# Contents

Abbreviations
Preface to the second edition
Organic chemistry and this book

**1 What is organic chemistry? 1**
- Organic chemistry and you 1
- Organic compounds 2
- Organic chemistry and industry 6
- Organic chemistry and the periodic table 11
- Organic chemistry and this book 13
- Further reading 13

**2 Organic structures 15**
- Hydrocarbon frameworks and functional groups 16
- Drawing molecules 17
- Hydrocarbon frameworks 22
- Functional groups 27
- Carbon atoms carrying functional groups can be classified by oxidation level 32
- Naming compounds 33
- What do chemists really call compounds? 36
- How should you name compounds? 40
- Further reading 42

**3 Determining organic structures 43**
- Introduction 43
- Mass spectrometry 46
- Mass spectrometry detects isotopes 48
- Atomic composition can be determined by high-resolution mass spectrometry 50
- Nuclear magnetic resonance 52
- Regions of the $^{13}C$ NMR spectrum 56
- Different ways of describing chemical shift 57
- A guided tour of the $^{13}C$ NMR spectra of some simple molecules 57
- The $^{1}H$ NMR spectrum 59
- Infrared spectra 63
- Mass spectra, NMR, and IR combined make quick identification possible 72
- Double bond equivalents help in the search for a structure 74
- Looking forward to Chapters 13 and 18 78
- Further reading 78

**4 Structure of molecules 80**
- Introduction 80
- Electrons occupy atomic orbitals 83
- Molecular orbitals—diatomic molecules 88
- Bonds between different atoms 95
- Hybridization of atomic orbitals 99
- Rotation and rigidity 105
- Conclusion 106
- Looking forward 106
- Further reading 106

**5 Organic reactions 107**
- Chemical reactions 107
- Nucleophiles and electrophiles 111
- Curly arrows represent reaction mechanisms 116
- Drawing your own mechanisms with curly arrows 120
- Further reading 124

**6 Nucleophilic addition to the carbonyl group 125**
- Molecular orbitals explain the reactivity of the carbonyl group 125
- Attack of cyanide on aldehydes and ketones 127
- The angle of nucleophilic attack on aldehydes and ketones 129
- Nucleophilic attack by 'hydride' on aldehydes and ketones 130
- Addition of organometallic reagents to aldehydes and ketones 132
- Addition of water to aldehydes and ketones 133
- Hemiacetals from reaction of alcohols with aldehydes and ketones 135
- Ketones also form hemiacetals 137
- Acid and base catalysis of hemiacetal and hydrate formation 137
- Bisulfite addition compounds 138
- Further reading 140

**7 Delocalization and conjugation 141**
- Introduction 141
- The structure of ethene (ethylene, $CH_2$ $CH_2$) 142
- Molecules with more than one C=C double bond 143

The conjugation of two $\pi$ bonds 146
UV and visible spectra 148
The allyl system 150
Delocalization over three atoms is a common structural feature 154
Aromaticity 156
Further reading 162

**8 Acidity, basicity, and p$K_a$ 163**
Organic compounds are more soluble in water as ions 163
Acids, bases, and p$K_a$ 165
Acidity 165
The definition of p$K_a$ 168
Constructing a p$K_a$ scale 171
Nitrogen compounds as acids and bases 174
Substituents affect the p$K_a$ 175
Carbon acids 176
p$K_a$ in action—the development of the drug cimetidine 178
Lewis acids and bases 180
Further reading 181

**9 Using organometallic reagents to make C–C bonds 182**
Introduction 182
Organometallic compounds contain a carbon–metal bond 183
Making organometallics 184
Using organometallics to make organic molecules 189
Oxidation of alcohols 194
Looking forward 196
Further reading 196

**10 Nucleophilic substitution at the carbonyl group 197**
The product of nucleophilic addition to a carbonyl group is not always a stable compound 197
Carboxylic acid derivatives 198
Why are the tetrahedral intermediates unstable? 200
Not all carboxylic acid derivatives are equally reactive 205
Acid catalysts increase the reactivity of a carbonyl group 207
Acid chlorides can be made from carboxylic acids using $SOCl_2$ or $PCl_5$ 214
Making other compounds by substitution reactions of acid derivatives 216
Making ketones from esters: the problem 216
Making ketones from esters: the solution 218
To summarize... 220
And to conclude... 220
Further reading 220

**11 Nucleophilic substitution at C=O with loss of carbonyl oxygen 222**
Introduction 222
Aldehydes can react with alcohols to form hemiacetals 223
Acetals are formed from aldehydes or ketones plus alcohols in the presence of acid 224
Amines react with carbonyl compounds 229
Imines are the nitrogen analogues of carbonyl compounds 230
Summary 238
Further reading 239

**12 Equilibria, rates, and mechanisms 240**
How far and how fast? 240
How to make the equilibrium favour the product you want 244
Entropy is important in determining equilibrium constants 246
Equilibrium constants vary with temperature 248
Introducing kinetics: how to make reactions go faster and cleaner 250
Rate equations 257
Catalysis in carbonyl substitution reactions 262
Kinetic versus thermodynamic products 264
Summary of mechanisms from Chapters 6–12 266
Further reading 267

**13 $^1$H NMR: Proton nuclear magnetic resonance 269**
The differences between carbon and proton NMR 269
Integration tells us the number of hydrogen atoms in each peak 270
Regions of the proton NMR spectrum 272
Protons on saturated carbon atoms 272
The alkene region and the benzene region 277
The aldehyde region: unsaturated carbon bonded to oxygen 281
Protons on heteroatoms have more variable shifts than protons on carbon 282
Coupling in the proton NMR spectrum 285
To conclude 301
Further reading 301

**14 Stereochemistry 302**
Some compounds can exist as a pair of mirror-image forms 302

Diastereoisomers are stereoisomers that are not enantiomers 311
Chiral compounds with no stereogenic centres 319
Axes and centres of symmetry 320
Separating enantiomers is called resolution 322
Further reading 327

**15 Nucleophilic substitution at saturated carbon 328**
Mechanisms for nucleophilic substitution 328
How can we decide which mechanism ($S_N1$ or $S_N2$) will apply to a given organic compound? 332
A closer look at the $S_N1$ reaction 333
A closer look at the $S_N2$ reaction 340
Contrasts between $S_N1$ and $S_N2$ 342
The leaving group in $S_N1$ and $S_N2$ reactions 347
The nucleophile in $S_N1$ reactions 352
The nucleophile in the $S_N2$ reaction 353
Nucleophiles and leaving groups compared 357
Looking forward: elimination and rearrangement reactions 358
Further reading 359

**16 Conformational analysis 360**
Bond rotation allows chains of atoms to adopt a number of conformations 360
Conformation and configuration 361
Barriers to rotation 362
Conformations of ethane 363
Conformations of propane 365
Conformations of butane 365
Ring strain 366
A closer look at cyclohexane 370
Substituted cyclohexanes 374
To conclude... 381
Further reading 381

**17 Elimination reactions 382**
Substitution and elimination 382
How the nucleophile affects elimination versus substitution 384
E1 and E2 mechanisms 386
Substrate structure may allow E1 388
The role of the leaving group 390
E1 reactions can be stereoselective 391
E2 eliminations have anti-periplanar transition states 395
The regioselectivity of E2 eliminations 398
Anion-stabilizing groups allow another mechanism—E1cB 399
To conclude 404
Further reading 406

**18 Review of spectroscopic methods 407**
There are three reasons for this chapter 407
Spectroscopy and carbonyl chemistry 408
Acid derivatives are best distinguished by infrared 411
Small rings introduce strain inside the ring and higher s character outside it 412
Simple calculations of C=O stretching frequencies in IR spectra 413
NMR spectra of alkynes and small rings 414
Proton NMR distinguishes axial and equatorial protons in cyclohexanes 415
Interactions between different nuclei can give enormous coupling constants 415
Identifying products spectroscopically 418
Tables 422
Shifts in proton NMR are easier to calculate and more informative than those in carbon NMR 425
Further reading 426

**19 Electrophilic addition to alkenes 427**
Alkenes react with bromine 427
Oxidation of alkenes to form epoxides 429
Electrophilic addition to unsymmetrical alkenes is regioselective 433
Electrophilic addition to dienes 435
Unsymmetrical bromonium ions open regioselectively 436
Electrophilic additions to alkenes can be stereospecific 439
Adding two hydroxyl groups: dihydroxylation 442
Breaking a double bond completely: periodate cleavage and ozonolysis 443
Adding one hydroxyl group: how to add water across a double bond 444
To conclude...a synopsis of electrophilic addition reactions 447
Further reading 447

**20 Formation and reactions of enols and enolates 449**
Would you accept a mixture of compounds as a pure substance? 449
Tautomerism: formation of enols by proton transfer 450
Why don't simple aldehydes and ketones exist as enols? 451

Evidence for the equilibration of carbonyl compounds with enols 451
Enolization is catalysed by acids and bases 452
The intermediate in the base-catalysed reaction is an enolate ion 452
Summary of types of enol and enolate 454
Stable enols 456
Consequences of enolization 459
Reaction with enols or enolates as intermediates 460
Stable equivalents of enolate ions 465
Enol and enolate reactions at oxygen: preparation of enol ethers 467
Reactions of enol ethers 468
To conclude 470
Further reading 470

**21 Electrophilic aromatic substitution 471**

Introduction: enols and phenols 471
Benzene and its reactions with electrophiles 473
Electrophilic substitution on phenols 479
A nitrogen lone pair activates even more strongly 482
Alkyl benzenes also react at the *ortho* and *para* positions 484
Electron-withdrawing substituents give *meta* products 486
Halogens show evidence of both electron withdrawal and donation 489
Two or more substituents may cooperate or compete 491
Some problems and some opportunities 492
A closer look at Friedel–Crafts chemistry 492
Exploiting the chemistry of the nitro group 494
Summary 495
Further reading 497

**22 Conjugate addition and nucleophilic aromatic substitution 498**

Alkenes conjugated with carbonyl groups 498
Conjugated alkenes can be electrophilic 499
Summary: factors controlling conjugate addition 509
Extending the reaction to other electron-deficient alkenes 510
Conjugate substitution reactions 511
Nucleophilic epoxidation 513
Nucleophilic aromatic substitution 514
The addition–elimination mechanism 515
The $S_N$1 mechanism for nucleophilic aromatic substitution: diazonium compounds 520
The benzyne mechanism 523
To conclude... 526
Further reading 527

**23 Chemoselectivity and protecting groups 528**

Selectivity 528
Reducing agents 530
Reduction of carbonyl groups 530
Hydrogen as a reducing agent: catalytic hydrogenation 534
Getting rid of functional groups 539
Dissolving metal reductions 541
Selectivity in oxidation reactions 544
Competing reactivity: choosing which group reacts 546
A survey of protecting groups 549
Further reading 561

**24 Regioselectivity 562**

Introduction 562
Regioselectivity in electrophilic aromatic substitution 563
Electrophilic attack on alkenes 570
Regioselectivity in radical reactions 571
Nucleophilic attack on allylic compounds 574
Electrophilic attack on conjugated dienes 579
Conjugate addition 581
Regioselectivity in action 582
Further reading 583

**25 Alkylation of enolates 584**

Carbonyl groups show diverse reactivity 584
Some important considerations that affect all alkylations 584
Nitriles and nitroalkanes can be alkylated 585
Choice of electrophile for alkylation 587
Lithium enolates of carbonyl compounds 587
Alkylations of lithium enolates 588
Using specific enol equivalents to alkylate aldehydes and ketones 591
Alkylation of β-dicarbonyl compounds 595
Ketone alkylation poses a problem in regioselectivity 598
Enones provide a solution to regioselectivity problems 601
Using Michael acceptors as electrophiles 605
To conclude... 612
Further reading 613

**26 Reactions of enolates with carbonyl compounds: the aldol and Claisen reactions 614**

Introduction 614
The aldol reaction 615
Cross-condensations 618

Specific enol equivalents can be used to control aldol reactions 624
How to control aldol reactions of esters 631
How to control aldol reactions of aldehydes 632
How to control aldol reactions of ketones 634
Intramolecular aldol reactions 636
Acylation at carbon 640
Crossed ester condensations 643
Summary of the preparation of keto-esters by the Claisen reaction 647
Controlling acylation with specific enol equivalents 648
Intramolecular crossed Claisen ester condensations 652
Carbonyl chemistry—where next? 654
Further reading 654

**27 Sulfur, silicon, and phosphorus in organic chemistry 656**

Useful main group elements 656
Sulfur: an element of contradictions 656
Sulfur-stabilized anions 660
Sulfonium salts 664
Sulfonium ylids 665
Silicon and carbon compared 668
Allyl silanes as nucleophiles 675
The selective synthesis of alkenes 677
The properties of alkenes depend on their geometry 677
Exploiting cyclic compounds 678
Equilibration of alkenes 679
*E* and *Z* alkenes can be made by stereoselective addition to alkynes 681
Predominantly *E* alkenes can be formed by stereoselective elimination reactions 684
The Julia olefination is regiospecific and connective 686
Stereospecific eliminations can give pure single isomers of alkenes 688
Perhaps the most important way of making alkenes—the Wittig reaction 689
To conclude 693
Further reading 693

**28 Retrosynthetic analysis 694**

Creative chemistry 694
Retrosynthetic analysis: synthesis backwards 694
Disconnections must correspond to known, reliable reactions 695
Synthons are idealized reagents 695
Multiple step syntheses: avoid chemoselectivity problems 698
Functional group interconversion 699
Two-group disconnections are better than one-group disconnections 702
C—C disconnections 706
Available starting materials 711
Donor and acceptor synthons 712
Two-group C—C disconnections 712
1,5-Related functional groups 719
'Natural reactivity' and 'umpolung' 719
To conclude... 722
Further reading 722

**29 Aromatic heterocycles 1: reactions 723**

Introduction 723
Aromaticity survives when parts of benzene's ring are replaced by nitrogen atoms 724
Pyridine is a very unreactive aromatic imine 725
Six-membered aromatic heterocycles can have oxygen in the ring 732
Five-membered aromatic heterocycles are good at electrophilic substitution 733
Furan and thiophene are oxygen and sulfur analogues of pyrrole 735
More reactions of five-membered heterocycles 738
Five-membered rings with two or more nitrogen atoms 740
Benzo-fused heterocycles 745
Putting more nitrogen atoms in a six-membered ring 748
Fusing rings to pyridines: quinolines and isoquinolines 749
Aromatic heterocycles can have many nitrogens but only one sulfur or oxygen in any ring 751
There are thousands more heterocycles out there 753
Which heterocyclic structures should you learn? 754
Further reading 755

**30 Aromatic heterocycles 2: synthesis 757**

Thermodynamics is on our side 758
Disconnect the carbon—heteroatom bonds first 758
Pyrroles, thiophenes, and furans from 1,4-dicarbonyl compounds 760
How to make pyridines: the Hantzsch pyridine synthesis 763
Pyrazoles and pyridazines from hydrazine and dicarbonyl compounds 767
Pyrimidines can be made from 1,3-dicarbonyl compounds and amidines 770
Unsymmetrical nucleophiles lead to selectivity questions 771
Isoxazoles are made from hydroxylamine or by cycloaddition 772
Tetrazoles and triazoles are also made by cycloadditions 774
The Fischer indole synthesis 775

Quinolines and isoquinolines 780
More heteroatoms in fused rings mean more choice in synthesis 784
Summary: the three major approaches to the synthesis of aromatic heterocycles 785
Further reading 788

**31 Saturated heterocycles and stereoelectronics 789**
Introduction 789
Reactions of saturated heterocycles 790
Conformation of saturated heterocycles 796
Making heterocycles: ring-closing reactions 805
Ring size and NMR 814
Geminal ($^2J$) coupling 817
Diastereotopic groups 820
To summarize... 824
Further reading 824

**32 Stereoselectivity in cyclic molecules 825**
Introduction 825
Stereochemical control in six-membered rings 826
Reactions on small rings 832
Regiochemical control in cyclohexene epoxides 836
Stereoselectivity in bicyclic compounds 839
Fused bicyclic compounds 841
Spirocyclic compounds 846
Reactions with cyclic intermediates or cyclic transition states 847
To summarize... 851
Further reading 851

**33 Diastereoselectivity 852**
Looking back 852
Prochirality 856
Additions to carbonyl groups can be diastereoselective even without rings 858
Stereoselective reactions of acyclic alkenes 865
Aldol reactions can be stereoselective 868
Single enantiomers from diastereoselective reactions 871
Looking forward 876
Further reading 876

**34 Pericyclic reactions 1: cycloadditions 877**
A new sort of reaction 877
General description of the Diels–Alder reaction 879
The frontier orbital description of cycloadditions 886
Regioselectivity in Diels–Alder reactions 889
The Woodward–Hoffmann description of the Diels–Alder reaction 892
Trapping reactive intermediates by cycloadditions 893
Other thermal cycloadditions 894
Photochemical [2 + 2] cycloadditions 896
Thermal [2 + 2] cycloadditions 898
Making five-membered rings: 1,3-dipolar cycloadditions 901
Two very important synthetic reactions: cycloaddition of alkenes with osmium tetroxide and with ozone 905
Summary of cycloaddition reactions 907
Further reading 908

**35 Pericyclic reactions 2: sigmatropic and electrocyclic reactions 909**
Sigmatropic rearrangements 909
Orbital descriptions of [3,3]-sigmatropic rearrangements 912
The direction of [3,3]-sigmatropic rearrangements 913
[2,3]-Sigmatropic rearrangements 917
[1,5]-Sigmatropic hydrogen shifts 919
Electrocyclic reactions 922
Further reading 930

**36 Participation, rearrangement, and fragmentation 931**
Neighbouring groups can accelerate substitution reactions 931
Rearrangements occur when a participating group ends up bonded to a different atom 937
Carbocations readily rearrange 940
The pinacol rearrangement 945
The dienone-phenol rearrangement 949
The benzilic acid rearrangement 950
The Favorskii rearrangement 950
Migration to oxygen: the Baeyer–Villiger reaction 953
The Beckmann rearrangement 958
Polarization of C—C bonds helps fragmentation 960
Fragmentations are controlled by stereochemistry 962
Ring expansion by fragmentation 963
Controlling double bonds using fragmentation 965
The synthesis of nootkatone: fragmentation showcase 966
Looking forward 969
Further reading 969

**37 Radical reactions 970**
Radicals contain unpaired electrons 970
Radicals form by homolysis of weak bonds 971

Most radicals are extremely reactive... 974
How to analyse the structure of radicals: electron spin resonance 975
Radical stability 977
How do radicals react? 980
Radical–radical reactions 980
Radical chain reactions 984
Chlorination of alkanes 986
Allylic bromination 989
Reversing the selectivity: radical substitution of Br by H 990
Carbon–carbon bond formation with radicals 992
The reactivity pattern of radicals is quite different from that of polar reagents 997
Alkyl radicals from boranes and oxygen 998
Intramolecular radical reactions are more efficient than intermolecular ones 999
Looking forward 1002
Further reading 1002

**38 Synthesis and reactions of carbenes 1003**

Diazomethane makes methyl esters from carboxylic acids 1003
Photolysis of diazomethane produces a carbene 1005
How do we know that carbenes exist? 1006
Ways to make carbenes 1006
Carbenes can be divided into two types 1010
How do carbenes react? 1013
Carbenes react with alkenes to give cyclopropanes 1013
Insertion into C–H bonds 1018
Rearrangement reactions 1020
Nitrenes are the nitrogen analogues of carbenes 1022
Alkene metathesis 1023
Summary 1027
Further reading 1027

**39 Determining reaction mechanisms 1029**

There are mechanisms and there are mechanisms 1029
Determining reaction mechanisms: the Cannizzaro reaction 1031
Be sure of the structure of the product 1035
Systematic structural variation 1040
The Hammett relationship 1041
Other kinetic evidence for reaction mechanisms 1050
Acid and base catalysis 1053
The detection of intermediates 1060
Stereochemistry and mechanism 1063
Summary of methods for the investigation of mechanism 1067
Further reading 1068

**40 Organometallic chemistry 1069**

Transition metals extend the range of organic reactions 1069
The 18 electron rule 1070
Bonding and reactions in transition metal complexes 1073
Palladium is the most widely used metal in homogeneous catalysis 1078
The Heck reaction couples together an organic halide or triflate and an alkene 1079
Cross-coupling of organometallics and halides 1082
Allylic electrophiles are activated by palladium(0) 1088
Palladium-catalysed amination of aromatic rings 1092
Alkenes coordinated to palladium(II) are attacked by nucleophiles 1096
Palladium catalysis in the total synthesis of a natural alkaloid 1098
An overview of some other transition metals 1099
Further reading 1101

**41 Asymmetric synthesis 1102**

Nature is asymmetric 1102
The chiral pool: Nature's chiral centres 'off the shelf' 1104
Resolution can be used to separate enantiomers 1106
Chiral auxiliaries 1107
Chiral reagents 1113
Asymmetric catalysis 1114
Asymmetric formation of carbon–carbon bonds 1126
Asymmetric aldol reactions 1129
Enzymes as catalysts 1132
Further reading 1133

**42 Organic chemistry of life 1134**

Primary metabolism 1134
Life begins with nucleic acids 1135
Proteins are made of amino acids 1139
Sugars—just energy sources? 1142
Lipids 1147
Mechanisms in biological chemistry 1149
Natural products 1156
Fatty acids and other polyketides are made from acetyl CoA 1161
Terpenes are volatile constituents of plants 1164
Further reading 1167

**43 Organic chemistry today** **1169**

Science advances through interaction between disciplines 1169

Chemistry vs viruses 1170

The future of organic chemistry 1179

Further reading 1181

Figure acknowledgements [illegible]

Periodic table of the elements [illegible]

Index [illegible]