et \xrightarrow[EtOH]{NaOEt} CH_3\overset{O}{\overset{\|}{C}}\underset{CO_2Et}{\underset{|}{C}}HCH_2CH_2CO_2Et \xrightarrow[\Delta]{H_3O^+}$$

$$\left[CH_3\overset{O}{\overset{\|}{C}}\underset{CO_2H}{\underset{|}{C}}HCH_2CH_2CO_2H\right] \longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CO_2H + CO_2$$

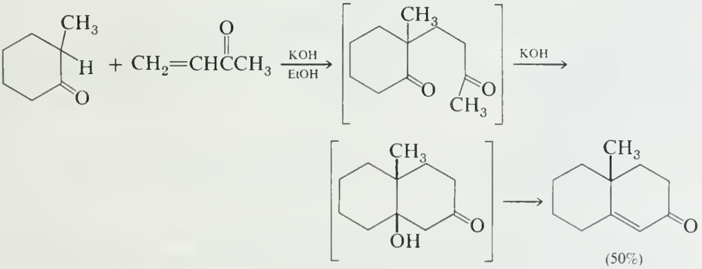
Although the Michael addition is most successful when the carbon acid is relatively acidic, such as a 1,3-dicarbonyl compound, the reaction also occurs with simple ketones.



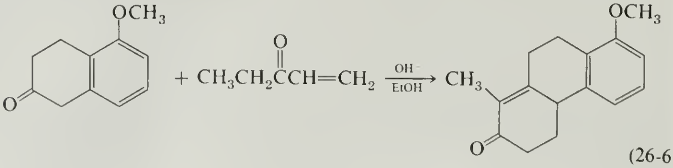


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3 + \underset{(excess)}{CH_2{=}CHCN} \xrightarrow[t\text{-}BuOH]{KOH} CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}}(CH_2CH_2CN)_2$$

A useful variant of the Michael addition occurs with methyl vinyl ketone and its derivatives. The initially formed 1,5-diketone undergoes a subsequent intramolecular aldol condensation to yield a cyclohexenone ring. The process is essentially a combination of the Michael reaction and aldol condensation and is called **Robinson annelation.**



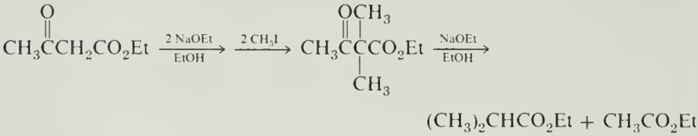
The Robinson annelation sequence has been very useful in building up the carbon framework of complex natural products such as steroids. An example of the use of the reaction as the first step in the laboratory synthesis of a steroid is given in (26-6).



(26-6)

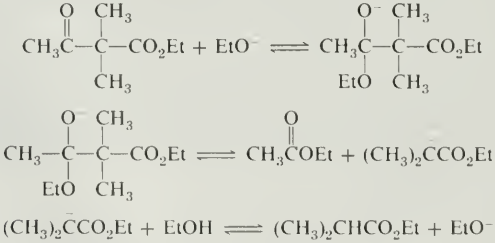
G. *Reverse Claisen Condensation*

As we saw in Section 26.3.A, the driving force for the Claisen condensation is provided by the conversion of the product β-keto ester into its conjugate base; when the product has no protons between the two carbonyl groups, the overall equilibrium constant is unfavorable. Such a fully alkylated system is said to be a nonenolizable β-keto ester. Nonenolizable β-keto esters may be prepared by the alkylation of a β-keto ester, as discussed in Section 26.4.D. At the end of the alkylation, the base has all been consumed and the product is stable. If a catalytic amount of sodium ethoxide is now added, a reverse Claisen condensation occurs.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2Et \xrightarrow[EtOH]{2\ NaOEt} \xrightarrow{2\ CH_3I} CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\overset{CH_3}{C}}CO_2Et \xrightarrow[EtOH]{NaOEt} (CH_3)_2CHCO_2Et + CH_3CO_2Et}$$

Only a catalytic amount of sodium ethoxide is required for the reverse Claisen because no base is consumed in the overall reaction.

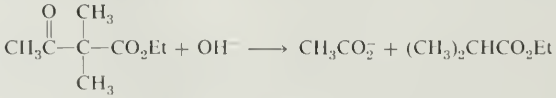


$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et + EtO^- \rightleftharpoons CH_3\underset{EtO}{\overset{O^-}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et}$$

$$\mathrm{CH_3-\underset{EtO}{\overset{O^-}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}OEt + (CH_3)_2\overset{-}{C}CO_2Et}$$

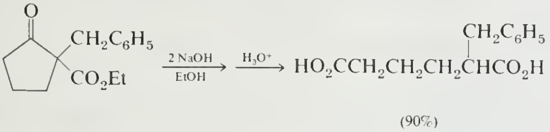
$$\mathrm{(CH_3)_2\overset{-}{C}CO_2Et + EtOH \rightleftharpoons (CH_3)_2CHCO_2Et + EtO^-}$$

If sodium hydroxide is used, a full equivalent of base is consumed, because one of the products is acetic acid.

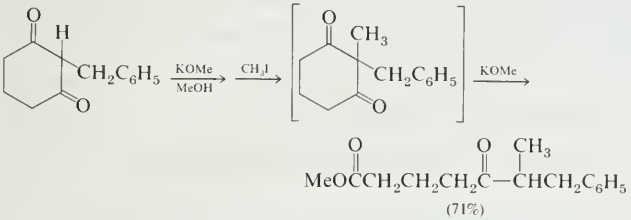


$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CO_2Et + OH^- \longrightarrow CH_3CO_2^- + (CH_3)_2CHCO_2Et}$$

The reverse Claisen condensation is a common side reaction that is observed when nonenolizable β-keto esters are hydrolyzed under basic conditions; it competes with hydrolysis especially well when the β-keto ester is cyclic. For this reason, it is usually best to hydrolyze such compounds under acidic conditions.


(26-7)

The reaction is not only an annoying side reaction, but it can be used as synthesis of dicarboxylic acids, as shown in equation (26-7). The same principles apply to nonenolizable β-diketones. An example of such a reaction, which yields a keto ester, is given in (26-8).

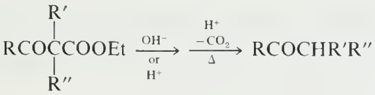

(26-8)

26.5
Summary

In this chapter we have covered a diverse but important array of reactions. We can now review these reactions briefly in the context of final products.

Ketones

To the various syntheses discussed in Chapter 15, add the decarboxylation of β-ketoacids.



$$\mathrm{RCO\overset{R'}{\underset{R''}{C}}COOEt} \xrightarrow[\substack{\text{or}\\ H^+}]{OH^-} \xrightarrow[\Delta]{\substack{H^+\\ -CO_2}} \mathrm{RCOCHR'R''}$$

Carboxylic acids

To the methods of Chapter 17, add the decarboxylation of malonic acids.

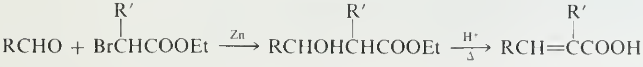
$$\mathrm{RR'C(COOEt)_2} \xrightarrow{OH^-} \xrightarrow[\Delta]{\substack{H^+\\ -CO_2}} \mathrm{RR'CHCOOH}$$

α,β-Unsaturated Acids

1. Hell-Vollhard-Zelinsky halogenation and dehydrohalogenation (Sections 17.7.B and 20.3.B)

$$\mathrm{RCH_2CH_2COOH} \xrightarrow[P]{Br_2} \mathrm{RCH_2CHBrCOOH} \xrightarrow{\text{base}} \mathrm{RCH{=}CHCOOH}$$

2. Reformatsky reaction and dehydration (Sections 24.5.A and 24.5.B)



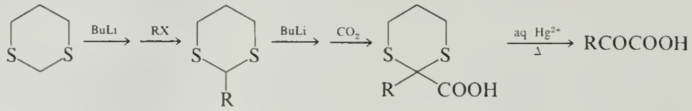
$$\mathrm{RCHO + Br\overset{R'}{C}HCOOEt} \xrightarrow{Zn} \mathrm{RCHOH\overset{R'}{C}HCOOEt} \xrightarrow[\Delta]{H^+} \mathrm{RCH{=}\overset{R'}{C}COOH}$$

3. Knoevenagel Condensation (Section 26.4.E).

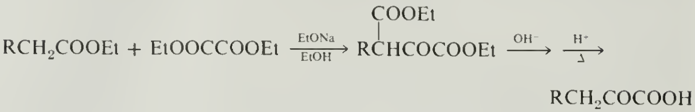
$$\mathrm{RCHO + CH_2(COOH)_2 \xrightarrow[\Delta]{\text{pyridine}} RCH{=}CHCOOH}$$

α-Keto Acids

1. Alkylation of dithianes (Section 26.3.B)



2. Claisen condensation with diethyl oxalate (Section 26.3.A)



$$\mathrm{RCH_2COOEt + EtOOCCOOEt \xrightarrow[EtOH]{EtONa} R\overset{COOEt}{\overset{|}{C}}HCOCOOEt \xrightarrow{OH^-} \xrightarrow[\Delta]{H^+} RCH_2COCOOH}$$

3. Acyl chlorides and cyanide (Section 26.3.B)

$$\mathrm{RCOCl + CN^- \longrightarrow RCOCN \xrightarrow{H^+} RCOCOOH}$$

α-Diketones

1. Acyloin condensation (Section 24.4.A) and oxidation (Section 26.3.B)

$$\mathrm{RCHO \xrightarrow[ether]{Na} RCOCHOHR \xrightarrow{[O]} RCOCOR}$$

2. Benzoin condensation (Section 24.4.A) and oxidation (Section 26.3.B)

$$\mathrm{C_6H_5CHO \xrightarrow{CN^-} C_6H_5COCHOHC_6H_5 \xrightarrow{[O]} C_6H_5COCOC_6H_5}$$

3. Selenium dioxide oxidation (Section 26.3.B)

$$\mathrm{RCH_2COR \xrightarrow{SeO_2} RCOCOR}$$

1,3-Diacids

1. Claisen condensation with diethyl carbonate (Section 26.3.A).

$$\mathrm{RCH_2COOEt + (EtO)_2CO \xrightarrow{NaOEt} RCH(COOEt)_2}$$

2. Alkylation of malonic ester (Section 26.4.D)

$$\mathrm{CH_2(COOEt)_2 \xrightarrow[EtOH]{EtONa} \xrightarrow{RX} RCH(COOEt)_2}$$

1,3-Keto Acids

1. Claisen condensation (Section 26.3.A)

$$\mathrm{2\,RCH_2COOEt \xrightarrow[EtOH]{NaOEt} RCH_2COCHRCOOEt}$$

2. Alkylation of β-keto esters (Section 26.4.D)

$$\mathrm{RCOCH_2COOEt \xrightarrow[EtOH]{NaOEt} \xrightarrow{R'X} RCOCHR'COOEt}$$

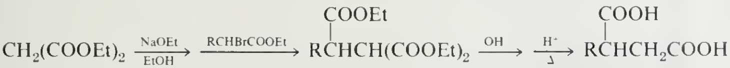
1,3-Diketones or Keto Aldehydes

Condensation of ketones with esters (Section 26.3.A)

$$\mathrm{RCOCH_3 + R'COOEt \xrightarrow[EtOH]{NaOEt} RCOCH_2COR'}$$

1,4-Diacids

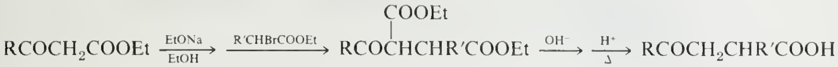
Alkylation of malonic ester with α-halo esters (Section 26.4.D)



$$CH_2(COOEt)_2 \xrightarrow[EtOH]{NaOEt} \xrightarrow{RCHBrCOOEt} R\overset{\displaystyle COOEt}{\overset{|}{C}}HCH(COOEt)_2 \xrightarrow{OH} \xrightarrow[\Delta]{H^+} R\overset{\displaystyle COOH}{\overset{|}{C}}HCH_2COOH$$

1,4-Keto Acids

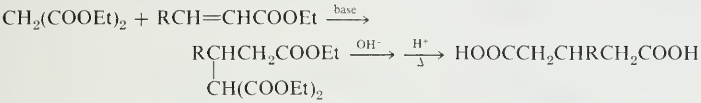
Alkylation of β-keto esters with α-halo esters (Section 26.4.D)



$$RCOCH_2COOEt \xrightarrow[EtOH]{EtONa} \xrightarrow{R'CHBrCOOEt} RCO\overset{\displaystyle COOEt}{\overset{|}{C}}HCHR'COOEt \xrightarrow{OH^-} \xrightarrow[\Delta]{H^+} RCOCH_2CHR'COOH$$

1,5-Diacids

Michael addition of malonic ester and α,β-unsaturated ester (Section 26.4.F)

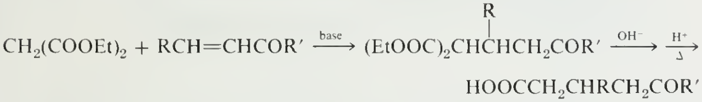


$$CH_2(COOEt)_2 + RCH{=}CHCOOEt \xrightarrow{base}$$

$$\underset{\displaystyle CH(COOEt)_2}{\underset{|}{R C}}HCH_2COOEt \xrightarrow{OH^-} \xrightarrow[\Delta]{H^+} HOOCCH_2CHRCH_2COOH$$

1,5-Keto Acids

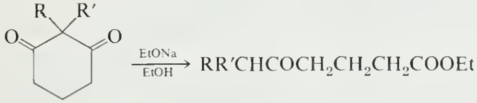
1. Michael addition of malonic ester and α,β-unsaturated aldehydes or ketones (Section 26.4.F)



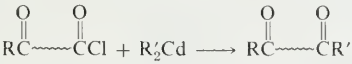
$$CH_2(COOEt)_2 + RCH{=}CHCOR' \xrightarrow{base} (EtOOC)_2CH\overset{\displaystyle R}{\overset{|}{C}}HCH_2COR' \xrightarrow{OH^-} \xrightarrow[\Delta]{H^+}$$

$$HOOCCH_2CHRCH_2COR'$$

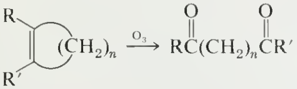
2. Reverse Claisen on 1,3-cyclohexanediones (Section 26.4.G)



In addition, many of the preparations of simple carbonyl compounds and carboxylic acids can also be applied in the preparation of dicarbonyl compounds. For example

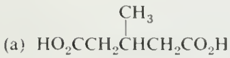


$$R\overset{\displaystyle O}{\overset{\|}{C}}\sim\!\sim\!\sim\overset{\displaystyle O}{\overset{\|}{C}}Cl + R'_2Cd \longrightarrow R\overset{\displaystyle O}{\overset{\|}{C}}\sim\!\sim\!\sim\overset{\displaystyle O}{\overset{\|}{C}}R'$$

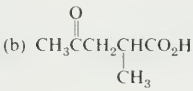


P R O B L E M S

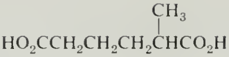
1. Name each compound.



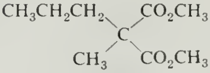
(a) $HO_2CCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CO_2H$

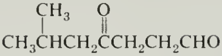


(b) $CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2H$

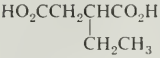
(c) 
$HO_2CCH_2CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCO_2H$

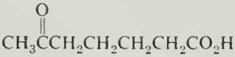
(d) $NCCH_2CH_2CH_2CN$

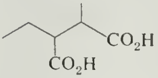
(e) 

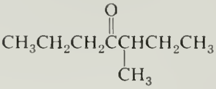
(f) 
$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CHO$

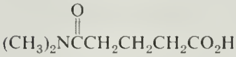
2. Show how each of the following compounds may be synthesized from compounds containing five or fewer carbons.

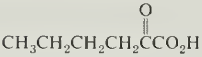
(a) 
$HO_2CCH_2\underset{CH_2CH_3}{\underset{|}{C}}HCO_2H$

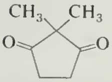
(b) 
$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2CO_2H$

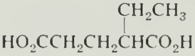
(c) 

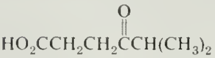
(d) 
$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}}HCH_2CH_3$

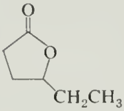
(e) 
$(CH_3)_2N\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CO_2H$

(f) 
$CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CO_2H$

(g) 

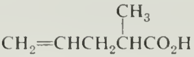
(h) 
$HO_2CCH_2CH_2\overset{CH_2CH_3}{\overset{|}{C}}HCO_2H$

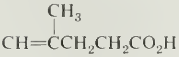
(i) 
$HO_2CCH_2CH_2\overset{O}{\overset{\|}{C}}CH(CH_3)_2$

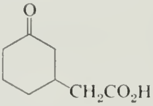
(j) 

3. Show how each of the following compounds may be prepared starting with diethyl malonate.

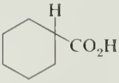
(a) $(CH_3)_2CHCH_2CH_2CO_2H$

(b) 
$CH_2{=}CHCH_2\overset{CH_3}{\overset{|}{C}}HCO_2H$

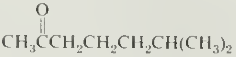
(c) 
$CH{=}\overset{CH_3}{\overset{|}{C}}CH_2CH_2CO_2H$

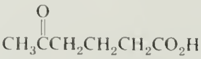
(d) 

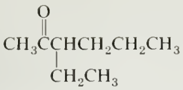
(e) $HO_2CCH_2CH_2CH_2CO_2H$

(f) 

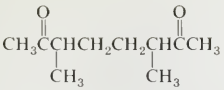
4. Show how each of the following compounds may be prepared starting with ethyl acetoacetate.

(a) 
$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH(CH_3)_2$

(b) 
$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CO_2H$

(c) 

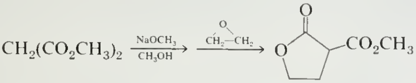
$CH_3C(=O)CH(CH_2CH_3)CH_2CH_2CH_3$

(d) 

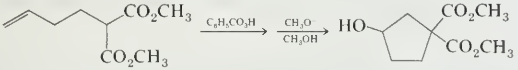
$CH_3C(=O)CH(CH_3)CH_2CH_2CH(CH_3)C(=O)CH_3$

5. When ethyl acetoacetate is treated with 1,3-dibromopropane and 2 moles of sodium ethoxide in ethanol, a product (A) is produced that has the formula $C_9H_{14}O_3$. Compound A has an infrared spectrum that shows only one carbonyl absorption and no OH bond. Suggest a structure for A and rationalize its formation.

6. Write a reasonable mechanism for the following reactions.

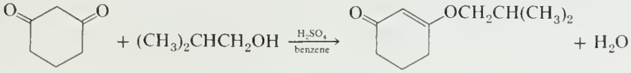
(a) 

CH₂(CO₂CH₃)₂
NaOCH₃
CH₃OH
O
CH₂—CH₂
O
O
CO₂CH₃

(b) 

CO₂CH₃
CO₂CH₃
C₆H₅CO₃H
CH₃O⁻
CH₃OH
HO
CO₂CH₃
CO₂CH₃

7. 1,3-Cyclohexanedione reacts with isobutyl alcohol and sulfuric acid in benzene in the following way. Write a mechanism for the reaction.

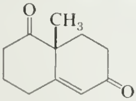


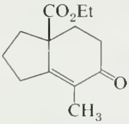
O
O
+ (CH₃)₂CHCH₂OH
H₂SO₄
benzene
O
OCH₂CH(CH₃)₂
+ H₂O

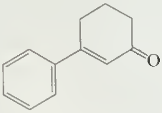
8. (a) Phthalimide (page 741) has a pK_a of 8.3. Explain why this compound is so acidic.
(b) Outline a scheme whereby phthalimide might be used as a reagent to prepare primary amines, that is, compounds of the general formula RNH_2.

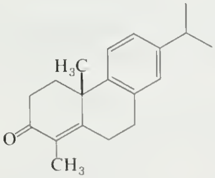
9. Suggest an explanation for the fact that β-keto acids undergo decarboxylation at lower temperatures than β-diacids.

10. Show how the Robinson annelation may be used to prepare each compound.

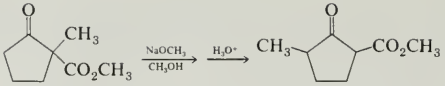
(a) 

(b) 

(c) 

(d) 

11. When 2-methyl-2-methoxycarbonylcyclopentanone is treated with sodium methoxide in refluxing methanol and the solution is then neutralized, 5-methyl-2-methoxycarbonylcyclopentanone is produced. Write a mechanism for the reaction and explain.



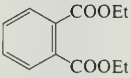
12. A side reaction in the alkylation of malonic ester is dialkylation:

$$(\mathrm{EtOOC})_2\mathrm{CH}^- + \mathrm{RX} \longrightarrow (\mathrm{EtOOC})_2\mathrm{CHR} + \mathrm{X}^-$$
$$(\mathrm{EtOOC})_2\mathrm{CHR} + (\mathrm{EtOOC})_2\mathrm{CH}^- \rightleftharpoons (\mathrm{EtOOC})_2\mathrm{CR}^- + (\mathrm{EtOOC})_2\mathrm{CH}_2$$
$$(\mathrm{EtOOC})_2\mathrm{CR}^- + \mathrm{RX} \longrightarrow (\mathrm{EtOOC})_2\mathrm{CR}_2 + \mathrm{X}^-$$

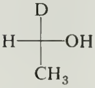
In the preparation of butylmethylmalonic ester (page 752) it is better to alkylate first with butyl bromide and then with methyl iodide rather than in the reverse sequence. Can you explain why based on the side reaction just mentioned?

13. Explain why succinic acid does not lose CO_2 as readily as malonic acid on heating.

14. Give the structure of the principal reaction product of each of the following reaction sequences:

(a) 

$+ \mathrm{EtOOC(CH_2)_3COOEt} \xrightarrow[\mathrm{EtOH}]{\mathrm{EtONa}} \xrightarrow[\Delta]{\text{dil H}^+} \mathrm{C_{11}H_{10}O_2}$

(b) 

$\mathrm{H{-}C(D)(CH_3){-}OH} \xrightarrow[\text{pyridine}]{\mathrm{C_6H_5SO_2Cl}} \xrightarrow[\mathrm{EtONa\ EtOH}]{\mathrm{CH_2(COOEt)_2}} \xrightarrow[\Delta]{\text{dil H}^+} \mathrm{C_4H_7DO_2}$

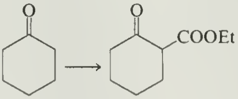
optically active

(c) $2\,\mathrm{CH_2(COOEt)_2} + \mathrm{C_6H_5CHO} \xrightarrow[\mathrm{EtOH}]{\mathrm{EtONa}} \xrightarrow[\Delta]{\text{dil H}^+} \mathrm{C_{11}H_{12}O_4}$

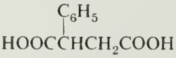
(d) $\mathrm{C_6H_5COCH_2COOEt} \xrightarrow[\mathrm{EtOH}]{\mathrm{EtONa}} \xrightarrow{\mathrm{CH_3CH_2I}} \xrightarrow[\mathrm{EtOH}]{\mathrm{EtONa}} \xrightarrow{\mathrm{CH_3I}} \xrightarrow[\Delta]{\mathrm{H^+}} \mathrm{C_{11}H_{14}O}$

(e) $\mathrm{EtOOCCOOEt} + \mathrm{CH_3COOEt} \xrightarrow[\mathrm{EtOH}]{\mathrm{EtONa}}$

15. Show how one may accomplish each of the following conversions in a practical manner.

(a) 

(b) $\mathrm{C_6H_5CH_2COOEt} \longrightarrow \mathrm{C_6H_5CH(COOEt)_2}$

(c) $\mathrm{C_6H_5CH(COOEt)_2} \longrightarrow$ 
$\mathrm{HOOC\overset{\displaystyle C_6H_5}{\overset{|}{C}}HCH_2COOH}$

CHAPTER 27
Amines

27.1
Structure

Amines are compounds in which one or more alkyl groups are attached to nitrogen. They may be considered as the organic relatives of ammonia, in the same way that alcohols and ethers are related to water.

$$\underset{\text{water}}{H_2O} \qquad \underset{\text{alcohols}}{ROH} \qquad \underset{\text{ethers}}{R_2O}$$

$$\underset{\text{ammonia}}{NH_3} \qquad \underbrace{RNH_2 \quad R_2NH \quad R_3N}_{\text{amines}}$$

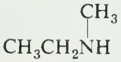
Amines are classified as **primary, secondary,** or **tertiary,** according to the number of alkyl groups that are joined to the nitrogen. Note that these descriptive adjectives are used here to denote the *degree of alkyl substitution* on nitrogen, not the nature of the alkyl groups. In secondary and tertiary amines, the alkyl groups may be the same or different.

Some Primary Amines

$CH_3NH_2 \qquad (CH_3)_2CHNH_2 \qquad (CH_3)_3CNH_2$

Some Secondary Amines

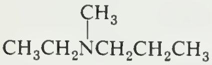
$(CH_3)_2NH \qquad (CH_3CH_2)_2NH$



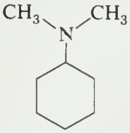
$CH_3CH_2\overset{\overset{CH_3}{|}}{N}H$

Some Tertiary Amines

$(CH_3)_3N$



$CH_3CH_2\overset{\overset{CH_3}{|}}{N}CH_2CH_2CH_3$



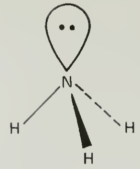
Quaternary ammonium compounds are related to simple inorganic ammonium salts. Again, the four alkyl groups joined to nitrogen in the ammonium ion may be the same or different.

Some Quaternary Ammonium Compounds

$(CH_3)_4N^+Cl^- \qquad CH_3CH_2CH_2N(CH_3)_3^+\ OH^-$

$(CH_3CH_2)_2N(CH_3)_2^+\ Br^-$

Recall that ammonia has a pyramidal shape. The N—H bond length is 1.008 Å and the HNH bond angle is 107.3°.



ammonia

The hybridization of nitrogen is approximately sp^3. It forms three approximately sp^3-s σ bonds to hydrogen and has a **nonbonding electron pair** which occupies the other approximately sp^3 orbital. Amines have similar structures, as shown in Figures 27.1 and 27.2 for methylamine and trimethylamine.

Bond Length, Å		Bond Angle, deg	
NH	1.011	HNH	105.9
CN	1.474	HNC	112.9

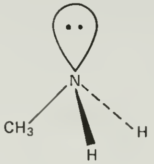


FIGURE 27.1 *Structure of methylamine.*

Bond Length, Å		Bond Angle, deg	
CN	1.47	CNC	108

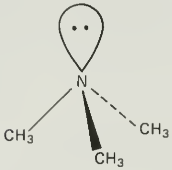


FIGURE 27.2 *Structure of trimethylamine.*

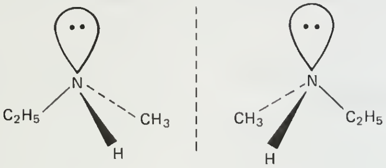
The nonbonding electron pair is extremely important in the chemistry of amines, since it is responsible for the typical basic and nucleophilic properties of these compounds.

Consider the following progression of bond lengths:

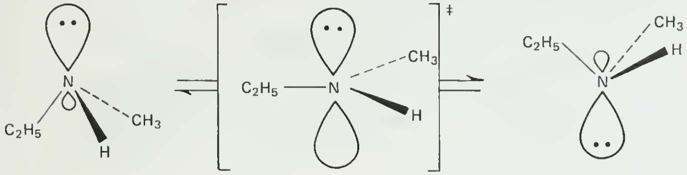
	Length, Å		Length, Å
CH_3-CH_3	1.531	$H-CH_3$	1.085
CH_3-NH_2	1.474	$H-NH_2$	1.012
CH_3-OH	1.427	$H-OH$	0.957
CH_3-F	1.385	$H-F$	0.917

As we proceed along the first row of the periodic table, the increasing nuclear charge causes the electron orbitals to shrink and result in shorter bonds.

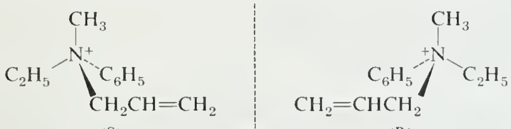
Because of the pyramidal geometry, an amine with three different groups joined to nitrogen is chiral (alternatively, amines may be regarded as approximately tetrahedral, with the nonbonding pair being the fourth "group").



Recall that enantiomeric carbon compounds may be separated and that the individual enantiomers are quite stable because it is necessary to break and reform bonds to interconvert them. In contrast, the two enantiomers of a chiral amine are readily interconvertible by a process known as **nitrogen inversion.** For simple amines, the activation energy required for inversion is rather small, on the order of 6 kcal mole^{-1}. In the planar transition state for inversion, the nitrogen has sp^2 hybridization with the lone pair in the p_z orbital.



For quaternary ammonium compounds, such inversion is not possible, and chiral ions may be separated into enantiomers that are relatively stable.



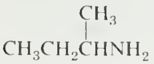
(S) (R)

27.2 Nomenclature of Amines

As with many other classes of organic compounds, there are several systems for naming amines. The simplest and most consistent system is the IUPAC system, but it is rarely used for simple amines. Under the IUPAC rules, amines are named as derivatives of a parent hydrocarbon; the NH_2 group is denoted by the prefix **amino.**

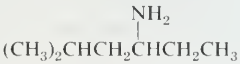
CH_3NH_2

aminomethane



$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HNH_2$

2-aminobutane



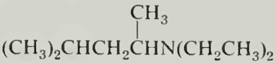
$(CH_3)_2CHCH_2\overset{\overset{NH_2}{|}}{C}HCH_2CH_3$

4-amino-2-methylhexane

Secondary and tertiary amines are named by using a compound prefix that includes the names of all but the largest alkyl group.

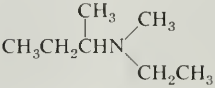
$CH_3CH_2N(CH_3)_2$

dimethylaminoethane

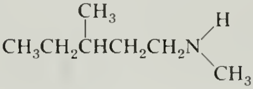


$$(CH_3)_2CHCH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HN(CH_2CH_3)_2$$

4-(diethylamino)-2-methylpentane



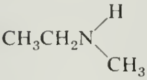
2-(ethylmethylamino)butane



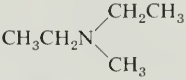
1-(methylamino)-3-methylpentane

The simple amines are usually referred to by common names, which are derived by using the suffix **-amine**, preceded by the name or names of the alkyl groups. The names are written as one word.

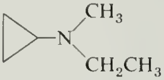
CH_3NH_2	$(CH_3CH_2)_2NH$	$(CH_3CH_2CH_2)_3N$
methylamine	diethylamine	tri-*n*-propylamine



ethylmethylamine



diethylmethylamine



cyclopropylethylmethylamine

27.3
Physical Properties of Amines

A. *Colligative Properties*

The melting points, boiling points, and densities of some simple amines are collected in Table 27.1. As with other classes of compounds, certain trends are evident in the properties. All three properties increase with molecular weight, as a consequence of the greater intermolecular attraction with the larger members in the series.

Like alcohols, the lower amines show the effect of hydrogen bonding (Section 11.3). Since nitrogen is not as electronegative as oxygen, the N—H···N hydrogen bond is not as strong as the analogous O—H···O bond. Thus, primary amines have boiling points that are intermediate between those of alkanes and alcohols of comparable molecular weight (Figure 27.3) just as ammonia, b.p. −33°, is intermediate between methane, b.p. −161°, and water, b.p. 100°.

Hydrogen bonding is more important with primary than with secondary amines and is not possible at all with tertiary amines. Thus, a primary amine always boils higher than a secondary or tertiary amine of the same molecular weight (Figure 27.4).

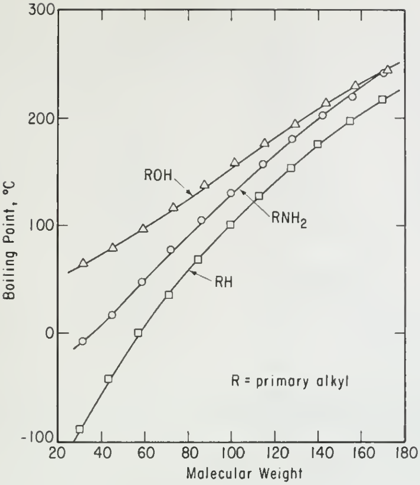


FIGURE 27.3 *Boiling points of alkanes, alcohols, and primary amines.*

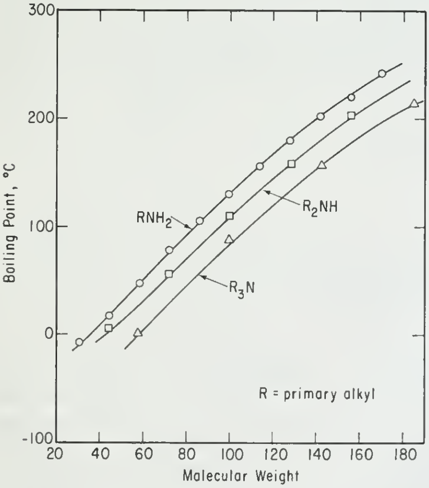


FIGURE 27.4 *Boiling points of primary, secondary, and tertiary amines.*

TABLE 27.1
Physical Properties of Amines

	Molecular Weight	Melting Point, °C	Boiling Point, °C	Density
Primary Amines				
CH_3NH_2	31	−94	−6.3	0.6628
$CH_3CH_2NH_2$	45	−81	16.6	0.6829
$CH_3CH_2CH_2NH_2$	59	−83	47.8	0.7173
$(CH_3)_2CHNH_2$	59	−95	32	0.8889
$CH_3CH_2CH_2CH_2NH_2$	73	−49	77.8	0.7414
$(CH_3)_3CNH_2$	73	−68	44.4	0.6958
$CH_3(CH_2)_4NH_2$	87	−55	104	0.7547
$CH_3(CH_2)_5NH_2$	101	−19	130	0.7660
$CH_3(CH_2)_6NH_2$	115	−18	157	0.7754
$CH_3(CH_2)_7NH_2$	129	0	180	0.7826
$CH_3(CH_2)_8NH_2$	143	−1	202	0.7886
$CH_3(CH_2)_9NH_2$	157	17	221	0.7936
Secondary Amines				
$(CH_3)_2NH$	45	−93	7.4	0.6804
$(CH_3CH_2)_2NH$	73	−48	56.3	0.7056
$(CH_3CH_2CH_2)_2NH$	101	−40	110	0.7400
$(CH_3CH_2CH_2CH_2)_2NH$	129	−60	159	0.7670
Tertiary Amines				
$(CH_3)_3N$	59	−117	2.9	0.6356
$(CH_3CH_2)_3N$	101	−114	89.3	0.7256
$(CH_3CH_2CH_2)_3N$	143	−94	155	0.7558
$(CH_3CH_2CH_2CH_2)_3N$	185		213	0.7771

B. *Spectroscopic Properties*

1. **INFRARED SPECTRA.** The characteristic infrared absorptions of amines are associated with the N—H and C—N bonds. Typical bands are summarized in Table 27.2. For diagnostic purposes, the C—N absorptions are not very useful, because these bands occur in a spectral region that normally contains many bands for other types of compounds as well. Particularly useful absorptions are the weak N—H stretching bands of primary amines, the N—H bending mode of primary amines, and the N—H wagging mode for primary and secondary amines. The N—H stretch of secondary amines is so weak that it is often not observed. Infrared spectroscopy is useful in diagnosing the presence of a tertiary amino group only in an indirect sense; if an amine does not show ir absorption bands characteristic for primary or secondary amines, it may be concluded that it is tertiary. An example is the spectrum of *n*-hexylamine, which is shown in Figure 27.5.

TABLE 27.2
Infrared Spectra of Amines

Wave Number, cm^{-1}	Intensity	Assignment	Compound Type
3500, 3400 (doublet)	weak	N—H stretching	primary
3310–3350	very weak	N—H stretching	secondary
1580–1650	medium to strong	N—H bending	primary
1020–1250	weak to medium	C—N stretching	primary, secondary
666–909	medium to strong	N—H wagging	primary, secondary

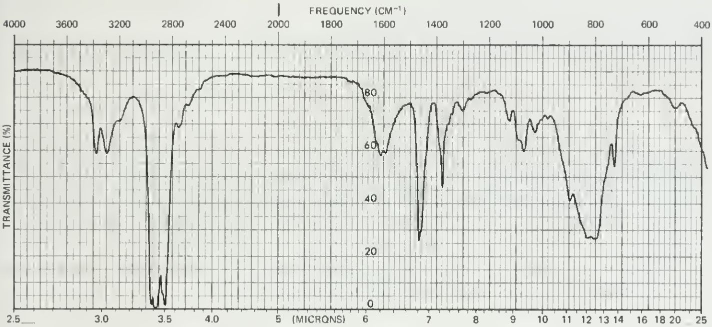


FIGURE 27.5 *Infrared spectrum of* n-*hexylamine.*

2. NUCLEAR MAGNETIC RESONANCE SPECTRA. Since nitrogen is more electronegative than carbon, the protons near the amino group are deshielded. The downfield shifts are not as pronounced as in the case of alcohols and ethers (Sections 11.5 and 11.9). As with alcohols and ethers, the exact chemical shift is dependent upon whether the protons are part of a CH_3, a CH_2, or a CH group:

	CH_3NR_2	$R'CH_2NR_2$	R'_2CHNR_2
δ, ppm:	2.2	2.4	2.8

Protons β to nitrogen are affected to a much smaller extent; they are normally seen in the range $\delta = 1.1\text{–}1.7$ ppm.

Protons bound directly to the nitrogen in primary and secondary amines may resonate anywhere in the region from $\delta = 0.6$ ppm to $\delta = 3.0$ ppm. The exact resonance position is dependent on the purity of the sample, the nature of the solvent, the concentration, and the temperature at which the measurement is made. As with alcohols, coupling of the type H—C—N—H is generally not observed because of proton exchange. The spectrum of di-*n*-propylamine is shown in Figure 27.6.

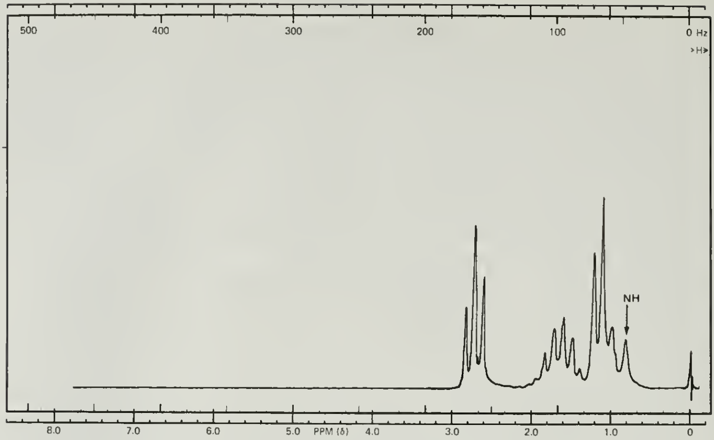


FIGURE 27.6 Nmr *spectrum of* $(CH_3CH_2CH_2)_2NH$.

3. MASS SPECTRA. Mass spectroscopy is often a useful technique for establishing the presence of nitrogen in an organic compound. Hydrocarbons and oxygen-containing compounds always have *even molecular weights,* but compounds containing an odd number of nitrogen atoms have odd molecular weights.

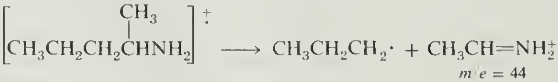
> The student should convince himself of the truth of this statement by adding up the molecular weights of some randomly selected compounds.

Thus, the molecular ion of a monoamine is always odd, and such an observation can be used to conclude that a molecule contains an odd number of nitrogens. Unfortunately, the parent molecular ions of simple amines tend to have low intensity because there is a favorable fragmentation pathway. For this reason, the absence of an odd molecular ion does not establish that a molecule is not a monoamine.

The chief fragmentation mode is cleavage of the molecular ion at the α—β C—C bond to give an alkyl radical and an **immonium ion.** Primary amines which are not branched at the α-carbon give a strong fragment with $m/e = 30$.

$$[CH_3CH_2CH_2NH_2]^{+\cdot} \longrightarrow CH_3CH_2\cdot + \underset{m/e\,=\,30}{CH_2{=}NH_2^+}$$

When the amine is branched at the α-carbon, an analogous cleavage occurs, leading to a homologous immonium ion; loss of the larger group is preferred.



$$\left[CH_3CH_2CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HNH_2\right]^{+\cdot} \longrightarrow CH_3CH_2CH_2\cdot + \underset{m/e\,=\,44}{CH_3CH{=}NH_2^+}$$

These cleavage patterns are illustrated by the spectra of isobutylamine and *t*-butylamine, shown in Figures 27.7 and 27.8.

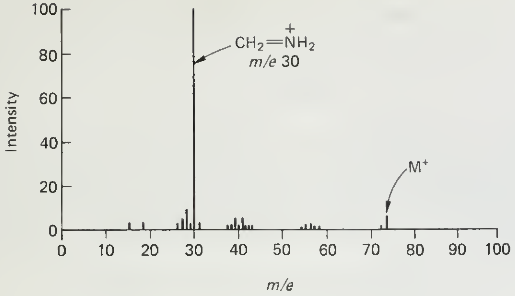


FIGURE 27.7 *Mass spectrum of isobutylamine,* $(CH_3)_2CHCH_2NH_2$.

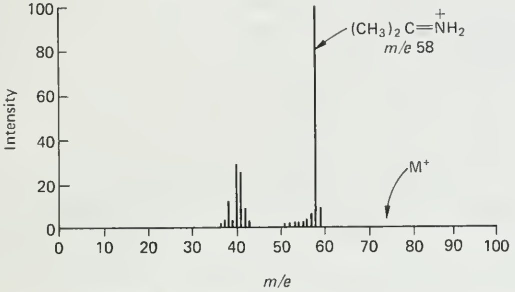


FIGURE 27.8 *Mass spectrum of* t-*butylamine,* $(CH_3)_3CNH_2$.

27.4
Basicity

Because of the presence of a nonbonding electron pair on nitrogen, amines are Lewis bases, just like alcohols and ethers (Sections 11.7.B and 18.7). Nitrogen is not as electronegative as oxygen, and amines have a greater tendency to react with a proton than alcohols. Looking at it another way, alkyloxonium ions are more acidic than alkylammonium ions.

$$\underset{\text{less basic}}{CH_3OH} + H^+ \rightleftharpoons \underset{\text{more acidic}}{CH_3\overset{+}{O}H_2}$$

$$\underset{\text{more basic}}{CH_3NH_2} + H^+ \rightleftharpoons \underset{\text{less acidic}}{CH_3\overset{+}{N}H_3}$$

Since amines are much more basic than water, aqueous solutions of amines have basic properties. The equilibrium constant for the acid-base reaction of an amine with water is called K_b.

$$RNH_2 + H_2O \overset{K_b}{\rightleftharpoons} RNH_3^+ + OH^-$$

$$K_b = \frac{[RNH_3^+][OH^-]}{[RNH_2]}$$

As usual in such expressions, the concentration of water is not included in the equilibrium expression because it is present in large excess and is essentially constant (Section 17.4). It is often convenient to refer to the dissociation constant of the corresponding ammonium ion when comparing base strengths of amines. This equilibrium constant, like other dissociation constants, is called K_a.

$$RNH_3^+ + H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]}$$

K_b for an amine and K_a for the corresponding ammonium ion are related by expression (27-1)

$$K_aK_b = 10^{-14}\ M^2$$

or (27-1)

$$pK_a + pK_b = 14$$

The student should derive this relationship by using the foregoing equations and the relationship for the dissociation of water, $K_w = [H_3O^+][OH^-] = 10^{-14}\ M^2$.

The pK_bs for some typical amines and the pK_as for the corresponding ammonium ions are collected in Table 27.3.

TABLE 27.3
Basicity of Some Amines

Amine	pK_b, 25°	Conjugate Acid	pK_a, 25°
NH_3	4.76	NH_4^+	9.24
CH_3NH_2	3.38	$CH_3NH_3^+$	10.62
$CH_3CH_2NH_2$	3.36	$CH_3CH_2NH_3^+$	10.64
$(CH_3)_3CNH_2$	3.32	$(CH_3)_3CNH_3^+$	10.68
$(CH_3)_2NH$	3.27	$(CH_3)_2NH_2^+$	10.73
$(CH_3CH_2)_2NH$	3.06	$(CH_3CH_2)_2NH_2^+$	10.94
$(CH_3)_3N$	4.21	$(CH_3)_3NH^+$	9.79
$(CH_3CH_2)_3N$	3.25	$(CH_3CH_2)_3NH^+$	10.75

The pK_b for ammonia and the pK_a for ammonium ion are included in Table 27.3 for reference. Notice that the simple alkylammonium ions all have pK_as in the range 10–11 and are therefore slightly *less acidic* than NH_4^+ itself. In other words, amines are only slightly more basic than NH_3.

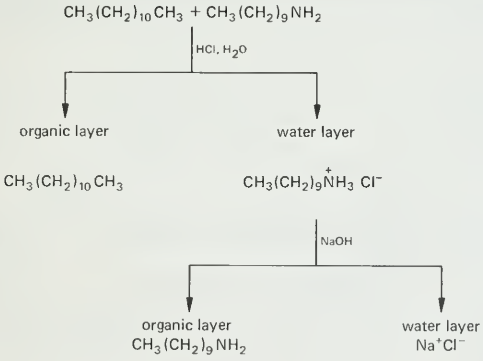
It is important to distinguish between K_a for the dissociation of NH_4^+ and K_a for NH_3 itself and not to confuse them. Ammonia itself is an extremely weak acid; the pK_a for NH_3 is about 35 and the pK_b for NH_2^-, correspondingly, is −21. Analogous anions derived by deprotonation of amines are known and are useful reagents for some organic reactions. Because amines are such feeble acids, powerful bases are needed for deprotonation; alkyllithium compounds are commonly used.

$$\underset{\substack{\text{dipropylamine}\\ \mathrm{p}K_a \approx 40}}{(CH_3CH_2CH_2)_2NH} + \underset{\text{butyllithium}}{n\text{-}C_4H_9Li} \longrightarrow \underset{\substack{\text{lithium}\\ \text{dipropylamide}}}{(CH_3CH_2CH_2)_2N^- \; Li^+} + \underset{\substack{\text{butane}\\ \mathrm{p}K_a \approx 50}}{C_4H_{10}}$$

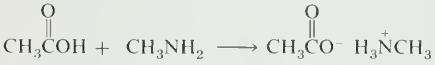
Because of their basic properties, amines form salts with acids. Since these salts are ionic compounds, they are usually water soluble, even in cases where the corresponding amine is insoluble in water.

$$\underset{\substack{n\text{-decylamine}\\ \text{(insoluble in } H_2O)}}{CH_3(CH_2)_9NH_2} + HCl \longrightarrow \underset{\substack{n\text{-decylammonium chloride}\\ \text{(soluble in } H_2O)}}{CH_3(CH_2)_9\overset{+}{N}H_3 \; Cl^-}$$

This property provides a convenient method for separating amines from neutral organic compounds. For example, a mixture of *n*-decylamine (b.p. 221°) and dodecane (b.p. 216°) is difficult to separate by fractional distillation. The two compounds may be separated easily by *extracting* the mixture with sufficient 10% aqueous hydrochloric acid to convert all of the amine into the ammonium salt. The alkane, being insoluble in water, is unaffected by this treatment, and the ammonium salt dissolves in the water layer. The layers may be separated by use of a separatory funnel to give the pure alkane. A strong base such as sodium hydroxide is then added to the aqueous solution to neutralize the ammonium salt and liberate the free amine. The water-insoluble amine now forms a separate layer that may be separated.



Amines also form salts with carboxylic acids. Again, the salts are ionic and are often water soluble.

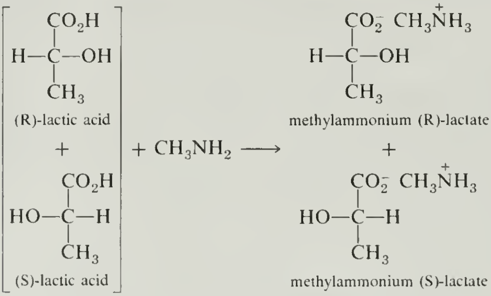


$$\underset{\substack{\text{acetic}\\ \text{acid}}}{CH_3\overset{\overset{\displaystyle O}{\|}}{C}OH} + \underset{\text{methylamine}}{CH_3NH_2} \longrightarrow \underset{\substack{\text{methylammonium}\\ \text{acetate}}}{CH_3\overset{\overset{\displaystyle O}{\|}}{C}O^- \; H_3\overset{+}{N}CH_3}$$

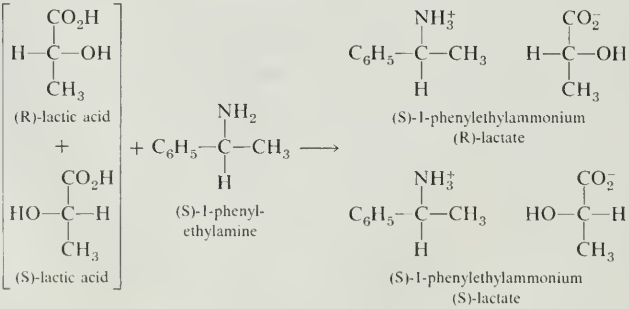
This salt-forming reaction is often used as a method for **resolving** racemic mixtures of organic acids.

The student should review the basic principles of stereochemistry in Chapter 7. **Resolution** is the term used to describe the separation of two enantiomers from each other.

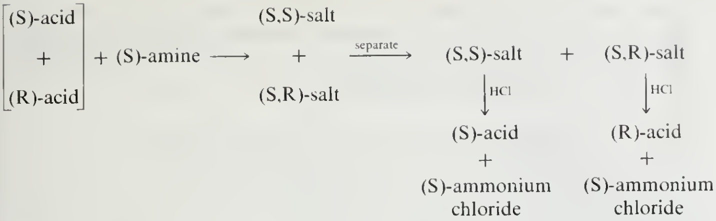
Consider a racemic mixture of α-hydroxypropionic acids (lactic acids). Recall that the two enantiomers have identical physical properties and cannot be separated by crystallization or distillation techniques. The mixture will react with methylamine to give a racemic mixture of methylammonium lactates, which also cannot be separated by physical methods.


(R)-lactic acid
(S)-lactic acid
+ CH_3NH_2
methylammonium (R)-lactate
methylammonium (S)-lactate

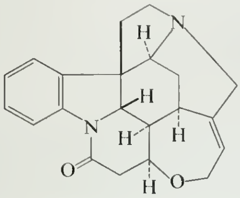
However, consider the situation when one enantiomer of a chiral amine is used to form the salt.


(R)-lactic acid
(S)-lactic acid
(S)-1-phenylethylamine
(S)-1-phenylethylammonium (R)-lactate
(S)-1-phenylethylammonium (S)-lactate

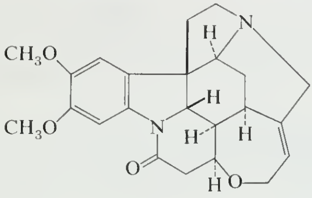
The two salts are now diastereomeric, rather than enantiomeric, and they have different physical properties. For example, the (S,R) salt may be more soluble in some solvents than the (S,S) salt. Because of this difference in solubility, the two salts can be separated by fractional crystallization. Each of the diastereomeric salts can then be treated with a strong acid such as hydrochloric or sulfuric acid to liberate the free carboxylic acid. Acidification of the (S,R) salt gives enantiomerically pure (R)-lactic acid, whereas similar treatment of the (S,S) salt gives pure (S)-lactic acid.



Of course, in order to use this technique for resolution, suitable optically active amines must be available. Fortunately, a number of such compounds are readily available and relatively inexpensive. A particularly useful source of such resolving agents is the class of naturally occurring amines called alkaloids, which occur in nature in only one enantiomeric form. Examples are strychnine and brucine.

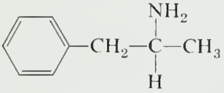


strychnine



brucine

Another frequently used resolving agent is 1-phenyl-2-aminopropane (amphetamine). Although not a natural product, synthetic amphetamine is readily available in both enantiomeric forms.



amphetamine

27.5
Nucleophilicity of Amines: Quaternary Ammonium Compounds

Recall that there is a correlation between Lewis basicity and the nucleophilicity of a species (Section 8.4). Amines are more basic than alcohols or ethers, and they are also more nucleophilic. For example, a mixture of diethyl ether and methyl iodide does not react under ordinary conditions, but triethylamine and methyl iodide react violently at room temperature. If the reaction is carried out in a solvent to moderate its vigor, the product, which is a tetraalkylammonium iodide, may be obtained in good yield.

$$(C_2H_5)_2O + CH_3I \xrightarrow{25^\circ} \text{no reaction}$$

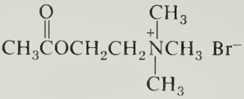
$$(C_2H_5)_3N + CH_3I \xrightarrow[\text{ether}]{25^\circ} (C_2H_5)_3\overset{+}{N}CH_3\ I^-$$

methyltriethylammonium iodide

Such compounds, which have four alkyl groups replacing the four hydrogens of the ammonium ion, are called **quaternary ammonium compounds.** Since they are ionic, they are generally water soluble and have fairly high melting points. They often decompose at the melting point.

$(CH_3)_4N^+Cl^-$	$(CH_3CH_2CH_2)_4N^+Br^-$
tetramethylammonium chloride m.p. 420°	tetrapropylammonium bromide m.p. 252°

Quaternary ammonium compounds are important as intermediates in some reactions that we shall encounter and also occur in nature. Acetylcholine, which is important in the neural transport system of mammals, is an example.



$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2\overset{CH_3}{\overset{+|}{\underset{\underset{CH_3}{|}}{N}}}CH_3\ Br^-$$

acetylcholine bromide

In Section 8.3 it was mentioned that ammonia reacts with primary alkyl halides by the S_N2 mechanism to give an alkylammonium halide. In principle, this type of displacement reaction might be used as a way of synthesizing primary amines.

$$CH_3CH_2Br + NH_3 \longrightarrow CH_3CH_2NH_3^+\ Br^- \xrightarrow{NaOH} CH_3CH_2NH_2$$

In practice, this method is not very useful because of the side reactions that occur. The product alkylammonium ion is fairly acidic and may transfer a proton to a molecule of ammonia which has not yet reacted to give the primary amine and the ammonium ion. Since the primary amine is also nucleophilic, it may undergo further reaction giving a secondary amine. By similar equilibria and further alkylation, the tertiary amine and even the quaternary ammonium compound may be formed. The actual result is a complex mixture even when equivalent molar amounts of ammonia and alkyl halide are used.

$$\begin{aligned}
RBr + NH_3 &\longrightarrow RNH_3^+\ Br^- \\
RNH_3^+ + NH_3 &\rightleftharpoons RNH_2 + NH_4^+ \\
RNH_2 + RBr &\longrightarrow R_2NH_2^+\ Br^- \\
R_2NH_2^+ + NH_3 &\rightleftharpoons R_2NH + NH_4^+ \\
R_2NH + RBr &\longrightarrow R_3NH^+Br^- \\
R_3NH^+ + NH_3 &\rightleftharpoons R_3N + NH_4^+ \\
R_3N + RBr &\longrightarrow R_4N^+Br^-
\end{aligned}$$

The "overalkylation" may be suppressed by using a large excess of ammonia or the amine being alkylated. This ploy is only practical in cases where the amine is relatively inexpensive and sufficiently volatile so that the unreacted excess may be easily removed. In many cases where a pure primary, secondary, or tertiary amine is desired, direct alkylation is not a practical synthetic method. Several indirect methods have been devised to accomplish this purpose; we shall study some of them in the next section.

27.6
Synthesis of Amines

A. *Direct Alkylation of Ammonia or Other Amines*

As mentioned in the previous section, the nucleophilic displacement of alkyl halides by ammonia or amines constitutes a method for the synthesis of amines. In practice, the procedure is complicated by overalkylation. If a large excess of ammonia or amine is used, the overalkylation is suppressed; however, the yield of desired product is still on the low side. An example is the preparation of *n*-butylamine by the reaction of *n*-butyl bromide with ammonia.

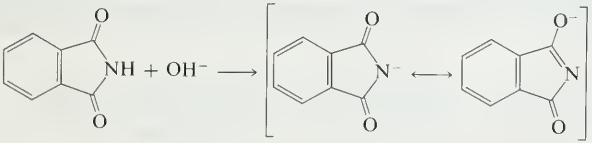
$$CH_3CH_2CH_2CH_2Br + NH_3 \longrightarrow \xrightarrow{NaOH} \underset{(47\%)}{CH_3CH_2CH_2CH_2NH_2}$$

> A solution of 300 g of NH_3 (20 moles) in 8 liters of 90% aqueous ethanol is prepared. *n*-Butyl bromide is added slowly until 1507 g (11 moles) has been added. The reaction mixture is stirred at 25° for 48 hr and then made basic with aqueous NaOH. Fractional distillation of the organic layer gives 388 g of *n*-butylamine (47%), along with some di-*n*-butylamine and tri-*n*-butylamine, which have higher boiling points.

Secondary and tertiary amines may also be prepared this way, but the yields are again often low due to overalkylation. Also, if the amine is not readily available or is expensive, it is undesirable to use it in excess.

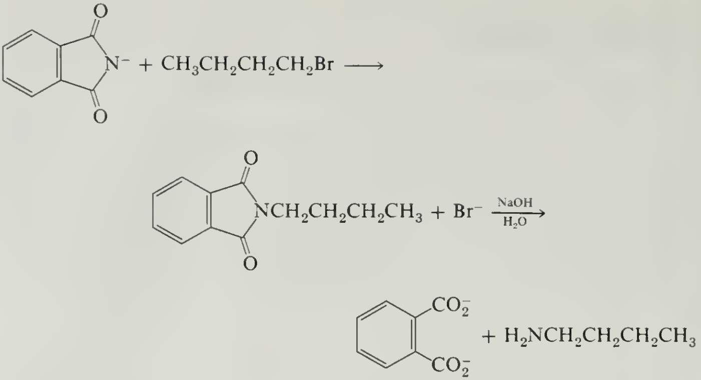
B. *Indirect Alkylation: The Gabriel synthesis*

Pure primary amines can be prepared in good yield by a method called the **Gabriel synthesis.** The compound phthalimide (Section 26.2.C) is prepared from ammonia and the dicarboxylic acid phthalic acid. Such imides have acidic properties because the negative charge on the conjugate base is delocalized over both oxygens and the nitrogen. They are nitrogen analogs of 1,3-diketones, and, since nitrogen is more electronegative than carbon, they are even more acidic than 1,3-diketones; the pK_a of phthalimide is 8.3. In aqueous basic solution, the compound is converted almost completely into the anion.



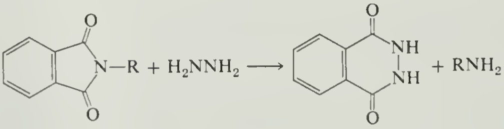
phthalimide

The phthalimide anion has nucleophilic properties and can enter into displacement reactions with alkyl halides. Reaction could in principle take place on either oxygen or nitrogen, but, since nitrogen is more nucleophilic, it occurs mostly on nitrogen. Further alkylation cannot occur because there are no acidic protons. The product is an N-alkylphthalimide, and hydrolysis gives the amine and phthalic acid.



The best solvent for the alkylation appears to be dimethylformamide, $HCON(CH_3)_2$. The Gabriel synthesis is frequently used in the preparation of α-amino carboxylic acids and we shall encounter it again in that context in Chapter 28.

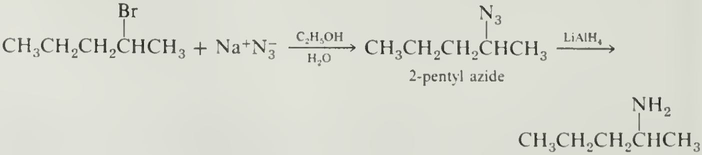
In many cases, the alkaline hydrolysis of the alkylphthalimide is very slow. An alternative procedure for recovering the amine is called the Ing-Manske modification and involves the use of hydrazine. The product is the amine and a cyclic diamide of hydrazine.



phthalhydrazide

C. *Reduction of Alkyl Azides*

Alkyl azides are obtained by the S_N2 reaction of azide ion, N_3^-, with alkyl halides (Section 8.3). The azido group may be reduced by several reagents to give an amino group. The most convenient reducing agent is $LiAlH_4$, but catalytic hydrogenation is also used.

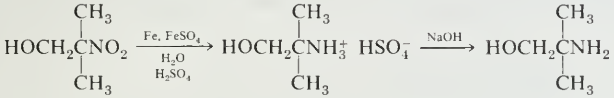


$$CH_3CH_2CH_2\overset{\overset{\displaystyle Br}{|}}{C}HCH_3 + Na^+N_3^- \xrightarrow[H_2O]{C_2H_5OH} \underset{\text{2-pentyl azide}}{CH_3CH_2CH_2\overset{\overset{\displaystyle N_3}{|}}{C}HCH_3} \xrightarrow{LiAlH_4} CH_3CH_2CH_2\overset{\overset{\displaystyle NH_2}{|}}{C}HCH_3$$

The method has one particularly nice feature in addition to the fact that pure primary amines result. Azide ion is an extremely good nucleophile and it is relatively nonbasic. Therefore, alkyl azides can be prepared in good yield from alkyl halides which are normally subject to much competing dehydrohalogenation when more basic nucleophiles are used. For this reason, the method is useful for preparing primary amines from secondary and β-branched alkyl halides (see Section 8.7). A major drawback of the azide method is the explosive nature of organic azides, especially those of low molecular weight (Section 27.8.A). Consequently, the route is seldom used on a large scale, even though the yields may be high.

D. *Reduction of Nitro Compounds*

Nitro compounds, RNO_2, may also be reduced to give primary amines. This method is most useful as a route to aromatic primary amines and we shall return to it in Section 32.1.C. It is less useful for the synthesis of aliphatic amines, because the corresponding nitro compounds are not as generally available (Section 27.8.C). An especially efficient reducing agent is a mixture of iron powder and ferrous sulfate in aqueous acidic solution.



$$HOCH_2C(CH_3)_2NO_2 \xrightarrow[H_2O,\ H_2SO_4]{Fe,\ FeSO_4} HOCH_2C(CH_3)_2NH_3^+\ HSO_4^- \xrightarrow{NaOH} HOCH_2C(CH_3)_2NH_2$$

(90%)

2-amino-2-methyl-1-propanol

E. *Reduction of Nitriles*

Nitriles are reduced by hydrogen and a catalyst or by lithium aluminum hydride in an ether solvent to give primary amines.

$$RC{\equiv}N \xrightarrow[\text{or } LiAlH_4]{H_2\text{-cat.}} RCH_2NH_2$$

An example is the $LiAlH_4$ reduction of butyronitrile, which affords *n*-butylamine in high yield.

$$CH_3CH_2CH_2C{\equiv}N \xrightarrow{LiAlH_4} \underset{(86\%)}{CH_3CH_2CH_2CH_2NH_2}$$

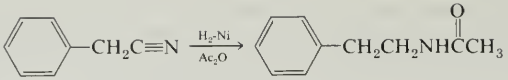
In the catalytic hydrogenation procedure, secondary amines are often produced as by-products. The initially produced imine may disproportionate by reaction with some of the primary amine already produced in the reduction to give a new imine. Hydrogenation of this imine gives the secondary amine.

(1) $RCN + H_2 \longrightarrow RCH{=}NH$
(2) $RCH{=}NH + H_2 \longrightarrow RCH_2NH_2$
(3) $RCH{=}NH + RCH_2NH_2 \rightleftharpoons RCH{=}NCH_2R + NH_3$
(4) $RCH{=}NCH_2R + H_2 \longrightarrow RCH_2NHCH_2R$

This side reaction may be supressed by carrying out the hydrogenation in the presence of excess NH_3, which forces equilibrium (3) to the left.

$$RCN \xrightarrow[EtOH,NH_3]{H_2\text{-Pd/C}} RCH_2NH_2$$

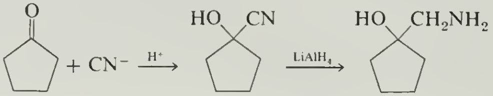
Secondary amine formation may also be minimized by carrying out the reaction in acetic anhydride as solvent. The primary amine produced is rapidly converted into the amide.



(97%)

The amine may then be obtained by hydrolysis of the amide. Since nitriles are easily available by several methods, many primary amines may be synthesized by this procedure.

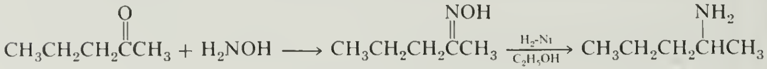
$$\mathrm{(CH_3)_2CHCH_2CH_2Br \xrightarrow{CN^-} (CH_3)_2CHCH_2CH_2CN \xrightarrow{LiAlH_4} (CH_3)_2CHCH_2CH_2CH_2NH_2}$$



Notice that the cyano group, CN^-, is thus synthetically equivalent to $-CH_2NH_2$.

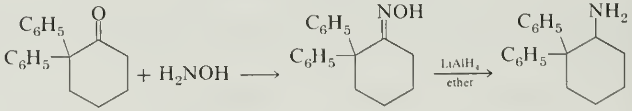
F. *Reduction of Oximes*

Aldoximes and ketoximes, which may be prepared from aldehydes or ketones by reaction with hydroxylamine (Section 15.7.C), are reduced by lithium aluminum hydride or hydrogen to primary amines. Since oximes are easily generated in high yield, this method is a useful synthetic method.



$$\mathrm{CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 + H_2NOH \longrightarrow CH_3CH_2CH_2\overset{NOH}{\overset{\|}{C}}CH_3 \xrightarrow[C_2H_5OH]{H_2\text{-}Ni} CH_3CH_2CH_2\overset{NH_2}{\overset{|}{C}}HCH_3}$$

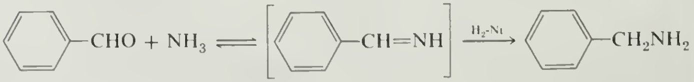
(85%)



(80%)

G. *Reduction of Imines: Reductive Amination*

Ammonia and primary amines condense with aldehydes and ketones to give imines (Section 15.7.C). In the case of ammonia, the imines are unstable and cannot be isolated. However, if a mixture of a carbonyl compound and ammonia is treated with hydrogen and a suitable hydrogenation catalyst, the C=N bond of the unstable imine is reduced and an amine results. The process is often called "reductive amination."

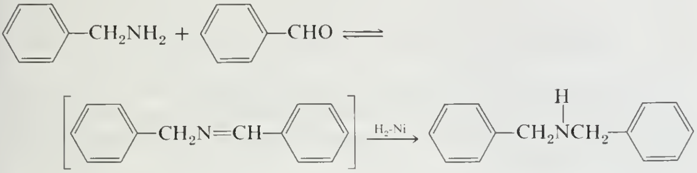


(89%)

benzaldehyde

benzylamine

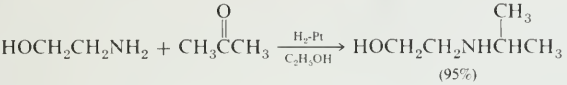
A significant side reaction complicates the reductive amination method. As the primary amine begins to build up, it may condense with the starting aldehyde to give a different imine. Reduction of this imine gives a secondary amine.



dibenzylamine

This side reaction may be minimized by using a large excess of ammonia in the reaction medium.

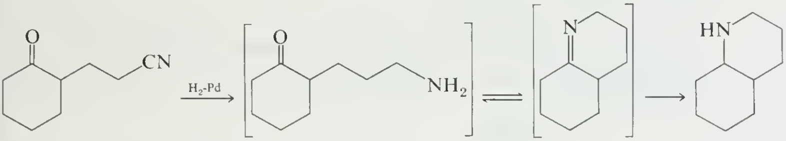
The foregoing side reaction may actually be exploited and used as a method for the synthesis of secondary amines, as shown by reaction (27-2). The example also demonstrates that ketones may be used as well as aldehydes.



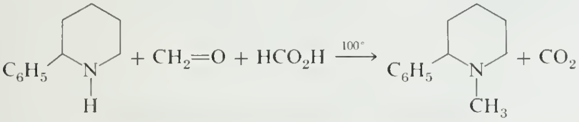
$$HOCH_2CH_2NH_2 + CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[C_2H_5OH]{H_2\text{-Pt}} HOCH_2CH_2NH\overset{\overset{CH_3}{|}}{C}HCH_3 \qquad (27\text{-}2)$$

(95%)

An interesting application of reductive amination occurs with the following cyano ketone. After hydrogenation of the nitrile function, the intermediate amino ketone condenses to a cyclic imine, which is reduced to a cyclic amine.

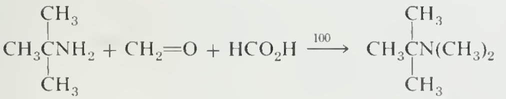


One version of reductive amination which is frequently employed for the synthesis of tertiary amines where at least one of the alkyl groups is methyl, is the **Eschweiler-Clarke** reaction. Instead of hydrogen, the reducing agent is formic acid, which is oxidized to carbon dioxide.



(27-3)

(94%)



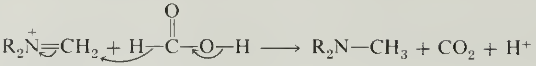
$$CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}NH_2 + CH_2{=}O + HCO_2H \xrightarrow{100} CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}N(CH_3)_2 \qquad (27\text{-}4)$$

(95%)
t-butyldimethylamine

As shown by equations (27-3) and (27-4), the reaction proceeds in excellent yield. The intermediate that is reduced is an **immonium ion** and the reduction may be visualized as follows:

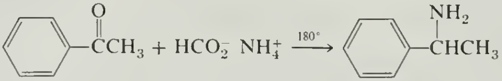
$$R_2NH + CH_2{=}O \overset{H^+}{\rightleftharpoons} R_2N{-}CH_2OH$$

$$R_2N{-}CH_2OH \overset{H^+}{\rightleftharpoons} R_2\overset{+}{N}{=}CH_2 + H_2O$$

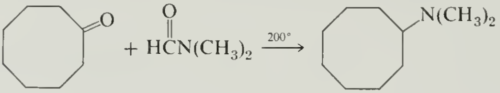


$$R_2\overset{+}{N}{=}CH_2 + H{-}\overset{O}{\overset{\|}{C}}{-}O{-}H \longrightarrow R_2N{-}CH_3 + CO_2 + H^+$$

An earlier version of this reaction, called the **Leukart** reaction, gives lower yields, but is more general. It can be used to prepare primary, secondary, or tertiary amines. In this method, the ketone is heated with a formate salt or a formamide at 180-200°.



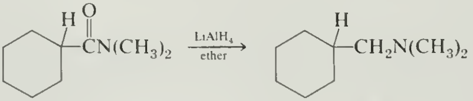
(60–66%)



(75%)
(dimethylamino)cyclooctane

H. *Reduction of Amides*

Amides are reduced by lithium aluminum hydride in refluxing ether to give amines. The reduction is unusual in that a C=O group is reduced to CH_2. Yields are generally good.

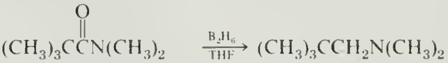


(88%)

N,N-dimethylcyclohexane-carboxamide

(cyclohexylmethyl)dimethylamine

Diborane, B_2H_6, may also be used as the reducing agent.



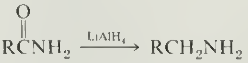
$$(CH_3)_3C\overset{O}{\overset{\|}{C}}N(CH_3)_2 \xrightarrow[THF]{B_2H_6} (CH_3)_3CCH_2N(CH_3)_2$$

(79%)

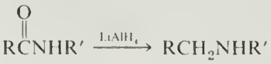
N,N,2,2-tetramethylpropanamide

dimethylneopentylamine

The method also serves as a method to prepare primary or secondary amines, depending on the structure of the amide used.



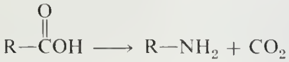
$$R\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$



$$R\overset{O}{\overset{\|}{C}}NHR' \xrightarrow{LiAlH_4} RCH_2NHR'$$

I. *Preparation of Amines from Carboxylic Acids: the Hofmann, Curtius, and Schmidt Rearrangements*

These three reactions all accomplish the same overall process—conversion of a carboxylic acid to a primary amine with *loss of the carboxy carbon* of the acid.



$$R{-}\overset{\overset{\large O}{\|}}{C}OH \longrightarrow R{-}NH_2 + CO_2$$

Examples of the three reactions are shown.

Hofmann

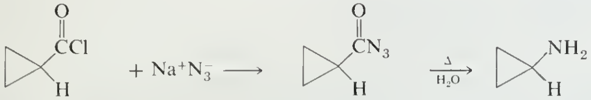
$$CH_3(CH_2)_7CH_2CONH_2 + Cl_2 + OH^- \longrightarrow CH_3(CH_2)_7CH_2NH_2$$

(66%)

decanamide

1-aminononane

Curtius



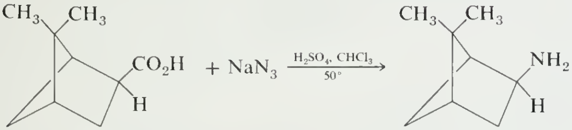
(60%)

cyclopropanecarbonyl chloride

cyclopropanecarbonyl azide

cyclopropylamine

Schmidt



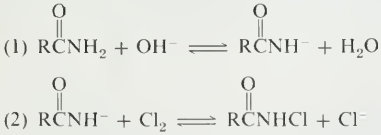
(61%)

exo-5,5-dimethylbicyclo[2.1.1]-hexane-2-carboxylic acid

exo-2-amino-5,5-dimethylbicyclo[2.1.1]hexane

Although the Hofmann rearrangement begins with an amide, the Curtius reaction with an acyl azide, and the Schmidt reaction with an acid, the three reactions are related mechanistically. In each case, the crucial intermediate is probably the same, an **acyl nitrene.**

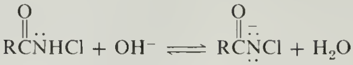
The probable mechanism for the Hofmann rearrangement is outlined as follows. The first two steps are simply the base-catalyzed halogenation of the amide, which is mechanistically related to the base-catalyzed halogenation of ketones (Section 15.6.D).



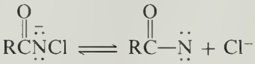
$$(1)\ R\overset{\overset{O}{\|}}{C}NH_2 + OH^- \rightleftharpoons R\overset{\overset{O}{\|}}{C}NH^- + H_2O$$

$$(2)\ R\overset{\overset{O}{\|}}{C}NH^- + Cl_2 \rightleftharpoons R\overset{\overset{O}{\|}}{C}NHCl + Cl^-$$

The N-chloroamide is more acidic than the starting amide and also reacts with base to give the corresponding anion. This intermediate loses chloride ion to give a highly reactive intermediate called a **nitrene.** Nitrenes are neutral molecules in which the nitrogen has only six electrons; they are structurally similar to carbenes (Section 23.5.A).

(3) 

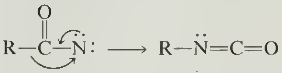
$$\mathrm{R\overset{\overset{O}{\|}}{C}\ddot{N}HCl + OH^- \rightleftharpoons R\overset{\overset{O}{\|}}{C}\overset{-}{\underset{..}{\ddot{N}}}Cl + H_2O}$$

(4) 

$$\mathrm{R\overset{\overset{O}{\|}}{C}\overset{-}{\underset{..}{\ddot{N}}}Cl \rightleftharpoons R\overset{\overset{O}{\|}}{C}{-}\underset{..}{\ddot{N}} + Cl^-}$$

an acyl
nitrene

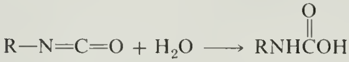
Acyl nitrenes undergo a rapid rearrangement to give a compound called an **isocyanate** which is similar to an allene (Section 20.2.C) or a ketene (Section 20.3.C).

(5) 

$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\ddot{N}\!: \longrightarrow R{-}\ddot{N}{=}C{=}O}$$

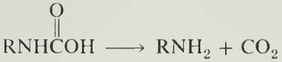
an isocyanate

Like ketenes, isocyanates react rapidly with water; the products in this case are **carbamic acids**, which are thermally unstable. Decarboxylation of the carbamic acid occurs to give the amine and carbon dioxide.

(6) 

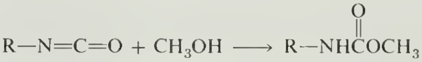
$$\mathrm{R{-}N{=}C{=}O + H_2O \longrightarrow RNH\overset{\overset{O}{\|}}{C}OH}$$

a carbamic
acid

(7) 

$$\mathrm{RNH\overset{\overset{O}{\|}}{C}OH \longrightarrow RNH_2 + CO_2}$$

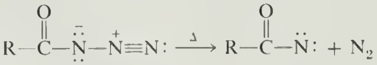
If the Hofmann rearrangement is carried out in alcohol solution rather than in water, steps (6) and (7) are not possible. Instead, the isocyanate adds the alcohol to give the ester of the carbamic acid, which is stable and may be isolated.

(6′) 

$$\mathrm{R{-}N{=}C{=}O + CH_3OH \longrightarrow R{-}NH\overset{\overset{O}{\|}}{C}OCH_3}$$

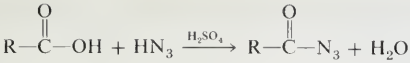
a methyl
carbamate

In the Curtius reaction, the acyl azide loses nitrogen upon heating to give the acyl nitrene directly. The remaining steps (5) through (7) are the same. Acyl azides are potentially explosive and the decomposition is therefore somewhat hazardous to carry out.



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\overset{-}{\underset{..}{\ddot{N}}}{-}\overset{+}{N}{\equiv}N\!: \xrightarrow{\Delta} R{-}\overset{\overset{O}{\|}}{C}{-}\ddot{N}\!: + N_2}$$

The Schmidt reaction also proceeds by way of the acyl azide, which is formed by reaction of the carboxylic acid with hydrazoic acid, HN_3, under the acidic conditions of the reaction.

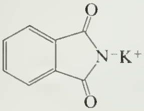


$$R-\overset{O}{\overset{\|}{C}}-OH + HN_3 \xrightarrow{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-N_3 + H_2O$$

J. *Summary of Amine Syntheses*

The various preparative methods for the syntheses of amines are summarized in Table 27.4 for the different classes of amines: primary, secondary, tertiary.

TABLE 27.4
Summary of Amine Preparations

Primary Amines
- Displacement methods
  - $RX + NH_3$ (excess)
  - RX +  (Gabriel synthesis)
  - $RX + N_3^-$
- Reduction methods
  - nitroalkanes: $RNO_2 + Fe, Fe^{2+}, H^+$
  - nitriles: $RCN + H_2/cat + NH_3$
    - $RCN + LiAlH_4$
  - amides: $RCONH_2 + LiAlH_4$
  - oximes: $RR'C{=}NOH + H_2/cat$
    - $RR'C{=}NOH + LiAlH_4$
  - reductive amination:
    - $RCOR' + NH_3$ (excess) $+ H_2/cat$
- Rearrangement
  - $RCONH_2 + OH^-, X_2$ (Hofmann)
  - $RCOCl + N_3^-$ (Curtius)
  - $RCOOH + HN_3, H_2SO_4$ (Schmidt)

Secondary Amines
- Displacement method
  - $RNHTs + OH^-, R'X$ (Section 27.7.A)
- Reduction
  - amide, $RCONHR' + LiAlH_4$
  - reductive amination:
    - $R'COR'' + RNH_2 + H_2/cat$

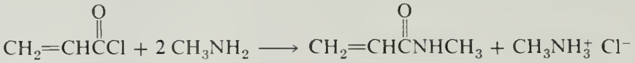
Tertiary Amines
- Reduction
  - amide, $RCONR'R'' + LiAlH_4$
  - RNH_2 or $RR'NH + CH_2O, HCOOH$ (Eschweiler-Clarke)

27.7
Reactions of Amines

Several important reactions of amines have already been discussed and will not be discussed further here. These are the reaction with protons (Section 27.4) and with alkyl halides (Sections 27.5 and 27.6.A).

A. *Formation of Amides*

Recall that ammonia and primary and secondary amines react with acyl halides and with acid anhydrides to give amides (Section 18.9.C). If an acyl halide is used, the hydrohalic acid produced will neutralize an additional equivalent of amine.

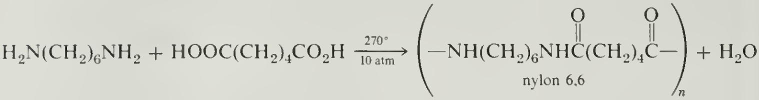


$$CH_2{=}CH\overset{O}{\overset{\|}{C}}Cl + 2\,CH_3NH_2 \longrightarrow CH_2{=}CH\overset{O}{\overset{\|}{C}}NHCH_3 + CH_3NH_3^+\ Cl^-$$

acrylyl chloride N-methylacrylamide

The student should review Section 18.9.C for further examples.

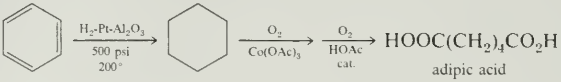
Polyamides are an important class of commercial polymers. The best known is nylon 6,6, which is a copolymer formed from 1,6-diaminohexane and adipic acid. The polymer is manufactured by heating an equimolar mixture of the two monomers at 270° under a pressure of about 10 atm.



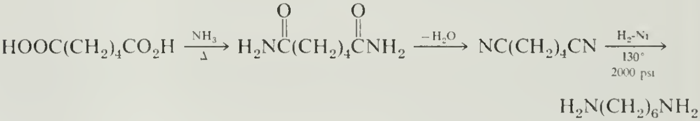
$$H_2N(CH_2)_6NH_2 + HOOC(CH_2)_4CO_2H \xrightarrow[10\text{ atm}]{270^\circ} \left(-NH(CH_2)_6NH\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}- \right)_n + H_2O$$

nylon 6,6

The molten polymer is then spun into fibers. The two monomers have both been produced commercially from benzene. The benzene is first reduced to give cyclohexane, which is oxidized in a two-stage process to adipic acid, one of the monomers.

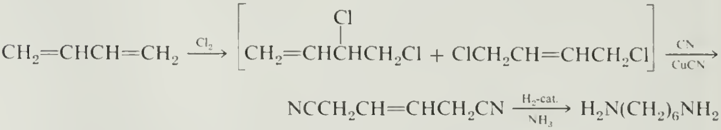


The 1,6-diaminohexane can be produced from adipic acid by converting it into the diamide, which is dehydrated to adiponitrile. Reduction of the dinitrile gives the diamine.



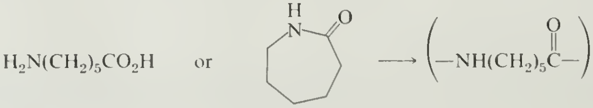
$$HOOC(CH_2)_4CO_2H \xrightarrow[\Delta]{NH_3} H_2N\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{-H_2O} NC(CH_2)_4CN \xrightarrow[\substack{130^\circ \\ 2000\text{ psi}}]{H_2\text{-Ni}} H_2N(CH_2)_6NH_2$$

The diamine is also prepared from butadiene by the following route.



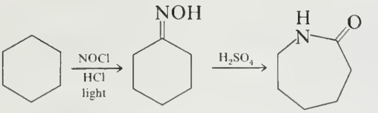
$$CH_2{=}CHCH{=}CH_2 \xrightarrow{Cl_2} \left[CH_2{=}CH\overset{Cl}{\overset{|}{C}}HCH_2Cl + ClCH_2CH{=}CHCH_2Cl \right] \xrightarrow[CuCN]{CN^-} NCCH_2CH{=}CHCH_2CN \xrightarrow[NH_3]{H_2\text{-cat.}} H_2N(CH_2)_6NH_2$$

Another form of nylon is nylon 6, which is produced by polymerization of the amino acid, 6-aminohexanoic acid. The actual monomer used is the cyclic amide, caprolactam.

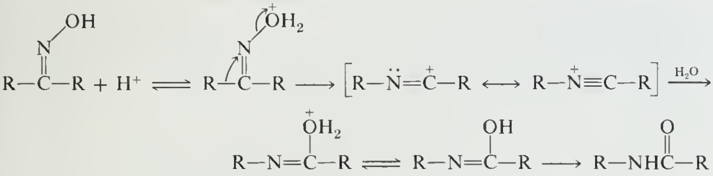


6-aminohexanoic acid caprolactam nylon 6

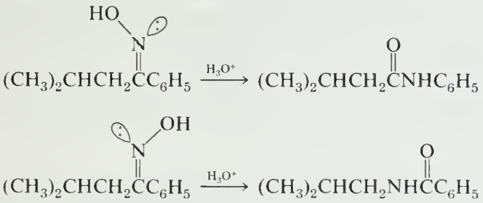
Caprolactam is also produced commercially from cyclohexane. Free radical nitrosation gives cyclohexanone oxime, which is then treated with concentrated sulfuric acid to give the lactam.


NOCl
HCl
light
NOH
H_2SO_4
H
N
O

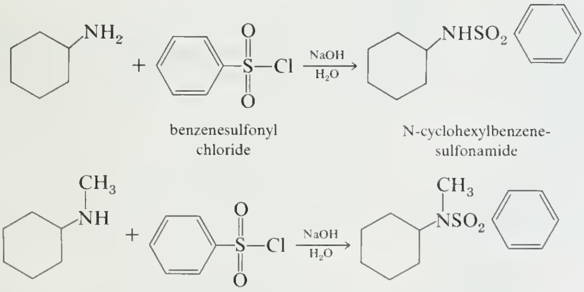
The last reaction is an example of the **Beckmann rearrangement**, which is a general reaction of oximes. The mechanism involves alkyl migration to an electron-deficient nitrogen, formed by loss of water from the protonated oxime. The initially formed cation reacts with water to give the enol form of an amide.



The Beckmann rearrangement is a stereospecific reaction; the group that migrates is the one which is *trans,* or *anti,* to the hydroxy group in the oxime.

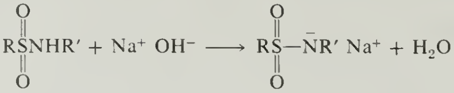


Amines also react with sulfonyl chlorides, which are acid chlorides of sulfonic acids. An example is benzenesulfonyl chloride, which reacts with primary or secondary amines to give N-alkylsulfonamides.


NH_2
+
O
S—Cl
O
NaOH
H_2O
$NHSO_2$
benzenesulfonyl chloride
N-cyclohexylbenzenesulfonamide
CH_3
NH
+
O
S—Cl
O
NaOH
H_2O
CH_3
NSO_2

A tertiary amine can give neither an amide nor a sulfonamide, because there is no replaceable hydrogen on nitrogen.

Sulfonamides which have at least one hydrogen on nitrogen are weak acids, with pK_as of about 10–11; for example, the pK_a of $CH_3SO_2NH_2$ is 10.8 and of $C_6H_5SO_2NH_2$ is 10.1. They are sufficiently acidic to be completely ionized in aqueous hydroxide and are therefore soluble in dilute alkali solutions:



$$R\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}NHR' + Na^+\ OH^- \longrightarrow R\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-\bar{N}R'\ Na^+ + H_2O$$

ionic salt,
water soluble

On the other hand, sulfonamides derived from secondary amines have no acidic proton and are insoluble in aqueous base.

This phenomenon was once used as a qualitative test to distinguish among primary, secondary, and tertiary amines (the **Hinsberg test**). In the Hinsberg test, the unknown amine is shaken in a test tube with a mixture of benzenesulfonyl chloride and aqueous sodium hydroxide. If all of the organic material dissolves and the mixture becomes homogeneous, it may be concluded that the amine is primary and that a base-soluble sulfonamide has been formed. If an insoluble organic layer remains, then it may be concluded that the amine is either secondary, in which case an insoluble sulfonamide has been formed, or that the amine is tertiary and no reaction has occurred. One may distinguish between these latter two possibilities by removing the insoluble organic layer and testing it for solubility in dilute acid. If the material dissolves, it is an unreacted tertiary amine; if it does not, it is a neutral sulfonamide. Although the Hinsberg test is rarely used in these days of powerful spectroscopic tools, it provides a good illustration of how structural information may be gained by observing the way in which an unknown compound reacts with various reagents.

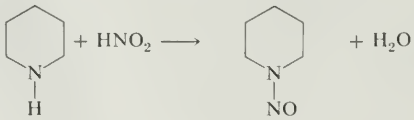
Synthetic use can be made of the sulfonamide salts of primary amines. These anions are nucleophilic and react with primary alkyl halides. The products can be hydrolyzed to give secondary amines:

$$R'NHSO_2R \xrightarrow{^-OH} R'\overset{-}{\underset{\cdot\cdot}{\ddot{N}}}SO_2R \xrightarrow{R''X} R'R''NSO_2R \xrightarrow[\Delta]{H^+} \xrightarrow{OH^-} R'R''NH$$

For this purpose, the toluenesulfonamides (RNHTs) are convenient.

B. *Reaction with Nitrous Acid*

Primary and secondary amines react with nitrous acid, HNO_2. With secondary amines, the product of this reaction is an N-nitroso compound, which is usually yellow.



piperidine

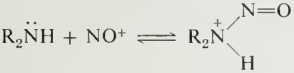
N-nitrosopiperidine
(yellow)

It is convenient to regard the reaction simply as a combination of the nucleophilic nitrogen with the nitrosonium ion, NO^+. The reaction mechanism is actually somewhat more complex and will be discussed in further detail in connection with the more important reaction with aromatic amines (Section 32.2.G).

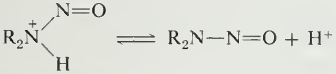
$$(1)\ HO{-}N{=}O + H^+ \rightleftharpoons H_2\overset{+}{O}{-}N{=}O$$

$$(2)\ H_2\overset{+}{O}{-}N{=}O \rightleftharpoons H_2O + {}^{+}\ddot{N}{=}\ddot{\underset{..}{O}}$$

(3)



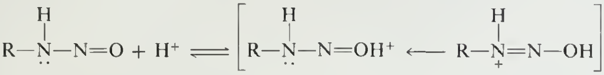
(4)



Since tertiary amines have no proton on nitrogen, step (4) is blocked and no overall reaction occurs.

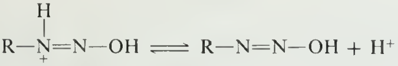
With primary amines, the reaction proceeds further, and an alkanediazonium compound is produced.

(5)



$$(5)\ R{-}\underset{..}{\overset{H}{\overset{|}{N}}}{-}N{=}O + H^+ \rightleftharpoons \left[R{-}\underset{..}{\overset{H}{\overset{|}{N}}}{-}N{=}OH^+ \longleftarrow R{-}\underset{+}{\overset{H}{\overset{|}{N}}}{=}N{-}OH\right]$$

(6)

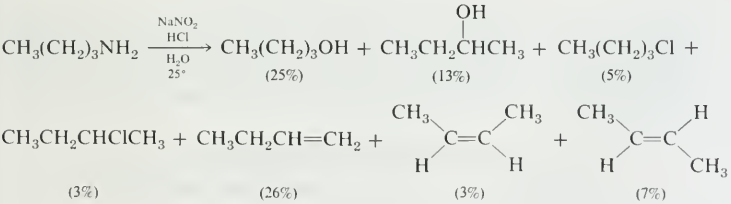


$$(6)\ R{-}\underset{+}{\overset{H}{\overset{|}{N}}}{=}N{-}OH \rightleftharpoons R{-}N{=}N{-}OH + H^+$$

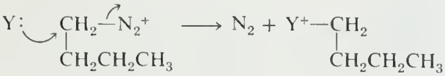
$$(7)\ R{-}\ddot{N}{=}\ddot{N}{-}OH + H^+ \rightleftharpoons R{-}\ddot{N}{=}\ddot{N}{-}OH_2^{\ +}$$

$$(8)\ R{-}\ddot{N}{=}\ddot{N}{-}OH_2^{\ +} \rightleftharpoons H_2O + \underset{\text{alkanediazonium cation}}{R{-}\overset{+}{N}{\equiv}\ddot{N}}$$

Alkanediazonium compounds are exceedingly unstable and decompose, even at low temperatures, to give nitrogen and carbonium ions, which then react by the normal pathways of substitution, elimination, and rearrangement. An example is the reaction of *n*-butylamine with nitrous acid, generated *in situ* from sodium nitrite and aqueous hydrochloric acid.

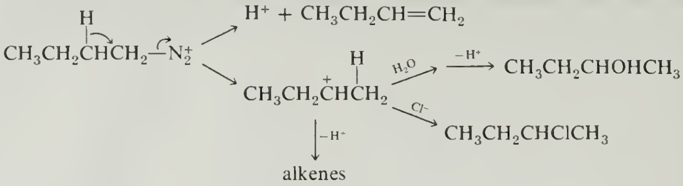


The primary alkyl products are derived from displacement reactions by water or chloride ion:



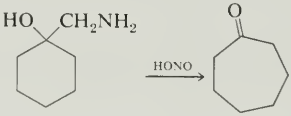
$$Y{:}\ \underset{CH_2CH_2CH_3}{\underset{|}{CH_2}}{-}N_2^{\ +} \longrightarrow N_2 + Y^+{-}\underset{CH_2CH_2CH_3}{\underset{|}{CH_2}}$$

Elimination of a proton and rearrangements are important alternative pathways:

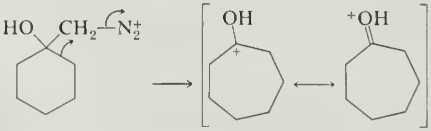

H
CH₃CH₂CHCH₂—N₂⁺
H⁺ + CH₃CH₂CH=CH₂
H
CH₃CH₂CHCH₂
H₂O
−H⁺
CH₃CH₂CHOHCH₃
Cl⁻
CH₃CH₂CHClCH₃
−H⁺
alkenes

Nitrogen is such a stable molecule that it constitutes a highly reactive leaving group. Alternative modes of reaction differ little in activation energy; hence, many pathways compete. Because such diazotizations give complex mixtures of products, the reaction is not generally a useful one with aliphatic amines. However, it is very useful with aromatic amines, and we shall return to the subject in Section 32.3.G.

One diazotization reaction of aliphatic amines that is useful, however, is that with 1,2-aminoalcohols; for example


HO
CH₂NH₂
HONO
O

This reaction is a useful procedure for ring expansion (see Section 23.7) and succeeds because rearrangement produces a highly stable carbonium ion—the protonated ketone:

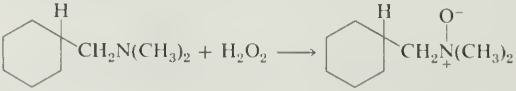

HO
CH₂—N₂⁺
OH
+
⁺OH

C. *Oxidation of Amines: The Cope Reaction*

Because of their basic nature, amines are oxidized with ease. With primary amines, oxidation is complicated by the variety of reaction paths that are available. Few useful oxidation reactions are known for this class. Secondary amines are easily oxidized to hydroxylamines. Again, yields are generally poor due to over-oxidation.

$$R_2NH + H_2O_2 \longrightarrow R_2NOH + H_2O$$

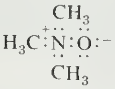
Tertiary amines are oxidized cleanly to tertiary amine oxides. Useful oxidants are H_2O_2 or organic peroxyacids, RCO_3H.


H
CH₂N(CH₃)₂ + H₂O₂
H
O⁻
CH₂N(CH₃)₂
+

(90%)

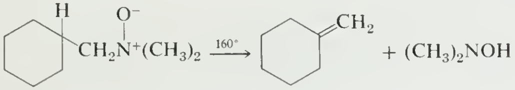
A mixture of 49 g of N,N-dimethylcyclohexylmethylamine, 45 ml of methanol, and 120 g of 30% aqueous H_2O_2 is kept at room temperature for 36 hr. The excess H_2O_2 is destroyed by the addition of a small amount of colloidal platinum. The solution is then filtered and evaporated to obtain the crude amine oxide in greater than 90% yield.

Amine oxides fall into the class of organic compounds for which no completely uncharged Lewis structure may be written. The Lewis electron dot representation of trimethylamine oxide shows that both the oxygen and the nitrogen have octet configurations and that they bear (−) and (+) formal charges, respectively.



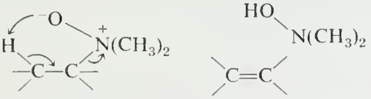
trimethylamine oxide

Amine oxides having at least one hydrogen β to the nitrogen undergo thermal elimination when heated at 150–200°. The elimination is called the **Cope reaction**, after its discoverer, and is a useful way to remove nitrogen from a compound. It is also a useful method for the synthesis of certain alkenes.



Crude N,N-dimethylcyclohexylmethylamine oxide (about 50 g) is placed in a flask that has been evacuated to a pressure of about 10 torr. The liquified amine oxide is heated at 160° for 2 hr. Water is added and the alkene layer is separated and distilled to obtain 30 g of methylenecyclohexane (98%).

Amine oxide pyrolysis is similar mechanistically to ester pyrolysis (Section 18.12). The mechanism is probably a sort of internal E2 elimination where the oxide oxygen acts as the attacking base.



This mechanism is supported by experiments that clearly show that the elimination is *syn* (see Section 18.12).

D. *Decomposition of Quaternary Ammonium Hydroxides: The Hofmann Degradation*

Quaternary ammonium hydroxides when heated undergo a β elimination reaction.

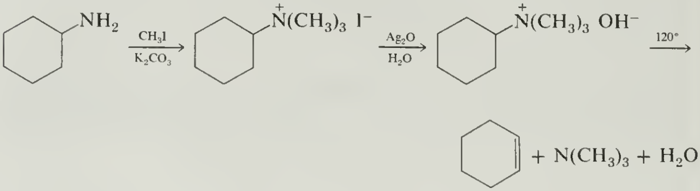
$$CH_3CH_2\overset{+}{N}(CH_2CH_3)_3\ OH^- \xrightarrow{\Delta} CH_2{=}CH_2 + N(CH_2CH_3)_3 + H_2O$$

tetraethylammonium hydroxide triethylamine

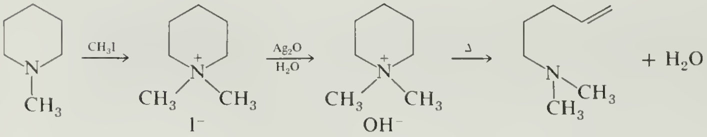
The reaction is an E2 elimination in which hydroxide ion is the attacking base.

$$HO^- + H{-}CH_2{-}CH_2{-}\overset{+}{N}R_3 \longrightarrow \left[\overset{\delta-}{HO}\cdots H\cdots CH_2\text{=-}CH_2\cdots\overset{\delta+}{NR_3}\right]^{\ddagger} \longrightarrow HOH + CH_2{=}CH_2 + NR_3$$

The elimination reaction itself is the final step in a process known as **Hofmann exhaustive methylation** or **Hofmann degradation.** In the process, a primary, secondary, or tertiary amine is first treated with enough methyl iodide to convert it into the quaternary ammonium iodide. Then the iodide is converted into the hydroxide with silver oxide and water. The elimination is finally effected by heating the dry quaternary ammonium hydroxide at 100° or higher. In the process the C—N bond is broken and an amine and an alkene are produced.


NH_2
CH_3I
K_2CO_3
$\overset{+}{N}(CH_3)_3\ I^-$
Ag_2O
H_2O
$\overset{+}{N}(CH_3)_3\ OH^-$
120°
$+ N(CH_3)_3 + H_2O$

If the amine is cyclic, then the product is an amino alkene.


N
CH_3
CH_3I
$\overset{+}{N}$
CH_3
CH_3
I^-
Ag_2O
H_2O
$\overset{+}{N}$
CH_3
CH_3
OH^-
Δ
N
CH_3
CH_3
$+ H_2O$

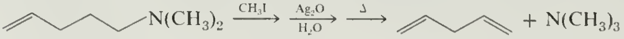
(27-6)

N-methyl-piperidine

N,N-dimethyl-piperidinium iodide

5-(dimethylamino)-1-pentene

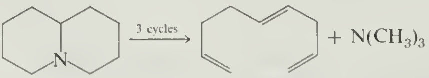
The process may be repeated with the product of (27-6) to yield a diene, liberating the nitrogen as trimethylamine (27-7).


$N(CH_3)_2$
CH_3I
Ag_2O
H_2O
Δ
$+ N(CH_3)_3$

(27-7)

1,4-pentadiene

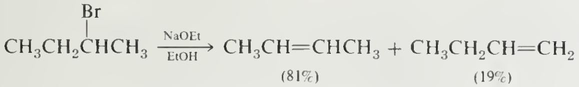
For bicyclic amines in which the nitrogen is a part of both rings, three cycles are required to remove the nitrogen completely.


N
3 cycles
$+ N(CH_3)_3$

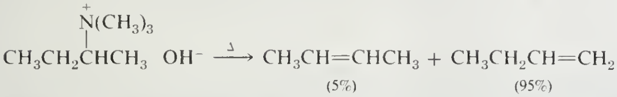
A side reaction that may occur is S_N2 displacement. This is seldom a significant reaction except in cases where there are no β-hydrogens.

$$(CH_3)_3\overset{+}{N}{-}CH_3 \ \ OH^- \xrightarrow[\Delta]{H_2O} (CH_3)_3N + CH_3OH$$

When the quaternary ammonium hydroxide has two or more different β-hydrogens, more than one alkene may be formed in the elimination. Unlike normal E2 eliminations with alkyl halides, the Hofmann elimination gives predominately the less highly substituted alkene, as comparison of (27-8) and (27-9) shows.

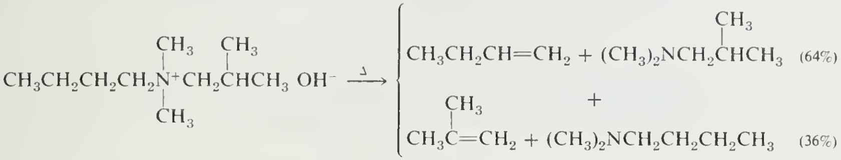


$$CH_3CH_2\overset{Br}{\overset{|}{C}}HCH_3 \xrightarrow[EtOH]{NaOEt} \underset{(81\%)}{CH_3CH{=}CHCH_3} + \underset{(19\%)}{CH_3CH_2CH{=}CH_2} \qquad (27\text{-}8)$$



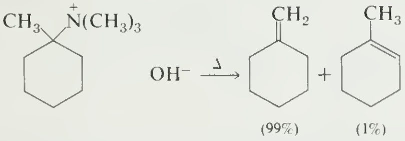
$$CH_3CH_2\overset{\overset{+}{N}(CH_3)_3}{\overset{|}{C}}HCH_3\ \ OH^- \xrightarrow{\Delta} \underset{(5\%)}{CH_3CH{=}CHCH_3} + \underset{(95\%)}{CH_3CH_2CH{=}CH_2} \qquad (27\text{-}9)$$

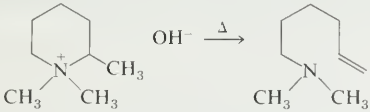
This type of behavior is also seen when the ammonium compound contains two different alkyl groups that may be lost as the alkene.



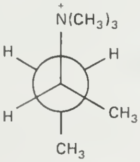
$$CH_3CH_2CH_2CH_2\overset{CH_3}{\underset{CH_3}{N^+}}CH_2\overset{CH_3}{C}HCH_3\ OH^- \xrightarrow{\Delta} \left\{ \begin{array}{l} CH_3CH_2CH{=}CH_2 + (CH_3)_2NCH_2\overset{CH_3}{C}HCH_3 \quad (64\%) \\ \qquad\qquad\qquad + \\ CH_3\overset{CH_3}{C}{=}CH_2 + (CH_3)_2NCH_2CH_2CH_2CH_3 \quad (36\%) \end{array}\right.$$

For ammonium hydroxides having only simple alkyl groups, such as the foregoing examples, the mode of elimination may be generalized as follows (**Hofmann rule**): "*In the decomposition of quaternary ammonium hydroxides, the hydrogen is lost most easily from CH_3, next from RCH_2— and least easily from R_2CH—.*" The direction of elimination in the Hofmann reaction is probably governed mostly by steric factors. The generality of the rule is shown by the following additional examples.

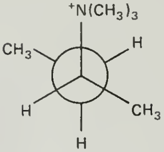


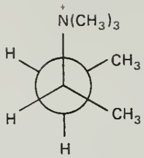


One way in which steric effects contribute to this preference for the less substituted olefin is by their effect on the populations of different conformations. For example, in the 2-butyl case (27-9), the most stable conformation may be represented by a Newman projection of the C_2—C_3 bond as

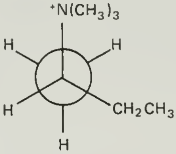


but this conformation has no *anti* hydrogen at C_3. *Trans* elimination can only occur in the two conformations:


⁺N(CH₃)₃
CH₃
H
H
CH₃
H

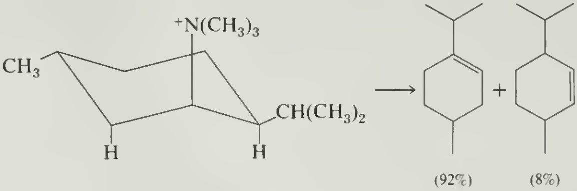

N(CH₃)₃
H
CH₃
H
CH₃
H

Both of these conformations have a methyl group *gauche* to the bulky trimethylammonium group—this group is comparable in size to *t*-butyl. Hence, the populations of these conformations are small. On the other hand, all conformations with respect to the $C_1—C_2$ bond have an *anti* hydrogen.


⁺N(CH₃)₃
H
H
H
CH₂CH₃
H

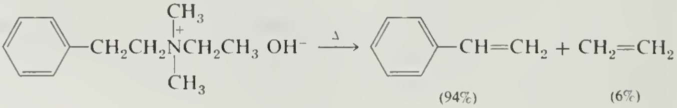
Although the reaction at C-3 would be faster because a more stable disubstituted ethylene results (Section 12.5.A), the population of conformations with *anti* hydrogen at C-3 is so small that the inherently slower reaction at C-1 dominates.

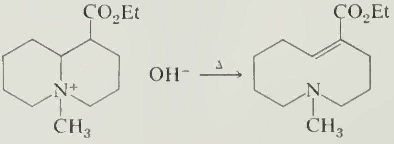
An interesting example is the elimination reaction of the cyclohexane compound


⁺N(CH₃)₃
CH₃
CH(CH₃)₂
H
H
(92%)
(8%)

This compound has a fixed conformation with two *anti* hydrogens, one secondary and one tertiary. Reaction at the tertiary hydrogen is faster and gives the more highly substituted olefin.

When electron-withdrawing groups are attached to one of the β-carbons, the Hofmann rule is not followed.


CH₃
CH₂CH₂NCH₂CH₃ OH⁻
CH₃
Δ
CH=CH₂ + CH₂=CH₂
(94%)
(6%)


CO₂Et
N+
CH₃
OH⁻
Δ
CO₂Et
N
CH₃

27.8
Other Nitrogen Compounds

There are a number of less common functional groups that contain nitrogen. We introduce some of these nitrogen containing functions at this point, but the scope of this text precludes an extensive discussion.

A. *Azides*

Organic azides are compounds with the general formula RN_3. They are related to the inorganic acid, hydrazoic acid, HN_3. Azide ion, N_3^-, is a resonance hybrid of the following important dipolar structures:

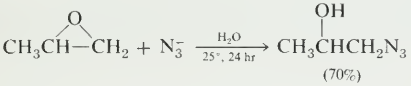
$$\left[:N{\equiv}\overset{+}{N}{-}\overset{\cdot\cdot\,2-}{\underset{\cdot\cdot}{N}}: \longleftrightarrow :\overset{-}{\underset{\cdot\cdot}{N}}{=}\overset{+}{N}{=}\overset{-}{\underset{\cdot\cdot}{N}}: \longleftrightarrow {}^{2-}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}{-}\overset{+}{N}{\equiv}N:\right]$$

This anion is relatively nonbasic for anionic nitrogen (the pK_a of HN_3 is 11) and is a good nucleophile. Alkyl azides are best prepared by nucleophilic displacement on alkyl halides.

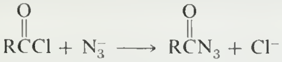
$$CH_3CH_2CH_2CH_2Br + N_3^- \xrightarrow[H_2O]{CH_3OH} CH_3CH_2CH_2CH_2N_3 + Br^-$$

A mixture of 34.5 g of NaN_3, 68.5 g of *n*-butyl bromide, 70 ml of water, and 25 ml of methanol is refluxed for 24 hr. The *n*-butyl azide separates as an oily layer. It is dried and distilled behind a safety barricade to obtain 40 g of pure *n*-butyl azide (90%).

Azide ion is also sufficiently nucleophilic to open the epoxide ring. β-Hydroxyalkyl azides may be prepared in this way.



Acyl azides may be prepared from acyl halides and azide ion (Section 27.6.I).

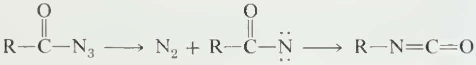


$$R\overset{O}{\overset{\|}{C}}Cl + N_3^- \longrightarrow R\overset{O}{\overset{\|}{C}}N_3 + Cl^-$$

Alkyl azides are reduced by lithium aluminum hydride or by catalytic hydrogenation to give the corresponding amines (Section 27.6.C).

$$RN_3 \xrightarrow{LiAlH_4} RNH_2$$

Both alkyl and acyl azides are thermally unstable and lose nitrogen on heating. In some cases, particularly when the nitrogen content of the molecule is higher than about 25%, the decomposition can occur with explosive violence. Decomposition of alkyl azides gives a complex mixture of products. Acyl azides decompose to the acyl nitrene, which rearranges to an **isocyanate** (Section 27.6.I).



$$R{-}\overset{O}{\overset{\|}{C}}{-}N_3 \longrightarrow N_2 + R{-}\overset{O}{\overset{\|}{C}}{-}\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}} \longrightarrow R{-}N{=}C{=}O$$

an isocyanate

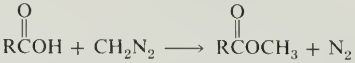
B. *Diazo Compounds*

Diazo compounds have the general formula $R_2C{=}N_2$. The electronic structure of diazomethane, the simplest diazo compound, shows that the carbon has nucleophilic properties.

$$\left[{}^{-}\ddot{C}H_2{-}\overset{+}{N}{\equiv}N\!:\ \longleftrightarrow\ CH_2{=}\overset{+}{N}{=}\underset{\cdot\cdot}{N}\!:^{-}\right]$$

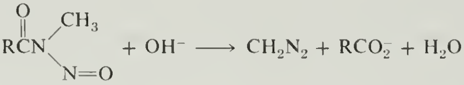
diazomethane

We have encountered diazomethane previously as a reagent for converting carboxylic acids into methyl esters (Section 17.7.A).



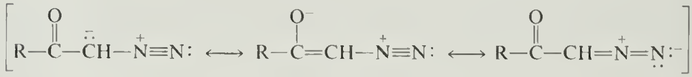
$$R\overset{O}{\overset{\|}{C}}OH + CH_2N_2 \longrightarrow R\overset{O}{\overset{\|}{C}}OCH_3 + N_2$$

Diazomethane is prepared by treating an N-methyl-N-nitrosoamide with concentrated potassium hydroxide solution.



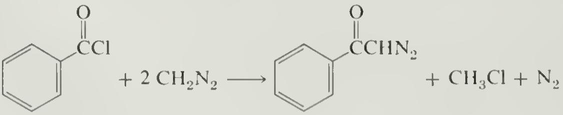
The preparation is carried out in a two-phase mixture consisting of ether and aqueous KOH. The diazomethane dissolves in the ether as it is formed and it is generally used as an ether solution (Section 17.7.A).

Other diazo compounds are also known. α-Diazo ketones and α-diazo esters are more stable since the carbonyl group can delocalize the carbanionic electron pair.

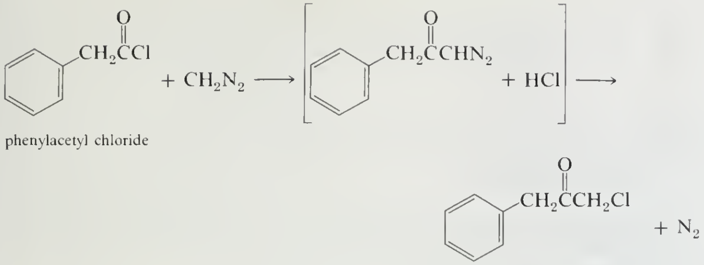


$$\left[R{-}\overset{O}{\overset{\|}{C}}{-}\overset{..}{\underset{-}{C}}H{-}\overset{+}{N}{\equiv}N\!:\ \longleftrightarrow\ R{-}\overset{O^-}{\overset{|}{C}}{=}CH{-}\overset{+}{N}{\equiv}N\!:\ \longleftrightarrow\ R{-}\overset{O}{\overset{\|}{C}}{-}CH{=}\overset{+}{N}{=}\underset{\cdot\cdot}{N}\!:^{-}\right]$$

This type of diazo compound is conveniently prepared by the reaction of diazomethane with an acyl halide.



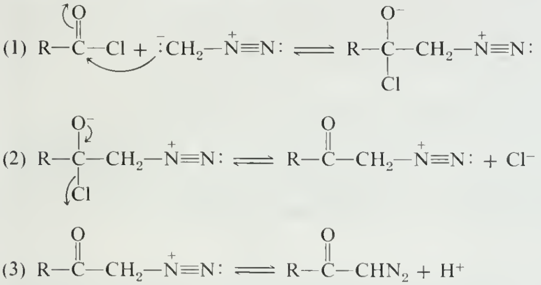
Excess diazomethane must be used to react with the HCl which is produced in the reaction. If only one equivalent of diazomethane is used, a chloromethyl ketone results.



phenylacetyl chloride

(83–85%)
α′-chloro-α-phenylacetone
3-chloro-1-phenyl-2-propanone

The reaction of diazomethane with acyl halides is another reaction that shows the nucleophilic nature of the carbon in this compound. The mechanism of the reaction may be visualized as follows:

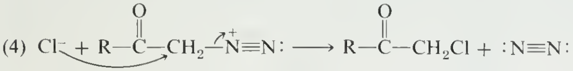


$$(1)\ R-\overset{\overset{O}{\|}}{C}-Cl + \overset{-}{:}CH_2-\overset{+}{N}\equiv N: \rightleftharpoons R-\underset{\underset{Cl}{|}}{\overset{\overset{O^-}{|}}{C}}-CH_2-\overset{+}{N}\equiv N:$$

$$(2)\ R-\underset{\underset{Cl}{|}}{\overset{\overset{O^-}{|}}{C}}-CH_2-\overset{+}{N}\equiv N: \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-CH_2-\overset{+}{N}\equiv N: + Cl^-$$

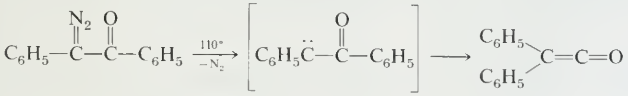
$$(3)\ R-\overset{\overset{O}{\|}}{C}-CH_2-\overset{+}{N}\equiv N: \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-CHN_2 + H^+$$

If there is no excess diazomethane to react with the proton liberated in step (3), the chloride ion displaces nitrogen to give the chloro ketone.



$$(4)\ Cl^- + R-\overset{\overset{O}{\|}}{C}-CH_2-\overset{+}{N}\equiv N: \longrightarrow R-\overset{\overset{O}{\|}}{C}-CH_2Cl + :N\equiv N:$$

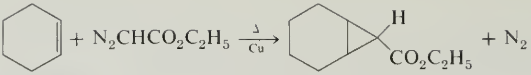
Like azides, diazo compounds lose nitrogen either thermally or when irradiated with ultraviolet light. The decomposition is catalyzed by copper powder. The initial product is a carbene (Section 23.5.A), which then reacts further. In the case of α-diazo ketones, the resulting acylcarbene rearranges to give a ketene (See the Curtius rearrangement, page 786).



$$C_6H_5-\overset{\overset{N_2}{\|}}{C}-\overset{\overset{O}{\|}}{C}-C_6H_5 \xrightarrow[-N_2]{110^\circ} \left[C_6H_5\ddot{C}-\overset{\overset{O}{\|}}{C}-C_6H_5\right] \longrightarrow (C_6H_5)_2C{=}C{=}O$$

(65%)
diphenylketene

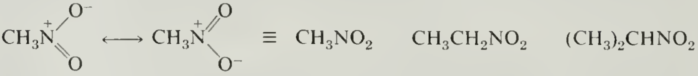
The carbenes derived from some diazo compounds may be trapped by reaction with an alkene; the products are cyclopropane derivatives.



ethyl 7-bicyclo[4.1.0]-heptanecarboxylate

C. *Nitro Compounds*

Nitroalkanes are relatively rare, although a few of the simpler ones are commercially available. Examples are nitromethane, which is used as a high-power fuel in racing engines, nitroethane, and 2-nitropropane.



$$CH_3\overset{+}{N}O_2 \equiv CH_3NO_2 \qquad CH_3CH_2NO_2 \qquad (CH_3)_2CHNO_2$$

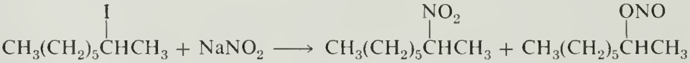
nitromethane nitroethane 2-nitropropane

Aromatic nitro compounds are much more common because they are easily prepared by the electrophilic nitration of aromatic compounds (Section 21.2.C). We shall discuss the chemistry of aromatic nitro compounds in Section 32.1.

Nitroalkanes are prepared industrially by the free radical nitration of alkanes (see problem 10, page 93).

$$CH_4 + HNO_3 \xrightarrow{400^\circ} CH_3NO_2 + H_2O$$

Some nitro compounds may be prepared in the laboratory by the displacement of alkyl halides with nitrite ion. Since nitrite is an ambident anion, some alkyl nitrite is usually produced as a by-product (Section 8.4).

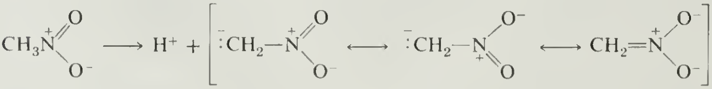


$$CH_3(CH_2)_5\overset{I}{C}HCH_3 + NaNO_2 \longrightarrow \underset{(58\%)}{CH_3(CH_2)_5\overset{NO_2}{C}HCH_3} + \underset{(30\%)}{CH_3(CH_2)_5\overset{ONO}{C}HCH_3}$$

Yields of nitroalkane are higher when silver nitrite is used, but this added economy is tempered by the cost of the silver salt.

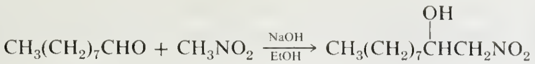
$$CH_3(CH_2)_6CH_2I + AgNO_2 \longrightarrow \underset{(83\%)}{CH_3(CH_2)_6CH_2NO_2} + \underset{(11\%)}{CH_3(CH_2)_6CH_2ONO}$$

The most striking chemical property of nitroalkanes is their acidity. The pK_a of nitromethane is 10.2, that of nitroethane is 8.5, and that of 2-nitropropane is 7.8. Thus, one nitro group has as great an acidifying effect as two carbonyl groups (Section 26.4.C). 2-Nitropropane is so acidic that it is 50% ionized at pH 7.8. Like carboxylic acids and ketones, nitro compounds owe their acidity to the fact that the conjugate base is resonance-stabilized.



methylnitronate ion

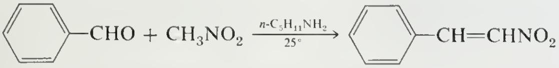
The anions derived from nitroalkanes are nucleophilic and enter into typical nucleophilic reactions. One particularly useful reaction is analogous to the aldol condensation.



$$CH_3(CH_2)_7CHO + CH_3NO_2 \xrightarrow[EtOH]{NaOH} CH_3(CH_2)_7\overset{OH}{\overset{|}{C}}HCH_2NO_2$$

(80%)
1-nitro-2-decanol

Since nitro compounds are so acidic, only weakly basic catalysts are required. In the case of aromatic aldehydes, dehydration of the initial β-hydroxy nitro compound usually results.



(75%)
β-nitrostyrene

Another general reaction of nitro compounds is reduction to the corresponding amine (Section 27.6.D). Reduction of β-hydroxynitroalkanes produced by the aldol condensation provides a convenient method for preparing 1,2-amino alcohols (page 781).

D. *Isocyanates, Carbamates, and Ureas*

We have encountered alkyl isocyanates previously as intermediates in the Hofmann rearrangement of amides (Section 27.6.I). They may also be prepared by S_N2 displacement of alkyl halides with cyanate ion. This ion is ambident and reacts preferentially at the nitrogen end.

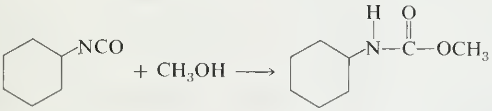
$$CH_3CH_2CH_2CH_2Br + Na^+NCO^- \longrightarrow CH_3CH_2CH_2CH_2NCO$$

n-butyl isocyanate

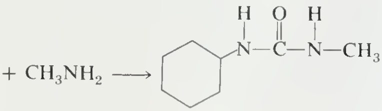
Isocyanates react with water to give N-alkyl carbamic acids which are unstable and spontaneously lose carbon dioxide to give the corresponding amine.

$$R{-}NCO + H_2O \longrightarrow [R{-}NHCO_2H] \longrightarrow RNH_2 + CO_2$$

With alcohols, isocyanates give carbamate esters and with amines, they give ureas.

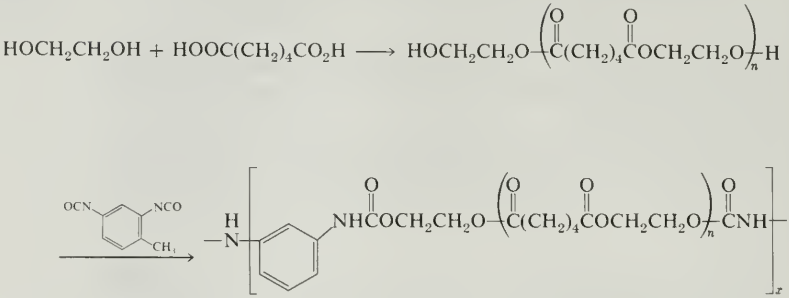


methyl N-cyclohexylcarbamate



N-methyl-N′-cyclohexylurea

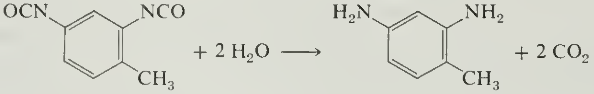
Carbamate esters are also called **urethanes.** An important class of commercial polymers is the **polyurethanes,** which are formed from an aromatic diisocyanate and a diol. One type of diol used is actually a low molecular weight copolymer made from ethylene glycol and adipic acid. When this polymer, which has free hydroxy end groups, is mixed with the diisocyanate, a larger polymer is produced.



$$\mathrm{HOCH_2CH_2OH + HOOC(CH_2)_4CO_2H \longrightarrow HOCH_2CH_2O\left(\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}OCH_2CH_2O\right)_{n}H}$$

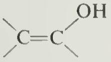
a polyurethane

In the manufacturing process, a little water is mixed in with the diol. Some of the diisocyanate reacts with water to give an aromatic diamine and carbon dioxide. The carbon dioxide forms bubbles that are trapped in the bulk of the polymer as it solidifies. The result is a spongy product called **polyurethane foam.**

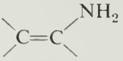


E. *Enamines*

Enamines are compounds in which an amino group is attached directly to a C=C double bond. They are the nitrogen analogs of enols.

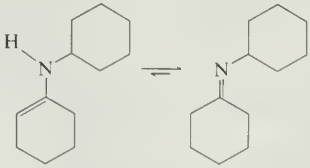


an enol

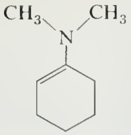


an enamine

Like enols, enamines are generally unstable and undergo rapid conversion into the imine tautomer.

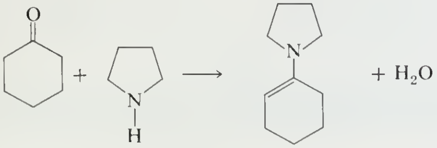


When the nitrogen of an enamine is tertiary, such tautomerism cannot occur and the enamine may be isolated and handled.



1-(dimethylamino)cyclohexene

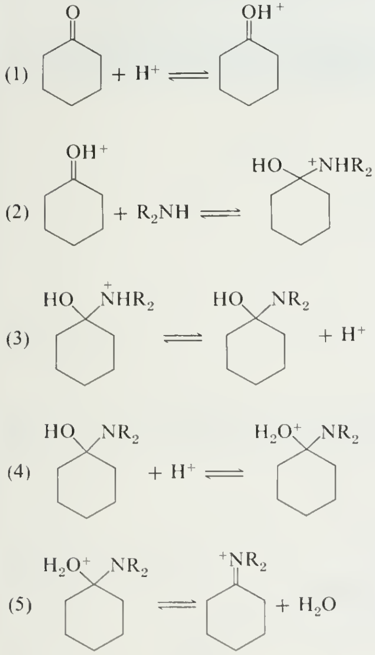
Tertiary enamines are prepared by reaction of a secondary amine with an aldehyde or ketone. Water must be removed as it is formed in order to shift the equilibrium to the enamine product (page 374). Cyclic secondary amines are commonly used.

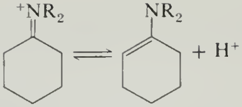


pyrrolidine

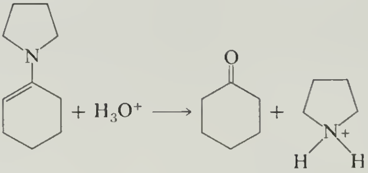
N-(1-cyclohexenyl)pyrrolidine

The mechanism for enamine formation is similar to the mechanism for formation of an imine; the reaction is subject to both acid and base catalysis (Section 15.7.C).

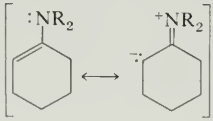


(6) 

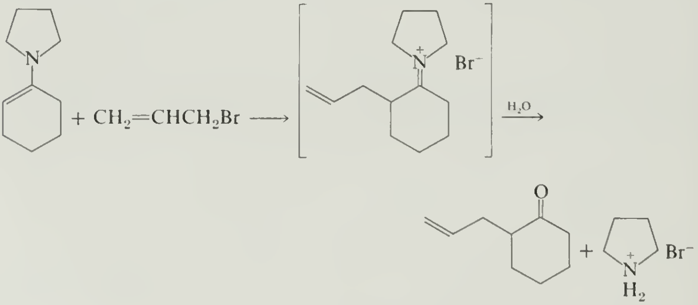
The products are sensitive to aqueous acid and revert to the carbonyl compound and the amine in dilute acid.



Enamines are useful intermediates in some reactions, because the β-carbon of the double bond has nucleophilic character, as shown in the following resonance structures.

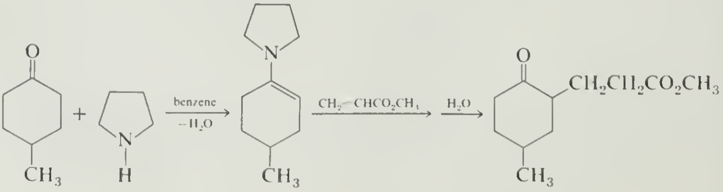


Reaction occurs rapidly with reactive alkyl halides to give alkylated immonium compounds, which undergo facile hydrolysis to give the alkylated ketone.


N
$+ CH_2{=}CHCH_2Br$
$\overset{+}{N}$
Br^-
H_2O
O
+
$\overset{+}{N}$
H_2
Br^-

2-allylcyclohexanone

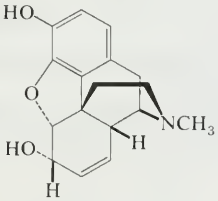
Enamines are most useful in the Michael addition reaction with α,β-unsaturated ketones, esters, and nitriles.


O
CH_3
+
N
H
benzene
$-H_2O$
N
CH_3
$CH_2{=}CHCO_2CH_3$
H_2O
O
$CH_2CH_2CO_2CH_3$
CH_3

27.9
Alkaloids

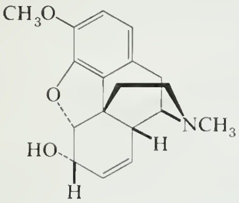
Alkaloids constitute a class of basic, nitrogen containing plant products that have complex structures and possess significant pharmacological properties. The name alkaloid, or "alkali-like," was first proposed by the pharmacist W. Meissner in the early nineteenth century before anything was known about the chemical structures of the compounds.

The first alkaloid isolated in a pure state was morphine, by Sertürner in 1805. The compound occurs in poppies and is responsible for the physiological effect of opium.

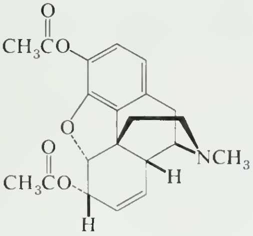


morphine

Other members of the morphine family are the O-methyl derivative, codeine, and the diacetyl derivative, heroin.



codeine



heroin

The stereo structure of codeine hydrobromide is shown in Figure 27.9.

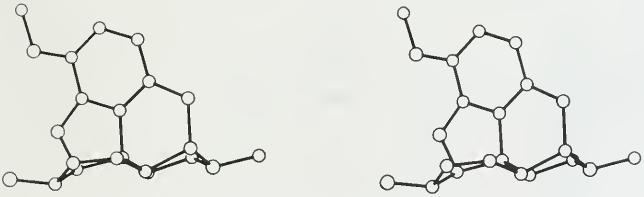
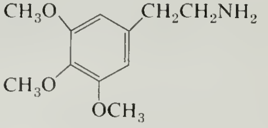


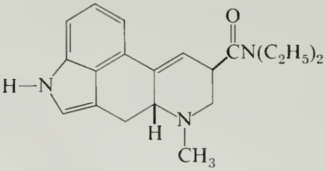
FIGURE 27.9 *Stereo structure of codeine hydrobromide. Hydrogens are not shown. [Reproduced with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.*]

Another common family of rather simple alkaloids are related to phenylethylamines. An example is mescaline, which occurs in several species of cactus. It is the active principle in mescal buttons, which were once used by some American

Indians in religious rites. It has more recently gained notoriety as an illegal hallucinogen. Recent studies have shown that virtually all "mescaline" in street sales is actually LSD (lysergic acid diethylamide), which is an even more potent hallucinogen.



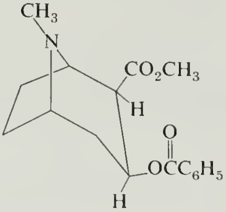
mescaline



lysergic acid diethylamide
"LSD"

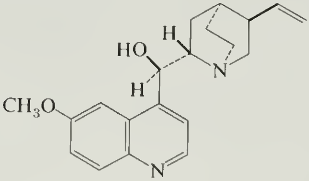
Note that both of these hallucinogens contain a β-phenylethylamine grouping, as does amphetamine (page 777).

Another representative alkaloid is the tropane alkaloid cocaine, which has important anesthetic properties.



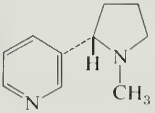
cocaine

Quinine is an alkaloid from cinchona bark which has had an important use as an antimalarial agent.



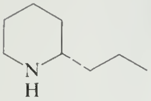
quinine

Nicotine is the chief alkaloid of the tobacco plant.

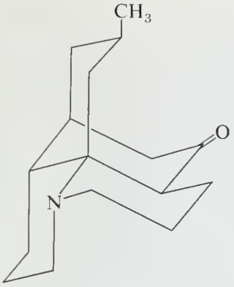


nicotine

Other important alkaloid structures are strychnine and brucine, mentioned previously in connection with their use as resolving agents (Section 27.4), coniine, the poisonous principle of poison hemlock, and lycopodine, which has the interesting tetracyclic structure shown on page 807.



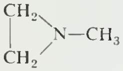
coniine



lycopodine

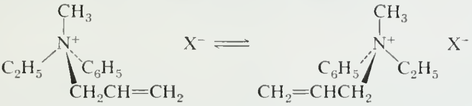
PROBLEMS

1. Although the inversion barrier for trimethylamine is only 6 kcal mole^{-1}, that for the heterocyclic tertiary amine N-methylaziridine is about 19 kcal mole^{-1}. Propose an explanation.

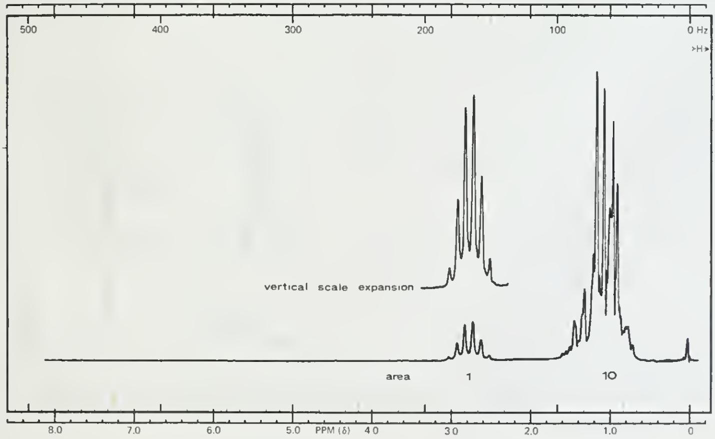


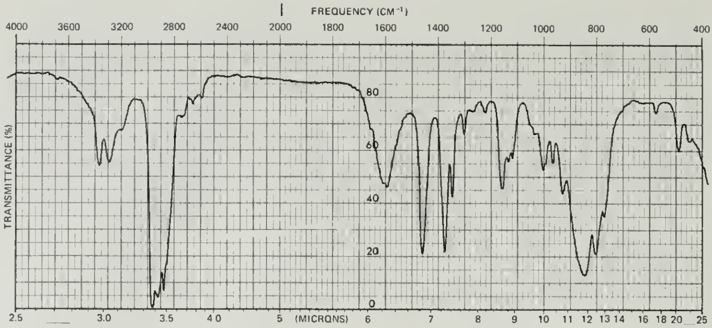
N-methylaziridine

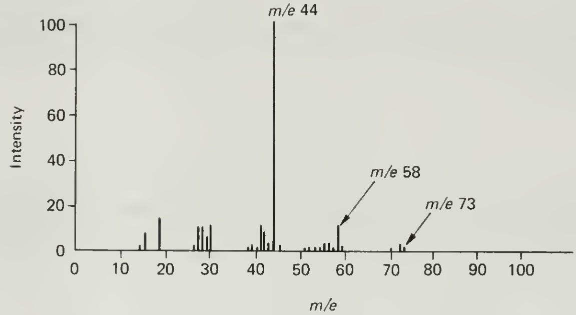
2. Quaternary ammonium salts that have four different groups on nitrogen are chiral and may be resolved. The optically active allylethylmethylphenylammonium halides racemize slowly in solution. The rate of racemization is temperature dependent and is faster for the iodide than for the bromide. Propose a mechanism for the racemization.



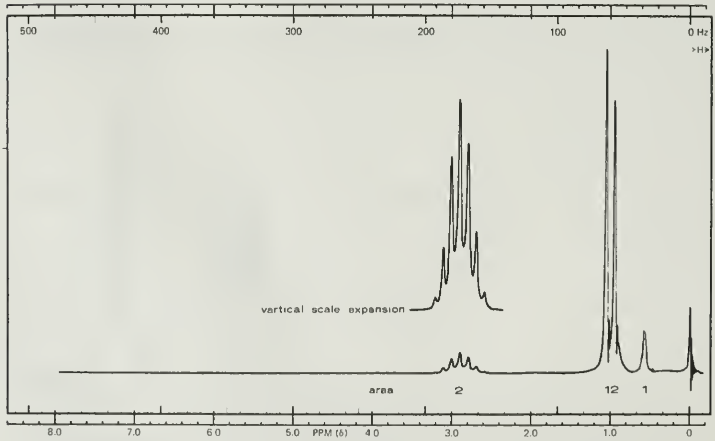
3. The nmr, ir, and mass spectra of an unknown compound are shown below. Propose a structure for the compound.

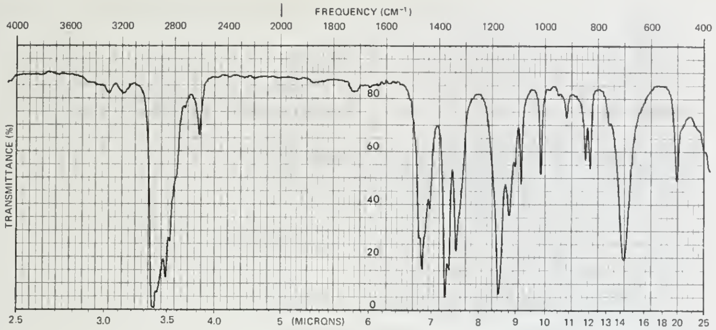


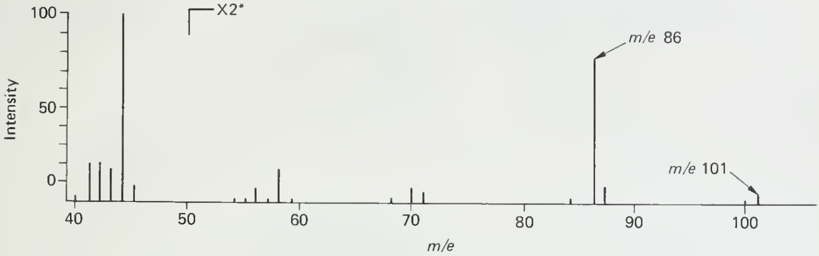




4. The nmr, ir, and mass spectra of an unknown compound are shown below. Propose a structure for the compound.







*The vertical scale is expanded by a factor of 2 above *m/e* 50.

5. Consider a solution of methylamine in water.
   (a) At what pH are the CH_3NH_2 and $CH_3NH_3^+$ concentrations exactly equal.
   (b) Calculate the $[CH_3NH_2]/[CH_3NH_3^+]$ ratio at pH 6, 8, 10, and 12.

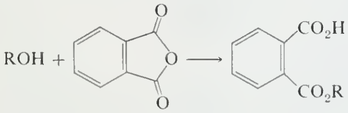
6. Consider the reaction of methylamine with acetic acid.

$$CH_3NH_2 + CH_3CO_2H \overset{K}{\rightleftharpoons} CH_3NH_3^+ + CH_3CO_2^-$$

   (a) Using the data in Tables 17.2 and 27.3, calculate K.
   (b) At what pH does $[CH_3CO_2^-] = [CH_3NH_3^+]$.

7. Propose a method for separating a mixture of cyclohexanecarboxylic acid, tributylamine, and decane.

8. Alcohols react with phthalic anhydride to give monophthalate esters (Section 26.4.A).

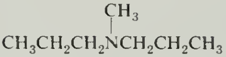


Suggest a method for the resolution of racemic 2-octanol.

9. Propose a synthesis of each of the following compounds from alcohols containing five or fewer carbon atoms.

(a) $CH_3(CH_2)_4NH_2$

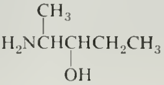
(b) $CH_3(CH_2)_4N(CH_3)_2$

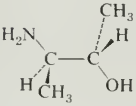
(c) 
$CH_3CH_2CH_2N(CH_3)CH_2CH_2CH_3$

(d) $(CH_3)_2CHCH_2CH_2NHCH_2CH_3$

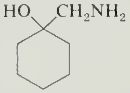
10. Propose a method for the stereospecific conversion of
(a) (R)-2-octanol into (S)-2-octylamine
(b) (R)-2-octanol into (R)-2-octylamine

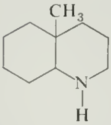
11. Propose a synthesis for each of the following compounds.

(a) 
$H_2NCH(CH_3)CH(OH)CH_2CH_3$ (mixture of diastereomers)

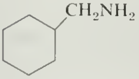
(b) 

(indicated diastereomer only)

(c) 

(d) 

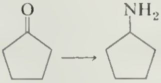
(*Hint:* See Section 26.4.F).

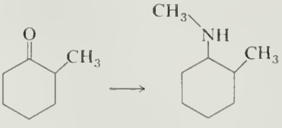
(e) 

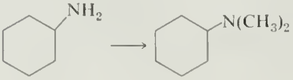
(*Hint:* See Section 26.2.A).

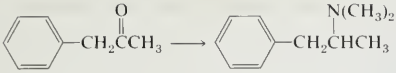
(f) $H_2NCH_2CH_2CH_2CH_2CH_2NH_2$

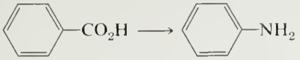
12. Show how to accomplish each of the following conversions.
(a) $CH_2{=}CHCO_2C_2H_5 \longrightarrow H_2NCH_2CH_2CH_2CH_2N(CH_3)_2$

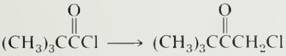
(b) 

(c) 

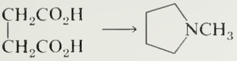
(d) 

(e) 

(f) 

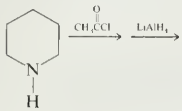
(g) 
$(CH_3)_3C\overset{\displaystyle O}{\overset{\|}{C}}Cl \longrightarrow (CH_3)_3C\overset{\displaystyle O}{\overset{\|}{C}}CH_2Cl$

(h) $(CH_3)_2CHCO_2H \longrightarrow (CH_3)_2CHNHCO_2CH_3$

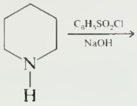
(i) 

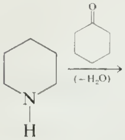
(j) $C_6H_5CH_2COCH_2C_6H_5 \longrightarrow C_6H_5CH_2NH_2$

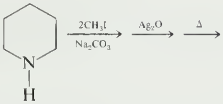
13. What is the expected product when piperidine is subjected to each of the following sets of reactions.

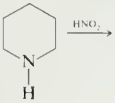
(a) 

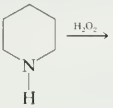
piperidine

(d) 

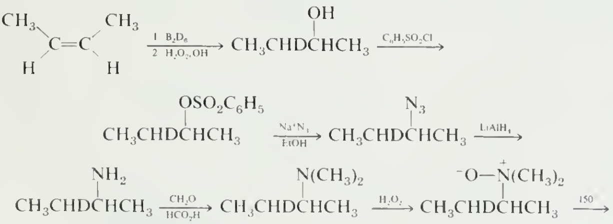
(b) 

(e) 

(c) 

(f) 

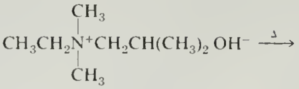
14. *cis*-2-Butene is subjected to the following sequence of reactions:


$$\xrightarrow[2\ H_2O_2,\ OH^-]{1\ B_2D_6} CH_3CHD\overset{\displaystyle OH}{\overset{|}{C}}HCH_3 \xrightarrow{C_6H_5SO_2Cl}$$
$$CH_3CHD\overset{\displaystyle OSO_2C_6H_5}{\overset{|}{C}}HCH_3 \xrightarrow[EtOH]{Na^+N_3^-} CH_3CHD\overset{\displaystyle N_3}{\overset{|}{C}}HCH_3 \xrightarrow{LiAlH_4}$$
$$CH_3CHD\overset{\displaystyle NH_2}{\overset{|}{C}}HCH_3 \xrightarrow[HCO_2H]{CH_2O} CH_3CHD\overset{\displaystyle N(CH_3)_2}{\overset{|}{C}}HCH_3 \xrightarrow{H_2O_2} CH_3CHD\overset{\displaystyle ^-O-\overset{+}{N}(CH_3)_2}{\overset{|}{C}}HCH_3 \xrightarrow{150^\circ}$$

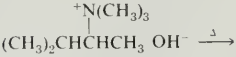
1-butene + *cis*-2-butene + *trans*-2-butene

Two of the butene isomers produced in the pyrolysis contain one atom of deuterium per molecule and the other isomer contains only hydrogen. Which isomer contains no deuterium? Explain.

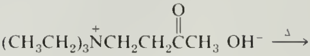
15. Predict the major product in each of the following elimination reactions:

(a) 

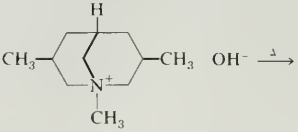
$CH_3CH_2\overset{CH_3}{\underset{CH_3}{N^+}}CH_2CH(CH_3)_2\ OH^- \xrightarrow{\Delta}$

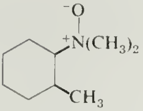
(b) 

$(CH_3)_2CH\overset{^+N(CH_3)_3}{C}HCH_3\ OH^- \xrightarrow{\Delta}$

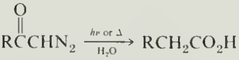
(c) 

$(CH_3CH_2)_3\overset{+}{N}CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3\ OH^- \xrightarrow{\Delta}$

(d) 

(e) 

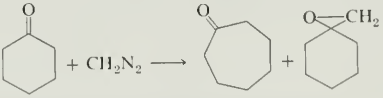
16. When α-diazoketones are irradiated or heated in aqueous solution, the product obtained is a carboxylic acid:



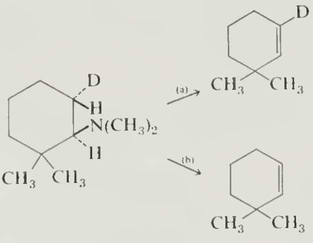
$$R\overset{O}{\overset{\|}{C}}CHN_2 \xrightarrow[H_2O]{h\nu \text{ or } \Delta} RCH_2CO_2H$$

(a) Propose a mechanism for the transformation.
(b) Predict the product when diazoacetone is irradiated in methanol solution.

17. When cyclohexanone is treated with diazomethane, a mixture of cycloheptanone and methylenecyclohexane oxide is produced. Propose a mechanism.



18. Show how to accomplish each of the following conversions:



19. Reaction of (cyclopentylmethyl)amine with aqueous nitrous acid gives a mixture of two alcohols and three olefins. Deduce their structures using a reasonable reaction mechanism.

20. Which member of each of the following pairs of substituted ammonium ions is the more acidic? Explain briefly.

(a) $ClCH_2CH_2NH_3^+$; $CH_3CH_2CH_2NH_3^+$

(b) $CH_3ONH_3^+$; $CH_3NH_3^+$

(c) $CH_3CONH_3^+$; $CH_3CH_2NH_3^+$

(d) $CH_2{=}NH_2^+$; $CH_3NH_3^+$

(e) $CH_3OOCCH_2NH_3^+$; $CH_3CH_2CH_2NH_3^+$

(f) $CH_2{=}CHNH_3^+$; $CH_3CH_2NH_3^+$

(g) $CH_3SO_2NH_3^+$; $CH_3CONH_3^+$

21. Granatine, $C_9H_{17}N$ is an alkaloid that occurs in pomegranate. Two stages of the Hofmann exhaustive methylation removes the nitrogen and yields a mixture of cyclooctadienes identified by catalytic hydrogenation to cyclooctane. The ultraviolet spectrum of the mixture shows the absence of the conjugated diene, 1,3-cyclooctadiene. Deduce the structure of granatine.

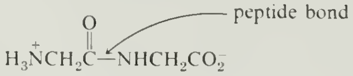
CHAPTER 28
Amino Acids, Peptides, and Proteins

28.1
Introduction

Amino acids constitute a particularly important class of difunctional compounds because they are the building blocks from which proteins are constructed. Since the two functional groups in an amino acid are, respectively, basic and acidic, the compounds are **amphoteric,** and in fact exist as **zwitterions** or **inner salts.** For example, glycine, the simplest amino acid, exists mostly in the form shown, rather than as aminoacetic acid.

$$\underset{\text{zwitterion form}}{\underset{\text{glycine}}{H_3\overset{+}{N}CH_2CO_2^-}} \rightleftharpoons \underset{\text{amino acid form}}{\underset{\text{glycine}}{H_2NCH_2CO_2H}}$$

Amino acids owe their important place in nature to the fact that they may form amide bonds between two molecules. Such a linkage is also called a **peptide bond,** and the resulting compounds are called **peptides.** For example, the peptide formed from two molecules of glycine is glycylglycine, a **dipeptide.** Like glycine, it is amphoteric and exists as a zwitterion.

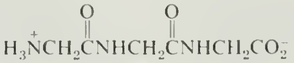


$$H_3\overset{+}{N}CH_2\overset{\overset{O}{\|}}{C}-NHCH_2CO_2^-$$

peptide bond

glycylglycine
a dipeptide

Higher peptides are also possible; a **tripeptide** contains three amino acid building blocks, a **tetrapeptide** four, and so on.



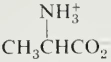
$$H_3\overset{+}{N}CH_2\overset{\overset{O}{\|}}{C}NHCH_2\overset{\overset{O}{\|}}{C}NHCH_2CO_2^-$$

glycylglycylglycine
a tripeptide

As more units are added to the chain, a polymer of any length may be achieved. Such polymers are called, as a class, **polypeptides. Proteins** are special types of polypeptides that are composed primarily of about 20 different specific amino acids. They are large molecules, with molecular weights from 6000 to more than 1,000,000 (from about 50 to more than 8000 amino acids per molecule).

28.2
Structure, Nomenclature, and Physical Properties of Amino Acids

Most of the important natural amino acids are α-amino acids; that is, the amino group occurs at the position adjacent to the carboxy function.


$CH_3\overset{NH_3^+}{\overset{|}{C}}HCO_2^-$

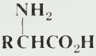
alanine
an α-amino acid

$H_3\overset{+}{N}CH_2CH_2CO_2^-$

β-alanine
a β-amino acid

The important natural amino acids are listed in Table 28.1, along with the three letter code that is conventionally used as an abbreviation for the name of each. The structures are all written in the amino acid form, rather than as zwitterions, since alternative zwittionic structures are possible for some.

TABLE 28.1

Common Amino Acids,  $R\overset{NH_2}{\overset{|}{C}}HCO_2H$

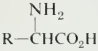
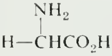
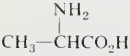
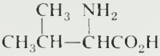
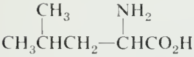
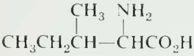
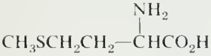
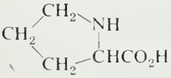
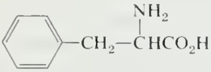
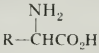
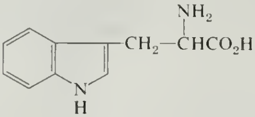
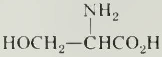
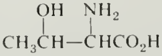
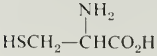
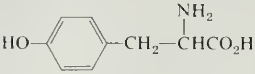
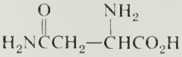
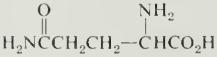
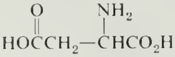
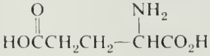
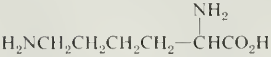
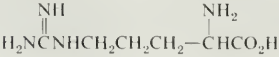
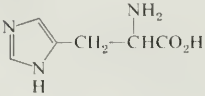
 $R{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	Name	Abbreviation
 $H{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	glycine	gly
 $CH_3{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	alanine	ala
 $CH_3\overset{CH_3}{\overset{|}{C}}H{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	valine	val
 $CH_3\overset{CH_3}{\overset{|}{C}}HCH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	leucine	leu
 $CH_3CH_2\overset{CH_3}{\overset{|}{C}}H{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	isoleucine	ile
 $CH_3SCH_2CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H$	methionine	met
	proline	pro
	phenylalanine	phe

TABLE 28.1 (continued)

 $\mathrm{R{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	Name	Abbreviation
	tryptophan	trp
 $\mathrm{HOCH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	serine	ser
 $\mathrm{CH_3\overset{OH}{\overset{|}{C}}H{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	threonine	thr
 $\mathrm{HSCH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	cysteine	cys
	tyrosine	tyr
 $\mathrm{H_2N\overset{O}{\overset{\|}{C}}CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	asparagine	asn
 $\mathrm{H_2N\overset{O}{\overset{\|}{C}}CH_2CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	glutamine	gln
 $\mathrm{HO\overset{O}{\overset{\|}{C}}CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	aspartic acid	asp
 $\mathrm{HO\overset{O}{\overset{\|}{C}}CH_2CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	glutamic acid	glu
 $\mathrm{H_2NCH_2CH_2CH_2CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	lysine	lys
 $\mathrm{H_2N\overset{NH}{\overset{\|}{C}}NHCH_2CH_2CH_2{-}\overset{NH_2}{\overset{|}{C}}HCO_2H}$	arginine	arg
	histidine	his

The inner salt nature of the amino acids results in physical properties that are somewhat different from the properties normally found in organic compounds. Zwitterions are highly polar substances for which intermolecular electrostatic attractions lead to rather strong crystal lattice structures. Consequently, melting points are generally high. Most amino acids decompose instead of melting, and it is customary to record decomposition points (Table 28.2). In general, decomposition points are dependent on the rate of heating of the sample and are not reliable physical properties.

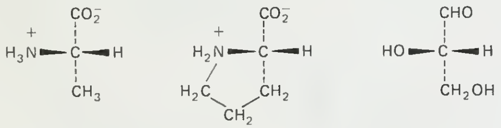
TABLE 28.2

Physical Properties of Amino Acids

Amino Acid	Decomposition point, °C	Water Solubility, g/100 ml H_2O at 25°	$[\alpha]_D^{25}$	pK_1	pK_2	pK_3
glycine	233	25		2.35	9.78	
alanine	297	16.7	+8.5	2.35	9.87	
valine	315	8.9	+13.9	2.29	9.72	
leucine	293	2.4	−10.8	2.33	9.74	
isoleucine	284	4.1	+11.3	2.32	9.76	
methionine	280	3.4	−8.2	2.17	9.27	
proline	220	162	−85.0	1.95	10.64	
phenylalanine	283	3.0	−35.1	2.58	9.24	
tryptothan	289	1.1	−31.5	2.43	9.44	
serine	228	5.0	−6.8	2.19	9.44	
threonine	225	very	−28.3	2.09	9.10	
cysteine			+6.5	1.86	8.35	10.34
tyrosine	342	0.04	−10.6	2.20	9.11	10.07
asparagine	234	3.5	−5.4	2.02	8.80	
glutamine	185	3.7	+6.1	2.17	9.13	
aspartic acid	270	0.54	+25.0	1.99	3.90	10.00
glutamic acid	247	0.86	+31.4	2.13	4.32	9.95
lysine	225	very	+14.6	2.16	9.20	10.80
arginine	244	15	+12.5	1.82	8.99	13.20
histidine	287	4.2	−39.7	1.81	6.05	9.15

Most of the amino acids are only sparingly soluble in water, again as a consequence of the strong intermolecular forces acting in the crystal lattice. Exceptions are glycine, alanine, proline, lysine, and arginine, which are all quite soluble in water.

With the exception of glycine, all of the common amino acids are chiral molecules. The naturally occurring compounds all have the (S) configuration at the asymmetric carbon. As with carbohydrates, it is traditional to use the D and L nomenclature with amino acids. Natural amino acids belong to the L series (Figure 28.1). The stereo structure of L-proline is shown in Figure 28.2. Optical rotations for the natural L-amino acids are given in Table 28.2.



L-alanine L-proline L-glyceraldehyde

FIGURE 28.1 *Showing the relationship of L-alanine and L-proline to L-glyceraldehyde.*

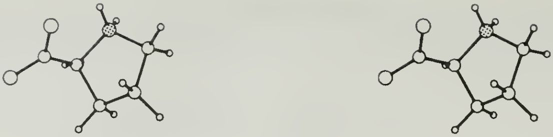


FIGURE 28.2 *Stereo structure of* L*-proline.* [*Reproduced with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.*]

28.3
Acid-Base Properties of Amino Acids

Amino acids show both acidic and basic properties **(amphoterism).** In acidic solution, the amino acid is completely protonated and exists as the conjugate acid.

$$H_3\overset{+}{N}CH_2CO_2^- + H^+ \longrightarrow H_3\overset{+}{N}CH_2CO_2H$$

The titration curve for glycine hydrochloride is shown in Figure 28.3. The salt behaves as a typical dihydric acid.

$$H_3\overset{+}{N}CH_2CO_2H \overset{K_1}{\rightleftharpoons} H^+ + H_3\overset{+}{N}CH_2CO_2^-$$

$$H_3\overset{+}{N}CH_2CO_2^- \overset{K_2}{\rightleftharpoons} H^+ + H_2NCH_2CO_2^-$$

$$K_1 = \frac{[H^+][H_3\overset{+}{N}CH_2CO_2^-]}{[H_3\overset{+}{N}CH_2CO_2H]}$$

$$K_2 = \frac{[H^+][H_2NCH_2CO_2^-]}{[H_3\overset{+}{N}CH_2CO_2^-]}$$

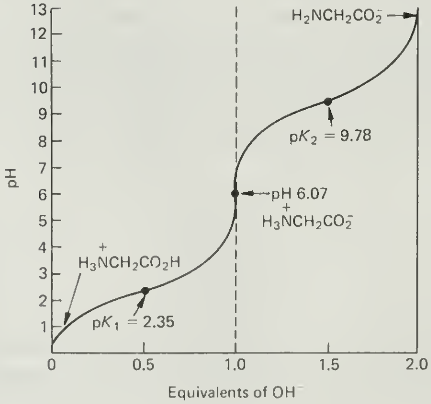


FIGURE 28.3 *Titration curve for glycine hydrochloride.*

When the hydrochloride has been half neutralized, $[H_3\overset{+}{N}CH_2CO_2H] = [H_3\overset{+}{N}CH_2CO_2^-]$. The pH of the solution at this point is equal to pK_1. This first dissociation constant refers to ionization of the CO_2H, which is the more acidic of the two acidic groups in the dibasic acid. Note that glycine is substantially more acidic than acetic acid, which has $pK_a = 4.76$, due to the large inductive effect of the $-NH_3^+$ group (see Sections 11.6.A and 17.4.B).

After one equivalent of base has been added, the chief species in solution is the zwitterionic form of the amino acid itself. The pH of the solution at this point is simply the pH of a solution of the amino acid in pure water. This point represents the pH at which the solubility of the amino acid is at a minimum, and is called the **isoelectric point.**

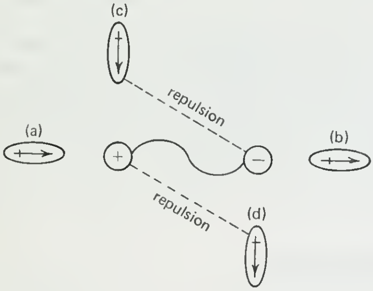
Addition of a further half equivalent of base corresponds to half neutralization of the acid $H_3\overset{+}{N}CH_2CO_2^-$. At this point $[H_3\overset{+}{N}CH_2CO_2^-] = [H_2NCH_2CO_2^-]$ and the pH of the solution is equal to pK_2, the dissociation constant for the protonated amino group. Note that pK_2 for glycine, 9.78, is slightly lower than that for the conjugate acid of methylamine, which has $pK_a = 10.4$.

$$H_3\overset{+}{N}CH_2CO_2^- \rightleftharpoons H^+ + H_2NCH_2CO_2^- \qquad pK_a = 9.8$$

$$H_3\overset{+}{N}CH_3 \rightleftharpoons H^+ + H_2NCH_3 \qquad pK_a = 10.4$$

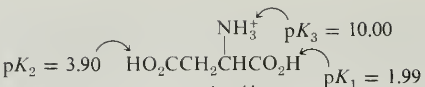
Thus, glycine is a slightly stronger acid than the methylammonium ion.

It may seem surprising that a carboxylate anion with its negative charge should make an ammonium cation *more* acidic. The explanation probably has to do with solvation effects. A dipolar or zwittionic compound with the charges sufficiently separated can have both ionic centers solvated in a normal fashion—as if the charges were in separate molecules. When the two charges are close together, however, solvation becomes less efficient. As shown in the illustration, solvent dipoles (a) and (b) provide normal solvation. Solvent dipoles (c) and (d), however, provide a stabilizing Coulombic attraction to one charge but repulsion with the other. As a result, a dipolar system of this type is less stabilized by solvation and is less favored in an equilibrium.



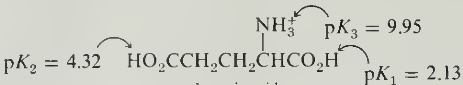
Solvation effects in a zwitterion

As shown in Table 28.2, most of the amino acids show similar values of pK_1 and pK_2. Aspartic and glutamic acids each have an additional carboxy group, with pK_as of 3.90 and 4.32, respectively.



$$\mathrm{p}K_2 = 3.90 \quad HO_2CCH_2\overset{\overset{NH_3^+}{|}}{C}HCO_2H \quad \mathrm{p}K_3 = 10.00 \quad \mathrm{p}K_1 = 1.99$$

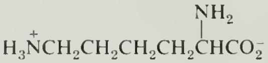
aspartic acid



$$\mathrm{p}K_2 = 4.32 \quad HO_2CCH_2CH_2\overset{\overset{NH_3^+}{|}}{C}HCO_2H \quad \mathrm{p}K_3 = 9.95 \quad \mathrm{p}K_1 = 2.13$$

glutamic acid

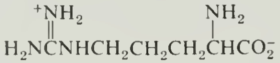
Lysine has two amino groups with pK_as of 9.20 and 10.8. The more basic group is probably the one most remote from the carboxy group. Consequently, the zwitterionic form of lysine is probably



$$H_3\overset{+}{N}CH_2CH_2CH_2CH_2\overset{\overset{NH_2}{|}}{C}HCO_2^-$$

lysine

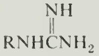
Arginine contains the strongly basic guanadino group, corresponding to pK_a 13.2. It exists in the following zwitterionic form



$$H_2N\overset{\overset{^+NH_2}{\|}}{C}NHCH_2CH_2CH_2\overset{\overset{NH_2}{|}}{C}HCO_2^-$$

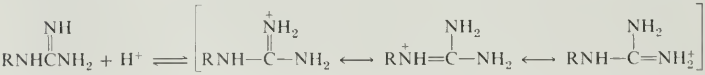
arginine

Guanidines are compounds of the general formula



$$RNH\overset{\overset{NH}{\|}}{C}NH_2$$

Protonation of the guanidino group on the imino nitrogen results in a cation that is highly resonance-stabilized. Guanidines are among the strongest organic bases.



$$RNH\overset{\overset{NH}{\|}}{C}NH_2 + H^+ \rightleftharpoons \left[RNH-\overset{\overset{\overset{+}{N}H_2}{\|}}{C}-NH_2 \longleftrightarrow R\overset{+}{N}H=\overset{\overset{NH_2}{|}}{C}-NH_2 \longleftrightarrow RNH-\overset{\overset{NH_2}{|}}{C}=NH_2^+\right]$$

The high pK_3 for arginine shows that the guanidino group is half protonated even at pH 13.2.

Tyrosine and histidine also contain other titratable groups, corresponding to the pK_as of 10.07 and 6.05, respectively. These ionization constants refer to the phenolic hydroxy in tyrosine and the imidazole ring in histidine. We shall discuss these two types of weak acids in later sections. The third titratable group in cysteine is the SH, which has a pK_a of 10.34, a normal value for a mercaptan.

28.4
Synthesis of Amino Acids

A. *Commercial Availability*

All of the common amino acids are available from chemical suppliers in optically active form. Table 28.3 lists the price per 100 g of the amino acids which

TABLE 28.3
Prices of Amino Acids

	Price per 100 g		
Amino Acid	L-enantiomer	D-enantiomer	Racemate
glycine			$ 0.76
alanine	$28.40	$ 78.10	3.40
valine	16.50	135.00	5.40
leucine	4.70	145.00	5.40
isoleucine	71.20		18.20
methionine	16.20	78.70	1.60
proline	35.00		242.00
phenylalanine	20.40	77.60	9.70
tryptothan	56.00	53.20	17.20
serine	51.70	531.00	9.90
threonine	43.50	142.00	18.50
cysteine	12.90	3355.00*	209.00*
tyrosine	4.40	705.00	11.00
asparginine	5.30	16.50	8.80
glutamine	40.60	605.00	63.80
aspartic acid	12.50	43.00	9.60
glutamic acid	1.05	198.00	9.90
lysine	3.14*	638.00*	9.90*
arginine	10.70	1035.00*	129.00*
histidine	17.30	86.90*	22.00

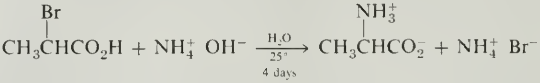
* Hydrochloride salt.

were quoted by one supplier in October, 1973. The prices in Table 28.3 reflect several factors. All of the racemic amino acids are synthetic and are prepared commercially by methods to be outlined later in this section. The prices of the synthetic amino acids reflect both the ease of synthesis and demand for the various compounds. Note that the most expensive racemic amino acid is the cyclic compound proline, which cannot be easily prepared by the standard methods that serve for the other amino acids.

Some of the available L-amino acids are isolated from natural sources; this is generally true when the price is lower than that for the racemate. The relatively low price of glutamic acid is a consequence of the fact that monosodium glutamate (MSG) is widely used as flavor enhancer in food preparation. The L-amino acid is prepared by a fermentation process in tonnage quantities, and its low price reflects this volume. Some of the commercially available L-amino acids and all of the D-enantiomers are prepared by resolution of the synthetic racemates. Their high costs result from the additional expenses incurred in the resolution process (see Section 28.4.F).

B. *Amination of α-Halo Acids*

α-Halo acids are available by the Hell-Volhard-Zelinsky halogenation of carboxylic acids (Section 17.7.B). Recall that the direct alkylation of ammonia or an amine is not generally a satisfactory method for preparing amines due to the overalkylation problem (Section 27.5). The reaction is somewhat better for preparing α-amino acids, because the amino group in the product amino acids is less basic (by about 0.8 pK_a units) than the amine itself. Thus, the second alkylation reaction is now slower than the first. A number of α-amino acids may be prepared in this way.

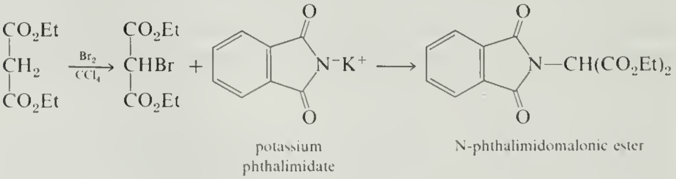


$$CH_3\overset{\overset{\displaystyle Br}{|}}{C}HCO_2H + NH_4^+\ OH^- \xrightarrow[25^\circ,\ 4\text{ days}]{H_2O} CH_3\overset{\overset{\displaystyle NH_3^+}{|}}{C}HCO_2^- + NH_4^+\ Br^-$$

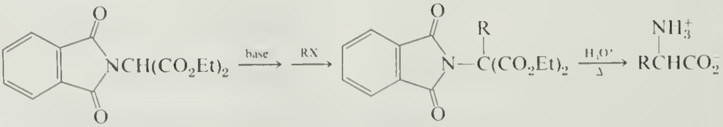
α-Bromopropionic acid (153 g) is added to 5.8 liters of concentrated aqueous ammonia and the resulting solution is kept at room temperature for 4 days. The solution is evaporated to dryness and extracted with warm absolute ethanol to remove ammonium bromide. The amino acid is obtained as a white crystalline mass. Yield, 50 g (56%).

C. *Alkylation of N-Substituted Aminomalonic Esters*

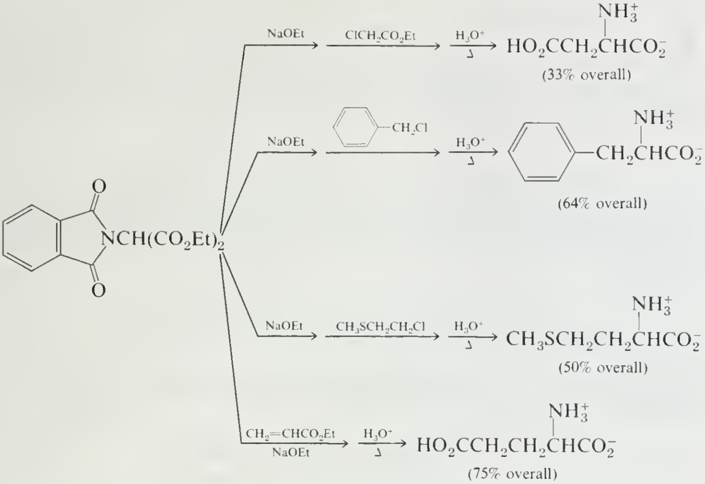
An especially general and useful method for the synthesis of α-amino acids involves a variation of the malonic ester synthesis (Section 26.4.D). Diethyl malonate may be monobrominated to yield a bromide that enters into the S_N2 reaction with the potassium salt of phthalimide to give N-phthalimidomalonic ester.



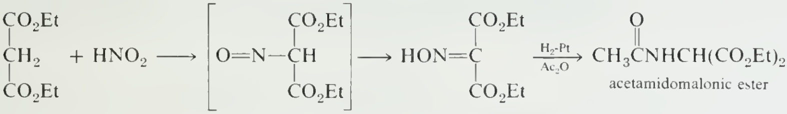
This substance may be alkylated by a variety of alkyl halides or α,β-unsaturated carbonyl compounds. Vigorous acid hydrolysis causes hydrolysis of both esters and the phthalimido group and decarboxylation of the resulting malonic acid. The product is an α-amino acid.



A few specific examples are given.


NCH(CO2Et)2
NaOEt
ClCH2CO2Et
H3O+
Δ
NH3+
HO2CCH2CHCO2−
(33% overall)
NaOEt
CH2Cl
H3O+
Δ
NH3+
CH2CHCO2−
(64% overall)
NaOEt
CH3SCH2CH2Cl
H3O+
Δ
NH3+
CH3SCH2CH2CHCO2−
(50% overall)
CH2=CHCO2Et
NaOEt
H3O+
Δ
NH3+
HO2CCH2CH2CHCO2−
(75% overall)

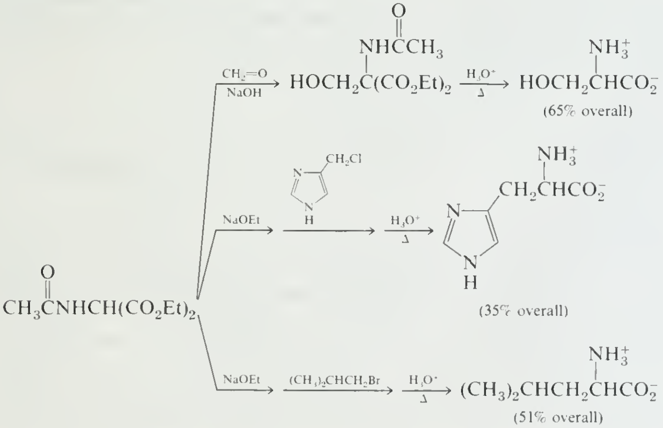
Other procedures similar to this are also useful. The best method utilizes the N-acetamido, rather than the N-phthalimido derivative. The starting material is prepared from malonic ester in the following way: Treatment of the diester with nitrous acid gives a nitroso derivative, which tautomerizes to the oxime. Hydrogenation of the oxime in acetic anhydride solution gives acetamidomalonic ester.



$$\begin{array}{c}CO_2Et\\|\\CH_2\\|\\CO_2Et\end{array} + HNO_2 \longrightarrow \left[O{=}N{-}\begin{array}{c}CO_2Et\\|\\CH\\|\\CO_2Et\end{array}\right] \longrightarrow HON{=}\begin{array}{c}CO_2Et\\|\\C\\|\\CO_2Et\end{array} \xrightarrow[Ac_2O]{H_2\text{-}Pt} CH_3\overset{\overset{O}{\|}}{C}NHCH(CO_2Et)_2$$

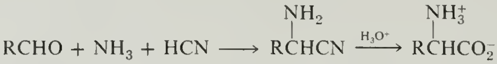
acetamidomalonic ester

The acetamidomalonic ester is alkylated and the resulting product is hydrolyzed and decarboxylated to obtain the amino acid.


CH3CNHCH(CO2Et)2
O
CH2=O
NaOH
NHCCH3
O
HOCH2C(CO2Et)2
H3O+
Δ
NH3+
HOCH2CHCO2−
(65% overall)
NaOEt
CH2Cl
N
N
H
H3O+
Δ
NH3+
CH2CHCO2−
N
N
H
(35% overall)
NaOEt
(CH3)2CHCH2Br
H3O+
Δ
NH3+
(CH3)2CHCH2CHCO2−
(51% overall)

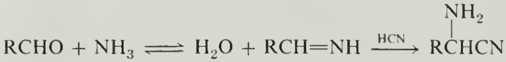
D. *Strecker Synthesis*

Another method of some generality for the preparation of α-amino acids is the hydrolysis of α-amino nitriles, which are available by the treatment of aldehydes with ammonia and HCN (Strecker synthesis).



$$\mathrm{RCHO + NH_3 + HCN \longrightarrow R\overset{NH_2}{\overset{|}{C}}HCN \xrightarrow{H_3O^+} R\overset{NH_3^+}{\overset{|}{C}}HCO_2^-}$$

The mechanism of formation of the α-amino nitrile probably involves the addition of HCN to the imine, which is formed by condensation of the aldehyde with ammonia.

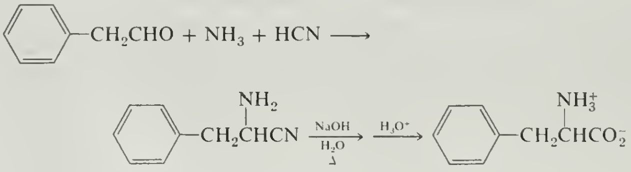


$$\mathrm{RCHO + NH_3 \rightleftharpoons H_2O + RCH{=}NH \xrightarrow{HCN} R\overset{NH_2}{\overset{|}{C}}HCN}$$

Examples of amino acids that have been prepared by the Strecker synthesis are given in (28-1) and (28-2).

$$\mathrm{CH_2{=}O + NH_4^+\ CN^- \xrightarrow{H_2SO_4} H_2NCH_2CN \xrightarrow[H_2O,\ \Delta]{BaO} H_3\overset{+}{N}CH_2CO_2^-}\quad (28\text{-}1)$$

(42%)

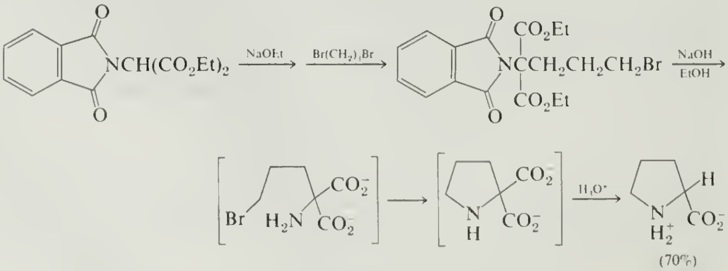


(28-2)

(74%)

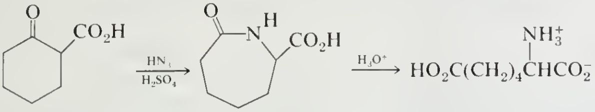
E. *Miscellaneous Methods*

The foregoing methods are of general applicability for the synthesis of the simpler amino acids, either natural or unnatural. Some of the more complicated structures must be prepared in other ways. For example, the heterocyclic amino acid proline has been synthesized by the following route.

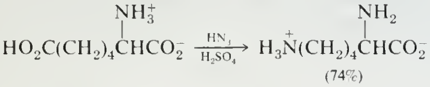


(70%)

The basic amino acid lysine has been prepared in a variety of ways. One interesting method involves application of the Schmidt reaction (Section 27.6.1) to 2-cyclohexanonecarboxylic acid. The product is a cyclic amide acid, which may be hydrolyzed to an amino dicarboxylic acid.



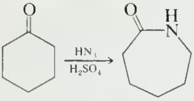
A second application of the Schmidt reaction yields lysine. Fortunately, only the carboxy group that is not α to the amino group reacts; in fact, α-amino acids fail to react at all in the Schmidt reaction.



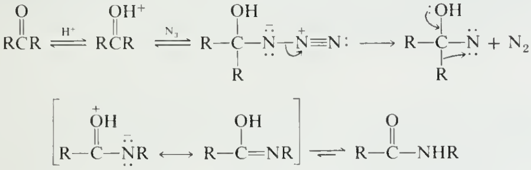
$$HO_2C(CH_2)_4\overset{\overset{NH_3^+}{|}}{C}HCO_2^- \xrightarrow[H_2SO_4]{HN_3} H_3\overset{+}{N}(CH_2)_4\overset{\overset{NH_2}{|}}{C}HCO_2^-$$

(74%)

The Schmidt reaction, introduced in Section 27.6.I as a reaction of carboxylic acids, also may be applied to ketones. It is a general method for the conversion of ketones to amides.



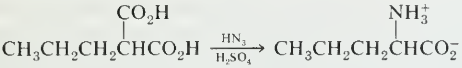
A probable mechanism for the conversion is



$$R\overset{\overset{O}{\|}}{C}R \underset{}{\xrightleftharpoons{H^+}} R\overset{\overset{OH^+}{\|}}{C}R \xrightleftharpoons{N_3^-} R-\underset{\underset{R}{|}}{\overset{\overset{OH}{|}}{C}}-\ddot{\overset{-}{N}}-\overset{+}{N}\equiv N: \longrightarrow R-\underset{\underset{R}{|}}{\overset{\overset{\ddot{O}H}{|}}{C}}-\ddot{N} + N_2$$

$$\left[R-\overset{\overset{\overset{+}{O}H}{\|}}{C}-\ddot{\overset{-}{N}}R \longleftrightarrow R-\overset{\overset{OH}{|}}{C}=NR\right] \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-NHR$$

The Schmidt reaction may also be used for the synthesis of simple amino acids if it is applied to an alkylated malonic acid.

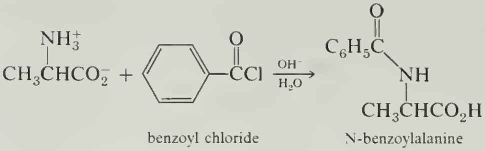


$$CH_3CH_2CH_2\overset{\overset{CO_2H}{|}}{C}HCO_2H \xrightarrow[H_2SO_4]{HN_3} CH_3CH_2CH_2\overset{\overset{NH_3^+}{|}}{C}HCO_2^-$$

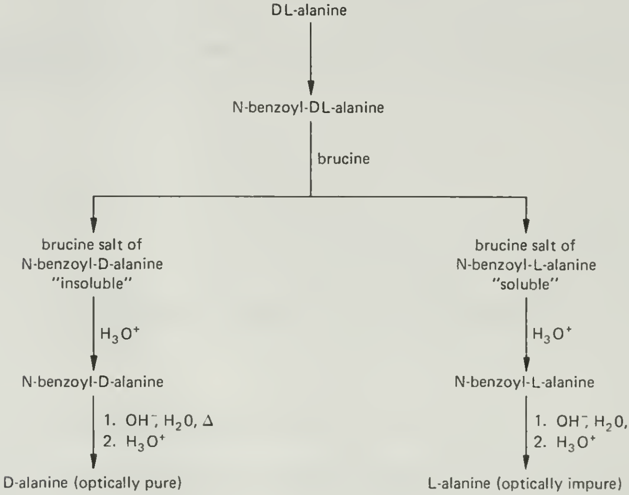
F. *Resolution*

Amino acids that are synthesized by the methods outlined in the preceding sections are obtained as racemates. It is usually desirable to have one of the two enantiomers, usually the L-enantiomer. For this reason, a good deal of attention has been paid to the problem of **resolving** racemic amino acids.

One method that may be used for the resolution of amino acids involves converting them into diastereomeric salts (Section 27.4). The amino group is usually converted into an amide so that the material is not amphoteric. For example, alanine reacts with benzoyl chloride in aqueous base to give N-benzoylalanine, which is a typical acid.


NH_3^+
$CH_3CHCO_2^-$
+
O
CCl
OH^-
H_2O
O
C_6H_5C
NH
CH_3CHCO_2H
benzoyl chloride
N-benzoylalanine

The racemic N-benzoylalanine is resolved in the normal way (Section 27.4) with brucine or strychnine. If brucine is used, it is the brucine salt of D-alanine that is less soluble. If strychnine is used, the strychnine salt of L-alanine crystallizes. Acidification of the salts yields the D- and L-enantiomers of N-benzoylalanine. Basic hydrolysis then affords the pure enantiomeric amino acids. The process is outlined schematically as follows:


DL-alanine
N-benzoyl-DL-alanine
brucine
brucine salt of
N-benzoyl-D-alanine
"insoluble"
brucine salt of
N-benzoyl-L-alanine
"soluble"
H_3O^+
H_3O^+
N-benzoyl-D-alanine
N-benzoyl-L-alanine
1. OH^-, H_2O, Δ
2. H_3O^+
1. OH^-, H_2O, Δ
2. H_3O^+
D-alanine (optically pure)
L-alanine (optically impure)

In cases such as that outlined, the enantiomer that forms the less soluble salt is usually obtained in an optically pure state. The other enantiomer is usually obtained in an impure state, because some of the less soluble salt invariably remains in solution. In the case diagrammed, the impure N-benzoyl-L-alanine may be treated with strychnine to give the insoluble strychnine salt. In this way, both enantiomers may be obtained in an optically pure state.

For all its simplicity, the **method of diastereomeric salts** suffers from several severe drawbacks. The less soluble diastereomeric salt is usually contaminated with the other salt, and several tedious recrystallizations may be required in order to purify it. These repetitive crystallizations are wasteful of both time and material, which may often be quite valuable. There is no way to predict which chiral base will give well-defined crystals with a given amino acid or which enantiomer of the amino acid will form the less soluble salt.

Various biological procedures are much more useful for the routine large-scale resolution of amino acids. The success of biological resolution stems from the fact that organisms are generally capable of utilizing only one enantiomer of a racemic substance. Thus, if a racemic amino acid is fed to an animal, the L-enantiomer will be consumed by the animal and the D-enantiomer will often be excreted. The optically pure D-enantiomer may then be isolated from the urine of the animal.

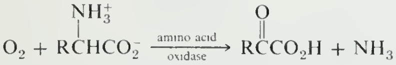
In practice, the procedure of using the whole animal for resolution is of only limited value. A more useful adaptation of the basic principle employs the use of crude enzyme preparations that catalyze some reaction on only one enantiomer. An example is the resolution of DL-leucine by *hog renal acylase,* an enzyme isolated from hog kidneys. The enzyme functions as a catalyst for the hydrolysis of amide linkages and is specific for amides of L-amino acids. For resolution, the racemic amino acid is first converted into the N-acetyl derivative, which is then incubated with a small amount of the crude enzyme preparation. The enzyme catalyzes hydrolysis of N-acetyl-L-leucine to the amino acid, leaving N-acetyl-D-leucine unchanged. The two enantiomers are easily separable, since one is acidic and the other is amphoteric.

$$\text{DL-leucine} \xrightarrow{\text{Ac}_2\text{O}} \text{N-acetyl-DL-leucine} \xrightarrow[\text{acylase}]{\text{hog renal}} \left\{ \begin{array}{c} \text{L-leucine} \\ + \\ \text{N-acetyl-D-leucine} \end{array} \right.$$

A suspension of 17.3 g of N-acetyl-DL-leucine in 1 liter of water is adjusted to pH 7.0 with NH_4OH solution, and 0.012 g of hog renal acylase powder is added. The mixture is agitated at 38° for 24 hr. The mixture is acidified with 10 ml of acetic acid, filtered, and evaporated under vacuum to a volume of about 50 ml. Upon addition of ethanol, L-leucine crystallizes. The semipure amino acid is recrystallized from ethanol-water to give 5 g (80%) of optically pure L-leucine.

The filtrates from the foregoing process are acidified to pH 2 with HCl and chilled, whereupon N-acetyl-D-leucine crystallizes. One recrystallization from water gives 7 g (80%) of optically pure product. It may be hydrolyzed by refluxing with 2 N HCl to obtain pure D-leucine.

Another biological process employs enzymes that specifically *destroy* one of the enantiomers. An example of such an enzyme is L-*amino acid oxidase,* which is obtained from rattlesnake venom. The enzyme catalyzes the oxidation of the amino acid to an α-keto acid and ammonia and is specific for L-enantiomers.



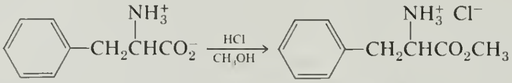
$$O_2 + R\overset{\overset{NH_3^+}{|}}{C}HCO_2^- \xrightarrow[\text{oxidase}]{\text{amino acid}} R\overset{\overset{O}{\|}}{C}CO_2H + NH_3$$

Analogous enzymes, such as hog kidney D-amino acid oxidase, perform the same function on the other enantiomer. The chief advantages of this method are its simplicity (it is not necessary to convert the amino acid into a derivative prior to resolution), and the extremely high stereospecificity that is observed. The chief drawbacks are the relative unavailability of the necessary enzymes and the fact that one of the two enantiomers is destroyed.

28.5
Reactions of Amino Acids

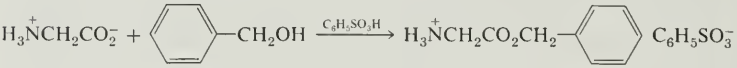
A. *Esterification*

The carboxy group of an amino acid may be esterified in the normal way. Methyl, ethyl, and benzyl esters are employed extensively as intermediates in the synthesis of peptides (Section 28.6). The methyl and ethyl esters are normally prepared by treating a suspension of the amino acid in the appropriate alcohol with anhydrous hydrogen chloride. The amino acid ester is isolated as the crystalline hydrochloride salt.



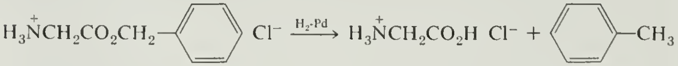
(90%)
phenylalanine methyl
ester hydrochloride

Benzyl esters are usually prepared using benzenesulfonic acid as the catalyst. The water produced in the reaction is removed by azeotropic distillation, thus avoiding the use of a large excess of benzyl alcohol.



(90%)
glycine benzyl ester
benzenesulfonate

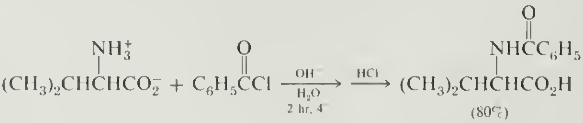
As we shall see later, the benzyl esters are especially useful derivatives because they may be converted back to acids by nonhydrolytic methods. For example, glycine benzyl ester reacts with hydrogen in the presence of palladium to give glycine and toluene.



This is an example of **hydrogenolysis** (cleavage of a σ bond by hydrogen) and is discussed further in Section 30.6.B.

B. *Amide formation*

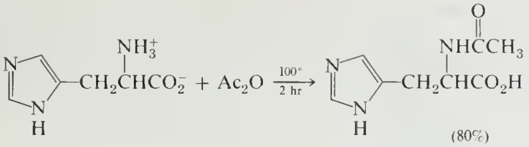
Acylation of the amino group in amino acids is best carried out under basic conditions, so that a substantial concentration of the free amino form is present. An example is N-benzoylation under Schotten-Baumann conditions (Section 18.9.C).



$$(\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{NH_3^+}}{\overset{|}{\mathrm{C}}}\mathrm{HCO_2^-} + \mathrm{C_6H_5}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{Cl} \xrightarrow[\mathrm{H_2O}\ 2\ \mathrm{hr},\ 4]{\mathrm{OH^-}} \xrightarrow{\mathrm{HCl}} (\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{NH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{C_6H_5}}{\overset{|}{\mathrm{C}}}\mathrm{HCO_2H}$$

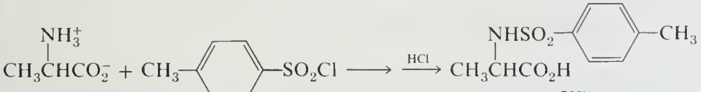
(80%)
N-benzoylvaline

Amides may also be prepared by reaction with acetic anhydride.



(80%)
N-acetylhistidine

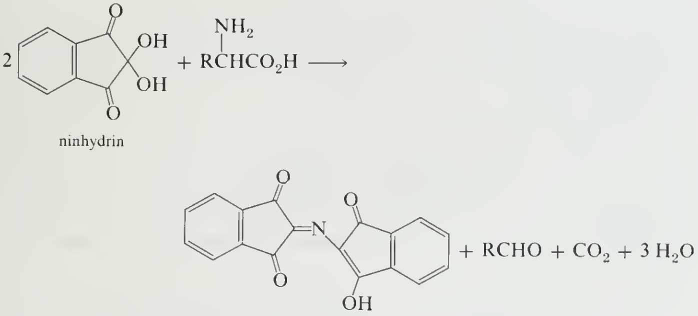
Sulfonamides may also be prepared.



(70%)

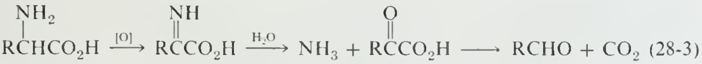
C. *Ninhydrin Reaction*

When an aqueous solution of an α-amino acid is treated with triketohydrindene hydrate (ninhydrin), a violet color is produced. The net reaction is outlined as



The reaction mechanism is complicated and we shall not go into it here. Note that only the nitrogen of the amino acid appears in the product responsible for the violet color produced. The manner in which this nitrogen becomes separated from the amino acid is known and is an example of a reaction of α-amino acids that is biologically important.

In the first stages of the ninhydrin reaction, the amino acid is oxidized to give an α-imino acid. In aqueous solution, this imino acid is hydrolyzed to an α-keto acid and ammonia. The ammonia reacts further to give the purple pigment and the α-keto acid decarboxylates to give an aldehyde.



$$\mathrm{R\overset{NH_2}{\overset{|}{C}}HCO_2H} \xrightarrow{[O]} \mathrm{R\overset{NH}{\overset{\|}{C}}CO_2H} \xrightarrow{H_2O} \mathrm{NH_3} + \mathrm{R\overset{O}{\overset{\|}{C}}CO_2H} \longrightarrow \mathrm{RCHO} + \mathrm{CO_2} \quad (28\text{-}3)$$

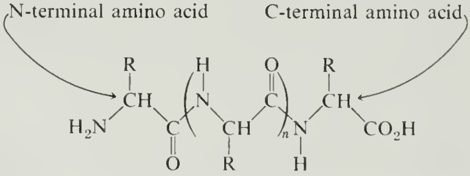
The process of **oxidative deamination,** outlined in (28-3), is an important pathway for the biodegradation of α-amino acids.

The ninhydrin reaction is important because it may be used as an analytical method for α-amino acids. The violet solutions that are produced show a significant absorption at 570 nm, and the intensity of the absorption is proportional to the amount of α-amino acid present. The reaction is not given by proline, in which the α-amino group is secondary. Another reaction occurs with proline to give a product that can be assayed at another wavelength.

28.6
Peptides

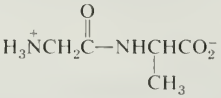
A. *Structure and Nomenclature*

Peptides, also called polypeptides, are amino acid polymers containing from 2 to about 50 individual units. The individual amino acids are connected by amide linkages from the amino group of one unit to the carboxy group of another. Unless a polypeptide is cyclic, it will contain a free $-NH_3^+$ group (the N-terminal end) and a free $-CO_2^-$ group (the C-terminal end).



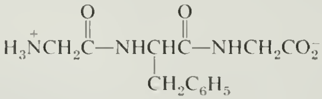
a polypeptide

By convention, peptide structures are always written with the N-terminal unit on the left and the C-terminal unit on the right. They are named by prefixing the name of the C-terminal unit with the group names of the other amino acids, beginning with the N-terminal unit. Since the names tend to become rather unintelligible, a shorthand notational system is used employing the three letter codes given in Table 28.1.



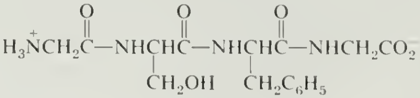
$$H_3\overset{+}{N}CH_2\overset{\overset{\displaystyle O}{\|}}{C}-NH\underset{\underset{\displaystyle CH_3}{|}}{C}HCO_2^-$$

glycylalanine
gly · ala



$$H_3\overset{+}{N}CH_2\overset{\overset{\displaystyle O}{\|}}{C}-NH\underset{\underset{\displaystyle CH_2C_6H_5}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}-NHCH_2CO_2^-$$

glycylphenylalanylglycine
gly · phe · gly



$$H_3\overset{+}{N}CH_2\overset{\overset{\displaystyle O}{\|}}{C}-NH\underset{\underset{\displaystyle CH_2OH}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}-NH\underset{\underset{\displaystyle CH_2C_6H_5}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}-NHCH_2CO_2^-$$

glycylserylphenylalanylglycine
gly · ser · phe · gly

The stereo structure of gly · phe · gly is shown in Figure 28.4.

Peptides are formed by partial hydrolysis of proteins, which are also amino acid polymers of much higher molecular weight (more than 50 amino acid units). Upon hydrolysis of a protein, some amide linkages are broken and a complex mixture of peptides results. Complete hydrolysis gives a mixture of amino acids. Some peptides are also important natural products. An example is the nonapep-

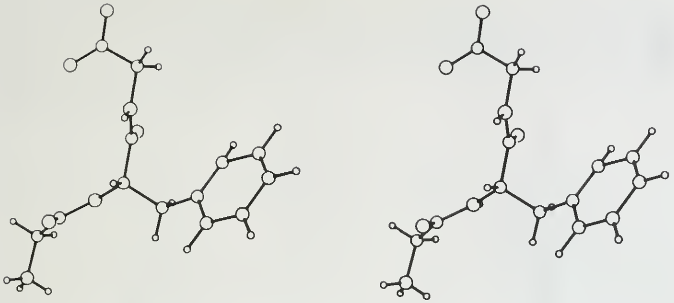
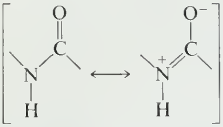


FIGURE 28.4 *Stereo structure of gly · phe · gly. [Reproduced with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.]*

tide bradykinin, which occurs in blood plasma and is involved in the regulation of blood pressure.

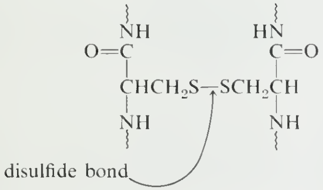
arg · pro · pro · gly · phe · ser · pro · phe · arg
bradykinin

The central feature of the polypeptide chain is the succession of amide linkages. Recall from our previous study (Chapter 18) that the C—N bond in an amide has a high degree of "double bond character," resulting from delocalization of the nitrogen lone pair into the carbonyl group. This delocalization reduces the basicity of the nitrogen and causes restricted rotation about the C—N bond.



The latter property of the amide linkage has an important consequence on the three-dimensional structure of proteins, as we shall see later.

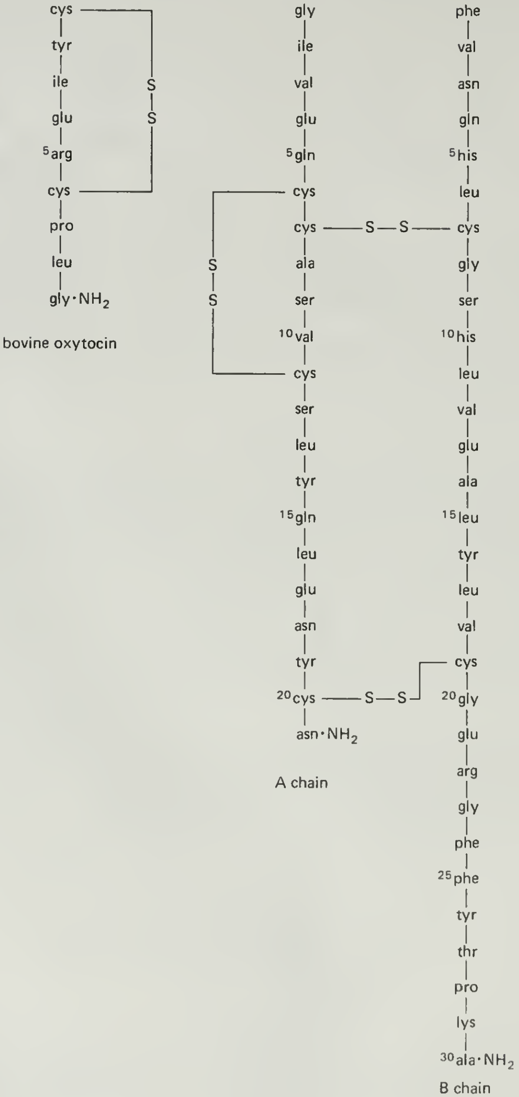
The only other type of covalent bond between amino acids in proteins and peptides is the disulfide linkage between two cysteine units.



Recall that disulfides, R—S—S—R, are formed by the mild oxidation of thiols (Section 11.15). The disulfide linkage is easily reduced to regenerate the thiols.

$$2\,\mathrm{RSH} \underset{\text{reduction}}{\overset{\text{oxidation}}{\rightleftharpoons}} \mathrm{RSSR}$$

When such a disulfide bond occurs between two cysteine residues that are in the same chain, a "loop" results, as in the posterior pituitary hormone oxytocin. If the cysteine units are in different chains, the disulfide link may bind the two chains together, as in the A and B chains of insulin (Figure 28.5).


cys
tyr
ile
glu
5arg
cys
pro
leu
gly·NH2
S
S
gly
ile
val
glu
5gln
cys
cys
ala
ser
10val
cys
ser
leu
tyr
15gln
leu
glu
asn
tyr
20cys
asn·NH2
S
S
S—S
S—S
phe
val
asn
gln
5his
leu
cys
gly
ser
10his
leu
val
glu
ala
15leu
tyr
leu
val
cys
20gly
glu
arg
gly
phe
25phe
tyr
thr
pro
lys
30ala·NH2

bovine oxytocin

A chain

B chain

bovine insulin

FIGURE 28.5 *Amino acid sequence and disulfide bridges of bovine oxytocin and bovine insulin. The N-terminal units are at the top and the C-terminal units are at the bottom. All three C-terminal units occur as amides.* —CONH$_2$.

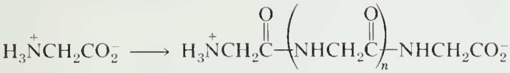
Like the simpler amino acids, peptides are amphoteric compounds, since they still contain a free amino and a free carboxy group; they exist as zwitterions. The pK_as for the two functions in a few simple peptides are listed in Table 28.4. Also included are the isoelectric points, pH_I, the pH at which the peptide is least soluble in aqueous solution.

TABLE 28.4
pK_a Values for Some Peptides

Peptide	pK_1 CO_2H	pK_2 NH_3^+	Isoelectric Point, pH_I
gly · gly	3.14	8.25	5.70
gly · ala	3.15	8.23	5.69
ala · gly	3.17	8.18	5.68
gly · gly · gly	3.23	8.09	5.66
ala · ala · ala · ala	3.42	7.94	5.68

B. *Synthesis of Peptides*

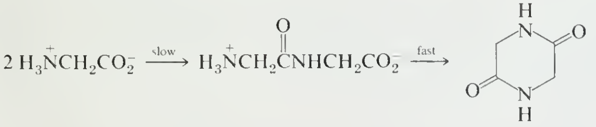
The simplest method for the synthesis of peptides is the polymerization of an amino acid. The resulting **homopolymer** is a mixture of peptides of variable chain length. Such homopolymers are not found in nature, but the synthetic ones have been useful in understanding some of the physical and spectral properties of proteins.



$$H_3\overset{+}{N}CH_2CO_2^- \longrightarrow H_3\overset{+}{N}CH_2\overset{\overset{O}{\|}}{C}\left(NHCH_2\overset{\overset{O}{\|}}{C}\right)_n NHCH_2CO_2^-$$

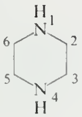
polyglycine

The first product formed when two amino acids condense is a dipeptide. The terminal amino and carboxy groups are now situated so that they can interact to form a six-membered ring diamide. Thus, when glycine is heated, the cyclic dimer 2,5-diketopiperazine is produced.


2 $H_3\overset{+}{N}CH_2CO_2^-$
slow
$H_3\overset{+}{N}CH_2\overset{\overset{O}{\|}}{C}NHCH_2CO_2^-$
fast
H
N
O
O
N
H

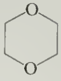
2,5-diketopiperazine
"glycine anhydride"

Piperazine is a heterocyclic diamine, which is numbered as shown.



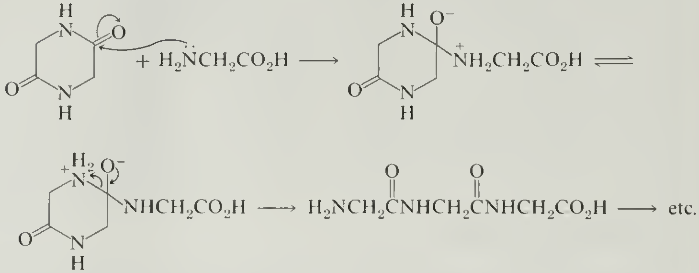
piperazine

It is the nitrogen analog of 1,4-dioxane.

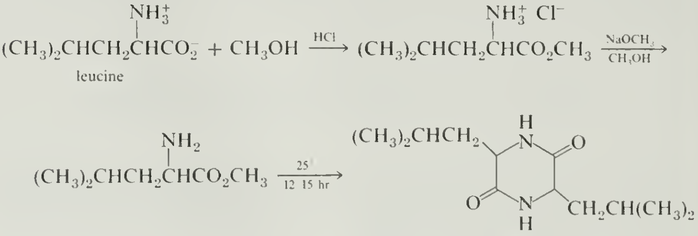


1,4-dioxane

Polymerization probably involves initial diketopiperazine formation, followed by opening of the ring by another amino acid or by the growing polymer chain.

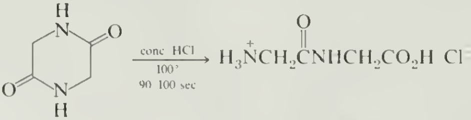


Diketopiperazines are best prepared from the corresponding amino acid esters. These compounds are stable indefinitely as the hydrochloride salts, but the free amines spontaneously dimerize to give the 2,5-diketopiperazine.



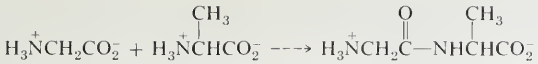
(60% overall)
leucine anhydride

Hydrolysis of one of the amide bonds in a 2,5-diketopiperazine is one method for preparing simple dipeptides.



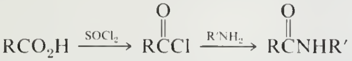
(90%)
glycylglycine hydrochloride

The rational synthesis of peptides is a challenging task that has only been solved in the past few decades. In order to illustrate the difficulty, consider the synthesis of the simple dipeptide glycylalanine from glycine and alanine. The problem is to form an amide linkage between the carboxy group of glycine and the amino group of alanine.



$$H_3\overset{+}{N}CH_2CO_2^- + H_3\overset{+}{N}\underset{}{\overset{CH_3}{\overset{|}{C}}}HCO_2^- \dashrightarrow H_3\overset{+}{N}CH_2\overset{O}{\overset{\|}{C}}{-}NH\overset{CH_3}{\overset{|}{C}}HCO_2^-$$

The normal method for converting a carboxylic acid into an amide is to activate the carboxy group by converting it to an acyl halide and then to add the amine.



$$RCO_2H \xrightarrow{SOCl_2} R\overset{O}{\overset{\|}{C}}Cl \xrightarrow{R'NH_2} R\overset{O}{\overset{\|}{C}}NHR'$$

But an amino acid cannot be converted into an acyl halide; polymerization would result. Another possibility would be the direct formation of the amide link by treatment of a mixture of the two amino acids with some dehydrating agent to remove the water produced. However, such a direct approach will give a mixture of four different dipeptides. Furthermore, each of these dipeptides can react further to give higher peptides.

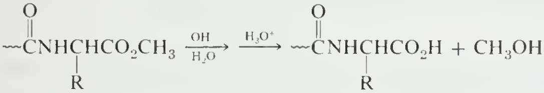
$$\text{glycine} + \text{alanine} \xrightarrow{-H_2O} \text{gly}\cdot\text{gly} + \text{ala}\cdot\text{ala} + \text{gly}\cdot\text{ala} + \text{ala}\cdot\text{gly}$$

An additional complication enters in with amino acids which have other reactive functional groups, such as serine, threonine, lysine, and aspartic acid.

The general method that has been developed to avoid these difficulties involves the use of protecting groups. Protecting groups have been developed for both the amino and carboxy groups, as well as for the other groups that occur in the side chains of the various amino acids. A suitable protecting group must fulfill several criteria:

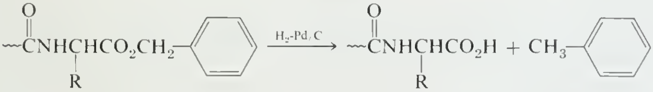
1. The protecting group must be easy to introduce into the molecule.
2. It must protect the functional group under conditions of amide formation.
3. It must be removable under conditions that leave the newly created amide link intact.

Carboxy groups are normally protected by conversion into the methyl, ethyl, or benzyl ester. Since esters are hydrolyzed more easily than amides, the protecting group can be removed by alkaline hydrolysis.

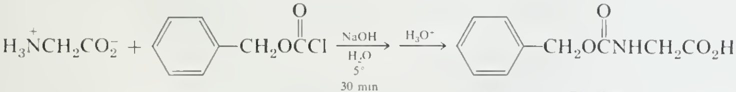


$$\sim\overset{O}{\overset{\|}{C}}NH\underset{\underset{R}{|}}{C}HCO_2CH_3 \xrightarrow[H_2O]{OH^-} \xrightarrow{H_3O^+} \sim\overset{O}{\overset{\|}{C}}NH\underset{\underset{R}{|}}{C}HCO_2H + CH_3OH$$

Benzyl esters may be cleaved by hydrogenolysis (Section 30.6.B).



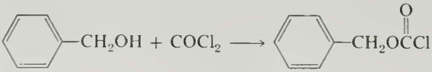
Of the many amino protecting groups that have been developed, we shall discuss only two, the benzyloxycarbonyl ("carbobenzoxy", cbz) and the *t*-butoxycarbonyl (boc) groups. The benzyloxycarbonyl group is introduced by treating the amino acid with benzyl chloroformate in alkaline solution.



benzyl
chloroformate

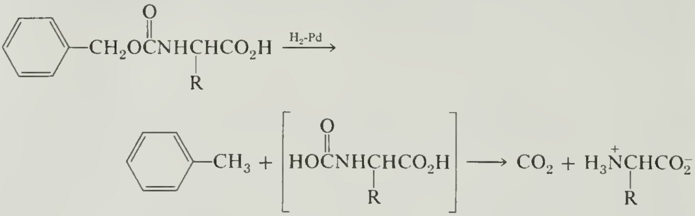
(70–80%)
benzyloxycarbonylglycine
cbz · gly

Benzyl chloroformate is the half benzyl ester, half acyl chloride of carbonic acid. It is prepared by treating benzyl alcohol with phosgene.

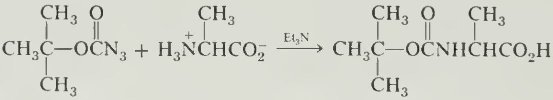


(95–99%)

The new C—N linkage in a benzyloxycarbonyl amino acid is part of a carbamate grouping (Sections 18.11 and 27.6.I). Like amides, carbamates hydrolyze with great difficulty. However, the benzyl-oxygen bond can be cleaved by catalytic hydrogenolysis, yielding the unstable carbamic acid, which undergoes decarboxylation (Section 27.6.I).



The *t*-butoxycarbonyl group is introduced by treating the amino acid with *t*-butyl azidoformate.



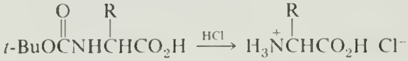
$$\mathrm{CH_3}\underset{\underset{\textstyle CH_3}{|}}{\overset{\overset{\textstyle CH_3}{|}}{\mathrm{C}}}\mathrm{-O}\overset{\overset{\textstyle O}{\|}}{\mathrm{C}}\mathrm{N_3} + \mathrm{H_3}\overset{+}{\mathrm{N}}\overset{\overset{\textstyle CH_3}{|}}{\mathrm{C}}\mathrm{HCO_2^-} \xrightarrow{\mathrm{Et_3N}} \mathrm{CH_3}\underset{\underset{\textstyle CH_3}{|}}{\overset{\overset{\textstyle CH_3}{|}}{\mathrm{C}}}\mathrm{-O}\overset{\overset{\textstyle O}{\|}}{\mathrm{C}}\mathrm{NH}\overset{\overset{\textstyle CH_3}{|}}{\mathrm{C}}\mathrm{HCO_2H}$$

t-butyl azidoformate

t-butoxycarbonylalanine
boc·ala

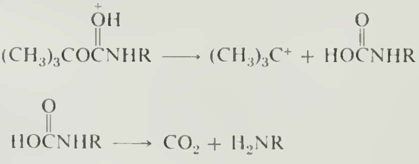
t-Butyl azidoformate is a commercially available material. *t*-Butyl chloroformate is too unstable to use in the reaction.

The *t*-butoxycarbonyl group is removed by treating the protected amino acid or peptide with hydrogen chloride in acetic acid, ether, ethyl acetate, or nitromethane as solvent.



$$t\text{-BuO}\overset{\overset{\textstyle O}{\|}}{\mathrm{C}}\mathrm{NH}\overset{\overset{\textstyle R}{|}}{\mathrm{C}}\mathrm{HCO_2H} \xrightarrow{\mathrm{HCl}} \mathrm{H_3}\overset{+}{\mathrm{N}}\overset{\overset{\textstyle R}{|}}{\mathrm{C}}\mathrm{HCO_2H\ Cl^-}$$

The initial reaction is hydrolysis of the *t*-butylcarbamate, which occurs with cleavage of the alkyl-oxygen bond (Section 18.9.A). The resulting carbamic acid then decarboxylates, giving the amine.

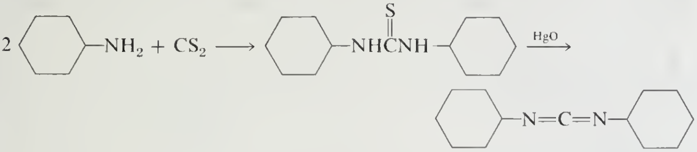


$$\mathrm{(CH_3)_3CO}\overset{\overset{\textstyle \overset{+}{O}H}{\|}}{\mathrm{C}}\mathrm{NHR} \longrightarrow \mathrm{(CH_3)_3C^+} + \mathrm{HO}\overset{\overset{\textstyle O}{\|}}{\mathrm{C}}\mathrm{NHR}$$

$$\mathrm{HO}\overset{\overset{\textstyle O}{\|}}{\mathrm{C}}\mathrm{NHR} \longrightarrow \mathrm{CO_2} + \mathrm{H_2NR}$$

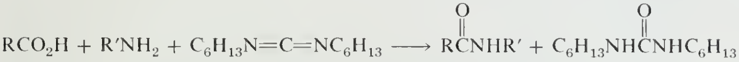
The most generally useful coupling reagent is dicyclohexylcarbodiimide (DCC).

a commercially available reagent that is prepared from cyclohexylamine and carbon disulfide by the route indicated.



(86%)
dicyclohexylcarbodiimide
(DCC)

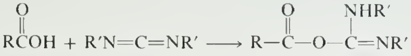
DCC is an effective catalyst for condensation of carboxylic acids with alcohols and amines. Thus, an equimolar mixture of a carboxylic acid, an amine, and DCC results in the corresponding amide and the highly insoluble N,N′-dicyclohexylurea.



$$\mathrm{RCO_2H + R'NH_2 + C_6H_{13}N{=}C{=}NC_6H_{13} \longrightarrow R\overset{\overset{O}{\|}}{C}NHR' + C_6H_{13}NH\overset{\overset{O}{\|}}{C}NHC_6H_{13}}$$

N,N′-dicyclohexylurea

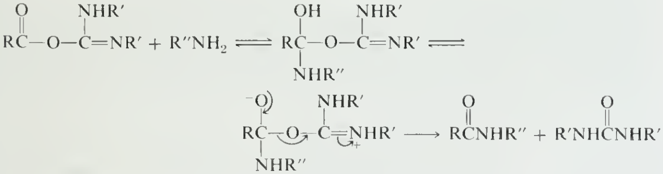
The probable mechanism for the DCC coupling reaction is outlined as follows. Addition of the carboxylic acid to the diimide gives the ester of isourea, an O-acylisourea.



$$\mathrm{R\overset{\overset{O}{\|}}{C}OH + R'N{=}C{=}NR' \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{NHR'}{|}}{C}{=}NR'}$$

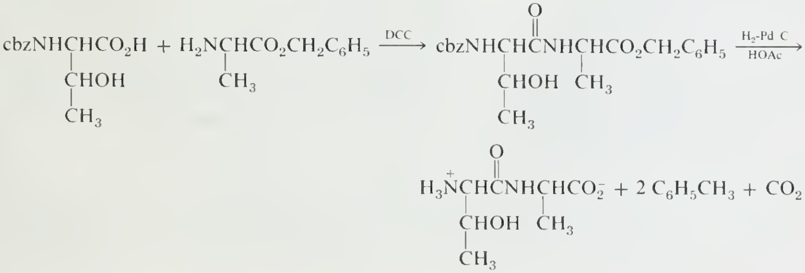
an O-acylisourea

The intermediate O-acylisourea is an activated carboxylic acid derivative similar in reactivity to an anhydride or an acyl halide. Nucleophilic substitution by the amine yields the amide and the dialkylurea.



$$\mathrm{R\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{NHR'}{|}}{C}{=}NR' + R''NH_2 \rightleftharpoons R\underset{\underset{NHR''}{|}}{\overset{\overset{OH}{|}}{C}}{-}O{-}\overset{\overset{NHR'}{|}}{C}{=}NR' \rightleftharpoons R\underset{\underset{NHR''}{|}}{\overset{\overset{^-O}{|}}{C}}{-}O{-}\overset{\overset{NHR'}{|}}{C}{=}\overset{+}{N}HR' \longrightarrow R\overset{\overset{O}{\|}}{C}NHR'' + R'NH\overset{\overset{O}{\|}}{C}NHR'}$$

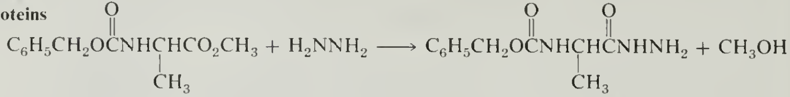
An example of the synthesis of a dipeptide utilizing this method is the synthesis of threonylalanine (thr · ala) from benzyloxycarbonylthreonine and alanine benzyl ester.



$$\mathrm{cbzNH\underset{\underset{\underset{CH_3}{|}}{\underset{CHOH}{|}}}{C}HCO_2H + H_2N\underset{\underset{CH_3}{|}}{C}HCO_2CH_2C_6H_5 \xrightarrow{DCC} cbzNH\underset{\underset{\underset{CH_3}{|}}{\underset{CHOH}{|}}}{C}H\overset{\overset{O}{\|}}{C}NH\underset{\underset{CH_3}{|}}{C}HCO_2CH_2C_6H_5 \xrightarrow[HOAc]{H_2\text{-}Pd\ C}}$$

$$\mathrm{H_3\overset{+}{N}\underset{\underset{\underset{CH_3}{|}}{\underset{CHOH}{|}}}{C}H\overset{\overset{O}{\|}}{C}NH\underset{\underset{CH_3}{|}}{C}HCO_2^- + 2\ C_6H_5CH_3 + CO_2}$$

Another widely used method for coupling the two protected amino acids involves activation of the carboxy group by conversion into an acyl azide. The N-protected amino acid ester is treated with hydrazine to give the acyl hydrazide.



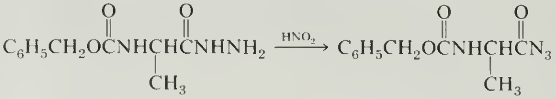
$$C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{CH_3}{\underset{|}{C}}HCO_2CH_3 + H_2NNH_2 \longrightarrow C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}NHNH_2 + CH_3OH$$

(80-90%)

benzyloxycarbonylalanine methyl ester

benzyloxycarbonylalanylhydrazide

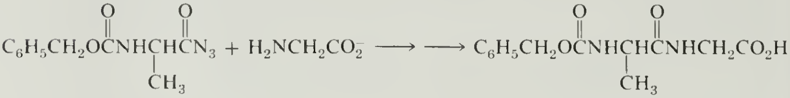
The hydrazide is treated with nitrous acid to give the acyl azide.



$$C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}NHNH_2 \xrightarrow{HNO_2} C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}N_3$$

benzyloxycarbonylalanyl azide

Acyl azides are less reactive than acyl halides and more reactive than esters. A typical nucleophilic substitution occurs when the acyl azide is treated with an amino acid in alkaline solution.

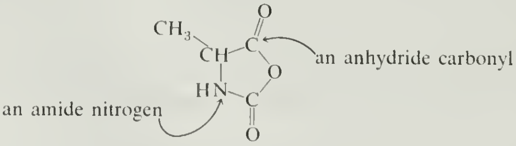


$$C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}N_3 + H_2NCH_2CO_2^- \longrightarrow \longrightarrow C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}NHCH_2CO_2H$$

benzyloxycarbonylalanylglycine
cbz·ala·gly

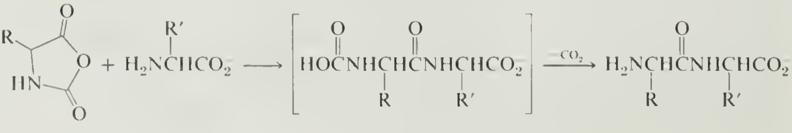
When using the acyl azide coupling, it is not necessary to employ a carboxy protecting group.

Another elegant method for peptide synthesis involves the use of amino acid N-carboxyanhydrides (**NCAs, or Leuchs' anhydrides**). The additional carbonyl group serves the dual function of protecting the nitrogen and activating the carbonyl.

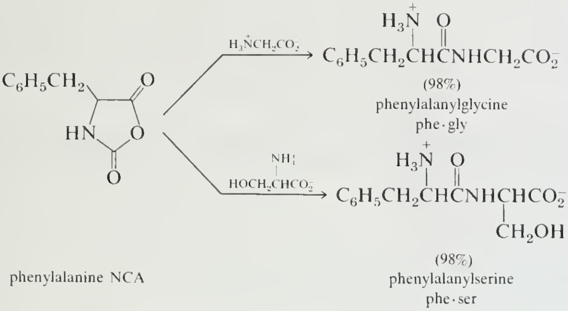


alanine NCA

When the NCA is slowly added to an aqueous solution of an amino acid at 0° and pH 10, an excellent yield of dipeptide is produced. The amino group of the amino acid undergoes a nucleophilic substitution reaction on the anhydride carbonyl group, yielding a carbamic acid, which decarboxylates as usual.



Examples of dipeptides prepared in this manner are


$H_3\overset{+}{N}CH_2CO_2^-$
$HOCH_2\overset{NH_3^+}{CH}CO_2^-$
(98%)
(98%)

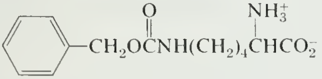
phenylalanine NCA

phenylalanylglycine
phe·gly

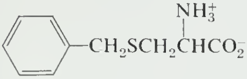
phenylalanylserine
phe·ser

The NCA method can also be used to prepare higher peptides, if a peptide, rather than an amino acid, is used in the coupling step. In fact, the conditions of the reaction must be carefully controlled to prevent further reaction of the initially formed peptide. The chief drawback of the NCA method is the fact that NCAs of all of the common amino acids are not available.

Thus far, we have discussed peptide synthesis only with amino acids containing no other reactive groups. When there is another functional group present in the molecule, it too must be protected until after the peptide has been formed. Typical protecting groups are benzyloxycarbonyl for the second amino group in lysine and benzyl for the sulfur in cysteine.



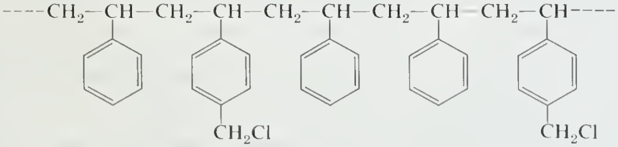
ε-benzyloxycarbonyllysine



S-benzylcysteine

Both protecting groups are removable by cleavage with anhydrous acids such as hydrogen bromide in acetic acid. The second carboxy group in aspartic acid or glutamic acid is usually protected as a methyl or benzyl ester.

A recent development that has revolutionized peptide synthesis is the **solid-phase technique,** introduced by R. B. Merrifield at Rockefeller University. In the Merrifield method, the peptide or protein is synthesized on the surface of an insoluble polymer. The polymer used is polystyrene (page 295) in which some of the benzene rings are substituted by —CH_2Cl groups. The polystyrene used is crosslinked with about 2% of divinylbenzenes. The particle sizes range from diameters of 20–70 μ.

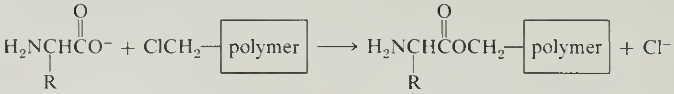


chloromethylated polystyrene

Actually, about one out of every 100 phenyl groups is chloromethylated.

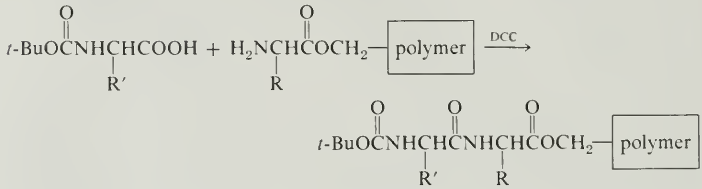
The C-terminal amino acid of the desired peptide is bound to the polymer by shaking an aqueous solution of the amino acid salt with the insoluble polymer.

The product is an amino acid ester in which the alkyl group is the polymer itself.



$$\mathrm{H_2N\underset{R}{CH}\overset{O}{\overset{\|}{C}}O^-} + \mathrm{ClCH_2}\text{—}\boxed{\text{polymer}} \longrightarrow \mathrm{H_2N\underset{R}{CH}\overset{O}{\overset{\|}{C}}OCH_2}\text{—}\boxed{\text{polymer}} + \mathrm{Cl^-}$$

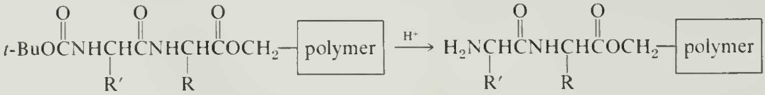
The polymer is filtered and added to a solution of an N-protected amino acid, with a coupling agent, and the heterogeneous mixture is shaken until coupling is complete.



$$t\text{-}\mathrm{BuO\overset{O}{\overset{\|}{C}}NH\underset{R'}{CH}COOH} + \mathrm{H_2N\underset{R}{CH}\overset{O}{\overset{\|}{C}}OCH_2}\text{—}\boxed{\text{polymer}} \xrightarrow{\text{DCC}}$$

$$t\text{-}\mathrm{BuO\overset{O}{\overset{\|}{C}}NH\underset{R'}{CH}\overset{O}{\overset{\|}{C}}NH\underset{R}{CH}\overset{O}{\overset{\|}{C}}OCH_2}\text{—}\boxed{\text{polymer}}$$

The polymer, now bound to an N-protected dipeptide, is again filtered and washed and a strong anhydrous acid, usually trifluoroacetic acid, is added to remove the protecting group.



$$t\text{-}\mathrm{BuO\overset{O}{\overset{\|}{C}}NH\underset{R'}{CH}\overset{O}{\overset{\|}{C}}NH\underset{R}{CH}\overset{O}{\overset{\|}{C}}OCH_2}\text{—}\boxed{\text{polymer}} \xrightarrow{\mathrm{H^+}} \mathrm{H_2N\underset{R'}{CH}\overset{O}{\overset{\|}{C}}NH\underset{R}{CH}\overset{O}{\overset{\|}{C}}OCH_2}\text{—}\boxed{\text{polymer}}$$

The process may now be repeated to add the third amino acid, and so on. At the end of the synthesis, the peptide is removed from the resin by treatment with anhydrous hydrogen fluoride. At the same time, all side-chain protecting groups are also removed. This final cleavage step does not affect the amide linkages of the peptide chain. The synthetic peptide is then purified by a suitable chromatographic method.

The great advantage of the solid phase technique is the ease of operation and the high overall yield that may be realized. Since the growing peptide chain is bound to the highly insoluble polystyrene resin, no mechanical losses are entailed in the intermediate isolation and purification stages. Furthermore, since the method involves the repetitive use of a small number of similar operations, the synthesis is easily automated. Almost all synthetic peptides are now made by the solid-phase technique.

The most impressive accomplishment to date using the method was Merrifield's synthesis of the enzyme bovine pancreatic ribonuclease, a protein having 124 amino acid units (Figure 28.6). The synthesis required 369 different chemical reactions, including coupling and various deprotection steps. A total of 11,931 operations of the automated peptide synthesis machine were entailed, including injection of reagents, filtrations, washings, and so on. The overall yield of synthetic protein, before cleavage from the resin, was 17%, corresponding to a yield of $>99\%$ for each step.

At the same time that the Merrifield synthesis was announced, another group,

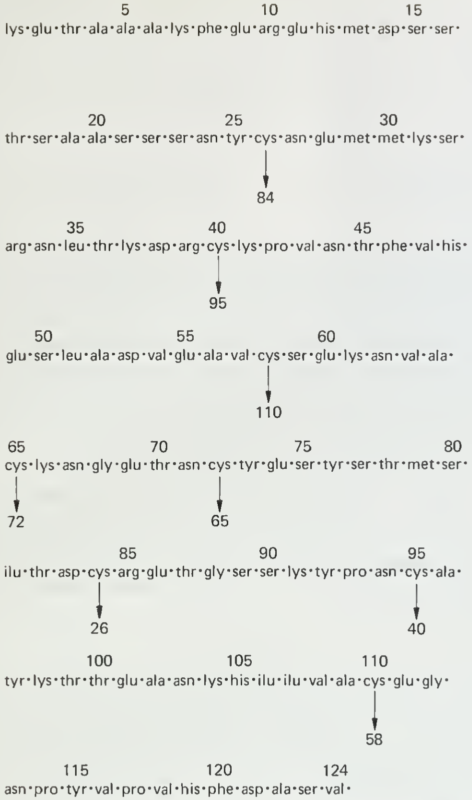
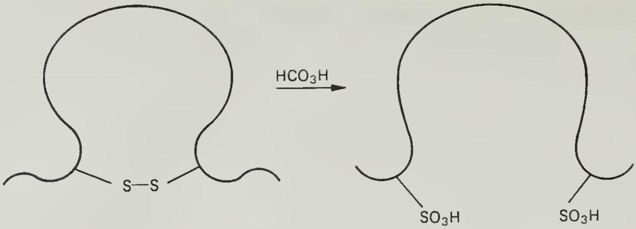

5 10 15
lys·glu·thr·ala·ala·ala·lys·phe·glu·arg·glu·his·met·asp·ser·ser·
20 25 30
thr·ser·ala·ala·ser·ser·ser·asn·tyr·cys·asn·glu·met·met·lys·ser·
84
35 40 45
arg·asn·leu·thr·lys·asp·arg·cys·lys·pro·val·asn·thr·phe·val·his·
95
50 55 60
glu·ser·leu·ala·asp·val·glu·ala·val·cys·ser·glu·lys·asn·val·ala·
110
65 70 75 80
cys·lys·asn·gly·glu·thr·asn·cys·tyr·glu·ser·tyr·ser·thr·met·ser·
72
65
85 90 95
ilu·thr·asp·cys·arg·glu·thr·gly·ser·ser·lys·tyr·pro·asn·cys·ala·
26
40
100 105 110
tyr·lys·thr·thr·glu·ala·asn·lys·his·ilu·ilu·val·ala·cys·glu·gly·
58
115 120 124
asn·pro·tyr·val·pro·val·his·phe·asp·ala·ser·val·

Figure 28.6 *Amino acid sequence of bovine pancreatic ribonuclease A. In the native protein, there are four disulfide loops, involving the cysteine units at positions 26, 40, 58, 65, 72, 84, 95, and 110. The disulfide bridges are indicated by arrows in the chart.*

at Merck and Company, also reported a synthesis of ribonuclease. The Merck synthesis was done by a classical approach in which various segments of the chain were synthesized and then coupled together.

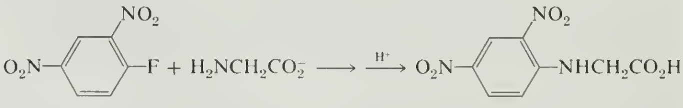
C. *Structure Determination*

1. **Amino Acid Analysis.** The first step in determining the structure of a polypeptide or protein is the cleavage of any disulfide bridges that may be present. This reaction is commonly done by oxidizing the substance with peroxyformic acid, which converts the two cysteine units into cysteic acid units. If the compound contains no disulfide bridges, this step is not necessary.



The next analytical step is to determine the total amino acid composition. The material is subjected to total hydrolysis by some suitable method, typically heating with 6 *N* HCl at 100–120° for 10–24 hr. The hydrolysate is then purified and analyzed by a chromatographic technique. The analytical method currently in use employs a commercial instrument called an **amino acid analyzer.** The mixture of amino acids is chromatographed on an ion exchange column, using an aqueous buffer solution as eluent. The effluent from the column is automatically mixed with ninhydrin solution and the presence of an amino acid is indicated by the typical violet color produced in the reaction (Section 28.5.C). The effluent is monitored at appropriate wavelengths with a visible spectrometer and the optical density is plotted by a recorder as a function of time. By comparing the chromatogram of an unknown mixture with that of a mixture of known composition, the analyst may arrive at a quantitative analysis of his mixture. The chromatogram determined for a standard mixture of amino acids is shown at the right in Figure 28.7. The left chromatogram curve is a chromatogram of hydrolyzed bradykinin (page 831).

2. IDENTIFICATION OF THE N-TERMINAL AMINO ACID. There are two methods available for identifying the amino acid unit that occupies the N-terminal position in the polypeptide chain. The first is called the **Sanger method.** The $—NH_2$ group in amino acids and peptides reacts with 2,4-dinitrofluorobenzene to form yellow 2,4-dinitrophenyl (DNP) derivatives. The reaction, illustrated for glycine, is an example of aromatic nucleophilic substitution and will be discussed in Section 30.3.A.



2,4-dinitrofluorobenzene

N-(2,4-dinitrophenyl)glycine
(yellow)

If the Sanger reaction is carried out on a peptide, the only α-amino group that undergoes the reaction is the free group on the N-terminal end. Total hydrolysis of the DNP labeled peptide then gives a mixture of amino acids, only one of which is labeled with the DNP function on the α-amino group. By knowing which amino acid bears the label, the investigator knows which amino acid is at the N-terminal end of the peptide.

The other technique for N-terminal analysis, which is actually more useful, is called the **Edman degradation.** In the Edman degradation, the peptide is allowed to react with phenylisothiocyanate, $C_6H_5N{=}C{=}S$. The terminal NH_2 group reacts to form the phenylthiocarbamoyl derivative of the peptide. The labeled peptide is then treated with anhydrous HCl in an organic solvent. Although these condi-

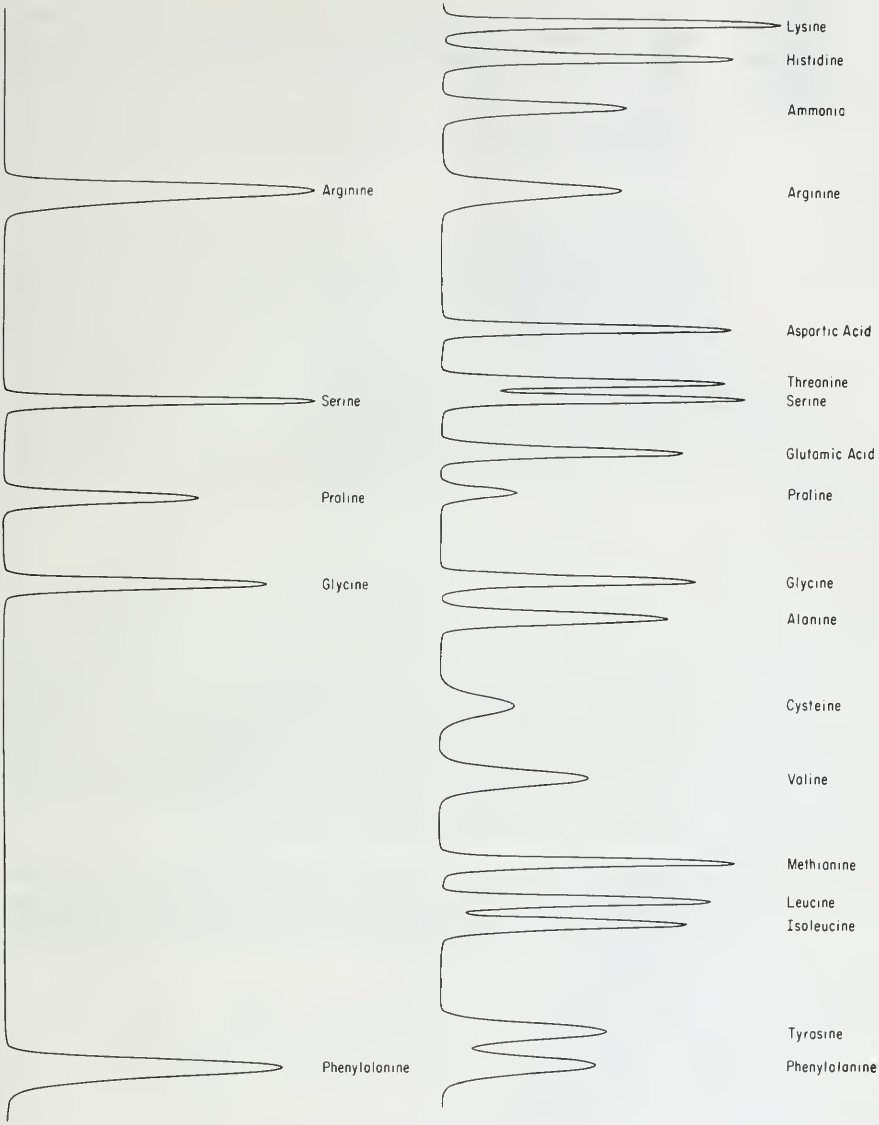
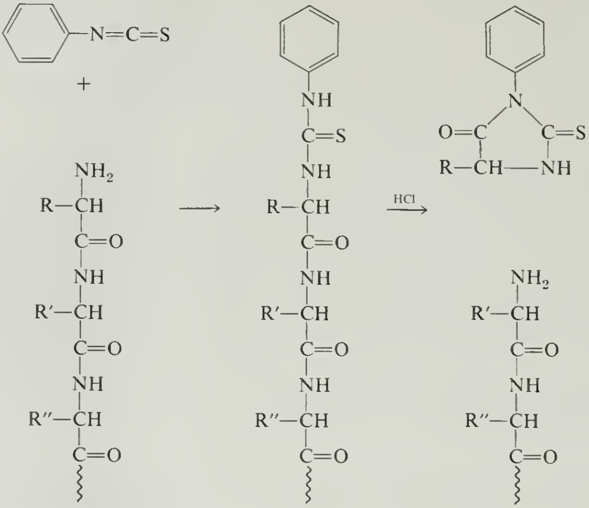


FIGURE 28.7 *Amino acid analyzer traces. The right curve is an equimolar mixture. The left curve is the analysis of a sample of hydrolyzed bradykinin.*

tions do not hydrolyze the amide linkages, the labeled amino acid undergoes a cyclization reaction, giving a phenylthiohydantoin. In the process, the end group also becomes separated from the remainder of the peptide chain.



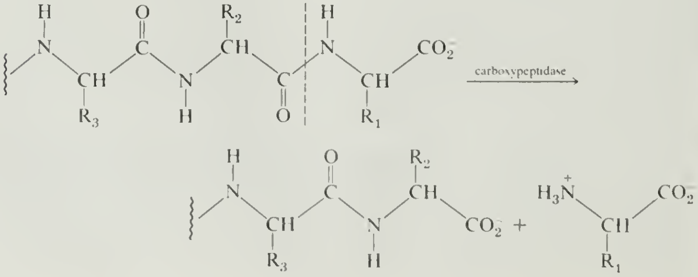
phenylisothiocyanate
+
peptide

phenylthiocarbamoyl-
peptide

phenylthiohydantoin
+
shorter peptide

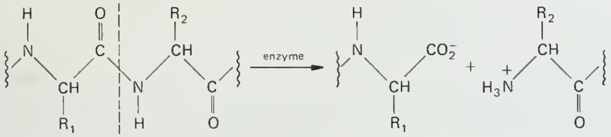
The substituted phenylthiohydantoin produced can be identified chromatographically by comparing it with known materials. Furthermore, the degraded peptide can be isolated and subjected to another cycle of the Edman degradation to identify the new N-terminal unit. The process has been automated and has been used to identify the first 60 amino acids in whale myoglobin, a protein that contains 153 amino acids in its chain. In practice, the repetitive degradation is usually not very reliable beyond about 15 cycles.

3. IDENTIFICATION OF THE C-TERMINAL AMINO ACID. The C-terminal amino acid may be identified by hydrolyzing with the enzyme **carboxypeptidase**, which specifically catalyzes the hydrolysis of the C-terminal amide link in a peptide or protein chain.



Thus, when the material is incubated with carboxypeptidase, the first free amino acid to appear in solution is the one that occupies the C-terminal position. Of course, once that amino acid has been removed from the chain, the enzyme continues to function and goes to work on the next residue, and so on. Eventually, the entire peptide or protein will be hydrolyzed to the constituent amino acids. By measuring the rate of appearance of amino acids in the hydrolysate, the C-terminal unit may be identified. In favorable cases, the first three or four units may be identified in this way.

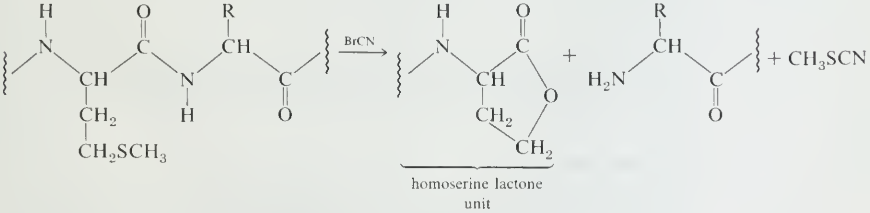
4. FRAGMENTATION OF THE PEPTIDE CHAIN. Several methods are available that may be used to fragment a polypeptide or protein chain into smaller peptides. The most useful method is enzymatic hydrolysis. There are several enzymes available, called **proteolases,** that catalyze hydrolysis of the peptide chain, usually at specific positions. For example, the enzyme **trypsin,** which occurs in the intestines of mammals, causes cleavage of peptide bonds only when the carbonyl group is part of a lysine or arginine unit. In a similar way, **chymotrypsin,** another intestinal enzyme, catalyzes hydrolysis of phenylalanine, tryptophan, and tyrosine positions. **Pepsin,** a gastric proteolase, is much less specific, causing rupture of the chain wherever there is phenylalanine, tryptophan, tyrosine, leucine, aspartic acid, or glutamic acid (Figure 28.8). Abnormal cleavage is sometimes observed.



Enzyme	*R₁*
trypsin	lys, arg
chymotrypsin	phe, trp, tyr
pepsin	phe, trp, tyr, leu, asp, glu

FIGURE 28.8 *Specificity of proteolases.*

Another useful method for selective cleavage of polypeptide chains employs **cyanogen bromide,** BrCN. This reagent cleaves the chain only at the carbonyl group of methionine units; the methionine is converted into a C-terminal homoserine lactone unit.



Partial degradation of the polypeptide chain, using one of the aforementioned methods, is a crucial step in determining the proper amino acid sequence of the molecule. Usually, the purified polypeptide or protein is first incubated with trypsin, the most selective proteolase. The resulting mixture of peptide fragments is chromatographed and the pure fragments are isolated. The peptides produced will usually contain from 2 to about 20 units. If the polypeptide chain is very long and if it contains relatively few lysine and arginine units, much larger fragments may be produced. The purified fragments are then analyzed for total amino acid content and subjected to repetitive Edman degradation to determine their structures.

The process is then repeated using a different cleavage method, usually cyanogen bromide. This second set of peptide fragments is then analyzed and sequenced. The various peptide blocks from the two degradation methods are then fitted together to produce a structure that unequivocally satisfies both sets of data.

As an example of the reasoning employed, consider a hypothetical eicosapeptide (20 amino acid units) having the amino acid composition (gly$_2$, ala$_4$, leu$_4$, phe$_3$, trp, lys$_2$, met$_2$, ser, arg). End group analysis shows that the polypeptide has alanine at the N-terminus (Sanger method) and phenylalanine at the C-terminus (carboxypeptidase). The material is hydrolyzed with trypsin to give four fragments, a tripeptide, two pentapeptides, and a heptapeptide. The four peptide fragments are each sequenced by repetitive Edman degradation and found to have the following structures.

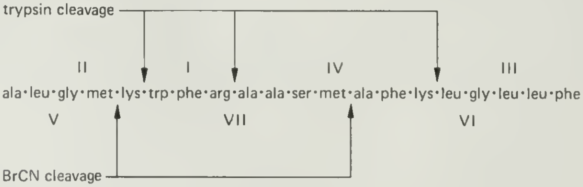
I trp · phe · arg
II ala · leu · gly · met · lys
III leu · gly · leu · leu · phe
IV ala · ala · ser · met · ala · phe · lys

At this point, the investigator knows that fragment III must correspond to the last five amino acids in the chain because trypsin does not cleave a chain at a phenylalanine carbonyl. Furthermore, fragment II or IV must correspond to the N-terminal end, but it is not possible with this information alone to write a unique complete sequence.

The intact polypeptide is then cleaved with cyanogen bromide and the fragments are isolated, purified, and sequenced as before. Three fragments are produced, having the structures

V ala · leu · gly · met
VI ala · phe · lys · leu · gly · leu · leu · phe
VII lys · trp · phe · arg · ala · ala · ser · met

The four fragments in the first degradation and the three fragments in the second are then ordered in an overlapping way to arrive at an unambiguous structure:


trypsin cleavage
II
I
IV
III
ala·leu·gly·met·lys·trp·phe·arg·ala·ala·ser·met·ala·phe·lys·leu·gly·leu·leu·phe
V
VII
VI
BrCN cleavage

In actual operation, the process of identifying the complete sequence of a complicated polypeptide or protein is rarely as simple as this example, and the actual process is usually tedious and time consuming. It often happens that almost the entire sequence is elucidated, but the exact positions of a few amino acids remain doubtful. The general process is still being improved and routine sequencing will undoubtedly become less tedious and more efficient during the next few years.

The first major structure determination that was accomplished was that of insulin (page 832), by Sanger in 1953. The next significant accomplishment in this area was the sequencing of adrenocorticotrophin (39 amino acid units), the hormone produced in the anterior pituitary gland which stimulates the adrenal cortex.

5 10
ser · tyr · ser · met · glu · his · phe · arg · trp · gly · lys · pro · val ·

15 20 25
gly · lys · lys · arg · arg · pro · val · lys · val · tyr · pro · asp · ala ·

30 35 39
gly · glu · asp · glu · ser · ala · glu · ala · phe · pro · leu · glu · phe

human adrenocorticotrophin

Using techniques such as these, such large proteins as bovine chymotrypsinogen (245 amino acid units) and glyceraldehyde 3-phosphate dehydrogenase (333 amino acid units) have been sequenced.

28.7
Proteins

A. *Molecular Shape*

Proteins serve two important biological functions. On the one hand, they serve as structural material. The structural proteins tend to be **fibrous** in nature. That is, the long polypeptide chains are lined up more or less parallel to each other and are bonded one to another by hydrogen bonds. Depending on the actual three-dimensional structure of the individual protein molecule and its interaction with other similar molecules, a variety of structural forms may result. Examples are the protective tissues such as hair, skin, nails, and claws (α- and β-keratins), connective tissues such as tendon (collagen), or the contractile material of muscle (myosin). Fibrous proteins are usually insoluble in water.

The other important function of proteins is their role as biological regulators. They are responsible for regulating the speed of biochemical reactions and the transport of various materials throughout the organisms. The catalytic proteins (**enzymes**) and transport proteins tend to be **globular** in nature. The polypeptide chain is folded around itself in such a way as to give the entire molecule a rounded shape. Each globular protein has its own characteristic geometry, which is a result of interactions between different sites on the chain. The intrachain interactions may be of three types: disulfide bridging, hydrogen bonding, or van der Waals attraction.

The globular proteins are water soluble. Sometimes each molecule of a globular protein consists of a single long polypeptide chain twisted about and folded back upon itself. In other cases, the molecule is composed of several subunits. Each subunit is a single polypeptide chain that has adopted its own unique three-dimensional geometry. Several of the subunits are then bonded together by secondary forces (hydrogen bonding and van der Waals attraction) to give the total globular unit.

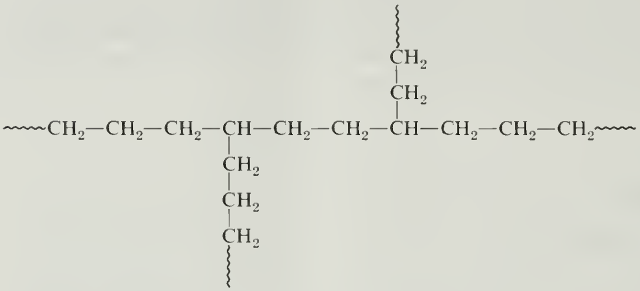
Globular proteins often carry a nonprotein molecule (the **prosthetic** group) as a part of their structure. The prosthetic group may be covalently bonded to the polypeptide chain, or it may be held in place by other forces.

B. *Factors Which Influence the Molecular Shape*

As we saw in the previous section, proteins are amino acid polymers containing more than about 50 individual units per chain. A polymer may be **linear** or **branched** (Section 12.6.F).

$$\sim\sim CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2\sim\sim$$

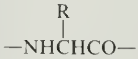
linear polyethylene



$$\sim\sim CH_2-CH_2-CH_2-\underset{\begin{array}{c}|\\CH_2\\|\\CH_2\\|\\CH_2\\\wr\end{array}}{CH}-CH_2-CH_2-\overset{\begin{array}{c}\wr\\CH_2\\|\\CH_2\\|\end{array}}{CH}-CH_2-CH_2-CH_2\sim\sim$$

branched polyethylene

Proteins are linear polymers. The backbone of the polymer chain is the repeating unit



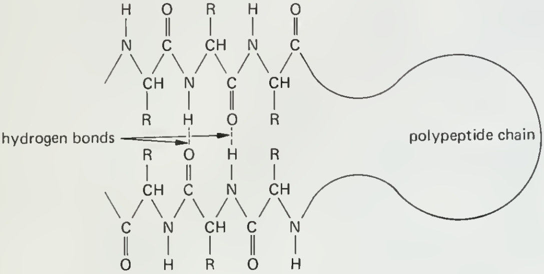
$$-NH\overset{\begin{array}{c}R\\|\end{array}}{C}HCO-$$

In addition to the rigidity imparted to the polymer chain by the restricted rotation about the amide bond (Sections 18.1 and 28.6), the three-dimensional structure of the macromolecule is determined by two factors:

1. SECONDARY INTER- OR INTRACHAIN BONDING. Disulfide bridges that occur between cysteine units in separate chains lead to a type of cross linking. An example is seen in insulin (Figure 28.5), in which the A and B chains are bonded together by two disulfide links. When the two cysteine units are in the same chain, as in oxytocin, in the A chain of insulin (Figure 28.5), or in ribonuclease (Figure 28.6), disulfide bridging results in loops in the chain. The result is that the polypeptide chain is forced to coil back on itself.

Hydrogen bonding is another type of secondary bonding that may occur between two different chains or between different regions of the same chain.

Although hydrogen bonds are inherently weak (about 5 kcal mol^{-1} per hydrogen bond), a polypeptide chain contains many C=O and N—H groups that may engage in such bonding. The total amount of bonding that results from many small interactions is substantial and plays an important role in the actual shape or conformation of the molecule. Reciprocal hydrogen bonding may occur between the C=O and N—H groups of different chains and thus bind them together. Intrachain hydrogen bonding causes the chain to fold back on itself in some specific fashion.



2. ELECTRONIC AND STERIC PROPERTIES OF THE SIDE CHAIN GROUPS. Some of the side chain groups that project from the polypeptide backbone are nonpolar (Figure 28.9). Such nonpolar, or **hydrophobic,** groups tend to attract each other by van der Waals forces. In the globular proteins, they are more likely to be found in the interior of the molecule, rather than on the surface where the environment is largely aqueous.

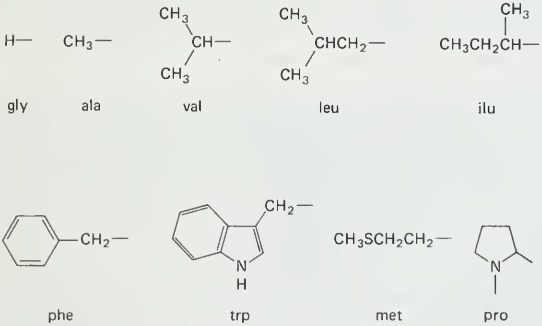


FIGURE 28.9 *Nonpolar side chains.*

Other side chains are polar and profit from hydrogen bonding to water molecules. Since the globular proteins exist mainly in aqueous solutions, the polar side chains prefer to be on the outer surface of the molecule. The polar, or **hydrophilic,** side chains are listed in Figure 28.10. Some are neutral, and others bear either a negative or a positive charge at neutral pH.

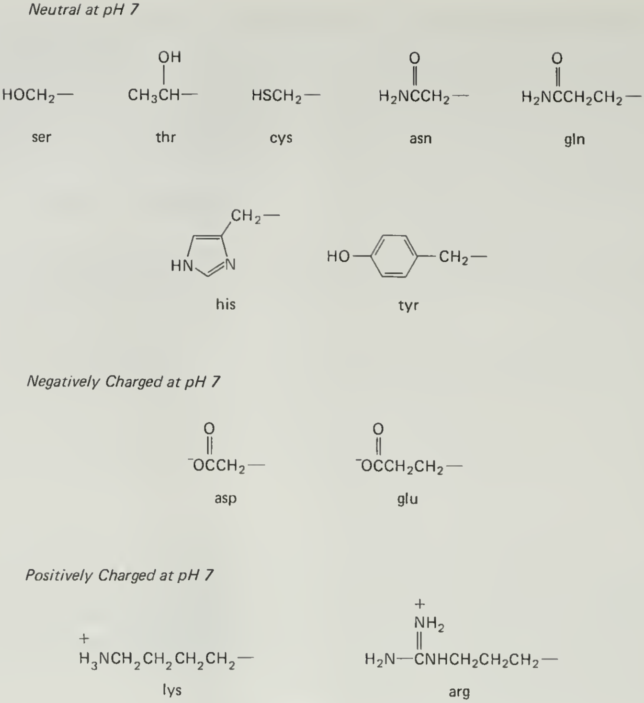

Neutral at pH 7
HOCH2—
ser
OH
CH3CH—
thr
HSCH2—
cys
O
H2NCCH2—
asn
O
H2NCCH2CH2—
gln
CH2—
HN
N
his
HO
CH2—
tyr
Negatively Charged at pH 7
O
⁻OCCH2—
asp
O
⁻OCCH2CH2—
glu
Positively Charged at pH 7
+
H3NCH2CH2CH2CH2—
lys
+
NH2
H2N—CNHCH2CH2CH2—
arg

FIGURE 28.10 *Polar side chains.*

C. *Structure of the Fibrous Proteins*

The most important type of conformation found in fibrous proteins is the α-helix. In this structure, the polypeptide chain coils about itself in a spiral manner. The spiral or helix is held together by intrachain hydrogen bonding. The α-helix is "right-handed" and has a pitch of 5.4 Å or 3.6 amino acid units (Figure 28.11). Although a right-handed α-helix can form from either D- or L-amino acids (but not from DL), the right-handed version is more stable with the natural L-amino acids. A dramatic demonstration of the α-helix is shown by the stereo representation of polyalanine in Figure 28.12.

Not all polypeptide chains can form a stable α-helix. The stability of the coil is governed by the nature of the side chain groups and their sequence along the chain. Polyalanine, where the side chains are small and uncharged, forms a stable α-helix. However, polylysine does not. At pH 7, the terminal amino groups in the lysine side chains are all protonated. Electrostatic repulsion between the neighboring ammonium groups disrupts the regular coil and forces polylysine to adopt a **random coil** conformation. At pH 12, the lysine amino groups are uncharged and the material spontaneously adopts the α-helical structure. In a similar way, polyglutamic acid exists as a random coil at pH 7, where the terminal carboxy groups are ionized, and as an α-helix at pH 2, where they are uncharged.

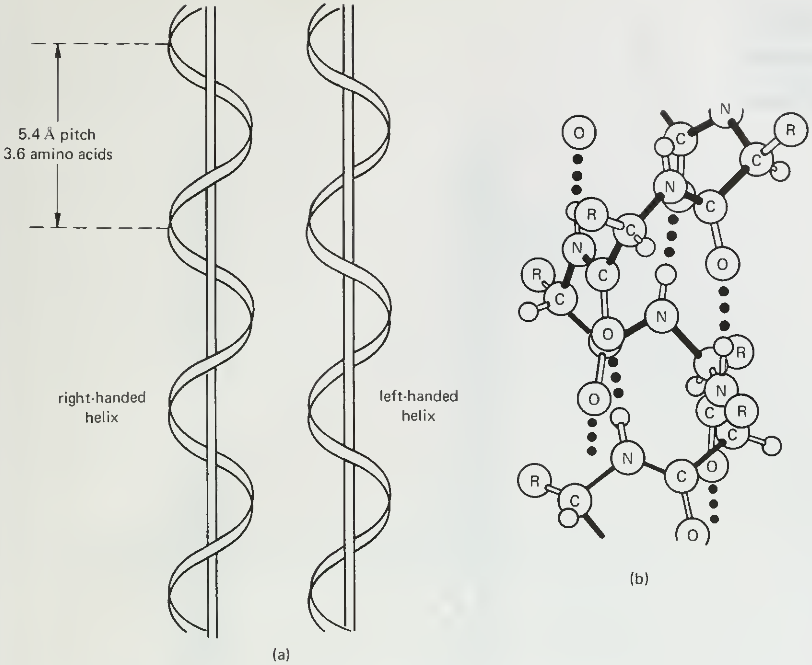


Figure 28.11 (a) *Right-handed and left-handed helix. Note that ordinary screws are right-handed helices.* (b) *Diagram of a peptide α-helix. [Adapted with permission from S. J. Baum:* Introduction to Organic and Biological Chemistry. *The Macmillan Company, 1970.]*

Proline is a particularly interesting case. Since the α-amino group in proline is part of a five-membered ring, rotation about the C—N bond is impossible. Furthermore, the amide nitrogen in polyproline has no hydrogens and intrachain hydrogen bonding is not possible. Wherever proline occurs in a polypeptide chain, the α-helix is disrupted and a "kink" or "bend" results (Figure 28.13).

In some cases, such as the keratins of hair and wool, several α-helices coil about one another to produce a **super helix.** In other cases, the helices are lined up parallel to one another and are held together by intercoil hydrogen bonding.

Another type of conformation found in the fibrous proteins is the β or **pleated sheet** structure of β-keratin (silk). In the β structure, the polypeptide chains are extended in a "linear" or zig-zag arrangement. Neighboring chains are bonded together by reciprocal interchain hydrogen bonding. The result is a structure resembling a pleated sheet (Figure 28.14). Side chain groups extend alternately above and below the general plane of the sheet. The pleated sheet structure results in the side chain groups being fairly close together. For this reason, side chains that are bulky or have like charges disrupt the arrangement. In the β-keratin of silk fibroin, 86% of the amino acid residues are glycine, alanine, and serine, all of which have small side chains.

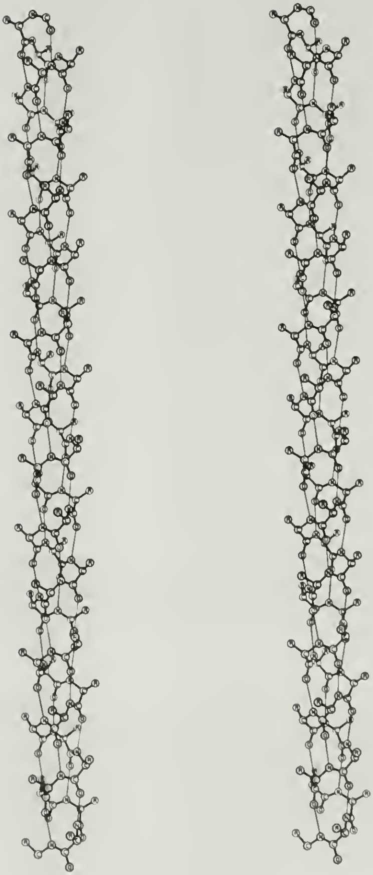
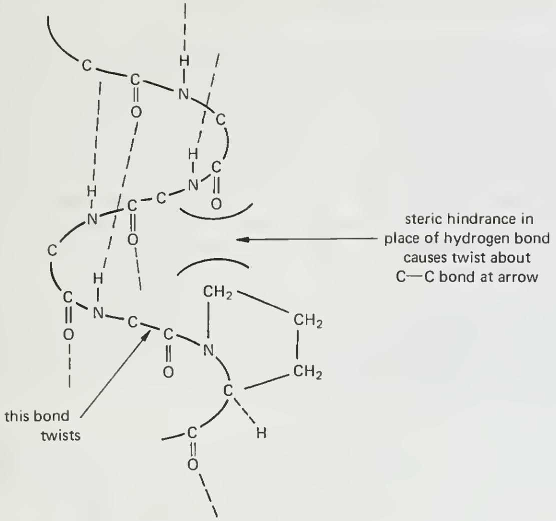


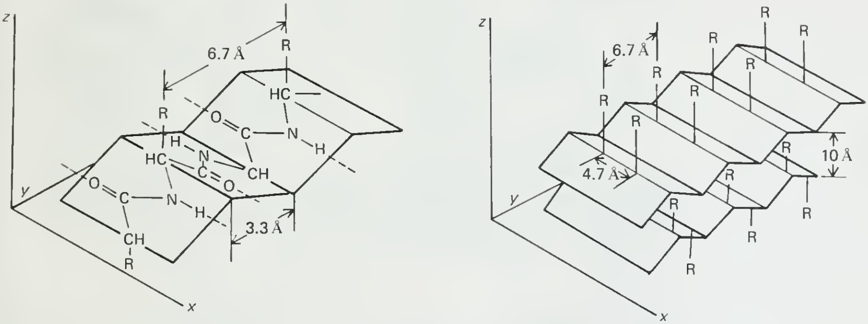
FIGURE 28.12 *Stereo representation of polyalanine. [Courtesy of C.K. Johnson, Oak Ridge National Laboratory.]*


C
C
O
H
N
C
H
C
N
O
H
N
C
C
O
C
H
C
N
C
C
O
N
CH2
CH2
CH2
C
H
C
O
O

steric hindrance in place of hydrogen bond causes twist about C—C bond at arrow

this bond twists

FIGURE 28.13 *Showing the origin of a kink in a α-helix at proline. The proline unit in a peptide chain has no* N—H *for hydrogen bonding.*


z
y
x
6.7 Å
R
HC
O
C
N
H
R
H
HC
N
C
O
CH
O
C
N
H
CH
R
3.3 Å
z
y
x
6.7 Å
R
4.7 Å
10 Å

extended polypeptide chain

array of chains to give pleated sheets

FIGURE 28.14 *Schematic diagrams of pleated-sheet structure of polypeptides. The peptide bonds lie in the plane of the pleated sheet; the side chains lie above and below the sheet alternately. The polypeptide chains are held together by interchain hydrogen bonds, shown as dotted lines. [Adapted from T. P. Bennett,* Graphic Biochemistry, *Vol 1. Macmillan Publishing Co.: New York, 1968.]*

D. *Structure of the Globular Proteins*

Globular proteins are designed to be soluble in the aqueous body fluids. They also must have a unique structure that creates an **active site** where the catalytic or transport function of the protein is carried out. The specific coiling that produces the proper geometry of the protein results from a delicate interplay of all the forces we have discussed up until now. Some folding is imposed by interchain disulfide bridges. The molecule tends to orient itself so that the nonpolar side chains lie inside the bulk of the structure where they attract each other by van der Waals forces. The polar side chains tend to be on the surface of the molecule where they can hydrogen bond to the solvent molecules and confer the necessary water solubility. Further coiling and compacting of the structure results from interchain hydrogen bonds between the amide linkages inside the bulk of the molecule. Some segments of the polypeptide chain may have the typical α-helical structure and others may be random coil. In other cases, the chain may fold back on itself in the β or pleated sheet fashion. A schematic representation of a globular protein is shown in Figure 28.15.

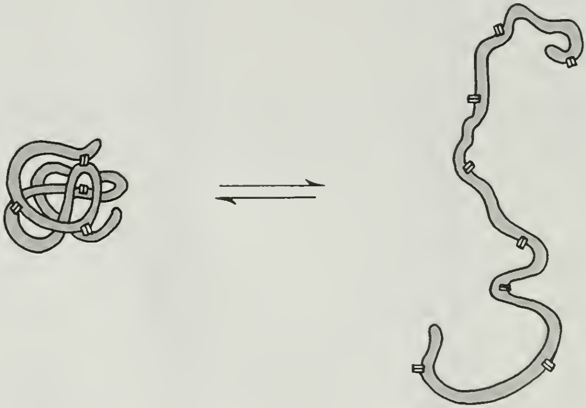


Figure 28.15 *Schematic diagram of a globular protein with intrachain bonds (hydrogen bonds, van der Waals forces, and so on), showing reversible denaturation to random coil chain. [Adapted with permission from S. J. Baum:* Introduction to Organic and Biological Chemistry. *The Macmillan Company, 1970.]*

If the protein contains a prosthetic group, it will be imbedded at some point within the overall three-dimensional structure of the protein, either covalently bonded to the polypeptide chain or simply held by secondary forces. An example of a prosthetic group is heme, which is found in hemoglobin and myoglobin (Figure 28.16).

In these proteins, both of which are oxygen carriers, myoglobin in muscle and hemoglobin in the blood stream, the function of the prosthetic group is to bind an oxygen molecule. In both cases, the polypeptide chain folds in such a way as to leave a hydrophobic "pocket" into which the heme just fits. The heme pocket is equipped with a histidine situated in such a way that its imidazole nitrogen can act as a fifth ligand for the ferrous ion in the center of the heme molecule.

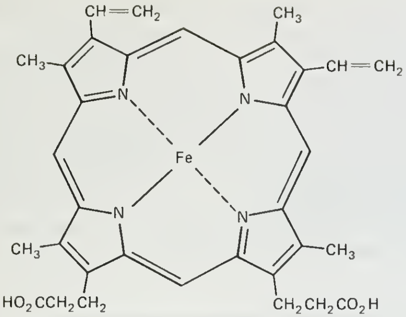


FIGURE 28.16 *Hemin, the prosthetic group of hemoglobin and myoglobin.*

The prosthetic group is further held in its pocket by hydrogen bonding between the two propionic acid side chains and other appropriate side chains within the pocket.

The stereo representation of myoglobin in Figure 28.17 shows only the backbone of the polypeptide chain and the heme; substituent groups have been deleted for clarity. Note how the globular protein coils up on itself. There are several α-helical regions in the chain. An extensive one is seen at the top of the molecule and is viewed almost end-on in this representation. The imidazole "fifth ligand" (not shown) is just above the heme.

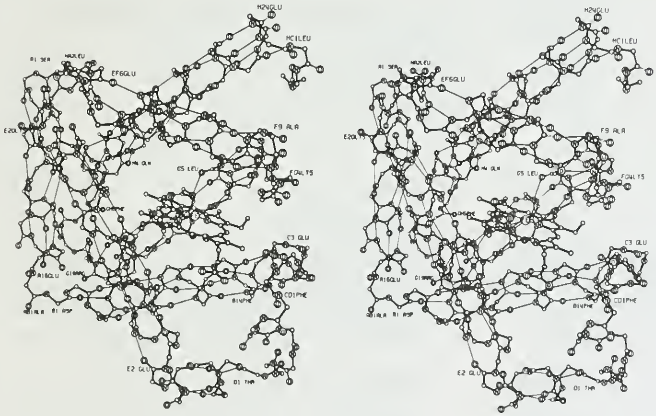


FIGURE 28.17 *Stereo representation of myoglobin* (*side chain substituents deleted*). [*Courtesy of C. K. Johnson, Oak Ridge National Laboratory.*]

Under proper conditions, the delicate three-dimensional structure of globular proteins may be disrupted. This process is called **denaturation.** Denaturation commonly occurs when the protein is subjected to extremes in temperature or pH. It is usually attended by a dramatic decrease in the water solubility of the protein. An example is the coagulation that results when skim milk is heated or acidified (denaturation of lactalbumin). A similar process is involved in the hardening of the white and the yolk of an egg upon heating.

Until fairly recently, it was believed that denaturation was an irreversible process. It now appears, however, that in some cases the process is reversible. The reverse process is called **renaturation.** Many cases are now known in which a denatured protein reverts to its natural folded geometry when the pH and temperature are adjusted back to the point where the native protein is stable. Thus, the three-dimensional structure of a protein seems to be a natural consequence of the specific amino acid sequence in its polypeptide chain; that is, the unique conformation of each protein is simply the most stable structure that molecule can have under biological conditions.

E. *Biological Function of Proteins—An Overview*

Although a complete discussion of the biological function of proteins is beyond the scope of this book, we shall give a brief tabular summary of the topic here. As discussed previously, one important function is structural. Some examples of structural proteins are listed in Table 28.5.

The regulatory proteins serve an immense variety of purposes. A few examples are illustrated in Table 28.6.

TABLE 28.5
Structural Proteins

Example	Function
α-keratin	structural component of skin, hair, feathers, nails
collagen	connective tissues, tendon, bone, cartilage
fibroin	silk of spider webs, cocoons
sclerolin	exoskeletons of insects
myosin	stationary component of muscle
actin	contractile component of muscle

TABLE 28.6
Regulatory Proteins

Example	Type	Function
carboxypeptidase	enzyme	catalyzes hydrolysis of polypeptide chains
trypsin	enzyme	catalyzes hydrolysis of polypeptide chains
hemoglobin	transport	carries oxygen in the bloodstream
myoglobin	transport	carries oxygen in muscles
cytochrome C	transport	carries electrons
ovalbumin	storage	food storage in egg white
casein	storage	milk protein
antibodies	protective	form insoluble complexes with foreign substances in the bloodstream
insulin	hormone	regulates the metabolism of glucose

PROBLEMS

1. Commit to memory the names, structures, and abbreviations of the 20 common amino acids in Table 28.1.

2. For each of the following compounds write the structure of the principal ionic species present in aqueous solution at pH 2, 7, and 12.
   (a) isoleucine
   (b) aspartic acid
   (c) lysine
   (d) glycylglycine (gly · gly)
   (e) lysylglycine (lys · gly)
   (f) alanylaspartylvaline (ala · asp · val)

3. Show how the isoelectric point of an amino acid can be computed from pK_1 and pK_2.

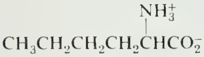
4. The pK_as for β-alanine and α-amino-*n*-butyric acid are shown below. Compare these values with the pK_as for the α-amino acids in Table 28.2 and explain the differences.

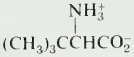
$H_3\overset{+}{N}CH_2CH_2CO_2^-$	$H_3\overset{+}{N}CH_2CH_2CH_2CO_2^-$
β-alanine	γ-aminobutyric acid
pK_1 = 3.55	pK_1 = 4.03
pK_2 = 10.24	pK_2 = 10.56

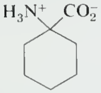
What are the isoelectric points for these two amino acids?

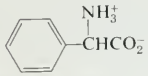
5. The dipeptide gly · asp has three known pK_a values, 2.81, 4.45, and 8.60. Associate each pK_a with the appropriate functional group in the structure of this peptide. Give a practical synthesis of this peptide starting with the amino acids.

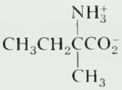
6. Propose syntheses for the following amino acids.

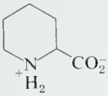
(a) 
$CH_3CH_2CH_2CH_2\overset{\overset{NH_3^+}{|}}{C}HCO_2^-$

(c) 
$(CH_3)_3C\overset{\overset{NH_3^+}{|}}{C}HCO_2^-$

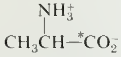
(e) 

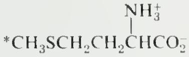
(b) 

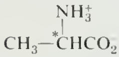
(d) 
$CH_3CH_2\underset{\underset{CH_3}{|}}{\overset{\overset{NH_3^+}{|}}{C}}CO_2^-$

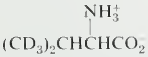
(f) 

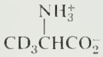
7. The following isotopically labeled amino acids are desired for biochemical research. Show how each may be prepared. The only acceptable sources of ^{14}C are $Ba^{14}CO_3$ and $Na^{14}CN$. The ^{14}C-labeled atom is marked with an asterisk in each case. Deuterated compounds may be prepared using D_2O, $LiAlD_4$, or D_2.

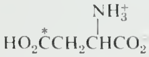
(a) 
$CH_3\overset{\overset{NH_3^+}{|}}{C}H\text{—}{}^*CO_2^-$

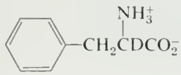
(e) 
${}^*CH_3SCH_2CH_2\overset{\overset{NH_3^+}{|}}{C}HCO_2^-$

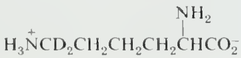
(b) 
$CH_3\text{—}\overset{\overset{NH_3^+}{|}}{\overset{*}{C}}HCO_2$

(f) 
$(CD_3)_2CH\overset{\overset{NH_3^+}{|}}{C}HCO_2$

(c) 
$CD_3\overset{\overset{NH_3^+}{|}}{C}HCO_2^-$

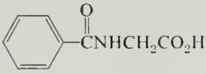
(g) 
$HO_2\overset{*}{C}CH_2\overset{\overset{NH_3^+}{|}}{C}HCO_2$

(d) 

(h) 
$H_3\overset{+}{N}CD_2CH_2CH_2CH_2\overset{\overset{NH_2}{|}}{C}HCO_2^-$

8. Glycine undergoes acid-catalyzed esterification more slowly than does propionic acid. Explain.

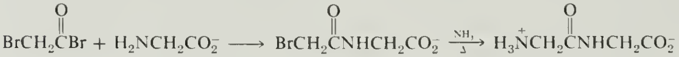
9. Explain why the benzoyl group cannot be used as a N-protecting group for peptide synthesis, for example N-benzoylglycine.



N-benzoylglycine

10. In 1914, Maillard reported a study of the polymerization of glycine. The amino acid was heated in glyerol solution. The main product of the reaction was found to be 2,5-diketopiperazine. A polypeptide fraction was produced in low yield. The predominant peptides in this fraction were found to be the even peptides, tetraglycine and hexaglycine. Explain.

11. In 1903, Emil Fischer introduced a rational method for the stepwise construction of peptides. The process, known as the α-haloacyl halide method, is outlined below in a synthesis of glycylglycine.



$$\mathrm{BrCH_2\overset{O}{\overset{\|}{C}}Br + H_2NCH_2CO_2^- \longrightarrow BrCH_2\overset{O}{\overset{\|}{C}}NHCH_2CO_2^- \xrightarrow[\Delta]{NH_3} H_3\overset{+}{N}CH_2\overset{O}{\overset{\|}{C}}NHCH_2CO_2^-}$$

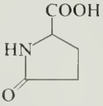
(a) Show how the α-haloacyl halide method can be used to synthesize glycyl-L-alanine and glycylglycyl-L-alanine.
(b) Which α-haloacyl halides would be used to add alanyl or valyl units?
(c) If the method is applied to L-alanine using the acyl halides in part (b), what will the products be?
(d) What would be the chief problem in applying the α-haloacyl halide method to a fairly complex polypeptide like ala · val · phe · ala · ala?

12. Write out all of the steps in a rational synthesis of the pentapeptide ala · val · phe · ala · ala. For N-protecting groups use the benzyloxycarbonyl group and for coupling use DCC.

13. Propose a synthesis for the pentapeptide in problem 12 using N-carboxy anhydrides. Assume that the necessary anhydrides are commercially available.

14. Propose a synthesis of the decapaptide ala · val · phe · ala · ala · ala · val · phe · ala · ala.

15. Pyroglutamic acid, pyroglu, is a cyclic lactam obtained by heating glutamic acid.



pyroglu

This derivative of proline occurs in an important tripeptide, thyrotropin-releasing hormone, TRH, which occurs in brain tissue. It also occurs in the anterior lobe of the pituitary gland where it stimulates the secretion of several other hormones. TRH has been shown to be pyroglutamyl-histidyl-prolineamide. Write out the structure of TRH. A sensitive assay method has been developed that makes use of synthetic hormone. Propose a synthesis of TRH from pyroglutamic acid and other required reagents.

16. The cyanogen bromide method for cleavage of peptide chains involves reaction of the nucleophilic sulfur of a methionine unit with the carbon of BrCN. Write out the complete reaction mechanism.

17. What polypeptide fragments will be produced when ribonuclease A (Figure 28.6) is partially hydrolyzed with (a) trypsin, (b) chymotrypsin, or (c) cyanogen bromide. Assume that the disulfide bonds are cleaved prior to hydrolysis.

18. Gastrins are heptadecapeptide (17 amino acid units) hormones that stimulate the secretion of gastric acid in the stomach of mammals. Feline gastrin has the empirical amino acid composition (ala$_2$asp$_1$gly$_2$glu$_5$leu$_1$met$_1$phe$_1$pro$_1$trp$_2$tyr$_1$). The peptide was digested with chymotrypsin and four peptide fragments were isolated. The four fragments were sequenced and found to be:

I glu · gly · pro · trp
II gly · trp
III met · asp · phe
IV leu · glu · glu · glu · glu · ala · ala · tyr

End group analysis revealed that the N-terminal unit is glu and the C-terminal unit is phe. What two structures for feline gastrin are compatible with the foregoing evidence?

19. Porcine pancreatic secretory trypsin inhibitor I is a protein containing 56 amino acid units. Acidic hydrolysis, followed by amino acid analysis, gave the following empirical composition: asp$_4$thr$_6$ser$_6$glu$_7$pro$_5$gly$_4$ala$_1$val$_4$cys$_6$ile$_3$leu$_2$tyr$_2$lys$_4$arg$_2$. (*Note:* Complete hydrolysis does not distinguish gln from glu or asn from asp). After cleavage of disulfide bridges, the protein was digested with trypsin. Nine fragments were isolated and purified by chromatography. The nine fragments were each sequenced by repetitive Edman degradation. Eight of the fragments were found to be

T-1 lys
T-2 arg
T-3 ser · gly · pro · cys
T-4 thr · ser · pro · gln · arg
T-5 gln · thr · pro · val · leu · ile · gln · lys
T-6 ser · asn · glu · cys · val · leu · cys · ser · glu · asn · lys
T-7 ile · tyr · asn · pro · val · cys · gly · thr · asp · gly · ile · thr · tyr
T-8 glu · ala · thr · cys · thr · ser · glu · val · ser · gly · cys · pro · lys

The ninth fragment contained 24 amino acid units and had the empirical composition asp$_4$thr$_2$ser$_2$glu$_2$pro$_1$gly$_2$val$_2$cys$_3$ile$_2$leu$_1$tyr$_2$lys$_1$. Seven cycles of Edman degradation showed that the N-terminal end of fragment T-9 had the composition

T-9 ile · tyr · asn · pro · val · cys · gly · · ·

Edman degradation of the intact protein showed the N-terminal unit to be thr. The C-terminal residue was shown to be cys.

The protein was then digested with chymotrypsin and three peptide fragments were isolated. The three chymotryptic fragments were each subjected to total hydrolysis and analyzed for amino acid composition. They were also subjected to three cycles of Edman degradation to identify the N-terminal sequence and incubated with carboxypeptidase to identify the C-terminal unit. The partial structures of the three fragments were found to be

Ch-1 thr · ser · pro(thr$_2$ser$_2$glu$_3$pro$_1$gly$_1$ala$_1$val$_1$cys$_2$ile$_1$lys$_1$arg$_1$)tyr
Ch-2 asn · pro · val(asp$_1$thr$_2$gly$_2$cys$_1$ile$_1$)tyr
Ch-3 ser · asn · glu(asp$_1$thr$_1$ser$_2$glu$_3$pro$_2$gly$_1$val$_2$cys$_2$ile$_1$leu$_2$lys$_3$arg$_1$)cys

The intact protein was then treated with methyl isothiocyanate. This reagent modifies the lysine side chains so that they are not cleaved by trypsin. The modified protein was digested with trypsin and three fragments were isolated. The three fragments were isolated, hydrolyzed, and analyzed and shown to have the following empirical compositions:

*T-1 $\text{thr}_1\text{ser}_1\text{pro}_1\text{arg}_1\text{glu}_1$
*T-2 $\text{thr}_1\text{ser}_1\text{glu}_2\text{pro}_2\text{gly}_1\text{val}_1\text{cys}_1\text{ile}_1\text{leu}_1\text{lys}_1$
*T-3 $\text{asp}_4\text{thr}_4\text{ser}_4\text{glu}_4\text{pro}_2\text{gly}_3\text{ala}_1\text{val}_3\text{cys}_5\text{ile}_2\text{leu}_1\text{tyr}_2\text{lys}_3\text{arg}_1$

From the data, what is the complete amino acid sequence of the protein?

CHAPTER 29

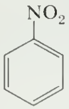
Substituted Benzenes and Electrophilic Aromatic Substitution

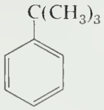
29.1

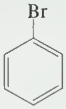
Nomenclature

A. *Monosubstituted Benzene Derivatives*

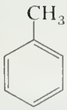
Benzene derivatives are named in a systematic manner by combining the substituent prefix with the word benzene. The names are written as one word, with no spaces. Since benzene has sixfold symmetry, there is only one monosubstituted benzene for each substituent, and no position number is necessary.

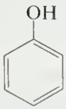

nitrobenzene

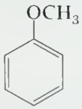

t-butylbenzene

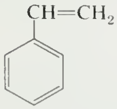

bromobenzene

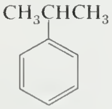
A number of monosubstituted benzene derivatives have special names that are in such common use that they have IUPAC sanction; these names should be learned.

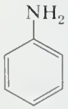

toluene
(methylbenzene)

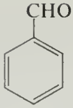

phenol
(hydroxybenzene)


anisole
(methoxybenzene)

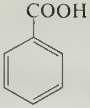

styrene
(vinylbenzene or
phenylethylene)


cumene
(isopropylbenzene)

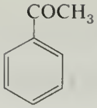

aniline
(aminobenzene)



benzaldehyde
(benzenecarboxaldehyde)

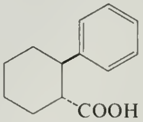


benzoic acid
(benzenecarboxylic acid)

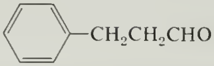


acetophenone
(phenyl methyl ketone)

In some cases, it is necessary to name compounds that contain a benzene ring as derivatives of another compound. In such cases, the prefix **phenyl-** is used.



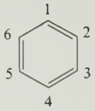
trans-2-phenylcyclohexanecarboxylic acid



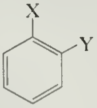
β-phenylpropionaldehyde
3-phenylpropanal

B. *Disubstituted Benzene Derivatives*

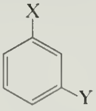
When there are two or more substituents, some specification of position is required. The numbering system is straightforward.



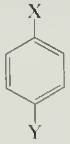
For disubstituted benzene derivatives, the three possible isomers are named using the Greek prefixes **ortho-**, **meta-**, and **para-**.



ortho- or *o-*

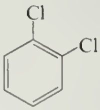


meta- or *m-*

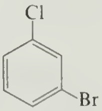


para- or *p-*

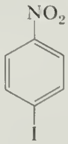
The following examples illustrate the use of these prefixes.



ortho-dichlorobenzene
o-dichlorobenzene

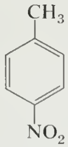


meta-bromochlorobenzene
m-bromochlorobenzene

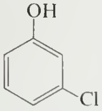


para-iodonitrobenzene
p-iodonitrobenzene

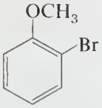
Note that the substituent prefixes are ordered alphabetically. When one of the substituents corresponds to a monosubstituted benzene that has a special name, the disubstituted compound is named as a derivative of that parent.



p-nitrotoluene

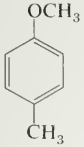


m-chlorophenol

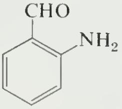


o-bromoanisole

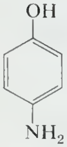
When two different substituents in a disubstituted compound each correspond to a special parent, there is an ambiguity in deciding which one to name as a derivative of the other. In such cases, that substituent that is normally treated as a suffix takes precedent. Some examples are



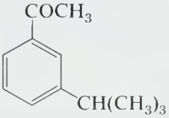
p-methylanisole



o-aminobenzaldehyde

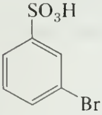


p-aminophenol

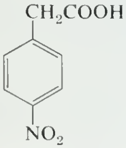


m-isopropyl-acetophenone

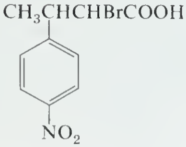
In many other cases, the systematic IUPAC name of the parent is in common use and derivatives are named accordingly.



m-bromobenzenesulfonic acid



p-nitrophenylacetic acid

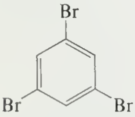


2-bromo-3-(*p*-nitrophenyl) butanoic acid

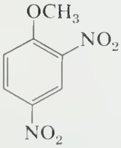
Some disubstituted benzene derivatives have common or trivial names that are in common use and should be learned. These special names will be discussed in subsequent chapters dealing with the chemistry of such compounds.

C. *Polysubstituted Benzene Derivatives*

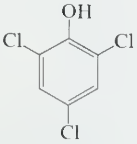
For polysubstituted benzenes, the numbering system should be used.



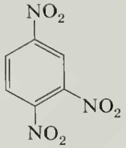
1,3,5-tribromobenzene



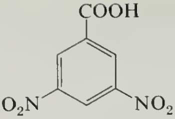
2,4-dinitroanisole



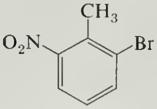
2,4,6-trichlorophenol



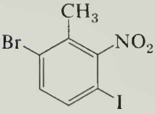
1,2,4-trinitrobenzene
(not 1,3,4-trinitrobenzene;
the lower numbers are used)



3,5-dinitrobenzoic acid



2-bromo-6-nitrotoluene
(prefixes are alphabetic)



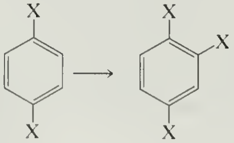
6-bromo-3-iodo-2-nitrotoluene

29.2
Determination of Structure

A. *Körner's Absolute Method*

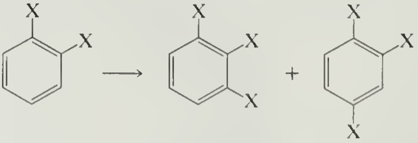
One of the classical methods for distinguishing *ortho, meta,* and *para* disubstituted benzenes is based on a simple logical corollary of a hexagonally symmetrical benzene and is known as Körner's absolute method. The method depends on the following simple principles applied to disubstituted benzenes where both substituents are the same:

1. In a *para* disubstituted benzene, all four hydrogens are equivalent. Further substitution can only lead to a single trisubstituted benzene.



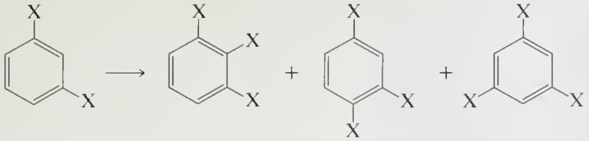
para 1,2,4-trisubstituted

2. In an *ortho* disubstituted benzene, there are two types of hydrogen, and further substitution can, in principle, lead to two isomeric trisubstituted benzenes.



ortho 1,2,3-trisubstituted 1,2,4-trisubstituted

3. In a *meta* disubstituted benzene there are three nonequivalent hydrogens, and further substitution can lead to three different trisubstituted benzenes:



meta 1,2,3-trisubstituted 1,2,4-trisubstituted 1,3,5-trisubstituted

Furthermore, only one trisubstituted isomer, the 1,2,4-, is given by all three disubstituted compounds. In practice, the application of this method requires careful work because the possible products are generally not formed in comparable amounts. The existing groups on a benzene ring provide strong orientation specificity, to be discussed in detail later, that strongly directs an incoming group to given positions. In practice, some isomers may be formed in such small quantity as to defy detection. This was especially true in earlier years when actual isolation was required. Nevertheless, by careful work the structures of many disubstituted benzenes were established early in the history of modern organic chemistry. By interconversion of functional groups, the structures of many other substituted benzenes could also be assigned.

Korner's absolute method is now only of historical interest as a valuable example of chemical logic. It is now generally feasible to convert an unknown benzene derivative into one of the many known derivatives or to use spectroscopic methods, primarily nmr and ir.

B. *Spectroscopic Methods*

Benzenoid hydrogens have nmr δ values in the 7–8 ppm range. The total area in this region provides a measure of the number of such hydrogens. In some monosubstituted benzenes, all five benzenoid hydrogens have approximately the same chemical shift and a relatively sharp singlet results. This simple result commonly occurs when the substituent has approximately the same electronegativity as carbon. An example is toluene, whose nmr spectrum is shown in Figure 29.1.

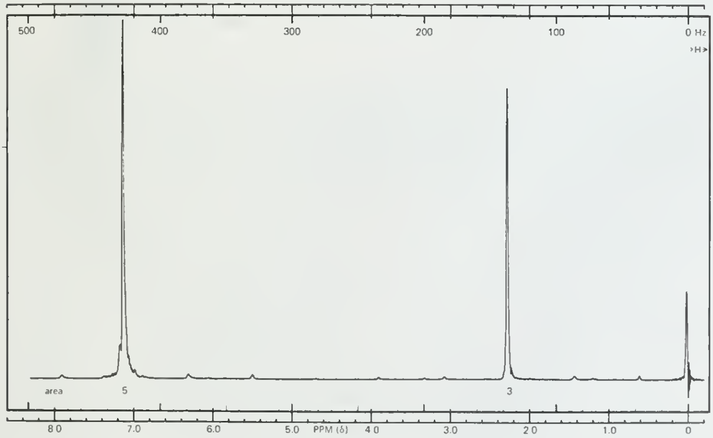


FIGURE 29.1 *Nmr Spectrum of toluene,* $C_6H_5CH_3$.

Also note in Figure 29.1 that the methyl group attached to the benzene ring resonates at $\delta = 2.32$ ppm. This is about 1.4 ppm downfield from the resonance position of a methyl group in an alkane. The main cause of this downfield shift is the diamagnetic anisotropy or ring current of the aromatic ring (Section 21.1.E), the same effect that is primarily responsible for the low-field resonance position of the benzenoid hydrogens. The effect is not as great with the methyl group because these hydrogens are farther from the circulating electrons than the benzenoid hydrogens.

When the substituent in a monosubstituted benzene is sufficiently electronegative or electropositive relative to carbon, the *ortho*-, *meta*-, and *para*-hydrogens have significantly different chemical shifts and the nmr spectrum becomes more complex. Such a spectrum is shown by nitrobenzene, Figure 29.2.

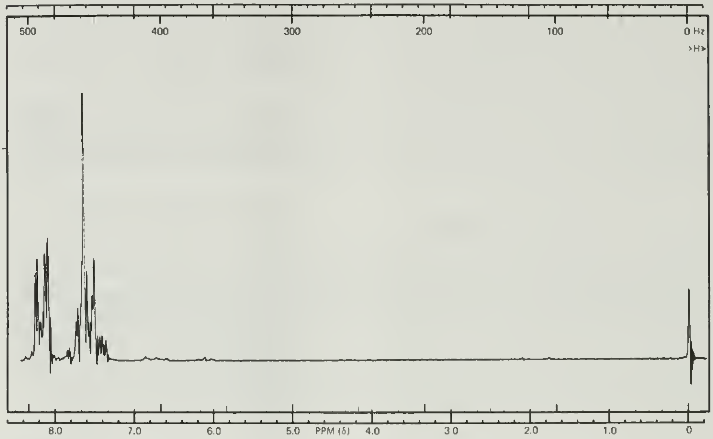


FIGURE 29.2 *Nmr spectrum of nitrobenzene,* $C_6H_5NO_2$.

The spectra of disubstituted benzenes can sometimes be rather complex. In *p*-dichlorobenzene, the four benzenoid hydrogens are equivalent and the nmr spectrum is a sharp singlet (Figure 29.3). On the other hand, there are 24 lines in the nmr spectrum of *o*-dichlorobenzene (Figure 29.4). Some of these signals are of low intensity and others are so close together that they appear merged if instrument resolution is inadequate. The analysis of such complex splitting patterns is beyond the scope of this text, but the student should know that such spectra can be analyzed and interpreted by experts to give structural information.

When the two substituents are of different electronegativity, the nmr spectra are sometimes sufficiently simple as to be interpretable by a "first-order" approximation. An example is the spectrum of *p*-nitrotoluene, shown in Figure 29.5. To a first approximation, the benzenoid region in *p*-nitrotoluene may be regarded as a pair of doublets, arising from coupling between the hydrogens on C-2 and C-3, with $J = 8$ Hz. Each doublet has an intensity of 2, relative to 3 for the methyl group because the hydrogens at C-2 and C-6 are equivalent and the hydrogens at C-3 and C-5 are equivalent.

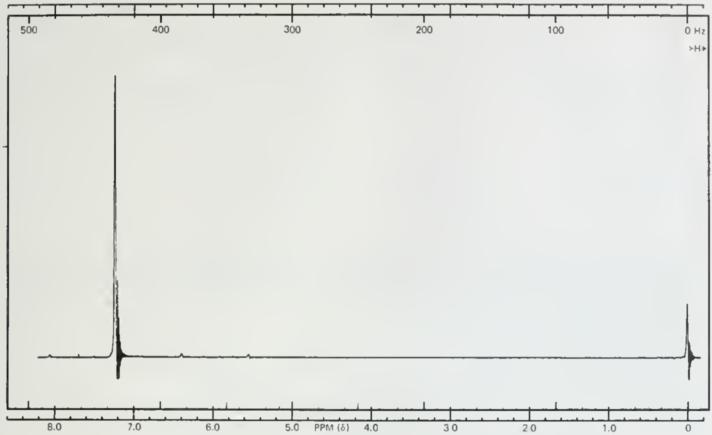


FIGURE 29.3 *Nmr spectrum of* p*-dichlorobenzene,* p-$Cl_2C_6H_4$.

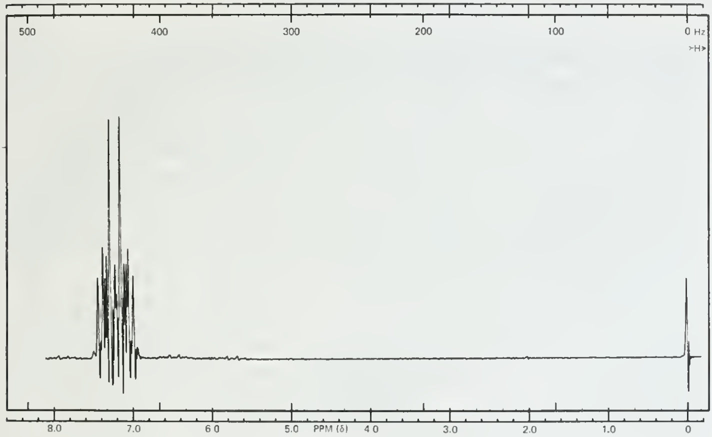
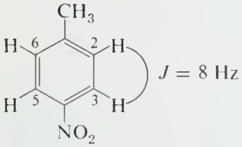


FIGURE 29.4 *Nmr spectrum of* o*-dichlorobenzene,* o-$Cl_2C_6H_4$.



Infrared spectra of aromatic hydrogens are more straightforward in use. Aromatic C—H bonds have a stretching frequency at about 3030 cm^{-1}. This is the same region as alkene C—H stretching bands. Both bonds are close to C_{sp^2}-H_{1s} in character. Aromatic C—H bonds also give rise generally to a series of low-

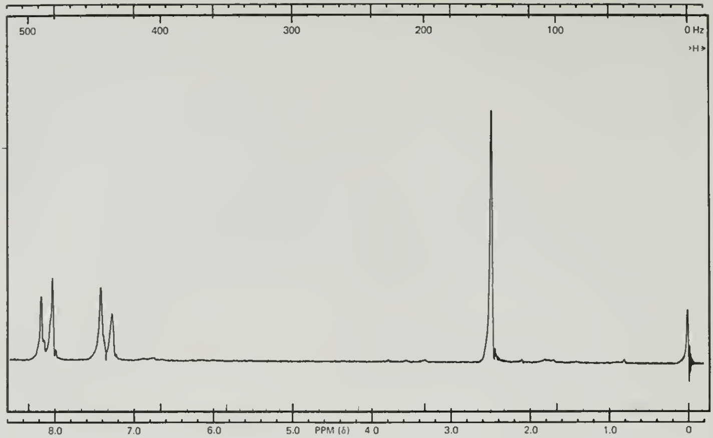


Figure 29.5 *Nmr spectrum of* p-*nitrotoluene,* p-$NO_2C_6H_4CH_3$.

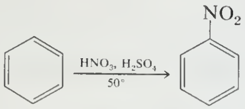
intensity combination and overtone bands at 2000–1660 cm^{-1} (5–6 μ). A further set of one or more intense bands in the 700–900 cm^{-1} region results from out-of-plane bending. These last absorptions are especially valuable because neighboring C—H's couple together to give bands whose absorption frequency is characteristic of the number of vicinal or adjacent C—H's in the ring. For example, four adjacent C—H's, as in an *ortho* disubstituted benzene, give absorption at about 750 cm^{-1}, whereas three adjacent C—H's, as in a *meta* disubstituted benzene, give absorption at somewhat higher frequency. Table 29.1 summarizes the one or two ir absorption bands generally found in this region for different substitution patterns on the benzene ring.

Table 29.1
Infrared Absorption of Benzene Derivatives

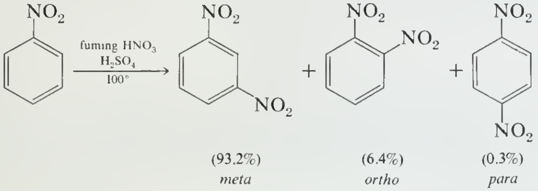
Substitution	Out-of-plane Bending Frequencies, cm^{-1}
mono-	770–730, 710–690
ortho-	770–735
meta-	810–750, 710–690
para-	840–810
1,2,3-	780–760, 745–705
1,3,5-	865–810, 730–675
1,2,4-	825–805, 885–870
1,2,3,4-	810–800
1,2,4,5-	870–855
1,2,3,5	850–840
penta-	870

29.3
Orientation in Electrophilic Aromatic Substitution

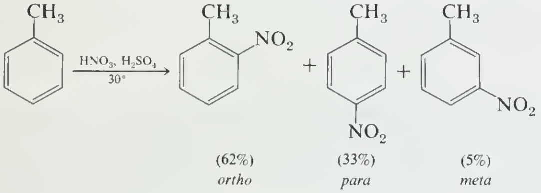
Benzene is nitrated by a mixture of concentrated nitric and sulfuric acids at 50° (page 586).



Further nitration of nitrobenzene is considerably more difficult. Stronger acid and higher temperatures are required. The product is primarily *m*-dinitrobenzene.



On the other hand, toluene undergoes nitration *more* rapidly than benzene. In this case, the predominant products are the *ortho* and *para* isomers.



As shown by these examples, the reactivity of an aromatic ring is influenced by the groups attached to it. Furthermore, the orientation of an incoming group is also a function of the substituent already present. Substituents are generally characterized as being ***ortho,para*** or ***meta* directors.** Note that *ortho* and *para* are produced together, although the *ortho*/*para* ratio may vary with different groups and under different conditions. Substituents may also be characterized as **activating** or **deactivating,** relative to benzene itself. We may distinguish three different classes:

1. ***Ortho,para directing and activating.*** Functional groups in this category include R (alkyl), NH$_2$, NR$_2$ and NHCOR (amino, alkylamino and amide). OH, OR and OCOR (hydroxy, alkoxy and ester).
2. ***Ortho,para directing and deactivating.*** The most important functional groups in this category are the halogens, F, Cl, Br and I.
3. ***Meta directing and deactivating.*** This group includes NO$_2$ (nitro), SO$_3$H (sulfonic acid), and all carbonyl compounds: COOH, COOR, CHO and COR (carboxylic acids and esters, aldehydes and ketones).

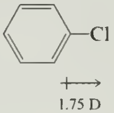
Note that all activating groups are *ortho,para* directors and all *meta* directors are deactivating. These generalizations derive from many experimental observations and form a set of empirical and useful rules. However, these rules are also subject to a consistent and satisfying interpretation by the modern theory of organic chemistry. This theory has its basis in the electron-donating and electron-attracting character of different functional groups, as discussed in the next section.

29.4
Dipole Moments of Benzene Derivatives

Methyl chloride has a dipole moment of 1.94 D in the gas phase. The experimental measurement of the dipole moment gives only its magnitude and not its direction. Nevertheless, there is no doubt that the dipole moment in methyl chloride is oriented from carbon to chlorine:

$$\underset{1.94\ \mathrm{D}}{\underset{+\!\!\!\longrightarrow}{\mathrm{CH_3{-}Cl}}}$$

This orientation agrees with quantum-mechanical calculations and with spectroscopic interpretations of related compounds. Chlorobenzene has a dipole moment of 1.75 D in the gas phase. The direction of the dipole is undoubtedly also from carbon to chlorine:



The magnitude of the dipole moment of chlorobenzene is smaller than that of methyl chloride for two reasons. The C—Cl bond in methyl chloride may be represented approximately as C_{sp^3}-Cl_p. The bond in chlorobenzene is approximately C_{sp^2}-Cl_p. The higher *s* character of the benzene orbital makes it more electronegative than an sp^3 orbital; hence, the electronegativity difference with the more electronegative chlorine orbital is reduced. The second contribution to the reduced dipole moment in chlorobenzene results from conjugation of one of the chlorine lone pairs with the benzene π system, illustrated in Figure 29.6. The lone pair is actually part of the π system and may be represented in terms of resonance structures by

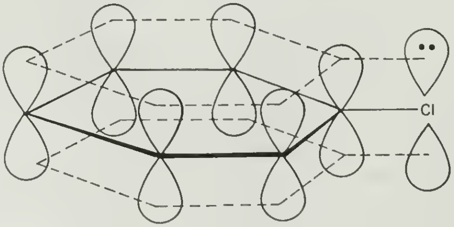
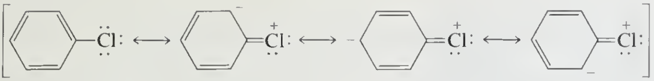
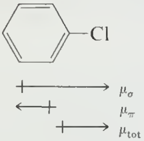


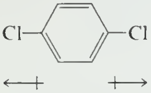
FIGURE 29.6 *Conjugation of a chlorine lone pair with the benzene π system. Actually, a chlorine* 3p *orbital is involved and the additional node is not shown for simplicity.*



The effect of conjugation is small; the ionic structures contribute only a slight amount to the overall electronic structure. This slight conjugation, however, is equivalent to a dipole moment for the π system, μ_π, oriented in the opposite direction from that associated with the C—Cl σ bond, μ_σ. The net dipole moment is the vector sum and is less than that of μ_σ alone.



Dipole moments of some other benzene derivatives in the gas phase are summarized in Table 29.2. The dipole moments of multiply substituted benzenes are generally close to the vector sum of the constituent dipoles. p-Dichlorobenzene has a net dipole moment of zero because the two component C—Cl dipoles oppose and cancel each other.



net $\mu = 1.75 + (-1.75) = 0$

TABLE 29.2
Dipole Moments of Substituted Benzenes

Compound	μ, D (gas phase)	Compound	μ, D (gas phase)
C_6H_6	0	p-$C_6H_4Cl_2$	0
C_6H_5F	1.63	o-$CH_3C_6H_4Cl$	1.57
C_6H_5Cl	1.75	p-$CH_3C_6H_4Cl$	2.21
C_6H_5Br	1.72	o-$CH_3C_6H_4F$	1.35
C_6H_5I	1.71	m-$CH_3C_6H_4F$	1.85
$C_6H_5CH_3$	0.37	p-$CH_3C_6H_4F$	2.01
$C_6H_5NO_2$	4.28	m-$ClC_6H_4NO_2$	3.72
o-$C_6H_4Cl_2$	2.52	p-$ClC_6H_4NO_2$	2.81
m-$C_6H_4Cl_2$	1.68		

Because of the geometry of the hexagonal benzene ring, *ortho* and *meta* vector sums are given simply as

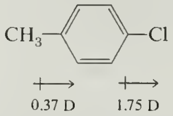
$$\mu = (\mu_1^2 + \mu_2^2 \pm \mu_1\mu_2)^{1/2} \qquad \begin{matrix} + \text{ ortho} \\ - \text{ meta} \end{matrix}$$

This equation generally is quite satisfactory for *meta* groups, but is frequently inadequate for *ortho* groups. *Ortho* groups are so close to each other that electronic effects are mutually perturbed. For example, this equation applied to o- and *m*-dichlorobenzenes gives

$$\mu_o = [1.75^2 + 1.75^2 + (1.75)(1.75)]^{1/2} = 3.03 \text{ D}$$
$$\mu_m = [1.75^2 + 1.75^2 - (1.75)(1.75)]^{1/2} = 1.75 \text{ D}$$

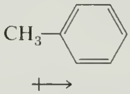
The *meta* result is close to the experimental value of 1.68 D, but the calculated *ortho* value is substantially higher than the experimental value of 2.52 D.

Toluene has a small but distinct dipole moment of 0.37 D. We note from the data in Table 29.2 that the dipole moment of *p*-chlorotoluene is approximately that of the sum of the dipole moments of toluene and chlorobenzene; hence, both component dipoles are operating in the same direction.

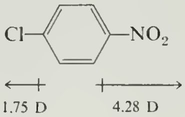


$0.37 + 1.75 = 2.12$ D (experimental $\mu = 2.21$ D)

The dipole moment of toluene results in part from the character of the $C_{\text{methyl}}—C_{\text{ring}}$ bond. This bond can be described approximately as C_{sp^3}-C_{sp^2}. The sp^2 orbital is more electronegative than the sp^3 orbital, and produces an electronic displacement corresponding to the direction of the dipole moment indicated for toluene.

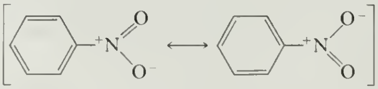


The same approach applied to nitrobenzene derivatives shows that the direction of the dipole in nitrobenzene is away from the benzene ring.



$\mu_{\text{net}} = 4.28 - 1.75 = 2.53$ D (experimental $\mu = 2.81$ D)

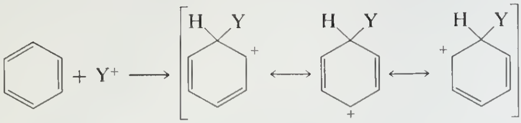
The direction thus derived for the dipole moment in nitrobenzene is that which we would have expected from the electronic structure of the nitro group



The relatively high magnitude of μ for nitrobenzene also follows from the formal charges required in the Lewis structures for the nitro group.

29.5
Theory of Orientation in Electrophilic Aromatic Substitution

In Chapter 21, we learned that the mechanism of electrophilic aromatic substitution involves combination of a positive or electrophilic species with a pair of π electrons of the benzene ring to form an intermediate having a pentadienyl cation structure.



The transition state leading to the pentadienyl cation intermediate may be assumed to be close to the intermediate in energy and structure. This assumption is implied in the energy profile for the reaction shown in Figure 29.7. The modern electronic theory of orientation in electrophilic aromatic substitution involves an assessment of the effect of a substituent on the relative energies of the pentadienyl cation-like transition state for reaction at different possible positions.

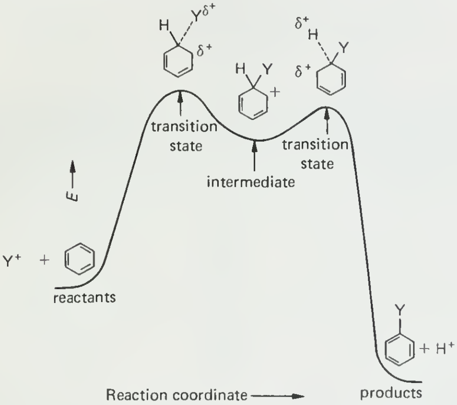
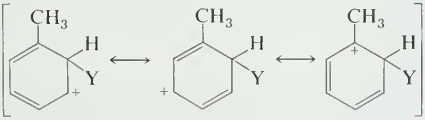


FIGURE 29.7 *Energy profile for electrophilic substitution on benzene.*

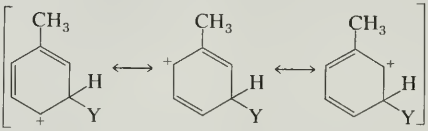
For example, reaction at the *ortho* position of toluene gives rise to a transition state that resembles the intermediate



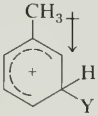
Two of the structures are those of secondary carbonium ions, but the third corresponds to a more stable tertiary carbonium ion. As a result, this intermediate, and *hence also the transition state that leads to it* are more stable—have lower energy—than the corresponding intermediate and transition state for benzene, in which all three resonance structures are those of secondary carbonium ions. The *ortho* position of toluene is therefore expected to be more reactive than a single position of benzene.

This argument must be put on a per-hydrogen basis. Without specific orientation preferences, statistics alone would give a reactivity ratio for benzene: *ortho* : *meta* : *para* of 6:2:2:1.

Reaction at the *meta* position gives rise to the following resonance structures:

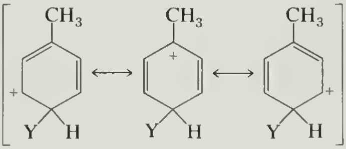


All three structures are those of secondary carbonium ions. Each structure is stabilized slightly by the C_{methyl}-C_{ring} dipole:



Correspondingly, the *meta* position of toluene is expected to be somewhat more reactive than a benzene position, but not nearly so reactive as an *ortho* position.

Finally, we apply this approach to the *para* position to generate the resonance structures



Here again we find two secondary carbonium ion structures, and one tertiary carbonium ion. The overall energy of the transition state is comparable to that for *ortho* substitution. Indeed, this approach does not distinguish between preference for *ortho* relative to *para* substitution, but does indicate why substituents divide into the two broad groups of *ortho,para* and *meta* directors.

The resulting energy profile for reaction at toluene is compared with that for benzene in Figure 29.8. The differences between the alternative structures are somewhat less in the transition state than in the intermediate because the amount of positive charge to be distributed is greater in the intermediate in which a fully formed C—Y bond is developed. We have chosen to examine the intermediates, but only for the convenience of symbolism. The same arguments apply to the developing positive charge on the benzene ring in the transition states. The net result is that of predominant *ortho,para* orientation; although the *meta* position is more reactive than a single benzene position, the *ortho,para* positions are even more so.

We next apply this approach to the corresponding reaction at the *ortho,para*

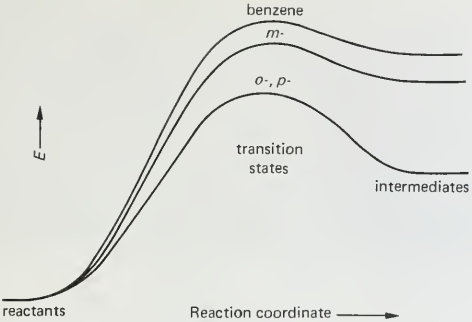
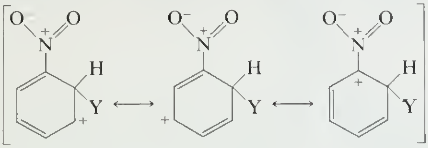


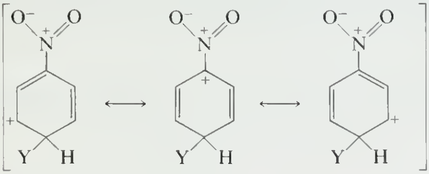
FIGURE 29.8 *Energy profile for reaction at* ortho,para *and* meta *positions of toluene compared to benzene.*

and *meta* positions of nitrobenzene and derive three sets of resonance structures for the intermediates (and transition states) involved:

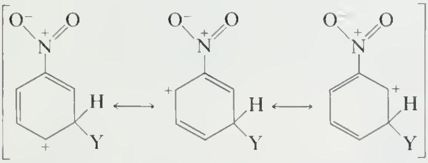
ortho



para



meta



All of these structures involve the electrostatic repulsion of the carbonium ion charge with the strong dipole of the nitro group.

$$(+) \qquad \overset{+\!\!\longrightarrow}{C{-}NO_2}$$

That is, every one of these structures is substantially less stable than the corresponding structure for reaction at benzene; hence, all positions in nitrobenzene are expected to be deactivated relative to benzene. For reaction at the *ortho* and *para* positions, however, one structure is that of a carbonium ion right next to the positive nitrogen of the nitro group. This structure in each case is of such high energy compared to the other structures, in which the positive charges are separated by one or more atoms, that it contributes very little to the overall resonance hybrid. The *meta* reaction involves only structures in which the positive charges are separated; thus, although the transition state for *meta* substitution is of higher energy than for reaction at benzene, it is of lower energy than those for reaction at the *ortho* or *para* positions. We can phrase this result in another way: the *meta* reaction is deactivated less than *ortho* or *para* reaction. The corresponding reaction profiles are summarized in Figure 29.9.

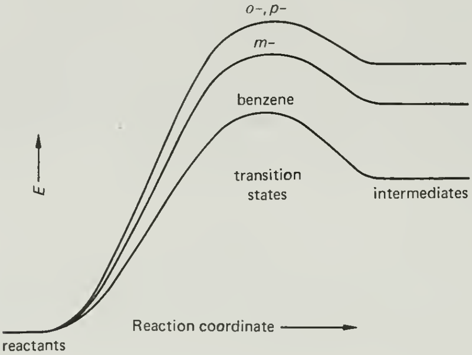
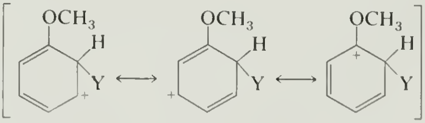


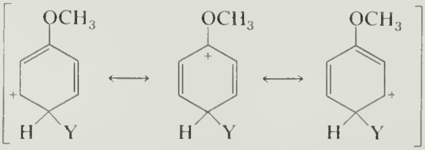
Figure 29.9 *The intermediate derived from* meta *reaction of nitrobenzene is formed less readily than that from attack at benzene itself, but more readily than that from reaction at the* ortho *or* para *positions.*

These principles apply generally to other types of substituents. For anisole, we may write the same sets of three resonance structures:

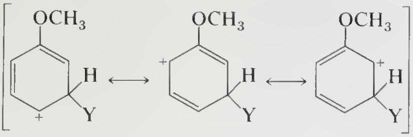
ortho



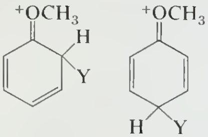
para



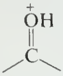
meta



All of these structures are expected to be somewhat destabilized by the electrostatic interaction with the C—O dipole, but reaction at the *ortho* and *para* positions also corresponds to oxonium ions.



These additional structures greatly stabilize the intermediates and the transition states leading to them. Similar structures are involved in acid-catalyzed reactions of carbonyl compounds.



The oxonium ion structures so dominate the system that the *ortho* and *para* positions of anisole are highly activated compared to benzene. We shall see in Chapter 33 that electrophilic substitution reactions at these positions in phenols and phenyl ethers and esters are accomplished under rather mild conditions. On the other hand, reaction at the *meta* positions is expected to be somewhat less facile than in benzene. The resulting reaction profile is shown in Figure 29.10.

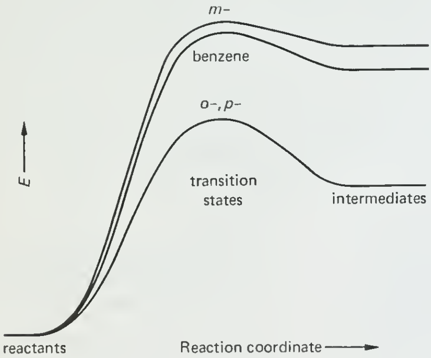
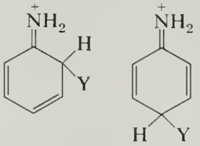


FIGURE 29.10 Reaction profile for reaction at the *ortho,para, and* meta *positions of anisole compared to benzene. The same figure would apply to reaction of phenol and aniline.*

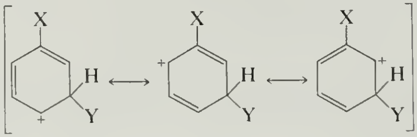
Reactions at the *ortho* and *para* positions of aromatic amines involve related immonium ion structures, for example,



Consequently, these positions are also highly activated relative to benzene.

Let us now apply the procedure to a halobenzene. Reaction at the *meta* position gives the three structures

meta

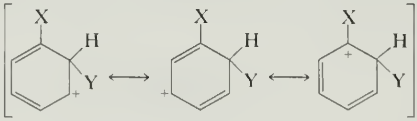


All three structures are strongly destabilized by electrostatic interaction of the positive charge with the C—X dipole:

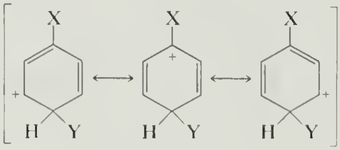
$$(+)\qquad \overset{+\!\!\longrightarrow}{\mathrm{C{-}X}}$$

Accordingly, the *meta* position in the halobenzene is strongly deactivated relative to benzene. Reaction at the *ortho* and *para* positions involve similar carbonium ion structures destabilized by interaction with the C—X dipole:

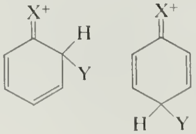
ortho



para



In both cases, however, one structure is that of an α-halocarbonium ion in which interaction with a halogen lone pair is possible to give the halonium ion structures.



Such halonium ion structures are not nearly so stable as related oxonium and immonium ions. In practice, the additional contribution of such structures does not compensate for the deactivating effect of the C—X dipoles on the other structures, but it does make reaction at the *ortho* and *para* positions far more facile than at the *meta* position. The corresponding reaction profile is shown in Figure 29.11.

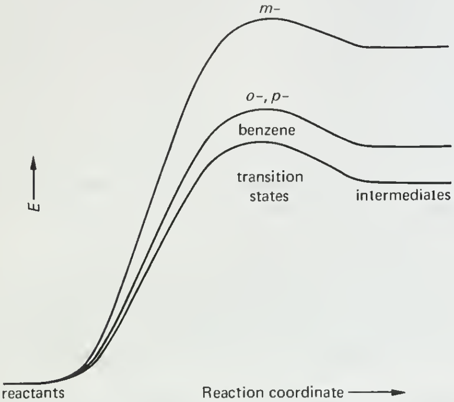


Figure 29.11 *Energy profile for reaction of a halobenzene compared to benzene.*

29.6
Quantitative Reactivities: Partial Rate Factors

Nitration reactions have been studied extensively for many aromatic compounds, and relative reactivities at different positions have been determined. Furthermore, by studying the reaction of a mixture of benzene and some other compound, it is often possible to determine the quantitative reactivities of various positions relative to a benzene position. These statistically corrected relative reactivities are known as partial rate factors.

For example, the reaction of equimolar amounts of toluene and benzene with a small amount of nitric acid in acetic anhydride at 30° gives one part of nitrobenzene to 27 parts of nitrotoluenes. The nitrotoluenes formed are 58.1% *ortho*, 3.7% *meta*, and 38.2% *para*. The partial rate factors, f_i, are calculated as follows:

$$f_o = (\text{fraction } o)\left(\frac{\text{no. benzene positions}}{\text{no. } o \text{ positions}}\right)\left(\frac{\text{toluene reactivity}}{\text{benzene reactivity}}\right)$$

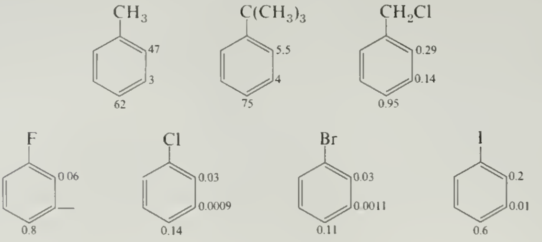
$$= (0.581)(\tfrac{6}{2})(27) = 47$$
$$f_m = (0.037)(\tfrac{6}{2})(27) = 3$$
$$f_p = (0.382)(\tfrac{6}{1})(27) = 62$$

Note that the *meta* position is more reactive than a benzene position, as predicted by the theory developed in Section 29.5.

Partial rate factors for nitration of several substituted benzenes are summarized in Table 29.3. Some effects are clearly apparent in these results. For example, a *t*-butyl group has much the same effect as a methyl group in the *meta* and *para* positions, but at the *ortho* position, *t*-butylbenzene is much less reactive than

Table 29.3

Partial Rate Factors for Nitration



toluene. The difference is clearly to be attributed to steric hindrance caused by the bulky *t*-butyl group. At the distant *meta* and *para* positions the size of the alkyl group has little effect.

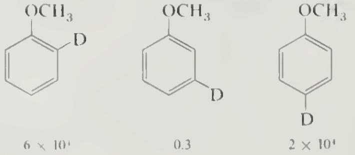
The halobenzenes follow the theory outlined in Section 29.5. All positions are less reactive than benzene, but the *meta* positions are more strongly deactivated than *ortho* and *para*. The chloromethyl group is of especial interest since the stabilizing effect of an alkyl group is superimposed on the deactivating effect of the C—Cl dipole. The result is a net *ortho,para* orientation with a little net deactivation.

But the quantitative data are sparse. The amounts formed of some isomers are so minute as to defy detection, even by modern gas chromatography analytical methods. One approach to obtaining quantitative reactivity results for all positions in a given molecule, even when they differ greatly in reactivity, has been to study the simplest possible electrophilic aromatic substitution reaction, the replacement of one hydrogen isotope by another. Examples of this reaction were given in Section 21.2.

In principle, it is possible to prepare a variety of specifically labeled aromatic compounds and to study quantitatively the rate of loss of the hydrogen isotope under a consistent set of acidic conditions. A comparison of the rates of replacement of deuterium by hydrogen of specifically deuterated anisoles with the corresponding rate for deuterobenzene in aqueous perchloric acid gives the results displayed in Table 29.4. These results demonstrate the high reactivity of the *ortho* and *para* positions, compared to benzene, and the lower reactivity in the *meta* position. These same relative rates are expected to correspond approximately to nitration as well and imply that nitration of anisole gives only a few parts per million of *m*-nitro product. This minute quantity is extremely difficult to detect directly in the product mixture.

Table 29.4

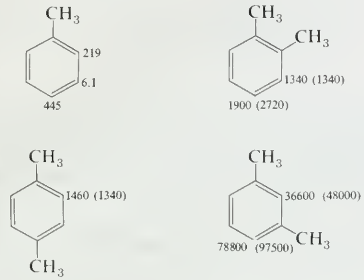
Rates of Dedeuteration in Aqueous Perchloric Acid Compared to Benzene



29.7
Effects of Multiple Substituents

The relative rates of replacement of tritium by hydrogen in trifluoroacetic acid for toluene and the dimethylbenzenes compared to benzene are summarized in Table 29.5. The energy effects of two methyl groups are approximately additive compared to the effect of one methyl group in toluene. For example, the 3-position in *o*-dimethylbenzene is *ortho* to one methyl and *meta* to the other. The predicted reactivity is, therefore, (219)(6.1) = 1340, which agrees exactly with the experimental reactivity.

TABLE 29.5
Relative Rates of Protodetritiation in Trifluoroacetic Acid



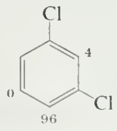
The product of the two partial rate factors is taken because it is the activation energy quantities that are additive:

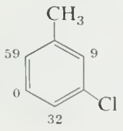
$$\Delta E^{\ddagger}\text{ (3-position in }o\text{-dimethylbenzene)} = \Delta E^{\ddagger}(o\text{-}) + \Delta E^{\ddagger}(m\text{-})$$

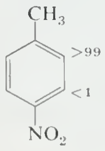
The energies are related to the logarithms of the rate constants:

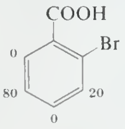
$$\begin{aligned} RT \ln k(\text{3-position}) &= RT \ln (o\text{-}) + RT \ln (m\text{-}) \\ \log f\text{ (3-position)} &= \log f_o + \log f_m = \log f_o f_m \\ f(\text{3-position}) &= f_o f_m \end{aligned}$$

The relative reactivities of the toluene positions were used as partial rate factors to derive the predicted reactivities of the dimethylbenzenes given in parentheses in Table 29.5. The approximate agreement can be generalized to electrophilic substitution reactions of polysubstituted benzenes. That is, the net orientation effects of two or more substituents can be predicted approximately by examining the effects of each substituent separately. If all substituents orient preferentially to the same positions, such positions are strongly preferred. For example, nitration of the following disubstituted benzenes gives the percentage of nitration at each position as indicated:







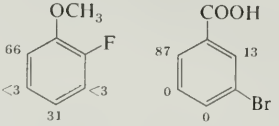


In *m*-chlorotoluene, the 5-position is *meta* both to chlorine and to methyl, and no significant reaction occurs at this position. The other positions are all *ortho* or *para* to both groups, and a disagreeable mixture results. In *p*-nitrotoluene, however, the highly favored 2-position is *ortho* to the *ortho,para* directing methyl and *meta* to the *meta* directing nitro.

If the groups already present have conflicting orientation preferences, it is helpful to divide substituents into three classes:

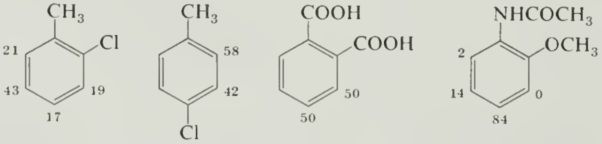
1. Strongly activating *ortho,para* directors, such as OR and NR_2
2. Alkyl groups and halogens
3. All *meta* directors

If two substituents belong to different classes, the orientation effect of the superior class dominates. The following nitration results are examples:

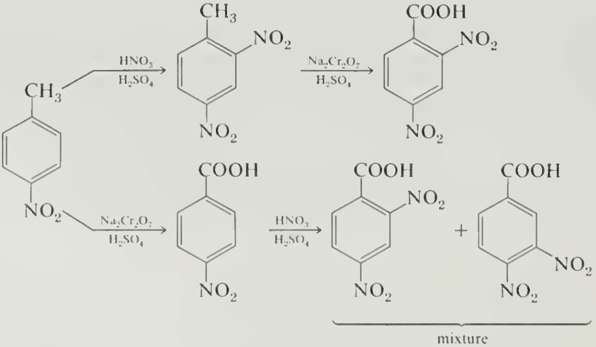

OCH3
F
66
<3
<3
31
COOH
87
13
0
Br
0

Note that the effects of all *ortho,para* directors dominate over *meta* directors.

Finally, if both substituents are in the same class, all bets are off and horrible mixtures can be anticipated. The following nitration results are examples:


CH3
Cl
21
43
19
17
CH3
58
42
Cl
COOH
COOH
50
50
NHCOCH3
OCH3
2
14
0
84

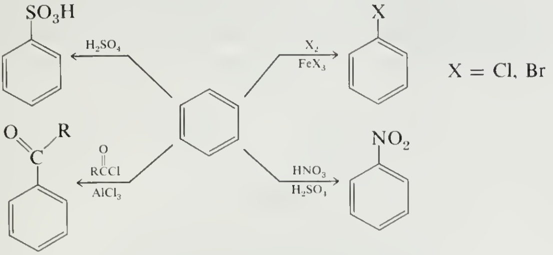
In our subsequent studies of the reactions of functional groups on benzene rings, we shall see that many syntheses can be accomplished by aromatic substitution reactions combined with functional group transformations. In such sequences, the order in which reactions are accomplished is of great importance, because of the orientation preferences of different groups. One example will demonstrate this point.


CH3
NO2
HNO3
H2SO4
CH3
NO2
NO2
Na2Cr2O7
H2SO4
COOH
NO2
NO2
Na2Cr2O7
H2SO4
COOH
NO2
HNO3
H2SO4
COOH
NO2
NO2
+
COOH
NO2
NO2
mixture

The first route is clearly to be preferred as a preparation of 2,4-dinitrobenzoic acid.

29.8
Synthetic Utility of Electrophilic Aromatic Substitution

In Chapter 21, we saw that a variety of simple monosubstituted benzene derivatives may be prepared by electrophilic substitution on benzene. Important examples of such synthetically useful reactions are halogenation, nitration, sulfonation, and Friedel-Crafts acylation.

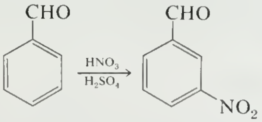


In Chapters 30–33, we shall see that these important functional groups may be modified in many ways to provide syntheses of even more benzene derivatives.

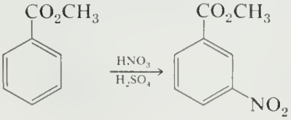
In this chapter, we have considered the effect on orientation and reactivity when the aromatic ring already has one or more substituents. Thus far, our discussion has been mainly a mechanistic one. How may the electrophilic substitution reaction be used in a practical sense to prepare polysubstituted benzenes? To some extent, the answer to this question depends on the modification and interrelation of functional groups, as demonstrated by the example at the end of Section 29.7. However, we may briefly consider at this time how the process may be used in some cases to provide practical syntheses of pure compounds.

Remember that the goal of any chemical synthesis is generally to prepare **one pure compound** for some purpose. Therefore, one must use reactions that do not give mixtures of isomers whenever possible. When there is no known method that provides only one isomer, a synthesis may still be acceptable if the desired isomer is produced in substantial amounts (hopefully as the *major* product) and if it may be separated in some way from the unwanted isomers.

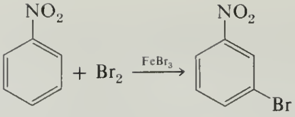
Some electrophilic substitution reactions fit the first criterion; that is, one of the possible isomers is produced almost exclusively. Substitution on *meta*-orienting compounds usually falls into this category. Thus, the following substitution reactions are all good preparative reactions.



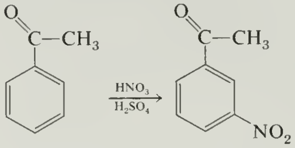
(75–84%)

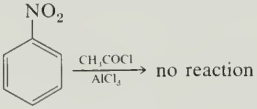


(81–85%)



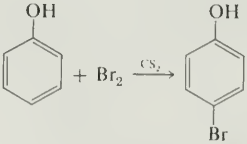
It is important to note that the Friedel-Crafts acylation reaction *does not work when the ring already contains a meta directing group*. Thus, *m*-nitroacetophenone may be prepared by nitration of acetophenone ($COCH_3$ is *meta*-orienting), but *not* by Friedel-Crafts acylation of nitrobenzene.

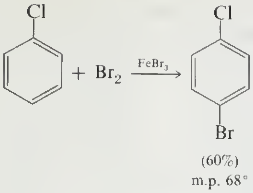




In many of these reactions, a few per cent of the *ortho* and *para* isomers are produced. However, if the major isomer is crystalline, as is usually the case, it may easily be purified by recrystallization.

When the substituent already in the ring is an *ortho,para* director, mixtures invariably result, as we have seen in previous sections. In such cases, direct electrophilic substitution is less satisfactory as a synthetic method. However, some benzene derivatives may still be obtained in this manner, particularly the *para* isomers. Because of its symmetrical nature, the *para* isomer usually has a significantly higher melting point than the *ortho* or *meta* isomer. Some representative data are summarized in Table 29.6. Recall that a higher melting point represents a more stable crystal lattice and lower solubility. Consequently, the higher melting *para* isomer may often be crystallized from the mixture of *ortho* and *para* products of direct substitution. It is generally *not possible* to isolate the *ortho* isomer in a pure state by this technique.





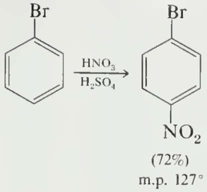


Table 29.6
Melting Points of Disubstituted Benzenes

	Melting Point °C		
Substituents	*ortho*	*meta*	*para*
Br, Br	7	−7	87
Cl, Cl	−17	−25	53
Br, Cl	−12	−22	68
CH_3, Br	−26	−40	29
CH_3, NO_2	−10	16	55
Br, NO_2	43	56	127
Cl, NO_2	35	46	84
Br, COOH	150	155	255
Cl, COOH	142	158	243
OH, Br	6	33	66

Since *ortho* and *para* isomers usually have closely similar boiling points, fractional distillation is usually *not* a satisfactory method for separation of such isomer mixtures, but there are exceptions to this generalization. Some representative data collected in Table 29.7 show that *o*- and *p*-nitrotoluenes differ sufficiently in boiling point to be separable by fractional distillation. On the other hand, the melting points of the bromotoluenes are too low for effective crystallization and their boiling points are too close for simple fractionation; hence, the bromination of toluene is *not* a satisfactory route to any of the bromotoluenes.

In summary, direct electrophilic substitution is a useful synthetic method as such if only one isomer is produced or if the mixture can be conveniently separated by physical means. To predict whether such a reaction will be useful, the chemist must consider the mechanism of the reaction, that is, what the isomer distribution is expected to be, and also the probable physical properties of the expected products. We shall see in future chapters that the utility of electrophilic substi-

TABLE 29.7
Boiling Points of Disubstituted Benzenes

Substituents	Boiling Point, °C		
	ortho	*meta*	*para*
Br, Br	225	218	219
Cl, Cl	181	173	174
Br, Cl	204	196	196
CH_3, Br	182	184	184
CH_3, Cl	159	162	162
Br, NO_2	258	265	256
Cl, NO_2	246	236	242
CH_3, NO_2	220	233	238
NO_2, NO_2	319	291	299
OCH_3, NO_2	277	258	274

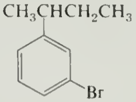
tution may be extended by modification and interrelation of functional groups and by a technique in which one or more positions on the ring are temporarily deactivated or blocked.

PROBLEMS

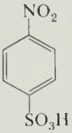
1. Write structures corresponding to each of the following names:
   - (a) *m*-fluoroanisole
   - (b) 2,4,6-tribromobenzoic acid
   - (c) 2,4-dinitrotoluene
   - (d) *m*-nitrobenzenesulfonic acid
   - (e) *m*-divinylbenzene
   - (f) *p*-cyanophenylacetylene
   - (g) *o*-diisopropylbenzene
   - (h) 2-bromo-6-chloroaniline

2. Give an acceptable name for each of the following structures:

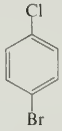
(a)



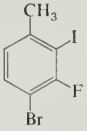
(b)



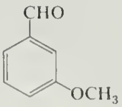
(c)



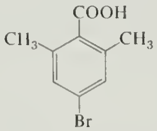
(d)



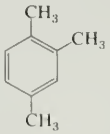
(e)



(f)



(g)



3. The dipole moment of *p*-fluoronitrobenzene in the gas phase, 2.87 D, differs significantly from the vector sum of fluorobenzene and nitrobenzene. Explain why, using resonance structures where appropriate.

4. Use the dipole moments of fluorobenzene and toluene (Table 29.2) to calculate the dipole moments of the three fluorotoluenes. Compare with the experimental values.

5. The following are some dipole moments determined in benzene solution (note that

solution values sometimes differ by a few tenths of a Debye from gas phase values because of solvent effects):

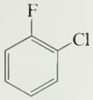
C_6H_5CN	3.93 D
$C_6H_5CH_3$	0.43 D
C_6H_5Br	1.56 D
p-BrC_6H_4CN	2.66 D
p-$CH_3C_6H_4CN$	4.40 D

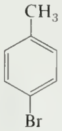
(a) What is the direction of the dipole in benzonitrile? Rationalize this result using resonance structures.

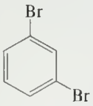
(b) Why does the vector sum of the dipole moments of benzonitrile and bromobenzene differ significantly from the experimental value for *p*-bromobenzonitrile (compare problem 3)?

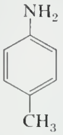
(c) On the basis of the direction of the dipole moment of benzonitrile, is the CN group expected to be an *ortho,para* or a *meta* director? Explain.

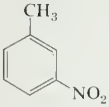
6. Indicate the principal mononitration product or products expected from each of the following compounds.

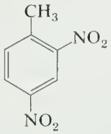
(a)


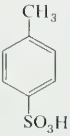
(b)


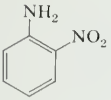
(c)


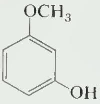
(d)


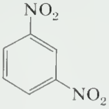
(e)


(f)


(g)


(h)


(i)


(j)


7. Using resonance structures where desirable, show that styrene is an *ortho,para* director.

8. Biphenyl, $C_6H_5—C_6H_5$, may be considered as a benzene with a phenyl substituent. Show why this hydrocarbon is expected to direct to the *ortho,para* positions, using resonance structures.

9. Use resonance structures to show why the aldehyde group in benzaldehyde is a *meta* director.

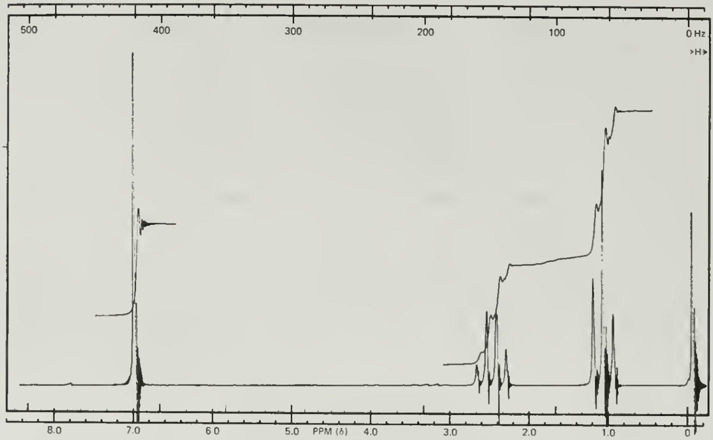
10. The bond dissociation energy of the C—Cl bond in chlorobenzene, about 96 kcal mole^{-1}, is 15 kcal mole^{-1} greater than that in isopropyl chloride. Explain briefly.

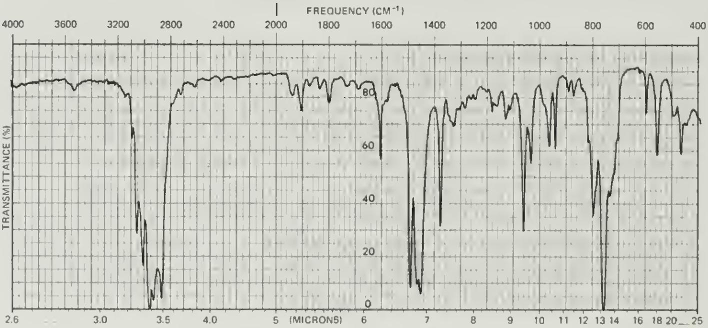
11. Toluene is 605 times as reactive as benzene towards bromination in aqueous acetic acid. The bromotoluenes produced are 32.9% *ortho*, 0.3% *meta*, and 66.8% *para*. Calculate the partial rate factors.

12. (a) The partial rate factors for chlorination of toluene are: *ortho*, 620; *meta*, 5.0; *para*, 820. Calculate the isomer distribution in chlorination of *m*-xylene (*m*-dimethylbenzene). The experimental result is 77% 4-, 23% 2-, and ≈0% 5-.

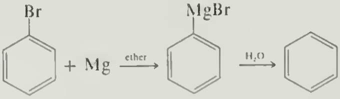
(b) The partial rate factors for chlorination of chlorobenzene are: *ortho,* 0.1; *meta,* 0.002; *para,* 0.41. Calculate the isomer distribution in chlorination of *p*-chlorotoluene (the experimental result is 77% 2,4-dichlorotoluene and 23% 3,4-dichlorotoluene).

13. A compound, $C_{10}H_{14}$, has the following nmr and ir spectra. Determine the structure of the compound.



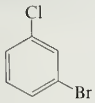


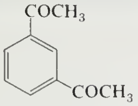
14. One general reaction of halobenzenes is the formation of Grignard reagents (Section 30.3.B). Thus, bromobenzene gives a Grignard reagent, which is hydrolyzed by water to give benzene.

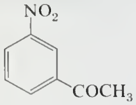


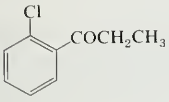
All six isomers of bromodimethylbenzene [$BrC_6H_3(CH_3)_2$] are known. Show how the above reaction, with Körner's absolute method, may be used to establish the structures of the three isomeric dimethylbenzenes.

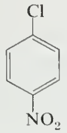
15. Which of the following compounds can probably be prepared in a pure state from benzene by using two successive electrophilic substitution reactions? For each compound, write out the reaction sequence and describe how the intermediates and products would be purified.

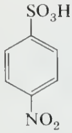
(a)


(b)

COCH3
COCH3

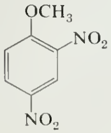
(c)


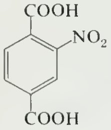
(d)

Cl
COCH2CH3

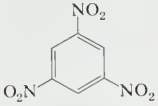
(e)


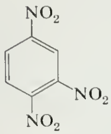
(f)


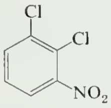
16. Which of the following compounds can probably be prepared in a pure state by electrophilic substitution on a disubstituted benzene? Outline the method in each case.

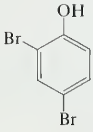
(a)

OCH3
NO2
NO2

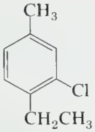
(b)

COOH
NO2
COOH

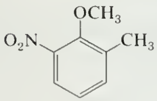
(c)


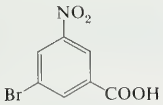
(d)


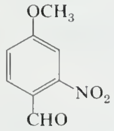
(e)


(f)


(g)

CH3
Cl
CH2CH3

(h)

OCH3
O2N
CH3

(i)


(j)

OCH3
NO2
CHO

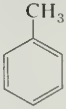
17. Toluene is *ortho,para* directing, whereas trifluoromethylbenzene, $C_6H_5CF_3$, is *meta* directing. Explain.

18. Körner's absolute method may be applied just as logically to the determination of the structures of trisubstituted benzenes. Consider a case in which three isomers, A, B, C, of $C_6H_3Y_3$ are all in hand. Each is allowed to react to introduce another Y group. There are three possible tetrasubstituted benzenes, $C_6H_2Y_4$, P, Q, and R. Reaction of A gave only P. Reaction of B or C gave a mixture of P and Q. Unfortunately, R could not be isolated. From these data determine the structures of all six compounds insofar as possible.

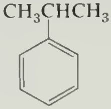
CHAPTER 30
Benzene Hydrocarbons and Halides

30.1
Nomenclature

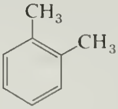
Aromatic hydrocarbons have the generic name of **arene,** to distinguish them from the alkanes. Accordingly, for many purposes the abbreviation, Ar, for aryl is used just as R is used for alkyl; thus, the symbol ArR refers to arylalkanes. Many alkylbenzenes have common names which have become so entrenched in the chemical literature that they are official IUPAC names for the compounds. The important ones are listed below.



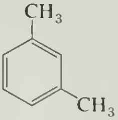
toluene



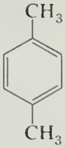
cumene



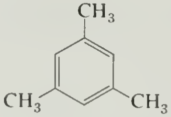
o-xylene



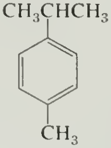
m-xylene



p-xylene

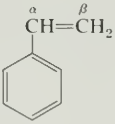


mesitylene
1,3,5-trimethylbenzene


CH3CHCH3
CH3

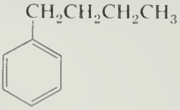
p-cymene
1-isopropyl-
4-methylbenzene

In addition, the accepted IUPAC name of vinylbenzene is **styrene.**

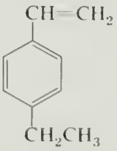


styrene

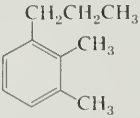
Other substituted benzenes are named as derivatives of benzene or of one of the foregoing hydrocarbons.


CH2CH2CH2CH3

butylbenzene

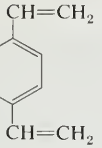

CH=CH2
CH2CH3

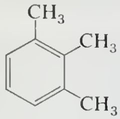
p-ethylstyrene


CH2CH2CH3
CH3
CH3

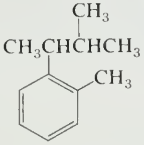
3-propyl-*o*-xylene, or
1,2-dimethyl-3-propylbenzene

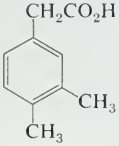
However, if the substituent introduced is the same as one already present, the compound is named as a derivative of benzene.

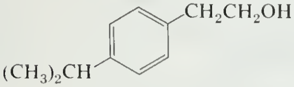

p-divinylbenzene
(not *p*-vinylstyrene)

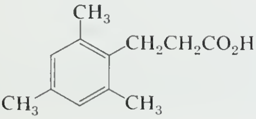

1,2,3-trimethylbenzene
(not 3-methyl-*o*-xylene)

Derivatives of toluene, cumene, the xylenes, and mesitylene, where the additional substituent is attached to the ring, may be named by using the prefixes **tolyl-, cumenyl-, xylyl-,** or **mesityl-.**

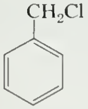

2-methyl-3-*o*-tolylbutane

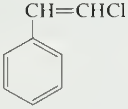

3,4-xylylacetic acid

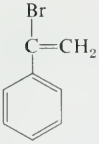

2-(*p*-cumenyl)ethanol

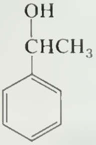

3-mesitylpropanoic acid

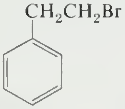
Certain other radical names are used for derivatives of these hydrocarbons when the substituent is attached to a side chain.

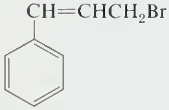

benzyl chloride
α-chlorotoluene


β-styryl chloride
β-chlorostyrene


α-styryl bromide
α-bromostyrene


α-phenethyl alcohol


β-phenethyl bromide


cinnamyl bromide

$(C_6H_5)_2CHOOCCH_3$
benzhydryl acetate
diphenylmethyl acetate

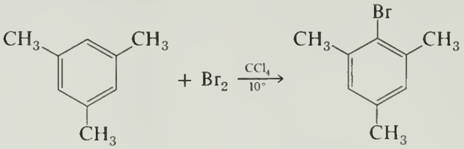
$(C_6H_5)_3CONO_2$
trityl nitrate
triphenylmethyl nitrate

30.2
Preparation of Halobenzenes

Functional groups on the side chain behave more or less as typical aliphatic functions. The presence of a benzene ring close to the functional group does have some important effects that we will take up later in this chapter. However, the chemistry of a halogen attached to a benzene ring is sufficiently different from side chain halides that we will study them independently. The ring halides are important intermediates that can be converted to other compounds.

A. *Electrophilic Aromatic Substitution*

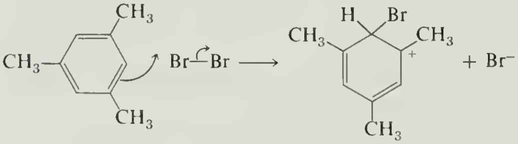
One important preparation of ring halides is by electrophilic aromatic substitution (Section 21.2.A). The active reagent in these reactions is an actual or incipient halonium ion. For sufficiently activated rings, halogenation may be accomplished using the halogen alone.


CH$_3$
CH$_3$
CH$_3$
+ Br$_2$
CCl$_4$
10°
Br
CH$_3$
CH$_3$
CH$_3$

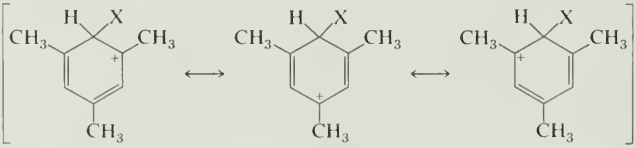
(79–82%)

mesitylene bromomesitylene

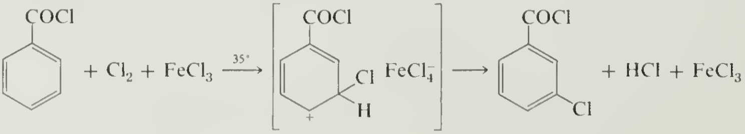
In such a case, the reaction may be considered to be a displacement reaction on halogen with the ring acting as a nucleophile.


CH$_3$
CH$_3$
CH$_3$
Br—Br
H
Br
CH$_3$
CH$_3$
+
CH$_3$
+ Br$^-$

Mesitylene is especially reactive because the intermediate produced is highly stabilized; all three of the usual resonance structures correspond to tertiary carbonium ions.


H X
CH$_3$
CH$_3$
+
CH$_3$
H X
CH$_3$
CH$_3$
+
CH$_3$
H X
CH$_3$
CH$_3$
+
CH$_3$

For less reactive rings, a Lewis acid such as a ferric salt is used to catalyze the reaction


COCl
+ Cl$_2$ + FeCl$_3$
35°
COCl
Cl
H
+
FeCl$_4^-$
COCl
Cl
+ HCl + FeCl$_3$

Iodobenzene can be prepared by a special reaction from iodine and an oxidizing agent under acidic conditions. Suitable oxidizing agents include nitric acid or arsenic acid (H_3AsO_4).

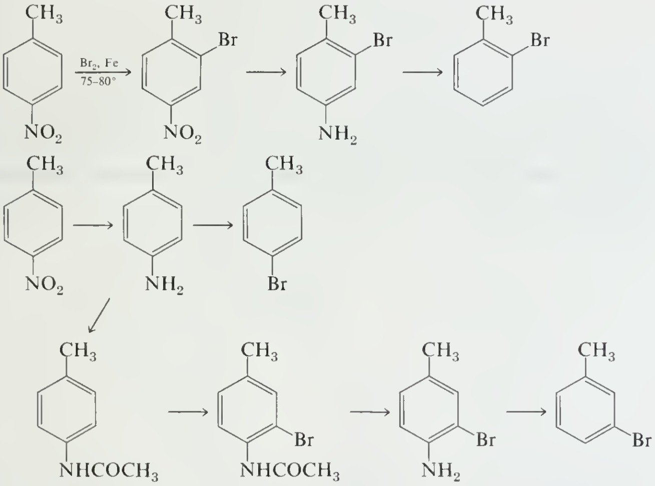
$$C_6H_6 + I_2 + HNO_3 \xrightarrow{50^\circ} NO + NO_2 + \underset{(86\text{–}87\%)}{C_6H_5I}$$

The reaction involves a normal aromatic electrophilic substitution by iodonium ion obtained by oxidation

$$I_2 \xrightarrow{-2e} 2\ I^+$$

B. *Use of Aromatic Amines*

Direct electrophilic aromatic substitution is most useful when the product is essentially a single compound. In many cases of *ortho,para* orientation the mixture of *ortho* and *para* compounds produced cannot be separated by practical means. Other routes involve the chemistry of aromatic amines and will be discussed in Chapter 32. The value of the amines comes from their ease of preparation from nitro compounds and from the reactions available for conversion to other functions. A single example at this time will emphasize this point.



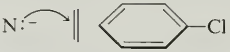
The boiling points of *o*- and *p*-nitrotoluene differ sufficiently so that these isomers can be separated by fractional distillation (Section 29.8). By the general routes shown above, all of the individual pure bromotoluenes can be prepared.

30.3
Reactions of Halobenzenes

A. *Substitution Reactions*

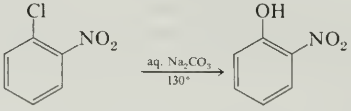
The halogen of an aryl halide can be replaced by other nucleophiles. However, such substitution reactions do *not* occur by the S_N2 mechanism. Like vinyl halides

(Section 13.7), aryl halides cannot achieve the geometry necessary for a backside displacement; the ring shields the rear of the C—X bond.

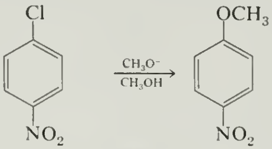


Instead, nucleophilic substitution occurs by two other mechanisms, **addition-elimination** and **elimination-addition.**

1. THE ADDITION-ELIMINATION MECHANISM. Aryl halides that have electron-attracting groups in the positions *ortho* and *para* to the halogen undergo substitution under rather mild conditions. The most effective groups are nitro and carbonyl groups.

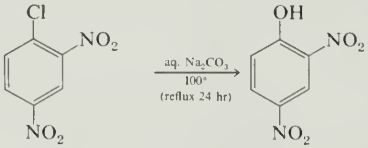


o-nitrochlorobenzene *o*-nitrophenol

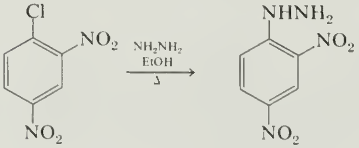


p-nitrochlorobenzene *p*-nitroanisole

With two nitro groups in conjugating positions, this type of displacement reaction is quite facile



2,4-dinitrochlorobenzene 2,4-dinitrophenol

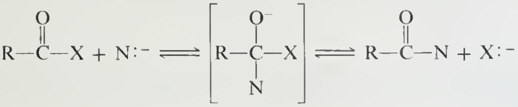


(30-1)

2,4-dinitrophenylhydrazine

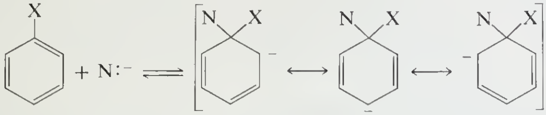
2,4-Dinitrophenylhydrazine prepared as shown in (30-1) is a common reagent used for preparing the corresponding 2,4-dinitrophenylhydrazone derivatives of aldehydes and ketones (see Section 15.7.C). These derivatives are usually crystalline compounds with well-defined melting points and are useful for characterizing aldehydes and ketones; the 2,4-dinitrophenylhydrazones are commonly abbreviated as DNPs.

The mechanism of these substitution reactions involves two steps, an addition followed by an elimination. It is analogous to the nucleophilic addition-elimination mechanism so prevalent in the chemistry of carboxylic acids and derivatives of carboxylic acids (Chapter 18).

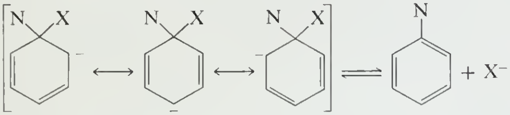


$$R-\overset{O}{\overset{\|}{C}}-X + N:^- \rightleftharpoons \left[R-\underset{N}{\overset{O^-}{C}}-X\right] \rightleftharpoons R-\overset{O}{\overset{\|}{C}}-N + X:^-$$

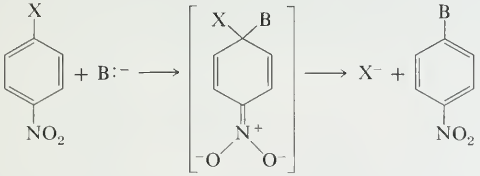
In the first step, the attacking nucleophile adds to the benzene ring to give a resonance-stabilized pentadienyl anion.



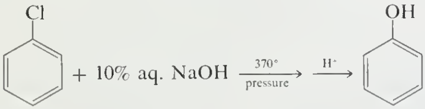
The pentadienyl anion can eject the nucleophile, regenerating the reactants, or it can eject halide ion, giving the substitution product.



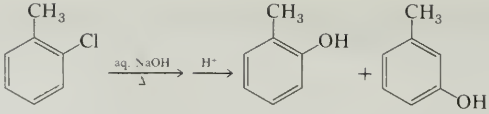
However, even a conjugated pentadienyl anion is not sufficiently stable for this mechanism to operate with such simple aryl halides as chlorobenzene or *o*-bromotoluene. Electron-attracting groups provide further resonance stabilization of the anion, thus lowering its energy enough for it to be formed as a reaction intermediate. As the foregoing resonance structures show, the nitro or carbonyl groups are most effective when they are *ortho* or *para* to the leaving group.



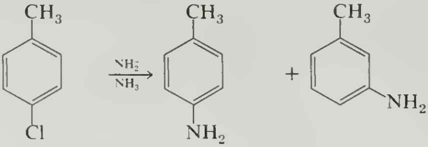
2. THE ELIMINATION-ADDITION MECHANISM; BENZYNE. With this type of background, it may seem surprising that one commercial preparation of phenol involves heating chlorobenzene itself with aqueous sodium hydroxide.

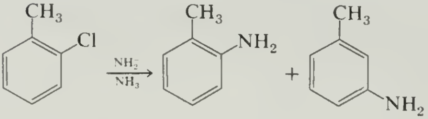


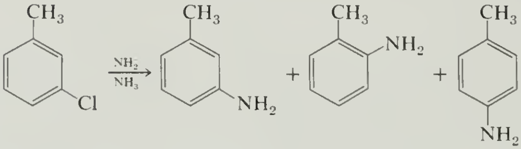
However, this reaction is not a simple displacement of chloride by hydroxide. *o*-Chlorotoluene, for example, gives not just *o*-methylphenol in this reaction, but a mixture of *o*- and *m*-methylphenol.


CH3
Cl
aq. NaOH
Δ
H+
CH3
OH
+
CH3
OH

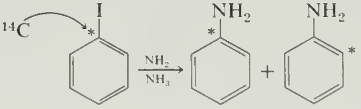
An analogous reaction occurs under milder conditions with amide ion in liquid ammonia.


CH3
Cl
NH2−
NH3
CH3
NH2
+
CH3
NH2

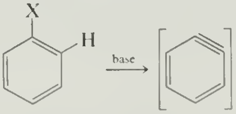

CH3
Cl
NH2−
NH3
CH3
NH2
+
CH3
NH2


CH3
Cl
NH2−
NH3
CH3
NH2
+
CH3
NH2
+
CH3
NH2

The remarkable feature of these reactions is that the entering group substitutes not only at the position of the displaced halide, but also at the ring position adjacent to the original halide. Even iodobenzene shows this behavior, as has been demonstrated using ^{14}C-labeled materials.

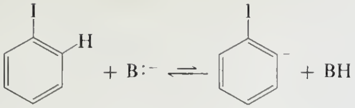

14C
I
*
NH2−
NH3
NH2
*
+
NH2
*

These results are rationalized by the involvement as a reactive intermediate of the product of an elimination reaction—dehydrobenzene or "benzyne."

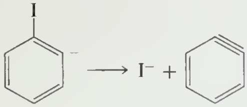


"benzyne"

The detailed mechanism involves a series of steps. Benzene itself is a weak acid, but its pK_a of 43 corresponds to a much higher acidity than the alkanes (p$K_a \approx 50$). The close proximity of an electronegative halogen renders an adjacent hydrogen sufficiently acidic that it is removed by a strong base such as NH_2^-.



The intermediate iodophenyl anion can itself pick up a proton to regenerate the original iodobenzene, *or it can lose iodide ion.*



The driving force for this reaction is the formation of a stable halide ion. The "benzyne" generated is a very reactive intermediate; recall that cyclooctyne is the smallest ring with a stable triple bond (Section 23.7). By special techniques benzyne has been detected spectroscopically.

The electronic structure of benzyne may be visualized readily as a distorted acetylene. A triple bond has two π bonds, as shown in Figure 30.1. One π bond is constructed from p orbitals perpendicular to the plane of the paper (dotted line in Figure 30.1); the other π bond derives from overlap of p orbitals in the plane of the page, as illustrated. When the triple bond is distorted from linearity, one π bond is essentially unchanged, but the other π bond now involves hybrid orbitals directed away from each other with consequent reduced overlap. Reduced overlap means a weaker and more reactive bond. Benzyne is related in this sense to the distorted acetylenes. The two orbitals shown in Figure 30.1 provide inefficient overlap and a weak, reactive bond. The resulting strained triple bond reacts readily with any available nucleophilic reagent *at either end of the triple bond.*

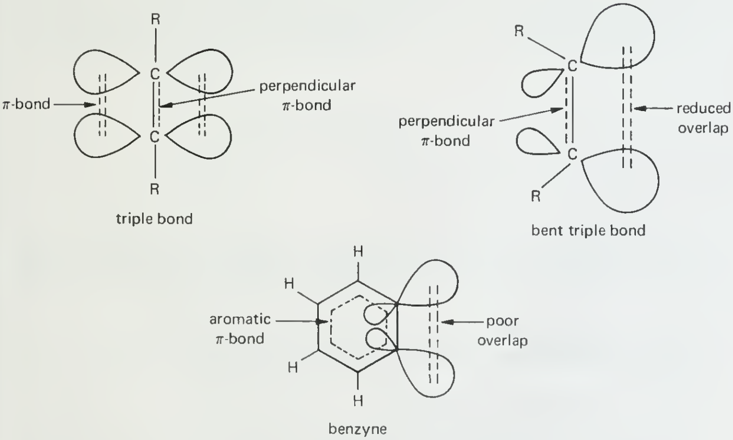
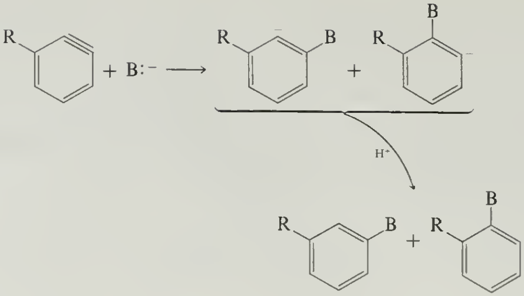
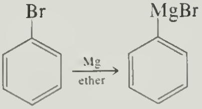


FIGURE 30.1 *Electronic structure of benzyne.*

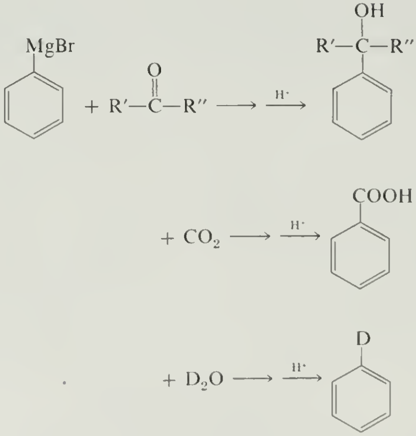

R
+ B:⁻
R
B
+
R
B
H⁺
R
B
+
R
B

B. *Metallation and Transmetallation*

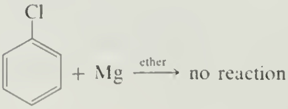
1. **GRIGNARD REAGENTS.** Aryl bromides form Grignard reagents in a normal fashion with magnesium in ether.


Br
Mg
ether
MgBr

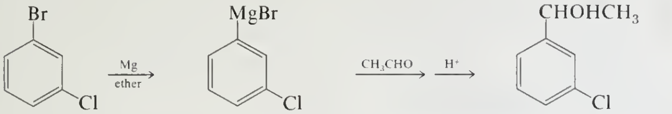
Such Grignard reagents undergo all the usual reactions of alkyl Grignard reagents: they react with aldehydes, ketones, CO_2, halogens, D_2O, and so on.


MgBr
+ R′—C—R″
O
H⁺
OH
R′—C—R″
+ CO₂
H⁺
COOH
+ D₂O
H⁺
D

Chlorobenzenes do not normally form Grignard reagents in ether.


Cl
+ Mg
ether
no reaction

Consequently, a bromochlorobenzene will form a chloro-Grignard reagent.

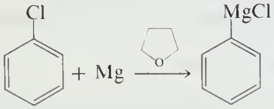


(82–88%)

m-chlorophenylmagnesium bromide

1-(*m*-chlorophenyl)ethanol

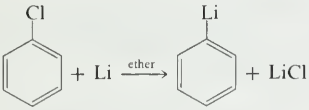
Grignard reagents can be prepared from aryl chlorides by using tetrahydrofuran (THF) as the solvent.



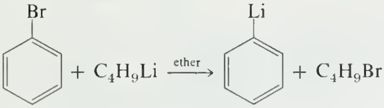
Of course, the formation of the Grignard reagent is successful only if no functional groups are present that will react with such reagents: examples of such reactive groups are NO_2, NO, COR, SO_3R, CN, OH and NH_2.

The formation of aryl Grignard reagents is restricted to bromides and chlorides. Iodides give poor yields and fluorides do not react.

2. **Aryllithium Reagents.** Aryllithium reagents can be prepared by reaction of lithium metal with aryl bromides or chlorides.



The lithium reagents generally undergo the same reactions as the Grignard reagents. Furthermore, aryllithiums can be prepared by **transmetallation** of an aryl bromide or iodide with an alkyllithium.



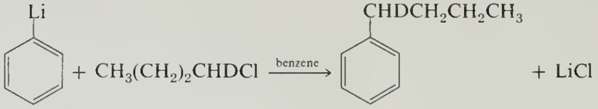
(85%)

With aryl bromides or iodides the reaction is rapid, even at low temperature. The reaction may be regarded as a displacement reaction on halogen to form the lithium salt of a more stable anion.

$$ArX + R^-Li^+ \longrightarrow Ar^-Li^+ + RX$$

This reaction is most successful with aromatic bromides and iodides; the chlorides do not react as cleanly or rapidly.

The resultant aryllithium reagents are nucleophilic reagents that can undergo displacement reactions on reactive alkyl halides or sulfonate esters. Such reactions are typical S_N2 displacement reactions in which the aryllithiums are the nucleophilic reagents. Since these reagents may be regarded as the lithium salts of strong bases, the reactions are most successful with simple primary halides; other halides give concurrent E2 elimination reactions.



S-(+)-1-chlorobutane-1-*d*

R-(−)-1-phenylbutane-1-*d*

3. **Wurtz-Fittig Reaction.** A variation of the reaction of aryllithiums with alkyl halides is the Wurtz-Fittig reaction, in which a mixture of aryl and primary alkyl halides is treated with sodium metal.

$$C_6H_5Br + CH_3(CH_2)_3CH_2Br + 2\ Na \xrightarrow[20^\circ]{\text{ether}} \underset{(65\text{–}70\%)}{C_6H_5(CH_2)_4CH_3} + 2\ NaBr$$

In this reaction the sodium reacts first with the aryl bromide to form the arylsodium, which then reacts with the alkyl bromide by the S_N2 mechanism.

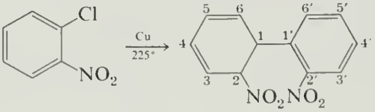
$$ArBr + 2\ Na \longrightarrow ArNa + NaBr$$
$$Ar^-Na^+ + RX \longrightarrow ArR + NaX$$

Under the proper conditions, the yields are quite good; this reaction is related to, but is considerably better than, the Wurtz reaction of alkyl halides with sodium (Section 9.4.A).

4. **Ullmann Reaction.** The Ullmann reaction appears superficially to be closely related to the Wurtz reaction.

$$2\ ArI + Cu \xrightarrow{\Delta} ArAr + CuI_2$$

The product of this reaction is a biaryl in which two benzene rings are joined together.

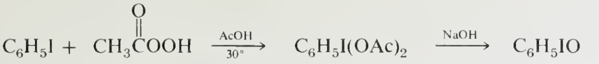


2,2′-dinitrobiphenyl

The chemistry of biaryls will be detailed in a subsequent chapter (Chapter 34). The Ullmann reaction works well with chlorides, bromides, and iodides and is facilitated by electron-attracting groups such as NO_2 and CN functions. The reaction involves the formation of an arylcopper intermediate which undergoes a free-radical-like coupling, probably while still coordinated to copper.

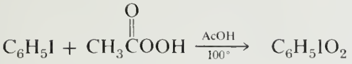
C. *Oxidation of Aryl Iodides*

Aryl iodides can be oxidized to form a series of interesting higher-valent iodine compounds.



$$C_6H_5I + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OOH \xrightarrow[30^\circ]{AcOH} C_6H_5I(OAc)_2 \xrightarrow{NaOH} C_6H_5IO$$

peroxyacetic acid — (83–91%) iodobenzene diacetate — (85–93%) iodosobenzene



$$C_6H_5I + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OOH \xrightarrow[100^\circ]{AcOH} C_6H_5IO_2$$

(72–80%)
iodoxybenzene

These higher valent states can also be prepared by direct reaction with chlorine.

$$C_6H_5I + Cl_2 \xrightarrow{CHCl_3} C_6H_5ICl_2$$

(87–94%)
iodobenzene dichloride

The dichloride can be hydrolyzed to iodosobenzene with aqueous sodium hydroxide in the same way as the diacetate. Iodoso- and iodoxybenzene explode on heating above about 200°. They do not represent important classes of compounds, but they do lead to an interesting class of iodonium salts.

$$C_6H_5IO + C_6H_5IO_2 \xrightarrow{aq.\ NaOH} (C_6H_5)_2I^+\ IO_3^- \xrightarrow{KI} (C_6H_5)_2I^+\ I^-$$

diphenyliodonium iodate — (70–72%) diphenyliodonium iodide

The product diphenyliodonium iodide is a crystalline salt isomeric with iodobenzene, which reverts to iodobenzene on heating.

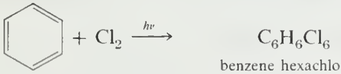
30.4
Preparation of Side Chain Halides

A. *Free Radical Halogenation*

Benzene itself does not undergo the type of free radical chlorination typical of alkanes. The bond dissociation energy of the phenyl-hydrogen bond is rather high ($DH^\circ = 112$ kcal mole^{-1}), undoubtedly because the bond involved is C_{sp^2}-H_{1s} and has extra s character. Consequently, the hydrogen transfer reaction is endothermic.

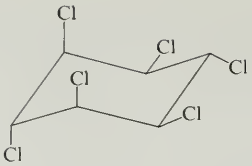
$$C_6H_5{-}H + Cl\cdot = C_6H_5\cdot + HCl \qquad \Delta H^\circ = +9 \text{ kcal mole}^{-1}$$

Instead, chlorine atoms tend to add to the ring with the ultimate formation of a hexachlorocyclohexane.



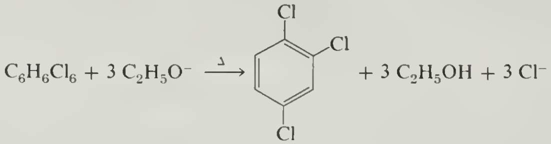
$C_6H_6Cl_6$
benzene hexachloride
1,2,3,4,5,6-hexachlorocyclohexane

Eight geometric isomers are possible. The so-called γ isomer **(gammexane, lindane)** has insecticidal properties and constitutes 18% of the mixture.

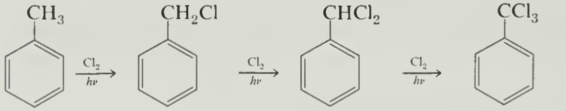

Cl
Cl
Cl
Cl
Cl
Cl

γ-benzene hexachloride

Reaction of the benzene hexachlorides with hot alcoholic potassium hydroxide gives 1,2,4-trichlorobenzene.


$C_6H_6Cl_6 + 3\ C_2H_5O^- \xrightarrow{\Delta}$
Cl
Cl
Cl
$+ 3\ C_2H_5OH + 3\ Cl^-$

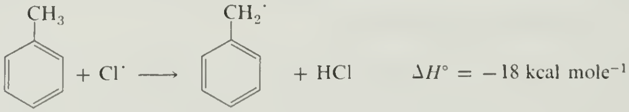
In contrast, toluene undergoes smooth free radical chlorination on the methyl group to give benzyl chloride. Benzyl chloride undergoes further halogenation to give benzal chloride and benzotrichloride.


CH_3
$\xrightarrow[h\nu]{Cl_2}$
CH_2Cl
$\xrightarrow[h\nu]{Cl_2}$
$CHCl_2$
$\xrightarrow[h\nu]{Cl_2}$
CCl_3

benzyl chloride   benzal chloride   benzotrichloride

The extent of chlorination may be controlled by monitoring the amount of chlorine used.

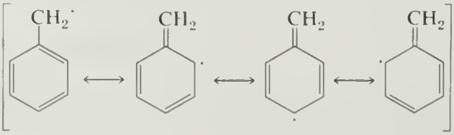
The reaction of toluene with chlorine atoms occurs exclusively at the methyl group because of the low bond dissociation energy of the benzyl-hydrogen bond ($DH° = 85$ kcal mole^{-1})


CH_3
$+ Cl^{\cdot} \longrightarrow$
$CH_2^{\cdot}$
$+ HCl$
$\Delta H° = -18$ kcal mole^{-1}

benzyl radical

The benzyl radical is especially stable for the same reason the allyl radical is stabilized (Section 20.1.D). Delocalization of the odd electron into the ring spreads out and diffuses the free radical character of the molecule. This conjugation can be represented by orbital overlap between the carbon $2p$ orbital containing the odd electron and the ring π system, as in Figure 30.2.

Alternatively, the conjugated system can be represented by resonance structures.


$CH_2^{\cdot}$
CH_2
CH_2
CH_2

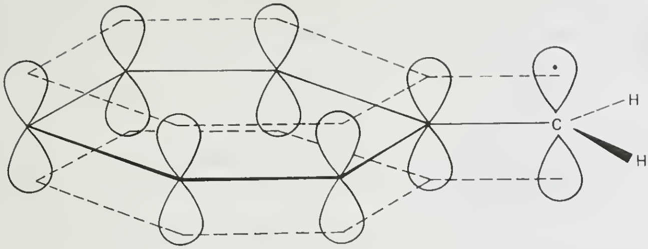
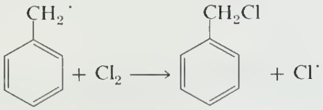
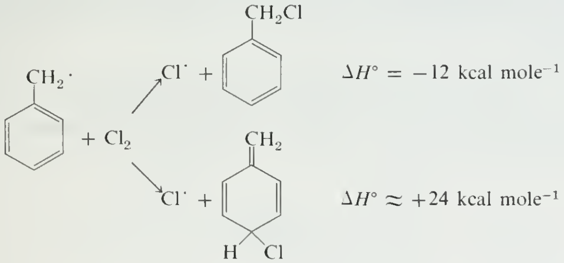


Figure 30.2 *Delocalization of the benzyl radical.*

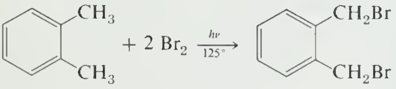
In the next step of the chain halogenation reaction, benzyl radical reacts with chlorine to regenerate a chlorine atom, which then continues the chain.


CH₂·
+ Cl₂
CH₂Cl
+ Cl·

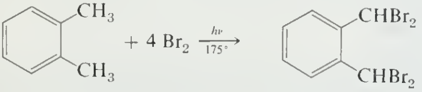
Note that benzyl radical reacts exclusively at the exocyclic position. The *ortho* and *para* positions do have odd-electron character, but reaction at these positions produces a chloride that does not have the aromatic stability of a benzene ring. The resulting effect on the thermodynamics of reaction is substantial.


CH₂·
+ Cl₂
Cl· +
CH₂Cl
ΔH° = −12 kcal mole⁻¹
Cl· +
CH₂
H
Cl
ΔH° ≈ +24 kcal mole⁻¹

The free radical chain bromination of toluene is exactly analogous and is a suitable route to benzyl bromide. With xylene, the two methyl groups undergo successive halogenation.

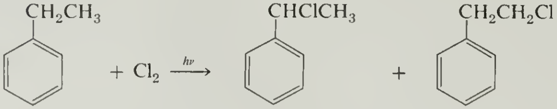

CH₃
CH₃
+ 2 Br₂
hν
125°
CH₂Br
CH₂Br

(48–53%)
α,α′-dibromo-*o*-xylene


CH₃
CH₃
+ 4 Br₂
hν
175°
CHBr₂
CHBr₂

(74–80%)
α,α,α′,α′-tetrabromo-*o*-xylene

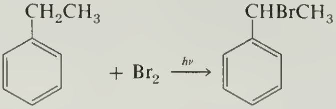
With the higher alkylbenzenes, chlorination is limited in its synthetic utility because reaction along the alkyl chain occurs in addition to reaction at the benzylic position.



(56%)
α-chloroethylbenzene
1-chloro-1-phenylethane

(44%)
β-chloroethylbenzene
2-chloro-1-phenylethane

However, bromination occurs exclusively at the benzylic position.



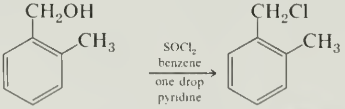
This difference in behavior again reflects the greater reactivity of chlorine atoms compared to bromine; recall that bromine generally is a more selective reagent than chlorine (Section 5.3.B).

B. *Side Chain Halides from Alcohols*

The reaction of phenyl-substituted alcohols to prepare the corresponding halides is generally a straightforward reaction that corresponds to the general reaction of alcohols.

$$C_6H_5CH_2CH_2OH + SOCl_2 \xrightarrow{\text{pyridine}} C_6H_5CH_2CH_2Cl$$

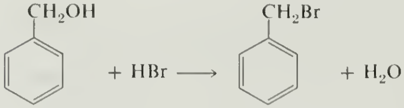
The corresponding reactions of benzylic alcohols are especially facile.



(75–89%)

o-methylbenzyl alcohol

α-chloro-*o*-xylene

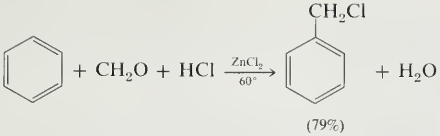


benzyl alcohol

benzyl bromide

C. *Chloromethylation*

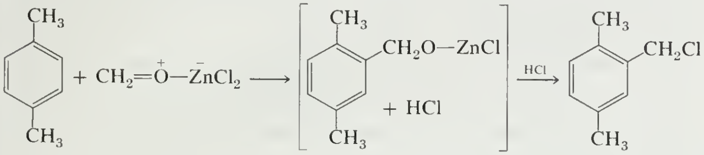
The direct introduction of a $ClCH_2$— group into an aromatic compound can frequently be accomplished by the reaction of formaldehyde, hydrogen chloride, and a Lewis acid, such as $ZnCl_2$.



The reaction is an electrophilic aromatic substitution, probably by the oxonium ion formed by coordination of the formaldehyde with the Lewis acid.

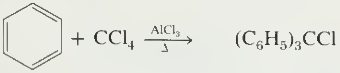
$$[H_2C=\overset{+}{O}-\overset{-}{Zn}Cl_2 \longleftrightarrow H_2\overset{+}{C}-O-\overset{-}{Zn}Cl_2]$$

The resulting reagent will react with aromatic rings which are at least as reactive as benzene. The product of electrophilic aromatic substitution by the coordinated aldehyde is the corresponding alcohol, but this alcohol is benzylic, and in the presence of $ZnCl_2$-HCl it is converted rapidly to the corresponding chloride.



The chloromethylation reaction must be conducted in an efficient hood and with extreme care. Under these reaction conditions bis-chloromethyl ether, $ClCH_2OCH_2Cl$, is produced. This compound is a potent carcinogen and should be avoided wherever possible.

An important side reaction in chloromethylation reactions is the further alkylation of another ring by the chloromethyl group to produce a diarylmethane. A related reaction is the Friedel-Crafts alkylation (Section 30.6.A) with carbon tetrachloride.

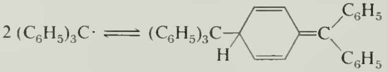


(84-86%)
triphenylmethyl chloride

Triphenylmethyl chloride, or "trityl" chloride, is a colorless crystalline solid, m.p. 111-112°, which forms the starting point of a fascinating chapter of organic chemistry. In experiments reported in 1900, Moses Gomberg treated triphenylmethyl chloride with finely divided silver in an inert atmosphere to obtain a white solid hydrocarbon formulated as hexaphenylethane. In organic solvents, this hydrocarbon gives yellow solutions which rapidly absorb oxygen from the atmosphere. These solutions contain a relatively stable free radical, triphenylmethyl:

$$(C_6H_5)_3C-C(C_6H_5)_3 \rightleftharpoons 2\,(C_6H_5)_3C^{\cdot} \xrightarrow{O_2} \underset{\text{bis-triphenylmethyl peroxide}}{(C_6H_5)_3COOC(C_6H_5)_3}$$

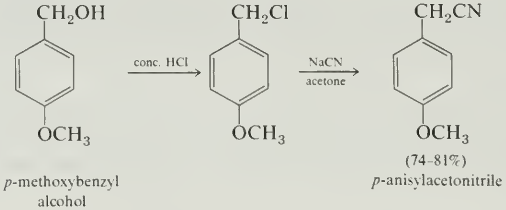
The stability of triphenylmethyl radical stems from π conjugation in the radical and steric hindrance in the dimer. Equilibrium studies showed the central bond in the dimer to have a strength of only 11 kcal mole^{-1}. A most remarkable epilog to this story was provided by recent structural studies based primarily on nmr evidence that show that the hydrocarbon considered to be hexaphenylethane for the better part of a century does not have this structure at all, but is instead the product of dimerization at one *para* position:



In other words, hexaphenylethane is so congested that it is less stable than the isomer shown despite the loss of the resonance energy of one benzene ring in this structure!

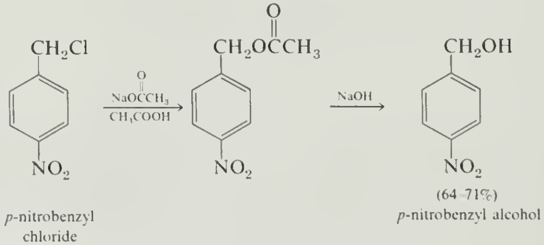
30.5
Reactions of Side Chain Halides

The reactions of phenylalkyl halides are comparable to those of alkyl halides —they undergo displacement reactions, eliminations, formation of Grignard reagents, and so on. However, when the halogen is α to a benzene ring the compounds are especially reactive. Benzyl halides are generally at least a hundred times as reactive as ethyl halides in S_N2 displacement reactions. This high reactivity is attributed to conjugation of the ring π electrons in the transition state (Figure 30.3). Accordingly, such displacement reactions are straightforward and facile. Some examples are



p-methoxybenzyl alcohol

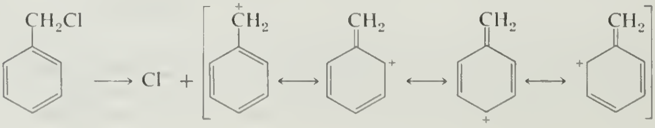
p-anisylacetonitrile



p-nitrobenzyl chloride

p-nitrobenzyl alcohol

Benzylic compounds also react rapidly by the S_N1 mechanism because of the relative stability of the benzyl cation.



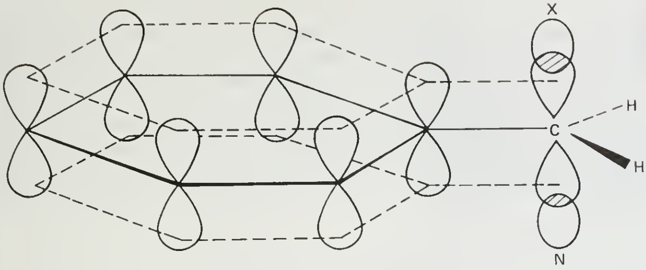


Figure 30.3 *Transition state for* S_N2 *reaction with a benzyl halide.*

In fact, the gas phase enthalpy of ionization of benzyl chloride is more comparable to that of secondary alkyl chlorides than to that of primary alkyl chlorides.

	$\Delta H°$, *kcal mole*$^{-1}$
$C_6H_5CH_2Cl \rightleftharpoons C_6H_5CH_2^+ + Cl^-$	165
$C_2H_5Cl \rightleftharpoons C_2H_5^+ + Cl^-$	192
$(CH_3)_2CHCl \rightleftharpoons (CH_3)_2CH^+ + Cl^-$	170
$(CH_3)_3CCl \rightleftharpoons (CH_3)_3C^+ + Cl^-$	157

When the carbonium ion center is conjugated with two or three benzene rings, the positive charge is distributed to a still greater extent. For example, triphenylmethyl cation has ten resonance structures in which the charge is spread to six *ortho* and three *para* positions. Consequently, triphenylmethyl chloride ionizes readily and shows exceptional reactivity. A liquid sulfur dioxide solution is colored yellow and conducts electricity because of the triphenylmethyl cations and chloride ions present.

$$(C_6H_5)_3CCl \xrightleftharpoons{SO_2} \underset{\text{(yellow color)}}{(C_6H_5)_3C^+} + Cl^-$$

$$K = \frac{[(C_6H_5)_3C^+][Cl^-]}{[(C_6H_5)_3CCl]} = 4 \times 10^{-5}\,M$$

Similarly, triphenylmethanol is converted into substantial amounts of triphenylmethyl cation in strong aqueous sulfuric acid.

$$(C_6H_5)_3COH + H^+ \rightleftharpoons (C_6H_5)_3C^+ + H_2O$$

$$K = \frac{[(C_6H_5)_3C^+]}{[(C_6H_5)_3COH][H^+]} = 2 \times 10^{-7}\,M^{-1}$$

To give some idea of relative magnitudes of reactivity, benzyl chloride undergoes S_N1 type reactions much more slowly than *t*-butyl chloride, diphenylmethyl chloride is 10^1 to 10^3 times faster than *t*-butyl chloride, and triphenylmethyl chloride is 10^6 to 10^7 times more reactive than *t*-butyl chloride.

Order of S_N1 reactivity:

$$(C_6H_5)_3CCl > (C_6H_5)_2CHCl > (CH_3)_3CCl > C_6H_5CH_2Cl$$

In fact, the rate of S_N1 reaction of triphenylmethyl chloride with ethanol is comparable to the rate at which the solid triphenylmethyl chloride dissolves.

The most effective conjugation between the carbonium ion center and the benzene π electrons in triphenylmethyl cation requires that the whole molecule be coplanar. In this type of structure, however, the *ortho*-hydrogens of the phenyl groups are only about 0.5 Å apart; the resulting steric repulsion forces the rings to tilt apart. The actual structure of triphenylmethyl cation is that of a three-bladed propeller, as shown by the stereo plot of tris-*p*-aminophenylmethyl cation in Figure 30.4. This twisting of the phenyl groups does somewhat diminish the magnitude of conjugation between the central carbon and each ring, but the effect is not large.

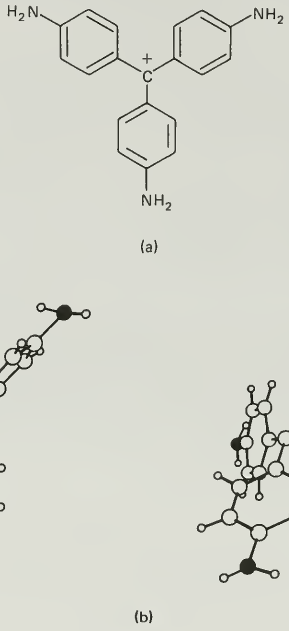
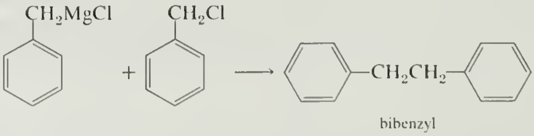


Figure 30.4 *Tris-p-aminophenylmethyl cation:* (a) *conventional structure;* (b) *stereo structure.*

The reaction of benzyl chloride with magnesium closely resembles the reaction of allyl chloride (Section 20.1.C). Benzylmagnesium chloride forms and reacts with benzyl chloride to produce 1,2-diphenylethane (bibenzyl).

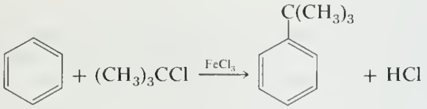


In the same manner as with the allylic systems special care and techniques are required to prepare benzylic Grignard reagents.

30.6 Preparation of Aromatic Hydrocarbons

A. *Friedel-Crafts Alkylation*

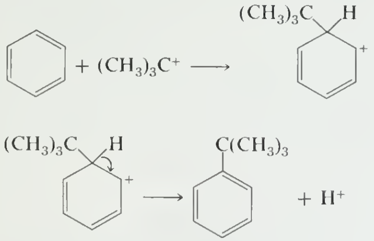
Benzene and some substituted benzenes undergo alkylation when treated with an alkyl halide and a Lewis acid catalyst such as $FeBr_3$ or $AlCl_3$. For example, benzene reacts with *t*-butyl chloride to give *t*-butylbenzene.



> To a mixture of 25 g of anhydrous ferric chloride (or 50 g of anhydrous aluminum chloride) in 200 ml of benzene cooled to 10° is added slowly and with stirring 50 g of *t*-butyl chloride. The mixture is allowed to warm to room temperature and when no further HCl is evolved, ice, water, and dilute hydrochloric acid are added. The organic layer is washed, dried, and distilled to give *t*-butylbenzene, b.p. 168.5°.

Such reactions are called **Friedel-Crafts alkylations** and occur by a mechanism similar to that involved in the Friedel-Crafts acylation reaction (Section 21.2.E). In this case, *t*-butyl chloride reacts with the Lewis acid to give the *t*-butyl cation. In the absence of other nucleophiles, this electrophilic species reacts with the aromatic ring.

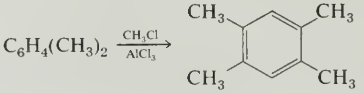
$$(CH_3)_3CCl + FeCl_3 \rightleftharpoons (CH_3)_3C^+FeCl_4^-$$



The Friedel-Crafts alkylation has two important limitations that severely restrict its usefulness and render the reaction generally less valuable than Friedel-Crafts acylation. Alkylbenzenes are generally *more* reactive in electrophilic aromatic substitution than is benzene itself (Section 29.3); hence, the alkylbenzene reaction product tends to react to give di- and higher alkylated products.

$$C_6H_6 \xrightarrow[(CH_3)_3CCl]{FeCl_3} C_6H_5C(CH_3)_3 \xrightarrow[\substack{(CH_3)_3CCl \\ \text{(faster)}}]{FeCl_3} C_6H_4[C(CH_3)_3]_2$$

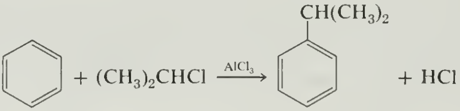
The only practical way of controlling such additional reactions is to keep benzene in large excess. This approach is practical with benzene itself, an inexpensive compound often used as a solvent, but it is impractical with substituted benzenes which are more expensive. Multiple alkylation can sometimes be made a practical preparation, for example



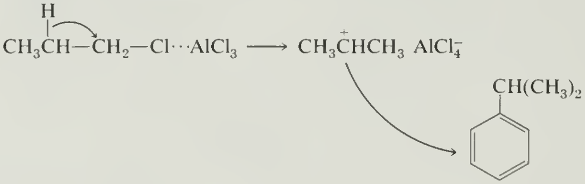
1,2,4,5-tetramethylbenzene
(durene)

In this preparation a mixture of xylenes may be used. Durene has a rather high melting point (m.p. 79°; the other two tetramethylbenzene isomers are liquids. Note the high symmetry of durene.). It may therefore be frozen out of the rather complex product mixture. Further alkylation can be accomplished to give pentamethylbenzene, m.p. 54°, or hexamethylbenzene, m.p. 165°.

Another important limitation of Friedel-Crafts alkylations relates to an alternative reaction of many carbonium ions, particularly in the absence of reactive nucleophiles, namely, rearrangement to isomeric carbonium ions. Isopropyl chloride or bromide reacts normally with aluminum chloride and benzene to give isopropylbenzene.

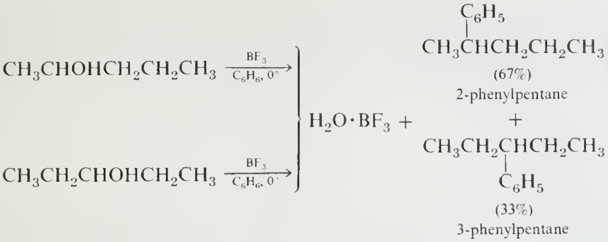


However, 1-chloropropane also gives isopropylbenzene under these conditions. Rearrangement to the secondary carbonium ion is essentially complete.



Primary alkyl halides are less reactive than secondary or tertiary halides, and higher temperatures are normally required. Under some conditions, the rearrangement of primary systems is only partial. Under these conditions, a displacement reaction by benzene on the alkyl halide coordinated with the Lewis acid competes with carbonium ion rearrangement. It should be emphasized, however, that at least some rearrangement always occurs with suitable primary systems and greatly limits the utility of this reaction.

Friedel-Crafts alkylations may also be accomplished with alcohols and a catalyst such as aluminum chloride or boron trifluoride. The reaction has the same limitations as the alkyl halide reactions in requiring a large excess of benzene and in giving rearrangement products in suitable cases. In addition, one reaction product is water which coordinates with Lewis acids. Thus, with alcohols a stoichiometric amount of Lewis acid is required:



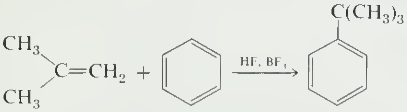
$$\left.\begin{array}{l} CH_3CHOHCH_2CH_2CH_3 \xrightarrow[C_6H_6,\,0^\circ]{BF_3} \\ \\ CH_3CH_2CHOHCH_2CH_3 \xrightarrow[C_6H_6,\,0^\circ]{BF_3} \end{array}\right\} H_2O\cdot BF_3 + \begin{array}{c} CH_3\overset{C_6H_5}{\overset{|}{C}}HCH_2CH_2CH_3 \\ (67\%) \\ \text{2-phenylpentane} \\ + \\ CH_3CH_2\underset{C_6H_5}{\underset{|}{C}}HCH_2CH_3 \\ (33\%) \\ \text{3-phenylpentane} \end{array}$$

Note that equilibration of the isomeric pentyl cations is rapid compared to alkylation of benzene.

$$CH_3\overset{+}{C}HCH_2CH_2CH_3 \rightleftharpoons CH_3CH_2\overset{+}{C}HCH_2CH_3 \rightleftharpoons CH_3CH_2CH_2\overset{+}{C}HCH_3$$

Since both cations are secondary, they are of comparable stability and the observed product ratio (2:1) reflects the 2:1 statistical bias in favor of the 2-pentyl cation.

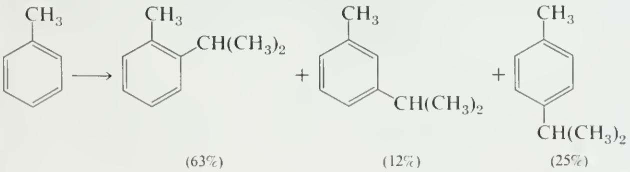
Alkylation reactions can also be accomplished with alkenes. Typical catalysts used, HF-BF_3 and HCl-$AlCl_3$, generate carbonium ions in the usual way.



$$[(CH_3)_2C{=}CH_2 + HF + BF_3 \rightleftharpoons (CH_3)_3C^+BF_4^-$$

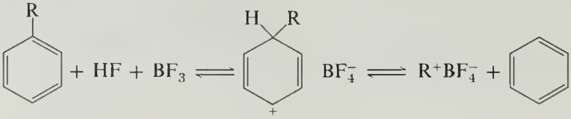
This reaction is used industrially to prepare alkylbenzenes, but it is not an important laboratory reaction.

Friedel-Crafts alkylations of substituted benzenes tend to be relatively nonspecific because of the high reactivity and low selectivity of alkyl cations. Often, the orientations observed appear to be quite unusual. For example, under mild conditions with aluminum chloride in acetonitrile, isopropylation of toluene gives predominantly the expected *ortho,para* orientation but with substantial amounts of *meta* product.



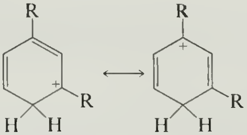
Under more vigorous conditions such as $AlCl_3$ + HCl or BF_3 + HF, the product is exclusively the *meta* isomer. In fact, all of the cymenes rearrange to *m*-cymene under these conditions.

This example again points up the difference between kinetic and thermodynamic control. The first-formed products are those formed fastest, but, if the reaction is reversible, the thermodynamically most stable product is produced. Alkylbenzenes with secondary or tertiary alkyl substituents form the corresponding carbonium ions reversibly under Friedel-Crafts conditions, for example



Secondary and tertiary carbonium ions are sufficiently stable for this type of reversibility to be important.

Nevertheless, if we consult available thermodynamic data on *o*-, *m*-, and *p*-dialkylbenzenes, we find the heats of formation of the isomers to be much the same. The *ortho* compounds tend to have ΔH_f° slightly higher than the *meta* and *para*-isomers, undoubtedly because of steric repulsion between neighboring alkyl groups, but the data summarized in Table 30.1 do not provide an explanation for the exclusive formation of *m*-dialkylbenzenes under equilibrium conditions with strong Lewis acids. The important further information is that 1 mole of reagent, such as $AlCl_3$-HCl or BF_3-HF, is required to obtain the *meta* isomers exclusively. The actual reaction product is not the hydrocarbon itself, but the protonated compound.



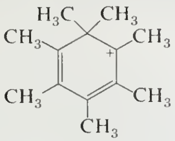
Only for the *m*-dialkylbenzene can the positive charge in the protonated complex be represented as a tertiary carbonium ion with respect to both alkyl groups.

In addition to rearrangements produced by *intermolecular* reversible carbonium ion alkylation reactions, *intramolecular* rearrangements can be observed in some

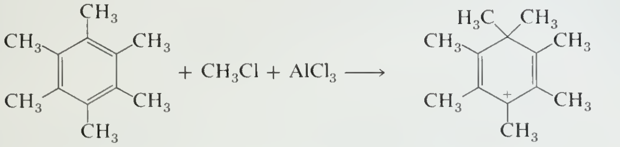
Table 30.1
Heats of Formation of Aromatic Hydrocarbons

Hydrocarbon	ΔH_f°, gas, 25° kcal mole^{-1}
benzene	19.8
toluene	12.0
ethylbenzene	7.2
o-xylene	4.6
m-xylene	4.1
p-xylene	4.3
propylbenzene	1.9
cumene	1.0
1-ethyl-2-methylbenzene	0.4
1-ethyl-3-methylbenzene	0.4
1-ethyl-4-methylbenzene	−0.8

cases. Such reactions are especially common for methyl groups. A striking example is provided by heptamethylbenzenonium ion,



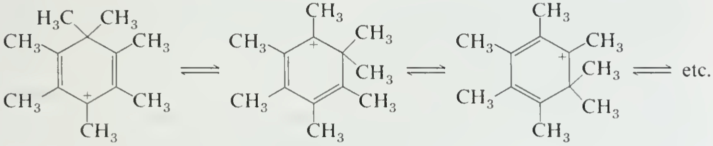
This ion is directly analogous to the protonated alkylbenzenes that are intermediates or products in Friedel-Crafts alkylations, and is prepared in an analogous fashion by reaction of hexamethylbenzene with methyl chloride and aluminum chloride.



hexamethylbenzene

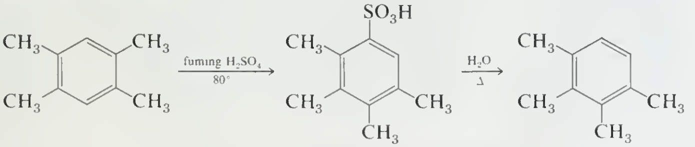
heptamethylbenzenonium cation

In the cation, the methyl groups undergo rearrangement.



Each rearrangement step is directly analogous to the 1,2-shifts that we have studied previously as frequent concomitants of carbonium ion reactions (Sections 11.7.B and 12.5.B). At room temperature, a solution of heptamethylbenzenonium cation shows four different methyl group signals in the ratio of 2:2:2:1; but at elevated temperatures, these signals collapse into a single band. At room temperature, rearrangement is slow on the nmr time scale; but at higher temperatures, rearrangement is sufficiently fast that nmr spectroscopy "sees" only one kind of methyl group. Note that rearrangements all around the ring have the effect of making all methyl groups equivalent.

Preparative use can be made of intramolecular methyl group rearrangements in polymethylbenzenes by reaction with sulfuric acid.

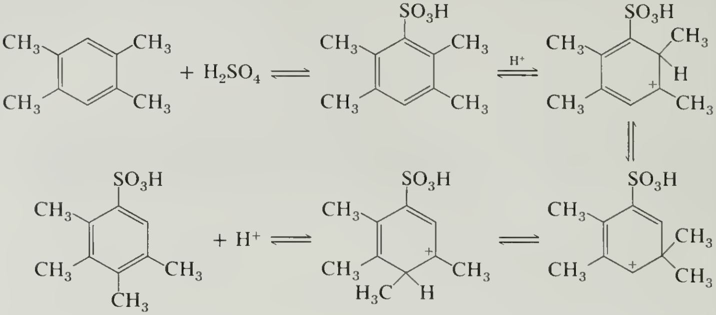


durene

2,3,4,5-tetramethylbenzenesulfonic acid

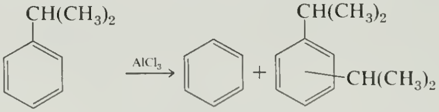
1,2,3,4-tetramethylbenzene (prehnitene)

The first-formed product is durenesulfonic acid, in which the bulky sulfonic acid group is flanked by two methyl groups. Rearrangement of a methyl group in the protonated compound gives the less strained sulfonic acid. We shall learn in greater detail later (Section 31.6.A) that sulfonation reactions are reversible and that the hydrocarbons can generally be regenerated by hydrolysis with water. This rearrangement of polyalkylbenzenes by use of sulfuric acid is known as the **Jacobsen reaction.**



Durene and prehnitene are trivial names for the tetramethylbenzenes shown that are not sanctioned by IUPAC. These names, however, are found in the chemical literature. The trivial name of the remaining isomer, 1,2,3,5-tetramethylbenzene, is isodurene.

For alkyl groups, intramolecular 1,2-shifts around the benzene ring are generally relatively slow and require rather vigorous conditions. Nevertheless, such rearrangements are generally faster for methyl groups than intermolecular rearrangements or transfers of methyls from one ring to another. For secondary and tertiary alkyl groups, the carbonium ions are sufficiently stable that intermolecular transfers from one ring to another, via the reversibility of alkylation discussed previously, are generally faster than intramolecular rearrangements around a benzene ring. Intermolecular rearrangements under the action of strong acids or Lewis acids results in **disproportionation,** for example



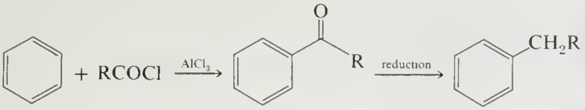
mixture of all three di-isopropylbenzenes

Disproportionation also occurs with primary alkyl groups higher than methyl, but by a special mechanism which we will not discuss.

The foregoing discussions should indicate that Friedel-Crafts alkylation reactions are useful for some preparations, but that the reaction is actually rather limited and requires rather careful characterization of the precise reaction conditions. The reaction is of great importance in industrial preparations, especially with alkenes as reagents, because the starting materials are usually available and inexpensive commodities.

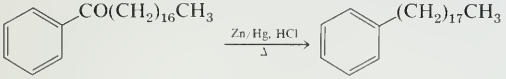
B. *Reduction of Aldehydes, Ketones, and Alcohols*

A particularly important synthetic route to pure alkylbenzenes involves the reduction of aryl ketones produced by the Friedel-Crafts acylation (Sections 21.2.E and 31.2.B).

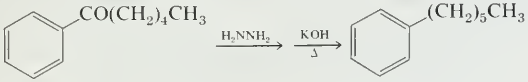

+ RCOCl
AlCl$_3$
O
R
reduction
CH$_2$R

In contrast to Friedel-Crafts alkylation, the product of the acylation reaction is less reactive than the reactant. Therefore, where they are applicable, Friedel-Crafts acylations are usually clean, high-yield reactions.

The direct reduction of carbonyl groups to hydrocarbons can be accomplished by the Wolff-Kishner or Clemmensen reductions (Sections 15.8.E and F). Both procedures are generally applicable to aromatic systems with the usual precautions. That is, the Wolff-Kishner reduction involves strongly basic conditions, whereas the Clemmensen reduction takes place in acid medium. Other functional groups present in the molecule must be stable to the conditions chosen. Some examples of these reductions follow:

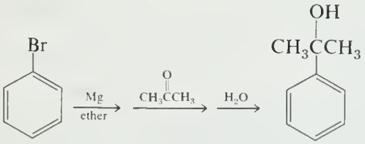

CO(CH$_2$)$_{16}$CH$_3$
Zn/Hg, HCl
Δ
(CH$_2$)$_{17}$CH$_3$

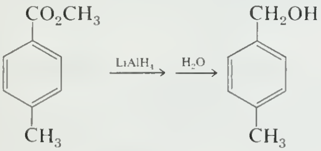
(77%)
octadecylbenzene

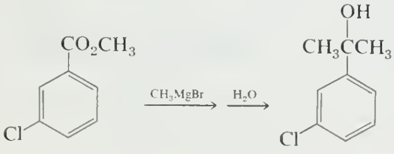

CO(CH$_2$)$_4$CH$_3$
H$_2$NNH$_2$
KOH
Δ
(CH$_2$)$_5$CH$_3$

(82%)
hexylbenzene

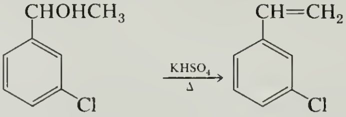
Benzylic alcohols are also readily available intermediates, as indicated by the following examples.


Br
Mg
ether
O
CH$_3$CCH$_3$
H$_2$O
OH
CH$_3$CCH$_3$


CO$_2$CH$_3$
CH$_3$
LiAlH$_4$
H$_2$O
CH$_2$OH
CH$_3$


CO$_2$CH$_3$
Cl
CH$_3$MgBr
H$_2$O
OH
CH$_3$CCH$_3$
Cl

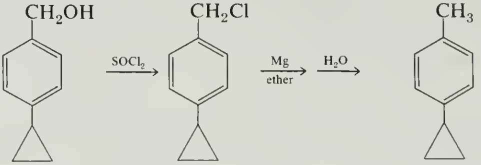
Such alcohols may be dehydrated directly to give arylalkanes, or they may be converted to halides for E2 elimination.


CHOHCH3
Cl
KHSO4
Δ
CH=CH2
Cl

1-(*m*-chlorophenyl)ethanol

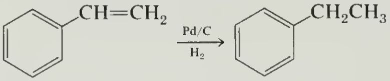
(80–82%)
m-chlorostyrene

The corresponding halides can be converted to hydrocarbons by reactions we have encountered previously.

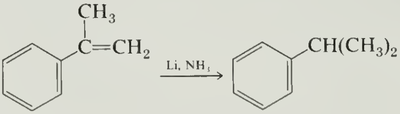

CH2OH
SOCl2
CH2Cl
Mg
ether
H2O
CH3

p-cyclopropyltoluene

Alternatively, phenylalkenes can be hydrogenated to the corresponding phenylalkanes; the benzene ring is more difficult to hydrogenate than double bonds.


CH=CH2
Pd/C
H2
CH2CH3

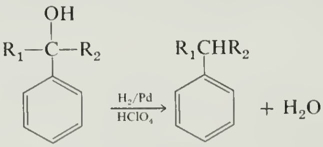
Double bonds conjugated to an aromatic ring can also be reduced by alkali metals in liquid ammonia (see Sections 13.6.A and 20.3.A).


CH3
C=CH2
Li, NH3
CH(CH3)2

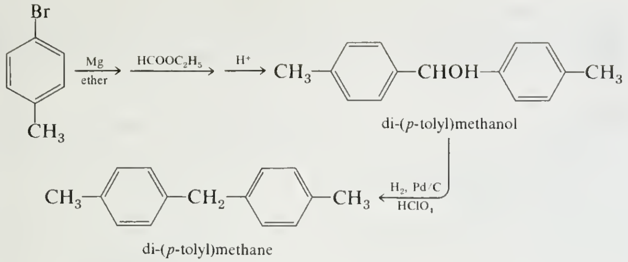
(80%)

Nonconjugated double bonds are stable to these conditions. Although the benzene ring is also reduced by lithium in ammonia (Section 30.7.D), it is not as reactive as the conjugated double bond. Thus, the selective reduction is possible.

Benzylic alcohols can be reduced directly by hydrogenation with palladium catalysts in the presence of some perchloric acid.

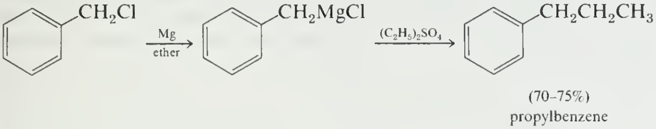

OH
R1—C—R2
H2/Pd
HClO4
R1CHR2
+ H2O

This type of process, in which hydrogen breaks a single bond, is known as **hydrogenolysis**. Another example using this process is

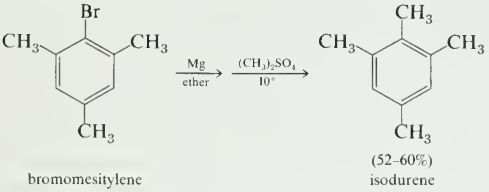

Br
CH3
Mg
ether
HCOOC2H5
H+
CH3
CHOH
CH3
di-(p-tolyl)methanol
H2, Pd/C
HClO4
CH3
CH2
CH3
di-(p-tolyl)methane

C. *Organometallic Intermediates*

Some alkylaromatic compounds can be prepared directly by displacement of organolithium compounds or Grignard reagents with alkyl halides or sulfonate esters. For example, benzylmagnesium halides react with primary alkyl halides or related compounds to give the corresponding phenylalkane.


CH2Cl
Mg
ether
CH2MgCl
(C2H5)2SO4
CH2CH2CH3
(70–75%)
propylbenzene

A similar reaction can be accomplished with arylmagnesium halides.

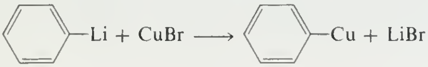

Br
CH3
CH3
CH3
bromomesitylene
Mg
ether
(CH3)2SO4
10°
CH3
CH3
CH3
CH3
(52–60%)
isodurene

Recall that this type of reaction of Grignard reagents is limited to certain types of systems; it is *not* a general reaction for all Grignard reagents. The reaction may be regarded as an S_N2 displacement by the magnesium salt of a carbanion on the alkyl carbon. Some examples in which this reaction works well are

$$RMgX + CH_2{=}CHCH_2Cl \longrightarrow RCH_2CH{=}CH_2 \qquad \text{(Section 20.1.B)}$$
$$C_6H_5CH_2MgX + \text{prim-}RX \longrightarrow C_6H_5CH_2R$$
$$C_6H_5MgX + \text{prim-}RX \longrightarrow C_6H_5R$$

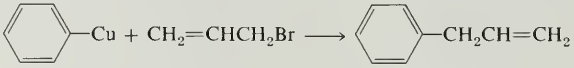
In other cases, yields of "coupling" products are variable and the reactions are complicated by side reactions involving radicals. The analogous reactions of aryllithium reagents (Section 30.3.B) and the Wurtz-Fittig reaction (Section 30.3.B) were discussed previously.

Aryl halides may also be converted into organocopper compounds by way of the Grignard reagent or aryllithium compound.


Li + CuBr
Cu + LiBr

A suspension of 1.0 g of cuprous bromide in ether is treated with 6.7 ml of 1 *M* phenyllithium solution. The CuBr becomes yellow and dissolves to give a brown-red solution which then turns green. Phenylcopper precipitates as a white powder in 90% yield.

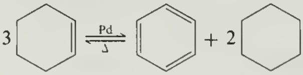
The arylcopper compounds undergo coupling with reactive halides in high yield.



(99%)
allylbenzene
3-phenyl-1-propene

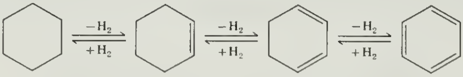
D. *Dehydrogenation of Cyclohexyl Compounds*

Six-membered rings can be dehydrogenated to the corresponding aromatic rings with palladium catalysts or with sulfur or selenium. The palladium-catalyzed reaction is an equilibrium process that is the same as that involved in hydrogenation. In the presence of hydrogen, cyclohexene is hydrogenated with palladium metal to cyclohexane. In the absence of hydrogen, cyclohexene disproportionates to benzene and cyclohexane.

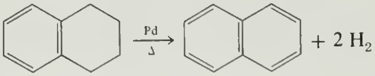


$\Delta H^\circ = -35.9 \text{ kcal mole}^{-1}$

This disproportionation is the net result of a series of hydrogenation-dehydrogenation equilibria:



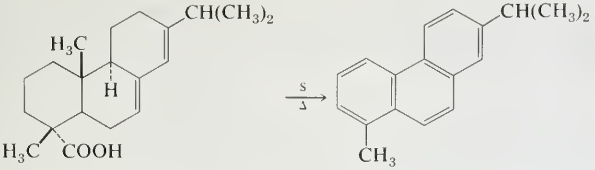
With higher boiling compounds or by bubbling carbon dioxide through a refluxing mixture, the hydrogen produced in the equilibrium is removed and the product is the aromatic product of dehydrogenation.



naphthalene

We shall see (Section 34.3.B) that such dehydrogenation reactions are especially useful in the preparation of polycyclic aromatic hydrocarbons.

The comparable dehydrogenations with sulfur and selenium are reactions in which the formation of hydrogen sulfide or hydrogen selenide provides an important driving force for reaction. The reactions are complex and involve intermediate organosulfur and organoselenium compounds. Yields are often poor, but the reaction has been useful for structure proofs of natural products. Dehydrogenation gives an aromatic hydrocarbon that often helps to determine the carbon skeleton of the natural product. An example of the use of this method is the identification of the carbon skeleton of abietic acid, a diterpene acid that occurs in rosin.



abietic acid

1-methyl-7-isopropylphenanthrene
(retene)

Note that quaternary carbons (a methyl and a COOH) are lost under the reaction conditions. Selenium gives a better yield of retene.

> Rosin is a pale yellow-to-amber glassy residue that remains after removal of the volatile component (turpentine) from the viscous exudate of incisions in pine trees. It has many commercial uses and consists largely of abietic acid.

Phenanthrene is a tricyclic benzenoid hydrocarbon that we will discuss in greater detail in Chapter 34.

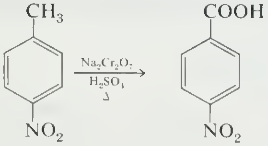
Catalytic dehydrogenation is one of the reactions that occurs in petroleum "reforming." The alkanes and cycloalkanes in petroleum fractions are treated at high temperature with appropriate catalysts to promote cyclization and dehydrogenation to yield benzene, toluene, and xylenes.

30.7
Reactions of Alkylbenzenes

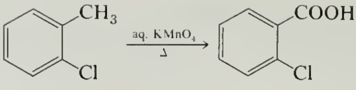
Electrophilic substitutions on benzene rings containing alkyl groups have already been discussed in detail. In this section, we will treat only one reaction involving the benzene ring directly, the reduction to hydroaromatic compounds. The other reactions involve the side chain carbons, particularly the position adjacent or conjugated to the ring, the benzylic position. We will find that the acidity of such hydrogens is greater than that of alkanes and that the corresponding carbanions are synthetically useful. Oxidation of side chain positions is also a more preparatively useful reaction than that of alkanes.

A. *Oxidation*

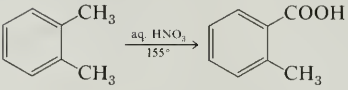
The benzene ring is rather stable to oxidizing agents, and, under appropriate conditions, side chain alkyl groups are oxidized instead. Sodium dichromate in aqueous sulfuric acid or acetic acid is a common laboratory procedure, but aqueous nitric acid or potassium permanganate has also been used.



(82 86%)
p-nitrobenzoic acid



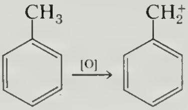
(76–78%)
o-chlorobenzoic acid



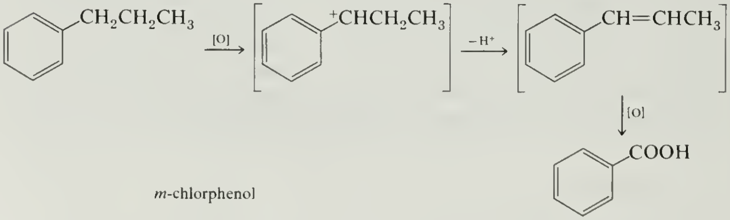
(53–55%)
o-toluic acid

The detailed reaction mechanisms by which these oxidations occur are rather complex. They involve numerous intermediates including chromate and permanganate esters.

In general, such oxidations proceed by way of an intermediate benzyl cation.

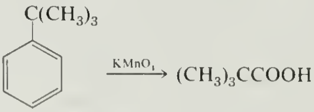


As we have seen, this carbonium ion is relatively stable because of conjugation of the positive charge with the benzene ring. Reaction with water yields benzyl alcohol, which can oxidize further. Larger side chains can also be oxidized completely so long as there is one benzylic hydrogen for the initial oxidation. Cleavage reactions of larger side chains probably involve the formation of an intermediate alkene.



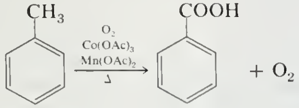
m-chlorphenol

The more extensive oxidation required in these reactions often results in lower yields so that they are not so useful for laboratory preparations as they are for structural identification. When there is no benzylic hydrogen, the side chain resists oxidation. For example, vigorous conditions are required for the oxidation of *t*-butylbenzene, and the product is trimethylacetic acid, the product of oxidation of the benzene ring.



pivalic acid
trimethylacetic acid

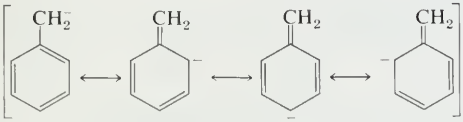
Oxidation of side chain methyl groups is an important industrial route to aromatic carboxylic acids. The most important oxidizing agent for such reactions is air.



The most important industrial reaction of this general type is the oxidation of *p*-xylene to the dicarboxylic acid (Section 31.5.A).

B. *Acidity of Alkylbenzenes*

Benzyl anion is stabilized by delocalization of the negative charge into the benzene ring.



As a result, toluene is more acidic than the alkanes. Its pK_a is about 41, compared to a value of about 50 for ethane. Toluene is still a very weak acid and is not significantly converted to the anion even with $NaNH_2$ in liquid ammonia. As additional benzene rings are added, however, the acidity increases markedly. Some relevant pK_a data are summarized in Table 30.2.

TABLE 30.2
Acidity of Some Hydrocarbons

Hydrocarbon	Conjugate Base	pK_a
ethane	$CH_3CH_2^-$	≈50
benzene	$C_6H_5^-$	43
toluene	$C_6H_5CH_2^-$	41
diphenylmethane	$(C_6H_5)_2CH^-$	34
triphenylmethane	$(C_6H_5)_3C^-$	31.5

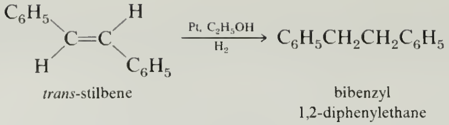
Di- and triphenylmethane are sufficiently acidic to be converted significantly to the corresponding carbanions with sodium amide. Hence, syntheses may be accomplished with these anions. One example is

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{NaNH_2} \xrightarrow[(C_2H_5)_2O]{CH_3(CH_2)_2CH_2Br} (C_6H_5)_2CH(CH_2)_3CH_3$$

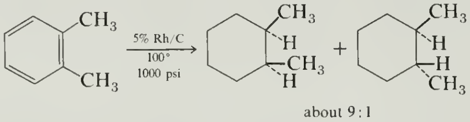
(92%)
1,1-diphenylpentane

C. *Catalytic Hydrogenation*

Benzene rings are substantially more resistant to catalytic hydrogenation than alkenes or alkynes. In molecules that contain both a double bond and a benzene ring, the double bond may be preferentially hydrogenated without difficulty.

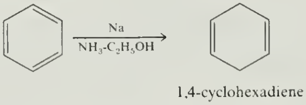

C_6H_5
H
H
C_6H_5
Pt, C_2H_5OH
H_2
$C_6H_5CH_2CH_2C_6H_5$
trans-stilbene
bibenzyl
1,2-diphenylethane

Hydrogenation of the benzene ring occurs under more vigorous conditions and yields the corresponding cyclohexane. It is generally impractical to stop the reaction at an intermediate stage, since cyclohexadienes and cyclohexenes hydrogenate more readily than benzenes. Dialkylbenzenes tend to give predominantly the *cis*-dialkylcyclohexane, although the exact stereochemistry of the reduction depends on the reaction conditions and catalysts used. Platinum or palladium catalysts may be used at temperatures near 100°; acetic acid is a common solvent. Nevertheless, these conditions are often inconveniently slow and ruthenium or rhodium on carbon are often more successful for hydrogenation of aromatic rings.

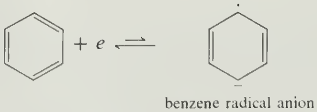

CH_3
CH_3
5% Rh/C
100°
1000 psi
CH_3
H
CH_3
H
+
CH_3
H
H
CH_3
about 9:1

D. *Birch Reduction*

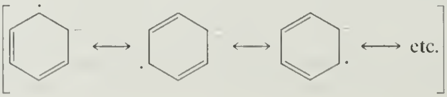
Aromatic rings can be reduced by alkali metals in a mixture of liquid ammonia and alcohol. The product of this reduction is an unconjugated cyclohexadiene.


Na
NH_3-C_2H_5OH
1,4-cyclohexadiene

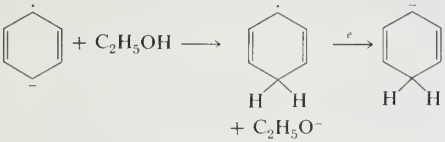
Recall that a similar reduction is used to prepare *trans*-alkenes from alkynes (Section 13.6.A). A solution of sodium in liquid ammonia contains solvated electrons which add to a benzene ring to give a radical anion. Benzene and alkylbenzenes are not readily reduced and the equilibrium lies far to the left.


+ e
benzene radical anion

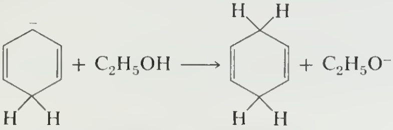
Note that the radical anion has seven electrons in the benzene π system. The extra electron has added to the lowest empty molecular orbital in benzene, an antibonding π molecular orbital (see Figure 21.3). The radical anion is still highly conjugated and many resonance structures can be written for it; some of these structures are



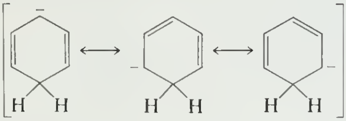
Because the odd electron is in an antibonding orbital, benzene radical anion is less stable than benzene. The ion reacts readily with proton donors. Ammonia itself is too weakly acidic to react, but ethanol is a sufficiently strong acid.



The resulting cyclohexadienyl radical immediately reacts with another solvated electron to form the corresponding cyclohexadienyl anion. This anion is a strong base that reacts immediately with ethanol and is protonated to give 1,4-cyclohexadiene.

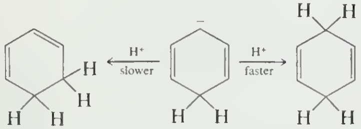


Cyclohexadienyl anion is a conjugated carbanion of the allylic type, and the negative charge is correspondingly distributed over several carbons, as indicated by the resonance structures

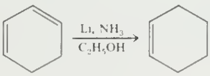


Protonation at the central carbon is much faster than at the end carbons of the conjugated chain. This result is quite general, even though the product of protonation at the terminal carbon of the conjugated chain produces the generally more stable conjugated diene. The reason is not readily apparent, although various more or less sophisticated explanations have been given for this unusual effect.

Since the product contains isolated double bonds, no further reduction takes place, and the cyclohexadiene may be isolated in good yield. On prolonged contact with base, the carbanion is reformed and will produce some of the conjugated diene.

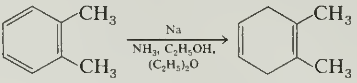


Conjugated dienes are reduced by solvated electrons in liquid ammonia to form the monoene.



Thus, by a proper choice of solvent and temperature, one may reduce the benzene ring to either the 1,4-cyclohexadiene or the cyclohexene.

With substituted benzenes, a single product is often formed in good yield. For example, the reduction of *o*-xylene is an excellent route to 1,2-dimethyl-1,4-cyclohexadiene.


CH3
CH3
Na
NH3, C2H5OH, (C2H5)2O
CH3
CH3

(77–92%)
1,2-dimethyl-1,4-cyclohexadiene

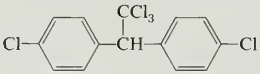
> Sodium is added in pieces to a mixture of liquid ammonia, ether, ethanol and *o*-xylene cooled in a Dry Ice bath. The ammonia is allowed to evaporate, water is added, and the washed and dried organic layer is distilled.

Of course, the Birch reduction cannot be applied to systems containing reducible functions such as halogens, nitro groups, ketones, and aldehydes.

PROBLEMS

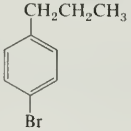
1. Give an acceptable name for each of the following structures:

(a)

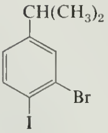

CCl3
Cl
CH
Cl

(DDT)

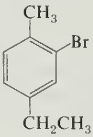
(b)


CH2CH2CH3
Br

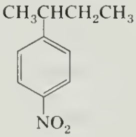
(c)



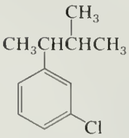
(d)


CH3
Br
CH2CH3

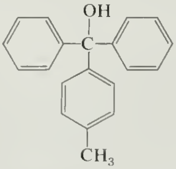
(e)


CH3CHCH2CH3
NO2

(f)

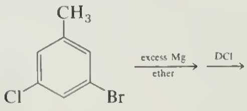

CH3
CH3CHCHCH3
Cl

(g)

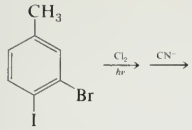


2. Give the principal product of the following reactions or reaction sequences:

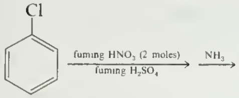
(a)


CH3
Cl
Br
excess Mg
ether
DCl

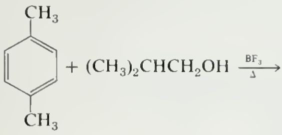
(b)


CH3
Br
I
Cl2
hν
CN⁻

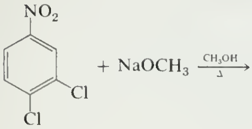
(c)


Cl
fuming HNO3 (2 moles)
fuming H2SO4
NH3

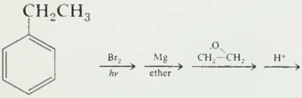
(d)


CH3
CH3
+ (CH3)2CHCH2OH
BF3
Δ

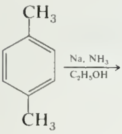
(e)


NO2
Cl
Cl
+ NaOCH3
CH3OH
Δ

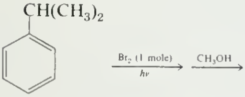
(f)


CH2CH3
Br2
hν
Mg
ether
O
CH2—CH2
H⁺

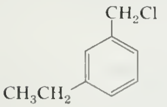
(g)


CH3
CH3
Na, NH3
C2H5OH

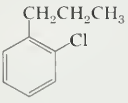
(h)


CH(CH3)2
Br2 (1 mole)
hν
CH3OH

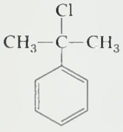
3. There are many isomers of $C_9H_{11}Cl$, even when we specify the presence of a benzene ring. One such compound is 2-chloro-1,3,5-trimethylbenzene.
   (a) Sketch its expected nmr spectrum.
   Other isomers are


CH2Cl
CH3CH2

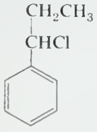
A


CH2CH2CH3
Cl

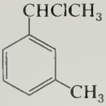
B



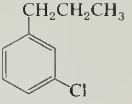
C


CH2CH3
CHCl

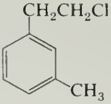
D



E



F



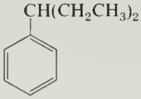
G

Associate these isomers with the properties listed. For those questions that have more than one correct answer, list all of the correct structures.

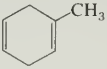
(b) Most reactive in carbonium ion reactions (one answer).
(c) Does not react with alcoholic silver nitrate.
(d) Nmr spectrum contains two triplets.
(e) Can give direct substitution reaction (S_N2), but not elimination (E2).
(f) Can give both S_N2 and E2 reactions.

4. Show how one may synthesize each of the following compounds, starting with benzene, toluene, xylene, or any required halobenzene or halotoluene.

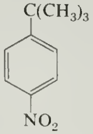
(a)



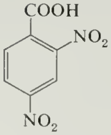
(b)



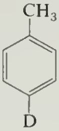
(c)



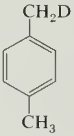
(d)



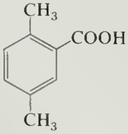
(e)



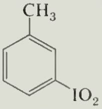
(f)



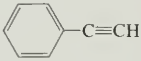
(g)



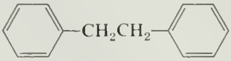
(h)



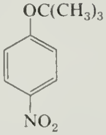
(i)



(j)



(k)



5. (a) Write out the steps of the free radical chain bromination of toluene to give benzyl bromide.
(b) From ΔH_f° and DH° values listed in Appendices I and II calculate ΔH° for the reactions in part (a).
(c) Compare these values with those for ethane and the tertiary position of isobutane. How feasible are these brominations?

6. The solvolysis reaction of 2-chloro-2-phenylpropane in aqueous acetone is an S_N1 carbonium ion process that yields 2-phenyl-2-propanol as the principal product.
(a) Write out the mechanism of this reaction, showing any intermediates involved.

(b) The rate of reaction depends markedly on substituents in the phenyl group. The order of reactivity given by *p*-substituents is

$$CH_3O > CH_3 > H > NO_2$$

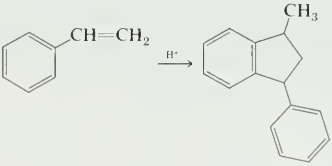
Explain, using resonance structures.

7. When a solution of *p*-di-(3-pentyl)benzene in benzene is treated with aluminum chloride at 25°, a rapid transfer of a pentyl group occurs to give monopentylbenzene. The reaction product is approximately one part of 2-phenylpentane and two parts of 3-phenylpentane. Account for these results with a reasonable reaction mechanism.

8. The Sanger method for identifying the N-terminal amino acid of a peptide involves reaction with 2,4-dinitrofluorobenzene (Section 28.6.C). Write a plausible mechanism for this reaction.

9. In chloromethylation reactions using formaldehyde, HCl, and $ZnCl_2$, the potent carcinogen bis-chloromethyl ether, $ClCH_2OCH_2Cl$, is produced. Write a plausible mechanism for this formation of this compound, showing each intermediate involved.

10. On heating with aqueous sulfuric acid, styrene reacts to form a dimer in good yield.



(77–81%)

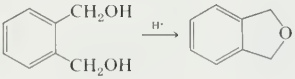
Write a reasonable mechanism, showing all intermediates involved.

11. When 2,4,6-trinitroanisole is treated with methoxide in methanol, a red anion having the composition $(C_8H_8O_8N_3)^-$ is produced. Such anions are called Meisenheimer complexes after the chemist who first suggested the correct structure. What structure do you think he suggested? One of Meisenheimer's experiments compared the product of reaction of 2,4,6-trinitroanisole with ethoxide ion with the product of 2,4,6-trinitrophenyl ethyl ether with methoxide ion. What do you think he found?

12. The reaction of chlorobenzene with hot aqueous sodium hydroxide actually goes in part by way of a benzyne intermediate and in part by nucleophilic aromatic substitution. Reaction of chlorobenzene labeled with ^{14}C at the 1-position with 4 *M* NaOH at 340° gives phenol in which 58% of the ^{14}C remains at the 1-position and 42% is at the 2-position. Calculate the fraction of reaction going by way of nucleophilic aromatic substitution compared to the benzyne mechanism.

13. Write structures for the eight possible benzene hexachlorides. Which one is capable of optical isomerism? Which one is slowest to react in E2 elimination reactions?

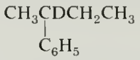
14. *o*-Phthalyl alcohol, 1,2-bis-(hydroxymethyl)benzene, on treatment with acid, gives the corresponding cyclic ether.



Give a reasonable mechanism for this reaction.

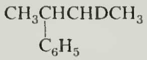
15. (a) Write a Lewis structure for diphenyliodonium cation. Each atom should have a normal octet of electrons. Which atom has the formal positive charge?
(b) Write a Lewis structure for iodosobenzene in which each atom has an octet of electrons.
(c) Write a Lewis structure for iodoxybenzene in which each atom has an octet of electrons. Would you expect the iodoxy group to be an electron-donating or an electron-attracting substituent?

16. (a) The reaction of 2-butanol and BF_3 with benzene at 0° gives a good yield of 2-phenylbutane. When 2-butanol-2-*d*, $CH_3CDOHCH_2CH_3$, is used, a mixture of deuterated compounds is obtained that includes major amounts of
Explain.



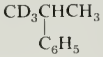
$CH_3\underset{\substack{|\\ C_6H_5}}{C}DCH_2CH_3$

and



$CH_3\underset{\substack{|\\ C_6H_5}}{C}HCHDCH_3$

(b) By contrast, the reaction of $CD_3CHOHCH_3$ with benzene and BF_3 gives a good yield of



$CD_3\underset{\substack{|\\ C_6H_5}}{C}HCH_3$

with no deuterium scrambling. How do you account for this difference?
(c) 2-Propanol-1-d_3, $CD_3CHOHCH_3$, has an asymmetric carbon and significant optical activity. According to the mechanism of the alkylation reaction, what do you expect for the steric course of the reaction of this optically active alcohol with benzene and BF_3?

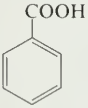
CHAPTER 31

Aromatic Carbonyl Compounds and Sulfonic Acids

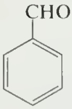
The conjugation of carbonyl and other functional groups with the benzene ring provides a characteristic chemistry that differs in some respects from that of corresponding aliphatic compounds. A number of preparative methods are unique to the aromatic functions. In this chapter we will examine this special chemistry for aromatic aldehydes and ketones, carboxylic acids, and sulfonic acids.

31.1
Nomenclature

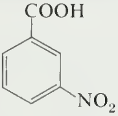
The naming of these compounds generally follows conventions already established. Benzenecarboxylic acid is commonly known as benzoic acid, and this name has IUPAC sanction. Similarly, benzaldehyde is the accepted name for the corresponding parent aldehyde. Derivatives are named accordingly.



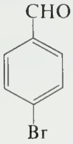
benzoic acid



benzaldehyde

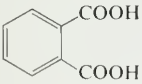


m-nitrobenzoic acid

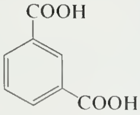


p-bromobenzaldehyde

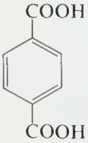
Several aromatic carboxylic acids have trivial names that are in common use. For the examples that follow, the trivial names have received IUPAC sanction and are preferred to the systematic names.



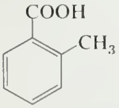
phthalic acid
1,2-benzenedicarboxylic acid



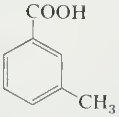
isophthalic acid
1,3-benzenedicarboxylic acid



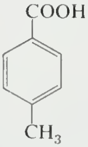
terephthalic acid
1,4-benzenedicarboxylic acid



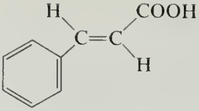
o-toluic acid
o-methylbenzoic acid



m-toluic acid
m-methylbenzoic acid

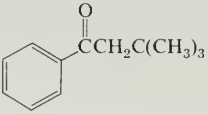


p-toluic acid
p-methylbenzoic acid

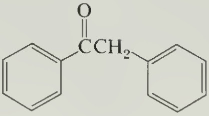


cinnamic acid
(E)-3-phenylpropenoic acid

Common names of aryl ketones are derived from the names of the two aryl or alkyl groups and the word **ketone.** In the IUPAC systems, aryl ketones are named as substituted alkanones.

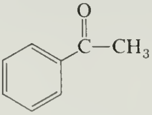


1-phenyl-3,3-dimethyl-1-butanone
phenyl neopentyl ketone

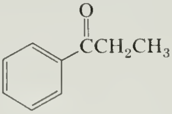


1,2-diphenylethanone
phenyl benzyl ketone

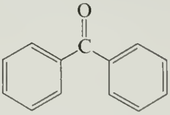
When a benzene ring is attached directly to the carbonyl carbon, the ketone may be named as a "phenone" derivative of the other acyl group. The **-ic** or **-oic** ending of the corresponding carboxylic acid is replaced by the ending **-ophenone.** These phenone names are generally preferred in the IUPAC rules.



acetophenone

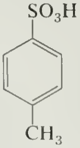


propiophenone
(note exception; not propionophenone)

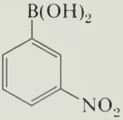


benzophenone

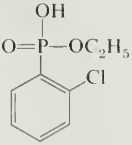
Finally, other acids are named using the appropriate arene stem.



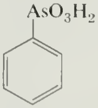
p-toluenesulfonic acid



m-nitrobenzeneboronic acid



ethyl *o*-chlorobenzene-phosphonate

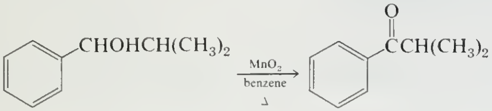


benzenearsonic acid

31.2
Preparation of Aromatic Ketones

A. *General Methods*

Many of the preparations of aromatic ketones are directly related to preparations of aliphatic ketones. Some examples illustrate these general methods.

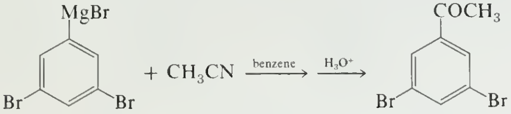


(77%)
isobutyrophenone

Note that benzyl alcohols are oxidized by manganese dioxide in the same way as allyl alcohols (Section 20.3.A). Conjugation to a benzene ring is similar in many respects to conjugation to a single double bond.

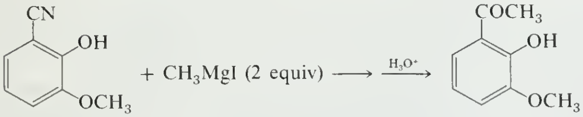
$$C_6H_5COCl + (C_2H_5)_2Cd \xrightarrow{\text{benzene}} \xrightarrow{H_3O^+} C_6H_5COCH_2CH_3$$

(84%)
propiophenone



(52%)
3,5-dibromoaceto-
phenone

This reaction of Grignard reagents works especially well with benzonitriles.

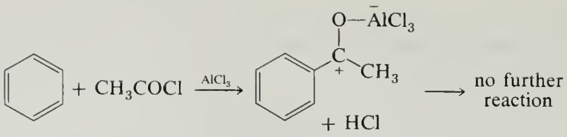


2-hydroxy-3-methoxy-
acetophenone

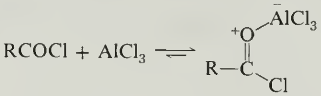
Two moles of Grignard reagent are required because the first mole reacts with the phenolic OH to produce methane and the magnesium salt of the phenol.

B. *Friedel-Crafts Acylation*

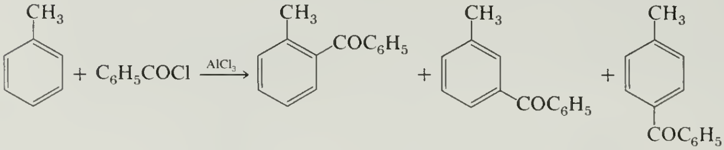
The reaction of aromatic rings with acid chlorides or anhydrides and a Lewis acid is generally an excellent one in the absence of *meta* directing groups. The reaction is especially clean because the product ketone is coordinated to a Lewis acid; the resulting positive charge is distributed to the ring and inhibits further electrophilic substitution.



The reactive reagent is an electrophilic complex between the acid chloride or anhydride and the Lewis acid.



This species appears to be effectively rather bulky; *para* substitution tends to dominate substantially over *ortho*. That is, in Friedel-Crafts acylation reactions with substituted benzenes, the *para* acylation product is often obtainable both pure and in high yield.

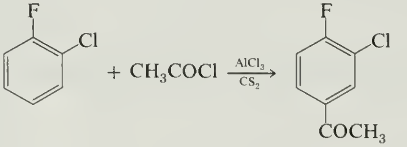


(31-1)

(9%) *o*-methyl benzophenone

(1%) *m*-methyl-benzophenone

(90%) *p*-methyl-benzophenone

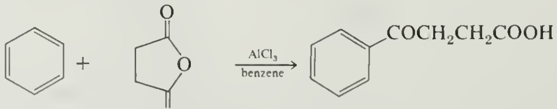


(31-2)

(80%) 3-chloro-4-fluoro-acetophenone

In reaction (31-2) note that the fluorine controls the orientation, probably because the fluorine $2p$ electrons are more available for π bonding with the ring than the more diffuse $3p$ orbitals of chlorine.

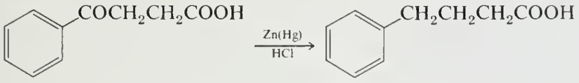
Cyclic anhydrides generally work quite well in Friedel-Crafts acylations.



succinic anhydride

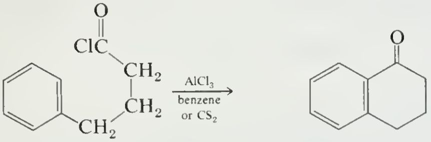
(84%) 4-phenyl-4-oxobutanoic acid
β-benzoylpropionic acid

The keto-acids produced in such acylations can be reduced to the corresponding acids by the Clemmensen or Wolff-Kishner methods (Sections 15.8.E and F).



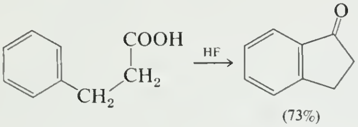
(82–89%)
4-phenylbutanoic acid
γ-phenylbutyric acid

An important property of such phenyl substituted acids is the ease with which they undergo intramolecular Friedel-Crafts acylation reactions to form five- and six-membered cyclic ketones.



(70–90%)
1-oxo-1,2,3,4-tetrahydronaphthalene
α-tetralone

Such cyclizations are generally excellent preparative methods when the product is a five- or six-membered ring ketone. Commonly used reagents are $AlCl_3$ with the acid chloride, and sulfuric acid, polyphosphoric acid, or liquid hydrogen fluoride with the free acid.

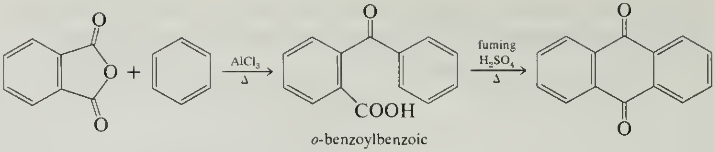


(73%)
1-indanone

The carboxylic acid is weighed into a polyethylene beaker and, in an efficient hood, liquid HF is added from an inverted tank previously cooled to 5° (use polyethylene or rubber gloves). The mixture is stirred and the HF is allowed to evaporate over the course of several hours. The residue is mixed with aqueous Na_2CO_3 and extracted with benzene. The product is obtained by distillation or crystallization. Yields are typically 70–90%. This is one of the best and simplest procedures for Friedel-Crafts cyclizations.

Anhydrous HF is a low boiling liquid, b.p. 19°, available in cylinders. It is highly corrosive to glass and tissue and must be handled with due caution. The liquid is an excellent solvent for oxygen containing organic compounds (hydrogen bonding). It does not attack polyethylene or Teflon, and these polymers make suitable reaction vessels. Because of the etching of glass windows, it is generally best to use one specific hood in a laboratory for HF reactions. The vapors should not be inhaled and the material causes severe burns on contact with skin.

Hot sulfuric acid is useful for some special cases. Reaction of phthalic anhydride with benzene gives a keto-acid that cyclizes in sulfuric acid to give a high yield of anthraquinone.

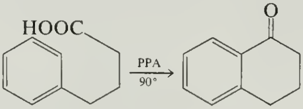


o-benzoylbenzoic acid

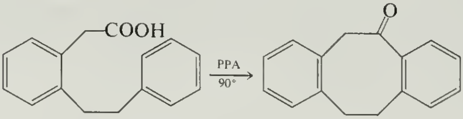
(81–90%)
anthraquinone

> This reaction is an apparent exception to the generalization that Friedel-Crafts acylations do not occur on aromatic ketones. However, in this case, both reactants are in the same molecule and ring formation provides an additional driving force.

Polyphosphoric acid (Section 18.13.B) is also a convenient reagent for carrying out such cyclizations.



(75–86%)

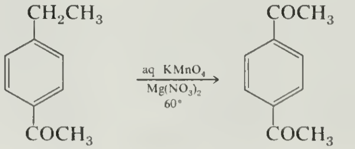


(93%)

Intramolecular Friedel-Crafts cyclizations such as these constitute one of the most important routes to polycyclic aromatic systems (Chapter 34).

C. *Oxidation of Hydrocarbons*

Aromatic ketones with the carbonyl group adjacent to a benzene ring can often be prepared by oxidation of a suitable hydrocarbon. This reaction is not generally applicable to aliphatic ketones.



p-ethylacetophenone

p-diacetylbenzene

Various oxidizing agents have been used, but the method is still limited in its usefulness.

31.3 Preparation of Aromatic Aldehydes

As in the case of ketones, many of the preparations of aliphatic aldehydes apply as well to aromatic aldehydes. A number of such reactions have already been discussed (Section 15.5). Aromatic carboxylic acid chlorides and nitriles may be reduced to aldehydes by the methods discussed in Section 18.10.

$$\mathrm{ArCOCl} \xrightarrow[\mathrm{Pd/BaSO_4}]{\mathrm{H_2}} \mathrm{HCl} + \mathrm{ArCHO}$$

$$\mathrm{ArCOCl} \xrightarrow{\mathrm{LiAlH(OBu\text{-}}t)_3} \mathrm{ArCHO}$$

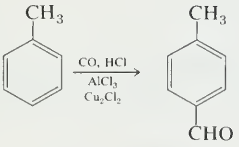
$$\mathrm{ArCN} \xrightarrow[\text{benzene}]{(i\text{-Bu})_2\mathrm{AlH}} \mathrm{ArCHO}$$

In addition, there are at least two dozen special preparations that apply primarily to aromatic aldehydes of specific types. Many of these reactions are "name" reactions such as the Sommelet, Vilsmeier, Sonn-Müller, and McFadyen-Stevens reactions, the Etard oxidation, and the Stephen reduction. There is both a Gattermann and a Gattermann-Koch synthesis. We will not detail all of these varied methods, but will discuss several of the most general and useful preparations.

A. *Friedel-Crafts Acylation*

Two important methods are available for the direct introduction of an aldehyde group into an aromatic ring. Both methods apply best to benzene rings without deactivating substituents.

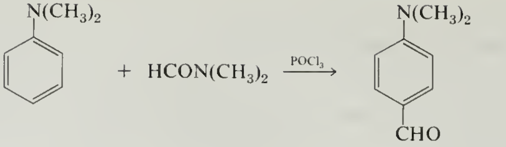
The **Gattermann-Koch** reaction is the reaction of an aromatic hydrocarbon with carbon monoxide and hydrogen chloride in the presence of a Lewis acid such as aluminum chloride. The reaction is equivalent to a Friedel-Crafts acylation with formyl chloride, HCOCl.



(46–51%)
p-tolualdehyde

This reaction is primarily of industrial importance.

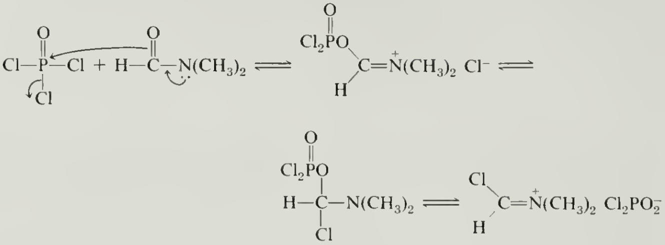
A related reaction is the **Vilsmeier** reaction, which involves the treatment of a reactive aromatic ring with dimethylformamide and phosphorus oxychloride. The reaction does not work with simple benzene hydrocarbons but requires activating substituents.



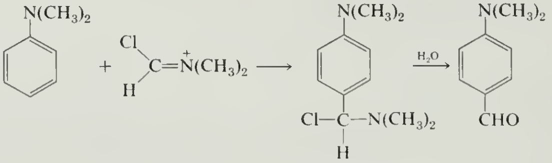
(80–84%)

dimethylaniline dimethylformamide (DMF) *p*-dimethylaminobenzaldehyde

The electrophilic reagent in the Vilsmeier reaction appears to be a chloroimmonium ion, formed in the following manner:

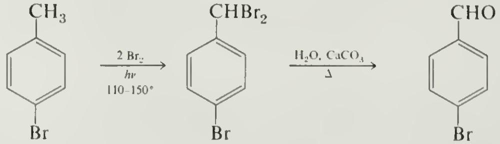


This species reacts with aromatic rings that contain highly activating substituents such as OH and NR_2. The initial product is an α-chloroamine, which rapidly hydrolyzes to the aldehyde.



B. *Oxidation of Methylarenes*

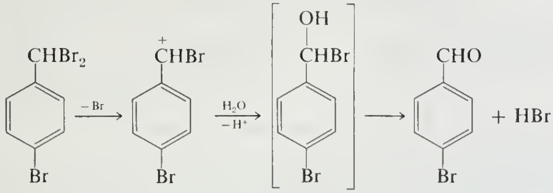
Aromatic aldehydes can be prepared from methyl substituents in two general ways. One procedure involves side chain halogenation to the dihalide, followed by hydrolysis.



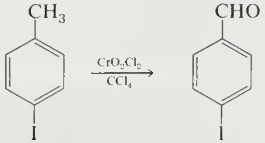
(60–69%)

p-bromotoluene *p*-bromobenzal bromide *p*-bromobenzaldehyde

Hydrolysis of benzal halides is an S_N1 process because a benzylic cation is involved as an intermediate. Calcium carbonate is used to react with the hydrohalic acid liberated.



Alternatively, the methyl group can be oxidized by chromyl chloride, CrO_2Cl_2 **(Etard's reagent).**



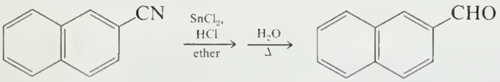
(58–64%)

p-iodotoluene *p*-iodobenzaldehyde

Chromyl chloride is a red volatile liquid. Its use is limited to compounds that are otherwise stable to strong oxidizing agents.

C. *Reduction of Nitriles*

In addition to other methods for reducing carboxylic acid derivatives to aldehydes, the **Stephen reduction** of nitriles has been applied primarily to aromatic systems, although some aliphatic examples are known. The reaction involves treatment with stannous chloride and hydrogen chloride in an inert solvent such as ether or ethyl acetate.



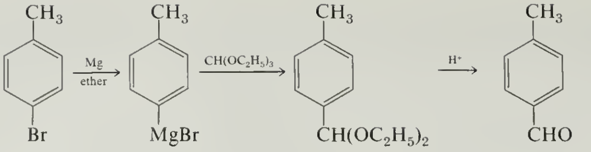
naphthalene-2-carbonitrile naphthalene-2-carboxaldehyde

The reaction involves reduction to an intermediate immonium salt which is readily hydrolyzed.

$$RCN \longrightarrow (RCH{=}NH_2^+)_2\ SnCl_6^{2-} \xrightarrow{H_2O} RCHO$$

D. *Grignard Reaction*

The final preparation of aromatic aldehydes involves reaction of a Grignard reagent with ethyl orthoformate.



(74%)
p-tolualdehyde

The method can also be applied to aliphatic aldehydes.

Ethyl orthoformate is an example of an orthoester; orthoesters bear the same relationship to esters as acetals do to aldehydes. Ethyl orthoformate is the most important member of this otherwise obscure class of compounds. It is a liquid, b.p. 146°, prepared by reaction of chloroform with ethanolic sodium ethoxide.

$$CHCl_3 + 3\ C_2H_5O^- \longrightarrow CH(OC_2H_5)_3 + 3\ Cl^-$$

The compound hydrolyzes readily in dilute acid to give first ethyl formate, then, upon further hydrolysis, formic acid.

$$CH(OC_2H_5)_3 + H_2O \xrightarrow{H^+} HCO_2C_2H_5 + 2\ C_2H_5OH$$

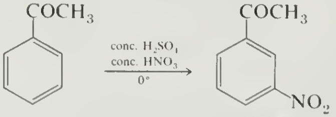
$$HCO_2C_2H_5 + H_2O \xrightarrow{H^+} HCO_2H + C_2H_5OH$$

31.4
Reactions of Aromatic Aldehydes and Ketones

Aromatic aldehydes and ketones undergo the normal carbonyl reactions of aldehydes and ketones generally. The aldehydes are oxidized readily to carboxylic acids. Normal carbonyl derivatives such as oximes, hydrazones, and bisulfite addition compounds may be prepared. They undergo normal addition reactions with Grignard reagents and reductions with lithium aluminum hydride or sodium borohydride. The additional kinds of reactions displayed by the aromatic compounds depend either on the benzene ring and its reactions or on the fact that the benzene ring conjugated with a carbonyl group does not provide hydrogens α to the carbonyl group.

A. *Benzene Ring Reactions*

The carbonyl group is *meta* directing. Aromatic aldehydes and ketones undergo many electrophilic substitution reactions to give *meta* products. A typical example is



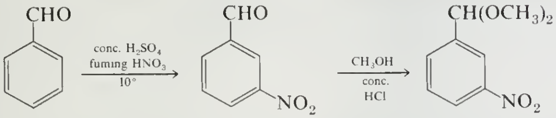
(55%)

acetophenone

m-nitroacetophenone

This nitration appears to require surprisingly mild conditions for a deactivated ring. However, the carbonyl group provides enhanced solubility in protonic solvents via hydrogen bonding.

A related example is provided by the following sequence:



m-nitrobenzaldehyde

(76–85%)
m-nitrobenzaldehyde dimethyl acetal

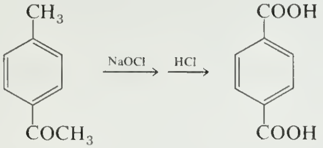
This example also shows that the aromatic aldehyde function forms normal acetal derivatives.

B. *Side Chain Reactions*

A number of side chain reactions have been discussed previously. For example, aryl methyl ketones undergo reaction with sodium hypohalite to produce carboxylic acids in good yield (Section 15.6.D):

$$\text{Ar-COCH}_3 \xrightarrow{\text{NaOCl}} \xrightarrow{\text{HCl}} \text{Ar-COOH} + \text{CHCl}_3$$

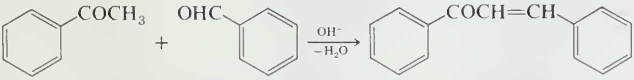
The efficacy of the method is limited by the fact that hypohalite often oxidizes side chain methyl groups as well as acyl groups.



(47%)
terephthalic acid

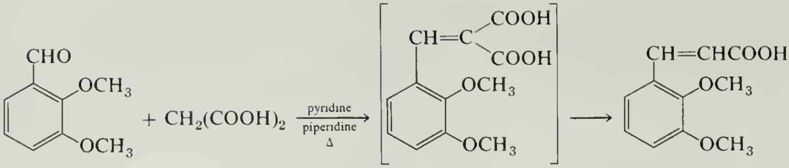
Because of the ready availability of some aryl methyl ketones by Friedel-Crafts acetylation, the procedure does find some use, especially with polycyclic aromatic hydrocarbons (Chapter 34).

Condensation reactions are especially important because reaction takes place unambiguously on one side of the carbonyl group.



benzalacetophenone

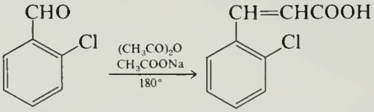
Aromatic aldehydes are especially useful in condensation reactions because the absence of α-hydrogens limits possible side reactions.



2,3-dimethoxy-benzaldehyde

(87–98%)
2,3-dimethoxy-cinnamic acid

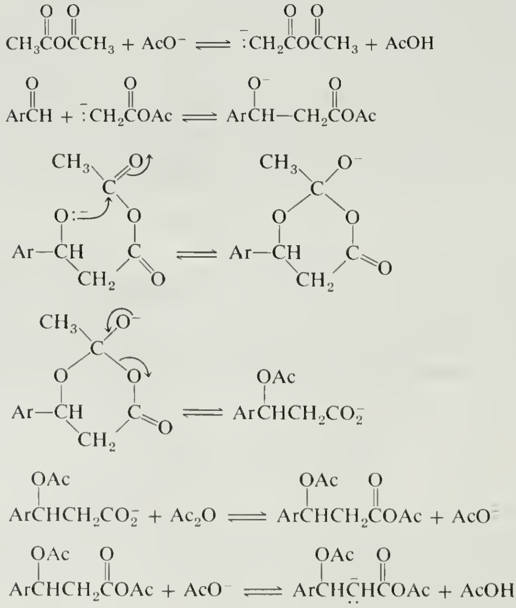
A condensation of this type that depends on the absence of α-hydrogens in aromatic aldehydes is the **Perkin reaction**, a reaction in which the aromatic aldehyde is heated with an acid anhydride and its corresponding sodium salt. Acetic anhydride and sodium acetate are used most commonly.



(72%)
o-chlorocinnamic acid

The reaction is a typical base-catalyzed condensation in which the enolate ion of an acid anhydride is an intermediate.

The Perkin reaction appears to proceed by way of the following interesting mechanism:



$$(1)\ CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 + AcO^- \rightleftharpoons \overset{-}{:}CH_2\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 + AcOH$$

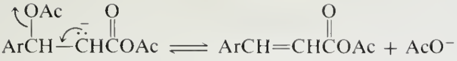
$$(2)\ Ar\overset{O}{\overset{\|}{C}}H + \overset{-}{:}CH_2\overset{O}{\overset{\|}{C}}OAc \rightleftharpoons Ar\overset{O^-}{\overset{|}{C}}H{-}CH_2\overset{O}{\overset{\|}{C}}OAc$$

(3)

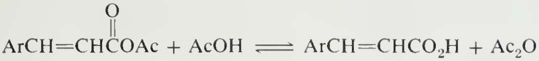
(4)

$$(5)\ Ar\overset{OAc}{\overset{|}{C}}HCH_2CO_2^- + Ac_2O \rightleftharpoons Ar\overset{OAc}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}OAc + AcO^-$$

$$(6)\ Ar\overset{OAc}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}OAc + AcO^- \rightleftharpoons Ar\overset{OAc}{\overset{|}{C}}H\underset{..}{\overset{-}{C}}H\overset{O}{\overset{\|}{C}}OAc + AcOH$$

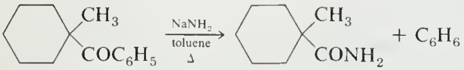
(7) 

$$\mathrm{Ar\overset{\overset{OAc}{|}}{C}H-\overset{-}{C}H\overset{\overset{O}{\|}}{C}OAc \rightleftharpoons ArCH{=}CH\overset{\overset{O}{\|}}{C}OAc + AcO^-}$$

(8) 

$$\mathrm{ArCH{=}CH\overset{\overset{O}{\|}}{C}OAc + AcOH \rightleftharpoons ArCH{=}CHCO_2H + Ac_2O}$$

Finally, aromatic ketones with no α-hydrogens undergo a remarkable cleavage reaction when treated with a strong base such as sodium amide.

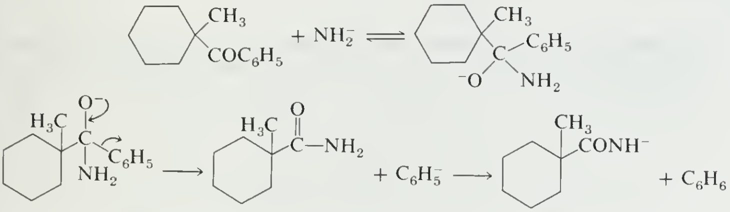

CH3
COC6H5
NaNH2
toluene
Δ
CH3
CONH2
+ C6H6

(88%)

1-methylcyclohexyl phenyl ketone

1-methylcyclohexanecarboxamide

The reaction involves addition of amide ion to the carbonyl group, followed by cleavage with formation of the more stable carbanion.

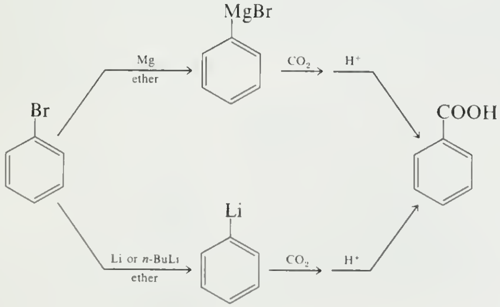

CH3
COC6H5
+ NH2−
CH3
C6H5
−O
NH2
H3C
O−
C6H5
NH2
H3C
O
C—NH2
+ C6H5−
CH3
CONH−
+ C6H6

Benzene is more acidic than an alkane, and phenyl anion is formed in preference to the alkyl anion. Phenyl anion immediately abstracts a proton from the more acidic amide nitrogen to give benzene and the amidate ion.

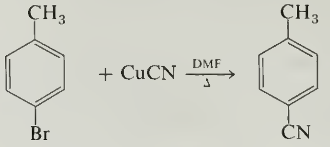
31.5
Aromatic Carboxylic Acids

A. *Preparation*

Aromatic carboxylic acids also show the general properties of carboxylic acids. They can be prepared by reaction of aryllithium or Grignard reagents with carbon dioxide just as their aliphatic counterparts.


MgBr
Mg
ether
CO2
H+
Br
COOH
Li
Li or n-BuLi
ether
CO2
H+

Although aryl halides do not undergo S_N2 displacement reactions, aryl bromides and iodides do undergo a facile substitution with cuprous cyanide.



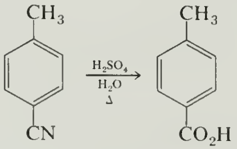
(91%)

p-bromotoluene *p*-tolunitrile

The mechanism of this substitution is not completely understood. It is not of the S_N2-type but probably involves organocopper intermediates. The reaction is less practical for aryl chlorides unless electron-attracting groups are present. Aryl cyanides are also readily available from the corresponding aromatic amines, as we shall see in Section 32.3.C.

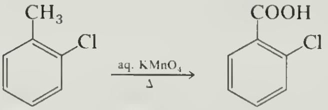
$$ArNH_2 \longrightarrow ArN_2^+ \longrightarrow ArCN$$

The resulting aryl cyanides may be hydrolyzed in the normal manner (Section 18.9.A) to give the corresponding aromatic carboxylic acids.



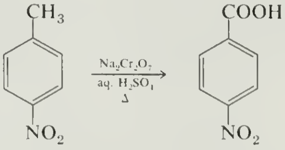
p-tolunitrile *p*-toluic acid

An important preparation of aromatic carboxylic acids is based on oxidation of methylarenes. A number of oxidizing agents have been used in laboratory preparations, including aqueous $KMnO_4$, aqueous HNO_3, and $Na_2Cr_2O_7$-H_2SO_4.



(76–78%)

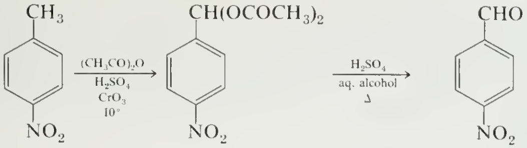
o-chlorotoluene *o*-chlorobenzoic acid



(82–86%)

p-nitrotoluene *p*-nitrobenzoic acid

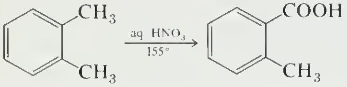
If the Cr(VI) oxidation is carried out in acetic anhydride, the product is the diester of the aldehyde hydrate. Hydrolysis of this diester affords the aromatic aldehyde.


CH3
NO2
(CH3CO)2O
H2SO4
CrO3
10°
CH(OCOCH3)2
NO2
H2SO4
aq. alcohol
Δ
CHO
NO2

(65–66%)

(89–94%)
p-nitrobenzaldehyde

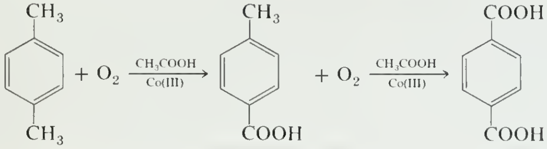
If the ring contains two methyl groups, the oxidation proceeds in steps, with the first alkyl group being oxidized more rapidly than the second. In such cases, the singly oxidized product can usually be isolated in moderate yield.


CH3
CH3
aq HNO3
155°
COOH
CH3

(53–55%)
o-toluic acid

Indeed, this difficulty in oxidizing the second methyl group has important chemical and financial implications in the industrial oxidation of *p*-xylene to terephthalic acid. This process is carried out on an enormous scale because of the commercial importance of terephthalic acid and its dimethyl ester. At the present time, the only industrially feasible oxidizing agent for the conversion of *p*-xylene to terephthalic acid is air, although nitric acid is used in some older processes.

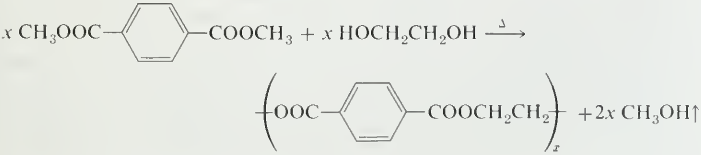
The air oxidation of *p*-xylene to *p*-toluic acid occurs readily; acetic acid is a convenient solvent and a cobalt compound is used as a catalyst.


CH3
CH3
+ O2
CH3COOH
Co(III)
CH3
COOH
+ O2
CH3COOH
Co(III)
COOH
COOH

p-toluic acid

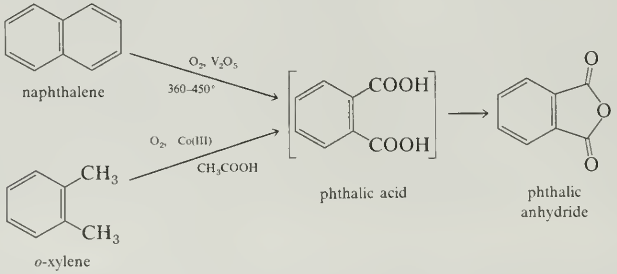
terephthalic acid

The subsequent oxidation of *p*-toluic acid is far more difficult and requires such high temperatures that oxidation of the acetic acid solvent becomes a significant cost concern and corrosion of reaction vessels is a problem. United States production of terephthalic acid and dimethyl terephthalate in 1973 was 5 billion lb. Much of this production was used for making a synthetic fiber variously known as polyester, Dacron, Terylene, and so on. This fiber is a condensation polymer with ethylene glycol, and one procedure for its synthesis involves a transesterification with dimethyl terephthalate.


x CH3OOC
COOCH3 + x HOCH2CH2OH
Δ
OOC
COOCH2CH2
x
+2x CH3OH↑

The same polymer is also used in Mylar film.

Phthalic acid is another important industrial product. Various high boiling esters, particularly the bis-2-ethylhexyl ester, are widely used as plasticizers. Phthalic acid is prepared commercially by the oxidation of naphthalene (Section 34.3.C) or *o*-xylene. It loses water readily on heating to produce phthalic anhydride, a compound with a characteristic odor that forms long colorless needles on sublimation.



Phthalic anhydride is used in the manufacture of glyptal resins, highly crosslinked, infusible polyesters prepared by heating the anhydride with glycerol. Potassium hydrogen phthalate is a well-characterized compound available in pure anhydrous form. It is used as a primary standard in titrations with bases.

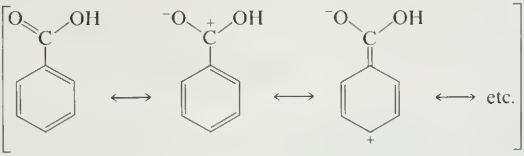
B. *Acidity of Substituted Benzoic Acids*

Phenylacetic acid ($K_a = 4.9 \times 10^{-5} M$, p$K_a$ = 4.31) is somewhat more acidic than acetic acid ($K_a = 1.8 \times 10^{-5}$ M, pK_a = 4.74). The sp^2 hybrid carbons of the benzene ring are effectively more electronegative than sp^3 hybrid carbons. This electron-attracting effect of a phenyl group was noted earlier in the dipole moment of toluene (Section 29.4). The phenyl group behaves as a normal type of substituent in that the acid-strengthening effect is attenuated rapidly down an alkyl chain, as shown by the acidity data displayed in Table 31.1.

TABLE 31.1
Acidity of Phenylalkanoic Acids

	K_a, M	pK_a
CH_3COOH	1.8×10^{-5}	4.74
C_6H_5COOH	6.3×10^{-5}	4.20
$C_6H_5CH_2COOH$	4.9×10^{-5}	4.31
$C_6H_5CH_2CH_2COOH$	2.2×10^{-5}	4.66
$C_6H_5CH_2CH_2CH_2COOH$	1.8×10^{-5}	4.76

Extrapolating in the other direction, putting the benzene ring still closer to the COOH group, we would expect benzoic acid to be much stronger acid than acetic acid. Benzoic acid ($K_a = 6.3 \times 10^{-5}$ M, pK_a = 4.20) is somewhat stronger than acetic acid, but the difference is much less than an extrapolation from Table 31.1 would suggest. The reason for the difference lies in the conjugation of the benzene ring with the carboxy group. This conjugation is less effective in the negatively charged carboxylate ion and renders the carboxy group effectively less acidic (compare α,β-unsaturated acids, Section 20.3.B).



Quantitative acidity measurements have been obtained for a variety of substituted benzoic acids because of the theoretical significance of aromatic chemistry and especially of the effect of structure on reactivity in these geometrically rigid and well-defined compounds. A number of the available pK_a measurements for *ortho, meta,* and *para* substituted benzoic acids are summarized in Table 31.2 and compared with the corresponding substituted acetic acids.

TABLE 31.2
Acidities of Substituted Benzoic and Acetic Acids

Substituent Y	pK_a at 25°			
		$Y{-}C_6H_4COOH$		
	$Y{-}CH_2COOH$	*ortho*	*meta*	*para*
H	4.74	4.20	4.20	4.20
CH_3	4.87	3.91	4.27	4.38
C_2H_5	4.82	3.79	4.27	4.35
F	2.59	3.27	3.86	4.14
Cl	2.85	2.92	3.83	3.97
Br	2.90	2.85	3.81	3.97
I	3.18	2.86	3.85	4.02
CN	2.47	3.14	3.64	3.55
CF_3	3.06		3.77	3.66
HO	3.83	2.98	4.08	4.57
CH_3O	3.57	4.09	4.09	4.47
C_6H_5	4.31	3.46	4.14	4.21
NO_2		2.21	3.49	3.42

Interesting comparisons may be made by plotting the pK_as of substituted benzoic acids against those of the corresponding acetic acids. Figure 31.1 shows such a plot for *meta* substituted benzoic acids. A fair linear correlation is obtained, with a slope of about 0.2. A similar plot for *para* substituted benzoic acids, Figure 31.2, shows much more scatter. Indeed, the points seem to form no consistent pattern. Electronegative atoms such as the halogens do increase the acidity of both acids, but the oxygen atoms in hydroxy and alkoxy groups cause substantial decreases in acidity. Furthermore, such strongly electron-attracting groups as CN and CF_3 have a greater effect on the acidity of benzoic acid in the *para*

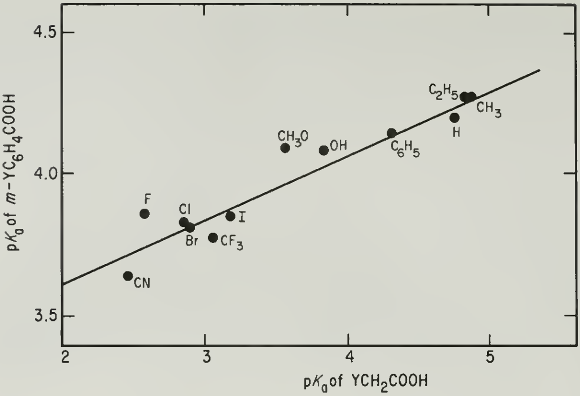


FIGURE 31.1 *Comparison of acidities of* meta *substituted benzoic acids to corresponding substituted acetic acids.*

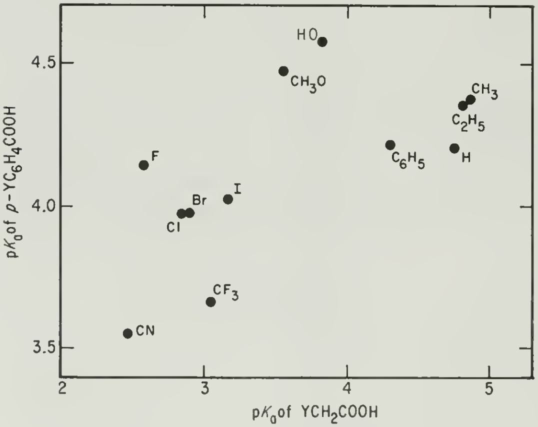
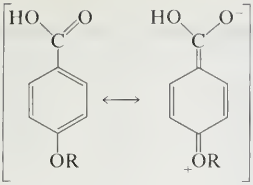


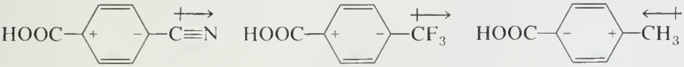
FIGURE 31.2 *Comparison of acidities of* para *substituted benzoic acids to corresponding substituted acetic acids.*

position than in the *meta*, even though the *para* position is one carbon atom farther removed from the carboxy group.

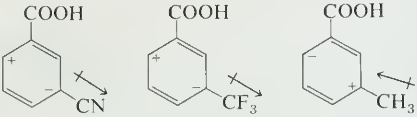
Reason is restored when we recognize that the *para* position is directly conjugated with the reaction center, whereas the *meta* position is not. The pronounced acid-weakening effect of RO groups can be interpreted on the basis of conjugative electron donation.



Benzene π electrons may be considered to be rather polarizable, and the effects of many substituents can be interpreted through the contribution of resonance structures that show such polarization. For example, polarization structures such as



help to explain the enhanced effect of substituents in the *para* position. In the *meta* position, such polarization is less efficient in relaying the dipolar nature of a substituent to the reaction center.



Ortho substituents present an additional complication. The steric hindrance provided by the close proximity of substituent and carboxyl group prevents the carboxy group from achieving complete coplanarity with the benzene ring. That is, the carboxy group in these compounds is no longer as conjugated with the benzene ring, and the differential stabilization of the carboxylic acid relative to the carboxylate ion is lost. Consequently, all *ortho* substituents, including alkyl groups, cause an increase in the acidity of benzoic acid. Because steric effects are involved as well as electronic effects, there is no useful correlation with the acidities of other substituted acids.

C. *The Hammett $\sigma\rho$ Equation*

Comparison of the acidities of substituted benzoic acids with substituted acetic acids has shown some important parallels but more important differences. We next inquire as to the effect of a substituent in other phenyl compounds compared to the effect in benzoic acid. For example, the acidities of some substituted phenylacetic acids are summarized in Table 31.3. Figure 31.3 shows a plot of these acidities compared to the corresponding benzoic acids. The *meta* and *para* groups form an excellent linear correlation, but the *ortho* groups deviate substantially. The *meta* and *para* positions are sufficiently removed from the center of reaction that only electronic effects are important; the *ortho* position involves steric effects as well. The important conclusion to be drawn from Figure 31.3 is that, in the *meta* and *para* positions, the electronic effects of a substituent in one system are proportional to the effects in another. The slope of the line in Figure 31.3, 0.46, shows that a given substituent has only half the effect in modifying the acidity of phenylacetic acid that it has on benzoic acid.

TABLE 31.3
Acidities of Substituted Phenylacetic Acids

	pK_a of Y—$C_6H_4CH_2COOH$		
Substituent, Y	*ortho*	*meta*	*para*
H	4.31	4.31	4.31
CH_3	4.35		4.37
F			4.25
Cl	4.07	4.14	4.19
Br	4.05		4.19
I	4.04	4.16	4.18
NO_2	4.00	3.97	3.85
CH_3O			4.36

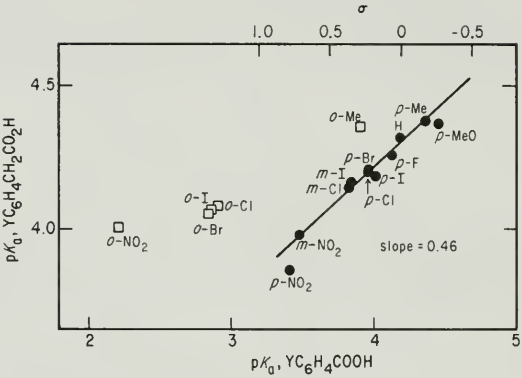


FIGURE 31.3 *Comparison of acidities of substituted phenylacetic acids to corresponding substituted benzoic acids.*

This type of interrelationship has been demonstrated for a wide variety of reactions and equilibria, and has been formulated as equation (31-3) by Professor L. P. Hammett. Equation (31-3) is now known as the Hammett equation.

$$\log K_i/K_H = \rho\sigma_i \tag{31-3}$$

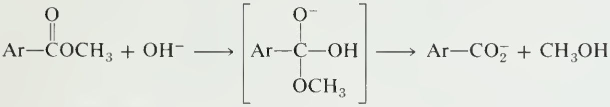
In this equation, K_i is the equilibrium or rate constant given by substituent i, compared to that for the unsubstituted compound (substituent = H). The Greek letter sigma, σ_i, is a number characteristic of the substituent, whereas rho, ρ, is a number characteristic of the reaction. For the acidities of benzoic acids in water at 25°, ρ is *defined* as unity; thus, σ_i values are given directly as the pK_a difference, pK_a(benzoic acid) − pK_a(substituted benzoic acid). Table 31.4 summarizes σ values for a number of *meta* and *para* substituents. A negative σ value signifies an electron-donating group; a positive σ value signifies an electron-attracting group. The larger the magnitude of σ, the greater is the effect of the substituent.

Figure 31.3 corresponds to a Hammett plot with $\rho = 0.46$. The magnitude of

TABLE 31.4
Hammett Substituent Constants, σ

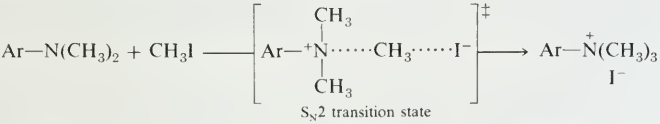
Group	σ_m	σ_p
CH_3	−0.069	−0.170
$C(CH_3)_3$	−0.10	−0.197
C_6H_5	0.06	−0.01
CF_3	0.43	0.54
CN	0.56	0.660
$COCH_3$	0.376	0.502
NH_2	−0.16	−0.66
NO_2	0.710	0.778
OCH_3	0.115	−0.268
OH	0.121	−0.37
F	0.337	0.062
Cl	0.373	0.227
Br	0.391	0.232
I	0.352	0.18

ρ indicates the sensitivity of a given equilibrium or reaction to a given substituent. A positive ρ value signifies that the equilibrium or reaction is aided by electron-attracting substituents. As an example, the rates of hydrolysis of substituted methyl benzoates by hydroxide ion in aqueous acetone solution follow a $\sigma\rho$-correlation with $\rho = 2.23$. This result means that the transition state has substantial negative charge (positive ρ; stabilization by electron-attracting substituents), and is consistent with our view of such hydrolyses proceeding through an anionic tetrahedral intermediate.



$$\mathrm{Ar{-}\overset{\overset{O}{\|}}{C}OCH_3 + OH^- \longrightarrow \left[Ar{-}\underset{\underset{OCH_3}{|}}{\overset{\overset{O^-}{|}}{C}}{-}OH\right] \longrightarrow Ar{-}CO_2^- + CH_3OH}$$

Conversely, the reaction of substituted dimethylanilines with methyl iodide in aqueous acetone to give the trimethylanilinium iodide has $\rho = -3.30$. In this case electron-donating substituents help to stabilize the developing positive charge close to the ring and lead to a negative ρ value.

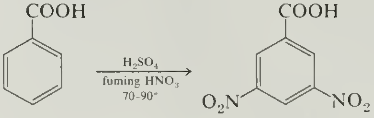


$$\mathrm{Ar{-}N(CH_3)_2 + CH_3I \longrightarrow \left[Ar{-}\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{{}^+N}}\cdots\cdots CH_3\cdots\cdots I^-\right]^{\ddagger} \longrightarrow Ar{-}\overset{+}{N}(CH_3)_3\ I^-}$$

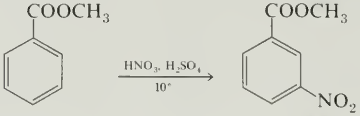
S_N2 transition state

D. *Reactions of Aromatic Carboxylic Acids*

The reactions of carboxylic acid groups do not change significantly by virtue of attachment to benzene rings. They form typical carboxylic acid derivatives such as acid halides, amides, esters, and so on. Indeed, many of the examples used previously for exemplifying such reactions utilized aromatic carboxylic acids. The carboxylic acid group does affect the reactivity of the aromatic ring. Like carbonyl functions generally, the carboxylic acid or ester group is *meta* directing in electrophilic aromatic substitution reactions. Many such reactions can be carried out smoothly. Some examples are

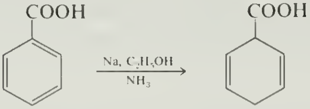


(54–58%)
3,5-dinitrobenzoic acid



(81–85%)
methyl *m*-nitrobenzate

Benzoic acid undergoes the Birch reduction (Section 30.7.D) with sodium and ethanol in liquid ammonia to give an unconjugated cyclohexadienecarboxylic acid.



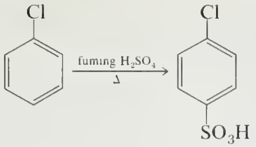
(89–95%)
2,5-cyclohexadiene-1-carboxylic acid

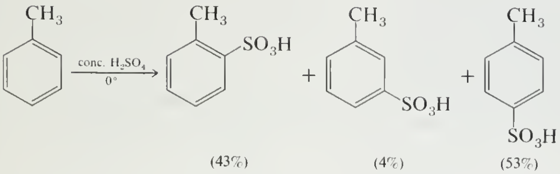
31.6
Sulfonic Acids

Alkanesulfonic acids have been discussed previously (Section 18.13.A). Arenesulfonic acids are much more common, and their chemistry will be discussed in this section.

A. *Preparation of Arenesulfonates*

The aromatic sulfonic acids are normally obtained by direct sulfonation of aromatic rings, using sulfuric acid or its derivatives. The reaction is a normal electrophilic aromatic substitution in which the electrophilic reagent is sulfur trioxide (Section 21.2.D). Some examples are



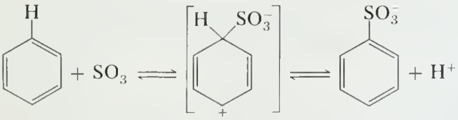


The isomer distribution often depends on the exact experimental conditions; for example, the product composition from toluene at 100° is 13% *ortho*, 8% *meta*, and 79% *para*. The sulfonation reaction is reversible and the product depends on whether the reaction conditions favor kinetic or thermodynamic control. In the sulfonation of toluene at low temperature, the reaction product is the product of kinetic control; that is, the product composition reflects relative energies of transition states. At higher temperatures, the reverse reaction has a significant rate, and the reaction takes on the aspects of an equilibrium.

$$\mathrm{Ar{-}H} + SO_3 \underset{\substack{\uparrow \\ \text{important at high} \\ \text{temperatures}}}{\rightleftharpoons} \mathrm{Ar{-}SO_3H}$$

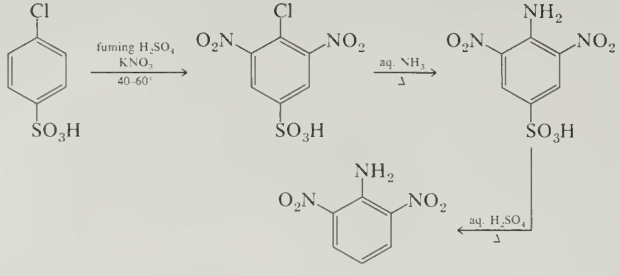
The sulfonic acid group is a rather bulky group and steric hindrance interaction with *ortho* substituents is significant. At equilibrium, the relatively unhindered *p*-toluenesulfonic acid dominates over *o*-toluenesulfonic acid. Such steric hindrance effects are much less evident at the transition state for sulfonation; hence, *o*- and *p*-toluenesulfonic acids are formed at comparable rates.

According to the principle of microscopic reversibility (Section 5.3.A), the back reaction must be the exact reverse of the forward reaction. The forward reaction is a reaction with sulfur trioxide to form a dipolar, neutral intermediate which loses a proton to form the arenesulfonate ion.



Consequently, the reverse reaction involves reaction by a proton at a ring carbon of the sulfonate ion. This reverse reaction is faster for a more hindered *ortho* substituted sulfonic acid, because steric congestion effects are relieved in the dipolar intermediate. Other consequences of steric hindrance effects in *ortho* substituted sulfonic acids were discussed previously in connection with the Jacobsen rearrangement (Section 30.6.A).

The reversal of sulfonation can be carried out by heating the sulfonic acid in dilute aqueous sulfuric acid. In this way the sulfonic acid group can serve as a protecting group to direct aromatic substitution into other positions. The following reaction sequence is a pertinent example:



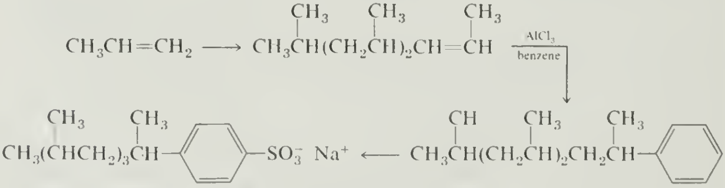
2,6-dinitroaniline

The presence of the SO_3H group in the *para* position results in dinitration in the positions *ortho* to the chlorine. These nitro groups are in positions to facilitate nucleophilic aromatic substitution of chloride by ammonia, and the sulfonic acid group is finally removed by a reversal of a sulfonation reaction.

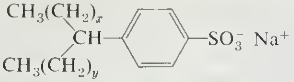
Arenesulfonic acids are strong acids, about as strong as hydrochloric acid. They are completely dissociated in aqueous solution and, indeed, the resulting solubility presents problems in isolations. Consequently, the products of sulfonation reactions are usually isolated as salts. The sodium salts, like all sodium salts, are water soluble, but they are generally not as soluble as sodium sulfate or sodium chloride. The solubility products of sodium arenesulfonates are sufficiently low that these salts can be "salted out" by addition of more soluble sodium salts to an aqueous solution.

$$ArSO_3^- + Na^+ \rightleftharpoons ArSO_3^-\ Na^+\downarrow$$

The sodium salts of benzenesulfonic acid containing a long alkyl side chain behave as detergents. The sulfonate end is hydrophilic and dissolves in water. The alkane end is hydrophobic and fat soluble and the combination serves to emulsify fatty materials (Section 17.4.D). At one time the alkane side chain was made by the carbonium ion polymerization of propylene to give a tetrameric olefin which was used to alkylate benzene; this alkylate was then sulfonated to give the product, which was widely used in many common household detergents.



The widespread use of large quantities of this material caused problems in the purification of sewage effluent because the branched chains were only slowly biodegradable. The detergent industry has now completely replaced this product with one prepared from a straight chain C_{12} to C_{15} alkane. The hydrocarbon is chlorinated and used for Friedel-Crafts alkylation of benzene followed by sulfonation to give a product that has the linear character necessary for rapid biodegradability by bacteria.

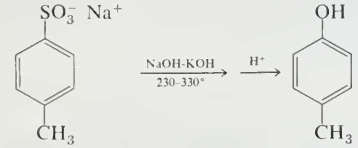


modern household detergent

p-Toluenesulfonic acid is available as the crystalline monohydrate, $C_7H_7SO_3^- \ H_3O^+$, m.p. 105°. It is prepared by salting out the sulfonation product from toluene with concentrated hydrochloric acid. Alternatively, the barium salt is treated with the stoichiometric amount of sulfuric acid and the insoluble barium sulfate is filtered. The filtrate is a strong acid, and concentrated solutions will dehydrate cellulose (filter paper!) just like sulfuric acid. Indeed, *p*-toluenesulfonic acid is used as an acid catalyst in place of sulfuric acid in cases where the oxidizing character of sulfuric acid is deleterious.

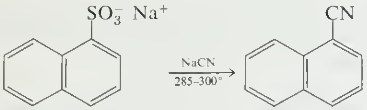
B. *Reaction of Arenesulfonic Acids*

The sulfonate group in aromatic sulfonic acids can be replaced by nucleophilic aromatic substitution reactions. The conditions are drastic: fusion with alkali hydroxide or other salts at temperatures of 200–350°. For example



sodium *p*-toluenesulfonate

(63–72%) *p*-cresol

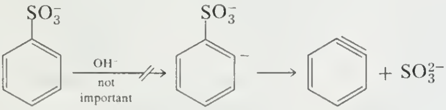


sodium 1-naphthalene-sulfonate

(60–70%) 1-naphthonitrile

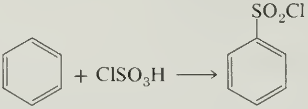
The method is used primarily for preparing phenols and nitriles. The reaction conditions required are tolerated by few other functional groups; hence, the scope of the reaction is limited.

One interesting feature in this reaction is the relative absence of benzyne intermediates, particularly with monosulfonates. Under these conditions, aryl halides give extensive elimination to benzynes. The negative charge on the sulfonate group and steric hindrance to *ortho* attack undoubtedly contribute to the absence of reaction via benzyne.

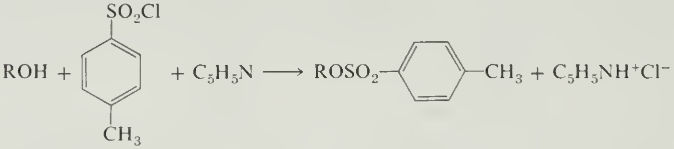


However, another difference lies in the nature of the reaction. Sodium arenesulfonates are salts and, as such, dissolve readily in fused salt systems. Such liquids are composed almost wholly of ions and constitute media quite different from normal liquids. In particular, neutral organic compounds are not generally soluble in such highly polar ionic media; hence, we have encountered them only rarely for organic reactions. Fused salt media are useful in organic chemistry only when the organic compound itself is a salt.

One of the most important reactions of these acids is the conversion to the acid chloride. In fact, this reaction is most conveniently carried out on the sodium salt by treatment with PCl_5 or $POCl_3$. The product can be distilled or crystallized from benzene: benzenesulfonyl chloride, b.p. 251.5°; *p*-toluenesulfonyl chloride, m.p. 68°. Alternatively, the acid chloride may be prepared by direct sulfonation with chlorosulfonic acid.



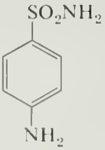
p-Toluenesulfonyl chloride (tosyl chloride) is used to prepare tosyl esters from alcohols. The procedure involves combining the reagents with excess pyridine at room temperature. Pyridinium chloride separates from solution; the mixture is then added to dilute hydrochloric acid and the product tosylate is filtered or extracted into ether.



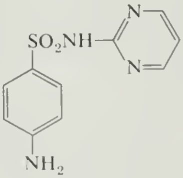
The sulfonyl chloride may in turn be used in a Friedel-Crafts reaction to produce a class of compounds known as sulfones:

$$C_6H_5SO_2Cl \xrightarrow[C_6H_6]{AlCl_3} \underset{\text{phenyl sulfone}}{C_6H_5SO_2C_6H_5}$$

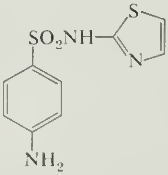
Reaction of sulfonyl chlorides with ammonia or amines gives the corresponding sulfonamides. Many such compounds have found important medicinal use as antibacterial agents. Examples of such compounds are sulfanilamide (*p*-aminobenzenesulfonamide), sulfadiazine [*p*-amino-N-(2-pyrimidyl)benzenesulfonamide], and sulfathiazole [*p*-amino-N-(2-thiazolyl)benzenesulfonamide].



sulfanilamide



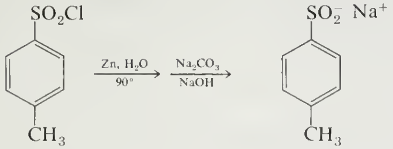
sulfadiazine



sulfathiazole

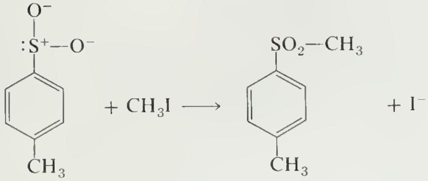
They are no longer used in human medicine because of side reactions and the development of antibiotics, but they are still used in veterinary medicine.

Reduction of a sulfonyl chloride with zinc and water gives a sulfinic acid.


SO₂Cl
Zn, H₂O
90°
Na₂CO₃
NaOH
SO₂⁻ Na⁺
CH₃
CH₃

(64%)
sodium *p*-toluenesulfinate

Sulfinic acids are a generally unimportant class of compounds, but the salts show one interesting feature. As nucleophilic reagents reacting with alkyl halides, reaction occurs on sulfur rather than oxygen to produce a sulfone; that is, sulfinates are another example of ambident anions (Section 8.4).


O⁻
:S⁺—O⁻
CH₃
+ CH₃I
SO₂—CH₃
CH₃
+ I⁻

methyl *p*-tolyl sulfone

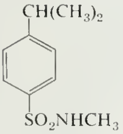
Under more strongly reducing conditions, sulfonyl chlorides give the corresponding thiols.

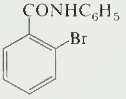
$$C_6H_5SO_2Cl \xrightarrow[0^\circ]{Zn,\ H_2SO_4} C_6H_5SH$$

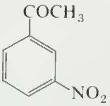
(96%)
thiophenol

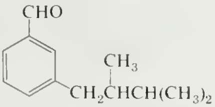
PROBLEMS

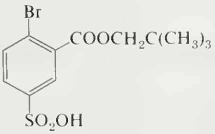
1. Give an acceptable name for each of the following structures:

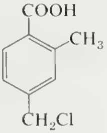
(a)

CH(CH₃)₂
SO₂NHCH₃

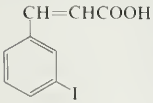
(b)

CONHC₆H₅
Br

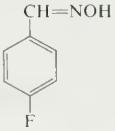
(c)


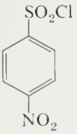
(d)

CHO
CH₃
CH₂CHCH(CH₃)₂

(e)

Br
COOCH₂C(CH₃)₃
SO₂OH

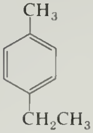
(f)

COOH
CH₃
CH₂Cl

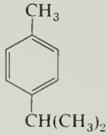
(g)


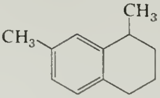
(h)


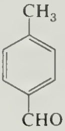
(i)


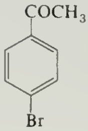
2. Show how each of the following compounds may be prepared in a practical manner, starting with benzene, toluene, and any required aliphatic or inorganic reagents.

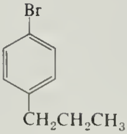
(a)


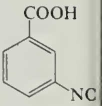
(b)


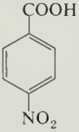
(c)


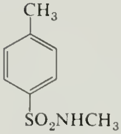
(d)


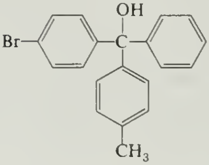
(e)


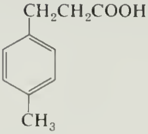
(f)

Br
CH2CH2CH3

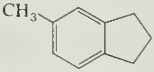
(g)


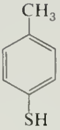
(h)


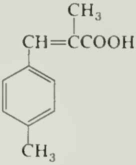
(i)

CH3
SO2NHCH3

(j)


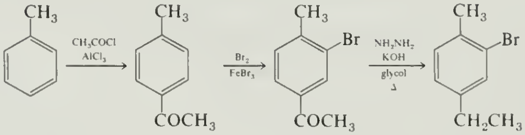
(k)

CH2CH2COOH
CH3

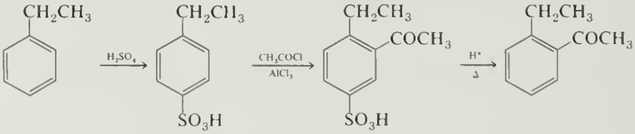
(l)


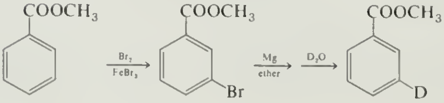
(m)


(n)

CH3
CH=CCOOH
CH3

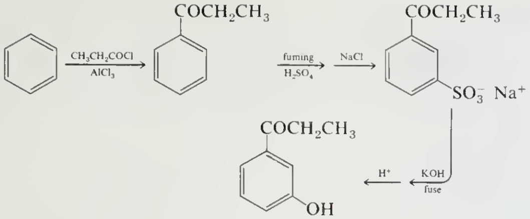
3. The following reaction sequences are impractical. Determine what is wrong in each case.

(a)

CH3
CH3COCl
AlCl3
CH3
COCH3
Br2
FeBr3
CH3
Br
COCH3
NH2NH2
KOH
glycol
Δ
CH3
Br
CH2CH3

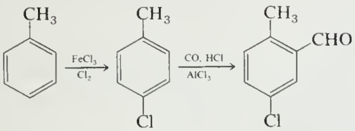
(b)

CH2CH3
H2SO4
CH2CH3
SO3H
CH3COCl
AlCl3
CH2CH3
COCH3
SO3H
H+
Δ
CH2CH3
COCH3

(c)

COOCH3
Br2
FeBr3
COOCH3
Br
Mg
ether
D2O
COOCH3
D

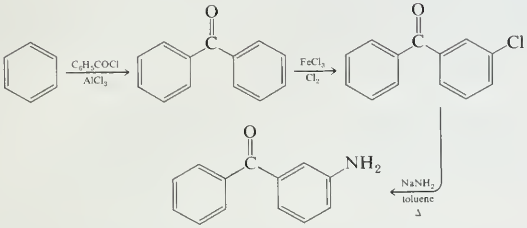
(d)


COCH2CH3
CH3CH2COCl
AlCl3
fuming
H2SO4
NaCl
COCH2CH3
SO3- Na+
KOH
fuse
H+
COCH2CH3
OH

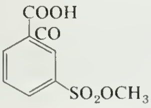
(e)


CH3
FeCl3
Cl2
CH3
Cl
CO, HCl
AlCl3
CH3
CHO
Cl

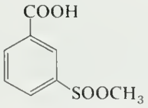
(f)


C6H5COCl
AlCl3
O
C
FeCl3
Cl2
O
C
Cl
NaNH2
toluene
Δ
O
C
NH2

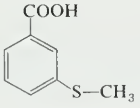
4. In each of the following series, rank in order of increasing acidity and give a reasonable explanation.
   (a) phthalic acid, isophthalic acid, benzoic acid
   (b) *p*-iodobenzoic acid, *p*-iodosobenzoic acid, *p*-iodoxybenzoic acid
   (c) benzoic acid, *m*-trifluoromethylbenzoic acid, *p*-trifluoromethylbenzoic acid
   (d)


COOH
CO
SO2OCH3

m-(methoxysulfonyl)-
benzoic acid

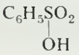

COOH
SOOCH3

m-(methoxysulfinyl)-
benzoic acid

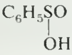


m-(methylthio)-
benzoic acid

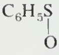
   (e) acetoacetic ester, 5-oxohexanoic acid, *m*-acetylbenzoic acid, benzoic acid
   (f)



$C_6H_5SO_2OH$



C_6H_5SOOH



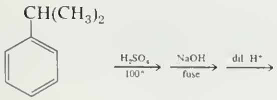
C_6H_5SOH

benzenesulfenic acid

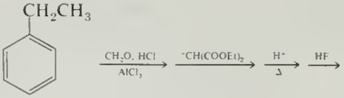
   (g) benzenesulfonic acid, *p*-methoxybenzenesulfonic acid, *m*-fluorobenzenesulfonic acid.

5. In each of the following sequences, the starting compound is transformed to a single principal product. Give its structure.

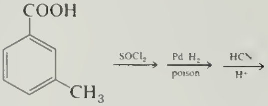
(a)


CH(CH3)2
H2SO4
100°
NaOH
fuse
dil H+

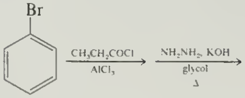
(b)



(c)

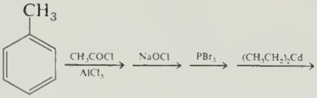


(d)

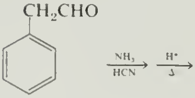


(e) $C_6H_5CHO \xrightarrow[\Delta]{\substack{(CH_3CH_2CO)_2O \\ CH_3CH_2COO^- \ Na^+}} \xrightarrow{Pd\ H_2} \xrightarrow{SOCl_2} \xrightarrow{NH_3} \xrightarrow{Br_2,\ OH^-}$

(f)



(g)



6. Compound A, $C_{14}H_{22}O_2$, on treatment with dilute HCl, gave B, $C_{10}H_{12}O$, which when treated with bromine and NaOH gave an acid, C, $C_9H_{10}O_2$. On heating with hydrazine and KOH in glycol, B gave D, $C_{10}H_{14}$. On treatment with benzaldehyde and dilute NaOH, B gave E, $C_{17}H_{16}O$. Compounds A, B, C, and D all gave phthalic acid on vigorous oxidation. Derive the structures of A through E and formulate the transformations involved.

7. Benzaldehyde reacts smoothly with acetophenone and aqueous sodium hydroxide to produce benzalacetophenone, $C_6H_5CH{=}CHCOC_6H_5$, in high yield. Write the mechanism of this reaction, showing all intermediates involved. Benzalacetophenone can be nitrated to give mononitration. Which ring reacts? What is the expected orientation?

8. The carboxy group in mesitoic acid (2,4,6-trimethylbenzoic acid) is so hindered that normal esterification with methanol and acid takes a very long time. Review the other methods of conversion of carboxylic acids to esters that we have studied and suggest those that are expected to be more successful with such highly hindered acids. Explain why these methods are more successful.

9. Explain why methyl benzoate is *meta* directing in electrophilic aromatic substitution reactions using resonance structures where desirable.

10. Compare the relative acidities of benzenesulfonic acid with benzoic acid and of benzenesulfonamide with benzamide. Predict the relative acidities of acetophenone and phenyl methyl sulfone.

11. Cleavage of *o*-methoxybenzophenone with sodium amide gives benzamide almost exclusively. What does this experiment reveal about the relative acidities of benzene and the *ortho*-hydrogen in anisole? Is this result reasonable on the basis of analogies known to you?

12. Oxalyl chloride reacts with mesitylene in the presence of $AlCl_3$ to give 2,4,6-trimethylbenzoyl chloride and carbon monoxide. Write a plausible reaction mechanism for this reaction. The corresponding acid, 2,4,6-trimethylbenzoic acid, dissolves in concentrated H_2SO_4 to form the ion, $(CH_3)_3C_6H_2CO^+$. Write the equilibrium reaction involved. When this solution is poured into methanol, the methyl ester, $(CH_3)_3C_6H_2COOCH_3$, is formed quantitatively. Write the reaction mechanism involved.

13. In the *meta* and *para* positions, hydroxybenzoic and methoxybenzoic acids have comparable acidities. In the *ortho* position, however, they differ by more than 1 pK unit (Table 31.2). Can you explain this difference? (*Hint:* the answer involves hydrogen-bonding.)

14. On heating an aqueous solution of sodium 2,4,6-trinitrobenzoate, sodium bicarbonate is produced, together with a good yield of 1,3,5-trinitrobenzene. What mechanism can you suggest for this reaction?

15. The pK_as of m- and p-iodoxybenzoic acids in water at 25° are 3.50 and 3.44, respectively. Calculate σ_m and σ_p for the iodoxy group, $—IO_2$. Give a rationalization of the approximate magnitude on the basis of Lewis structures of the $—IO_2$ group.

16. (a) What is the sign of ρ for the reaction

$$\text{Ar—CH}_2\text{NMe}_2 + \text{CH}_3\text{I} \longrightarrow \text{Ar—CH}_2\text{N(CH}_3)_3^+\ \text{I}^-$$

(b) How does this magnitude of ρ compare with that for the reaction

$$\text{Ar—CH}_2\text{CH}_2\text{NMe}_2 + \text{CH}_3\text{I} \longrightarrow \text{Ar—CH}_2\text{CH}_2\text{N(CH}_3)_3^+\ \text{I}^-$$

(c) What is the sign of ρ for the reaction

$$\text{Ar—SO}_2\text{OCH}_3 + \text{C}_2\text{H}_5\text{O}^- \longrightarrow \text{Ar—SO}_3^- + \text{CH}_3\text{OC}_2\text{H}_5$$

(d) The first-order rate constants for solvolysis of isopropyl esters of substituted benzenesulfonic acids in 50% aqueous ethanol at 25° are given:

Substituent	$10^5\,k$, sec^{-1}
H	2.50
p-CH_3	1.47
p-Br	7.30
m-NO_2	34.2
p-NO_2	44.4

Calculate ρ for this reaction and predict the solvolysis rate of isopropyl m-trifluoromethylbenzenesulfonate.

17. Reaction of 2-bromo-5-nitroacetophenone with hydroxylamine gives two oximes, called α and β. The α-oxime on treatment with base gives a compound, $C_8H_6N_2O_3$, and on treatment with acid undergoes Beckmann rearrangement to N-methyl-2-bromo-5-nitrobenzamide. The β-oxime on Beckmann rearrangement gives N-(2-bromo-5-nitrophenyl) acetamide. Deduce the structures of the two oximes and the stereochemical course of the Beckmann rearrangement.

CHAPTER 32

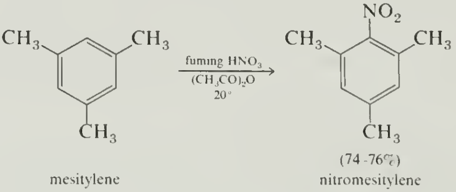
Aromatic Nitrogen Compounds

32.1

Nitroarenes

A. *Preparation*

We have already seen many examples of the preparation of aromatic nitro compounds. By far the most important route to such compounds is electrophilic aromatic nitration with nitric acid. For benzene itself and for derivatives of comparable reactivity, a mixture of concentrated nitric and sulfuric acids is the reagent generally used. Less reactive aromatic rings require the use of fuming nitric or fuming sulfuric acids or both. For more reactive rings, nitric acid in acetic acid or acetic anhydride are useful reagents.

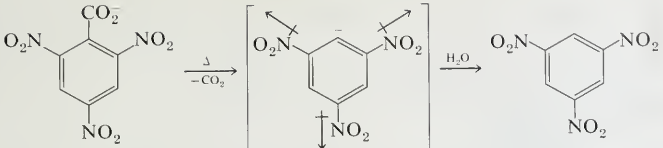


Minor methods of preparation that are useful for special cases involve conversion of an —NH_2 group to the —NO_2 group. Two such methods will be described in later sections.

B. *Properties of Nitro Compounds*

Nitrobenzene and related nitro compounds are generally high boiling liquids. Nitrobenzene is a pale yellow oil, b.p. 210–211°, having a characteristic odor of almonds. It was used at one time in shoe polish, but is readily absorbed through the skin and is poisonous.

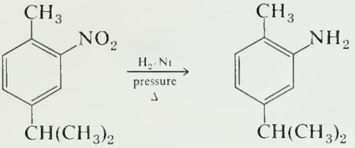
2,4,6-Trinitrotoluene, TNT, is an important explosive. It is relatively insensitive to shock and is used with a detonator. It melts at 81°, and it can be poured as the melt into containers such as bombs and hand grenades. 1,3,5-Trinitrobenzene is less sensitive than TNT to shock and has more explosive power, but is more difficult to prepare. Direct introduction of the third nitro group into toluene is assisted by the methyl group. Small amounts of 1,3,5-trinitrobenzene are prepared by oxidation of TNT to trinitrobenzoic acid. 2,4,6-Trinitrobenzoic acid is a strong acid ($pK_a = 0.7$) whose anion decomposes on heating to liberate carbon dioxide and form a phenyl anion which is stabilized by the electron-attracting inductive effect of the three nitro groups.



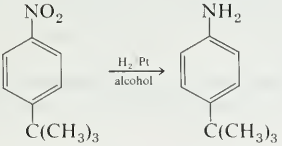
1,3,5-trinitrobenzene

C. *Reactions of Nitroarenes*

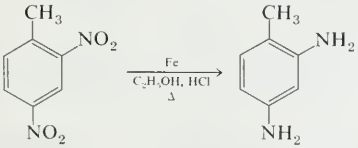
The nitro group is relatively stable to many reagents. It is generally inert to acids and most electrophilic reagents; hence, it may be present in a ring when reactions with such reagents are used. The nitro group is also stable to most oxidizing agents, but it reacts with Grignard reagents and strongly basic reagents and interferes with Friedel-Crafts reactions. The most important reaction of the nitro group in aromatic compounds is reduction, but the reduction product depends on the reaction conditions used. Catalytic hydrogenation and chemical reducing agents in acidic media give the corresponding amines in high yield.



(87–90%)
2-methyl-5-isopropylaniline

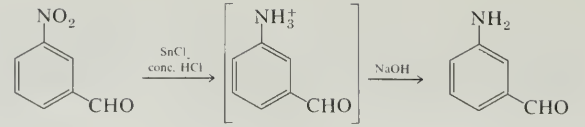


(100%)
p-t-butylaniline



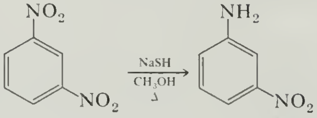
(74%)
2,4-diaminotoluene

Many chemical reducing agents have been used for the conversion of aromatic nitro groups to amines. Among the most common are metals and acid, usually iron or zinc and dilute hydrochloric acid. Stannous chloride, $SnCl_2$, and hydrochloric acid are an especially useful combination when other reducible groups, such as carbonyl groups, are present.



m-nitrobenzaldehyde *m*-aminobenzaldehyde

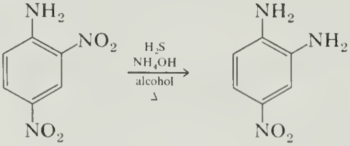
Sodium or ammonium sulfide or hydrosulfide is useful for reducing one of the nitro groups in dinitro compounds.



(79-85%)

m-dinitrobenzene *m*-nitroaniline

The method can be applied to unsymmetrical dinitro compounds as well and selective reductions are sometimes possible.

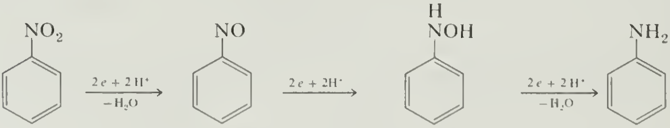


(52-58%)

2,4-dinitroaniline 1,2-diamino-4-nitrobenzene

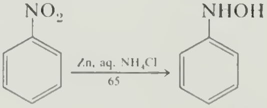
The reduction of aromatic nitro compounds is an important synthetic process because nitro groups can often be introduced directly by electrophilic aromatic nitration, and the amino group can in turn be converted into a host of other functional groups.

Reduction of the nitro group actually proceeds in a series of two-electron steps. In acid the intermediate compounds cannot be isolated, but are reduced rapidly in turn.



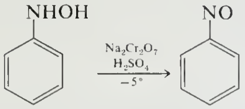
nitrobenzene nitrosobenzene phenylhydroxylamine aniline

In neutral media, a higher reduction potential is required and reduction is readily stopped at the hydroxylamine stage.



(62-68%)

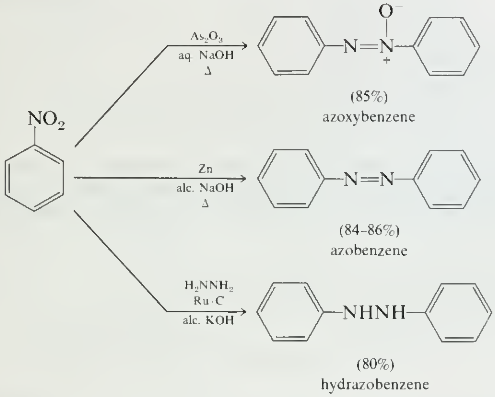
Aromatic hydroxylamines are relatively unimportant compounds. Phenylhydroxylamine is a water soluble, crystalline solid, m.p. 82°, that deteriorates in storage. It may be oxidized to nitrosobenzene.


NHOH
NO
$Na_2Cr_2O_7$
H_2SO_4
−5°

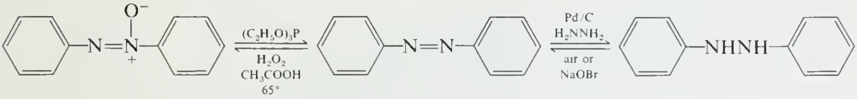
(65-70%)

Nitrosoarenes also are not important compounds, but some nitrosoamines (Section 32.2.G) and nitrosophenols (Section 33.3.C) have significant uses. Both hydroxylamino and nitroso groups are readily reduced to amines by chemical reduction in acid or by catalytic hydrogenation.

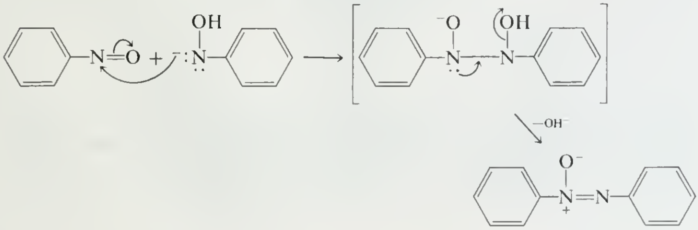
Reduction in basic media gives binuclear compounds.


NO_2
As_2O_3
aq. NaOH
Δ
O^-
N=N
+
(85%)
azoxybenzene
Zn
alc. NaOH
Δ
N=N
(84-86%)
azobenzene
H_2NNH_2
Ru/C
alc. KOH
NHNH
(80%)
hydrazobenzene

All of these compounds are reduced to aniline under acidic conditions. They may also be interconverted by the following reactions:

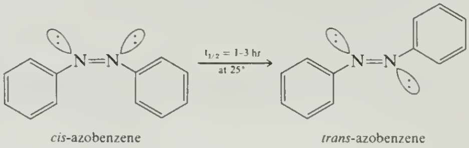

O^-
N=N
+
$(C_2H_5O)_3P$
H_2O_2
CH_3COOH
65°
N=N
Pd/C
H_2NNH_2
air or
NaOBr
NHNH

These binuclear compounds may best be considered to arise by condensation reactions during reduction.

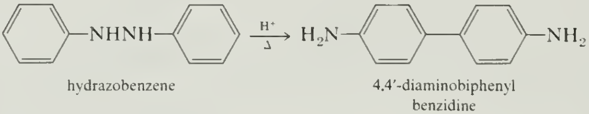

N=O
+
OH
N
^-O
OH
N
N
−OH⁻
O^-
N=N
+

In fact, azoxybenzene can be prepared by the base-catalyzed condensation of phenylhydroxylamine with nitrosobenzene. The azoxy function is the least important functional group among these compounds. Azobenzene is a bright orange-red solid; although this parent compound has only limited significance, the azo linkage is an important component of azo dyes (Section 36.4).

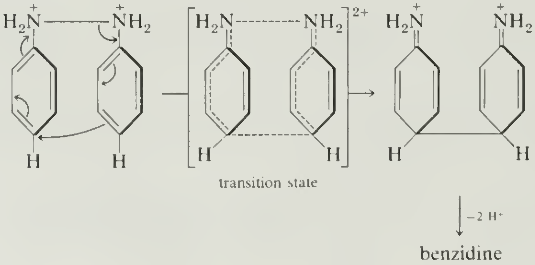
Many azo compounds show *cis-trans* isomerism. The *trans* isomer is generally the more stable, and the activation energy for the conversion is sufficiently low that the *cis* isomer is generally not seen. For example, azobenzene can be converted in part to the *cis* isomer by photolysis, but the activation energy required to convert back to *trans*-azobenzene is only 23–25 kcal mole^{-1} in various solvents. This reaction has a half-life on the order of hours at room temperature.


N=N
$t_{1/2}$ = 1-3 hr
at 25°
N=N
cis-azobenzene
trans-azobenzene

Hydrazobenzene or 1,2-diphenylhydrazine is a colorless solid that air oxidizes on standing to azobenzene. It is significant principally because of a rearrangement that it undergoes in strongly acidic solution, the **benzidine rearrangement.**


NHNH
H⁺
Δ
H₂N
NH₂
hydrazobenzene
4,4′-diaminobiphenyl
benzidine

This remarkable reaction involves the mono- or diprotonated salt in which bonding occurs between the para positions as the N—N bond is broken.


H₂N⁺
N⁺H₂
H
H
H₂N
NH₂
2+
H
H
transition state
H₂N⁺
N⁺H₂
H
H
−2 H⁺
benzidine

Benzidine has important uses as an intermediate in dye manufacture, but the compound has recently been demonstrated to be carcinogenic. Its place is being taken by dichlorobenzidine, but it now appears that this analog may also be a carcinogen.

Azoxybenzene, azobenzene, and hydrazobenzene are all conveniently reduced to aniline with sodium hydrosulfite.

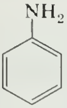
$$C_6H_5{-}N{=}N{-}C_6H_5 + 2Na_2S_2O_4 + 2H_2O \longrightarrow 2C_6H_5NH_2 + 4NaHSO_3$$

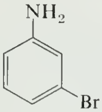
Sodium hydrosulfite, or sodium dithionite, is a useful reagent in neutral or alkaline solution. At acid pH's, it decomposes with the liberation of sulfur. It is especially useful in the reductive cleavage of the azo groups in azo dyes. These dyes are generally water soluble and it suffices simply to add sodium hydrosulfite to an aqueous solution until the color of the dye has been discharged. The products are the corresponding amines.

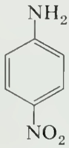
32.2
Aromatic Amines

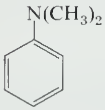
A. *Nomenclature*

Many simple aminobenzene compounds can be named as derivatives of aniline, the IUPAC sanctioned name of aminobenzene.

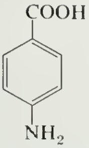

aniline

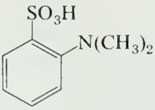

m-bromoaniline

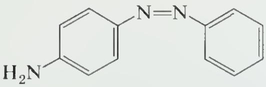

p-nitroaniline


N,N-dimethylaniline

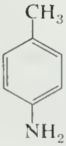
Others can generally be named by using the prefix, amino-, for example

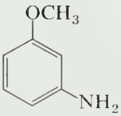

p-aminobenzoic acid

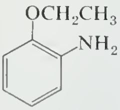

o-(dimethylamino)benzene-sulfonic acid

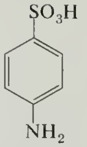

p-aminoazobenzene

A number of aromatic amines have trivial names that have received IUPAC sanction. Some of the more important examples are

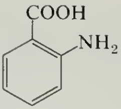

p-toluidine
p-aminotoluene


m-anisidine
m-methoxyaniline


o-phenetidine
o-ethoxyaniline

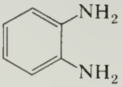


sulfanilic acid
p-aminobenzenesulfonic acid



anthranilic acid
o-aminobenzoic acid

The diaminobenzenes are known as phenylenediamines.



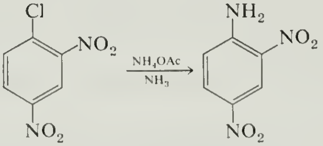
o-phenylenediamine
o-diaminobenzene

B. *Preparation*

The most important route to aromatic amines is the reduction of nitroarenes, as detailed in Section 32.1.C.

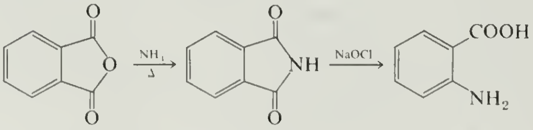
$$\mathrm{ArNO_2} \longrightarrow \mathrm{ArNH_2}$$

Another route is useful only for aromatic rings that are highly activated for nucleophilic aromatic substitution by ammonia.



(68–76%)
2,4-dinitroaniline

The use of the Hofmann rearrangement (Section 18.11) is exemplified by a convenient preparation of anthranilic acid.

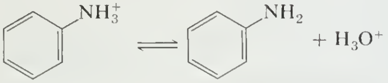


phthalic anhydride
phthalimide
(95%)
anthranilic acid

The lower amines are high boiling liquids. For example, aniline boils at 184°. Cyclohexylamine, which has comparable size, has a boiling point of 134.5°. The higher boiling point of aniline is probably associated with the higher polarizability of the benzene ring. Aniline is colorless when pure, but air oxidation produces highly colored products which, even in trace quantity, render aniline yellow or brown. This behavior is typical of amines. For example, *p*-toluidine forms colorless leaves, m.p. 43.5°, that turn brown on exposure to air. Aniline itself and most substituted anilines are poisonous and should be handled with care. Chronic exposure to aniline can give rise to bladder tumors. Many other aromatic amines are known or suspected carcinogens.

C. *Basicity of Aromatic Amines*

Aniline is a substituted ammonia with a lone pair of electrons and has basic properties as expected for such functions. However, the basicity of aniline in aqueous solution is much less than that of comparable primary aliphatic amines. Correspondingly, the acidity of anilinium ion is substantially greater than that of alkylammonium ions.



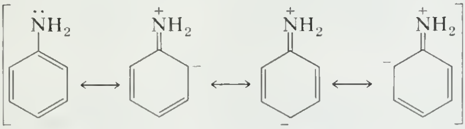
$$K_a = 2.5 \times 10^{-5}\ M \qquad pK_a = 4.60$$

$$(CH_3)_2CHNH_3^+ \rightleftharpoons (CH_3)_2CHNH_2 + H_3O^+$$

$$K_a = 2.5 \times 10^{-12}\ M \qquad pK_a = 11.60$$

Aliphatic amines have basicity comparable to dilute solutions of sodium hydroxide; the basicity of aniline is comparable to sodium acetate.

The reduced basicity of aniline compared to aliphatic amines may be attributed in part to the electron-attracting inductive effect of a phenyl group; recall that phenylacetic acid ($pK_a = 4.31$) is more acidic than acetic acid ($pK_a = 4.76$). However, this effect is small compared to the effect of delocalization of the nitrogen lone pair into the benzene ring.



This delocalization renders the lone pair less accessible for bonding. Alternatively, and equivalently, this delocalization effect can be expressed as a resonance stabilization of the amine that is not present in the ammonium ion. This energy effect is illustrated in Figure 32.1. The resonance energy of conjugation results in displacement of the protonation equilibrium towards the amine.

Ammonia itself and amines generally have a pyramidal structure (Section 27.1): the H—N—H bond angle in ammonia is 107.1°. The most effective conjugation of the nitrogen lone pair with the benzene ring would be obtained for a lone pair in a p orbital parallel to the p orbitals of the aromatic π system. However, lone pairs are generally more stable in orbitals having some s character. In the case of aniline, an energy compromise is reached in which the lone pair orbital has more p character than in ammonia but in which the orbital retains some s character. As a result, the NH_2 group in aniline is still pyramidal, but with a larger H—N—H bond angle (113.9°) than in ammonia. The H—N—H plane intersects the plane of the benzene ring at an angle of 39.4°. The orbital structure of aniline is represented in Figure 32.2.

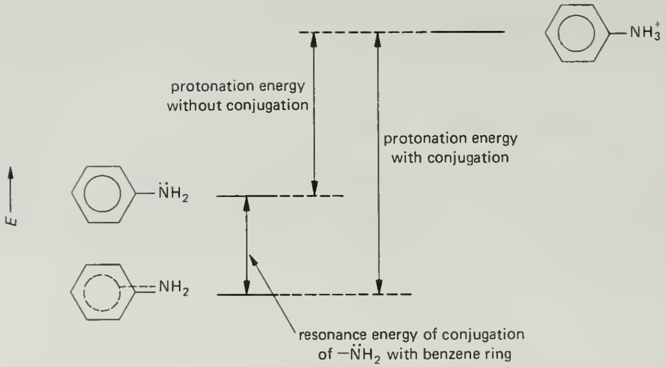

protonation energy without conjugation
protonation energy with conjugation
E
NH_3^+
$\dot{N}H_2$
NH_2
resonance energy of conjugation of $-\dot{N}H_2$ with benzene ring

FIGURE 32.1 *Conjugation with the phenyl ring decreases the basicity of the amino group in aniline.*

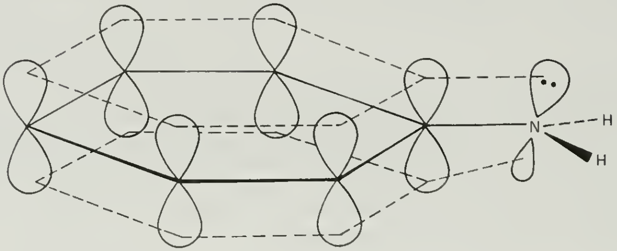


FIGURE 32.2 *The partially pyramidal amino group in aniline can still conjugate with the phenyl π system.*

Substituents on the aniline ring affect basicity in ways that are generally interpretable with the principles of substituent effects discussed previously. Table 32.1 summarizes the pK_a values of a number of substituted anilinium ions.

Ortho substituents sometimes give unexpected results because of steric effects; for example, *o*-methylaniline is less basic than aniline, whereas in the *meta* and *para* positions a methyl substituent exerts its typical electron-donating effect to give enhanced basicity. Bromo, chloro, iodo, and CF_3 groups show normal electron-attracting inductive effects that decrease the basicity of aniline. The nitro group has an especially potent effect in the *para* position that is attributed to direct conjugation with the amino group.

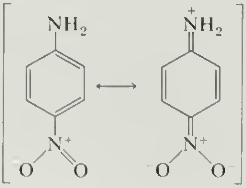


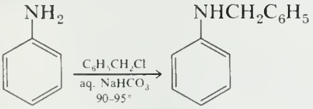
TABLE 32.1
pK_as of Anilinium Ions

Substituent	pK_a, 25°		
	ortho	*meta*	*para*
H	4.60	4.60	4.60
benzoyl			2.17
bromo	2.53	3.58	3.86
chloro	2.65	3.52	3.98
cyano	0.95	2.75	1.74
fluoro	3.20	3.57	4.65
iodo	2.60	3.60	3.78
methoxy	4.52	4.23	5.34
methyl	4.44	4.72	5.10
nitro	−0.26	2.47	1.00
trifluoromethyl		3.20	2.75

Aniline is essentially completely protonated in 0.1 *M* HCl solution (pH = 1). Hence, although aniline is only slightly soluble in water, it dissolves completely in dilute hydrohalic and sulfuric acids. The nitroanilines are less basic but also dissolve in strong acids. 2,4-Dinitroanilinium ion has $pK_a = -4.4$; this amine is soluble only in rather concentrated acids.

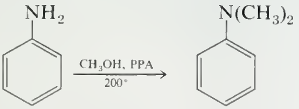
D. *Alkylation and Acylation*

Aromatic primary amines react with alkyl halides and sulfonates to form the expected secondary or tertiary amines or quaternary salts. These alkylation reactions are exactly analogous to those of aliphatic amines (Section 27.5).



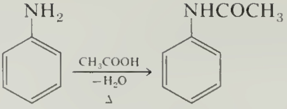
(85–87%)
N-benzylaniline

For the preparation of methylated amines, dimethyl sulfate or a mixture of methanol and polyphosphoric acid (Section 18.13.B) is convenient.

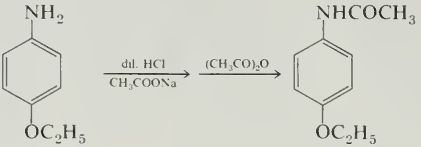


(66%)
N,N-dimethylaniline

Similarly, aromatic amines can be converted to amides by reaction with acid chlorides or anhydrides. We shall find that this is frequently a useful procedure because the amide group moderates the high reactivity of the amine in many reactions. For this *moderating* purpose the acetyl group is most often used and is usually introduced with acetic anhydride. The acetyl amide can also be prepared by direct heating of the amine with acetic acid, but this process is generally slower.



acetanilide



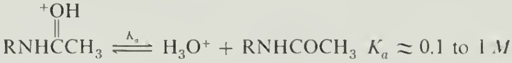
p-phenetidine
p-ethoxyaniline

phenacetin
p-ethoxyacetanilide

Phenacetin has been used as an analgesic and in mixture with aspirin and caffeine as formerly popular over-the-counter analgesic pills (the "P" in APC). It has since been removed from such compositions because of suspected side effects.

The mixture of HCl and sodium acetate creates a buffered medium that keeps the amine in solution as the ammonium salt in equilibrium with a small amount of free amine. The free amine reacts rapidly with acetic anhydride to form the amide in high yield and in a pure state. Acetic anhydride hydrolyzes slowly under these conditions. The amide can be hydrolyzed back to the amine by heating with alcoholic HCl.

Acetanilide is a colorless crystalline solid, m.p. 114°, that behaves as a neutral compound under normal conditions. The basic character of aniline is reduced by the acetyl group. The conjugate acids of aliphatic amides have pK_as of about 0 to +1; that is, they are extensively protonated in 10% sulfuric acid.



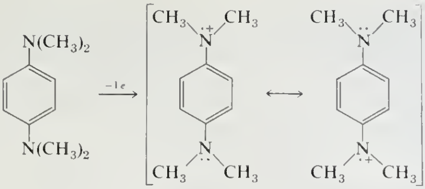
$$\mathrm{RNH}\overset{\overset{+}{\mathrm{O}}\mathrm{H}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_3} \overset{K_a}{\rightleftharpoons} \mathrm{H_3O^+} + \mathrm{RNHCOCH_3} \quad K_a \simeq 0.1 \text{ to } 1\ M$$

Acetanilide is a somewhat weaker base, just as aniline is a weaker base than aliphatic amines; the pK_a of the conjugate acid of acetanilide is about −1 to −2. It is protonated by strong sulfuric acid solutions. Acetanilide is also a weak acid with a pK_a that is estimated to be about 15. It is not appreciably soluble in dilute aqueous alkali hydroxides and requires more basic conditions to form the conjugate anion.

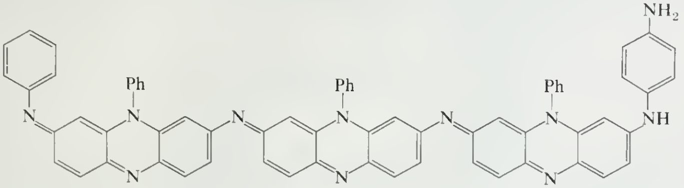
E. *Oxidation*

Aromatic amines are readily oxidized by a variety of oxidizing agents, as well as by air. As a result, the oxidation of other functional groups cannot usually be carried out as satisfactorily if amino groups are also present.

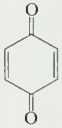
The nature of amine oxidations is demonstrated by oxidation of *p*-bis-(dimethylamino)benzene, which gives a relatively stable radical cation called Wurster's Blue.


Wurster's Blue

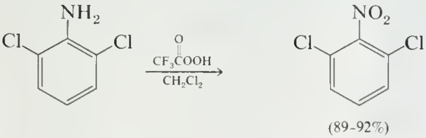
Radical cations were encountered previously as gas phase species in mass spectroscopy (Chapter 16). Wurster's Blue is an example of a radical cation that is stable in solution. Other examples are now known to be important intermediates in various oxidation reactions. For example, the radical cation formed from aniline reacts further with aniline to produce highly colored polymeric compounds. On treatment with acidic potassium dichromate, aniline gives a black insoluble dye, Aniline Black, that is difficult to characterize. A proposed structure for the compound is



Further oxidation gives some *p*-benzoquinone, a compound that we will consider in detail in the next chapter.


p-benzoquinone

The facile oxidation of amines often gives rise to undesired by-products in the course of other preparations, but there are some oxidation reactions of the amino group itself that have some preparative significance. One example is the direct oxidation to a nitro group by the action of trifluoroperoxyacetic acid.


2,6-dichloroaniline

(89-92%)
2,6-dichloronitrobenzene

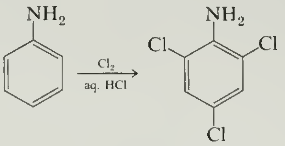
Trifluoroperoxyacetic acid is prepared as needed by stirring trifluoroacetic anhydride in CH_2Cl_2 with 90% hydrogen peroxide. The amine to be oxidized is added to the

> resulting solution and heated to reflux. Trifluoroperoxyacetic acid is another of the reagents that find limited but important use in organic chemistry. It is the best reagent, for example, for the direct oxidation of an arylamine to the nitroarene.

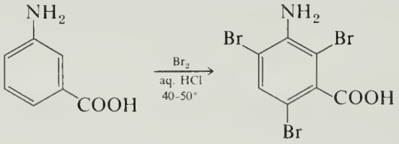
This oxidation reaction works best with arylamines that have electron-attracting groups such as halogen, nitro, cyano, and so on.

F. *Electrophilic Aromatic Substitution*

Aromatic amines are highly activated towards substitution in the ring by electrophilic reagents. Reaction with such amines generally occurs under rather mild conditions. For example, halogenation is so facile that all unsubstituted *ortho* and *para* positions become substituted.

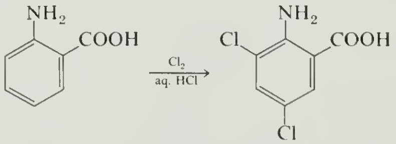


2,4,6-trichloroaniline



m-aminobenzoic acid

3-amino-2,4,6-tribromo-benzoic acid

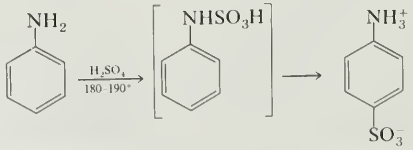


(69-78%)

anthranilic acid

2-amino-3,5-dichloro-benzoic acid

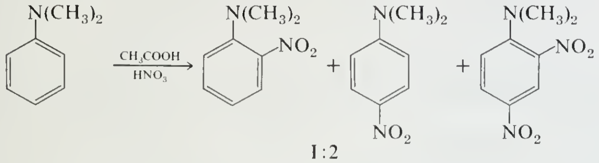
Sulfonation with sulfuric acid involves reaction first at the basic amino group; the initial product must be heated to give the ring-substituted product.



sulfanilic acid

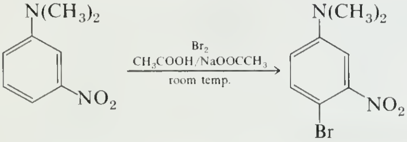
Note that sulfanilic acid contains an acidic and basic group in the same molecule and exists in the zwitterion, or inner-salt, form.

Nitration of aromatic primary amines is not generally a useful reaction because nitric acid is an oxidizing agent and amines are sensitive to oxidation. A mixture of aniline and nitric acid can burst into flame. Nitration of tertiary aromatic amines can be accomplished conveniently and in good yield; a satisfactory method is nitration in acetic acid.


N(CH3)2
CH3COOH
HNO3
N(CH3)2
NO2
+
N(CH3)2
NO2
+
N(CH3)2
NO2
NO2
1:2

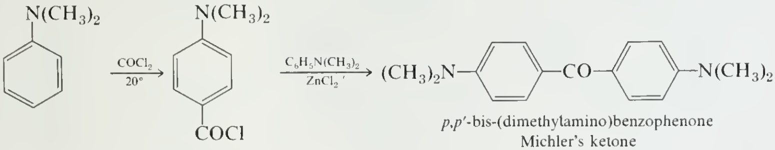
The *ortho*:*para* ratio is 1:2 and the amount of 2,4-dinitro-N,N-dimethylaniline depends on the reaction conditions.

In general, electrophilic aromatic substitution reactions can be applied to tertiary aromatic amines. Furthermore, the dialkylamino group is such a strongly activating substituent that rather mild reaction conditions may be used.


N(CH3)2
NO2
Br2
CH3COOH/NaOOCCH3
room temp.
N(CH3)2
NO2
Br

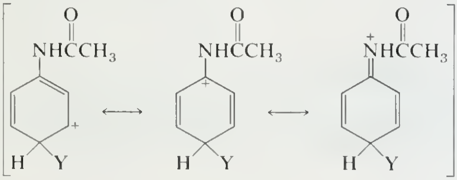
In this example, no additional Lewis acid catalyst is required, even with a deactivating nitro group in the ring.

Friedel-Crafts acylations can also be accomplished under mild conditions, for example

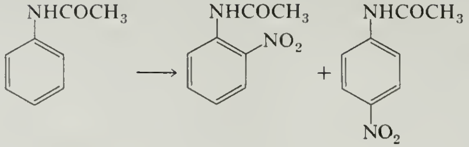

N(CH3)2
COCl2
20°
N(CH3)2
COCl
C6H5N(CH3)2
ZnCl2
(CH3)2N
CO
N(CH3)2

p,p'-bis-(dimethylamino)benzophenone
Michler's ketone
(a dye intermediate)

The sensitivity of the aromatic ring to oxidizing agents and to electrophilic reagents is reduced when the amine is converted to an amide. The nitrogen lone pair that is so available to help stabilize the electrophilic substitution transition state is partially tied up by the carbonyl group of the amide. Amide groups are still active *ortho,para* directors, but the reaction is now readily controlled. In the transition state for *ortho* or *para* reaction with an electrophilic reagent, the amide nitrogen has additional ammonium ion character adjacent to the positive carbon of the carbonyl group; some illustrative resonance structures are

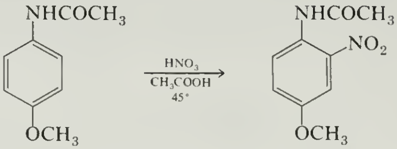

O
NHCCH3
+
H Y
O
NHCCH3
+
H Y
O
+
NHCCH3
H Y

Some examples of the use of aromatic amides in electrophilic substitutions are


NHCOCH3
NHCOCH3
NO2
NHCOCH3
NO2
+

90% aq. HNO_3, −20°	(23%)	(77%)
HNO_3, Ac_2O, 20°	(68%)	(30%)

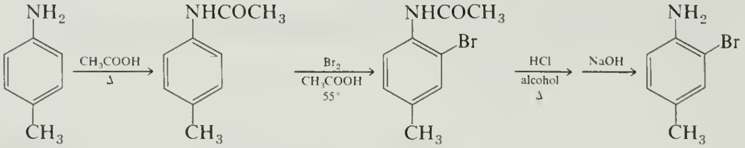
Note that by proper choice of reaction conditions, either the *ortho* or *para* nitration product of acetanilide can be made to dominate.


NHCOCH3
OCH3
HNO3
CH3COOH
45°
NHCOCH3
NO2
OCH3

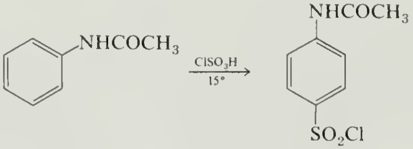
(75–79%)

p-methoxyacetanilide

2-nitro-4-methoxyacetanilide


NH2
CH3
CH3COOH
Δ
NHCOCH3
CH3
Br2
CH3COOH
55°
NHCOCH3
Br
CH3
HCl
alcohol
Δ
NaOH
NH2
Br
CH3

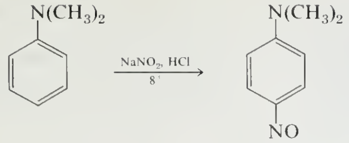
(60–67%)
2-bromo-4-methylaniline


NHCOCH3
ClSO3H
15°
NHCOCH3
SO2Cl

(77–81%)
p-acetylamino-benzenesulfonyl chloride

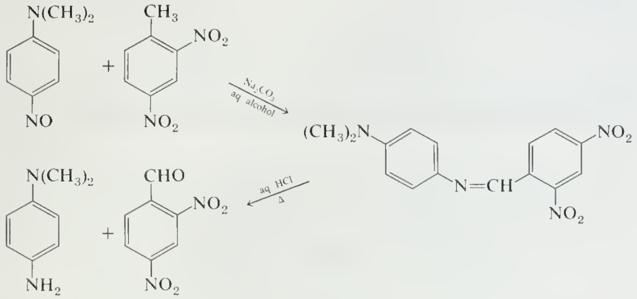
G. *Reaction with Nitrous Acid*

Tertiary aromatic amines react with nitrous acid as an electrophilic substitution reagent to give ring substitution.


N(CH3)2
NaNO2, HCl
8°
N(CH3)2
NO

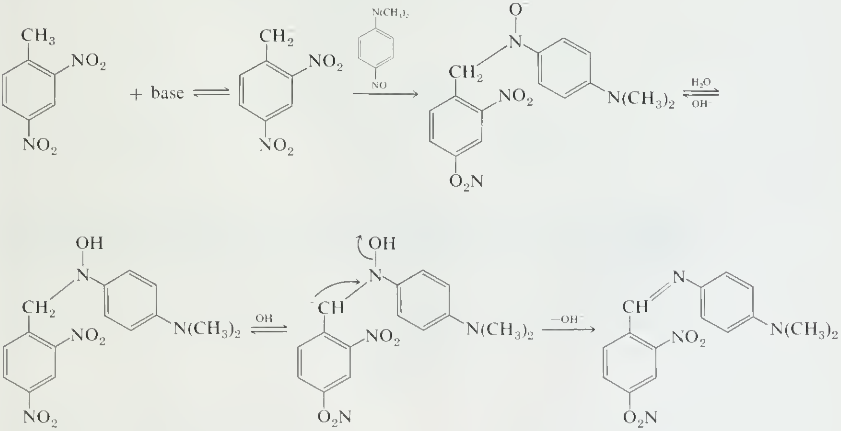
(80–89%)
p-nitrosodimethylaniline

p-Nitrosodimethylaniline has some uses as an organic intermediate, based on condensation reactions with suitable carbanions.

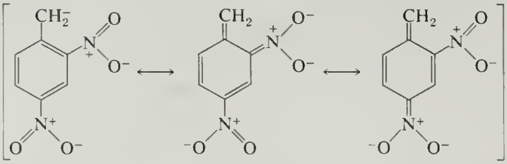

N(CH3)2
NO
CH3
NO2
NO2
Na2CO3
aq alcohol
(CH3)2N
N=CH
NO2
NO2
aq HCl
Δ
N(CH3)2
NH2
CHO
NO2
NO2

(29–38%)
2,4-dinitrobenzaldehyde

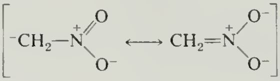
The first step of this sequence involves condensation of the nitroso group with the conjugate base of 2,4-dinitrotoluene.


CH3
NO2
NO2
+ base
CH2−
NO2
NO2
N(CH3)2
NO
O−
N
CH2
NO2
O2N
N(CH3)2
H2O
OH−
OH
N
CH2
NO2
NO2
N(CH3)2
OH
OH
N
−CH
NO2
O2N
N(CH3)2
−OH−
N
CH
NO2
O2N
N(CH3)2

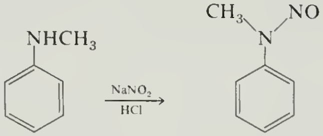
The condensation product is an imine that hydrolyzes to give a carbonyl compound and an amine. The overall result is a mild oxidation of a suitably activated methyl group to an aldehyde. 2,4-Dinitrotoluene can be used in this reaction because of the relatively high acidity of the methyl group. The negative charge of the anion can be shared with both nitro groups as shown by the following resonance structures:



That is, this anion can be considered to be *vinylogous* to that of nitromethane (Section 27.8.C).

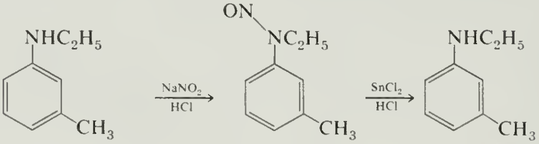


Secondary amines react with nitrous acid to give N-nitroso compounds (Section 27.7.B).



N-nitroso-N-methylaniline

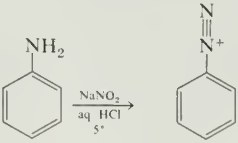
The nitrosoamine group can be cleaved by reductive methods; the overall procedure then serves as a method for purifying secondary amines.



N-ethyl-*m*-toluidine
N-ethyl-*m*-methylaniline

(63–66%)

The most important of these reactions is without doubt the reaction of primary aromatic amines with nitrous acid to give the corresponding arenediazonium ion.



benzenediazonium cation

The process of converting an amine to the diazonium salt is called **diazotization.** Although this example is shown with sodium nitrite and hydrochloric acid to generate nitrous acid, other strong mineral acids such as sulfuric, perchloric, and fluoboric (HBF_4) acids may be used.

Nitrous acid, O=NOH, is known only as a gas phase species or under special conditions at very low temperatures or in dilute aqueous solution. These solutions are generally prepared from the reaction of alkali nitrites (nitrite ion, NO_2^-) and strong acids. Nitrous acid is a weak acid with $pK_a = 3.23$. In solution, it is in equilibrium with several other species, such as dinitrogen trioxide, the anhydride of nitrous acid.

$$2\ HONO \rightleftharpoons H_2O + N_2O_3$$

With halide ions, the equilibria contain the nitrosyl halides which are the mixed anhydrides of nitrous acid and hydrohalic acids.

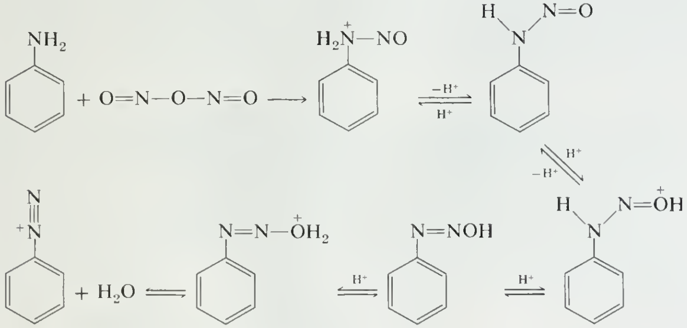
$$HONO + HX \rightleftharpoons ONX + H_2O$$

Nitrous acid is an intermediate oxidation state of nitrogen and disproportionates to nitric oxide and nitric acid.

$$3\ HONO \longrightarrow 2\ NO + H_3O^+ + NO_3^-$$

The rate of this reaction is temperature dependent and is also strongly dependent on the concentration of nitrous acid—the rate is proportional to $[HONO]^4$. Consequently, nitrous acid solutions are usually kept cold and dilute and are used immediately.

The actual nitrosating agent has been shown to be N_2O_3, although, in solutions containing halide ion, the corresponding nitrosyl halide may also play a role. The reaction starts by combination of the basic amine with the nitrosating agent, followed by a series of rapid proton transfers.



Arenediazonium salts are unstable; the dry salts are generally rather sensitive and can explode at a touch. Among the most stable of the diazonium salts are the tetrafluoroborates, $ArN_2^+\ BF_4^-$. Diazonium salts undergo a variety of important reactions, but they are rarely isolated. Instead, the solutions in which they are prepared are used directly. These reactions of diazonium salts are so varied and so important that they will be discussed separately in the next section.

32.3
Arenediazonium Salts

A. *Acid-base Equilibria*

In acid solution, arenediazonium salts have the diazonium ion structure, with a linear C—N—N bond system. The diazonium ion has a π system that can conjugate with the aromatic π system (Figure 32.3). This conjugation is responsible in part for the relative stability that these compounds have. Recall that aliphatic diazonium ions are not at all stable and generally react immediately upon formation (Section 27.7.B).

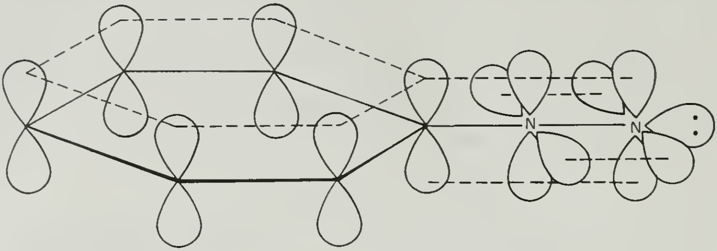


FIGURE 32.3 *Orbital structure of benzenediazonium cation.*

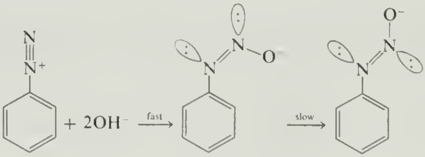
Arenediazonium ions behave as dibasic acids. The two steps in the equilibria are represented as

$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N} + 2\,\mathrm{H_2O} \overset{K_1}{\rightleftharpoons} \underset{\text{arenediazohydroxide}}{\mathrm{Ar{-}N{=}NOH}} + \mathrm{H_3O^+}$$

$$\mathrm{Ar{-}N{=}NOH} + \mathrm{H_2O} \overset{K_2}{\rightleftharpoons} \underset{\text{arenediazotate ion}}{\mathrm{Ar{-}N{=}N{-}O^-}} + \mathrm{H_3O^+}$$

The diazonium ions represent an unusual class of dibasic acids in that $K_2 \gg K_1$; that is, the arenediazohydroxide is present only in small amount. For the phenyl group, equal concentrations of benzenediazonium ion and benzenediazotate are present at a pH of 11.9. Even in neutral solutions with pH = 7, the diazonium ions are generally the most predominant species present.

Benzenediazotate ion exists in *syn* and *anti* forms, in common with other compounds containing C=N and N=N bonds. The *anti* form is the more stable, but the less stable *syn* isomer is that formed first by reaction of the diazonium cation with hydroxide ion.



syn-benzenediazotate ion

anti-benzenediazotate ion

Alkanediazonium ions react by S_N2 displacement, S_N1 formation of carbonium ions, E1 and E2 eliminations, and by carbonium ion rearrangements (Section 27.7.B). None of these pathways is readily available to arenediazonium ions. The most likely reaction, formation of an aryl cation, is limited by the high energy of these species. In phenyl cation, the empty orbital has approximately sp^2 hybridization and cannot conjugate with the π electronic system (Figure 32.4).

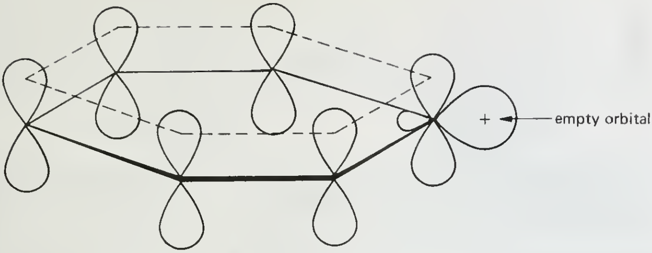


FIGURE 32.4 *Orbital diagram of phenyl cation.*

For example, the enthalpy of formation in the gas phase of phenyl cation from chlorobenzene is about the same as that for the ionization of vinyl chloride and is almost as high as the enthalpy of formation of methyl cation from methyl chloride.

$$\begin{aligned} C_6H_5Cl &\longrightarrow C_6H_5^+ + Cl^- &\quad \Delta H^\circ &= 223 \text{ kcal mole}^{-1} \\ CH_2{=}CHCl &\longrightarrow C_2H_3^+ + Cl^- &\quad \Delta H^\circ &= 223 \text{ kcal mole}^{-1} \\ CH_3Cl &\longrightarrow CH_3^+ + Cl^- &\quad \Delta H^\circ &= 227 \text{ kcal mole}^{-1} \end{aligned}$$

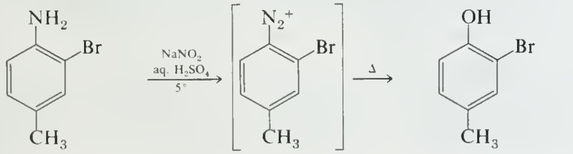
Nevertheless, many reactions of diazonium ions are the reactions expected if aryl cations were intermediates. In many preparative methods, however, the aryl cation is not free, but is combined as a complex with a metal, often copper. Other reactions involve free radical intermediates. All of the following types of compounds can be prepared by appropriate reactions of the arenediazonium ions, ArN_2^+:

ArOH
ArI
ArSH
ArCl
ArBr
ArCN
ArF
$ArNO_2$
ArH
Ar-Ar
Ar-Ar′
$ArNHNH_2$
ArN_3
ArN=NAr′

B. *Formation of ArOH, ArI, and ArSH: Hydrolysis of Diazonium Ions*

Aqueous solutions of arenediazonium ions are not stable. Nitrogen gas is evolved slowly in the cold and rapidly on heating. The net reaction is that of hydrolysis.

$$ArN_2^+ \xrightarrow{H_2O} ArOH + N_2$$

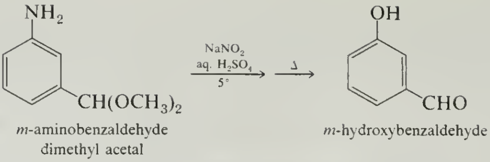


(32-1)

(80–92%)

2-bromo-4-methylaniline

2-bromo-4-methylphenol



(32-2)

In (32-2), the hot dilute acid also hydrolyzes the acetal function that protects the aldehyde group from the action of nitrous acid.

Aqueous sulfuric acid is used for the diazotization because the hydrolysis of the diazonium ion appears to be an S_N1 type of process involving the aryl cation.

$$ArN_2^+ \longrightarrow N_2 + Ar^+$$

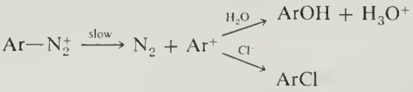
The aryl cation forms, despite its high energy, because of the great stability of nitrogen; that is, the formation of N_2 is a powerful driving force for the decomposition of diazonium ions. The aryl cation intermediate is highly reactive and reacts rapidly with water to form the corresponding phenol.

$$Ar^+ + H_2O \longrightarrow Ar{-}OH_2^+ \rightleftharpoons ArOH + H^+$$

However, the aryl cation does react with other nucleophilic reagents which may be present—such as halide ion. If HCl is used in the diazotization, some chloroarene is also produced.

$$Ar^+ + Cl^- \longrightarrow ArCl$$

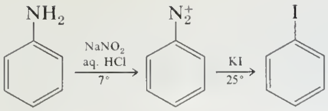
When aqueous solutions of diazonium ions containing chloride ion are allowed to decompose, the rate of reaction is independent of the chloride ion concentration, but the amount of chloroarene formed is proportional to $[Cl^-]$. Thus, the rate-determining step does not depend on chloride ion, but the product-determining steps do. This result is interpretable by the scheme



$$Ar{-}N_2^+ \xrightarrow{\text{slow}} N_2 + Ar^+ \begin{array}{l} \xrightarrow{H_2O} ArOH + H_3O^+ \\ \xrightarrow{Cl^-} ArCl \end{array}$$

The competition of chloride ion with water for the intermediate aryl cation is usually inadequate for this method to be a successful preparation of chloroarenes; the Sandmeyer reaction (Section 32.3.C) is generally better. However, this competition does represent a yield loss of the phenol; hence, the reaction is usually carried out with sulfuric acid. Sulfate and bisulfate ion are less nucleophilic and compete poorly with water for the aryl cation. The resulting reaction is a satisfactory route for the overall conversion, $ArNH_2 \longrightarrow ArOH$, and constitutes one general preparation of phenols (Section 33.2.A). The principal side reaction is the reaction of the product phenol with the diazonium ion to form an azo dye (Section 33.3.B); however, these highly colored and higher molecular weight by-products can usually be readily separated from the more volatile phenol.

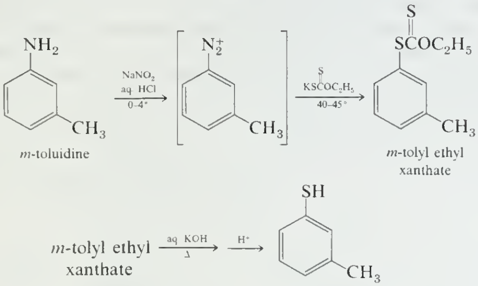
Highly nucleophilic anions can compete successfully with water for the intermediate aryl cation, and lead to satisfactory syntheses. A useful example is iodide ion:



(74–76%)

In this case HCl is used for the diazotization and the resulting solution contains Cl$^-$; nevertheless, the more nucleophilic I$^-$ dominates the reaction. The diazotization could have been accomplished with hydriodic acid, but this acid is far more expensive than HCl.

Reaction of aqueous diazonium salts with HS$^-$ or with metal polysulfides has been used for preparation of thiophenols, but violent reactions and explosions have been reported and the method is not recommended. An alternative route involves potassium ethyl xanthate, $KSCSOC_2H_5$, which is available commercially from the reaction of potassium ethoxide with carbon disulfide.



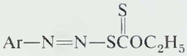
m-toluidine

m-tolyl ethyl xanthate

m-tolyl ethyl xanthate

(63–75%)
m-methylthiophenol
m-thiocresol

This reaction involves a variation of the hydrolysis reaction above. Reaction of the diazonium ion with the ethyl xanthate ion gives first the diazoxanthate,

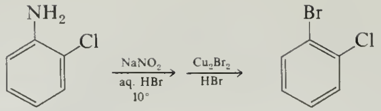


$$Ar{-}N{=}N{-}S\overset{\overset{\displaystyle S}{\|}}{C}OC_2H_5$$

which then decomposes with liberation of nitrogen by an ion pair or radical mechanism. Even this method is hazardous because the intermediate diazoxanthate can detonate and should be allowed to decompose as formed. The use of traces of nickel—even a nichrome stirrer—has been recommended to facilitate the controlled decomposition.

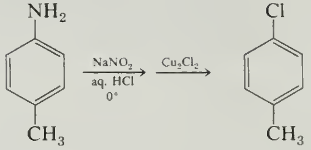
C. *Preparation of Chlorides, Bromides, and Nitriles: the Sandmeyer Reaction*

The decomposition of diazonium salts is catalyzed by cuprous salts. In laboratory practice, the cold diazonium solution is added dropwise to a hot suspension of cuprous bromide, chloride, or cyanide to give the corresponding aromatic product in a method known as the **Sandmeyer reaction.** Some examples of Sandmeyer reactions are



(89–95%)

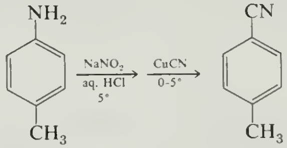
o-chloroaniline *o*-bromochlorobenzene



(70–79%)

p-toluidine *p*-chlorotoluene

Note in these cases that the hydrohalic acid is used to correspond to the halogen introduced; the use of HCl with Cu_2Br_2 would give a mixture of chloro and bromo product. Incidentally, this route to *o*- or *p*-chlorotoluene (or the bromotoluenes) gives the individual pure isomers. The sequence starts with the nitration of toluene and the separation of *o*- and *p*-nitrotoluenes by distillation. Recall (Section 29.8) that halogenation of toluene gives a mixture of isomers that is difficult to separate.



(64–70%)

p-tolunitrile

Note that the decomposition with CuCN occurs even in the cold.

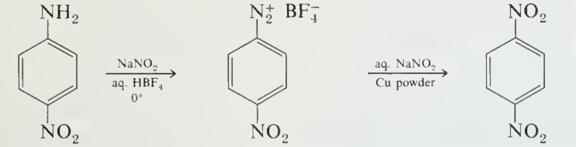
> Cupric chloride is normally obtained as a blue-green hydrate, $CuCl_2 \cdot 2H_2O$. This color is characteristic of many cupric salts. Cupric chloride and bromide are readily soluble in water. Cuprous bromide and chloride are white insoluble powders prepared by reducing an aqueous solution of cupric sulfate and sodium bromide or chloride with sodium bisulfite. The cuprous halide precipitates as a white powder which is filtered and used directly. On standing in air, the white cuprous salts darken by oxidation. Cuprous cyanide is prepared by treating an aqueous suspension of cuprous chloride with sodium cyanide. Cuprous cyanide is also insoluble in water, but dissolves in excess sodium cyanide with formation of a complex, $Cu(CN)_2^-$. This solution is used directly in the Sandmeyer reaction.

The aromatic nitriles prepared by the Sandmeyer reaction can, of course, be hydrolyzed to carboxylic acids, reduced to benzylamines, or treated with Grignard reagents to produce ketones, and so on. Consequently, the diazonium salts provide an entry to a host of aromatic compounds.

D. *Preparation of Fluoro- and Nitroarenes*

Some diazonium salts are fairly stable and can be isolated and handled. One such salt is the fluoborate. This salt is prepared by diazotization with sodium nitrate and fluoboric acid. The diazonium fluoborate usually precipitates and is filtered. The isolated salt is useful in two significant reactions.

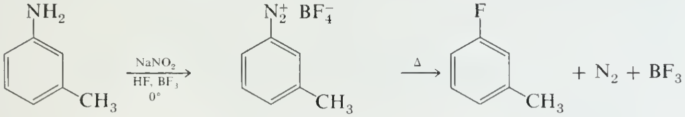
In one reaction, a suspension of the diazonium fluoborate in aqueous sodium nitrite is treated with copper powder. Nitrogen is evolved and the corresponding nitro compound is produced.



p-nitroaniline
p-nitrobenzenediazonium fluoborate
p-dinitrobenzene

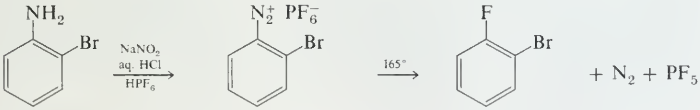
The use of copper powder is common in many diazonium reactions. It can be used in plece of cuprous salts to prepare the bromide and chloride, and then becomes the **Gatterman reaction**, but this variant is not so successful as the Sandmeyer reaction. This method of effecting the conversion $ArNH_2 \longrightarrow ArNO_2$ is an alternative to oxidation with trifluoroperoxyacetic acid (Section 32.2.E). Both reactions are successful with amines containing electron-attracting groups, but only the diazonium reaction can be applied to amines with electron-donating groups.

The isolated diazonium fluoborate can be decomposed thermally either as the dry salt or in an inert solvent such as THF to provide a satisfactory preparation of aryl fluorides (**Schiemann reaction**).



(76–84%)
m-toluidine
m-methylbenzenediazonium fluoborate
m-fluorotoluene

An improved procedure makes use of hexafluorophosphoric acid, HPF_6. The corresponding diazonium salts are less soluble than the fluoborates and are obtained in generally higher yield. The dry salt is thermally decomposed to form the aryl fluoride.

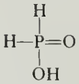


(76–78%)
o-bromoaniline
o-bromobenzenediazonium hexafluorophosphate
o-bromofluorobenzene

E. *Replacement by Hydrogen*

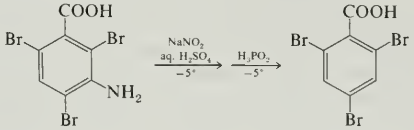
One of the most useful reactions of diazonium salts is the replacement of the diazonium group by hydrogen. This reaction allows use of the amino group to direct the orientation of an electrophilic aromatic substitution reaction, followed by removal of the amino group. The most generally useful reagent for the reaction is hypophosphorous acid, H_3PO_2.

Hypophosphorous acid is a low melting (m.p. 26.5°) crystalline solid having a structure with two P—H bonds,



$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle OH}{P}}{=}O}$$

Salts are prepared by treating white phosphorus with alkali or alkaline earth hydroxides. The free acid can be liberated from the water soluble calcium salt with sulfuric acid. Aqueous solutions are available commercially and can be used directly. The monobasic acid has $pK_a = 1.2$ and is a powerful reducing agent.

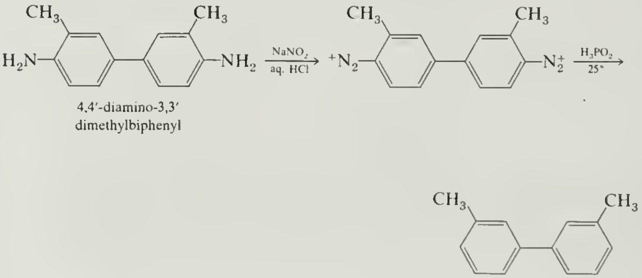


3-amino-2,4,6-tribromo-benzoic acid

2,4,6-tribromo-benzoic acid

(32-3)

In (32-3) the amino group was used to direct the facile introduction of three bromines (Section 32.2.F). The yield of the tribromobenzoic acid is 70–80% from *m*-aminobenzoic acid.



4,4′-diamino-3,3′ dimethylbiphenyl

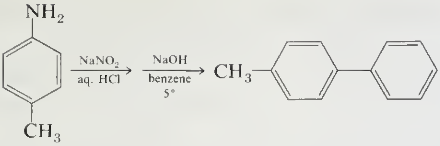
3,3′-dimethyl-biphenyl

(32-4)

Equation (32-4) shows that a diamine can be "tetrazotized" and reaction can be accomplished at both diazonium groups.

F. *Arylation Reactions*

This useful reaction provides a convenient preparation of unsymmetrical biaryls in which the diazonium group is replaced by an aromatic ring. Diazotization is carried out in the usual way, except that a minimum of water is used. The solution is made basic and the resulting concentrated aqueous solution is stirred in the cold with a liquid aromatic compound.



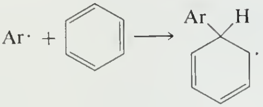
(21%)
4-methylbiphenyl

The yields are generally fairly poor, but the starting materials are usually available and there are few other routes to such biaryls (Section 34.2.A).

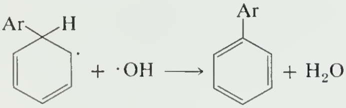
The reaction mechanism involves free radicals. The diazohydroxide is extracted into the organic phase, where homolytic fission occurs to give the radical intermediates. An important driving force for the reaction is the formation of highly stable nitrogen.

$$\mathrm{Ar{-}N{=}N{-}OH} \longrightarrow \mathrm{Ar}\cdot + \mathrm{N_2} + \cdot\mathrm{OH}$$

The aryl radical reacts with the benzene ring in the solvent.

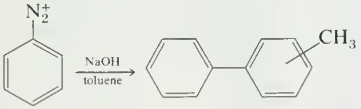


Reaction with another radical gives the final product, the net result being that of homolytic or radical aromatic substitution.



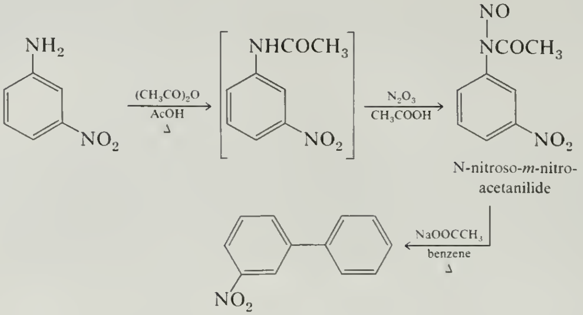
Note that this process is not a radical chain reaction. If chain reactions are involved, the chains are rather short. The concentration of radicals in this reaction is generally higher than that in most radical chain reactions. The yields in this **Gomberg-Bachmann** reaction are relatively low because so many alternative reactions are available to the radicals involved.

Because the aromatic substitution involves radicals, the normal orientation rules do not hold; almost all substituents tend to give *ortho* and *para* orientation, and mixtures of products are common. In using this method to prepare an unsymmetrical biaryl, it is best to start with the substituents on the diazonium ring and to keep the ring to be added as simple as possible.



66% *o*-, 19% *m*-, 14% *p*-

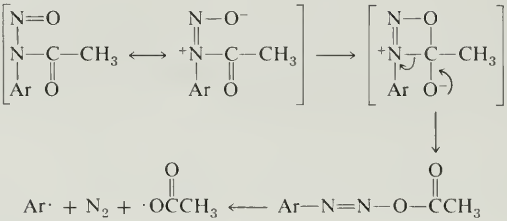
The same reaction can usually be carried out in better yield by using an N-nitrosoamide. This intermediate is prepared in straightforward fashion from the amine and is heated in an aromatic solvent. The N-nitrosoamide rearranges to a diazo ester, which forms the same aryl radical intermediate involved in the Gomberg-Bachmann reaction.


NH$_2$
NO$_2$
(CH$_3$CO)$_2$O
AcOH
Δ
NHCOCH$_3$
NO$_2$
N$_2$O$_3$
CH$_3$COOH
NO
NCOCH$_3$
NO$_2$
NaOOCCH$_3$
benzene
Δ
NO$_2$

N-nitroso-*m*-nitroacetanilide

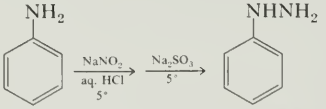
(56–60%)
3-nitrobiphenyl

The rearrangement of the intermediate nitrosoamide can be regarded as an intramolecular transesterification.


N=O
N—C—CH$_3$
Ar O
N—O$^-$
$^+$N—C—CH$_3$
Ar O
N—O
$^+$N—C—CH$_3$
Ar O$^-$
Ar· + N$_2$ + ·OCCH$_3$
O
Ar—N=N—O—CCH$_3$
O

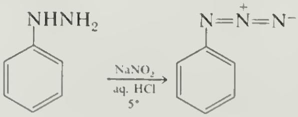
G. *Miscellaneous Reactions*

The diazonium group can be reduced with sodium sulfite to give arylhydrazines in good yield.


NH$_2$
NaNO$_2$
aq. HCl
5°
Na$_2$SO$_3$
5°
NHNH$_2$

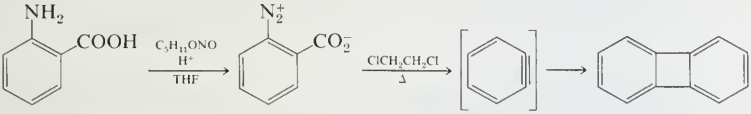
(80–84%)
phenylhydrazine

The phenylhydrazine in turn may be converted to phenyl azide by reaction with nitrous acid.


NHNH$_2$
NaNO$_2$
aq. HCl
5°
N=$\overset{+}{N}$=N$^-$

(65–68%)
phenyl azide

The diazonium salt derived from anthranilic acid provides a source of benzyne on thermal decomposition. This diazonium compound is an inner salt and is insoluble. The dry salt will detonate and must be kept moist and handled with care. The controlled decomposition in ethylene chloride provides the unusual strained hydrocarbon, biphenylene.



anthranilic acid

benzyne

(21-30%)
biphenylene

In this preparation, no nucleophilic reagents are present to react with benzyne (compare Section 30.3.A under the Elimination-Addition Mechanism), hence, the dimerization reaction occurs to a significant extent.

H. *Diazonium Ions as Electrophilic Reagents: Azo Compounds*

The diazonium cation bears a resemblance to some other species that are known as intermediates in electrophilic aromatic substitution reactions. Compare

$$\text{Ar}-\overset{+}{\text{N}}\equiv\text{N}: \qquad \text{R}-\text{C}\equiv\overset{+}{\text{O}}: \qquad \overset{+}{\text{O}}\equiv\text{N}:$$

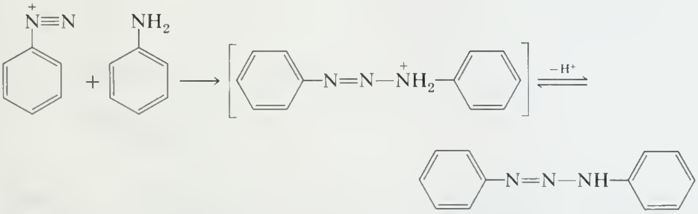
Arenediazonium ions can react as electrophilic reagents in aromatic substitutions, but they are such mild reagents that only the most activated rings can be used. In practice, such reactions are limited primarily to aromatic amines and phenols. This lack of reactivity was already apparent in the chemistry of the diazonium salts already discussed. They do not react with the mild base, water,

$$\text{Ar}-\overset{+}{\text{N}}\equiv\text{N} + \text{H}_2\text{O} \rightleftharpoons \text{Ar}-\text{N}=\text{N}-\overset{+}{\text{O}}\text{H}_2$$

and water is a stronger base than most aromatic rings. Note that the central nitrogen is analogous to an ammonium salt and that the reaction with bases that does occur is exclusively at the terminal nitrogen.

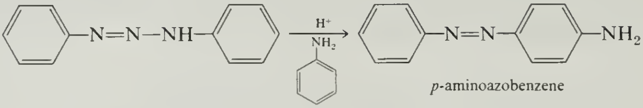
$$\text{Ar}-\overset{+}{\text{N}}\equiv\text{N} + {}^{-}\text{OH} \rightleftharpoons \text{Ar}-\text{N}=\text{N}-\text{OH}$$

Reaction with primary aromatic amines occurs in a related manner, with the amino nitrogen as a base, to give a derivative of a **triazene.**

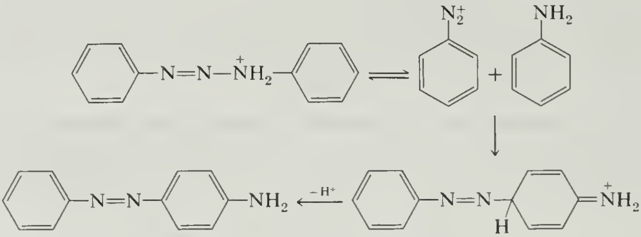


(82-85%)
diazoaminobenzene
1,3-diphenyltriazine

Diazoaminobenzene reacts with excess aniline and acid to give the aromatic substitution product *p*-aminoazobenzene.

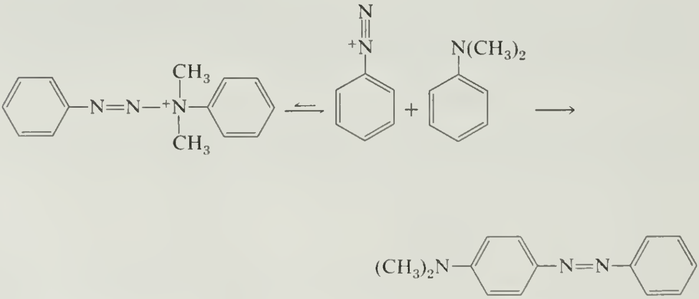


This reaction is usually assumed to involve a reversal of diazoaminobenzene formation, followed by the slower reaction of benzenediazonium cation with the *para* position of aniline.



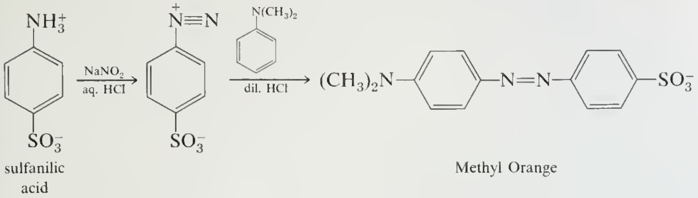
This mechanism incorporates the frequently encountered distinction between kinetically controlled and thermodynamically controlled reactions and explains many features of the reaction; however, the reaction also produces a variety of minor by-products that suggest a more complex reaction mechanism.

With N,N-dimethylaniline, the triazene is so unstable that it is not observed, and the net observed reaction is that of aromatic substitution.



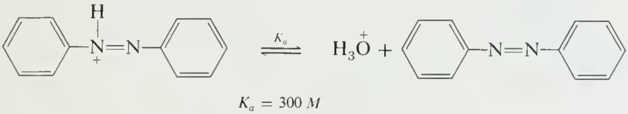
p-dimethylaminoazobenzene
Butter Yellow

Butter Yellow was used at one time as a yellow food coloring, but as a suspected carcinogen it is no longer used for this purpose. Substituted azoarenes form an important class of dyes (Section 36.4.C). Several are also useful as indicators in the laboratory. Methyl Orange, *p*-dimethylaminoazobenzene-*p*′-sulfonic acid, is prepared from diazotized sulfanilic acid and N,N-dimethylaniline.

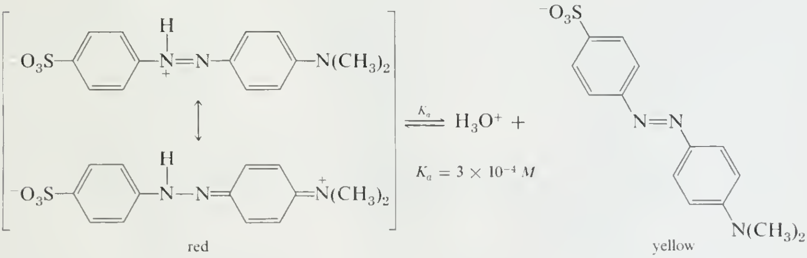


The product is isolated as the sodium salt by salting out with sodium chloride. Note that these so-called "coupling reactions" of diazonium salts occur almost exclusively at the *para* position. Reaction occurs generally at the *ortho* position only when the *para* position is blocked.

The azo group has nitrogen lone pairs and is expected to show basic properties. However, each of these lone pairs is in an approximately sp^2 orbital and is less basic than an amino lone pair, in which the orbital has less *s* character. Furthermore, the adjacent nitrogen further reduces the basicity. As a result, the azo group in azobenzene itself is a rather weak base; the pK_a of the protonated compound is -2.5.



Azobenzene itself is protonated only in rather strong acid. Methyl Orange has a pK_a of 3.5; this value refers to the protonated azo group, not to the dimethylamino or sulfonic acid groups. At pH's much above 3.5, Methyl Orange is in the yellow azo form. At pH's lower than 3.5 it is present instead in the red protonated form.

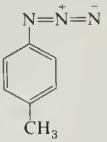


Note that the azo-protonated form of Methyl Orange is stabilized by the *p*-$N(CH_3)_2$ group. This stabilization renders the protonated form less acidic than protonated azobenzene.

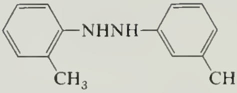
PROBLEMS

1. Name each of the following compounds

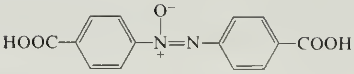
(a)



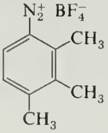
(b)



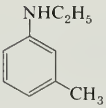
(c)



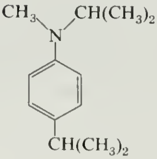
(d)



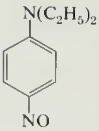
(e)



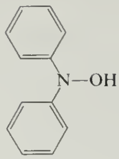
(f)



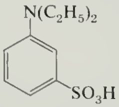
(g)



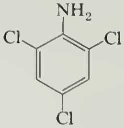
(h)



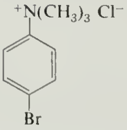
(i)



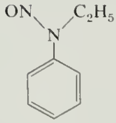
(j)



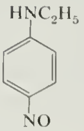
(k)



(l)

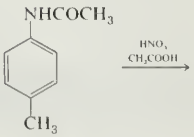


(m)

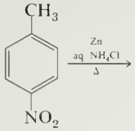


2. What is the principal organic product(s) of each of the following reactions:

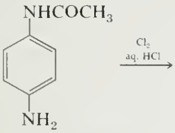
(a)



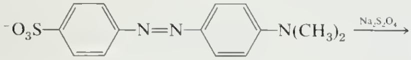
(b)


CH3
NO2
Zn
aq NH4Cl
Δ

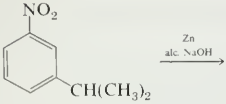
(c)


NHCOCH3
NH2
Cl2
aq. HCl

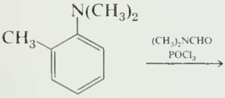
(d)


⁻O3S
N=N
N(CH3)2
Na2S2O4

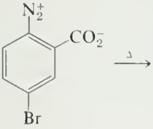
(e)


NO2
CH(CH3)2
Zn
alc. NaOH

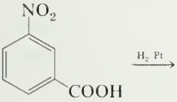
(f)


N(CH3)2
CH3
(CH3)2NCHO
POCl3

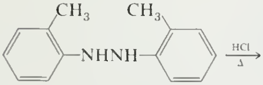
(g)


N2+
CO2⁻
Br
Δ

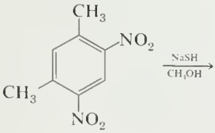
(h)

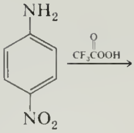

NO2
COOH
H2 Pt

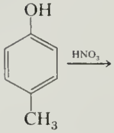
(i)


CH3
CH3
NHNH
HCl
Δ

(j)


CH3
NO2
CH3
NO2
NaSH
CH3OH

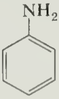
(k) 
NH2
CF3COOH
NO2

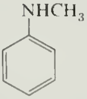
(l) 

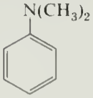
3. Give the principal reduction product from *m*-nitrotoluene under each of the following conditions:
   - (a) Zn, alc. NaOH
   - (b) Pt/H_2
   - (c) Zn, aq. NH_4Cl
   - (d) $SnCl_2$, HCl
   - (e) H_2NNH_2, Ru/C, alc. KOH
   - (f) As_2O_3, aq. NaOH

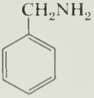
4. What is the principal product obtained from *p*-toluenediazonium cation with each of the following reagents:
   - (a) I^-
   - (b) CuCN
   - (c) OH^- (cold)
   - (d) H_2O (hot)
   - (e) Cu_2Br_2
   - (f) $NaNO_2$, Cu powder
   - (g) aq. NaOH, benzene, 5°
   - (h) (1) $NaBF_4$; (2) heat
   - (i) H_3PO_2
   - (j) Na_2SO_3
   - (k) N,N-diethylaniline
   - (l) (1) HPF_6; (2) heat

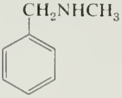
5. Compare the behavior towards aqueous nitrous acid of each of the following compounds:

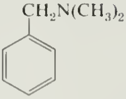
(a) 

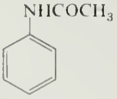
(b) 

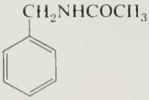
(c) 

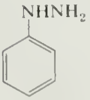
(d) 

(e) 

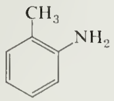
(f) 

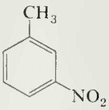
(g) 

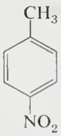
(h) 
CH2NHCOCH3

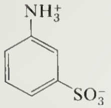
(i) 

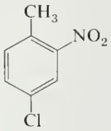
6. Each of the following compounds is a significant dye intermediate. Give a practical laboratory preparation for each starting with benzene or toluene.

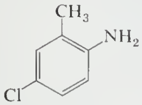
(a)


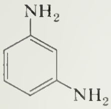
(b)


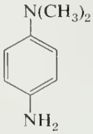
(c)


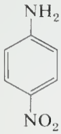
(d)


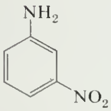
(e)


(f)


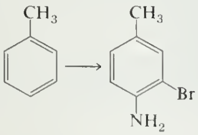
(g)


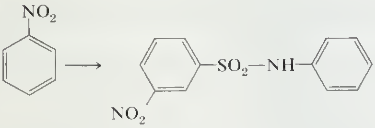
(h)


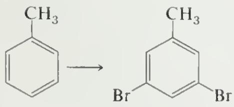
(i)


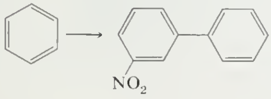
(j)


7. Show how each of the following conversions can be accomplished in a practical manner:

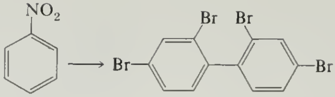
(a)

CH3
CH3
Br
NH2

(b)

NO2
SO2—NH
NO2

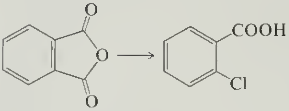
(c)

CH3
CH3
Br
Br

(d)


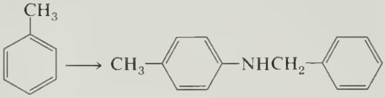
(e)



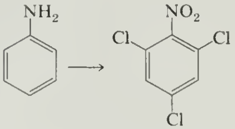
(f)



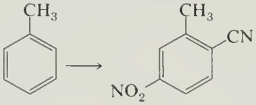
(g)



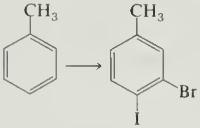
(h)



(i)



(j)



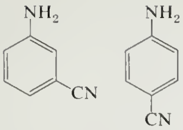
8. The dipole moment of *p*-(N,N-dimethylamino)benzonitrile, 6.60 D, is substantially greater than the sum of the dipole moments of N,N-dimethylaniline, 1.57 D, and benzonitrile, 3.93 D. Explain.

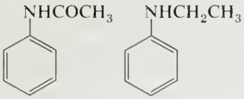
9. Write out the mechanism for bromination of N,N-dimethylaniline in the *para* position with Br_2 and show why this compound is so much more reactive than benzene.

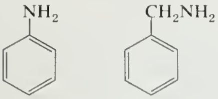
10. Although *o*-methylaniline ($pK_a = 4.44$) is a somewhat weaker base than aniline ($pK_a = 4.60$), *o*-methyl-N,N-dimethylaniline ($pK_a = 6.11$) is a much stronger base than N,N-dimethylaniline ($pK_a = 5.15$). Give a rational explanation.

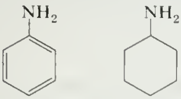
11. Plot the pK_as of *meta* and *para* substituted anilines against the corresponding σ values. How does the magnitude of ρ compare with that for benzoic acids? How do you explain the difference in magnitude? The points that deviate farthest from the linear correlation are those for *p*-CN and *p*-NO_2. Explain why these groups deviate in the direction they do. Table 31.4 gives σ values for some substituents not given in Table 32.1 and for which pK_a values of anilines could be calculated using your $\sigma\rho$ correlation. For which substituents would such a calculation be unreliable?

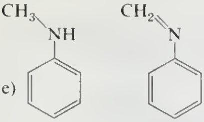
12. In each of the following pairs of compounds, which is the more *basic* in aqueous solution. Give a brief explanation.

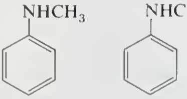
(a)


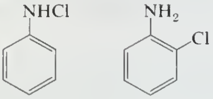
(b)


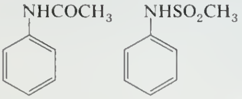
(c)


(d)


(e)


(f)


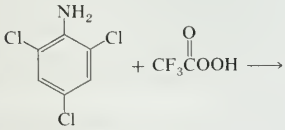
(g)


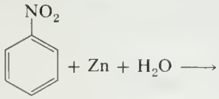
(h)


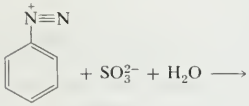
13. Diphenylamine, $(C_6H_5)_2NH$, is a rather weak base; the pK_a of the conjugate acid, 0.79, shows that diphenylamine is about 10^{-4} as basic as aniline. Give a reasonable explanation.

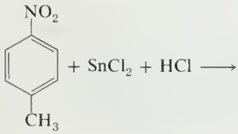
14. A small amount of Methyl Orange is added to a solution containing equimolar amounts of acetic acid and sodium acetate. Is this solution yellow or red?

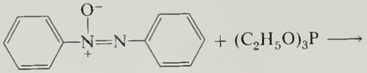
15. Write balanced equations for the following oxidation-reductions:

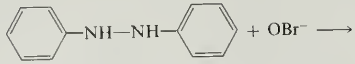
(a)


(b)


(c)


(d)


(e) 

(f) 

16. A diazonium salt prepared from *p*-nitroaniline, when decomposed in nitrobenzene, gives a 69% yield of 4,4′-dinitrobiphenyl. That is, reaction of the aryl radical formed from the diazonium salt occurs primarily at the *para* position of the nitrobenzene. Give a reasonable explanation of this orientation behavior.

17. The trimethylanilium cation, $C_6H_5N(CH_3)_3^+$ is prepared by an S_N2 reaction of dimethylaniline with a methyl halide or sulfonate. The compound undergoes a number of electrophilic substitution reactions such as nitration. Write out the resonance structures involved for reaction at the *meta* and *para* positions and determine whether the trimethylammonium group is activating or deactivating, and *ortho, para,* or *meta* directing.

18. A student tried to prepare *p*-bromocumene by diazotizing *p*-aminocumene with a mixture of aqueous sodium nitrite and hydrochloric acid at 0° followed by reaction with hot cuprous bromide, but he or she obtained a mixture of products. What was the nature of the mixture?

★19. Thermal decomposition of N-nitrosoacetanilide in carbon tetrachloride yields chlorobenzene. Write a reasonable mechanism for this reaction.

★20. (a) *p*-Nitroso-N,N-dimethylaniline reacts with aqueous hydroxide ion to form dimethylamine and *p*-nitrosophenol. The reaction involves a nucleophilic aromatic substitution. Give the structure of the nucleophilic addition intermediate, and show how the *p*-nitroso group provides stabilization for the intermediate. This reaction was used at one time as a preparation of secondary aliphatic amines. Show how this general reaction may be used to prepare diethylamine, starting with aniline.

(b) The example in (a) shows that the nitroso group is an electron-attracting group in nucleophilic aromatic substitution. Nevertheless, the nitroso group is also an *ortho, para* director in electrophilic aromatic substitution. Explain.

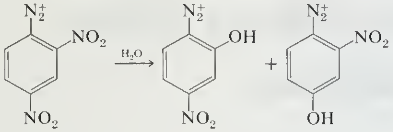
★21. For the diazonium ion–diazotate ion equilibrium expressed as

$$ArN_2^+ \overset{K}{\rightleftharpoons} ArN_2O^- + 2\,H^+$$

show that $\frac{1}{2}\log[ArN_2O^-]/[ArN_2^+] = pH - \frac{1}{2}pK$. Some values of $\frac{1}{2}pK$ for substituted benzenediazo compounds at 25° are as follows: *p*-NO_2, 9.44; *m*-Cl, 10.70; H, 11.90; *m*-CH_3, 12.12. Plot these values against the appropriate σ values and calculate ρ for this equilibrium. Does ρ have the sign you would have expected?

★22. N-Chloroacetanilide is converted to a mixture of 32% *o*-chloroacetanilide and 68% *p*-chloroacetanilide in the presence of HCl. The use of ^{36}Cl-enriched HCl finds the isotopic Cl incorporated into the product. The reaction of acetanilide with chlorine under the same reaction conditions gives the same product composition. Write a reaction mechanism for the rearrangement of N-chloroacetanilide (Orton rearrangement) to account for these facts.

★**23.** Diazotization of 2,4-dinitroaniline in aqueous solution is accompanied by some conversion to phenols in which a nitro group is replaced by a hydroxy group.

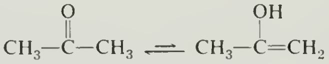

N_2^+
NO_2
NO_2
H_2O
N_2^+
OH
NO_2
+
N_2^+
NO_2
OH

Give a reasonable mechanism for this reaction.

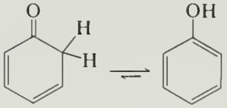
CHAPTER 33

Phenols, Phenyl Ethers and Quinones

The term phenol is used for the parent compound, hydroxybenzene, and also as a generic term for the class of compounds that have a hydroxy group attached to a benzene ring. Hydroxybenzenes may be regarded as enols, as the name **phenol** implies. However, unlike simple ketones, which are usually far more stable than their corresponding enols, the tautomeric equilibria in the aromatic series lie far on the side of the enol. The reason for this difference is the resonance energy of the benzene ring which provides an important stabilization of the enol form.



$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 \rightleftharpoons CH_3-\overset{\overset{OH}{|}}{C}=CH_2 \qquad \Delta H^\circ \approx +14\ \text{kcal mole}^{-1}$$

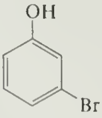


$\Delta H^\circ \approx -16$ kcal mole^{-1}

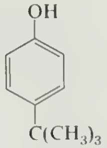
The relationship of hydroxyarenes to enols is reflected in much of the chemistry of these systems to be discussed in this chapter.

33.1 Nomenclature

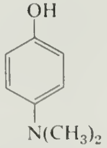
Since the functional group occurs as a suffix in **phenol**, many compounds containing an aromatic hydroxy group are named as derivatives of the parent compound phenol.



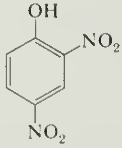
m-bromophenol



p-*t*-butylphenol

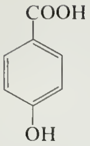


p-dimethylaminophenol

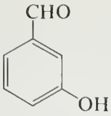


2,4-dinitrophenol

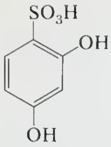
Suffix groups such as sulfonic acid, carboxylic acid, and so on, take priority, and when these groups are present the hydroxy group is used as a modifying prefix.



p-hydroxybenzoic acid

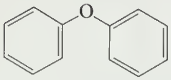


m-hydroxybenzaldehyde

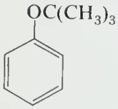


2,4-dihydroxybenzene-sulfonic acid

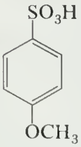
Phenyl ethers are named in the IUPAC system as alkoxyarenes, although the "ether" nomenclature is used for some compounds.



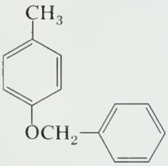
phenyl ether



t-butoxybenzene

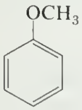


p-methoxybenzene-sulfonic acid

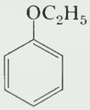


p-benzyloxytoluene

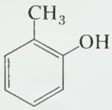
Phenols and their ethers are widespread in nature, and, as is usual for such compounds, trivial names abound. Many of these names are in such common use that they should be learned.



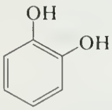
anisole
methoxybenzene



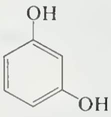
phenetole
ethoxybenzene



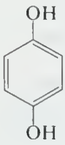
o-cresol
o-methylphenol



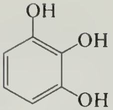
catechol
o-dihydroxybenzene



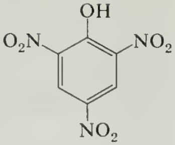
resorcinol
m-dihydroxybenzene



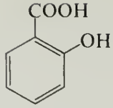
hydroquinone
p-dihydroxybenzene



pyrogallol
1,2,3-trihydroxybenzene

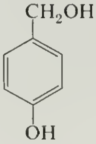


picric acid
2,4,6-trinitrophenol

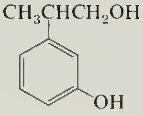


salicylic acid
o-hydroxybenzoic acid

Note that compounds with more than one hydroxy group are named with the hydroxy prefix. Terms such as "phen-diol" or "benzene-triol" are *not* used. Phenols differ from alcohols in much of their chemistry, and alcohol nomenclature does *not* apply to hydroxyarenes.

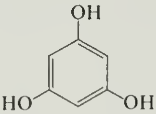


p-hydroxybenzyl alcohol

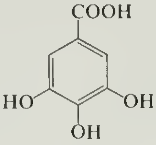


2-(*m*-hydroxyphenyl)-1-propanol

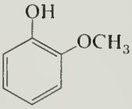
Other trivial names are common and the student can expect to find them in the current literature.



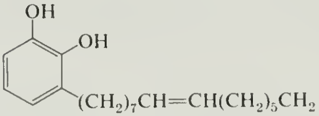
phloroglucinol



gallic acid



guaiacol



a urushiol

Urushiol is the active constituent of the allergenic oil of poison ivy and probably also of poison oak. It is a mixture of several compounds in which the long side chain varies in degree of saturation. One of the constituents is that shown above. It causes skin reactions typical of poison ivy.

33.2
Preparation and Properties of Phenols and Ethers

A. *Preparation of Phenols*

All of the important preparations of phenols involve reactions that have already been discussed.

$$\text{ArSO}_3^- \xrightarrow[\Delta]{\text{NaOH}} \text{ArOH}$$

The fusion of arenesulfonic acids with alkali hydroxide is an excellent route for systems that are available by sulfonation and contain no base-sensitive functions (Section 31.6.B).

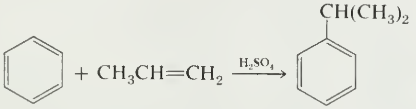
$$\mathrm{ArCl} \xrightarrow[\Delta]{\mathrm{NaOH}} \mathrm{ArOH}$$

The hydrolysis of haloarenes with alkali under high temperature conditions is a commercial preparation but is not suitable for general laboratory use because of the involvement of benzyne intermediates and the formation of mixtures of isomeric phenols (Section 30.3.A). An exception occurs in those systems that contain strongly electron-attracting groups, such as nitro groups, conjugated with the halogen. In such cases, nucleophilic aromatic substitution proceeds smoothly to give the hydroxy compound (Section 30.3.A).

$$\mathrm{ArN_2^+} \xrightarrow[\Delta]{\mathrm{H_2O}} \mathrm{ArOH} + \mathrm{H_3O^+} + \mathrm{N_2}$$

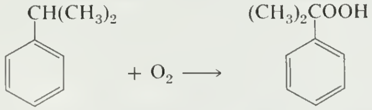
The hydrolysis of arenediazonium salts is a good route to many phenols and has been discussed in Section 32.3.B.

An important industrial preparation of phenol involves the oxidation of cumene, an inexpensive hydrocarbon which may be prepared by alkylation of benzene (Section 30.6.A).



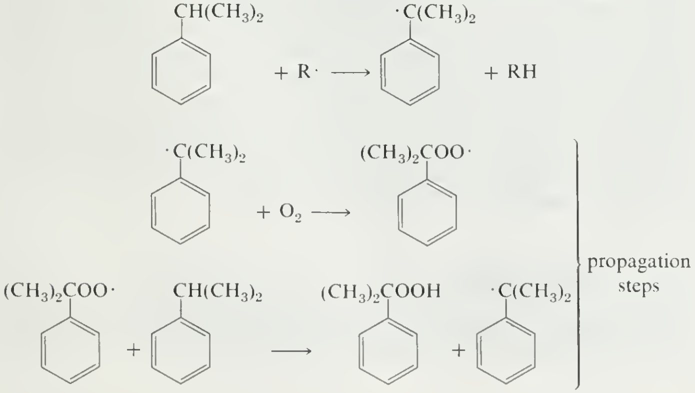
cumene

Cumene is air oxidized (Section 11.11) to obtain cumene hydroperoxide.

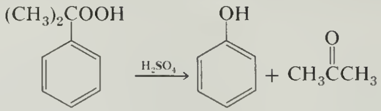


cumene hydroperoxide

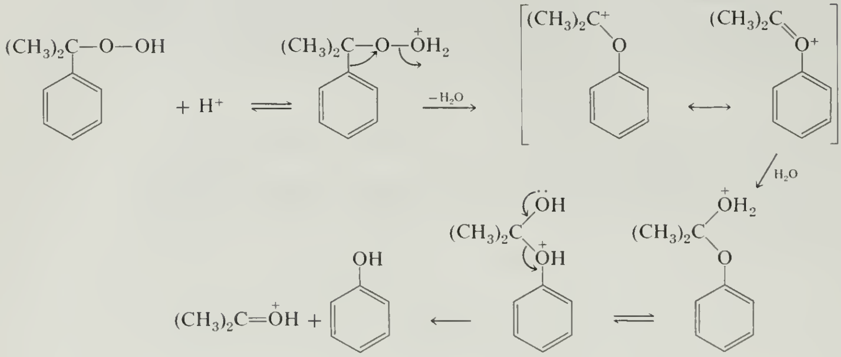
The oxidation is a typical free radical chain process. It is especially facile because the intermediate cumyl radical is tertiary and benzylic.



The cumene hydroperoxide is treated with sulfuric acid to obtain phenol and acetone.



This interesting fragmentation probably occurs by the following mechanism:

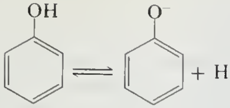


The cumene process is a good example of the economics of industrial organic synthesis. It owes its economic feasibility in part to the fact that *two* important commercial products are formed. Note that in the overall process, from benzene and propylene to phenol and acetone, the only reagent that is consumed is oxygen. In fact, the overall process amounts to a circuitous oxidation of both starting hydrocarbons. The sulfuric acid that is used both in the alkylation and in decomposition of the hydroperoxide is recycled.

Phenols are generally crystalline compounds with distinctive odors. Phenol itself melts at 40.9°, but is often found to be semiliquid because of the presence of water which lowers the melting point; it is completely liquified by the addition of 8% of water. It is soluble to the extent of 6.7 g per 100 ml of cold water and is totally miscible with hot water. The lower alkylphenols are sparingly soluble in water; for example, *o*-cresol dissolves to the extent of 2.5 g per 100 ml of water at 25°. Phenol and the cresols are widely used in commercial disinfectants. Phenol turns pink on exposure to air because of oxidation. The sensitivity of phenols to air oxidation is enhanced by the presence of more than one hydroxy group and by alkali. An alkaline solution of pyrogallol rapidly removes oxygen from a stream of air, and it is often used for this purpose. The oxidation of phenols to quinones will be discussed in Section 33.4.B. Phenols are sufficiently acidic that they are caustic toward flesh and are poisonous.

B. *Acidity of Phenols*

Phenol has $pK_a = 10.00$. The pK_as of some substituted phenols are summarized in Table 33.1; most values are in the range from 8 to 10.



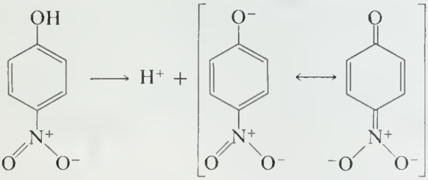
$K_a = 1.0 \times 10^{-10}\,M \qquad \mathrm{p}K_a = 10.00$

Phenols are generally several orders of magnitude less acidic than carboxylic acids but are far more acidic than alcohols. If we recall that the value of the pK_a corresponds to that pH at which the conjugate acid and base are in equal concentrations, pK_as of 8–10 imply that phenols will dissolve in dilute alkali hydroxide solutions (pH 12–14); however, water insoluble phenols will not dissolve in aqueous sodium bicarbonate (pH ≈ 6–7). Carboxylic acids dissolve in aqueous bicarbonate.

TABLE 33.1
Acidities of Phenols

	pK_a, 25°		
Substituent	*ortho*	*meta*	*para*
H	10.00	10.00	10.00
methyl	10.29	10.09	10.26
fluoro	8.81	9.28	9.81
chloro	8.48	9.02	9.38
bromo	8.42	8.87	9.26
iodo	8.46	8.88	9.20
methoxy	9.98	9.65	10.21
methylthio		9.53	9.53
cyano			7.95
nitro	7.22	8.39	7.15

Ring substituents show effects that follow the general pattern established in other systems. The methyl group is acid weakening. Halogens increase acidity, and strongly electron-attracting groups, such as cyano and nitro, have pronounced effects. With these substituents, the negative charge in the anion can be delocalized onto the oxygen or nitrogen of the substituent.



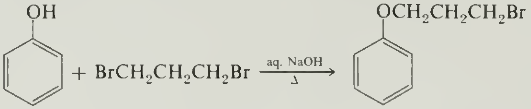
Note that a nitro group is more acid strengthening when it is *ortho* or *para* to the hydroxy group. Dinitrophenols are comparable to carboxylic acids in acidity; for example, the pK_a of 2,4-dinitrophenol is 4.09. Picric acid, 2,4,6-trinitrophenol, has pK_a = 0.25 and is a rather strong acid, comparable to trifluoroacetic acid.

C. *Preparation of Ethers*

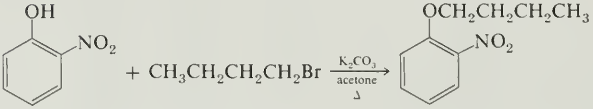
Alkyl phenyl ethers can be prepared by the Williamson synthesis—the S_N2 reaction of phenoxide ions with alkyl halides. As is usually the case with S_N2 reactions, this preparation works best for primary halides and is least successful with tertiary alkyl halides. The reaction can be run in water, acetone, dimethylformamide, or dimethyl sulfoxide. The reaction is even feasible in alcohol; because of the difference in acidities of alcohols and phenols, equilibrium (33-1) lies far to the left.

$$ArO^- + ROH \rightleftharpoons ArOH + RO^- \tag{33-1}$$

Thus, reaction of the alkyl halide with alkoxide ion is not an important side reaction. Some examples of preparations of aryl ethers are

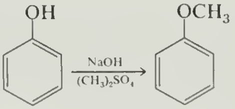


(84–85%)
1-bromo-3-phenoxypropane



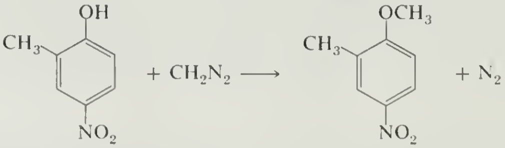
(75–80%)
1-butoxy-2-nitrobenzene

For the preparation of aryl methyl ethers, dimethyl sulfate is especially convenient.



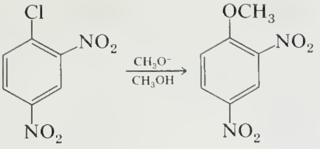
(72–75%)

Diazomethane may also be used to prepare aryl methyl ethers. Because of its expense, toxicity, and the hazards involved in its use (Sections 17.7.A and 27.8.B), it is used only for the small scale methylation of relatively precious phenols.



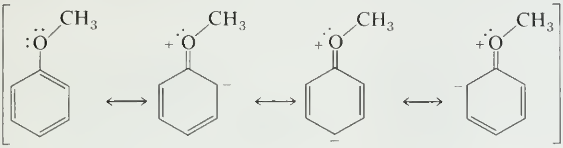
2-methyl-4-nitrophenol
2-methyl-4-nitroanisole

Ethers can also be prepared by nucleophilic aromatic substitution in suitable cases (see Section 30.3.A).



2,4-dinitroanisole

The lower phenyl ethers are liquids; for example, anisole boils at 154°. Unlike phenols, the ethers are essentially insoluble in water. They lack the hydroxy group of phenol, which can hydrogen bond to water oxygens. The ether oxygens have relatively low basicity and form only weak hydrogen bonds to water hydrogens. The low basicity of the oxygens of phenyl ethers compared to aliphatic ethers stems from conjugation of a lone pair with the aromatic ring. The same phenomenon is responsible for the reduced basicity of aromatic amines compared to aliphatic amines.



Aryl ethers are also more stable to oxidation than phenols.

33.3
Reactions of Phenols and Ethers

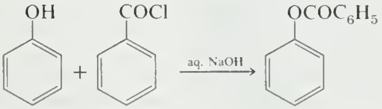
A. *Esterification*

Phenols can be converted to esters but *not* by direct reaction with carboxylic acids. Although the esterification equilibrium is exothermic for alcohols, it is slightly endothermic for phenols. For example, in the gas phase

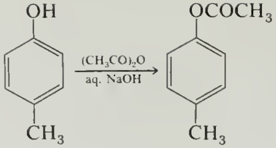
$$C_6H_5OH + CH_3COOH \rightleftharpoons C_6H_5OOCCH_3 + H_2O \qquad \Delta H^\circ = +1.5 \text{ kcal mole}^{-1}$$

$$C_2H_5OH + CH_3COOH \rightleftharpoons C_2H_5OOCCH_3 + H_2O \qquad \Delta H^\circ = -4.6 \text{ kcal mole}^{-1}$$

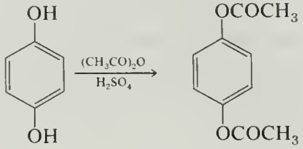
This example again demonstrates the significant differences between alcohols and phenols. Aryl esters can be prepared by allowing the phenol to react with an acid chloride or anhydride under basic or acid catalysis. Some typical examples are



phenyl benzoate

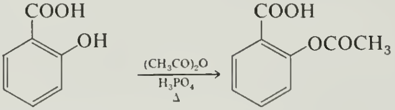


p-tolyl acetate



hydroquinone diacetate

One of the best known aromatic acetates is acetylsalicylic acid, or aspirin, which is prepared by the acetylation of salicylic acid.



salicylic acid
o-hydroxybenzoic acid

aspirin
acetylsalicylic acid
o-acetoxybenzoic acid

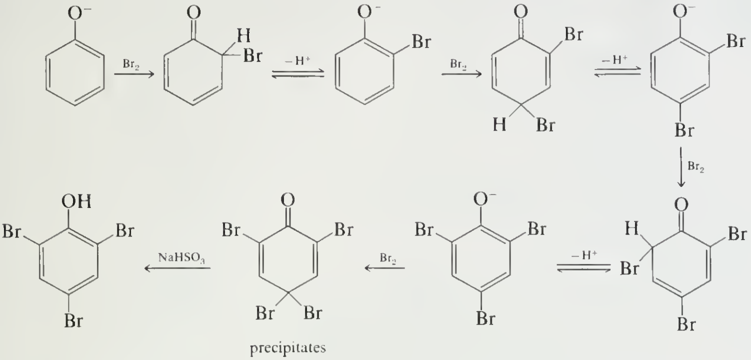
Aspirin is widely used, primarily for its analgesic effect but also as an antipyretic and antirheumatic. It is not so innocuous a drug as one might imagine from its widespread use and ready availability. Repeated use may cause gastrointestinal bleeding, and large doses can provoke a host of reactions including vomiting, diarrhea, vertigo, and hallucinations. The average dose is 0.3 to 1 g; single doses of 10–30 g are usually fatal.

B. *Reactions of Phenolate Ions*

Phenolate ions may be considered as enolate ions and many of the reactions of phenolate ions point up this relationship. It is convenient to distinguish such reactions from those of the conjugate acids, the phenols. Many of the reactions of phenols resemble those of the corresponding ethers and may be considered together.

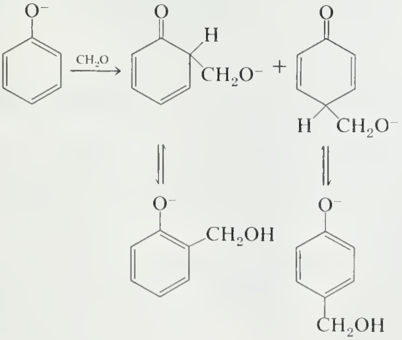
1. HALOGENATION. The reaction of an aqueous solution of phenol with bromine gives a precipitate of 2,4,4,6-tetrabromocyclohexa-2,5-dienone. This precipitate is normally washed with aqueous sodium bisulfite to generate 2,4,6-tribromophenol. The reaction appears to be a reaction of bromine with phenolate anion. As each successive bromine is introduced, the product is progressively more acidic, a greater fraction is present as the phenolate anion, and additional halo-

genation results. The net reaction is similar to the bromination of a ketone under basic conditions (Section 15.6.D).

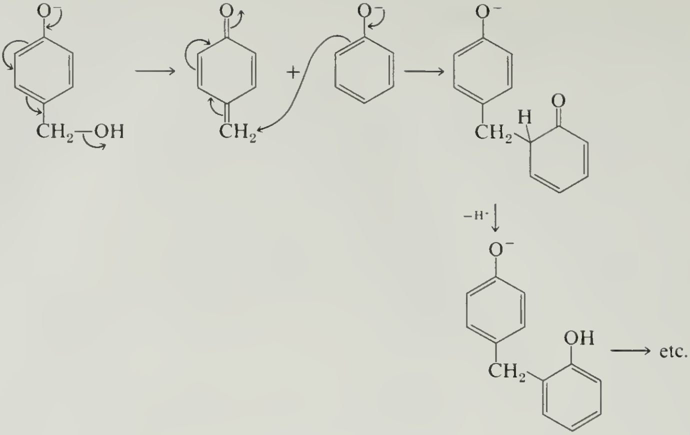


Corresponding reactions occur with chlorine and iodine and with other phenols. The net reaction is halogenation of all available *ortho* and *para* positions. Halogenation of phenol is possible under acid conditions, and the incorporation of successive halogens can be controlled (Section 33.3.C). Here also we see an analogy to the acid-catalyzed, as well as the base-catalyzed, halogenation of carbonyl compounds (Section 15.6.D).

2. CONDENSATION WITH ALDEHYDES. A characteristic of enolate ions from aldehydes and ketones is the condensation with other carbonyl groups as in the aldol condensation (Section 15.7.G). A similar reaction occurs with phenolate ions. Phenol reacts with formaldehyde in the presence of dilute alkali to give a mixture of *o*- and *p*-hydroxybenzyl alcohols.



The reaction difficult to control because of further condensations that lead to a polymeric product.


O⁻
CH₂—OH
O
CH₂
+
O⁻
O⁻
H
O
CH₂
−H⁺
O⁻
OH
CH₂
etc.

Note the relationship of the further condensations to the Michael addition (Section 26.4.F). Under proper conditions, the final product is a dark, brittle, crosslinked polymer known as Bakelite, one of the oldest commercial plastics. The general class of such polymers is now called phenol-formaldehyde resins (Figure 33.1).

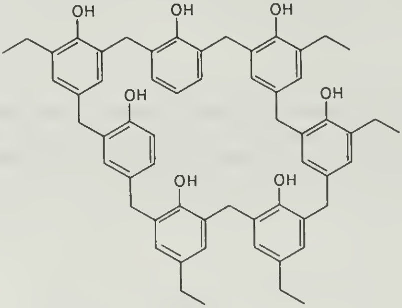
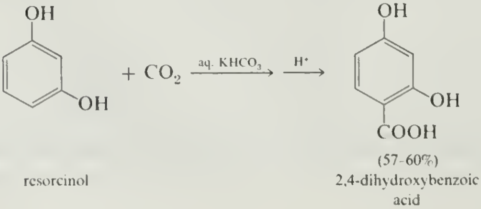
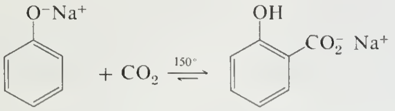

OH
OH
OH
OH
OH
OH
OH

FIGURE 33.1 *Partial structure of a phenol-formaldehyde resin.*

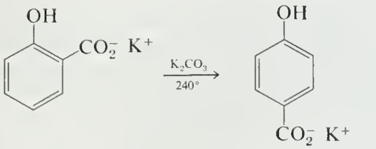
3. **KOLBE SYNTHESIS.** The reaction of carbanions with carbon dioxide to give carboxylate salts has its counterpart in the reactions of phenolate ions.


OH
OH
+ CO₂
aq. KHCO₃
H⁺
OH
OH
COOH
(57-60%)
resorcinol
2,4-dihydroxybenzoic acid

The reaction of phenolate ion with carbon dioxide is called the Kolbe synthesis; the reaction product depends on the conditions, especially temperature. Carbonation of sodium phenolate at relatively low temperatures gives sodium salicylate in a reversible reaction. At higher temperatures, potassium salicylate may be smoothly isomerized to the *para* isomer.



sodium salicylate
sodium *o*-hydroxybenzoate



potassium salicylate

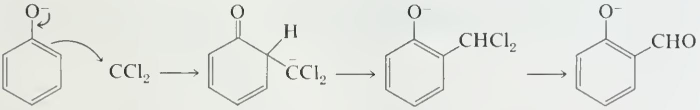
potassium *p*-hydroxybenzoate

Although the Kolbe synthesis may be written simply as the enolate condensation of phenolate ion with carbon dioxide, it is clear that coordination phenomena are involved. However, these mechanistic details are not yet fully understood.

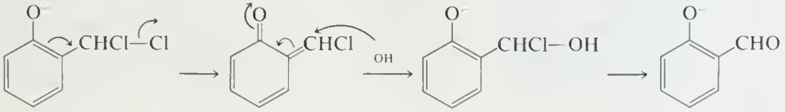
4. **Reimer-Tiemann Reaction.** The Reimer-Tiemann reaction is the reaction of a phenol with chloroform in basic solution to give a hydroxybenzaldehyde. Reaction occurs primarily in an *ortho* position unless both are blocked. The reaction mechanism involves the prior formation of dichlorocarbene by the reaction of chloroform with alkali (Section 23.5.A).

$$\mathrm{CHCl_3 + OH^- \rightleftharpoons CCl_3^- \longrightarrow \underset{\text{dichlorocarbene}}{:CCl_2}}$$

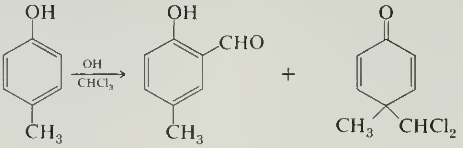
The dichlorocarbene then reacts with the phenolate ion to give a dichloromethyl compound, which rapidly hydrolyzes.



The final hydrolysis reaction is undoubtedly facilitated by the phenoxide ion in the following way:



The essential correctness of the overall mechanism is revealed by an interesting by-product of the Reimer-Tiemann reaction on *p*-cresol.

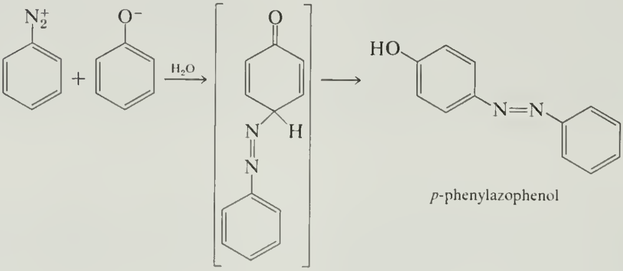


(5%)

2-hydroxy-5-methyl-benzaldehyde

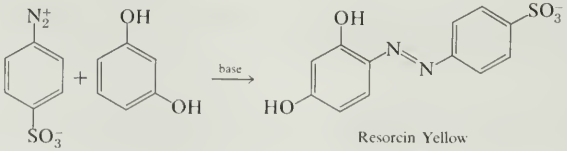
4-methyl-4-dichloromethyl-cyclohex-2,5-dienone

5. **Diazonium Coupling.** Phenols react in basic solution with diazonium salts to give the corresponding arylazophenols. The reaction is an electrophilic aromatic substitution reaction by a weak electrophile, the diazonium ion, on an aromatic ring which is highly activated by the oxide anion.



p-phenylazophenol

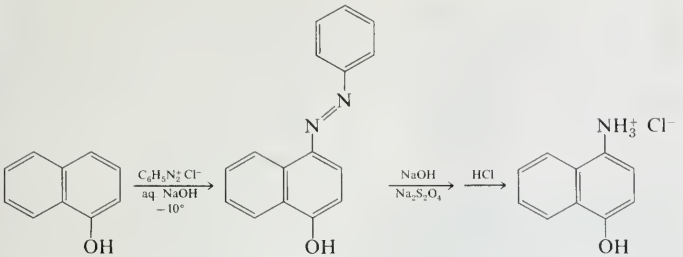
The product is almost exclusively the *para* isomer; the *ortho* isomer is formed to the extent of only 1%.



Resorcin Yellow
(silk and leather dye)

Arylazophenols constitute an important class of azo dyes. However, most of the important examples are naphthalene rather than benzene derivatives (Section 36.4.C).

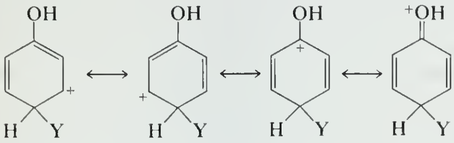
Arylazophenols can be reduced to aminophenols by sodium hydrosulfite. Yields are generally high and the reaction is one of the best methods for the synthesis of many aminophenols.



1-naphthol 4-phenylazo-1-naphthol (85–90%) 4-amino-1-naphthol hydrochloride

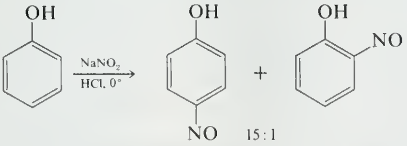
C. *Electrophilic Substitutions of Phenols and Ethers*

In acidic solutions, electrophilic substitutions occur on the unionized phenol. Such substitutions are still rather facile because of the activating nature of the hydroxy group, which is a strong *ortho,para* director. Reaction at one of these positions gives an intermediate cation that is essentially a protonated carbonyl group.



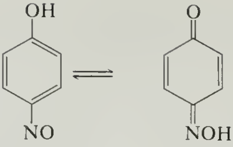
The last structure shows the role of an oxygen lone pair in stabilizing the intermediate and the transition state leading to it. Exactly the same phenomenon applies to the aromatic ethers; that is, alkoxy groups are also powerful *ortho,para* directors. Consequently, for many electrophilic aromatic substitution reactions, phenols and ethers can be considered together. The principal difference between the two groups of compounds lies in the greater water solubility of the phenols. Many electrophilic reactions of phenols can be carried out in aqueous solutions.

1. **Nitrosation.** Phenols react with nitrous acid in aqueous or acetic acid solution to give mostly *p*-nitrosophenols, with some *ortho* isomer:



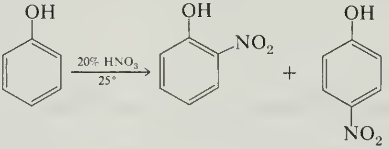
p-nitrosophenol *o*-nitrosophenol

Nitrosophenols are of interest principally because of their tautomeric equilibria with quinone monooximes.



p-benzoquinoneoxime

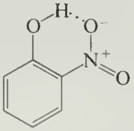
2. **Nitration.** Phenol is nitrated by dilute aqueous nitric acid, even at room temperature.



(30–40%) *o*-nitrophenol (15%) *p*-nitrophenol

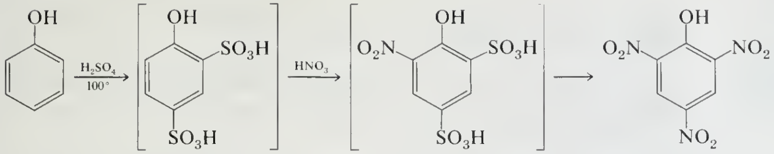
The reaction appears to be catalyzed by nitrous acid. That is, the reaction may first involve a nitrosation, followed by oxidation of the nitroso group by nitric acid to a nitro group. The ratio of *ortho* and *para* products depends on the concentration of nitrous acid in solution. The reaction is also accompanied by varying amounts of tarry by-products produced by oxidation of phenol. Nevertheless, the reaction is satisfactory for preparing both *o*- and *p*-nitrophenol because the isomers can be readily separated and purified.

o-Nitrophenol has lower solubility and higher volatility because of the **chelation** or intramolecular hydrogen bonding between the hydroxy group and the nitro group. Chelation (Gr., *chele,* claw) refers to formation of a ring by coordination with a pair of electrons.



Because the acceptor hydrogen of *o*-nitrophenol is involved in chelation it is not available for hydrogen bonding to solvent water molecules. The resulting lower solubility and higher volatility are such that *o*-nitrophenol can be steam-distilled from the reaction mixture. The *o*- and *p*-nitrophenols are also available by hydrolysis of *o*- and *p*-chloronitrobenzene (Section 30.3.A). Similarly, although 2,4-dinitrophenol can be prepared by nitration of phenol with somewhat stronger nitric acid, it is more conveniently prepared by hydrolysis of 2,4-dinitrochlorobenzene.

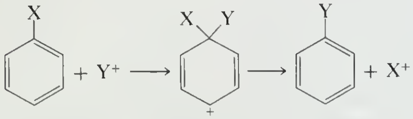
Picric acid is prepared by first treating phenol with concentrated sulfuric acid at 100°. Nitric acid is added to the cooled mixture which is then heated again. The reaction involves first the formation of the disulfonic acid which is then nitrated. At higher temperatures nitration involves replacement of sulfonic acid groups by nitro groups.



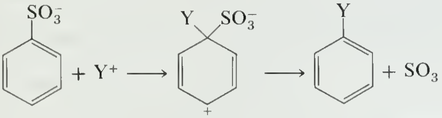
4-hydroxybenzene-1,3-disulfonic acid

(90%)
picric acid

The reaction in which a sulfonic acid group is replaced by a nitro group is not uncommon in electrophilic aromatic substitutions but occurs more often as a side reaction rather than the main reaction. The mechanism is exactly the same as for substitution of a proton, except that a different cation is lost.

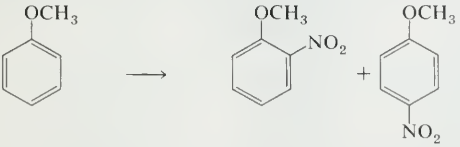


The reaction is most prevalent when strong *ortho,para* directing groups such as —OR and —NR_2 are present and with functions that form relatively stable electrophilic molecules. The sulfonic acid group is prone to such replacement because it is lost as a neutral molecule, SO_3.



Picric acid forms yellow crystals, m.p. 123°. It explodes at temperatures above 300° and was once used as a synthetic dye. It is now important principally because of the molecular complexes it forms with many compounds, especially with polycyclic aromatic hydrocarbons and their derivatives. These complexes are of the 'charge-transfer' type to be discussed in Section 33.4D. Such picric acid complexes are called picrates. They can be crystallized and are useful for purification purposes. On treatment with base, the picric acid component is converted to picrate ion which does not form complexes; thus, the other component of the complex is readily recovered.

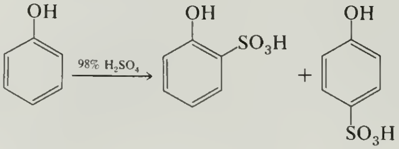
Anisole is readily nitrated to give a mixture of *o*- and *p*-nitroanisole. The composition of the mixture depends on the reaction conditions; nitric and sulfuric acids give more *para* substitution, whereas nitration in acetic anhydride gives more *ortho*.



HNO_3—H_2SO_4, 45°	(31%)	(67%)
HNO_3, Ac_2O, 10°	(71%)	(28%)

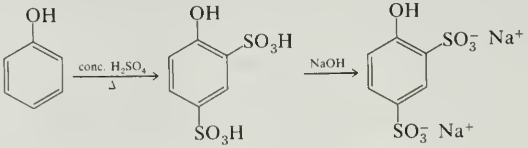
These compounds are also available from the corresponding chloronitrobenzenes by substitution with methoxide ion (Section 30.3.A).

3. **Sulfonation.** The monosulfonation of phenol shows the typical behavior of a kinetically versus thermodynamically controlled reaction that we have seen before in sulfonations (Section 31.6.A).

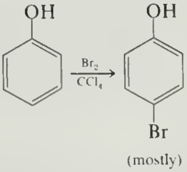

OH
98% H_2SO_4
OH
SO_3H
+
OH
SO_3H

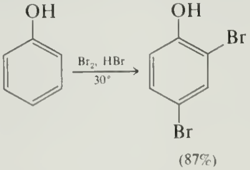
20°	(49%)	(51%)
100°	(10%)	(90%)

With concentrated sulfuric acid the disulfonic acid is formed. This product can be isolated as the sodium salt or can be used directly for further reactions as in the preparation of picric acid (page 1012).

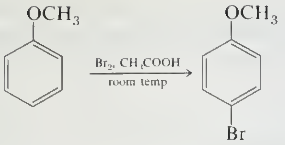

OH
conc. H_2SO_4
Δ
OH
SO_3H
SO_3H
NaOH
OH
SO_3^- Na^+
SO_3^- Na^+

4. **Halogenation.** In acidic solution the phenol rather than phenolate ion is involved in electrophilic halogenation. By proper choice of conditions one, two, or three halogens can be introduced in the available *ortho,para* positions.


OH
Br_2
CCl_4
OH
Br
(mostly)

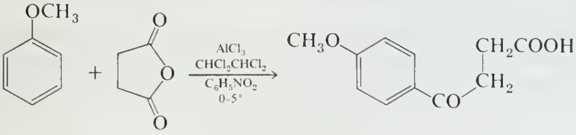

OH
Br_2, HBr
30°
OH
Br
Br
(87%)

Bromination of phenyl ethers also gives the *para* product in preference to the *ortho*.


OCH3
Br2, CH3COOH
room temp
OCH3
Br

The *p*-bromoanisole obtained in this reaction contains 10% of *ortho* isomer; the pure *para* compound is obtained by fractional freezing (*o*-, m.p. 2.5°; *p*-, m.p. 13°).

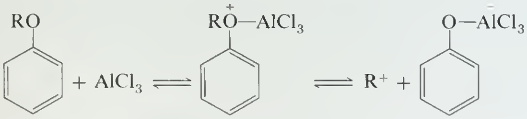
5. **Friedel-Crafts Acylations.** Anisole and primary alkyl aryl ethers undergo Friedel-Crafts acylation reactions in a straightforward way.


OCH3
O
O
O
AlCl3
CHCl2CHCl2
C6H5NO2
0-5°
CH3O
CH2COOH
CH2
CO

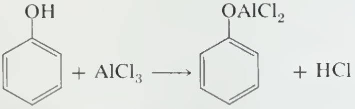
succinic anhydride

(85%)
β-(*p*-methoxybenzoyl)-propionic acid

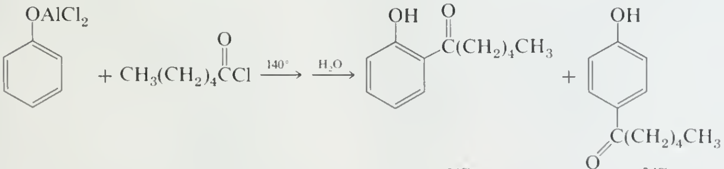
The conditions are mild because the alkoxy group is highly activating. The most important limitation in these reactions is acid-catalyzed cleavage of the ether linkage (Section 33.3.D). Such cleavage reactions are especially important for the ethers of secondary and tertiary alkyl groups because of the ease with which they form carbonium ions under these conditions.


RO
+ AlCl3
RO—AlCl3
R+ +
O—AlCl3

Friedel-Crafts acylations of phenol present problems. Phenol itself reacts with aluminum chloride to give phenoxyaluminum dichloride.

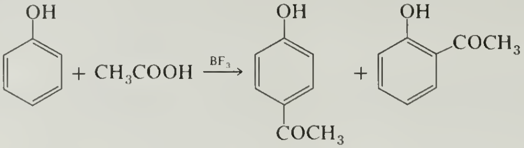

OH
+ AlCl3
OAlCl2
+ HCl

If this salt is heated to 120–140° in the presence of an acyl halide, acylation occurs in moderate yield.


OAlCl2
O
+ CH3(CH2)4CCl
140°
H2O
OH
O
C(CH2)4CH3
+
OH
C(CH2)4CH3
O

(56%) (34%)

A more successful method of direct acylation employs boron trifluoride or polyphosphoric acid as the catalyst. With the former reagent, a high preference for *para*-acylation is observed.

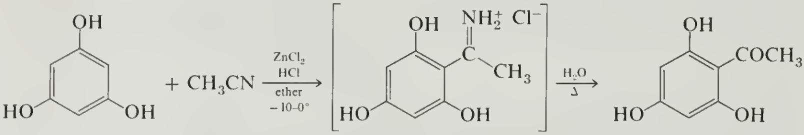

OH
+ CH_3COOH
BF_3
OH
COCH$_3$
+
OH
COCH$_3$

(95%)
p-hydroxyacetophenone

(trace)
o-hydroxyacetophenone

However, many phenol acylations proceed in low yield. One problem is esterification of the hydroxy group.

An alternative acylation method that avoids the problem of esterification is the **Houben-Hoesch synthesis.** In this reaction, the phenol is treated with a nitrile instead of an acyl halide or anhydride. The usual catalyst is zinc chloride.

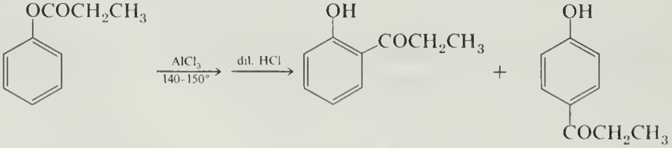

OH
HO
OH
+ CH_3CN
$ZnCl_2$
HCl
ether
−10–0°
OH
NH_2^+ Cl^-
C
CH_3
HO
OH
H_2O
Δ
OH
COCH$_3$
HO
OH

phloroglucinol

(74–87%)
2,4,6-trihydroxyacetophenone

The reaction is generally not as useful for monohydric phenols as it is for di- and polyhydric phenols; it may also be applied to many of the phenyl ethers.

Phenyl esters undergo a Lewis acid-catalyzed rearrangement which is essentially an intramolecular Friedel-Crafts acylation. The reaction is known as the **Fries rearrangement** and is usually carried out by heating the ester with aluminum chloride, often in the absence of solvent.

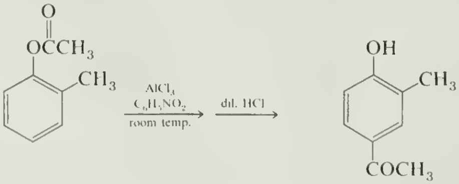

OCOCH$_2$CH$_3$
$AlCl_3$
140–150°
dil. HCl
OH
COCH$_2$CH$_3$
+
OH
COCH$_2$CH$_3$

phenyl propionate

(32–35%)
o-hydroxypropiophenone

(45–50%)
p-hydroxypropiophenone

The two products can be conveniently separated by fractional distillation. In many cases a single product is formed in good yield.

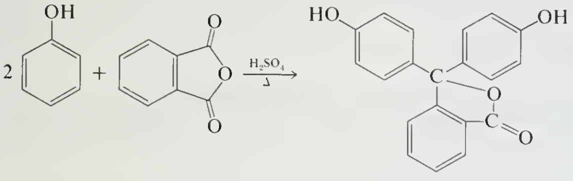

O
OCCH$_3$
CH$_3$
$AlCl_3$
$C_6H_5NO_2$
room temp.
dil. HCl
OH
CH$_3$
COCH$_3$

(80–85%)

o-tolyl acetate

3-methyl-4-hydroxyacetophenone

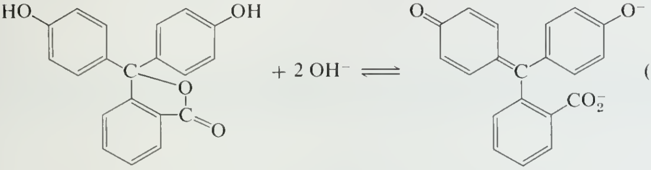
Phenols undergo a special Friedel-Crafts acylation with phthalic anhydride and sulfuric acid or zinc chloride. In this case, two molecules of phenol condense with one molecule of phthalic anhydride to give triarylmethane derivatives known as **phthaleins.**



(33-2)

phenolphthalein
(colorless lactone form)

The phthaleins are an important class of indicators and dyes. For example, phenolphthalein has the colorless lactone structure shown in (33-2) in solutions below pH 8.5. Above pH 9, two protons are lost to form an intensely colored red dianion (33-3).

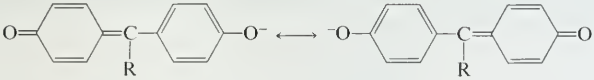


(33-3)

colorless

red

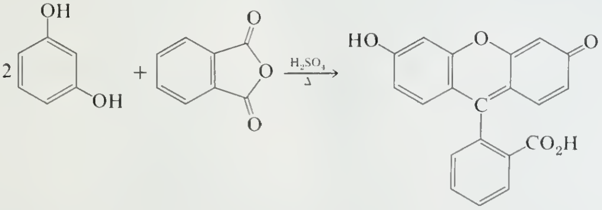
The red color comes from an electronic transition in the visible region associated with the extended π system of the ion:



Highly conjugated anions or cations of this type are invariably highly colored.

Phenolphthalein is used medicinally as a laxative and is the principal active ingredient in some proprietary preparations sold as laxative agents.

The condensation of resorcinol and phthalic anhydride gives an intensely fluorescent dye, fluorescein.



resorcinol

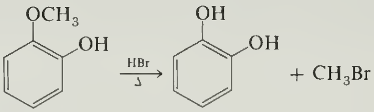
fluorescein

The yellowish-green fluorescence of fluorescein is detectable even in extremely dilute solutions and has been used for tracing the course of underground rivers. Fluorescein also finds use in ophthalmology. A minute amount added to the eye assists the visual fitting of contact lenses under ultraviolet illumination.

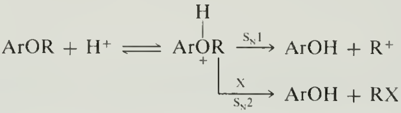
D. *Reactions of Ethers*

Aryl ethers show several important reactions not shared by phenols. These reactions include ether cleavage to phenols (the reverse of ether formation), a significant intramolecular rearrangement of aryl allyl ethers, ring metallation, and the Birch reduction.

1. **Ether Cleavage Reactions.** Aryl alkyl ethers are cleaved by acid just as are the aliphatic ethers. The most commonly used reagents are hydrobromic or hydriodic acids.

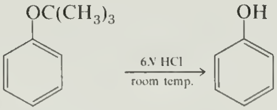


The reaction mechanism is the same as for aliphatic ethers; the protonated ether undergoes S_N1 or S_N2 cleavage. Because the phenyl group is not susceptible to either S_N1 or S_N2 reaction, cleavage of the aliphatic C—O bond always occurs.



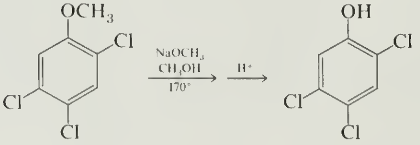
$$\mathrm{ArOR} + \mathrm{H}^+ \rightleftharpoons \mathrm{Ar}\overset{\mathrm{H}}{\underset{+}{\mathrm{O}}}\mathrm{R} \xrightarrow{S_N1} \mathrm{ArOH} + \mathrm{R}^+$$
$$\xrightarrow[S_N2]{\mathrm{X}^-} \mathrm{ArOH} + \mathrm{RX}$$

When R is a tertiary alkyl group, the ether cleavage is especially facile; cleavage occurs by the S_N1 mechanism.



phenyl *t*-butyl ether

Aliphatic ethers are stable to alkali, but aryl alkyl ethers can be cleaved by strongly basic reagents.



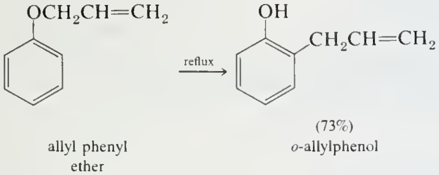
(58%)

2,4,5-trichloroanisole

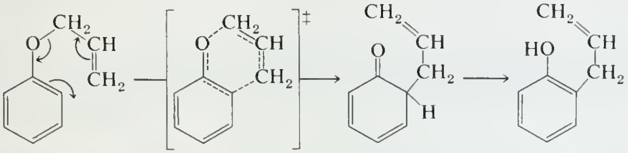
2,4,5-trichlorophenol

The reaction is an S_N2 reaction on the methyl group by methoxide ion; the other product is dimethyl ether. Because of the difference in basicity, phenoxide ions are much better leaving groups than alkoxide ions in S_N2 displacement reactions.

2. **Claisen Rearrangement.** The Claisen rearrangement is an intramolecular thermal rearrangement of aryl allyl ethers to give the corresponding allylphenol. Reaction occurs *ortho* if an *ortho* position is available. If both *ortho* positions are occupied, reaction occurs in the *para* position.



The reaction mechanism is known to involve a concerted formation of a C—C bond between the *ortho*-carbon and the terminal position of the allyl group as the C—O bond is broken.



The transition state has the six-electron aromatic conjugation characteristic of benzene. A related type of transition state was noted earlier in the Diels-Alder reaction (Section 23.4.B). An orbital description of the Claisen rearrangement transition state is shown in Figure 33.2.

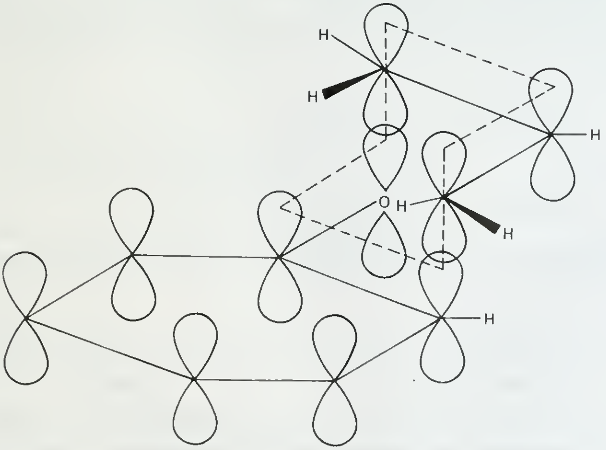
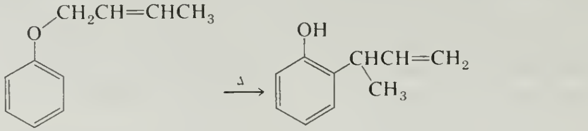


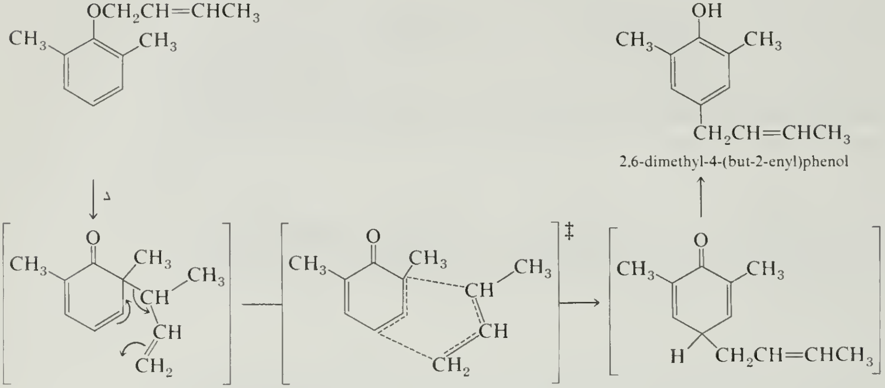
Figure 33.2 *Transition state for Claisen rearrangement. Dotted line shows the orbital interactions important in the reaction zone only.*

Note that the γ-carbon of the allyl group becomes attached to the benzene ring. The allylic rearrangement is observable with an unsymmetrical allyl group.


CH₂CH=CHCH₃
O
OH
CHCH=CH₂
CH₃
Δ

o-(α-methylallyl)phenol

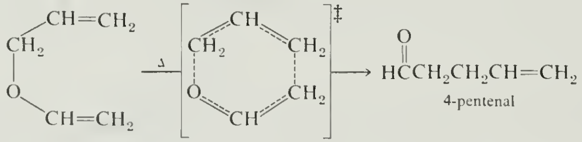
If no *ortho*-hydrogens are available, enolization to the phenol cannot occur, and a second rearrangement occurs to the *para*-position.


OCH₂CH=CHCH₃
CH₃
CH₃
Δ
O
CH₃
CH₃
CH₃
CH
CH
CH₂
O
CH₃
CH₃
CH
CH₃
CH
CH₂
‡
O
CH₃
CH₃
H
CH₂CH=CHCH₃
OH
CH₃
CH₃
CH₂CH=CHCH₃

2,6-dimethyl-4-(but-2-enyl)phenol

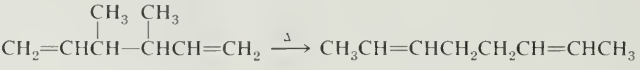
Note that two successive allylic rearrangements restore the original orientation of the allylic group. In the second rearrangement the transition state involves a six-membered ring of carbon atoms.

Both types of rearrangements have their counterparts in aliphatic systems. The rearrangement of allyl ethers of enols is another example of a Claisen rearrangement.


CH=CH₂
CH₂
O
CH=CH₂
Δ
CH
CH₂
CH₂
O
CH₂
CH
‡
O
HCCH₂CH₂CH=CH₂

4-pentenal

The all-carbon rearrangement is known as the Cope rearrangement and is a general thermal reaction of 1,5-dienes.



$$CH_2{=}CH\overset{CH_3}{\overset{|}{C}}H-\overset{CH_3}{\overset{|}{C}}HCH{=}CH_2 \xrightarrow{\Delta} CH_3CH{=}CHCH_2CH_2CH{=}CHCH_3$$

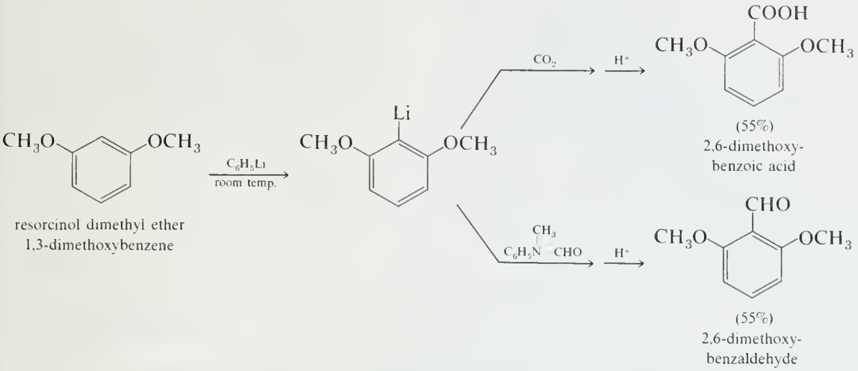
3,4-dimethyl-1,5-hexadiene 2,6-octadiene

The reaction can be observed for 1,5-hexadiene itself with deuterium labeling:

$$CD_2{=}CHCH_2CH_2CH{=}CD_2 \overset{\Delta}{\rightleftharpoons} CH_2{=}CHCD_2CD_2CH{=}CH_2$$

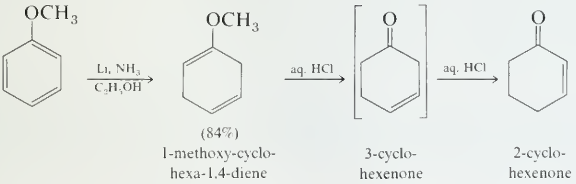
The mechanism of these **sigmatropic rearrangements** is discussed in more detail in Section 36.2.

3. **METALATION.** Resorcinol dimethyl ether is readily metalated by butyllithium or phenyllithium at the position *ortho* to both methoxy groups.


CH_3O
OCH_3
C_6H_5Li
room temp.
resorcinol dimethyl ether
1,3-dimethoxybenzene
Li
CH_3O
OCH_3
CO_2
H^+
COOH
CH_3O
OCH_3
(55%)
2,6-dimethoxy-
benzoic acid
CH_3
C_6H_5N CHO
H^+
CHO
CH_3O
OCH_3
(55%)
2,6-dimethoxy-
benzaldehyde

The electronegative oxygens provide an important electron-attracting inductive effect that makes the 2-position of 1,3-dimethoxybenzene significantly more acidic than benzene itself. Anisole itself is not metalated as readily as the di- and trimethoxybenzenes.

4. **BIRCH REDUCTION.** Anisole is reduced by lithium metal in liquid ammonia and alcohol in a reaction that was discussed previously in the reduction of aromatic hydrocarbons (Section 30.7.D) and acids (Section 31.5.D). The product is an enol ether that hydrolyzes readily (Section 15.7.B) to give 3-cyclohexenone. Under the acidic conditions, the double bond moves into conjugation with the carbonyl group (Section 20.3.A).


OCH_3
Li, NH_3
C_2H_5OH
OCH_3
(84%)
1-methoxy-cyclo-
hexa-1,4-diene
aq. HCl
O
3-cyclo-
hexenone
aq. HCl
O
2-cyclo-
hexenone

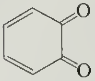
The reaction is a useful route to cyclohexane derivatives.

33.4
Quinones

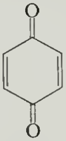
A. *Nomenclature*

Quinones are cyclohexadiendiones, but they are named as derivatives of aromatic systems: benzoquinones are derived from benzene, toluquinones from toluene, naphthoquinones from naphthalene, and so on. "Quinone" is used both as a generic term and for *p*-benzoquinone.

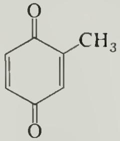
Many quinones and especially hydroxyquinones occur in nature. Some examples are



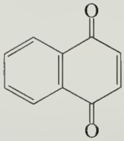
o-benzoquinone



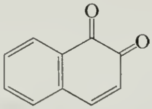
p-benzoquinone
or quinone



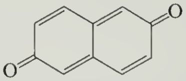
toluquinone
2-methyl-1,4-benzoquinone



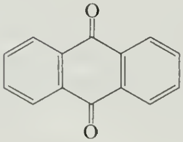
1,4-naphthoquinone



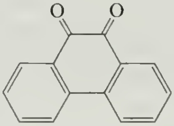
1,2-naphthoquinone



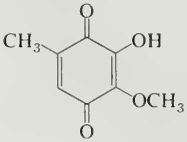
2,6-naphthoquinone



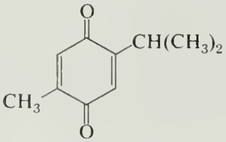
9,10-anthraquinone



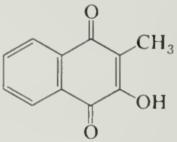
9,10-phenanthraquinone



fumigatin
(antibiotic substance)
3-hydroxy-2-methoxy-5-methyl-1,4-benzoquinone

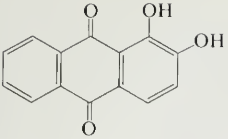


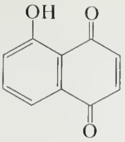
thymoquinone
(a terpene)
5-isopropyl-2-methyl-1,4-benzoquinone

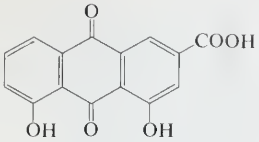


phthiocol
(antibiotic substance)
2-hydroxy-3-methyl-1,4-naphthoquinone

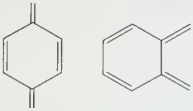
Hydroxynaphthoquinones and hydroxyanthraquinones are especially common, either free or as glycosides. Many natural pigments have quinone structures.


alizarin
(madder root)


juglone
(walnut shells)


rhein
(rhubarb)

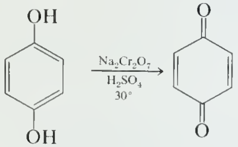
Quinone structures are frequently associated with color and the structural units



are referred to as "quinoid" structures.

B. *Preparation*

The only important method for the preparation of quinones is oxidation of aromatic hydroxy and amino compounds. Substituted phenols or aniline derivatives can be used with some oxidizing agents. For example, *p*-benzoquinone can be prepared by oxidation of benzene or aniline with a variety of oxidizing agents, but the usual laboratory preparation involves the oxidation of hydroquinone.

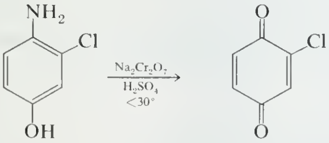


hydroquinone

(86–92%)
quinone

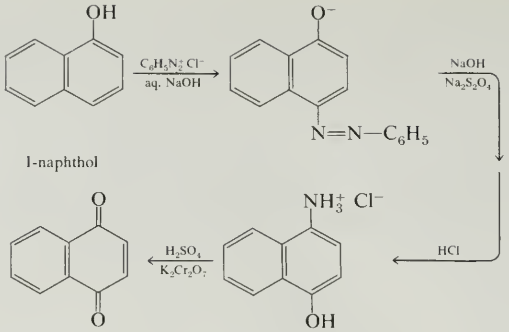
p-Benzoquinone forms yellow crystals, m.p. 115.7°, that are slightly soluble in water and can be sublimed or steam-distilled.

Aminophenols are easily oxidized to quinones, and this route constitutes one of the best methods for the preparation of some substituted quinones.



2-chloro-1,4-benzoquinone

The aminophenols can frequently be obtained by reaction of phenols with diazonium salts (Section 33.3.B under Diazonium Coupling). An example is the synthesis of naphthoquinone from 1-naphthol.

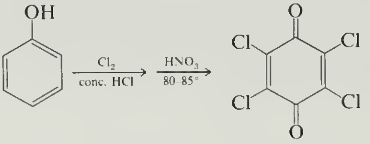

OH
$C_6H_5N_2^+Cl^-$
aq. NaOH
O^-
$N{=}N{-}C_6H_5$
NaOH
$Na_2S_2O_4$
HCl
$NH_3^+ Cl^-$
OH
H_2SO_4
$K_2Cr_2O_7$
O
O

1-naphthol

(78–81%)
1,4-naphthoquinone

4-amino-1-naphthol
hydrochloride

Other oxidizing agents which are used for the preparation of quinones are ferric ion, nitrogen tetroxide (N_2O_4), and sodium chlorate–vanadium pentoxide. Many other oxidizing agents have also been used, and the best one for any given compound must be determined by experiment. For example, the preparation indicated in (33-4) makes advantageous use of nitric acid.

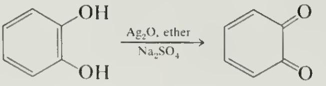

OH
Cl_2
conc. HCl
HNO_3
80–85°
O
Cl
Cl
Cl
Cl
O

(33-4)

(60%)
2,3,5,6-tetrachloro-1,4-
benzoquinone
chloranil

Chloranil is commercially available and has several uses in organic chemistry that we will encounter later (Sections 33.4.D and 34.3.B).

The oxidation of *o*-dihydroxybenzenes to *o*-quinones can be carried out with silver oxide in ether.


OH
OH
Ag_2O, ether
Na_2SO_4
O
O

(33-5)

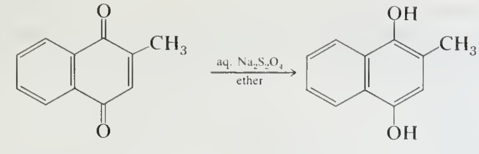
catechol

o-benzoquinone

o-Benzoquinone forms red crystals that are water sensitive; anhydrous sodium sulfate is used in the preparation (33-5) to remove the water formed in the oxidation.

C. *Reduction-Oxidation Equilibria*

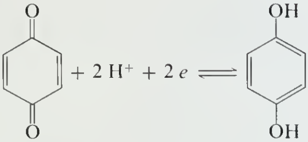
Just as 1,2- and 1,4-dihydroxybenzenes are readily oxidized to quinones, the quinones are readily reduced back to dihydroxy compounds. This reduction can be carried out chemically.



2-methyl-1,4-naphthoquinone

(95%)
2-methyl-1,4-dihydroxynaphthalene

However, the most important aspect of this redox system is that it is electrochemically reversible.



The electrical potential of this cell is given by the Nernst equation (33-6)

$$E = E_0 + \frac{2.303\ RT}{n\mathfrak{F}} \log \frac{[\text{quinone}][\text{H}^+]^2}{[\text{hydroquinone}]} \tag{33-6}$$

in which $\mathfrak{F}$ is the Faraday. At 25°, equation (33-6) may be written as (33-7), in which the electrical potential is given in volts.

$$E^{25^\circ} = E_0 - 0.059\ \text{pH} + 0.0296 \log \frac{[\text{quinone}]}{[\text{hydroquinone}]} \tag{33-7}$$

The standard potential, E_0, is that given at unit hydrogen ion concentration and equal concentrations of quinone and hydroquinone. Some values of E_0 are listed in Table 33.2. The more positive the value of the potential, the more readily the quinone is reduced. Note that electron-donating groups such as methyl and hydroxy stabilize the quinone form relative to the hydroquinone and result in lowering the reduction potential; electron-attracting groups such as halogen have the opposite effect.

TABLE 33.2
Reduction Potentials of Quinones

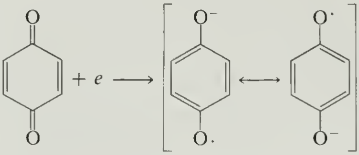
Quinone	Reduction Potential, E_0 at 25°, volts
1,4-benzoquinone	0.699
2-methyl	0.645
2-hydroxy	0.59
2-bromo	0.715
2-chloro	0.713
1,2-benzoquinone	0.78
1,4-naphthoquinone	0.47
1,2-naphthoquinone	0.56
9,10-anthraquinone	0.13
9,10-phenanthraquinone	0.44

The reduction potentials in Table 33.2 allow one to see a clear parallel between redox phenomena in organic compounds and those observed with inorganic species. Recall that oxidation corresponds to the loss of electrons, and reduction to the gain of electrons:

$$Fe^{2+} \underset{\text{reduction}}{\overset{\text{oxidation}}{\rightleftharpoons}} Fe^{3+} + e$$

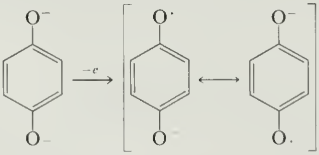
The more electron-rich a species is, the easier is its oxidation and the more difficult is its reduction. In Table 33.2, we see that the electron-attracting substituents chloro and bromo do indeed cause the quinone to be reduced more easily (more positive reduction potential). Similarly, the electron-donating substituents hydroxy and methyl cause the quinone to be reduced less easily.

The reduction of quinone occurs in two one-electron steps. The product of the first step is a radical anion that can be detected in dilute solution by the technique of electron spin resonance spectroscopy.

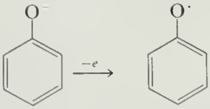


Electron spin resonance or esr is closely related to nuclear magnetic resonance. Electrons, like protons, have spin and in molecules with an odd number of electrons (radicals) the resulting net electronic spin is aligned with or against an applied magnetic field. With commercial magnets the energy difference between the two states is in the microwave region of electromagnetic radiation. The resulting esr spectra have been extremely useful not only for detecting small concentrations of radicals but the details of the spectra provide important information about the electronic structures of radicals. These details, however, are beyond the scope of an introductory textbook.

The same radical anions are produced by one-electron oxidations of hydroquinone dianions.



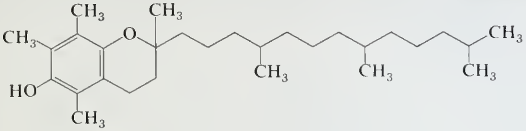
Phenols are also subject to one-electron oxidation to give the corresponding neutral radicals.



phenoxy radical

Such radicals are involved in many of the reactions of phenols including reactions of naturally occurring phenols.

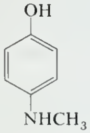
Vitamin E or α-tocopherol is a phenol that is widespread in plant materials. It appears to have several functions in animals but one important function seems to be as a radical scavenger. The corresponding phenoxy radical is less reactive and less damaging to body constituents. Free radicals have been implicated in the aging process.



α-tocophenol; vitamin E

Quinone-hydroquinone redox systems have a number of important uses. Hydroquinone itself, for example, is an important photographic developer.

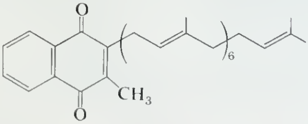
Silver bromide crystals that have become photoactivated by exposure to light are reduced by hydroquinone. The photoactivated silver bromide is reduced to black silver metal and the hydroquinone is oxidized to *p*-benzoquinone. The residual silver bromide is then removed by "hypo," sodium hyposulfite, which forms a soluble complex with silver cation. The result is a black image where the silver bromide emulsion was exposed to light. Some developer formulas include *p*-methylaminophenol, usually as the sulfate (Elon, Metol) which also oxidizes to *p*-benzoquinone.



p-methylaminophenol

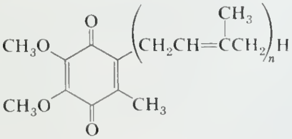
The oxidation-reduction of hydroquinone and quinone derivatives play an important role in physiological redox processes.

Vitamin K is actually many vitamins; for example, K_1, K_2, K_3, and so on. They are all related to 1,4-naphthoquinone or compounds that are oxidized to it. For example, one of the vitamin K_2s is



Others vary in the length of the side chain. The K vitamins are present in blood as coagulation factors.

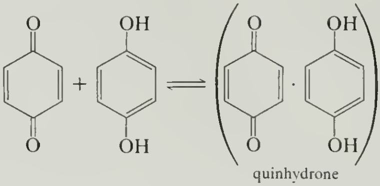
A related series of compounds is coenzyme Q, which occurs in many kinds of cells with $n = 6$, 8, or 10 ($n = 10$ in mammalian cells); indeed, when first discovered, it was called **ubiquinone** because it was so ubiquitous in cells. Coenzyme Q is involved in electron-transport systems, and the long isoprenoid chain is undoubtedly designed to promote fat solubility.



coenzyme Q

D. *Charge-Transfer Complexes*

An equimolar mixture of *p*-benzoquinone and hydroquinone forms a dark green crystalline molecular complex, "quinhydrone," having a definite melting point of 171°. This material dissolves in hot water, and the solution is largely dissociated into its components.



The buffered solution has been used as a standard reference electrode.

The structure of the crystals consists of alternating molecules of quinone and hydroquinone with the rings parallel to each other (Figure 33.3). This complex is only one example of many complexes now known as **charge-transfer** complexes. Such complexes are characterized by one component that is electron-rich (the donor) and another component that is strongly electron-attracting (the acceptor): hence, such complexes are also known as donor-acceptor complexes. In resonance language the complexes are characterized as a hybrid of two resonance structures:

$$\mathrm{D\!:\,A} \longleftrightarrow \overset{+}{\mathrm{D}}\cdot\ \overset{-}{\mathrm{A}}\cdot$$

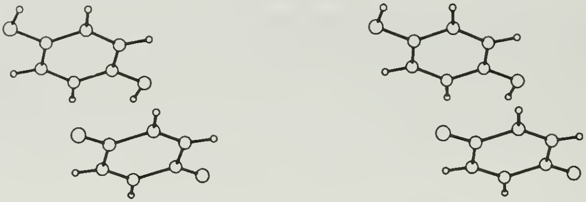


FIGURE 33.3 *Stereo diagram of quinhydrone. [Adapted with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.]*

The second structure, the "charge-transfer structure," makes only a small contribution to the total electronic structure; that is, it is this second structure that provides the bonding that holds the two components together but the bond strength involved is only a few kcal mole^{-1}.

In molecular orbital language, the donors have a filled high energy orbital in which electrons are held rather loosely; that is, this "highest occupied" molecular orbital has a low ionization potential. The acceptors have a relatively low lying vacant molecular orbital; in fact, common acceptors frequently form radical anions readily on one-electron reduction in which the electron enters this "lowest vacant" orbital. In the complex, there is some overlap of the highest occupied orbital of the donor with the lowest vacant orbital of the acceptor that results in transfer of some electron density from donor to acceptor. The amount of charge transferred is small and corresponds typically to a small fraction (≈ 0.05) of an electron. The molecular orbital approach is entirely equivalent to the resonance interpretation.

Typical donors that form charge-transfer complexes are benzene rings with electron-donating groups such as —OH, $—OCH_3$, $—N(CH_3)_2$, $—CH_3$, and so on. Common acceptors are compounds with several nitro groups, such as 1,3,5-trinitrobenzene and picric acid or quinones. Especially potent are quinones with additional electron-attracting groups; chloranil (tetrachloro-*p*-benzoquinone) is an important example. The structure of the complex formed from hexamethylbenzene and chloranil is shown in Figure 33.4; this complex has a bond strength of about 5 kcal mole^{-1}. Compounds with several CN groups are also used as acceptors. Some examples are tetracyanoethylene and 2,3-dicyano-1,4-benzoquinone.

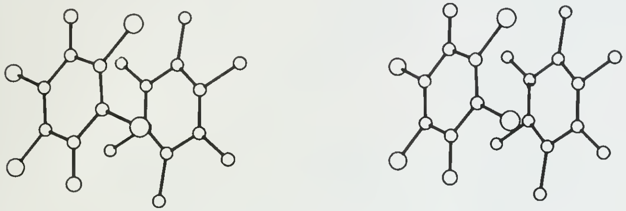
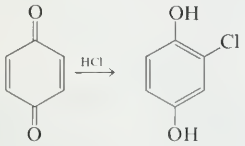


FIGURE 33.4 *Stereo diagram of hexamethylbenzene-chloranil complex. [Adapted with permission from* Molecular Structure and Dimensions. *International Union of Crystallography, 1972.]*

Charge-transfer complexes are often intensely colored. The color is associated with an electronic transition in which a substantial fraction of an electron is transferred from donor to acceptor. Charge transfer interactions are now recognized as being important in other solid state structures in which the interactions are weaker. Furthermore, many reactions and reaction mechanisms are now recognized to involve charge-transfer phenomena; however, a detailed treatment of such phenomena must be deferred to advanced organic chemistry texts.

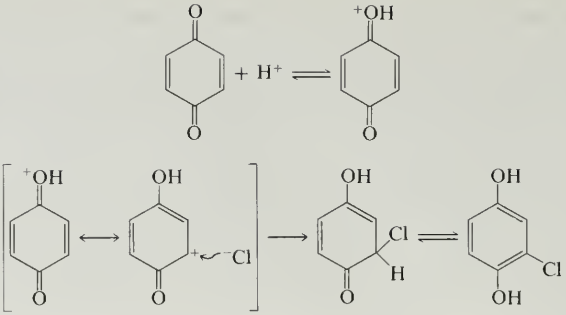
E. *Reactions of Quinones*

Quinones are α,β-unsaturated carbonyl compounds and show double bond reactions typical of such structures. One significant reaction is addition of hydrogen chloride.

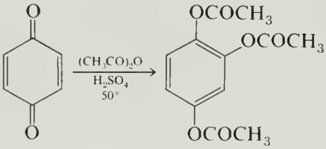


chlorohydroquinone

This reaction is simply an acid-catalyzed Michael addition (see Section 26.4.F).

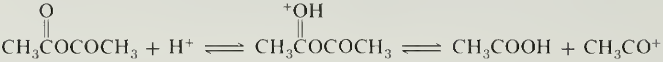


Another example involves addition of acetic acid.

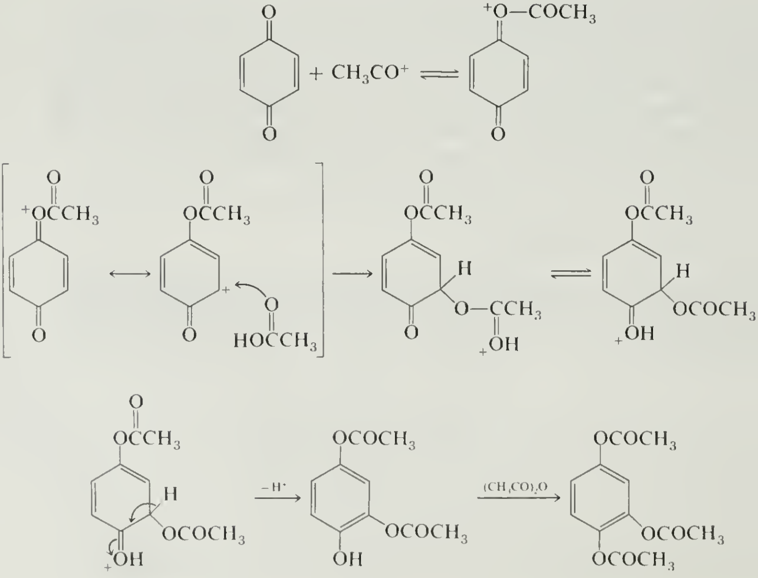

(CH₃CO)₂O
H₂SO₄
50°

(86–87%)
1,2,4-triacetoxybenzene

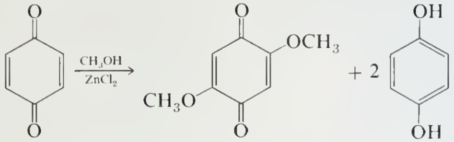
This reaction may be rationalized by the following mechanism sequence:



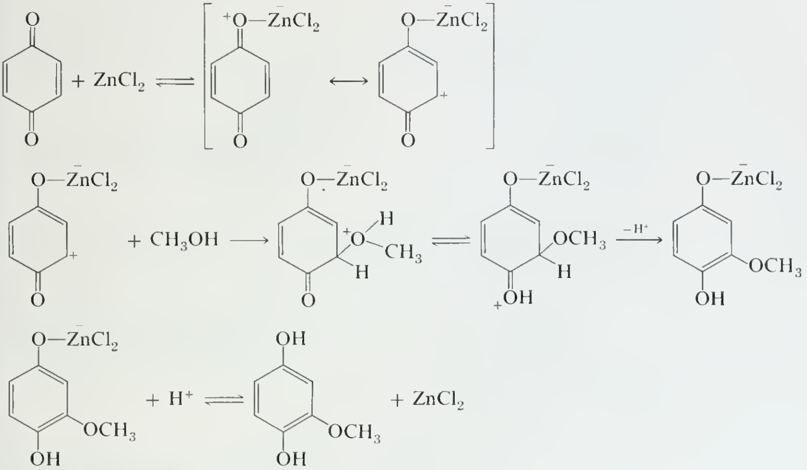
$$CH_3\overset{O}{\overset{\|}{C}}OCOCH_3 + H^+ \rightleftharpoons CH_3\overset{^+OH}{\overset{\|}{C}}OCOCH_3 \rightleftharpoons CH_3COOH + CH_3CO^+$$


+ CH₃CO⁺
HOCCH₃
−H⁺
(CH₃CO)₂O

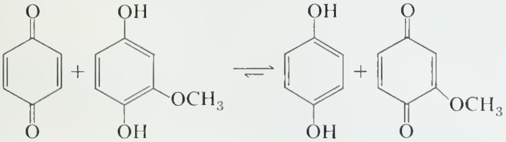
Another interesting example shows the importance of redox reactions in quinone-hydroquinone systems.



This reaction starts with a normal Lewis acid-catalyzed Michael addition.



The next step is a redox equilibrium with quinone; the presence of the methoxy group causes the equilibrium to shift to the right (Section 33.4.C).



A second Michael addition takes place with the methoxyquinone, followed by a second oxidation.

PROBLEMS

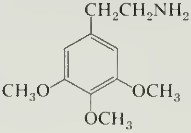
1. Write structures for each of the following names:
- (a) *m*-cresol
- (b) 3-hydroxybenzenesulfonamide
- (c) 3-chloro-1,2-benzoquinone
- (d) *o*-methoxyphenol
- (e) *p*-(*p*-tolyl)azophenol
- (f) benzyl phenyl ether
- (g) 3-(*o*-hydroxyphenyl)pentanoic acid
- (h) *p*-isobutylphenol
- (i) 2-methoxy-1,4-naphthoquinone
- (j) 2,5-dichloro-1,4-benzoquinone

2. Write the principal reaction product or products, if any, of *o*-cresol with the following reagents:
   - (a) $(CH_3O)_2SO_2$, NaOH
   - (b) $Na_2S_2O_4$
   - (c) $SnCl_2$, HCl
   - (d) $Na_2Cr_2O_7$, H_2SO_4
   - (e) $C_6H_5N_2^+$, aq. NaOH
   - (f) CH_3COOH, H_2SO_4, Δ
   - (g) aq. NH_3
   - (h) 98% H_2SO_4, 25°
   - (i) $KMnO_4$, Δ
   - (j) cold dilute HNO_3
   - (k) Br_2, H_2O
   - (l) $(CH_3CO)_2O$
   - (m) $CHCl_3$, aq. NaOH
   - (n) HONO
   - (o) $LiAlH_4$
   - (p) HNO_3 (2 moles) in CH_3COOH
   - (q) HBr, Δ
   - (r) CO_2, K_2CO_3, 240°
   - (s) Br_2 (1 mole), CCl_4

3. Write the principal reaction product or products, if any, when 2-methylanisole is subjected to the following conditions:
   - (a) $Na_2S_2O_4$
   - (b) conc. H_2SO_4
   - (c) HBr, Δ
   - (d) Br_2, CH_3COOH
   - (e) HNO_3 (2 moles) in CH_3COOH
   - (f) $LiAlH_4$
   - (g) $(CH_3CO)_2O$
   - (h) CH_3COCl, $ZnCl_2$
   - (i) phthalic anhydride, $C_6H_5NO_2$, $AlCl_3$, 0°
   - (j) Na, liquid NH_3

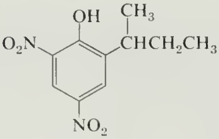
4. Each of the following phenol or quinone derivatives has the common or trivial name shown and is a compound of some significance. Provide the IUPAC name and synthesize each from the starting material given.

(a)



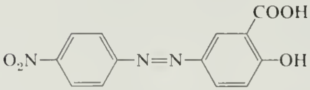
Mescaline is the active ingredient in peyote (mescal buttons) and is used as a psychotomimetic (that is, mimics psychosis) drug. Prepare from gallic acid.

(b)



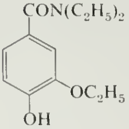
The ester of this phenol with 3-methylbut-2-enoic acid is **binapacryl**, which is used as a fungicide and mitocide. Synthesize the phenolic portion shown from phenol.

(c)



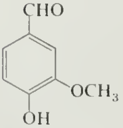
Alizarine Yellow R is used as an indicator in alkaline solutions. The color changes from yellow to red over the pH range from 10 to 12. Synthesize from aniline.

(d)



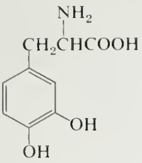
Anacardiol is a drug that acts as a stimulant on the central nervous system. Prepare from catechol.

(e)



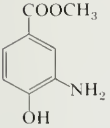
Vanillin occurs naturally in vanilla and other plant materials, and is used as a flavoring agent. Prepare from guaiacol.

(f)


NH2
CH2CHCOOH
OH
OH

Dopa having levorotation (**L-Dopa**) is found in some beans. It is used in a treatment of Parkinson's disease. Prepare the racemic compound from catechol.

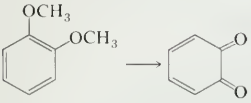
(g)


COOCH3
NH2
OH

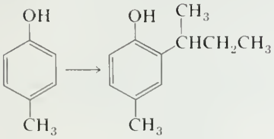
Orthocaine is used as a surface anesthetic. Prepare from phenol.

5. Accomplish each of the following conversions in a practical manner:

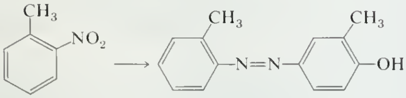
(a)


OCH3
OCH3
O
O

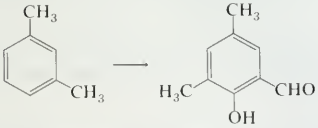
(b)


OH
CH3
OH
CH3
CHCH2CH3
CH3

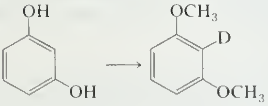
(c)


CH3
NO2
CH3
N=N
CH3
OH

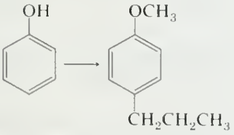
(d)


CH3
CH3
CH3
H3C
CHO
OH

(e)

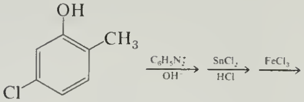

OH
OH
OCH3
D
OCH3

(f)


OH
OCH3
CH2CH2CH3

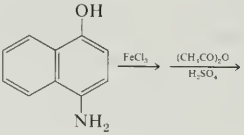
6. What is the principal organic product of each of the following sequences?

(a)

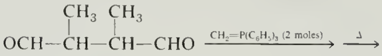


(b) $C_6H_5CH{=}CHCH_2Cl \xrightarrow{C_6H_5O^-} \xrightarrow{\Delta}$

(c)



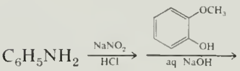
(d)



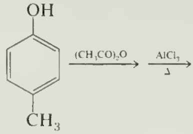
$\mathrm{OCH{-}\underset{\displaystyle CH_3}{CH}{-}\underset{\displaystyle CH_3}{CH}{-}CHO} \xrightarrow{CH_2{=}P(C_6H_5)_3\ (2\ \text{moles})} \xrightarrow{\Delta}$

(e) $(CH_3)_2C{=}CHCH_2OCH{=}CH_2 \xrightarrow{\Delta} \xrightarrow{CH_2{=}P(C_6H_5)_3} \xrightarrow{\Delta}$

(f)



(g)



7. 2,6-Dichlorophenol is present in some ticks and is thought to be a sex pheromone. Devise a practical synthesis from phenol.

8. In Table 29.4, the relative rates of protodedeuteration of *o*-, *m*-, and *p*-anisole-*d* are summarized. Show how each of these deuterated anisoles can be prepared uncontaminated by the other isomers.

9. Another component of urushiol, the active constituent of the irritating oil of poison ivy, is 3-pentadecyl-1,2-dihydroxybenzene. Synthesize this compound from catechol (be careful in handling the product!).

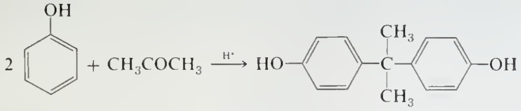
10. The reaction of *p*-benzoquinone with hydrogen chloride gives monochlorohydroquinone, whereas the reaction with methanol and $ZnCl_2$ gives dimethoxyhydroquinone (Section 33.4.E). Explain.

11. When *n*-butyl benzenesulfonate is heated with an ethanolic solution of potassium benzyloxide, the product is a mixture of *n*-butyl ethyl ether and *n*-butyl benzyl ether. However, if the isomeric salt, potassium *p*-methylphenolate, is used, the product is almost exclusively *n*-butyl *p*-methylphenyl ether. Explain.

12. *p*-Benzoquinone reacts with aniline to give 2,5-bis-(phenylamino)-1,4-benzoquinone. Write a reasonable reaction mechanism, showing all intermediates involved.

13. Acetanilide is oxidized in the body by oxygen and a hydroxylase enzyme to *p*-hydroxyacetanilide. Show how this compound can be synthesized from phenol.

14. 2,2-Bis-(*p*-hydroxyphenyl)propane or "Bisphenol A", used commercially in the manufacture of epoxy resins and as a fungicide, is prepared by the reaction of phenol with acetone in acid.



Bisphenol A

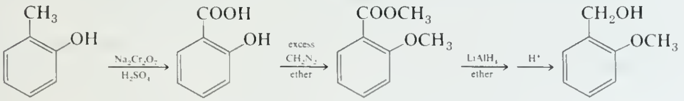
Write out the mechanism of this reaction, showing all intermediates involved.

15. The sulfonation of *p*-cymene (1-methyl-4-isopropylbenzene) gives the 2-sulfonic acid. Is this the expected orientation? Explain. Use this fact to synthesize carvacrol, 2-methyl-5-isopropylphenol, from *p*-cymene. Carvacrol is found in the essential oils from thyme, marjoram, and summer savory. It has a pleasant thymol-like odor.

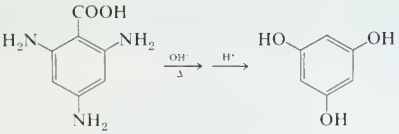
16. 4-Hexylresorcinol is used medicinally as an antiseptic. Suggest a practical synthesis from resorcinol.

17. Rank in order of increasing acidity:
(a) phenol, 3-acetylphenol, 4-acetylphenol
(b) *p*-dimethylaminomethylphenol, *p*-dimethylaminophenol, trimethyl-(*p*-hydroxyphenyl)ammonium ion
(c) 2-hydroxy-1,4-benzoquinone, 2,5-dimethoxyphenol, 4-hydroxy-1,2-benzoquinone

18. A student attempted the following synthesis of *o*-methoxybenzyl alcohol from *o*-cresol, but got essentially no yield. What went wrong?



19. Hydrolysis of 2,4,6-triaminobenzoic acid by refluxing with dilute NaOH gives phloroglucinol.



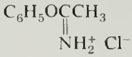
Write a reasonable mechanism for this reaction (*Hint:* the reaction involves the nonaromatic keto forms).

20. Plot the pK_as of the substituted phenols against the corresponding σ values and determine ρ. Why is ρ greater than that for the pK_as of benzoic acids? Compare this value of ρ with that for the pK_a of anilinium ions. Which substituents deviate most seriously from the σρ correlation? Explain briefly using resonance structures where desirable.

21. Calculate the pH of a 0.1 *M* solution of phenol in water. What is the pH of a solution containing 0.1 *M* phenol and 0.1 *M* sodium phenolate?

22. *o*-Phenylazophenol is readily separable from the *para* isomer by steam distillation. Give a reasonable explanation for the greater volatility of the *ortho* isomer. Can this explanation also be used to explain the greater volatility of *o*-hydroxypropiophenone compared to the *para* isomer?

23. Write out the mechanism of both steps involved in the Hoesch reaction of phloroglucinol with acetonitrile, shown in Section 33.3.C under Friedel-Crafts Acylations. The corresponding reaction of phenol gives mostly the iminoether hydrochloride,



$$C_6H_5OC(=NH_2^+)CH_3 \; Cl^-$$

Write out the mechanism for the formation of this product. How do you account for the difference between these two cases?

24. (a) Write out a reasonable mechanism for the sulfuric acid catalyzed condensation of phenol with phthalic acid. Be sure to show all intermediates.
(b) Phenol does not form diphenyl ether with sulfuric acid, yet the condensation of resorcinol with phthalic anhydride to give fluorescein includes the formation of an ether link from two phenolic hydroxy groups. Give a reasonable explanation.

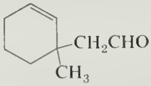
25. Equimolar mixtures of *p*-benzoquinone with hydroquinone and of 2-chloro-1,4-benzoquinone with chlorohydroquinone in the same buffer solution are contained in separate beakers. The beakers are connected by a salt bridge and the potential difference between them is measured. What is this potential difference? Which beaker constitutes the negative end (cathode) of this battery?

26. Allyl chloride labeled with ^{14}C is allowed to react with the anion from 2-methyl-6-allylphenol to form the corresponding ether. When this ether is heated, the Claisen rearrangement product, 2-methyl-4,6-diallylphenol, is formed. More than half, but not all, of the ^{14}C is found in the allyl group in the 4-position. Explain.

27. Vinyl ethers are readily available by an alcohol exchange reaction using commercially available ethyl vinyl ether.

$$ROH + C_2H_5OCH{=}CH_2 \xrightarrow{Hg^{2+}} ROCH{=}CH_2 + C_2H_5OH$$

(a) Write a mechanism that accounts for the mercuric ion catalysis (*Hint:* the Hg^{2+} first adds to the enol ether to give a mercuricarbonium ion).
(b) If ROH is an allyl alcohol, the resulting allyl vinyl ether can undergo the Claisen rearrangement. Show how this sequence may be used in a synthesis of (1-methyl-2-cyclohexenyl)acetaldehyde,



28. Tri-*o*-cresyl phosphate, $(o\text{-}CH_3C_6H_4O)_3PO$, is used as a gasoline additive. Suggest a preparation.

CHAPTER 34

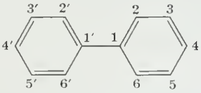
Polycyclic Aromatic Hydrocarbons

34.1

Nomenclature

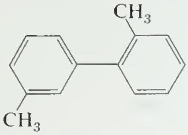
Polycyclic aromatic hydrocarbons may be dissected into two broad classes: the biaryls and the condensed benzenoid hydrocarbons. The latter class is by far the larger and more important group.

The biaryls are benzenoid compounds in which two rings are linked together by a single bond. The parent system of this class is biphenyl. In numbering the ring positions, the rings are considered to be joined at the 1-position, and the two rings are distinguished by the use of primes.



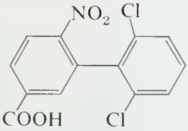
biphenyl

Simple derivatives can be named by use of *ortho*, *meta*, *para* nomenclature.



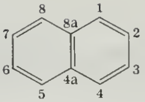
o,*m*′-dimethylbiphenyl

More complex compounds are named using numbers. Again, substituents in one ring are designated by the use of primes.

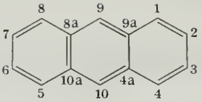


2′,6′-dichloro-6-nitrobiphenyl-3-carboxylic acid

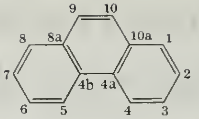
The condensed benzenoid compounds are characterized by two or more benzene rings **fused** or superimposed together at *ortho* positions in such a way that each pair of rings share two carbons. The simplest members of this group are naphthalene, with two rings, and anthracene and phenanthrene, with three rings. In the IUPAC systematic names, all carbons that may bear a substituent are numbered. Carbons that are part of a ring junction are denoted by a lower case a or b following the number of the immediately preceeding carbon. The numbering systems for naphthalene, anthracene, and phenanthrene are



naphthalene

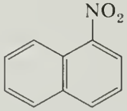


anthracene

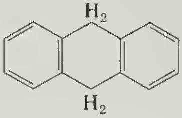


phenanthrene

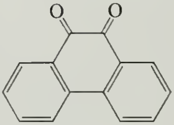
Derivatives are named using these numbering systems.



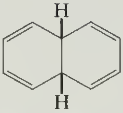
1-nitronaphthalene



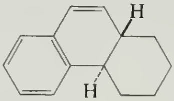
9,10-dihydroanthracene



9,10-phenanthraquinone



cis-4a,8a-dihydro-
naphthalene



trans-1,2,3,4,4a,10a-
hexahydrophenanthrene

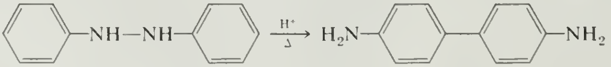
34.2
Biphenyl

A. Synthesis

Biphenyl is prepared commercially by the pyrolysis of benzene.

$$2\,C_6H_6 \xrightarrow{\Delta} C_6H_5{-}C_6H_5 + H_2$$

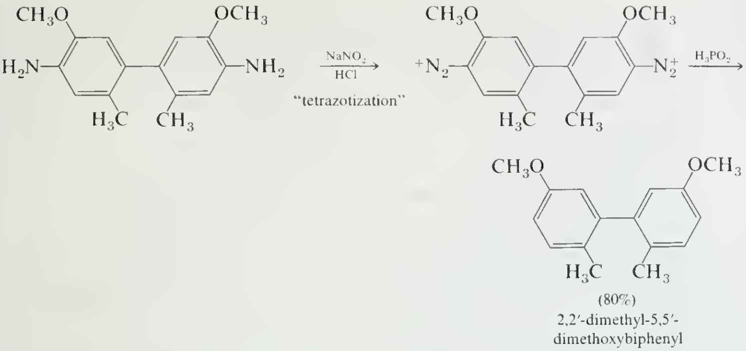
It is a colorless crystalline solid with a melting point of 70°. Substituted biphenyls are prepared by electrophilic aromatic substitution reactions on the parent hydrocarbon (Section 34.2.C) or from benzene derivatives using reactions we have already studied. One of the most useful methods is the benzidine rearrangement (Section 32.1.C).



hydrazobenzene

benzidine

The amino groups in benzidine can be converted to many other functional groups via the bis-diazonium salt.



The Ullmann reaction (Section 30.3.B) is useful for the preparation of some symmetrically substituted biphenyls, whereas the Gomberg-Bachmann reaction (Section 32.3.F) is suitable for the preparation of unsymmetrical biphenyls.

B. Structure

In the crystal, both benzene rings of biphenyl lie in the same plane. However, in solution and in the vapor phase, the two rings are twisted with respect to each other by an angle of about 45° (Figure 34.1). This twisting is the result of steric interactions between the 2,2′ and 6,6′ pairs of hydrogens (Figure 34.2). The magnitude of these repulsions is relatively small, only a few kilocalories per mole, and in the crystal is less than the stabilization obtained by stacking biphenyls together in coplanar arrays. Of course, these crystal packing forces do not exist in the vapor phase, and the twisting of the rings causes greater separation of the hydrogens.

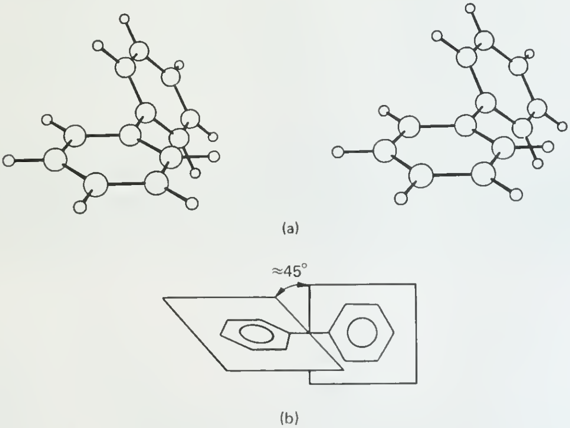


FIGURE 34.1 *Structure of biphenyl in the solution or vapor phase:* (a) *stereo representation;* (b) *perspective diagram.*

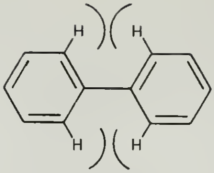


FIGURE 34.2 *Steric interactions between* ortho-*hydrogens in biphenyl.*

These repulsion effects are enhanced by *ortho* substituents larger than hydrogen. When the groups are sufficiently large, rotation of the phenyl rings with respect to each other is hindered or prevented. For example, 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid can be resolved into its enantiomers and each enantiomer is stable indefinitely (Figure 34.3). The nitro and carboxylic acid groups are so bulky that they cannot pass by each other, and rotation about the bond joining the two rings is prevented.

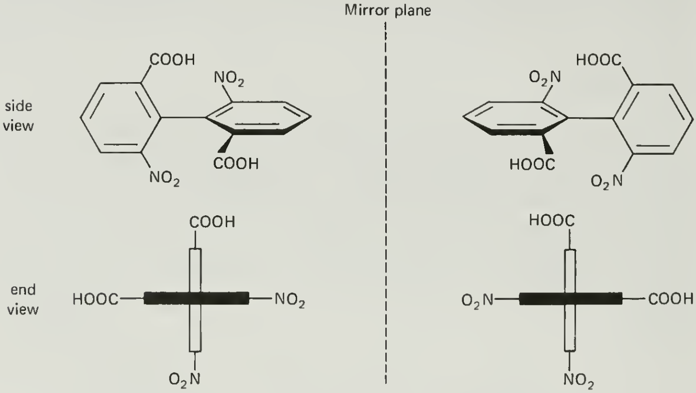
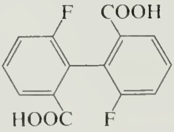


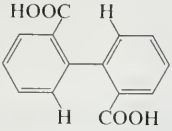
FIGURE 34.3 *Enantiomers of 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid.*

If the bulky nitro groups are replaced by the smaller fluorine atoms, the resulting compound, 6,6′-difluorobiphenyl-2,2′-dicarboxylic acid, can still be obtained in optically active form. However, the compound racemizes readily; that is, the enantiomers are readily interconverted. The racemization process involves squeezing the fluorines past the adjacent COOH groups via a planar transition state.



6,6′-difluorobiphenyl-2,2′-dicarboxylic acid

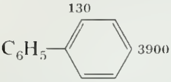
This transition state is congested and requires bending bonds. The process takes energy and is measurably slow. On the other hand, all attempts to resolve iphenyl-2,2′-dicarboxylic acid (diphenic acid) have failed. The process of slipping small hydrogen past the carboxylic acid group is so facile that racemization f enantiomers occurs rapidly.



diphenic acid

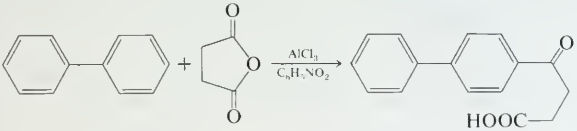
C. *Reactions*

Biphenyl undergoes electrophilic aromatic substitution more readily than enzene; a phenyl substituent is activating and is an *ortho,para* director (see hapter 29, problem 8, page 887). Nitration in acetic anhydride solution gives rimarily 2-nitrobiphenyl, but most other substitution reactions give primarily *ara* orientation. Bromination, for example, gives almost wholly 4-bromobiphenyl, nd excess reagent leads readily to 4,4′-dibromobiphenyl. Typical partial rate actors are



for Br_2 in 50% aqueous acetic acid

riedel-Crafts acylation with acetyl chloride and $AlCl_3$ yields 4-acetyl and ,4′-diacetylbiphenyl depending on the conditions. Reaction with succinic anhyride is another example.

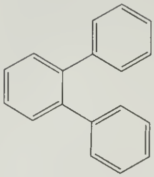


(70–90%)
4-oxo-4-(4-biphenylyl)butanoic acid

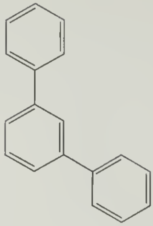
In general, 4-substituted and 4,4′-disubstituted biphenyls can often be prepared y way of electrophilic substitution reactions of biphenyl. Other derivatives are onstructed from benzene compounds by way of the syntheses described in Section 4.2.A.

D. *Related Compounds*

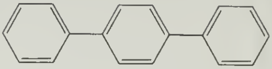
The terphenyls have three benzene rings linked together. All three possible somers, *ortho*, *meta*, and *para*, are known. Note how the higher symmetry of he *para* isomer confers a much higher melting point.



o-terphenyl
m.p. 57°



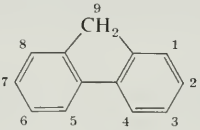
m-terphenyl
m.p. 87°



p-terphenyl
m.p. 171°

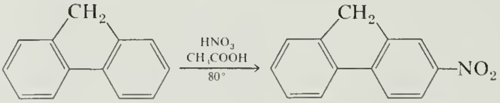
Many of the higher polyphenyls are known, especially for the *para* isomers. *p*-Quaterphenyl has four phenyl groups linked and melts at 320°. These compounds are generally such insoluble materials that they are difficult to work with.

Fluorene is a biphenyl in which two *ortho* positions are linked by a methylene group. It is obtained commercially from coal tar.



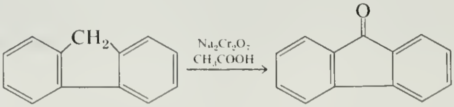
fluorene

The 2- and 7-positions correspond to the *para* positions of biphenyl and are, accordingly, the most reactive positions in electrophilic aromatic substitution reactions. Most such substitutions on fluorene give predominantly the 2-substituted or 2,7-disubstituted compounds, for example



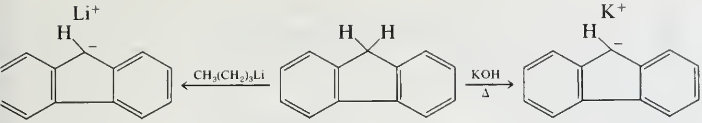
(79%)
2-nitrofluorene

The methylene group is an important center for other reactions. Oxidation gives the corresponding yellow ketone, fluorenone.



fluorenone

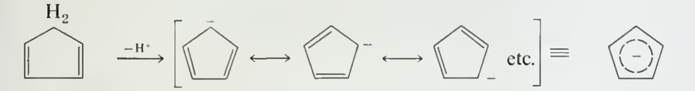
One of the especially interesting aspects of the chemistry of fluorene is its relatively high acidity. The pK_a value of 23 puts the methylene group of this hydrocarbon in the same range as ketones and esters. Alkali metal salts can be prepared by melting with potassium hydroxide or by treatment with butyllithium.



9-fluorenyllithium 9-fluorenylpotassium

The reason for this remarkably high acidity is related to the central five-membered ring structure. Cyclopentadiene is a highly acidic hydrocarbon with a pK_a of 16—an acidity comparable to that of water and alcohols. Cyclopentadienyl anion is a cyclic conjugated system with six π electrons, just as benzene.

The molecular orbitals of cyclopentadienyl anion have nodal character similar to those of benzene and resemble those shown in Figure 21.3 in energy. The six π electrons form a filled shell just as in the case of all cyclic π systems having $4n + 2$ electrons.

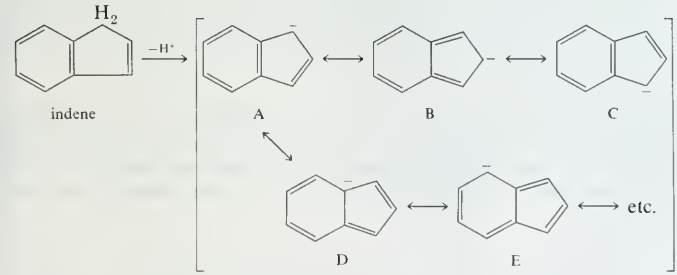


cyclopentadiene

cyclopentadienyl anion

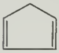
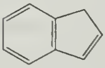
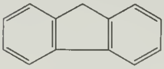
The resulting "aromatic" character of this electronic system stabilizes the anion relative to the hydrocarbon. The anion is less basic and the hydrocarbon is more acidic than would be expected in the absence of such stabilization. (See also Section 36.1).

If one or both double bonds in cyclopentadiene are replaced by benzene rings, the corresponding anion has reduced stability relative to its conjugate acid because the delocalization of negative charge disrupts the benzene conjugation.



Indene, unlike cyclopentadiene, has a benzene ring. Structures A and C of indenyl anion also have benzene rings, but the other structures, B, D, E, and so on, have no benzene rings and are expected to be much less stable. The same principles apply to fluorene and fluorenyl anion. The corresponding pK_a values are summarized in Table 34.1 and compared with several other hydrocarbons for reference.

TABLE 34.1
Acidities of Some Hydrocarbons

Formula	Name	pK_a
	cyclopentadiene	16
	indene	20
	fluorene	23
$(C_6H_5)_3CH$		31.5
$(C_6H_5)_2CH_2$		34
$C_6H_5CH_3$		41

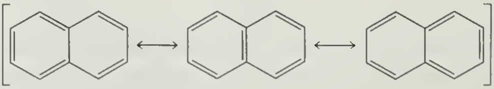
34.3 Naphthalene

A. *Structure and Occurrence*

Naphthalene is a colorless crystalline hydrocarbon, m.p. 80°. It sublimes readily and is isolated in quantity from coal tar.

Coal tar is obtained from the conversion of bituminous coal to coke. The coal is heated in the absence of oxygen, giving gas and a distillate boiling over a wide range. The low boiling range contains benzene, toluene, and xylenes. A fraction boiling at 195–230°, called naphthalene oil, yields crude naphthalene on cooling. The higher boiling coal tar is a black odiferous complex mixture containing many polycyclic hydrocarbons and heterocyclic compounds.

Naphthalene is the parent hydrocarbon of the series of fused benzene polycyclic structures. X-ray analysis shows it to have the structure shown in Figure 34.4. The bonds are not all of the same length but are close to the benzene value of 1.397 Å. Naphthalene can be considered to be resonance hybrid of three structures:



Accordingly, it has an empirical resonance energy of about 60 kcal mole^{-1}, a value somewhat greater than that of benzene (Section 21.1.B).

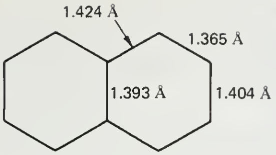
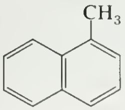
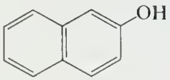

1.424 Å
1.365 Å
1.393 Å
1.404 Å

FIGURE 34.4 *Structure of naphthalene.*

Substituted naphthalenes are named using the numbering system given in Section 34.1. Monosubstituted naphthalenes are often named using α and β nomenclature for the 1- and 2-positions, respectively, for example



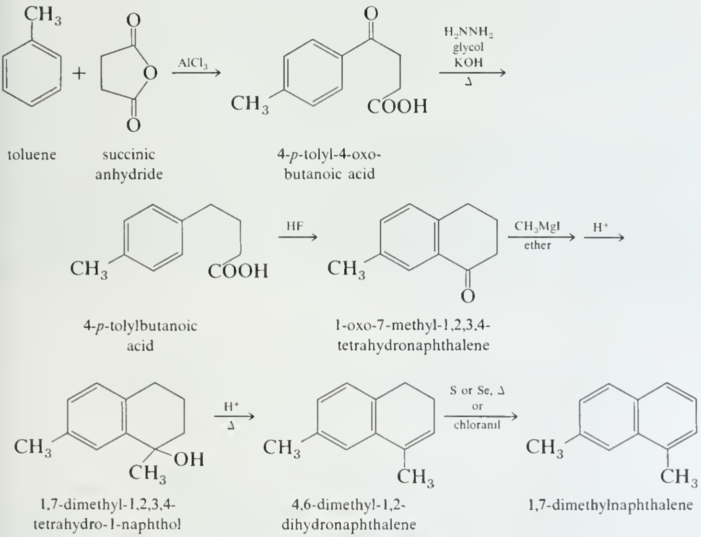
α-methylnaphthalene
1-methylnaphthalene



β-naphthol
2-naphthol

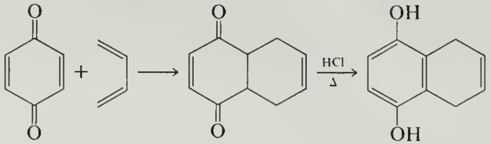
B. *Synthesis*

The naphthalene ring system can be prepared from suitable benzene derivatives. The following sequence is an example:


CH_3
+
O
O
O
$AlCl_3$
O
CH_3
COOH
H_2NNH_2
glycol
KOH
Δ
toluene
succinic anhydride
4-*p*-tolyl-4-oxobutanoic acid
CH_3
COOH
HF
CH_3
O
CH_3MgI
ether
H^+
4-*p*-tolylbutanoic acid
1-oxo-7-methyl-1,2,3,4-tetrahydronaphthalene
CH_3
OH
CH_3
H^+
Δ
CH_3
CH_3
S or Se, Δ
or
chloranil
CH_3
CH_3
1,7-dimethyl-1,2,3,4-tetrahydro-1-naphthol
4,6-dimethyl-1,2-dihydronaphthalene
1,7-dimethylnaphthalene

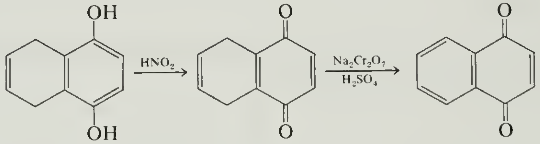
The use of sulfur or selenium for dehydrogenation was discussed previously (Section 30.6.D). Reactive quinones such as tetrachloro-*p*-benzoquinone (chloranil) (Section 33.4.B) are frequently useful for the same purpose. Note that the preceding reaction sequence is subject to wide variation for the synthesis of many naphthalene hydrocarbons. It is less useful for the introduction of functional groups because of the sensitivity of most groups to several of the reactions involved.

Another important way of building up the second ring makes use of the Diels-Alder reaction (Section 23.4.B). *p*-Benzoquinone is an excellent dienophile and reacts with a wide range of conjugated dienes.



(88%)

The product is a dihydroxydihydronaphthalene which can be converted in good yield to 1,4-naphthoquinone.

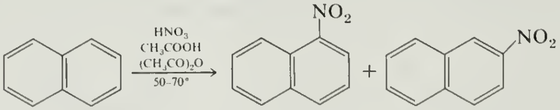


(91–97%)

(88%)
1,4-naphthoquinone

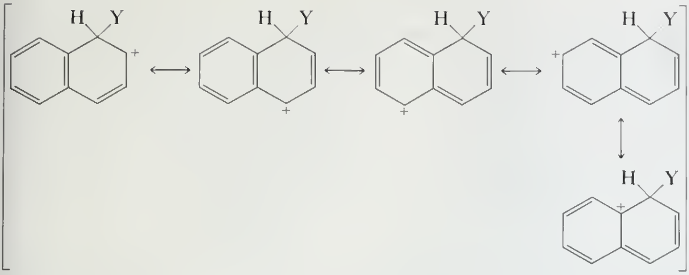
C. *Reactions of Naphthalene*

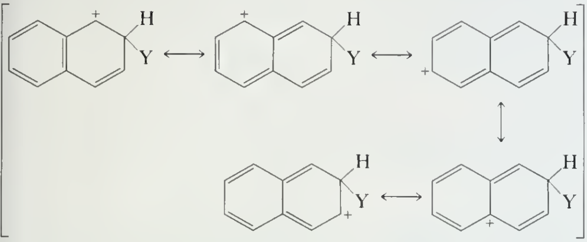
1. Electrophilic Substitution. Naphthalene undergoes a number of the usual electrophilic aromatic substitution reactions such as nitration, halogenation, sulfonation, and Friedel-Crafts acylation. The 1-position is the more reactive, for example



10:1
1-nitronaphthalene 2-nitronaphthalene

The reason for the generally greater reactivity of the 1-position can be seen by examination of the resonance structures for the two transition states or the intermediates resulting from them.

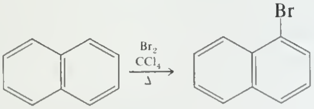




In both cases the positive charge can be distributed to five different positions, but these carbonium ion structures are not equivalent in energy. In the *α* case the first two structures still have an intact benzene ring and are, consequently, much more stable than the remaining three structures. The first two structures contribute much more to the overall resonance hybrid. In the *β* case, however, only the first structure has an intact benzene ring; the resulting resonance hybrid has higher energy than in the *α* case.

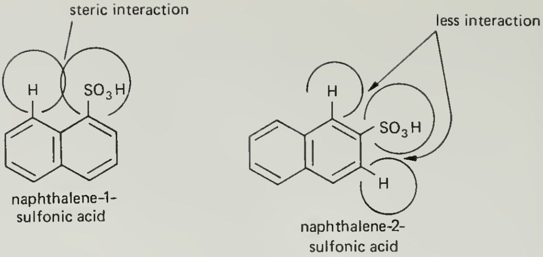
In the nitration reaction, the small amount of 2-nitronaphthalene formed is readily removed by recrystallization; hence, the nitration reaction is a satisfactory route to 1-nitronaphthalene. More vigorous nitration conditions give mixtures of 1,5- and 1,8-dinitronaphthalenes. Since the nitro group is a deactivating group, the second nitro group enters the other ring.

Bromination is also an excellent reaction and gives substantially pure 1-bromonaphthalene.

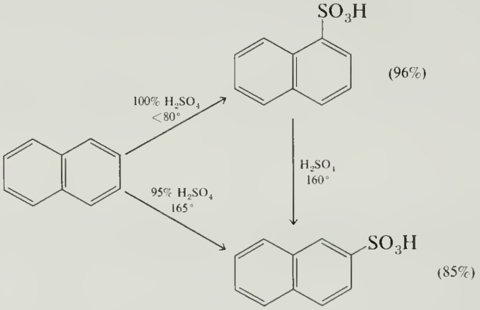


(72–75%)
1-bromonaphthalene

Sulfonation under mild conditions gives the 1-sulfonic acid. However, at higher temperature naphthalene-2-sulfonic acid results. This pattern is the same phenomenon of kinetic versus thermodynamic control which we have seen previously for sulfonations (Section 31.6.A). The 1-position is the more reactive but 1-naphthalenesulfonic acid is more hindered and less stable than the 2-acid because the

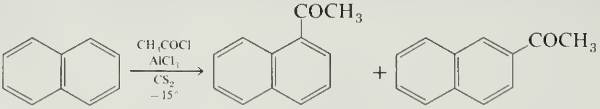

steric interaction
H
SO_3H
naphthalene-1-sulfonic acid
less interaction
H
SO_3H
H
naphthalene-2-sulfonic acid

bulky sulfonic acid group is within the van der Waals radius of the 8-hydrogen. Under conditions where the sulfonation reaction is reversible, the 2-acid is the dominant product.

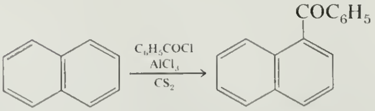

SO_3H
(96%)
100% H_2SO_4
<80°
H_2SO_4
160°
95% H_2SO_4
165°
SO_3H
(85%)

More vigorous sulfonation conditions give di- and trisulfonic acids whose structures are highly dependent on the precise reaction conditions. Several such reaction conditions have been worked out in detail to lead primarily to individual isomers for the preparation of several naphthalenedisulfonic acids which are useful intermediates for the preparation of dyes.

Friedel-Crafts acylation reactions also frequently give mixtures. In general, use of $AlCl_3$ with CS_2 as solvent gives predominantly the α product but purification from the β product also produced can be difficult or impractical.

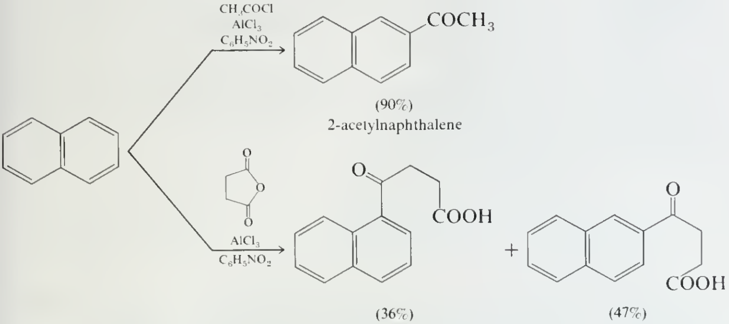

$COCH_3$
CH_3COCl
$AlCl_3$
CS_2
−15°
+
$COCH_3$

3 : 1
difficult to separate


COC_6H_5
C_6H_5COCl
$AlCl_3$
CS_2

(81%)
1-benzoylnaphthalene

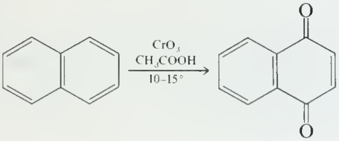
Use of nitrobenzene as solvent generally leads to the β isomer. These generalizations are only approximate. The reaction products depend on the reaction conditions and the concentrations of reagents. These reactions are not simple, and the nature of the rate-determining step can differ for α and β reaction. Some useful specific examples are


CH_3COCl
$AlCl_3$
$C_6H_5NO_2$
$COCH_3$
$AlCl_3$
$C_6H_5NO_2$
O
O
O
COOH
O
COOH

(90%)
2-acetylnaphthalene

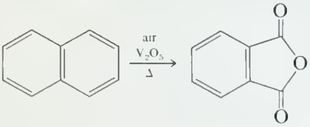
(36%) (47%)
can be separated by crystallization

2. Oxidation. Under many oxidation conditions, naphthalene is oxidized to 1,4-naphthoquinone, but the yields are frequently rather poor.


CrO_3
CH_3COOH
10–15°
O
O

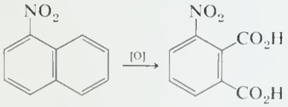
(18–22%)

More vigorous oxidation results in loss of one ring and constitutes one commercial preparation of phthalic anhydride.

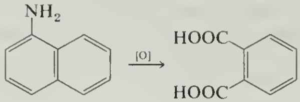

air
V_2O_5
Δ
O
O
O

phthalic anhydride

When a substituted naphthalene is oxidized, either ring may be destroyed depending on the substituent present. For example


NO_2
[O]
NO_2
CO_2H
CO_2H

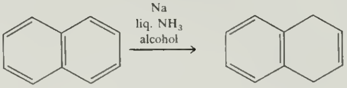
1-nitronaphthalene 3-nitrophthalic acid



1-aminonaphthalene phthalic acid

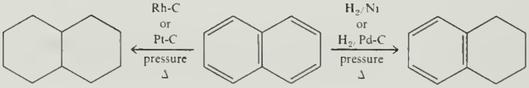
Here again, we see a connection between electron density and the ease of oxidation (see page 1026). In both compounds it is the more electron-rich ring that is oxidized.

3. **Reduction.** The Birch reduction (Section 30.7.D) of naphthalene yields 1,4-dihydronaphthalene. Note that in this product an isolated double bond is produced that does not reduce further.



1,4-dihydronaphthalene

Catalytic hydrogenation gives either 1,2,3,4-tetrahydronaphthalene (tetralin) or decahydronaphthalene (decalin) depending on catalyst or conditions.

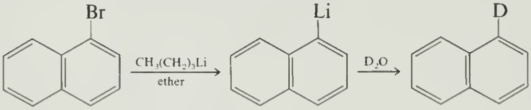


decalin tetralin

Decalin exists as *cis* and *trans* isomers (Section 23.8). The *cis* isomer is the predominant product of complete hydrogenation. Tetralin and the decalins are liquids that find some use as solvents.

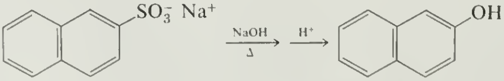
D. *Substituted Naphthalenes*

Functional groups on a naphthalene ring behave more or less as their benzenoid analogs. For example, nitro groups can be reduced to amines and bromides can be converted to Grignard or lithium reagents.



naphthalene-1-*d*

An especially useful reaction is the fusion of the sulfonic acids with sodium or potassium hydroxide.

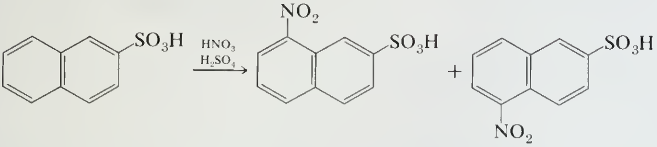


2-naphthol

Since both naphthalenesulfonic acids are available by sulfonation under different conditions (Section 34.3.C under Electrophilic Substitution) this reaction provides a route to either α-naphthol or β-naphtol.

In the further electrophilic substitution reactions of monosubstituted naphthalenes some simple generalizations can be made:

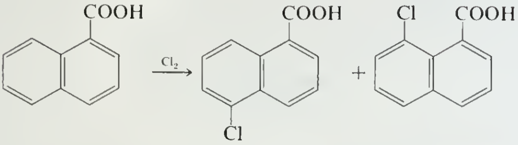
1. *Meta* directing substituents in either the 1- or 2-positions generally direct to the 5- and 8-positions, the α-positions of the other ring. Examples:


SO3H
HNO3
H2SO4
NO2
SO3H
+
SO3H
NO2

2-naphthalenesulfonic acid

8-nitronaphthalene-2-sulfonic acid

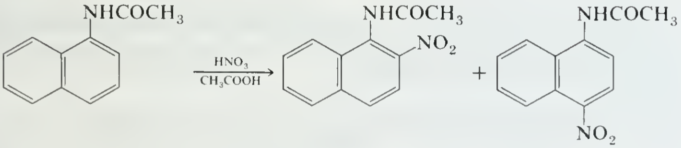
5-nitronaphthalene-2-sulfonic acid


COOH
Cl2
COOH
Cl
+
Cl
COOH

5-chloro-1-naphthoic acid

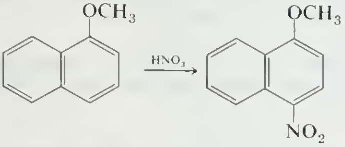
8-chloro-1-naphthoic acid

2. *Ortho,para* directing groups in the 1-position direct principally to the 4-position, but also occasionally to the 2-position as well. Examples:


NHCOCH3
HNO3
CH3COOH
NHCOCH3
NO2
+
NHCOCH3
NO2

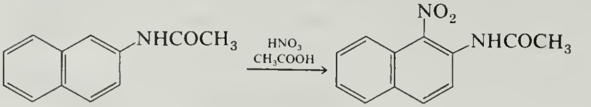
2-nitro-1-acetylaminonaphthalene

4-nitro-1-acetylaminonaphthalene

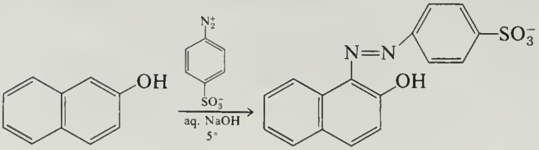

OCH3
HNO3
OCH3
NO2

4-nitro-1-methoxynaphthalene

3. *Ortho,para* directors in the 2-position generally direct to the 1-position. Examples:

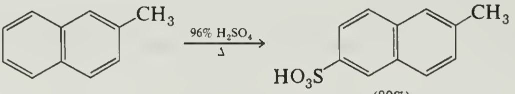

NHCOCH3
HNO3
CH3COOH
NO2
NHCOCH3

(plus some 5- and 8-nitro)

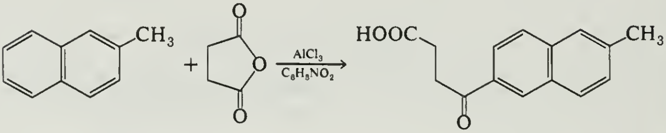

OH
N2+
SO3-
aq. NaOH
5°
N=N
SO3-
OH

Orange II

Exceptions to these generalizations are not uncommon, especially in Friedel-Crafts acylations and sulfonation.

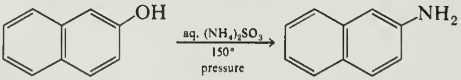

CH3
96% H2SO4
Δ
CH3
HO3S

(80%)
6-methylnaphthalene-2-sulfonic acid


CH3
+
O
O
O
AlCl3
C6H5NO2
HOOC
CH3
O

(60–79%)

One of the important reactions in naphthalene chemistry, the **Bucherer** reaction, involves the interconversion of naphthols and aminonaphthalenes and does not apply generally in benzene chemistry.

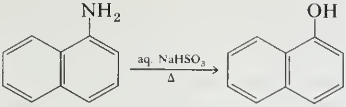

OH
aq. (NH4)2SO3
150°
pressure
NH2

2-naphthol 2-aminonaphthalene

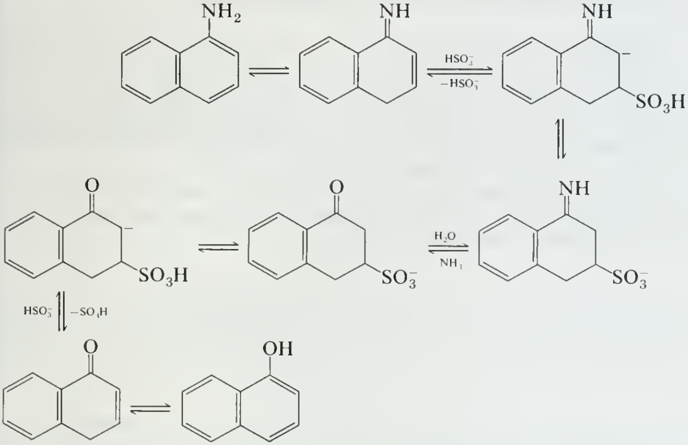
2-Naphthol is readily available from 2-naphthalenesulfonic acid; hence, the Bucherer reaction provides a simple route to 2-aminonaphthalene, which, in turn, can be converted to many other functions via the diazonium ion.

2-Naphthylamine is a powdery solid that at one time was widely used as an important intermediate in dye chemistry. This amine is carcinogenic and now sees only limited industrial use.

The reaction is reversible and also provides a hydrolytic route from amine to naphthol.



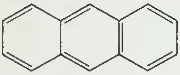
The sulfite or bisulfite ion is essential in this reaction. The amine and naphthol are in equilibrium with a small amount of the imine or keto form, an α,β-unsaturated system that undergoes conjugate addition by bisulfite ion much as in the formation of bisulfite addition compounds of aldehydes and ketones (Section 18.13.A).



34.4
Anthracene and Phenanthrene

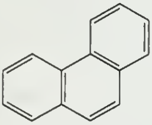
A. *Structure and Stability*

The isomeric tricyclic benzenoid hydrocarbons differ significantly in thermodynamic stability; the linear system, anthracene, is almost 6 kcal mole^{-1} less stable than the angular system, phenanthrene.



anthracene

$\Delta H_f^\circ = +55.2$ kcal mole^{-1}



phenanthrene

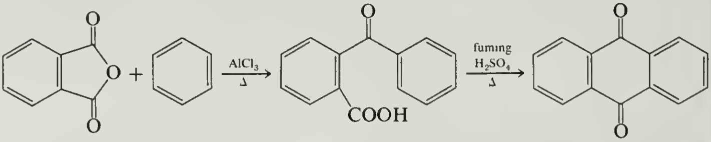
$\Delta H_f^\circ = +49.5$ kcal mole^{-1}

The empirical resonance energies show a corresponding change; one set of values is 84 kcal mole^{-1} for anthracene and 91 kcal mole^{-1} for phenanthrene. The empirical resonance energy of benzene calculated in the same way is 36 kcal mole^{-1}. The resonance energies of anthracene and phenanthrene are not much more than that of two benzene rings; that is, the third ring contributes relatively little additional resonance stabilization. We shall see that this characteristic is reflected in the reactivities of these hydrocarbons.

B. *Preparation of Anthracenes and Phenanthrenes*

Anthracene and phenanthrene are both available from coal tar in grades that are suitable for most reactions. Commercial material requires extensive further treatment to obtain the pure hydrocarbons. When pure, anthracene, m.p. 216°, exhibits a beautiful blue fluorescence. This fluorescence is diminished or altered by impurities in the commercial material. Phenanthrene also is a colorless crystalline solid, m.p. 101°, and it does not fluoresce.

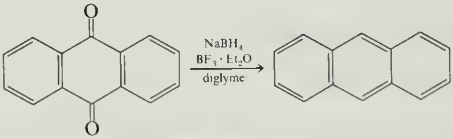
Both ring systems can be built up from simpler compounds. Anthracene and many derivatives are available from phthalic anhydride and benzene compounds via benzoylbenzoic acid (Section 31.2.B).



benzoylbenzoic acid

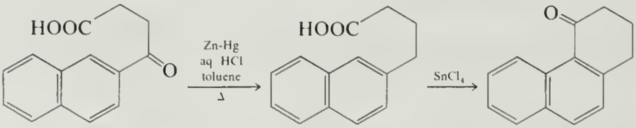
anthraquinone

Anthraquinones can be reduced directly to anthracene by several reducing agents, but the use of sodium borohydride and boron fluoride etherate is convenient.



(73%)

The phenanthrene ring system can be built up from naphthalene.



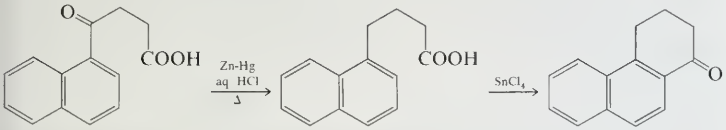
β-(2-naphthoyl)-propionic acid
4-oxo-4-(2-naphthyl)-butanoic acid

(91%)
4-(2-naphthoyl)-butanoic acid

(88%)
4-oxo-1,2,3,4-tetrahydrophenanthrene

Note that the cyclization goes exclusively to the 1-position of naphthalene (Section

34.3.D). A similar sequence starting from the 1-substituted naphthalene also gives the phenanthrene ring system.

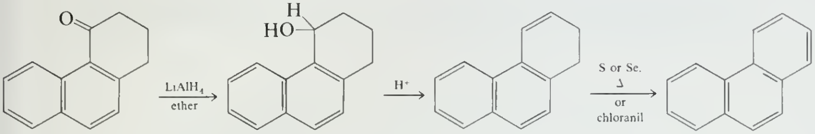

O
COOH
Zn-Hg
aq HCl
Δ
COOH
SnCl$_4$
O

β-(1-naphthoyl)-propionic acid
4-oxo-4-(1-naphthyl)-butanoic acid

(70%)
4-(1-naphthyl)-butanoic acid

(92–94%)
1-oxo-1,2,3,4-tetrahydrophenanthrene

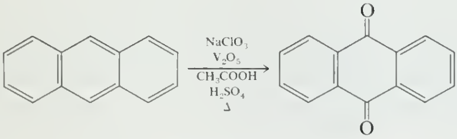
The cyclic ketones can be converted to phenanthrene by successive reduction, dehydration, and dehydrogenation.


O
LiAlH$_4$
ether
H
HO
H$^+$
S or Se.
Δ
or
chloranil

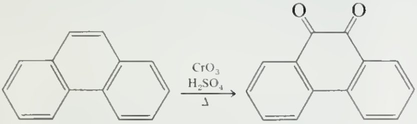
Many substituted phenanthrenes may be synthesized by variations of this general sequence.

C. *Reactions*

Anthracene and phenanthrene undergo ready oxidation to the corresponding quinones.

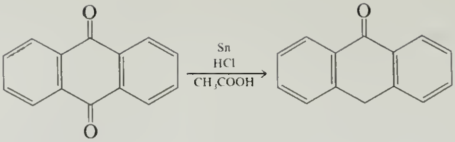

NaClO$_3$
V$_2$O$_5$
CH$_3$COOH
H$_2$SO$_4$
Δ
O
O

(88–91%)
9,10-anthraquinone


O
O
CrO$_3$
H$_2$SO$_4$
Δ

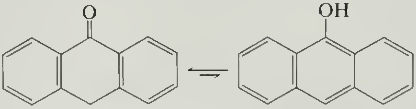
(44–48% from technical grade phenanthrene)
9,10-phenthraquinone

Anthraquinone can be partially reduced to give anthrone.



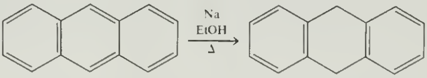
(82%)
anthrone

Anthrone is the keto form of 9-anthranol; both isomers can be isolated but anthrone is the stable form.

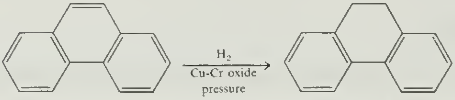


anthrone   9-anthranol

Both hydrocarbons can be reduced readily to dihydro compounds.

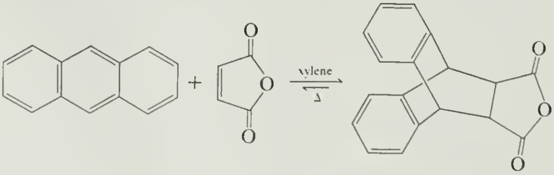


(75–79%)
9,10-dihydroanthracene



(70–77%)
9,10-dihydrophenanthrene

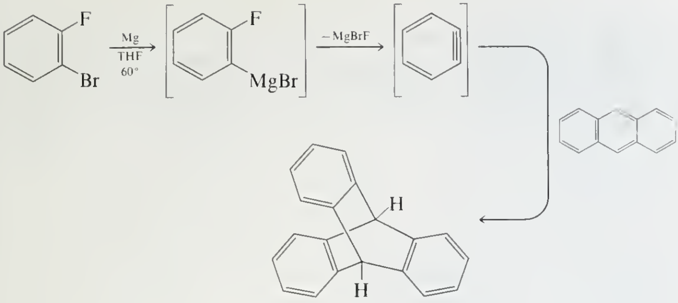
These reactions show the distinctive reactivity of the 9,10-positions of both compounds, a reactivity inherent in the low resonance stabilization contributed by the third benzene ring (Section 34.4.A). This reactivity is also demonstrated by the ability of anthracene to undergo Diels-Alder reactions as a diene. The reaction with maleic anhydride is an equilibrium which favors the adduct.



(99%)

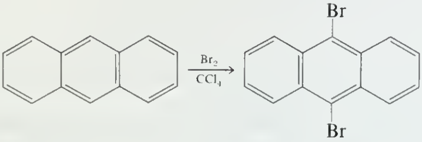
maleic
anhydride

A novel reaction of this type is with benzyne (Section 30.3.A) to give the unusual hydrocarbon, triptycene.

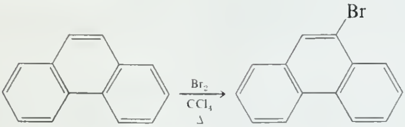


(28%)
triptycene

Electrophilic aromatic substitution reactions with anthracene and phenanthrene occur most readily in the 9-position and frequently give disubstitution products.



(83–88%)
9,10-dibromoanthracene

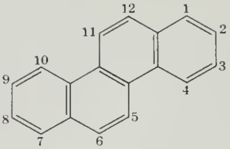


(90–94%)
9-bromophenanthrene

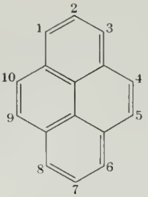
Because of the reactivity of polybenzenoid aromatic hydrocarbons special conditions must frequently be established for individual reactions. A detailed discussion of this chemistry is beyond the scope of this book.

34.5
Higher Polybenzenoid Hydrocarbons

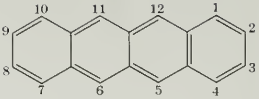
A large number of polybenzenoid hydrocarbons are known compounds, and some are relatively important. Some ring systems with established common names and their numbering systems are



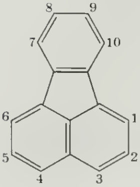
chrysene



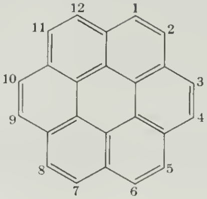
pyrene



tetracene



fluoranthene



coronene

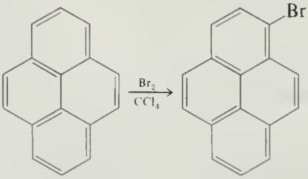
Some of these hydrocarbons are available from coal tar; others are prepared from simpler systems by building up rings in the manner shown in the preceding section for anthracene and phenanthrene.

Tetracene is an orange compound that shows much of the chemistry of anthracene. Oxidation and reduction occurs readily at the 5,12-positions and the hydrocarbon reacts readily as a Diels-Alder diene. Higher linear **acenes** are known; pentacene with five fused benzene rings in a row is blue, hexacene is green, and heptacene is a deep greenish black. The higher linear acenes are reactive, air sensitive and difficult to obtain pure.

Chrysene is similar to phenanthrene in its reactions; it can be oxidized to the 5,6-quinone. Pyrene is among the most important of these hydrocarbons.

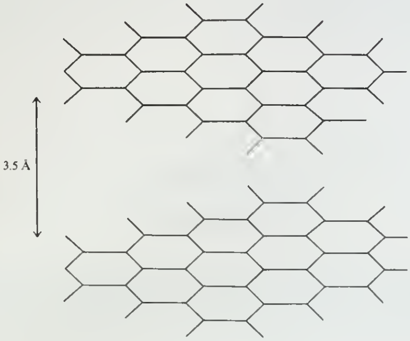
Two numbering systems have been used for pyrene and care must be taken in reading the literature, particularly the older literature, to establish the numbering system used. The system shown is the accepted IUPAC numbering, but even today references will be found with the older nomenclature.

Pyrene undergoes the usual electrophilic aromatic substitution reactions such as halogenation, nitration, Friedel-Crafts acylation, and so on. These reactions occur exclusively at the 1-position.



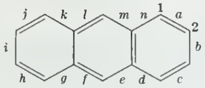
(78–86%)
1-bromopyrene

Polycyclic systems much larger than coronene are known. The large polycyclic hydrocarbons have low solubility and few are significant in organic chemistry. Their properties start to approach those of graphite, an allotrope of carbon that consists of infinite planes of benzene rings with the planes separated by 3.5 Å. This distance is usually taken as the total width of the π electronic system of benzene.

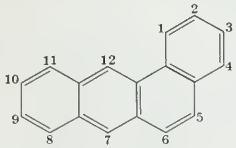


graphite

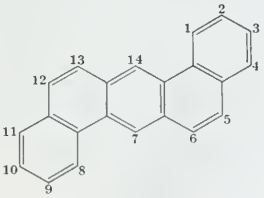
A number of polycyclic aromatic hydrocarbons are named as **benz-** derivatives of simpler systems. The position of fusion of the benz-ring is represented by a lower case letter that designates the side around the periphery of the parent system used for the fusion. For example, the sides in anthracene are lettered starting with side *a* between positions 1 and 2



In this way the following hydrocarbons are derived



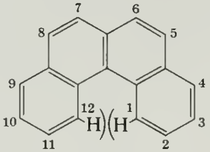
benz[*a*]anthracene



dibenz[*a,h*]anthracene

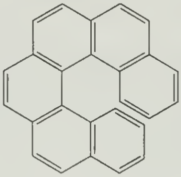
Some polycyclic aromatic hydrocarbons are highly carcinogenic compounds. Minute amounts painted on the skin of mice will produce skin tumors (epithelioma) in the course of a few months. Some of the most potent of the carcinogenic hydrocarbons are dibenz[*a,h*]anthracene (but not dibenz[*a,c*]anthracene), benzo[*a*]pyrene (but not benzo[*e*]pyrene), dibenzo[*a,i*]pyrene, and benzo[*b*]fluoranthene. These compounds occur in coal tar and in soot. A high incidence of scrotal cancer in chimney sweeps was noticed in England as early as 1775. All of these carcinogenic hydrocarbons have been detected in minute quantity in tobacco smoke. The way in which these compounds induce malignant tumors has been of interest for several decades and is still a topic of active research.

Benzo[*c*]phenanthrene presents a further aspect of interesting chemistry.



benzo[*c*]phenanthrene

The hydrogen atoms at the 1- and 12-positions interact significantly, and the molecule is forced to twist somewhat from coplanarity. With two additional benzene rings we obtain the spirally *fused* hydrocarbon, hexahelicene.



hexahelicene

If this molecule were planar two sets of CH groups would have to exist in the same space. In practice the hydrocarbon adopts a spiral structure which is also chiral. The enantiomers of this hydrocarbon have been obtained and have enormous optical rotations, $[\alpha]_D$ 3700°. The spiral structure has been demonstrated experimentally by the x-ray structure determination of 2-methylhexahelicene as shown in the stereo plot in Figure 34.5.

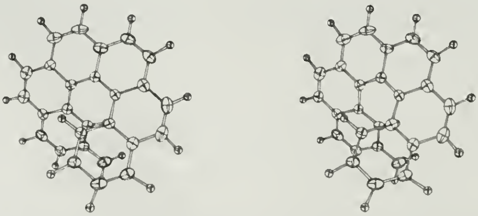
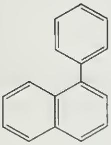


Figure 34.5 *Stereo structure of 2-methylhexahelicene. [Reproduced with permission from K. N. Trueblood,* et al.: Acta Cryst., **B29**; *223 (1973).]*

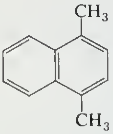
PROBLEMS

1. Show a practical synthesis of each of the following compounds starting with a suitable benzene derivative.

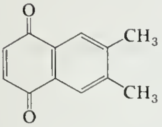
(a)



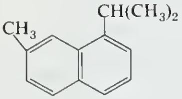
(b)



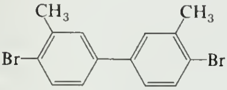
(c)



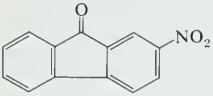
(d)



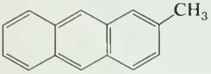
(e)



(f)



(g)



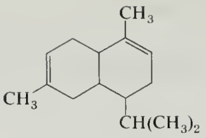
2. 6,6′-Dinitrobiphenyl-2,2′-dicarboxylic acid can be prepared by the Ullmann reaction on 2-iodo-3-nitrobenzoic acid. Give a reasonable preparation of this compound from available materials.

3. Substitution reactions of 2-methylnaphthalene with bulky electrophilic reagents tend to occur at the 6-position. Explain why this position is preferred to the sterically equivalent 7-position.

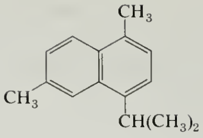
4. Write out the mechanism for the conversion of 2-naphthol to 2-aminonaphthalene showing every intermediate involved in the Bucherer reaction.

5. The heat of formation of naphthalene, ΔH_f°, is 36.1 kcal mole^{-1}; ΔH_f° for *trans*-decalin is -43.5 kcal mole^{-1}.
   (a) Calculate the heat of hydrogenation of naphthalene to *trans*-decalin.
   (b) Using the heat of hydrogenation of cyclohexene as a comparison standard, what is the estimated heat of hydrogenation of naphthalene in the absence of any conjugation stabilization?
   (c) Compare (a) and (b) to derive the corresponding empirical resonance energy of naphthalene.

6. Cadinene, $C_{15}H_{24}$, is a sesquiterpene occurring in the essential oils of junipers and cedars. Dehydrogenation gives the naphthalene hydrocarbon cadalene.
   (a) What is the IUPAC name for cadalene.
   (b) Give a rational synthesis of cadalene from toluene and any necessary aliphatic compounds.



cadinene

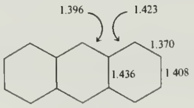


cadalene

7. Provide a practical synthesis of each of the following compounds from naphthalene:
   - (a) 2-bromonaphthalene
   - (b) 1-methylnaphthalene
   - (c) 1-isopropylnaphthalene
   - (d) 1-naphthyl propyl ketone
   - (e) 2-phenylnaphthalene
   - (f) 1,2-naphthoquinone
   - (g) 1-naphthoic acid
   - (h) 2-naphthoic acid
   - (i) ethyl α-naphthoylacetate

8. 2-Naphthyl allyl ether undergoes the Claisen rearrangement to give exclusively 1-allyl-2-naphthol. Give a reasonable explanation for the decided preference of this reaction over the alternative reaction to 3-allyl-2-naphthol.

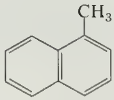
9. The difference in empirical resonance energies of anthracene and phenanthrene can be accounted for on the basis of resonance structures. Whereas we can write two benzenoid resonance structures for benzene (Section 21.1.A) and three for naphthalene (Section 34.3.A), there are four structures for anthracene and five for phenanthrene.
   - (a) Write out both sets of resonance structures for anthracene and phenanthrene.
   - (b) For each of the five different C—C bonds in anthracene compare the number of resonance structures in which each is single or double and determine the fraction of double bond character (bond order). Compare with the bond lengths determined by x-ray crystal structure techniques as



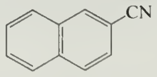
bond distances in Å

10. Give the expected dominant product or products in mononitration of each of the following compounds:

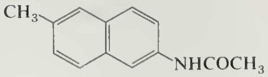
(a)



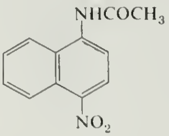
(b)



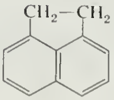
(c)



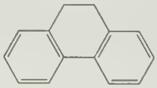
(d)

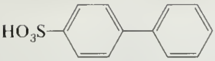


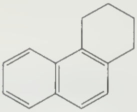
(e)

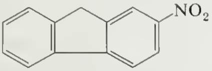


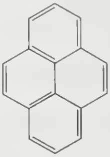
(f)

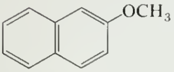


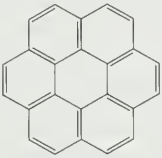
(g) 

(h) 

(i) 

(j) 

(k) 

(l) 

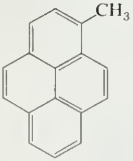
11. Acetylation of phenanthrene with acetyl chloride and $AlCl_3$ in nitrobenzene gives primarily 3-acetylphenanthrene. 2-Acetylphenanthrene is best prepared by Friedel-Crafts acetylation of 9,10-dihydrophenanthrene (Note that this hydrocarbon is a biphenyl compound and the 2-position corresponds to the *para* position of biphenyl) followed by dehydrogenation with Pd/C. Show how to prepare each of the following phenanthrene derivatives.

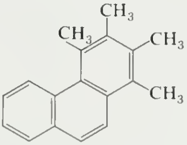
(a) 2- and 3-phenanthrenecarboxylic acid
(b) 2- and 3-aminophenanthrene
(c) 2- and 3-bromophenanthrene
(d) phenanthrene-2-*d* and phenanthrene-3-*d*

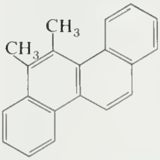
12. (a) Starting from naphthalene or monomethylnaphthalenes show how to prepare all five possible methylphenanthrenes. [*Note:* Some of these are harder than others.]
(b) α-Methylsuccinic anhydride reacts with naphthalene and $AlCl_3$ in nitrobenzene to give about equal amounts of 4-oxo-4-(1-naphthyl)-2-methylbutanoic acid and 4-oxo-4-(2-naphthyl)-2-methylbutanoic acid. These acids can be separated and used as starting materials for problem (a). Which of the methylphenanthrenes can be prepared in this way?

13. Show how anthraquinone can be prepared from 1,4-naphthoquinone.

14. (a) Write out the structures of the four carcinogenic hydrocarbons listed on page 1060.
(b) The following methyl derivatives have been shown to be carcinogenic. Supply an adequate name for each compound.





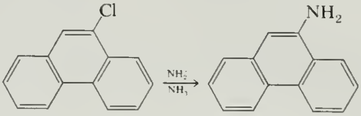


15. (a) Cyclopentadiene dimerizes readily on standing in a Diels-Alder reaction. Write the structure of the dimer.

(b) Work out a practical synthesis of indene starting with a C_6 or C_7 benzene derivative.

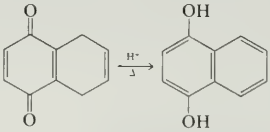
16. The acidity of fluorene is sufficiently high that it will undergo condensation reactions as do esters in alcoholic sodium ethoxide. Show how such condensation reactions can be utilized for the preparation of the following compounds:
    (a) fluorene-9-carboxylic acid
    (b) 9-methylfluorene-9-carboxylic acid
    (c) 9-benzoylfluorene
    (d) fluorene-9-carboxaldehyde

17. (a) Write a reasonable mechanism for the following reaction showing all intermediates involved:



(b) On the basis of this mechanism what would be the course of reaction for 2-methyl-9-chlorophenanthrene?

18. Give a reasonable mechanism for the following reaction, showing all intermediates involved:



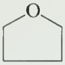
19. 2,6-Naphthoquinone is reduced more readily than 1,2-naphthoquinone. Explain.

CHAPTER 35
Heterocyclic Compounds

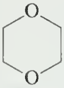
35.1 Introduction

Heterocyclic compounds are cyclic compounds in which one or more ring atoms are not carbon (that is, *hetero* atoms). Although heterocycles are known that incorporate many different elements into cyclic structures (for example, N, O, S, B, Al, Si, P, Sn, As, Cu), we shall consider only some of the more common systems in which the hetero atom is N, O, or S.

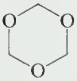
Heterocycles are conveniently grouped into two classes, nonaromatic and aromatic. The nonaromatic compounds have physical and chemical properties that are typical of the particular hetero atom. Thus, tetrahydrofuran and 1,4-dioxane are typical ethers, whereas 1,3,5-trioxane behaves as an acetal.



tetrahydrofuran

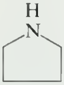


1,4-dioxane

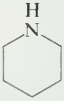


1,3,5-trioxane

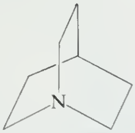
Pyrrolidine and piperidine are typical secondary amines and the bicyclic compound quinuclidine is a tertiary amine.



pyrrolidine



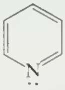
piperidine



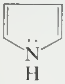
quinuclidine

Since the chemistry of these compounds parallels the chemistry of their acyclic relatives, we shall treat them here only briefly.

The aromatic heterocycles include such compounds as pyridine, where nitrogen replaces one of the CH groups in benzene, and pyrrole, in which the aromatic sextet is supplied by the four electrons of the two double bonds and the lone pair on nitrogen.

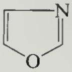


pyridine

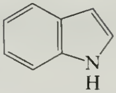


pyrrole

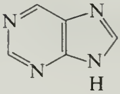
Other aromatic heterocycles contain more than one hetero atom, and still others contain fused aromatic rings. Examples which we will treat in more detail later include:



oxazole

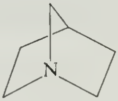


indole

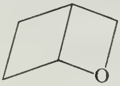


purine

The nomenclature of these heterocyclic series is a vast sea of special names for individual ring systems and trivial names for individual compounds. In the course of developing the chemistry of some important groups of compounds we will treat the associated nomenclature. There is only one naming scheme common to all of these compounds that is, unfortunately, used only in cases where alternative nomenclature based on special names is awkward. This scheme is based on the corresponding hydrocarbon. The compound formed by replacing a carbon by a hetero atom is named by an appropriate prefix: **aza** for nitrogen, **oxa** for oxygen and **thia** for sulfur. Some examples are

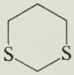


1-azabicyclo[2.2.1]heptane

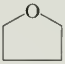


2-oxabicyclo[2.2.0]hexane

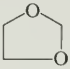
Saturated monocyclic rings are named according to ring size as 3-, **-iran**; 4-, **-etan**; 5-, **-olan**; and 6-, **-ane**. Even this system does not apply to nitrogen-containing rings and finds only limited use in common practice. Some examples of this nomenclature are:



1,3-dithiane
(used commonly)



oxolane
(rarely used)



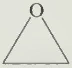
1,3-dioxolane
(used commonly)

The commonly used names for monocyclic rings with a single hetero atom will be discussed in the next section.

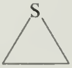
35.2
Nonaromatic Heterocycles

A. *Nomenclature*

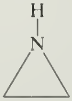
Names in common use of some fully saturated heterocycles containing only one hetero atom are shown below.



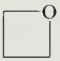
oxirane

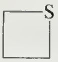


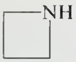
thiirane

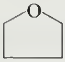


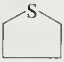
aziridine

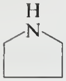

oxetane

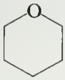

thietane

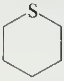

azetidine

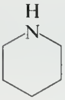

tetrahydrofuran


tetrahydrothiophene

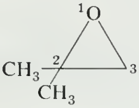

pyrrolidine

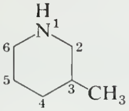

tetrahydropyran


tetrahydrothiopyran


piperidine

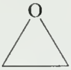
In naming substituted derivatives, the ring is numbered beginning with the hetero atom.

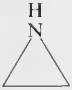

1
O
2
3
CH3
CH3
2,2-dimethyloxirane

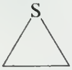

H
N
1
2
3
4
5
6
CH3
3-methylpiperidine

B. *Three-Membered Rings*

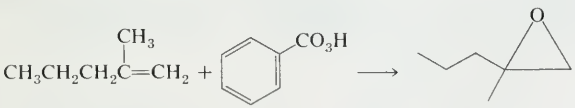
The common three-membered heterocycles are ethylene oxide (oxirane), ethyleneimine (aziridine), and ethylene sulfide (thiirane).

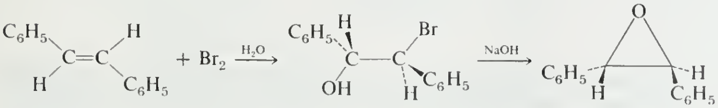

ethylene oxide
oxirane


ethyleneimine
aziridine

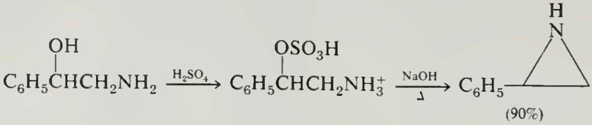

ethylene sulfide
thiirane

Ethylene oxides have been discussed previously (Section 23.10.A). Recall that the two most general syntheses are the oxidation of alkenes with peroxyacids, and the base-catalyzed cyclization of halohydrins (Section 23.10.A).


CH3
CH3CH2CH2C=CH2 +
CO3H
O
2-methyl-2-propyloxirane

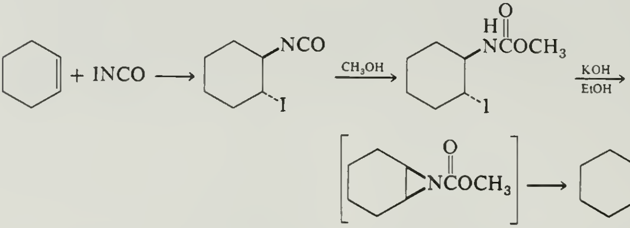

C6H5
H
C=C
H
C6H5
+ Br2
H2O
C6H5
H
C
OH
Br
C
H
C6H5
NaOH
O
C6H5
H
H
C6H5
trans-2,3-diphenyloxirane

Aziridines are most commonly prepared by related cyclization reactions. A classical method (the **Wenker synthesis**) consists of converting a β-amino alcohol into a β-amino hydrogen sulfate, which is cyclized by treatment with strong base.


OH
$C_6H_5CHCH_2NH_2$
H_2SO_4
OSO_3H
$C_6H_5CHCH_2NH_3^+$
NaOH
Δ
H
N
C_6H_5

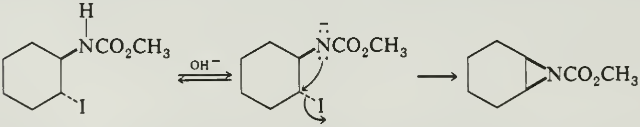
(90%)
2-phenylaziridine

They may also be prepared by cyclization of β-haloalkylamines and their derivatives. An example is the conversion of an alkene into an aziridine via the iodo isocyanate and iodo carbamate.

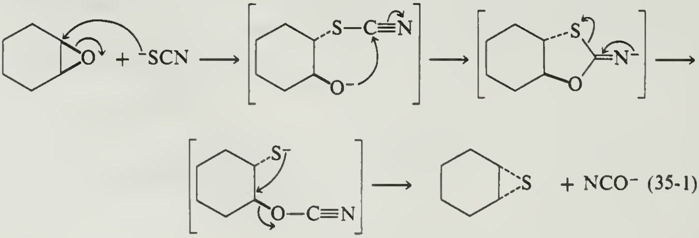

+ INCO
NCO
I
CH_3OH
H O
$NCOCH_3$
I
KOH
EtOH
O
$NCOCH_3$
NH

cyclohexeneimine

Under basic conditions, the NH of the carbamate grouping is partially deprotonated ($pK_a \approx 15$). The resulting anion accomplishes an internal S_N2 displacement, leading to the cyclized carbamate, which hydrolyzes to the aziridine.


H
NCO_2CH_3
I
OH^-
NCO_2CH_3
I
NCO_2CH_3

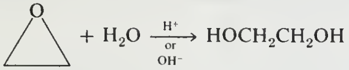
Thiiranes are most conveniently prepared from the corresponding oxirane. An especially useful method involves treating the epoxide with sodium thiocyanate. The reaction is formulated as shown in (35-1)


O
+ ⁻SCN
S—C≡N
O⁻
S
N⁻
O
S⁻
O—C≡N
S
+ NCO⁻

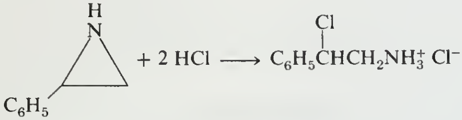
(35-1)

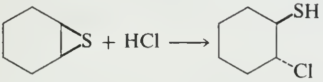
cyclohexene sulfide

The most striking chemical property of the three-membered heterocycles is their extraordinary reactivity. This enhanced reactivity has its origin in the relief of ring strain that occurs when the ring is cleaved. Recall that ethylene oxide is much more reactive than normal ethers, and undergoes ring opening by dilute acid or by base (Section 23.10.A).


O
+ H₂O
H⁺
or
OH⁻
HOCH₂CH₂OH

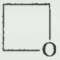
Similar reactivity is observed with aziridines and with thiiranes.


H
N
C₆H₅
+ 2 HCl
Cl
C₆H₅CHCH₂NH₃⁺ Cl⁻

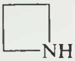


C. *Four-Membered Rings*

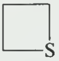
The four-membered ring heterocycles are rarer, mainly because of the greater difficulty of preparing four-membered rings (Sections 23.3 and 23.6.A).



oxetane

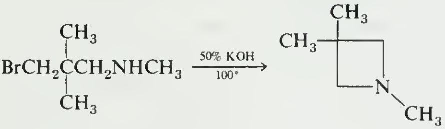


azetidine

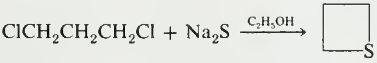


thietane

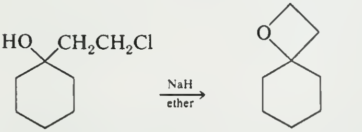
In some favorable cases, the rings may be formed by direct ring closure, but yields in such reactions are often low.


CH₃
BrCH₂CCH₂NHCH₃
CH₃
50% KOH
100°
CH₃
CH₃
N
CH₃

(80%)
1,3,3-trimethylazetidine

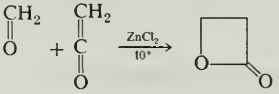

ClCH₂CH₂CH₂Cl + Na₂S
C₂H₅OH
S

(20–30%)
thietane

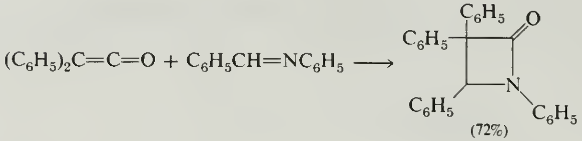

HO
CH₂CH₂Cl
NaH
ether
O

(55%)
1-oxaspiro[5.3]nonane

Another approach to generation of the four-membered ring heterocycles is by the union of two double bonds, a cycloaddition reaction. Examples are the formation of β-lactones and β-lactams.

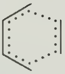


(88%)
β-propiolactone

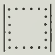

$(C_6H_5)_2C{=}C{=}O + C_6H_5CH{=}NC_6H_5 \longrightarrow$

(72%)
1,3,3,4-tetraphenyl-azetidin-2-one

The cycloaddition reactions of these examples are *not* analogous to Diels-Alder reactions. Diels-Alder reactions are examples of 4 + 2 cycloaddition reactions and involve a cyclic six-electron transition state related to benzenoid aromatic systems (Sections 23.4.B and 36.2). An analogous transition state for the present 2 + 2 cycloadditions has only four electrons and is not aromatic.

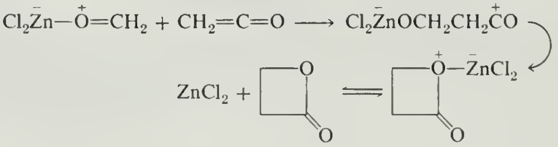


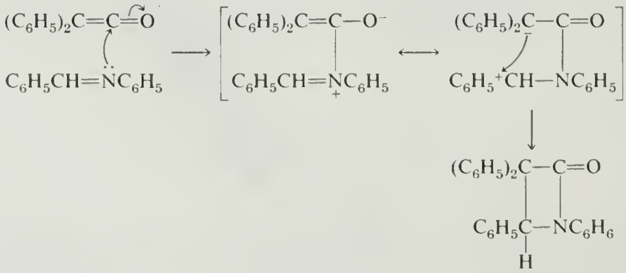
six-electron aromatic
transition state for
4 + 2 Diels-Alder
reaction



four-electron transition
state for a concerted
2 + 2 cycloaddition—
nonaromatic

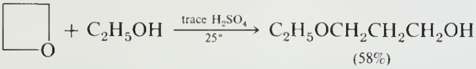
Instead, stepwise mechanisms are involved.

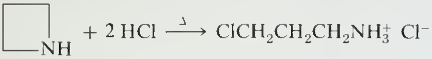

$Cl_2\overset{-}{Zn}{-}\overset{+}{O}{=}CH_2 + CH_2{=}C{=}O \longrightarrow Cl_2\overset{-}{Zn}OCH_2CH_2\overset{+}{C}O$
ZnCl$_2$ +



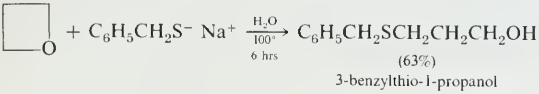
The stepwise processes also rationalize the observed modes of addition.

Like the three-membered ring analogs, oxetanes, azetidines, and thietanes are susceptible to acid-catalyzed ring opening reactions.


O
+ C₂H₅OH
trace H₂SO₄
25°
C₂H₅OCH₂CH₂CH₂OH
(58%)


NH
+ 2 HCl
Δ
ClCH₂CH₂CH₂NH₃⁺ Cl⁻

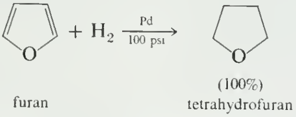
They are also more reactive than their open chain relatives in nucleophilic reactions but are much less reactive than the analogous three-membered ring compounds. Note the strenuous conditions required in the example (35-2).

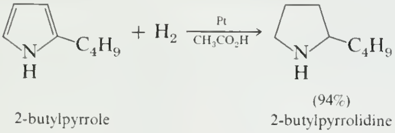

O
+ C₆H₅CH₂S⁻ Na⁺
H₂O
100°
6 hrs
C₆H₅CH₂SCH₂CH₂CH₂OH
(63%)
3-benzylthio-1-propanol

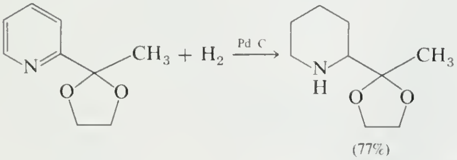
(35-2)

D. *Five- and Six-Membered Rings*

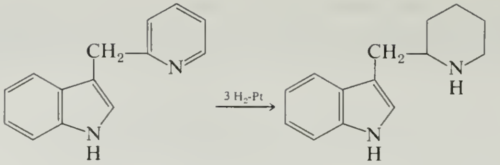
One source of the saturated five-membered ring heterocycles is the reduction of the available aromatic compounds derived from furan and pyrrole.


O
+ H₂
Pd
100 psi
O
(100%)
furan
tetrahydrofuran


N
H
C₄H₉
+ H₂
Pt
CH₃CO₂H
N
H
C₄H₉
(94%)
2-butylpyrrole
2-butylpyrrolidine

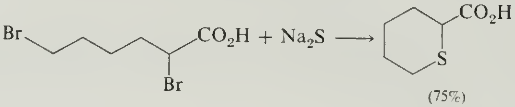

N
O
O
CH₃ + H₂
Pd C
N
H
O
O
CH₃
(77%)

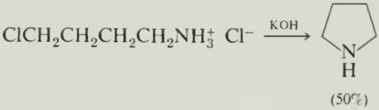
The pyridine ring is more easily reduced than indole or pyrrole. For example, the selective reduction (35-3) may be carried out in high yield.

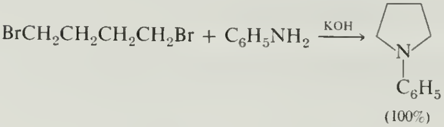


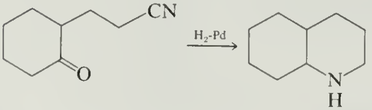
(35-3)

Aside from reduction of aromatic heterocycles, the main synthetic route to the five and six-membered ring saturated compounds is by ring closure of suitable difunctional compounds. Some examples are



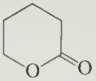




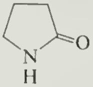


(page 783)

Cyclic esters (lactones) and amides (lactams) are also examples of heterocyclic compounds.



δ-valerolactone

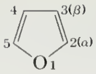


γ-butyrolactam
(2-pyrrolidone)

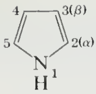
35.3
Furan, Pyrrole, and Thiophene

A. *Structure and Properties*

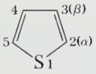
The structures of these three heterocycles would suggest that they have highly reactive diene character.



furan



pyrrole



thiophene

However, like benzene, many of their chemical properties are not typical of dienes. They undergo substitution rather than addition reactions, and they show the effect of a ring current in their nmr spectra. In short, these heterocycles have characteristics associated with aromaticity.

From an orbital point of view, pyrrole has a planar pentagonal structure in which the four carbons and the nitrogen have sp^2 hybridization. Each ring atom forms two sp^2-sp^2 σ bonds to its neighboring ring atoms, and each forms one sp^2-s σ bond to a hydrogen. The remaining p_z orbitals on each ring atom overlap to form a π molecular system in which the three lowest molecular orbitals are bonding. The six π electrons (one for each carbon and two for nitrogen) fill the three bonding orbitals and give the molecule its aromatic character. Pyrrole (Figure 35.1) is isoelectronic with cyclopentadienyl anion, an unusually stable carbanion that also has a cyclic π electronic system with six electrons (Section 34.2.D).

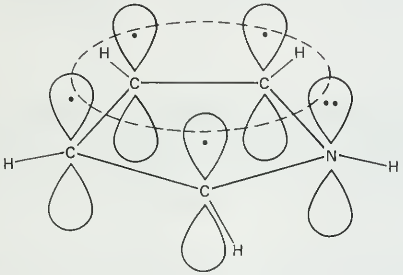
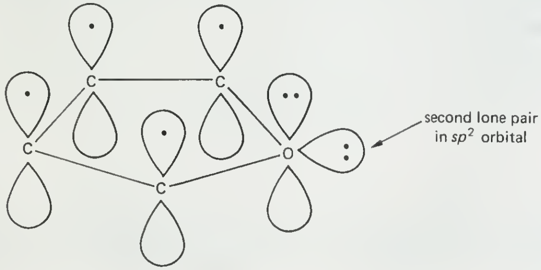


FIGURE 35.1 *Orbital structure of pyrrole.*

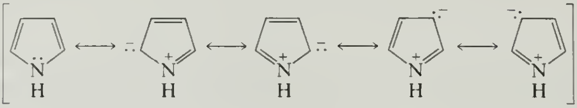
Furan and thiophene have similar structures. In these cases, the second lone pair on the heteroatom may be considered to occupy an sp^2 orbital that is perpendicular to the π system of the ring (Figure 35.2).



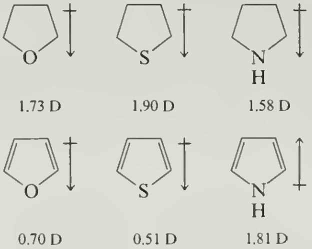
second lone pair in sp^2 orbital

FIGURE 35.2 *Orbital structure of furan.*

The aromatic character of these heterocycles may also be expressed using resonance structures, which show that a pair of electrons from the hetero atom is delocalized around the ring.



This delocalization of the lone pair electrons away from the heteroatom can be inferred from the dipole moments of these aromatic heterocycles and their non-aromatic counterparts.

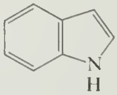


In the saturated compounds, the heteroatom is at the negative end of the dipole. In the aromatic heterocycles the dipole moment associated with the π system opposes the σ moment. As a result, the net dipole moment of furan and thiophene is reduced. In pyrrole, the π moment is larger than the σ moment so that the direction of the net dipole moment is actually reversed from its saturated counterpart!

Empirical resonance energies for furan, pyrrole, and thiophene may be computed from the heats of combustion for the compounds. In all cases, there is a substantial stabilization energy, although of considerably smaller magnitude than for benzene.

The physical properties of some furan, pyrrole, and thiophene derivatives are listed in Table 35.1. Most of the simple derivatives are liquids.

As mentioned earlier, furan, pyrrole, and thiophene show the effect of a ring current in their nmr spectra. The spectra of furan, thiophene, and indole, which are reproduced in Figures 35.3 through 35.5, show the low-field resonance position of the ring hydrogens.



indole

Although pyrrole is an amine, it is an extremely nonbasic one because the nitrogen lone pair is involved in the aromatic sextet and is thereby less available for bonding to a proton. The pK_a of its conjugate acid is 0.4. In fact, this pK_a

Table 35.1
Physical Properties of Some Furans, Pyrroles, and Thiophenes

Compound	Melting Point, °C	Boiling Point, °C
furan	−86	31
2-chlorofuran	—	78
3-chlorofuran	—	79
2-methylfuran	—	63
3-methylfuran	—	66
2-nitrofuran	29	135
pyrrole	—	131
1-methylpyrrole	—	115
2-methylpyrrole	—	148
3-methylpyrrole	—	143
1-phenylpyrrole	62	234
2-phenylpyrrole	129	271
thiophene	−38	84
2-chlorothiophene	−72	128
2-methylthiophene	−63	113
3-methylthiophene	−69	115
2-nitrothiophene	46	225
2,4-dimethylthiophene	—	141

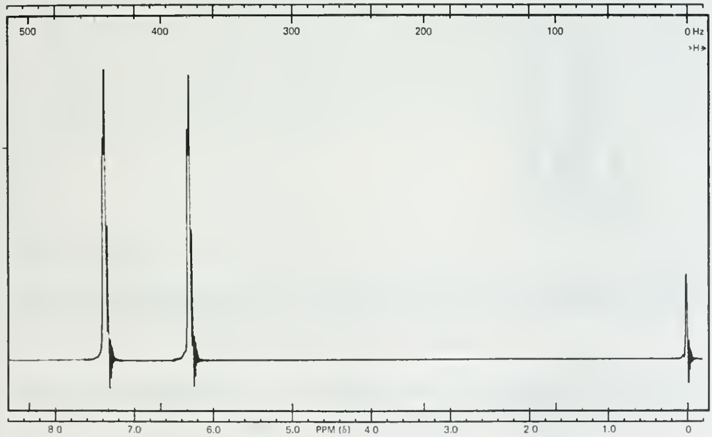


Figure 35.3 *Nmr spectrum of furan.*

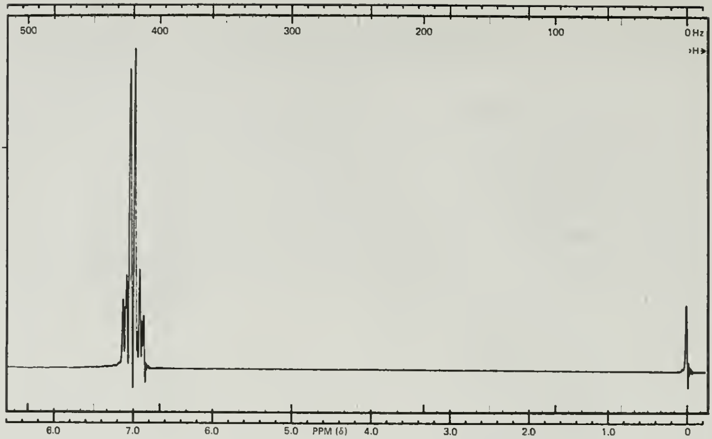


FIGURE 35.4 *Nmr spectrum of thiophene.*

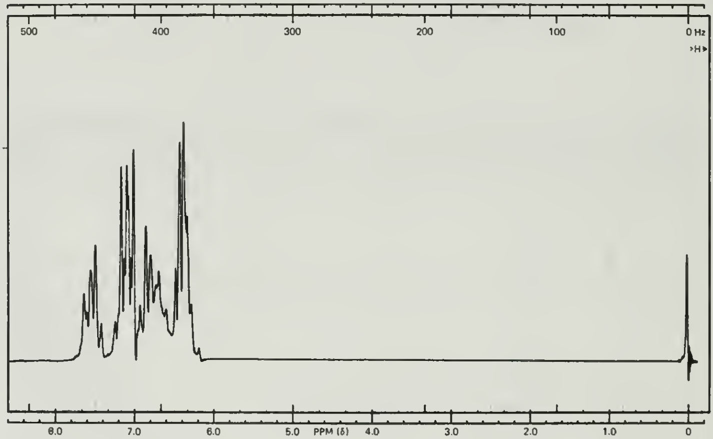
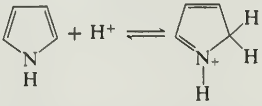


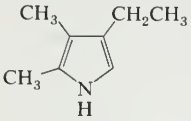
FIGURE 35.5 *Nmr spectrum of indole.*

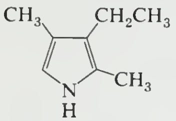
corresponds to a conjugate acid in which protonation has occurred predominantly on carbon rather than on nitrogen.

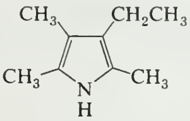


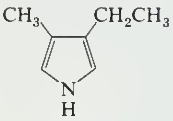
$pK_a = 0.4$

Pyrrole compounds occur widely in living systems. One of the more important pyrrole compounds is the porphyrin **hemin**, the prosthetic group of hemoglobin and myoglobin (see Figure 28.16). A number of simple alkylpyrroles have played an important role in the elucidation of the porphyrin structures. Thus, drastic reduction of hemin gives a complex mixture from which the four pyrroles, hemopyrrole, cryptopyrrole, phyllopyrrole, and opsopyrrole, have been isolated.


hemopyrrole


cryptopyrrole

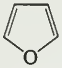

phyllopyrrole

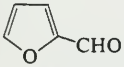

opsopyrrole

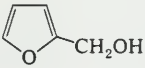
The function of hemoglobin in an organism is to transport oxygen; 1 g of hemoglobin absorbs 1.35 ml of oxygen at STP, corresponding to exactly one molecule of O_2 per iron. The oxygen binds to the hemoglobin molecule in the vicinity of the iron, and the binding constant is proportional to the partial pressure of oxygen. In the lungs, where the partial pressure of oxygen is high, hemoglobin binds oxygen. In the tissues served by the blood stream, the oxyhemoglobin dissociates back into O_2 and hemoglobin, which returns to the lungs for another load. Carbon monoxide is a poison because it forms a tight complex with the iron of hemoglobin and prevents it from binding oxygen.

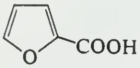
B. *Synthesis*

Furan, 2-furaldehyde (furfural), 2-furylmethanol, and 2-furoic acid are all inexpensive commercial items.

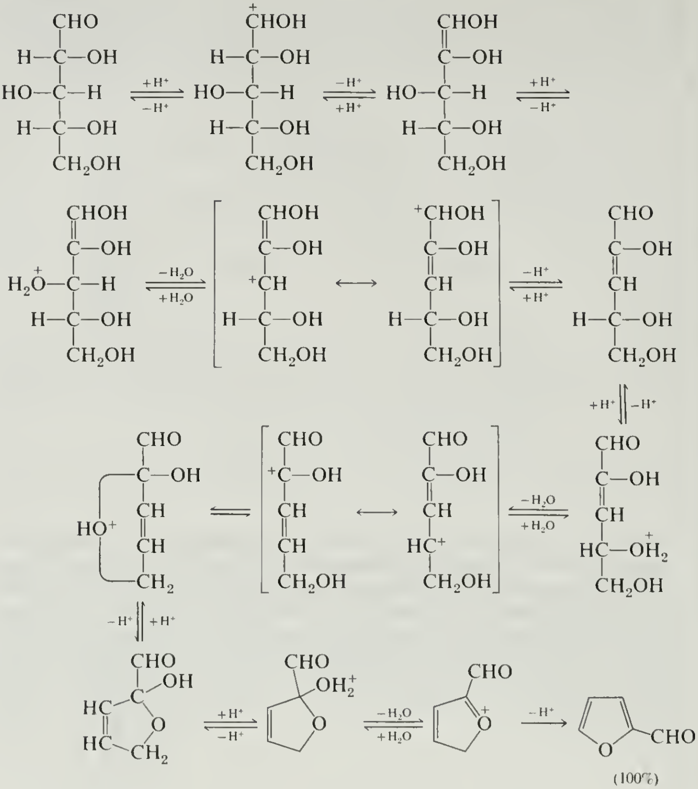

furan


2-furaldehyde
furfural


2-furylmethanol

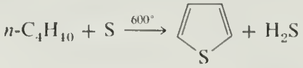

2-furoic acid

The ultimate source of these heterocycles is furfural, which is obtained industrially by the acid hydrolysis of the polysaccharides of oat hulls, corn cobs, or straw. These polysaccharides are built up from pentose units. Dehydration of the pentose may be formulated as follows:

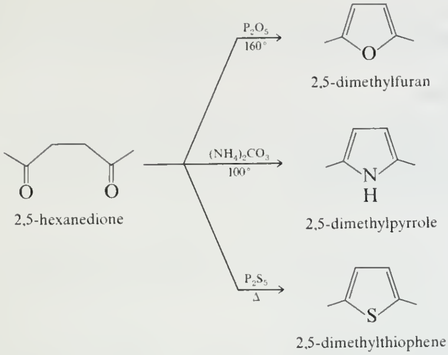


Pyrrole is prepared commercially by the fractional distillation of coal tar, or by passing a mixture of furan, ammonia, and steam over a catalyst at 400°.

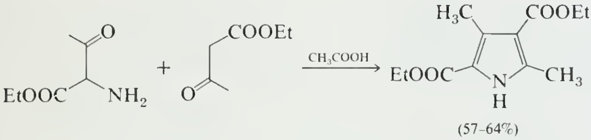
Thiophene is prepared industrially by passing a mixture of butane, butenes, or butadiene and sulfur through a reactor heated at 600° for a contact time of about 1 sec.



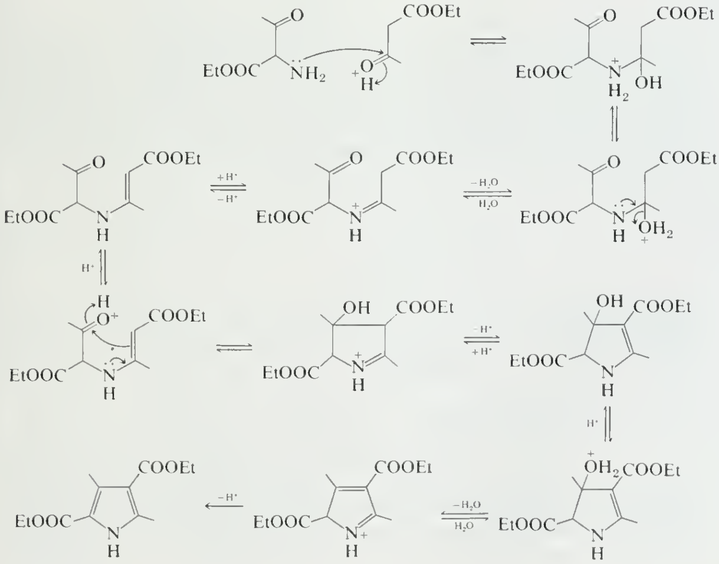
Substituted furans, pyrroles, and thiophenes may be prepared by electrophilic substitution on one of the available materials discussed or by a variety of cyclization reactions. The most general is the **Paal-Knorr** synthesis, in which a 1,4-dicarbonyl compound is heated with a dehydrating agent, ammonia, or an inorganic sulfide to produce the furan, pyrrole, or thiophene, respectively.


P_2O_5
160°
2,5-dimethylfuran
2,5-hexanedione
$(NH_4)_2CO_3$
100°
2,5-dimethylpyrrole
P_2S_5
Δ
2,5-dimethylthiophene

Another general method for the synthesis of substituted pyrroles is the **Knorr pyrrole synthesis,** the condensation of an α-aminoketone with a β-keto ester. The method is illustrated in a synthesis of diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate.


EtOOC
NH_2
COOEt
CH_3COOH
H_3C
CH_3
(57–64%)

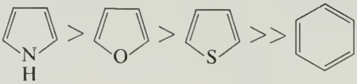
The probable mechanism of the Knorr synthesis is


EtOOC
COOEt
$-H_2O$
H_2O
$+H^+$
$-H^+$
H^+

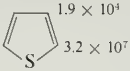
Notice how each individual step involves either an oxonium ion or an ammonium ion. No unstabilized carbonium ions are involved.

C. *Reactions*

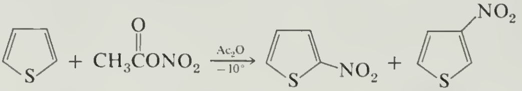
The most typical reaction of furan, pyrrole, and thiophene is electrophilic substitution. All three heterocycles are much more reactive than benzene, the reactivity order being



To give some idea of the magnitude of this reactivity order, partial rate factors (reactivities relative to benzene) for tritium exchange with trifluoroacetic acid (page 881) for thiophene are

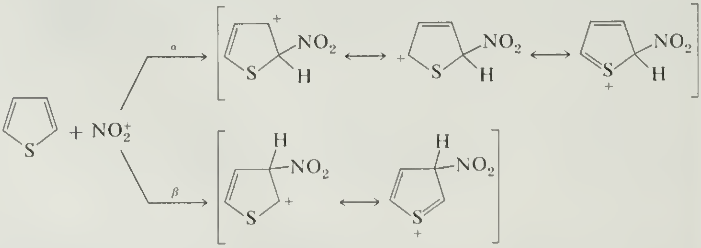


Because of this high reactivity, even mild electrophiles suffice to cause reaction. Substitution occurs predominantly at the α-position (C-2).

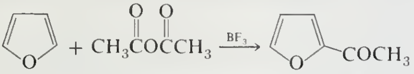


acetyl nitrate (70%) 2-nitrothiophene (5%) 3-nitrothiophene

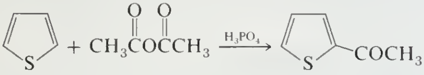
This orientation is understandable in terms of the mechanism of electrophilic aromatic substitution. The α/β ratio is determined by the relative energies of the transition states leading to the two isomers. As in the case of substituted benzenes (Section 29.5), we may estimate the relative energies of these two transition states by considering the actual reaction intermediates produced by attack at the α- or β-positions. The important resonance structures for these two cations are



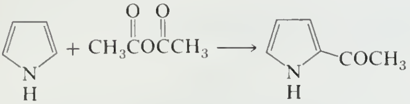
Of these structures, the most important are the two with the positive charge on sulfur because, in these two sulfonium cation structures, all atoms have octets of electrons. Nevertheless, as the sets of resonance structures show, the charge on the cation resulting from attack at the α-position is more extensively delocalized than that for the cation resulting from attack at the β-position. The following examples further demonstrate the generality of α-attack.


O
+ CH3COCCH3
BF3
COCH3

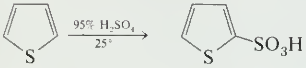
(75–92%)
2-acetylfuran


S
+ CH3COCCH3
H3PO4
COCH3

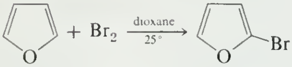
(94%)
2-acetylthiophene


N
H
+ CH3COCCH3
COCH3

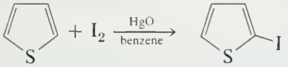
(60%)
2-acetylpyrrole


S
95% H2SO4
25°
SO3H

(69–76%)
thiophene-2-sulfonic acid


O
+ Br2
dioxane
25°
Br

(75%)
2-bromofuran

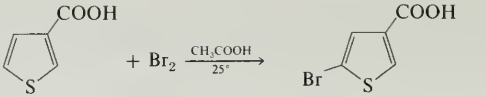

S
+ I2
HgO
benzene
I

(75%)
2-iodothiophene

In the last example, note that 2-iodothiophene is the sole product of iodination, even though the reaction is carried out in benzene as solvent; that is, thiophene is so much more reactive than benzene that no significant amount of iodobenzene is formed.

The position of second substitution in a monosubstituted furan, pyrrole, or thiophene is governed by a combination of the directing effect of the group present and the inherent α-directing effect of the heteroatom.

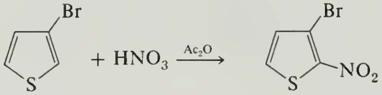
Substitution on 3-substituted compounds occurs exclusively at an α-position. When the substituent present is electron attracting (*meta* directing), reaction occurs at the nonadjacent α-position (that is, *meta* to the group present). An example is (35-4).


COOH
S
+ Br2
CH3COOH
25°
COOH
Br
S

(35-4)

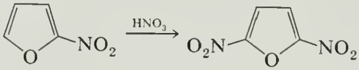
(69%)
5-bromo-3-thiophenecarboxylic acid

When the 3-substituent is electron donating (*ortho,para* directing), substitution occurs at the adjacent α-position (that is, *ortho* to the group present).


Br
S
+ HNO3
Ac2O
Br
NO2
S

(55–60%)
3-bromo-2-nitrothiophene

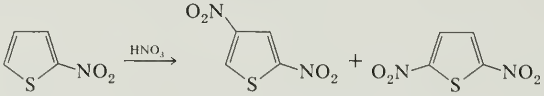
Further substitution on 2-substituted furans tends to occur at the other α-position.


NO2
O
HNO3
O2N
O
NO2

2-nitrofuran

2,5-dinitrofuran

With 2-substituted pyrroles and thiophenes, attack can occur at C-4 or C-5 when the group present is *meta* directing, or at C-3 and C-5 when the group present is *ortho,para* directing. Examples are (35-5) and (35-6).

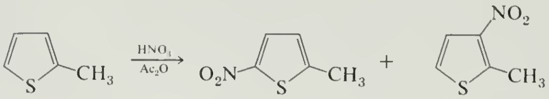

S
NO2
HNO3
O2N
S
NO2
+
O2N
S
NO2

(35-5)

2-nitrothiophene

(85%)
2,4-dinitrothiophene

(15%)
2,5-dinitrothiophene


S
CH3
HNO3
Ac2O
O2N
S
CH3
+
NO2
S
CH3

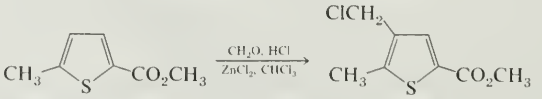
(35-6)

2-methylthiophene

(70%)
2-methyl-5-nitrothiophene

(30%)
2-methyl-3-nitrothiophene

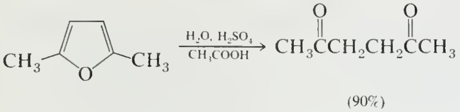
When both α-positions are occupied, further substitution occurs at a β-position, the direction of attack being governed by the directing effect of the two groups present.


CH3
S
CO2CH3
CH2O, HCl
ZnCl2, CHCl3
ClCH2
CH3
S
CO2CH3

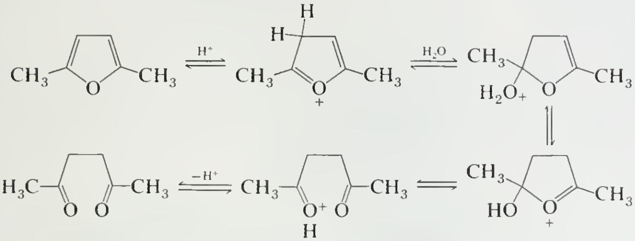
methyl 5-methylthiophene-2-carboxylate

(93%)
methyl 5-methyl-4-chloromethyl-2-carboxylate

Hydrolytic ring opening is a typical reaction of furans. In essence, the reaction is the reverse of the Paal-Knorr synthesis. Careful hydrolysis of furans can lead to the corresponding 1,4-dicarbonyl compounds in good yield.

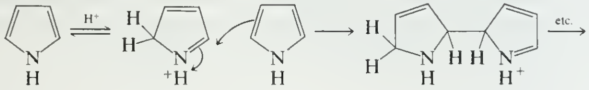

CH3
CH3
O
H2O, H2SO4
CH3COOH
CH3CCH2CH2CCH3
(90%)

The hydrolysis is initiated by electrophilic attack on the ring.


H+
H2O
−H+
H2O+
HO

This hydrolysis, of course, is the microscopic reverse process of the Paal-Knorr synthesis (Section 35.3.B).

Pyrroles are polymerized by even dilute acids, probably by a mechanism such as the following:

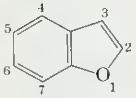


Thiophenes are more stable and do not undergo hydrolysis.

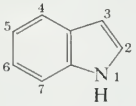
35.4
Condensed Furans, Pyrroles, and Thiophenes

A. *Structure and Nomenclature*

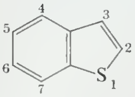
Benzofuran, indole, and benzothiophene are analogous to naphthalene. As with the simple heterocycles, the rings are numbered beginning with the heteroatom; carbazole is an exception.



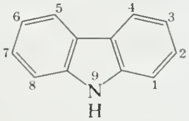
benzofuran



indole

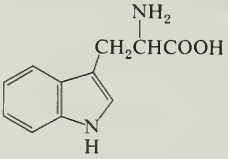


benzothiophene

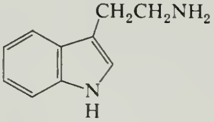

1
2
3
4
5
6
7
8
9
N
H

carbazole

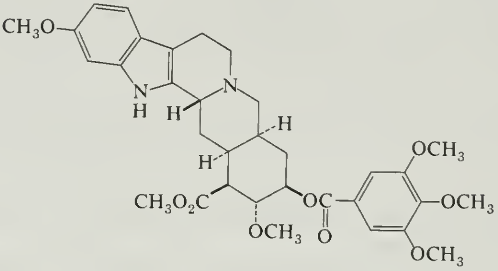
Of the four systems, indoles are by far the most important. Many natural products have indole structures (see also Section 27.9).


NH₂
CH₂CHCOOH
N
H

tryptophan


CH₂CH₂NH₂
N
H

tryptamine

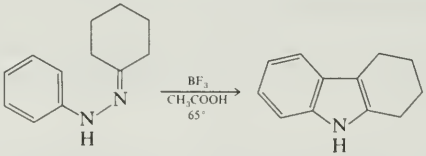

CH₃O
N
H
H
N
H
H
OCH₃
CH₃O₂C
OC
O
OCH₃
OCH₃
OCH₃

reserpine

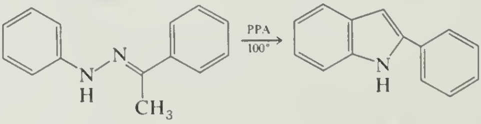
From a chemical standpoint, the chief effect of fusing the benzene ring onto the simple heterocycle is to increase its stability and to change the preferred orientation in electrophilic substitution from C-2 to C-3 (Section 35.4.C).

B. *Synthesis*

The most general synthesis of indoles is the **Fischer indole synthesis**, in which the phenylhydrazone of an aldehyde or ketone is treated with a catalyst such as BF_3, $ZnCl_2$, or polyphosphoric acid (PPA).

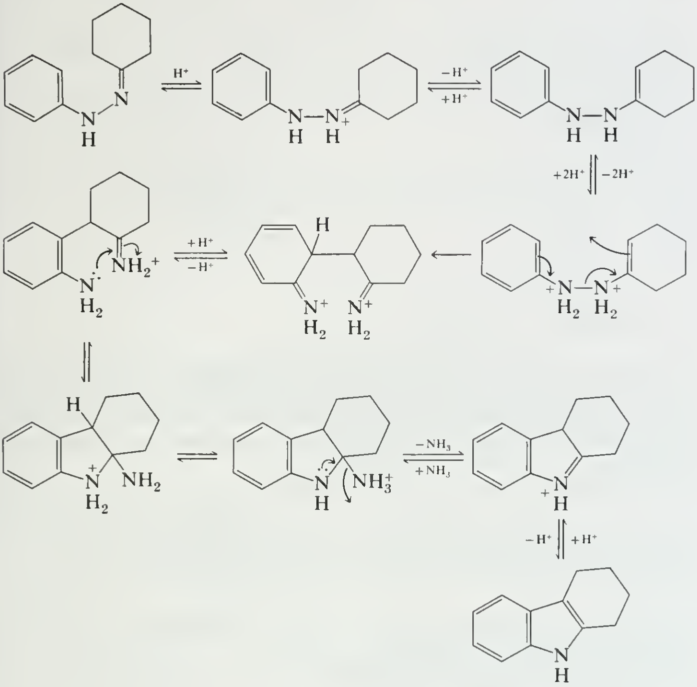

N
N
H
BF₃
CH₃COOH
65°
N
H

(93%)
1,2,3,4-tetrahydrocarbazole

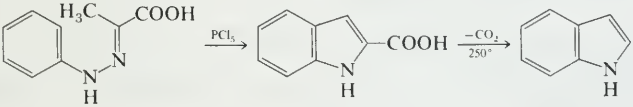

N
N
H
CH₃
PPA
100°
N
H

(73%)
2-phenylindole

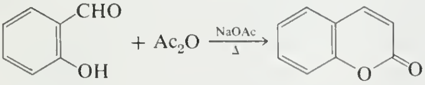
The mechanism of the Fischer synthesis has been the subject of much study. The available evidence is in accord with a pathway involving a benzidine-like rearrangement (Section 32.1.C):



The reaction fails with the phenylhydrazone of acetaldehyde and, thus, cannot be used to prepare indole itself. However, the phenylhydrazone of pyruvic acid does react to yield indole-2-carboxylic acid, which can be decarboxylated to give indole.

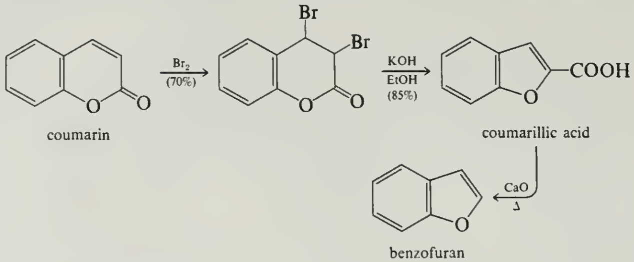


Benzofuran is prepared from coumarin, which in turn is prepared from salicyladehyde by the Perkin synthesis (Section 31.4.B).



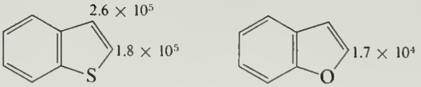
coumarin

Coumarin reacts with bromine to give a dibromide, which undergoes an interesting ring contraction when treated with ethanolic potassium hydroxide to give benzofuran-2-carboxylic acid. The acid may be decarboxylated by distillation over calcium oxide.


Br
Br
Br_2
(70%)
KOH
EtOH
(85%)
COOH
CaO
Δ
O
coumarin
coumarillic acid
benzofuran

C. *Reactions*

All three condensed heterocycles undergo electrophilic substitution in the heterocyclic ring rather than in the benzene ring. However, each is markedly less reactive than the corresponding monocyclic heterocycle. Some partial rate factors for protodetritiation with trifluoroacetic acid are available for benzothiophene and benzofuran:


2.6 × 10⁵
1.8 × 10⁵
S
1.7 × 10⁴
O

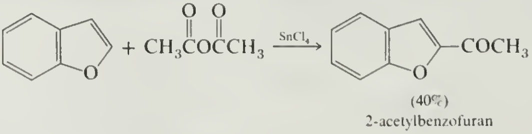
These values are at least two orders of magnitude smaller than that for the α-position of thiophene (Section 35.3.C).

The preferred orientation in electrophilic substitution reactions in these compounds can be summarized as follows:

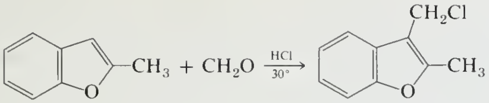
The most reactive position in benzofuran is C-2.
In benzothiophene, C-2 and C-3 have comparable reactivities, with C-3 being somewhat the more reactive.
In indole, the most reactive position is C-3.

The way in which these generalizations apply in practice will be illustrated with some specific examples.

Electrophilic substitution in benzofuran occurs predominantly at C-2, just as in furan itself.

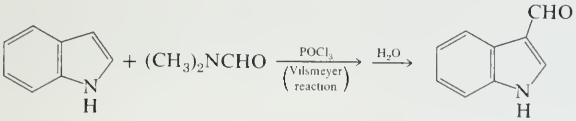

+ CH_3COCCH_3
O O
$SnCl_4$
$COCH_3$
O
(40%)
2-acetylbenzofuran

If the 2-position is occupied, reaction occurs at C-3.

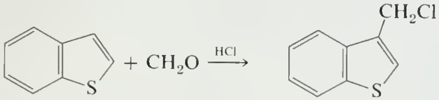

CH3
CH2O
HCl
30°
CH2Cl
CH3
O
O

(70%)
2-methyl-3-chloromethylbenzofuran

The preferred reaction at C-3 in indole and benzothiophene is illustrated by


N
H
(CH3)2NCHO
POCl3
(Vilsmeyer reaction)
H2O
CHO
N
H

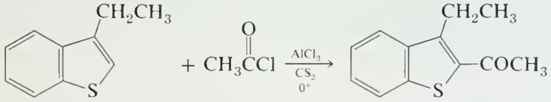
(97%)
indole-3-carboxaldehyde


S
CH2O
HCl
CH2Cl
S

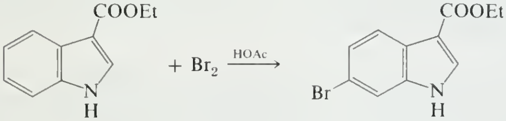
(56%)
3-chloromethylbenzothiophene

With benzothiophene, other isomers are usually produced as well, but are not always detected or isolated.

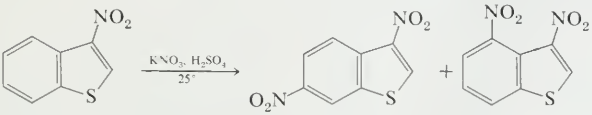
When C-3 is occupied, reaction occurs at C-2 if the 3-substituent is activating or in the benzene ring (C-4 or C-6) if the 3-substituent is deactivating. Some examples are


CH2CH3
S
CH3CCl
O
AlCl3
CS2
0°
CH2CH3
COCH3
S

2-acetyl-3-ethylbenzothiophene


COOEt
N
H
Br2
HOAc
COOEt
Br
N
H

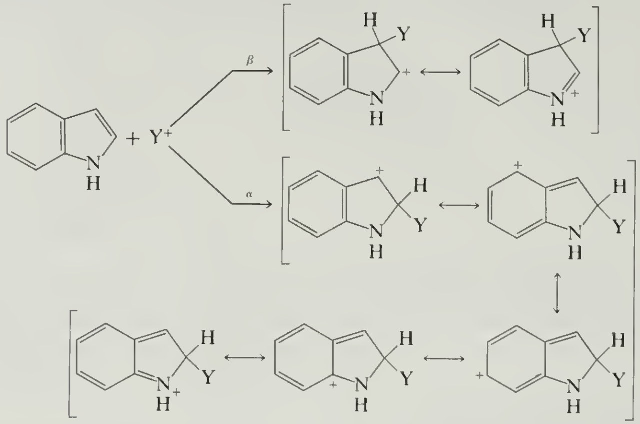
ethyl 6-bromoindole-3-carboxylate


NO2
S
KNO3, H2SO4
25°
NO2
O2N
S
NO2
NO2
S

3,6-dinitrobenzothiophene (minor)

3,4-dinitrobenzothiophene (major)

These orientation specificities can be rationalized by considering the intermediate ions produced by attack at C-2 and C-3. Reaction at C-2 gives a carbonium ion in which the charge is distributed to the benzene ring and to the heteroatom; however, the structure with the charge on the heteroatom no longer has a benzene ring. In contrast, reaction at C-3 does not permit effective distribution of charge around the benzene ring, but the electron pair on the heteroatom is utilized efficiently without disruption of the benzene resonance.

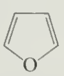


The relative reactivities depend on the balance of these contrasting effects. The experimental results suggest that for indole the direct involvement of the basic nitrogen lone pair is much more important than conjugation with the benzene ring, whereas, with benzofuran, the oxygen lone pair is less basic and the involvement of the benzene ring now dominates. In the case of benzothiophene, the two effects are roughly comparable in magnitude.

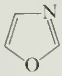
35.5
Azoles

A. *Structure and Nomenclature*

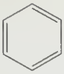
Azoles are five-membered ring aromatic heterocycles containing two nitrogens, one nitrogen and one oxygen, or one nitrogen and one sulfur. They are named and numbered as shown in Table 35.2. They may be considered as aza analogs of furan, pyrrole, and thiophene, in the same way that pyridine is an aza analog of benzene (see Section 35.6).



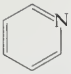
furan



oxazole
(3-azafuran)



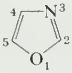
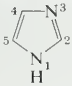
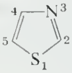
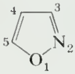
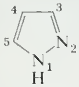
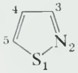
benzene



pyridine
(azabenzene)

From a molecular orbital standpoint, the azoles are similar to the simpler aromatic heterocycles. For example, in imidazole, each carbon and nitrogen may be considered to be sp^2 hybridized. One nitrogen makes two sp^2-sp^2 σ bonds to carbon and one sp^2-s σ bond to hydrogen. The other nitrogen has its lone pair in the third sp^2 orbital. The π molecular orbital system is made up from the p_z orbitals from each ring atom (Figure 35.6). Six π electrons (one from each carbon and from one nitrogen, two from the other nitrogen) complete the aromatic shell.

TABLE 35.2
Names and Physical Properties of Azoles

		
oxazole b.p. 70°	imidazole b.p. 263° m.p. 90°	thiazole b.p. 117°
		
isoxazole b.p. 95°	pyrazole b.p. 188° m.p. 70°	isothiazole b.p. 113°

An examination of the physical properties of the simple azoles, given in Table 35.2, reveals that imidazole and pyrazole have anomalously high boiling points. They are also the only simple azoles which are solids at room temperature. These properties clearly result from intermolecular hydrogen bonding. With imidazole,

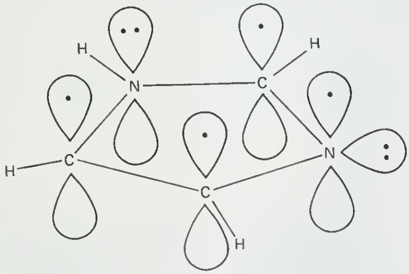
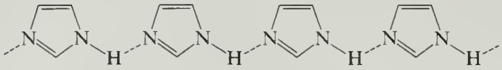
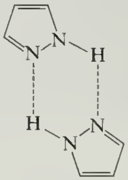


FIGURE 35.6 *Orbital structure of imidazole.*

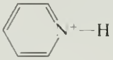
the hydrogen bonding is of a linear polymer, whereas pyrazole seems to exist largely as the dimer.



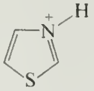


Like pyridine (pK_a 5.2, Section 35.6.A), thiazole (pK_a 2.4), pyrazole (pK_a 2.5), and isoxazole (pK_a 1.3) are weak bases. As in pyridine, the nitrogen lone pair is in an sp^2 orbital. Recall that greater s character of lone pair electrons is associated with heightened stability and lower basicity (Sections 13.4 and 18.7). A similar trend obtains with nitrogen acids (Table 35.3).

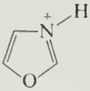
TABLE 35.3
Hybridization and Acidity

Orbital	Carbon Acid	pK_a	Nitrogen Acid	pK_a
sp	$HC\equiv CH$	25	$CH_3C\equiv\overset{+}{N}H$	−10
sp^2	$CH_2=CH_2$	44		5
sp^3	CH_3-CH_3	50	$(CH_3)_3\overset{+}{N}H$	10

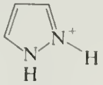
The higher s character of the pyridine lone pair compared to aliphatic amines is sufficient to account for a decrease in basicity of several powers of ten. In pyrazole, thiazole, and isoxazole, the basicity of the nitrogen lone pair is further reduced by the presence of the other heteroatom.



pK_a 2.4

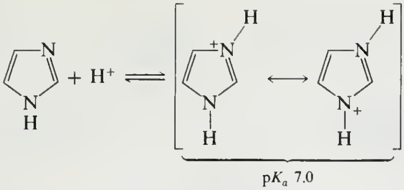


pK_a 1.3

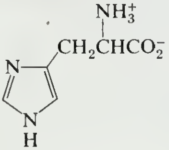


pK_a 2.5

In marked contrast to these results, imidazole seems to be abnormally basic for a compound with sp^2 hybridized nitrogen (pK_a 7.0). The enhanced basicity of imidazole is presumably due to the symmetry of the conjugate acid and the consequent resonance stabilization.

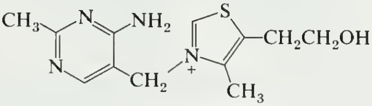


Its pK_a of 7.0 means that imidazole is half protonated in neutral water. As a result, the basicity of imidazole plays an important role in biological processes. The imidazole ring in the amino acid histidine is often involved as a proton acceptor in the active site of enzymes (see Section 18.9.A for an example).



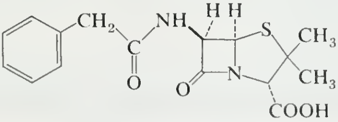
histidine

The thiazole ring is also important in nature. It occurs, for example, in vitamin B_1, thiamine, a coenzyme required for the oxidative decarboxylation of α-keto acids.



thiamine

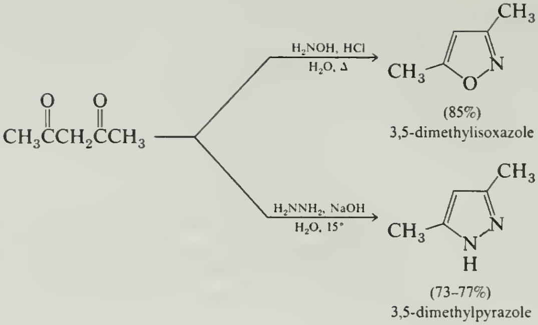
A tetrahydrothiazole also appears in the skeleton of penicillin, one of the first and still most important of the broad-spectrum antibiotics.



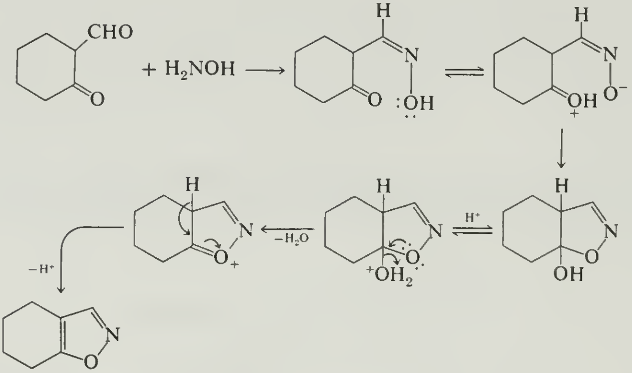
benzylpenicillin

B. *Synthesis*

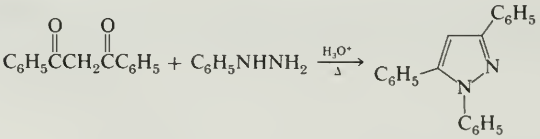
Pyrazoles and isoxazoles may be synthesized by the reaction of hydrazine or hydroxylamine with a 1,3-dicarbonyl compound or its equivalent.


CH₃CCH₂CCH₃
H₂NOH, HCl
H₂O, Δ
(85%)
3,5-dimethylisoxazole
H₂NNH₂, NaOH
H₂O, 15°
(73–77%)
3,5-dimethylpyrazole

The reaction proceeds through an oxime or hydrazone, which undergoes cyclization.

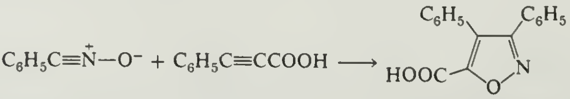

CHO
+ H₂NOH
H⁺
−H₂O
−H⁺

If a substituted hydrazine is used, a 1-substituted pyrazole results.



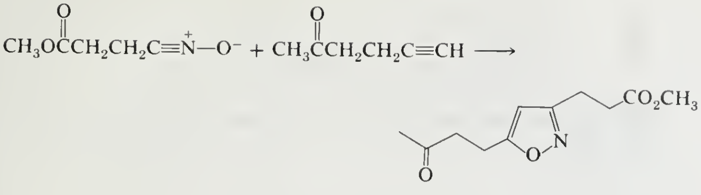
1,3,5-triphenylpyrazole

An alternative synthesis of isoxazoles involves the cycloaddition of a nitrile oxide to an acetylene.



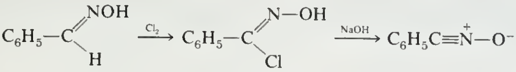
benzonitrile oxide

3,4-diphenylisoxazole-5-carboxylic acid

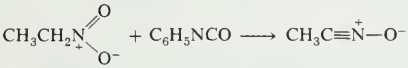

$CH_3OCCH_2CH_2C{\equiv}\overset{+}{N}{-}O^- + CH_3CCH_2CH_2C{\equiv}CH \longrightarrow$

(50%)

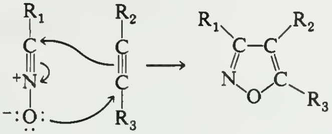
Nitrile oxides are unstable compounds generated *in situ* by the dehydration of a hydroxamic acid chloride, which is prepared by chlorination of an aldoxime.



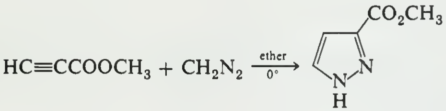
An alternative preparation involves dehydration of a nitroalkane.



The reaction is an example of a **1,3-dipolar cycloaddition,** and is analogous to the Diels-Alder reaction (Section 23.4.B; see also Section 36.2).

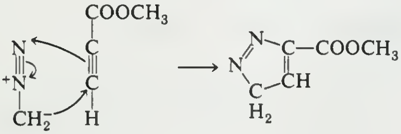


Pyrazoles may also be prepared by a 1,3-dipolar cycloaddition, this time between diazomethane and an acetylene.

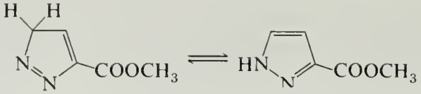


(80%)
methyl pyrazole-3-carboxylate

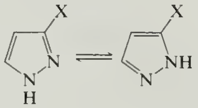
The reaction is formulated in a completely analogous manner:



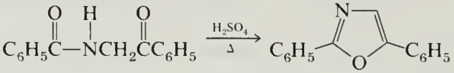
The initially-formed product tautomerizes to the more stable aromatic system.



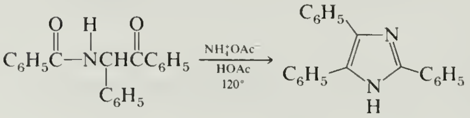
3-Substituted pyrazoles bearing a proton on nitrogen are in rapid equilibrium with the 5-isomers.



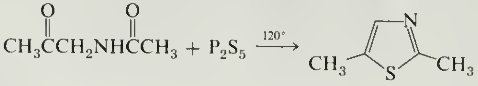
The most general synthesis of the 1,3-azoles is the dehydration of 1,4-dicarbonyl compounds, a form of Paal-Knorr cyclization.



2,5-diphenyloxazole



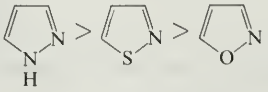
(93%)
2,4,5-triphenylimidazole



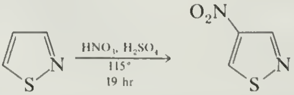
2, 5-dimethylthiazole

C. *Reactions*

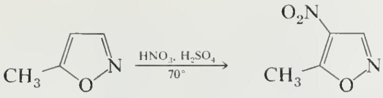
The azoles are markedly less reactive than furan, pyrrole, and thiophene. The reduced reactivity is due to the electronegative azole nitrogen. For the 1,2-azoles, the reactivity order is



Electrophilic substitution takes place exclusively at C-4.

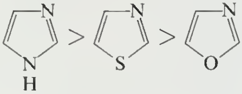


(97%)
4-nitroisothiazole

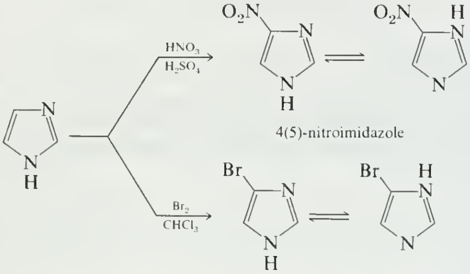


5-methylisoxazole 4-nitro-5-methylisoxazole

For the 1,3-azoles, the reactivity order seems to be

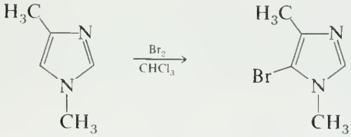


For imidazoles, which have been studied most extensively, substitution occurs preferentially at C-4 (equivalent to C-5).



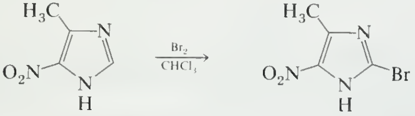
4(5)-nitroimidazole

4(5)-bromoimidazole



1,4-dimethylimidazole 5-bromo-1,4-dimethylimidazole

When both C-4 and C-5 are blocked, substitution occurs at C-2.



4-methyl-5-nitroimidazole 2-bromo-4-methyl-5-nitroimidazole

35.6
Pyridine

A. *Structure and Physical Properties*

Pyridine is an analog of benzene in which one of the CH units is replaced by nitrogen (Figure 35.7). The nitrogen lone pair is located in an sp^2 hybrid orbital

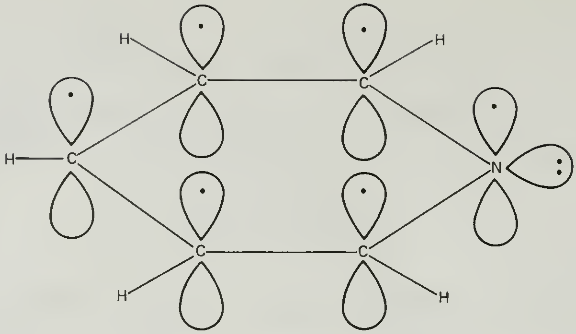
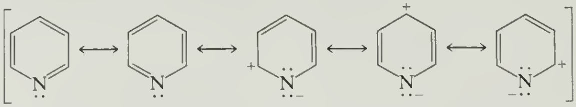
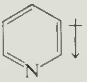


FIGURE 35.7 *Orbital; structure of pyridine.*

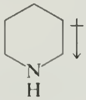
which is perpendicular to the π system of the ring. The effect on the basicity of the nitrogen (pK_a 5.2) has been discussed in Section 35.5.A. Various values have been deduced for the empirical resonance energy of pyridine, but it would appear to be roughly comparable to benzene. The resonance stabilization is shown by the two equivalent Kekulé structures and the three zwitterionic forms with negative charge on nitrogen.



The surplus negative charge on nitrogen is manifest in the dipole moment of pyridine, which is substantially greater than that of piperidine, the nonaromatic analog. That is, the π moment is in the same direction as the σ moment and the net moment is additive.



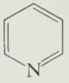
2.26 D



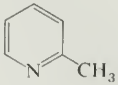
1.17 D

As the charged resonance structures and the dipole moment show, the ring in pyridine is relatively electron deficient. This deficiency is reflected in many of the reactions of pyridine (Section 35.6.C).

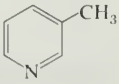
Alkylpyridines have the trivial names of picolines (C_6H_7N), lutidines (C_7H_9N), or collidines ($C_8H_{11}N$).



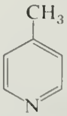
pyridine
b.p. 115°



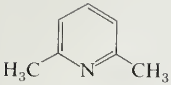
α-picoline
b.p. 128°

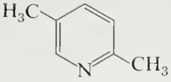


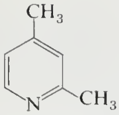
β-picoline
b.p. 144°

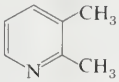


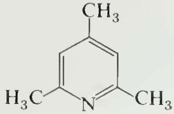
γ-picoline
b.p. 144°

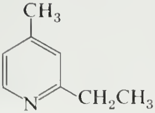

2,6-lutidine
b.p. 144°

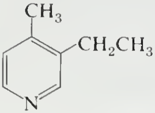

2,5-lutidine
b.p. 157°


2,4-lutidine
b.p. 157°


2,3-lutidine
b.p. 163°


sym-collidine
b.p. 170°

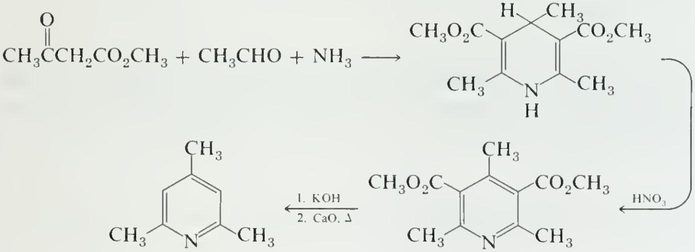

α-collidine
b.p. 179°


β-collidine
b.p. 196°

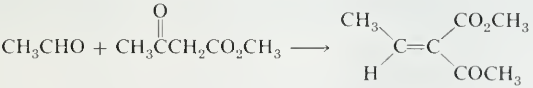
B. *Synthesis*

Pyridine itself and most of the simpler alkylpyridines are available from coal tar distillates. Several syntheses are available for deriving substituted pyridines from other compounds.

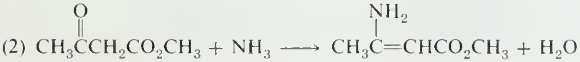
The most general technique for constructing the ring is the **Hantzsch pyridine synthesis.** Although numerous variations are known, the simplest consists of the condensation of a β-keto ester with an aldehyde and ammonia. The product is a 1,4-dihydropyridine, which is subsequently aromatized by oxidation.



A reasonable mechanism for the Hantzsch reaction is outlined as follows. The first step is probably a Knoevenagel condensation of the aldehyde (Section 26.4.E) with the β-keto ester.

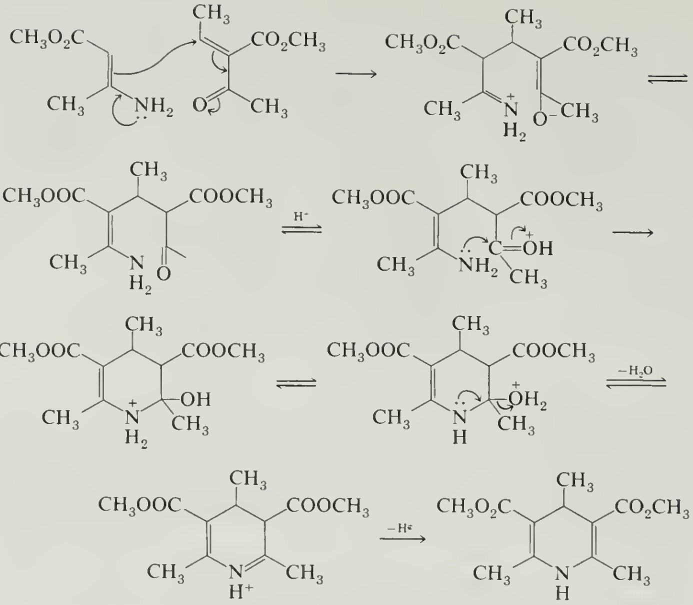
(1) 

This unsaturated keto ester undergoes a condensation with the enamine produced from ammonia and the original keto ester.



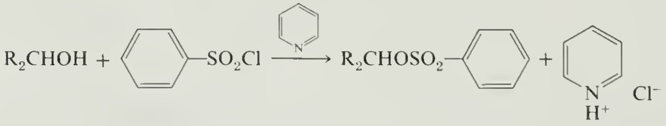
$$(2)\quad CH_3\overset{\overset{O}{\|}}{C}CH_2CO_2CH_3 + NH_3 \longrightarrow CH_3\overset{\overset{NH_2}{|}}{C}{=}CHCO_2CH_3 + H_2O$$

(3)



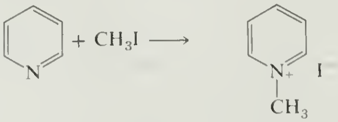
C. *Reactions*

The nitrogen lone pair has basic and nucleophilic properties, although both are diminished by the hybridization effect. Pyridines form salts with acids and are widely used as catalysts and "acid scavengers" in reactions where strong acids are produced.



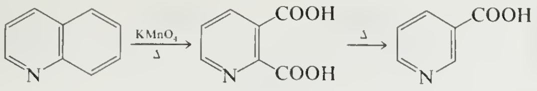
pyridinium chloride

The nitrogen may be alkylated by primary alkyl halides, leading to N-alkylpyridinium salts.



N-methylpyridinium iodide

Pyridines are rather resistant to oxidation, as reaction (35-7) demonstrates.



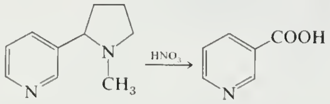
(35-7)

quinoline

(65–70%)
quinolinic acid

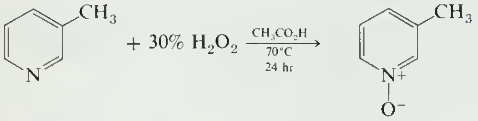
nicotinic acid (niacin)

Reaction (35-7) provides a route to *β*-pyridine derivatives. Nicotinic acid is present in minute amounts in all living cells. The corresponding amide, niacinamide, is an essential B vitamin. Nicotinic acid is also produced by oxidation of nicotine, an alkaloid present to the extent of 2–8% in the dried leaves of *Nicotiana tabacum*. Nicotine is used as an agricultural insecticide but is also toxic to man; the fatal dose is about 40 mg.



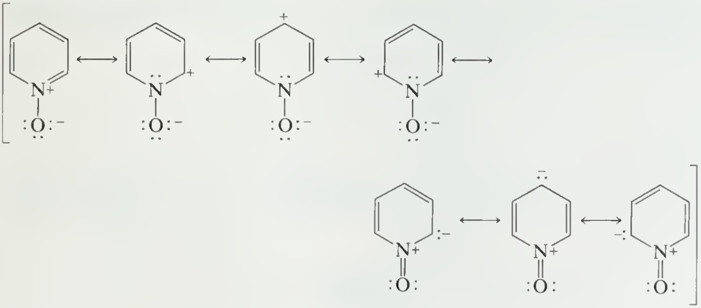
nicotine

Because of its resistance to oxidation, pyridine is commonly used as a solvent for chromium trioxide oxidations (Sarrett procedure, see also Section 15.5.A). However, under the proper conditions, the nitrogen is oxidized to the N-oxide, as are other tertiary amines (Section 27.7.C).

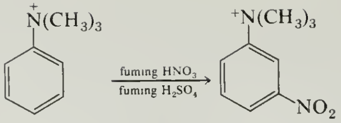


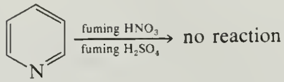
(75%)
3-methylpyridine N-oxide

As we shall see later, pyridine N-oxides are important synthetic intermediates. The electronic structure may be described by the following resonance forms:

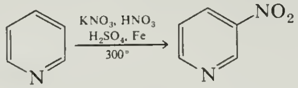


Pyridine is resistant to electrophilic aromatic substitution conditions, not only because of the electron deficient ring but also because under the acidic conditions of such reactions the nitrogen is protonated or complexed with a Lewis acid. In general, pyridine is *less* reactive in such reactions than trimethylanilinium ion.

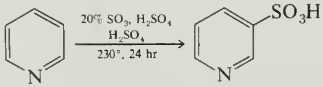

$\overset{+}{N}(CH_3)_3$
fuming HNO_3
fuming H_2SO_4
$^+N(CH_3)_3$
NO_2


N
fuming HNO_3
fuming H_2SO_4
no reaction

Substitution is achieved only under the most drastic conditions, for example

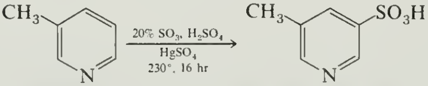

N
KNO_3, HNO_3
H_2SO_4, Fe
300°
NO_2
N

(22%)
3-nitropyridine


N
20% SO_3, H_2SO_4
H_2SO_4
230°, 24 hr
SO_3H
N

(71%)
pyridine-3-sulfonic acid

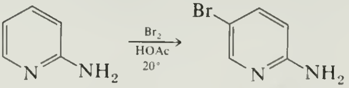
Alkyl and amino groups activate the ring toward electrophilic substitution. In the alkylpyridines, the ring nitrogen directing influence predominates (C-3 or C-5 attack) regardless of the position of alkylation.


CH_3
N
20% SO_3, H_2SO_4
$HgSO_4$
230°, 16 hr
CH_3
SO_3H
N

β-picoline

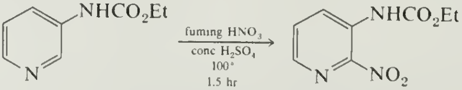
5-methylpyridine-3-sulfonic acid

Amino groups, either free or acylated, govern the position of further substitution (*ortho* or *para* to the amino).


N
NH_2
Br_2
HOAc
20°
Br
N
NH_2

2-aminopyridine

(90%)
5-bromo-2-aminopyridine

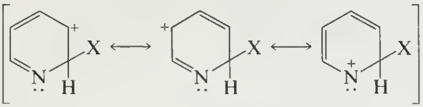

$NHCO_2Et$
N
fuming HNO_3
conc H_2SO_4
100°
1.5 hr
$NHCO_2Et$
N
NO_2

ethyl N-(3-pyridyl)-carbamate

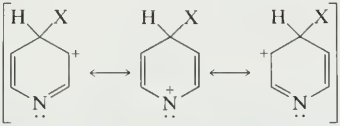
(61%)
ethyl N-(2-nitro-3-pyridyl)-carbamate

The predominant 3-substitution in pyridine is explainable in terms of the resonance structures of the intermediate ions, and the corresponding transition states, produced by electrophilic attack at the three positions.

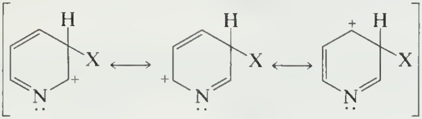
Attack at C-2



Attack at C-4

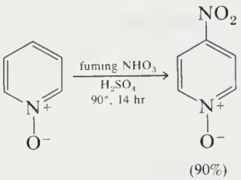


Attack at C-3

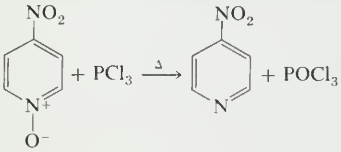


Compared to the ion produced from benzene, all three ions are destabilized by the inductive effect of the nitrogen, especially if it is protonated or coordinated with a Lewis acid. However, the situation is much worse when attack is at C-2 or C-4 than at C-3. In the two former cases, one of the structures of the intermediate ion has the positive charge on an electron deficient nitrogen. Thus, the situation in pyridine is similar to that in nitrobenzene. Electrophilic attack is retarded at all positions, but especially at C-2 and C-4.

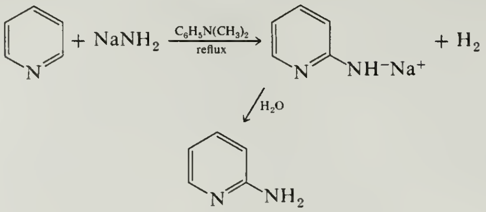
Pyridine N-oxides undergo electrophilic substitution somewhat more readily. Reaction generally occurs at C-4.



The N-oxide can often be used as an "activated" form of the pyridine. Treatment of the substituted N-oxide with PCl_3 results in deoxygenation.

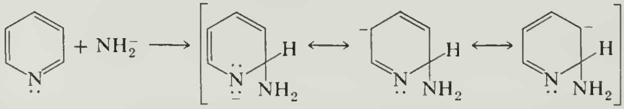


The electron deficient nature of the pyridine ring is also manifest in the ease with which pyridines undergo **nucleophilic substitution**. A particularly useful and unusual example is the synthesis of aminopyridines by the reaction of a pyridine with an alkali metal amide **(Chichibabin reaction).**

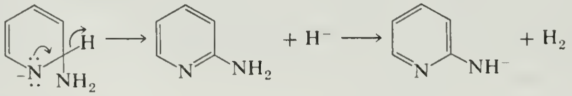

N
+ NaNH2
C6H5N(CH3)2
reflux
N
NH⁻Na⁺
+ H2
H2O
N
NH2

(70–80%)
2-aminopyridine

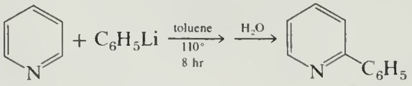
Attack occurs at C-2 or C-6, unless both positions are occupied. In such cases, substitution can occur at C-4. The reaction is initiated by attack by the nucleophile at C-2 or C-4. Attack occurs at these positions because the negative charge can be delocalized onto the ring nitrogen.


N
+ NH2⁻
N
H
NH2
N
H
NH2
N
H
NH2

The second step is elimination of hydride ion, which reacts with the aminopyridine to give H_2. The driving force for the elimination of hydride ion is, of course, the formation of the aromatic cycle.

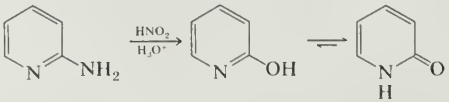

H
N
NH2
N
NH2
+ H⁻
N
NH⁻
+ H2

Chichibabin-like reactions are also observed with organolithium compounds.

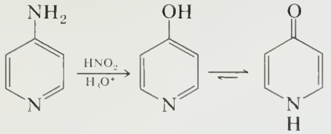

N
+ C6H5Li
toluene
110°
8 hr
H2O
N
C6H5

(50%)
2-phenylpyridine

Diazotization of the 2- and 4-aminopyridines yields the 2- and 4-hydroxypyridines, which exist completely in the keto form (for example, α-pyridone, γ-pyridone).

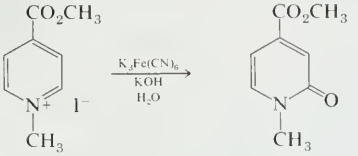

N
NH2
HNO2
H3O⁺
N
OH
N
H
O

α-pyridone



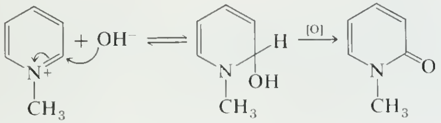
γ-pyridone

N-Alkylated α-pyridones may be produced by the ferricyanide oxidation of N-alkylpyridinium salts.

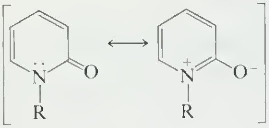


(96%)
methyl N-methyl-2-pyridone-4-carboxylate

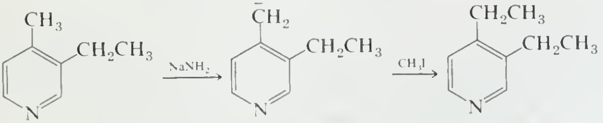
The oxidation occurs by initial addition of hydroxide to give a dihydropyridine, which is then oxidized to the pyridone. Even though the simple pyridones exist



in the tautomeric form with hydrogen attached to nitrogen (amide form), they still have extensive aromatic character as shown by the important dipolar resonance structure:

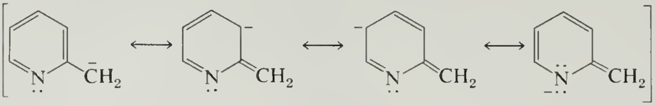


A final feature of the pyridine ring is of interest. The methyl groups in α- and γ-picoline are comparable in acidity to methyl ketones and readily undergo base-catalyzed reactions.

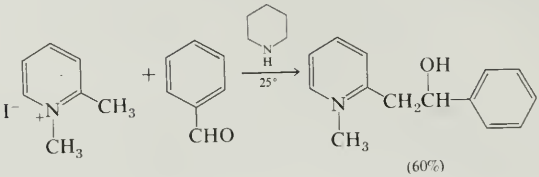


(80%)
3,4-diethylpyridine

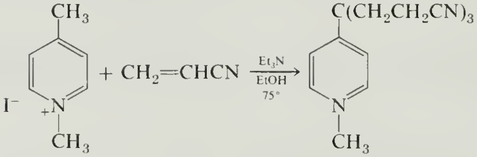
The enhanced acidity at these positions is again attributed to delocalization of negative charge in the intermediate anion into the ring and especially onto the nitrogen.


N
CH₂
N
CH₂
N
CH₂
N
CH₂

This side chain acidity is enhanced in the N-alkylpyridinium compounds.


I⁻
N
CH₃
CH₃
CHO
N
H
25°
OH
N
CH₂CH
CH₃

(60%)

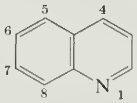

CH₃
I⁻
N
CH₃
+ CH₂=CHCN
Et₃N
EtOH
75°
C(CH₂CH₂CN)₃
N
CH₃

(92%)

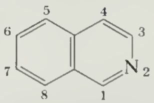
35.7
Quinoline and Isoquinoline

A. *Structure and Nomenclature*

Quinoline and isoquinoline are benzopyridines.



quinoline
b.p. 238°
pK_a 4.8



isoquinoline
b.p. 243°
pK_a 5.4

The orbital structures of both compounds are related to those of pyridine (Section 35.6.A) and naphthalene (Section 34.3.A). Both are weak bases, with pK_as comparable to that of pyridine. Alkaloids based on the quinoline and isoquinoline skeleton are widespread in the plant kingdom (Section 27.9).

The nmr spectrum of quinoline is shown in Figure 35.8. Note the downfield position of the resonances, a consequence of the electron attracting effect of the pyridine nitrogen.

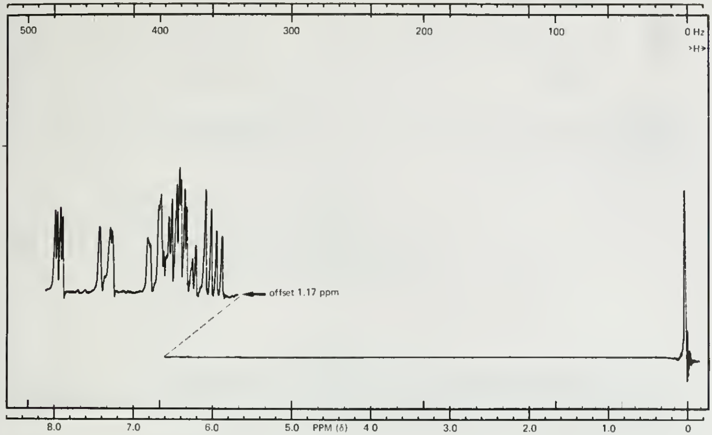
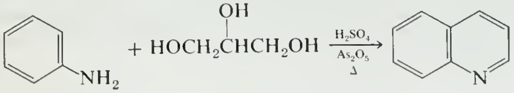


FIGURE 35.8 *Nmr spectrum of quinoline.*

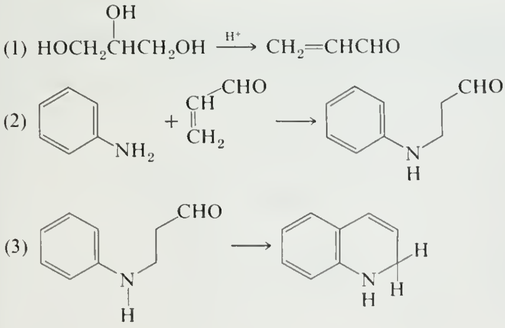
B. *Synthesis*

The most general method for synthesizing quinolines is the **Skraup reaction,** in which aniline or a substituted aniline is treated with glycerol, sulfuric acid, and an oxidizing agent such as As_2O_5, ferric salts, or the nitro compound corresponding to the amine used.

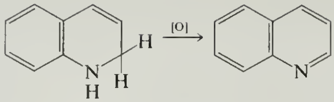


(84–91%)

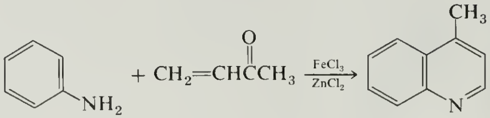
The mechanism of the Skraup reaction probably involves initial dehydration of the glycerol to give acrolein, which undergoes a 1,4-addition by the aniline. The resulting β-anilinopropionaldehyde is then cyclized to a dihydroquinoline, which is finally oxidized to give the product.



(1) $HOCH_2\overset{OH}{\overset{|}{C}}HCH_2OH \xrightarrow{H^+} CH_2{=}CHCHO$

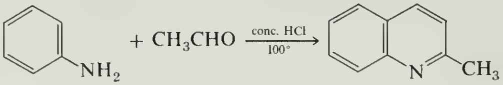
(4) 

Identical results are obtained if an α,β-unsaturated ketone or aldehyde is substituted for the glycerol.


NH2
+ CH2=CHCCH3
O
FeCl3
ZnCl2
CH3
N

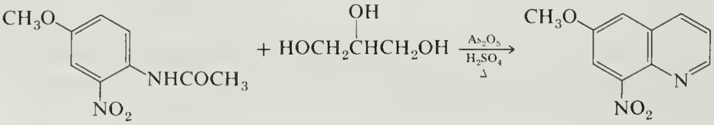
(73%)
lepidine

If a saturated aldehyde is used, an initial aldol condensation occurs to give an α,β-unsaturated aldehyde which engages in the normal condensation **(Döbner-Miller reaction).**


NH2
+ CH3CHO
conc. HCl
100°
N
CH3

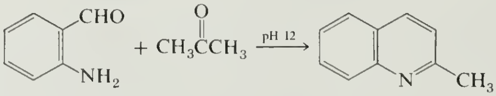
(32%)
quinaldine

In some of these cases an oxidizing agent is not included; in these cases unsaturated reaction intermediates probably serve as oxidizing agents, but this point has not been established. The Skraup synthesis is extremely versatile; almost any desired quinoline may be prepared by using the proper combination of aniline and aldehyde, so long as the reagents will survive the hot acid conditions. A more complex example is

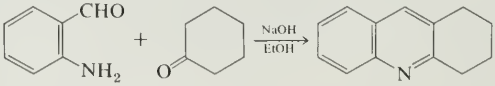

CH3O
NHCOCH3
NO2
OH
+ HOCH2CHCH2OH
As2O5
H2SO4
Δ
CH3O
N
NO2

(67%)
6-methoxy-8-nitroquinoline

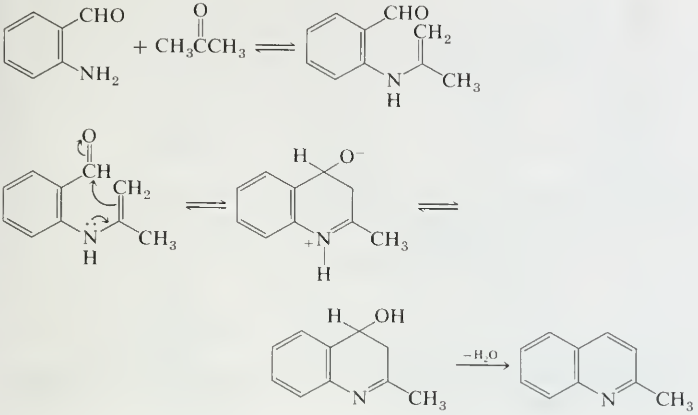
A second general preparation of quinolines is the **Friedländer synthesis.** In this method an *o*-aminobenzaldehyde is condensed with a ketone.


CHO
NH2
O
+ CH3CCH3
pH 12
N
CH3

(85%)

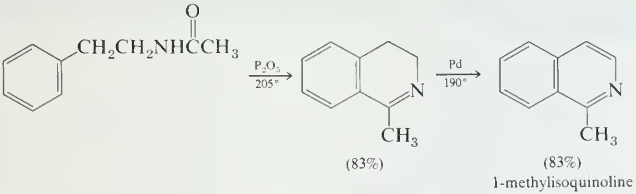

CHO
NH2
+
O
NaOH
EtOH
N

The Friedländer synthesis probably involves the following reaction steps:


CHO
NH₂
+ CH₃CCH₃
CHO
CH₂
N
H
CH₃
O
CH
CH₂
N
H
CH₃
H
O⁻
+N
H
CH₃
H
OH
N
CH₃
−H₂O
N
CH₃

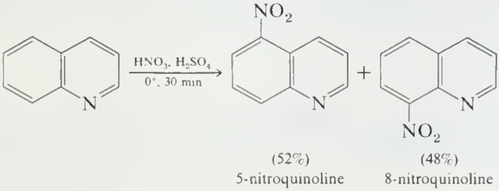
Although substituted *o*-aminobenzaldehydes are not readily available, the parent compound is, and the reaction occurs smoothly with a variety of aldehydes and ketones. It constitutes a good method for the synthesis of quinolines substituted in the pyridine ring.

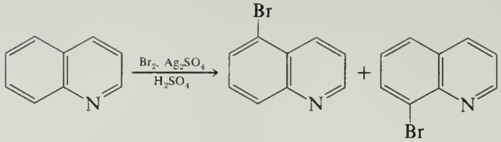
Isoquinolines are most easily prepared by a reaction known as the **Bischler-Napieralski synthesis.** An acyl derivative of a β-phenylethylamine is treated with a dehydrating agent to give a dihydroisoquinoline, which is dehydrogenated to the isoquinoline.


O
CH₂CH₂NHCCH₃
P₂O₅
205°
N
CH₃
(83%)
Pd
190°
N
CH₃
(83%)
1-methylisoquinoline

C. *Reactions*

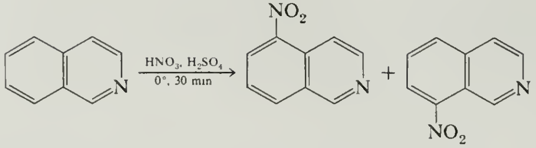
Quinoline and isoquinoline are considerably more reactive than pyridine in electrophilic substitution reactions. For reactions carried out in strongly acidic solution, reaction occurs on the protonated form and substitution occurs in the benzene ring at C-5 and C-8.


N
HNO₃, H₂SO₄
0°, 30 min
NO₂
N
+
N
NO₂
(52%)
5-nitroquinoline
(48%)
8-nitroquinoline


Br
Br_2, Ag_2SO_4
H_2SO_4
N
+
Br

(51%)
5-bromoquinoline

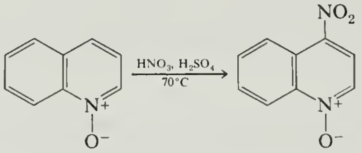
(49%)
8-bromoquinoline


NO_2
HNO_3, H_2SO_4
0°, 30 min
N
+
NO_2

(90%)
5-nitroisoquinoline

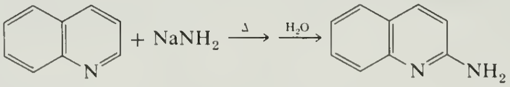
(10%)
8-nitroisoquinoline

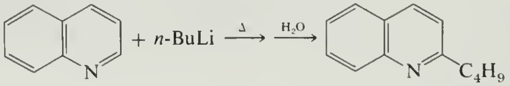
As with pyridine N-oxide, quinoline N-oxide undergoes nitration considerably more easily; reaction occurs at C-4.

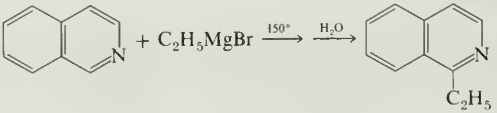

HNO_3, H_2SO_4
70°C
NO_2
N+
O⁻

(67%)

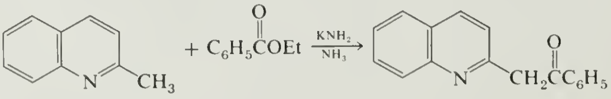
Both compounds readily undergo nucleophilic substitution reactions of the Chichibabin type.


+ $NaNH_2$
Δ
H_2O
N
NH_2


+ n-BuLi
Δ
H_2O
N
C_4H_9

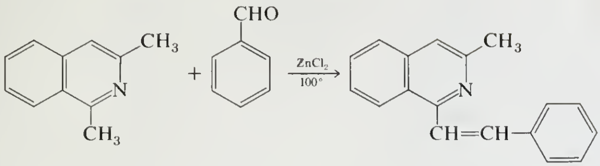

+ C_2H_5MgBr
150°
H_2O
N
C_2H_5

As with 2- and 4-alkylpyridines, 2- and 4-alkylquinolines and 1-alkylisoquinolines have α-hydrogens that are significantly acidic and enter into base-catalyzed reactions.

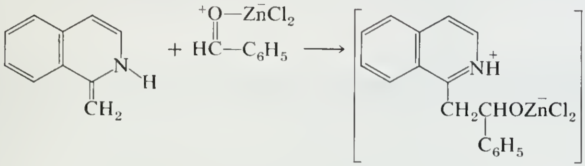

CH_3
+ $C_6H_5\overset{O}{\overset{\|}{C}}OEt$
KNH_2
NH_3
N
$CH_2\overset{O}{\overset{\|}{C}}C_6H_5$

(60%)

Acid-catalyzed analogs also occur, for example



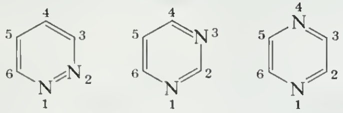
This reaction probably involves the alkylation of an intermediate enamine tautomer (see Section 27.8.E).



35.8 Diazines

A. *Structure and Occurrence*

In this section, we shall take a brief look at another class of heterocycles, the diazines. The three types of diazabenzenes are

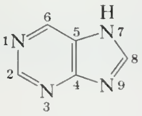


pyridazine
b.p. 208°
pK_a 2.3

pyrimidine
b.p. 134°
pK_a 1.3

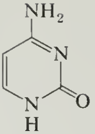
pyrazine
b.p. 118°
pK_a 0.7

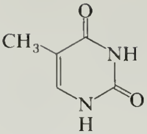
In addition to these three diazines, the bicyclic tetraaza compound, purine, is an important heterocyclic system.

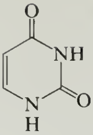


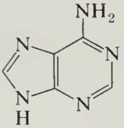
purine
m.p. 217°
pK_a 2.3

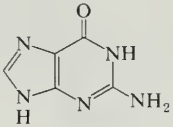
These ring systems, particularly that of pyrimidine, occur commonly in natural products. The pyrimidines, cytosine, thymine, and uracil are especially important because they are components of nucleic acids, as are the purine derivatives adenine and guanine (Section 36.3).


cytosine

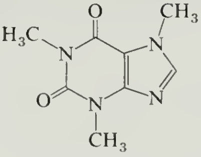

thymine

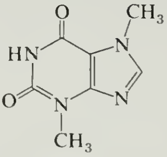

uracil


adenine


guanine

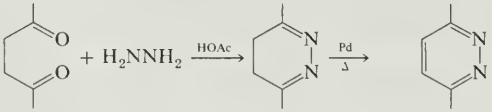
The purine nucleus also occurs in such compounds as caffeine (coffee and tea) and theobromine (cacao beans).

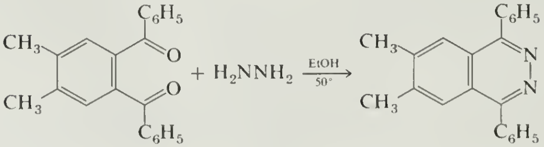

caffeine


theobromine

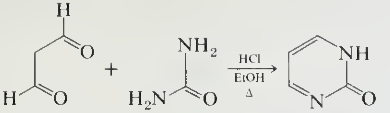
B. *Synthesis*

Pyridazines are prepared by the reaction of hydrazine with 1,4-dicarbonyl compounds.

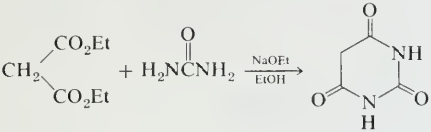

2,5-dimethylpyridazine


1,4-diphenyl-6,7-dimethylphthalazine

Pyrimidines may be most easily prepared by condensations between 1,3-dicarbonyl compounds and a material containing the general structure N—C—N, such as urea.



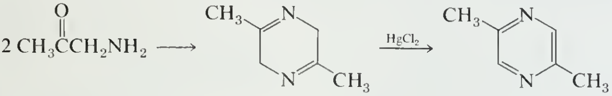
(73%)
2-pyrimidone



(72–78%)
barbituric acid

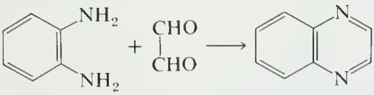
Note that the C-2 oxygenated pyrimidine, like the C-2 oxygenated pyridine, exists in the keto form.

Pyrazines result from the dimerization of α-aminocarbonyl compounds. The initial dihydropyrazines may be oxidized to obtain the pyrazine.



2,5-dimethylpyrazine

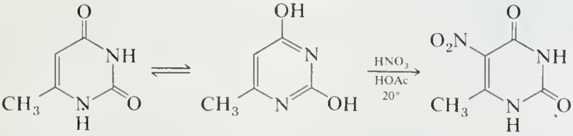
Pyrazines are also obtained from the condensation of 1,2-diamines with 1,2-dicarbonyl compounds. When 1,2-diaminobenzene (*o*-phenylenediamine) is used, the product is a benzopyrazine (quinoxaline). The reaction has been used as a diagnostic test for such 1,2-dicarbonyl compounds.



(85–90%)
quinoxaline

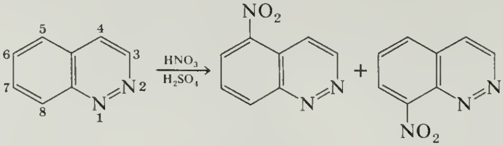
C. *Reactions*

Because of the second nitrogen in the ring system, the diazines are even less reactive than pyridine towards electrophilic substitution. When activating groups are present on the ring, such substitutions may occur.

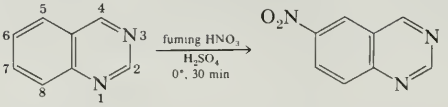


(85%)

As with quinoline and isoquinoline, attack on the benzodiazines occur in the benzene ring.


5
4
6
3
7
2
8
1
N
N
HNO_3
H_2SO_4
NO_2
+
NO_2

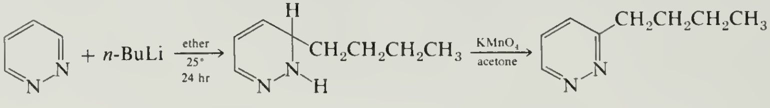
cinnoline 5-nitrocinnoline 8-nitrocinnoline


5
4
6
N3
7
2
8
N
1
fuming HNO_3
H_2SO_4
0°, 30 min
O_2N
N
N

(56%)

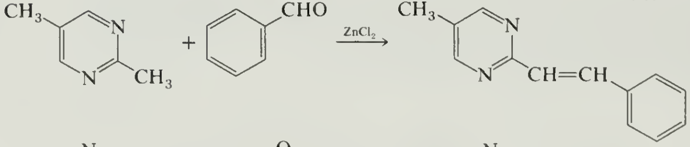
quinazoline 6-nitroquinazoline

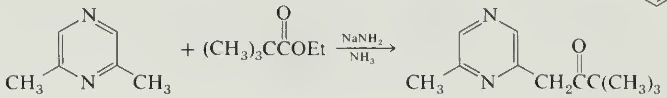
Many other reactions of the diazines and their benzo derivatives are similar to those observed with pyridine, quinoline, and isoquinoline. The following reactions illustrate some of these similarities.


+ n-BuLi
ether
25°
24 hr
H
$CH_2CH_2CH_2CH_3$
H
$KMnO_4$
acetone
$CH_2CH_2CH_2CH_3$
N
N

(66%)

(77%)
3-butylpyridazine

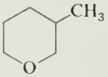

CH_3
N
N
CH_3
+
CHO
$ZnCl_2$
CH_3
N
N
CH=CH

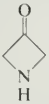

N
CH_3
N
CH_3
O
$+ (CH_3)_3CCOEt$
$NaNH_2$
NH_3
N
CH_3
N
O
$CH_2CC(CH_3)_3$

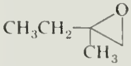
(81%)

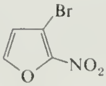
PROBLEMS

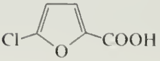
1. Name each of the following compounds.

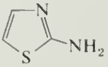
(a)


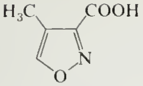
(b)


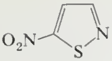
(c)

CH_3CH_2
O
CH_3

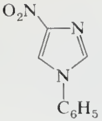
(d)


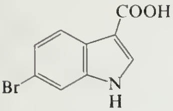
(e)


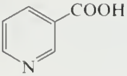
(f)


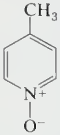
(g)


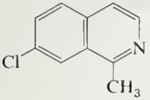
(h)


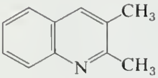
(i)


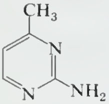
(j)


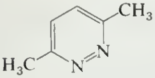
(k)


(l)


(m)


(n)


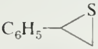
(o)


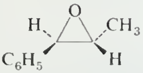
(p)


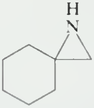
2. Write a structure for each compound.

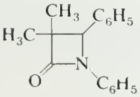
(a) 1,2-diphenylaziridine
(b) 2,5-dihydrofuran
(c) 1-methyl-2-pyridone
(d) 8-bromoisoquinoline
(e) 7-methyl-6-aminopurine
(f) 2-aminopurine
(g) (3-indolyl)acetic acid
(h) 4-nitroquinoline-1-oxide
(i) 4-chlorothiophene-2-carboxylic acid
(j) 2-methyl-5-phenylpyrazine
(k) 5-nitroquinoline-2-carboxylic acid
(l) 2-nitrothiazole
(m) 3-cyanoisoxazole

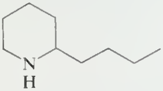
3. Outline a synthesis for each of the following compounds.

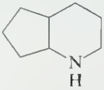
(a)


(b)

O
H
CH3
C6H5
H

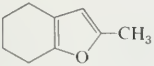
(c)


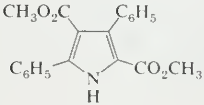
(d)

CH3
C6H5
H3C
N
O
C6H5

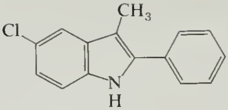
(e)


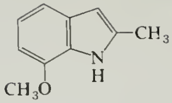
(f)


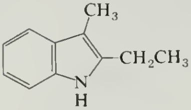
4. Outline a synthesis for each of the following compounds, starting from nonheterocyclic precursors.

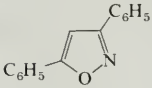
(a)


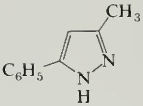
(b)

CH3O2C
C6H5
C6H5
CO2CH3
N
H

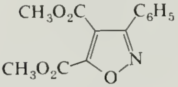
(c)


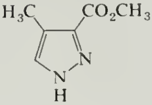
(d)


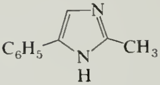
(e)

CH$_3$
CH$_2$CH$_3$
N
H

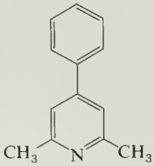
(f)

C$_6$H$_5$
C$_6$H$_5$
O
N

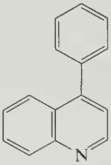
(g)

CH$_3$
C$_6$H$_5$
N
N
H

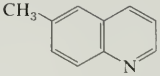
(h)

CH$_3$O$_2$C
C$_6$H$_5$
CH$_3$O$_2$C
O
N

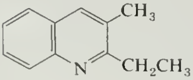
(i)

H$_3$C
CO$_2$CH$_3$
N
N
H

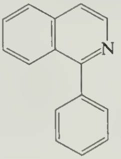
(j)

N
C$_6$H$_5$
CH$_3$
N
H

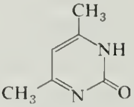
(k)


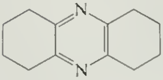
(l)


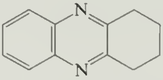
(m)


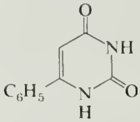
(n)

CH$_3$
N
CH$_2$CH$_3$

(o)


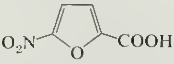
(p)

CH$_3$
NH
CH$_3$
N
O

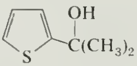
(q)


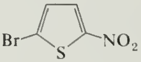
(r)


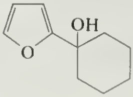
(s)

O
NH
C$_6$H$_5$
N
O
H

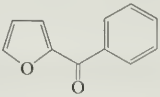
5. Outline a synthesis for each of the following compounds from the corresponding unsubstituted or alkyl-substituted heterocyclic system.

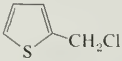
(a)


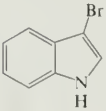
(b)


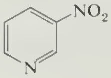
(c)


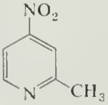
(d)


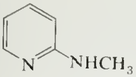
(e)


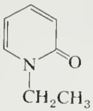
(f)


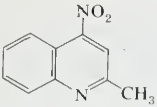
(g)


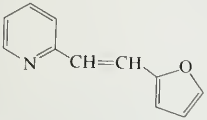
(h)


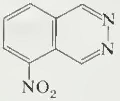
(i)


(j)


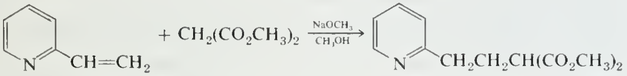
(k)


(l)


(m)


(n)


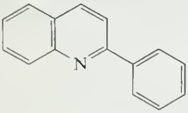
6. Write a reasonable mechanism that explains the following reaction:

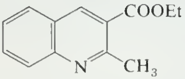


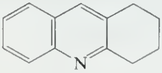
7. *o*-Aminobenzaldehyde is a useful starting material in the Friedländer synthesis of quinolines.

(a) Synthesize this compound from available materials.

(b) Use *o*-aminobenzaldehyde in the synthesis of the following compounds:

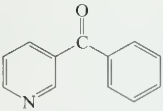




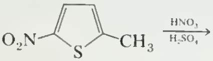


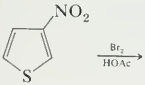
(c) The mechanism of the Friedländer synthesis given on page 1107 was abbreviated. Write out the complete mechanism, showing all of the intermediates involved.

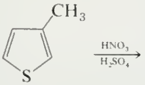
8. The pyridine ring is so inert that Friedel-Crafts reactions fail completely. Suggest a method to synthesize phenyl 3-pyridyl ketone.

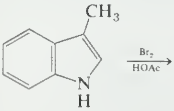


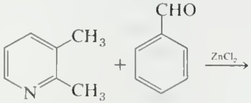
9. Predict the major product from each of the following reactions.

(a)


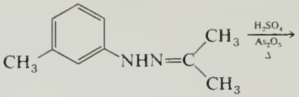
(b)


(c)


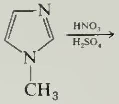
(d)


(e)


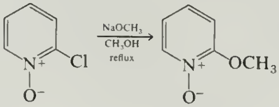
(f)


CH3
NHN=C
CH3
CH3
H2SO4
As2O5
Δ

(g)

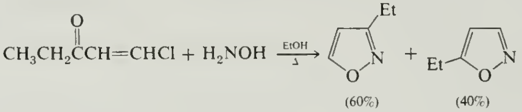

N
N
CH3
HNO3
H2SO4

10. Write a reasonable mechanism for the following reaction:

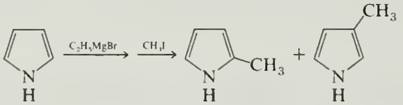

N+
O−
Cl
NaOCH3
CH3OH
reflux
N+
O−
OCH3

11. Pyridine N-oxide reacts with benzyl bromide to give N-benzyloxypyridinium bromide. Treatment of this salt with strong base gives benzaldehyde (92%) and pyridine. Rationalize with a reasonable mechanism.

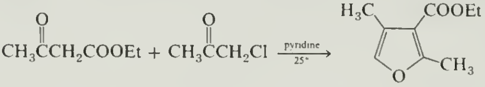
12. Write a mechanism, showing all steps, that explains the following reaction.


O
CH3CH2CCH=CHCl + H2NOH
EtOH
Δ
Et
N
O
+
Et
N
O
(60%)
(40%)

13. Pyrrole reacts with ethylmagnesium bromide, followed by methyl iodide, to give a mixture of 2- and 3-methylpyrrole. Rationalize this result, using resonance structures where desirable.


N
H
C2H5MgBr
CH3I
N
H
CH3
+
CH3
N
H

14. Write a mechanism for the following reaction in which a furan is produced:

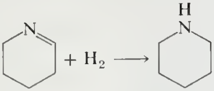

O
CH3CCH2COOEt + CH3CCH2Cl
O
pyridine
25°
H3C
COOEt
CH3
O

15. Explain why the methyl protons in 1-methylisoquinoline are more acidic than the methyl protons in 3-methylisoquinoline.

16. Heats of formation for some five-membered ring compounds are given in the table below. Compare the heats of hydrogenation of furan, pyrrole, and thiophene with that of cyclopentadiene. Derive the corresponding empirical resonance energies assuming that cyclopentadiene has no aromatic resonance energy.

Compound	ΔH_f° (gas, 25°), kcal mol^{-1}
cyclopentadiene	31.4
cyclopentane	−18.4
furan	−8.3
tetrahydrofuran	−44.0
thiophene	27.6
tetrahydrothiophene	−8.1
pyrrole	25.9
pyrrolidine	−0.8

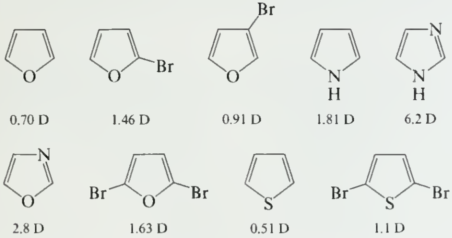
17. Heats of formation, ΔH_f°, are pyridine, +34.6, and piperidine, −11.8 kcal mole⁻¹. Before these data can be used to estimate the empirical resonance energy of pyridine, we need a value for the heat of hydrogenation of a C=N double bond. Unfortunately, little good data are available for such bonds, but the thermodynamic data that are available suggest a value of −20 kcal mole⁻¹ for ΔH° for the reaction



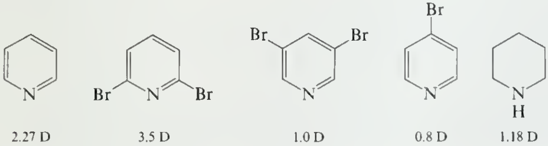
(a) Use this information together with corresponding results for the heat of hydrogeneration of cyclohexene (Appendix I) and derive an empirical resonance energy for pyridine.

★(b) An alternative method for calculating the empirical resonance energy is to compare the experimental heat of atomization with that obtained by use of a table of average bond energies, such as that in Appendix III. Compare the value you calculate by this method with the commonly quoted value for the resonance energy of pyridine of 23 kcal mole⁻¹. To get some insight into the source of the discrepancy, compare the calculated and observed heats of atomization of piperidine. How accurate are the results expected from the use of average bond energies?

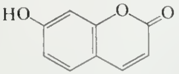
18. Dipole moments of furan, thiophene, and pyrrole were discussed in Section 35.3.A, and the assignments of directions of the dipoles were presented. Given the following dipole moment data, deduce whether the directions assigned are correct.



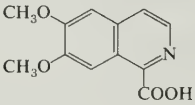
19. Given the following dipole moments, deduce the direction of the dipole moment of pyridine. Compared to the dipole moment of piperidine, is this direction reasonable?

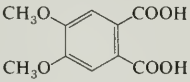


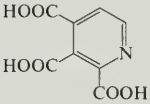
20. Umbelliferone is a coumarin derivative present as a glucoside in many plants, for example, in several species of japonica. It is used commercially as a sun-screen in lotions. Show how it may be synthesized from resorcinol.

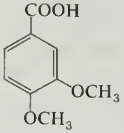


21. Papaverine, $C_{20}H_{21}O_4N$, is an alkaloid present in opium and is used as a muscle relaxant. It is nonaddicting but is classified as a narcotic. Reaction with excess hydriodic acid gives 4 moles of CH_3I and shows the presence of 4 CH_3O groups (Zeisel determination). Oxidation with $KMnO_4$ gives first a ketone, $C_{20}H_{19}O_5N$, which on continued oxidation gives a mixture from which the compounds shown below were isolated and identified. Deduce the structure of papaverine and interpret the reactions described.


CH3O
CH3O
N
COOH


CH3O
COOH
CH3O
COOH


HOOC
HOOC
N
COOH


COOH
OCH3
OCH3

22. Write a mechanism for the base-catalyzed chlorination of an oxime to give a hydroxamic acid chloride (page 1093).

CHAPTER 36
Special Topics

36.1
Aromaticity

A. *The Hückel 4n + 2 Rule*

In Section 21.1.C, we learned that the π electronic system of benzene consists of a pair of electrons of opposite spin contained in each of three π molecular orbitals having quantum numbers of 0, +1, and −1. In general, for all cyclic π electronic systems, successive molecular orbitals can be characterized by quantum numbers of $\pm n$, where n is any integer.

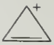
> The absolute value of the quantum number, n, indicates the number of nodal planes that bisect the ring. Alternatively, and equivalently, we can consider the quantum number to represent the angular momentum of an electron circling round the ring. The lowest level then corresponds to an electron having zero angular momentum. Thereafter, the momentum can be represented clockwise or counterclockwise about the ring; hence, above zero the quantum numbers come as ± integer pairs.

A filled orbital shell corresponds to a relatively stable electronic configuration. Examples in atomic orbitals are the filled $1s$ shell of helium and the filled $2p$ shell or neon. Similarly, filled π molecular orbital shells give the stability associated with "aromatic" systems and bestow that stabilization commonly known as aromatic character or aromaticity. It takes two electrons of opposite spin to fill the lowest π molecular orbital level for which $n = 0$. Thereafter, four electrons are required to give a filled π molecular orbital shell. That is, filled shells are associated with a total of $4n + 2$ electrons, or two ($n = 0$), six ($n = 1$), ten ($n = 2$), fourteen ($n = 3$), and so on, electrons. This rule is known as the Hückel $4n + 2$ rule after Erich Hückel, the German theoretical chemist who first developed the rule in the mid-1930s.

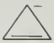
Many examples of compounds are now known to which the Hückel rule can be applied. The results are truly remarkable for such a simple rule; a vast amount of experimental chemistry can be summarized by the generalization that *those monocyclic π systems with $4n + 2$ electrons show relative stability compared to acyclic analogs.* Furthermore, those monocyclic systems with other than $4n + 2$ electrons appear to be destabilized relative to acyclic analogs and can be said to have "antiaromatic" character. In succeeding sections we will summarize some of the experimental evidence for several values of n.

B. *Two-Electron Systems*

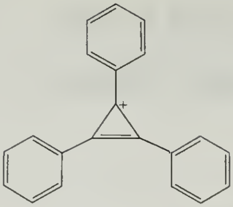
One two-electron cyclic π system is obviously ethylene, a well-known and relatively stable compound. However, another cyclic π system with two electrons is cyclopropenyl cation, a rather stable carbonium ion.



cyclopropenyl cation



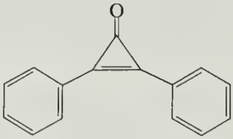
cyclopropenyl anion



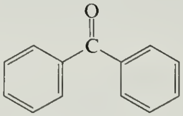
triphenylcyclopropenyl cation

Triphenylcyclopropenyl cation is such a stable carbonium ion that many of its salts can be isolated and stored in bottles. On the other hand, the cyclopropenyl anion is unknown. The acidity of the methylene group in the known hydrocarbon cyclopropene has been deduced from several experiments to be *less* than that of alkanes.

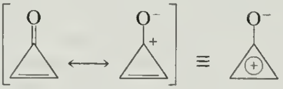
The generalization makes its appearance in some subtle ways. For example, compounds containing the cyclopropenone ring system have unusually high dipole moments; this result is explained on the basis that the dipolar resonance structure contributes more to the resonance hybrid of cyclopropenone because it embodies the "aromatic" cyclopropenyl cation.



$\mu = 5.08$ D
diphenylcyclopropenone



$\mu = 2.97$ D
benzophenone

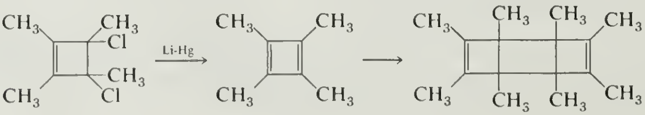


(36-1)

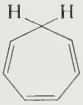
Example (36-1) also illustrates the use of an inscribed circle to represent an aromatic cycle of $4n + 2$ electrons.

C. *Six-Electron Systems*

The most important π cycle with six electrons is, of course, benzene, and its stability and "aromatic character" are now well-known to us. By contrast, both cyclobutadiene with four electrons and cyclooctatetraene with eight electrons are known hydrocarbons and behave as reactive polyolefins. Cyclobutadiene, for example, can be captured only at very low temperatures. Under most conditions it has but a fleeting existence and yields only dimeric products. This same reactivity is characteristic of various substituted derivatives, for example



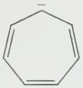
Some other six-electron systems are ions. Cyclopentadienyl anion was discussed earlier (Section 34.2.D) as a rather stable carbanion whose conjugate acid, cyclopentadiene, is an unusually acidic hydrocarbon with a pK_a of 16. The related isoelectronic heterocyclic compounds, furan and pyrrole, were discussed in the last chapter (Section 35.5.3). By contrast, cycloheptatriene is a nonacidic hydrocarbon; it appears to be less acidic than the open chain heptatriene. The cycloheptatrienyl anion has seven equivalent resonance structures of the type shown (36-2) and would be expected to have a well-distributed negative charge. But it also has an incomplete molecular orbital shell with its eight π electrons, and this property conveys antiaromatic character (Figure 36.1).



cycloheptatriene

$CH_3CH{=}CHCH{=}CHCH{=}CH_2$

heptatriene



cycloheptatrienyl anion

(36-2)

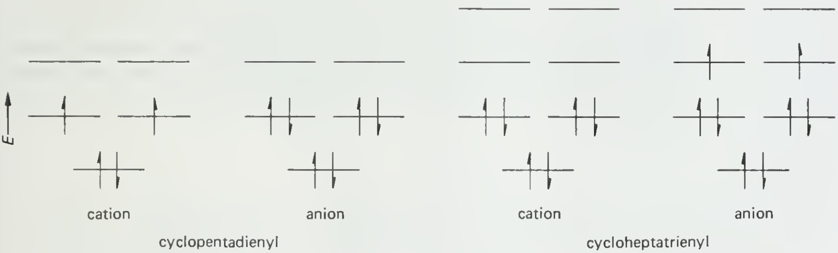
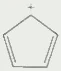
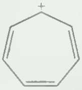


FIGURE 36.1 *Molecular orbital energy levels for cyclopentadienyl and cycloheptatrienyl ions showing filled molecular orbital shells for six π electrons.*

Figure 36.1 also shows that the situation is reversed for the corresponding cations. Cyclopentadienyl cation is highly reactive and difficult to prepare. It has only four π electrons. On the other hand cycloheptatrienyl cation has six π electrons and is a remarkably stable carbonium ion. It is readily prepared by oxidation of cycloheptatriene and many of its salts are stable crystalline compounds.



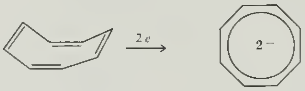
cyclopentadienyl
cation



cycloheptatrienyl
cation

D. *Ten-Electron Systems*

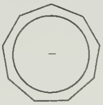
Cyclooctatetraene is a polyolefinic liquid with a tub shape and alternating single and double bonds (Section 21.1.C). Its reaction with alkali metals to give a stable, planar dianion having the structure of a regular octagon was mentioned earlier.



cyclooctatetraene   cyclooctatetraene dianion

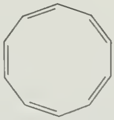
This dianion is a filled shell $4n + 2$ system with ten electrons and $n = 2$. Salts of the dianion are known; in fact the dipotassium salt can be sublimed without decomposition.

Cyclononatetraenyl anion has been prepared and gives evidence of having a planar nonagon structure, despite the high angle strain in such a ring system.

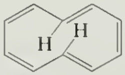


cyclononatetraenyl anion

A neutral ten-π-electron hydrocarbon homologous to benzene would be cyclodecapentaene. The planar all-*cis* structure has highly strained bond angles. The alternative structure with two *trans* double bonds cannot achieve planarity because of interaction between the two interior hydrogens. As a result, cyclodecapentaene does not have the expected aromatic stability, but is instead a highly reactive hydrocarbon.

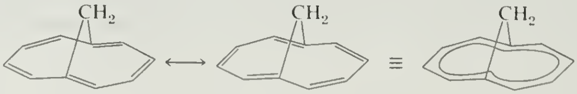


all-*cis* or all-(Z)- cyclodecapentaene



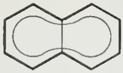
(Z,Z,E,Z,E)-cyclodecapentaene

An unusual hydrocarbon has been prepared in which the two interior hydrogens have been replaced by a bridging methylene group. This hydrocarbon cannot have a completely coplanar π system, but enough cyclic overlap occurs to give the compound significant aromatic character.



bicyclo[4.4.1]undeca-1,3,5,7,9-pentaene

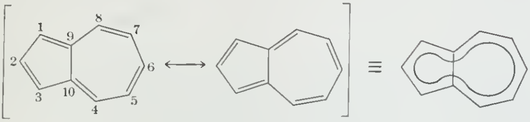
In a related manner, naphthalene could be considered to be a perturbed cyclodecapentaene; naphthalene has a ten-electron periphery.



naphthalene as a modified $4n + 2$ cycle

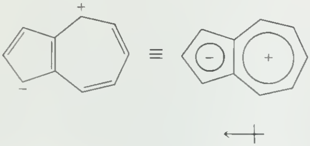
In the case of naphthalene, however, the 9,10-bond is so short, 1.39 Å, that this viewpoint is not necessarily accurate or useful.

The isomeric hydrocarbon, azulene, is a fascinating molecule, not the least interesting feature of which is its brilliant blue color!



azulene

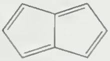
Two Kekulé structures can be written as shown. In both structures the 9,10-bond is a single bond. Its experimental bond length of 1.46 Å suggests that azulene could be considered to be an aromatic cyclodecapentaene structure. There is more to the story, however. If we separate charges, we can write azulene as having fused cyclopentadienyl anion and cycloheptatrienyl cation rings.



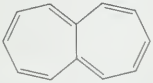
$\mu = 1$ D

Remarkably enough, azulene has a dipole moment of 1.0 D, an unusually high value for a hydrocarbon; comparison of derivatives shows that the dipole moment is oriented as shown, exactly as expected for a contribution by ionic structures having $4n + 2$ cycles.

Azulene may be contrasted with two other related hydrocarbons, pentalene and heptalene. Pentalene is a lower homolog of naphthalene with two fused five-membered rings; heptalene is a higher homolog with two fused seven-membered rings.



pentalene



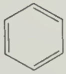
heptalene

Both compounds are known. Pentalene is highly reactive and dimerizes rapidly. Heptalene also behaves as a polyolefin. Neither compound shows any semblance of aromatic character. Note that pentalene has a periphery of eight π electrons, whereas heptalene has a 12-π-electron periphery; neither has a $4n + 2$ cycle.

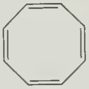
E. *Larger Cyclic π Systems*

Benzene and cyclooctatetraene are two members of monocyclic $(CH)_n$ compounds known as annulenes. Benzene is [6]annulene and cyclobutadiene is [4]annulene.

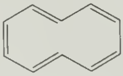
cyclobutadiene
[4]annulene



benzene
[6]annulene

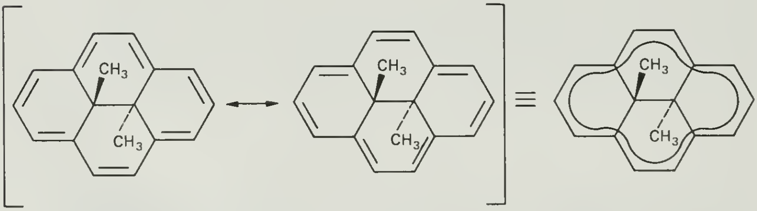


cyclooctatetraene
[8]annulene



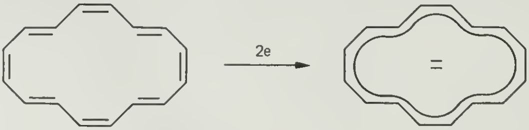
cyclodecapentaene
[10]annulene

A number of larger annulenes are known that further confirm the generality of the $4n + 2$ rule. Cyclododecahexaene, [12]annulene, is a polyolefinic compound that reacts with alkali metals to give a dianion which, with 14 electrons, follows the $4n + 2$ rule. The bridged hydrocarbon *trans*-10b,10c-dimethyl-10b,10c-dihydropyrene has a 14-electron π system and is a stable molecule that has the properties of an aromatic system. The periphery is a [14]annulene that follows the $4n + 2$ rule.



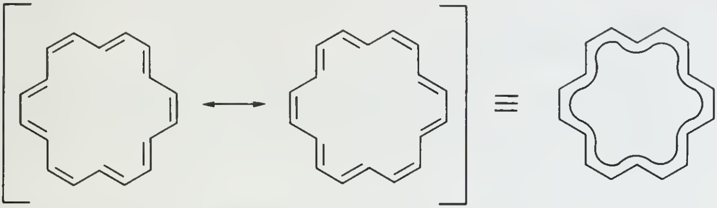
trans–10b,10c-dimethyl-10b,10c-dihydropyrene

Cyclohexadecaoctaene, [16]annulene, with 16 π electrons, does not fit the $4n + 2$ rule. It has polyolefinic behavior but reacts with alkali metals to form the aromatic cyclic dianion with 18 π electrons.



cyclohexadecaoctaene
[16] annulene

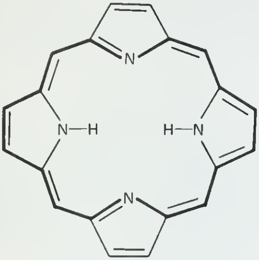
The corresponding neutral 18-π-electron hydrocarbon, cyclooctadecanonaene, [18]annulene, has been synthesized as a relatively stable brown-red compound. X-ray structure analysis shows that the bonds have equal length; however, this result has been questioned by some theoretical calculations and the aromaticity of this hydrocarbon is still controversial.



[18]annulene

Note that [18]annulene has the periphery of coronene (Section 34.5).

An especially important 18-electron cycle is that of the porphyrins (see hemin, Section 28.7.D, page 855). These metal complexes constitute part of the active site of a number of enzymes. They may be regarded as salts of derivatives of the parent heterocycle, porphine. The conjugating system of 18 π centers is readily traced in this compound.



porphine

This section provides only a brief introduction to a wealth of fascinating chemistry stimulated by the recognition of the Hückel $4n + 2$ rule. The story extends far beyond these limits and is a continuing one. Much of the chemistry discussed in this chapter was revealed only within the past decade. Some of the important results were published in 1973, only shortly before these pages were written.

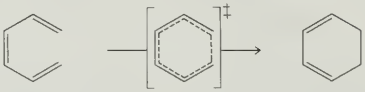
36.2
Pericyclic Transition States

In our study of organic chemistry we have encountered a number of reactions that proceed through cyclic transition states. Examples are the Diels-Alder reaction (Section 23.4.B), and the Claisen and Cope rearrangements (Section 33.3.D). These transition states were related to benzene and the facility of these reactions was compared to the aromatic character of benzene. The comparison is accurate and, indeed, these and many other reactions, including a number we have already studied, can be treated as cyclic electronic systems *to which the*

Hückel 4n + 2 rule can be applied. In this section we shall demonstrate this generality and show its application to several important types of reaction.

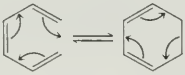
A. *Electrocyclic Reactions*

cis-1,3,5-Hexatriene undergoes a facile transformation on heating to give 1,3-cyclohexadiene. This type of isomerization is known as an **electrocyclic** reaction. The reaction can be perceived as proceeding through a cyclic six-membered transition state.

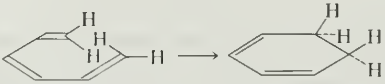


cis-1,3,5-hexatriene 1,3-cyclohexadiene

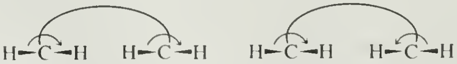
Moreover, if we follow the electrons involved by the conventional symbolism of a curved arrow for each pair of electrons involved, we find that three arrows are required. That is, six electrons participate in the transformation and hint at the involvement of $4n + 2$ in some manner.



There is a complication, however, as regards stereochemistry. In the open chain hexatriene, best π overlap of the double bonds is achieved when all six carbons and eight hydrogens lie in the same plane—including both terminal CH_2 groups. In the cyclohexadiene, however, the two methylene groups form part of a ring and are no longer coplanar. That is, in the transformation from hexatriene to cyclohexadiene, the terminal methylene groups must rotate out of coplanarity.

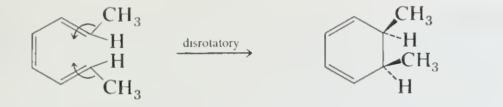


In principle, these rotations can take two possible modes. They can both rotate in the same sense when viewed from the same direction **(conrotatory motion)**, or in the opposite sense **(disrotatory motion)**



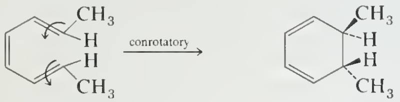
conrotatory motion disrotatory motion

In the simple case of hexatriene itself, these alternative modes of rotation cannot be distinguished, but substituted compounds would lead to different isomers. Consider the (E,E)-1,6-dimethyl compound as an example. If both end groups rotate in opposite directions in disrotatory fashion, the product is the *cis*-dimethylcyclohexadiene. If they rotate together in conrotatory fashion, the product is the *trans*-dimethylcyclohexadiene.



(E,Z,E)-octa-2,4,6-triene

cis-5,6-dimethylcyclohexa-1,3-diene



trans-5,6-dimethylcyclohexa-1,3-diene

The reaction involves the conversion of the two terminal *p*-orbitals from π bonding to σ bonding. At this point it is important to examine the signs of the orbital wave functions to determine whether the orbital overlaps involved are bonding (positive) or antibonding (negative) (Figure 36.2). In the starting hexatriene, the *p* orbitals have signs assigned to the wave functions to provide the most positive overlaps and lead to a set of π molecular orbitals that describe the electronic structure. Note that for clarity only the overlap (dotted line) at the top is shown. In disrotatory motion, both terminal CH_2 groups rotate so that the positive lobes interact to give positive overlap throughout, exactly as in the related benzene system included for comparison in Figure 36.2. Even though the orbitals in the transition state for electrocyclic reaction are not aligned exactly as in benzene, the all-important overlap characteristics are the same in both; that is, the orbital overlaps are all positive around the ring.

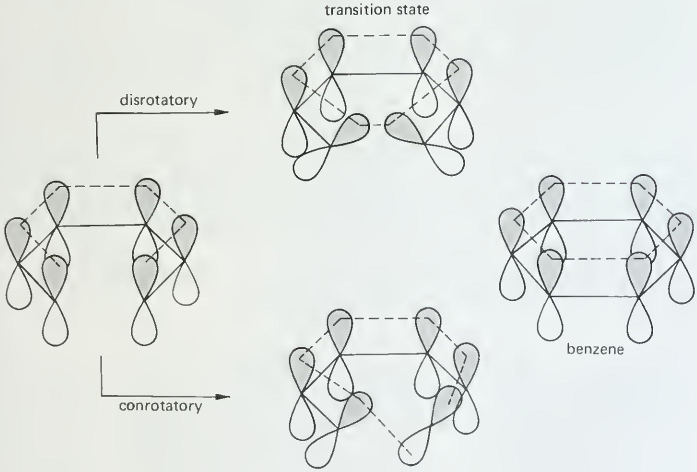


FIGURE 36.2 *Orbital interactions involved in disrotatory and conrotatory ring closure of 1,3,5-hexatriene, compared to benzene. Shaded lobes represent positive wave functions; unshaded lobes represent negative wave functions.*

This result is to be contrasted with the pattern for conrotatory motion. In this case the positive lobe of one terminal *p* orbital starts to overlap with the negative lobe of the other terminal p orbital. The disrotatory transition state clearly more closely resembles orbital interactions in benzene and, indeed, the electrocyclic reaction of hexatrienes is completely disrotatory. The product of the dimethyl case shown is *exclusively* the *cis*-dimethylcyclohexadiene, even though this product is thermodynamically less stable than the alternative *trans* structure.

The substantial difference in activation energies for the two cases is directly related to the stabilization energies of aromatic systems having cyclic π systems with $4n + 2$ electrons. Recall that a cyclic system of p orbitals gives rise to a pattern of molecular orbitals in a distinctive manner. There is a lowest-lying molecular orbital with zero nodes and thereafter the molecular orbitals occur as degenerate pairs having one, two, and so on, nodes (Section 36.1.). In the benzene-like transition state for disrotatory ring closure in Figure 36.2, this symmetry is disturbed so that the higher molecular orbitals no longer occur as degenerate pairs, but the molecular orbitals within each pair still have energies that are close together. As such they still represent orbital "shells" that provide aromatic-like stability when filled. The molecular orbital energies of the disrotatory transition state of Figure 36.2 are illustrated in Figure 36.3a.

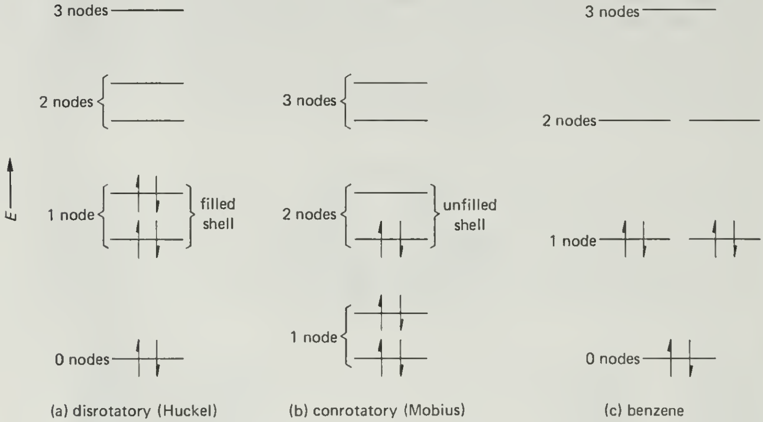


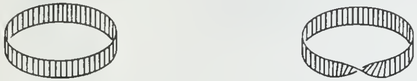
FIGURE 36.3 *Energy level diagram for alternative transition states for ring closure of hexatriene, compared to that for benzene.*

The negative overlap required for the conrotatory ring closure gives rise to an entirely different pattern of molecular orbital energies. The negative overlap constitutes a node; hence, there cannot be any molecular orbital with zero nodes. Instead, we find a pair of molecular orbitals of similar energy with one node each, a higher pair with two nodes, and so on. This pattern is illustrated in Figure 36.3b. Six electrons leave the second shell unfilled, a condition that represents relative instability.

It is convenient to have names for these two possible patterns of molecular orbital levels. The pattern for disrotatory closure is a **Hückel molecular orbital system** and gives filled molecular orbital shells with $4n + 2$ electrons. The conrotatory pattern in Figure 36.3b is frequently referred to as a **Möbius molecular**

orbital system, and has the important characteristic of giving filled molecular orbital shells with $4n$ electrons.

This name derives from the topology of a **Möbius strip.** A Möbius strip is formed by taking a circular band, cutting in one place, giving one twist, and rejoining at the cut. The resulting strip has no inside nor outside! Both are joined in one continuous manner (Figure 36.4). In a Hückel molecular orbital system, the p orbitals are set up with a positive "top" and negative "bottom." In the Möbius system, the negative overlap joins the "top" and the "bottom" in a manner that resembles the joining of the inside and outside of a Möbius strip.



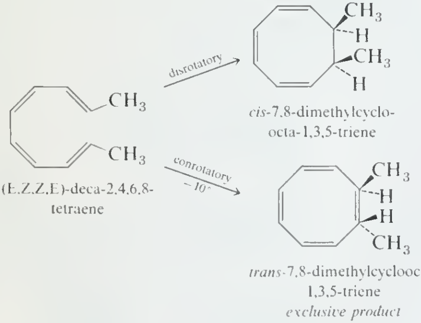
strip having inside and outside

Möbius strip inside is the outside

FIGURE 36.4 *Illustrating the surfaces of a Möbius strip.*

Note that this point also emphasizes the difference between setting up atomic orbitals, such as p orbitals, to overlap in a given fashion (basis functions) and the set of molecular orbitals that results from such overlaps. If we start with n interacting atomic orbitals, we must end up with n molecular orbitals. The energies of the molecular orbitals depend on how the starting atomic orbitals overlap. We may summarize this discussion as follows: A set of p orbitals overlapping in a cyclic manner with zero (or an even number) of negative overlaps gives rise to a Hückel pattern of molecular orbital energy levels to which quantum numbers can be assigned as: 0, ± 1, ± 2, and so on. Cyclic interaction of a set of p orbitals with one (or an odd number) of negative overlaps gives rise to a set of molecular orbitals having the Möbius pattern of energy levels to which quantum numbers can be assigned as ± 1, ± 2, and so on.

Let us now apply these principles to the corresponding electrocyclic ring closure of 1,3,5,7-octatetraene to 1,3,5-cyclooctatriene. In contrast to the (E,Z,E)-dimethylhexatriene case discussed previously, the (E,Z,Z,E)-dimethyloctatetraene compound shown (36-3) gives, as the first product of thermal electrocyclic reaction, *exclusively* the *trans*-dimethylcyclooctatriene, the product of *conrotatory* motion!



(E,Z,Z,E)-deca-2,4,6,8-tetraene

cis-7,8-dimethylcycloocta-1,3,5-triene

trans-7,8-dimethylcycloocta-1,3,5-triene
exclusive product

(36-3)

To see why this system changes so dramatically from the hexatriene case, we again look at the orbital overlaps involved (Figure 36.5). In disrotatory motion,

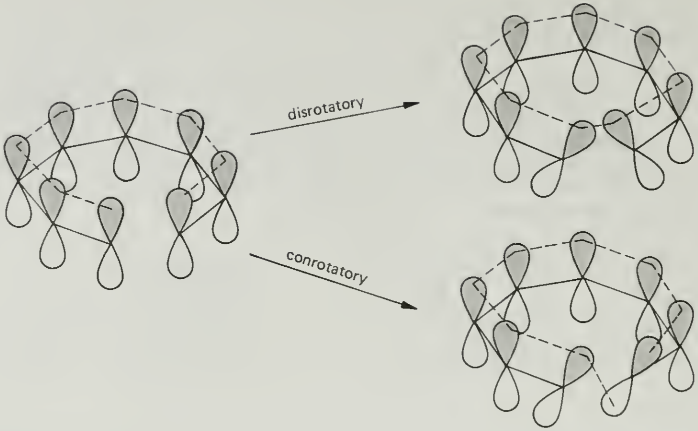

disrotatory
conrotatory

Figure 36.5 *Orbital overlaps involved in cyclization of octatetraene.*

the overlaps involved are again all positive, and give rise to a Hückel pattern of molecular orbital energy levels. But the eight electrons now involved no longer fit the $4n + 2$ rule. The result is the instability associated with an unfilled orbital shell. On the other hand, the conrotatory transition state gives rise to a Möbius pattern of molecular orbital levels. The eight electrons fill the first two shells and have the stability associated with filled orbital shells (Figure 36.6); that is, con-

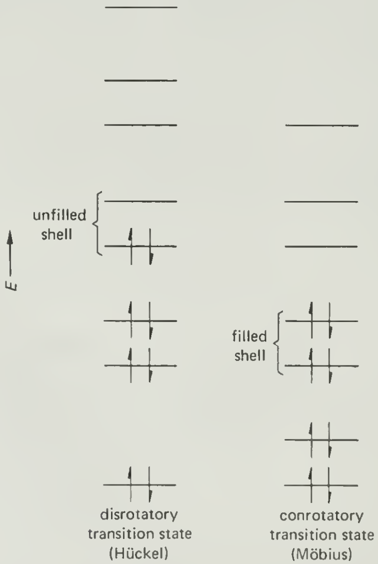
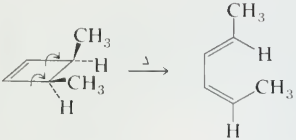

unfilled shell
E
filled shell
disrotatory transition state (Hückel)
conrotatory transition state (Möbius)

Figure 36.6 *Energy level pattern of molecular orbitals for cyclization of octatetraene.*

rotatory ring closure of octatetraene involves a transition state that has Möbius aromatic character and is energetically more favorable than the Hückel antiaromatic character of the transition state for disrotatory ring closure.

This result may be generalized. *Those thermal electrocyclic reactions that involve $4n + 2$ electrons react with disrotatory motion* so that the orbitals involved can overlap in the Hückel sense. *Those thermal electrocyclic reactions that involve $4n$ electrons react with conrotatory motion* so that the orbitals involved can overlap in the Möbius sense. These generalizations hold whether the reaction involved is that of ring closure or ring opening (principle of microscopic reversibility).

The thermal ring opening of cyclobutenes provide a further example. On heating, *cis*-3,4-dimethylcyclobutene is smoothly converted to (E,Z)-hexa-2,4-diene.


CH_3
H
CH_3
H
Δ
CH_3
H
CH_3
H

cis-3,4-dimethyl-cyclobutene

(E,Z)-hexa-2,4-diene

The reaction involves a four-electron cycle. The filled shell molecular orbital system of the transition state thus requires Möbius overlap and conrotatory motion (Figure 36.7). Disrotatory ring opening would give a Hückel cyclic system, which, with four electrons, would be antiaromatic (Figure 36.7).

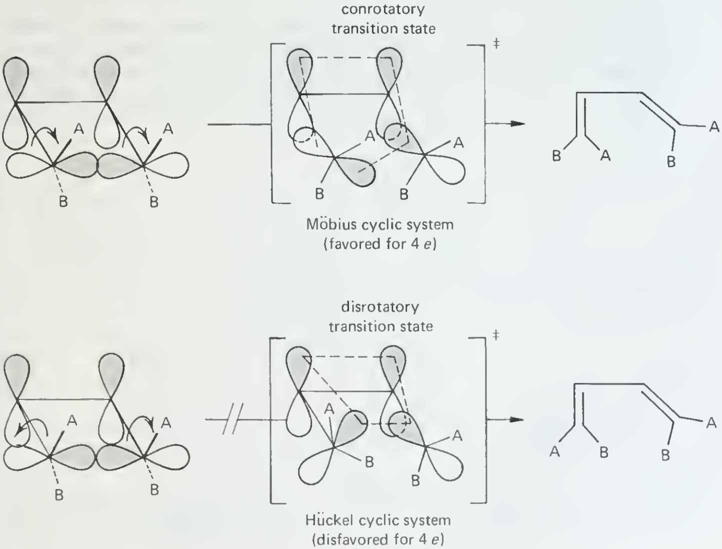

conrotatory transition state
‡
A
A
B
B
A
A
B
B
A
B
A
B
Möbius cyclic system (favored for 4 e)
disrotatory transition state
‡
A
A
B
B
A
A
B
B
A
B
B
A
Hückel cyclic system (disfavored for 4 e)

FIGURE 36.7 *Orbital interactions for electrocyclic ring openings of cyclobutene.*

If this example is approached from the microscopically reverse direction, ring closure of butadiene, we obtain the equivalent result (Figure 36.8). This transition state looks superficially different from that derived from ring opening (Figure 36.7); that is, the + and − labeling of different lobes is different, but both pictures have one negative overlap and correspond to a Möbius cyclic system. Moreover, they give rise to precisely the same set of four molecular orbitals. In the approach shown here, it is only necessary to determine whether a given transition state is a Möbius or Hückel cyclic system. Other approaches based on detailed consideration of the symmetries of individual molecular orbitals may also be applied, but the present $4n$ versus $4n + 2$ approach is exactly equivalent and simpler to use in practice.

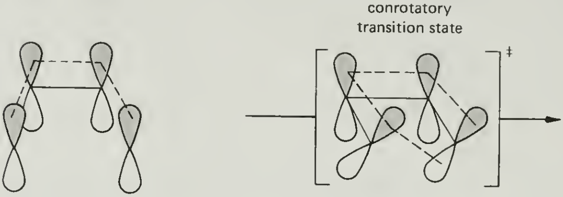
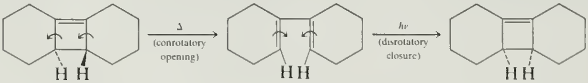


Figure 36.8 *Orbital interactions for ring closure of butadiene.*

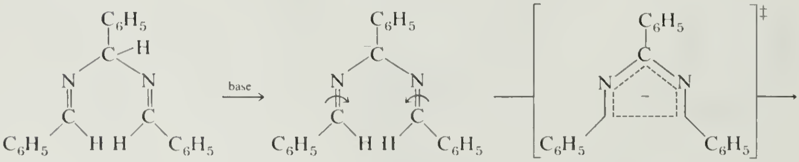
The foregoing considerations lead to the following generalizations for thermal electrocyclic reactions:

$4n$ electrons (4, 8, 12, etc.)	conrotatory motion
$4n + 2$ electrons (2, 6, 10, 14, etc.)	disrotatory motion

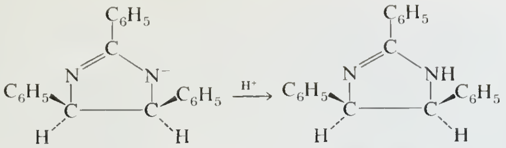
These rules apply to thermal reactions only. For photochemical reactions, the rules are usually exactly opposite, because electronic excited states have some important symmetry differences from ground states that we will not explore here. Furthermore, photochemical electrocyclic reactions are often not concerted reactions (Section 36.3). Thermal and photochemical reactions can sometimes be combined to give interesting results, for example



Some additional examples (36-4) and (36-5) follow:

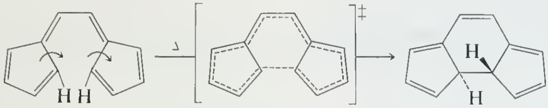


6 e cyclic system ≡ $4n + 2$
therefore Hückel and disrotatory



(36-4)

cis product
amarine

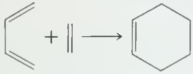


(36-5)

12 e cyclic system ≡ 4*n*
therefore Möbius and conrotatory

B. *Cycloaddition Reactions*

The Diels-Alder reaction is an example of a cycloaddition reaction.



Diels-Alder reactions involve the formation of two σ bonds and one π bond from the two π bonds of a diene and the π bond of a monoene. Accordingly, the common Diels-Alder reaction can be referred to as a $({}_4\pi + {}_2\pi)$ cycloaddition reaction. If we label the orbitals involved, we can see that the normal Diels-Alder reaction involves a Hückel cyclic electronic system with six electrons; that is, the transition state is aromatic (Figure 36.9).

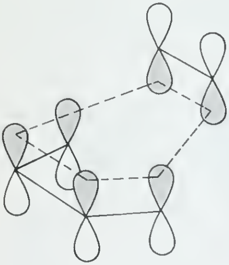
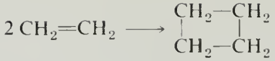


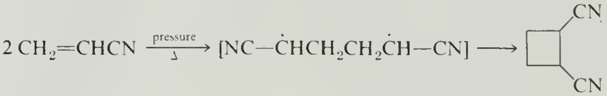
FIGURE 36.9 *Transition state for* $({}_4\pi + {}_2\pi)$ *cycloaddition reaction; all overlaps are positive.*

On the other hand, $({}_2\pi + {}_2\pi)$ cycloaddition reactions are unknown. Ethylene, for example, does not dimerize even under high pressure, despite the large favorable enthalpy for forming cyclobutane.

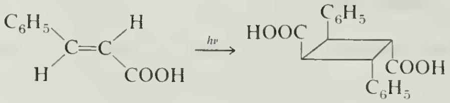


$\Delta H^\circ = -18.2 \text{ kcal mole}^{-1}$

Cycloaddition in the $({}_2\pi + {}_2\pi)$ manner involves a transition state of the antiaromatic Hückel type (four electrons $\neq 4n + 2$). Instead, ethylene undergoes linear polymerization to form polyethylene. Examples of thermal cycloadditions to form cyclobutanes are known, but in virtually every case the mechanism appears to involve a diradical intermediate rather than a concerted reaction via a cyclic transition state.

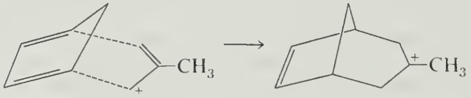


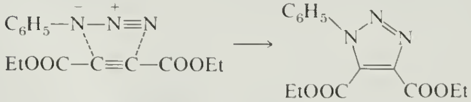
However, many photochemical $({}_2\pi + {}_2\pi)$ cycloadditions are known. In photochemical reactions, a $4n$ cyclic transition state is acceptable, although many of these reactions may also involve diradical intermediates. One example of a photochemical cycloaddition occurs when cinnamic acid is exposed to sunlight:



trans-cinnamic acid α-truxillic acid

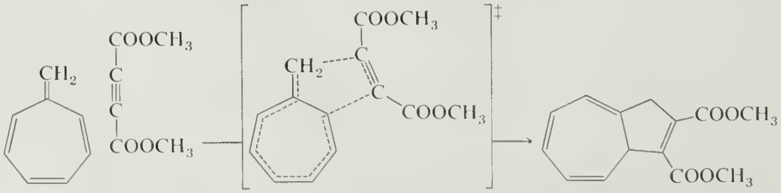
Many variations of $({}_4\pi + {}_2\pi)$ cycloadditions are known. Two further examples are



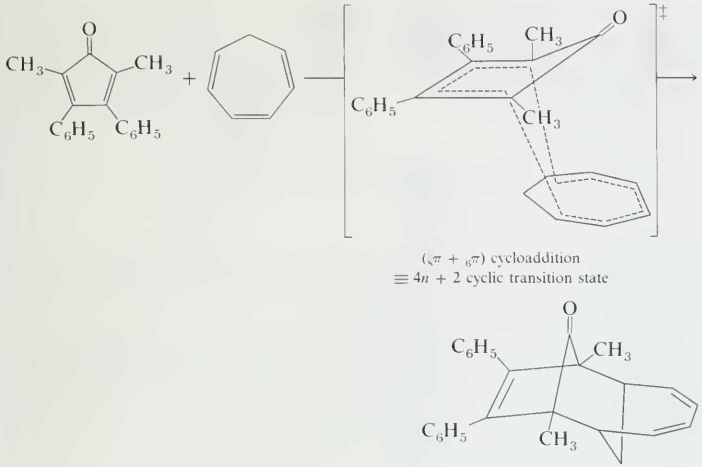


Other examples of dipolar cycloaddition reactions were discussed in the previous chapter (Section 35.5.B); these examples are all of the $({}_4\pi + {}_2\pi)$ type.

Still other examples involve higher $4n + 2$ cyclic electronic transition states.

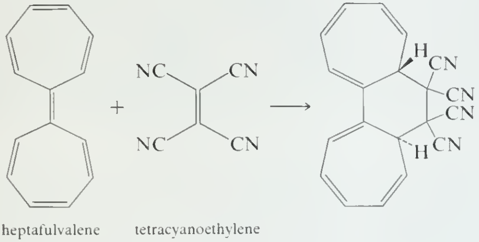


$({}_4\pi + {}_2\pi)$ cycloaddition
$\equiv 4n + 2$ cyclic transition state


O
CH_3
CH_3
C_6H_5
C_6H_5
+
C_6H_5
CH_3
O
C_6H_5
CH_3
‡
O
C_6H_5
CH_3
C_6H_5
CH_3

(${}_4\pi + {}_6\pi$) cycloaddition
≡ $4n + 2$ cyclic transition state

A remarkable exception would appear to be reaction (36-6), which involves a (${}_{14}\pi + {}_2\pi$) cycloaddition and does not fit the $4n + 2$ rule.


+
NC
CN
NC
CN
H
CN
CN
CN
H
CN
heptafulvalene
tetracyanoethylene

(36-6)

However, note that the product is the result of *trans* addition. The corresponding transition state (Figure 36.10) involves a negative overlap which would correspond to a Möbius cyclic electronic system, a favorable transition state for a 16-electron cyclic system!

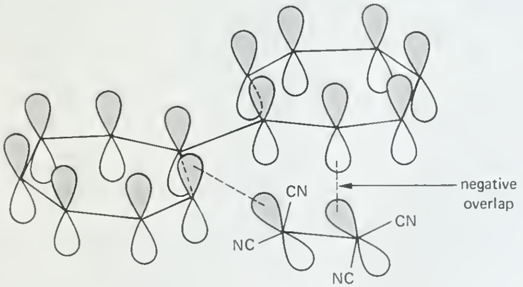

CN
negative overlap
CN
NC
NC

Figure 36.10 *Orbital interactions for* trans *addition of tetracyanoethylene to heptafulvalene.*

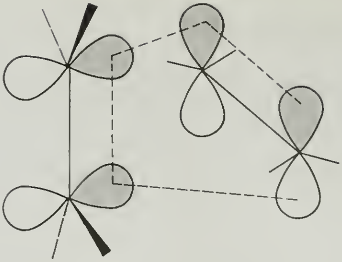


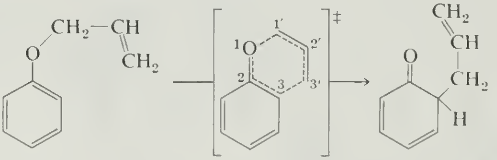
FIGURE 36.11 *Orbital interactions for the hypothetical* trans *or* $({}_2\pi_a + {}_2\pi_s)$ *cycloaddition of one ethylene with another.*

In principle, ethylene could dimerize if the positive lobes of one molecule could overlap with the opposite lobes of another (Figure 36.11). The resulting transition state has one negative overlap and creates a Möbius molecular orbital system. However, the steric constraints of such a four-membered cyclic system mean that it possesses energy that is too high for it to compete with alternative modes of reaction.

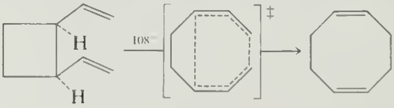
Addition to the same side of a π system is called **suprafacial** and is symbolized with a subscript *s*; addition to opposite sides of a π system is called **antarafacial** and is symbolized with a subscript *a*. Hence, the normal Diels-Alder reaction is an example of a $({}_4\pi_s + {}_2\pi_s)$ cycloaddition. Reaction (36-6) of heptafulvalene with tetracyanoethylene discussed previously is an example of a $({}_{14}\pi_a + {}_2\pi_s)$ cycloaddition. In general, $({}_p\pi_s + {}_q\pi_s)$ cycloadditions are thermally "allowed" when $p + q = 4n + 2$, whereas $({}_p\pi_a + {}_q\pi_s)$ thermal cycloadditions, a somewhat rarer breed, are thermally allowed when $p + q = 4n$.

C. *Sigmatropic Rearrangements*

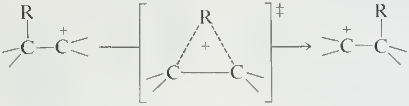
A **sigmatropic rearrangement** of order $[p,q]$ is defined as a concerted rearrangement in which a bond between two conjugated systems is broken at the same time that a new one is formed at the *p*th atom of one of the systems and the *q*th atom of the other. For example, the Claisen rearrangement (Section 33.3.D) is an example of a [3,3]sigmatropic rearrangement.



The Cope rearrangement is also a [3,3]sigmatropic rearrangement.



We have alluded earlier to the benzene-like or aromatic character of such transition states. Indeed, we expect such aromatic character whenever $4n + 2$ electrons are involved. One well-known example that fits this pattern is the familiar carbonium ion rearrangement, a reaction that could be termed a two-electron [2,1]sigmatropic rearrangement.



The orbital picture of the transition state follows in straightforward fashion (Figure 36.12). Only positive orbital overlaps are involved; hence, the system is of the Hückel type and has aromatic stabilization for two electrons. Note that the migrating group is still pyramidal and the cyclic system is derived from hybrid orbitals rather than pure *p* orbitals.

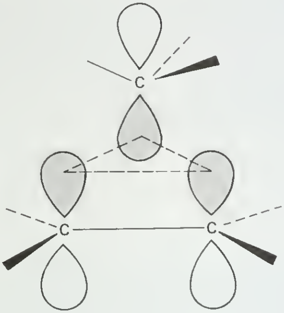
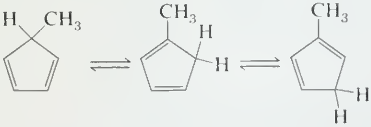


FIGURE 36.12 *Orbital interactions in a [2.1]sigmatropic rearrangement.*

Such rearrangements are common for carbonium ions but do not occur for carbanions. The 1,2-rearrangement of carbanions would be described as a four-electron [2,1]sigmatropic rearrangement and would be antiaromatic.

Another sigmatropic rearrangement that involves a Hückel six-electron transition state is a 1,5-hydrogen shift, a [5,1]sigmatropic rearrangement. An example of this reaction is afforded by 5-methyl-1,3-cyclopentadiene, which rearranges readily, first to 1-methyl-1,3-cyclopentadiene and then to an equilibrium mixture that contains 2-methyl-1,3-cyclopentadiene.



The [5,1]sigmatropic character of the transition state is apparent when written as in Figure 36.13. All overlaps involved are positive; hence, the system is Hückel and aromatic for six electrons.

The benzidine rearrangement (Section 32.1.C) is an example of a [5,5]sigmatropic rearrangement and is aromatic for a Hückel ten-electron cycle.

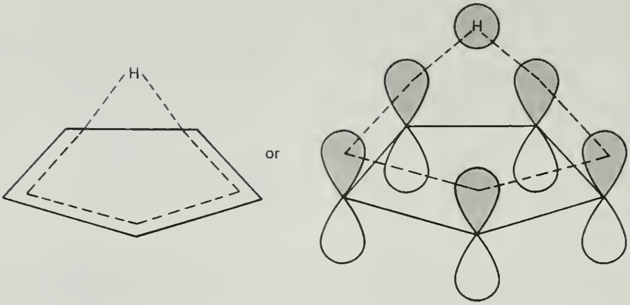
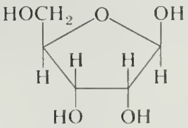


Figure 36.13 *Orbital interactions for a [5,1]sigmatropic rearrangement.*

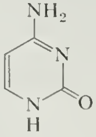
In this chapter we have only touched on what has become a vast and growing field, a subject of much current research in organic chemistry. The unifying concepts that have brought such order to a hitherto mysterious collection of experimental results are only a few years old. The vitality and growth of modern organic chemistry are emphasized by the realization that the interpretation of pericyclic transition states given in these pages was unknown in the organic chemistry of only a decade ago!

36.3
Nucleic Acids

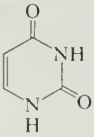
Nucleic acids are important biomolecules that play a crucial role in the storage of genetic information and in protein biosynthesis. There are two types of nucleic acid, ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Both are biopolymers in which the repeating monomer units are called **nucleotides.** A nucleotide, in turn, is a complex molecule made up of one unit each of phosphate, a pentose, and a heterocyclic base. For each class of nucleic acid, there are four main nucleotide monomers. For RNA, the pentose is ribose and the heterocyclic bases are the pyrimidines, uracil or cytosine, or the purines, adenine or guanine.



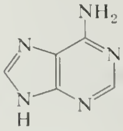
ribose



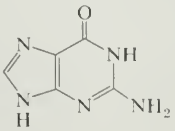
cytosine



uracil

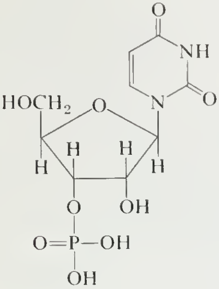


adenine

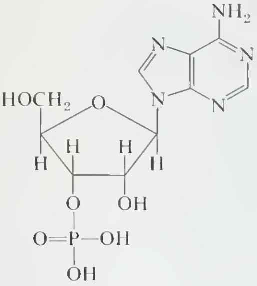


guanine

The nucleotides themselves are called urydilic acid, cytidilic acid, and so on.

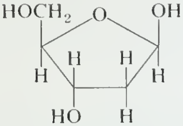


urydilic acid

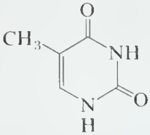


adenylic acid

For DNA, the pentose is 2-deoxyribose and the heterocyclic bases are the same, except that thymine replaces uracil.

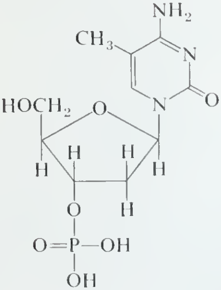


2-deoxyribose



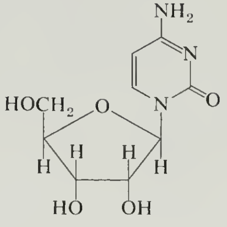
thymine

The nucleotides are called 2-deoxythymidilic acid, 2-deoxycytidilic acid, and so on.

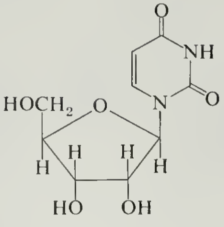


2-deoxythymidilic acid

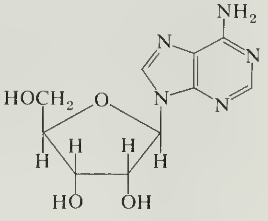
Base-catalyzed hydrolysis of a nucleotide removes the phosphate group and yields a **nucleoside**, which is a glycoside formed from the pentose and the heterocyclic base. The nucleosides may also be obtained by hydrolysis of the appropriate nucleic acid itself. The nucleosides of RNA are cytidine, uridine, adenosine, and guanosine.


NH2
N
N
O
HOCH2
O
H
H
H
H
HO
OH

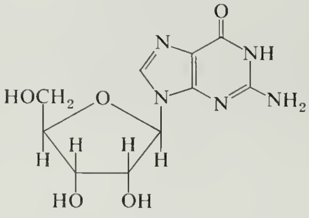
cytidine


O
NH
N
O
HOCH2
O
H
H
H
H
HO
OH

uridine

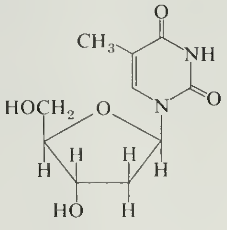

NH2
N
N
N
N
HOCH2
O
H
H
H
H
HO
OH

adenosine


O
N
NH
N
N
NH2
HOCH2
O
H
H
H
H
HO
OH

guanosine

For DNA, the nucleosides are the corresponding 2-deoxy analogs, with 2-deoxythymidine replacing uridine.


O
CH3
NH
N
O
HOCH2
O
H
H
H
H
HO
H

2-deoxythymidine

The nucleic acids may be extremely large molecules, with molecular weights up to 4 billion. Thus, the nucleic acid backbone is a copolymer of phosphoric acid and either ribose or 2-deoxyribose molecules, with one of the four heterocycles, adenine, guanine, cytosine, and uracil (or thymine), linked to C-1 of each of the pentose units (see Figure 36.14).

DNA occurs in the nuclei of all cells and is the molecule in which genetic information is stored. In the precise sequence of purine and pyrimidine bases along its phosphodiester backbone, it carries the information necessary for the exact duplication of the cell, and, in fact, for the construction of the entire organism. DNA is actually a double-stranded helix of two individual molecules

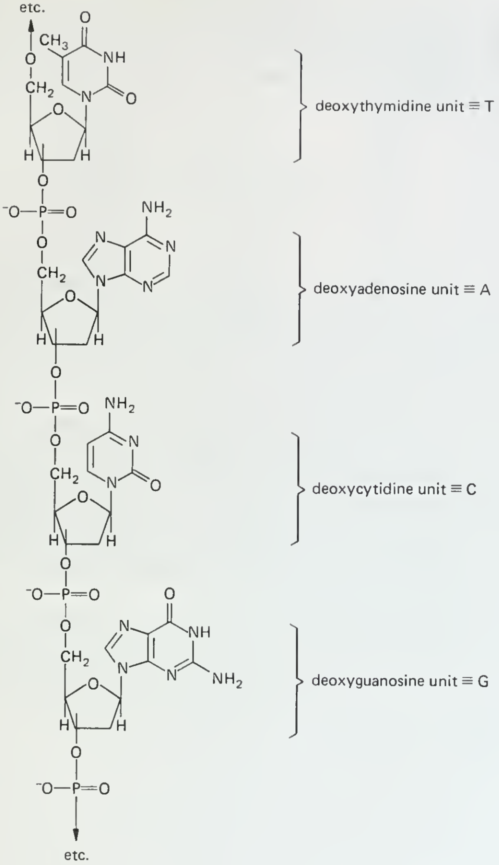
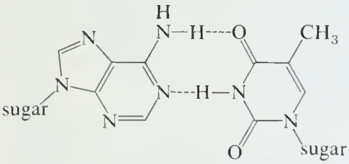
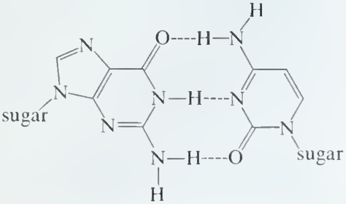

etc.
deoxythymidine unit ≡ T
deoxyadenosine unit ≡ A
deoxycytidine unit ≡ C
deoxyguanosine unit ≡ G
etc.

FIGURE 36.14 *Illustrating a portion of deoxyribonucleic acid (DNA) molecule.*

about 20 Å apart. The two chains are held together by reciprocal hydrogen bonding between pairs of bases in opposite positions in the two chains. The molecular geometry is such that adenine forms a strong reciprocal bond to thymine (AT) and guanine to cytosine (GC).

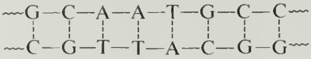

sugar
sugar

adenine-thymine bond (AT)


sugar
sugar

guanine-cytosine bond (GC)

The two interwoven chains have *exactly complementary structures*. Thus, if a segment of one molecule has the base sequence —G—C—A—A—T—G—C—C—, then the complementary chain has the corresponding base sequence —C—G—T—T—A—C—G—G—, and the two chains are hydrogen-bonded together as symbolized by



Genetic information is passed from cell to cell in a process called **DNA replication.** As one of the essential steps in cell mitosis, the nuclear DNA helicies separate. Each of the separate chains then functions as a template upon which another chain exactly complementary to itself is constructed. The end result is that one DNA double helix is transformed into two. In this way, each daughter cell acquires an identical set of nuclear DNA molecules.

RNA is similar to DNA except that the pentose units are ribose instead of deoxyribose. Unlike DNA, RNA molecules seem to exist as single strands with rather irregular structures. There appear to be three general types. Ribosomal RNA constitutes the major amount, and seems to serve some structural function. Messenger RNA functions as a template for the synthesis of proteins in the polyribosomes. Soluble RNA, or transfer RNA, is also involved in protein synthesis. These small RNA molecules bind to individual amino acids and guide them into place on the growing protein chain.

Many fascinating details of DNA and RNA chemistry have been worked out over the last 15 years. Much of the story of the genetic code and how it functions has been unraveled, and much more remains to be learned. Although we cannot even scratch the surface of this intriguing story here, suffice it to say that the unique hydrogen bonding that is possible between the complementary purines and pyrimidines is crucial to life as we know it.

36.4
Organic Coloring Matters

A. *Color*

As discussed in Chapter 22, all compounds can be excited electronically by electromagnetic radiation. For most organic compounds, such transitions are in the ultraviolet region of the spectrum, and such compounds are white or colorless. However, when an electronic transition is in the visible range (about 400–750 nm) the compound will appear to us as colored. The color perceived for different wavelengths of light are summarized in Table 36.1.

Light of a given wavelength is perceived as the colors indicated. However, if that wavelength is *absorbed*, we perceive the complementary color. Some compounds appear to have a yellow color even though their λ_{max} are all in the ultraviolet region. In such cases, a "tail" of an absorption band stretches into

TABLE 36.1
Color and Wavelength

Wavelength of light, nm	Color	Complementary color
400–430	violet	green-yellow
430–480	blue	yellow
480–490	green-blue	orange
490–510	blue-green	red
510–530	green	purple
530–570	yellow-green	violet
570–580	yellow	blue
580–600	orange	green-blue
600–680	red	blue-green
680–750	purple	green

the visible. Since the light absorbed is violet or blue, we see the compound as the complementary color of yellow.

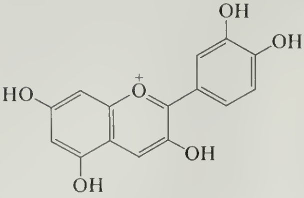
Intensely colored materials have absorptions in the visible region. For organic compounds, such electronic absorptions are generally $\pi \rightarrow \pi^*$ or $n \rightarrow \pi^*$ transitions and involve extended π electronic systems. That is, color in organic compounds is generally a property of π structure. If the absorption band is narrow or sharp, the color will appear to us as bright or brilliant and clean. A broad absorption band, or more than one band in the visible region, gives colors that we perceive as dull or "muddy."

B. *Natural Coloring Matters*

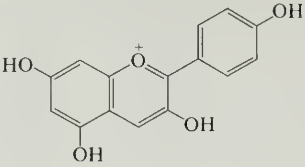
A large number of naturally occurring organic compounds are brightly colored. Some find a role in nature because of their color. Examples are the colors of flowers to attract bees and the camouflage of some insects and animals. Not all colors in nature are due to chemicals. Some colors depend on architectural design to produce color by diffraction of light. Examples are the blue feathers of the bluejay and the colors of hummingbirds, peacocks, and some butterflies and beetles. More often, however, specific organic compounds are involved. A few of the important classes of compounds with representative examples will be summarized here.

Anthocyanins provide much of the color of the plant world. They are responsible for the red color of buds and young shoots and of the purple of autumn leaves as the green chlorophyll decomposes with the approach of winter. Their colors depend in part on the pH of their environment. For example, the blue cornflower and red rose have the same anthocyanin, cyanin. The blue color is that of the potassium salt. Anthocyanins are actually present as glycosides. Hydrolysis gives the corresponding anthocyanidins; that is, anthocyanidins are the aglycones of anthocyanins.

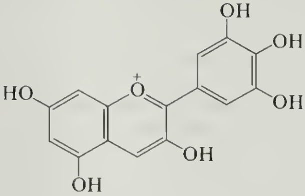
Only three anthocyanidins are important: cyanidin (crimson to blue-red flowers, cherries, cranberries), pelargonidin (pelargonium, geranium) and delphinidin (delphinium, pansy, grape). These compounds have the following structures:



cyanidin

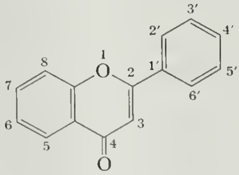


pelargonidin



delphinidin

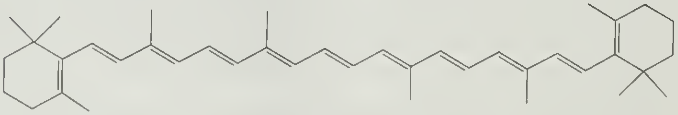
These pyrylium salts (Section 35.6.A) are generally considered as derivatives of a parent structure, flavone, a nucleus that is widespread in nature.



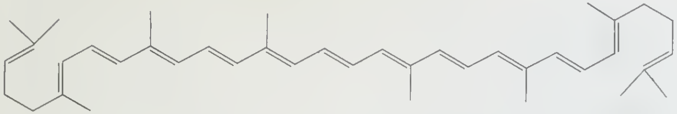
flavone

In the corresponding glycosides, the sugar units are attached at the 3- and 5-positions.

Carotenoids are also widespread in nature from bacteria and fungi to vegetable and animal life. Examples are β-carotene, which is a precursor for vitamin A, and lycopene, which occurs in tomatoes and ripe fruit. The color of these hydrocarbons clearly comes from $\pi \rightarrow \pi^*$ transitions of the long conjugated system. Note that these compounds are terpenes (Section 23.9). Carotenoids also occur in marine



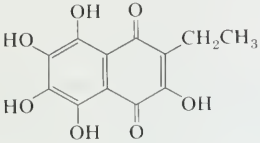
β-carotene



lycopene

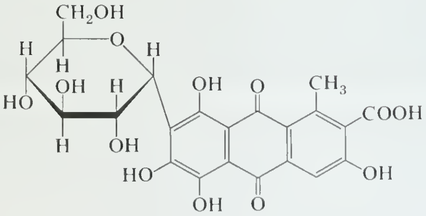
biology, for example, in the skins of fish, sea stars, anemones, corals, and crustaceans, frequently in combination with proteins. Denaturation of the protein in boiling water frees the carotenoid and unmasks its color as in the red color of boiled lobster.

Naphthoquinones and **anthraquinones** also occur in both animal and vegetable worlds. Some examples were given in Section 33.4.A. Echinochrome is a polyhydroxynaphthoquinone that occurs as a red pigment in the sea urchin and sand dollar.



echinochrome

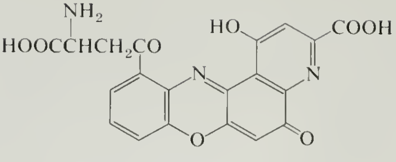
Cochineal is a dried female insect, *Coccus cacti L.*, used for a red coloring in food products, cosmetics, and pigments. The principal constituent is carminic acid, a polyhydroxyanthraquinone attached to glucose.



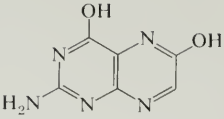
carminic acid

Melanins are complex quinoidal compounds derived from the oxidation and polymerization of tyrosine. Melanins occur in such varied places as feathers, hair, and eyes, and the ink of cephalopods. They occur in the skin of all humans, except albinos, and are responsible for the varied skin coloration among the races of man. Albinos and certain white animals lack an enzyme required to convert tyrosine.

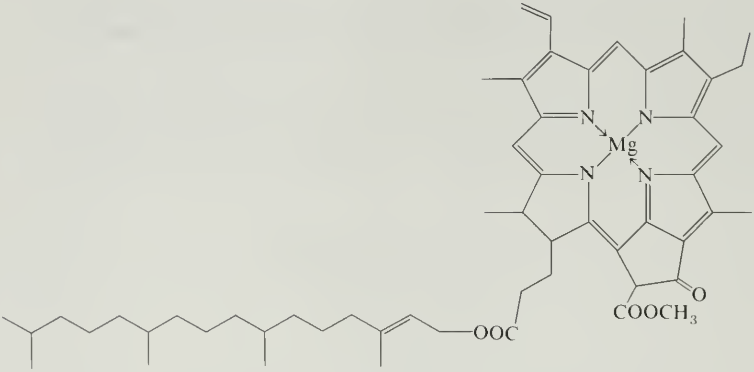
Other types of natural pigments include the **ommochromes** (xanthommatin, a yellow pigment from insect eyes), **pterins** (xanthopterin, yellow pigment in butterfly wings), **porphyrins** (hemin, page 855, chlorophyll) and **indigoids** (indigotin or indigo, occurs as glucoside in many plants; used as a blue dye; see next section).



xanthommatin



xanthopterin

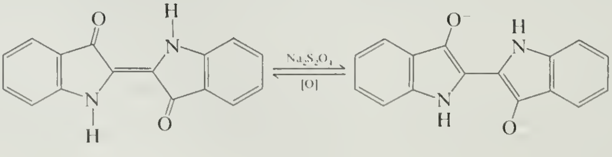


chlorophyll A

C. *Dyes and Dyeing*

Dyes are coloring matters that will bind in some manner to a substrate, usually a fiber or cloth, and are fast to light and to washing. Dyes have been known to man for thousands of years. Early dyes were entirely of natural origin, but common dyes in use today are almost all synthetic. Different methods were and still are used for combining the dye with the fiber. Some of the principal categories follow.

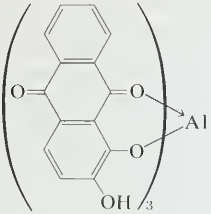
Vat dyes are exemplified by indigo, a highly insoluble blue compound known to the ancient world. It is also the *woad* of ancient Britain. A warm suspension of indigo with other materials was allowed to ferment for several days. This process produced a reduced and soluble "leuco" compound that is colorless. The material to be dyed was immersed in this solution and then exposed to air to reoxidize the leuco base. Indigo is now produced synthetically and is reduced to the leuco form with sodium hydrosulfite. It can be oxidized by exposure to air or more quickly by use of an oxidizing agent such as sodium perborate. The insoluble blue pigment so produced is "locked" within the fiber.



indigotin
indigo

leuco form

Mordant dyes are used in conjunction with a mordant (Latin, *mordere*, to bite), usually a metal salt that forms an insoluble complex or "lake" with the dye. The dye is applied to fiber or cloth that has been pretreated with a metal salt. An example known to the ancient world was the extract of the madder root, which was mordanted with aluminum salts to produce a color known as turkey red. Other metal salts give different colors. The actual dye that coordinates with the metal is alizarin. Alizarin was first synthesized in 1869, and shortly thereafter synthetically manufactured material drove the natural product from the market with important economic repercussions.

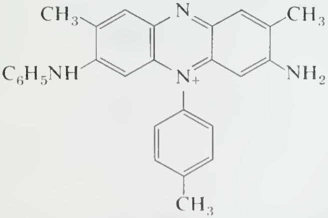


alizarin mordanted with Al^{3+}

Direct dyes can be applied to the fiber directly from an aqueous solution. This process is especially applicable to wool and silk. These fibers are proteins that incorporate both acidic and basic groups that can combine with **basic** and **acid dyes**, respectively. An example is **mauve**, the dye that started the modern synthetic dyestuff industry but is no longer used.

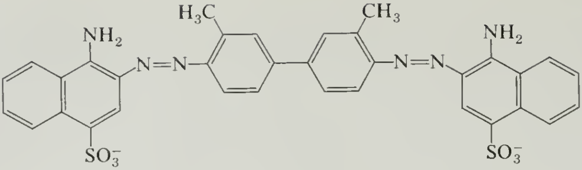
William Henry Perkin was a student at the Royal College of Chemistry when, in 1856 in his home laboratory, at the age of 18, he treated aniline sulfate with sodium dichromate and obtained a black precipitate from which he extracted a purple compound. This material showed promise as a dye and he resigned his position to manufacture it. The product was successful and cloth dyed with mauve was even worn by Queen Victoria. Not long afterwards, additional synthetic dyes were synthesized by German chemists and the synthetic dyestuff industry gradually became a German industry. By the time of World War I, almost all of the world production of synthetic dyes was German.

Perkin's success in the discovery of mauve was based on the fact that his "aniline" was impure. It was prepared by nitrating and reducing "benzene" that contained substantial amounts of toluene!



mauve

Mauve is an example of a basic dye that can ion-pair with acidic centers of the fiber. An example of a direct acid dye is Benzopurpurin 4B whose sulfonate ion groups can pair with cationic centers in the fiber.

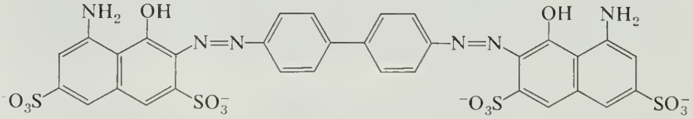


Benzopurpurin 4B

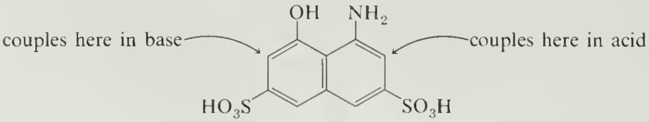
Disperse dyes are used as aqueous dispersions of finely divided dyes or colloidal suspensions that form solid solutions of the dye within the fiber. They are especially useful for polyester synthetic fibers. These fibers have no acid or basic groups for use with direct dyes and are sensitive to hydrolysis in the strongly alkaline conditions of vat dyeing. Disperse dyes tend to have important limitations. They frequently lack fastness to washing, tend to sublime out on ironing and are subject to fading with NO_2 or ozone in the atmosphere, a condition known as *gas fading*.

Dyes are also classified on the basis of chemical structure. These structures frequently contain a functional group that is principally involved in the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions that give rise to the color. Examples of such groups, called **chromophores**, are the azo group, —N=N—, the carbonyl groups in quinones, and extended chains of conjugation. Some of the principal chemical classes of dyes follow.

Azo dyes form the largest chemical class of dyestuffs. These dyes number in the thousands. They consist of a diazotized amine coupled to an amine or a phenol and have one or more azo linkages. An example of a disazo dye, a dye with two azo groups, is Direct Blue 2B, prepared by coupling tetrazotized benzidine with H-acid (8-amino-1-naphthol-3,6-disulfonic acid) in alkaline solution. If H-acid is coupled with a diazonium ion in dilute acid solution, reaction occurs next to the amino group. Both positions can be coupled to different diazonium salts.

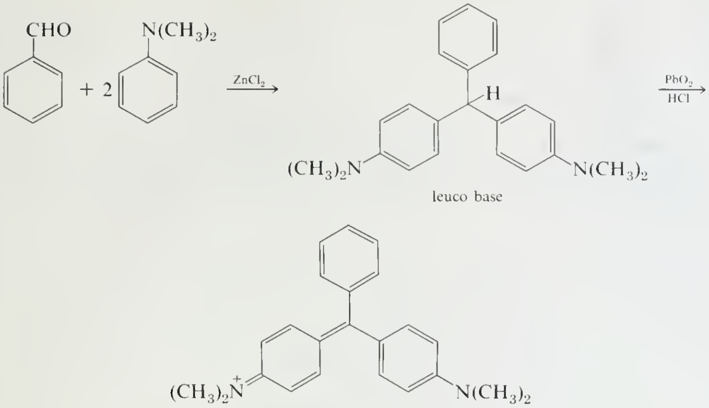


Direct Blue 2B



H-acid

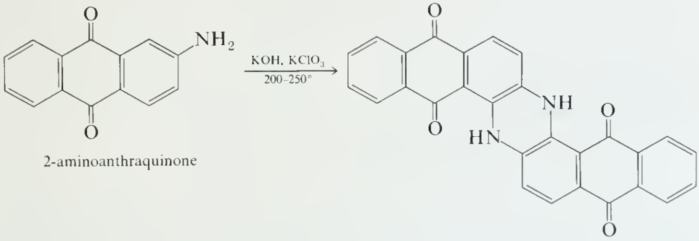
Triphenylmethane dyes are derivatives of triphenylmethyl cation. They are basic dyes for wool or silk or for suitably mordanted cotton. Malachite green is a typical example that is prepared by condensing benzaldehyde with dimethylaniline and oxidizing the intermediate leuco base.



leuco base

malachite green

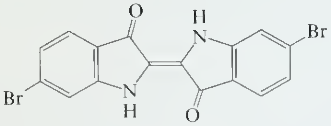
Anthraquinone dyes are generally vat dyes as exemplified by alizarin. More complex examples are higher molecular weight compounds prepared by oxidizing anthraquinone derivatives under basic conditions.



2-aminoanthraquinone

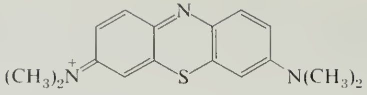
indanthrone
Indanthrene Blue R

Indigoid dyes are also vat dyes, as represented by indigo itself. A dibromoindigo has historical interest as the Tyrian purple of the ancient world. This dye was laboriously isolated from a family of mollusks (*Murex*). Its use was restricted to the wealthy. It is now a relatively inexpensive dye that still finds some use.



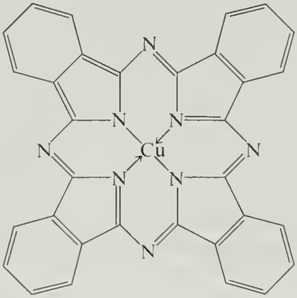
Tyrian Purple
6,6′-dibromoindigo

Azine dyes are derivatives of phenoxazine, phenothiazine, or phenazine. Mauve and aniline black (page 971) are derivatives of phenazine. Methylene blue is a thiazine derivative used as a bacteriological stain.



methylene blue

Phthalocyanines are used as pigments rather than dyes. An important member of this class is copper phthalocyanine, a brilliant blue pigment that can be prepared by heating phthalonitrile with copper.



copper phthalocyanine

36.5
Photochemistry

A. *Electronically Excited States*

Most organic molecules have an even number of electrons with all electrons paired. Within each pair, the opposing electron spins cancel, and the molecule has no net electronic spin. Such an electronic structure is called a **singlet** state. When a ground state singlet absorbs a photon of sufficient energy, it is converted to an excited singlet state. The process is a **vertical transition;** that is, electronic excitation is so fast that the excited state has the same geometry of bond distances and bond angles. The most stable geometry of the excited state often differs from that of the ground state with the result that the excited electronic state is often formed in an excited vibrational state as well. These relationships are illustrated in Figure 36.15. A vertical transition of the type illustrated is also known as a **Franck-Condon transition.**

Figure 36.15 is simplified in showing energy levels as a function of a single bond coordinate. For real molecules, there are many bonds and the resulting pattern of energy levels is multidimensional and complex. Furthermore, there are many excited singlet states, which may be represented collectively as S_i. The lowest excited singlet state is then represented as S_1.

The first formed excited state generally gives up its extra vibrational energy to other bonds in the molecule and falls to the lowest vibrational level of this state. The time required for this process is very short, about 10^{-13} sec, the time required for a single vibration. In the next step, this electronic excited state gives up more energy to other vibrational modes in the molecule or in collisions with

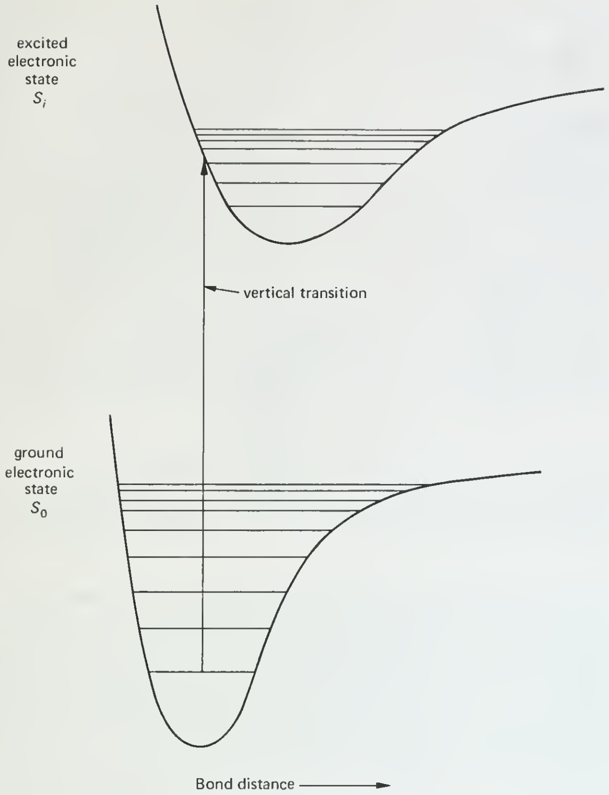


Figure 36.15 *Vertical or Franck-Condon electronic transition.*

solvent and becomes an excited vibrational level of the lowest excited state, S_1. This excited vibrational state again gives up vibrational energy until it reaches the lowest vibrational level of S_1. The change from S_i to S_1 is called **internal conversion** and takes about 10^{-11} sec, or about 10^2 vibrations.

The lifetime of the S_1 state in its lowest vibrational level is longer, about 10^{-8} to 10^{-7} sec. During this time, one of four possibilities can occur. These alternatives are discussed below with the help of a Jablonski diagram, Figure 36.16.

1. S_1 can emit a photon and undergo an electronic transition to the ground state, a process called **fluorescence.** Because the excited state has lost energy before fluorescence occurs, the fluorescence photon has less energy than the originally exciting photon. Fluorescent light has longer wavelength than the light required for the original excitation.
2. S_1 can give up energy to other vibrations or to solvent and become an excited vibrational state of the ground state, S_0. This is an internal conversion and is a nonradiative process. The excited vibrational level again gives energy to its environment until it achieves an equilibrium distribution with the

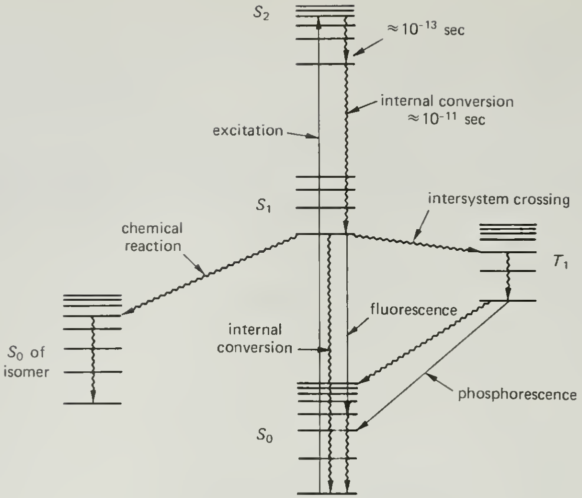


FIGURE 36.16 *Jablonski diagram. Nonradiative processes are shown as wavy lines.*

lowest vibrational level. The net result of all of these changes is the conversion of the original light quantum into heat.

3. S_1 can undergo internal conversion to an excited vibrational level of the ground state of a different compound, an isomer whose lowest vibrational level of S_0 corresponds to a different geometry than our starting material. Alternatively, S_1 can react on collision with another molecule. In either case, we have achieved a photochemical reaction.
4. S_1 can undergo **intersystem crossing** to the triplet state, T_1. A triplet state is one in which one electron spin has been changed so that the molecule has two electrons that cannot pair. The lowest triplet state is usually of higher energy than the ground state (the rare exceptions are compounds with "ground state triplets"). Nevertheless T_1 is of lower energy than S_1. Electrons with the same spin tend to stay apart because of the Pauli principle. As a result, the electrostatic energy of electronic repulsion is less than in comparable singlet states.

In many compounds, the switching of an electronic spin is an improbable process, and triplet states are not important in the photochemistry of such compounds. In certain other compounds, particularly $\pi \rightarrow \pi^*$ states of polycyclic aromatic hydrocarbons and $n \rightarrow \pi^*$ states of many ketones, the process of intersystem crossing is more probable. The process can take as little as 10^{-9} sec. Since the lifetime of S_1 is generally in the range of 10^{-7} to 10^{-8} sec, in such cases almost all of the excited states intersystem cross to T_1.

Triplet states are fairly long lived, with lifetimes of greater than 10^{-5} sec, and, in some cases up to a second or so. One reason for such long lifetimes is that conversion to S_0 again requires switching an electronic spin. The rate at which intersystem crossing takes place depends in large part on the energy difference between the two states. The energy difference between S_1 and T_1 is generally much less than between T_1 and S_0; hence, the latter intersystem crossing is much less probable.

Triplet states themselves have four possible ways for shedding their excess energy:

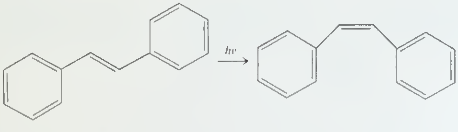
1. T_1 can thermally decay to S_0. The net result in this case is again the conversion of a light quantum to heat.
2. T_1 can emit a photon. This process is called phosphorescence. As in the case of fluorescence, the wavelength of the phosphorescent light is longer than that of the initially exciting light. Phosphorescence is a low-probability event because of the change in electron spin required. It is generally observed only at low temperature for which thermal events have been slowed.
3. T_1 can convert to T_1 of an isomeric molecule or it can intersystem cross to S_0 of an isomer. Either process results in a photochemical isomerization. Alternatively, T_1 can react on collision with another molecule to provide a photochemical reaction.
4. T_1 can transfer its electronic spin to another molecule and become converted to S_0. This process is called *triplet energy transfer* and is symbolized as

$$T_1 + S_0' \longrightarrow S_0 + T_1'$$

   This reaction is actually an equilibrium governed by the usual free energy requirements, but is usually important only when the reaction shown is exothermic.

B. *Photochemical Reactions*

Some photochemical reactions involve simple isomerizations. An example is the *cis-trans* interconversion of alkenes. In this case, the excited state involves a twisted double bond (an example is Figure 12.8), and conversion to the ground state has an equal probability of going *cis* and *trans*. If a wavelength of light can be chosen at which the *trans* isomer absorbs and the *cis* does not, a *trans* isomer can be converted completely to the *cis*. In other cases, a photochemical **stationary state** is achieved.



trans-stilbene *cis*-stilbene

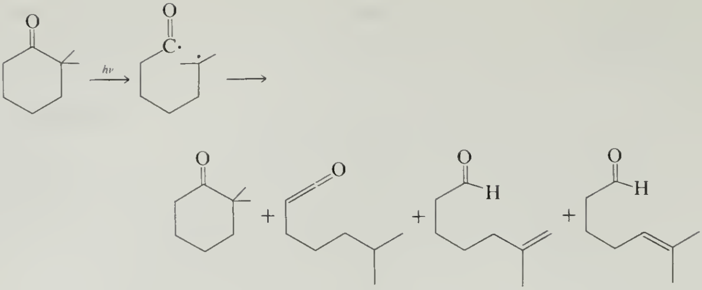
The breaking of bonds is a common photochemical reaction. We saw an early example in the dissociation of chlorine to initiate free radical chain reactions (Section 5.3.A). This reaction is also common for ketones and is called a **Norrish type I** reaction.

$$CH_3COCH_3 \xrightarrow{h\nu} CH_3CO\cdot + CH_3\cdot$$

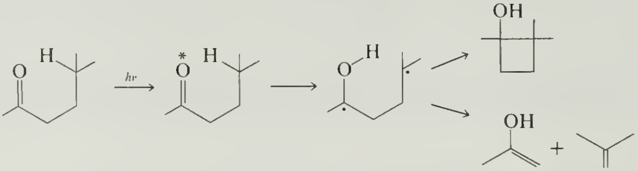
$$CH_3CO\cdot \longrightarrow CH_3\cdot + CO$$

$$2\,CH_3\cdot \longrightarrow CH_3CH_3$$

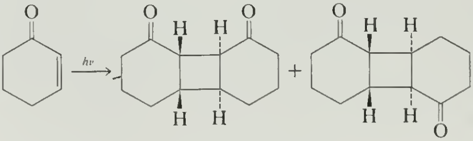
For cyclic ketones, the photochemical product is a **diradical** that can undergo further reactions.


O
hν
O
C·
O
O
O
H
O
H

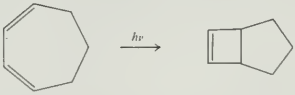
Another reaction that ketones undergo involves intramolecular hydrogen atom transfer via a six-membered ring transition state to form another diradical. This reaction is called a **Norrish type II** process.


H
O
hν
*
O
H
H
O
OH
OH

α,β-Unsaturated carbonyl compounds can undergo a photochemical dimerization with the formation of a four-membered ring.

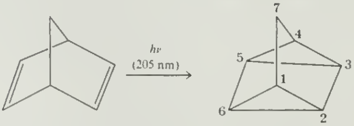

O
hν
O
H
H
O
O
H
H
H
H
H
H
O

The formation of four-membered rings is also common with dienes.



1,3-cycloheptadiene

bicyclo[3.2.0]hept-6-ene

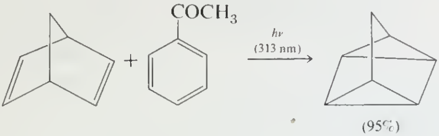

hν
(205 nm)
7
4
5
3
1
6
2

norbornadiene
bicyclo[2.2.1]-
hepta-2,5-diene

quadricyclene
tetracyclo[2.2.1.0^{2,6}.0^{3,5}]-
heptane

Quadricyclene is an unusual hydrocarbon given its trivial name from its tetracyclic nature. The compound is considered to be tetracyclic because four C—C bonds must be broken to obtain an acyclic system. Note how the systematic name is generated from a bicyclic parent. This last reaction is a slow process and the compound is formed in low yield. Most of the light quanta absorbed end up as heat and the **quantum yield** is low. The quantum yield is defined as the number of product molecules divided by the number of light quanta absorbed.

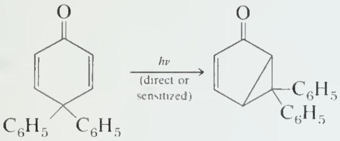
This reaction becomes much more efficient by triplet energy transfer.



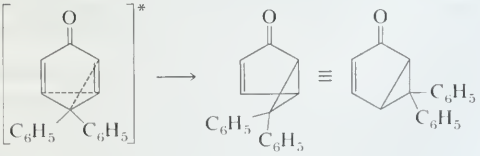
Norbornadiene is transparent to light of 313 nm wavelength. The ketone, however, absorbs this light in an $n \rightarrow \pi^*$ transition. Intersystem crossing occurs readily to T_1 of the ketone. On colliding with a molecule of norbornadiene, the ketone T_1 gives up its triplet character and is converted back to the ground state. Norbornadiene is converted to its T_1, which undergoes the changes in geometry required to intersystem cross to the ground state of quadricyclene. In this example, the acetophenone functions as a **triplet sensitizer.**

> Sensitizers work in the same fashion in photography. The direct photoexcitation of a grain of silver bromide by light (page 1027) is an inefficient process and long exposure times would be required. In modern photography, a light photon first excites a dye molecule and its excited state transfers its excitation energy to a silver bromide grain which is then developed as usual. The dye functions as the sensitizer.

Some photochemical reactions involve rather deep-seated rearrangements.



This reaction can be rationalized by the following bond-switching process in the excited state:

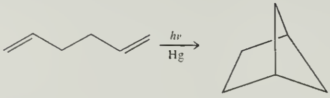


Mercury vapor is often used as a photosensitizer.

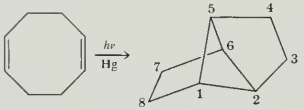
$$\mathrm{Hg} \xrightarrow[\text{(253.7 nm)}]{h\nu} \mathrm{Hg}^*$$

$$\mathrm{Hg}^* + \mathrm{A} \longrightarrow \mathrm{Hg} + \mathrm{A}^*$$

Small amounts of mercury vapor suffice to make the following reactions preparatively useful:



bicyclo[2.1.1]hexane



tricyclo[3.3.0.0^{2,6}]octane

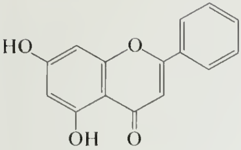
36.6 Biosynthesis

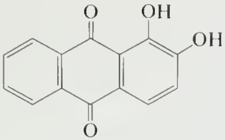
Metabolism is the collection of chemical processes by which an organism creates and maintains its substance and obtains energy in order to grow and function. Almost all of these chemical processes involve organic compounds and reactions and naturally fall under the purview of the organic chemist. The metabolic processes of various organisms are varied and complex and, in fact, the study of these processes is the subject of an entire discipline of science—biochemistry. However, many of the end products of metabolism are readily isolable organic compounds and have historical importance in organic chemistry. These compounds are grouped together under the broad heading of **natural products.**

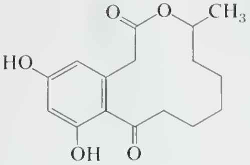
There are many different classes of naturally occurring compounds, and some have already been encountered in this book. Some, such as fats (Section 18.14.B), carbohydrates (Chapter 25), proteins (Chapter 28), and nucleic acids (Section 36.3) have obvious roles in the functioning of organisms. These natural products, together with a relatively small number of related substances, occur in almost all organisms and they are called **primary metabolites.** The processes whereby they are produced are called **primary metabolic processes.** That is, most living organisms, regardless of species, produce the common sugars and sugar derivatives, the 20 or so "essential" amino acids, the common fatty acids, and the simple carboxylic acids.

There is a second class of natural products which are called **secondary metabolites.** They are not necessarily of secondary importance to the organism, but their distribution in nature tends to be much more species dependent. They are the product of **secondary metabolic** processes of the organism. Examples of such secondary metabolites are the acetogenins, the terpenes and steroids, and the alkaloids.

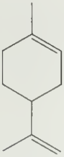
Acetogenins

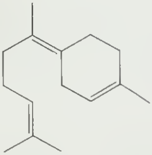

chrysin
(plant pigment)

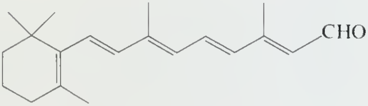

alizarin
(plant pigment)

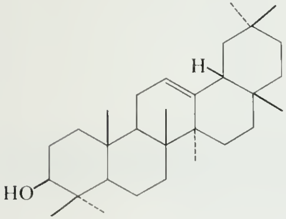

curvularin
(a fungal metabolite)

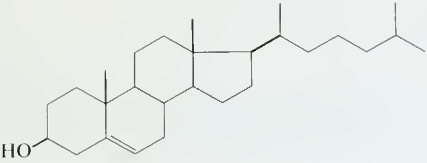
Terpenoids and Steroids


limonene
(a monoterpene)

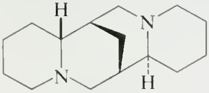

γ-bisabolene
(a sesquiterpene)

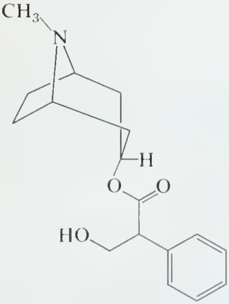

retinal
(a diterpene)


β-amyrin
(a triterpene)


cholesterol
(a steroid)

Alkaloids


sparteine


atropine

In most cases, the functions of the primary metabolites are understood, at least in broad outline. However, it is not yet known what role many of the secondary metabolites play.

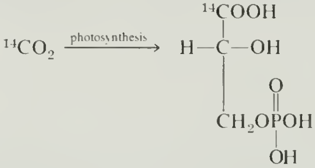
It is not within the scope of this book to go into full details on metabolic processes. However, the elucidation of the pathways by which natural products are constructed by organisms **(biosynthesized)** is a major area of current research. For that reason, we shall survey briefly one area of biosynthesis, that of the terpenes and steroids.

The basic raw material of the higher plants is carbon dioxide. This basic building unit is reduced in a process called **photosynthesis,** to give simple sugars and sugar derivatives.

$$n\ CO_2 + n\ H_2O \longrightarrow (CH_2O)_n + n\ O_2 \qquad (36\text{-}7)$$

The process described in equation (36-7) is wonderfully complex, and its details have been mostly elucidated. The conversion is catalyzed by the green pigment chlorophyll and various enzymes, and numerous other cellular constituents are involved. The energy required for the functioning of the photosynthetic apparatus is supplied by the light of the sun.

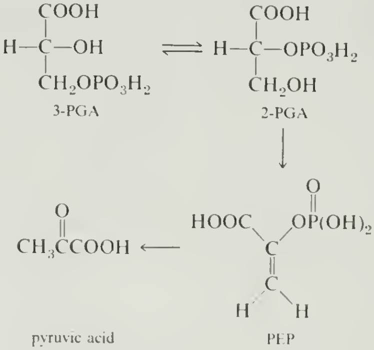
One of the first stable products of photosynthesis that can be identified is 3-phosphoglyceric acid (3-PGA). If $^{14}CO_2$ is "fed" to a plant, the 3-phosphoglyceric acid is labelled initially in the carboxy group.



$$^{14}CO_2 \xrightarrow{\text{photosynthesis}} \begin{array}{c} ^{14}COOH \\ | \\ H{-}C{-}OH \\ | \\ CH_2OP(=O)(OH)OH \end{array}$$

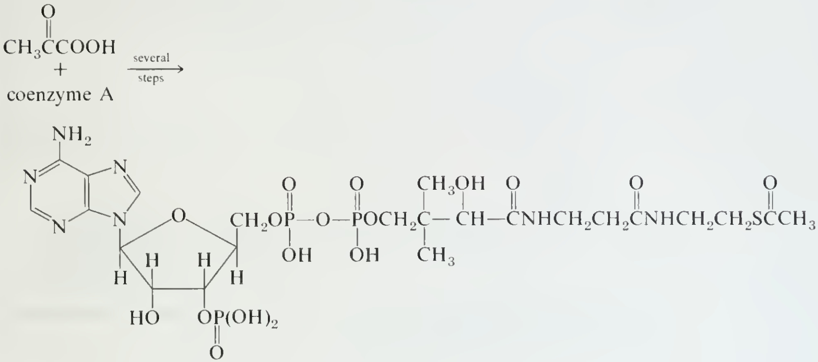
3-phosphoglyceric acid

This substance is isomerized to 2-phosphoglyceric acid (2-PGA), which undergoes dehydration to give phosphoenolpyruvic acid (PEP). The phosphoenolpyruvic acid is then hydrolyzed to give pyruvic acid and phosphate ion.



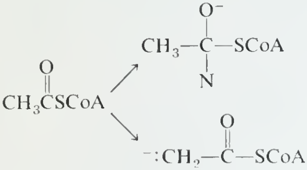
All of these reactions, like almost all biological reactions, are mediated by enzymes. Enzymes function as catalysts and merely lower the activation energy for a reaction, thereby allowing it to occur more rapidly. An enzyme cannot make a thermodynamically unfavorable process favorable. All biological processes are inherently exothermic. However, just as in any multistep reaction, a given step may be endothermic. In writing reactions in this section, we shall omit the enzymes from the equations.

Pyruvic acid, PEP, 2-PGA, and 3-PGA are all involved in a number of primary metabolic processes that we shall not consider. We shall look only at one reaction of pyruvic acid, a reaction which leads us further down the path from CO_2 to the terpenes and steroids. In a complex series of steps, which are generally understood, the α-keto acid is oxidatively decarboxylated and coupled with the —SH group of coenzyme A to give a substance known as **acetyl coenzyme A,** or $CH_3COSCoA$.

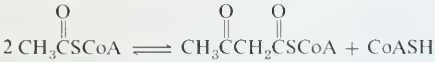


acetyl coenzyme A, $CH_3\overset{O}{\overset{\|}{C}}SCoA$

Acetyl coenzyme A is a **thioester.** In essence, it is the biological equivalent of ethyl acetate. The —SR group serves two functions; it activates the acetyl group for nucleophilic attack and it renders the $—CH_3$ protons more acidic for enolization.



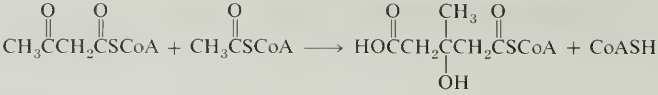
We have already seen in Section 26.3.B how these properties are utilized in the formation of fatty acids. The first step of this process is a biological version of the Claisen condensation, affording acetoacetyl coenzyme A.



$$2\,CH_3\overset{O}{\overset{\|}{C}}SCoA \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}SCoA + CoASH$$

acetoacetyl
coenzyme A

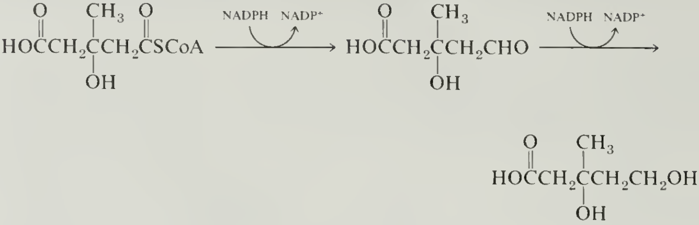
This substance reacts with another molecule of acetyl CoA in a form of aldol condensation to give β-hydroxy-β-methylglutaryl CoA.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}SCoA + CH_3\overset{O}{\overset{\|}{C}}SCoA \longrightarrow HO\overset{O}{\overset{\|}{C}}CH_2\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2\overset{O}{\overset{\|}{C}}SCoA + CoASH}$$

β-hydroxy-β-methyl-
glutaryl CoA

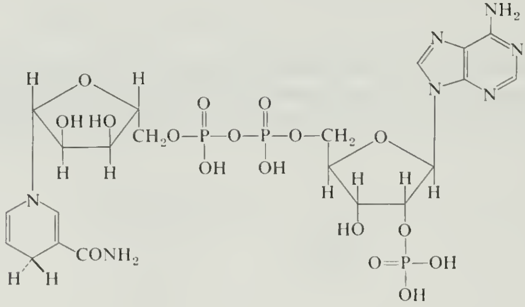
The thioester grouping is reduced, first to a hydroxy aldehydo acid, then to a dihydroxy acid, **mevalonic acid.**



$$\mathrm{HO\overset{O}{\overset{\|}{C}}CH_2\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2\overset{O}{\overset{\|}{C}}SCoA \xrightarrow{NADPH\quad NADP^+} HO\overset{O}{\overset{\|}{C}}CH_2\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2CHO \xrightarrow{NADPH\quad NADP^+} HO\overset{O}{\overset{\|}{C}}CH_2\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2CH_2OH}$$

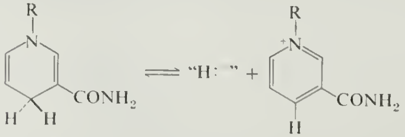
(R)-3,5-dihydroxy-
3-methylpentanoic
acid
mevalonic acid

The biological reducing agent in these two reductions is **nicotinamide adenine dinucleotide phosphate,** NADPH.



NADPH

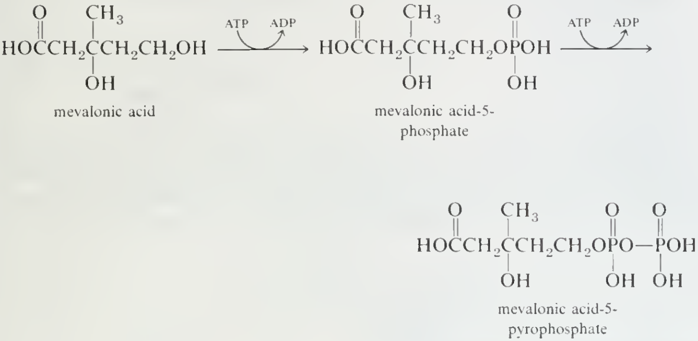
It is classified as a coenzyme and functions with the aid of an enzyme. It functions as a reducing agent in the following manner.



NADPH NADP⁺

Biological reactions involving oxidation or reduction are conventionally written as indicated, the curved arrow symbolizing that NADPH is consumed and $NADP^+$ is produced in the reaction.

Mevalonic acid is converted, in two steps, into mevalonic acid-5-pyrophosphate.

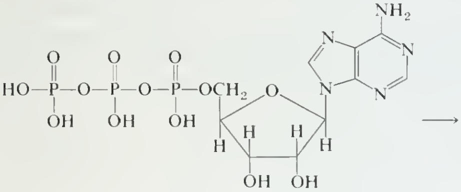


mevalonic acid

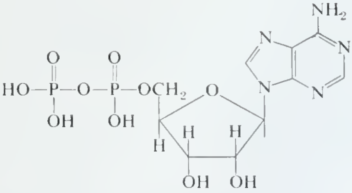
mevalonic acid-5-phosphate

mevalonic acid-5-pyrophosphate

Phosphorylation is accomplished with the aid of another coenzyme, adenosine triphosphate (ATP). The by-product of each phosphorylation step is adenosine diphosphate (ADP).

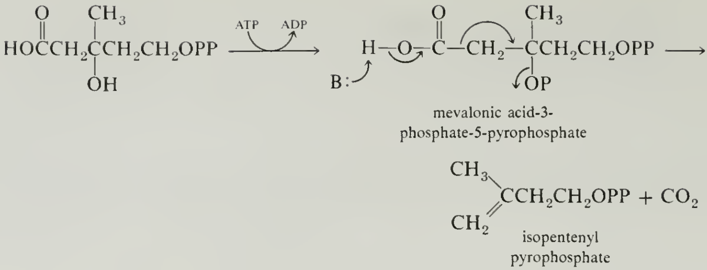


adenosine triphosphate
ATP

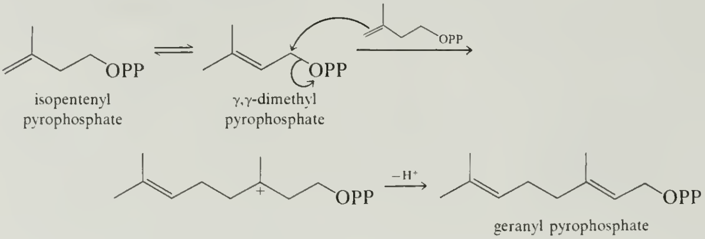


adenosine diphosphate
ADP

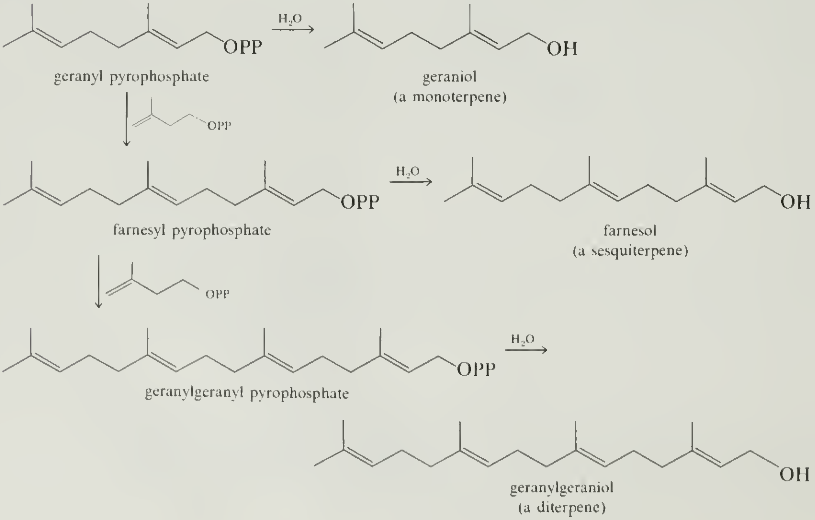
Mevalonic acid-5-pyrophosphate is phosphorylated once again to yield mevalonic acid-3-phosphate-5-pyrophosphate, which undergoes "decarboxylative elimination" to yield isopentenyl pyrophosphate (Section 20.2.E).


ATP
ADP
B:
mevalonic acid-3-phosphate-5-pyrophosphate
isopentenyl pyrophosphate

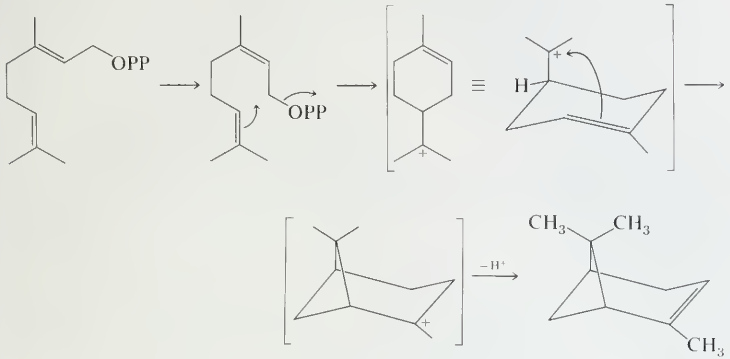
Isopentenyl pyrophosphate is the biological "isoprene unit." It undergoes isomerization to γ,γ-dimethylallyl pyrophosphate, which is highly activated toward S_N1 and S_N2 reactions (Section 20.2.E). Coupling of γ,γ-dimethylallyl pyrophosphate with isopentenyl pyrophosphate gives geranyl pyrophosphate.


OPP
isopentenyl pyrophosphate
γ,γ-dimethyl pyrophosphate
−H⁺
geranyl pyrophosphate

By successive alkylations of isopentenyl pyrophosphate, farnesyl pyrophosphate and geranylgeranyl pyrophosphate are elaborated. Hydrolysis of these three pyrophosphates yields the acyclic terpene alcohols geraniol, farnesol, and geranylgeraniol.

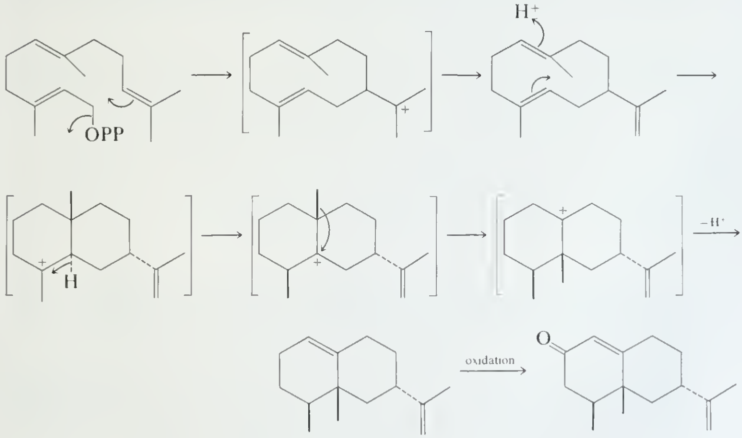

H₂O
OPP
OH
geranyl pyrophosphate
geraniol (a monoterpene)
farnesyl pyrophosphate
farnesol (a sesquiterpene)
geranylgeranyl pyrophosphate
geranylgeraniol (a diterpene)

The three acyclic pyrophosphates undergo a marvelous assortment of subsequent reactions to yield the cyclic monoterpenes, sesquiterpenes, and diterpenes that are so widespread in the plant kingdom. For example, double bond isomerization, followed by two successive enzyme-catalyzed cyclizations, converts geranyl pyrophosphate into α-pinene, the familiar fragrant principle of turpentine.



α-pinene

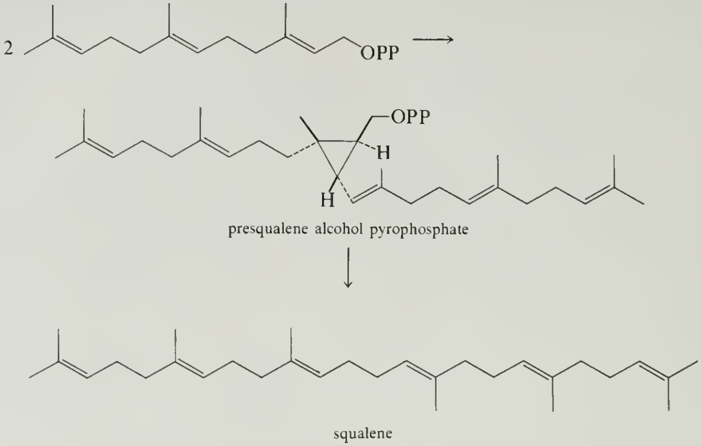
The following sequence of steps may be envisioned from farnesyl pyrophosphate to nootkatone, which is responsible for the aroma and taste of grapefruit.



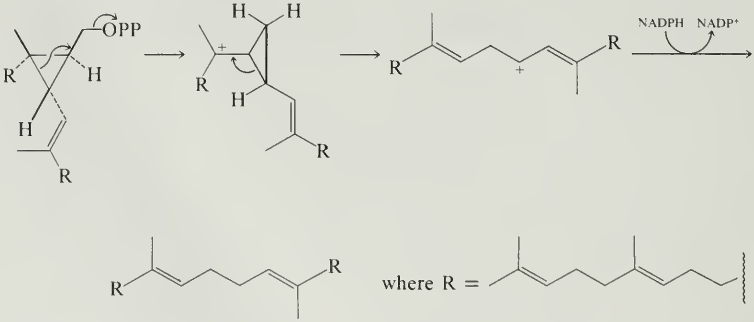
nootkatone

Similar cyclizations yield the diterpenes. The foregoing metabolic paths are common to many plants. Differences occur mainly in the ways in which geranyl pyrophosphate and farnesyl pyrophosphate are converted into the various terpenes.

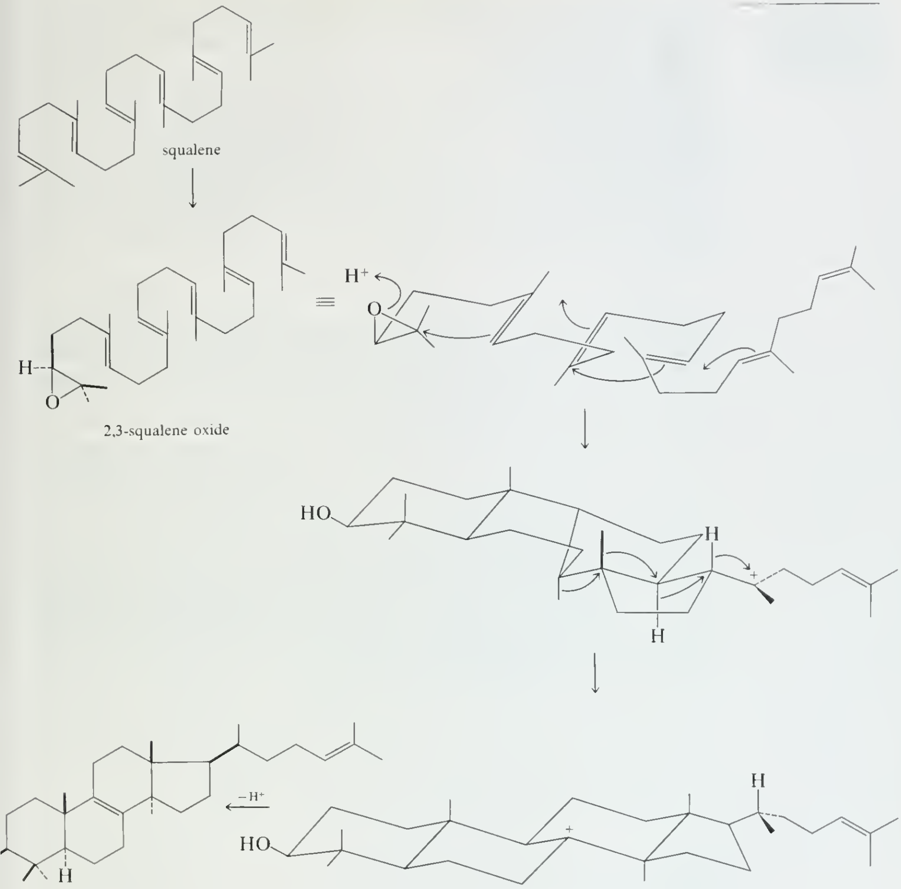
Farnesyl pyrophosphate undergoes another biological reaction—reductive coupling. The initial product of this coupling process is a cyclopropylmethyl pyrophosphate, presqualene alcohol pyrophosphate, which is then converted into squalene (Section 20.2.E).



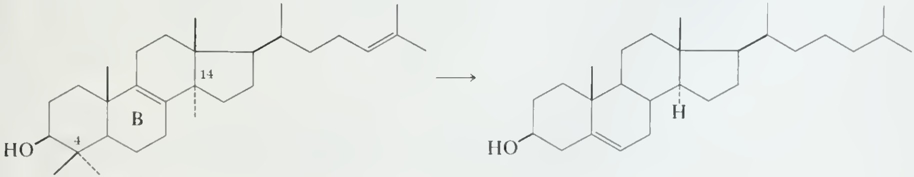
The exact mechanism whereby presqualene alcohol pyrophosphate is converted into squalene is still unknown, but it may reasonably be formulated as follows:



Squalene was once regarded as a curious terpenoid polyene that occurs in shark oil. It is now recognized to be the precurser to the whole family of steroids (Section 23.9). Squalene is elaborated by plants by the biosynthetic path outlined previously, beginning with carbon dioxide. In animals, its biosynthesis is similar, except that the beginning raw materials are more complicated foodstuffs than carbon dioxide. Oxidation of one of the squalene double bonds yields squalene oxide, which undergoes an enzymic cyclization. The cyclization is a complex reaction in which the squalene oxide chain must be folded in a precise manner. The initial product is a tetracyclic carbonium ion that undergoes the indicated "backbone rearrangement" to afford lanosterol.


squalene
2,3-squalene oxide
H
O
≡
H+
O
HO
H
H
+
− H+
H
HO
H
+
lanosterol

Since the oxidation of squalene is an enzymic process, the squalene oxide is chiral, as is the lanosterol produced by its cyclization. Lanosterol is converted into cholesterol by the loss of the three methyl groups at C-4 and C-14, isomerization of the double bond in ring B, and reduction of the double bond in the side chain.


14
B
4
HO
lanosterol
HO
H
cholesterol

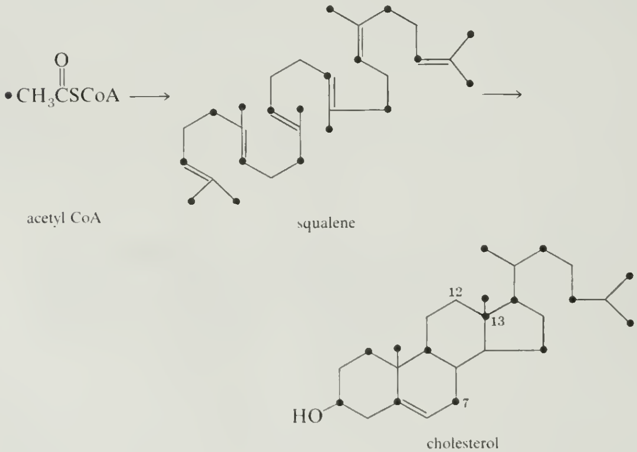
The exact mechanisms of these final steps have not yet been elucidated, but it is known that the three methyl groups are first oxidized to carboxy groups and then lost as carbon dioxide.

The foregoing discussion illustrates in broad outline the **biosynthesis** of one complex natural product. Similar biosynthetic routes have been elucidated for dozens of other natural products. Many kinds of experiments go into the elucidation of such a pathway, and we do not have space to consider them in detail. One type of experiment that has been extremely useful involves the incorporation of radioactive precursers. We shall illustrate the use of this technique in sorting out the various intermediates involved in the biosynthesis of cholesterol. The pathway proposed above for the final steps is

$$\text{squalene} \longrightarrow \text{2,3-squalene oxide} \longrightarrow \text{lanosterol} \longrightarrow \text{cholesterol}$$

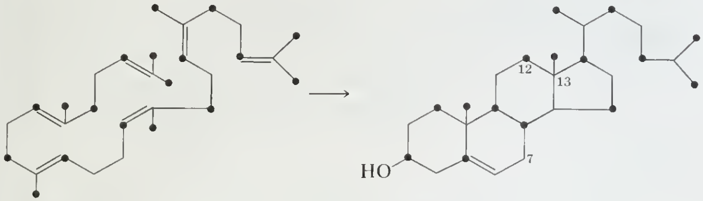
An organism that is producing cholesterol is fed squalene labeled with ^{14}C. After a suitable period, cholesterol is isolated and its radioactivity is determined. Incorporation of the label is taken as evidence that squalene is a biological precurser. Similar experiments may be carried out using labeled squalene oxide and labeled lanosterol. Incorporation studies can also be done to establish the intermediate stages; labeled squalene oxide can be administered and lanosterol is isolated. Studies such as these have been used to work out the entire metabolic path from carbon dioxide to the various terpenes and steroids, at least in gross detail. In many cases, gaps still exist. For example, we still do not know the precise steps that occur between lanosterol and cholesterol.

Incorporation studies can provide even more detailed information on metabolic pathways, as illustrated by the following example. If acetyl coenzyme A, labeled with ^{14}C in the acetyl methyl group, is administered, then the cholesterol produced should have ^{14}C in the positions indicated by black dots in (36-8), if the biosynthetic path outlined in this section is correct.



(36-8)

This experiment has been done and the cholesterol produced was subjected to a lengthy multistep degradation. The degradation was carried out in such a way that each of the 27 carbons could be examined separately for radioactivity. The label was found precisely where it is predicted to be on the basis of the biosynthetic hypothesis. In particular, the experiment ruled out an earlier hypothesis regarding the possible biosynthesis of cholesterol, which may be summarized as



Note the different labeling pattern at C-7, C-12, and C-13 that would result from this model. In fact, the degradation revealed that C-7 and C-13 are labeled, whereas C-12 is not, thus refuting this earlier hypothesis.

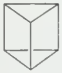
36.7
Stereospecific Synthesis

In the preceding section, we considered the question of how organisms synthesize complex organic molecules. We saw that the chemical reactions involved are the same reactions we use in the laboratory—aldol condensations, Claisen condensations, oxidations and reductions, and so on. Only the reagents and catalysts are different. Organisms make use of highly complex reagents to achieve rapid and specific reactions. An example is the biological reducing agent nicotinamide adenine dinucleotide phosphate (NADPH)—the organic chemist uses $NaBH_4$ or $LiAlH_4$. Although $NaBH_4$ and $LiAlH_4$ are much simpler molecules than NADPH, they are not nearly as specific. Under the influence of various enzyme catalysts, NADPH can perform selective reductions that the chemist cannot yet hope to achieve with our laboratory reducing agents.

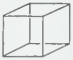
In fact, one of the major goals of organic chemists who specialize in synthetic methods is to duplicate or surpass the finesse with which nature can construct complicated molecules. In many areas, we are far from that goal, although significant advances have been made. For example, in 1973 a team of organic chemists headed by Professor R. B. Woodward at Harvard University and Professor Albert Eschenmoser at the Swiss Federal Institute of Technology completed a laboratory synthesis of vitamin B_{12} (Figure 36.17).

The synthesis was a notable achievement. In terms of effort expended, it is undoubtedly the most impressive organic synthesis ever done. More than 90 separate synthetic reactions were required and dozens of highly trained chemists labored for years to bring it to completion. However, compared with the ease with which nature elaborates this complex molecule, the organic chemist must still take second place.

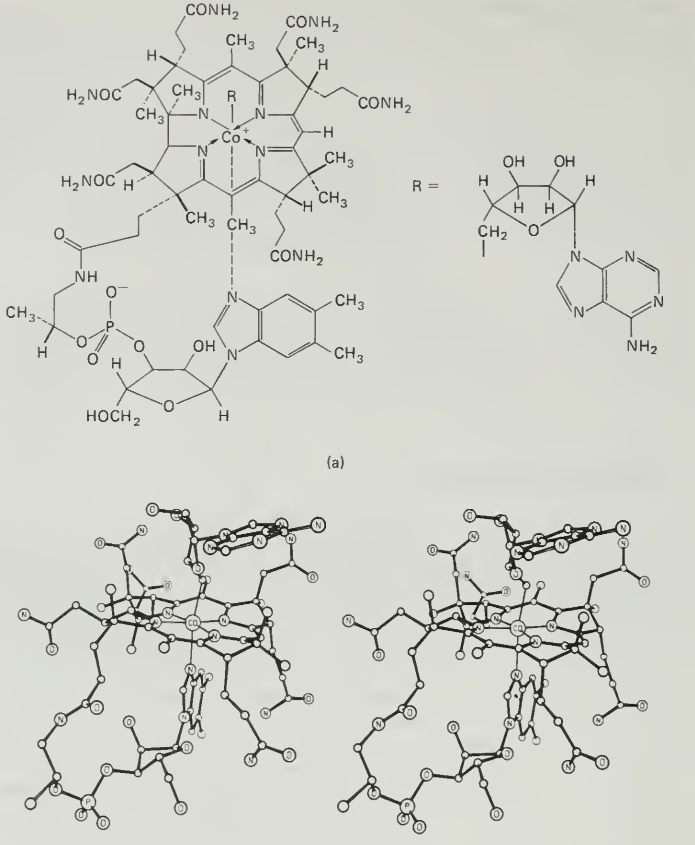
However, chemists *have* been able to synthesize many interesting molecules



prismane, C_6H_6



cubane, C_8H_8



(a)

(b)

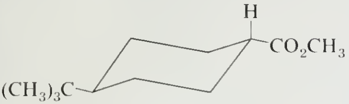
Figure 36.17 *Vitamin* B_{12}*:* (a) *structure;* (b) *stereo structure.* [*Courtesy of C. K. Johnson, Oak Ridge National Laboratory*].

that are not produced by nature (perhaps because nature has no need for them). Examples are the highly strained hydrocarbons prismane and cubane.

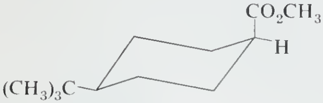
As we pointed out in Chapter 19, when we first surveyed the problem of designing the synthesis of an organic compound, several interrelated factors must be considered. Two of these factors are construction of the carbon skeleton and placement of the desired functional groups in their proper positions. In the intervening chapters, we have encountered many more reactions that can be used to accomplish both of these ends.

The third major consideration in synthetic design that we mentioned in Chapter 19 is stereochemical control. At the time, we had studied relatively few reactions that could be used to establish stereochemistry. Our repertoire is now more suited for a discussion of that problem, and we shall examine it briefly. In general, stereochemistry may be controlled in two ways: thermodynamically or kinetically.

1. **THERMODYNAMIC CONTROL.** If the stereoisomer we wish to synthesize is the more stable stereoisomer, we may carry out the synthesis in such a way that the product, or one of its precursers, may equilibrate with its stereoisomers. For example, suppose we wish to synthesize methyl *trans*-4-*t*-butylcyclohexanecarboxylate. Since both substituents are equatorial in the *trans* stereoisomer, it is more stable than the *cis* isomer (Section 23.4.A).

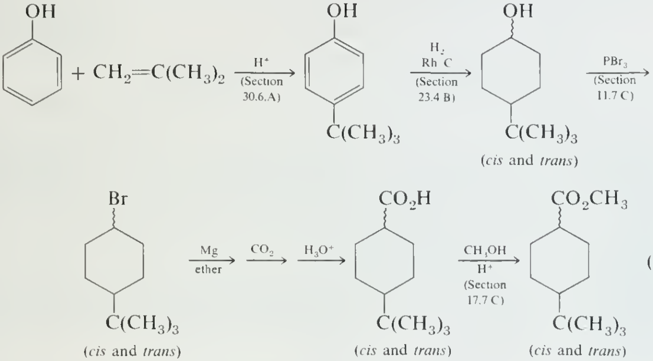

H
CO_2CH_3
$(CH_3)_3C$

trans stereoisomer
(more stable)


CO_2CH_3
H
$(CH_3)_3C$

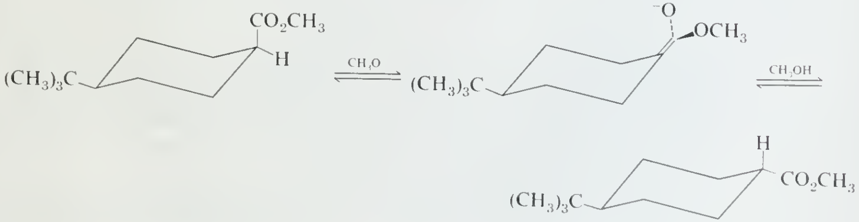
cis stereoisomer
(less stable)

We may take advantage of this information in our synthesis. A reasonable synthesis of the compound, beginning with phenol, is outlined (36-9).

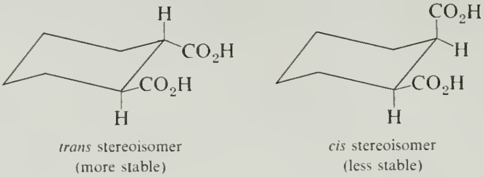

OH
$+ CH_2{=}C(CH_3)_2$
H^+
(Section 30.6.A)
OH
$C(CH_3)_3$
H_2
Rh/C
(Section 23.4.B)
OH
$C(CH_3)_3$
(*cis* and *trans*)
PBr_3
(Section 11.7.C)
Br
$C(CH_3)_3$
(*cis* and *trans*)
Mg
ether
CO_2
H_3O^+
CO_2H
$C(CH_3)_3$
(*cis* and *trans*)
CH_3OH
H^+
(Section 17.7.C)
CO_2CH_3
$C(CH_3)_3$
(*cis* and *trans*)

(36-9)

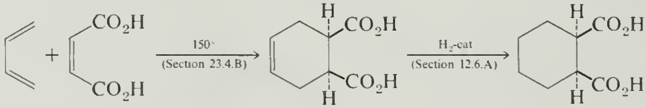
The synthetic design is straightforward, and makes use of five reactions we have encountered previously. However, it is difficult to predict the stereochemical outcome, and a mixture of *cis* and *trans* isomers will probably result. Since the more stable *trans* isomer is the desired product, obtaining a mixture of stereoisomers presents no problem. One may simply equilibrate the product by treating the final mixture with sodium methoxide in anhydrous methanol. The more stable *trans* isomer predominates at equilibrium.


CO_2CH_3
H
$(CH_3)_3C$
CH_3O^-
^-O
OCH_3
$(CH_3)_3C$
CH_3OH
H
CO_2CH_3
$(CH_3)_3C$

2. **Kinetic Control.** In cases where the desired stereoisomer is *not* the more stable one, we must carry out the synthesis in such a way that the less stable stereoisomer is produced more rapidly than the more stable stereoisomer. As an example, consider the synthesis of *cis*-cyclohexane-1,2-dicarboxylic acid. The desired product is less stable than the *trans* stereoisomer, so we must introduce stereochemistry by a kinetic method.

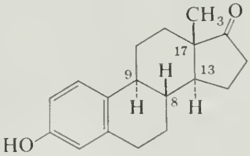


We may synthesize the diacid by the following route, which assures the desired stereochemistry:



Stereochemistry is established in the Diels-Alder reaction (step 1). Since this pericyclic reaction proceeds through an aromatic $4n + 2$ transition state, the *cis* isomer is produced much more rapidly than the *trans*. Hydrogenation of the double bond affords the desired product.

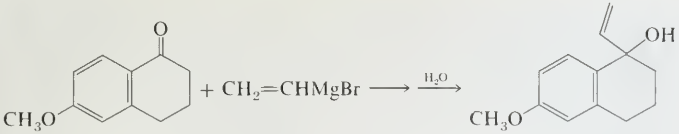
Let us consider one example of the laboratory synthesis of a complex organic compound where such principles of stereochemical control are practiced. The example is that of estrone, which we have previously encountered as an important sex hormone (Section 23.9).



estrone

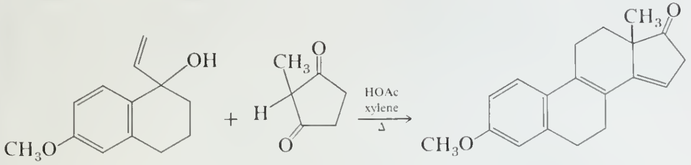
The molecule has four asymmetric centers, and there are therefore 16 stereoisomers (Section 7.5). Only the isomer shown has significant physiological activity. There have been numerous syntheses of estrone, but by far the most efficient is one discovered by the Russian chemist I. V. Torgov and perfected by various other workers. In fact, the Torgov synthesis of estrone is so efficient that it is used as a commercial preparation for the steroid.

The Torgov synthesis begins with 6-methoxy-1-tetralone, a substance readily available from naphthalene. The ketone is treated with vinylmagnesium bromide to give an allylic alcohol.


O
CH$_3$O
+ CH$_2$=CHMgBr
H$_2$O
OH
CH$_3$O

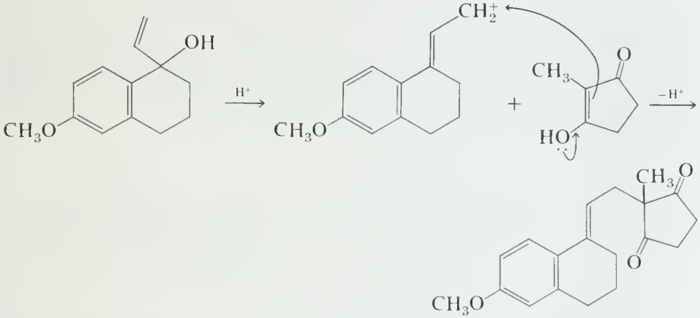
6-methoxy-1-tetralone

When this alcohol is heated in xylene with 2-methyl-1,3-cyclopentanedione and acetic acid, a crystalline tetracyclic ketone is produced in 70% yield.

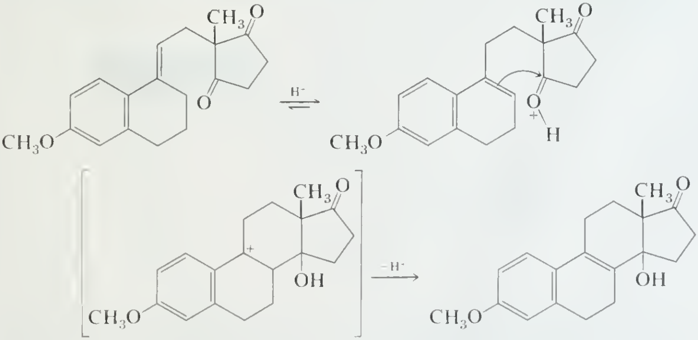

OH
CH$_3$O
+
CH$_3$
O
H
O
HOAc
xylene
Δ
CH$_3$
O
CH$_3$O

(70%)

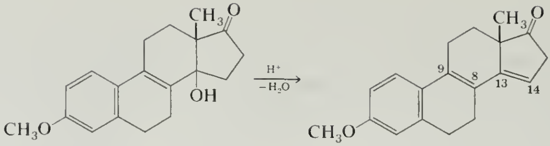
The mechanism of this reaction involves an acid-catalyzed ionization of the allylic alcohol (Section 20.1.A), which reacts with the enol form of the 1,3-diketone (Section 26.4.B).


OH
CH$_3$O
H$^+$
CH$_2^+$
CH$_3$O
+
CH$_3$
O
HO
−H$^+$
CH$_3$
O
O
CH$_3$O

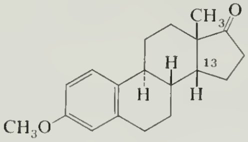
The double bond then undergoes acid-catalyzed isomerization, and a type of Friedel-Crafts alkylation reaction follows (Section 30.6.A).


CH$_3$
O
O
CH$_3$O
H$^+$
CH$_3$
O
O
H
CH$_3$O
CH$_3$
O
OH
CH$_3$O
−H$^+$
CH$_3$
O
OH
CH$_3$O

Finally, the allylic alcohol dehydrates to give the diene.

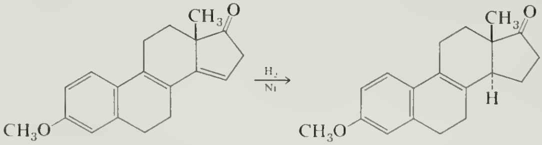


With the carbon skeleton of estrone elaborated, and the functional groups in their proper position, it remains only to reduce the two double bonds in such a way that the proper stereoisomer is produced. At this point, we should mention that estrone is *not* the most stable of the 16 stereoisomers. Rather, 13-isoestrone is the most stable isomer. Therefore, chirality must be imparted to C-13 by some kinetic method.

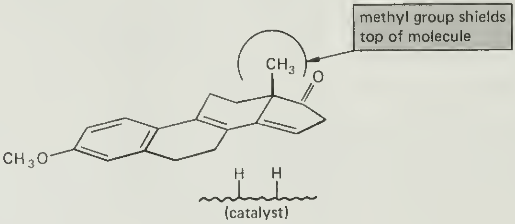


13-isoestrone

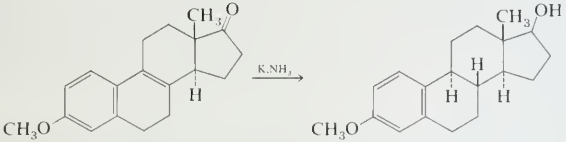
This is readily achieved by a selective catalytic hydrogenation of the diene system. The more reactive double bond is the one between C-13 and C-14, since it is more easily accessible. When the tetracyclic dienone is reduced with hydrogen in the presence of Raney nickel, and the reduction is stopped after the uptake of one equivalent of H_2, the 13—14 double bond is reduced cleanly and stereospecifically.



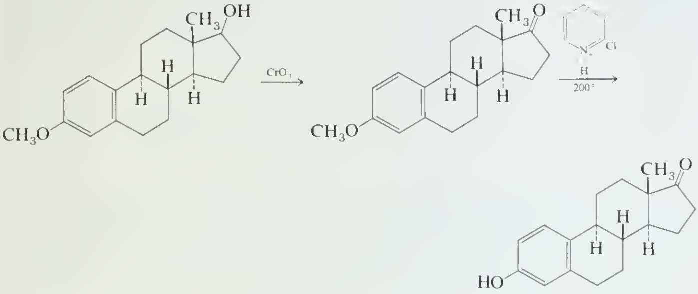
In this case, the methyl group, which projects over the top of the nearly flat molecule, shields that side of the molecule from the surface of the catalyst. Thus, the less stable stereoisomer is produced more rapidly and stereospecificity is achieved.



The remaining double bond between C-8 and C-9 may be reduced under conditions of thermodynamic control, because the desired stereochemistry at these centers is the thermodynamically favored stereochemistry. This is achieved by treating the compound with potassium in liquid ammonia. Both the ketone and the double bond are reduced in this reaction, but the important feature is the stereochemistry. The alkali metal–ammonia reducing medium has the important property of producing the most stable reduction product (for example, see Section 13.6.A). Thus, the stereochemistry at C-8 and C-9 is that desired.


CH3
O
H
CH3O
K, NH3
CH3
OH
H
H
H
CH3O

The secondary alcohol is oxidized back to a ketone, and the aryl methyl ether is cleaved (Section 33.3.D) to complete the synthesis.


CH3
OH
H
H
H
CH3O
CrO3
CH3
O
H
H
H
CH3O
N
H
Cl
200°
CH3
O
H
H
H
HO

estrone

In the introductory chapter to this book, we spoke of organic chemistry as an *art form*. It is altogether fitting that we conclude our survey of organic chemistry with a look at one such work of art.

CHAPTER 37
The Chemical Literature

37.1
Research Journals

The total knowledge of chemistry is contained in hundreds of thousands of books and journals that are known collectively as **the literature.** New knowledge is communicated to the world for the first time as a **paper** or **communication** in a **research journal.** There are perhaps 10,000 journals that publish original articles on chemical topics, but only about 50 are of general interest to most chemists. Some journals, such as the *Journal of the American Chemical Society,* publish articles in all branches of chemistry. Others, such as the *Journal of Organic Chemistry,* only publish articles dealing with a specific area. A partial listing of typical journals that would be of interest to an organic chemist, with the normal abbreviation printed in italic type, is given. The language(s) used in each journal is also indicated.

1. *Angew*andte *Chem*ie (German)
2. *Angew*andte *Chem*ie *Int*ernational *Ed*ition in *Eng*lish (English)
3. Justus Liebig's *Ann*alen der Chemie (German)
4. *Bull*etin of the *Chem*ical *Soc*iety of *Jap*an (English)
5. *Can*adian *J*ournal of *Chem*istry (English, French)
6. *Chem*ische *Ber*ichte (German)
7. *Chem*ical *Commun*ications (English)
8. *Coll*ection of *Czech*oslovak *Chem*ical *Commun*ications (English)
9. *Compt*es *rend*us hebdomadaries, *Ser*ies *C* (French)
10. *Helv*etica *Chim*ica *Acta* (German, French, English)
11. *J*ournal of the *Am*erican *Chem*ical *Soc*iety (English)
12. *J*ournal of the *Chem*ical *Soc*iety, Section *B*, Physical-Organic Chemistry (English)
13. *J*ournal of the *Chem*ical *Soc*iety, Section *C*, Organic Chemistry (English)
14. *J*ournal of *Heterocycl*ic *Chem*istry (English)
15. *J*ournal of the *Indian Chem*ical *Soc*iety (English)
16. *J*ournal of *Med*icinal *Chem*istry (English)
17. *J*ournal of *Organometal*lic *Chem*istry (English, German, French)
18. *J*ournal of *Org*anic *Chem*istry (English)
19. *Synthesis* (English)
20. *Syn*thetic *Commun*ications (English)
21. *Tetrahedron* (English, German, French)
22. *Tetrahedron Lett*ers (English, German, French)

An original article in a research journal may be in the form of a **full paper,** a **note,** or a **communication.** A full paper is a complete report on a research project, with full experimental details and interpretation. It is always accompanied by a short abstract, written by the authors. A note is a final report on a project of smaller scope. It includes experimental details but has no abstract. A communication is a preliminary report on a finding of unusual significance. Communications are extremely concise, usually less than 1000 words, and have little or no experimental detail. In most cases, a communication will be followed later by a full paper after the project has been completed. Some journals, such as *J. Am. Chem. Soc.* and *J. Org. Chem.* publish both papers and communications and others, such as *Tetrahedron Lett.* and *Chem. Commun.* publish only communications. Research articles are documented with references to the literature, to other research articles, and to books. The form of such a **literature citation** used in the American Chemical Society journals is: Authors, *journal abbreviation*, **volume number**, page number (year). For example

H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2052 (1965).

If a practicing chemist is to keep abreast of the developments in his field, it is essential that he peruse a number of research journals regularly, as they appear. All of the journals listed above appear periodically, usually weekly, semimonthly, or monthly. Most chemists regularly scan the tables of contents of a dozen or so journals that publish articles in areas of interest to them.

37.2
Books and Review Articles

The original research journals comprise the **primary literature** of chemistry; they are the ultimate source that must be consulted for authoritative information on any subject. A second category of chemical literature is classed as **secondary literature.** The secondary literature consists of reference books and review articles in which the primary literature is collated and interpreted.

A. *Handbooks*

There are a number of excellent handbooks that compile data about individual organic compounds. The most extensive and most useful is the *Handbuch der Organischen Chemie,* commonly known as *Beilstein,* after its first editor. *Beilstein* is a multivolume handbook that lists all known organic compounds, together with their physical properties, methods of preparation, chemical properties, and any other available information. The main disadvantage of *Beilstein* is the fact that it is not up to date. All of the literature through 1929 is completely covered, and a supplement covering the period 1930–1949 is partially completed. We shall consider the use of *Beilstein* in Section 37.4.

The Handbook of Chemistry and Physics, published by the Chemical Rubber Publishing Company, Cleveland, Ohio, is revised regularly. It contains a useful collection of data and a copy may be found on the desk of almost all practicing chemists. The most important table for organic chemists is "Physical Constants of Organic Compounds," which occupies a major portion of the book. This table contains the name, formula, color, and several important physical properties for several thousand common organic compounds. Compounds are listed alphabetically, using the IUPAC names. A similar volume is Lange's *Handbook of Chemistry*, McGraw-Hill Book Company, New York.

The Dictionary of Organic Compounds, edited by Heilbron, Cook, Bunbury, and Hey, is a five-volume handbook published by Oxford University Press, New York. It contains names, formulas, physical properties, and references for about

40,000 organic compounds. Compounds are listed alphabetically and there is no index.

The Merck Index of Chemicals and Drugs, is published periodically by Merck and Company, Rahway, New Jersey. It concentrates on compounds of medicinal importance, but covers most simple organic compounds, whether or not they have significant physiological properties. In addition to names and formulas, the *Merck Index* lists physical properties, methods of synthesis, physiological properties and medicinal uses, and also gives the generic and trade names for all compounds that are used as drugs.

B. *Review Articles*

A review article is a survey of a single limited topic. For example, a chemist may assemble all the information available on a topic by reading the original research articles, and condense the information into a review article, frequently with his own interpretation. There are several periodicals that specialize in publishing review articles. A few important to organic chemists are

1. *Chem*ical *Rev*iews (English)
2. *Chem*ical *Soc*iety *Rev*iews (English)
3. *Angew*andte *Chem*ie (German)
4. *Angew*andte *Chem*ie *Int*ernational *Ed*ition in *Eng*lish (English)
5. *Fortschr*itte der *Chem*ischen *Forsch*ung (German)
6. *Rev*iews of *Pure* and *Appl*ied *Chem*istry (English)
7. *Synthesis* (English)
8. *Organometal*lic *Chem*istry *Rev*iews (English)

In addition to review journals such as these, there are a number of open-ended serial publications that are published at somewhat irregular intervals in hardbound form. These books are similar in content and format to the normal review journals. A few examples are

1. *Advan*ces in *Carbohyd*rate *Chem*istry
2. *Advan*ces in *Free Radical Chem*istry
3. *Advan*ces in *Photochem*istry
4. *Progr*ess in *Phys*ical *Org*anic *Chem*istry
5. *Advan*ces in *Phys*ical *Org*anic *Chem*istry
6. *Org*anic *React*ions
7. *Progr*ess in *Org*anic *Chem*istry
8. *Progr*ess in *Stereochem*istry
9. *Top*ics in *Stereochem*istry

Organic Reactions is a particularly important reference source for organic chemists. It is published approximately yearly and contains review articles on general reactions, for example, "The Wittig Reaction," "The Clemmensen Reaction." The articles are accompanied by extensive tables of applications of the reaction.

C. *Monographs*

There are a large number of excellent books available that provide in-depth surveys of specific areas. The number of such monographs is far too great even to attempt to list here, and the student is referred to the card catalog in his own library. Several examples, merely to indicate the types of topics covered, are:

1. H. C. Brown: *Hydroboration.* Benjamin, New York, 1962.
2. E. L. Eliel: *Stereochemistry of Carbon Compounds.* McGraw-Hill, New York, 1962.
3. H. O. House: *Modern Synthetic Reactions.* Benjamin, New York, 1971.
4. A. Streitwieser, Jr.: *Molecular Orbital Theory for Organic Chemists.* Wiley, New York, 1961.
5. N. J. Turro: *Molecular Photochemistry.* Benjamin, New York, 1965.

D. *Books Covering Methods and Reagents*

There are several useful books that are devoted to synthetic methods or to reagents used in organic reactions. *Organic Syntheses* is published by John Wiley and Sons, New York. It is a collection of procedures for the preparation of specific compounds. The work has appeared annually since 1921. The procedures for each 10-year period are collected in cumulative volumes, of which five now exist. The procedures in *Organic Syntheses* are submitted by any chemist who wishes to do so, and are then tested in the laboratory of a member of the editorial board. Although the methods given pertain to specific compounds, an attempt is made to include procedures that have general applicability. For this reason, *Organic Syntheses* is a useful source of model procedures when the chemist wishes to carry out a new preparation. The cumulative volumes are thoroughly indexed.

Theilheimer, *Synthetic Methods of Organic Chemistry,* S. Karger Verlag, Basel, is an annual compilation of synthetic methods. It is organized by way of a system based upon types of bond formations or bond cleavages. There is an index with each volume and a cumulative index after each fifth volume.

Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Wiley, New York, is an exceedingly useful compendium of reagents and catalysts used in organic chemistry. In addition to the main volume, three supplements are now available. The work gives information of how each reagent is prepared, commercial suppliers, and references to its uses.

37.3
Abstract Journals

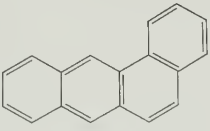
Abstract Journals are periodicals that publish short abstracts of articles which appear in the original research journals. There are currently three such publications devoted to the coverage of the original chemical literature, of which the most important is *Chemical Abstracts.* Others are *Chemisches Zentralblatt* (German) and *Referativnyi Zhurnal* (Russian).

Chemical Abstracts is published weekly by the American Chemical Society and contains abstracts in English of nearly every paper that contains chemical information, regardless of the original language. Abstracts appear from 3 to 12 months after the appearance of the original paper. The abstracts are grouped into 80 sections, of which sections 21–34 pertain to organic chemistry. Each individual abstract is preceeded by the authors' names, the authors' address, the journal citation, and the language of the original article.

Although many chemists use *Chemical Abstracts* routinely as a method to keep abreast of a broad area of chemistry, it is most useful because of its indexes. From its beginning in 1907 until 1961 there were annual indexes. Since 1962, there have been semiannual indexes, covering the periods January–June and July–December. From 1907 until 1956 there were published additional 10-year indexes. Since 1957, the cumulative indexes have appeared at 5-year intervals. The most recent complete index is the *Eighth Collective Index,* covering the period 1967–1971. Each annual and collective index has a subject index and an author index. Formula indexes for the periods 1920–1946, 1947–1956, 1957–1961, 1962–1966, and 1967–1971 are also available. The most useful of the indexes is the subject index. Each compound referred to in any paper abstracted during the index period is listed alphabetically. Following each entry is an abstract number.

To search *Chemical Abstracts* for information concerning a given compound, one looks up the name of the compound in each of the collective indexes, and then in the semiannual indexes that have appeared since the last collective index. The abstract numbers are then used to locate the abstracts, and these are scanned. If it appears from an abstract that the original paper contains information of use the original paper is consulted.

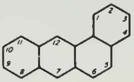
For example, suppose we wish to know what has been published regarding the carcinogenic (tumor-producing) properties of the hydrocarbon benz[a]anthracene during the period 1967–1971.



benz[a]anthracene

Consulting the *Eighth Collective Index,* which covers the period, we find the listing:

Benz[*a*]anthracene [*56 –55 –3*]



[a]

Following this listing, there are a number of indexed topics, in alphabetical order. A portion is shown.

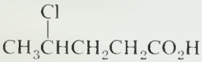
- bond length and heat of dissocn. of, **69:** 35282v
- bond length in, **72:** 6380g
- bond lengths and energy levels of, **75:** 5052b
- bond order and localization energy of, in excited state, polarizability in relation to, **68:** 62565d
- bromination of, mechanism of, **66:** 37049m
- bud induction by, in tobacco callus culture, **74:** 2887w
- butoxyphenyl siloxanes contg., degradation of, **72:** 133523f
- carbonate dehydratase inhibition by, **67:** 115102k
- carcinogenesis by, two-stage process in relation to, **73:** 33378q
- carcinogenic activity of
  - **67:** 98520a; **72:** 10910x
  - activation energy of elec. conduction in relation to, **70:** 42062x
  - mol. orbitals in relation to, **72:** 64737q
- carcinogenic activity of hydrocarbons and, **72:** 53064s
- carcinogenic and menadione reductase-inducing activities of, **68:** 47948j
- as carcinogen in human environment, **69:** 25669n
- cell invasiveness in presence of, **68:** 103288h
- cell protection against dimethylbenzanthracene by, aryl hydroxylase formation in, **71:** 122020t
- cheese contamination with, from wax coating, **72:** 109888h
- chem. shifts of, mol. orbital calcn. in relation to, **73:** 55252w

The number after each topic indicates the *Chemical Abstracts* volume number and abstract number where the information will be found. For example, the listing 67:98520a means that abstract 98520 in volume 67 contains information on the carcinogenic activity of benz[a]anthracene. Going to volume 67 of the abstracts (1967), we find the following abstract:

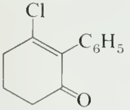
> **98520a The carcinogenic activities in mice of compounds related to benz[a]anthracene.** E. Boyland and P. Sims (Roy. Cancer Hosp., London). *Int. J. Cancer* 2(5), 500–4(1967)(Eng). The carcinogenic activities of 18 aromatic hydrocarbons and their metabolic intermediates were compared after 3–10 s.c. injections of 1 mg. into C57 black mice. The monohydroxymethyl derivs. of 7,12-dimethylbenz[*a*]anthracene and some related compds. were active carcinogens, but were much less so than the parent hydrocarbon. Epoxides formed at the 5,6-bond (K-region) of chrysene, benz[*a*]anthracene, 7-methylbenz[*a*]anthracene, and dibenz[*a,h*]anthracene produced tumors when given at high dose levels, but were not as active as the parent hydrocarbons. The epoxide derived from phenanthrene was inactive. All of the compds. were prepd. by known methods with the exception of 7,12-dimethylbenz[*a*]anthracene, dibenz[*a,h*]anthracene, and chrysene which were obtained com. and 7-(diacetoxymethyl)benz[*a*]anthracene which was prepd. by heating benz[*a*]anthracene-7-carboxaldehyde under reflux with Ac_2O for 6 hrs. It sepd. from EtOH in needles, m. 196°. CTJN

If we desire more complete information, we may consult the original article, which was published in the *International Journal of Cancer Research*, volume **2**, on page 500, in 1967.

In order to use *Chemical Abstracts* efficiently, one must have a good command of organic nomenclature. All compounds are listed as derivatives of a parent compound, for example



$$CH_3\overset{\overset{\large Cl}{|}}{C}HCH_2CH_2CO_2H \equiv \text{valeric acid, 4-chloro}$$



≡ 2-cyclohexen-1-one, 3-chloro, 2-phenyl

Note that *Chemical Abstracts* does not always use IUPAC nomenclature. At the beginning of each collective index, there is an extensive section dealing with the system of nomenclature used in indexing. In cases where it is not clear which name is used for indexing a particular compound, the formula index is useful. However, the formula index is much more tedious to use, because one must often sift through an extensive list of isomers. It is also less reliable than the subject index, since omissions are more frequent.

The physical size of the Subject Index has necessitated some format changes to maintain optimal useability of this important access point to the chemical literature. Consequently since the issuance of the volume indexes covering the January–June 1972 period, the Subject Index has been issued in 3 parts: The Chemical Substance Index, the General Subject Index, and the Index Guide. All references to distinct, definable chemical substances are collected in the Chemical Substance Index, and all entries pertinent to any other topics (concepts, processes, organism names, diseases, reactions, generalized classes of compounds, and so on) are found in the General Subject Index. The Index Guide serves to guide the user quickly and efficiently to the proper headings in these two indexes. The Index Guide can be used to find a Chemical Substance Index name for trivial-, commercial-, and other nonsystematically-named substances. It represents a compilation of indexing cross-references, preferred index headings, synonyms, and general index notes on thousands of chemical terms and names and should be consulted before using either the Chemical Substance or General Subject Indexes. The Index Guide is supplemented annually to cover additions and changes that may occur within a volume indexing period.

37.4
Beilstein

Beilstein's *Handbuch der Organischen Chemie* is shelved in the reference section of most chemical libraries. There have been four editions of the work and the first three are obsolete. The fourth edition (*vierte Auflage*) consists of a main series (*das Hauptwerk*) and three supplementary series (*erstes, zweites,* and *drittes Ergänzungswerk*). The periods covered by the various series are

Main series:	antiquity–1909
First supplement:	1910–1919
Second supplement:	1920–1929
Third supplement:	1930–1949 (incomplete)

A fourth supplement, covering the period 1950–1959, has just begun to appear. The main series consists of 27 volumes (*Bands*), each bound as a separate book. Each supplementary series also consists of 27 volumes, and entries in the supplements are cross referenced to the main series. Volumes in the supplementary series are sometimes bound as more than one book and in some cases, two or more volumes are bound together.

Compounds are grouped into three major divisions, in the following manner:

Division	Volumes
Acyclishe reihe, Acyclic compounds	1–4
Isocyclishe reihe, Carbocyclic compounds	5–16
Heterocyclishe reihe, Heterocyclic compounds	17–27

There is a fourth minor division, carbohydrates, rubber-like compounds, and carotenoids, contained in volumes 30 and 31, which only appears with the main series.

Volumes 28 and 29 are a subject index (*Generalsachregister*) and a formula index (*Generalformelregister*), respectively. The most recent indexes are part of the second supplement and they cover the main series and the first and second supplements, that is, through 1929. Earlier versions of the indexes are obsolete. One cannot rely completely on the indexes, because only representative compounds are indexed. However, they are useful to obtain rapidly the approximate location of a compound in the handbook, particularly for heterocyclic compounds. The index listing gives the volume and page numbers where the compound will be found. Bold type indicates the volume number and normal type indicates the page number, supplementary series page numbers are preceeded by the appropriate Roman numeral. For example, volume **28** of the second supplementary series contains the listing:

Indol **20**, 304, I 121, II 196; **21** II 567.

Thus, we find indole listed on page 304 in volume **20** of the main series, on page 121 of volume **20** of the first supplementary series, and on page 196 of volume **20** of the second supplementary series. The final entry refers to a correction, which appeared on page 567, at the end of volume **21** of the second supplementary series. We find the same listing in volume **29** of the second supplementary series, which is the formula index, under C_8H_7N, the formula of indole.

Although the *Beilstein* indexes are useful, one should become familiar with the basic organizational system of the handbook if it is to be used to best advantage. In each of the first two major divisions, acyclic compounds and carbocyclic compounds, compounds are listed according to the following order of basic classes:

1. Hydrocarbons (*Kohlenwasserstoffe*), RH.
2. Hydroxy compounds (*Oxyverbindungen*), ROH.
3. Carbonyl compounds (*Oxoverbindungen*), $R_2C{=}O$.
4. Carboxylic acids (*Carbonsäuren*), RCOOH.
5. Sulfinic acids (*Sulfinsäuren*), RSO_2H.
6. Sulfonic acids (*Sulfonsäuren*), RSO_3H.
7. Selenium acids (*Seleninsäuren* and *Selenosäuren*), $RSeO_2H$ and $RSeO_3H$.
8. Amines (*Amine*), RNH_2, R_2NH, R_3N.
9. Hydroxylamines (*Hydroxylamine*), RNHOH.
10. Hydrazines (*Hydrazine*), $RNHNH_2$.
11. Azo compounds (*Azo-Verbindungen*), $RN{=}NH$.

Following these basic classes, there are a further 27 rare classes, which we shall not list.

The handbook begins with acyclic hydrocarbons; the very first entry is methane, CH_4. After all of the derivatives of methane have been listed, one finds ethane, followed by its derivatives, and so on, through all the hydrocarbons having the empirical formula C_nH_{2n+2}. When all alkanes and their substitution derivatives have been listed, hydrocarbons with the formula C_nH_{2n} follow, beginning with ethylene (C_2H_4), and going on up in carbon number. Next are listed hydrocarbons with the formula C_nH_{2n-2}. In this section we find alkynes and dienes; the first entry is acetylene, C_2H_2. The following group of compounds has the general formula C_nH_{2n-4}, then C_nH_{2n-6}, and so on. Thus, within a class of compounds, such as hydrocarbons, compounds are listed in order of *increasing unsaturation*. The general formula for the compounds listed on a given pair of pages is printed at the top of the left-hand page.

After all hydrocarbons and their derivatives have been listed, the hydroxy compounds are listed. In the acyclic division, the first hydroxy compound is methanol, CH_3OH, which has the empirical formula $C_nH_{2n+2}O$. Following the alcohols of this formula, one finds alcohols with the formula $C_nH_{2n}O$, and so on. When all mono alcohols have been listed, the diols are listed, beginning with the $C_nH_{2n+2}O_2$ compounds. Next come the triols, tetraols, and so on. When the alcohols have been exhausted, the aldehydes and ketones are listed, and so on down the list of classes of compounds.

Polyfunctional compounds are indexed *under the class that occurs last in the listing*. For example, hydroxycarboxylic acids are indexed under carboxylic acids, amino sulfonic acids under amines, and so on. When three or more of the basic functional groups are present, the same rule applies; a hydroxy amino acid will be found under the amines.

Following each compound in the handbook, one will find its derivatives. The derivatives are of three types, and are listed in the following order.

1. **FUNCTIONAL DERIVATIVES.** These compounds are derivatives of the basic functional group and are hydrolyzable (in principle) to the parent compound. For example, dimethyl ether and methyl nitrate are both considered as functional derivatives of methyl alcohol and are indexed after it.

$$CH_3OCH_3 \xrightarrow{H_2O} 2\,CH_3OH$$

$$CH_3ONO_2 \xrightarrow{H_2O} CH_3OH + HNO_3$$

2. **SUBSTITUTION DERIVATIVES.** These are compounds in which a C—H has been replaced by C—X, C—NO, C—NO_2, or C—N_3. They are listed in the order:

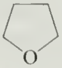
1. Halides
   (a) Fluorides; such as, CH_3F.
   (b) Chlorides; such as, CH_3Cl.
   (c) Bromides; such as, CH_3Br.
   (d) Iodides; such as, CH_3I.
2. Nitroso derivatives; such as, CH_3NO.
3. Nitro derivatives; such as, CH_3NO_2.
4. Azido derivatives; such as, CH_3N_3.

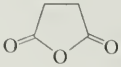
When there is more than one of the same group attached to the basic compound, the polysubstituted compounds follow the monosubstituted compound. For example, the fluorinated methanes appear in the order: CH_3F, CH_2F_2, CHF_3, CF_4. When two different substitution groups are present, the compound is listed under the group which *occurs last* in the foregoing list. Thus, fluorochloromethane, CH_2FCl, appears immediately after methyl chloride, CH_3Cl; in effect, CH_2FCl is considered as a substitution derivative of CH_3Cl. Likewise, chloronitromethane, $ClCH_2NO_2$, follows nitromethane in the listing. One must be careful not to confuse substitution derivatives with functional derivatives. For example, methyl hypochlorite, CH_3OCl, is listed with the functional derivatives of methyl alcohol because, in principle, it is hydrolyzable to methyl alcohol.

$$CH_3OCl \xrightarrow{H_2O} CH_3OH + HOCl$$

3. **SULFUR AND SELENIUM COMPOUNDS.** These compounds are listed as replacement derivatives under the corresponding oxygen compound. For example, methyl mercaptan, CH_3SH, and dimethyl selenide, $(CH_3)_2Se$, are listed last under the derivatives of methyl alcohol. Similarly, dithioacetic acid, CH_3CS_2H, is found among the final listings that follow acetic acid.

A similar organization is followed with the carbocyclic compounds. For heterocyclic compounds, the same scheme is used, but there is an additional division into *hetero numbers*. Most practicing chemists do not use the hetero numbers, but rely on the subject or formula index to locate the parent heterocycle in the handbook. One must remember that many familiar compounds not normally thought of as heterocyclic compounds, indeed are. For example, succinic anhydride will be found in the third division, as a dicarbonyl derivative of the heterocycle tetrahydrofuran.


tetrahydrofuran


succinic anhydride

APPENDIX I

Heats of Formation

ΔH_f° *(gas, 25° C), kcal mole*$^{-1}$

Alkanes

methane	—17.9	2,2-dimethylpropane	—40.3
ethane	—20.2	hexane	—39.9
propane	—24.8	2-methylpentane	—41.8
butane	—30.4	3-methylpentane	—41.1
2-methylpropane	—32.4	2,2-dimethylbutane	—44.5
pentane	—35.1	2,3-dimethylbutane	—42.6
2-methylbutane	—36.9		

Cycloalkanes

cyclopropane	12.7	methylcyclopentane	—25.3
cyclobutane	6.8	methylcyclohexane	—37.0
cyclopentane	—18.4	ethylcyclohexane	—41.0
cyclohexane	—29.5	1,1-dimethylcyclohexane	—43.2
cycloheptane	—28.2	*cis*-1,2-dimethylcyclohexane	—41.1
cyclooctane	—29.7	*trans*-1,2-dimethylcyclohexane	—43.0
cyclononane	—31.7	*cis*-1,3-dimethylcyclohexane	—44.1
cyclodecane	—36.9	*trans*-1,3-dimethylcyclohexane	—42.2
		cis-1,4-dimethylcyclohexane	—42.2
		trans-1,4-dimethylcyclohexane	—44.1

Alkenes

ethylene	12.5	2-methyl-1-butene	— 8.6
propylene	4.9	2-methyl-2-butene	—10.1
1-butene	— 0.2	cyclobutene	37.5
cis-2-butene	— 1.9	cyclopentene	8.2
trans-2-butene	— 3.0	cyclohexene	— 1.1
2-methylpropene	— 4.3	1-methylcyclohexene	—10.3
1-pentene	— 5.3	cycloheptene	— 2.2
cis-2-pentene	— 7.0	cyclooctene	— 6.5
trans-2-pentene	— 7.9		

Alkynes and Polyenes

acetylene	54.3	*cis*-1,3-pentadiene	19.1
propyne	44.4	*trans*-1,3-pentadiene	18.1
1-butyne	39.5	1,4-pentadiene	25.3
2-butyne	34.7	2-methyl-1,3-butadiene	18.1
allene	45.6	cyclopentadiene	31.9
1,2-butadiene	38.8	1,3-cyclohexadiene	25.4
1,3-butadiene	26.1	1,3,5,7-cyclooctatetraene	71.1
1,2-pentadiene	33.6		

Aromatic Hydrocarbons

benzene	19.8	styrene	35.3
toluene	12.0	naphthalene	36.1
o-xylene	4.6	1,2,3,4-tetrahydronaphthalene	7.3
m-xylene	4.1	anthracene	55.2

p-xylene	4.3	9,10-dihydroanthracene	38.2
ethylbenzene	7.1	phenanthrene	49.5

Alcohols

methanol	—48.1	*t*-butyl alcohol	—74.7
ethanol	—56.2	cyclopentanol	—58.0
allyl alcohol	—29.6	cyclohexanol	—68.4
1-propanol	—61.2	benzyl alcohol	—24.0
2-propanol	—65.1	ethylene glycol	—93.9

Ethers

dimethyl ether	—44.0	1,1-dimethoxyethane	— 93.3
ethylene oxide	—12.6	2,2-dimethoxypropane	—101.9
tetrahydrofuran	—44.0	anisole	— 17.3
diethyl ether	—60.3		

Aldehydes and Ketones

formaldehyde	—26.0	butanal	—49.0
acetaldehyde	—39.7	cyclopentanone	—46.0
propionaldehyde	—45.5	cyclohexanone	—54.0
acetone	—51.9	benzaldehyde	— 8.8
2-butenal	—24.0		

Other Oxygen Compounds

formic acid	— 90.6	benzoic acid	— 70.1
acetic acid	—103.3	acetic anhydride	—137.1
vinyl acetate	— 75.5	furan	— 8.3
ethyl acetate	—106.3	phenol	— 23.0

Nitrogen Compounds

methylamine	— 5.5	pyridine	34.6
dimethylamine	— 4.7	piperidine	—11.8
trimethylamine	— 5.7	aniline	20.8
ethylamine	—11.4	benzonitrile	51.5
acrylonitrile	44.1	dimethylformamide	—45.8
acetonitrile	21.0	acetanilide	—30.8
propionitrile	12.1	methyl nitrite	—15.8
pyrrole	25.9	nitromethane	—17.9
pyrrolidine	— 0.8	glycine	—93.7

Halogen Compounds

methyl chloride	—20.6	bromobenzene	25.2
methylene chloride	—23.0	chlorobenzene	12.2
chloroform	—24.6	acetyl chloride	—58.4
carbon tetrachloride	—25.2	methyl bromide	— 9.1
vinyl chloride	8.6	methyl iodide	3.4
ethyl chloride	—26.1	ethyl bromide	—15.2
n-propyl chloride	—31.0	benzyl chloride	4.5
isopropyl chloride	—33.6		

Inorganic Compounds

CO_2	—94.05	NH_3	—10.9
H_2O	—57.80	CO	—26.42

HCl	-22.1	NO_2	7.9
Br_2	7.4	HF	-65.0
HBr	-8.7	HNO_3	-32.1
I_2	14.9	HNO_2	-18.4
HI	6.3	H_2O_2	-32.53
		NO	21.6

Atoms and Radicals

H	52.1	$CH_3\cdot$	34
Li	38.4	$C_2H_5\cdot$	26
C	170.9	$(CH_3)_2CH\cdot$	18
N	113.0	$(CH_3)_3C\cdot$	7
O	59.6	$CH_2{=}CH\cdot$	68
F	18.9	$CH_2{=}CHCH_2\cdot$	40
Cl	28.9	$C_6H_5CH_2\cdot$	45
Br	26.7	$C_6H_5\cdot$	80
I	25.5	$CH_3CO\cdot$	-5
		$CH_3CO_2\cdot$	-50
		$CH_3O\cdot$	4
		$C_2H_5O\cdot$	-5

APPENDIX II

Bond Dissociation Energies

DH°, kcal mole^{-1} for A—B bonds

A	(52.1) B: H	(18.9) F	(29.0) Cl	(26.7) Br	(25.5) I	(9.3) OH	(40.1) NH_2	(34) CH_3	(26) C_2H_5	(18) i-C_3H_7	(7) t-C_4H_9	(80) C_6H_5	(109) CN
(34) CH_3	104	109	84	70	56	91	80	88	85	84	81	102	122
(26) C_2H_5	98	107	81	68	53	91	77	85	82	80	77	99	123
(21) n-C_3H_7	98	107	81	68	53	91	78	85	82	80	77	99	122
(18) i-C_3H_7	95	106	80	68	53	92	78	84	80	78	73	97	121
(7) t-C_4H_9	91	108	79	65	50	91	76	81	77	73	68	92	
(80) C_6H_5	112	127	97	82	66	112	99	102	99	97	92	117	137
(45) $C_6H_5CH_2$	85		70	55	45	78		72	69	68		88	
(40) allyl	87		69	55	42	79		74	71	70	66		
(−5) CH_3CO	87	120	82	67	50	108		81	77	75	71	95	
(−5) C_2H_5O	103					43		81	81			101	
(68) $CH_2{=}CH$	108		88	76				97	94	93	86	113	133
(52.1) H	104.2	135.8	103.2	87.5	71.3	119.2	103.2	104.0	98	95	91	112	130

Numbers in parentheses are the heats of formation, ΔH_f°, for the corresponding atom or radical.

APPENDIX III

Average Bond Energies

Average Bond Energies, kcal mole^{-1}

H	C	N	O	F	Si	S	Cl	Br	I	
104	99	93	111	135	76	83	103	87	71	H
	83[a]	73[b]	86[c]	116[d]	72	65	81	68	52	C
		39	53[e]	65			46			N
			47	45	108		52	48	56	O
				37	135					F
					53		91	74	56	Si
						60	61	52		S
							58			Cl
								46		Br
									36	I

[a] C=C 146, C≡C 200

[b] C=N 147, C≡N 213

[c] C=O 176 (aldehydes), 179 (ketones)

[d] In CF_4

[e] In nitrites and nitrates

APPENDIX IV
Acidity and Basicity

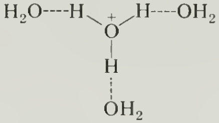
One definition of acidity is based on the tendency to lose a proton. Such reactions can be measured for the gas phase but are invariably highly *endothermic*. For example,

$$HCl(g) \rightleftharpoons H^+(g) + Cl^-(g) \qquad \Delta H^\circ = 328.8 \text{ kcal mole}^{-1}$$

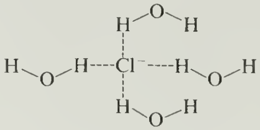
This reaction is highly endothermic because a bond is broken and charges are separated; both of these processes require energy. In aqueous solution, acidity is defined in terms of a dissociation equilibrium as in the example,

$$HCl(aq) \rightleftharpoons H^+(aq) + Cl^-(aq)$$

In this case, the H^+ is bound to water as H_3O^+, which is further solvated by hydrogen bonds to the oxygens of other water molecules.



Similarly, the Cl^- ion is solvated by hydrogen bonds to water molecules.



These **solvation** bonds are sufficiently strong in the aggregate to compensate for the H—Cl bond strength and the electrostatic energy required to separate negative from positive charges.

The equilibrium can also be described as a proton transfer from an acid to a base.

$$\underset{\text{acid}}{HCl} + \underset{\text{base}}{H_2O} \rightleftharpoons \underset{\text{acid}}{H_3O^+} + \underset{\text{base}}{Cl^-}$$

The equilibrium constant for aqueous HCl is large, about 10^7, and the equilibrium position lies far to the right. We speak of HCl as a strong acid and Cl^- as a weak base; more properly we should speak of HCl as a strong acid relative to H_3O^+, and Cl^- as a weak base relative to H_2O.

In general, the acidity of an acid HA in water is defined as the equilibrium constant for

$$HA(aq) \overset{K}{\rightleftharpoons} H^+(aq) + A^-(aq)$$

$$K = \frac{[H^+][A^-]}{[HA]}$$

Note that K normally has units of M or mole liter^{-1}.

Acidity equilibrium constants vary over a wide range. Acids with $K > 1$ are referred to as strong acids; acids with $K < 10^{-4}$ are weak acids, and many compounds are very weak acids for which K is exceedingly small. Methane, for example, is a very weak acid,

$K \simeq 10^{-49}$. This number is so small (it corresponds to approximately one pair of dissociated ions per universe of solution) that it is known only approximately and must be measured indirectly.

Acidity equilibrium constants are usually expressed as an exponent of 10 in order to accommodate this large range of possible values. The pK is defined as the negative exponent of ten, or as

$$\mathrm{p}K = -\log K$$

The pK of HCl is about -7 and that of methane is approximately 49. The smaller or more negative the pK, the stronger the acid.

pK values of some common inorganic acids are summarized in the table that follows. The strong acids HI, HBr, HCl, H_2SO_4, $HClO_4$, and HNO_3 are usually referred to as "mineral acids." The table gives second and third dissociation constants where appropriate; thus, HSO_4^- with pK = 1.99 is about as acidic as the first dissociation of H_3PO_4, pK = 2.15. The acidity of $H_2PO_4^-$, pK = 7.20, is comparable to H_2S, pK = 6.95. Both have pKs that are comparable to the pH of neutral water, 7. The significance of this point is apparent from the following analysis. When an acid is exactly 50% dissociated, the remaining acid concentration, [HA], is equal to the concentration of the conjugate anion, [A^-]. For such a case, the hydrogen ion concentration of the solution is numerically equal to the acidity constant, or pH = pK.

$$K = \frac{\cancel{[A^-]}[H^+]}{\cancel{[HA]}}$$

$$\mathrm{p}K = -\log K = -\log\,[H^+] = \mathrm{pH}$$

For aqueous solutions, pK values in the range of about 2-12 are known fairly accurately. The acidity constants of stronger acids (p$K < 2$) are known with less precision because such acids are extensively dissociated in aqueous solution. Sulfuric acid is an important special case. Its acidity in water corresponds to $K_1 \simeq 1.4 \times 10^5\,M$, but in concentrated solutions the effective acidity or protonating power increases markedly. Ordinary concentrated sulfuric acid is about 98% H_2SO_4 and has an "effective pH" or "acidity function" of 10. The protonating power is increased further by addition of SO_3. The basicities of many of the weak organic bases (strong acids) given in the table were measured in sulfuric acid solutions.

Finally, note that the K defined above is often expressed as K_a, a more specific symbol for the acid dissociation constant. In general, pK refers to pK_a.

Acidities of Inorganic Acids at 25°

Name	Formula	pK_a
ammonium ion	NH_4^+	9.24
boric acid	H_3BO_3	9.24
carbon dioxide	CO_2	6.35[a]
cyanic acid	HOCN	3.46
hydrazinium ion	$H_2NNH_3^+$	7.94
hydrazoic acid	HN_3	4.68
hydriodic acid	HI	$\simeq -9.5$
hydrobromic acid	HBr	$\simeq -9$
hydrochloric acid	HCl	-7
hydrocyanic acid	HCN	9.22
hydrofluoric acid	HF	3.18

Acidities of Inorganic Acids at 25°

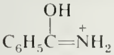
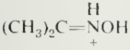
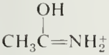
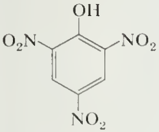
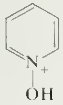
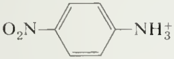
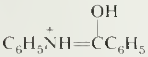
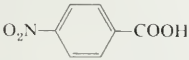
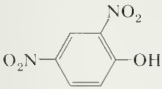
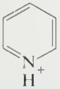
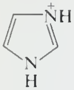
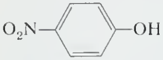
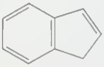
Name	Formula	pK_a
hydrogen peroxide	H_2O_2	11.65
hydrogen selenide	H_2Se	3.71
hydrogen sulfide	H_2S	6.97
hydroxylammonium ion	$H_3\overset{+}{N}OH$	5.95
hypobromous acid	$HOBr$	8.6
hypochlorous acid	$HOCl$	7.53
hypophosphorus acid	H_3PO_2	1.2
nitric acid	$HONO_2$	1.3
nitrous acid	$HONO$	3.23
phosphonium ion	PH_4^+	≈ -14
phosphoric acid	$(HO)_3PO$	2.15 (7.20, 12.38)[b]
sulfuric acid	$(HO)_2SO_2$	≈ -5.2 (1.99)[b]
sulfurous acid	$(HO)_2SO$	1.8 (7.2)[b]
thiocyanic acid	$HCNS$	−1.9

[a] For the equilibrium $CO_2(aq) = H^+(aq) + HCO_3^-(aq)$.
[b] Second and third acidity constants in parentheses.

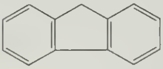
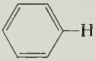
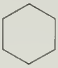
Acidities of Organic Acids at 25°

Acid	pK_a	Acid	pK_a
$CH_3\underset{+}{\overset{O}{\overset{\Vert}{N}}}OH$	−11.9	$CH_3\overset{OC_2H_5}{\overset{\vert}{C}}=\underset{+}{O}H$	−6.5
$C_6H_5\underset{+}{\overset{O}{\overset{\Vert}{N}}}OH$	−11.3	$C_6H_5N=\underset{+}{\overset{OH}{\overset{\vert}{N}}}C_6H_5$	−6.45
$C_6H_5C\equiv\overset{+}{N}H$	−10.5	$C_6H_5\overset{^{+}OH}{\overset{\Vert}{C}}CH_3$	−6.2
$CH_3C\equiv\overset{+}{N}H$	−10.1	$CH_3\overset{^{+}OH}{\overset{\Vert}{C}}OH$	−6.1
$CH_3\overset{H}{\overset{\vert}{C}}=\overset{+}{O}H$	≈ -8	$(CH_3)_2\overset{+}{S}H$	−5.4
$C_6H_5\overset{OH}{\overset{\vert}{C}}=\underset{+}{O}H$	−7.3	$(CH_3)_3C\overset{+}{O}H_2$	−3.8
$(CH_3)_2C=\overset{+}{O}H$	−7.2	$(CH_3CH_2)_2\overset{+}{O}H$	−3.6
$C_6H_5\overset{H}{\overset{\vert}{C}}=\overset{+}{O}H$	−7.1	$(CH_3)_2CHOH_2^+$	−3.2
$CH_3\overset{+}{S}H_2$	−6.8	$C_6H_5N=\underset{+}{\overset{H}{N}}C_6H_5$	−2.9
$C_6H_5\overset{+}{O}H_2$	−6.7	$C_2H_5OH_2^+$	−2.4
$C_6H_5\underset{+}{\overset{H}{O}}CH_3$	≈ -6.5	$CH_3OH_2^+$	−2.2

Acidities of Organic Acids at 25° (continued)

Acid	pK_a
 $C_6H_5\overset{OH}{\overset{\vert}{C}}=\overset{+}{N}H_2$	−2.0
 $(CH_3)_2C=\overset{H}{\underset{+}{N}}OH$	−1.9
CH_3SO_3H	≈ −1.2
 $CH_3\overset{OH}{\overset{\vert}{C}}=NH_2^+$	≈0
$CH_3(CH_2)_3PH_3^+$	0
$(CH_3)_2\overset{+}{S}OH$	0
CF_3COOH	0.2
	0.25
	0.79
$(C_6H_5)_2NH_2^+$	0.8
	1.00
 $C_6H_5\overset{+}{N}H=\overset{OH}{\overset{\vert}{C}}C_6H_5$	2.17
	3.42
$CH_2(NO_2)_2$	3.57
	4.09
$C_6H_5NH_3^+$	4.60
$(CH_3)_3\overset{+}{N}OH$	4.7
CH_3COOH	4.74
	5.29
$(CH_3CO)_3CH$	5.85
	7.0
	7.15
C_6H_5SH	7.8
$(CH_3CO)_2CH_2$	9
$(CH_3)_3NH^+$	9.79
C_6H_5OH	10.00
CH_3NO_2	10.21
CH_3CH_2SH	10.60
$CH_3NH_3^+$	10.62
$(CH_3)_2NH_2^+$	10.73
$CH_3COCH_2COOC_2H_5$	11
$CH_2(CN)_2$	11.2
CF_3CH_2OH	12.4
$CH_2(COOC_2H_5)_2$	13.3
$(CH_3SO_2)_2CH_2$	14
CH_3OH	15.5
C_2H_5OH	15.9
	16
$(CH_3)_3COH$	18
CH_3COCH_3	20
	20

Acidities of Organic Acids at 25° (continued)

Acid	pK_a	Acid	pK_a
	23	$C_6H_5CH_3$	41
$CH_3SO_2CH_3$	23		43
$CH_3COOC_2H_5$	24.5	$CH_2{=}CH_2$	44
$HC{\equiv}CH$	≈25		46
CH_3CN	≈25	CH_4	≈49
$(C_6H_5)_3CH$	31.5	C_2H_6	≈50
$(C_6H_5)_2CH_2$	34		≈52
$C_2H_5NH_2$	~35		

Appendix V
Proton Chemical Shifts

Proton Chemical Shifts, δ, ppm, for C—H

Y	$\mathrm{CH_3Y}$	$\mathrm{CH_3{-}C{-}Y}$	$\mathrm{CH_3{-}C{-}C{-}Y}$	$\mathrm{R{-}CH_2{-}Y}$	$\mathrm{RCH_2{-}C{-}Y}$	$\mathrm{R_2CH{-}Y}$
H	0.23	0.9	0.9	0.9	1.3	1.3
$\mathrm{CH{=}CH_2}$	1.71	1.0		2.0		1.7
$\mathrm{C{\equiv}CH}$	1.80	1.2	1.0	2.1	1.5	2.6
$\mathrm{C_6H_5}$	2.35	1.3	1.0	2.6	1.7	2.9
F	4.27	1.2		4.4		
Cl	3.06	1.5	1.1	3.5	1.8	4.1
Br	2.69	1.7	1.1	3.4	1.9	4.2
I	2.16	1.9	1.0	3.2	1.9	4.2
OH	3.39	1.2	0.9	3.5	1.5	3.9
OR	3.24	1.2	1.1	3.3	1.6	3.6
OAc	3.67	1.3	1.1	4.0	1.6	4.9
CHO	2.18	1.1	1.0	2.4	1.7	2.4
$\mathrm{COCH_3}$	2.09	1.1	0.9	2.4	1.6	2.5
COOH	2.08	1.2	1.0	2.3	1.7	2.6
$\mathrm{NH_2}$	2.47	1.1	0.9	2.7	1.4	3.1
$\mathrm{NHCOCH_3}$	2.71	1.1	1.0	3.2	1.6	4.0
SH	2.00	1.3	1.0	2.5	1.6	3.2
CN	1.98	1.4	1.1	2.3	1.7	2.7
$\mathrm{NO_2}$	4.29	1.6	1.0	4.3	2.0	4.4

Proton Chemical Shifts for Y—H

Group Type	δ, ppm
ROH	0.5–5.5
ArOH	4–8
RCOOH	10–13
$\mathrm{R_2C{=}NOH}$	7.4–10.2
RSH	0.9–2.5
ArSH	3–4
$\mathrm{RSO_3H}$	11–12
$\mathrm{RNH_2}$, $\mathrm{R_2NH}$	0.4–3.5
$\mathrm{ArNH_2}$, ArRNH	2.9–4.8
$\mathrm{RCONH_2}$	5.0–6.5
RCONHR	6.0–8.2
RCONHAr	7.8–9.4

APPENDIX VI

Infrared Bands

TABLE A
Characteristic Stretching Frequencies

Bond	$\tilde{\nu}$, cm^{-1}
1. C—H	
(a) C_{sp^3}-H	2800–3000
(b) C_{sp^2}-H	3000–3100
(c) C_{sp}-H	3300
2. C—C	
(c) C—C	1150–1250
(b) C=C	1600–1670
(c) C≡C	2100–2260
3. C—N	
(a) C—N	1030–1230
(b) C=N	1640–1690
(c) C≡N	2210–2260
4. C—O	
(a) C—O	1020–1275
(b) C=O	1650–1800 (see also **Table C**)
5. C—X	
(a) C—F	1000–1350
(b) C—Cl	800–850
(c) C—Br	500–680
(d) C—I	200–500
6. N—H	
(a) RNH_2, R_2NH	3400–3500 (two)
(b) $R\overset{+}{N}H_3$, $R_2\overset{+}{N}H_2$, $R_3\overset{+}{N}H$	2250–3000
(c) $RCONH_2$, $RCONHR'$	3400–3500
7. O—H	
(a) ROH	3610–3640 (free)
	3200–3400 (H-bonded)
(b) RCO_2H	2500–3000
8. N—O	
(a) RNO_2	1350, 1560
(b) $RONO_2$	1620–1640, 1270–1285
(c) RN=O	1500–1600
(d) RO—N=O	1610–1680 (two), 750–815
(e) C=N—OH	930–960
(f) $R_3\overset{+}{N}—O^-$	950–970

Table A (continued)

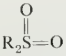
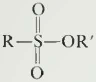
Bond	$\tilde{\nu}$, cm^{-1}
9. S—O	
(a) $R_2\overset{+}{S}-O^-$	1040–1060
(b)  $R_2\overset{\overset{\displaystyle O}{\Vert}}{S}=O$	1310–1350, 1120–1160
(c)  $R-\underset{\underset{\displaystyle O}{\Vert}}{\overset{\overset{\displaystyle O}{\Vert}}{S}}-OR'$	1330–1420, 1145–1200
10. Cumulated systems	
(a) $C=C=C$	1950
(b) $C=C=O$	2150
(c) $R_2C=\overset{+}{N}=N^-$	2090–3100
(d) $RN=C=O$	2250–2275
(e) $RN=\overset{+}{N}=N^-$	2120–2160

Table B
Useful C—H Out-of-Plane Bending Vibrations

Bond	$\tilde{\nu}$, cm^{-1}
1. Alkynes, $C\equiv C-H$	600–700
2. Alkenes	
(a) $RCH=CH$	910, 990
(b) $R_2C=CH_2$	890
(c) *trans*-$RCH=CHR$	970
(d) *cis*-$RCH=CHR$	725–675
(e) $R_2C=CHR$	790–840
3. Aromatic	
(a) mono-	730–770, 690–710 (two)
(b) *o*-	735–770
(c) *m*-	750–810, 690–710 (two)
(d) *p*-	810–840
(e) 1,2,3-	760–780, 705–745 (two)
(f) 1,3,5-	810–865, 675–730 (two)
(g) 1,2,4-	805–825, 870,885 (two)
(h) 1,2,3,4-	800–810
(i) 1,2,4,5-	855–870
(j) 1,2,3,5	840–850
(k) penta-	870

TABLE C
Summary of Carbonyl Stretching Frequencies

Compound Type	$\tilde{\nu}$, cm^{-1}
1. Aldehydes	
(a) RCHO	1725
(b) $C{=}CCHO$	1685
(c) ArCHO	1700
2. Ketones	
(a) $R_2C{=}O$	1715
(b) $C{=}C{-}C{=}O$	1675
(c) $Ar{-}C{=}O$	1690
(d) four-membered cyclic	1780
(e) five-membered cyclic	1745
(f) six-membered cyclic	1715
3. Carboxylic acids	
(a) RCOOH	1760 (monomer)
	1710 (dimer)
(b) $C{=}C{-}COOH$	1720 (monomer)
	1690 (dimer)
(c) RCO_2^-	1550–1610, 1400 (two)
4. Esters	
(a) RCOOR	1735
(b) $C{=}C{-}COOR$	1720
(c) ArCOOR	1720
(d) γ-Lactone	1770
(e) δ-Lactone	1735
5. Amides	
(a) $RCONH_2$	1690 (free)
	1650 (associated)
(b) RCONHR′	1680 (free)
	1655 (associated)
(c) $RCONR'_2$	1650
(d) β-lactam	1745
(e) γ-lactam	1700
(f) δ-lactam	1640
6. Acid anhydrides	1820, 1760 (two)
7. Acyl halides	1800

APPENDIX VII

Symbols and Abbreviations

Å	Angstroms (10^{-8} cm)
Ac	acetyl group, CH_3CO—
Ar	aryl radical
$[\alpha]$	specific optical activity
aq	aqueous
boc	*t*-butoxycarbonyl group, $(CH_3)_3COCO$—
n-Bu	*n*-butyl group, $CH_3CH_2CH_2CH_2$—
t-Bu	*t*-butyl group, $(CH_3)_3C$—
cmr	^{13}C magnetic resonance
cbz	benzyloxycarbonyl group, $C_6H_5CH_2OCO$—
D	Debye (10^{-18} esu-cm); measure of dipole moment
DCC	dicyclohexylcarbodiimide, $C_6H_{11}N{=}C{=}NC_6H_{11}$
δ	delta, chemical shift downfield from TMS, given as ppm
Δ	Delta; symbol for heat supplied to a reaction
ΔG°	standard Gibb's free energy of reaction
$\Delta G^\ddagger$	Gibb's free energy of activation
ΔH°	standard enthalpy of reaction
ΔH_f°	enthalpy of formation from standard states
$\Delta H^\ddagger$	enthalpy of activation
ΔS°	standard entropy of reaction
$\Delta S^\ddagger$	entropy of activation
DH°	bond dissociation energy
DIBAL	diisobutylaluminum hydride, $[(CH_3)_2CHCH_2]_2AlH$
diglyme	bis-(2-methoxyethyl) ether, $(CH_3OCH_2CH_2)_2O$
DMF	dimethylformamide, $(CH_3)_2NCHO$
DMSO	dimethyl sulfoxide, $(CH_3)_2SO$
DNP	2,4-dinitrophenyl group, 2,4-$(O_2N)_2C_6H_3$— or 2,4-dinitrophenylhydrazone, 2,4-$(O_2N)C_6H_3NHN$=
E	*entgegen*, opposite sides in (E,Z) nomenclature of alkenes
E1	unimolecular elimination reaction mechanism
E2	bimolecular elimination reaction mechanism
EA	electron affinity
Et	ethyl group, CH_3CH_2—
eu	entropy units, cal deg^{-1} mole^{-1}
f_i	partial rate factor at position i
glyme	1,2-dimethoxyethane, $CH_3OCH_2CH_2OCH_3$
H	magnetic field
HMPT	hexamethylphosphoric triamide, $[(CH_3)_2N]_3PO$
$h\nu$	symbol for light
Hz	Hertz (sec^{-1} or cycles per second)
IP	ionization potential
ir	infrared
J	coupling constant, usually in Hz
k	rate constant for reaction
K	equilibrium constant for reaction
K_a	acid dissociation constant
LDA	lithium diisopropylamide, $LiN[CH(CH_3)_2]_2$
Me	methyl group, CH_3—
m/e	mass-to-charge ratio in mass spectroscopy

MHz	megaHertz ≡ 10^6 Hz
μ	dipole moment
nmr	nuclear magnetic resonance
NR	no reaction
Ph	phenyl radical, C_6H_5—
pH	measure of acidity ≡ —log $[H^+]$
pK_a	measure of acid strength ≡ —log K_a
pmr	proton magnetic resonance
PPA	polyphosphoric acid
ψ	Greek *psi;* wave function or orbital
R	alkyl or cycloalkyl group
(R,S)	designation of stereochemical configuration
S_N1	unimolecular nucleophilic substitution mechanism
S_N2	bimolecular nucleophilic substitution mechanism
τ	Greek *tau;* chemical shift ≡ 10 − δ ppm
THF	tetrahydrofuran, $\overline{CH_2CH_2CH_2CH_2O}$
TMS	tetramethylsilane, $(CH_3)_4Si$
Ts	tosyl or *p*-toluenesulfonyl group, *p*-$CH_3C_6H_5SO_2$—
uv	ultraviolet
X	halogen group
xs	excess
Z	*zusammen,* same side in (E,Z) nomenclature of alkenes
↷	symbol for flow of electron pair

APPENDIX VIII
Summary of Functional Group Preparations

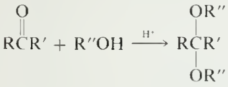
Functional group interconversions can be discussed as reactions of one function or preparations of another. The following summary lists the preparations of various functional groups discussed in this textbook with reference to each place the reaction is used. Products shown are those for normal work-up of the reaction. Although examples are included with more than one functional group, specific reactions of polyfunctional compounds are not included. Abbreviations used are

R = alkyl and cycloalkyl; for some cases may also apply to R = H, R = Ar
Ar = aryl
X = halide
Y = leaving group; may be X, sulfonate, and so on
[H] = several reducing agents
[O] = several oxidizing agents

The importance of a given type of reaction or functional group transformation can be gauged roughly from the number of times it is cited.

Acetals and Ketals

Aldehydes or ketones



$R\overset{\overset{O}{\|}}{C}R' + R''OH \xrightarrow{H^+} R\overset{\overset{OR''}{|}}{\underset{\underset{OR''}{|}}{C}}R'$

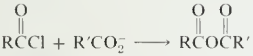
372–376, 526, 673, 680, 700, 701, 705–707, 939

Ethyl orthoformate

$ArMgX + CH(OEt)_3 \longrightarrow ArCH(OEt)_2$ 938

Acid Anhydrides

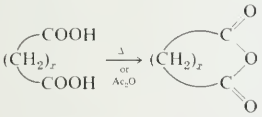
Acyl Halides



$R\overset{\overset{O}{\|}}{C}Cl + R'CO_2^- \longrightarrow R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R'$

462, 485

Carboxylic acids



$x = 2$ or 3

462, 739, 740, 944

Acyl Halides

Arenes

$ArH + COCl_2 \xrightarrow{\text{Lewis acid}} ArCOCl$ 973

Carboxylic acids

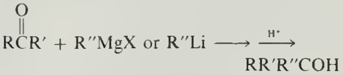
$RCOOH + SOCl_2 \longrightarrow RCOCl$ 444, 445, 461, 480, 484, 835

$RCOOH + PCl_5 \longrightarrow RCOCl$ 444, 461, 480

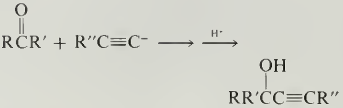
$RCOOH + PBr_3 \longrightarrow RCOBr$ 444, 461, 470, 562

Alcohols

Aldehydes and ketones: Carbanion additions

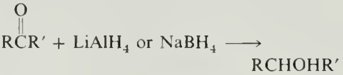


$R\overset{O}{\overset{\|}{C}}R' + R''MgX \text{ or } R''Li \longrightarrow \xrightarrow{H^+} RR'R''COH$ 381–383, 524, 556, 557, 680, 898, 899, 915, 1045, 1171

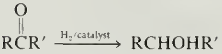


$R\overset{O}{\overset{\|}{C}}R' + R''C{\equiv}C^- \longrightarrow \xrightarrow{H^+} RR'\overset{OH}{\overset{|}{C}}C{\equiv}CR''$ 383, 516, 517, 546, 653

Aldehydes and ketones: Reductions



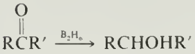
$R\overset{O}{\overset{\|}{C}}R' + LiAlH_4 \text{ or } NaBH_4 \longrightarrow RCHOHR'$ 394, 395, 490, 558, 636, 664, 670, 680, 696, 708, 709, 1055



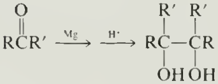
$R\overset{O}{\overset{\|}{C}}R' \xrightarrow{H_2/\text{catalyst}} RCHOHR'$ 395, 396, 680, 709

$RCHO \xrightarrow{OH^-} RCOOH + RCH_2OH$ 396, 397
(Cannizzaro reaction)

$RCHO + H_2C{=}O \xrightarrow{OH^-} RCH_2OH$ 397
(crossed Cannizzaro)



$R\overset{O}{\overset{\|}{C}}R' \xrightarrow{B_2H_6} RCHOHR'$ 441

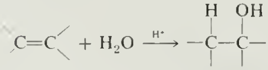


$R\overset{O}{\overset{\|}{C}}R' \xrightarrow{Mg} \xrightarrow{H^+} R\underset{OH}{\overset{R'}{C}}{-}\underset{OH}{\overset{R'}{C}}R$ 670, 674

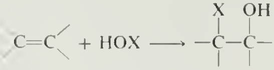
Alkanes

$RH + O_2 \xrightarrow{\text{catalyst}} ROOH \xrightarrow{H_2/\text{cat}} ROH$ 223

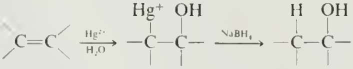
Alkenes



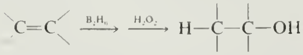
$>C{=}C< + H_2O \xrightarrow{H^+} -\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{OH}{\overset{|}{\underset{|}{C}}}-$ 279



$>C{=}C< + HOX \longrightarrow -\overset{X}{\overset{|}{\underset{|}{C}}}-\overset{OH}{\overset{|}{\underset{|}{C}}}-$ 282

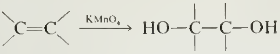
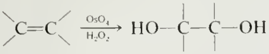
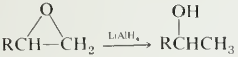
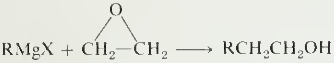
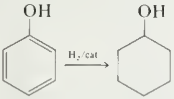


$>C{=}C< \xrightarrow[H_2O]{Hg^{2+}} -\overset{Hg^+}{\overset{|}{\underset{|}{C}}}-\overset{OH}{\overset{|}{\underset{|}{C}}}- \xrightarrow{NaBH_4} -\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{OH}{\overset{|}{\underset{|}{C}}}-$ 283



$>C{=}C< \xrightarrow{B_2H_6} \xrightarrow{H_2O_2} H-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OH$ 287–289, 519

$RCH{=}CHR \xrightarrow{O_3} \xrightarrow{NaBH_4} RCH_2OH$ 292

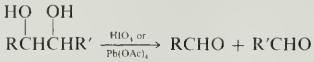
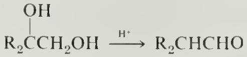
	289, 667–669
	290, 519, 668, 669, 671
Carboxylic acids	
RCOOH $\xrightarrow{LiAlH_4}$ RCH_2OH	440
RCOOH $\xrightarrow{B_2H_6}$ RCH_2OH	440, 441
Esters	
R′COOR $\xrightarrow[H_2O]{H^+ \text{ or } OH^-}$ R′COOH + ROH	48, 49, 222, 474, 475, 507, 518, 634, 685, 949
R′COOR $\xrightarrow[\text{or } LiBH_4]{LiAlH_4}$ $R'CH_2OH$ + ROH	395, 491, 670, 915
R′COOR $\xrightarrow{B_2H_6}$ $R'CH_2OH$ + ROH	441
RCOOEt + R′MgX or R′Li $\longrightarrow$ $\xrightarrow{H^+}$ RR'_2COH	487, 488, 524, 915, 917
RMgX + $(EtO)_2C{=}O$ $\longrightarrow$ R_3COH	488
R′COOR $\xrightarrow[\text{or } H_2 \text{ cat}]{\text{Na EtOH}}$ $R'CH_2OH$ + ROH	491
Halides and sulfonates	
RY $\xrightarrow{H_2O \text{ or } OH^-}$ ROH	42–47, 127, 132, 151, 221, 222, 518, 529, 530, 682
RX $\xrightarrow[\text{ether}]{Mg}$ $\xrightarrow{O_2}$ $\xrightarrow{H^+}$ ROH	222
Oxiranes	
	652
	652
Peroxides	
ROOR′ $\xrightarrow{H_2 \text{ cat}}$ ROH + R′OH	223
Phenols	
	623, 1169

Aldehydes

Acetals	
$RCH(OR')_2$ $\xrightarrow{H^+}$ RCHO + R′OH	702, 704, 705, 938
Acid derivatives	
RCOCl $\xrightarrow[Li(t\text{-}BuO)_3AlH]{H_2 \text{ cat, or}}$ RCHO	359, 489, 490, 935
$RCONR'_2$ $\xrightarrow{LiAlH(OEt)_3}$ RCHO	493

$\text{RCN} \xrightarrow{\text{DIBAL}} \text{RCHO}$	493, 935
$\text{ArCN} \xrightarrow{\text{SnCl}_2,\ \text{HCl}} \text{ArCHO}$ (Stephen reduction)	937
$\text{ArMgX} + \text{CH(OEt)}_3 \longrightarrow \text{ArCHO}$	938

Alcohols

$\text{RCH}_2\text{OH} \xrightarrow{[\text{O}]} \text{RCHO}$	232–234, 357, 358, 554, 555
 $\text{R}\overset{\text{HO}}{\overset{\vert}{\text{C}}}\text{H}\overset{\text{OH}}{\overset{\vert}{\text{C}}}\text{HR}' \xrightarrow[\text{Pb(OAc)}_4]{\text{HIO}_4\text{ or}} \text{RCHO} + \text{R}'\text{CHO}$	671, 672, 712–714
 $\text{R}_2\overset{\text{OH}}{\overset{\vert}{\text{C}}}\text{CH}_2\text{OH} \xrightarrow{\text{H}^+} \text{R}_2\text{CHCHO}$	674

Alkenes

$\text{RCH=CHR} \xrightarrow{\text{O}_3} \xrightarrow[(\text{CH}_3)_2\text{S}]{\text{Zn AcOH or}} \text{RCHO}$	291, 358

Alkynes

$\text{RC}\equiv\text{CH} \xrightarrow{\text{B}_2\text{H}_6} \xrightarrow[\text{OH}^-]{\text{H}_2\text{O}_2} \text{RCH}_2\text{CHO}$	317, 359, 521

Arenes

$\text{ArH} + \text{CO} + \text{HCl} \xrightarrow{\text{AlCl}_3} \text{ArCHO}$	590, 935
$\text{ArH} + \text{HCON(CH}_3)_2 \xrightarrow{\text{POCl}_3} \text{ArCHO}$ (Vilsmeier reaction)	935, 936
$\text{ArCH}_3 \xrightarrow{\text{CrO}_2\text{Cl}_2} \text{ArCHO}$	937
$\text{ArCH}_3 \longrightarrow \text{ArCH(OAc)}_2 \xrightarrow[\text{H}_2\text{O}]{\text{H}^+} \text{ArCHO}$	943

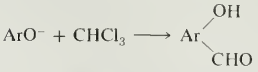
Enol ethers

$\text{R}_2\text{C=CHOR}' \xrightarrow[\text{H}_2\text{O}]{\text{H}^+} \text{R}_2\text{CHCHO}$	377

Halides

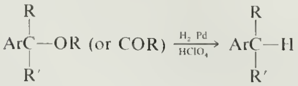
$\text{ArCHX}_2 \xrightarrow[\text{CaCO}_3]{\text{H}_2\text{O}} \text{ArCHO}$	936, 937

Phenols

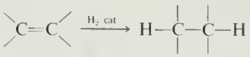
 (Riemer-Tiemann reaction)	1009, 1010

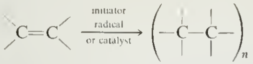
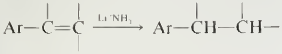
Alkanes and Arenes

Alcohols

 $\text{Ar}\underset{\text{R}'}{\underset{\vert}{\overset{\text{R}}{\overset{\vert}{\text{C}}}}}\text{—OR (or COR)} \xrightarrow[\text{HClO}_4]{\text{H}_2\ \text{Pd}} \text{Ar}\underset{\text{R}'}{\underset{\vert}{\overset{\text{R}}{\overset{\vert}{\text{C}}}}}\text{—H}$	828, 835, 836, 916, 917

Alkenes

	276, 277, 518, 916, 918, 922

	292–296
 $\mathrm{Ar{-}C{=}C} \xrightarrow{\mathrm{Li/NH_3}} \mathrm{Ar{-}CH{-}CH{-}}$	916

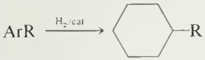
Alkynes

$RC\equiv CR' \xrightarrow{H_2\ \mathrm{cat.}} RCH_2CH_2R'$	311

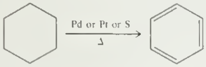
Amines

$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow{H_3PO_2} ArH$	984, 1039

Arenes

	623, 738, 788, 922, 1050, 1069

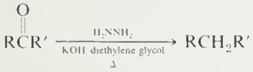
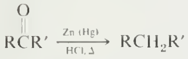
Cyclohexanes

	581, 918, 919, 1045, 1055

Halides and sulfonates

$ArLi$ or $ArMgX + RX \longrightarrow ArR$	900, 917
$ArX + RX \xrightarrow{Na} ArR$ (Wurtz-Fittig reaction)	900
$ArI + Cu \longrightarrow Ar{-}Ar$ (Ullmann reaction)	900
$ArH + RX \xrightarrow{AlCl_3} ArR + ArR'$ (Friedel-Crafts alkylation)	909–911
$ArCH_2MgX$ or $ArCH_2Li + RX \longrightarrow ArCH_2R$	908, 917
$Ar_2CH_2 \xrightarrow{NaNH_2} \xrightarrow{RX} Ar_2CHR$	921

Ketones

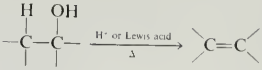
 $R\overset{O}{\overset{\Vert}{C}}R' \xrightarrow[\text{KOH diethylene glycol, }\Delta]{H_2NNH_2} RCH_2R'$ (Wolff-Kishner reduction)	397, 398, 518, 636, 915, 1045
 $R\overset{O}{\overset{\Vert}{C}}R' \xrightarrow[HCl,\ \Delta]{Zn(Hg)} RCH_2R'$ (Clemmensen reduction)	398, 915, 933, 1054, 1055

Organometallics

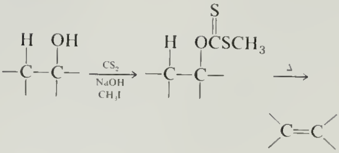
$RMgX$ or $RLi \xrightarrow{R'OH} RH$	163, 898, 916, 1050

Alkenes

Alcohols

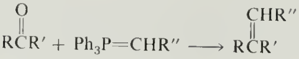

H⁺ or Lewis acid
Δ

272–275, 518, 525, 546, 678, 679, 687, 759, 916, 1045, 1055


CS₂
NaOH
CH₃I
Δ

497

Aldehydes and ketones

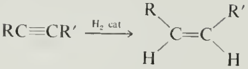


$$\overset{O}{\overset{\|}{RCR'}} + Ph_3P{=}CHR'' \longrightarrow \overset{CHR''}{\overset{\|}{RCR'}}$$

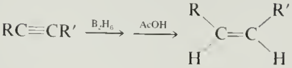
(Wittig reaction)

388–390, 517, 524, 546

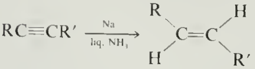
Alkynes



311–313, 519, 525, 546

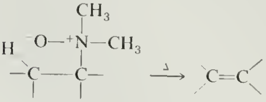


317



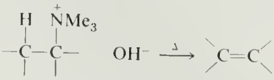
312, 313, 519

Amine oxides



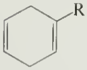
496, 793

Ammonium hydroxides



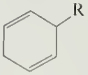
793–796

Arenes



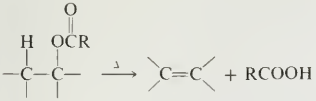
922–924, 1021, 1050

$ArR \xrightarrow[NH_3]{Na}$ or



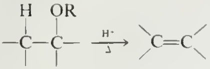
(for R = COOH) 950

Esters



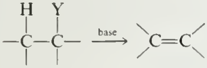
$-\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}-\overset{\displaystyle O\overset{O}{\overset{\|}{C}}R}{\overset{|}{\underset{|}{C}}}- \xrightarrow{\Delta} \;\rangle C{=}C\langle\; + RCOOH$ 495–498, 546

Ethers

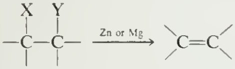


$-\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}-\overset{\displaystyle OR}{\overset{|}{\underset{|}{C}}}- \xrightarrow[\Delta]{H^+} \;\rangle C{=}C\langle$ 239, 240

Halides and sulfonates (X = halogen; Y = X or sulfonate)



$-\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}-\overset{\displaystyle Y}{\overset{|}{\underset{|}{C}}}- \xrightarrow{\text{base}} \;\rangle C{=}C\langle$ 145, 146, 151–153, 221, 224, 237, 266–272, 282, 318, 319, 519, 562, 564, 628, 682, 795



$-\overset{\displaystyle X}{\overset{|}{\underset{|}{C}}}-\overset{\displaystyle Y}{\overset{|}{\underset{|}{C}}}- \xrightarrow{\text{Zn or Mg}} \;\rangle C{=}C\langle$ 283, 563, 636

$RMgX + CH_2{=}CHCH_2Y \longrightarrow RCH_2CH{=}CH_2$ 532, 533, 546, 915

$ArCu + CH_2{=}CHCH_2Y \longrightarrow ArCH_2CH{=}CH_2$ 918

Alkynes

$RCX_2CH_2R' \xrightarrow{\text{base}} RC{\equiv}CR'$ 308, 309, 390

$RCHXCHXR' \xrightarrow{\text{base}} RC{\equiv}CR'$ 307, 308

$RC{\equiv}C^- + R'Y \longrightarrow RC{\equiv}CR'$ 309, 310, 521, 526

Amides

Acid anhydrides

$(RCO)_2O + R'NH_2 \longrightarrow RCONHR'$ 461, 483, 484, 827, 829, 970

Acyl halides

$RCOCl + R'NH_2 \longrightarrow RCONHR'$ 461, 483, 788, 826, 828, 835

Carboxylic acids

$RCOOH + R'NH_2 \xrightarrow{\Delta} RCONHR'$ 439, 440, 461, 788, 833, 834, 970, 974

$\xrightarrow{\text{DCC}} RCONHR'$ 837, 840

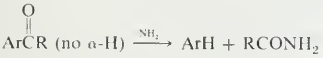
Esters

$RCOOR' + R''NH_2 \longrightarrow RCONHR''$ 484, 834

Ketones

$R_2C{=}O + HN_3 \xrightarrow{H^+} RCONHR$ 825

(Schmidt reaction)



$Ar\overset{O}{\overset{\|}{C}}R \text{ (no } \alpha\text{-H)} \xrightarrow{NH_2^-} ArH + RCONH_2$ 941

Nitriles

$RCN \xrightarrow[\text{or } H_2O_2\text{-}OH^-]{H^+} RCONH_2$ 461, 479, 562, 741

Oximes

$R_2C{=}NOH \xrightarrow{H^+} RCONHR$ 789

(Beckmann rearrangement)

Amines

Acyl halides

$RCOCl + N_3^- \longrightarrow RCON_3 \xrightarrow[H_2O]{\Delta} RNH_2$ 785–787, 797

(Curtius reaction)

Amides

$RCONR'R'' \xrightarrow{LiAlH_4} RCH_2NR'R''$ 491, 492, 784, 787

$RCONH_2 + Br_2 \xrightarrow{NaOH} RNH_2$ 494, 495, 785–787, 966

(Hofmann rearrangement)

Amines

$RNH_2 \xrightarrow[PPA]{CH_3OH} RN(CH_3)_2$ 969

$RNH_2 \text{ (or } RR'NH) \xrightarrow[\Delta]{CH_2O,\ HCOOH}$

$RN(CH_3)_2 \text{ (or } RR'NCH_3)$ 783, 784, 787

(Eschweiler-Clark reaction)

Carboxylic acids

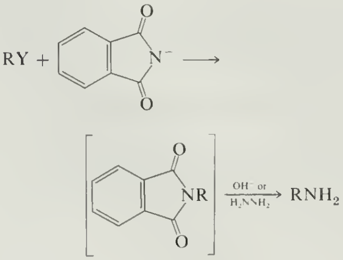
$RCOOH + NH_3 \xrightarrow[\Delta]{H^+} RNH_2$ 785–787, 825

(Schmidt reaction)

Halides and sulfonates

$RY + R'NH_2 \text{ (or } NH_3) \longrightarrow$

$RR'NH \text{ (or } RNH_2)$ 132, 152, 616, 778, 779, 787, 822, 824, 969



779, 780, 787, 822, 823

$RY + R'\bar{N}SO_2Ar \longrightarrow$

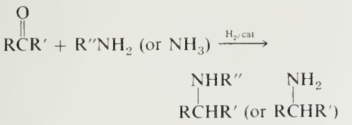
$RR'NSO_2Ar \xrightarrow[OH^-]{H^+ \text{ or}} RR'NH$ 787, 790

$RY + N_3^- \longrightarrow [RN_3] \xrightarrow[\text{or } LiAlH_4]{H_2 \text{ cat}} RNH_2$ 780, 787, 797

$ArX + NH_3 \longrightarrow ArNH_2$ 952, 966

$ArX + NH_2^- \xrightarrow{\text{liq } NH_3} ArNH_2 + Ar'NH_2$ 896

Ketones



$RC(=O)R' + R''NH_2 \text{ (or } NH_3) \xrightarrow{H_2/cat} RCH(NHR'')R' \text{ (or } RCH(NH_2)R')$ 782, 783, 787

Nitriles

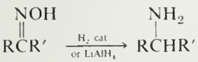
$RCN \xrightarrow{B_2H_6} RCH_2NH_2$ 441

$RCN \xrightarrow[H_2, cat.]{LiAlH_4 \text{ or}} RCH_2NH_2$ 493, 781–783, 787, 788

Nitro compounds

$RNO_2 \xrightarrow[H_2/cat \text{ or other } [H]]{Fe, H^+ \text{ or}} RNH_2$ 781, 787, 961, 962, 966

Oximes



$RC(=NOH)R' \xrightarrow[\text{or } LiAlH_4]{H_2, cat} RCH(NH_2)R'$ 782, 787, 823

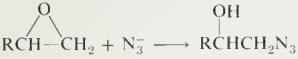
Phenols

$ArOH \xrightarrow[\Delta]{(NH_4)_2SO_3} ArNH_2$ 1052, 1053

(Bucherer reaction)

Azides

$RY + N_3^- \longrightarrow RN_3$ 132, 143, 144, 664, 780, 797



$RCH(O)CH_2 + N_3^- \longrightarrow RCH(OH)CH_2N_3$ 797

$ArNHNH_2 + HONO \longrightarrow ArN_3$ 986

Carboxylic Acids

Acid anhydrides

$(RCO)_2O + H_2O \longrightarrow RCOOH$ 472

Acyl halides

$RCOCl + H_2O \longrightarrow RCOOH$ 472

Alcohols

$RCH_2OH \xrightarrow{[O]} RCOOH$ 234, 435, 711, 712, 719, 721

$RCHOHCH_2R' \xrightarrow{[O]} RCOOH + R'COOH$ 233

$RCHOHCH_3 \xrightarrow{X_2, OH^-} RCOOH$ 368

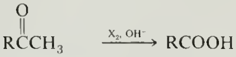
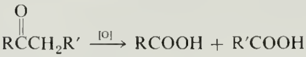
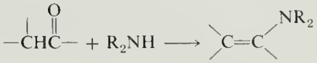
(Haloform reaction)

Aldehydes

$RCHO \xrightarrow{[O]} RCOOH$ 391, 392, 435, 521, 555, 710–712, 716, 717, 719, 721, 723

Alkenes

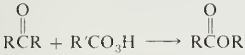
$RCH{=}CHR' \xrightarrow{KMnO_4} RCOOH + R'COOH$ 290, 737

Alkynes	
$RC\equiv CH \xrightarrow{R'MgX} \xrightarrow{CO_2} RC\equiv CCOOH$	307
$RC\equiv CR' \xrightarrow{KMnO_4} RCOOH + R'COOH$	317
Amides	
$RCONH_2 \xrightarrow[\text{or HONO}]{H^+ \text{ or } OH^-} RCOOH$	477, 478
Arenes	
$ArR \xrightarrow{[O]} ArCOOH$	882, 919–921, 939, 942–944
Esters	
$RCOOR' \xrightarrow{H^+ \text{ or } OH^-} RCOOH + R'OH$	48, 49, 222, 473–475, 507, 628, 634, 685, 753, 761, 835, 906, 949
Halides	
$RX \xrightarrow[\text{ether}]{Mg} [RMgX] \xrightarrow{CO_2} RCOOH$	434, 517, 521, 522, 898, 941, 1169
$ArX \xrightarrow{n\text{-BuLi}} \xrightarrow{CO_2} ArCOOH$	941
Ketones	
 $R\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{X_2,\ OH^-} RCOOH$ (Haloform reaction)	367, 368, 561, 939
 $R\overset{O}{\overset{\|}{C}}CH_2R' \xrightarrow{[O]} RCOOH + R'COOH$	393, 394, 737
Nitriles	
$RCN \xrightarrow{H^+ \text{ or } OH^-} RCOOH$	433, 434, 479, 517, 561, 634, 683, 716, 737, 746, 942
Enamines	
	803, 804
Esters	
Acid anhydrides	
$(RCO)_2O + R'OH \longrightarrow RCOOR'$	461, 481, 944
Acyl halides	
$RCOCl + R'OH \longrightarrow RCOOR'$	461, 480, 518, 562, 672, 680
Alcohols and phenols	
$ROH + R'COOH \xrightarrow{H^+} R'COOR$	229, 441–444, 460, 522, 685, 687, 828, 834
$ROH + R'COCl \longrightarrow R'COOR$	461, 480, 518, 672, 738, 1005
$ROH + (R'CO)_2O \longrightarrow R'COOR$	461, 481, 628, 708, 718, 728, 1006
Amides	
$RCONH_2 + R'OH \xrightarrow{H^+} RCOOR'$	482, 562
Carboxylic acids	
$RCOOH + CH_2N_2 \longrightarrow RCOOCH_3$	436, 437, 460, 798
$RCOOH + R'OH \xrightarrow{H^+} RCOOR'$	441–444, 460, 522, 685, 687, 828, 834, 1169

Esters

$RCOOR' + R''OH \xrightleftharpoons{H^+ \text{ or } R''O^-} RCOOR'' + R'OH$	460, 481, 482, 943

Ketones

 $R\overset{O}{\overset{\|}{C}}R + R'CO_3H \longrightarrow R\overset{O}{\overset{\|}{C}}OR$	392, 393

Nitriles

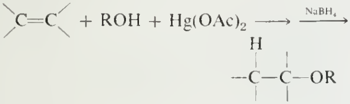
$RCN + R'OH \xrightarrow{H^+} RCOOR'$	482

Ethers

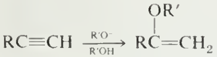
Alcohols

$ROH \xrightarrow[\Delta]{H^+} R_2O$	228, 237, 238, 674

Alkenes

 $>C=C< + ROH + Hg(OAc)_2 \longrightarrow \xrightarrow{NaBH_4} -\overset{H}{\overset{\|}{\underset{\|}{C}}}-\overset{\|}{\underset{\|}{C}}-OR$	238

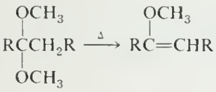
Alkynes

 $RC\equiv CH \xrightarrow[R'OH]{R'O^-} R\overset{OR'}{\overset{\|}{C}}=CH_2$	316, 377

Halides and sulfonates

$RY + R'O^- \text{ (or } R'OH) \longrightarrow ROR'$	132, 141, 143, 147, 148, 151–153, 224, 236, 237, 500, 654, 655, 665, 704, 707, 723
$RY + ArO^- \longrightarrow ROAr$	1004

Ketals

 $R\overset{OCH_3}{\overset{\|}{\underset{\underset{OCH_3}{\|}}{C}}}CH_2R \xrightarrow{\Delta} R\overset{OCH_3}{\overset{\|}{C}}=CHR$	376

Phenols

$ArOH + CH_2N_2 \longrightarrow ArOCH_3$	1004

Halogen Compounds

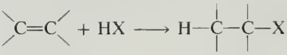
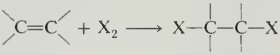
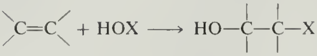
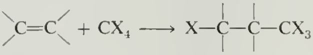
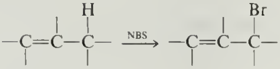
Alcohols

$ROH + HX \longrightarrow RX$	225–227, 231, 232, 529, 530, 904, 906
$ROH + SOCl_2 \longrightarrow RCl$	230, 231, 532, 904, 916
$ROH + PCl_5 \longrightarrow RCl$	230
$ROH + PBr_3 \longrightarrow RBr$	230–232, 518, 635, 1169
$ROH + PI_3 \longrightarrow RI$	230, 231

Alkanes

$RH + X_2 \xrightarrow{h\nu} RX$	77–87, 119–124, 145, 518, 634

Alkenes

	278, 279, 284, 285, 313, 315, 542–544, 645
	280, 281, 314, 519, 536, 543, 544, 555, 581, 630
	282
	285, 286
 $-\mathrm{C}{=}\mathrm{C}{-}\overset{\mathrm{H}}{\mathrm{C}}- \xrightarrow{\mathrm{NBS}} -\mathrm{C}{=}\mathrm{C}{-}\overset{\mathrm{Br}}{\mathrm{C}}-$	536, 537

Alkynes

$\mathrm{RC{\equiv}CR' + HX \longrightarrow RCH{=}CXR'}$	313–316, 318
$\mathrm{RC{\equiv}CR' + X_2 \longrightarrow RCX{=}CXR'}$	314, 315
$\mathrm{RC{\equiv}CH \xrightarrow{R'_2BH} \xrightarrow{Br_2} \xrightarrow[\text{or } \Delta]{NaOH} RCH{=}CHBr}$	319, 320

Amines

$\mathrm{ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow{I^-} ArI}$	981
$\mathrm{ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow[\Delta]{CuX} ArX}$ $(\mathrm{X = Cl, Br})$	980–982
$\mathrm{ArNH_2 \xrightarrow[BF_3 (or\ HPF_6)]{HONO} ArN_2^+\,BF_4^-\ (or\ PF_6^-) \xrightarrow{\Delta} ArF}$	983

Arenes

$\mathrm{ArH + X_2 \longrightarrow ArX}$	582–584, 883–885, 892, 893, 972–974, 1006, 1007, 1014, 1015, 1024, 1041, 1047, 1051, 1057, 1058, 1087, 1108
$\mathrm{ArH + CH_2O + HCl \xrightarrow{ZnCl_2} ArCH_2Cl}$	590, 905
$\mathrm{ArCH_3 + Cl_2 \xrightarrow{h\nu} ArCH_2Cl}$	902, 903
$\mathrm{ArCHR_2 + Br_2 \xrightarrow{h\nu} ArCBrR_2}$	903, 904, 936
$\mathrm{ArH + CCl_4 \xrightarrow{AlCl_3} Ar_3CCl}$	905

Carboxylic acids

$\mathrm{RCH_2COOH + Br_2 \xrightarrow{PBr_3} RCHBrCOOH}$ (Hell-Vollhard-Zelinsky reaction)	438
$\mathrm{RCOOH \xrightarrow{Ag^+} \xrightarrow[CCl_4]{Br_2} RBr}$	445
$\mathrm{RCOOH \xrightarrow[Br_2]{HgO} RBr}$	445
$\mathrm{RCOOH \xrightarrow[LiCl]{Pb(OAc)_4} RCl}$	446

Ethers

$ROR' + HX \longrightarrow ROH + R'X$ or $RX + R'X$ 239

Halides and sulfonates

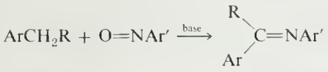
$RY + X^- \longrightarrow RX$ 127–130, 143, 146, 152, 231, 232, 518, 532

Ketones

$R_2C{=}O + PCl_5 \longrightarrow R_2CCl_2$ 390, 391

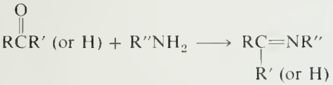
Imines and Derivatives

Arenes

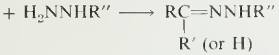


975

Aldehydes and ketones



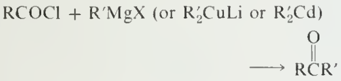
$R\overset{\displaystyle O}{\overset{\|}{C}}R'\ (\text{or H}) + R''NH_2 \longrightarrow R\underset{\underset{\displaystyle R'\ (\text{or H})}{|}}{C}{=}NR''$ 378–380



$+\ H_2NNHR'' \longrightarrow R\underset{\underset{\displaystyle R'\ (\text{or H})}{|}}{C}{=}NNHR''$ 379, 714, 1110

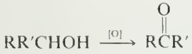
Ketones

Acyl Halides

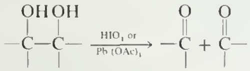


$RCOCl + R'MgX\ (\text{or } R'_2CuLi \text{ or } R'_2Cd) \longrightarrow R\overset{\displaystyle O}{\overset{\|}{C}}R'$ 486, 487, 517, 525, 761, 931

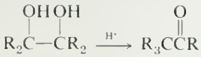
Alcohols



$RR'CHOH \xrightarrow{[O]} R\overset{\displaystyle O}{\overset{\|}{C}}R'$ 232–234, 357, 525, 623, 708, 746, 931

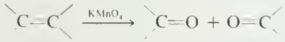


$-\underset{|}{\overset{\overset{\displaystyle OH}{|}}{C}}-\underset{|}{\overset{\overset{\displaystyle OH}{|}}{C}}- \xrightarrow[Pb(OAc)_4]{HIO_4 \text{ or}} -\underset{|}{\overset{\overset{\displaystyle O}{\|}}{C}} + \underset{|}{\overset{\overset{\displaystyle O}{\|}}{C}}-$ 671

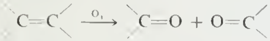


$R_2\overset{\overset{\displaystyle OH}{|}}{C}-\overset{\overset{\displaystyle OH}{|}}{C}R_2 \xrightarrow{H^+} R_3C\overset{\displaystyle O}{\overset{\|}{C}}R$ 674, 675

Alkenes

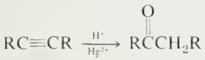


290

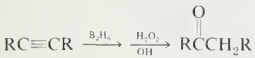


290, 291, 358, 636, 761

Alkynes

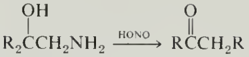


$RC{\equiv}CR \xrightarrow[Hg^{2+}]{H^+} R\overset{\displaystyle O}{\overset{\|}{C}}CH_2R$ 315, 358, 359



$RC{\equiv}CR \xrightarrow{B_2H_6} \xrightarrow[OH^-]{H_2O_2} R\overset{\displaystyle O}{\overset{\|}{C}}CH_2R$ 317

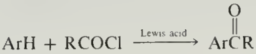
Amino Alcohols



$$R_2\overset{OH}{\overset{|}{C}}CH_2NH_2 \xrightarrow{HONO} R\overset{O}{\overset{\|}{C}}CH_2R$$

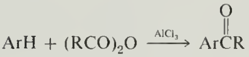
792

Arenes



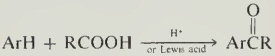
$$ArH + RCOCl \xrightarrow{\text{Lewis acid}} Ar\overset{O}{\overset{\|}{C}}R$$

588, 589, 883, 884, 915, 932, 933, 973, 1015, 1048, 1049



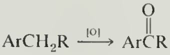
$$ArH + (RCO)_2O \xrightarrow{AlCl_3} Ar\overset{O}{\overset{\|}{C}}R$$

932, 934, 1015, 1017, 1041, 1045, 1049, 1052, 1054



$$ArH + RCOOH \xrightarrow[\text{or Lewis acid}]{H^+} Ar\overset{O}{\overset{\|}{C}}R$$

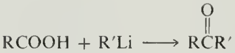
933, 934, 1016, 1045, 1049, 1054, 1055



$$ArCH_2R \xrightarrow{[O]} Ar\overset{O}{\overset{\|}{C}}R$$

934, 1042

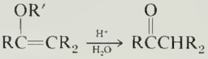
Carboxylic acids



$$RCOOH + R'Li \longrightarrow R\overset{O}{\overset{\|}{C}}R'$$

441, 517, 525

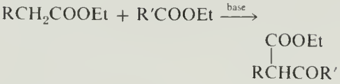
Enol ethers



$$R\overset{OR'}{\overset{|}{C}}{=}CR_2 \xrightarrow[H_2O]{H^+} R\overset{O}{\overset{\|}{C}}CHR_2$$

377, 1021

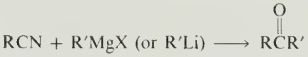
Esters



$$RCH_2COOEt + R'COOEt \xrightarrow{base} R\overset{COOEt}{\overset{|}{C}}HCOR'$$

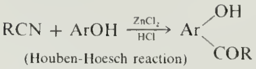
638

Nitriles



$$RCN + R'MgX\ (\text{or } R'Li) \longrightarrow R\overset{O}{\overset{\|}{C}}R'$$

488, 489, 525, 931



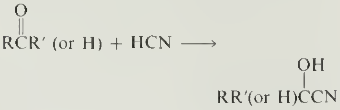
$$RCN + ArOH \xrightarrow[HCl]{ZnCl_2} Ar(OH)COR$$

(Houben-Hoesch reaction)

1016

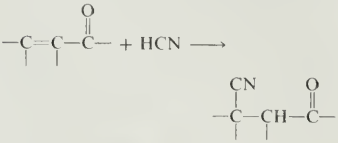
Nitriles

Aldehydes and ketones



$$R\overset{O}{\overset{\|}{C}}R'\ (\text{or } H) + HCN \longrightarrow RR'(\text{or } H)\overset{OH}{\overset{|}{C}}CN$$

383–385, 562, 716



$$-\underset{|}{C}{=}\underset{|}{C}-\overset{O}{\overset{\|}{C}}- + HCN \longrightarrow -\underset{|}{\overset{CN}{\overset{|}{C}}}-\underset{|}{C}H-\overset{O}{\overset{\|}{C}}-$$

556, 737

Amides

$RCONH_2 \xrightarrow[SOCl_2]{P_2O_5 \text{ or}} RCN$	494, 788

Amines

$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow{CuCN} ArCN$ (Sandmeyer reaction)	981, 982

Halides and sulfonates

$RY + CN^-$ (or CuCN) $\longrightarrow RCN$	132, 138, 143, 282, 434, 462, 516, 521, 561, 737, 788, 906
$ArX + CuCN \longrightarrow ArCN$	942

Oximes

$RCH{=}NOH \xrightarrow{Ac_2O} RCN$	718

Sulfonic acids

$ArSO_3H \xrightarrow[\Delta]{NaCN} ArCN$	953

Nitro Compounds

Amines

$ArNH_2 \xrightarrow{CF_3CO_3H} ArNO_2$	971
$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow[Cu]{NO_2^-} ArNO_2$	983

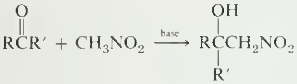
Arenes

$ArH + HNO_3 \longrightarrow ArNO_2$	586, 587, 869, 879–884, 938, 939, 950, 960, 973, 974, 1012, 1013, 1042, 1046, 1051, 1052, 1087, 1107, 1108

Halides and sulfonates

$RY + NO_2^- \longrightarrow RNO_2$	137, 800

Ketones

 $R\overset{O}{\overset{\Vert}{C}}R' + CH_3NO_2 \xrightarrow{base} R\overset{OH}{\overset{\vert}{\underset{R'}{\underset{\vert}{C}}}}CH_2NO_2$	801

Organometallics

Boron

$RCH{=}CH_2 + B_2H_6 \longrightarrow (RCH_2CH_2)_3B$	286, 287, 319
$RC{\equiv}CR + B_2H_6 \longrightarrow (RCH{=}CR)_3B$	316, 317, 319

Cadmium

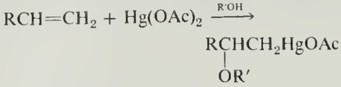
$RMgX + CdCl_2 \longrightarrow R_2Cd$ (R = prim.)	162, 486

Copper

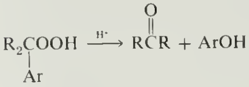
$RLi + CuI$ (or CuBr) $\longrightarrow RCu$	162, 917, 918
$RLi + CuI \longrightarrow R_2CuLi$	165

Lead

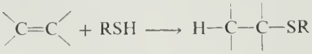
$RCl + Na\text{-}Pb \longrightarrow R_4Pb$	161

Lithium	
$RX + Li \xrightarrow{\text{ether}} RLi$	159, 899, 941
$ArBr + RLi \longrightarrow ArLi$	899, 941, 1050
Magnesium (Grignard reagents)	
$RX + Mg \xrightarrow{\text{ether}} RMgX$	158, 159, 898, 899, 917, 938, 941
Mercury	
$RMgX + HgCl_2 \longrightarrow R_2Hg$	162
 $RCH{=}CH_2 + Hg(OAc)_2 \xrightarrow{R'OH} \underset{\displaystyle OR'}{RCHCH_2HgOAc}$	166, 283
Sodium	
$R_2Hg + Na \longrightarrow RNa$	163
Tin	
$RLi + SnCl_4 \longrightarrow R_4Sn$	162

Phenols

Amines	
$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow[\Delta]{H_2O} ArOH$	979, 980, 1001
$ArNH_2 \xrightarrow[\Delta]{HSO_3^-} ArOH$	1053
Ethers	
$ArOR + HX \longrightarrow ArOH + RX$	1018
Halides	
$ArX \xrightarrow{OH^-} ArOH$	894, 1001
Hydroperoxides	
 $\underset{\displaystyle Ar}{R_2COOH} \xrightarrow{H^+} R\overset{\displaystyle O}{\overset{\Vert}{C}}R + ArOH$	1002
Sulfonic acids	
$ArSO_3H \xrightarrow[\Delta]{NaOH} ArOH$	953, 1000, 1050

Sulfur Compounds

Disulfides	
$2\,RSH \xrightarrow{[O]} RSSR$	243
Sulfides	
$RS^- + R'Y \longrightarrow RSR'$	242, 243
 $>C{=}C< + RSH \longrightarrow H{-}\overset{\vert}{\underset{\vert}{C}}{-}\overset{\vert}{\underset{\vert}{C}}{-}SR$	285
Sulfonamides	
$RSO_2Cl + R'NH_2 \longrightarrow RSO_2NHR'$	789, 829, 954

Sulfonate esters

$ArSO_2Cl + ROH \xrightarrow{\text{pyridine}} ArSO_2OR$	501, 532, 954, 1098

Sulfones

$R_2SO \xrightarrow{R'CO_3H} R_2SO_2$	244
$R_2S \xrightarrow{KMnO_4} R_2SO_2$	247
$ArSO_2Cl + Ar'H \xrightarrow{AlCl_3} ArSO_2Ar'$	954

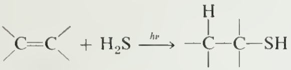
Sulfonic acids

$RSH \xrightarrow{KMnO_4} RSO_3H$	247
$RY + SO_3^{2-} \longrightarrow RSO_3^-$	137, 500
$ArH + H_2SO_4 \longrightarrow ArSO_3H$	587, 883, 913, 914, 950–952, 972, 974, 1013, 1014, 1047, 1048, 1052

Sulfoxides

$R_2S \xrightarrow{H_2O_2} R_2SO$	244

Thiols

$RY + HS^- \longrightarrow RSH$	132, 242
$RY + H_2NCSNH_2 \longrightarrow \xrightarrow{OH^-} RSH$	242, 243
$RX \longrightarrow RMgX \xrightarrow{S} RSH$	243
	285
$ArSO_2Cl \xrightarrow[H^+]{Zn} ArSH$	955
$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow[EtOCS_2^-,\ OH^-]{HS^-\ \text{or}} ArSH$	981

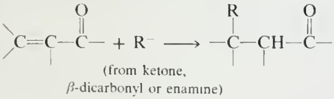
Formation of C—C Bonds

Acyloin Condensation

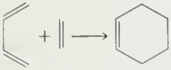
$RCOOEt \xrightarrow[\text{ether}]{Na} RCOCHOHR$	675, 760

Alkene Addition Reactions

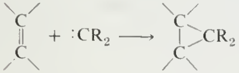
Michael additions

	756–758, 761, 804

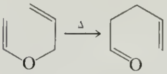
Diels-Alder cycloaddition

	624–627, 642, 643, 737, 740, 1046, 1056, 1057, 1170

Carbenoid additions

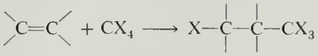
	630–632, 642, 800

Claisen rearrangement



1020

Carbon tetrahalide addition



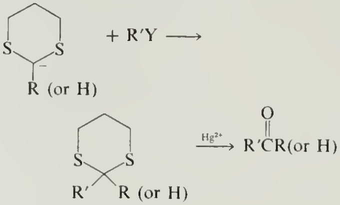
$\rangle C=C\langle + CX_4 \longrightarrow X-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-CX_3$ 285, 286

Alkylation of Carbon Acids

Acetylides

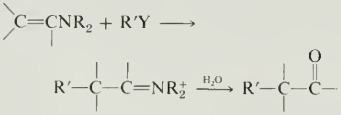
$RC\equiv C^- + R'Y \longrightarrow RC\equiv CR'$ 309, 310, 516, 521, 526

Dithianes



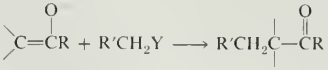
676, 677, 760

Enamines



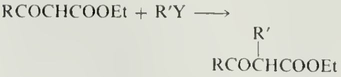
$\rangle C=\underset{|}{C}NR_2 + R'Y \longrightarrow R'-\overset{|}{\underset{|}{C}}-\overset{|}{C}=NR_2^+ \xrightarrow{H_2O} R'-\overset{|}{\underset{|}{C}}-\overset{O}{\overset{\|}{C}}-$ 804

Enolates



$\rangle C=\overset{O^-}{\overset{|}{C}}R + R'CH_2Y \longrightarrow R'CH_2\overset{|}{\underset{|}{C}}-\overset{O}{\overset{\|}{C}}R$ 517, 523, 753

$(EtOOC)_2CH^- + RY \longrightarrow (EtOOC)_2CHR$ 637, 638, 751, 752, 754, 760, 761, 823

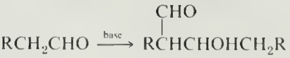


$RCO\bar{C}HCOOEt + R'Y \longrightarrow RCO\overset{R'}{\overset{|}{C}}HCOOEt$ 752-754, 760, 761

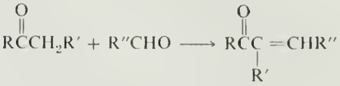
$RCHCOOEt + R'Y \longrightarrow RR'CHCOOEt$ 470, 517, 523

Carbonyl Condensation Reactions

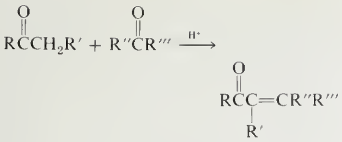
Aldol type



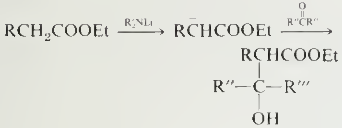
$RCH_2CHO \xrightarrow{base} R\overset{CHO}{\overset{|}{C}}HCHOHCH_2R$ 385, 386, 397, 518, 670, 677



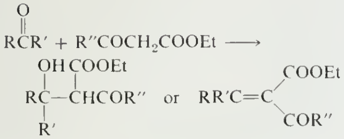
$R\overset{O}{\overset{\|}{C}}CH_2R' + R''CHO \longrightarrow R\overset{O}{\overset{\|}{C}}\underset{R'}{\underset{|}{C}}=CHR''$ 387, 388, 677, 939



$R\overset{O}{\overset{\|}{C}}CH_2R' + R''\overset{O}{\overset{\|}{C}}R''' \xrightarrow{H^+} R\overset{O}{\overset{\|}{C}}\underset{R'}{\underset{|}{C}}{=}CR''R'''$ 387, 553, 554, 757



$RCH_2COOEt \xrightarrow{R'_2NLi} R\bar{C}HCOOEt \xrightarrow{R''\overset{O}{\overset{\|}{C}}R''} \begin{array}{c} RCHCOOEt \\ | \\ R''-C-R''' \\ | \\ OH \end{array}$ 470, 684

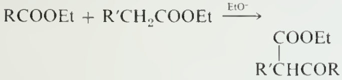


$R\overset{O}{\overset{\|}{C}}R' + R''COCH_2COOEt \longrightarrow R\underset{R'}{\underset{|}{\overset{OH}{\overset{|}{C}}}}-\overset{COOEt}{\overset{|}{C}}HCOR'' \text{ or } RR'C{=}C\begin{array}{l} \diagup COOEt \\ \diagdown COR'' \end{array}$ 754, 755

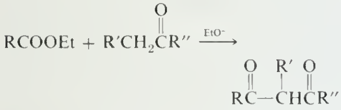
Benzoin

$ArCHO \xrightarrow{CN^-} ArCOCHOHAr$ 675, 676, 760

Claisen condensation



$RCOOEt + R'CH_2COOEt \xrightarrow{EtO^-} \begin{array}{c} COOEt \\ | \\ R'CHCOR \end{array}$ 470, 638, 741–744, 760

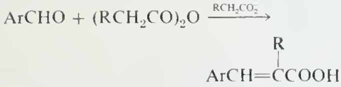


$RCOOEt + R'CH_2\overset{O}{\overset{\|}{C}}R'' \xrightarrow{EtO^-} R\overset{O}{\overset{\|}{C}}-\overset{R'}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}R''$ 744, 745, 760

Knoevenagel

$RCHO + CH_2(COOH)_2 \xrightarrow{\text{amine}} RCH{=}C(COOH)_2$ 755, 760, 940

Perkin



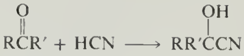
$ArCHO + (RCH_2CO)_2O \xrightarrow{RCH_2CO_2^-} ArCH{=}\overset{R}{\overset{|}{C}}COOH$ 940, 941

Wittig

$Ph_3P{=}CHR + R'_2C{=}O \longrightarrow R'_2C{=}CHR$ 389, 390, 517, 524, 546

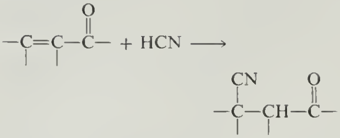
Cyanide Reactions

$RY + CN^- \longrightarrow RCN$ 132, 138, 143, 282, 434, 516, 521, 561, 737, 782, 788, 906



$$R\overset{\overset{O}{\|}}{C}R' + HCN \longrightarrow RR'\overset{\overset{OH}{|}}{C}CN$$

383–385, 516, 562, 716, 782

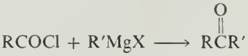


$$-\underset{|}{C}=\underset{|}{C}-\overset{\overset{O}{\|}}{C}- + HCN \longrightarrow -\underset{|}{\overset{\overset{CN}{|}}{C}}-\underset{|}{CH}-\overset{\overset{O}{\|}}{C}-$$

556, 737

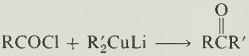
Grignard and Related Organometallic Reactions

Acyl halides



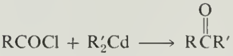
$$RCOCl + R'MgX \longrightarrow R\overset{\overset{O}{\|}}{C}R'$$

486, 517



$$RCOCl + R_2'CuLi \longrightarrow R\overset{\overset{O}{\|}}{C}R'$$

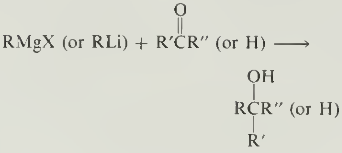
487, 517



$$RCOCl + R_2'Cd \longrightarrow R\overset{\overset{O}{\|}}{C}R'$$

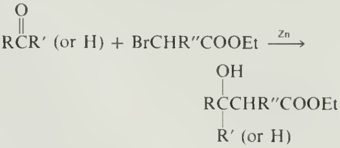
486, 517, 525, 761, 931

Aldehydes and ketones



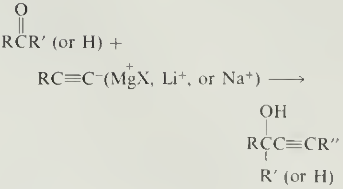
$$RMgX \text{ (or RLi)} + R'\overset{\overset{O}{\|}}{C}R'' \text{ (or H)} \longrightarrow R\underset{\underset{R'}{|}}{\overset{\overset{OH}{|}}{C}}R'' \text{ (or H)}$$

381–383, 517, 524, 525, 556, 557, 898, 899, 915, 1045



$$R\overset{\overset{O}{\|}}{C}R' \text{ (or H)} + BrCHR''COOEt \xrightarrow{Zn} R\underset{\underset{R' \text{ (or H)}}{|}}{\overset{\overset{OH}{|}}{C}}CHR''COOEt$$

684, 759



$$R\overset{\overset{O}{\|}}{C}R' \text{ (or H)} + RC\equiv C^-(\overset{+}{M}gX, Li^+, \text{ or } Na^+) \longrightarrow R\underset{\underset{R' \text{ (or H)}}{|}}{\overset{\overset{OH}{|}}{C}}C\equiv CR''$$

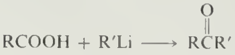
383, 517

Carbon dioxide

$RMgX$ (or RLi) $\xrightarrow{CO_2}$ RCOOH 434, 517, 521, 522, 526, 898, 941, 1021

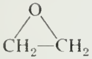
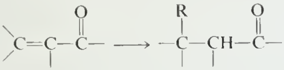
$RC\equiv C^-(MgX^+, Li^+, \text{ or } Na^+) \xrightarrow{CO_2} RC\equiv CCOOH$ 307

Carboxylic acids



$$RCOOH + R'Li \longrightarrow R\overset{\overset{O}{\|}}{C}R'$$

517, 525

Esters	
$RCOOEt + R'MgX \text{ (or } R'Li) \longrightarrow RR'_2COOH$	487, 488, 517, 524, 915, 917
$RMgX + (EtO)_2C{=}O \longrightarrow R_3COH$	488
Halides	
$RMgX + CH_2{=}CHCH_2X \longrightarrow RCH_2CH{=}CH_2$	532, 533, 546, 917
$RMgX + ArCH_2X \longrightarrow ArCH_2R$	908
$ArCH_2MgX + RX \longrightarrow ArCH_2R$	908, 917
Nitriles	
$RCN + R'MgX \text{ (or } R'Li) \longrightarrow R\overset{\overset{O}{\parallel}}{C}R'$	517, 525, 931
Orthoesters	
$ArMgX + HC(OEt)_3 \longrightarrow \xrightarrow{H^+} ArCHO$	938
Oxirane	
 $RMgX + CH_2(O)CH_2 \longrightarrow RCH_2CH_2OH$	652
Unsaturated ketones	
$RMgX \text{ (or } R_2CuLi) +$  $>C{=}\underset{\vert}{C}{-}\overset{\overset{O}{\parallel}}{C}{-} \longrightarrow {-}\overset{R}{\underset{\vert}{\overset{\vert}{C}}}{-}\underset{\vert}{C}H{-}\overset{\overset{O}{\parallel}}{C}{-}$	557, 558, 664

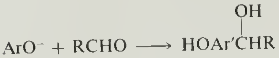
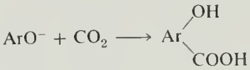
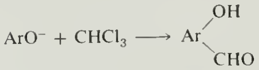
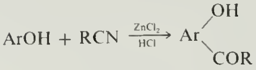
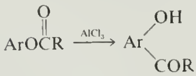
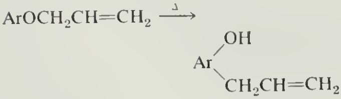
Formation of C—C Bonds to Aromatic Rings

Amine derivatives	
$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow{CuCN} ArCN$	981, 982
$ArNH_2 \xrightarrow{HONO} ArN_2^+ \xrightarrow[OH^-]{Ar'H} Ar{-}Ar'$	984–986
$ArNHNHAr \xrightarrow{H^+} H_2NAr'Ar'NH_2$ (benzidine rearrangement)	964, 1038
Arenes	
$ArH + RCOCl \text{ (or } (RCO)_2O) \xrightarrow{\text{Lewis acid}} Ar\overset{\overset{O}{\parallel}}{C}R$	588, 589, 883, 884, 915, 932–934, 973, 1015–1017, 1041, 1045, 1048, 1049, 1052, 1054
$ArH + CO + HCl \xrightarrow[AlCl_3]{ZnCl_2 \text{ or}} ArCHO$	590, 935
$ArH + HCON(CH_3)_2 \xrightarrow{POCl_3} ArCHO$	935, 936
$ArH + CH_2O + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$	590, 905
$ArH + RX \xrightarrow{AlCl} ArR \ (+ Ar'R + ArR')$	905, 909–911
$Ar_2CH_2 \text{ (or } Ar_3CH) \xrightarrow{NaNH_2} \xrightarrow{RX} Ar_2CHR \text{ (or } Ar_3CR)$	921

Aryl halides and organometallics

$\mathrm{ArMgX\ (or\ ArLi) + RY \longrightarrow ArR}$	900, 917
$\mathrm{ArX + RX \xrightarrow{Na} ArR}$	900
$\mathrm{ArX \xrightarrow{Cu} ArAr}$	900
$\mathrm{ArCH_2MgX + RX \longrightarrow ArCH_2R}$	908, 917
$\mathrm{ArCu + CH_2{=}CHCH_2Br \longrightarrow ArCH_2CH{=}CH_2}$	918
$\mathrm{ArX \xrightarrow{BuLi} \xrightarrow{CO_2} ArCOOH}$	941
$\mathrm{ArX \xrightarrow{CuCN} ArCN}$	942

Phenols

 $\mathrm{ArO^- + RCHO \longrightarrow HOAr'\overset{OH}{C}HR}$	1007, 1008
 $\mathrm{ArO^- + CO_2 \longrightarrow Ar}\begin{array}{l}\diagup \mathrm{OH}\\ \diagdown \mathrm{COOH}\end{array}$	1008, 1009
 $\mathrm{ArO^- + CHCl_3 \longrightarrow Ar}\begin{array}{l}\diagup \mathrm{OH}\\ \diagdown \mathrm{CHO}\end{array}$	1009, 1010
 $\mathrm{ArOH + RCN \xrightarrow[HCl]{ZnCl_2} Ar}\begin{array}{l}\diagup \mathrm{OH}\\ \diagdown \mathrm{COR}\end{array}$	1016
 $\mathrm{ArO\overset{\overset{O}{\Vert}}{C}R \xrightarrow{AlCl_3} Ar}\begin{array}{l}\diagup \mathrm{OH}\\ \diagdown \mathrm{COR}\end{array}$	1016
 $\mathrm{ArOCH_2CH{=}CH_2 \xrightarrow{\Delta} Ar}\begin{array}{l}\diagup \mathrm{OH}\\ \diagdown \mathrm{CH_2CH{=}CH_2}\end{array}$ (Claisen rearrangement)	1019, 1020, 1136

INDEX

(*Boldface entries refer to definitions of terms in the text.*)

A

- Abietic acid, 919
- ABS (plastic polymer), 562
- Absolute configuration, **111**
- Absolute stereostructure, 110
- Acenes, 1058
- Acetaldehyde
  - nmr spectrum, 355
  - physical properties, 352 *t*
  - preparation, 315
  - polymerization, 378
  - stereoscopic figure, 348
- Acetals, 372–378
  - as protecting groups, 707
  - from diols, 672–673
  - from monosaccharides, 705–708
  - glycosides, 700–702
  - pyrolysis, 376–377
- Acetamide
  - hydrogen bonding, 457–458
  - physical properties, 458 *t*
- Acetamidomalonic ester, 823
- Acetanilide
  - biological oxidation, 1034
  - nitration, 973
  - properties, 970
- Acetate ion
  - electronic structure, 428
  - resonance stabilization, 427–428
- Acetic acid, 439
  - glacial, **446**
  - in biosynthesis of rubber, 548
  - ionization, 426–427
  - natural occurrence, 446
  - physical properties, 426 *t*
  - pK_a, 738
  - substituted, acidity, 428–429, 945 *t*
- Acetic anhydride, 451
  - in cyclic anhydride formation, 740
  - industrial synthesis, 564
- Acetic formic anhydride, 485
- Acetoacetic ester, 742
  - in Michael addition, 757
  - pK_a, 742, 751
  - condensation (*see also*, Claisen condensation), 742
  - synthesis, 751
- Acetoacetyl coenzyme A, 1159
- Acetogenins, 1157
- Acetone, 29
  - acidity, 361–362, 468
  - basicity, 349–350
  - condensation, 552–554
  - electronic transitions, 597
  - physical properties, 352 *t*
  - pyrolysis, 563
  - reaction with galactose, 706
- Acetone [*cont.*]
  - resonance structures, 370
  - ultraviolet spectroscopy, 596–597
- Acetone anion, 361
- Acetonitrile, 143, 144
  - reaction with organometallic compounds, 488
  - structure, 453
  - use as solvent, 458
- Acetonitrile oxide, 14
- Acetophenone, 862, 930
  - nitration, 884
- Acetophenones, as triplet sensitizer, 1155
- *o*-Acetoxybenzoic acid (aspirin), 1006
- Acetylacetone (*see*, 2,4-Pentanedione)
- *p*-Acetylaminobenzenesulfonyl chloride, 974
- 4-Acetylbiphenyl, 1041
- Acetyl chloride, 453
  - hydrolysis, 472
  - in cyclic anhydride formation, 740
- Acetylcholine, 778
- Acetyl CoA (*see*, Acetyl coenzyme A), 745
- Acetyl coenzyme A, 1159
- Acetylene, 29
  - handling and storage, 307–308
  - hydration of, 315
  - industrial source, 307
  - in preparation of chloroprene, 547
  - in synthesis of acrylonitrile, 562
  - ionization potential, 410 *t*
  - Lewis structure, 8
  - physical properties, 303 *t*, 307–308
  - pK_a, 467
  - preparation, 307
  - reactions, 310
  - structure, 301–302
- Acetylenes
  - cyclic polymers, 318
  - cycloaddition to diazomethane, 1093
  - cycloaddition to nitrile oxides, 1092–1093
  - ultraviolet spectroscopy, 602
- Acetylide ions, 306, 309–310
  - addition, to aldehydes and ketones, 383
- N-Acetyl-*dl*-leucine, resolution of, 827
- 2-Acetylnaphthalene, 368, 1049
- Acetyl nitrate, 1080
- 2-Acetylpyrrole, 1081
- Acetylsalicylic acid (aspirin), 1006
- 2-Acetylthiophene, 1081
- Achirality, **105**
- Acid anhydrides, **451**
  - cyclic, 462
    - in Friedel-Crafts acylations, 932–934
  - hydrolysis, 472
  - infrared spectroscopy, 459
  - nomenclature, 455
  - preparation
    - from acetic anhydride, 485
    - from acyl halides and carboxylate salts, 485

Acid anhydrides, preparation [*cont.*]
    summary, 462
  reactions
    with alcohols, 480–481
    with amines and ammonia, 483–484
  solubility, 458
  ultraviolet spectroscopy, 602
Acid, conjugate, 132–133
Acid dissociation constant, **215**, 426
Acid halides (*see,* Acyl halides)
Acidity, **215**
  effect of alkyl groups, 217
  of acetic acids, substituted, 945 *t*
  of alcohols, 214–217, 427
  of aldehydes, 467–468
  of alkylbenzenes, 921
  of alkylsulfuric acids, 499
  of alkynes, 306
  of amides, 494
  of amino acids, 817 *t*, 818–820
  of benzoic acids, 944–948, 945 *t*
  of carboxylic acid derivatives, 467–471
  of carboxylic acids, 426–432
    inductive effects, 428–429
  of chlorobutyric acids, 429
  of β-dicarbonyl compounds, 750–751
  of dicarboxylic acids, 738–739
  of ketones, 467–468
  of oxonium ions, 465
  of phenols, 1002–1003
  of phenylacetic acids, 948 *t*
  of phenylalkanoic acids, 944 *t*
  of phosphates, 502
  of propylene, 534
  of protonated carbonyl compounds, 463–467
  of substituted acetic acids, 429 *t*
  pK_a, **215**
    of acetic acid, 427
    of acetylene, 306, 467
    of ammonium ions, 774
    of anilinium ions, substituted, 969
    of chlorobutyric acids, 429
    of chloroform, 631
    of β-dicarbonyl compounds, 750–751
    of dimethyl phosphate, 502
    of methane, 467
    of methanol, 439
    of methyl phosphate, 502
    of orthophosphoric acid, 502
    of protonated compounds, 464
    of substituted acetic acids, 429 *t*
Acidity constant, 132
  of conjugate acids of common bases, 133 *t*
  of inorganic acids (*see* Appendix IV in the text)
  relation to standard free energy, 133
Acrilan, 562
Acrolein, 1105
  dimerization, 625
  in Michael addition, 756
  preparation, 554, 567
Acrylic acid, 562
Acrylonitrile
  industrial preparation, 562
  polymerization, 562
Acrylyl chloride, 788
Actin, function, 856
Activated complex (*see also,* Transition state), 46–47
Activation energy, 44, 46, 268–269
Active site, in proteins, 854
Acyl ammonium salts, 483
Acylation, Friedel-Crafts (*see,* Friedel-Crafts acylation)
Acyl azides, 838
  in Curtius rearrangement, 786
  preparation, 797
Acyl bromides, 438, 451
Acyl chlorides, **451**
  physical properties, 456–458
  preparation, 444–445
  reaction with sodium peroxide, 649
  structure, 453
  ultraviolet spectroscopy, 602
Acyl cyanides, hydrolysis, 746
Acyl group, 588
Acyl halides, 34, **451**
  acidity, 468–469
  dehalogenation, 563–564
  enol form, 470–471
  hydrolysis, 472
  infrared spectroscopy, 459
  NMR spectroscopy, 458
  nomenclature, 454–455
  physical properties, 456–458
  preparation, 444–445
    summary, 461
  reactions
    with alcohols, 480
    with amines and ammonia, 482–483
    with azide ion, 797
    with carboxylate salts, 485
    with diazomethane, 798
    with organometallic compounds, 485–489
  reduction, 489–490
  solubility, 458
  structure, 453
Acyl hydrazides, 838
O-Acylisoureas, 837
Acylium ions, 443–444, 471, 478, 588
  resonance structures, 444
Acyl nitrenes, 785
Acyloin condensation, 675
Acyloins, 675
Acyloxonium ions, 465
Adamantane, 72
Adams catalyst (*see also,* Platinum), 276
Addition reactions (*see also,* Electrophilic addition; Radicals, addition reactions)
  of aldehydes and ketones, 368–391
  of alkenes, 276–296
  of alkynes, 313–317
  of conjugated dienes, 542–544
  of cyclohexene, 630
  of unsaturated aldehydes and ketones, 555–560
Adenine, 1110, 1138
Adenosine, 1140
Adenosine diphosphate (ADP), 1161
Adenosine triphosphate (ATP), 693, 1161

S-Adenosylmethionine, 244–245
Adenylic acid, 1139
Adipaldehyde, 672
Adipic acid, 233, 393–394, 435, 736
  acidity, 738
  esters, Dieckmann condensation of, 743
  industrial preparation, 788
  in nylon structure, 788
  in polyurethanes, 801
  preparation, 738
Adiponitrile, 788
Adrenocorticotrophin, sequence of, 847
Aerosol propellants, 102
Aglycon, **731**
-al, as suffix, 667
L-Alanine, 815–817
  physical properties, 817 *t*
  preparation, 822
  resolution, 826
β-Alanine, 815
Alanylglycine, p*K* values for, 833
Albinism, 1145
Alchemy, 1–2
Alcohols, **32–33, 206**
  acidity, 214–217, 427
  addition to aldehydes and ketones, 372–376
  addition to alkynes, 377
  alkyl halides from, 224–227, 228–232
  basicity, 463, 464
  dielectric constants, 213–214
  esterification (*see*, Esterification of alcohols)
  hydrogen bonding, 213
  infrared spectroscopy, 338–340
  mass spectroscopy, 414–416
  NMR spectroscopy, 218–220
  nomenclature
    carbinol system, 209
    common system, 207–209
    IUPAC system, 209–211
  oxidation, 357–358
  physical properties, 211–214
  preparation, 220–224
    from alkyl halides, 132, 221–223
    from Grignard synthesis, 381–383
    from hydrocarbons, 223
    hydration of alkenes, 279
    hydroboration-oxidation of alkenes, 286–289
    oxidation of Grignard reagents, 222–223
    oxymercuration-reduction of alkenes, 283–284
    reduction of acyl halides, 490
    reduction of aldehydes and ketones, 394–398
    reduction of carboxylic acids, 440–441
    reduction of esters, 490–491
    special preparations, 223–224
    summary, 220–221
  reactions, 224–234
    addition to nitriles, 482
    alkoxide ions, 224
    alkyloxonium salts, 224–229
    dehydration, 228–229, 237–238, 497
    elimination, 272–275
    formation of inorganic esters, 229–231
Alcohols, reactions [*cont.*]
    oxidation, 232–234, 435
    transesterification, 481–482
    with acyl halides, 229
    with alkali metals, 216
    with carboxylic acid derivatives, 480–482
    with carboxylic acids, 229
    with nitric acid, 505
    with phosgene, 488, 738
  secondary, preparation of formic esters and Grignard reagents, 487–488
  S_N2 reactions, 142
  structure, 206
  tertiary, preparation of
    from acyl halides and Grignard reagents, 486
    Grignard reagents and esters, 487–488
  ultraviolet spectroscopy, 602
  use as solvents, 214
Aldehydes, 32–34
  acidity, 467–468
  addition
    of acetylide anions, 383
    of alcohols, 372–376
    of ammonia derivatives, 378–381, 783
    of cyanide, 383–384
    of 1,3-dithianyl anions, 676
    of Grignard reagents, 381–383
  aldol condensation, 385–388, 397
  α-amino nitriles from, 824
  aromatic
    benzoin condensation, 675–676
    Perkin reaction, 940
    preparation, 935–938
      Gatterman-Koch synthesis, 590
    reactions, 938–941
  Baeyer-Villiger oxidation, 392
  basicity of, 463–464
  Cannizzaro reaction, 396–397
  catalytic hydrogenation, 395
  Clemmensen reduction, 398
  condensation
    with malonic esters, 754–755
    with phenols, 1007–1008
  2,4-dinitrophenylhydrazone derivatives, 894
  enolization, 360–368
  exchange reaction with water, 371–372
  halogenation
    acid catalysis, 366–367
    base catalysis, 366–367
  hydration, 357–358
    equilibrium, 368–369, 371
    rate, 368, 371–372
  hydroxy, 675–681
  in enamine formation, 803
  infrared spectroscopy, 355–357
  in Strecker synthesis, 824
  Knoevenagel condensation, 754–755
  mass spectroscopy, 416–417
  NMR spectroscopy, 354–355
  nomenclature
    common system, 350
    IUPAC, 351–352
  oxidation, 391–392, 435–436
  physical properties, 352–354

- Aldehydes [*cont.*]
  - polymerization, 377–378
  - preparation, 357–359
    - hydration of alkynes, 315, 359
    - hydroboration of alkynes, 317, 359
    - oxidation of alcohols, 232, 234, 357–358
    - oxidation of alkenes, 358
    - ozonolysis of alkenes, 291
    - reduction of acyl halides, 489–490
    - reduction of amides, 492–493
    - reduction of nitriles, 493
  - reactions, 360–398
    - addition of bisulfite, 500–501
    - reduction
      - to alcohols, 394–398
      - to alkanes, 397–398
    - Reformatsky reaction, 684
    - Wittig reaction, 388–390
  - stability versus ketones, 370, 375
  - structure, 348–349
  - ultraviolet spectroscopy, 596–599
  - unsaturated (*see*, α,β-Unsaturated aldehydes and ketones)
- Alditols, 709
- Aldohexose, **694**
- Aldohexoses
  - α- and β-anomers, **698**
  - conformations, 702–703
  - number of, 695
- Aldol (*see*, β-Hydroxy aldehydes)
- Aldol condensation, 385–388, 397, 552–554, 677, 744
  - intramolecular, 617–618
  - mixed, 386–388
- Aldonic acids, 709–711, 716, 717
- Aldopentoses, **694**
  - number of, 695
- Aldoses, **694**
  - carbon-chain lengthening, 714–717
  - chain shortening, 717–718
  - glycosides, 700–702
  - methylation, 704–705
  - oxidation, 709–714
    - by Fehling's reagent, 710
    - by Tollens reagent, 710–711
- Aldotetroses, **694**
  - number of, 695
- Aldotrioses, **694**
  - number of, 695
- Aldoximes (*see*, Oximes)
- Aliphatic compounds (*see also*, Alkanes; Cycloalkanes), **35**
- Alizarin, 1023, 1147, 1157
- Alizarine Yellow R, 1032
- Alkali metals
  - electropositivity of, 6
  - reaction
    - with alcohols, 31
    - with nitric acid, 30
    - with sulfuric acid, 30
    - with water, 30
- Alkaloids, 777, 805–807, 1157
- Alkanes, **32**, 53–71
  - branched chain, 62–67
  - bromination, 85–87
- Akanes [*cont.*]
  - chlorination, 77–84
  - combustion, 87–89
  - conformations, 57–62, 66–67
  - cyclic (*see also*, Cycloalkanes), 68–69
  - dehydrogenation, 580–581
  - halogenation, 77–87
  - infrared spectroscopy, 333
  - mass spectroscopy, 410–414
  - NMR characteristics, 191 *t*
  - nomenclature, 53–54, 62–66, 68–69
    - IUPAC, 64–66
  - normal (*n*-), **53**, 54–61
  - occurrence, 69–71
  - physical properties, 54–57, 67, 68
  - preparation
    - by hydrogenation of alkenes, 276–277
    - from alkyl halides, 167
    - reduction of aldehydes and ketones, 397–398
  - pyrolysis, 76–77
  - saturated, **53**
  - straight-chain, **53**
  - structure, 54, 55, 56, 57
- Alkanesulfonic acids, 500–501
- Alkenes (*see also*, Dienes), **32–33**, 251–296
  - addition reactions
    - alkoxymercuration, 238
    - anti-Markovnikov, 284–285, 288
    - halohydrin formation, 282
    - hydration, 279
    - hydroboration-oxidation, 286–289
    - hydrogenation, 276–277
    - Markovnikov, 278
    - of carbenes, 631–632
    - of carbon tetrabromide, 285
    - of carbon tetrachloride, 285
    - of halogens, 280–281, 318–319, 581–582
    - of hydrogen bromide, 278–279, 284–286
    - of hydrogen chloride, 278–279
    - of hydrogen iodide, 278
    - of hydrogen sulfide, 285
    - of mercuric acetate, 283–284
    - of nitric acid, 586
    - of polyhaloalkanes, 285
    - of sulfuric acid, 587
    - of thiols, 285
    - peroxide effect, 284–285
    - polymerization, 292–296
    - radical, 284–286
    - stereochemistry, hydroxylation, 667–669
    - telomer products, 285–286
  - *cis-trans* isomerism, effect of excitation, 603
  - cleavage, 671–672
  - conversion into aziridines, 1068
  - cyclopropyl rings from, 630–632
  - dipole moment, 259–260
  - electronic structure, 251–256
  - from Hofmann elimination, 793–796
  - heat of hydrogenation, 311
  - hydroxylation, 667–669
  - infrared spectroscopy, 334–336
  - in Friedel-Crafts alkylation, 911
  - NMR spectroscopy, 260–264
  - nomenclature, 256–258

Alkenes, nomenclature [*cont.*]
    common system, 256-257
    IUPAC system, 257-258
  oxidation, 289-292, 358
  ozonolysis, 290-292
  physical properties, 258-264
  preparation, 266-275
    allyl halides and Grignard reagents, 532-533
    dehydration of alcohols, 272-275
    dehydrohalogenation of alkyl halides, 145-147, 266-272
    disproportionation of alkanes, 76-77
    from alkenyl chlorides, 323
    from amines, 793
    hydroboration-protonolysis of alkynes, 317
    industrial, 275
    pyrolytic elimination of esters, 495-498
    selective hydrogenation of alkynes, 311-312
    Wittig reaction, 388-390
  reactions, 275-296
    with peroxycarboxylic acids, 649-650
  relative stability, 264-266
Alkenyl chlorides, conversion to alkenes, 323
Alkenyl dihalides (*see*, Alkenyl halides)
Alkenyl halides
  preparation, 313-315, 318-321
  reactions, 320-321
Alkoxides, 216
  stabilization, 217
Alkoxy, as prefix, 241
Alkoxymercuration-demercuration, 283-284
Alkylaluminum compounds (*see*, Organoaluminum compounds)
Alkyl anions, 398
Alkylating agents, 500, 501
Alkylation
  of ammonia, 778
  of β-dicarbonyl compounds, 751-754
  of malonic esters, 822-823
Alkyl azides
  decomposition, 797
  preparation, 797
    from alkyl halides, 780
  reduction, 780
Alkylbenzenes
  acidity, 921
  Birch reduction, 922-924
  catalytic hydrogenation, 921-922
  Friedel-Crafts alkylation, 909
  halogenation, 902-904
  heats of formation, 912
  nomenclature, 890-891
  oxidation, 919-921
  preparation
    from benzylic alcohols, 916
    from organometallics, 917-918
    reduction of aryl carbonyls, 914-915
  reactions, 919-924
  rearrangements, 913-914
Alkyl benzenesulfonates, 431
  in S_N2 reactions, 141
Alkylboranes (*see*, Organoboron compounds)
Alkylcadmium compounds (*see*, Organocadmium compounds)
Alkyl chlorides
  enthalpy of ionization, 149 *t*
  preparation, 390-391
    from alkanes, 83-84
Alkylcopper compounds (*see*, Organocopper compounds)
Alkyl dihalides (*see also*, Alkyl halides)
  preparation, 308
Alkyl fluorides
  ineffectiveness in S_N2 reaction, 142
  uses, 102
Alkyl halides, 33 *t*, 95-104
  boiling point, 99 *t*
  carbonium ions from, 147-151
  conformations, 100-102
  dehydrohalogenation, 318-319, 437
  displacement
    with cyanate ion, 801
    with nitrite ion, 800
  displacement reactions, 127-145, 152-153
  elimination, 145-153, 267
    E1 mechanism, 151-153
    E2 mechanism, 145-147, 266-272
    stereochemistry, 267, 269-272
    versus substitution, 145-147, 152-153
  from radical addition to alkenes, 284-286
  hybrid orbitals, 96
  hydrolysis, 221-222
  infrared spectroscopy, 337
  in Friedel-Crafts alkylation, 909-914
  in Williamson ether synthesis, 236-237
  IUPAC nomenclature, 95-96
  NMR characteristics, 191 *t*
  nomenclature, 95-96
  nucleophilic substitution, S_N2
    kinetics, 127-128
    rate of racemization, 128-129
    relative reactivities, 138-140
    solvents for, 143-144
    stereochemistry, 128-131
    steric hindrance, 138-140
    transition state, 130-131
    versus elimination, 152-153
  nucleophilic substitution, S_N1, 147-151
    carbonium ions, 147-151
    rate, 148
    versus elimination, 152-153
  α-phenylalkyl halides (*see*, Benzylic halides)
  physical properties, 98-100
  preparation
    by halide exchange, 127, 143
    degradation of carboxylic acids, 445-446
    from alcohols, 224-227, 230-232
    from alkanes, 77-79, 82-87
    from alkenes, 278-279
    from sulfonate esters, 231-232
    halogenation of alkanes, 77-87, 100
  reactions, 127-153
    dehydrohalogenation, 308-309, 318-319
    displacement (*see also* specific nucleophiles below), 127-145, 152-153
      with nitrite ion, 137
      with sulfate ion, 136
      with sulfite ion, 137
      with thiosulfate ion, 137

Alkyl halides, reactions, displacement [*cont.*]
    with alkoxides, 236–237
    with amines, 616
    with ammonia, 778
    with aryllithiums, 899–900
    with azide ion, 780, 797
    with hydroxide ion, 127
    with metals, 158–161
    with phosphines, 388
    with phthalimide, 779–780
    with silver nitrate, 505
    with silver oxide, 529
  S_N2 reaction, reactivity, 143–144
  solvolysis reaction, 148, 151
  stability, 99
  structure, 96–98
  ultraviolet spectroscopy, 602
  uses, 102–104
  Wurtz-Fittig reactions, 900
  Wurtz reaction, 167
Alkyl hydroperoxides, 88
Alkyl isocyanates, 495
Alkyl isoquinolines, acidity, 1108–1109
Alkyllithium compounds (*see,* Organolithium compounds)
Alkyllithium reagents (*see,* Organolithium compounds)
  reaction with carboxylic acids, 441
Alkylmagnesium compounds (*see,* Grignard reagents)
Alkylmagnesium halides (*see,* Grignard reagents)
Alkylmercury compounds, uses, 166
Alkyl methanesulfonates, in S_N2 reactions, 141
Alkyl nitrates, in S_N2 reactions, 141
Alkyl nitrites, 800
Alkyloxonium salts, **225**
Alkylperoxy radicals, 88
Alkyl pyrophosphates, 504
Alkylpyridines (*see,* Picolines; Lutidines; Collidine)
N-Alkylpyridinium salts (*see,* Pyridinium salts)
Alkyl radicals, 74, 75
  abbreviation for, 159
  combination with oxygen, 88
  disproportionation, 76
  recombination, 76
  stability, 75
Alkylsodium compounds (*see,* Organosodium compounds)
  reaction with alkyl halides, 168
Alkyl sulfonates
  in S_N2 reactions, 141
  preparation, 501, 1098
Alkylsulfuric acids, 228, 499
Alkylthio prefix, **241**
Alkyl *p*-toluenesulfonates (*see,* Alkyl sulfonates)
Alkyl vinyl ethers (*see,* Enol ethers)
Alkynes, **32–33,** 301–321
  acidity, 306–307
  addition of alcohols, 377
  dipole moments, 304
  electronic structure, 301–302
Alkynes [*cont.*]
  Glaser reaction, 317
  heat of hydrogenation, 311
  heavy metal salts, 307
  hydration, 358–359
  hydroboration, 359
  infrared spectroscopy, 336–337
  Nieuwland enyne synthesis, 318
  NMR spectroscopy, 304–306
  nomenclature, 302–303
  physical properties, 303–306
  preparation, 307–310
    dehydrohalogenation of alkyl dihalides, 308–309
    from acetylides, 309–311
    from ketones, 390–391
  purification, 307
  reactions, 311–318
    addition of alkoxides, 316
    addition of halogens, 313–315
    addition of hydrogen halides, 313–315
    hydroboration, 316–317, 319
    hydrogenation, 311–312
    oxidation, 317–318
    protonation of Grignard reagents, 306
  stability, 308
  terminal, 306
Alkynylcarbinols, 383
Allenes, 545–546
  chirality, 545
  electronic structure, 545
  stability, 545–546
  stereoscopic figure, 545
D-(+)-Allose, 697, 702
  synthesis from D-glucose, 707–708
Allyl alcohol, preparation, 537
Allyl anion, 534, 535
  π molecular orbitals, 538
  resonance structures, 535
Allylbenzene, 918
Allyl bromide, reaction with azide ion, 664
Allyl cation, 415, 530–531, 634
  electronic structure, 530–531
  π molecular orbitals, 538
  resonance structures, 535
  stability, 531
  stereoscopic figure, 531
  structure, 531
Allyl chloride, preparation, 537
Allylcyclopentane, 532
Allyl halides, reaction with Grignard reagents, 532–533, 546
Allylic alcohols
  oxidation, 554–555
  reaction with hydrogen bromide, 529
Allylic anions, 533–535
  resonance stabilization, 534
Allylic cations (*see also,* Allyl cation), 529–532
Allylic radicals, 535–537
  resonance stabilization, 535
Allylic rearrangement, 531–532
Allylic systems, 529–540
  molecular orbital description, 537–540
  S_N2 reactions, 532–533

o-Allylphenol, 1019
Allyl phenyl ether, 1019
Allylphosphoranes, in Wittig reactions, 546
Allyl radical
  in nomenclature, 531
  π molecular orbitals, 538
Almonds, glycosides in, 731
D-(+)-Altrose, 697
Alumina, 274
Aluminum carbide, hydrolysis, 71
Aluminum chloride, 588
Aluminum hydride, 492
Aluminum oxide, 274
Amalgam, 398
Amalgamated zinc, 398
Ambident nucleophilicity, **138**
Amidate ions, resonance stabilization, 534
Amide, aromatic
  as suffix, 454, 667
  electrophilic substitution, 973–974
Amide ion, 295
Amides, 34, **451**
  acidity, 468, 494
  aromatic, preparation from amines, 969–970
  basicity, 466–467
  carboxylic acid, preparation of by pyrolysis of ammonium carboxylates, 439–440
  cyclic (*see,* Lactams)
  dehydration, 494
  from amino acids, 828–829
  Hofmann degradation, 494–495
  Hofmann rearrangement, 785–786
  hydrogen bonding, 457–458
  hydrolysis, 477, 478
  infrared spectroscopy, 459–460
  NMR spectroscopy, 458
  nomenclature, 454
  polymers, 788
  preparation
    from carboxylic acid derivatives, 482–485
    Schotten-Baumann method, 483
    summary, 461
    transamination, 484
  reaction with alcohols, 482
  rearrangement to amines, 785–786
  reduction, 491–493, 784
  resonance structures, 535
  solubility, 458
  structure, 456
Amidine, **485**
Amination, of α-halo acids, 821–822
-amine, as suffix, 667, 768
Amine oxides, 496
  Cope elimination, 793
  Lewis structure, 793
Amines, 765–807
  aromatic, 965–977
    acylation, 969–970
    alkylation, 969–970
    amide formation, 969–970
    basicity, 967–969
    diazotization (*see also,* Diazotization; Arenediazonium salts), 976–977
    electrophilic substitution, 878, 972–974
Amines, Aromatic [*cont.*]
    Friedel-Crafts acylation, 973
    halogenation, 972
    nitration, 973
    nomenclature, 965–966
    oxidation, 970–972
    physical properties, 967–969
    preparation, 961–962, 966
    reaction with nitrous acid, 974–977
    sulfonation, 972
  aromatic halobenzenes from, 893
  basicity, 773–774
  chirality, 767
  classification, 765
  cyclic, preparation, 153, 1068, 1069, 1072
  enamine formation, 803
  Hinsberg test for, 790
  Hofmann degradation, 793–796
  hydrogen bonding, 768
  nitrogen inversion, 767
  nomenclature, 767–768
  nucleophilicity, 777–778
  oxidation, 792–793
  oxides (*see,* Amine oxides)
  physical properties, 768–770
  preparation
    alkylation of ammonia, 778
    Curtius rearrangement, 785–786
    Eschweiler-Clarke reaction, 783
    from carboxylic acids, 785–786
    Gabriel synthesis, 779–780
    Hofmann rearrangement, 785–786
    Leukart reaction, 784
    reduction
      of alkyl azides, 780
      of amides, 491–492, 784
      of imines, 782–783
      of nitriles, 781–782
      of nitro compounds, 781
      of oximes, 782
    reductive amination, 782–783
    Schmidt rearrangement, 785, 786–787
    summary, 787
  primary, **34**
  purification, 775
  reactions, 787–796
    amide formation, 787–790
    with alkyl halides, 616
    with carboxylic acid derivatives, 482–485
    with isocyanates, 801
    with nitrous acid, 790–792
    with sulfonyl chlorides, 789–790
  salts
    formation, 775
    solubility, 775
    sulfonamide, 790
  secondary, **34**
  spectroscopy
    infrared, 770–771
    mass, 772–773
    NMR, 771–772
  structure, 765–767
  tertiary, **34**
  transamination, 484

Amino, as prefix, 667, 767
L-Amino acid oxidase, 827
Amino acids, 452–453, 814–830
  acid-base properties, 818–820
    isoelectric point, 819
    p*K* values for, 817 *t*
  alkylation of amino malonic esters, 822–823
  amide formation, 828-829
  analyzers, 842
  commercial availability, 820–821
  DNP derivatives, 842
  esterification, 827–828
  importance, 814
  in peptides (*see,* Peptides)
  in proteins (*see,* Proteins)
  ninhydrin reaction for, 829–830
  nomenclature, 815-816
  phenylthiohydantoin formation, 844
  physical properties of, 817 *t*
  polymerization
    coupling agents, 836–839
    α-haloacyl halide method, 858
    into homopolymers, 833–834
    into peptides, 835–841
    protecting groups, 835–836, 840
    solid-phase technique, 839–840
  preparation, 821–825
    amination of α-halo acids, 821–822
    resolution of enantiomers, 825–827
    Schmidt rearrangement, 825
    Strecker synthesis, 824
  protecting groups for, 835–836, 840
  reactions, 827–830
  resolution, 825–827
    enzymatic, 827
  side-chain groups, 849-850
  specific rotations, 817 *t*
  stereochemistry, 817
  structure, 815
  zwitterionic form, 814, 816
1,2-Amino alcohols, 792
  preparation, 801
p-Aminoazobenzene, preparation, 988
o-Aminobenzaldehyde, in Friedländer synthesis, 1106–1107
Aminobenzene (*see,* Aniline)
p-Aminobenzenesulfonamide (*see,* Sulfanilamide)
p-Aminobenzenesulfonic acid (*see,* Sulfanilic acid)
m-Aminobenzoic acid, bromination, 972
o-Aminobenzoic acid (*see,* Anthranilic acid)
1-Amino-4-bromobutane, cyclization, 616
1-Amino-5-bromopentane, cyclization, 617
α-Aminobutyric acid, p*K*, 857
Amino group, protecting groups for, 835–836, 840
Aminomalonic esters, alkylation, 822–823
Aminomethane (*see,* Methylamine)
1-Aminonaphthalene, oxidation, 1050
2-Aminonaphthalene, 1052
α-Amino nitriles, Strecker synthesis, 824
Aminophenols
  oxidation, 1023
  preparation, 1010, 1023
2-Aminopyridine, 1102
Aminopyridines, Chichibabin synthesis, 1101–1102
Aminotoluenes (*see, p*-Toluidine)
3-Amino-2,4,6-tribromobenzoic acid, 972
Ammonia
  alkylation, 778
  geometry, 766
  liquid, 310
  p*K*'s 774
  reaction with alkyl halides, 778
Ammonium carboxylates, pyrolysis, 439–440
Ammonium ions, acidity, 774
Ammonium salts, quaternary (*see,* Quaternary ammonium compounds)
Amphetamine, 777
Amphoterism, 814, **818**
Amygdalin, 731
Amylopectin, 728–729
Amylose, 728–729
β-Amyrin, 1157
Anacardiol, 1032
Analysis
  combustion, 35–37
  determination of structure, 35–37, 169–170
  elemental
    qualitative 35-37
    quantitative, 35–37
  of geometric structure, 9–10
  spectroscopic (*see,* Infrared spectroscopy; Mass spectroscopy; Ultraviolet spectroscopy; Nuclear magnetic resonance spectroscopy)
Androgens, 647
Androsterone, 647
Anesthetics, 102, 103
Angle of rotation (α), **108**, 109
Angle strain, 23
Anhydrides
  carboxylic, 451, 455, 462, 472, 480, 483, 485
  phosphoric, 502
Aniline, 861, 965
  basicity, 967–969
  delocalization, 967–968
  diazotization, 977
  from reduction of nitrobenzene, 962
  geometry, 967
  ionization potential, 410 *t*
  orbital structure 967–968
  p*K*, 994
  properties, 966
Aniline black, 971, 1149
Anilines, in Skraup reaction, 1105–1106
Anilinium ion, acidity, 967
Anilinium ions, substituted, pK_a, 969
Anionic polymerization, 295-296
m-Anisidine, 965
Anisole, 861, 999
  Birch reduction, 1021
  boiling point, 1005
  electrophilic substitution, 876–877
  Friedel-Crafts acylation, 1015
  metalation, 1021
  nitration, 880, 1013
Anisotropic polarization, **108**
Annelation, Robinson, 757

Annulenes, 592, 1124–1125
  [4] annulene (*see*, Cyclobutadiene), 1124
  [6] annulene (*see*, Benzene), 1124
  [8] annulene (*see*, Cyclooctatetraene), 1124
  [10] annulene, 1124
  [12] annulene, 1124
  [14] annulene, 1124
Anomalous dispersion, **110**
Anomers, **698**
  D-glucose, 698–699
  interconversion of, 699–700
Anopheles, 103
Antarafacial addition, **1136**
Anthocyanidins, 1143–1144
Anthocyanins, 1143
Anthracene, 1038
Anthracenes
  in Diels-Alder reactions, 1056–1057
  lettering system, 1059
  numbering system, 1038
  preparation, 1054–1055
  reactions, 1055–1057
  structure and stability, 1053–1054
Anthranilic acid, 966
  biphenylene from, 987
  chlorination, 972
9-Anthranol, 1056
Anthraquinone, 934, 1054
9,10-Anthraquinone, 1022, 1055
Anthraquinone dyes, 1149
Anthraquinones, colored, 1145
Anthrone, 1056
Anti addition, 632
Antibodies, function, 856
Antibonding molecular orbital (*see*, Molecular orbitals, antibonding)
Anti conformation, **59**, 60–61, 101
Antifreeze, 666
Antimalarial agents, 806
Anti-Markovnikov addition, 284–285, 288
APC, 970
Aprotic solvents, 365
Ar, symbol for aryl group, 890
D-(−)-Arabinose, 697, 717
  chain extension of, 716, 720
Arbuzov-Michealis reaction, 504–505
Arenediazohydroxides, 978
Arenediazonium salts, 977–989
  acid-base equilibria, 978
  arylhydrazines from, 986
  as electrophilic reagents, 987
  biphenyls from, 984–986
  coupling with phenols, 989, 1010–1011
  fluoborates, 982–983
  haloarenes from, 980–982, 981–983
  hydrolysis, 979–980
  nitriles from, 982
  nitroarenes from, 983
  phenols from, 979–980
  properties, 977
  reactions, 979–989
  Sandmeyer reactions, 981–982
  tetrafluoroborates, 977
  thiophenols from, 981
Arenediazoxanthates, 981
Arenes
  nomenclature, 890–891
  oxidation
    to acids, 942–944
    to aldehydes and ketones, 934, 936–937
  preparation, 909–919
    Friedel-Crafts alkylation, 909–914
Arginine, 816
  physical properties, 817 *t*
  p*K* values, 817, 820
Aristotle, 1
Armstrong, Henry Edward, 570
Armstrong's centroid structure of benzene, 570
Aromatic compounds, **35**, 577
  history, 569
  molecular orbital theory, 574–578
  NMR spectroscopy, 579–580
  stability, 575–578
  symbolism of, 578
Aromatic hydrocarbons, 890, 909–924
Aromaticity, 1119–1125
  Hückel $4n + 2$ rule, 1119–1125
Arylazophenols
  preparation, 1010
  reduction, 1010
Arylcopper compounds (*see*, Organocopper compounds)
Aryl cyanides (*see*, Cyanobenzenes)
Aryl halides (*see*, Halobenzenes)
Aryllithium compounds (*see*, Organolithium compounds)
Asparagine, 816
  physical properties, 817 *t*
Aspartic acid, 816
  physical properties, 817 *t*
  p*K* values, 817, 819–820
  protecting groups for, 839
Astatine, 347
Asymmetric carbon atom, **105**
Asymmetric induction, **124**
Atomic orbitals, 15–28
  amplitude, 15
  combining of, 534–535
  electron density of, 17, 19
  electron density plots, 19
  energies, 17, 19, 20
  hybridization, 23–28
  perspective plots, 18
  quantum numbers, 16
  shells, 577
  sign of, **16**
  symbolic representation, 17
Atomist school, 1
Atropine, 1157
Automobile polish, 506
Autoxidation, **240**
Average bond energy, 92
  difference from bond dissociation energy, 92
Axial bonds, 612, 613
Aza-, as prefix, **1066**
Azabenzene (*see*, Pyridine)
3-Azafuran (*see*, Oxazole)
Azelaic acid, 736
Azeotropic distillation, 374–375
Azetidine, 1067

- Azetidines
  - preparation, 1069
  - ring opening, 1071
- Azide ion, 132
  - displacement on alkyl halides, 132, 797
  - reaction with acyl halides, 797
  - reaction with allyl bromide, 664
  - reaction with propyl bromide, 664
  - resonance structures for, 797
- Azides, preparation, 132, 664, 797
- Azimuthal or angular momentum quantum number, 16
- Azine dyes, 379, 1149–1150
- Aziridine, 1066, 1067
- Aziridines
  - preparation, 1068
  - ring opening, 1069
- Azobenzene, 963–965, 989
- Azo compounds, 963–965, 988–989
  - as dyes, 1148
  - *cis-trans* isomerism, 964
- Azo dyes, 981, 988–989, 1010, 1148
- Azoles
  - electrophilic substitution, 1094–1095
  - nomenclature, 1088
  - physical properties, 1089
  - preparation, 1091–1094
  - structure, 1089
- Azoxybenzene, 963–965
- Azulene, aromaticity, 1123

B

- Baeyer-Villiger oxidation, 392–393
- Bakelite, 1008
- Balsam oil, 644
- Bands
  - bending, 328
  - stretching, 328
- Barbituric acid, 1111
- Base
  - conjugate, 132–133
  - Lewis, **132**
  - strong, 132–133
  - weak, 132–133, 142
- Base peak, in mass spectroscopy, **407**
- Basicity (*see also*, Nucleophilic substitution), 133, **134**, 141
  - conjugation effects, 465
  - dissociation constant, (K_b), 773
  - hybrid orbitals and, 306, 464
  - in elimination reaction, 145–146
  - measure of, 132–133
  - of alcohols, 463, 464
  - of aldehydes and ketones, 463–464
  - of amines, 773–774
  - of aromatic amines, 967–969
  - of azoles, 1090
  - of carbonyl group, 349–350
  - of carbonyl oxygen, 463–464
  - of carboxylic acid derivatives, 463–467
  - of phenyl ethers, 1005
  - pK_b, of amines, 774
- Beckmann rearrangement, 789
- Beer's law, 598
- Beeswax, structure, 506
- Beilstein, 1175, 1180–1182
- Benzalacetone, 388
- Benzalacetophenone, 939, 958
- Benzal chloride, 902
- Benzaldehyde, 590, 862, 929
  - acetal formation, 707
  - in benzoin condensation, 675
  - ultraviolet spectrum, 596
- Benz[a]anthracene, 1178
- Benzene, 569–590
  - Armstrong's centroid formula, 570
  - aromaticity, 1120
  - Birch reduction, 922–924
  - bromination, 581–584
  - chlorination, 584
  - chloromethylation, 589–590, 904–905
  - commercial source, 581
  - derivatives (*see also,* Halobenzenes; Alkylbenzenes)
    - boiling point, 886 *t*
    - dipole moments, 870–872, 887
    - *o, m, p*-directors, 869
    - electrophilic aromatic substitution, 869–870
      - orientation, 873–879, 881–882
    - Friedel-Crafts alkylation, 911–913
    - hydrogenation, 623
    - ir spectroscopy, 868
    - melting point, 885 *t*
    - nitration, 869
      - partial rate factors, 879–880
    - NMR spectroscopy, 865–868
    - nomenclature, 861–864, 890–891
    - structural determination, 864–868
  - dipole moment, 871
  - electrophilic aromatic substitution, 581–590, 873
  - Friedel-Crafts acylation, 588–589
  - Friedel-Crafts alkylation, 904–914
  - Gatterman-Koch synthesis, 590
  - halogenation, 901–902
  - history, 569–571
  - hydrogenation, 572–573
  - ionization potential, 410 *t*
  - Ladenburg's prismane structure, 570
  - mercuration, 591
  - molecular orbital theory, 574–575
  - nitration, 586–587, 869
  - NMR spectrum, 579
  - physical properties, 569
  - π bonding, 571
  - pK_a, 896, 920
  - preparation, 580–581
  - protonation, 584–586
  - pyrolysis, 1038
  - resonance energy, 572–573
  - stability, 569
  - structure, 571
  - sulfonation, 587, 951
  - ultraviolet spectroscopy, 595, 599–600
- Benzenearsonic acid, 930

Benzenecarboxylic acid (*see*. Benzoic acid)
Benzenediazonium cation, 976
  orbital structure, 978
Benzenediazotate ion, *anti* and *syn*, 978
1,2-Benzenedicarboxylic acid (*see*, Phthalic acid)
Benzene-d_6, 585
Benzene hexachlorides, 901–902
Benzene radical anion, resonance stabilization, 922
Benzene ring, symbolism for, 578
Benzenesulfenic acid, 957
Benzenesulfonic acid, 587
Benzenesulfonyl chloride, 231, 789, 954
Benzhydryl acetate, 891
Benzidine, 1038
Benzidine rearrangement, 964
  as sigmatropic rearrangement, 1137
  biphenyls from, 1038
Benzil, 683
Benzilic acid, 683
Benzilic acid rearrangement, 683
Benzofuran
  electrophilic substitution, 1086–1087
  numbering system, 1083
  preparation, 1085–1086
Benzofuran-2-carboxylic acid, 1086
Benzoic acid, 434, 862, 929
  acidity, 944
  Birch reduction, 950
  hydrogenation of, 623
  substituted, acidity and Hammett relation, 944–948, 948 *t*
Benzoic anhydride, 485
Benzoin, 675
Benzoin condensation, 675–676
Benzol, 569
Benzonitrile, 931
  dipole moment, 994
Benzonitrile oxide, 1092
Benzophenone, 930
  dipole moment, 1120
Benzopurpurin 4B, 1148
Benzopyrazine, 1111
Benzo[a]pyrene, 39
p-Benzoquinone, 971, 1022, 1023
  in naphthalene preparation, 1046
  in photography, 1027
  oxime, 1012
  quinhydrone complex, 1028
o-Benzoquinone, 1022, 1024
Benzothiophene
  electrophilic substitution, 1086–1087
  numbering system, 1083
Benzotrichloride, 902
N-Benzoylalanine, 826
Benzoyl chloride, 826
β-Benzoylpropionic acid, 932
N-Benzoylvaline, 828
Benzyl alcohol, 209, 828
Benzylamine, 782
N-Benzylaniline, 969
Benzyl anion, resonance stabilization, 921
Benzyl cation, 920
  stability, 906–907
Benzyl chloride, 590
  enthalpy of ionization, 907
  nitration, 880
  preparation, 902–903, 905
  reaction with sodium cyanide, 143
Benzyl chloroformate, 836
Benzyl cyanide, preparation, 143
Benzylic alcohols, 915
  conversion into halides, 904
  hydrogenolysis, 916
Benzylic halides
  hydrolysis, 937
  preparation, 902–905
  reactions, 906–908
2,4-O-Benzylidine-D-glucose, 733
Benzylmagnesium chloride, 908
Benzyloxycarbonyl (cbz) group, as protecting group, 835–836
Benzyl radical, conjugation in, 902–903
Benzyne, 896–897, 987, 1057
  electronic structure, 897
Beryllium carbide, hydrolysis, 71
Beryllium hydride, bonding in, 23, 24, 25
Betaines, 389
Biallyl, 533
Biaryls (*see*, Biphenyls)
Bibenzyl, 908, 922
Bicyclic compounds, 639–643
  cis and *trans* fusion, 640
  IUPAC nomenclature, 639–640
  Karplus curve, 658
  preparation, 641–643
Bicyclo, as prefix, 639
Bicyclo[4.4.0]decane (*see*, Decalin)
Bicyclo[4.1.0]heptane, 642
Bicyclo[2.2.1]heptane (norbornane), 640
Bicyclo[3.2.1]hept-6-ene, 1154
Bicyclo[2.1.1]hexane, 1156
Bicyclo[2.2.2]octan-2-one, 656
Bicyclo[4.4.1]undeca-1,3,5,7,9-pentaene, aromaticity, 1122
Bifunctional compounds (*see*, Difunctional compounds)
Bijvoet, J. M., 719
Bile salts, 646–647
Bimolecular displacement reaction (*see*, Nucleophilic substitution)
Bimolecular homolytic substitution, 145
Bimolecular mechanism, **128**
Binapacryl, 1032
Biodegradable soaps, 431
Biosynthesis, 1156–1167
  stereospecificity, 1167
Biphenylene, preparation, 987
Biphenyls
  nomenclature, 1037
  optically active, 1040–1041
  preparation, 1038–1039
    from diazonium salts, 984–986
    Gomberg-Bachmann reaction, 985–986
    Ullmann reaction, 900
  reactions, 1041
  stereoscopic figure, 1039
  structure, 1039–1040

Birch reduction, 922–924
  of naphthalene, 1050
  phenyl ethers, 1021
γ-Bisabolene, 1157
Bischler-Napieralski synthesis, 1107
Bis-β-chloroethyl sulfide (mustard gas), 249
Bis-chloroethyl ether, 905, 927
p-Bis-(dimethylamino)benzene, oxidation, 971
p,p'-Bis-(dimethylamino)benzophenone, 973
Bis-2-ethylhexyl phthalate, 295
2,2-Bis-hydroxymethyl-1,3-propanediol (*see*, Pentaerythritol)
Bis-β-methoxyether ether (diglyme), 236
Bis-pyridinechromium(VI) oxide, 358
Bis-triphenylmethyl peroxide, 905
Bisphenol A, 1035
Bisulfate ion, 14, 136
Bisulfite ion, 137
Blasting powder, 728
Bleach, 144
Boat conformation, 621–622
Bohr model of the atom, 15
Boiling point (*see also* specific compounds), **54**
  alcohols versus alkanes, 212
  alcohols versus alkyl chlorides, 211–213
  chain branching and, 67, 99
  chain length and, 54–56, 98–99
  dipole-dipole interaction, 211–213
  hydrogen bonding, intermolecular, 213, 457
  Van der Waals forces and, 98–99
Boltzmann distribution function, 44
Bond, **20–28**
Bond angle, and hybridization, 96
Bond dissociation energy (for specific compounds, see Appendix II of the text), **73**, 74–75
  difference from average bond energy, 92
Bonding molecular orbital (*see*, Molecular orbitals, bonding)
Bond order, 11
Bond rotation
  barriers, 57–62, 66–67
    in alkyl halides, 101 *t*
Bonds
  bent, 140, 251–252, 608
  covalent (*see*, Covalent bond)
  dative, **8**
  from overlap of orbitals, 20–28
  hybrid orbitals and, 23–28
  ionic (*see*, Ionic bonding)
  peptide (*see*, Peptide bonds)
  π (*see*, π bonding)
  polarity, 97–98
  σ (*see*, σ bonds)
  stretching of, 73, 268–269, 327–328
  vibration, 268, 327–329
Bond strengths (see Appendix III of the text)
Borane, 157, 286
Boron-oxygen bond, 287
Boron trifluoride, 293
  in acylations, 1016
Boron trifluoride etherate, 293, 1054
Bouveault-Blanc reaction, 491
Bradykinin
  amino acid analysis, 842, 843
  sequence of, 831
Bromination (*see also*, Halogenation)
  Hell-Volhard-Zelinsky reaction, 437–438, 470
  of alkanes, 85–87
  of alkenes, 581–582
  of allylic systems, 535–536
  of carboxylic acids, 437–438, 470
  of cyclohexene, 630
  of isobutane, 87
  of methane, 85
  of naphthalene, 1047
  of phenyl ethers, 1014–1015
  of propane, 85–86
  of toluene, 903
  of 2,2,3-trimethylbutane, 87
Bromine
  abundance of isotopes, 409 *t*
  addition to dienes, 543–544
  addition to double bonds, 536, 581–582
  reactivity, compared to chlorine, 904
Bromine water, 717
α-Bromoacyl bromides, 438, 470
N-Bromoamides, 494–495
p-Bromoanisole, preparation, 1014–1015
p-Bromobenzaldehyde, 936
Bromobenzene, 582
  aryllithium formation, 899
  dipole moment, 871
  Grignard formation, 898–899
  nitration, 880, 885
  transmetallation, 899
Bromobenzoic acids, nitration, 881, 882
4-Bromobiphenyl, preparation, 1041
Bromochlorobenzene, 885, 982
  Grignard formation, 899
1-Bromo-3-chloropropane, 637
  NMR spectrum, 189
Bromoethers, from bromination of alkenes, 281–282
o-Bromofluorobenzene, 983
Bromoform, addition to alkenes, 631
Bromoformyl, as prefix, 456
1-Bromo-1-hexene, 319
2-Bromo-1-hexene, 314
4(5)-Bromoimidazole, 1095
Bromomesitylene, 892
1-Bromonaphthalene, 1047
p-Bromonitrobenzene, 885
Bromonium ions, 280–281
2-Bromopentane, 279
3-Bromopentane, 279
9-Bromophenanthrene, 1057
p-Bromophenol, 884
1-Bromopropane, mass spectrum, 409
1-Bromopropene, 315
α-Bromopropionic acid, amination of, 882
1-Bromopyrene, 1058
5-Bromoquinoline, 1108
8-Bromoquinoline, 1108
N-Bromosuccinimide, 536

Bromotoluene, preparation, 893
Brucine, 777, 806, 826
Bucherer reaction, 1052–1053
Buna S (synthetic rubber), 547
1,2-Butadiene (methylallene), 545
1,3-Butadiene, 275, 788
  addition of bromine, 543–544
  Diels-Alder reactions of, 624, 740
  electronic states of, 595
  heat of hydrogenation, 563
  industrial preparation, 547
  physical properties, 547
  π bonding in, 540–542
  polymerization of, 547, 562
  stability, 540–542
  structure, 540–542
  ultraviolet spectroscopy, 594
Butadienes, alkyl-substituted, ultraviolet absorption, 600–602
Butane, 53
  chlorination, 119–120
  combustion, 88–89
  component of crude oil, 70
  conformations, 56, 60, 106–107
    stereoscopic figure, 56, 60
  disproportionation of, 90
  hydrogenation, 89–90
  isomers, 62–63
  physical properties, 55 *t*
  pK_a, 775
1,4-Butanediol, 653
2,3-Butanediol, 668
Butanoic acid (*see*, Butyric acid)
1-Butanol, infrared spectrum, 338
2-Butanol, infrared spectrum, 339
1-Butanol-1-d, optical activity, 250
2-Butanone
  mass spectrum, 407
  physical properties, 352 *t*
1-Butene
  heat of hydrogenation, 563
  physical properties, 259 *t*
cis-2-Butene
  hydroxylation of, 668
  physical properties, 259 *t*
  steric hindrance in, 264–265
trans-2-Butene
  hydroxylation of, 668
  physical properties, 259 *t*
  steric hindrance in, 264–265
3-Butenoic acid, 561
t-Butoxycarbonyl (boc) group, as protecting group, 836
Butter Yellow, 988
t-Butyl acetate, 470, 480
  hydrolysis of, 474–475
n-Butyl alcohol, 225
  physical properties 211 *t*
  reaction with sulfuric acid, 228
sec-Butyl alcohol, physical properties, 211 *t*
t-Butyl alcohol
  infrared spectrum, 339
  physical properties, 211 *t*
n-Butylamine
  physical properties, 770 *t*
  preparation, 779, 781
  reaction with nitrous acid, 791
t-Butylamine
  mass spectrum, 773
  physical properties, 770 *t*
  pK_b, 774
t-Butylammonium ion, 774
p-*t*-Butylaniline, 961
n-Butyl azide, preparation, 797
t-Butyl azidoformate, 836
t-Butylbenzene
  nitration, 880
  oxidation, 920
  preparation, 909, 911
n-Butyl bromide
  preparation, 225
  reaction
    with ammonia, 779
    with azide ion, 797
    with lithium, 159
    with sodium methoxide, 143
t-Butyl bromide
  S_N1 reaction, 147–148
  Solvolysis, 148, 151
t-Butyl cation, 149, 474
t-Butyl chloride, 278, 907, 909
  in chlorination of isobutane, 82
  reaction
    with hydroxide ion, 51–52
    with magnesium, 158
t-Butyl chloroformate, 836
n-Butyl chlorosulfite, 230
trans-4-*t*-Butylcyclohexanecarboxylic acid, methyl ester, synthesis, 1169
3-*t*-Butylcyclohexanol, *cis*- and *trans*-isomers, acetylation of, 628
4-*t*-Butylcyclohexyl toluenesulfonate, conformational analysis, 628–629
t-Butyldimethylamine, 783
n-Butyl ether, preparation, 228
t-Butyl ethers, as protecting groups, 527
n-Butyl isocyanate, 801
t-Butyl isopropyl ether, preparation, 238
t-Butyl lithioacetate, 470
n-Butyllithium, 775
  metal exchange reaction, 162
  physical properties, 158 *t*
  preparation, 159
t-Butyllithium, 383
  reaction with ethylene, 295–296
t-Butylmagesium chloride, preparation, 158
s-Butyl radical, 64
t-Butyl radical, 64
2-Butyn-1,4-diol, 653
Butyne, physical properties, 306 *t*
Butyraldehyde, 232
  mass spectrum, 416–417
  McLafferty rearrangement, 416
  physical properties, 352 *t*
Butyric acid, 424
  chlorination, 437

- Butyric acid [*cont.*]
  - natural occurrence, 446
  - physical properties, 426 *t*
  - reaction with ammonia, 439
- γ-Butyrolactone, 685
- Butyronitrile, reduction, 781

C

- Cadalene, 1061
- β-Cadinene, 644, 1061
- Caffeine, 1110
- Calcium carbide, 307
- Calculi, 737
- Camphene, 645
- Camphene hydrochloride, rearrangement, 645
- Camphor, 40, 639
  - infrared spectroscopy, 656
- Cane sugar, 681
- Cannizzaro, Stanislao, 3
- Cannizzaro reaction, 396–397
  - crossed, 396–397
- Capric acid (*see also,* Decanoic acid), 424
  - physical properties, 426 *t*
- Caproic acid (*see also,* Hexanoic acid), 424
  - natural occurrence, 446
  - physical properties, 426 *t*
- Caprolactam, 789
- Caprylic acid, 424
  - physical properties, 426 *t*
- Carbamates, in pesticides, 103
- Carbamic acids, **495**, 786, 801, 836
- Carbamoyl-, as prefix, 456, 667
- Carbanions (*see also* individual anions)
  - aromatic, 1121, 1122
  - from terminal alkynes, 306
  - in polymerization of alkenes, 295–296
  - stability, 306
- Carbazole, numbering system, 1083
- Carbenes, 631
- Carbenium ion, **149**
- Carbenoid, 632
- Carbinol (*see,* Methyl alcohol)
- Carbinol system of nomenclature, 209
- Carbocation, **149**
- Carbocyclic compounds, 387
- Carbocyclic rings, 606
- Carbohydrates, 693–732
  - classification, 693–695
  - D,L notation, 695
  - definition, **693**
  - in nature, 693
  - stereochemistry, 693
- Carbon
  - abundance of isotopes, 409 *t*
  - catenation of, 29
- Carbonate ion
  - resonance structures, 11
- Carbonates, preparation, 488
- Carbonation, of organometallic reagents, 434
- Carbon branching
  - in elimination reactions, 146
  - in nucleophilic substitution reactions, 138–140
- Carbon-carbon bond-forming reactions (*see also* Appendix VIII in text)
  - summary, 516–518
- Carbon-carbon bond lengths
  - of alkanes, 54
  - of alkenes, 251
  - of alkynes, 301
- Carbon-carbon bond rotation
  - in alkanes, 57–62
  - in alkenes, 255–256
- Carbon-carbon double bond
  - barriers to rotation, 253–256
  - bent bond model, 251–252
  - cleavage of, 671–672
  - conjugated (*see,* Dienes)
  - cumulated, 545
  - electron density, 253–255
  - in allene, 545
  - inductive effects, 429
  - in ethylene, 607, 608
  - in nmr, 261
  - length, 252
  - Lewis bases, 278
  - π-bond model, 252–254
  - reactivity, 251, 276–276
  - rearrangement in unsaturated carbonyl compounds, 550–552
  - strength, 275–276
  - test for, 280
- Carbon-carbon single bond
  - cleavage, 671, 681
  - in cyclobutane, 610
  - in cyclopropane, 608, 633
  - length, 29
- Carbon-carbon triple bond
  - electron density, 302
  - inductive effects, 429
  - method for location, 317
  - orbitals, 301–302
  - test for, 307
- Carbon chain lengthening
  - of aldoses, 714–717
  - of alkynes, 309–310
- Carbon chain shortening (*see also,* Degradation reactions)
  - in amides, 495
  - in carboxylic acids, 495
  - of aldoses, 717–718
- Carbon-deuterium bond, in elimination reaction, 268–269
- Carbon dioxide, in Kolbe synthesis, 1008–1009
- Carbon disulfide, 497, 837
- Carbon-halogen bond
  - in acyl halides, 453, 510
  - in alkyl halides, 96–98
  - in vinyl halides, 320–321
- Carbon-halogen bond length
  - in acyl halides, 453, 510
  - in methyl halides, 97 *t*
- Carbon-hydrogen bond
  - in alkanes, 75
  - in cyclopropane, 608–609
  - in elimination reaction, 268–269
  - in methane, 73, 79

Carbon-hydrogen bond lengths
  of alkanes, 54
  of alkenes, 251
  of alkynes, 301
  s-character and, 301
Carbonic acid, 738
-carbonitrile, as suffix, 667
Carbonium ions (*see also* specific cations), 147–151
  aromatic, 1120, 1121
  conjugated (*see*, Allyl cation)
  dispersal of charge, 150–151
  from alcohols, 225–229
  from alkyl halides, 147–150, 529
  from alkynes, 314
  in fragmentation, 412–414
  in S_N2 reaction, 147–151
  orbital interactions, 150–151
  polymerization, 292–293
  primary, **149**
  reactions of, 583
  rearrangement of, 226–228, 1137
  relative stabilities, 150
  secondary, **149**
  stability of, 150, 314
  structure, **12**, 149–151
  tertiary, **149**
  versus radical cations, 404
Carbonium oxide, 349
Carbon-metal bonds
  covalency of, 156–157
  in organometallic compounds, 156, 162
  ionic character, 156
Carbon monoxide, poisoning, 1077
Carbon-nitrogen bond
  in amides, 452
  in methyleneimine, 13
  in peptide bonds, 831
Carbon-oxygen bond
  in aldehydes and ketones, 348–350
  in carbonate ion, 11
  in carboxylate ion, 428
  in protonated formaldehyde, 12
Carbon-phosphorus bond, 389
Carbon tetrachloride, 96
  boiling point, 77
  in chlorination of methane, 77
  solvent for infrared studies, 338
  uses of, 102
-carbonyl chloride, as suffix, 667
Carbonyl compounds (*see also,* Aldehydes; Ketones; Carboxylic acids; Esters; Amides)
  aromatic, 929–950
  nomenclature, 929–930
Carbonyl group, **32**, 34
  as a *meta* director, 938
  basicity of, 349–350, 463–467
  bonding in, 348–349
  dipolar character, 372
  geometry, 348
  in aldehydes and ketones, 348–350
  in carboxylic acids, 438
  infrared spectroscopy, 355–357, 655–657
Carbonyl group [*cont.*]
  in NMR spectroscopy, 354 355
  lone-pair (n) system, 597
  π system, 597
  protonated, 463–467
  resonance structures of, 369–370
  ultraviolet spectroscopy, 596–599
Carbonyl hydrates, 368–372
-carboxaldehyde, as suffix, **351**, 667
-carboxamide, as suffix, 455, 667
Carboxy-, as prefix, 667
N-Carboxyanhydrides (NCA), 838
Carboxy group (*see also,* Carboxylic acids), 33, 34, **423**
  bonding in, 423
  geometry of, 423
  inductive effect, 738
  in nomenclature, 425
  nucleophilic addition to, 438–445
  protecting groups for, 835
Carboxylate ion, resonance stabilization, 534, 535
Carboxylate salts, reactions, 485
Carboxyl group (*see*, Carboxy group)
-carboxylic acid, as suffix, 667
Carboxylic acids, 32, 34, 423–446
  acidity, 426–432
    inductive effects in, 428–429
  aromatic, 941–950
    nomenclature, 929
    preparation, 920, 941–944
    preparation from methyl ketones, 939
    reactions, 949–950
  biosynthesis of, 424
  carbon chain shortening, 445–446
  conversion
    into acyl chlorides, 444–445
    into alkyl halides, 445–446
    into amides, 439–440
    into amines, 785–786
    into esters, 436–437, 441–444
    into salts, 430, 436
  degradation of, 445
    Hunsdiecker reaction, 445
    Kochi reaction, 446
  dimerization of, 423
  esterification, 436–437, 441–444
  functional derivatives, 451–498
    acid anhydrides (*see*, Acid anhydrides)
    acyl halides (*see*, Acyl halides)
    amides (*see*, Amides, carboxylic acid)
    basicity, 463–467
    esters (*see*, Esters, carboxylic acid)
    hydrolysis of, 472–479
    infrared spectroscopy, 459–460
    nitriles (*see*, Nitriles)
    NMR spectroscopy, 458–459
    nomenclature, 454–456
    nucleophilic substitution, 471–472
    physical properties, 456–458
    preparation of, summary, 460–462
    reactions, 463–498
      with alcohols, 480–482
      with organometallic compounds, 485–489

- Carboxylic acids, functional derivatives [*cont.*]
    - solubility, 458
    - structure, 451–454
    - ultraviolet spectroscopy, 602
    - unsaturated (*see,* Unsaturated carboxylic acids and derivatives)
  - halogenation, 437
    - Hell-Volhard-Zelinsky reaction, 437–438, 470
  - Hofmann rearrangement, 785–786
  - hydrogen bonding in, 423, 457
  - hydroxy, 681–687
  - infrared spectroscopy, 433
  - ionization, 426–429
  - natural occurrence of, 446
  - NMR spectroscopy, 432, 458
  - nomenclature, 423–425
  - physical properties, 425–426, 456–458
  - preparation, 433–436
    - carbonation of organometallic reagents, 434
    - from malonic esters, 752
    - hydrolysis of nitriles, 433–434
    - oxidation of alcohols, 233–234, 357–358
    - oxidation of aldehydes and ketones, 368, 391–394, 435–436
    - oxidation of alkenes, 290, 292
    - oxidation of alkynes, 317
    - oxidation of primary alcohols, 435
  - reactions, 436–446
    - with alkyllithium reagents, 441
    - with ammonia or amines, 439–440
    - with bases, 436
    - with diazomethane, 436–437
    - with phosphorus pentachloride, 444
    - with phosphorus tribromide, 445
    - with thionyl chloride, 444–445
  - reduction, 440–441
    - by diborane, 440–441
    - by lithium aluminum hydride, 440
  - resonance structures of, 535
  - salts, 430, 436, 439
    - as soaps, 430–432
    - nomenclature, 430
    - reactions, 485
  - solubility, 430
    - salts, 430
  - structure, 423
  - ultraviolet spectroscopy, 602
  - unsaturated (*see,* Unsaturated carboxylic acids and derivatives)
- Carboxypeptidase, 844–845, 856
- Cardiac glycosides, 648
- Carminic acid, 1145
- Carnuba wax, 506
- β-Carotene, 1144–1145
  - visible light absorption, 596, 599–600
- Carotenoids, 1144–1145
- Carson, Rachel, 103
- Carvacrol, 1035
- Caryophyllene, 639
- Casein, 856
- Castor oil, 563
- Catalysts, poisoned, 277, 311, 489
- Catalytic hydrogenation (*see,* Hydrogenation)
- Catalytic reforming, in cracking of crude oil, 77
- Cat cracker, in pyrolysis of crude oil, 77
- Catechol, 999, 1024
- Cationic polymerization, 292–293
- Cedar oil, 644
- Celcon, 377
- Cellobionic acid, 724
- Cellobiose, 724
  - in cellulose, 727
  - oxidation, 724
  - stereoscopic figure, 724
- Cellulases, 728
- Celluloid, 728
- Cellulose
  - acetylation, 728
  - nitrated, 728
  - structure, 727–728
- Cellulose triacetate, 728
- Cellulose trinitrate, 728
- Cetyl palmitate, 506
- Chain initiating step, **78**
- Chain propagating step, **78**, 284
- Chain reaction, **78**
  - allylic halogenation, 536–537
  - chlorination of methane, 78–82
  - heat of reaction, 80–81
  - initiators of, 84
  - pyrolysis of acetone, 563
  - radical addition to alkenes, 284–286
- Chain terminating step, **78**
- Chair conformation, of cyclohexane, 611
- Chamomile oil, 644
- Charge-transfer complexes, 1028–1029
- Chelation, **1012**
- Chemical Abstracts, 66, 1177–1180
  - carboxylic acids nomenclature in, 424–425
  - organometallic nomenclature in, 157
- Chemical shift, of functional groups (*see* Appendix V of the text)
- Chemical shifts, in NMR spectroscopy, 174–178
- Chenodesoxycholic acid, 646
- Chichibabin reaction, 1101–1102, 1108
- Chirality, **105**
- Chloral, 370
- Chloral hydrate, 370
- Chloranil, 1045–1046
  - complexed with hexamethylbenzene, 1029
  - preparation, 1024
- Chlorinated hydrocarbons, uses of, 102–104
- Chlorination
  - of alkanes, 77–84
  - of benzene, 584
  - of carboxylic acids, 437
  - of cyclohexane, 83, 84
  - of cyclopropanes, 634
  - of ethane, 82
  - of isobutane, 82–83, 87
  - of methane, 77–82
    - stereoscopic figure, 79, 81
  - of neopentane, 83
  - of propane, 82
  - of toluene, 902–903
  - relative reactivity of hydrocarbons in, 82–83

- Chlorine
  - abundance of isotopes, 409 *t*
  - excitation of, 603
  - industrial production, 102
  - reactivity, compared to bromine, 904
- Chloro-, as prefix, 667
- Chloroacetaldehyde, 370
  - resonance structures of, 370
- Chloroacetic acid, 737
  - inductive effects in, 428
  - pK_a, 429 *t*
- Chloroacetyl hydrazide, 484
- *cis*-3-Chloroacrylonitrile, NMR spectrum, 263
- *trans*-3-Chloroacrylonitrile, NMR spectrum, 263
- 1-Chloro alcohols, 383–384
- Chloroarenes, from arenediazonium salts, 980
- Chlorobenzene
  - aryllithium formation, 899
  - bromination, 885
  - chlorination, 888
  - dipole moment, 870, 871
  - Grignard formation, 898–899
  - nitration, 880
  - phenol from, 895
  - reaction with sodium hydroxide, 927
  - resonance structures, 870
- 2-Chloro-1,3-butadiene
  - polymerization of, 547
  - preparation of, 547
- 1-Chlorobutane-1-d, 900
- Chlorobutyric acids, acidity of, 429
- Chlorocarbene, 632
- Chlorocyclopropane, 634
- Chloroethanol, inductive effects in, 428
- Chloroform, 29
  - acidity, 631
  - boiling point, 77
  - in chlorination of methane, 77
  - NMR spectrum, 202
  - Reimer-Tiemann reaction, 1009–1010
  - stability of, 99
- Chloroformyl-, as prefix, 456, 667
- Chlorofuran, physical properties, 1075
- Chlorohydrins, **282**
- Chlorohydroquinone, 1029
- Chloromethylation, of benzene, 589–590, 905
- Chloromethyl ketones, 798
- Chloronitrobenzene
  - dipole moment, 871
  - hydrolysis, 1012
- 2-Chlorooctane, 160
- *m*-Chloroperoxybenzoic acid, 649
- *m*-Chlorophenylmagnesium bromide, 899
- Chlorophyll, 1146, 1158
- Chlorophyll A, 1146
- Chloroprene
  - polymerization, 547
  - preparation, 547
- 1-Chloropropane, NMR spectrum, 171, 190
- 2-Chloropropane
  - mass spectrum, 409
  - NMR spectrum, 172, 190
- 3-Chloropropanoic acid, 435
- Chlorospiropentane, 93
- Chlorosulfonic acid, 954
- 2-Chlorothiophene, physical properties, 1075
- Chlorotoluene, 942, 982
  - dipole moment, 871
  - nitration, 880, 881
- α-Chlorotoluene (*see*, Benzyl chloride)
- Chlorotrifluoromethane (Freon 13), 102
- Chlorotrimethylsilane, 675
- 7-Cholestanone, bromination, 663
- Cholesterol, 40, 481, 646, 1157
  - biosynthesis, 1158–1166
- Cholesteryl acetate, preparation, 481
- Cholic acid, 646
- Chromate, oxidation, of naphthalene, 1049
- Chromic acid, oxidation, of alcohols, 232–233
- Chromium trioxide, 232
  - oxidations, 358, 1099
- Chromophores, 1148
- Chromyl chloride, 937
- Chrysene, 1058
  - numbering system, 1058
- Chrysin, 1157
- Chugaev reaction, 497
- Chymotrypsin, 476, 845
- Chymotrypsinogen, 847
- Cinnamic acid, 637, 930
  - photochemical cycloaddition, 1134
- Cinnamyl bromide, 891
- Cinnoline, 1112
- *Cis* addition, 632
- *Cis* and *trans* isomers, 257–258
- *Cis*-, as prefix, **257**
- Citric acid, 682
- Citronellal, 644
- Cladinose, 732
- Claisen condensation, 470, 741–745
  - cyclic (*see*, Dieckmann condensation)
  - in biological systems, 745
  - mixed, 743–745
    - intramolecular, 744
  - reverse, 758–759
- Claisen rearrangement
  - aliphatic allyl ethers, 1020
  - as sigmatropic rearrangement, 1136
  - phenyl allyl ethers, 1019–1020
- Cleavage
  - of alkenes, 671–672
  - of diols, 671–672
  - of halogenated ketones, 367–368
  - of α-hydroxy aldehydes and ketones, 681
  - of ketones, 393–394
- Clemmensen reduction, 398
  - of aromatic carbonyls, 915
- Cloves, oil of, 639
- CMR (*see*, Nuclear magnetic resonance, carbon)
- Coal tar, 1044
- Cocaine, 41, 806
- Cochineal, 1145
- Codeine, 805
- Codeine hydrobromide, 805
  - stereoscopic figure, 805
- Coenzyme A (CoA), 745
- Coenzyme Q, 1027
- Collagen, 847, 856

Collidine, 1097
Color (*see also,* Dyes, Pigments), 596
  and wavelength, 1142–1143
Combination band, 329
Combustion
  of alkanes, 87–89
  of butane, 88–89
  of gasoline, 88
  of isobutane, 88–89
  of methane, 35
Combustion analysis, 35–37
Condensation reactions, **378**
  acyloin, 675
  aldol, 385–388
  benzoin, 675–676
  Dieckmann, 622, 638
Condensed formulas, **28–29**
Configuration, absolute, 111
Configurational isomers, **256**
  cis-trans nomenclature, 256–257
  of alkenes, 264–266
Conformational isomers, **67**, **256**
Conformations, **58**, **67**
  anti, 101
  gauche, 101
Conformers, **67**
Coniine, 807
Conjugate acid, 132–133
Conjugate base, 132–133
Conjugated systems, π bonding in, 428
Conjugation, 529–565
  allylic systems, 529–540
  crossed, **560**
  dienes, 540–550
  linear, **560**
  π-bonding, 537–540
  polyenes, 564–565
  unsaturated carbonyl compounds, 550–565
Conrotatory motion, **1126**
Contraceptives, 647
Coordinate covalence bond, **8**
Copaene, 644
Cope reaction, 793
Cope rearrangement, 1020
  as sigmatropic rearrangement, 1136
Copper-chromium oxide, as catalyst, 277
Copper phthalocyanine, 1150
Corey-Pauling-Koltun molecular models, 30–31
Coronene, 577, 1125
  numbering system, 1058
Cosmic rays, 325
Cotton, cellulose in, 727
Cottonseed oil, 508
Coulomb's law, 212–213, **213–214**
Coumarillic acid, 1086
Coumarin, Perkin synthesis of, 1085
Couper, Archibald Scott, 3
Coupling constant
  and dihedral angle of vicinal protons, 658
  for vinyl protons, 261 *t*
Coupling reactions, amino acid, 836–839
Covalent bond, **6**, 21
Cracking of alkanes (*see,* Pyrolysis of alkanes)
Cresols, 953
  properties, 1002
  Reimer-Tiemann reaction in, 1010
Crotonaldehyde, 551
Crotyl bromide, 543, 544
Crown ethers, 654–655
  preparation, 655–656
  solvation of ions, 654
18-Crown-6, 654
Crude oil, 70
  composition of, 70
  from manure, 70–71
  production, 70
  pyrolysis (cracking) of, 77
Cryptopyrrole, 1077
Cubane, 1167
Cumene, 861, 890
  oxidation to phenol, 1001–1002
  preparation, 1001
Cumene hydroperoxide, 1001–1002
Cumenyl, as prefix, **891**
Cuprates
  preparation, 165
  structure, 165
  uses, 166
Cupric acetate, as oxidant, 746
Cupric chloride, 982
Cupric ion, in Fehling's test, 710
Cuprous cyanide, 982
Cuprous halides, 982
Curtin, David Y., 498
Curtius rearrangement, 785, 786
Curvularin, 1157
Cyanate ion, displacement on alkyl halides, 801
Cyanide ion
  addition to α,β-unsaturated esters, 737
  in benzoin condensation, 675–676
  reaction with methyl iodide, 137–138
Cyanidin, 1144
Cyano-, as prefix, 456, 667
Cyanoacetic acid, 737
Cyanoalcohols (*see,* Cyanohydrins)
Cyanobenzenes, preparation, 942
Cyano compounds (*see,* Nitriles)
Cyanogen bromide, cleavage of polypeptides, 845
Cyanohydrins, 383–385
  compared to 1-chloro alcohols, 384
  hydrolysis of, 682–683
  in Kiliani-Fischer synthesis, 715–717
  preparation, 682
Cyclic aliphatic hydrocarbons, dehydrogenation, 580–581
Cyclic alkenes, oxidation, 737–738
Cyclic anhydrides, 462
  preparation, 462, 739–740
Cyclic bromonium ion, 280, 543
Cyclic compounds (*see also,* Cycloalkanes; Heterocyclic compounds; Polycyclic aromatic hydrocarbons; and specific compounds), 606–659
  aromaticity, 1119–1125
  infrared spectroscopy, 655–657
  NMR spectroscopy, 657–659

Cyclic diketones, keto-enol equilibria, 750
Cyclic ethers, 648–655
  epoxides, 648–652
  furans, 653
  nomenclature, 648, 653, 654
  oxetanes, 653
  preparation, 674
Cyclic halonium ions, 280–281
Cyclic imides, preparation, 740–741
Cyclic ketones, oxidation, 737–738
Cyclization
  aliphatic hydrocarbons, 580–581
  conrotatory motion, 1126
  Dieckmann condensation, 622, 638
  disrotatory motion, 1126
  intramolecular aldol condensation, 617–618
  of ω-bromoalkylamines, 616
  of diols, 672–673, 674
  of hexatriene, 1126–1129
  of octatetraene, 1129–1131
  rate, and ring size, 616–617
Cyclo-, as prefix, **68**
Cycloaddition reactions, 1070, 1133–1136
  antarafacial addition, **1136**
  suprafacial addition, **1136**
Cycloalkanes (*see also,* Alkanes, cyclic; Bicyclic compounds), **32**, 68–69
  conformations, 608–616
  heats of formation, 608
  large ring, 615–616
    preparation, 638
  nomenclature, 68–69, 257
  physical properties, 68
  preparation, 617–618
  ring strain in, 607–608
  symbols for, 69
Cycloalkenes
  reaction with carbenes, 641–642
  stability, 638
Cycloalkyl radical, in nomenclature, 69
Cycloalkynes, stability, 638
Cyclobutadiene, reactivity, 1120
Cyclobutane
  hydrogenation, 637
  physical properties, 68 *t*
  preparation, 635, 636
  reactions, 637
  ring strain in, 608, 610
  stereoscopic figure, 610
  structure, 610
Cyclobutanol, 395, 636
Cyclobutanone, 636
Cyclobutenes, ring opening, 1131–1132
Cyclodecane, ring strain in, 608
Cyclodecapentaene, 1122
Cyclododecahexaene, 1124
Cyclododecane, ring strain in, 608
trans,trans,cis-1,5,9-Cyclododecatriene, synthesis, 638
1,3-Cycloheptadiene, 1154
Cycloheptane
  conformations of, 615
  physical properties, 68 *t*
Cycloheptane [*cont.*]
  ring strain in, 608, 615
  stereoscopic figure, 615
Cycloheptatriene, 1121
Cycloheptatrienyl anion, 1121
Cycloheptatrienyl cation, stability, 1121
Cyclohexadecane, ring strain in, 608
Cyclohexadecaoctaene, 1124
1,3-Cyclohexadiene
  from hexatriene, 1126–1129
  heat of hydrogenation, 572–573
1,4-Cyclohexadiene, 922
Cyclohexadienes, from reduction of benzenes, 922
Cyclohexadienyl anion, 922
Cyclohexane, 618–630
  axial bonds, 612, 613
  boat conformation, 621–622
    stereoscopic figure, 622
  chair conformation, 611
    stereoscopic figure, 612, 613
  chlorination of, 83, 84
  conformations, 611–615
  dehydrogenation, 580–581
  derivatives
    conformational analysis, 618–620
    conformational energies for, 619
    preparation, 622–627
    reactions, 627–630
    stereoisomerism, 620–621
  equatorial bonds, 612, 613
    energy compared to axial, 620
  from hydrogenation of benzenes, 922
  NMR and conformations of, 614–615
  oxidation, 737
  physical properties, 68 *t*, 618
  ring strain in, 608, 611
Cyclohexanecarboxylic acid, 623
cis-Cyclohexane-1,2-dicarboxylic acid, 1170
cis-1,2-Cyclohexanediol, 289, 290, 667
Cyclohexane-d_{11}, NMR spectrum, 614
Cyclohexanes, NMR spectroscopy, 657–658
Cyclohexanol, 233, 623
  dehydration of, 273
2-Cyclohexanonecarboxylic acid, 805
Cyclohexatriene (*see*, Benzene)
Cyclohexene, 237, 273
  addition reactions, 630
  bromination, 630
  disproportionation, 918–919
  heat of hydrogenation, 572–573
  hydroxylation, 667
  in Lemieux-Johnson reaction, 672
  oxidation, 737
  ozonolysis of, 292
  reaction with hydrogen iodide, 278
  stereoscopic figure, 629
  structure, 629
Cyclohexeneimine, 1068
Cyclohexene oxide, 649
Cyclohexene sulfide, 1068
2-Cyclohexen-1-one, 1021
Cyclohexylamine, 837, 966
Cyclohexyl chloride, 83, 84

Cyclohexyl iodide, 278
Cyclohexylmethanol, 381
Cyclononane, 398
  ring strain in, 608
Cyclononatetraenyl anion, aromaticity, 1122
Cyclooctadecanonaene, stability, 1124–1125
Cyclooctane
  conformations of, 615–616
    stereoscopic figures, 616
  physical properties, 68 *t*
  ring strain in, 608, 615
1,2-Cyclooctanediol, 668
Cyclooctatetraene
  reactions, 577
  stereoscopic figure, 576
  structure, 575–576, 1122
  synthesis, 638
Cyclooctatetraene dianion, 577
  aromaticity, 1122
1,3,5-Cyclooctatriene, from octatetraene, 1129
Cyclooctene, 638, 668
Cyclooctyne, 638, 897
Cyclopentadecane, ring strain in, 608
Cyclopentadiene, 642, 643
  acidity, 1043
  dimerization of, 643
Cyclopentadienyl anion, 1043, 1121
Cyclopentadienyl cation, 1121
Cyclopentane
  conformations, 610–611
  physical properties, 68 *t*
  ring strain in, 608, 610
  stereoscopic figure, 611
Cyclopentanol, 234
Cyclopentanone, 234
Cyclopentene
  chlorohydrin, 282
  reaction with bromine, 281
1,2-Cyclopentenophenanthrene, 646
Cyclopropane
  from diazo compounds, 800
  geometric structure, 608–609
  NMR spectroscopy, 657
  physical properties, 68 *t*
  preparation, 630–632
  reactions, 632–635
  ring strain in, 608–609, 633
  stereoscopic figure, 609
Cyclopropanecarboxaldehyde diethyl acetal, 631
Cyclopropanes
  addition of hydrogen bromide, 633–634
  chlorination, 634
  hydrogenation, 633
  natural occurrence of, 635
  ring opening, 633–634
  ring strain in, 608–610
Cyclopropenyl anion, 1120
Cyclopropenyl cation, aromaticity, 1119–1120
Cyclopropyl chloride, 634
Cyclopropylmethyl cation
  orbital representation, 634
  rearrangements of, 634–635
  stereoscopic figure, 348
Cyclotetradecane, ring strain in, 608
Cyclotridecane, ring strain in, 608
Cycloundecane, ring strain in, 608
p-Cymene, 890
  preparation, 911
α-Cyperone, ultraviolet absorption, 605
Cysteic acid, 841
Cysteine, 816
  disulfide linkages, 831, 848
  physical properties of, 817 *t*
  p*K* values, 817 *t*, 820
  protecting groups for, 839
Cytidine, 1140
Cytochrome C, 856
Cytosine, 1110, 1138

D

D,L notation, 695
-d, symbol for deuterium, 163
Dacron, 943
Dative bond, **8**
DDT, 103–104
Dean-Stark trap, 374–375
Debye, Peter, 98
Decaborane, 286
Decalin, 641–642, 1050
  stereoscopic figures, 641, 642
Decanal, physical properties, 352 *t*
Decane, 53
  physical properties, 55 *t*
Decanoic acid (*see also,* Capric acid), physical properties, 426 *t*
2-Decanone, physical properties, 353 *t*
Decarboxylation
  of β-diacids, 748
  of β-keto acids, 747–748
  of carbamic acids, 495
n-Decylamine, physical properties, 770 *t*
n-Decyl cyanide, hydrolysis of, 434
Degeneracy
  of atomic orbitals, 574–575
  of energy levels, **329**
Degradation reactions, **445**
  Edman degradation, 842–844
  Hofmann degradation, 494–495
  Hunsdiecker reaction, 445
  Kochi reaction, 446
  Ruff degradation, 717
Dehalogenation, of α-haloacyl halides, 563–564
Dehydration
  of alcohols, 272–275, 497
  of amides, 494
  of diols, 673–674
  of hydroxy acids and esters, 562
  of hydroxy aldehydes and ketones, 678–679, 687
  rearrangements of carbonium ions, 274–275
Dehydrogenation
  of alkanes, 580–581
  of cyclohexyl derivatives, 918–919
Dehydrohalogenation
  of alkyl halides, 266–272, 282, 437
  of dihalides, 308–309, 318–319

Delocalization energy, **573**
Delphinidin, 1144
Delrin, 377
δ scale, in NMR, 177
Democritus, 1
Denaturation, 854, 855
Denatured alcohol, **223-224**
Density (*see* specific compounds)
Deoxyadenosine, 1141
Deoxycytidine, 1141
Deoxyguanosine, 1141
Deoxyribonucleic acid (DNA), 730, 1138-1142
  replication, 1142
  structure, 1140-1142
Deoxyribose, 710, 1139
Deoxythymidillic acid, 1139
Deoxythymidine, 1140, 1141
Desoamine, 732
Desoxycholic acid, 646
6-Desoxygalactose, 732-733
Detergents, 431-432, 952-953
  linear alkanesulfonate, 432
Deuterioethanol, 469
  preparation, 514
Deuterium, 268
  as macroscopic isotope, 585
  exchange with carbonyl α-protons, 362-363, 551-552
Deuterium exchange, 362-363
  in unsaturated carbonyl compounds, 551-552
Deuterium oxide, 163
Deuterium sulfate, 585, 587
Dextrorotatory, **108**
Dextrose (*see,* D-(+)-Glucose)
Diacetone alcohol, 387, 553
4,4′-Diacetylbiphenyl, 1041
Diacyl peroxides, 649
Dialdehydes, nomenclature, 735-736
Dialkyl carbonates, 488
Diaminobenzenes (*see,* Phenylenediamines)
4,4′-Diaminobiphenyl (*see,* Benzidine)
1,6-Diaminohexane
  industrial preparation, 788
  in nylon structure, 788
Diastereomers, **116**
Diazines, 1109-1112
  preparation, 1110-1111
  reaction, 1111-1112
  structure and occurrence, 1109-1110
Diazoaminobenzene, 987
Diazo compounds, 798-799
  decomposition, 799-800
  electronic structure, 798
  preparation, 798
α-Diazo esters, 798
α-Diazo ketones, 798
Diazomethane, 14, 436
  cycloaddition to acetylenes, 1093
  electronic structure, 798
  in preparation of phenyl ethers, 1004
  preparation, 798
  reaction with acyl halides, 798
  reaction with carboxylic acids, 436-437
Diazonium compounds (*see also,* Arenediazonium salts), from amines, 791
Diazonium ions, alkyl, reactions, 791, 978
Diazotization, **976**
  fluoborate salts from, 983
  in biaryl preparation, 984-986
  in Sandmeyer reactions, 981-982
  of aminopyridines, 1102-1103
  of aromatic amines, 976-977
DIBAL (diisobutylaluminum hydride), 493
Dibenzalacetone, 388
Diborane, 286
  reduction of amides, 784
  reduction of carboxylic acids, 440-441
  relative reactivity of various compounds, 441 *t*
9,10-Dibromoanthracene, 1057
4,4′-Dibromobiphenyl, preparation, 1041
1,3-Dibromobutane, reaction with zinc, 635
1,4-Dibromobutane, 638
  reaction with zinc, 635
trans-1,2-Dibromocyclohexane, 630
trans-1,2-Dibromocyclopentane, 281
Dibromocyclopropanes, preparation, 631
6,6′-Dibromoindigo, 1149
1,3-Dibromopropane, cyclization of, 630
α,α-Dibromo-*o*-xylene, 903
Di-*n*-butylamine, physical properties of, 770 *t*
trans-1,3-Di-*t*-butylcyclohexane, conformations of, 621
Di-*t*-butyl ketone, 383, 487
Dicarbonyl compounds (*see also,* Diketones; Dialdehydes; Dicarboxylic acids; Diesters; Keto acids; Keto esters), 735-761
  acidity, 750-751
  alkylation, 751-754
  in Michael addition, 755-757
  keto-enol tautomerism, 748-750
  Knoevenagel condensation, 754-755
  nomenclature, 735-736
  preparation by Claisen condensation, 741-745
  reactions, 747
  reverse Claisen condensation, 758-759
  summary, 759-761
1,2-Dicarbonyl compounds, test for, 1111
1,5-Dicarbonyl compounds, preparation by Michael addition, 757
Dicarboxylic acids
  acidity, 738-739
  cyclic anhydride formation, 739-740
  decarboxylation, 739, 747-748
  decomposition, 739-741
  functional derivatives, nomenclature, 736
  natural occurrence, 737
  nomenclature, 735-736
  preparation, 737-738, 760, 761
  reverse Claisen condensation, 759
Dichlorobenzene
  dipole moment, 871
  nitration, 881
  NMR spectrum of, 867
7,7-Dichlorobicyclo[4.1.0]heptane, synthesis, 642
1,4-Dichloro-2-butene, preparation of, 547

Dichlorocarbene, 631
  electronic structure, 631
  in Reimer-Tiemann reaction, 1009
2,2-Dichloro-1,1-dimethylcyclopropane, 631
1,1-Dichloroethane, in chlorination of ethane, 82
1,2-Dichloroethane
  conformations of, 101
  in chlorination of ethane, 82
  use in industry, 294
Dichlorofluoromethane (Freon 12), 102
2,6-Dichlorophenol, natural occurrence, 1034
1,3-Dichloropropane, NMR spectrum of, 189
Dichromate, oxidation
  of alcohols, 232–233
  of amino phenols, 1023
  of benzene derivatives, 920, 942
  of hydroquinone, 1023
2,3-Dicyano-1,4-benzoquinone, in charge-transfer complexes, 1029
1,3-Dicyanopropane, hydrolysis, 737
Dicyclohexylcarbodiimide (DCC), 836–837
N,N-Dicyclohexylurea, 837
Dicyclopentadiene, 643
Dideuterioethylene, stereoisomers, 253–255
Dieckmann condensation, 622, 638, 743
Dielectric constant, 213–214
  of alcohols, 214 *t*
  of water, 214 *t*
Diels-Alder reaction, 624–627, 1070
  anthracenes, 1056–1057
  as cycloaddition reaction, 1133
  bicyclic compounds from, 642–643
  mechanism, 625–626
  naphthalene preparation, 1046
  orientation, 624–625
  stereochemistry, 627, 642–643
  transition state, 626
Dienes
  addition reactions, 542–544
  conjugated, 540
  Cope rearrangement, 1020
  cumulated (*see*, Allenes)
  photochemical reactions, 1154–1155
  polymerization of, 547–548
  preparation of, 546
    from allyl halides, 546
    Wittig reaction, 546
  stability, 540
  structure of, 540, 542
Dienophile, in Diels-Alder reaction, 624
Diesters, nomenclature, 736
Diethyl acetylenedicarboxylate, 625
Diethyl adipate, 638
Diethylamine
  physical properties of, 770 *t*
  pK_b, 774
Diethylammonium ion, pK_a, 774
Diethylcadmium, physical properties of, 158 *t*
Diethyl 1,1-cyclobutanedicarboxylate, 637
Diethyl cyclohexa-1,4-diene-1,2-dicarboxylate, 625
Diethyl 1,1-cyclopentanedicarboxylate, 638
Diethyl disulfide, 243
Diethylene glycol, 397
  preparation, 651
Diethylene glycol dimethyl ether (*see*, Diglyme)
Diethyl ether, 132
  physical properties of, 235 *t*
  uses, 235
Diethyl malonate, 637, 751
  in amino acid preparation, 822–823
  in Michael addition, 755–757
Diethylmercury
  physical properties of, 158 *t*
  preparation of, 163
  reaction with sodium, 163
Diethyl phenylmalonate, 743
3,4-Diethylpyridine, 1103
Diethyl sulfate, preparation and uses, 500
Diethylzinc, physical properties of, 158 *t*
Difluoromethane, PMR spectrum of, 205
Difunctional compounds (*see also*, Diols; Hydroxy aldehydes; Hydroxy ketones; Hydroxy acids; Dicarboxylic acids; Diesters; Keto acids; Diketones), 644–687, 735–761
  general chemistry, 664–665
  nomenclature, 665–667, 735–736
Digitalis, 648
Digitoxigenin, 648
Digitoxin, hydrolysis, 648
Diglyme, 236
  preparation, 651
Dihaloalkanes, preparation of, 315
1,2-Dihaloalkanes (*see*, Vicinal dihalides; Alkyl halides)
Dihaloalkenes, preparation of, 315
Dihalomethylene (*see*, Carbenes)
9,10-Dihydroanthracene, 1056
Dihydronaphthalene, 1038, 1050
9,10-Dihydrophenanthrene, 1056
o-Dihydroxybenzene, oxidation to quinones, 1024
o-Dihydroxybenzene (*see*, Catechol)
p-Dihydroxybenzene (*see*, Hydroquinone)
2,4-Dihydroxybenzoic acid, 1008
Diisobutylaluminum hydride (DIBAL), 493
Diisobutylenes, 292
Diisopropylamine, 523
Diisopropyl ether
  NMR spectrum of, 236
  physical properties of, 235 *t*
Diketones
  alkylation, 753
  cyclic, preparation, 745
  keto-enol equilibria, 748–750
  preparation, 741, 744, 745
    1,2-diketones, 317, 746, 760
    1,3-diketones, 741, 744, 745, 760
2,5-Diketopiperazines, 833, 858
  preparation, 833
Dilution principle, 533
Dimerization, of alkenes, 292
2,6-Dimethoxybenzoic acid, 1021
1,2-Dimethoxyethane (glyme), 236

N,N-Dimethylacetamide
  physical properties of, 458 *t*
  use as solvent, 458
β,β-Dimethylacrylic acid, 561
α,β-Dimethyladipic acid, 737
Dimethylallyl alcohol, 548
γ,γ-Dimethylallyl pyrophosphate, 548, 1162
Dimethylamine
  physical properties of, 770 *t*
  pK_b, 774
p-Dimethylaminoazobenzene, 988
p-Dimethylaminoazobenzene-*p'*-sulfonic acid, 989
p-Dimethylaminobenzaldehyde, 936
p-(N,N-Dimethylamino)benzonitrile, dipole moment, 994
Dimethylammonium ion, pK_a, 774
N,N-Dimethylaniline, 969
  dipole moment, 994
m-Dimethylbenzene (*see also*, *o*-Xylene), 881
o-Dimethylbenzene (*see also*, *m*-Xylene), 881
p-Dimethylbenzene (*see also*, *p*-Xylene), 881
3,3'-Dimethylbiphenyl, 984
2,3-Dimethyl-1,3-butadiene, 546
2,2-Dimethylbutane, physical properties of, 67 *t*
2,3-Dimethylbutane, physical properties of, 67 *t*
2,3-Dimethylbutane-2,3-diol (pinacol), 673
3,3-Dimethylbutanoic acid, 368
3,3-Dimethyl-2-butanone, 487
3,3-Dimethyl-1-butene, NMR spectrum of, 262
3,3-Dimethyl-1-butyne, NMR spectrum of, 305
Dimethylcadmium, physical properties of, 158 *t*
Dimethyl carbonate, 488
cis-3,4-Dimethylcyclobutene, 1131
1,3-Dimethylcyclohexane, 621
1,4-Dimethylcyclohexane, conformations of, 620–621
2,2-Dimethyl-1,3-cyclohexanedione, 753
Dimethyl ether
  geometry, 207
  physical properties, 235 *t*
Dimethylformamide (DMF), 143, 144, 936
  use as solvent, 458, 780
2,5-Dimethylfuran, 1075
3,4-Dimethyl-1,5-hexadiene, rearrangement of, 1020
1,4-Dimethylimidazole, 1095
3,5-Dimethylisoxazole, 1092
Dimethylketene, 563
Dimethyl ketone (*see*, Acetone)
Dimethylmagnesium, physical properties, 158 *t*
Dimethylmercury
  dipole moment, 167
  physical properties, 158 *t*
  reaction with ethyllithium, 163
1,7-Dimethylnaphthalene, 1045
Dimethylneopentylamine, 784
α,β-Dimethyloxysuccinic acid, 734
4,4-Dimethyl-2-pentanone, 368
Dimethyl phosphate, pK_a, 502
2,2-Dimethyl-1,3-propanediol, 386
2,5-Dimethylpyrazine, 1111
3,5-Dimethylpyrazole, 1092
2,5-Dimethylpyridazine, 1110
2,5-Dimethylpyrrole, 1079
Dimethyl sulfate, 499
  in S_N2 reactions, 141
  preparation and uses, 500
Dimethyl sulfide, geometry, 207
Dimethyl sulfone, 244
  Lewis structures of, 244
Dimethyl sulfoxide (DMSO), 143, 144, 244
  Lewis structures of, 244
Dimethyl terephthalate, industrial production, 943
2,5-Dimethylthiazole, 1094
2,4-Dimethylthiophene, physical properties of, 1075
2,5-Dimethylthiophene, 1079
Dimethylzinc, physical properties of, 158 *t*
2,6-Dinitroaniline, 952
2,4-Dinitroaniline, 966
2,4-Dinitroanilinium ion, pK_a, 969
2,4-Dinitrobenzaldehyde, 975
Dinitrobenzene, 869, 983
2,4-Dinitrobenzoic acid, preparation, 882
3,5-Dinitrobenzoic acid, 950
3,4-Dinitrobenzothiophene, 1087
3,6-Dinitrobenzothiophene, 1087
2,4-Dinitrochlorobenzene, hydrolysis, 1012
2,4-Dinitrofluorobenzene, 842
2,5-Dinitrofuran, 1082
1,5-Dinitronaphthalene, preparation, 1047
1,8-Dinitronaphthalene, 1047
2,4-Dinitrophenol
  pK_a, 1003
  preparation, 1012
2,4-Dinitrophenylhydrazine, 894
2,4-Dinitrophenylhydrazone derivatives (DNP), 894
2,4-Dinitrothiophene, 1082
2,5-Dinitrothiophene, 1082
Diols, 667–674
  acetal and ketal formation, 672–673
  cleavage, 671–672
  cyclization, 674
  dehydration, 673–674
  nomenclature, 665–666
  oxidation, 671–672
  pinacol rearrangement, 673–674
  preparation
    from aldol condensation, 670
    hydroxylation of alkenes, 667–669
    opening of epoxides, 669
    pinacol reaction, 670
    reduction of dicarbonyl compounds, 670
  reaction with phosgene, 672
  reactions, 671–674
1,4-Dioxane, 221, 236, 834, 1065
1,3-Dioxolane, 1066
Dipeptides, **814**, 833
  from Diketopiperazines, 834
Diphenic acid, 1041
Diphenylacetaldehyde, 689
Diphenylacetylene, physical properties of, 303 *t*
Diphenylcyclopropenone, dipole moment, 1120

1,1-Diphenyl-1,2-ethanediol, 689
1,2-Diphenylethanol, 652
1,2-Diphenylethylene (*see*, Stilbene)
Diphenyliodonium ion, 901
Diphenylketene, 799
Diphenylmethane, pK_a, 920
Diphenylmethyl chloride, 907
2,5-Diphenyloxazole, 1094
1,3-Diphenyltriazine, 987
Dipole-dipole repulsion, conformation stability and, 101–102
Dipole moments, **98**
  alkenes, 259–260
  alkynes, 304
  and molecular vibration, 327–328
  cis-trans isomers, 259–260
  of carbonyl compounds, 349
  of methyl halides, 98 *t*
Di-*n*-propylamine
  NMR spectrum of, 772
  physical properties of, 770 *t*
  pK_a, 774
Dipropyl ether, physical properties of, 235 *t*
Dipropylzinc, physical properties of, 158 *t*
Direct Blue 2B, 1148
Disaccharides (*see also,* Maltose; Cellulose; Lactose; Sucrose), **694,** 722–726
Dispersive force, **55**
Displacement reactions (*see,* Nucleophilic substitution)
Disproportionation, **76**
  of butane, 91
Disproportionation reaction, Cannizzaro reaction, 396–397
Disrotatory motion, **1126**
Dissociation constant, 214–216
Disulfides, **34**
  in proteins, 831
  oxidation, 841
Diterpenes, **643**
1,3-Dithiane, 676–677, 1066
  α-keto acids from, 746
  preparation, 676
  substituted, 676–677
DMSO (*see,* Dimethyl sulfoxide)
Döbner-Miller reaction, 1106
5,7-Dodecadiyne, 318
1-Dodecanal, 491
  physical properties, 352 *t*
Dodecane, 53
n-Dodecane
  fragmentation, 412, 413
  mass spectrum, 412, 413
  physical properties, 55 *t*
1-Dodecanethiol, 243
Dodecanoic acid (*see also,* Lauric acid), physical properties, 426 *t*
2-Dodecanone, physical properties, 353 *t*
Doeicosane, 53
L-Dopa, 1033
Drieding stereomodels, 30–31
Drying oil, 563
Durene, 913–914
Durenesulfonic acid, 913
Dyes (*see also,* Pigments)
  categories, 1146–1150
  leuco, 1146
Dyne, **331**

E

Echinochrome, 1145
Eclipsed structure, 57, 58
Edman degradation, 842–844
Eicosane, 53
  physical properties of, 55 *t*
E isomer, **258**
Elasticity, of polymers, 548
Elastomers, 547–548
Electrical scanning, in mass spectroscopy, 406
Electrocyclic reactions, 1126–1133
  photochemical, 1132
Electromagnetic radiation, 325–327
  relation between energy and frequency, 326
  relation between wave length and frequency, 326
  speed of, 325, 326
  wave number, **326**
Electromagnetic spectrum, 325
Electron
  nonbonded pairs (*see also,* Lone pair electrons), 8, 26, 28
  octets, **6**
    expanded, 14
    stability and, 6
  probability distribution for, 15
  sharing, 6
  shells, **5,** 20, 577
  spin, 16, 17
  valence (*see,* Valence electrons)
  wave function of, 15
  wave motion of, 15
Electron affinity, **6**
Electron configurations, of various elements, 20
Electron correlative effect, **55**
Electron density, 28
Electron density distribution, 15
Electronegativity, **6, 156**
  of hybrid orbitals, 429
  Pauling values for some elements, 156 *t*
Electron flow, distinguished from electrical current, 175
Electronic configuration of atoms, 19–20
Electronic configuration of noble gases, 5
Electronic states
  excited states, 1150–1153
  triplet states, 1152–1153
Electronic transitions, 593–599
  and color, 1142–1143
  and excited states, 1150–1153
  Franck-Condon (vertical), 1150
  $n \rightarrow \pi^*$, 596–599
  orbital nodes in, 594
  $\pi \rightarrow \pi^*$, 594–596
  $\sigma \rightarrow \sigma^*$, 593–594

Electron octet
  in resonance structures, 13, 14
  stability and, 6, 8
Electron pushing, 144
Electron spin
  in singlet state, 1150
  in triplet state, 1152
Electron spin resonance spectroscopy (ESR), 1026
Electrophilic addition
  to alkenes, 278-284
  to alkynes, 313-315
Electrophilic aromatic substitution
  anisole, 876-877
  anthracene, 1057
  aromatic amides, 973-974
  aromatic amines, 972-974
  azoles, 1094-1095
  benzene, 581-590
  benzene derivatives
    o,m,p-directors, 869
    orientation, 869-870, 873-879, 881-882
  benzofuran, 1086-1087
  benzothiophene, 1086-1087
  biphenyls, 1041
  carbonium ions in, 583-584
  chloromethylation, 588-589
  diazines, 1111-1112
  five-membered ring heterocycles, 1080-1083
  Friedel-Crafts acylation, 588-589
  halobenzenes, 878-879
  indole, 1086-1088
  isoquinolines, 1107-1108
  napthalene, 1046-1049
  naphthalenes, substituted, 1051-1052
  nitrobenzene, 875-876
  phenanthrene, 1057
  pyrene, 1058
  pyridine N-oxides, 1101
  pyridines, 1100-1101
  quinoline, 1107-1108
  synthetic utility, 883-886
  toluene, 873-875
Electrophilic substitution, 164
Electropositivity, **6**
Elemental analysis, 35
Elements, periodic table of (*see also* end paper), 5
Elimination reaction (*see also*, Dehydrohalogenation), 145-153, 266-272
  Dehydration of alcohols, 272-275, 497
  E1 mechanism, 151-153, 267
  E2 mechanism, 145-147, 266-272, 628
  α-halo acids and esters, 561-562
  of alkyl halides, 145-153, 266-272
  pyrolytic (*see*, Pyrolytic elimination)
  stereochemistry, 267, 269-272, 498
  syn-anti, 270
  versus substitution, 145-147, 152-153
Elon, 1027
Elostearic acid, 507
Empirical formula, determination of, 36
Emulsifying agents, biological, 646-647
Enamines, 802-804
  in Michael addition, 804
  preparation, 803
  reaction with alkyl halides, 804
  resonance structures for, 804
  tautomerization with imine form, 802
Enanthic acid (*see*, Heptanoic acid)
Enantiomers, **105**
  comparison of properties, 107, 110, 116
  interconversion of, 107
  nomenclature of, 110-114
  optical activity of, 107-110
  relation to diastereomers, 116
  relative reactivity of, 124
Encephalitis, 103
Endothermic reaction, 43
-ene, as suffix, 667
Energy
  of activation, **44**
  of electromagnetic radiation, 326
  sources of, 70-71
  units of, 326
Energy barriers, in reactions, 44, 48
Energy of activation (*see*, Activation energy)
Enolate ions, **361**, 363-365
  esters, 684
  resonance stabilization, 534, 535
Enol ethers, 376-377
Enolization, 360-368, 382
Enol-keto equilibrium, 360-363
Enols, intramolecular hydrogen bonding in, 749-750
Enthalpy (*see also*, Heat of reaction) 43, 46, 90
Enthalpy of activation (*see also*, Activation energy), **44**
Entropy, 43, 90
  of melting, 67
  role of equilibria, 374-376
Entropy units, 44
Envelope structure, of cyclopentane, 610-611
Environmental Protection Agency (EPA), 104
Enzymatic hydrolysis
  of cellulose, 728
  of glycosides, 702
  of lactose, 724
  of maltose, 724
  of raffinose, 726
  of sucrose, 726
Enzymes, 693, 847
  as catalysts, 90
  hydrolytic, 476-477
  in metabolism, 1158-1159
Epoxides, 648-652
  NMR spectroscopy, 657
  nomenclature, 648
  preparation, 648-650
  protonated, rearrangement of, 652
  ring opening, 1069
    acid or base catalyzed, 650-651
    by organometallics, 652
    reduction, 652
    stereochemistry, 669
Equatorial bonds, 612, 613

- Equilibrium, 46, 90
  - reaction, 42–44
- Equilibrium concentrations, as a function of free energy, 266
- Equilibrium constant, **42–43**, 90
  - K_b, **773**
- Erythritol, 696
- *erythro* isomers, **669**
- Erythromycin, 732
- D-(−)-Erythrose, 697, 718
  - oxidation, 716, 719
  - reduction, 696
- L-(+)-Erythrose
  - oxidation, 719
  - reduction, 696
- Eschenmoser, Albert, 1167
- Eschweiler-Clarke reaction, 783
- Essential oils, 643
- Esterification
  - of alcohols, 441–444
    - by acyl halides, 480
    - by amides, 482
    - by anhydrides, 480–481
    - by isocyanates, 801
    - transesterification, 481–482
  - of amino acids, 827–828
  - of cyclohexyl hydroxy groups, 628
  - of monosaccharides, 708–709
  - of phenols, 1005–1006
- Esters
  - boric acid, in hydroboration-oxidation, 288
  - carbamate (urethanes), 801
  - carbonate, 692
  - carboxylic acid, 34, **451**
    - acidity, 468–470
    - acyloin condensation, 675
    - anions, reactions, 470
    - Claisen condensation, 741–745
    - cyclic (*see*, Lactones)
    - fats, 506–509
    - hydrolysis of, 473–477
    - infrared spectroscopy, 459–460
    - keto (*see*, β-Keto esters)
    - NMR spectroscopy, 458
    - nomenclature, 454
    - physical properties of, 456–458
    - preparation, 229, 393
      - acid-catalyzed esterification of carboxylic acids, 441–444
      - alcohols and acyl halides, 480
      - alcohols and amides, 482
      - alcohols and anhydrides, 480–481
      - alkyl halides and carboxylate salts, 132, 437
      - diazomethane and carboxylic acids, 436–437
      - summary, 460–461
      - transesterification, 481–482
    - pyrolytic elimination, 495–497
    - reactions
      - Claisen condensation, 470
      - with amines and ammonia, 484
      - with base, 470
      - with organometallic compounds, 487–488
- Esters, carboxylic acid, reactions [*cont.*]
      - reduction, 490–491
    - solubility, 458
    - waxes, 506
  - dicarboxylic acid, Dieckmann condensation, 622, 638
  - imino, 482
  - phosphonic acid (*see*, Phosphonates)
  - phosphoric acid (*see*, Phosphates)
  - preparation of, 736–738, 760–761
  - pyrophosphoric acid, 502
  - sulfonic acid (*see*, Sulfonates)
    - in S_N2 reactions, 141
  - sulfuric acid, 499–500
- Estrogens, 647
- Estrone, 647
  - Torgov synthesis, 1170–1173
- Et, symbol for ethyl group, 159, 742
- Etard's reagent, 937
- Ethane, 53, 74
  - chlorination, 82
  - conformations, 57–58
  - cracking, 275
  - entropy, 57
  - from hydrogenation of butane, 90
  - from hydrogenation of ethylene, 90
  - physical properties of, 55 *t*
  - pK_a, 920
  - rotational barrier, 57–59
  - stereoscopic figure, 57
- Ethanethiol, 132
- Ethanoic acid, (*see*, Acetic acid)
- Ethanol, (*see*, Ethyl alcohol)
- Ethene, (*see*, Ethylene)
- Ethers (*see also*, Acetals; Ketals), 32, 34, 206
  - aromatic (*see*, Phenyl ethers)
  - as solvents, 235–236
  - cyclic, 648–655
  - infrared spectroscopy, 338
  - mass spectroscopy, 415
  - NMR spectroscopy, 236
  - nomenclature, 234
  - oxidation (autoxidation), 240–241
  - physical properties, 235–236
  - preparation, 236–238
    - alkoxymercuration of alkenes, 238, 283–284
    - dehydration of alcohols, 228, 237–238
    - from alkyl halides, 132, 236–237
    - Williamson synthesis, 236–237
  - reaction with acids, 239–240
  - removal of peroxides, 240–241
  - silyl, 527
  - structure of, 206–207
  - symmetrical, 234
- ultraviolet spectroscopy, 602
- Ethoxide ion, 427
- *o*-Ethoxyaniline (*see*, *o*-Phenetidine)
- Ethoxybenzene (*see*, Phenetole)
- Ethoxycarbonyl-, as prefix, 456
- Ethyl acetate, 132, 441–442
  - acidity of, 469
  - condensation, 741
  - hydrolysis of, 48–49
  - use as solvent, 458

Ethyl acetoacetate, 741, 751, 752
Ethyl alcohol, 223–224
  dehydration of, 272–273
  denatured, 224
  dipole moment, 250
  industrial production of, 499
  NMR spectra of, 218, 219
  physical properties of, 211 *t*
  reaction with acetic acid, 441–442
  vapor pressures of, 250
Ethylamine
  physical properties of, 770 *t*
  pK_b, 774
Ethylammonium ion, pK_a, 774
Ethyl anion, 361
Ethyl azide, 132
Ethylbenzene, 398
Ethyl benzoylacetate, 743
Ethyl bromide
  displacement reactions of, 132 *t*
  hydrolysis of, 224–225
  reaction with iodide ion, 127
  S_N2 reaction of, 146–147
Ethyl 6-bromoindole-3-carboxylate, 1087
Ethyl 4-*t*-butylcyclohexanecarboxylate, hydrolysis of *cis* and *trans* isomers, 628
Ethyl cation, 149
Ethyl chloride, 54
  anesthetic effect of, 103
  NMR spectrum of, 185
Ethyl cyanide, 132
Ethylene, 29, 256
  air oxidation, 648
  bond bending in, 608
  dimerization, 1134
  electronic structure, 251–255
  geometric structure, 251
  hydration, 279
  hydrogenation, 90
  in Diels-Alder reaction, 624
  industrial uses, 275
  ionization potential, 410 *t*
  Lewis structure, 8, 251
  physical properties, 259 *t*
  polymerization, 292, 293–294, 296
  sources, 275
  stereoscopic figure, 251
  substituted, stability of, 264–265
  ultraviolet spectroscopy, 595
Ethylene carbonate, 672
Ethylene dichloride (*see*, 1,1- and 1,2-Dichloroethane)
Ethylene glycol, 673
  crown ethers from, 654–655
  in polyurethanes, 801
Ethyleneimine (*see*, Aziridine)
Ethylene oxide, 648
  industrial preparation, 648
  polymerization of, 651
  preparation, 1067
  reaction with Grignard reagents, 652
Ethylene sulfide (*see*, Thiirane)
Ethyl ether, preparation of, 228
Ethyl formate, in mixed Claisen condensation, 744
Ethyl β-D-glucoside, hydrolysis of, 702
2-Ethyl-2-hexenal, 385
Ethyl iodide
  from ethyl bromide, 127
  NMR spectrum of, 185
Ethyl isobutyrate, Claisen condensation, 742
Ethyllithium
  physical properties of, 158 *t*
  reaction with dimethylmercury, 163
Ethylmagnesium bromide, hydrolysis of, 163
Ethylmercuric chloride, physical properties of, 158 *t*
Ethylmercuric iodide, physical properties of, 158 *t*
Ethyl methyl ether, physical properties of, 235 *t*
Ethyl 2-methylhexanoate, 470
Ethyl nitrate, 132
Ethyl octanoate, infrared spectrum of, 460
Ethyl orthoacetate, 514
Ethyl orthoformate, 938
Ethyl 3-oxobutanoate (*see*, Ethyl acetoacetate)
Ethyloxonium bromide, 132
Ethyl pentenoates, heats of formation, 560
Ethyl radical, 54
Ethylsodium, preparation of, 163
Ethylsulfuric acid, industrial use, 499
Ethyl thiocyanate, 132
Ethyltrimethylphosphonium bromide, 132
Ethyl vinyl ether, 377
Ethyne (*see*, Acetylene)
Ethynylacetic acid
  inductive effects in, 429
  pK_a of, 429 *t*
1-Ethynylcyclohexanol, 383
Excited state, 1150–1153
  of molecules, 327, 593–600, 602–603
Exhaustive methylation (*see*, Hofmann degradation)
Exothermic reaction, 43
Explosives, 960
Extinction coefficient, 597–599

F

Faraday, Michael, 569
Farnesol, 549, 550, 1162
Farnesyl pyrophosphate, 549, 1162, 1163, 1164
Fats, 506–509
  alkaline hydrolysis (saponification), 507
  composition, 563
  decomposition, 554
  hydrogenation (hardening), 507–508
  melting point, 507
Fatty acids, 430, **506**
  biosynthesis, 745
  unsaturated, 507
Fehling's test, 710
Ferricyanide oxidation, N-alkylpyridinium salts, 1103
Fibroin, 856
Fingernail polish remover, 458

- Glycine anhydride, 833
- Glycine benzyl ester, hydrogenolysis, 828
- Glycine hydrochloride, titration of, 818–819
- glycogen, 693, 729
  - biosynthesis, 730
  - degradation, 729
- Glycolic acid, 681
- Glycols (*see also,* Diols), **289**
  - preparation of, 289–290, 651
- Glycolysis, 729
- Glycosides, **700**
  - as nonreducing sugars, 711
  - formation, 701
  - hydrolysis, 731–732
    - acidic, 701–702
    - enzymatic, 702
  - naturally occurring, 731–732
  - periodate oxidation, 712–714
  - stability towards bases, 711
- Glycosyl residue, **731**
- Glycylalanine, 830
  - p*K* values, 833
- Glycylaspartic acid, p*K* values, 857
- Glycylglycine, 814
  - p*K* values, 833
  - synthesis, 834
- Glyme, 236
  - preparation, 651
- Glyoxylic acid, 379
- Glyptal resins, 944
- Gomberg, Moses, 905
- Gomberg-Bachmann reaction, 985
  - biphenyls from, 1039
- Goodyear, Charles, 547
- Granatine, 813
- Graphite, 1059
- Greek alphabet, 208 *t*
  - in nomenclature, 208
- Grignard reagents, **157**
  - acetylenyl, 306–307
  - allyl, 533–534
  - aromatic, 917
  - aromatic acids from, 941
  - aryl, 898–899
  - benzylic, preparation, 908
  - bonds in, 159
  - from halobenzenes, 888
  - from vinyl halides, 321
  - hydrolysis, 163
  - in alcohol synthesis, 381–383
  - Lewis structure, 159
  - metal exchange reaction, 162
  - preparation, 159–160, 381
  - reactions
    - with aldehydes and ketones, 381–383
    - with alkynes, 306
    - with allyl halides, 532–533
    - with cadmium chloride, 162
    - with carboxylic acid derivatives, 485–489
    - with epoxides, 652
    - with ethyl orthoformate, 937–938
    - with hydroxylic compounds, 163
- Grignard synthesis, of alcohols, 381–383
- Grivich, Peter, 3
- Ground state, of molecules, 593, 595, 597, 602
- GRS (synthetic rubber), 547
- Guaiacol, 1000
- Guanidines, 820
- Guanidino group, 820
- Guanine, 1110, 1138
- Guanosine, 1140
- D-(−)-Gulose, 697
- L-(+)-Gulose
  - in Fischer proof, 721
  - reduction of, 709
- Gum benzoin, 569
- Gutta-percha, 548, 644
  - biosynthesis of, 548

H

- Halides, relative reactivity of, 141
- Hallucinogens, 806
- Halo acids, hydrolysis, 682
- α-Halo acids
  - amination, 821–822
  - Hell-Volhard-Zelinsky reaction, 437–438, 470
- β-Halo acids, elimination in, 682
- α-Haloacyl halide method, 858
- Haloalkanes (*see,* Alkyl halides)
- Haloarenes
  - from diazonimm salts, 981–983
  - hydrolysis to phenols, 894–896, 1001
- Halobenzenes
  - acidity, 896
  - aryllithium formation, 899
  - conversion to nitriles, 942
  - electrophilic substitution, 878–879
  - Grignard formation, 888, 898
  - nitration, 880
  - organocopper compounds from, 918
  - preparation, 892–893
  - reactions, 893–897
    - addition-elimination mechanism, 894–895
    - elimination-addition mechanism, 895–898
  - transmetallation, 899
- Haloform reaction, 367–368
- Halogenation
  - of aldehydes and ketones, 366–368
  - of alkanes, 77–87
  - of alkenes, 280–281
  - of alkyl benzenes, 902–904
  - of allylic systems, 535–536
  - of aromatic amines, 972
  - of benzene, 581–584, 901–902
  - of phenols
    - in acidic medium, 1014–1015
    - in basic medium, 1006–1007
  - of phenyl ethers, 1014–1015
- Halogens
  - addition to alkenes, 280–281
  - electronegativity, 6
  - formation of hypohalous acids, 282
  - size, 97
- Halohydrins
  - epoxides from, 648–649
  - halomethylene, (*see,* Carbenes)

Halonium ions, 280–282
Halothane, 102
Hammett, Louis P., 947
Hammett equation, 947–950
Hammett substituent constants, 949 *t*
Handedness (*see*, Chirality)
Hantzsch pyridine synthesis, 1097–1098
Hardening, of fats, 507–508
Harmonic oscillator approximation, 330–331
Haworth, Walter N., 699
Haworth projections, 699
Heat, **73**
Heat of atomization, 92
Heat of combustion, **88**, 90
  relation to heats of formation, 90
Heat of formation (*see* Appendix I of the text for specific compounds), **89**, 90
  and stability, 264
  use in calculating heats of atomization, 92
  use in estimating possible reaction, 89–90
Heat of hydrogenation, 300
  alkenes and dienes, 540
Heat of reaction (**see also**, Enthalpy), **43**
  role in equilibria, 374–376
Heavy water, 163–164
Heisenberg uncertainty principle, 15, 61, 73, 178
α-Helix, in proteins, 850, 852
Hell-Volhard-Zelinsky reaction, 437–438
Hemiacetals, 372–373
  cyclic
    preparation, 679–680
    reactions, 680
  α- and β-D-glucose, 698–699
Hemiaminals, 380
Hemiketals, 372–373
  cyclic, 679–680
Hemin, 855, 1077
Hemoglobin, 855, 1077
  function, 856
Hemopyrrole, 1077
Heneicosane, 53
Heptacene, 1058
Heptadecanoic acid, physical properties, 426 *t*
Heptalene, 1123
Heptamethylbenzenonium ion, 913
Heptanal, 291
  physical properties, 352 *t*
n-Heptane, 53
  infrared spectrum, 331
  in gasoline, 88
  physical properties, 55 *t*
Heptanoic acid, physical properties, 426 *t*
2-Heptanone
  infrared spectrum, 356
  physical properties, 353 *t*
Heptatriene, 1121
n-Heptylamine, physical properties, 770 *t*
Herbicides, 103
Heroin, 805
Heteroatom, **606**, 648
Heterocyclic compounds, **606**, 1065–1112
  aromatic
    condensed five-membered rings, 1083–1088
    five-membered rings, 1072–1083
Heterocyclic compounds [*cont.*]
  azoles, 1088–1095
  classification, 1065
  cyclic ethers, 648–655
  diazines, 1109–1112
  isoquinoline, 1104–1109
  nomenclature, 1066
  nonaromatic
    five- and six-membered rings, 1071–1072
    four-membered rings, 1069–1071
    nomenclature, 1066–1067
    three-membered rings, 1067–1069
  pyridine, 1095–1104
  quinoline, 1104–1109
Heterogeneous reaction, **158**
Heterolysis, **78**
Heterolytic cleavage, **78**
Hexaborane, 286
Hexacene, 1058
1,2,3,4,5,6-Hexachlorocyclohexane, preparation, 901–902
Hexadecanoic acid (*see also*, Palmitic acid), physical properties, 426 *t*
1,5-Hexadiene (biallyl), 533
  rearrangement, 1020
(E,Z)-Hexa-2,4-diene, 1131
Hexahelicene, 1060
Hexamethylbenzene, 585, 913
  complexed with chloranil, 1029
    stereoscopic figure, 1029
  preparation, 910
Hexamethylphosphoric triamide (HMPT), 143, 144
Hexanal, physical properties, 352 *t*
Hexane, 53
  physical properties, 55 *t*
Hexanedioic acid, 435
1,6-Hexanediol, 292
2,5-Hexanedione, in Paal-Knorr synthesis, 1078
Hexanoic acid (*see also*, Caproic acid)
  infrared spectrum, 433
  physical properties, 426 *t*
2-Hexanol, preparation, 283
2-Hexanone, physical properties, 353 *t*
3-Hexanone, physical properties, 353 *t*
Hexaphenylethane, 905
1,3,5-Hexatriene
  electronic states, 595
  ultraviolet spectroscopy, 594
cis-1,3,5-Hexatriene, ring closure, 1126–1129
1-Hexene, oxymercuration-demercuration, 283
Hexoses, **694**
n-Hexyl alcohol, physical properties, 211 *t*
n-Hexylamine
  IR spectrum, 771
  physical properties, 770 *t*
1-Hexyne, 310
  NMR spectrum, 305
  physical properties, 306 *t*
  purification, 307
2-Hexyne, physical properties, 306 *t*
3-Hexyne, physical properties, 306 *t*
Hinsberg test, 790

Glycine anhydride, 833
Glycine benzyl ester, hydrogenolysis, 828
Glycine hydrochloride, titration of, 818–819
glycogen, 693, 729
  biosynthesis, 730
  degradation, 729
Glycolic acid, 681
Glycols (*see also,* Diols), **289**
  preparation of, 289–290, 651
Glycolysis, 729
Glycosides, **700**
  as nonreducing sugars, 711
  formation, 701
  hydrolysis, 731–732
    acidic, 701–702
    enzymatic, 702
  naturally occurring, 731–732
  periodate oxidation, 712–714
  stability towards bases, 711
Glycosyl residue, **731**
Glycylalanine, 830
  p*K* values, 833
Glycylaspartic acid, p*K* values, 857
Glycylglycine, 814
  p*K* values, 833
  synthesis, 834
Glyme, 236
  preparation, 651
Glyoxylic acid, 379
Glyptal resins, 944
Gomberg, Moses, 905
Gomberg-Bachmann reaction, 985
  biphenyls from, 1039
Goodyear, Charles, 547
Granatine, 813
Graphite, 1059
Greek alphabet, 208 *t*
  in nomenclature, 208
Grignard reagents, **157**
  acetylenyl, 306–307
  allyl, 533–534
  aromatic, 917
  aromatic acids from, 941
  aryl, 898–899
  benzylic, preparation, 908
  bonds in, 159
  from halobenzenes, 888
  from vinyl halides, 321
  hydrolysis, 163
  in alcohol synthesis, 381–383
  Lewis structure, 159
  metal exchange reaction, 162
  preparation, 159–160, 381
  reactions
    with aldehydes and ketones, 381–383
    with alkynes, 306
    with allyl halides, 532–533
    with cadmium chloride, 162
    with carboxylic acid derivatives, 485–489
    with epoxides, 652
    with ethyl orthoformate, 937–938
    with hydroxylic compounds, 163
Grignard synthesis, of alcohols, 381–383
Grivich, Peter, 3
Ground state, of molecules, 593, 595, 597, 602
GRS (synthetic rubber), 547
Guaiacol, 1000
Guanidines, 820
Guanidino group, 820
Guanine, 1110, 1138
Guanosine, 1140
D-(−)-Gulose, 697
L-(+)-Gulose
  in Fischer proof, 721
  reduction of, 709
Gum benzoin, 569
Gutta-percha, 548, 644
  biosynthesis of, 548

H

Halides, relative reactivity of, 141
Hallucinogens, 806
Halo acids, hydrolysis, 682
α-Halo acids
  amination, 821–822
  Hell-Volhard-Zelinsky reaction, 437–438, 470
β-Halo acids, elimination in, 682
α-Haloacyl halide method, 858
Haloalkanes (*see,* Alkyl halides)
Haloarenes
  from diazonimm salts, 981–983
  hydrolysis to phenols, 894–896, 1001
Halobenzenes
  acidity, 896
  aryllithium formation, 899
  conversion to nitriles, 942
  electrophilic substitution, 878–879
  Grignard formation, 888, 898
  nitration, 880
  organocopper compounds from, 918
  preparation, 892–893
  reactions, 893–897
    addition-elimination mechanism, 894–895
    elimination-addition mechanism, 895–898
  transmetallation, 899
Haloform reaction, 367–368
Halogenation
  of aldehydes and ketones, 366–368
  of alkanes, 77–87
  of alkenes, 280–281
  of alkyl benzenes, 902–904
  of allylic systems, 535–536
  of aromatic amines, 972
  of benzene, 581–584, 901–902
  of phenols
    in acidic medium, 1014–1015
    in basic medium, 1006–1007
  of phenyl ethers, 1014–1015
Halogens
  addition to alkenes, 280–281
  electronegativity, 6
  formation of hypohalous acids, 282
  size, 97
Halohydrins
  epoxides from, 648–649
  halomethylene, (*see,* Carbenes)

Halonium ions, 280–282
Halothane, 102
Hammett, Louis P., 947
Hammett equation, 947–950
Hammett substituent constants, 949 *t*
Handedness (*see*, Chirality)
Hantzsch pyridine synthesis, 1097–1098
Hardening, of fats, 507–508
Harmonic oscillator approximation, 330–331
Haworth, Walter N., 699
Haworth projections, 699
Heat, **73**
Heat of atomization, 92
Heat of combustion, **88**, 90
  relation to heats of formation, 90
Heat of formation (*see* Appendix 1 of the text for specific compounds), **89**, 90
  and stability, 264
  use in calculating heats of atomization, 92
  use in estimating possible reaction, 89–90
Heat of hydrogenation, 300
  alkenes and dienes, 540
Heat of reaction (**see also**, Enthalpy), **43**
  role in equilibria, 374–376
Heavy water, 163–164
Heisenberg uncertainty principle, 15, 61, 73, 178
α-Helix, in proteins, 850, 852
Hell-Volhard-Zelinsky reaction, 437–438
Hemiacetals, 372–373
  cyclic
    preparation, 679–680
    reactions, 680
  α- and β-D-glucose, 698–699
Hemiaminals, 380
Hemiketals, 372–373
  cyclic, 679–680
Hemin, 855, 1077
Hemoglobin, 855, 1077
  function, 856
Hemopyrrole, 1077
Heneicosane, 53
Heptacene, 1058
Heptadecanoic acid, physical properties, 426 *t*
Heptalene, 1123
Heptamethylbenzenonium ion, 913
Heptanal, 291
  physical properties, 352 *t*
n-Heptane, 53
  infrared spectrum, 331
  in gasoline, 88
  physical properties, 55 *t*
Heptanoic acid, physical properties, 426 *t*
2-Heptanone
  infrared spectrum, 356
  physical properties, 353 *t*
Heptatriene, 1121
n-Heptylamine, physical properties, 770 *t*
Herbicides, 103
Heroin, 805
Heteroatom, **606**, 648
Heterocyclic compounds, **606**, 1065–1112
  aromatic
    condensed five-membered rings, 1083–1088
    five-membered rings, 1072–1083
Heterocyclic compounds [*cont.*]
  azoles, 1088–1095
  classification, 1065
  cyclic ethers, 648–655
  diazines, 1109–1112
  isoquinoline, 1104–1109
  nomenclature, 1066
  nonaromatic
    five- and six-membered rings, 1071–1072
    four-membered rings, 1069–1071
    nomenclature, 1066–1067
    three-membered rings, 1067–1069
  pyridine, 1095–1104
  quinoline, 1104–1109
Heterogeneous reaction, **158**
Heterolysis, **78**
Heterolytic cleavage, **78**
Hexaborane, 286
Hexacene, 1058
1,2,3,4,5,6-Hexachlorocyclohexane, preparation, 901–902
Hexadecanoic acid (*see also*, Palmitic acid), physical properties, 426 *t*
1,5-Hexadiene (biallyl), 533
  rearrangement, 1020
(E,Z)-Hexa-2,4-diene, 1131
Hexahelicene, 1060
Hexamethylbenzene, 585, 913
  complexed with chloranil, 1029
    stereoscopic figure, 1029
  preparation, 910
Hexamethylphosphoric triamide (HMPT), 143, 144
Hexanal, physical properties, 352 *t*
Hexane, 53
  physical properties, 55 *t*
Hexanedioic acid, 435
1,6-Hexanediol, 292
2,5-Hexanedione, in Paal-Knorr synthesis, 1078
Hexanoic acid (*see also*, Caproic acid)
  infrared spectrum, 433
  physical properties, 426 *t*
2-Hexanol, preparation, 283
2-Hexanone, physical properties, 353 *t*
3-Hexanone, physical properties, 353 *t*
Hexaphenylethane, 905
1,3,5-Hexatriene
  electronic states, 595
  ultraviolet spectroscopy, 594
cis-1,3,5-Hexatriene, ring closure, 1126–1129
1-Hexene, oxymercuration-demercuration, 283
Hexoses, **694**
n-Hexyl alcohol, physical properties, 211 *t*
n-Hexylamine
  IR spectrum, 771
  physical properties, 770 *t*
1-Hexyne, 310
  NMR spectrum, 305
  physical properties, 306 *t*
  purification, 307
2-Hexyne, physical properties, 306 *t*
3-Hexyne, physical properties, 306 *t*
Hinsberg test, 790

Histidine, 476, 816, 1091
  in heme, 854
  physical properties of, 817 *t*
  p*K* values, 817 *t*, 820
Hofmann degradation, 494–495, 793–796
  Hofmann rule, 795
  stereochemistry, 795–796
Hofmann exhaustive methylation (*see,* Hofmann degradation)
Hofmann rearrangement, 785–786
Hog kidney D-amino acid oxidase, 827
Hog renal acylase, 827
Homocuprates (*see,* Cuprates)
Homolog, **53**
Homologous series, **53**
Homolysis, **78**
Homolytic cleavage, **78**
Homolytic substitution, biomolecular (*see also,* Halogenation), 145
Homoserine lactone, 845
Honey, composition, 726
Hooke's law, model of vibration, 330–331
Houben-Hoesch synthesis, 1016
Hückel, Erich, 1119
Hückel MO system, 1128–1129
Hückel $4n + 2$ rule, 577, 1119–1125
  in cycloaddition reactions, 1133–1136
  in ring closure, 1126–1136
Hughes, Edward D., 129
Hund's rule, 575
Hunsdiecker reaction, 445
Hybrid orbitals, 23–28
  and bond angles, 96
  energies of, 26, 28
  in alkyl halides, 96
  p character of, 26, 28
  relative electronegativities of, 429
  s character of, 26, 28
  sp, 23–25
  sp^2, 25–26
  sp^3, 25–27
Hydration
  of aldehydes and ketones, 368–372
  of alkenes, 279
  of alkynes, 358–359
Hydrazine, 379
  in Gabriel synthesis, 780
  preparation from Raschig process, 144–145
Hydrazine hydrate, 397
Hydrazines, aromatic, from diazonium salts, 986
Hydrazobenzene, 963–965
  benzidine rearrangement, 1038
  reduction, 965
Hydrazoic acid, 786, 797
  pK_a, 797
Hydrazone, in Wolff-Kishner reduction, 397–398
Hydrazones, 379
Hydroboration
  of alkenes, 286–289
  of alkynes, 316–317, 319, 359
Hydrocarbons (*see also,* Alkanes; Alkenes, etc.; Polycyclic aromatic hydrocarbons)
  branched (*see,* Alkanes)
  saturated, 32, **53**
Hydrofluoric acid, 293
Hydroforming process, 581
Hydrogen, abundance of isotopes, 409 *t*
α-Hydrogen, acidity, 361–362
Hydrogenation
  catalysts, 276–277
  heat of, 300
  of acyl halides, 489
  of aldehydes and ketones, 395–396
  of alkenes, 276–277
  of alkylbenzenes, 921–922
  of alkynes, 311–312
  of benzene, 572–573
  of benzene derivatives, 623
  of butane, 89–90
  of cyclobutane, 637
  of cyclopropanes, 633
  of esters, 491
  of ethylene, 90
  of fats (hardening), 507–508
  of furan, 653
  of nitroarenes, 961
  of unsaturated carbonyl compounds, 559
  stereochemistry, 277
Hydrogen bonding
  anion solvation and, 143
  in alcohols, 213
  in amides, 457–458
  in amines, 768
  in carboxylic acids, 423, 457
  in DNA, 1141–1142
  in enols, 745
  in proteins, 848–849
Hydrogen bromide
  addition to 1,3-dienes, 542–543
  1,2- versus 1,4-addition, 544
  reaction with allylic alcohols, 529
Hydrogen cyanide
  addition to aldehydes and ketones, 682
  addition to unsaturated aldehydes and ketones, 555–556
  in situ generation, 384
Hydrogen fluoride, 933
Hydrogen halides, addition to alkenes, 278–279
Hydrogenolysis, 827, 913
Hydrogen peroxide, 9, 287–288
  oxidation of aldehydes, 391
  oxidation of alkylboranes, 287–288
  oxidation of amines, 792–793
Hydrolysis
  of acid anhydrides, 472
  of acyl cyanides, 746
  of acyl halides, 472
  of alkyl halides, 221–222
  of amides, 477–478
  of arenediazonium salts, 979–980
  of benzylic halides, 934
  of cyanohydrins, 682–683
  of cyclopropanecarboxylic acid esters, 634
  of enol ethers, 377
  of esters, 48–49, 473–477
  of fats (saponification), 507
  of glycosides, 701–702
  of halo acids, 682

Hydrolysis [*cont.*]
  of isomeric ethyl
    4-*t*-butylcyclohexanecarboxylates, 628
  of lactones, 684–685
  of nitriles, 433–434, 478–479, 737
  of phosphates, 503–504
  of phosphonates, 505
  of organometallic compounds, 163–165
Hydronium ion, Lewis structure, 12
Hydroperoxides, 222–223, 240
Hydrophilic groups in proteins, **849**
Hydrophobic groups in proteins, **849**
Hydroquinone, 999
  acetate, 1006
  in quinhydrone complex, 1028
  oxidation, 1023
Hydroxy-, as prefix, 667
Hydroxyacetophenone, 1016
Hydroxy acids, 681–687
  dehydration, 687
  lactide formation, 687
  lactone formation, 685–687
  natural occurrence, 681–682
  polymerization, 687
  preparation, 682–685
  reactions, 685–687
Hydroxy aldehydes, 675–681
  cleavage, 681
  cyclic hemiacetals from, 679–680
  dehydration, 678–679
  oxidation, 681
  preparation, 675–677
  reactions, 678–681
β-Hydroxy aldehydes, 385
α-Hydroxyalkanesulfonic acids, 500
Hydroxyanthraquinones, 1022
m-Hydroxybenzaldehyde, 979
N-Hydroxybenzamide, 484
Hydroxybenzene (*see*, Phenol)
o-Hydroxybenzoic acid (*see*, Salicylic acid)
γ-Hydroxybutyric acid, 685
Hydroxycarbonium ion, 372
Hydroxy ketones, 675–681
  cleavage, 681
  cyclic hemiketals from, 679–680
  dehydration, 678–679
  oxidation, 681
  preparation, 675–677
  reactions, 678–681
α-Hydroxy ketones, oxidation, 746
β-Hydroxy ketones, 385
Hydroxylamine, 9, 379, 484
Hydroxylamines, 792–793
  aromatic, preparation, 962
Hydroxylammonium ion, 9
β-Hydroxy-β-methylglutaryl CoA, 1159–1160
4-Hydroxy-4-methyl-2-pentanone (*see*,
    Diacetone alcohol)
Hydroxynaphthoquinones, 1022
15-Hydroxypentadecanoic acid, 685
  lactone, 685
α-Hydroxyphenylacetic acid (mandelic acid),
    683
α-Hydroxypropionic acid (*see*, Lactic acid)
Hydroxypyridines, 1102–1103
Hydroxyquinones, 1022
α-Hydroxy sulfonic acids, 500
Hyperconjugation, 600, 601
Hypo (sodium hyposulfite), 1027
Hypochlorite, preparation, 144
Hypohalite, oxidation
  of aromatic ketones, 939
  of methyl ketones, 561
Hypohalous acids, 282
Hypophosphorous acid, 984

I

α-D-Idose, conformations, 703
D-(−)-Idose, 697
Imidazole
  basicity, 1090–1091
  electrophilic substitution, 1094–1095
  hydrogen bonding in, 1090
  in histidine, 1091
  numbering system, 1089
  orbital structure, 1089
Imidazole ring, 476
Imidazoles, preparation, 1094
Imines, 34, 378–379, 493
  in reduction of nitriles, 781
  reduction, 782–783
Imino esters, 482
Immonium ion, 772, 783
1-Indanone, 933
Indanthrene Blue R, 1149
Indanthrone, 1149
Indene, 1043
Indicators, 989
  acid-base, 1017
Indigo, 1145, 1146
Indigoid dyes, 1145, 1149
Indole, 1066
  electrophilic substitution, 1086–1088
  NMR spectroscopy, 1076
  numbering system, 1083
  preparation, 1085
Indole-3-carboxaldehyde, 1087
Indole-2-carboxylic acid, 1085
Indoles
  natural occurrence, 1084
  preparation, 1084–1085
Inductive effects, 217
  and acidity of alcohols, 428
  and acidity of carboxylic acids, 428–429
  and carbonium ion stability, 370
  carboxy groups, 738
Infrared active transitions, **328**
Infrared inactive transitions, **328**
Infrared radiation, 170, 325–327, 593
  regions of spectrum, 326–327
Infrared spectroscopy (*see also* specific families,
    specific compounds, and Appendix VI
    of the text), 325–342
  absorption bands
    cell length and, 329–330
    combination bands, **329**

Infrared spectroscopy [*cont.*]
    overtone, 329
    representation of, 329
  analysis of spectra, 332–333
  spectrometers, 341–342
  theory, 327–332
  use in alcohol analysis, 342
Initiation step, 78
Initiator, 84
Inner salts (*see,* Zwitterions)
Insecticides, 103
Insulin, 847
  amino acid sequence, 832
  disulfide bridges in, 848
  function, 856
Integrator, 179
Interference of wave functions, 22
Intermolecular forces
  polar, 457
  Van der Waals (*see*, Van der Waals forces)
Internal conversion, **1151**
Intoxalyzer, 342
Invertases, 726
Iodic acid, 671, 689
Iodination (*see also,* Halogenation), of methane, 85
Iodine, abundance of isotopes, 409 *t*
p-Iodobenzaldehyde, 937
Iodobenzene
  dipole moment, 871
  nitration, 880
  preparation, 893
Iodobenzene diacetate, 901
Iodobenzene dichloride, 901
Iodobenzenes
  oxidation, 900
  transmetallation, 899
2-Iodobutane
  chirality, 105–106
  optical rotation, 110
  stereoscopic figures, 106
Iodoform, 96
Iodoform test
  alcohols, 368
  ketones, 368
Iodomethylzinc iodide, 630
Iodosobenzene, 901
2-Iodothiophene, 1081
Iodoxybenzene, 901
Iodoxybenzoic acid, pK_a, 959
Ionic bonding, **6**
Ionization, 404
Ionization potential, **5**, 404
  of some compounds, 410 *t*
Ion pair, **217**
Ion product constant (*see*, Dissociation constant)
IR (*see*, Infrared)
Iridium, as catalyst, 277
Iso-, as prefix, **63**
Isobornyl chloride, 645
Isobutane, 75
  alkylation with isobutylene, 293
  bromination, 87
  chlorination, 82–83, 87
Isobutane [*cont.*]
  combustion, 88–89
  physical properties, 67 *t*
Isobutyl alcohol, reaction with phosphorous tribromide, 230
Isobutylamine, mass spectrum, 773
Isobutyl bromide, preparation, 230
Isobutyl chloride, in chlorination of isobutane, 82
Isobutylene, 239, 256
  polymerization of, 292–293
  reaction with hydrogen chloride, 228
Isobutylene oxide, ring opening of, 651
Isobutyl halides, in S_N2 reactions, 138
Isobutyl radical, 64
Isobutyraldehyde, 386
Isobutyric acid, NMR spectrum of, 432
Isocyanates, 495, 786
  carbamate ester formation, 801
  polyurethane production, 802
  preparation, 801–802
  reaction with water, 801
Isodurene, 914, 917
Isoelectric point, **819**
1,3-Isoestrone, 1172
Isohexane, 63
Isoleucine, 815
  physical properties of, 817 *t*
Isomerism (*see also,* Keto-enol tautomerism; Stereoisomerism), **2**
  cis-trans, 256–257
    cyclohexane derivatives, 620–621
    in photochemical reactions, 1153
Isomers (*see also,* Stereoisomers; Conformational isomers; Configurational isomers), **62**
  conformational, **67**
  possible number of, 63
  structural, **67**
Isooctane, standard for octane ratings, 292
Isopentane,
  conformations, 66–67
  physical properties, 67 *t*
Isopentenyl pyrophosphate, 548, 1162
Isophthalic acid, 735, 929
Isoprene
  in Diels-Alder reaction, 624
  polymerization of, 547–548
  preparation of, 546
Isoprene unit, 643, 1162
Isopropyl alcohol, physical properties, 211 *t*
Isopropylamine, physical properties, 770 *t*
Isopropylbenzene (*see also*, Cumene), preparation, 910
Isopropyl bromide
  in bromination of propane, 85
  reaction with ethoxide, 299
  reaction with sodium thiocyanate, 143
Isopropyl cation, 149
Isopropyl chloride
  in chlorination of propane, 82
  NMR spectrum, 172
Isopropyl halides, in Friedel-Crafts alkylation, 910

- 1-Isopropyl-4-methylbenzene (*see*, *p*-Cymene)
- 2-Isopropyl-5-methylcyclohexanol (*see*, Menthol)
- Isopropyl radical, 64
- Isopropyl thiocyanate, preparation, 143
- Isoquinolines
  - preparation, 1104, 1107
  - reactions, 1104, 1107–1109
- Isothiazole
  - electrophilic substitution, 1094–1095
  - numbering system, 1089
- Isotope effects, in elimination reaction, 267, 268–269
- Isotopes, natural abundance, 409 *t*
- Isotopically labelled compounds, nomenclature, 163
- Isotopically labelled hydrocarbons, preparation of, 163–164
- Isotopic tracers, in protonation of benzene, 585
- Isoxazole
  - basicity, 1090
  - electrophilic substitution, 1094–1095
  - numbering system, 1089
- Isoxazoles, preparation, 1092–1093
- IUPAC (International Union of Pure and Applied Chemistry), **64**
- IUPAC nomenclature (*see* specific families)

J

- Jablonski diagram, 1152
- Jacobsen reaction, 914
- Joule, **326**
- Juglone, 1023
- Juvabione, 446
- Juvenile hormone, 446

K

- Karplus curve, 658
- Kekulé, Friedrich August, 3, 8, 569
- Kekulé structures, **8**
- Kekulé theory of valence, 569–570
- Keratins, 847
- α-Keratins
  - function, 856
  - α-helix in, 851
- β-Keratins, pleated sheet structure, 851
- Kerosene, **70**
- Ketals, 372–378
  - from diols, 672–673
  - from monosaccharide, 705–708
  - pyrolysis, 376–377
  - use as protecting group, 376, 526–527, 707
- Ketene, 563
  - orbital structure, 564
- Ketenes, 563–564
  - from diazo compounds, 799
  - preparation of, 563–564
  - reactions, 564
- Keto-, as prefix, 667
- 1,2-Keto acids, preparation, 746, 760
- 1,3-Keto acids
  - decarboxylation, 747–748
  - preparation, 760
- 1,5-Keto acids, preparation, 757
- α-Keto aldehydes, preparation, 746
- β-Keto aldehydes
  - keto-enol equilibria, 750
  - preparation, 744, 760
- Keto-enol tautomerism
  - acid-base catalysis, 361–362
  - dicarbonyl compounds, equilibria, 748–750
  - equilibria, 360–363
  - phenols, 998
  - racemization in, 365
- β-Keto esters, 470
  - alkylation, 753
  - cyclic, preparation, 743
  - keto-enol equilibria, 748–750
  - preparation, 743–745
  - reverse Claisen condensation, 758–759
- Keto esters
  - intramolecular Claisen condensation, 743, 744
- α-Ketoglutaric acid, 379
- Ketohexoses, **694**
- Ketones, **32–34**, 348–398
  - acidity of, 467–468
  - addition
    - of acetylide anions, 383
    - of alcohols, 372–376
    - of ammonia derivatives, 378–381, 783
    - of cyanide, 383–385
    - of 1,3-dithianyl anions, 677
    - of Grignard reagents, 381–383
    - of phosphorus pentachloride, 390–391
  - aldol condensation, 386–388, 744
  - aromatic
    - cleavage of, 941
    - nomenclature, 930
    - preparation, 931–934
      - Friedel-Crafts acylation, 588–589
    - reactions, 938–941
    - reduction, 914–915
  - Baeyer-Villiger oxidation, 392–393
  - catalytic hydrogenation, 395–396
  - Clemmensen reduction, 398
  - condensation, with malonic esters, 754–755
  - conversion into amides (Schmidt reaction), 825
  - cyclic, infrared spectroscopy, 655–656
  - 2,4-dinitrophenylhydrazone derivatives, 894
  - enolization, 360–368
  - exchange reaction with water, 371–372
  - from enamines, 804
  - haloform reaction, 367–368
  - halogenation, 366–368
  - hydration, 368–372
  - hydroxy, 675–681
  - in enamine formation, 803
  - infrared spectroscopy, 355–357, 655–656
  - Knoevenagel condensation, 754–755
  - mass spectroscopy, 416–417
  - mixed Claisen condensation, 743–745
  - NMR spectroscopy, 354–356
  - nomenclature

Ketones [*cont.*]
    common system, 350-351
    IUPAC, 351-352
  Norrish type reactions, 1153-1154
  oxidation, 368, 392-394
  physical properties of, 352-354
  preparation of, 357-359
    from carboxylic acids and alkyllithium reagents, 441
    from ethyl acetoacetate, 752
    from organometallic compounds and acyl halides, 485-487
    from organometallic compounds and esters, 487-488
    from organometallic compounds and nitriles, 488-489
    hydration of alkynes, 315, 358-359
    hydroboration-oxidation of alkynes, 317
    oxidation of alcohols, 232-234, 357-358
    oxidation of alkenes, 290-291, 358
  reactions, 360-398
    addition of bisulfite, 500-501
  reduction
    to alcohols, 394-398
    to alkanes, 397-398
    to pinacols, 670
  Reformatsky reaction, 684
  stability versus aldehydes, 370, 375
  structure, 348-349
  ultraviolet spectroscopy, 596-599
  unsaturated, 550-560
  Wittig reaction, 388-390
  Wolff-Kishner reduction, 397-398
Ketopentoses, 694
Ketoses, **694**
Ketoximes (*see,* Oximes)
Ketyl, 670
Kiliani-Fischer synthesis, 715-717
Kinetic energy, 73
Kinetic energy of molecules, 44
  energy factor in reaction rates, 45
Kinetic order, 135
Kinetics
  second-order, **127-128**
  versus thermodynamic control, 543
Knockout drops, 370
Knoevenagel condensation, 754-755
Knorr pyrrole synthesis, 1079
Kolbe synthesis, 1008-1009
Kochi reaction, 446
Körner's absolute method, 864-865

L

Lacquers, 728
Lactalbumin, 856
Lactams, 1072
β-Lactams, preparation, 1070
Lactic acid, 681, 729
  lactide formation, 687
  resolution, 776
Lactides, 687
  preparation, 687
Lactobionic acid, 724
Lactones
  from aldonic acids, 710
  from hydroxy acids, 685-687
  hydrolysis of, 684-685
  infrared spectroscopy, 657
  preparation, 393
β-Lactones, preparation, 1070
γ-Lactones, 685
δ-Lactones, 685
Lactonization, 685-687
Lactose, 724-725
Ladenburg, Albert, 570
Ladenburg benzene, 570
Lanosterol, 1165
Latex, 547
Lauric acid (*see also,* Dodecanoic acid), 424, 507
  physical properties, 426 *t*
Lavoisier, Antoine Laurent, 2, 35
LCAO (*see,* Linear combination of atomic orbitals)
LDA (*see,* Lithium diisopropylamide)
L-Dopa, 1033
Lead tetraacetate, oxidation of diols, 671
Leaving group, **128**
  and basicity, 141-142
Le Bel-Van't Hoff theory, 718
Le Chatelier principle, 441
Lemieux-Johnson reaction, 671-672
Lemon oil, 644
Lepidine, synthesis, 1106
Leuchs' anhydrides, 838
Leucine, 815
  physical properties, 817 *t*
  polymerization, 834
L-Leucine, 827
Leucine anhydride, 834
Leukart reaction, 784
Leuco base, 1149
Levorotatory, **108**
Levulose (*see,* D-(−)-Fructose)
Lewis base, **132**
Lewis structures, 5-8, **6**, 9-10
  and resonance structures, 10-11
  charge separation in, 13, 14
  formal charge in, 7, 8
  rules for deriving, 7
  use in interpreting bond distances, 9-10
von Liebig, Justus, 35
Light
  electric and magnetic fields in, 107
  monochromatic, **108**
  plane polarized, **107-108**
Light petroleum ether, 70
Ligroin, **70**
Limonene, 1157
Lindane, 901
Lindlar's catalyst, 311
Linear combination of atomic orbitals (LCAO), 534-535
Linear polyethylene, 294, 296
Linoleic acid, 563
Linolenic acid, 507, 563

Linseed oil, 563
Lipid, **508**
Liquefied petroleum gas (LPG), 69
Literature, 66, 1174–1182
Lithium aluminum hydride, 394
  compared with lithium borohydride, 491
  reduction
    of acyl halides, 490
    of aldehydes and ketones, 394–395
    of alkyl azides, 797
    of amides, 491–492, 784
    of benzylic esters, 915
    of carboxylic acids, 440
    of epoxides, 652
    of esters, 491
    of nitriles, 493, 781–782
    of oximes, 782
    of unsaturated ketones, 558
    of various functional groups, 395 *t*
Lithium-ammonia reduction, of unsaturated carbonyl compounds, 559–560
Lithium borohydride, 491
  reduction of epoxides, 652
Lithium dialkylcuprates, 486–487
  addition to unsaturated carbonyl compounds, 557–558
  preparation, 557
Lithium diisopropylamide (LDA), 363–364
  preparation of, 523
Lithium dimethylcopper, preparation, 165
Lithium isopropylcyclohexylamide, 470
Lithium tri-*t*-butoxyaluminum hydride, 490
London force, **55**
Lone pair electrons (*see also*, Electrons, nonbonded pairs), 8
  nucleophilicity of, 135
  stability, 467
Longifolene, 645
LSD (*see*, Lysergic acid diethylamide)
Lucas reagent, **225**
Lucite, 562–563
Lutidines, 1097
Lycopene, 1144–1145
Lycopodine, 807
Lysergic acid diethylamide (LSD), 806
Lysine, 816, 860
  physical properties, 817 *t*
  pK values, 817 *t*, 820
  preparation, 825
  protecting groups for, 839
D-(−)-Lyxose, 697

M

Magnesium, reaction with alkyl halides, 158–159
Magnetic quantum number, 16
Magnetic scanning, in mass spectroscopy, 406
Malachite green, 1149
Malaria, 103
Maleic acid, 735
Maleic anhydride, 740, 1056
Malic acid, 681
Malonic acid, 736
  acidity, 738
  decarboxylation, 739, 748
  preparation, 737
Malonic esters, alkylation, 757, 822–823
Malonic ester synthesis, 757
Maltobionic acid, 723
  methylation, 723
Maltose
  α and β anomers, 722
  from starch, 729
  hydrolysis, 694, 724
  oxidation, 722–723
  structure, 722–724
Mandelic acid, 681, 683, 692
Manganese dioxide, 554–555
  oxidation of allylic alcohols, 554–555
D-Mannitol, 709
D-(+)-Mannose, 697, 700, 717
  anomers, specific rotations, 734
  chain shortening, 717
  mannoside formation, 700–701
  phenylosazone formation, 715
  reduction of, 709
Mannosides, **700**
  formation, 701
Markovnikov's rule, 278
Marsh gas, 69
Mass spectrometers, 404–407
Mass spectroscopy, 404–417
  base peak, **407**
  fragmentation, 404, 410–417
  instrumentation, 405–407
  ionization in, 404, 410
  isotope peaks, 407–410
  McLafferty rearrangement, **416**
  molecular ion, **407**
  separation of ions, 405–406
Mass spectrum, **404**
Mass-to-charge ratio, 404, 406
Matricarin, 644
Mauve, 1147, 1149
McFadyen-Steven reaction, 935
McLafferty rearrangement, **416**
Me, symbol for methyl group, 159
Meisenheimer complexes, 927
Meissner, William, 805
Melanins, 1145
Melibiose, 734
Melting, entropy of, 67
Melting point (*see also*, specific compounds), chain branching and, 67
Membranes, cellular, 509
Menthol, 357, 644
Menthone, preparation, 357
Mercaptans (*see also*, Thiols), preparation from alkyl halides, 132
Mercapto-, as prefix, 667
Merck Index, 1176
Mercuric ion, 283
  as catalyst, 324
Mercurochrome, 166
Mercury vapor, as photosensitizer, 1155–1156
Merrifield, Robert B., 839

Merrifield method (*see,* Solid-phase technique)
Merthiolate, 166
Mescal buttons, 805
Mescaline, 41, 806, 1032
Mesitoic acid, 959
Mesityl-, as prefix, **891**
Mesitylene, 890
  halogenation of, 892
  nitration, 960
Mesityl oxide, 554
  ultraviolet spectra, 598
Meso compounds, **117**
  in carbohydrate chemistry, 696
  optical inactivity, 117–118
  symmetry in, 117–118
Mesylates, **501**
Mesyl chloride, 501
Metabolic processes, 1156
Metabolism, **1156**
Metabolites
  primary, **1156**
  secondary, **1156**
meta-directors, 869
meta-isomer, 862
Metaldehyde, 378
Methane, 53, 73
  bromination, 85
  chloroination, 77–82
  combustion, 35
  electronic transition, 593–594
  enthalpies of halogenation, 84 *t*
  fluorination, 84
  fragmentation, 404, 410–411
  iodination, 85
  ionization potential, 410 *t*
  mass spectrum, 411
  natural occurrence, 69, 71
  physical properties, 55 *t*
  pK_a, 467
  production from beryllium carbide, 71
  pyrolysis, 307
  sp^3 hybridization, 25–27
  stereoscopic figure, 27
Methanesulfonate ion, 137
Methanesuflonic acid, 500, 501
Methanesulfonyl chloride (mesyl chloride), 501
Methanethiol, IR vibration frequency, 347
Methanoic acid (*see,* Formic acid)
Methanol (*see also,* Methyl alcohol)
  ionization potential, 410 *t*
  pK_a, 439
  reaction with potassium, 31
Methionine, 40, 815, 845
  physical properties, 817 *t*
m-Methoxyaniline (*see, m*-Anisidine)
Methoxybenzene (*see,* Anisole)
β-(*p*-Methoxybenzoyl)propionic acid, 1015
Methoxycarbonyl-, as prefix, 456
1-Methoxycyclohexene, 376
2-Methoxy-3-hydroxy-5-methyl-1,4-benzoquinone (*see,* Fumigatin)
Methoxymalonic acid, 734
6-Methoxy-1-tetralone, 1170–1171
N-Methylacetamide, physical properties, 458 *t*
Methyl acrylate, 642
α-Methylacrylic acid, 562
Methyl alcohol, 9, 54, 223
  geometry, 206
  physical properties, 211 *t*
  reaction with iodine, 231
Methylallyl cation, 531
o-(α-Methylallyl)phenol, 1020
Methylaluminum dichloride, physical properties, 158 *t*
Methylamine, 13
  basicity, 774, 819
  physical properties, 770 *t*
  structure, 766
p-Methylaminophenol, 1027
Methylammonium ion, pK_a, 774, 819
o-Methylaniline, basicity, 968, 994
Methyl anion, 306
Methylation, of monosaccharides, 704–705
Methylbenzene (*see,* Toluene)
Methylbenzoic acid (*see,* Toluic acid)
2-Methyl-1,4-benzoquinone (*see,* Toluquinone)
4-Methylbiphenyl, 985
Methyl bromide, 97 *t*
  IR vibration frequency, 347
2-Methyl-1,3-butadiene (*see,* Isoprene)
3-Methyl-1,2-butadiene, 567
2-Methylbutanal, McLafferty rearrangement in, 416
3-Methylbutanal, McLafferty rearrangement in, 416
2-Methyl-2-butanol, mass spectrum, 414–415
3-Methyl-1-butanol, mass spectrum, 415–416
3-Methyl-2-butanol, 381
2-Methyl-2-butene, physical properties, 259 *t*
3-Methyl-2-butenoic acid, 561
3-Methyl-1-buten-3-ol, 546
3-Methyl-3-buten-2-one, 679
cis-4-Methyl-1-*t*-butylcyclohexane, conformational analysis, 621
Methyl *n*-butyl ether, preparation, 143
Methyl *t*-butyl ketone (pinacolone), 673
3-Methyl-1-butyn-3-ol, 546
Methylcarbinol group, test for, 368
Methyl cation, 149, 404, 411
  Lewis structure of, 8, 12
  sp^2 hybridization in, 26
Methyl chloride, 42, 97 *t*
  boiling point, 77
  dipole moment, 870
  in chlorination of methane, 77
  ionization potential, 410 *t*
  IR stretching frequency, 347
  reaction with hydroxide ion, 127
Methylcopper, 162, 165
Methyl cyanide (*see also,* Acetonitrile), 138
Methylcyclohexane, 623
  conformations, 618–619
  Newman projections, 619
2-Methyl-1,3-cyclohexanedione, 753
4-Methylcyclohexanol, 623
Methyl 4-cyclohexenecarboxylate, 624
trans-2-Methylcyclopentanol, 287
1-Methylcyclopentene, hydroboration, 287

o-Methyl-N,N-dimethylanilinium ion, pK_a, 994
2-Methyldodec-2-enoic acid, 562
Methylene blue, 1150
Methylene bromide, 96
Methylene chloride
  boiling point, 77
  in chlorination of methane, 77
  reaction with organolithium compounds, 632
Methylenecyclobutane, 636
Methylenecyclohexane, 793
Methylene group, vibrational modes for, 328
Methyleneimine, 13
  protonated (*see*, Protonated methyleneimine)
Methyl fluoride, 97 *t*
  hybrid orbitals, 96
Methyl formate, structure, 452
2-Methylfuran, physical properties, 1075
3-Methylfuran, physical properties, 1075
Methyl α-D-galactoside, acetal formation, 707
Methyl β-D-galactoside, 701
Methyl α-D-glucopyranoside, 702
Methyl β-D-glucopyranoside, 702
3-O-Methylglucose, synthesis of, 707
2-Methylheptane, 71
2-Methyl-1-heptene, infrared spectrum, 334
6-Methyl-1-heptene, 358
  ozonolysis, 291
2-Methylhexahelicene, 1060
  stereoscopic figure, 1060
5-Methylhexanal, 291, 358
2-Methyl-2-hydroxybutanoic acid, 683
Methyl iodide, 97 *t*
  IR vibration frequency, 347
  preparation of, 231
  reaction with cyanide ion, 137–138
  reaction with nitrite ion, 137
  reaction with sulfate ion, 136
  reaction with sulfite ion, 137
  reaction with thiosulfate, 137
Methyl isocyanide, 138
2-Methyl-5-isopropylaniline, 961
Methyl isopropyl ketone, NMR spectrum, 355
1-Methyl-7-isopropylphenanthrene, 919
Methyl isothiocyanate, 860
Methyl ketone group, test for, 368
Methyllithium, 165
  hydrolysis of, 163
  metal exchange reaction, 162
Methyl α-*d*-mannoside, 701
Methyl β-*d*-mannoside, 701
Methyl mercaptan, geometry, 207
Methylmercury, toxicity of, 166–167
Methyl methacrylate
  polymers of, 562–563
  preparation of, 562
Methyl nitrite, 93, 137
Methyl *m*-nitrobenzoate, 950
Methylnitronate ion, resonance structures, 800
2-Methyl-3-nitrothiophene, 1082
2-Methyl-5-nitrothiophene, 1082
Methyl Orange, 989
2-Methylpentane
  mass spectrum, 413
  physical properties, 67 *t*
3-Methylpentane
  mass spectrum, 413
  physical properties, 67 *t*
4-Methyl-1-pentanol, 288
2-Methyl-2-pentene, infrared spectrum, 336
4-Methyl-1-pentene
  hydroboration-oxidation, 288
  reaction with hydrogen bromide, 278
p-Methylphenol, hydrogenation of, 623
Methylphenols (*see*, Cresols)
Methyl phosphate, pK_a, 502
2-Methyl-2-propanol (*see also*, *t*-Butyl alcohol), 339
  infrared spectrum, 339
2-Methyl-1-propene, physical properties, 259 *t*
Methyl propionate, NMR spectrum, 459
Methyl pyrazole-3-carboxylate, 1093
3-Methylpyridine N-oxide, 1099
5-Methylpyridine-3-sulfonic acid, 1100
Methylpyrroles, physical properties, 1075
Methyl radical, 54, 74, 404, 411
  in chlorination of methane, 78
  Lewis structure, 8
  structure, 74, 79
Methyl sulfate ion, 136, 141
Methylthiophenes, physical properties, 1075
m-Methylthiophenol, 981
Methyl thiosulfate ion, 137
Methyl urea, 484
Methyl vinyl ketone
  electronic transitions in, 597
  in Diels-Alder reaction, 624
  in Michael addition, 757
  ultraviolet spectroscopy, 596–597
Methyl β-D-xyloside, methylation, 704
Metol, 1027
Mevalonic acid, 1160
Mevalonic acid-5-phosphate, 1161
Mevalonic acid-3-phosphate-5-pyrophosphate, 1161–1162
Mevalonic acid-5-pyrophosphate, 1161
Micelles, **430**, 508, 509
Michael addition, 755–758
  mechanism 756
  quinones, 1029–1030
  with enamines, 804
Michler's ketone, 973
Microanalysis, 37
Micron, **326**
Microwave radiation, 170, 325
  energy of, 593
Microwave spectroscopy, 170
Migratory aptitude, 393
Milk, 681
  lactose in, 724
Mitscherlich, E. A., 569, 682
Möbius MO system, 1128–1129
Möbius strip, 1129
Molecular formula
  determination of, 37
  from mass spectroscopy, 407
Molecular ion, in mass spectroscopy, **407**
Molecularity, **135**
Molecular models, 30–31

Molecular orbital, 21
Molecular orbitals, 21
  antibonding, 21, 22, 594
  bonding, 22, 594
  energies of, 22
  localization, 28
  π (*see,* π-Molecular orbitals)
Molozonide, 291
Monochromator, 341
Monomer, **292**
Monosaccharides, **693**
  acetal and ketal formation, 750–708
  anomers, 698–699
  chain extension, 715–717
  chain shortening, 717–718
  classification, 694
  esterification, 708–709
  ether formation, 704–705
  Fehling's test, 710
  Fischer projections, 693, 698
  Haworth projections, 699
  Kiliani-Fischer synthesis, 715–717
  methylation, 704–705
  osazone formation, 714–715
  oxidation
    by periodic acid, 712–714
    to aldonic acids, 709–711
    to saccharic acids, 711–712, 719, 721
  phenylhydrazone formation, 714–715
  protecting groups for, 707
  reactions, 704–718
  reducing and nonreducing, **711**
  reduction, 709
  ring forms
    furanose, 699
    pyranose, 699, 702–703
  Ruff degradation, 717
  stereochemistry, 695–697
    Fischer proof, 718–722
  structure, as cyclic hemiacetals, 698
  Tollen's test, 710
  Wohl degradation, 718
Monosodium glutamate (MSG), 821
Monoterpenes, **549**, **643**
Mordant dyes, 1147
Morphine, 40, 805
  derivatives, 805
Mosquito, control of, 103
Motion
  molecular, 170
  rotational, 57–62, 170
  vibrational (*see,* Vibrational motion)
Mucic acid, 711
Murex, 1149
Muscalure, 323
Mustard gas, 40, 249
Mutarotation, **699**
Mylar film, 943
Myoglobin, 844, 855, 1077
  function, 856
  stereoscopic figure, 855
Myosin, function, 856
Myristic acid, 424, 507
  physical properties, 426 *t*

N

n-, as prefix, 454
NADP (*see,* Nicotinamide adenine dinucleotide phosphate)
Naphthalene, 1038
  aromaticity, 1123
  preparation, 918
Naphthalene-1-*d*, 1050
Naphthalenes
  Bucherer reaction, 1052–1053
  electrophilic substitution, 1046–1049
  Friedel-Crafts acylation, 1048–1049
  nomenclature, 1045
  numbering system, 1038
  oxidation, 944, 1049–1050
  reactions, 1046–1053
  reduction, 1050
  substituted,
    reactions, 1050–1053
Naphthalenesulfonic acids, 1048
  naphthols from, 1050
1-Naphthol, 1050
2-Naphthol, 1045, 1052
1-Naphthonitrile, 953
1,4-Naphthoquinone, 1022, 1024, 1046, 1049
Naphthoquinones, 1022
  colored, 1145
2-Naphthylamine, 1052
Natural gas, **69**
Neo-, as prefix, **63**
Neohexane, 63
Neopentane, 63
  chlorination, 83
  physical properties, 67 *t*
Neopentyl alcohol, physical properties, 211 *t*
Neopentyl chloride, in chlorination of neopentane, 83
Neopentyl halides, in S_N2 reactions, 139
Neopentyloxonium ion, 227, 228
Neopentyl radical, 64
Neoprene, 547
Nernst equation, 1025
Newman projections, **58**
Niacin, 1099
Niacinamide, 1099
Nickel, as catalyst, 277
Nicol prism, 108
Nicotinamide adenine dinucleotide phosphate (NADP), 1160
Nicotine, 806
  oxidation, 1099
Nicotinic acid (niacin), 1099
Nieuwland enyne synthesis, 318
Ninhydrin, 829
Ninhydrin reaction, 829–830
Nitrate ion, 132
Nitrates, 505
  preparation, 132, 505
  uses, 505
Nitration
  of aromatic amines, 973
  of benzene, 586–587
  of benzene derivatives, 869

- Nitration [*cont.*]
    - partial rate factors, 880
  - of naphthalene, 1046
  - of phenols and phenyl ethers, 1012–1014
- Nitrenes, 495, 785
- Nitric acid
  - addition to alkenes, 586
  - as oxidizing agent, 435
  - oxidation
    - of alcohols, 233–234
    - of aldehydes, 435
    - of benzene derivatives, 919, 942
    - of cyclohexanone, 393–394
    - of glycosides, 711–712
    - of monosaccharides, 711–712, 719, 721
  - reaction with alcohols, 505
- -nitrile, as suffix, 667
- Nitrile oxides
  - cycloaddition to acetylenes, 1092–1093
  - preparation, 1093
- Nitriles, 34, 451
  - acidity of, 469
  - anions, reactions, 470
  - aromatic
    - from halobenzenes, 942
    - from Sandmeyer reaction, 982
    - Stephen reduction, 937
  - basicity, 467
  - hydrolysis, 433–434, 478–479, 737
  - infrared spectroscopy, 460
  - NMR spectroscopy, 458
  - nomenclature, 455
  - orbital structure, 453
  - physical properties, 456–458
  - preparation, 434
    - from alkyl halides, 132
    - dehydration of amides, 494
    - summary, 462
  - reactions, 982
    - addition of ammonia, 485
    - addition of alcohols, 482
    - with organometallic compounds, 488–489
  - reduction, 493, 781–782
  - solubility, 458
  - ultraviolet spectroscopy, 602
- Nitrite ion
  - displacement on alkyl halides, 800
  - reaction with methyl iodide, 137
  - resonance stabilization, 534, 535
  - resonance structure of, 137
- Nitrites, 587
- *m*-Nitroacetophenone, 938
  - preparation, 884
- Nitroalkanes
  - acidity, 800
  - preparation, 800–801
  - reactions, 801
- *m*-Nitroaniline, 962
- *p*-Nitroaniline, 968
- Nitroanisoles, preparation, 1013
- Nitroarenes, 960–965
  - from amines, 971
  - preparation, 960, 982–983
  - properties, 960–961
- Nitroarenes [*cont.*]
  - reactions, 961–965
  - reduction, 961–962
- *m*-Nitrobenzaldehyde, 374, 939
- *p*-Nitrobenzaldehyde, 943
- *m*-Nitrobenzaldehyde dimethyl acetal, 374
- Nitrobenzene, 586, 962
  - dipole moment, 871
  - electrophilic substitution, 875–876
  - nitration, 869
  - NMR spectrum, 866
  - properties, 960
  - resonance structures for, 872
- *p*-Nitrobenzoic acid, 919, 942
- 2-Nitrobiphenyl, preparation, 1041
- 3-Nitrobiphenyl, 986
- Nitro compounds, 34, 800–801
  - reactions, 801
  - reduction, 781
- Nitroethane, pK_a, 800
- 2-Nitrofuran, physical properties, 1075
- Nitrogen, abundance of isotopes, 409 *t*
- Nitrogen dioxide, 93
- Nitrogen inversion, 767
- Nitrogen narcosis, 102
- Nitrogen-oxygen bonds, 9, 10, 11
- Nitrogen tetroxide, 1024
- Nitroglycerin, 505–506
- Nitro group
  - in electrophilic aromatic substitution, 586–587, 875–876
  - resonance structures, 586
- Nitromesitylene, 960
- Nitromethane
  - pK_a, 800
  - preparation, 93
  - resonance structures, 137
- aci-Nitromethane, 361
- 2-Nitro-4-methoxyacetanilide, 974
- 1-Nitronaphthalene, 1046
  - oxidation, 1049
- 2-Nitronaphthalene, 1046
- Nitronium ion, 586
  - Lewis structure, 9
- *o*-Nitrophenol, 1012
  - chelation in, 1012
- *p*-Nitrophenol, 1012
- 2-Nitropropane, pK_a, 800
- 3-Nitropyridine, 1100
- N-Nitrosamides, in biphenyl preparation, 985–986
- Nitrosation, of phenols and phenyl ethers, 1011–1012
- Nitrosoarenes, 963
- Nitrosobenzene, 962
- Nitroso compounds
  - aromatic, preparation, 975–976
  - from amines, 790
- *p*-Nitrosodimethylaniline, 975
  - condensation reactions, 975–976
- N-Nitroso-N-methylaniline, 976
- Nitrosonium ion, 790
- Nitrosophenols, 1011
  - preparation, 1011

β-Nitrostyrene, 801
Nitrosyl halides, 977
2-Nitrothiophene, 1080
  physical properties, 1075
3-Nitrothiophene, 1080
m-Nitrotoluene, 869
o-Nitrotoluene, 869
p-Nitrotoluene, 869
  nitration, 881
  NMR spectrum, 868
Nitrous acid, 137, 977
  hydrolysis of amides, 478
  reaction with amines, 790–792
Nitryl chloride
  geometric structure, 10
  Lewis structure, 10–11
  resonance structures, 10–11
NMR (*see*, Nuclear magnetic resonance)
Noble gases, inertness, 5
Node, **15**
Nomenclature
  Greek alphabet, 208
  in chemical literature, 66
Nonactin, 655
1,8-Nonadiyne, 318
Nonanal, physical properties, 352 *t*
Nonane, 53
  physical properties, 55 *t*
Nonanoic acid, physical properties, 426 *t*
5-Nonanol, 488
2-Nonanone, physical properties, 353 *t*
n-Nonylamine, physical properties, 770 *t*
Nootkatone, 1163
Norbornadiene, 1154
Norbornane, 640
  stereoscopic figure, 640
Nonbornanone, 671
  infrared spectroscopy, 656
Norethindrone, 41, 647
Norlutin, 647
Norrish type I reaction, 1153
Norrish type II reaction, 1154
Novocaine, 40
Nuclear magnetic resonance
  absorption frequency, 173–174
  carbon (CMR), 192–195
  carbon-proton off-resonance decoupling, **194**
  chemical shift (*see also* Appendix V of the text), 174–178, 183, 184, 191
  δ scale, **177**
  reference standard, 176
  τ scale, **177**
  complex splitting, 187–190
  conformational analysis, 177–178
  coupling constant, **182**, 184, 186–190
  downfield shift, **176**
  energy units, 173–174
  fluorine (F-NMR), 192
  Karplus curve, 658
  magnetic field strength, 173–174
  magnetic moment, 172
  magnetic moments, 181
  magnetic properties of nuclei, 192 *t*
Nuclear magnetic resonance [*cont.*]
  magnetogyric ratio, 173
  peak area and proton counting, 178–179
  peak codes, 191–192
  peak spacing (*see*, Coupling constant)
  problem solving, 190–192
  proton (PMR), 192
  protons
    aldehyde, 354–355
    alkyne, 304–306
    amine, 771
    aromatic, 579–580
    axial versus equatorial, 657
    benzene, 865–868
    carboxylic acids, 432
    chemical shifts, 174–178
    counting by peak area, 178–179
    diamagnetic shielding, **174–175**
    exchange with deuteroxide, 219–220
    magnetic equivalence, 178, 188
    nonequivalent, 180
    resonance, 181
    resonance value, **175**
    shielded, 174–175
    vinyl, 260–264
  shielding, 174–175
  signals, 181–182
    intensities, 178–179
    number of, 184
    positions of, 176–177
    splitting of, 180–190
  spectrometer, 175
  spectroscopy, 171–195
  spin flipping, 172, 174
  spin of nuclei, 172–174
  spin-spin coupling, 180–190
  spin states, 172–173
    energy difference, 173–174, 179
    population differences, 179
    saturation, 179–180
  theory, 171–174
  time scale, 178
  types of, 192
Nucleic acids, 693, 1110, 1138–1142
Nucleophilic addition
  base-catalyzed, 439–441
  to alkynes, 316
  to carboxylic acids, acid-catalyzed, 441–444
Nucleophilicity, 134–135, 135–138, 144
Nucleophilic substitution (*see also*, S_N1 mechanism; S_N2 mechanism)
  acid catalysts, 142
  alcohols, 142
  alkyl halides, 127–145, 152–153
  alkyl nitrates, 141
  alkyl sulfonates, 141
  allylic systems, 532–533
  at atoms other than carbon, 144–145
  basicity, **134**
  basicity versus reactivity, 133–134
  bimolecular displacement mechanism in, 127–131
  carboxylic acid derivatives, 471–489

Nucleophilic substitution [*cont.*]
  dimethyl sulfate, 141
  effect of substrate structure, 138–140
  frontal attack mechanism, 128–129
  kinetics, 127–128
  leaving groups in, 128, 129, 141–142
  nucleophilic addition-elimination mechanism, 471–472
  nucleophilicity versus basicity, 135–137
  rate, 127–128
  rate of racemization in, 128–129
  similarity to S_E2, 164
  S_N2 mechanism, **135**
  S_N1 mechanism, 127–131
  solvent polarity, 143–144
  stereochemistry, 128–131
  steric hindrance, 138–140
  transition state in, 129–131, 141–142
  versus elimination, 145–147, 152–153
Nucleosides, 1139
Nucleotides, 1138
Nylon, 738
  synthesis of, 547
Nylon 6, preparation, 788
Nylon 6,6, preparation, 788

O

Occupational Safety and Health Administration (OSHA), 294
(Z,Z)-9,12-Octadecadienoic acid, 507
1-Octadecanethiol, 242
Octadecanoic acid (*see also,* Stearic acid), physical properties, 426 *t*
Z,E,E-9,11,13-Octadecatrienoic acid, 507
Z,Z,Z-9,12,15-Octadecatrienoic acid, 507
1-Octadecene, infrared spectrum, 332
Z-9-Octadecenoic acid, 507
2,6-Octadiene, 1020
Octanal
  physical properties, 352 *t*
  preparation, 358
n-Octane, 53
  infrared spectrum, 329, 330
  physical properties, 55 *t*
Octane ratings, 88
  of gasoline, 292
Octanoic acid (*see also,* Caprylic acid), physical properties, 426 *t*
2-Octanone
  mass spectrum, 421
  physical properties, 353 *t*
1,3,5,7-Octatetraene
  ring closure, 1129–1131
  ultraviolet spectroscopy, 595
1-Octene
  infrared spectrum, 332
  ozonolysis of, 291
cis-4-Octene, infrared spectrum, 335
trans-4-Octene, infrared spectrum, 335
Octet (*see,* Electron, octet)
n-Octylamine, physical properties, 770 *t*
1-Octyne, infrared spectrum, 337
2-Octyne, infrared spectrum, 337
4-Octyne, 310
-oic acid, as suffix, 667
Oils, 507
-ol, as suffix, 667
Olefins (*see also,* Alkenes), **256**
Oleic acid, 507, 563
Oligosaccharides (*see also,* Disaccharides), **694**, 722–726
Olive oil, 549
ω-, in nomenclature, 208
Ommochromes, 1145
-one, as suffix, 667
Opium, 805
Opsin, 603
Opsopyrrole, 1077
Optical activity, **108**
  measurement of, 108–110
  symbols for, 108–109
Orbitals
  angle strain and, 23
  overlap principle in, 22, 23
  p, 17–19
  s, 17–19
  sp, 23–25
  sp^2, 25–26
  sp^3, 25–27
Organic compounds
  definition, **2**
  history, 2
Organoaluminum compounds, 547
  hydrolysis, 163
  reaction with hydroxylic compounds, 163
Organoboron compounds, reaction with alkaline hydrogen peroxide, 287–288
Organocadmium compounds
  preparation from Grignard reagents, 162
  preparation of, 486
  reactions with acyl chlorides, 486
  uses of, 166
Organocopper compounds
  aryl, 918
  from halobenzenes, 918
  reaction with alkyllithium compounds, 165
Organofluorine compounds, 84
Organolithium compounds
  addition to unsaturated carbonyl compounds, 557
  aryl, 917
  carbonation of, 434
  Chichibabin type reactions, 1102, 1108
  hydrolysis, 163
  in alcohol synthesis, 383
  metal exchange reaction, 162
  preparation from alkyl halides, 159–160
  preparation from aryl halides, 899
  reactions, 899–900
    with alkylcopper compounds, 165
    with carboxylic acids, 441
    with epoxides, 652
    with hydroxylic compounds, 163
    with methylene chloride, 632

- Organomagnesium compounds (*see*, Grignard reagents)
- Organometallic compounds, **34**, **156**, 156–158
  - addition to unsaturated carbonyl compounds, 556–558
  - nomenclature, 157
  - physical properties, 157-158
  - preparation
    - by metalation, 161–162
    - disproportionation of organometallics, 162–163
    - free metal and organometallics, 162–163
    - from alkyl halides, 158–161
  - reactions, 163–165
    - carbonation, 434
    - hydrolysis, 163–164
    - with carboxylic acid derivatives, 485-489
    - with halogens, 164
    - with organometallic compounds, 165
    - with oxygen, 165
    - with salts, 161–162
  - resonance structures, 156
  - structure, 156–157
  - uses of, 165–167
- Organometallic reagents, carbenoid, 632
- Organophosphorus compounds, in pesticides, 103
- Organopotassium compounds, 160
- Organosilicon compounds, preparation from Grignard reagents, 162
- Organosodium compounds, reaction with alkyl halides, 168
- Orlon, 562
- Orthocaine, 1033
- *ortho*-directors, 869
- Orthoesters, 514, 938
- *ortho*-isomer, **862**
- Orthophosphoric acid (phosphoric acid), 501–502
- Osazones, 714
- Osmic acid (*see*, Osmium tetroxide)
- Osmium tetroxide, 290
- Ovalbumin, function, 856
- Overtones, of infrared absorption bands, 329
- Oxa-, as prefix, **1066**
- Oxalic acid, 736
  - acidity, 738
  - decomposition, 739
  - natural occurrence, 737
- Oxalyl chloride, 736
- Oxaphosphetanes, 389
- 1-Oxaspira[5.3]nonane, 1069
- Oxazole, 1066
  - numbering system, 1089
- Oxazoles, preparation, 1094
- Oxetane, 653, 1067
- Oxetanes, 653
  - preparation, 1069
  - ring opening, 1071
- Oxidation
  - of alcohols, 232–234, 357–358, 435
  - of aldehydes, 391–394, 435–436
  - of alkenes, 289–292, 358
  - of alkylbenzenes, 919–921
- Oxidation [*cont.*]
  - of alkynes, 317–318
  - of allylic alcohols, 554–555
  - of amines, 792
  - of arenes
    - to acids, 942–944
    - to aldehydes and ketones, 934, 936–937
  - of aromatic amines, 970–972
  - of benzyl alcohols, 931
  - of cumene, 1001–1002
  - of diols, 671–672
  - of ethers, 240–241
  - of hydroxy aldehydes and ketones, 681
  - of iodobenzenes, 900–901
  - of ketones, 368, 391–394
  - of methyl ketones, 561
  - of monosaccharides, 709–714
  - of naphthalene, 1049–1050
  - of propylene, 562
  - of sulfides, 244
  - of thiols, 243–244
- Oxidation-reduction reactions, balancing, 232–233
- Oxidative coupling reaction, 317–318
- Oxidative deamination, 829
- Oximes, 379, 718
  - Beckmann rearrangement, 789
  - reduction, 782
  - unsaturated, 555
- Oxirane, 1066
- Oxo-, as prefix, 351–352, 667
- Oxolane, 1066
- Oxonium ions, 414, 554
  - acidity, 465
  - acyl, 465
- Oxygen, abundance of isotopes, 409 *t*
- Oxygen-hydrogen bond length
  - constancy of, 9
  - in various compounds, 9 *t*
- Oxytocin, 832
- -oyl chloride, as suffix, 667
- Ozonator, 291
- Ozone, 290–291, 292
- Ozonide, 291
- Ozonolysis of alkenes, 290–292

P

- Paal-Knorr synthesis, 1078
  - of azoles, 1094
- Paint, 563
- Paint remover, 458
- Palladium, as catalyst, 277, 311
- Palmitic acid, 424, 507
  - physical properties, 426 *t*
- Palm oil, composition of, 507
- Papaverine, 1117–1118
- *para*-directors, 869
- Paraformaldehyde, 377
- *para*-isomer, **862**
- Paraldehyde, 378
- Partial rate factors, **879**
- Pasteur, Louis, 681

Pauli principle, **17**, 538, 576
Peanut oil, 508
Pectins, 693
Pelargonadin, 1144
Pelargonic acid (*see also*, Nonanoic acid), 424
Penicillin, 40, 1091
Pentaborane, 286
Pentacene, 1058
Pentadecane, 53
Pentadecanoic acid, physical properties, 426 *t*
1,5-Pentadial (*see*, Glutaraldehyde)
Penta-2,3-diene, optical activity, 545
1,4-Pentadiene, 564
Pentadienyl cation, stability, 564–565
Pentaerythritol, 397, 635
Pentaerythritol tetranitrate, 505–506
Pentalene, 1123
Pentamethylbenzene, preparation, 910
Pentamethyleneketene, 564
Pentane
  conformations, 62, 67
  isomers, 63
  physical properties, 55 *t*
  stereoscopic figure, 62
2,3-Pentanediols, diastereomers, 669
2,4-Pentanedione, keto-enol equilibrium, 749
Pentanoic acid (*see also*, Valeric acid), 434
2-Pentanol
  dehydration, 273
  physical properties of, 211 *t*
  reaction with sulfuric acid, 229
3-Pentanol
  physical properties of, 211 *t*
  reaction with sulfuric acid, 229
2-Pentanone, physical properties, 353 *t*
3-Pentanone, physical properties, 353 *t*
1-Pentene, physical properties, 259 *t*
2-Pentenes, preparation, 229
cis-2-Pentene
  hydroxylation, 669
  physical properties, 259 *t*
trans-2-Pentene,
  hydroxylation, 669
  physical properties, 259 *t*
n-Pentyl alcohol, physical properties, 211 *t*
n-Pentylamine, physical properties, 770 *t*
t-Pentyl bromide, 227
1-Pentyne
  preparation, 153
  physical properties, 303 *t*
2-Pentyne, physical properties, 303 *t*
Peonin, 732
Peony, 731
Peppermint oil, 644
Pepsin, 845
Peptide bonds, 814
Peptides, 478, **814**, 830
  amino acid analysis, 841–842
  amphoteric properties, 833
  classification, 814
  Edman degradation, 842–844
  fragmentation, 845–847
  from hydrolysis of proteins, 830
  nomenclature, 830
Peptides [*cont.*]
  p*K* values, 833 *t*
  preparation
    α-haloacyl halide method, 858
    NCA method, 839–840
    solid-phase technique, 839–840
  Sanger reaction, 842
  sequencing, 845–847
  structure, 830–847
  synthesis, 833–841
  C-terminal identification, 844–845
  N-terminal identification, 842, 844
Per-, as prefix, 295
Perchloric acid, 295
Perchloroethylene (*see*, Tetrachloroethylene)
Periodic acid oxidation
  of diols, 671
  of glycosides, 712–714
  of α-hydroxy aldehydes and ketones, 681
  of monosaccharides, 712–714
Periodic table of the elements (*see also*, Endpaper), 5
Perkin, William Henry, 1147
Perkin reaction, 940
Perkin synthesis, of coumarin, 1085
Permanganate, oxidation
  of alcohols, 435
  of alkenes, 289, 290
  of alkynes, 317
  of benzene derivatives, 919, 942
Peroxide effect, 284–285
Peroxides, analysis for
  in ethers, 240–241
  as initiators of chain reaction, 84
Peroxyacetic acid, 649, 901
  oxidation, of aldehydes, 391
Peroxycarboxylic acids, 391–393
  as oxidants, 792
  oxidation of alkanes, 1067
  preparation, 649
  reaction with alkenes, 649–650
Peroxyformic acid, oxidation of polypeptides, 841
Peroxysulfuric acid, 295
Pesticides, 103, 446
PETN (*see*, Pentaerythritol tetranitrate)
Petroleum, 70
Phenacetin, 970
Phenanthraquinone, 1022, 1055
Phenanthrene, 1038
Phenanthrenes
  numbering system, 1038
  preparation, 1054–1057
  reactions, 1055–1057
  structure and stability, 1053–1054
Phenazine, dyes from, 1149
Phenetidine, 970
Phenetole, 999
Phenol, 209, 861
  bromination, 884
  commercial preparation, 895
  condensation with formaldehyde, 1007–1008
  hydrogenation, 623
  industrial preparation, 1002

Phenol [*cont.*]
  pK_a, 1003
  properties, 1002
Phenol-formaldehyde resins, 1008
Phenolphthalein, 1017
Phenols, 998–1021
  acidity, 1002–1003
  as enols, 998
  condensation with aldehydes, 1007–1008
  diazonium coupling, 1010–1011
  electrophilic substitution, 1011–1018
  esterification, 1005–1006
  esters, Fries rearrangement, 1016
  Friedel-Crafts acylation, 1015–1018
  halogenation
    in acidic medium, 1014–1015
    in basic medium, 1006–1007
  in Houben-Hoesch synthesis, 1016
  in Kolbe synthesis, 1008–1009
  nitration, 1012–1014
  nitrosation, 1011–1012
  nomenclature, 209, 998–1000
  oxidation to radicals, 1026
  preparation, 1000–1002
    from arenediazonium salts, 979–980
    oxidation of cumene, 1001–1002
  properties, 1002
  reactions, 1005–1018
    as phenolate ions, 1006–1011
    with chloroform, 1009–1010
  Reimer-Tiemann reactions, 1009–1010
  sulfonation, 1014
Phenone, nomenclature, 930
Phenothiazine, dyes from, 1149
Phenoxazine, azine dyes, 1149
Phenoxyaluminum dichloride, 1015
Phenoxy radical, 1026
Phenyl-, as prefix, 862
Phenylacetic acid
  pK_a, 944
  preparation from phenylacetonitrile, 433–434
Phenylacetic acids, substituted
  acidities, 948 *t*
Phenylacetonitrile, hydrolysis, 433–434
Phenylacetylene, physical properties, 303 *t*
Phenylalanine, 815
  physical properties, 817 *t*
Phenylalanylglycine, 839
Phenylalkyl halides, reactions, 906–908
1-Phenyl-2-aminopropane (amphetamine), 777
Phenyl azide, 986
p-Phenylazophenol, 1010
cis-4-Phenyl-1-*t*-butylcyclohexane,
    conformational analysis, 621
γ-Phenylbutyric acid, 933
  pK_a, 944
Phenyl cation, 911
  orbital structure, 979
Phenylcopper, preparation, 918
Phenylenediamines, 966, 1111
Phenyl ethers
  Birch reduction, 1021
  Claisen rearrangement, 1019–1020
  cleavage reactions, 1018

Phenyl ethers [*cont.*]
  electrophilic substitution, 1011–1018
  Friedel-Crafts acylation, 1015
  halogenation, 1014–1015
  metalation, 1021
  nitration, 1012–1014
  nomenclature, 999–1000
  preparation, 1004
    Williamson synthesis, 1004
  properties, 1005
  reactions, 1011–1021
  sulfonation, 1014
Phenylethylamines, 776, 806
Phenylethylene (*see*, Styrene)
Phenyl group, inductive effect, 944
Phenylhydrazine, 379, 380, 714
  preparation, 986
Phenylhydrazones, 380, 714–715
Phenylhydroxylamine, properties, 962
Phenylisothiocyanate, 842, 844
Phenyl ketones, from Friedel-Crafts acylation,
    588–589
Phenyllithium, 434, 652
β-Phenylpropionic acid, pK_a, 944
2-Phenylpyridine, 1102
1-Phenylpyrrole, physical properties, 1075
2-Phenylpyrrole, physical properties, 1075
Phenyl radical, 209, 569
Phenyl sulfone, 954
Phenylthiohydantoins, 844
Pheromone, **71**
Phloroglucinol, 1000
Phosgene, 488
  industrial preparation, 738
  reaction with alcohols, 738
  reaction with diols, 672
Phosphates
  acidity, 502
  hydrolysis, 503–504
  preparation, 503
Phosphatidic acids, 508
  natural occurrence, 508
  stereochemistry, 508
Phosphatidyl choline, 508
Phosphatidyl ethanolamine, 508
Phosphine, 388
Phosphites, 504–505
  conversion into phosphanates, 504–505
  preparation, 504
Phosphoenolpyruvic acid (PEP), 1158, 1159
2-Phosphoglyceric acid (2-PGA), 1158, 1159
3-Phosphoglyceric acid (3-PGA), 1158, 1159
Phosphoglycerides, 508
  bilayer formation, 509
  micelle formation, 508, 509
  structure of, 508–509
Phospholipids (*see*, Phosphoglycerides)
Phosphonates
  hydrolysis, 505
  preparation, Arbuzov-Michealis reaction,
    504–505
Phosphonic acids, 504
Phosphonium salts, 388
Phosphoranes, 388–389

Phosphorescence, 1152
Phosphoric acids, 501
Phosphorochloridates, 503
Phosphorus, 501
Phosphorus oxychloride, 230, 503, 935
Phosphorus pentachloride, 14, 230, 444
Phosphorus pentoxide, 502
Phosphorus tribromide, 229, 444
  in Hell-Volhard-Zelinsky reaction, 470
Phosphorus triiodide, 230
Phosphorylation, biological, 1161
Photochemical reactions, 602–603, 1132, 1134, 1153–1156
  isomerism of alkenes, 603
Photochemistry (*see also*, Photochemical reactions), 1150–1156
Photographic developer, 1027
Photosynthesis, 1158
Phthaleins, preparation, 1017
Phthalhydrazide, 780
Phthalic acid, 735, 929
  industrial uses, 944
Phthalic anhydride
  anthraquinone from, 934
  in acylation of phenol, 1017
  preparation, 1049
Phthalic anhydrides, industrial production and uses, 944
Phthalimide, 966
  in Gabriel synthesis, 779
  pK_a, 763, 779
  preparation, 741
N-Phthalimidomalonic ester, 822
Phthalocyanines, 1150
Phthalonitrile, 1150
o-Phthalyl alcohol, 927
Phthiocol, 1022
Phyllopyrrole, 1077
π bonding, 252–256
  in allylic systems, 537–540
  in benzene, 571
  in carbon-carbon triple bond, 301–302
  in dienes, 540–542
  in multiply-conjugated systems, 564–565
Picolines, 1096
  acidity, 1103–1104
  electrophilic substitution, 1100
Picrates, 1013
Picric acid, 1000
  in charge-transfer complexes, 1029
  pK_a, 1003
  preparation, 1012–1013
  properties, 1013
Pigments, 1142–1143
  theory, 1142–1143
Pill, the, 647
Pimelic acid, 736
  esters, Dieckmann condensation of, 743
π-molecular orbitals, 538–540
  Hückel $4n + 2$ rule, 1119–1125
  in benzene, 574–575
  in cyclooctatetraene, 575–576
  in dienes, 540–542
Pinacol, 670
Pinacol reaction, 670
Pinacol rearrangement, 673, 689
α-Pinene, 639, 1163
Piperazine, numbering for, 833
Piperdine, 1065, 1067
Pituitary hormones, 831, 847, 858
Pivalaldehyde, 493
Pivalic acid, 920
Planck's constant, 170, 326
Plane of polarization, **107-108**
Plane polarized light, **107-108**
Plants
  carbohydrates in, 693
  cellulose in, 727
  essential oils, 643
Plasticizers, 295, 944
Platforming, in pyrolysis of crude oil, 77, 581
Platinum, as catalyst, 276–277
Plexiglass, 562–563
Plus-minus (±) as prefix, for racemates, 114
PMR (*see*, Nuclear magnetic resonance, proton)
Poison hemlock, 806
Poison ivy, active ingredients, 1000
Polar bonds, 156–157
Polarimeter, 109–110
Polarizability, of electrons, 99, 101–102
Polaroid lens, 108
Polyalanine
  α-helix formation, 850, 852
  Stereoscopic figure, 852
Polyamides, 788
Polychloromethanes, industrial production, 102
Polycyclic aromatic hydrocarbons, 1037–1060
  anthracenes, 1053–1057
  biphenyls, 1038–1041
  carcinogenicity, 1059–1060
  fluorenes, 1042–1043
  higher polybenzenoid compounds, 1057–1060
  naphthalenes, 1044–1053
  nomenclature, 1037–1038, 1059
  phenanthrenes, 1053–1057
  quaterphenyls, 1041–1042
  terphenyls, 1041–1042
Polyenes, 564–565
  π-molecular orbitals in, 594–596
  polymerization, 565
  ultraviolet spectroscopy, 594–596, 601, 605
Polyester, 943
Polyether alcohols 651
Polyethylene, 275, 292, 293–294, 296
  branched, 848
  linear, 848
  physical properties, 55 *t*
Polyglutamic acid, conformations, 850
Polyglycine, 833
Polyhalomethanes, 96
Polyisoprene, 547–548
Polylysine, random coil, 850
Polymerization (*see also*, Carbonium ions, polymerization; Radical polymerization; Carbanions, in polymerization of alkenes)
  of aldehydes, 377–378
  of alkenes, 292–296

Polymerization [*cont.*]
  of amino acids into homopolymers, 833–834
  of amino acids into peptides, 835–841
  of ethylene oxide, 651
  of hydroxy acids, 687
  of polyenes, 564–565
  vulcanization, 547–548
Polymers, **292**
  crosslinking in, 547–548
  cyclic acetylene, 318
  diene, 547–550
  elastomers, 547–548
  end groups in, 295
  formation, 292
  industrial, 292–296
  of acrylonitrile, 562
  of methyl methacrylate, 562–563
  phenol-formaldehyde resins, 1008
  physical properties of, 296
Poly (methyl methacrylate), 562–563
Polypeptides (*see also,* Peptides; Proteins), **814**, **830**
Polyphosphoric acid (PPA), 502
  in acylations, 1016
  in ketone preparation, 934
Polypropylene, 275
Polysaccharides (*see also,* Cellulose; Starch; Glycogen) **694**, 726–729
  types, 726–727
Polystyrene, 295
  chloromethylated, 839
  in peptide synthesis, 839
Polytetrafluoroethylene (Teflon), 295
Polyurethane foam, 802
Polyurethanes, 801
Polyvinyl chloride, 294–295
p orbitals, electrons in, 306
Porphine, 1125
Porphyrins, 1077
  aromaticity, 1125
  color, 1145, 1146
Potassium
  lab use of, 216
  reaction with hydroxy group, 30–31
Potassium *t*-butoxide, 216
  use in dehydrohalogenation, 224, 267
Potassium cation, solvation by crown ethers, 654
Potassium dichromate, 232
Potassium ethyl xanthate, 981
Potassium hydride, 364
Potassium hydrogen phthalate, 944
Potassium *t*-pentoxide, use in dehydrohalogenation, 224
Potassium permanganate, 289
Potassium phthalimidate, 822
Potassium triphenylmethide, 364
Potential energy, of ethanes as function of C—C bond rotation, 58–59
PPA (*see,* Polyphosphoric acid)
Pregl, Fritz, 37
Prehnitene, 913
Presqualene alcohol pyrophosphate, 1164
Pressure, standard atmospheric **54**
Principle of microscopic reversibility, **80**, 951, 1132
Principle of vinylogy, **749**
Prismane, 570, 1167
Progesterone, 647
L-Proline, 815–817
  in polypeptide chains, 851, 853
  physical properties, 817 *t*
  preparation, 824
  stereoscopic figure, 818
1,2-Propadiene (allene), 545
Propagation step, 78
Propane, 53
  bromination, 85–86
  chlorination, 82, 83, 169
  conformations, 59
  physical properties, 55 *t*
  use as LPG, 70
1,3-Propanedithiol, 677
Propanoic acid (*see,* Propionic acid)
Propenal (acrolein), 554
Propene (*see,* Propylene)
Propenoic acid, 562
2-Propen-1-yl cation (allyl cation), 530–531
β-propiolactone, 1070
Propionaldehyde
  physical properties, 352 *t*
  resonance structures, 370
Propionic acid, physical properties, 426 *t*
Propionitrile, 132
Propiophenone, 930, 931
n-Propyl alcohol
  dehydration, 273
  physical properties, 211 *t*
n-Propylamine, physical properties, 770 *t*
n-Propyl bromide, 54
  in bromination of propane, 85
  reaction with azide ion, 664
  reaction with sodium, 160
n-Propyl chloride
  in chlorination of propane, 82
  NMR spectrum, 171
Propylene, 256
  acidity, 534
  conformations, 298–299
  oxidation, 562
  physical properties, 259 *t*
  polymerization, 952
  sources and uses, 275
n-Propyl halides, in S_N2 reactions, 138
Propyl radical, 54
Propyne, physical properties, 303 *t*
Protecting groups
  acetals, 376
  t-butyl ethers, 239–240, 527
  criteria for, 835
  for alcohols, 239–240
  for aldehydes and ketones, 376
  for amino group, 835–836
  for carboxy group, 835
  for sugars, 707
  ketals, 376, 526–527
  silyl ethers, 527
  sulfonic acid, 952
  use of, 376
Proteins, 452, 478, 847–856
  biological functions, 847, 856

Proteins [*cont.*]
  chain interactions in, 848–856
  conformations of, 847
  denaturation-renaturation, 854, 855–856
  fibrous, 847
    conformations, 850–851
  globular, 847, 849
    active sites, 854
    structure, 854–856
  α-helix, 850, 852
  hydrolysis, 830
  pleated sheet structure, 851, 853
  prosthetic groups, 848, 854–855
  random coil conformation, 850
  regulatory, 856
  sequencing of, 845–847
  structural, 856
  super helix, 851
Proteolases, 845
Protonated formaldehyde
  carbonium ion structure, 12
  Lewis structure, 11, 12
  oxonium ion structure, 12
  resonance structures, 12
Protonated methyleneimine, resonance structures, 13
Protonolysis, of vinylboranes, 317
Pseudorotation, **611**
Pterins, 1145
Purine, 1066
  numbering system, 1109
Purines, natural occurrence, 1110
Purple foxglove, 648
Pyran, 699
Pyranose rings, 699
  conformations, 702–703
Pyrazine, numbering system, 1109
Pyrazines, preparation, 1111
Pyrazole
  basicity, 1090
  hydrogen bonding in, 1090
  numbering system, 1085
Pyrazoles
  interconversion of 3- and 5-isomers, 1094
  preparation, 1091–1092
Pyrene, 1058
Pyridazines
  numbering system, 1109
  preparation, 1110
Pyridine, 1065, 1089, 1095–1104
  as catalyst, 755
  basicity, 1090
  Chichibabin reaction, 1101–1102
  preparation, 1097–1098
  reactions, 1098–1104
  resonance forms, 1096
  salt formation, 1098
  structure and properties 1095–1097
Pyridine N-oxides
  deoxygenation, 1101
  electronic structure, 1099
  electrophilic substitution, 1101
  preparation, 1099
Pyridines (*see also*, Picolines; Lutidines; Collidine)
Pyridines [*cont.*]
  electrophilic substitution, 1100–1101
  nucleophilic substitution, 1101
  oxidation, 1098–1099
  reduction, 1071–1072
Pyridine-3-sulfonic acid, 1100
Pyridinium salts
  acidity, 1103–1104
  oxidation, 1103
  preparation, 1098
Pyridones, 1102–1103
Pyrimidines
  numbering system, 1109
  occurrence, 1109
  preparation, 1110–1111
2-Pyrimidone, 1111
Pyrogallol, 1000
Pyroglutamic acid, 858
Pyrolysis, 74, **76**
  of acetals and ketals, 376–377
  of acetone, 563
  of amine oxides, 793
  of ammonium carboxylates, 439–440
  of crude oil, 77
Pyrolysis (cracking), of alkanes, 76–77
Pyrolytic elimination, 495–498
  of esters, 495–498
  transition state, 496
Pyrophosphoric acid, 501–502
Pyrrole, 1065
  acidity, 1076
  electrophilic substitution, 1080–1083
  natural occurrence, 1076–1077
  physical properties, 1075
  preparation, 1079
  structure, 1072–1073
Pyrroles
  polymerization, 1083
  properties, 1074–1075
  reduction, 1071–1072
Pyrrolidine, 803, 1065, 1067
Pyrrolidines, preparation, 1071
Pyruvic acid, 746, 1158
Pyrylium salts, 1144

Q

Quadricyclene, numbering system, 1154
Quantum mechanics, 15
Quantum numbers
  atomic, 15
    azimuthal or angular momentum, 16
    principal, 16
    spin, 16 *t*
  relations to nodes, 16
Quantum yield, **1155**
Quaternary ammonium compounds, 765 **778**
Quaternary ammonium hydroxides, Hofmann degradation, 793–796
p-Quaterphenyl, 1042
Quinaldine, synthesis, 1106
Quinazoline, 1112
Quinhydrone, 1028
  stereoscopic figure, 1028

Quinine, 806
Quinoid structures, 1023
Quinoline
  as catalyst poison, 311
  NMR spectrum, 1105
  nomenclature, 1104
  oxidation, 1099
  properties, 1104
  reactions, 1107–1109
Quinoline N-oxide, 1108
Quinolines
  preparation, 1105–1107
  Friedländer synthesis, 1106–1107
  Skraup reaction, 1105–1106
Quinolinic acid, 1099
Quinone, 1022
Quinones, 1021–1031
  charge-transfer complexes, 1028–1029
  nomenclature, 1021–1023
  preparation, 1023–1024
  quinoid structures, 1023
  radical anions from, 1026
  reactions, 1029–1031
  reduction, 1025–1026
  reduction-oxidation equilibria, 1024–1027
Quinoxaline, preparation, 1111
Quinuclidine, 1065

R

R, prefix for absolute configuration, **111**
  symbol for alkyl group, 32
Racemate, **114**
Racemic acid, 682
Racemic compounds, **115**
  melting characteristics, 115
Racemic mixtures, **114**
  melting characteristics, 115
  physical properties, 115
  symbol for, 114
Racemization, **116**
  in enolization, 365
  rate constant for, **128**
Radical additions (*see*, Radicals, addition reactions)
Radical anion (ketyl), 670
Radical cation, **404**
Radical cations
  dyes, 971
  versus carbonium ions, 404
Radical initiators, 284–285
Radical polymerization, of dienes, 547
Radical reactions, allylic halogenation, 536–537
Radicals, **54**
  addition reactions
    to alkenes, 284–286
    to alkynes, 315–316
  alkyl, 54
  allylic, 535–537
  in polymerization of alkenes, 292, 293–294
  nomenclature, 54, 64–65, 69
Raffinose, 726
Raney nickel, 277
Raschig process, 144–145
Rate constant, 45, 46–47
  relation to free energy of activation, 133
Rate-determining step, 48
Rate equation, 45
Rate expression, 45, 49
Rate of reaction, 42, 45, 46–47, 48
  concentration of reactants, 45
  effect of temperature change, 45
  energy barrier, 48
  transition state, 46–47
  units of, 45
Rattlesnake venom, 827
Rayon, 728
Reaction
  abbreviations used for, 48–49
  coordinate, **46**
  driving force, 43
  endothermic, 43
  energy barriers, 44, 48
  energy changes, 43, 46–47
  equilibrium (*see*, Equilibrium)
  exothermic, 43
  first-order, **45–46**
  heat of (*see*, Enthalpy, heat of reaction)
  intermediates, 46–47
  kinetics, 44–46
  mechanism 47–49
  oxidation-reduction, 232–233
  principles of, 42–50
  profile, 46–49
  psuedo first order, 46
  second-order, **45–46**
  structure in, 46–47
Reaction rate (*see also*, Rate of reaction), activation energy and, 128
Reactions, kinetic versus thermodynamic control, 543
Rearrangements
  allylic, 531–532
  Cope, 1020
  in dehydration of alcohols, 274–275
  in Hofmann degradation, 495
  McLafferty, 416
  of hydroperoxides, 287
  of triple bonds in alkynes, 308–309
  sigmatropic, 1021, 1136–1138
Reduction (*see also*, Hydrogenation)
  Bouveault-Blanc reaction, 491
  lithium aluminum hydride, 394–395
  of acyl halides, 489–490
  of aldehydes and ketones, 394–398
  of amides, 491–493, 784
  of aromatic nitriles, 937
  of azides, 780
  of carboxylic acids, 440–441
  of esters, 490–491
  of imines, 782–783
  of monosaccharides, 709
  of naphthalenes, 1050
  of nitriles, 493, 781–782
  of nitroarenes, 961–962
  of nitro compounds, 781
  of oximes, 782
  Rosenmund reduction, 489
Reduction potentials, of quinones, 1025 *t*

Reductive alkylation (*see,* Reductive amination)
Reductive amination, 782–783
Reductive dimerization, of ketones, 670
Reformatsky reaction, 684
Reforming, of petroleum, 76–77, 581, 919
Refrigerants, 102
Reimer-Tiemann reaction, 1009–1010
Renaturation, 856
Reserpine, 1084
Resolution, **776**
  of amino acids, 825–827
Resonance, uses of term, 572–573
Resonance energy, **572**
  benzene, 572–573
  versus delocalization energy, 573
Resonance hybrid, **10–11**
Resonance stabilization
  acetate ion, 427–428
  allyl anion, 534
  allyl cation, 531
  allylic radicals, 535
  amidate ions, 534
  and acidity, 534, 535
  carboxylate ion, 534, 535
  enolate ions, 534, 535
  nitrite ions, 534, 535
  polyenes, 564–565
  $4n + 2$ rule, 477
Resonance structures (*see also* specific compounds) 10–14, 534–535, 539–540
  charge separation in, 13, 14
  electron octets in, 13, 14
  relative importance of, 13, 14
  symbolism of, 10,11
Resorcinol, 999
Resorcinol dimethyl ether, metallation, 1021
Resorcin Yellow, 1010
Retene, 919
Retina, 603
Retinal (retinene, vitamin A aldehyde), 555, 1157
  cis and *trans* forms, 603
Retinal isomerase, 603
Rhein, 1023
Rhodium, as catalyst, 277
Rhodopsin (visual purple), 603
Ribonuclease A
  sequence, 841
  synthesis, 840–841
Ribonucleic acid (RNA), 730, 1138
  types of, 1142
D-(−)-Ribose, 697, 1138
  chain shortening of, 718
Ribulose, 695
Rice bran oil, 549
Ricinoleic acid, 563
Ring compounds (*see,* Cyclic compounds, rings)
Ring expansion, 638
  1,2-amino alcohols, 792
Ring formation, 616–618
  acyloin condensation, 675
  anthracenes, 1054–1055
  azetidine, 1069
  aziridine, 1068
  bicyclic, 641–643
  biphenyl, 1038
Ring formation [*cont.*]
  Bischler-Napieralski synthesis, 1107
  Claisen condensation, 743, 745
  conrotatory, **1126**
  cyclization of bromoalkylamines, 616–617
  cyclobutane, 635–637
  cyclohexane, 622–627
  cyclohexenone, 757
  cyclopentane, 638
  cyclopropane, 630–632
  diazines, 1110–1111
  Dieckmann condensation, 622, 638
  Diels-Alder reaction, 624–627, 642–643
  disrotatory, **1126**
  epoxide, 1067
  epoxides, 648–650
  Fischer indole synthesis, 1084–1085
  Friedlañder synthesis, 1106–1107
  furan, 653, 1077–1078
  Hantzsch pyridine synthesis, 1097–1098
  Hückel $4n + 2$ rule, 1126–1136
  imidazole, 1094
  indole, 1084–1085
  intramolecular aldol condensation, 617–618
  isoquinoline, 1107
  isoxazole, 1092–1093
  Knorr pyrrole synthesis, 1079
  lactides, 687
  lactones, 685–687
  large rings, 638
  naphthalene, 1045–1046
  oxazole, 1094
  oxetane, 653, 1069
  Paal-Knorr synthesis, 1078
  phenanthrenes, 1054–1055
  pyrazole, 1091–1092
  pyridine, 1097–1098
  pyrrole, 1079
  pyrrolidine, 1071
  quinoline, 1105–1107
  Robinson annelation, 757
  Skraup reaction, 1105
  tetrahydrofuran, 1071
  thiazole, 1094
  thietane, 1069
  thiirane, 1068
  thiophene, 1078
Ring opening
  azetidine, 1071
  aziridines, 1069
  cyclobutane, 637
  cyclobutenes, 1131–1132
  epoxides, 650–652, 669, 1069
  furans, 1083
  oxetane, 1071
  thietane, 1071
  thiiranes, 1069
Rings
  acenes, 1058
  anthracene, 1053
  azoles, 1088–1095
  biphenyl, 1038
  chrysene, 1058
  coronene, 1058
  cyclobutane, 610

Rings [*cont.*]
  cyclohexane, 611-615
  cyclopentane, 610-611
  cyclopropane, 608-609
  diazine, 1109-1112
  fluoranthene, 1058
  fluorene, 1042-1043
  furan, 653, 1073
  heterocyclic, 1065-1112
  isoquinoline, 1104
  naphthalene, 1044-1045
  phenanthrene, 1053
  pyrene, 1058
  pyridine, 1095-1096
  pyrrole, 1072
  quinoline, 1104
  terphenyl, 1041-1042
  thiophene, 1073
Ring strain
  in cycloalkanes, 607-608
  infrared spectroscopy, 655-657
Ritter reaction, 513
Robinson annelation, 757
Rodenticides, 103
Rose oil, 644
Rosenmund reduction, 489
Rosin, 919
Rotational motion (*see*, Motion, rotational)
R-S convention (*see*, Sequence rule)
Rubber
  natural, 644
    biosynthesis of, 548
    structure, 547
  synthetic, 547
Ruff degradation, 717
Ruthenium, as catalyst, 277
Ruthenium tetroxide, as oxidizing agent, 708

S

S, prefix for absolute configuration, **111**
Saccharic acids, **711,** 719
Saccharides (*see also*, Sugars; Monosaccharides; Disaccharides, etc.), 693
Salicylaldehyde, coumarin from, 1085
Salicylic acid, 1006
  salts, 1009
Sandalwood oil, 644
Sandmeyer reactions, 981-982
Sanger, Frederick, 842
Sanger reaction, 842
β-Santalol, 644
Saponification, 507
Sarrett procedure, 1099
Saturated hydrocarbons, 32, **53**
Saturation of spin states in NMR, 179-180
Sausage formula, 3
Sawhorse structures, **58**
Schiemann reaction, 983
Schiff base, 378
Schmidt rearrangement, 785, 786-787
  converting ketones to amides, 825
  preparation of amino acids, 825
Schotten-Baumann reaction, 483, 828
Scintillation counter, 585
Sclerolin, 856
Seaweed, 635
Sebacic acid, 736
Second-order reaction, **45**
Selection rule, **328**
Selenium dioxide
  as oxidant, 746
  oxidation of ketones, 746
S_E1 mechanism, 164
S_E2 mechanism, 164
Semicarbazide, 379, 380
Semicarbazones, 380
Sequence rule, 111-114
  for configurations, 111
Serine, 476, 816
  physical properties, 817 *t*
Serturner, Friedrich Wilhelm, 805
Sesquiterpenes, **549, 643**
Sex attractants
  for greater wax moth, 403
  for honey bees, 39
  for housefly, 323
  for Tiger moth, 323
Sex hormones, 647
Shale oil, **70**
Shark liver oil, 559
S_H2 mechanism, 145
σ antibonding orbital, 593, 594
σ bonding orbital, 593, 594
σ bonds, 252
Sigmatropic rearrangement (*see*, Rearrangements, sigmatropic)
Silane, 157
Silk, pleated sheet structure, 851, 853
Silver bromide, in photography, 1027
Silver ion, in Tollens' test, 710-711
Silver nitrate, 505
Silver oxide, 435-436
  oxidation
    of aldehydes, 391, 435-436
    of *o*-dihydroxybenzenes, 1024
    of unsaturated aldehydes, 555
  reaction with alkyl halides, 529
Simmons, Howard, 630
Simmons-Smith reagent, 630-631
Singlet electronic state, **1150**
SI system of units, 326
Skew boat structure, of cyclohexane, 621-622
Skraup reaction, 1105
Smith, Ronald, 630
S_N1 mechanism, 147-151
  carbonium ions in, 148-149
  evidence for, 147
  kinetics, 147-148
  rate-limiting step, 148
  versus E1, 152-153
S_N2 mechanism, 127-131, **135,** 152-153
  acid catalysis, 142
  cyclohexane derivatives, 628
  kinetics, 127-128
  of cyclobutanes, 637
  reactivity, 143-144

S_N2 mechanism [*cont.*]
  similarity to S_E2 mechanism, 164
  solvent polarity, 143–145
  stereochemistry, 128–131
  steric factors, 138–140, 152–153
  transition state for, 142
    stereoscopic figure, 131
  versus E2 mechanism, 152–153
Soaps, 430–432, 507
Sodium amalgam, 716
Sodium amide, 308–309
Sodium-ammonia, reduction
  of alkynes, 312–313
  of naphthalene, 1050
Sodium ammonium racemate, 682
Sodium ammonium tartrate, 681
Sodium borohydride, 284
  compared with lithium aluminum hydride, 395
  reduction
    of aldoses, 696, 709
    of anthraquinones, 1054
    of unsaturated ketones, 558–559
  reduction of unsaturated carbonyl compounds, 558–559
Sodium dichromate, 232
Sodium dithionite, 965
Sodium ethoxide, 216
Sodium hydrosulfite, 965
Sodium methoxide, 216
Sodium peroxide, reaction with acyl chlorides, 649
Sodium sulfide, reduction of nitro compounds, 962
Sodium triphenylmethide, 742–743
Solid-phase technique, 839
Solubility, structure and, 214
Solvation, **44**
Solvent
  aprotic, 143
  polar aprotic, 143–144
Solvolysis reaction, **148**, 151
Sommelet reaction, 935
Sonn-Müller reaction, 935
s orbitals
  electrons in, 306
D-Sorbitol (*see*, D-Glucitol)
Space-filling models, 30–31
Sparteine, 1157
Specific deuteration, 163
Specific rotation, **109**
Spectropolarimeters, 109
Spectroscopy (*see also*, Nuclear magnetic resonance; Microwave spectroscopy; Infrared spectroscopy; Ultraviolet spectroscopy; Mass spectroscopy), **170**, 325–326
  and structure, 169–170
  for conjugated multiple bonds, 594–603
  theory, 170–171
  types of, 170–171
Spermaceti, 506
sp hybrid orbitals, 23–25
sp^2 hybrid orbitals, 25, 26
sp^3 hybrid orbitals, 25–27
Spin quantum number, 16
Spiro compounds, **641**
Spiro[4.5]decan-6-one, 674
Spiropentane, 93
Squalene, 549, 550, 1164
2,3-Squalene oxide, 1165
Staggered structure, 57, 58
Stahl, Georg E., 446
Standard atmospheric pressure, **54**
Standard free energy, **43**
  relation to acidity constant, 133
Standard reduction potentials, 161–162
  of chlorine, 164
  of quinones, 1025 *t*
  of various metals, 161 *t*
Standard states of elements, 89
Stannane, 157
Stannous chloride
  as reducing agent, 961
  reduction of nitriles, 937
Starch 728–729, 730
Stearic acid (*see also*, Octadecanoic acid), 424, 507, 563
  physical properties, 426 *t*
Stephen reduction, 937
Stereochemistry, 119–124
  cis-trans nomenclature, 632
  in alkaline hydrolysis of esters, 222
  in nucleophilic substitution, 519
  of catalytic hydrogenation, 277
  of dehydrohalogenation of alkyl halides, 267, 269–272
  of elimination reactions, 267, 269–272
  of halogen addition to alkenes, 280–281
  of hydroboration, 287
  of hydrogenation of alkynes, 312
  of oxidation of alkenes, 289–290
  resolution, **776**
  stereospecific reactions, 518–519
  syn-anti nomenclature, 632
  transition states in, 120–124
Stereoisomerism, **105**, 105–126, 254
  diastereomers (*see*, Diastereomers)
  enantiomers (*see*, Enantiomers)
  in chemical reactions (*see*, Stereochemistry)
Stereoisomers, 105, 254
  configurational (*see*, Configurational isomers)
  conformational (*see*, Conformational isomers)
  geometric
    cis-trans nomenclature, 256–258
    E-Z nomenclature, 258
  possible number of, 116–117
Stereoscopic figures (*see* page 5 of the text for general instructions on use)
  acetaldehyde, 348
  allene, 545
  allyl cation, 531
  biphenyl, 1039
  butane conformations, 56, 60
  cellobiose, 724
  chlorination of methane, transition state, 79, 81
  codeine hydrobromide, 805

Stereoscopic figures [*cont.*]
  cyclobutane, 610
  cycloheptane, 615
  cyclohexane
    boat conformation, 622
    chair conformation, 612,613
  cyclohexene, 629
  cyclooctane, 616
  cyclooctatetraene, 576
  cyclopentane, 611
  cyclopropane, 609
  cyclopropylmethyl cation, 634
  cis-decalin, 642
  trans-decalin, 641
  E2 mechanism, transition state, 271
  electrophilic aromatic substitution, intermediate, 583
  ethane, 57
  ethylene, 251
    twisted, 256
  β-D-glucose, 703
  glycylphenylalanylglycine, 831
  α-helix, polyalanine, 852
  hexahelicene, 2-methyl, 1060
  hexamethylbenzene-chloranil complex, 1029
  2-iodobutane, R and S, 106
  longifolene hydrochloride, 645
  methane, 27
  2-methylhexahelicene, 1060
  myoglobin, 855
  neopentyl rearrangement, transition state, 228
  norbornane, 640
  pentane, 62
  polyalanine, α-helix, 852
  L-proline, 818
  quinhydrone, 1028
  RS nomenclature, 112
  S_N2 mechanism, transition state, 131
  sucrose, 725
  transition states
    chlorination of methane, 79, 81
    E2 mechanism, 271
    neopentyl cation rearrangement, 228
    S_N2 mechanism, 131
  tris-(*p*-aminophenyl)methyl cation, 908
  vitamin B_{12}, 1168
Stereospecificity, in synthesis, 1167–1173
Stereostructure (*see*, Absolute stereostructure)
Steric factors, in S_N2 reaction, 138–140, 152–153
Steric hindrance, 264
  in substituted alkenes, 264–265
Steroids, 645–648, 1157
  bile salts, 646–647
  biosynthesis, 549, 1158–1167
  cholesterol, 646
  general formula, 604
  general structure, 646
  laboratory preparation, 758
  plant, 648
  sex hormones, 647
  stereochemistry, 646
Stilbene, 308
  cis-trans isomerism, 1153
cis-Stilbene
  isomerism to *trans*, 603
  ultraviolet spectroscopy, 599
trans-Stilbene, 257, 649
  hydrogenation, 922
  ultraviolet spectroscopy, 599
Strecker synthesis, 824
Structural formulas, **28**
Structural isomers, **67**
Structure
  determination (*see also*, Nuclear magnetic resonance; Mass spectometry; Infrared spectroscopy; Ultraviolet spectroscopy), 35–37
  geometric, 9, 10
  in reaction, 46–47
  representations, 28–29
Strychnine, 41, 777, 806, 826
Styrene, 257, 861, 890
  as monomer, 295
  heat of hydrogenation, 573
  polymerization, 562
  polymers, 547
  ultraviolet spectroscopy, 596, 599
Suberic acid, 736
Sublimation, 67
Substitution reactions
  addition-elimination mechanism, 894–895
  elimination-addition mechanism, 895–898
  electrophilic (*see*, Electrophilic substitution)
    bimolecular (*see*, S_E2 mechanism)
    unimolecular (*see*, S_E1 mechanism)
  homolytic, 145
  nucleophilic
    bimolecular (*see*, S_N2 mechanism)
    unimolecular (*see*, S_N1 mechanism)
Succinic acid, 736
  acidity, 738
  cyclic anhydride formation, 739–740
  cyclic imide formation, 740
  preparation, 737
Succinic anhydride, 932, 1015
  preparation, 739–740
Succinimide, 536
  preparation, 740
Sucrose
  degradation, 731
  in plants, 693
  inversion, 726
  specific rotation, 725–726
  stereoscopic figure, 725
  structure, 725
Sugar beets, sucrose from, 725
Sugar cane, sucrose from, 725
Sugar phosphates, 729–731
  biological importance, 729–730
Sugars
  invert, **726**
  nonreducing, **711**
  reducing, **711**
Sulfadiazine, 954
Sulfanilamide, 954
Sulfanilic acid, 966, 972
  methyl orange from, 989

Sulfate ion
  Lewis structure, 7, 8
  reaction with methyl iodide, 136
  reaction with proton, 136
Sulfates, 498–500
Sulfathiazole, 954
Sulfides, **34**, **206**
  nomenclature, 241
  physical properties of, 242
  preparation of, 243
  reactions, 243–245
    oxidation, 243–244
    with alkyl halides, 244–245
  structure, 206–207
  ultraviolet spectroscopy, 602
Sulfinic acids, 955
Sulfite ion
  reaction with methyl iodide, 137
  reaction with proton, 137
Sulfo-, as prefix, 667
Sulfonamides, 954
  from amino acids, 829
  in Hinsberg test, 790
  pK_a, 789–790
  preparation, 789–790
  synthetic uses, 790
Sulfonates, 501
Sulfonation
  of arenes, 951
  of aromatic amines, 972
  of benzene, 587
  of naphthalene, 1048
  of phenols and phenyl ethers, 1014
Sulfones, 34, 244, 954
-sulfonic acid, as suffix, 667
Sulfonic acid group, as protecting group, 951–952
Sulfonic acids, 34, **500**, 950–954
  aromatic
    preparation, 950–951
    reactions, 953–954
    salts, 952
  in S_N2 reactions, 141
  nomenclature, 500, 930
  preparation, 500
Sulfonyl chlorides, 954
  preparation, 501
  reaction with amines, 789–790
Sulfoxides, 244
Sulfur, abundance of isotopes, 409 *t*
Sulfur dioxide, 587
Sulfur hexafluoride, 14
Sulfuric acid, 498–499
  addition to alkenes, 587
  commercial preparation, 587
  fuming, 587
  hydration of alkynes, 315
  in elimination of alcohols, 237–238
  resonance structures, 14
Sulfur trioxide, 587, 951
Sulfuryl chloride, 84
Supersonic transport (SST), 290
Suprafacial addition, **1136**
Symmetry-forbidden absorption, **599**
syn-addition, 632
Synthesis, 516–528
  carbon-carbon formation, 516–518
  control of stereochemistry, 518–519
  functional group placement, 518
  industrial, 527–528
  kinetic control, 1170
  stereospecific, 1167–1173
  thermodynamic control, 1169
  use of protecting groups, 526–527
Système International de Unites, 326

T

-t, symbol for tritium, 163
D-(+)-Talose, 697
Tartaric acid, 681–682
  enantiomers, 681, 719
  pyruvic acid from, 746
  stereoisomers, 681–682
Taurine, 646
τ scale, in NMR, 177
Tautomerism, **360–361**
  enol-keto, 360–368
Teflon, 295
Telomerization, 285–286, 293–294
Telomers, 285
Terephthalic acid, 735, 929, 939
  industrial preparation, 943
Termination step, 78
Terpenes, 549, 643–645, 1144, 1157
  biosynthesis, 643, 1158–1164
Terphenyls, 1041–1042
Testosterone, 647
2,4,4,6-Tetrabromocyclohexa-2,5-dienone, 1006
$\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene, 903
Tetrabutylstannane, preparation, 162
Tetracene
  numbering system, 1058
  properties, 1058
2,3,5,6-Tetrachloro-1,4-benzoquinone (*see*, Chloranil)
1,1,1,3-Tetrachlorononane, 285
Tetracontane, 53
Tetracyanoethylene, 1135
  in charge-transfer complexes, 1029
Tetradecane, 53
  physical properties, 55 *t*
Tetradecanoic acid (*see also*, Myristic acid), physical properties, 426 *t*
Tetraethylammonium bromide, 132
Tetraethyllead, 40
  in gasoline, 88
  preparation, 161
Tetraethylsilane, physical properties, 158 *t*
Tetrafluoroborate salts, 977
Tetrafluoroethylene, 295
Tetrafluoromethane (Freon 14), 102
Tetraglycine, 858
Tetrahydroaluminate ion, 440
1,2,3,4-Tetrahydrocarbazole, 1084
Tetrahydrofuran (THF), 235, 1065, 1067
  preparation, 653, 1071
  uses, 653

Tetrahydropyran, 1067
Tetrahydrothiazole, in penicillin, 1091
Tetrahydrothiophene, 1067
Tetrahydrothiopyran, 1067
Tetralin, 1050
α-Tetralone, 933
Tetramethylammonium chloride, 778
1,2,3,4-Tetramethylbenzene, 913
1,2,4,5-Tetramethylbenzene (*see also,* Durene), 914
2,2,3,3-Tetramethylbutane, physical properties, 67 *t*
Tetramethylsilane (TMS)
  NMR spectrum, 176
  physical properties, 158 *t*
  preparation, 162
Tetrapropylammonium bromide, 778
Tetrasaccharides, **694**
Tetrazotization, 1039
Theobromine, 1110
Theory of absolute rates, 46–47
Thermal cycloaddition reaction, 625–626
Thermal ellipsoids, 719
THF (*see,* Tetrahydrofuran)
Thia-, as prefix, **1066**
Thiamine, 1091
Thiazole
  basicity, 1090
  in thiamine, 1091
  numbering system, 1089
Thiazoles, preparation, 1094
Thietane, 1067
  preparation, 1069
Thietanes
  preparation, 1069
  ring opening, 1071
Thiirane, 1066, 1067
Thiiranes
  preparation, 1068
  ring opening, 1069
m-Thiocresol, 981
-thiol, as suffix, 667
Thiols, **34**, **206**
  nomenclature, 241
  odor, 242
  physical properties, 242
  preparation, 242–243
  reactions, 243–245
  structure, 206–207
  thiol-disulfide redox system, 242–243
Thionyl chloride, 229, 444–445
Thiophene
  electrophilic substitution, 1080–1083
  NMR spectrum, 1076
  physical properties, 1075
  preparation, 1078
  structure, 1073
Thiophenes, properties, 1074–1075
Thiophenol, 955
Thiophenols, preparation, 981
Thiosulfate ion, reaction with methyl iodide, 137
Thiourea, 242–243
Thorium oxide, in dehydration of alcohols, 274–275
Threitol, 696
threo isomer, **669**
Threonine, 816
  physical properties, 817 *t*
Threonylalanine, synthesis, 837
Threose, 697
  oxidation, 716, 719
  reduction, 696
Thymine, 1110, 1139
Thymoquinone, 1022
Thyrotropin-releasing hormone (TRH), 858
Titanium, 296
TMS (*see,* Tetramethylsilane)
TNT, 960
α-Tocopherol, 1027
Tollens' test, 710
p-Tolualdehyde, 935, 938
Toluene, 861, 890
  bromination, 887, 903
  chlorination, 887, 902–903
  dipole moment, 871
  electrophilic substitution, 873–875
  Friedel-Crafts alkylation, 911–912
  hydrogenation of, 623
  nitration, 869, 880
  NMR spectrum, 865
  pK_a, 920
  sulfonation, 951
p-Toluenesulfonic acid, 679, 930, 953
Toluenesulfonic acids, preparation, 951
p-Toluenesulfonyl chloride (tosyl chloride), 231
  melting point, 954
m-Toluic acid, 929
o-Toluic acid, 920, 929, 943
p-Toluic acid, 929, 942
  from *p*-xylene, 943
  industrial oxidation, 943
p-Toluidine, 965
  properties, 966
p-Toluonitrile, 942, 982
Toluquinone, 1022
Tolyl-, as prefix, **891**
Torgov, I.V., 1170
Torgov synthesis of estrone, 1170–1173
Torr, **54**
Torsional motion, energy states of, 61
Tosyl chloride, 954
trans addition, 632
Transamination, 379, 484
Transesterification, 481–482
Transition state, 46–47, **130**
  cyclic four-center, 276
  for formation of dibromobutenes, 543–544
  for interconversion of dideuterio ethylenes, 256
  for pyrolytic elimination, 496
  in E2 mechanism, 270–271
    stereoscopic figure, 271
  in S_N2 mechanism, 130–131
    stereoscopic figure, 131
  six-center, 496, 497, 498
Transmetallation, 899
Transmittance of light, 597
trans-, as prefix, **257**
TRH (thyrotropin-releasing hormone), 858

1,2,4-Triacetoxybenzene, 1030
Triacontane, 53
  physical properties, 55 *t*
Trialkyl phosphates, hydrolysis of, 503–504
Trialkylsulfonium salts, 244–245
Triazene, 987
2,4,6-Tribromobenzoic acid, 984
3,4,4-Tribromo-2,2-dimethylbutane, NMR spectrum, 180
2,4,6-Tribromophenol, 1007
Tri-*n*-butylamine, physical properties, 770 *t*
Tri-*t*-butylcarbinol, 383
Trichloroacetaldehyde (chloral), 370
2,4,6-Trichloroaniline, 972
1,2,4-Trichlorobenzene, 902
1,1,1-Trichloro-2,2-bis-(*p*-chlorophenyl)ethane (DDT), 103–104
1,1,2-Trichloroethane
  NMR spectrum, 183
  spin-spin splitting analysis, 183–184
Trichlorofluoromethane (Freon 11), 102
2,4,5-Trichlorophenol, 1018
1,1,2-Trichloropropane, NMR spectrum, 190
1,2,2-Trichloropropane
  CMR spectrum, 193–194
  conformations, 178
  PMR spectrum, 176
cis-9-Tricosene, 323
Tri-*o*-cresyl phosphate, 1036
Tricyclo[3.3.0.$0^{2,6}$]octane, 1156
Tridecane, 53
  physical properties, 55 *t*
Tridecanoic acid, physical properties, 426 *t*
Triethylaluminum, 556
Triethylamine, 132, 756
  physical properties, 770 *t*
  pK_b, 774
  reaction with methyl iodide, 777
Triethylammonium ion, pK_a, 774
Triethylcarbinol, 488
Triethylene glycol, 654
  preparation, 651
Triethylene glycol ditosylate, 654
Triethylphosphonoacetate, 505
Trifluoroacetic acid, 840
β,β,β-Trifluoroethyl alcohol, inductive effects in, 217
Trifluoromethanesulfonic acid, 500
Trifluoromethyl cation, 13
Trifluoroperoxyacetic acid, 971–972
Triglycerides, 507
Triglyme, 651
2,4,6-Trihydroxyacetophenone, 1016
1,2,3-Trihydroxybenzene (*see*, Pyrogallol)
Triisobutylenes, 292
Triketohydrindene hydrate (*see*, Ninhydrin)
Trimerization, of alkenes, 292
2,3,4-Trimethoxyglutaric acid, 705
Trimethylacetic acid, 920
Trimethylaluminum
  hydrolysis, 163
  physical properties, 158 *t*
Trimethylamine
  physical properties, 770 *t*
Trimethylamine [*cont.*]
  pK_b, 774
  structure, 766
Trimethylammonium ion, pK_a, 774
Trimethylanilinium iodide, 949
Trimethylanilinium ion, 996, 1100
1,3,5-Trimethylbenzene (*see*, Mesitylene)
2,2,3-Trimethylbutane, bromination, 87
Trimethylchlorosilane, 527
Trimethylene glycol, 666
2,2,4-Trimethylpentane (isooctane), standard for octane ratings, 292
2,3,4-Trimethyl-2-pentene, infrared spectrum, 336
Trimethylphosphine, 132
Trimethylsilyl ethers, 527
2,3,4-Tri-O-methyl-α-D-xylose, 705
2,3,4-Tri-O-methyl-β-D-xylose, 705
Trimyristin, 514
2,4,6-Trinitroanisole, 927
1,3,5-Trinitrobenzene, 961
  in charge-transfer complexes, 1029
2,4,6-Trinitrobenzoic acid, pK_a, 960
2,4,6-Trinitrophenol (*see*, Picric acid)
2,4,6-Trinitrotoluene (TNT), 960
1,3,5-Trioxane, 378, 1065
Triphenylcyclopropenyl cation, stability, 1120
2,4,5-Triphenylimidazole, 1094
Triphenylmethane, pK_a, 742–743, 920
Triphenylmethane dyes, 1148–1149
Triphenylmethanol, 907
Triphenylmethyl cation, 907–908
Triphenylmethyl chloride, 905, 907
Triphenylmethyl radical, stability, 905
Triphenylphosphine, 388
Triphenylphosphine oxide, 389
1,3,5-Triphenylpyrazole, 1092
Triplet energy transfer, **1153**
Triplet sensitizer, **1155**
Triplet states, 1152–1153
Tripolyphosphoric acid, 502
Tri-*n*-propylamine, physical properties, 770 *t*
Triptycene, preparation, 1057
Tris-(p-amino phenyl) methyl cation, 908
  stereoscopic figure, 908
Trisaccharides (*see also*, Raffinose), **694**
Triterpene, **549**
Tritium, as a tracer isotope, 585
Trityl chloride, 905
Trityl nitrate, 891
Truxillic acid, 637, 1134
Trypsin, 845
  function, 856
Tryptamine, 1084
Tryptophan, 816, 1084
  physical properties, 817 *t*
Tung oil, 507
Turkey red, 1147
Turpentine, 639
Twist boat form of cyclohexane, 621–622
Tyrian purple, 1149
Tyrosine, 816, 1145
  physical properties 817 *t*
  pK values, 817 *t*, 820

U

- Ubiquinone 1027
- Ullmann reaction, 900
  - biphenyls from, 1039
- Ultraviolet light, 171
- Ultraviolet radiation, 325
  - energy of, 593
- Ultraviolet spectroscopy, 171, 593–603
  - absorption bands
  - intensity of, 597–599
    - relation to conjugated bonds, 594–596
  - alkyl substituents, 600–602
  - benzene rings in, 599–600
  - carbonyl group in, 596–599, 602
  - *cis-trans* isomerism in, 599–600
  - conjugated bonds in, 594–596, 602
  - electronic transitions in, 593–599
  - solvents used, 602
  - symmetry-forbidden absorption, **599**
  - wavelengths used, 594
  - Woodward's rules, 601–602
- Umbelliferone, 1117
- Undecanal
  - as sex-attractant, 403
  - physical properties, 352 *t*
- Undecane, 53
  - physical properties, 55 *t*
- Undecanoic acid
  - physical properties, 426 *t*
  - preparation from *n*-decyl cyanide, 433
- 2-Undecanone
  - physical properties, 353 *t*
- 5-Undecyne, 310
- α,β-Unsaturated acids
  - from Knoevenagel condensation, 755
  - preparation, 759
- α,β-Unsaturated aldehydes and ketones
  - aldol condensation, 552–554, 677
  - conjugation in, 550–552
  - oxidation of allylic alcohols, 554–555
  - preparation, 552–554, 677
  - reactions, 555–560
    - addition of hydrogen cyanide, 555–556
    - addition of organometallic reagents, 556–558
    - 1,2- versus 1,4-addition, 555–560
  - reduction, 558–560
  - structure, 550
  - ultraviolet spectroscopy, 596, 600–602
- α,β-Unsaturated carbonyl compounds, 385–388, 550–565
  - deuterium exchange, 551–552
  - double bond migration in, 550–552
  - interconversion of, 550–552
  - Michael addition, 755–758
  - photochemical reactions, 1154
- Unsaturated carboxylic acids and derivatives, 560–564
  - addition of cyanide, 737
  - conjugated system, 560–563
  - from dehydration of hydroxy acids, 687
  - natural occurrence of, 563
  - preparation, 561–562
- Uracil, 1110, 1138
- Urea, 2, 243, 738, 1111
- Ureas, preparation, 801
- Urethanes, 801
- Uridine, 1140
- Urushiol, 1034
- Urydilic acid, 1139

V

- Vacuum ultraviolet radiation, 594
- Valence electrons, **6**, 7
- Valeraldehyde, physical properties, 352 *t*
- Valeric acid, 424
  - physical properties, 426 *t*
- Valine, 815
  - physical properties, 817 *t*
- Vanadium pentoxide, 393–394
  - oxidation of naphthalene, 1049
- Van der Waals forces, 54–57, 96–97, 456
  - and boiling point, 54–57, 98–99
  - and melting point, 57
  - in branched chain alkanes, 63, 67
  - in conformation stability, 101–102
  - in elasticity of polymers, 548
  - in proteins, 849
- Van der Waals radius, **96–97**
  - of various elements, 97 *t*
- Vanillin, 1032
- Vapor pressure, relationship to intermolecular attractive force, 54
- Varnish, 563
- Vegetable oils, 508
- Vertical electronic transitions, 1150
- Vibrational energy, 268, 593, 603
  - excited states, 1150–1152
  - internal conversion, **1151**
- Vibrational motion, 73, 170, 268, 327–329
  - bending, 328
  - energy differences in, 170
  - frequency of, 330–331
  - fundamental vibrational modes, 328
  - models of, 330–331
  - quantization of, 327–328
  - stretching, 328
- Vibrational transitions
  - infrared active, **328**
  - infrared inactive, **328**
- Vibration of bonds, energy differences in, 170
- *Vic-*, as prefix, 308
- Vicinal dihalides
  - dehydrohalogenation, 282
  - nucleophilic displacement, 282
  - preparation of, 280–281
  - reaction with magnesium, 283
- Vicinal diols (*see*, Glycols)
- Vilsmeier reaction, 935–936
- Vinegar, 446
- Vinyl, **313**
- Vinylacetic acid, 561
  - inductive effects in, 429
  - pK_a, 429 *t*

Vinylacetylene, 547
  industrial preparation, 318
Vinyl alcohols, 315, 358
Vinyl anion, 306, 312-313
Vinylbenzene (*see*, Styrene)
Vinylboranes, 316-317
Vinyl bromides, preparation of, 319
Vinyl cations, **314**, 320-321
  electronic structure, 314
  reactions, 314-315
Vinyl chloride
  as human carcinogen, 294
  as monomer, 294
Vinyl ethers, preparation of, 316
Vinyl halides, 318-321
  preparation of, 314-315
Vinyl hydrogens, **260**
  in NMR spectroscopy, 260-264
Vinylogs, **749**
Vinyl radical, 257, 312-313
Vinyl radicals, stability 312-313
Visible light, 171
  and color, 1142-1143
  energy of, 593
  wavelength, 594
Vision, photochemical reactions in, 603
Visual purple (rhodopsin), 603
Vital force, 2
Vitamin A_1, 41, 555, 564, 603
Vitamin A_1 aldehyde (retinal), 555, 603
Vitamin B_1 (thiamine), 1091
Vitamin B_{12}
  stereoscopic figure, 1168
  synthesis, 1167
Vitamin C, 40
Vitamin E, 1027
Vitamin K, 1027
von Liebig, Justus, 35
Vulcanization, 547-548

W

Water
  dielectric constant, 213-214
  dissociation constant, 774
  heavy oxygen isotope, 371
  structure, 9
Wave function (*see also*, Atomic orbitals), **15**
Wave functions, combining of, 20, 21, 534-535
Wave motion of electron, 15
Wave number, **326**
Waxes, 506
Wenker synthesis, 1068
Wheat germ oil, 549
Whey, lactose from, 724
Williamson, A. W., 236
Williamson ether synthesis, 236-237
Wittig reaction, 388-390, 546
Woehler, Friedrich, 2
Wohl degradation, 718
Wolff-Kishner reduction, 397-398
  of aryl carbonyls, 915
Wood, cellulose in, 727
Woodward, R. B., 1167
Woodward's rules, 601-602
Wurster's blue, 971
Wurtz-Fittig reaction, 900
Wurtz reaction, 167

X

X, symbol for halogen, 96
Xanthates, 497
  preparation of, 497
  pyrolytic elimination (Chugaev reaction), 497
Xanthommatin, 1145, 1146
Xanthopterin, 1145, 1146
Xenon, anesthetic effect of, 102
X-ray diffraction, 725
X rays, 325
o-Xylene, 890
  Birch reduction of, 924
  halogenation, 903
  oxidation, 944
p-Xylene, 890
  industrial oxidation of, 943
D-(+)-Xylose, 697
Xylyl-, as prefix, **891**

Y

Yeast, 549
Yellow fever, 103
Ylids, 388-389
-yne, as suffix, 667

Z

Zeisel determination, 1118
Zero point energy, 61, 73, 268-269
  effect on activation energy, 268-269
Ziegler-Natta catalysts, 547
Zinc chloride, 225, 590
Zinc-copper couple, 630
Zingiberene, 644
Z isomer, **258**
Zwitterions, 814, 816

TABLE OF BOND DISSOCIATION ENERGIES

DH°, kcal mole^{-1} for A—B bonds

			(52.1)	(29.0)	(26.7)	(25.5)	(9.3)	(40.1)	(34)	(80)	(109)
	A	B:	H	Cl	Br	I	OH	NH_2	CH_3	C_6H_5	CN
(34)	CH_3—		104	84	70	56	91	80	88	102	122
(26)	C_2H_5—		98	81	68	53	91	77	85	99	123
(18)	i-C_3H_7 —		95	80	68	53	92	78	84	97	121
(7)	t-C_4H_9 —		91	79	65	50	91	76	81	92	
(80)	C_6H_5—		112	97	82	66	112	99	102	117	137
(45)	$C_6H_5CH_2$—		85	70	55	45	78		72	88	
(40)	$CH_2{=}CHCH_2$—		87	69	55	42	79		74		
(−5)	CH_3CO—		87	82	67	50	108		81	95	
(−5)	C_2H_5O—		103				43		81	101	
(68)	$CH_2{=}CH$—		108	88	76				97	113	133
(52.1)	H—		104.2	103.2	87.5	71.3	119.2	103.2	104.0	112	130

Numbers in parentheses: (ΔH_f°) for $A^\cdot$ or $B^\cdot$

David Applegarth

PERIODIC TABLE OF THE ELEMENTS

			1 **H** 1.008														2 **He** 4.003
3 **Li** 6.94	4 **Be** 9.01											5 **B** 10.81	6 **C** 12.011	7 **N** 14.01	8 **O** 16.00	9 **F** 19.00	10 **Ne** 20.18
11 **Na** 22.99	12 **Mg** 24.31											13 **Al** 26.98	14 **Si** 28.09	15 **P** 30.97	16 **S** 32.06	17 **Cl** 35.45	18 **Ar** 39.95
19 **K** 39.10	20 **Ca** 40.08	21 **Sc** 44.96	22 **Ti** 47.90	23 **V** 50.94	24 **Cr** 52.00	25 **Mn** 54.94	26 **Fe** 55.85	27 **Co** 58.93	28 **Ni** 58.71	29 **Cu** 63.55	30 **Zn** 65.37	31 **Ga** 69.72	32 **Ge** 72.59	33 **As** 74.92	34 **Se** 78.96	35 **Br** 79.90	36 **Kr** 83.80
37 **Rb** 85.47	38 **Sr** 87.62	39 **Y** 88.91	40 **Zr** 91.22	41 **Nb** 92.91	42 **Mo** 95.94	43 **Tc** 98.91	44 **Ru** 101.07	45 **Rh** 102.91	46 **Pd** 106.4	47 **Ag** 107.87	48 **Cd** 112.40	49 **In** 114.82	50 **Sn** 118.69	51 **Sb** 121.75	52 **Te** 127.60	53 **I** 126.90	54 **Xe** 131.30
55 **Cs** 132.91	56 **Ba** 137.34	57 **La** 138.91	72 **Hf** 178.49	73 **Ta** 180.95	74 **W** 183.85	75 **Re** 186.2	76 **Os** 190.2	77 **Ir** 192.22	78 **Pt** 195.09	79 **Au** 196.97	80 **Hg** 200.59	81 **Tl** 204.37	82 **Pb** 207.2	83 **Bi** 208.98	84 **Po** (209)	85 **At** (210)	86 **Rn** (222)
87 **Fr** (223)	88 **Ra** 226.03	89 **Ac** (227)	104 **(Rf)** (261)	105 **(Ha)** (262)	106												

Lanthanides	58 **Ce** 140.12	59 **Pr** 140.91	60 **Nd** 144.24	61 **Pm** (145)	62 **Sm** 150.4	63 **Eu** 151.96	64 **Gd** 157.25	65 **Tb** 158.93	66 **Dy** 162.50	67 **Ho** 164.93	68 **Er** 167.26	69 **Tm** 168.93	70 **Yb** 173.04	71 **Lu** 174.97
Actinides	90 **Th** 232.04	91 **Pa** 231.04	92 **U** 238.03	93 **Np** 237.05	94 **Pu** (244)	95 **Am** (243)	96 **Cm** (247)	97 **Bk** (249)	98 **Cf** (249)	99 **Es** (254)	100 **Fm** (257)	101 **Md** (258)	102 **No** (259)	103 **Lr** (260)

(available radioactive isotope of longest half-life)

41801