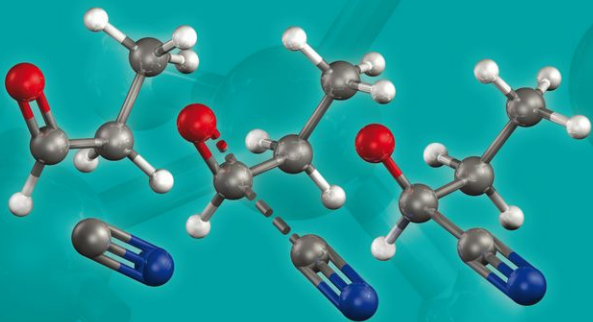


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ORGANIC CHEMISTRY

SECOND
EDITION



Jonathan Clayden, Nick Greeves,
and Stuart Warren

Organic Chemistry

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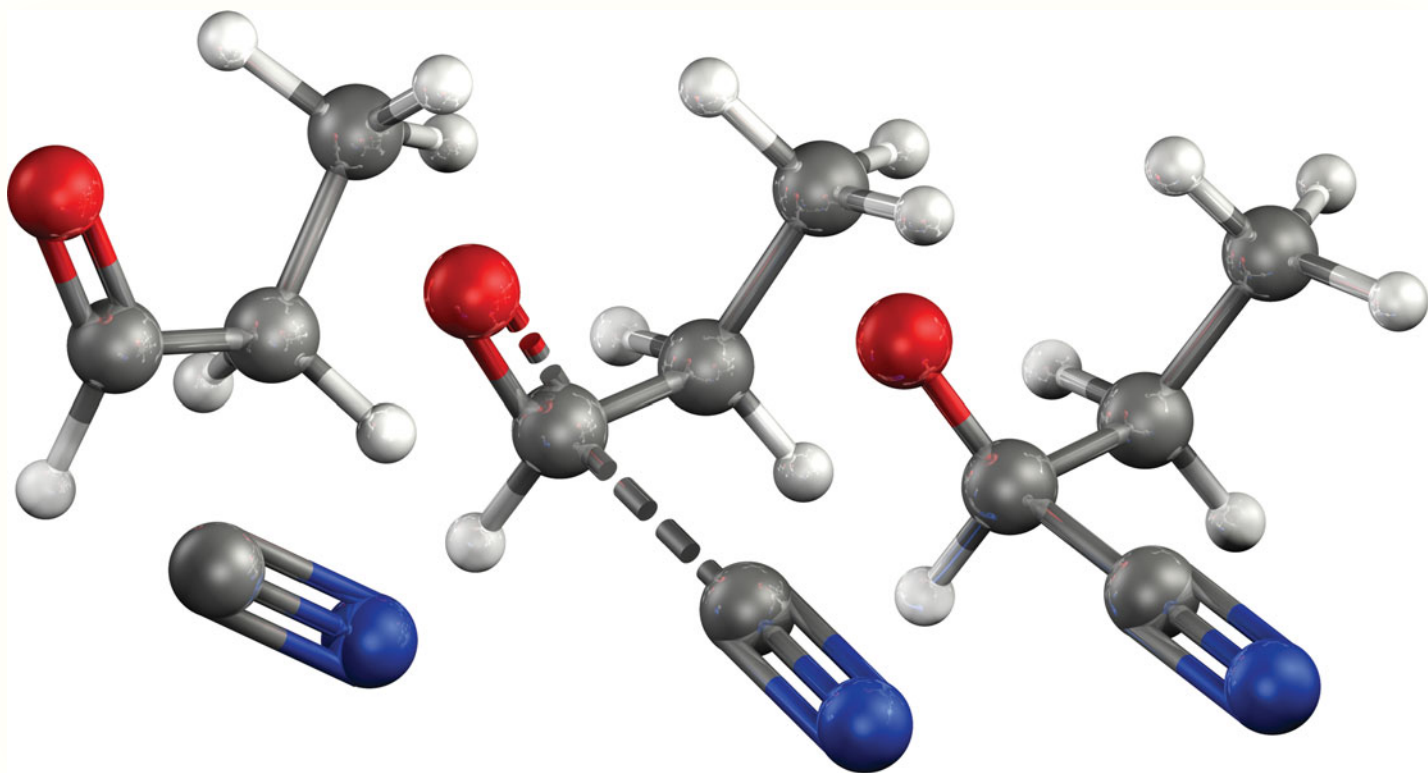
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SECOND
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Abbreviations

Ac	Acetyl	DMS	Dimethyl sulfide
Acac	Acetylacetonate	DMSO	Dimethyl sulfoxide
AD	Asymmetric dihydroxylation	DNA	Deoxyribonucleic acid
ADP	Adenosine 5'-diphosphate	E1	Unimolecular elimination
AE	Asymmetric epoxidation	E2	Bimolecular elimination
AIBN	Azobisisobutyronitrile	E _a	Activation energy
AO	Atomic orbital	EDTA	Ethylenediaminetetraacetic acid
Ar	Aryl	EPR	Electron paramagnetic resonance
ATP	Adenosine triphosphate	ESR	Electron spin resonance
9-BBN	9-Borabicyclo[3.3.1]nonane	Et	Ethyl
BHT	Butylated hydroxy toluene (2,6-di- <i>t</i> -butyl-4-methylphenol)	FGI	Functional group interconversion
BINAP	Bis(diphenylphosphino)-1,1'-binaphthyl	Fmoc	Fluorenylmethyloxycarbonyl
Bn	Benzyl	GAC	General acid catalysis
Boc, BOC	<i>tert</i> -Butyloxycarbonyl	GBC	General base catalysis
Bu	Butyl	HMPA	Hexamethylphosphoramide
<i>s</i> -Bu	<i>sec</i> -Butyl	HMPT	Hexamethylphosphorous triamide
<i>t</i> -Bu	<i>tert</i> -Butyl	HOBt	1-Hydroxybenzotriazole
Bz	Benzoyl	HOMO	Highest occupied molecular orbital
Cbz	Carboxybenzyl	HPLC	High performance liquid chromatography
CDI	Carbonyldiimidazole	HIV	Human immunodeficiency virus
CI	Chemical ionization	IR	Infrared
CoA	Coenzyme A	KHMDS	Potassium hexamethyldisilazide
COT	Cyclooctatetraene	LCAO	Linear combination of atomic orbitals
Cp	Cyclopentadienyl	LDA	Lithium diisopropylamide
DABCO	1,4-Diazabicyclo[2.2.2]octane	LHMDS	Lithium hexamethyldisilazide
DBE	Double bond equivalent	LICA	Lithium isopropylcyclohexylamide
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene	LTMP, LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	LUMO	Lowest unoccupied molecular orbital
DCC	<i>N,N</i> -dicyclohexylcarbodiimide	<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	Me	Methyl
DEAD	Diethyl azodicarboxylate	MO	Molecular orbital
DIBAL	Diisobutylaluminum hydride	MOM	Methoxymethyl
DMAP	4-Dimethylaminopyridine	Ms	Methanesulfonyl (mesyl)
DME	1,2-Dimethoxyethane	NAD	Nicotinamide adenine dinucleotide
DMF	<i>N,N</i> -Dimethylformamide	NADH	Reduced NAD
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone	NBS	<i>N</i> -Bromosuccinimide
		NIS	<i>N</i> -Iodosuccinimide
		NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide

NMR	Nuclear magnetic resonance	SOMO	Singly occupied molecular orbital
NOE	Nuclear Overhauser effect	STM	Scanning tunnelling microscopy
PCC	Pyridinium chlorochromate	TBDMS	<i>Tert</i> -butyldimethylsilyl
PDC	Pyridinium dichromate	TBDPS	<i>Tert</i> -butyldiphenylsilyl
Ph	Phenyl	Tf	Trifluoromethanesulfonyl (triflyl)
PPA	Polyphosphoric acid	THF	Tetrahydrofuran
Pr	Propyl	THP	Tetrahydropyran
<i>i</i> -Pr	<i>iso</i> -Propyl	TIPS	Triisopropylsilyl
PTC	Phase transfer catalysis	TMEDA	<i>N,N,N',N'</i> -tetramethyl-1,2-ethylenediamine
PTSA	<i>p</i> -Toluenesulfonic acid	TMP	2,2,6,6-Tetramethylpiperidine
Py	Pyridine	TMS	Trimethylsilyl, tetramethylsilane
Red Al	Sodium <i>bis</i> (2-methoxyethoxy) aluminum hydride	TMSOTf	Trimethylsilyl triflate
RNA	Ribonucleic acid	TPAP	Tetra- <i>N</i> -propylammonium perruthenate
SAC	Specific acid catalysis	Tr	Triphenylmethyl (trityl)
SAM	<i>S</i> -Adenosyl methionine	TS	Transition state
SBC	Specific base catalysis	Ts	<i>p</i> -Toluenesulfonyl, tosyl
S_N1	Unimolecular nucleophilic substitution	UV	Ultraviolet
S_N2	Bimolecular nucleophilic substitution	VSEPR	Valence shell electron pair repulsion

Preface to the second edition

Students of chemistry are not hard-pressed to find a text to support their learning in organic chemistry through their years at university. The shelves of a university bookshop will usually offer a choice of at least half a dozen—all entitled ‘Organic Chemistry’, all with substantially more than 1000 pages. Closer inspection of these titles quickly disappoints expectations of variety. Almost without exception, general organic chemistry texts have been written to accompany traditional American sophomore courses, with their rather precisely defined requirements. This has left the authors of these books little scope for reinvigorating their presentation of chemistry with new ideas.

We wanted to write a book whose structure grows from the development of ideas rather than being dictated by the sequential presentation of facts. We believe that students benefit most of all from a book which leads from familiar concepts to unfamiliar ones, not just encouraging them to *know* but to *understand* and to understand *why*. We were spurred on by the nature of the best modern university chemistry courses, which themselves follow this pattern: this is after all how science itself develops. We also knew that if we did this we could, from the start, relate the chemistry we were talking about to the two most important sorts of chemistry that exist—the chemistry that is known as life, and the chemistry as practised by chemists solving real problems in laboratories.

We aimed at an approach which would make sense to and appeal to today’s students. But all of this meant taking the axe to the roots of some long-standing textbook traditions. The best way to find out how something works is to take it apart and put it back together again, so we started with the tools for expressing chemical ideas: structural diagrams and curly arrows. Organic chemistry is too huge a field to learn even a small part by rote, but with these tools, students can soon make sense of chemistry which may be unfamiliar in detail by relating it to what they know and understand. By calling on curly arrows and ordering chemistry according to mechanism we allow ourselves to discuss mechanistically (and orbitally) simple reactions (addition to C=O, for example) before more complex and involved ones (such as S_N1 and S_N2).

Complexity follows in its own time, but we have deliberately omitted detailed discussion of obscure reactions of little value, or of variants of reactions which lie a simple step of mechanistic logic from our main story: some of these are explored in the problems associated with each chapter, which are available online.¹ We have similarly aimed to avoid exhuming principles and rules (from those of Le Châtelier through Markovnikov, Saytseff, least motion, and the like) to explain things which are better understood in terms of unifying fundamental thermodynamic or mechanistic concepts.

All science must be underpinned by evidence, and support for organic chemistry’s claims is provided by spectroscopy. For this reason we first reveal to students the facts which spectroscopy tells us (Chapter 3) before trying to explain them (Chapter 4) and then use them to deduce mechanisms (Chapter 5). NMR in particular forms a significant part of four chapters in the book, and evidence drawn from NMR underpins many of the discussions right through the book. Likewise, the mechanistic principles we outline in Chapter 5, firmly based in the orbital theories of Chapter 4, underpin all of the discussion of new reactions through the rest of the book.

We have presented chemistry as something whose essence is truth, of provable veracity, but which is embellished with opinions and suggestions to which not all chemists subscribe. We aim to avoid dogma and promote the healthy weighing up of evidence, and on occasion we are content to leave readers to draw their own conclusions. Science is important not just to scientists, but to society. Our aim has been to write a book which itself takes a scientific

¹ See www.oxfordtextbooks.co.uk/orc/clayden2e/.

standpoint—‘one foot inside the boundary of the known, the other just outside’²—and encourages the reader to do the same.

The authors are indebted to the many supportive and critical readers of the first edition of this book who have supplied us over the last ten years with a stream of comments and corrections, hearty encouragements and stern rebukes. All were carefully noted and none was overlooked while we were writing this edition. In many cases these contributions helped us to correct errors or make other improvements to the text. We would also like to acknowledge the support and guidance of the editorial team at OUP, and again to recognize the seminal contribution of the man who first nurtured the vision that organic chemistry could be taught with a book like this, Michael Rodgers. The time spent on the preparation of this edition was made available only with the forbearance of our families, friends and research groups, and we thank all of them for their patience and understanding.

Changes for this edition

In the decade since the publication of the first edition of this book it has become clear that some aspects of our original approach were in need of revision, some chapters in need of updating with material which has gained in significance over those years, and others in need of shortening. We have taken into account a consistent criticism from readers that the early chapters of the first edition were too detailed for new students, and have made substantial changes to the material in Chapters 4, 8, and 12, shifting the emphasis towards explanation and away from detail more suitably found in specialised texts. Every chapter has been rewritten to improve clarity and new explanations and examples have been used widely. The style, location, and content of the spectroscopy chapters (3, 13, 18, and 31) have been revised to strengthen the links with material appearing nearby in the book. Concepts such as conjugate addition and regioselectivity, which previously lacked coherent presentation, now have their own chapters (22 and 24). In some sections of the first edition, groups of chapters were used to present related material: these chapter groups have now been condensed—so, for example, Chapters 25 and 26 on enolate chemistry replace four previous chapters, Chapters 31 and 32 on cyclic molecules replace three chapters, Chapter 36 on rearrangements and fragmentations replaces two chapters, and Chapter 42 on the organic chemistry of life replaces three chapters (the former versions of which are available online). Three chapters placed late in the first edition have been moved forward and revised to emphasize links between their material and the enolate chemistry of Chapters 25 and 26, thus Chapter 27 deals with double-bond stereocontrol in the context of organo-main group chemistry, and Chapters 29 and 30, addressing aromatic heterocycles, now reinforce the link between many of the mechanisms characteristic of these compounds and those of the carbonyl addition and condensation reactions discussed in the previous chapters. Earlier discussion of heterocycles also allows a theme of cyclic molecules and transition states to develop throughout Chapters 29–36, and matches more closely the typical order of material in undergraduate courses.

Some fields have inevitably advanced considerably in the last 10 years: the chapters on organometallic chemistry (40) and asymmetric synthesis (41) have received the most extensive revision, and are now placed consecutively to allow the essential role of organometallic catalysis in asymmetric synthesis to come to the fore. Throughout the book, new examples, especially from the recent literature of drug synthesis, have been used to illustrate the reactions being discussed.

² McEvedy, C. *The Penguin Atlas of Ancient History*, Penguin Books, 1967.

Organic chemistry and this book

You can tell from the title that this book tells you about organic chemistry. But it tells you more than that: it tells you *how we know* about organic chemistry. It tells you facts, but it also teaches you how to find facts out. It tells you about reactions, and teaches you how to predict which reactions will work; it tells you about molecules, and it teaches you how to work out ways of making them.

We said 'it tells' in that last paragraph. Maybe we should have said 'we tell' because we want to speak to you through our words so that you can see how we think about organic chemistry and to encourage you to develop your own ideas. We expect you to notice that three people have written this book, and that they don't all think or write in the same way. That is as it should be. Organic chemistry is too big and important a subject to be restricted by dogmatic rules. Different chemists think in different ways about many aspects of organic chemistry and in many cases it is not yet, and may never be, possible to be sure who is right. In many cases it doesn't matter anyway.

We may refer to the history of chemistry from time to time but we are usually going to tell you about organic chemistry as it is now. We will develop the ideas slowly, from simple and fundamental ones using small molecules to complex ideas and large molecules. We promise one thing. We are not going to pull the wool over your eyes by making things artificially simple and avoiding the awkward questions. We aim to be honest and share both our delight in good complete explanations and our puzzlement at inadequate ones.

The chapters

So how are we going to do this? The book starts with a series of chapters on the structures and reactions of simple molecules. You will meet the way structures are determined and the theory that explains those structures. It is vital that you realize that theory is used to explain what is known by experiment and only then to predict what is unknown. You will meet mechanisms—the dynamic language used by chemists to talk about reactions—and of course some reactions.

The book starts with an introductory section of four chapters:

1. What is organic chemistry?
2. Organic structures
3. Determining organic structures
4. Structure of molecules

Chapter 1 is a 'rough guide' to the subject—it will introduce the major areas where organic chemistry plays a role, and set the scene by showing you some snapshots of a few landmarks. In Chapter 2 you will look at the way in which we present diagrams of molecules on the printed page. Organic chemistry is a visual, three-dimensional subject and the way you draw molecules shows how you think about them. We want you too to draw molecules in the best way possible. It is just as easy to draw them well as to draw them in an old-fashioned or inaccurate way.

Then in Chapter 3, before we come to the theory which *explains* molecular structure, we shall introduce you to the experimental techniques which *tell us about* molecular structure. This means studying the interactions between molecules and radiation by spectroscopy—using the whole electromagnetic spectrum from X-rays to radio waves. Only then, in Chapter 4, will we go behind the scenes and look at the theories of why atoms combine in the ways they do. Experiment comes before explanation. The spectroscopic methods of Chapter 3 will still be telling the truth in a hundred years' time, but the theories of Chapter 4 will look quite dated by then.