Contents

Preface ..... **v**

Acknowledgment and Personal Statement ..... **vii**

Introduction ..... **ix**

Chapter 1. Chemical Bonding and Molecular Structure **1**

Introduction 1
1.1. Description of Molecular Structure Using Valence Bond Concepts 2
1.1.1. Hybridization 4
1.1.2. The Origin of Electron-Electron Repulsion 7
1.1.3. Electronegativity and Polarity 8
1.1.4. Electronegativity Equalization 11
1.1.5. Differential Electronegativity of Carbon Atoms 12
1.1.6. Polarizability, Hardness, and Softness 14
1.1.7. Resonance and Conjugation 18
1.1.8. Hyperconjugation 22
1.1.9. Covalent and van der Waals Radii of Atoms 24
1.2. Molecular Orbital Theory and Methods 26
1.2.1. The Hückel MO Method 27
1.2.2. Semiempirical MO Methods 32
1.2.3. Ab Initio Methods 32
1.2.4. Pictorial Representation of MOs for Molecules 35
1.2.5. Qualitative Application of MO Theory to Reactivity: Perturbational MO Theory and Frontier Orbitals 41
1.2.6. Numerical Application of MO Theory 50
1.3. Electron Density Functionals 54
1.4. Representation of Electron Density Distribution 57
1.4.1. Mulliken Population Analysis 60
1.4.2. Natural Bond Orbitals and Natural Population Analysis 61

1.4.3. Atoms in Molecules 63
1.4.4. Comparison and Interpretation of Atomic Charge Calculations 70
1.4.5. Electrostatic Potential Surfaces 73
1.4.6. Relationships between Electron Density and Bond Order 76
Topic 1.1. The Origin of the Rotational (Torsional) Barrier in Ethane and Other Small Molecules 78
Topic 1.2. Heteroatom Hyperconjugation (Anomeric Effect) in Acyclic Molecules 81
Topic 1.3. Bonding in Cyclopropane and Other Small Ring Compounds 85
Topic 1.4. Representation of Electron Density by the Laplacian Function 92
Topic 1.5. Application of Density Functional Theory to Chemical Properties and Reactivity 94
T.1.5.1. DFT Formulation of Chemical Potential, Electronegativity, Hardness and Softness, and Covalent and van der Waal Radii 95
T.1.5.2. DFT Formulation of Reactivity—The Fukui Function 97
T.1.5.3. DFT Concepts of Substituent Groups Effects 100
General References 106
Problems 106

Chapter 2. Stereochemistry, Conformation, and Stereoselectivity 119

Introduction 119
2.1. Configuration 119
2.1.1. Configuration at Double Bonds 119
2.1.2. Configuration of Cyclic Compounds 121
2.1.3. Configuration at Tetrahedral Atoms 122
2.1.4. Molecules with Multiple Stereogenic Centers 126
2.1.5. Other Types of Stereogenic Centers 128
2.1.6. The Relationship between Chirality and Symmetry 131
2.1.7. Configuration at Prochiral Centers 133
2.1.8. Resolution—The Separation of Enantiomers 136
2.2. Conformation 142
2.2.1. Conformation of Acyclic Compounds 142
2.2.2. Conformations of Cyclohexane Derivatives 152
2.2.3. Conformations of Carbocyclic Rings of Other Sizes 161
2.3. Molecular Mechanics 167
2.4. Stereoselective and Stereospecific Reactions 169
2.4.1. Examples of Stereoselective Reactions 170
2.4.2. Examples of Stereospecific Reactions 182
2.5. Enantioselective Reactions 189
2.5.1. Enantioselective Hydrogenation 189
2.5.2. Enantioselective Reduction of Ketones 193
2.5.3. Enantioselective Epoxidation of Allylic Alcohols 196
2.5.4. Enantioselective Dihydroxylation of Alkenes 200
2.6. Double Stereodifferentiation: Reinforcing and Competing Stereoselectivity 204

Topic 2.1. Analysis and Separation of Enantiomeric Mixtures 208
T.2.1.1. Chiral Shift Reagents and Chiral Solvating Agents 208
T.2.1.2. Separation of Enantiomers 211
Topic 2.2. Enzymatic Resolution and Desymmetrization 215
T.2.2.1. Lipases and Esterases 216
T.2.2.2. Proteases and Acylases 222
T.2.2.3. Epoxide Hydrolases 224
Topic 2.3. The Anomeric Effect in Cyclic Compounds 227
Topic 2.4. Polar Substituent Effects in Reduction of Carbonyl Compounds 234
General References 239
Problems 240

Chapter 3. Structural Effects on Stability and Reactivity 253

Introduction 253
3.1. Thermodynamic Stability 254
3.1.1. Relationship between Structure and Thermodynamic Stability for Hydrocarbons 256
3.1.2. Calculation of Enthalpy of Formation and Enthalpy of Reaction 257
3.2. Chemical Kinetics 270
3.2.1. Fundamental Principles of Chemical Kinetics 270
3.2.2. Representation of Potential Energy Changes in Reactions 273
3.2.3. Reaction Rate Expressions 280
3.2.4. Examples of Rate Expressions 283
3.3. General Relationships between Thermodynamic Stability and Reaction Rates 285
3.3.1. Kinetic versus Thermodynamic Control of Product Composition 285
3.3.2. Correlations between Thermodynamic and Kinetic Aspects of Reactions 287
3.3.3. Curtin-Hammett Principle 296
3.4. Electronic Substituent Effects on Reaction Intermediates 297
3.4.1. Carbocations 300
3.4.2. Carbanions 307
3.4.3. Radical Intermediates 311
3.4.4. Carbonyl Addition Intermediates 319
3.5. Kinetic Isotope Effects 332
3.6. Linear Free-Energy Relationships for Substituent Effects 335
3.6.1. Numerical Expression of Linear Free-Energy Relationships 335
3.6.2. Application of Linear Free-Energy Relationships to Characterization of Reaction Mechanisms 342
3.7. Catalysis 345
3.7.1. Catalysis by Acids and Bases 345
3.7.2. Lewis Acid Catalysis 354

3.8. Solvent Effects 359
3.8.1. Bulk Solvent Effects 359
3.8.2. Examples of Specific Solvent Effects 362
Topic 3.1. Acidity of Hydrocarbons 368
General References 376
Problems 376

Chapter 4. Nucleophilic Substitution 389

Introduction 389
4.1. Mechanisms for Nucleophilic Substitution 389
4.1.1. Substitution by the Ionization (S_N1) Mechanism 391
4.1.2. Substitution by the Direct Displacement (S_N2) Mechanism 393
4.1.3. Detailed Mechanistic Description and Borderline Mechanisms 395
4.1.4. Relationship between Stereochemistry and Mechanism of Substitution 402
4.1.5. Substitution Reactions of Alkyldiazonium Ions 405
4.2. Structural and Solvation Effects on Reactivity 407
4.2.1. Characteristics of Nucleophilicity 407
4.2.2. Effect of Solvation on Nucleophilicity 411
4.2.3. Leaving-Group Effects 413
4.2.4. Steric and Strain Effects on Substitution and Ionization Rates 415
4.2.5. Effects of Conjugation on Reactivity 417
4.3. Neighboring-Group Participation 419
4.4. Structure and Reactions of Carbocation Intermediates 425
4.4.1. Structure and Stability of Carbocations 425
4.4.2. Direct Observation of Carbocations 436
4.4.3. Competing Reactions of Carbocations 438
4.4.4. Mechanisms of Rearrangement of Carbocations 440
4.4.5. Bridged (Nonclassical) Carbocations 447
Topic 4.1. The Role Carbocations and Carbonium Ions in Petroleum Processing 454
General References 459
Problems 459

Chapter 5. Polar Addition and Elimination Reactions 473

Introduction 475
5.1. Addition of Hydrogen Halides to Alkenes 476
5.2. Acid-Catalyzed Hydration and Related Addition Reactions 482
5.3. Addition of Halogens 485
5.4. Sulfenylation and Selenenylation 497
5.4.1. Sulfenylation 498
5.4.2. Selenenylation 500
5.5. Addition Reactions Involving Epoxides 503
5.5.1. Epoxides from Alkenes and Peroxidic Reagents 503
5.5.2. Subsequent Transformations of Epoxides 511

5.6. Electrophilic Additions Involving Metal Ions 515
5.6.1. Solvomercuration 515
5.6.2. Argentation—the Formation of Silver Complexes 520
5.7. Synthesis and Reactions of Alkylboranes 521
5.7.1. Hydroboration 522
5.7.2. Reactions of Organoboranes 526
5.7.3. Enantioselective Hydroboration 529
5.8. Comparison of Electrophilic Addition Reactions 531
5.9. Additions to Alkynes and Allenes 536
5.9.1. Hydrohalogenation and Hydration of Alkynes 538
5.9.2. Halogenation of Alkynes 540
5.9.3. Mercuration of Alkynes 544
5.9.4. Overview of Alkyne Additions 544
5.9.5. Additions to Allenes 545
5.10. Elimination Reactions 546
5.10.1. The E2, E1 and E1cb Mechanisms 548
5.10.2. Regiochemistry of Elimination Reactions 554
5.10.3. Stereochemistry of E2 Elimination Reactions 558
5.10.4. Dehydration of Alcohols 563
5.10.5. Eliminations Reactions Not Involving C−H Bonds 564
General References 569
Problems 569

Chapter 6. Carbanions and Other Carbon Nucleophiles 579

Introduction 559
6.1. Acidity of Hydrocarbons 579
6.2. Carbanion Character of Organometallic Compounds 588
6.3. Carbanions Stabilized by Functional Groups 591
6.4. Enols and Enamines 601
6.5. Carbanions as Nucleophiles in S_N2 Reactions 609
6.5.1. Substitution Reactions of Organometallic Reagents 609
6.5.2. Substitution Reactions of Enolates 611
General References 619
Problems 619

Chapter 7. Addition, Condensation and Substitution Reactions of Carbonyl Compounds 629

Introduction 629
7.1. Reactivity of Carbonyl Compounds toward Addition 632
7.2. Hydration and Addition of Alcohols to Aldehydes and Ketones 638
7.3. Condensation Reactions of Aldehydes and Ketones with Nitrogen Nucleophiles 645
7.4. Substitution Reactions of Carboxylic Acid Derivatives 654
7.4.1. Ester Hydrolysis and Exchange 654
7.4.2. Aminolysis of Esters 659
7.4.3. Amide Hydrolysis 662
7.4.4. Acylation of Nucleophilic Oxygen and Nitrogen Groups 664

7.5. Intramolecular Catalysis of Carbonyl Substitution Reactions 668
7.6. Addition of Organometallic Reagents to Carbonyl Groups..... 676
7.6.1. Kinetics of Organometallic Addition Reactions 677
7.6.2. Stereoselectivity of Organometallic Addition Reactions..... 680
7.7. Addition of Enolates and Enols to Carbonyl Compounds: The Aldol Addition and Condensation Reactions 682
7.7.1. The General Mechanisms 682
7.7.2. Mixed Aldol Condensations with Aromatic Aldehydes 685
7.7.3. Control of Regiochemistry and Stereochemistry of Aldol Reactions of Ketones 687
7.7.4. Aldol Reactions of Other Carbonyl Compounds 692
General References 698
Problems 698

Chapter 8. Aromaticity 713

Introduction 713
8.1. Criteria of Aromaticity..... 715
8.1.1. The Energy Criterion for Aromaticity..... 715
8.1.2. Structural Criteria for Aromaticity 718
8.1.3. Electronic Criteria for Aromaticity 720
8.1.4. Relationship among the Energetic, Structural, and Electronic Criteria of Aromaticity 724
8.2. The Annulenes 725
8.2.1. Cyclobutadiene..... 725
8.2.2. Benzene..... 727
8.2.3. 1,3,5,7-Cyclooctatetraene 727
8.2.4. [10]Annulenes—1,3,5,7,9-Cyclodecapentaene Isomers..... 728
8.2.5. [12], [14], and [16]Annulenes 730
8.2.6. [18]Annulene and Larger Annulenes 733
8.2.7. Other Related Structures..... 735
8.3. Aromaticity in Charged Rings..... 738
8.4. Homoaromaticity..... 743
8.5. Fused-Ring Systems..... 745
8.6. Heteroaromatic Systems 758
General References 760
Problems..... 760

Chapter 9. Aromatic Substitution 771

Introduction 771
9.1. Electrophilic Aromatic Substitution Reactions 771
9.2. Structure-Reactivity Relationships for Substituted Benzenes..... 779
9.2.1. Substituent Effects on Reactivity 779
9.2.2. Mechanistic Interpretation of the Relationship between Reactivity and Selectivity..... 787
9.3. Reactivity of Polycyclic and Heteroaromatic Compounds 791

9.4. Specific Electrophilic Substitution Reactions 796
9.4.1. Nitration 796
9.4.2. Halogenation 800
9.4.3. Protonation and Hydrogen Exchange 804
9.4.4. Friedel-Crafts Alkylation and Related Reactions 805
9.4.5. Friedel-Crafts Acylation and Related Reactions 809
9.4.6. Aromatic Substitution by Diazonium Ions 813
9.4.7. Substitution of Groups Other than Hydrogen 814
9.5. Nucleophilic Aromatic Substitution 816
9.5.1. Nucleophilic Aromatic Substitution by the Addition-Elimination Mechanism 817
9.5.2. Nucleophilic Aromatic Substitution by the Elimination-Addition Mechanism 821
General References 824
Problems 824

Chapter 10. Concerted Pericyclic Reactions 833

Introduction 833
10.1. Cycloaddition Reactions 834
10.2. The Diels-Alder Reaction 839
10.2.1. Stereochemistry of the Diels-Alder Reaction 839
10.2.2. Substituent Effects on Reactivity, Regioselectivity and Stereochemistry 843
10.2.3. Catalysis of Diels-Alder Reactions by Lewis Acids 848
10.2.4. Computational Characterization of Diels-Alder Transition Structures 851
10.2.5. Scope and Synthetic Applications of the Diels-Alder Reaction 860
10.2.6. Enantioselective Diels-Alder Reactions 865
10.2.7. Intramolecular Diels-Alder Reactions 868
10.3. 1,3-Dipolar Cycloaddition Reactions 873
10.3.1. Relative Reactivity, Regioselectivity, Stereoselectivity, and Transition Structures 874
10.3.2. Scope and Applications of 1,3-Dipolar Cycloadditions 884
10.3.3. Catalysis of 1,3-Dipolar Cycloaddition Reactions 886
10.4. [2 + 2] Cycloaddition Reactions 888
10.5. Electrocyclic Reactions 892
10.5.1. Overview of Electrocyclic Reactions 892
10.5.2. Orbital Symmetry Basis for the Stereospecificity of Electrocyclic Reactions 894
10.5.3. Examples of Electrocyclic Reactions 903
10.5.4. Electrocyclic Reactions of Charged Species 906
10.5.5. Electrocyclization of Heteroatomic Trienes 910
10.6. Sigmatropic Rearrangements 911
10.6.1. Overview of Sigmatropic Rearrangements 911
10.6.2. [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts of Hydrogen and Alkyl Groups 912

10.6.3. Overview of [3,3]-Sigmatropic Rearrangements 919
10.6.4. [2,3]-Sigmatropic Rearrangements 939
Topic 10.1. Application of DFT Concepts to Reactivity and Regiochemistry of Cycloaddition Reactions 945
Problems 951

Chapter 11. Free Radical Reactions 965

Introduction 965
11.1. Generation and Characterization of Free Radicals 967
11.1.1. Background 967
11.1.2. Long-Lived Free Radicals 968
11.1.3. Direct Detection of Radical Intermediates 970
11.1.4. Generation of Free Radicals 976
11.1.5. Structural and Stereochemical Properties of Free Radicals 980
11.1.6. Substituent Effects on Radical Stability 986
11.1.7. Charged Radicals 988
11.2. Characteristics of Reactions Involving Radical Intermediates 992
11.2.1. Kinetic Characteristics of Chain Reactions 992
11.2.2. Determination of Reaction Rates 995
11.2.3. Structure-Reactivity Relationships 1000
11.3. Free Radical Substitution Reactions 1018
11.3.1. Halogenation 1018
11.3.2. Oxygenation 1024
11.4. Free Radical Addition Reactions 1026
11.4.1. Addition of Hydrogen Halides 1026
11.4.2. Addition of Halomethanes 1029
11.4.3. Addition of Other Carbon Radicals 1031
11.4.4. Addition of Thiols and Thiocarboxylic Acids 1033
11.4.5. Examples of Radical Addition Reactions 1033
11.5. Other Types of Free Radical Reactions 1037
11.5.1. Halogen, Sulfur, and Selenium Group Transfer Reactions 1037
11.5.2. Intramolecular Hydrogen Atom Transfer Reactions 1040
11.5.3. Rearrangement Reactions of Free Radicals 1041
11.6. $S_{RN}1$ Substitution Processes 1044
11.6.1. $S_{RN}1$ Substitution Reactions of Alkyl Nitro Compounds 1045
11.6.2. $S_{RN}1$ Substitution Reactions of Aryl and Alkyl Halides 1048
Topic 11.1. Relationships between Bond and Radical Stabilization Energies 1052
Topic 11.2. Structure-Reactivity Relationships in Hydrogen Abstraction Reactions 1056
General References 1062
Problems 1063

Chapter 12. Photochemistry 1073

Introduction 1073
12.1. General Principles 1073

12.2. Photochemistry of Alkenes, Dienes, and Polyenes 1081
12.2.1. *cis-trans* Isomerization 1081
12.2.2. Photoreactions of Other Alkenes 1091
12.2.3. Photoisomerization of 1,3-Butadiene 1096
12.2.4. Orbital Symmetry Considerations for Photochemical Reactions of Alkenes and Dienes 1097
12.2.5. Photochemical Electrocyclic Reactions 1100
12.2.6. Photochemical Cycloaddition Reactions 1109
12.2.7. Photochemical Rearrangements Reactions of 1,4-Dienes 1112
12.3. Photochemistry of Carbonyl Compounds 1116
12.3.1. Hydrogen Abstraction and Fragmentation Reactions 1118
12.3.2. Cycloaddition and Rearrangement Reactions of Cyclic Unsaturated Ketones 1125
12.3.3. Cycloaddition of Carbonyl Compounds and Alkenes 1132
12.4. Photochemistry of Aromatic Compounds 1134
Topic 12.1. Computational Interpretation of Diene and Polyene Photochemistry 1137
General References 1145
Problems 1146

References to Problems 1155

Index 1171