CONTENTS

Preface xxv

INTRODUCTION 1
The Origins of Organic Chemistry 1 Berzelius, Wöhler, and Vitalism 1 The Structural Theory 3 Electronic Theories of Structure and Reactivity 3 The Influence of Organic Chemistry 4
Computers and Organic Chemistry 4
Challenges and Opportunities 5
Where Did the Carbon Come From? 6
CHAPTER 1
CHEMICAL BONDING 7
1.1 Atoms, Electrons, and Orbitals 7
1.2 Ionic Bonds 11
1.3 Covalent Bonds 12
1.4 Double Bonds and Triple Bonds 14
1.5 Polar Covalent Bonds and Electronegativity 15
1.6 Formal Charge 16
1.7 Structural Formulas of Organic Molecules 191.8 Constitutional Isomers 22
1.8 Constitutional Isomers 22 1.9 Resonance 23
1.10 The Shapes of Some Simple Molecules 26
Learning By Modeling 27
1.11 Molecular Dipole Moments 30
1.12 Electron Waves and Chemical Bonds 31
1.13 Bonding in H ₂ : The Valence Bond Model 32
1.14 Bonding in H ₂ : The Molecular Orbital Model 34
1.15 Bonding in Methane and Orbital Hybridization 35 1.16 sp ³ Hybridization and Bonding in Ethane 37
1.16 sp ³ Hybridization and Bonding in Ethane 37 1.17 sp ² Hybridization and Bonding in Ethylene 38
1.18 sp Hybridization and Bonding in Acetylene 40
1.19 Which Theory of Chemical Bonding Is Best? 42
1.20 SUMMARY 43
PROBLEMS 47

CHAPTER 2

ALKANES 53

- 2.1 Classes of Hydrocarbons 53
- 2.2 Reactive Sites in Hydrocarbons 54
- 2.3 The Key Functional Groups 55
- 2.4 Introduction to Alkanes: Methane, Ethane, and Propane 56
- 2.5 Isomeric Alkanes: The Butanes 57

Methane and the Biosphere 58

xii CONTENTS

2.6	Higher <i>n</i> -Alkanes 59
2.7	The C ₅ H ₁₂ Isomers 59
2.8 2.9	IUPAC Nomenclature of Unbranched Alkanes 61 Applying the IUPAC Rules: The Names of the C ₆ H ₁₄ Isomers 62
2.5	A Brief History of Systematic Organic Nomenclature 63
2.10	Alkyl Groups 65
2.11	IUPAC Names of Highly Branched Alkanes 66
2.12	Cycloalkane Nomenclature 68
2.13	Sources of Alkanes and Cycloalkanes 69
2.14 2.15	Physical Properties of Alkanes and Cycloalkanes 71 Chemical Properties. Combustion of Alkanes 74
	Thermochemistry 77
2.16	Oxidation–Reduction in Organic Chemistry 78
2.17	SUMMARY 80
	PROBLEMS 83
CHA	APTER 3
CON	FORMATIONS OF ALKANES AND CYCLOALKANES 89
3.1	Conformational Analysis of Ethane 90
3.2	Conformational Analysis of Butane 94
	Molecular Mechanics Applied to Alkanes and Cycloalkanes 96
3.3	Conformations of Higher Alkanes 97
3.4 3.5	The Shapes of Cycloalkanes: Planar or Nonplanar? 98 Conformations of Cyclohexane 99
3.6	Axial and Equatorial Bonds in Cyclohexane 100
3.7	Conformational Inversion (Ring Flipping) in Cyclohexane 103
3.8	Conformational Analysis of Monosubstituted Cyclohexanes 104
	Enthalpy, Free Energy, and Equilibrium Constant 106
3.9	Small Rings: Cyclopropane and Cyclobutane 106
3.10	Cyclopentane 108
3.11 3.12	Medium and Large Rings 108 Disubstituted Cycloalkanes: Stereoisomers 108
3.13	Conformational Analysis of Disubstituted Cyclohexanes 110
3.14	Polycyclic Ring Systems 114
3.15	Heterocyclic Compounds 116
3.16	SUMMARY 117
	PROBLEMS 120
CHA	APTER 4
ALCC	PHOLS AND ALKYL HALIDES 126
4.1	IUPAC Nomenclature of Alkyl Halides 127
4.2 4.3	IUPAC Nomenclature of Alcohols 127 Classes of Alcohols and Alkyl Halides 128
4.3 4.4	Bonding in Alcohols and Alkyl Halides 129
4.5	Physical Properties of Alcohols and Alkyl Halides: Intermolecular Forces 130
4.6	Acids and Bases: General Principles 133
4.7	Acid-Base Reactions: A Mechanism for Proton Transfer 136
4.8	Preparation of Alkyl Halides from Alcohols and Hydrogen Halides 137
4.9 4.10	Mechanism of the Reaction of Alcohols with Hydrogen Halides 139 Structure, Bonding, and Stability of Carbocations 140
7.10	Structure, bolianing, and stability of Carbocations 140

CONTENTS xiii

4.11 4.12 4.13 4.14 4.15 4.16 4.17 4.18 4.19 4.20	Potential Energy Diagrams for Multistep Reactions: The S _N 1 Mechanism 143 Effect of Alcohol Structure on Reaction Rate 145 Reaction of Primary Alcohols with Hydrogen Halides: The S _N 2 Mechanism 146 Other Methods for Converting Alcohols to Alkyl Halides 147 Halogenation of Alkanes 148 Chlorination of Methane 148 Structure and Stability of Free Radicals 149 Mechanism of Methane Chlorination 153 From Bond Energies to Heats of Reaction 155 Halogenation of Higher Alkanes 156 SUMMARY 159 PROBLEMS 163
STRU	PTER 5 CTURE AND PREPARATION OF ALKENES: ELIMINATION TIONS 167
5.1	Alkene Nomenclature 167
	Ethylene 168
5.2	Structure and Bonding in Alkenes 170
5.3	Isomerism in Alkenes 172
5.4	Naming Stereoisomeric Alkenes by the <i>E–Z</i> Notational System 173
5.5	Physical Properties of Alkenes 174
5.6	Relative Stabilities of Alkenes 176
5.7	Cycloalkenes 180
5.8	Preparation of Alkenes: Elimination Reactions 181
5.9	Dehydration of Alcohols 182
5.10	Regioselectivity in Alcohol Dehydration: The Zaitsev Rule 183
5.11	Stereoselectivity in Alcohol Dehydration 184 The Mashanism of Asid Catalyzad Dehydration of Alsohols 185
5.12 5.13	The Mechanism of Acid-Catalyzed Dehydration of Alcohols 185 Rearrangements in Alcohol Dehydration 187
5.14	Dehydrohalogenation of Alkyl Halides 190
5.15	Mechanism of the Dehydrohalogenation of Alkyl Halides: The E2
3.13	Mechanism 192
5.16	Anti Elimination in E2 Reactions: Stereoelectronic Effects 194
5.17	A Different Mechanism for Alkyl Halide Elimination: The E1
	Mechanism 196
5.18	SUMMARY 198
	PROBLEMS 202
CHA	PTER 6
REAC	TIONS OF ALKENES: ADDITION REACTIONS 208
6.1	Hydrogenation of Alkenes 208
6.2	Heats of Hydrogenation 209
6.3	Stereochemistry of Alkene Hydrogenation 212
6.4	Electrophilic Addition of Hydrogen Halides to Alkenes 213
6.5	Regioselectivity of Hydrogen Halide Addition: Markovnikov's Rule 214
6.6	Mechanistic Basis for Markovnikov's Rule 216
	Rules, Laws, Theories, and the Scientific Method 217
6.7	Carbocation Rearrangements in Hydrogen Halide Addition to Alkenes 219
6.8	Free-Radical Addition of Hydrogen Bromide to Alkenes 220

xiv CONTENTS

6.9 6.10 6.11 6.12 6.13 6.14 6.15 6.16 6.17 6.18 6.20 6.21	Addition of Sulfuric Acid to Alkenes 223 Acid-Catalyzed Hydration of Alkenes 225 Hydroboration—Oxidation of Alkenes 227 Stereochemistry of Hydroboration—Oxidation 229 Mechanism of Hydroboration—Oxidation 230 Addition of Halogens to Alkenes 233 Stereochemistry of Halogen Addition 233 Mechanism of Halogen Addition to Alkenes: Halonium lons 234 Conversion of Alkenes to Vicinal Halohydrins 236 Epoxidation of Alkenes 238 Ozonolysis of Alkenes 240 Introduction to Organic Chemical Synthesis 243 Reactions of Alkenes with Alkenes: Polymerization 244 Ethylene and Propene: The Most Important Industrial Organic Chemicals 248
6.22	SUMMARY 249
	PROBLEMS 252
CHA	PTER 7
	OCHEMISTRY 259
7.1	Molecular Chirality: Enantiomers 259
7.2	The Stereogenic Center 260
7.3 7.4	Symmetry in Achiral Structures 264 Properties of Chiral Molecules: Optical Activity 265
7. 4 7.5	Properties of Chiral Molecules: Optical Activity 265 Absolute and Relative Configuration 267
7.6	The Cahn–Ingold–Prelog <i>R–S</i> Notational System 268
7.7	Fischer Projections 271
7.8	Physical Properties of Enantiomers 272
	Chiral Drugs 273
7.9 7.10	Reactions That Create a Stereogenic Center 274
7.10 7.11	Chiral Molecules with Two Stereogenic Centers 276 Achiral Molecules with Two Stereogenic Centers 279
	Chirality of Disubstituted Cyclohexanes 281
7.12	Molecules with Multiple Stereogenic Centers 282
7.13	Reactions That Produce Diastereomers 284
7.14	Resolution of Enantiomers 286
7.15	Stereoregular Polymers 288
7.16	-
7.17	SUMMARY 290 PROBLEMS 293
	FRODLEINIS 255
	PTER 8 EOPHILIC SUBSTITUTION 302
8.1	Functional Group Transformation by Nucleophilic Substitution 302
8.2	Relative Reactivity of Halide Leaving Groups 305
8.3 8.4	The S_N 2 Mechanism of Nucleophilic Substitution 306 Stereochemistry of S_N 2 Reactions 307
8.5	How S _N 2 Reactions Occur 308
8.6	Steric Effects in S _N 2 Reactions 310
8.7	Nucleophiles and Nucleophilicity 312
	An Enzyme-Catalyzed Nucleophilic Substitution of an Alkyl Halide 314

CONTENTS xv

8.8 8.9 8.10 8.11 8.12 8.13 8.14 8.15	The S _N 1 Mechanism of Nucleophilic Substitution 315 Carbocation Stability and S _N 1 Reaction Rates 315 Stereochemistry of S _N 1 Reactions 318 Carbocation Rearrangements in S _N 1 Reactions 319 Effect of Solvent on the Rate of Nucleophilic Substitution 320 Substitution and Elimination as Competing Reactions 323 Sulfonate Esters as Substrates in Nucleophilic Substitution 326 Looking Back: Reactions of Alcohols with Hydrogen Halides 329
8.16	SUMMARY 330 PROBLEMS 332
CHA ALKY	PTER 9
9.1 9.2 9.3 9.4	Sources of Alkynes 339 Nomenclature 340 Physical Properties of Alkynes 341 Structure and Bonding in Alkynes: <i>sp</i> Hybridization 341
0.5	Natural and "Designed" Enediyne Antibiotics 344
9.5 9.6	Acidity of Acetylene and Terminal Alkynes 344 Preparation of Alkynes by Alkylation of Acetylene and Terminal Alkynes 346
9.7 9.8 9.9 9.10 9.11 9.12 9.13 9.14	Preparation of Alkynes by Elimination Reactions 348 Reactions of Alkynes 350 Hydrogenation of Alkynes 350 Metal-Ammonia Reduction of Alkynes 351 Addition of Hydrogen Halides to Alkynes 352 Hydration of Alkynes 355 Addition of Halogens to Alkynes 356 Ozonolysis of Alkynes 357
9.15	SUMMARY 357
	PROBLEMS 358
CONJ	PTER 10 UGATION IN ALKADIENES AND ALLYLIC SYSTEMS 365
10.1 10.2 10.3 10.4 10.5 10.6 10.7 10.8 10.9 10.10 10.11 10.12	Addition of Hydrogen Halides to Conjugated Dienes 379
	Diene Polymers 383
10.14	The π Molecular Orbitals of Ethylene and 1,3-Butadiene 386 A π Molecular Orbital Analysis of the Diels–Alder Reaction 388
10.15	SUMMARY 390 PRORIEMS 393

CONTENTS χvi

CHAPTER	11	
ADENIEC AND	A DOBA ATICITY	_

	ES AND AROMATICITY 398
11.1	Benzene 399
11.2	Kekulé and the Structure of Benzene 399
	Benzene, Dreams, and Creative Thinking 401
11.3 11.4 11.5 11.6 11.7 11.8	A Resonance Picture of Bonding in Benzene 402 The Stability of Benzene 403 An Orbital Hybridization View of Bonding in Benzene 405 The π Molecular Orbitals of Benzene 405 Substituted Derivatives of Benzene and Their Nomenclature 406 Polycyclic Aromatic Hydrocarbons 408
	Carbon Clusters, Fullerenes, and Nanotubes 410
11.11 11.12 11.13 11.14 11.15 11.16 11.17 11.18 11.19 11.20 11.21 11.22	Physical Properties of Arenes 411 Reactions of Arenes: A Preview 411 The Birch Reduction 412 Free-Radical Halogenation of Alkylbenzenes 414 Oxidation of Alkylbenzenes 416 Nucleophilic Substitution in Benzylic Halides 417 Preparation of Alkenylbenzenes 419 Addition Reactions of Alkenylbenzenes 419 Polymerization of Styrene 421 Cyclobutadiene and Cyclooctatetraene 422 Hückel's Rule: Annulenes 423 Aromatic Ions 426 Heterocyclic Aromatic Compounds 430 Heterocyclic Aromatic Compounds and Hückel's Rule 432 SUMMARY 433
	PROBLEMS 437
CHA	PTER 12
REAC	TIONS OF ARENES: ELECTROPHILIC AROMATIC
SUBS.	TITUTION 443
12.1	Representative Electrophilic Aromatic Substitution Reactions of
12.2 12.3 12.4 12.5	Benzene 444 Mechanistic Principles of Electrophilic Aromatic Substitution 444 Nitration of Benzene 447 Sulfonation of Benzene 448 Halogenation of Benzene 448
12.6	Friedel–Crafts Alkylation of Benzene 450
12.7	Friedel–Crafts Acylation of Benzene 453
12.8	Synthesis of Alkylbenzenes by Acylation–Reduction 455
12.9	Rate and Regioselectivity in Electrophilic Aromatic Substitution 457
12.10	
12.11	Rate and Regioselectivity in the Nitration of (Trifluoromethyl)benzene 461
	Substituent Effects in Electrophilic Aromatic Substitution: Activating Substituents 463
12.13	Substituent Effects in Electrophilic Aromatic Substitution: Strongly Deactivating Substituents 466

12.14 Substituent Effects in Electrophilic Aromatic Substitution: Halogens 469

12.15 Multiple Substituent Effects 470

12.16 Regioselective Synthesis of Disubstituted Aromatic Compounds 472

CONTENTS xvii

Substitution in Naphthalene 474 Substitution in Heterocyclic Aromatic Compounds 475
SUMMARY 477
PROBLEMS 480
TROBLEMS 400
PTER 13 TROSCOPY 487
Principles of Molecular Spectroscopy: Electromagnetic Radiation 488 Principles of Molecular Spectroscopy: Quantized Energy States 489 Introduction to ¹ H NMR Spectroscopy 490 Nuclear Shielding and ¹ H Chemical Shifts 493 Effects of Molecular Structure on ¹ H Chemical Shifts 494 Interpreting Proton NMR Spectra 497 Spin–Spin Splitting in NMR Spectroscopy 500 Splitting Patterns: The Ethyl Group 503 Splitting Patterns: The Isopropyl Group 505 Splitting Patterns: Pairs of Doublets 505 Complex Splitting Patterns 507 ¹ H NMR Spectra of Alcohols 509 NMR and Conformations 510 ¹³ C NMR Spectroscopy 510 ¹³ C Chemical Shifts 512 ¹³ C NMR and Peak Intensities 513
¹³ C— ¹ H Coupling 515
Using DEPT to Count the Hydrogens Attached to ¹³ C 515
Magnetic Resonance Imaging 517
Infrared Spectroscopy 518 Ultraviolet-Visible (UV-VIS) Spectroscopy 522 Mass Spectrometry 526
Gas Chromatography, GC/MS, and MS/MS 530
Molecular Formula as a Clue to Structure 532
SUMMARY 533
PROBLEMS 536
ANOMETALLIC COMPOUNDS 546
Organometallic Nomenclature 547 Carbon–Metal Bonds in Organometallic Compounds 547 Preparation of Organolithium Compounds 549 Preparation of Organomagnesium Compounds: Grignard Reagents 550 Organolithium and Organomagnesium Compounds as Brønsted Bases 551 Synthesis of Alcohols Using Grignard Reagents 553 Synthesis of Alcohols Using Organolithium Reagents 554 Synthesis of Acetylenic Alcohols 556 Retrosynthetic Analysis 557 Preparation of Tertiary Alcohols from Esters and Grignard Reagents 560 Alkane Synthesis Using Organocopper Reagents 561 An Organozinc Reagent for Cyclopropane Synthesis 563 Carbenes and Carbenoids 565 Transition-Metal Organometallic Compounds 566 Ziegler–Natta Catalysis of Alkene Polymerization 567

xviii CONTENTS

An Organometallic Compound That Occurs Naturally: Coenzyme B_{12} 568

14.16 SUMMARY 570

PROBLEMS 573

CHAPIER IS	CH	A	P1	ſΕ	R	1	5
------------	----	---	----	----	---	---	---

ALCC	OHOLS, DIOLS, AND THIOLS	579
4 - 4	C	

- 15.1 Sources of Alcohols 579
- 15.2 Preparation of Alcohols by Reduction of Aldehydes and Ketones 583
- 15.3 Preparation of Alcohols by Reduction of Carboxylic Acids and Esters 587
- 15.4 Preparation of Alcohols from Epoxides 587
- 15.5 Preparation of Diols 589
- 15.6 Reactions of Alcohols: A Review and a Preview 590
- 15.7 Conversion of Alcohols to Ethers 590
- 15.8 Esterification 593
- 15.9 Esters of Inorganic Acids 595
- 15.10 Oxidation of Alcohols 596

Economic and Environmental Factors in Organic Synthesis 598

619

- 15.11 Biological Oxidation of Alcohols 600
- 15.12 Oxidative Cleavage of Vicinal Diols 602
- 15.13 Preparation of Thiols 603
- 15.14 Properties of Thiols 604
- 15.15 Spectroscopic Analysis of Alcohols 605
- 15.16 SUMMARY 607

PROBLEMS 611

CHAPTER 16

ETHERS, EPOXIDES, AND SULFIDES

- 16.1 Nomenclature of Ethers, Epoxides, and Sulfides 619
- 16.2 Structure and Bonding in Ethers and Epoxides 621
- 16.3 Physical Properties of Ethers 622
- 16.4 Crown Ethers 622

Polyether Antibiotics 624

- 16.5 Preparation of Ethers 625
- 16.6 The Williamson Ether Synthesis 626
- 16.7 Reactions of Ethers: A Review and a Preview 627
- 16.8 Acid-Catalyzed Cleavage of Ethers 628
- 16.9 Preparation of Epoxides: A Review and a Preview 630
- 16.10 Conversion of Vicinal Halohydrins to Epoxides 630
- 16.11 Reactions of Epoxides: A Review and a Preview 632
- 16.12 Nucleophilic Ring-Opening Reactions of Epoxides 633
- 16.13 Acid-Catalyzed Ring-Opening Reactions of Epoxides 635
- 16.14 Epoxides in Biological Processes 637
- 16.15 Preparation of Sulfides 638
- 16.16 Oxidation of Sulfides: Sulfoxides and Sulfones 639
- 16.17 Alkylation of Sulfides: Sulfonium Salts 640
- 16.18 Spectroscopic Analysis of Ethers 641
- 16.19 SUMMARY 643

PROBLEMS 647

CONTENTS xix

	-			_
_				

ALDEHYDES AND KETONES: NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP 654

- 17.1 Nomenclature 654
- 17.2 Structure and Bonding: The Carbonyl Group 657
- 17.3 Physical Properties 658
- 17.4 Sources of Aldehydes and Ketones 659
- 17.5 Reactions of Aldehydes and Ketones: A Review and a Preview 661
- 17.6 Principles of Nucleophilic Addition: Hydration of Aldehydes and Ketones 663
- 17.7 Cyanohydrin Formation 667
- 17.8 Acetal Formation 668
- 17.9 Acetals as Protecting Groups 671
- 17.10 Reaction with Primary Amines: Imines 672
- 17.11 Reaction with Secondary Amines: Enamines 674

Imines in Biological Chemistry 675

- 17.12 The Wittig Reaction 677
- 17.13 Planning an Alkene Synthesis via the Wittig Reaction 678
- 17.14 Stereoselective Addition to Carbonyl Groups 681
- 17.15 Oxidation of Aldehydes 682
- 17.16 Baeyer-Villiger Oxidation of Ketones 683
- 17.17 Spectroscopic Analysis of Aldehydes and Ketones 684
- 17.18 SUMMARY 688

PROBLEMS 691

CHAPTER 18

ENOLS AND ENOLATES

701

- 18.1 The α -Carbon Atom and Its Hydrogens 702
- 18.2 α Halogenation of Aldehydes and Ketones 703
- 18.3 Mechanism of α Halogenation of Aldehydes and Ketones 703
- 18.4 Enolization and Enol Content 705
- 18.5 Stabilized Enols 707
- 18.6 Base-Catalyzed Enolization: Enolate Anions 708
- 18.7 The Haloform Reaction 711

The Haloform Reaction and the Biosynthesis of Trihalomethanes 713

- 18.8 Some Chemical and Stereochemical Consequences of Enolization 713
- 18.9 The Aldol Condensation 715
- 18.10 Mixed Aldol Condensations 719
- 18.11 Effects of Conjugation in α , β -Unsaturated Aldehydes and Ketones 720
- 18.12 Conjugate Addition to α , β -Unsaturated Carbonyl Compounds 722
- 18.13 Additions of Carbanions to α,β -Unsaturated Ketones: The Michael Reaction 724
- 18.14 Conjugate Addition of Organocopper Reagents to α,β -Unsaturated Carbonyl Compounds 724
- 18.15 Alkylation of Enolate Anions 725
- 18.16 SUMMARY 726

PROBLEMS 726

XX CONTENTS

	PTER 19 OXYLIC ACIDS 736
19.1	Carboxylic Acid Nomenclature 737
19.2	Structure and Bonding 738
19.3	Physical Properties 739
19.4 19.5	Acidity of Carboxylic Acids 740 Salts of Carboxylic Acids 742
19.5	•
	Quantitative Relationships Involving Carboxylic Acids 743
19.6	Substituents and Acid Strength 745
19.7 19.8	Ionization of Substituted Benzoic Acids 747 Dicarboxylic Acids 748
19.8	Carbonic Acid 749
	Sources of Carboxylic Acids 750
	Synthesis of Carboxylic Acids by the Carboxylation of Grignard Reagents 750
19.12	Nitriles 752
	Reactions of Carboxylic Acids: A Review and a Preview 753
	Mechanism of Acid-Catalyzed Esterification 754
	Intramolecular Ester Formation: Lactones 758
19.16	α Halogenation of Carboxylic Acids: The Hell–Volhard–Zelinsky Reaction 759
19.17	Decarboxylation of Malonic Acid and Related Compounds 760
	Spectroscopic Analysis of Carboxylic Acids 763
	SUMMARY 765
	PROBLEMS 768
	PROBLEMS 768
	PTER 20
CARB	PTER 20 OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL
CARB SUBS	PTER 20 OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774
CARB SUBS 20.1	PTER 20 OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775
CARB SUBS 20.1 20.2	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777
20.1 20.2 20.3	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780
20.1 20.2 20.3 20.4	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783
20.1 20.2 20.3	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780
20.1 20.2 20.3 20.4 20.5	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784
20.1 20.2 20.3 20.4 20.5 20.6	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13 20.14	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800 Lactams 803
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13 20.14 20.15	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800 Lactams 803 Imides 804
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13 20.14 20.15 20.16	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800 Lactams 803
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13 20.14 20.15 20.16	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800 Lactams 803 Imides 804 Hydrolysis of Amides 804 The Hofmann Rearrangement 807
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13 20.14 20.15 20.16 20.17	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800 Lactams 803 Imides 804 Hydrolysis of Amides 804 The Hofmann Rearrangement 807 Condensation Polymers: Polyamides and Polyesters 809
20.1 20.2 20.3 20.4 20.5 20.6 20.7 20.8 20.9 20.10 20.11 20.12 20.13 20.14 20.15 20.16 20.17	OXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL TITUTION 774 Nomenclature of Carboxylic Acid Derivatives 775 Structure of Carboxylic Acid Derivatives 777 Nucleophilic Substitution in Acyl Chlorides 780 Preparation of Carboxylic Acid Anhydrides 783 Reactions of Carboxylic Acid Anhydrides 784 Sources of Esters 787 Physical Properties of Esters 788 Reactions of Esters: A Review and a Preview 790 Acid-Catalyzed Ester Hydrolysis 791 Ester Hydrolysis in Base: Saponification 794 Reaction of Esters with Ammonia and Amines 799 Thioesters 800 Preparation of Amides 800 Lactams 803 Imides 804 Hydrolysis of Amides 804 The Hofmann Rearrangement 807

CONTENTS xxi

20.21	Spectroscopic Analysis of Carboxylic Acid Derivatives 817	
20.22	SUMMARY 819	
	PROBLEMS 822	
CHAPTER 21 ESTER ENOLATES 831		
	The Claisen Condensation 832 Intramolecular Claisen Condensation: The Dieckmann Reaction 835 Mixed Claisen Condensations 836 Acylation of Ketones with Esters 837 Ketone Synthesis via β-Keto Esters 838 The Acetoacetic Ester Synthesis 839 The Malonic Ester Synthesis 842 Barbiturates 845 Michael Additions of Stabilized Anions 846 α Deprotonation of Carbonyl Compounds by Lithium Dialkylamides 847 SUMMARY 850 PROBLEMS 853	
CHA AMIN	PTER 22 ES 858	
22.1 22.2 22.3 22.4 22.5	9	
	Amines as Natural Products 869	
22.11	Tetraalkylammonium Salts as Phase-Transfer Catalysts 871 Reactions That Lead to Amines: A Review and a Preview 872 Preparation of Amines by Alkylation of Ammonia 872 The Gabriel Synthesis of Primary Alkylamines 875 Preparation of Amines by Reduction 877 Reductive Amination 879 Reactions of Amines: A Review and a Preview 881	
22.13 22.14 22.15 22.16 22.17 22.18	Reaction of Amines with Alkyl Halides 883 The Hofmann Elimination 883 Electrophilic Aromatic Substitution in Arylamines 886 Nitrosation of Alkylamines 888 Nitrosation of Arylamines 891 Synthetic Transformations of Aryl Diazonium Salts 892 Azo Coupling 895	
	From Dyes to Sulfa Drugs 896	
22.20	Spectroscopic Analysis of Amines 897	
	SUMMARY 900	
	PROBLEMS 907	
CHAPTER 23 ARVI HALIDES 917		

- 23.1 Bonding in Aryl Halides 91723.2 Sources of Aryl Halides 918

xxii CONTENTS

23.3	Physical Properties of Aryl Halides 918
23.4	Reactions of Aryl Halides: A Review and a Preview 919
23.5	Nucleophilic Substitution in Nitro-Substituted Aryl Halides 922
23.6	The Addition–Elimination Mechanism of Nucleophilic Aromatic
	Substitution 923
23.7	Related Nucleophilic Aromatic Substitution Reactions 926
23.8	The Elimination–Addition Mechanism of Nucleophilic Aromatic Substitution:
	Benzyne 927
23.9	Diels–Alder Reactions of Benzyne 931
23.10	SUMMARY 932
	PROBLEMS 934
CHA PHEN	PTER 24 OLS 939
24.1	Nomenclature 939
24.2	Structure and Bonding 940
24.3	Physical Properties 941
24.4	Acidity of Phenols 942
24.5	Substituent Effects on the Acidity of Phenols 944
24.6	Sources of Phenols 946
24.7	Naturally Occurring Phenols 946
24.8	Reactions of Phenols: Electrophilic Aromatic Substitution 948
24.9	Acylation of Phenols 949
	Carboxylation of Phenols: Aspirin and the Kolbe–Schmitt Reaction 952
24.11	Preparation of Aryl Ethers 954
	Agent Orange and Dioxin 955
24.12	Cleavage of Aryl Ethers by Hydrogen Halides 956
	Claisen Rearrangement of Allyl Aryl Ethers 957
24.14	Oxidation of Phenols: Quinones 958
24.15	Spectroscopic Analysis of Phenols 960
24.16	SUMMARY 962
	PROBLEMS 965
	PTER 25
CARB	OHYDRATES 972
25.1	Classification of Carbohydrates 972
25.2	Fischer Projections and the D-L Notation 973
25.3	The Aldotetroses 974
25.4	Aldopentoses and Aldohexoses 976
25.5	A Mnemonic for Carbohydrate Configurations 978
25.6	Cyclic Forms of Carbohydrates: Furanose Forms 978
25.7	Cyclic Forms of Carbohydrates: Pyranose Forms 981
25.8 25.9	Mutarotation 985 Ketoses 986
25.10	
	Amino Sugars 988
	Branched-Chain Carbohydrates 988
	Glycosides 988
	Disaccharides 991
	Polysaccharides 993
	Cell-Surface Glycoproteins 995
	Carbohydrate Structure Determination 996
25.18	Reduction of Carbohydrates 996

CONTENTS xxiii

	How Sweet It Is! 997		
25.20	Oxidation of Carbohydrates 998 Cyanohydrin Formation and Carbohydrate Chain Extension 1001 Epimerization, Isomerization, and Retro-Aldol Cleavage Reactions of Carbohydrates 1003		
	Acylation and Alkylation of Hydroxyl Groups in Carbohydrates 1004 Periodic Acid Oxidation of Carbohydrates 1005		
25.24	SUMMARY 1006		
	PROBLEMS 1008		
CHAPTER 26 LIPIDS 1015			
26.1	Acetyl Coenzyme A 1016		
26.2 26.3	Fats, Oils, and Fatty Acids 1017 Fatty Acid Biosynthesis 1019		
26.3 26.4	Phospholipids 1022		
26.5	Waxes 1024		
26.6	Prostaglandins 1024		
26.7	Terpenes: The Isoprene Rule 1025		
26.8	Isopentenyl Pyrophosphate: The Biological Isoprene Unit 1028		
26.9 26.10	Carbon–Carbon Bond Formation in Terpene Biosynthesis 1029 The Pathway from Acetate to Isopentenyl Pyrophosphate 1032		
26.10	Steroids: Cholesterol 1034		
	Good Cholesterol? Bad Cholesterol? What's the Difference? 1038		
26 12	Vitamin D 1038		
	Bile Acids 1039		
26.14	Corticosteroids 1040		
26.15	Sex Hormones 1040		
	Anabolic Steroids 1041		
26.16	Carotenoids 1042		
26.17	SUMMARY 1042		
	PROBLEMS 1045		
	PTER 27 O ACIDS, PEPTIDES, AND PROTEINS. NUCLEIC ACIDS 1051		
27.1	Classification of Amino Acids 1052		
27.2	Stereochemistry of Amino Acids 1052		
27.3	Acid–Base Behavior of Amino Acids 1057		
	Electrophoresis 1060		
27.4	Synthesis of Amino Acids 1061		
27.5	Reactions of Amino Acids 1063		
27.6 27.7	Some Biochemical Reactions of Amino Acids 1063 Peptides 1067		
27.7 27.8	Introduction to Peptide Structure Determination 1070		
27.9	Amino Acid Analysis 1070		
	Partial Hydrolysis of Peptides 1071		
27.11	End Group Analysis 1071		
	Insulin 1073		
27.13 27.14	The Edman Degradation and Automated Sequencing of Peptides 1074 The Strategy of Peptide Synthesis 1076		
۷1.14	The strategy of repute synthesis 10/0		

xxiv CONTENTS

27.16 27.17 27.18 27.19 27.20 27.21 27.22 27.23 27.24 27.25 27.26 27.27	Amino Group Protection 1077 Carboxyl Group Protection 1079 Peptide Bond Formation 1079 Solid-Phase Peptide Synthesis: The Merrifield Method 1082 Secondary Structures of Peptides and Proteins 1084 Tertiary Structure of Peptides and Proteins 1086 Coenzymes 1088 Protein Quaternary Structure: Hemoglobin 1089 Pyrimidines and Purines 1090 Nucleosides 1091 Nucleotides 1092 Nucleic Acids 1093 Structure and Replication of DNA: The Double Helix 1094 DNA-Directed Protein Biosynthesis 1096
27.20	AIDS 1098
27.29	DNA Sequencing 1100
27.30	SUMMARY 1103
	PROBLEMS 1106
APPEN	IDIX 1 PHYSICAL PROPERTIES A-1
APPEN	IDIX 2 ANSWERS TO IN-TEXT PROBLEMS A-9
APPEN	IDIX 3 LEARNING CHEMISTRY WITH MOLECULAR MODELS: Using SpartanBuild and SpartanView A-64

GLOSSARY G-1 CREDITS C-1 INDEX I-1