CHEMISTRY OF THE CARBONYL GROUP
A STEP-BY-STEP APPROACH TO UNDERSTANDING ORGANIC REACTION MECHANISMS

TIMOTHY K. DICKENS
STUART WARREN

WILEY
CHEMISTRY OF THE CARBONYL GROUP
CHEMISTRY OF THE CARBONYL GROUP
A step-by-step approach to understanding Organic Reaction Mechanisms

Revised Edition

Timothy K. Dickens
Fellow and Director of Studies in Chemistry
Peterhouse, Cambridge

Stuart Warren
Retired Fellow
Churchill College, Cambridge

WILEY
To Sophie Jackson and
Chris Lester
## CONTENTS

**PREFACE** xi  
**ACKNOWLEDGEMENTS** xiii  
**SOME HELP THAT YOU MAY NEED** xv  
**WHAT DO YOU NEED TO KNOW BEFORE YOU START?** xvii  
**INTRODUCTION** xix  

1 Nucleophilic Addition to the Carbonyl Group 1  
Nucleophilic addition: what it is and how it happens 3  
Alcohols as nucleophiles: acetal formation 6  
Some carbon–carbon bond-forming reactions with carbon nucleophiles: cyanide ion, acetylide ion and Grignard reagents 10  
Hydride ion and its derivatives LiAlH₄ and NaBH₄. Reduction of aldehydes and ketones 17  
Meerwein–Ponndorf reduction and Oppenauer oxidation, with a branch program on how to draw transition states 19  
Two general revision problems 25
## CONTENTS

### 2 Nucleophilic Substitution 29
- Substitution: how it happens 31
- LiAlH₄ reduction of esters 33
- Reaction of Grignard reagents with esters 34
- Alkaline hydrolysis of esters 38
- Acid hydrolysis of amides 39
- Summary of acid and base catalysis 41
- Reaction between carboxylic acids and thionyl chloride 41
- Synthesis of esters and anhydrides from carboxylic acids 43
- Review questions 45

### 3 Nucleophilic Substitution at the Carbonyl Group with Complete Removal of Carbonyl Oxygen 49
- Imine formation from aldehydes and ketones 51
- Oxime formation and the structure of oximes 53
- Hydrazono and semicarbazone formation 54
- Reduction of C=O to CH₂ 56
- Conversion of C=O to CCl₂ 60
- DDT synthesis 64
- Chloromethylation of aromatic compounds 65
- Review questions 66

### 4 Carbanions and Enolisation 69
- Carbanions 71
- Tautomerism 72
- Equilibration and racemisation of ketones by enolisation 73
- Halogenation of ketones 78
- Formation of bromo-acid derivatives 83
- Organo-zinc derivatives and their use in synthesis 85
- Review questions 87
5 Building Organic Molecules from Carbonyl Compounds

Using enols as nucleophiles to attack other carbonyl groups 92
The aldol reaction 92
The Claisen ester condensation 93
Acid catalysed condensation of acetone 94
Self-condensation reactions 96
Elaboration of a skeleton in synthesis 97
Cross-condensations with molecules which cannot enolise 98
Mannich reaction 103
Perkin reaction 105
Stable enols from β-dicarbonyl compounds 108
Knoevenagel reaction 110
Alkylation of β-dicarbonyl compounds 113
Michael reaction 116
Decarboxylation 125
Base cleavage of β-dicarbonyl compounds 131
Cyclisation reactions: the Dieckmann condensation 134
Cyclisation of diketones 136
The dimedone synthesis 137
Ring opening by base cleavage of β-dicarbonyl compounds 141
Revision questions 142
Examples of syntheses: two steroid syntheses 145
Stork’s cedrene synthesis 150

INDEX 155
Understanding the movement of electrons as a reaction takes place is perhaps the hardest general concept in Organic Chemistry. This is often referred to as ‘pushing curly arrows’. Once this concept has been grasped, it becomes possible to rationalise what is happening in a chemical reaction and predictions can start to be made. In *Chemistry of the Carbonyl Group*, five chemical reactions are explored. These are nucleophilic addition, nucleophilic substitution, nucleophilic substitution with complete removal of carbonyl oxygen, carbanions and enolisation. With these reactions, it is possible to design and build organic molecules from carbonyl compounds. The last section of the book covers this. This understanding of the processes behind reactions by extrapolation can be used to rationalise organic reactions involving heteroatoms such as nitrogen, phosphorus and sulphur. Other types of chemical reactions, such as electrophilic substitution and addition, become easy to comprehend.
It is the authors’ firm belief that the most effective way to learn is by practice and interaction. With this in mind, the reader is asked to predict what would happen under a specific set of reaction conditions. The book is divided into frames. These frames pose a question and invite the reader to predict what will happen. Subsequent frames give the solution but then pose more questions to develop a theme further. Therefore, the book should be worked through with pen and paper.

The reactions of the carbonyl group are some of the first reactions that a student studying Chemistry at university will encounter. As such, this book should be tackled just before, or when, a student is starting Organic Chemistry. Indeed, at Peterhouse, first year Natural Science students taking Chemistry are encouraged to work through this book during the Christmas break. Students who do this make substantially faster progress with the Cambridge Organic Chemistry course during the Lent term. The book could also be used by gifted or curious sixth-form students who are keen to broaden their knowledge of Organic Chemistry beyond the A-level syllabus.

This book was first published in 1974. After some discussion, it was decided not to change the text substantially. The motivation was very much to improve the layout of the book; hence all the diagrams have been redrawn using ChemDraw and the text formatted using the text mark-up language \LaTeX. One area that it might have been appropriate to develop is a discussion of the frontier orbitals; this would lead to an understanding of why the “magic angle” of attack in nucleophilic addition\textsuperscript{1–3} is $107^\circ$. However, this could be seen as an unnecessary distraction, depending on what other Chemistry topics the reader is already familiar with.

Timothy K. Dickens, Cambridge February 2018

ACKNOWLEDGEMENTS

This edition has largely been developed by T.K.D. As the revising author, he is indebted to a number of people, including his son, Alex, who first drew T.K.D.’s attention to it whilst he was assigned this book as a Christmas break exercise when studying Chemistry at New College, Oxford. T.K.D. wishes to express his gratitude to Dr Peter Wothers (Teaching Fellow at the Department of Chemistry at Cambridge) for general advice, to Professor Jonathan Clayden for the discussion on the representation of tetrahedral angles and charges on atoms, to Jenny Cossham, the publisher of this book at Wiley, for her warm encouragement and discussion on layout and presentation of material in this revised edition, to Dr James Keeler (Director of Teaching at the Department of Chemistry) who got the author started with using \LaTeX{} and especially to Dr Russell Currie who provided much detailed technical help with the package and for meticulously proof reading drafts of this edition. T.K.D. is indebted
to Dr Roger Mallion for the thoroughness with which he checked the manuscript for grammatical and chemical errors. However, the two people whom he would chiefly like to thank are Dr Stuart Warren for all his wonderful help, insight, support and ever helpful encouragement and Catherine, his wife, for her patience every time he disappeared into his study to work on this volume.
SOME HELP THAT YOU MAY NEED

Throughout this book, several references are made to consulting an advisor. An advisor is someone who can guide the reader if a concept is not fully understood or more detail is required. An advisor could be a college tutor or supervisor, lecturer, graduate student or even a student in a later year who has a passion for chemistry. If the book is being tackled by a sixth former, then perhaps his or her chemistry teacher could act in the role of an advisor.

Books that you might find useful:

General Organic Chemistry Textbooks:


The solutions to the problems posed in these books can be found in:


For those who wish to gain a better grasp of using Molecular Orbitals to describe reactions in Organic Chemistry see:

WHAT DO YOU NEED TO KNOW BEFORE YOU START?

The program is about only a small part of organic chemistry, and we have to assume that you know certain facts and appreciate certain concepts. In case you feel uncertain about any of these, here is a list of them with appropriate remedies in each case.\(^1\)

We assume you can:

- Draw and recognise structures of simple organic compounds (an aldehyde, acetone, \(n\)-butanol, etc.). Any organic textbook will tell you about this.