Modern Physical Organic Chemistry

Eric V. Anslyn
University of Texas, Austin

Dennis A. Dougherty
California Institute of Technology



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Contents

List of Highlights xix
Preface xxiii
Acknowledgments xxv
A Note to the Instructor xxvii

PART I
MOLECULAR STRUCTURE AND THERMODYNAMICS

CHAPTER 1: Introduction to Structure and Models of Bonding 3

Intent and Purpose 3

1.1 A Review of Basic Bonding Concepts 4
1.1.1 Quantum Numbers and Atomic Orbitals 4
1.1.2 Electron Configurations and Electronic Diagrams 5
1.1.3 Lewis Structures 6
1.1.4 Formal Charge 6
1.1.5 VSEPR 7
1.1.6 Hybridization 8
1.1.7 A Hybrid Valence Bond / Molecular Orbital Model of Bonding 10
Creating Localized σ and π Bonds 11
1.1.8 Polar Covalent Bonding 12
Electronegativity 12
Electrostatic Potential Surfaces 14
Inductive Effects 15
Group Electronegativities 16
Hybridization Effects 17
1.1.9 Bond Dipoles, Molecular Dipoles, and Quadrupoles 17
Bond Dipoles 17
Molecular Dipole Moments 18
Molecular Quadrupole Moments 19
1.1.10 Resonance 20
1.1.11 Bond Lengths 22
1.1.12 Polarizability 24
1.1.13 Summary of Concepts Used for the Simplest Model of Bonding in Organic Structures 26

1.2 A More Modern Theory of Organic Bonding 26
1.2.1 Molecular Orbital Theory 27
1.2.2 A Method for QMOT 28
1.2.3 Methyl in Detail 29
Planar Methyl 29
The Walsh Diagram: Pyramidal Methyl 31
"Group Orbitals" for Pyramidal Methyl 32
Putting the Electrons In—The MH_3 System 33
1.2.4 The CH_2 Group in Detail 33
The Walsh Diagram and Group Orbitals 33
Putting the Electrons In—The MH_2 System 33

1.3 Orbital Mixing—Building Larger Molecules 35
1.3.1 Using Group Orbitals to Make Ethane 36
1.3.2 Using Group Orbitals to Make Ethylene 38
1.3.3 The Effects of Heteroatoms—Formaldehyde 40
1.3.4 Making More Complex Alkanes 43
1.3.5 Three More Examples of Building Larger Molecules from Group Orbitals 43
Propene 43
Methyl Chloride 45
Butadiene 46
1.3.6 Group Orbitals of Representative π Systems: Benzene, Benzyl, and Allyl 46
1.3.7 Understanding Common Functional Groups as Perturbations of Allyl 49
1.3.8 The Three Center–Two Electron Bond 50
1.3.9 Summary of the Concepts Involved in Our Second Model of Bonding 51

1.4 Bonding and Structures of Reactive Intermediates 52
1.4.1 Carbocations 52
Carbenium Ions 53
Interplay with Carbonium Ions 54
Carbonium Ions 55
1.4.2 Carbanions 56
1.4.3 Radicals 57
1.4.4 Carbenes 58

1.5 A Very Quick Look at Organometallic and Inorganic Bonding 59

Summary and Outlook 61

EXERCISES 62
FURTHER READING 64

CHAPTER 2: Strain and Stability 65

Intent and Purpose 65

2.1 Thermochemistry of Stable Molecules 66
2.1.1 The Concepts of Internal Strain and Relative Stability 66
2.1.2 Types of Energy 68
Gibbs Free Energy 68
Enthalpy 69
Entropy 70
2.1.3 Bond Dissociation Energies 70
Using BDEs to Predict Exothermicity and Endothermicity 72
2.1.4 An Introduction to Potential Functions and Surfaces—Bond Stretches 73
Infrared Spectroscopy 77
2.1.5 Heats of Formation and Combustion 77
2.1.6 The Group Increment Method 79
2.1.7 Strain Energy 82

The Trustees of Columbia Univ. Ex. 2047 - Page 3 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

2.2 Thermochemistry of Reactive Intermediates 82
2.2.1 Stability vs. Persistence 82
2.2.2 Radicals 83
BDEs as a Measure of Stability 83
Radical Persistence 84
Group Increments for Radicals 86
2.2.3 Carbocations 87
Hydride Ion Affinities as a Measure of Stability 87
Lifetimes of Carbocations 90
2.2.4 Carbanions 91
2.2.5 Summary 91

2.3 Relationships Between Structure and Energetics—Basic Conformational Analysis 92
2.3.1 Acyclic Systems—Torsional Potential Surfaces 92
Ethane 92
Butane—The Gauche Interaction 95
Barrier Height 97
Barrier Foldedness 97
Tetraalkylethanes 98
The g+g− Pentane Interaction 99
Allylic ($A^{1,3}$) Strain 100
2.3.2 Basic Cyclic Systems 100
Cyclopropane 100
Cyclobutane 100
Cyclopentane 101
Cyclohexane 102
Larger Rings—Transannular Effects 107
Group Increment Corrections for Ring Systems 109
Ring Torsional Modes 109
Bicyclic Ring Systems 110
Cycloalkenes and Bredt's Rule 110
Summary of Conformational Analysis and Its Connection to Strain 112

2.4 Electronic Effects 112
2.4.1 Interactions Involving π Systems 112
Substitution on Alkenes 112
Conformations of Substituted Alkenes 113
Conjugation 115
Aromaticity 116
Antiaromaticity, An Unusual Destabilizing Effect 117
NMR Chemical Shifts 118
Polycyclic Aromatic Hydrocarbons 119
Large Annulenes 119
2.4.2 Effects of Multiple Heteroatoms 120
Bond Length Effects 120
Orbital Effects 120

2.5 Highly-Strained Molecules 124
2.5.1 Long Bonds and Large Angles 124
2.5.2 Small Rings 125
2.5.3 Very Large Rotation Barriers 127

2.6 Molecular Mechanics 128
2.6.1 The Molecular Mechanics Model 129
Bond Stretching 129
Angle Bending 130
Torsion 130
Nonbonded Interactions 130
Cross Terms 131
Electrostatic Interactions 131
Hydrogen Bonding 131
The Parameterization 132
Heat of Formation and Strain Energy 132
2.6.2 General Comments on the Molecular Mechanics Method 133
2.6.3 Molecular Mechanics on Biomolecules and Unnatural Polymers—"Modeling" 135
2.6.4 Molecular Mechanics Studies of Reactions 136

Summary and Outlook 137

EXERCISES 138
FURTHER READING 143

CHAPTER 3: Solutions and Non-Covalent Binding Forces 145

Intent and Purpose 145

3.1 Solvent and Solution Properties 145
3.1.1 Nature Abhors a Vacuum 146
3.1.2 Solvent Scales 146
Dielectric Constant 147
Other Solvent Scales 148
Heat of Vaporization 150
Surface Tension and Wetting 150
Water 151
3.1.3 Solubility 153
General Overview 153
Shape 154
Using the "Like-Dissolves-Like" Paradigm 154
3.1.4 Solute Mobility 155
Diffusion 155
Fick's Law of Diffusion 156
Correlation Times 156
3.1.5 The Thermodynamics of Solutions 157
Chemical Potential 158
The Thermodynamics of Reactions 160
Calculating $\Delta H°$ and $\Delta S°$ 162

3.2 Binding Forces 162
3.2.1 Ion Pairing Interactions 163
Salt Bridges 164
3.2.2 Electrostatic Interactions Involving Dipoles 165
Ion–Dipole Interactions 165
A Simple Model of Ionic Solvation—The Born Equation 166
Dipole–Dipole Interactions 168
3.2.3 Hydrogen Bonding 168
Geometries 169
Strengths of Normal Hydrogen Bonds 171
i. Solvation Effects 171
ii. Electronegativity Effects 172
iii. Resonance Assisted Hydrogen Bonds 173
iv. Polarization Enhanced Hydrogen Bonds 174
v. Secondary Interactions in Hydrogen Bonding Systems 175

The Trustees of Columbia Univ. Ex. 2047 - Page 4 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

vi. Cooperativity in Hydrogen Bonds 175
Vibrational Properties of Hydrogen Bonds 176
Short–Strong Hydrogen Bonds 177
3.2.4 π Effects 180
Cation–π Interactions 181
Polar–π Interactions 183
Aromatic–Aromatic Interactions (π Stacking) 184
The Arene–Perfluoroarene Interaction 184
π Donor–Acceptor Interactions 186
3.2.5 Induced-Dipole Interactions 186
Ion–Induced-Dipole Interactions 187
Dipole–Induced-Dipole Interactions 187
Induced-Dipole–Induced-Dipole Interactions 188
Summarizing Monopole, Dipole, and Induced-Dipole Binding Forces 188
3.2.6 The Hydrophobic Effect 189
Aggregation of Organics 189
The Origin of the Hydrophobic Effect 192

3.3 Computational Modeling of Solvation 194
3.3.1 Continuum Solvation Models 196
3.3.2 Explicit Solvation Models 197
3.3.3 Monte Carlo (MC) Methods 198
3.3.4 Molecular Dynamics (MD) 199
3.3.5 Statistical Perturbation Theory / Free Energy Perturbation 200

Summary and Outlook 201

EXERCISES 202
FURTHER READING 204

CHAPTER 4: **Molecular Recognition and Supramolecular Chemistry** 207

Intent and Purpose 207

4.1 Thermodynamic Analyses of Binding Phenomena 207
4.1.1 General Thermodynamics of Binding 208
The Relevance of the Standard State 210
The Influence of a Change in Heat Capacity 212
Cooperativity 213
Enthalpy–Entropy Compensation 216
4.1.2 The Binding Isotherm 216
4.1.3 Experimental Methods 219
UV/Vis or Fluorescence Methods 220
NMR Methods 220
Isothermal Calorimetry 221

4.2 Molecular Recognition 222
4.2.1 Complementarity and Preorganization 224
Crowns, Cryptands, and Spherands—Molecular Recognition with a Large Ion–Dipole Component 224
Tweezers and Clefts 228
4.2.2 Molecular Recognition with a Large Ion Pairing Component 228
4.2.3 Molecular Recognition with a Large Hydrogen Bonding Component 230
Representative Structures 230
Molecular Recognition via Hydrogen Bonding in Water 232
4.2.4 Molecular Recognition with a Large Hydrophobic Component 234
Cyclodextrins 234
Cyclophanes 234
A Summary of the Hydrophobic Component of Molecular Recognition in Water 238
4.2.5 Molecular Recognition with a Large π Component 239
Cation–π Interactions 239
Polar–π and Related Effects 241
4.2.6 Summary 241

4.3 Supramolecular Chemistry 243
4.3.1 Supramolecular Assembly of Complex Architectures 244
Self-Assembly via Coordination Compounds 244
Self-Assembly via Hydrogen Bonding 245
4.3.2 Novel Supramolecular Architectures—Catenanes, Rotaxanes, and Knots 246
Nanotechnology 248
4.3.3 Container Compounds—Molecules within Molecules 249

Summary and Outlook 252

EXERCISES 253
FURTHER READING 256

CHAPTER 5: **Acid–Base Chemistry** 259

Intent and Purpose 259

5.1 Brønsted Acid–Base Chemistry 259

5.2 Aqueous Solutions 261
5.2.1 pK_a 261
5.2.2 pH 262
5.2.3 The Leveling Effect 264
5.2.4 Activity vs. Concentration 266
5.2.5 Acidity Functions: Acidity Scales for Highly Concentrated Acidic Solutions 266
5.2.6 Super Acids 270

5.3 Nonaqueous Systems 271
5.3.1 pK_a Shifts at Enzyme Active Sites 273
5.3.2 Solution Phase vs. Gas Phase 273

5.4 Predicting Acid Strength in Solution 276
5.4.1 Methods Used to Measure Weak Acid Strength 276
5.4.2 Two Guiding Principles for Predicting Relative Acidities 277
5.4.3 Electronegativity and Induction 278
5.4.4 Resonance 278
5.4.5 Bond Strengths 283
5.4.6 Electrostatic Effects 283
5.4.7 Hybridization 283

The Trustees of Columbia Univ. Ex. 2047 - Page 5 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

5.4.8 Aromaticity 284
5.4.9 Solvation 284
5.4.10 Cationic Organic Structures 285

5.5 Acids and Bases of Biological Interest 285

5.6 Lewis Acids/Bases and Electrophiles/ Nucleophiles 288
5.6.1 The Concept of Hard and Soft Acids and Bases, General Lessons for Lewis Acid–Base Interactions, and Relative Nucleophilicity and Electrophilicity 289

Summary and Outlook 292

EXERCISES 292
FURTHER READING 294

CHAPTER 6: Stereochemistry 297

Intent and Purpose 297

6.1 Stereogenicity and Stereoisomerism 297
6.1.1 Basic Concepts and Terminology 298
Classic Terminology 299
More Modern Terminology 301
6.1.2 Stereochemical Descriptors 303
R,S System 304
E,Z System 304
D and L 304
Erythro and Threo 305
Helical Descriptors—M and P 305
Ent and Epi 306
Using Descriptors to Compare Structures 306
6.1.3 Distinguishing Enantiomers 306
Optical Activity and Chirality 309
Why is Plane Polarized Light Rotated by a Chiral Medium? 309
Circular Dichroism 310
X-Ray Crystallography 310

6.2 Symmetry and Stereochemistry 311
6.2.1 Basic Symmetry Operations 311
6.2.2 Chirality and Symmetry 311
6.2.3 Symmetry Arguments 313
6.2.4 Focusing on Carbon 314

6.3 Topicity Relationships 315
6.3.1 Homotopic, Enantiotopic, and Diastereotopic 315
6.3.2 Topicity Descriptors—Pro-*R*/Pro-*S* and *Re*/*Si* 316
6.3.3 Chirotopicity 317

6.4 Reaction Stereochemistry: Stereoselectivity and Stereospecificity 317
6.4.1 Simple Guidelines for Reaction Stereochemistry 317
6.4.2 Stereospecific and Stereoselective Reactions 319

6.5 Symmetry and Time Scale 322

6.6 Topological and Supramolecular Stereochemistry 324
6.6.1 Loops and Knots 325
6.6.2 Topological Chirality 326
6.6.3 Nonplanar Graphs 326
6.6.4 Achievements in Topological and Supramolecular Stereochemistry 327

6.7 Stereochemical Issues in Polymer Chemistry 331

6.8 Stereochemical Issues in Chemical Biology 333
6.8.1 The Linkages of Proteins, Nucleic Acids, and Polysaccharides 333
Proteins 333
Nucleic Acids 334
Polysaccharides 334
6.8.2 Helicity 336
Synthetic Helical Polymers 337
6.8.3 The Origin of Chirality in Nature 339

6.9 Stereochemical Terminology 340

Summary and Outlook 344

EXERCISES 344
FURTHER READING 350

PART II
REACTIVITY, KINETICS, AND MECHANISMS

CHAPTER 7: Energy Surfaces and Kinetic Analyses 355

Intent and Purpose 355

7.1 Energy Surfaces and Related Concepts 356
7.1.1 Energy Surfaces 357
7.1.2 Reaction Coordinate Diagrams 359
7.1.3 What is the Nature of the Activated Complex/Transition State? 362
7.1.4 Rates and Rate Constants 363
7.1.5 Reaction Order and Rate Laws 364

7.2 Transition State Theory (TST) and Related Topics 365
7.2.1 The Mathematics of Transition State Theory 365
7.2.2 Relationship to the Arrhenius Rate Law 367
7.2.3 Boltzmann Distributions and Temperature Dependence 368
7.2.4 Revisiting "What is the Nature of the Activated Complex?" and Why Does TST Work? 369
7.2.5 Experimental Determinations of Activation Parameters and Arrhenius Parameters 370
7.2.6 Examples of Activation Parameters and Their Interpretations 372
7.2.7 Is TST Completely Correct? The Dynamic Behavior of Organic Reactive Intermediates 372

7.3 Postulates and Principles Related to Kinetic Analysis 374
7.3.1 The Hammond Postulate 374
7.3.2 The Reactivity vs. Selectivity Principle 377

The Trustees of Columbia Univ. Ex. 2047 - Page 6 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

7.3.3 The Curtin–Hammett Principle 378
7.3.4 Microscopic Reversibility 379
7.3.5 Kinetic vs. Thermodynamic Control 380

7.4 Kinetic Experiments 382
7.4.1 How Kinetic Experiments are Performed 382
7.4.2 Kinetic Analyses for Simple Mechanisms 384
First Order Kinetics 385
Second Order Kinetics 386
Pseudo-First Order Kinetics 387
Equilibrium Kinetics 388
Initial-Rate Kinetics 389
Tabulating a Series of Common Kinetic Scenarios 389

7.5 Complex Reactions—Deciphering Mechanisms 390
7.5.1 Steady State Kinetics 390
7.5.2 Using the SSA to Predict Changes in Kinetic Order 395
7.5.3 Saturation Kinetics 396
7.5.4 Prior Rapid Equilibria 397

7.6 Methods for Following Kinetics 397
7.6.1 Reactions with Half-Lives Greater than a Few Seconds 398
7.6.2 Fast Kinetics Techniques 398
Flow Techniques 399
Flash Photolysis 399
Pulse Radiolysis 401
7.6.3 Relaxation Methods 401
7.6.4 Summary of Kinetic Analyses 402

7.7 Calculating Rate Constants 403
7.7.1 Marcus Theory 403
7.7.2 Marcus Theory Applied to Electron Transfer 405

7.8 Considering Multiple Reaction Coordinates 407
7.8.1 Variation in Transition State Structures Across a Series of Related Reactions—An Example Using Substitution Reactions 407
7.8.2 More O'Ferrall–Jencks Plots 409
7.8.3 Changes in Vibrational State Along the Reaction Coordinate—Relating the Third Coordinate to Entropy 412

Summary and Outlook 413

EXERCISES 413
FURTHER READING 417

CHAPTER 8: **Experiments Related to Thermodynamics and Kinetics** 421

Intent and Purpose 421

8.1 Isotope Effects 421
8.1.1 The Experiment 422
8.1.2 The Origin of Primary Kinetic Isotope Effects 422
Reaction Coordinate Diagrams and Isotope Effects 424
Primary Kinetic Isotope Effects for Linear Transition States as a Function of Exothermicity and Endothermicity 425
Isotope Effects for Linear vs. Non-Linear Transition States 428
8.1.3 The Origin of Secondary Kinetic Isotope Effects 428
Hybridization Changes 429
Steric Isotope Effects 430
8.1.4 Equilibrium Isotope Effects 432
Isotopic Perturbation of Equilibrium—Applications to Carbocations 432
8.1.5 Tunneling 435
8.1.6 Solvent Isotope Effects 437
Fractionation Factors 437
Proton Inventories 438
8.1.7 Heavy Atom Isotope Effects 441
8.1.8 Summary 441

8.2 Substituent Effects 441
8.2.1 The Origin of Substituent Effects 443
Field Effects 443
Inductive Effects 443
Resonance Effects 444
Polarizability Effects 444
Steric Effects 445
Solvation Effects 445

8.3 Hammett Plots—The Most Common LFER. A General Method for Examining Changes in Charges During a Reaction 445
8.3.1 Sigma (σ) 445
8.3.2 Rho (ρ) 447
8.3.3 The Power of Hammett Plots for Deciphering Mechanisms 448
8.3.4 Deviations from Linearity 449
8.3.5 Separating Resonance from Induction 451

8.4 Other Linear Free Energy Relationships 454
8.4.1 Steric and Polar Effects—Taft Parameters 454
8.4.2 Solvent Effects—Grunwald–Winstein Plots 455
8.4.3 Schleyer Adaptation 457
8.4.4 Nucleophilicity and Nucleofugality 458
Basicity/Acidity 459
Solvation 460
Polarizability, Basicity, and Solvation Interplay 460
Shape 461
8.4.5 Swain–Scott Parameters—Nucleophilicity Parameters 461
8.4.6 Edwards and Ritchie Correlations 463

8.5 Acid–Base Related Effects—Brønsted Relationships 464
8.5.1 β_{Nuc} 464
8.5.2 β_{LG} 464
8.5.3 Acid–Base Catalysis 466

8.6 Why do Linear Free Energy Relationships Work? 466
8.6.1 General Mathematics of LFERs 467
8.6.2 Conditions to Create an LFER 468
8.6.3 The Isokinetic or Isoequilibrium Temperature 469

The Trustees of Columbia Univ. Ex. 2047 - Page 7 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.6.4 Why does Enthalpy–Entropy Compensation Occur? 469
Steric Effects 470
Solvation 470

8.7 Summary of Linear Free Energy Relationships 470

8.8 Miscellaneous Experiments for Studying Mechanisms 471
8.8.1 Product Identification 472
8.8.2 Changing the Reactant Structure to Divert or Trap a Proposed Intermediate 473
8.8.3 Trapping and Competition Experiments 474
8.8.4 Checking for a Common Intermediate 475
8.8.5 Cross-Over Experiments 476
8.8.6 Stereochemical Analysis 476
8.8.7 Isotope Scrambling 477
8.8.8 Techniques to Study Radicals: Clocks and Traps 478
8.8.9 Direct Isolation and Characterization of an Intermediate 480
8.8.10 Transient Spectroscopy 480
8.8.11 Stable Media 481

Summary and Outlook 482

EXERCISES 482
FURTHER READING 487

CHAPTER 9: **Catalysis** 489

Intent and Purpose 489

9.1 General Principles of Catalysis 490
9.1.1 Binding the Transition State *Better* than the Ground State 491
9.1.2 A Thermodynamic Cycle Analysis 493
9.1.3 A Spatial Temporal Approach 494

9.2 Forms of Catalysis 495
9.2.1 "Binding" is Akin to Solvation 495
9.2.2 Proximity as a Binding Phenomenon 495
9.2.3 Electrophilic Catalysis 499
Electrostatic Interactions 499
Metal Ion Catalysis 500
9.2.4 Acid–Base Catalysis 502
9.2.5 Nucleophilic Catalysis 502
9.2.6 Covalent Catalysis 504
9.2.7 Strain and Distortion 505
9.2.8 Phase Transfer Catalysis 507

9.3 Brønsted Acid–Base Catalysis 507
9.3.1 Specific Catalysis 507
The Mathematics of Specific Catalysis 507
Kinetic Plots 510
9.3.2 General Catalysis 510
The Mathematics of General Catalysis 511
Kinetic Plots 512
9.3.3 A Kinetic Equivalency 514
9.3.4 Concerted or Sequential General-Acid–General-Base Catalysis 515
9.3.5 The Brønsted Catalysis Law and Its Ramifications 516
A Linear Free Energy Relationship 516
The Meaning of α and β 517
$\alpha+\beta=1$ 518
Deviations from Linearity 519
9.3.6 Predicting General-Acid or General-Base Catalysis 520
The Libido Rule 520
Potential Energy Surfaces Dictate General or Specific Catalysis 521
9.3.7 The Dynamics of Proton Transfers 522
Marcus Analysis 522

9.4 Enzymatic Catalysis 523
9.4.1 Michaelis–Menten Kinetics 523
9.4.2 The Meaning of K_M, k_{cat}, and k_{cat}/K_M 524
9.4.3 Enzyme Active Sites 525
9.4.4 [S] vs. K_M—Reaction Coordinate Diagrams 527
9.4.5 Supramolecular Interactions 529

Summary and Outlook 530

EXERCISES 531
FURTHER READING 535

CHAPTER 10: **Organic Reaction Mechanisms, Part 1: Reactions Involving Additions and/or Eliminations** 537

Intent and Purpose 537

10.1 Predicting Organic Reactivity 538
10.1.1 A Useful Paradigm for Polar Reactions 539
Nucleophiles and Electrophiles 539
Lewis Acids and Lewis Bases 540
Donor–Acceptor Orbital Interactions 540
10.1.2 Predicting Radical Reactivity 541
10.1.3 In Preparation for the Following Sections 541

—ADDITION REACTIONS— 542

10.2 Hydration of Carbonyl Structures 542
10.2.1 Acid–Base Catalysis 543
10.2.2 The Thermodynamics of the Formation of Geminal Diols and Hemiacetals 544

10.3 Electrophilic Addition of Water to Alkenes and Alkynes: Hydration 545
10.3.1 Electron Pushing 546
10.3.2 Acid-Catalyzed Aqueous Hydration 546
10.3.3 Regiochemistry 546
10.3.4 Alkyne Hydration 547

10.4 Electrophilic Addition of Hydrogen Halides to Alkenes and Alkynes 548
10.4.1 Electron Pushing 548

The Trustees of Columbia Univ. Ex. 2047 - Page 8 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

10.4.2 Experimental Observations Related to Regiochemistry and Stereochemistry 548
10.4.3 Addition to Alkynes 551

10.5 Electrophilic Addition of Halogens to Alkenes 551
10.5.1 Electron Pushing 551
10.5.2 Stereochemistry 552
10.5.3 Other Evidence Supporting a σ Complex 552
10.5.4 Mechanistic Variants 553
10.5.5 Addition to Alkynes 554

10.6 Hydroboration 554
10.6.1 Electron Pushing 555
10.6.2 Experimental Observations 555

10.7 Epoxidation 555
10.7.1 Electron Pushing 556
10.7.2 Experimental Observations 556

10.8 Nucleophilic Additions to Carbonyl Compounds 556
10.8.1 Electron Pushing for a Few Nucleophilic Additions 557
10.8.2 Experimental Observations for Cyanohydrin Formation 559
10.8.3 Experimental Observations for Grignard Reactions 560
10.8.4 Experimental Observations in LAH Reductions 561
10.8.5 Orbital Considerations 561
The Bürgi–Dunitz Angle 561
Orbital Mixing 562
10.8.6 Conformational Effects in Additions to Carbonyl Compounds 562
10.8.7 Stereochemistry of Nucleophilic Additions 563

10.9 Nucleophilic Additions to Olefins 567
10.9.1 Electron Pushing 567
10.9.2 Experimental Observations 567
10.9.3 Regiochemistry of Addition 567
10.9.4 Baldwin's Rules 568

10.10 Radical Additions to Unsaturated Systems 569
10.10.1 Electron Pushing for Radical Additions 569
10.10.2 Radical Initiators 570
10.10.3 Chain Transfer vs. Polymerization 571
10.10.4 Termination 571
10.10.5 Regiochemistry of Radical Additions 572

10.11 Carbene Additions and Insertions 572
10.11.1 Electron Pushing for Carbene Reactions 574
10.11.2 Carbene Generation 574
10.11.3 Experimental Observations for Carbene Reactions 575

—ELIMINATIONS— 576

10.12 Eliminations to Form Carbonyls or "Carbonyl-Like" Intermediates 577
10.12.1 Electron Pushing 577
10.12.2 Stereochemical and Isotope Labeling Evidence 577
10.12.3 Catalysis of the Hydrolysis of Acetals 578
10.12.4 Stereoelectronic Effects 579
10.12.5 CrO_3 Oxidation—The Jones Reagent 580
Electron Pushing 580
A Few Experimental Observations 581

10.13 Elimination Reactions for Aliphatic Systems—Formation of Alkenes 581
10.13.1 Electron Pushing and Definitions 581
10.13.2 Some Experimental Observations for E2 and E1 Reactions 582
10.13.3 Contrasting Elimination and Substitution 583
10.13.4 Another Possibility—E1cB 584
10.13.5 Kinetics and Experimental Observations for E1cB 584
10.13.6 Contrasting E2, E1, and E1cB 586
10.13.7 Regiochemistry of Eliminations 588
10.13.8 Stereochemistry of Eliminations—Orbital Considerations 590
10.13.9 Dehydration 592
Electron Pushing 592
Other Mechanistic Possibilities 594
10.13.10 Thermal Eliminations 594

10.14 Eliminations from Radical Intermediates 596

—COMBINING ADDITION AND ELIMINATION REACTIONS (SUBSTITUTIONS AT sp^2 CENTERS)— 596

10.15 The Addition of Nitrogen Nucleophiles to Carbonyl Structures, Followed by Elimination 597
10.15.1 Electron Pushing 598
10.15.2 Acid–Base Catalysis 598

10.16 The Addition of Carbon Nucleophiles, Followed by Elimination—The Wittig Reaction 599
10.16.1 Electron Pushing 600

10.17 Acyl Transfers 600
10.17.1 General Electron-Pushing Schemes 600
10.17.2 Isotope Scrambling 601
10.17.3 Predicting the Site of Cleavage for Acyl Transfers from Esters 602
10.17.4 Catalysis 602

10.18 Electrophilic Aromatic Substitution 607
10.18.1 Electron Pushing for Electrophilic Aromatic Substitutions 607
10.18.2 Kinetics and Isotope Effects 608
10.18.3 Intermediate Complexes 608
10.18.4 Regiochemistry and Relative Rates of Aromatic Substitution 609

10.19 Nucleophilic Aromatic Substitution 611
10.19.1 Electron Pushing for Nucleophilic Aromatic Substitution 611
10.19.2 Experimental Observations 611

The Trustees of Columbia Univ. Ex. 2047 - Page 9 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

10.20 Reactions Involving Benzyne 612
10.20.1 Electron Pushing for Benzyne Reactions 612
10.20.2 Experimental Observations 613
10.20.3 Substituent Effects 613

10.21 The $S_{RN}1$ Reaction on Aromatic Rings 615
10.21.1 Electron Pushing 615
10.21.2 A Few Experimental Observations 615

10.22 Radical Aromatic Substitutions 615
10.22.1 Electron Pushing 615
10.22.2 Isotope Effects 616
10.22.3 Regiochemistry 616

Summary and Outlook 617

EXERCISES 617
FURTHER READING 624

CHAPTER 11: Organic Reaction Mechanisms, Part 2: Substitutions at Aliphatic Centers and Thermal Isomerizations/ Rearrangements 627

Intent and Purpose 627

—SUBSTITUTION α TO A CARBONYL CENTER: ENOL AND ENOLATE CHEMISTRY— 627

11.1 Tautomerization 628
11.1.1 Electron Pushing for Keto–Enol Tautomerizations 628
11.1.2 The Thermodynamics of Enol Formation 628
11.1.3 Catalysis of Enolizations 629
11.1.4 Kinetic vs. Thermodynamic Control in Enolate and Enol Formation 629

11.2 α-Halogenation 631
11.2.1 Electron Pushing 631
11.2.2 A Few Experimental Observations 631

11.3 α-Alkylations 632
11.3.1 Electron Pushing 632
11.3.2 Stereochemistry: Conformational Effects 633

11.4 The Aldol Reaction 634
11.4.1 Electron Pushing 634
11.4.2 Conformational Effects on the Aldol Reaction 634

—SUBSTITUTIONS ON ALIPHATIC CENTERS— 637

11.5 Nucleophilic Aliphatic Substitution Reactions 637
11.5.1 S_N2 and S_N1 Electron-Pushing Examples 637
11.5.2 Kinetics 638
11.5.3 Competition Experiments and Product Analyses 639
11.5.4 Stereochemistry 640
11.5.5 Orbital Considerations 643
11.5.6 Solvent Effects 643
11.5.7 Isotope Effect Data 646
11.5.8 An Overall Picture of S_N2 and S_N1 Reactions 646
11.5.9 Structure–Function Correlations with the Nucleophile 648
11.5.10 Structure–Function Correlations with the Leaving Group 651
11.5.11 Structure–Function Correlations with the R Group 651
Effect of the R Group Structure on S_N2 Reactions 651
Effect of the R Group Structure on S_N1 Reactions 653
11.5.12 Carbocation Rearrangements 656
11.5.13 Anchimeric Assistance in S_N1 Reactions 659
11.5.14 S_N1 Reactions Involving Non-Classical Carbocations 661
Norbornyl Cation 662
Cyclopropyl Carbinyl Carbocation 664
11.5.15 Summary of Carbocation Stabilization in Various Reactions 667
11.5.16 The Interplay Between Substitution and Elimination 667

11.6 Substitution, Radical, Nucleophilic 668
11.6.1 The SET Reaction—Electron Pushing 668
11.6.2 The Nature of the Intermediate in an SET Mechanism 669
11.6.3 Radical Rearrangements as Evidence 669
11.6.4 Structure–Function Correlations with the Leaving Group 670
11.6.5 The $S_{RN}1$ Reaction—Electron Pushing 670

11.7 Radical Aliphatic Substitutions 671
11.7.1 Electron Pushing 671
11.7.2 Heats of Reaction 671
11.7.3 Regiochemistry of Free Radical Halogenation 671
11.7.4 Autoxidation: Addition of O_2 into C–H Bonds 673
Electron Pushing for Autoxidation 673

—ISOMERIZATIONS AND REARRANGEMENTS— 674

11.8 Migrations to Electrophilic Carbons 674
11.8.1 Electron Pushing for the Pinacol Rearrangement 675
11.8.2 Electron Pushing in the Benzilic Acid Rearrangement 675
11.8.3 Migratory Aptitudes in the Pinacol Rearrangement 675
11.8.4 Stereoelectronic and Stereochemical Considerations in the Pinacol Rearrangement 676
11.8.5 A Few Experimental Observations for the Benzilic Acid Rearrangement 678

11.9 Migrations to Electrophilic Heteroatoms 678
11.9.1 Electron Pushing in the Beckmann Rearrangement 678
11.9.2 Electron Pushing for the Hofmann Rearrangement 679
11.9.3 Electron Pushing for the Schmidt Rearrangement 680
11.9.4 Electron Pushing for the Baeyer–Villiger Oxidation 680
11.9.5 A Few Experimental Observations for the Beckmann Rearrangement 680

The Trustees of Columbia Univ. Ex. 2047 - Page 10 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

11.9.6 A Few Experimental Observations for the Schmidt Rearrangement 681
11.9.7 A Few Experimental Observations for the Baeyer–Villiger Oxidation 681

11.10 The Favorskii Rearrangement and Other Carbanion Rearrangements 682
11.10.1 Electron Pushing 682
11.10.2 Other Carbanion Rearrangements 683

11.11 Rearrangements Involving Radicals 683
11.11.1 Hydrogen Shifts 683
11.11.2 Aryl and Vinyl Shifts 684
11.11.3 Ring-Opening Reactions 685

11.12 Rearrangements and Isomerizations Involving Biradicals 685
11.12.1 Electron Pushing Involving Biradicals 686
11.12.2 Tetramethylene 687
11.12.3 Trimethylene 689
11.12.4 Trimethylenemethane 693

Summary and Outlook 695

EXERCISES 695
FURTHER READING 703

CHAPTER 12: Organotransition Metal Reaction Mechanisms and Catalysis 705

Intent and Purpose 705

12.1 The Basics of Organometallic Complexes 705
12.1.1 Electron Counting and Oxidation State 706
Electron Counting 706
Oxidation State 708
d Electron Count 708
Ambiguities 708
12.1.2 The 18-Electron Rule 710
12.1.3 Standard Geometries 710
12.1.4 Terminology 711
12.1.5 Electron Pushing with Organometallic Structures 711
12.1.6 *d* Orbital Splitting Patterns 712
12.1.7 Stabilizing Reactive Ligands 713

12.2 Common Organometallic Reactions 714
12.2.1 Ligand Exchange Reactions 714
Reaction Types 714
Kinetics 716
Structure–Function Relationships with the Metal 716
Structure–Function Relationships with the Ligand 716
Substitutions of Other Ligands 717
12.2.2 Oxidative Addition 717
Stereochemistry of the Metal Complex 718
Kinetics 718
Stereochemistry of the R Group 719
Structure–Function Relationship for the R Group 720
Structure–Function Relationships for the Ligands 720
Oxidative Addition at sp^2 Centers 721
Summary of the Mechanisms for Oxidative Addition 721
12.2.3 Reductive Elimination 724
Structure–Function Relationship for the R Group and the Ligands 724
Stereochemistry at the Metal Center 725
Other Mechanisms 725
Summary of the Mechanisms for Reductive Elimination 726
12.2.4 α- and β-Eliminations 727
General Trends for α- and β-Eliminations 727
Kinetics 728
Stereochemistry of β-Hydride Elimination 729
12.2.5 Migratory Insertions 729
Kinetics 730
Studies to Decipher the Mechanism of Migratory Insertion Involving CO 730
Other Stereochemical Considerations 732
12.2.6 Electrophilic Addition to Ligands 733
Reaction Types 733
Common Mechanisms Deduced from Stereochemical Analyses 734
12.2.7 Nucleophilic Addition to Ligands 734
Reaction Types 735
Stereochemical and Regiochemical Analyses 735

12.3 Combining the Individual Reactions into Overall Transformations and Cycles 737
12.3.1 The Nature of Organometallic Catalysis—Change in Mechanism 738
12.3.2 The Monsanto Acetic Acid Synthesis 738
12.3.3 Hydroformylation 739
12.3.4 The Water-Gas Shift Reaction 740
12.3.5 Olefin Oxidation—The Wacker Process 741
12.3.6 Palladium Coupling Reactions 742
12.3.7 Allylic Alkylation 743
12.3.8 Olefin Metathesis 744

Summary and Outlook 747

EXERCISES 748
FURTHER READING 750

CHAPTER 13: Organic Polymer and Materials Chemistry 753

Intent and Purpose 753

13.1 Structural Issues in Materials Chemistry 754
13.1.1 Molecular Weight Analysis of Polymers 754
Number Average and Weight Average Molecular Weights—M_n and M_w 754
13.1.2 Thermal Transitions—Thermoplastics and Elastomers 757
13.1.3 Basic Polymer Topologies 759

The Trustees of Columbia Univ. Ex. 2047 - Page 11 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

13.1.4 Polymer–Polymer Phase Behavior 760
13.1.5 Polymer Processing 762
13.1.6 Novel Topologies—Dendrimers and Hyperbranched Polymers 763
Dendrimers 763
Hyperbranched Polymers 768
13.1.7 Liquid Crystals 769
13.1.8 Fullerenes and Carbon Nanotubes 775

13.2 Common Polymerization Mechanisms 779
13.2.1 General Issues 779
13.2.2 Polymerization Kinetics 782
Step-Growth Kinetics 782
Free-Radical Chain Polymerization 783
Living Polymerizations 785
Thermodynamics of Polymerizations 787
13.2.3 Condensation Polymerization 788
13.2.4 Radical Polymerization 791
13.2.5 Anionic Polymerization 793
13.2.6 Cationic Polymerization 794
13.2.7 Ziegler–Natta and Related Polymerizations 794
Single-Site Catalysts 796
13.2.8 Ring-Opening Polymerization 797
13.2.9 Group Transfer Polymerization (GTP) 799

Summary and Outlook 800

EXERCISES 801
FURTHER READING 803

PART III
ELECTRONIC STRUCTURE: THEORY AND APPLICATIONS

CHAPTER 14: Advanced Concepts in Electronic Structure Theory 807

Intent and Purpose 807

14.1 Introductory Quantum Mechanics 808
14.1.1 The Nature of Wavefunctions 808
14.1.2 The Schrödinger Equation 809
14.1.3 The Hamiltonian 809
14.1.4 The Nature of the ∇^2 Operator 811
14.1.5 Why do Bonds Form? 812

14.2 Calculational Methods—Solving the Schrödinger Equation for Complex Systems 815
14.2.1 *Ab Initio* Molecular Orbital Theory 815
Born–Oppenheimer Approximation 815
The Orbital Approximation 815
Spin 816
The Pauli Principle and Determinantal Wavefunctions 816
The Hartree–Fock Equation and the Variational Theorem 818
SCF Theory 821
Linear Combination of Atomic Orbitals—Molecular Orbitals (LCAO–MO) 821
Common Basis Sets—Modeling Atomic Orbitals 822
Extension Beyond HF—Correlation Energy 824
Solvation 825
General Considerations 825
Summary 826
14.2.2 Secular Determinants—A Bridge Between *Ab Initio*, Semi-Empirical / Approximate, and Perturbational Molecular Orbital Theory Methods 828
The "Two-Orbital Mixing Problem" 829
Writing the Secular Equations and Determinant for Any Molecule 832
14.2.3 Semi-Empirical and Approximate Methods 833
Neglect of Differential Overlap (NDO) Methods 833
i. CNDO, INDO, PNDO (C = Complete, I = Intermediate, P = Partial) 834
ii. The Semi-Empirical Methods: MNDO, AM1, and PM3 834
Extended Hückel Theory (EHT) 834
Hückel Molecular Orbital Theory (HMOT) 835
14.2.4 Some General Comments on Computational Quantum Mechanics 835
14.2.5 An Alternative: Density Functional Theory (DFT) 836

14.3 A Brief Overview of the Implementation and Results of HMOT 837
14.3.1 Implementing Hückel Theory 838
14.3.2 HMOT of Cyclic π Systems 840
14.3.3 HMOT of Linear π Systems 841
14.3.4 Alternate Hydrocarbons 842

14.4 Perturbation Theory—Orbital Mixing Rules 844
14.4.1 Mixing of Degenerate Orbitals—First-Order Perturbations 845
14.4.2 Mixing of Non-Degenerate Orbitals—Second-Order Perturbations 845

14.5 Some Topics in Organic Chemistry for Which Molecular Orbital Theory Lends Important Insights 846
14.5.1 Arenes: Aromaticity and Antiaromaticity 846
14.5.2 Cyclopropane and Cyclopropylcarbinyl—Walsh Orbitals 848
The Cyclic Three-Orbital Mixing Problem 849
The MOs of Cyclopropane 850
14.5.3 Planar Methane 853
14.5.4 Through-Bond Coupling 854
14.5.5 Unique Bonding Capabilities of Carbocations—Non-Classical Ions and Hypervalent Carbon 855
Transition State Structure Calculations 856
Application of These Methods to Carbocations 857
NMR Effects in Carbocations 857
The Norbornyl Cation 858
14.5.6 Spin Preferences 859
Two Weakly Interacting Electrons: H_2 vs. Atomic C 859

The Trustees of Columbia Univ. Ex. 2047 - Page 12 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

14.6 Organometallic Complexes 862
14.6.1 Group Orbitals for Metals 863
14.6.2 The Isolobal Analogy 866
14.6.3 Using the Group Orbitals to Construct Organometallic Complexes 867

Summary and Outlook 868

EXERCISES 868
FURTHER READING 875

CHAPTER 15: **Thermal Pericyclic Reactions** 877

Intent and Purpose 877

15.1 Background 878

15.2 A Detailed Analysis of Two Simple Cycloadditions 878
15.2.1 Orbital Symmetry Diagrams 879
[2+2] 879
[4+2] 881
15.2.2 State Correlation Diagrams 883
[2+2] 883
[4+2] 886
15.2.3 Frontier Molecular Orbital (FMO) Theory 888
Contrasting the [2+2] and [4+2] 888
15.2.4 Aromatic Transition State Theory / Topology 889
15.2.5 The Generalized Orbital Symmetry Rule 890
15.2.6 Some Comments on "Forbidden" and "Allowed" Reactions 892
15.2.7 Photochemical Pericyclic Reactions 892
15.2.8 Summary of the Various Methods 893

15.3 Cycloadditions 893
15.3.1 An Allowed Geometry for [2+2] Cycloadditions 894
15.3.2 Summarizing Cycloadditions 895
15.3.3 General Experimental Observations 895
15.3.4 Stereochemistry and Regiochemistry of the Diels–Alder Reaction 896
An Orbital Approach to Predicting Regiochemistry 896
The Endo Effect 899
15.3.5 Experimental Observations for [2+2] Cycloadditions 901
15.3.6 Experimental Observations for 1,3-Dipolar Cycloadditions 901
15.3.7 Retrocycloadditions 902

15.4 Electrocyclic Reactions 903
15.4.1 Terminology 903
15.4.2 Theoretical Analyses 904
15.4.3 Experimental Observations: Stereochemistry 906
15.4.4 Torquoselectivity 908

15.5 Sigmatropic Rearrangements 910
15.5.1 Theory 911
15.5.2 Experimental Observations: A Focus on Stereochemistry 913
15.5.3 The Mechanism of the Cope Rearrangement 916
15.5.4 The Claisen Rearrangement 921
Uses in Synthesis 921
Mechanistic Studies 923
15.5.5 The Ene Reaction 924

15.6 Cheletropic Reactions 924
15.6.1 Theoretical Analyses 926
15.6.2 Carbene Additions 927

15.7 In Summary—Applying the Rules 928

Summary and Outlook 928

EXERCISES 929
FURTHER READING 933

CHAPTER 16: **Photochemistry** 935

Intent and Purpose 935

16.1 Photophysical Processes—The Jablonski Diagram 936
16.1.1 Electromagnetic Radiation 936
Multiple Energy Surfaces Exist 937
16.1.2 Absorption 939
16.1.3 Radiationless Vibrational Relaxation 944
16.1.4 Fluorescence 945
16.1.5 Internal Conversion (IC) 949
16.1.6 Intersystem Crossing (ISC) 950
16.1.7 Phosphorescence 951
16.1.8 Quantum Yield 952
16.1.9 Summary of Photophysical Processes 952

16.2 Bimolecular Photophysical Processes 953
16.2.1 General Considerations 953
16.2.2 Quenching, Excimers, and Exciplexes 953
Quenching 954
Excimers and Exciplexes 954
Photoinduced Electron Transfer 955
16.2.3 Energy Transfer I. The Dexter Mechanism—Sensitization 956
16.2.4 Energy Transfer II. The Förster Mechanism 958
16.2.5 FRET 960
16.2.6 Energy Pooling 962
16.2.7 An Overview of Bimolecular Photophysical Processes 962

16.3 Photochemical Reactions 962
16.3.1 Theoretical Considerations—Funnels 962
Diabatic Photoreactions 963
Other Mechanisms 964
16.3.2 Acid–Base Chemistry 965

The Trustees of Columbia Univ. Ex. 2047 - Page 13 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

16.3.3 Olefin Isomerization 965
16.3.4 Reversal of Pericyclic Selection Rules 968
16.3.5 Photocycloaddition Reactions 970
Making Highly Strained Ring Systems 973
Breaking Aromaticity 974
16.3.6 The Di-π-Methane Rearrangement 974
16.3.7 Carbonyls Part I: The Norrish I Reaction 976
16.3.8 Carbonyls Part II: Photoreduction and the Norrish II Reaction 978
16.3.9 Nitrobenzyl Photochemistry: "Caged" Compounds 980
16.3.10 Elimination of N_2: Azo Compounds, Diazo Compounds, Diazirines, and Azides 981
Azoalkanes (1,2-Diazenes) 981
Diazo Compounds and Diazirines 982
Azides 983

16.4 Chemiluminescence 985
16.4.1 Potential Energy Surface for a Chemiluminescent Reaction 985
16.4.2 Typical Chemiluminescent Reactions 986
16.4.3 Dioxetane Thermolysis 987

16.5 Singlet Oxygen 989

Summary and Outlook 993

EXERCISES 993
FURTHER READING 999

CHAPTER 17: Electronic Organic Materials 1001

Intent and Purpose 1001

17.1 Theory 1001
17.1.1 Infinite π Systems—An Introduction to Band Structures 1002
17.1.2 The Peierls Distortion 1009
17.1.3 Doping 1011

17.2 Conducting Polymers 1016
17.2.1 Conductivity 1016
17.2.2 Polyacetylene 1017
17.2.3 Polyarenes and Polyarenevinylenes 1018
17.2.4 Polyaniline 1021

17.3 Organic Magnetic Materials 1022
17.3.1 Magnetism 1023
17.3.2 The Molecular Approach to Organic Magnetic Materials 1024
17.3.3 The Polymer Approach to Organic Magnetic Materials—Very High-Spin Organic Molecules 1027

17.4 Superconductivity 1030
17.4.1 Organic Metals/Synthetic Metals 1032

17.5 Non-Linear Optics (NLO) 1033

17.6 Photoresists 1036
17.6.1 Photolithography 1036
17.6.2 Negative Photoresists 1037
17.6.3 Positive Photoresists 1038

Summary and Outlook 1041

EXERCISES 1042
FURTHER READING 1044

APPENDIX 1: **Conversion Factors and Other Useful Data** 1047

APPENDIX 2: **Electrostatic Potential Surfaces for Representative Organic Molecules** 1049

APPENDIX 3: **Group Orbitals of Common Functional Groups: Representative Examples Using Simple Molecules** 1051

APPENDIX 4: **The Organic Structures of Biology** 1057

APPENDIX 5: **Pushing Electrons** 1061
A5.1 The Rudiments of Pushing Electrons 1061
A5.2 Electron Sources and Sinks for Two-Electron Flow 1062
A5.3 How to Denote Resonance 1064
A5.4 Common Electron-Pushing Errors 1065
Backwards Arrow Pushing 1065
Not Enough Arrows 1065
Losing Track of the Octet Rule 1066
Losing Track of Hydrogens and Lone Pairs 1066
Not Using the Proper Source 1067
Mixed Media Mistakes 1067
Too Many Arrows—Short Cuts 1067
A5.5 Complex Reactions—Drawing a Chemically Reasonable Mechanism 1068
A5.6 Two Case Studies of Predicting Reaction Mechanisms 1069
A5.7 Pushing Electrons for Radical Reactions 1071
Practice Problems for Pushing Electrons 1073

APPENDIX 6: **Reaction Mechanism Nomenclature** 1075

Index 1079

The Trustees of Columbia Univ. Ex. 2047 - Page 14 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

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CHAPTER 8

Experiments Related to Thermodynamics and Kinetics

Intent and Purpose

The intent of this chapter is to teach several of the experimental tools routinely applied by physical organic chemists in the study of reaction mechanisms. The majority of these methods build upon an analysis of kinetics and thermodynamics, providing a natural progression from the previous chapter. Both the theory behind the methods and their application are covered, and many methods are illustrated by example.

The first topic is isotope effects. We consider the origin of isotope effects, what information they provide, and how they are analyzed. This includes solvent isotope effects, which are very relevant to the analysis of enzymatic reactions. After isotope effects, we delve into linear free energy relationships (LFERs), and show how structural changes can be used in a systematic way to gain insight into the nature of reactive intermediates. Electronic substituent effects (Hammett plots) are discussed in detail, but we also examine how structural changes in the solvent, nucleophile, and nucleofuge (a synonym for leaving group) can be used to probe a reaction mechanism. It is particularly instructive within the context of linear free energy relationships to examine trends in reactivity. Hence, in this chapter we also discuss the general effects of electron withdrawing and donating groups, changes in the ionizing power of the solvent, steric effects, and changes in nucleophilicity and leaving group ability (nucleofugality). The notions are not specific to individual reaction types, so they are discussed here instead of being examined only in the context of specific mechanisms in the next chapters. Finally, a variety of experiments that do not fit under any single heading are examined, such as cross-over experiments, scrambling experiments, clocks, etc. These experiments can be extremely important. We delineate the general approach used in each experimental type, but teach the methods mostly by example.

In all the sections of this chapter, examples are drawn from the literature. In doing so, we show that the tools of physical organic chemistry are used in most chemical subdisciplines. Our examples come from enzymology, bioorganic chemistry, organometallic chemistry, and traditional small molecule organic chemistry. Our intention is for the student to learn how general the experiments discussed herein are, so that he or she will immediately incorporate them into his or her repertoire for studying chemical reactivity.

8.1 Isotope Effects

In our analysis of kinetics in the last chapter, we emphasized that the information gained is limited, and that most studies of mechanisms involve other techniques. One piece of information that cannot be gained from a kinetic study is what bonds have been broken, formed, or rehybridized during the rate-determining step. Isotope effects can provide just this kind of information. Substituting one isotope for another at or near an atom at which bonds are breaking or rehybridizing typically leads to a change in the rate of the reaction. When the bonds being broken or formed involve those to hydrogen, the effect of replacing H with D often is relatively large and can be measured routinely. Isotope effects with other atoms have

The Trustees of Columbia Univ. Ex. 2047 - Page 15 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

also been studied, but the effects are typically small and sometimes difficult to quantify. Therefore, our discussion of isotope effects will focus on hydrogen, although we give a brief introduction to heavy atom isotope effects later.

8.1.1 The Experiment

An isotope effect is measured to determine if the bond at which the isotopic substitution is being made changes in some manner during the rate-determining step. We express an isotope effect as a ratio of rate constants, where the numerator is the rate constant for the reaction with the natural abundance isotope, and the denominator is the rate constant for the reaction with the altered isotope. For example, when measuring isotope effects for reactions involving a substitution of hydrogen with deuterium, the isotope effect would be expressed as k_H/k_D. Measuring an isotope effect, therefore, typically requires us to run two kinetic analyses or to design a clever competition experiment.

For a hydrogen isotope effect, typically a first order (or pseudo-first order) rate constant for the reaction of interest is determined with the bond that is being analyzed (X–H) having a natural abundance distribution of isotopes. This is because the natural abundance of deuterium and tritium (0.015% and 1×10^{-4}%, respectively) is so low that their contribution to the rate is negligible. Next, the rate constant for the same reaction is determined with a version of the molecule in which synthesis (or solvent exchange; see Section 8.1.6) has introduced nearly 100% deuterium in place of the hydrogen.

The magnitude of the isotope effect (the variation of k_H/k_D from unity) gives us information about the reaction mechanism. If k_H/k_D is 1, one conclusion would be that the bond where the substitution occurred is not changing during the rate-determining step. However, it may just be that the isotope effect is too small to be measured accurately. If the ratio of k_H/k_D is different from one, more solid conclusions can be drawn. When k_H/k_D is greater than one, we call the isotope effect **normal**. When k_H/k_D is less than one, we call the isotope effect **inverse**. When the isotope effect can be attributed to a bond breaking event at the X–H/X–D bond, it is referred to as a **primary isotope effect**. When the effect is attributed to a rehybridization or arises from isotopic substitution remote from the bonds undergoing reaction, it is referred to as a **secondary isotope effect**. The situation we have discussed thus far, in which the isotope substitution changes the rate of the reaction, is called a **kinetic isotope effect** (KIE). When the interchange of isotopes alters the position of an equilibrium, we call it an **equilibrium isotope effect**.

8.1.2 The Origin of Primary Kinetic Isotope Effects

The origin of all isotope effects is the difference in frequencies of various vibrational modes of a molecule that arise when one isotope is substituted with another. Let's first analyze a bond that is breaking during the rate-determining step of a reaction (a primary kinetic isotope effect). To a good approximation, the potential energy of the system does not change with substitution of one isotope for another. In other words, the relative energies of the minima and maxima on the energy surface do not change with isotopic substitution. However, we noted in Chapter 7 that the *shapes* of the potential wells on an energy surface are composites of the various vibrational states of the molecule. When considering a reaction, it is sufficient to consider the shapes of these wells as being dominated by the vibrational modes that are undergoing the most change during the reaction.

Recall from our discussion of IR spectroscopy (Section 2.1.4) that vibrational states are quantized, and that each potential energy well has several rungs that represent different energies for that vibrational mode (Figure 2.2). The formula for the quantized energies (e_n) of the vibrational modes is given in Eq. 8.1, where ν is the frequency of the vibrational mode being considered. These energies are measured from the lowest point in the potential energy well. At ambient temperature, the vibrational modes for bond stretches are dominated by $n = 0$, with $e_0 = \frac{1}{2}h\nu$. This energy is referred to as the **zero-point energy** (ZPE).

$$e_n = \left(n + \frac{1}{2}\right) h\nu \quad n = 0,1,2, \cdots \qquad \text{(Eq. 8.1)}$$

The Trustees of Columbia Univ. Ex. 2047 - Page 16 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

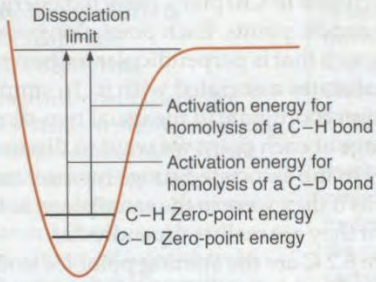


Figure 8.1
A Morse potential for a C–H bond showing that the activation energy for homolysis of a C–D bond is larger than for a C–H bond.

For a bond breaking event, the stretching vibration of that bond is defined as the reaction coordinate. As was discussed in Chapter 2, the frequency of a stretching vibration is modeled by the classic equation for the stretching of a spring with a mass attached at both ends (Eq. 8.2). In Eq. 8.2 ν is expressed in s^{-1}, whereas in IR spectroscopy the frequency is expressed in cm^{-1}, and is called $\bar{\nu}$ (where $\bar{\nu} = \nu/c$ and c, the speed of light, is given in cm/s).

The frequency is directly proportional to the square root of the force constant for the bond, and inversely proportional to the square root of the reduced mass. The reduced mass for a bond between a heavy atom such as C, N, or O with a light atom such as H is significantly affected when the H atom is changed to D. The stretching frequency of a bond with deuterium is lower due to the heavier mass, and hence the zero-point energy for the bond is lower also. We denote this on a potential energy well by showing a second rung that is lower in energy for the deuterium-containing bond (Figure 8.1).

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{m_r}} \quad \text{where } m_r = \frac{m_1 m_2}{m_1 + m_2} \qquad \text{(Eq. 8.2)}$$

In a homolysis reaction that forms two radicals, the stretching vibration in the reactant is converted to a translational degree of freedom. Comparing a C–H and C–D bond (as done in Figure 8.1) shows a larger activation energy for the C–D bond. In this case, the full difference in ZPE establishes the magnitude of the isotope effect, and k_H/k_D is greater than 1. There are no vibrations for the bond that is breaking when the reaction is done, and therefore the force constant associated with this bond has gone to zero, after full bond cleavage. By assuming that the bond of interest is 100% broken at the transition state (typically not the case), we can calculate the maximum possible isotope effect using Eqs. 8.1 and 8.2 (left as an Exercise at the end of this chapter). The expectation is that an isotope effect measured at 298 K for a homolysis reaction involving a C–H bond, whose IR stretch appears at 3000 cm^{-1}, should be approximately $k_H/k_D = 6.5$. This is a relatively large primary kinetic isotope effect, because we assumed that the bond was completely broken.

Most isotope effects are attenuated from this value because reactions typically do not involve bonds that are completely broken in the transition state. An example of a reaction with a relatively large isotope effect is the hydroxylation reaction given in the Connections highlight on page 425. To understand any kinetic phenomenon, one always compares reactant with transition state. For isotope effects we compare the ZPEs of the various vibrations of the reactant and the activated complex. Usually the bond is only partially broken at the transition state, or another bond is starting to form at the transition state. Both of these will attenuate the isotope effect from that of total homolysis. To visualize this attenuation, we need to examine reaction coordinate diagrams and the associated vibrational modes.

The Trustees of Columbia Univ. Ex. 2047 - Page 17 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

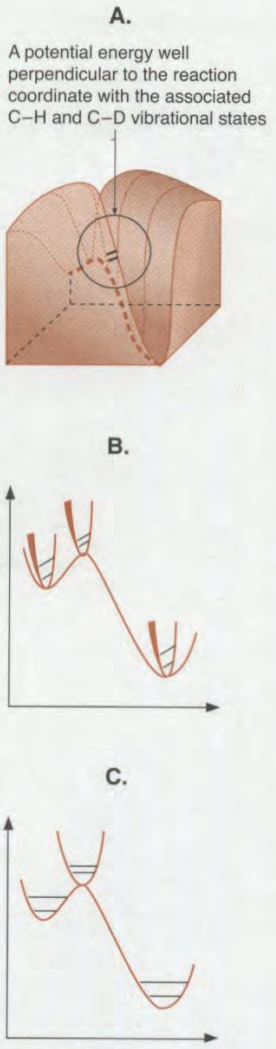


Figure 8.2
Various images of three- and two-dimensional reaction coordinate diagrams.
A. Showing the C–H and C–D ZPE levels within the troughs on the energy surface. **B.** Picture of the troughs and rungs at the reactant, T. S., and product, perpendicular to the reaction coordinate. **C.** Drawing the troughs and rungs in the same plane as the reaction coordinate.

Reaction Coordinate Diagrams and Isotope Effects

The energy surfaces discussed in Chapter 7 depicted energy wells from which troughs are traversed to achieve the saddle points. Each point along a reaction coordinate is associated with a potential energy well that is perpendicular to the reaction coordinate (Figure 8.2 **A**). Each well has vibrational states associated with it. To simplify these pictures for rapid drawing, we draw the reaction coordinate in the usual two-dimensional sense, and place a well perpendicular to the page at each point we want to discuss on the reaction coordinate (Figure 8.2 **B**). We then draw in the associated rungs representing the vibrational states. We now draw these same wells as if they were in the same plane as the reaction coordinate (Figure 8.2 **C**), fully realizing that they are really perpendicular.

Drawings such as Figure 8.2 **C** are the starting point for understanding the magnitudes of conventional isotope effects. In this figure we are achieving a transition state where there is still some bonding between the H or D and a heavy atom, such as carbon. Activated complexes have vibrational modes with ZPEs, just like any other molecule. For every vibrational mode there is a ZPE difference for C–H vs. C–D. However, the only vibrational modes we need consider are those that are undergoing a *change* along the reaction coordinate (see below). These will give a *differential* ZPE difference between C–H and C–D at the transition state vs. the reactant, and can thereby produce a kinetic isotope effect.

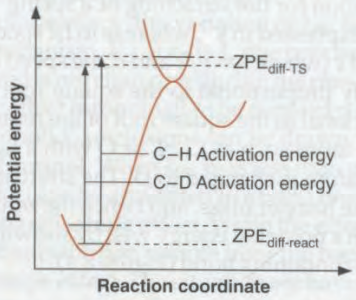


Figure 8.3
Diagram showing that a residual ZPE difference between C–H and C–D bonds at the transition state diminishes the isotope effect.

With primary kinetic isotope effects (Figure 8.3) the ZPE difference in the activated complex ($ZPE_{diff-TS}$) is smaller than in the reactants ($ZPE_{diff-react}$). The activation free energy for the deuterium case is still larger than the hydrogen case, but the isotope effect is reduced from that associated with a full homolysis reaction by the amount of ZPE difference that is residual in the transition state. In other words, the difference in free energy of activation for the C–H and C–D reactions ($\Delta\Delta G_{CH/CD}^{\circ\ddagger}$) is the difference between the ZPE differences in the reactant and the activated complex (Eq. 8.3).

$$\Delta\Delta G_{CH/CD}^{\circ\ddagger} = ZPE_{diff-react} - ZPE_{diff-TS} \qquad \text{(Eq. 8.3)}$$

In summary, then, the magnitude of a primary kinetic isotope effect depends upon differences in the ZPEs in the reactant and activated complex for all the vibrational modes of the reactant and activated complex. The changes in vibrations for the bonds undergoing transformations during the reaction dominate the isotope effect. We need to identify these vibrational modes and understand how their force constants change during the reaction. We focus on the force constants because the frequencies of the vibrational modes are related to the force constants via equations such as Eq. 8.2. As is discussed below, the proper vibrational modes to consider can be a function of the angle of collision between the reactants. Further, the extent of change in the force constants is a function of the extent of bond breaking and forming in the transition state.

The Trustees of Columbia Univ. Ex. 2047 - Page 18 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

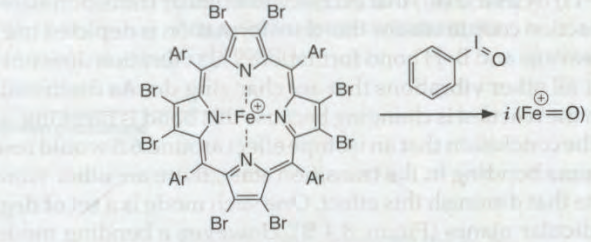
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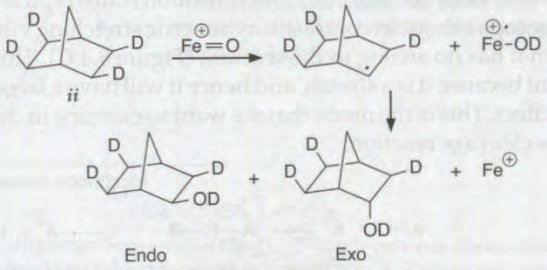
The Use of Primary Kinetic Isotope Effects to Probe the Mechanism of Aliphatic Hydroxylation by Iron(III) Porphyrins

One reaction that is uncommon in organic chemistry but is common in biological systems in the hydroxylation of alkanes to form alcohols. Cytochrome P-450, a heme containing enzyme, catalyzes this reaction. Large primary isotope effects are found, as well as an absence of carbocation-like skeletal rearrangements and loss of stereochemistry. These observations led researchers to conclude that a **radical cage mechanism** is operative. A radical cage mechanism is one in which radicals are created and react together before diffusing apart.

Several models of this heme enzyme are based upon substituted porphyrins. For example, compound *i* (oxidized Fe in porphyrin ligand shown) catalyzes the oxidation of norbornane to norboran-2-ol with iodosobenzene as oxidant. With the deuterionorbornane shown (*ii*), a mixture of endo- and exo-norboran-2-ols is produced, and a primary kinetic isotope effect of 5 is measured. This is similar to the isotope effect found for the enzyme-catalyzed reaction, suggesting that *i* is a good model for the natural reaction. The large isotope effect supports a mechanism involving hydrogen atom abstraction in the rate-determining step followed by a rapid transfer of the hydroxyl from the iron to the carbon-based radical (hence the radical cage description). Furthermore, note that no carbon skeletal rearrangements were found, as would be expected for a norbornyl cation (see Chapter 11). This supports a mechanism that does not involve carbocations.

Traylor, T. G., Hill, K. W., Fann, W.-P., Tsuchiya, S., and Dunlap, B. E. "Aliphatic Hydroxylation Catalyzed by Iron(III) Porphyrins." *J. Am. Chem. Soc.*, **114**, 1308–1312 (1992).





Primary Kinetic Isotope Effects for Linear Transition States as a Function of Exothermicity and Endothermicity

To analyze which vibrational modes are relevant to an isotope effect, we must have a reference point to compare to the transition state, and we must identify the reaction coordinate. The Hammond postulate tells us that the structure of the activated complex most resembles the structure of the molecule to which it is closest in energy. This means that we can estimate the vibrational modes in the activated complex by making comparisons to the vibrational modes for the reactants and products (remembering that in this context the "product" might actually be a reactive intermediate). The force constants for the transition state will be most similar to the force constants in the structure that the transition state is closest to in energy. We must also identify the vibrational mode that is the reaction coordinate, because this vibration will not contribute to the isotope effect at the transition state. This is because the

The Trustees of Columbia Univ. Ex. 2047 - Page 19 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

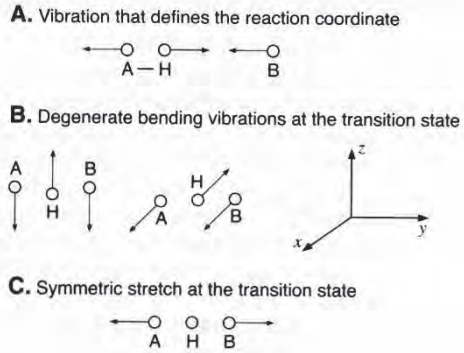
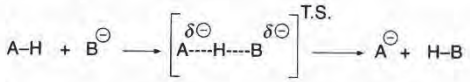


Figure 8.4
Vibrational modes relevant to kinetic primary isotope effects. **A.** Vibration that defines the reaction coordinate. **B.** In-plane and out-of-plane bends at the transition state. **C.** Symmetric stretch that forms at the transition state.

reaction coordinate is not a vibration present in the transition state, but instead defines the reaction.

The normal modes we must pay the most attention to are those that are changing in the reactant and developing in the activated complex. Consider a deprotonation reaction of an acid (A–H) by a base (B^-) that occurs with a linear transition state (Eq. 8.4). The vibration that is the reaction coordinate for this transformation is depicted in Figure 8.4 **A**, leading to A–H bond cleavage and B–H bond formation. This vibration does not contribute to the isotope effect, but all other vibrations that are changing do. As discussed above, the A–H stretching mode in the reactant is changing because this bond is breaking, and a simple analysis would lead to the conclusion that an isotope effect around 6.5 would result. However, because there is still some bonding in the transition state, there are other vibrational modes in the transition state that diminish this effect. One such mode is a set of degenerate bends that occur in perpendicular planes (Figure 8.4 **B**). However, a bending mode also exists in the reactant, and bending modes have significantly lower force constants than stretches. Therefore, differences in bends between reactants and transition states typically do not contribute greatly to primary isotope effects. In contrast, a symmetric stretching vibration develops at the transition state that has no analog in the reactant (Figure 8.4 **C**). This new vibration has a large force constant because it is a stretch, and hence it will have a large effect on the magnitude of the isotope effect. This is the mode that we want to examine in detail as a function of the free energy of the cleavage reaction.



(Eq. 8.4)

If the deprotonation is very exothermic, the transition state resembles the reactants; that is, very little bond breaking has occurred at the acid and very little bond formation has occurred at the base (Figure 8.5 **A**). Hence, the bond holding the hydrogen to the complex still greatly resembles the bond in the reactant. The newly forming symmetric stretch involves almost as much movement of the hydrogen as does the bond stretch in the reactant. The magnitude of the isotope effect is therefore predicted to be small, because the *difference* in ZPE H/D differences for the reactant and transition state is small.

When the reaction is very endothermic, the bond between the proton and the base has been almost completely formed at the transition state (Figure 8.4 **B**). Hence, the symmetric stretch at the transition state greatly resembles the normal bond stretch in the product. When examining a reaction where the force constant of the B–H bond is similar to that of the A–H bond, the force constant for the symmetric stretch at the transition state would therefore be similar to that for the A–H bond. Again, we find little difference in ZPE differences between the reactant and the activated complex, leading to a small isotope effect.

The situation is much more interesting when the reaction is thermoneutral or close to it (Figure 8.4 **C**). Now the bond that holds the hydrogen in the activated complex has the hy-

The Trustees of Columbia Univ. Ex. 2047 - Page 20 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

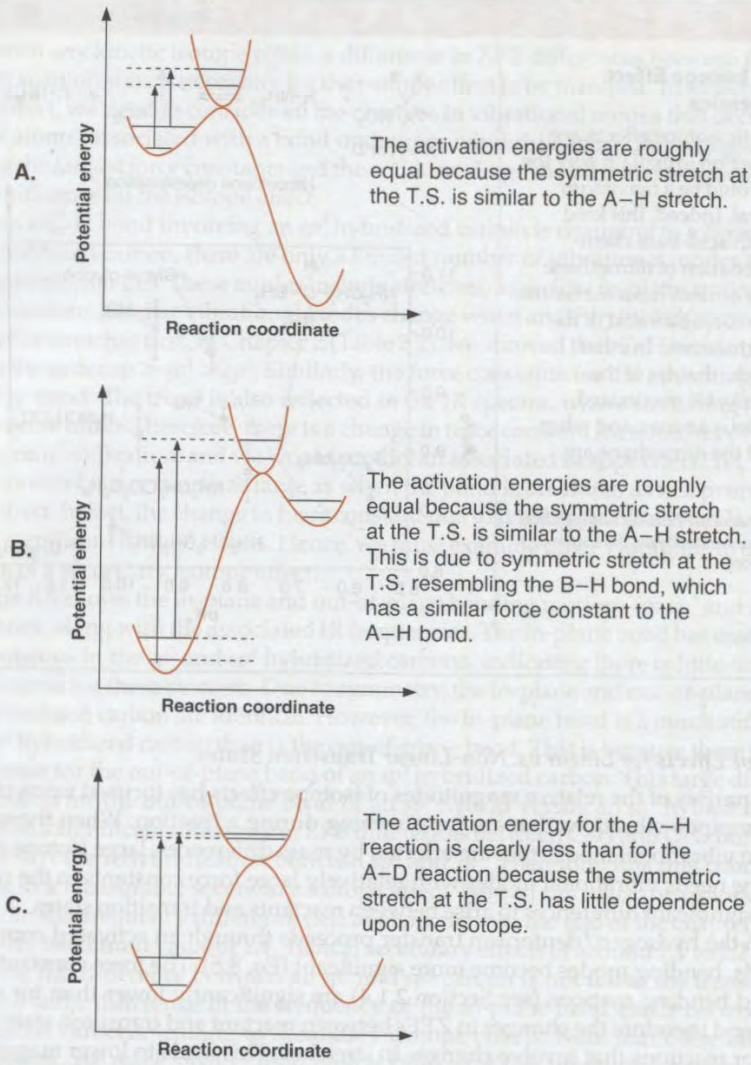


Figure 8.5
Diagrams showing how the ZPE difference between C–H and C–D bonds between the reactant and transition state changes as a function of the free energy of the reaction. **A.** Exothermic reaction, **B.** Endothermic reaction, and **C.** Thermoneutral reaction. The symmetric stretch referred to in the figure is that of Figure 8.4 **C**.

drogen almost equally shared between A and B, and the symmetric stretch (Figure 8.4 **C**) is centered around the hydrogen with little or no movement of the hydrogen. Therefore, the frequency of this stretch does not depend strongly upon the isotope. Now the ZPE difference at the transition state is very small. The resulting isotope effect is therefore predicted to be large, possibly approaching 6.5. Note that this analysis tells us that the magnitude of the isotope effect is a rough measure of the position of the transition state along the reaction coordinate; that is, large isotope effects are found for reactions with nearly symmetrical transition states, and smaller effects are observed as the transition state moves toward reactant or product. An example of this in a proton transfer reaction is described in the following Connections highlight.

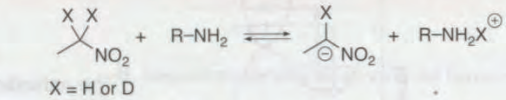
The Trustees of Columbia Univ. Ex. 2047 - Page 21 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

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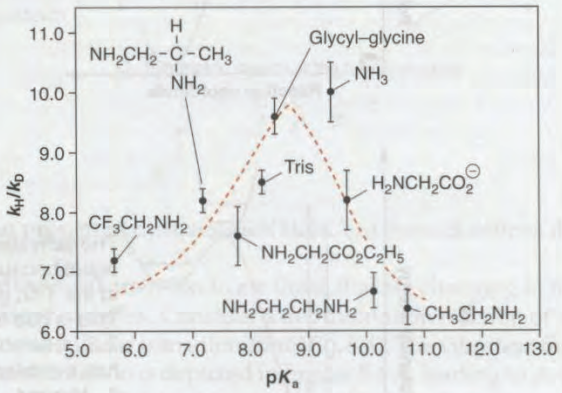
An Example of Changes in the Isotope Effect with Varying Reaction Free Energies

In our discussion of primary kinetic isotope effects, we used a hypothetical acid–base reaction to explain why the magnitude of the isotope effect would be a maximum when the reaction is thermoneutral. Indeed, this kind of effect has often been observed in acid–base chemistry. As one example, the deprotonation of nitroethane ($CH_3CH_2NO_2$ or $CH_3CD_2NO_2$) by amines has a maximum isotope effect when the pK_a of the conjugate acid of the amine base matches the pK_a of nitroethane. In other words, when the acid strength on both sides of the reaction is the same, the isotope effect is maximized. The graph to the right shows various amines, and when the acidity of the ammonium and the nitroethane are close, the largest KIE is found.

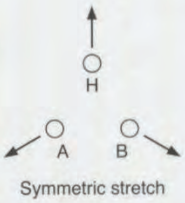
Dixon, J. E., and Bruice, T. C. "Dependence of the Primary Isotope Effect (k^H/k^D) on Base Strength for the Primary Amine Catalyzed Ionization of Nitroethane." *J. Am. Chem. Soc.*, **92**, 905 (1970).



Nitroethane deprotonation



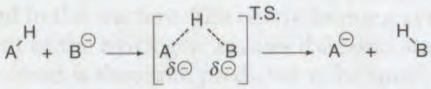
Isotope Effects for Linear vs. Non-Linear Transition States



Symmetric stretch

Our analysis of the relative magnitudes of isotope effects has focused upon changes in ZPEs for various vibrations that are transforming during a reaction. When there are large changes in vibrational modes that are affected by mass differences, large isotope effects are found. One needs vibrational modes with relatively large force constants in the reactant in order for significant differences to arise between reactants and transition states.

When the hydrogen/deuterium transfer proceeds through an activated complex with bent bonds, bending modes become more significant (Eq. 8.5). The force constants for scissoring and bending motions (see Section 2.1.4) are significantly lower than for stretching motions, and therefore the changes in ZPEs between reactant and transition state are not as large as for reactions that involve changes in stretches. This leads to lower magnitudes for primary kinetic isotope effects. Moreover, the hydrogen in the symmetric stretch (the bent analog to Figure 8.4 **C**) still has a significant movement. Therefore, this vibration still has a mass dependence, and will diminish the magnitude of the isotope effect relative to a linear transition state. Hence, hydrogen transfers that proceeds through non-linear transition states have lower KIEs.



(Eq. 8.5)

8.1.3 The Origin of Secondary Kinetic Isotope Effects

Secondary kinetic isotope effects arise from isotopic substitution at a bond that is not being broken, and typically involve a change in bond hybridization or involvement of the bond in hyperconjugation. They are defined as α or β **secondary isotope effects**. The terms refer to whether the isotope is on a position α or β to the bond that is changing. An α effect occurs when the atom undergoing reaction has the associated isotope, whereas a β effect occurs when the neighboring atom has the isotope. An example of how to use a secondary isotope effect in deciphering a mechanism is given in the Connections highlight on page 431.

The Trustees of Columbia Univ. Ex. 2047 - Page 22 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Hybridization Changes

As with any kinetic isotope effect, a difference in ZPE differences between the reactant and the transition state is necessary for the isotope effect to be manifest. To understand a secondary effect, we need to consider all the changes in vibrational modes that occur when an atom (or atoms) associated with a bond undergoes rehybridization. The vibrational modes that have the largest force constants and those that undergo the largest changes will have the greatest influence on the isotope effect.

When a C–H bond involving an sp^3 hybridized carbon is changing to a bond involving an sp^2 hybridized carbon, there are only a limited number of vibrational modes that are undergoing large changes. These modes include stretches, as well as in-plane and out-of-plane bending motions. Similar vibrational modes change when an sp^2 hybrid changes to sp. Let's consider the stretches first. In Chapter 2 (Table 2.2), we showed that C–H bond strengths decrease in the order $sp > sp^2 > sp^3$. Similarly, the force constants for the stretching vibrations follow this trend. The trend is also reflected in the IR spectra, where stretching frequencies have the same order. Therefore, there is a change in force constant for stretches of a bond undergoing rehybridization, and we would predict an associated isotope effect. Yet, the change in force constant is not nearly as large as when the bond is breaking, as in a primary kinetic isotope effect. In fact, the change in force constant due to rehybridization is not large enough to create significant isotope effects. Hence, we must examine other vibrations to understand the origin of a secondary isotope effect.

Figure 8.6 shows the in-plane and out-of-plane bending motions for sp^3 and sp^2 hybridized carbons, along with the associated IR frequencies. The in-plane bend has essentially the same frequency in the sp^3 and sp^2 hybridized carbons, indicating there is little difference in force constants for these motions. Due to symmetry, the in-plane and out-of-plane bends for an sp^3 hybridized carbon are identical. However, the in-plane bend is a much stiffer motion for the sp^2 hybridized carbon than is the out-of-plane bend. This is because there is little steric hindrance for the out-of-plane bend of an sp^2 hybridized carbon. This large difference in force constant for the out-of-plane bend of an sp^3 hybrid versus an sp^2 hybrid means that there will be a significant difference in ZPE differences between C–H and C–D bonds in reactions that involve rehybridization between sp^3 and sp^2. Therefore, it is this bending mode that leads to a measurable secondary isotope effect. We can calculate the isotope effect expected from this frequency difference (left as an Exercise at the end of the chapter), and find a theoretical maximum value of 1.4. Typical secondary effects of around 1.1 to 1.2 are found, because the full difference between an sp^3 and sp^2 carbon is not felt at the transition state. Similarly, a large difference in the frequency of the in-plane bend exists between sp^2 and sp hybridized carbons, leading to secondary isotope effects. Note that these effects, even at their largest, are *much* smaller than typical primary KIEs, presenting a more significant challenge to the experimentalist. A Going Deeper highlight on page 432 describes an ingenious method for measuring very small isotope effects.

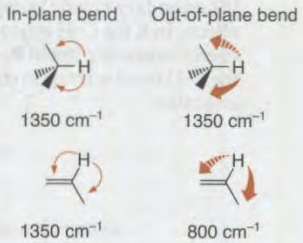


Figure 8.6
In-plane and out-of-plane bending vibrations for C–H bonds on sp^3 and sp^2 hybridized carbons.

We have just explained that a secondary kinetic isotope effect arises from differences in bending vibrations. One draws this difference using the typical reaction coordinate diagrams. In Figure 8.7, we plot the potential energy wells for the vibrational states undergoing change, but now we are plotting bending motions. Since the transition state is developing sp^2 character at the carbon where the isotopic substitution has been made, the force constant is weaker at the transition state than for the reactant (Figure 8.7 **A**). We find that the reaction is slower when the reaction has a deuterium on the carbon undergoing rehybridization. This is a normal secondary kinetic isotopic effect.

Consider now a reaction that is the opposite from above—that is, one that involves rehybridization from sp^2 to sp^3 (Figure 8.7 **B**). Now the force constant for the bending motion is getting larger at the transition state because the vibration is becoming stiffer. In this scenario the ZPE difference is larger at the transition state than at the reactant, which means that the reaction actually proceeds faster with deuterium than with hydrogen. This is an inverse kinetic isotope effect. Isotope effect values of around 0.8 to 0.9 are common in these cases.

A secondary kinetic isotope effect can also arise from the involvement of a C–H(D) bond in hyperconjugation in a rate-determining step. For example, in an S_N1 reaction a carbocat-

The Trustees of Columbia Univ. Ex. 2047 - Page 23 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

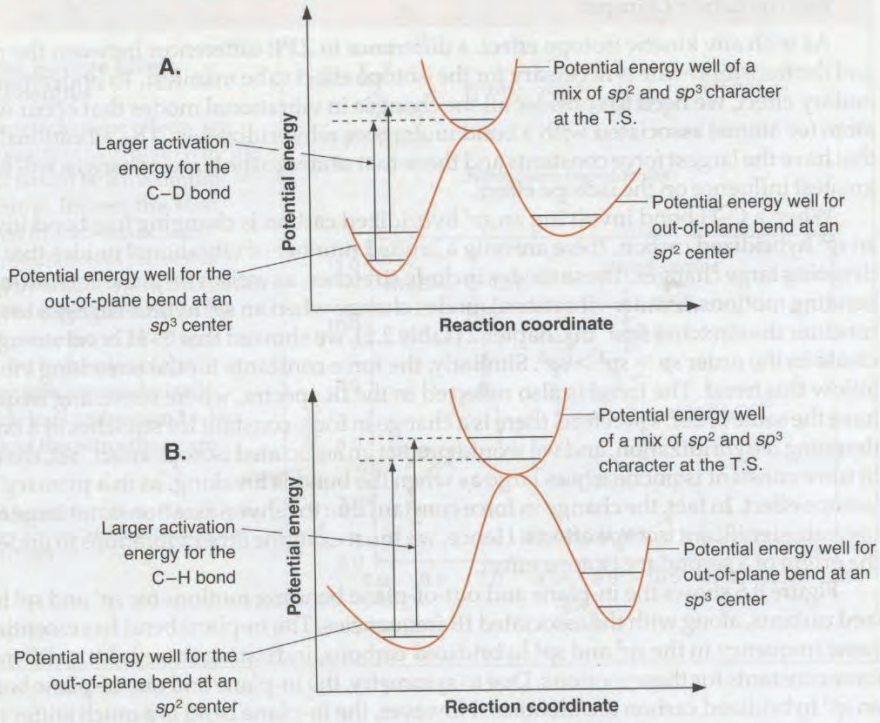


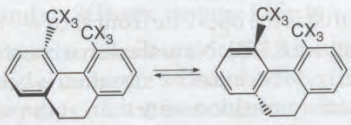
Figure 8.7
Diagrams showing the origin of normal **(A)** and inverse **(B)** secondary kinetic isotope effects. In **A** the C–H activation energy is smaller, but in **B** the C–D bond activation energy is smaller.

ion is created in the slow step, and C–H(D) bonds β to the cationic center stabilize the cation by hyperconjugation (see Section 1.4.1). This weakens the C–H(D) bonds, which will lead to a normal secondary kinetic isotope effect.

Steric Isotope Effects

There is an alternative mechanism by which we can see isotope effects in cases that do not involve breaking or making C–H bonds. This is a steric effect, in which the differing effective steric sizes of H vs. D come into play. In a C–H vs. a C–D bond, not only is the ZPE less for D, but we should also anticipate that the vibrational amplitude should be less for D than for H. This in turn should make D appear to be smaller than H in some contexts.

A classic demonstration of this effect is in the racemization of the chiral biphenyl compound characterized by Mislow and shown in Eq. 8.6. Rotation about the central bond racemizes the material and forces a severe steric clash between the two methyl groups in the transition state. Indeed, it is found that the deuterio compound racemizes faster than the protio, consistent with the notion that D is effectively smaller than H. The effect is certainly not a large one, as only a 15% difference is seen in a system with a really severe steric interaction and with multiple H/D substitutions. Nevertheless, steric isotope effects can be comparable to other secondary isotope effects, and so should be considered when evaluating experimental data.



(Eq. 8.6)

$$\frac{k\,(X = D)}{k\,(X = H)} = 1.15$$

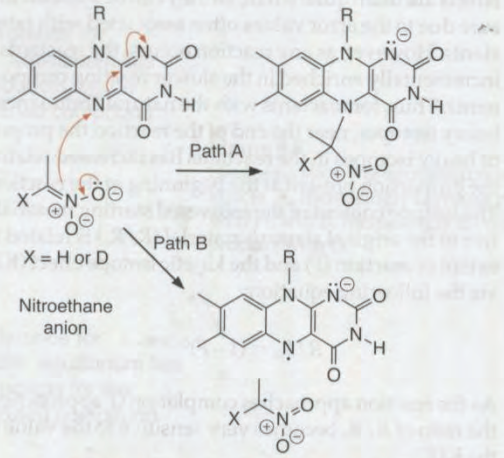
The Trustees of Columbia Univ. Ex. 2047 - Page 24 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

The Use of an Inverse Isotope Effect to Delineate an Enzyme Mechanism

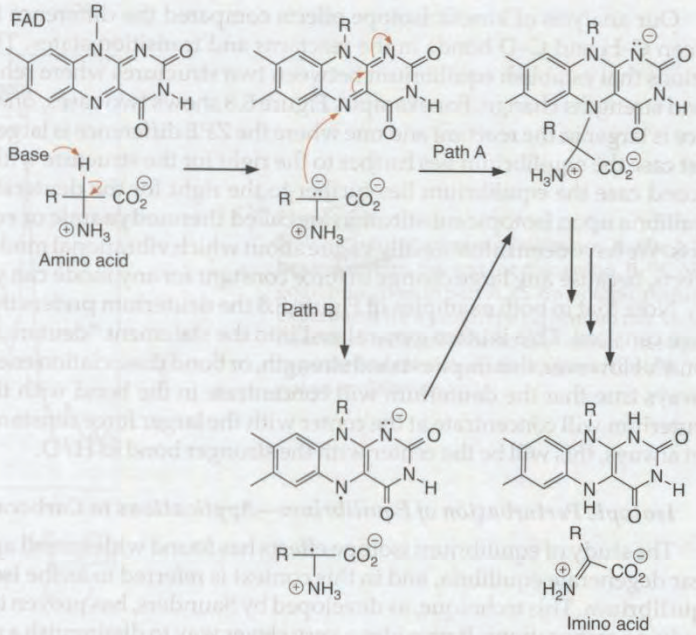
D-Amino acid oxidase catalyzes the oxidation of amino acids to imino acids via the transfer of a hydride to the coenzyme flavin adenine dinucleotide (FAD). The mechanism first involves deprotonation of the amino acid to create a carbanion (see below). This carbanion can then undergo either a nucleophilic addition to the flavin of FAD (Path A) or an electron transfer to the flavin, creating radicals that combine to give the same product as the nucleophilic addition (Path B). Expulsion of the flavin as a leaving group, concomitant with some proton transfers, gives the oxidized imino acid product.

To distinguish whether the reaction involves nucleophilic attack or radical intermediates, the conjugate base of nitroethane was used as a substrate for the enzyme (see to the right). In this case the enzyme does not need to deprotonate the substrate because it is a carbanion to begin with. This carbanion is sp^2 hydridized at the anionic carbon, and nucleophilic attack on the flavin would transform this carbon to sp^3 (Path A). Since the hybridization changes from sp^2 to sp^3, an inverse isotope effect is predicted. However, the alternative wherein a radical is formed from the carbanion keeps the hybridization state of the α-carbon roughly the same (Path B), giving little if any isotope effect. Following the kinetics of the reaction of nitroethane anion (α-H or D) with FAD and D-amino acid oxidase revealed a secondary inverse kinetic isotope effect of 0.84. This is relatively large for a secondary isotope effect, and so the data were interpreted to support the nucleophilic mechanism (Path A).



Probing radical vs. nucleophilic mechanisms

Kurtz, K. A., and Fitzpatrick, P. F. "pH and Secondary Kinetic Isotope Effects on the Reaction of D-Amino Acid Oxidase with Nitroalkane Anions: Evidence for Direct Attack on the Flavin by Carbanions." *J. Am. Chem. Soc.*, **119**, 1155 (1997).



The Trustees of Columbia Univ. Ex. 2047 - Page 25 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Going Deeper

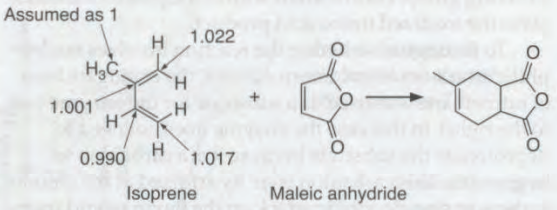
An Ingenious Method for Measuring Very Small Isotope Effects

Heavy atom and secondary hydrogen kinetic isotope effects are often quite small, so they can be difficult to measure due to the error values often associated with rate constants. However, as any reaction occurs, the reactants are incrementally enriched in the slower reacting components. Thus, for reactants with the natural abundance of heavy isotopes, near the end of the reaction the proportion of heavy isotopes in the reactants has increased relative to the proportion present at the beginning of the reaction. The isotope content of the recovered starting material relative to the original starting material (R/R_o) is related to the extent of reaction (F) and the kinetic isotope effect (KIE) via the following equation:

$$R/R_o = (1-F)^{(1/\mathrm{KIE})-1}$$

As the reaction approaches completion (F approaches 1), the ratio of R/R_o becomes very sensitive to the value of the KIE.

Using this method, the kinetic isotope effects of ^2H and ^{13}C at each atom in isoprene for the Diels–Alder reaction with maleic anhydride were determined. NMR spectroscopy was used to measure the ^2H and ^{13}C content at each atom in the initial starting material, and in recovered starting material after the reaction had proceeded to 98.9% completion. The ratio of isotopic abundance at each carbon and hydrogen was used in the above equation to give the isotope effect at each center. The ^{13}C isotope effects for each carbon are shown below. Using this very clever method, one can now routinely measure very small isotope effects, as long as the reaction is sufficiently scalable to allow for recovery of enough starting material for NMR analysis.



Singleton, D. A., and Thomas, A. A. "High-Precision Simultaneous Determination of Multiple Small Kinetic Isotope Effects at Natural Abundance." *J. Am. Chem. Soc.*, **117**, 9357–9358 (1995).

8.1.4 Equilibrium Isotope Effects

Our analysis of kinetic isotope effects compared the difference in ZPE differences between C–H and C–D bonds in the reactants and transition states. There are also many reactions that establish equilibrium between two structures where rehybridization occurs or bond strengths change. For example, Figure 8.8 shows two cases, one where the ZPE difference is larger in the reactant and one where the ZPE difference is larger in the product. In the first case the equilibrium lies further to the right for the structure with hydrogen, and in the second case the equilibrium lies further to the right for the deuterated structure. Shifts in equilibria upon isotopic substitution are called **thermodynamic** or **equilibrium isotope effects**. We have been intentionally vague about which vibrational modes lead to these isotope effects, because any large change in force constant for any mode can yield such effects.

Note that in both examples of Figure 8.8 the deuterium prefers the bond with the larger force constant. This is often generalized into the statement "deuterium prefers the stronger bond". However, this implies bond strength, or bond dissociation energy (BDE), and it is not always true that the deuterium will concentrate in the bond with the larger BDE. Rather, deuterium will concentrate at the center with the larger force constants overall. Usually, but not always, this will be the center with the stronger bond to H/D.

Isotopic Perturbation of Equilibrium—Applications to Carbocations

The study of equilibrium isotope effects has found widespread application in analyzing near degenerate equilibria, and in this context is referred to as the **isotopic perturbation of equilibrium**. This technique, as developed by Saunders, has proven to be a powerful tool for studying carbocations. It provides a very clever way to distinguish a rapid equilibrium from a single, symmetrical structure. The method is best described by considering some specific examples, shown in Figure 8.9.

The Trustees of Columbia Univ. Ex. 2047 - Page 26 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

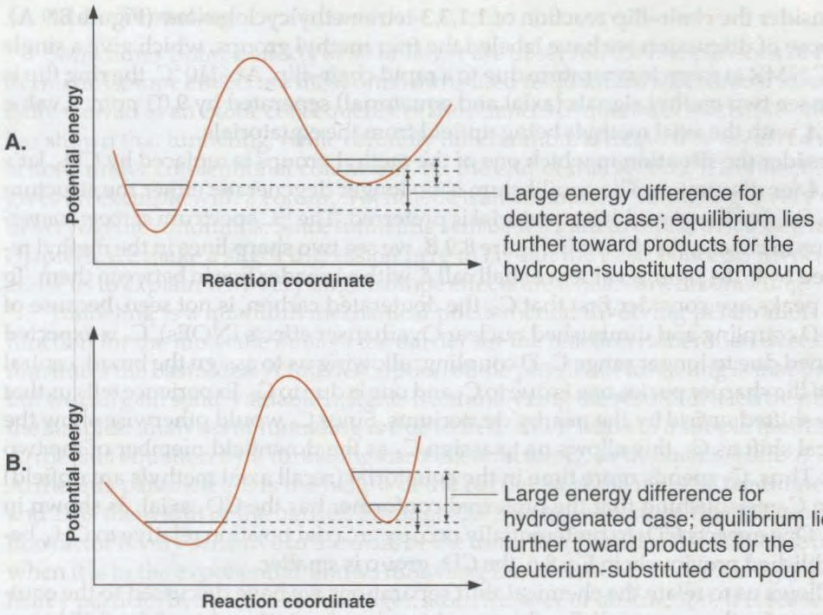


Figure 8.8
Diagrams showing equilibrium isotope effects. **A.** Increasingly favoring product with H, and **B.** Increasingly favoring product with D.

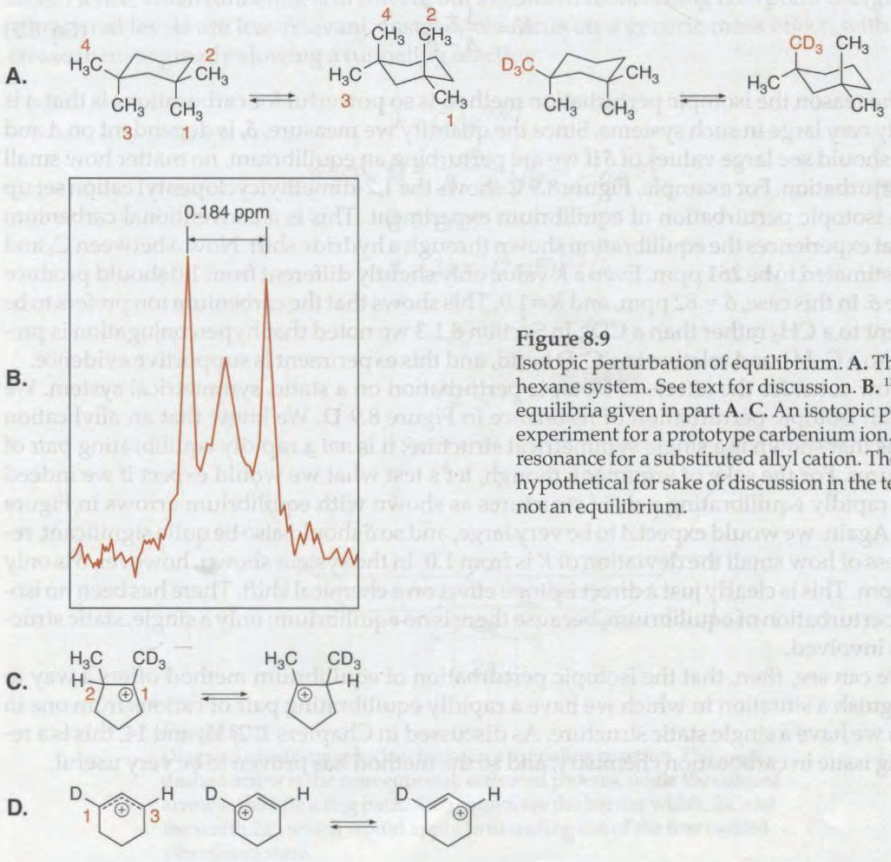


Figure 8.9
Isotopic perturbation of equilibrium. **A.** The 1,1,3,3-tetramethylcyclohexane system. See text for discussion. **B.** ^{13}C NMR spectra used to study equilibria given in part **A**. **C.** An isotopic perturbation of equilibrium experiment for a prototype carbenium ion. **D.** Isotopic perturbation of resonance for a substituted allyl cation. The equilibrium arrows are hypothetical for sake of discussion in the text. It is really resonance, not an equilibrium.

The Trustees of Columbia Univ. Ex. 2047 - Page 27 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

First, consider the chair–flip reaction of 1,1,3,3-tetramethylcyclohexane (Figure 8.9 **A**). For the purpose of discussion we have labeled the four methyl groups, which give a single line in the ^{13}C NMR at room temperature due to a rapid chair–flip. At –110 °C, the ring flip is slow, and we see two methyl signals (axial and equatorial) separated by 9.03 ppm, a value we shall call Δ, with the axial methyls being upfield from the equatorials.

Now consider the situation in which one of the methyl groups is replaced by CD_3, let's say position 4 for discussion. The equilibrium is no longer degenerate; either the structure with the CD_3 axial or the one with it equatorial is preferred. The ^{13}C spectrum *at room temperature* allows us to choose. As shown in Figure 8.9 **B**, we see two sharp lines in the methyl region separated by 0.184 ppm, a value we shall call δ, with a broader line in between them. To assign these peaks, we consider first that C_4, the deuterated carbon, is not seen, because of extensive C–D coupling and diminished nuclear Overhauser effects (NOEs). C_3 is expected to be broadened due to longer range C–D coupling, allowing us to assign the broad, central peak to C_3. Of the sharper peaks, one is due to C_1 and one is due to C_2. Experience tells us that C_3 should be shifted *upfield* by the nearby deuteriums. Since C_3 would otherwise show the same chemical shift as C_1, this allows us to assign C_1 as the downfield member of the two sharp peaks. Thus, C_1 spends more time in the equatorial (recall axial methyls are upfield) position than C_2, establishing that the preferred conformer has the CD_3 axial, as shown in Figure 8.9 **A**. One expects CD_3 to preferentially occupy an axial position relative to CH_3, because as established previously in Eq. 8.6, the CD_3 group is smaller.

Eq. 8.7 allows us to relate the chemical shift separations we have discussed to the equilibrium constant for the process, K. For this case, inserting $\Delta = 9.03$ ppm and $\delta = 0.184$ ppm gives $K = 1.042 \pm 0.001$. This corresponds to an energy difference of 0.024 kcal/mol! The isotopic perturbation of equilibrium method has allowed us to measure a very small deviation of an equilibrium constant from a value of 1.

$$K = \frac{\Delta + \delta}{\Delta - \delta} \qquad \text{(Eq. 8.7)}$$

The reason the isotopic perturbation method is so powerful for carbocations is that Δ is usually *very* large in such systems. Since the quantity we measure, δ, is dependent on Δ and K, we should see large values of δ if we are perturbing an equilibrium, no matter how small the perturbation. For example, Figure 8.9 **C** shows the 1,2-dimethylcyclopentyl cation set up for an isotopic perturbation of equilibrium experiment. This is a conventional carbenium ion that experiences the equilibration shown through a hydride shift. Now Δ between C_1 and C_2 is estimated to be 261 ppm. Even a K value only slightly different from 1.0 should produce a large δ. In this case, $\delta = 82$ ppm, and $K = 1.9$. This shows that the carbenium ion prefers to be adjacent to a CH_3 rather than a CD_3. In Section 8.1.3 we noted that hyperconjugation is preferred to a C–H bond relative to a C–D bond, and this experiment is supportive evidence.

Now consider the effects of isotopic perturbation on a static, symmetrical system. We show an isotopic perturbation of resonance in Figure 8.9 **D**. We know that an allyl cation such as that shown is a single symmetrical structure; it is *not* a rapidly equilibrating pair of structures. For the sake of argument, though, let's test what we would expect if we indeed had a rapidly equilibrating pair of structures as shown with equilibrium arrows in Figure 8.9 **D**. Again, we would expect Δ to be very large, and so δ should also be quite significant, regardless of how small the deviation of K is from 1.0. In the system shown, however, δ is only 0.33 ppm. This is clearly just a direct isotope effect on a chemical shift. There has been no isotopic perturbation of equilibrium, because there is no equilibrium; only a single, static structure is involved.

We can see, then, that the isotopic perturbation of equilibrium method offers a way to distinguish a situation in which we have a rapidly equilibrating pair of cations from one in which we have a single static structure. As discussed in Chapters 1, 2, 11, and 14, this is a recurring issue in carbocation chemistry, and so the method has proven to be very useful.

The Trustees of Columbia Univ. Ex. 2047 - Page 28 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.1.5 Tunneling

Sometimes isotope effects of 50 or larger are observed for comparisons of H vs. D. Such dramatic isotope effects are most often attributed to quantum mechanical tunneling. Originally viewed as an exotic consequence of the nuances of quantum mechanics, detailed study has shown that tunneling, while certainly not common, is frequently involved in organic reactions under conventional conditions. At the end of this section, a Connections highlight gives an example with a common synthetic transformation. Tunneling is very common under cryogenic conditions. Since tunneling will be relevant to topics discussed in subsequent chapters, we make a slight digression here to lay out the basic concepts involved. This will allow us to explain why very large isotope effects are a hallmark of tunneling.

Tunneling is a quantum mechanical phenomenon involving penetration of the wavefunction for the molecule *through* the barrier for the reaction rather than over it. Figure 8.10 illustrates the basic idea. A full description of the physics of tunneling is inappropriate here, but we can gain some valuable insights from analyzing the results of such treatments. One of the simplest analyses of tunneling is due to Bell, and it leads to a simple modification of the Arrhenius equation by a tunneling correction factor, Q, as in Eq. 8.8. Here A is the normal Arrhenius parameter, E is the height of the barrier, m is the mass of the tunneling particle, and $2a$ is the width of the barrier. Through the β term, we can see that the tunneling correction factor is very sensitive to the mass of the tunneling particle. The influence of β is greatest when it is in the exponential, and so tunneling is much more likely for a light particle than a heavy particle. In a proton or hydrogen atom transfer or abstraction, it is reasonable to consider the hydrogen as the tunneling particle, and so we have a very light tunneling particle with a mass of 1. This is why tunneling is usually associated with proton or hydrogen transfers or electron transfers, but there are important exceptions. On going to deuterium, we double the mass, and the exponential dependence on m can produce very large isotope effects. Hence, when tunneling is involved, our arguments concerning zero point energies and vibrational levels are less relevant. Instead, we focus on a generic mass effect, with an increase in mass greatly slowing a tunneling reaction.

$$k = QAe^{-E/RT}$$

$$\text{where, } Q = \frac{e^{\alpha}}{\beta - \alpha}\left(\beta e^{-\alpha} - \alpha e^{-\beta}\right) \qquad \text{(Eq. 8.8)}$$

$$\alpha = E/RT$$

$$\beta = 2a\pi^2 (2mE)^{1/2}/h$$

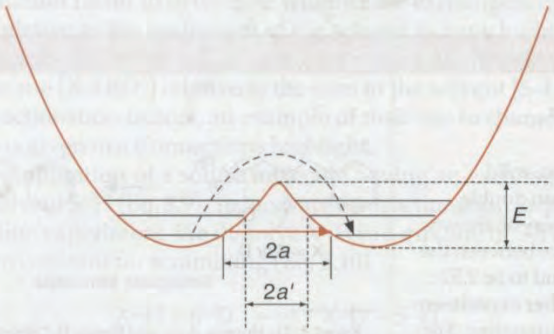


Figure 8.10
Diagram illustrating the key terms in a tunneling reaction. The gray, dashed arrow is the conventional, activated process, while the colored arrow is the tunneling path. Also shown are the barrier width, $2a$, and the width $2a'$, which would apply to tunneling out of the first excited vibrational state.

The Trustees of Columbia Univ. Ex. 2047 - Page 29 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Eq. 8.8 reveals another interesting feature of tunneling. As with m, tunneling will be most effective when the barrier width, $2a$, is small (that is, the barrier is narrow). However, while the β term varies as the square root of m, it depends linearly on the barrier width, $2a$. As such, it is generally true that tunneling is much more sensitive to changes in barrier width than to mass. In fact, we will see that in certain cases particles much heavier than H/D can tunnel, as long as they are tunneling through a narrow barrier.

How do we think about the barrier width? Remember, the x axis in Figure 8.10 is a geometrical coordinate. A narrow barrier implies that nuclei must move only short distances to tunnel from one well to another. So, if we have a reaction in which only small nuclear movements can get us from one minimum to another, then tunneling might be important.

The tunneling correction term Q is *much* less sensitive to temperature than the Arrhenius component of Eq. 8.8. Thus, while conventional reactions slow down dramatically as we lower the temperature, tunneling reaction rates hardly change at all. As a result, tunneling is often much more important at very low temperatures, where even the smallest barrier could not be overcome, but it can be tunneled through.

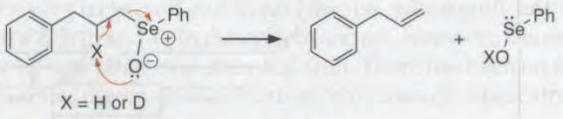
Where does the generally small temperature dependence of tunneling come from? A particle tunneling through a barrier is a quantum mechanical effect, resulting from the fact that the true wavefunction of the reactant is not confined to the energy well of Figure 8.10, but can leak out into the next minimum. In this view, hydrogen tunnels well because its light mass gives it a very large de Broglie wavelength. Such a process should not be temperature dependent. However, consider the consequences of adding thermal energy to Figure 8.10. This could lead to a slight population of the second vibrational level ($n = 1$; remember that the lowest level is $n = 0$, the zero point). In a conventional, activated process, this excitation would have only a small influence on the rate, and that increase will be comparable to the Boltzmann factor disfavoring population of $n = 1$. In other words, this is not an issue for conventional reactions. However, for a tunneling reaction, the difference between $n = 1$ and $n = 0$ could be immense. This is because the *barrier width* is significantly diminished on going to the higher vibrational state; note how much smaller $2a'$ is than $2a$ in Figure 8.10. The shrinking of the barrier width can dramatically increase the tunneling rate, such that even a very small population of an excited vibrational state would dominate the tunneling process. It is in this way that tunneling reactions are sometimes found to have shallow, but non-zero temperature dependencies.

There are certain criteria used to determine if a large H/D isotope reflects a reaction that involves tunneling. First, the difference in the activation energies for the hydrogen- and deuterium-containing compound must be greater than the difference in their ZPEs. Second, tunneling reactions still proceed at low temperatures, as discussed above. This odd temperature dependence is supported by a deviation from linearity in an Eyring plot, where the slope becomes less negative at lower temperatures. Third, anomalously large differences in

Connections

An Example of Tunneling in a Common Synthetic Organic Reaction

The elimination of a selenoxide is a common, mild method for the formation of a carbon–carbon double bond, occuring via a syn-elimination pathway as shown to the right. The activation energy difference between the H- and D-substituted compounds was found to be 2.52 kcal/mol, giving an isotope effect of 74. Other experimental parameters were also found to support tunneling. For example, the A_H/A_D is 0.092, considerably different from 1. Furthermore, a barrier width for the reaction was calculated to be 0.82 Å, definitely less than the length of a common C–H bond (1.1 Å).



Selenoxide elimination

Kwart, L. D., Horgan, A. G., and Kwart, H. "Structure of the Reaction Barrier in the Selenoxide-Mediated Formation of Olefins." *J. Am. Chem. Soc.*, **103**, 1232–1234 (1981).

The Trustees of Columbia Univ. Ex. 2047 - Page 30 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

the Arrhenius pre-exponential factors are found, meaning A_D/A_H does not equal 1 as predicted by collisional theory. Remember, in an experimental determination, the product of Q and A (Eq. 8.8) will be the multiplier of the exponential. Since Q varies considerably for D vs. H, the empirically determined A factor will also vary considerably. Similarly, a large negative entropy of activation is indicative of barrier tunneling, recalling the connection between $\Delta S^{\ddagger}$ and the pre-exponential term. A large negative entropy of activation is interpreted to mean that a precise arrangement of the H must occur to permit tunneling through the barrier. Finally, the geometries of the reactants and products are usually very similar, meaning that the heavy atoms do not significantly change position during the reaction; instead, only the hydrogen moves.

8.1.6 Solvent Isotope Effects

The introduction of an isotope into a specific position (or positions) in a molecule in order to measure an isotope effect can sometimes be a synthetically challenging task. However, when the position to be deuterated is readily exchangeable with the solvent, stirring the reactant in a deuterated protic solvent will deuterate the reactant. For example, alcohol OHs, amine NHs, amide NHs, thiol SHs, etc., will all quite rapidly scramble the hydrogen atoms for deuterium atoms when placed in D_2O or deuterated alcohols such as CH_3OD. Reactions such as these are also excellent candidates for observing **solvent isotope effects**, which are changes in rates or equilibria that are seen in comparing normal vs. deuterated solvents.

Often the solvent is actually involved in the mechanism of the reaction, in which case isotope effects clearly can arise. Furthermore, one sometimes finds a solvent isotope effect when solvation of a transition state is different with the labeled and unlabeled solvent. The isotope effects can be primary, secondary, normal, or inverse depending upon the role that the solvent plays. As expected, direct bond cleavage of a hydrogen or deuterium atom in the solvent or of an exchangeable position in the rate-determining step will lead to a primary kinetic isotope effect. A protonation in an equilibrium prior to a rate-determining step can give either a normal or inverse effect depending upon how the equilibrium is shifted due to the isotopic substitution.

Fractionation Factors

As mentioned above, reactions involving a scrambling of the protons and deuterons between the reactant and solvent are good candidates for significant KIEs. This scrambling does not necessarily lead to a statistical distribution of the exchangeable entities; instead, equilibrium isotope effects are common. In these kinds of reactions, it is generally true that deuterium will prefer the site with the larger force constants. Measurable equilibrium isotope effects most often occur when the two basic centers exchanging the proton (or deuteron) are of different chemical types, such as oxygen or nitrogen. We measure what is known as a **fractionation factor** to determine whether the exchangeable site prefers hydrogen or deuterium relative to the preference of the solvent to have hydrogen or deuterium. The fractionation factors, therefore, tell us about the sum of all the different force constants in the exchangeable site [X–H(D)] relative to the sum in the solvent [S–H(D)]. At the end of the discussion of fractionation factors, an example of their use to characterize the strengths of hydrogen bonds is given in a Connections highlight.

Consider the equilibration of a solute molecule having an exchangeable X–H bond in the exchangeable solvent S–H (Eq. 8.9). To measure the fractionation factor, denoted as ϕ, we perform a competition experiment. We dissolve X–H in a mixture of S–H and S–D and measure the equilibrium constant for scrambling (Eq. 8.10).

$$\text{X–H} + \text{S–D} \rightleftharpoons \text{X–D} + \text{S–H} \qquad \text{(Eq. 8.9)}$$

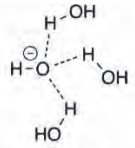
$$K_{eq} = \phi = \frac{[\text{S–H}][\text{X–D}]}{[\text{S–D}][\text{X–H}]} = \frac{\dfrac{[\text{X–D}]}{[\text{X–H}]}}{\dfrac{[\text{S–D}]}{[\text{S–H}]}} \qquad \text{(Eq. 8.10)}$$

The Trustees of Columbia Univ. Ex. 2047 - Page 31 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Table 8.1
Fractionation Factors*

Bond type	ϕ
RO–H(D)	1.0
HO^-	0.5
$RO–H_2(D_2)^+$	0.69
$R_3C–H(D)$	0.69
$R_2N–H(D)$	0.92
$R_3N–H(D)^+$	0.97
RS–H(D)	0.42

*Gold, V. "Proteolytic Processes in H_2O–D_2O Mixtures." *Adv. Phys. Org. Chem.*, 7, 259 (1969).



Hydrogen bonding to hydroxide

A fractionation factor greater than 1 means that the deuterium prefers site X over site S. Conversely, values less than 1 mean the deuterium prefers the solvent. Table 8.1 lists a few fractionation factors where the solvent is water. Alcohols statistically distribute deuterium with water ($\phi = 1.0$) because the vibrational modes in alcohols and water are all nearly identical. Carbon, nitrogen, and sulfur show a preference for hydrogen, meaning that the overall force constants are larger in water. Hydronium and hydroxide both show a preference for hydrogen. The bond in hydronium is predicted to be weaker than in water due to the positive charge, and since deuterium prefers sites with stronger bonds it makes good sense that the fractionation factor is less than 1.

Yet, it may seem odd that deuterium also prefers water over hydroxide. To understand this, remember that the deuterium concentrates where the overall force constants are larger, including the force constants for all intramolecular and intermolecular vibrations. Hence, we must examine hydroxide and its interactions with water. Approximately three hydrogen bonds are formed to the oxygen of hydroxide in water. These hydrogen bonds from water to hydroxide lower the force constants for the O–H bonds within the three respective waters. Apparently, this results in an overall preference for hydrogen in hydroxide. This means that the force constants for water hydrogen bonded to just water are larger overall than those for the hydroxide hydrogen bonded to water. In fact, if we assume a fractionation factor of 1.2 for the O–H bond in hydroxide and three fractionation factors of 0.7 for each hydrogen bond from water, the product of these four ($1.2 \times 0.7 \times 0.7 \times 0.7$) leads to the observed fractionation factor. Hence, we always use the product of fractionation factors for all the individual exchangeable sites to get the overall fractionation factor.

We can use the ratio of fractionation factor products to predict relative equilibrium constants for reactions in H_2O or D_2O. Consider the dissociation of an acid in H_2O or D_2O. Eq. 8.11 tells us that the ratio of equilibrium constants for a reaction in pure D_2O (K_D) to that in pure H_2O (K_H) is the ratio of the mathematical products of fractionation factors for the products (ϕ_i^P) and reactants (ϕ_j^r). Letters i and j are running tags of each exchangeable site in the product and reactant, respectively. In essence, the ratio between the equilibrium constants in these two solvents reflects the relative ability of the products and reactants to accept deuterium over hydrogen. We ask you to derive Eq. 8.11 in Exercise 4 at the end of the chapter.

$$\frac{K_D}{K_H} = \frac{\Pi_i^P \phi_i^P}{\Pi_j^r \phi_j^r} \qquad \text{(Eq. 8.11)}$$

Extending the concept to kinetics requires us to remember the tenets of transition state theory (TST). With TST we assume that there is an equilibrium between the transition state and the reactants. Therefore, we write Eq. 8.12 analogous to Eq. 8.11, where k_D is for the reaction with deuterium and k_H is for the reaction with hydrogen. As a result, we obtain the inverse of the kinetic isotope effect, because KIE = k_H/k_D.

$$\frac{k_D}{k_H} = \frac{\Pi_i^\ddagger \phi_i^\ddagger}{\Pi_i^r \phi_i^r} \qquad \text{(Eq. 8.12)}$$

Proton Inventories

Competition experiments between S–H and S–D for scrambling of an exchangeable site on a reactant X–H can be used to determine how many protons are being transferred or associated with rehybridation during the rate-determining step of a reaction. We demonstrate this below by examining an enzymatic reaction in a Connections highlight. To understand this experiment, we must consider measuring the rate constant for a reaction involving a change in the X–H(D) bond, where the molecules in solution are actually a mixture of X–H and X–D. The rate constant would be a weighted mean of the rate constants for the X–H and X–D molecules (Eq. 8.13). Letter n in Eq. 8.13 is the mole fraction of D at the exchangeable site, established both by the mole fraction of D in the solvent and the equilibrium fractionation factor for placing D at this site. We define a kinetic fractionation factor for the reaction as

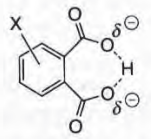
The Trustees of Columbia Univ. Ex. 2047 - Page 32 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

Using Fractionation Factors to Characterize Very Strong Hydrogen Bonds

Recall from Chapter 3 the debate in enzymology about the relevance of a particular type of hydrogen bond known as a "low-barrier hydrogen bond" (LBHB) or "short–strong hydrogen bond". These hydrogen bonds can possess bond strengths on the order of 40 kcal/mol in the gas phase. In these bonds the barrier to hydrogen exchange between the donor (Dn) and acceptor atom (:Ac) is close to or lower than the ZPE of the bonds to the H. The force constant for the stretch involving H is smaller for the LBHB compared to a normal hydrogen bond, because the potential well that describes that bond vibration is wider with a LBHB.

One way that is used to characterize these hydrogen bonds is to measure a fractionation factor. Given the above analysis, a low isotope fractionation factor is predicted, because the force constant is smaller for the LBHB (look back at the potential wells for LBHBs in Chapter 3). For example, the observation that the fractionation factors for various substituted phthalate monoanions were between 0.5 to 0.6 was used to support the existence of LBHBs in these structures.



Strong hydrogen bond system

This example highlights the fact that we want to consider the force constants for vibrations to predict the site that the deuterium will prefer. LBHBs are very strong hydrogen bonds, but the force constant for the vibration of the hydrogen between the heavy atoms is low. Hence, fractionation factors are less than 1. The deuterium actually prefers the solvent.

Shan, S.-O., Loh, S., and Herschlag, D. "The Energetics of Hydrogen Bonds in Model Systems: Implications for Enzymatic Catalysis." *Science*, **222**, 97–101 (1996).

$\phi = k_D/k_H$. Here again the ratio is the inverse of the definition of the isotope effect. This leads to Eq. 8.14 and subsequently to Eq. 8.15 upon rearrangement. Eq. 8.15 makes good sense; when no D_2O is added, $n = 0$ and $k_n = k_H$. Conversely, when the reaction is run in pure D_2O, $n = 1$ and $k_n = k_D$.

$$k_n = k_H(1 - n) + k_D(n) \qquad \text{(Eq. 8.13)}$$

$$k_n = k_H(1 - n) + \phi k_H(n) \qquad \text{(Eq. 8.14)}$$

$$k_n = k_H(1 - n + n\phi) \qquad \text{(Eq. 8.15)}$$

Using analogous logic, we rewrite Eqs. 8.11 and 8.12, giving Eqs. 8.16 and 8.17, respectively.

$$\frac{K_n}{K_H} = \frac{\Pi_i^P(1 - n + n\phi_i^P)}{\Pi_j^r(1 - n + n\phi_j^r)} \qquad \text{(Eq. 8.16)}$$

$$\frac{k_n}{k_H} = \frac{\Pi_i^{\ddagger}(1 - n + n\phi_i^{\ddagger})}{\Pi_i^r(1 - n + n\phi_i^r)} \qquad \text{(Eq. 8.17)}$$

Eq. 8.17 tells us that ratio of rate constants in mixtures of protio and deuterio solvents relative to a pure protio solvent depends upon each exchangeable site that has a fractionation factor different from unity between the transition state and the reactant. In practice, only those exchangeable sites that are undergoing either a bond cleavage or a rehybridization will have fractionation factors that differ between reactant and transition state. Hence, they are the only sites that typically need to be considered as contributing to Eq. 8.17. We call these protons ones that are "moving" or are "in flight" during the reaction. Very often it is assumed that the fractionation factors for the exchangeable sites on the reactant are close to unity because the respective bond strengths relative to the bond strengths in the solvent are

The Trustees of Columbia Univ. Ex. 2047 - Page 33 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

similar, an assumption that is good for simple O–H and N–H bonds (see Table 8.1). This reasoning allows us to neglect the denominator of Eq. 8.17, thus leading to Eq. 8.18, where each term represents one of the protons that is moving in the transition state.

$$\frac{k_n}{k_H} = (1 - n + n\phi_1)(1 - n + n\phi_2)(1 - n + n\phi_3) \ldots \qquad \text{(Eq. 8.18)}$$

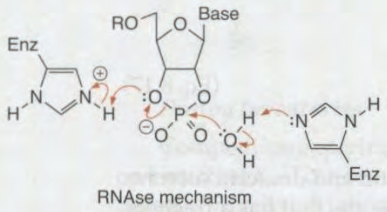
Each ϕ is the fractionation factor for a given proton that is moving—that is, the inverse of the isotope effect for each proton that is moving. If only one proton moves, a plot of n versus k_n/k_H is linear; if two protons move, the plot is quadratic in n; and if three protons move, the plot is cubic in n, etc. Hence, the term **proton inventory** is applied to such an experiment and plot. The shape of the curve allows us to inventory the number of protons that are moving, and fitting the curve can extract the individual fractionation factors.

Many reaction mechanisms involve the movement of one or more protons, so this technique is applicable to a vast number of reactions, particularly so in enzymology, where catalysis often involves the coupling of several proton transfers in a single step (see Chapter 9). Therefore, the proton inventory is an extremely powerful physical organic chemistry technique that has found use in an untraditional physical organic field.

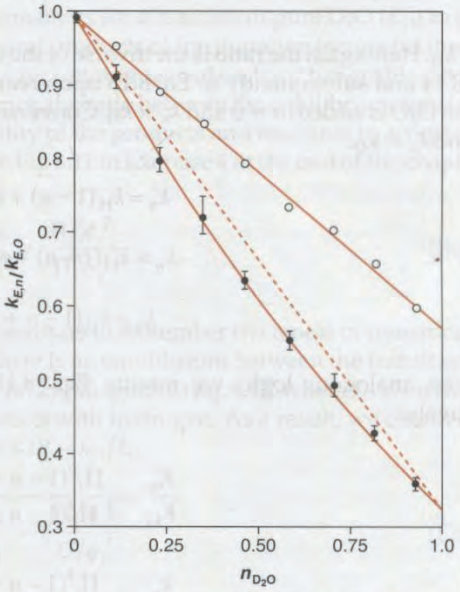
Connections

The Use of a Proton Inventory to Explore the Mechanism of Ribonuclease Catalysis

The enzyme ribonuclease A cleaves single-stranded RNA and opens up 2′,3′-cyclic phosphodiesters. The classic mechanism for the ring opening involves an imidazole acting as a base to deprotonate water during nucleophilic attack, and an imidazolium protonating the leaving group (see below). If such a mechanism is operative, two protons are moving in the rate-determining step, and hence a two proton inventory should be found. Indeed, when plotting the catalytic rate constant ($k_{E,n}$) for this ring opening in various mixtures of D_2O and H_2O relative to the rate constant in pure H_2O ($k_{E,O}$), a curved plot was found, as shown to the right. The plot was fit using two ϕ values, both of 0.58. The inverse of the ϕ values can be considered as the isotope effect for each proton that is moving, giving in this case two isotope effects of 1.75. The results clearly support two simultaneous proton transfers in the rate-determining step.



RNAse mechanism



Closed circles represent the data used to fit a proton inventory of two protons moving in the rate-determining step. The open circles are the square root of the values for the closed circles. The dashed line simply shows a linear connection between the first and last points, thereby accentuating the curvature in the plot of the closed circles.

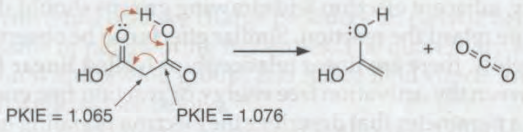
Matta, M. S., and Vo, D. T. "Proton Inventory of the Second Step of Ribonuclease Catalysis." *J. Am. Chem. Soc.*, **108**, 5316 (1986).

The Trustees of Columbia Univ. Ex. 2047 - Page 34 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

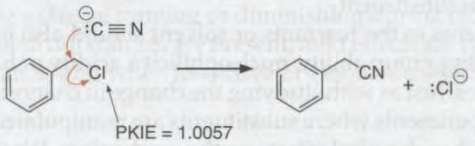
8.1.7 Heavy Atom Isotope Effects

Our discussion of isotope effects has focused upon hydrogen versus deuterium. Isotope effects for other elements are possible, however, and experiments involving isotopes of C, O, N, and Cl are somewhat common. The problem becomes one of the sensitivity of the technique used to measure the isotope effects, because they are very small (see the earlier Going Deeper highlight entitled "An Ingenious Method for Measuring Very Small Isotope Effects", page 432). Recall that the stretching frequency of the bond undergoing cleavage in an experiment involving a primary kinetic isotope effect is given by Eq. 8.2, where the reduced mass of the bond is in the denominator. The difference in frequency of bonds with different isotopes arises from differences in the reduced masses. When comparing hydrogen to deuterium, there is a 100% increase in mass, which has a reasonable effect on the size of the two reduced masses. However, when comparing ^{13}C to ^{12}C, there is only an 8% change in mass, which has little effect on the reduced masses, and therefore very small primary isotope effects are found. Furthermore, secondary isotope effects are almost completely negligible.

Consider two examples—a decarboxylation and an S_N2 reaction. The primary kinetic isotope effects (PKIE, k_{12}/k_{14} for ^{14}C relative to the natural abundance C, which is mostly ^{12}C) at the methylene and carboxyl carbons in the decarboxylation of malonic acid are 1.076 and 1.065, respectively (Eq. 8.19). The values are very close, indicating that a bond to each of these carbons breaks in the rate-determining step. The ^{37}Cl isotope effect (k_{35}/k_{37}) in the displacement of chloride from benzyl chloride by cyanide is 1.0057, indicating that the bond to chlorine breaks in the rate-determining step (Eq. 8.20).



(Eq. 8.19)



(Eq. 8.20)

8.1.8 Summary

The study of isotope effects is extremely valuable in deciphering mechanisms. Such studies are necessary whenever we suspect that a bond to a hydrogen is moving or rehybridizing during a rate-determining step. A kinetic isotope effect greater than 1 is good evidence of a bond cleavage or rehybridization. A kinetic isotope effect less than 1 is good evidence of a rehybridization to a bond that has one or more stiffer vibrational modes.

8.2 Substituent Effects

So far, we have considered two types of experiments for studying reaction mechanisms. First was an analysis of kinetics (Chapter 7), which can give the order of reactants involved in a mechanism prior to or during the rate-determining step. Second, we now have a method to determine if a bond to hydrogen has been broken or rehybridized. This latter experiment gives us some limited structural information about the activated complex.

More in-depth analysis of the structure of the transition state is obtained from studies of substituent effects. A **substituent** is any group on a molecule, such as a methyl, nitro, hydroxy, etc. A **substituent effect** is the manner in which the reactivity of the molecule changes when substituents are changed. Note the conceptual difference here from the two methods

The Trustees of Columbia Univ. Ex. 2047 - Page 35 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

presented thus far. In order to investigate the mechanism of a reaction using substituent effects, we are going to study a *different* reactant, one in which a substituent has been added or changed. It should be appreciated from the outset that this is a fundamentally different approach (we don't consider the H/D substitution associated with isotope effect studies to be a substituent effect), and one that is considerably less direct than kinetic or isotope effect studies. As such, studies of substituent effects are susceptible to misinterpretation and abuse; caution is in order. Nevertheless, studies of substituent effects represent a key pillar of physical organic chemistry. When they are carefully applied, substituent effects are used to determine how the free energies of reaction and activation vary as a function of chemical structure. In either a kinetic or thermodynamic analysis, we change the structure of the reactant or solvent and see how this changes the function (reactivity) of the molecule; hence the terms **structure–function relationship** or **structure–reactivity relationship**. In the context of pharmaceutical studies, where activity, bioavailability, and other medicinally related data are collected as a function of the chemical structure of the drug, the substituent effect studies are referred to as **structure–activity relationships (SARs)**. Most important for physical organic chemistry, the nature of the structure–reactivity relationship is often informative about the mechanism of the reaction.

The logic of conventional structure–function relationships should be familiar. Experiments can be designed to test for changes in charges along a reaction coordinate by interchanging functional groups, such as switching an electron donating group to an electron withdrawing group. If a positive charge is being created in a rate–determining step, then adjacent electron donating groups should stabilize the transition state and the reaction should speed up. Conversely, adjacent electron withdrawing groups should destabilize the transition state and therefore retard the reaction. Similar effects can be observed for equilibria.

As we will see below, there are linear relationships (called **linear free energy relationships** or **LFERs**) between the activation free energy or reaction free energy change induced by a substituent and a parameter that describes the electron donating or electron withdrawing characteristics of the substituent.

Changing substituents in the reactants or solvent should also influence the steric congestion, solvation, leaving group ability, nucleophilicity, acidity or basicity, and a variety of other chemical attributes. Just as with studying the change in charge along a reaction coordinate, we can design experiments where substituents are manipulated in order to determine the influence of these other chemical effects on the mechanism. We will show that there are LFERs for activation free energies and reaction free energies with parameters that describe all these chemical effects. In each analysis, the goal of changing substituents is to determine how that change affects the activation free energy (and thus the structure of the activated complex), or affects the equilibrium for the reaction.

As mentioned above, there are LFERs that correlate free energies with parameters that describe the character of substituent effects. It has been experimentally determined that in most cases, individual substituents influence reactions in a consistent manner. For example, electron withdrawing groups are consistently electron withdrawing, no matter what reaction they are involved in. What varies from one reaction to another is the magnitude of this influence. Sometimes a reaction is very sensitive to changes in substituents, and sometimes there is little or no effect.

When performing structure–function experiments we must remember that any structural change results in a perturbation of the energy surface. You can't do a structure–function study without changing structures, and hence the energy surface. Such perturbations for S_N2 and S_N1 reactions were analyzed in Section 7.8.1. In that example, the change of hydrogen substituents to alkyl substituents shifted the position of the S_N2 transition state on a three-dimensional reaction coordinate diagram. There was a point where additional alkyl substituents retarded the S_N2 route enough, and sped up the S_N1 route to such an extent that the mechanism changed. The interchange of substituents is always susceptible to such changes to the energy surface, and we must always be alert to a possible mechanism change.

The Trustees of Columbia Univ. Ex. 2047 - Page 36 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

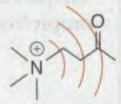
In order to design successful experiments by varying substituents, we should start with a good understanding of how different groups influence structure and bonding and of the various mechanisms by which substituents can influence the rate of a reaction.

8.2.1 The Origin of Substituent Effects

In Chapter 1 two different views of bonding were described: valence bond theory (VBT) and molecular orbital theory (MOT). In MO theory there are orbitals that are spread out over all atoms in a molecule. When adding or changing substituents, new molecular orbitals are created that involve the atomic orbitals on the substituents. Although this theory can be used to analyze substituent effects successfully, the concept of delocalized molecular orbitals presents difficulties in visualizing localized changes in a molecule brought about by a substituent change. Thus, substituent effects are almost always discussed in terms of our hybrid VBT/MOT approach, wherein localized bonding effects and isolated bonds between atoms are considered.

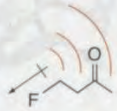
Field Effects

When one substituent is changed to another, bond dipoles can change in magnitude and direction, or formal charges can change. Localized charges resulting from bond dipoles and formal charges present electric fields that can have an effect on a remote site in a molecule. A **field effect** is one that originates from such a through-space interaction. For example, a quaternary ammonium with a full positive charge produces an electric field that can influence distant atoms in the same or neighboring molecules. The quaternary ammonium group is also a strongly electron withdrawing group, and hence field effects are often very hard to separate from inductive effects (see below).



Field effects

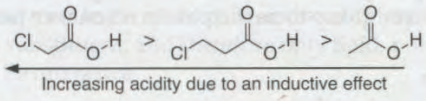
Usually, however, the field effect is associated with a bond dipole that is aligned so as to stabilize or destabilize a charge forming or diminishing during crossing of the transition state. Except in cases where full charges are present, field effects are typically small and rapidly diminish with distance, and when inductive or resonance effects are also present, the latter dominate.



Dipole field effects

Inductive Effects

An **inductive effect** (introduced in Chapter 1) results from the ability of an atom or group of atoms to withdraw or donate electrons through σ bonds. Strongly electronegative atoms or groups are best at drawing electrons to themselves (see Section 1.1.8). Conversely, a group can donate electrons via the σ bond framework. The further away the group from the site of reaction, the lower its ability to affect the reaction via induction. For example, chloroacetic acid is substantially more acidic than acetic acid. However, the increase in acidity induced by the electronegative chlorine diminishes the further away from the carboxyl it is positioned (see other examples in Chapter 5, and recall from Chapter 5 that entropy effects are likely important in this example, too). An interesting example of an inductive effect is given in the Connections highlight below, where an important biomaterial is examined.



Convenient scales have been developed to indicate the relative inductive effects of substituents (see Tables 1.1 and 1.2 for atom and group electronegativities). In the present chapter, however, we will define a new scale called sigma (σ), to relate the different electron donating or electron withdrawing abilities of atoms and groups.

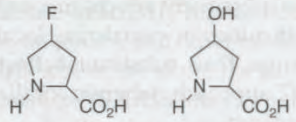
The Trustees of Columbia Univ. Ex. 2047 - Page 37 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

A Substituent Effect Study to Decipher the Reason for the High Stability of Collagen

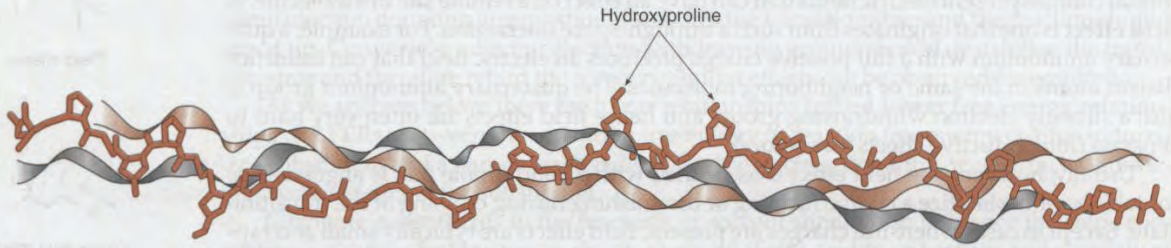
Collagen is the most abundant protein in animals. It forms connective tissue of high tensile strength and thermal stability, such as cartilage. Collagen consists of three protein strands wrapped together to form a tight triple helix (see below). The sequences of the individual strands have glycine as every third amino acid with intervening prolines and hydroxyprolines. For some time it was thought that the hydroxyprolines led to the high structural stability by being involved in a network of hydrogen bonds between strands. However, to test whether the inductive nature of the hydroxyl substituent influenced the stability, this substituent was switched to fluorine, a group that is poor at making hydrogen bonds (see Chapter 3) but is still electronegative.

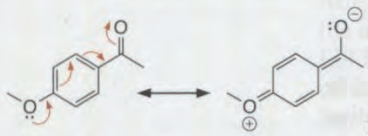
It was found that the circular dichoism spectra (see Chapter 6) are identical whether the strands possess fluoroproline or hydroxyproline. In fact, it was found that the fluoroproline-containing strands created even more stable collagen. The conclusion was that the trans conformation of the hydroxyprolyl peptide bond (see the Connections highlight in Section 1.1.10 for definitions of cis/trans peptide bonds), required in collagen formation, is preferred with increasing electron withdrawing groups, thereby stabilizing the overall peptide structure. This simple structure–function study greatly increased our knowledge of a very important biomaterial.



Fluoroproline Hydroxyproline

Holmgren, S. K., Taylor, K. M., Bretscher, L. E., and Raines, R. T. "Code for Collagen's Stability Deciphered." *Nature*, **392**, 666 (1998).





A common resonance effect

Resonance Effects

A **resonance effect** reflects the ability of an atom or group of atoms to withdraw or donate electrons through π bonds. This is also sometimes referred to as a **mesomeric effect** in older literature. This effect is solely a valence bond concept that describes the electronic structure of a molecule when more than one canonical structure of a molecule can be drawn (see Chapter 1 again). Resonance effects can be important for understanding charge distributions in molecules that result from substituent changes quite remote from the site of reaction. A typical example is shown in the margin, in which methoxy induces increased negative charge on a carbonyl group remote on a benzene ring. Scales have been developed that relate the ability of an atom or group to participate in resonance (see below).

Polarizability Effects

Another change that results when substituents are interchanged is the polarizability of the molecule. The polarizability of a molecule is defined as the extent to which the electron cloud of the structure can undergo distortion, and the polarizability of molecules and groups was extensively discussed in Section 1.1.12. A hard compound, in which the electron cloud is tightly held, is not very polarizable (see the discussion of hard and soft acids and bases in Section 5.6.1). Conversely, a soft compound is one in which the electron cloud is more diffuse, and therefore polarizable. Differences in polarizability influence nucleophile

The Trustees of Columbia Univ. Ex. 2047 - Page 38 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

and nucleofuge properties, and relative solvation. For example, a sulfide is more polarizable than an alkoxide, making the sulfide a better nucleophile and a better leaving group, because in both leaving group departure and nucleophilic attack the electron clouds are distorting.

Steric Effects

Steric effects can also have a dramatic influence on the rate of a reaction, as well as conformations (see Chapter 2). Large atoms or groups influence the manner in which molecules collide, often deflecting the reactants away from the angle or depth of collision necessary for the reaction to occur. For example, the S_N2 reaction becomes slower due to steric effects as the carbon with the leaving group is more highly substituted with alkyl groups (see Chapter 11). The nucleophile cannot penetrate to the carbon with the leaving group when larger groups are attached. Again, scales have been developed to measure steric effects. You have already been introduced to one such scale; the *A* values given in Section 2.3.2 indicated the bias for equatorial versus axial substitution on a cyclohexane ring. A new scale, called the Taft parameters, is given below.

Solvation Effects

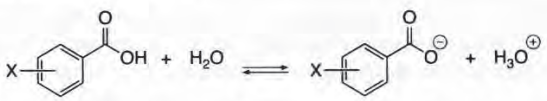
Finally, experiments involving changes in substituents are not just confined to the reactants. Changing groups in the solvent or completely switching solvents can also be considered to be a substituent effect. The five parameters—field, inductive, resonance, polarizability, and steric—all still play roles. However, now field effects can become quite important because the solvent dipoles can become directly involved in the reaction. The effects that changing the solvent have on the activation or reaction free energies are called **solvent effects**, to specifically distinguish them from substituent effects.

8.3 Hammett Plots—The Most Common LFER. A General Method for Examining Changes in Charges During a Reaction

Substituent effects come in the five kinds mentioned previously: field, resonance, inductive, polarizability, and steric. The first four can all be considered as electronic effects, whereas steric effects largely depend upon the size of the substituent. Hence, there is the often quoted notion that "trends in chemistry can be explained by either electronic or steric effects". However, even steric effects are electronic in origin. They are repulsions brought about by atoms approaching within their respective van der Waals contact distances, where the electron clouds of the groups involved repel each other. Most chemists, however, separate the concepts of sterics and electronics.

8.3.1 Sigma (σ)

To picture how reaction mechanisms vary as a function of the electronic changes induced by substituents, chemists use **Hammett plots**. Hammett defined a scale that measured the ability of substituents to influence the acidity of benzoic acid (Eq. 8.21). The substituents are placed meta or para to the carboxylic acid to eliminate any possible steric effects associated with an ortho substituent, and therefore only field, polarizability, inductive, and resonance effects should be operative.



(Eq. 8.21)

Eq. 8.22 was used to define a **substituent parameter** σ_X for each substituent X. Hydrogen is the reference substituent. Thus, all acidity equilibrium constants for the substituted benzoic acids are compared to the equilibrium constant for benzoic acid itself ($\sigma_H = 0$ by defi-

The Trustees of Columbia Univ. Ex. 2047 - Page 39 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

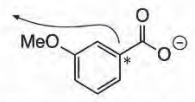
Table 8.2
σ Values for Several Commonly Encountered Substituents*†

Substituent	σ_{meta}	σ_{para}	σ^+	σ^-
$-NH_2$	−0.09	−0.30	−1.3	
−OH	0.13	−0.38	−0.92	
$-OCH_3$	0.10	−0.12	−0.78	
$-C(CH_3)_3$	−0.09	−0.15	−0.26	
$-CH_3$	−0.06	−0.14	−0.31	
$-Si(CH_3)_3$	−0.04	−0.17		
$-NHC(O)CH_3$	0.14	0.0	−0.6	0.47
−Ph	0.05	0.05	−0.18	0.08
−I	0.35	0.18	0.13	
−Br	0.37	0.26	0.15	
−Cl	0.37	0.24	0.11	
−F	0.34	0.15	−0.07	
$-C(O)CH_3$	0.36	0.47		0.82
$-OC(O)CH_3$	0.39	0.31	0.18	
−C(O)OH	0.35	0.44		0.73
$-CF_3$	0.46	0.53		0.74
−CN	0.62	0.70		0.99
$-NO_2$	0.71	0.81		1.23
$-N(CH_3)_3^+$	0.99	0.96		

*Ritchie, C. D., and Sager, W. F. "An Examination of Structure–Reactivity Relationships." *Prog. Phys. Org. Chem.*, **2**, 323 (1964).
†σ^* and σ^- are for para substitution.

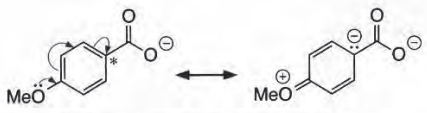
nition). Table 8.2 gives a number of σ values (σ^+ and σ^- values will be discussed later in this chapter). More extensive compilations are given in references at the end of the chapter. A different set of σ values is necessary for each different position on the benzoic acid, because the ability of a substituent to influence the acidity of benzoic acid depends upon its position relative to the carboxyl group. When σ is negative, the substituted benzoic acid is less acidic than benzoic acid itself, and when σ is positive, the substituted benzoic acid is more acidic. Note that electron donating groups have negative σ values and electron withdrawing groups have positive σ values. This trend is exactly as predicted, because electron withdrawing groups should stabilize the negative charge of the carboxylate and electron donating groups should destabilize this charge.

$$\log\left(\frac{K_X}{K_H}\right) = \sigma_X \qquad \text{(Eq. 8.22)}$$



Pulling electrons via induction

One interesting feature about the ionization of benzoic acids becomes apparent upon studying Table 8.2. The σ_{para} values generally reflect a larger influence of the substituent at this position than do the σ_{meta} values (the absolute value of $\sigma_{para} > \sigma_{meta}$), even though the meta position is closer to the ionizing group than is the para position. This difference in part reflects the ability of the para position to influence charge at the starred carbon (see margin) via resonance, an influence that is not possible for the meta position. This difference is clearly evident with the hydroxy and methoxy groups. In the meta position these groups are found to be electron withdrawing toward the starred carbon, an inductive effect. In the para position, these groups are electron donating, a resonance effect. Note that while this is a reso-



Donation of electrons via resonance

The Trustees of Columbia Univ. Ex. 2047 - Page 40 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

nance effect, it is *not* resonance with the carboxylate anion. The negative charge of benzoate anion is not in conjugation with the aromatic ring, and so cannot be stabilized by resonance.

8.3.2 Rho (ρ)

Now that a scale for substituent effects has been established, we can determine if other reactions respond to substituents the way benzoic acid does. The goal is to use benzoic acid ionization as a reference reaction that creates a negative charge and compare other reactions to it as a means to see if they also create a negative charge, or conversely, a positive charge. Furthermore, we want to determine if different reactions are more or less sensitive to the substituents than are the acidities of benzoic acid derivatives. To do this, we use the Hammett relationships given in Eqs. 8.23 and 8.24 for thermodynamic and kinetic analyses, respectively. To determine ρ, plot $\log(K_X/K_H)$ or $\log(k_X/k_H)$ versus σ_X for the new reaction under study. Rho (ρ) is simply the slope of this plot.

$$\log\left(\frac{K_X}{K_H}\right) = \rho\sigma_X \qquad \text{(Eq. 8.23)}$$

$$\log\left(\frac{k_X}{k_H}\right) = \rho\sigma_X \qquad \text{(Eq. 8.24)}$$

Rho describes the sensitivity of the new reaction to substituent effects relative to the influence of the substituent on the ionization of benzoic acid. It is called the **reaction constant** or **sensitivity constant** for each new reaction under study. The following values of ρ lead to the associated conclusions:

a. When $\rho > 1$, the reaction under study is more sensitive to substituents than benzoic acid, and negative charge is building during the reaction.

b. When $0 < \rho < 1$, the reaction is less sensitive to substituents than benzoic acid, but negative charge is still building.

c. When ρ is equal to or close to 0, the reaction shows no substituent effects.
This can mean no change in charge occurs in the equilibrium or rate-determining step.

d. When ρ is negative, the reaction is creating positive charge.

Figure 8.11, for example, shows a plot of the log of ionization constants of substituted phenylacetic acids in water, and the ionization of substituted benzoic acids in ethanol. The ρ for phenylacetic acid derivatives is 0.56, while that for benzoic acid derivatives in ethanol is

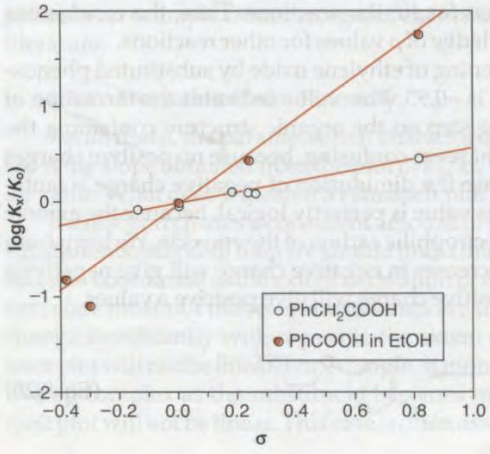


Figure 8.11
Hammett plots. For phenylacetic acid ionization constants and for benzoic acid in ethanol. Data to generate these plots were taken from Bright, W. L., and Briscoe, H. T. "The Acidity of Organic Acids in Methyl and Ethyl Alcohols." *J. Phys. Chem.*, **37**, 787 (1933), and Dippy, J. F., and Williams, F. R. "Chemical Composition and Dissociation Constants of Mono-Carboxylic Acids. Part I. Some Substituted Phenylacetic Acids." *J. Chem. Soc.*, 161 (1934).

The Trustees of Columbia Univ. Ex. 2047 - Page 41 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

2.25. These indicate much lower and higher sensitivities of the acidities to the substituent effects, respectively. The smaller ρ for phenylacetic acid derives from the more remote position of the substituents to the carboxyl group relative to that in benzoic acid. The larger ρ value for the ionization of benzoic acid in ethanol reflects reduced stabilization of the negative charge in the carboxylate product in ethanol relative to that in water (remember $\rho = 1$ in H_2O). Hence, the substituents become more important in stabilizing or destabilizing the negative charge in the product. Interestingly, the lines are linear even though the ρ values are derived from σ-values of benzoic acid ionization in water. The linear behavior is indicative of the general mathematics of LFERs, which we discuss in Section 8.6.1.

Very often the magnitude of ρ is used as a guide to the amount of charge that has developed in a transition state or in the product. Such an interpretation must be made with caution, because ρ really only relates the sensitivity of ionization to the substituents. In the examples just discussed, the amount of charge on the products is the same in all three reactions (phenylacetic acid, and benzoic acid in ethanol or water), but the ρ values are significantly different.

8.3.3 The Power of Hammett Plots for Deciphering Mechanisms

More interesting than the ionization of carboxylic acids is the application of Hammett plots to reactions that have no resemblance to an acid–base reaction. In fact, as has been alluded to, the σ values can be used to analyze the kinetics of reactions, even though they are based upon the analysis of the thermodynamics of an acid dissociation reaction. When a linear Hammett correlation is found for the kinetics of a reaction, the ρ value gives us information about the change in charge during the rate-determining step. We use the four scenarios labeled a–d in the preceding section to draw conclusions about the new reaction under study. Let's consider a few organic chemistry examples in detail.

The rate constants for the base-induced hydrolysis of methyl benzoate in water produce a ρ value of 2.23. This value tells us that the rate-determining step for this hydrolysis creates negative charge. Mechanisms involving nucleophilic displacement on the methyl group or addition to the carbonyl (Figures 8.12 **A** and **B**) are both consistent with this ρ value, because a full negative charge is created on the product. Here, the ρ value supports either mechanism, and other techniques are needed to distinguish the two possibilities.

The ρ value for the reaction of diphenylmethyl chloride with ethanol is –5.09. A large and negative ρ value indicates significant positive charge building in the rate-determining step. Both an S_N1 and S_N2 pathway create positive charge on the organic structure containing the substituents (Figures 8.12 **C** and **D**). It is the magnitude of the ρ value in this case that is informative. Such a large negative ρ is consistent with an S_N1-like mechanism, wherein a carbocation is forming. It is inconsistent with an S_N2 mechanism involving little or no change in charge on the carbon undergoing substitution.

You might be wondering what are considered large, medium, and small ρ values. As with many parameters in chemistry, there is no certain cut-off, but instead we consider a ρ value large or small relative to other ρ values for similar reactions. Thus, the conclusions drawn above are partially based upon knowledge of ρ values for other reactions.

As a final example, consider the ring opening of ethylene oxide by substituted phenoxides (Eq. 8.25). The ρ value for this reaction is –0.95. This value indicates the formation of positive charge during the rate-determining step on the organic structure containing the substituents. At first this interpretation might seem confusing, because no positive charges are involved in this reaction at all. In this case the diminution of negative charge is tantamount to the creation of positive charge. This value is perfectly logical, because the anionic oxygen of the nucleophile is adding to the electrophilic carbon of the epoxide. We learn from this example that we must be aware that decreases in negative charge will give negative ρ values, and correspondingly decreases in positive charge will give positive ρ values.



(Eq. 8.25)

The Trustees of Columbia Univ. Ex. 2047 - Page 42 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

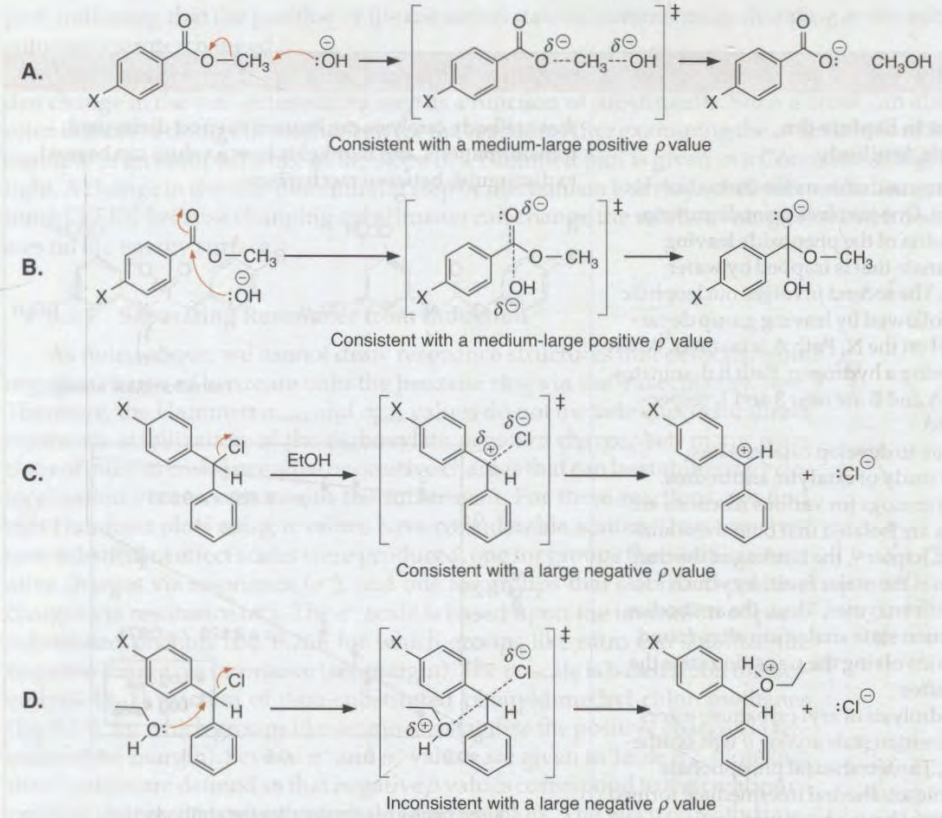


Figure 8.12
Examples of reactions and expected ρ values. A ρ value of 2.33 for the reactions shown in **A** and **B** does not distinguish between these two mechanistic alternatives. A ρ value of –5.09 for the first step of the substitution reaction given in **C** and **D** supports alternative **C**.

These examples highlight the power of LFERs, particularly Hammett plots. They indicate the change in charge when comparing the reactant to the transition state or product. This physical organic technique has often been applied (or in some cases "rediscovered") in fields well outside of traditional organic chemistry. The following Connections highight presents an example from bioorganic chemistry, but numerous others can be found in the literature.

8.3.4 Deviations from Linearity

Recall that ρ, the parameter that characterizes a particular reaction in a Hammett analysis, is the slope obtained from the plot of k_X/k_H vs. σ. The plot must give a straight line to get a ρ value. What does it mean if a Hammett plot is not linear?

If a reaction creates a consistent amount of charge in its transition state regardless of the substituents attached, then we should find a linear Hammett plot. Therefore, if we define the reaction coordinate as the extent of creation of charge on the transition state, then the transition state must not move as substituents are interchanged. When the transition state does change significantly with regard to the extent of charge development, however, the Hammett plot will not be linear. For example, if more and more negative charge resides on the activated complex as the substituent becomes increasingly electron withdrawing, the Hammett plot will not be linear. This case is often associated with a gradual curve in the Hammett

The Trustees of Columbia Univ. Ex. 2047 - Page 43 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

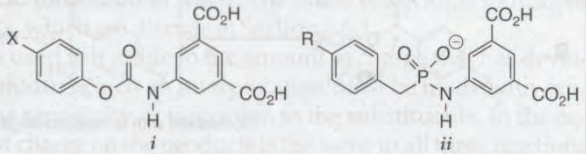
Connections

Using a Hammett Plot to Explore the Behavior of a Catalytic Antibody

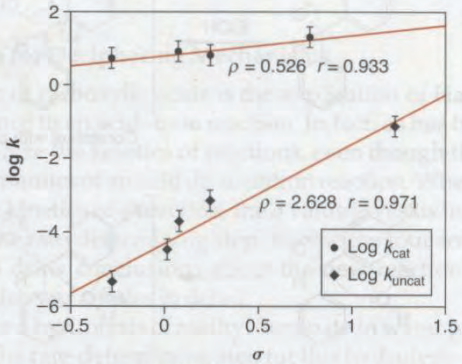
There are two competing mechanisms for the hydrolysis of aryl carbamate esters. One involves prior deprotonation followed by expulsion of the phenoxide leaving group to give an isocyanate that is trapped by water (Path A shown below). The second involves nucleophilic attack at the carbonyl followed by leaving group departure (Path B). With an H on the N, Path A is favored. When the carbamate N is missing a hydrogen, Path B dominates. The ρ values for Paths A and B are near 3 and 1, respectively (X = substituents).

Recently, a new way to develop catalysts has emerged known as the study of **catalytic antibodies**. Herein, transition state analogs for various reactions are created, and antibodies are isolated that bind these analogs. As we will see in Chapter 9, the binding of the transition state of a reaction is the major factor by which catalysis is achieved with enzymes. Thus, the antibodies created to bind a transition state analog are often found to catalyze the reaction involving the transition state the analog was patterned after.

To catalyze the hydrolysis of aryl carbamate esters such as *i* via Path B, transition state analog *ii* was synthesized (see above right). The tetrahedral phosphonate anion mimics the anionic tetrahedral intermediate formed along Path B. Carbamates *i* have a hydrogen on the N, and therefore are expected to hydrolyze via Path A in solution, and indeed a ρ value of 2.628 was found. Yet, a Hammett plot for the hydrolysis of carbamates catalyzed by antibodies that bind *ii* gave a ρ value of 0.526 (see plot at right). This value supports Path B, indicating that the use of transition state analog *ii* redirected the antibody-catalyzed mechanism to the less favored pathway. This study shows that antibody catalysis can be used to effect disfavored transformations, and highlights how ρ values can be used to distinguish between mechanisms.

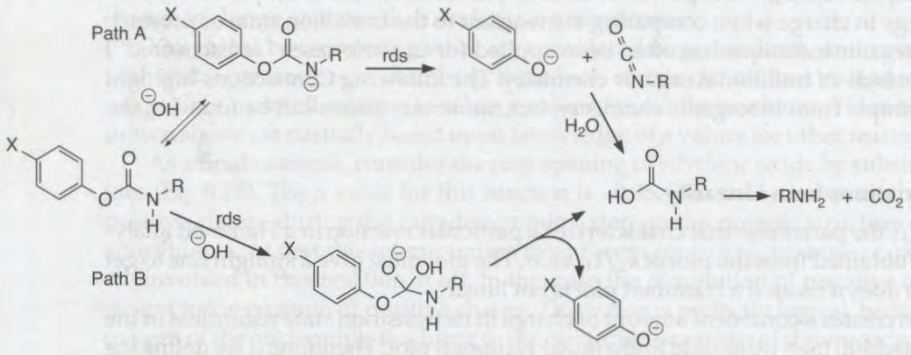


Transition state analog



Closed circles are the data for the antibody-catalyzed pathway. The diamonds are the data for the reaction in solution.

Wentworth, P., Jr., Datta, A., Smith, S., Marshall, A., Partridge, L. J., and Blackburn, G. M. "Antibody Catalysis of $B_{Ac}2$ Aryl Carbamate Ester Hydrolysis: A Highly Disfavored Chemical Process." *J. Am. Chem. Soc.*, **119**, 2315–2316 (1997).



Competing hydrolysis mechanisms

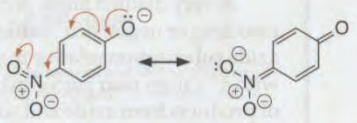
The Trustees of Columbia Univ. Ex. 2047 - Page 44 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

plot, indicating that the position of the transition state is incrementally changing as the substituents are interchanged.

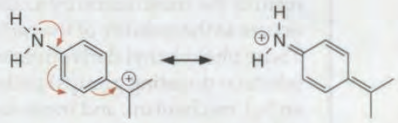
An abrupt change in the slope of the plot with two intersecting lines can indicate a sudden change in the rate-determining step as a function of substituents. Such a break can also often indicate a change in mechanism for the reaction. After examining the σ^+ scale below, an example of an abrupt change in the slope of a Hammett plot is given in a Connections highlight. A change in the rate-determining step or mechanism is always of concern when examining LFERs, because changing substituents can change the relative energies of intermediates on the energy surface.

8.3.5 Separating Resonance from Induction

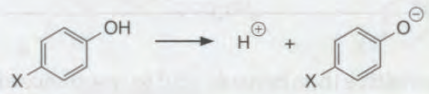
As noted above, we cannot draw resonance structures that delocalize the negative charge of benzoate onto the benzene ring via the π electron system. Therefore, the Hammett σ_{meta} and σ_{para} values do not include effects for direct resonance stabilization of the carboxylate negative charge. Yet, many reactions of interest create negative or positive charges that can be stabilized by delocalization via resonance with the substituent. For these reactions, we find that Hammett plots using σ values have considerable scatter. Therefore, two new substituent effect scales were produced, one for groups that stabilize negative charges via resonance (σ^-), and one for groups that stabilized positive charges via resonance (σ^+). The σ^- scale is based upon the ionization of para-substituted phenols (Eq. 8.26), for which groups like nitro can stabilize the negative charge via resonance (see margin). The σ^+ scale is based upon the heterolysis (S_N1) reaction of para-substituted phenyldimethyl chloromethanes (Eq. 8.27), for which groups like amino can stabilize the positive charge via resonance (see margin). Several σ^+ and σ^- values are given in Table 8.2. Note that the σ^+ values are defined so that negative ρ values correspond to the creation of positive charge, just as with normal Hammett plots. The electron withdrawing groups have positive σ^+ values, and the electron donating groups have negative σ^+ values, just as with σ values. One example of the use of the σ^+ scale is shown in the next Connections highlight.



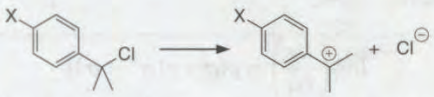
p-Nitrophenolate



p-Aminobenzylic cation



(Eq. 8.26)



(Eq. 8.27)

When examining a brand new reaction, we often do not know which set of σ values is the most appropriate to use. However, the experimental measurements we make (rates or equilibria with varying substituents) are the same no matter what σ values are applied. Therefore, one develops plots based upon the various σ values and determines which has the least amount of scatter, thereby indicating if the stabilization of the charges involved is dominated by inductive or resonance effects.

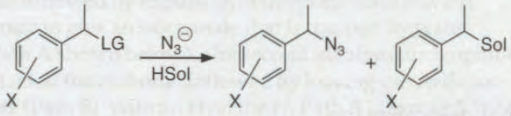
A method for separating inductive effects from resonance effects was proposed by Yukawa and Tsuno (Eq. 8.28). Here the "r" value expresses the influence of resonance on the new reaction relative to the influence with benzoic acid. Since r is multiplied by the difference between the resonance and inductive substituent constants (σ^+ and σ, respectively), it describes the sensitivity of the reaction to resonance. When r is equal to zero, there is no difference in resonance effects for the new reaction compared to benzoic acid, but when $r > 0$,

The Trustees of Columbia Univ. Ex. 2047 - Page 45 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

An Example of a Change in Mechanism in a Solvolysis Reaction Studied Using σ^+

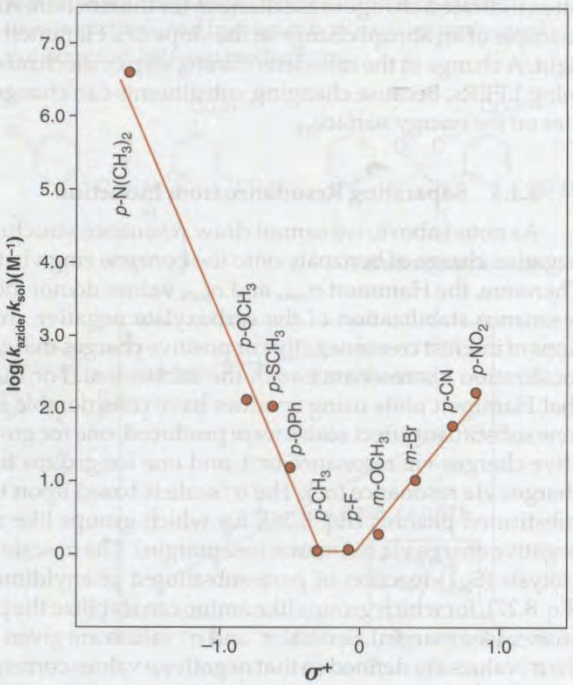
The substitution of various leaving groups from 1-phenylethyl by azide or solvent (a 50:50 mixture of trifluoroethanol and water) was studied as a function of σ^+, and the results obtained are shown at right.



This plot is a slight variation from that described for a basic σ^+ plot, in that the reaction with solvent is used as the reference reaction and not a comparison to one single substituent.

A very distinct break occurs. Those substituents with near zero or negative σ^+ values show rapidly increasing azide substitution relative to solvent. Those substituents with σ^+ values near zero produce nearly equal mixtures of products from azide and solvent, and finally, as σ^+ becomes more positive, the azide substitution again dominates but with a lower absolute value of the slope than with the negative σ^+ value substituents.

The data are consistent with a change in the mechanism of the substitution by azide from S_N1 to S_N2, which occurs as the stability of the carbocation is decreased. Those phenylethyl derivatives with negative σ^+ values (electron donating groups) undergo the substitution via an S_N1 mechanism, and those substituents with positive σ^+ values proceed via an S_N2 pathway. Furthermore, the data support a very clear reactivity–selectivity relationship. As the carbocation becomes more stable (the left side of the graph), it becomes more selective for the better nucleophile (azide).



Richard, J. P., and Jencks, W. P. "A Simple Relationship between Carbocation Lifetime and Reactivity–Selectivity Relationships for the Solvolysis of Ring–Substituted 1-Phenylethyl Derivatives." *J. Am. Chem. Soc.*, **104**, 4689–4691 (1982).

the new reaction is more sensitive than benzoic acid to resonance effects, and when $r < 0$, the new reaction is less sensitive.

$$\log\left(\frac{k_X}{k_H}\right) = \rho[\sigma + r(\sigma^+ - \sigma)] \qquad \text{(Eq. 8.28)}$$

The concept of separating the influence of resonance and induction on a reaction is quite appealing, because it tells us how the charge on the transition state is distributed. In fact, breaking down a substituent effect into all the different individual effects (resonance, induction, field, polarizability, steric) can be quite informative. For example, Swain and Lupton separated electronic LFERs into two substituent parameters: F (field or inductive) and R (resonance), with sensitivity factors f and r (Eq. 8.29), respectively. The F and R parameters can be found in references given at the end of the chapter. In this analysis, one can let the $fF + rR$ term equal the traditional $\rho\sigma$ values, thereby deciphering what fraction of the ρ value derives from resonance or induction. The following Connections highlight shows the use of this approach in an organometallic example.

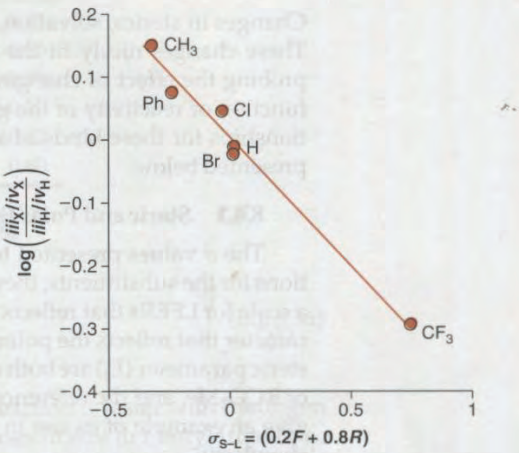
$$\log\left(\frac{k_X}{k_H}\right) = fF + rR, \text{ where } fF + rR = \rho\sigma \qquad \text{(Eq. 8.29)}$$

The Trustees of Columbia Univ. Ex. 2047 - Page 46 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

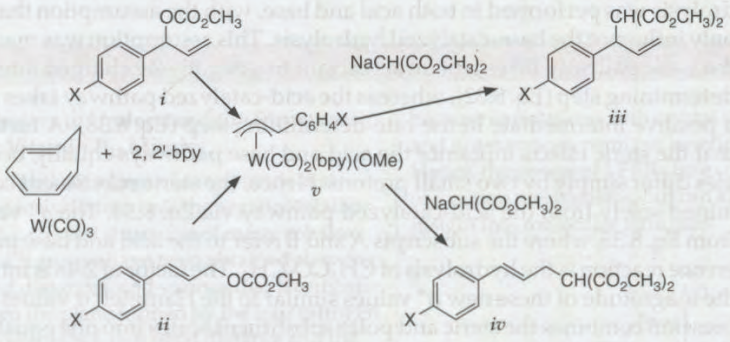
Connections

A Swain–Lupton Correlation for Tungsten-Bipyridine-Catalyzed Allylic Alkylation

One very useful reaction in organic synthesis is the allylic alkylation of allyl carbonates catalyzed by various metal complexes (see Chapter 12 for mechanistic details). In the case of the alkylation of carbonates such as *i* and *ii*, catalyzed by the tungsten complex shown, the ratio of the two products was found to depend upon the para-substituent on the phenyl ring of the reactants. To understand the influence of the substitutent, a Hammett plot was derived based upon the Swain–Lupton parameters *F* and *R*. In this case, a plot of the ratio of *iii* to *iv* for the various substituents (with the reference substitutent being hydrogen) versus *F* and *R* was made. The overall slope of the line (ρ) was –2.5 with the *R* constant being dominant (giving 80% of the slope). These data lead to the conclusion that there is a significant amount of positive charge on the benzylic carbon that is stabilized by resonance during the formation of the transition state that sets the regiochemistry.



Lehman, J., and Lloyd-Jones, G. C. "Regiocontrol and Stereoselectivity in Tungsten-Bipyridine Catalyzed Allylic Alkylation." *Tetrahedron*, 8863–8874 (1995).



Allylic alkylation

Taft and Topsom broke the substituent constants into four parameters (Eq. 8.30), reflecting contributions from field (*F*), induction (*x*), polarizability (*a*), and *R* (resonance), along with appropriate sensitivity factors (these substituent constants are also given in references at the end of the chapter).

$$\log\left(\frac{k_X}{k_H}\right) = \rho_F\sigma_F + \rho_x\sigma_x + \rho_a\sigma_a + \rho_R\sigma_R \qquad \text{(Eq. 8.30)}$$

Although these multi-parameter approaches are intriguing, the overwhelming majority of electronic LFERs used in modern physical organic chemistry rely simply on σ, σ^+, and σ^- values, and therefore we do not explore the multi-parameter approaches to separating inductive and resonance in any more depth. However, the notion of separating reactivity into the various components remains appealing, and examples involving steric effects and solvent effects are given below.

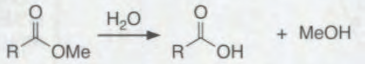
The Trustees of Columbia Univ. Ex. 2047 - Page 47 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.4 Other Linear Free Energy Relationships

Changes in sterics, solvation, nucleophilicity, etc., can all be viewed as substituent effects. These changes nicely fit the concept of a structure–reactivity relationship, where we are probing the effect of changing steric size, solvating ability, nucleophilicity, etc., upon the function or reactivity of the groups undergoing change. Therefore, linear free energy relationships for these kinds of substituent effects have also been developed, and several are presented below.

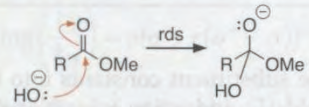
8.4.1 Steric and Polar Effects—Taft Parameters

The σ values presented to this point include field, inductive, and resonance contributions for the substituents; they do not give the influence of sterics. Taft, however, developed a scale for LFERs that reflects the steric influence of substituents on various reactions. A parameter that reflects the polar nature (i.e., field and induction) of the substituent (σ^*) and a steric parameter (E_s) are both defined. The defining reaction is the acid-catalyzed hydrolysis of RCO_2Me, and the reference R group is methyl (Eq. 8.31). After examining this LFER, we give an example of its use in a Connections highlight concerned with structural inorganic chemistry.

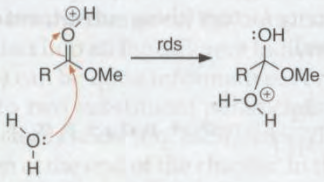


(Eq. 8.31)

To measure the polar and steric substituent constants for the R groups in Eq. 8.31, the hydrolysis was performed in both acid and base, with the assumption that polar effects would only influence the base-catalyzed hydrolysis. This assumption was made due to the fact that the basic pathway takes a neutral reactant to a negatively charged intermediate in the rate-determining step (Eq. 8.32), whereas the acid-catalyzed pathway takes a positive reactant to a positive intermediate in the rate-determining step (Eq. 8.33). A further assumption was that the steric effects influence the acid and base pathways equally, because the intermediates differ simply by two small protons. Hence, the steric substituent constant E_s was determined solely from the acid-catalyzed pathway via Eq. 8.34. The σ^* values are determined from Eq. 8.35, where the subscripts A and B refer to the acid and base pathways, and the reference reaction is the hydrolysis of $CH_3CO_2CH_3$. The factor of 2.48 is introduced just to make the magnitude of these new σ^* values similar to the Hammett σ values. The general Taft expression combines the steric and polar substituent scales into one equation (Eq. 8.36), where ρ^* and δ are the sensitivity factors for a new reaction under study to polar and steric effects, respectively. Table 8.3 gives several E_s and σ^* values.



(Eq. 8.32)



(Eq. 8.33)

$$\log\left(\frac{k_s}{k_{CH_3}}\right) = E_s \qquad \text{(Eq. 8.34)}$$

$$\sigma^* = \frac{1}{2.48}\left[\log\left(\frac{k}{k_o}\right)_B - \log\left(\frac{k}{k_o}\right)_A\right] \qquad \text{(Eq. 8.35)}$$

The Trustees of Columbia Univ. Ex. 2047 - Page 48 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Table 8.3
Selected Taft Parameters[‡]

R group	E_s	σ^*
–H	1.24	0.49
–Et	–0.07	–0.10
–*i*Pr	–0.47	–0.19
–*t*-Bu	–1.54	–0.30
$-CH_2Ph$	–0.38	0.22
–Ph	–2.55	0.60

[‡]Taft, R. W. in *Steric Effects in Organic Chemistry*, M. S. Newman (ed.), John Wiley & Sons, New York, 1956.

$$\log\left(\frac{k_s}{k_{CH_3}}\right) = \rho^*\sigma^* + \delta E_s \qquad \text{(Eq. 8.36)}$$

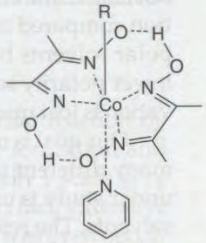
These parameters show that the rate of the hydrolysis reaction is faster with hydrogen than methyl, and slows as the R group incrementally increases in size to *t*-butyl (that is, E_s becomes more negative). Phenyl, however, comes out surprisingly large in this analysis ($E_s = -2.55$). In Chapter 2 we noted that efforts to characterize the steric size of a group will be strongly context dependent, and this is an example. In an alternative measure of the steric size of substituents—the cyclohexane *A* value (Table 2.14)—phenyl is much smaller than *t*-butyl.

Connections

Using Taft Parameters to Understand the Structures of Cobaloximes; Vitamin B_{12} Mimics

Cobaloximes (see right) are a class of compounds that have been used extensively to mimic the organometallic cofactor vitamin B_{12}. Crystal structures of many cobaloximes with different R groups have been obtained showing various Co–R bond distances, and various displacements of the Co atom from the plane formed by the four nitrogen ligands. Correlations of the Co–R bond distance and the displacement of the Co atom were created using a multiparameter approach. The Co–R bond distances gave a linear correlation to σ values describing the electron donating and withdrawing ability of the R group, with varying influences from resonance and induction. However, the displacement of the Co from the plane formed by the four nitrogens correlated best with the Taft E_s parameters, indicating that the steric bulk of the R group primarily determined the positioning of the Co atom within the ligand.

This study is an interesting application of LFERs, because correlations with crystal structure information and not thermodynamic or kinetic data were made. Hence, the power of LFERs far exceeds just the analysis of reaction mechanisms, but can also be used to provide insight into molecular structure.



A cobaloxime

Randaccio, L., Geremia, S., Zangrando, E., and Ebert, C. "Quantitative Rationalization of Solution and Solid State Properties in Cobaloximes, $RCo(DH)_2L$, as a Function of the Electronic and Steric Properties of R." *Inorg. Chem.*, 33, 4641–4650 (1994).

8.4.2 Solvent Effects—Grunwald–Winstein Plots

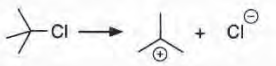
The Hammett LFER gives us a powerful tool for analyzing the changes in charge during a reaction. However, if we vary the structure of the solvent instead of varying the structure of the reactant, and follow the kinetics or thermodynamics of a reaction, we can also gain insight into changes in charge. We can determine whether charges form along the reaction co-

The Trustees of Columbia Univ. Ex. 2047 - Page 49 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

ordinate, and how the solvent influences the formation of these charges. Such an LFER was developed by Grunwald and Winstein.

Many S_N1 reactions involve the formation of positive and negative species in the rate-determining step. Greater solvent polarity accelerates the rate of such reactions by stabilizing the transition states, which are highly charged. You might predict that the rates of these reactions would nicely correlate with the dipole moment of the solvent molecules (μ), the dielectric constant of the solvent (ε), or any one of the other solvent scales [such as Z, π^*, or $E_T(30)$; see Table 3.1]. However, none of these scales correlates well with chemical reactions. This lack of correlation reflects the fact that solvents do not just stabilize or destabilize point charges in a remote or "innocent" manner. Instead, the solvent often directly assists the reaction. With regard to an ionization such as the S_N1 reaction, an electrophilic solvent can directly coordinate with the leaving group as it departs. Furthermore, a nucleophilic solvent can directly coordinate in a loose manner with the carbocation as it forms, a process called **nucleophilic assistance**. None of these factors is directly taken into account with the scales of solvent polarity, dielectric constant, or polarizability. Thus, Grunwald and Winstein defined a new scale that was directly based on an ionization reaction.

The reference reaction chosen was the S_N1 reaction of *t*-BuCl (Eq. 8.37). This reaction was chosen because it was assumed that very little if any S_N2 pathway occurred. The reference solvent was 80% ethanol/20% water, both of which could act as a nucleophile to add to the incipient *t*-butyl carbocation. Hence, the LFER given in Eq. 8.38 was defined. Here, $k_{t\text{-BuCl, sol}}$ is the rate of the reaction in the solvent being analyzed, and $k_{t\text{-BuCl, 80\% EtOH}}$ is the rate of the reaction in 80% ethanol. Thus, Y reflects the ability of the new solvent to influence the rate of the reference reaction compared to 80:20 ethanol:water. Table 8.4 lists a variety of Y values.



(Eq. 8.37)

$$\log\left(\frac{k_{t\text{-BuCl, sol}}}{k_{t\text{-BuCl, 80\% EtOH}}}\right) = Y \qquad \text{(Eq. 8.38)}$$

Several interesting trends are revealed in Table 8.4. First, pure water is the most ionizing solvent of all, with the ability to enhance the rate of the S_N1 reaction of *t*-BuCl by a factor of $10^{3.49}$ relative to 80% ethanol. Formic acid is a good ionizing solvent, too—better than ethanol and acetic acid. Acetic acid, ethanol, and 90% acetone, on the other hand, slow the reaction compared to 80% ethanol. There are two contributions to these trends. The first is that polar solvents better solvate charges, and hence speed the ionization. The second is that lower polarity solvents solvate neutral organic species, but a significant amount of this solvation is lost upon formation of a cation and halide anion, hence retarding ionization.

Our goal is not to study just the S_N1 reaction of *t*-BuCl, but instead to apply the LFER to many different reactions. Hence, an LFER with a sensitivity factor m for any new reaction under study is used (Eq. 8.39). Here, k_{new} is the rate constant for the new reaction in various solvents. The reference solvent is still 80% ethanol. Although the majority of the studies using this equation have been S_N1 and S_N2 reactions (see examples in Chapter 11), it is in principle applicable to any reaction.

$$\log\left(\frac{k_{new, sol}}{k_{new, 80\% EtOH}}\right) = mY \qquad \text{(Eq. 8.39)}$$

Since the Y parameter was based upon a reaction that has little nucleophilic assistance, those reactions that have m values near 1 reflect nearly full ionization in the rate-determining step. For those reactions that have an m value less than 1, the reaction is not as sensitive to the ionizing ability of the solvent as is *t*-BuCl. This means less charge has been created in the transition state, which is most often accomplished by some degree of nucleophilic assistance (Chapter 11 discusses the shades of grey between pure S_N1 and pure S_N2 reaction mechanisms). Hence, a reaction with some S_N2 character will have a reduced extent of charge development in the transition state and therefore an m value less than unity. More-

The Trustees of Columbia Univ. Ex. 2047 - Page 50 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Table 8.4
Values of Solvent Ionizing Ability as Defined by LFERs Eqs. 8.38, 8.39 and 8.41*

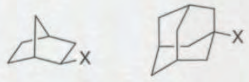
Solvent	Y	Y_{OTs}	N_{OTs}
CF_3CO_2H	1.84	4.57	–5.56
H_2O	3.49	4.0	–0.41
CF_3CH_2OH	1.04	1.80	–3.0
HCO_2H	2.05	3.04	–2.35
CH_3CO_2H	–1.68	–0.61	–2.35
EtOH	–2.03	–1.75	0.00
Mixed solvent systems (all expressed as percent co-solvent in water)			
98% EtOH	–1.68		0.00
80% EtOH	0.00	0.00	0.00
50% EtOH	1.66	1.29	–0.09
80% HCO_2H	2.32		
50% HCO_2H	2.64		
50% CH_3CO_2H	1.94		
25% CH_3CO_2H	2.84		
90% Acetone	–1.86		
50% Acetone	1.40		
20% Acetone	2.91		

*Fainberg, A. H., and Winstein, S. "Correlation of Solvolysis Rates. III. *t*-Butyl Chloride in a Wide Range of Solvent Mixtures." *J. Am. Chem. Soc.*, **78**, 2770 (1956). Schadt, F. L., Bentley, T. W., and Schleyer, P. v. R. "The S_N2–S_N1 Spectrum. 2. Quantitative Treatments of Nucleophilic Solvent Assistance. A Scale of Solvent Nucleophilicities." *J. Am. Chem. Soc.*, **98**, 7667 (1976).

over, the m values of two different reactions in solvents of the same Y value but different nucleophilicities should be the same if ionization is rate-determining, but different if nucleophilic attack or assistance is involved.

8.4.3 Schleyer Adaptation

As stated above, many solvents can directly participate in an ionization reaction by coordination to the leaving group or carbocation. Schleyer noted that the ionization and rearrangement of norbornane derivatives did not fit the Grunwald–Winstein Y scale very well, and that nucleophilic assistance was likely occurring (see margin). In fact, extensive studies of solvolysis reactions began to indicate that nucleophilic assistance was even occurring to some extent in the Grunwald–Winstein reference reaction of *t*-BuCl. Therefore, Schleyer defined a scale (Eq. 8.40) based upon the ionization of 1-adamantyl chloride, a reactant for which no nucleophilic assistance can occur because the nucleophile cannot penetrate the adamantyl group to reach the backside of the C–Cl bond. Here, the Y_{Cl} parameter gives a measure of the solvent ionizing power on 1-adamantylchloride with no nucleophilic assistance, relative to 80% ethanol. Similarly, Y_{OTs} values have been measured for 1-adamantyl tosylate. These Y scales reflect only ionization.



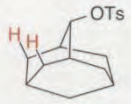
Norbornane derivatives

1-Adamantyl system

$$\log\left(\frac{k_{\text{1-AdaCl, sol}}}{k_{\text{1-AdaCl, 80\% EtOH}}}\right) = Y_{Cl} \qquad \text{(Eq. 8.40)}$$

Although the 1-adamantyl system seems ideal, the ionization of 2-adamantyl systems has become the most widely accepted system for separating the effects of ionizing power and nucleophilic assistance. Again, the reference solvent is 80% ethanol. It may not be imme-

The Trustees of Columbia Univ. Ex. 2047 - Page 51 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313



2-Adamantyl tosylate

diately apparent, but backside attack is also impossible in the 2-adamantyl system due to the axial hydrogens shown in color. We know that backside attack is not possible because the Y_{OTs} values based upon 2-adamantyl tosylate correlate very well with the Y_{OTs} values based upon 1-adamantyl tosylate. Furthermore, in the solvents 98:2 ethanol/water and acetic acid, the rates of ionization of 2-adamantyl tosylate are the same even though the ethanol/water mixture is more nucleophilic. In addition, the 2-adamantyl tosylate system gives a very large secondary isotope effect (1.23), indicating a large extent of rehybridization to sp^2 in the transition state. The reason 2-adamantyl is preferred over 1-adamantyl is primarily due to the fact that 2-adamantyl derivatives are more synthetically accessible than 1-adamantyl derivatives. Table 8.4 lists some Y_{OTs} values based upon 2-adamantyl tosylate.

Once again, the goal is to study the charge build-up on reactions other than the reference reaction. We compare the rate constants for the new reaction under study in a variety of solvents ($k_{new, sol}$) to the parameters developed from an analysis of the adamantyl systems. Most reactants, however, are not as restricted as the 1- or 2-adamantyl systems to only an ionization. Therefore, a substituent constant, called N_{OTs}, is also included. N_{OTs} gives the ability of the solvent to participate in nucleophilic assistance. N_{OTs} is determined from a reaction that is solely nucleophilic in nature, the S_N2 displacement of tosylate from methyltosylate (Eq. 8.41). In Eq. 8.41 the $0.3Y$ corrects the sensitivity of the rate of reaction of methyltosylate to the solvent ionizing power (Y in this case comes from the Grunwald–Winstein equation). Eq. 8.42 thus reflects both a factor for pure ionization (mY_{Cl}, where Y_{Cl} comes from the ionization of 1- or 2-adamantyl chloride) and a factor for pure nucleophilic assistance (lN_{OTs}, where N_{OTs} comes from S_N2 displacement on MeOTs). Table 8.4 lists some N_{OTs} values. We will look at various l and m sensitivity constants in Chapters 10 and 11. For now, the Connections highlight below describes one use of the Schleyer approach to solvent ionizing scales.

$$N_{OTs} = \log\left(\frac{k_{sol}}{k_{80\%\ EtOH}}\right) - 0.3Y \qquad \text{(Eq. 8.41)}$$

$$\log\left(\frac{k_{new, sol}}{k_{new, 80\%\ EtOH}}\right) = lN_{OTs} + mY_{Cl} \qquad \text{(Eq. 8.42)}$$

We have separated the ability of the solvent to assist in carbocation formation by electrostatics and nucleophilic assistance, but we have not considered the ability of the solvent to stabilize the leaving group. In fact, it has been found that the Y scales do not correlate well with reactions when the leaving group is different from that upon which the scale is based. Solvents that can directly assist the leaving group as it departs can do so to varying extents depending upon the structure of the leaving group. For example, electrophilic solvents can stabilize a small chloride anion better than a large tosylate anion. As a result, many scales based upon different leaving groups have been developed (such as Y_{Br}, Y_I, and Y_{OTs}).

In summary, we have defined another tool for studying the charges that change during a mechanism. Several LFERs were discussed that give one the ability to determine both the extent of ionization at the transition state of a specific reaction and how much nucleophilic assistance has occurred, all just by changing the structure of the solvent.

8.4.4 Nucleophilicity and Nucleofugality

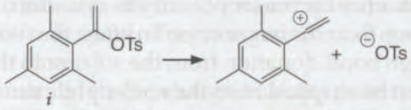
In several of the reactions that you learned in introductory organic chemistry, and many of those that are discussed in Chapters 10 and 11, nucleophilic attack on an electron deficient center such as a carbocation or a polarized σ or π bond occurs. The ability of nucleophiles to participate in these reactions depends upon their molecular structure. A structural dependence suggests that there should be scales of relative nucleophilicity that depend upon the sterics, polarizability, and inductive/resonance properties of the nucleophile. Hence, changing the nucleophile becomes one of the tools that we have to study reactions. As with solvent and electronic substituent effects, LFERs provide insight into how the change in nucleophile structure affects the reaction. Similarly, the ability of a leaving group to depart

The Trustees of Columbia Univ. Ex. 2047 - Page 52 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

The Use of the Schleyer Method to Determine the Extent of Nucleophilic Assistance in the Solvolysis of Arylvinyl Tosylates

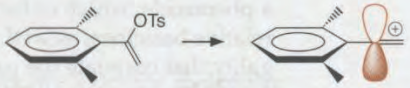
The solvolysis of vinyl tosylate *i* proceeds via an *sp* hybridized carbocation. The Grunwald–Winstein *m* value for this reaction was found to be small (0.62) for such an ionization reaction, indicating much less stabilization from the solvent than occurs in the ionization of *t*-butylchloride. This small *m* value could be due to increased nucleophilic assistance, or stabilization of the carbocation by some other factor, making the role of the solvent less important.



i

Solvolysis of a vinyl tosylate

Typically, C(sp^2)–X bonds as in *i* are very sluggish in solvolysis reactions compared to analogous C(sp^3)–X bonds. This sluggish behavior can be ascribed to less effective backside solvation of the developing carbocation with the sp^2 system, and the higher energy of an *sp* cation compared with an analogous trisubstituted "normal" sp^2 carbenium ion. Yet, with *i*, the steric congestion presented by the methyl groups on the phenyl ring results in a conformation where the vinyl group is initially perpendicular to the benzene, while the vinyl cation becomes increasingly planar, allowing for resonance stabilization from the benzene. This stabilization by the phenyl ring could account for the low *m* values, because less stabilization by the solvent is required.



Stabilization of a vinyl cation via conjugation with phenyl

To discover if any nucleophilic assistance occurs with *i*, the Schleyer method was used. Instead of plotting an entire series of solvents with different *Y* and *N* values, followed by the application of Eq. 8.42, the investigators simply chose two solvent systems with the same *Y* values, but different nucleophilicities. Ethanol/water (98:2) and acetic acid both have *Y* values of –1.68, but N_{OTs} values of 0.0 and –2.35, respectively (see Table 8.4). Following the kinetics of solvolysis of *i* revealed a difference in rate constants in the two solvents of only 25%. Given the large difference in *N* values, the small difference in rate constants indicates that nucleophilic assistance does *not* occur in the solvolysis of *i*. Therefore, the stabilization imparted by the benzene ring is the reason for the low *m* values.

Yates, K., and Périé, J.-J. "Solvolysis of Arylvinyl Bromides and Tosylates." *J. Org. Chem.*, **39**, 1902 (1974).

from a structure should depend upon the electronics of the leaving group. In other words, the nucleofugalities of different groups should correlate with parameters that describe the properties of the leaving groups. Therefore, changing leaving groups is another tool for studying reactions.

Once again, as with all LFERs, the goal is to change the structure of the reactants, in this case the nucleophile and nucleofuge, and have parameters for relative nucleophilicity and nucleofugality that can be applied to many different reactions. Before describing the scales that have been developed for analyzing the ability of different atoms or molecules to act as nucleophiles or leaving groups, it is instructive to discuss what makes a good nucleophile or leaving group. The attributes of reactivity discussed below can be applied to all reactions involving nucleophiles, and hence we discuss them here as part of our tools for studying mechanisms, rather than discussing them in the context of specific reactions in future chapters.

Basicity/Acidity

First of all, there should be a relationship between nucleophilicity and basicity, and a correlation between nucleofugality and the acidity of the conjugate acid of the leaving group. Both basicity and nucleophilicity involve the donation of electrons to an electrophile. Likewise, a leaving group and an acid both accept electrons as they depart or lose a proton, respectively. Since nucleophiles and nucleofuges behave oppositely with regard to electron donation and acceptance, good nucleophiles are often poor leaving groups and vice versa. However, there are many exceptions, which we will discuss below.

Nucleophiles that have the same nucleophilic atom are better when the nucleophilic atom is negative compared to neutral. This charge dependence is the same for the relative

The Trustees of Columbia Univ. Ex. 2047 - Page 53 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

basicity of the nucleophile. The opposite is true for leaving groups; that is, neutral is better than negative when the same atom is being compared.

When proceeding from left-to-right across a row in the periodic table, the atoms further to the left are more nucleophilic ($H_3C^- > H_2N^- > HO^- > F^-$). This trend correlates again with the basicity of the group, and the opposite trend is found for leaving group ability.

The more stable the negative charge of the nucleophilic atom, the less nucleophilic it is. For example, due to differing resonance stabilization, an alkoxide is more nucleophilic than a phenoxide, which in turn is more nucleophilic than a carboxylate. This trend reflects the relative basicities, as well. Below we will describe LFERs for nucleophilicity and nucleofugality that correlate the pK_as of the conjugate acids of the nucleophiles and nucleofuges to sensitivity parameters (β_{nuc} and β_{LG}).

Solvation

Another factor that has a dramatic influence on nucleophilicity is solvation. Solvation forces are stronger for small nucleophilic ions than for larger ones, an effect that is especially true in polar protic solvents where hydrogen bond donation from the solvent to the nucleophile is stabilizing. Because the solvent must be stripped from the nucleophile during the attack on the electrophile, the well solvated smaller ions are poor nucleophiles. Therefore, the more "naked" (less solvated) the nucleophile, the better it becomes. Hence, nucleophiles are consistently more reactive in aprotic solvents of low polarity. However, very often the nucleophile will not be soluble in these solvents because many nucleophiles are negatively charged (they are part of salts). Hence, solvents such as DMF and DMSO are commonly used. These are aprotic but polar enough to solubilize the nucleophile, and high reactivity is found.

Similar to the solvation effect, counterion effects can influence nucleophilicity. A tight ion pair between a negative nucleophile and a positive counterion will decrease the nucleophilicity (unless the counterion is involved in the reaction; see examples in Chapters 10 and 11). Conversely, if one can effectively solvate and perhaps even fully encapsulate the counterion, so that no coordination to the nucleophile is possible, the nucleophilicity will increase (see Section 4.2.1 on crown ethers).

Another interesting effect on nucleophilicity that arises in part from a solvation effect is called the α-effect. The **α-effect** arises when two nucleophilic atoms are adjacent to one another. This dramatically increases the nucleophilicity. For example, although hydroxide is about 16,000 times more basic than hydroperoxide (HOO^-), hydroperoxide is approximately 200 times more nucleophilic. Similarly, the amine groups in hydroxylamines ($HONR_2$) or hydrazines (NR_2NR_2) are more nucleophilc than simple amines. There are two explanations for this effect. In one explanation the existence of lone pair electrons directly adjacent to the nucleophilic site is believed to destabilize the ground state, making the nucleophile more reactive. However, whereas the α-effect trend is seen in solution with hydroxide and hydroperoxide, hydroxide is the better nucleophile in the gas phase. Apparently, the inductive withdrawal of the negative charge by the adjacent electronegative oxygen in hydroperoxide makes this nucleophile less solvated, and hence more reactive in solution.

Polarizability, Basicity, and Solvation Interplay

A comparison of nucleophiles in which the nucleophilic atoms bear the same charge, and are in the same column of the periodic table, indicates that the nucleophilicity increases as one proceeds down the column. For example, the order of nucleophilicities for the halide anions is $I^- > Br^- > Cl^- > F^-$ in polar protic solvents. As discussed above, in these solvents, the anions are well solvated, and fluoride makes stronger bonds with the solvent because the anionic charge is more localized. This trend is opposite of that expected if there was a strict correlation between basicity and nucleophilicity (the order of basicity is $F^- > Cl^- > Br^- > I^-$). Similarly, thiolate anions are consistently better nucleophiles than analogous alkoxides, even though the alkoxides are significantly more basic. The increased nucleophilicity

The Trustees of Columbia Univ. Ex. 2047 - Page 54 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

upon going down a column in the periodic table is due, in part, to a polarizability effect. The atom with the higher polarizability (see Chapter 1) forms the incipient covalent bond to the electrophile more easily because its electron cloud more readily accommodates changes in shape.

When polar aprotic solvents are used, anionic nucleophiles are not well solvated. In these cases, the nucleophilicity is more often found to track basicity. For example, in DMSO it can be found that $F^- > Cl^- > Br^- > I^-$ is the order of nucleophilicity for various reactions.

Shape

As a last example of a factor that influences nucleophilicity, we examine molecular shape. A nucleophile is required to penetrate the solvent shell around an electrophile, and often to hone in on an electrophilic center that may be sterically congested. In this regard, large bulky nucleophiles are not very effective, but small, "bullet" (linear) shaped nucleophiles can be quite effective. For example, the nucleophiles cyanide (NC^-) and azide (N_3^-) are particularly good. They are much more nucleophilic than would be predicted based upon their basicity.

In summary, shape, charge, basicity, polarizability, and solvation are all factors that determine the nucleophilicity of compounds. Understanding these factors allows us to use the differences to our advantage when probing mechanisms.

The LFERs that have been developed for structure–function relationships for nucleophiles do not universally correlate reactions of different types and in different solvents. As one changes from one electrophile to another, changes solvent, or changes counterions, the nucleophilicity parameters based upon a different type of reference reaction do not apply as uniformly as, for example, the Hammett parameters apply to reactions that have no resemblance to the ionization of benzoic acid. However, once armed with these caveats, there are nucleophilicity parameters that have found general use, and they are good tools for you to consider when studying any reaction that involves a nucleophilic attack prior to or during the rate-determining step.

8.4.5 Swain–Scott Parameters—Nucleophilicity Parameters

To create an LFER for nucleophilicity, Swain and Scott defined the reference reaction to be the S_N2 nucleophilic displacement of bromide from methyl bromide by the reference nucleophile water. A more widely accepted scale based upon methyl iodide is now used (Eq. 8.43). Eq. 8.44 shows the LFER, with n_X as the parameter for nucleophile X, and s is the sensitivity parameter for any new reaction under study. Additionally, $k_{\text{new, Nuc}_X}$ is the rate constant for the new reaction under study with each nucleophile X, while $k_{\text{new, H}_2\text{O}}$ is the rate constant for the same reaction with water as the nucleophile. Table 8.5 gives a series of n_X values for various nucleophiles (based upon CH_3I), and the pK_as of the conjugate acids. Note, as discussed above, that the pK_as do not necessarily correlate with the nucleophilicities, and that the effects of resonance on nucleophilicity are well accounted for with the n values (compare the n values for acetate, phenoxide, and methoxide).

$$\log\left(\frac{k_{\text{CH}_3\text{–I, Nuc}_X}}{k_{\text{CH}_3\text{–I, H}_2\text{O}}}\right) = n_X \qquad \text{(Eq. 8.43)}$$

$$\log\left(\frac{k_{\text{new, Nuc}_X}}{k_{\text{new, H}_2\text{O}}}\right) = sn_X \qquad \text{(Eq. 8.44)}$$

Recall that the substituent parameters in LFERs define a logarithmic scale. Hence, in general, methoxide is a better nucleophile than methanol by a factor of $10^{6.29}$, and iodide is a better nucleophile than fluoride by a factor of $10^{4.72}$. We will look at a few s values in Chapter 11 when substitution reactions are considered. Here, we simply give one example in the context of an acetal substitution reaction (see the Connections highlight on the following pages).

The Trustees of Columbia Univ. Ex. 2047 - Page 55 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Table 8.5
Swain–Scott Parameters (n_X Values) for the S_N2 Reaction of CH_3I*

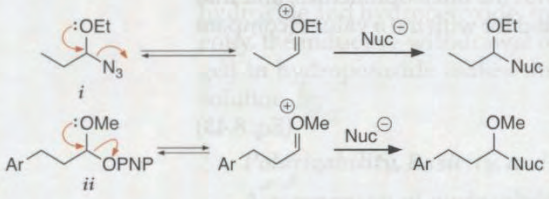
Nucleophile	n_X	pK_a of conjugate acid
F^-	2.7	3.45
Cl^-	4.37	–5.7
Br^-	5.79	–7.77
I^-	7.42	–10.7
N_3^-	5.78	4.74
NC^-	6.70	9.3
CH_3OH	near 0.0	–1.7
H_2O	0.0	–1.7
$CH_3CO_2^-$	4.3	4.75
PhO^-	5.75	9.89
CH_3O^-	6.29	15.7
Pyridine	5.23	5.23
Aniline	5.70	4.58
$(Et)_3N$	6.66	10.7
PhSH	5.70	—
PhS^-	9.92	6.52

*Pearson, R. G., Sobel, H., and Songstad, J. "Nucleophilic Reactivity Constants Toward Methyl Iodide and *trans*-Dichlorodi(pyridine)platinum(II)." *J. Am. Chem. Soc.*, **90**, 319 (1968).

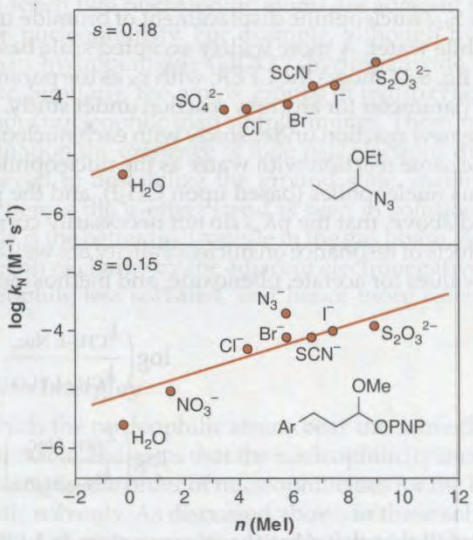
Connections

The Use of Swain–Scott Parameters to Determine the Mechanism of Some Acetal Substitution Reactions

Compounds *i* and *ii* (PNP = *p*-nitrophenyl) undergo reactions with neutral and anionic nucleophiles giving substitution products. The reactions are second order with a first-order dependence on nucleophile, consistent with an S_N2 mechanism. However, reasonable S_N1 mechanisms can be written, given that the leaving groups are very good.



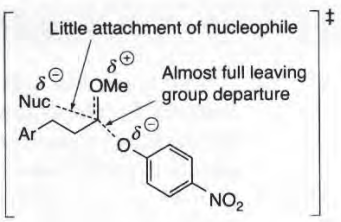
To determine the extent to which a nucleophile is involved in the transition state for S_N2 reactions of *i* and *ii*, Swain–Scott plots were generated (see right). The slopes of the plots (*s* values) for *i* and *ii* are only 0.15 and 0.18, respectively, meaning that the rate of the reaction does not depend very much upon the reactivity of the nucleophile.



The Trustees of Columbia Univ. Ex. 2047 - Page 56 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

The clear first-order kinetic dependence upon the nucleophile means that it has to be involved in the rate-determining step, as in an S_N2 mechanism. Yet, the very low *s* values indicate an early transition state with little bonding to the nucleophile at the transition state. The transition state has almost full loss of the leaving group with little nucleophilic attack (see right), analogous to an S_N1 reaction. This interpretation shows that the *s* value can provide insight into the extent of nucleophilic attack at a transition state relative to the extent of attack during the reference reaction.

Amyes, T. L., and Jencks, W. P. "Concerted Bimolecular Substitution Reactions of Acetal Derivatives of Propionaldehyde and Benzaldehyde." *J. Am. Chem. Soc.*, **111**, 7900 (1989).



8.4.6 Edwards and Ritchie Correlations

Although there have been many attempts to provide a multi-parameter approach for correlating relative nucleophilicity, only one is examined here. We examine only this one because it gives insight into how oxidation potential, a molecular property not yet discussed, can influence nucleophilicity. Edwards and Ritchie considered that nucleophilicity arises from two parameters that reflect the ability of the nucleophile to donate electrons: basicity and oxidation potential. To the extent that a nucleophilic attack on an electrophile resembles the loss of electrons from the nucleophile to the electrophile, then the oxidation potential of the nucleophile should correlate with its reactivity. Thus, two substituent parameters were defined—E_n for oxidation potential and H for basicity, with corresponding sensitivity factors α and β (Eq. 8.45). Because Eq. 8.45 incorporates oxidation potential and basicity, it is referred to as the **oxibase scale**. The parameters E_n and H are based upon the pK_a of the conjugate acid (Eq. 8.46) and the oxidation potential of the nucleophile, as given in Eq. 8.47 (where E_o is the standard oxidation potential). A reference reaction and nucleophile are still needed, and S_N2 attack on CH_3I with water were used. This method has been found to nicely correlate a variety of different S_N2 reactions.

$$\log\left(\frac{k_{\mathrm{Nuc_X}}}{k_{\mathrm{H_2O}}}\right) = \alpha E_n + \beta H \qquad \text{(Eq. 8.45)}$$

$$H = \mathrm{p}K_a + 1.74 \qquad \text{(Eq. 8.46)}$$

$$E_n = E_o + 2.60 \qquad \text{(Eq. 8.47)}$$

The Trustees of Columbia Univ. Ex. 2047 - Page 57 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.5 Acid–Base Related Effects—Brønsted Relationships

A final linear free energy relationship that we cover is one that is still extensively used in modern research—almost as much as Hammett plots. It is called a Brønsted plot, and it relates acidity or basicity to other kinds of reactions. The reason that this LFER is still actively used is in part because this relationship is essential to an understanding of acid–base catalysis in enzymology. However, the same relationship can be used to study nucleophilicity and leaving group ability. We describe all three uses below, but we leave a more detailed analysis of the use of this relationship in studies of acid–base catalysis to Chapter 9.

8.5.1 β_{Nuc}

Some of the earliest correlations between nucleophilicity and reactivity focused solely on the pK_a of the conjugate acid of the nucleophile. If one keeps the electronic and steric properties of a series of nucleophiles similar, and uses the same solvent for the analyses, reactivity does nicely correlate with the basicity of the nucleophile (K_b; see Chapter 5). An LFER as defined in Eq. 8.48 can be used to correlate the data. This structure–function relationship is called a **Brønsted relationship**.

$$\log(k) = \beta_{Nuc} \log(K_b) + \log(C)$$
$$\text{or } \log(k) = \beta_{Nuc}\, pK_a + \log(C') \qquad \text{(Eq. 8.48)}$$

In this equation k is the rate constant for the reaction under study. In place of a substituent parameter, we use $\log(K_b)$. Therefore, the reference reaction is the deprotonation of water by the nucleophile (Eq. 8.49). Log(C) is the y intercept of the plot, and has no physical meaning. Finally, β_{Nuc} is the sensitivity factor. Plotting the pK_a of the conjugate acid of the nucleophile ($\log K_b = pK_a + \log K_w$) versus $\log(k)$ should give a straight line when the dominant factor in determining how the structure of the nucleophile affects the reaction is basicity. When $\beta_{Nuc} = 1$, the full effect of the change in basicity is reflected in the nucleophilicity, meaning that a nucleophile that is 100 times more basic than another will speed up a reaction by a factor of 100. When $\beta_{Nuc} < 1$, then the sensitivity of the nucleophilic attack on the basicity of the nucleophile is diminished.

$$Nuc^{\ominus} + H_2O \rightleftharpoons NucH + OH^{\ominus} \qquad \text{(Eq. 8.49)}$$

8.5.2 β_{LG}

Just as nucleophilicity can be found to correlate directly with basicity, the ability of a leaving group to depart is often found to correlate directly with the acidity of its conjugate acid. The same kind of equation used to correlate nucleophilicity with pK_a is used to correlate nucleofugality with pK_a (Eq. 8.50). In this case a β_{LG} is measured, which gives the sensitivity of the reaction to the acidity of the conjugate acid of the leaving group. Since the leaving group ability should increase with lower pK_as of the conjugate acid, Eq. 8.50 tells us that the β_{LG} values will be negative. It is very common to measure both β_{LG} and β_{Nuc} values when implementing a mechanistic analysis, since their comparison gives good insight into the relative amounts of nucleophilic attack and leaving group departure at the rate-determining step. An example is given in the next Connections highlight in the context of an important biochemical reaction, the hydrolysis of ATP.

$$\log(k) = \beta_{LG}(pK_a) + \log(C) \qquad \text{(Eq. 8.50)}$$

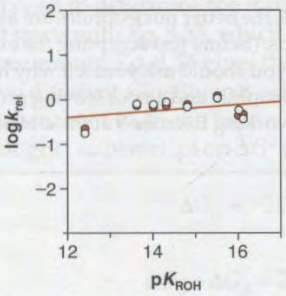
The Trustees of Columbia Univ. Ex. 2047 - Page 58 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

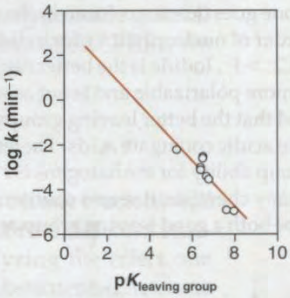
Connections

ATP Hydrolysis—How β_{LG} and β_{Nuc} Values Have Given Insight into Transition State Structures

The phosphoryl transfer reaction from ATP is one of the most common biological reactions, being used to store energy, generate concentration gradients, and to transduce signals. The extent of bond breaking and forming that occurs at the transition state for phosphoryl transfer to alcohols has been studied to give insight into transition state structures during enzyme-catalyzed processes.

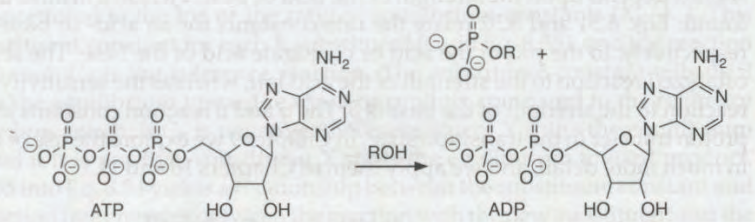
Shown below is the Brønsted plot for the reaction of ATP^{4-}, and the complex between Mg^{2+} and ATP^{4-}, as a function of the pK_a of primary alcohol nucleophiles (closed and open circles, respectively). The values of β_{Nuc} are 0.07 and 0.06, respectively, reflecting that the nucleophilicity of the alcohols has little effect on the rate of the reaction. This indicates very little bond formation to the nucleophiles in the transition state.

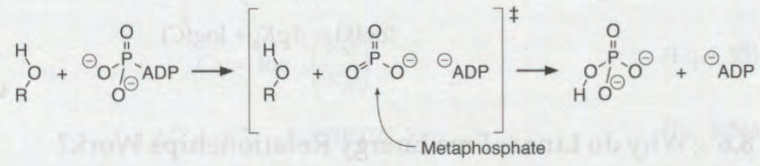




Shown above is a Brønsted plot for the hydrolysis reaction (phosphoryl transfer to water) of various phosphoanhydrides as a function of leaving group pK_a. The slope of the line (β_{LG}) is near –1.1. This value is large, indicating that there is a significant amount of bond cleavage to the leaving group at the transition state. In fact, because the absolute value is greater than 1, this leaving group departure is actually more sensitive to the structure and nature of the anion than is the reference deprotonation reaction of water. The small β_{Nuc} and large β_{LG} were interpreted to support a dissociative mechanism for the hydrolysis of ATP, with a transition state involving considerable metaphosphate-like character (see below).

Herschlag, D., and Admiraal, S. J. "Mapping the Transition State for ATP Hydrolysis: Implications for Enzymatic Catalysis." *Curr. Biol.*, **2**, 729–739 (1995).



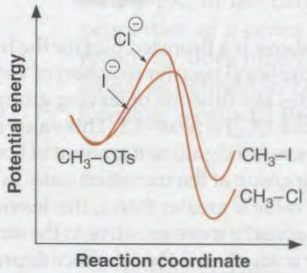


The Trustees of Columbia Univ. Ex. 2047 - Page 59 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Going Deeper

How Can Some Groups be Both Good Nucleophiles and Good Leaving Groups?

As noted earlier, nucleophilicity in polar protic solvents increases as one goes down a column in the periodic table. Hence, the order of nucleophilicity for halide anions is $I^- > Br^- > Cl^- > F^-$. Iodide is the better nucleophile because it is more polarizable and is not as well solvated. We also stated that the better leaving groups are those that have the more acidic conjugate acids. Therefore, the order of leaving group ability for the halogens is $I^- > Br^- > Cl^- > F^-$, also. To many chemists, it seems counterintuitive that a group can be both a good leaving group and a good nucleophile.



To understand this dichotomy we must understand that by "good" we mean faster—the groups are kinetically "good". It does not mean that the bond being formed or broken is particularly strong or weak. To see this, let's examine the hypothetical reaction coordinate diagrams for the S_N2 substitution reactions of methyl tosylate with iodide and chloride shown to the side. A C–Cl bond is stronger than a C–I bond, so methyl chloride is placed lower in energy on the diagram. We find from experiment that the barrier to the reaction is lower with iodide than with chloride even though the product is more stable with chloride. Iodide is therefore a better nucleophile.

Now consider the reverse reaction—that of tosylate displacing chloride or iodide. Due to microscopic reversibility, the reverse reactions have to proceed through the same transition states. Therefore, the barrier to the reverse reaction is also lower for iodide, and hence, iodide is the better leaving group. Once you tie the concept of microscopic reversibility to both nucleophilicity and leaving group ability, it is clear that in going down a column in the periodic table, the better nucleophiles are also the better leaving groups. (Before just accepting the explanation given above, you should ask yourself why hydroxide is a good nucleophile and a poor leaving group. Alternatively, try working Exercise 9 at the end of the chapter.)

8.5.3 Acid–Base Catalysis

Recall that Eqs. 8.48 and 8.50 are called Brønsted linear free energy relationships. If an acid or base is involved in the rate-determining step of a reaction, the rate of that reaction should depend upon the strength of the acid or base. Hence, a Brønsted correlation is often found. Eqs. 8.51 and 8.52 relate the rate constants for an acid- or base-catalyzed reaction, respectively, to the pK_a of the acid or conjugate acid of the base. The sensitivity of an acid-catalyzed reaction to the strength of the acid is α, whereas the sensitivity of a base-catalyzed reaction to the strength of the base is β. The α and β reaction constants indicate the extent of proton transfer in the transition state. In Chapter 9 we explore the use of these two equations in much more detail, and we apply them in Chapters 10 and 11.

$$\log(k) = -\alpha pK_a + \log(C) \qquad \text{(Eq. 8.51)}$$

$$\log(k) = \beta pK_a + \log(C) \qquad \text{(Eq. 8.52)}$$

8.6 Why do Linear Free Energy Relationships Work?

All the LFERs given above included a reaction constant that gave the sensitivity of the reaction to the change in substituent, and each substituent behaved the same in each reaction. It seems reasonable that an electron donating or electron withdrawing group should be electron donating or electron withdrawing regardless of the reaction. Similarly, a good leaving group is always a good leaving group, regardless of the reaction. Yet, why is the *relative* influence of the groups the same in each reaction, and why is their degree of influence the same? For example, why shouldn't nitro be more electron withdrawing than a cyano in one

The Trustees of Columbia Univ. Ex. 2047 - Page 60 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

reaction, and vice versa in a different reaction? Further, why shouldn't one reaction be very sensitive to the addition of electron withdrawing groups and not electron donating groups, while another reaction is very sensitive to electron donating groups but not electron withdrawing groups? In general, we do not find this behavior. An LFER, such as a linear Hammett plot, Swain–Scott plot, or Brønsted plot, means that the relative influence of the substituents is always the same. To understand this behavior, we must first analyze some general mathematics that is the basis of all LFERs. After deriving the general form of all LFERs, we can return to this issue.

8.6.1 General Mathematics of LFERs

We first need to understand why the effect of changing substituents on one reactant will be similar to the effect on another reactant, even when the sensitivity of two different reactions to a change in substituents is quite different. Let's start by analyzing the effect one would expect on the free energy of a reaction due to a change in a substituent. The same analysis can be applied to the activation energy of a reaction. To determine how substituents affect equilibria, we need two reference points. First, we need a reference substituent, and second, we need a reference reaction. For example, in a Hammett analysis, the substituent that all other substituents are compared to is hydrogen, and the reaction that all reactions are compared to is the dissociation of benzoic acid. Here, we keep the analysis general.

The method used to determine the influence of new substituents compared to the reference substituent starts with Eq. 8.53, which gives the relationship of an equilibrium constant to the reaction free energy. Eq. 8.54 gives the difference in reaction free energies for the same reaction with two different substituents where ΔG_o is for the reference substituent and ΔG_X is for the new substituent X. In the following analysis, for simplicity of notation, we have dropped the "nought" superscript on ΔG^o that indicates standard conditions.

$$\Delta G_o = -2.303RT \log_{10}(K_o) \qquad \text{(Eq. 8.53)}$$

$$\Delta G_o - \Delta G_X = 2.303RT \log_{10}\left(\frac{K_X}{K_o}\right) \qquad \text{(Eq. 8.54)}$$

Eq. 8.54 tells us that the difference in free energies of two reactions with different substituents is directly proportional to the log of the ratio of equilibrium constants (K_X/K_o). This quantity is the **substituent constant** for each X substituent (C_X in Eq. 8.55), and the reaction we use to measure each C_X is the **reference reaction**. The substituent constant tells us if substituent X shifts the equilibrium toward reactant or product compared to the reference substituent, and by how much. If C_X is negative, then substituent X shifts the equilibrium toward reactant, and if it is positive, substituent X shifts the equilibrium toward product. Substituting Eq. 8.55 into Eq. 8.54 yields a relationship between the substituent constant and the difference in reaction free energies between the reaction with the new substituent and the reaction with the reference substituent (Eq. 8.56).

$$C_X = \log_{10}\left(\frac{K_X}{K_o}\right) \qquad \text{(Eq. 8.55)}$$

$$\Delta G_o - \Delta G_X = 2.303RT(C_X) \qquad \text{(Eq. 8.56)}$$

The next step is to see if the various substituents influence a different reaction in the same manner as they influence the reference reaction. Another equation identical to Eq. 8.56 is written for the new reaction under study, but we designate it with primes on the variables (Eq. 8.57). As discussed earlier, this reaction can be totally unrelated to the reference reaction. Because we want to know the relative effect of the substituents on the two reactions, we take a ratio of Eqs. 8.56 and 8.57, giving Eq. 8.58. This equation states that the ratio of the free energy differences for the two reactions under comparison is the ratio of the log of the equilib-

The Trustees of Columbia Univ. Ex. 2047 - Page 61 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

rium constants of the new reaction to the log of the equilibrium constants for the reference reaction (C_X'/C_X). In our analysis, this ratio is defined as the **reaction constant** (Q in this generalized example). The ratio Q directly tells us if the reaction under study is more or less sensitive to a change in substituents than the reference reaction. If Q is greater than one, the substituents affect the thermodynamics of the new reaction to a greater extent than the substituents affect the reference reaction. Conversely, if Q is less than one, the reaction is less sensitive to changes in substituents than the reference reaction. Hence, we have also called Q the **sensitivity factor**. Rearranging Eq. 8.58 to 8.59 and simplifying to Eq. 8.60 gives further insight into LFERs. We now see that the extent to which the free energy of the new reaction is changed, via a change in substituent, is proportional to the extent to which the reference reaction was changed by the same substitution, but enhanced or diminished by Q.

$$\Delta G_o' - \Delta G_X' = 2.303RT(C_X') \qquad \text{(Eq. 8.57)}$$

$$\frac{\Delta G_o' - \Delta G_X'}{\Delta G_o - \Delta G_X} = \frac{C_X'}{C_X} = Q \qquad \text{(Eq. 8.58)}$$

$$(\Delta G_o' - \Delta G_X') = Q(\Delta G_o - \Delta G_X) \qquad \text{(Eq. 8.59)}$$

$$\Delta\Delta G' = Q\Delta\Delta G$$
$$\text{where } (\Delta G_o' - \Delta G_X') = \Delta\Delta G' \text{ and } (\Delta G_o - \Delta G_X) = \Delta\Delta G \qquad \text{(Eq. 8.60)}$$

The LFERs given in Eqs. 8.57 and 8.59 are not those routinely applied to experiments, such as a Hammett plot. Instead, a form that relates the sensitivity factor Q and the substituent constant C_X to a number that can be experimentally determined is used. To derive this form of the LFER, we perform some algebraic manipulations (left as an Exercise at the end of the chapter) to derive Eq. 8.61. This final form of an LFER is the one used in most such analyses (see Sections 8.3–8.5). An identical equation can be written for rate constants (Eq. 8.62).

$$\log_{10}\left(\frac{K_X'}{K_o'}\right) = QC_X \qquad \text{(Eq. 8.61)}$$

$$\log_{10}\left(\frac{k_X'}{k_o'}\right) = QC_X \qquad \text{(Eq. 8.62)}$$

8.6.2 Conditions to Create an LFER

In principle, the reaction constant Q does not have to be a constant for all substituents, because LFERs do not derive from any thermodynamic law. However, chemists find empirically that it most often is. When Q is constant, it means that two different reactions respond to all substituents in the same manner, but just to differing extents. To understand how this can be possible, we must substitute $\Delta G = \Delta H - T\Delta S$ into Eq. 8.60, giving Eq. 8.63.

$$(\Delta\Delta H' - T\Delta\Delta S') = Q(\Delta\Delta H - T\Delta\Delta S) \qquad \text{(Eq. 8.63)}$$

Eq. 8.63 has two independent variables, $\Delta\Delta H'$ and $\Delta\Delta S'$ ($\Delta\Delta H$ and $\Delta\Delta S$ are already determined) and therefore can only hold when one of three conditions are met.

- First, the $\Delta\Delta H$s are coincidentally the same for both the new reaction under study and the reference reaction, and the $\Delta\Delta S$s are linearily proportional for the two reactions being compared.
- Second, the $\Delta\Delta S$s are coincidentally the same for both reactions and the $\Delta\Delta H$s are linearily proportional.

The Trustees of Columbia Univ. Ex. 2047 - Page 62 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

- Or third, the $\Delta\Delta H$s and $\Delta\Delta S$s are linearly related to each other for both the reference reaction and the new reaction. That is, for each reaction, as ΔH goes up ΔS increases also. In other words, they scale proportionately. In this scenario, the enthalpy and entropy compensate for each other, because in the Gibbs free energy equation ($\Delta G = \Delta H - T\Delta S$) the enthalpy and entropy terms have opposite algebraic signs. This is actually the most common situation, and is referred to as the **enthalpy–entropy compensation effect** (see Chapter 4).

Before exploring why enthalpy–entropy compensation effects exist, it is instructive to delineate the temperature dependence of LFERs. Because temperature dependence has been mostly explored with regard to kinetics, we present this discussion below in terms of activation parameters, but it also applies to reaction free energies.

8.6.3 The Isokinetic or Isoequilibrium Temperature

If we assume a linear relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the same reaction but with different substituents we can obtain Eq. 8.64. For most reactions, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are unknown. However, for those cases where these parameters have been measured and an LFER was found to hold, Eq. 8.64 does indeed correlate the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ parameters. The slope β is a proportionality constant between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, telling us how sensitive the compensation effect is between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Eq. 8.64 tells us that as the enthalpy of activation becomes larger and less favorable, the entropy of activation becomes larger, too, but is more favorable, leading to a compensating effect.

$$\Delta H^{\ddagger} = \beta\Delta S^{\ddagger} + \Delta H_o^{\ddagger} \qquad \text{(Eq. 8.64)}$$

Using the Gibbs free energy equation ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) in combination with Eq. 8.64 leads to Eq. 8.65. Now the proportionality constant β is seen to have units of temperature, and is referred to as the **isokinetic** or **isoequilibrium temperature** for kinetic or thermodynamic LFERs, respectively.

$$\Delta G^{\ddagger} = \Delta H_o^{\ddagger} - (T - \beta)\Delta S^{\ddagger} \qquad \text{(Eq. 8.65)}$$

Eq. 8.65 states that the Gibbs free energies of activation for the same reaction with different substituents can be considered to be made up of two terms. One is constant, regardless of the substituent ($\Delta H_o^{\ddagger}$), and one is an entropy term that is different for each substituent. The extent that the entropy influences the reaction depends upon the difference between the experimental temperature T and the isotemperature β. A corollary of Eq. 8.65 is that LFERs should be interpreted with care when measured at temperatures near the isokinetic or isoequilibrium temperature. In other words, for the same reaction with varying substituents or in different solvents, if the enthalpy is linearly related to the entropy via a relationship such as Eq. 8.64, there will be a temperature where changes in substituents or solvent will not affect the rate or equilibrium at all. Therefore, when one measures any reaction constant and that value is near zero, it could simply be that the temperature of analysis is coincidentally near or at the isokinetic or isoequilibrium temperature. Hence, small reaction constants (such as ρ, s, m, β_{LG}, etc.) should be interpreted with care when drawing conclusions about reaction mechanisms. However, having stated this caveat related to LFERs, it is true that for most common organic reactions the isokinetic or isoequilibrium temperature is outside of experimentally accessible conditions.

8.6.4 Why does Enthalpy–Entropy Compensation Occur?

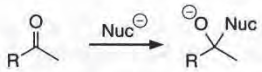
We have presented the fact that most reactions for which an LFER can correlate rate constants or equilibrium constants have linear relationships between ΔH and ΔS as described by Eq. 8.64. Because increases in $\Delta H^{\ddagger}$ impede a reaction while increases in $\Delta S^{\ddagger}$ assist a reaction, the two affects are compensating. This compensation is a general phenomenon,

The Trustees of Columbia Univ. Ex. 2047 - Page 63 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

one that is often neglected when chemists attempt to improve the rate or yield of a reaction by changing substituents or reaction conditions. The most common rationalizations of enthalpy–entropy compensation invoke steric or solvation effects, and we discuss both briefly here.

Steric Effects

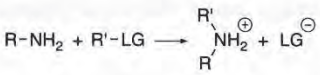
Consider what happens when you increase the steric hindrance to attack of a nucleophile on a carbonyl by increasing the size of the R group (Eq. 8.66). A larger R group would lead to a more crowded transition state, thereby raising the $\Delta H^{\ddagger}$. However, the nucleophile is further away from the carbonyl carbon at the transition state, and therefore it would be less tightly held at the transition state than the reaction with the smaller R group. These structural issues manifest themselves as a lower loss in entropy and therefore a more favorable entropy of activation.



(Eq. 8.66)

Solvation

Let's examine an S_N2 reaction between an amine and an alkyl halide to illustrate enthalpy–entropy compensation effects due to differential solvation (Eq. 8.67). The transition state is polar relative to the reactants, so the enthalpy of activation should be lower in increasingly polar solvents. In addition, the developing charges in the transition state will cause the solvent to be more constrained than when solvating the neutral amine or alkyl halide, and this effect will be greater with the more polar solvent. Hence, a higher polarity solvent leads to a lower $\Delta H^{\ddagger}$, but also makes $\Delta S^{\ddagger}$ more unfavorable; as a result, these are compensating effects.



(Eq. 8.67)

These two examples are indicative of a general phenomenon. When enthalpy becomes more favorable (stronger bonding) the system typically becomes more organized (meaning less entropy). Conversely, when the enthalpy change is slight there is often more disorganization at the transition state. We encountered this same phenomenon when we discussed binding in Chapter 4. Stronger intramolecular forces lead to stronger binding, but also more restricted movement of the compounds involved in the binding event, therefore compensating for each other with respect to the Gibbs free energy.

8.7 Summary of Linear Free Energy Relationships

A large number of LFERs were discussed above; many more can be found in the literature or other physical organic chemistry texts. This is especially true for Hammett-related sigma constants. For example, here is an abbreviated list of some you may encounter in the literature: σ^0, σ^n, and σ_I for the ionization of carboxylic acids other than benzoic acid; σ_I^q for inductive effects; σ^I and σ' for the effects of acidities in bicyclic compounds; and σ_R, σ_R^o, $\sigma_{R(BA)}$, σ_R^+, and σ_R^- for various resonance effects. The number of these scales and their uses quickly become confusing.

Our intent here was to focus only on those that are still commonly used, and on the conceptual foundation of the methodology. The student should now be prepared to understand any new LFERs encountered in the literature. At this point, though, it may be helpful to tabulate the LFERs we have discussed in one place, so that their uses can be quickly deciphered

The Trustees of Columbia Univ. Ex. 2047 - Page 64 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Table 8.6
A Summary of the Most Common LFERs Used*

LFER	Substituent constant	Reference reaction	Used to study	Reaction constant and its meaning relative to the reference reaction
Hammett	σ	Ionization of benzoic acid	Inductive effects	$\rho > 1$, more sensitive $0 < \rho < 1$, less sensitive $\rho = 0$, not sensitive $\rho < 0$, positive charge created
Hammett	σ^-	Ionization of phenol	Resonance in addition to induction	Same as above
Hammett	σ^+	Ionization of phenyldimethyl chloromethane	Resonance in addition to induction	Same as above
Taft	E_s	Hydrolysis of methyl esters	Steric size	$\delta > 1$, more sensitive $\delta < 1$, less sensitive
Grunwald–Winstein	Y	Ionization of *t*-BuCl in 80:20 $EtOH/H_2O$	Ionizing power of solvent	$m > 1$, more sensitive $m < 1$, less sensitive
Swain–Scott	n	S_N2 reaction of methyl iodide in water	Nucleophilicity	$s > 1$, more sensitive $s < 1$, less sensitive
Brønsted	pK_a	Acidity in water	Nucleophilicity	$\beta_{Nuc} > 1$, more sensitive $\beta_{Nuc} < 1$, less sensitive
Brønsted	pK_a	Acidity in water	Leaving group departure	$\beta_{LG} > -1$, more sensitive $\beta_{LG} < -1$, less sensitive
Brønsted	pK_a	Acidity in water	Acid catalysis	$\alpha > 1$, more sensitive $\alpha < 1$, less sensitive
Brønsted	pK_a	Acidity in water	Basic catalysis	$\beta > 1$, more sensitive $\beta < 1$, less sensitive

*Not all of the LFERs discussed in the text are included in Table 8.6. Only those most likely to be encountered in modern research are included.

when one is designing experiments. Table 8.6 gives the names of the major LFERs, the substituent constant, the reference reaction, the kinds of effects they are used to explore, and the meaning of the reaction constant.

8.8 Miscellaneous Experiments for Studying Mechanisms

A large number of experiments have been presented in Chapters 7 and 8 for the study of reaction mechanisms—namely, kinetic analyses, isotope effects, and structure–function analyses. These are standard experimental tools associated with physical organic chemistry. However, the experimentalist can often devise studies that are completely different from any of those presented thus far, depending upon his or her imagination and chemical ingenuity. In this section we summarize some of the more common approaches. We first analyze the most obvious experiments to perform, such as product and intermediate identification, but also more subtle experiments such as cross-over and isotope scrambling. Unlike our analyses of the isotope effect and substituent effects, the following techniques are given only brief general discussions, followed by one or more examples in Connections highlights. For most of the techniques mentioned, we give more examples in Chapters 9–12.

The Trustees of Columbia Univ. Ex. 2047 - Page 65 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.8.1 Product Identification

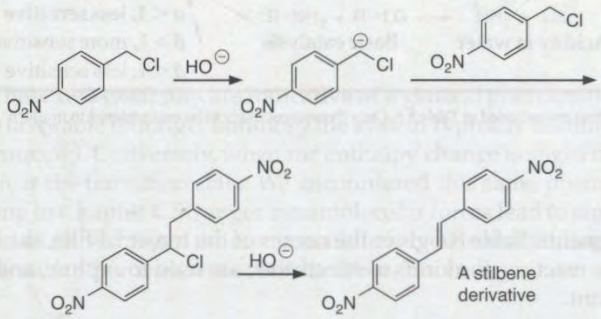
The experiment that should be performed first in the analysis of any mechanism is the determination of the products of the reaction. This experiment may seem obvious, but it is worth stating because failure to do so can cause problems (see the Connections highlight below). In particular, as much as possible, it is important to identify *all* the products of a reaction. Doing so is equivalent to ensuring that the **mass balance** of the reaction is complete; that is, everything that goes in as a reactant comes out as a product. Sometimes, identification of a minor product will provide a valuable clue as to the kind(s) of mechanistic pathways that are going on in the reaction. Alternatively, it is dangerous to make sweeping mechanistic conclusions based on a product that is present in only very low yield if we don't know the other products of the reaction.

Connections

An Example of an Unexpected Product

In the reaction of hydroxide with *p*-nitrobenzyl chloride, you might expect *p*-nitrobenzyl alcohol to be the major product via a simple S_N2 reaction. However, *p*-nitrobenzyl chloride is acidic enough to be deprotonated by hydroxide, leading to a carbon nucleophile that reacts with a second equivalent of *p*-nitrobenzyl chloride, subsequently giving the stilbene via elimination. Thus, without identification of the product one might have interpreted the kinetic data incorrectly.

Tewfik, R., Fouad, F. M., and Farrell, P. G. "Elimination Reactions. I. Reaction of Bis(4-nitrophenyl)methyl Chloride with Sodium Hydroxide in Aqueous Dioxane." *J. Chem. Soc., Perkin Trans.*, **2**, 31 (1974).



The Trustees of Columbia Univ. Ex. 2047 - Page 66 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.8.2 Changing the Reactant Structure to Divert or Trap a Proposed Intermediate

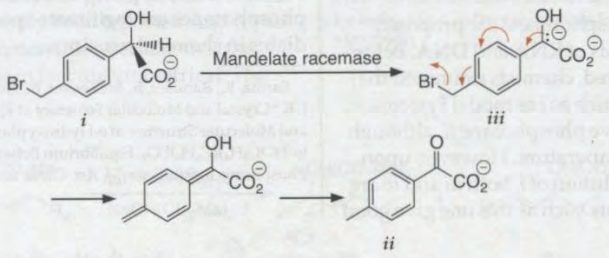
The nature of an intermediate can sometimes be deciphered by synthesizing a new reactant that is similar to the actual reactant under study, but for which the intermediate being proposed can react in a new and predictable manner. There are no standard ways to approach this kind of experiment, and you must design your own experiments on a case-by-case basis. We draw upon an enzymatic reaction as an example of the application of this technique.

Connections

Designing a Method to Divert the Intermediate

The enzyme mandelate racemase interconverts the enantiomers of mandelate ion (2-hydroxyphenylacetic acid). A carbanion alpha to the carboxylate was proposed as the intermediate formed. To test for the presence of this intermediate, an analog of mandelate ion, *i*, was synthesized and subjected to racemization by the enzyme. The product isolated was *ii*, which can result from formation of a carbanion and a subsequent 1,6-elimination of bromide followed by tautomerization. The result supported the intermediacy of carbanion *iii* in the mandelate ion pathway.

Lin, D. T., Powers, V. M., Reynolds, L. J., Whitman, C. P., Kozarich, J. W., and Kenyon, G. L. "Evidence for the Generation of .Alpha.-carboxy-.alpha.-hydroxy-*p*-xylylene from *p*-(Bromomethyl)mandelate by Mandelate Racemase." *J. Am. Chem. Soc.*, **110**, 323 (1988).

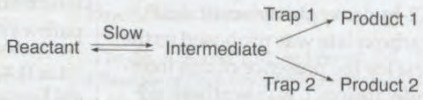


The Trustees of Columbia Univ. Ex. 2047 - Page 67 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.8.3 Trapping and Competition Experiments

A common method for intermediate identification is trapping of the intermediate with an added reagent. Several radical traps exist (see Section 8.8.8), and many good nucleophiles make viable traps for transient electrophiles such as carbocations. You should use your own chemical insight to devise traps for intermediates such as carbanions, carbenes, etc. Reactive intermediates are short lived, though, so the trap must be very reactive to compete with the standard reaction path of the reactive intermediate. Also, because the trapping reaction will typically be bimolecular, high concentrations of trap will often be required. Alternatively, the trap could be covalently tethered to the reactant, facilitating capture of the reactive intermediate.

A variant of a trapping experiment is a **competition experiment**. In our analysis of kinetic experiments in Chapter 7, we said that steps beyond the rate-determining step do not affect the kinetics, and thus information about them cannot be obtained. This lack of a kinetic dependence often leaves a large portion of the mechanism invisible to kinetic analysis. One way to probe chemical steps past the rate-limiting step is to use competition experiments. A competition experiment involves the addition of two or more reagents that compete for one or more intermediates. It is a variant on the trapping experiment, where now more than one trap is used (Eq. 8.68). The ratio of products derived from the different traps tells the ratio of rate constants for the reaction of the traps with the intermediate. From this ratio, some insight into the nature of the intermediate can be gained. The experiment is viable only when the trapping reaction is under kinetic control.



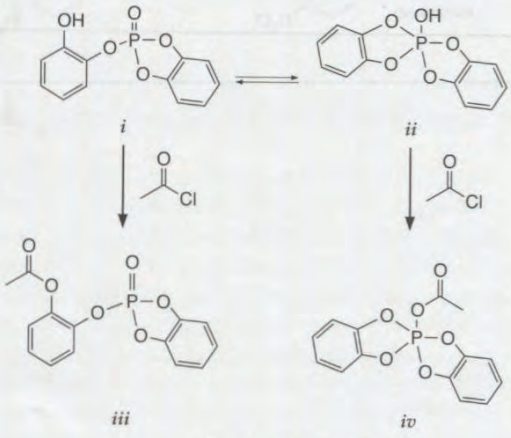
(Eq. 8.68)

Connections

Trapping a Phosphorane Legitimizes Its Existence

Pentacoordinate species (phosphoranes) are proposed intermediates in the hydrolysis of RNA and DNA. Before such species were well accepted, chemists examined the chemistry of phosphoesters such as *i* as model systems. Compound *i* can cyclize to give phosphorane *ii*, although *ii* was never seen at room termperature. However, upon adding acetyl chloride to a solution of *i*, both *iii* and *iv* are isolated. Trapping experiments such as this one give good evidence that *ii* is present in a solution of *i*, showing that phosphoranes are legitimate species and possible intermediates in chemical reactions.

Sarma, R., Ramirez, F., McKeever, B., Nowakowski, M., and Marecek, J. F. "Crystal and Molecular Structure of Phosphate Esters. 9. Crystal and Molecular Structure of *o*-Hydroxyphenyl-*o*-phenylene Phosphate, (o-HOC_6H_4)(C_6H_4)PO_4. Equilibrium Between Pentavalent and Tetravalent Phosphorus in Solutions." *J. Am. Chem. Soc.*, **100**, 5391 (1978).



Phosphorane trapping

The Trustees of Columbia Univ. Ex. 2047 - Page 68 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

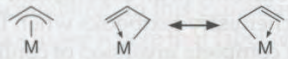
8.8.4 Checking for a Common Intermediate

Often similar reactions proceed via the same intermediate. For example, the S_N1 solvolysis of *t*-butyl bromide and *t*-butyl iodide in water would both be presumed to proceed via the *t*-butyl cation. We could easily verify this conclusion by performing a competition experiment where the addition of two nucleophilic traps would give two products resulting from the same intermediate in the same ratio. Any deviation in products and ratios would indicate different intermediates. This is exactly the same concept that was used in our example of competition experiments, except now we compare the product ratio from two different reactants.

Connections

Checking for a Common Intermediate in Rhodium-Catalyzed Allylic Alkylations

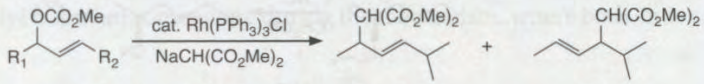
A very common structure in organometallic transformations is the π-allyl complex (see Chapter 12). Such a structure is a resonance hybrid of two forms with σ and π bond character. These structures are formed from allylcarbonates and can undergo attack by various carbon-based nucleophiles to give extended allylic systems.



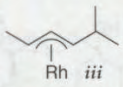
π-Allyl complex — Individually known as σ + π complexes

A rhodium-based system that gives excellent control of stereochemistry has recently been reported, and it was shown by testing for a common intermediate that the putative allyl–Rh species is in fact unsymmetrical. The experiment consisted of subjecting the unsymmetrical secondary allylic carbonates *i* and *ii* to reaction with catalytic $Rh(PPh_3)_3Cl$. Conventional wisdom predicted the two would form the same π-allyl complex *iii*. If so, compound *iii* should give upon reaction with the nucleophile the two products shown in the same ratio regardless of whether *i* or *ii* is the starting material. Instead, the reactions of *i* and *ii* retained regiochemistry, with the nucleophile in both cases attached to the carbon that possessed the leaving group in the starting material. Hence, a common intermediate such as *iii* is *not* formed. The authors interpreted this result to support distinct σ + π intermediates instead of symmetric π-allyl complexes.

Evans, P. A., and Nelson, J. D. "Conservation of Absolute Configuration in the Acyclic Rhodium-Catalyzed Allylic Alkylation Reaction: Evidence for an Enyl (σ + π) Organorhodium Intermediate." *J. Am. Chem. Soc.*, **120**, 5581 (1998).



i: R_1 = Me, R_2 = *i*Pr	97	3
ii: R_1 = *i*Pr, R_2 = Me	3	97



Symmetrical π-allyl intermediate

The Trustees of Columbia Univ. Ex. 2047 - Page 69 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

8.8.5 Cross-Over Experiments

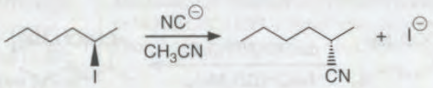
A cross-over experiment is used to determine if a reactant breaks apart to form intermediates that are released to solution before they recombine to give product. To accomplish this kind of experiment, we use two similar reactants, one that is labeled in some manner to distinguish it from the other. The label can be a different substituent or an isotope; the more subtle the variation the better. Consider a simple reaction in which A–B reacts to give C–D. We want to know whether the A and B fragments, which give rise to C and D, respectively, are ever free in the flask. The reactant (A–B) and its labeled variant (A*–B* in Eq. 8.69) are mixed together, and we analyze the products. No scrambling of the labeled and unlabeled portions of the reactant indicates no free intermediates to cross over between the two reactions (Eq. 8.69). When intermediates are released to solution, scrambling can occur (Eq. 8.70). However, sometimes the observation of no scrambling can still be consistent with fragmentation, where recombination of the intermediates occurs faster than diffusion of the intermediates into bulk solution. As always, a negative result should be interpreted with caution. In favorable cases, however, a cross-over experiment gives us information about whether a reaction occurs by an intramolecular or intermolecular process (look at Section 12.2.3 for examples).

$$\text{A–B} + \text{A*–B*} \longrightarrow \text{C–D} + \text{C*–D*} \qquad \text{(Eq. 8.69)}$$

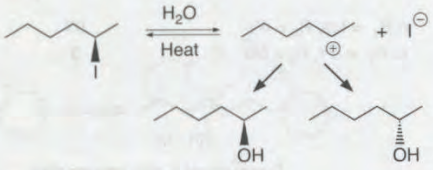
$$\text{A–B} + \text{A*–B*} \longrightarrow \text{C–D} + \text{C*–D*} + \text{C*–D} + \text{C–D*} \qquad \text{(Eq. 8.70)}$$

8.8.6 Stereochemical Analysis

Very often the existence of an intermediate and/or the nature of a reaction can be deciphered from an analysis of the stereochemical outcome of an experiment. This type of experiment is covered in all introductory organic chemistry textbooks when the S_N2 and S_N1 reactions are first introduced. The observation of complete inversion of configuration in the product derived from an enantiomerically pure reactant is indicative of no intermediate and a concerted displacement of the leaving group by the nucleophile (Eq. 8.71, S_N2). On the other hand, complete or partial racemization is indicative of a planar intermediate (Eq. 8.72, S_N1). This simple but elegant probe into the existence and nature of an intermediate can be extended to much more complicated reactions, and stereochemical analysis is one of the most powerful mechanistic probes. We give a biochemical example in the Connections highlight, and we will see many examples of stereochemical analyses in subsequent chapters.



(Eq. 8.71)



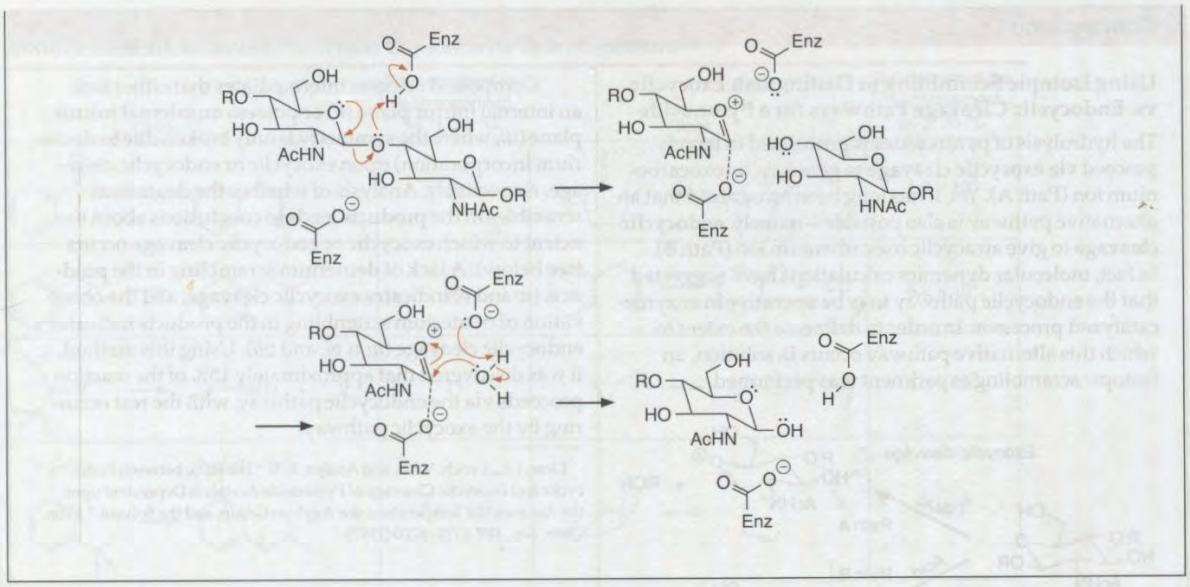
(Eq. 8.72)

Connections

Pyranoside Hydrolysis by Lysozyme

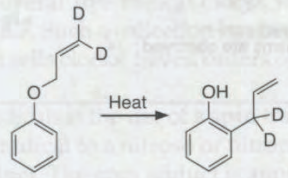
The hydrolysis of β-pyranosides by lysozyme occurs strictly with retention of configuration at the anomeric center, giving a β-hemiacetal product. To explain the retention, the following mechanism is postulated. Protonation of the **aglycon group** (the leaving group attached to the anomeric center) by an enzyme carboxylic acid occurs during leaving group departure. Either backside nucleophilic attack or ion pairing with an enzyme carboxylate protects one face of the anomeric carbon from reaction with water. Thus, replacement of the departing saccharide with water leads to addition from the same face as the leaving group, giving a **double inversion** and hence overall retention. This study is a classic case of examining the stereochemical outcome of an enzyme-catalyzed reaction, providing support for a particular mechanistic scenario.

The Trustees of Columbia Univ. Ex. 2047 - Page 70 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

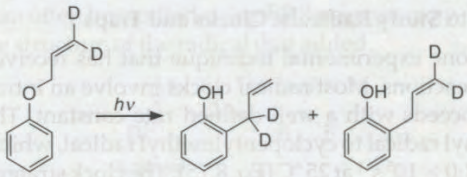


8.8.7 Isotope Scrambling

A related tool that can give us insight into the involvement of symmetrical intermediates is isotope scrambling. In this experiment one isotopically labels one portion of the reactant and checks to see where that label resides in the product. The position of the label in the product can tell us about the nature of the intermediate and / or whether dissociation has occurred to give a symmetrical intermediate. The classic check for a tetrahedral intermediate in an acyl transfer experiment is a good example (see Section 10.17.2). For another example, consider the thermal and photochemical Claisen rearrangements shown in Eqs. 8.73 and 8.74. Labeling the terminal position of the allyl group of the reactant and analyzing the products gives insight into the nature of the intermediates. The label cleanly migrates to only one place in the thermal rearrangement, suggesting a concerted mechanism with no free symmetric allyl fragment (see Section 15.5.4). However, the photochemical rearrangement gives a 50:50 scrambling of the label on both ends of the allyl fragment, suggesting the intermediacy of a symmetric allyl fragment somewhere during the mechanism, where both ends can react equally.



(Eq. 8.73)



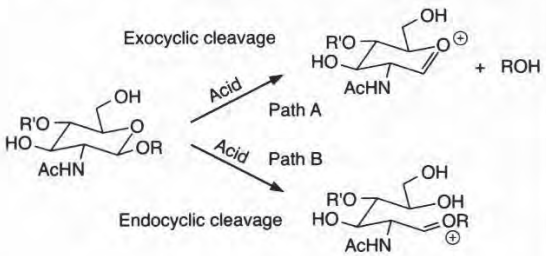
(Eq. 8.74)

The Trustees of Columbia Univ. Ex. 2047 - Page 71 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

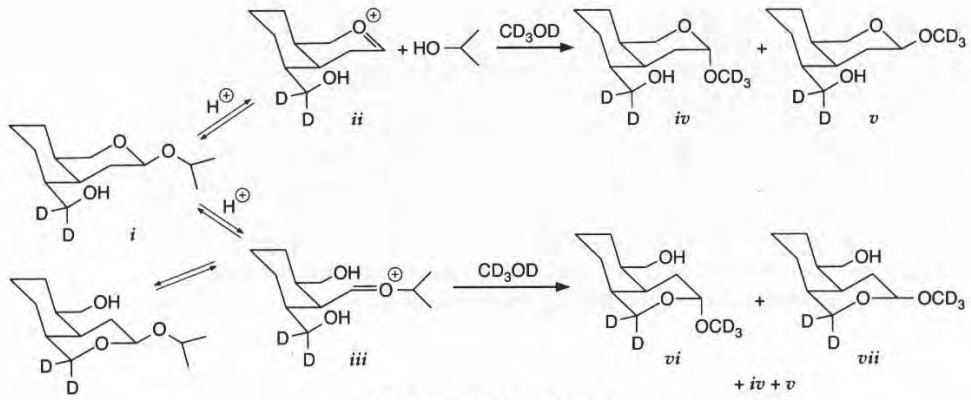
Using Isotopic Scrambling to Distinguish Exocyclic vs. Endocyclic Cleavage Pathways for a Pyranoside

The hydrolysis of pyranosides is postulated to largely proceed via **exocyclic cleavage** to give a cyclic oxocarbenium ion (Path A). Yet, it has long been recognized that an alternative pathway is also possible—namely, **endocyclic cleavage** to give an acyclic oxocarbenium ion (Path B). In fact, molecular dynamics calculations have suggested that the endocyclic pathway may be operative in enzyme-catalyzed processes. In order to delineate the extent to which this alternative pathway occurs in solution, an isotopic scrambling experiment was performed.



Compound *i* creates intermediates that either lack an internal mirror plane (*ii*) or possess an internal mirror plane (*iii*, where the symmetry is only broken due to deuterium incorporation) upon exocyclic or endocyclic cleavage, respectively. Analysis of whether the deuterium scrambles in the products leads to conclusions about the extent to which exocyclic or endocyclic cleavage occurs (see below). A lack of deuterium scrambling in the products (*iv* and *v*) indicates exocyclic cleavage, and the observation of deuterium scrambling in the products indicates endocyclic cleavage (*iv*, *v*, *vi*, and *vii*). Using this method, it was discovered that approximately 15% of the reaction proceeds via the endocyclic pathway, with the rest occurring by the exocyclic pathway.

Liras, J. L., Lynch, V. M., and Anslyn, E. V. "The Ratio between Endocyclic and Exocyclic Cleavage of Pyranoside Acetals is Dependent upon the Anomer, the Temperature, the Agylcon Group, and the Solvent." *J. Am. Chem. Soc.*, **119**, 8191–8200 (1997).



Both mechanisms are observed

8.8.8 Techniques to Study Radicals: Clocks and Traps

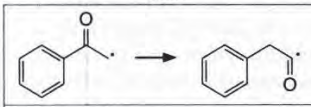
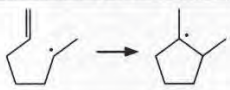
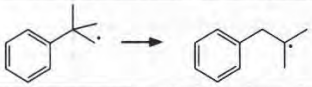
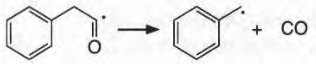
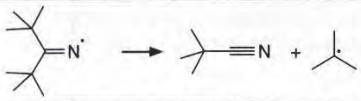
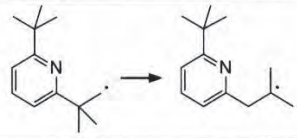
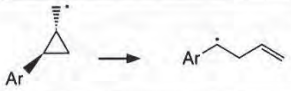
Radical clocks are one experimental technique that has received considerable use in the analysis of radical reactions. Most radical clocks involve an intramolecular free radical rearrangement that proceeds with a well-defined rate constant. The prototype is the rearrangement of 5-hexenyl radical to cyclopentylmethyl radical, which occurs with a unimolecular rate constant of $1.0 \times 10^5\ s^{-1}$ at 25 °C (Eq. 8.75). The clock strategy is to embed a 5-hexenyl unit into the reactive system of interest. If a radical forms, and if its lifetime is comparable to or greater than 10^{-5} s, cyclopentylmethyl-derived products should form.



(Eq. 8.75)

The Trustees of Columbia Univ. Ex. 2047 - Page 72 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

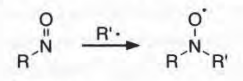
Table 8.7
Various Radical Clocks and Their Rate Constants for Rearrangements*

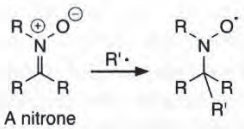
Clock	Rate constant for rearrangement (s^{-1}), 25 °C	Clock	Rate constant for rearrangement (s^{-1}), 25 °C
	10		1.3×10^5
	59		5.2×10^7
	71		1.3×10^8
	7.8×10^2		2×10^9
	1.3×10^3		$(5–8) \times 10^{10}$
	9.8×10^3		$(1–4) \times 10^{11}$
	3.3×10^4		

*Griller, D., and Ingold, K. U. "Free Radical Clocks." *Acc. Chem. Res.*, **13**, 317 (1980). Newkomb, M., and Toy, P. H. "Hypersensitive Radical Probes and the Mechanisms of Cytochrome P450-Catalyzed Hydroxylation Reactions." *Acc. Chem. Res.*, **33**, 449 (2000).

In order to study the lifetimes of various radicals in new reactions, one requires several radical clocks with varying lifetimes. Incorporation of these clocks into the molecules under study is used both to show that radical intermediates do or do not exist, and if they do, their lifetimes relative to the clock. Several free radical clocks with their rate constants for rearrangement are shown in Table 8.7. Such a collection has been termed an **horlogerie**, after a French term for a small shop that sells clocks. Seven orders of magnitude can be spanned by choosing the correct clocks.

Another tool for studying radicals is the use of a **spin trap**, in an experiment called **spin trapping**. The addition of a free radical to a nitroso or nitrone group (the spin trap; see Eqs. 8.76 and 8.77) creates a **spin adduct**. The spin adduct is another radical, but it is typically a long lived radical that can often be studied using EPR spectroscopy. The EPR spectrum can be informative about the structure of the radical that added.


A nitroso (Eq. 8.76)


A nitrone (Eq. 8.77)

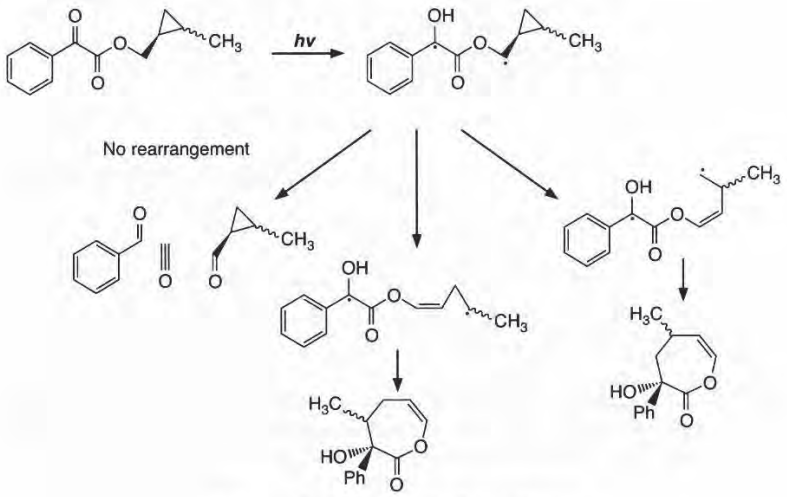
The Trustees of Columbia Univ. Ex. 2047 - Page 73 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

Connections

Determination of 1,4-Biradical Lifetimes Using a Radical Clock

The photolysis of ketones leads to reactions that we will call Norrish type II in Chapter 16. The reaction involves carbonyl excitation followed by hydrogen atom abstraction from a γ-carbon. Imbedded carbon monoxide, in the form of an ester, placed between the ketone and the γ-carbon is known to accelerate the decay of the resulting 1,4-biradical by allowing a fragmentation pathway. To ascertain the lifetime of the radical intermediates formed from the photolysis of the following α-keto ester, the incorporation of a radical clock was performed. Upon photolysis, three products are found, one that results from no opening of the radical clock, and two that result from the opening. Hence, the ring opening of the clock competes with the fragmentation. As seen in Table 8.7, the radical clocks of this type open with rate constants near 10^8. In this particular case, the rate constant is $9.4 \times 10^7\ s^{-1}$. Hence, the lifetime for fragmentation of the kinds of biradical created upon photolysis of α-ketoesters is in the range of 1 to 4 ns.

Hu, S., and Neckers, D. C. "Lifetimes of the 1,4-Biradical Derived from Alkyl Phenylglyoxylate Triplets: An Estimation Using the Cyclopropylmethyl Radical Clock." *J. Org. Chem.*, **62**, 755–757 (1997).



Using a radical clock to probe the mechanism

8.8.9 Direct Isolation and Characterization of an Intermediate

If an intermediate is stable enough to be isolated, then common spectroscopic and other characterization techniques can be used to identify it. However, we must demonstrate that under the established reaction conditions the isolated intermediate proceeds to the same products as the reactants to be confident that it is an intermediate and not just a by-product. Conversely, if one suspects that a certain compound is an intermediate in a reaction, the suspected intermediate can be synthesized by an independent route and subjected to the experimental conditions of the reaction under study. If the correct product(s) is(are) produced, this gives good but not conclusive evidence (it may be coincidental that they give the same product) that the structure in question is an intermediate. If the proposed intermediate gives a different product, on the other hand, it is good evidence that it is not an intermediate in the reaction under study.

8.8.10 Transient Spectroscopy

For short lived reactive intermediates, simple isolation and characterization is not an option, so we must resort to other techniques. As we noted in Chapter 7, fast spectroscopy methods have allowed chemists to obtain real-time characterization of many types of reac-

The Trustees of Columbia Univ. Ex. 2047 - Page 74 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

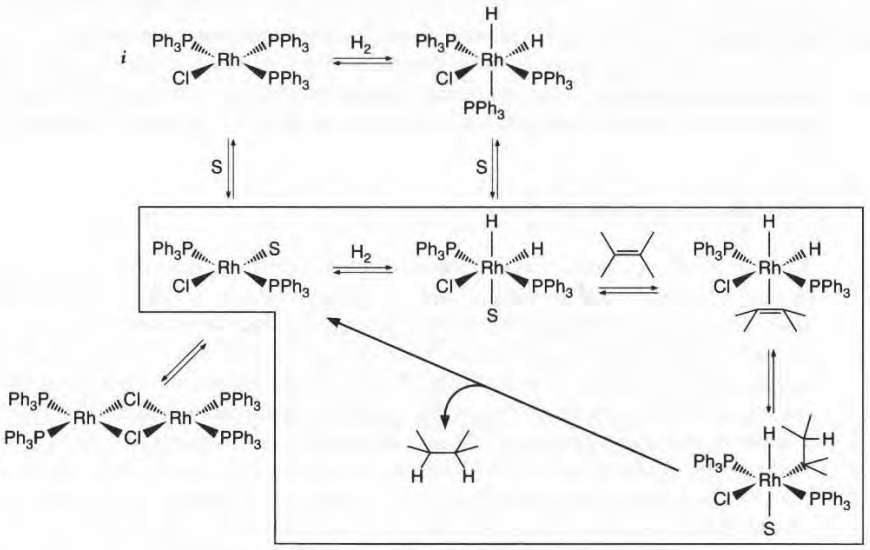
Connections

The Identification of Intermediates from a Catalytic Cycle Needs to be Interpreted with Care

The mechanism of hydrogenation of alkenes using Wilkinson's catalyst (*i*) is shown below. The two other species outside the box have been either detected in, or isolated from, solutions undergoing catalysis (S = solvent). However, the actual catalytic cycle is given within the box. The species outside the box were found to be too sluggish to react as competent intermediates in the rapidly proceeding catalytic cycle. Hence, they are simply by-products of some of the catalytically active species. Their accumulation actually slows the rate of the catalytic reaction.

This example shows that the identification of a detectable species in a catalytic system can lead to misinterpretations of the catalytic cycle. Being able to detect an intermediate often means that it is stable, and therefore may not be active, especially in a catalytic system. We must always show that the species are kinetically competent to participate in the cycle.

Halpern, J. "Mechanism and Stereoselectivity of Asymmetric Hydrogenation." *Science*, **217**, 401 (1982).



Hydrogenation mechanism

tive intermediates. Just as with isolating intermediates, we must demonstrate that the intermediate observed by the fast spectroscopy is indeed an intermediate involved in the mechanism under study. Furthermore, we should demonstrate that the spectroscopy is of the intermediate we are proposing and not of some other unknown species. These two proofs are often challenging, but careful experimental design can provide convincing support.

8.8.11 Stable Media

Another strategy for characterizing reactive intermediates that are short lived is to generate them in an environment in which there are no available reaction paths. If there is nothing the reactive intermediate can do, it will persist. There are two basic strategies. The first, typified by the **stable ion media** used so successfully to study carbocations, is to simply remove all possible species that could react with the reactive intermediate. For carbocations, this means removing all nucleophiles. This approach is only viable if the reactive intermediate cannot react with itself, either bimolecularly (dimerization) or unimolecularly (rearrangement). For example, because free radicals can usually dimerize readily, there is no

The Trustees of Columbia Univ. Ex. 2047 - Page 75 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

such thing as "stable radical media". However, radicals can be observed in a frozen matrix (see below). Still, when a stable medium can be found for a reactive intermediate, the full array of spectroscopic tools becomes available, including NMR, IR, UV / vis, etc.

For extremely reactive structures for which no stable fluid medium can be envisioned, the technique of **matrix isolation** is useful. This approach combines two features to make the reactive intermediate observable. First, the reactive intermediate is generated in a solid (frozen) solvent. 2-Methyltetrahydrofuran forms a particularly useful glass at low temperature. The matrix suppresses all bimolecular reactions. Often this is enough to stabilize the intermediate, if the reactive intermediate has no unimolecular decomposition pathways. For example, methyl radical is incredibly reactive. But, if it is generated locked in a rigid glass, there is really nothing it can do. It can't rearrange, and it isn't photoreactive. Indeed, samples of methyl radical in glass are indefinitely stable at room temperature. This example highlights the distinction between stability and persistence given in Section 2.2.1.

More typically, highly reactive intermediates also have unimolecular decomposition pathways that need to be suppressed. For this purpose, matrix isolation experiments are typically carried out at extremely low temperatures. For example, temperatures as low as 4 K are not uncommon. Note that at these low temperatures, inert gasses such as Ar are rigid solids, and they make perfect inert matrices. You should convince yourself that at 4 K a barrier as small as 1 kcal / mol is completely insurmountable. The matrix isolation methodology is technically demanding, and it is best suited to IR, UV / vis, and EPR characterization.

Summary and Outlook

Kinetics, isotope effects, linear free energy relationships, and the varied experiments discussed in the last section of this chapter make up the vast majority of the methods chemists use to decipher reaction mechanisms. The level at which we discussed these techniques was aimed at setting the stage for a more detailed analysis of many of the common organic and organometallic reaction mechanisms. By having the chapters on experimental tools behind us, we are ready to examine how these tools are used to delineate the details of mechanisms. However, many organic reactions, as well as most biochemical reactions, are catalyzed. We still need to understand catalysis before examining common organic mechanisms. Therefore, we now examine general methods of catalysis (Chapter 9). After this, we look at the mechanisms of substitutions, eliminations, and additions (Chapters 10 and 11). Looking forward even further to Chapters 12 and 13, you will see the application of mechanistic tools in organometallic and polymerization reactions, respectively. Therefore, you may consider Chapters 7 and 8 the "bread and butter" of classical physical organic chemistry, and the subsequent chapters as the applications to classical and modern topics.

Exercises

1. One equation often used to calculate kinetic isotope effects is given below. Derive this equation.

$$k_H / k_D = \exp[hc(\bar{\nu}_H - \bar{\nu}_D) / 2kT]$$

2. For a C–H bond with a stretching frequency of 3000 cm^{-1}, use the equation in Exercise 1 to calculate the expected isotope effect at 298 K for a full bond homolysis.

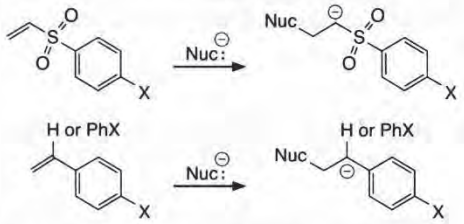
3. Given the frequencies of the out-of-plane bending modes in Figure 8.4, calculate the maximum secondary isotope effect that could arise during a reaction with a C–H(D) bond that rehybridizes from sp^3 to sp^2 at 298 K. (*Hint*: Although Eq. 8.2 was introduced in relation to stretching vibrations, it may also be used for bending vibrations.)

4. From our discussion of fractionation factors, derive Eq. 8.11. Here, assume two reactants and two products, each with only one exchangeable hydrogen.

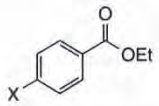
5. Derive the Hammett equation in terms of rate constants instead of equilibrium constants. Use the discussion given in Section 8.6.1 as your guideline.

The Trustees of Columbia Univ. Ex. 2047 - Page 76 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

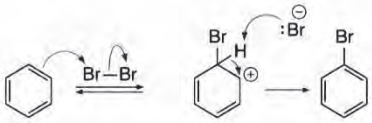
6. Steric effects are commonly dominated by differences in entropy. Taft parameters are dominated by entropy until the steric effect becomes very large, and then enthalpy effects start to dominate the steric effects.
   a. Using an entropy–enthalpy compensation analysis, explain why a linear free energy relationship for steric effects works at all.
   b. Explain how entropy–enthalpy compensation is involved in the Grunwald–Winstein LFER.
7. Consider a unimolecular reaction with an Arrhenius A value of 10^{13} s^{-1} and E_a of 0.5 kcal / mol. What is the half-life of this species at 4 K? At 8 K? Why is there such a large rate change in response to raising the temperature only 4 K?
8. A major research area is the consideration of the kinds of organic chemistry that might go on in interstellar space. It is possible that organic molecules formed in space could have been carried to earth on comets or meteorites, seeding prebiotic organic chemistry. Also, the organics in space can be a signature of star formation or collapse. In interstellar organic chemistry, tunnelling is often given much more consideration than in conventional, terrestrial chemistry. Why should this be so?
9. In the Going Deeper highlight on page 466 that discusses why a good leaving group can also be a good nucleophile, we tie the answer to the principle of microscopic reversibility. At first glance, reading this highlight may lead one to believe that all good nucleophiles are good leaving groups. This is not true, however, because hydroxide is a better nucleophile than water, but water is the better leaving group. Use reaction coordinate diagrams to explain when a good nucleophile is a good leaving group and when a good nucleophile is a poor leaving group.
10. Explain why the relief of ring strain or steric strain in an S_N1 reaction can often lead to small m values (reaction constants in Grunwald–Winstein plots).
11. In the nucleophilic addition to substituted alkenes, the ρ values are larger when the substituent is aryl than when the substituent is arylsulfonyl. This is also true if there is a second aryl group (denoted PhX). Why is this so?



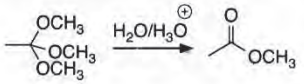
12. The acid-catalyzed hydrolysis of substituted ethylbenzoates has a ρ value of 0.14, whereas the base-catalyzed hydrolysis of the same series of compounds shows a ρ value of 2.19. Why is there such a difference?



13. It is often stated that deuterium prefers the strongest bond. This implies that one should use bond strengths (meaning bond dissociation energies) to predict where deuterium will concentrate during a reaction that is in equilibrium and where the deuterium changes positions between two bonds. Explain what is not quite correct about this statement, and give an explanation of a better way to predict which bond deuterium would prefer.
14. Explain how one would experimentally perform a Hammett plot study for the following reaction. Do you expect a positive or negative ρ value?



15. How can one distinguish experimentally if the ortho ester shown below hydrolyzes in acidic water by an S_N1 or S_N2 mechanism? There are actually two possible S_N2 mechanisms, but recall that an S_N2 at a tertiary carbon is uncommon, and therefore this is not one of the two choices that we are trying to distinguish.

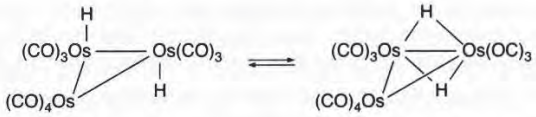


The Trustees of Columbia Univ. Ex. 2047 - Page 77 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

16. a. Given that a primary carbocation is less stable than a tertiary carbocation, would you expect that a reaction that creates a primary cation would be more or less responsive to solvent polarity than a reaction that creates a tertiary cation?

b. Now give some reasons why the *m* value for ethyltosylate is less than the standard (*t*-butyl chloride) on which this free energy relationship is based. Does this experimental result agree with your answer to part a of this question?

17. In the following equilibrium the hydrogens (or deuteria) can be found in either terminal or bridging positions. It is harder to break the bond(s) to the H or D when they are bridging between the metals, and due to this, the reaction is slightly exothermic in the direction shown (from left-to-right) because the hydrogens are bound more strongly.

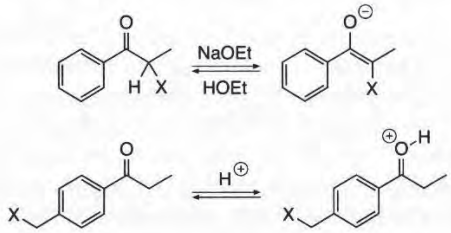


A. Terminal hydrogens **B.** Bridging hydrogens

a. Is the equilibrium constant for this reaction larger or smaller when one has D instead of H? Consider the equilibrium expression as $K_{eq} = [B]/[A]$.

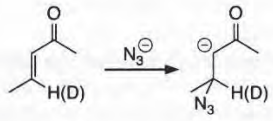
b. Draw a reaction coordinate diagram showing the relative shapes of the potential wells for the Os–H(D) bonds in the reactants and products, and the proper zero point energy levels within these wells. The Os–H bonds do not break and form in sequential steps. Use this diagram to explain your answer to part a.

18. In the following reactions substituent X was varied between electron donating and electron withdrawing. If you use the usual σ values, do you expect a positive or negative ρ value for each equilibrium? Should each reaction be more sensitive or less sensitive to the X substituent than benzoic acid? Explain your reasoning for each answer.

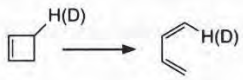


19. State whether the following reactions will show a normal or inverse, primary or secondary, kinetic isotope effect. Explain your reasoning.

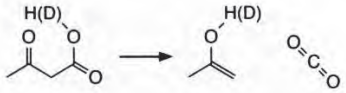
a.



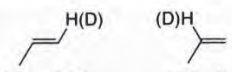
b.



c.



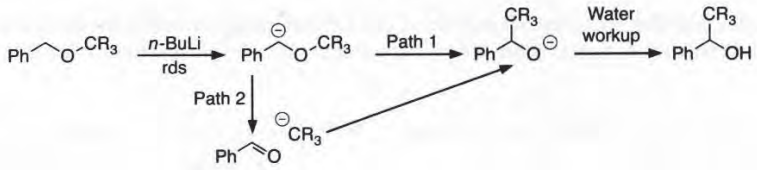
20. The following isotope effects are found for the ozonolysis of various deuterium-substituted propenes. What do these isotope effects tell you about the mechanism?



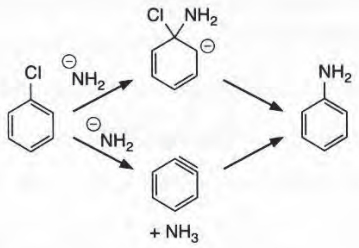
KIE = 0.88 KIE = 0.88

The Trustees of Columbia Univ. Ex. 2047 - Page 78 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

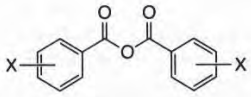
21. Two possible mechanisms for the Wittig rearrangement of benzyl ethers are shown below. Path 1 involves concerted intramolecular migration of CR_3, whereas Path 2 involves a heterolysis. In either mechanism, the deprotonation step is rate-determining. How would you apply the following experiments to distinguish between the two mechanisms: cross-over, trapping, and stereochemistry?



22. The treatment of chlorobenzene with potassium amide in liquid ammonia results in the formation of aniline. Propose four experiments discussed in this chapter, or others you can devise, that can be used to distinguish between the two mechanisms given below.

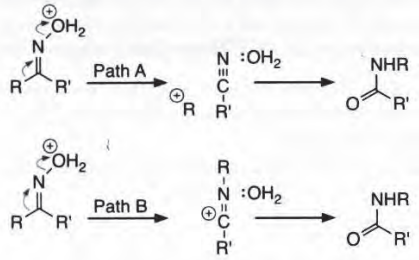


23. The hydrolysis of the following anhydrides gave the activation parameters listed. What is the isokinetic temperature for this reaction?

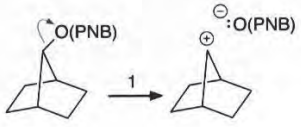


Substituent	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)
m-Methyl	17.8	−31.4
p-Methoxy	20.1	−27.8
m-Nitro	11.6	−38.8
p-Nitro	10.7	−40.5

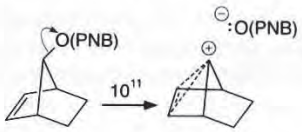
24. The acid-catalyzed Beckmann rearrangement of oximes to amides (see Chapter 11) has two possible rate-determining steps, the first one in each path shown below. Explain how you would use a Hammett plot analysis to distinguish these possibilities. It may be helpful to know that the R group trans to the departing water is the only one that migrates.



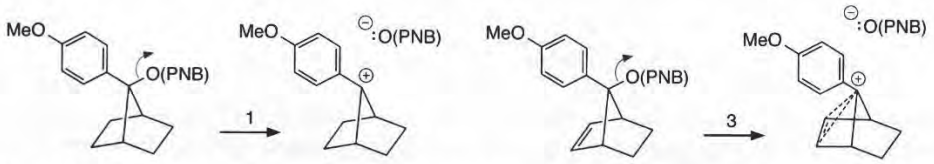
25. The relative rates of the S_N1 reactions of the following two alkyl *p*-nitrobenzoates (PNB) are as shown over the arrows below. The reason for the dramatic difference in the rate of departure of the nitrobenzoate leaving groups is the stabilization from the alkene to form a non-classical carbocation (recall non-classical carbocations from Chapters 1 and 2).



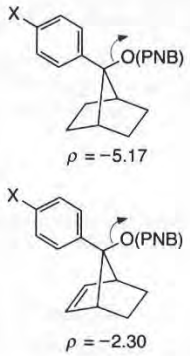
The Trustees of Columbia Univ. Ex. 2047 - Page 79 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313



a. When *p*-anisyl is placed in the reactant as shown below, the 10^{11} rate enhancement by the double bond is reduced to only a factor of 3. Explain why introduction of this substituent changes the relative reactivity from the example given above.



b. The ρ values for the S_N1 reaction of the following compounds were measured using σ^+ values. Interpret these values in light of the information given above. Do these ρ values support or contradict the conclusions based upon the difference in relative rates of the two comparisons given above?

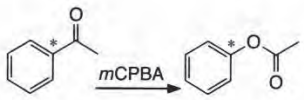


c. When H and CF_3 are the X groups shown above, the relative rates of the S_N1 reaction of the norbornene structure compared to the norbornane analog are 41 and 35,000, respectively. Why are these relative rates higher than when X = OMe?

d. The data given in this problem have led to the **rule of increasing electron demand** for the extent of neighboring group participation. We will examine neighboring group participation in Chapter 11. Consider the alkene in the above reactants as a "neighboring group" that participates in the stabilization of the carbocation. Use all the data presented above to make a guess as to what the rule of increasing electron demand must state.

26. Draw two curves associated with proton inventory studies where two protons are "in flight" in the rate-determining step. In the first case each proton has an associated isotope effect of 2, while in the second case one isotope effect is 1.5 and the other is 2.5. Using a proton inventory analysis, can you differentiate the two possibilities?

27. The following reaction is an example of the Baeyer–Villager oxidation (see Chapter 11; *m*CPBA = *m*-chloroperbenzoic acid). A heavy atom isotope effect for the carbon labeled was found to be $k_{12}/k_{14} = 1.048$. What does this tell you about the mechanism (do not write the entire mechanism)?



28. In general, how would you use radical clocks to measure the rate constant for the following radical rearrangement? Give one specific example.



The Trustees of Columbia Univ. Ex. 2047 - Page 80 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

29. In an S_N2 reaction it is commonly observed that β_{Nuc} values are larger for reactions with poorer leaving groups. Similarly, β_{LG} values are larger for reactions involving weaker nucleophiles. Such interrelationships are called **Bema Hapothle** effects (an acronym of chemists' names). Explain the interdependence between β_{Nuc} and β_{LG} for S_N2 reactions.

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The Trustees of Columbia Univ. Ex. 2047 - Page 82 of 82
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313