

Table of Contents

Chapter 1: Introduction to organic structure and bonding I

Introduction

Section 1: Atomic orbitals and electron configuration

- A: The atom
- B: Atomic orbitals
- C: Electron configuration

Section 2: Chemical Bonds

- A: Ionic bonds
- B: Covalent bonds and Lewis structures
- C: Formal charges

Section 3: Drawing organic structures

- A: Common bonding patterns in organic structures
- B: Using the 'line structure' convention
- C: Constitutional isomers
- D: The Index of Hydrogen Deficiency

Section 4: Functional groups and organic nomenclature

- A: Common functional groups in organic compounds
- B: Naming organic compounds
- C: Abbreviated organic structures

Section 5: Valence bond theory

- A: Formation of sigma bonds: the H₂ molecule
- B: Hybrid orbitals: sp³ hybridization and tetrahedral bonding
- C: Formation of pi bonds: sp² and sp hybridization
- D: The valence bonding picture in carbocations, carbanions, and carbon free radicals

Chapter 2: Introduction to organic structure and bonding II

Introduction

Section 1: Molecular orbital theory

- A: Another look at the H₂ molecule: bonding and antibonding sigma molecular orbitals
- B: MO theory and pi bonds: conjugation
- C: Aromaticity

Section 2: Resonance

- A: The meaning of resonance contributors: benzene and its derivatives
- B: Resonance contributors of the carboxylate group
- C: Rules for drawing resonance structures
- D: Major vs minor resonance contributors - four more rules to follow
- E: More examples of resonance: peptide bonds, enolates, and carbocations

Section 3: Non-covalent interactions

- A: Dipoles
- B: Ion-ion, dipole-dipole and ion-dipole interactions
- C: van der Waals forces
- D: Hydrogen bonds

Section 4: The relationship between noncovalent interactions physical properties

- A: Solubility
- B: Illustrations of solubility concepts - metabolic intermediates, lipid bilayer membranes, soaps and detergent
- C: Boiling points and melting points
- D: The melting behavior of lipid structures

Chapter 3: Conformations and Stereochemistry

Introduction

Section 1: Conformations of straight-chain organic molecules

- A: Conformations of ethane
- B: Conformations of butane

Section 2: Conformations of cyclic organic molecules

- A: Introduction to sugars and other cyclic molecules
- B: Ring size
- C: Conformations of glucose and other six-membered ring structures
- D: Conformations of pentose and other five-membered ring structures
- E: The importance of conformation in organic reactivity (*isoprenoid cyclases*)

Section 3: Stereoisomerism – chirality, stereocenters, enantiomers (*thalidomide*)

Section 4: Defining stereochemical configuration - the Cahn-Ingold-Prelog system

Section 5: Interactions between chiral molecules and proteins (*ibuprofen, carvone*)

Section 6: Optical activity

Section 7: Diastereomers

- A: Compounds with multiple stereocenters (*erythrose, threose, other sugars*)
- B: *Meso* compounds (*tartaric acid*)
- C: Stereoisomerism of alkenes (*trans-fatty acids, retinal, rubber*)

Section 8: Fischer projections

Section 9: Stereochemistry and organic reactivity

Section 10: Prochirality

- A: Prochiral substituents on tetrahedral carbons (*NADH, DHAP, GAP*)
- B: The prochirality of planar functional groups

Chapter 4: Structure determination part I: Infrared spectroscopy, UV-visible spectroscopy, and mass spectrometry

Introduction

Section 1: Introduction to molecular spectroscopy

- A: The electromagnetic spectrum
- B: Molecular spectroscopy – the basic idea

- Section 2: Infrared spectroscopy (*identifying forged paintings*)
- Section 3: Ultraviolet and visible spectroscopy
 - A: Electronic transitions
 - B: Electronic transitions in conjugated π -bonded systems
 - C: Looking at UV-vis spectra
 - D: Applications of UV spectroscopy in organic and biological chemistry (*measuring DNA concentration, observing DNA unfolding*)
- Section 4: Mass Spectrometry
 - A: The elements of a mass spectrometry instrument
 - B: Looking at mass spectra
 - C: Gas Chromatography - Mass Spectrometry
 - D: Mass spectrometry of proteins - applications in proteomics (*MALDI-TOF, identifying biomarkers for diseases, sequencing T. Rex proteins*)

Chapter 5: Structure determination part II- Nuclear magnetic resonance spectroscopy

Introduction

- Section 1: The origin of the NMR signal
 - A: NMR-active nuclei
 - B: Nuclear precession, spin states, and the resonance condition
- Section 2: Chemical equivalence
- Section 3: The NMR experiment
 - A: The basics of an NMR experiment
 - B: The chemical shift
 - C: Signal integration
- Section 4: The basis for differences in chemical shift
 - A: Diamagnetic shielding and deshielding
 - B: Diamagnetic anisotropy
 - C: Hydrogen-bonded protons
- Section 5: Spin-spin coupling
 - A: The source of spin-spin coupling
 - B: Coupling constants
 - C: Complex coupling
- Section 6: ^{13}C -NMR spectroscopy
 - A: The basics of ^{13}C -NMR spectroscopy
 - B: ^{13}C -NMR in isotopic labeling studies
- Section 7 : Determining unknown structures
- Section 8: NMR of phosphorylated molecules

Chapter 6: Introduction to organic reactivity and catalysis

- Section 1: Introduction to reaction mechanisms
 - A: An acid-base (proton transfer) reaction
 - B: A one-step nucleophilic substitution reaction
 - C: A two-step nucleophilic substitution reaction
- Section 2: Describing the thermodynamics and kinetics of chemical reactions - energy diagrams

- Section 3: Enzymatic catalysis - the basic ideas
- Section 4: Protein structure
 - A: Amino acids and peptide bonds
 - B: Visualizing protein structure: X-ray crystallography
 - C: The four levels of protein structure
 - D: The molecular forces that hold proteins together
- Section 5: How enzymes work
 - A: The active site
 - B: Transition state stabilization
 - C: Site-directed mutagenesis
 - D: Enzyme inhibition
 - E: Catalysts in the laboratory

Chapter 7: Organic compounds as acids and bases

Introduction

- Section 1: The 'basic' idea of an acid-base reaction
 - A: The Brønsted-Lowry definition of acidity
 - B: The Lewis definition of acidity
- Section 2: Comparing the acidity and basicity of organic functional groups– the acidity constant
 - A: Defining K_a and pK_a
 - B: Using listed pK_a values to predict reaction equilibria
 - C: pK_a and pH: the Henderson-Hasselbalch equation
- Section 3: Structural effects on acidity and basicity
 - A: Periodic trends
 - B: The resonance effect
 - C: The inductive effect
- Section 4: Resonance-based effects involving aromatic compounds
 - A: The acidity of phenols
 - B: More on the basicity of nitrogen-containing groups: aniline, pyridine, and pyrrole
- Section 5: Carbon acids and enolate ions
- Section 6: Polyprotic acids
- Section 7: The effects of solvent and enzyme microenvironment on acidity

Chapter 8: Nucleophilic substitution reactions part I

Introduction

- Section 1: Introduction to the nucleophilic substitution reaction
- Section 2: Two mechanistic models for a nucleophilic substitution reaction
 - A: Associative nucleophilic substitution: the S_N2 reaction
 - B: Dissociative nucleophilic substitution: the S_N1 reaction
 - C: Nucleophilic substitutions occur at sp^3 -hybridized carbons
- Section 3: More about nucleophiles
 - A: What makes a nucleophile?
 - B: Protonation states and nucleophilicity
 - C: Periodic trends in nucleophilicity

- D: Resonance effects on nucleophilicity
- E: Steric effects on nucleophilicity
- Section 4: Electrophiles and carbocation stability
 - A: Steric effects on electrophilicity
 - B: Stability of carbocation intermediates
- Section 5: Leaving groups and solvent effects
 - A: What makes a good leaving group?
 - B: Synthetic parallel - conversion of alcohols to alkyl halides, tosylates and mesylates
 - C: The effect of solvent on nucleophilic substitutions
 - D: Predicting S_N1 vs S_N2 mechanisms, and competition with elimination
- Section 6: Epoxides as substrates in nucleophilic substitution reactions
 - A: Epoxide structure
 - B: Epoxide ring-opening reactions - S_N1 vs S_N2 , regioselectivity, and stereoselectivity

Chapter 9: Nucleophilic substitution reactions part II

Introduction

- Section 1: Methyl group transfers: examples of S_N2 reactions
 - A: SAM methyltransferase
 - B: Synthetic parallel – the Williamson ether synthesis
- Section 2: Digestion of starch by glycosidases - an S_N1 reaction
- Section 3: Protein prenyltransferase - a hybrid S_N1/S_N2 substitution
 - A: The biological relevance of the protein prenyltransferase reaction
 - B: Determining the mechanism of protein prenyltransferase with fluorinated substrate analogs
 - C: The zinc-thiolate interaction in protein prenyltransferase - 'tuning' the nucleophile
- Section 4: Biochemical nucleophilic substitutions with epoxide electrophiles
 - A: Hydrolysis of stearic acid epoxide: investigating the mechanism with kinetic isotope effect experiments
 - B: Fosfomycin - an epoxide antibiotic
- Section 5: Nucleophilic substitution over conjugated pi systems - the S_N1 mechanism (*anthranilate synthase, thebaine synthase*).

Chapter 10: Phosphoryl transfer reactions

Introduction: Abundance of phosphoryl groups in metabolic intermediates

- Section 1: Overview of phosphates and phosphoryl transfer reactions
 - A: Nomenclature and abbreviations
 - B: Acid constants and protonation states
 - C: The orbital picture for phosphoryl groups
 - D: Phosphoryl transfer reactions - the general picture (Mg^{2+} activation, sp^3d TS, inversion)
 - E: Phosphoryl transfer reactions - associative, addition-elimination, or dissociative?
- Section 2: Phosphorylation reactions - kinase enzymes
 - A: ATP - the principle phosphoryl group donor
 - B: Monophosphorylation of alcohols (glucose kinase, serine/threonine kinase, protein phosphorylation as on-off switch)

- C: Diphosphorylation of alcohols (*phosphomevalonate kinase, PRPP synthetase*)
- D: Conversion of carboxylates to acyl phosphates (*glutamine synthase*)
- E: Generation of nucleotide phosphates (*asparagine synthetase, diphosphocytidyl-methylerythritol synthase*)
- F: Regeneration of ATP (*ATP synthase, 3-phosphoglycerate kinase, pyruvate kinase*)
- Section 3: Dephosphorylation reactions - phosphatases
 - A: G6P phosphatase: (*¹⁸O experiments to confirm phosphorus as electrophile, retention of configuration; evidence for covalent intermediate*)
 - B: Alkaline phosphatase (*retention of config, isolation of phosphorylated enzyme*)
 - C: Serine/threonine phosphatases (*direct hydrolysis, evidence for inversion; fructose 1,6-bisphosphate phosphatase*).
- Section 4: Phosphate diesters
 - A: The role of phosphate diesters as the DNA backbone (*relative stability of DNA/RNA*)
 - B: The chemistry of genetic engineering: (*endonucleases, ligases, polymerases, alkaline phosphatase*).

Chapter 11: Nucleophilic carbonyl addition reactions

Introduction

Section 1: Nucleophilic additions to aldehydes and ketones: the general picture

Section 2: Stereochemistry of the nucleophilic addition reaction

Section 3: Hemiacetals, hemiketals, and hydrates

A: The general picture

B: Simple sugars are hemiacetals and hemiketals

Section 4: Acetals and ketals

A: Glycosidic bonds revisited

B: Synthetic parallel: cyclic acetals/ketals as 'protecting groups' for ketones and aldehydes

Section 5: N-glycosidic bonds (*glutamine phosphoribosyl amidotransferase*)

Section 6: Imine (Schiff base) formation

A: The general picture

B: PLP coenzyme links to enzymes via Schiff base

C: Schiff base formation in aldolase reactions

Section 7: A look ahead: when the nucleophile in a carbonyl addition reaction is a carbanion or hydride

Chapter 12: Acyl substitution reactions

Introduction

Section 1: Introduction to carboxylic acid derivatives and the nucleophilic acyl substitution reaction

A: Carboxylic acid derivatives and acyl groups

B: The nucleophilic acyl substitution reaction

C: The relative reactivity of carboxylic acid derivatives

Section 2: Acyl phosphates: activated carboxylic acids

A: Glutamine synthetase

B: Asparagine synthetase

- C: Glycinamide ribonucleotide synthetase
- 12.2D: Synthetic parallel - activated carboxylic acids in the lab
- Section 3: Thioesters
 - A: Introduction to thioesters and Coenzyme A
 - B: Activation of fatty acids by coenzyme A - a thioesterification reaction (*acyl-SCoA synthetase*)
 - C: Transfer of fatty acyl groups to glycerol: a thioester to ester substitution (*monoacylglycerol acyltransferase*)
 - D: More transthioesterification reactions (*acyl carrier proteins, pyruvate dehydrogenase complex, E2 reaction*).
 - E: Hydrolysis of thioesters (*citrate synthase*)
- Section 4: Esters
 - A: Nonenzymatic esterification: synthesis of 'banana oil'
 - B: Nonenzymatic ester hydrolysis: making soap
 - C: Enzymatic ester hydrolysis: acetylcholinesterase and sarin nerve gas
 - D: More enzymatic ester hydrolysis: lipase, the resolution of enantiomers, and dehalogenation
 - E: Transesterification: the chemistry of aspirin and biodeisel
- Section 5: Nucleophilic acyl substitution reactions involving peptide bonds
 - A: Formation of peptide bonds on the ribosome (*mechanism of puromycin*)
 - B: Hydrolysis of peptide bonds: HIV protease
 - C: The chemical mechanism of penicillin
- Section 6: Activated amide groups (*arginosuccinate synthase*)
- Section 7: A look ahead: when the nucleophile in an acyl substitution reaction is a carbanion or hydride

Chapter 13: Reactions with stabilized carbanion intermediates, part I - isomerizations, aldol, and Claisen reactions

Introduction

Section 1: Tautomers

- A: Enolates and keto-enol tautomerization
- B: Imine/enamine tautomerization

Section 2: Isomerization *via* enolate and enol intermediates

- A: Carbonyl isomerization (*triose-phosphate isomerase, glucose-6-phosphate isomerase*)
- B: Stereoisomerization at chiral carbons (*ribulose-5-phosphate-4-epimerase, glutamate racemase*).

Section 3: Aldol reactions

- A: The general mechanism for an aldol reaction
- B: Typical aldolase reactions: three different strategies for stabilizing the carbanion intermediate (*fructose 1,6-bisphosphate aldolase, type II (gluconeogenesis direction), fructose 1,6-bisphosphate aldolase, type I (gluconeogenesis direction), citrate synthase*)
- C: Going backwards: the retroaldol reaction (*fructose 1,6-bisphosphate aldolase, type II (glycolytic direction); 2-keto-3-deoxy-6-phosphogluconate aldolase, tryptophan synthase*)
- D: Going both ways: transaldolase

Section 4: Claisen reactions

- A: Claisen condensations (*acetoacetyl CoA acetyltransferase*)
- B: Retro-Claisen cleavages (*β -ketothiolase, funarylacetoacetate hydrolase*)
- C: Enolates as nucleophiles in S_N2 displacements (*indol-pyruvate methylase*)

Section 5: Carboxylation and decarboxylation reactions

- A: The metabolic context of carboxylation and decarboxylation
- B: The carboxylation mechanism of Rubisco
- C: Decarboxylation (*isocitrate dehydrogenase, phosphogluconate dehydrogenase, acetoacetate decarboxylase, acetoacetyl-ACP synthesis, prephenate decarboxylase*)

Section 6: Synthetic parallel - carbon nucleophiles in the lab

- A: Lab reactions with enolate /enamine intermediates
- B: The Wittig reaction
- C: Terminal alkynes as carbon nucleophiles
- D: Grignard, Gilman, and organolithium reagents

Chapter 14: Reactions with stabilized carbanion intermediates, part II: Michael additions, eliminations, and electron sink cofactors

Introduction

Section 1: Michael additions and β -eliminations

- A: Overview of mechanisms; 5-dehydroquinone synthase and the requirement for a β -carbonyl
- B: Stereochemistry of alkene additions and eliminations (*syn addition: enoyl-CoA hydratase, anti elimination: trans- crotonyl ACP synthase*).
- C: NMR experiments to determine the stereochemistry of a Michael addition
- D: More examples of elimination and addition reactions (*DHQ dehydratase, argininosuccinase lyase, aconitase*)

Section 2: Other variations on the Michael reaction

- A: *Cis/trans* alkene isomerization (*Maleylacetoacetate isomerase*)
- B: Nucleophilic aromatic substitution (*N-terminal labeling, inosine monophosphate dehydrogenase*)

Section 3: Elimination by the E1 and E2 mechanisms

- A: E1 and E2 reactions in the laboratory
- B: Enzymatic E1 and E2 reactions (*EPSP synthase, chorismate synthase, mevalonate diphosphate decarboxylase, prephenate decarboxylase*)

Section 4: Pyridoxal phosphate - an electron sink cofactor

- A: PLP and the Schiff-base linkage to lysine
- B: PLP-dependent amino acid racemases
- C: PLP-dependent decarboxylation (*diaminopimelate decarboxylase*)
- D: PLP-dependent retroaldolases (*serine hydroxymethyltransferase*)
- E: PLP-dependent transaminase reactions (*aspartate aminotransferase*)
- F: PLP-dependent β -elimination (*serine dehydratase*); β -substitution (*O-acetylserine sulfhydrylase*)
- G: PLP-dependent γ -elimination (*cystathionine γ -lyase*); γ -substitution (*cystathionine γ -synthase*)
- H: Altering the course of a PLP reaction through site-directed mutagenesis

- Section 5: Thiamine diphosphate-dependent reactions
 A: Benzoin condensation
 B: Transketolase
 C: Pyruvate decarboxylase
 D: Synthetic parallel - carbonyl nucleophiles *via* dithiane anions
- Section 6: The transition state geometry of reactions involving π -bonds
 A: Transition state geometry of E2 reactions
 B: Transition state geometry of PLP-dependent reactions

Chapter 15: π electrons as nucleophiles: electrophilic additions, addition/eliminations, and rearrangements

Introduction

- Section 1: An overview of the different types of electrophilic reactions
- Section 2: Electrophilic addition
 A: Electrophilic addition - the general picture
 B: The regiochemistry of electrophilic addition
 C: Enzymatic electrophilic additions (*methylation of an alkene by SAM, DAHP synthase, linalyl diphosphate to α -terpineol (a conjugated electrophilic addition)*).
 D: Electrophilic additions in the laboratory
- Section 3: Electrophilic isomerization and substitution (addition/elimination)
 A: Alkene isomerization by electrophilic addition/elimination (*isopentenyl diphosphate isomerase*)
 B: Substitution by electrophilic addition/elimination (*geranyl diphosphate synthase*)
- Section 4: Another kind of electrophilic addition-elimination - Shikimate to chorismate
- Section 5: Electrophilic aromatic substitution
 A: Electrophilic aromatic substitution - the general picture
 B: Some important enzymatic electrophilic aromatic substitutions (*tryptophan-DMAPP transferase, phenol alkylation in vitamin K synthesis, porphobilinogen condensation, tryptophan synthase (PLP-dependent S_EAr), aromatic alkylation-decarboxylation (indole-3-glycerol phosphate synthase)*)
- Section 6: Synthetic parallel - electrophilic aromatic substitution in the lab
 A: Friedel-Crafts reactions and other S_EAr reactions
 B: Ring directing effects in S_EAr reactions
- Section 7: Carbocation rearrangements
 A: Hydride and alkyl shifts
 B: Enzymatic reactions with carbocation rearrangement steps (*HBA synthase, oxidosqualene cyclase, pentalanene synthase*).
 C: The acyloin, pinacol, and Hoffman rearrangements (*isoleucine biosynthesis*).
- Section 8: Cation- π interactions and the stabilization of carbocation intermediates
- Section 9: Outside the box - 1,3-elimination and rearrangement in squalene synthase
- Section 10: The Diels-Alder reaction and other pericyclic reactions

Chapter 16: Oxidation and reduction reactions

Introduction

Section 1: Oxidation and reduction of organic compounds - an overview

Section 2: The importance of redox reactions in metabolism

Section 3: Thinking outside the box - methanogenesis

Section 4: Hydrogenation/dehydrogenation reactions of carbonyls, imines, and alcohols

A: Nicotinamide adenine dinucleotide - a hydride transfer coenzyme

B: Carbonyl hydrogenation and alcohol dehydrogenation - the general picture

C: Stereochemistry of carbonyl hydrogenation and alcohol dehydrogenation

D: Examples of redox reactions involving alcohols, carbonyl groups, and imines (*(R)*-GP dehydrogenase, *(S)*-GP dehydrogenase, alcohol dehydrogenase, proline synthetase, glutamate dehydrogenase, HMG CoA reductase, glutamate semialdehyde synthase, GAP dehydrogenase).

Section 5: Hydrogenation of alkenes and dehydrogenation of alkanes

A: Alkene hydrogenation in fatty acid synthesis (*crotonyl ACP reductase*)

B: The flavin coenzymes

C: Alkane dehydrogenation in fatty acid degradation (*acyl-CoA dehydrogenase*, *succinate dehydrogenase*)D: More examples of enzymatic alkene hydrogenation (*dihydropyrimidine dehydrogenase* (alkene hydrogenation by $FMN H_2$), *2,4-dienoyl-CoA reductase* (hydrogenation at the γ - δ position), *biliverdin reductase*, *geranylgeranyl reductase* (hydrogenation of isolated double bonds)).Section 6: Additional examples of enzymatic hydride transfer reactions (*squalene synthase*, *inosine monophosphate dehydrogenase*, an oxidative S_NAr step).Section 7: NAD(P)H, FADH₂ and metabolism - a second lookA: NADH and FADH₂ as carriers of hydrides from fuel molecules to water

B: The pentose phosphate pathway as a source of NADPH for reductive biosynthesis

Section 8: Observing the progress of hydrogenation and dehydrogenation reactions by UV assay

Section 9: Hydrogenation/dehydrogenation reactions and renewable energy technology (*biohydrogen*)Section 10: Oxygenase reactions- flavin-dependent monooxygenases (*squalene epoxidase*, *kynurenine-3-monooxygenase*)

Section 11: Halogenation of organic compounds

A: Enzymatic halogenation (*tryptophan halogenase*)

B: Synthetic parallel - halogenation of alkenes in the lab

Section 12: Redox reactions involving thiols and disulfides

A: Disulfide bridges in proteins (*lipoamide dehydrogenase*, *glutathione reductase*, *thioredoxin*, β -mercaptoethanol)

B: The role of disulfides in the pyruvate dehydrogenase reaction

Section 13: Redox reactions in the organic synthesis laboratory

A: Metal hydride reducing agents

B: Catalytic hydrogenation and the *trans* fat issue

C: Reduction of carbonyl carbons to methylene

D: Laboratory oxidation reactions

Chapter 17: Radical reactions

Introduction

Section 1: Structure and reactivity of radical species

- A: The definition of free radical
- B: Geometry and relative stability of carbon radicals.
- C: The diradical character of triplet oxygen

Section 2: Radical chain reactions

- A: The three phases of radical chain reactions
- B: Radical halogenation in the lab
- C: Useful polymers formed by radical chain reactions
- D: Destruction of the ozone layer by CFC radicals
- E: Harmful radical species in cells and natural antioxidants (*reactive oxygen species, lipid peroxidation, polyphenol radical scavengers*)

Section 3: Enzymatic reactions with free radical intermediates

- A: Hydroxylation of alkanes
- B: Reductive dehydroxylation of alcohols (*ribonucleotide reductase*)
- C: Radical mechanisms for flavin-dependent reactions (*acyl CoA dehydrogenase alternate mechanism, chorismate synthase*)

Tables

Table 1: Some characteristic absorption frequencies in IR spectroscopy

Table 2: Typical values for ^1H -NMR chemical shifts

Table 3: Typical values for ^{13}C -NMR chemical shifts

Table 4: Typical coupling constants in NMR

Table 5: The 20 common amino acids

Table 6: Structures of common coenzymes

Table 7: Representative acid constants

Table 8: Some common laboratory solvents, acids, and bases

Inside front cover: The periodic table of the elements

Inside back cover: The common functional groups in organic chemistry